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Air Pollution, Oxidative Stress, and Diabetes: a Life Course Epidemiologic Perspective

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Abstract

Purpose of Review Ambient air pollution is strongly linked to cardiovascular and respiratory diseases. We summarize available published evidence regarding similar associations with diabetes across the life course.

Recent Findings We performed a life-course survey of the recent literature, including prenatal, gestational, childhood/adolescence, and adult exposures to air pollution. Oxidative stress is identified as a key factor in both metabolic dysfunction and the effects of air pollution exposure, especially from fossil fuel combustion products, providing a plausible mechanism for air pollution-diabetes associations. The global burden of diabetes attributed to air pollution exposure is substantial, with a recent estimate that ambient fine particulate matter ($PM_{2.5}$) exposure contributes to more than 200,000 deaths from diabetes annually.

Summary There is a growing body of literature linking air pollution exposure during childhood and adulthood with diabetes etiology and related cardiometabolic biomarkers. A small number of studies found that exposure to air pollution during pregnancy is associated with elevated gestational diabetes risk among mothers. Studies examining prenatal air pollution exposure and diabetes risk among the offspring, as well as potential transgenerational effects of air pollution exposure, are very limited thus far. This review provides insight into how air pollutants affect diabetes and other metabolic dysfunction-related diseases across the different life stages.

Keywords Air pollution · Diabetes · Particulate matter · Oxidative stress

Introduction

The global prevalence of metabolic syndrome disorders, including diabetes mellitus (DM), has increased over time due to aging populations, growing levels of urbanization, and increasing intake of obesogenic diets. The diabetes epidemic is one of the greatest challenges faced by the world's health care systems [1]. Type 2 diabetes (T2DM) is characterized by high levels of circulating glucose and overall insulin resistance, which relates to the development of vascular and metabolic dysfunctions [2]. Increased oxidative stress has a central role in metabolic syndrome and its component pathologies, and may be a shared underlying actor in their progressions [3]. There is an emerging body of literature implicating ambient air pollution exposure as a potential risk factor for diabetes, as demonstrated by several literature reviews and meta-analyses [4, 5]. The global disease burden of diabetes attributed to air pollution exposure is substantial, with a recent study estimating that ambient fine particulate matter ($PM_{2.5}$) contributes to 3.2 million incident cases of diabetes and more than 200,000 deaths from diabetes annually [6••]. Although the majority of the current evidence is based on studies of adults, recent results suggest that air pollution can adversely affect cardiometabolic health and elevate diabetes risk earlier in life, beginning with in utero exposures. Here, we review, summarize, and synthesize recent findings (from 2015 forward) on potential health effects of exposure to air pollution on diabetes risk during different stages of the life course: prenatal, gestational, childhood/adolescence, and adulthood. We also discuss the oxidative stress mechanism potentially underlying these associations.

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Air Pollution and Exposure Assessment

Studies included in this literature review analyzed multiple air pollutants and their associations with diabetes risk. $PM_{2.5}$ refers to fine particulate matter, with aerodynamic diameter of less than 2.5 μm, which can penetrate deep into the lungs. $PM_{2.5}$ composition and toxicity can vary depending on its source. NO_x refers to nitrogen oxides, which are byproducts of high-temperature combustion process, and is a marker of traffic-related air pollution. BC is black carbon, a component of particulate matter formed during diesel fuel combustion, and is another marker of traffic, but one more specific to diesel traffic. Ground-level ozone (O_3) forms when NO_2 and volatile organic compounds react with sunlight and heat. SO_2 is sulfur dioxide, which is formed as a byproduct of fossil fuel combustion mainly from industrial sources. Air pollution exposure assessment is traditionally done via linking measurements from nearby stationary-site monitors to study participants, often at their location of residence. To improve exposure estimates, most recent studies rely on statistical models based on land use information and data from monitoring networks, chemical transport models, and remote sensing data from satellites. Personal-level monitoring, where study participants each carry a portable instrument, is another potential approach, although such applications are usually not feasible due to prohibitive costs.

Epidemiological Studies of Air Pollution's Effects on Diabetes

In this review, we performed a comprehensive survey of the literature published since 2015. We selected this date as it is after a recent meta-analysis [5], and since the majority of the studies has been generated thereafter. We searched the PubMed database for articles that contained the terms in the title and/or abstract that were relevant to the current review. The search terms included air pollution AND (diabetes or diabetes mellitus or gestational diabetes). This resulted in 408 articles that were individually evaluated for their relevance; of these, we included 43 studies that included both relevant exposure information and health endpoints and organized them into different life stages. We also added and described studies analyzing cardiometabolic risk factors (e.g., obesity) when the evidence is limited for a life stage. We summarize our findings in Table 1, and the individual papers are listed and described in Appendix Table 2.

Prenatal Exposure

Prenatal exposure to air pollution could adversely affect cardiometabolic health. As the prenatal period is a critical period for cardiovascular growth and development, fetuses may be especially vulnerable to the adverse health effects of ambient air pollution. Although numerous studies have demonstrated that air pollution exposure during this period can have transgenerational effects on offspring health outcomes (e.g., higher risk of low birthweight and birth defects), evidence linking prenatal exposure to air pollutants and increased risk of diabetes among offspring is very limited. A single study in Sweden found that maternal exposures to NO_x during third trimester pregnancy and to O_3 during second trimester were associated with offspring risk of developing type 1 diabetes (T1D), after controlling for genetic predisposition of disease [7•]. Exposure to particulate matter (PM) air pollution, but not NO_2, during pregnancy was associated with increased levels of cord plasma insulin at birth among 590 newborns in Belgium, suggesting that prenatal exposure could increase the risk of cardiometabolic dysfunction later in life [8].

Recent studies have also linked in utero exposure with diabetes risk factors such as obesity and high blood pressure, suggesting that exposure during this critical period could contribute to the underlying pathophysiology of diabetes. Prenatal exposure could potentially influence body weight and BMI trajectory, as demonstrated by an analysis of the Children's Health Study finding that near-road freeway NO_x exposure during pregnancy was associated with increased rate of change of childhood BMI and higher attained BMI at age 10, independent of later childhood exposures [9]. The Project Viva cohort in Boston, a prospective cohort of prenatal exposures, pregnancy outcomes, and offspring health exposed to low levels of air pollution, offers detailed insights regarding the potential pathways by which prenatal air pollution exposure could induce adverse cardiometabolic outcomes among the offspring. Among infants exposed to higher traffic-related pollution during the third trimester in this cohort, fetal growth was inhibited while rapid postnatal weight gain was observed [10]. Children whose mothers lived close to a major roadway at the time of pregnancy also had higher markers of cardiovascular risk in early and mid-childhood, including higher BMI, larger waist circumference, and higher leptin concentration [11]. However, the investigators did not find evidence for an effect of prenatal exposure to traffic pollution on BMI trajectory from birth through mid-childhood [12].

Prenatal exposure to air pollution is also linked with elevated blood pressure among the offspring [13–15]. These studies found significant associations between air pollution exposure and elevated offspring blood pressure during the third trimester exposure, but not first or second trimesters, suggesting that this may be the most etiologically relevant

Table 1 Summary of evidence for the association between air pollution and diabetes risk across the life-course

Life-stage	# of studies evaluated	Summary
Prenatal	2, and additional 7 studies on cardiometabolic risk factors	Evidence examining air pollution exposure during pregnancy and diabetes risk among offspring is limited to only two studies that examined T1D risk and cord plasma insulin levels. Multiple studies have evaluated and found associations between prenatal air pollution exposure and cardiometabolic risk factors among offspring, suggesting that transgenerational effects on diabetes risk is plausible.
Gestational	6	There is limited but an emerging body of evidence suggesting that air pollution exposure during pregnancy could lead to gestational diabetes. Additional confirmatory studies are still needed, especially to ascertain the etiologically relevant window of exposure prior to and during pregnancy.
Children/adolescents	7, and additional 3 studies on cardiometabolic risk factors	There is growing evidence linking air pollution exposure with metabolic dysfunction among children and adolescents. Other studies also observed significant associations between air pollution and cardiometabolic risk factors.
Adults	28	The evidence regarding air pollution exposure and diabetes prevalence, incidence, and mortality is generally positive. Several studies also examined the effects of co-exposures, such as noise, with mixed findings. Multiple studies have also evaluated cardiometabolic biomarkers related to diabetes risk. Many of the newer studies were conducted in Asia, but evidence from other regions of the world remains very limited.

time window. Epidemiological studies examining whether prenatal exposures to air pollutants could confer elevated diabetes risk later in life and during adulthood among offspring have not been carried out to date and remains a topic of future research.

Gestational Diabetes

Pregnancy is an especially vulnerable period for development of abnormal glycemia because insulin resistance increases as part of adaption to ensure adequate supply of nutrients to the fetus [16]. Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition in pregnancy, affecting up to 8% of pregnancies in the USA [17]. Women with GDM are more likely to develop preeclampsia and diabetes in the years following pregnancy, and their children are at increased risk of stillbirth, delivery by Cesarean section, macrosomia, overweight, impaired glucose tolerance, and diabetes later in life [18].

Findings from recent studies suggest that exposure to air pollutants during pregnancy may be associated with increased risk of developing GDM. In a study of 410,267 women in Florida, exposures to $PM_{2.5}$ and O_3 during first and second trimesters in single-pollutant models were associated with increased risk of GDM [19]. Exposure to higher CO, NO, and NO_x levels during pregnancy during first trimester and SO_2 and NO during second trimester increased the risk of GDM among 19,606 women in Taiwan [20]. Maternal exposure to NO_x and SO_2 before conception and during first trimester increased GDM risks among mothers in the USA (n = 219,952), but a negative association was found for preconception exposure to O_3 [21]. An analysis of 72,745 pregnancies in Denmark found that NO_2 exposure was significantly associated with GDM, although after adjusting for road traffic noise, the associations became non-significant (HR: 1.22; 95% CI = 0.98–1.53) [22]. Exposures to $PM_{2.5}$ during the second trimester and NO_2 during the first trimester were significantly associated with higher risk of GDM among women in New York City, with stronger associations observed in women who were younger, not receiving Medicaid, and overweight [23]. In the aforementioned Project Viva cohort, exposure to $PM_{2.5}$ among women was generally not associated with GDM, although they found evidence of second trimester exposure and GDM among younger women [24]. Overall, the evidence linking air pollution exposure with GDM is generally positive and growing, but additional studies are still needed, especially to ascertain the etiologically relevant window of exposure prior to and during pregnancy.

Children and Adolescents

A number of recent studies, mostly with cross-sectional or observational study designs, have examined and found significant associations between air pollution exposure during childhood and adolescence with diabetes risk. Chronic exposure to PM_{10}, but not NO_x, CO, and O_3, contributed to the incidence rate of type 1 diabetes among children aged between 0 and 14 years old in Southern Italy [25]. A cross-sectional study of 837 children in two German cohorts found that NO_2 and $PM_{2.5}$ exposures were associated with higher HOMA-IR (homeostatic model assessment for insulin resistance), which remained after adjusting for greenspace [26]. Another cross-sectional study found that among 429 overweight and obese African-American and Latino youth in urban Los Angeles, elevated exposure to $PM_{2.5}$ and NO_2 was associated with a metabolic profile characteristic of increased risk for type 2 diabetes, such as higher fasting insulin, lower insulin sensitivity, higher acute insulin response to glucose, and higher fasting glucose [27]. High exposure to the traffic-related air pollutants PM_{10}, NO_2, and potentially $PM_{2.5}$ accelerated the manifestation of T1D, but only in very young children, independent of levels of urbanization [28]. However, a study of 6807 participants aged 0 to 19 years old at diagnosis in Germany did not find such an association between exposure to air pollutants and acceleration of manifestation of type 1 diabetes [29]. An analysis of 37,372 individuals with type 1 diabetes aged < 21 years in a cross-sectional study also observed negative findings, with accumulated exposure to ozone associated with lower HbA1c and no significant associations observed with PM_{10} and NO_2 [30].

Longitudinal investigations in children have been limited to a recent study of 314 overweight and obese Latino children in Los Angeles [31••], which found that $PM_{2.5}$ and NO_2 exposures were associated with faster decline in insulin sensitivity and lower insulin sensitivity at age 18 years, independent of adiposity. Declines in insulin sensitivity were compensated by increases in insulin secretion, including increased fasting insulin levels and acute insulin response to glucose, and higher levels of exposures were also associated with a higher BMI and body fat at age 18. In addition, NO_2 exposure negatively influenced β-cell function, measured by a faster decline in disposition index (DI) and a lower DI at age 18, suggesting that higher exposures to air pollutants may contribute to development of type 2 diabetes.

Air pollution exposure may also contribute to development of diabetes risk factors in children. In a longitudinal study of 4550 children living in Southern California, traffic-related air pollution exposure during childhood was positively associated with BMI, suggesting that air pollution exposure could contribute to obesity in children [32]. Another study of 130 children found that same-day exposure to higher concentrations of ultrafine particles, but not $PM_{2.5}$, was associated with higher systolic blood pressure in children [33]. Interaction between air pollution exposure and obesity on blood pressure and hypertension was also observed in a study of 9354 Chinese children [34].

Adults

Numerous investigations found significant associations between multiple air pollutants with diabetes prevalence, incidence, and mortality risk [5, 35, 36, 37•, 38–42]. Recent studies of biomarkers have also improved our understanding of the potential pathways underlying air pollution-induced diabetes. For example, among 1023 Mexican Americans, short-term exposure to $PM_{2.5}$ was associated with lower insulin sensitivity and HDL-to-LDL (low density lipoprotein-to-high density lipoprotein) cholesterol ratio, and higher fasting glucose and insulin, HOMA-IR, total cholesterol, and LDL cholesterol, although the study did not find any associations between traffic-related air pollution and metabolic outcomes [43]. Living closer to a major roadway or acute exposure to traffic-related air pollutants was associated with dysregulated glucose homeostasis, but not with adipokines [44]. A study of 4052 participants in persons without diabetes in Germany found that several diabetes-related biomarkers were associated with air pollution, finding that exposures were negatively associated with adiponectin and positively associated with IL-1RA [45]. In another study of 551 nondiabetic participants, $PM_{2.5}$ was associated with higher fasting blood glucose and higher odds of impaired fasting glucose [46]. PM_{10} and NO_2 were associated with Hb1A1c, but not prevalent DM, in a cross-sectional study of 2895 participants in Northern France [47]. An analysis of 2944 participants in Germany found that PM_{10} was associated with higher HOMA-IR, and NO_2 was associated with HOMA-IR, glucose, insulin, and leptin levels, with stronger associations among those with prediabetes [48]. Another analysis of 73,117 participants in Southern Israel found that 3-month average PM_{10} was associated with elevated serum glucose, HbA1c, low-density lipoprotein, and triglycerides, with elevated associations observed among subjects with diabetes [49].

Notably, many of the newer studies were conducted in Asia, where potential risk factors for diabetes differ and both diabetes prevalence and ambient air pollution levels are substantially higher than Europe and North America, where most of past studies have been conducted. Among longitudinal studies, air pollution exposures were significantly associated with fasting blood glucose levels, and both prevalent and incident DM [50–54]. A cross-sectional study of 11,847 adults in China found that exposure to elevated $PM_{2.5}$ levels was significantly associated with increased T2DM prevalence and elevated levels of fasting glucose and HbA1c [55]. Another cross-sectional study of 15,477 participants in 33 communities in China found that PM_1, $PM_{2.5}$, and PM_{10} were significantly associated with increased diabetes prevalence, and that air pollution exposure was associated with altered lipid profiles and dyslipidemias, especially among overweight or obese participants [56]. Studies elsewhere in the world examining the air pollution-diabetes association are very limited. In one of the only studies conducted in the Middle East, an analysis of 2025 participants in Jeddah, Saudi Arabia found that $PM_{2.5}$, especially from road dust and traffic sources, was associated with metabolic syndrome, hyperglycemia, and hypertension prevalence [57].

Several of recent studies also evaluated and identified potentially vulnerable subpopulations, although consistent evidence of effect modification is limited. Risk of diabetes associated with air pollution exposure was different across sexes [39, 50] and BMI levels [52, 56]. Studies reported elevated risks among younger populations and those with pre-diabetes and metabolic syndrome [48, 52, 56]. Dietary habits, such as fruit and alcohol consumption, also modified the air pollution-diabetes associations [42, 52, 54]. DM patients were found to be more susceptible to the air pollution-induced serum glucose variations, and Metformin treatment had a protective effect [58]. Genetic risk for T2DM may also modify susceptibility to air pollution through alternations in insulin sensitivity [46, 59].

Recent studies have also evaluated and found significant associations between diabetes risk and co-exposures, including ultrafine particles, temperature, and noise. A study of all residents residing in Toronto, Canada, found that exposures to ultrafine particles and NO_2 were significantly associated with incident diabetes [60]. $PM_{2.5}$ was associated with risk of developing metabolic syndrome and hypertriglyceridemia, and higher levels of $PM_{2.5}$ and temperature were both associated with elevated risk of developing elevated fasting blood glucose [61]. An analysis of a population-based cohort in Vancouver found that diabetes incidence was associated with noise exposures, but not with traffic-related air pollutants [62]. Another analysis of a Swiss cohort did not find a relationship between NO_2 and diabetes incidence, but did find a positive association with noise exposure [63]. Analyses of two Danish cohorts also reported mixed findings regarding potential associations between noise exposure and diabetes incidence [64, 65].

Oxidative Stress as a Factor Across the Metabolic Syndrome Effects of Air Pollution

There is a strong biologic rationale for the associations between air pollution exposure and increased diabetes risk. In addition to causing harm by directly impacting our lungs, inhaling air pollutants such as $PM_{2.5}$ and gases can induce systemic effects, including metabolic dysfunction [66]. A mediator of metabolic syndrome is insulin resistance, which relates to the development of vascular and metabolic dysfunctions that can lead to manifest cardiovascular disease and T2DM [2]. Although the exact biological mechanism(s) involved in the associations between increased air pollution exposure and greater risk of metabolic dysfunction-related diseases remain a subject of research, available evidence to date points to air pollution-induced inflammation and resulting oxidative stress as a major pathway [67].

Air pollution exposure has been found to cause oxidative stress in the body, and oxidative stress is a known risk factor for metabolic dysfunction diseases. Oxidative stress can result in lipid peroxidation, depletion of antioxidants, and activation of pro-inflammatory signaling, which can set off a cascade of biological events that can affect distant organs [68]. It contributes to many adverse health conditions, including cancer, atherosclerosis, hypertension, ischemia/perfusion, diabetes, and asthma [69]. Air pollution exposure has also been found to cause broad metabolic derangements in glucose and insulin homoeostasis (including glucose intolerance, decreased insulin sensitivity, and impaired secretion) and increased blood lipid concentrations [6]. This provides biological mechanistic plausibility to the observed association between air pollution exposure and diabetes.

Of the various air pollutants, exposure to fine particulate matter ($PM_{2.5}$) air pollution resulting from the combustion of fossil fuels is strongly associated with the induction of both systemic inflammation and oxidative stress. The proposed mechanism is that fossil fuel particulate matter, especially coal combustion $PM_{2.5}$, is enriched in

both metals and sulfur [70], which can cause oxidative stress, and sulfur, which induces acidity, making the oxidative metals even more bioavailable to cause systemic damage [71]. These metals and their associated oxidative stress have been found in animal studies to mediate the adverse effects of particulate matter exposures [72].

A key test as to whether oxidative stress is the primary pathway of air pollution's effects on metabolic dysfunction-related diseases is to evaluate if diminishing oxidative stress reduces the adverse health effects of air pollution. In fact, recent considerations of dietary and genetic variant evidence validates this specific pathway's importance. Considering the large, well characterized NIH-AARP Diet and Health Cohort, Thurston et al. (2016) [73] showed $PM_{2.5}$ exposure was related to increase risk of cardiovascular death, with subsequent analyses finding that a diet rich in anti-oxidants reduced both the diabetes and the cardiovascular mortality in this cohort [42, 74]. After adjusting for both individual- and contextual-level covariates, $PM_{2.5}$ was found to be significantly associated with diabetes-related mortality (HR = 1.19 per 10 μg/m^3; 95% CI: 1.03–1.39). However, the strength of the $PM_{2.5}$-diabetes mortality association was greater in subjects who consumed less than 2.5 servings of fruits per day (HR = 1.28; 95% CI: 1.08–1.53), as compared to those who consumed greater amounts (HR = 0.93; 95% CI: 0.69–1.27) (p-interaction = 0.01), for whom the $PM_{2.5}$ effect became non-significant. Similarly, Wenton et al. (2009) [75] found that the respiratory effects of oxidative stress-inducing air pollutants were increased among elementary school children when the catalase (CAT) enzymatic (anti-oxidant) protection gene variant was absent. Thus, both the toxicology and the epidemiology of air pollution effects are consistent in indicating that oxidative stress is an important causal pathway in the associations found between air pollution exposures and increased risk of diabetes.

Future Directions

Important advances have been made in regards to our understanding of the relationship between air pollution exposure and diabetes risk during different, distinct stages of life. At the same time, oxidative stress has been identified as a risk factor for metabolic syndrome, and as an effect of air pollution exposure, especially from fossil fuel combustion particulate matter. This provides a plausible mechanism for the observed associations between air pollution and diabetes. However, this review also highlights the considerable gaps in current knowledge, especially in regards to limited evidence examining whether early life exposures subsequently affect cardiometabolic endpoints and diabetes risk in adulthood, and the need to investigate the transgenerational effects of air pollution in the etiology of diabetes. Results from animal studies suggest this may be plausible; for example, Woodward et al. (2019) [76] reported that chronic nano-particulate matter exposure from gestation to early adulthood in male mice promoted metabolic dysregulation, food intake, and adiposity, in part through modulation of feeding behavior. Chen et al. (2018) [77] also found that prenatal exposure to diesel exhaust $PM_{2.5}$ caused offspring β-cell dysfunction in adulthood. As established pregnancy and pediatric cohorts are followed for a longer period of time to adolescence and adulthood and exposure assessment methods continue to improve, the potential transgenerational effects will be better understood in the future. This review also found that, despite the emerging body of evidence examining the air pollution-diabetes association in Asia, studies in developing countries and other regions in the world are still very limited. Studies examining potential interactions and/or confounding effects with co-exposures such as noise and temperature are also lacking, as well as studies assessing air pollution mixtures and specific $PM_{2.5}$ components and air pollution sources. As the built environment and neighborhood socioeconomic status are significant predictors of diabetes risk [78], their potentially interactive effects with air pollution exposure could also be examined in further detail. The emerging concept of the 'exposome,' defined as the totality of environmental exposures from conception onwards [79], could provide improved understanding of the association between multiple exposures and diabetes risk. Overall, this review provides insight into how, and to what extent, air pollution causes and exacerbates diabetes and other metabolic dysfunction-related diseases during the life-course, as well as the potential underlying pathophysiology due to oxidative stress from air pollutants.

Compliance with Ethical Standards

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Conflict of Interest The authors declare that they have no conflict of interest.

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.

Appendix

Table 2 Recent studies of the association between air pollution and diabetes risk (from 2015 forward)

Reference	Study Design	Location	Sample Size	Pollutants Evaluated	Main findings
Prenatal/Gestational					
Malmqvist et al., (2015) [7•]	Observational	Skane, Sweden	84,039	NO_x, O_3	Maternal exposure to air pollutants was associated with increased T1D risk among offspring. Highest vs lowest exposure group odds ratio of 1.62 (0.99–2.65) for O_3 during 2nd trimester and 1.58 (1.06–2.35) for NO_x in the 3rd trimester.
Madhloum et al., (2017) [8]	Observational	Genk, Belgium	590 mother-infant pairs	$PM_{2.5}$, PM_{10}, NO_2	Cord plasma insulin levels increased 15.5% (7.8 to 24.4) for each SD increment in $PM_{2.5}$ levels during entire pregnancy, and effects were most pronounced during 2nd trimester; similar effects found for PM_{10}.
Hu et al., (2015) [19]	Observational	Florida, U.S	410,267	$PM_{2.5}$, O_3	Both $PM_{2.5}$ and O_3 exposures during 1st, 2nd, and entire pregnancy were associated with GDM.
Pan et al., (2017) [20]	Observational	Taiwan	19,606	NO, NO_2, NO_x, O_3, SO_2, PM_{10}	NO exposure during first second trimester associated with GDM in both single and two-pollutant models.
Robledo et al., (2015) [21]	Observational	U.S	219,952	$PM_{2.5}$, $PM_{2.5}$ constituents, PM_{10}, NO_x, CO SO_2, O_3	Preconception and 1st trimester maternal exposures to NO_X and SO_2 were associated with increased risk of subsequent GDM. Preconception O_3 was associated with lower risk of subsequent GDM. Of $PM_{2.5}$ constituents, sulfates (preconception and 1st trimester) were negatively associated with GDM, while nitrates (1st trimester) were positively associated with GDM.
Pedersen et al., (2017) [22]	Observational	Denmark	72,745 births	NO_2, noise	NO_2 exposure during 1st trimester was associated with increased risk of GDM (OR = 1.24; 1.03–1.49); effect was attenuated (OR = 1.22; 0.98–1.53) adjusting for noise.
Fleisch et al., (2016) [24]	Observational	Massachusetts, USA	159,373	$PM_{2.5}$	No association with GDM in the full cohort; women aged less than 20 years old had increased GDM risk with second semester $PM_{2.5}$ exposure.
Choe et al., (2019) [23]	Observational	New York City, U.S.	256,372 births	$PM_{2.5,}$ NO_2	

Table 2 (continued)

Reference	Study Design	Location	Sample Size	Pollutants Evaluated	Main findings
					1st trimester NO_2 exposure and 2nd trimester $PM_{2.5}$ exposure were associated with elevated GDM risk. $PM_{2.5}$-GDM association was elevated in younger women and non-Medicaid recipients; NO_2-GDM association was elevated in overweight and multiparous women.
Children/Adolescents					
Di Ciaula, (2016) [25]	Observational	Apulia, Italy	631,275	PM_{10}, NO_x, O_3, CO	Long-term PM_{10} exposure associated with T1D incidence rate.
Thiering et al., (2016) [26]	Cross-sectional	Germany	837	NO_2, PM_{10}, $PM_{2.5}$	NO_2 associated with higher HOMA-IR levels.
Toledo-Corral et al., (2016) [27]	Cross-sectional	Los Angeles, California, U.S	429	$PM_{2.5}$, NO_2, NO_x	Air pollution exposure was associated with elevated fasting insulin, lower insulin sensitivity, higher acute insulin response to glucose, and higher fasting glucose in overweight/obese Latino children.
Lanzinger et al., (2018) [30]	Cross-sectional	Germany	37,372	O_3	Inverse relationship between ozone and HbA1c levels observed in those with type 1 diabetes.
Alderete et al., (2017) [31]	Longitudinal	Los Angeles, CA, U.S	314	NO_2, $PM_{2.5}$	$PM_{2.5}$ and NO_2 associated with faster decline in S1 and lower S1 at age 18 years. NO_2 associated with negatively affected beta-cell function, faster decline in disposition index and lower DI at age 18.
Beyerlein et al., (2015) [28]	Observational	Bavaria, Germany	671	PM_{10}, $PM_{2.5}$, NO_2	Exposures to the traffic-related air pollutants PM_{10}, NO_2, and possibly $PM_{2.5}$ accelerate the manifestation of T1D, but only in very young children.
Rosenbauer et al., (2016) [29]	Observational	North Rhine-Westphalia, Germany	6807	PM_{10}, NO_2, O_3	Exposure to air pollution was not associated with age at onset of T1D.
Adults					
Park et al. (2015) [35]	Longitudinal	U.S	5839	$PM_{2.5}$ and NO_x	Significant association observed with T2DM prevalence, but not incidence, in a multi-ethnic cohort.
Coogan et al. (2016) [36]	Longitudinal	U.S	43,003	NO_2	Did not find association with diabetes incidence in a cohort of Black women.
Jerrett et al., (2017) [37•]	Longitudinal	U.S	45,231	O_3	

Table 2 (continued)

Reference	Study Design	Location	Sample Size	Pollutants Evaluated	Main findings
					Observed significant association between O_3 with diabetes incidence in a cohort of Black women.
Bowe et al., (2018) [6••]	Longitudinal	U.S	1,729,108	$PM_{2.5}$	Significant association with diabetes incidence in a cohort of U.S veterans.
Renzi et al., (2018)	Longitudinal	Rome, Italy	1,425,580	O_3, PM_{10}, $PM_{2.5–10}$, $PM_{2.5}$, NO_2, and NO_x	NO_x and O_3 were significantly associated with diabetes incidence. The association between O_3 and incident diabetes was stronger in women and younger (<50 years) participants.
Weinmayr et al., (2015) [39]	Longitudinal	Bochum, Essen, and Mulheim, Germany	3607	PM_{10}, $PM_{2.5}$	Increased diabetes incidence risk associated with PM_{10} and $PM_{2.5}$; those living closer to a busy road had elevated risks.
Hansen et al. (2016) [41]	Longitudinal	Denmark	28,731	$PM_{2.5}$, PM_{10}, NO_x, NO_2	Diabetes incidence was significantly associated with $PM_{2.5}$, while elevated but non-significant associations were observed with other pollutants.
Qiu et al., (2018) [50]	Longitudinal	Hong Kong	61,447	$PM_{2.5}$	Significant association with both diabetes prevalence and incidence.
Lim et al., (2018)	Longitudinal	U.S	549,735	$PM_{2.5}$, NO_2, O_3	Significant association between $PM_{2.5}$ and NO_2 with diabetes mortality; higher associated risks among the obese and those with smaller fruit consumption.
Yitshak-Sade et al., (2015) [58]	Cross-sectional	Southern Israel	131,882	PM_{10}, CO, SO_2, O_3, NO_2	NO_2 and SO_2 were significantly associated with increased levels of serum glucose.
Honda et al., (2017) [40]	Observational	U.S	4121	$PM_{2.5}$, NO_2	$PM_{2.5}$ and NO_2 exposures both associated with diabetes prevalence and HbA1c levels, in both diabetic and non-diabetic participants.
Eze et al., (2016) [59]	Observational	Switzerland	1524	PM_{10}	Significant association between diabetes and PM_{10} exposure; interaction observed between PM_{10} and genetic risk score, with odds of diabetes risk increasing per T2DM risk allele.
Chen et al., (2016)	Cross-sectional	Southern California, U.S	1023	NO_2, O_3, $PM_{2.5}$	Short-term $PM_{2.5}$ exposure was associated with lower insulin sensitivity and HDL-to-LDL cholesterol ratio and higher fasting glucose and insulin,

Table 2 (continued)

Reference	Study Design	Location	Sample Size	Pollutants Evaluated	Main findings
					HOMA-IR, total cholesterol, and LDL cholesterol.
Annual $PM_{2.5}$ associated with higher fasting glucose, HOMA-IR, and LDL-C.					
Li et al., (2018) [44]	Observational	Massachusetts, US	5958	$PM_{2.5}$, BC, SO_2, NO_x, O_3	Living closer to a major roadway or acute exposure to traffic-related air pollutants (NO_x, BC) were significantly associated with dysregulated glucose homeostasis but not with adipokines.
Chen et al., (2016)	Longitudinal	China	27,685	PM_{10}, SO_2, NO_2	Exposures to NO_2, SO_2, and PM_{10} were associated with increased fasting glucose levels in single-pollutant models.
Peng et al., (2016) [46]	Observational	Boston, Massachusetts, U.S	551	$PM_{2.5}$	Exposure to $PM_{2.5}$ was associated with higher fasting glucose in a group of non-diabetics.
Yitshak-Sade et al., (2016) [49]	Longitudinal	Southern Israel	71,117	$PM_{2.5}$, PM_{10}	Three-month average, but not short-term, exposure to PM_{10} was associated with increases in serum glucose, HbA1c, low-density lipoprotein and triglycerides, and decrease of high-density lipoprotein.
Lucht et al., (2019) [45]	Cross-sectional	Bochum, Essen, and Mulheim, Germany	4052	PM_{10}, $PM_{2.5}$, NO_2	All pollutants were negatively associated with adiponectin and positively associated with IL-1RA and hsCRP levels; no consistent patterns with fibrinogen.
Riant et al., (2018) [47]	Cross-sectional	Northern France	2895	NO_2, PM_{10}, SO_2	PM_{10} and NO_2 associated with HbA1c increase.
Liu et al., (2016) [55]	Cross-sectional	China	11,847	$PM_{2.5}$	Significant associations with T2DM prevalence, fasting glucose, and HbA1c.
Wolf et al., (2016) [48]	Cross-sectional	Southern Germany	2944	$PM_{2.5}$, PM_{10}, NO_2, NO_x	$PM_{2.5}$ associated with elevated HOMA-IR and insulin; NO_2 with HOMA-IR, glucose, insulin, and leptin. Associations were higher for those with prediabetes.
Liang et al., (2019) [53]	Longitudinal	China	88,397	$PM_{2.5}$	Significant association with diabetes incidence. Larger effects in females, rural residents, non-smokers, younger subjects, those without hypertension, and BMI less than 25 kg/m^3.
Yang et al., (2018) [54]	Cross-sectional	China	15,477	PM_1, $PM_{2.5}$, PM_{10}	

Table 2 (continued)

Reference	Study Design	Location	Sample Size	Pollutants Evaluated	Main findings
					Significant associations with prevalence, fasting glucose, 2 h glucose, and 2 h insulin.
Lao et al., (2019) [52]	Longitudinal	Taiwan	147,908	$PM_{2.5}$	Long-term $PM_{2.5}$ exposure was associated with diabetes incidence. Those who drank occasionally/regularly or had a lower BMI (<23 kg/m2) were more susceptible to the long-term effects of exposure to ambient $PM_{2.5}$.
Shamy et al., (2019) [57]	Cross-sectional	Jeddah, Saudi Arabia	2025	$PM_{2.5}$, PM_{10} and their sources	$PM_{2.5}$ was associated with metabolic syndrome, hyperglycemia, and hypertension. $PM_{2.5}$ from soil/road dust was associated with hyperglycemia and hypertension, and $PM_{2.5}$ from traffic was associated with hyperglycemia.
Wallwork et al., (2016) [61]	Longitudinal	New England, U.S.	587	$PM_{2.5}$	$PM_{2.5}$ was associated with elevated risk of developing metabolic syndrome, elevated fasting blood glucose level, and hypertriglyceridemia. Temperature was also associated with developing elevated fasting blood glucose level.
Bai et al., (2019) [60]	Longitudinal	Toronto, Canada	1,056,012	NO_2, UFP, $PM_{2.5}$	NO_2 and UFP both associated with diabetes incidence.
Eze et al., (2017) [63]	Longitudinal	Switzerland	2631	NO_2	NO_2 exposure not associated with diabetes incidence after adjusting for noise.

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