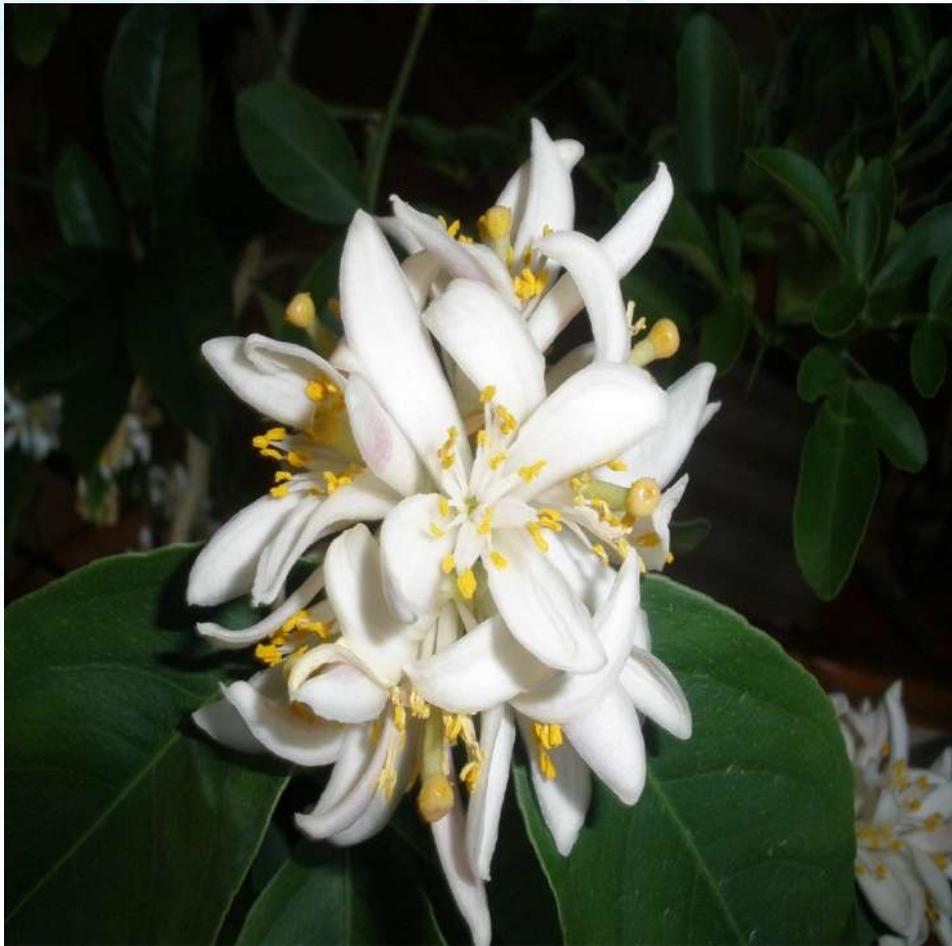


Muchas gracias!



*Santé et qualité de l'air: enjeu de  
société majeur*

## **Air Pollution: Brain Impact**

**Lilian Calderón-Garcidueñas MA, MD, PhD**

# Criteria Air Pollutants

- EPA uses 6 pollutants (ozone, PM 2.5/10, sulfur dioxides, carbon monoxide, nitrogen dioxide and lead) as indicators of air quality and has established for each of them a maximum concentration above which adverse effects on human health may occur.
- These thresholds concentrations are called the National Ambient Air Quality Standards (NAAQS).
- Ozone: new 8 hour standard  $<0.070$  ppm. Annual-fourth-highest daily maximum 8-hour concentration, averaged over 3 years
- PM<sub>2.5</sub> Annual Primary  $12 \mu\text{g}/\text{m}^3$ , 24h  $35 \mu\text{g}/\text{m}^3$ . Annual mean averaged over 3 years

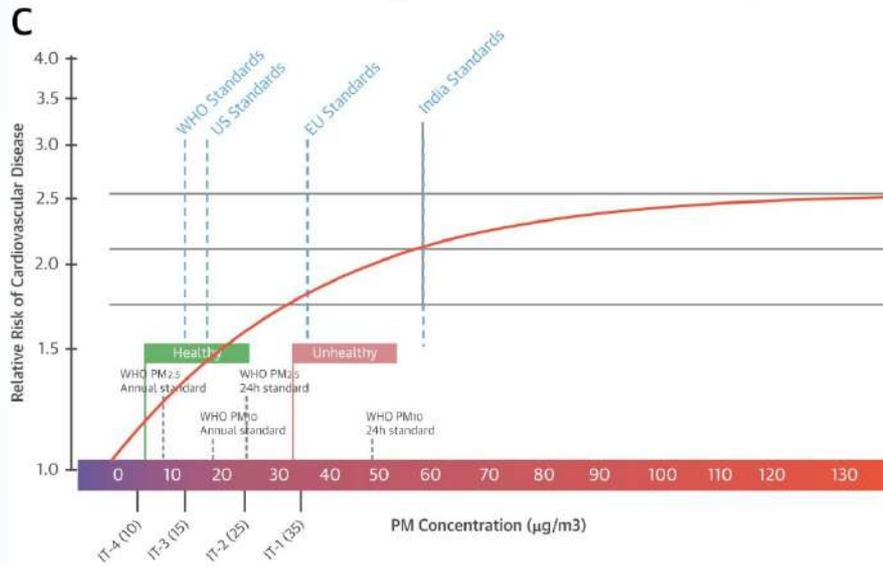
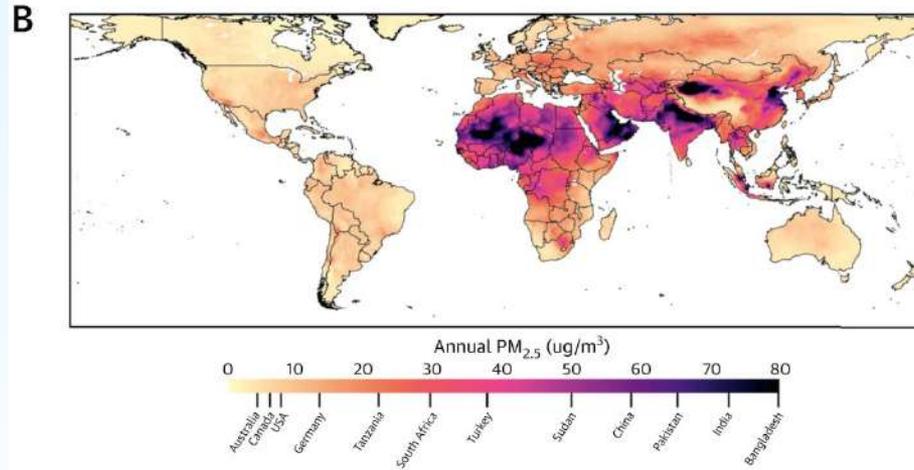
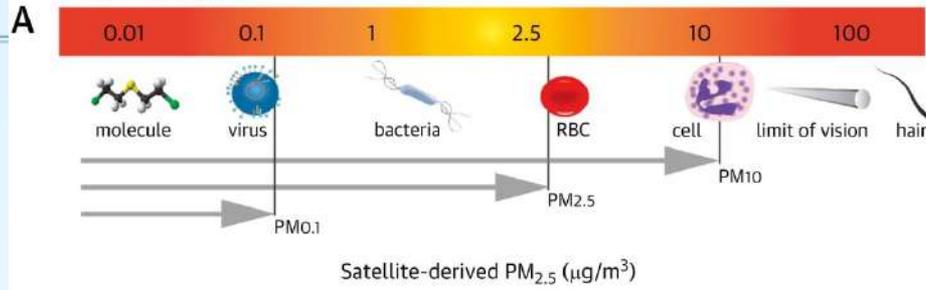
# FACTS

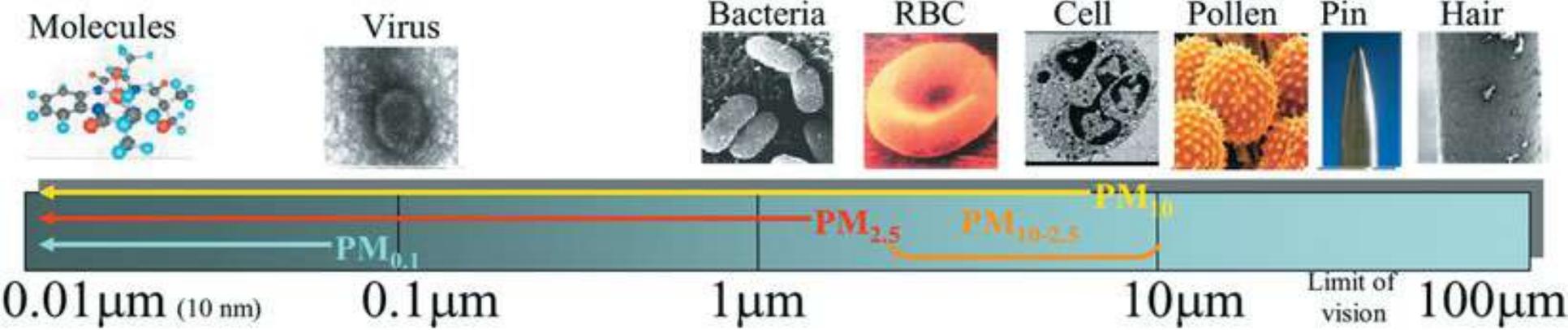
- More than 4 in 10 people (nearly 44 %) in the United States live in counties that have unhealthy levels of either ozone or particle pollution.
- Nearly 138.5 million Americans live in 287 counties where they are exposed to unhealthy levels of air pollution in the form of **either ozone or short-term or year-round levels of particles.**
- Nearly 17.8 million people (5.6%) in the United States live in 12 counties with unhealthy levels of **all three: ozone and short-term and year-round particle pollution.**
- **The vast majority of diesel trucks, buses, and heavy equipment will likely be in use for thousands more miles, spewing dangerous diesel exhaust into communities and**

# FACT

- Ultrafine particulate matter ( $\leq 100$  nm) is largely from the combustion of fossil fuels, biomass, landfills, agricultural activities, tobacco smoke and E-cigarettes and it is not regulated. Current ambient air quality standards across the world are mass-based and restricted to PM<sub>2.5</sub> and PM<sub>10</sub> fractions. Current standards are unable to effectively monitor and control nanoparticle concentrations from combustion sources.
- Iron-rich, strongly magnetic, combustion and friction-derived nanoparticles (CFDNPs) are

Particle size ( $\mu\text{m}$ )





Brooks et al.2010

**PM<sub>2.5</sub>**  
Fine particles

**Constituents:**  
Organic/elemental carbon  
Organic compounds, hydrocarbons  
Ultrafine particle aggregates  
Biological material – Endotoxin  
Ions: NH<sub>4</sub>-Sulfate, nitrate  
Metals: Fe, Al, Ni, Zn, V, Cu, Si

**Sources:**  
Primary from all combustion sources  
Coal, oil, gas, wood, industry, fires  
Secondary gas-to-particle conversion

**Lifetime:** Days-to-weeks.  
Distributed regionally (1000 or more Km)

**UFP (PM<sub>0.1</sub>)** Ultrafine particles

**Constituents:**  
Primary combustion – hydrocarbons, metals, organic carbon

**Sources:**  
Secondary photochemical formation from gases, VOC/SVOC  
Fresh automobile and combustion emissions

**Lifetime:** Minutes to hours. Distributed 100s of meters from source

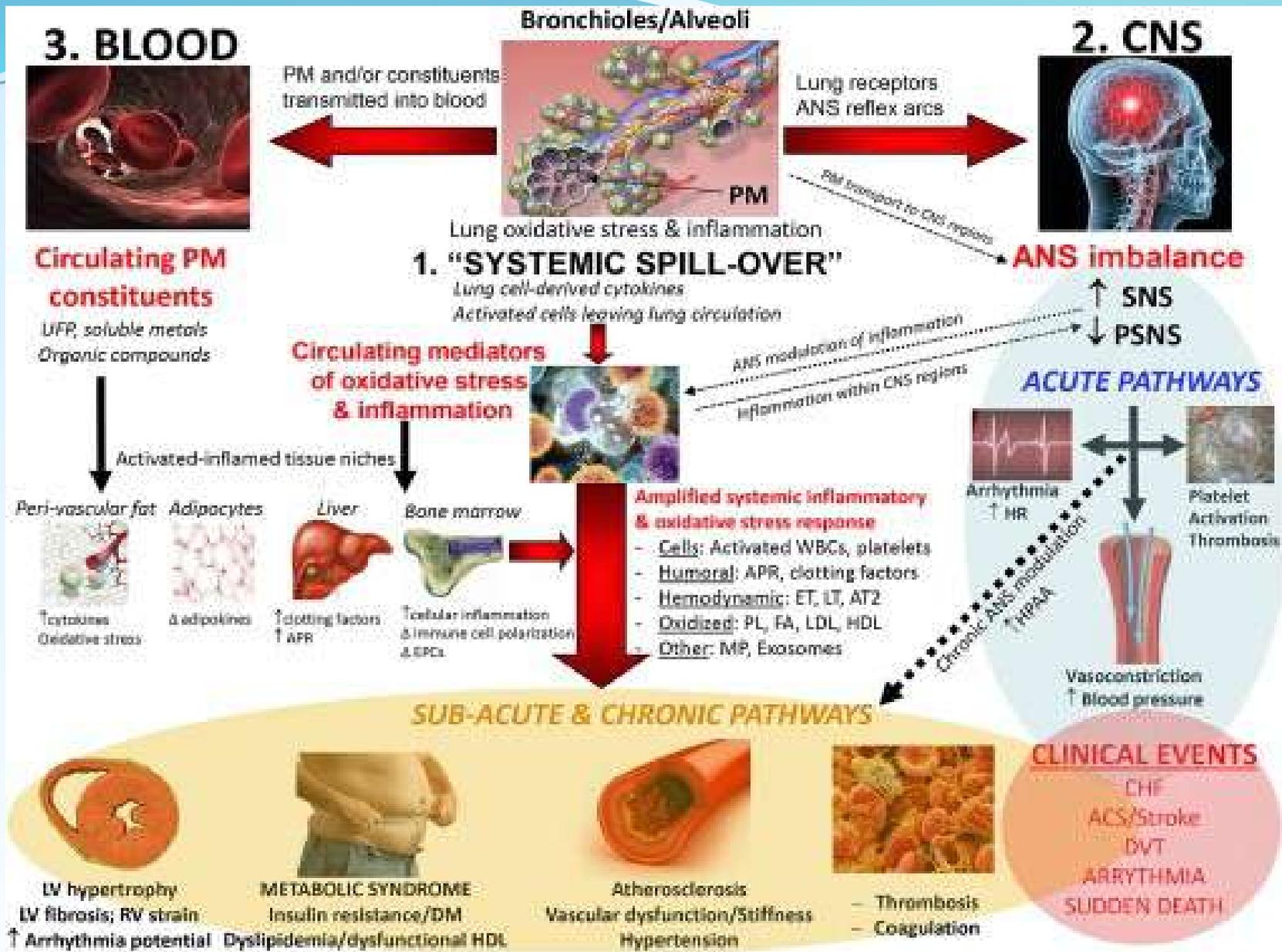
**Human hair (70 μm)**

**PM<sub>10-2.5</sub>**  
Coarse fraction

**Constituents:**  
Dust, endotoxin, pollen, fungi debris, ground materials  
metals (Si, Al, Ca, Fe)

**Sources:**  
Agriculture, soil, road dust, sea spray, suspension in air from grinding and erosion

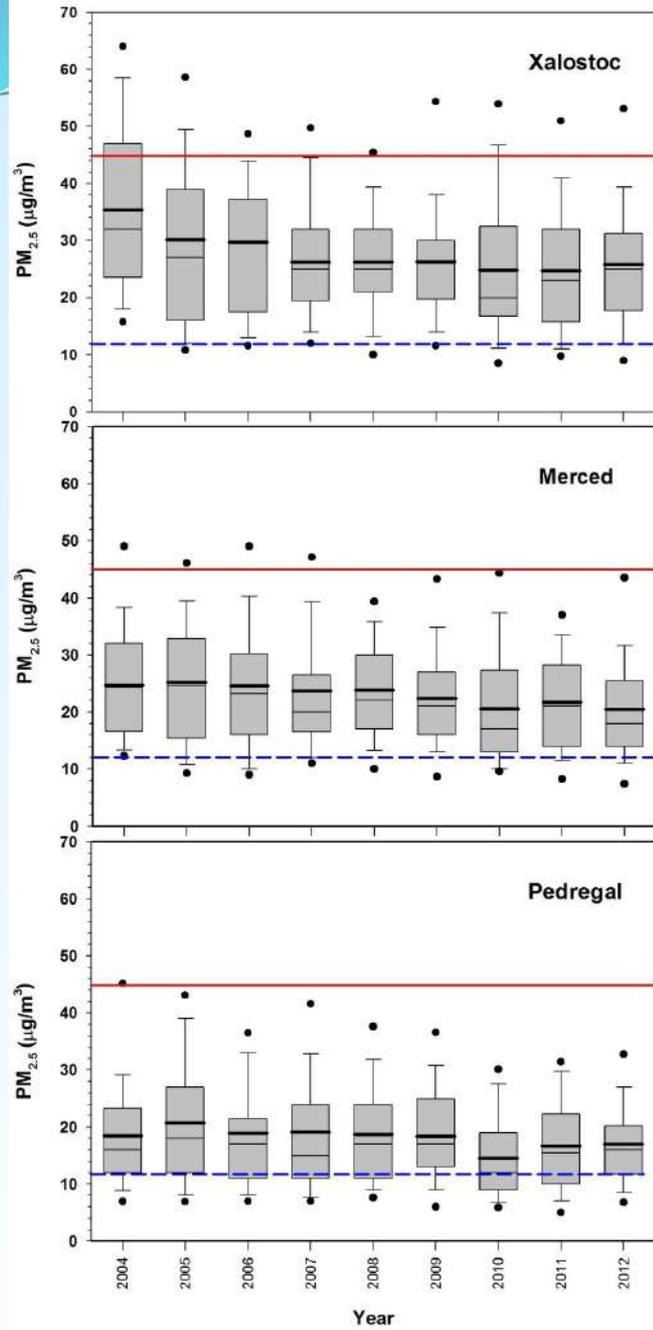
**Lifetime:** hours-to-days  
Distribute 10-100 Km



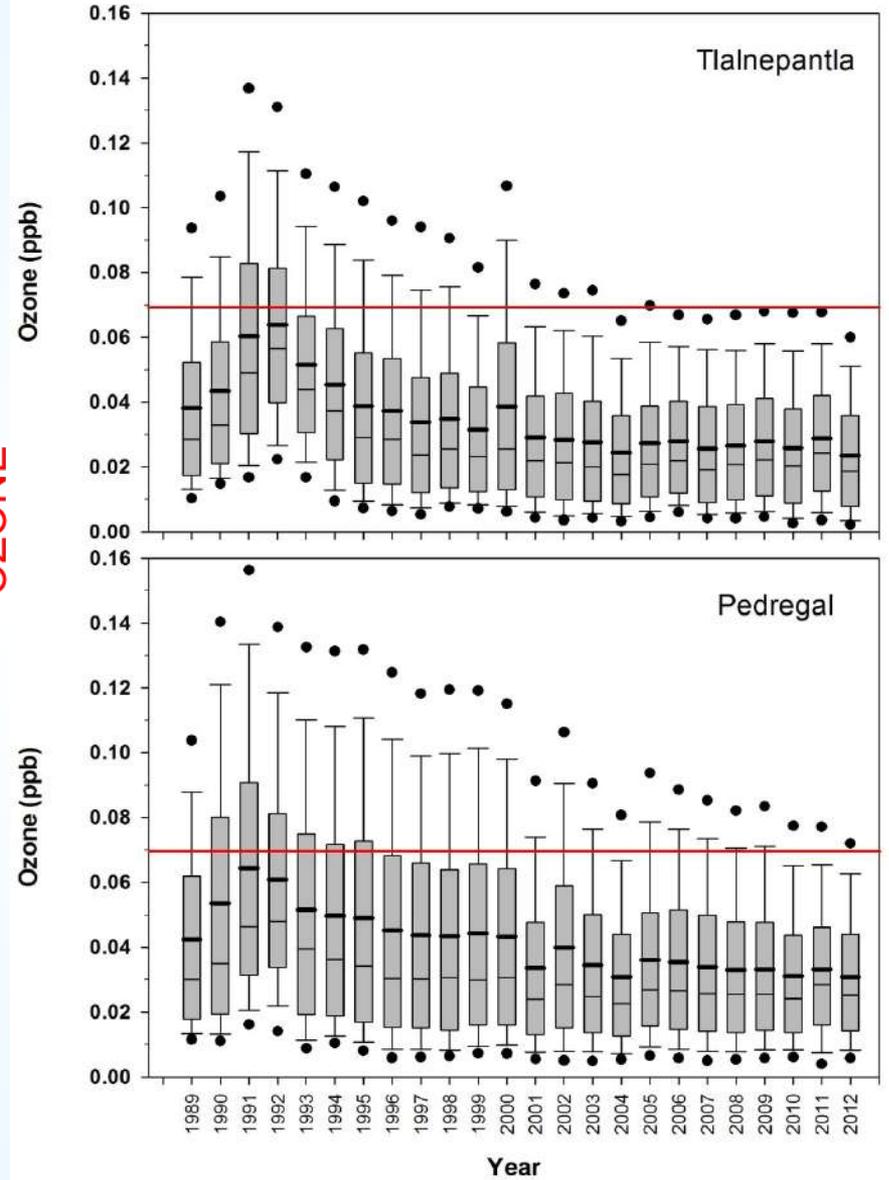
# Mexico City



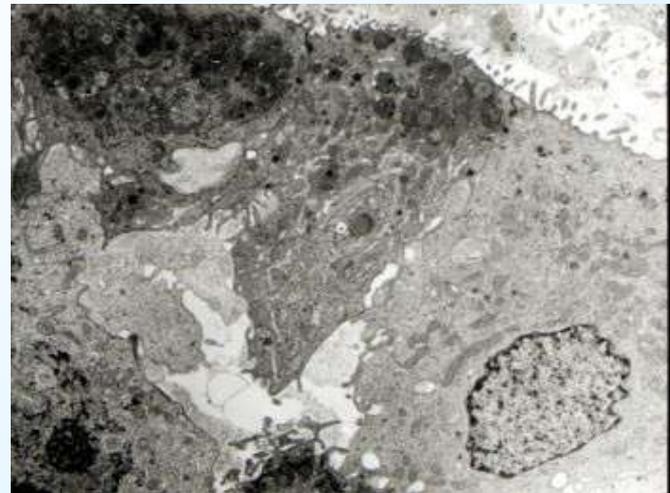
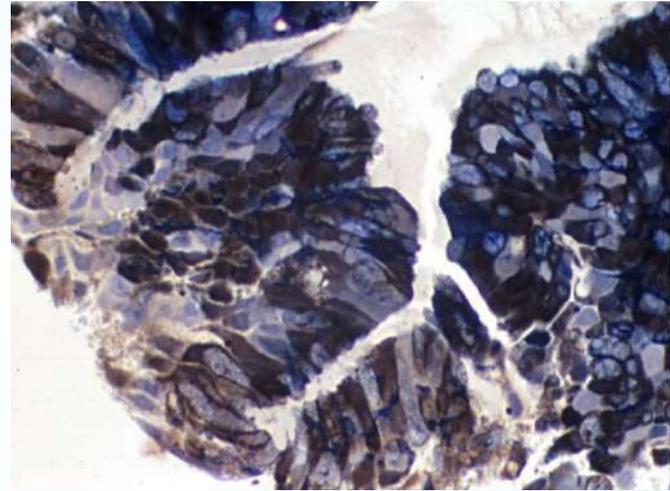
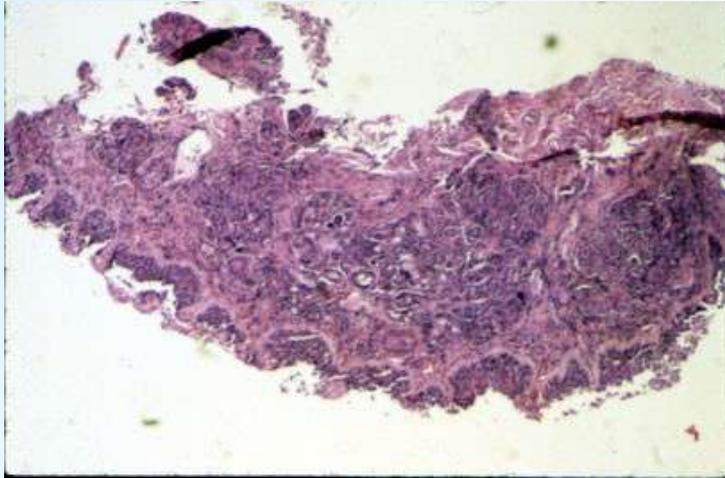
PM2.5



OZONE



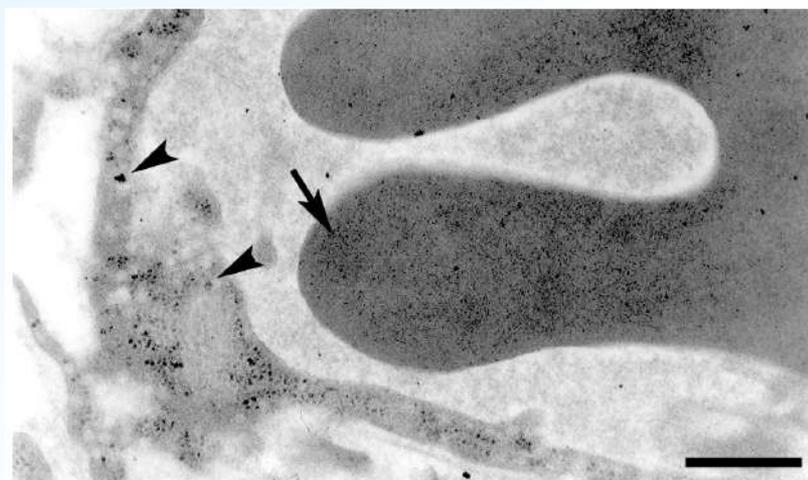
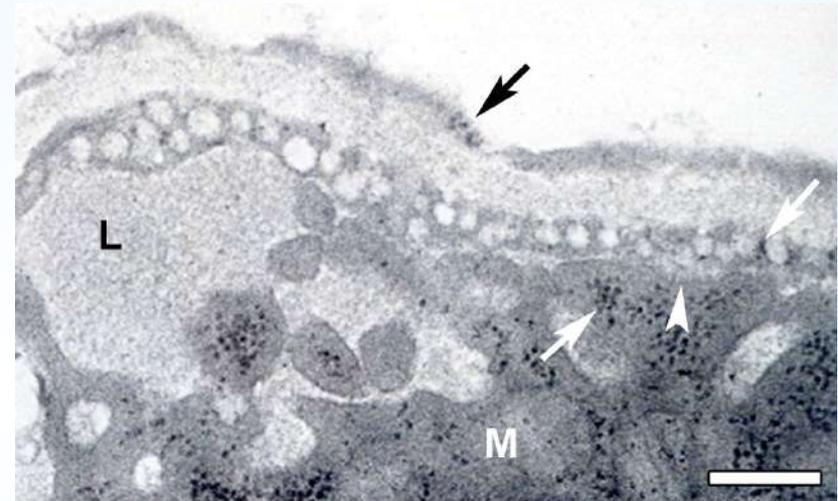
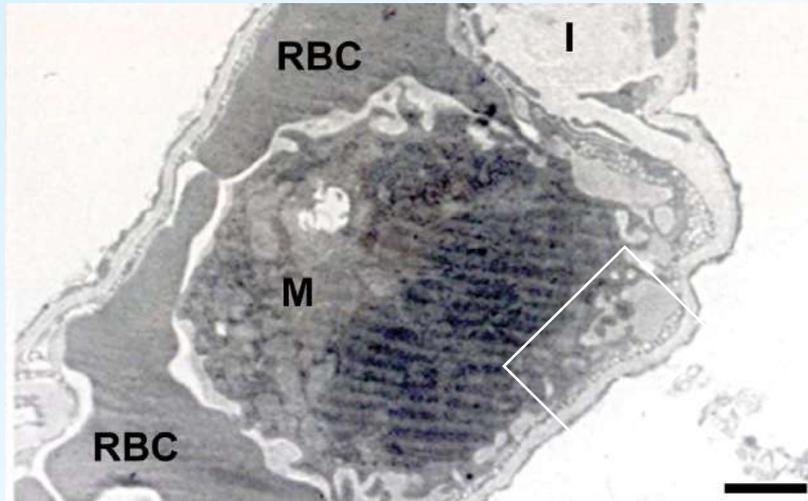
# Breakdown of the nasal respiratory mucosa



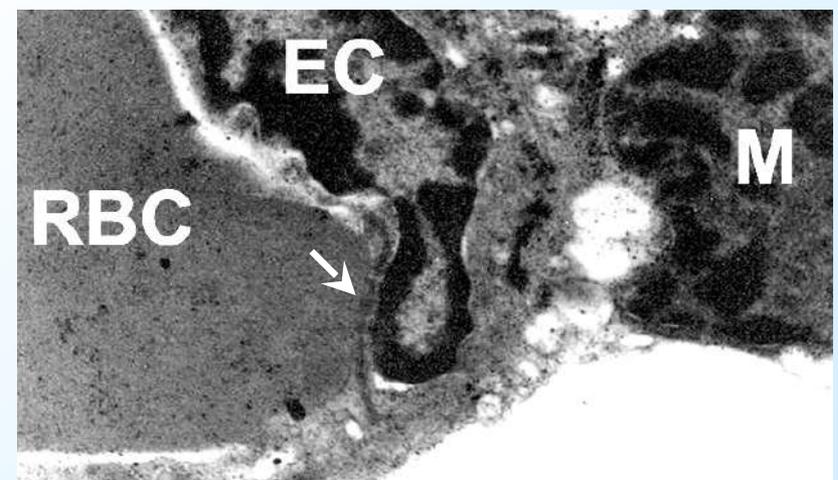
# Ultrafine Particulate Matter Air Pollution was Present in a Variety of Tissues in Mexico City

## Dogs and Humans

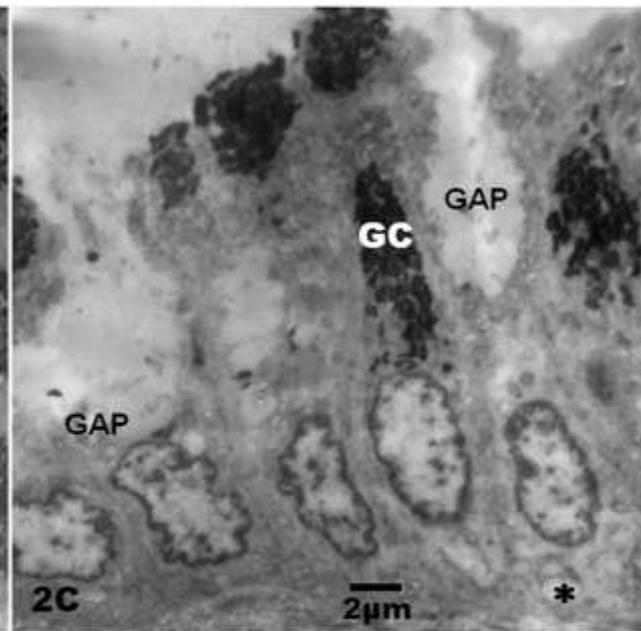
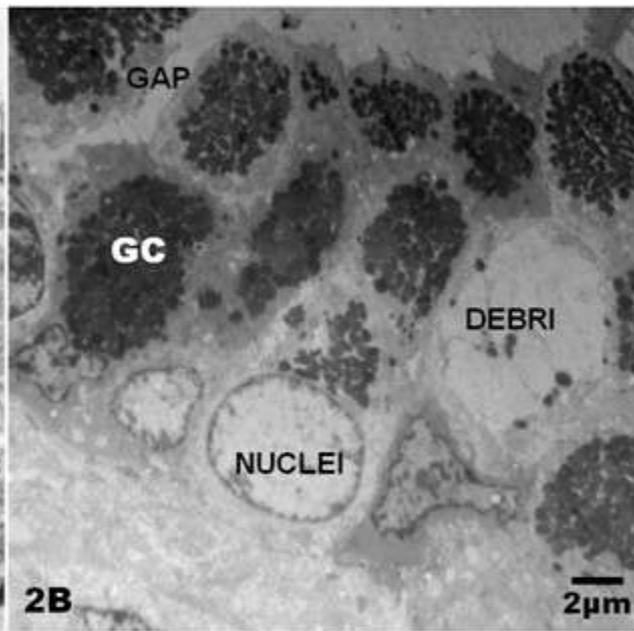
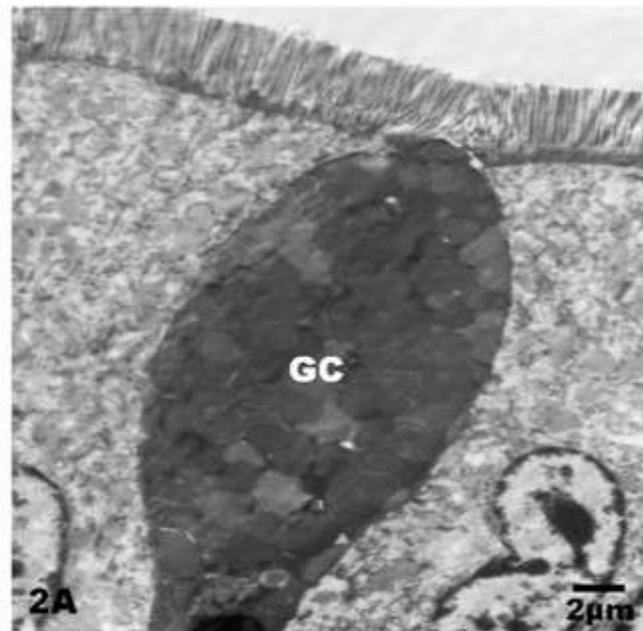
### *Dog lung capillaries*



*Dog heart capillary*



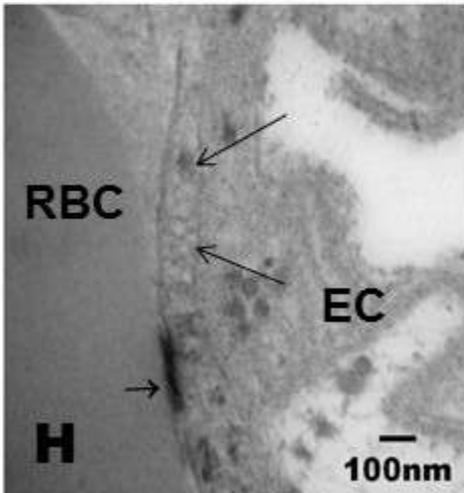
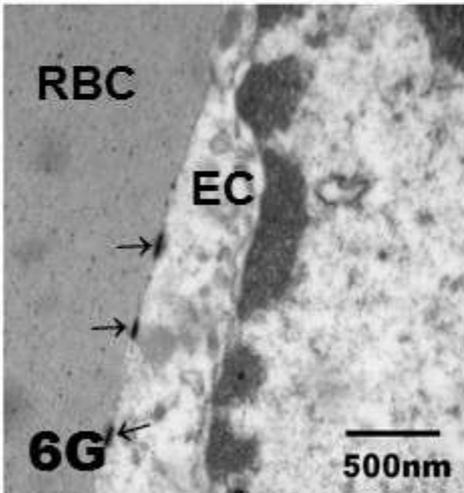
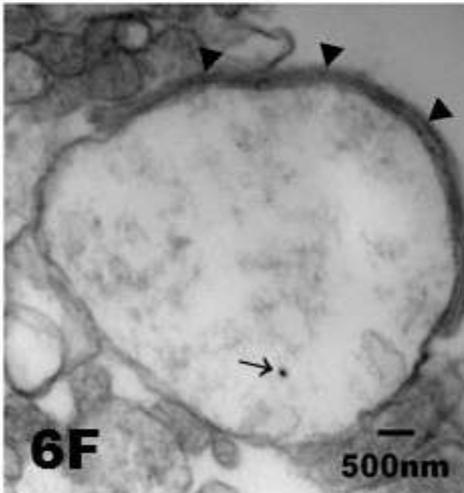
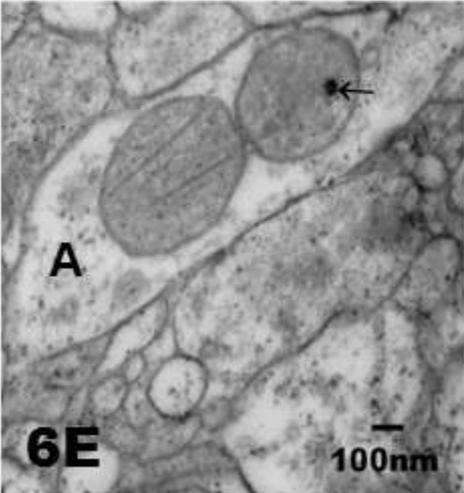
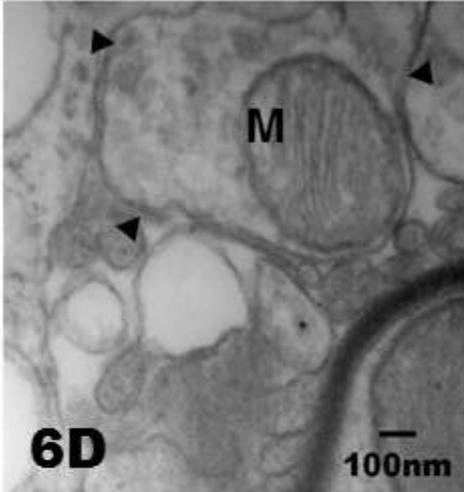
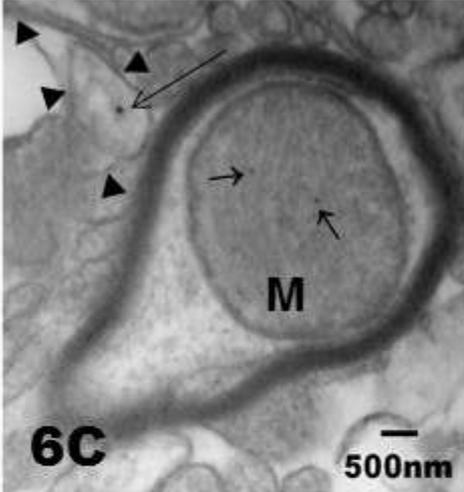
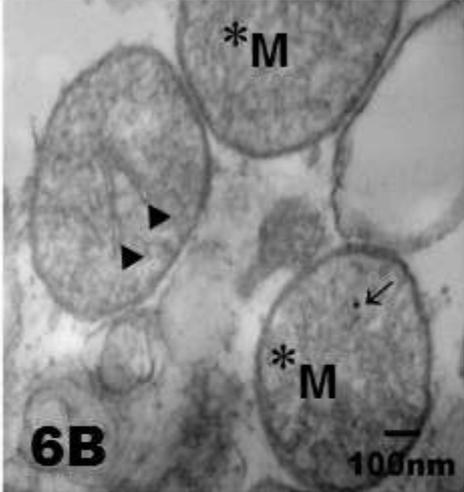
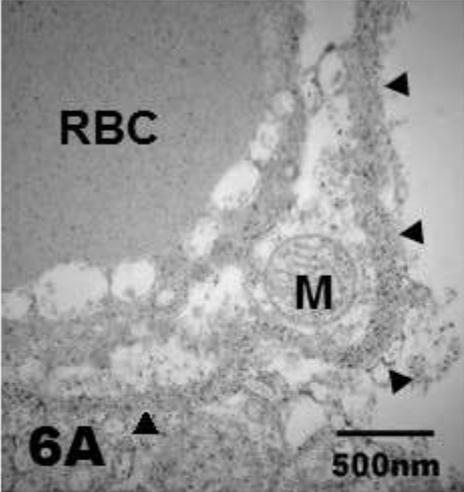
*Human frontal cortex capillaries*



Clean air control

Mexico City resident

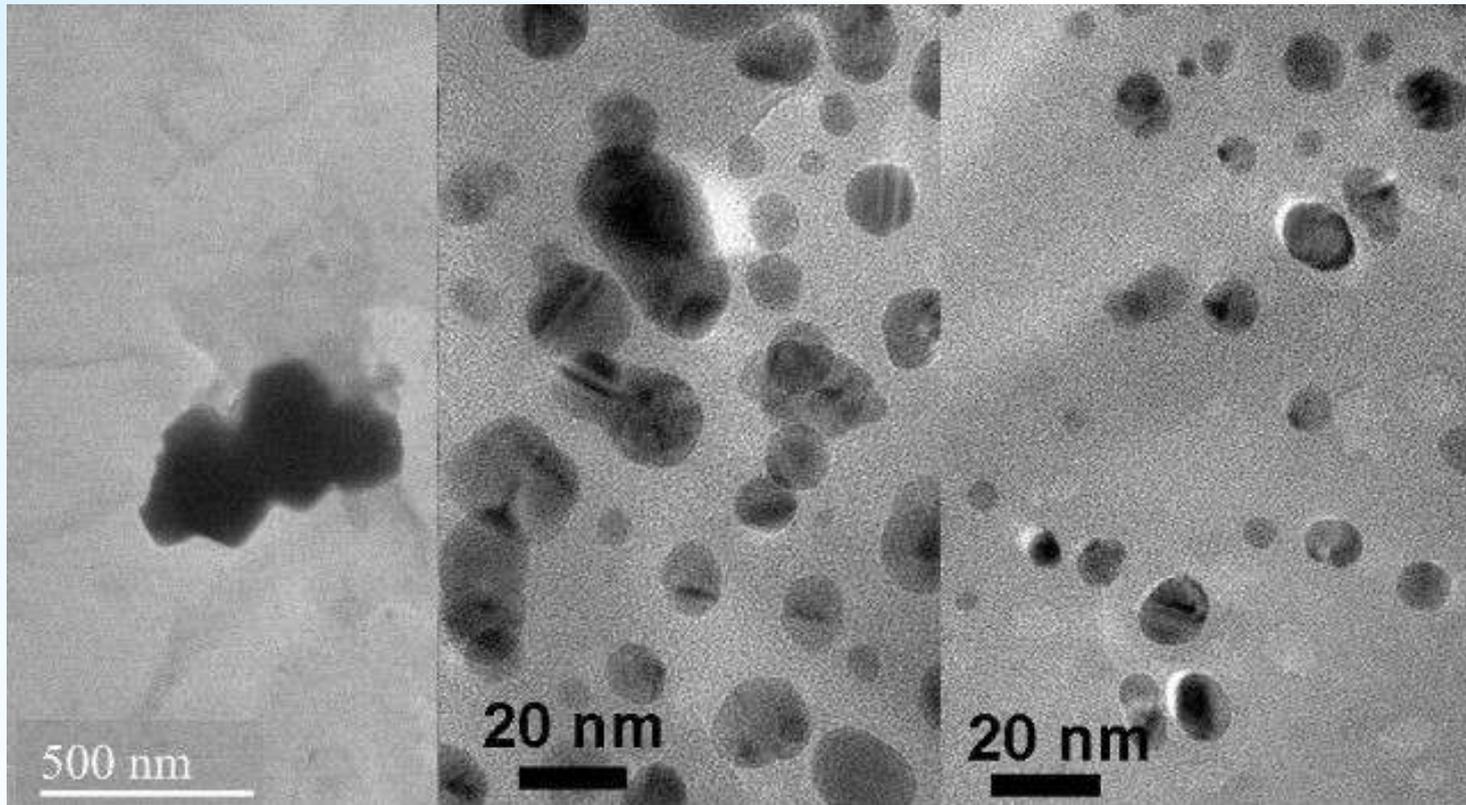
NANOPARTICLES IN BRAIN ORGANELLES, AXONS, DENDRITES AND CAPILLARIES



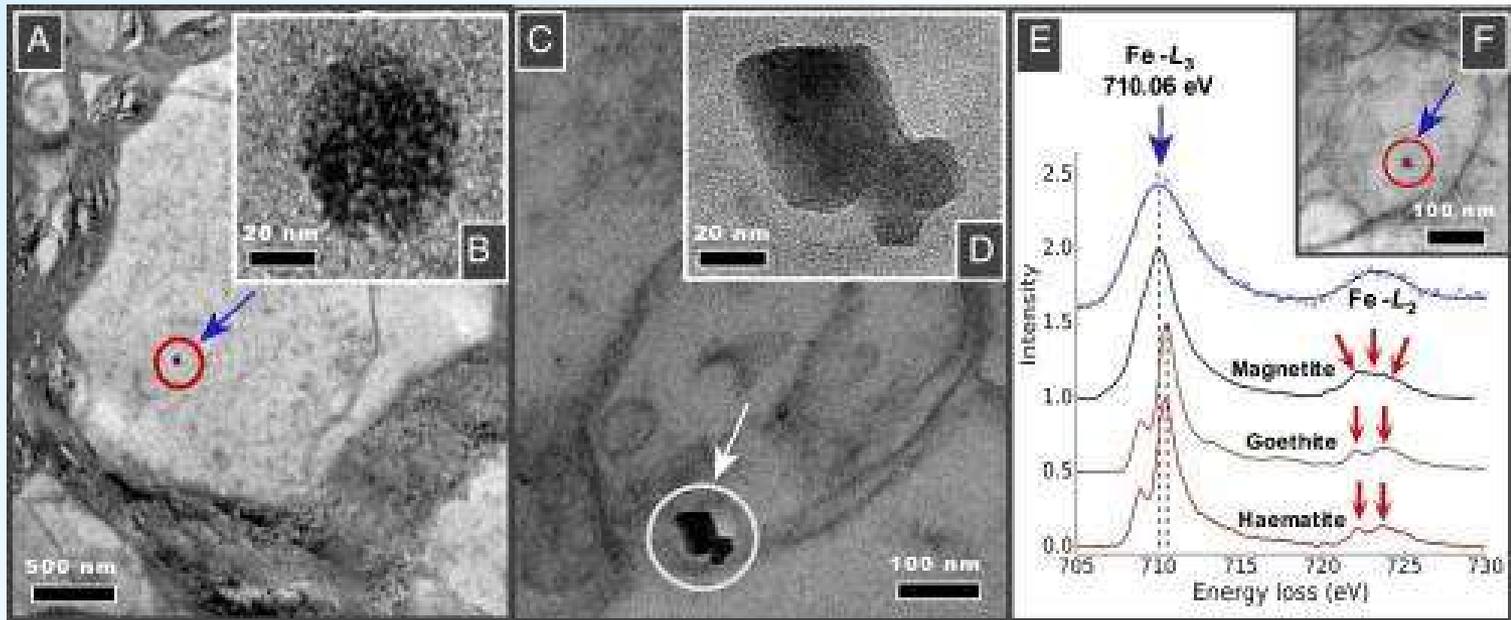
27;113(39):10797-801.

# Magnetite pollution nanoparticles in the human brain.

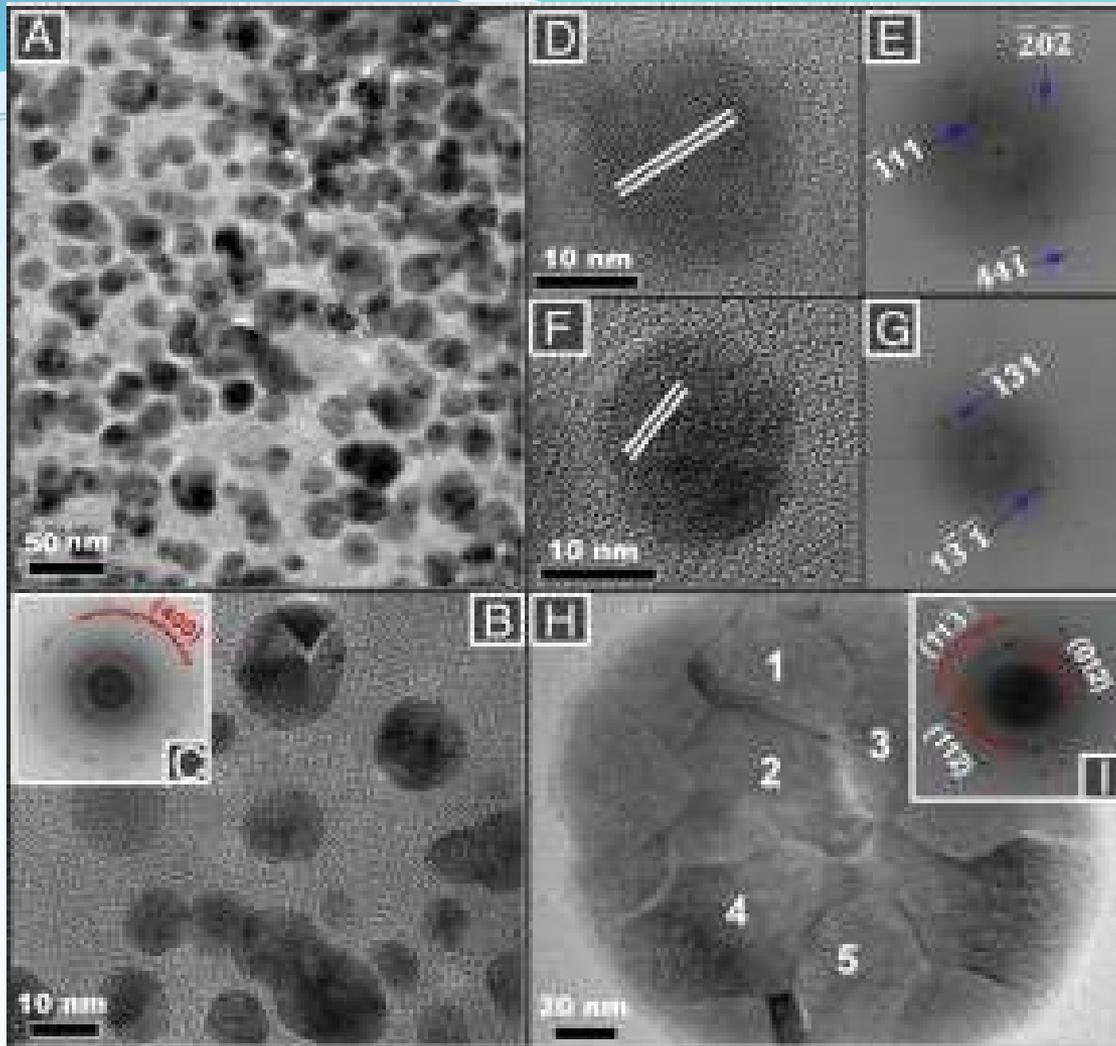
Maher BA.....Calderón-Garcidueñas L.



Angular endogenous magnetite AND **Iron rich magnetite euhedral particles with** rounded crystal morphologies and fused surface textures, reflect crystallization upon cooling from an initially heated, iron-bearing source material. These particles have HIGH redox activity, surface charge, and strongly magnetic behavior.



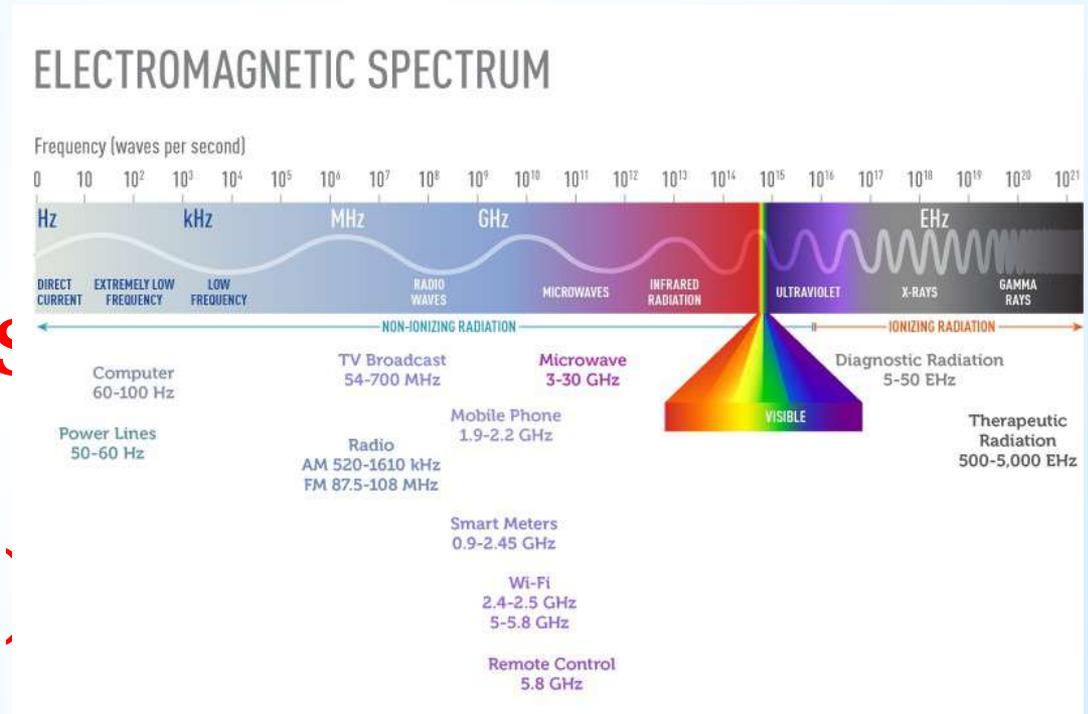
Transmission electron micrographs of brain thin sections, identifying two distinct types of magnetite morphologies within frontal cells: (A and F) rounded particles (A shown at higher magnification in B); and (C) angular, euhedral particles, which we attribute to endogenous formation (particles from C shown at higher magnification in D). (E) EELS spectra (in blue) for the rounded particle shown in F and for standard iron oxide species. The position of the Fe-L<sub>3</sub> edge absorption peak, the broad feature of the Fe-L<sub>2</sub> (compared with the sharp edges, arrowed, of the fully oxidized Fe<sup>3+</sup> phases), and the integrated areas of the L<sub>3</sub>/L<sub>2</sub> (5.5) and the Fe/O (0.56) are all consistent with magnetite.



Transmission electron micrographs of rounded particles magnetically extracted from human brain samples: (A, D, F, and H) Mexico City cases; (B) Manchester case. (H) A large (~150-nm diameter) spherical particle with fused, interlocking magnetite/maghemite surface crystallites. (C, E, and G) Indexing of the lattice fringes of the brain particles is consistent with the (400) reflection of magnetite and (I) mixed magnetite and maghemite of selected areas 1–5 in H.

# BRAIN NANOPARTICLES

Magnetite  
average  
concentrations  
271 ng/gr dry  
tissue (frontal)



# **Adverse Health Effects in Children Chronically Exposed to Severe Air Pollution**

## **Respiratory Tract Effects**

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- ❖ Breakdown of the nasal epithelial and olfactory barriers**
- ❖ Hyperinflation and interstitial lines on chest x-rays**
- ❖ Abnormal high resolution lung computed tomography scans**
- ❖ Abnormal spirometry (restricted**

# **Adverse Health Effects in Children Chronically Exposed to Severe Air Pollution**

## **Systemic and Cardiovascular Effects**

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- ❖ **Systemic inflammation**
- ❖ **Elevated plasma endothelin-1 and pulmonary arterial pressure (endothelial dysfunction)**
- ❖ **Altered systemic expression of lipopolysaccharide-binding proteins**
- ❖ **Supraventricular arrhythmias, and decreased cardiac vagal tone**

# Adverse Health Effects in Mexico City Dogs

## Neuropathological Effects



- ❖ **Neuroinflammation**
  - Nuclear NF- $\kappa$ B RelA (p65)
  - Elevated COX-2 mRNA
- ❖ **Elevated Metallothionein I-II protein expression**
- ❖ **Endothelial Damage**
- ❖ **Genomic DNA damage in Frontal Cortex**
- ❖ **Accumulation of A $\beta$ 42 in neurons and in diffuse plaques**

# **Adverse Health Effects in Adult Humans Exposed to Severe Air Pollution**

## **Neuropathological Effects**

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- ❖ **19 Adults average age  $54 \pm 4.7$ y (10 high exposure and 9 low exposure)**
- ❖ **Neuroinflammation**
  - **Elevated COX-2 mRNA expression in frontal cortex and olfactory bulb**
- ❖ **Genomic DNA damage in frontal cortex**
- ❖ **Accumulation of A $\beta$ 42 in neurons and diffuse and mature plaques in frontal cortex**

# Mexico City Children and Young Adults

## Neuropathological Effects

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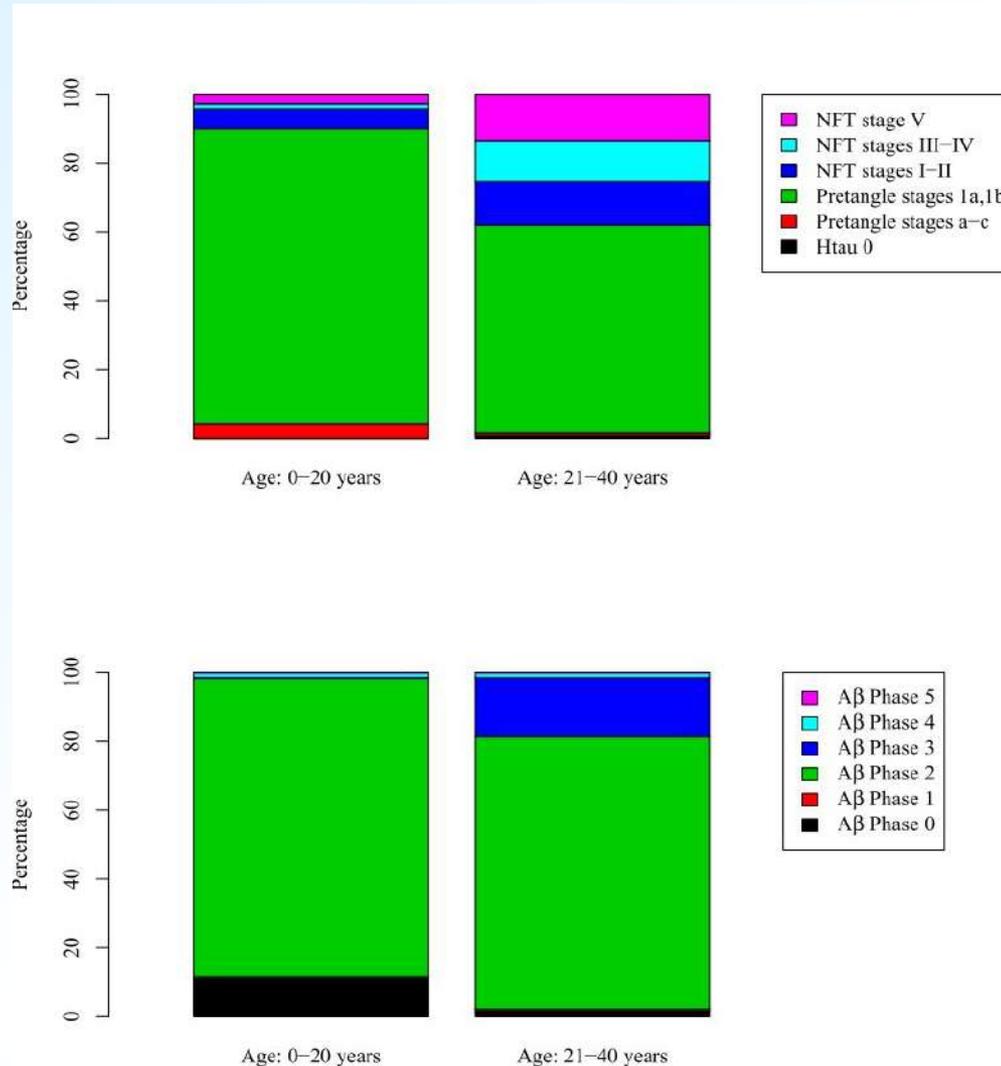
- ❖ Autopsy study of 12 controls & 35 MC subjects age  $25.1 \pm 1.5$  y
  - 12 children ages 2-17, 4 in the control and 8 in the MC group, average age  $13.2 \pm 7.5$  and  $12.3 \pm 5.4$  respectively  $p=0.81$
- ❖ **Upregulation of COX-2, IL-1 $\beta$  and CD14 in target brain areas**
  - Prefrontal Cortex
  - Olfactory bulb
  - Substantia nigrae
  - Vagus nerves

Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the BBB, ultrafine particulate deposition, and accumulation of amyloid  $\beta$  42 and  $\alpha$  synuclein in children and young adults. ToxPath2008

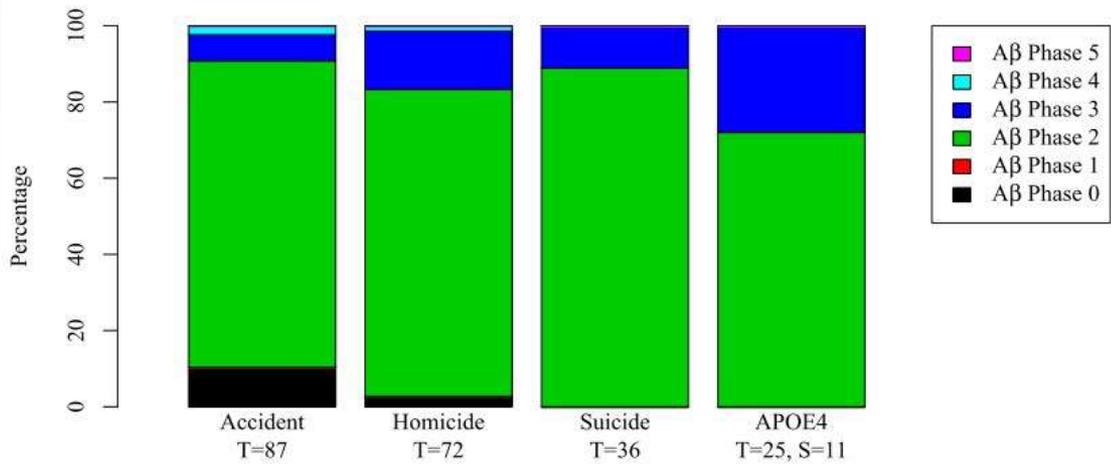
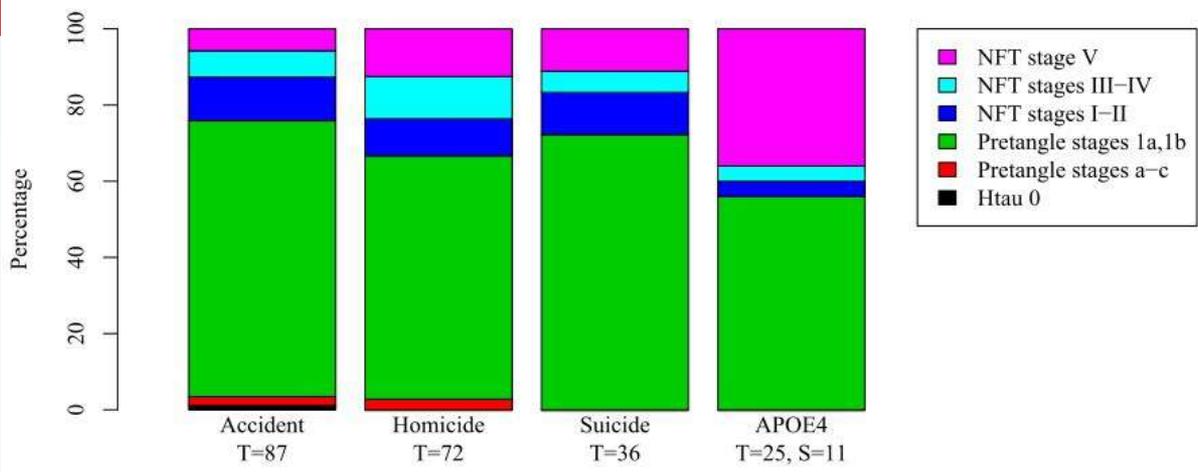
Anatomical region and gene	Controls	Mexico City residents	Statistical significance
COX-2 lung *	15.9±6.7 x10 <sup>6</sup>	42.3±7.4 x10 <sup>6</sup>	0.015
IL-1β lung *	3.08±1.87 x10 <sup>6</sup>	4.51±2.6 x10 <sup>6</sup>	0.60
COX-2 Olf bulb *	12.9±3.0 x 10 <sup>5</sup>	38.7±5.5 x 10 <sup>5</sup>	0.0002
IL-1β Olf bulb *	3.4±0.8 x 10 <sup>4</sup>	7.7±1.0 x 10 <sup>4</sup>	0.003
CD14 Olf bulb §	0.01±0.001	0.04±0.01	0.04
COX-2 frontal *	2.6±0.4x 10 <sup>5</sup>	5.0±0.7 x 10 <sup>5</sup>	0.008
IL-1β frontal *	0.6±0.2 x10 <sup>4</sup>	6.2±1.3 x10 <sup>4</sup>	0.0002
COX-2 hippocampus *	1.9±0.5x 10 <sup>5</sup>	1.6±8.7 x 10 <sup>5</sup>	0.1
IL-1β Hippocampus *	1.8±0.2 x10 <sup>4</sup>	3.0±0.5 x10 <sup>4</sup>	0.06
COX-2 Substantia nigrae *	0.16±0.06	0.97±0.2	0.03

\* The amount of COX-2, IL1β, CD14 was normalized to the amount of GAPDH cDNA, index femtomol/GAPDH rRNA

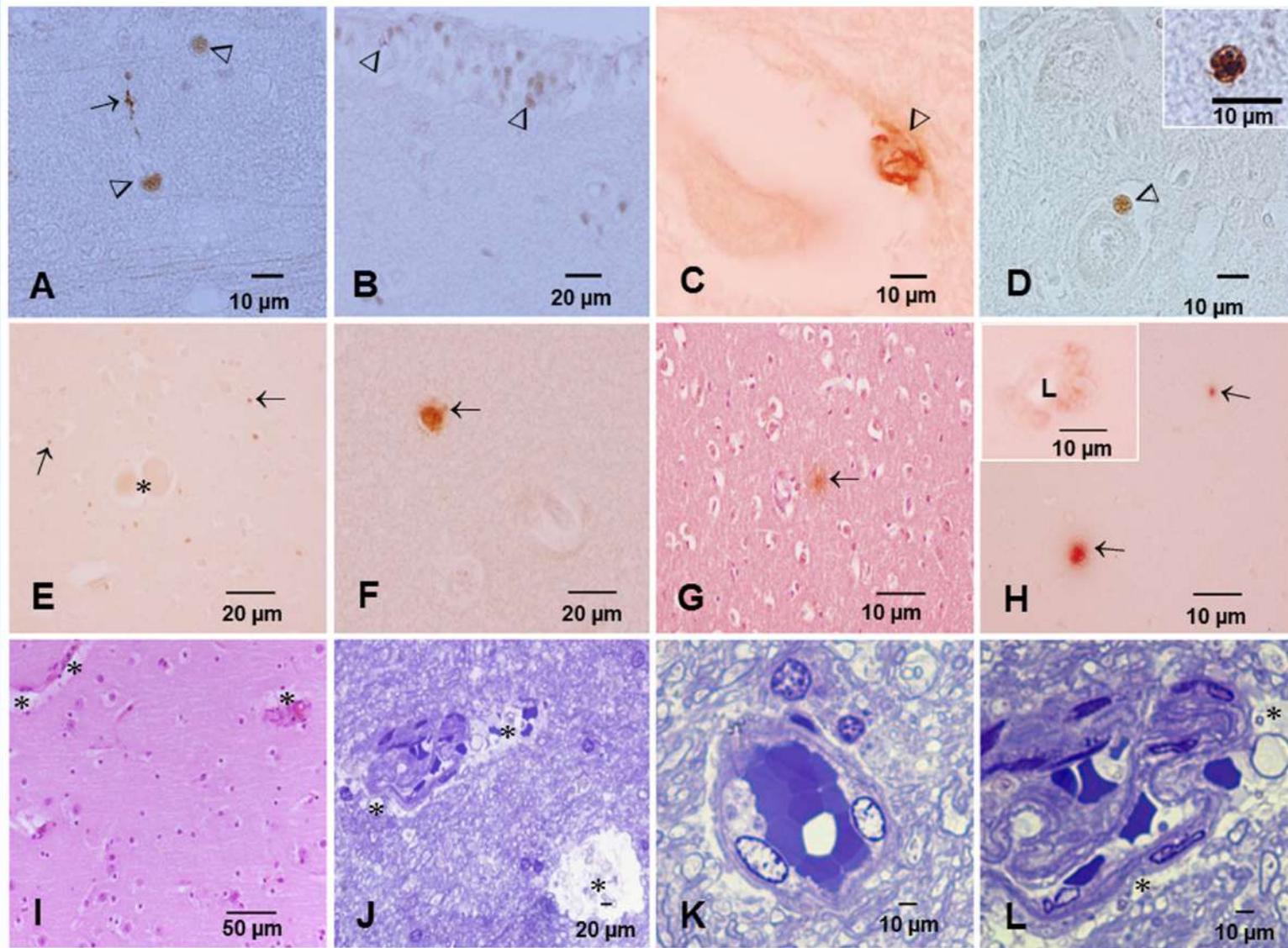
# Alzheimer's disease and alpha-synuclein pathology in the olfactory bulbs of infants, children, teens and adults $\leq 40$ years in Metropolitan Mexico City. APOE4 carriers at higher risk of suicide accelerate their olfactory bulb pathology. ER 2018

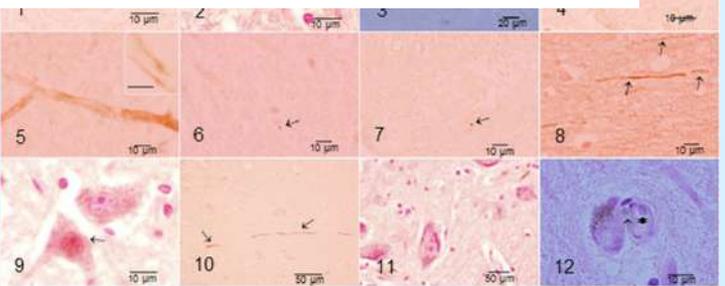
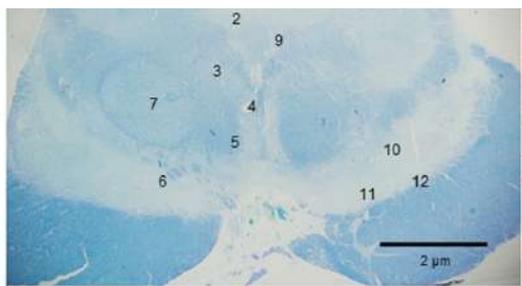
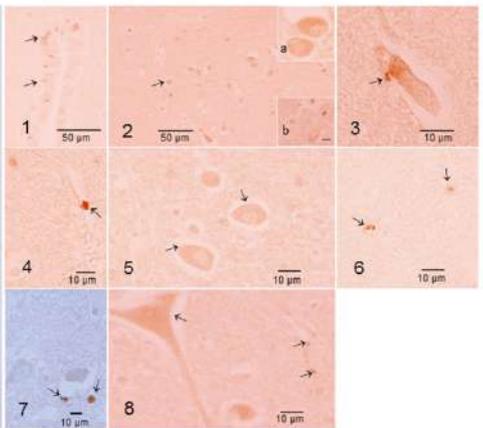
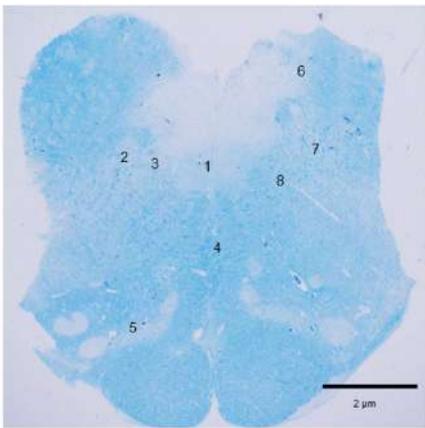
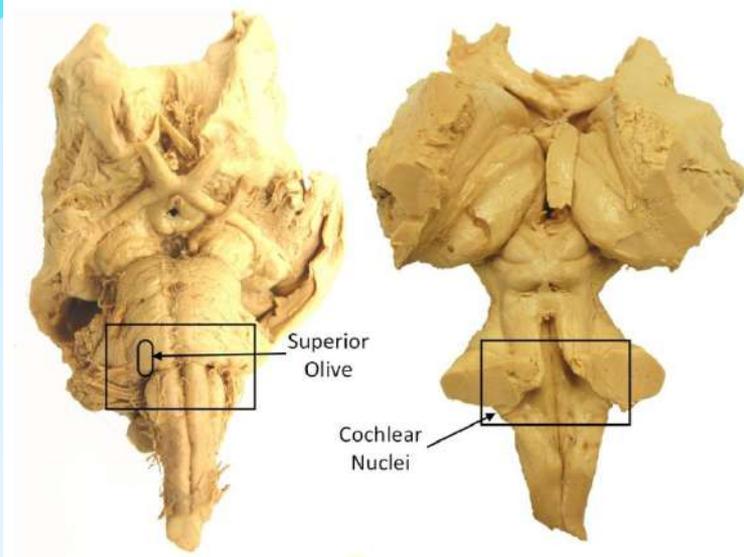


# Alzheimer's disease and alpha-synuclein pathology in the olfactory bulbs of infants, children, teens and adults $\leq 40$ years in Metropolitan Mexico City. APOE4 carriers at higher risk of suicide accel



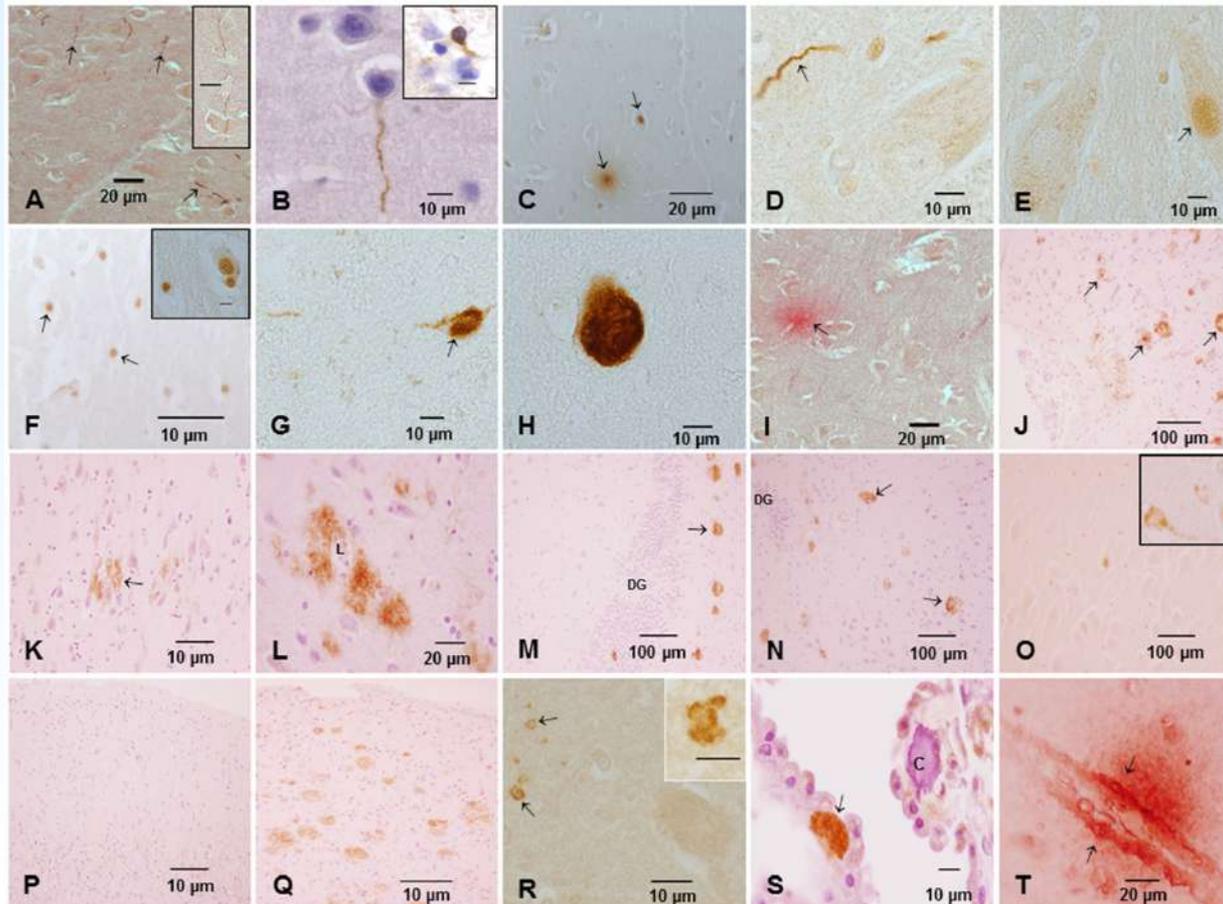
Alzheimer's disease and alpha-synuclein pathology in the olfactory bulbs of infants, children, teens and adults  $\leq 40$  years in Metropolitan Mexico City. APOE4 carriers at higher risk of suicide accelerate their olfactory bulb pathology.





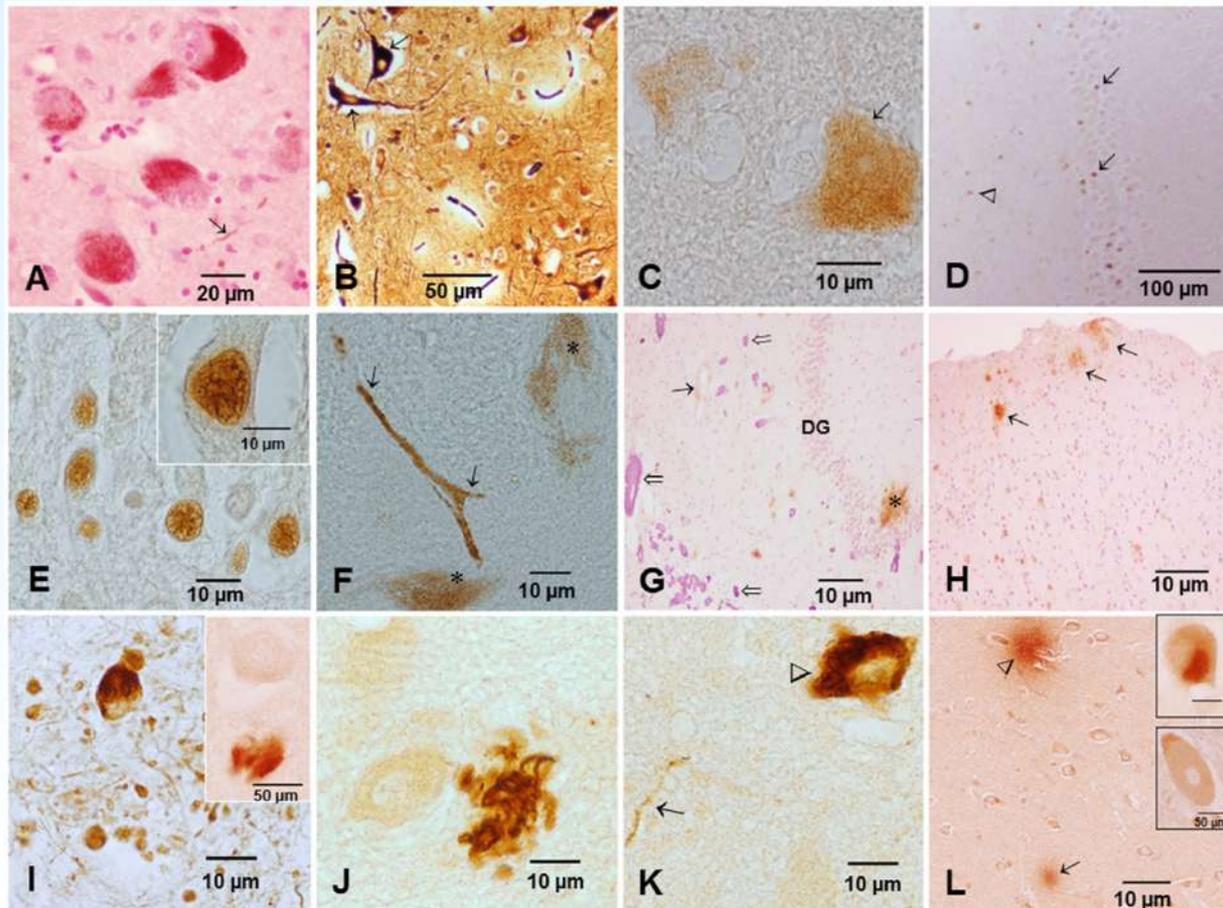
Alzheimer's disease and alpha-synuclein pathology in the olfactory bulbs of infants, children, teens and adults  $\leq 40$  years in Metropolitan Mexico City. APOE4 carriers at higher risk of suicide accelerate their olfactory bulb pathology.

## 2 sd decade



Alzheimer's disease and alpha-synuclein pathology in the olfactory bulbs of infants, children, teens and adults  $\leq 40$  years in Metropolitan Mexico City. APOE4 carriers at higher risk of suicide accelerate their olfactory bulb pathology.

### 3<sup>rd</sup> and 4<sup>th</sup> decades



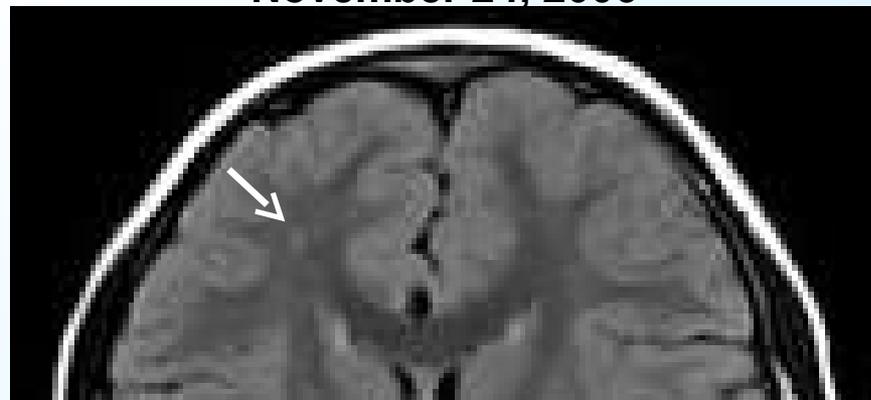
# Fifty-Six Percent (20/35) of Mexico City Children had White Matter Hyperintense Lesions on MR Images



July 13, 2006

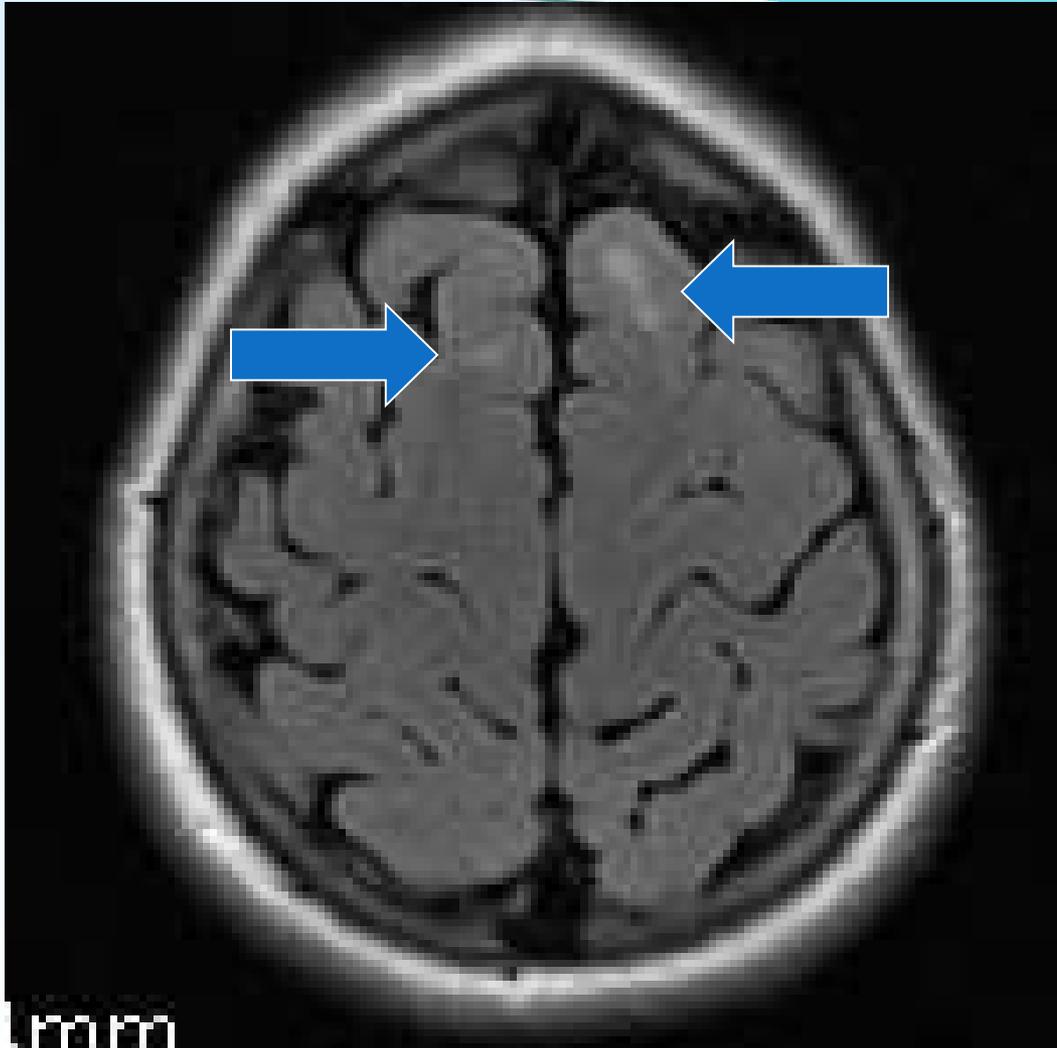


November 24, 2006



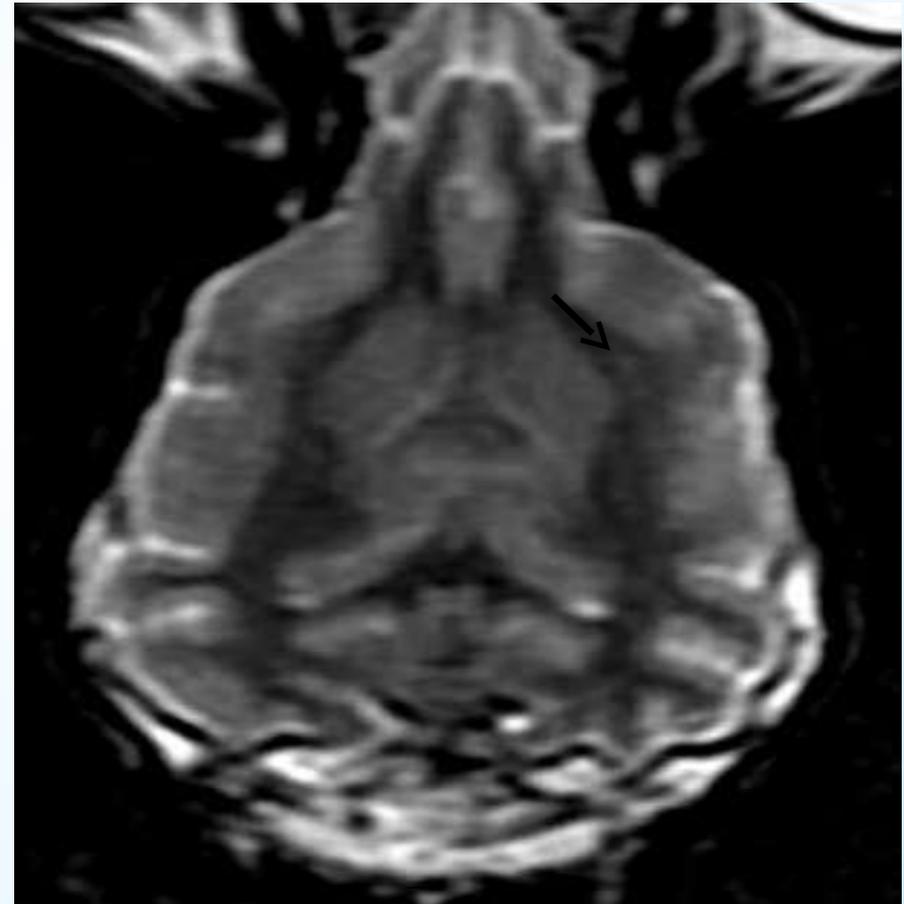
September 25, 2010

8.02 y old girl, IQ Global 113, verbal 56 and performance 57. She performs behind her chronological age for Object assembly 6.16 y, and Similarities 7.08y.

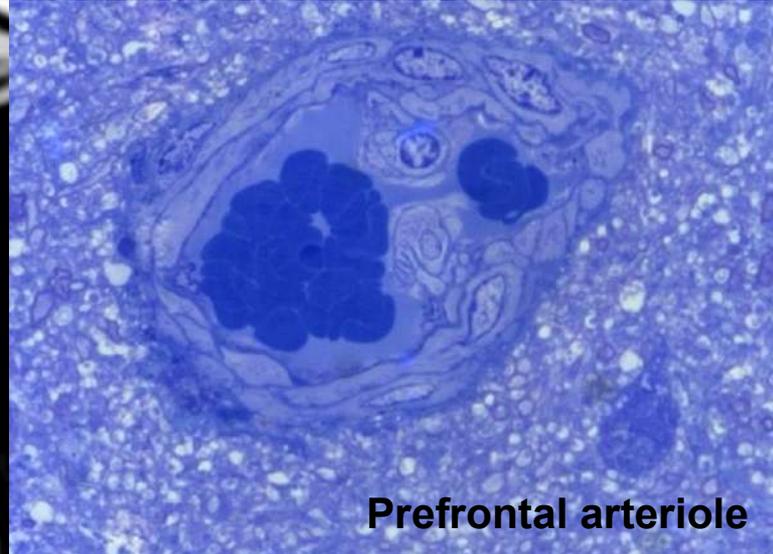
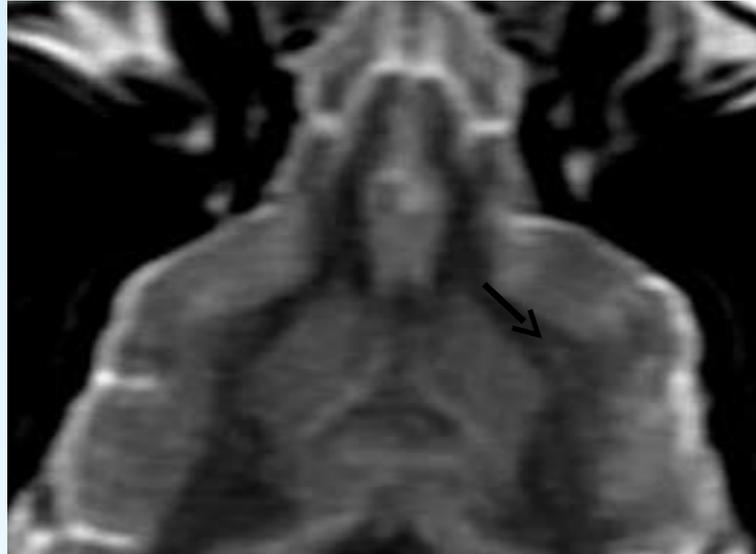


Niña de 10 años, IQ 111. Verbal 115, Ejecución 104, escala en límites bajos en retención de dígitos, composición de objetos, claves y laberintos.

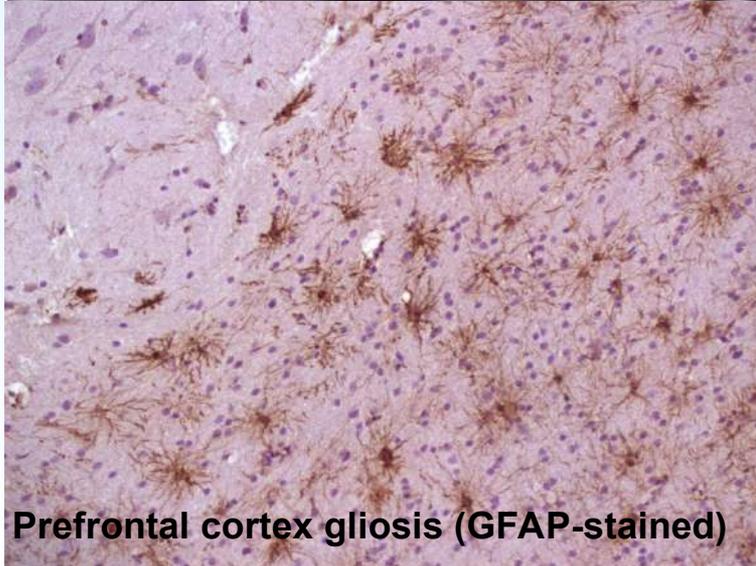
# White Matter Hyperintense Lesions were Present in Fifty-Seven Percent (4/7) of Mexico City Dogs



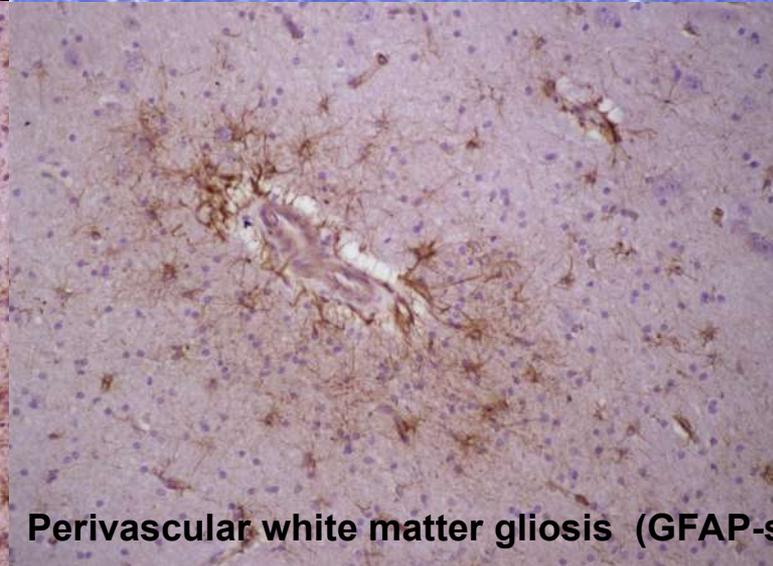
# In Dogs the White Matter Lesions were Sites of Endothelial Hyperplasia and Gliosis (Reactive Astrocytosis)



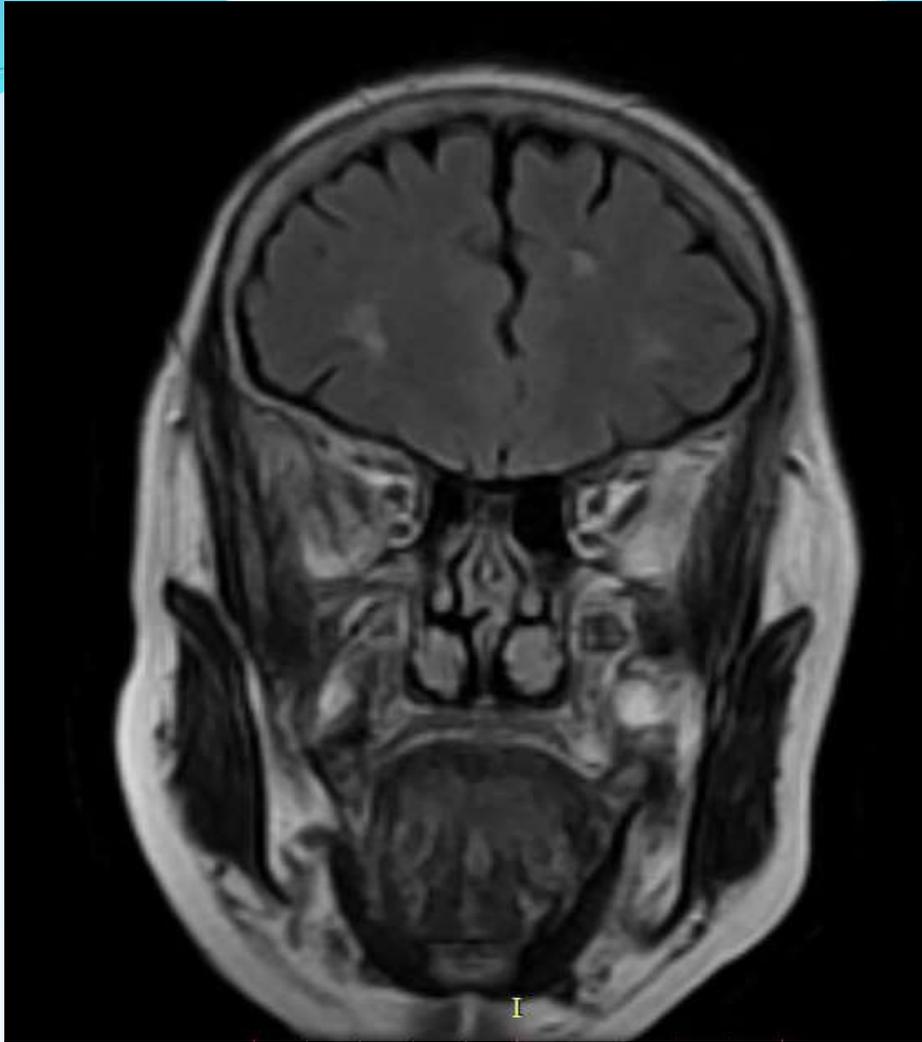
Prefrontal arteriole



Prefrontal cortex gliosis (GFAP-stained)

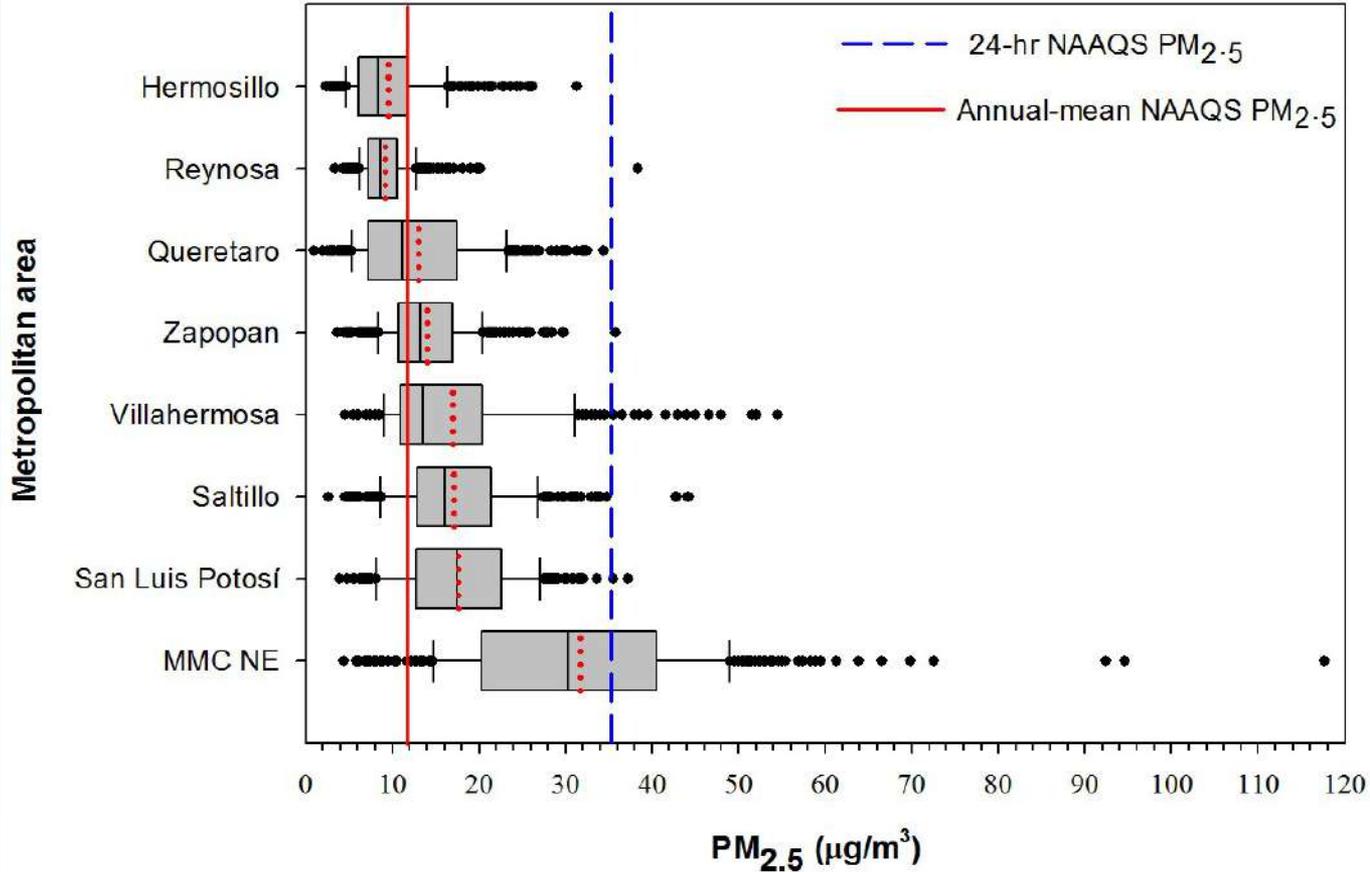


Perivascular white matter gliosis (GFAP-stained)



60 y old female

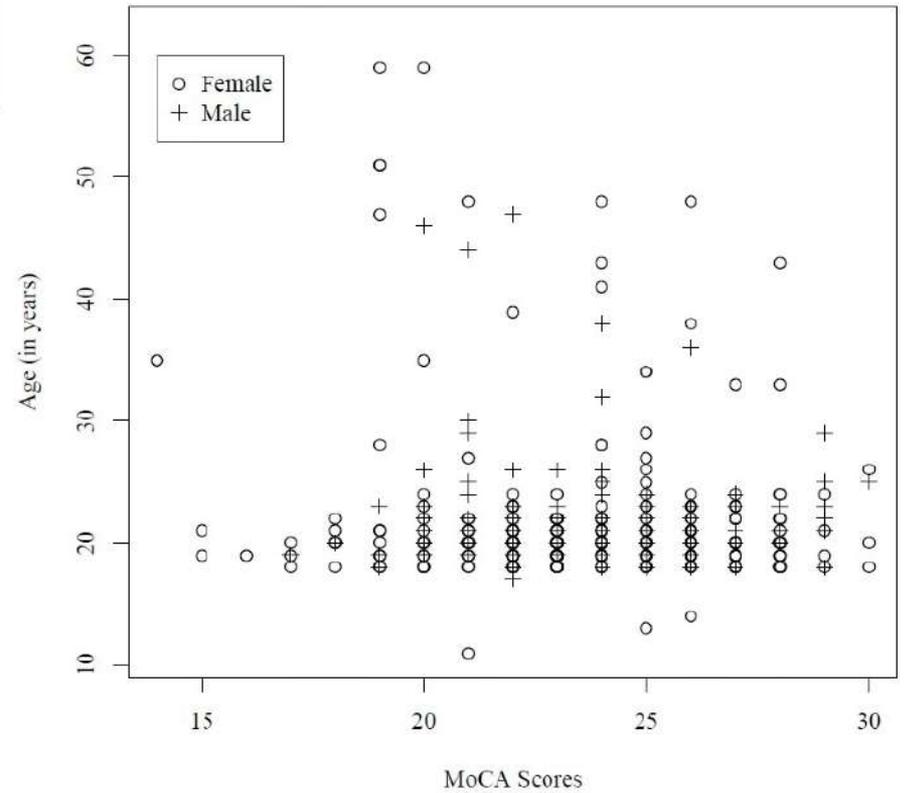
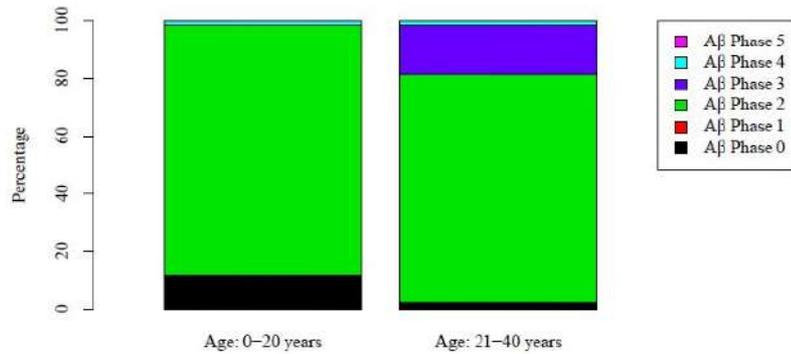
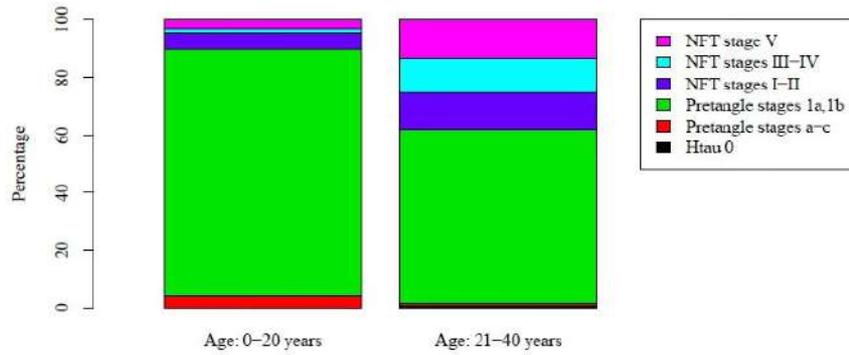
# Mild Cognitive Impairment and Dementia Involving Multiple Cognitive Domains in Mexican Urbanites.



## **181208. Mild Cognitive Impairment and Dementia Involving Multiple Cognitive Domains in Mexican Urbanites.**

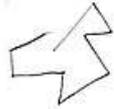
- **The Montreal Cognitive Assessment (MoCA) was administered to 517 urbanites, age  $21.60 \pm 5.88$  years, with  $13.69 \pm 1.28$  formal education years, in Mexican PM2.5 polluted cities.**
- **Normal MoCA score: 26-30**
- **MoCA score was  $23.92 \pm 2.82$ , and 24.7% and 30.3% scored  $\leq 24$  and  $\leq 22$ , respectively (MCI  $\leq 24$ , AD  $\leq 22$ )**

- Cognitive deficits progressively targeted Visuospatial, Executive, Language, and Memory domains, body mass index (BMI) impacting total scores negatively ( $p = 0.0008$ ), aging driving down Executive, Visuospatial, and Language index scores ( $p < 0.0001$ ,  $0.0037$ , and  $0.0045$ ), and males performing better in Executive tasks. Average age for AD MoCA scores was  $22.38 \pm 7.7$  years.
- Residency in polluted cities is associated with progression of multi-domain cognitive impairment affecting 55% of Mexican seemingly healthy youth





(21)



(28)



(26)



(22)



(25)



(25)



(20)



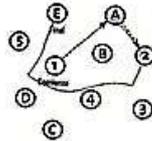
(14)



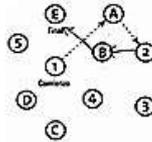
Draw CLOCK  
(Ten past eleven)



(24)



(19)

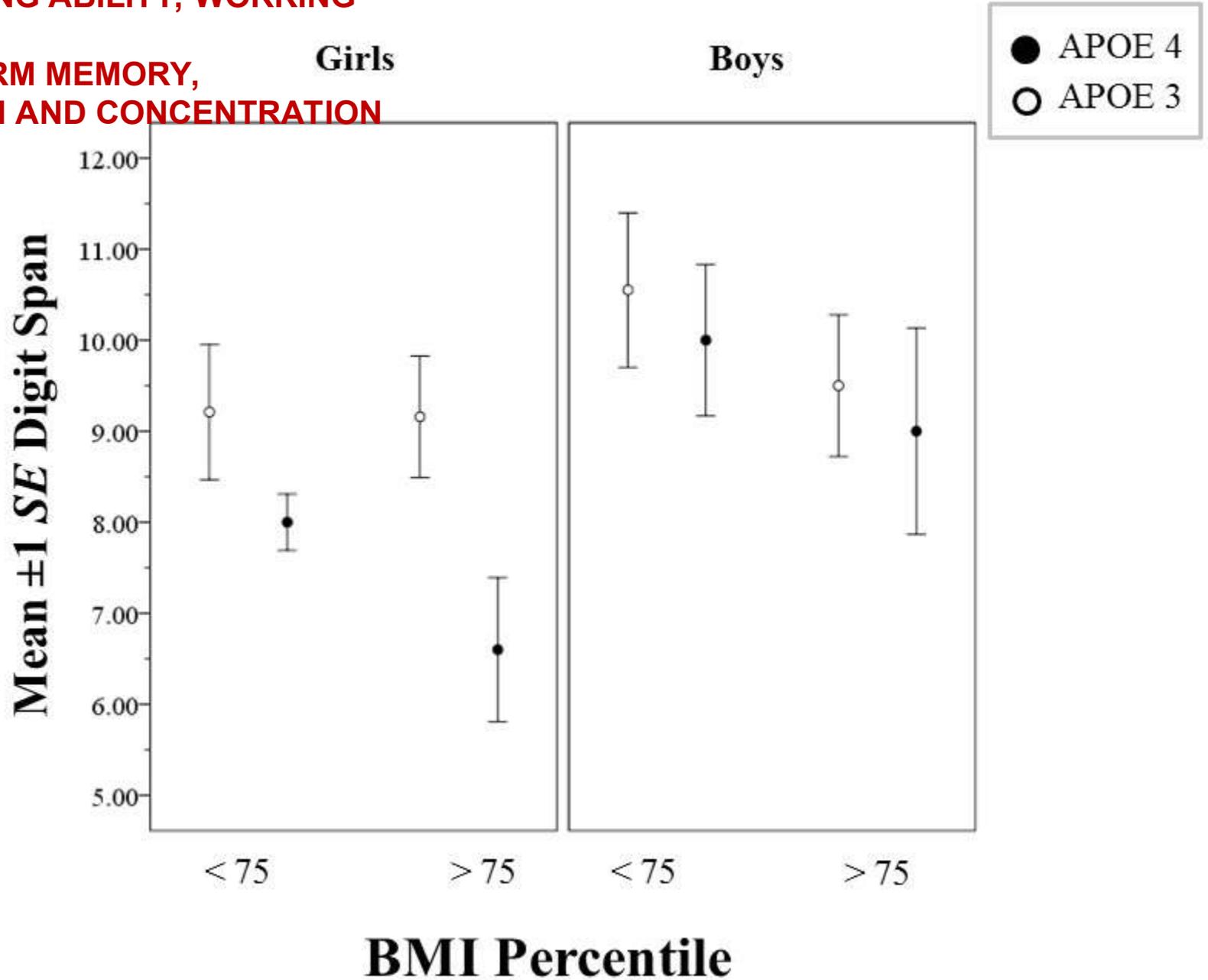


Interactive and additive influences of gender, BMI and Apolipoprotein on cognition in children chronically exposed to high concentrations of PM2.5 and ozone. APOE4 females are at the highest risk in Mexico City. ER 2016;150:411-422

- We assessed whether gender, BMI, APOE and metabolic variables in healthy urban children with high exposures to ozone and PM2.5 influence cognition.
- 69 APOE3/3 children and 36 APOE 3/4 children ages  $12.32 \pm 5.4y$
- Applied the WISC-R
- APOE4 females had higher BMI and females with BMI between 75-94% had the highest deficits in Performance IQ, Total IQ, Digit Span, Picture Arrangement, Block Design and Object Assembly.

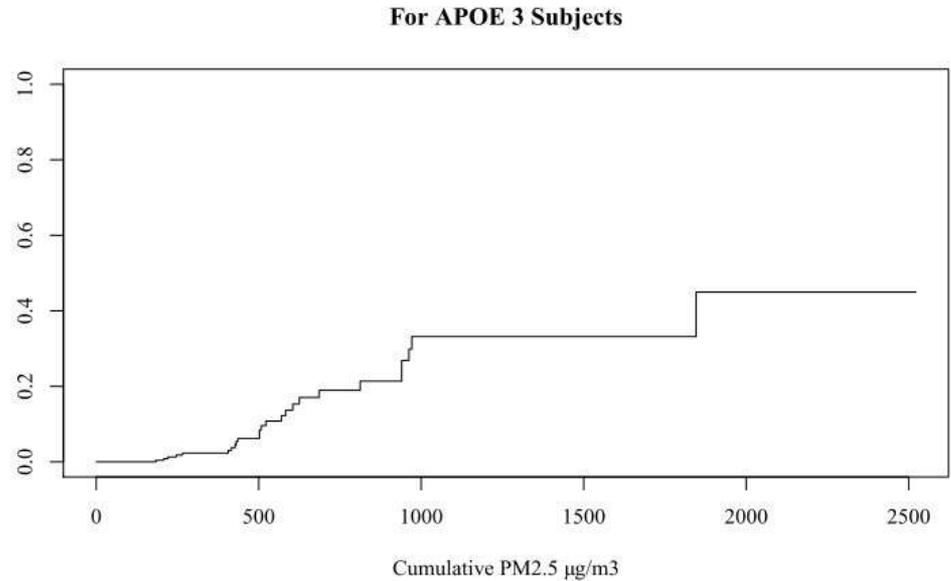
- FASTING GLUCOSE was significantly higher in APOE4 children  $p=0.006$ , while GENDER was the main variable accounting for the difference in insulin, HOMA-IR and leptin.
- APOE4 heterozygous females with  $>75 <94\%$  BMI percentiles **are at the highest risk of SEVERE cognitive deficits 1.5- 2 SD from average IQ**

**SEQUENCING ABILITY, WORKING  
MEMORY,  
SHORT TERM MEMORY,  
ATTENTION AND CONCENTRATION**

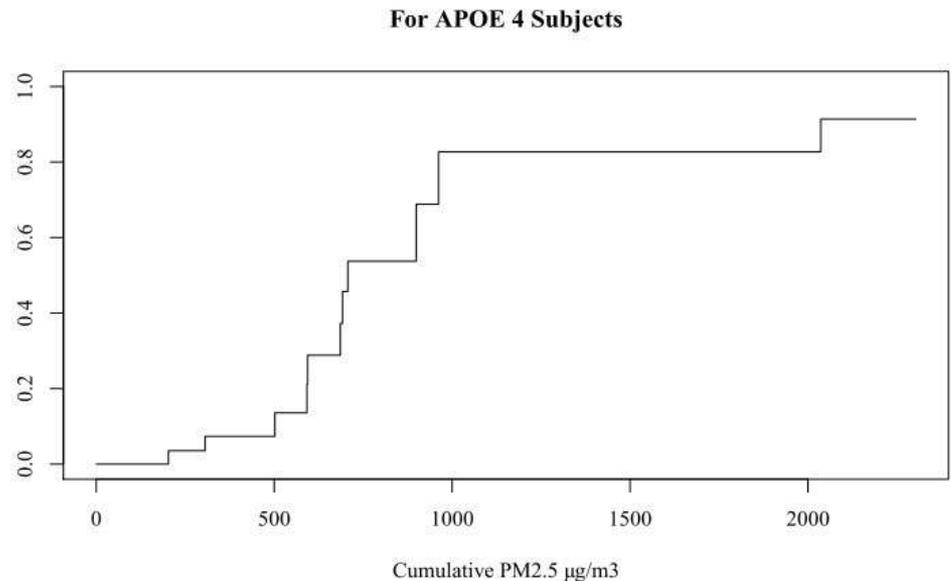


**Cumulative  
PM 2.5  
Suicide  
Probability in  
males carrying  
one APOE 4 allele  
APOE4 carriers  
were 4.57 times  
more likely than  
non-carriers to die  
by suicide**

Cumulative suicide probability of APOE 3 subjects adjusted for Age



Cumulative suicide probability of APOE 4 subjects adjusted for Age





**How early?**

**How badly?**

**Air pollution affects  
children's brains**



# Nanoparticles

- Redox-active, strongly magnetic, combustion and friction-derived nanoparticles (CFDNPs) are abundant in particulate matter air pollution.
- Urban children and young adults with Alzheimer disease continuum have higher numbers of brain CFDNPs versus clean air controls.

- CFDNPs surface charge, dynamic magnetic susceptibility, iron content and redox activity contribute to ROS generation, neurovascular unit (NVU), mitochondria, and endoplasmic reticulum (ER) damage, and are catalysts for protein misfolding, aggregation and fibrillation.

- **CFDNPs respond to external magnetic fields and are involved in cell damage by agglomeration/clustering, magnetic rotation and/or**

- **Critical information includes how these NPs overcome all barriers, the NPs protein corona changes as they cross the NVU and the complexity of NPs interaction with soluble proteins and key organelles.**
- **Oxidative, ER and mitochondrial stress, and a faulty complex protein quality control are at the core of Alzheimer and Parkinson's diseases and NPs mechanisms of action and toxicity are strong candidates for early development and progression of both fatal diseases.**
- **Nanoparticle exposure regardless of sources carries a high risk for the developing brain homeostasis and ought to be included in the AD and PD research framework.**

# Ultrafine PM Research Gaps



**MERCI!**  
**Thank you!**  
**¡Muchas Gracias!**

