The development and convergence of co-pathologies associated with Tau, Ab, a-synuclein and TDP-43 proteinopathies in Metropolitan Mexico City children and young adults: a health crisis is in progress. Nanoparticles a common denominator?

Lilian Calderón-Garcidueñas MA, MD PhD, Angélica González-Maciel MS, Rafael Reynoso-Robles BS, Partha S Mukherjee PhD

Session 5: Health and Toxicity
Wed, 23.06.2021, 13:20 (CEST)

METROPOLITAN MEXICO CITY

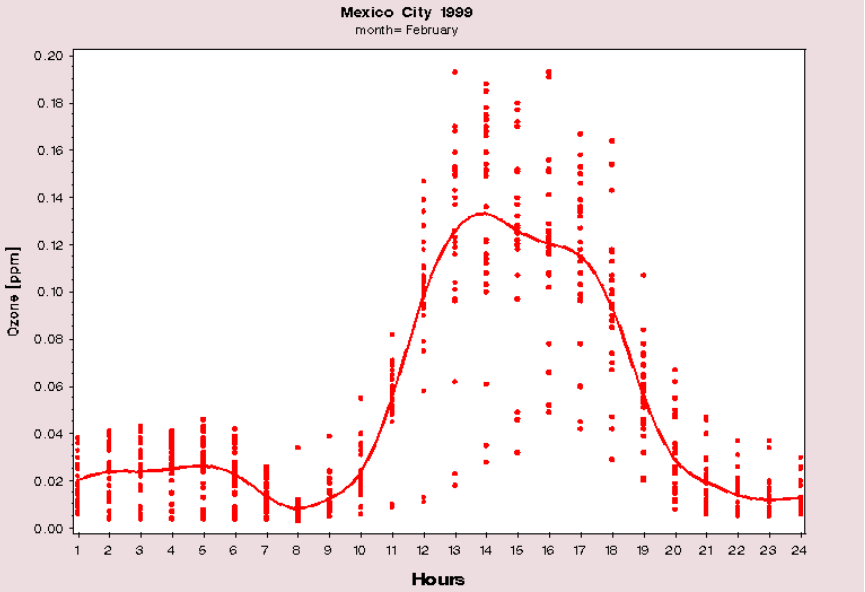
Consumption of > 40 million liters of petroleum fuels per day

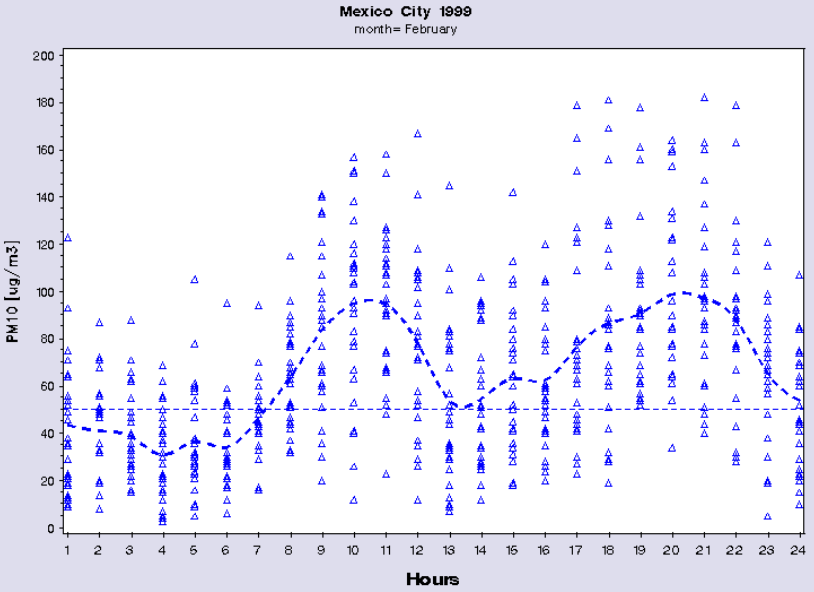
> 50,000 industries and > 6 million cars

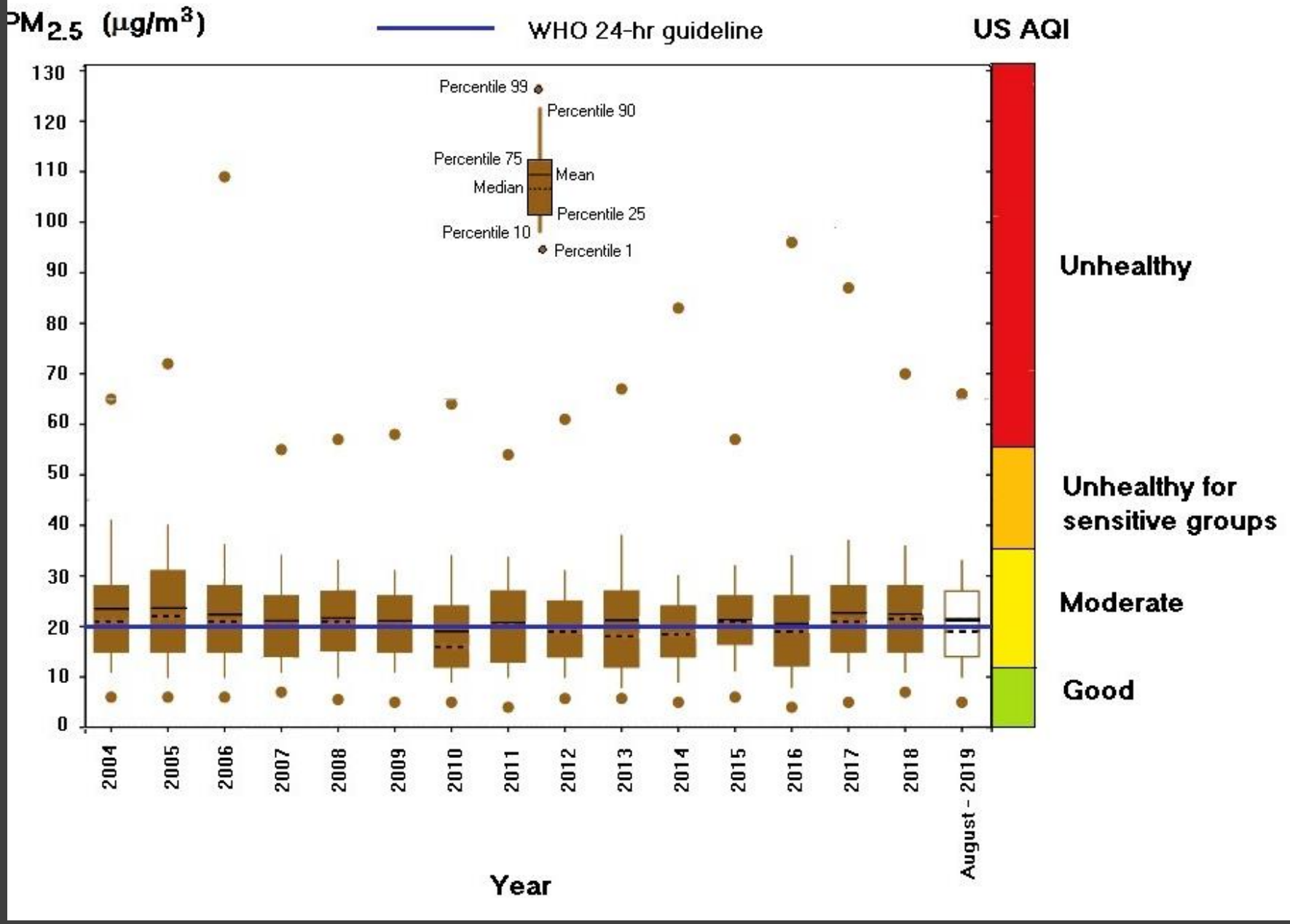
Valley with obstruction of air movement, at 7350 feet

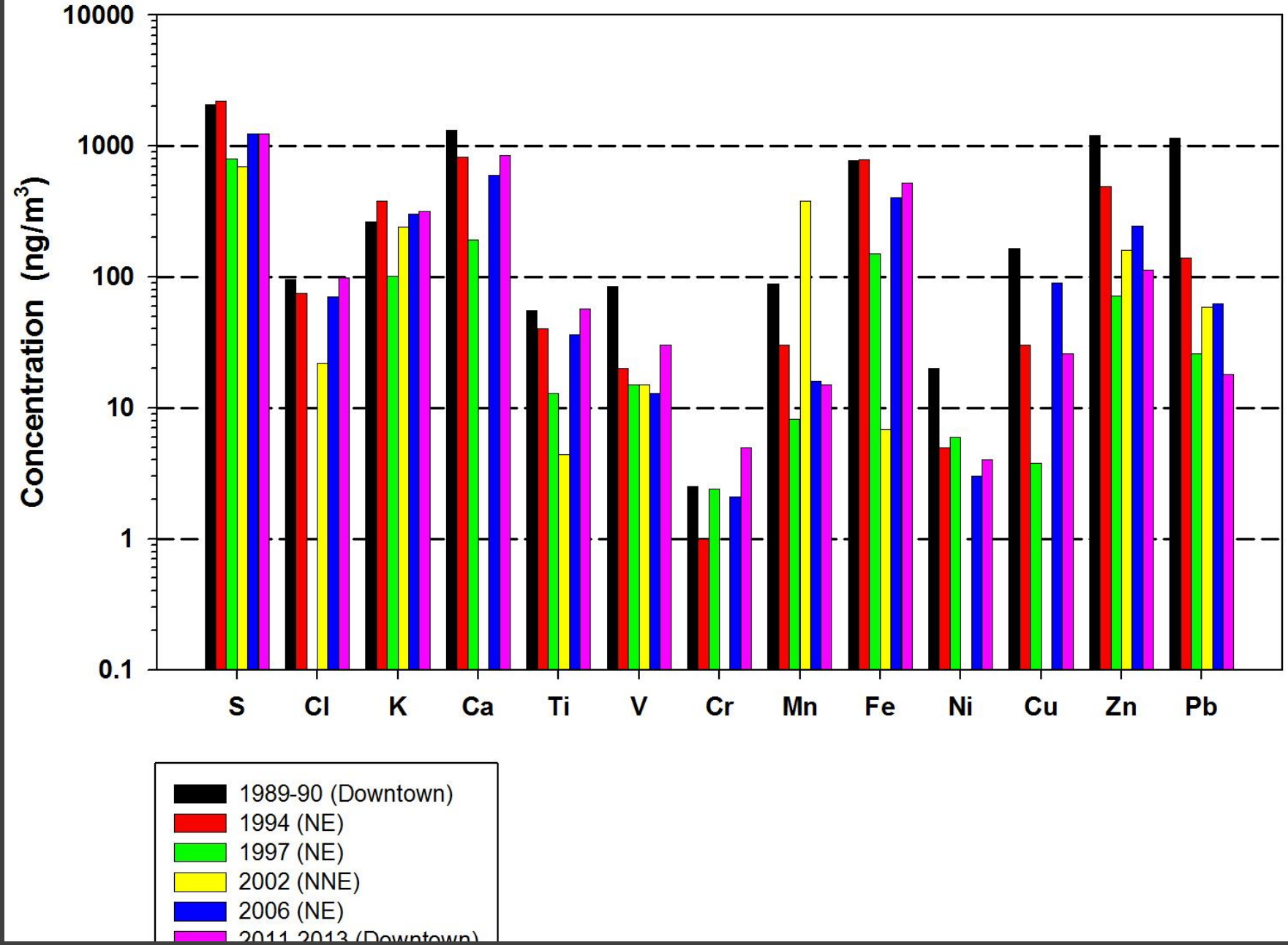
An involuntary, very effective exposure chamber for 21.8 million people

Metropolitan Mexico City 21.8 million people.
Typical Day ozone and PM






PM2.5 (µg/m3)
WHO 24-hr guideline
US AQI
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Percentile 99
Percentile 90
Percentile 75
Mean
Median
Percentile 25
Percentile 10
Percentile 1
Unhealthy
Unhealthy for sensitive groups
Moderate
Good
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
August - 2019
Year


10000
1000
100
10
1
0.1
Concentration (ng/m3)
S
Cl
K
Ca
Ti
V
Cr
Mn
Fe
Ni
Cu
Zn
Pb
1989-90 (Downtown)
1994 (NE)
1997 (NE)
2002 (NNE)
2006 (NE)
2011-2013 (Downtown)

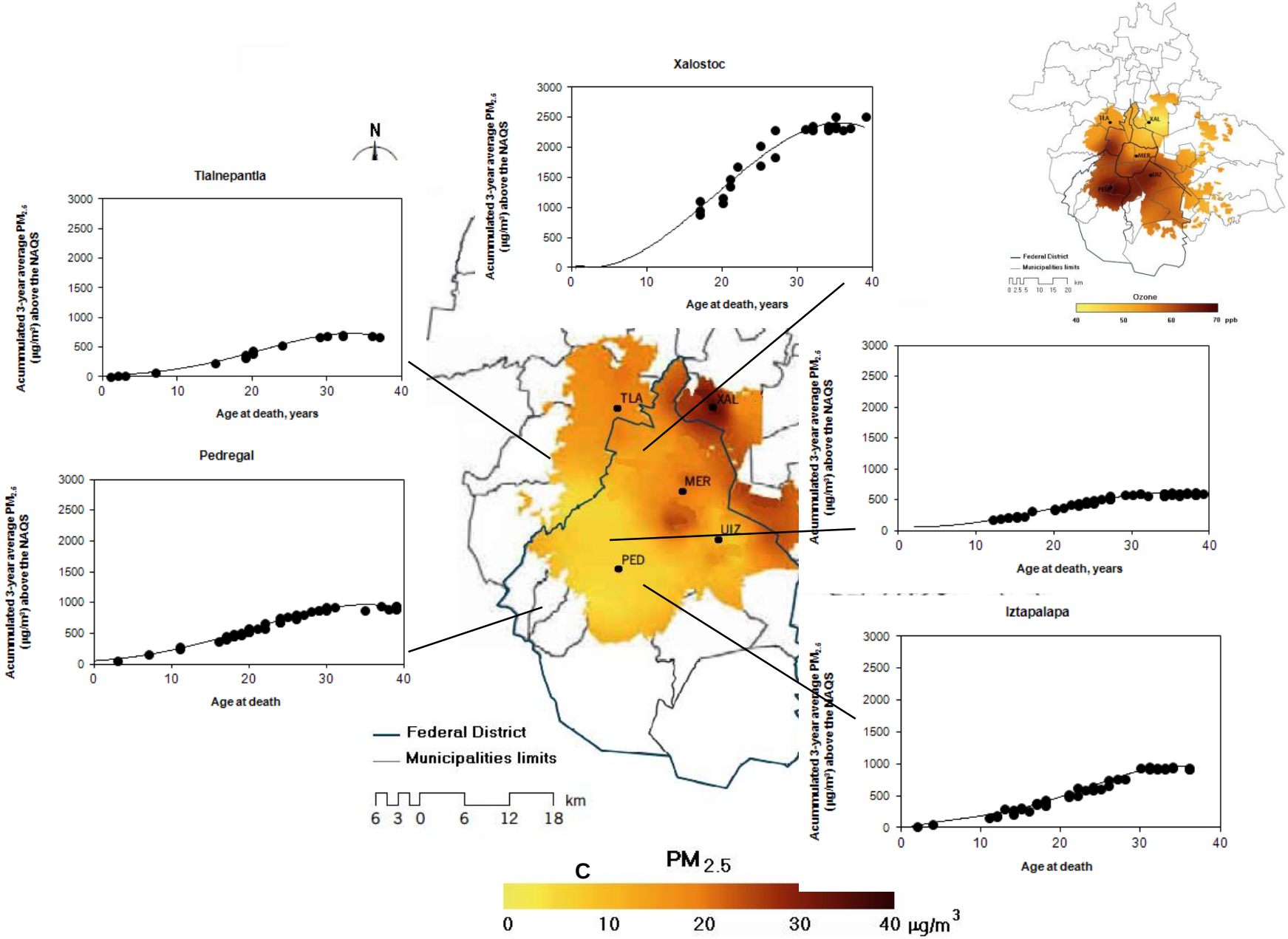
Environ Res 2018

Hallmarks of Alzheimer disease are evolving relentlessly in Metropolitan Mexico City infants, children and young adults. APOE4 carriers have higher suicide risk and higher odds of reaching NFT stage V at ≤ 40 years of age.

203 consecutive autopsies age 25.36 ± 9.23 years, including 44 children age 12.9±4.9 years

Quadruple abnormal protein aggregates in brainstem pathology and exogenous metal-rich magnetic nanoparticles (and engineered Ti-rich nanorods). ER 2020

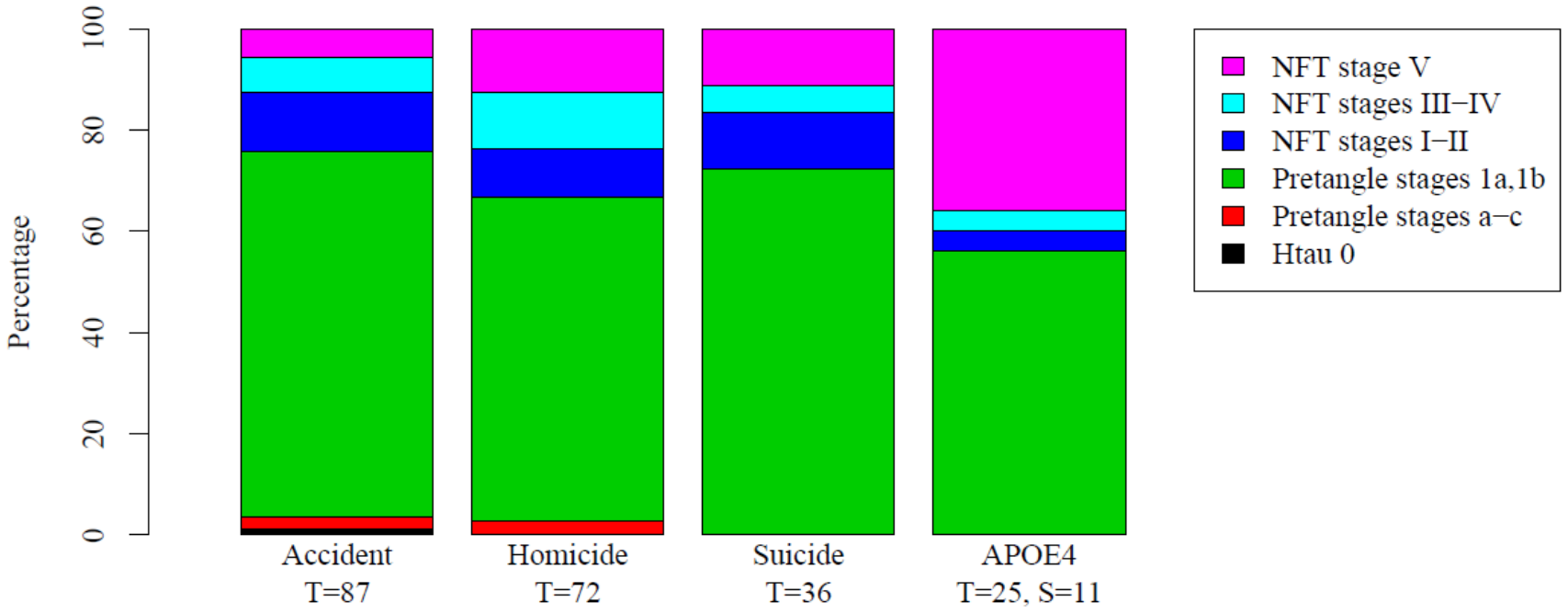
Neuropath golden markers for Alzheimer, Parkinson and TDP-43 (frontotemporal dementia and ALS)


Xalostoc
Tlalnepantla
Pedregal
Iztapalapa
Acummulated 3-year average PM2.5 (µg/m³) above the NAQS
Age at death, years
Age at death
N
TLA
XAL
MER
UIZ
PED
Federal District
Municipalities limits
km
6 3 0 6 12 18
Ozone
40 50 60 70 ppb
C
PM 2.5
0 10 20 30 40 µg/m3

Primary outcomes: staging of Htau and beta amyloid (Braak et al.,) per decade and cumulative $PM_{2.5}$ ($CPM_{2.5}$) above standard. Apolipoprotein E allele 4 (APOE4), age and cause of death were secondary outcomes.

203 FORENSIC AUTOPSIES AVERAGE AGE:

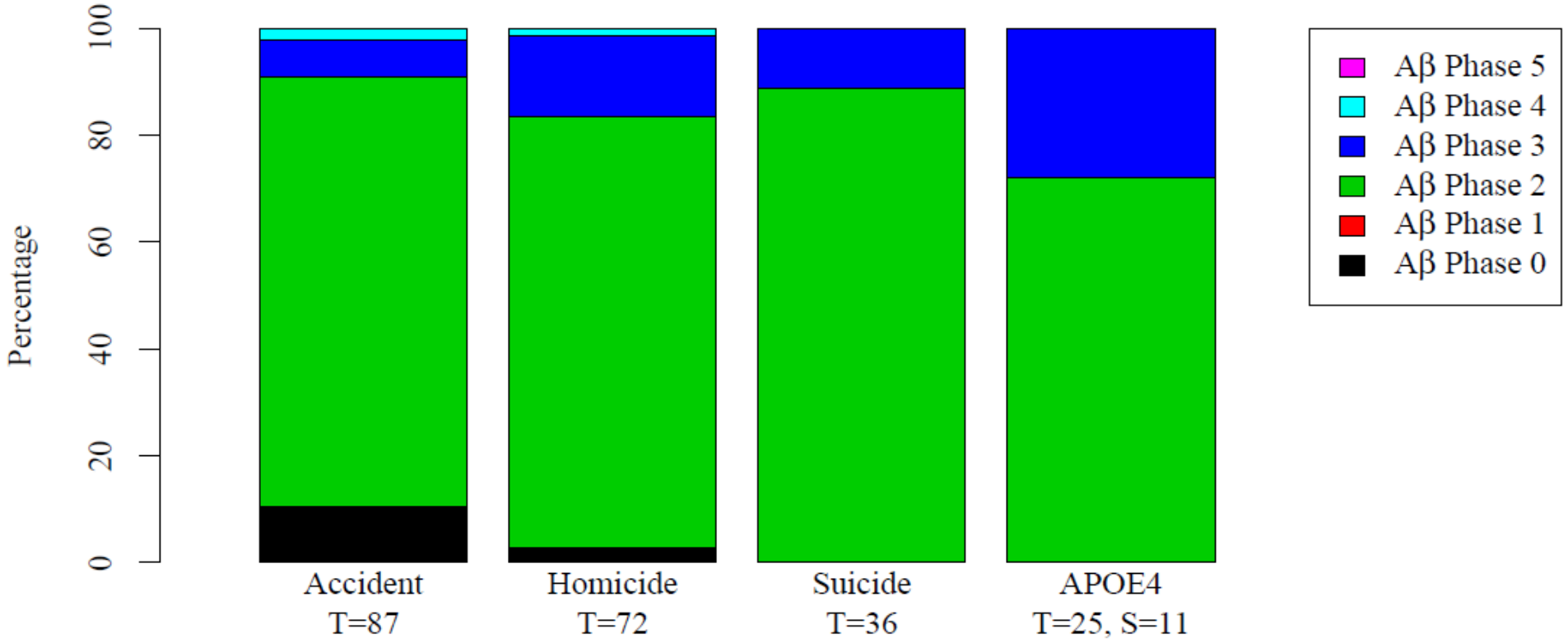
25.36 ± 9.23 years, 44 children age 12.9±4.9 years



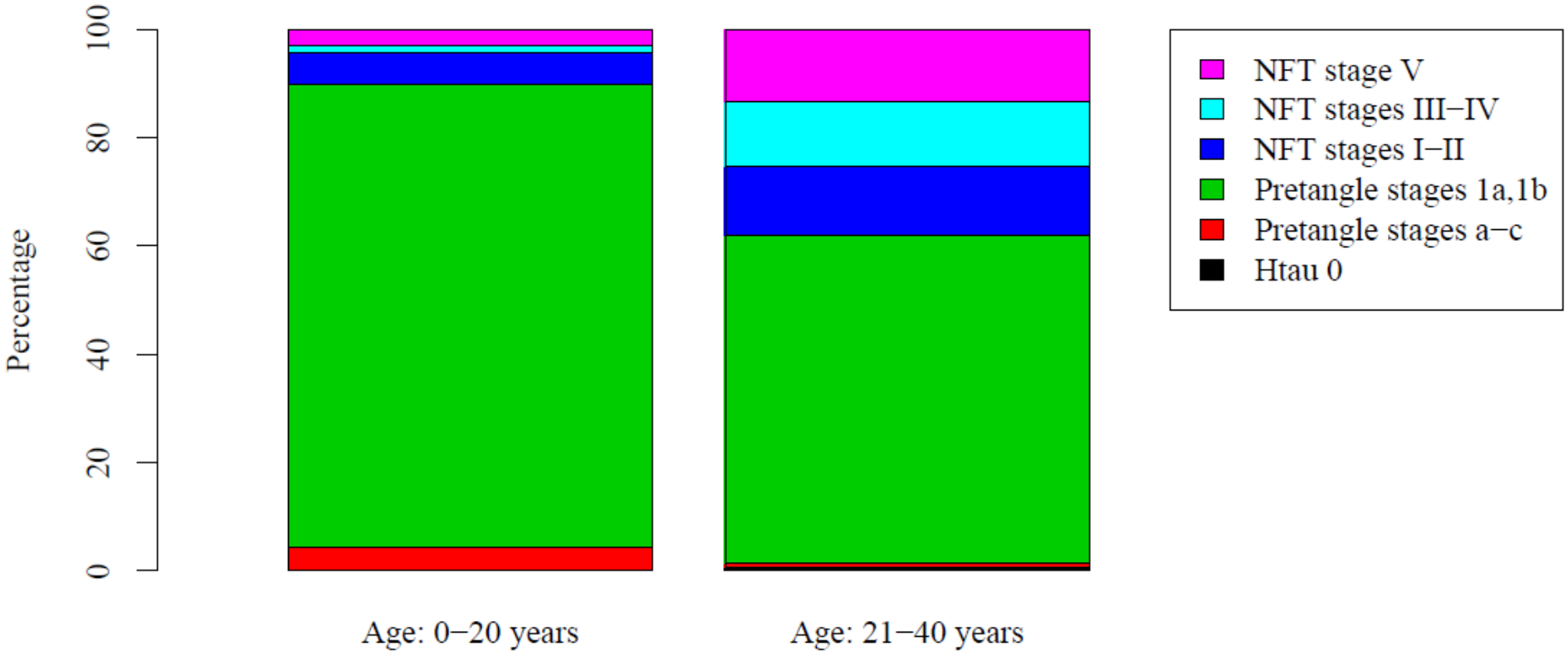
HYPERPHOSPHORYLATED TAU

FORENSIC AUTOPSIES

Extracellular deposits of insoluble amyloid-beta (Abeta)

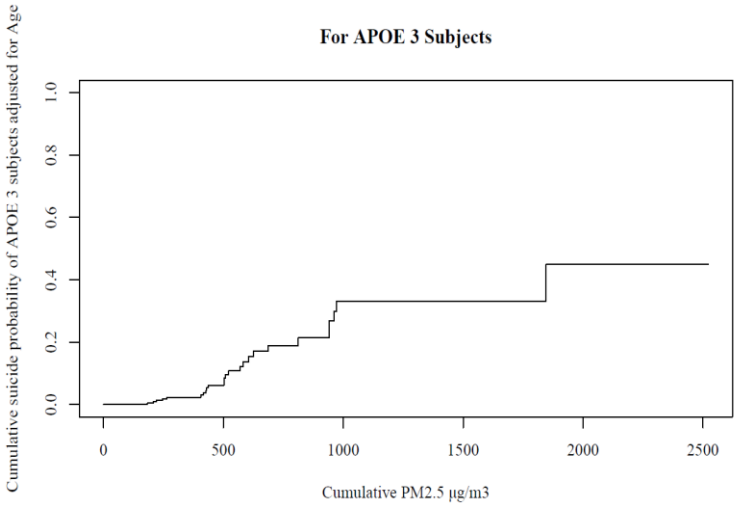


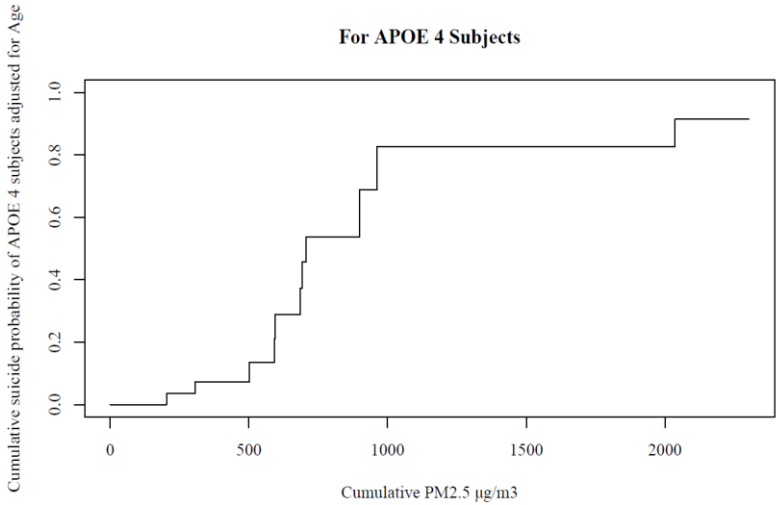
Tau per decades



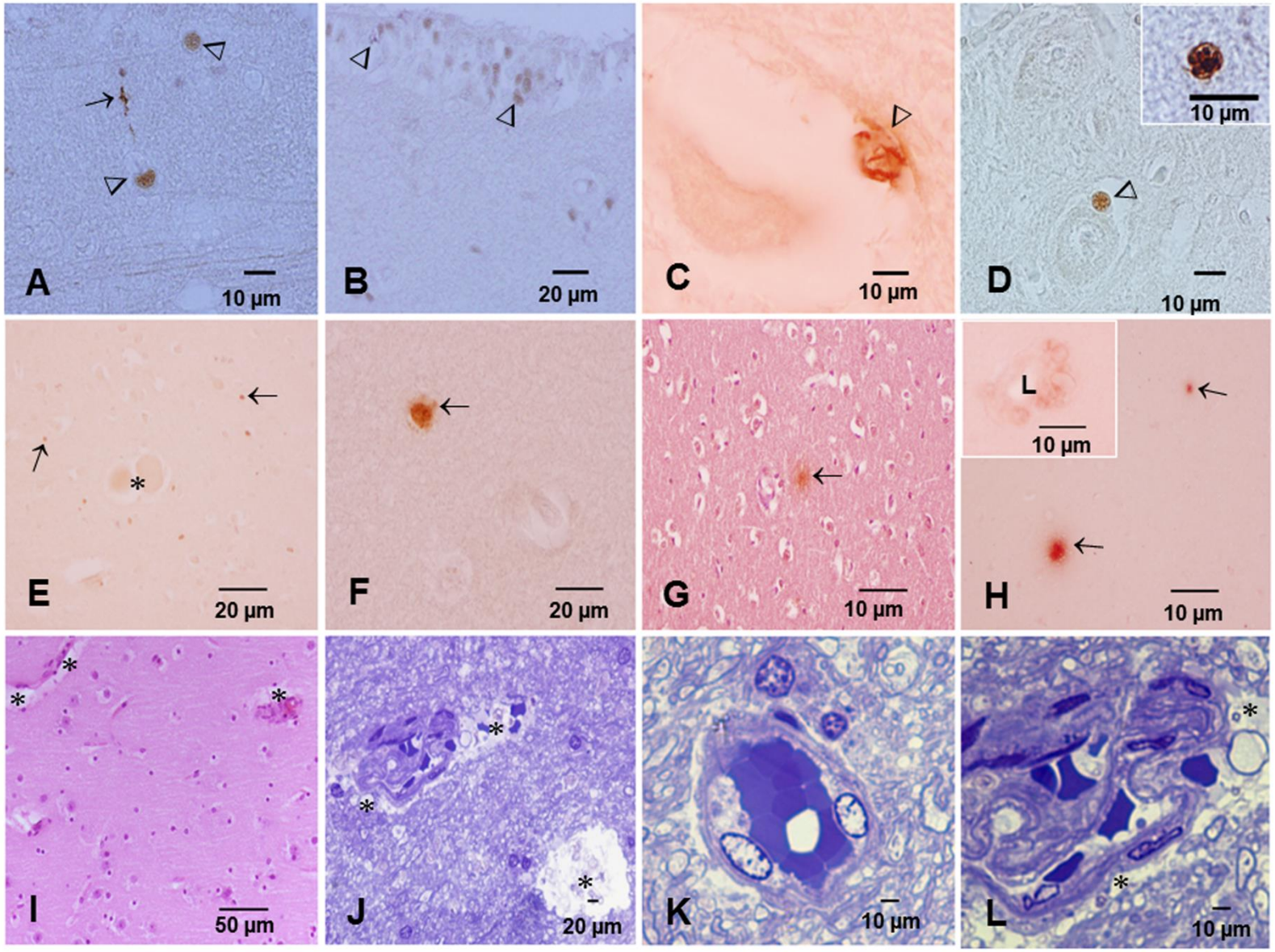
Beta amyloid per decades

ACCUMULATIVE SUICIDE RISK

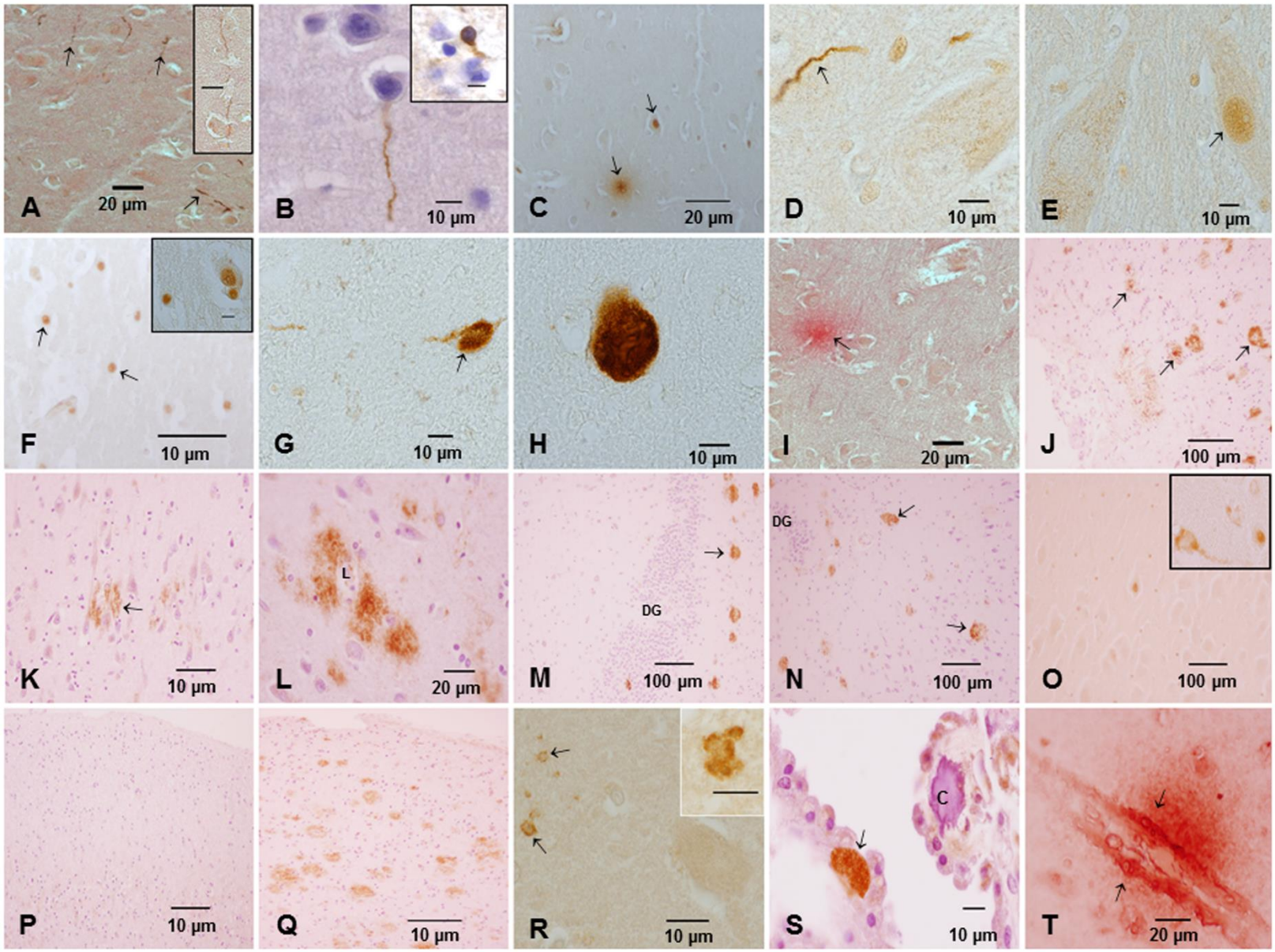




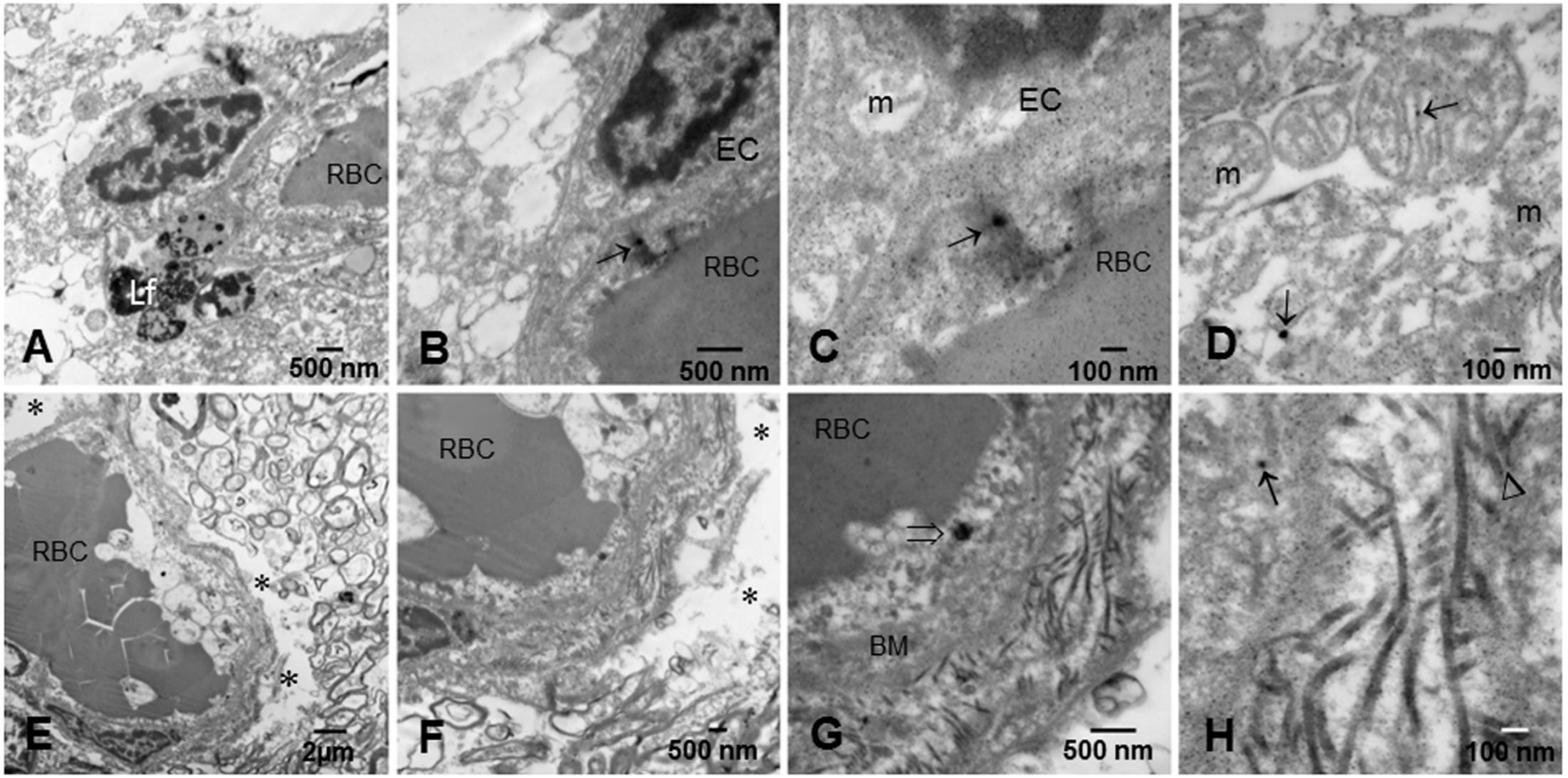
Immunohistochemistry and Electron Microscopy. First decade of life



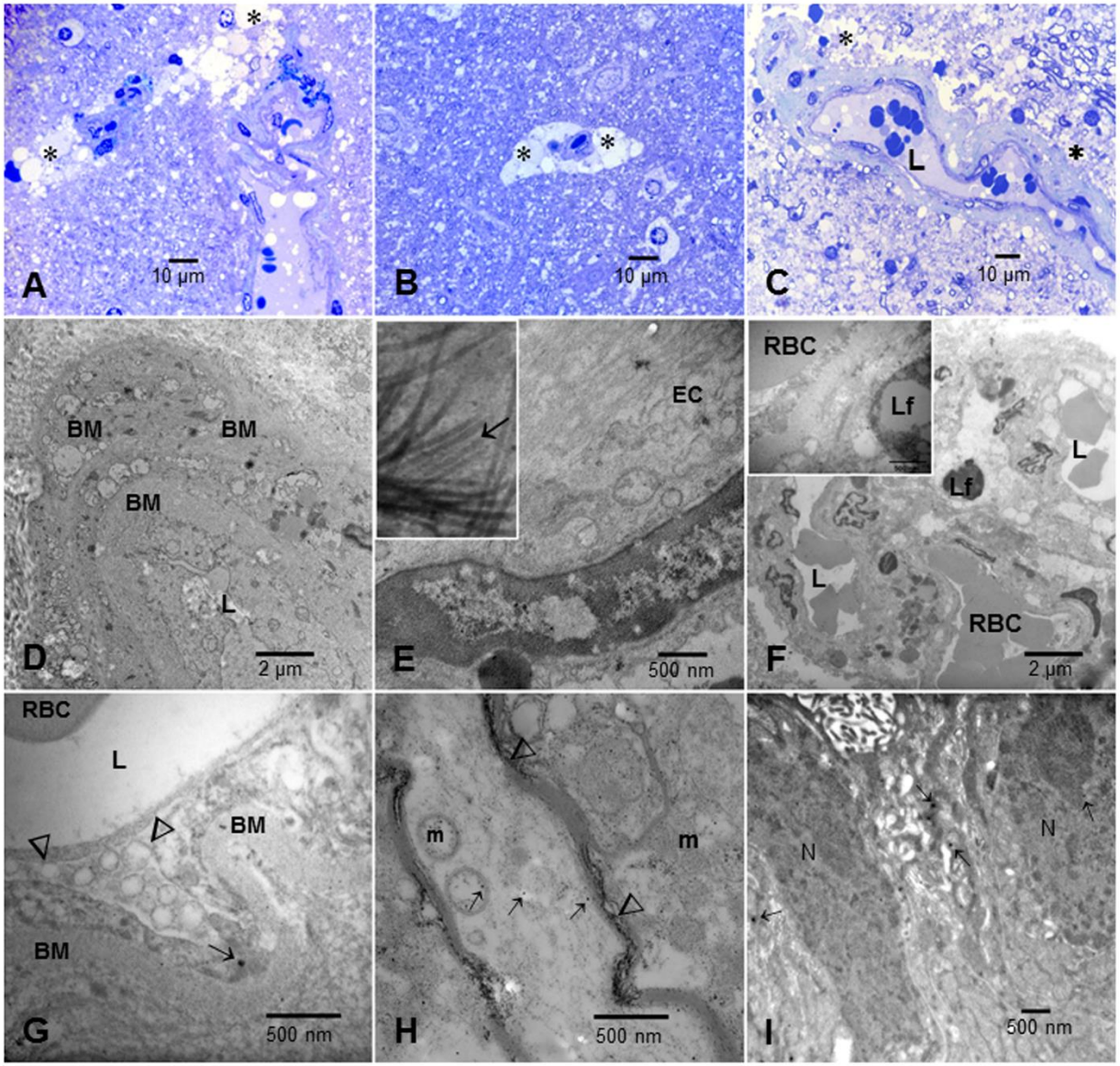
Immunohistochemistry and Electron Microscopy. Second decade of life



Electron Microscopy. First decade of life



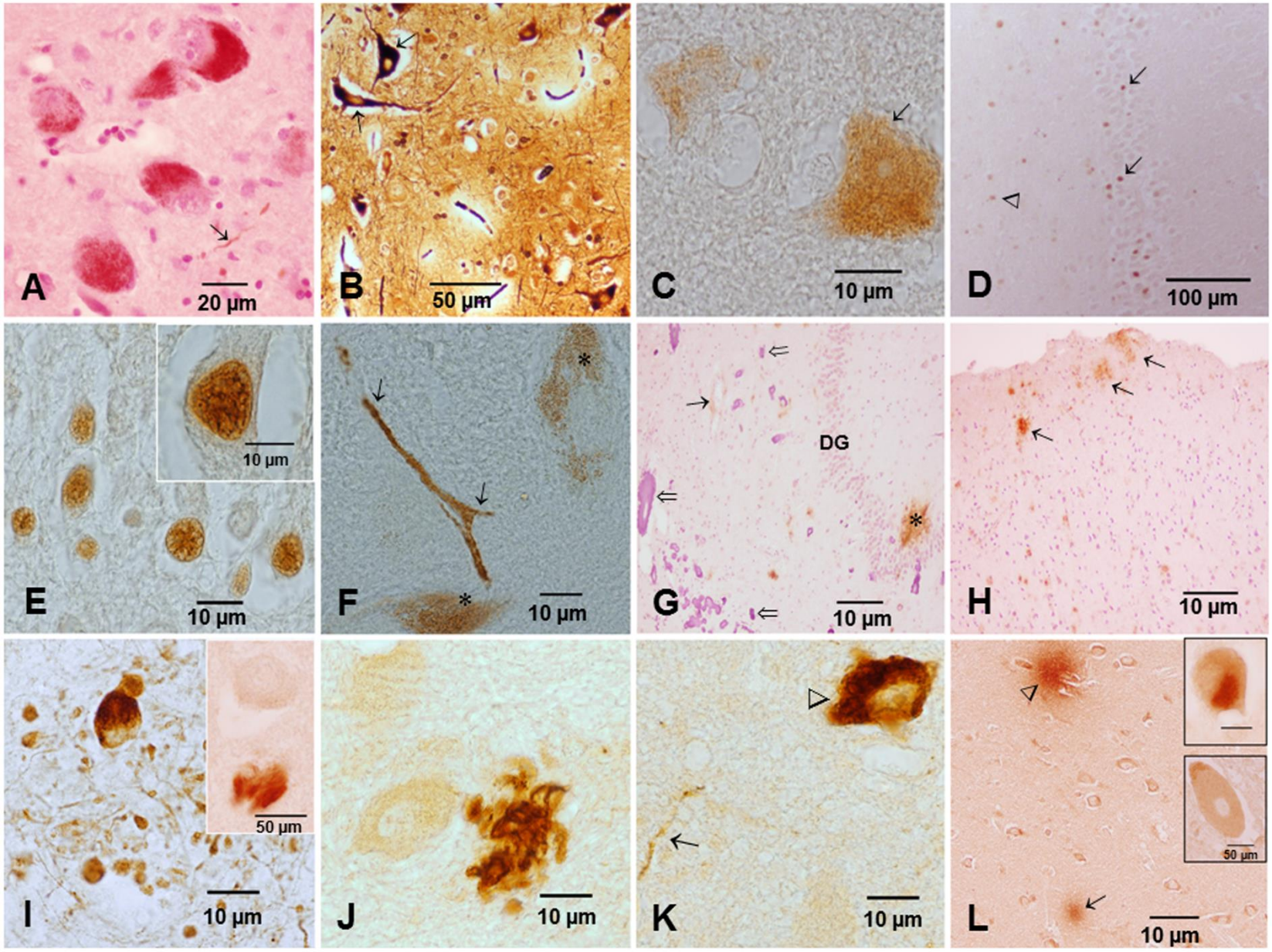
Electron Microscopy and Toluidine 1um sections. 1st and 2sd decades of life

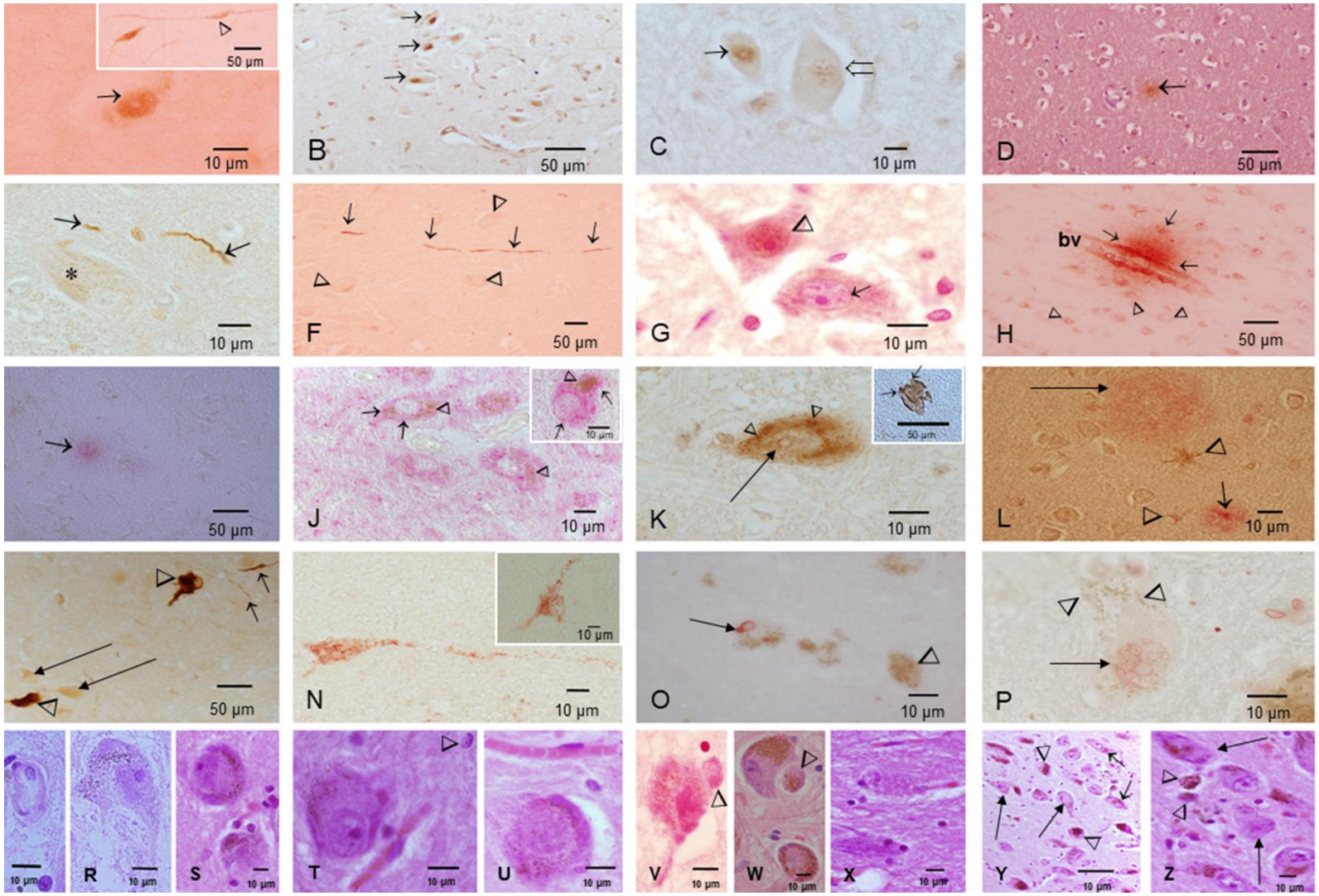


Neurofibrillary tangles (NFT) Stages I-II, amyloid phases 1-2, Htau in substantia nigrae, auditory, oculomotor, trigeminal and autonomic systems in the 2nd decade.

NFT stages III-V was present in 24.8% of 30-40 y old subjects.

Immunohistochemistry
3rd and 4th decades of life





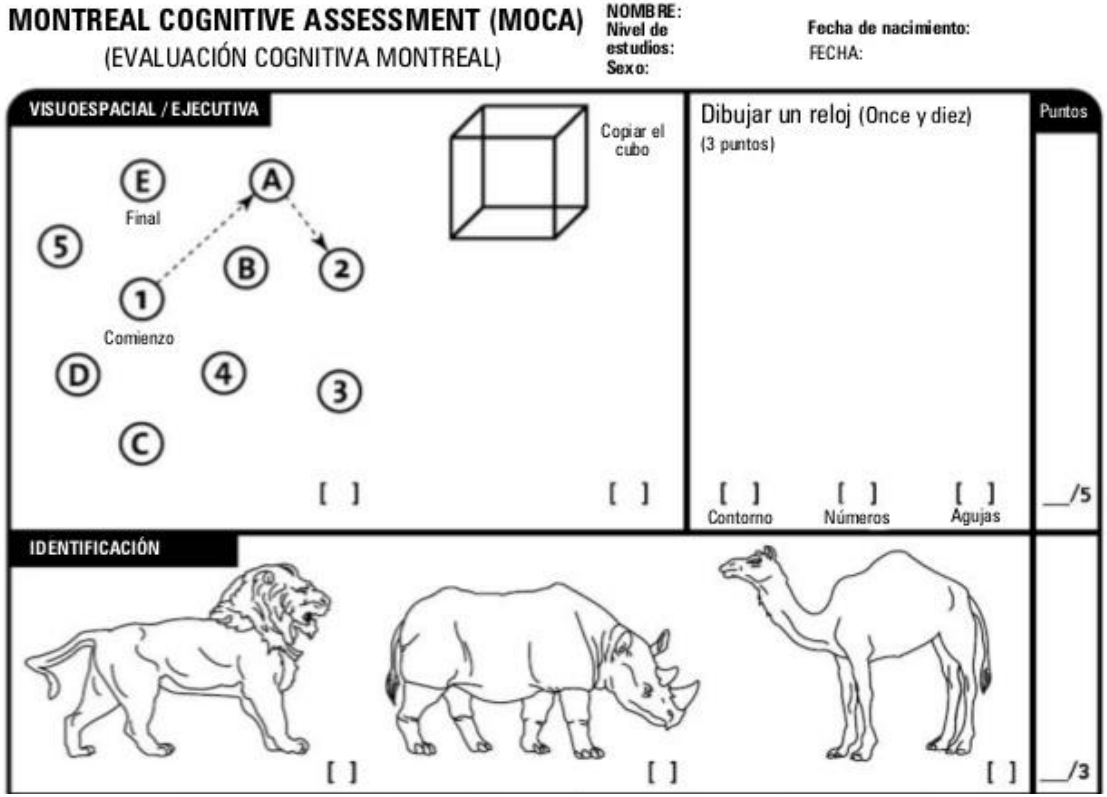
Quadruple pathology overlap

ALZHEIMER (99.5%),PARKINSON (23%)AND TDP-43 PATHOLOGY (18%) (FRONTOTEMPORAL DEMENTIA AND ALS).

Quadruple abnormal protein aggregates in brainstem pathology and exogenous metal-rich magnetic nanoparticles (and engineered Ti-rich nanorods). The substantia nigrae is a very early target in young urbanites and the gastrointestinal tract a key brainstem portal.

Mild Cognitive Impairment and Dementia Involving Multiple Cognitive Domains in Mexican Urbanites. Journal of Alzheimer's Disease 2019;68(3):1113-1123.

The Montreal Cognitive Assessment (MoCA) was administered to 517 urbanites, age 21.60±5.88 years, with 13.69±1.28 formal education years, in Mexican PM2.5 polluted cities.



MoCA Normal scores

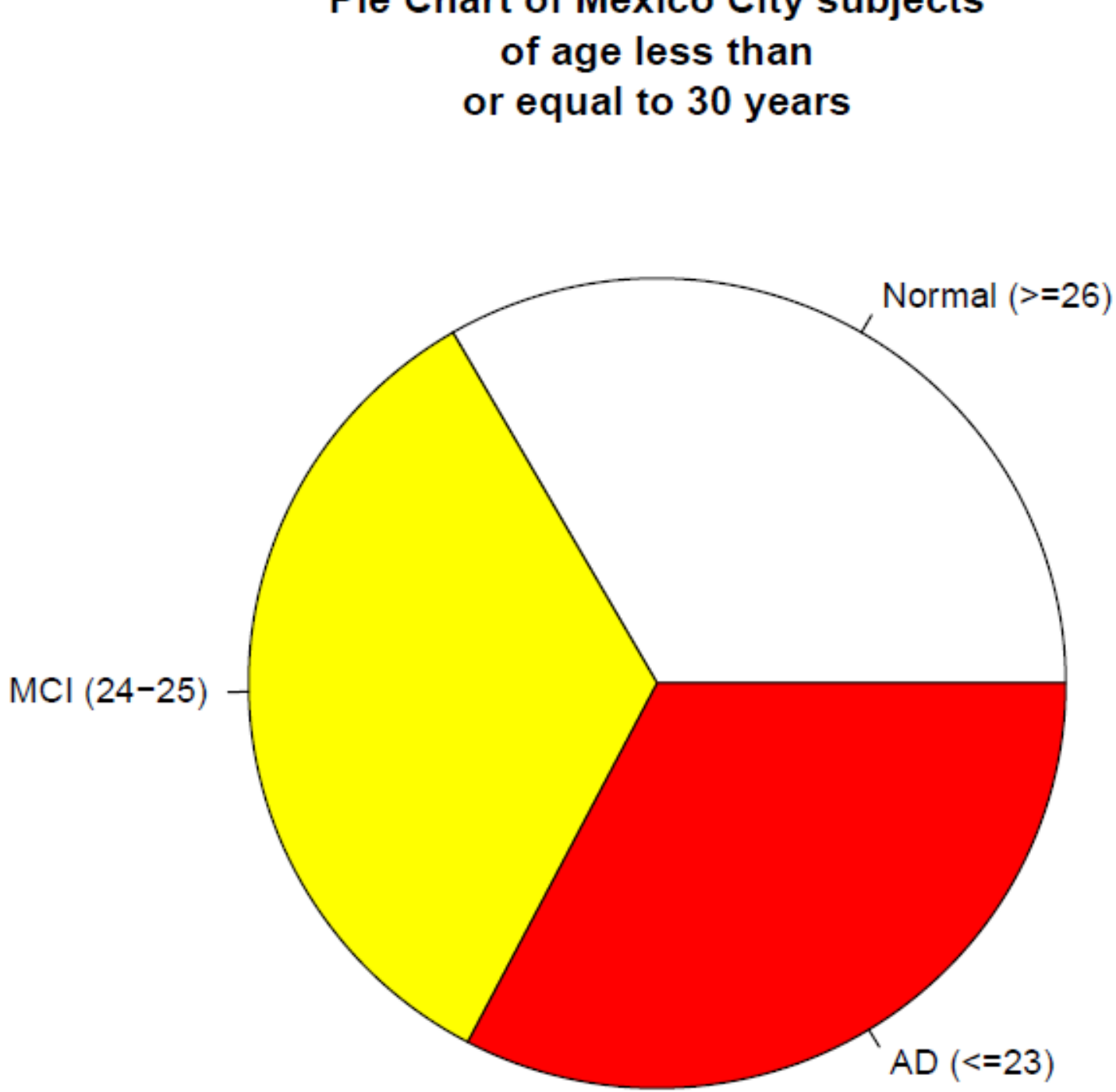
- NORMAL COGNITION 26-30
- MILD COGNITIVE IMPAIRMENT 24-25
- DEMENTIA SCORES ≤23

RESULTS

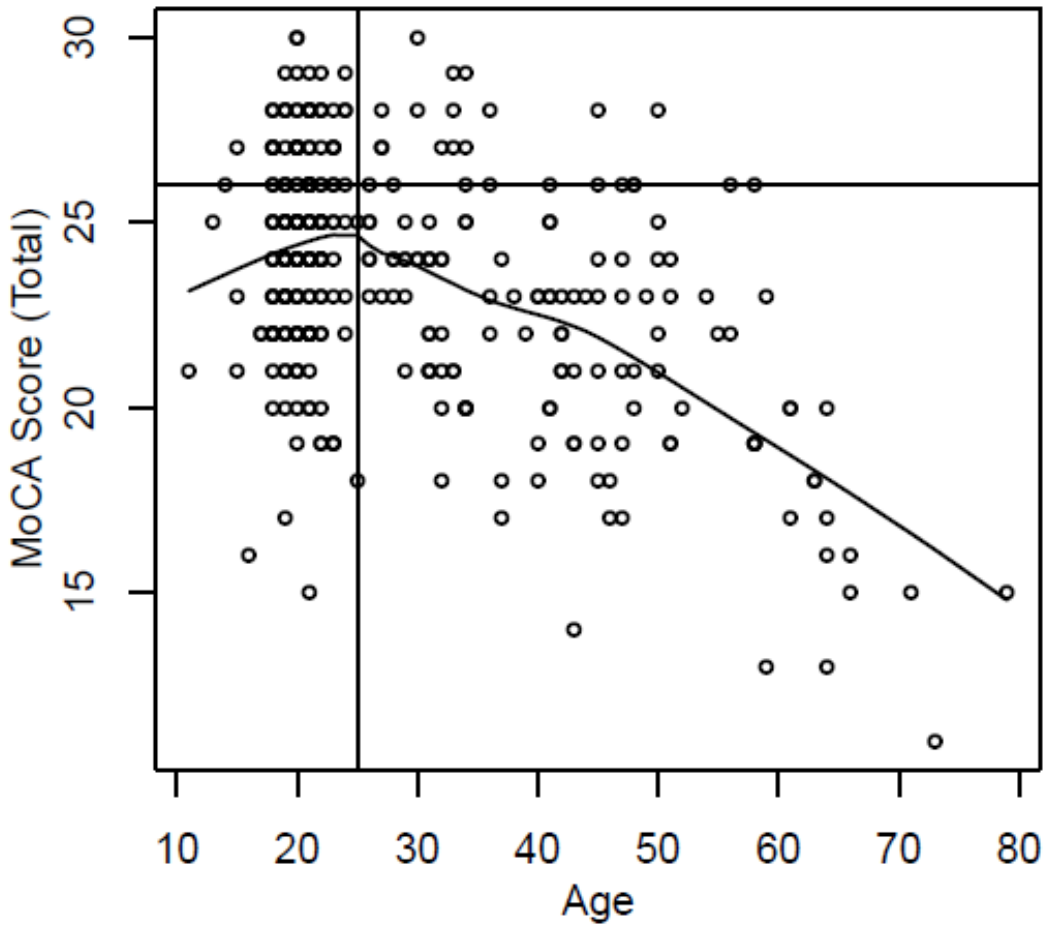
Residency in polluted cities is associated with progression of multi-domain cognitive impairment affecting 55% of Mexican seemingly healthy youth age 21.60±5.88 years, with 13.69±1.28 y of formal education.

MoCA score was 23.92±2.82, and 24.7% and 30.3% scored ≤24 and ≤22, respectively (MCI≤24, AD≤22).

Average age for dementia MoCA scores was 22.38±7.7 years.


Pie Chart of Mexico City subjects
of age less than
or equal to 30 years
Normal (>=26)
MCI (24−25)
AD (<=23)

MoCA total scores
517 urbanites, age 21.60±5.88 years

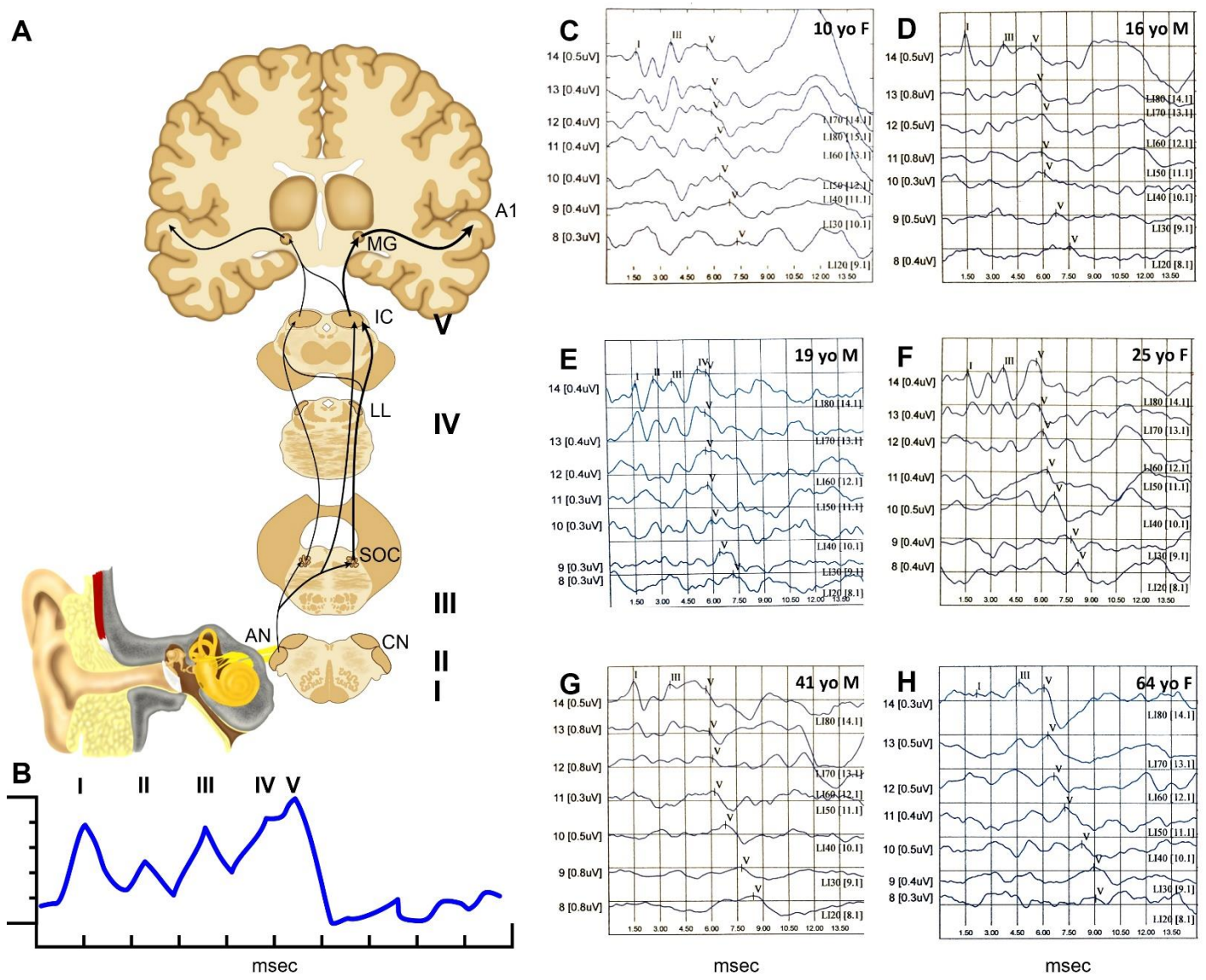


•. 2019

Increased Gain in the Auditory Pathway, Alzheimer's Disease Continuum, and Air Pollution: Peripheral and Central Auditory System Dysfunction Evolves Across Pediatric and Adult Urbanites. JAD 2019;70:1275-86

A major impediment in early diagnosis of Alzheimer's disease (AD) is the lack of robust non-invasive biomarkers of early brain dysfunction.

We measured brainstem auditory evoked potentials in MMC clinically healthy children (8.52±3.3 years) and adults (21.08±3.0 years, 42.48±8.5 years, and 71.2±6.4 years) compared to clean air controls


A
A1
MG
IC
V
LL
IV
SOC
III
AN
CN
II
I
B
I
II
III
IV V
msec
C
10 yo F
D
16 yo M
E
19 yo M
F
25 yo F
G
41 yo M
H
64 yo F
msec
msec

MMC children had decreased latency to wave I, delays in waves III and V, and longer latencies for interwave intervals, consistent with delayed central conduction time of brainstem neural transmission.

Young adults have significantly shortened interwave intervals I-III and I-V. By the 5th decade, wave V and interval I-V were significantly shorter, while the elderly cohort had significant delay in mean latencies and interwave intervals.

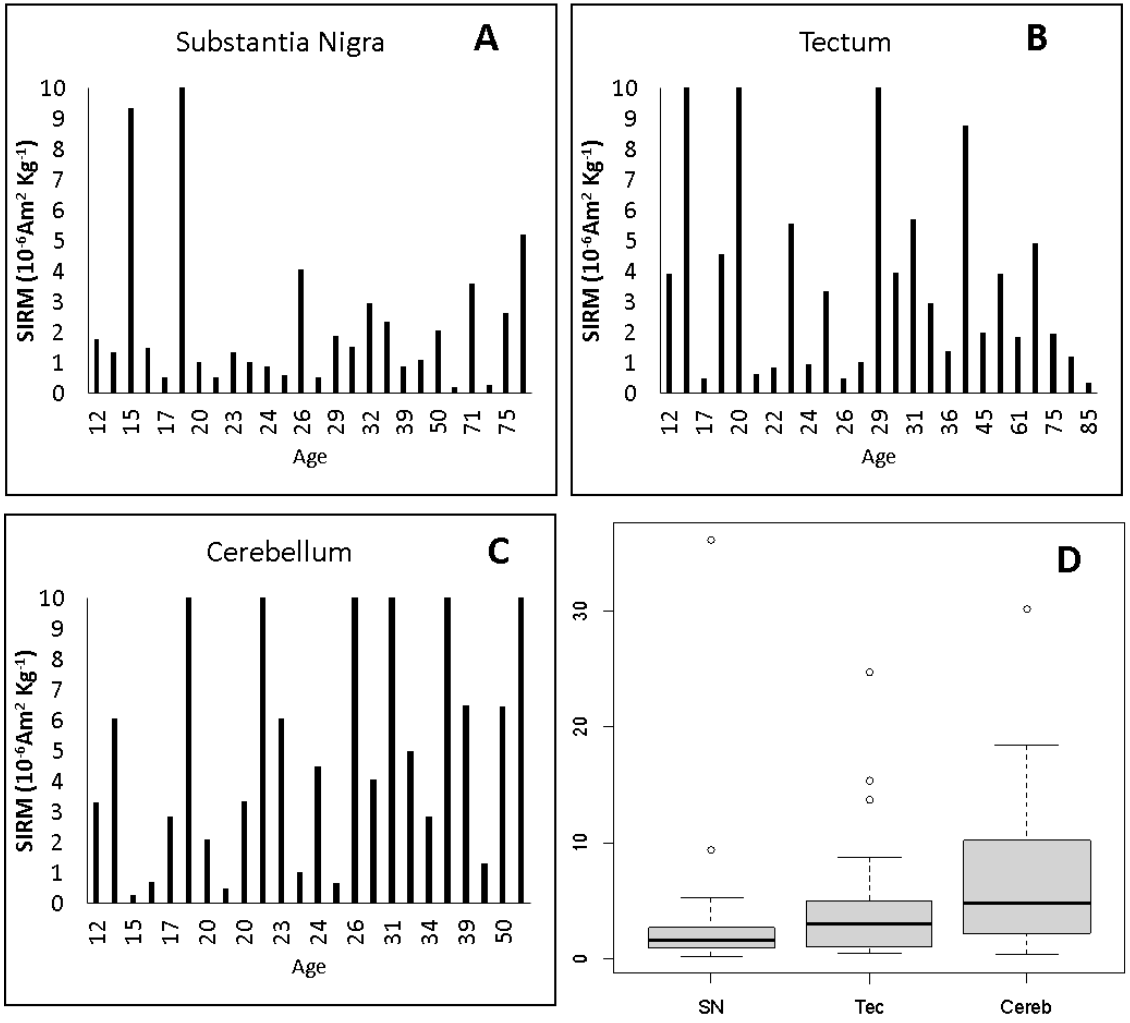
Compensatory plasticity, increased auditory gain, cochlear synaptopathy, neuroinflammation, and AD continuum likely play a role in the evolving distinct auditory

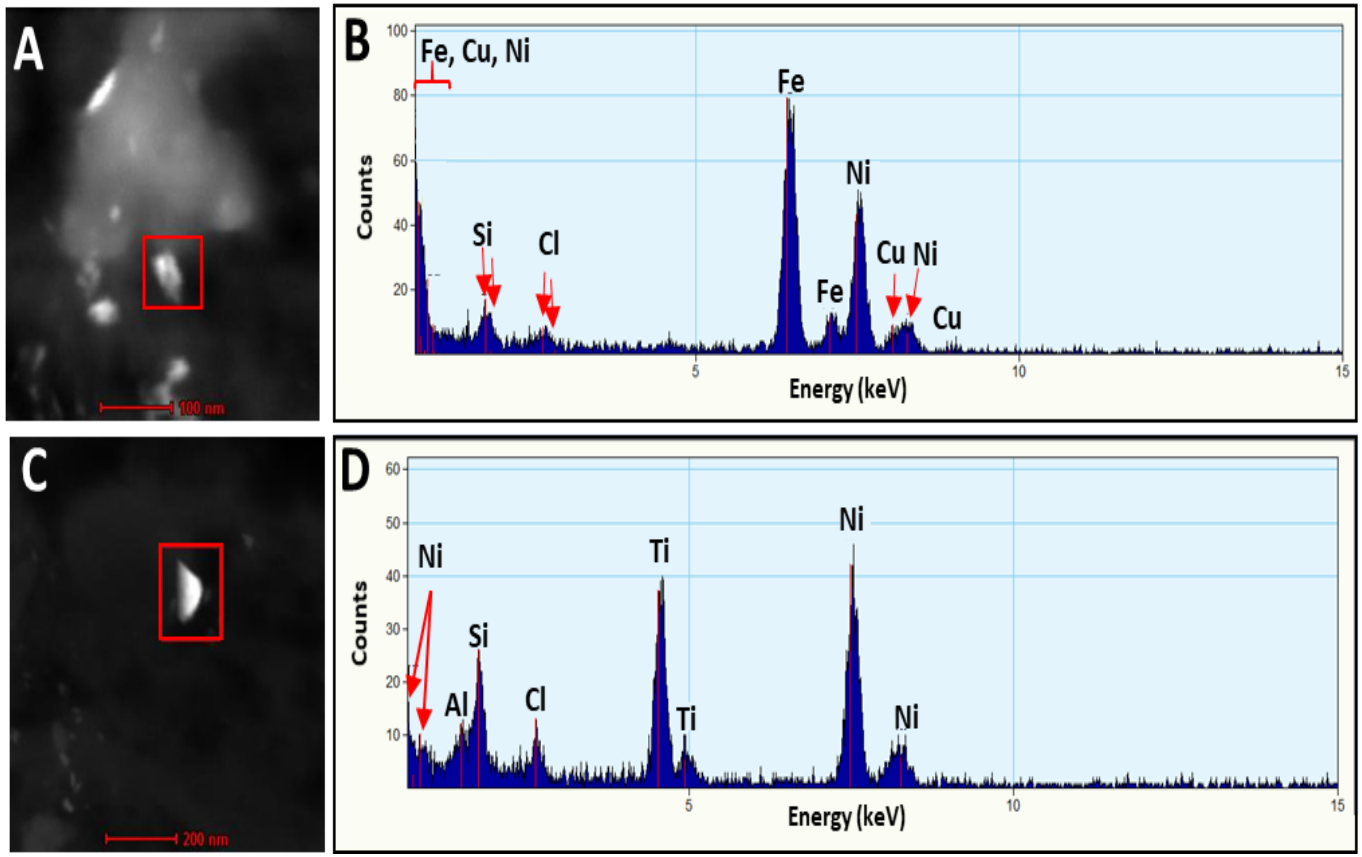
Gait and balance disturbances are common in young urbanites and associated with cognitive impairment. Air pollution and the historical development of Alzheimer's disease in the young. ER 2020

We tested gait and balance with Tinetti and Berg tests in 575 clinically healthy subjects, age 21.0 ± 5.7 years who were residents in Metropolitan Mexico City, Villahermosa and Reynosa.

In the 575 cohort, 75.4% and 34.4% had abnormal total Tinetti and Berg scores and high risk of falls in 17.2% and 5.7%

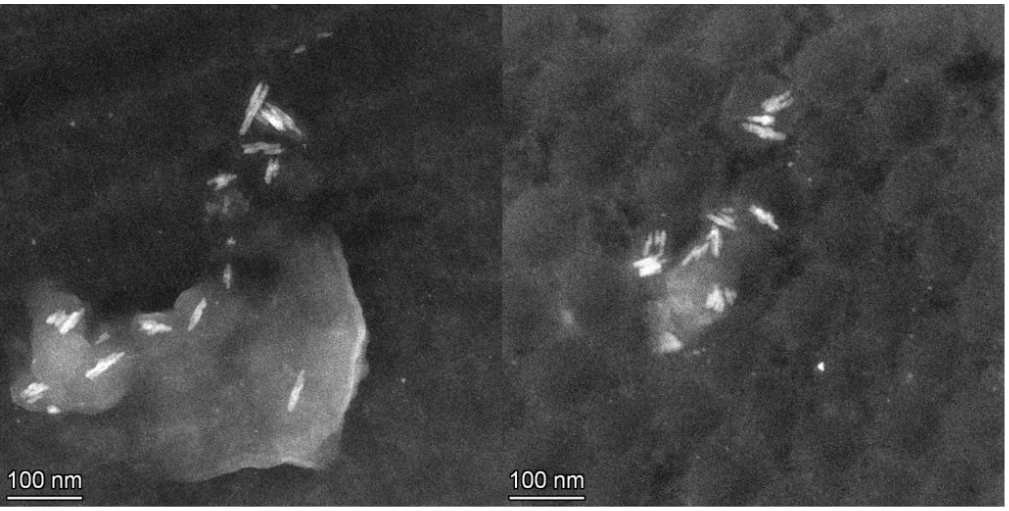
Magnetic nanoparticles in targeted brain areas

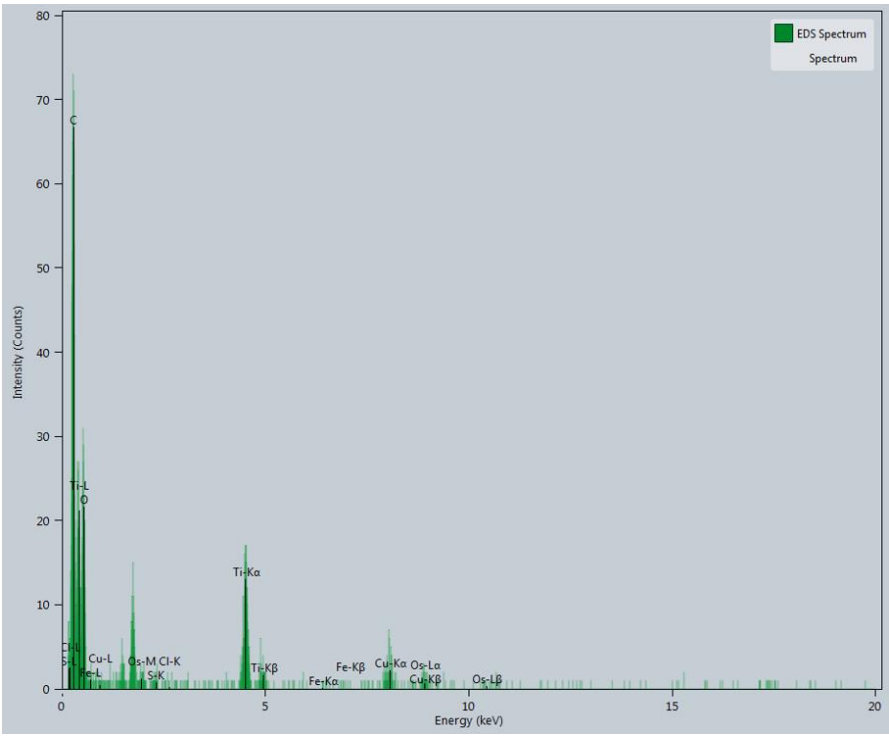




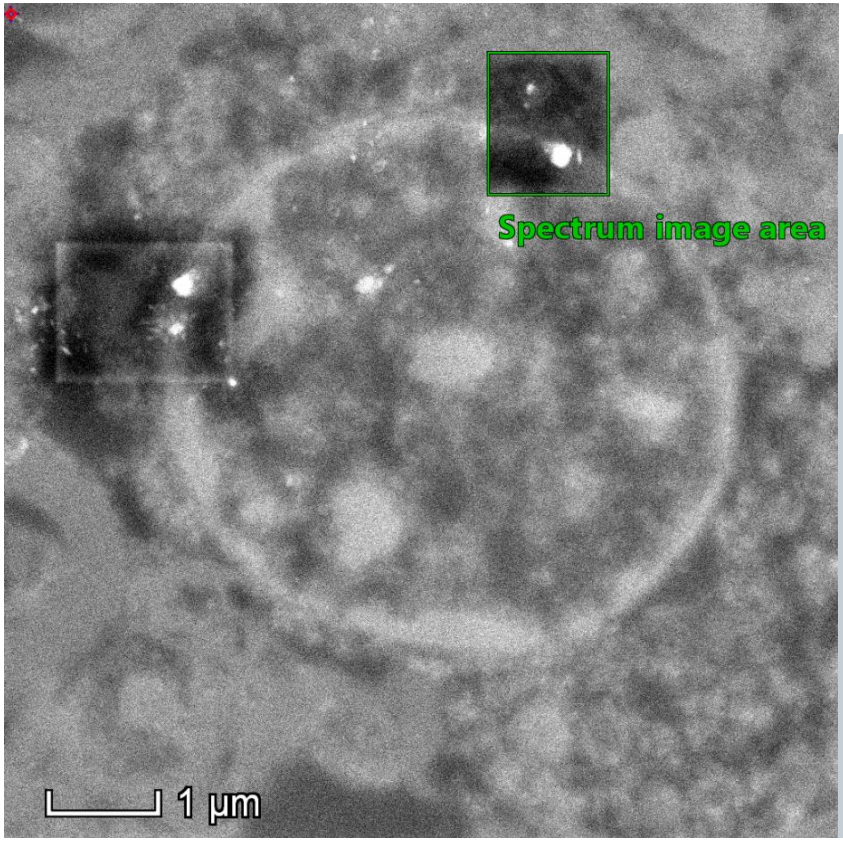
NP characterization by TEM and EDXS in human granular cell layer, cerebellum. (A) A cluster of NPs in granular cells observed by TEM and indicated by red square. (B) EDXS identifies the cluster composition: Fe and traces of Cu and Si. (C) A spherical ~80 nm NP (red square). (D) Typical rounded crystal morphologies and fused surface textures of combustion and friction derived nanoparticles (CFDNPs) are co-associated with other reactive metals including Ti and Al, as well as metalloid elements like Si. (B, D) Ni traces reflect the Ni TEM support grid.

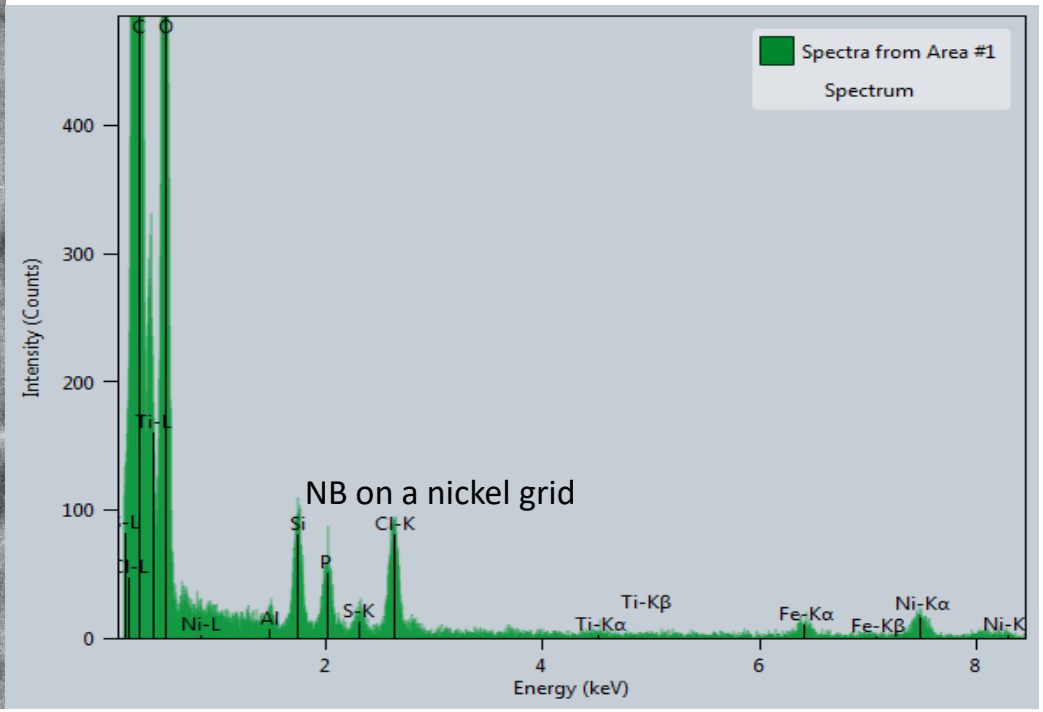
HAADF-STEM neuroenteric sample Ti nanorods and Fe NPs. ER 2020





Metal and non-metal nanoparticles in mitochondria. ER 2020





Sources of nanoparticles in MMC

Emissions from internal combustion engines burning fossil fuels in motor vehicles- unregulated diesel engines and equipment are responsible for total regional and urban MMC pollution.

Fixed sources

E-Waste

Food, cosmetic, pharmaceutical, and medical utilization

Nanoparticles as a sink for organic and inorganic co-contaminants.

NPs Damage to the brain

- Oxidative damage i.e., formation of free radicals
- Direct damage of membrane organelles
- Interference with metabolic processes
- *de novo* mutations of DNA
- Apoptosis, autophagy, immune-responses, neuroinflammation and brain-blood-barrier BBB damage
- Magnetic damage i.e., heat production, alignment and /or rotation in response to magnetic fields.

Neurodegenerative diseases

Exposure to air pollutants has been associated with the most common neurodegenerative fatal diseases affecting millions of people across the world:

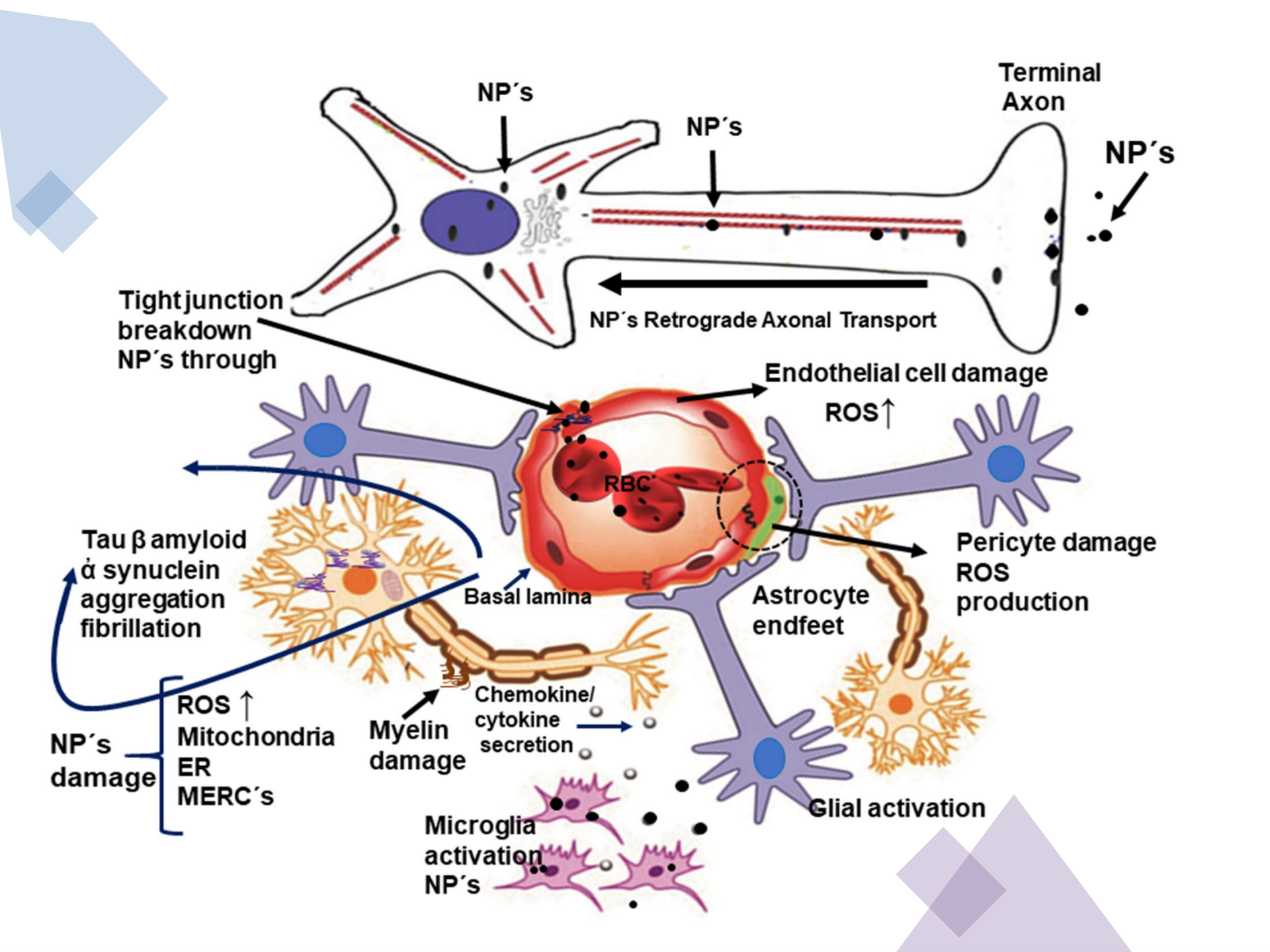
Alzheimer and Parkinson's diseases, Fronto-temporal dementia and ALS.

To date, NPs remain an underexplored environmental toxicant in the development of common neurodegenerative diseases.

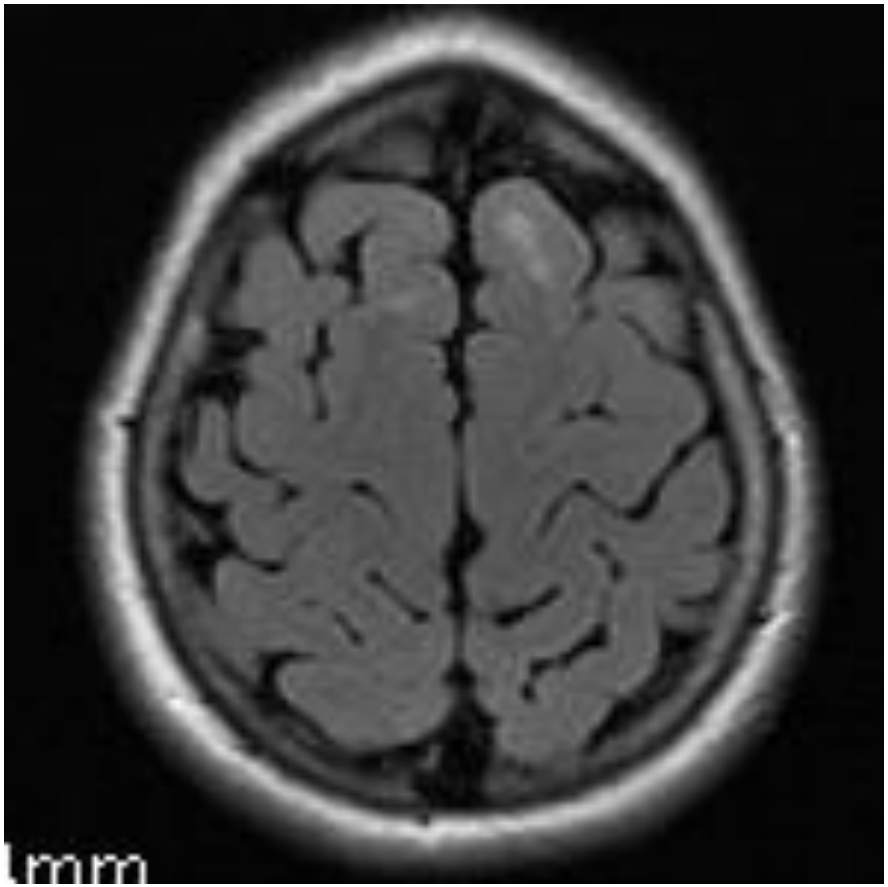
Environmental NPs and body distribution

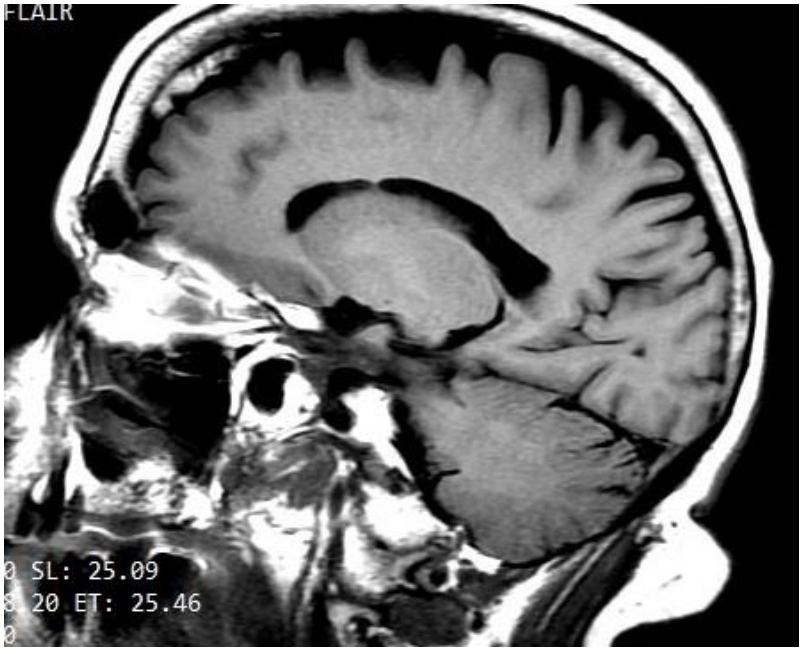
For health purposes, it is critical to understand entry routes and profiles of NPs capable of crossing different barriers. Toxic NPs are typically smaller, inorganic in nature and water insoluble and toxicity appears linked to exposure dose and frequency.

Neural damage and neuropathology could depend on NP characteristics, genetic susceptibility, comorbidities and the differential access and targets achieved via their portals of entry


NP´s
NP´s
Terminal Axon
NP´s
NP´s Retrograde Axonal Transport
Tight junction breakdown NP´s through
Endothelial cell damage
ROS↑
RBC
Pericyte damage ROS production
Tau β amyloid ά synuclein aggregation fibrillation
Basal lamina
Astrocyte endfeet
ROS ↑ Mitochondria ER MERC´s
NP´s damage
Myelin damage
Chemokine/ cytokine secretion
Glial activation
Microglia activation NP´s

Human Brains exposed to NPs





45Y FEMALE, MoCA 21

10y old boy, IQ 111, several targeted cognitive deficits

NANOPARTICLES

We need to characterize UFP exposures in urban populations

We desperately need to quantify and characterize NPs concentrations, composition, size, shape and location in neural cells in specific brain target areas in exposed individuals.

We need working hypothesis establishing the association between nanoparticles and neuropathology hallmarks taking into account there is considerable overlap between misfolded protein pathologies.

We need support from multidisciplinary groups and resources to do the research.

Highly polluted city exposures consequences

1. OLFACTORY DEFICITS
2. COGNITIVE DEFICITS
3. VESTIBULAR AND AUDITORY ALTERATIONS
4. SYSTEMIC INFLAMMATION
5. BRAIN INFLAMMATION
6. HEART INFLAMMATION
7. RESPIRATORY AND CARDIOVASCULAR MORBILITY AND MORTALITY
8. **NEURODEGENERATIVE DISEASES INCLUDING Alzheimer and Parkinson**

- **Etc., etc., etc.,**

Detail of a Painting by Lilian Calderon-Garciduenas.

The girl in blue