Exposure to iron-rich air pollution nanoparticles: a specific risk to human brains and hearts?

Professor Barbara A. Maher
Lancaster Environment Centre
University of Lancaster
UK LA1 4YQ
B.MAHER@LANCASTER.AC.UK

Contributing colleagues

- Lancaster Environment Centre: Vassil Karloukovski, Tomasz Gonet
- Lancaster Biological Sciences: Jess Hammond, David Allsop

- Leeds University: Zabeada Aslam, Nanoscience and Nanotechnology Facility (LENNF)
- Oxford University: Imad Ahmed
- Internationally: Lilian Calderon-Garciduenas (Mexico, Montana), Angélica González-Maciel, Rafael Reynoso-Robles, Ricardo Torres-Jardón PhD (Mexico), Partha S. Mukherjee India)

Airborne Particulate Matter (PM)

- A ‘cocktail’ of organic (C-rich aerosols) +
- inorganic, primary & secondary components.
-
- Urban PM enriched in metals (Fe, Cu, Pb, Zn, Ba, Mn, Cd Cr)……and invariably, in ***magnetic PM***.

- Sources?
- Combustion, abrasion, corrosion – e.g. vehicle brake wear, exhausts, tyre wear, road dust……

NB. ~10% of solid PM = *iron-rich, strongly magnetic nanoparticles (< 100 nm)*

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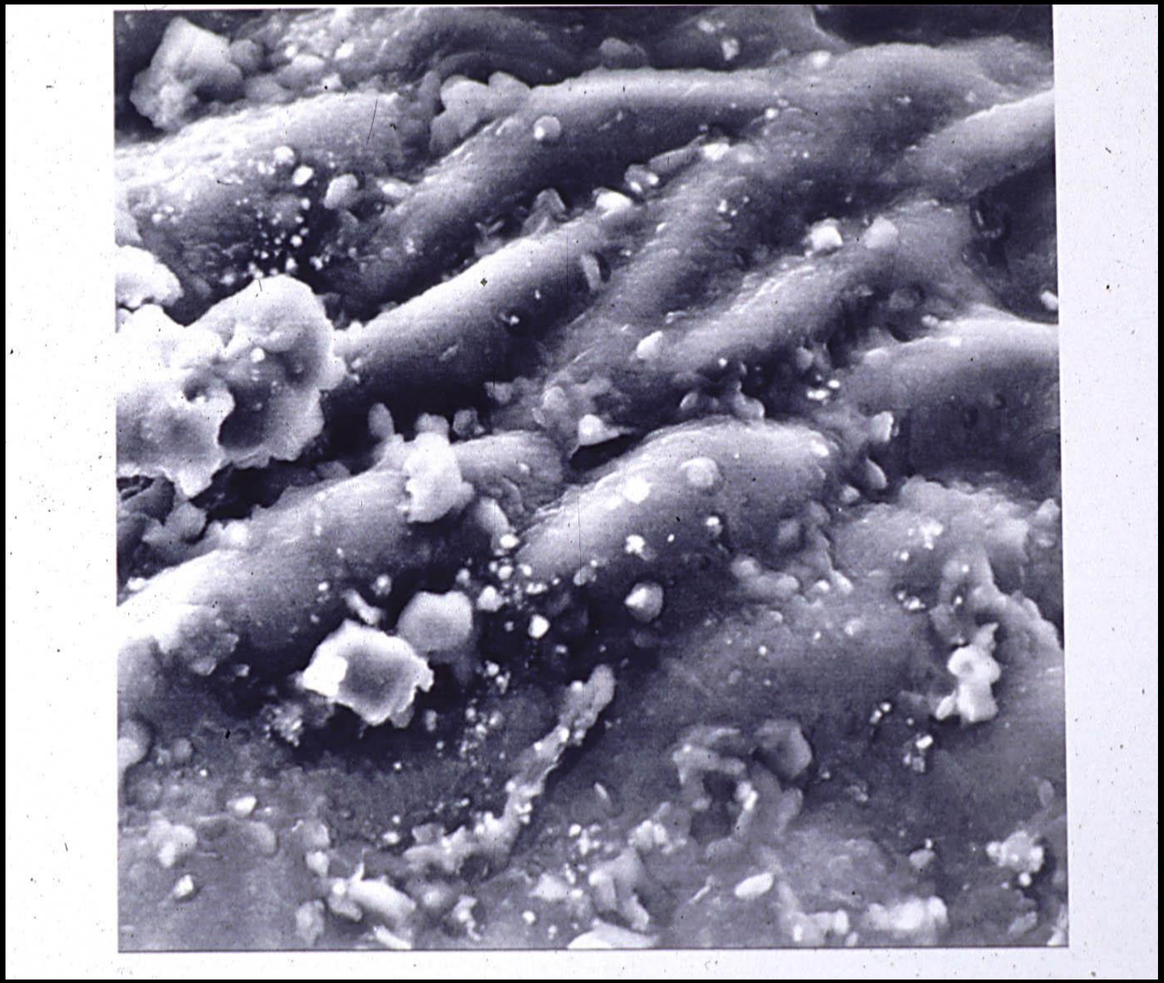
Air pollution particles on roadside birch leaf
(Norwich, UK, scanning electron micrograph, micrograph width = 60 µm)



Magnetic content and Pb, leaf-deposited PM (roadside, Norwich, UK)

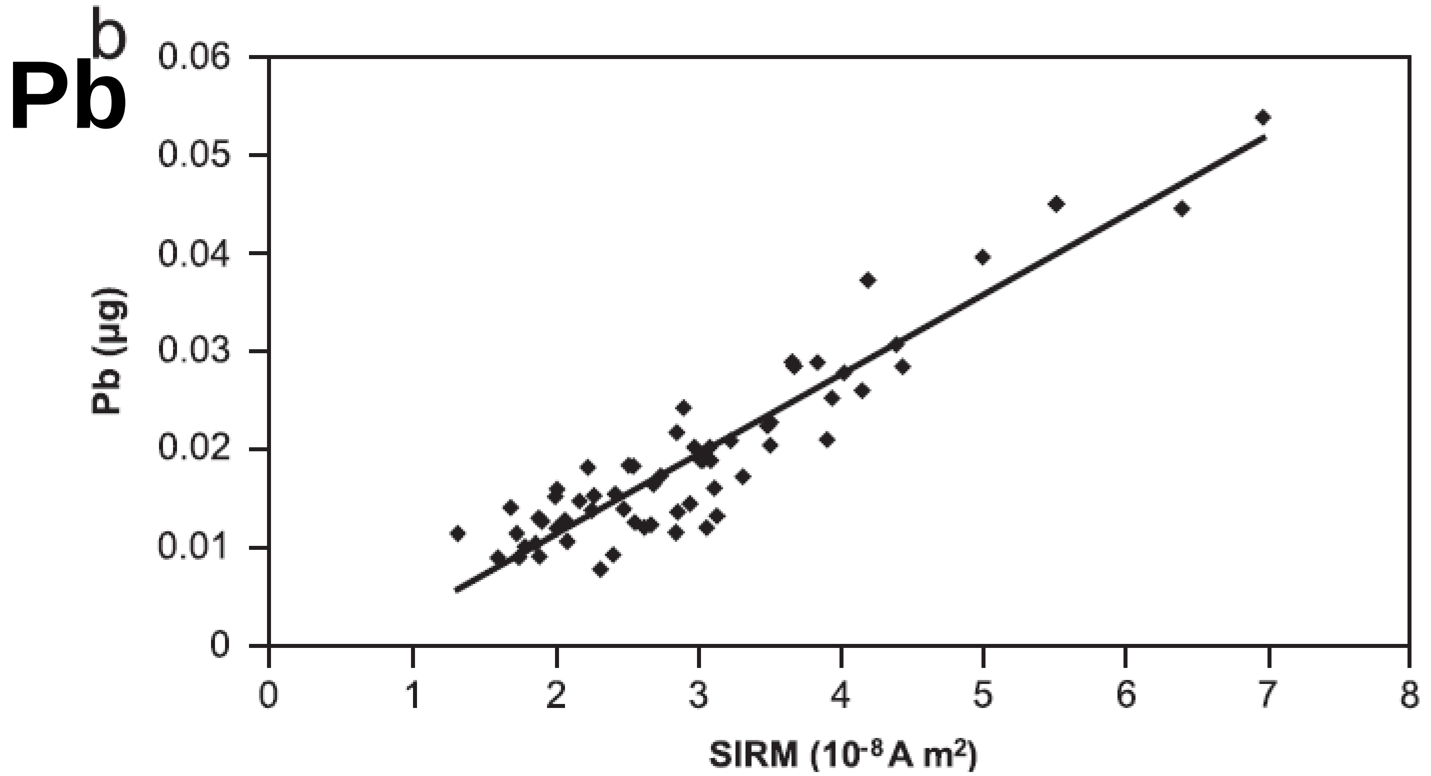
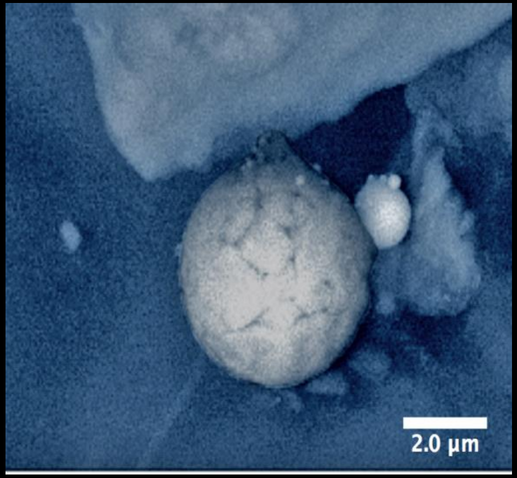
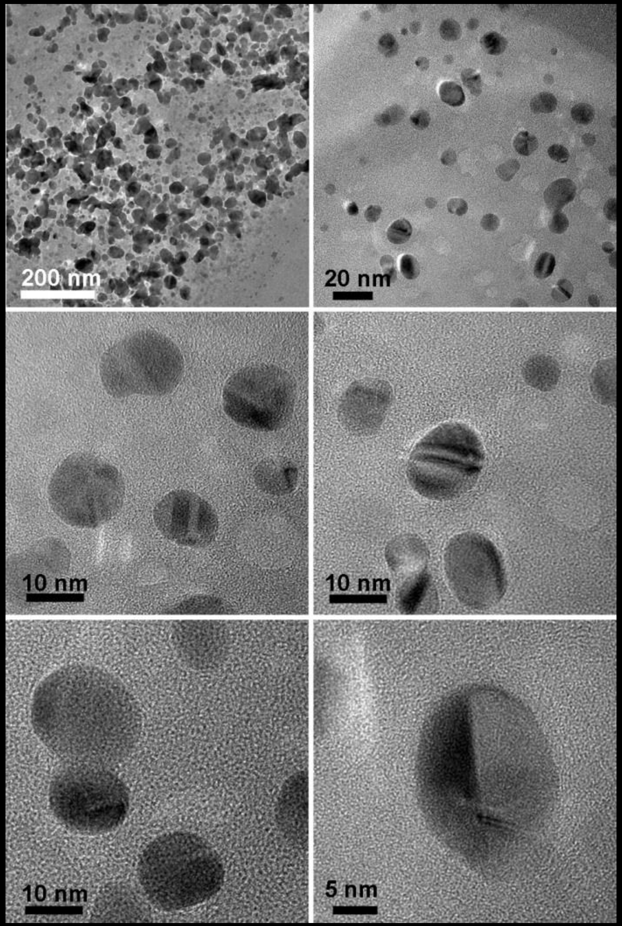


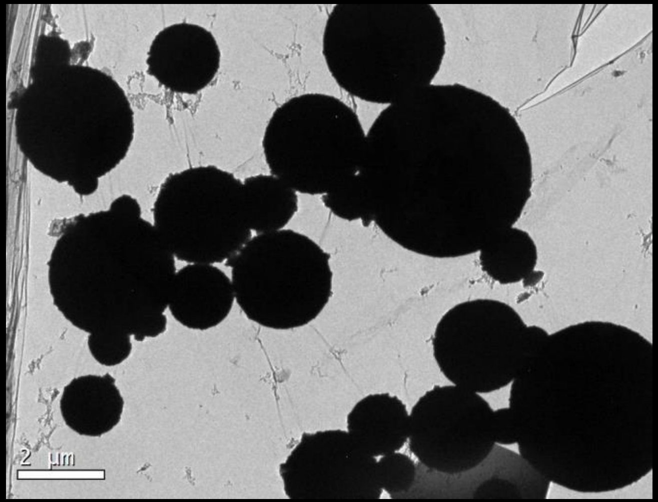
Fig. 3. Correlations between leaf particulate metal concentrations and SIRM, Grapes Hill, Norwich: (a) all analysed metals ($n = 40$, shaded boxes with significance <0.05) and (b) Pb concentration and SIRM ($n = 40$, $p \leqslant 0.0005$).

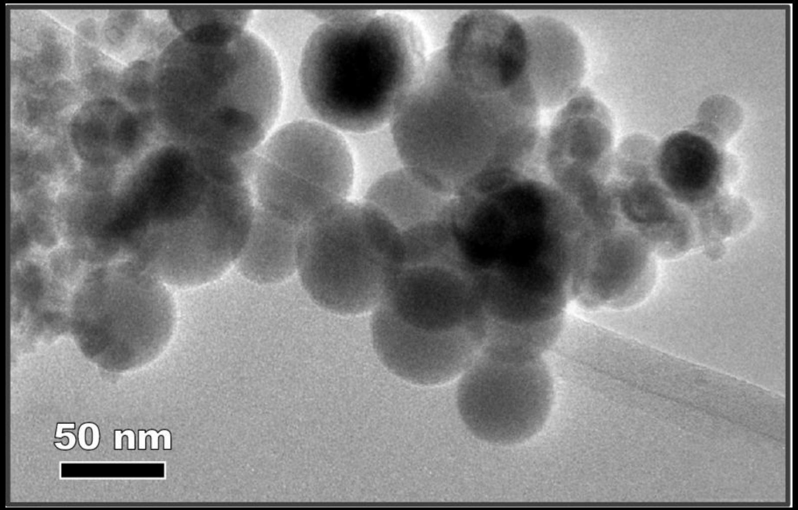
Iron-rich air pollution particles

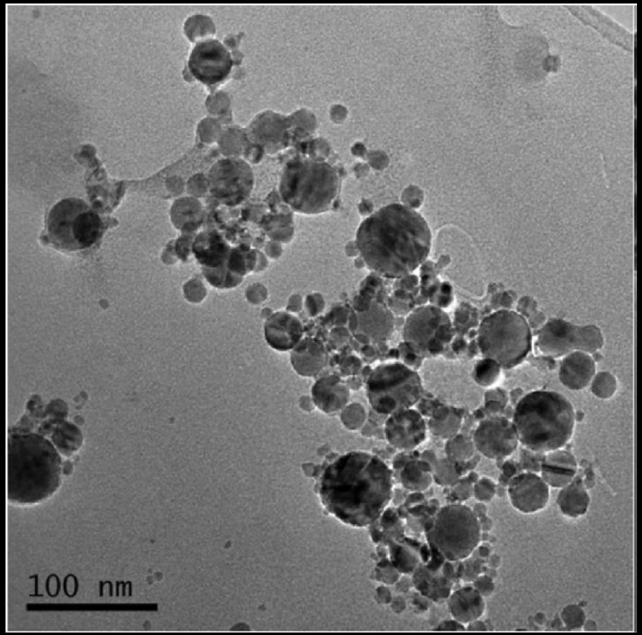
magnetite ‘nanospheres’ – ubiquitous and abundant in urban, airborne pollution.





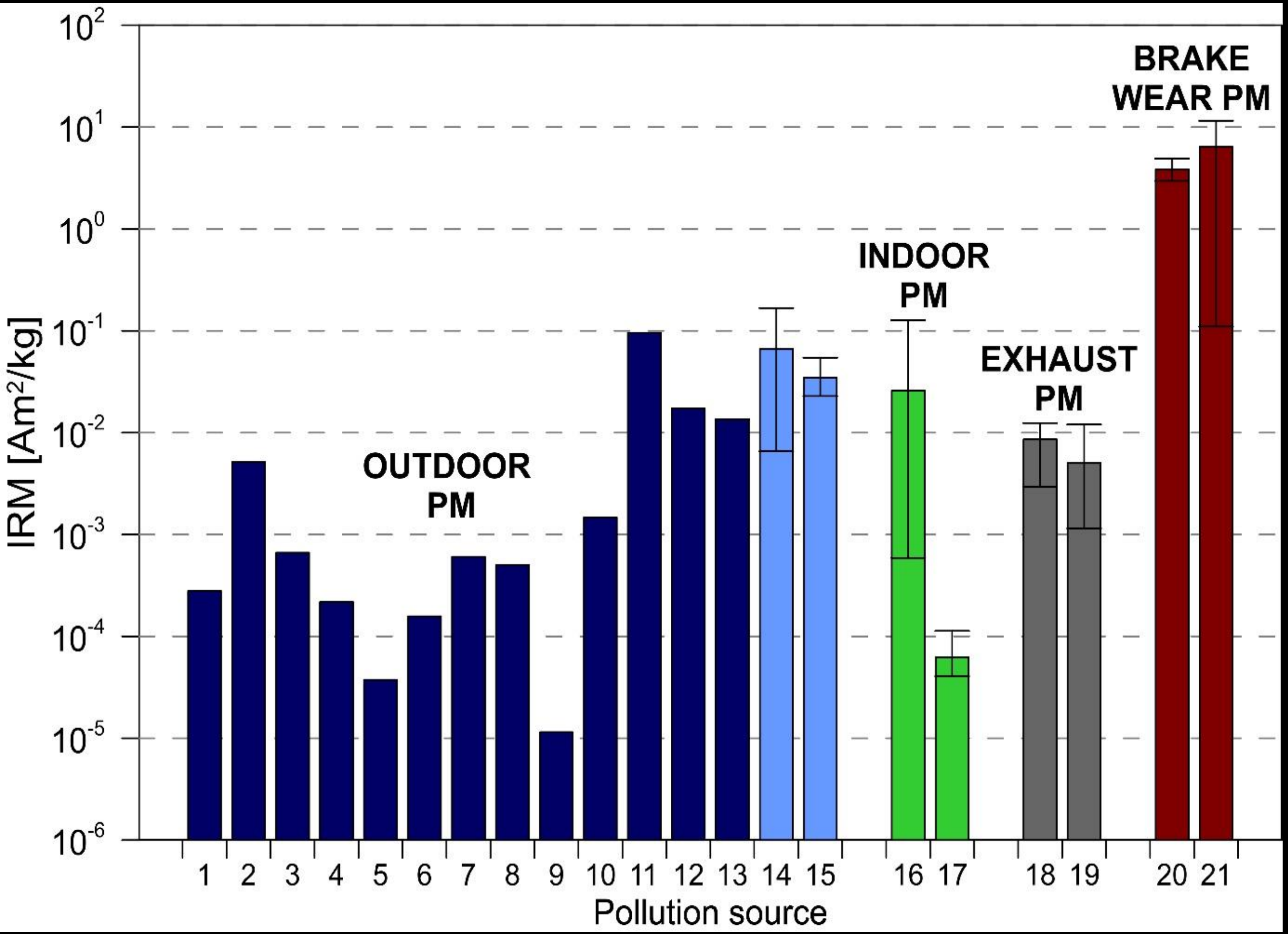




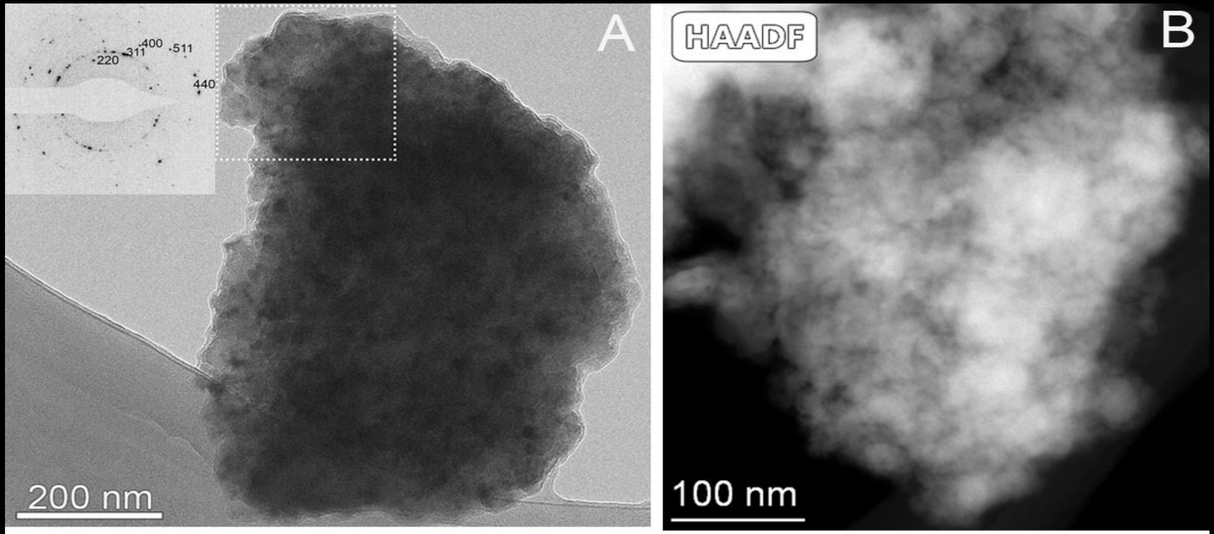


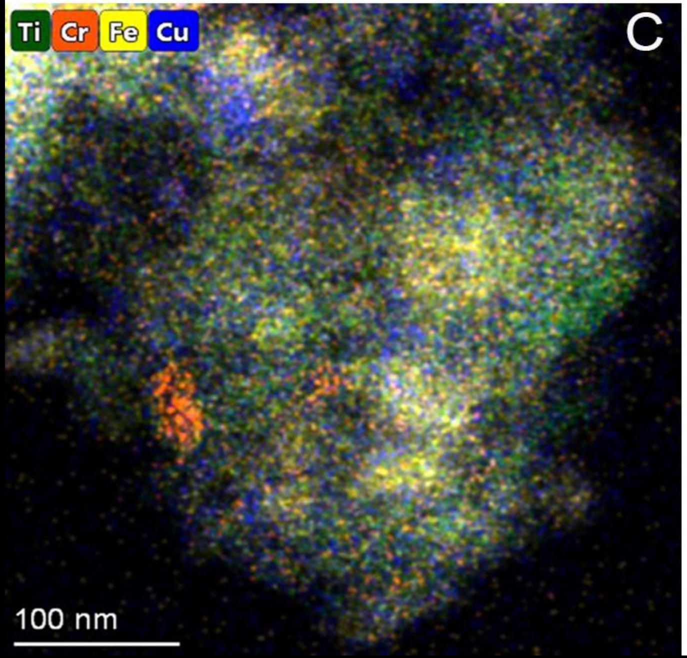
Magnetic content of PM from different sources

NOTE LOG SCALE!



CO-ASSOCIATION OF MAGNETITE WITH OTHER METAL SPECIES: BRAKEWEAR





Element	Atomic Fraction (%)	Atomic Error (%)
C	43	4.84
O	28.51	6.53
Mg	1.17	0.27
Si	1.82	0.41
S	1.73	0.38
Ti	1.86	0.32
Fe	16.61	2.88
Cu	5.29	0.92

(A) TEM of UFP agglomerate, & selected-area electron diffraction pattern corresponding to an ensemble of randomly oriented magnetite nanocrystals; (B) high-angle annular dark-field (HAADF) image of UFP agglomerate from stage 10 (～1.6 µm) and (C) its EDS elemental map, showing distributions of Cr, Fe, Cu and Ti, & composition of the entire agglomerate.

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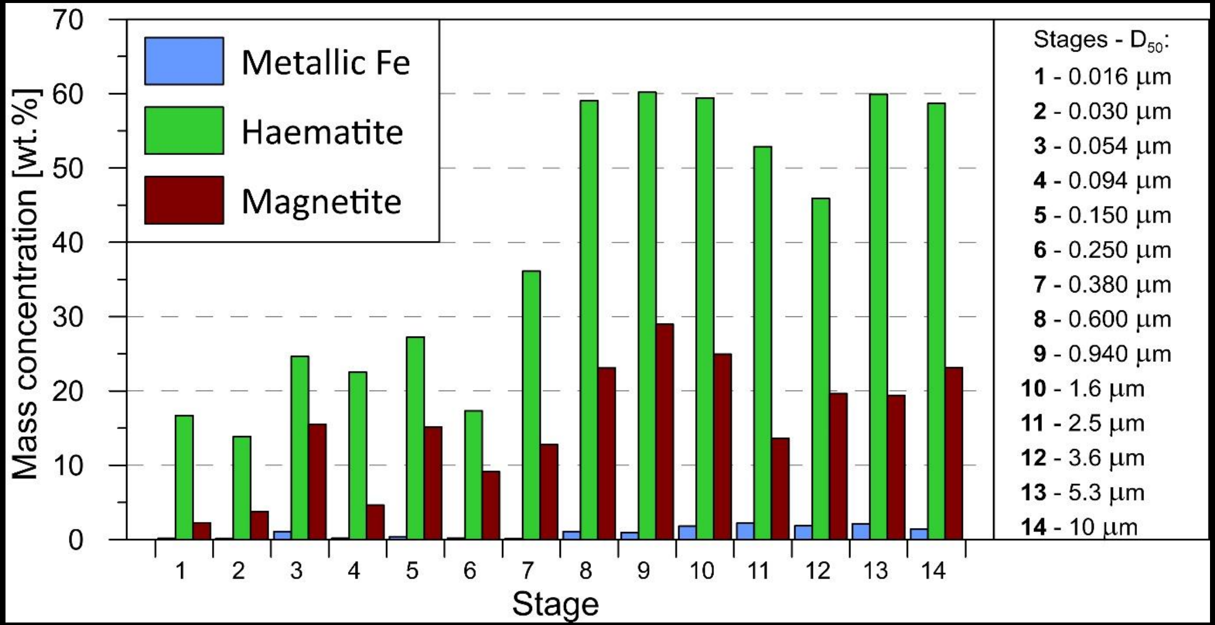
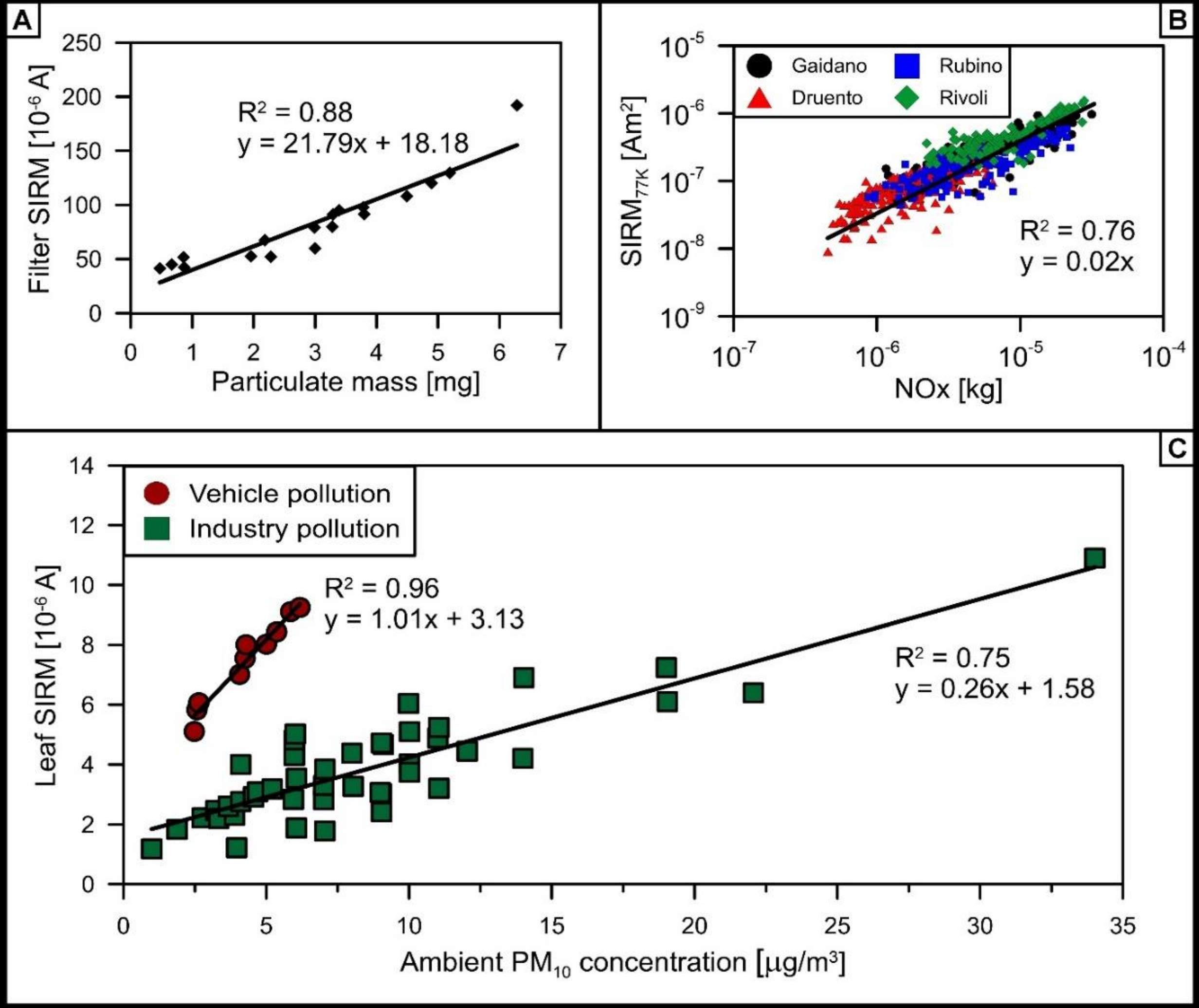
MAGNETITE, HAEMATITE & METALLIC FE IN BRAKEWEAR PM

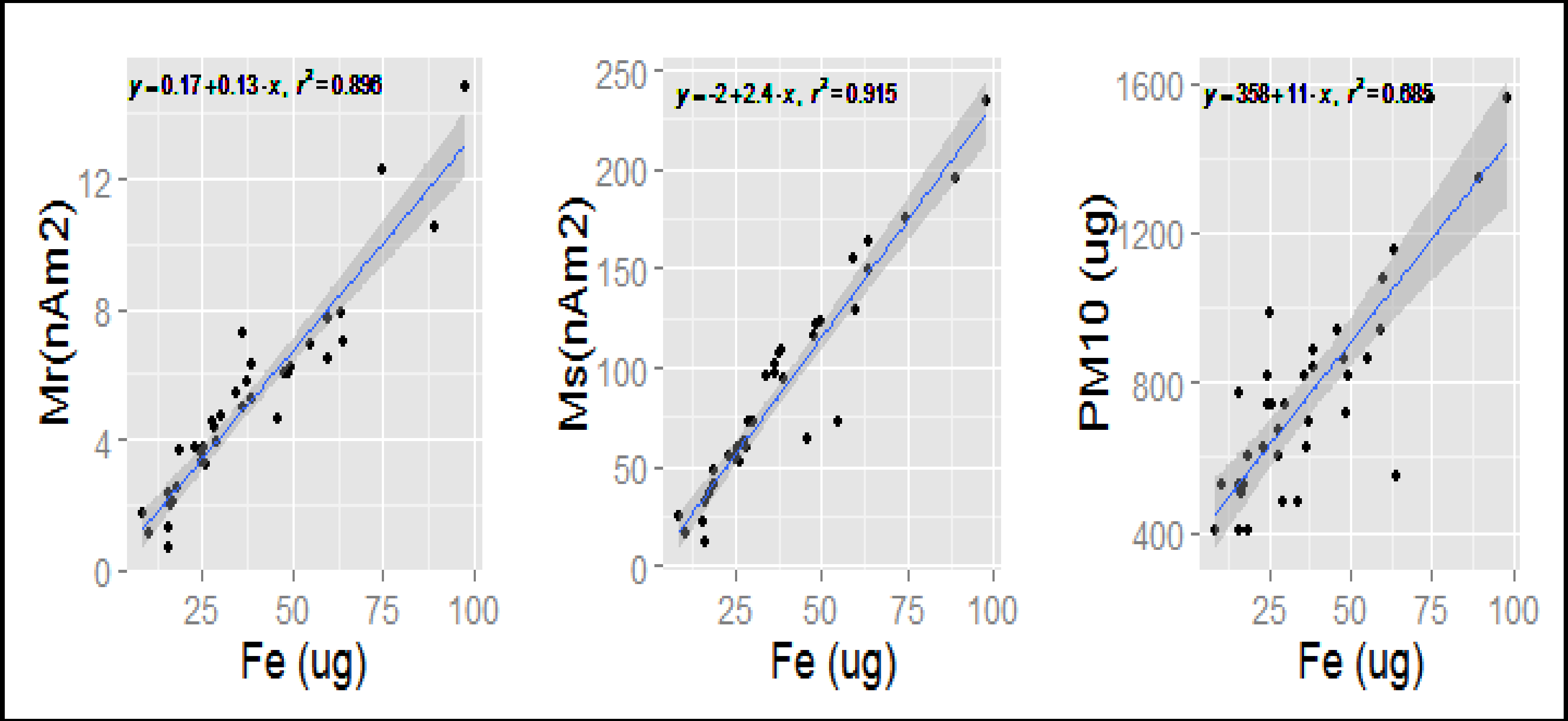


Mass concentration (wt.%) of metallic Fe, magnetite and haematite in dynamometer-derived, size-fractionated particulate brake emissions, estimated from magnetic component analysis. Gonet et al., 2021

Magnetic content OF AIR POLLUTION correlates with e.g. PM mass, NOx content…



Magnetic properties of PM, Marylebone Road, London, U.K.



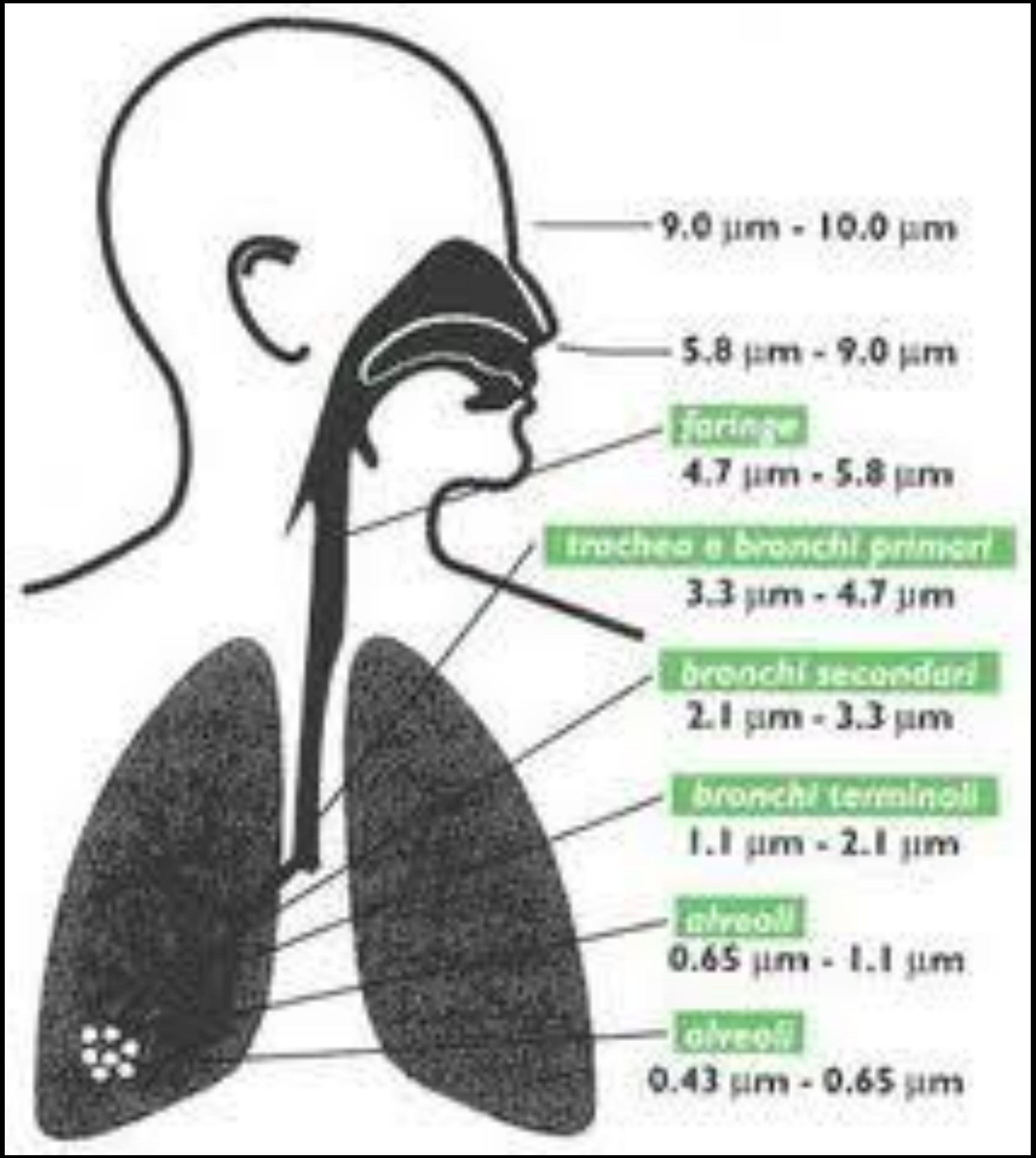
Potential health significance of *iron-rich* air pollution particles?

- Iron-bearing particles often *the most abundant composition* of the solid (non-volatile) urban PM.

- Iron is an essential element in all human tissues, especially the brain…….BUT toxic when not safely stored/transported/ regulated.

- Causes excess formation of damaging reactive oxygen species:
- $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH + HO\cdot$

Of course, not just particle composition but *particle size* important…



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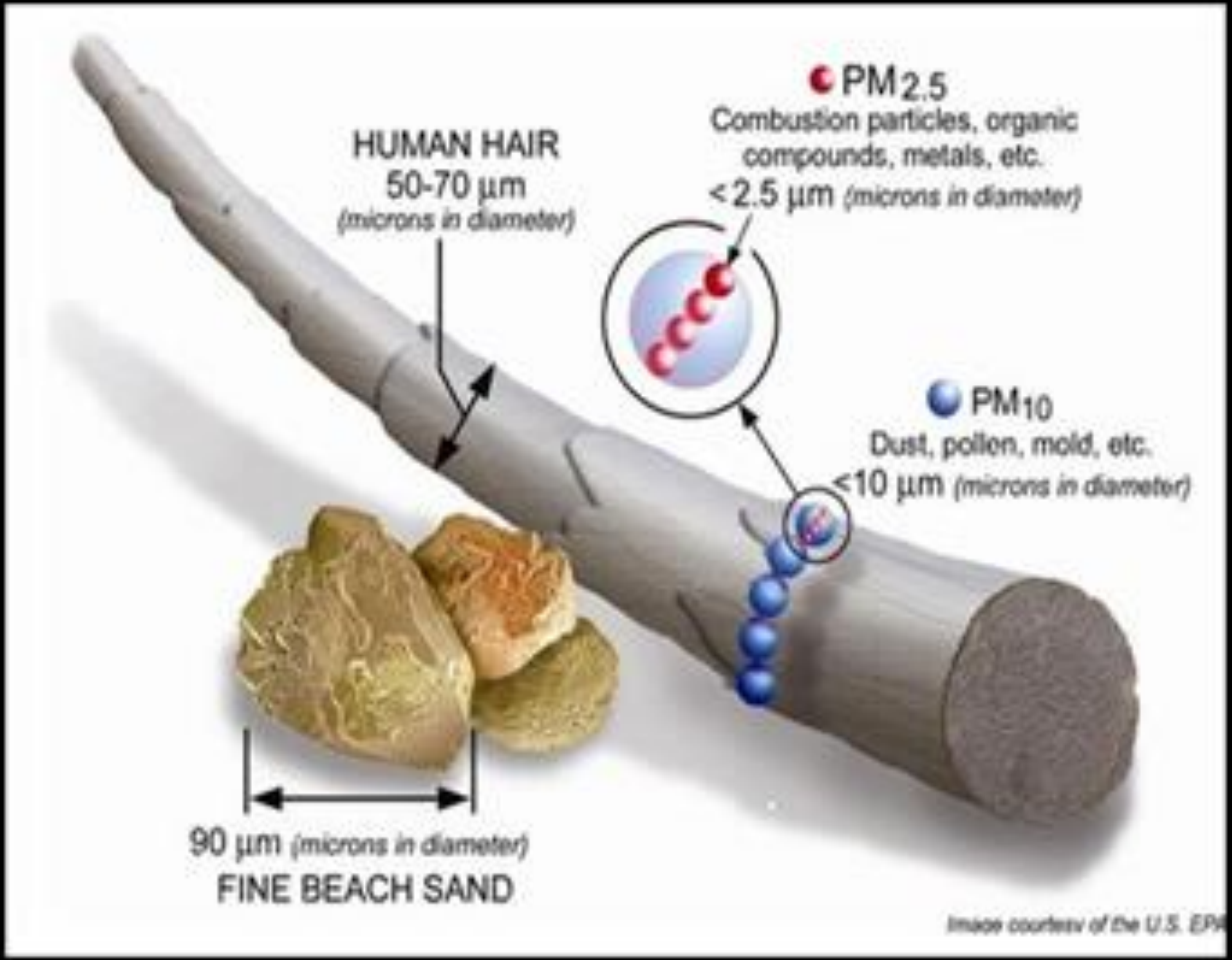

BUT WHAT ABOUT THE NANOPARTICLES?

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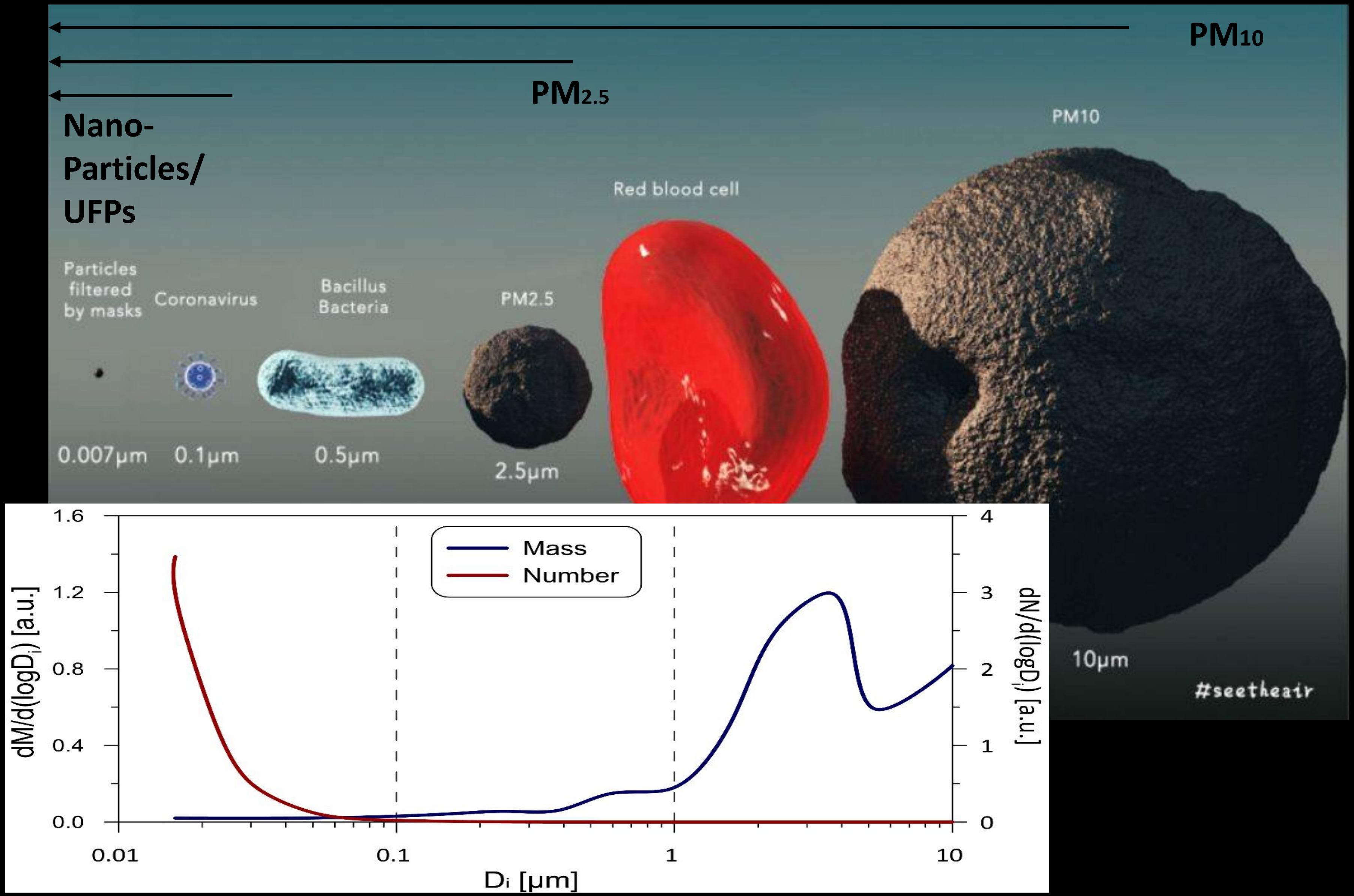
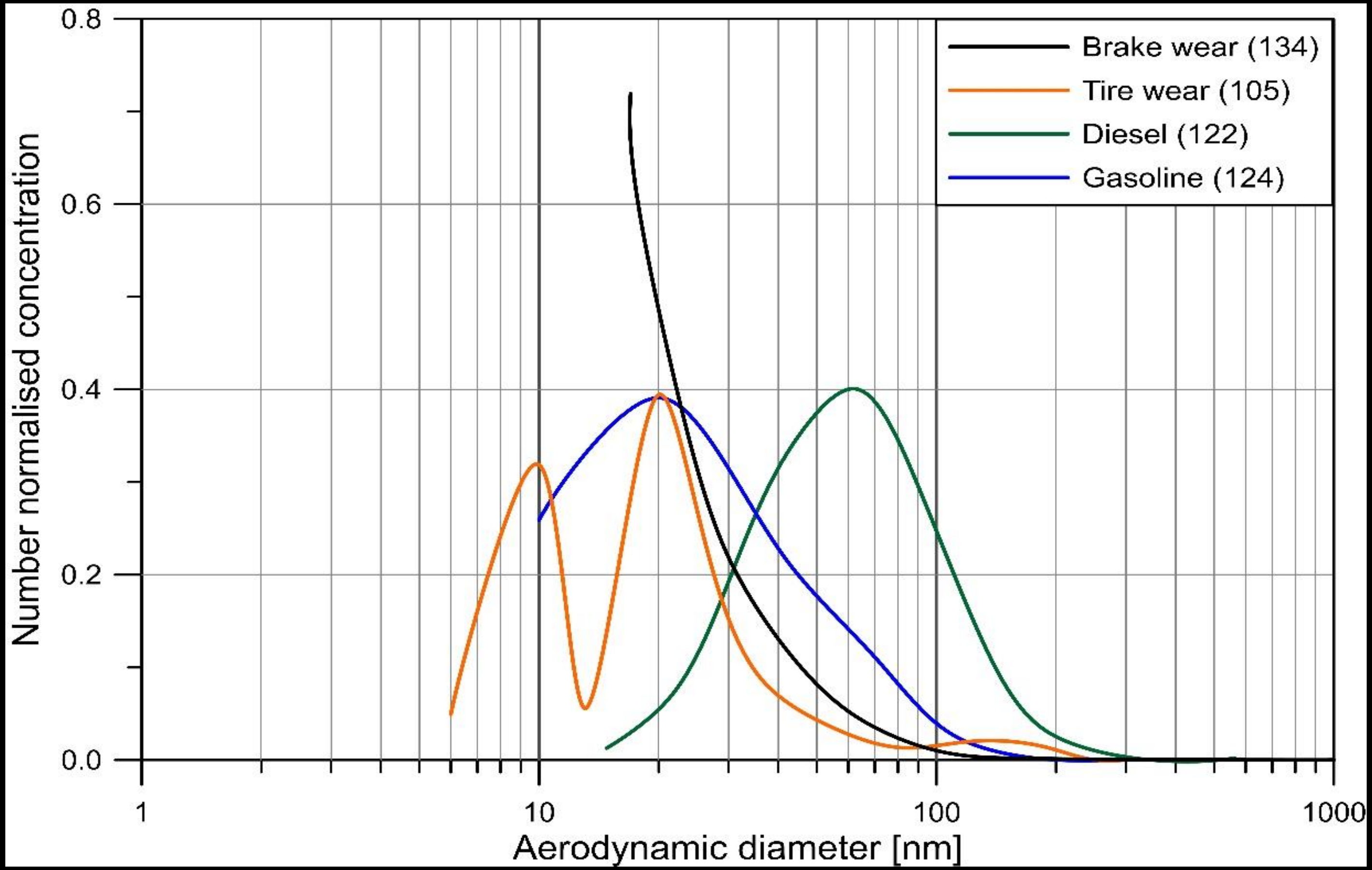
N.B. NANOPARTICLE *NUMBERS* VS PARTICLE *MASS*



Most traffic-derived air pollution particles are nanoparticles



Airborne Particulate Matter (PM) and neurodegenerative disease?

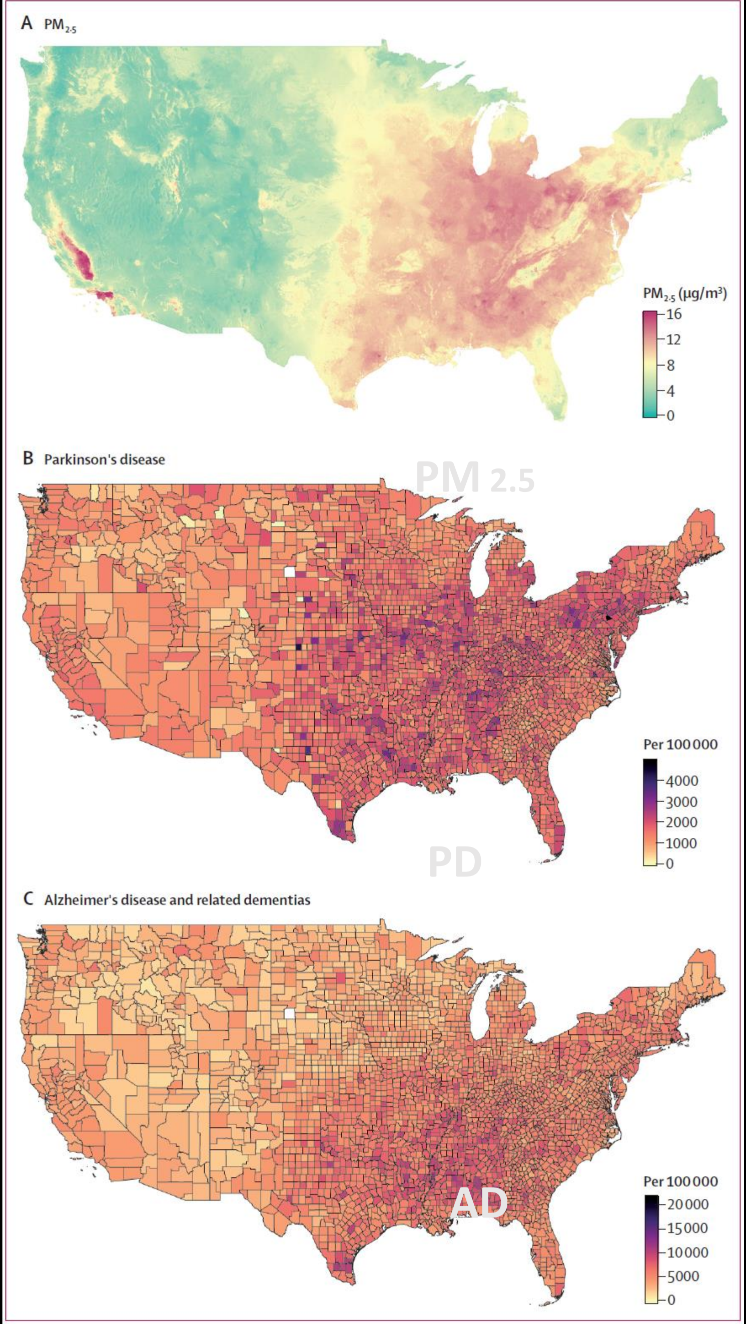


Figure 1: Nationwide concentrations of $PM_{2.5}$, and occurrences of Parkinson's disease and Alzheimer's disease and related dementias across the contiguous United States
(A) 17-year mean of annual $PM_{2.5}$ concentrations (μg/m³). (B) Occurrence of first Parkinson's disease hospital admissions per 100 000 Medicare beneficiaries. (C) Occurrence of first Alzheimer's disease and related dementias hospital admissions per 100 000 Medicare beneficiaries (2000–16).

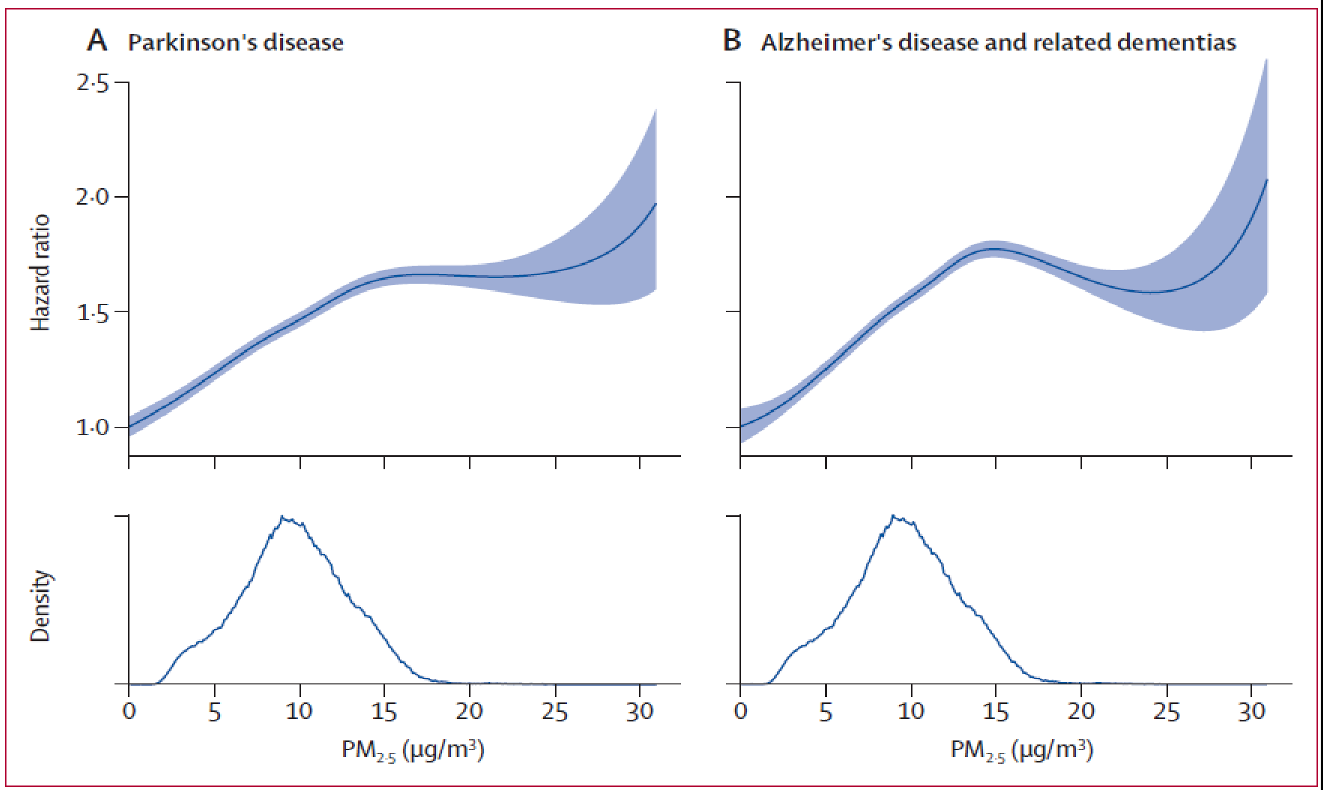


Figure 2: Concentration–response curves of the association between long-term $PM_{2.5}$ exposure and neurological disorders

Shi et al., October 19, 2020 https://doi.org/10.1016/S2542-5196(20)30227-8

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The Lancet Jan 2017

Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study

Hong Chen, Jeffrey C Kwong, Ray Copes, Karen Tu, Paul J Villeneuve, Aaron van Donkelaar, Perry Hystad, Randall V Martin, Brian J Murray, Barry Jessiman, Andrew S Wilton, Alexander Kopp, Richard T Burnett

centres and those who never moved. Although the increase in risk might appear moderate (eg, HRs varied from 1·07–1·12 for living <50 m away from a major road, depending on the region), this translates to 7–11% of dementia cases in patients who live near major roads attributable to traffic exposure (appendix). The associations

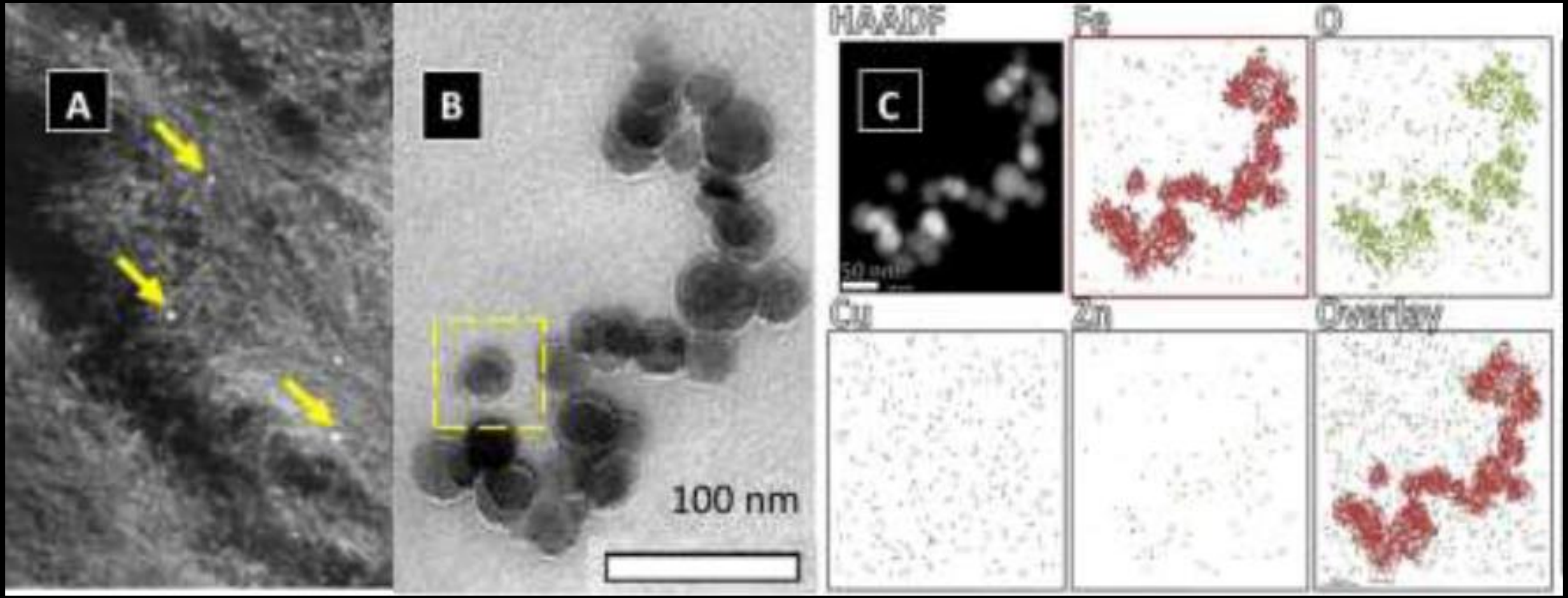
MAGNETITE AND ALZHEIMER’S DISEASE (AD)?

- Fe concentration in AD plaques (~1 mmoL L-1) is higher than in normal brain tissue (~0.35 mmol L-1)

- Fe^{2+} an effective catalyst for production of damaging reactive oxygen species (incl. free radicals) in brain tissues.

- Magnetite particles found directly associated with AD plaques; may enhance toxicity of the plaque-forming protein, β-amyloid.

Magnetite found directly associated with Alzheimer's disease plaques



Plascencia-Villa et al., Nature SciReps, 2016

METALLIC FE & CU ALSO FOUND IN AMYLOID PLAQUES FROM HUMAN BRAINS

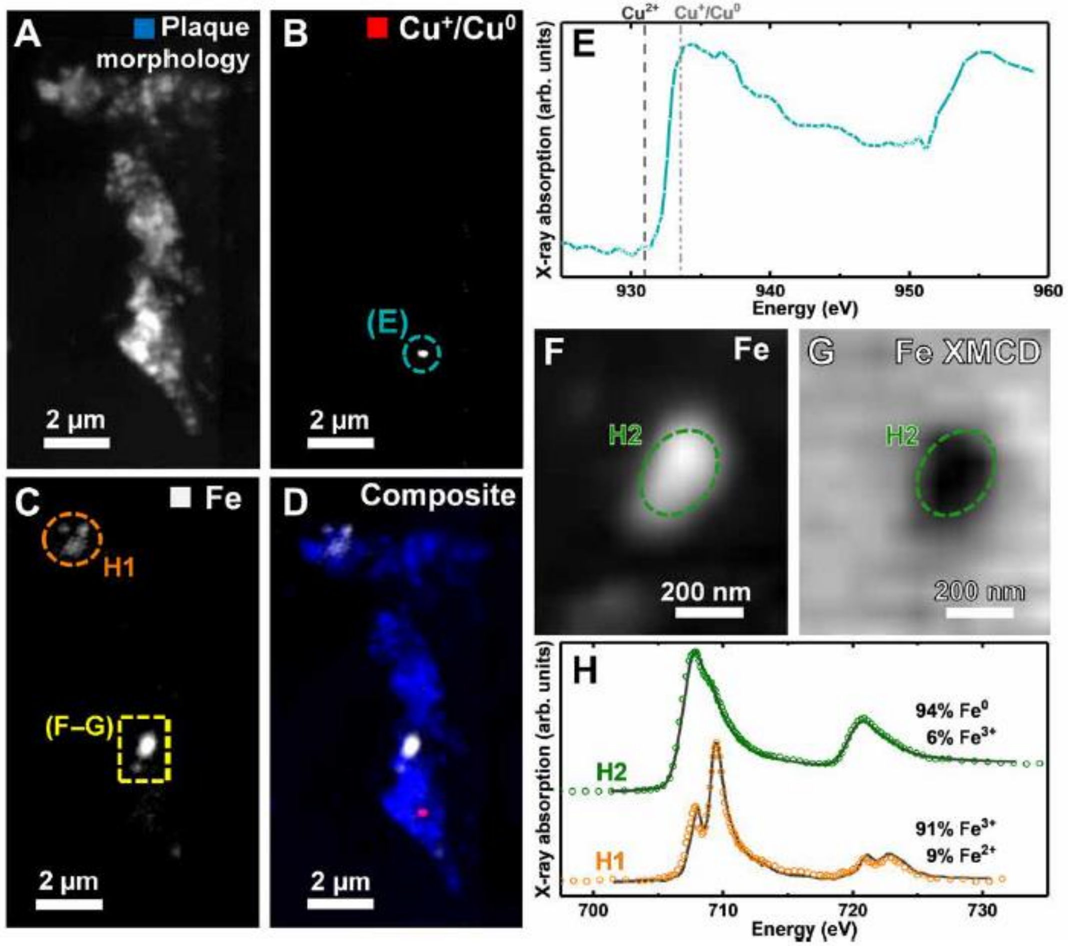


Fig. 3. STXM images, metal maps, and copper and iron x-ray absorption spectra from a subject X amyloid plaque core. (**A**) Overall plaque morphology. (**B**) Cu^{+}/Cu^{0} map. (**C**) Iron map. (**D**) Composite STXM image showing plaque morphology (blue), Cu^{+}/Cu^{0} (red), and iron (gray) content. (**E**) Copper x-ray absorption spectrum from the copper deposit highlighted in (B). The energies corresponding to Cu^{2+} and Cu^{+}/Cu^{0} content are shown by the dashed and dotted-dashed lines, respectively. (**F**) High-resolution iron map and (**G**) iron XMCD map from the region highlighted in yellow in (C). In the XMCD map, areas of bright and dark contrast represent the presence of magnetic iron. (**H**) Iron x-ray absorption spectra from the iron deposits highlighted in (C), (F), and (G).

APPLIED SCIENCES AND ENGINEERING

Biogenic metallic elements in the human brain?

James Everett[1,2], Frederik Lermyte[2,3], Jake Brooks[2], Vindy Tjendana-Tjhin[2], Germán Plascencia-Villa[4], Ian Hands-Portman[5], Jane M. Donnelly[2], Kharmen Billimoria[2,6,7], George Perry[4], Xiongwei Zhu[8], Peter J. Sadler[6], Peter B. O'Connor[6], Joanna F. Collingwood[2], Neil D. Telling[1]*

The chemistry of copper and iron plays a critical role in normal brain function. A variety of enzymes and proteins containing positively charged Cu^{+}, Cu^{2+}, Fe^{2+}, and Fe^{3+} control key processes, catalyzing oxidative metabolism and neurotransmitter and neuropeptide production. Here, we report the discovery of elemental (zero–oxidation state) metallic Cu^{0} accompanying ferromagnetic elemental Fe^{0} in the human brain. These nanoscale biometal deposits were identified within amyloid plaque cores isolated from Alzheimer's disease subjects, using synchrotron x-ray spectromicroscopy. The surfaces of nanodeposits of metallic copper and iron are highly reactive, with distinctly different chemical and magnetic properties from their predominant oxide counterparts. The discovery of metals in their elemental form in the brain raises new questions regarding their generation and their role in neurochemistry, neurobiology, and the etiology of neurodegenerative disease.

The unexpected identification of Cu^{0} and Fe^{0} within AD amyloid plaques suggests that biogenic metallic elements, previously observed only in microorganisms, viruses, and plants, can also occur in humans. The reactivity of these metallic phases differs from their metal oxide counterparts previously detected in the human brain and has the scope to redefine our understanding of metal neurochemistry and the role of metal toxicity in neurodegenerative diseases.

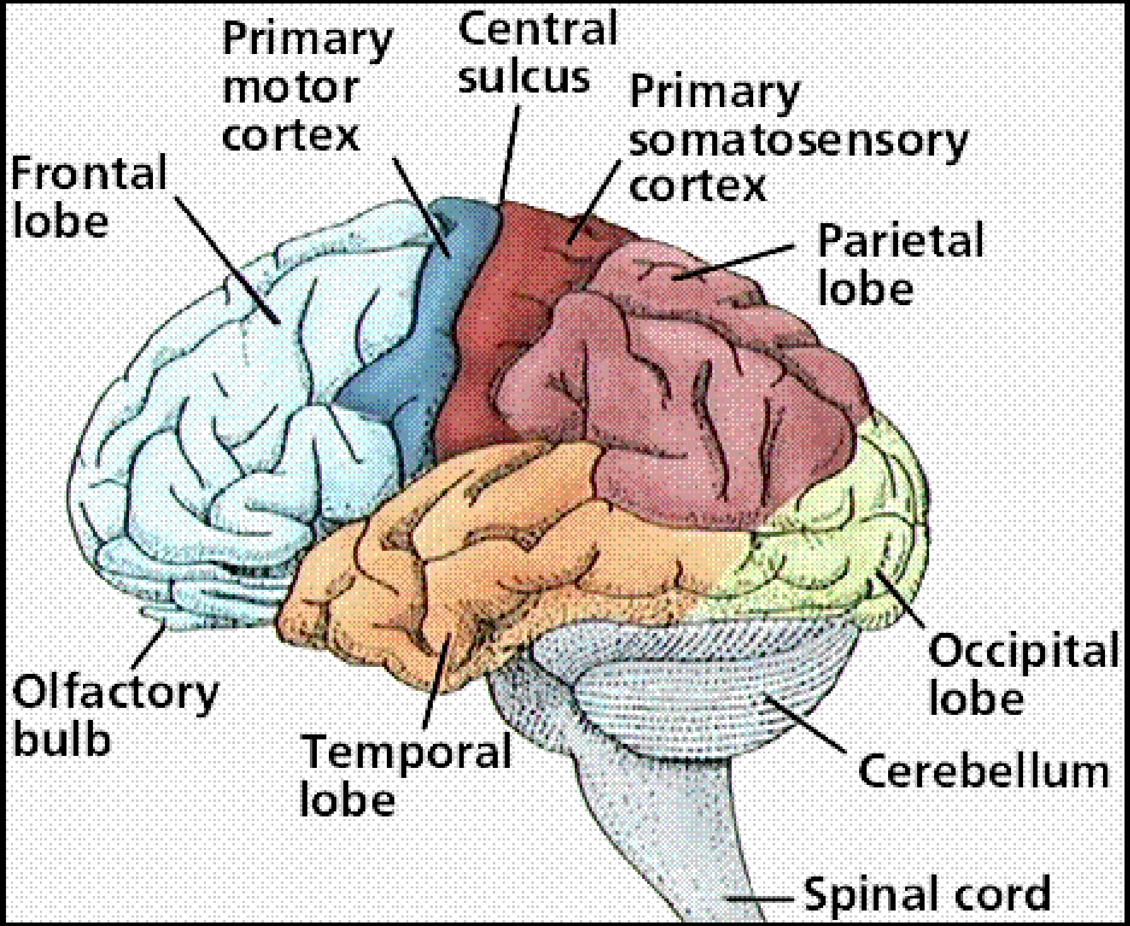
Existing paradigm?

- All brain magnetite/metallic Fe (and Cu) formed *in situ*, of biogenic, possibly pathological, origin...

NEW HYPOTHESIS

Brain contains varying concentrations of externally-sourced magnetite (and other Fe-bearing) pollution NPs, typically co-associated with range of other, including non-physiological, metal species (Maher et al., 2016)

Magnetic and HRTEM analyses, human brain samples



1. 'natural'/biogenic magnetite

WHO? WHY?

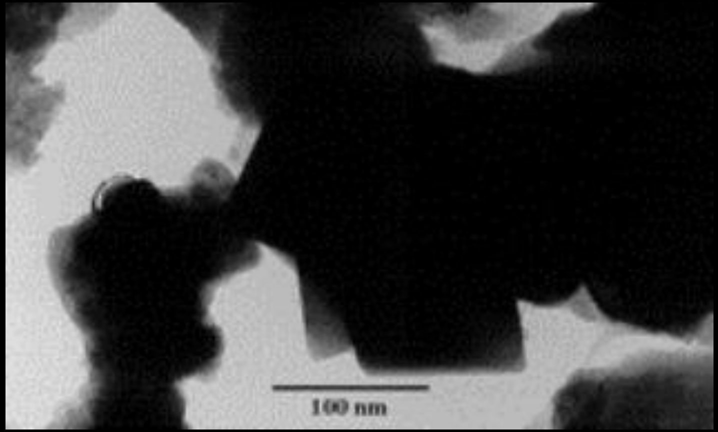
Proc. Natl. Acad. Sci. USA
Vol. 89, pp. 7683–7687, August 1992
Biophysics

Magnetite biomineralization in the human brain

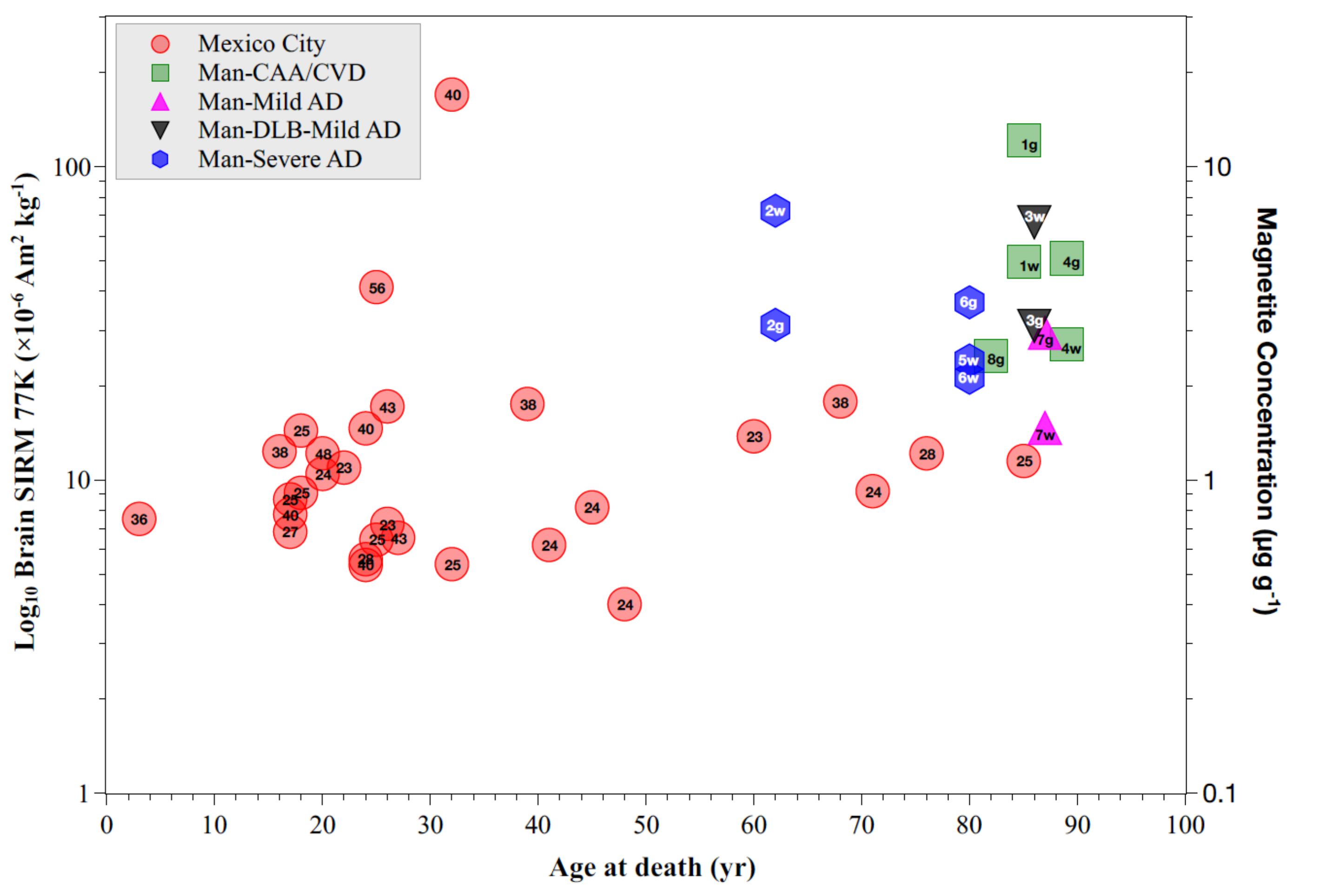
(iron/extremely low frequency magnetic fields)

Joseph L. Kirschvink, Atsuko Kobayashi-Kirschvink, and Barbara J. Woodford*

Division of Geological and Planetary Sciences, The California Institute of Technology, Pasadena, CA 91125

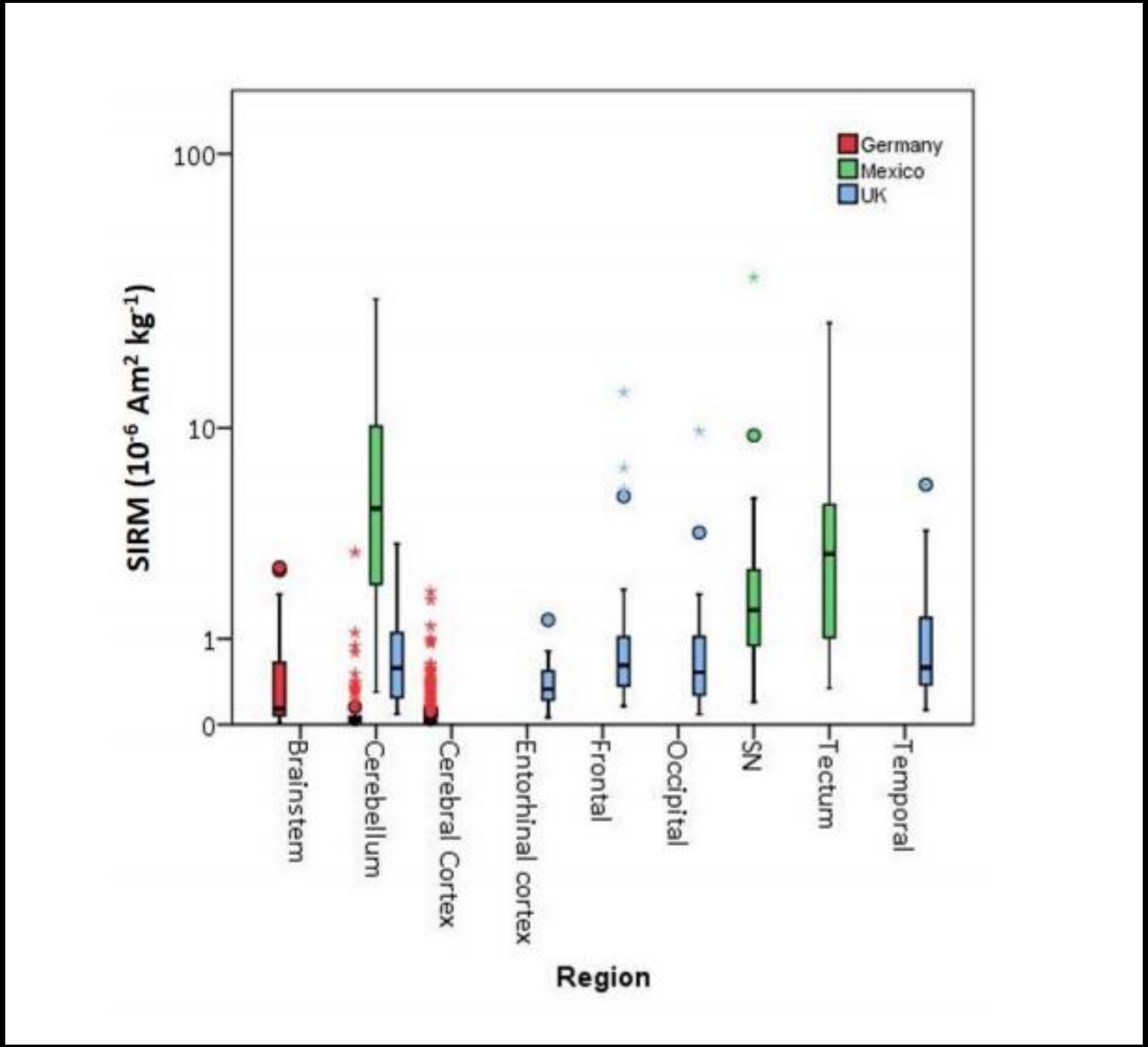


But 2. Brain magnetic content (SIRM, 77 K) vary by individual



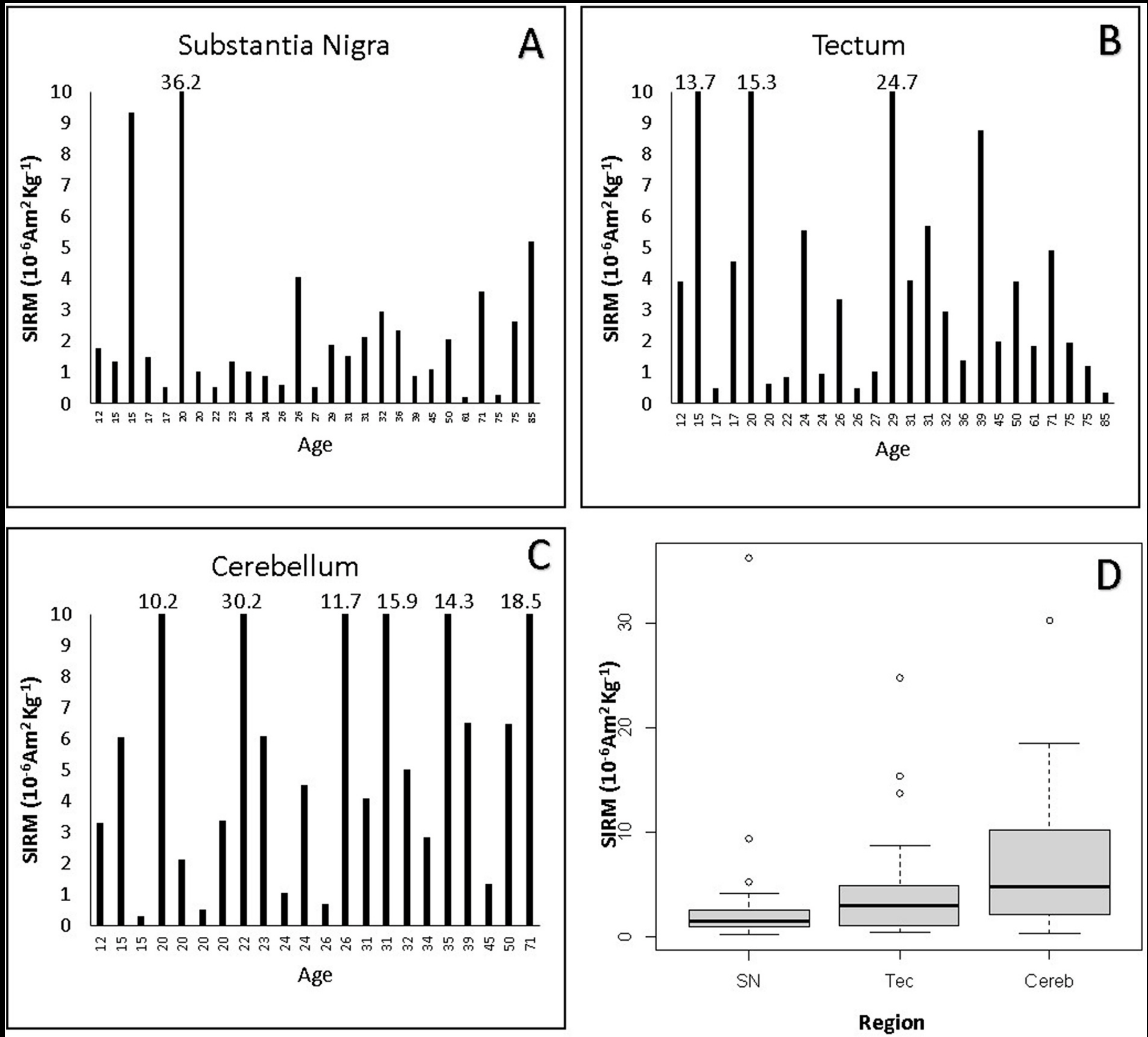
Many of the highly magnetic brain samples were from young (< 40 years at death) Mexico City residents exposed to high levels of airborne particulate pollution, & those with severe to moderate AD in the older Manchester cases (> 65 years at death).

MAGNETIC CONTENT BY BRAIN REGION AND GEOGRAPHIC SOURCE

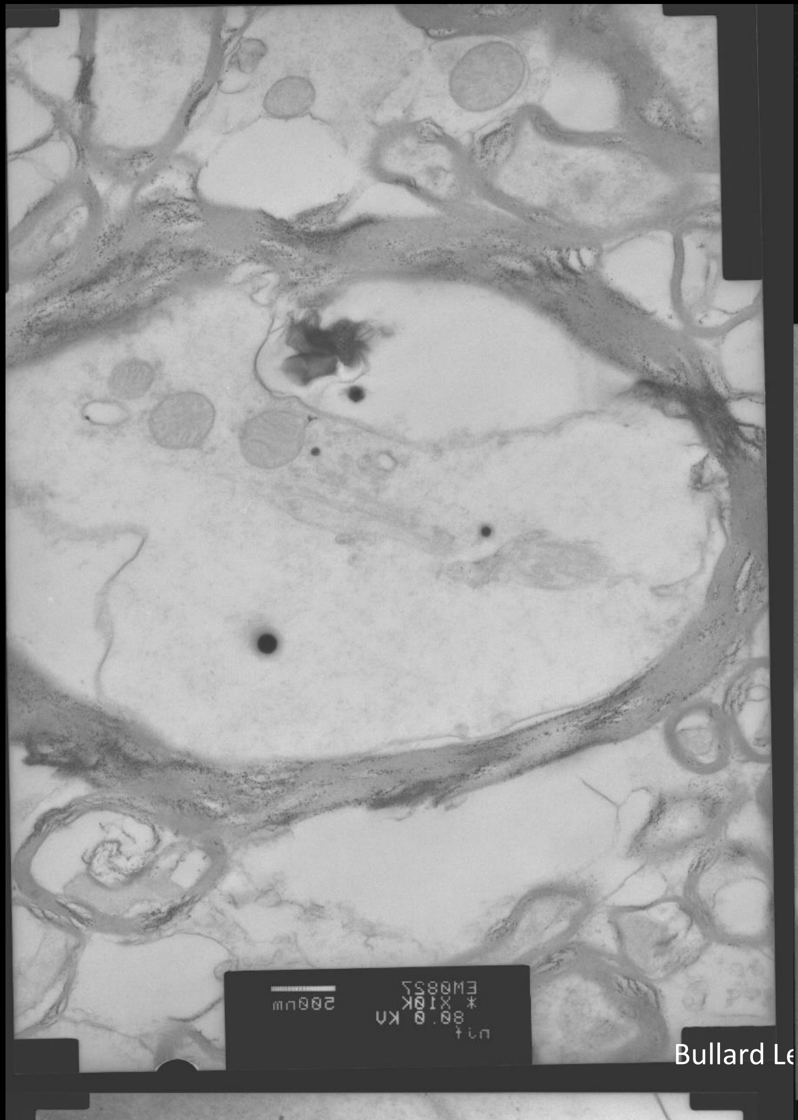


Hammond et al., 2020

Magnetic content (MMC)
by brain region

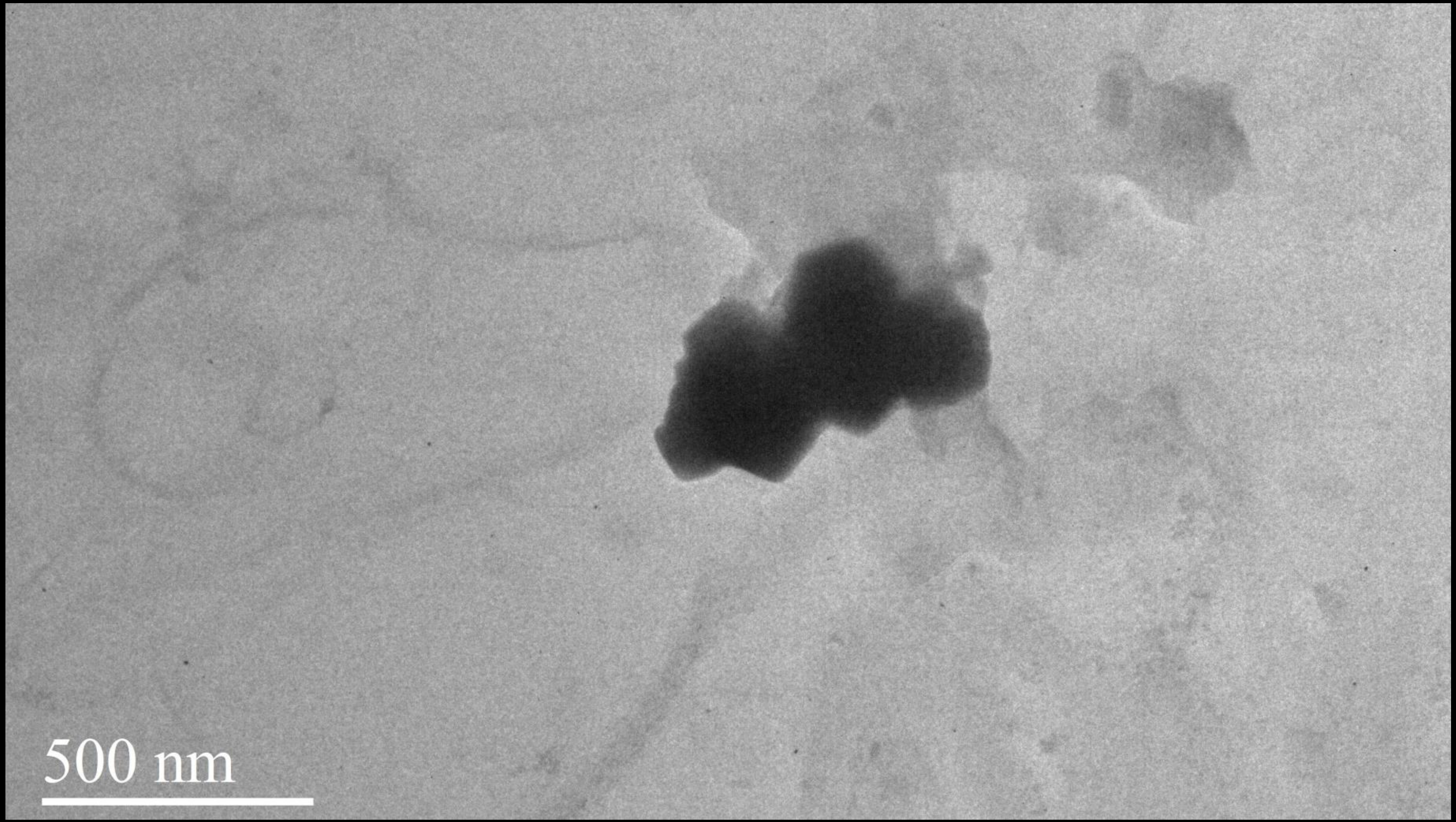


Electron microscopy, frontal cortex (possible olfactory portal of entry)

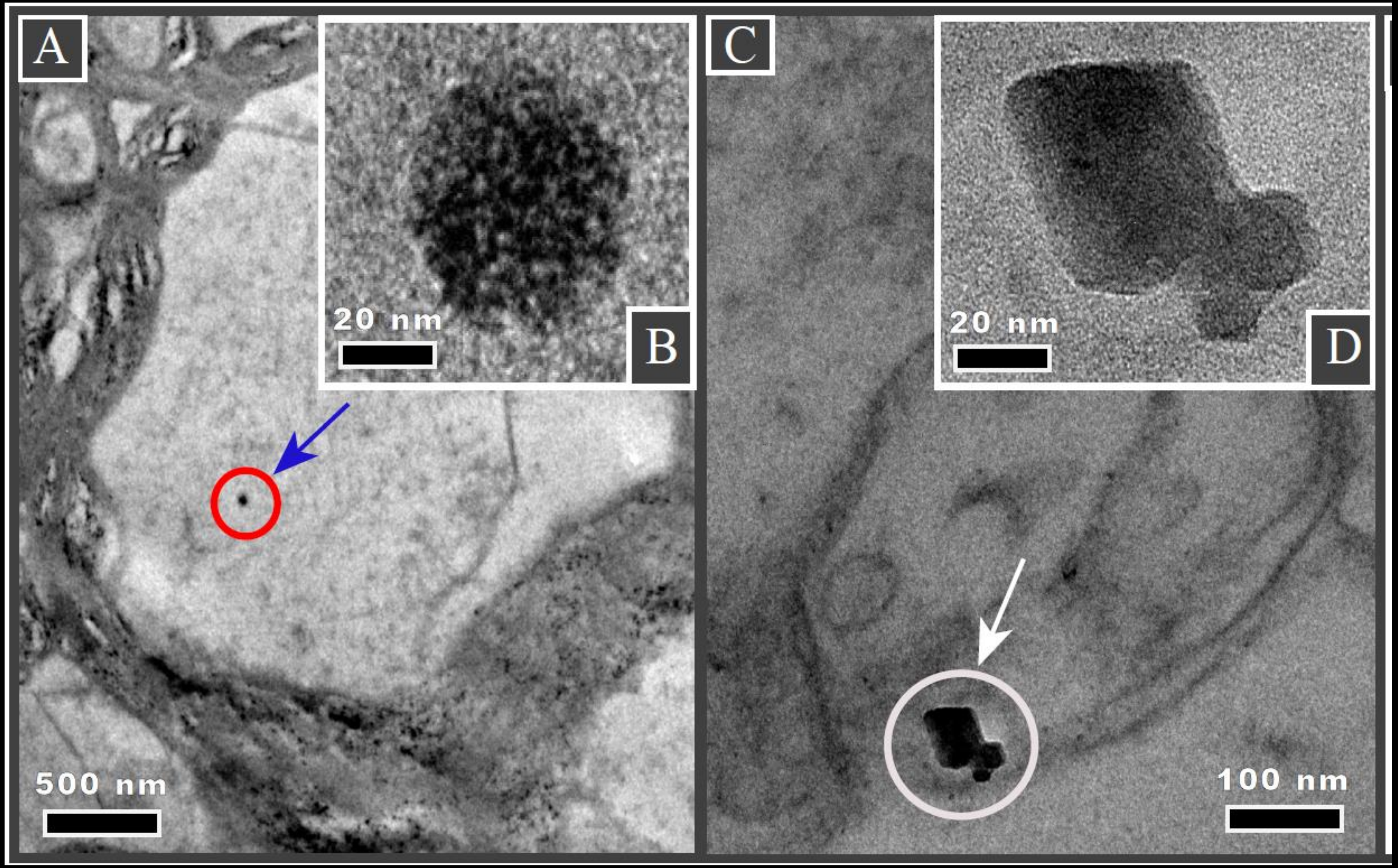


Bullard Le

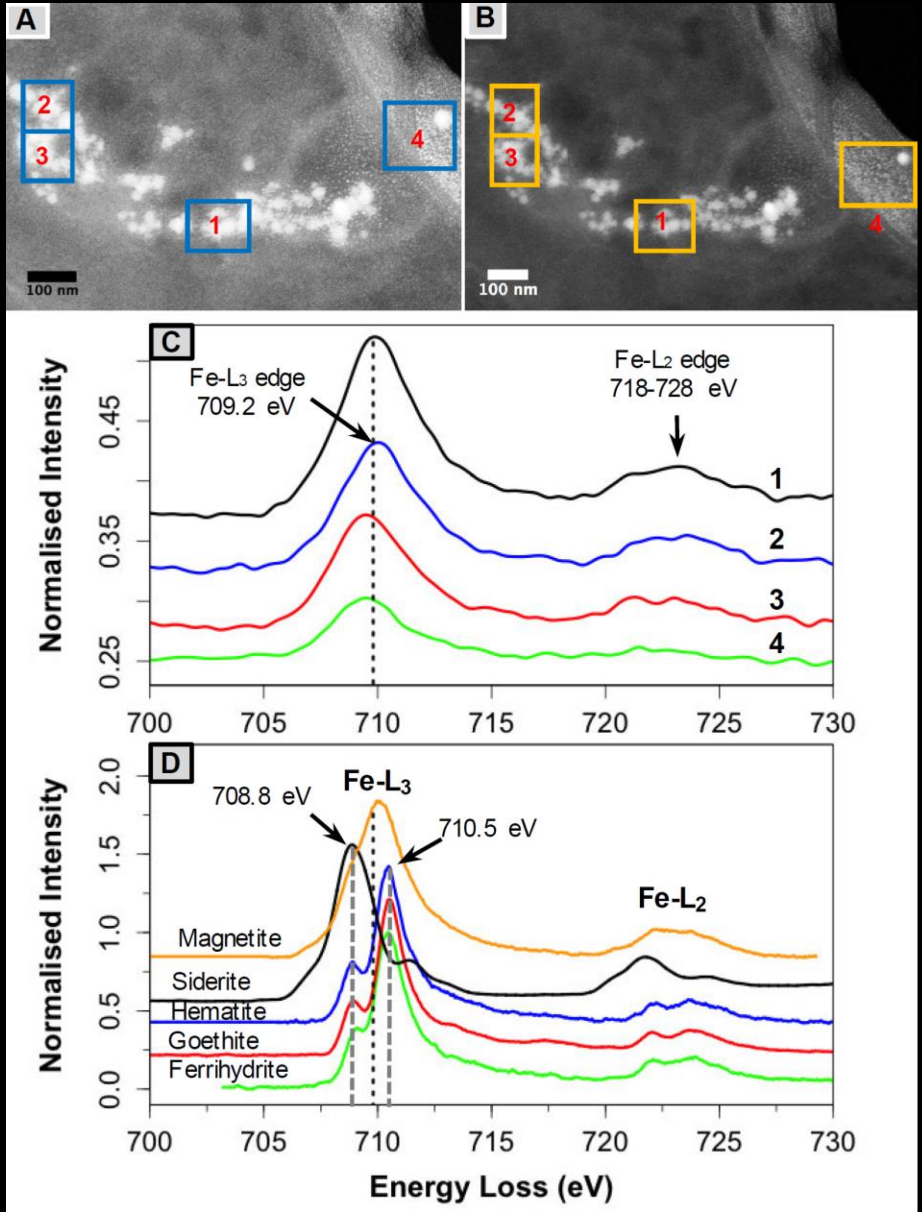
Biogenic brain magnetite



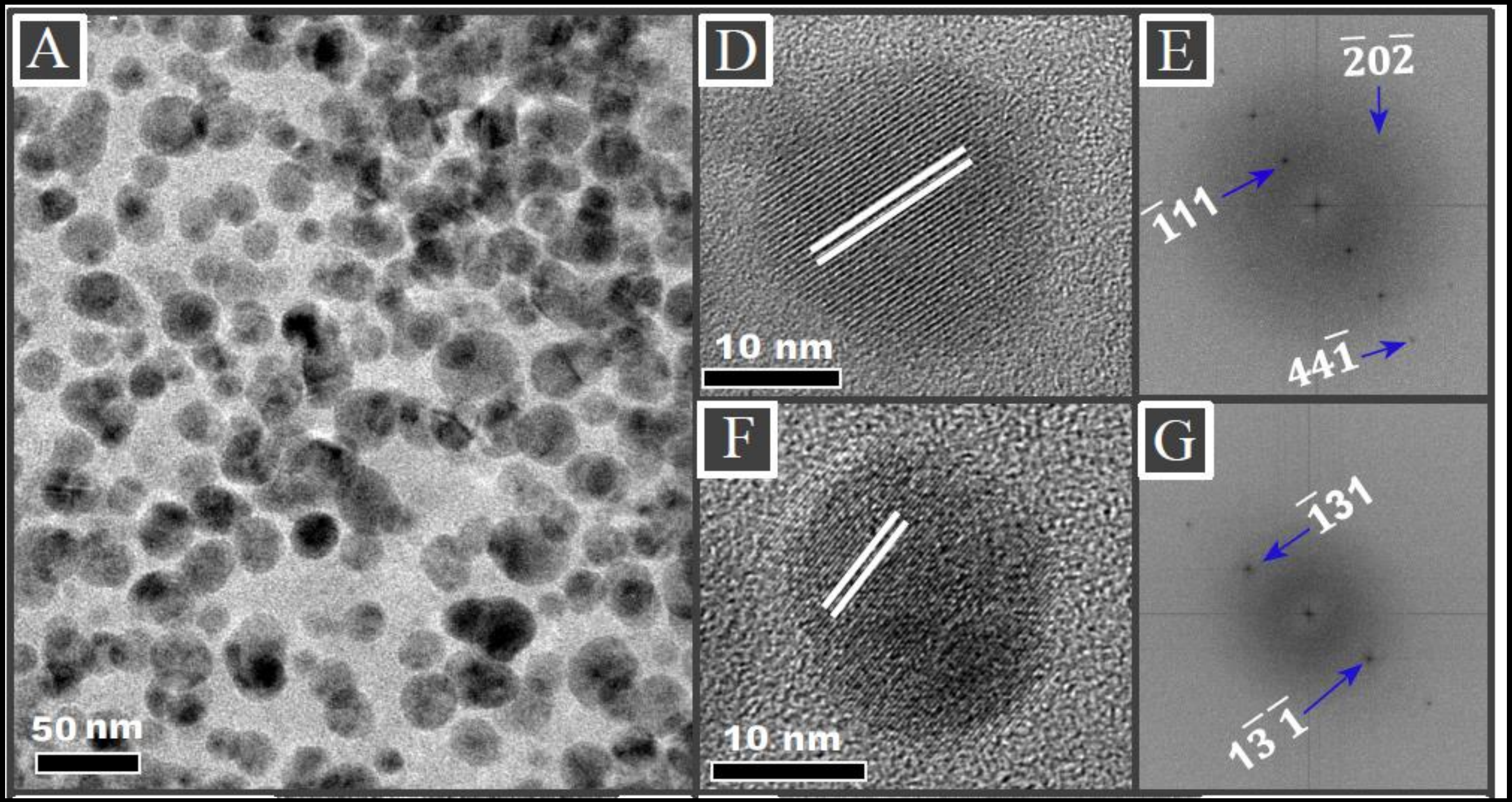
C/W Non-biogenic brain magnetite



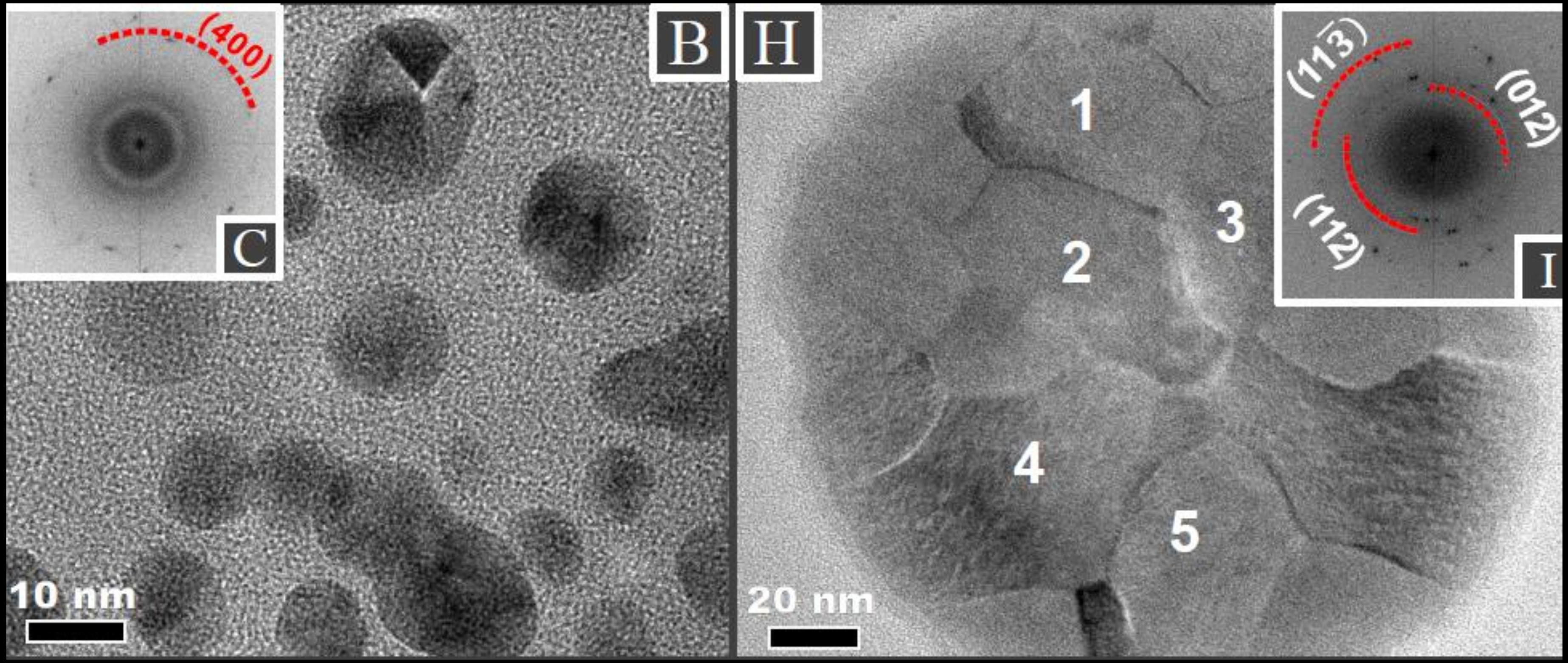
Abundant abiogenic magnetite nanoparticles in (some)brains



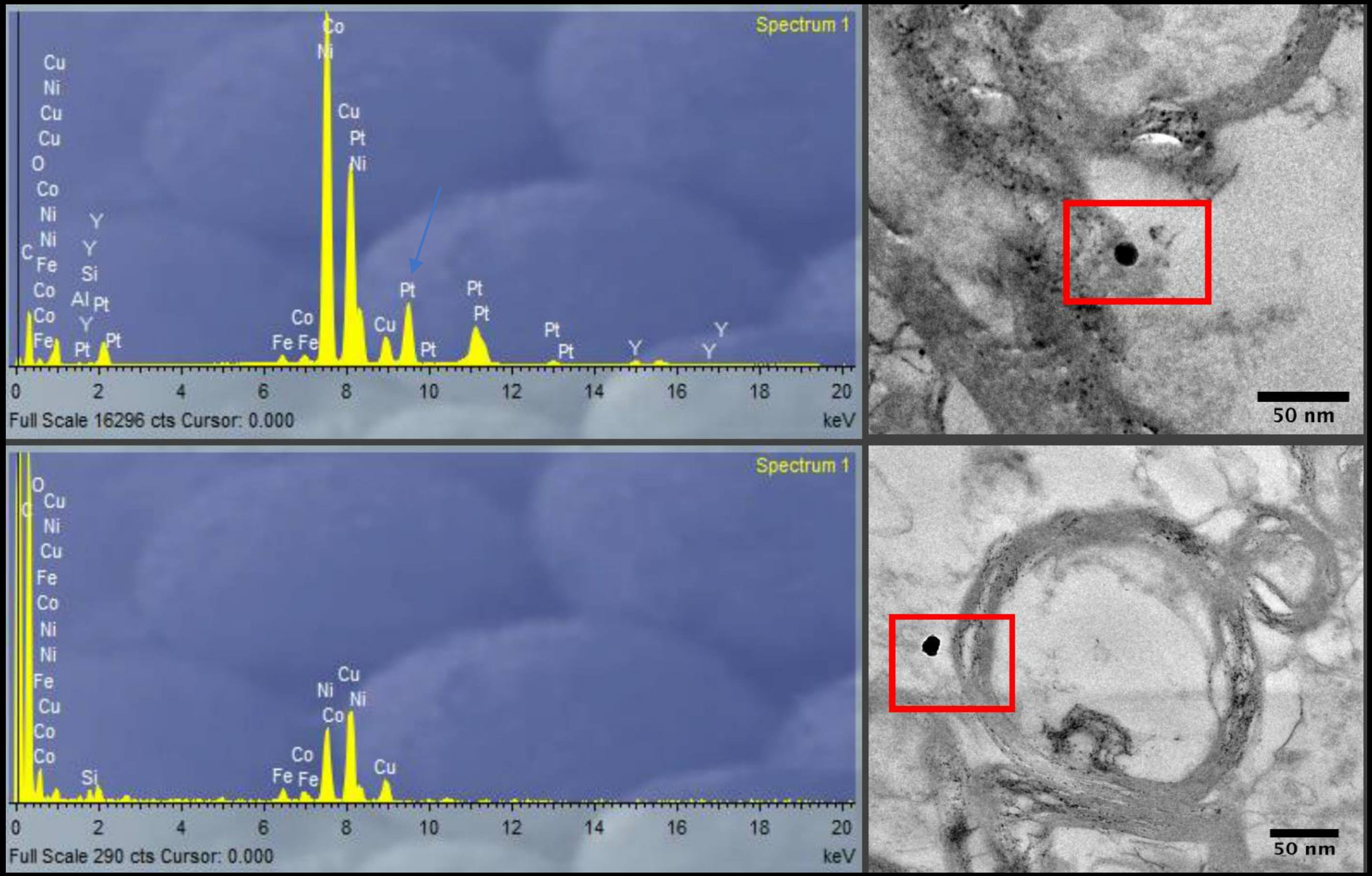
TEM, brain magnetic extracts…10^9/g tissue



TEM, Brain magnetic extracts



FRONTAL CORTEX NPs CONTAIN RANGE OF CO-ASSOCIATED METAL SPECIES



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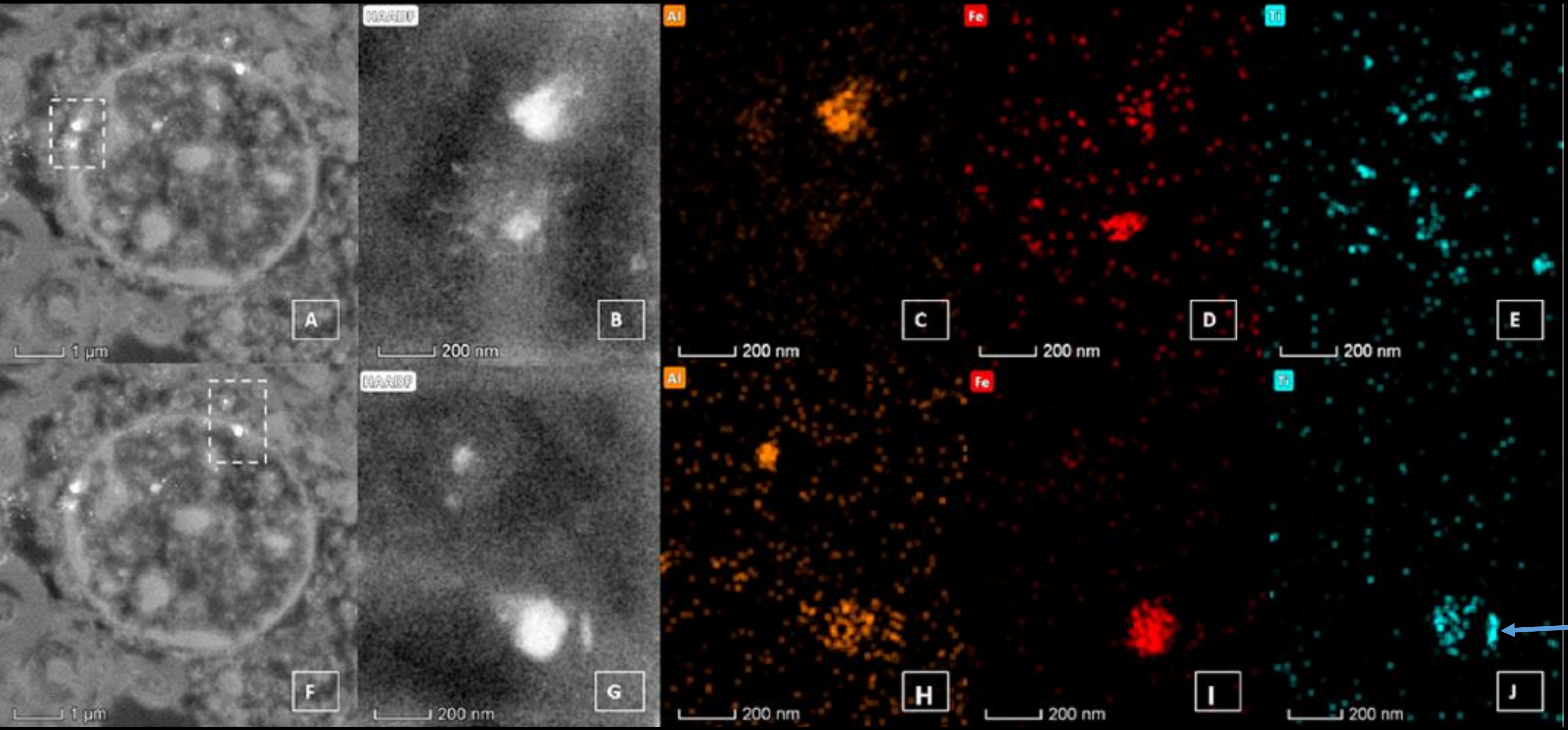
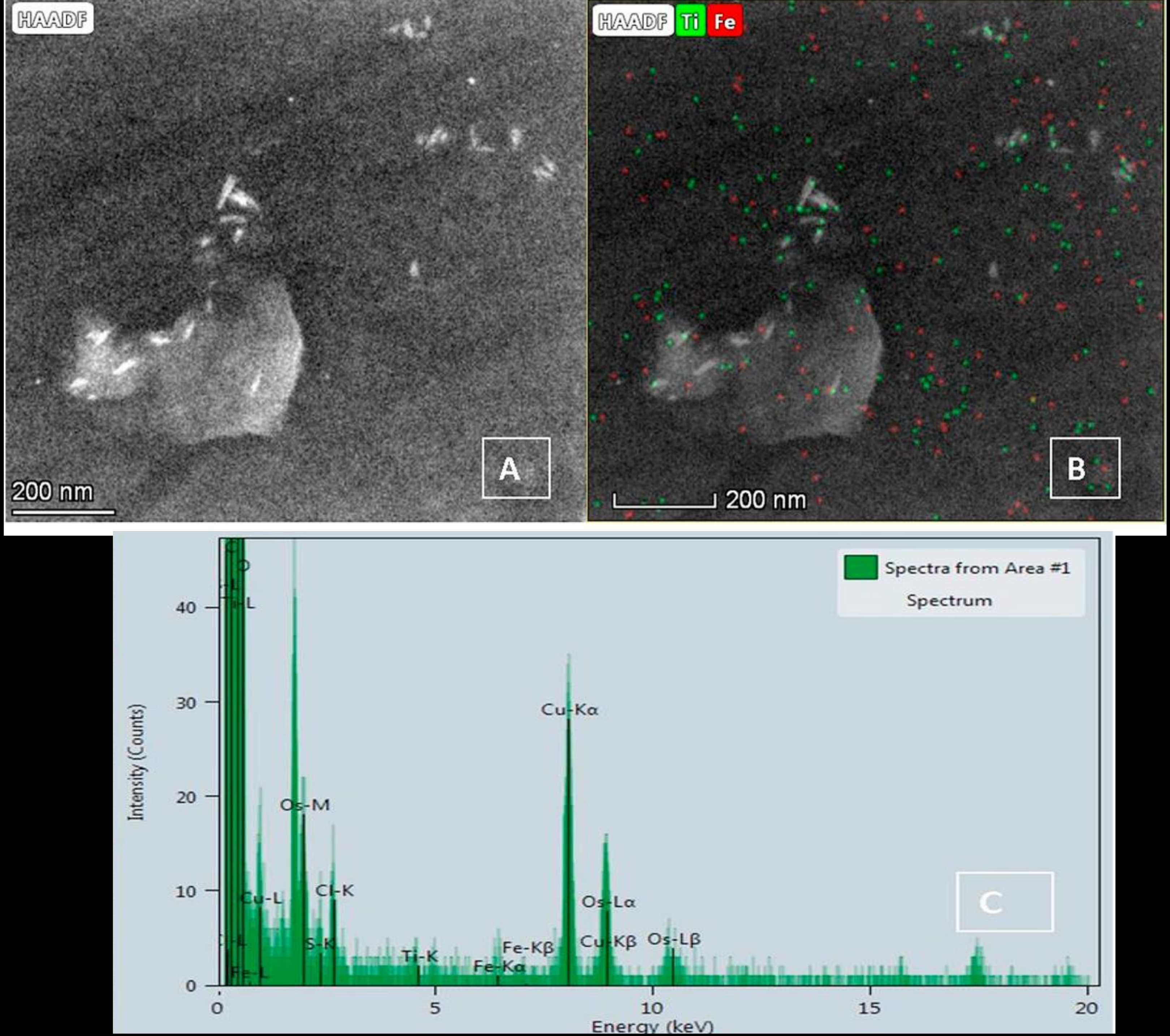
BRAINSTEM METAL NANOPARTICLES



Calderon-Garciduenas et al., 2020

Acicular Ti-rich NPs

Iron most common, + Al, Ti

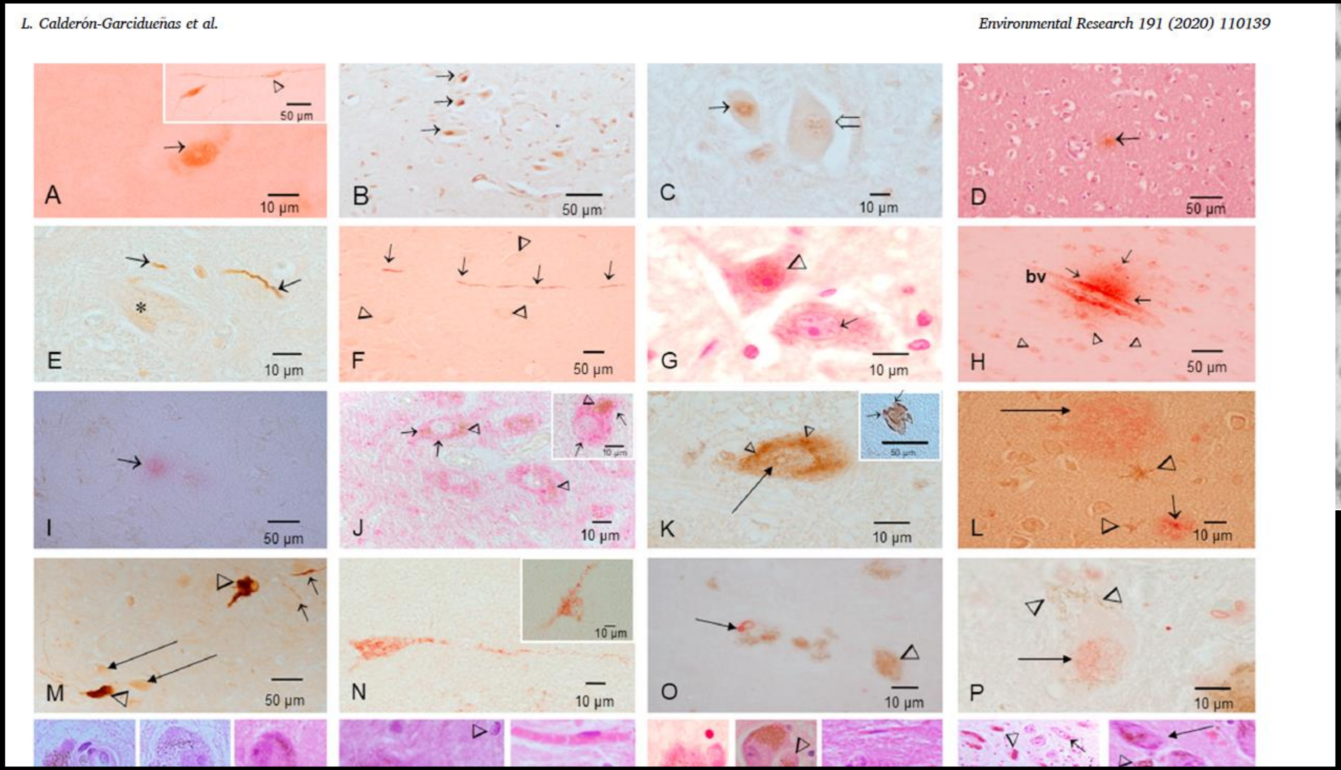

HAADF
200 nm
A
HAADF Ti Fe
200 nm
B
Spectra from Area #1
Spectrum
Intensity (Counts)
Energy (keV)
O
Ti-L
Os-M
Cu-L
Cl-K
S-K
Ti-K
Fe-L
Fe-Kα
Fe-Kβ
Cu-Kα
Os-Lα
Cu-Kβ
Os-Lβ
C

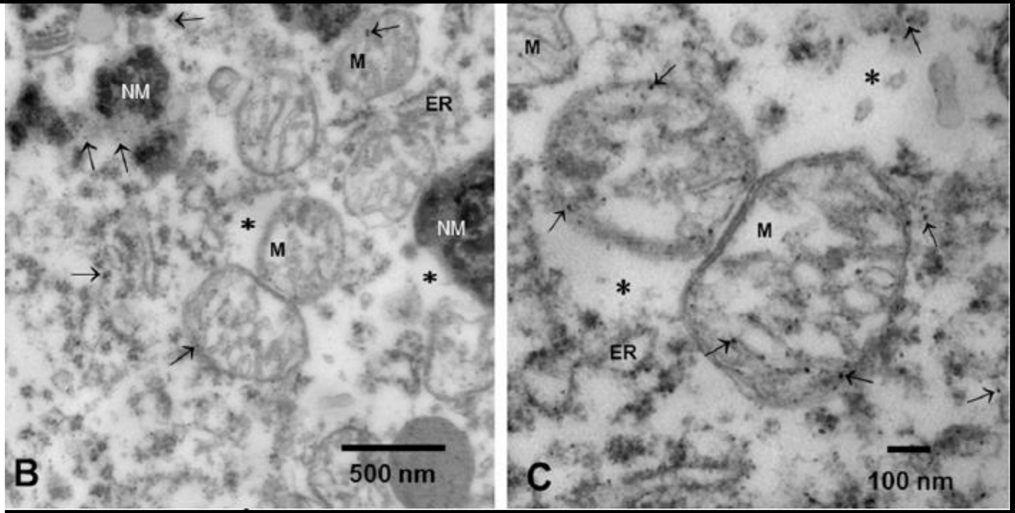
EM SUMMARY

Many, not all, of the brain magnetite particles:

- Rounded/spherical
- Diameters range widely, from 5 to 150 nm
- Some display fused surface crystallites
- Found associated with nanoparticles containing other metals, such as platinum, titanium, nickel, and cobalt

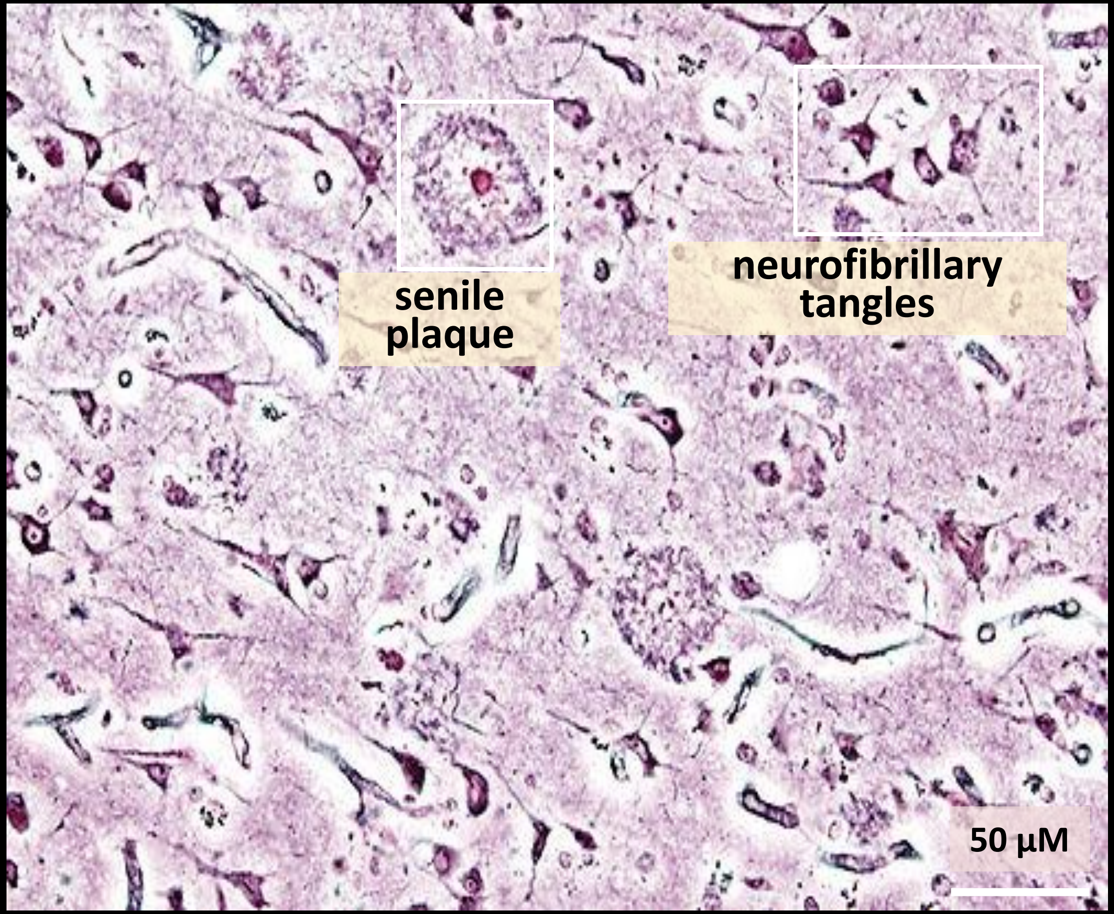
Fe-, Al- & Ti-bearing NPs directly associated with damaged brainstem organelles/ structures, & presence of AD, PD & MND pathology

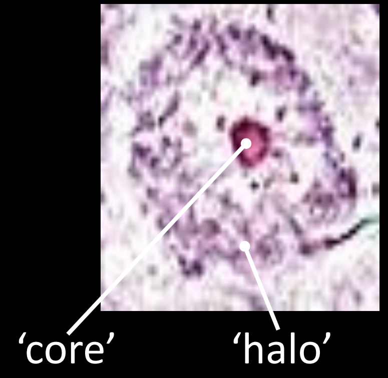




Calderon-Garciduenas et al., 2020

Senile plaques and neurofibrillary tangles





Contain β-amyloid (Aβ)

Tau filaments inside nerve cells

Both plaques and tangles are sites of metal accumulation

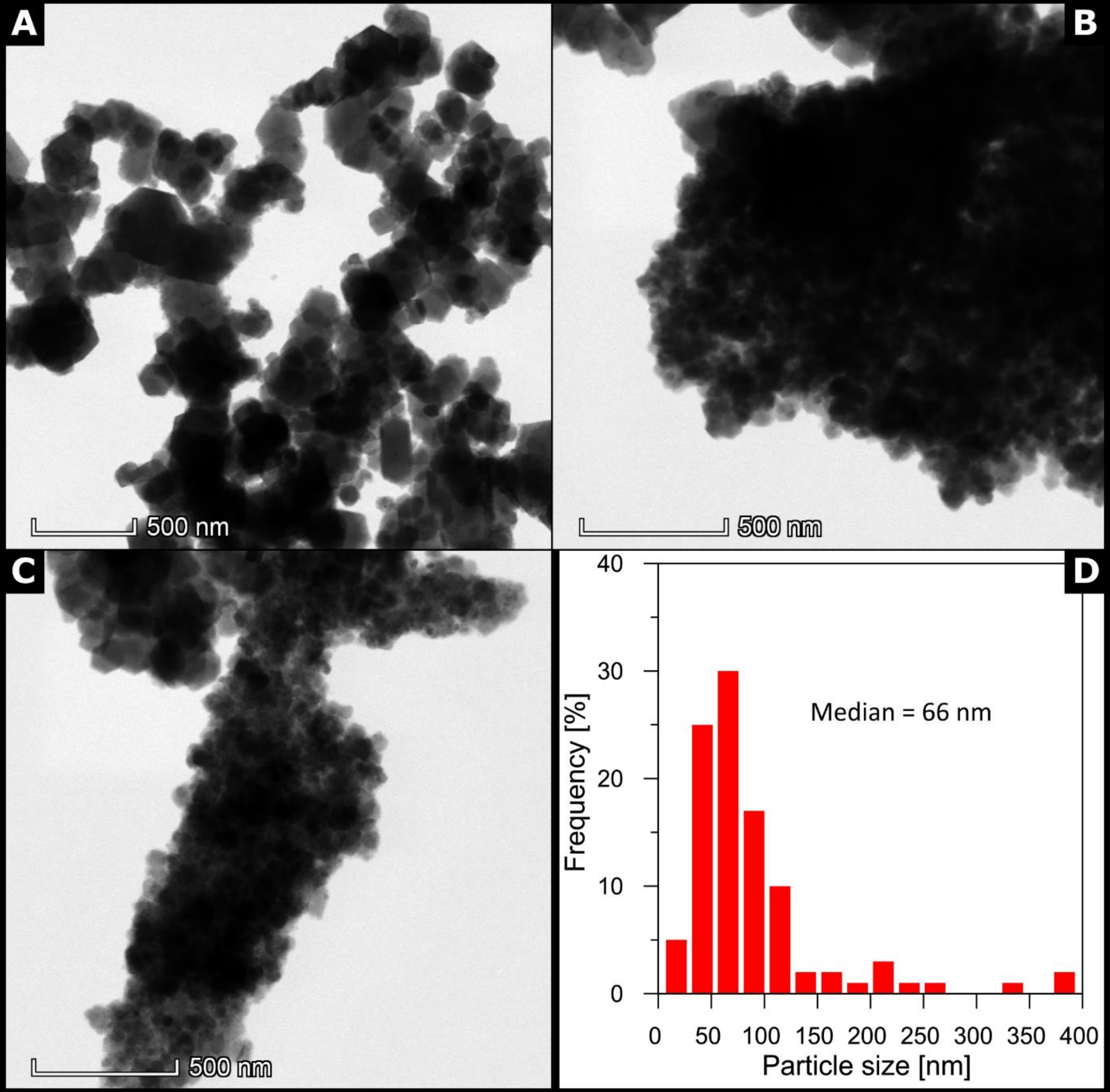
IRON- AND CO-ASSOCIATED METAL-RICH AIR POLLUTION NANOPARTICLES

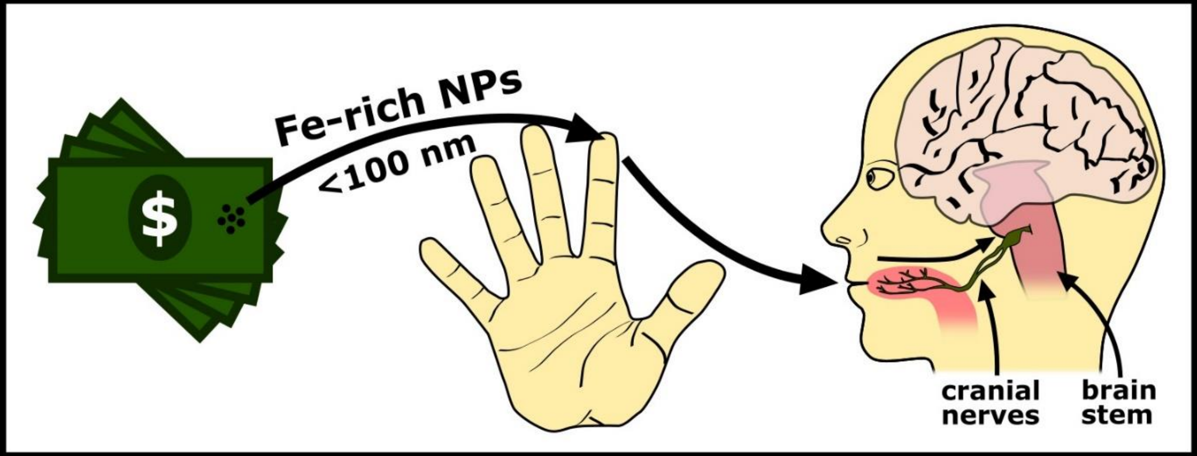
- Appear to be capable of evading all body defences

- We have now found them in the brain, heart, placenta…

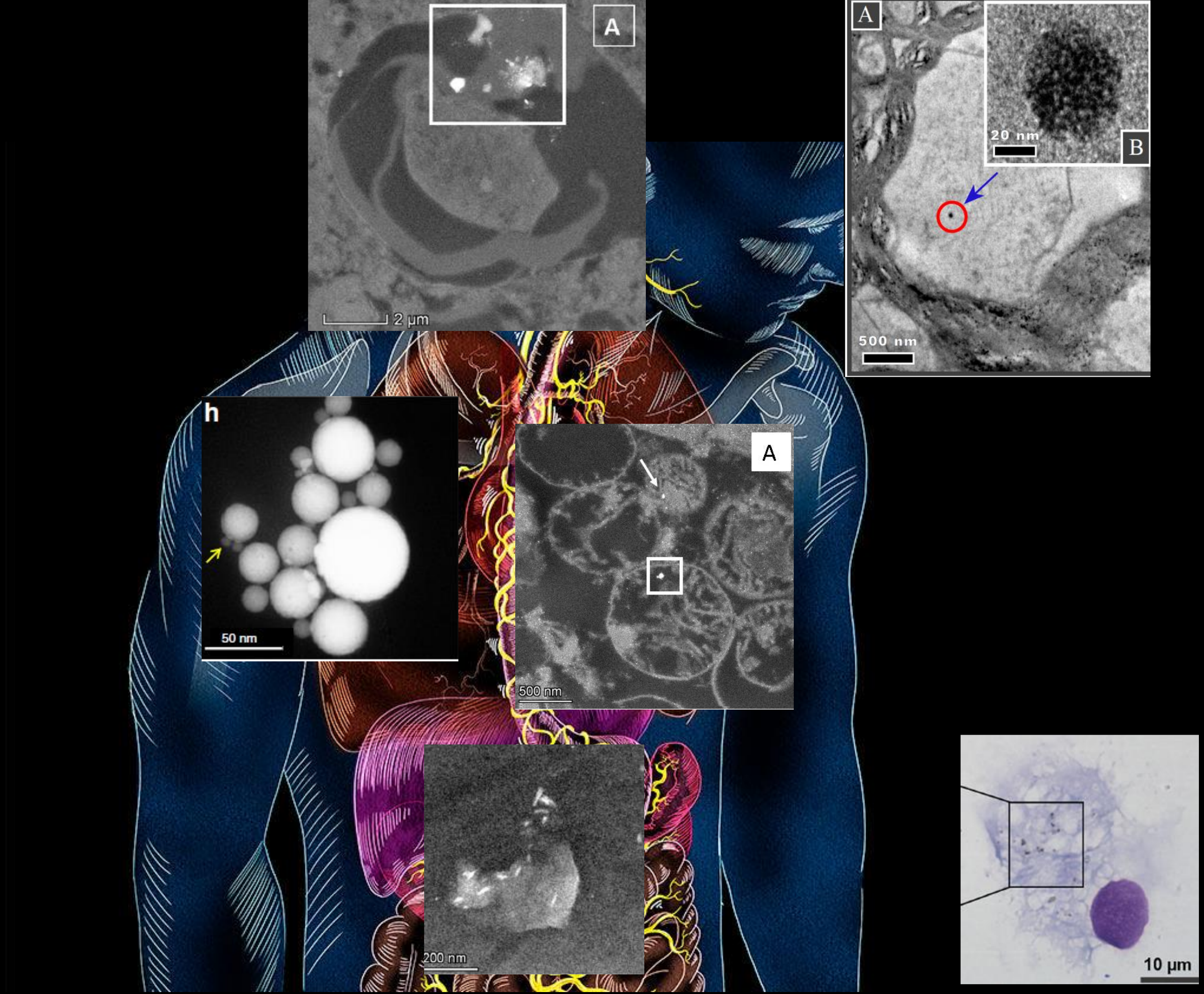
- Others now identifying them in lung effusions, bloodstream, CSF….

- N.B. Magnetic and EM data indicate different portals of NP entry: inhalation to lungs/circulation (likely most important); direct olfactory nerve uptake; ingestion (e.g. to brainstem via neuroenteric system)



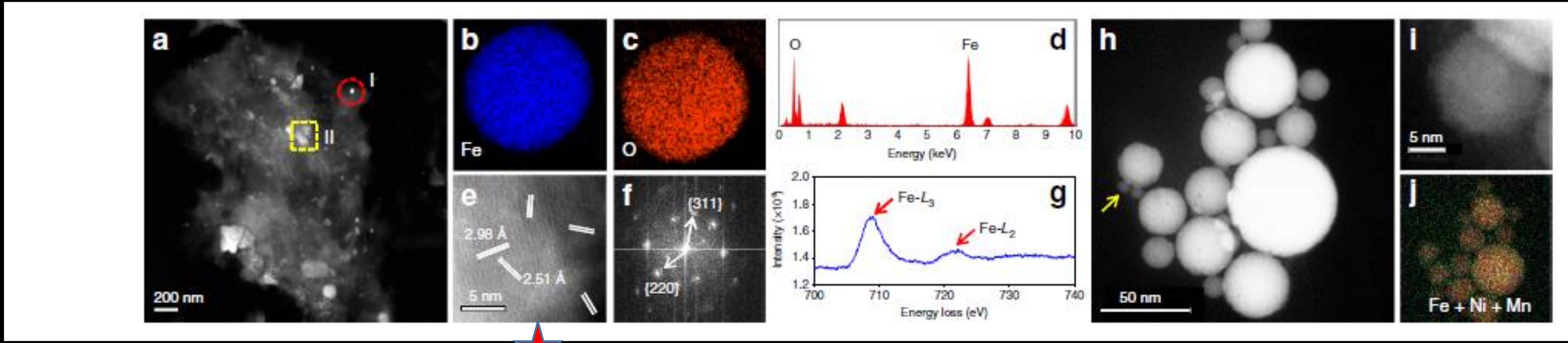


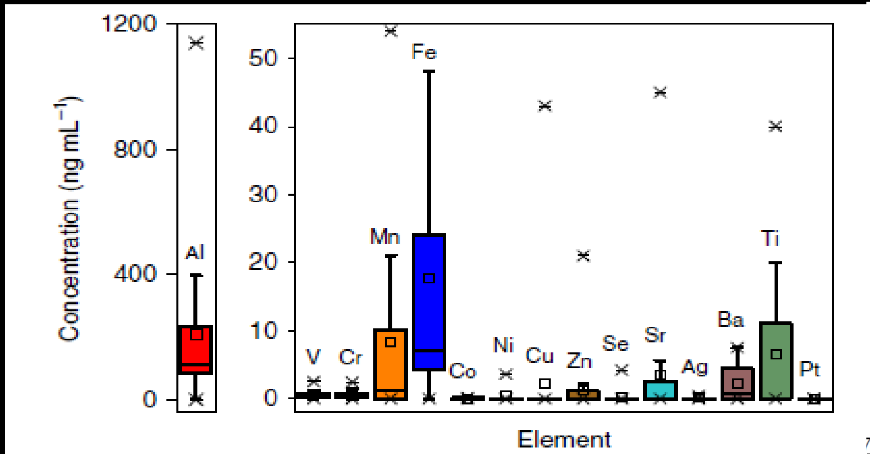
Gonet & Maher, 2020

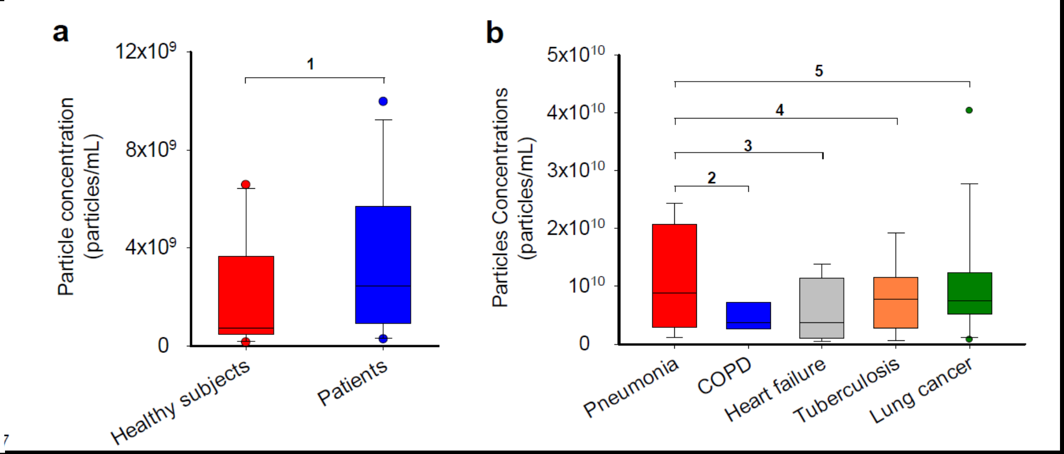


All micrographs from Maher et al, except h, Lu et al, 2020

https://doi.org/10.1038/s41467-020-16427-x







UFP 2022

https://doi.org/10.1038/s41467-020-16427-x OPEN

Chemical multi-fingerprinting of exogenous ultrafine particles in human serum and pleural effusion

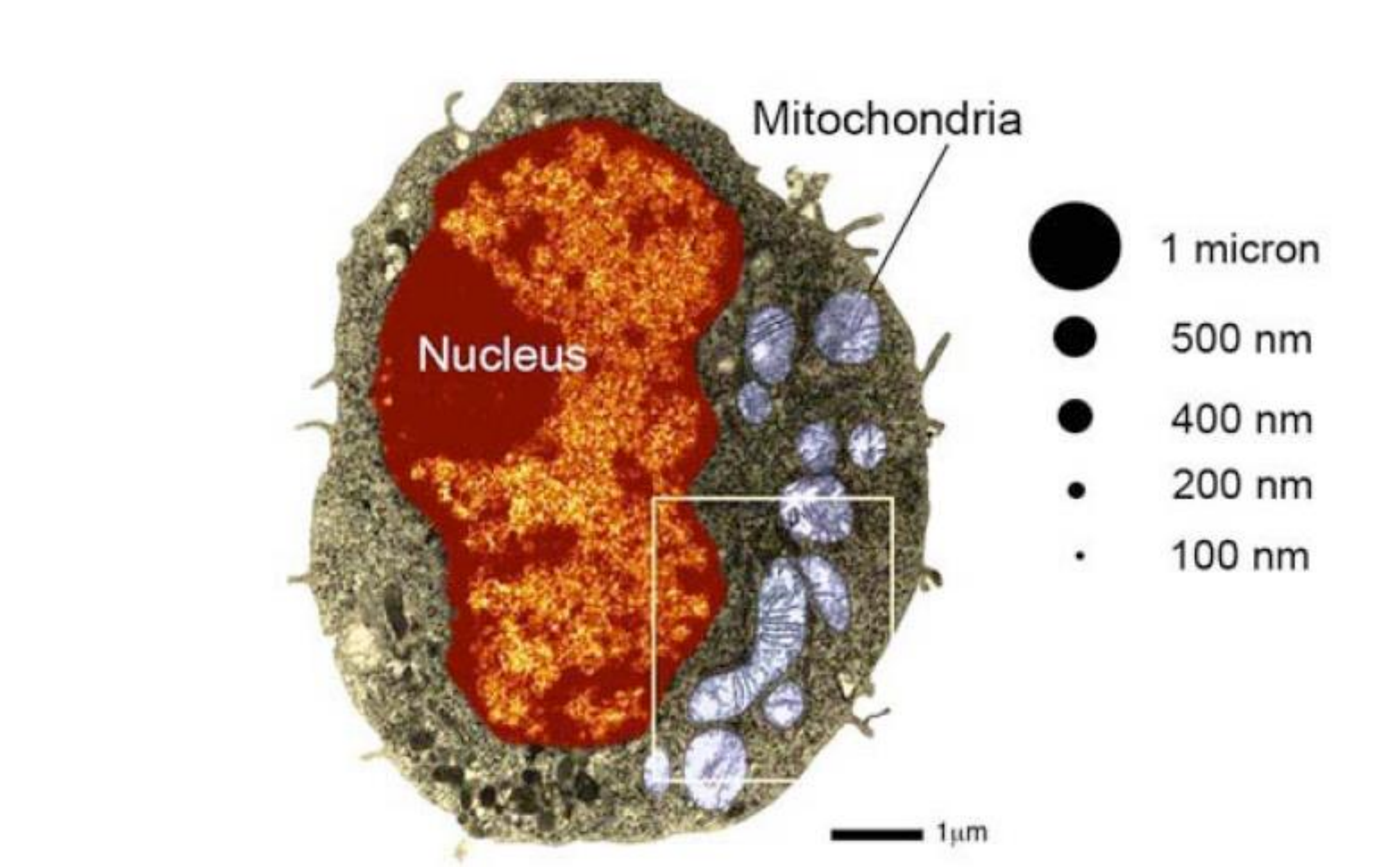
Dawei Lu [1,2], Qian Luo[3], Rui Chen[4], Yongxun Zhuansun[4], Jie Jiang[5], Weichao Wang[1,2], Xuezhi Yang[1,2], Luyao Zhang[1,2], Xiaolei Liu[1,2], Fang Li[3], Qian Liu [1,2,6✉] & Guibin Jiang[1,2✉]

Air pollution and CV disease

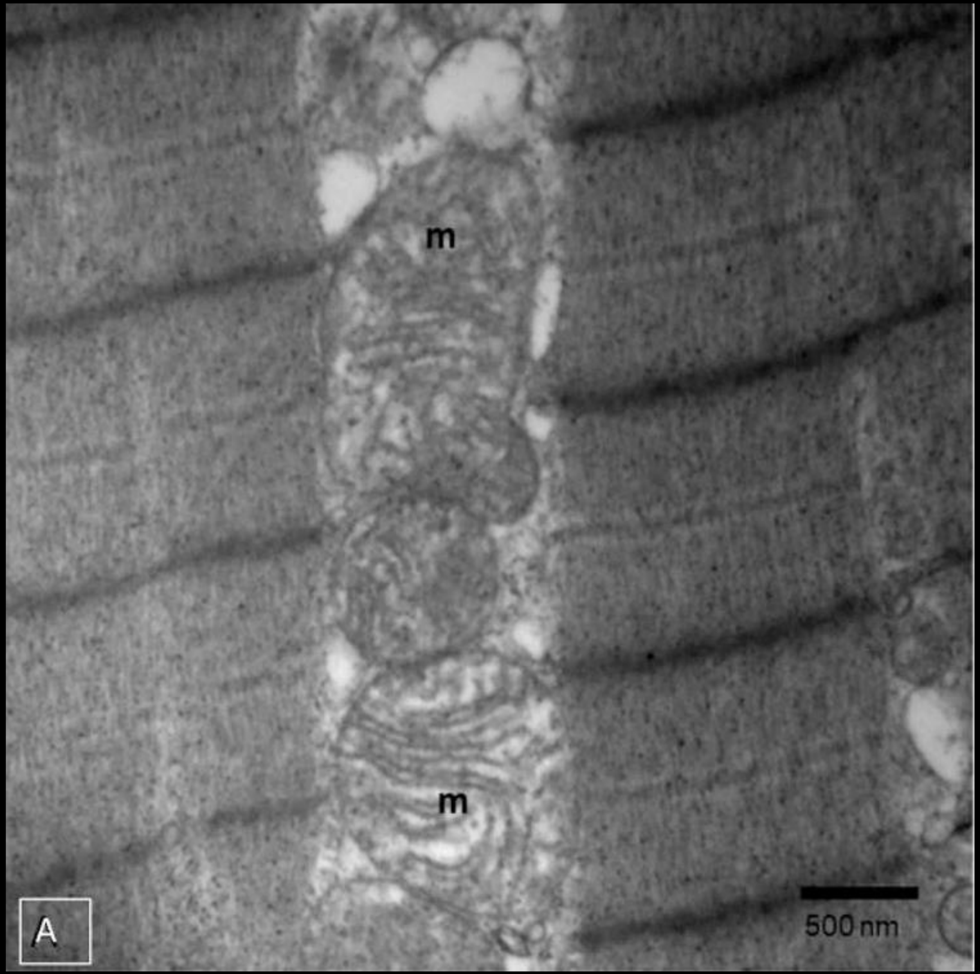
- Annual excess mortality rate from ambient air pollution (mainly $PM_{2.5}$) in Europe = 790,000 [95% confidence interval 645,000–934,000]…

- of which between 40 and 80% are due to cardiovascular events, which dominate health outcomes

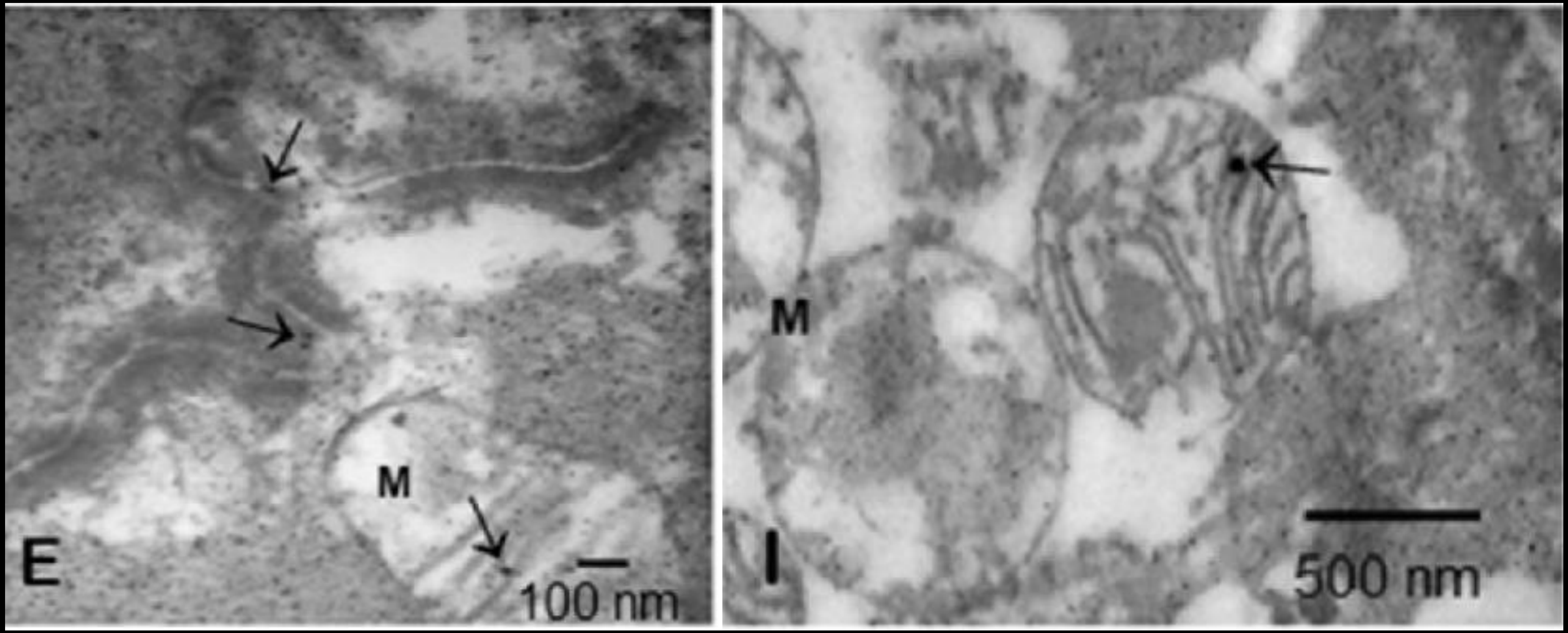
- (Lelieveld et al., 2019).


Mitochondria
Nucleus
1 micron
500 nm
400 nm
200 nm
100 nm
1μm

Intact myocardial mitochondria, low-pollution control…metal NP_s absent



METAL-RICH NPs IN DAMAGED MYOCARDIAL MITOCHONDRIA



Associated with significant up-regulation of GRP78, a marker of endoplasmic reticulum stress

Maher et al., 2020

Fe-rich NPs in myocardial mitochondria

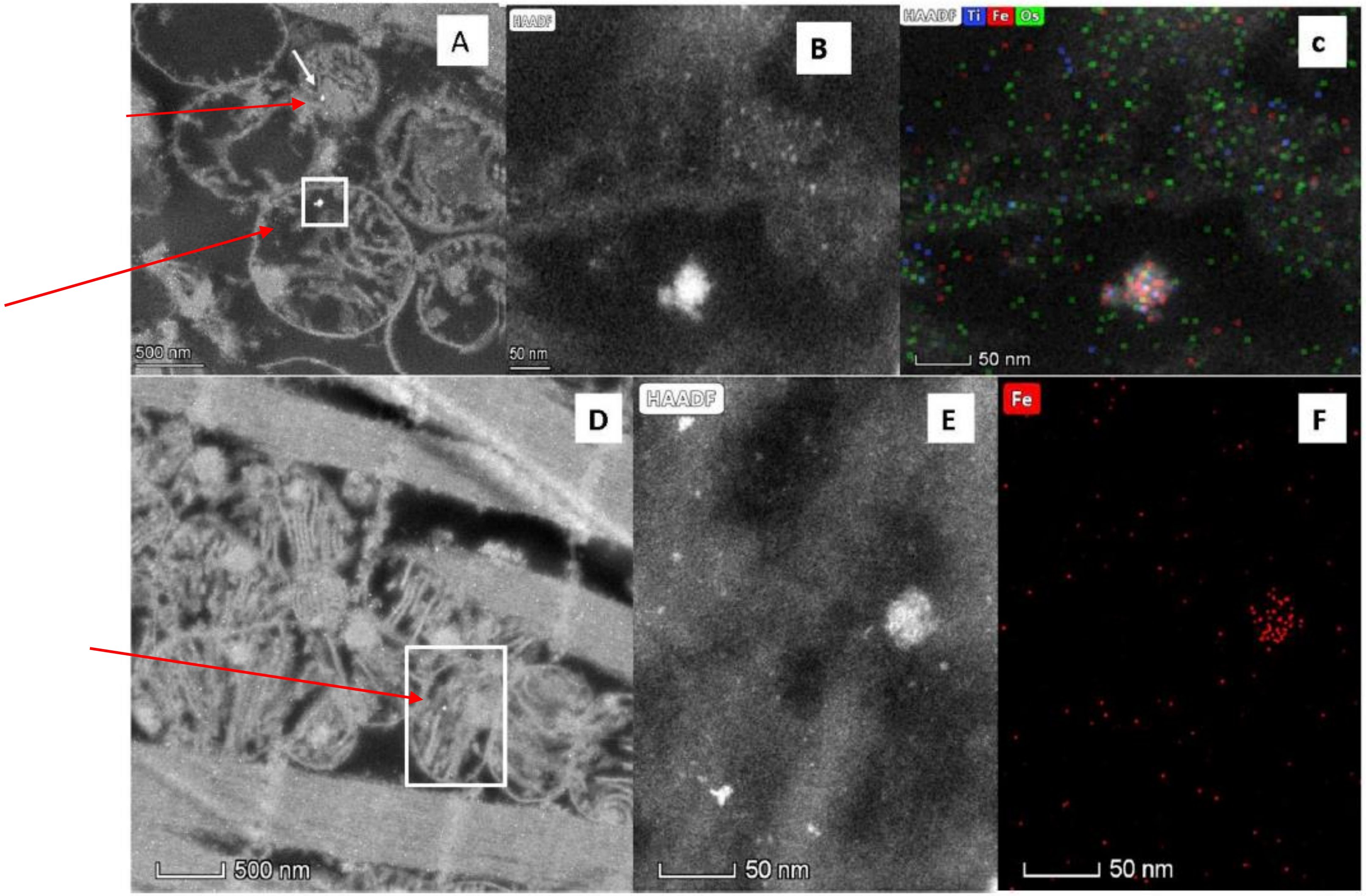


Fig. 2. High-angle annular dark-field scanning/transmission electron microscopy (HAADF-STEM) of left ventricle tissue, 3 y old (A–C) and 26 y old (D–F) MMC cases. A, B, D and E: Bright, electrodense NPs (white arrow and boxes), between ~15 and 40 nm, inside mitochondria; C and F: Elemental maps showing the iron-rich composition of the NPs shown in white boxes in A and D. (The smallest electrodense particles, < 10 nm, comprise osmium tetroxide used to stain the tissue).

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Iron-rich air pollution nanoparticles: An unrecognised environmental risk factor for myocardial mitochondrial dysfunction and cardiac oxidative stress

B.A. Maher[a,1,*], A. González-Maciel[b], R. Reynoso-Robles[b], R. Torres-Jardón[c], L. Calderón-Garcidueñas[d,e,1]

[a] Centre for Environmental Magnetism and Palaeomagnetism, Lancaster Environment Centre, University of Lancaster, LA1 4YQ, UK
[b] Instituto Nacional de Pediatría, 04530, Mexico
[c] Centro de Ciencias de La Atmósfera, Universidad Nacional Autónoma de México,04310, Ciudad de México, Mexico
[d] The University of Montana, Missoula, MT, 59812, USA
[e] Universidad Del Valle de México, 14370, Mexico

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ABSTRACT

Exposure to particulate air pollution is a major environmental risk factor for cardiovascular mortality and morbidity, on a global scale. Both acute and chronic cardiovascular impacts have so far been attributed to particulate-mediated oxidative stress in the lung and/or via 'secondary' pathways, including endothelial dysfunction, and inflammation. However, increasing evidence indicates the translocation of inhaled nanoparticles to major organs via the circulation. It is essential to identify the composition and intracellular targets of such particles, since these are likely to determine their toxicity and consequent health impacts. Of potential major concern is the abundant presence of iron-rich air pollution nanoparticles, emitted from a range of industry and traffic-related sources. Bioreactive iron can catalyse formation of damaging reactive oxygen species, leading to oxidative stress and cell damage or death.

Here, we identify for the first time, *in situ*, that exogenous nanoparticles (~15–40 nm diameter) within

Fe-rich air pollution NPs a plausible and pervasive risk factor for ND and CV diseases

BECAUSE of their ultrafine size

catalysis of ROS formation

ubiquity within airborne PM

- exposure to magnetite (and associated metal-bearing) nanoparticles might be an environmental risk factor for diseases associated with cascading inflammation and oxidative stress, including CVD and neurodegeneration.

- Exposure to higher concentrations of magnetite pollution nanoparticles in:
- Some occupational settings
- Indoors, from open fires or poorly-sealed stoves
- Outdoors, from vehicle and/or industrial PM sources.

Lancaster University

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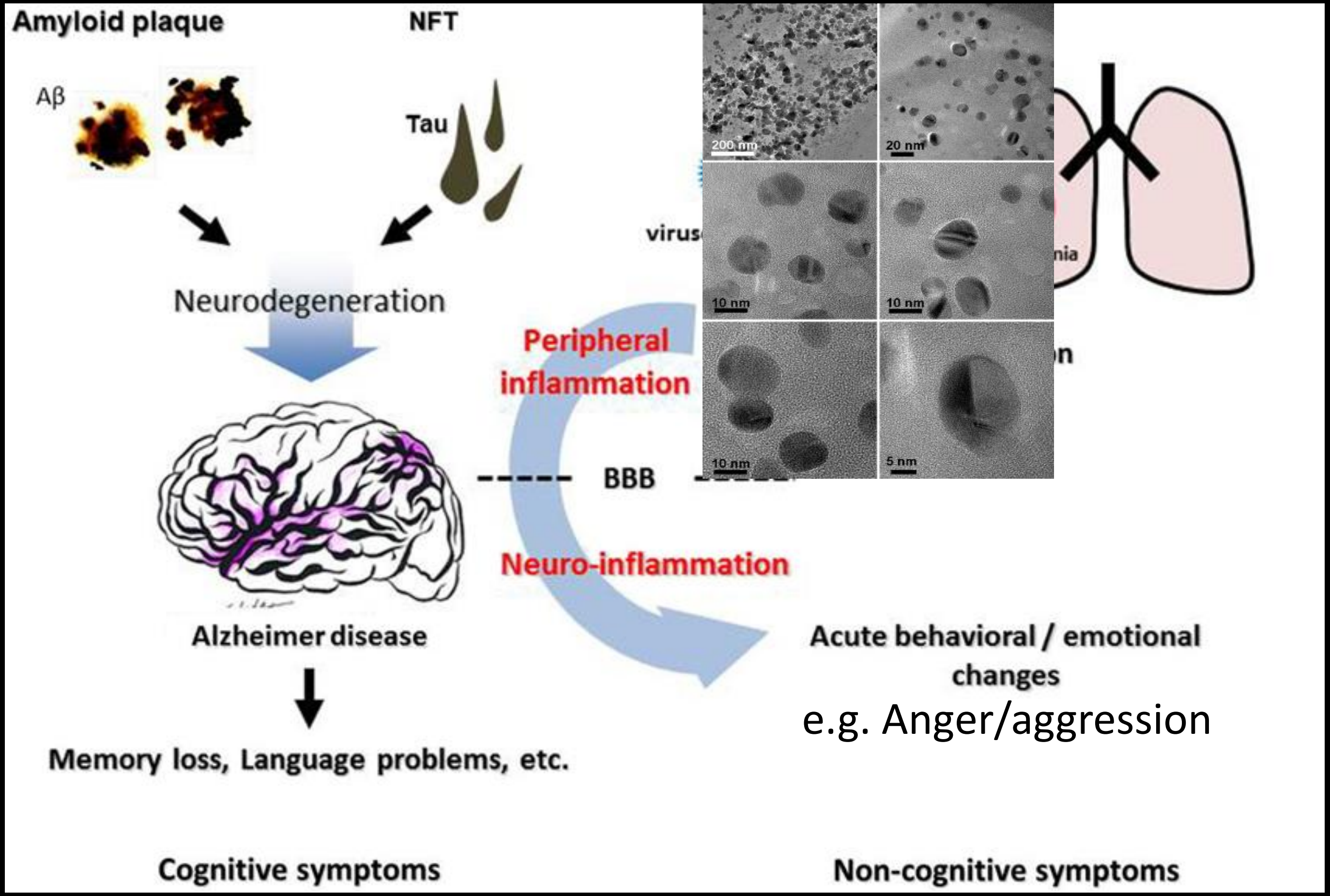
IOS Press

Review

Airborne Magnetite- and Iron-Rich Pollution Nanoparticles: Potential Neurotoxicants and Environmental Risk Factors for Neurodegenerative Disease, Including Alzheimer's Disease

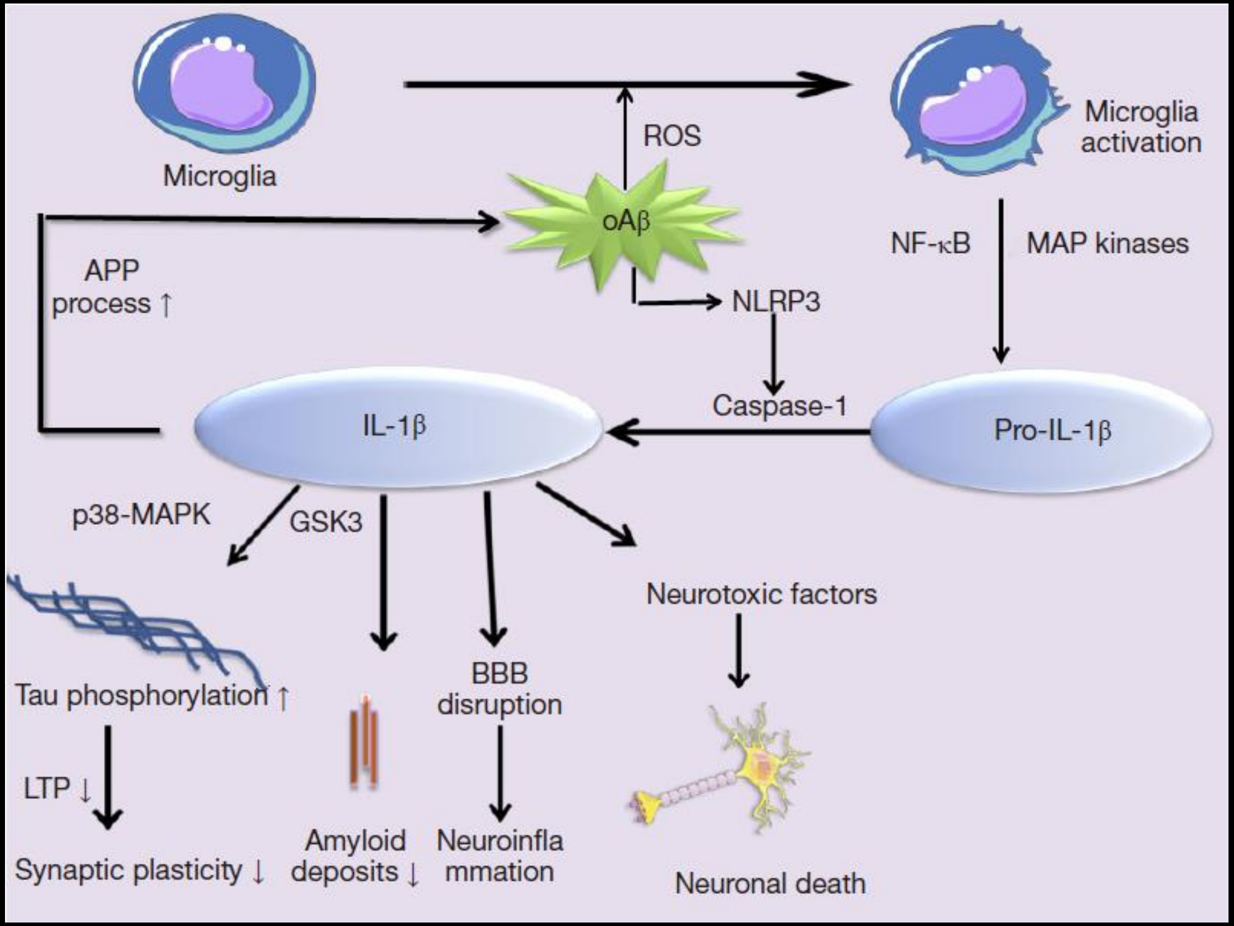
Barbara A. Maher*
Lancaster Environment Centre, University of Lancaster, UK

Chronic insult from inhaled metal-rich NP_s, resultant inflammation?

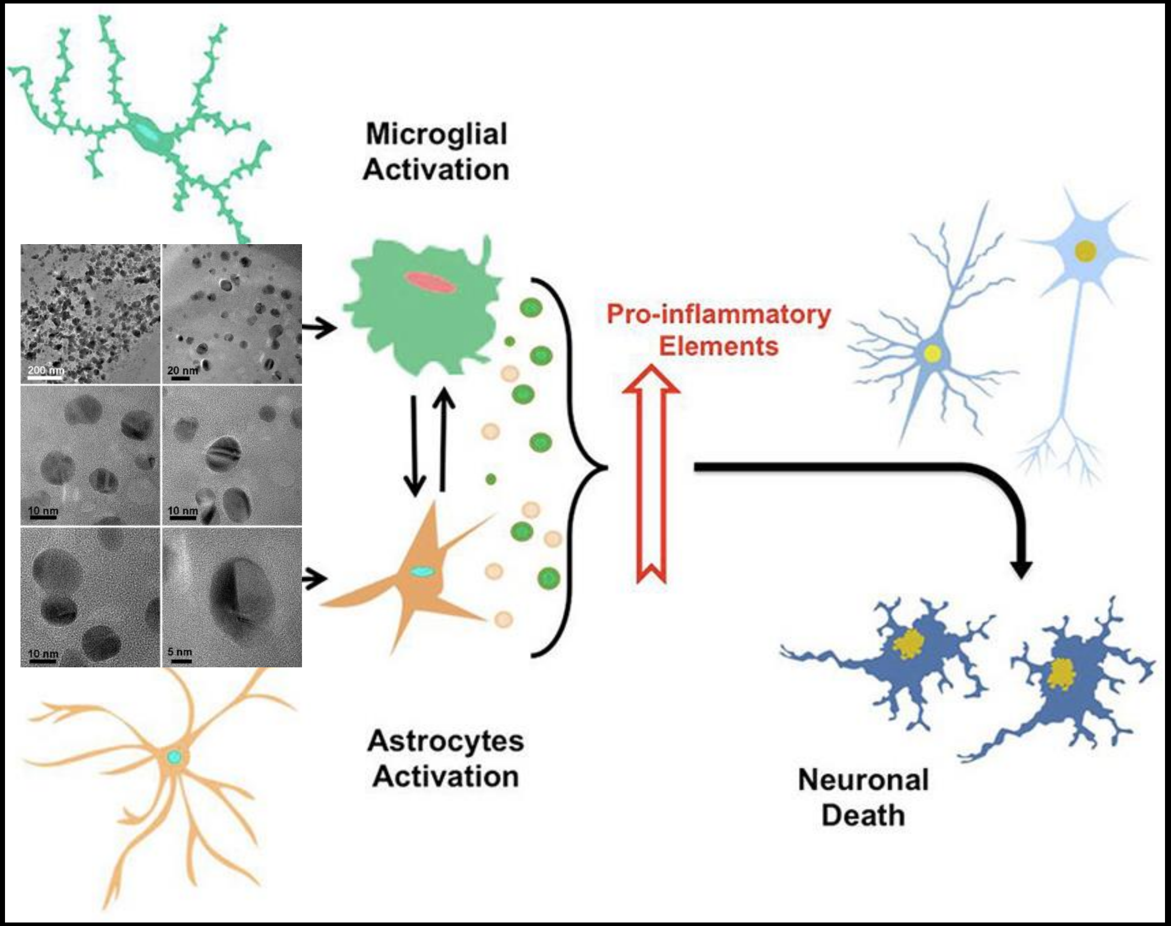


(Modified from Takeda et al., 2014)

Magnetite, ROS catalysis (Fenton reaction)



Microglial activation, excess inflammation



(Adapted from Morales et al., 2014)

Cancer and chronic exposure to Fe-rich NP_s?

- Repeated inflammatory response, oxidative stress, constant Fe replenishment…..possible progress from neurodegeneration to carcinogenesis (Maher, J Alzh Disease, 2019).

Conclusions

- Of the mix of components which contribute to airborne particulate pollution, magnetite and associated Fe- and metal-rich, redox-active nanoparticles may represent a key driver of excess ROS production, oxidative stress and inflammation.

- Hence, exposure to such NPs from road traffic and other emitting sources may be an environmental risk factor for CV and neurodegenerative diseases, including AD, PD and MND.

Thank you for your time and attention