Ambient Air Pollution and Type 2 Diabetes: Do the Metabolic Effects of Air Pollution Start Early in Life?

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The adverse health effects of ambient (outdoor) air pollution have been recognized since increased mortality due to smog was reported in London in 1952 (1). Suspended particles (particulate matters) from soot were associated with increased mortality and morbidity related to both respiratory and cardiovascular disorders (1). Since then, great efforts have been made to control ambient air pollution on a national level. For example, the Clean Air Act in the U.S. resulted in improvements in ambient air quality. Between 1990 and 2015, annual concentrations of particulate matter <10 μm in aerodynamic diameter (PM_{10}) dropped by 39% in the U.S. (2). Nonetheless, ambient air pollution is still one of the leading causes of global disease burden (3,4). In fact, the World Health Organization has estimated that ambient air pollution is responsible for more than 3 million deaths, representing 5.4% of total deaths in 2012 (5).

Recently, scientific communities have suggested that ambient air pollution may increase the risk of type 2 diabetes. Animal models have provided convincing evidence and suggested potential mechanisms including particle-mediated alterations in glucose homeostasis, inflammation in visceral adipose tissue, endoplasmic reticulum stress in liver and lung, mitochondrial dysfunction and brown adipose tissue dysfunction, inflammation mediated through Toll-like receptors and nucleotide-binding oligomerization domain-like receptors, and inflammatory signaling in key regions of the hypothalamus (6). Although the evidence is still limited, epidemiological studies have also supported the hypothesis that ambient air pollution exposure is associated with elevated risk for type 2 diabetes (7–9).

Important questions not fully addressed by the literature include the following: *1*) what are the potential mechanisms supported by human population data? and *2*) when do the adverse metabolic effects of ambient air pollution start? In this issue of *Diabetes*, Alderete et al. (10) address these questions by evaluating the associations between long-term ambient air pollution exposure and longitudinal measures of insulin resistance, β-cell functions, and adiposity in 314 overweight and obese Latino children aged 8 to 15 years at baseline in Los Angeles, California. This study evaluated two air pollutants: nitrogen dioxide (NO_2), a measure of traffic-related exposure, and $PM_{2.5}$, an indicator of both traffic-related and regionally transported particles. Long-term exposure to these air pollutants were computed as yearly concentrations averaged over an individual's follow-up. This study is unique in that direct measures of glucose homeostasis based on the frequently sampled intravenous glucose tolerance test were used rather than indirect estimates from fasting glucose and insulin (i.e., HOMA of insulin resistance). In addition, the measures were longitudinally assessed for an average of 3.4 years with an average of four repeated measurements, allowing the investigators to evaluate whether higher exposure to ambient air pollution accelerates impairments in insulin sensitivity and β-cell function.

The authors report that higher exposure to both NO_2 and $PM_{2.5}$ were statistically significantly associated with a faster decline in the whole-body insulin sensitivity measure. NO_2, but not $PM_{2.5}$, was statistically significantly associated with a faster decline in the disposition index, an indicator of β-cell function. These associations were observed after adjustment for important confounding factors such as social position and body fat percent, suggesting that the observed associations are independent of socioeconomic status and adiposity, although residual confounding by built environment and residential noise could not be ruled out (11,12). In addition, both NO_2 and $PM_{2.5}$ were statistically significantly associated with faster increases in BMI and subcutaneous abdominal adipose tissue. This study failed to show that either NO_2 or $PM_{2.5}$ was statistically significantly associated with visceral fat increments, a potential mechanism supported by animal studies (13,14). Traditionally,

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visceral fat has been considered a major contributing factor for insulin resistance, but a growing body of evidence suggests that abdominal subcutaneous fat may also play a critical role in the development of insulin resistance (15).

These findings shed light on potential mechanisms by which ambient air pollution exposure, especially traffic-related pollution, influences type 2 diabetes risk. Long-term air pollution exposure may *1*) diminish insulin-dependent glucose uptake, leading to insulin resistance; *2*) impair β-cell function, resulting in reduced insulin secretion; and *3*) promote subcutaneous fat accumulation. Upstream pathways linking air pollution exposure and insulin resistance, β-cell dysfunction, and adiposity suggested by animal studies (e.g., oxidative stress, systemic inflammation, inhibition of insulin signaling, adipose tissue inflammation) remain to be elucidated in humans.

The observed findings in overweight and obese children raise the question of whether ambient air pollution is sufficient to disrupt glucose homeostasis or if it worsens glucose homeostasis only in metabolically predisposed individuals. Two population-based studies conducted in children 10–15 years of age in German birth cohorts reported a significant positive association between NO_2 and insulin resistance (16,17). This association remained significant even after adjustment for green spaces such as natural vegetation, parks, and gardens (17). This finding suggests that traffic-related exposure is at least a sufficient cause of insulin resistance. More studies are warranted to confirm whether adiposity confers susceptibility to air pollution exposure–related β-cell dysfunction.

The study by Alderete et al. (10) suggests childhood exposure to ambient air pollution between the ages of 10 and 18 may be responsible for rapid metabolic dysfunction. How important is early air pollution exposure? Because residential history was not available, this study could not evaluate or account for earlier exposure in childhood or prenatal exposure. A birth cohort study conducted in the Bronx and Northern Manhattan, New York, reported that higher maternal exposure to ambient polycyclic aromatic hydrocarbons (chemicals created during incomplete combustion processes) during pregnancy was associated with higher risk for obesity at 7 years of age (18). This finding was replicated in another prospective birth cohort study in Massachusetts, Project Viva, which showed that prenatal exposure to traffic-related pollution was associated with more rapid postnatal weight gain and higher midchildhood cardiometabolic risk including total fat mass and leptin concentrations (19,20). Together, these data and those from the study by Alderete et al. suggest that there is no specific window of susceptibility to the metabolic effects of air pollution during childhood. Traffic-related pollution may be a previously unrecognized contributor to the epidemic of pediatric obesity and related metabolic conditions in the U.S.

In summary, the findings of Alderete et al. (10) suggest that current urban air quality in the U.S. may not be safe enough for overweight and obese children who are vulnerable to cardiometabolic diseases later in life. If this is true, changes in diet and physical activity at the individual level may be insufficient to prevent obesity and type 2 diabetes in children and adolescents. This study and other recent work provide important scientific evidence that population-wide policies enforcing or even tightening national ambient air quality standards by the U.S. Environmental Protection Agency are critical to protect our next generation.

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