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Interactive and additive influences of Gender, BMI and Apolipoprotein 4 on cognition in children chronically exposed to high concentrations of $PM_{2.5}$ and ozone. APOE 4 females are at highest risk in Mexico City

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ABSTRACT

Children's air pollution exposures are associated with systemic and brain inflammation and the early hallmarks of Alzheimer's disease (AD). The Apolipoprotein E (APOE) 4 allele is the most prevalent genetic risk for AD, with higher risk for women. We assessed whether gender, BMI, APOE and metabolic variables in healthy children with high exposures to ozone and fine particulate matter ($PM_{2.5}$) influence cognition. The Wechsler Intelligence Scale for Children (WISC-R) was administered to 105 Mexico City children (12.32 ± 5.4 years, 69 APOE 3/3 and 36 APOE 3/4). APOE 4v 3 children showed decrements on attention and short-term memory subscales, and below-average scores in Verbal, Performance and Full Scale IQ. APOE 4 females had higher BMI and females with normal BMI between 75–94% percentiles had the highest deficits in Total IQ, Performance IQ, Digit Span, Picture Arrangement, Block Design and Object Assembly. Fasting glucose was significantly higher in APOE 4 children $p=0.006$, while Gender was the main variable accounting for the difference in insulin, HOMA-IR and leptin ($p<.05$).

Gender, BMI and APOE influence children's cognitive responses to air pollution and glucose is likely a key player. APOE 4 heterozygous females with $>75\%$ to $<94\%$ BMI percentiles are at the highest risk of severe cognitive deficits (1.5–2SD from average IQ). Young female results highlight the urgent need for gender-targeted health programmes to improve cognitive responses. Multidisciplinary intervention strategies could provide paths for prevention or amelioration of female air pollution targeted cognitive deficits and possible long-term AD progression.

1. Introduction

Systemic inflammation, metabolic imbalance, brain damage, neuroinflammation, and neurodegeneration, have been associated with exposure to urban air pollution (Calderón-Garcidueñas et al., 2008a, 2008b, 2010, 2011, 2012a, 2012b, 2012c, 2013a, 2015a, 2015b, 2015c, 2015d). Jung et al. (2015) have estimated a 211% risk of increase of Alzheimer's disease (AD) per increase of 10.91 ppb in ozone (O_3) and a 138% risk of increase of AD per increase of 4.34 μg/m^3 in particulate matter <2.5 μm ($PM_{2.5}$) in their cohort's 9 year follow-up period. Jung et al. findings in 95,690 individuals (with age ≥ 65 years) suggest long-term exposure to O_3 and $PM_{2.5}$ above the current US EPA standards is associated with increased risk of AD.

Air pollutants have serious pediatric detrimental effects on the brain that can be modulated by gender and genetic factors. For example, we have shown that the Apolipoprotein E (APOE) ε4 allele is related to increases in Alzheimer disease-related protein aggregates within the frontal lobe of both children and young

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adults exposed to O_3 and $PM_{2.5}$ concentrations above the accepted US standards in Mexico City Metropolitan Area (MCMA) (Calderón-Garcidueñas et al., 2012a). MCMA APOE ε4 carriers had more hyperphosphorylated tau and diffuse amyloid-β ($Aβ_{1–42}$) plaques than ε3 carriers. These findings in highly exposed Mexico City children and young adults are absent in low pollution-exposed age, gender and socio-economic status matched individuals (Calderón-Garcidueñas et al., 2012a). The APOE 4 allele is the strongest known genetic risk factor for late and early onset AD, influencing Aβ clearance and aggregation and impacting AD pathology independently of Aβ (Michaelson, 2014; Huang and Mahley, 2014; Kanekiyo et al., 2014; Malkki, 2015; Zhu et al., 2015). While gender cognitive stereotypes are controversial (Hyde, 2016), we have a consensus in terms of the APOE key role in coordinating the mobilization and redistribution of cholesterol, phospholipids and fatty acids, cholinergic function, and the capacity to clear Aβ plaques. There is also agreement in that age, APOE 4 and chromosomal sex are well-established risk factors for AD (Mahley and Rall, 2000; Michaelson, 2014; Huang and Mahley, 2014; Kanekiyo et al., 2014; Riedel et al., 2016; Dolejší et al., 2016; Simonovitch et al., 2016). Over 60% of AD patients carry at least one APOE-4 allele and moreover, sex-based prevalence of AD is well documented with over 60% of persons with AD being female (Riedel et al., 2016). APOE 4 is playing a role in our children's response to their cumulative air pollution exposures and the impact of the carrier status is an early event, as nicely described by Dean et al. (2014a, 2014b).

A piece of information of utmost relevance is the concept that APOE 4 young adult carriers exhibit compensatory or non-selective mechanisms during working memory testing (Han et al., 2008; Borghesani et al., 2008; Filbey et al., 2010). Matura et al. (2014) reported APOE 4 carriers performing significantly poorer than non-carriers in wordlist recognition and cued recall and showing increased connectivity relative to ε4 non-carriers between the posterior cingulate cortex (PCC) seed region and left-hemispheric middle temporal gyrus (MTG). Kunz et al. (2015) found that young APOE-4adults exhibit reduced grid-cell-like representations and altered navigational behavior in a virtual arena, associated with impaired spatial memory performance. Kunz et al. (2015) also reported reduced grid-cell-like representations were related to increased hippocampal activity, potentially reflecting compensatory mechanisms that prevent overt spatial memory impairment in APOE-4 carriers, decades before potential disease onset.

The issue of compensatory phenomena described in APOE-4 carriers is at the core of this research. Children in MCMA live under hostile air pollution chronic exposures and we have previously reported APOE 4 versus 3 children had a reduced NAA/Cr ratio in the right frontal white matter (Calderón-Garcidueñas et al., 2015b). While the NAA/Cr ratio in right hippocampus in clean air controls versus APOE 4 MCMA children and in left hippocampus in MCMA APOE 4 parents versus their children was significantly different after adjusting for age, gender, and BMI (Calderón-Garcidueñas et al., 2015c). The NAA/Cr ratio is reflective of neuronal density/functional integrity/loss of synapses/higher pTau burden, thus a significant decrease in frontal and hippocampal NAA/Cr ratios may constitute a spectral marker of early neurodegeneration in young urbanites and likely relates to decrements on attention, short-term memory, and below-average scores in Verbal and Full Scale IQ. Moreover, the neuropathological description of frontal hyperphosphorylated tau and diffuse amyloid-β ($Aβ_{1–42}$) plaques predominantly in young 4 MCMA carriers, strongly suggests APOE4 children and adolescents are being negatively impacted by the polluted atmosphere and compensatory phenomena are not working. In the UK, Taylor et al. (2011) published an interesting work in 5995 children from the Avon Longitudinal Study of Parents and Children covering an area of relatively low air pollution. Taylor et al. showed a strong relationships between APOE genotype and low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides, however reported no strong evidence to suggest that APOE genotype was associated with IQ, memory function, or school attainment test results. Their results are indeed in keeping with ours for low pollution control cities (Calderón-Garcidueñas et al., 2015b, 2015c, 2015d).

An issue of great concern for pediatricians across North-America are the reports on American, Mexican, Mexican-American and African-American children showing higher rates of overweight and obesity and the clear links between traffic-related air pollution and metabolic syndrome, obesity, hypertension, and diabetes mellitus (DM) (Iriart et al., 2013; Jerrett et al., 2014; Falkner and Cossrow, 2014). Traffic pollution has been positively associated with growth in BMI in children aged 5–11 years in Southern California (Jerrett et al., 2014). It is also clear that in experimental animal models and epidemiological studies, PM and gaseous air pollutants -even at concentrations below air quality standards-, exacerbate the metabolic imbalance in diabetes mellitus (DM), impair glucose tolerance during pregnancy, and increase DM risk (Vella et al., 2015; Fleisch et al., 2014; Eze et al., 2015).

The relationship between BMI and cognition is another critical aspect, since the literature suggests there are shared genetic contributions to BMI and cognitive function (Marioni et al., 2016; Wang et al., 2016), and episodic memory deficits are seen in obese teens and young adults (Qavam et al., 2015; Cheke et al., 2016). Adipose tissue, macrophages and immune cells are a source of potent inflammatory mediators, key to metabolic homeostasis, food intake, immune cell function, and a driving force for the development of insulin resistance, type 2 DM and Alzheimer's disease (Boutens and Stienstra, 2016; Booth et al., 2016; Chami et al., 2016).

Thus, severe exposure to air pollutants such as $PM_{2.5}$ and ozone could exert its impact on the cognitive functions of the developing brain in association with multiple variables. The purpose of the present study was to assess, in APOE ε4 versus ε3 matched clinically healthy children severely exposed to air pollution, the influence of APOE status, together with gender and body mass index as well as metabolic variables, on cognition. Previous research has studied the relevance of one or two of these variables separately. The novel contribution of the present study was to examine the interactive and cumulative influences of the entire set of variables on the risk of developing cognitive deficits. The gained knowledge can guide target experimental interventions to prevent or delay the early onset of certain neurodegenerative processes in subpopulations of children that are at particular risk.

2. Methods

This prospective study was approved by the review boards and ethics committees at the University of Montana, written consent was obtained from parents, and verbal consent from children.

2.1. Study areas

MCMA is the largest urban center in North America, a prime example of extreme urban growth and massive chronic exposure of 24 million people to concentrations of O_3 and $PM_{2.5}$ above the Environmental Protection Agency (EPA) Standards (Calderón-Segura et al., 2004; Dzepina et al., 2007; Valle-Hernández et al., 2010; Mugica-Álvarez et al., 2012; US EPA, 2014). The metropolitan area of over 2000 square kilometers lies in an elevated basin 2240 m above sea level surrounded on three sides by mountain

ridges, a broad opening to the north, and a narrower gap to the south-southwest. The MCMA 24 million inhabitants, over 50,000 industries, thousands of tons of garbage in dumping sky-exposed grounds (i.e., Bordo Poniente), and >5 million vehicles produce an estimated annual emission of 2.6 thousand tons of pollutants, including coarse and fine PM gaseous pollutants, polycyclic aromatic hydrocarbons, elemental carbon, endotoxins, and metals. Vehicles consume more than 40 million liters of petroleum fuels *per day* (Calderón-Segura et al., 2004; Dzepina et al., 2007; Valle-Hernández et al., 2010; Mugica-Álvarez et al., 2012). $PM_{2.5}$ concentrations peak toward the north-northeast area because the stronger emitters of PM such as industries and heavy duty diesel trucks are located in this zone, while ozone concentrations peak toward the downwind southwest area in the afternoon as a result of the typical diurnal wind transport of air polluted masses rich in precursors coming from the north and the center of the urban area.

2.2. Participant children

This work includes data from 105 Mexico City clinically healthy, right handed children and teens (*Mean age*=12.32 *SD*=5.4 years). We identified 69 children with an APOE ε3/ε3, and 36 with an APOE ε3/ε4. Children's clinical inclusion criteria were: no history of smoking or environmental tobacco exposure, lifelong residency in MCMA, residency within 5 miles of the city monitoring stations, full term birth, and unremarkable clinical histories, including absence of history of hospitalizations for respiratory illnesses, systemic or respiratory viral diseases, surgery, head trauma, and personal and family histories of neurologic or psychiatric diseases. We specifically excluded children with active participation in team sports with high incidence of head trauma, including soccer. Mothers had resided in Mexico City, in the same neighborhood for their entire life, including their pregnancy time, had full term pregnancies with uncomplicated vaginal deliveries and took no drugs, including alcohol. These children had a history of breast feeding for a minimum of 6 months and were introduced to solid foods after age 4 months. Participants were from middle socioeconomic class families living in single-family homes with no indoor pets, used natural gas for cooking, and kitchens were separated from the living and sleeping areas. The APOE ε3 and ε4 cohorts were matched for age, gestational duration, birth weight, gender ratio, maternal age, and education.

2.3. Pediatric examination

Children had complete clinical histories and physical examinations by a pediatrician. The heights and weights used in this study were measured during the pediatric clinical care visit the same week as the neurocognitive testing. Age and gender specific BMI percentiles were calculated with the year 2000 modified 10/16/00, Centers for Disease Control and Prevention Growth Charts (Kuczmarski et al., 2002). BMI was classified in two categories: healthy 25–74th and high healthy and overweight combined 75–94th percentiles. This work does not include children with BMI equal or greater than the 95th percentile. All included children were clinically healthy and actively engaged in daily outdoor activities.

2.4. Peripheral blood analysis

Blood samples were taken after 10–12 h of fasting between 7 and 9am during the school working days. Comprehensive Metabolic Panel (CMP) and custom made human Multiplexing Laser Bead Technology, Bio-Rad Human Diabetes (Eve Technologies Corporation, Calgary, Alberta, Canada) were done for the quantification of the following markers: Glucagon, Insulin, and Leptin. Endothelin-1 was measured using a QuantiGlo ELISA kit from R&D Systems, Minneapolis, MN, USA (detection limit .102 pg/mL), and 25-OH-Vitamin D ELISA (detection limit 1.6 ng/mL) from Diagnostika GMBH, Adlerhorst, Hamburg, Germany. The HOMA-IR Homeostatic Model Assessment of Insulin Resistance was calculated.

2.5. Wechsler Intelligence Scale for Children-Revised (WISC-R)

We used the Spanish version of the Wechsler Intelligence Scale for Children-Revised WISC-R (Wechsler, 1974).

2.6. Apolipoprotein E genotyping

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

2.7. Data analysis

We performed four types of analyses: 1) Parametric planned t-tests to compare variables of interest between APOE 3 and 4 carriers; 2) a multifactorial analysis of variance (MANOVA), with metabolic ratios as dependent variables and with APOE and gender as independent variables; 3) Univariate ANOVAs testing Between-Subjects effects following up to MANOVA models and 4) Pearson correlation coefficients for measuring the association between BMI and cognitive performance on IQ subtests and quotients split in subgroups APOE type by gender. For all analyses, significance was assumed when the p-value $p < .05$, and the test is assumed to be two-sided; to correct for multiple comparisons we performed the Simes-Bonferroni correction (Simes, 1986).

3. Results

3.1. Air pollution levels

Children in this study have been exposed to concentrations of $PM_{2.5}$ and O_3, above the current EPA standards for their entire life (Figs. 1 and 2). The climatic conditions in MCMA are relatively stable through the year thus pollutant concentrations are relatively uniform without strong variations. According to data from the government air quality monitoring network (SMA 2014), during the 1997–2014 period that includes the period the children have lived in MCMA (Fig. 1), the $PM_{2.5}$ three-year averages of annual average concentrations in the representative monitoring stations were always above the respective primary $PM_{2.5}$ US EPA annual standard of 12 $\mu g/m^3$. This standard is attained when the 3-year average of annual means is less than or equal to the above mentioned concentration. In addition, the four highest daily maximum eight-hour average concentrations for each of 3 consecutive years for ozone in the same monitoring sites for the 1997–2014 period (Fig. 2) were above the current 8-h average ozone NAAQS of 75 ppb.

3.2. Demographic data and physical exams

Table 1 summarizes the characteristics of the selected children cohorts. Vital signs and the physical examination results were unremarkable in all participant children. APOE ε4 children had higher body mass index (BMI) v APOE ε3 children. APOE 4 females had significantly higher BMI than their ε3 counterparts ($p < .01$). Females had higher mean BMI percentile than males. The APOE ε3

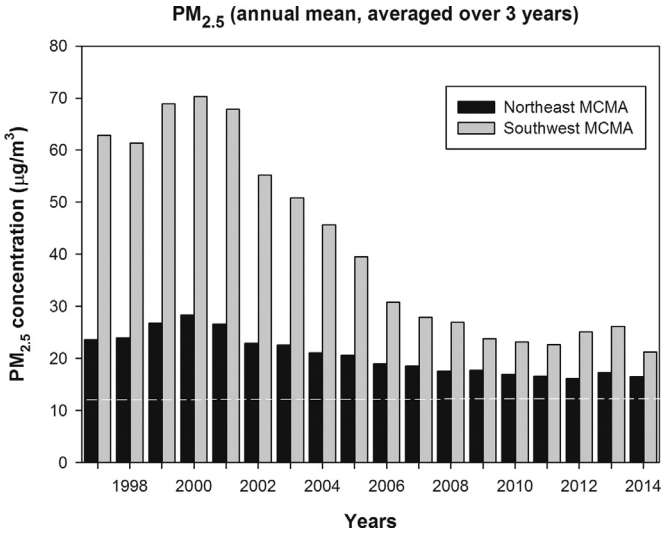

Fig. 1. Three-year average $PM_{2.5}$ annual mean concentration registered at the northeast and southwest Mexico City Metropolitan Area (MCMA) from 1997 to 2014. The dashed lines represent the respective US-EPA National Air Quality Standards. Since $PM_{2.5}$ measurements began in 2004, data from 2004 to 2009 were obtained from the slope of the correlation PM_{10} v $PM_{2.5}$.

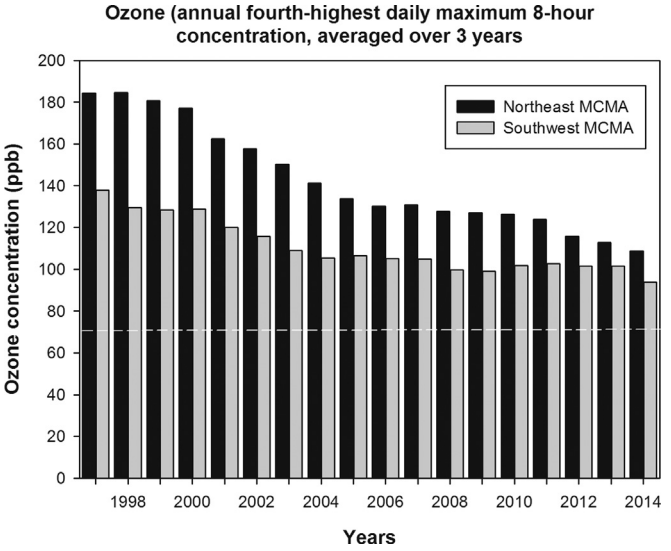

Fig. 2. Three year average 4th highest 8-h ozone annual mean concentration registered at the northeast and southwest Mexico City Metropolitan Area (MCMA) from 1997 to 2014.
O^3 and $PM_{2.5}$ concentrations were obtained from the Air Quality Monitoring Network of the Government of Mexico City.

and ε4 cohorts had no significant differences in age, gestational duration, birth weight, gender ratio, maternal age, education, and maternal socioeconomic status as indicated by years of education. Consistent with the report of the *Institute Of Medicine Of The National Academies*, and with Kuczmarski and colleagues paper, we have followed their established criteria: children and adolescents with a BMI equal to or greater than the 95th percentile are categorized as obese, and those with a BMI between the 85th and 94th percentiles are considered to be at risk for obesity (IOM, 2005; Kuczmarski et al., 2002). For statistical purposes, evaluation of APOE, gender and cognition was done on the bases of BMI% classified in two categories: healthy 25–74th and high healthy and overweight combined 75th to 94th percentiles.

Table 1
Characteristics of the 105 Mexico City Metropolitan Area APOE 3 and 4 children studied.

	APOE 3/3	APOE 3/4
n	69	36
Age (years)	11.89 ± 4.1	12.7 ± 6.7
Weight (kg)	19.4 ± 4.2	21.0 ± 4.8
Height (m)	1.44 ± 0.1	1.48 ± 0.1
BMI	19.1 ± 3.6	22.5 ± 4.6*
BMI Females	20.07 ± 5.1	22.3 ± 4.7*
BMI Males	18.6 ± 2.6	19.9 ± 4.8
BMI %	66.6 ± 27.2	68.78 ± 29.1
BMI % Females	70.07 ± 27.9[a]	71 ± 28.6[a]
BMI% Males	62.2 ± 25.9[b]	66.7 ± 30.3[b]
Gender	39F/30M	17F/19M
Birth weight (grams)	3234 ± 341	3340 ± 398
Gestational duration (weeks)	38.8 ± 1.6	38.8 ± 1.4
Mother's age	38.05 ± 6.7	39.4 ± 7.0
Mother's education years	11.07 ± 2.3	11.62 ± 1.9

[a vs. b] Effect of Gender ($F(1, 101)=143.15$; $MSE=844.65$; $p=0.05$).
Note. The numerical values shown in the table represent means (± 1 standard deviation). % indicates percentile.
* $p < .05$ (with Simes-Bonferroni correction) $t(103) > 2.18$.

Table 2
Means and standard deviations for Vitamin D, adipokines, Comprehensive Metabolic Panel and HOMA-IR values in 105 APOE 3 versus APOE4 Metropolitan Mexico City 12.32 ± 5.4 years children.

Serum variables	MCMA APOE3	MCMA APOE 4
Vitamin D* ng/mL	23.0 ± 12.4	28.3 ± 23.7
Glucagon pg/mL	168.9 ± 25.9	154.2 ± 40.6
Insulin pg/mL	351.0 ± 257.6	346.9 ± 147
Leptin pg/mL	6607.2 ± 9229	6616 ± 6416
ET-1 pg/mL	2.2 ± 0.9	2.5 ± 0.6
Fasting blood sugar mg/dL	82.8 ± 8.7	90.5 ± 6.8
HOMA-IR	1.69 ± 1.17	1.85 ± 0.7
Cholesterol mg/dL	159.6 ± 26.6	171 ± 19.7
Triglycerides mg/dL	101.5 ± 51.2	113.1 ± 46.4
AST[a] U/L	29.3 ± 4.2	32.2 ± 4.8
ALT[b] U/L	16.5 ± 2.6	16.6 ± 3.1
Calcium mg/dL	9.7 ± 0.31	9.9 ± 0.31
Phosphorus mg/dL	4.9 ± 0.2	4.9 ± 0.1
Magnesium mg/dL	2.2 ± 1.1	2.2 ± 0.1

Note. For APOE 3n=25, APOE 4n=13. Females=22; Males=16.
* Vitamin D Normal > 30 ng/mL, Insufficiency 21–29 ng/mL, Deficiency < 20ng/mL.
[a] AST = Aspartate aminotransferase.
[b] ALT = Alanine aminotransferase.

3.3. Laboratory findings

Table 2 shows the concentrations, means and SD ± in the selected laboratory variables in MCMA APOE 3 versus APOE 4 children. Multivariate analysis revealed no interactions between APOE and Gender and no main effects, except for a significant additive effect of APOE and Gender on glucose ($F(1, 34)=3.372$; $MSE=67.18$; $p=0.03$; $\eta^2=0.23$). The follow up univariate analysis showed that glucose was significantly different in APOE 4 children $p=0.006$ (Table 3) while Gender was the main variable accounting for the difference in insulin ($p=0.035$), HOMA-IR ($p=0.037$) and leptin ($p=0.048$). No other univariate effects were significant.

3.4. WISC-R results

The WISC-R results for APOE 3/3 versus carriers of an allele ε4 are shown in Table 4. APOE ε3 female and male subjects significantly outperformed their APOE ε4 counterparts in five subtests: Arithmetic, Information, Picture Completion, and most and

Table 3
Multivariate analysis for variables in Table 2 comparing APOE 3 versus APOE 4, APOE and Gender, significant results in bold, corrected for multiple tests and type 1 and 2 errors.

	Source	MSE	F (1, 34)	p
APOE	Glucagon	44.099	.027	.871
	Insulin	739.001	.015	.902
	HOMAIR	.437	.418	.522
	Leptin	14128983.161	.216	.645
	Vit. D	497.300	1.445	.238
	ET1	1.025	2.411	.130
	glucose	580.337	8.638	**.006**
	Cholesterol	920.648	1.470	.234
	Triglyc	3477.815	1.402	.245
	AST	71.109	3.536	.069
	ALT	2.120	.308	.583
	Ca	.009	.102	.752
	P	.019	.294	.591
	Mg	.015	.700	.408
Gender	Glucagon	748.331	.457	.503
	Insulin	230786.455	4.814	**.035**
	HOMAIR	4.947	4.728	**.037**
	Leptin	274128724.184	4.188	**.048**
	Vit. D	62.927	.183	.672
	ET1	.306	.719	.402
	Glucose	88.985	1.325	.258
	Cholesterol	1375.744	2.197	.147
	Triglyc	433.155	.175	.679
	AST	31.089	1.546	.222
	ALT	3.760	.546	.465
	Ca	.011	.120	.732
	P	.000	.001	.981
	Mg	.000	.006	.937
APOE X Gender	Glucagon	103.631	.063	.803
	Insulin	1871.792	.039	.845
	HOMAIR	.092	.088	.769
	Leptin	19147136.853	.293	.592
	Vit. D	76.883	.223	.640
	ET1	.003	.007	.932
	Glucose	24.892	.371	.547
	Cholesterol	132.011	.211	.649
	Triglyc	970.295	.391	.536
	AST	32.175	1.600	.214
	ALT	4.547	.660	.422
	Ca	.068	.727	.400
	P	.012	.184	.671
	Mg	.010	.447	.508
	Glucagon	1636.263		
	Insulin	47945.656		
	HOMAIR	1.046		
	Leptin	65452055.511		
Error	VitD	344.239		
	ET_1	.425		
	Glucose	67.183		
	Cholesterol	626.202		
	Triglyc	2481.101		
	AST	20.109		
	ALT	6.891		
	Ca	.093		
	P	.066		
	Mg	.022		

foremost on Digit Span, a measure of short and working memory. Table 5 shows the results of Verbal, Performance and Total IQ tests of multivariate and univariate analysis between-subjects effects of APOE 3/3 versus APOE 4 Mexico City children. The interaction of Gender and APOE and their combined separate effects had a strong impact upon Performance and Full IQ, with APOE having strongest effect on Full IQ, while the strongest effect of Gender was on Performance IQ.

Table 6 shows the results of the multivariate and univariate tests of Between-Subjects effects APOE 3/3 versus APOE 3/4

Table 4
WISC-R subtest normalized results in APOE 3/3 versus APOE 3/4 Mexico City children.

	APOE 3		APOE 4	
	Males	Females	Males	Females
Information	10.8 ± 2.4	9.6 ± 2.9	9.0 ± 2.8	8.35 ± 3.7
Similarities	13.2 ± 3.3	12.3 ± 4.2	11.84 ± 5.2	10.11 ± 5.1
Arithmetic	11.5 ± 3.1	10.2 ± 3.2	10.3 ± 3	8.9 ± 3.1
Vocabulary	12.6 ± 2.8	12.1 ± 2.2	12.4 ± 2.9	11.1 ± 3.9
Comprehension	13.1 ± 3.2	12.7 ± 3.0	13.3 ± 3.1	12.0 ± 3.4
Digit Span	10.2 ± 3.3	**9.2 ± 3.0**	9.5 ± 2.9	**7.1 ± 2.0**
Picture Completion	13.1 ± 2.8	12.9 ± 2.8	13.4 ± 3.1	11.1 ± 2.9
Picture Arrangement	11.6 ± 3.0	**10.8 ± 3.4**	11.9 ± 2.6	**7.7 ± 2.5**
Block Design	12.1 ± 2.4	**11.2 ± 2.7**	12.5 ± 3.2	**9.7 ± 2.5**
Object Assembly	11.4 ± 2.6	**10.1 ± 2.7**	11.2 ± 2.6	**7.5 ± 2.3**
Coding	10.2 ± 2.6	11.1 ± 2.9	10.4 ± 2.9	9.8 ± 2.2
Mazes	11.8 ± 3.1	11.0 ± 4	12.9 ± 2.8	10.6 ± 2.5
Verbal IQ	113.1 ± 13.5	108.2 ± 14.6	108.2 ± 15.6	99.5 ± 19.5
Performance IQ	112.3 ± 13.6	**109.1 ± 15.6**	113.7 ± 14.6	**94.4 ± 14.1**
Full Scale IQ	113.9 ± 12.5	**109.4 ± 15.6**	112.1 ± 15.8	**96.9 ± 16.2**

Note. The numerical valuems shown in the table represent means (± 1 standard deviation). Significant targeted contrasts between Females APOE 4 vs APOE 3 are flagged in bold.

Table 5
ANOVA results: multivariate and univariate tests of between-subjects effects on WISC-R IQ in APOE 3/3 versus APOE 4/3 Mexico City children.

Source	Dependent variable	F	MSE	p	η^2
Multivariate		df (3,101)			
	Verbal IQ	2.803	666.884	**.044**	.077
	Performance IQ	6.692	1441.655	**.000**	.166
	FULL IQ	5.055	1132.968	**.003**	.131
Univariate		df (1,101)			
APOE[a]	Verbal IQ	4.543	1080.744	**.035**	.043
	Performance IQ	4.704	1013.471	**.032**	.045
	FULL IQ	5.396	1209.288	**.022**	.051
Gender[b]	Verbal IQ	4.552	1082.894	**.035**	.043
	Performance IQ	13.808	2974.748	**.000**	.120
	FULL IQ	10.155	2275.941	**.002**	.091
APOE X Gender[c]	Verbal IQ	.350	83.159	.556	.003
	Performance IQ	7.078	1524.978	**.009**	.065
	FULL IQ	2.960	663.427	.088	.028
Error	Verbal IQ		237.895		
	Performance IQ		215.438		
	FULL IQ		224.112		

Note. Multivariate tests, *Hotelling's Trace*,
[a] .061.
[b] .143.
[c] .095.

Mexico City children in individual IQ subtests. Gender strongly affected Object Assembly, Picture Arrangement, Block Design and Digit Span. Additional to and independent of Gender, APOE had the largest effects upon Information, Object Assembly, and Digit Span. While an interaction of APOE and Gender strongly affected Picture Arrangement. The combined significant effects as reflected by the corrected MANOVA models explained between 8% and 20% of the variance. Table 7 show the Pearson correlation coefficients measuring the association between BMI and cognitive performance on IQ subtests and quotients split in subgroups APOE type by gender. There are very strong negative correlations between BMI and targeted subtests in APOE 4 females. Performance and Full IQ are strongly negatively affected.

Finally, the effect of percentile of BMI (BMI %) upon the targeted WISC-R subtest is shown in Fig. 3. The impact of a BMI% > 75% is

Table 6
Tests of multivariate and univariate tests between-subjects effects on WISC-R specific subtest for APOE 3/3 versus APOE 3/4 Mexico City children.

Source	IQ Subtests	MSE	F	p	η^2
Multivariate			df (3,101)		
	Information	26.227	2.972	.035	.081
	Similarities	35.331	1.853	.142	.052
	Arithmetic	25.779	2.561	.059	.071
	Vocabulary	8.818	1.064	.368	.031
	Comprehension	6.356	.627	.599	.018
	Digit Span	34.075	3.801	.013	.101
	PictureCompl	19.997	2.393	.073	.066
	PictureArrngm	69.643	7.459	.000	.181
	BlockDesign	30.828	4.142	.008	.110
	ObjectAssmb	59.209	8.420	.000	.200
	Coding	8.198	1.051	.373	.030
	Mazes	10.667	.936	.426	.027
Univariate			df (1,101)		
APOE[a]					
	Information	56.233	6.372	.013	.059
	Similarities	73.860	3.874	.052	.037
	Arithmetic	37.829	3.758	.055	.036
	Vocabulary	9.525	1.149	.286	.011
	Comprehension	2.020	.199	.656	.002
	Digit Span	42.806	4.775	.031	.045
	PictureCompl	12.028	1.439	.233	.014
	PictureArrngm	48.584	5.203	.025	.049
	BlockDesign	7.602	1.021	.315	.010
	Object Assmb	45.370	6.452	.013	.060
	Coding	5.930	.761	.385	.007
	Mazes	.062	.005	.942	.000
Gender[b]					
	Information	20.409	2.313	.131	.022
	Similarities	40.178	2.108	.150	.020
	Arithmetic	43.151	4.287	.041	.041
	Vocabulary	18.119	2.186	.142	.021
	Comprehension	16.558	1.632	.204	.016
	Digit Span	65.694	7.329	.008	.068
	PictureCompl	37.645	4.505	.036	.043
	PictureArrngm	145.364	15.569	.000	.134
	BlockDesign	83.985	11.283	.001	.100
	Object Assmb	137.610	19.569	.000	.162
	Coding	.374	.048	.827	.000
	Mazes	31.916	2.802	.097	.027
APOE xGender[c]					
	Information	1.912	.217	.643	.002
	Similarities	4.063	.213	.645	.002
	Arithmetic	.119	.012	.914	.000
	Vocabulary	4.235	.511	.476	.005
	Comprehension	5.314	.524	.471	.005
	Digit Span	12.488	1.393	.241	.014
	PictureCompl	27.862	3.334	.071	.032
	PictureArrngm	72.107	7.723	.007	.071
	BlockDesign	22.605	3.037	.084	.029
	Object Assmb	33.847	4.813	.031	.045
	Coding	14.146	1.814	.181	.018
	Mazes	3.738	.328	.568	.003
Error					
	Information	8.825			
	Similarities	19.063			
	Arithmetic	10.066			
	Vocabulary	8.288			
	Comprehension	10.144			
	Digit Span	8.964			
	PictureCompl	8.356			
	PictureArrngm	9.337			
	Block Design	7.443			
	ObjectAssmb	7.032			
	Coding	7.798			
	Mazes	11.392			

Note. PictureCompl = Picture Completion; PictureArrngm = Picture Arrangement; ObjectAssmb = Object Assembly.
Multivariate tests, *Hotelling's Trace*:
[a] .179;
[b] .374;
[c] .173.

Table 7
Pearson correlation coefficients measuring the association between BMI and cognitive performance on IQ subtests and quotients split in subgroups APOE type by gender.

	BMI			
	APOE 3		APOE 4	
	Males (n=30)	Females (n=39)	Males (n=19)	Females (n=17)
IQ subtests				
DigitSpan	−0.522**	−0.379*	−0.374	−0.680**
PictureCompl	−0.155	−0.120	−0.206	−0.591*
PictureArrngm	−0.599**	−0.012	−0.619**	−0.610**
BlockDesign	−0.187	.319	−0.126	−0.763**
ObjectAssmb	−0.272	.049	−0.587**	−0.682**
IQ quotients				
Verbal	−0.166	.073	−0.131	−0.464
Performance	−0.309	.114	−0.374	−0.748**
Full	−0.304	.070	−0.276	−0.623**

Note.
* $p < .05$.
** $p < .01$.

observed in Digit Span, Block Design, Picture Arrangement and Object Assembly. Fig. 4 illustrates the impact of BMI % upon Performance (Fig. 4(A)), Verbal (Fig. 4(B)) and Full IQ (Fig. 4(C)).

4. Discussion

The present findings show underperformance in cognitive processes as a function of gender, BMI and APOE status in clinically healthy urban children chronically exposed to concentrations of fine particulate matter and ozone above current US Environmental Protection Agency standards. The cognition deficits impact predominantly females, and specific WISC-R subtests i.e., Object Assembly, Picture Arrangement, Block Design and Digit Span. Fasting glucose is significantly different in APOE 4 children and female gender is the main variable accounting for the difference in insulin, HOMA-IR and leptin.

According to our findings, gender is critical in the scenario of air pollution metabolic and central nervous system (CNS) detrimental impact. Being a young female in Mexico City is associated with strong negative effects at all levels of IQ, with the strongest effect on Performance IQ. Although there is an extensive literature examining gender and neurocognitive function (Linn and Petersen, 1985; Suades-González et al., 2015; Yasen et al., 2015; Miraglia et al., 2015; Newman, 2015; Sano and Gandy, 2016; Triviño-Paredes et al., 2016; Mansouri et al., 2016; Riedel et al., 2016), there is scarce literature identifying air pollution as a risk factor for gender related cognition deficits in children (Jiménez-Pavón et al., 2013). Some authors propose that sex differences in selective attention for example, are caused by underlying sex differences in core abilities, such as spatial or verbal cognition (Stoet, 2016), while others include variables such as exercise regime, duration, and intensity playing a role in hippocampal structural plasticity and in adult hippocampal neurogenesis (Triviño-Paredes et al., 2016). Equally important during brain development, gender differences in volume and surface area are observed across time suggesting few cerebral regions exhibit cortical developmental changes as a function of gender (Vijayakumar et al., 2016). The Gender Similarities Hypothesis states that males and females are quite similar on most-but not all-psychological variables (Hyde, 2016). However, when one considers retrospective life-span data on the dementia risk in both sexes, there are clear differences in the modulation of

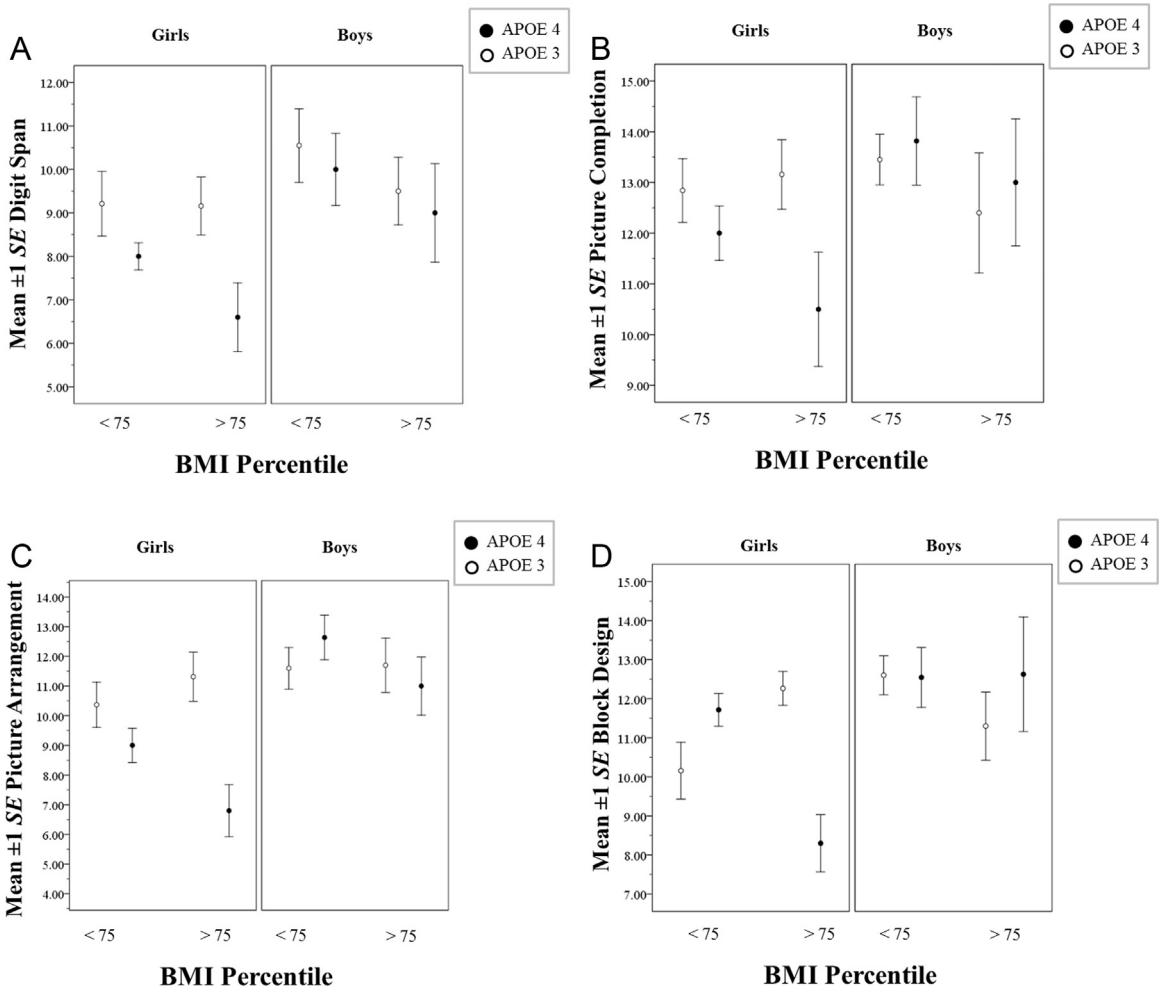

Fig. 3. Means and standard errors of standardized scaled scores on IQ subtests as a function of BMI percentile category and Gender in APOE 3 and 4 Mexico City children. Each separate panel corresponds to a different IQ subtest: A: Digit Span; B: Picture Completion; C: Picture Arrangement; D: Block Design.

redox proteins and sex-specific alterations in the white matter and mitochondria proteomes of female patients (Gallart-Palau et al., 2016). Laws et al. (2016) have reported that men outperform women at the same stage of AD in several cognitive domains including episodic memory, visuospatial tasks, language and semantic abilities.

The available evidence points at complex relationships and interactions between age, APOE genotype and gender that support a medical approach that cuts across these three main risk factors for Alzheimer's disease. In this context, it will be critical to define if compensatory mechanisms that prevent overt cognitive impairments evolve in APOE4 children, particularly in girls at some time during childhood. Therefore, we review how current evidence applies to the *pediatric exposure model* of Mexico City. Subsequently, we outline the progress we are making in linking such model to the implementation of an *integrative targeted prevention approach*.

4.1. Mexico City Pediatric Exposure Model

Gene/environment GXE interactions are key for air pollution health effects. We have reported in Mexico City APOE 4 versus 3 children reduction in right frontal white matter NAA/Cr ratio associated with decrements on attention, short-term memory, and below-average scores in Verbal and Full Scale IQ. APOE modulated the group effects between WISC-R and left frontal and parietal white matter, and hippocampus metabolites (Calderón-Garcidueñas et al., 2015b, 2015c). The striking ε4 carriers' underperformance in IQ subscales tapping on attention, short term memory, and learning abilities goes along with the NAA/Cr decreased ratios in frontal brain regions that sub-serve higher cognitive functions and impulse control.

Of note, neuroinflammation, beta amyloid diffuse plaques and hyperphosphorilated tau- the latter two, key pathology hallmarks of AD- are already present in MCMA children and are significantly worse in APOE ε4 children (Calderón-Garcidueñas et al., 2012a). Moreover, the impact of APOE4 in relationship with air pollution affected both children and parents sharing the allele 4 (Calderón-Garcidueñas et al., 2015c).

Reynolds results suggested APOE may represent a variability gene for depressive symptoms and spatial reasoning, but not for BMI (Reynolds et al., 2016). Ihle et al. (2012) found no APOE4 –related cognitive effects in children adolescents and young adults, while Heise et al. (2011) found a general reduction of fractional anisotropy and increase in mean diffusivity using diffusion tensor imaging in healthy 20–35 and 50–78 y adults, in APOE 4 carriers relative to non-carriers. Interestingly, they found no significant interactions between genotype and age, suggesting that differences in white matter (WM) structure between APOE 4-carriers and non-carriers do not undergo significant differential changes with age. The early reduction of fractional anisotropy and increase in mean diffusivity values in APOE4 carriers is very relevant for our MCMA cohorts, since white matter metabolic and structural alterations impact cognition (Heise et al., 2011; Calderón-Garcidueñas et al.,

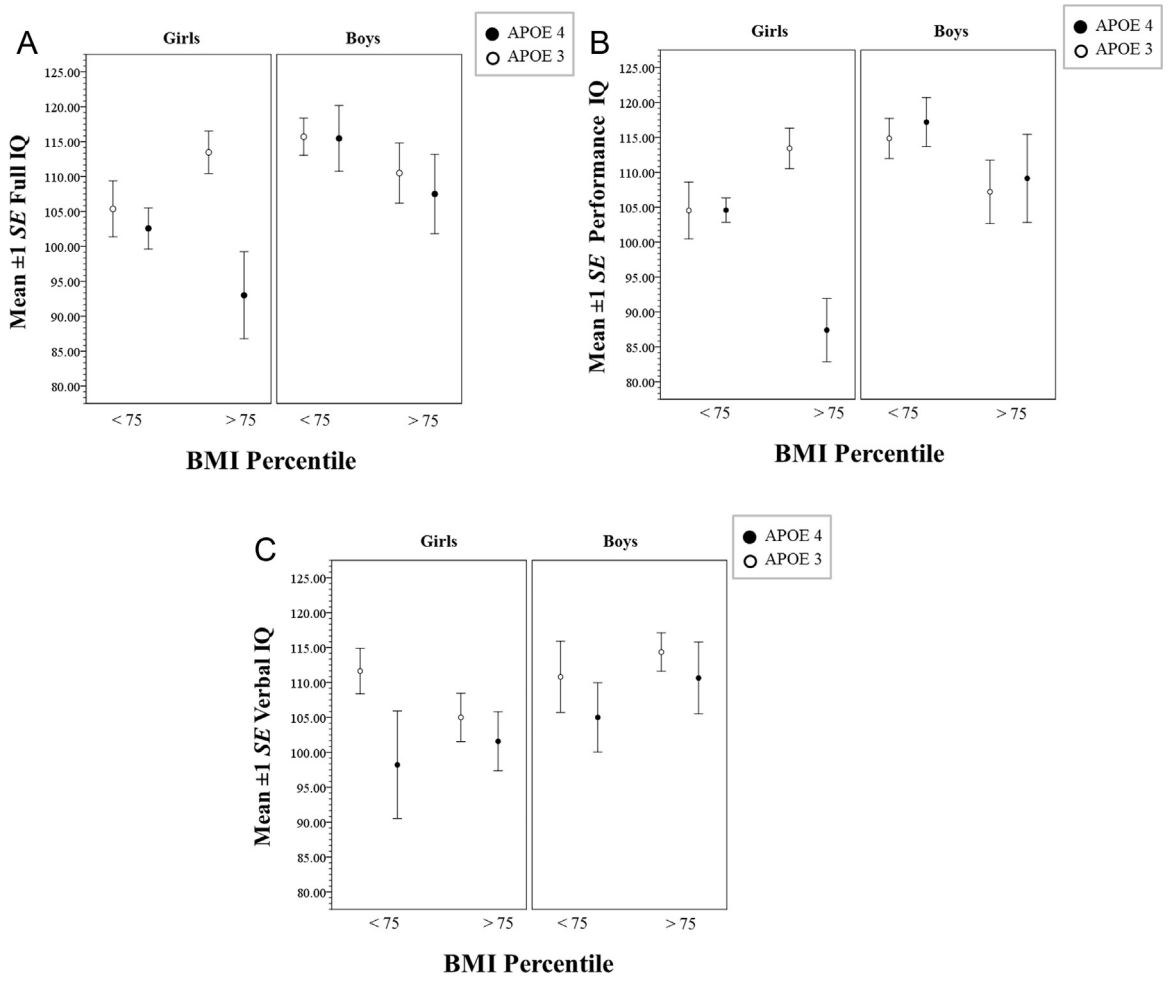

Fig. 4. Means and standard errors of IQ scales as a function of BMI percentile category and Gender in APOE 3 and 4 Mexico City children. Each separate panel corresponds to a different IQ scale: A: Full IQ quotient; B: Verbal IQ; C Performance IQ.

2012b; Bjartmar et al., 2002; Haier, 2004; Schmithorst et al., 2005; Moffett et al., 2007; Braak et al., 2011; Braak and Del Tredeci, 2011; Penke et al., 2012; Lyall et al., 2014; Kantarci, 2007, 2013a, 2013b, Kantarci et al., 2013; Rohn, 2014).

Thus, in evaluating cognitive functions, the interaction between air pollution and APOE gene variants has to be taken into account at all ages (Calderón-Garcidueñas et al., 2015b, 2015c; Schikowski et al., 2015). The key aspect in the present work is that APOE4 children had higher BMI v APOE3 counterparts, the statistical significance driven by APOE4 females. APOE4 allele is a risk factor for cardiovascular disease and analysis of 4408 men showed a gene dose-dependent association between APOE4 and increased risk for metabolic syndrome (MetS) (Torres-Pérez et al., 2016). This association is primarily derived from the overweight individuals. The same researchers evaluated 3908 healthy young individuals from the Coronary Artery Risk Development in Young Adults cohort for 25 years, and APOE4 presence significantly increased the risk of developing MetS. Interplay between APOE4 and the longitudinal development of fatness towards the onset of MetS occurred throughout the study. The authors concluded APOE4 carrier status increases MetS in a dose-dependent manner.

This substantiates our findings: female gender is the main variable accounting for the difference in insulin, HOMA-IR and leptin, while APOE 4 is critical for the fasting glucose levels. Thus, we are dealing with an unfortunate interplay of gender, APOE4 and metabolic abnormalities in young girls living in a polluted city. Compensatory mechanisms that prevent overt cognitive impairments in APOE4 young females don't seem to be in place.

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). 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 (Jiménez-Pavón et al., 2013). The issue is very relevant because we already have evidence that systemic inflammation and immunodysregulation are important early findings in MCMA children (Calderón-Garcidueñas et al., 2008a, 2009) and since overweight and obesity causes low grade systemic inflammation -associated to a dysfunctional adipose tissue-(Pérez et al., 2016; Varma et al., 2016) consideration for a synergistic effect with air pollution inflammation is warranted (Wei et al., 2016).

Lean Mexico City children 11.1 ± 3.3y olds, show high blood leptin and food reward hormone dysregulation versus clean air controls, and leptin is strongly positively associated to $PM_{2.5}$ cumulative exposures (Calderón-Garcidueñas et al., 2015d). Thus, the trajectory defined so far, indicates that high blood leptin and food reward hormone dysregulation in MCMA children is present in the early pubertal stage (11.1 ± 3.2 years), before these children start putting on weight (12.32 ± 5.4 years in this study). Moreover, in a similar cohort (11.9 ± 4.7 years), MCMA children already show

lower cerebrospinal fluid (CSF) concentrations of the biomarker for Alzheimer's disease amyloid beta 1–42 protein ($A\beta_{1-42}$) ($p=0.001$) versus clean air controls (Calderón-Garcidueñas et al., 2015e).

Supporting our work, Lavigne et al. (2016) found significant associations between air pollution variables and cord blood leptin levels adjusted for birth weight z-score among 1257 mother-infant pairs from the Maternal-Infant Research on Environmental Chemicals Study, conducted in Canada between 2008 and 2011 Thus, we agree with Lavigne et al. that prenatal exposure is also of extreme importance for the potential development of childhood obesity.

Obesity is increased in minority, low SES populations, and 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; Safdie et al., 2013; Fowler et al., 2013; Rossen, 2014; Bauer et al., 2014).

MCMA children have two serious problems:

1. They are unable to play outdoors due to the high pollution levels and violence on the streets, and
2. Their current high fructose consumption.

Mexico City has witnessed a steady increase in violent crime in the last few years along with a negative trust on authorities (Muggah and Vilalta, 2016; Blanco, 2016). Armed robberies, kidnappings, car thefts, and various forms of residential/street crime are daily concerns (OSAC, 2015). Homicides were up 20% in 2015, one third of the MCMA population has been a victim of a crime. Muggah and Vilalta discussed the strong relationships between high-crime areas and underdevelopment, income, and family disruption. All these factors are negatively impacting children and teens, decreasing their interactions outside the home, as it happens in other well-known violent Mexican cities (Hernandez and Grineski, 2012). Mexico is the world's biggest per capita consumer of soft drinks and the recent change from cane sugar to high fructose corn syrup will aggravate obesity, chronic metabolic disease, cognitive decline and the risk of AD (Lustig, 2013; Regnault et al., 2013; Sloboda et al., 2014).

Compounding the problem, is the documentation that $>85\%$ of Mexico City children and teens of 25-hydroxyvitamin D serum concentrations below <30 ng/mL (Calderón-Garcidueñas et al., 2015d). Vitamin D synthesis is greatly influenced by outdoor pollution, latitude, altitude, darker skin pigmentation and deficient nutritional intake (Wacker et al., 2013; Calderón-Garcidueñas et al., 2013b; Kelishadi et al., 2014).

4.2. From evidence to prevention

An emerging theme for the development of neurodegenerative diseases is the characterization of individuals' APOE genotype to identify at-risk participants for preventive intervention (Torres-Pérez et al., 2016). Currently, our team is making progress in identifying young APOE 3/4 girls with significant cognitive deficits, with historical documentation in similar cohorts of reduced NAA/Cr ratio in the right frontal white matter and right hippocampus, considered reflective of neuronal density/functional integrity/loss of synapses/higher pTau burden (Calderón-Garcidueñas et al., 2015b, 2015c). These metabolic changes may constitute a spectral marker of early neurodegeneration in young urbanites and they correlate well with cognitive function, behavioral symptoms, and in older cohorts with dementia severity. Sampedro et al. (2015) argue the impact of APOE4 on brain metabolism and structure is modified by sex. In their work, healthy elderly female APOE4 carriers had lower CSF $A\beta_{1-42}$ and higher CSF p-tau181p values than non-carriers and APOE4 females exhibited greater hypometabolism and atrophy than male carriers (Sampedro et al., 2015). We have shown that Mexico City APOE4 carriers have greater hyperphosphorylated tau and diffuse Aβ plaques versus E3 carriers ($Q=7.82$, $p=0.005$) (Calderón-Garcidueñas et al., 2012a).

The overall picture in Mexico City children, particularly girls, could signal their future trajectory towards the development of progressively worse cognitive impairment, insulin resistance, obesity, type II diabetes, premature cardiovascular disease, and Alzheimer's disease.

This is complicated by underprovided public schools, poor in the development of executive function skills with a resultant lack of cognitive reserves (Calderón-Garcidueñas and Torres-Jardón, 2012c), deficits in Verbal, Performance and Total IQ tests in APOE 4 children with a resultant negative impact on a projected 2.16 million MCMA APOE ε4 pediatric carriers.

An optimist approach to this issue is the roughly 50 year window of opportunity between the time urban children might be experiencing the detrimental effects we are describing and when they might undergo neurologic assessment, allowing for:

1. Targeted preventive intervention of vitamin D deficiency and insufficiency.
2. Access to indoor spaces for exercise away from air pollutants.
3. Public school curricula improvement to build executive function skills and increase their cognitive reserves.
4. Good nutrition: low price school lunches.
5. Good pediatric care including mental health services.

All preventive measures should be integrated in health and educational agendas targeting Mexico City children, especially girls. The need for interventions aimed at breaking the cycle of childhood poverty, food insecurity, high unemployment, violence, addictions, air pollution, and their negative health consequences becomes heightened.

5. Conclusions

In summary, adding to the already accumulating evidence of detrimental neural effects of air pollutants, we have shown data which document the interactive and additive influences of Gender, BMI and Apolipoprotein 4 on cognition in Mexico City children who are chronically exposed to high concentrations of $PM_{2.5}$ and ozone, also showing that APOE 4 females are at highest risk. We have detailed a pediatric exposure model that maps out the neurodevelopmental changes associated with the complex relationships within the system of variables exerting influences at multiple levels in children, and as logical follow up we have discussed an ongoing feasible preventive approach targeting the most vulnerable.

With the approach proposed here, we argue that pediatric air pollution research requires support and extensive multidisciplinary collaborations to accomplish a critical goal: to protect exposed children through multidimensional interventions having both broad impact and reach. Such overarching goals not only imply increased efforts to decrease pediatric $PM_{2.5}$ and ozone exposures to levels below the USA standard, but also to deliver health interventions prior to the development of overweight and obesity and mitigate environmental factors influencing metabolic syndrome, obesity and Alzheimer disease.

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