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Mexico City normal weight children exposed to high concentrations of ambient $PM_{2.5}$ show high blood leptin and endothelin-1, vitamin D deficiency, and food reward hormone dysregulation versus low pollution controls. Relevance for obesity and Alzheimer disease

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ABSTRACT

Millions of Mexico, US and across the world children are overweight and obese. Exposure to fossil-fuel combustion sources increases the risk for obesity and diabetes, while long-term exposure to fine particulate matter ($PM_{2.5}$) and ozone (O_3) above US EPA standards is associated with increased risk of Alzheimer's disease (AD). Mexico City Metropolitan Area children are chronically exposed to $PM_{2.5}$ and O_3 concentrations above the standards and exhibit systemic, brain and intrathecal inflammation, cognitive deficits, and Alzheimer disease neuropathology. We investigated adipokines, food reward hormones, endothelial dysfunction, vitamin D and apolipoprotein E (APOE) relationships in 80 healthy, normal weight 11.1 ± 3.2 year olds matched by age, gender, BMI and SES, low (n: 26) versus high (n:54) $PM_{2.5}$ exposures. Mexico City children had higher leptin and endothelin-1 ($p < 0.01$ and $p < 0.000$), and decreases in glucagon-like peptide-1 (GLP 1), ghrelin, and glucagon (< 0.02) versus controls. BMI and leptin relationships were significantly different in low versus high $PM_{2.5}$ exposed children. Mexico City APOE 4 versus 3 children had higher glucose ($p = 0.009$). Serum 25-hydroxyvitamin D < 30 ng/mL was documented in 87% of Mexico City children. Leptin is strongly positively associated to PM $_{2.5}$ cumulative exposures. Residing in a high $PM_{2.5}$ and O_3 environment is associated with 12 h fasting hyperleptinemia, altered appetite-regulating peptides, vitamin D deficiency, and increases in ET-1 in clinically healthy children. These changes could signal the future trajectory of urban children towards the development of insulin resistance, obesity, type II diabetes, premature cardiovascular disease, addiction-like behavior, cognitive impairment and Alzheimer's disease. Increased efforts should be made to decrease pediatric $PM_{2.5}$ exposures, to deliver health interventions prior to the development of obesity and to identify and mitigate environmental factors influencing obesity and Alzheimer disease.

1. Introduction

Environmental pollutants have a negative health impact upon children ranging from impaired systemic immunity, delayed psychomotor development, hypertension, insulin dysregulation, reduced lung function, preterm birth, cognitive and olfaction deficits, white matter volumetric changes, systemic inflammation, neuroinflammation, and the hallmarks of Alzheimer disease

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(Gehring et al., 2013; Pedersen et al., 2013; Guxens et al., 2014; Liu et al., 2014a, 2014b, 2014c; Vella et al., 2014; Calderón-Garcidueñas et al., 2007, 2008a, 2008b, 2010, 2011a, 2011b, 2012a, 2012b, 2013a, 2013b, 2015a, 2015b). Sources of air pollutants include common environmental pollutants, molds, and outdoor and indoor fine particulate matter ($PM_{2.5}$) (Baxi et al., 2013; Amato et al., 2014). $PM_{2.5}$ is particularly important for children's health and particle size range, source category, residency within a city, and season have a different impact upon adverse health effects (Calderón-Garcidueñas and Torres-Jardón, 2012, 2015; Amato et al., 2014).

Significant concerns among Mexican, American, Mexican–American and African–American children include their higher rates of obesity and the link between traffic-related air pollution and metabolic syndrome (MetS), obesity, hypertension, and diabetes mellitus (DM) (Iriart et al., 2013; Li et al., 2014a, 2014b; Jerrett et al., 2014; Falkner and Cossrow, 2014). Traffic pollution has been positively associated with growth in BMI in children aged 5–11 years in Southern California (Jerrett et al., 2014). It is also clear that in experimental animal models and epidemiological studies, PM and gaseous air pollutants, even at concentrations below air quality guidelines, exacerbate the metabolic imbalance in diabetes mellitus, impair glucose tolerance during pregnancy, and increase DM risk (Vella et al., 2014; Fleisch et al., 2014; Liu et al., 2014a, 2014b, 2014c; Eze et al., 2014).

In the setting of severe air pollution, a serious concern is vitamin D deficiency in close association with indoor confinement during the day, residency at higher altitudes, darker skin pigmentation and poor nutritional intake (Alvær et al., 2007; Balasubramanian and Ganesh, 2008; Calderón-Garcidueñas et al., 2013a, 2013b; Christakos et al., 2013; Kelishadi et al., 2014; Miñambres et al., 2014). Vitamin D deficiency in Metropolitan Mexico City area (MCMA) children is important because well-known metabolic and dementia links (Annweiler et al., 2013; Anastasiou et al., 2014; Bishnoi et al., 2014; Bartali et al., 2014).

With this background, we focused on the impact of lifelong exposures to $PM_{2.5}$ upon adipokines, endothelial dysfunction, APOE and vitamin D status in low versus high air pollution exposed children age 11.1 ± 3.2 years matched by age, gender, weight, height, BMI, and socioeconomic status (SES). The APOE ε4 allele is the strongest known genetic risk factor for late and early onset AD (Michaelson, 2014; Huang and Mahley, 2014), and given our previous reports of Mexico City APOE 4 young carriers accelerating their expression of AD neuropathological markers (Calderón-Garcidueñas et al., 2008a, 2008b, 2010, 2012a, 2012b, 2013a, 2013b), APOE genotyping was included in this work. Likewise, high concentrations of endothelin-1 (ET-1), a marker of endothelial dysfunction and exposure to severe air pollution obligated its inclusion (Calderón-Garcidueñas et al., 2007). The primary aim of this study was to measure 12 h fasting adipokines, lipids, glucose and ET-1 from clinically healthy MCMA children versus controls (i.e., all criteria pollutants below the current US standards). Concurrently, we measured vitamin D playing critical roles in insulin metabolism and cognitive responses. Finally, in keeping with the fact Mexico City children are at high risk of obesity, we wanted to define their profile of food reward hormones, an issue of pressing importance given their restricted physical activity, unbalanced diets and a record of the world highest per capita intake of commercial carbonated beverages (Barquera et al., 2008; Bonvecchio et al., 2009; Piernas et al., 2014; Duffey et al., 2014). Effective January 2014, a significant increment in the cost of soft drinks by the 8% federal tax, resulted in the substitution of sugar cane by high-fructose corn syrup (HFCS) by the soft drink industry in Mexico. An increase in HFCS will severely aggravate the obesity, chronic metabolic disease, cognitive decline and risk of Alzheimer's disease in exposed children (Lakhan and Kirchgessner, 2013; Lustig, 2013; Regnault et al., 2013; Sloboda et al., 2014). The complexity of the systemic inflammation, neuroinflammation and the early hallmarks of AD in Mexico City teens is worsen by data supporting that adipokines mediate inflammation and insulin resistance (Kwon and Pessin,2013) and deficient brain insulin signaling pathways are critical etiological factors in Alzheimer's disease (Lee et al., 2013; De la Monte, 2014). Short and long-term health implications of our findings are serious especially in view of the social segregation in health care (Cotlear et al., 2014).

2. Procedure

2.1. Study cities and air quality

Mexico City Metropolitan Area (MCMA) is an example of extreme urban growth and accompanying environmental pollution (Molina et al., 2007). The metropolitan area of over 2000 square kilometers lies in an elevated basin 2240 m above mean sea level, 24 million inhabitants, over 50,000 industries and >5 million vehicles consume more than 40 million liters of petroleum fuels per day producing millions of tons of pollutants including coarse and fine particulate matter, gaseous pollutants, polycyclic aromatic hydrocarbons, and lipopolysaccharides. The higher short term (i.e., hourly averages) fine particulate matter (particles with a diameter less than 2.5 μm, $PM_{2.5}$) concentrations coincide with the times children are outdoors during school recess and physical education periods and when they go home (Villarreal-Calderón et al., 2002). Recent studies on the composition of $PM_{2.5}$ with regards to sites and samples collected in 1997 show that composition has not changed during the last decade (Molina et al., 2010). Contrary to higher latitude polluted urban areas that during the winter season generally have lower pollution levels, the seasonal climatic conditions in MCMA are relatively stable and thus pollutant concentrations are above standards all through the year, and year after year. An important observation affecting MCMA residents is that due to high traffic density and increased energy usage, exposures to high levels of particulate black carbon (BC) are common (Molina et al., 2007). BC is the dominant light-absorbing aerosol species produced by diesel engines within the urban area and by incomplete combustion of fossil fuel biomass burning in the surroundings rural areas. The absorption of solar light by freshly emitted BC aerosols is broadband, although they are more efficient in the UVB range (280–315 nm). The presence of highly absorbing fine mode aerosols in MCMA is expected to reduce the UV flux at ground level and therefore to reduce the photochemical production of oxidants such as ozone (Li et al., 2011). However, under certain meteorological circumstances, the presence of fine mode scattering aerosols in the boundary layer in the MCMA air basin that approach the same size as the wavelength of the incoming UV radiation may also increase in the UV-B flux at ground level due to their ability to strongly scatter light towards the forward direction. In turn, this increase in UV-B flux leads to an increase in photochemical pollution (Marley et al., 2009). Nevertheless, the net reduction effect in UV-B radiation predominates. The control city Polotitlán, is a small town 2300 meters above mean sea level, 73 miles Northwest of Mexico City with an estimated population of 13,000 residents. Its main activity is agriculture with a few small dairy plants. In contrast to Mexico City, historical monitoring data in Polotitlán as well as mathematical modeling of air pollutants covering the central region of Mexico indicate that air quality for all criteria pollutants in this part of the country has been typically below the equivalent US EPA air quality standards (Ali et al., 2010; GEM, 2008).