MECHANISMS IN ENDOCRINOLOGY

Main air pollutants and diabetes-associated mortality: a systematic review and meta-analysis

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Abstract

Objective: Exposure to high levels of air pollutants may be linked to diabetes-associated mortality, but the associations remain unclear. To assess the associations between main air pollutants and diabetes-associated mortality, a systematic review and meta-analysis was performed.

Methods: PubMed, Embase and Web of Science were searched for studies investigating the associations between increments in gaseous (nitrogen dioxide (NO₂), sulphur dioxide, ozone (O₃) and carbon monoxide) and particulate matter (PM; diameter <2.5 µm (PM_{2.5}) or <10 µm (PM₁₀)) air pollutants and diabetes-associated mortality. Using a random-effects model, relative risks (RRs) and 95% CIs were calculated per interquartile range (IQR) increment or per 10 µg/m³ increment in pollutant concentrations.

Results: Out of 925 identified articles, 36 were reviewed in depth and 12 studies from 13 articles satisfying the inclusion criteria (five time-series, five case-crossovers and two cohorts) were finally included. Increased risk of diabetes-associated mortality was associated with higher levels of PM_{2.5} (per 10 µg/m³: RR = 1.123, 95% CI 1.036–1.217, *P* = 0.005, *I*² = 96.1%), PM₁₀ (per 10 µg/m³: RR = 1.008, 95% CI 1.004–1.013, *P* < 0.001, *I*² = 0%), NO₂ (per 10 µg/m³: RR = 1.024, 95% CI 1.007–1.041, *P* = 0.006, *I*² = 49.7%) and O₃ (per IQR increment: RR = 1.065, 95% CI 1.017–1.115, *P* = 0.007, *I*² = 0.0%). No obvious risk of publication bias was observed.

Conclusions: Exposure to high levels of air pollutants is significantly associated with an increased risk of diabetes-associated mortality.

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Introduction

Diabetes mellitus is a serious public health issue worldwide and has caused serious damages to public health (1, 2). There were over 366 million people diagnosed with diabetes mellitus worldwide in 2011 (3, 4). Though obesity is a major risk factor leading to increasing incidence of type 2 diabetes, other potential risk factors have been proposed, such as air pollution (5, 6). Air pollution is a more and more serious problem worldwide, and one in

eight deaths worldwide can be attributed at least in part to air pollution (7). There were approximately seven million people dying from exposure to air pollution in 2012 (7). Previous studies have shown that air pollution can cause several adverse effects, including cardiovascular diseases, lung cancer and early mortality (8, 9, 10, 11). However, the relationship between air pollution and diabetes-associated mortality has not been well established (5). Several studies

of exposures to air pollution have included diabetes-associated mortality, although it has not been the primary focus in most analyses (12, 13, 14, 15, 16, 17, 18, 19, 20). We therefore systematically reviewed the evidence examining the association between air pollution and diabetes-associated mortality. In the present meta-analysis, we focused on the associations between increments in gaseous (nitrogen dioxide (NO₂), sulphur dioxide (SO₂), ozone (O₃) and carbon monoxide (CO)) and particulate matter (PM, diameter <2.5 µm (PM_{2.5}) or <10 µm (PM₁₀)) air pollutants and diabetes-associated mortality. This study is registered in the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42014009162.

Methods

Search strategy and study selection

Pubmed, Embase and Web of Science were searched for observational studies assessing the associations of diabetes-associated mortality with increments in gaseous (NO₂, SO₂, O₃ and CO) and particulate (PM_{2.5} and PM₁₀) air pollutants. We also searched abstracts from the 2012 and 2013 meetings of the American Diabetes Association and the European Association for the Study of Diabetes. The search time was from their commencements to February 26, 2014, and there was no language restriction. The following keywords were used: 'diabetes', 'diabetic', 'air pollution', 'particulate matter', 'PM_{2.5}', 'PM₁₀', 'sulphur dioxide', 'ozone', 'carbon monoxide' and 'nitrogen dioxide'. Hand searching of selected journals and checking of bibliographies in relevant published reviews or articles were also performed to supplement the electronic searches. After removal of duplicate references, initial screening of titles and abstracts was performed by two members of the review team. Potentially relevant articles were obtained in full text and assessed independently by two members of the review team. Any disagreements were settled by discussion among all members of the review team.

The inclusion criteria were as following: i) case-crossover, time-series, nested case-control, or cohort studies; ii) estimation of the effect of exposures to air pollution, including gaseous (NO₂, SO₂, O₃ and CO) and particulate (PM_{2.5} and PM₁₀) air pollutants, on diabetes-associated mortality; iii) the outcome was diabetes-associated mortality; iv) reported relative risks (RRs) or hazard ratios with 95% CIs for diabetes-associated mortality, or other sufficient data to estimate these data.

Case-control and cross-sectional studies were all excluded. In addition, studies without usable data or of low quality were also excluded. For multiple reports from the same study, only the article with the largest dataset 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. There was an agreement value (κ) of 94% in the studies selected by these two investigators for detailed analysis. Data extraction using a standardised form included a full description of the study characteristics: first author, publication year, country, ethnic origin, study design, baseline characteristics, exposure type, data type, events of diabetes-associated mortality, adjustments in analyses and adjusted RRs with 95% CIs. This study collected data for maximally adjusted risk estimates, if available. We contacted authors for additional data or clarification where needed.

As there were no validated scales to evaluate the methodological quality of time-series studies and case-crossover studies, we used a quality scale that was based on validated scales for other types of epidemiological studies and used in the study by Mustafic *et al.* (9). We evaluated three components (the validation of diabetes-associated mortality (0–1 point), the quality of air pollutant measurements (0–1 point) and the extent of adjustment for confounders (0–3 points)) (9). Quality was graded as excellent with five points, good with 3–4 points and suboptimal with 0–2 points. Only studies with excellent or good quality were finally included into the analysis.

Statistical methods

We used RR as a measure of effect size because it was an intuitive and commonly used measure in the medical and public health literature. Many studies used generalised linear models and, therefore, we assumed a linear relation between exposure and outcome, and RRs were further expressed for a standardised increment in the pollutant concentration by 10 µg/m³ each for PM_{2.5}, PM₁₀ and NO₂. Standardised risk estimates were calculated for each study using the following formula: $RR_{(standardised)} = RR_{(original)}^{increment(10)/increment(original)}$ (8). The pooled RRs with 95% CIs were calculated using a random-effects model for all analyses (21). 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 (22). I^2 values of 25% or less, 50% and 75% or more represent low, moderate and high heterogeneity respectively (22). The associations of increments in the three main air pollutants, PM_{2.5}, PM₁₀ and NO₂, with diabetes-associated mortality were first assessed by per interquartile range (IQR) increment and then by standardised increment (per 10 µg/m³ increment). We also did subgroup analyses stratifying studies by study design (time-series, nested case-control, case-crossover or cohort). To assess the potential for publication bias, we visually inspected funnel plots. However, because of the limitations of funnel plot, we also used the Egger regression test to test the symmetry of funnel plot (23). In addition, the trim and fill method was also used to simulate those studies that may be missing from the literature, and we estimated the pooled RR after adding those 'missing' studies (24). 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 925 articles were assessed, and 36 studies were selected for in-depth review, with 23 studies not fulfilling the inclusion criteria (Fig. 1). Two articles evaluated three different pollutants from the same study (12, 25). Thus, 12 studies from 13 articles were finally included into the meta-analysis (12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 26, 27, 28). The main characteristics of those 12 studies included in the meta-analysis are shown in Table 1. Those 12 studies involved a total of 582 197 events of diabetes-associated mortality (12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 26, 27). Of those 12 studies, there were five time-series studies (12, 14, 19, 25, 26, 27), five case-crossover studies (13, 15, 16, 17, 28) and two cohort studies (18, 20). Four of these studies were from Canada (12, 14, 18, 19, 25), four from USA (13, 16, 27, 28), two from Italy (15, 17), one from Denmark (20) and one from China (26) (Table 1). All studies reported adjusted estimates, but the adjusted factors were of various types and different from each other (Table 1). There were five studies evaluating PM_{2.5} (18, 19, 25, 27, 28), four studies evaluating PM₁₀ (13, 15, 25, 26), five studies evaluating NO₂ (14, 17, 19, 20, 26), three studies evaluating SO₂ (14, 19, 26), two studies evaluating O₃ (12, 16) and two studies evaluating CO (14, 19) respectively (Table 1). According to the quality of

Figure 1

Flow chart of study selection in the meta-analysis.

criteria, there were two studies with an excellent quality (18, 20) and the other ten studies were of good quality (12, 13, 14, 15, 16, 17, 19, 25, 26, 27, 28) (Table 1).

PM_{2.5} and diabetes-associated mortality

Meta-analysis of those four studies (18, 19, 25, 27, 28) evaluating PM_{2.5} showed that a high level of PM_{2.5} was significantly associated with an increased risk of diabetes-associated mortality (per IQR or 10 µg/m³: RR=1.079, 95% CI 1.032–1.128, $P=0.001$, $I^2=95.4\%$; per 10 µg/m³: RR=1.081, 95% CI 1.034–1.131, $P=0.001$, $I^2=95.4\%$) (Fig. 2). After excluding the study by Brook *et al.* (18), a high level of PM_{2.5} was still found to be significantly associated with an increased risk of diabetes-associated mortality (per IQR or 10 µg/m³: RR=1.021, 95% CI 1.004–1.038, $P=0.016$, $I^2=70.0\%$; per 10 µg/m³: RR=1.023, 95% CI 1.005–1.042, $P=0.011$, $I^2=74.2\%$). Subgroup analyses by study design showed similar obvious associations (time-series studies 3: RR=1.029, 95% CI 1.007–1.052, $P=0.009$; cohort study 1: RR=1.49, 95% CI 1.37–1.62, $P<0.001$; case-crossover study 1: RR=1.008, 95% CI 1.004–1.011, $P<0.001$). There was no obvious risk of publication bias in the funnel plot for the association between PM_{2.5} and diabetes-associated mortality, and the

Table 1 Characteristics of 12 studies included in the meta-analysis.

Study	Country	Study design	Period	Pollutants	Events	Data type	Adjustment	Quality ^a
(28)	USA	Case-crossover	1999–2000	PM2.5	442 622	Per 10 µg/m ³	Seasonal, days of the week and weather	4
(19)	Canada	Time-series	1990–2003	NO ₂ , CO, SO ₂ , PM2.5	38 883	Per IQR	Temporal variability and maximum temperature	4
(18)	Canada	Cohort	1991	PM2.5	5200	Per 10 µg/m ³	Adults with less than high school diploma, adults in the lowest low-income cut-off quintile and adults unemployed determined at both the census divisions and census tract levels	5
(20)	Denmark	Cohort	1993–1997	NO ₂	122	Per 10 µg/m ³	Sex, age, calendar year, length of school attendance, occupation with potential for exposure to smoke and fumes, smoking status, smoking intensity, smoking duration, environmental tobacco smoking, intake of alcohol, fat, fruit and vegetables, BMI, waist circumference, physical activity with sport, hypertension and hypercholesterolaemia at baseline	5
(17)	Italy	Case-crossover	2001–2005	NO ₂	30 620	Per 10 µg/m ³	Temporal variability and maximum temperature	4
(16)	USA	Case-crossover	1995–2002	O ₃	3845	Per IQR	Linear and quadratic apparent temperature and days of the week	3
(15)	Italy	Case-crossover	1997–2004	PM10	30 173	Per 10 µg/m ³	Time, population changes and meteorological conditions	4
(27)	USA	Time-series	1999–2002	PM2.5	10 400	Per 10 µg/m ³	Daily average temperature and humidity data at weather stations	4
(14)	Canada	Time-series	1984–1993	NO ₂ , CO, SO ₂	3677	Per IQR	Seasonal and sub-seasonal trends, calendar year, days of the week and weather variables	4
(26)	China	Time-series	2001–2002	NO ₂ , SO ₂ , PM10	NA	Per 10 µg/m ³	Long-term trends, weather variables and days of the week	3
(13)	USA	Case-crossover	1988–1991	PM10	12 978	Per 10 µg/m ³	Temperature, humidity and pressure	4
(12, 25)	Canada	Time-series	1984–1993	O ₃ , PM2.5, PM10	3677	Per IQR	Seasonal, sub-seasonal variations (temporal filter) and weather variables	4

IQR, interquartile range.

^aQuality was assigned as A or excellent with five points, B or good with 3–4 points and C or suboptimal with 0–2 points.

Figure 2

Association between the high level of PM_{2.5} and diabetes-associated mortality.

P value for Egger's test was 0.127. When using the trim and fill method, no possible 'missing' study was added.

PM₁₀ and diabetes-associated mortality

Meta-analysis of those four studies (13, 15, 25, 26) on PM₁₀ indicated that a high level of PM₁₀ was significantly associated with an increased risk of diabetes-associated mortality (per IQR or 10 µg/m³: RR=1.010, 95% CI 1.002–1.019, $P=0.021$, $I^2=56.2\%$; per 10 µg/m³: RR=1.008, 95% CI 1.004–1.013, $P<0.001$, $I^2=0\%$) (Fig. 3). Subgroup analyses by study design showed similar obvious associations (case-crossover studies 2: RR=1.011, 95% CI 1.004–1.018, $P=0.002$). There was no obvious risk of publication bias in the funnel plot for the association between PM₁₀ and diabetes-associated mortality, and the P value for Egger's test was 0.150. When using the trim and fill method, two possible 'missing' studies were added, and a high level of PM₁₀ was still significantly associated with an increased risk of diabetes-associated mortality (per 10 µg/m³: RR=1.008, 95% CI 1.003–1.012, $P<0.001$).

NO₂ and diabetes-associated mortality

Meta-analysis of those five studies on NO₂ (14, 17, 19, 20, 26) indicated that a high level of NO₂ was significantly associated with an increased risk of diabetes-associated mortality (per IQR or 10 µg/m³: RR=1.036, 95% CI 1.013–1.060, $P=0.002$, $I^2=71.2\%$; per 10 µg/m³: RR=1.024, 95% CI 1.007–1.041, $P=0.006$, $I^2=49.7\%$) (Fig. 4). After excluding the study by Raaschou-Nielsen *et al.* (20), a

high level of NO₂ was significantly associated with an increased risk of diabetes-associated mortality (per IQR or 10 µg/m³: RR=1.034, 95% CI 1.012–1.056, $P=0.002$, $I^2=73.2\%$; per 10 µg/m³: RR=1.022, 95% CI 1.008–1.036, $P=0.002$, $I^2=41.7\%$). Subgroup analyses by study design showed similar obvious associations in the analyses of time-series (studies 2: RR=1.037, 95% CI 1.004–1.070, $P=0.027$) and case-crossover (study 1: RR=1.036, 95% CI 1.017–1.055, $P<0.001$) studies. There was no obvious risk of publication bias in the funnel plot for the association between NO₂ and diabetes-associated mortality, and the P value for Egger's test was 0.135. When using the trim and fill method, two possible 'missing' studies were added, and exposure to a high level of NO₂ was still significantly associated with an increased risk of diabetes-associated mortality (per 10 µg/m³: RR=1.021, 95% CI 1.003–1.040, $P<0.001$).

Other air pollutants and diabetes-associated mortality

Meta-analysis of those three studies on SO₂ (14, 19, 26) indicated that a high level of SO₂ was not significantly associated with an increased risk of diabetes-associated mortality (per IQR increment: RR=1.027, 95% CI 0.998–1.058, $P=0.070$, $I^2=66.9\%$).

Meta-analysis of those three studies on O₃ (12, 16) showed that a high level of O₃ was significantly associated with an increased risk of diabetes-associated mortality (per IQR increment: RR=1.065, 95% CI 1.017–1.115, $P=0.007$, $I^2=0.0\%$).

Meta-analysis of those three studies on CO (14, 19) showed that a high level of CO was not significantly

Figure 3

Association between the high level of PM₁₀ and diabetes-associated mortality.

Figure 4
Association between the high level of NO₂ and diabetes-associated mortality.

associated with an increased risk of diabetes-associated mortality (per IQR increment: RR=1.044, 95% CI 0.996–1.093, $P=0.073$, $I^2=47.3\%$).

Discussion

Currently, there is no definite conclusion on the influence of air pollutants on diabetes-associated mortality. This study is a comprehensive meta-analysis aimed to assess the associations between main air pollutants and diabetes-associated mortality. Eleven studies involving a total of 582 197 events of diabetes-associated mortality were finally included in the meta-analysis (12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 26, 27, 28). The findings from the meta-analysis suggested that an increased risk of diabetes-associated mortality was associated with increases in PM_{2.5} (per 10 µg/m³: RR=1.123, 95% CI 1.036–1.217, $P=0.005$, $I^2=96.1\%$), PM₁₀ (per 10 µg/m³: RR=1.008, 95% CI 1.004–1.013, $P<0.001$, $I^2=0\%$), NO₂ (per 10 µg/m³: RR=1.024, 95% CI 1.007–1.041, $P=0.006$, $I^2=49.7\%$) and O₃ (per IQR increment: RR=1.065, 95% CI 1.017–1.115, $P=0.007$, $I^2=0.0\%$) (Figs 2, 3 and 4). Thus, the findings from the meta-analysis prove the obvious influence of air pollutants on diabetes-associated mortality and exposure to high levels of air pollutants results in an increased risk of diabetes-associated mortality.

In the present meta-analysis, the associations were first assessed by per IQR increment and then by standardised increment (per 10 µg/m³ increment) for PM_{2.5}, PM₁₀ and NO₂. However, the method described above was not used for the other three pollutants because

there were limited studies and obviously discrepancy in the IQR for O₃, SO₂ and CO. More studies are needed to assess the effects of O₃, SO₂ and CO on the risk of diabetes-associated mortality. In addition, most included studies used generalised linear models to assess the associations of PM_{2.5}, PM₁₀ and NO₂ with diabetes-associated mortality; we thus used standardised risk estimates by a standardised increment in the pollutant concentration by 10 µg/m³ each for PM_{2.5}, PM₁₀ and NO₂. There was no obvious discrepancy in the pooled results of meta-analyses by different data types (per IQR or per 10 µg/m³), which suggested the stability of overall risk estimates.

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, 8, 10, 11, 29, 30). The findings from the meta-analysis further add strong evidence for the adverse effect of air pollution on diabetes-associated mortality. In addition, there are also many studies showing the possible associations of air pollutants with the risk of diabetes (31, 32, 33, 34, 35), which further indicate the adverse effects of air pollution on diabetes. The adverse effect of exposures to air pollution on diabetes-associated mortality is of much importance, given the extraordinary confluence of air pollutants worldwide (36).

Air pollution is a more and more serious problem worldwide, especially in the developing or rapidly urbanising countries, such as China (36, 37, 38). The adverse effect of exposure to air pollution on diabetes-associated mortality is of much more importance for those countries with serious air pollution. Air pollution in China is a significant public health burden, and the mean annual averages of PM_{2.5}, PM₁₀ and NO₂ among 74 major cities from China in 2013 were 72.4, 118.5 and 43.7 µg/m³ (39), which were roughly fivefold higher than the USA National Ambient Air Quality Standard of 15 µg/m³ for PM_{2.5} and the WHO standard of 10 µg/m³. 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 strong evidence for the clear adverse effect of air pollution on diabetes-associated mortality, thus improvement of air quality through positive environmental policy or interventions are needed to gain public health benefits and substantial health-care cost savings.

Several limitations of the meta-analysis should be considered when interpreting the results. First, most included studies were time-series studies or case-crossover

studies, while only two studies used cohort design. To get a more precise assessment on the effects of main air pollutants on diabetes-associated mortality, more well-designed studies with a large sample size are needed. Secondly, most studies included for the meta-analysis were done in developed countries, and there was only one study from the developing countries. However, the data from developing countries may be more concerning because these regions are affected mostly by air pollution and may have the greatest potential to improve health by controlling air pollution and improving air quality (40). More studies from developing countries are needed to provide a more precise assessment of the influence of air pollution on diabetes-associated mortality. Finally, the potential additive effects of multiple pollutants on diabetes-associated mortality were not assessed owing to the lack of relevant data in those included studies. Future studies may further assess the possible additive effects of multiple pollutants on diabetes-associated mortality, which may help us better understand the adverse influence of air pollution on public health (41).

In conclusion, the findings from the meta-analysis suggest that exposure to high levels of air pollutants is significantly associated with an increased risk of diabetes-associated mortality. Higher levels of PM_{2.5}, PM₁₀, NO₂ and O₃ are all associated with the risk of diabetes-associated mortality. However, future studies are needed to further assess the effects of SO₂ and CO on the risk of diabetes-associated mortality. In addition, more well-designed studies with a large sample size are needed to provide a more precise assessment of the influence of air pollution on diabetes-associated mortality.

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

B Wang, C Li and Y Wang were the project lead for the main systematic review. B Wang, C Li and D Xu searched databases, assessed the study eligibility and performed data extraction. Quality of data extraction and checking were carried out by B Wang, D Fang, S Yan, S Zhao and Y Wang. Statistical analysis was performed by B Wang and D Xu. B Wang, C Li and D Fang wrote and revised the manuscript. All authors reviewed the manuscript and contributed to the preparation of the manuscript.

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