

1 **Is standard deviation of daily PM_{2.5} concentration associated with respiratory**
2 **mortality?**

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23 **ABSTRACT**

24 Studies on health effects of air pollution often use daily mean concentration to
25 estimate exposure while ignoring daily variations. This study examined the health
26 effects of daily variation of PM_{2.5}. We calculated daily mean and standard deviations
27 of PM_{2.5} in Hong Kong between 1998 and 2011. We used a generalized additive
28 model to estimate the association between respiratory mortality and daily mean and
29 variation of PM_{2.5}, as well as their interaction. We controlled for potential
30 confounders, including temporal trends, day of the week, meteorological factors, and
31 gaseous air pollutants. Both daily mean and standard deviation of PM_{2.5} were
32 significantly associated with mortalities from overall respiratory diseases and
33 pneumonia. Each 10 ug/m³ increment in daily mean concentration at lag 2 day was
34 associated with a 0.61% (95% CI: 0.19%, 1.03%) increase in overall respiratory
35 mortality and a 0.67% (95% CI: 0.14%, 1.21%) increase in pneumonia mortality. And
36 a 10 ug/m³ increase in standard deviation at lag 1 day corresponded to a 1.40% (95%
37 CI: 0.35%, 2.46%) increase in overall respiratory mortality, and a 1.80% (95% CI:
38 0.46%, 3.16%) increase in pneumonia mortality. We also observed a positive but
39 non-significant synergistic interaction between daily mean and variation on
40 respiratory mortality and pneumonia mortality. However, we did not find any
41 significant association with mortality from chronic obstructive pulmonary diseases.
42 Our study suggests that, besides mean concentration, the standard deviation of PM_{2.5}
43 might be one potential predictor of respiratory mortality in Hong Kong, and should be
44 considered when assessing the respiratory effects of PM_{2.5}.

45

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

49

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

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54 **1. Introduction**

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

63 It is reasonable to hypothesize that daily variation of PM_{2.5} might be
64 independently associated with health outcomes. Consider the following hypothetical
65 scenarios, where each day is divided into three equal periods and under the
66 simplifying assumption that all covariates are held constant. Under this framework,
67 suppose that the mortality count (on the logarithmic scale) is 100 when PM_{2.5}
68 concentration is 50 for each of the three time periods, and that the RR per 10 ug/m³
69 increase in PM_{2.5} is 2. In our first scenario, suppose that the PM_{2.5} concentration is
70 stable at 60 ug/m³, resulting in a mortality count of 600 (100*RR*3 time periods
71 =100*2*3=600). In the second scenario, suppose that the mean concentration is the
72 same as the first scenario (60 ug/m³), yet with large variability between the three time
73 periods, 50, 60 and 70 ug/m³, respectively. The mortality count would be 700 [100+
74 (100*2) + (100*4) =700], which is considerably larger than the mortality in the first
75 scenario. These hypothetical scenarios suggest that variations in PM_{2.5} throughout a

76 given day should not be ignored as it may directly impact health outcomes.

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

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

92

93 **2. Materials and methods**

94 *2.1 Air Pollution Data*

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

98 2012). In brief, there are 14 air monitoring stations in Hong Kong, each of which
99 collected four major air pollutants (PM₁₀, NO₂, SO₂, and O₃). Hourly concentrations
100 of PM_{2.5} have been monitored in four stations (Tsuen Wan (TW), Tap Mun (TM),
101 Tung Chung (TC) and Central (CL)) since 1998 (Fig. 1). We used the average of daily
102 mean and variation of these four stations in the main model to approximate PM_{2.5}
103 concentrations for all of Hong Kong.

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

109 We also calculated daily mean concentrations of NO₂, SO₂ and 8-hour mean
110 (10:00 to 18:00) concentrations of O₃ using data from these four stations. Daily
111 meteorological data for the same period, including daily mean temperature (°C),
112 relative humidity (%) and wind speed (m/s), were also obtained from the Hong Kong
113 Observatory.

114

115 *2.2 Mortality Data*

116 Daily mortality data, which covered all deaths in Hong Kong over the period of
117 1998-2011, were obtained from the Hong Kong Census and Statistics Department.
118 They were coded according to the 9th revision (1998-2000) or 10th revision
119 (2001-2011) of the International Classification of Diseases (ICD). Overall respiratory

120 deaths (ICD-9: 460-519 or ICD-10: J00-J99, 519, excluding influenza), chronic
121 obstructive pulmonary diseases (COPD, ICD-9: 491-492, and 496 or ICD-10:
122 J40-J44), and pneumonia (ICD-9: 480-486 or ICD-10: J12-J18) were extracted to
123 construct the corresponding time series. We excluded influenza because previous
124 studies suggested that influenza epidemics may confound the associations between air
125 pollution and respiratory mortality (Ren et al. 2006, Qiu et al. 2012). Therefore, daily
126 hospital admissions for influenza were abstracted and used to identify influenza
127 outbreaks, which were then treated as a potential confounder in the analysis (Thach et
128 al. 2010).

129

130 2.3 Statistical methods

131 We examined the short-term association between daily mean and variation of
132 $PM_{2.5}$ concentrations and respiratory mortalities using generalized additive models
133 (GAM), and a quasi-Poisson link function was applied to account for over-dispersion
134 in daily respiratory mortality (Zanobetti and Schwartz 2008, Stieb et al. 2009). We
135 used a penalized smoothing spline to filter out seasonality and long-term trends in
136 daily mortality, as well as temperature and relative humidity. We included day of the
137 week and public holidays in the model as dummy variables (Schwartz and Morris
138 1995). To adjust for the potential confounding effect of influenza outbreaks, we
139 entered a dummy variable for weeks with the number of influenza hospital admissions
140 exceeding the 75th percentile in a year into the model (Wong et al. 2002).

141 To reduce the potential concerns associated with multiple testing and model

142 selection, we selected *a priori* model specification and degrees of freedom (df) for
143 temporal trends and meteorological factors, as has been done by others (Bell et al.
144 2008, Peng et al. 2008, Tian et al. 2013). We used a df of 6 per year for time trends to
145 filter out the information at time scales of 2 months, a df of 6 for mean temperature of
146 current day temperature (Temp₀) and previous 3 days' moving average (Temp₁₋₃) and
147 a df of 3 for current day's relative humidity (Humidity₀). For temperatures, 6 df was
148 chosen to account for potential nonlinear relationship between temperature and
149 mortality (Curriero et al. 2002). Briefly, we set up a core model to remove the
150 long-term trends, seasonal variations and to adjust for time varying confounders as
151 follows:

$$\begin{aligned} 152 \log[E(Y_t)] = & \alpha + s(t, \text{df}=6/\text{year}) + s(\text{Temp}_0, \text{df}=6) + s(\text{Temp}_{1-3}, \text{df}=6) \\ 153 & + s(\text{Humidity}_0, \text{df}=3) + \beta_1 * \text{DOW} + \beta_2 * \text{PH} + \beta_3 * \text{Influenza}, \end{aligned}$$

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

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

160 We estimated the linear effects with different lag structures including both
161 single-day lag (from the current day (lag₀) up to three lag days (lag₃)), as previous
162 studies in China showed little evidence of association with a lag beyond 3 days (Kan
163 et al. 2007, Lin et al. 2016). We also examined the respiratory mortality impacts of

164 multi-day lags (moving averages for the current day and the previous 1, 2 and 3 days:
165 lag₀₁, lag₀₂, and lag₀₃).

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

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

182 Our analysis suggested that they were independent (controlling for daily mean
183 concentration of PM_{2.5} did not change the risk estimates of daily PM_{2.5} SD, as shown
184 in Table 3), so we further examined their interaction using an additive model proposed
185 by Andersson (Andersson et al. 2005), and calculated three measures of additive

186 interactions: relative excess risk due to interaction (RERI), attributable proportion
187 (AP) and synergy index (SI). When RERI and AP were equal to 0 and SI equal to 1,
188 we considered that to be absence of additive interaction; while additive interaction
189 was present if RERI and AP did not equal 0 and SI exceeded unity. Furthermore, an SI
190 greater than 1 denoted a synergetic interaction, which implied that the joint effects of
191 two factors in an additive model was greater than sum of their individual effects. On
192 the other hand, if SI was smaller than 1, it implied an antagonistic interaction,
193 indicating that in the presence of two exposures in an additive model, one factor
194 decreased the effect of the other (Lundberg et al. 1996, Zhang et al. 2016).

195

196 *2.4 Sensitivity analysis*

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

208 All analyses were conducted using the “mgcv” package in R. We reported the
 209 results as excess relative risk (ERR) in respiratory mortality for each 10 $\mu\text{g}/\text{m}^3$
 210 increase in daily $\text{PM}_{2.5}$ variation. Statistical significance was defined as $p < 0.05$.

211

212 3. Results

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

217

218 Table 1

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

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

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

223

224 During the study period, there were 190 days with missing information at TW
 225 station, 90 days at TM station, 456 days at TC station, and 44 days at CL station,
 226 accounting for 3.7%, 1.8%, 8.9% and 0.9% of the observation days, respectively.
 227 However, there was only 1 day for the entire study period where monitoring stations
 228 were unable to collect air pollution measurements. The daily mean and standard
 229 deviation of PM_{2.5} concentration were 37.5 and 10.5 ug/m³. Supplementary Figure s1
 230 shows the time series of daily mean and standard deviation of PM_{2.5} concentrations in
 231 Hong Kong during the study period. There were seasonal patterns for both mean and
 232 standard deviation of PM_{2.5} with higher concentrations in the cold season. The daily
 233 mean concentrations of NO₂, SO₂ and O₃ were 55.5, 17.6, and 31.1 ug/m³,
 234 respectively. The daily mean temperature and relative humidity were 23.5 °C and
 235 77.9%, respectively.

236 Generally, the standard deviation of PM_{2.5} was moderately to highly correlated

237 with the mean concentration of PM_{2.5} (correlation coefficient, $r = 0.67$) and was also
 238 correlated with other covariates (for example, $r=0.63$ for SO₂, and $r = 0.17$ for O₃).
 239 There were low to moderate correlations between other pollutants and weather
 240 covariates, except between SO₂ and O₃ (Table 2).

241

242 **Table 2**

243 Pearson correlation coefficients between PM_{2.5} variation, air pollutants, and weather
 244 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**

245 ** $p < 0.01$, * $P < 0.05$.

246

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

252 PM_{2.5} deviation than PM_{2.5} mean. For example, a 10 ug/m³ increase in daily mean
 253 concentration of PM_{2.5} at lag 2 day corresponded to a 0.61% (95% CI: 0.19%, 1.03%)
 254 and 0.67% (95% CI: 0.14%, 1.21%) increase in mortalities from overall respiratory
 255 diseases and pneumonia, respectively. And a 10 ug/m³ increase in daily standard
 256 deviation of PM_{2.5} at lag 1 day corresponded to a 1.40% (95% CI: 0.35%, 2.46%) and
 257 1.80% (95% CI: 0.46%, 3.16%) increase in mortalities from overall respiratory
 258 diseases and pneumonia, respectively. In the models, we did not find any effects on
 259 mortality from COPD. In the two-pollutant models with adjustment for daily mean
 260 concentrations of NO₂, SO₂ or O₃, their effects changed very little and remained
 261 statistical significant (Table 3).

262

263 **Table 3**

264 ERR in mortality for an 10 ug/m³ increase in daily standard deviation of PM_{2.5} in
 265 different models.

Models	Overall respiratory mortality	Pneumonia mortality
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)

266 * Results obtained from single-pollutant models.

267 Abbreviations: ERR, excess relative risk; df, degree of freedom; "Model w/SO₂"

268 means results from model with SO₂ being controlled for; "Model w/ws" means results

269 from the model with wind speed being controlled for; "Nearby TW" means results

270 from model with subjects around Tsuen Wan Station.

271

272 Fig. 3 shows the smoothing curves of the concentration-response curves for the

273 effects of daily mean and standard deviation of PM_{2.5} on mortalities from overall

274 respiratory diseases and pneumonia. The concentration-response curves, while not

275 perfect, suggested an approximately linear relationships.

276 In the sensitivity analyses, we used standard deviation of PM_{2.5} at day time as an

277 exposure indicator and produced comparable results: each 10 ug/m³ increase in daily

278 standard deviation of PM_{2.5} corresponded to a 1.35% (0.21%, 2.50%) and 1.40%

279 (0.35%, 2.46%) increase in mortalities from overall respiratory diseases and

280 pneumonia, respectively. And when we controlled for daily mean concentration of

281 PM_{2.5}, the risk estimates of daily PM_{2.5} SD remained similar: the ERRs were 1.39%

282 (95% CI: 0.27%, 2.52%) and 1.35% (95% CI: 0.21%, 2.50%) for mortalities from

283 overall respiratory diseases and pneumonia, respectively. We used alternative degrees

284 of freedom to adjust for temporal trends (5, 7 and 8 per year), with most of the results
 285 largely unaffected (Table 3). The model using only air pollution data from the TW
 286 station and the model controlling for wind speed both yielded results comparable to
 287 those from the main model. All these suggested that the association between daily
 288 PM_{2.5} variation and overall respiratory diseases and pneumonia obtained from the
 289 main models was robust.

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

296

297 **Table 4**

298 The interactive effects between daily mean and standard deviation of PM_{2.5} on
 299 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)			

300 Abbreviations: ERR, excess relative risk; RERI, relative excess risk due to interaction;

301 AP, attributable proportion.

302

303 **Discussion**

304 To our knowledge, this is the first study to report the association between daily
305 standard deviation of PM_{2.5} concentrations and respiratory mortality and its possible
306 interaction with daily mean concentration of PM_{2.5}. Using 14 years of data with about
307 96,000 deaths in Hong Kong, our study suggested that, besides daily mean
308 concentration of PM_{2.5}, standard deviation of PM_{2.5} might be another respiratory
309 health predictor; and it appears that these two factors might have some positive, but
310 non-significant, synergistic interaction in terms of their effects on respiratory

311 mortality. These findings provided additional insights into the deleterious respiratory
312 health effects of air pollution.

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

319 Our results of the association between daily variation of $PM_{2.5}$ and respiratory
320 mortality, particularly pneumonia, could not be explained by their correlation with
321 daily mean $PM_{2.5}$. We proposed a novel method to examine the individual effect of
322 two moderately/highly correlated factors, which has not been previously reported. We
323 also observed more acute effects of $PM_{2.5}$ SD (0-1 lag days) than those of $PM_{2.5}$ mean
324 (2-3 lag days), and the model controlling for daily mean concentration of $PM_{2.5}$
325 showed a similar effect of daily standard deviation of $PM_{2.5}$, all these supported that
326 the effects of $PM_{2.5}$ SD were not due to its correlation with $PM_{2.5}$ mean.

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

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

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

345 The adverse respiratory effects of larger variation in PM_{2.5} concentration were
346 biologically plausible. It was likely that during the days with higher standard
347 deviation, people may have higher levels of exposure to PM_{2.5} and inhale more
348 particles. Some vulnerable subgroups may be less acclimatized to significant swings
349 in PM_{2.5} and thus led to more adverse health outcomes. Another possibility might be
350 that increased daily variation of PM_{2.5} concentrations may stress the ability of the
351 respiratory system to adapt to extremely high levels of PM_{2.5} concentrations, which
352 happen frequently within a relatively short time period (which is more often observed
353 in day time with more outdoor human activities, and thus more exposure to traffic
354 exhausts). Such adaptation ability may be reduced in the presence of another illness,

355 such as respiratory conditions. Recently, one Japanese study suggested that exposure
356 to high levels of suspended particulate matter with a lag of 2 hours was associated
357 with higher mortality risk among patients with hemorrhagic stroke (Yamazaki et al.
358 2007), and in one experimental study, inhalation of diesel exhaust was shown to
359 impair the regulation of vascular tone 2 hours after exposure (Mills et al. 2005). The
360 mechanisms for the observed positive interaction between daily mean and standard
361 deviation of PM_{2.5} concentrations remained largely unknown. However, it is possible
362 that, in Hong Kong, when both larger variations and higher daily mean concentrations
363 of PM_{2.5} occur simultaneously, the participants would be exposed to higher levels of
364 ambient air pollution. This exposure would lead to enhanced acute mortality effects,
365 especially for those who are the most vulnerable and susceptible, such as the elderly
366 and those with chronic medical conditions. More studies are warranted to further
367 investigate this research question. We found significant effects on mortalities from
368 overall respiratory diseases and pneumonia, while no significant effect was detected
369 for COPD. The underlying reasons remained unclear; it was possible that people with
370 COPD had relatively fewer outdoor activities and were less affected by variation in
371 ambient PM_{2.5} concentrations. More studies are warranted to further investigate the
372 underlying mechanisms.

373 This study had several strengths. Firstly, this study calls for consideration of
374 daily variation of air pollution in future studies; based on a long time series data in
375 Hong Kong, our study found a significant association between daily standard
376 deviation of PM_{2.5} and respiratory mortality, which has not been reported. Secondly,

377 we proposed a novel and easy method to differentiate the effects of two correlated
378 factors, which is often one concern in environmental epidemiological studies. Thirdly,
379 this study explored the interactive effects of PM_{2.5} mean and standard deviation on the
380 risk of respiratory mortality, which further improved our understanding of the
381 association between PM_{2.5} and respiratory mortality. More importantly, findings from
382 this study have some important public health implications. The variation of PM_{2.5}
383 concentrations should be considered as an important indicator in the future air
384 pollution management and health protection measures. Practically, to reduce the daily
385 variation of PM_{2.5} concentrations, the air pollution controlling policies should pay
386 more attention to vehicle emissions, which produced common cause of peak
387 concentrations of PM_{2.5} in Hong Kong (Cheng et al. 2006).

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

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

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

404

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409

410 **Conflicts of interest and source of funding**

411 None declared.

412

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514

515 **Figure legend:**

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

518

519 **Fig. 2.** Percentage change in respiratory mortalities for per 10 $\mu\text{g}/\text{m}^3$ increase in daily
520 mean and standard deviation of $\text{PM}_{2.5}$ at different lag days in single-pollutant models.

521

522 **Fig. 3.** Exposure-response curves for daily mean and standard deviation of $\text{PM}_{2.5}$ and
523 mortalities for overall respiratory diseases and pneumonia. A natural spline smoother
524 with 3 df was applied.

525

526 Fig. s1. Time series of daily mean and standard deviation of $\text{PM}_{2.5}$ concentration in
527 Hong Kong, 1998-2011.