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<http://dx.doi.org/10.1289/ehp.1307823>

Received: 30 October 2013

Accepted: 26 January 2015

Advance Publication: 27 January 2015

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Association between Ambient Air Pollution and Diabetes Mellitus in Europe and North America: Systematic Review and Meta-Analysis

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Running title: Ambient air pollution and diabetes: systematic review

Acknowledgment: The Federal Office for Forest, Environment and Landscape provided support for the salary costs related to this study. SAPALDIA is supported by the Swiss National Science Foundation; the Federal Office for Forest, Environment and Landscape; the Federal Office of Public Health; the Federal Office of Roads and Transport; the cantonal government of Aargau, Basel-Stadt, Basel-Land, Geneva, Luzern, Ticino and Zurich; the Swiss Lung League and the Lung Leagues of Basel-Stadt/Basel-Landschaft, Geneva, Ticino and Zurich. HCB and LGH are supported by unrestricted grants from Santésuisse.

Competing Financial Interest: The authors declare they have no actual or potential competing financial interests.

Abstract

Background: Air pollution is hypothesized to be a risk factor for diabetes. Epidemiological evidence is inconsistent and has not been systematically evaluated.

Objectives: We systematically reviewed epidemiological evidence on the association between air pollution and diabetes, and synthesized results of studies on type 2 diabetes (T2DM).

Methods: We systematically searched electronic literature databases (last search 29 April 2014) for studies reporting the association between air pollution (particle concentration or traffic exposure) and diabetes (type 1, type 2 or gestational). We systematically evaluated risk of bias and role of potential confounders in all studies. We synthesized reported associations with T2DM in meta-analyses using random effect models and conducted various sensitivity analyses.

Results: We included 13 studies (eight on T2DM, two on type 1, three on gestational diabetes), all conducted in Europe or North-America. Five studies were longitudinal, five cross-sectional, two case-control and one ecologic. Risk of bias, air pollution assessment, and confounder control varied across studies. Dose-response effects were not reported. Meta-analyses of three studies on PM_{2.5} (particulate matter <2.5 µm in diameter) and four studies on NO₂ (nitrogen dioxide) showed increased risk of T2DM by 8-10% per 10 µg/m³ increase in exposure [PM_{2.5}: 1.10 (95% CI: 1.02, 1.18); NO₂: 1.08 (95% CI: 1.00, 1.17)]. Associations were stronger in females. Sensitivity analyses showed similar results.

Conclusion: Existing evidence indicates a positive association of air pollution and T2DM risk albeit there is high risk of bias. High quality studies assessing dose-response effects are needed. Research should be expanded to developing countries where outdoor and indoor air pollution are high.

Introduction

Ambient air pollution ranks high among risk factors for the global burden of disease (Lim et al. 2012) and is linked to several chronic non-communicable conditions such as cardiovascular diseases (Bauer et al. 2010; Brook et al. 2010; Künzli et al. 2010), asthma (Bui et al. 2013; Jacquemin et al. 2012; Künzli et al. 2009), chronic obstructive pulmonary diseases (COPD) (Andersen et al. 2011; Schikowski et al. 2014; Zanobetti et al. 2008) and cancers including lung (Raaschou-Nielsen et al. 2013a), cervical and brain cancers (Raaschou-Nielsen et al. 2011). Persons with type 2 diabetes (T2DM) are at increased risk to develop micro- and macro vascular diseases and reduced lung function (Jones et al. 2014; Kinney et al. 2014). Air pollution has also been shown, to be more detrimental to diabetic patients, worsening their clinical outcomes (O'Neill et al. 2005; Raaschou-Nielsen et al. 2013b; Whitsel et al. 2009; Zanobetti and Schwartz 2001).

More recent evidence is supportive of an air pollution effect on diabetes risk. Experimental evidence show that possible pathways may include endothelial dysfunction, over-activity of the sympathetic nervous system (Rajagopalan and Brook 2012), immune response alterations in visceral adipose tissues; endoplasmic reticulum stress resulting in alterations in insulin transduction (Sun et al. 2009), insulin sensitivity and glucose metabolism; alterations in mitochondria and brown adipocytes (Liu et al. 2013; Rajagopalan and Brook 2012).

Papazafiropoulou et al (Papazafiropoulou et al. 2011) systematically reviewed the aetiologic association between environmental pollution and diabetes, taking into account studies on organic pollutants and secondary effects of air pollution on diabetic patients, published up to November 2010. They described a positive association between environmental pollution and prevalent diabetes, as well as increased morbidity and mortality among diabetic patients. A number of

pertinent studies have been published since this review and thus far there is, to the best of our knowledge, no meta-analysis of the available evidence. We therefore systematically identified and reviewed the epidemiological evidence on the association between air pollution and diabetes mellitus, and synthesized the results of studies on the association with type 2 diabetes.

Methods

Search strategy

We systematically searched electronic literature databases (MEDLINE, EMBASE and ISI web of knowledge) for pertinent literature published up to 03 February 2014. Terms used in this search included ‘air pollution’, ‘air pollutants’, ‘particulate matter’, ‘PM₁₀’, ‘PM_{2.5}’, ‘nitrogen dioxide’, ‘NO₂’, ‘NO_x’, ‘ozone’, ‘soot’, ‘smog’, ‘diabetes mellitus’, ‘diabetes’, ‘T1DM’, ‘T2DM’, ‘type 1 DM’, ‘type 2 DM’, ‘IDDM’, ‘NIDDM’, alone and in combination. We applied no filters for study designs. Reference lists of eligible articles were searched for further pertinent articles. After de-duplication, titles and abstracts were screened for eligibility and potentially relevant articles were retrieved as full texts. Screening was performed independently by two reviewers and any discrepancies were resolved by discussion.

Inclusion and exclusion criteria

We included only original research published in English as full publication in a peer-reviewed journal. We accepted any type of study design. In eligible studies, the definition of air pollution and diabetes mellitus had to be clearly stated. Air pollution had to be outdoor (ambient, including traffic-related) and we accepted any type of assessment including particle concentration in the air or indicators of long-term traffic exposure. Diabetes mellitus had to be physician-diagnosed or based on the use of anti-diabetic medications. We included any type of diabetes mellitus (type 1,

type 2 and gestational). Eligible studies had to report quantitative measures of association between air pollution and diabetes mellitus, and their 95% confidence intervals (or enough data to allow derivation of this association). We excluded studies that were based on the effect on blood markers, and not clearly defining clinical outcomes. Studies testing only whether diabetes status would modify the association between air pollution and health outcomes were not considered in this review. Animal studies were excluded.

For the meta-analysis, only studies on individual type 2 diabetes risk were included. We included all studies that quantified particle concentrations as ‘per x $\mu\text{g}/\text{m}^3$ ’ or ‘ppb’. If the diabetes type was not clearly stated, we considered diagnoses of diabetes in non-pregnant adults (≥ 18 years age) as diagnoses of T2DM since $>90\%$ of new diagnosis of adult diabetes is usually type 2 diabetes (Alberti and Zimmet 1998).

Data extraction

We extracted the following data from the eligible studies: year of study, study setting, study design, year of publication, population demographics, study definition of diabetes and assessment of air pollution exposure, confounder adjustments and effect modification assessments. We extracted data on the effect estimates (unadjusted and final model) of the association (and their 95% confidence intervals) between air pollution and diabetes.

Data were extracted independently by two reviewers and disagreements were resolved by discussion.

Meta-analysis

We used random-effects models to synthesize the associations between air pollution and T2DM (Lau et al. 1997). Random-effect models give more weight to smaller studies and have typically

wider confidence intervals because in addition to the within-study variance, they also consider potential variation between the true effects that all included studies estimate. We used fixed-effect models (which assume that all studies share a common true effect) in a sensitivity analysis.

We used risk ratios as measure of association across all studies. When hazard ratios and incidence risk ratios were reported, we directly considered them as risk ratios. Since diabetes is not very common, we considered reported odds ratios as equivalent to risk ratios. For studies with estimates of association from multiple particle concentration sources, we chose the estimates modelled at participants' residences (land-use regression, kriging or satellite-based estimates). We used the effect estimates reported by the study authors as "main model" or "fully adjusted model". We used estimates of association and their standard errors reported as 'per $10\mu\text{g}/\text{m}^3$ ' of exposure and we converted other reported quantities or units where necessary.

We described the between study heterogeneity using the I^2 metric and the between studies' variance using Tau^2 . We assessed publication bias using the Egger's test for asymmetry (Egger et al. 1997). We conducted sensitivity analyses including only studies that: (1) measured air pollution exposure before DM diagnosis; (2) comprised both males and females; (3) were longitudinal and (4) we applied a fixed-effect analysis. All analyses were performed with Stata version 12 (Stata Corporation, Texas) using the "metan" command. P values were two-tailed and $p < 0.05$ was considered nominally statistically significant.

For reporting, we followed the Meta-analysis of Observational Studies in Epidemiology (Stroup et al. 2000) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (Moher et al. 2010) guidelines.

Results

The database search yielded 636 records after de-duplication, which were screened on title/abstract level for eligibility (Figure 1). 16 potentially eligible articles were screened on full-text level and three were excluded (Figure 1). Thirteen studies were included (Table 1). There were five longitudinal studies (Andersen et al. 2012; Chen et al. 2013; Coogan et al. 2012; Krämer et al. 2010; Puett et al. 2011), five cross-sectional studies (Brook et al. 2008; Dijkema et al. 2011; Fleisch et al. 2014; Malmqvist et al. 2013; van den Hooven et al. 2009), two case-control studies (Hathout et al. 2002; Hathout et al. 2006) and one ecologic study (Pearson et al. 2010). Two studies were on type 1 diabetes (Hathout et al. 2002; Hathout et al. 2006); three studies on gestational diabetes (GDM) (Fleisch et al. 2014; Malmqvist et al. 2013; van den Hooven et al. 2009) and eight studies on T2DM (Andersen et al. 2012; Brook et al. 2008; Chen et al. 2013; Coogan et al. 2012; Dijkema et al. 2011; Krämer et al. 2010; Pearson et al. 2010; Puett et al. 2011). Seven non-ecological studies on T2DM were selected for quantitative synthesis (with the exclusion of Pearson et al. 2010). Air pollution estimates from these studies were based on Land-use regression (Andersen et al. 2012; Brook et al. 2008; Dijkema et al. 2011; Krämer et al. 2010; Puett et al. 2011), Kriging (Coogan et al. 2012) and satellite-derived estimates (Chen et al. 2013). All studies were conducted in Europe or North America. Tables 1, 2 and Supplemental Material, Table S1 provide an overview of the 13 eligible studies. Table 3 summarizes the data reported in the studies synthesized in meta-analyses.

Supplemental Material Table S2 provides an overview of potential sources of bias and how they were assessed by the 13 studies. These are discussed in detail below.

Bias due to outcome assessment

Some studies relied on self-reported, physician-diagnosed DM (Coogan et al. 2012; Dijkema et al. 2011; Krämer et al. 2010), while others linked participants to established databases to identify cases (Andersen et al. 2012; Brook et al. 2008; Chen et al. 2013; Hathout et al. 2002; Hathout et al. 2006; Malmqvist et al. 2013) [Table 2]. Additional steps were taken by some studies with self-reported outcomes, to test the validity of the DM diagnosis. These steps included sending a follow-up questionnaire with same questions about diabetes (Krämer et al. 2010) and confirmation from medical records provided by physicians (Coogan et al. 2012). Dijkema and colleagues further tested participants who did not report physician-diagnosed diabetes, to identify undiagnosed cases (Dijkema et al. 2011).

Bias due to exposure assessment

The reviewed studies used different approaches to assess exposure of participants to air pollution, including modelled concentrations of various particulate matters, NO_x, sulphates, ozone and various proxies to estimate traffic-related pollution, with varying buffer levels. The studies are also heterogeneous with regard to the lag time considered for exposure assessment. Only the Danish Cohort (Andersen et al. 2012) assessed the impact of different lag times, albeit with little evidence for substantial differences in effects [see Supplemental Material, Table S1]. In the absence of a biological basis for the latency between exposure and diagnosis of diabetes, different lag times should be tested. Overall, the diversity of exposure measurement makes it difficult to compare the reported effect estimates across these studies.

Bias due to confounder adjustment

1. Indoor air pollution and smoking

Beyond adjustment for basic DM risk factors at baseline [see Supplemental Material, Table S2], Krämer et al also adjusted for environmental tobacco smoking (ETS), indoor heating with fossil fuels, as well as occupational exposure to dust, fumes and extreme temperatures (Krämer et al. 2010), while Andersen et al also adjusted for ETS (Andersen et al. 2012). One study done in children considered ETS exposure (Hathout et al. 2006).

2. Demographics, physical activity and dietary factors

The longitudinal studies uniformly adjusted for age, body mass index (BMI) and sex (when study population includes both sexes). The studies on women did not adjust for dietary factors, and all longitudinal studies but one adjusted for alcohol consumption and physical activity [see Supplemental Material, Table S1]. The other studies assessed confounding by age and BMI except the case-control studies which did not consider the children's BMI in their models. The GDM studies mostly considered maternal alcohol consumption (but not dietary factors) whereas the cross-sectional T2DM studies did not consider both factors [see Supplemental Material, Table S1].

3. Socio-economic status

There was a uniform adjustment for socio-economic status in all studies, although on different scales. At the individual level, educational attainment as a socio-economic determinant was most commonly used across studies and a few studies additionally considered household income and ethnicity [see Supplemental Material, Table S1]. Few studies considered spatial socio-economic confounding in forms of unemployment rate, urban/rural residence, neighbourhood income and

neighbourhood socio-economic status score [see Supplemental Material, Table S1]. Overall, there was sufficient consideration for individual-level socio-economic status but the insufficient control of area-level socioeconomic status may increase the risk of bias.

4. Co-morbidities

Some co-morbidities associated with diabetes may also be associated with air pollution. These co-morbidities may include hypertension, myocardial infarction, stroke, asthma and chronic obstructive pulmonary disease (Brook et al. 2010; Pelle et al. 2012; Vojtkova et al. 2012). The longitudinal studies considered some of these co-morbidities [see Supplemental Material, Table S1]. Participants with co-morbidities were not excluded from any T2DM study.

Effect modification

Several studies reported stronger effects in women compared to men (Andersen et al. 2012; Brook et al. 2008; Chen et al. 2013; Dijkema et al. 2011). Other subgroups reported with potentially increased susceptibility include subjects with low education (Andersen et al. 2012; Chen et al. 2013; Krämer et al. 2010), COPD (Andersen et al. 2012; Chen et al. 2013), asthma (Andersen et al. 2012), non-smokers (Andersen et al. 2012), higher waist-to-hip ratio (Andersen et al. 2012), higher level of subclinical inflammation (Krämer et al. 2010) and subjects aged less than 50 years or more than 65 years (Chen et al. 2013) [see Supplemental Material, Table S1]. No study assessed interaction between different air pollutants, air pollutants and noise, or interaction between air pollutants and genetic polymorphisms.

Loss to follow-up

Losses to follow-up and healthy survivor bias present common problems in epidemiological studies. Puett et al reported a loss of less than 10 % in both studied cohorts over 20 years of

follow-up (Puett et al. 2011) while Coogan et al reported less than 20% loss of cohort over 10 years of follow-up (Coogan et al. 2012) . The other longitudinal studies did not report losses to follow-up. None of the studies included sensitivity analyses to estimate the effect of the healthy survivor bias.

Publication bias

Although selective reporting and publication bias cannot be ruled out, considering a high probability that negative findings will not be published, we found no indication for such sources of bias (p-value of Egger's test >0.2). Some studies reported negative findings. However, most studies had several markers of air pollution available and it remains unclear if some markers have been measured but not reported, thus, some selective reporting may have occurred.

Meta-analysis of studies reporting the association of air pollution and risk of type 2 diabetes.

Results of seven studies reporting on risk of type 2 diabetes (three on PM_{2.5} and four on NO₂) were considered for quantitative synthesis. All studies synthesized for PM_{2.5} were longitudinal. For NO₂, two were longitudinal and two were cross-sectional.

The pooled relative risks of type 2 diabetes per 10 µg/m³ increase in exposure to PM_{2.5} (Figure 2) and NO₂ (Figure 3) were 1.10 (95% CI: 1.02, 1.18) and 1.08 (95% CI: 1.00, 1.17) respectively. The effect was more pronounced in females than in males [NO₂: 1.15 (95% CI: 1.05, 1.27) vs. 0.99 (95% CI: 0.93, 1.07); PM_{2.5}: 1.14 (95% CI: 1.03, 1.26) vs. 1.04 (95% CI: 0.93, 1.17)] respectively per 10µg/m³ increase in exposure. The relative risks were similar across all sensitivity analyses (Table 4). We observed substantial statistical heterogeneity with NO₂ studies (Table 4). Egger's test was consistently >0.2 (p-value) in all cases.

Discussion

This systematic review considered 13 studies on different types of diabetes. The identified epidemiological evidence is highly diverse: levels, timing and assessment of exposure varied as well as the outcome definitions, measures of association and degree of confounder control. The studies included persons with different age ranges and settings, and some population included only women. While there is a risk of bias, the results of the meta-analyses indicate a positive association between traffic-related air pollution and T2DM.

Pathophysiologic mechanisms of DM- air pollution association

There is strong evidence supporting the role of inflammation in T2DM (Donath and Shoelson 2011; Sjöholm and Nystrom 2006). Chronic activation of inflammatory mechanisms can contribute to chronic insulin resistance and subsequent T2DM. Air pollution has been shown to be inflammatory (Liu et al. 2013; Rajagopalan and Brook 2012). Its potential mechanisms in mediating type 2 diabetes include pulmonary and systemic inflammation, directly releasing cytokines, alterations in glucose homeostasis through defective insulin signalling in tissues, immune cells activation in visceral adipose tissues potentiating inflammation (Sun et al. 2009; Xu et al. 2010; Yan et al. 2011), and endoplasmic reticulum stress in the lung and liver in relation with hepatocyte and alveolar cells (Liu et al. 2013; Rajagopalan and Brook 2012). PM_{2.5} also acts as a hypothalamic stressor, inducing peripheral inflammation and abnormalities in glucose metabolism (Liu et al. 2013; Purkayastha et al. 2011). PM_{2.5} was also shown to mediate dysfunctional brown adipose and mitochondrial tissues (Liu et al. 2013; Rajagopalan and Brook 2012), which is one of the systemic pathologies in type 2 diabetes (Lowell and Shulman 2005).

Chuang and colleagues demonstrated that exposure to air pollution (PM₁₀ and O₃) exposure leads to alteration in blood pressure, blood lipids and haemoglobin A1c (Chuang et al. 2010), a marker

of blood glucose control. Kelishadi and colleagues found positive associations between exposure to PM₁₀, NO₂, and insulin resistance among children in Iran (Kelishadi et al. 2009). Thiering et al later found a positive association between residential proximity to traffic, particulate matter (PM₁₀), NO₂ and risk of insulin resistance (HOMA-IR) among children that were part of a birth cohort in Germany (Thiering et al. 2013). Exposure to traffic-related air pollution is also associated with impaired glucose tolerance in pregnancy (Fleisch et al. 2014). Experimental evidence also exists for the association of air pollution and type 1 diabetes. Ozone is known to alter T cell dependent immune response, predisposing to autoimmune diseases (Krishna et al. 1998). It may also damage the beta cells of the insulin possibly as a result of pulmonary reactive oxidative species production and oxidative stress, leading to reduced insulin secretion (Brenner et al. 1993; Kelishadi et al. 2009). Together with SO₄, it may have apoptotic properties on the beta cells (Hathout et al. 2006). The use of antioxidant prophylaxis for T1DM also points to the possibility of oxidative or inflammatory mechanisms in T1DM (Albright and Goldstein 1996).

Strengths and limitations

Although we have applied a very broad search strategy and accepted any study design, there are few published studies on the association of air pollution with T1DM or GDM. In addition, some studies did not allow distinguishing adult T1DM from T2DM. Only three of the seven synthesized studies explicitly analysed the T2DM risk (Coogan et al. 2012; Dijkema et al. 2011; Krämer et al. 2010). However, since >90% of adult diabetes diagnoses are T2DM, this is unlikely to substantially impact the conclusions. Overall, the available data are not sufficient to evaluate associations with these diabetes types.

Our analysis on the association with T2DM was based on results from primary studies with unclear to high risk of bias and high diversity among the included studies. We took this into

account by using effect estimates modelled to participants' residences, converting all effect estimates to a comparable unit (per 10 $\mu\text{g}/\text{m}^3$ of exposure), stratifying analyses by sex, including only longitudinal studies and performing other sensitivity analyses.

The high diversity among the studies was reflected in our observation of substantial heterogeneity in the meta-analysis for NO_2 [Table 4], which synthesized longitudinal and cross-sectional data. This was not observed for $\text{PM}_{2.5}$ where all studies were longitudinal. However, the number of studies was too small to further analyse this heterogeneity

Prospects

Future studies should report scales of exposure assessment (pollutant quantification and traffic exposure proxies) that allow direct comparisons with existing evidence. It would be important to apply comparable models in assigning exposure to participants. Ideally, traffic distance measures should be replaced by objective particle concentration measures and models of near-road traffic-related pollutants such as ultrafine particles of elemental carbon. Also, it would be important to consider various time lags for exposure.

The studies on T1DM found associations with ozone and sulphates. These pollutants can be included in the future models for T2DM, since pollutants usually occur together in different proportions. Carbon monoxide, lead, oxidative metals, volatile organic compounds and polycyclic aromatic hydrocarbons are other traffic-related pollutants, which may be more deleterious to health but have been given less consideration.

Adjusting for noise exposure is also essential since air pollution and noise can be correlated (Foraster 2013; Kim et al. 2012; Ross et al. 2011; Tetreault et al. 2013) and share health effects. Sorensen et al (Sorensen et al. 2013) recently reported a positive association between road-traffic

noise and incident diabetes while another large meta-analysis of 10 epidemiologic studies by Cappuccio et al found that both quality and quantity of sleep, which are related to noise, were significant predictors of the risk of T2DM (Cappuccio et al. 2010). Consideration of noise is thus necessary in assessing the health effects of air pollution.

Also, socio-economic variables should be adjusted on the spatial scale, apart from individual-level adjustment. Consideration for this spatial confounding is necessary when individual differences in health outcome are associated with neighbourhood characteristics such as neighbourhood socio-economic status (Sheppard et al. 2012). It is crucial that studies on diabetes risk consider established diabetes risk factors including obesity, physical activity and nutrition. Active and passive smoking should be considered when the assessing the effect of air pollution. Lack of information on these creates a high risk for bias.

Other forms of bias such as the healthy survivor effect should be taken into account especially by longitudinal studies. Raaschou-Nielsen and colleagues (Raaschou-Nielsen et al. 2013b) demonstrated associations between diabetes mortality and NO_x exposure, thus, diabetes patients exposed to air pollution could die and no longer participate, resulting in incorrect estimates of association if not taken into consideration.

No included study on this topic was done in developing countries. For generalizability of evidence, research should be extended to developing countries where air pollution (including indoor) is high. This could also help in understanding effects of different air pollution compositions. Indoor air pollution is also associated with diabetes as well as cardiovascular diseases (Lee et al. 2012) and is highly prevalent in the developing nations (Lim et al. 2012).

Considering the ambiguity in dose-response relationship in air pollution studies (Smith and Peel 2010), future studies should assess air pollution diabetes association in a dose-response manner. This will help in identifying the point in the dose spectrum where control will yield the most benefits for health policy (Smith and Peel 2010).

Overall, the existing evidence indicates a positive association of air pollution and T2DM risk, although there is high risk of bias. High quality longitudinal studies are needed (taking into consideration sources and composition of air pollution as well as biomarkers) to improve our understanding of this association.

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Table 1. Characteristics of the studies on the relationship between air pollution and diabetes mellitus.

Source	Location	Year of study	Study design and duration of follow up	Population (N) and age of participants
Krämer et al. 2010 ^a	Ruhrgebiet, Germany	1990-2006	Longitudinal - Study on the Influence of Air Pollution on Lung Inflammation and Aging. Follow-up: 16 years	N= 1775 Caucasian women without T2DM at baseline, aged 54-55 years.
Andersen et al. 2012 ^a	Copenhagen and Aarhus, Denmark	(1993-1997) -2006	Longitudinal- Danish Diet, Cancer and Health cohort. Follow-up: 9.7 years	N=51,818 Caucasians without DM at baseline, aged 50-65 years
Puett et al. 2011 ^a	Metropolitan Statistical Areas (MSA) in North-Eastern and Mid-Western states of USA	1989-2009	Longitudinal, with 2 cohorts- Nurses' Health Study and Health Professionals Follow-up Study. Follow-up: 20 years.	N=74,412 female nurses aged 30-55 years and 15,048 male health professionals aged 40-75 years, without T2DM at baseline.
Coogan et al. 2012 ^a	Los Angeles, USA	1995-2005	Longitudinal - Black Women's Health Study. Follow-up: 10 years	N=3992 African-American women, without DM at baseline and aged 21-69 years.
Chen et al. 2013 ^a	Ontario, Canada	(1996-2005) – 2010	Longitudinal. Follow-up: 8 years.	N= 62,012 Canadians without DM, aged >=35 years.
Brook et al. 2008 ^a	Hamilton and Toronto, Ontario, Canada	1992-1999	Cross-sectional.	N=7634 patients who attended two respiratory clinics in Hamilton and Toronto, aged 40 and above.
van den Hooven et al. 2009	Rotterdam, Netherlands	2002-2006	Cross-sectional- Generation R study.	N=7,399 pregnant women, who had delivery date in the study period, aged 21-38 years.
Dijkema et al. 2011	Westfriesland, Netherlands	1998-2000	Cross-sectional- Hoorn Screening Study for T2DM.	N=8018 Caucasians residents aged 50-75 years.
Malmqvist et al. 2013	Scania, Sweden	1999-2005	Cross-sectional- The Swedish Medical Birth Registry.	N=81,110 women who had singleton deliveries during the study period.
Hathout et al. 2006	California, USA	2002-2003	Case-Control Follow-up: Retrospectively from birth till diagnosis of T1DM.	N= 402 children (102 with T1DM and 300 age- matched controls), aged 1-12 years, receiving care at Loma Linda University Paediatric Centre.

Source	Location	Year of study	Study design and duration of follow up	Population (N) and age of participants
Hathout et al. 2002	California, USA	2002	Case-control. Follow-up: Retrospectively from birth till diagnosis of T1DM.	N=100 children (61 cases: 30 had onset <or= 5 years and 31> 5 years) (39 age-matched controls: 19 were <or= 5 years and 20 were >5 years) receiving care at Loma Linda University Paediatric Centre.
Fleisch et al. 2014	Boston, USA	1999-2002	Cross-sectional. Project Viva Cohort	N=2093 second-trimester pregnant women without known diabetes.
Pearson et al. 2010	USA	2004-2005	Ecologic	N=3082 counties of USA

T2DM: Type 2 diabetes mellitus.

^aIncluded in meta-analysis.

Table 2. Exposure and outcome definitions.

Source	Outcome	Definition of outcome	Exposure	Definition of exposure	Exposure estimates
Krämer et al. 2010 ^a	Incident T2DM	Self-reported, physician-diagnosed T2DM	PM ₁₀ , PM, PM _{2.5} , NO ₂ and traffic exposure	5-year means of PM ₁₀ and NO ₂ in an 8km grid from monitoring stations, prior to baseline.	Median(P25-P75) Monitoring stations (µg/m ³): PM ₁₀ : 46.9 (44-54.1) NO ₂ : 41.7 (23.3-48.2)
				Traffic PM and NO ₂ in a 1km grid, in 1 year, from emission inventory.	Traffic emission inventory (tons/year/ km ²): PM:0.54 (0.22-1.09)
				Traffic PM _{2.5} and NO ₂ ^b from a (1-year measurement) LUR model. Distance from the next major road with >10,000 cars per day.	NO ₂ :12 (5.4-24.4) LUR Soot (10 ⁻⁵ m): 1.89 (1.67-2.06) NO ₂ (µg/m ³): 34.5 (23.8-38.8) % of participants living <100m from busy road: 15.8
Andersen et al. 2012 ^a	Incident DM	Confirmed DM cases from the Danish National Diabetes Register.	NO ₂ , NO _x , Traffic exposure	35 ^b - and 15-year mean levels of NO ₂ and NO _x , from the Danish AirGIS model prior to baseline.	Median (IQR) 35-year NO ₂ and NO _x (µg/m ³): 14.5 (4.9) and 20.9 (11.4). 15-year NO ₂ and NO _x (µg/m ³): 15.3 (5.6) and 22.1 (12).
				1-year mean NO ₂ and NO _x at baseline	1-year NO ₂ and NO _x at baseline (µg/m ³): 15.4 (5.6) and 20.3 (10.9)
				1-year mean NO ₂ and NO _x at follow-up	1-year NO ₂ and NO _x at follow-up (µg/m ³): 15.2 (5.7) and 21.5 (12)
				Major road (with annual traffic density of ≥10,000) within 50m of residence	% major road within 50m: 8.1
				Traffic load within 100m of residence (10 ³ vehicle km/day)	Traffic load within 100m ((10 ³ vehicle km/day): 0.34 (1.3)
Puett et al. 2011 ^a	Incident T2DM	DM according to the National Diabetes Data Group Criteria ^c	PM _{2.5} , PM ₁₀ , PM _{10-2.5}	Average PM _{2.5} ^b , PM ₁₀ and PM _{10-2.5} concentrations, from LUR model, 12 months prior to diagnosis.	Means (SD) PM _{2.5} (µg/m ³): 18.3 (3.1) for HPFS and 17.5 (2.7) for NHS. PM ₁₀ (µg/m ³): 28.5 (5.5) for HPFS and 26.9 (4.8) for NHS. PM _{10-2.5} (µg/m ³): 10.3 (3.3) for HPFS and 9.4 (2.9) for NHS.

Source	Outcome	Definition of outcome	Exposure	Definition of exposure	Exposure estimates
Coogan et al. 2012 ^a	Incident T2DM	Self-reported, physician-diagnosed T2DM	PM _{2.5} , NO _x , traffic exposure	1 year-mean PM _{2.5} ^b during follow-up, assigned by kriging model.	Means (SD) PM _{2.5} (µg/m ³): 20.7 (2.1) Median (P25-P75) PM _{2.5} (µg/m ³): 21.1(20.3-21.6)
				1 year-mean NO _x the year after follow-up, assigned by LUR model.	Means (SD) NO _x (ppb): 43.3 (11). Median (P25-P75) NO _x (ppb): 41.6 (36.9-49.2).
Chen et al. (2013) ^a	Incident DM	Physician-diagnosed DM from Ontario database	PM _{2.5}	6-year mean PM _{2.5} ^b during baseline/ follow-up, obtained from satellite-based estimates at 10x10 km resolution.	Mean (range) PM _{2.5} (µg/m ³): 10.6 (2.6-19.1)
Brook et al. (2008) ^a	Prevalent DM	Physician-diagnosed DM from Ontario Health Insurance Plan and Ontario Health Discharge Database.	NO ₂	NO ₂ ^b assigned by LUR models developed from mean field measurements within 3 years, from Hamilton and Toronto.	Median (P25-P75) NO ₂ (ppb) Males: Hamilton: 15.2 (13.9-17.1). Toronto: 23 (20.8-25) Females: Hamilton: 15.3 (14-17). Toronto: 22.9 (20.8-24.7).
van den Hooven et al. 2009	Prevalent gestational DM (GDM)	GDM diagnosed according to the Dutch midwifery and obstetric guidelines	Traffic exposure	Distance-weighted traffic density (DWTd) within a 150-meter radius around residence (vehicles/24h*m).	Median (P25-P75) DWTd (vehicles/24h*m): 5.5x10 ⁵ (1.6x10 ⁵ -1.2x10 ⁶).
				Proximity to a major road (>10,000 vehicles/day)	Proximity to a major road (m): 143 (74-225).
Dijkema et al. 2011	Prevalent T2DM	Self-reported physician-diagnosed T2DM. Laboratory-based diagnosis for undetected cases.	NO ₂ , Traffic exposure	1 year mean NO ₂ assigned by LUR model.	Median (P25-P75) NO ₂ (µg/m ³): 15.2 (14.2-16.5).
				Distance to the nearest main road (≥5,000 vehicles/day).	Distance to nearest main road (m): 140 (74-220).
				Traffic flow at the nearest main road (vehicles/24h).	Traffic flow at the nearest main road (10 ³ vehicles/ 24h): 7.31 (5.87-9.67).
				Total traffic per 24 hours on all roads within a 250 m circular buffer around the address.	Traffic within 250m buffer (10 ³ vehicles/24h): 680 (516-882).

Source	Outcome	Definition of outcome	Exposure	Definition of exposure	Exposure estimates
Malmqvist et al. 2013	Prevalent GDM	GDM as defined in the Swedish Medical Birth Registry	NO _x , Traffic exposure	Monthly and Trimester means of NO _x assigned by dispersion modelling at a spatial resolution of 500x500 m over the duration of the pregnancy.	Quartiles of NO _x exposure (µg/m ³): Q1: 2.5-8.9 Q2: 9.0-14.1 Q3: 14.2-22.6 Q4: >22.7
				Traffic density within a 200m radius.	Categories of traffic density within 200 m (vehicles/min): 1: no road 2: <2 3: 2-5 4: 5-10 5: >10
Hathout et al. 2006	Prevalent T1DM	Physician-diagnosed T1DM from the database of Loma Linda University Paediatric Centre.	O ₃ , NO ₂ , SO ₂ , SO ₄ and PM ₁₀	Average monthly pollutant exposure (obtained from Environmental Protection Agency and California Air Resources Board) from birth till diagnosis for cases and till enrolment for controls, assigned to residential zip codes.	Mean (95% CI) For Cases: O ₃ : 29.4(28, 30.8) ppb SO ₄ : 3.6(3.4, 3.87) µg/m ³ SO ₂ : 1.6(1.41, 1.75) ppb NO ₂ : 30.3(28.4, 32.3) ppb PM ₁₀ : 48.6 (45.9, 51.3) µg/m ³ . For Controls: O ₃ : 25.8(25.2, 26.3) ppb SO ₄ : 3.3(3.2, 3.36) µg/m ³ SO ₂ : 1.5(1.42, 1.5) ppb NO ₂ : 29.7(29.1, 30.4) ppb PM ₁₀ : 47.4(46.3, 48.5) µg/m ³
Hathout et al. 2002	Prevalent T1DM	Physician-diagnosed T1DM from the database of Loma Linda University Paediatric Centre.	O ₃ , NO ₂ , SO ₂ , SO ₄ and PM ₁₀	Average monthly pollutant exposure (obtained from Environmental Protection Agency and California Air Resources Board) from birth till diagnosis for cases and till enrolment for controls, assigned to residential zip codes.	Mean (SD) For Cases: O ₃ : 32.5 (5.22) ppb SO ₄ : 5.52 (0.75) µg/m ³ SO ₂ : 0.67 (0.55) pphm NO ₂ : 23.7 (7.91) ppb PM ₁₀ : 59.3 (12.9) µg/m ³ . For Controls: O ₃ : 26.7 (9.6) ppb SO ₄ : 5.88 (1.04) µg/m ³ SO ₂ : 1.29 (0.92) pphm NO ₂ : 24.7 (7.26) ppb PM ₁₀ : 49.6 (14.7) µg/m ³

Source	Outcome	Definition of outcome	Exposure	Definition of exposure	Exposure estimates
Fleisch et al. 2014	Prevalent GDM	Failed GCT ^d with ≥ 2 high values on the OGTT ^e		PM _{2.5} and black carbon from central sites within 40km of residence.	Mean (SD) From central sites: PM _{2.5} : 10.9 (1.4) $\mu\text{g}/\text{m}^3$ Black carbon: 0.9 (0.1) $\mu\text{g}/\text{m}^3$.
				PM _{2.5} and black carbon from spatio-temporal models	From spatio-temporal models: PM _{2.5} : 11.9 (1.4) $\mu\text{g}/\text{m}^3$ Black carbon: 0.7 (0.2) $\mu\text{g}/\text{m}^3$.
				Neighbourhood traffic density [(vehicles/day)*km] within 100m.	Traffic density: 1,621(2,234) [(vehicles/day)*km]
				Home roadway proximity ($\leq 200\text{m}$)	Roadway proximity: 281(13)
Pearson et al. 2010	Prevalent DM	County-level DM prevalence from the Centers for Disease Control and Prevention.	PM _{2.5}	County annual mean level of PM _{2.5} obtained from EPA as 36 km model, 12 km model and surface monitor data.	PM _{2.5} ($\mu\text{g}/\text{m}^3$): 2004: 36km model: Q1 mean=7.71; Q4 mean=12.11. 12km model: Q1 mean=7.78; Q4 mean=11.77. Ground data: Q1 mean=9.43; Q4 mean=12.69. 2005: 36km model: Q1 mean=7.69; Q4 mean=12.75. 12km model: Q1 mean=8.41; Q4 mean=12.38. Ground data: Q1 mean=9.51; Q4 mean=13.65.

PM: particulate matter; PM₁₀: particulate matter <10 μm in diameter; PM_{10-2.5}: particulate matter between 2.5 and 10 μm in diameter; PM_{2.5}: particulate matter <2.5 μm in diameter; NO₂: nitrogen dioxide; NO_x: nitrogen oxides; O₃: ozone; SO₂: sulphur dioxide; SO₄: sulphate; DM: diabetes mellitus; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; GDM: gestational diabetes mellitus; LUR: land-use regression; AirGIS: Air geographic information system; EPA: Environmental Protection Agency.

^aStudies included in meta-analysis; ^bAir pollution estimates pooled in the meta-analysis; ^cElevated plasma glucose concentration on at least two different occasions, one or more DM symptoms and a single elevated plasma glucose concentration, or treatment with hypoglycaemic medication.

^dGlucose challenge test: serum glucose 1hour after a non-fasting 50g oral glucose load; ^eOral glucose tolerance test: serum glucose 3hours after a fasting 100g glucose load. P25: 25th percentile; P75: 75th percentile.

Table 3. Data synthesized for meta-analysis.

Source	Population	Pollutant	Assignment of individual exposure	Reported fully-adjusted estimate [OR (95% CI)] / [HR (95% CI)] / [IRR (95% CI)] ^a
Krämer et al. 2010	Females	NO ₂	Land-use regression model	1.42 (1.16, 1.73) per 15 µg/m ³ of exposure
Andersen et al. 2012	Females	NO ₂	Land-use regression model	1.07 (1.01, 1.13) per 4.9 µg/m ³ of exposure
	Males	NO ₂	Land-use regression model	1.01 (0.97, 1.07) per 4.9 µg/m ³ of exposure
	Both	NO ₂	Land-use regression model	1.04 (1.00, 1.08) per 4.9 µg/m ³ of exposure
Brook et al. 2008	Females	NO ₂	Land-use regression model	1.04 (1.00, 1.08) per 1 ppb of exposure
	Males	NO ₂	Land-use regression model	0.99 (0.95-1.03) per 1 ppb of exposure
	Both	NO ₂	Land-use regression model	1.015 (0.98, 1.049) per 1 ppb of exposure
Puetz et al. 2011	Females	PM _{2.5}	Land-use regression model	1.02 (0.94, 1.09) per 4 µg/m ³ of exposure
	Males	PM _{2.5}	Land-use regression model	1.07 (0.92, 1.24) per 4 µg/m ³ of exposure
	Both	PM _{2.5}	Land-use regression model	1.03 (0.96, 1.10) per 4 µg/m ³ of exposure
Chen et al. 2013	Females	PM _{2.5}	Satellite-based estimates	1.17 (1.03, 1.32) per 10 µg/m ³ of exposure
	Males	PM _{2.5}	Satellite-based estimates	1.03 (0.91, 1.16) per 10 µg/m ³ of exposure
	Both	PM _{2.5}	Satellite-based estimates	1.11 (1.02, 1.21) per 10 µg/m ³ of exposure
Coogan et al. 2012	Females	PM _{2.5}	Kriging model	1.63 (0.78, 3.44) per 10 µg/m ³ of exposure
Dijkema et al. 2011	Females	NO ₂	Land-use regression model	1.03 (0.90, 1.16) per 10 µg/m ³ of exposure
	Males	NO ₂	Land-use regression model	0.97 (0.87, 1.09) per 10 µg/m ³ of exposure
	Both	NO ₂	Land-use regression model	1.00 (0.94, 1.06) per 10 µg/m ³ of exposure

^aAll estimates were converted to per 10µg/m³ of exposure for meta-analysis. PM_{2.5}: particulate matter <2.5µm in diameter; NO₂: nitrogen dioxide. Estimates from Dijkema et al were derived from reported non-linear estimates.

Table 4. Sensitivity analyses and heterogeneity measures.

Analyses	Population	NO ₂ OR [95% CI]	Heterogeneity measures (I ² (%); p-value; Tau ²)	PM _{2.5} OR [95% CI]	Heterogeneity measures (I ² (%); p-value; Tau ²)
Main model (random-effects)	Males	0.99 [0.93, 1.07]	0; 0.744; 0	1.04 [0.93, 1.17]	0; 0.486; 0
	Females	1.15 [1.05, 1.27]	46.1; 0.135; 0.0042	1.14 [1.03, 1.26]	0; 0.405; 0
	Overall	1.08 [1.00, 1.17]	58.4; 0.025; 0.0063	1.10 [1.02, 1.18]	0; 0.473; 0
Studies assessing air pollution before DM diagnosis	Males	1.02 [0.92, 1.13]	NA; NA; 0	1.04 [0.93, 1.17]	0; 0.486; 0
	Females	1.20 [1.10, 1.30]	12.5; 0.285; 0.0006	1.13 [1.02, 1.25]	0; 0.344; 0
	Overall	1.12 [1.05, 1.19]	69.8; 0.036; 0.008	1.09 [1.01, 1.18]	0; 0.489; 0
Studies including both men and women	Males	0.99 [0.93, 1.07]	0; 0.744; 0	1.04 [0.93, 1.17]	0; 0.486; 0
	Females	1.11 [1.01, 1.23]	30.2; 0.238; 0.0023	1.13 [1.02, 1.25]	0; 0.344; 0
	Overall	1.05 [0.98, 1.12]	34.9; 0.175; 0.0024	1.09 [1.01, 1.18]	0; 0.489; 0
Only longitudinal studies	Males	1.02 [0.92, 1.13]	NA; NA; 0	1.04 [0.93, 1.17]	0; 0.486; 0
	Females	1.20 [1.10, 1.30]	12.5; 0.285; 0.0006	1.14 [1.03, 1.26]	0; 0.405; 0
	Overall	1.12 [1.05, 1.19]	69.8; 0.036; 0.008	1.10 [1.02, 1.18]	0; 0.473; 0
Meta-analysis using fixed effect model	Males	1.00 [0.93, 1.07]	0; 0.744	1.04 [0.93, 1.17]	0; 0.486
	Females	1.15 [1.07, 1.23]	46.1; 0.135	1.14 [1.03, 1.26]	0; 0.405
	Overall	1.07 [1.02, 1.13]	58.4; 0.025	1.10 [1.02, 1.18]	0; 0.473

I² is the proportion of total variability explained by heterogeneity. Tau² is a measure of among-study variance.

NA-not applicable.

Figure Legends

Figure 1. Results of systematic literature search.

Figure 2. PM_{2.5} and risk of type 2 diabetes. Where I-square is the variation in effect estimates attributable to heterogeneity, D+L overall is the pooled random effect estimate of all studies. I-V overall is the pooled fixed effects estimate of all studies. %Weight (D+L) is the weight assigned to each study, based on the inverse of the within- and between-study variance. The size of the grey boxes around the point estimates reflects the weight assigned to each study. The summarised studies were adjusted for: age, sex, body mass index, smoking, alcohol consumption and socio-economic status.

Figure 3. NO₂ and risk of type 2 diabetes. Where I-square is the variation in effect estimates attributable to heterogeneity, D+L overall is the pooled random effects estimate of all studies. I-V overall is the pooled fixed effects estimate of all studies. %Weight (D+L) is the weight assigned to each study, based on the inverse of the within- and between-study variance. The size of the grey boxes around the point estimates reflects the weight assigned to each study. The summarised studies were adjusted for: age, sex, body mass index, smoking and socio-economic status.

Figure 1: Results of systematic literature search.

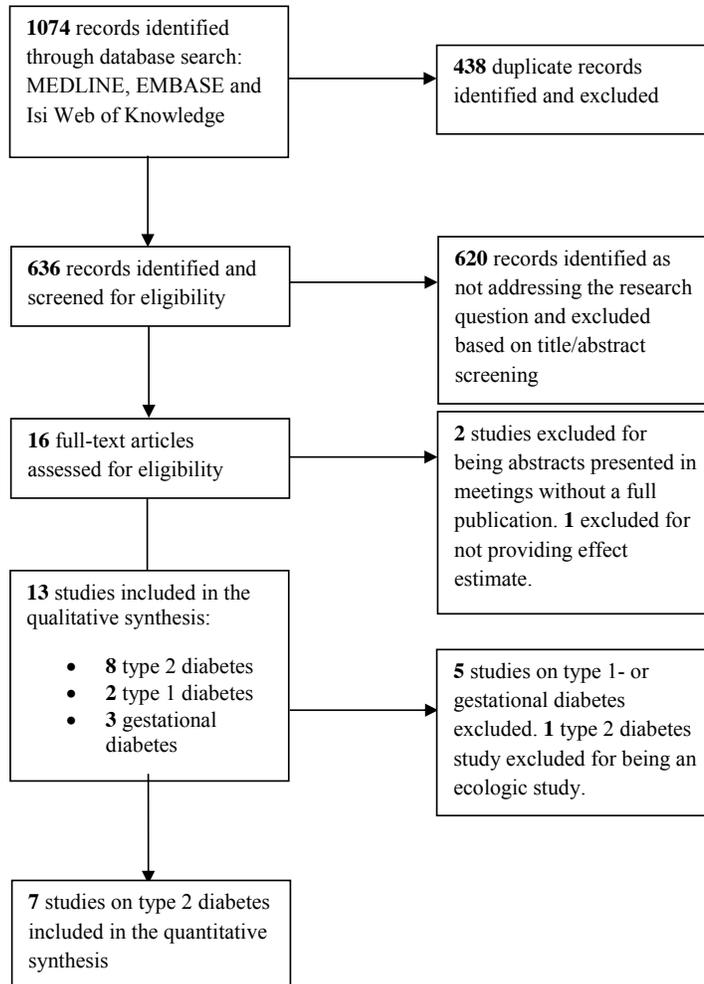


Figure 2.

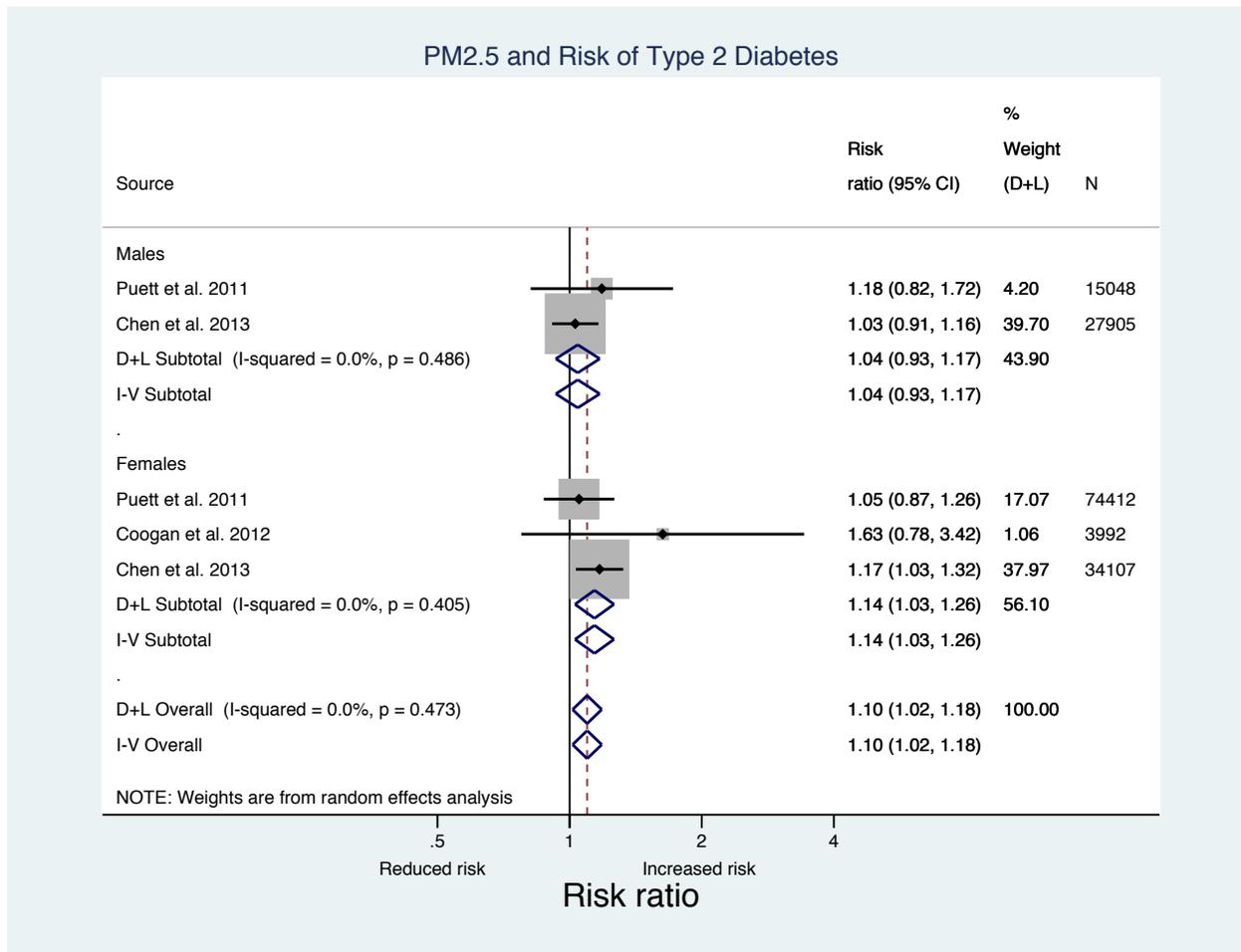


Figure 3.

