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 (PM2.5) 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 PM2.5 (per 10 µg/m³: RR=1.123, 95% CI 1.036–1.217, P=0.005, I²=96.1%), PM10 (per 10 µg/m³: RR=1.008, 95% CI 1.004–1.013, P<0.001, I²=0%), NO₂ (per 10 µg/m³: RR=1.024, 95% CI 1.007–1.041, P=0.006, I²=49.7%) and O₃ (per IQR increment: RR=1.065, 95% CI 1.017–1.115, P=0.007, I²=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.

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 (NO\textsubscript{2}), sulphur dioxide (SO\textsubscript{2}), ozone (O\textsubscript{3}) and carbon monoxide (CO)) and particulate matter (PM, diameter <2.5 \mu m (PM2.5) or <10 \mu m (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 (NO\textsubscript{2}, SO\textsubscript{2}, O\textsubscript{3} and CO) and particulate (PM2.5 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’, ‘PM2.5’, ‘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 (NO\textsubscript{2}, SO\textsubscript{2}, O\textsubscript{3} and CO) and particulate (PM2.5 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. 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 \mu g/m\textsuperscript{3} each for PM2.5, PM10 and NO\textsubscript{2}. Standardised risk estimates were calculated for each study using the following formula: \[ RR_{\text{standardised}} = \frac{RR_{\text{increment}(10)/\text{increment}(\text{original})}}{\text{original}} \] (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, PM2.5, PM10 and NO$_2$, with diabetes-associated mortality were first assessed by per interquartile range (IQR) increment and then by standardised increment (per 10 $\mu$g/m$^3$ 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 plot, we also used the Egger regression test to test the associations (time-series studies 3: RR $Z=1.023$, 95% CI 1.005–1.042, $P=0.011$, $I^2=95.4%$; per 10 $\mu$g/m$^3$: 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 PM2.5 was still found to be significantly associated with an increased risk of diabetes-associated mortality (per IQR or 10 $\mu$g/m$^3$: RR=1.079, 95% CI 1.032–1.128, $P=0.001$, $I^2=95.4%$; per 10 $\mu$g/m$^3$: 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 PM2.5 and diabetes-associated mortality, and the

**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, 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, 25, 26, 27, 28). 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 PM2.5 (18, 19, 25, 27, 28), four studies evaluating PM10 (13, 15, 25, 26), five studies evaluating NO$_2$ (14, 17, 19, 20, 26), three studies evaluating SO$_2$ (14, 19, 26), two studies evaluating O$_3$ (12, 16) and two studies evaluating CO (14, 19) respectively (Table 1). According to the quality of 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).

**PM2.5 and diabetes-associated mortality**

Meta-analysis of those four studies (18, 19, 25, 27, 28) evaluating PM2.5 showed that a high level of PM2.5 was significantly associated with an increased risk of diabetes-associated mortality (per IQR or 10 $\mu$g/m$^3$: 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 PM2.5 and diabetes-associated mortality, and the
Table 1 Characteristics of 12 studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study design</th>
<th>Period</th>
<th>Pollutants</th>
<th>Events</th>
<th>Data type</th>
<th>Adjustment</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>(28)</td>
<td>USA</td>
<td>Case-crossover</td>
<td>1999–2000</td>
<td>PM2.5</td>
<td>442</td>
<td>Per 10 μg/m³</td>
<td>Seasonal, days of the week and weather temperature</td>
<td>4</td>
</tr>
<tr>
<td>(19)</td>
<td>Canada</td>
<td>Time-series</td>
<td>1990–2003</td>
<td>NO₂, CO, SO₂, PM2.5</td>
<td>38 883</td>
<td>Per IQR</td>
<td>Temporal variability and maximum temperature</td>
<td>4</td>
</tr>
<tr>
<td>(18)</td>
<td>Canada</td>
<td>Cohort</td>
<td>1991</td>
<td>PM2.5</td>
<td>5200</td>
<td>Per 10 μg/m³</td>
<td>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</td>
<td>5</td>
</tr>
<tr>
<td>(20)</td>
<td>Denmark</td>
<td>Cohort</td>
<td>1993–1997</td>
<td>NO₂</td>
<td>122</td>
<td>Per 10 μg/m³</td>
<td>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</td>
<td>5</td>
</tr>
<tr>
<td>(17)</td>
<td>Italy</td>
<td>Case-crossover</td>
<td>2001–2005</td>
<td>NO₂</td>
<td>30 620</td>
<td>Per 10 μg/m³</td>
<td>Temporal variability and maximum temperature</td>
<td>4</td>
</tr>
<tr>
<td>(16)</td>
<td>USA</td>
<td>Case-crossover</td>
<td>1995–2002</td>
<td>O₃</td>
<td>3845</td>
<td>Per IQR</td>
<td>Linear and quadratic apparent temperature and days of the week</td>
<td>3</td>
</tr>
<tr>
<td>(15)</td>
<td>Italy</td>
<td>Case-crossover</td>
<td>1997–2004</td>
<td>PM10</td>
<td>30 173</td>
<td>Per 10 μg/m³</td>
<td>Time, population changes and meteorological conditions</td>
<td>4</td>
</tr>
<tr>
<td>(27)</td>
<td>USA</td>
<td>Time-series</td>
<td>1999–2002</td>
<td>PM2.5</td>
<td>10 400</td>
<td>Per 10 μg/m³</td>
<td>Daily average temperature and humidity data at weather stations</td>
<td>4</td>
</tr>
<tr>
<td>(14)</td>
<td>Canada</td>
<td>Time-series</td>
<td>1984–1993</td>
<td>NO₂, CO, SO₂, PM10</td>
<td>3677</td>
<td>Per IQR</td>
<td>Seasonal and sub-seasonal trends, calendar year, days of the week and weather variables</td>
<td>4</td>
</tr>
<tr>
<td>(26)</td>
<td>China</td>
<td>Time-series</td>
<td>2001–2002</td>
<td>NO₂, SO₂, PM10</td>
<td>NA</td>
<td>Per 10 μg/m³</td>
<td>Long-term trends, weather variables and days of the week</td>
<td>3</td>
</tr>
<tr>
<td>(13)</td>
<td>USA</td>
<td>Case-crossover</td>
<td>1988–1991</td>
<td>PM10</td>
<td>12 978</td>
<td>Per 10 μg/m³</td>
<td>Temperature, humidity and pressure</td>
<td>4</td>
</tr>
<tr>
<td>(12, 25)</td>
<td>Canada</td>
<td>Time-series</td>
<td>1984–1993</td>
<td>O₃, PM2.5, PM10</td>
<td>3677</td>
<td>Per IQR</td>
<td>Seasonal, sub-seasonal variations (temporal filter) and weather variables</td>
<td>4</td>
</tr>
</tbody>
</table>

IQR, interquartile range.
*Quality was assigned as A or excellent with five points, B or good with 3–4 points and C or suboptimal with 0–2 points.
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, I² = 56.2%; per 10 µg/m³: RR = 1.008, 95% CI 1.004–1.013, P < 0.001, I² = 0%) (Fig. 3). Subgroup analyses by study design showed similar obvious associations (case-crossover studies: 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 exposure to a high level of PM10 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).

**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 = 1.034, 95% CI 1.012–1.056, P = 0.002, I² = 73.2%; per 10 µg/m³: RR = 1.022, 95% CI 1.008–1.036, P = 0.002, I² = 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).
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 PM2.5 (per 10 $\mu g/m^3$: $RR = 1.123$, 95% CI 1.036–1.217, $P = 0.005$, $I^2 = 96.1\%$), PM10 (per 10 $\mu g/m^3$: $RR = 1.088$, 95% CI 1.004–1.103, $P < 0.001$, $I^2 = 0\%$), NO2 (per 10 $\mu g/m^3$: $RR = 1.024$, 95% CI 1.007–1.041, $P = 0.006$, $I^2 = 47.9\%$) and O3 (per IQR increment: $RR = 1.065$, 95% CI 1.017–1.115, $P = 0.007$, $I^2 = 0\%$) (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 $\mu g/m^3$ increment) for PM2.5, 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 PM2.5, PM10 and NO2 with diabetes-associated mortality; we thus used standardised risk estimates by a standardised increment in the pollutant concentration by 10 $\mu g/m^3$ each for PM2.5, PM10 and NO2. There was no obvious discrepancy in the pooled results of meta-analyses by different data types (per IQR or per 10 $\mu g/m^3$), 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 consequence 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 PM2.5, PM10 and NO2 among 74 major cities from China in 2013 were 72.4, 118.5 and 43.7 $\mu g/m^3$ (39), which were roughly fivefold higher than the USA National Ambient Air Quality Standard of 15 $\mu g/m^3$ for PM2.5 and the WHO standard of 10 $\mu g/m^3$. 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, which have limitations of reverse causality and selection bias. In addition, the association of air pollution and diabetes should be further studied with more advanced epidemiological methods.

### Table: Summary of Studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldberg MS 2013 (19)</td>
<td>1.03 (1.01, 1.06)</td>
<td>27.99</td>
</tr>
<tr>
<td>Raaschou-Nielsen O 2013 (11)</td>
<td>1.01 (0.98, 1.03)</td>
<td>33.13</td>
</tr>
<tr>
<td>Chiuolo M 2011 (17)</td>
<td>1.04 (1.02, 1.06)</td>
<td>100.00</td>
</tr>
<tr>
<td>Goldberg MS 2006 (14)</td>
<td>1.12 (1.04, 1.20)</td>
<td>8.42</td>
</tr>
<tr>
<td>Ken H 2004 (25)</td>
<td>1.01 (1.00, 1.03)</td>
<td>37.73</td>
</tr>
<tr>
<td>Subtotal</td>
<td>1.04 (1.01, 1.06)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Note: weights are from random effects analysis.

### Figure 4

Association between the high level of NO2 and diabetes-associated mortality.
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 PM2.5, 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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