

## Mini Review

# Urban Air Pollution and Type 1 Diabetes: There is Still a Long Way to Go

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Italy**Received:** May 18, 2017; **Accepted:** June 06, 2017;**Published:** June 13, 2017**Abstract**

Immune-mediated Type 1 diabetes is characterized by permanent insulin deficiency and absolute requirement for insulin replacement therapy. Autoimmune destruction of beta cells has been related to multiple genetic predispositions and poorly defined environmental determinants.

Exposure to air pollution (gaseous pollutants and/or particulate matter) has been associated with diabetes incidence, prevalence and mortality. Most human studies referred to diabetes mellitus, with no distinction between Type 1 and Type 2 diabetes. Few studies focused specifically on the role of air pollutants in the development of Type 1 diabetes with inconclusive results. Based on animal model studies, hypothesized mechanisms of air pollution-mediated metabolic disease included oxidative stress, adipose tissue inflammation, mitochondrial dysfunction, insulin resistance, and pancreas toxicity. Major difficulties in establishing a relationship between air pollution and Type 1 diabetes are: the retrospective design of epidemiological studies, unwatched pollution, and long-term exposure misclassification.

**Keywords:** Type 1 diabetes; Air pollution; Risk factors**Introduction**

Immune-mediated Type 1 diabetes is characterized by permanent insulin deficiency and absolute requirement for insulin replacement therapy. Autoimmune destruction of beta cells has been related to multiple genetic predispositions and poorly defined environmental determinants [1-2]. The incidence of Type 1 diabetes is increasing in many countries and the reasons for this remain unknown: changes in environmental risk factors and/or viral infections? [3].

Exposure to air pollution (gaseous pollutants and/or particulate matter) has been associated with diabetes incidence, prevalence and mortality [1,4-7]. Most studies referred to diabetes mellitus, with no distinction between Type 1 and Type 2 diabetes. Few studies focused specifically on the role of air pollutants in the development of Type 1 diabetes with inconclusive results [4,6,8-10].

As far back as 1970, Sultz et al. evaluated the effect of continued exposure to air pollution on the incidence of chronic allergic disease in children under 15 years of age from the Erie County Study of Long-Term Childhood Diseases [11]. The average annual incidence rates for children hospitalized with diabetes mellitus by air pollution level (carbon monoxide, ozone, and particulate matter  $\leq 2.5\mu\text{m}$  in diameter or PM<sub>2.5</sub>) and social class revealed no association. In 2006, a retrospective study of 402 children suggested that cumulative exposure to ozone and sulfate in ambient air could “predispose to the development of Type 1 diabetes in children” [6]. Insulin resistance evaluated using the homeostasis model assessment-estimated insulin resistance (HOMA-IR) index in 397 10-year-old children was associated with long-term exposure to PM<sub>10</sub> and nitric dioxide [12]. The land use regression models were used to estimate long-term spatial variability of nitric dioxide, PM<sub>10</sub>, PM<sub>2.5</sub>, and PM<sub>2.5</sub> absorbance; air pollution concentrations were measured at the birth address of each

individual some years after the birth of the children. Thus, a notable study limitation was the potential for exposure misclassification due to changes in infrastructure or residential address over time. According to Malmqvist et al. mothers of offspring who developed Type 1 diabetes (n = 324) “more often had lived in areas with elevated levels of nitrogen oxides during the third trimester or ozone during the second trimester, compared to mothers of children who had not developed the disease” (n = 930). Mother’s residential coordinates (yearly updated in Sweden) were linked to the air pollution databases in order to individually assess exposure [4]. In a study population of 671 children who were positive for at least 1 islet autoantibody, exposure to traffic related pollutants (PM<sub>10</sub>, nitrogen dioxide, and possibly PM<sub>2.5</sub>) accelerated “the manifestation of Type 1 diabetes but only in very young children” [9].

Several possible mechanisms whereby air pollution could contribute to the development of diabetes have been suggested: adipose inflammation and insulin resistance, mitochondrial dysfunction, impaired endothelial reactivity, oxidative stress, and pancreatic damage [13-16].

In a mouse model of diet-induced obesity, PM<sub>2.5</sub> potentiated whole-body insulin resistance, increased visceral adiposity and inflammation, induced vascular relaxation abnormalities, and enhanced monocyte adhesion to microcirculatory beds, thus providing potential contributors to diabetes development [13]. Subsequently, in the same animal model, Xu et al. observed that PM<sub>2.5</sub> exposure decreased mitochondrial number in white adipose tissue, reduced mitochondrial size in brown adipose tissue, lowered uncoupling protein 1 expression and induced down-regulation of brown adipose-specific gene profiles [14]. Diesel exhaust particles caused adverse effects on the pancreas of streptozotocin-induced Type

1 diabetic mice, including a marked decrease in the size and number of islet cells with cellular vacuolation and increase of apoptotic islet cells. Elevated concentrations of 8-isoprostane along with decreased SOD activity and concentration of reduced GSH in the pancreas suggested a role of oxidative stress [15]. On the basis of findings in literature, PM<sub>2.5</sub> exposure has been considered a modifiable cardiovascular risk factor [16]. In a streptozotocin-induced Type 1 diabetes rat model, sub-chronic exposure to continuous, real world, non-concentrated (similar to the current air quality standards) PM<sub>2.5</sub> affected glucose homeostasis and caused inflammation, multi-organ macro- and micro-vascular complications [17].

## Conclusions

The demonstration of a significant correlation between Type 1 diabetes and pollution is an arduous endeavor due to the complexity of both diabetes pathogenesis and atmospheric chemistry. Well-designed, long-term prospective studies should be required to precisely estimate the relative risk of an outcome based on exposure, but the outcome of interest should be common (that is not the case of Type 1 diabetes). Moreover, epidemiological studies that investigate air-pollution-related health effects are facing several additional methodological problems:

1) The number of air quality indicators and the performance of air pollution sensors. There are six criteria air pollutants (ozone, carbon monoxide, sulfur dioxide, particulate matter, lead, and nitrogen dioxide) [18] but additional 187 toxic air pollutants from industrial sources [19] and the toxicity of all components is not identical. Air pollutants include gases or particle components that are directly emitted by the sources as well as secondary components that are formed by chemical and physical transformation. Thus, the performance of air pollution sensors is important in view of co-pollutants and interferences [20].

2) The selection of appropriate models for estimating individual exposure as a function of the relevant human factors and the measured pollutant concentrations [21] in order to avoid long-term exposure misclassification of modeled air pollution concentrations from several sources. Significant challenges in this respect include: characterizing place of birth or current residence as a location of long-term exposure whereas people are moving, failed geocoding of an address or mobile, lack information regarding indoor air pollution exposures, work address, exposure to air pollution at work, transportation habits, outdoor activities, incomplete dataset of annual mean pollutant concentrations, etc. [22].

## References

- Butalia S, Kaplan GG, Khokhar B, Rabi DM. Environmental Risk Factors and Type 1 Diabetes: Past, Present, and Future. *Can J Diabetes*. 2016; 40: 586-593.
- Rewers M, Ludvigsson J. Environmental risk factors for type 1 diabetes. *Lancet*. 2016; 387: 2340-2348.
- IDF Diabetes Atlas Seventh Edition. 2015.
- Malmqvist E, Larsson HE, Jönsson I, Rignell-Hydbom A, Ivarsson SA, Tinnerberg H, et al. Maternal exposure to air pollution and type 1 diabetes—Accounting for genetic factors. *Environmental Research*. 2015; 140: 268-274.
- Bhatnagar A. Could dirty air cause diabetes? *Circulation*. 2009; 119: 492-494.
- Hathout EH, Beeson WL, Ischander M, Rao R, Mace JW. Air pollution and type 1 diabetes in children. *Pediatric Diabetes*. 2006; 7: 81-87.
- Brook RD, Cakmak S, Turner MC, Brook JR, Crouse DL, Peters PA, et al. Long-term fine particulate matter exposure and mortality from diabetes in Canada. *Diabetes Care*. 2013; 36: 3313-3320.
- Di Ciaula A. Type I diabetes in paediatric age in Apulia (Italy): Incidence and associations with outdoor air pollutants. *Diabetes Research and Clinical Practice*. 2016; 111: 36-43.
- Beyerlein A, Krasmann M, Thiering E, Kusian D, Markevych I, D'Orlando O, et al. Ambient air pollution and early manifestation of type 1 diabetes. *Epidemiology*. 2015; 26: 31-32.
- Rosenbauer J, Tamayo T, Bächle C, Stahl-Pehe A, Landwehr S, Sugiri D, et al. Re: Ambient Air Pollution and Early Manifestation of Type 1 Diabetes. *Epidemiology*. 2016; 27: 25-26.
- Sultz HA, Feldman JG, Schlesinger ER, Mosher WE. An effect of continued exposure to air pollution on the incidence of chronic childhood allergic disease. *American Journal of Public Health and the Nation's Health*. 1970; 60: 891-900.
- Thiering E, Cyrys J, Kratzsch J, Meisinger C, Hoffmann B, Berdel D, et al. Long-term exposure to traffic-related air pollution and insulin resistance in children: results from the GINIplus and LISAPlus birth cohorts. *Diabetologia*. 2013; 56: 1696-1704.
- Sun Q, Yue P, Deuliais JA, Lumeng CN, Kampfrath T, Mikolaj MB, et al. Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. *Circulation*. 2009; 119: 538-546.
- Xu X, Liu C, Xu Z, Tzan K, Zhong M, Wang A, et al. Long-term exposure to ambient fine particulate pollution induces insulin resistance and mitochondrial alteration in adipose tissue. *Toxicological Sciences*. 2011; 124: 88-98.
- Nemmar A, Al-Salam S, Beegam S, Yuvaraju P, Yasin J, Ali BH. Pancreatic effects of diesel exhaust particles in mice with type 1 diabetes mellitus. *Cellular Physiol and Biochem*. 2014; 33: 413-422.
- Brook RD, Rajagopalan S, Pope CA, Brook JR, Bhatnagar A, Diez-Roux AV, et al. American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation*. 2010; 121: 2331-2378.
- Yan YH, C-K Chou C, Wang JS, Tung CL, Li YR, Lo K, et al. Sub chronic effects of inhaled ambient particulate matter on glucose homeostasis and target organ damage in a type1diabeticratmodel. *Toxicol Appl Pharmacol*. 2014; 281: 211-220.
- United States Environmental Protection Agency (EPA). Criteria air pollutants.
- United States Environmental Protection Agency (EPA). Initial list of hazardous air pollutants with modifications.
- Baltensperger U. Spiers Memorial Lecture. Introductory lecture: chemistry in the urban atmosphere. *Faraday Discussion*. 2016; 189: 9-29.
- United States Environmental Protection Agency (EPA). Human exposure modeling – General.
- Chang ET, Adami HO, Bailey WH, Boffetta P, Krieger RI, Moolgavkar SH, et al. Validity of geographically modeled environmental exposure estimates. *Crit Rev Toxicol*. 2014; 44: 450-466.