

Does near-roadway air pollution contribute to childhood obesity?

R. McConnell^{1,2}, F.D. Gilliland^{1,2}, M. Goran^{1,2}, H. Allayee^{1,2}, A. Hricko^{1,2} and S. Mittelman^{1,3,4}

¹Southern California Children's Environmental Health Center, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; ²Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; ³Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; ⁴The Saban Research Institute, Children's Hospital Los Angeles, Los Angeles, CA, USA

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The prevailing model of the epidemic of childhood obesity is that increased energy intake combined with a sedentary lifestyle results in positive energy balance and excess fat storage (1). Increased caloric density of food found in fast food restaurants and decreased opportunities for physical activity common in inner-city areas with high rates of obesity are likely important determinants of positive energy balance. However, emerging evidence indicates that other factors may affect food consumption, absorption, basal metabolism and adipose deposition, which could therefore be additional contributors to the epidemic. These factors include the *in utero* environment (2), neonatal feeding practices (3), dietary composition (1) and the gut microbiome (4). Furthermore, recent evidence from studies in animal models also supports the premise that a broad spectrum of environmental chemicals and chemical mixtures have 'obesogenic' properties and alter the metabolic profile of adipose tissue (5).

Animal models and human epidemiological investigations indicate that maternal smoking during pregnancy causes subsequent childhood obesity (6). Recently, prospective epidemiological studies have found associations of childhood obesity and trajectory of body mass index (BMI, calculated as weight in kg/[height in m]²) with another anthropogenic combustion source, near-roadway air pollution (NRAP). NRAP is a complex mixture, including particulate and gaseous combustion products in fresh vehicle emissions, debris from tires and brake wear, and metals from engine wear (7). Among Southern California children, increased NRAP exposure was associated with a higher BMI trajectory over the course of primary school (8). In older children followed through adolescence, exposure to NRAP (but not regional urban particulate matter), second-hand tobacco smoke (SHS) and maternal smoking during pregnancy were associated with BMI growth trajectory and attained BMI at the conclusion of follow-up at age 18 (9). More notably, synergistic effects of co-exposure to SHS and high NRAP were estimated to account for 6 kg of excess body weight in an obese young adult male.

While evidence points to nicotine as a driver of obesity associated with *in utero* exposure to maternal smoking (6), the synergistic effects of SHS and NRAP suggest that similar biological pathways may be involved in each. As there is no nicotine in NRAP, other products of these two anthropogenic combustion sources may be responsible for the observed associations, if they are indeed causal. Combustion-related polycyclic aromatic hydrocarbons, for example, are present in both NRAP and SHS. Among children in a New York City pregnancy cohort, being in the top tertile of the polycyclic aromatic hydrocarbon exposure distribution was associated with greater than twofold increased risk of obesity at age 7 (10).

Together, these observations challenge the view that childhood obesity is due solely to increased caloric intake and reduced physical activity, or even food composition and feeding practices. In addition, they cast doubt on the usual explanation that *in utero* exposure to nicotine is the only cause of the well-recognized obesogenic effects of early life tobacco smoke exposure.

There are several possible mechanisms for obesogenic effects of combustion products. NRAP-associated weight gain in animals could be mediated by effects on the brain (11), possibly through effects on appetite or on anxiety-associated overeating. For example, mice exposed *in utero* to diesel exhaust particulate, a model near-roadway air pollutant, had an increase in fetal brain inflammatory cytokines and subsequent increased adult microglial activation and increased anxiety induced by a high fat diet than mice exposed to filtered air during gestation (11). Exposed mice gained more weight during early life, and the early life exposure to diesel exhaust particulate also primed mice to gain more weight when placed on a high fat diet later in life.

Alternative explanations include NRAP-induced changes in basal metabolism. Polycyclic aromatic hydrocarbons inhibit catecholamine-induced lipolysis, resulting in weight gain in experimental animals (in the absence of increased caloric intake) (12). Animal studies have also shown that early life exposure to urban particulate matter causes mitochondrial

damage and increased accumulation of white adipose tissue relative to metabolically active brown adipose tissue (13–15), potentially skewing overall metabolic balance from energy utilization more towards storage. *In utero* exposure to particles also results in less DNA methylation and higher gene expression of PPAR γ , effects of which were shown to extend transgenerationally (16). Ambient particulate matter has also been found to have oestrogenic effects (17), and *in utero* exposure to environmental oestrogens cause subsequent obesity in an animal model (18). Finally, exposure to urban particulate matter led to marked increases in visceral adipose tissue and adipose tissue inflammation, both of which are considered to be determinants of the development of the associated insulin resistance and metabolic abnormalities (15). However, urban background particle-exposed animals in general did not gain more weight compared with those exposed to filtered air. This raises the intriguing possibility that NRAP causes obesity, while urban background particulate contributes to obesity-associated metabolic and inflammatory sequelae, if not obesity itself.

In conclusion, new epidemiological findings and animal models suggest that there may be large obesogenic effects of NRAP. The results of such studies could have large public health implications, since NRAP and SHS exposure are both prevalent in the most at-risk populations. It is likely that neither regional urban exposure to particulate matter nor SHS by themselves are important causes of the epidemic of childhood obesity, at least in the United States because levels of regional pollution and smoking rates have both declined over the course of the epidemic. However, there are many toxicologically relevant compounds in the complex mixture of NRAP, which has not been well characterized, and there has been a large temporal increase in number of vehicle miles travelled over the past several decades corresponding well to the time course of the epidemic (19). Heavy NRAP-generating traffic corridors are ubiquitous in poor urban areas where the epidemic is most acute. A role for NRAP in the epidemic, perhaps in combination with increased caloric intake and changing dietary composition in an environment not conducive to physical activity, or in synergy with stable or decreasing levels of tobacco smoke exposure, merits further investigation to identify novel mechanisms of obesogenic effects and potential targets for intervention.

Conflict of Interest Statement

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