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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) v controls. BMI and leptin relationships were significantly different in low v high $PM_{2.5}$ exposed children. Mexico City APOE 4 v 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.

Keywords: Alzheimer, children, fructose, leptin, APOE, $PM_{2.5}$ air pollution, Mexico City, obesity, vitamin D

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 (Gehring et al., 2013; Pedersen et al., 2013;Guxens et al., 2014; Liu et al., 2014;Vella et al., 2014; Calderón-Garcidueñas et al., 2007, 2008, 2010,2011,2012,2013,2015). 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; 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., 2014; Jerret 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 (Jerret 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., 2014; 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., 2013;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 v 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., 2008, 2010,2012,2013), 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 v 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 50000 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 2.5μm, $PM_{2.5}$) 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 13000 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).

2.2 Participants

Study Areas and Children's Cohorts

This prospective protocol was approved by the review boards and ethics committee at the University of Montana and the Hospital Central Militar, written consent was obtained from parents and verbal consent from children. MCMA and controls belong to the same SES and attended public schools with identical academic and physical education curricula. We included data from 54 MCMA children (*Mean age* = 11.69 years, *SD* = 3.61) and 26 controls (*Mean age* = 10.53 years, *SD* = 2.95). Clinical inclusion criteria were: negative smoking history and environmental tobacco exposure, lifelong residency in MCMA or in the control city, residency within 5 miles of the closest monitoring station, full term birth, breastfeed for ≥ 6 to ≤ 12 months, and unremarkable clinical histories. Exclusion criteria included: i. premature birth, ii. any systemic disease, iii. intake of any medications prescribed or over the counter, including vitamins and dietary supplements. Mothers were permanent residents in either the control city or in Mexico City, had unremarkable, full term pregnancies with uncomplicated vaginal deliveries and took no drugs, including tobacco and alcohol. Mothers were not exposed to second or third hand tobacco smoke. Participants were from middle class families living in single-family, non-smoking homes with no indoor pets, used natural gas for cooking and kitchens were separated from the living and sleeping areas. Outdoor daily exposures in hours per day were recorded by the mother for 7 days, including the transit time to and from school, the time spent in recess and physical education during school, and the outdoor time while playing and engaging in other activities. The amount of time spent in PE and the type of activity was given by the PE teacher in charge of the student. The low v high exposure cohorts were matched for age, gestational duration, birth weight, gender ratio, maternal age, education, and SES.

Pediatric and Dermatological Examination

Children had complete clinical histories and physical examinations including recording the type of skin according with the Fitzpatrick Classification Scale (Fitzpatrick, 1988). The anthropometric measurements in the fasting state, included weight measured without shoes and to the nearest 0.05kg and height measured barefoot to the nearest 0.1cm in the horizontal plane. BMI was calculated as body mass (kg) divided by height (m) squared ($kg.m^{-2}$). Twelve hour fasting blood samples were collected between 7:00 and 9:00 am.

Peripheral Blood Analysis

Blood samples were taken for a Comprehensive Metabolic Panel (CMP) and custom made human Multiplexing Laser Bead Technology, Bio-Rad Human Diabetes (Eve Technologies Corporation, Calgary, Alberta, Canada) for the quantification of the following markers: C-Peptide, Ghrelin (active), Gastric Inhibitory peptide GIP (total), Glucagon-like peptide 1 GLP-1 (active), Glucagon, Insulin, Leptin, Plasminogen activator inhibitor 1 PAI-1(total), Resistin, and Visfatin. Endothelin-1, QuantiGlo ELISA from R&D Systems, Minneapolis, MN, USA (detection limit 0.102 pg/mL), and 25-OH-Vitamin D ELISA (detection limit 1.6 ng/mL) from Diagnostika GMBH, Adlerhorst, Hamburg, Germany were done following the supplier instructions.

Apolipoprotein E Genotyping

Peripheral blood samples were APOE genotyped using Taqman ready to use assays from both SNP's that constitute the APOE genotype according to TaqMan Gene Expression Assays, Applied Biosystems, 2006.

Data Analysis

The univariate descriptive measurements of characteristic variables of the two groups were calculated along with 95% confidence intervals and p values of two sample t-test for difference between two group means. The Gaussian distribution was assumed in the inference procedures, i.e., confidence intervals and two sample t-tests. The laboratory data were analyzed using the same method as the characteristic variables assuming Gaussian distribution. Pearson Chi-Square values were calculated to define the differences among groups for age, weight, height and BMI between Controls and Metropolitan Mexico City children. Multiple comparisons Post Hoc focused analyses between controls and MCMA children were done using Games-Howell test.

The r-squares of linear regression and p values for testing linear relationship were calculated. Statistical analyses were performed using R version 2.13 (http://www.r-project.org/). Univariate descriptive measurements were summarized as mean values ±standard deviations. Significance was assumed either if 95% confidence intervals do not cover zero or at $p<0.05$. We also modeled leptin concentrations as a function of age and the annual mean $PM_{2.5}$ concentrations in Southwest Mexico City using a non-linear correlation surface map resulting in a 3D Gaussian graphic.

The strength of simple linear relationship was summarized as r-squares.

3. Results

Air Pollution Levels

Mexico City Metropolitan Area children in this study have been exposed to significant concentrations of $PM_{2.5}$ and O_3 for their entire life (Molina et al., 2010). In the last decade, that includes the average age of the participants, $PM_{2.5}$ annual average concentrations in SWMC were from 22.3 (± 9.9) $\mu g/m^3$ in 2002 to 16.8 (± 8.3) $\mu g/m^3$ in 2012 (the respective US EPA annual standard calls for an $PM_{2.5}$ annual average limit of 12 $\mu g/m^3$ averaged over 3 years). In addition, the 4th highest daily maximum 8-hr average ozone concentration for the same period in the same MCMA sector were from 0.165 ppm to 0.129 ppm (the ozone US EPA air quality standard stands for an annual fourth-highest daily maximum 8-hr concentration of 0.075 ppm averaged over 3 years). Figures 1 and 2 show the $PM_{2.5}$ annual average concentrations and the 4th highest daily maximum 8-hr average ozone concentrations from 2002 to 2012 in southwest MCMA. UV-B levels at ground level have been lower in MCMA than in the surrounding rural locations because of the attenuation effect of the polluted urban air in Mexico City, including the presence of highly absorbing aerosols (Li et al., 2011; Acosta et al., 2000). Short term PM_{10}, O_3, SO_2 and NO_2 monitoring campaigns performed by the Government of the State of Mexico in the control city Polotitlán before 2005 (Secretaría de Ecología, 2005), recent measurements of PM_{10} and O_3 in San Juan del Río, 24 km to the northwest of Polotitlán (Valtierra et al., 2011), and mathematical modeling of ozone air quality in the center of Mexico (Ali et al., 2010) indicate that criteria pollutant control levels are below the USA EPA air quality standards due to the combination of few contributing emission sources from industry and cars and good ventilation conditions due to regional winds.

Demographic Data and Physical Exams

Table 1 summarizes the characteristics of the matched samples. There were 26 controls (12 females, 14 males) and 54 MCMA children (34 females, 20 males). Controls spend more time outdoors than MCMA children (CTL 4.3±0.5, MCMA 3.5±0.2, $p<0.001$). We found no differences among groups for age, gender, weight, height and BMI. The predominant skin type was type IV with 13 % type III (Fitzpatrick, 1988).

Laboratory findings

Tables 2-4 show the concentrations and values of the selected variables in MCMA v controls. MCMA children (Table 4) exhibited significantly higher ET-1 ($p<0.0001$), leptin and glucose ($p= 0.01$), while they had significant reductions in ghrelin ($p= 0.005$), GLP-1 ($p= 0.003$), and glucagon ($p= 0.02$). Multiple Comparisons Post hoc focused analyses (Table 5) between MCMA APOE 3 and 4 carriers showed higher concentrations of glucose ($p=0.009$) in ε4 carriers. Significant differences in cholesterol and GLP-1 ($p=0.009$), glucose ($p=0.016$), ghrelin ($p=0.024$), leptin ($p=0.027$) and glucagon ($p=0.041$) were seen between controls and APOE 4 MCMA children, and between controls and MCMA APOE 3 children: C peptide ($p=0.028$) and leptin ($p=0.005$). Leptin was significantly higher in females v males adjusting for age in MCMA children ($p=0.02$). BMI /leptin, BMI/HOMA-IR and leptin/insulin are significantly related after adjusting age and gender ($p <0.0001$, 0.026, 0.0009) respectively in all children. BMI and leptin and GLP1/ glucose relationships are significantly different in control v Mexico City children ($p=0.006$ and <0.0001 respectively). Figure 3 illustrates a 3D mesh plot of simultaneous measurements of leptin and BMI with regards to the age of each participant for the study areas. Figure 4 shows the 3D Gaussian non-linear correlation surface map ($R2 = 0.58$) of the modeled leptin concentration as a function of age and the annual mean $PM_{2.5}$ concentrations in southwest Mexico City. There are significant differences in APOE 4 v 3 MCMA children in the relationships between BMI and glucose ($p=0.006$), BMI and GLP-1 ($p=0.023$) and GLP1 and insulin ($p= 0.042$).

Normal values of vitamin D were seen in 31% and 13% respectively in control and MCMA children. Vitamin values below 20 ng/ml indicative of deficiency were recorded in 46% of MCMA children, while 41% fell in the insufficiency values (21 and 29 ng/ml) (Table 6).

4. Discussion

Seemingly healthy normal weight children with prenatal and lifetime exposures to fine particulate matter ($PM_{2.5}$) and ozone above current US safety standards are showing high levels of leptin, a powerful pro-inflammatory adipokine implicated in brain development, neuroplasticity, insulin resistance, obesity, type 2 diabetes and cardiovascular disease (Steppan and Swick,1999; De la Monte,2014; Stieg et al. 2015). Mexico City children showed dysregulation of feeding regulatory hormones including glucagon-like peptide-1, ghrelin, and glucagon, also involved in the modulation of reward processes, motivated behaviors and cognitive performances (Monteleone and Maj, 2013). Residency in a polluted environment results in altered appetite-regulating peptides and increases in endothelin-1- a powerful vasoconstrictor and pro-inflammatory mediator (Teder and Noble, 2000; Freeman et al., 2014; Bickford et al., 2014). To worsen the scenario, these children also have marked vitamin D deficiency. Not unexpectedly, apolipoprotein E (APOE) 4 allele, the strongest known genetic risk factor for late and early onset AD (Michaelson, 2014; Huang and Mahley, 2014; Calderón-Garcidueñas et al., 2015), is playing a role in a child metabolic responses to lifelong residency in a polluted environment.

Fasting high leptin concentrations in normal weight urban children is a finding with important health implications in the setting of air pollution, systemic inflammation, neuroinflammation and the early hallmarks of Alzheimer's disease (Calderón-Garcidueñas et al., 2002, 2004, 2008, 2012, 2013). Leptin is an anorexigenic pleiotropic hormone, a potent insulin sensitizer, released by white adipose tissue signaling states of negative energy balance and decreased energy stores (Zhang et al., 1994; Rosenbaum and Leibel, 2014; Farr et al., 2014). Circulating leptin signals to the brain the amount of stored energy in body fat (Farr et al., 2014). Leptin plays a key role in inflammatory processes involving either innate or adaptive immune responses (Gainsford et al., 1996; Lago et al., 2008; Kwon and Pessin, 2013; Conde et al., 2014),its effects on circulating immune cells contribute to the promotion of inflammation in obese children (Inzaugarat et al., 2013) and other inflammatory mediators such as TNF α and lipopolysaccharides (LPS) stimulate the expression of both leptin and leptin receptors (Grunfeld et al., 1996; Gan et al., 2012). Obese rodents and humans have high circulating leptin, suggesting obesity is associated with leptin resistance (Friedman and Halaas, 1998). Indeed, obese children have higher leptin and soluble leptin receptor levels, making it a useful marker of metabolic syndrome and insulin resistance and a player in innate and adaptive immune responses involved in the maintenance of low grade inflammation (Inzaugarat et al., 2013; Catli et al., 2014; Goodson et al., 2014; Gonzaga et al., 2014). Leptin has central key actions (Farr et al., 2014) including brain development and neuroplastic events, and crosses the blood-brain-barrier (BBB) through saturable, receptor-mediated transport (Banks et al., 1996; Caro et al., 1996; Pan et al., 2008, 2014; Bouret, 2010). Central resistance to leptin in obese subjects is associated with peripheral hyperleptinaemia usually linked to decreased leptin BBB transport efficiency (Elmquist et al., 1998; Baharami et al., 2014). Plausible factors potentially affecting leptin regulation, BBB transport, and activation/uncoupling ligand leptin brain receptors (Li et al., 2013; Zabeau et al., 2014), in urban children may include: i. Diffuse neuroinflammation involving supra and infratentorial brain structures, ii. Lipopolysaccharide-associated particulate matter immune stress, iii. Significant increases in the potent vasoconstrictor endothelin-1, and iv. Brain endothelium damage resulting in a disrupted BBB (Calderón-Garcidueñas et al., 2007, 2008, 2012;Sachot et al., 2004; Qin et al., 2007; Pan et al., 2008; Brook and Rajagopalan, 2012; Iwasa et al., 2014; Pohl et al., 2014). Harris has shown that simultaneous activation of leptin receptors in supra and infratentorial key regions modulates an integrated response to leptin concentrations (Harris, 2013), thus any process, i.e., air pollution-associated diffuse neuroinflammation (Calderón-Garcidueñas et al., 2007, 2008, 2012), altering this balance could result in a disrupted leptin action. Highly exposed Mexico City children v controls exhibit prefrontal up-regulation of gene network clusters IL1, NFκB, TNF, IFN, TLRs and inflammasomes (Calderón-Garcidueñas et al., 2012). Their brainstem is at the core of the neuroinflammatory process with high immunoreactivity for 8 hydroxi-deoxyguanosine, activated microglia and accumulation of alpha synuclein involving the ventral tegmental area, substantia nigrae, nucleus ambiguus, and the dorsal motor nucleus of the vagus, among others. The anatomical areas involved in Mexico City children overlap the well described leptin cellular targets (Steppan and Swick, 1999; Grill and Hayes, 2009; Scott et al., 2009; Bouret, 2013). The arcuate nucleus of the hypothalamus, hippocampus, cortical neurons, insular cortex, lateral septal nucleus, ventral tegmental area and midbrain dopaminergic neurons express leptin receptors and are influenced by signals that carry information about nutritional and metabolic states (Pan et al., 2008; Scott et al., 2009;Bouret, 2009, 2013). Sachot et al (2004) have

shown that endotoxins induce leptin synthesis and secretion in the periphery and leptin is a neuroimmune mediator of LPS-induced inflammation. The issue becomes complicated in diet-induced obese animals, in whom leptin plays a key role in modulating the late portion of the fever response to LPS through hypothalamic IL6 induction (Pohl et al., 2014).

Why is this leptin-LPS relationship particularly relevant for Mexico City children? Because Mexico City children cohorts exhibit an endotoxin tolerance-like state, and systemic inflammation, along with increased numbers of mCD14+ monocytes, the key membranous receptor involved in LPS binding (Calderón-Garcidueñas et al., 2009). Children in this study are historically exposed to significant concentrations of lipopolysaccharides associated with PM (Bonner et al., 1998; Osornio-Vargas et al., 2003). Thus, exposed children could have LPS-PM-induced immune stress that impacts the synthesis and secretion of leptin, and relates to their CD14 and inflammasome brain up-regulation (Calderón-Garcidueñas et al., 2008,2012; Steinstra et al., 2011; Iwasa et al., 2014). The complexity of the LPS-PM exposures is highlighted when we reviewed prenatal rat exposures to LPS combined with a high fat diet (Hao et al., 2014). The striking results observed in 3 month old offspring rats combined insulin resistance and impaired liver function (Hao et al., 2014). Hao and his group make a very important conclusion: prenatal exposure to LPS (as in pregnant Mexico City mothers and their fetuses), concomitantly with a high-fat diet results in offspring with insulin resistance. Thus, we have a potential evolving high leptin scenario in highly exposed urban children that actually could start *in utero*.

Like new and exciting observations, this study prompts many additional questions. For example, do we have a central leptin resistance in urban children *before weight changes* take place? If so, since leptin plays a key role in the developing brain (Steppan and Swick, 1999; Stieg et al., 2015; Farr et al., 2014; Bouret, 2010; Johnston et al., 2014; Pérez-Gónzalez et al., 2011; Busch et al., 2011; Folch et al., 2012; Zhang et al., 2013; Mancini et al., 2014; Davis et al., 2014) are the high leptin concentrations in serum associated with high CSF leptin and low leptin receptors mRNA in target areas like hippocampus as in Alzheimer's patients? (Bonda et al., 2014). If indeed, aberrant leptin signaling is present in urban children as in patients with neuroinflammatory entities, i.e., AIDS and Alzheimer's disease (Bonda et al., 2014; Huang et al., 2007; Johnston et al., 2014) will children's brain development be compromised? Given that leptin dysregulation is a key finding in AD (Bonda et al., 2014; Farr et al., 2014; Irving et al., 2013; Arnoldussen et al., 2014; Ríos et al., 2014), experimental AD mouse models exhibit dysregulated adipokine pathways in hippocampus (Pedrós et al., 2015) and high serum leptin concentrations have been recently linked to long-term exposure to ambient air pollution in older adults (Wang et al., 2014), the answer to our question is urgent.

The issue of urban children having significant endothelial damage, and the presence of nano size PM in their brain endothelium are critical (Calderón-Garcidueñas et al., 2008, 2011, 2012). It is well known that common urban air pollutants like diesel exhaust impair endothelial progenitor cells, neoangiogenesis and increase atherosclerotic lesions (Pöss et al., 2013). Exposures to ozone and PM rapidly modulate the expression of genes involved in key vasoregulatory pathways in the brain and pituitary, substantiating the notion that inhaled pollutants induce cerebrovascular effects and adding to the neuroinflammatory changes seen in exposed urbanites (Thomson et al., 2007; Karthikevan et al., 2013). ET-1 blood levels alter key regulatory mechanisms of the cerebral circulation by modulating endothelial NO synthase phosphorylation and NO production through Rho-associated protein kinase (Faraco et al., 2013). The significant vasoconstrictive and pro-inflammatory ET-1 effects at selected brain loci could also alter leptin regulatory circuits and BBB transport in urban children (Freeman et al., 2014; Faraco et al., 2013; Kurokawa et al., 1997; Mathison et al., 2007; Rossi et al., 2008). The ET1-induced cerebrovascular dysfunction may contribute to the vascular alterations associated with neuroinflammation. Indeed, hyperleptinemia *per se* is an important mediator of endothelial dysfunction and causes deleterious effects on endothelium and vascular smooth muscle cells (Payne et al., 2014). Hyperleptinemia has negative associations with vasodilatation in resistance arteries in conjunction with arterial stiffness, hypertension and sympathetic nervous system activation (Beltowski et al., 2012; Wang et al., 2013; Gónzalez et al., 2013). The relationship between ET-1 and leptin is clearly shown in spontaneously hypertensive rat's thoracic aorta and pulmonary arteries responses. Decreased leptin receptors were simultaneous with high expression of ET-1 A and B receptors and inducible nitric oxide synthase (Gomart et al., 2014). These observations are very relevant to our work because high ET-1 and leptin characterize MCMA exposed children and we have shown repeatedly that exposure to $PM_{2.5}$ is associated with increased levels of circulating endothelin-1 and elevated mean pulmonary arterial pressure in similar cohorts (Calderón-Garcidueñas et al., 2007, 2009).

We are aware food reward hormone imbalance is associated with overweight, obese or anorexic individuals, thus our findings in normal weight healthy MCMA children can't be dismissed as they could signal the future trajectory of these children towards the development of insulin resistance, metabolic syndrome, obesity, type II diabetes, and premature cardiovascular disease. Their appetite-regulating peptide imbalance is interesting: leptin promotes suppression of appetite, in contrast to ghrelin secreted by the stomach and being a potent and effective appetite stimulant. GLP-1 originating in the duodenal L-cells, small and large intestinal mucosa and in the caudal brainstem and hypothalamus, suppresses appetite and reduces the rate of food absorption into the blood by lowering the rate of gastric emptying. GLP-1 secretion depends on meal content and it is particularly high with high-fat meals. Glucagon on the other hand, enhances glucose synthesis and release in the liver and suppresses appetite and causes weight loss (Cegla et al., 2014). Thus, high leptin and low ghrelin suppress the appetite, while low GLP-1 and glucagon contribute to appetite stimulation. The final effect on a child will also depend on meal content, the amount of high-fat and sugar, including fructose, the amount and distribution of body and liver fat content, the effects on insulin sensitivity and glucose metabolism, the basal nutritional status, gonadal status, exercise level, the integrity of the brain-gut axis, and their genetic susceptibility for diabetes mellitus (Bouret, 2013; Peltus et al., 2013; Korek et al., 2013; Shah and Vella, 2014; Liu et al., 2014; Laughlin,2014). Low levels of ghrelin are of concern in children given its involvement in the regulation of growth hormone, memory and learning, food addiction and neuroprotection (Albarran-Zeckler et al., 2011). Since ghrelin is more than a promoter of feeding and appetite, its participation in brain growth, neurogenesis, pancreas and gastrointestinal tract developmental processes, higher brain functions, including sleep-wake state, learning and memory and its link between metabolism and neurodegeneration (Folch et al., 2012; Stewlorum and Bouret,2011; Stoyanova,2014) makes it a key follow-up marker in exposed children.

Evidence is accumulating of the close relationship between hormones involved in feeding behavior and neural systems that modulate dopaminergic and opioidergic brain systems, thus our findings beg the important question of whether the dysregulation in feeding behavior hormones seen in young urbanites will impact overeating, obesity and the development of addiction-like behavior (Daws et al., 2011). Hormones controlling feeding behavior interact with or modulate neural systems implicated in reward function (Daws et al., 2011). Since overeating, particularly of highly palatable foods, can affect the dopaminergic and opioidergic brain systems, the development of addiction-like behavior has to be considered (Daws et al., 2011). The issue is critical in urban youngsters because the behavioral and neurochemical overlap between overeating highly palatable foods, alcohol and cocaine drug addiction, insulin signaling and regulation of dopamine neurotransmission (Daws et al., 2011; Engel and Jerlhag, 2014; Blum et al., 2014; García-García et al., 2014; Burghardt et al., 2012). The Reward Deficiency Syndrome (RDS) results from an impairment of the brain reward circuitry with a hypo-dopaminergic function (Blum et al., 2014). The link with RDS, leptin, insulin resistance, overeating and obesity is difficult to ignore in exposed youngsters. Reward signaling and sensitivity and the leptin's ability to modulate dopaminergic responses (Burghardt et al., 2012) could be impaired. Future examination of these mechanistic pathways, appear warranted in urban teens and young adults.

C peptide, a product of the insulin pro-hormone (Yosten et al., 2014), seems to be an interesting player in urban children. Higher C peptide concentrations in MCMA APOE 3 v controls could represent an evolving insulin resistance state (Lebbherz and Marx, 2013). Lack of C-peptide is a key factor in the development of microvascular complications in type 1 diabetes and its anti-inflammatory activity on dysfunctional endothelium is clearly applicable to alleviate or prevent the occurrence of these complications (Luppi et al., 2013). C-peptide has been associated in a contrasting manner to pro-atherogenic and anti-atherogenic effects (Lebbherz and Marx, 2013). The pro-atherogenic effects are dose-related and produce increased chemotactic activity, proliferation of aortic smooth muscle cells, and activation of key inflammatory mediators involved in atherogenic processes, including the NFκ B factor (Lebbherz and Marx, 2013). Positive correlations of high C-peptide levels with cardiovascular deaths are stronger than fasting glucose levels, homeostatic model assessment index or insulin in adult non-diabetics (Patel et al., 2012; Min and Min, 2013). High fasting C-peptide concentrations are also related to risk of liver and biliary tract cancer and low cognition scores in middle age subjects with insulin resistance (Pedersen et al., 2012; Aleksandrovaet et al., 2014). Of deep concern in cognitively normal individuals is the strong correlation between C-peptide and brain regional cortical thinning (Yoon et al., 2014).

Recent work has highlighted the importance of vitamin D deficiency, dysfunctional adipose tissue and the negative correlation between vitamin D concentrations, leptin and resistin in obese subjects (Edita et al., 2014). Vitamin D synthesis is greatly influenced by outdoor pollution, latitude, altitude, darker skin pigmentation and deficient

nutritional intake (Alvær et al., 2007; Balasubramanian and Ganesh,2008; Christakos et al., 2013; Calderón-Garcidueñas et al., 2013; Kelishadi et al., 2014). We are particularly concerned with the associations between hypovitaminosis D and proatherogenic cardiometabolic risk profile, metabolic syndrome, insulin resistance and DM risk (Christakos et al., 2013; Miñambres et al., 2014;Mezza et al., 2012; Stokić et al., 2014; Badawi et al., 2014). A key paper associating leptin, vitamin D and insulin resistance in European adolescents demonstrates leptin as the only risk factor for insulin resistance in male adolescents, while in females, leptin, vitamin D and fitness were independent risk factors for insulin resistance (Jiménez-Pavón et al., 2013). This paper is important for two main reasons: gender is critical for insulin resistance in adolescents and relationships between obesity/adiposity and vitamin D reservoirs along with expression of insulin receptors and glucose transport could play major roles in insulin resistance (Mezza et al., 2012; Jiménez-Pavón et al., 2013). More important from the point of view of public health: preventive strategies should be implemented across risk populations (Jiménez-Pavón et al., 2013). Research investigating the relationship between hypovitaminosis D, Alzheimer, memory and executive dysfunction has established plausible associations that certainly justify immediate supplementation in deficient subjects (Mosconi et al., 2014; Schneider et al., 2014;Annweiler et al., 2013; Anastasiou et al., 2014; Bishnoi et al., 2014; Bartali et al., 2014).

We have shown that APOE ε4 is related to increases in AD-related protein aggregates within the frontal lobe of MCMA children and young adults (Calderón-Garcidueñas et al., 2008, 2012). We were not surprised APOE 4 v 3 carriers had significantly higher fasting blood sugar and significant differences in the relationships between BMI and glucose, BMI and GLP-1 and GLP1 and insulin. The implications of these findings are interesting in view of the MCMA APOE 4 v 3 children >10 point deficit in Verbal and Full Scale IQ along reduced NAA/Cr ratio in the right frontal white matter (Calderón-Garcidueñas et al., 2015). APOE4 carriers display enhanced lipid binding ability, APOE4 binds better than APOE3 to the surface of very low density lipoprotein (VLDL) particles and impairs their lipolytic processing in the circulation, the result is a pro-atherogenic lipoprotein-cholesterol distribution (Phillips, 2014). Intracellular APOE modulate cellular processes, including cytoskeletal assembly and stability, mitochondrial integrity and function, and dendritic morphology and function (Huang and Mahley, 2014). Recent works suggest higher glucose levels may be a risk factor for dementia, even in the absence of diabetes mellitus (Crane et al., 2013), and their association with lower memory and reduced hippocampal microstructure (Kerti et al., 2013) and cerebral hypometabolism in AD target regions (Burns et al., 2013), pose a special threat for young urban APOE4 carriers. Since dyslipidemia is associated with high glucose and insulin resistance (Li et al., 2014), young APOE 4 urban carriers are immediate candidates for neuroprotection.

Strong and consistent evidence supports a link between oxidative stress, abnormal lipid, glucose and insulin metabolism and Alzheimer's disease (Nunomura et al., 2012; De la Monte, 2014; Castellani and Perry, 2014; Bonda et al., 2014; Butterfield et al., 2014; Wang et al., 2014). In the setting of severe air pollution or in experimental models exposed to air pollution components (Levesque et al., 2011a,b), the notion that AD is indicative of an active host response or environmental adaptation (Castellani and Perry, 2014), is biologically plausible and thus metabolic derangements involving inflammatory adipokines, insulin resistance and endothelial dysfunction in urban children are representing a vicious downward spiral involving the interactions between air pollutants, oxidative stress, genetics, and nutritional deficiencies. The work of Matarese, Pucino, and Procaccini groups is of critical importance to us, because adipokines like leptin are a prime example of a link between environment, CNS and the immune systems (Matarese et al., 2012; Pucino et al., 2014; Procaccini et al., 2014). In this context, is imperative not to ignore that early metabolic changes, dysregulated pathways, immune self-tolerance, and low chronic inflammatory states in urban children may pave the way for serious CNS consequences decades later.

Obesity is increasing in minority, low SES populations, an ominous predictor of a surge in metabolic syndrome, type 2 diabetes, cardiovascular disease and dementia. The problem is certainly a deep concern in Mexicans and Mexican-Americans for whom socioeconomic disadvantage, race/ethnic disparities and genetics play a key role in overweight and obesity status (Bonvecchio et al., 2009; Piernas et al., 2014; Fowler et al., 2013; Rossen, 2014; Bouer et al., 2014). Compounding the problem in Mexican children is their current high fructose consumption: Mexico is the world's biggest per capita consumer of soft drinks and the change from cane sugar to high fructose corn syrup will aggravate obesity, chronic metabolic disease, cognitive decline and increase the risk of Alzheimer's disease (Lakhan and Kirchgessner, 2013; Lustig, 2013; Regnault et al., 2013; Sloboda et al., 2014).

We have a 50 year window of opportunity between the time urban children have the metabolic detrimental effects we are describing here, and the day they will present with mild cognitive impairment and dementia. We have an even shorter window for similarly exposed adults. The current metabolic evidence impacting the health of millions of urban children obligates to take immediate action if we are aiming our efforts to identify and mitigate environmental factors influencing obesity, cardio-metabolic disease, diabetes mellitus and Alzheimer's.

Conflict of Interest

None

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FIGURES

Figure 1. $PM_{2.5}$ annual mean concentrations from 2002 through 2012 that includes the average age of participating children, at the Pedregal monitoring site in Southwest Mexico City.

Figure 2. Four highest daily maximum eight-hour average ozone concentrations from 1997 through 2012 at the monitoring site of Pedregal in southwest Mexico City. Data from the government of Mexico City air quality monitoring network

Figure 3. 3D mesh plot of simultaneous measurements of leptin and BMI with regards to the age of each participant for the study areas of (a) southwest Mexico City and (b) Polotitlán.

Figure 4. 3D Gaussian non-linear correlation surface map (R2 = 0.58) of the modeled leptin concentration as a function of age and the annual mean PM2.5 concentrations in southwest Mexico City. The modeled leptin was obtained from the respective 3D Gaussian non-linear correlation of age and the observed BMI and leptin levels (R2 = 0.56) in southwest Mexico City.