Association between air pollution and type 2 diabetes: an updated review of the literature

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***Abstract*:** Air pollution and type 2 diabetes mellitus (T2DM) are critical public health issues worldwide. A large number of epidemiological studies have highlighted the adverse effects of air pollution on diabetes, and include risk profiles for different exposure durations, study design types, subgroup populations, and effects of air pollution components. We researched PubMed, Google Scholar, and Web of Science to identify studies on the association between air pollution and T2DM from January 2009 to January 2019. The aim of this review is to provide a brief overview of epidemiological and experimental studies on air pollution associated with T2DM from the latest research, which may provide practical information about this relationship and possible mechanisms. Current cumulative evidence appears to suggest that T2DM-related biomarkers increase with increasing exposure duration and concentration of air pollutants. The chemical constituents of the air pollutant mixture may affect T2DM to varying degrees. The suggested mechanisms whereby air pollutants induce T2DM include increased inflammation, oxidative stress, and endoplasmic reticulum stress.

Keywords: air pollution, fine particulate matter, insulin resistance, type 2 diabetes mellitus

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Introduction

Along with rapid socioeconomic development worldwide, the harmful health effects of air pollutants have received increasing attention.[1] On the basis of their existing state in the atmosphere, pollutants can be divided into gaseous pollutants and atmospheric particulates. Gaseous pollutants include sulfur compounds, nitrogen compounds, carbon oxides, hydrocarbons, and halogen compounds; atmospheric particulates comprise total suspended particulates, inhalable particles (PM10), fine particulate matter (PM2.5), and ultrafine particulate matter. Reports from the Global Burden of Disease, Injuries, and Risk Factors Study 2017 indicated that air pollution was the eighth leading risk factor for death.[2] A total of 2.94 million deaths have been attributed to ambient particulate matter pollution globally.[2] Furthermore, a large number of studies have found that air pollution has been linked to respiratory disease,[3] cardiovascular and cerebrovascular diseases,[4] and metabolic syndrome.[5]

Diabetes is a metabolic disorder caused by genetic and environmental factors that results in insufficient insulin secretion and impaired biological effects, and is considered one of the major contributors to the global burden of disease and premature death.[6] In recent years, the prevalence of diabetes has progressed incessantly in both developed and developing nations.[7] Furthermore, current studies indicate that air pollutants may be associated with impaired glucose metabolism, insulin resistance (IR), and type 2 diabetes mellitus (T2DM).[5,8] Previous studies on associations between air pollution and T2DM were conducted mainly in developed countries, and this evidence should be balanced by studies in developing and underdeveloped countries. A literature search of electronic databases (PubMed, Google Scholar, and Web of Science) was conducted to identify relevant studies published between January 2009 and January 2019. The terms used in this research were as follows: ('air pollution' or 'air pollutants' or 'particulate matter' or 'PM10' or 'PM2.5' or

'NO2' or 'NOX' or 'ozone' or 'SO2' or 'CO') and ('diabetes mellitus' or 'type 2 diabetes' or 'T2DM'). The literature search was restricted to papers published in English. Only high-quality studies with sample sizes over 1000 participants were included. In this review, we focus on the latest epidemiological and experimental studies (Table 1) that have evaluated air pollution as a causal mechanism in order to provide a brief overview of the influence of air pollution on T2DM and the possible mechanisms.

Epidemiological evidence between air pollution and T2DM

Effect on T2DM of air pollution exposure duration and dose response

To investigate the relationship between long-term exposure to ambient particulate matter (PM) on the prevalence of T2DM, Hassanvand and colleagues conducted a cross-sectional study of 2916 adult participants in Iran from 2006 to 2011, and showed that previous exposure to ambient PM10 for 5 years might be associated with higher odds of developing T2DM [odds ratio (OR) = 1.32, 95% confidence interval (CI): 1.03–1.69].[9] A prospective cohort study conducted in Hong Kong with a mean follow up of 9.8 years demonstrated that long-term exposure to a high level of PM2.5 may increase the risk of both prevalence and incidence of T2DM.[10] Although large numbers of studies have provided significant associations between air pollution and T2DM for long-term exposure, population growth and aging are important contributors to the increase in T2DM development that should be taken into consideration (see Table 1). A few other studies have not found a consistent significantly increased risk. Andersen and colleagues conducted a cohort study with a mean follow up of 9.7 years among Copenhagen or Arhus residents aged 50–65 years, and showed that air pollution was not significantly associated with confirmed cases of T2DM [hazard ratio (HR): 1.04, 95% CI: 1.00–1.08].[11] Another long-term effect study conducted by Wolf and colleagues suggested an association between PM10 and IR in the general population, but no association was found for hemoglobin A1c (HbA1c).[12] This discrepancy might be due to the biological mechanism of HbA1c since the lifespan of a typical red blood cell is approximately 115 days. Thus, medium-term exposure would be more likely to show an association than long-term exposure. Lucht and colleagues performed an analysis on medium-term (28- and 91-day means) air pollution and glucose metabolism, and showed that medium-term PM and accumulation mode particle number exposures were positively associated with fasting blood glucose (FBG) levels (28-day PM2.5: 0.91 mg/dl per 5.7 μg/m^3) and HbA1c [91-day PM2.5: 0.07 percentage points (p.p.) per 4.0 μg/m^3] in nondiabetic adults.[13] The impact of short-term (no more than 16 days) air pollution exposure on T2DM-related length of stay and hospitalization expenses incurred by patients showed that sulfur dioxide (SO2) and carbon monoxide (CO) were significantly positively associated with the presence of T2DM, length of stay, and expenses.[14] A recent study revealed different patterns of significant associations between PM, nitrogen dioxide (NO2) and diabetic-related biomarkers across a range of exposure windows (short, medium, and long term) among individuals without T2DM.[15] They found that medium-term exposures were associated most strongly with HbA1c.[15] Kim and colleagues evaluated the association between air pollutants and IR markers with different exposure periods, and found that PM10, O3, and NO2 may increase IR depending on the lag period.[16] However, they recruited only subjects aged 60 years or older; if age modifies the effect of air pollution on IR, their results may not be generalizable to younger people.

Considering the ambiguity in the dose-response relationship between in air pollution and cardiovascular disease mortality, recent studies have explored the dose–response relationship of concentrations between air pollution and T2DM.[38] Bowe and colleagues built a nonlinear integrated exposure response function to characterize the relationship between all concentrations of PM2.5 exposure, providing quantitative evidence for a substantial increase in the risk of T2DM with PM2.5 above 2.4 μg/m^3, and then showed a moderate increase at concentrations above 10 μg/m^3 with PM2.5.[17] In addition, significant dose–response relationships were also identified between HbA1c and NO2 and PM2.5 in T2DM participants, and NO2 in nondiabetic participants.[18] In a further investigation, Tan and colleagues provided evidence that a dose–response relationship exists between fasting blood glucose and the duration of PM2.5 exposure.[19] These findings indicated that a reduction in PM2.5 exposure will yield health benefits.

Table 1. Characteristic of included epidemiological studies.

Author	Study type	Population	Country	No. of subjects	Specific air pollutant	Outcome	Main findings[a]	Exposure duration
Effect of air pollution exposure duration and dose–response on T2DM								
Hassanvand[9]	Cross-sectional study	Iranian adults	Iran	2916	PM10	OR	T2DM [1.32 (95% CI 1.03, 1.69)]	Long-term (6 years)
Qiu[10]	Cohort study	Aged 65+	Hong Kong	61,447	PM2.5	OR, HR	Prevalence of T2DM [PM2.5 1.06 (95% CI 1.01, 1.11)]; incidence of T2DM [PM2.5 1.15 (95% CI 1.05, 1.25)]	Long-term (1 year)
Andersen[11]	Cohort study	Aged 50–65	Denmark	57,053	NO2	HR	T2DM [1.04 (95% CI 1.00, 1.08)]	Long-term (9.7 year)
Wolf[12]	Cross-sectional study	German adults	Germany	3080	PM10	Beta coefficient	HOMA-IR [15.6% (95% CI 4.0, 28.6)] HbA1c [0.5% (95% CI –0.5, 1.5)]	Long-term (3 years)
Lucht[13]	Cohort study	Nondiabetic patients	Germany	7108	PM2.5	Beta coefficient	FBG [28-day 0.91 (95% CI 0.38, 1.44) 91-day 0.81 (95% CI 0.05, 1.58)] HbA1c [28-day 0.03 (95% CI 0.01–0.05); 91-day 0.07 (95% CI 0.04, 0.10)]	Medium-term (28–91 days)
Li[14]	Cross-sectional study	T2DM patients	China	2840	PM2.5, PM10, SO2, CO	Beta coefficient	LOS [PM2.5 (+) PM10 (+) SO2 + CO +]; hospitalization costs [PM2.5 (–) PM10 (–) SO2 + CO +]	Short-term (up to 16 days)
Lucht[15]	Cohort study	Aged 45–75	Germany	6727	PM2.5, PM10, NO2	Beta coefficient	Adiponectin [PM2.5 (–) PM10 – NO2 –] IL-1RA; (PM2.5 + PM10 + NO2 +)	1–365 days
Kim[16]	Cohort study	Aged 60+	Korea	1560	PM10, NO2, O3, SO2	Beta coefficient	IR [PM10 + NO2 + O3 + SO2 (+)]	Short-term (up to 10 days)
Bowe[17]	Cohort study	US veterans without diabetes	United States	172,9108	PM2.5	Response function	Incidence of T2DM +	Long-term (more than 1 year)
Honda[18]	Cross-sectional study	Aged 57+	United States	4121	PM2.5, NO2	Prevalence; OR	T2DM [PM2.5 1.35 (95% CI 1.19, 1.53); NO2 1.27 (1.10, 1.48)]	Long-term (more than 1 year)

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Table 1. (Continued)

Author	Study type	Population	Country	No. of subjects	Specific air pollutant	Outcome	Main findings[a]	Exposure duration
Tan[19]	Cross-sectional study	Policemen	China	1271	PM2.5	Beta coefficient	FBG [0.005% (95% CI 0.0004%, 0.009%)]	Long-term (more than 1 year)
Effects of air pollution exposure on T2DM in subpopulations								
Qiu[10]	Cohort study	Aged 65+	Hong Kong	61,447	PM2.5	OR, HR	Prevalence of T2DM [PM2.5 1.06 (95% CI 1.01, 1.11)]; incidence of T2DM [PM2.5 1.15 (95% CI 1.05, 1.25)]	Long-term (1 year)
Honda[18]	Cohort study	Aged 57+	United States	4121	PM2.5, NO2	Beta coefficient, OR	HbA1c for diabetic (PM2.5 + NO2 +); HbA1c for nondiabetic [PM2.5 (+) NO2 +]; T2DM [PM2.5 1.35 (95% CI 1.19, 1.53); NO2 1.27 (1.10, 1.48)]	Long-term (more than 1 year)
Yang[20]	Cross-sectional study	Aged 50+	China	11,504	PM2.5	OR	T2DM [1.27 (95% CI 1.12, 1.43)]	Long-term (3 years)
Shen[21]	Case-control study	Female	Taiwan	6717	PM2.5, SO2	OR	GDM [PM2.5 1.10 (95% CI 1.03, 1.18); SO2 1.37 (95% CI 1.30, 1.45)]	Medium-term (12 weeks)
van den Hooven[22]	Cohort study	Pregnant women	Netherlands	7339	Traffic density	Beta coefficient	GDM (0)	Long-term (more than 1 year)
Fleisch[23]	Cohort study	Pregnant women	United States	2093	PM2.5	OR	IGT [2.63 (95% CI 1.15, 6.01)]; GDM [0.71 (95% CI 0.35, 1.42)]	Long-term (more than 1 year)
Hansen[24]	Cohort study	Female nurses	Denmark	24,174	PM2.5 PM10 NO2 NOX	HR	T2DM [PM2.5 1.11 (95% CI 1.02, 1.22); PM10 1.06 (95% CI 0.98, 1.14); NO2 1.05 (95% CI 0.99, 1.12); NOX 1.01 (95% CI 0.98, 1.05)]	Long-term (5 years)
Eze[25]	Meta-analysis	N/A	Europe and North America	N/A	PM2.5, NO2	OR	T2DM [PM2.5 1.10 (95% CI 1.02, 1.18); NO2 1.08 (95% CI 1.00, 1.17)]	Long-term (more than 1 year)
Lim[26]	Cohort study	Aged 50+	United States	549,735	PM2.5 NO2 03	HR	Diabetes mortality [PM2.5 1.19 (95% CI 1.03, 1.39); NO2 1.09 (95% CI 1.01, 1.18); O3 0.96 (95% CI 0.88, 1.04)]	Long-term (30 years)

(Continued)

Table 1. (Continued)

Author	Study type	Population	Country	No. of subjects	Specific air pollutant	Outcome	Main findings[a]	Exposure duration
Effect of air pollution exposure on T2DM in countries on different economic development levels								
Bai[27]	Cohort study	Aged 30+	Canada	105,6012	NO2	HR	T2DM [1.06 (95% CI 1.05, 1.07)]	Long-term (more than 1 year)
Hernandez[28]	Cross-sectional study	Adults	United States	862,519	PM2.5, O3	Prevalence ratio	T2DM (PM2.5 1.10 (95% CI 1.03, 1.17); O3 1.06 (95% CI 1.03, 1.09)]	Long-term (7 years)
Eze[29]	Cross-sectional study	Adults	Swiss	6392	PM10, NO2	OR	T2DM [PM10 1.40 (95% CI 1.17, 1.67); NO2 1.19 (95% CI 1.03, 1.38)]	Long-term (10 years)
Renzi[30]	Cohort study	Aged 35+	Italy	65,955	NO2, NOX, O3	OR, HR	Prevalence of T2DM [NO2 1.010 (95% CI 1.002, 1.017); NOX 1.015 (95% CI 1.009, 1.021)]; incidence of T2DM [NOX 1.011 (95% CI 1.003, 1.019); O3 1.015 (95% CI 1.002, 1.027)]	Long-term (3 years)
Kramer[8]	Cohort study	Nondiabetic women	Germany	1775	PM10, NO2	HR	T2DM [PM10 1.16 (95% CI 0.81, 1.65); NO2 1.34 (95% CI 1.02, 1.76)]	Long-term (5 years)
Coogan[31]	Cohort study	Black women	United States	4204	PM2.5	Incidence rate ratios	T2DM [1.63 (95% CI 0.78, 3.44)]	Long-term (1 year)
Puett[32]	Cohort study	Female nurses	United States	74,412	PM2.5, PM10	HR	T2DM [PM2.5 1.02 (95% CI 0.94, 1.09); PM10 1.03 (95% CI 0.98, 1.09)]	Long-term (1 year)
Dijkema[33]	Cross-sectional study	Aged 50–75	Netherlands	8018	NO2	OR	T2DM [0.80 (95% CI 0.63, 1.02)]	Long-term (2 years)
Yang[20]	Cross-sectional study	Aged 50+	China	11,504	PM2.5	OR	T2DM [1.27 (95% CI 1.12, 1.43)]	Long-term (3 years)
Yang[6]	Cross-sectional study	Adults	China	15,477	PM1, PM2.5, PM10	OR	T2DM [PM1 1.13 (95% 1.04, 1.22); PM2.5 1.14 (95% CI 1.03, 1.25); PM10 1.20 (95% CI 1.12, 1.28)]	Long-term (3 years)

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Table 1. (Continued)

Author	Study type	Population	Country	No. of subjects	Specific air pollutant	Outcome	Main findings[a]	Exposure duration
Effects of different air pollution components								
Weinmayr[34]	Cohort study	Individuals without diabetes	Germany	3607	PM2.5 PM10	Relative risk	T2DM [PM2.5 1.03 (95% CI 0.95, 1.12); PM10 1.05 (95% CI 1.00, 1.10)]	Long-term (1 year)
Strak[35]	Cross-sectional study	Adults	Netherlands	289,703	PM2.5 PM10 NO2	OR	T2DM [PM2.5 1.01 (95% CI 0.99, 1.03); PM10 1.04 (95% CI 1.02, 1.06); NO2 1.07 (95% CI 1.05, 1.09)]	Long-term (more than 1 year)
Sun[36]	Cross-sectional study	Aged 65+	Hong Kong	40,150	Elemental carbon, organic carbon, nitrate, and nickel	Excess risk	T2DM admissions [elemental carbon 3.79% (95% CI 1.63, 5.95); organic carbon 3.74% (95% CI 0.83, 6.64); nitrate 4.58% (95% CI 2.17, 6.99); nickel 1.91% (95% CI 0.43, 3.38)]	Short-term (24 h)
Zanobetti[37]	Cross-sectional study	Adults	United States	46,192	Elemental carbon, organic carbon, As, SO_4^{2-}	Excess risk	T2DM admissions [organic carbon −2.42% (95% CI −3.79, −1.06); elemental carbon −2.12% (95% CI −3.84, −0.39); As 2.16% (95% CI 0.11, 4.21); SO_4^{2-} 2.91% (95% CI 0.92, 4.89)]	Short-term (48 h)

[a]The direction of the effect is denoted by – for significant negative association; (–) for negative association; (0) for no association; + for significant positive association; (+) for positive association.
As, arsenic; CI, confidence interval; CO, carbon monoxide; FBG, fasting blood glucose; GDM, gestational diabetes mellitus; Hb1Ac, hemoglobin 1Ac; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio; IGT, impaired glucose tolerance; IL-IRA, interleukin 1RA; IR, insulin resistance; LOS, length of stay; NO2 nitrogen dioxide; NOX, nitrogen oxides; O3, ozone; OR, odds ratio; PM2.5, fine particulate matter; PM10, inhalable particles; SO2 sulfur dioxide; T2DM, type 2 diabetes mellitus.

While the ability of short- and long-term exposure to air pollution to cause inflammation has consistently been reported in *in vivo* and *in vitro* studies,[39] evidence from several epidemiologic studies supports this connection between air pollution and glucose metabolism, given that researchers have observed associations between short-, medium- and long-term air pollution exposure and increased inflammation.[40] In addition, the increasing concentration of air pollutants can lead to clinically significant disturbances in the autonomic nervous system, oxidative stress, inflammation, endoplasmic reticulum stress (ERS), apoptosis, and broad metabolic derangements in glucose and insulin homeostasis, including glucose intolerance, decreased insulin sensitivity and impaired secretion, and increased blood lipid concentrations. Such changes provide biological mechanistic plausibility in the dose relationship of the association between PM2.5 exposure and risk of T2DM.[6,12,40,41] Current cumulative evidence appears to suggest that T2DM-related biomarkers increase with increasing exposure duration and concentration of air pollutants. Epidemiological studies of short-term exposures to diabetic indicators are limited and need to be further investigated.

Effects of air pollution exposure on T2DM in subpopulations

Subpopulations were also studied to investigate the association between air pollution and T2DM among women in general, pregnant women, obese individuals, and elderly people. Honda and colleagues evaluated the association between long-term average air pollutant levels and the prevalence of T2DM and HbA1c levels among older Americans, and found that air pollution was associated with abnormal glucose metabolism and T2DM in elderly participants.[18] This association was stronger among elderly individuals and was supported by previous studies.[10,20] Shen and colleagues conducted a case-control study on 6717 mothers with gestational diabetes mellitus (GDM) in Taiwan, and concluded that higher maternal pre- and postpregnancy exposures to PM2.5 and SO2 were associated with a modestly elevated, but significant, risk of GDM.[21] A large cross-sectional study in Sweden including 81,110 pregnant women showed that the prevalence of GDM during the second trimester increased with NOx exposure (OR = 1.69, 95% CI: 1.41–2.03). However, a cohort study of more than 7000 pregnant women in the Netherlands found no association between air pollution exposure and GDM.[22] Another study in the United States of 2093 women showed that exposure to air pollutants during pregnancy was associated with impaired glucose tolerance (IGT) (OR = 2.63, 95% CI: 1.15–6.01) but not GDM (OR = 0.71, 95% CI: 0.35–1.42).[23] In addition, evidence in the Danish Nurse Cohort Study showed that PM may be the most relevant pollutant for diabetes development among women, and that nonsmokers, obese women, and heart disease patients may be more susceptible.[24] Although several previous studies did not find significant evidence of an association between T2DM and air pollutants among women, a meta-analysis that included the above studies showed that the association was stronger in women than in men.[25] Interestingly, Lim and colleagues found that the diabetes mortality risk attributable to air pollution was significantly decreased among those who consumed higher levels of fruits and had a lower BMI, suggesting that higher fruit consumption and weight loss are recommended, especially for susceptible populations.[26]

The sex-, age- and BMI- specific differences seen in some of these studies may relate to true differences in biologic susceptibility. The current studies noted that elderly, female, and obese participants were more susceptible to T2DM under exposure to air pollution. On the other hand, it is also possible that subpopulations may be subject to exposure assessment error, particularly men, younger people, and individuals with lower BMIs who tend to be more mobile than other subpopulations. Research on GDM and air pollution is scarce, with inconsistent estimates, and this specific subpopulation is of concern and merits further investigation.

Effects of air pollution exposure on T2DM in countries with different economic development levels

Air pollutants vary between developed and developing countries. A population-based cohort study conducted in Canada to investigate the link between exposure to ultrafine particles and NO2 and T2DM showed that air pollution may increase the risk of T2DM.[27] Hernandez and colleagues used data from the US Centers for Disease Control to conduct a Poisson regression analysis examining associations between each air pollutant (per 10-unit increase) and T2DM, and found that

the diabetes prevalence ratios of PM2.5 and ozone were 1.10 and 1.06, respectively.[28] Another cross-sectional study in a Swiss population also found a similar significant relationship between PM10 and T2DM.[29] A large cohort study evaluated the link between long-term exposure to air pollution and the occurrence of T2DM in Rome, and found that long-term exposure to nitrogen oxides was associated with prevalent diabetes, while NOx and O3 exposures were associated with incident T2DM.[30] However, the few cohort studies conducted in developed countries indicated no significant association between PM and T2DM. Kramer and colleagues conducted a cohort study among 1775 nondiabetic women in Germany to examine the association between traffic-related air pollution and incident T2DM, and showed that PM10 was not significantly associated with T2DM (HR = 1.16, 95% CI: 0.81–1.65).[8] Similar null results were also presented by three additional studies.[31–33] These inconsistent conclusions might be explained by the subgroup populations being targeted and the different methodologies used.[8,31–33] Yang and colleagues examined the association between exposure to PM2.5 and T2DM among 11,504 Chinese adults in a large cross-sectional study, finding that PM2.5 was significantly associated with T2DM (adjusted OR was 1.27 for each 10 $\mu g/m^3$ increase in ambient PM2.5).[20] A large cross-sectional study conducted in China with 15,477 adult participants using a random number generator and multistage cluster sampling method also demonstrated that long-term exposure to air pollution was associated with an increased risk of T2DM in a Chinese population.[6] Studies focusing on this link in developing countries are mainly documented in mainland China, which may contribute to a high risk of bias.[6,14,20] Further studies in developing countries are needed to expand the conclusions, given that both T2DM prevalence and air pollution concentrations are reported to be much higher in those countries.[42,43] The burden of T2DM attributed to PM2.5 exposure varied substantially between geographical locations, and was more serious in low-income and lower-to-middle income countries.[17] However, high-quality studies in underdeveloped countries are scarce and these areas require further research.

No studies to date have directly compared the effect of air pollution on T2DM in countries with different economic levels. However, previous studies have suggested that populations from underdeveloped and developing countries may be more vulnerable.[44] The forces of demographic expansion, aging, epidemiological transition, and rapid industrialization in low-income and lower-to-middle income countries will probably increase the burden of health loss and death due to air pollution. The burden of health loss from diabetes attributable to PM2.5 pollution is not insignificant in well-developed countries, and in geographical areas with relatively lower air pollution. Nevertheless, no conclusions can be drawn due to the limited number of studies. Moreover, Chen and colleagues found that the effect was not modified by sociodemographic covariates at the individual level.[45] The effect of air pollution on T2DM seems to exist generally in both developed and developing countries. Although ambient air pollutants are maintained at a relatively lower level in developed countries, more existing evidence still indicates a positive association between air pollution and T2DM risk.[25] Studies with comparisons of different economic development levels on this relationship are needed to draw definitive conclusions in the future.

Effects of different air pollution components

Previous studies suggest that the effects on T2DM of polluting particles may differ with composition.[34] Strak and colleagues conducted a cross-sectional study to investigate the association between multiple air pollutants and T2DM among 289,703 Dutch adults, and found an association with the oxidative potential of fine particles but not with PM2.5, which suggested that particle composition may play a crucial role in a potential link with T2DM.[35] A Poisson time-series model used to examine the association between 17 chemical components of PM10 and daily emergency hospital admissions for T2DM among elderly individuals in Hong Kong indicated that exposure to specific PM10 chemical components, such as elemental carbon and nitrate, was associated with a higher risk of acute complications or exacerbation of symptoms in T2DM patients.[36] Another study conducted in 26 US communities reported that PM2.5 was higher in elemental carbon, and that organic carbon was associated with lower rates of T2DM admissions, whereas PM2.5 higher in SO_4^{2-} and arsenic (As) was associated with higher rates of T2DM.[37] These results suggested that the chemical constituents of the air pollutant mixture may affect T2DM to varying degrees. This effect may be due to particles from different sources inducing variation in markers of

inflammation in association with an acute phase response in patients.[46] Some chemical species significantly modify the association between PM2.5 and T2DM-related indices, which illustrates that mass alone is not a sufficient metric to use when evaluating the health effects of PM exposure.

In summary, the available evidence highlights the association between air pollution and T2DM. Although a causal relationship is not established so far, it may be discussed. In addition, not all aspects of this relationship have been reported consistently or revealed fully at this time. The varying associations noted among studies may be related to multiple causes, including study design, population characteristics, air pollution types, seriousness of exposure, and technical aspects of the measuring methods. The application of negative exposure and outcome controls is especially important for identifying noncausal associations, and serves as an important complement to other epidemiological methods for improving causal inference.[47] Individuals' risk for T2DM is shaped by lifestyle factors such as participation in physical activity. Some studies have suggested that rates of outdoor physical activity may be lower in areas where air pollution is getting heavier. The relationship between air pollution and T2DM might actually be mediated by physical activity. In addition, air pollution is causally related to traffic and emission conditions; that increased traffic burden is inversely related to decreased physical activity, and decreased physical activity is inversely related to insulin resistance and T2DM. Although some studies estimated the T2DM attributable to air pollution after adjustment for personal physical activity level, further longitudinal research is needed to investigate mediation by physical activity and other factors. Epidemiological and experimental investigations revealed a relationship between IR and decreasing insulin sensitivity and air pollution. Mechanisms of air pollution and T2DM are not well known, and inflammation, oxidative stress, and ERS may play an important role in the pathological progression of these effects.

Possible mechanisms of air-pollution-induced diabetes

Inflammation may play a role in air-pollution-mediated glucose metabolism

Air pollutants act first on the lungs and are deposited easily in the bronchioles and alveolar tissues after inhalation. Studies have shown that exposure to air particles can induce the release of cytokines and inflammatory factors, such as interleukin (IL)-8, IL-6, monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein 2 (MIP2), and tumor necrosis factor-α (TNF-α), which induce inflammation mediated by increasing levels of C-reactive protein (CRP) in the blood, reduce insulin sensitivity, and block the uptake of glucose in peripheral tissues, increasing the risk of T2DM.[48] Wang and colleagues suggested that inflammation is one of the reasons for IR.[49] They conducted a meta-analysis, including 10 prospective studies with 19,709 participants and 4480 patients, and found a significant dose–response association of IL-6 levels with T2DM [relative risk (RR) 1.31 (95% CI 1.17–1.46)]. Another study, involving 22 cohorts of 40,735 participants and 5753 patients, showed that elevated levels of CRP were significantly associated with a higher risk of T2DM [1.26 (1.16–1.37)]. This meta-analysis suggests that elevated levels of CRP and IL-6 were significantly associated with a higher risk of T2DM and that chronic inflammation is a predictor of the development of T2DM. A study evaluated the associations between long- and short-term air pollution concentration and inflammatory markers, and showed that PM2.5 measured on the day of blood draw was associated with CRP.[50] A study of the effects of different sources of PM10 on inflammatory responses in rats found that PM10 from dust, cigarettes, and cooking fumes could increase the number of leukocytes, macrophages, lymphocytes, and neutrophils in bronchoalveolar lavage fluid in rats, and that the activity of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in lung tissue was decreased; however, malondialdehyde (MDA) and neutrophil chemoattractant were elevated, which indicated that PM10 from the above sources may play an important role in increasing inflammation and oxidative stress in rodents.[51] Adipose tissue performs major metabolic and endocrine functions, and plays a vital role in the control of lipid homeostasis and energy balance.[52] In mammals, adipocytes are divided into two types: white adipose tissue (WAT), the main site of energy storage; and brown adipose tissue (BAT), which is specialized for energy expenditure.[53] The physiological role of BAT is the metabolism of fatty acids and the generation of heat.[53] Given their functional differences, the imbalance between WAT and BAT affects the balance of systemic energy, and, thus, may contribute to IR and adiposity development. Xu and colleagues studied the effects of PM2.5 exposure over

a substantial proportion of the rodent lifespan, and evaluated the impact of long-term exposure on the structure and function of adipose tissue.[54] Their findings suggested that long-term ambient PM2.5 exposure promotes IR, IGT, inflammation, and mitochondrial alteration, which is a risk factor for T2DM development.[55] Zheng and colleagues found that mice showed impaired hepatic glycogen storage, glucose intolerance, and IR after PM2.5 exposure.[56] Exposure to PM2.5 activates inflammatory response pathways mediated through JNK, NF-κB, and TLR4, but inhibits insulin receptor substrate 1 (IRS1)-mediated signal transduction. Furthermore, PM2.5 exposure inhibited the expression of the peroxisome proliferator-activated receptors PPARγ and PPARα in the liver. Further investigation revealed that PM2.5 resulted in significant increases in the expression of the proinflammatory genes TNF-α and IL-6 (M1), while there was no change in the expression of nitric oxide synthase-2. In contrast, IL-10 and the alternative (M2) macrophage activation marker galactose-*N*-acetylgalactosamine-specific lectin (Mgl1) were significantly downregulated,[41] suggesting that the inflammatory signaling pathway could be activated by PM2.5. In addition, the difference between focal (lung-specific) and systemic (systemic glucose metabolism) effects should be considered. Chen and colleagues conducted an experimental study to explore whether lung-specific inflammation is sufficient to induce adverse glucose effects. A study has shown that pulmonary inflammation caused by lung-specific overexpression of IKK2ca is sufficient to increase circulating levels of TNFα and IL-6, adipocyte expression of IL-6 mRNA and Tnfα, aortic endothelial dysfunction and systemic IR. The authors unexpectedly found no significant changes in hypothalamic expression of Tnfα and IL-6 mRNA and glucose tolerance in mice. Lung-specific inflammation is sufficient to cause systemic inflammation and IR; however, it does not induce glucose intolerance.[53] In conclusion, air pollution exposure may mediate the systemic inflammatory response, causing abnormal glucose tolerance, fat metabolism disorder, and an increase in the IR index, which significantly increases the risk of diabetes.

PM2.5-mediated oxidative stress in insulin and fat metabolism

Oxidative stress reflects an imbalance between the systemic manifestation of reactive oxygen species (ROS)/reactive nitrogen species (RNS) and the ability of biological systems to readily detoxify reactive intermediates or repair the resulting damage. The anti-free radical protection system comprises two types. One is the antioxidant enzyme system, including SOD, GSH-Px, and endogenous antioxidants (uric acid, glutathione, coenzyme Q, etc.). The other includes nonenzymatic defense systems such as vitamin C and vitamin E,[57] which play an important role in free radical scavenging and the protection of tissue cells. Under certain adverse conditions, an increase in free radicals, or a decrease in antioxidant function, may cause oxidative damage to biological macromolecules, leading to cell degeneration and apoptosis, which may lead to disease. Studies have shown that exposure to PM2.5 can induce rodent tissue cells to produce ROS, which plays a crucial role in oxidative damage.[54,56] Cellular experiments have shown that PM2.5 acts mainly through the mitochondrial electron transport chain to generate ROS, leading to oxidative stress.[58] The β cells in the pancreas are sensitive to ROS due to low levels of antioxidant enzymes such as catalase (CAT) and GSH-Px and poor antioxidant capacity. Oxidative stress reportedly results in β-cell dysfunction, and ROS could directly cause β-cell damage, especially the destruction of the mitochondrial structure in cells.[59]

ROS could also interfere with the insulin signaling pathway, indirectly inhibiting β cell function by activating the NF-κB signaling pathway and triggering β cell inflammatory responses.[56] ROS also appear to depress the expression of pancreas duodenum homeobox-1 (PDX-1) mRNA, which may reduce the synthesis and secretion of insulin.[60] A previous study also showed that reduced insulin-stimulated tyrosine phosphorylation is mediated by phosphorylation of IRS-1atSer307 *via* activation of JNK activity.[61] Furthermore, ROS and RNS indirectly induce damage to tissues by activating a number of cellular stress-sensitive pathways, such as p38 mitogen-activated protein kinase and hexosamines. Moreover, phosphatidylinositol-3-kinase is decreased, resulting in reduced insulin action, which may lead to IR.[62] Nuclear factor erythroid 2-related factor 2 (Nrf2) is a redox-sensitive transcription factor that plays an important role in tissue damage caused by oxidative stress. The Nrf2 pathway is the most important endogenous antioxidant stress pathway currently known.[60] Xu and colleagues found that long-term PM2.5 exposure induced a significant increase in SOD levels in mice, and resulted in

high expression levels of the oxidative stress marker 3-nitrotyrosinein the BAT depot and increased expression of the transcription factor Nrf2 in WAT and BAT.[54] The above results indicate that long-term PM2.5 exposure activates oxidative stress signaling pathways, induces oxidative stress in visceral adipose tissue, and interferes with fat metabolism. A previous study also indicated that PM2.5 exposure (within 2 months) could cause an increase in ROS production in BAT, a decrease in the expression of uncoupling protein 1 (UCP1) in WAT, and a significant decrease in the number of mitochondria in BAT and WAT, causing a functional decrease in antioxidant stress and adipose tissue in BAT that leads to IR.[63]

Endoplasmic reticulum stress involved in PM2.5-induced glucose metabolism

The endoplasmic reticulum (ER) is a locus where proteins are modified and folded and calcium is saved, playing a crucial role in the homeostasis of the intracellular environment. The ERS response can be triggered by ischemia, hypoxia, hyperglycemia, and abnormal Ca^{2+} concentrations. Proteins are transported from the rough ER to the Golgi apparatus when they fold properly. ERS can be triggered by disorders of glucose deprivation, calcium regulation, redox regulation, and viral infection,[64] or the overexpression of proteins,[65] which is an adaptive condition that slows down the rate of protein folding and results in the accumulation of unfolded proteins. This mechanism indicates a potential reason for IR.[66] The unfolded protein response (UPR) is activated in response to ERS, which can effectively remove unfolded, or misfolded, proteins in the lumen of the ER and reduce protein synthesis. On the other hand, the UPR can strengthen the ability of ER biosynthesis and increase the production of molecular chaperones, thus rebuilding the balance to achieve the goal of relieving ERS and protecting cells. If the duration of ERS is too long, or the intensity is too high, the dynamic balance of homeostasis cannot be reconstructed. In this case, the UPR activates an apoptotic signaling pathway, such as the C/EBP homologous protein (CHOP) and inositol-requiring enzyme 1 (IRE1)-JNK pathway. In addition, glucose-regulated protein78 (GRP78), also called immunoglobulin heavy chain-binding protein (BiP), is a central regulator of the UPR. The main function of islet cells is to secrete insulin; thus, they have a highly developed ER, and are, therefore, very sensitive to the ERS response. There is increasing evidence that airborne-mediated liver and pancreatic cell ERS may be an important mechanism in the development of T2DM.[67] Mendez and colleagues found that exposure to long-term PM2.5 induces inflammatory responses and activation of ERS in mouse WAT.[66] Furthermore, PM2.5 exposure induces two distinct UPR signaling pathways mediated through inositol-requiring 1α (IRE1α), that is, unfolded or misfolded proteins and regulated IRE1-dependent decay (RIDD) of mRNAs. The lung is the primary target organ of gaseous pollutants, and the liver is the main organ for chemical and lipid metabolism and detoxification. PM2.5 may target the lung and liver, activate macrophages, ERS, and UPR, and stimulate lipogenesis, lipid deposition, and adipocyte differentiation, as well as visceral fat inflammation, IR, brown fat mitochondrial fat changes, and ERS in the liver, and eventually lead to diabetes. To clarify the air-pollution-exposure-mediated mouse ERS signaling pathway, Laing and colleagues studied the impact of PM2.5 exposure on intracellular stress signaling pathways in animal models and cultured cells, and found that PM2.5 exposure induces the ERS response and activates the UPR in the lung and liver tissue.[68] In general, air pollution can mediate the ERS and UPR, further inducing apoptosis of islet β cells, causing impaired insulin secretion and leading to diabetes.

Although cell culture and animal experimental models are usually used to explore the possible health effect on humans due to environmental and occupational exposure to air pollutants, their applicability to the 'real world' is limited, which should be considered when we attempt to summarize the experimental studies of air pollutants for possible mechanisms regarding health effects. To better address the knowledge gaps, the focus of exploration should be on the molecular mechanisms by which air pollutants and their components affect T2DM.

Conclusion

In brief, the existing epidemiological evidence appears to suggest that the T2DM-related biomarkers increase with increasing exposure duration and concentration of air pollutants. The chemical constituents of the air pollutant mixture may affect T2DM to varying degrees. Experimental studies

support the adverse effects of air pollution on T2DM through multiple molecular mechanisms, signaling pathways, and interactive effects. Given the massive global population that is likely exposed to air pollution, even conservative estimates of OR would still translate into a substantial increase in the population-attributable and preventable fraction of diabetes related to air pollutants. Studies are warranted to gain greater insight into the effect of combined exposure on mixtures, maternal exposure, and susceptible factors. Future studies are also needed to establish proven and effective air pollution control measures that may reduce the global T2DM-related burden of disease.

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Author Contribution Statement

Weiping Teng and Cheng Han conceived and designed the study. Yongze Li drafted the manuscript. Yongze Li, Zhongyan Shan and Lu Xu revised the manuscript. All authors read and approved the final version of the manuscript.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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