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Long-term exposure to fine particulate matter air pollution and type 2 diabetes mellitus in elderly: A cohort study in Hong Kong☆,☆☆,★

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ABSTRACT

Background: Evidence for the link between long-term air pollution exposure and occurrence of diabetes is limited and the results are mixed.
Objectives: We aimed to assess the association of long-term residential exposure to fine particulate matter ($PM_{2.5}$) with the prevalence and incidence of type 2 diabetes mellitus (DM).
Methods: This is a prospective cohort study. We studied 61,447 participants of the Chinese Elderly Health Services cohort in Hong Kong enrolled 1998–2001 and followed participants without DM at baseline to 31 December 2010 to ascertain the first hospital admissions for type 2 DM. Yearly mean residential $PM_{2.5}$ exposure was predicted based on satellite data. Logistic regression and time-varying Cox regression model were used to evaluate the prevalence and incidence risk of DM associated with $PM_{2.5}$ while adjusting for potential individual and neighborhood confounders.
Results: There were 61,447 participants included in the study of prevalent DM, and in 53,905 participants without DM at baseline we studied incident type 2 DM. Over a mean follow-up of 9.8 years, we ascertained 806 incident cases of type 2 DM. After adjusting for potential confounders, the odds ratio (OR) for every interquartile range (3.2 $\mu g/m^3$) increase of $PM_{2.5}$ concentration was 1.06 (95% confidence interval (CI): 1.01–1.11) for prevalent DM, while the corresponding hazard ratio (HR) was 1.15 (95% CI: 1.05–1.25) for incident type 2 DM.
Conclusions: Long-term exposure to high levels of $PM_{2.5}$ may increase the risk of both prevalence and incidence of type 2 diabetes mellitus in Hong Kong elderly population.

1. Introduction

An estimated 422 million adults were living with diabetes in 2014 globally compared to 108 million in 1980, according to the WHO Global Report on Diabetes. The global age-standardized prevalence of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population (World Health Organization, 2016). Type 2 diabetes mellitus (DM), or adult-onset diabetes, is a group of metabolic disorders characterized by high blood glucose levels caused by a combination of resistance to insulin action and an inadequate compensatory insulin secretory response, which is the most common type of DM accounting for about 90–95% of all DM cases (American Diabetes Association, 2014).

Type 2 DM is undoubtedly attributable to modifiable lifestyle behaviors and can be prevented or delayed by maintaining a normal body weight through physical exercise and healthy diet (Colberg et al., 2010; Mayor, 2015). Air pollution has also been proposed as an emerging global risk factor for the development of type 2 DM (Rajagopalan and Brook, 2012). Increasing evidence from epidemiological studies links long-term air pollution exposure with type 2 DM, however, the findings are not definitive. Associations of long-term $PM_{2.5}$ exposure with the development of DM were observed in Canada (Brook et al., 2013; Chen

Abbreviations: AOD, Aerosol Optical Depth; CI, Confidence Interval; DM, diabetes mellitus; ICD-9, International Classification of Diseases, 9th version; IQR, interquartile range; HR, hazard ratio; OR, odds ratio; $PM_{2.5}$, fine particulate matter with aerodynamic diameter ≤ 2.5 Microns; SEC, Surface extinction coefficients; TPU, Tertiary Planning Units

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et al., 2013), Denmark (Hansen et al., 2016), as well as in China (Liu et al., 2016) but not in some US cohort studies (Coogan et al., 2012; Park et al., 2015; Puett et al., 2011). Although there have systematic reviews and meta-analyses reported the statistically significant pooled estimates of association between long-term $PM_{2.5}$ exposure and diabetes (Eze et al., 2015; Wang et al., 2014), the studies included in these reviews were quite limited and the results of each individual study were diverse. In this situation where observations are conflicting, evidence from different settings, with different levels of exposure, patterns of DM and potential biases may provide clarification.

The Hong Kong Chinese elderly health service cohort was set up by the Department of Health in July 1998, with the purpose to promote understanding of aging in Hong Kong where the patterns of common chronic diseases and their determinants may differ from those in the West (Schooling et al., 2016). Hong Kong is an economically developed non-Western setting with high levels of diabetes, without corresponding levels of obesity and high levels of exposure to $PM_{2.5}$ (Schooling et al., 2016). We took advantage of this long-running cohort to assess the association of long-term residential exposure to $PM_{2.5}$ with both the prevalence and incidence of type 2 DM. Given that some previous studies reported a significant association between air pollution and DM only among women (Eze et al., 2015; Hansen et al., 2016; Krämer et al., 2010), we conducted stratified analyses by sex to explore effect modification.

2. Materials and methods

2.1. Study population

An elderly Chinese cohort of 66,820 older adults who aged 65 years or above was set up by the Elderly Health Service (EHS) of the Department of Health in Hong Kong from July 1998 to December 2001. The participants were recruited on voluntary basis. Elderly Health Centre (EHC) that located in each of the 18 districts in Hong Kong provides health assessment, using standardized and structured interviews, and comprehensive clinical examinations. Information on sociodemographics, lifestyles, and disease history was collected by doctors and nurses, as described in a previous study using the data collected by registered nurses (Schooling et al., 2016). The protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster and the ethics committee of the Department of Health. This is an analysis of routinely collected data, the participants implicitly agreed to their data being used for research by using the service.

2.2. Outcome ascertainment

The prevalent cases of diabetes were identified as those with self-reported diabetes mellitus (DM) receiving regular health care at baseline in the questionnaire survey. Almost all of the DM cases in the elderly population can be assumed to be type 2 DM (Park et al., 2015). The participants without DM at baseline were followed up to ascertain incident type 2 DM. New occurrences of type 2 DM from 1998 to 2010 was obtained from hospitalization records of the Hospital Authority, which manages all 42 public hospitals in the entire territory of Hong Kong. All hospital discharges are coded using the International Classification of Diseases, Ninth Revision (ICD-9), with 250.x0 and 250.x2 (x = 0–9) for type 2 DM (Centers for Disease Control and Prevention, 2011). We identified participants who had the hospital admissions for type 2 DM during 1998 and 2010, and their date of first admission.

2.3. Exposure assessment for residential $PM_{2.5}$

Satellite-based estimates of long-term $PM_{2.5}$ exposure from 1998 to 2010 were obtained from satellite sensing calibrated against surface measurements, as previously descripted (Wong et al., 2015). Briefly, Aerosol Optical Depth (AOD), an indicator of $PM_{2.5}$ levels in the troposphere, was retrieved from remote sensing by two NASA Earth Observing System satellites (NASA, 2015). Surface extinction coefficients (SEC) obtained from AOD at 1 × 1 km resolution, controlling for humid and rainy days, were used to predict $PM_{2.5}$ (HKUST, 2015). Excluding roadside stations, Hong Kong Environmental Protection Department (EPD) provided four general stations for $PM_{2.5}$ measurement during the study period. We calculated annual mean $PM_{2.5}$ concentrations from 1998 to 2010 for each general monitoring station from hourly concentrations and then regressed on the corresponding annual mean SEC, which was the exposure model. The validity of this approach has been confirmed by cross-validation tests in previous study (Wong et al., 2015).

The residential addresses for all participants were geo-coded and linked with SEC data. Then the annual $PM_{2.5}$ exposures at geographical locations of individual participants were estimated using the same exposure model with annual SEC as the explanatory variable for each year. $PM_{2.5}$ concentrations averaged over the baseline years between 1998 and 2001 were used as the proxy of exposure to examine the association with prevalent DM, while the annual mean $PM_{2.5}$ exposure over the follow-up period (1998–2010) as a time-varying variable was used to examine the association with incident type 2 DM. About 13.3% patients in this Elderly Cohort had their residential addresses changed between 1998 and 2010. We have taken the residential movement into account in the estimation of $PM_{2.5}$ exposure by year (Qiu et al., 2017).

2.4. Other covariates

We included individual covariates of age, gender, body mass index (BMI), smoking status, alcohol drinking, exercise frequency, education level and personal monthly expenditure. Active diseases were defined as self-reported hypertension, heart diseases, COPD/asthma, or cerebrovascular accident at baseline. We also included neighborhood characteristics, including percentage of older people (aged 65+ years), percentage with tertiary education and with monthly domestic household income higher than US$ 1923, based on small area statistics (Census and Statistics Department, 2002) (197 Tertiary Planning Units (TPU)) from the census. Environmental characteristics included percentages of smokers (aged 15+) in the 18 districts of Hong Kong to indicate exposure to environmental tobacco smoke (ETS) at baseline years (Census and Statistics Department, 2011).

2.5. Statistical analysis

To estimate the association of baseline $PM_{2.5}$ with prevalence of DM (Park et al., 2015), we used logistic regression. To estimate the association of annual exposure to $PM_{2.5}$ with incidence of type 2 DM we used time-varying Cox regression (Andersen et al., 2012), with attained age as the underlying time scale, because it accounts better adjustment for potential confounding by age (Thiebaut and Benichou, 2004). Using attained age as the time scale provides the flexible control for age effect while avoiding the need to include an effect of age when considering the lifetime exposure (Griffin et al., 2013). Attained age was calculated as the age of first hospital admission for type 2 DM, age at death or age at end of follow-up on 2010-12-31.

We estimate the odds ratio (OR) and hazard ratio (HR) per interquartile range (IQR, 3.22 $\mu g/m^3$) increase of $PM_{2.5}$ concentrations in three different models, while adjusting for an increasing number of potential confounders obtained from the literature as possible common causes of $PM_{2.5}$ exposure and diabetes (Andersen et al., 2012; Chen et al., 2013). Model 1 adjusted for age and sex in logistic model, or sex and calendar year of entry in Cox model while using attained age as the underlying time scale (Stafoggia et al., 2014). Model 2 additionally adjusted for body mass index (BMI), smoking status, alcohol drinking, physical exercise, education, monthly expenses, medication taken and self-reported comorbidities including hypertension, heart diseases,

COPD/asthma, or cerebrovascular accident at baseline. Model 3 additionally adjusted for small area characteristics (% 65+ years, % with tertiary education and income ≥ US$ 1923/month) and district smoking rate. We didn't collect the information on diet pattern, traffic noise, neighborhood walkability and greenness, and could not adjust them in the regression model which might also confound the association of air pollution with diabetes (Clark et al., 2017; Mayor, 2015).

To assure detection of associations and to control for competing diseases, we performed sensitivity analyses excluding participants with death or occurrence of type 2 DM in the first year after entry (Wong et al., 2015). Time-independent Cox proportional hazard model using annual mean $PM_{2.5}$ at baseline (1998–2001) as proxy for long-term exposure was also performed (Wong et al., 2015).

The exposure-response relationship between $PM_{2.5}$ and type 2 DM were plotted using natural cubic spline with three degree of freedom for $PM_{2.5}$ exposure term in the fully adjusted logistic and Cox model, respectively (Wong et al., 2015). Linearity was tested by comparing the model fit of the linear and the spline model using a log likelihood ratio Chi-square test (Abrahamowicz et al., 2003). To explore potential gender difference, we conducted subgroup analyses stratified by sex. The p-value for the difference was obtained from the interaction term of sex and $PM_{2.5}$ in Model 3.

All analyses were conducted in R statistical environment version 3.3.3, with packages 'survival' for survival analysis, 'rms' and 'Hmisc' for plotting the exposure-response relationship curves.

3. Results

Of the total of 66,820 older people initially enrolled, we excluded 1932 (2.9%) people without sufficient address information for geo-coding, 3420 (5.1%) with wrong geo-coding or without $PM_{2.5}$ exposure estimates due to lack of satellite data, and 21 (0.03%) with missing covariates, giving a final sample of 61,447 (92.0%) people with complete data.

The correlation between the annual $PM_{2.5}$ concentrations obtained from the general monitoring stations and from the adjusted satellite-based SEC on dry days in the same 1 × 1 km grid from 1998 to 2010 was 0.625 (p-value < .001). The mean estimated annual $PM_{2.5}$ concentration at baseline years was 35.8 $\mu g/m^3$ with an IQR of 3.2 $\mu g/m^3$. The annual mean concentrations of $PM_{2.5}$ over the study period were varying temporally, and the individual $PM_{2.5}$ exposure for cohort participants was normally distributed (Fig. 1).

At baseline mean age was 72 years and about 65.9% were women. There were 20,921 (34.0%) overweight participants with BMI between 25.0 and 30.0 kg/m^2, and 3788 (6.2%) obese participants with BMI ≥ 30.0 kg/m^2. There were 9.6% current smokers and 19.3% former smokers. Only 8461 (13.8%) were former or regular drinkers, and 44,252 (72%) did daily physical exercise. Most participants (82.9%) had primary school education or below. About half the participants took regular medication (53.1%) and reported active diseases (45.6%), including hypertension, heart disease, COPD/asthma, or a cerebrovascular accident. 7542 (12.3%) participants reported prevalent diabetes at baseline. The characteristics of study participants at baseline by DM status are shown in Table 1. Both prevalent and incident DM cases tended to be more overweight and obese.

In the cross-sectional analysis residential $PM_{2.5}$ exposure was associated with prevalent DM. The OR per IQR increment of $PM_{2.5}$ averaged from 1998 to 2001 (baseline years) was similar in all models, 1.06 with 95% CI from 1.01 to 1.11 in Model 3 (Table 2). We then followed up the 53,905 participants without DM at baseline and identified 806 incident type 2 DM cases over a mean follow-up of 9.8 years totaling 529,783 person-years of observation. Using yearly mean $PM_{2.5}$ as a time-varying exposure, residential $PM_{2.5}$ exposure was associated with incident type 2 DM. Estimates were similar in all three models, with a HR of 1.15 (95% CI: 1.05–1.25) per IQR increment of $PM_{2.5}$ in Model 3 (Table 3). Sensitivity analysis excluding participants with new occurrence of type 2 DM or death in the first year after entry, or using annual mean $PM_{2.5}$ at baseline (1998–2001) as a time-independent variable to proxy long-term exposure gave similar associations (Table 3). Stratified analyses by sex showed the associations of long-term residential $PM_{2.5}$ exposure with prevalence and incidence of type 2 TD were only statistically significant among women (Tables 2 & 3). However, the p-values for the interaction by sex were > 0.05.

Comparison of the linear and spline models suggested the exposure-response relationship was essentially linear for both prevalence of DM (p-value = .623) and incidence of type 2 DM (p-value = .951) (Fig. 2).

4. Discussion

In this large population-based elderly cohort from an under-studied non-Western population, we found long-term exposure to $PM_{2.5}$ associated with both prevalence and incidence of type 2 diabetes, especially in women. This finding is consistent with several cross-sectional and cohort studies from Western settings, but adds by showing a similar association in a different non-Western setting with relatively high levels of $PM_{2.5}$.

Our findings are generally consistent with the limited epidemiological evidence linking long-term residential $PM_{2.5}$ exposure with diabetes prevalence (Eze et al., 2014; Liu et al., 2016; Park et al., 2015; Pearson et al., 2010). A cross-sectional analysis of 5839 participants included in the Multi-Ethnic Study of Atherosclerosis in 6 US cities found significant associations between $PM_{2.5}$ and prevalent DM (Park et al., 2015). Each interquartile-range increase of annual average $PM_{2.5}$ (2.43 $\mu g/m^3$) was associated with prevalent DM (OR = 1.09 with 95% CI: 1.00–1.17), while another cross-sectional analysis of 6392 participants of a Swiss Cohort reported similar association between average

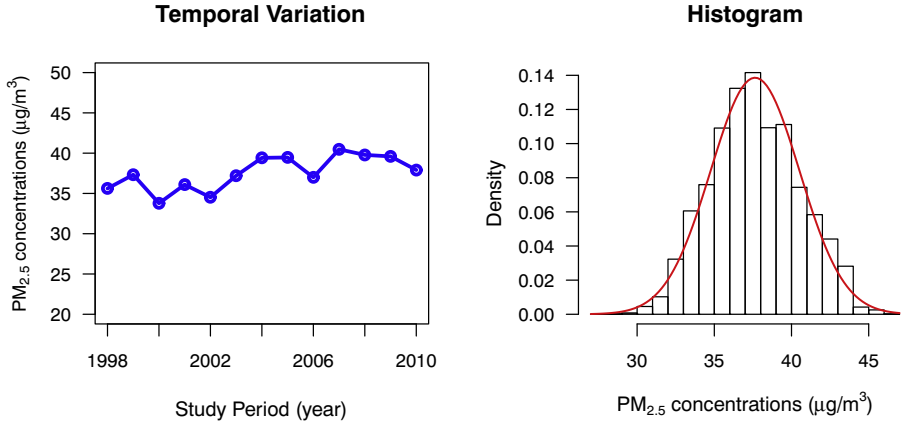

Fig. 1. Annual mean concentrations of $PM_{2.5}$ exposure estimated for cohort participants, 1998–2010.

Table 1
Characteristics of study participants at baseline by diabetes mellitus status, Hong Kong Elderly Health Services Cohort, 1998–2001.

Variables	DM at baseline (N = 61,447)		DM during follow-up (N = 53,905)	
	Yes (n = 7542)	No (n = 53,905)	Yes (N = 806)	No (N = 53,099)
$PM_{2.5}$ concentrations (mean ± SD)				
Averaged over 1998–2001 (μg/m^3)	35.83 ± 1.92	35.77 ± 1.91	–	–
Yearly mean at entry (μg/m^3)	–	–	35.92 ± 2.49	35.79 ± 2.40
Averaged over 1998–2010 (μg/m^3)	–	–	38.24 ± 2.82	37.64 ± 2.88
Individual level covariates				
Age at entry (mean ± SD)	72.0 ± 5.3	72.1 ± 5.7	72.4 ± 5.5	72.1 ± 5.7
Gender: Male (%)	2472 (32.8)	18,461 (34.2)	278 (34.5)	18,183 (34.2)
Female (%)	5070 (67.2)	35,444 (65.8)	528 (65.5)	34,916 (65.8)
BMI quartiles:				
Underweight [< 19.0] (%)	238 (3.2)	4130 (7.7)	19 (2.4)	4111 (7.7)
Normal [≥ 19.0 & < 25.0] (%)	3844 (51.0)	28,526 (52.9)	339 (42.1)	28,187 (53.1)
Overweight [≥ 25.0 & < 30.0] (%)	2886 (38.3)	18,035 (33.5)	348 (43.2)	17,687 (33.3)
Obese [≥30.0] (%)	574 (7.6)	3214 (6.0)	100 (12.4)	3114 (5.9)
Smoking status				
Never (%)	5526 (73.3)	38,143 (70.8)	524 (65.0)	37,619 (70.8)
Former (%)	1486 (19.7)	10,385 (19.3)	167 (20.7)	10,218 (19.2)
Current (%)	530 (7.0)	5377 (10.0)	115 (14.3)	5262 (9.9)
Alcohol drinking				
Never/social drinker (%)	6452 (85.6)	46,534 (86.3)	663 (82.3)	45,871 (86.4)
Former/regular drinker (%)	1090 (14.5)	7371 (13.7)	143 (17.7)	7228 (13.6)
Exercise in days/week				
Never [0] (%)	951 (12.6)	8455 (15.7)	142 (17.6)	8313 (15.7)
Medium [1–6] (%)	936 (12.4)	6853 (12.7)	88 (10.9)	6765 (12.7)
High [7] (%)	5655 (75.0)	38,597 (71.6)	576 (71.5)	38,021 (71.6)
Education				
Below primary (%)	3544 (47.0)	24,698 (45.8)	430 (53.3)	24,268 (45.7)
Primary (%)	2694 (35.7)	19,962 (37.0)	269 (33.4)	19,693 (37.1)
Secondary or above (%)	1304 (17.3)	9245 (17.2)	107 (13.3)	9138 (17.2)
Expenses/month in US$				
Low [< 128] (%)	1409 (18.7)	8713 (16.2)	148 (18.4)	8565 (16.1)
Medium [128–384] (%)	5044 (66.9)	37,108 (68.8)	553 (68.6)	36,555 (68.9)
High [≥385] (%)	1089 (14.4)	8084 (15.0)	105 (13.0)	7979 (15.0)
Medication taken	6822 (90.5)	25,806 (47.9)	458 (56.8)	25,348 (47.7)
Self-reported diabetes	7542 (100.0)	–	–	–
Active diseases[a]	5207 (69.0)	22,908 (42.5)	424 (52.6)	22,484 (42.3)
TPU level covariates (mean)				
Prevalence of age ≥ 65	12.18	12.11	12.20	12.11
Prevalence of tertiary education	12.07	13.01	12.45	13.00
Prevalence of income ≥ US$ 1923/m	58.48	59.53	59.08	59.52
District level covariate				
Smoking rate (mean)	11.56	11.55	11.58	11.55

[a] Active diseases were defined as self-reported hypertension, heart diseases, COPD/asthma, or cerebrovascular accident at baseline.

Table 2
Odds ratios (ORs) for the prevalence of diabetes mellitus at baseline per IQR (3.2 μg/m^3) increase of residential $PM_{2.5}$ exposure in Hong Kong Elderly Health Services Cohort (N = 61,447), 1998–2001.[a]

	No. of prevalent DM	OR (95% CI)	p-Value
$PM_{2.5}$ averaged over 1998–2001			
Model 1	7542	1.05 (1.01–1.10)	.0113
Model 2	7542	1.05 (1.01–1.10)	.0163
Model 3	7542	1.06 (1.01–1.11)	.0161
Stratified analyses (Model 3)[b]			
Men	2472	1.04 (0.96–1.13)	.3278
Women	5070	1.07 (1.01–1.13)	.0245

Model 1: only adjusted for age and sex;
Model 2: adjusted for covariates of individual level at baseline (age, sex, BMI, smoking status, alcohol drinking, physical exercise, education, monthly expenses, medication taken and self-reported active diseases including hypertension, heart diseases, COPD/asthma, or cerebrovascular accident at baseline).
Model 3: further adjusted for the TPU level covariates (prevalence of age ≥ 65, tertiary education and income ≥ US$ 1923/m) and smoking rate at district level, so-called fully adjusted model.
All covariates were included in the model as fixed values at baseline.
[a] Binary logistic regression models were used.
[b] p value for the interaction by sex is .758.

outdoor PM_{10} level and diabetes prevalence (Eze et al., 2014). Using a national wide baseline survey of 11,847 adults from China, Liu et al. found that $PM_{2.5}$ exposure was associated with increased type 2 DM prevalence and elevated levels of blood glucose (Liu et al., 2016). These studies used the baseline information of cohort participants and fitted binary logistic regression model for prevalent DM cases, which is the same approach as ours but with much smaller sample size. Using a different ecological study approach, Pearson et al. linked the exact county-level prevalence values of diagnosed DM in US with annual mean $PM_{2.5}$ level in each county, and reported that each 10 μg/m^3 increase in $PM_{2.5}$ exposure was associated with a 1% increase in diabetes prevalence rate (Pearson et al., 2010).

Our findings are also comparative with several prospective cohort studies that examined the effect of long-term $PM_{2.5}$ exposure on the incidence of type 2 DM (Chen et al., 2013; Hansen et al., 2016; Krämer et al., 2010). Cohort studies with adults living in Ontario Canada (Chen et al., 2013), Danish nurses (Hansen et al., 2016) and elder women from West Germany (Krämer et al., 2010) all started with non-diabetic participants at baseline, followed up to identify the incident DM cases, and provided evidence that long-term exposure to $PM_{2.5}$ may contribute to the development of diabetes. However, some other prospective cohort studies failed to observe the statistically significant associations of the long-term $PM_{2.5}$ exposure with incident DM (Coogan et al., 2012; Park

Table 3
Hazard ratios (HRs) for the Incidence of type 2 diabetes mellitus during follow-up per IQR (3.2 μg/m^3) increase of residential $PM_{2.5}$ exposure in Hong Kong Elderly Health Services Cohort (N = 53,905), 1998–2010.[a]

	No. of incident DM	HR (95% CI)	p-Value
Main analysis			
Model 1	806	1.13 (1.04–1.23)	.0030
Model 2	806	1.13 (1.04–1.22)	.0046
Model 3	806	1.15 (1.05–1.25)	.0016
Sensitivity analysis (Model 3)			
Excluding those with incident type 2 DM (n = 32) or died (n = 190) in the first year	774	1.19 (1.09–1.30)	.0002
Using annual mean $PM_{2.5}$ at baseline (1998–2001) as a time-independent exposure	806	1.13 (0.99–1.29)	0.0630
Stratified analyses (Model 3)[b]			
Men	278	1.08 (0.93–1.26)	.2855
Women	528	1.17 (1.02–1.34)	.0209

Model 1: only adjusted for sex and calendar year of entry;
Model 2: adjusted for covariates of individual level at baseline (sex, calendar year of entry, BMI, smoking status, alcohol drinking, physical exercise, education, monthly expenses, medication taken and self-reported active diseases including hypertension, heart diseases, COPD/asthma, or cerebrovascular accident at baseline).
Model 3: further adjusted for the TPU level covariates (prevalence of age ≥65, tertiary education and income ≥ US$ 1923/m) and smoking rate at district level, so-called fully adjusted model.
All covariates were included in the model as fixed values at baseline.
[a] Time-dependent Cox models were used with age as the underlying time scale; yearly mean $PM_{2.5}$ between 1998 and 2010 was treated as the time-varying exposure.
[b] p value for the interaction by sex is .197.

et al., 2015; Puett et al., 2011). In the Black Women's Health Study conducted in African American women living in Los Angeles (Coogan et al., 2012), researchers identified 183 incident cases of type 2 DM from 3992 nondiabetic women at baseline over a 10-year follow up, and reported the incident risk ratio of 1.63 (95% CI: 0.78–3.44) per 10 μg/m^3 increase of residential $PM_{2.5}$ exposure, where the non-statistically significant association was probably due to the small sample size. The up mentioned US six cities' Multi-Ethnic study (Park et al., 2015) found the association of long-term $PM_{2.5}$ exposure with DM prevalence but not incidence, the authors suggested longer follow-up time with higher level and greater range of exposure in additional studies. Cohorts of the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS) in US did not provide convincing evidence of an association between $PM_{2.5}$ exposure in the previous 12 months and incident DM (Puett et al., 2011). Not excluding the prevalent DM cases at baseline may probably dilute the true association, as in our cohort we did observe null association between $PM_{2.5}$ exposure and reoccurrence of DM in those participants with prevalent diabetes at baseline (data not shown). Although the previous systematic reviews and meta-analyses (Eze et al., 2015; Wang et al., 2014) reported the statistically significant pooled estimates of association between long-term $PM_{2.5}$ exposure and type 2 DM, the studies with different population characteristics, pollution profiles, exposure assessment methods, ascertainment of new cases, as well as the model specifications would contribute to the diverse results. It has also been suggested that "high-quality studies assessing dose-response effects are needed" (Eze et al., 2015). Compared with previous studies conducted in Western populations had $PM_{2.5}$ levels of 10–20 μg/m^3, our study adds new evidence that long-term exposure to high levels of $PM_{2.5}$ may increase the risk of type 2 DM.

The biological mechanisms linking long-term $PM_{2.5}$ exposure with the development of type 2 DM may occur through several pathways. Ambient fine particulate matter may exaggerate adipose inflammation, induce insulin resistance and oxidative stress, as well as alter mitochondrial functions and gene expression in adipose tissue (Sun et al., 2009; X. Xu et al., 2011; Z. Xu et al., 2011). Furthermore, diabetes and obesity may enhance the associations between $PM_{2.5}$ and biomarkers of systemic inflammation (Dubowsky et al., 2006), which in turn would lead to diminished insulin action (Meigs et al., 2015). Both of our cross-

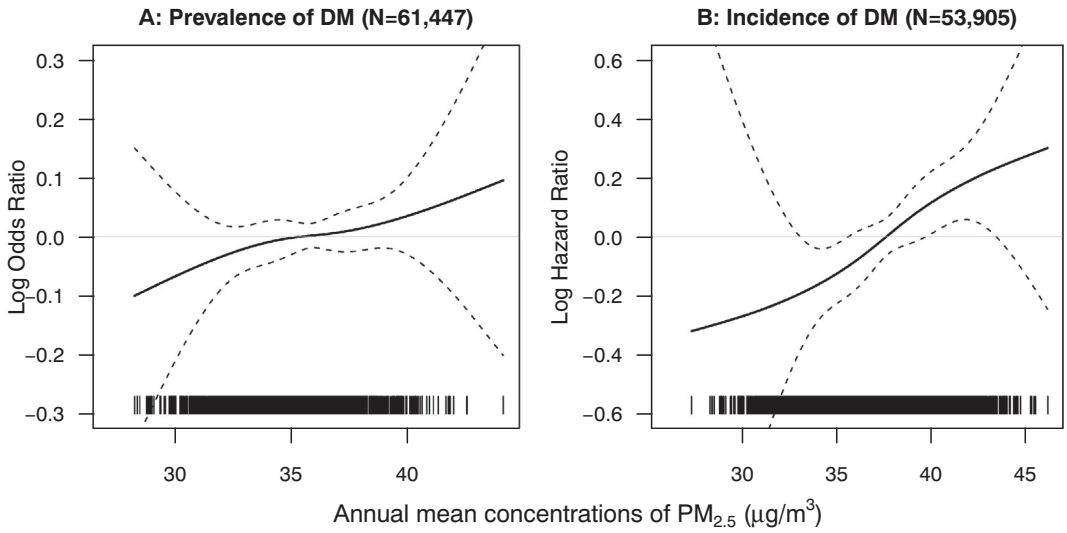

Fig. 2. Exposure-response relationship between long-term $PM_{2.5}$ exposure and (A) prevalence and (B) incidence of diabetes mellitus. The annual mean concentration averaged over the baseline years (1998–2001), and the annual mean concentration over the follow-up period (1998–2010) was used, respectively. The p-values of log likelihood Chi-square test for linear vs. natural spline model were: 0.623 for prevalence of DM and 0.951 for incidence of DM.

sectional and prospective findings are consistent with these hypotheses.

The greater and more significant association we observed in women than men in this study was consistent with previous studies (Eze et al., 2015; Hansen et al., 2016; Krämer et al., 2010), which may attribute to sex-linked biological differences in hormonal complement, body size and gender differences in activity patterns, co-exposures, or accuracy of exposure measurement (Clougherty, 2010). Evidence of air pollution epidemiological studies have supported the stronger effects among women, particularly for elders or where using residential exposure assessment (Clougherty, 2010). The suggested women's airway hyperresponsiveness, stronger responses to smoking (Kanner et al., 1994) and better accuracy in residential-based exposure assessment among homemakers would explain the stronger association of air pollution in women.

This study helps to address the linkage between long-term pollution exposure and both prevalence and incidence of DM. We took advantage of a very large cohort, where we were able to control for many individual and neighborhood level potential confounders, however, residual confounding was still possible as we did not collect the information of dietary, energy intake, traffic noise, or neighborhood-level factors such as walkability and greenness (Clark et al., 2017; Mayor, 2015). Some other limitations should be noted. First, prevalent diabetes at baseline was identified based on self-reported "receiving regular health care on diabetes mellitus" in a survey. As such, diabetes represents known treated diabetes, while a full clinical assessment would undoubtedly have found higher prevalence. However, given the comprehensive public provision of health care in Hong Kong, and the population density, there is no reason to think that whether or not people are diagnosed with diabetes depends on their exposure to air pollution. Second, during the follow up period we used the first hospital admission with discharge codes 250.x2 and 250.x2 (x = 0–9) to identify new occurrences of type 2 DM which were objective measures of confirmed type 2 DM cases. Nevertheless, we may have missed some cases with comorbidities whose underlying discharged diagnosis was other than diabetes or cases without severe symptoms who did not need to be admitted to hospital. So the incident type 2 DM cases we identified in this study may underestimate the true incidence rate in the older population. Third, the participants were enrolled at a preventive service, so they may be more health-conscious and perhaps less susceptible to the effects of air pollution than the general elderly population (Schooling et al., 2016), which would make our estimates more conservative. Although the proportion of women participants is relatively higher (65.9%) in this cohort than in the general older population, we stratified analysis by sex and cannot rule out $PM_{2.5}$ having a stronger effect in women, which needs further investigation. Fourth, yearly residential exposure to $PM_{2.5}$ was estimated from the linear relationship between local monitoring data measured by the Hong Kong Environmental Protection Department and SEC data from NASA satellites. Although the validity of this approach has been demonstrated in several previous studies (Brook et al., 2013; Chen et al., 2013; Wong et al., 2015), greater precision could be obtained from a three dimensional landscape exposure model (Barratt et al., 2017). However, such measurement error would bias towards the null for which our large sample size compensates. Finally, we only considered $PM_{2.5}$ so we cannot exclude the possibility that our findings are due to a different component of air pollution correlated with $PM_{2.5}$.

5. Conclusions

This study adds by showing long-term residential $PM_{2.5}$ exposure increases the risk of development of type 2 diabetes in older people from a developed non-Western setting with high levels of $PM_{2.5}$ exposure. Notably, air quality tends to be poorer in many settings with unexpectedly high rates of diabetes given their level of obesity (Yoon et al., 2006). As such $PM_{2.5}$ could be an additional modifiable factor contributing to diabetes, which may be particularly relevant in non-Western settings, further investigation and potentially action are required.

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Author contributions

HQ and CMS designed the study and wrote the manuscript; HQ and SS analyzed the data and interpreted the results; HT worked on data cleaning and preliminary analyses; YY co-worded on the interpretation of the results; CMS and RSL set up the cohort; CMW set up the method for exposure assessment; LT defined the research theme, reviewed the manuscript and approved the submission. All authors have no conflict of interest to declare.

Corresponding author, Dr. Linwei Tian, takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

References

Abrahamowicz, M., Schopflocher, T., Leffondré, K., du Berger, R., Krewski, D., 2003. Flexible modeling of exposure-response relationship between long-term average levels of particulate air pollution and mortality in the American Cancer Society study. J. Toxic. Environ. Health A 66, 1625–1654.

American Diabetes Association, 2014. Diagnosis and classification of diabetes mellitus. Diabetes Care 37, 81–90. http://dx.doi.org/10.2337/dc14-S081.

Andersen, Z.J., Raaschou-Nielsen, O., Ketzel, M., Jensen, S.S., Hvidberg, M., Loft, S., Tjønneland, A., Overvad, K., Sørensen, M., 2012. Diabetes incidence and long-term exposure to air pollution: a cohort study. Diabetes Care 35, 92–98. http://dx.doi.org/10.2337/dc11-1155.

Barratt, B., Lee, M., Wong, P., Tang, R., Tsui, T.H., Choi, C., Cheng, W., Yang, Y., Lai, P.-C., Tian, L., Thach, T.-Q., Allen, R., Brauer, M., 2017. HKD3D - a dynamic three-dimensional exposure model for Hong Kong. Res. Rep. Health Eff. Inst (Accepted).

Brook, R.D., Cakmak, S., Turner, M.C., Brook, J.R., Crouse, D.L., Peters, P.A., Van Donkelaar, A., Villeneuve, P.J., Brion, O., Jerrett, M., Martin, R.V., Rajagopalan, S., Goldberg, M.S., Pope, C.A., Burnett, R.T., 2013. Long-term fine particulate matter exposure and mortality from diabetes in Canada. Diabetes Care 36, 3313–3320. http://dx.doi.org/10.2337/dc12-2189.

Census and Statistics Department, 2002. Hong Kong 2001 population census: basic tables for tertiary planning units. [WWW document]. Gov. Hong Kong Spec. Adm. Reg. http://www.statistics.gov.hk/pub/B11200242001XXXXB0400.pdf, Accessed date: 10 August 2015.

Census and Statistics Department, 2011. Thematic household survey. Report no. 48. [WWW document]. Gov. Hong Kong Spec. Adm. Reg. http://smokefree.hk/UserFiles/resources/Statistics/Thematic_Household_Survey_No48.pdf, Accessed date: 10 August 2015.

Centers for Disease Control and Prevention, 2011. International classification of diseases, ninth revision, clinical modification (ICD-9-CM) [WWW document]. http://www.cdc.gov/nchs/icd/icd9cm.htm, Accessed date: 10 August 2015.

Chen, H., Burnett, R.T., Kwong, J.C., Villeneuve, P.J., Goldberg, M.S., Brook, R.D., van Donkelaar, A., Jerrett, M., Martin, R.V., Brook, J.R., Copes, R., 2013. Risk of incident diabetes in relation to long-term exposure to fine particulate matter in Ontario, Canada. Environ. Health Perspect. 121, 804–810. http://dx.doi.org/10.1289/ehp.1205958.

Clark, C., Sbihi, H., Tamburic, L., Brauer, M., Frank, L.D., Davies, H.W., 2017. Association of long-term exposure to transportation noise and traffic-related air pollution with the incidence of diabetes: a prospective cohort study. Environ. Health Perspect. 125, 1–10. http://dx.doi.org/10.1289/EHP1279.

Clougherty, J.E., 2010. A growing role for gender analysis in air pollution epidemiology. Environ. Health Perspect. 118, 167–176. http://dx.doi.org/10.1289/ehp.0900994.

Colberg, S.R., Sigal, R.J., Fernhall, B., Regensteiner, J.G., Blissmer, B.J., Rubin, R.R., Chasan-Taber, L., Albright, A.L., Braun, B., 2010. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. Diabetes Care 33, e147–e167. http://dx.doi.org/10.2337/dc10-9990.

Coogan, P.F., White, L.F., Jerrett, M., Brook, R.D., Su, J.G., Seto, E., Burnett, R., Palmer, J.R., Rosenberg, L., 2012. Air pollution and incidence of hypertension and diabetes mellitus in black women living in Los Angeles. Circulation 125, 767–772. http://dx.doi.org/10.1161/CIRCULATIONAHA.111.052753.Air.

Dubowsky, S.D., Suh, H., Schwartz, J., Coull, B.A., Gold, D.R., 2006. Diabetes, obesity, and hypertension may enhance associations between air pollution and markers of systemic inflammation. Environ. Health Perspect. 114, 992–998. http://dx.doi.org/10.1289/ehp.8469.

Eze, I.C., Schaffner, E., Fischer, E., Schikowski, T., Adam, M., Imboden, M., Tsai, M., Carballo, D., von Eckardstein, A., Künzli, N., Schindler, C., Probst-Hensch, N., 2014. Long-term air pollution exposure and diabetes in a population-based Swiss cohort. Environ. Int. 70, 95–105. http://dx.doi.org/10.1016/j.envint.2014.05.014.

Eze, I.C., Hemkens, L.G., Bucher, H.C., Hoffmann, B., Schindler, C., Kunzli, N., Schikowski, T., Probst-Hensch, N.M., 2015. Association between ambient air pollution and diabetes mellitus in Europe and North America: systematic review and meta-analysis. Environ. Health Perspect. 123, 381–389. http://dx.doi.org/10.1289/ehp.1307823.

Griffin, B.A., Anderson, G.L., Shih, R.A., Whitsel, E.A., Corporation, R., Beth, V., Griffin, A., Shih, R.A., Hutchinson, F., Hill, C., Carolina, N., Whitsel, E.A., 2013. Use of alternative time scales in Cox proportional hazard models: implications for time-varying environmental exposures. Stat. Med. 31, 3320–3327. http://dx.doi.org/10.1002/sim.5347.Use.

Hansen, A.B., Ravnskjær, L., Loft, S., Andersen, K.K., Bräuner, E.V., Baastrup, R., Yao, C., Ketzel, M., Becker, T., Brandt, J., Hertel, O., Andersen, Z.J., 2016. Long-term exposure to fine particulate matter and incidence of diabetes in the Danish Nurse Cohort. Environ. Int. 91, 243–250. http://dx.doi.org/10.1016/j.envint.2016.02.036.

HKUST, 2015. Institute for the Environment (IENV). Satellite information system for surface particulate matter distribution [WWW document]. http://envf.ust.hk/itf-si/index.py?where=Home&param=sec_dry, Accessed date: 10 August 2015.

Kanner, R., Connett, J., Altose, M., Buist, A., Lee, W., Tashkin, D., Wise, R., 1994. Gender difference in airway hyperresponsiveness in smokers with mild COPD. The Lung Health Study. Am. J. Respir. Crit. Care Med. 150, 956–961.

Krämer, U., Herder, C., Sugiri, D., Strassburger, K., Schikowski, T., Ranft, U., Rathmann, W., 2010. Traffic-related air pollution and incident type 2 diabetes: results from the SALIA cohort study. Environ. Health Perspect. 118, 1273–1279. http://dx.doi.org/10.1289/ehp.0901689.

Liu, C., Yang, C., Zhao, Y., Ma, Z., Bi, J., Liu, Y., Meng, X., Wang, Y., Cai, J., Chen, R., Kan, H., 2016. Associations between long-term exposure to ambient particulate air pollution and type 2 diabetes prevalence, blood glucose and glycosylated hemoglobin levels in China. Environ. Int. 92–93, 416–421. http://dx.doi.org/10.1016/j.envint.2016.03.028.Associations.

Mayor, S., 2015. Healthy diet markedly reduces type 2 diabetes risk in ethnic minority women, study finds. BMJ 350, h263. http://dx.doi.org/10.1136/bmj.h263.

Meigs, J.B., Hu, F.B., Rifai, N., Manson, J., 2015. Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. JAMA, J. Am. Med. Assoc. 291, 1978–1986.

NASA, 2015. NASA's Earth Observing System [WWW document]. Homepage. http://eospso.nasa.gov/, Accessed date: 4 February 2016.

Park, S.K., Adar, S.D., O'Neill, M.S., Auchincloss, A.H., Szpiro, A., Bertoni, A.G., Navas-Acien, A., Kaufman, J.D., Diez-Roux, A.V., 2015. Long-term exposure to air pollution and type 2 diabetes mellitus in a multiethnic cohort. Am. J. Epidemiol. 181, 327–336. http://dx.doi.org/10.1093/aje/kwu280.

Pearson, J., Bachireddy, C., Shyamprasad, S., Goldfine, A., Brownstein, J., 2010. Association between fine particulate matter and diabetes prevalence in the U.S. Diabetes Care 33, 2196–2201. http://dx.doi.org/10.2337/dc10-0698.

Puett, R.C., Hart, J.E., Schwartz, J., Hu, F.B., Liese, A.D., Laden, F., 2011. Are particulate matter exposures associated with risk of type 2 diabetes? Environ. Health Perspect. 119, 384–389. http://dx.doi.org/10.1289/ehp.1002344.

Qiu, H., Sun, S., Tsang, H., Wong, C.-M., Lee, R.S., Schooling, C.M., Tian, L., 2017. Fine particulate matter exposure and incidence of stroke: a cohort study in Hong Kong. Neurology 88, 1709–1717.

Rajagopalan, S., Brook, R.D., 2012. Air pollution and type 2 diabetes: mechanistic insights. Diabetes 61, 3037–3045. http://dx.doi.org/10.2337/db12-0190.

Schooling, C., Chan, W., Leung, S., Lam, T., Lee, S., Shen, C., Leung, J., Leung, G., 2016. Cohort profile: Hong Kong Department of Health Elderly Health Service Cohort. Int. J. Epidemiol. 45, 64–72. http://dx.doi.org/10.1093/ije/dyu227.

Stafoggia, M., Cesaroni, G., Peters, A., Andersen, Z.J., Badaloni, C., Beelen, R., Caracciolo, B., Cyrys, J., de Faire, U., de Hoogh, K., Eriksen, K.T., Fratiglioni, L., Galassi, C., Gigante, B., Havulinna, A.S., Hennig, F., Hilding, A., Hoek, G., Hoffmann, B., Houthuijs, D., Korek, M., Lanki, T., Leander, K., Magnusson, P.K., Meisinger, C., Migliore, E., Overvad, K., Ostenson, C.G., Pedersen, N.L., Pekkanen, J., Penell, J., Pershagen, G., Pundt, N., Pyko, A., Raaschou-Nielsen, O., Ranzi, A., Ricceri, F., Sacerdote, C., Swart, W.J.R., Turunen, A.W., Vineis, P., Weimar, C., Weinmayr, G., Wolf, K., Brunekreef, B., Forastiere, F., 2014. Long-term exposure to ambient air pollution and incidence of cerebrovascular events: results from 11 European cohorts within the ESCAPE project. Environ. Health Perspect. 122, 919–925. http://dx.doi.org/10.1289/ehp.1307301.

Sun, Q., Yue, P., Deiuliis, J.A., Lumeng, C.N., Kampfrath, T., Mikolaj, M.B., Cai, Y., Ostrowski, M.C., Lu, B., Parthasarathy, S., Brook, R.D., Moffatt-Bruce, S.D., Chen, L.C., Rajagopalan, S., 2009. Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. Circulation 119, 538–546. http://dx.doi.org/10.1161/CIRCULATIONAHA.108.799015.Ambient.

Thiebaut, A.C.M., Benichou, J., 2004. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. Stat. Med. 23, 3803–3820. http://dx.doi.org/10.1002/sim.2098.

Wang, B., Xu, D., Jing, Z., Liu, D., Yan, S., Wang, Y., 2014. Effect of long-term exposure to air pollution on type 2 diabetes mellitus risk: a systemic review and meta-analysis of cohort studies. Eur. J. Endocrinol. 171, R173–82. http://dx.doi.org/10.1530/EJE-14-0365.

Wong, C.M., Lai, H.K., Tsang, H., Thach, T.Q., Neil Thomas, G., Lam, K.B.H., Chan, K.P., Yang, L., Lau, A.K.H., Ayres, J.G., Lee, S.Y., Chan, W.M., Hedley, A.J., Lam, T.H., 2015. Satellite-based estimates of long-term exposure to fine particles and association with mortality in elderly Hong Kong residents. Environ. Health Perspect. 123, 1167–1172. http://dx.doi.org/10.1289/ehp.1408264.

World Health Organization, 2016. Global Report on Diabetes. WHO Library Cataloguing-in-Publication Data (doi:ISBN 978 92 4 156525 7).

Xu, X., Liu, C., Xu, Z., Tzan, K., Zhong, M., Wang, A., Lippmann, M., Chen, L.C., Rajagopalan, S., Sun, Q., 2011a. Long-term exposure to ambient fine particulate pollution induces insulin resistance and mitochondrial alteration in adipose tissue. Toxicol. Sci. 124, 88–98. http://dx.doi.org/10.1093/toxsci/kfr211.

Xu, Z., Xu, X., Zhong, M., Hotchkiss, I.P., Lewandowski, R.P., Wagner, J.G., Bramble, L.A., Yang, Y., Wang, A., Harkema, J.R., Lippmann, M., Rajagopalan, S., Chen, L.-C., Sun, Q., 2011b. Ambient particulate air pollution induces oxidative stress and alterations of mitochondria and gene expression in brown and white adipose tissues. Part. Fibre Toxicol. 8, 20. http://dx.doi.org/10.1186/1743-8977-8-20.

Yoon, K.H., Lee, J.H., Kim, J.W., Cho, J.H., Choi, Y.H., Ko, S.H., Zimmet, P., Son, H.Y., 2006. Epidemic obesity and type 2 diabetes in Asia. Lancet 368, 1681–1688. http://dx.doi.org/10.1016/S0140-6736(06)69703-1.