

7-1-2015

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

Partha S. Mukherjee
Boise State University

Publication Information

Mukherjee, Partha S. (2015) "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". *Environmental Research*, 140, 579-592. <http://dx.doi.org/10.1016/j.envres.2015.05.012>

This is an author-produced, peer-reviewed version of this article. © 2015, Elsevier. Licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International license. Details regarding the use of this work can be found at: <http://creativecommons.org/licenses/by-nc-nd/4.0/>. The final, definitive version of this document can be found online at *Environmental Research*, doi: 10.1016/j.envres.2015.05.012

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

***Lilian Calderón-Garcidueñas**

The Center for Structural and Functional
Neurosciences
The University of Montana
Missoula, MT
lilian.calderon-garciduenas@umontana.edu

and

Hospital Central Militar
Mexico City, Mexico

Maricela Franco-Lira

Hospital Central Militar
Mexico City, Mexico

Amedeo D'Angiulli

Department of Neuroscience
Carleton University, Ottawa, Canada

Joel Rodríguez-Díaz

Escuela de Ciencias de la Salud
Universidad del Valle de México
Saltillo, Coahuila, México

Eleonore Blaurock-Busch

Clinical and Environmental Laboratory Micro Trace
Minerals (MTM)
Hersbruck, Germany

Yvette Busch

Clinical and Environmental Laboratory Micro Trace
Minerals (MTM)
Hersbruck, Germany

Chih-kai Chao

The Center for Structural and Functional
Neurosciences
The University of Montana
Missoula, MT

Charles Thompson

The Center for Structural and Functional
Neurosciences
The University of Montana
Missoula, MT

Partha S. Mukherjee

Mathematics Department
Boise State University
Boise, Idaho

Ricardo Torres-Jardón

Centro de Ciencias de la Atmósfera
Universidad Nacional Autónoma de México
Mexico

George Perry

College of Sciences
University of Texas at San Antonio
San Antonio, TX

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 (O₃) 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 O₃ 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 O₃ 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 (Alvæ 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 worsened 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 ($\text{kg}\cdot\text{m}^{-2}$). 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 \pm 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 O₃ 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 (\pm 9.9) $\mu\text{g}/\text{m}^3$ in 2002 to 16.8 (\pm 8.3) $\mu\text{g}/\text{m}^3$ in 2012 (the respective US EPA annual standard calls for an PM_{2.5} annual average limit of 12 $\mu\text{g}/\text{m}^3$ 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 PM₁₀, O₃, SO₂ and NO₂ 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 PM₁₀ and O₃ in San Juan del Rio, 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 \pm 0.5, MCMA 3.5 \pm 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 $\epsilon 4$ 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 ($R^2 = 0.58$) 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 (Elmqvist 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, NF κ B, 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-González 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; Karthikeyan 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; González 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 NF κ 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; Aleksandrova 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 (Alv er et al., 2007; Balasubramanian and Ganesh,2008; Christakos et al., 2013; Calder n-Garcidue nas 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; Mi ambres et al., 2014;Mezza et al., 2012; Stoki c 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 (Jim nez-Pav n 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; Jim nez-Pav n et al., 2013). More important from the point of view of public health: preventive strategies should be implemented across risk populations (Jim nez-Pav n 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 ϵ 4 is related to increases in AD-related protein aggregates within the frontal lobe of MCMA children and young adults (Calder n-Garcidue nas 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 (Calder n-Garcidue nas 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

Funding Sources

Support for Dr. George Perry was given by the Semmes Foundation, Alzheimer's Association and NIH G12-MD007591.

References

- Acosta LR, Evans WFJ. Design of the Mexico City UV monitoring network: UV-B measurements at ground level in the urban environment. *J. Geophys Res* 116: 5017-5026 (2000).
- Albarran-Zeckler RG, Sun Y, Smith RG. Physiological roles revealed by ghrelin and ghrelin receptor deficient mice. *Peptides* 32:2229-2235(2011).
- Aleksandrovaet K, Boeing H, Nöthlings U, Jenab M, Fedirko V, Kaaks R, Lukanova A, Trichopoulou A, Trichopoulos D, Boffetta P, Trepo E, Westphal S, Duarte-Salles T, Stepien M, Overvad K, Tjønneland A, Halkjaer J, Boutron-Ruault MC, Dossus L, Racine A, Lagiou P, Bamia C, Benetou V, Agnoli C, Palli D, Panico S, Tumino R, Vineis P, Bueno-de-Mesquita B, Peeters PH, Gram IT, Lund E, Weiderpass E, Quirós JR, Agudo A, Sánchez MJ, Gavrila D, Barricarte A, Dorronsoro M, Ohlsson B, Lindkvist B, Johansson A, Sund M, Khaw KT, Wareham N, Travis RC, Riboli E, Pischon T. Inflammatory and metabolic biomarkers and risk of liver and biliary tract cancer. *Hepatology* 60(3):858-871(2014).
- Ali S, Chen G, Zhang H, Ying Q, Cureño IV, Marín A. High resolution air quality modeling for the Mexico City Metropolitan Zone using a source-oriented CMAQ model – Part I: Emission inventory and base case model results. 9th Annual CMAS Conference, Chapel Hill, NC (2010).
- Alvær K, Meyer HE, Falch JA, Nafstad P. Outdoor air pollution and bone mineral density in elderly men-the Oslo Health Study. *Osteoporos Int* 18:1669-1674(2007).
- Amato F, Rivas I, Viana M, Moreno T, Bousso L, Reche C, Álvarez-Pedrerol M, Alastuey A, Sunyer J, Querol X. Sources of indoor and outdoor PM2.5 concentrations in primary schools. *Sci Total Environ* 490: 757-765(2014).
- Anastasiou CA, Yannakoulia M, Scarmeas N. Vitamin D and cognition: An update of the current evidence. *J Alzheimers Dis* 42 Suppl 3:S71-80 (2014).
- Annweiler C, Llewellyn DJ, Beauchet O. Low serum vitamin D concentrations in Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimer Dis* 33:659-674 (2013).
- Arnoldussen IA, Kiliaan AJ, Gustafson DR. Obesity and dementia: Adipokines interact with the brain. *Eur Neuropsychopharmacol* doi:10.1016/j.euroneuro.2014.03.002 (2014).
- Badawi A, Sayegh S, Sadoun E, Al-Thani M, Arora P, Haddad PS. Relationship between insulin resistance and plasma vitamin D in adults. *Diabetes Metab Syndr Obes* 7:297-303(2014).
- Balasubramanian S, Ganesh R. Vitamin D deficiency in exclusively breast-fed infants. *Indian J Med Res* 127:250-255 (2008).
- Bahrami E, Mirmoghtadaee P, Ardalan G, Zarkesh-Esfahani H, Tajaddini MH, Haghjooy-Javanmard S, Najafi H, Kelishadi R. Insulin and leptin levels in overweight and normal-weight Iranian adolescents: The CASPIAN-III study. *J Res Med Sci* 19:387-390 (2014).
- Banks WA, Kastin AJ, Huang W, Jaspan JB, Maness LM. Leptin enters the brain by a saturable system independent of insulin. *Peptides* 17:305-311(1996).
- Barquera S, Hernández-Barrera L, Tolentino ML, Espinosa J, Ng SW, Rivera JA, Popkin BM. Energy intake from beverages is increasing among Mexican adolescents and adults. *J Nutr* 138:2454-2461(2008).
- Bartali B, Devore E, Grodstein F, Kang JH. Plasma vitamin D levels and cognitive function in aging women: the nurses' health study. *J Nutr Health Aging* 18:400-406 (2014).

- Bauer CC, Moreno B, González-Santos L, Concha L, Barquera S, Barrios FA. Child overweight and obesity are associated with reduced executive cognitive performance and brain alterations: a magnetic resonance imaging study in Mexican children. *Pediatr Obes* doi: 10.1111/ijpo.241(2014).
- Baxi SN, Muilenberg ML, Rogers CA, Sheehan WJ, Gaffin J, Permaul P, Kopel LS, Lai PS, Lane JP, Bailey A, Petty CR, Fu C, Gold DR, Phipatanakul W. Exposures to molds in school classrooms of children with asthma. *Pediatr Allergy Immunol* 24:697-703 (2013).
- Beltowski J. Leptin and the regulation of endothelial function in physiological and pathological conditions. *Clin Exp Pharmacol Physiol* 39: 168-178 (2012).
- Bickford JS, Ali NF, Nick JA, Al-Yahia M, Beachy DE, Doré S, Nick HS, Waters MF. Endothelin-1 mediated vasoconstriction alters cerebral gene expression in iron homeostasis and eicosanoid metabolism. *Brain Res* 1588:25-36 (2014).
- Bishnoi RJ, Palmer RF, Royall DR. Vitamin D binding protein as a serum biomarker of Alzheimer's disease. *J Alzheimers Dis* July 30 (2014).
- Blum K, Thanos PK, Gold MS. Dopamine and glucose, obesity and reward deficiency syndrome. *Front Psychol* doi: 10.3389/fpsyg.2014.00919 (2014).
- Bonda DJ, Wang X, Lee HG, Smith MA, Perry G, Zhu X. Neuronal failure in Alzheimer's disease: a view through the oxidative stress looking-glass. *Neurosci Bull* 30:243-252 (2014).
- Bonda DJ, Stone JG, Torres SL, Siedlak SL, Perry G, Jicha G, Casadesus G, Smith MA, Zhu X, Lee HG. Dysregulation of leptin signaling in Alzheimer disease: evidence for neuronal leptin resistance. *J Neurochem* 128:162-172(2014).
- Bonner JC, Rice AB, Lindroos PM, O'Brien PO, Dreher KL, Rosas I, Alfaro-Moreno E, Osornio-Vargas AR. Induction of the lung myofibroblast PDGF receptor system by urban ambient particles from Mexico City. *Am J Respir Cell Mol Biol* 19:672-680 (1998).
- Bonvecchio A, Safdie M, Monterrubio EA, Gust T, Villalpando S, Rivera JA. Overweight and obesity trends in Mexican children 2 to 18 years of age from 1988 to 2006. *Salud Publica Mex* 51 Suppl 4:S586-594 (2009).
- Brook RD, Rajagopalan S. Chronic air pollution exposure and endothelial dysfunction: what you can't see-can harm you. *J Am Coll Cardiol* 60:2167-2169 (2012).
- Bouret SG. Early life origins of obesity: role of hypothalamic programming. *J Pediatr Gastroenterol Nutr* 48: S31-S38 (2009).
- Bouret SG. Neurodevelopmental actions of leptin. *Brain Res* 1350:2-9 (2010).
- Bouret SG. Organizational actions of metabolic hormones. *Front Neuroendocrinol* 34:18-26(2013).
- Busch HJ, Schirmer SH, Jost M, van Stijn S, Peters SL, Piek SL, Bode C, Buschmann IR, Mies G. Leptin augments cerebral hemodynamic reserve after three-vessel occlusion: distinct effects on cerebrovascular tone and proliferation in a nonlethal model of hypoperfused rat brain. *J Cereb Blood Flow Metab* 31:1085-1092(2011).
- Butterfield DA, Di Domenico F, Barone E. Elevated risk of type 2 diabetes for development of Alzheimer disease: a key role for oxidative stress in brain. *Biochim Biophys Acta* 1842: 1693-1706(2014).
- Burghardt PR, Love TM, Stohler CS, Hodgkinson C, Shen PH, Enoch MA, Goldman D, Zubieta JK. Leptin regulates dopamine responses to sustained stress in humans. *J Neurosci* 32 :15369-15376(2012).
- Burns CM, Chen K, Kaszniak AW, Lee W, Alexander GE, Bandy D, Fliesher AS, Caselli RJ, Reiman EM. Higher serum glucose levels are associated with cerebral hypometabolism in Alzheimer regions. *Neurology* 80: 1557-1564(2013).
- Calderón-Garcidueñas L, Azzarelli B, Acuna H, Garcia R, Gambling TM, Osnaya N, Monroy S, Del Tizapantzi MR, Carson JL, Villarreal-Calderon A, Rewcastle B. Air pollution and brain damage. *Toxicol Pathol* 30:373-389(2002).
- Calderón-Garcidueñas L, Reed W, Maronpot RR, Henríquez-Roldán C, Delgado-Chavez R, Calderón-Garcidueñas A, Dragustinovis I, Franco-Lira M, Aragón-Flores M, Solt AC, Altenburg M, Torres-Jardón R, Swenberg JA. Brain inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. *Toxicol Pathol* 32:650-658(2004).
- Calderón-Garcidueñas L, Vincent R, Mora-Tiscareño, A, Franco-Lira M, Henríquez-Roldán C, Garrido-Garcia L, Camacho-Reyes L, Valencia-Salazar G, Paredes R, Romero L, Osnaya H, Villarreal-Calderon R, Torres-Jardon R, Hazucha MJ, Reed W. Elevated plasma endothelin-1 and pulmonary arterial pressure in children exposed to air pollution. *Environ Health Perspect* 115:1248-1253(2007).

- Calderón-Garcidueñas L, Mora-Tiscareño A, Gómez-Garza G, Broadway J, Chapman S, Valencia-Salazar G, Jewells V, Maronpot RR, Torres-Jardon R, Gonzalez-Maciél A, Reynoso-Robles R, Villarreal-Calderon R, Solt AC, Engle RW. Air pollution, cognitive deficits and brain abnormalities: A pilot study with children and dogs. *Brain and Cognition* 68:117-127(2008).
- Calderón-Garcidueñas L, Solt AC, Henríquez-Roldán C, Torres-Jardón R, Nuse B, Villarreal-Calderón R. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain-barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. *Toxicol Pathol* 36: 289-310 (2008).
- Calderón-Garcidueñas L, Macías-Parra M, Hoffmann HJ, Valencia-Salazar G, Henríquez-Roldán C. Immunotoxicity and environment: immunodysregulation and systemic inflammation in children. *Toxicol Pathol* 37:161-169(2009).
- Calderón-Garcidueñas L, Franco-Lira M, Henríquez-Roldán C, González-Maciél A, Reynoso-Robles R, Villarreal-Calderon R. Urban air pollution: influences on olfactory function and pathology in exposed children and young adults. *Exp Toxicol Pathol* 62: 91-102(2010).
- Calderón-Garcidueñas L, D'Angiulli A, Kulesza RJ, Torres-Jardón R, Osnaya N, Romero L. Air pollution is associated with brainstem auditory nuclei pathology and delayed brainstem auditory evoked potentials. *Int J Dev Neurosci* 29: 365-375(2011).
- Calderón-Garcidueñas L, Engle R, Mora-Tiscareño A, Styner M, Gomez-Garza G, Zhu H, et al. Exposure to severe urban pollution influences cognitive outcomes, brain volume and systemic inflammation in clinically healthy children. *Brain Cognition* 77:345-355(2011).
- Calderón-Garcidueñas L, Torres-Jardón R. Air pollution, socioeconomic status and children's cognition in megacities: The Mexico City scenario. *Front Psychol* 3:217(2012). doi: 10.3389/fpsyg.2012.00217.
- Calderón-Garcidueñas L, Mora-Tiscareño A, Styner M, Gómez-Garza G, Zhu H, Torres-Jardón R. White matter hyperintensities, systemic inflammation, brain growth and cognitive functions in children exposed to air pollution. *J Alzheimer Dis* 31:183-191(2012).
- Calderón-Garcidueñas L, Kavanaugh M, Block ML, D'Angiulli A, Delgado-Chávez R, Torres-Jardón R. Neuroinflammation, hyperphosphorylated tau, diffuse amyloid plaques and down-regulation of the cellular prion protein in air pollution exposed children and adults. *Journal of Alzheimer Disease* 28: 93-107(2012).
- Calderón-Garcidueñas L, Franco-Lira M, Mora-Tiscareño A, Medina-Cortina H, Torres-Jardón R, Kavanaugh M. Early Alzheimer's and Parkinson's disease pathology in urban children: Friend versus Foe responses-it is time to face the evidence. *Biomed Res Int* doi: 10.1155/2013/161687 (2013).
- Calderón-Garcidueñas L, Mora-Tiscareño A, Francolira M, Torres-Jardón R, Peña-Cruz B, Palacios-López C. Exposure to urban air pollution and bone health in clinically healthy six-year old children. *Arh Hig Rada Toksikol* 64:23-34(2013).
- Calderón-Garcidueñas L, Vojdani A, Blaurock-Busch E, Busch Y, Friedle A, Franco-lira M, Sarathi-Mukherjee P, Park SB, Torres-Jardon R, D'Angiulli A. Air pollution and children: neural and tight junction antibodies and combustion metals, the role of barrier breakdown and brain immunity in neurodegeneration. *J Alzheimers Dis* 43: 1039-58 (2015).
- Calderón-Garcidueñas L, Mora-Tiscareño A, Franco-Lira M, Zhu H, Lu Z, Solorio E, Torres-Jardón R, D'Angiulli A. Decreases in short term memory, IQ and altered brain metabolic ratios in urban Apolipoprotein ϵ 4 children exposed to air pollution. *J Alzheimers Dis.* (2015)
- Calderón-Garcidueñas L, Torres-Jardón R. The impact of air pollutants on the brain. *JAMA Psychiatry* doi: 10.1001/jamapsychiatry.2015.0192 (2015).
- Caro JF, Kolaczynski JW, Nyce MR, Ohannesian JP, Opentanova I, Goldman WH, Lynn RB, Zhang PL, Sinha MK, Considine RV. Decreased cerebro-spinal fluid /serum leptin ratio in obesity: a possible mechanism for leptin resistance. *Lancet* 348:159-161(1996).
- Castellani RJ, Perry G. The complexities of the pathology-pathogenesis relationship in Alzheimer disease. *Biochem Pharmacol* 88:671-676(2014).
- Catli G, Anik A, Tuhhan HU, Kume T, Bober E, Abaci A. The relation of leptin and soluble leptin receptor levels with metabolic and clinical parameters in obese and healthy children. *Peptides* 56:72-76(2014).
- Cegla J, Troke RC, Jones B, Tharakan G, Kenkre J, McCullough KA, Lim CT, Parvizi N, Hussein M, Chambers ES, Minnion J, Cuenco J, Ghatei MA, Meeran K, Tan TM, Bloom SR. Co-infusion of low dose glucagon – like peptide (GLP-1) and glucagon in man result in a reduction in food intake. *Diabetes* 63(11):3711-3720 (2014).
- Christakos S, Hewison M, Gardner DG, Wagner CL, Sergeev IN, Rutten E, Pittas AG, Boland R, Ferruci L, Bikle DD. Vitamin D: beyond bone. *Ann NY Acad Sci* 1287:45-58(2013).

- Conde J, Scotece M, Abella V, López V, Pino J, Gómez-Reino JJ, Gualillo O. An update on leptin as immunomodulator. *Expert Rev Clin Immunol* Aug 7:1-6 (2014).
- Cotlear D, Gómez-Dantés O, Knaul F, Atun R, Barreto IC, Cetrángolo O, Cueto M, Francke P, Frenz P, Guerrero R, Lozano R, Marten R, Sáenz R. Overcoming social segregation in health care in Latin America. *Lancet* 2014; doi: 10.1016/S0140-6736(14)61647-0.
- Crane PK, Walker R, Hubbard RA, Li G, Nathan DM, Zheng H, Haneuse S, Craft S, Montine TJ, Kahn SE, McCormick W, McCurry W, Bowen JD, Larson EB. Glucose levels and risk of dementia. *N Engl J Med* 369: 540-548(2013).
- Davis C, Mudd J, Hawkins M. Neuroprotective effects of leptin in the context of obesity and metabolic disorders. *Neurobiol Dis* 72 Pt A: 61-71(2014).
- Daws LC, Avison MJ, Robertson SD, Niswender KD, Galli A, Saunders C. Insulin signaling and addiction. *Neuropharmacol* 61:1123-1128(2011).
- De la Monte SM. Type 3 diabetes is sporadic Alzheimer's disease: Mini-Review. *Eur Neuropsychopharmacol* 24(12):1954-1960 (2014).
- Duffey KJ, Rivera JA, Popkin BM. Snacking is prevalent in Mexico. *J Nutr* 144:1843-1849(2014).
- Edita S, Aleksandar K, Dragana TN, Dragana S, Branka KZ, Biljana SG, Sanja S, Esma IR. Vitamin D and dysfunctional adipose tissue in obesity. *Angiology* pii: 0003319714543512(2014).
- Elmqvist JK, Bjørbæk C, Ahima RS, Flier JS, Saper CB. Distributions of leptin receptor mRNA isoforms in the rat brain. *J Comp Neurol* 395:535-547(1998).
- Engel JA, Jerlhag E. Role of appetite-regulating peptides in the pathophysiology of addiction: implications for pharmacotherapy. *CNS Drugs* 28: 875-886(2014).
- Eze IC, Schaffner E, Fischer E, Schikowski T, Adam M, Imboden M, Tsai M, Carballo D, von Eckardstein A, Kunzli N, Schinler C, Probst-Hensch N. Long-term air pollution exposure and diabetes in a population-based Swiss cohort. *Environ Int* 70:95-105(2014).
- Falkner B, Cossrow ND. Prevalence of metabolic syndrome and obesity-associated hypertension in the racial ethnic minorities of the United States. *Curr Hypertens Rep* 16:449 (2014). doi: 10.1007/s11906-014-0449-5.
- Faraco G, Moraga A, Moore J, Anrather J, Pickel VM, Iadecola C. Circulating endothelin-1 alters critical mechanisms regulating cerebral microcirculation. *Hypertension* 62:759-766(2013).
- Farr OM, Tsoukas MA, Mantzoros CS. Leptin and the brain: Influences on brain development, cognitive functioning and psychiatric disorders. *Metabolism* 64(1):114-30(2014).
- Fitzpatrick TB. The validity and practicality of sun-reactive skin type I through VI. *Arch Dermatology* 124:869-871(1988).
- Fleisch AF, Gold DR, Rifas-Shiman SL, Koutrakis P, Schwartz JD, Kloog I, Melly S, Coull BA, Zanobetti A, Gillman MW, Oken E. Air pollution exposure and abnormal glucose tolerance during pregnancy: the project Viva cohort. *Environ Health Perspect* 122: 378-383(2014).
- Freeman BD, Machado FS, Tanowitz HB, Desruisseaux MS. Endothelin 1 and its role in the pathogenesis of infectious diseases. *Life Sci* 118(2):110-119(2014).
- Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. *Nature* 395: 763-770(1998).
- Folch J, Pedrós I, Patracá I, Sureda F, Junyent F, Beas-Zarate C, Verdager E, Pallàs M, Auladell C, Camins A. Neuroprotective and anti-ageing role of leptin. *J Mol Endocrinol* 49:R149-156(2012).
- Fowler SP, Puppala S, Arya R, Chittoor G, Farook VS, Schneider J, Resendez RG, Upadhayay RP, Vandeberg J, Hunt KJ, Bradshaw B, Cersosimo E, Vandeberg JL, Almasly L, Curran JE, Comuzzie AG, Lehman DM, Jenkinson CP, Lynch JL, Defronzo RA, Blangero J, Hale DE, Duggirala R. Genetic epidemiology of cardiometabolic risk factors and their clustering patterns in Mexican American children and adolescents: the SAFARI study. *Human Genet* 132: 1059-1071(2013).
- Gan L, Guo K, Cremona ML, McGraw TE, Leibel RL, Zhang Y. TNF- α up-regulates protein level and cell surface expression of the leptin receptor by stimulating its export via a PKC-dependent mechanism. *Endocrinology* 153:5821-5833(2012).
- Gainsford T, Willson TA, Metcalf D, Handman E, McFarlane C, Ng A, Nicola NA, Alexander WS, Hilton DJ. Leptin can induce proliferation, differentiation, and functional activation of hemopoietic cells. *Proc Natl Acad Sci USA* 93:14564-14568(1996).
- García-García I, Hosrtmann A, Jurado MA, Garolera M, Chaudhry SJ, Margulies DS, Villringer A, Neumann J. Reward processing in obesity, substance addiction and non-substance addiction. *Obes Rev* 15:853-869(2014).

- Gehring U, Gruziova O, Agius RM, Beelen R, Custovic A, Cyrus J, Eeftens M, Flexeder C, Fuertes E, Heinrich J, Hoffmann B, de Jongste JC, Kerkhof M, Klümper C, Korek M, Mölter A, Schultz ES, Simpson A, Sugiri D, Svartengren M, von Berg A, Wijga AH, Pershagen G, Brunekreef B. Air pollution exposure and lung function in children: the ESCAPE project. *Environ Health Perspect* 121: 1357-1364 (2013).
- GEM Diagnóstico Ambiental. Región I. Atlacomulco. Dirección General de Prevención y Control de la Contaminación Atmosférica. Gobierno del Estado de México (2008).
- Gomart S, Damoiseaux C, Jaspers P, Makanga M, Labranche N, Pochet S, Michaux C, Berkenboom G, Naeije R, McEntee K, Dewachter L. Pulmonary vasoactivity in spontaneously hypertensive rats-effects of endothelin-1 and leptin. *Respir Res* doi: 10.1186/1465-9921-15-12(2014).
- Gonzaga NC, Medeiros CC, de Carvalho DF, Alves JG. Leptin and cardiometabolic risk factors in obese children and adolescents. *J Paediatr Child Health* 50:707-712(2014).
- Gonzalez M, Lind L, Söderberg S. Leptin and endothelial function in the elderly: the prospective Investigation of the vasculature in Uppsala Seniors (PIVUS) study. *Atherosclerosis* 228: 485-490(2013).
- Goodson JM, Kantarci A, Hartman ML, Denis GV, Stephens D, Hasturk H, et al. Yaskell T, Vargas J, Wang X, Cugini M, Barake R, Alsmadi O, Al-Mutawa S, Ariga J, Soparkar P, Behbehani J, Behbehani K, Welty F. Metabolic disease risk in children by salivary biomarker analysis. *PLoS One* 9: e987999(2014).
- Grill HJ, Hayes MR. The nucleus tractus solitarius: a portal for visceral afferent signal processing, energy status assessment and integration of their combined effects on food intake. *Int J Obes (Lond)* 33 Suppl 1: S11-S15(2009).
- Grunfeld C, Zhao C, Fuller J, Pollack A, Moser A, Friedman J, Feingold KR. Endotoxin and cytokines induce expression of leptin, the ob gene product in hamsters. *J Clin Invest* 97:2152-2157(1996).
- Guxens M, Garcia-Esteban R, Giorgis-Allemand L, Forn J, Badaloni C, Ballester F, Beelen R, Cesaroni G, Chatzi L, de Agostini M, de Nazelle A, Eeftens M, Fernandez MF, Fernández-Somoano A, Forastiere F, Gehring U, Ghassabian A, Heude B, Jaddoe VW, Klümper C, Kogevinas M, Krämer U, Larroque B, Lertxundi A, Lertxuni N, Murcia M, Navel V, Nieuwenhuijsen M, Porta D, Ramos R, Roumeliotaki T, Slama R, Sørensen M, Stephanou EG, Sugiri D, Tardón A, Tiemeier H, Tiesler CM, Verhulst FC, Vrijkotte T, Wilhelm M, Brunekreef B, Pershagen G, Sunyer J. Air pollution during pregnancy and childhood cognitive and psychomotor development: six European birth cohorts. *Epidemiology* 25:636-647(2014).
- Hao XQ, Du JX, Li Y, Zhang SY. Prenatal exposure to lipopolysaccharide combined with pre and post-natal high-fat diet result in lowered blood pressure and insulin resistance in offspring rats. *PLoS One* e88127(2014).
- Harris RB. Evidence that leptin-induced weight loss requires activation of both forebrain and hindbrain receptors. *Physiol Behav* 120:83-92(2013).
- Huang JS, Letendre S, Marquie-Beck J, Cherner M, McCutchan JA, Grant I, Ellis R. Low CSF leptin levels are associated with worse learning and memory performance in HIV-infected men. *J Neuroimmune Pharmacol* 2:352-358 (2007).
- Huang Y, Mahley RW. Apolipoprotein E: Structure and function in lipid metabolism, neurobiology, and Alzheimer's disease. *Neurobiol Dis* 72 Pt A:3-12 (2014).
- Inzaugarat ME, Billordo LA, Vodánovich F, Cervini GM, Casavalle PL, Vedire C, Cherňavsky AC. Alterations in innate and adaptive immune leukocytes are involved in pediatric obesity. *Pediatr Obes* doi: 10.1111/j.2047-6310.2013.00179x (2013).
- Iriart C, Boursaw B, Rodrigues GP, Handal AJ. Obesity and malnutrition among Hispanic children in the United States: double burden on health inequities. *Rev Panam Salud Publica* 34(4):235-243(2013).
- Irving AJ, Harvey J. Leptin regulation of hippocampal synaptic function in health and disease. *Philos Trans R Soc Lond B Biol Sci* 2;369(1633):20130155 (2013).
- Iwasa T, Matsuzaki T, Munkhzaya M, Tungalagsuvd A, Murakami M, Kato T, Kuwashara A, Yasui T, Irahara M. Changes in leptin production/secretion induced in response to septic doses of lipopolysaccharides in gonadally intact and ovariectomized female rats. *J Reprod Immunol* 104-105:92-95(2014).
- Jerrett M, McConnell R, Wolch J, Chang R, Lam C, Dunton G, Gilliland F, Lurmann F, Islam T, Berhane K. Traffic-related air pollution and obesity formation in children: a longitudinal, multilevel analysis. *Environ Health* doi: 10.1186/1476-069X-13-49(2014).
- Jiménez-Pavón D, Ruiz JR, Ortega FB, Martínez-Gómez D, Moreno S, Urzanqui A, Gottrand F, Molnár D, Castillo MJ, Sjöström M, Moreno LA; HELENA Study group. Physical activity and markers of insulin resistance in adolescents: role of cardiorespiratory fitness levels-The HELENA study. *Pediatr Diabetes* 14(4):249-258(2013).

- Johnston JM, Hu WT, Fardo DW, Greco SJ, Perry G, Montini TJ, Trojanowski JQ, Shaw LM, Ashford JW, Tezapsidis N. Alzheimer's Disease Neuroimaging Initiative. Low plasma leptin in cognitively impaired ADNI subjects: gender differences and diagnostic and therapeutic potential. *Curr Alzheimer Res* 11:165-174(2014).
- Karthikevan S, Thompson EM, Kumarathan P, Guenette J, Rosenblatt D, Chan T, Rideout G, Vincent R. Nitrogen dioxide and ultrafine particles dominate the biological effects of inhaled diesel exhaust treated by a catalyzed diesel particulate filter. *Toxicol Sci* 135:437-450(2013).
- Kelishadi R, Moeini R, Poursafa P, Farajian S, Yousefy H, Okhovat-Souraki AA. Independent association between air pollutants and vitamin D deficiency in young children in Isfahan, Iran. *Paediatr Int Child Health* 34:50-55 (2014).
- Kerti L, Witte AV, Winkler A, Grittner U, Rujescu D, Flöel A. Higher glucose levels associated with lower memory and reduced hippocampal microstructure. *Neurology* 81:1746-1752(2013).
- Korek E, Krauss H, Gibas-Dorna M, Kupsz J, Piateck M, Piatek J. Fasting and postprandial levels of ghrelin, leptin and insulin in lean, obese and anorexic subjects. *Prz Gastroenterol* 8:383-389(2013).
- Kurokawa K, Yamada H, Ochi J. Topographical distribution of neurons containing endothelin type A receptor in the rat brain. *J Comp Neurol* 389: 348-360(1997).
- Kwon H, Pessin JE. Adipokines mediate inflammation and insulin resistance. *Frontiers Endocrinology* doi: 10.3389/fendo.2013.00071(2013).
- Lago R, Gómez R, Lago F, Gómez-Reino J, Gualillo O. Leptin beyond body weight regulation-current concepts concerning its role in immune function and inflammation. *Cell Immunol* 252:139-145(2008).
- Lakhan SE, Kirchgessner A. The emerging role of dietary fructose in obesity and cognitive decline. *Nutr J* doi: 10.1186/1475-2891-12-114(2013).
- Laughlin MR. Normal roles for dietary fructose in carbohydrate metabolism. *Nutrients* 6:3117-3129(2014).
- Lebbherz C, Marx N. C-peptide and its career from innocent bystander to active player in diabetic atherogenesis. *Curr Atheroscler Rep* 15(7):339 (2013).
- Lee S, Tong M, Hang S, Deochand C, de la Monte S. CSF and brain indices of insulin resistance, oxidative stress and neuroinflammation in early versus late Alzheimer's disease. *J Alzheimers Dis Parkinsonism* 3: 128 (2013).
- Levesque S, Surace MJ, McDonald J, Block ML. Air pollution and the brain: Subchronic diesel exhaust exposure causes neuroinflammation and elevates early markers of neurodegenerative disease. *J Neuroinflammation* doi: 10.1186/1742-2094-8-105(2011).
- Levesque S, Taetsch T, Lull ME, Kodavanti U, Stadler K, Wagner A, et al. Diesel exhaust activates and primes microglia: air pollution, neuroinflammation and regulation of dopaminergic neurotoxicity. *Environ Health Perspect* 119:1149-1155(2011).
- Li G, Bei N, Tie X, Molina LT. Aerosol effects on the photochemistry in Mexico City during MCMA-2006/MILAGRO campaign. *Atmos Chem Phys* 11:5169-5182(2011).
- Li N, van der Sijde MR, Lifelines Cohort Study Group, Bakker SJ, Dullaart RP, van der Harst P. Pleiotropic effects of lipid genes on plasma glucose, HbA1c and HOMA-IR levels. *Diabetes* 63:3149-3158(2014).
- Li Y, Robinson LE, Carter WM, Gupta R. Childhood obesity and community food environments in Alabama's Black Belt region. *Child Care Health Dev* Oct 16 doi: 10.1111/cch.12204 (2014).
- Li Z, Ceccarini G, Eisenstein M, Tan K, Friedman JM. Phenotypic effects of an induced mutation of the ObRa isoform of the leptin receptor. *Molecular Metabolism* 2:364-375(2013).
- Liu C, Fuentes E, Tiesler CM, Birk M, Babisch W, Bauer CP, Koletzko S, von Berg A, Hoffmann B, Heinrich J, GINIplus and LISApplus Study Groups. The associations between traffic-related air pollution and noise with blood pressure in children: results from the GINIplus and LISApplus studies. *Int J Hyg Environ Health* 217(4-5):499-505(2014).
- Liu C, Bai Y, Xu X, Sun L, Wang A, Wang TY, Maurya SK, Periasamy M, Morishita M, Harkema J, Ying Z, Sun Q, Rajagopalan S. Exaggerated effects of particulate matter air pollution in genetic type II diabetes mellitus. *Part Fibre Toxicol* doi: 10.1186/1743-8977-11-27(2014).
- Liu Y, Wei R, Hong TP. Potential roles of glucagon-like peptide-1 based therapies in treating non-alcohol fatty liver disease. *World J Gastroenterol* 20:9090-9097(2014).
- Luppi P, Kallas A, Wahren J. Can C-peptide mediated anti-inflammatory effects retards the development of microvascular complications of type 1 diabetes? *Diabetes Metab Res Rev* 29:357-362(2013).
- Lustig RH. Fructose: it's "alcohol without the buzz". *Adv Nutr* 4:226-235(2013).

- Mancini M, Soldovieri MV, Gessner G, Wissuwa B, Barrese V, Boscia F, Secondo A, Miceli F, Franco C, Ambrosino P, Canzoniero LM, Bauer M, Hoshi T, Heinemann SH, Tagliatalata M. Critical role of large-conductance calcium and voltage-activated potassium channels in leptin-induced neuroprotection of N-methyl-d-aspartate exposed cortical neurons. *Pharmacol Res* 87: 80-86(2014).
- Matarese G, Procaccini C, De Rosa V. At the crossroad of T cells, adipose tissue and diabetes. *Immunol Rev* 249: 116-134(2012).
- Marley NA, Gaffney JS, Castro T, Salcido A, Frederick JE. Measurements of aerosol absorption and scattering in the Mexico City Metropolitan Area during the MILAGRO field campaign: a comparison of results from the T0 and T1 sites. *Atmos Chem Phys* 9:189-206(2009).
- Mathison Y, del Garrido MR, Israel A. Multiple signaling pathways involved in the effects of endothelin type B receptor in the rat median eminence. *Acta Biol Hung* 58: 139-150(2007).
- Mezza T, Muscogiuri G, Sorice GP, Priolella A, Salomone E, Pontecorvi A, Giaccari A. Vitamin D deficiency: a new risk factor for type 2 diabetes? *Ann Nutr Metab* 61:337-348(2012).
- Michaelson DM. ApoE4: The most prevalent yet understudied risk factor for Alzheimer's disease. *Alzheimers Dement* doi: 10.1016/j.jalz.2014.06.015(2014).
- Min JY, Min KB. Serum c-peptide levels and risk of death among adults without diabetes mellitus. *CMAJ* 185:E402-408(2013).
- Miñambres I, de Leiva A, Pérez A. Hypovitaminosis D and metabolic syndrome. *Med Clin (Barc)* doi: 10.1016/j.medcli.2013.12.012(2014).
- Molina LT, Kolb CE, de Foy B, Lamb BK, Brune WH, Jimenez JL. Air quality in North America's most populous city – overview of the MCMA-2003 campaign. *Atmos Chem Phys* 7: 2447-2473(2007).
- Molina LT, Madronich SJ, Gaffney JS, Apel E, de Foy B, Fast J. An overview of the MILAGRO 2006 Campaign: Mexico City emissions and their transport and transformation. *Atmos Chem Phys* 10: 8697–8760(2010).
- Monteleone P, Maj M. Dysfunctions of leptin, ghrelin, BDNF and endocannabinoids in eating disorders: Beyond the homeostatic control of food intake. *Psychoneuroendocrinology* 38:312-330(2013).
- Mosconi L, Murray J, Davies M, Williams S, Pirraglia E, Spector N, Tsui WH, Li Y, Butler T, Osorio RS, Glodzik L, Vallabhajosula S, McHugh P, Marmar CR, de Leon MJ. Nutrient intake and brain biomarkers of Alzheimer's disease in at-risk cognitively normal individuals: a cross-sectional neuroimaging pilot study. *BMJ Open* doi: 10.1136/bmjopen-2014-004850(2014).
- Murray S, Tulloch A, Gold MS, Avena NM. Hormonal and neural mechanisms of food reward, eating behaviour and obesity. *Nat Rev Endocrinol* 10(9):540-552(2014).
- Nunomura A, Moreira PI, Castellani RJ, Lee HG, Zhu X, Smith MA, Perry G. Oxidative damage to RNA in aging and neurodegenerative disorders. *Neurotox Res* 22:231-248(2012).
- Osornio-Vargas AR, Bonner JC, Alfaro-Moreno E, Martinez L, Garcia-Cuellar C, Ponce de Leon Rosales S. Proinflammatory and cytotoxic effects of Mexico City air pollution particulate matter in vitro are dependent on particle size and composition. *Environ Health Perspect* 111:1289-93(2003).
- Pan W, Hsueh H, Tu H, Kastin AJ. Developmental changes of leptin receptors in cerebral microvessels: Unexpected relation to leptin transport. *Endocrinology* 149: 877-885(2008).
- Pan H, Guo J, Su Z. Advances in understanding the interrelations between leptin resistance and obesity. *Physiol and Behavior* 130:157-169(2014).
- Patel N, Taveira TH, Choudhary G, Whitlatch H, Wu WC. Fasting serum C-peptide levels predict cardiovascular and overall death in nondiabetic adults. *J Am Heart Assoc* 1:e003152 (2012).
- Payne GA, Tune JD, Knudson JD. Leptin-induced endothelial dysfunction: a target for therapeutic interventions. *Curr Pharm Des* 20:603-608(2014).
- Pedersen M, Pedersen KK, Bruunsgaard H, Krabbe KS, Thomsen C, Faerch K, Pedersen BK, Mortensen EL. Cognitive functions in middle aged individuals are related to metabolic disturbances and aerobic capacity: a cross-sectional study. *PLoS One* doi: 10.1371/journal.pone.0051132(2012).
- Pedersen M, Giorgis-Allemand L, Bernard C, Aguilera I, Andersen AM, Ballester F. Ambient air pollution and low birth weight: a European cohort study (ESCAPE). *Lancet Respir Med* 1:695-704 (2013).
- Pedros I, Petrov D, Artiach G, Abad S, Ramon-Duaso C, Sureda F, Pallàs M, Beas-Zarate C, Folch J, Camins A. Adipokine pathways are altered in hippocampus of an experimental mouse model of Alzheimer's disease. *J Nutr Health Aging* 2015; 19:403-412
- Pérez-González R, Antequera D, Vargas T, Spuch C, Bolós M, Carro E. Leptin induces proliferation of neuronal progenitors and neuroprotection in a mouse model of Alzheimer's disease. *J Alzheimer Dis* 24 Suppl 2:17-25(2011).
- Pettus J, Hirsch I, Edelman S. GLP-1 agonists in type 1 diabetes. *Clin Immunol* 149: 317-323(2013).

- Phillips MC. Apolipoprotein E isoforms and lipoprotein metabolism. *IUBMB Life* 66:616-623(2014).
- Piernas C, Barquera S, Popkin BM. Current patterns of water and beverage consumption among Mexican children and adolescents aged 1-18 years: analysis of the Mexican National Health and Nutrition Survey 2012. *Public Health Nutr* 1-10(2014).
- Pohl J, Woodside B, Luheshi GN. Leptin modulates the late fever response to LPS in diet-induced obese animals. *Brain Behav Immun* 42:41-47(2014).
- Pöss J, Lorenz D, Werner C, Pavlikova V, Gensch C, Speer T, Alessandrini F, Berezowski V, Kuntz M, Mempel M, Endres M, Böhm M, Laufs U. Diesel exhaust particles impair endothelial progenitor cells, compromise endothelial integrity, reduce neoangiogenesis, and increase atherogenesis in mice. *Cardiovasc Toxicol* 13:290-300(2013).
- Procaccini C, Pucino V, Mantzoros CS, Matarese G. Leptin in autoimmune diseases. *Metabolism* doi: 10.1016/j.metabol.2014.10.014 (2014).
- Pucino V, De Rosa V, Procaccini C, Matarese G. Regulatory T cells, leptin and angiogenesis. *Chem Immunol Allergy* 99:155-69 (2014).
- Qin L, Wu X, Block ML, Liu Y, Breese GR, Hong JS, Knapp DJ, Crews FT. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. *Glia* 55:453-462(2007).
- Regnault TR, Gentili S, Sarr O, Toop CR, Sloboda DM. Fructose, pregnancy and later life impacts. *Clin Exp Pharmacol Physiol* 40:824-837(2013).
- Rios JA, Cisternas P, Arrese M, Barja S, Inestrosa NC. Is Alzheimer's disease related to metabolic syndrome? A Wnt signaling conundrum. *Prog Neurobiol* <http://dx.doi.org/10.1016/j.pneurobio.2014.07.004>(2014).
- Rosenbaum M, Leibel RL. The role of leptin in energy homeostasis in humans. *J Endocrinol pii: JOE-14-0358*(2014).
- Rossen LM. Neighborhood economic deprivation explains racial/ethnic disparities in overweight and obesity among children and adolescents in the USA. *J Epidemiol Community Health* 68:123-129(2014).
- Rossi NF, Maliszewska-Scislo M. Role of paraventricular nucleus vasopressin V1A receptors in the response to endothelin-1 activation of the subfornical organ in the rat. *J Physiol Pharmacol* 59:47-59(2008).
- Sachot C, Poole S, Luheshi GN. Circulating leptin mediates lipopolysaccharide-induced anorexia and fever in rats. *J Physiol* 561:263-272(2004).
- Schneider AL, Lutsey PL, Alonso A, Gottesman RF, Sharrett AR, Carson KA, Gross M, Post WS, Knopman DS, Mosley TH, Michos ED. Vitamin D and cognitive function and dementia risk in a biracial cohort: the ARIC Brain MRI Study. *Eur J Neurol* 21(9):1211-8, e69-70(2014).
- Scott MM, Lachey JL, Sternson SM, Lee CE, Elias CF, Friedman JM, Elmquist JK. Leptin targets in the mouse brain. *J Comp Neurol* 514:518-532(2009).
- Secretaría de Ecología. Gobierno del Estado de México. Medición de la calidad del aire y parámetros meteorológicos en el Municipio de Polotitlán. Departamento de Monitoreo Ambiental. Dirección General de Prevención y Control de la Contaminación Atmosférica. Gobierno del Estado de México. Toluca, Edo. de México (2005).
- Shah M, Vella A. Effects of GLP-1 on appetite and weight. *Rev Endocr Metab Disord* 15:181-187(2014).
- Sloboda DM, Li M, Patel R, Clayton ZE, Yap C, Vickers MH. Early life exposure to fructose and offspring phenotype: implications for long term metabolic homeostasis. *J Obes* 2014:203474 doi: 10.1155/2014/203474(2014).
- Steculorum SM, Bouret SG. Developmental effects of ghrelin. *Peptides* 32: 2362-2366 (2011).
- Steppan CM, Swick AG. A role for leptin in brain development. *Biochem Biophysical Res Commun* 256:600-602(1999).
- Stieg MR, Sievers C, Farr O, Stalla GK, Mantzoros CS. Leptin: A hormone linking activation of neuroendocrine axes with neuropathology. *Psychoneuroendocrinology* 51: 47-57(2015).
- Stienstra R, van Diepen JA, Tack CJ, Zaki MH, van de Veerdonk FL, Perera D, Neale GA, Hooiveld GJ, Hijmans A, Vroegrijk I, van den Berg S, Romijn J, Rensen PC, Joosten LA, Netea MG, Kannekanti TD. Inflammasome is a central player in the induction of obesity and insulin resistance. *Proc Natl Acad Sci USA* 108: 15324-15329(2011).
- Stokić E, Kupusinac A, Tomić-Naglić D, Zavišić BK, Mitrović M, Smiljenić D, Soskić S, Isenović E. Obesity and vitamin D deficiency: Trends to promote a more proatherogenic cardiometabolic risk profile. *Angiology* 66(3):237-43 (2014)
- Stoyanova II. Ghrelin: A link between ageing, metabolism and neurodegenerative disorders. *Neurobiology Dis* doi: 10.1016/j.nbd.2014.08.026(2014).

- Teder P, Noble PW. A cytokine reborn? Endothelin-1 in pulmonary inflammation and fibrosis. *Am J Respir Cell Mol Biol*. 23:7-10(2000).
- Thomson EM, Kumarathasan P, Calderon-Garciduenas L, Vincent R. Air pollution alters brain and pituitary endothelin-1 and inducible nitric oxide synthase gene expression. *Environ Res* 105: 224-233(2007).
- Valtierra JG, de la Lata GR, Medina LSE, Bayona CA, Toral LMA, Muñoz AG. Diagnóstico Ambiental Integral de la Ciudad de San Juan del Río, Querétaro. Tomo XVII: Centro Queretano de Recursos Naturales. Published by the Consejo de Ciencia y Tecnología del Estado de Querétaro, Santiago de Querétaro, Qro., México (2011).
- Vella RE, Pillon NJ, Zarrouki B, Croze ML, Koppe L, Guichardant M, Pesenti S, Chauvin MA, Rieusset J, Géoën A, Soulage CO. Ozone exposure triggers insulin resistance through muscle c-Jun N-terminal Kinases (JNKs) activation. *Diabetes* 64(3):1011-1024(2014).
- Villarreal-Calderón A, Acuña H, Villarreal-Calderón J, Garduño M, Henriquez-Roldán CF, Calderón-Garcidueñas L, Valencia-Salazar G. Assessment of physical education time and after-school outdoor time in elementary and middle school students in South Mexico City: the dilemma between physical fitness and adverse health effects of outdoor pollutant exposure. *Arch Environ Health* 57:450-460 (2002).
- Wang J, Wang H, Luo W, Guo C, Wang J, Chen YE, Chang L, Eitzman DT. Leptin-induced endothelial dysfunction is mediated by sympathetic nervous system activity. *J Am Heart Assoc* 2013;2:e000299 doi: 10.1161/JAHA.113.000299.
- Wang Y, Eliot MN, Kuchel GA, Schwartz J, Coull BA, Mittleman MA, Lipsitz LA, Wellenius GA. Long-term exposure to ambient air pollution and serum leptin in older adults: results from the MOBILIZE Boston Study. *JOEM* 56:73-77(2014).
- Wang X, Wang W, Li L, Perry G, Lee HG, Zhu X. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. *Biochim Biophys Acta* 1842:1240-1247(2014).
- Yoon CW, Kang M, Shin HY, Jeon S, Yang JJ, Kim ST, Noh Y, Kim GH, Kim HJ, Kim YJ, Kim JH, Cho H, Ye BS, Lee JM, Choi SH, Im K, Moon HS, Na DL, Seo SW. Higher C-peptide levels are associated with regional cortical thinning in 1093 cognitively normal subjects. *Eur J Neurol* 21(10):1318-1323(2014).
- Yosten G, Marie-Bilkan C, Luppi P, Wahren J. Physiological effects and therapeutic potential of proinsulin C-peptide. *Am J Physiol Endocrinol Metab* doi: 10.1152/ajpendo.00130.2014.
- Zabeau L, Jensen CJ, Seeuws S, Venken K, Verhee A, Cateeuw D, van Loo G, Chen H, Walder K, Hollis J, Foote S, Morris MJ, Van der Heyden J, Peelman F, Oldfield BJ, Rubio JP, Elewaut D, Tavernier J. Leptin's metabolic and immune functions can be uncoupled at the ligand/receptor interaction level. *Cell Mol Life Sci* 72(3):629-644 (2014)
- Zhang J, Deng Z, Liao J, Song C, Liang C, Xue H, Wang L, Zhang K, Yan G. Leptin attenuates cerebral ischemia injury through the promotion of energy via the P13K/Akt pathway. *J Cereb Blood Flow Metab* 33:567-574(2013).
- Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 372:425-432 (1994).

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 ($R^2 = 0.58$) of the modeled leptin concentration as a function of age and the annual mean PM_{2.5} 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 ($R^2 = 0.56$) in southwest Mexico City.