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Ambient Air Pollution and Type 2 Diabetes: A Systematic Review of Epidemiologic Research

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Abstract

Recent experimental and epidemiologic studies have suggested air pollution as a new risk factor for type 2 diabetes mellitus (T2DM). We conducted a systematic review of the epidemiologic studies on the association of air pollution with T2DM and related outcomes published by December 2013. We identified 22 studies: 6 prospective studies on incident T2DM; 2 prospective study on diabetes mortality; 4 cross-sectional studies on prevalent T2DM; 7 ecological studies on mortality or morbidity from diabetes; and 3 studies on glucose or insulin levels. The evidence of the association between long-term exposure to fine particles ($PM_{2.5}$) and the risk of T2DM is suggestive. The summary hazard ratio of the association between long-term $PM_{2.5}$ exposure and incident T2DM was 1.11 (95% CI, 1.03–1.19) for a 10 μg/m^3 increase. The evidence on the association between long-term traffic-related exposure (measured by nitrogen dioxide or nitrogen oxides) and the risk of T2DM was also suggestive although most studies were conducted in women. For short-term effects of air pollution on diabetes mortality or hospital/emergency admissions, we conclude that the evidence is not sufficient to infer a causal relationship. Because most studies were conducted in North America or in Europe where exposure levels are relatively low, more studies are needed in recently urbanized areas in Asia and Latin America where air pollution levels are much higher and T2DM is an emerging public health concern.

Keywords

Air pollution; meta-analysis; nitrogen dioxide; particulate matters; systematic review; type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by high glucose levels in the blood caused by insulin resistance and relative insulin deficiency [1]. There are

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Conflict of Interest
Sung Kyun Park and Weiye Wang declare that they have no conflict of interest.

Compliance with Ethics Guidelines
Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

currently 347 million people with diabetes around the world and T2DM consists of approximately 90% of people with diabetes [2]. High fasting blood glucose was ranked as the 7th risk factor for global disease burden and accounted for 3.4 million deaths and 3.6% of disability-adjusted life years (DALYs) in 2010 [3]. While recent genome-wide association studies have uncovered genetic variants associated with T2DM risk [4, 5], these variants collectively account for only a small proportion of T2DM risk, suggesting a substantial role of modifiable risk factors in the development of T2DM. Although diet and physical activity are well established risk factors for T2DM [6], there is growing evidence that environmental pollutants also play an important role in the pathogenesis of T2DM [7].

Air pollution has been suggested as a risk factor for T2DM. Recent reviews based on animal studies summarized potential biological mechanisms of air pollution-induced insulin resistance and T2DM [8, 9] including particle-mediated alterations in glucose homeostasis, inflammation in visceral adipose tissue, endoplasmic reticulum stress in liver and lung, mitochondrial dysfunction and brown adipose tissue dysfunction, inflammation mediated through toll-like receptors and nucleotide oligomerization domain receptors, and inflammatory signaling in key regions of the hypothalamus. Epidemiologic studies of air pollution and T2DM have provided mixed results [10–29]. Some studies have reported significant positive associations, but others found no associations. To summarize epidemiologic findings, we conducted a systematic review of the epidemiologic studies on the association between ambient air pollution and T2DM. We searched for studies on incidence and prevalence of T2DM, diabetes mortality and glucose homeostatic measures such as fasting glucose, insulin, homeostatic model assessment-insulin resistance (HOMA-IR), and hemoglobin A1c (HbA1c). Because of small numbers of studies identified in each outcome and heterogeneity in air pollutants, we conducted a meta-analysis only for long-term exposure to fine particles ($PM_{2.5}$) and incident T2DM to compute a summary measure of association. For other outcomes, we summarized each study findings descriptively.

METHODS

Search Strategy and Data Extraction

We conducted a literature search in PubMed and Web of Science on January 7, 2014 using the following key words: (air pollution OR particulate matter OR PM_{10} OR $PM_{2.5}$ OR nitrogen oxides OR nitrogen dioxide OR fine particles OR coarse particles OR ozone OR traffic particle OR traffic exhaust NOT nitric oxide) AND (type 2 diabetes OR diabetes mellitus OR insulin OR glucose). We searched publications between January 1990 and December 2013 given that epidemiologic studies of air pollution and type 2 diabetes received attention just recently. In the Web of Science, we restricted articles from the following categories: Environmental sciences; Pharmacology pharmacy; Toxicology; Endocrinology metabolism; Public environmental occupational health; Cardiac cardiovascular system; Medicine general internal; Multidisciplinary science. A total of 933 articles from PubMed and 481 from Web of Science were identified and the abstracts were reviewed. Only human studies that included original data were considered. We also excluded studies conducted in children or pregnant women (gestational diabetes), studies with no air pollution data, studies with no effect estimate in relation to air pollution

exposure, or studies that examined T2DM as an effect modifier. Finally 21 original studies were included in this review. We extracted the following information from each study and summarized by study design: first author, year of publication, study population, sample size, study (follow-up) period, age, percent of female subjects, exposure distribution (median (interquartile range (IQR)), mean±standard deviation (SD), or range), number of cases, covariates adjusted, and measures of association. We only considered exposure measures from ambient concentrations of air pollutants (i.e. studies on indoor air pollution were excluded) and did not include exposure measures from emission inventory.

Statistical Analysis

To make the reported measures of association (e.g., hazard ratio (HR), odds ratio (OR), percent change) across studies comparable, we rescaled the effect estimates for an interquartile range (IQR) increase and for a 10 unit ($\mu g/m^3$ or ppb) increase. We conducted a meta-analysis of the association between $PM_{2.5}$ and incident T2DM with the identified 4 cohort studies [13, 15, 26]. We used a random-effects model to compute a summary HR. Two studies reported HRs from a multi-pollutant model [15, 26]. We extracted all reported HRs but considered the HRs from a single pollutant model in the meta-analysis. Because the number of studies for the meta-analysis was small, we did not perform a test for publication bias. R version 3.0.2 (R Foundation for Statistical Computing, http://www.w-project.org) with the package metafor was used.

RESULTS

We included 6 prospective cohort studies on incident T2DM; 2 prospective cohort study on diabetes mortality; 4 cross-sectional studies on prevalence of T2DM or impaired glucose metabolism (IGM: fasting glucose≥100 mg/dL or physician-diagnosis); 3 studies on continuous measures of glucose homeostasis; 4 ecological studies on mortality from diabetes; and 3 ecological studies on hospital/emergency admissions for diabetes.

Long-Term Exposure to Air Pollution and Incidence of Type 2 Diabetes

We identified 6 cohort studies of incident T2DM (Table 1) [10, 13, 15, 23, 26]. Two independent cohort studies (the Nurses' Health Study (NHS) and the Health Professional Follow-up Study (HPFS)) were examined in a study by Puett and colleagues [26]. Three studies were performed in the U.S. and one each in Germany, Denmark and Canada. Three cohort studies (SALIA (Study on the Influence of Air Pollution on Lung, Inflammation and Aging), BWHS (Black Women's Health Study), and NHS) included only women and the HPFS included only men. Incidence rates ranged from 402 per 100,000 subjects in HPFS to 1,302 per 100,000 in the Ontario residents' study. Four studies examined either $PM_{2.5}$ (annual mean ranged from 10.6 $\mu g/m^3$ to 21.1 $\mu g/m^3$) or PM_{10} (26.9 $\mu g/m^3$ to 46.9 $\mu g/m^3$); three studies examined either NO_x (41.6 ppb) or NO_2 (15.4 to 34.5 $\mu g/m^3$). For PM, all four studies found weak positive associations and only the Ontario residents' study reported a statistically significant association (adjusted hazard ratio (HR)=1.06 (95% confidence interval (CI), 1.01, 1.11) for an IQR increase in $PM_{2.5}$ (5.4 $\mu g/m^3$); HR=1.11 (95% CI, 1.02, 1.21) for a 10 $\mu g/m^3$ increase) [13]. The random-effect summary HR for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was 1.11 (95% CI, 1.03, 1.19), with no evidence of heterogeneity among the three

studies with $PM_{2.5}$ measures available (test for heterogeneity: $Q_{df=3} = 1.08$, p-value=0.78) (Figure 1). For NO_2 or NO_x (traffic-related particles), two studies conducted in women's cohorts reported significant positive associations (HR=1.42 (95% CI, 1.16, 1.73) for NO_2 (IQR=15 μg/m^3) in SALIA; HR=1.25 (95% CI, 1.07, 1.46) for NO_x (IQR=12.4 ppb) in BWHS), whereas the Danish Diet, Cancer, and Health (DCH) study found no association when all cases of T2DM were examined but found a weak marginal association when only confirmed T2DM cases were considered (HR=1.04 (95% CI, 1.00, 1.08) for NO_2 (IQR=4.9 μg/m^3)).

Two studies examined long-term exposure to air pollution and incident diabetes mortality [30, 27]. In a study conducted in Denmark (the DHC cohort study followed from 1993 to 2009, N=52,061, 122 cases), an IQR increase in NO_2 (IQR=4.9 μg/m^3) averaged from 1971 to the follow-up period was associated with a HR for diabetes equal to 1.14 (95% CI, 0.99, 1.32) [27]. A large national follow-up study conducted in Canada (The 1991 Canadian census mortality follow-up from 1991 to 2001, N=2,145,400, 5,200 cases) found a significant positive association between average concentrations of $PM_{2.5}$ for the period from 2001 to 2006 and diabetes mortality (HR=1.28 (95% CI, 1.22, 1.35) for an IQR increase in $PM_{2.5}$ (6.2 μg/m^3) [30].

Long-Term Exposure to Air Pollution and Prevalence of Type 2 Diabetes

Four studies (three observational and one ecological) reported cross-sectional associations between long-term air pollution and prevalence of T2DM or IGM (Table 1). Two observational cross-sectional studies performed in Canada and The Netherlands examined annual NO_2 concentrations as the exposure measure, whereas the SALIA study (Germany) examined various air pollution measures including $PM_{2.5}$, $PM_{10–2.5}$, PM_{10}, NO_2 and NO_x. The ecological study conducted in the U.S. was based on county-levels of diabetes prevalence and $PM_{2.5}$ annual concentrations in 2004 and 2005 (n=2,754 counties). In patients from a respiratory disease clinic from Hamilton (N=5,228, prevalence of T2DM=15%) and Toronto (N=2,406, prevalence of T2DM=17%), Canada, an IQR increase in NO_2 was positively associated with T2DM among women (OR=1.08 (95% CI, 0.94, 1.26) in Hamilton; OR=1.23 (95% CI, 1.00, 1.50) in Toronto) but not men (OR=1.03 (95% CI, 0.85, 1.20) in Hamilton; OR=0.92 (95% CI, 0.74, 1.09) in Toronto) [11]. In a study of 8,018 residents (prevalence of T2DM=8%) from Westfriesland, Netherlands, NO_2 was not associated with the prevalence of T2DM [17]. A study conducted in the SALIA cohort, Germany (N=363, 100% women, prevalence of IGM=48%) found significant positive associations of IGM with NO_2 (OR=1.47 (95% CI, 1.05, 2.05) per IQR increase) and NO_x (OR=1.41 (95% CI, 1.01, 1.97)) [28]. Finally, in an ecological study of the association between county-level $PM_{2.5}$ concentrations and diabetes prevalence in the US [25], a 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 1.15% (95% CI, 1.02, 1.32%) increase in the diabetes prevalence in 2004 and a 0.92% (95% CI, 0.75, 1.13%) increase in 2005.

Air Pollution and Measures of Glucose Homeostasis

Three studies evaluated continuous measures of glucose homeostasis (Table 2) [12, 14, 21]. A study from Taiwan examined the associations with long-term exposures (annual concentrations) to 5 criteria pollutants ($PM_{2.5}$, PM_{10}, NO_2, SO_2 and O_3), whereas two

studies from Korea and Michigan, U.S. examined short-term exposures (up to 7-day lags of PM_{10}, NO_2, SO_2 and O_3 in the Korean study; 5-day long exposure to $PM_{2.5}$ in the U.S. study). All three examined fasting glucose levels; a study from Taiwan additionally examined hemoglobin A1c (HbA1c), a measure of glycated hemoglobin in red blood cells that reflects average glucose level over the previous 3 months [31]; two studies from Korea and Michigan, U.S. examined fasting insulin and an indicator of insulin resistance (homeostatic model assessment-insulin resistance (HOMA-IR)) [12, 21]. In a study of 1,023 participants from the Social Environment and Biomarkers of Aging Study in Taiwan, fasting glucose and HbA1c were associated with all criteria pollutants except SO_2 [14]. A study of 560 older people in Korea reported that short-term exposure to PM_{10}, NO_2 and O_3 but not SO_2 were associated with increased fasting glucose, insulin and HOMA-IR, which suggests reduced metabolic insulin sensitivity [21]. A human panel study with 25 healthy non-smoking adults conducted in Michigan, U.S. also found that sub-acute exposure to $PM_{2.5}$ (5-day-long cumulative exposure) was associated with increased fasting glucose, insulin and HOMA-IR [12].

Short-Term Exposure to Air Pollution and Mortality from Diabetes

We identified four ecological studies (Poisson time-series or case-crossover design studies) of short-term exposure to air pollution and mortality from diabetes (Table 3) [18–20, 24]. These studies included both type-1 and type 2 diabetes. In a study conducted in Montreal, Canada between 1984 and 1993, the estimated percent change in daily diabetes mortality for an IQR increase in air pollution was 13.2% (95% CI, 2.69%, 24.8%) for PM_{10}, 12.0% (95% CI, 3.01%, 21.8%) for $PM_{2.5}$, and 3.79%, (95% CI, 0.69%, 6.98%) for sulfate (predicted from $PM_{2.5}$). In a latter study conducted between 1990 and 2003 the corresponding percent changes were 3.45% (95% CI, 1.29%, 5.66%) for NO_2, 2.74% (95% CI, 0.75%, 4.77%) for CO and 1.89%, (95% CI, 0.05%, 3.76%) for SO_2 [19]. In a time-series study using daily mortality from diabetes between 2001 and 2002 conducted in Shanghai, China observed marginal associations with PM_{10} (4.18% (95% CI, 0.00%, 8.54%) per IQR increase) and SO_2 (3.82%, (95% CI, 0.00%, 7.78%)) [20]. In Massachusetts, U.S., black carbon (5.7%, (95% CI, −1.7%, 13.7%)) and sulfate (2.9%, (95% CI, −3.1%, 9.5%)) were positively but non-significantly associated with the deaths from diabetes for the years 1995–2002 [24].

Short-Term Exposure to Air Pollution and Hospital/Emergency Admissions for Diabetes

Three studies examined hospital/emergency admissions for diabetes using the time-series Poisson model analysis or the case-crossover design (Table 3) [16, 22, 29]. These studies also included both type-1 and type 2 diabetes. Two studies by Zanobetti et al. [29] and Dales et al. [16] examined short-term exposures to air pollution and one study by Kloog et al. [22] examined both short-term and long-term effects of $PM_{2.5}$. Zanobetti et al. found that a 10 $\mu g/m^3$ increase in 2-day averaged $PM_{2.5}$ was associated with a 2.74% (95% CI, 1.30, 4.20%) increase in emergency admissions for diabetes in 26 U.S. communities between 2000 and 2003 [29]. In a study from Santiago, Chile between 2001 and 2008, Dales et al. found that IQR increases in criteria pollutants except ozone were associated with an 11% to a 15% increase in the risk for hospitalization for diabetes [16]. In a study conducted in New England, U.S., a 10 $\mu g/m^3$ increase in short-term and long-term $PM_{2.5}$ was associated with a

0.96% (95% CI, 0.62%, 1.30%) and a 6.33% (95% CI, 3.22%, 9.53%) increase in the risk for diabetes hospitalization, respectively [22].

DISCUSSION

In general, two different study designs were used to examine the association between air pollution and T2DM: observational studies of incidence, prevalence or mortality from T2DM or continuous measures of insulin resistance in relation to long-term exposure to air pollution; and ecological studies of daily mortality or hospital/emergency admissions in relation to short-term exposure. For the incidence and prevalence studies and observational diabetes mortality studies, either annual concentrations of particulate matters (mostly $PM_{2.5}$ or PM_{10} and $PM_{10–2.5}$ (coarse particles)) or nitrogen oxides (NO_x or NO_2) which were estimated using land-use regression [10, 11, 15, 17, 26–28, 30] or satellite-based approach [13] were used as exposure metrics, whereas ecological studies of DM mortality or hospital/emergency admissions (except the study by Kloog et al. [22]) used daily concentrations of criteria pollutants ($PM_{2.5}$, PM_{10}, NO_2, CO, SO_2, and O_3) based on central monitoring or the nearest monitors. Given the differences in study design and disease etiology between long-term air pollution effects on the development of T2DM vs. short-term air pollution effects on daily diabetes mortality or morbidity, we discussed causal relationships based on epidemiologic findings by these two study designs separately.

Observational Studies in Relation to Long-Term Exposure

Consistency—For $PM_{2.5}$, all studies showed positive associations with either incident T2DM [13, 15, 23, 26], diabetes mortality [30] or prevalent IGM [28]. Our meta-analysis suggests an association between $PM_{2.5}$ and incident T2DM with a small summary HR of 1.11 (95% CI, 1.03, 1.19). One large national-level study examined more than 2 millions of Canadians showed a strong positive association between $PM_{2.5}$ and diabetes mortality. For NO_2 or NO_x, a measure of traffic particle exposure, three studies from two women's cohorts (SALIA and BWHS) reported a significant association with incident T2DM [15, 23] or prevalent IGM [28], and one relatively large study from Denmark (approximately 52,000 participants) also reported a significant association with confirmed T2DM (but not with all cases of T2DM) [10] or diabetes mortality [27]. Two other cross-sectional studies also found a suggestive association with prevalent T2DM only among women [11, 17].

Strength—One Canadian census mortality study and two women's cohort studies (SALIA and BWHS) reported relatively strong associations (HRs from 1.25 to 1.42 for an IQR increase in $PM_{2.5}$, NO_x or NO_2), whereas other studies reported modest associations (i.e., HRs or ORs <1.1). Although most studies used land-use regression models to generate improved exposure estimates, the use of stationary monitoring data rather than personal monitoring may lead to exposure measurement error. Another potential source of exposure measurement error is that one year average concentrations prior to baseline or at any given year are used as proxies for the long-term exposure. Exposure measurement error may occur if individual exposure levels have changed over time before baseline, for example, if individuals have moved often before baseline. These errors generally bias the observed association towards the null.

Temporality—Eight prospective studies have examined incident T2DM or diabetes mortality which supports the temporality issue that the cause precedes the effect in time. Reverse causation is unlikely given that onset of T2DM may not lead to an increase in air pollution exposure.

Biological Plausibility—As introduced early, several animal studies support potential biological mechanisms, for example, cumulative exposure to air pollution can lead to a reduction in Akt phosphorylation in the liver, skeletal muscle and white adipose tissue which influences insulin signaling pathway and apoptosis [32, 33]. Fine particulate matter exposure can induce inflammation in visceral adipose tissue by increasing adipose tissue macrophages [34]. $PM_{2.5}$ exposure may also induce endoplasmic reticulum (ER) stress not only in the lung but in the liver which induces hepatic insulin resistance [35]. These mechanisms eventually affect insulin resistance and cause T2DM [8, 9].

Causal Inference—Based on consistency of the observed findings, the evidence of the association between long-term exposure to $PM_{2.5}$ and the risk of T2DM is suggestive. The vast majority of studies were conducted in North America or Europe and little evidence was reported from other areas. The evidence on the association between long-term traffic-related exposure (measured by nitrogen dioxide or nitrogen oxides) and the risk of T2DM is also suggestive although most studies were conducted in women. The fact that two primary studies showing significant associations between traffic exposure and incident T2DM were conducted in women's cohorts and most other studies have reported a significant association only among women suggests that women may be more susceptible to air pollution-related response to T2DM. It is unclear that the stronger associations in women are consequences of sex-related biological differences or gender-related behavioral or social differences [36] which needs further investigation.

Ecological Studies in Relation to Short-Term Exposure

Consistency and Strength—For mortality from T2DM, three studies examined either PM_{10} or $PM_{2.5}$: a time-series study from Shanghai, China found a marginal association [20]. In studies done in Montreal, Canada, the earlier study that examined mortality between 1984 and 1993 in which the median concentrations of $PM_{2.5}$ and PM_{10} were 28.5 and 14.7 $\mu g/m^3$ reported a significant association (12% and 13% increases in DM mortality per IQR increase in $PM_{2.5}$ and PM_{10}, respectively) [18], whereas a more recent study that examined mortality between 1990 and 2003 in which the median $PM_{2.5}$ concentration was 6.9 $\mu g/m^3$ found no association [19]. For hospital/emergency admissions, all three studies reported significant associations with $PM_{2.5}$. Two U.S. studies where $PM_{2.5}$ concentrations were 9 to 15 $\mu g/m^3$ reported weak positive associations (0.96% and 2.74% per 10 $\mu g/m^3$ increase in $PM_{2.5}$), whereas a time-series study done in Santiago, Chile where $PM_{2.5}$ concentrations were two-fold higher (the median $PM_{2.5}$ =31.5 $\mu g/m^3$) found a 6% increased risk per 10 $\mu g/m^3$ increase in $PM_{2.5}$.

Biological Plausibility—For short-term exposure, it is unclear if mortality from diabetes or hospital/emergency admissions to diabetes was due to diabetes-related complications by dysfunctions of serum glucose control or due to acute exacerbation of other pre-existing

diseases [16]. Short-term exposure to particulate matters or ozone is known to induce oxidative stress, systemic inflammation, endothelial dysfunction, and cardiac autonomic nervous system dysfunction [37], which may lead to insulin dysregulation [38, 39]. A human panel study conducted in Michigan, U.S. found that sub-acute exposure to $PM_{2.5}$ was associated with reduced metabolic insulin sensitivity as measured by increased HOMA-IR and reduced heart rate variability [12], which supports the plausibility that air pollution, not only long-term but relatively short-term exposure, could influence insulin and glucose homeostasis.

Temporality—The temporality issue in ecological time-series studies has been assured by examining the lagged effects [40]. Nonetheless, most studies explored only short lagged-exposure periods, such as 0 or 1-day lag or a 2-day distributed lag because many previous studies of total and cardiovascular mortality and morbidity reported larger associations with particle exposures at 0 to 2-day lags. Whether short-term air pollution exposure has immediate effects on glucose and insulin functions or more delayed effects remains to be explored in the future.

Causal Inference—We conclude that the evidence is not sufficient to infer a causal relationship of short-term exposure to air pollution and mortality or hospital/emergency admissions to diabetes. Although a few studies suggest potential mechanisms, those are not specific to glucose and insulin actions and direct mechanisms are unknown. Most previous studies examined diabetes mortality and morbidity along with cardiovascular and respiratory outcomes.

CONCLUSION

Our systematic review suggests that the evidence is suggestive to infer causal relationship between fine particle exposure and the risk of T2DM and there is suggestive evidence of the association between traffic-related exposure and incident T2DM especially in women. Because most studies were conducted in North America or in Europe where exposure levels are relatively low, more studies are needed in recently urbanized areas in Asia and Latin America where air pollution levels are much higher and T2DM is an emerging public health concern [41, 42] to increase the power and to determine the dose-response relationships.

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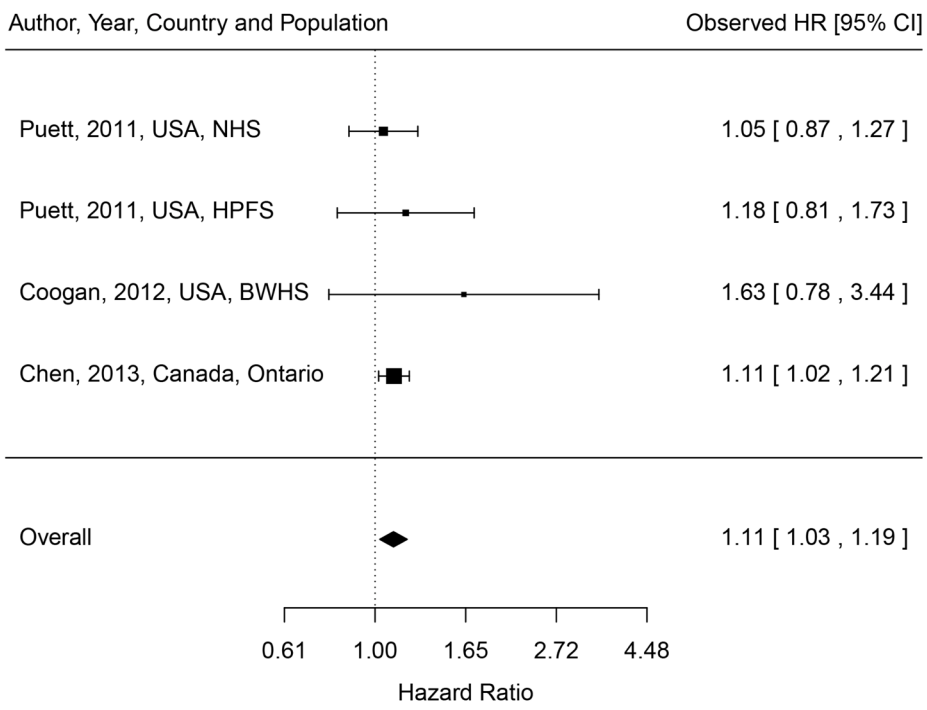

Figure 1.

Meta-analysis of the association between PM2.5 and incident diabetes. Hazard ratios (HRs) were based on a 10 μg/m3 increase. Random effect model was used to compute the overall (summary) HR.

Table 1

Observational cohort studies of long-term air pollution exposure and diabetes mellitus (DM)

1st author, Year [ref]	Population	Sample size	Study (follow-up) period	Age (y) Female (%)	Outcome Definition	No of cases (IR or %)	Exposure	Median (IQR) or Mean±SD (IQR)[g]	Adjusted RR (95% CI) per IQR increase	Adjusted RR (95% CI) per 10 unit increase	Covariate adjusted
Prospective Study on Incident DM											
Kramer, 2010 [23]	SALIA, Germany	1,775	1990–2006	54–55 100%	Self-reported physician diagnosis	187 (658/10^5 py)	Monitor PM_{10} NO_2 LUR Soot NO_2	46.9 (10) 41.7 (25) 1.89 (0.39)×10^{-5}m 34.5 (15)	1.16 (0.81, 1.65) 1.34 (1.02, 1.76) 1.27 (1.09, 1.48) 1.42 (1.16, 1.73)	1.16 (0.81, 1.65) 1.12 (1.01, 1.25) 1.26 (1.10, 1.44)	Age, BMI, education, smoking, heating w/ fossil fuels, workplace exposure w/ dust/fumes, extreme temperature
Puett, 2011 [26]	NHS, US	74,412	1989–2002	55±7 100%	↑ plasma glucose on ≥2 different occasions[a], DM symptoms and a single ↑ plasma glucose, or Hypoglycemic medication	3,784 (448/10^5 py)	LUR $PM_{2.5}$ PM_{10} $PM_{10–2.5}$	17.5±2.7 (4.3) 26.9±4.8 (6.3) 9.4±2.9 (3.7)	1.02 (0.94, 1.09) 1.03 (0.98, 1.09) 1.04 (0.98, 1.10)	1.05 (0.87, 1.22) 1.05 (0.97, 1.15) 1.11 (0.95, 1.29)	Age, BMI, smoking, alcohol, physical activity, diet, hypertension, season, calendar year, residence state
Puett, 2011 [26]	HPFS, US	15,048	1989–2002	57±10 0%		688 (402/10^5 py)	LUR $PM_{2.5}$ PM_{10} $PM_{10–2.5}$	18.3±3.1 (4.0) 28.5±5.5 (7.2) 10.3±3.3 (4.2)	1.07 (0.92, 1.24) 1.06 (0.94, 1.20) 1.04 (0.93, 1.16)	1.18 (0.81, 1.71) 1.08 (0.92, 1.29) 1.10 (0.84, 1.42)	Age, BMI, smoking, alcohol, physical activity, diet, hypertension, season, calendar year, residence state
Andersen, 2012 [10]	DCH, Denmark	51,818	1993/97–June 2006 (mean=9.7 yrs)	56±8 52.6%	All cases in the National Diabetes Registry (NDR)[b] Confirmed DM: excluding those included in NDR only because of a blood glucose test	All cases 4,040 (800/10^5 py) Confirmed 2877 (570/10^5 py)	LUR NO_2 ('71-[e]) NO_2 ('91-[e]) NO_2 (1-[e]$_{yr}$)	14.5 (4.9) 15.3 (5.6) 15.4 (5.6)	All cases 1.00 (0.97, 1.03) 1.00 (0.97, 1.04) 0.98 (0.95, 1.01) Confirmed DM 1.04 (1.00, 1.08) 1.04 (1.01, 1.07) 1.02 (0.98, 1.05)	All cases 1.00 (0.94, 1.06) 1.00 (0.95, 1.07) 0.96 (0.91, 1.02) Confirmed DM 1.08 (1.00, 1.17) 1.07 (1.02, 1.13) 1.04 (0.96, 1.10)	Age, sex, BMI, waist-to-hip ratio, education, smoking, SHS, alcohol, physical activity, fruit, fat, calendar year
Coogan, 2012 [15]	BWHS, Los Angeles, US	3,992	1995–2005 (mean=10 yrs)	21–69 100%	Self-reported physician diagnosis at ≥30 yrs of age (96% confirmed)	183 (458/10^5 py)	LUR $PM_{2.5}$ NO_x	21.1 (1.3) 41.6 (12.4) ppb	Single pollutant 1.07 (0.97, 1.17) 1.25 (1.07, 1.46) Multi-pollutant[i] 1.02 (0.92, 1.13) 1.24 (1.05, 1.45)	Single pollutant 1.63 (0.78, 3.44) 1.20 (1.06, 1.36) Multi-pollutant[i] 1.15 (0.51, 2.58) 1.19 (1.04, 1.36)	Age, BMI, education, income, No of people/ household, neighborhood SES, smoking, alcohol, physical activity, family history
Chen, 2013 [13]	Residents in Ontario, Canada	62,012	1996/2005–2010 (mean=8 yrs)	55±14 55%	Ontario Diabetes Database[c]	6,310 (1302/10^5 py)	Satellite $PM_{2.5}$	Mean=10.6 (5.4)[h] (range: 2.6–19.1)	1.06 (1.01, 1.11)	1.11 (1.02, 1.21)	Age (strata), sex, race, marital status, BMI, education, income, smoking, physical activity, alcohol, diet, hypertension, urban residency
Prospective Study on Mortality from DM											
Raaschou-Nielsen, 2013 [27]	DCH, Denmark	52,061	1993/97–2009 (mean=13 yrs)	56.1 52.5%	Danish Register of Causes of Death (ICD-10 E10–E14)	122 (18/10^5 py)	LUR NO_2 ('71-[e]) NO_2 ('91-[e]) NO_2 (1-yr[e])	15.1 14.5 16.6	1.14 (0.99, 1.32) 1.10 (0.95, 1.27) 1.08 (0.94, 1.23)	1.31 (0.98, 1.76) 1.18 (0.92, 1.50) 1.14 (0.90, 1.44)	Age (time scale), sex, BMI, waist circumference, education, smoking, SHS, physical activity, alcohol, fruit, fat, hypertension, hypercholesterolemia, calendar year

1st author, Year [ref]	Population	Sample size	Study (follow-up) period	Age (y) Female (%)	Outcome Definition	No of cases (IR or %)	Exposure	Median (IQR) or Mean±SD (IQR)[g]	Adjusted RR (95% CI) per IQR increase	Adjusted RR (95% CI) per 10 unit increase	Covariate adjusted
Brook, 2013 [30]	The 1991 Canadian census mortality follow-up, Canada	2,145,400	1991–2001	≥25 51%	Canadian Mortality Database (ICD-9 250; ICD-10 E10–E14)	5,200 (2.4/10^5 py)	Satellite $PM_{2.5}$ (2001–2006)	8.7±3.9 (6.2)	1.28 (1.22, 1.35)	1.49 (1.37, 1.62)	Age (strata), sex (strata), aboriginal ancestry, visible minority, marital status, education, employment, occupation, income, contextual covariates
Cross-sectional study on prevalent DM											
Brook, 2008 [11]	Respir disease clinic patients from Hamilton and Toronto, Canada	Hamilton M: 2306 F: 2922 Toronto M: 1146 F: 1260	1992–1999	Median M: 61.5 F: 60.4 56% M: 61.2 F: 59.8 52%	Ontario Health Insurance Plan physician billing database and hospital discharge database (ICD-9 250)[d]	M: 395 (17) F: 445 (15) M: 227 (20) F: 185 (15)	LUR NO_2	M: 15.2 (3.2) F: 15.3 (3.0) M: 23.0 (4.2) F: 22.9 (3.9)	1.03 (0.85, 1.20) 1.08 (0.94, 1.26) 0.92 (0.74, 1.09) 1.23 (1.00, 1.50)	1.10 (0.60, 1.79) 1.33 (0.82, 2.16) 0.82 (0.48, 1.22) 1.71 (0.99, 2.84)	Age, BMI, neighborhood income
Dijkema, 2011 [17]	Residents of Westfriesland, Netherlands	8,018	1998–2000	Median: 58 (50–75) 51%	Self-reported physician diagnosis + fasting plasma glucose	619 (8)	LUR NO_2	15.2 (2.3) 140 (146) m	Q1: Reference Q2: 1.03 (0.82, 1.31) Q3: 1.25 (0.99, 1.56) Q4: 0.80 (0.63, 1.02)		Age, sex, income
Teichert, 2013 [28]	SALIA, Germany	363	2008–2009	74±2.6 100%	Fasting glucose ≥100 mg/dL or physician-diagnosis	174 (48.3)	LUR NO_2 NO_x $PM_{2.5(abs)}$[f] $PM_{2.5}$ $PM_{10-2.5}$ PM_{10}	37.8±9.8 69.3±30.0 2.8±0.8 34.0±3.1 18.2±3.3 51.0±4.9	1.47 (1.05, 2.05) 1.41 (1.01, 1.97) 1.26 (0.95, 1.67) 1.15 (0.81, 1.63) 1.13 (0.79, 1.60) 1.21 (0.87, 1.68)		Age, BMI, education, smoking, SHS, indoor mold, season of blood sampling
Ecological study on prevalent DM											
Pearson, 2010 [25]	All U.S. counties	2,754 counties	2004–2005	≥20 –	County-level prevalence of self-reported physician-diagnosis	Range: 3.0–14.8	Fused model, $PM_{2.5}$	County-level, Range: 2.5–17.7 15.1 14.5 16.6		2004: 1.15 (1.02, 1.32) 2005: 0.92 (0.75, 1.13)	Median age, % men, per capita income, % population >25 yrs with a high school diploma, race/ethnicity, health insurance, obesity, physical activity, latitude, population density

SALIA, Study on the Influence of Air Pollution on Lung, Inflammation and Aging; NHS, Nurses Health Study; HPFS, Health Professional Follow-up Study; DCH, Danish Diet, Cancer, and Health; BWHS, Black Women's Health Study; LUR, land-use regression; ICD, International Classification of Disease; IQR, interquartile range; SD, standard deviation; M, male; F, female; IR, incident rate; py, person-years; BMI, body mass index; SHS, second-hand smoke; SES, socioeconomic status; RR, relative risk.

[a] An elevated plasma glucose concentration was defined as a fasting plasma glucose > 140 mg/dL for cases diagnosed before or during 1997 or > 126 mg/dL for cases diagnosed after 1997, a random plasma glucose concentration > 200 mg/dL, or a plasma glucose concentration > 200 mg/dL after >2 hr of oral glucose tolerance testing.

[b] The National Diabetes Registry (NDR) included 1) diabetes hospital discharge diagnoses in the National Patient Register defined as ICD-10 (DE10-14, DH36.0, DO24) or ICD-8 (249 and 250); 2) chiropody for diabetes patients, five blood glucose measurements within 1 year, or two blood glucose measurements per year for 5 consecutive years, registered in the National Health Insurance Registry; or 3) second purchase of insulin or oral glucose-lowering drugs within 6 months, registered in the Register of Medicinal Product Statistics. Type 1 and type 2 diabetes are not distinguishable from NDR.

[c] The Ontario Diabetes Database included information on hospital admission with a diagnosis of diabetes (ICD-9 250 or ICD-10 E10–E14) or ≥2 physician claims for diabetes within a 2-year period. Gestational diabetes was excluded. It has been validated (86% sensitivity and 97% specificity).

[d] Subjects were classified as diabetic if the diagnosis had been made in two or more claim submissions by a general practitioner, one claim submission by a specialist, or in any hospitalization.

[e] Andersen et al [10] and Raaschou-Nielsen et al [27] examined three NO_2 variables averaged from 1971 to follow-up (NO_2 ('71-)), from 1991 to follow-up (NO_2 ('91-)) and a 1-yr before baseline (NO_2 (1-yr)).

[f] $PM_{2.5}$ based on filter absorbance (soot).

[g] Unit is $\mu g/m^3$ unless otherwise specified.

[h] IQR data for Chen (2013) obtained directly from the authors; IQR data for Raaschou-Nielsen (2013) assumed the same as those in Andersen (2012) given the same DCH cohort.

[i] Multi-pollutant models included two pollutants in models simultaneously.

Table 2

Observational studies of air pollution exposure and continuous glucose/insulin measures

1st author, Year [ref]	Population	Sample size	Study year	Age (y), Female (%)	Outcomes, mean±SD	Exposure	Lag or duration	Median (IQR) or Mean±SD[a]	Adjusted change (95% CI) per IQR increase	Adjusted change (95% CI) per 10 unit increase	Covariate adjusted
Chuang, 2011 [14]	SEBAS, Taiwan	1,023	2000	69±8.7 (54–90) 42.3%	Glucose: 107±37 mg/dl HbA1c: 5.8±1.4%	Monitor PM_{10} $PM_{2.5}$ NO_2 SO_2 O_3	1-y 1-y 1-y 1-y 1-y	67.8±33.5 35.3±15.9 24.5±9.5 ppb 4.9±3.6 ppb 23.0±6.8 ppb	Glucose: 22.9 (14.9, 30.8) 36.6 (19.2, 53.9) 17.0 (10.4, 23.7) 4.95 (−7.05, 17.0) 21.1 (12.0, 30.2) HbA1c: 1.40 (1.11, 1.69) 2.24 (1.47, 3.00) 1.08 (0.84, 1.33) 0.20 (−0.23, 0.64) 1.30 (0.97, 1.63)	Glucose: 4.8 (3.1, 6.4) 17.9 (9.4, 26.4) 13.3 (8.1, 18.5) 15.6 (−22.2, 53.3) 23.6 (13.4, 33.7) HbA1c: 0.29 (0.23, 0.35) 1.10 (0.72, 1.47) 0.84 (0.65, 1.03) 0.63 (−0.72, 1.98) 1.45 (1.08, 1.82)	Age, sex, BMI, smoking, alcohol, smooth functions of visit date, yearly temperature
Kim, 2012 [21]	KEEP, Korea	560	2008–2010	70.7 (60–87) 73.9%	Glucose: 96±21 mg/dl Insulin: 6.9±6.0 μU/ml HOMA-IR: 1.7±1.7	Monitor PM_{10} NO_2 O_3	Lag 4-d 7-d 5-d	39.9 (20.8) 35.2 (10.8) ppb 19.3 (15.1) ppb	Glucose: 1.98 (0.90, 3.06) 1.98 (0.90, 3.06) 3.42 (1.62, 5.04) Insulin: 0.21 (−0.22, 0.64) 0.72 (0.29, 1.14) 0.71 (0.02, 1.39) HOMA-IR: 0.14 (−0.003, 0.29) 0.28 (0.13, 0.42) 0.30 (0.06, 0.53)	Glucose: 0.95 (0.43, 1.47) 1.83 (0.83, 2.83) 2.26 (1.07, 3.34) Insulin: 0.10 (−0.11, 0.31) 0.67 (0.27, 1.06) 0.47 (0.01, 0.92) HOMA-IR: 0.07 (−0.001, 0.14) 0.26 (0.12, 0.39) 0.20 (0.04, 0.35)	Age, sex, BMI, cotinine, outdoor temperature, dew point temperature
Brook, 2013 [12]	Healthy adults living in rural Michigan	25	2009–2010	38±12 68% G: 84±8 mg/dl I: 15±6 μU/ml H: 3.3±1.5 Exposure G: 74±6 mg/dl I: 13±5 μU/ml H: 2.4±1.0 Post-exposure G: 79±7 mg/dl I: 15±6 μU/ml H: 2.8±1.2	Pre-exposure	Monitor $PM_{2.5}$	5-d long exposure	11.5±4.8		G: 5.4 (0.5, 10.3) I: 2.9 (0.2, 5.6) H: 0.7 (0.1, 1.3)	Age, BMI

SEBAS, Social Environment and Biomarkers of Aging Study; KEEP, Korean Elderly Environmental Panel Study; IQR, interquartile range; SD, standard deviation; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment-insulin resistance; exp, exposure; G, glucose; I, insulin; H, HOMA-IR; BMI, body mass index..

[a] Unit is $\mu g/m^3$ unless otherwise specified.

Table 3

Ecological studies of short-term air pollution exposure and diabetes mortality and morbidity

1st author, Year [ref]	Population	Study period	Age (y) Female (%)	Outcome	Total cases (/day)	Exposure[b]	Lag	Median (IQR) or Mean±SD[c]	Adjusted percent change (95% CI) per IQR increase	Adjusted percent change (95% CI) per 10 unit increase	Covariate adjusted
Ecological Study on Mortality from Diabetes											
Goldberg, 2001 [18]	Montreal, Canada	1984–1993	–	ICD-9: 250	3677	PM_{10} $PM_{2.5}$ $PM_{2.5\ (pred)}$[a] Sulfate $Sulfate_{(pred)}$[a]	1-d	28.5 (21.3) 14.7 (12.5) 15.4 (9.5) 2.2 (2.5) 3.1 (2.9)	13.2 (2.69, 24.8) 12.0 (3.01, 21.8) 5.94 (1.69, 10.4) 2.39 (−0.28, 5.13) 3.79 (0.69, 6.98)	5.99 (1.25, 11.0) 9.49 (2.40, 17.1) 6.26 (1.78, 10.9) 9.91 (−1.12, 22.2) 13.7 (2.40, 26.2)	Long-term trend, weather
Kan, 2004 [20]	Shanghai, China	2001–2002	–	ICD-9: 250	434 (0.59/day)	PM_{10} NO_2 SO_2	1-d	73 (68.5) 64 (29) 40 (31)	4.2 (0.0, 8.5) 3.8 (0.0, 7.8) 3.5 (−3.1, 10.4)	0.6 (0.0, 1.2) 1.3 (0.0, 2.6) 1.1 (−1.0, 3.2)	Long-term trend, weather, day of week
Maynard, 2007 [24]	Massachusetts, US	1995–2002	76.6 57%	ICD-9: 250, ICD-10: E10–E14	2,694	BC Sulfate	1-d	0.218 (0.203) 2.378 (2.259)	5.7 (−1.7, 13.7) 2.9 (−3.1, 9.5)		Apparent temperature, day of week
Goldberg, 2013 [19]	Montreal, Canada	1990–2003	65 and older –	ICD-10: E10–E14	38,883 (7.6/day)	$PM_{2.5}$ NO_2 CO SO_2 O_3	2-d distributed lags	6.9 (6.9) 36.0 (17.6) 5.4 (3.3) 11.5 (8.9) 29.8 (22.4)	1.83 (−0.53, 4.25) 3.45 (1.29, 5.66) 2.74 (0.75, 4.77) 1.89 (0.05, 3.76) −0.84 (−3.48, 1.88)	2.66 (−0.77, 6.21) 1.95 (0.73, 3.18) 8.54 (2.29, 15.2) 2.13 (0.06, 4.24) −0.38 (−1.57, 0.83)	Temporal variability, maximum temperature
Ecological Study on Hospital/Emergency Admissions for Diabetes											
Zanobetti, 2009 [29]	26 US communities	2000–2003	65 and older –	ICD-9: 250	46,192 (1.2/day)	$PM_{2.5}$ All Winter Spring Summer Autumn	2-d moving average	15.3±8.2 (range: 6.1–24)		2.74 (1.30, 4.20) −0.52 (−3.20, 2.24) 5.43 (1.97, 9.02) 1.85 (−1.02, 4.80) 4.78 (2.16, 7.46)	Long-term trend, season, temperature, dew-point temperature day of week,
Kloog, 2012 [22]	New England, US	2000–2006	77 (65 and older) 57%	ICD-9: 250	398,596	$PM_{2.5}$ $PM_{2.5}$	0-d 1-y average	8.55 (5.32) 9.65 (0.98)	0.51 (0.33, 0.69) 0.60 (0.31, 0.90)	0.96 (0.62, 1.30) 6.33 (3.22, 9.53)	Temperature, day of week, socioeconomic factors
Dales, 2012 [16]	Santiago, Chile	2001–2008	–	ICD-10: E10–E11	(1.79/day)	PM_{10} $PM_{2.5}$ NO_2 CO SO_2 O_3	6-d distributed lags	67.6 (27.7) 31.5 (16.7) 43.6 (25.0) ppb 0.96 (0.85)ppm 9.0 (4.7) ppb 64.4 (38.1) ppb	11.0 (6.9, 15.2) 10.8 (6.3, 15.5) 12.1 (5.0, 19.7) 14.6 (9.8, 19.7) 13.9 (6.4, 22.0) 6.9 (−1.8, 16.3)	3.8 (2.4, 5.3) 6.3 (3.7, 9.0) 4.7 (2.0, 7.5) –[d] 31.9 (14.1, 52.5) 1.8 (−0.48, 4.1)	Long-term trend, day of week, humidex

IQR, interquartile range; SD, standard deviation; ICD, International Classification of Disease.

All air pollution data used in ecological studies of short-term exposure were based on data from monitoring stations except $PM_{2.5}$(pred) and sulfate(pred).

[a] Predicted $PM_{2.5}$ and sulfate concentrations from $PM_{2.5}$ when measurements were not taken, based on coefficient of haze, the extinction coefficient and measured sulfate as predictors.

[b] All exposure measures in ecological studies of short-term air pollution were based on monitoring data.

[c] Unit is $\mu g/m^3$ unless otherwise specified.

[d] Percent change not reported because a 10-unit is too big compared to IQR (0.85).