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Impact of Polycyclic Aromatic Hydrocarbon exposure on Cognitive Function and Neurodegeneration in Humans. A Systematic Review and Meta-Analysis

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Abstract

This review documents an emerging body of evidence concerning the neurological effect of polycyclic aromatic hydrocarbon (PAH) exposure, with regard to cognitive function and increased risk of neurodegeneration. Two electronic databases PubMed and Web of Science were systematically searched. The 37/428 studies selected included outcomes measuring cognitive function, neurobehavioral symptoms of impaired cognition, and pathologies associated with neurodegeneration from prenatal (21/37 studies), childhood (14/37 studies), and adult (8/37 studies) PAH exposure. Sufficient evidence surrounding prenatal exposure negatively impacting child intelligence, mental development, average overall development, verbal IQ, memory impairment, externalizing, internalizing, anxious, depressed behaviours, behavioural development and child attentiveness was found. Evidence concerning exposure during childhood and as an adult was scarce and highly heterogeneous, however presence of neurodegenerative biomarkers and increased concentrations of cryptic "self" antigens in serum and cerebrospinal fluid samples suggest a higher risk of neurodegenerative disease. Associations with lowered cognitive ability, and impaired attentiveness were found in children and memory disturbances, specifically auditory memory, verbal learning and general memory in adults. Although evidence is not yet conclusive and further research is needed the studies included supported the hypothesis that PAH exposure negatively impacts cognitive function and increases the risk of neurodegeneration in humans, and recommends considering the introduction of a variable "rural vs. urban" as covariate for adjusting analyses where the neurological functions affected (as result of our review) are outcome variables.
Keywords: polycyclic aromatic hydrocarbons, particulate matter 2.5 (PM 2.5), cognition, neurodegeneration, neurology, air pollution, environment, rural, urban, neurocognitive development, neurodegeneration

Abbreviations

AD……..Alzheimer's Disease
ADHD……Attention deficit hyperactivity disorder
APOE4 ……..Apolipoprotein E4
A$\beta_{1\text{-}42}$……..Amyloid beta protein fragment 1-42
α-synuclein……..Alpha-synuclein
B[a]P……..Benzo[a]pyrene
BDNF…….Brain-Derived Neurotrophic Factor
CEREB IgG……..Cerebellar antigen
CO……..Carbon monoxide
CSF……Cerebrospinal Fluid
ETS…….....Environmental Tobacco Smoke

IFN γ……...Interferon gamma

IgA……..Immunoglobulin A

IgG…….Immunoglobulin G

IgM…….Immunoglobulin M

IL β…….Interleukin beta

IL 2…….Interleukin 2

IL 6…….Interleukin 6

IL 10……...Interleukin 10

IQ……Intelligence Quotient

MBP……...Myelin Basic Protein

MBP IgA……...Myelin Basic Protein Immunoglobulin A

MBP IgG……Myelin Basic Protein Immunoglobulin G

MCP-1……Monocyte Chemoattractant Protein-1

MOG IgG……..Myelin Oligodendrocyte Glycoprotein Immunoglobulin G

MOG IgM……..Myelin Oligodendrocyte Glycoprotein Immunoglobulin A

NHANES……National Health and Nutrition Examination Survey

Non-p-tau……Non-Phosphorylated Tau

NO_x…….Nitrogen Oxide species

NO_2…….Nitrogen Dioxide

OZ IgA……Occludin/ Zonulin Immunoglobulin A

OZ IgG……Occludin/ Zonulin Immunoglobulin G

PAH……Polycyclic Aromatic Hydrocarbons

PAH-DNA adducts….Polycyclic Aromatic Hydrocarbon- DNA adducts

PD……..Parkinson's Disease

PM……..Particulate Matter

$PM_{2.5}$……..Particulate Matter with an aerodynamic diameter > 2.5 micrometres

PM_{10}……...Particulate Matter with an aerodynamic diameter > 10 micrometres

p-tau……..Phosphorylated Tau

S-100 IgG……..Astrocytic protein Immunoglobulin G

S-100 IgM……Astrocytic protein Immunoglobulin M

TDP-43……..Transactive response DNA binding protein 43

TRAP……Traffic Related Air Pollution

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Introduction

Exposure to air pollution in the environment is now recognized globally by Governments, leading research scientists, and civil society, as one of the greatest public health hazards of the 21st century (Cohen et al. 2017). Legislation such as “The UK National Air Quality Strategy” (Department for Environment, Food and Rural Affairs, 2011), and the European Commission’s “Fourth Daughter Directive” (The European Parliament and The European Council of the European Union, 2015) have introduced standards to monitor and limit levels of air pollutants posing the greatest risk to human health. Polycyclic aromatic hydrocarbons (PAHs) are a group of pollutants included in such legislation. PAHs are atmospheric organic compounds composed of two or more benzene rings arranged in a variety of different configurations. Over 100 different PAHs have been identified to date (U.S. Department of health and human services, 1995). They are discharged from anthropogenic sources (Figure 1), involving the incomplete combustion and pyrolysis of hydrocarbons, predominantly found in: coal, oil, wood and petrol. PAHs exist in the atmosphere in a gaseous state or adsorbed to particulate matter. Over 80% of particulate-bound PAHs are associated with particulate matter of an aerodynamic diameter ≤ 2.5 μm (PM2.5) (Hassanvand et al. 2015).

Research surrounding PAH exposure and acute short-term health effects in humans has thus far focused on vulnerable individuals with pre-existing health conditions: thrombotic effects in individuals with pre-existing coronary heart disease and impaired lung function in asthma sufferers (American Conference of Governmental Industrial Hygienists (ACGIH), 2005). Chronic long-term exposure has implicated PAH’s reactive metabolites, to have the ability to bind to proteins and DNA, and exert carcinogenic effects (Bach et al. 2003). Such biochemical disruption and cellular damage has been most extensively researched in occupational studies, whereby high exposure has been associated with increased incidence of lung, bladder, skin, and gastrointestinal cancer (Boffetta et al. 1997) (Diggs et al. 2012) (Bach et al. 2003) (Olsson et al. 2010). Additionally, decreased immune function, cataracts, kidney and liver damage, including jaundice, have also been associated with high exposure (Kuo et al. 2012) (U.S. Department of health and human services, 1995). Whilst extensive research exists surrounding PAH’s genotoxic and carcinogenic properties, an emerging body of evidence concerns PAH’s neurotoxic effect through the induction of oxidative stress, inflammation (Saunders et al. 2006) and vascular injury within the brain (Hartz et al. 2008). Recently, research has emerged associating PAH exposure with impaired cognitive function and increased risk of neurodegeneration.

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To the best of our knowledge, from the large body of literature on the influence of air pollution in human health, the implications of PAH exposure specifically, on cognitive function and neurodegeneration in humans have not been systematically reviewed. Prior reviews have addressed the implications of PAH exposure on general health (Abdel-Shafy & Mansour, 2016; Kiim et al. 2013), and its carcinogenic outcomes (Armstrong et al. 2004) (Bosetti, et al., 2007). The reviews which have made cognitive function and neurodegeneration the outcome of interest, include exposures to a vast mixture of air pollutants (Peters et al. 2019) (Schikowski & Altug, 2020) (Kilian & Kitazawa, 2018) (Calderón-Garcidueñas et al. 2016). In doing so we aim to disentangle the unique neurotoxic effect of PAH's from other pollutants in specific age groups and cognitive-related functions to provide evidence for cognitive research and more vigilant monitoring and tighter restrictions on the main sources of emission. The Department for Environment, Food and Rural Affairs, currently considers annual monitoring of concentrations of one PAH, Benzo[a]pyrene (B[a]P), to be a sufficient representation of all atmospheric PAHs, and classifies the potential effect to human health of PAHs collectively, as 6 compounds, categorised as probably or possibly carcinogenic. No mention is made of the adverse neurological impact (Department for Environment, Food and Rural Affairs, 2011). A possible explanation is the consideration of concentration levels that constitute a risk for cancer, below which the effect of these pollutants can pass inadvertently. The UK national air quality objective for B[a]P is: 0.25ng.m^{-3}. However, emissions of B[a]P have been increasing since 2008, and exceed this limit in multiple locations at multiple time points (Department or Environment, Food and Rural Affairs, 2020). Atmospheric PAH concentrations are subject to seasonal variation and climate (Finardi S, 2017). A further aim is to explore the influence the difference in PAH concentration in rural vs. metropolitan areas, can have, on outcomes involving cognitive function and neurodegeneration, to inform further studies.

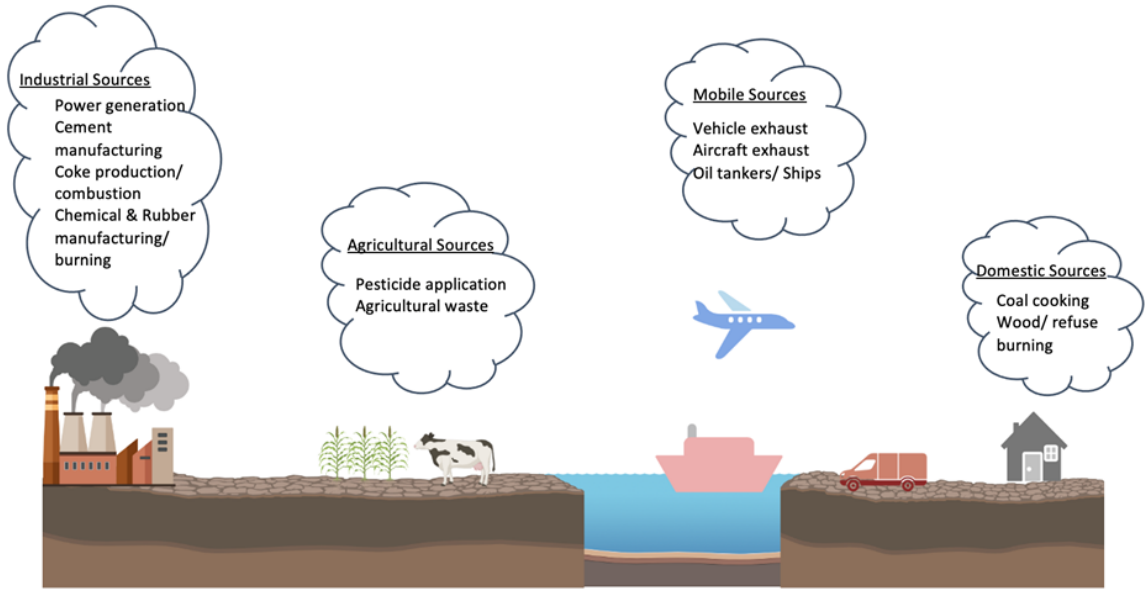

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Figure 1: Anthropogenic sources (Industrial, Mobile, Domestic and Agricultural Sources) of PAH release into the environment (figure made using: biorender.com).

Methods

Eligibility criteria

This review was conducted in line with the PRISMA guidelines (Liberati et al. 2009). Studies included were observational cohort studies of both male and female humans. Time of exposure was inclusive of the gestational period and stretched throughout life until death. Exposure quantification was limited to studies which measured the level of exposure to ambient PAHs, or PM2.5 through environmental air sampling or spatiotemporal modelling. Measures of exposure also included concentration of PAH metabolites in urine and dosimetry of PAH-DNA adducts, from DNA extracted from white blood cells. Outcomes included involved a formal assessment of outcomes of cognitive function, neurobehavioral symptoms of impaired cognition, and pathologies associated with neurodegeneration. Reports were limited to published scientific articles written in the English language. No publication dates were imposed. Studies were excluded if they did not fulfil the inclusion criteria, were not in humans, or where PAH exposure was measured as a component of diet, Environmental Tobacco Smoke (ETS) or Traffic Related Air Pollution (TRAP). Exposure via diet and ETS is not an appropriate representation of a major source of atmospheric PAH. Prior research has elucidated contaminating pollutants within TRAP composition detrimentally affecting cognitive function. Inclusion of such studies would confound results and prevent us from elucidating the specific impact of PAH on cognition.

Information Sources

Studies were identified by searching electronic databases: PubMed (1984- present) and Web of Science (1979- present). The last search was run on the 15th February 2021. “Polycyclic Aromatic Hydrocarbons” in addition to the following search terms: “brain”, “neurological”, “cognitive”, “cognition”, “neurodegenerative”, “neurodegeneration”, “neurodevelopment”, “neurodevelopmental” were used to identify articles in both databases. Limitations applied to the search included the fields searched being: Title and Abstract. In Web of Science the document type of: Articles was applied. In PubMed an additional limitation of the species selected being: Humans, was applied. Eligibility assessment was performed independently in an unbiased standardized manner by one reviewer. Ambiguity concerning the inclusion or exclusion of a study was resolved by a second

reviewer being consulted and a consensus taken. Initial screening was performed through reviewing the Title and Abstract, after which, the full manuscript was reviewed.

Data Collection process

A data extraction sheet was developed and pilot tested on 5 randomly selected included studies, before being refined accordingly. One review author extracted data from the included studies, a second was consulted where ambiguity arose surrounding the appropriate data to extract. One author was contacted via email to provide numerical data that had only been presented graphically. Information extracted from studies included: sample size, sample characteristics, gender ratio, mean age, age range, comorbidities, air pollution component, time of exposure, air pollution data acquisition method and outcome measured.

Risk of bias in individual studies

Risk of bias was assessed in line with the QADAS guidelines (University of Bristol, 2003). To ascertain the risk of bias within each study included, one reviewer working independently extracted the following information: participant inclusion/exclusion criteria explained, participant withdrawals from study explained, use of /comparison with a control/low exposure population, confounding variables identified, appropriate method/ analysis to adjust for confounding variables, outcome assessors aware of exposure status of study participant, intermediate or unexpected results explained/reported, and whether or not the methods of the study were reproducible.

Planned methods of analysis

Studies included were divided into 4 subgroups depending on the time at which the exposure was measured: prenatal, childhood, adult and finally childhood+ adult. The category childhood+ adult included studies whereby the cohort of people included was a mixture of individuals exposed only up until childhood, and others where exposure extended through to adulthood. Subsequently, studies were further divided into categories depending on the outcome measured: cognitive development, neurobehavioral development, general cognition and neurodegeneration. This subgroup division was conducted to adjust for heterogeneity between studies. The meta-analysis was performed by calculating odds ratios and 95% confidence for the effect sizes of reported outcomes. Forest plots were used to visualise differences in effect sizes between studies within the same subgroup.

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Results

Study Selection

The search of Web of Science and PubMed provided a total of 490 citations. After adjusting for duplicates 428 remained. Subsequent screening of the title and abstract resulted in a further 289 being discarded. Of the remaining 139, a further 102 were excluded upon further examination of the full manuscript and application of inclusion criteria. 1 reported data copied directly from a previous study (Tang *et al.* 2014). 16 were reviews, and did not include any primary data, 47 reported outcomes not relevant to cognitive function or neurodegeneration and in 38 the recorded exposure to PAH was not in keeping with the specified criteria. Resulting in a total of 37 studies included in this review. Subgroup division resulted in 21 prenatal exposure studies, 15 concerning cognitive development outcomes and 13 neurobehavioral development, 7 included measures of both. 11 childhood exposure studies, 3 general cognition, 5 neurobehavioral development and 3 neurodegeneration. 5 adult exposure studies all with outcomes of general cognition, and 3 childhood + adult studies all with measures of neurodegeneration. 1 study included measured outcomes for both prenatal and childhood exposure (Kerin *et al.* 2017) and 2 studies involved 2 different study cohorts one exposed only during childhood and the other included a mix of childhood and adult exposed subjects (Calderón-Garcidueñas *et al.* 2016; Calderón-Garcidueñas *et al.* 2018). Figure 2 depicts the flow chart for study inclusion and subgroup division. The full dataset can be found at the following link: https://doi.org/10.7488/ds/3031 .

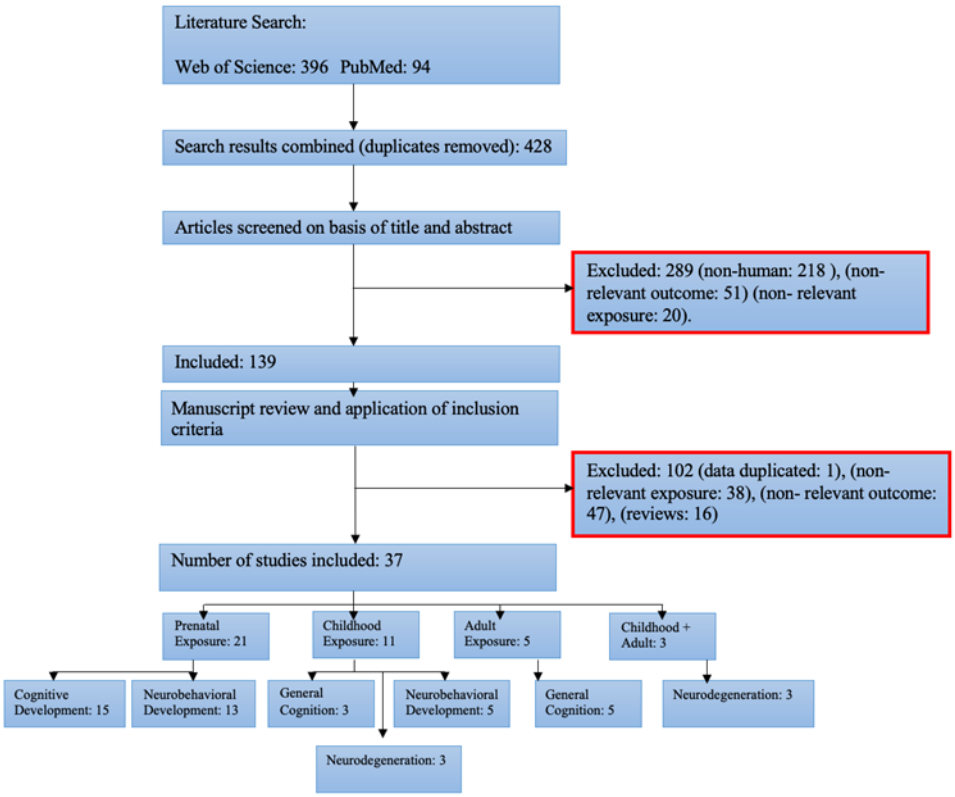

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Figure 2: Flow chart of the search, study inclusion and subgroup division.

Study Characteristics

The 37 studies, involved populations from 9 countries (figure 3). Study population characteristics including sample size and mean age (± SD) are displayed in figure 4.

11 included cohorts from the USA. 6 selected participants from the Columbia Centre for Children's Environmental Health cohort, however each selected different subgroups of the population, and measured different outcomes (Perera *et al.* 2006; Perera *et al.* 2018; Perera *et al.* 2015; Perera *et al.* 2012; Perera *et al.* 2011; Pagliaccio *et al.* 2020). 2 studies selected a subgroup of participants from the National Health and Nutrition Examination Survey 2001-2002 (NHANES) (Best *et al.* 2016), 1 of which included additional participants from the NHANES 2003-2004 cohort (Abid *et al.* 2014). The remaining 3 studies involved cohorts from the Childhood Autism Risks from Genetics and the Environment Study (Kerin *et al.* 2017), the Adolescent Brain Cognitive Development Study (Cserbik *et al.* 2020), and the Asthma Coalition on Community, Environment and Social Stress project (Chiu *et al.* 2016).

8 studies reported results from populations in China. 1 study involved a Taiyuan population (Niu *et al.* 2009) in addition to 2 selecting different subgroups from the Taiyuan Mother and Child Cohort Study (Cao *et al.* 2020; Nie *et al.* 2019). 3 involved populations from Tongliang (Perera *et al.* 2008; Tang *et al.* 2008; Tang *et al.* 2014), and the remaining 2 from Shanxi province (Du *et al.* 2020) and Qingdao City (Zhang *et al.* 2019).

5 studies involved populations from Spain. 2 involved a subgroup from the INfancia y Medio Ambiente Project (Lertxundi *et al.* 2015; Lertxundi *et al.* 2019) and the additional 3 participants from the Brian Development and Air Pollution Ultrafine Particles in School Children project (Mortamais *et al.* 2017; Rivas *et al.* 2019; Alemany *et al.* 2018).

4 studies reported on populations in Poland. 3 including participants from the Krakow Study (Jedrychowski *et al.* 2015; Edwards *et al.* 2010; Perera *et al.* 2013) and 1, the Polish Mother and Child Cohort Study (Polanska *et al.* 2013).

4 studies reported on populations in Mexico. All involved Mexico City residents (Calderón-Garcidueñas *et al.* 2020), and 1 of 6 (Calderón-Garcidueñas *et al.* 2015; Calderón-Garcidueñas *et al.* 2016), or 3 small Mexican cities (Calderón-Garcidueñas *et al.* 2018) respectively.

2 studies involved a Korean population (Cho *et al.* 2020; Ha *et al.* 2012). Further individual studies included populations from the Czech Republic (Blazkova *et al.* 2020), Kenya (Suter *et al.* 2017) and Belgium (Saenen *et al.* 2016).

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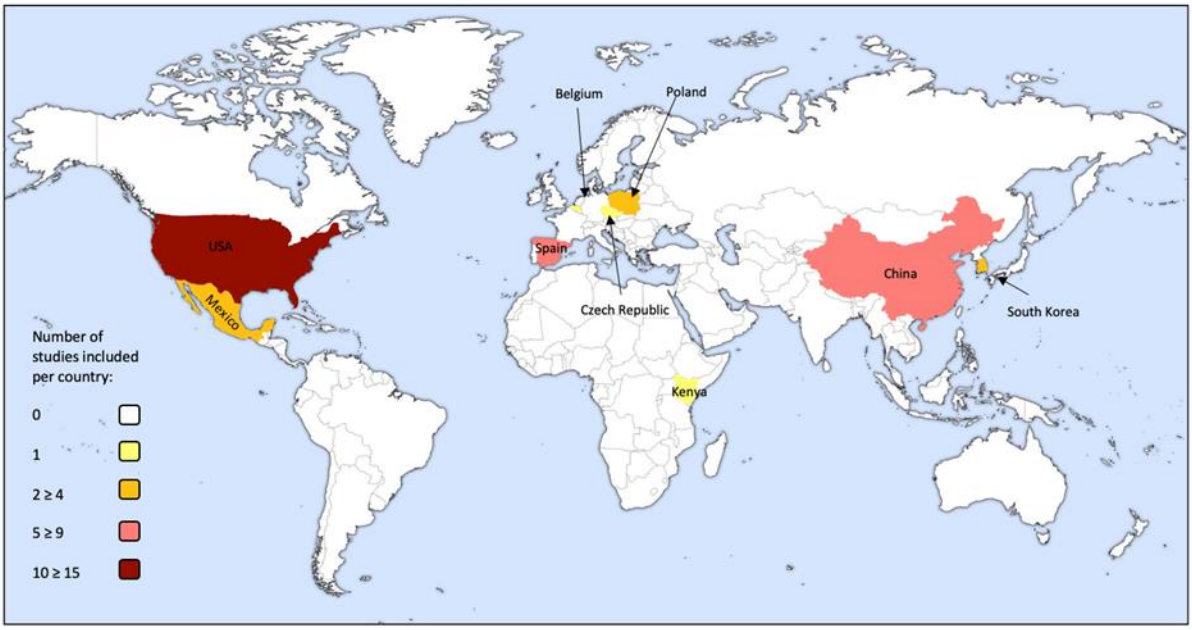

Figure 3: Global Distribution of the population cohorts in each of the 37 studies included in this review (figure made using: biorender.com).

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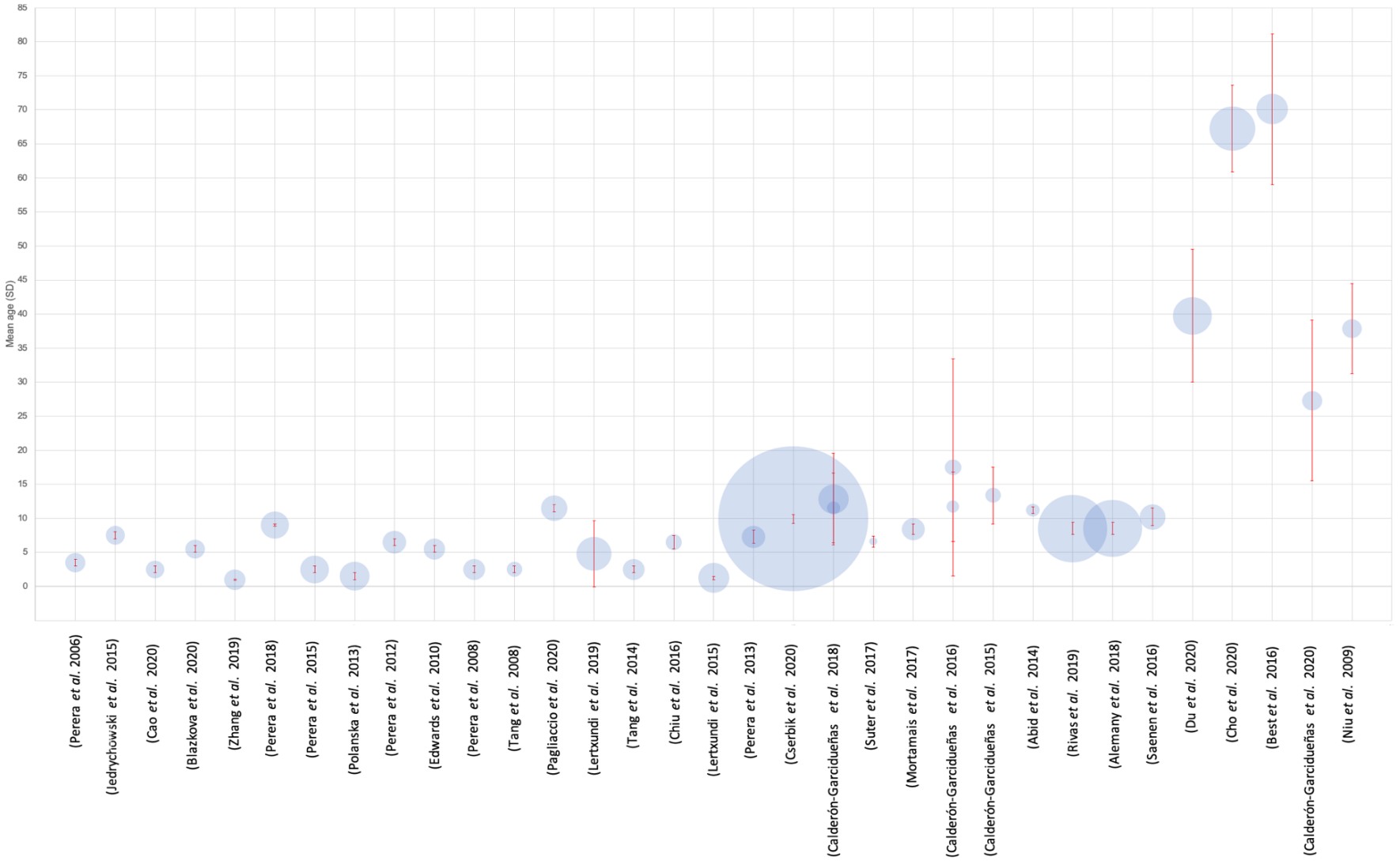

Figure 4: Characteristics of the study population involved in each study. Circle size is representative of the sample size. Red bars indicate mean age ± 1 SD. 4 studies were omitted from this analysis due to insufficient data (Kerin *et al.* 2017; Ha *et al.* 2012; Perera *et al.* 2011; Nie *et al.* 2019).

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Exposure assessment

Of the 37 studies included, 7 measured exposure through environmental PAH sampling, 5 by environmental $PM_{2.5}$ sampling, 7 by $PM_{2.5}$ spatiotemporal modelling, 10 by concentrations of PAH metabolites in urine and 8 using dosimetry to measure PAH-DNA adducts (figure 5).

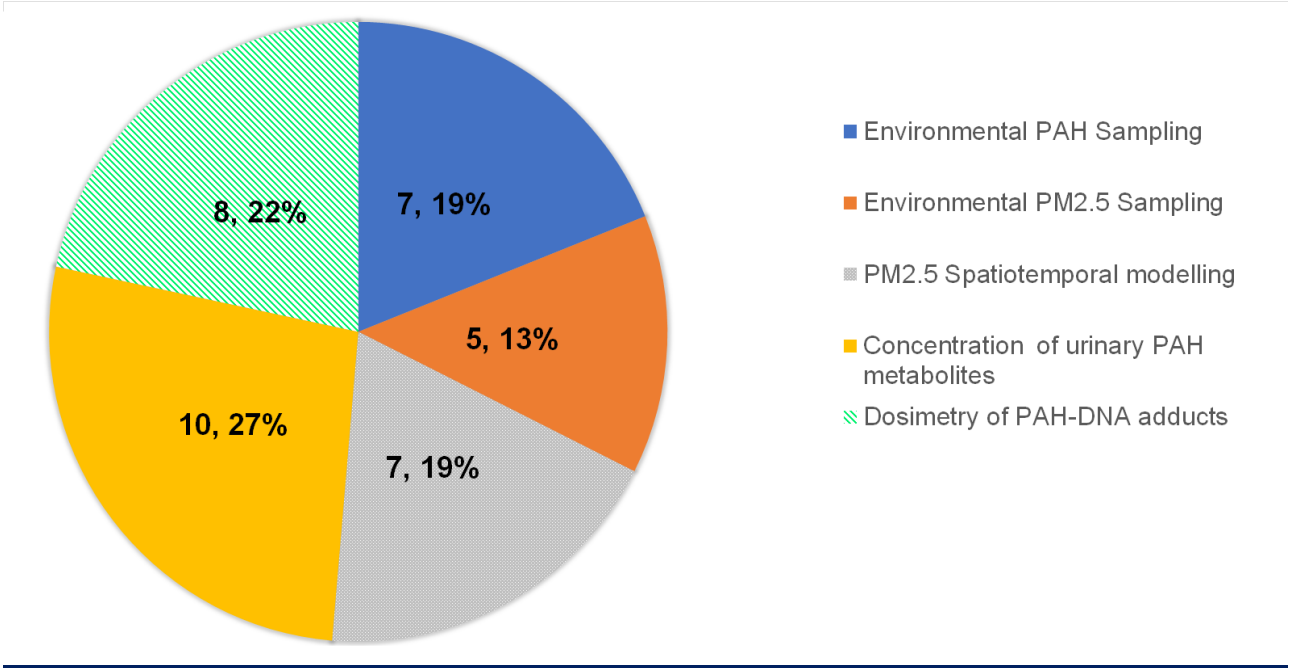

Figure 5: Pie chart representing the proportion of included studies measuring exposure to PAH as a measure of: environmental PAH Sampling, environmental $PM_{2.5}$ sampling, $PM_{2.5}$ spatiotemporal modelling, concentration of urinary PAH metabolites and dosimetry of PAH-DNA adducts.

Outcome assessment

Outcomes included 21 different tests measuring cognitive function, 9 different tests measuring neurobehavioral symptoms of impaired cognition and 3 different measures of pathologies associated with neurodegeneration (figure 6).

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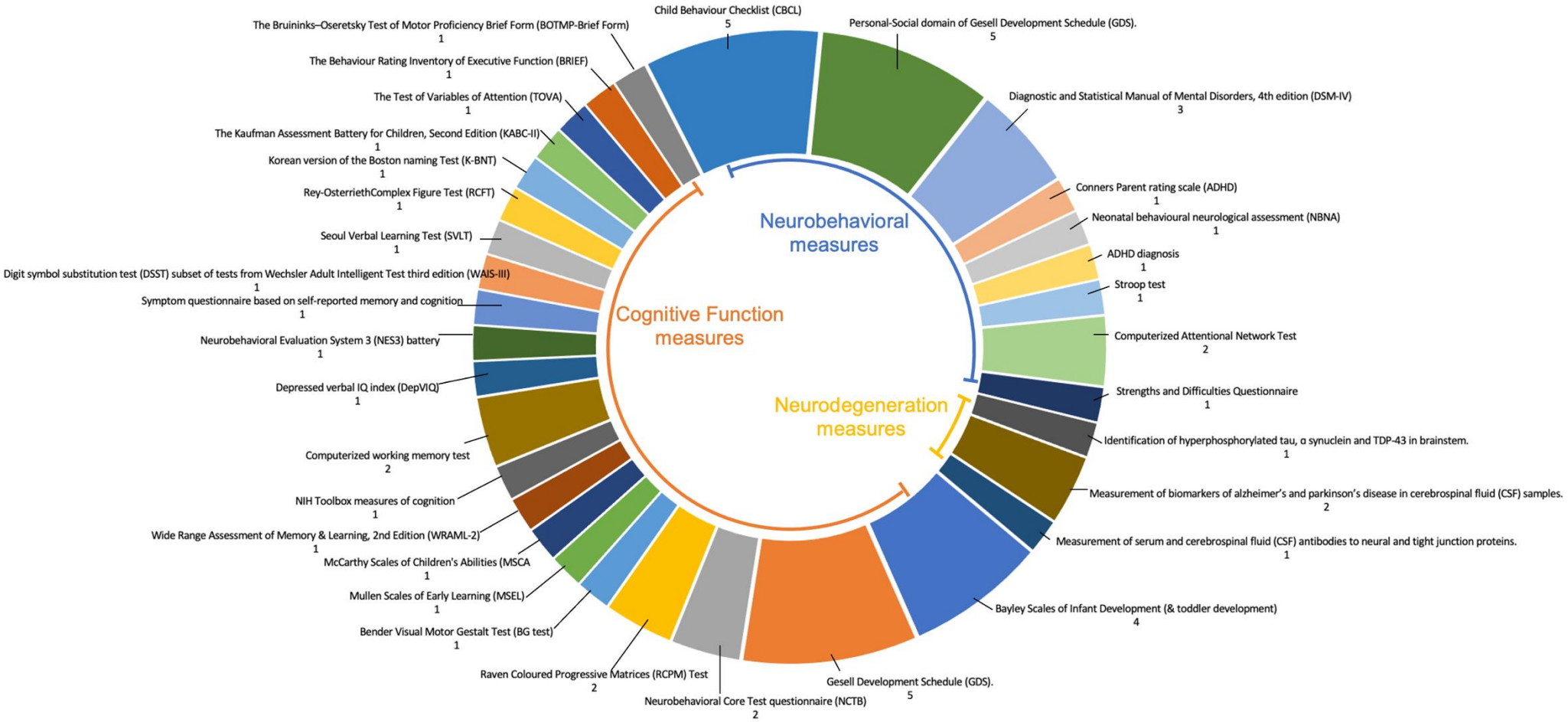

Figure 6: Pie chart representing the number of studies using different tests to measure outcomes. Measures include cognitive function, neurobehavioral symptoms of impaired cognition, and pathologies associated with neurodegeneration.

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Prenatal Exposure

Association between prenatal PAH exposure and cognitive development

Children with a high prenatal PAH exposure were found to have a delay in overall child intelligence (OR= 1.75, 95%CI, 1.11 to 2.71) (Edwards *et al.* 2010), mental development (OR= 0.65, Perera *et al.* 2015) and average overall development (Perera *et al.* 2008; Tang *et al.* 2014) (OR= 0.84, 95%CI, 0.52 to 1.36; OR= 1.85, 95%CI, 1.13 to 3.01 respectively). Specifically, the greatest negative effects reported were in verbal IQ (OR= 3.45, 95%CI, 0.95 to 12.49) (Jedrychowski *et al.* 2015) and language (OR= 5.99, 95%CI, 1.88 to 19.02) (Zhang *et al.* 2015). However, the latter could not be confirmed in 5/6 studies (Perera *et al.* 2008; Tang *et al.* 2008; Tang *et al.* 2014; Cao *et al.* 2020; Polanska *et al.* 2013). Two studies analysed the effect of PAH in general cognitive abilities with contradictory results: Perera *et al* (2006) reported a negative effect (OR= 2.89, 95%CI, 1.33 to 6.25) while Polanska *et al* (2013) reported no effect. PAH effect on impaired motor development was inconclusive, as it was confirmed by 4 studies (Perera *et al.* 2008; Tang *et al.* 2008; Tang *et al.* 2014; Cao *et al.* 2020) (OR= 0.95, 95%CI, 0.58 to 1.53; OR= 1.91, 95%CI, 1.22 to 2.97; OR= 1.63, 95%CI, 1.00 to 2.65; OR= 1.82, 95%CI, 3.21 to 1.03 respectively) whereas 3 others could not confirm it. No association was found between PAH exposure and developmental motor ability by Polanska *et al* (2013), fine and gross motor abilities by Zhang *et al* (2019) and psychomotor abilities by Perera *et al* (2006).

Only one study reported effect of PAH and reduced adaptive development (Tang *et al.* 2014) (OR= 1.77, 95%CI, 1.09 to 2.88) while 4/5 reported no association with adaptive domains (Zhang *et al.* 2019; Perera *et al.* 2008; Tang *et al.* 2008; Cao *et al.* 2020). Size effects reported by the studies mentioned are graphically represented in figure 7 and listed in table 1.

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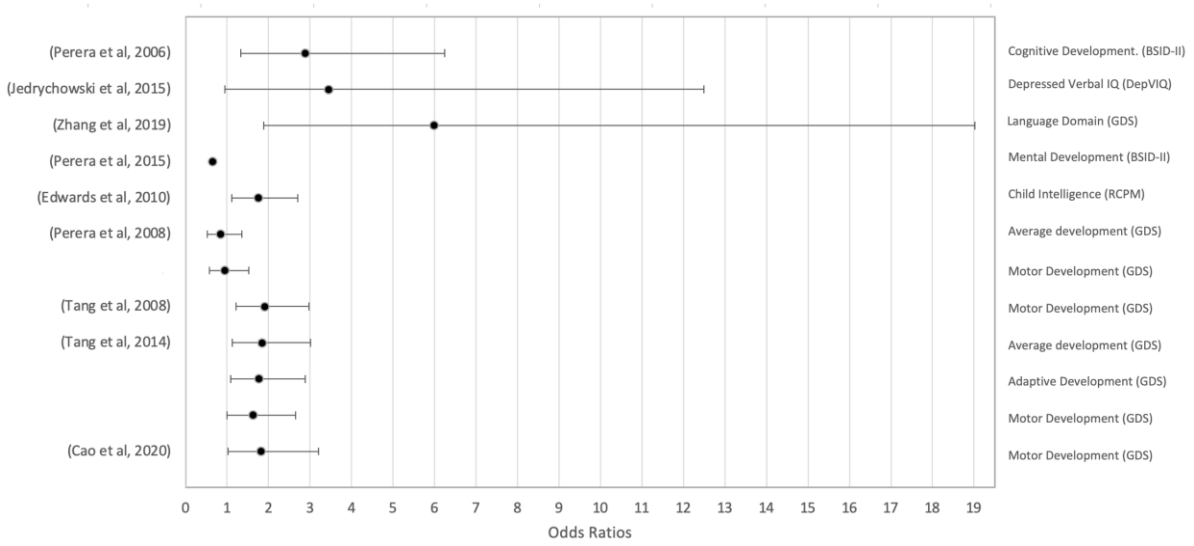

Figure 7 : Forest Plot of the calculated odds ratios (OR) and 95% confidence intervals (95% CI) for the association between prenatal exposure to PAH and measures of Cognitive Development. Bayley Scales of Infant Development- Revised (BSID-II), Depressed Verbal IQ Index (DepVIQ), Gesell Development Schedule (GDS), Raven Coloured Progressive Matrices Test (RCPM), Wechsler Intelligence Scale for Children IV (WISC-IV). 1 study had insufficient data to calculate 95% CI (Perera *et al.* 2015)

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Table 1: Studies with measured prenatal PAH exposure on cognitive development.

Citation	Sample Size	Sample Characteristics	Male: Female	Mean age (SD)	Age Range	Comorbidities	Air Pollution Data Acquisition Method
Perera *et al.* 2006	183	Children 3 years of age, mothers 18-35 years, non-smoking, free of diabetes, hypertension, or known HIV, African American and Dominican women residing for a minimum of a year in Washington Heights, Harlem or the South Bronx in New York City	84:99	3.5 (0.5)	3 years - 3 years 12 months	N/A	Environmental samples analysed for 8 PAHs
Jedrychowski *et al.* 2015	170	Children 7 years of age, mothers ≥18 years of age, non-smoking, singleton pregnancies, no history of illicit drug use, pregnancy related diabetes, or hypertension, no current occupational exposure to PAH or any other known developmental toxicants, and have been resident in Krakow, Poland for a minimum of a year	80:90	7.5 (0.5)	7 years - 7 years 12months	N/A	Cord blood PAH–DNA adduct
Zhang *et al.* 2019	211	Infants 12 months of age, free from delivery injuries, neonatal problems, acquired disabilities, developmental dysplasia or other developmental defects, Mothers resident in Qingdao city, China for at least 3 years, free from diabetes, known HIV and known neuropsychiatric disease.	192:156	1.0 (0.083)	1 year - 1 year 1 month	N/A	Cord blood Benzo[a]pyrene-DNA adducts (ng/mL)
Perera *et al.* 2015	380	Children 2 years of age, mothers 18-35 years, non-smoking, free of diabetes, hypertension, or known HIV, African American and Dominican women residing for a minimum of a year in Washington Heights, Harlem or the South Bronx in New York City.	N/A	2.5 (0.5)	2 years - 2 years 12 months	N/A	PAH/aromatic DNA adducts in umbilical cord blood samples
Polanska *et al.* 2013	406	Children 1-2 years of age, mothers had single pregnancy up to 12 weeks of gestation, no assisted conception, no pregnancy complications, no chronic disease, resident in Poland	192:214	1.5 (0.5)	1 year - 2 years 12 months	N/A	1-hydroxypyrene metabolites in mothers urine

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Edwards *et al.* 2010	214	Children 5 years of age, mothers ≥18 years of age, non-smoking, singleton pregnancies, no history of illicit drug use, pregnancy related diabetes, or hypertension, no current occupational exposure to PAH or any other known developmental toxicants, and have been resident in Krakow, Poland for a minimum of a year	103:111	5.5 (0.5)	5 years - 5 years 12 months	N/A	Environmental samples analysed for 8 PAHs
Perera *et al.* 2008	217	Children 2 years of age, born between either: March-June 2002 or March- May 2002, mothers ≥ 20 years, non-smoking, resident within 2km of Tongliang power plant	113: 104	2.5 (0.5)	2 years - 2 years 12 months	N/A	Cord blood Benzo[a]pyrene-DNA adducts (ng/mL)
Tang *et al.* 2008	110	Children 2 years of age, born between March- June 2002, Mothers ≥ 20 years, non-smoking, resident within 2km of Tongliang power plant	54:56	2.5 (0.5)	2 years - 2 years 12 months	N/A	Cord blood Benzo[a]pyrene-DNA adducts (ng/mL)
Tang *et al.* 2014	215	Children 2 years of age, born between either: March-June 2002 or March- May 2002, mothers ≥ 20 years, non-smoking, resident within 2km of Tongliang power plant	106:109	2.5 (0.5)	2 years - 2 years 12 months	N/A	Cord blood Benzo[a]pyrene-DNA adducts (ng/mL)
Cao *et al.* 2020	158	Children 2 years of age, mothers ≥18 years of age, non-smoking, resident in Taiyuan, Shanxi province, China for a minimum of 1 year	82:76	2.5 (0.5)	2 years - 2 years 12 months	N/A	The sum of the maternal concentrations of eleven urinary PAHs metabolites Σ-OHPAHs

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Association between prenatal PAH exposure and neurobehavioral development

Children with a high prenatal PAH exposure were found to exhibit externalizing and internalizing behavioural problems (OR= 2.49, 95%CI, 1.57 to 3.95; OR=2.39, 95%CI, 1.51 to 3.79 respectively) (Perera *et al.* 2013) and infants exhibited a decrease in behavioural development (OR= 2, 95%CI, 1.27 to 3.15) (Nie *et al.* 2019). Associations with anxious/ depressed behaviour were found in 3/4 studies (Perera *et al.* 2012; Perera *et al.* 2011; Perera *et al.* 2013) (OR=8.89, 95%CI, 1.7 to 46.51; OR= 8.14, 95%CI, 1.21 to 54.94; OR=1.7, 95%CI, 1.08 to 2.68 respectively) with no association found by Pagliaccio *et al* (2020). 3/5 studies reported negative effect on child attentiveness (Perera *et al.* 2018; Pagliaccio *et al.* 2020; Perera *et al.* 2012) (OR=1.34, 95%, 0.85 to 1.83; OR= 2.02, 95%, 1.35 to 3.03; OR=3.79, 95%CI, 1.14 to 12.66) whilst Perera *et al* (2011) and Perera *et al* (2013) reported no effect. Perera *et al* (2013) report of an effect in both withdrawn/ depressed and aggressive behaviour (OR=2, 95%CI, 1.27 to 3.16; OR=2.29, 95%CI, 1.45 to 3.62 respectively) was contradicted by Pagliaccio *et al* (2020) reporting no effect for either. Pagliaccio *et al* (2020) did however report an effect on impaired thought problems (OR= 1.95, 95%CI, 1.3 to 2.91) which was contradicted by Perera *et al* (2013). Only 1/7 studies reported an association between PAH and social problems (Perera *et al.* 2013) (OR= 1.57, 95%CI, 1.00 to 2.48), the remaining 6 reported no effect (Pagliaccio *et al.* 2020; Zhang *et al.* 2019, Perera *et al.* 2008; Tang *et al.* 2008; Tang *et al.* 2014; Cao *et al.* 2020). Both Perera *et al* (2013) and Pagliaccio *et al* (2020) found no effect on rule breaking behaviour or somatic complaints. Perera *et al* (2018) reported no associations with attention deficit hyperactivity disorder (ADHD) index scores, or hyperactive compulsive behaviour nor did Perera *et al* (2006) with total behavioural problems. Studies reporting neurobehavioral effects are reported in table 2, and effect sizes depicted in figure 8.

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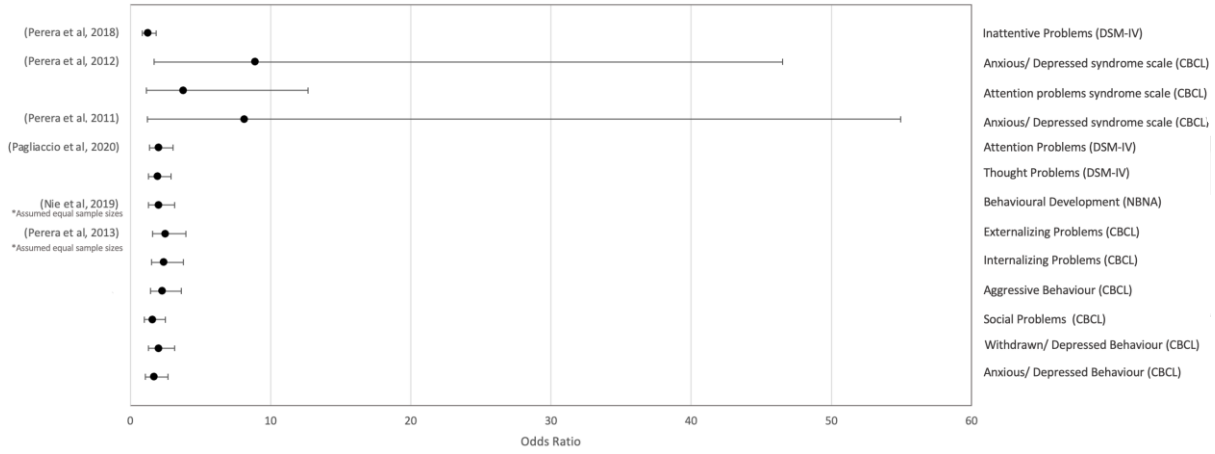

Figure 8: A Forest Plot of the calculated odds ratios (OR) and 95% confidence intervals (95% CI) for the association between prenatal exposure to PAH and measures of Neurobehavioral Development. Gesell Development Schedule, Diagnostic (GDS) and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), Child Behaviour Checklist (CBCL), Neonatal Behavioural Neurological Assessment (NBNA). *sample sizes were assumed equal

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Table 2: Studies with measured prenatal PAH exposure on neurobehavioral development.

Citation	Sample Size	Sample Characteristics	Male: Female	Mean age (SD)	Age Range	Comorbidities	Air Pollution Data Acquisition Method
Perera *et al.* 2018	351	Children 9 years of age, mothers 18-35 years, non-smoking, free of diabetes, hypertension, or known HIV, African American and Dominican women residing for a minimum of a year in Washington Heights, Harlem or the South Bronx in New York City.	163: 188	9.01 (0.19)	9 years- 9 years 12 months	N/A	Cord blood Benzo[a]pyrene-DNA adducts (ng/mL)
Perera *et al.* 2012	253	Children 6-7 years of age, mothers 18-35 years, non-smoking, free of diabetes, hypertension, or known HIV, African American and Dominican women residing for a minimum of a year in Washington Heights, Harlem or the South Bronx in New York City.	131:122	6.5 (0.5)	6 years - 7 years 12 months	N/A	Environmental samples analysed for 8 PAHs
Perera *et al.* 2011	215	Children 3 years 9 months- 5 years 11 months of age, mothers 18-35 years, non-smoking, free of diabetes, hypertension, or known HIV, African American and Dominican women residing for a minimum of a year in Washington Heights, Harlem or the South Bronx in New York City.	87: 128	4.8 (not reported)	3 years 9 months - 5 years 11 months	N/A	Cord blood Benzo[a]pyrene-DNA adducts (ng/mL)
Pagliaccio *et al.* 2020	319	Children 11 years old, mothers 18-35 years, non-smoking, free of diabetes, hypertension, or known HIV, African American and Dominican women residing for a minimum of a year in Washington Heights, Harlem or the South Bronx in New York City.	177: 142	11.5 (0.5)	11 years - 11 years 12 months	Early Life Stress	Environmental samples analysed for 8 PAHs
Nie *et al.* 2019	247	Infants 3 days of age, mothers ≥ 18 years, non-smoking, no chronic disease or family history of neurological disease, single gestational viable fetus, who delivered in the Sixth Hospital of Shanxi Medical University and the Eighth People's Hospital of Taiyua, resident in Taiyuan for at least a year	132: 115	3 days (not reported)	3 days	N/A	Urinary metabolite concentrations of 2-hydroxyfluorene

Perera *et al.* 2013	248	Children from Krakow, Poland, mothers ≥18 years, non-smoking	122: 126	7.28 (0.98)	6 years - 9 years 12 months	Maternal Psychological Distress	Personal air monitoring analysing concentrations of 8 PAHs
Tang *et al.* 2008	110	Children 2 years of age, born between March- June 2002, mothers ≥ 20 years, non-smoking, resident within 2km of Tongliang power plant	54:56	2.5 (0.5)	2 years - 2 years 12 months	N/A	Cord blood Benzo[a]pyrene-DNA adducts (ng/mL)
Zhang *et al.* 2019	211	Infants 12 months of age, free from delivery injuries, neonatal problems, acquired disabilities, developmental dysplasia or other developmental defects, mothers resident in Qingdao city, China for at least 3 years, free from diabetes, known HIV and known neuropsychiatric disease.	192:156	1.0 (0.083)	1 year - 1 year 1 month	N/A	Cord blood Benzo[a]pyrene-DNA adducts (ng/mL)
Perera *et al.* 2008	217	Children 2 years of age, born between either: March- June 2002 or March- May 2002, mothers ≥ 20 years, non-smoking, resident within 2km of Tongliang power plant	113: 104	2.5 (0.5)	2 years - 2 years 12 months	N/A	Cord blood Benzo[a]pyrene-DNA adducts (ng/mL)
Tang *et al.* 2014	215	Children 2 years of age, born between either: March- June 2002 or March- May 2002, mothers ≥ 20 years, non-smoking, resident within 2km of Tongliang power plant	106:109	2.5 (0.5)	2 years - 2 years 12 months	N/A	Cord blood Benzo[a]pyrene-DNA adducts (ng/mL)
Cao *et al.* 2020	158	Children 2 years of age, mothers ≥18 years of age, non-smoking, resident in Taiyuan, Shanxi province, China for a minimum of 1 year	82:76	2.5 (0.5)	2 years - 2 years 12 months	N/A	The sum of the maternal concentrations of eleven urinary PAHs metabolites Σ-OHPAHs
Perera *et al.* 2006	183	Children 3 years of age, mothers 18-35 years, non-smoking, free of diabetes, hypertension, or known HIV, African American and Dominican women residing for a minimum of a year in Washington Heights, Harlem or the South Bronx in New York City	84:99	3.5 (0.5)	3 years - 3 years 12 months	N/A	Environmental samples analysed for 8 PAHs

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Association between prenatal $PM_{2.5}$ exposure and cognitive and neurobehavioral development

Chiu *et al* (2016) examined high $PM_{2.5}$ exposure during: early, mid and late pregnancy with measures of: full-scale IQ score, inattentiveness and adverse memory performance. Boys highly exposed during late pregnancy exhibit lower IQ, and inattentiveness when exposure was from mid to late pregnancy. Girls highly exposed during early to mid-pregnancy exhibited adverse memory performance. No effect was reported for the remaining domains. Contradictory to this Lertxundi *et al* (2019) reported impaired memory in boys.
Lertxundi *et al* (2015)s finding of impaired motor development was not supported by Lertxundi *et al* (2019)s report. No effect was found on visual-motor functioning (Blazkova *et al.* 2020).
No association was observed in cognitive ability (Kerin *et al.* 2017), general cognitive index (Lertxundi *et al.* 2019) and mental scale (Lertxundi *et al.* 2015) nor, non-verbal intelligence (Blazkova *et al.* 2020), adaptive function, autism spectrum disorder (Kerin *et al.* 2017) and verbal, perceptive manipulative and numeric development (Lertxundi *et al.* 2019). Studies reporting prenatal $PM_{2.5}$ exposure can be found in table 3.

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Table 3: Studies with measured prenatal $PM_{2.5}$ exposure on cognitive and neurobehavioral development.

Citation	Sample Size	Sample Characteristics	Male: Female	Mean age (SD)	Age Range	Comorbidities	Air Pollution Data Acquisition Method
Blazkova *et al.* 2020	169	Children 5 years of age, born in the summer 2013 to winter 2014, non-smoking mothers, resident in Karvina and Ceske Budejovice, Czech Republic	78:90	5.5 (0.5)	5 years - 5 years 12 months	Viral Diseases Otitis Bronchitis GIS HCD	Analysis of 11 OH-PAHs in Urine
Kerin *et al.* 2017	325	Children 2-5 years, resident in catchment area of 20 counties in northern California, the central valley and parts of Los Angeles metropolitan area, US, Complete history of Environmental air exposure, lived with at least 1 biological parent who speaks English or Spanish.	281:44	(not reported)	2 years - 5 years 12 months	N/A	Residential addresses inputted into Tele Atlas database and software
Lertxundi *et al.* 2019	560	Children 4 years Male, mothers ≥ 16 years, resident in Valencia, Sabadell and Gipuzkoa in Spain	560:00	4.8 (4.9)	4 years - 4 years 12 months	N/A	Land use regression models
Lertxundi *et al.* 2015	438	Children aged approx. 15 months age, mothers ≥16 years, singleton pregnancies	198:240	1.25 (0.25)	1 year 1 month- 1 year 6 months	N/A	Environmental samples from Digital DHA-80 high-volume aerosol samplers
Chiu *et al.* 2016	119	Mothers ≥18 years, at 28.4 ± 7.9 weeks gestation between August 2002 and January 2000 in Boston.	00:119	6.5 (0.98)	6 years - 7 years 3 months	N/A	Use of a hybrid satellite based spatio-temporal prediction model and residential address during pregnancy

Childhood

Association between childhood PAH exposure and general cognition and neurobehavioral development.

Children exposed to high levels of PAH postnatally exhibited lower cognitive ability (Suter *et al.* 2017). Both Suter *et al* (2017) and Alemany *et al* (2018) reported increased inattentiveness, which was contradicted by Mortamais *et al* (2017). Alemany *et al* (2018) found an association with impaired working numeric memory, however no effect was reported on working verbal memory. Additionally, Suter *et al* (2017) reported an effect of delayed impaired memory, but not with short term memory.
The association with ADHD diagnosis, reported by Abid *et al* (2014) was not supported by 2 studies concerning symptom scores of ADHD (Mortamais *et al.* 2017; Alemany *et al.* 2018). No effect to learning performance (Suter *et al.* 2017), nor learning disability (Abid *et al.* 2014) was reported. Further to this, no association was found with visual spatial skills, non-verbal test performance, executive function, motor performance (Suter *et al.* 2017), or behavioural problems (Alemany *et al.* 2018). Studies reporting childhood PAH exposure can be found in table 4.

Association between childhood $PM_{2.5}$ exposure and general cognition and neurobehavioral development

Children exposed to high levels of $PM_{2.5}$ postnatally displayed impaired selective and sustained attention (Saenen *et al.* 2016). This was not supported by Rivas *et al* (2019) nor Cserbik *et al* (2020) reporting no effect on inattentiveness or attention and executive function respectively.
Saenen *et al* (2016) report of impaired visual information processing speed, was again contradicted by Cserbik *et al* (2020) reporting no association with processing speed.
No association was found with working memory (Rivas *et al.* 2019; Cserbik *et al.* 2020), episodic memory, language (Cserbik *et al.* 2020), cognitive ability, adaptive function or autism spectrum disorder (Kerin *et al.* 2017). Studies reporting postnatal $PM_{2.5}$ exposure on general cognition and neurobehavior can be found in table 5.

Association between childhood $PM_{2.5}$ exposure and neurodegeneration

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Children highly exposed to $PM_{2.5}$ postnatally exhibited lower amyloid beta protein fragment 1-42 ($A\beta_{1-42}$). and brain-derived neurotrophic factor (BDNF) (Calderón-Garcidueñas *et al.* 2018; Calderón-Garcidueñas *et al.* 2016) and higher interferon (IFN) γ concentrations in cerebrospinal fluid (CSF) (Calderón-Garcidueñas *et al.* 2018). No effect was found with regard to concentrations of biomarkers: non-phosphorylated tau (non-p-tau), vitamin D, tau phosphorylated at threonine 181 (Calderón-Garcidueñas *et al.* 2018), cellular prion protein, total tau, interleukin (IL) β, leptin (Calderón-Garcidueñas *et al.* 2016; Calderón-Garcidueñas *et al.* 2018), total alpha- synuclein (α-synuclein), oligodendrocyte α-synuclein, hyperphosphorylated tau, tumour necrosis factor alpha, IL 2, IL 6, IL 10 or monocyte chemoattractant protein-1 (MCP-1) (Calderón-Garcidueñas *et al.* 2016). Of 33 antibodies to neural and tight junction proteins actin immunoglobulin G (IgG), occludin/ zonulin (OZ) immunoglobulin A (IgA), OZ IgG, myelin oligodendrocyte glycoprotein (MOG) IgG, MOG immunoglobulin M (IgM), myelin basic protein (MBP) IgA, MBP IgG, astrocytic protein (S-100) IgG, S-100 IgM and cerebellar antigen (CEREB) IgG in serum and MBP antibodies in CSF were higher in children exposed to high levels of PAH compared to controls (Calderón-Garcidueñas *et al.* 2015). Studies reporting postnatal $PM_{2.5}$ exposure on neurodegeneration can be found in table 6.

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Table 4: Studies with measured childhood PAH exposure on general cognition and neurobehavioral development

Citation	**Sample Size**	**Sample Characteristics**	**Male: Female**	**Mean age (SD)**	**Age Range**	**Comorbidities**	**Air Pollution Data Acquisition Method**
Suter *et al.* 2017	31	Children aged 5-12 resident in Nairobi, Kenya, Infected with HIV and previously enrolled in the Optimizing HIV-1 Therapy Study	N/A	6.6 (0.8)	5 years - 12 years 12 months	HIV	Concentration of urinary PAH metabolite 1-hydroxypyrene (1-OHP)
Mortamais *et al.* 2017	242	Children 7- 10 years, resident and enrolled in one of 40 schools in Barcelona, Spain, no dental braces	123:119	8.4 (0.8)	7 years - 10 years 12 months	N/A	Environmental air sampling
Abid *et al.* 2014	83	Children 6-15 years of age, Part of a civilian population resident in the US	58:25	11.2 (0.5)	6 years - 15 years 12 months	N/A	Urinary metabolite concentrations of 2-napthol
Alemany *et al.* 2018	1589	Children aged 7-11, attending 1 of 38 schools in Barcelona, Spain, and 1 school in the adjacent municipality, Sant Cugat del Vallés	831: 758	8.52 (0.87)	7 years-11 years 12 months	APOE e4 allele	Environmental samples analysed for 7 PAHs

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Table 5: Studies with measured childhood $PM_{2.5}$ exposure on general cognition and neurobehavioral development.

Citation	**Sample Size**	**Sample Characteristics**	**Male: Female**	**Mean age (SD)**	**Age Range**	**Comorbidities**	**Air Pollution Data Acquisition Method**
Cserbik *et al.* 2020	10, 343	Children aged 9 to 10 years, resident in one of 21 study sites in the US	5410: 4933	9.93 (0.64)	9 years -10 years and 12 months	N/A	Ensemble-based model approach combining aerosol optical depth models, land-use regression, and chemical transport models
Kerin *et al.* 2017	325	Children 2-5 years, resident in catchment area of 20 counties in northern California, the central valley and parts of Los Angeles metropolitan area, US, Complete history of Environmental air exposure, lived with at least 1 biological parent who speaks English or Spanish	281:44	(not reported)	2 years -5 years 12 months	N/A	Residential addresses inputted into Tele Atlas database and software
Rivas *et al.* 2019	2,221	Children 7-10 years old, attending one of 39 schools in Barcelona, Catalonia, Spain, without special needs	1133: 1088	8.5 (0.9)	7 years - 10 years 12 months	N/A	Land use regression models
Saenen *et al.* 2016	310	Children in grades 3-6 in three primary schools, Flanders, Belgium.	158: 152	10.2 (1.3)	N/A	N/A	Chronic exposure: spatial temporal interpolation method to model the daily residential exposure. Recent exposure (at schools): portable devices

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Table 6: Studies with measured childhood $PM_{2.5}$ exposure on neurodegeneration.

Citation	Sample Size	Sample Characteristics	Male: Female	Mean age (SD)	Age Range	Comorbidities	Air Pollution Data Acquisition Method
Calderón-Garcidueñas *et al.* 2018	1) 426 2) 81	Children admitted to Mexico City hospital, resident in Mexico City Metropolitan area (MCMA) and other small cities in Mexico	1) 256: 161 2) 44:33	1) 13.36 (8.82) 2) 11.54 (5.1)	(not reported)	lymphoblastic leukaemia	Environmental air sampling, for regulating levels above the USEPA standards
Calderón-Garcidueñas *et al.* 2016	1) 73 2) 126	Children admitted to Mexico City hospital, resident in Mexico City Metropolitan area (MCMA) and other small cities in Mexico	1) 42:31 2) 59:70	1) 11.7 (5.14) 2) 17.49 (15.98)	(not reported)	lymphoblastic leukaemia	Environmental air sampling
Calderón-Garcidueñas *et al.* 2015	111	Children within 5 miles of Mexico City Metropolitan Area(MCMA) or small control cities in Mexico (Zacatlán and Huachinango, Puebla; Zitaácuaro, Michoacaán; Puerto Escondido, Oaxaca; Chalma, Veracruz; Tlaxcala, Tlaxcala), No ETS exposure, lived within 5 miles of an air monitoring station	54:57	13.37 (4.2)	(not reported)	N/A	Environmental air sampling

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Adult

Association between adult PAH exposure and general cognition

Adults highly exposed to PAH exhibited impaired auditory memory in 2 studies (Du *et al.* 2020; Niu *et al.* 2009), and individual accounts of memory disturbances (Ha *et al.* 2012) and impaired verbal learning and memory (Cho *et al.* 2020). However, there was no effect on working memory and executive function, visuospatial memory/attention & planning (Cho *et al*. 2020) nor a further 2 concurring accounts of no effect on visual perception memory (Du *et al.* 2020; Niu *et al.* 2009).
One account of impaired cognitive disturbances (Ha *et al.* 2012), was contradicted by 2 reports of no association with cognitive dysfunction (Cho *et al.* 2020; Best *et al.* 2016).
Both Niu *et al* (2009) and Du *et al* (2020) reported no association with mood state, attention/response speed, manual dexterity or perceptual motor speed. Additional individual accounts of no effect in approximate number system functioning (Niu *et al.* 2009), confrontational word retrieval, verbal fluency, delayed reaction time between congruent and incongruent stimuli, visual attention and task switching (Cho *et al.* 2020) were also reported. All studies involving adult PAH exposure and general cognition can be found in table 7.

Childhood and Adult

Association between childhood and adult $PM_{2.5}$ exposure and neurodegeneration

In a cohort of mixed exposure to $PM_{2.5}$, the presence of neurodegenerative biomarkers phosphorylated tau (p-tau), α-synuclein and transactive response DNA binding protein 43 (TDP-43) was confirmed in brainstems (Calderón-Garcidueñas *et al.* 2020). Faster increase in concentrations with regard to age of non-p-tau in CSF was also associated with increased exposure (Calderón-Garcidueñas *et al.* 2018). However, no association was found with regard to concentration of total and oligomer α-synuclein in CSF (Calderón-Garcidueñas *et al.* 2016). Studies reporting on cohorts inclusive of participants exposed to $PM_{2.5}$ only during childhood and some participants through to adulthood can be found in table 8.

Risk of bias within studies

All studies included were of a high quality with reproducible accounts of the method employed to assess relevant outcomes, and the inclusion/ exclusion criteria used to select

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the study population explained in sufficient detail. Where applicable all studies provided explanations for participant withdrawal, which were unrelated to both the exposure and the outcome being measured and reported intermediate or unexpected results. 54% of studies involved the use of a comparison with a low exposure or control population either by dichotomising exposure data or using a demographically matched control population. The remaining 46% of studies assessed PAH exposure as a continuous variable. All studies correctly identified confounding variables and the method and analysis was adjusted accordingly. There was however a considerable risk of information bias amongst studies, with only 16% of studies reporting the outcome assessor to be blinded and unaware of the exposure status of the study participant. 73% provided no indication as to whether they were or not, and in 11% the outcome assessors were confirmed unblinded.

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Table 7: Studies with measured adult PAH exposure on general cognition.

Citation	Sample Size	Sample Characteristics	Male: Female	Mean age (SD)	Age Range	Comorbidities	Air Pollution Data Acquisition Method
Du *et al.* 2020	697	Employed at a coking plant in Shanxi province, China for minimum of 1 year	470:227	39.73 (9.74)	24-64 years 12 months	N/A	The sum of the concentrations of eleven urinary PAHs metabolites Σ-OHPAHs
Cho *et al.* 2020	949	≥50 year-old individuals, no known neurological diseases, resident in Seoul, Incheon, Wonju and Pyeongchang, Republic of Korea.	421:528	67.24 (6.39)	≥50 years	Hypertension Diabetes Dyslipidaemia Angina Myocardial infarction	Concentrations of urinary PAHs metabolites including: 1-hydroxypyrene
Ha *et al.* 2012	565	Volunteers in the Hebei Spirit oil spill, 2007,near the shore of Taean, Korea.	275:288	N/A	N/A	Asthma	1-hydroxypyrene and 2-naphthol metabolites in urine
Niu *et al.* 2009	176	Male 23–48-year-old coke oven workers Taiyuan, China, employed for a minimum of 1-year, middle school educated.	176:00	37.86 (6.61)	23 years to 48 years 12 months	N/A	Concentration of urinary PAH metabolite 1-hydroxypyrene (1-OHP)
Best *et al.* 2016	454	≥60-year-old individuals without known neurological diseases, resident in 15 randomly selected states in the US	221:233	70.1 (0.02)	≥ 60 years	Hypertension Thyroid Disease Stroke Kidney Disease Liver Disease	The sum of the concentrations of eight urinary PAHs metabolites (Σ-OHPAHs)

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Table 8: Studies with measured cohorts inclusive of childhood and adult PM2.5 exposure on Neurodegeneration

Citation	Sample Size	Sample Characteristics	Male: Female	Mean age (SD)	Age Range	Comorbidities	Air Pollution Data Acquisition Method
Calderón-Garcidueñas *et al.* 2020	186	Metropolitan Mexico City residents, acute cause of death not involving the brain, autopsies were performed 3.7 ± 1.7 h after death, autopsy material examined between 2004 and 2008	162:186	27.29 (11.8)	11 months-40 years 12 months	N/A	Ministry of Environment of Mexico City monitoring stations
Calderón-Garcidueñas *et al.* 2018	1) 426 2) 81	Children admitted to Mexico City hospital, resident in Mexico City Metropolitan area (MCMA) and other small cities in Mexico	1) 256: 161 2) 44:33	1) 13.36 (8.82) 2) 11.54 (5.1)	N/A	lymphoblastic leukaemia	Environmental air sampling, for regulating levels above the USEPA standards
Calderón-Garcidueñas *et al.* 2016	1) 73 2) 126	Children admitted to Mexico City hospital, resident in Mexico City Metropolitan area (MCMA) and other small cities in Mexico	1) 42:31 2) 59:70	1) 11.7 (5.14) 2) 17.49 (15.98)	N/A	lymphoblastic leukaemia	Environmental air sampling

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Discussion

This review found sufficient evidence that prenatal PAH exposure negatively impacts cognitive function with specific regard to child intelligence, mental development, verbal IQ, memory impairment, average overall development, child attentiveness, behavioural development and externalizing, internalizing, anxious and depressed behavioural problems. Evidence concerning exposure during childhood and as an adult with cognitive function was insufficient to conduct a meta-analysis, due to a reduced number of studies, low consistency and high heterogeneity in results. However, associations can be observed such as exposure during childhood with lowered cognitive ability, and impaired child attentiveness, and exposure as an adult manifesting in memory disturbances with specific regard to auditory memory and verbal learning and memory.

Studies concerning PAH exposure during childhood, and as an adult were scarce, but found an increased risk of neurodegeneration via the presence of neurodegenerative biomarkers and increased concentrations of cryptic “self” antigens in serum and CSF, indicative of the neuroinflammatory pathology which precedes Alzheimer’s disease (AD) and Parkinson’s disease (PD).

This review disentangled the neurological impact of PAHs from other polluting compounds and can be used as evidence for policy surrounding the monitoring of PAHs specifically. In addition, it raises awareness of the potentially confounding effect, that different ambient PAH concentrations, in metropolitan and rural settings, can have on research assessing outcomes concerned with cognitive function and neurodegeneration in studies.

A previous review on the impact of PM2.5 in disease incidence did not stratify patients by age and neither considered differences between urban and rural areas, rather stratifying studies by the pollution level in which the country was considered (i.e., “lightly polluted” vs. “heavily polluted”) (Fu et al., 2019). Other reviews have highlighted general adverse health conditions such as chronic asthma, increased incidence of premature death and hospital admissions (Abdel-Shafy & Mansour, 2016), and kidney and liver damage (Kim et al. 2013). Some focussed specifically on the carcinogenic properties and resulting incidence of lung (Armstrong et al. 2004), urinary tract (Bosetti et al. 2007), skin and gastrointestinal tract cancers (Kim et al. 2013). Those that focussed on the neurological impact of air pollution, concerned a diverse mixture of compounds. Peters et al (2019) specifically focus on non-communicable diseases and the roles of Nitrogen dioxide (NO2), Nitrogen oxide species (NOx), Carbon monoxide (CO) and PM2.5. Schikowski & Altug, (2020) raise awareness concerning ambient pollutions adverse effect on cognitive decline and impairment,

concurring with findings from Calderón-Garcidueñas et al, (2016), where the emphasis was on ozone, PM2.5 and PM10. Kilian & Kitazawa, (2018) report NO2, NOx, black carbon and PMs role as potential risk factors for AD, PD and multiple sclerosis. Despite the outcomes assessed being orientated toward neurological health, the exposures measured either include multiple pollutants, or compounds NO2, NOx, CO, PM or black carbon, around which extensive research already exists and has culminated in tight air quality restrictions and monitoring, which is closely adhered to by governing bodies. This review raises awareness as to the neurological impact, PAH has independent of other pollutants, the importance of which is paramount with the current health effects of PAHs in the UK Air quality strategy detailed as “possibly” or “probably” carcinogenic, detracting from the seriousness of their impact on neurological human health (Department for Environment, Food and Rural Affairs, 2011). This review proceeds to categorise outcomes into subgroups depending on the time of exposure to provide further insight into the demographic most vulnerable and to differentiate between the areas of cognitive function and neurodegeneration most impacted, elucidating the potential mechanisms of neurotoxicity. Observation that the most profound effect of PAH exposure culminates from the prenatal period is in keeping with prior research, showing the fetal brain to be more vulnerable to environmental toxic insult than the adult. The increased permeability of the not yet fully formed blood-brain barrier combined with the rapid brain growth during the second trimester, means the period of most intense construction and brain architecture is also the time the brain is most vulnerable to passage of toxins and neurotoxicity (Lanphear BP, 2015).

Limitations

Studies included in the analysis were limited to those written in the English language. Publication bias, and selective reporting within studies cannot be discarded, nor can indexing issues, in which the search terms failed to identify relevant studies.
The study populations included only originated from 9 countries, of which the UK was not one. Findings are therefore limited to the environments and seasonal variations in climate found in these countries and no specific recommendations for UK can be made. Studies included also involved the use of different subgroup samples from the same large cohort, due to the necessity and availability of a limited number of longitudinal study databases. Sampling bias cannot therefore be disregarded.
To adjust for heterogeneity studies were stratified depending on the time point of exposure and outcome assessed, however this did not account for heterogeneity between evaluators and instruments used. In addition to this the use of 5 different measures to quantify levels of PAH exposure as well as the inclusion of quantification of $PM_{2.5}$ as a measure, resulted in

heterogeneity in exposure measurement instruments, and the inclusion of potential contaminating compounds within $PM_{2.5}$ which would confound results. Finally, there was insufficient data to calculate 95%CI for 1 study (Perera *et al.* 2015) and the request for numeric data from another study, received no response, hence the report of an effect on memory and cognitive disturbances was inferred from a figure with no confirmation from the raw data (Ha *et al.* 2012).

Future Research

The role of gender in the neurotoxic effects of PAH exposure requires further investigation. Sex stratification of data concerning memory impairment in prenatally exposed populations was contradictory. Further accounts of memory impairment following both childhood and adult exposure should be dichotomized according to gender to examine sensitivity between sexes. Prenatal PAH exposure effect on motor development was an area of controversy. Additional research is required in this domain to eliminate ambiguity, as well as further analysis following childhood and adult exposure. Individual reports of a lack of association with motor performance and perceptual motor speed respectively, were inadequate to clarify such controversy, or draw any conclusions.

In addition to this a more thorough examination of the timescale of PAH exposure is needed, utilising a smaller scale to determine critical windows. Stratification by pregnancy term elucidated to differential full-scale IQ, inattentiveness and memory performance results. No effect on concentration of non-p-tau in CSF was reported following childhood exposure, however when looked at in a mixed cohort of childhood and adult exposure, in relation to age progression an association was reported, indicative of a critical window of exposure. Further to this gene-environment interactions need further analysis, PAHs effect on the brain of genetically susceptible populations, such as carriers of the APOE4 allele.

Repeated future analysis on longitudinal cohorts is required to examine the impact of sustained high PAH exposure or subsequent markedly reduced exposure, and the effects such fluctuations can have on cognitive function and neurodegeneration and whether some adverse effects from prenatal or early life exposure are recoverable.

Future research should identify and analyse the individual contributions, and specific synergistic combinations of PAHs on neurological health. This would differentiate and determine the most neurotoxic PAHs, and provide evidence for an update in policy, requiring the monitoring of additional PAHs other than B[a]P. Additional research into the threshold at which PAH is capable of exerting neurotoxic effects would inform policy, with scientific backing on a safe limit with regard to neurological health and update the limit of $0.25ng.m^{-3}$ B[a]P set with regard only, to the carcinogenic properties. Further to this more studies are

needed concerning populations in the UK, to account for the local environment, climate and seasonal variations, capable of altering PAH's neurotoxic properties.

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