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ARTICLE

Long-term exposure to ambient fine particulate matter ($PM_{2.5}$) and incident type 2 diabetes: a longitudinal cohort study

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Abstract

Aims/hypothesis Information on the associations of long-term exposure to fine particulate matter (with an aerodynamic diameter less than 2.5 μm; $PM_{2.5}$) with the development of type 2 diabetes is scarce, especially for south-east Asia, where most countries are experiencing serious air pollution. This study aimed to investigate the long-term effects of exposure to ambient $PM_{2.5}$ on the incidence of type 2 diabetes in a population of Taiwanese adults.

Methods A total of 147,908 participants without diabetes, at least 18 years of age, were recruited in a standard medical examination programme between 2001 and 2014. They were encouraged to take medical examinations periodically and underwent at least two measurements of fasting plasma glucose (FPG). Incident type 2 diabetes was identified as FPG ≥7 mmol/l or self-reported physician-diagnosed diabetes in the subsequent medical visits. The $PM_{2.5}$ concentration at each participant's address was estimated using a satellite-based spatiotemporal model with a resolution of 1×1 km^2. The 2 year average of $PM_{2.5}$ concentrations (i.e. the year of and the year before the medical examination) was treated as an indicator of long-term exposure to ambient $PM_{2.5}$ air pollution. We performed Cox regression models with time-dependent covariates to analyse the long-term effects of exposure to $PM_{2.5}$ on the incidence of type 2 diabetes. A wide range of covariates were introduced in the models to control for potential effects, including age, sex, education, season, year, smoking status, alcohol drinking, physical activity, vegetable intake, fruit intake, occupational exposure, BMI, hypertension and dyslipidaemia (all were treated as time-dependent covariates except for sex).

Results Compared with the participants exposed to the first quartile of ambient $PM_{2.5}$, participants exposed to the second, third and fourth quartiles of ambient $PM_{2.5}$ had HRs of 1.28 (95% CI 1.18, 1.39), 1.27 (95% CI 1.17, 1.38) and 1.16 (95% CI 1.07, 1.26), respectively, for the incidence of type 2 diabetes. Participants who drank occasionally or regularly (more than once per week) or who had a lower BMI (<23 kg/m^2) were more sensitive to the long-term effects of exposure to ambient $PM_{2.5}$.

Conclusions/interpretation Long-term exposure to ambient $PM_{2.5}$ appears to be associated with a higher risk of developing type 2 diabetes in this Asian population experiencing high levels of air pollution.

Keywords Incident type 2 diabetes · Longitudinal cohort · Long-term exposure · $PM_{2.5}$

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Research in context

What is already known about this subject?

- Long-term exposure to fine particulate matter (with an aerodynamic diameter less than 2.5 μm; $PM_{2.5}$) is a novel risk for cardiovascular disease that is closely linked with type 2 diabetes
- There are limited data on the association between long-term exposure to $PM_{2.5}$ and the development of type 2 diabetes, especially for populations in south-east Asia

What is the key question?

- Is long-term exposure to ambient $PM_{2.5}$ associated with a higher risk of incident type 2 diabetes?

What are the new findings?

- Long-term exposure to ambient $PM_{2.5}$ is associated with a higher risk of developing type 2 diabetes in an adult population experiencing high levels of air pollution

How might this impact on clinical practice in the foreseeable future?

- Mitigation of global air pollution can help to prevent the current pandemic of type 2 diabetes

Abbreviations

AOD	Aerosol optical depth
FPG	Fasting plasma glucose
MET	Metabolic equivalent value
PM	Particulate matter
$PM_{2.5}$	Particulate matter with an aerodynamic diameter less than 2.5 μm

Introduction

The escalating pandemic of type 2 diabetes presents an enormous public health challenge around the world. There were estimated to be 383 million diabetic individuals and around 1.4 million deaths due to diabetes worldwide in 2016 [1, 2]. These numbers are expected to continue to rise rapidly, especially in middle- and low-income countries [3]. Type 2 diabetes can lead to a series of chronic complications, including vision loss, renal diseases, stroke and cardiovascular diseases, that pose an overwhelming burden on healthcare systems [4–6]. Several traditional cardiovascular risk factors are also risk factors for the development of type 2 diabetes, including obesity, high blood pressure and unhealthy lifestyles and behaviours, which have all been well investigated [7].

Air pollution is the largest single environmental risk in the world and it has recently been regarded as a novel risk factor for cardiovascular diseases. The American Heart Association states that exposure to particulate matter (PM) with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) is causally associated with an increased risk of cardiovascular morbidity and mortality [8]. Given the close linkage between type 2 diabetes and cardiovascular disease, $PM_{2.5}$ air pollution may also act as a risk factor for type 2 diabetes. Although a few studies have investigated long-term exposure to PM and the development, prevalence and mortality rate of diabetes [9–12], the results are inconsistent. Large-scale prospective cohort studies are necessary to provide stable results and precise estimates. Furthermore, most studies have been conducted in North America and Europe [13–16] and limited information is available from other regions, such as the WHO western Pacific and south-east Asia regions, where many countries are experiencing high levels of air pollution. At the same time, epidemics of type 2 diabetes are growing quickly in Asia. We therefore investigated the association of long-term exposure to $PM_{2.5}$ with the development of type 2 diabetes in a large longitudinal cohort of 147,908 adults in Taiwan.

Methods

Study participants This study was based on an ongoing large prospective cohort whose details were described previously [17–20]. In brief, this cohort study recruited more than 0.6 million participants between 1994 and 2014. A private firm, the MJ Health Management Institution, provided a standard medical screening programme. The participants were of Chinese descent residing in Taiwan. They were encouraged to visit the firm periodically through a paid membership and underwent a series of medical examinations at each visit, including anthropometric measurements, spirometry test, blood and urinary tests and imaging tests, and answered a standard self-administered questionnaire survey. This cohort is an open (dynamic) cohort with no end date. Each year there are around 20,000 new members recruited to the cohort, in addition to the revisits by existing members. Data generated from the medical examinations have been computerised since 1996. As of

December 2014, the database contained around 0.59 million Taiwan participants and had counted 1.35 million medical visits. Around 43.5% of the participants had attended at least two medical visits (range 2–28 visits). Each participant was required to sign an informed consent form before participation. We obtained ethical approval for this study from the Joint Chinese University of Hong Kong, New Territories East Cluster Clinical Research Ethics Committee.

The participant selection in this study is presented in ESM Fig. 1. In total, 418,811 participants at least 18 years of age with fasting plasma glucose (FPG) measurements were recruited during 2001–2014, when data on $PM_{2.5}$ concentration were available. We excluded 52,365 participants with incomplete information (2861 with $PM_{2.5}$ data due to a missing address and 49,504 based on the covariates). We further excluded 15,008 participants with self-reported physician-diagnosed cancer or cardiovascular diseases at their first medical visit because of the possible effects of comorbidities on type 2 diabetes. Among the remaining 351,438 participants, 194,975 were excluded because they visited the institution and received medical examination only once. For those who had at least two medical examination visits, 5488 participants were excluded because they had diabetes (defined as FPG ≥7 mmol/l, or self-reported physician-diagnosed diabetes) at their first visit [21]. Because the development of type 2 diabetes is a chronic process, we further excluded 3067 participants with a follow-up duration of less than 2 years. Finally, 147,908 participants with 548,429 FPG measurements were included in the present analysis. Compared with those participants excluded because of attending only one medical visit, the 147,908 participants included in the present study had similar baseline distributions of general characteristics (ESM Table 1). The follow-up duration of the 147,908 participants ranged from 2 to 13.9 years (mean 6.7 years). The number of medical visits ranged from 2 to 23 with a median of 3.0. The mean visit interval was 1.2 years (SD 4.1).

Exposure assessment We have described the detailed method for estimating $PM_{2.5}$ exposure in previous publications [17, 19, 22, 23]. In brief, the ambient $PM_{2.5}$ exposure at each participant's address was estimated by a satellite-based spatial-temporal model with high resolution (1×1 km^2) using the aerosol optical depth (AOD) data derived from the Moderate Resolution Imaging Spectroradiometer carried on US National Aeronautics and Space Administration satellites. The sample size for AOD data was around 300, which was similar to the general average level worldwide [24]. To address the issues of missing data and temporal limitation, we derived a correction factor using ground observations [23]. To calibrate the satellite-derived AOD data, we collected the ground observation of AOD from the aerosol robotic network (AERONET) in Taipei (EPA-NCU station, 24.97°N and 121.19°E), the capital city of Taiwan. Finally, we validated the model by comparing the estimated $PM_{2.5}$ exposure with the monitoring data from more than 70 ground-level air pollution monitoring stations. The correlation coefficients for yearly average concentration ranged from 0.72 to 0.83 [17, 18].

The address of each participant (either residential or business) was noted during each medical visit so that the medical report could be mailed to them. Thus, any change of address was recorded. If a participant reported a change of his/her address in a follow-up medical visit, the $PM_{2.5}$ concentration at the new address since the follow-up time point was applied in the data analysis. There were 29,032 (19.6%) participants who changed their address during this study. We geocoded each participant's address into latitude and longitude data, which were used to calculate the address-specific yearly average $PM_{2.5}$ concentration. The 2 year average concentration was then calculated based on the concentrations from the year of and the year before the medical examination as an indicator of long-term exposure to ambient $PM_{2.5}$ air pollution.

Outcome measurement Detailed information on the medical examination and quality control has been described in previous publications and in the Technical Reports published by the MJ Health Research Foundation [17, 18, 25]. An overnight fasting blood sample was taken in the morning and the plasma glucose level was measured enzymatically with a Hitachi 7150 analyser (Tokyo, Japan) if before 2005 or Toshiba C8000 analyser (Tokyo, Japan) if since 2005.

The health outcome in this study was incident type 2 diabetes. After the baseline assessment at the first visit, all the 147,908 non-diabetic participants were followed up, and incident type 2 diabetes was identified by medical assessment (defined as FPG ≥7 mmol/l, or self-reported physician-diagnosed diabetes) in subsequent visits [21]. The endpoint was the first occurrence of type 2 diabetes or the last visit if type 2 diabetes did not occur.

Contextual variables We collected information on the participants' demographic and socioeconomic characteristics, lifestyle and medical history by using a standard self-administered questionnaire at each visit. Height and weight were measured with participants wearing light indoor clothing without shoes. Seated blood pressure was measured using an auto-sphygmomanometer (CH-5000; Citizen, Tokyo, Japan). An overnight fasting blood sample was taken in the morning and a lipid profile was documented.

Based on previous literature [7, 26], we included the following factors as covariates in this study: age (years), sex (male or female), education (lower than high school [<10 years], high school [10–12 years], college or university [13–16 years] or postgraduate [>16 years]), smoking status (never, former or current), alcohol drinking (seldom [less than once per week], occasional [1–3 times/week] or regular [>3

times/week]), physical activity (defined as the product of metabolic equivalent value [MET; 1 MET = 1 kJ h^{-1} [kg bodyweight]$^{-1}$] and duration of exercise [h] [27]: inactive [<3.75 MET-h], low [3.75–7.49 MET-h], medium [7.50–16.49 MET-h], high [16.50–25.49 MET-h] or very high [≥25.50 MET-h]), vegetable intake (seldom [<1 serving/day], moderate [1–2 servings/day] or frequent [>2 servings/day]), fruit intake (seldom [<1 serving/day], moderate [1–2 servings/day] or frequent [>2 servings/day]), occupational exposure to dust or organic solvents in the workplace (yes or no; as obtained by asking, 'Are there any occupational hazards in your workplace?'), BMI (calculated as weight [kg] divided by the square of height [m]), hypertension (defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥90 mmHg or self-reported hypertension), dyslipidaemia (defined as total cholesterol ≥13.3 mmol/l, triacylglycerol ≥11.1 mmol/l or HDL-cholesterol <2.2 mmol/l), season of each visit (spring [March–May], summer [June–August], autumn [September–November], winter [December to February]) and calendar year at baseline.

Data analysis We used Cox regression models with time-dependent covariates to analyse the associations between long-term exposure to ambient $PM_{2.5}$ and the development of type 2 diabetes. The timescale used in the models was time-in-study (i.e. follow-up time). A crude model and three multivariable models were developed to compare the effects of covariates: Model 1 had no adjustment; Model 2 adjusted for demographic factors (age, sex and education), season and calendar year; Model 3 further adjusted for lifestyle factors (smoking status, alcohol drinking, physical activity, vegetable intake and fruit intake) and occupational exposure and Model 4 further adjusted for cardiovascular risk factors (BMI, hypertension and dyslipidaemia). All covariates were treated as time-dependent covariates except for sex. We estimated the HR with 95% CI as the risk of incident diabetes for $PM_{2.5}$ quartiles (first to fourth quartile [μg/m^3], respectively): <21.7, 21.7–<24.1, 24.1–<28.0, ≥28.0). We tested the linearity using likelihood ratio test and results showed that the associations deviated from linearity ($\chi^2 = 35.2$, $p < 0.05$). Therefore, we applied deciles to show the concentration–response associations between ambient $PM_{2.5}$ and incident type 2 diabetes (first to tenth deciles [μg/m^3], respectively: 5.7–<19.8, 19.8–<21.2, 21.2–<22.2, 22.2–<23.2, 23.2–<24.1, 24.1–<25.2, 25.2–<26.5, 26.5–<32.7, 32.7–<39.9 and 39.9–50.3).

We performed stratified analyses based on the following characteristics of the participants at baseline: sex (male vs female); education (<13 years vs ≥13 years); smoking status (never vs ever); alcohol drinking (seldom vs occasional/regular); physical activity (<7.5 MET-h vs ≥7.5 MET-h); BMI (<23 kg/m^2 vs ≥23 kg/m^2) [28]; hypertension (no vs yes) and dyslipidaemia (no vs yes). We stratified the participants into two subgroups according to the baseline cut off values of the aforementioned characteristics. We then performed data analyses separately within each subgroup using the Cox regression models with time-dependent covariates to derive the stratum-specific HR.

To test the stability of the associations, we further conducted sensitivity analyses by: (1) including participants with a follow-up of less than 2 years; (2) including only participants enrolled before 2005 whose FPG and lipids were measured with the Hitachi 7150; (3) including only the participants enrolled since 2005 whose FPG and lipids were measured with the Toshiba C8000; (4) excluding the participants with a business address to eliminate the potential misclassification of $PM_{2.5}$ exposure due to different types of addresses; (5) using annual average $PM_{2.5}$ concentration as an indicator for long-term exposure to $PM_{2.5}$; (6) excluding those participants who were younger than 30 years old to better distinguish between type 1 and type 2 diabetes; (7) further adjusting for region of participant's location (including five municipalities [Taipei, Taoyuan, Taichung, Tainan and Kaoshiung], ten counties [Hsinchu, Miaoli, Changhua, Nantou, Yunlin, Chiayi, Pingtung, Ilan, Hualien and Taitung] and one county-level city [Keelong]) to consider the effects of different regions; and (8) only including those participants with annual medical visit (interval of the medical visits ranged from 8 months to 16 months) to avoid delayed diagnosis of the disease.

All the statistical analyses were performed using R 3.3.2. (R Core Team, Vienna, Austria). The exposure and interaction effects were regarded as statistically significant at a two-tailed test level of 0.05 and 0.1, respectively.

Results

Table 1 shows the characteristics of all participants and participants with incident diabetes. The mean age of the participants was 38.3 years (SD 11.5 years) at baseline. The majority were well-educated, non-smokers and seldom drank alcohol; 4781 participants developed diabetes. At baseline, the participants who developed diabetes were generally older, had a lower level of education and were more likely to smoke and drink alcohol. They also had a higher prevalence of cardiovascular risk. The cumulative incidence was 3.2% with an incidence rate of 3.5 per 1000 person-years.

The locations of the participants are shown in Fig. 1. The participants mainly lived in the western part of Taiwan. In general, the south-western areas were the most heavily polluted and the middle and eastern areas were the least heavily polluted. The spatial pattern of exposure contrast throughout the island generally remained stable during the study period. The $PM_{2.5}$ concentrations increased slightly from 2001 to 2004 (the mean 2 year $PM_{2.5}$ was 24.8, 26.2, 28.7 and 29.6 μg/m^3, respectively, for participants enrolled in 2001,

Table 1 Characteristics of the participants

Characteristic	All participants at baseline[a] $N = 147,908$	All observations[b] $n = 548,429$	Incident diabetes[c] $n = 4781$
Age, years	38.3 (11.5)	41.8 (16)	46.7 (12.0)
Male sex, *n* (%)	74,142 (50.1)	279,528 (51.0)	3001 (62.8)
Education, *n* (%)			
Lower than high school	17,600 (11.9)	61,940 (11.3)	1294 (27.1)
High school	29,461 (19.9)	104,849 (19.1)	1059 (22.2)
College or university	82,278 (55.6)	305,167 (55.6)	2050 (42.9)
Postgraduate	18,569 (12.6)	76,473 (13.9)	378 (7.9)
Smoking status, *n* (%)			
Never	111,024 (75.1)	418,371 (76.3)	3166 (66.2)
Former	7764 (5.2)	31,679 (5.8)	326 (6.8)
Current	29,120 (19.7)	98,379 (17.9)	1289 (27.0)
Alcohol consumption, *n* (%)			
Seldom	127,433 (86.2)	468,629 (85.4)	3776 (79.0)
Occasional	14,015 (9.5)	54,462 (9.9)	618 (12.9)
Regular	6460 (4.4)	25,338 (4.6)	387 (8.1)
Physical activity, *n* (%)			
Inactive	74,407 (50.3)	247,310 (45.1)	2304 (48.2)
Low	31,669 (21.4)	112,080 (20.4)	953 (19.9)
Moderate	24,279 (16.4)	103,714 (18.9)	818 (17.1)
High	9770 (6.6)	41,747 (7.6)	420 (8.8)
Very high	7783 (5.3)	43,578 (7.9)	286 (6.0)
Vegetable intake, *n* (%)			
Seldom	20,376 (13.8)	60,853 (11.1)	631 (13.2)
Moderate	88,753 (60.0)	322,871 (58.9)	2866 (59.9)
Frequent	38,779 (26.2)	164,705 (30.0)	1284 (26.9)
Fruit intake, *n* (%)			
Seldom	48,643 (32.9)	151,980 (27.7)	1386 (29.0)
Moderate	81,054 (54.8)	316,796 (57.8)	2717 (56.8)
Frequent	18,211 (12.3)	79,653 (14.5)	678 (14.2)
Occupational exposure, *n* (%)[d]	12,272 (8.3)	42,330 (7.7)	384 (8.0)
BMI, kg/m^2	22.8 (3.5)	23.1 (4.5)	26 (3.7)
Hypertension, *n* (%)[e]	17,516 (11.8)	74,695 (13.6)	1558 (32.6)
Dyslipidaemia, *n* (%)[f]	33,291 (22.5)	125,444 (22.9)	2280 (47.7)
$PM_{2.5}$, $\mu g/m^3$[g]	26.8 (7.8)	26.5 (6.2)	26.5 (7.7)
Diabetes incidence rate, *n*/1000 person-years	–	3.5	–

[a] Baseline characteristics for all participants: values are shown as mean (SD) for continuous variables and count (%) for categorical variables

[b] Characteristics for all observations (i.e. all medical examinations of the 147,908 participants during the study period): values are shown as mean (interquartile range) for continuous variables and count (%) for categorical variables

[c] Baseline characteristics for participants who developed incident type 2 diabetes during the study period (fasting blood glucose ≥7 mmol/l or self-reported physician-diagnosed type 2 diabetes): values are shown as mean (SD) for continuous variables and count (%) for categorical variables

[d] Classified as exposure to dust or organic solvents in the workplace, established by asking, 'Are there any occupational hazards in your workplace?'

[e] Systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or reported physician-diagnosed hypertension

[f] Total cholesterol ≥13.3 mmol/l, triacylglycerol ≥11.1 mmol/l or HDL-cholesterol <2.2 mmol/l

[g] Average $PM_{2.5}$ level for the year of visit and the previous year

2002, 2003 and 2004) and then declined gradually from 2005 to 2014 (the mean 2 year $PM_{2.5}$ was 27.4, 26.9, 26.9, 26.7, 26.8, 25.8, 25.6, 25.0, 23.7 and 24.4 $\mu g/m^3$, respectively, for 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013 and 2014). The overall mean was 26.5 $\mu g/m^3$ (SD 7.4 $\mu g/m^3$) with an interquartile range of 21.7–28.0 $\mu g/m^3$.

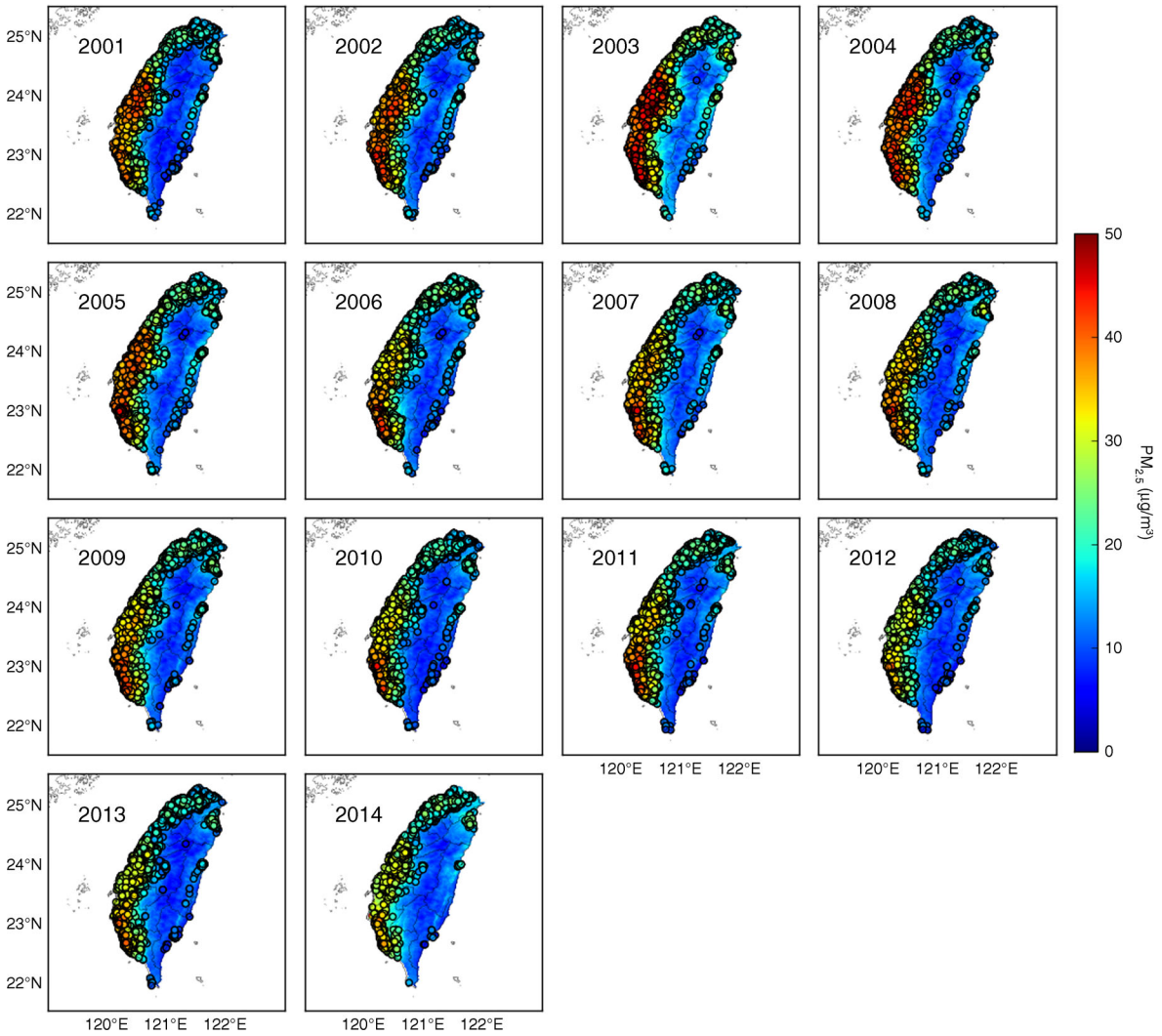

Fig. 1 Spatial distribution of the participants in Taiwan, by year. The spatial distribution of the 147,908 participants at baseline by year and mean $PM_{2.5}$ concentration at each location during that year. Circles indicate participant locations

Table 2 shows the associations between ambient $PM_{2.5}$ and the development of type 2 diabetes. Exposure to $PM_{2.5}$ was significantly associated with a higher risk of incident type 2 diabetes. Compared with the participants exposed to the first quartile of ambient $PM_{2.5}$, those exposed to the second, third and fourth quartiles of $PM_{2.5}$ were associated with HRs (95% CI) of 1.28 (1.18, 1.39), 1.27 (1.17, 1.38) and 1.16 (1.07, 1.26), respectively, for incident type 2 diabetes after adjusting for a wide range of covariates. The concentration–response association is presented in Fig. 2. No obvious effect threshold was observed.

The results of stratified analyses are presented in Table 3. Significant modified effects were observed for the categories of BMI and alcohol drinking. Long-term $PM_{2.5}$ exposure had a stronger association with the development of diabetes in participants with BMI <23 kg/m^2 or a habit of occasional or regular alcohol consumption. No significant modifying effects were observed for the other factors. Sensitivity analyses generally yielded similar results (ESM Table 2).

The associations between covariates and incident type 2 diabetes are presented in ESM Table 3.

Discussion

The results of this large prospective cohort study show that long-term exposure to ambient $PM_{2.5}$ appears to be associated with a higher risk of developing type 2 diabetes after controlling for a wide range of covariates. The associations remain robust in the stratified and sensitivity analyses.

Our results are in line with those of some previous studies [16, 29–31]. Three studies, in Canada, Denmark and the USA, found that a 10 μg/m^3 increase in $PM_{2.5}$ was associated with a higher risk of incident diabetes with the HR ranging from 1.11 to 1.52 [16, 29, 30]. In a Hong Kong elderly population, a significant association with an HR of 1.15 per interquartile range (3.2 μg/m^3) was also observed by Qiu et al [31]. The

Table 2 Associations of long-term exposure to ambient $PM_{2.5}$ with incident type 2 diabetes in Taiwanese adults

$PM_{2.5}$ quartiles	Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
1st quartile ($PM_{2.5}$ < 21.7 μg/m^3)	–	–	–	–	–	–	–	–
2nd quartile ($PM_{2.5}$ 21.7–<24.1 μg/m^3)	1.14 (1.06, 1.24)	0.001	1.26 (1.16, 1.36)	<0.001	1.26 (1.16, 1.36)	<0.001	1.28 (1.18, 1.39)	<0.001
3rd quartile ($PM_{2.5}$ 24.1–<28.0 μg/m^3)	1.18 (1.09, 1.29)	<0.001	1.25 (1.15, 1.36)	<0.001	1.25 (1.15, 1.36)	<0.001	1.27 (1.17, 1.38)	<0.001
4th quartile ($PM_{2.5}$ ≥ 28.0 μg/m^3)	1.17 (1.08, 1.27)	<0.001	1.16 (1.07, 1.26)	<0.001	1.17 (1.08, 1.27)	<0.001	1.16 (1.07, 1.26)	<0.001

Data are presented as HR of incident type 2 diabetes with 95% CI, using the first quartile of the $PM_{2.5}$ concentration as reference. Incident type 2 diabetes was defined as plasma glucose ≥7 mmol/l or self-reported physician-diagnosed type 2 diabetes

[a] Model 1 is the crude model

[b] Model 2 was adjusted for demographic factors (including age, sex, education), season and year

[c] Model 3 was further adjusted for lifestyle factors (smoking status, alcohol drinking, physical activity, vegetable intake and fruit intake) and occupational exposure

[d] Model 4 was further adjusted for BMI and health factors (including hypertension and dyslipidaemia)

larger HR in the Hong Kong study was possibly due to its elderly participants who were potentially more vulnerable. There are limited cohort studies in Asia but a few large-scale cross-sectional studies showed that $PM_{2.5}$ was significantly associated with higher risk of prevalence of diabetes [12, 32], supporting our findings. Several previous studies also found that traffic-related air pollution or other air pollutants, including NO_2 and O_3, were associated with incident diabetes [14, 33–35]. However, five previous studies did not find that PM significantly affected the development of diabetes [26, 35–38]. Many factors may contribute to this inconsistency, including the heterogeneity of the study populations, study regions, chemical components of PM, research methods and diagnostic criteria. Our study targeted a population in Taiwan, in which the $PM_{2.5}$ levels were higher than those in North America and Europe. One advantage of this study is that the exposure contrast among our participants was relatively large. The accuracy of the exposure estimate may also play an important role in the inconsistency among the studies. Some previous studies estimated PM exposure based on the proximity of residences to fixed monitoring stations, with the same exposure level assigned to an entire community (district, county or city). Such community-level exposure assessment (ecological fallacy) may mask the true spatial variation or introduce misclassification of exposure, thus leading to the inconsistent results. Finally, the effect sizes of $PM_{2.5}$ on incident type 2 diabetes are small. Thus, a large sample size is necessary to provide sufficient statistical power, yet many previous studies had relatively small sample sizes.

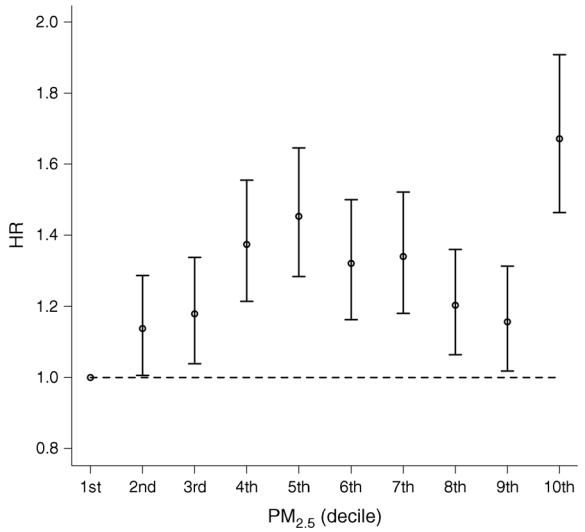

Fig. 2 The concentration–response association between ambient $PM_{2.5}$ and incident type 2 diabetes in the Taiwanese participants. The data are presented as estimated HR (95% CI) associated with $PM_{2.5}$ concentration deciles. The association was adjusted for age, sex, education, season, year, smoking status, alcohol drinking, physical activity, vegetable intake, fruit intake, occupational exposure, BMI, hypertension and dyslipidaemia. The $PM_{2.5}$ range (μg/m^3) of the first to tenth deciles, respectively, was: 5.7–<19.8, 19.8–<21.2, 21.2–<22.2, 22.2–<23.2, 23.2–<24.1, 24.1–<25.2, 25.2–<26.5, 26.5–<32.7, 32.7–<39.9 and 39.9–50.3

In this study, we categorised $PM_{2.5}$ into quartiles. It seems the HR values decreased slightly in participants with higher quartile exposure (HR 1.28, 1.27 and 1.16 for the second, third and fourth quartile, respectively). We do not know the exact reasons for this phenomenon, but we speculate that the use of category variable might lead to a loss of information and an increase in uncertainty. Because the likelihood ratio test show that the association marginally deviated from linearity ($\chi^2 = 35.2$, $p < 0.001$), we used $PM_{2.5}$ deciles to draw the concentration–response association (Fig. 2). The HR values decreased in the sixth to ninth deciles and jumped in the tenth decile. It is difficult to interpret this phenomenon but the non-linearity association might also be due to the heterogeneities of the populations in different cities/areas and other unidentified confounders (e.g. some factors might affect the health of people living in the same city but this may vary across the city). The high HR in the tenth decile of $PM_{2.5}$ concentration could be partially explained by the larger $PM_{2.5}$ concentration

Table 3 Stratified analyses of the associations between $PM_{2.5}$ and incident type 2 diabetes by covariates at baseline

Covariate	Counts/ population	IR (per 1000 person-years)	2nd $PM_{2.5}$ quartile		3rd $PM_{2.5}$ quartile		4th $PM_{2.5}$ quartile		p_{inter}
			HR	*p* value	HR	*p* value	HR	*p* value	
Sex									0.270
Male	3001/74,142	4.3	1.24 (1.12, 1.37)	<0.001	1.26 (1.14, 1.40)	<0.001	1.16 (1.05, 1.28)	0.005	
Female	1780/73,766	2.6	1.32 (1.16, 1.50)	<0.001	1.29 (1.13, 1.48)	<0.001	1.09 (0.95, 1.25)	0.201	
Education (years)									0.541
<13	2353/47,061	5.6	1.24 (1.11, 1.38)	<0.001	1.17 (1.04, 1.31)	0.008	1.14 (1.01, 1.28)	0.033	
≥13	2428/100,847	2.5	1.35 (1.21, 1.51)	<0.001	1.33 (1.18, 1.49)	<0.001	1.23 (1.10, 1.38)	<0.001	
Smoking status									0.830
Never	3166/111,024	3.0	1.24 (1.13, 1.37)	<0.001	1.23 (1.11, 1.36)	<0.001	1.15 (1.04, 1.27)	0.006	
Ever	1615/36,884	4.8	1.36 (1.18, 1.56)	<0.001	1.35 (1.17, 1.55)	<0.001	1.19 (1.04, 1.38)	0.015	
Alcohol drinking									0.038
Seldom	3776/127,433	3.2	1.28 (1.17, 1.40)	<0.001	1.29 (1.18, 1.41)	<0.001	1.13 (1.03, 1.24)	0.008	
Occasional or regular	1005/20,475	5.4	1.29 (1.08, 1.54)	0.005	1.23 (1.02, 1.47)	0.028	1.25 (1.05, 1.49)	0.012	
Physical activity (MET-h)									0.844
<7.5	3257/106,076	3.3	1.28 (1.16, 1.41)	<0.001	1.32 (1.20, 1.46)	<0.001	1.18 (1.07, 1.30)	0.001	
≥7.5	1524/41,832	3.9	1.33 (1.16, 1.54)	<0.001	1.22 (1.05, 1.41)	0.010	1.17 (1.01, 1.35)	0.035	
BMI									0.012
<23 kg/m^2	929/82,025	1.2	1.34 (1.11, 1.61)	0.002	1.21 (0.99, 1.46)	0.057	1.40 (1.17, 1.68)	<0.001	
≥23 kg/m^2	3852/65,883	6.3	1.27 (1.16, 1.39)	<0.001	1.28 (1.17, 1.40)	<0.001	1.07 (0.98, 1.18)	0.132	
Hypertension									0.952
No	3223/130,392	2.6	1.33 (1.21, 1.46)	<0.001	1.26 (1.14, 1.39)	<0.001	1.17 (1.06, 1.29)	0.002	
Yes	1558/17,516	10.2	1.25 (1.08, 1.44)	0.002	1.31 (1.14, 1.51)	<0.001	1.18 (1.02, 1.37)	0.023	
Dyslipidaemia									0.301
No	2501/114,617	2.3	1.21 (1.08, 1.35)	0.001	1.24 (1.11, 1.39)	<0.001	1.14 (1.02, 1.27)	0.023	
Yes	2280/33,291	7.6	1.36 (1.22, 1.53)	<0.001	1.31 (1.16, 1.48)	<0.001	1.19 (1.05, 1.34)	0.005	

Data are presented as HR of incident type 2 diabetes with 95% CI, using the first quartile of the $PM_{2.5}$ concentration as the reference. Incident type 2 diabetes was defined as plasma glucose ≥7 mmol/l or self-reported physician-diagnosed type 2 diabetes

HR was adjusted for age (not in age-stratified analysis), sex (not in sex-stratified analysis), education (not in education-stratified analysis), season, year, smoking status (not in smoking-stratified analysis), alcohol drinking (not in alcohol drinking-stratified analysis), physical activity (not in physical activity-stratified analysis), vegetable intake, fruit intake, occupational exposure, BMI (not in BMI-stratified analysis), hypertension (not in hypertension-stratified analysis) and dyslipidaemia (not in dyslipidaemia-stratified analysis)

IR, incidence rate; p_{inter}, *p* value for the interaction terms

range (39.9–50.3 μg/m^3) and the relatively smaller number of incident diabetes cases (there were 416 cases in the tenth decile, while the number in each of the first nine deciles ranged from 450 to 521). Nonetheless, further studies to illustrate the concentration–response relationship between $PM_{2.5}$ and type 2 diabetes are warranted.

The biological mechanism underlying the association between long-term exposure to $PM_{2.5}$ and the development of type 2 diabetes is not completely understood. Animal experiments have shown that $PM_{2.5}$ can produce hypothalamic inflammation and induce metabolic disorders, including autonomic imbalance, visceral adipose inflammation, endothelial dysfunction, insulin resistance and overt diabetes [39, 40]. One in vivo study noted that long-term exposure to $PM_{2.5}$ can further cause metabolic disorders by triggering the unfolded protein response and macrophage infiltration [41]. In addition, cardiovascular disease and diabetes may have similar mechanistic pathways (systematic inflammation and oxidative stress) [42]. Our previous study clearly showed that $PM_{2.5}$ may induce systemic inflammation [17, 43]. Thus, the systematic inflammation and oxidative stress induced by $PM_{2.5}$ may be the main mediators between $PM_{2.5}$ exposure and diabetes by disrupting insulin signalling [44, 45].

We also explored the potential modifying effects of a range of factors. Although no significant modifying effects were observed for sex, education, smoking status, physical activity, hypertension and dyslipidaemia, statistical significance was observed for the modifying effect of alcohol drinking. Presently, however, there is little information on the modifying effects of alcohol drinking. BMI was another significant

modifier in this study. Interestingly, the participants with a lower BMI had a higher risk of developing diabetes due to $PM_{2.5}$ exposure, even though BMI is a significant risk factor for diabetes development. This phenomenon has also been observed in previous studies but the modifying effects were generally insignificant [29, 32, 33, 46]. Further studies are warranted to assess the different modifying effects.

This study has several important strengths. First, it targeted a large general population in Asia, where type 2 diabetes epidemics are growing quickly and people are generally experiencing serious air pollution. Second, it used a longitudinal study design, and most incidences of type 2 diabetes were identified by FPG measurements. In comparison with self-reported diabetes, the FPG test is a relatively time-efficient way to minimise diagnostic misclassification and lessen the likelihood of underestimating the incidence of type 2 diabetes [34]. The longitudinal study design also enabled us to account for the effects related to the change of $PM_{2.5}$ exposure and a wide range of covariates. The associations did not change materially after including these covariates in the models. Third, the large sample size and the relatively long follow-up duration gave the study sufficient power to detect the small effects of ambient $PM_{2.5}$ on the development of type 2 diabetes. The large sample size also allowed us to generate stable results and precise estimates. Finally, we used a novel model based on satellite-derived AOD data with high resolution ($1 \times km^2$) to estimate individual exposure at the participants' addresses. This technology permitted us to overcome the spatial coverage limitation that typically occurs when using data obtained only from monitoring stations. The exposure data at individual level also enabled us to avoid ecological fallacies.

This study also has several limitations. First, we did not have information on indoor and gaseous pollutants. However, we included smoking as a covariate as it is an important source of household air pollution in developed economies. The generally high correlations between gaseous pollutants and $PM_{2.5}$ suggest that we should analyse their effects separately [16]. Second, the $PM_{2.5}$ exposure levels were calculated at the fixed addresses of the participants, and their daily activity patterns were not considered. More advanced technologies are needed for more accurate assessment of exposure in future studies. Third, we did not account for noise exposures due to the information being unavailable. Noise may be regarded as a potential risk of cardiovascular disease [47]. Fourth, it is difficult to distinguish between type 1 and type 2 diabetes in a large-scale epidemiological study with around 0.15 million participants. However, the targeted population were non-diabetic participants aged 18 years or above and therefore the majority of individuals who developed diabetes were likely to develop type 2 diabetes. The sensitivity analysis that excluded participants with a baseline age of <30 years yielded similar results (ESM Table 2), which further supported the association between $PM_{2.5}$ and the development of type 2 diabetes. Fifth, the follow-up frequency and interval of medical examinations varied among the participants. Thus, it is difficult to identify the exact onset date of the disease for those participants with a long interval between medical examinations. However, the sensitivity analysis that only included the participants with annual medical examination yielded similar results. Finally, the participants were relatively healthy and were educated to a high level. Therefore, we should be cautious when generalising the results to other populations.

In conclusion, we found long-term exposure to ambient $PM_{2.5}$ to be significantly associated with a higher risk of developing type 2 diabetes in a population from Asia, in which people in many of the region's countries are generally experiencing high levels of air pollution and the prevalence of diabetes is rising rapidly. We advocate urgent strategies to reduce global air pollution that can aid in preventing the current pandemic of type 2 diabetes.

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Data availability The datasets generated and/or analysed during the current study are available upon request.

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Contribution statement XQL conceived and designed the study and obtained the funding. L-YC, AKHL and XQL supervised this study. L-YC, AKHL and XQL acquired the data. CG, YB and ZZ searched the literature. ZZ, YB, YCC and WKJ cleaned the data. CL and AKHL estimated the $PM_{2.5}$ concentration. CG analysed the data. CG, XQL, TT, C-YL and TCC interpreted the results. CG and XQL drafted the manuscript. XQL, CG, TT, C-YL and TCC revised the manuscript. All authors contributed to the content and critical revision of the manuscript and agreed to submit the manuscript for publication. XQL is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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