DEVELOPMENT

Air pollution and your brain: what do you need to know right now

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Research links air pollution mostly to respiratory and cardiovascular disease. The effects of air pollution on the central nervous system (CNS) are not broadly recognized. Urban outdoor pollution is a global public health problem particularly severe in megacities and in underdeveloped countries, but large and small cities in the United States and the United Kingom are not spared. Fine and ultrafine particulate matter (UFPM) defined by aerodynamic diameter (<2.5-µm fine particles, $PM_{2.5}$, and <100-nm UFPM) pose a special interest for the brain effects given the capability of very small particles to reach the brain. In adults, ambient pollution is associated to stroke and depression, whereas the emerging picture in children show significant systemic inflammation, immuno-dysregulation at systemic, intratechal and brain levels, neuroinflammation and brain oxidative stress, along with the main hallmarks of Alzheimer and Parkinson's diseases: hyperphosphorilated tau, amyloid plaques and misfolded α-synuclein. Animal models exposed to particulate matter components show markers of both neuroinflammation and neurodegeneration. Epidemiological, cognitive, behavioral and mechanistic studies into the association between air pollution exposures and the development of CNS damage particularly in children are of pressing importance for public health and quality of life. Primary health providers have to include a complete prenatal and postnatal environmental and occupational history to indoor and outdoor toxic hazards and measures should be taken to prevent or reduce further exposures.

Key words: children; cognition and mood effects; neurodegeneration; neuroinflammation; particulate matter; stroke and depression; urban air pollution

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Introduction

Millions of people around the world, 74 million in the United States and 24 million people living in the Mexico City Metropolitan Area (MCMA) are involuntarily inhaling ambient concentrations of particulate matter (PM) above safety standards. In the United States, millions of people in busy corridors from New York–New Jersey–Long Island to relatively small cities like Provo, UT are chronically exposed to fine PM year after year (Chen and Kan, 2008). Well-documented air pollution events have been described in United Kingdom including the 1952 London episode with a high impact on public awareness of pollution (Bell *et al.*, 2004; Beelen *et al.*, 2013; Langrish and

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Mills, 2014). Cohort longitudinal studies across Europe show 7% increase in natural cause mortality with each 5 μg/m^3 in fine PM$_{2.5}$ (Beelen *et al.*, 2013; Langrish and Mills, 2014). According to a report by the European Topic Centre on Air and Climate Change (ETC/ACC), fine PM air pollution is associated with 455 000 premature deaths every year in the EU's 27 member states, including 46 200 in the United Kingdom (ETC/ACC, 2009 report). Air pollution levels have been decreasing in developed countries, while in developing countries and countries in transition, the problem is decreasing at a very low rate or even worsening. MCMA is an example of a polluted megacity with over 40 000 industries, >4 million vehicles that consume more than 40 million liters of petroleum fuels per day and produce thousands of tons of pollutants (INE, 2011). Since MCMA lies in an elevated basin 2240 m above sea level, surrounded on three sides by mountain ridges, surface, as well as surface-based air temperature inversions occur frequently, trapping pollutant emissions close to the surface and aggravating the pollution (Bravo-Alvarez and Torres-Jardón, 2002). MCMA geographical setting and the climatological characteristics along with the relatively little mobility of their residents allows for the opportunity of studying health effects associated to sustained yearlong exposures to concentrations of air pollutants above the current US National Ambient Air Quality Standards.

PM air pollution

Air pollution is a complex mixture of PM, gases, organic and inorganic compounds present in outdoor and indoor air. Urban outdoor pollution is a global public health problem (Molina and Molina, 2004). PM defined by aerodynamic diameter (>2.5 to <10-μm coarse particles, PM$_{10}$, <2.5-μm fine particles, PM$_{2.5}$, and <100-nm ultrafine particulate matter (UFPM)) poses a special interest for the brain effects given the capability of fine and UFPM to reach the brain (Block and Calderón-Garcidueñas, 2009). The major sources of fine and UFPM in the environment, that is, combustion sources from gas, oil, coal, industry and fires, metals and biological materials are common threat in urban and rural sites (Brook *et al.*, 2010). The smaller the particle, the larger the surface area, the

better lung penetration and diffusion and major particle deposition in the respiratory tract and direct translocation into the brain. A significant threat not contemplated by health care workers are man-made particles <100 nm. Nano-sized materials are included in many consumer products and daily use indoor machines produce them in significant amounts, and thus humans are being exposed on daily bases (ie, tooth paste, flavor enhancers, food additives, food and drink containers including baby bottles and pacifiers, laser printers, etc.; Hagens *et al.*, 2007; Benn *et al.*, 2010; Bergin and Witzmann, 2013). Most people spend >90% of their time indoors, so indoor air pollution is very important: smoking, cooking, candle/incense burning, cleaning and use of plastics and conglomerates all contribute to indoor pollution (Habre *et al.*, 2013). Poor air quality in schools and in-vehicle concentrations of pollutants are also of deep concern (Brown *et al.*, 2012; Annesi-Maesano *et al.*, 2013).

As in any city, air quality in MCMA is determined by the balance between pollutant emissions and the capacity of the geographical site to eliminate, disperse or concentrate those air pollutants. Despite MCMA rapid growth and development, air quality has improved during the past two decades. Nevertheless, residents remain exposed to concentrations of airborne pollutants exceeding ambient air quality standards, especially for PM and ozone, the two most important pollutants from the standpoint of public health (Brook *et al.*, 2010). The higher socioeconomic status (SES) MCMA population lives toward the south and west of the urban area with access to vegetation, water and better road networks. The industry is located primarily in the northeast and northwest, whereas the east side has been covered by large housing low SES developments in areas of difficult access and poor services. This distribution of the population, as well as the intensity and type of activities carried out, has great influence on the spatial distribution of emissions. According to the most recent emissions inventory for the MCMA (Secretaria de Medio Ambiente, Gobierno de Distrito Federal (SMA-GDF), 2008), the distribution of PM$_{10}$ depends largely on the activity of vehicles on paved and unpaved streets and roads, and in some urban areas of the northwest, these emissions are added with those generated by heavy industries. The fractional composition of PM$_{2.5}$ has been dominated by organic and black

carbon, sulfate, nitrate, ammonium and crustal components, with site- and time-dependent variations (Aiken *et al.*, 2009). Particle species are typically categorized as 'primary' if they are emitted in the particle phase and 'secondary' if their precursors (volatile organic compounds, NO_x, SO_2, NH_3 and others) are emitted in the gas-phase and subsequent chemical reactions bring them to the particle phase.

Diesel and gasoline exhausts emissions have been responsible for a significant fraction of the fine particle primary emissions in MCMA (Molina *et al.*, 2010). Polycyclic aromatic hydrocarbons (PAH) are a family of species, some of which are highly mutagenic and carcinogenic, that are generally associated with black carbon as their emissions are largely from combustion sources (Valle-Hernández *et al.*, 2010).

Peak concentrations of PAHs in MCMA are reached during the morning rush hour and are of the order of 120 ngm^{-3}, which is significantly higher than in United States (Marr *et al.*, 2004; Molina *et al.*, 2010). High levels of anthropogenic metals including chromium (Cr), zinc (Zn), copper, lead (Pb), antimony, arsenic, tin and barium complete the toxic potential of fine PM (Molina *et al.*, 2010). As expected, these metals exhibit strong temporal variations in concentration and are largely associated with industrial and mobile sources. Elements representing mostly road traffic, that is, Cr, Mn, Zn and Pb, are typically associated with engine emissions and abrasion of tires and brake pads. V and Ni are interpreted as tracers of long-range transport from the use of heavy fuel oil in the north of the basin (Querol *et al.*, 2008). Pb deserves a special mention. Before 1986, Pb was probably the most harmful pollutant in MCMA, associated with the exclusive use of leaded gasoline and resulting in Pb concentrations three times the air quality standard. In response to a very strong social pressure and to a growing international trend to control car emissions with catalytic converters, PEMEX, the federal Mexican oil company, was forced to reduce the gasoline content of tetra-ethyl-lead (Bravo-Alvarez and Torres-Jardón, 2002) resulting in Pb concentrations ~2 µg/m^3 in 1988 and reaching ~0.5 µg/m^3 by 1998. Although Pb is no longer an air pollutant problem, lipopolysaccharides (products of the outer membrane of Gram-negative bacteria) associated with PM, are detected in very high concentrations in southern Mexico City (Rosas-Pérez *et al.*, 2007). The grim scenario for MCMA residents is a sustained exposure to $PM_{2.5}$ several hours per day above the current standards, every year, in such a way that residents are living in a very effective exposure chamber from conception to death. Is this scenario exclusive for Mexico City residents? The answer is no, Salt Lake City, Tacoma, San Francisco Bay, Los Angeles, Fairbanks, London, Greater Manchester and Oxfordshire residents to name a few have similar scenarios, albeit less severe (Bell *et al.*, 2007; Maheswarang *et al.*, 2010; Williams *et al.*, 2011; Beelen *et al.*, 2013; UK Air Data). On the other hand, millions of Shanghai residents are covered with heavy haze substantially increasing cardiovascular, respiratory and cerebrovascular morbidity and mortality (Xu *et al.*, 2013).

The impact of polluted air on an adult brain

The first important statement to be made is that age and disease status are key factors on the impact of air pollutants. Associations between stroke, ambient pollution and coal fumes were suggested in the 1980s (Knox, 1981; Zhang *et al.*, 1988). Cigarette smoking as a stroke risk factor (and of course an excellent source of large amounts of PM) was published a decade later (Howard *et al.*, 1998). Ischemic stroke mortality and transient ischemic attacks relate to fine and UFPM exposures even at concentrations below the current standards (Hong *et al.*, 2002; Kettunen *et al.*, 2007; Lisabeth *et al.*, 2008; Bedada *et al.*, 2012; Leiva *et al.*, 2013) and very important from the clinical point of view, outdoor air pollution and proximity to high-traffic roadways impact stroke survival (Maheswarang *et al.*, 2010; Wilker *et al.*, 2013). The largest association between $PM_{2.5}$ and ischemic stroke risk was seen with stroke due to large-artery atherosclerosis and small-vessel occlusion: diabetic patients are particularly at risk (O'Donnell *et al.*, 2011). Moreover, the associations involve not only urban pollutants but also dust storms and unfortunate events like 9/11 World Trade Center (Yang *et al.*, 2005; Brackbill *et al.*, 2006). Although most of the literature associating stroke with air pollution emphasizes PM, ozone – a key photochemical pollutant affecting our populations in Mexico City, Los Angeles, San Joaquin Valley, Riverside, Sacramento, Baltimore, Dallas, south-east of England, etc. – is also a big player (Parrish, *et al.*, 2011; Carlsen *et al.*, 2013;

Suissa *et al.*, 2013). Depression and mood disorders have been associated with air pollution. Increases in PM_{10}, $PM_{2.5}$, NO_2, CO, SO_2, O_3 and biomass burning are associated with depression in the elderly, and emotional symptoms and suicide attempts in younger subjects (Szyszkowicz *et al.*, 2010; Wisnivesky *et al.*, 2011; Banerjee *et al.*, 2012; Lim *et al.*, 2012). Exposure of animal models to ambient $PM_{2.5}$ results in depressive responses and increase hippocampal pro-inflammatory cytokines (Fonken *et al.*, 2011), whereas prenatal nano-PM impacts neonatal neurons and adult behavior in mice (Davis *et al.*, 2013).

The impact of polluted air on a developing brain

Clean air is fundamental for children's health and well-being. Millions of children are showing an array of adverse short- and long-term health outcomes related to air pollution exposures. Widely recognized among pediatric health providers is the impact of intrauterine factors, parent–child interactions, cognitive stimulation, maternal SES during pregnancy and the child's nutrition and exposure to complex learning stimuli, all vital for brain development (Calderón-Garcidueñas and Torres-Jardón, 2012a). However, air pollution brain effects rooted in intrauterine life and childhood are not generally acknowledged. Air pollution is not broadly recognized in the context of children's brain effects including the presence of neuroinflammation, cognitive deficits, structural brain alterations and neuropathological hallmarks of Alzheimer (AD) and Parkinson's diseases (PD) (Calderón-Garcidueñas *et al.*, 2003; 2008a; 2008b; 2008c; 2009; 2010; 2011a; 2011b; 2012a; 2012b; 2012c; 2013a; 2013b).

A coherent pathway linking exposure to air pollution and brain damage starts with a chronic inflammatory process involving the respiratory upper and lower tracts, which result in a systemic inflammatory response with the production of inflammatory mediators capable of reaching the brain (Calderón-Garcidueñas *et al.*, 2003; 2008a; 2008b; 2008c; 2009; 2011a; 2011b; 2012a; 2012b; 2013a; 2013b). Continuous expression of potent inflammatory mediators in the central nervous system (CNS) and the formation of reactive oxygen species are major findings in urban residents

(Block and Calderón-Garcidueñas, 2009). UFPM, particulate matter-associated lipopolysaccharides, and metal uptake could take place through olfactory neurons, cranial nerves such as the trigeminal and vagus, the systemic circulation and macrophage-like cells loaded with PM from the lungs (Calderón-Garcidueñas *et al.*, 2008c; 2012a). Activation of the brain innate immune responses resulting from the interaction between circulating cytokines and constitutively expressed cytokine receptors located in brain endothelial cells is followed by activation of cells involved in adaptive immunity (Lampron *et al.*, 2013). Monocytes are the main innate immune response mediator cells, producing and secreting $TNF\alpha$, interleukin-1β (IL-1β) and IL-6, which in turn recruit and increase the activity of other immune cells. Fine and UFPM could serve as the crucial trigger for a chain of events leading to endothelial activation, disruption of blood–brain barrier (BBB), altered response of the innate immune system, production of autoantibodies to cell junction and neural proteins, neuroinflammation and neurodegeneration. These early changes, amenable to intervention and viewed initially as a compensatory phenomenon by some groups including ours (Perry *et al.*, 2002; Castellani *et al.*, 2006; Calderón-Garcidueñas *et al.*, 2012a; 2013a) are likely critical to onset and progression of the neurodegenerative changes and the full clinical picture seen in AD patients (Castellani *et al.*, 2006).

There is growing recognition of the role of systemic and neural inflammation and the interplay between immunity, neurodegeneration and maladaptive activation of innate/adaptive immunity as key pathogenic phenomenon in AD (Blasko *et al.*, 2004; Dik *et al.*, 2005; Finch and Morgan, 2007; Bonotis *et al.,* 2008; Gomez-Ravetti and Moscato, 2008; Cunningham *et al.*, 2009; Keene *et al.*, 2011). Likewise, change in immune status has been suggested as a plausible biological mechanism by which PM could cause adverse health effects (Eikelenboom *et al.*, 2011). PM has the capability of crossing barriers, including the BBB resulting in neuroinflammation and intrinsically disordered neural proteins associated with neurodegenerative diseases (Campbell, 2004; Win-Shwe *et al.*, 2008; Levesque *et al.*, 2011).

The emerging picture reveals highly exposed urban children exhibit significant neuroinflammation and brain oxidative stress (Calderón-G arcidueñas *et al.*, 2008c; 2012a; 2013a; 2013b). In addition, these

children have extensive abnormal white matter blood vessels, perivascular inflammation and a breakdown of the BBB (Calderón-Garcidueñas *et al.*, 2008c). Fine tuning of immune-to-brain communication is crucial to neural networks appropriate functioning, thus our recent finding of autoantibodies to actin and occludin/zonulin in the presence of BBB compromise might represent one more factor contributing to initiation and/or pathogenesis of neurodegenerative changes. Current data support a role for air pollution in CNS damage and urban children shared mechanistic pathways potentially conducting to AD and PD (Calderón-Garcidueñas *et al.*, 2013a).

The short- and long-term effects of air pollution upon the CNS

We have discussed plausible mechanistic pathways causing CNS effects associated with sustained exposures of ambient pollutants during a lifetime, however, it should be clear that acute, subchronic or chronic exposures to air pollutants all have detrimental CNS effects. An example of acute and subchronic massive exposures was the World Trade Center 9/11-related environmental disaster (Bills *et al.*, 2008; Jordan *et al.*, 2013; Ozbay *et al.*, 2013). Massive exposure to a complex mixture of inhalable fine PM, nanoparticles (NPs) and toxic chemicals, resulted in persistent mental detrimental effects and evolution toward unknown brain health outcomes beyond posttraumatic stress disorder (Bills *et al.*, 2008; Jordan *et al.*, 2013; Ozbay *et al.*, 2013).

The olfactory bulb (OB) pathology needs special attention because large segments of the world population inhale toxic substances on daily basis that have the potential for harming the olfactory system and penetrating the brain via the olfactory epithelium (Calderón-Garcidueñas *et al.*, 2010). The issue is very important in the context of air pollution because olfactory dysfunction is among the earliest '*pre-clinical*' features of AD and PD, occurring in ~90% of early onset cases (Wang *et al.*, 2010; Doty, 2012). Early olfactory deficits in MCMA young residents appear to be associated with the presence of *β*-amyloid, *α*- synuclein, PM in glomerular structures and the massive distortion of the OB organization (Calderón-Garcidueñas *et al.*, 2010). The central delayed brainstem auditory evoked potentials (BAEPs), auditory impairment and vestibular dysfunction in exposed children is likely related to the extensive brainstem inflammation with accumulation of *β*-amyloid and *α*-synuclein in key auditory and vestibular nuclei (Calderón-Garcidueñas *et al.*, 2011). Neurodegenerative changes in the dorsal motor nucleus of the vagus, the nucleus of the solitary tract, arcuate nucleus, raphe midline, and extra-raphe medial and lateral tegmental neurons (Calderón-Garcidueñas *et al.*, 2011) are similar to the PD stages I and II of Braak *et al.* (2004) in highly exposed children has strong links with both AD and PD (Braak *et al.*, 2004; 2011).

Recent studies have reported associations between prenatal and perinatal exposures to air pollutants and autism spectrum disorder (ASD) in children (van den Hazel *et al.*, 2006; Larsson *et al.*, 2009; Herbert, 2010; Volk *et al.*, 2011; 2013; 2014; Becerra *et al.*, 2013; Roberts *et al.*, 2013; Visser *et al.*, 2013). ASD is likely caused by complex interactions between genetic and environmental factors. ASD is associated to air pollution exposures during pregnancy in US cities with significant air pollution from traffic sources (Becerra *et al.*, 2013). Activation of the maternal immune system during pregnancy and abnormal behavioral development in Rhesus monkey offspring brings up key questions regarding the role of air pollution and autism among vulnerable populations (Bauman *et al.*, 2013). To complicate matters for clinicians in real-world settings, the changes in the diagnostic criteria for autism in DSM-5 is causing significant controversies and concerns among health providers without formal training in research instruments and complicated assessment processes (Hazen *et al.*, 2013).

Reflections from practice

This paper is the product of discussions among the authors, all of us familiar with MCMA air pollution. We are physicians, pathologists, neuropathologists, auditory system experts, toxicologists, psychologists and atmospheric researchers dealing with children, worried parents and school officials, looking at neurodegenerative pathologies in autopsy materials from seemingly healthy children dying in accidents and having significant trouble in explaining parents plausible biological pathways that will solve all their questions. Several concerns have been raised in this

short review about the influence of air pollutants upon the adult and the developing brain that involve a wide spectrum of pathologies the clinician should take into account for short- and long-term CNS impact.

In adults, it is imperative to take care of chronic diseases that aggravate vascular, metabolic and structural brain changes, while advising the patient about tobacco and cigarette smoking and harmful occupations and hobbies. In children, the cognitive, auditory and vestibular effects have immediate early school negative effects, while the prefrontal lesions and the diffuse cortical neuroinflammation will be reflected in decreased career opportunities, negative social health outcomes, including increases in delinquent or criminal activity and violence and consequently a major negative impact on the economy in which those individuals reside. An issue everybody ignores is that the teens reduced capacity to block impulsive antisocial behavior that accompanies impaired fluid cognition is having a significant impact on society.

Next, we review more in detail the specific air pollution effects of brain impairment on cognition and behavior that support the practical reflections presented in this paper. Table 1 summarizes in schematic form selected studies examining neuro-cognitive/neurophysiological effects of air pollution in children, adolescents and young adult populations. The table shows the populations and the air pollutants studied, the tests and deficits found, other tests used and the city/cities/country where the study took place. In what follows we will be focusing mainly on the available findings concerning MCMA children and mechanistic studies on brain development in animal research literature.

Making the links: detrimental brain effects and cognitive/behavioral functions

As we have already mentioned, depending on the pollutant component, doses, exposure protocol, age and gender, health status, etc., the detrimental effects range from endothelial dysfunction, BBB breakdown, dopaminergic neuronal damage, DNA damage, white matter lesions, neuroinflammation, formation of free radicals and oxidative stress, to the identification of early hallmarks of AD and PD (Campbell *et al.*, 2004; Fonken *et al.*, 2011;

Levesque *et al.*, 2011; Win-Shwe and Fujimaki, 2011; Wu *et al.*, 2011; Brun *et al.*, 2012; Guo *et al.*, 2012; Sharma and Sharma, 2012; Trickler *et al.*, 2012). The chronic effects of $PM_{2.5}$ in mice result in spatial learning and memory deficits with neuroinflammation and hippocampal dendritic alterations (Fonken *et al.*, 2011). Metal accumulation is associated with memory dysfunction, especially if the metal is administered during the neonatal period, a clear example being iron loading in rodents resulting in impaired spatial memory and in long-term retention of object recognition deficient memory (Schröder *et al.*, 2013). Equally important in the context of urban environments is the massive exposure to NPs entering the body mostly through inhalation (Win-Shwe *et al.*, 2011; Brun *et al.*, 2012). Gold and silver NPs have an effect on human embryonic neural precursor cell growth, suggesting a negative impact of NPs on the developing CNS (Söderstjerna *et al.*, 2013). Intense oxidative damage and lipid, protein and DNA peroxidation are observed in mice after intranasal administration of TiO_2 NPs (Ze *et al.*, 2014). Ferromagnetic mineral magnetite (Fe(3)O (4)) NPs cause structural changes of microtubule and tau protein, essential in the memory mechanism and memory dysfunction (Dadras *et al.*, 2013). Ozone, the main component of photochemical pollution in urban areas has been shown to alter adult neurogenesis and produce progressive hippocampal neurodegeneration along with memory deficits in rats exposed to low subchronic concentrations (Rivas-Arancibia *et al.*, 2010).

Clinically healthy urban children from MCMA selected by stringent criteria exhibited structural, neurophysiological and cognitive detrimental effects compared with matched SES, gender, age and mother's IQ low pollution exposed children (Calderón-Garcidueñas *et al.*, 2008a; Calderón-Garcidueñas *et al.*, 2011a). The cognitive deficits in MC children matched the magnetic resonance imaging (MRI) volumetric changes in their right parietal and bilateral temporal areas (Calderón-Garcidueñas *et al.*, 2012b). Highly exposed children without white matter hyperintensities (WMH−) displayed the profile of classical pro-inflammatory defensive responses: high IL-12, production of powerful pro-inflammatory cytokines and low concentrations of key cytokines and chemokines associated with neuroprotection. Conversely, children with WMH+ exhibited a response involved in

Table 1 Selected studies examining neurocognitive/neurophysiological effects of air pollution in children, adolescents and young adult populations. The table shows the populations and the air pollutants studied, the tests and deficits found, other tests used and the city/cities/country where the study took place

Study	Exposed/pollutants measured	Neurobehavioral/ neurophysiological tests	Neurocognitive/neurophysiological results	Other tests/laboratory longitudinal follow-up	City, country
Calderón-Garcidueñas *et al.* (2008a)	73 children 9.85 ± 2.15 years Urban Mexico City atmosphere	WISC-R	Deficits in a combination of fluid and crystallized cognition tasks: object assembly, picture arrangement, digit span, information, arithmetic, mazes, vocabulary	Brain MRI ApoE genotyping Comparative neuropathology Dog brain RT-PCR	Mexico City versus Control City, Mexico
Suglia *et al.* (2008)	202 children 9.7 ± 1.7 years Black carbon	Wide range assessment of memory and learning Kaufman Brief Intelligence Test	Decreases on the visual subscale and general index Decreases in vocabulary, matrices and composite intelligence quotient scores	na	Boston, MA, USA
Wang *et al.* (2009)	861 children 8–10 years NO_2 and $PM10$	Line discrimination (LDT) Visual retention (VRT) Visual simple reaction time, preferred hand (VRT-Prh) Visual simple reaction time, nonpreferred hand (VRT-Nprh) Continuous performance (CPT) Digit erase (DET) Digit symbol (DSB) Pursuit aiming (PAT) Sign register (SRT)	Visual simple reaction time with preferred hand and with nonpreferred hand, continuous performance, digit symbol, pursuit aiming, and sign register	na	Quanzhou, China
Calderón-Garcidueñas *et al.* (2010)	87 teens, young adults 21.2 ± 2.7 years Urban Mexico City atmosphere	The University of Pennsylvania Smell Identification Test (UPSIT)	Olfaction deficits in 35.5% of Mexico City subjects ApoE 4 carriers failed 10-items related to Alzheimer's disease $P = 0.01$ versus low air pollution controls	Olfactory bulb neuropathology in children and young adults: βA 1–42 and α-synuclein immunoreactivity, ultrafine particles and vascular changes ApoE genotyping	Mexico City versus Control City, Mexico
Freire *et al.* (2010)	210 children from rural and urban areas Five-year-olds NO_2	McCarthy Scales of Children's Abilities (MSCA)	Decreases in general cognitive scores and in quantitative, working memory and gross motor areas	One-year follow-up from age four years	Granada, Spain
Calderón-Garcidueñas *et al.* (2011)	51 children 8.0 ± 0.7 years Urban Mexico City atmosphere	Brainstem auditory evoked potentials (BAEPs)	Significant delays in wave III ($P < 0.0001$), and wave V ($P < 0.0001$) in Mexico City versus controls consisting with delayed central conduction time of brainstem neural transmission	Brainstem pathology in nine children aged 13.9 ± 4.0 years Brainstem inflammation and accumulation of βA 1–42 and α-synuclein in auditory and vestibular nuclei. α-synuclein in pigmented neurons of the substantia nigrae	Mexico City versus Control City, Mexico
Haynes *et al.* (2011)	Rate of criminal adjudications/10 000 people/10–19 years	Criminal behavior	Airborne exposure to Mn, Hg and PM are associated with increased risk of criminal activity adjudication	Antisocial behavior Ecological relationship between county-wide reported airborne emissions of air metals, PM and youth adjudicated for criminal activity	Ohio counties, USA

Table 1 Continued

Study	Exposed/pollutants measured	Neurobehavioral/ neurophysiological tests	Neurocognitive/neurophysiological results	Other tests/laboratory longitudinal follow-up	City, country
Calderón-Garcidueñas et al. (2011)	20 children 6.95 ± 0.67 years Urban Mexico City atmosphere One-year follow-up	WISC-R	Progressive deficits in digit span and vocabulary in Mexico City children versus controls The cognitive deficits in highly exposed children matched the significant differences in white matter volumes involving right parietal and bilateral temporal lobes	Brain MRI	Mexico City versus Control City, Mexico
Clark et al. (2012)	719 children 9–10 years 22 schools around London's Heathrow airport	Suffolk Reading Scale 2 Child Memory Scale The Search and Memory Task Health	Aircraft noise exposure at school was significantly associated with poorer recognition memory, reading comprehension, information recall, and conceptual recall	Parents completed a self-report questionnaire that included questions on sociodemographic factors, as well as questions on the perceived health of their children and psychological distress measured using the parental version of the Strengths and Difficulties Questionnaire	
Calderón-Garcidueñas et al. (2012c)	20 children 6.95 ± 0.67 years Urban Mexico City atmosphere Baseline and one-year follow-up	WISC-R	MC WMH− children displayed classical pro-inflammatory defensive responses versus WMH+ children responses involving resolution of inflammation, immunoregulation, and tissue remodeling. The MC WMH+ group responded to the air pollution-associated brain volumetric alterations with white and gray matter volume increases in temporal, parietal, and frontal regions and better cognitive performance compared to MC WMH−	Brain MRI Measurement of white matter hyperintensities (WMH) Inflammatory mediators	Mexico City versus Control City, Mexico
van Kempen et al. (2012)	553 children 10.5 ± 0.6 years Schiphol-Amsterdam Airport NO_2 exposures	Simple Reaction Time Test (SRTT) Switching Attention Test (SAT) Hand–Eye Coordination Test Symbol Digit Substitution Test (SDST) Digit Memory Span Test (DMST)	Exposure to NO_2 at school was statistically significantly associated with a decrease in the memory span length Statistically significant associations were observed between road and air traffic noise exposure at school and the number of errors made during the 'arrow' and 'switch' conditions of the SAT	na	Amsterdam, The Netherlands

The table shows the populations and the air pollutants studied, the tests and deficits found, other tests used and the city/cities/country where the study took place.

resolution of inflammation, immunoregulation and tissue remodeling. The WMH+ group responded to the air pollution-associated brain volumetric alterations with white and gray matter volume increases in temporal, parietal and frontal regions and better cognitive performance compared with the WMH− group. We conclude that complex modulation of cytokines and chemokines influences children's CNS structural and volumetric responses and cognitive correlates resulting from environmental pollution exposures. Regardless of the presence of prefrontal WMH, MC children performed more poorly across a variety of cognitive tests, compared with control children.

We have identified a number of abnormalities also within the auditory brainstem nuclei in children exposed to severe air pollution. Specifically, we have observed that neuronal cell bodies within the medial superior olive (MSO) are significantly smaller and more round than those in age-matched control brains (Calderón-Garcidueñas *et al*., 2011b). We interpret this dysmorphology to indicate injury and dysfunction in the MSO. The MSO is the largest nucleus within the human superior olivary complex and has clear roles in localization of sound sources, encoding temporal features of sound and likely plays an important role in brainstem encoding of speech. Incidentally, similar morphological alterations were observed in autistic children (Kulesza and Mangunay, 2008; Kulesza *et al*., 2011). Confirming brainstem pathology, MCMA children showed clearly abnormal BAEPs with delays in wave III and wave V but no delay in wave I. These findings are consistent with delayed central conduction time of brainstem neural transmission, and increased risk for auditory and vestibular impairment (Calderón-Garcidueñas *et al*., 2011b). We are assessing the integrity of the auditory system in highly exposed children through a number of noninvasive techniques, such as BAEPs, otoacoustic emissions, speech recognition tasks and listening in background noise.

It is clear that air pollution exposed children experience a chronic, intense state of oxidative stress and exhibit an early brain imbalance in genes involved in inflammation, innate and adaptive immune responses, cell proliferation and apoptosis. Neuroinflammation, endothelial activation and the breakdown of the BBB contribute to cognitive impairment and pathogenesis and pathophysiology of neurodegenerative states (Roher *et al*., 2012;

Jian *et al*., 2013). The associations between cognition and urban pollution has been established in cities like Boston, where black carbon – a marker for traffic PM – predicted decreased cognitive function across assessments of verbal and nonverbal intelligence and memory in nine-year-olds (Suglia *et al*., 2008).

A working framework for prevention and intervention

Although genetic factors play a key role in CNS responses (as evidenced by the acceleration of neurodegenerative pathology in children carrying an APOE 4 allele), studies such the above mentioned ones in Boston and others, sketch a complex scenario where air pollution and SES can influence neural development and cognition, as well as genetics, nutrition, access to a cognitively stimulating environment, thereby influencing and determining mental health, academic achievements and overall life performance (D'Angiulli *et al*., 2009; Siddique *et al*., 2011; Calderón-Garcidueñas & Torres-Jardón, 2012a; Becerra *et al*., 2013).

Thus, identification of children at risk for cognitive deficits, brain structural/volumetric and neurodegenerative accelerating changes should be prioritized in populations exposed to significant concentrations of air pollutants. There is growing public concern about the direct and indirect influences air pollution may have on several developmental outcomes such as school performance, behavioral changes and mood disorders in children and teens. Moreover, childhood aggression and teen delinquency are increasing in megacities, establishing early environmental health risk factors for violence prediction and prevention (Haynes *et al*., 2011; Liu, 2011) in populations at risk will be absolutely critical. New concerns involve the association between air pollution exposure and increased risk of attention deficit hyperactive disorder (Siddique *et al*., 2011) and autism (Becerra *et al*., 2013) in young and older children.

Strong support for the need of neurocognitive screening comes from a growing psychological and epidemiological literature suggesting evidence of suboptimal cognitive functioning across the developmental span in clinically healthy children (Guxens and Sunyer, 2012; Calderón-Garcidueñas

et al., 2012b). Importantly, a significant proportion of urban schools are situated near major traffic-related air pollution sources (Amram *et al.*, 2011; Amato *et al.*, 2014), and cognitive outcomes may be partly associated with air pollution levels around schools (Mohai *et al.*, 2011).

Consistent with these observations, the National Institute of Environmental Health Sciences/National Institute of Health panel on outdoor air pollution indicated cognitive, neuropsychological (and possibly neuroimaging) screening of children as one of the priority target areas for future research advocating a multidisciplinary collaborative approach wherein brain-related cognitive (henceforth, neurocognitive) development testing would have a prominent role (Block *et al.*, 2012).

Hence, the use of standard neurocognitive tasks to screen clinically healthy children in schools or pediatric offices seems not only desirable but also highly beneficial. Because the primary goal would be to identify children at risk, possibly at the largest scale, the first step could be to screen entire schools in different neighborhoods with different air pollutant profiles. Multidisciplinary approaches for early risk identification could include using air pollution databases from available monitoring stations to gather: (1) Air pollutant profiles in selected geographic area; (2) exposures to traffic-related air pollutants at each child's school and current residence with land use regression models that combine a geographic information system with ambient passive monitoring in the target area; (3) cumulative ambient exposures to fine $PM_{2.5}$; (4) robust baseline information on the oxidative potential and metal content of PM found in the targeted regions; (5) cognitive screening first and, when applicable, more elaborate neurocognitive/neurophysiological follow-ups, which could include EEG/ERPs, BAEPs, MRI, f MRI and MRS.

The first goal in targeted areas will be to define the cohorts with the most risk for neurocognitive deficits based on traffic emissions, fixed sources of contaminants, profile of toxic pollutant components (ie, metals) and cumulative concentrations of fine PM. The initial studies should be followed by interventions aimed at breaking the cycle of air pollution, indoor air pollution, tobacco use, high body mass index, low fruit and vegetable intake and physical inactivity. Since health risk factors are more likely to have a toll on low SES children, identification of spatial concentrations of low SES

Table 2 Suggested battery of neuropsychological and psychoeducational tests for the initial screening of school-aged children and teens exposed to urban air pollution

1. Rapid mental health screening tool for pediatric use that includes: education, activities/peers, drugs/alcohol, suicidality, emotions/behavior discharge resources like HEADS-ED (Cappelli *et al.*, 2012)
2. Test for episodic memory
   Rey Auditory Verbal learning Test (RAVLT): learning, immediate and delayed recall
   Weschler's Logical Memory (WLM): immediate and delayed recall
3. Speed/executive functions
   Digit symbol WAIS-R
4. Visuospatial function
   Rey Complex Figure Test
   Block design WAIS-R
5. Semantic memory/verbal functions
   Similarities WAIS-R
6. Verbal working memory/fluency
   Digit Span WAIS-R
   Word fluency (COWA)

pediatric populations at risk, should be prioritized (Forastiere *et al.*, 2007; Ou *et al.*, 2008).

According to the American Neuropsychiatric Association and the Shulman criteria (Malloy *et al.*, 1997; Shulman, 2000), the ideal cognitive screening instrument should (i) be relatively brief to administer; (ii) be easy to score; (iii) well tolerated and accepted by participants, in our cases both child and parent; (iv) test all targeted cognitive domains; (v) be valid and reliable; and (vi) relatively independent of or controlling for age and education.

A possible battery of tests (easily translatable in many languages) for the initial screening of school-aged children is described in Table 2. The measures in this table have reference to previous neuroimaging findings implicating functional, maturational or structural correlates of frontal, parietal and temporal regions and/or neurocognitive tests applied to air pollution studies in children as seen on Table 1. Because several studies link risk of negative effects of air pollution to early development, from infancy to preschool, screening could start in daycare or during transition from kindergarten to first grade, for example using tools such as the Early Development Instrument (D'Angiulli *et al.*, 2009). With advances in wireless neuroimaging technology, neurocognitive screening may even incorporate rapid EEG/ERP recording procedures.

In summary, air pollution effects on the developing brain may vary along a continuum from

minor subclinical deficits in cognitive functioning to significant cognitive deficits that are identified readily by parents and/or teachers. The detrimental effects may also worsen with the age of the child, thus selected neurocognitive tools ought to be useful for longitudinal studies, across educational backgrounds and expecting overlaps in the functional areas and tests affected. Complex cognitive responses that may be affected include attention and short-term memory, information processing speed and executive function, verbal abstraction and visuospatial and motor skills. We should also expect deficits in auditory and vestibular responses and sound localization, along with olfaction deficits. The diffuse nature of the neuroinflammation and the neurodegenerative changes observed in exposed children obligates us not to rely on a single study or measure but rather to employ a weight of evidence approach incorporating current clinical, neurophysiological, radiological and epidemiological research as well as the results of animal exposure studies to single pollutants/mixtures/or pollutant components. Inflammatory biomarkers play a key role in the identification of children with positive volumetric and cognitive responses to their lifelong pollutant exposures (Calderón-Garcidueñas *et al.*, 2012b) and since neuroinflammation/vascular damage/neurodegeneration go hand in hand (Calderón-Garcidueñas *et al.*, 2013a and 2013b), definition of inflammatory/ endothelial dysfunction biomarkers establishing an association between brain growth and cognition are urgently needed.

Of course, in light of the findings reviewed in the present paper, a pressing important question that jumps to mind is whether the prevalence of AD/ PD is increased in MCMA? Unfortunately we do not have accurate records from health institutions. Mexico health care is covered by both private and government hospitals and institutes and there is no universal statistical information regarding AD and PD prevalence. Empirically, however, neurologists and general practitioners report a significant increase in the number of cases for both neurodegenerative diseases (Victor Esquivel MD, Neurologist, personal communication). Death certificates that would be a source of information, unfortunately fail to list AD or PD in the certificate, basically because families are reluctant to link their patients to a disease with genetic implications, and so only allowed for the writing of acute causes of death like pneumonia, but not the base disease. Therefore, the answer to the central issue of incidence of AD/PD in MCMA is very much an open empirical question for future research.

Our ultimate goal is to protect exposed children through multidimensional interventions yielding both impact and reach: cognitive (Diamond and Lee, 2011), family participation (Josephson, 2013) and modifiable lifestyle factors such as diet and micronutrient supply (Villarreal-Calderon *et al.*, 2010; Calderón-Garcidueñas *et al.*, 2012c).

Air pollution brain effects on children and teens ought to be key public health targets.

Key points to remember

- Risk for stroke and depression are associated with common ambient air pollutants, including fine and UFPM and ozone.
- The stroke risk is present even at pollutant concentrations below the current standards, meaning there is a wide spectrum of susceptibility to pollutants likely related to factors such as the presence of chronic diseases, and genetic and nutrition variables.
- Stroke is not a stroke, *specific patient characteristics modify associations between air pollution and ischemic stroke* (Villeneuve *et al.*, 2012).
- Check for factors that will aggravate the neurological/psychiatric effects of air pollution such as diabetes, hypertension, infectious processes, residency in close proximity to a busy road, changes in occupation, etc.
- Keep an eye on the air quality index of your city, record proximity of the patient to high density traffic (Mohai *et al.*, 2011; van Kempen *et al.*, 2012) or fixed sources of pollutants, check for acute events such as forest fires or the arrival of fumes from a distant area (Chen *et al.*, 2013).
- PM occupational exposures and tobacco are to be taken into consideration as important sources of pollutants.
- The patient's occupation and hobbies are important. Is she an outdoor person? Is he protected against toxic substances at work? Is there a significant source of PM or NPs at the office? Where is the patient from? A good clinical history is a must.
- Parents and school officials should be aware of the high pollutant concentrations in their area and keep children indoors.

- Identification of children at risk for cognitive deficits, brain structural/volumetric and neurodegenerative accelerating changes should be prioritized in populations exposed to significant concentrations of air pollutants.
- Brain damage is cumulative and has deleterious effects on cognitive, emotional and behavioral areas.
- Preventive measures against the harmful effects of environmental pollution should be referred to and applied as early as the conception time.
- Finally, we must consider whether we want to pay the high price that involves ignoring the serious health impacts of environmental pollution.

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Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the institutional guidelines based on the Helsinki Declaration of 1975, as revised in 2008.

References

Aiken, A.C., Salcedo, D., Cubison, M.J., Huffman, A. and DeCarlo, P.E. 2009: Mexico City aerosol analysis during MILAGRO using high resolution aerosol mass spectrometry at the urban supersite (T0) e part 1: fine particle composition and organic source apportionment. *Atmospheric Chemistry and Physics* 9, 6633–53.

Amato, F., Rivas, I., Viana, M., Moreno, T., Bouso, L., Reche, C., Alvarez-Pedrerol, M., Alastuey, A., Sunyer, J., Querol, X. 2014: Sources of indoor and outdoor PM2.5 concentrations in primary schools. *Science of the Total Environment* 490C, 757–65.

Amram, O., Abernethy, R., Brauer, M., Davies, H. and Allen, R.W. 2011: Proximity of public elementary schools to major roads in Canadian urban areas. *International Journal of Health Geographics* 10, 68.

Annesi-Maesano, J., Baiz, N., Banerjee, S., Rudnai, P. and Rive, S., SINPHONIE Group. 2013: Indoor air quality and sources in schools and related health effects. *Journal of Toxicology and Environmental Health. Part B Critical Reviews* 16, 491–550.

Banerjee, M., Siddique, S., Dutta, A., Mukherjee, B. and Ray, M.R. 2012: Cooking with biomass increases the risk of depression in pre-menopausal women in India. *Social Science & Medicine* 75, 565–72.

Bauman, M.D., Iosif, A.M., Smith, S.E., Bregere, C., Amaral, D.G. and Patterson, P.H. 2013: Activation of the maternal immune system during pregnancy alters behavioral development of Rhesus monkey offspring. *Biological Psychiatry* 75, 332–41.

Becerra, T.A., Wilhelm, M., Olsen, J., Cockburn, M. and Ritz, B. 2013: Ambient air pollution and autism in Los Angeles county, California. *Environmental Health Perspectives* 121, 80–386.

Bedada, G.B., Smith, C.J., Tyrrell, P.J., Hirst, A.A. and Agius, R. 2012: Short-term effects of ambient particulates and gaseous pollutants on the incidence of transient ischemic attack and minor stroke: a case-crossover study. *Environmental Health*. doi: 10.1186/1476-069X-11-77.

Beelen, R., Raaschou-Nielsen, O., Stafoggia, M., Andersen, Z.J. 2013: Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicenter ESCAPE project. *Lancet* 383, 785–95.

Bell, M., Davis, D.L. and Fletcher, T. 2004: A retrospective assessment of mortality from the London smog episode of 1952: the role of influenza and pollution. *Environmental Health Perspectives* 112, 6–8.

Bell, M.L., Goldberg, R., Hogrefe, C., Kinney, P.L., Knowlton, K., Lynn, B., Rosenthal, J., Rosenzweig, C. and Patz, J.A. 2007: Climate change, ambient ozone, and health in 50 US cities. *Climatic Change* 82, 61–76.

Benn, T., Cavanagh, B., Hristovski, K., Posner, J.D. and Westerhoff, P. 2010: The release of nanosilver from consumer products used in the home. *Journal of Environmental Quality* 39, 1875–82.

Bergin, I.L. and Witzmann, F.A. 2013: Nanoparticle toxicity by the gastrointestinal route: evidence and knowledge gaps. *International Journal of Biomededical Nanoscience and Nanotechnology* 3, 1–2.

Bills, C.B., Levy, N.A., Sharma, V., Charney, D.S., Herbert, R., Moline, J. and Katz, C.L. 2008: Mental health of workers and volunteers responding to events of 9/11: review of the literature. *Mount Sinai Journal of Medicine* 75, 115–27.

Blasko, I., Stampfer-Kountchev, M., Robatscher, P., Veerhuis, R., Eikelenboom, P. and Grubeck-Loebenstein, B. 2004: How chronic inflammation can affect the brain and support the development of Alzheimer's disease in old age: the role of microglia and astrocytes. *Aging Cell* 3, 169–76.

Block, M.L. and Calderón-Garcidueñas, L. 2009: Air pollution: mechanisms of neuroinflammation and CNS disease. *Trends in Neurosciences* 32, 506–16.

Block, M.L., Elder, A., Auten, R.L., Bilbo, S.D., Chen, H., Chen, J.C., Cory-Slechta, D.A., Costa, D., Diaz-Sanchez, D., Dorman, D.C., Gold, D.R., Gray, K., Jeng, H.A., Kaufman, J.D., Kleinman, M.T., Kirshner, A., Lawler, C., Miller, D.S., Nadadur, S.S., Ritz, B., Semmens, E.O., Tonelli, L.H., Veronesi, B., Wright, R.O., Wright, R.J. 2012: The outdoor air pollution and brain health workshop. *Neurotoxicology* 33, 972–84.

Bonotis, K., Krikki, E., Holeva, V., Aggouridaki, C., Costa, V. and Baloyannis, S. 2008: Systemic immune aberrations in Alzheimer's disease patients. *Journal of Neuroimmunology* 193, 183–87.

Braak, H., Ghebremedhin, E., Rüb, U., Bratzke, H. and Del Tredeci, K. 2004: Stages in the development of Parkinson's disease-related pathology. *Cell and Tissue Research* 318, 121–34.

Braak, H., Thal, D.R., Ghebremedhin, E. and Del Tredeci, K. 2011: Stages of the pathological process in Alzheimer's disease: age categories from 1 to 100 years. *The Journal of Neuropathology & Experimental Neurology* 70, 960–69.

Brackbill, R.M., Thorpe, L.E., DiGrande, L., Perrin, M., Sapp, J.H. 2nd, Wu, D., Campolucci, S., Walker, D.J., Cone, J., Pulliam, P., Thalji, L., Farfel, M.R. and Thomas, P. 2006: Surveillance for World Trade Center disaster health effects among survivors of collapsed and damaged buildings. *MMWR Surveillance Summeries* 55, 1–18.

Bravo-Alvarez, H. and Torres-Jardón, R. 2002: Air pollution levels and trends in the México City metropolitan area. In Fenn, M.E., de Bauer, L.I. and Hernández-Tejeda, T., editors, *Urban air pollution and forest: resources at risk in the Mexico City air basin*. Ecological Studies, Chapter 6, Volume 156. New York: Springer-Verlag, 121–59.

Brook, R., Rajagopala, S., Pope, A., Brook, J.R., Bhatnagar, A., Diez-Roux, A.V., Holguin, F., Hong, Y., Luepker, R.V., Mittleman, M.A., Peters, A., Siscovick, D., Smith, S.C., Whitse, L. and Kaufman, J. 2010: Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation* 12, 2331–78.

Brown, K.W., Sarnat, J.A. and Koutrakis, K. 2012: Concentrations of PM2.5 mass and components in residential and non-residential indoor microenvironments: the Source and Composition of particulate exposure study. *Journal of Exposure Science & Environmental Epidemiology* 22, 161–72.

Brun, E., Carrière, M. and Mabondzo, A. 2012: In vitro evidence of dysregulation of blood-brain barrier function after acute and repeated/long term exposure to TiO2 nanoparticles. *Biomaterials* 33, 886–96.

Calderón-Garcidueñas, L., Mora-Tiscareño, A., Fordham, L.A., Valencia-Salazar, G., Chung, C.J., Rodriguez-Alcaraz, A., Paredes, R., Variakojis, D., Villarreal-Calderón, A., Flores-Camacho, L., Antunez-Solis, A., Henríquez-Roldán, C. and Hazucha, M.J. 2003: Respiratory damage in children exposed to urban pollution. *Pediatric Pulmonology* 36, 148–61.

Calderón-Garcidueñas, L., Mora-Tiscareño, A., Ontiveros, E., Gómez-Garza, G., Barragán-Mejía, G., Broadway, J., Chapman, S., Valencia-Salazar, G., Jewells, V., Maronpot, R.R., Henríquez-Roldán, C., Pérez-Guillé, B., Torres-Jardón, R., Herrit, L., Brooks, D., Osnaya-Brizuela, N., Monroy, M.E., González-Maciel, A., Reynoso-Robles, R., Villarreal-Calderon, R., Solt, A.C. and Engle, R.W. 2008a: Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. *Brain and Cognition* 68, 117–27.

Calderón-Garcidueñas, L., Villarreal-Calderon, R., Valencia-Salazar, G., Henríquez-Roldán, C., Gutiérrez-Castrellón, P., Torres-Jardón, R., Osnaya-Brizuela, N., Romero, L., Torres-Jardón, R., Solt, A. and Reed, W. 2008b: Systemic inflammation, endothelial dysfunction, and activation in clinically healthy children exposed to air pollutants. *Inhalation Toxicology* 20, 499–506.

Calderón-Garcidueñas, L., Solt, A., Franco-Lira, M., Torres-Jardón, R., Nuse, B., Herritt, L., Villarreal-Calderón, R., Osnaya, N., Stone, I., García, R., Brooks, D.M., González-Maciel, A., Reynoso-Robles, R., Delgado-Chávez, R. and Reed, W. 2008c: Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain-barrier, ultrafine particle deposition, and accumulation of amyloid beta 42 and alpha synuclein in children and young adults. *Toxicologic Pathology* 36, 289–310.

Calderón-Garcidueñas, L., Macias-Parra, M., Hoffmann, H.J., Valencia-Salazar, G., Henríquez-Roldán, C., Monte, O.C., Barragán-Mejía, G., Villarreal-Calderon, R., Romero, L., Granada-Macías, M., Torres-Jardón, R., Medina-Cortina, H. and Maronpot, R.R. 2009: Immunotoxicity and environment: immunodysregulation and systemic inflammation in children. *Toxicologic Pathology* 37, 161–69.

Calderón-Garcidueñas, L., Franco-Lira, M., Henríquez-Roldán, C., González-Maciel, A., Reynoso-Robles, R., Villarreal-Calderon, R., Herritt, L., Brooks, D., Keefe, S., Palacios-Moreno, J., Torres-Jardón, R., Medina-Cortina, H., Delgado-Chávez, R., Aiello-Mora, M., Maronpot, R.R. and Doty, R.L. 2010: Urban air pollution: influences on olfactory function and pathology in exposed children and young adults. *Experimental and Toxicologic Pathology* 62, 91–102.

Calderón-Garcidueñas, L., D'Angiulli, A., Kulesza, R.J., Torres-Jardón, R., Osnaya, N., Romero, L., Keefe, S., Herritt, L., Brooks, D.M., Avila-Ramirez, J., Delgado-Chávez, R., Medina-Cortina, H. and González-González, L.O. 2011a: Air pollution is associated with brainstem auditory nuclei pathology and delayed brainstem auditory evoked potentials. *International Journal of Developmental Neuroscience* 29, 365–75.

Calderón-Garcidueñas, L., Engle, R., Mora-Tiscareño, A., Styner, M., Gomez-Garza, G., Zhu, H., Jewells, V., Torres-Jardón, R., Romero, L., Monroy-Acosta, M.E., González-González, L.O., Medina-Cortina, H. and D'Angiulli, A. 2011b: Exposure to severe urban air pollution influences cognitive outcomes, brain volume and

systemic inflammation in clinically healthy children. *Brain and Cognition* 77, 345–55.

Calderón-Garcidueñas, L. and **Torres-Jardón, R.** 2012a: Air pollution, socioeconomic status and children's cognition in megacities: the Mexico City scenario. *Frontiers in Psychology* 3, 217.

Calderón-Garcidueñas, L., Kavanaugh, M., Block, M.L., D'Angiulli, A., Delgado-Chávez, R., Torres-Jardón, R., González-Maciel, A., Reynoso-Robles, R., Osnaya, N., Villarreal-Calderon, R., Guo, R., Hua, Z., Zhu, H., Perry, G. and **Diaz, P.** 2012b: Neuroinflammation, hyperphosphorilated tau, diffuse amyloid plaques and down-regulation of the cellular prion protein in air pollution exposed children and adults. *Journal of Alzheimer's Disease* 28, 93–107.

Calderón-Garcidueñas, L., Mora-Tiscareño, A., Styner, M., Gómez-Garza, G., Zhu, H., Torres-Jardón, R., Carlos, E., Solorio-López, E., Medina-Cortina, H., Kavanaugh, M. and **D'Angiulli, A.** 2012c: White matter hyperintensities, systemic inflammation, brain growth, and cognitive functions in children exposed to air pollution. *Journal of Alzheimer's Disease* 31, 183–91.

Calderón-Garcidueñas, L., Franco-Lira, M., Mora-Tiscareño, A., Medina-Cortina, H., Torres-Jardón, R. and **Kavanaugh, M.** 2013a: Early Alzheimer's and Parkinson's disease pathology in urban children: friend versus foe responses – it is time to face the evidence. *Biomed Research International*. doi: 10.1155/2013/161687.

Calderón-Garcidueñas, L., Cross, J.V., Franco-Lira, M., Aragón-Flores, M., Kavanaugh, M., Torres-Jardón, R., Chao, C.K., Thompson, C., Chang, J., Zhu, H. and **D'Angiulli, A.** 2013b: Brain immune interactions and air pollution: macrophage inhibitory factor (MIF), prion cellular protein (PrPc), interleukin-6 (IL6), interleukin 1 receptor antagonist (IL-1Ra) and interleukin-2 (IL2) in cerebrospinal fluid and MIF in serum differentiate urban children exposed to severe v low air pollution. *Frontiers in Neuroscience* 7, 183.

Campbell, A. 2004: Inflammation, neurodegenerative diseases and environmental exposures. *Annals of the New York Academy of Sciences* 1035, 117–32.

Cappelli, M., Gray, C., Zemek, R., Cloutier, P., Kennedy, A., Glennie, E., Doucet, G., Lyons, J.S. 2012: The HEADS-ED: a rapid mental health screening tool for pediatric patients in the emergency department. *Pediatrics* 130, e321–27.

Carlsen, H.K., Forsberg, B., Meister, K., Gislason, T. and **Oudin, A.** 2013: Ozone is associated with cardiopulmonary and stroke emergency hospital visits in Reykjavík, Iceland 2003-2009. *Environmental Health*. doi: 10.1186/1476-069X-12-28.

Castellani, R.J., Zhu, X., Zhu, X., Moreira, P.I., Perry, G. and **Smith, M.A.** 2006: Involvement of oxidative stress in Alzheimer disease. *The Journal of Neuropathology & Experimental Neurology* 65, 631–41.

Clark, C., Crombie, R., Head, J., van Kamp, I., van Kempen, E. and **Stansfeld, S.A.** 2012: Does traffic-related air pollution explain associations of aircraft and road traffic noise exposure on children's health and cognition? A secondary analysis of the United Kingdom sample from the RANCH project. *American Journal of Epidemiology* 176, 327–37.

Cunningham, C., Campion, S., Lunnon, K., Murray, C.L., Woods, J.F., Deacon, R.M., Rawlins, J.N. and **Perry, V.H.** 2009: Systemic inflammation induces acute behavioral and cognitive changes and accelerates neurodegenerative disease. *Biological Psychiatry* 65, 304–12.

Chen, B. and **Kan, H.** 2008: Air pollution and population health: a global challenge. *Environmental Health and Preventive Medicine* 13, 94–101.

Chen, L., Villeneuve, P.J., Rowe, B.H., Liu, L. and **Stieb, D.M.** 2013: The Air Quality Health Index as a predictor of emergency department visits for ischemic stroke in Edmonton, Canada. *Journal of Exposure Science & Environmental Epidemiology* 24, 358–64.

D'Angiulli, A., Warburton, W., Dahinten, S. and **Hertzman, C.** 2009: Population-level associations between preschool vulnerability and grade-four basic skills. *PLoS One* 4, e7692.

Dadras, A., Riazi, G.H., Afrasiabi, A., Naghshineh, A., Ghalandari, F. and **Mokhtari, F.** 2013: In vitro study of the alterations of brain tubulin structure and assembly affected by magnetite nanoparticles. *Journal of Biological Inorganic Chemistry* 18, 357–69.

Davis, D.A., Bortolato, M., Godar, S.C., Sander, T.K., Iwata, N., Pakbin, P., Shib, J.C., Berhane, K., McConnell, R., Sioutas, C., Finch, C.E., Morgan, T.E. and **Block, M.** 2013: Prenatal exposure to urban air nanoparticles in mice causes altered neuronal differentiation and depression-like responses. *PLoS One* 8, e64128.

Diamond, A. and **Lee, K.** 2011: Interventions shown to aid executive function development in children 4 to 12 years old. *Science* 333, 959–64.

Dik, M.G., Jonker, C., Hack, C.E., Smit, J.H., Comijs, H.C. and **Eikelenboom, P.** 2005: Serum inflammatory proteins and cognitive decline in older persons. *Neurology* 64, 1371–77.

Doty, R.L. 2012: Olfactory dysfunction in Parkinson disease. *Nature Reviews. Neurology* 8, 329–39.

European Topic Centre on Air and Climate Change (ETC/ACC). 2009 Report. Retrieved 18 June 2014 from http://acm.eionet.europa.eu/reports/ETCACC_TP_2009_1_European_PM2.5_HIA

Eikelenboom, P., van Exel, E., Veerhuis, R., Rozemuller, A.J., van Gool, W.A. and **Hoozemans, J.J.** 2011: Innate immunity and the etiology of late-onset Alzheimer's disease. *Neurodegenerative Disease* 10, 271–73.

Finch, C.E. and **Morgan, T.E.** 2007: Systemic inflammation, infection, ApoE alleles and Alzheimer disease: a position paper. *Current Alzheimer Research* 4, 185–89.

Fonken, L.K., Xu, X., Weil, Z.M., Chen, G., Sun, Q., Rajagopalan, S. and **Nelson, R.J.** 2011: Air pollution impairs cognition, provokes depressive-like behaviors and alters hippocampal cytokine expression and morphology. *Molecular Psychiatry* 16, 987–95.

Forastiere, F., Stafoggia, M., Tasco, C., Picciotto, S., Agabiti, N., Casaroni, G., Perucci, C.A. 2007: Socio-economic status, particulate air pollution, and daily mortality: differential exposure. *American Journal of Industrial Medicine* 50, 208–16.

Freire, C., Ramos, R., Puertas, R., Lopez-Espinoza, M.J., Julyez, J., Aguilera, I., Cruz, F., Fernandez, M.F., Sunyer, J. and Olea, N. 2010: Association of traffic-related air pollution with cognitive development in children. *Journal of Epidemiology and Community Health* 64, 223–28.

Gomez-Ravetti, M. and Moscato, P. 2008: Identification of a 5-protein biomarker molecular signature for predicting Alzheimer's disease. *PLoS One* 3, e3111.

Guo, L., Zhu, N., Guo, Z., Li, G.K., Chen, C., Sang, N. and Yao, Q.C. 2012: Particulate matter (PM10) exposure induces endothelial dysfunction and inflammation in rat brain. *Journal of Hazardous Materials* 213-214, 28–37.

Guxens, M. and Sunyer, J. 2012: A review of epidemiological studies on neuropsychological effects of air pollution. *Swiss Medical Weekly* 141, w13322.

Habre, R., Coull, B., Moshier, E., Godbold, J., Nath, A., Castro, W., Schachter, N., Rohr, A., Kattan, M., Spengler, J. and Koutrakis, P. 2013: Sources of indoor air pollution in New York City residences of asthmatic children. *Journal of Exposure Science & Environmental Epidemiology* 24, 269–78.

Hagens, W.I., Oomen, A.G., de Jong, W.H., Cassee, F.R. and Sips, A.J. 2007: What do we (need to) know about the kinetic properties of nanoparticles in the body? *Regulatory Toxicology and Pharmacology* 49, 217–29.

Haynes, E.N., Chen, A., Ryan, P., Succop, P., Wright, J. and Dietrich, K.N. 2011: Exposure to airborne metals and particulate matter and risk for youth adjudicated for criminal activity. *Environmental Research* 111, 1243–48.

Hazen, E.P., McDougle, C.J. and Volkmar, F.R. 2013: Changes in the diagnostic criteria for autism in DSM-5: controversies and concerns. *The Journal of Clinical Psychiatry* 74, 739–40.

Herbert, M.R. 2010: Contributions of the environment and environmentally vulnerable physiology to autism spectrum disorders. *Current Opinion in Neurology* 23, 103–10.

Hong, Y.C., Lee, J.T., Kim, H. and Kwon, H.J. 2002: Air pollution: a new risk factor in ischemic stroke mortality. *Stroke* 33, 2165–69.

Howard, G., Wagenknecht, L.E., Cai, J., Cooper, L., Kraut, M.A. and Toole, J.F. 1998: Cigarette smoking and other risk factors for silent cerebral infarction in the general population. *Stroke* 29, 913–17.

INE. 2011: Cuarto Almanaque de Datos y Tendencias de la Calidad del Aire en 20 Ciudades Mexicanas (2000–2009). first edition. Mexico D.F.: Instituto Nacional de Ecología.

Jian, H., Yi-Fang, W., Qi, L., Xiai-Song, H. and Gui-Yun, Z. 2013: Cerebral blood flow and metabolic changes in hippocampal regions of a modified rat model with chronic cerebral hypoperfusion. *Acta Neurologica Belgica* 113, 313–17.

Jordan, H.T., Stellman, S.D., Morabia, A., Miller-Archie, S.A., Alper, H., Laskaris, Z., Brackbill, R.M. and Cone, J.E. 2013: Cardiovascular disease hospitalizations in relation to exposure to the September 11, 2001 World Trade Center disaster and posttraumatic stress disorder. *Journal of American Heart Association* 2, e000431.

Josephson, A.M. 2013: Family intervention as a developmental psychodynamic therapy. *Child and Adolescent Psychiatric Clinics of North America* 22, 241–60.

Keene, C.D., Cudaback, E., Li, X., Montine, K.S. and Montine, T.J. 2011: Apolipoprotein E isoforms and regulation of the innate immune response in brain of patients with Alzheimer's disease. *Current Opinion in Neurobiology* 21, 920–28.

Kettunen, J., Lanki, T., Tiittanen, P., Aaalto, P.P., Koskentalo, T., Kulmala, M., Salomaa, V. and Pekkanen, J. 2007: Associations of fine and ultrafine particulate air pollution with stroke mortality in an area of low air pollution levels. *Stroke* 38, 918–22.

Knox, E.G. 1981: Metereological associations of cerebrovascular disease mortality in England and Wales. *Journal of Epidemiology Community Health* 35, 220–23.

Kulesza, R.J. and Mangunay, K. 2008: Morphological features of the medial superior olive in autism. *Brain Research* 1200, 132–37.

Kulesza, R.J. Jr, Lukose, R. and Stevens, L.V. 2011: Malformation of the human superior olive in autistic spectrum disorders. *Brain Research* 1367, 360–71.

Lampron, A., Elali, A. and Rivest, S. 2013: Innate immunity in the CNS: redefining the relationship between the CNS and its environment. *Neuron* 78, 214–32.

Langrish, J.P. and Mills, N.L. 2014: Air pollution and mortality in Europe. *Lancet* 383, 758–60.

Larsson, M., Weiss, B., Janson, S., Sundell, J. and Bornehag, C.G. 2009: Associations between indoor environmental factors and parental-reported autistic spectrum disorders in children 6–8 years of age. *Neurotoxicology* 30, 822–31.

Leiva, G.M.A., Santibañez, D.A., Ibarra, E.S., Matus, C.P. and Seguel, R. 2013: A five-year study of particulate matter (PM$_{2.5}$) and cerebrovascular diseases. *Environmental Pollution* 181, 1–6.

Levesque, S., Surace, M.J., McDonald, J. and Block, M.L. 2011: Air pollution and the brain: subchronic diesel exhaust exposure causes neuroinflammation and elevates early markers of neurodegenerative disease. *Journal of Neuroinflammation* 24, 105.

Lim, Y.H., Kim, H., Kim, J.H., Bae, S., Park, H.Y. and Hong, Y.C. 2012: Air pollution and symptoms of depression in elderly adults. *Environmental Health Perspectives* 120, 1023–28.

Lisabeth, L.D., Escobar, J.D., Dvonch, J.T., Sanchez, B.N., Majersik, J.J., Brown, D.L., Smith, M.A. and Morgenstern, L.B. 2008: Ambient air pollution and risk for ischemic stroke and transient ischemic attack. *Annals of Neurology* 64, 53–59.

Liu, J. 2011: Early risk factors for violence: conceptualization, review of the evidence and implications. *Agression and Violent Behavior* 16, 63–73.

Maheswarang, R., Pearson, T., Smeeton, N.C., Beevers, S.D., Campbell, M.J. and Wolfe, C.D. 2010: Impact of outdoor air pollution on survival after stroke: population-based cohort study. *Stroke* 41, 869–77.

Malloy, P.F., Cummings, J.L., Coffey, C.E., Duffy, J., Fink, M., Lauterbach, E.C., Lovell, M., Royall, D., Salloway, S. 1997: Cognitive screening instruments in neuropsychiatry: a report of the committee of research of the American Neuropsychiatric Association. *Journal of Neuropsychiatry and Clinical Neurosciences* 9, 189–97.

Marr, L.C., Grogan, L.A., Wohrnschimmel, H., Molina, L.T., Molina, M.J., Smith, T.J. and Garshick, E. 2004: Vehicle traffic as a source of particulate polycyclic aromatic hydrocarbon exposure in Mexico City. *Environmental Science and Technology* 38, 2584–92.

Mohai, P., Kweon, B.S., Lee, S. and Ard, K. 2011: Air pollution around schools is linked to poorer student health and academic performance. *Health Affairs* 30, 852–62.

Molina, J.M., Molina, L.T. 2004: Megacities and atmospheric pollution. *Journal of Air & Waste Management Association* 54, 644–80.

Molina, L.T., Madronich, S.J., Gaffney, J.S., Apel, E., de Foy, B., Fast, J., Ferrare, R., Herndon, S., Jimenez, J.L., Lamb, B., Osornio-Vargas, A.R., Russell, P., Schauer, J.J., Stevens, P.S., Volkamer, R. and Zavala, M. 2010: An overview of the MILAGRO 2006 Campaign: Mexico City emissions and their transport and transformation. *Atmospheric Chemistry and Physics* 10, 8697–760.

O'Donnell, M.J., Fang, J., Mittleman, M.A., Kapral, M.K. and Wellenius, G.A., **Investigators of the Registry of Canadian Stroke Network**. 2011: Fine particulate air pollution (PM2.5) and the risk of acute ischemic stroke. *Epidemiology* 22, 422–31.

Ou, C.Q., Hedley, A.J., Chung, R.Y., Thach, T.Q., Chau, Y.K., Chan, K.P., Yang, L., Ho, S.Y., Wong, C.M., Lam, T.H. 2008: Socioeconomic disparities in air pollution-associated mortality. *Environmental Research* 107, 237–44.

Ozbay, F., Aud der Heyde, T., Reissman, D. and Sharma, V. 2013: The enduring mental health impact of the September 11th terrorist attacks: challenges and lessons learned. *The Psychiatric Clinics of North America* 36, 417–29.

Parrish, D.D., Singh, H.B., Molina, L. and Madronich, S. 2011: Air quality progress in North American megacities: a review. *Atmospheric Environment* 45, 7015–25.

Perry, G., Nunomura, A., Hirai, K., Zhu, X., Pérez, M., Avila, J., Castellani, R.J., Atwood, C.S., Aliev, G., Sayre, L.M., Takeda, A. and Smith, M.A. 2002: Is oxidative damage the fundamental pathogenic mechanism of Alzheimer's and other neurodegenerative diseases? *Free Radical Biology & Medicine* 33, 1475–79.

Querol, X., Pey, J., Minguillón, M.C., Pérez, N., Alastuey, A., Viana, M., Moreno, T., Bernabé, R.M., Blanco, S., Cárdenas, B., Vega, E., Sosa, G., Escalona, S., Ruiz, H. and Artiñano, B. 2008: PM speciation and sources in Mexico

during the MILAGRO-2006 Campaign. *Atmospheric Chemistry and Physics* 8, 111–28.

Rivas-Arancibia, S., Guevara-Gúzman, R., Lopez-Vidal, Y., Rodriguez-Martinez, E., Zanardo-Gomez, M., Angoa-Pérez, M., Raisman-Vozari, R. 2010: Oxidative stress caused by ozone exposure induces loss of brain repair in hippocampus of adult rats. *Toxicological Sciences* 113, 187–97.

Roberts, A.L., Lyall, K., Hart, J.E., Laden, F., Just, A.C., Bobb, J.F., Koenen, K.C., Ascherio, A. and Weisskoof, M.G. 2013: Perinatal air pollutant exposures and autism spectrum disorder in the children of nurses' health study II participants. *Environmental Health Perspectives* 121, 978–84.

Roher, A.E., Debbins, J.P., Malek-Ahmandi, M., Chen, K., Pipe, J.G., Maze., S., Belden, C., Maarout, C.L., Thiyyagura, P., Mo, H., Hunter, J.M., Kokjohn, T.A., Walker, D.J., Kruchowsky, J.C., Belohlavek, M., Sabbagh, M.N., Beach, T.G. 2012: Cerebral blood flow in Alzheimer's disease. *Vascular Health & Risk Management* 8, 599–608.

Rosas-Pérez, I., Serrano, J., Alfaro-Moreno, E., Baumgardner, D., Garcia-Cuellar, C., Martin del Campo, J.M., Raga, G.B., Castillejos, M., Colin, R.D. and Osornio-Vargas, A.R. 2007: Relations between PM$_{10}$ composition and cell toxicity: a multivariate and graphical Approach. *Chemosphere* 67, 1218–28.

Schröder, N., Silva-Figueiredo, L. and Martins de Lima, M.N. 2013: Role of brain iron accumulation in cognitive dysfunction: evidence from animal models and human studies. *Journal of Alzheimer's Disease* 34, 797–812.

Sharma, H.S. and Sharma, A. 2012: Neurotoxicity of engineered nanoparticles from metals. *CNS & Neurological Disorders* 11, 65–80.

Shulman, K.I. 2000: Clock-drawing: is it the ideal cognitive screening test? *International Journal of Geriatric Psychiatry* 15, 548–61.

Siddique, S., Banerjee, M., Ray, M.R. and Lahiri, T. 2011: Attention-deficit hyperactivity disorder in children chronically exposed to high level of vehicular pollution. *European Journal of Pediatrics* 170, 923–29.

Secretaria de Medio Ambiente, Gobierno de Distrito Federal (SMA-GDF). 2008: Inventario de Emisiones de la Atmósfera. Zona Metropolitana del Valle de México 2006, Secretaria de Medio Ambiente, Gobierno de Distrito Federal, Mexoico D.F.

Suglia, S.F., Gryparis, A., Wright, R.O., Schwartz, J. and Wright, R.J. 2008: Association of black carbon with cognition among children in a prospective birth cohort study. *American Journal of Epidemiology* 167, 280–86.

Suissa, L., Fortier, M., Lachaud, S., Staccini, P. and Mahagne, M.H. 2013: Ozone air pollution and ischemic stroke occurrence: a case-crossover study in Nice, France. *BMJ Open* 3, e004060.

Söderstjerna, E., Johansson, F., Klefbohm, B. and Englund-Johansson, U. 2013: Gold and silver nanoparticles affect the growth characteristics of human embryonic neural precursor cells. *PLoS One* 8, e58211.

Szyszkowicz, M., Willey, J.B., Grafstein, E., Rowe, B.H. and Colman, I. 2010: Air pollution and emergency department

visits for suicide attempts in Vancouver, Canada. *Environmental Health Insights* 4, 79–86.

Trickler, W.J., Lantz, S.M. and Schrand, A.M. 2012: Effects of copper nanoparticles on rat cerebral microvessel endothelial cells. *Nanomedicine* 7, 835–46.

UK Air Data. http://uk-air-defra.gov.uk

U.S. Environmental Protection Agency. 2006: Particulate Matter (PM-2.5). Standard Nonattainment Areas. U.S. Environmental Protection Agency.

Valle-Hernández, B.L., Mugica-Alvarez, V., Salinas-Talavera, E., Amador-Muñoz, O., Murillo-Tovar, M.A., Villalobos-Pietrini, R. and De Vizcaya-Ruíz, A. 2010: Temporal variation of nitro-polycyclic aromatic hydrocarbons in PM10 and PM2.5 collected in Northern Mexico City. *The Science of the Total Environment* 408, 5429–38.

van den Hazel, P., Zuurbier, M., Babisch, W., Bartonova, A., Bistrup, M.L., Bolte, G., Busby, C., Butter, M., Ceccatelli, S., Fucic, A., Hanke, W., Johansson, C., Kohlhuber, M., Leijs, M., Lundqvist, C., Moshammer, H., Naginiene, R., Preece, A., Ronchetti, R., Salines, G., Saunders, M., Schoeters, G., Stilianakis, N., ten Tusscher, G. and Koppe, J.G. 2006: Today's epidemics in children: possible relations to environmental pollution and suggested preventive measures. *Acta Paediatrica Supplement* 95, 18–25.

Van Kempen, E., Fischer, P., Janssen, N., Houthuijis, D., van Kamp, I., Stansfeld, S., Cassee, F. 2012: Neurobehavioral effects of exposure to traffic-related air pollution and transportation noise in primary school children. *Environmental Research* 115, 18–25.

Villarreal-Calderón, R., Torres-Jardon, R., Palacios-Moreno, J., Perez-Guille, B., Maronpot, R.R., Reed, W., Zhu, H., Calderón-Garciduenas, L. 2010: Urban air pollution targets the dorsal vagal complex and dark chocolate offers neuroprotection. *International Journal of Toxicology* 29, 604–15.

Villeneuve, P.J., Johnson, J.Y., Pasichnvk, D., Lowes, J., Kirkland, S. and Rowe, B.H. 2012: Short term effects of ambient air pollution on stroke: who is most vulnerable? *The Science of the Total Environment* 430, 193–201.

Visser, J.C., Rommelse, N., Vink, L., Schrieken, M., Oosterling, I.J., van der Gaag, R.J. and Buitelaar, J.K. 2013: Narrowly versus broadly defined autism spectrum disorders: differences in pre and perinatal risk factors. *Journal of Autism Developmental Disorders* 43, 1505–16.

Volk, H.E., Hertz-Picciotto, I., Delwiche, L., Lurmann, F. and McConnell, R. 2011: Residential proximity to freeways and autism in the CHARGE study. *Environmental Health Perspectives* 119, 873–77.

Volk, H.E., Lurmann, F., Penfold, B., Hertz-Picciotto, I. and McConnell, R. 2013: Traffic-related air pollution, particulate matter and autism. *JAMA Psychiatry* 70, 71–77.

Volk, H.E., Kerin, T., Lurmann, F., Hertz-Picciotto, I., McConnell, R. and Campbell, D.B. 2014: Autism spectrum disorder: interaction of air pollution with the MET receptor tyrosine kinase gene. *Epidemiology* 25, 44–47.

Wang, S., Zhang, J., Zeng, X., Zeng, Y., Wang, S. and Chen, S. 2009: Association of traffic-related air pollution with children's neurobehavioral functions in Quanzhou, China. *Environmental Health Perspectives* 117, 1612–18.

Wang, J., Eslinger, P.J., Doty, R.L., Zimmerman, E.K., Grunfeld, R., Sun, X., Meadowcroft, M.D., Connor, J.R., Price, J.L., Smith, M.B. and Yang, Q.X. 2010: Olfactory deficit detected by fMRI in early Alzheimer's disease. *Brain Research* 1357, 184–94.

Wilker, E.H., Mostofsky, E., Lue, S.H., Gold, D., Schwartz, J., Wellenius, G.A. and Mittleman, M.A. 2013: Residential proximity to high-traffic roadways and poststroke mortality. *Journal of Stroke and Cerebrovascular Diseases* 22, e366–72.

Williams, L., Ulrich, C.M., Larson, T., Wener, M.H., Wood, B., Chen-Levy, Z., Campbell, P.T., Potter, J., McTiernan, A. and Roos, A.J. 2011: Fine particulate matter PM2.5 air pollution and immune status among women in the Seattle area. *Archives of Environmental Health* 66, 155–64.

Win-Shwe, T.T., Yamamoto, S., Fujitani, Y., Hirano, S. and Fujimaki, H. 2008: Spatial learning and memory function-related gene expression in the hippocampus of mouse exposed to nanoparticle-rich diesel exhaust. *Neurotoxicology* 29, 940–47.

Win-Shwe, T.T. and Fujimaki, H. 2011: Nanoparticles and neurotoxicity. *International Journal of Molecular Sciences* 12, 6267–80.

Wisnivesky, J.P., Teitelbaum, S.L., Todd, A.C., Boffetta, P., Crane, M., Crowley, L., de la Hoz, R.E., Dellenbaugh, C., Harrison, D., Herbert, R., Kim, H., Jeon, Y., Kaplan, J., Katz, C., Levin, S., Luft, B., Markowitz, S., Moline, J.M., Ozbay, F., Pietrzak, R.H., Shapiro, M., Sharma, V., Skloot, G., Southwick, S., Stevenson, L.A., Udasin, I., Wallenstein, S. and Landrigan, P.J. 2011: Persistence of multiple illnesses in World Trade center rescue and recovery workers: a cohort study. *Lancet* 378, 888–97.

Wu, J., Wang, C. and Sun, J. 2011: Neurotoxicity of silica nanoparticles: brain localization and dopaminergic neurons damage pathways. *ACS Nano* 5, 4476–89.

Xu, P. and Ye, X. 2013: Haze air pollution and health in China. *Lancet* 49, 217–29.

Yang, C.Y., Chen, Y.S., Chiu, H.F. and Goggins, W.B. 2005: Effects of Asian dust storm events on daily stroke admissions in Taipei, Taiwan. *Environ Res* 99, 79–84.

Ze, Y., Sheng, L., Zhao, X., Ze, X., Wang, X., Zhou, Q., Liu, J., Yuan, Y., Gui, S., Sang, X., Sun, Q., Hong, J., Yu, X., Wang, L., Li, B., Hong, F. 2014: Neurotoxic characteristics of spatial recognition damage of the hippocampus in mice following subchronic peroral exposure to TiO2 nanoparticles. *Journal of Hazardous Materials* 264, 219–29.

Zhang, Z.F., Yu, S.Z. and Zhou, G.D. 1988: Indoor air pollution of coal fumes as a risk factor of stroke, Shanghai. American Journal of Public Health 78, 975–77.