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MINI REVIEW

Particulate matter pollutants and risk of type 2 diabetes: a time for concern?

Katherine Esposito[1] · Michela Petrizzo[3] · Maria Ida Maiorino[2] · Giuseppe Bellastella[2] · Dario Giugliano[2]

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Abstract The World Health Organization estimates that worldwide in 2012 around 7 million deaths occurred prematurely due to air pollution, which is now the world's largest single environmental health risk. The higher premature mortality associated with air pollution is due to exposure to small particulate matter of 10 microns (PM_{10}) or less in diameter. Exposure to air pollution has also been suggested as a contributing to diabetes incidence and progression. There are a number of possible biological pathways linking air pollutants to diabetes, including endothelial dysfunction, dysregulation of the visceral adipose tissue through inflammation, hepatic insulin resistance, elevated hemoglobin A1c level, elevated blood pressure, and alterations in autonomic tone, which may increase insulin resistance. The risk of future diabetes associated with exposure to 10 μg/m^3 increase of $PM_{2.5}$ has been quantified in the range of 10 to 27 %; the risk of diabetes mortality associated with $PM_{2.5}$ appears to be quite lower, around 1 % for each increment exposure of 10 μg/m^3 of both $PM_{2.5}$ and PM_{10}. Limitations of the current epidemiological evidence include the complex mixture of pollutants, the different design of the studies, the limited data available for non Western populations, and the lack of demonstration that improvement of air quality is associated with a decrease incidence of type 2 diabetes. Although the most sources of outdoor air pollution are well beyond the control of individuals, people should be informed that there are means to reduce the burden of air pollutants on diabetes risk, including avoidance of passive smoking, adoption of an healthy diet, and increasing leisure-time physical activity.

Keywords Particulate matter pollutants · Air pollution · Type 2 diabetes · Incidence · Mortality

Introduction

The prevalence of diabetes is increasing rapidly all over the world, with an estimated 592 million cases suffering from type 2 diabetes by the year 2035 [1]. The combination of continued increase in prevalence of diagnosed diabetes with declining mortality have led to an acceleration of lifetime risk and more years spent with diabetes [2]. A report from the American Diabetes Association [3] confirmed that diabetes is a major factor in total economic costs in the U.S., totaling $245 billion in 2012 and accounting for 1 in every 10 health care dollars spent. At least US$147 billion was spent on diabetes health care in Europe [1]. The type 2 diabetes epidemic has been attributed to enhanced accessibility of unhealthy foods and sedentary lifestyles [4], which can lead to the occurrence of overweight or obesity. Exposure to air pollution has also been suggested as a contributing factor to diabetes incidence and progression [5, 6].

Ambient air pollution and particulate matter pollutants

Ambient air pollution is a major environmental health problem in developed and developing countries alike. The World Health Organization (WHO) estimates that

✉ Dario Giugliano
dario.giugliano@unina2.it

[1] Department of Clinical and Experimental Medicine, Second University of Naples, Naples, Italy

[2] Department of Medical, Surgical, Neurological, Metabolic Sciences and Geriatrics, Second University of Naples, Naples, Italy

[3] IOS and Coleman – Medicina Futura Medical Center, Centro Direzionale, Naples, Italy

worldwide in 2012, around 7 million deaths—one in eight of total global deaths—occurred prematurely due to air pollution [7], which is now the world's largest single environmental health risk. WHO also estimates [7] that some 80 % of outdoor air pollution-related premature deaths were due to ischemic heart disease and strokes, while 14 % of deaths were due to chronic obstructive pulmonary disease or acute lower respiratory infections, and 6 % of deaths were due to lung cancer.

The higher premature mortality associated with air pollution is due to exposure to small particulate matter (PM) of 10 microns (PM_{10}) or less ($PM_{2.5}$) in diameter [8]. Particulate matter pollutants consist of a complex mixture of solid and liquid particles of organic and inorganic substances suspended in the air, which mostly derived from fossil–fuel combustion by motor vehicles and stationary sources such as power plants. The major components of PM are sulfate, nitrates, ammonia, sodium chloride, black carbon, mineral dust, and water.

Routine air quality measurements typically describe such PM concentrations in terms of micrograms per cubic meter ($\mu g/m^3$). When sufficiently sensitive measurement tools are available, concentrations of fine particles ($PM_{2.5}$ or smaller) are also reported. Small particulate pollution have health impacts even at very low concentrations—indeed no threshold has been identified below which no damage to health is observed. Therefore, the WHO 2005 guideline limits aimed to achieve the lowest concentrations of PM possible. Guidelines values are 10 $\mu g/m^3$ annual mean for $PM_{2.5}$ and 20 $\mu g/m^3$ annual mean for PM_{10} [9].

Particulate matter pollutants and risk of diabetes: proposed mechanisms

Type 2 diabetes results from the interaction between genetic susceptibility, environmental factors, and lifestyle choices. Although genetic predisposition, obesity, poor diet, and lack of exercise are commonly accepted causes for the development of type 2 diabetes, it is argued that these factors alone cannot full explain the rapid rise in the prevalence of diabetes. The magnitude of the association between air pollutants and type 2 diabetes has received increasing attention in recent years, and existing evidence from mechanistic studies suggest a number of possible biological pathways linking air pollutants to diabetes [6].

One mechanism is endothelial dysfunction, which precedes insulin resistance. Particulate matter pollutants have been described as a mediator of endothelial dysfunction [10, 11], implicated in reduced peripheral glucose uptake. It has been suggested that early life may represent a vulnerable period of enhancement susceptibility to $PM_{2.5}$ exposure effect [6]. The second potential mechanism is a dysregulation of the visceral adipose tissue through inflammation [12]. There is evidence that exposure to ambient PM can be associated with elevated systemic proinflammatory biomarkers. Indeed, one study reported that the association of inflammation (as assessed by blood levels of complement fragment C3c) with propensity to diabetes was enhanced by exposure to particulate matters [13]. A recent meta-analysis of prospective studies identified two inflammatory markers, that is, interleukin-6 and C-reactive protein, significantly associated with diabetes, with an increased risk of 26 % for elevated C-reactive protein and 31 % for elevated interleukin-6 levels [14].

Hepatic insulin resistance is the third potential mechanism of diabetes pathogenesis due to pollutants. $PM_{2.5}$ exposure decreases tyrosine phosphorylation in the liver but does not affect insulin receptor substrate 1 (IRS-1) levels [15]. Similarly, short-term (5-day) exposure to low-dose $PM_{2.5}$ was shown to reduce metabolic insulin sensitivity in healthy individuals [16]. Other mechanisms proposed to play a role are elevated hemoglobin A1c level [6], elevated blood pressure [17], and alterations in autonomic tone [18], which may increase insulin resistance [12]. There is also evidence that changes in adiponectin, resistin, and leptin levels over time may contribute to the association between exposure to air pollution and diabetes [6, 12].

Although a number of plausible pathways related to these mechanisms, particularly inflammation and oxidative stress, have been proposed, the mechanisms underlying the observed associations remain unclear, both because of the complex nature of diabetes etiology and the heterogeneous composition of air pollution. Moreover, no studies to date have examined the effect of air pollution exposure on beta-cell function [19].

Particulate matter pollutants and risk of diabetes: the epidemiological evidence

The epidemiological evidence linking particulate matter air pollutants and diabetes has been summarized in many recent systematic reviews with meta-analyses [20–24], published mostly in 2014 and 2015. Obviously, many of these reviews made reference to the same studies; however, depending on inclusion and exclusion criteria, not all meta-analyses included the same studies. Table 1 summarizes the results of the five meta-analyses so far published on the relationship between exposure to particulate matter pollutants and diabetes. Risk of future diabetes was assessed specifically in three meta-analyses [20, 21, 24], while the other two meta-analyses has mortality as outcome, either alone [23] or combined with risk of diabetes [22].

Table 1 Summary of meta-analyses exploring the association between particulate matter pollutants and diabetes risk or mortality

Author, year (reference)	Design	Exposure	Variable	Effect size (95 % CI)	Heterogeneity I^2 (%)	Quality/risk of bias	Outcome
Balti [20]	Cohort ($n = 5$)	$PM_{2.5}$	10 μg/m^3 increase	HR: 1.11 (1.03–1.2)	0 %	NR	Risk of diabetes
Wang [21]	Cohort ($n = 5$)	$PM_{2.5}$	10 μg/m^3 increase	RR: 1.27 (0.97–1.66)	91.4	Good/excellent	Risk of diabetes
	Cohort (3)	PM_{10}	10 μg/m^3 increase	RR: 1.15 (1.02–1.30)	0	Good/excellent	Risk of diabetes
Janghobani [22]	Cohort ($n = 2$)	$PM_{2.5}$	10 μg/m^3 increase	RR: 1.05 (0.99–1.1)	43	Risk of bias	Risk of diabetes and mortality
	Time-series (2)		or IQR increase				
	Cohort ($n = 1$)	PM_{10}	10 μg/m^3 increase	RR: 1.008 (1.003–1.013)	0	Risk of bias	Risk of diabetes and mortality
	Time-series ($n = 1$)		or IQR increase				
	Case-cross ($n = 2$)						
Li [23]	Time-series ($n = 3$)	$PM_{2.5}$	10 μg/m^3 increase	RR: 1.08 (1.03–1.13)	95.8	Good/excellent	Mortality
	Cohort ($n = 1$)						
	Case-Cross ($n = 1$)						
	Time-series ($n = 2$)	PM_{10}	10 μg/m^3 increase	RR: 1.008 (1.004–1.013)	0	Good/excellent	Mortality
	Case-cross ($n = 2$)						
Eze [24]	Cohort ($n = 3$)	$PM_{2.5}$	10 μg/m^3 increase	RR: 1.10 (1.02–1.18)	0	High risk of bias	Risk of diabetes

Case-Cross Case-crossectional, *NR* not reported, *HR* hazard ratio, *RR* relative risk, *IQR* interquartile range

The risk of future diabetes associated with exposure to each 10 μg/m^3 increase of $PM_{2.5}$ has been quantified in the range of 10 % [24] to 27 % [21]; the risk of diabetes mortality associated with $PM_{2.5}$ appears to be quite lower, around 1 % for each increment exposure of 10 μg/m^3 of both $PM_{2.5}$ and PM_{10} [23]. Where reported [21–23], the risk of incident diabetes or diabetes mortality associated with PM_{10} was lower than that associated with $PM_{2.5}$. Heterogeneity was absent in some meta-analyses [20, 24], or high in other [21, 23]. The quality of studies included in the meta-analyses were said to be good on the average, although two meta-analyses acknowledged the possibility for risk of bias [22, 24].

To summarize, the results of five recent meta-analyses support a weak positive association between exposure to particulate pollutants and diabetes. The evidence was too limited to draw a robust conclusion, in part because of some inconsistency in study designs and potentially selective reporting of the results for some of the pollutants that were measured.

Limitations of the current evidence

There are several limitations to the current epidemiological evidence of the association between exposure to particulate matter pollutants and diabetes.

(a) Ambient air pollution comprises a complex mixture of pollutants, and it is impossible to separate the effects of one individual pollutant from those of others. The limitations of single-pollutant models in explaining health consequences have been recognized [25].(b) In most studies, only diagnosed cases of diabetes were considered, with no distinction between type 2 diabetes and type 1. However, 90–95 % of patients with diabetes have type 2 disease [26], and the reported associations probably describe the effects on type 2 diabetes.(c) All evidence reported to date comes from observational studies, making it difficult to draw conclusions regarding causality; moreover, the different design of the reported observational studies may be another cause of concern because they are subject to different types of confounding.(d) Most published papers were from the North American and Western European populations; limited data are available for other populations, particularly from non-Western populations. Indeed, air pollution in China is a significant public health burden, and the mean annual averages of $PM_{2.5}$ and PM_{10} in 2013 were 72.4 and 118.5 μg/m^3, respectively [23], which were fivefold higher than the USA National Ambient Air Quality Standard of 15 μg/m^3 for $PM_{2.5}$ and the WHO standard of 10 μg/m^3. Moreover, people living in low- and middle-income countries disproportionately experience the burden of outdoor air pollution, with 88 % of the

premature deaths occurring in these areas.(e) Exposure to air pollution may also vary among population subgroups according to socioeconomic status, educational level, air conditioning use, proximity to roadways, geographic location, level of physical activity, and work environment. Kramer et al. [13] found a positive association between proximity with busy roads and risk of diabetes in individuals with low educational status.(f) Finally, information is lacking about the effects of indoor air pollution on risk of incident diabetes.

A time for concern?

The implications of a link between PM pollutants exposure and type 2 diabetes are profound as air pollution is a pervasive risk factor throughout the world and even modest alleviation in exposure may provide substantial public health benefits. Given the enormous number of people who are likely exposed to air pollution, even conservative risk estimates would still translate into a substantial increase in the population attributable fraction of diabetes related to PM pollutants. The 2005 "WHO Air quality guidelines" [27] offer global guidance on thresholds and limits for key air pollutants that pose health risks. The Guidelines indicate that by reducing particulate matter (PM_{10}) pollution from 70 to 20 $\mu g/m^3$, we can cut air pollution-related deaths by around 15 %.

The logical conclusion of this scenario would be that health officials must develop policies to minimize air pollution in order to decrease the burden of associated diseases, including type 2 diabetes. However, this seems unlikely to happen in the near future, given the complex and coordinated actions that many national and international policymakers should demand in sector-like transport, energy waste management, buildings, and agriculture. Although most sources of outdoor air pollution are well beyond the control of people, individuals should be informed that there are means to reduce the burden of air pollutants on diabetes risk.

Is prevention possible?

A growing body of evidence from epidemiologic studies, combined with animal and toxicologic experiments, suggests that inflammatory responses to diet [28] and environmental factors [15] is the key mechanism that help explain the emerging epidemic of diabetes. Non-traditional factors, such as air pollution that are pervasive in the urban environment, may provide low-level synergism with other dominant factors in accelerating propensity for type 2 diabetes.

In a large population-based cohort of women from Ontario (Canada) with over 30 years of follow-up, it was observed a 28 % increased risk of type 2 diabetes per 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure; the risk was substantially larger among smokers and obese individuals [29]. Avoidance of smoking may represent a possible strategy to reduce the risk of future type 2 diabetes in those who cannot leave the dangerous environment. This choice will also benefit the people living inside the family, as passive smoking may amplify the risk of incident diabetes. A meta-analysis of 4 prospective cohort studies, with a total of 112,351 participants involved, shows that the risk of future diabetes is increased by 28 % in those who were exposed to passive smoking as compared with those who were not [30].

In the National Health and Nutrition Examination Survey 2003–2004 [31], increased fruit and vegetable intake, reflected by serum carotenoid concentrations, was associated with the reduced probability of developing type 2 diabetes in US adults with elevated serum concentrations of polychlorinated biphenyls, persistent organic pollutants. Although there are no reported studies about the possible synergism between poor dietary habits and PM exposure on the risk of type 2 diabetes, the larger risk in obese women [29] may suggest a possible role for poor diets. In general, adoption of healthy dietary patterns, such as Mediterranean diet, which may cut by 20–23 % the incidence of future diabetes [32]. Notably, worldwide, diets low in fruits rank third for deaths attributable to individual risk factors [4].

Finally, reducing time spent in sedentary behaviors (television viewing, overall sitting) may improve general health and reduce the burden of metabolic diseases [33]; for instance, a meta-analysis of prospective studies, including 64,353 participants and 11,271 incident cases, demonstrated that a high level of leisure-time physical activity was associated with a 20 % reduced risk of incident metabolic syndrome [34], a prediabetic state.

Future perspectives

Future studies are warranted to gain greater insight into the molecular mechanisms involved, the responsible pollutants, the role of combined exposures to mixtures, and susceptibility factors. Given the already established nature of the link between PM pollutants and cardiovascular disease [17], important public health issue will likely become of even greater concern in the future given the current trend towards global urbanization. At last, we need studies which demonstrate that effective interventions aimed at improving air quality are associated with a decrease incidence of type 2 diabetes.

Conflict of interest None.

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