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### **hospital admissions for Type II diabetes mellitus in Hong Kong**

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#### **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 20 ( $PM_{10}$ ), not simply  $PM_{10}$  mass, can exacerbate symptoms or cause acute complications for type II diabetes mellitus (T2DM).

 **Methods:** We used a Poisson time-series model to examine the association between 17 24 chemical components of  $PM_{10}$  and daily emergency hospital admissions for T2DM among residents aged 65 years or above from January 1998 to December 2007 in Hong Kong. We estimated excess risk (ER%) for T2DM hospitalizations per interquartile range (IQR) 27 increment in chemical component concentrations of days at  $\log_0$  through  $\log_3$ , and the moving 28 average of the same-day and previous-day  $(lag_{0-1})$  in single-pollutant models. To further 29 evaluate the independent effects of chemical components on T2DM, we controlled for  $PM_{10}$  mass and major  $PM_{10}$  chemical components and gaseous pollutants in two-pollutant models. 

 **Results:** In the single-pollutant models, PM10 components associated with T2DM admissions include: elemental carbon, organic carbon, nitrate, and nickel. The ER% estimates per IQR 34 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.

**Conclusions:** Short-term exposure to some PM<sub>10</sub> chemical components such as nitrate and elemental carbon increases the risk of acute complications or exacerbation of symptoms for the T2DM patients. These findings may have potential biological and policy implications. 

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

# 44 **List of abbreviations and their full forms**

# 45 **Abbreviations Full form**

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### **1. Introduction**

 The global diabetes epidemic is becoming a serious threat to public health. The first WHO 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, 2016). This number is projected to be 592 million in 2038 (International Diabetes Federation, 2013). Type II diabetes mellitus (T2DM) is a metabolic disorder characterized by high glucose levels in the blood caused by insulin resistance and relative insulin deficiency, accounting for more than 90% of all diabetes cases (American Diabetes Association, 2006). The increase in diabetes prevalence in recent years may be primarily attributable to modern lifestyles including obesity, physical inactivity, and the growing aging population (Van 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; Kan et al., 2004) particulate matter (PM) have been linked to diabetes, although there are still 60 a lot of inconsistencies among studies. For example, a 10  $\mu$ g/m<sup>3</sup> increment in long-term fine 61 particulate matter (PM<sub>2.5</sub>) exposure was associated with 1.49 fold higher risk (95% CI, 1.37, 1.62) for diabetes-related mortality in the 1991 Canadian follow-up study (Brook et al., 2013), while the findings were negative in the American Cancer Society Cancer Prevention II study 64 (Pope et al., 2004). Positive associations were reported for short-term  $PM_{10}$  exposure in Shanghai, China (Kan et al., 2004), but not in the ten metropolitan areas in the European Mediterranean region (Samoli et al., 2014).

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## *2.2. Type II diabetes mellitus hospitalizations*

 We computed daily counts of emergency hospital admissions for the elderly aged 65 years or 109 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

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., 2016). The Accident and Emergency (A&E) Departments in all publicly funded hospitals of 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 emergency attendance would not be treated in A&E Department but rather transferred to 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.

#### *2.3. Statistical analysis*

 PM<sub>10</sub> samples were collected on average every-sixth-day on a distinct sampling schedule for each of the six monitoring stations, thus for one particular day, there may be zero or multiple 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 125 occurrence in the time-series. To compute the territory-wide mean concentrations of PM<sub>10</sub> chemical components, we applied a centering method to remove the station-specific influence 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 129 time-series plots of PM<sub>10</sub> chemical components. All pollutant concentrations are expressed in  $\mu$ g/m<sup>3</sup> except for EC and OC, which are reported in μg carbon/m<sup>3</sup>. 

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

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

 T2DM. The same-day mean temperature (*Tmean0*) was used to control for the immediate effect of temperature, while the moving average of lag 1-3 days (*Tmean1-3*) was used to 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 cubic splines with 3 *df* for both *Tmean0* and *Tmean1-3* to account for the nonlinearity of temperature effect, and included them simultaneously in the model (Tian et al., 2014). We used natural cubic spline with three *df* to control for the same-day mean relative humidity (*rh*). We also adjusted for day of the week (*DOW*), public holidays (*Holiday*), and influenza epidemics (*influenza*) as dummy variables. Our model is shown as follows:  $log[E(Y)] = \mu + \beta_I COMP + ns (time, df = 8/year \times no. of year) + ns (Tmean_0, df = 3) +$  *ns(Tmean1-3, df = 3) + ns(rh, df = 3) + β2DOW + β3influenza + β4Holiday* -------  $(1)$ 147 where *COMP* represents  $PM_{10}$  chemical components, *ns(.)* denotes natural cubic splines, and *β<sup>i</sup>* indicates regression coefficients. We first used single-pollutant models to examine the association of emergency 151 hospitalizations for T2DM with each  $PM_{10}$  component on the same day (lag<sub>0</sub>) and the 152 previous 1-3 days (lag<sub>1</sub> to lag<sub>3</sub>), and the moving average of same-day and previous-day (lag<sub>0-1</sub>) while adjusting for time-varying confounders. For chemical components demonstrating 154 statistically significant associations at lag<sub>0-1</sub> in single-pollutant models, we further constructed 155 two-pollutant models. We adjusted one at a time for  $PM_{10}$  mass, the major  $PM_{10}$  components

156 (those contributing  $\geq 4\%$  to PM<sub>10</sub> mass: EC, OC, SO<sub>4</sub><sup>2</sup>, NO<sub>3</sub><sup>2</sup>, and NH<sub>4</sub><sup>+</sup>) and gaseous

![](_page_9_Picture_196.jpeg)

 The results were reported in terms of the percentage excess risk (ER%) increase in daily 166 T2DM emergency hospitalizations for an interquartile range (IQR) increment of  $PM_{10}$  chemical components, and respective 95% confidence intervals (CI). All statistical 168 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.

#### **3. Results**

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

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

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

- values for PM<sup>10</sup> chemical component concentrations. **Table 1** shows summary statistics of
- emergency hospital admissions for T2DM, meteorological conditions, and concentrations of
- 178 PM<sub>10</sub> mass and its chemical components. The daily mean temperature and relative humidity

179 were 23.6 °C and 78.0 %, respectively. Gaseous pollutants concentrations were 59.9, 20.2, 180 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> 181 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><sup>-</sup>, NH<sub>4</sub><sup>+</sup>, and Ni accounting for 7.18%, 15.62%, 182 6.28%, 19.39%, 5.39%, and 0.01% of the PM<sub>10</sub> mass, respectively.

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197 with  $SO_4^2$  (**Table 2**).

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

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

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- 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
- current study found no positive associations, in line with the multicity study conducted in the

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

### *4.2. Association between PM components and diabetes mellitus*

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

#### *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

(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 diabetes could be elevated on days with higher PM pollution.

 EC and OC are mainly from combustion-related source, such as local gasoline and diesel vehicle exhausts, and regional industrial and agricultural combustion (Pun et al., 2015). Exposure to EC and OC has a potential to increase oxidative stress, which is considered to be a major risk factor for both the onset and progress of T2DM (Rains and Jain, 2011) and its associated complications, such as endothelial dysfunction, systemic inflammation, and 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 epithelial BEAS-2B cells were exposed to particle extracts at 100 μg/ml for 8 hours (Huang 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 can alter endothelial function (Mills, 2005) and increase systemic inflammation makers (e.g., vascular endothelial growth factor, tumor necrosis factor-α) (Fang et al., 2012). OC may increase airway and systemic inflammation in elderly subjects (Delfino et al., 2010).

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 example, Wu et al. (2016) conducted a panel study using 40 healthy college students in 268 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 271 body's antioxidant system (Pandey and Rizvi, 2010). It suggested that nitrate in  $PM_{10}$  may 272 have a stronger potential to induce oxidative stress than other components in  $PM_{10}$ .

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

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

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
- 288 linking PM to diabetes (Rajagopalan and Brook, 2012). EC, OC,  $NO_3^-$ , 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.

 Our findings should be interpreted with caution for several reasons. First, although we used 294 six monitoring stations in one single city to measure  $PM_{10}$  chemical components, spatial 295 variability of  $PM_{10}$  chemical components cannot be fully captured. Ito et al. (2005) found that concentrations of EC, OC, and Ni (local combustion sources) tend to have low monitor-to- monitor temporal correlations. Thus, components from local combustion sources might be subject to more measurement error given their higher spatial heterogeneity. Second, components with very low ambient concentrations might be subject to more instrument or 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 hospitalizations due to the principal diagnosis of T2DM were included in the current study, but emergency visits due to hypoglycemia were not excluded. Hypoglycemia emergency hospitalizations are often associated with strict glycemic control (Leese et al., 2003), but not with air pollution.

#### **5. Conclusions**

308 Our findings add new evidence regarding the differential toxicity of  $PM_{10}$  constituents on 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

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![](_page_18_Picture_228.jpeg)

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

480 and concentrations of PM<sup>10</sup> 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

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![](_page_22_Picture_668.jpeg)

![](_page_22_Picture_669.jpeg)

487 Abbreviations: EC, elemental carbon; OC, organic carbon; NO<sub>3</sub>, 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;

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

- **Figure legends:**
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 **Fig. 1.** Percentage excess risk (ER %) of emergency hospital admission for type II diabetes mellitus per interquartile range (IQR) increment in the concentrations of respirable particulate 493 matter (PM<sub>10</sub>) and its chemical components on single-days (the lag<sub>0</sub> through lag<sub>3</sub>, and moving 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- 2007. Filled circle indicates that the risk estimate is not statistically significant while hollow 497 circle indicates it is statistically significant. EC, elemental carbon; OC, organic carbon;  $NO_3$ <sup>-</sup>, 498 nitrate;  $SO_4^2$ , sulfate; NH<sub>4</sub><sup>+</sup>, ammonium; Na<sup>+</sup>, sodium ion; K<sup>+</sup>, potassium ion; Cl<sup>-</sup>, chloride ion; Al, aluminum; As, arsenic, Ca, calcium; Cd, cadmium; Fe, iron; Mg, magnesium; Mn, manganese; Ni, nickel; Pb, lead.

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

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

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

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

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

507 the two-pollutant model while square denotes the correlation is  $\geq$  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

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

511 carbon; NO<sub>3</sub><sup>-</sup>, nitrate; SO<sub>4</sub><sup>2</sup><sup>-</sup>, sulfate; NH<sub>4</sub><sup>+</sup>, ammonium; Na<sup>+</sup>, sodium ion; K<sup>+</sup>, potassium ion;

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

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

![](_page_24_Figure_0.jpeg)

![](_page_25_Figure_0.jpeg)

![](_page_25_Figure_1.jpeg)

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