

MECHANISMS IN ENDOCRINOLOGY

Effect of long-term exposure to air pollution on type 2 diabetes mellitus risk: a systemic review and meta-analysis of cohort studies

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Abstract

Objective: To assess the effect of long-term exposure to air pollution on type 2 diabetes risk, a meta-analysis of prospective cohort studies was performed.

Methods: Literature search was conducted with Pubmed, Embase, and Web of Science for prospective cohort studies investigating the association of type 2 diabetes risk with increments in particulate matter (PM, diameter $<2.5\ \mu\text{m}$ (PM_{2.5}) or $<10\ \mu\text{m}$ (PM₁₀)) or nitrogen dioxide (NO₂). We used a random-effects model to calculate the overall relative risk (RR) with 95% CI.

Results: Of 808 identified articles, ten cohort studies were finally included, which involved a total of 2 371 907 participants and 21 095 incident cases of type 2 diabetes. Elevated risk of type 2 diabetes was significantly associated with long-term exposures to high levels of PM_{2.5} (RR = 1.28, 95% CI 1.06–1.55, $P=0.009$, $I^2=83.5\%$), PM₁₀ (RR = 1.15, 95% CI 1.02–1.30, $P=0.022$, $I^2=0\%$), and NO₂ (RR = 1.12, 95% CI 1.02–1.23, $P=0.015$, $I^2=63.5\%$). When using standardized risk estimates, the RRs of type 2 diabetes were significant for increments in concentrations of PM_{2.5} (1.39 per 10 $\mu\text{g}/\text{m}^3$ increment, 95% CI 1.14–1.68, $P=0.001$), PM₁₀ (1.34 per 10 $\mu\text{g}/\text{m}^3$ increment, 95% CI 1.22–1.47, $P<0.001$), and NO₂ (1.11 per 10 $\mu\text{g}/\text{m}^3$ increment, 95% CI 1.07–1.16, $P<0.001$). No obvious evidence of publication bias was observed.

Conclusion: Long-term exposure to high levels of main air pollutants is significantly associated with elevated risk of type 2 diabetes mellitus.

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Introduction

Type 2 diabetes mellitus is now a common disease in the world, and its prevalence is still increasing obviously in recent years (1, 2). The International Diabetes Federation reported that diabetes mellitus affected at least 366 million people worldwide in 2011, and that number was expected to reach 566 million by the year 2030 (3). Though the increasing incidence of type 2 diabetes may be a result of increasing obesity, other potential risk factors have been

proposed, such as air pollution (1, 2, 4). In recent years, several major epidemiological studies have showed that air pollution is obviously associated with increased risks of cardiovascular disease, lung cancer, and natural-cause mortality (5, 6, 7, 8, 9). However, the effect of air pollution on type 2 diabetes risk has not been clearly described. Several studies have assessed the association between long-term exposure to air pollution and risk of type 2

diabetes, but the association remains unclear owing to the conflicting results (10, 11, 12, 13, 14). To assess the effect of long-term exposure to air pollution on type 2 diabetes risk, a meta-analysis of prospective cohort studies was performed according to the standard guideline for conducting and reporting meta-analyses of observational studies. In this meta-analysis, we focused on the associations of type 2 diabetes with increments in the concentrations of particulate matter (PM, diameter $<2.5\ \mu\text{m}$ (PM_{2.5}) or $<10\ \mu\text{m}$ (PM₁₀)) or nitrogen dioxide (NO₂). This study is registered at International Prospective Register of Systematic Reviews (PROSPERO), number CRD42014009081.

Methods

Search strategy

The literature search was conducted with Pubmed, Embase, and Web of Science for prospective cohort studies assessing the associations of type 2 diabetes risk with increments in PM_{2.5}, PM₁₀, or NO₂. We also searched abstracts from the 2012 and 2013 meetings of the American Diabetes Association and the European Association for the Study of Diabetes for unpublished studies. The search time was from their commencements to February 16, 2014, and there was no language restriction. The last literature search was updated on June 16 2014. The following keywords were used: 'type 2 diabetes', 'diabetes mellitus', 'insulin resistance', 'air pollution', 'particulate matter', 'PM_{2.5}', 'PM₁₀', and 'NO₂'. Hand searching of selected journals and checking of bibliographies in relevant published reviews or articles were also performed to supplement the electronic searches.

Study selection

The inclusion criteria were as follows: i) prospective cohort studies; ii) estimated the effect of long-term exposure to air pollution, including PM_{2.5}, PM₁₀, and NO₂, on risk of type 2 diabetes; iii) the outcome was the development of type 2 diabetes at least 3 years after follow-up; iv) type 2 diabetes was defined with an oral glucose tolerance test or fasting plasma glucose concentration, or both, according to the National Diabetes Data Group, WHO criteria, countrywide guidelines, or specified local criteria; v) reported relative risks (RR) with 95% CIs for type 2 diabetes according to the concentrations of air pollutants. The exclusion criteria were retrospective cohort, case-control, cross-sectional, and time-series studies.

In addition, studies without usable data or low quality were also excluded. For multiple reports from the same cohort study, only the article with the longest follow-up for identical outcomes was included.

Data extraction and quality assessment

Data were extracted independently by two investigators and conflicts were adjudicated by a third investigator. Data extraction using a standardized form included a full description of the study characteristics: first author, publication year, country, study design, baseline characteristics, exposure type, data type, definition of diabetes, time of follow-up, number of participants, events of type 2 diabetes, adjustments used within analyses, and adjusted RRs with 95% CIs for diabetes risk. The maximally adjusted risk estimates were used in the meta-analysis. All pollutant concentrations were converted, if necessary, to $\mu\text{g}/\text{m}^3$. We contacted authors for additional data or clarification where needed.

The quality of included studies was assessed using the Newcastle Ottawa Scale as recommended by the Cochrane Non-Randomized Studies Methods Working Group (15). This scale awards a maximum of nine stars to each study: four stars for the adequate selection of cohort participants, two stars for comparability of cohort participants on the basis of the design and analysis, and three stars for the adequate ascertainment of outcomes. Quality was assigned as A or excellent with 7–9 stars, B or good with 4–6 stars, and C or suboptimal with 0–3 stars. Only studies with excellent or good quality were finally included into the analysis.

Statistical analysis

The overall RRs with 95% CIs were used to assess the effect of air pollution on type 2 diabetes risk. As Chen *et al.*'s study identified the linearity for the relationship between PM_{2.5} and diabetes, we assumed a linear relation between exposures and outcome, and RRs were further expressed for a standardized increment in pollutant concentration of per $10\ \mu\text{g}/\text{m}^3$ for PM_{2.5}, PM₁₀, and NO₂ (13). Standardized risk estimates were calculated for each study using the following formula: $\text{RR}_{(\text{standardized})} = \text{RR}_{(\text{original})}^{\text{increment}(10)/\text{increment}(\text{original})}$ (8). The overall RRs with 95% CIs were calculated using a random-effects model for all analyses (16). The significance of the pooled RR was determined by the Z test, and a *P* value of <0.05 was considered significant. Statistical heterogeneity across the studies was calculated by the I^2 statistic to quantify

inconsistencies between studies (17). I^2 values of 25% or less, 50%, and 75% or more represent low, moderate, and high heterogeneity respectively. Subgroup analysis was further performed by gender (males and females) and data type (per 10 $\mu\text{g}/\text{m}^3$ or interquartile range (IQR) increment). To assess the potential for publication bias, we visually inspected funnel plots. We also added the Egger regression test to test the symmetry of funnel plot (18). In addition, trim and fill method was also used to simulate those studies that may be missing from the literature, and estimated the pooled RR after adding those 'missing' studies (19). Statistical analyses were performed using Stata 12.0 (StataCorp, College Station, TX, USA). Statistical significance was taken as two-sided $P < 0.05$.

Results

Literature search and study characteristics

The abstracts of 808 articles were assessed, and 42 studies underwent in-depth review, with 33 studies not fulfilling the inclusion criteria. One article reported two individual cohort studies, and was extracted as two individual studies (14). Thus, ten prospective cohort studies from nine articles were finally included into the meta-analysis (10, 11, 12, 13, 14, 20, 21, 22, 23). Table 1 shows the main characteristics of those ten cohort studies included in the meta-analysis (Table 1). Those ten cohort studies involved a total of 2 371 907 participants and 21 095 incident cases of type 2 diabetes (10, 11, 12, 13, 14, 20, 21, 22, 23). Among those ten cohort studies, nine studies reported incident new cases of type 2 diabetes (10, 11, 13, 14, 20, 21, 22, 23), while the left one reported events of deaths coded as diabetes (12). There were three studies from USA (10, 14), three studies from Canada (12, 13, 20), two studies from Germany (21, 22), one from Denmark (11), and one from Switzerland (24) (Table 1). The time of follow-up of those ten cohort studies ranged from 6 to 16 years (Table 1). All studies reported adjusted estimates, but the adjusted factors were various and different from each other (Table 1). There were five cohort studies on PM_{2.5} (10, 12, 13, 14), six cohort studies on NO₂ (10, 11, 20, 21, 22, 23), and four cohort studies on PM₁₀ (14, 21, 23) respectively (Table 1). According to the quality criteria, there were seven cohort studies with A level quality (10, 11, 13, 14, 21, 23), and the other three studies with B level quality (12, 20, 22) (Table 1). Among those nine cohort studies, five studies provided data on incident cases of confirmed type 2 diabetes (10, 14, 21, 22), while the other five studies made no distinction between type 2 diabetes

and type 1 diabetes (11, 12, 13, 20, 23). Because the vast majority of those patients with diabetes were type 2 diabetes, the associations from those four studies likely described an effect of air pollution on risk of type 2 diabetes, and they were included into the meta-analysis. In the sensitivity analysis, those five studies were further excluded to get a more precise assessment on the effects of air pollutants on type 2 diabetes risk. Among those ten cohort studies, the average concentrations of PM_{2.5}, PM₁₀, and NO₂ were 15.2, 34.1, and 24.6 $\mu\text{g}/\text{m}^3$ respectively (Fig. 1).

PM_{2.5} and type 2 diabetes mellitus

Meta-analysis of those five studies (10, 12, 13, 14) on PM_{2.5} showed that long-term exposure to high levels of PM_{2.5} was significantly associated with elevated risk of type 2 diabetes (per 10 $\mu\text{g}/\text{m}^3$ or IQR increment RR=1.28, 95% CI 1.06–1.55, $P=0.009$, $I^2=83.5\%$; standardized RR=1.39, 95% CI 1.14–1.68, $P=0.001$, $I^2=86.3\%$; Fig. 2). After excluding Brook *et al.*'s study, long-term exposure to high levels of PM_{2.5} was significantly associated with elevated risk of type 2 diabetes (per 10 $\mu\text{g}/\text{m}^3$ or IQR increment RR=1.13, 95% CI 1.05–1.23, $P=0.001$, $I^2=0\%$; standardized RR=1.35, 95% CI 1.05–1.75, $P=0.020$, $I^2=81.1\%$). In addition, the pooled risk estimates were not significantly altered in the sensitivity analysis performed by omitting single study in turns. After excluding those two studies (12, 13) making no distinction between type 2 diabetes and type 1 diabetes, long-term exposure to high levels of PM_{2.5} was still significantly associated with elevated risk of type 2 diabetes (per 10 $\mu\text{g}/\text{m}^3$ or IQR increment RR=1.24, 95% CI 1.05–1.48, $P=0.014$, $I^2=0\%$).

Subgroup analysis by gender showed that long-term exposure to high levels of PM_{2.5} was associated with elevated risk of type 2 diabetes in females (per 10 $\mu\text{g}/\text{m}^3$ or IQR increment RR=1.28, 95% CI 1.10–1.50, $P=0.001$, $I^2=67.1\%$), but not in males (per 10 $\mu\text{g}/\text{m}^3$ or IQR increment RR=1.30, 95% CI 0.95–1.77, $P=0.103$, $I^2=90.4\%$). Meta-analysis of studies reporting data of per IQR increment showed an obvious association between long-term exposure to high levels of PM_{2.5} and risk of type 2 diabetes (per IQR increment RR=1.25, 95% CI 1.04–1.49, $P=0.014$, $I^2=0\%$), but meta-analysis of studies reporting data on per 10 $\mu\text{g}/\text{m}^3$ increment failed to identify an obvious association (per 10 $\mu\text{g}/\text{m}^3$ increment RR=1.27, 95% CI 0.97–1.66, $P=0.077$, $I^2=91.4\%$).

There was no obvious risk of publication bias in the funnel plot for the association between PM_{2.5} and type 2

Table 1 Characteristics of ten cohort studies included in the meta-analysis.

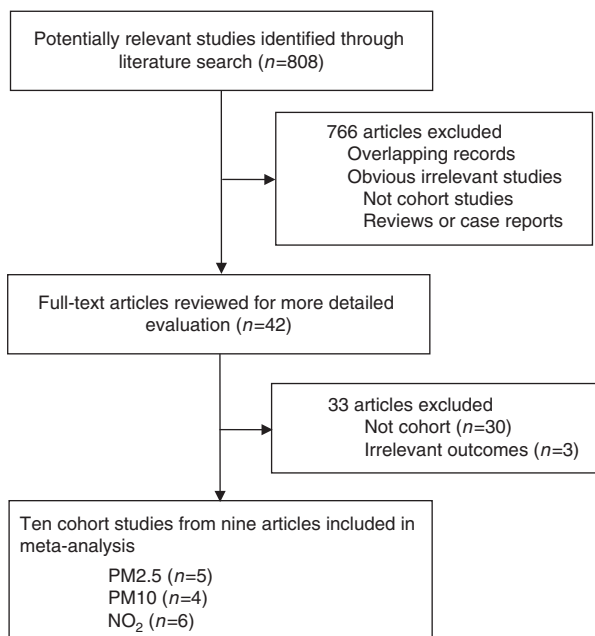
Study	Country	Study design	Pollutants (average exposure)	Participants (main age, year; male, %)	Events of diabetes	Definition of diabetes	Follow-up	Data type	Adjustment	Quality ^a
(23)	Switzerland	Prospective cohort	PM10 (22.5 µg/m ³), NO ₂ (26.7 µg/m ³)	6392 (52 years; 50%)	315 incident cases of diabetes	At least one of the following conditions: i) intake of any anti-diabetic medication; ii) self-reported, physician-diagnosed diabetes mellitus; iii) non-fasting blood glucose of N11.1 mmol/l; or iv) HbA1c of > 6.5%	10 years	Per 10 µg/m ³	Age, gender, educational level and neighborhood socio-economic index, lifestyle characteristics, BMI, noise, hypertension, hs-CRP, and dyslipidemia	8
(12)	Canada	Prospective cohort	PM2.5 (8.7 µg/m ³)	2 145 400 (44.3 years; 49%)	5200 deaths code as diabetes	Mortality from diabetes	Nearly 10 years	Per 10 µg/m ³	Adults with less than high school diploma, adults with low income cutoff quintile, and adults unemployed determined at both the census divisions and census tracts levels	6
(13)	Canada	Prospective cohort	PM2.5 (10.6 µg/m ³)	62 012 (54.9 years; 45%)	6310 incident cases of diabetes	At least one hospital admission with a diagnosis of diabetes or two or more physician claims for diabetes	8 years	Per 10 µg/m ³	Age, sex, BMI, education, race/ethnicity, household income adequacy, physical activity, smoking, and annual mean concentration of PM2.5	9
(10)	USA	Prospective cohort	PM2.5 (20.7 µg/m ³), NO _x (43.3 ppb)	3992 (54.5 years; 0.0%)	183 incident cases of type 2 diabetes	Self-report of doctor-diagnosed diabetes mellitus	10 years	Per 10 µg/m ³ for PM2.5; per IQR for NO ₂ (12.4 ppb)	Age, BMI, income, number of people in the household, history of diabetes mellitus, smoking, hours per week of vigorous physical activity, and neighborhood socioeconomic status score in quintiles	8
(12)	Denmark	Prospective cohort	NO ₂ (14.5 µg/m ³)	51 818 (56.1 years; 47.7%)	2877 incident cases of diabetes	Hospital admission for diabetes, diabetes medication, reimbursement for chiropody due to diabetes, or glucose blood tests	9.7 years	Per IQR (4.9 µg/m ³)	Sex, BMI, waist-to-hip ratio, smoking status, smoking duration, smoking intensity, environmental tobacco smoke, educational level, physical/sports activity in leisure time, alcohol consumption, fruit consumption, and fat consumption, and calendar year	8

Table 1 Continued

Study	Country	Study design	Pollutants (average exposure)	Participants (main age, year; male, %)	Events of diabetes	Definition of diabetes	Follow-up	Data type	Adjustment	Quality ^a
(22)	Germany	Prospective cohort	NO ₂ (NA)	3424 (NA; NA)	309 incident cases of type 2 diabetes	NA	6 years	Per IQR (5 µg/m ³)	Sex, age, BMI, education, occupational status, smoking status, physical activity, cholesterol, hypertension, and city of residence	6
(14) NHS	USA	Prospective cohort	PM2.5 (17.5 µg/m ³), PM10 (26.9 µg/m ³)	74 412 (55.1 years; 0%)	3784 incident cases of type 2 diabetes	Elevated plasma glucose concentrations on at least two different occasions, one or more diabetes symptoms and a single elevated plasma glucose concentration, or treatment with hypoglycemic medication	13 years	Per IQR (4 µg/m ³)	Age, season, calendar year, state of residence, time-varying cigarette smoking, time-varying hypertension, baseline BMI, time-varying alcohol intake, baseline physical activity, and time-varying diet	9
(14) HPFS	USA	Prospective cohort	PM2.5 (18.3 µg/m ³), PM10 (28.5 µg/m ³)	15 048 (57.3 years; 100%)	688 incident cases of type 2 diabetes	Elevated plasma glucose concentrations on at least two different occasions, one or more diabetes symptoms and a single elevated plasma glucose concentration, or treatment with hypoglycemic medication	13 years	Per IQR (7 µg/m ³)	Age, season, calendar year, state of residence, time-varying cigarette smoking, time-varying hypertension, baseline BMI, time-varying alcohol intake, baseline physical activity, and time-varying diet	9
(21)	Germany	Prospective cohort	PM10 (46.9 µg/m ³), NO ₂ (41.7 µg/m ³)	1775 (54.5 years; 0%)	187 incident cases of type 2 diabetes	Physician-diagnosed diabetes	16 years	Per IQR (10 µg/m ³) for PM2.5; per IQR for NO ₂ (24.9 µg/m ³)	Age, BMI, heating with fossil fuels, workplace exposure with dust/fumes, extreme temperatures, smoking, education	8
(20)	Canada	Prospective cohort	NO ₂ (17.6 µg/m ³)	7634 (60.5 years; 45.2%)	1242 incident cases of diabetes	The diagnosis of diabetes had been made in two or more claim submissions by a general practitioner, one claim submission by a specialist, or in any hospitalization	10 years	Per 1 ppb	Age, BMI, and neighborhood income	6

NA, Not available; IQR, Interquartile range; USA, United States of America; ppb, parts per billion.

^aQuality was assigned as A or excellent with 7–9 stars, B or good with 4–6 stars, and C or suboptimal with 0–3 stars.

**Figure 1**

Flow chart of study selection in the meta-analysis.

diabetes, and the P value for Egger's test was 0.98. When using the Trim and Fill method, one possible 'missing' study was added and long-term exposure to high levels of PM2.5 was still significantly associated with elevated risk of type 2 diabetes (per $10 \mu\text{g}/\text{m}^3$ or IQR increment $\text{RR}=1.26$, 95% CI 1.05–1.50, $P=0.011$).

NO₂ and type 2 diabetes mellitus

Meta-analysis of those six studies (10, 11, 20, 21, 22, 23) on NO₂ showed that long-term exposure to high levels of NO₂ was significantly associated with elevated risk of type 2 diabetes (per IQR increment $\text{RR}=1.12$, 95% CI 1.02–1.23, $P=0.015$, $I^2=63.5\%$; standardized $\text{RR}=1.11$, 95% CI 1.07–1.16, $P<0.001$, $I^2=43.6\%$; Fig. 3). In addition, the pooled risk estimates were not significantly altered in the sensitivity analysis performed by omitting single study in turns. After excluding those three studies (11, 20, 23) making no distinction between type 2 diabetes and type 1 diabetes, long-term exposure to high levels of NO₂ was still significantly associated with elevated risk of type 2 diabetes (per IQR increment $\text{RR}=1.17$, 95% CI 1.06–1.29, $P=0.001$, $I^2=19.5\%$).

Subgroup analysis by gender showed that long-term exposure to high levels of NO₂ was associated with elevated risk of type 2 diabetes in females (per IQR

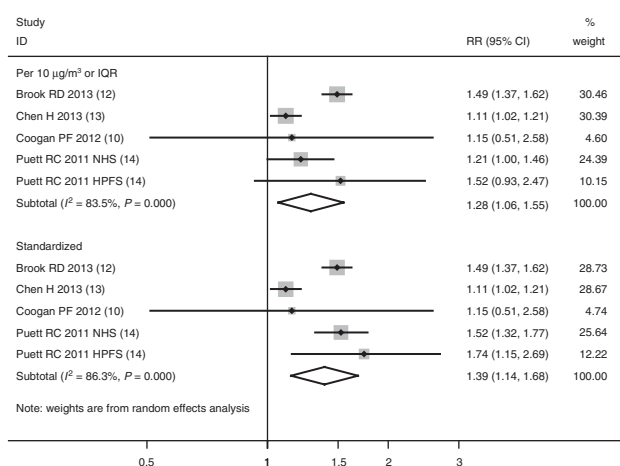
increment $\text{RR}=1.09$, 95% CI 1.02–1.15, $P=0.006$, $I^2=48.2\%$), but not in males (per IQR increment $\text{RR}=1.03$, 95% CI 0.96–1.10, $P=0.414$, $I^2=72.0\%$).

There was no obvious risk of publication bias in the funnel plot for the association between NO₂ and type 2 diabetes, and the P value for Egger's test was 0.11. When using the Trim and Fill method, three possible 'missing' studies were added, and long-term exposure to high levels of NO₂ was still significantly associated with elevated risk of type 2 diabetes (standardized $\text{RR}=1.09$, 95% CI 1.04–1.14, $P<0.001$).

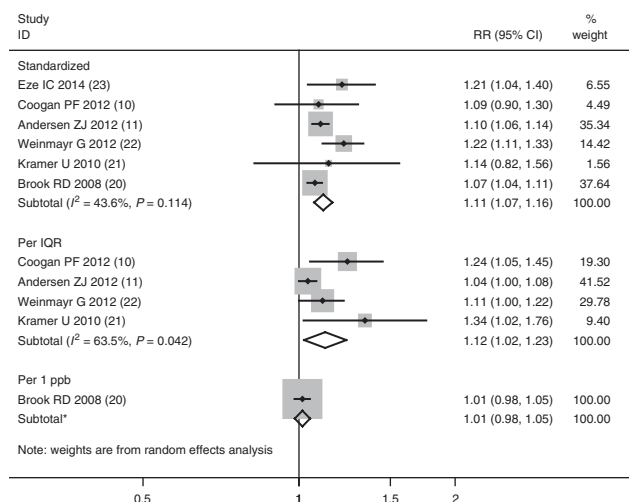
PM10 and type 2 diabetes mellitus

Meta-analysis of those four studies (14, 21, 23) on PM10 showed that long-term exposure to high levels of PM10 was significantly associated with elevated risk of type 2 diabetes (per IQR increase $\text{RR}=1.15$, 95% CI 1.02–1.30, $P=0.022$, $I^2=0\%$; standardized $\text{RR}=1.34$, 95% CI 1.22–1.47, $P<0.001$, $I^2=0\%$; Fig. 4). In sensitivity analysis by excluding the studies one by one, with the exception of NHS study by Puett *et al.* (14), the pooled RR for per IQR increment was not significant (per IQR increment $\text{RR}=1.22$, 95% CI 0.95–1.55, $P=0.112$, $I^2=0\%$), but the standardized RR was still significant (standardized $\text{RR}=1.36$, 95% CI 1.18–1.57, $P<0.001$, $I^2=0\%$).

Subgroup analysis by gender showed that the association between long-term exposure to high levels of PM10 and type 2 diabetes was marginally significant in females (per IQR increment $\text{RR}=1.09$, 95% CI 1.02–1.15,

**Figure 2**

Association between long-term exposure to high level of PM2.5 and type 2 diabetes risk.

**Figure 3**

Association between long-term exposure to high level of NO_2 and type 2 diabetes risk. * I^2 and P values are not available as there was only one study and heterogeneity could not be analysed.

$P=0.006$), but not in males (per IQR increment $\text{RR}=1.03$, 95% CI 0.96–1.10, $P=0.414$).

There was no obvious risk of publication bias in the funnel plot for the association between PM_{10} and type 2 diabetes, and the P value for Egger's test was 0.76. When using the Trim and Fill method, no possible 'missing' study was added.

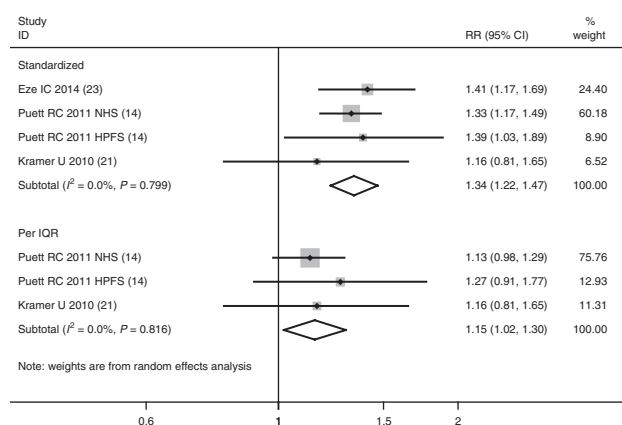
Discussion

Previous studies published to assess the association between long-term exposure to air pollution and type 2 diabetes risk reported conflicting results (10, 11, 12, 13, 14, 20, 21, 22, 23). The conflicting results may result from the low statistical power derived in a single study. Meta-analysis is a statistical method that focuses on contrasting and combining results from different studies and provides a more powerful estimate of the true effect size. Thus, to provide a more powerful estimate of the effect of long-term exposure to air pollution on type 2 diabetes risk, a meta-analysis of prospective cohort studies was performed in the study. To the best of our knowledge, the meta-analysis is the first to assess the quality and magnitude of the association between long-term exposure to air pollution and type 2 diabetes risk. The findings from the meta-analysis suggested that incident type 2 diabetes was significantly associated with long-term exposures to high levels of $\text{PM}_{2.5}$, PM_{10} , and NO_2 (Figs 2, 3 and 4). Pooled

results of standardized risk estimates also found the obvious associations of type 2 diabetes risk with long-term exposures to $\text{PM}_{2.5}$, PM_{10} , and NO_2 . In addition, sensitivity analyses further identified the obvious associations mentioned earlier. Thus, the meta-analysis suggests that long-term exposure to high levels of main air pollutants is significantly associated with increased risk of type 2 diabetes.

Subgroup analyses by gender showed that incident type 2 diabetes was significantly associated with long-term exposures to high levels of $\text{PM}_{2.5}$ or NO_2 in females, but not in males. The findings indicated that the effect of long-term exposure to air pollution on type 2 diabetes risk may be more profound in females than in males. The gender-specific difference in the effects of long-term exposure to air pollution on type 2 diabetes risk may relate to the differences in the biologic susceptibility to type 2 diabetes between males and females. In addition, it is also possible that the gender-specific difference may be related to the exposure assessment error, as male participants tend to be more mobile compared with female participants (4). However, considering the limited number of cohort studies on males, the findings from males are still not robust, and the effects of long-term exposure to air pollution on type 2 diabetes risk in males need further studies.

Though the risk of publication bias was not observed in the meta-analysis, the statistical power from Egger's test was limited, because there were only five studies evaluating $\text{PM}_{2.5}$, six studies evaluating NO_2 , and four studies evaluating PM_{10} respectively (Table 1). However, the findings after adding possible 'missing' studies through the Trim and Fill method suggested that incident type 2

**Figure 4**

Association between long-term exposure to high level of PM_{10} and type 2 diabetes risk.

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diabetes was still significantly associated with long-term exposures to high levels of PM_{2.5}, PM₁₀, and NO₂, which indicated that publication bias had little influence on the pooled estimates in the meta-analysis and that proved the creditability of the pooled results in the meta-analysis.

The adverse effect of long-term exposure to air pollution on type 2 diabetes risk is of much importance given the extraordinary confluence of high levels of air pollutants in urbanized environments, especially in rapidly urbanizing countries (23, 25, 26). Air pollution in China is a significant public health burden, especially in spring and winter (26, 27). The pooled results of standardized risk estimates in the present meta-analysis suggest an obvious association of type 2 diabetes risk with long-term exposure to PM_{2.5} (Fig. 2). Compared with the average concentration of PM_{2.5} in the five cohort studies, the mean annual average of PM_{2.5} in China is much higher, and it is no doubt that people from China will suffer much higher risk of type 2 diabetes. Indeed, the overall prevalence of diabetes in China has experienced a rapid increase during the past decade (from 5.5 to 11.6%) (24, 28, 29), and it is much higher than that of worldwide (6.4%) (3), which indirectly proves the rationality of the hypothesis mentioned earlier. Given the increasing burden of air pollution and its continuous and omnipresent nature, even a small adverse effect on health can represent an enormous public health issue and it should deserve rapid and positive response in public health policy. The findings from the meta-analysis provide a strong evidence for the obviously adverse effect of air pollution on type 2 diabetes mellitus; improving air quality is necessary in developing countries, which can lead to significant public health benefits. Currently, there are no trials designed to assess whether effective interventions that improve air quality are associated with a decreased incidence of type 2 diabetes. Further trials are needed to determine the effects of interventions aiming to improve air quality on risk of type 2 diabetes.

The adverse effects of air pollution on cardiovascular disease, lung cancer, and natural-cause mortality have been well established in several major epidemiological studies (5, 6, 7, 8, 9). The findings from the meta-analysis further add the evidence for the adverse effect of air pollution on risk of type 2 diabetes mellitus. In fact, the influence of air pollution on risk of type 2 diabetes may further result in an increased risk of cardiovascular disease, because diabetes and insulin resistance have fundamental roles in the pathophysiology of cardiovascular disease (4). In addition, there are also many studies showing the obvious associations of air pollutants with diabetes-related

mortality, which further indicate the adverse effects of air pollution on diabetes (30, 31, 32, 33). The obvious association of long-term exposures to air pollution with diabetes-related mortality has also been identified in two prospective cohort studies (12, 34).

Several possible mechanisms for the adverse effect of air pollution on type 2 diabetes mellitus reported herein have been suggested in recent studies. Insulin resistance is a main potential mechanism explaining the associations mentioned earlier. Both experimental and epidemiologic studies suggest that environmental exposures to air pollutants can increase the risk of insulin resistance, which may lead to an obvious link between air pollution and type 2 diabetes mellitus (35, 36, 37). Inflammation is another potential mechanism explaining the associations reported in this meta-analysis. There is high possibility for the activation of the inflammatory pathway and oxidative stress pathway by particulate matter (38, 39, 40). Previous studies also suggest that PM_{2.5} can recruit inflammatory cells via CC chemokine receptor 2-dependent mechanism, which is a known inflammatory mechanism in the pathogenesis underlying the association between air pollution and type 2 diabetes (35, 41). In addition, previous experimental studies also show that tumor necrosis factor- α , interleukin-6, and leptin levels are also elevated on exposure to PM_{2.5}, which suggests that exposure to ambient PM_{2.5} can be associated with elevated proinflammatory biomarkers and inflammatory responses (37, 39, 40). It is clear that further data from both experimental and epidemiologic studies are needed to provide more insights into the adverse effect of air pollution on type 2 diabetes risk.

Several limitations of the meta-analysis should be considered. First, there was lack of individual participant data. Some studies used the mean concentration of air pollutants, while other studies used peak concentration of air pollutant. The variables used in the adjusted risk estimates were also different among those included cohort studies, which could result in the high heterogeneity among those studies. A meta-analysis of individual participant data is needed, which may decrease the influence of heterogeneity among those studies, and could provide a more precise assessment on the effects of air pollution on type 2 diabetes risk. Second, all cohort studies included in the meta-analysis were done in developed countries, and there was lack of data from developing countries. However, the data from developing countries may be more concerning because those regions are affected most by air pollution and may have the greatest potential to improve health by improving air

quality. Larger cohort studies, especially from developing countries, are needed to provide a more precise assessment of the adverse effects of long-term exposure to air pollution on type 2 diabetes risk. Finally, meta-analysis of observational studies has limitations with inherent biases. The limitations of observational studies included the problem of residual confounding factors, which could also extend to the meta-analyses of observational studies and may cause some possible bias.

In conclusion, the study provides a strong evidence for the adverse effect of air pollution on type 2 diabetes risk, and long-term exposure to high levels of main air pollutants is significantly associated with elevated risk of type 2 diabetes mellitus. In addition, more prospective cohort studies with large numbers of participants, especially those from developing countries, are needed to provide a more precise assessment of the adverse effects of long-term exposure to air pollution on type 2 diabetes risk.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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Author contribution statement

The authors have made the following declarations about their contributions: B Wang and Y Wang were the project leads for the main systematic review. D Xu, D Liu, S Yan, and Z Jing searched databases, assessed the study eligibility, and performed data extraction. Quality of data extraction and checking was carried out by B Wang, D Xu, and Z Jing. Statistical analysis was undertaken by B Wang and D Xu. B Wang and Y Wang wrote the manuscript. All authors reviewed the manuscript and contributed to the preparation of the manuscript.

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