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1	<b>Chemical components</b>	of respirable	particulate matter	associated with	ith emergency
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## 2 hospital admissions for Type II diabetes mellitus in Hong Kong

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#### 15 Abstract

Background: Epidemiological studies have shown that short-term exposure to particulate
matter (PM) mass was associated with diabetes morbidity and mortality, although
inconsistencies still exist. Variation of chemical components in PM may have contributed to
these inconsistencies. We hypothesize that certain components of respirable particulate matter
(PM<sub>10</sub>), not simply PM<sub>10</sub> mass, can exacerbate symptoms or cause acute complications for
type II diabetes mellitus (T2DM).

22

23 Methods: We used a Poisson time-series model to examine the association between 17 chemical components of PM<sub>10</sub> and daily emergency hospital admissions for T2DM among 24 residents aged 65 years or above from January 1998 to December 2007 in Hong Kong. We 25 estimated excess risk (ER%) for T2DM hospitalizations per interquartile range (IQR) 26 increment in chemical component concentrations of days at lag<sub>0</sub> through lag<sub>3</sub>, and the moving 27 28 average of the same-day and previous-day  $(lag_{0-1})$  in single-pollutant models. To further evaluate the independent effects of chemical components on T2DM, we controlled for PM<sub>10</sub> 29 30 mass and major  $PM_{10}$  chemical components and gaseous pollutants in two-pollutant models. 31

**Results:** In the single-pollutant models, PM<sub>10</sub> components associated with T2DM admissions
include: elemental carbon, organic carbon, nitrate, and nickel. The ER% estimates per IQR
increment at lag<sub>0-1</sub> for these four components were 3.79% (1.63, 5.95), 3.74 (0.83, 6.64), 4.58
(2.17, 6.99), and 1.91(0.43, 3.38), respectively. Risk estimates for nitrate and elemental
carbon were robust to adjustment for co-pollutant concentrations.

37

38 **Conclusions:** Short-term exposure to some  $PM_{10}$  chemical components such as nitrate and 39 elemental carbon increases the risk of acute complications or exacerbation of symptoms for 40 the T2DM patients. These findings may have potential biological and policy implications. 41

Keywords: Particulate matter; Chemical component; Air pollution; Diabetes; Time-series
analysis

# 44 List of abbreviations and their full forms

# 45 Abbreviations Full form

$PM_{10}$	Particulate matter with aerodynamic diameter less than or equal to $10 \mu m$
T2DM	Type II diabetes mellitus
NO <sub>2</sub>	Nitrogen dioxide
$SO_2$	Sulfur dioxide
O <sub>3</sub>	Ozone
ICD-9	Ninth revision of the international classification of diseases
OC	Organic carbon
EC	Elemental carbon
NO <sub>3</sub> <sup>-</sup>	Nitrate
SO <sub>4</sub> <sup>2-</sup>	Sulfate
$\mathrm{NH_4}^+$	Ammonium
Ni	Nickel
Na <sup>+</sup>	Sodium ion
$\mathbf{K}^+$	Potassium ion
Cl	Chloride ion
Al	Aluminum
As	Arsenic
Ca	Calcium
Cd	Cadmium
Fe	Iron
Mg	Magnesium
Mn	Manganese
Pb	Lead

### 46 1. Introduction

The global diabetes epidemic is becoming a serious threat to public health. The first WHO 47 48 Global Report on Diabetes showed that the number of people living with diabetes almost quadrupled to 422 million in 2014 from 108 million in 1980 (World Health Organization, 49 2016). This number is projected to be 592 million in 2038 (International Diabetes Federation, 50 2013). Type II diabetes mellitus (T2DM) is a metabolic disorder characterized by high 51 glucose levels in the blood caused by insulin resistance and relative insulin deficiency, 52 53 accounting for more than 90% of all diabetes cases (American Diabetes Association, 2006). 54 The increase in diabetes prevalence in recent years may be primarily attributable to modern 55 lifestyles including obesity, physical inactivity, and the growing aging population (Van 56 57 Dieren et al., 2010). Both long-term (Anderson et al., 2012; Brook et al., 2013; Chen et al., 2016; Eze et al., 2014; Liu et al., 2016) and short-term exposure to (Goldberg et al., 2013; 58 Kan et al., 2004) particulate matter (PM) have been linked to diabetes, although there are still 59 a lot of inconsistencies among studies. For example, a 10  $\mu$ g/m<sup>3</sup> increment in long-term fine 60 particulate matter (PM<sub>2.5</sub>) exposure was associated with 1.49 fold higher risk (95% CI, 1.37, 61 1.62) for diabetes-related mortality in the 1991 Canadian follow-up study (Brook et al., 2013), 62 while the findings were negative in the American Cancer Society Cancer Prevention II study 63 (Pope et al., 2004). Positive associations were reported for short-term PM<sub>10</sub> exposure in 64 Shanghai, China (Kan et al., 2004), but not in the ten metropolitan areas in the European 65 Mediterranean region (Samoli et al., 2014). 66

68	The inconsistencies among previous studies might relate to numerous factors such as the
69	population susceptibilities, diabetes prevalence, sample size, exposure assessment, and
70	statistical methods in controlling for confounders. Another key factor is that PM composition
71	may vary from location to location because PM is a mixture of different components
72	associated with particular local and regional sources of air pollution.
73	
74	Emergency hospital admissions for diabetes are due to acute complications of diabetes (e.g.,
75	ketoacidosis, hyperosmolarity) and acute onset of chronic complications (e.g., renal
76	manifestations and peripheral circulatory disorders)(Amaize and Mistry, 2016). Time-series
77	analysis is well suited for evaluating short-term effects of time-varying exposures on health.
78	In the present study, we aimed to identify which chemical components of $PM_{10}$ (PM with a
79	diameter $< 10 \ \mu m$ ) are associated with T2DM emergency hospitalizations using 10 years of
80	daily time-series data from January 1, 1998 to December 31, 2007 in Hong Kong.
81	
82	2. Materials and Methods
83	2.1 Air pollution and meteorological data
84	The Hong Kong Environmental Protection Department (HKEPD) established the $PM_{10}$
85	chemical speciation network to measure twenty-six $PM_{10}$ chemical components, in addition
86	to $PM_{10}$ mass. $PM_{10}$ samples were collected with quartz filters using High Volume $PM_{10}$
87	samplers. The filters were analyzed for gravimetric mass, elements (e.g., nickel, aluminum)
88	by inductively coupled plasma atomic emission spectroscopy (ICP-AES), ions (e.g., sulfate,
89	nitrate) by ion chromatography (IC), and elemental carbon/organic carbon by a

90	thermal/optical transmittance method (Yuan et al., 2013). During the study period, 24-hour
91	$PM_{10}$ sampling was carried out at six air quality monitoring stations, these six monitoring
92	stations interspersed in different districts of Hong Kong, which include Yuen Long, Tsuen
93	Wan, Sham Shui Po, Tung Chung, Central Western, and Kwun Tong, and were reported to
94	well represent the general population exposure on a regular basis (Fig. S1) (Pun et al., 2014b).
95	After excluding those chemical components that had a contamination issue or that had more
96	than 25% of samples below the analytical detection limit or that had more than 25% of
97	missing values, in the end a total of 17 chemical components were retained for data analysis.
98	They were elemental carbon (EC), organic carbon (OC), nitrate $(NO_3^-)$ , sulfate $(SO_4^{2-})$ ,
99	ammonium ion $(NH_4^+)$ , chloride ion $(Cl^-)$ , sodium ion $(Na^+)$ , potassium ion $(K^+)$ , aluminum
100	(Al), arsenic (As), calcium (Ca), cadmium (Cd), iron (Fe), magnesium (Mg), manganese
101	(Mn), nickel (Ni), and lead (Pb). Nitrogen dioxide (NO <sub>2</sub> ), sulfur dioxide (SO <sub>2</sub> ), and ozone (O <sub>3</sub> )
102	were also monitored at the same day and the same monitoring stations with $PM_{10}$ chemical
103	components. Air pollutant concentrations generally had moderate-to-very high monitor-to-
104	monitor correlations (Table S1). We also obtained daily mean temperature and relative
105	humidity data from the Hong Kong Observatory for the same study period.

## 107 2.2. Type II diabetes mellitus hospitalizations

We computed daily counts of emergency hospital admissions for the elderly aged 65 years or
older with the principal diagnosis of T2DM [International Classification of Diseases, 9<sup>th</sup>
revision (ICD-9): 250.X0 and 250.X2, X=0-9] recorded in the Hospital Authority Corporate

111 Data Warehouse, which covered all publicly funded hospitals that provide 24-hour accident

and emergency services and cover 90% of hospital beds for Hong Kong residents (Tian et al., 112 2016). The Accident and Emergency (A&E) Departments in all publicly funded hospitals of 113 114 Hong Kong adopted a triage system to ensure that patients with more serious conditions were accorded higher priority in medical treatment (Ho, 2013). Patients who did not require 115 116 emergency attendance would not be treated in A&E Department but rather transferred to 117 public or private clinics. The diabetes patients included in the current study were those with acute complications or with acute symptoms related to chronic conditions. 118

119

#### 120 2.3. Statistical analysis

PM<sub>10</sub> samples were collected on average every-sixth-day on a distinct sampling schedule for 121 each of the six monitoring stations, thus for one particular day, there may be zero or multiple 122 123 samples taken from the whole territory. Collectively, 69% of the study days had speciation measurements from at least one station; there is not an obvious pattern for missing data 124 125 occurrence in the time-series. To compute the territory-wide mean concentrations of  $PM_{10}$ 126 chemical components, we applied a centering method to remove the station-specific influence 127 on the measurements of each component. Details of the centering method were reported elsewhere (Katsouyanni et al., 1996; Pun et al., 2014a; Wong et al., 2001). Fig. S2 shows 128 time-series plots of PM<sub>10</sub> chemical components. All pollutant concentrations are expressed in 129  $\mu g/m^3$  except for EC and OC, which are reported in  $\mu g$  carbon/m<sup>3</sup>. 130

131

132 This was a time-series study, and we used generalized additive models to estimate

associations between PM<sub>10</sub> chemical components and emergency hospital admissions for 133

effect of temperature, while the moving average of lag 1-3 days (*Tmean*<sub>1-3</sub>) was used to 135 136 control for the delayed effects of temperature. Natural cubic splines with 8 degrees of freedom (df) per year were used to control for time trend and seasonality. We used natural 137 cubic splines with 3 df for both  $Tmean_0$  and  $Tmean_{1-3}$  to account for the nonlinearity of 138 temperature effect, and included them simultaneously in the model (Tian et al., 2014). We 139 used natural cubic spline with three df to control for the same-day mean relative humidity 140 (rh). We also adjusted for day of the week (DOW), public holidays (Holiday), and influenza 141 142 epidemics (*influenza*) as dummy variables. Our model is shown as follows: 143  $\log[E(Y)] = \mu + \beta_1 COMP + ns(time, df = 8/year \times no. of year) + ns(Tmean_0, df = 3) + \beta_1 COMP + ns(time, df = 8/year \times no. of year) + ns(Tmean_0, df = 3) + \beta_1 COMP + ns(time, df = 8/year \times no. of year) + ns(Tmean_0, df = 3) + \beta_1 COMP + ns(time, df = 8/year \times no. of year) + ns(Tmean_0, df = 3) + \beta_1 COMP + ns(time, df = 8/year \times no. of year) + ns(Tmean_0, df = 3) + \beta_1 COMP + ns(time, df = 8/year \times no. of year) + ns(Tmean_0, df = 3) + \beta_1 COMP + ns(time, df = 8/year \times no. of year) + ns(Tmean_0, df = 3) + \beta_1 COMP + ns(time, df = 8/year \times no. of year) + ns(Tmean_0, df = 3) + \beta_1 COMP + ns(time, df = 8/year \times no. of year) + ns(Tmean_0, df = 3) + \beta_1 COMP + ns(time, df = 8/year \times no. of year) + ns(Tmean_0, df = 3) + \beta_1 COMP + ns(time, df = 8/year \times no. of year) + ns(Tmean_0, df = 3) + \beta_1 COMP + ns(time, df = 8/year \times no. of year) + ns(time, df = 8/year \times no. of year \times no. of year$ 144  $ns(Tmean_{1-3}, df = 3) + ns(rh, df = 3) + \beta_2 DOW + \beta_3 influenza + \beta_4 Holiday$ 145 146 ----- (1) where *COMP* represents  $PM_{10}$  chemical components, *ns(.)* denotes natural cubic splines, and 147  $\beta_i$  indicates regression coefficients. 148 149 150 We first used single-pollutant models to examine the association of emergency hospitalizations for T2DM with each  $PM_{10}$  component on the same day (lag<sub>0</sub>) and the 151 previous 1-3 days ( $lag_1$  to  $lag_3$ ), and the moving average of same-day and previous-day ( $lag_{0-1}$ ) 152 153 while adjusting for time-varying confounders. For chemical components demonstrating statistically significant associations at lag<sub>0-1</sub> in single-pollutant models, we further constructed 154 155 two-pollutant models. We adjusted one at a time for PM<sub>10</sub> mass, the major PM<sub>10</sub> components (those contributing  $\geq 4\%$  to PM<sub>10</sub> mass: EC, OC, SO<sub>4</sub><sup>2-</sup>, NO<sub>3</sub><sup>-</sup>, and NH<sub>4</sub><sup>+</sup>) and gaseous 156

T2DM. The same-day mean temperature (*Tmean*<sub>0</sub>) was used to control for the immediate

134

157	pollutants (SO <sub>2</sub> , NO <sub>2</sub> , and O <sub>3</sub> ). Risk estimates were treated with caution when correlation
158	between the two pollutants was $\geq 0.6$ (Bell et al., 2014; Mostofsky et al., 2012; Tian et al.,
159	2013). Besides that, we also included Ni which was significantly associated with diabetes
160	hospitalizations in the single-pollutant models. For sensitivity analysis, we reanalyzed the
161	time-series data using linear interpolation to fill in missing data for the days without data
162	from any stations via the <i>na.approx</i> function in the R <i>zoo</i> package (Pun et al., 2015; Pun et al.,
163	2014b).

The results were reported in terms of the percentage excess risk (ER%) increase in daily T2DM emergency hospitalizations for an interquartile range (IQR) increment of  $PM_{10}$ chemical components, and respective 95% confidence intervals (CI). All statistical significance tests were two-sided, and values of *p*<0.05 were considered statistically significant. The data were analyzed using the statistical software R (version 3.1.2), and the "mgcv" (version 1.8-12) package.

171

## 172 **3. Results**

173 During the 10-year study period of 3,652 days, we identified 40,150 T2DM emergency

admissions (11.0  $\pm$  3.8 admissions per day), with a mean age of 76 (range: 65-104) and

175 female percentage 57.4%. Among these 3,652 days, 2,520 (~69%) days had non-missing

- 176 values for  $PM_{10}$  chemical component concentrations. Table 1 shows summary statistics of
- 177 emergency hospital admissions for T2DM, meteorological conditions, and concentrations of
- 178  $PM_{10}$  mass and its chemical components. The daily mean temperature and relative humidity

were 23.6 °C and 78.0 %, respectively. Gaseous pollutants concentrations were 59.9, 20.2, and 30.1  $\mu$ g/m<sup>3</sup> for NO<sub>2</sub>, SO<sub>2</sub>, and O<sub>3</sub>, respectively. The daily mean concentrations of PM<sub>10</sub> was 55.7  $\mu$ g/m<sup>3</sup>, with EC, OC, NO<sub>3</sub><sup>-</sup>, SO<sub>4</sub><sup>2-</sup>, NH<sub>4</sub><sup>+</sup>, and Ni accounting for 7.18%, 15.62%, 6.28%, 19.39%, 5.39%, and 0.01% of the PM<sub>10</sub> mass, respectively.

183

184	Fig. 1 shows the ER (%) of T2DM emergency hospitalizations per IQR increment in the
185	concentrations of $PM_{10}$ chemical components using single-pollutant models. $PM_{10}$ mass was
186	associated with emergency hospital admissions for T2DM at $lag_2$ with ER (%) of 2.42 (95%
187	confidence interval (CI), 0.30, 4.53) per IQR (41.5 $\mu$ g/m <sup>3</sup> ). EC, OC, NO <sub>3</sub> <sup>-</sup> , Ni, and K <sup>+</sup> were
188	all significantly associated with T2DM hospitalizations at certain lags from $lag_0$ to $lag_3$ .
189	Based on previous studies in Hong Kong (Wong et al., 2008), we used $lag_{0-1}$ as a <i>priori</i> lag
190	structure and found EC, OC, NO <sub>3</sub> , and Ni were all associated with emergency hospital
191	admissions for T2DM (Fig. 1). With one IQR increment in pollution level at $lag_{0-1}$ , the ER (%)
192	of T2DM emergency admissions for EC, OC, $NO_3^-$ , and Ni were 3.79 (1.63, 5.95), 3.74 (0.83,
193	6.64), 4.58 (2.17, 6.99), and 1.91 (0.43, 3.38), respectively.
194	
195	We observed relatively high correlations ( $r > 0.8$ ) of PM <sub>10</sub> mass with OC and Mn. We
196	observed high correlations ( $r > 0.8$ ) of Fe with Al, Ca, and Mn, of Pb with K <sup>+</sup> , and of NH <sub>4</sub> <sup>+</sup>

197 with  $SO_4^{2-}$  (**Table 2**).

198

199 In the two-pollutant models, we further controlled for co-pollutants to examine the

200 independent effects of chemical components for EC, OC, NO<sub>3</sub><sup>-</sup>, and Ni. However, cautions

201	should be taken when interpreting the results due to the high correlations between pairs of
202	certain components. For example, it is possible that the non-statistically significant risk
203	estimate of OC after adjustment for $PM_{10}$ mass, $NO_3^-$ , or $NO_2$ may relate to over-adjustment.
204	In general, the associations of EC and $NO_3^-$ with T2DM hospitalizations were robust to co-
205	pollutant adjustment, while the risk estimates for Ni and OC lost statistical significance in the
206	two-pollutant models (Fig. 2). When linear interpolation was used to fill in missing values for
207	the concentrations of chemical components, the risk estimates for the chemical components
208	did not change substantially (Fig. S3).
209	
210	4. Discussion
211	We examined the effects of $PM_{10}$ chemical components on the emergency hospital
211 212	We examined the effects of $PM_{10}$ chemical components on the emergency hospital admissions for T2DM among residents aged 65 years or above in Hong Kong from 1998 to
<ul><li>211</li><li>212</li><li>213</li></ul>	We examined the effects of $PM_{10}$ chemical components on the emergency hospital admissions for T2DM among residents aged 65 years or above in Hong Kong from 1998 to 2007. This was one of the few studies in the literature to explore the association between
<ul><li>211</li><li>212</li><li>213</li><li>214</li></ul>	We examined the effects of PM <sub>10</sub> chemical components on the emergency hospital admissions for T2DM among residents aged 65 years or above in Hong Kong from 1998 to 2007. This was one of the few studies in the literature to explore the association between chemical components and emergency T2DM hospitalizations. EC, OC, NO <sub>3</sub> <sup>-</sup> , and Ni in PM <sub>10</sub>
<ul> <li>211</li> <li>212</li> <li>213</li> <li>214</li> <li>215</li> </ul>	We examined the effects of PM <sub>10</sub> chemical components on the emergency hospital admissions for T2DM among residents aged 65 years or above in Hong Kong from 1998 to 2007. This was one of the few studies in the literature to explore the association between chemical components and emergency T2DM hospitalizations. EC, OC, NO <sub>3</sub> <sup>-</sup> , and Ni in PM <sub>10</sub> were linked to increased risks of T2DM emergency admissions. The associations of EC and
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<ul> <li>211</li> <li>212</li> <li>213</li> <li>214</li> <li>215</li> <li>216</li> <li>217</li> </ul>	We examined the effects of PM <sub>10</sub> chemical components on the emergency hospital admissions for T2DM among residents aged 65 years or above in Hong Kong from 1998 to 2007. This was one of the few studies in the literature to explore the association between chemical components and emergency T2DM hospitalizations. EC, OC, NO <sub>3</sub> <sup>-</sup> , and Ni in PM <sub>10</sub> were linked to increased risks of T2DM emergency admissions. The associations of EC and NO <sub>3</sub> <sup>-</sup> with T2DM hospitalizations were robust to co-pollutant adjustment.
<ul> <li>211</li> <li>212</li> <li>213</li> <li>214</li> <li>215</li> <li>216</li> <li>217</li> <li>218</li> </ul>	We examined the effects of PM <sub>10</sub> chemical components on the emergency hospital admissions for T2DM among residents aged 65 years or above in Hong Kong from 1998 to 2007. This was one of the few studies in the literature to explore the association between chemical components and emergency T2DM hospitalizations. EC, OC, NO <sub>3</sub> <sup>-</sup> , and Ni in PM <sub>10</sub> were linked to increased risks of T2DM emergency admissions. The associations of EC and NO <sub>3</sub> <sup>-</sup> with T2DM hospitalizations were robust to co-pollutant adjustment.

- 220 mellitus mortality or hospital admission (**Table S2**). Most of the studies found positive
- association of PM mass with diabetes mellitus mortality or hospital admissions. But the
- 222 current study found no positive associations, in line with the multicity study conducted in the

European Mediterranean region (Samoli et al., 2014).

224

## 4.2. Association between PM components and diabetes mellitus

We identified only one earlier study on the associations between  $PM_{10}$  chemical components 226 227 and emergency hospital admissions for diabetes (Zanobetti et al., 2009). The study conducted in the 26 U.S. communities reported that PM<sub>2.5</sub> higher in EC and OC were associated with 228 lower rates of diabetes admissions whereas the  $PM_{2.5}$  higher in  $SO_4^{2-}$  and As were associated 229 with higher rates of diabetes. In our current study, the number of daily emergency hospital 230 admissions for T2DM was positively associated with  $NO_3^-$  and EC, but not with  $SO_4^{2-}$  or As. 231 Disparities in findings might be attributable to differences in sample size (e.g., daily average 232 counts of emergency hospital admissions for diabetes, and the number of years of the time-233 234 series), study population (e.g., population susceptibility), and air pollution characteristics (e.g., air pollutant concentrations and PM composition). The multicity study in America 235 (Zanobetti et al., 2009) used the proportion of chemical components to PM<sub>2.5</sub> mass to 236 investigate the modification of the PM2.5 mass association by PM2.5 composition, so the effect 237 estimates could not be quantitatively compared with ours, which explored directly the 238 component effect on Type II diabetes mellitus. 239

240

#### 241 *4.3. Biological mechanisms*

There is evidence that exposure to short-term PM can alter endothelial function (Schneider et
al., 2008), increase fasting glucose (Chen et al., 2016), and trigger systemic inflammation

244 (Gurgueira et al., 2002; Sun et al., 2013), and therefore may increase insulin resistance (Sun

et al., 2009). Thus, it is biologically plausible that the number of hospitalizations for diabetescould be elevated on days with higher PM pollution.

247

EC and OC are mainly from combustion-related source, such as local gasoline and diesel 248 vehicle exhausts, and regional industrial and agricultural combustion (Pun et al., 2015). 249 Exposure to EC and OC has a potential to increase oxidative stress, which is considered to be 250 a major risk factor for both the onset and progress of T2DM (Rains and Jain, 2011) and its 251 associated complications, such as endothelial dysfunction, systemic inflammation, and 252 253 dyslipidemia (Rajagopalan and Brook, 2012). One in vitro experimental study found that lipid peroxidation in BEAS-2B cells was associated with EC and OC when human bronchial 254 epithelial BEAS-2B cells were exposed to particle extracts at 100 µg/ml for 8 hours (Huang 255 256 et al., 2002). Epidemiological studies generally support pro-inflammatory effects of EC and OC. EC in particles is an indicator of emission sources from diesel exhaust. Diesel exhaust 257 can alter endothelial function (Mills, 2005) and increase systemic inflammation makers (e.g., 258 259 vascular endothelial growth factor, tumor necrosis factor- $\alpha$ ) (Fang et al., 2012). OC may 260 increase airway and systemic inflammation in elderly subjects (Delfino et al., 2010).

261



example, Wu et al. (2016) conducted a panel study using 40 healthy college students in Beijing, China and reported the strongest association of nitrate, among all  $PM_{10}$  chemical constituents, with activity changes in two enzymes: extracellular superoxide dismutase (EC-SOD) and glutathione peroxidase 1 (GPX1), the two enzymes that play central roles in the body's antioxidant system (Pandey and Rizvi, 2010). It suggested that nitrate in  $PM_{10}$  may have a stronger potential to induce oxidative stress than other components in  $PM_{10}$ .

273

274 The major source of Ni in PM is from residual oils used by marine vessels (Pun et al., 2015). 275 It was linked to diabetes hospitalizations, although the association lost statistical significant in the two-pollutant models. Animal experiments demonstrated that acute and subchronic 276 277 exposure to Ni could induce hyperglycemia by increasing hepatic glycogenolysis and 278 pancreatic release of glucagon, and decreasing peripheral utilization of glucose and gluconeogenesis (Tikare et al., 2008). One human epidemiological study also reported that Ni 279 was associated with T2DM even after the adjustment for traditional risk factors including 280 281 lifestyle, body mass index, family history of diabetes, and inflammatory biomarkers (Liu et al., 2015). 282

283

284 Exposure to long-term PM could instigate or accelerate chronic cardiovascular diseases,

285 while short-term exposure to PM could exacerbate existing cardiovascular disease and trigger

- acute cardiovascular events (Brook et al., 2010). Hypothesized biological mechanisms to
- explain the association between PM and cardiovascular diseases are also shared with those
- linking PM to diabetes (Rajagopalan and Brook, 2012). EC, OC, NO<sub>3</sub><sup>-</sup>, and Ni were all

associated with cardiovascular morbidity (e.g., emergency hospitalizations) and mortality in
the epidemiological studies (Kelly and Fussell, 2012), thus it is likely that these components
may contribute to diabetes exacerbation.

292

293 Our findings should be interpreted with caution for several reasons. First, although we used six monitoring stations in one single city to measure PM<sub>10</sub> chemical components, spatial 294 variability of PM<sub>10</sub> chemical components cannot be fully captured. Ito et al. (2005) found that 295 296 concentrations of EC, OC, and Ni (local combustion sources) tend to have low monitor-to-297 monitor temporal correlations. Thus, components from local combustion sources might be subject to more measurement error given their higher spatial heterogeneity. Second, 298 299 components with very low ambient concentrations might be subject to more instrument or 300 laboratory errors. These measurement errors may be one of the reasons for the non-significant associations of arsenic and cadmium with T2DM hospitalizations. Finally, all emergency 301 hospitalizations due to the principal diagnosis of T2DM were included in the current study, 302 303 but emergency visits due to hypoglycemia were not excluded. Hypoglycemia emergency 304 hospitalizations are often associated with strict glycemic control (Leese et al., 2003), but not with air pollution. 305

306

#### **5.** Conclusions

308 Our findings add new evidence regarding the differential toxicity of  $PM_{10}$  constituents on 309 Type II Diabetes mellitus and suggest  $PM_{10}$  constituents from combustion-related particles 310 (EC, OC,  $NO_3^-$  and Ni) may cause acute exacerbations of symptoms or complications for type

311	II diabetes mellitus. Air pollution control policies may target local gasoline and diesel vehicle
312	exhausts, residual oils from marine vessels, and regional industrial and agricultural
313	combustion.
314	
315	Conflict of interest
316	The authors declare no actual or potential conflicts of interest.
317	
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322	Protection Department for providing the air pollution monitoring data, and the Hong Kong
323	Observatory for providing the temperature and relative humidity data.

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No. of No. of			Percent of		Percentile	ercentile	
variable	days	Mean (SD)	PM <sub>10</sub> mass	25th	50th	75th	- IQK
Emergency hospital							
admissions (counts)							
T2DM	3,652	11.0 (3.8)	-	9	11	13	5
Meteorological							
conditions							
Temperature, °C	3,652	23.6 (4.9)	-	19.7	24.8	27.8	8.1
Relative humidity, %	3,652	78.0 (10.0)	-	73.5	79.1	84.7	11.2
Pollutant							
concentration, µg/m <sup>3</sup>							
Nitrogen dioxide	2,497	59.9 (24.7)	-	42.6	59.0	75.0	32.4
Sulfur dioxide	2,499	20.2 (16.1)	-	9.8	16.0	25.2	15.5
Ozone	2,497	30.1 (20.3)	-	15.0	25.4	40.0	25.0
$PM_{10}$	2,520	55.7 (30.8)	100.00	31.9	50.1	73.4	41.5
$SO_4^{2-}$	2,520	10.8 (7.0)	19.39	5.4	9.6	14.3	8.9
OC	2,511	8.7 (5.6)	15.62	4.5	7.4	11.5	7.0
EC	2,511	4.0 (1.8)	7.18	2.9	3.8	4.9	2.0
NO <sub>3</sub> <sup>-</sup>	2,520	3.5 (3.1)	6.28	1.5	2.5	4.8	3.3
$\mathrm{NH_4^+}$	2,520	3.0 (2.6)	5.39	1.0	2.5	4.4	3.3
$Na^+$	2,520	1.5 (1.0)	2.69	0.8	1.3	2.0	1.2
Cl	2,520	0.9 (1.1)	1.62	0.3	0.6	1.2	0.9
Ca	2,520	0.8 (0.6)	1.44	0.4	0.6	1.0	0.6
$\mathbf{K}^+$	2,520	0.6 (0.6)	1.08	0.2	0.4	0.9	0.7
Fe	2,520	0.5 (0.4)	0.90	0.3	0.4	0.7	0.4
Al	2,520	0.3 (0.3)	0.54	0.1	0.2	0.3	0.2
Mg	2,520	0.3 (0.2)	0.54	0.2	0.2	0.3	0.2
Pb	2,520	0.07 (0.07)	0.13	0.02	0.04	0.10	0.08
Mn	2,520	0.02 (0.02)	0.04	0.01	0.02	0.03	0.02
As	2,520	0.005 (0.006)	0.01	0.001	0.003	0.007	0.006
Ni	2,520	0.006 (0.006)	0.01	0.002	0.004	0.007	0.005
Cd	2,520	0.002 (0.003)	0.00	0.0	0.001	0.003	0.002

479 **Table 1.** Summary statistics of emergency hospital admissions, meteorological conditions,

480 and concentrations of  $PM_{10}$  and its chemical components in Hong Kong, China, 1998-2007.

481 Abbreviations: IQR, interquartile range; SD, standard deviation; T2DM, type II diabetes

482 mellitus; EC, elemental carbon; OC, organic carbon;  $NO_3^-$ , nitrate;  $SO_4^{2-}$ , sulfate;  $NH_4^+$ ,

483 ammonium; Na<sup>+</sup>, sodium ion; K<sup>+</sup>, potassium ion; Cl<sup>-</sup>, chloride ion; Al, aluminum; As, arsenic,

484 Ca, calcium; Cd, cadmium; Fe, iron; Mg, magnesium; Mn, manganese; Ni, nickel

486 **Table 2.** Pearson correlation of air pollutants.

	EC	OC	NO <sub>3</sub> <sup>-</sup>	Ni	SO4 <sup>2-</sup>	$\mathrm{NH_4}^+$	$Na^+$	$\mathbf{K}^+$	Cl	Al	As	Ca	Cd	Fe	Mg	Mn	Pb	$PM_{10}$	NO <sub>2</sub>	SO <sub>2</sub>	O <sub>3</sub>
EC	1.00														U						
OC	0.39	1.00																			
$NO_3^-$	0.30	0.69	1.00																		
Ni	0.31	0.40	0.37	1.00																	
$SO_4^{2-}$	0.22	0.64	0.53	0.43	1.00																
$\mathrm{NH_4}^+$	0.25	0.72	0.67	0.48	0.93	1.00															
$Na^+$	-0.12	-0.17	0.22	-0.05	0.09	-0.03	1.00														
$\mathbf{K}^+$	0.31	0.82	0.61	0.28	0.67	0.69	-0.12	1.00													
Cl	0.02	0.03	0.34	-0.01	-0.05	0.00	0.63	0.05	1.00												
Al	0.21	0.53	0.49	0.23	0.48	0.42	0.05	0.61	0.12	1.00											
As	0.29	0.73	0.51	0.40	0.69	0.73	-0.16	0.79	-0.01	0.54	1.00										
Ca	0.28	0.59	0.50	0.23	0.44	0.39	0.02	0.63	0.14	0.91	0.55	1.00									
Cd	0.26	0.60	0.45	0.28	0.50	0.53	-0.14	0.66	0.01	0.46	0.64	0.50	1.00								
Fe	0.32	0.67	0.58	0.31	0.58	0.54	0.00	0.69	0.10	0.93	0.64	0.93	0.55	1.00							
Mg	0.02	0.13	0.40	0.04	0.27	0.14	0.65	0.22	0.51	0.68	0.13	0.64	0.14	0.61	1.00						
Mn	0.30	0.72	0.59	0.30	0.68	0.66	-0.04	0.79	0.05	0.84	0.74	0.83	0.62	0.91	0.48	1.00					
Pb	0.33	0.80	0.59	0.34	0.68	0.71	-0.16	0.89	0.01	0.58	0.83	0.62	0.71	0.69	0.17	0.79	1.00				
$PM_{10}$	0.41	0.87	0.78	0.44	0.83	0.85	0.07	0.84	0.15	0.74	0.77	0.75	0.64	0.84	0.45	0.87	0.83	1.00			
$NO_2$	0.48	0.75	0.59	0.42	0.56	0.60	-0.08	0.56	-0.06	0.45	0.52	0.49	0.44	0.58	0.18	0.57	0.59	0.72	1.00		
$SO_2$	0.42	0.46	0.31	0.63	0.39	0.43	-0.14	0.32	-0.06	0.27	0.47	0.30	0.30	0.35	-0.02	0.34	0.39	0.45	0.47	1.00	
$O_3$	-0.11	0.17	0.11	0.06	0.52	0.37	0.20	0.32	-0.12	0.38	0.31	0.30	0.23	0.36	0.35	0.42	0.30	0.39	0.11	-0.06	1.00

487 Abbreviations: EC, elemental carbon; OC, organic carbon;  $NO_3^-$ , nitrate;  $SO_4^{2-}$ , sulfate;  $NH_4^+$ , ammonium;  $Na^+$ , sodium ion;  $K^+$ , potassium ion;

488 Cl<sup>-</sup>, chloride ion; Al, aluminum; As, arsenic, Ca, calcium; Cd, cadmium; Fe, iron; Mg, magnesium; Mn, manganese; Ni, nickel; Pb, lead.

- 489 **Figure legends:**
- 490

Fig. 1. Percentage excess risk (ER %) of emergency hospital admission for type II diabetes 491 mellitus per interquartile range (IQR) increment in the concentrations of respirable particulate 492 matter  $(PM_{10})$  and its chemical components on single-days (the lag<sub>0</sub> through lag<sub>3</sub>, and moving 493 494 average of lag<sub>0-1</sub>) in the single-pollutant models adjusted for meteorological factors, time trends, public holiday, day of the week, and influenza epidemic, Hong Kong, China, 1998-495 2007. Filled circle indicates that the risk estimate is not statistically significant while hollow 496 circle indicates it is statistically significant. EC, elemental carbon; OC, organic carbon; NO<sub>3</sub>, 497 nitrate; SO<sub>4</sub><sup>2-</sup>, sulfate; NH<sub>4</sub><sup>+</sup>, ammonium; Na<sup>+</sup>, sodium ion; K<sup>+</sup>, potassium ion; Cl<sup>-</sup>, chloride 498 ion; Al, aluminum; As, arsenic, Ca, calcium; Cd, cadmium; Fe, iron; Mg, magnesium: Mn. 499 500 manganese; Ni, nickel; Pb, lead.

501

502 Fig. 2. Percentage excess risk (ER %) of emergency hospital admission for type II diabetes

503 mellitus per interquartile range (IQR) increment in the concentrations of 2-day moving

average (current day and previous day,  $lag_{0-1}$ ) of daily respirable particulate matter (PM<sub>10</sub>)

and its chemical components with additional adjustment for co-pollutant in the two-pollutant

506 models. Circle indicates that correlation between the second pollutant and the first is <0.6 in

the two-pollutant model while square denotes the correlation is  $\ge 0.6$ . Filled circle or square represents the risk estimate is not statistically significant while hollow circle or square

indicates it is statistically significant. The vertical dash line denotes the point estimate of the

510 chemical components in the single-pollutant models. EC, elemental carbon; OC, organic

511 carbon;  $NO_3^-$ , nitrate;  $SO_4^{2^-}$ , sulfate;  $NH_4^+$ , ammonium;  $Na^+$ , sodium ion;  $K^+$ , potassium ion;

512 Cl<sup>-</sup>, chloride ion; Al, aluminum; As, arsenic, Ca, calcium; Cd, cadmium; Fe, iron; Mg,

513 magnesium; Mn, manganese; Ni, nickel; Pb, lead.







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