Review

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Epidemiology of air pollution and diabetes

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Air pollution affects a large proportion of the global population. Air pollutants are hypothesized to exert their effects via impaired endothelial function, elevated systemic inflammation, mitochondrial dysfunction, and oxidative stress, all of which are hallmarks of type 2 diabetes (T2D). Here we review epidemiological studies aimed at answering whether diabetes patients are more vulnerable to ambient (outdoor) air pollution exposure and whether air pollution is associated with diabetes development or other predisposing conditions for T2D. Current evidence suggests an association between air pollution exposure and T2D, but more critical analysis is warranted. Understanding the associations between air pollution exposure and the development of T2D is critical in our efforts to control sources of air pollution and their impact on the disease.

The diabetes epidemic and ubiquitous air pollution exposure

Air pollution is a ubiquitous exposure that affects large proportions of the global population [1]. Air pollutants are emitted from many sources, such as industrial facilities, cars, trucks, ships, and airplanes, but also from household combustion devices or during forest fires and volcanic eruptions. Ambient or outdoor air pollution (referred to as air pollution hereafter) comprises particulate matter (PM) (see Glossary) of various sizes [<10 μm in diameter, PM_{10}; <2.5 μm, $PM_{2.5}$; <100 nm, ultrafine particles (UFPs)], chemicals such as persistent organic pollutants (POPs), and gaseous compounds such as nitric oxides (NO_x), carbon monoxide (CO), ozone (O_3), and sulfur oxides (SO_x). These compounds differ in their dispersion, reactivity, and toxicity. Air pollution exposure has been linked to a reduced life expectancy, mainly attributable to cardiovascular and respiratory diseases such as heart disease and lung cancer [2–4], even among individuals exposed to annual average concentrations below the current air quality standards in Europe [5,6].

In 2010, more than 3.2 million deaths worldwide were attributed to outdoor PM exposure and 3.5 million deaths to indoor household air pollution from solid fuels [7]. Air pollution exposure also accounts for a large number of disease-adjusted life-years lost (29.4 million for PM pollution and 47.9 million for household air pollution from solid fuels, which are equivalent to 3% and 4.3% of the worldwide burden of disease, respectively). Newer data from 2012 revealed 3.7 million deaths attributable to ambient air pollution and 4.3 million to household air pollution [Global Health Observatory Data Repository (http://apps.

Glossary

Black carbon (BC): a fraction of $PM_{2.5}$ that is mainly emitted during open biomass burning and from diesel cars and trucks without soot particle filters.
Confidence interval (CI): an interval estimation of a parameter to show the reliability of the estimates. Typically, 95% CIs are reported, which represent an interval that contains the true value with a 95% probability.
Hazard ratio (HR): a measure of mortality risk between different groups corresponding to a certain period of time. It is defined as the ratio between two hazard rates and is typically estimated via proportional hazard models.
Interquartile range (IQR): the distance between the 75% percentile (third quartile) and 25% percentile (first quartile) of a distribution. Being a measure of dispersion it is often used to calculate effect sizes per increase in IQR to make them comparable between studies.
Mortality rate ratio (MRR): defines the ratio between two mortality rates corresponding to two subgroups or to different causes of death.
Nitric oxide (NO): a free radical and a byproduct of combustion in automobile engines and fossil-fuel power plants. In humans it is an important cellular signaling molecule and it is involved in many physiological processes. In the air it is rapidly oxidized to nitrogen dioxide (NO_2).
Ozone (O_3): also known as trioxygen; an inorganic molecule. At ground level O_3 is primarily formed by the action of sunlight on air containing hydrocarbons and NO_x from combustion processes. It is not emitted directly from car engines or industrial operations.
Particulate matter (PM): a complex mixture of small particles and liquid droplets. Particle pollution comprises numerous components, including acids (such as nitrates and sulfates), organic chemicals, metals, and soil or dust particles. These compounds can be directly emitted or formed through reactions with other compounds. The size of a particle is directly linked to its potential to penetrate the lung and cause health problems. Therefore, particles are divided into those of diameter <10 μm (PM_{10}), which can pass into the throat and nose and enter the lung, and those of diameter <2.5 μm ($PM_{2.5}$), which can additionally reach the alveolar region of the lung.
Sulfur (S): an abundant, multivalent, non-metal element. It is oxidized to sulfur dioxide (SO_2) during combustion processes. Major sources of SO_2 emissions are volcanic eruptions and fossil fuel combustion at power plants and industrial facilities. In the atmosphere SO_2 is converted to sulfate (SO_4).
Ultrafine particles (UFPs): defined as particles with aerodynamic diameter <0.1 μm and best characterized using particle number concentrations instead of particle mass.

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who.int/gho/data/node.main.122?lang=en)]. While household indoor air pollution from solid fuels plays a major role in Asia, Latin America, and Africa [8], outdoor air pollution from PM is of global importance.

Although there is strong evidence that air pollution adversely influences a broad spectrum of health indicators [2–6,9,10], links between air pollution exposure and T2D development have been only recently revealed. T2D affects approximately 9% of the global population [11] and accounts for 2.7% of global deaths (WHO, 2012). The number of affected people is expected to increase to 592 million by 2035 [12], with the steepest increases predicted in low- and middle-income countries. Changes in lifestyle factors due to urbanization, such as reduced physical activity, overnutrition, and obesity [13], were previously advanced as explanations for this trend. Recently, there is also interest in, and some evidence for, an association between air pollution exposure and T2D. Several biological mechanisms have been proposed to explain such a link. For example, PM exposure has been associated with impaired endothelial function, elevated systemic inflammation and oxidative stress, endoplasmic reticulum stress, cardiac autonomic nervous system dysfunction, and mitochondrial dysfunction [10,14–16]. Additionally, epigenetic changes leading to activation of key signaling pathways, or changes in markers of coagulation, inflammation, and endothelial function, have been described after exposure to air pollutants [17,18].

An ecological study by Alan Lockwood [19] was the first to link diabetes prevalence in adults to total air releases from all industries. More recently, several epidemiological studies varying in design, exposure, and outcome that are discussed below have explored the connection between air quality and diabetes.

In this review we focus on epidemiological studies that examined associations between outdoor air pollution exposure and T2D. We also consider mortality due to diabetes, diabetes-related traits, and gestational diabetes and comprehensively summarize the results of five previous meta-analyses [20–24]. We address three fundamental questions: are diabetes patients more vulnerable to air pollution exposure, is exposure to air pollution associated with diabetes development, and/or is it associated with other conditions that predispose to diabetes?

While most T2D determinants, such as inactivity or overweight, are individual factors, environmental hazards have a mostly involuntary nature. Therefore, policies that modify environmental risk factors can protect the general population. However, to fully evaluate potential public health impacts, better understanding of who is at risk [e.g., only predisposed subjects (for example, those having T2D) or also healthy individuals] is required.

Although the currently reported risk increases are relatively small, given the large proportion of subjects exposed to air pollution and the high prevalence of T2D establishing and modifying a link between these two factors could have a large impact on healthy living. Although the body of evidence for adverse health effects of air pollution, especially of PM, is increasing, results specific to diabetes-related outcomes could be used in the ongoing debate on air quality guidelines setting. Thus, evaluating whether air pollution is related to T2D is highly important and very timely.

Are diabetes patients more vulnerable to ambient air pollution exposure?

Mainly case-crossover and time-series study designs have been used to compare the effects of short-term exposure to air pollutants on all-cause mortality rates among the general population and diabetic patients. A total of seven studies have been conducted in American, Italian, Canadian, and European populations [25–32] involving between 12 978 [25] and 2935 647 [30] subjects with diabetes (for an overview see Figure 1A, for details see Table 1). Diabetes was not the original primary focus of these investigations with the exception of the study by Zanobetti *et al.* [30], in which 2935 647 subjects with a history of diabetes-related emergency hospital admission were followed. In other studies, death rates after days of high air pollution exposure among diabetic subjects were compared with those in the general population as a subgroup analysis. Among 65 180 elderly people who had a history of hospitalization for lung or heart disease, increased PM_{10} levels were positively associated with mortality risk for participants with a prior diagnosis of diabetes and this risk was greater than that observed among those without a prior diagnosis of diabetes [25]. Similar PM_{10} effects on mortality were seen in a study including nine Italian cities [26]. A national case-crossover analysis conducted in 121 cities in the USA observed associations between short-term $PM_{2.5}$ exposure and increased risk for diabetes-related hospitalization and all-cause mortality in subjects with a previous diabetes-related hospital admission [27]. Again, these $PM_{2.5}$-associated risks were greater than those observed among individuals without diabetes. Increased nonaccidental mortality among subjects previously diagnosed with diabetes was observed in association with higher $PM_{2.5}$ and SO_4 concentrations in a mortality time-series study in Montreal, Canada [28]. However, no increased risk was observed among subjects who had diabetes but not cancer, cardiovascular disease, or an airways disease. An extension of this study published in 2013, which included deaths in Montreal during a later time period, revealed similar but slightly decreased effect estimates [29].

Associations between mortality among diabetes patients and O_3 levels were also investigated. Higher average summer concentrations O_3 were positively associated with mortality risk among 2935 647 patients with a history of diabetes-related emergency hospital admission living in 105 cities in the USA [30]. A nonsignificantly increased mortality risk following higher short-term O_3 exposure was also seen among 14 350 subjects with diabetes in Italy [31].

Finally, a study on short-term NO_2 exposure effects reported an increase in all-cause mortality risk among subjects with diabetes that was greater than that reported among those without diabetes [32] (Figure 1A).

In summary, all seven studies investigating the effects of air pollution exposure on all-cause mortality observed a tendency for higher mortality rates among those with diabetes compared with those without. However, statistical significance ($P < 0.05$) was reached in only two of the