Sex Difference of Pre- and Post-Natal Exposure to Six Developmental Neurotoxicants on Intellectual Abilities: A Systematic Review and Meta-Analysis of Human Studies

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Abstract

Objective: To examine sex-specific effects of exposure to developmental neurotoxicants on IQ in a systematic review and meta-analysis.

Method: We screened abstracts published before December 31, 2021, for empirical studies of six neurotoxicants (lead, mercury, polychlorinated biphenyls, polybrominated diphenyl ethers, organophosphates, and phthalates) that (1) used an individualized biomarker; (2) measured exposure during the prenatal period or before age six; and (3) provided effect estimates on general, nonverbal, and/or verbal IQ by sex. We performed separate random effect meta-analyses by sex with subgroup analyses by neurotoxicant.

Results: Fifty-one studies were included in the systematic review and 22 in the meta-analysis. Prenatal exposure to neurotoxicants was associated with decreased general and nonverbal IQ in males, especially for lead. No significant effects were found for females or verbal IQ.

Conclusion: During fetal development, males may be more vulnerable than females to general and nonverbal intellectual deficits from neurotoxic exposures, especially from lead.

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List of Abbreviations

9CB	9 Chlorinated Biphenyls
ADHD	Attention-Deficit/Hyperactivity Disorder
ALSPAC	Avon Longitudinal Study of Parents and Children
AS	Achievement Score
ASD	Autism Spectrum Disorder
BDCIPP	Bis(1,3-dichloro-2-propyl) Phosphate
BDE	Brominated Diphenyl Ethers
BDE-47	Tetrabromodiphenyl Ether
CCCEH	Columbia Center for Children's Environmental Health
CHAMACOS	Center for the Health Assessment of Mothers and Children of Salinas
CI	Confidence Interval
CPF	Chlorpyrifos
C-WISC	Chinese Version of the Wechsler Intelligence Scale for Children
cx-MiNP	Mono-4-methyl-7-carboxyheptyl phthalate
CYP	Cytochrome
DACE	Development at Adolescence and Chemical Exposure
DAP	Dialkyl Phosphates
DEAP	Diethyl Alkyl Phosphates
DEDTP	Diethyl Dithiophosphate
DEHP	Bis(2-ethylhexyl) Phthalate
DEP	Diethyl phosphate
DETP	Diethyl Thiophosphate
DiNP	Diisononyl Phthalate
DMAP	Dimethyl Alkyl Phosphates
DMDTP	Dimethyl Dithiophosphate
DMP	Dimethyl Phosphate
DMTP	Dimethyl Thiophosphate
DNA	Deoxyribonucleic Acid
DPHP	Di(2-propylheptyl) Phthalate
ELEMENT	Early Life Exposures in Mexico to ENvironmental Toxicants
FRI	Fluid Reasoning Index
FSIQ	Full-Scale IQ
GCI	General Cognitive Index
HOME	Health Outcomes and Measures of the Environment
ID	Intellectual Disability
INMA	INfancia y Medio Ambiente (Environment and Childhood) Project
IOM	Institutes of Medicine
ip-PPP	2-((isopropyl) phenyl) Phenyl Hydrogen Phosphate

IQ	Intelligence Quotient
K-ABC	Kaufman Assessment Battery for Children
MABC	The Ma'anshan Birth Cohort
MBP	Monobutyl Phthalate
MBzP	Monobenzyl Phthalate
MCPP	Mono-(3-carboxypropyl) Phthalate
MECP2	Methyl CpG Binding Protein 2
MECPP	Mono(2-ethyl-5-carboxypentyl) Phthalate
MEHHP	Mono(2-ethyl-5-hydroxyhexyl) Phthalate
MEHP	Mono(2-ethylhexyl) Phthalate
MEOHP	Mono-(2-ethyl-5-oxohexyl) Phthalate
MEP	Mono-ethyl Phthalate
MiBP	Mono-isobutyl Phthalate
MIREC	Maternal-Infant Research on Environmental Chemicals
MMP	Mono-methyl Phthalate
MMCHP	Mono-2-methylcarboxyhexyl phthalate
MnBP	Mono-n-butyl Phthalate
MoBA	The Norwegian Mother & Child Cohort Study (den norske Mor & barn-undersøkelsen)
MoS	Motor Scale
MPS	Mental Processing Scale
MS	Memory Scale
MSCA	McCarthy Scales of Children's Abilities
NDD	Neurodevelopmental Disorder
OH-MiNP	Mono-4-methyl-7-hydroxyoctyl phthalate
OH-PCB	Hydroxylated Polychlorinated Biphenyls
OPP	Organophosphate Pesticides
oxo-MiNP	Mono-4-methyl-7oxooctyl phthalate
PBDE	Polybrominated Diphenyl Ethers
PCB	Polychlorinated Biphenyls
PIQ	Performance Intelligence
PON1	Paraoxonase 1
POP	Persistent Organic Pollutants
PPS	Perceptual Performance Scale
PPVT	Peabody Picture Vocabulary Test
PRI	Perceptual Reasoning Index
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSI	Processing Speed Index
QS	Quantitative Scale
SB5	Standford Binet 5
SCDS	Seychelles Child Development Study

SGOMSEC	Scientific Group on Methodologies for the Safety Evaluation of Chemicals
SMBCS	Sheyang Mini Birth Cohort Study
SON-R	Snijders-Oomen Nonverbal Intelligence Test
TENDR	Targeting Environmental Neuro-Development Risks
TMICS	Taiwan Maternal and Infant Cohort Study
TSCD	Tohoku Study of Child Development
UK	United Kingdom
USA	United States of America
VAS	Vibroacoustic Stimulation
VCI	Verbal Comprehension Index
VIQ	Verbal Intelligence
VS	Verbal Scale
VSI	Visual Spatial Index
WISC-III	Wechsler Intelligence Scale for Children, Third Edition
WISC-IV	Wechsler Intelligence Scale for Children, Fourth Edition
WISC-III-NL	Wechsler Intelligence Scale for Children, Third Edition, Netherlands Version
WISC-R	Wechsler Intelligence Scale for Children, Revised
WM	Working Memory
WMI	Working Memory Index
WPPSI-III	Wechsler Preschool & Primary Scale of Intelligence, Third Edition
WPPSI-R	Wechsler Preschool & Primary Scale of Intelligence, Revised
WRAT-III	Wide Range Achievement Test, Third Edition

Introduction

The prevalence of neurodevelopmental disorders (NDDs) is on the rise. From 1997 to 2017, the prevalence of having any one NDD increased from approximately 13% to 18% with especially increasing rates among males[2]. It is well known that males have a roughly twofold higher prevalence of NDDs compared to females due to a complex and dynamic interplay between genetic, hormonal, and environmental factors[3]. While a variety of environmental factors may contribute to the prevalence of NDDs, mounting evidence suggests that exposure to toxic chemicals during critical periods of development increases children's risk of NDDs, including intellectual disabilities, attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder (ASD)[4–6]. Moreover, experimental and epidemiological studies demonstrate that early-life exposure to toxic chemicals can impact males and females differently[7–9], potentially accounting for sex differences in a variety of NDDs. Nonetheless, the literature remains inconclusive regarding a sex-specific vulnerability. A better understanding of the impact of toxic chemicals on sex-specific differential susceptibility can provide critical insight into the mechanisms underlying risk of NDDs.

Developmental Neurotoxicity

Fetuses, infants, and young children are especially at risk of harm from toxic chemicals because their bodies and brains are still developing. Development is a period of rapid growth, when the blood-brain barrier is more permeable, and growing cells are more susceptible to toxic chemicals. Thus, as chemicals pass through the blood-brain barrier, they can interfere with sensitive biological processes such as neuronal migration, differentiation, proliferation, synaptogenesis, myelination, and apoptosis, resulting in deleterious effects on neurodevelopment[4]. Furthermore, during critical periods of development, immature metabolic

pathways and enzymes that metabolize and excrete toxic chemicals make it harder for a fetus, infant, or child to rid their body of toxicity[5]. As a result, the developing brain is more susceptible to even low levels of toxic chemicals that might not have an adverse effect on adults[10].

Unfortunately, despite the increased risk of toxic chemicals on fetal and infant development, biomonitoring data show that pregnant women and infants have widespread exposure to a variety of chemicals[11–13]. In an effort to reduce exposure and harm, Project TENDR (Targeting Environmental Neuro-Development Risks; 2016) identified a list of developmental neurotoxicants that were consistently shown to be associated with adverse neurodevelopmental outcomes. Developmental neurotoxicants are toxic chemicals that interfere with the developing central nervous system. Lead, mercury, polychlorinated biphenyls (PCBs), polybromide diphenyl ether (PBDE) flame retardants, organophosphate pesticides (OPPs), phthalates, and air pollution were all identified as developmental neurotoxicants[14].

The next section describes how these developmental neurotoxicants are widespread in the environment and can pass the placenta to alter brain or endocrine functioning even at low levels. Prenatal and early life exposure to these neurotoxicants is associated with cognitive or behavioural problems, indicators of children's brain health, and risk of NDDs[14–21]. Air pollution, which has been associated with adverse neurodevelopmental outcomes[22–24], is not reviewed below given a focus on exposure to neurotoxicants that can be measured with individualized biomarkers.

Heavy Metals

Lead and mercury are both heavy metals. Humans are ubiquitously exposed to heavy metals in the environment due to both natural and anthropogenic sources. Specifically, lead can be found in gasoline, paint, toys, jewelry, traditional medications, foods, and drinking water[25],

and mercury can be found in higher-trophic fish and marine mammals[26]. Despite that production of lead-based products has halted in many countries, remnants of lead continue to be a source of low-level exposure worldwide[25,27] and research indicates there is no "safe" level of lead exposure[28]. Moreover, it has been widely demonstrated that lead and methylmercury can easily cross the placenta and accumulate in placental tissues, amniotic fluid, and umbilical cord blood, thereby impacting fetal development[29,30]. Further, lead and mercury have been found to interfere with sensitive biological processes involved in brain development, such as synaptogenesis and neural differentiation[31]. As a result, lead and mercury exposure are associated with a variety of neurodevelopmental deficits[4,32–37].

Persistent Organic Pollutants (POPs)

PCBs and PBDEs belong to the class of chemicals called persistent organic pollutants (POPs), meaning they are resistant to biodegradation and thus are persistent in the environment. PCBs are synthetic hydrocarbons previously used as insulators in transformers and capacitors[38]. While PCBs have been banned in most industrialized countries for over thirty years, they continue to be a source of exposure due to consumption of contaminated foods and leakage and improper disposal of contaminated electrical equipment[38]. PBDEs are flame retardants widely used in a variety of consumer products such as furniture, mattresses, car seats, and electronic devices[39]. Both chemicals accumulate in cord blood and breast milk[40,41] and have neurological and endocrine-disrupting effects[18,39]. Specifically, PCBs and PBDEs have been found to disrupt thyroid hormone and calcium signaling and induce oxidative stress in neurons[18,39]. In-utero and early-life exposure to PCBs and PBDEs have been associated with poorer cognitive and behavioural development[18,20,42]

Organophosphate Pesticides (OPPs)

OPPs are chemical pesticides used in residential and agricultural settings for the control of pests[43]. Humans can be exposed to OPPs through a variety of sources including contaminated food, water, and the environment[43]. Prenatal exposure to OPPs has adverse neurodevelopmental effects at all stages of childhood including as neonates, in infancy, at pre-school, and school-age[19], which may be mediated by synaptic dysfunction[44]. Specifically, OPPs are associated with deficits in intelligence quotient (IQ) and mental development, as well as increases in attention problems[19,43]

Phthalates

Lastly, phthalates, used as plasticizers in polyvinyl chloride plastics, are found in a wide variety of consumer products, including food packaging, cosmetics, building materials, children's toys, and clothing[45]. Phthalates have become of increasing concern due to their widespread exposure[46], ability to pass through the placenta and breast milk[47], and their endocrine-disrupting effects[45]. A systematic review suggested that prenatal phthalate exposure is associated with adverse neurodevelopmental outcomes, including decreased IQ and social communication, as well as increased inattention and hyperactivity[21].

Sex Differences in Relation to Developmental Neurotoxicology

Sex differences emerge as early as fertilization with the genetic inequality of sex chromosomes, where females have two X chromosomes and males have one X and one Y chromosome[48]. The subsequent interplay between genes, hormones, and environmental factors triggers a variety of anatomical, physiological, and biochemical sex differences, both obvious and subtle, all of which can contribute to sex-linked variations in toxicokinetics and toxicodynamics[48,49]. Toxicokinetics refers to the absorption, distribution, metabolism, and

elimination of toxic chemicals[49]. Toxicodynamics refers to the biochemical and physiological effects of toxic chemicals and the mechanisms by which these chemicals produce their effects[49].

Males and females may differ in their patterns of exposure as hormonal and social influences shape behaviours, activities, and characteristics[50]. Once a toxic chemical is absorbed via inhalation, ingestion, or dermal absorption, sex differences can also be found in distribution and metabolism. On average, females have greater body fat than males[51,52]. As a result, females may be more vulnerable to lipophilic chemicals that preferentially accumulate in fat tissue[53]. Moreover, there is evidence for sex differences in the activity of various cytochrome P-450s (CYP450), the class of enzymes involved in the metabolism of toxic chemicals[54–56], as well as in the activity of glutathione peroxidase, which protects against oxidative damage[57]. Differential activity of detoxification mechanisms can place either males or females at heightened vulnerability depending on the chemical of exposure.

In recognition of sex-based biological differences, the Institute of Medicine (IOM) published a report in 2001 concluding that sex is a fundamental variable that should be considered at all levels of basic and clinical research[58]. In 2005, the Scientific Group on Methodologies for the Safety Evaluation of Chemicals (SGOMSEC) extended the arguments made by the IOM to toxicology and held a weeklong workshop on studying sex in toxicological research[59]. As of 2005, sex was often used as a confounder and relatively unexplored in epidemiologic and neurotoxicological studies. SGOMSEC recommended that future toxicological research consider sex when designing and analyzing their studies[59].

More recently, the importance of understanding sex differences in neurotoxicity has become increasingly recognized and many studies have questioned how toxic chemicals interfere with neurodevelopment as a function of sex. Nonetheless, the literature on sex differences in

response to neurotoxic exposure has remained inconclusive; some studies show evidence of a male vulnerability, some show evidence of a female vulnerability, and others have found no interactions by sex[7–9,60]. The inconsistency in findings may be due to a potential sex difference in vulnerable time windows (i.e., prenatal versus postnatal exposure) and to heterogeneity in the neurotoxic chemicals or neurodevelopmental endpoints assessed.

Sex-Specific Window of Susceptibility

Evidence for sex-specific vulnerabilities to prenatal risk factors has become increasingly prevalent[61]. Partly due to differences in placental function, maturation, epigenetic transmission, and hormonal responses, male fetuses appear to be more vulnerable to a wide variety of environmental insults than female fetuses[61]. For example, males born to mothers with asthma, stress, or gestational diabetes have worse developmental, neurocognitive, and neuromotor outcomes than females[61–64]. Whether this difference applies to prenatal exposure to developmental neurotoxicants is currently unknown.

Despite accumulating evidence that males may be more vulnerable to prenatal environmental insults, less is known about sex-specific effects of postnatal environmental insults. It is known, however, that there are sex differences in brain structure, organization, and perfusion that can evolve dynamically during childhood[65]. Further, during the early postnatal period, one study found that microglia volume and synapses in the hippocampus peaked earlier in female mice than male mice[66]. The relative sex differences in the timing of brain development may then create sex-specific windows of susceptibility to exposures during the postnatal period.

Indeed, one study found sex-specific windows of susceptibility to manganese exposure on intrinsic functional connectivity in areas of the brain associated with cognitive and motor function[67]. Another study found sex-specific windows of susceptibility to lead exposure, where

males' neurobehavior was more susceptible to prenatal exposure, while females' neurobehavior was more susceptible to postnatal exposure[68]. A similar pattern was reported with fluoride exposure[69]. Taken together, these findings suggest that sex-specific effects should be analyzed within the context of windows of exposure.

Neurodevelopmental Endpoints

In addition to window of exposure, the neurodevelopmental endpoint should also be considered when assessing sex-specific effects of neurotoxic exposures. *Neurodevelopment* is a broad term referring to the development of neurological pathways critical for performance and functioning. Neurodevelopment can encompass a wide variety of outcomes, including, but not limited to, attention, motor skills, intellectual functioning, social skills, reading ability, and memory. Sex-specific effects of neurotoxic exposures may vary depending on the specific neurodevelopmental outcome assessed due to differences in the genetics and neurological underpinnings of these outcomes[70]. Therefore**,** to better understand sex-specific vulnerability of neurotoxic exposures, it is valuable to home in on each neurodevelopmental outcome in isolation.

IQ is the most studied neurodevelopmental outcome in children[71]. Even mild IQ deficits predict poorer academic and occupational success and reduced emotional and physical well-being[72]. Given the large number of human neurotoxicology studies that use IQ as the outcome of interest, it is sensible to focus on sex-differences in IQ in response to neurotoxic exposure. However, while IQ is considered a highly significant outcome from a public health[4] and economic standpoint[73], a low IQ score does not convey specific information about the child's intellectual and cognitive profile. When there are strengths and weaknesses in a cognitive profile, the use of a composite score may have high sensitivity, but it also may obscure important aspects

of cognitive functioning[74]. Thus, it is also important to partition IQ into domain-specific intellectual abilities, such as verbal and nonverbal skills, which may reveal particular cognitive domains that are differentially affected by the sexes[75].

Rationale for Present Study

Although some studies have attempted to synthesize the literature on sex-dependent neurodevelopmental effects from toxic chemical exposure, they have aggregated data across a variety of endpoints or timing of exposure, often leaving vague conclusions[7–9,60]. Moreover, aggregating data in such a way has made it nearly impossible for researchers to conduct a meta-analysis to quantitatively assess the strength of evidence. Previous studies have also not considered risk of bias which may impact conclusions by placing equal importance on studies of varying quality. Without a better understanding of these sex effects, we may be overlooking a potentially harmful effect on one sex. Thus, a systematic review and meta-analysis of the data on sex-specific outcomes from neurotoxic exposure is of high research importance.

The present study is a systematic review and meta-analysis to determine the sex-specific effects of general, verbal, and nonverbal IQ deficits from pre- and postnatal exposure to six developmental neurotoxicants (lead, mercury, PCBs, PBDEs, OPPs, and phthalates).

A Note on Sex and Gender

There is controversy over whether to use the term *sex* or *gender* in reference to differences between males and females. Sex refers to the biological characteristics of an individual which differentiate them as male or female. Gender refers to socially constructed roles and a person's self-identification as male or female[76]. For the purposes of this study, we will use the term sex in reference to the biological differences between males and females.

Methods

Our systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Appendix A). The protocol for our review was registered with PROSPERO (CRD42020156526).

Search Strategy and Eligibility Criteria

Titles and abstracts from January 1, 1950, to December 31, 2021, were extracted from the electronic databases PubMed and PsycINFO. The search strategy was developed in collaboration with an academic librarian at York University. The following search terms were used: ("neurotoxic" or "mercury" or "PCB" or "polychlorinated biphenyl" or "PBDE" or "flame retardants" or phthalates" or "OP" or "organophosphates" or "pesticides" or "lead") and ("cogniti*" or "neurodev*" or "intell*" or "IQ"). Additional filters were applied to ensure we extracted English, peer-reviewed, human studies on children.

Abstracts were screened by three reviewers (JR, JJ, and CG) and then independently re-reviewed by a fourth reviewer (CG or RG) to determine whether they met the inclusion criteria. Studies were included based on the following criteria: (1) study examined exposure to one of the six neurotoxicants (i.e., lead, methylmercury, PCBs, PBDEs, OPPs, and phthalates); (2) study's outcome variable was related to neurodevelopment; (3) toxicant exposure was measured during the prenatal or early postnatal period (up to age six); (4) level of toxicant exposure was determined through an individualized biomarker (e.g., blood, hair, urine); (5) study was empirical (excluding case studies).

A full-text review was then independently carried out by two reviewers (CG and RG) for all study abstracts that met inclusion criteria. Included in the analysis were studies that (1) evaluated general, verbal, and/or nonverbal IQ and (2) reported the interaction by sex or effects separately by sex. A full-text review was also carried out for study abstracts in which there was

ambiguity concerning whether they met the inclusion criteria or in which no abstract was available.

Data Extraction

Two reviewers (CG and one of JJ, JR, RM, NS, and AD) independently extracted data on authors, publication year, study aim, design, population, sample size, exposure characteristics (toxicant, timing of exposure, biomarker, mean of exposure), outcome characteristics (IQ test, and age at IQ test), and results (regression coefficients, standard errors, p-values), using a standardized extraction form in Covidence (a systematic review software tool). A third reviewer (RG) settled any discrepancies. If a study was missing quantitative data, its corresponding author was contacted. If the author did not respond after three attempts of contact over the course of a two-month period, the data were considered unretrievable.

Risk of Bias

We evaluated risk of bias using Navigation Guide, a systematic review methodology developed by Woodruff and Sutton[1]. This systematic review tool was designed to evaluate evidence relating environmental exposures to adverse health outcomes and has been recommended for use over similar tools[77]. Nine domains were assessed for risk of bias: selection bias, blinding, confounding, exposure, outcome, incomplete outcome data, selective outcome reporting, conflict of interest, and other threats to internal validity. Each domain could be rated as “low”, “probably low”, “probably high”, or “high” risk of bias. Instructions for making risk of bias determinations were modified from Lam and colleagues’ systematic review[20] (Appendix B). Two reviewers (CG and one of JJ, JR, RM, NS, AD) independently made risk of bias determinations for each study and all discrepancies were resolved by a third reviewer (RG).

Data Analysis

Data analysis involved a three-step process. First, we decided studies suitable for quantitative synthesis. Second, effect sizes were transformed to homogenize the magnitude of effect observed in each study. Third, meta-analysis was used to statistically combine effect sizes across studies, in cases where sufficient data was available to do so. Each of these steps is described in detail below. All statistical analyses were run using Stata 17.0 (Stata Corporation, College Station, TX, U.S.A.). A p value < 0.05 was considered statistically significant for all analyses in our study.

Studies Suitable for Quantitative Synthesis

We decided studies suitable for quantitative synthesis based on the study features, exposure assessment, outcome assessment, and method of data analysis.

Exposure. We considered studies that measured the exposure at any point during pregnancy or at birth as combinable measures of prenatal exposure. We considered studies that measured the exposure at any point from infancy to age six years as combinable measures of postnatal exposure. When regression coefficients were available for groups of chemicals, for instance, PBDE, PCB, phthalate, and OPP congeners, we considered studies that evaluated the sum of exposures (i.e., ΣDEHPs for phthalates, ΣPCBs for PCBs, ΣBDEs for PBDEs and ΣDAPs for OPPs) as combinable.

Outcome. We considered Full-Scale IQ (FSIQ) evaluated by any Wechsler test and the General Cognitive Index (GCI) evaluated by the McCarthy Scale of Children's Abilities (MSCA) as combinable measures of general intelligence[78]. We considered verbal IQ (VIQ), or the Verbal Comprehension Index (VCI) evaluated by any Wechsler test and the Verbal Scale evaluated by the MSCA as combinable measures of verbal intelligence. We considered

performance IQ (PIQ) or the Perceptual Reasoning Index (PRI) evaluated by any Wechsler test, the Perceptual-Performance Scale (PPS) evaluated by the MSCA, and the Snijders-Oomen Non-Verbal Intelligence Test (SON-R) as combinable measures of nonverbal intelligence[79]. Since Weschler, MSCA, and SON-R tests are standardized with mean scores of 100 and a standard deviation of 15, they were not rescaled.

Method of Data Analysis. Studies that used linear regression techniques were considered combinable.

Handling of Multiple Effect Sizes. Some selected studies investigated different iterations of the same prospective cohort study. When multiple effect sizes were available from the same study or sample, effect sizes that most closely resembled the methodologies of the other included studies in the meta-analysis were selected to minimize heterogeneity among studies. For example, when effect sizes were available from multiple exposure periods (e.g., 1st, 2nd, or 3rd trimester) or age at outcome assessment (e.g., 4 and 6 years) in the same study, effect sizes from the trimester or outcome age most similar to other included studies for a given chemical were selected. If the same prospective cohort study included data on more than one neurotoxicant, they were considered as separate effects.

Effect Size Transformation

Studies used different transformations for the exposure variable (natural log, log base 10, or log base 2, or no transformation). Because a one unit increase in the logarithmically transformed variable is equivalent to multiplying the original variable by the base of the logarithm used, the different transformations affect effect size interpretation. To homogenize the magnitude of effect observed in each study, results were recalculated as an absolute change in the dependent variable (i.e., IQ) for a relative difference of $k = 1.5$ times in the exposure variable

(i.e., a 50% difference) [80]. To estimate the absolute change in Y for a relative difference of *k* times in *X*, as well as the 95% confidence interval, for untransformed exposure we used the following formulae:

$$\text{Absolute change in Y for a relative difference of k times in X} = (k-1)\cdot E[X]\cdot\hat{\beta}$$

$$95\%\ \text{CI} = (k-1)\cdot E[X]\cdot\left[\hat{\beta}\pm 1.96\cdot se(\hat{\beta})\right]$$

where *k* was set to 1.5, $E[X]$ is the mean of the exposure measure and $\hat{\beta}$ is the regression coefficient of the exposure. To estimate the absolute change in Y for a relative difference of *k* times in *X*, as well as the 95% confidence interval, for a log transformed exposure we used the following formulae:

$$\text{Absolute change in Y for a relative difference of k times in X} = log_b(k)\cdot\hat{\beta}$$

$$95\%\ \text{CI} = log_b(k)\cdot\hat{\beta}\cdot\left[\hat{\beta}\pm 1.96\cdot se(\hat{\beta})\right]$$

where *b* is the base of the log transformation.

Missing Data. For studies that did not report a standard error or confidence interval, we calculated the standard error as a function of the *t*-statistic for the regression coefficient of the exposure.

Meta Analysis

We ran separate random effects meta-analyses using the DerSimonian-Laird method[81] examining the male- and female-specific effects of prenatal exposures on general intelligence, nonverbal intelligence, and verbal intelligence. Further, given that each neurotoxicant may differ in their route of exposure and toxicological effects, we also ran subgroup analyses by neurotoxicant (for those with at least two studies). The subgroup analyses include neurotoxicant as a categorical moderator variable to compare the overall estimates across groups and to determine whether the considered grouping helps explain some of the observed between-study heterogeneity. Due to the limited number of studies available, we did not perform a separate

analysis of PCBs for any intelligence outcome, nor separate analyses of OPPs or PBDEs for verbal intelligence.

Some neurotoxicants (i.e., PCBs, BDEs, OPPs, and phthalates) are a part of a class of chemicals, composed of a variety of compounds. Therefore, we also conducted separate random-effects meta-analyses for each class of neurotoxicant, with subgroup analyses by compound, when additional data on individual compounds were available. Due to a lack of available data, we were only able to run a meta-analysis on phthalates with phthalate compounds as the categorical moderator variable [i.e., monobenzyl phthalate (MBzP), mono-(3-carboxypropyl) phthalate (MCPP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethylhexyl) phthalate (MEHP), mono-ethyl phthalate (MEP), mono-isobutyl phthalate (MiBP), mono-n-butyl phthalate (MnBP)].

Moreover, we ran separate random effects meta-analyses of the male- and female-specific effects of postnatal lead exposure on general intelligence. Due to the limited number of studies (i.e., fewer than two per neurotoxicant), we were unable to analyze postnatal effects of any of the other neurotoxicants. The results from the meta-analyses are graphed with forest plots.

Heterogeneity. We report τ^2 to show the between-study variance, H^2 to show the amount of heterogeneity, and I^2 to quantify the percentage of the total variation across studies that is due to heterogeneity [82]. I^2 values of 25%, 50%, and 75% have been purported to correspond with low, moderate, and high degrees of heterogeneity, respectively[83].

Publication Bias. We used Egger's Test to assess potential publication bias via funnel plot asymmetry[84].

Sensitivity Analyses

To examine the influence of each study on the overall effect-size estimate, we used the leave-one-out method. Leave-one-out meta-analysis performs multiple meta-analyses by excluding one study at a time, where the displayed effect size for each study corresponds to an overall effect size computed from a meta-analysis excluding that study[85]. Moreover, we ran additional meta-analyses in which only included studies rated as "low" or "probably" low risk of bias across all domains.

For studies in which there was more than one estimate that was equally combinable in the meta-analysis (i.e., the individual phthalate estimates for trimester 2 and 3 of Torres-Olascoaga, 2020[131] in predicting general intelligence), we ran sensitivity analyses to obtain separate results with each estimate.

Qualitative Synthesis

Studies not included in the meta-analysis were qualitatively described in a table with data on the country/cohort, biomarker, mean of exposure, outcome measure, and a general interpretation of the study findings.

Results

Study Selection

The PRISMA 2020 flow diagram is shown in Figure 1. Our search retrieved 2843 unique articles, of which 450 met the initial inclusion criteria and were included in the full-text review. Fifty-one articles fulfilled the full-text inclusion criteria and were included in the systematic review[86–137]. Of the 51 studies included in the systematic review, 17 pertained to lead, 13 mercury, nine phthalates, six OPPs, five PCBs, and five PBDEs. Four articles included data from exposure to more than one neurotoxicant, thus data on each neurotoxicant was included in the

systematic review[86-89]. Of the 51 studies included in the systematic review, 22 were included in the meta-analyses[88–90,92,98,99,101,102,104,108,111,114,115,118,123,125,130–132,132,134,136].

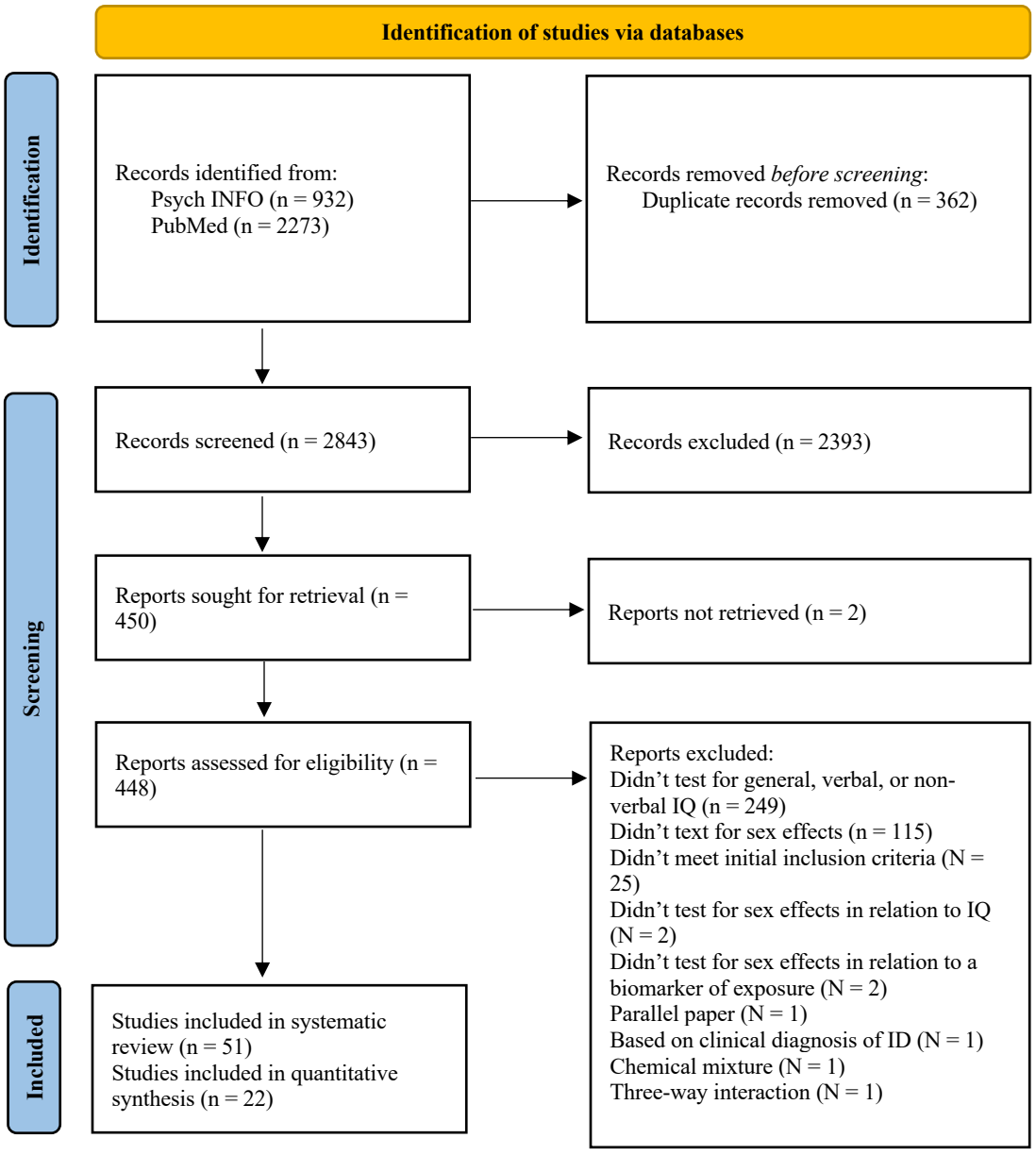


Figure 1. PRISMA 2020 Flow Diagram

Meta-Analysis Study Characteristics

Table 1 provides an overview of the studies included in the meta-analysis, including the country/cohort, biomarker, mean of exposure in parts per billion (ppb), and the outcome measure.

Included studies were published between 1987 and 2021 and involved between 188 and 1827 study participants from 15 different cohorts around the world. Ten studies were conducted in North America, seven in Europe, one in Australia, and four in Asia. Seven studies pertained to lead, four to mercury, two to PBDEs, three to OPPs, and seven to phthalates. Most studies measured neurotoxicant exposure in urine (n = 11), followed by blood (n = 9), incisor teeth (n =1) and umbilical cord tissue (n =1). Eighteen studies measured toxicant exposure during the prenatal period, three measured toxicant exposure during the postnatal period, and one measured toxicant exposure during both the prenatal and postnatal period. Five studies conducted intelligence assessments using the WPPSI-III, five using the WISC-IV, four using the MSCA, two using the SON-R, one using the WISC-III (UK version), two using the WISC-R, one using the WPPSI-R/WISC-III, one using the C-WISC, one using the Japanese version of the WISC-IV, and one using the Chinese version of the WISC-IV. Nineteen studies examined general intelligence, 14 examined nonverbal intelligence, and ten examined verbal intelligence.

Table 2 depicts the risk of bias ratings for the studies included in the meta-analysis. Ten studies were rated as “low” or “probably low” risk of bias in all domains assessed. Twelve studies were rated as “high” or “probably high” risk of bias in one or more domains. Many of the studies that had at least one rating of “probably high” risk of bias were rated as such in the domain of confounding.

Table. Meta-Analysis Study Characteristics

First Author, Year	Country (Cohort)	N ($\%_{males}$)	Neurotoxicant	Compound	Biomarker and Timing of Exposure	Median of Exposure (ppb)	Outcome Measure
Azar, 2021	Canada (MIREC)	584-589 (48.8-49.1)	PBDE	ΣPBDE[c]	1st trimester blood	12.9	FSIQ and PIQ on WPPSI-III at 3-4 years
Bouchard, 2011	USA (CHAMACOS)	297 (47.5)	OPP	∑DAP[d]	Mean of 5-27 weeks' gestation urine and 18-39 weeks' gestation urine	41.3	FSIQ on WISC-IV at 7 years
Desrochers-Couture, 2018	Canada (MIREC)	601-606 (~48.8)	Lead Lead	N/A N/A	Cord blood Child blood at 3-4 years	7.9 6.7	FSIQ, PIQ, and VIQ on WPPSI-III at 3-4 years
Dietrich, 1993	USA (Cincinnati Lead Study)	251 (N/A)	Lead	N/A	Cord Blood	83.0[a]	PIQ on WISC-R at 6.5 years
Eskenazi, 2013	USA (CHAMACOS)	231-256 (45.5-45.7)	PBDE	ΣPBDE[c]	2nd trimester blood or maternal blood at delivery	24.9	PIQ on WPPSI-III at 5 years and FSIQ on WISC-IV at 7 years
Factor-Litvak, 2014	USA (CCCEH)	328 (47.3)	Phthalate Phthalate Phthalate Phthalate Phthalate Phthalate	MnBP MBzP MEHHP MEHP MEP MiBP	3rd trimester urine 3rd trimester urine 3rd trimester urine 3rd trimester urine 3rd trimester urine 3rd trimester urine	38.0 14.4 21.8 4.9 141.5 9.2	FSIQ on WISC-IV at 7 years
Gascon, 2015	Spain (INMA-Sabadell)	367 (52.0)	Phthalate Phthalate Phthalate Phthalate Phthalate	MBzP MEP MiBP MnBP ΣDEHP[e]	Average of 1st and 3rd trimester urine Average of 1st and 3rd trimester urine Average of 1st and 3rd trimester urine Average of 1st and 3rd trimester urine Average of 1st and 3rd trimester urine	11,900 403,400 31,600 30,800 99,800	GCI, PPS, VS on MSCA at 4 years
Guo, 2020	China (SMBCS)	297 (~57.0)	Lead Mercury	N/A	Maternal urine at delivery Maternal urine at delivery	1.7 0.4	FSIQ, PRI, and VCI, on C-WISC at 7 years
Huang, 2012	Taiwan (N/A)	133 (~51.9)	Lead	N/A	Blood at 2-3 years Blood at 5-6 years	25.0 23.0	FSIQ on WPPSI-R at 5-6 years and WISC-III at 8-9 years

Hyland, 2019	USA (CHAMACOS)	321-323 (47.9- 48.5)	Phthalate	ΣDEHP[e]	Median of 13- and 26-week urine	78.1	FSIQ, PRI, PSI, VCI, and WMI on WISC-IV at 7 years and 10.5 years
Julvez, 2013	UK (ALSPAC)	914 (52.4)	Mercury	N/A	Umbilical cord tissue	26.0[a]	FSIQ on WISC-III short form at 8 years
Jusko, 2019	Netherlands (Generation R)	708 (51.3)	OPP	∑DAP[d]	Mean of three urines	~314 nmol/g	Mosaics and Categories subtests on SON-R at 6 years
Li, 2019	USA (HOME)	245-251 (~43.0-45.0)	Phthalate Phthalate Phthalate Phthalate Phthalate Phthalate	ΣDEHP[f] MBzP MCPP MEP MiBP MnBP	26 weeks' gestation urine 26 weeks' gestation urine 26 weeks' gestation urine 26 weeks' gestation urine 26 weeks' gestation urine 26 weeks' gestation urine	69.8 7.8 1.7 114.2 4.1 23.2	FSIQ on WPPSI-III at 5 years or WISC-IV at 8 years
Llop, 2017	Spain (INMA)	1362 (52.3)	Mercury	N/A	Cord blood	8.80[a]	GCI, PPS, VS on MSCA at 4 years
McMichael, 1992	Australia (Port Pirie Cohort Study)	548 (N/A)	Lead	N/A	Lifetime average blood up to 4 years	~190[a]	GCI on MSCA at 4 years
Ntantu Nkinsa, 2020	Canada (MIREC)	505-510 (48.5-48.8)	OPP	∑DAP[d]	1st trimester urine	27.8	FSIQ and PIQ on WPPSI-III at 3-4 years
Pocock, 1987	UK (The Institute of Child Health/Southampton Study)	402 (45.3)	Lead	N/A	Incisor teeth at 6 years	Males: 3980[b] Females: 4020[b]	FSIQ on WISC-R at 6 years
Tatsuta, 2020	Japan (TSCD)	289 (51.2)	Lead Mercury	N/A	Cord blood Cord blood	8.0 ~15.6	FSIQ, PRI, and VCI on Japanese version of the WISC-IV at 12 years
Taylor, 2017	UK (ALSPAC)	1826 (56.6)	Lead	N/A	1st trimester blood	34.1	FSIQ, PIQ, and VIQ on WISC-III (UK) at 8 years
Torres-Olascoaga, 2020	Mexico (ELEMENT)	188-214 (~46.8)	Phthalate Phthalate Phthalate Phthalate	ΣDEHP[e] MBzP MCPP MEHHP	2nd trimester urine 2nd trimester urine 2nd trimester urine 2nd trimester urine	N/A 0.0046[b] 0.0554[b] 0.0325[b]	GCI on MSCA at 4 years

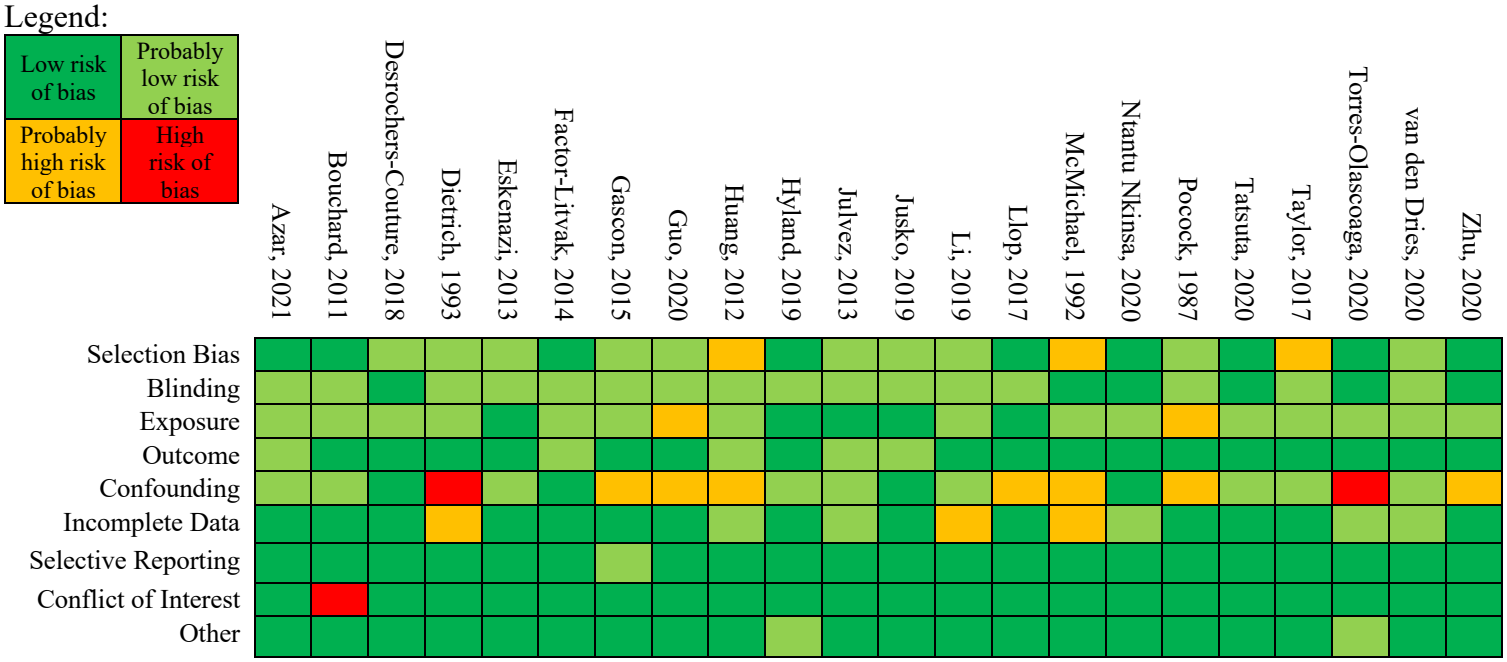
			Phthalate	MEHP	2nd trimester urine	0.0078[b]	
van den Dries, 2020	Netherlands (Generation R)	1269-1274 (~50.5)	Phthalate	ΣDEHP[e]	Mean of three urines	~0.042	Mosaics and Categories subtests on SON-R at 6 years
Zhu, 2020	China (MABC)	1865-2128 (~52.0)	Phthalate	MBzP	Mean of three urines	N/A	FSIQ, VCI, and VSI on WPPSI-IV (Chinese version) between 3 to 6 years
			Phthalate	MEHHP	Mean of three urines	N/A	
			Phthalate	MEHP	Mean of three urines	N/A	
			Phthalate	MEP	Mean of three urines	N/A	

[a]Arithmetic mean, [b]geometric mean

[c]ΣPBDE = BDE-47 + BDE-99 + BDE-100 + BDE-153; [d]ΣDAP = DMP + DMTP + DMDTP + DEP + DETP + DEDTP; [e]ΣDEHP = MEHHP + MEHP + MEOHP + MECPP; [f]ΣDEHP = MEOHP + MEHHP + MECPP

Abbreviations: ALSPAC: Avon Longitudinal Study of Parents and Children; BDE: Brominated Diphenyl Ethers; CCCEH: Columbia Center for Children's Environmental Health; CHAMACOS: Center for the Health Assessment of Mothers and Children of Salinas; C-WISC: Chinese Version of the Wechsler Intelligence Scale for Children; DAP: Dialkyl Phosphates; DEDTP: Diethyl Dithiophosphate; DEHP: Bis(2-ethylhexyl) Phthalate; DEP: Diethyl phosphate; DETP: Diethyl Thiophosphate; DMDTP: Dimethyl Dithiophosphate; DMP: Dimethyl Phosphate; DMTP: Dimethyl Thiophosphate; ELEMENT: Early Life Exposures in Mexico to ENvironmental Toxicants; FSIQ: Full-Scale IQ; GCI: General Cognitive Index; HOME: Health Outcomes and Measures of the Environment; INMA: INfancia y Medio Ambiente (Environment and Childhood) Project; IQ: Intelligence Quotient; MABC: The Ma'anshan Birth Cohort; MBzP: Monobenzyl Phthalate; MCPP: Mono-(3-carboxypropyl) Phthalate; MECPP: Mono(2-ethyl-5-carboxypentyl) Phthalate; MEHHP: Mono(2-ethyl-5-hydroxyhexyl) Phthalate; MEHP: Mono(2-ethylhexyl) Phthalate; MEOHP: Mono-(2-ethyl-5-oxohexyl) Phthalate; MEP: Mono-ethyl Phthalate; MiBP: Mono-isobutyl Phthalate; MIREC: Maternal-Infant Research on Environmental Chemicals; MnBP: Mono-n-butyl Phthalate; MSCA: McCarthy Scales of Children's Abilities; OPP: Organophosphate Pesticides; PBDE: Polybrominated Diphenyl Ethers; PCB: Polychlorinated Biphenyls; PIQ: Performance Intelligence; PPS: Perceptual Performance Scale; PRI: Perceptual Reasoning Index; SMBCS: Sheyang Mini Birth Cohort Study; SON-R: Snijders-Oomen Nonverbal Intelligence Test; TSCD: Tohoku Study of Child Development; UK: United Kingdom; USA: United States of America; VCI: Verbal Comprehension Index; VIQ: Verbal Intelligence; VS: Verbal Scale; VSI: Visual Spatial Index; WISC-III: Wechsler Intelligence Scale for Children, Third Edition; WISC-IV: Wechsler Intelligence Scale for Children, Fourth Edition; WISC-R: Wechsler Intelligence Scale for Children, Revised; WPPSI-III: Wechsler Preschool & Primary Scale of Intelligence, Third Edition; WPPSI-R: Wechsler Preschool & Primary Scale of Intelligence, Revised

Table 1. Risk of Bias Ratings for Studies Included in the Meta-Analysis



Prenatal Exposures

General Intelligence

The meta-analysis of prenatal exposures and general intelligence included 14 studies: four lead[88,89,98,130], four mercury[88,89,111,115], two PBDEs[90,101], two OPPs[92,123], and four phthalates[104,108,114,131]. Two articles included data from exposure to more than one neurotoxicant (i.e., lead and mercury), thus data on each neurotoxicant was included in the meta-analysis[88,89].

Males. The forest plot for the meta-analysis of prenatal exposures and general intelligence in males is shown in Figure 2. Prenatal exposure to developmental neurotoxicants was associated with decreased general intelligence in males (B = -0.38; 95% CI: -0.72, -0.04). In subgroup analyses, prenatal exposure to lead (B = -1.07; 95% CI: -1.63, -0.52), and ΣPBDEs (B = -0.57; 95% CI: -1.14, -0.01) were significantly associated with decreased general intelligence in males. Nonetheless, the effects did not significantly differ by neurotoxicant (Q_b = 7.77, p = .10), and effect sizes were largely negative across neurotoxicants.

There was a moderate degree of heterogeneity for the total pooled effect (I^2 = 57.08), and low to high degrees of heterogeneity for the pooled effects by neurotoxicant (I^2 = 0.00 to 63.02), especially mercury. Egger's test did not indicate significant funnel plot asymmetry (z = -0.42, p = .67); see Figure 3.

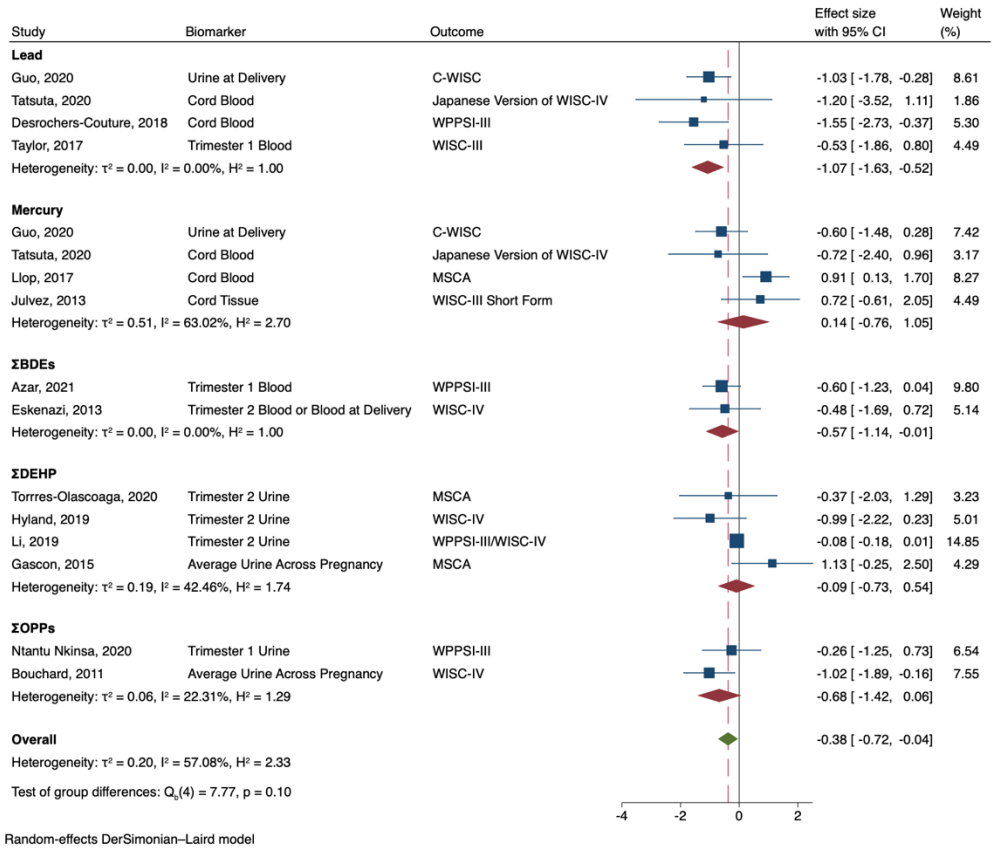


Figure 2. Random-Effects Meta-Analysis - General Intelligence in Males[1]

[1] The range of beta coefficient values is on the X-axis and the included references are listed on the Y-axis. The blue boxes correspond to each reference's beta coefficient and the size of the blue box represents the weight of the study in the meta-analysis, based on its' standard error. The error bars on each box represent the upper and lower 95% confidence intervals. The subgroup pooled estimates are each provided by red diamonds. The overall meta-analysis pooled estimate is provided by a green diamond and a vertical dashed red line. The 'line of no effect' (i.e., the line at which the beta coefficient equals 0) is represented by a black vertical line.

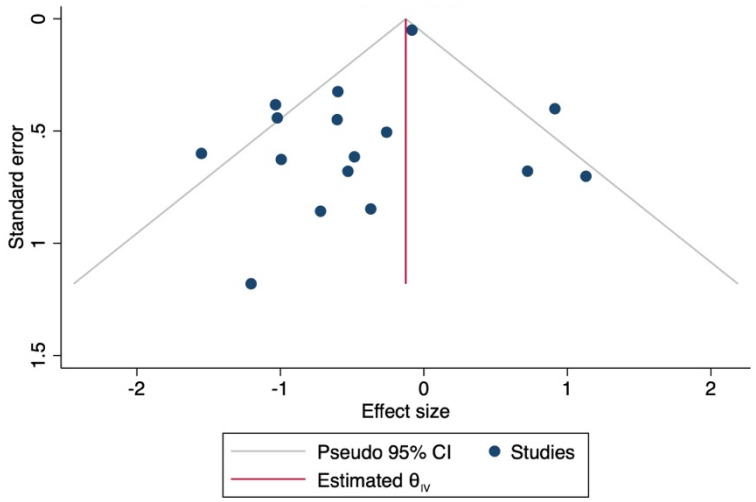


Figure 3. Funnel Plot - General Intelligence in Males

Females. The forest plot for the meta-analysis of prenatal exposures and general intelligence in females is shown in Figure 4. Prenatal exposure to developmental neurotoxicants was not significantly associated with general intelligence in females (B = 0.14; 95% CI: -0.14, 0.42). Effect sizes were either largely near zero or slightly positive, regardless of the neurotoxicant (Q_b = 4.00, p = .41). There was a moderate degree of heterogeneity for the total pooled effect (I^2 = 46.13), and low to high degrees of heterogeneity for the pooled effects by neurotoxicant (I^2 = 0.00 to 86.48). Specifically, there was a high degree of heterogeneity for the ΣPBDE pooled effect (I^2 = 86.48). Egger's test did not indicate substantial funnel plot asymmetry (z = -0.34, p = .735; see Figure 5).

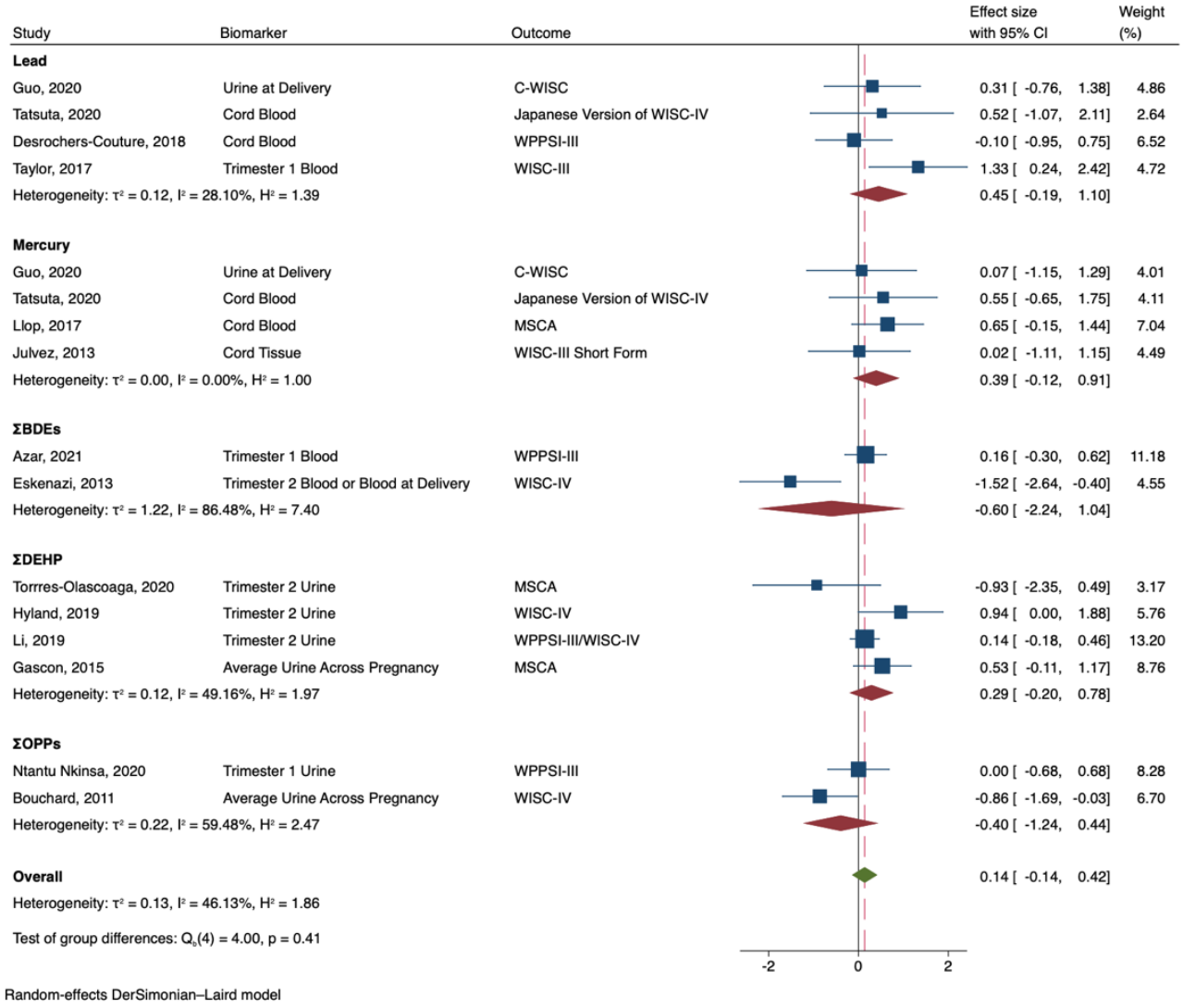


Figure 4. Random-Effects Meta-Analysis - General Intelligence in Females

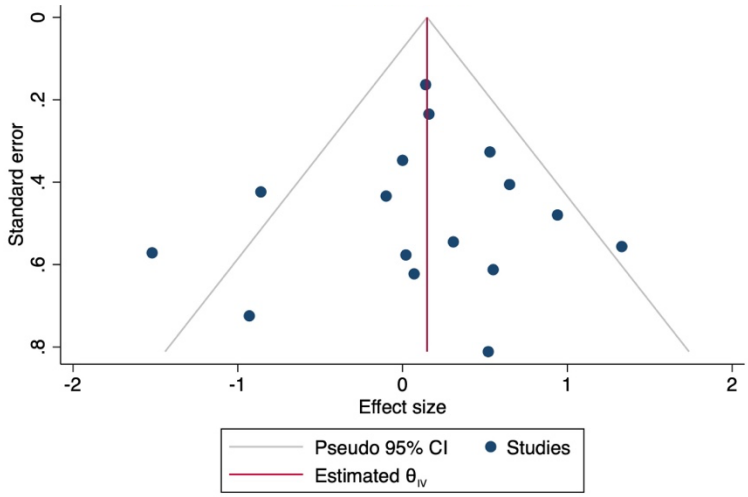


Figure 5. Funnel Plot - General Intelligence in Females

Nonverbal Intelligence

The meta-analysis of prenatal exposures and nonverbal intelligence included 13 studies: five lead[88,89,98,99,130], three mercury[88,89,115], two PBDEs[90,101], three phthalates[104,108,132], and two OPPs[112,123]. Two articles included data from exposure to more than one neurotoxicant (i.e., lead and mercury), so results for each neurotoxicant were included in the meta-analysis[88,89].

Males. The forest plot for the meta-analysis of prenatal exposures and nonverbal intelligence in males is shown in Figure 6. Prenatal exposure to developmental neurotoxicants was associated with decreased nonverbal intelligence in males (B = -0.42; 95% CI: -0.71, -0.14). In subgroup analyses, prenatal exposure to lead (B = -1.18; 95% CI: -1.78, -0.59) was significantly associated with decreased nonverbal intelligence. Nonetheless, effect sizes were largely negative across the neurotoxicants, and the effects did not significantly vary by neurotoxicant (Q_b = 8.27, p = .08). Heterogeneity ranged from I^2 = 0.00 to 54.86. Egger's test did not indicate substantial funnel plot asymmetry (z = -0.72, p = .260; see Figure 7).

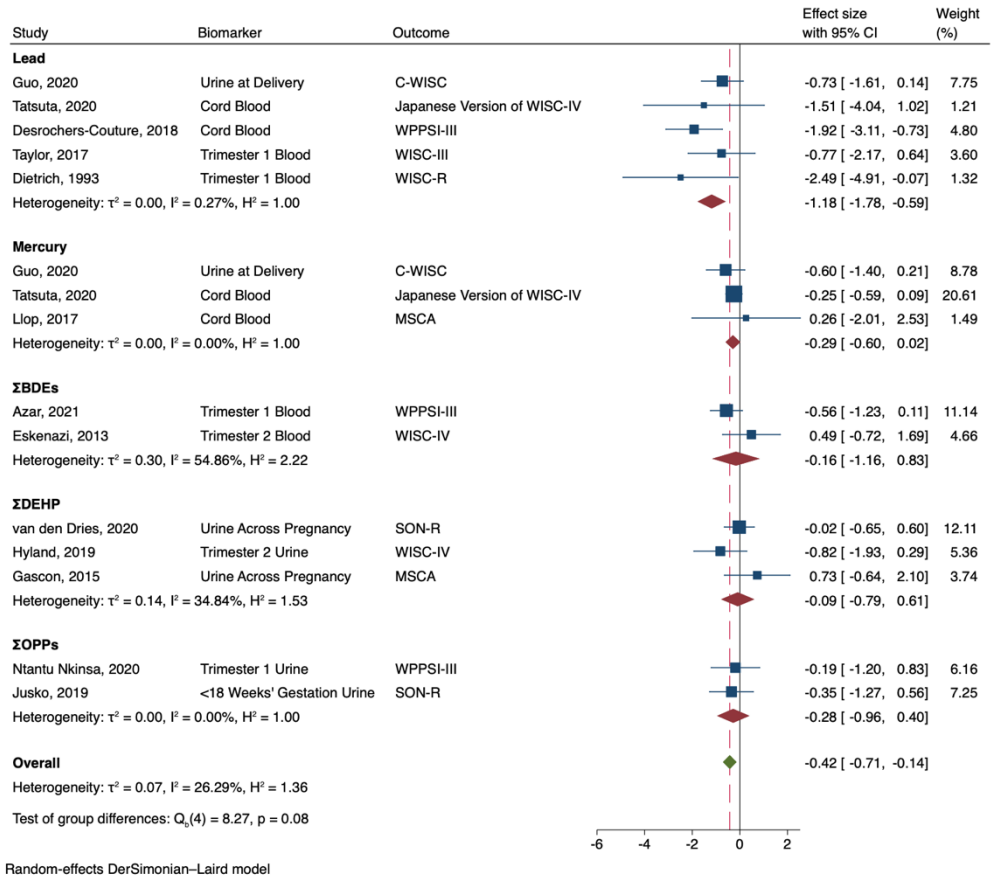


Figure 6. Random-Effects Meta-Analysis - Nonverbal Intelligence in Males

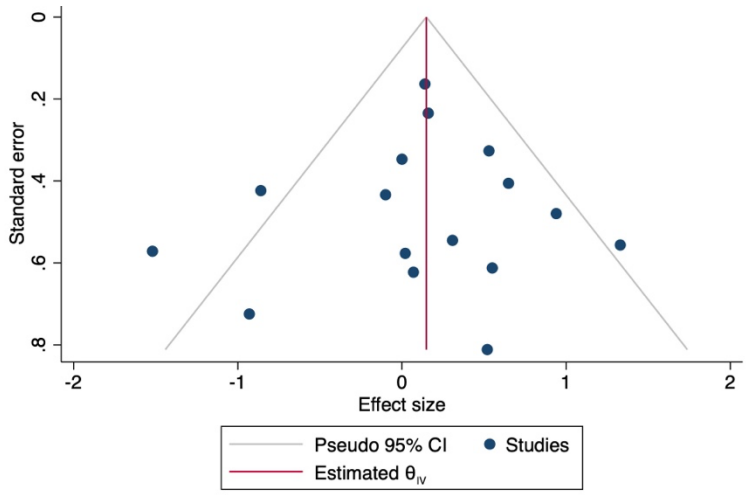


Figure 7. Funnel Plot - Nonverbal Intelligence in Males

Females. The forest plot for the meta-analysis in females is shown in Figure 8. Prenatal exposure to developmental neurotoxicants was not significantly associated with nonverbal intelligence in females (B = 0.14; 95% CI: -0.07, 0.34). In subgroup analyses, prenatal exposure to ΣDEHP (B = 0.62; 95% CI: 0.17, 1.08) was significantly associated with greater nonverbal intelligence in females; however, effect sizes did not significantly vary by neurotoxicant (Q_b = 7.02, p = .13). The degree of heterogeneity was low across all neurotoxicants (I^2 = 0.00 to 10.75). Egger's test did not indicate substantial funnel plot asymmetry (z = -0.31, p = .58; see Figure 9).

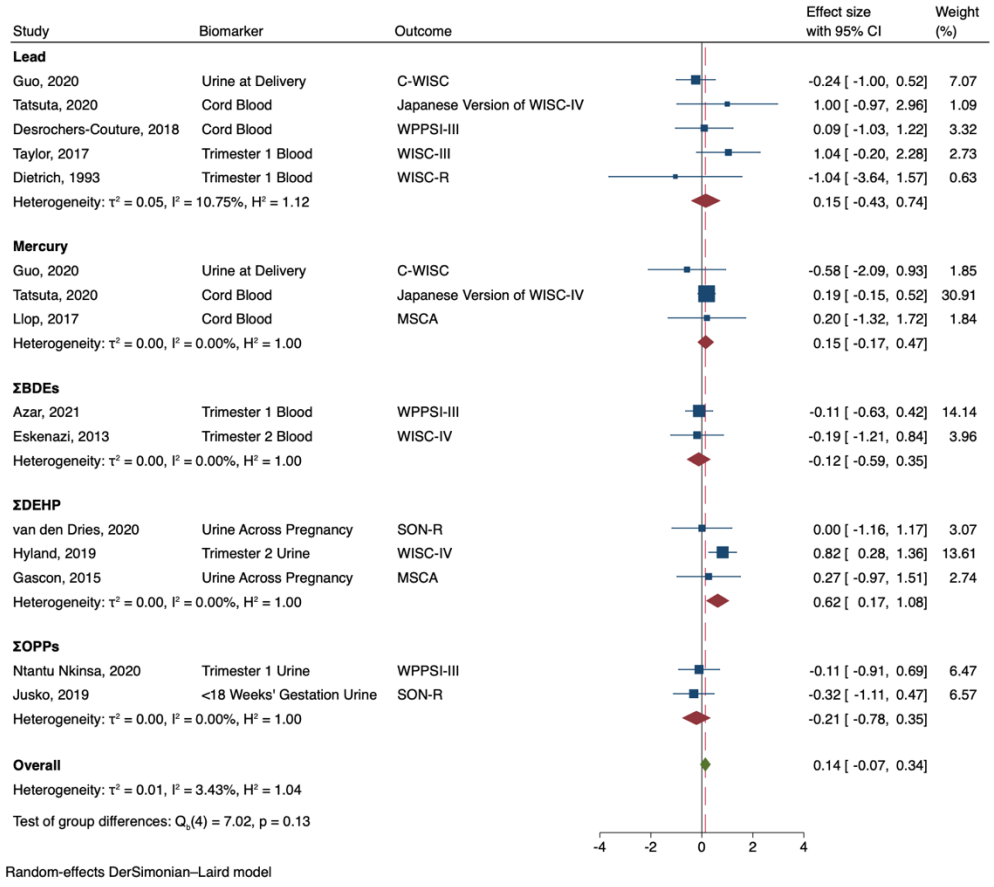


Figure 8. Random-Effects Meta-Analysis - Nonverbal Intelligence in Females

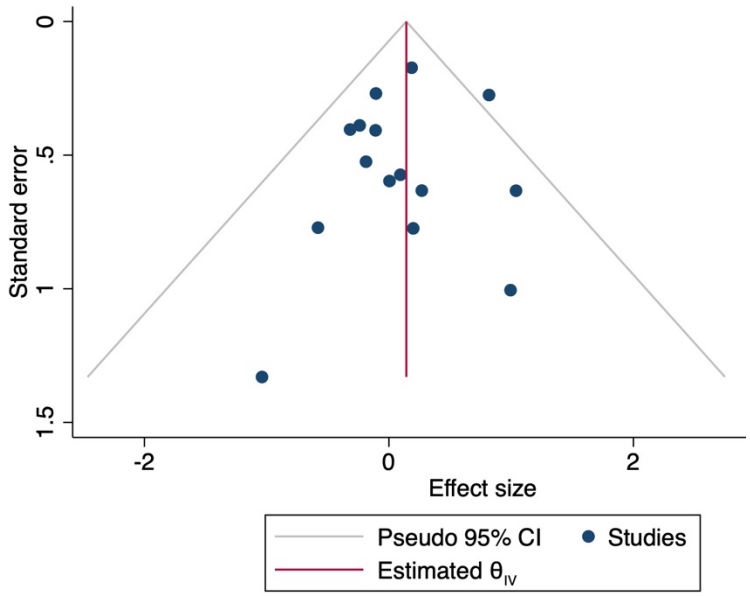


Figure 9. Funnel Plot - Nonverbal Intelligence in Females

Verbal Intelligence

The meta-analysis of prenatal exposures and verbal intelligence included seven studies: four pertaining to lead[88,89,98,130], three mercury[88,89,115], and two phthalates[104,108]. Two articles included data from exposure to more than one neurotoxicant (i.e., lead and mercury) so data on each neurotoxicant was included in the meta-analysis[88,89].

Males. The forest plot for the meta-analysis of prenatal exposures and verbal intelligence in males is shown in Figure 10. Prenatal exposure to developmental neurotoxicants was not significantly associated with verbal intelligence in males (B = -0.02; 95% CI: -0.28, 0.25), and effect sizes did not significantly vary by neurotoxicant (Q_b = 0.56, p = .76). Heterogeneity ranged from I^2 = 0.00 to 61.11. Egger's test did not indicate substantial funnel plot asymmetry (z = -0.83, p = .41; see Figure 11).

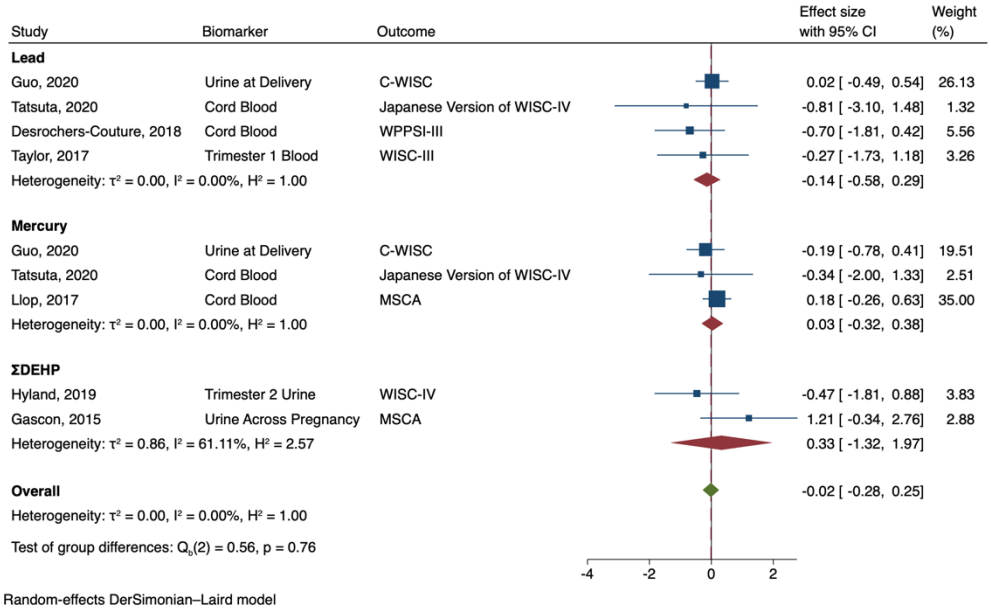


Figure 10. Random-Effects Meta-Analysis - Verbal Intelligence in Males

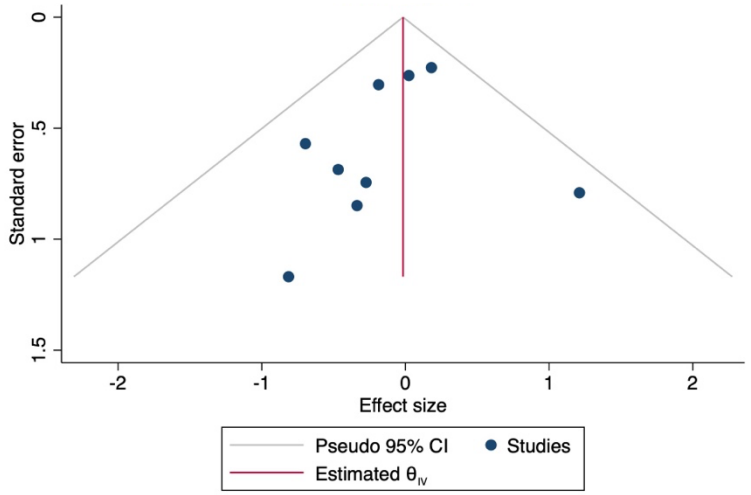


Figure 11. Funnel Plot - Verbal Intelligence in Males

Females. The forest plot for the meta-analysis of prenatal exposures and verbal intelligence in females is shown in Figure 12. Prenatal exposure to developmental neurotoxicants was not significantly associated with verbal intelligence in females (B = 0.19; 95% CI: -0.17, 0.56) and effect sizes did not significantly vary by neurotoxicant (Q_b = 0.70, p = .70).

Heterogeneity ranged from $I^2 = 0.00$ to 57.74. Egger's test did not indicate substantial funnel plot asymmetry ($z = 0.78$, $p = .435$; see Figure 13).

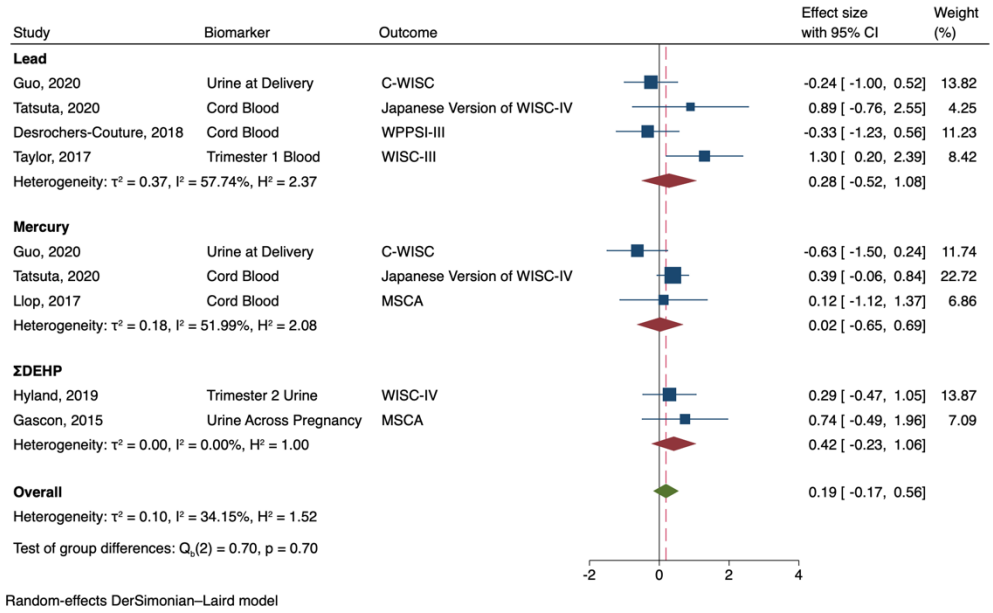


Figure 12. Random-Effects Meta-Analysis - Verbal Intelligence in Females

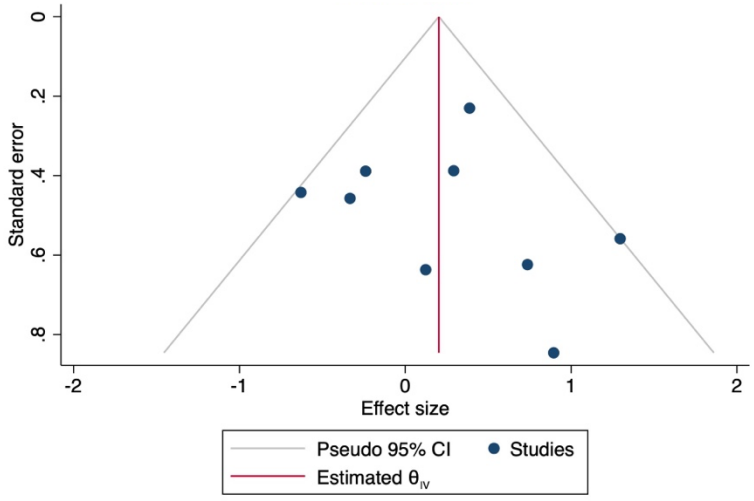


Figure 13. Funnel Plot - Verbal Intelligence in Females

Phthalate Exposure and General Intelligence

The meta-analysis of individual phthalate congeners and general intelligence included five studies[102,104,114,131,134].

Males. The forest plot for the meta-analysis of individual phthalate congeners and general intelligence in males is shown in Figure 14. Prenatal exposure to phthalates was not significantly associated with general intelligence in males (B = 0.02; 95% CI: -0.10, 0.13) and effect sizes did not significantly vary by individual phthalates (Q_b = 10.04, p = .12). There was a moderate degree of heterogeneity for the total pooled effect (I^2 = 38.26), and low to high degrees of heterogeneity for the pooled effects by individual phthalate (I^2 = 0.00 to 80.14). Specifically, there was a high degree of heterogeneity for the MiBP pooled effect (I^2 = 80.14). Egger's test did not indicate substantial funnel plot asymmetry (z = -0.90, p = .37; see Figure 15).

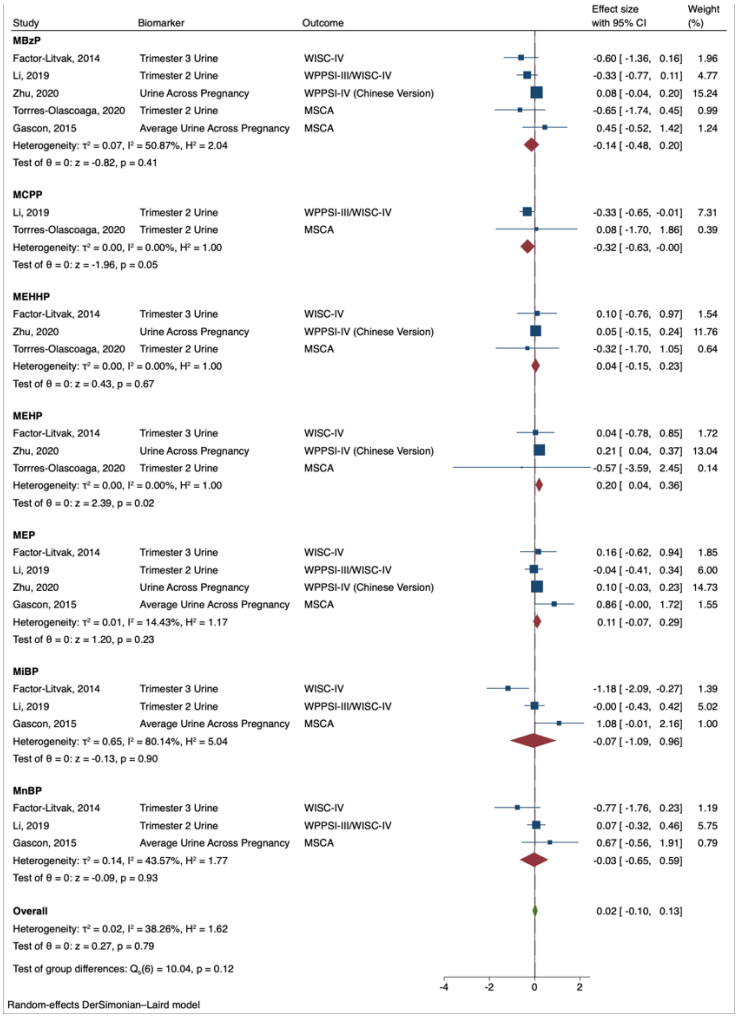


Figure 14. Random-Effects Meta-Analysis - Phthalates and General Intelligence in Males

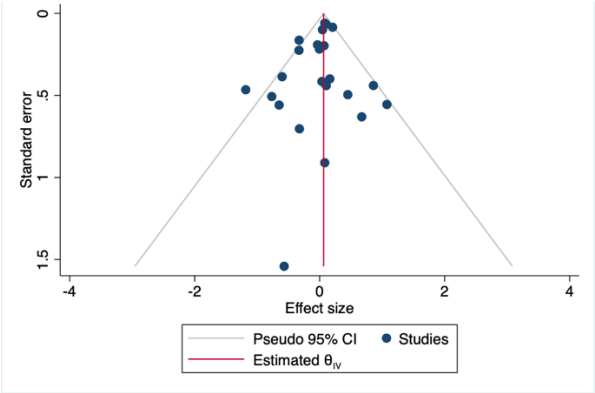


Figure 15. Funnel Plot - Phthalates and General Intelligence in Males

Females. The forest plot for the meta-analysis of individual phthalate compounds and general intelligence in females is shown in Figure 16. Prenatal exposure to phthalates was not significantly associated with general intelligence in females (B = 0.01; 95% CI: -0.04, 0.07) and effect sizes did not significantly vary by compound (Q_b =1.21, p = .98). There was a low degree of heterogeneity for the total pooled effect (I^2 = 0.00), and low to high degrees of heterogeneity for the pooled effects by compound (I^2 = 0.00 to 65.52). Specifically, there was a high degree of heterogeneity for the MnBP pooled effect (I^2 = 65.52). There was significant funnel plot asymmetry (z = -2.25, p = .02; see Figure 17)

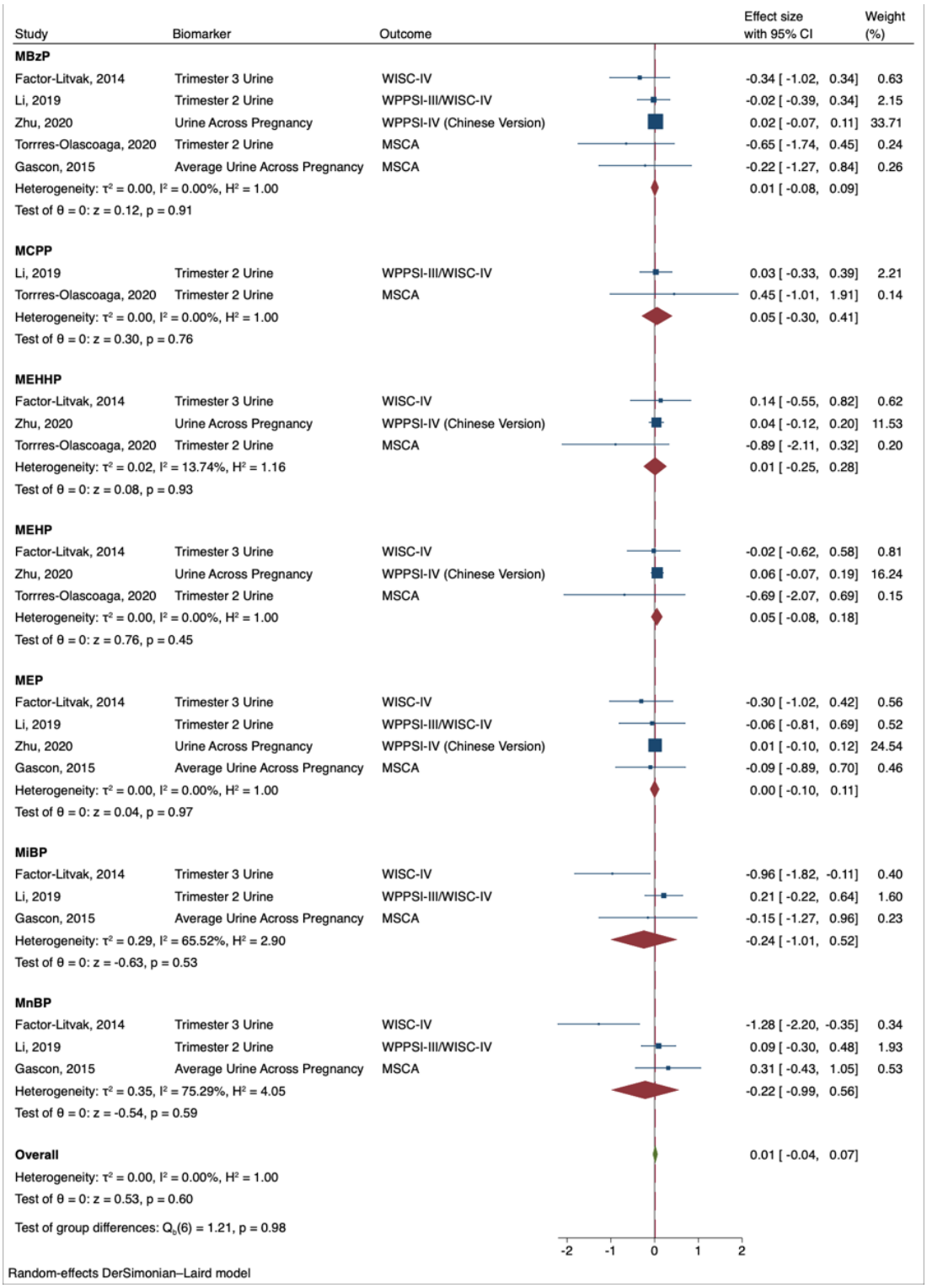


Figure 16. Random Effects Meta-Analysis - Phthalates and General Intelligence in Females

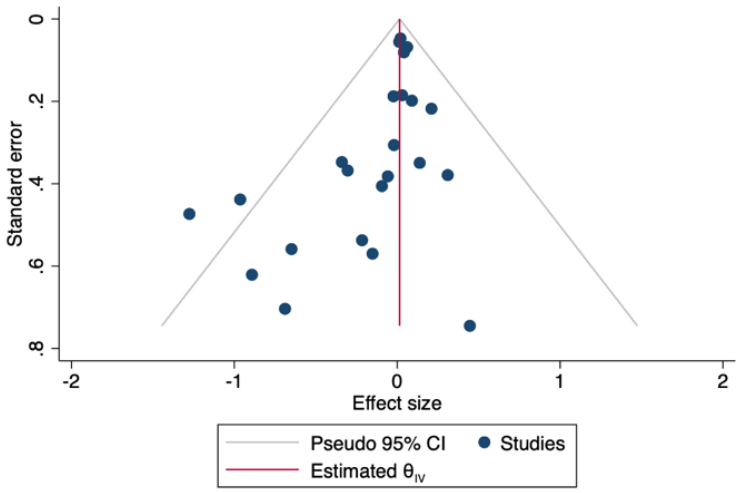


Figure 17. Funnel Plot - Phthalates and General Intelligence in Females

Postnatal Exposure

Lead and General Intelligence

The meta-analysis of postnatal lead exposure and general intelligence included four studies[98,118,125,136].

Males. The forest plot for the meta-analysis of postnatal lead exposure and general intelligence in males is shown in Figure 18. Postnatal exposure to lead was not significantly associated with general intelligence in males (B = -1.04; 95% CI: -2.21, 0.14), although the mean effect size was strongly negative and there was a moderate degree of heterogeneity (I^2 = 44.98). Egger's test did not indicate substantial funnel plot asymmetry (z = -0.46, p = .65; see Figure 19).

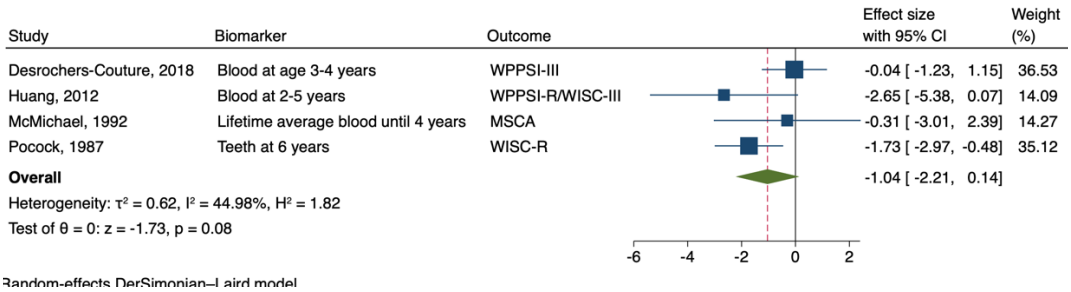


Figure 18. Random-Effects Meta-Analysis - Postnatal Lead and General Intelligence in Males

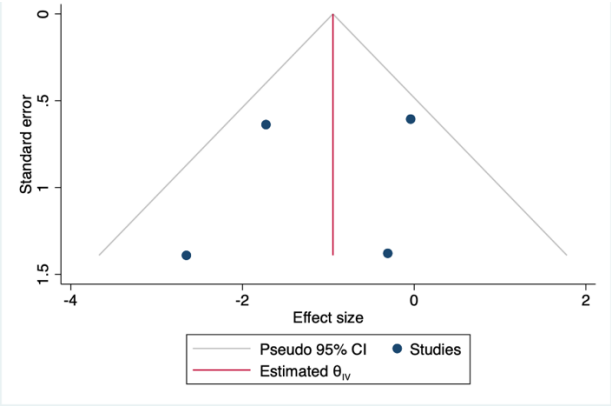


Figure 19. Funnel Plot - Postnatal Lead and General Intelligence in Males

Females. The forest plot for the meta-analysis of postnatal lead exposure and general intelligence in females is shown in Figure 20. Postnatal exposure to lead was not significantly associated with general intelligence in females (B = -0.51; 95% CI: -1.87, 0.85). There was a moderate to high degree of heterogeneity (I^2 = 60.92). Egger's test indicated significant funnel plot asymmetry (z = -2.66, p = .008; see Figure 21).

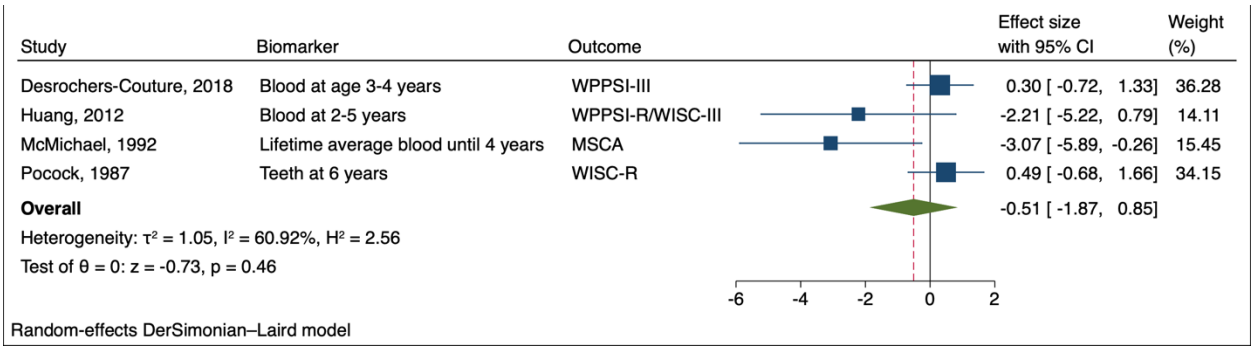


Figure 20. Random-Effect Meta-Analysis - Postnatal Lead and General Intelligence in Females

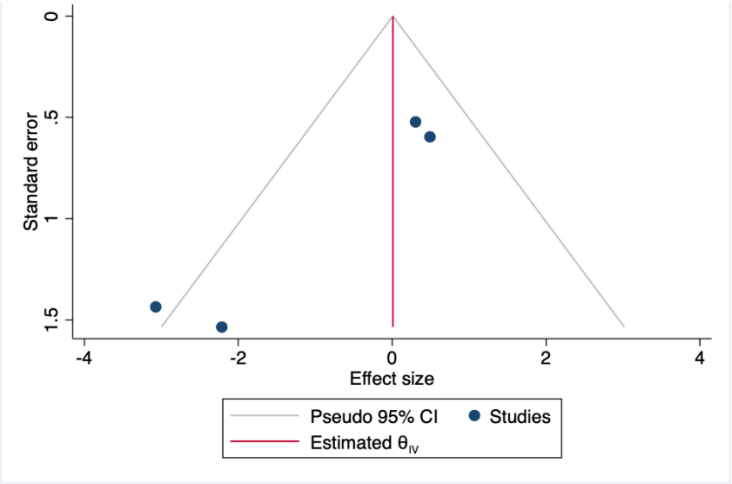


Figure 21. Funnel Plot - Postnatal Lead and General Intelligence in Females

Sensitivity Analyses

For studies in which there was more than one estimate that was combinable in the meta-analysis (i.e., the individual phthalate estimates for trimester 2 and 3 of Torres-Olascoaga, 2020[131] in predicting general intelligence), we ran results with both estimates and found that results did not meaningfully differ.

Leave-One-Out Meta-Analysis

Prenatal Exposures and General Intelligence. In males, the overall effect size varies from -0.31 to -0.49 depending on the study excluded (see Figure 22). Omitting Llop (2017) has a larger influence than other studies on the overall effect size, such that omitting this study causes the overall effect to increase from -0.38 to -0.49. In females, the overall effect size varies slightly from 0.08 to 0.21 (see Figure 23).

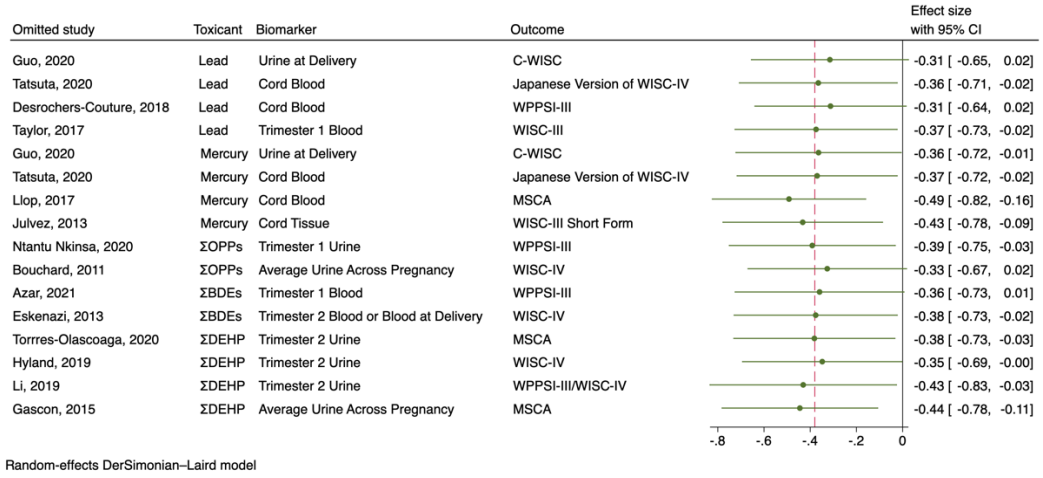


Figure 22. Leave One Out - General Intelligence in Males

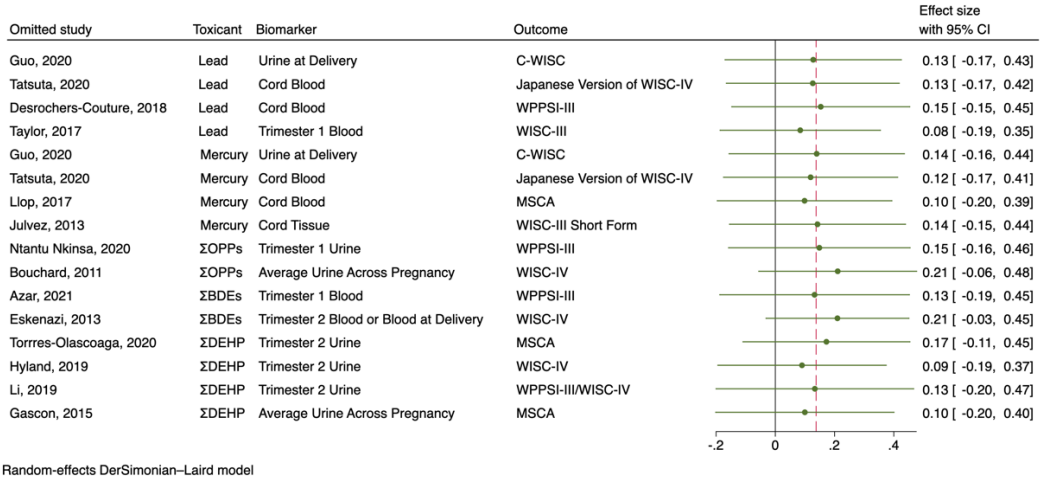


Figure 23. Leave One Out - General Intelligence in Females

Prenatal Exposures and Nonverbal Intelligence. In males, the overall effect size varies from -0.32 to -0.48 depending on the study excluded (see Figure 24). Omitting Desrochers-Couture (2018) has a larger influence than other studies on the overall effect size such that omitting this study causes the overall effect to decrease from -0.42 to -0.32. In females, the overall effect size varies from 0.4 to 0.18 (see Figure 25). Omitting Hyland (2019) has a larger influence than other studies on the overall effect size; omitting this study causes the overall effect to decrease from 0.14 to 0.04.

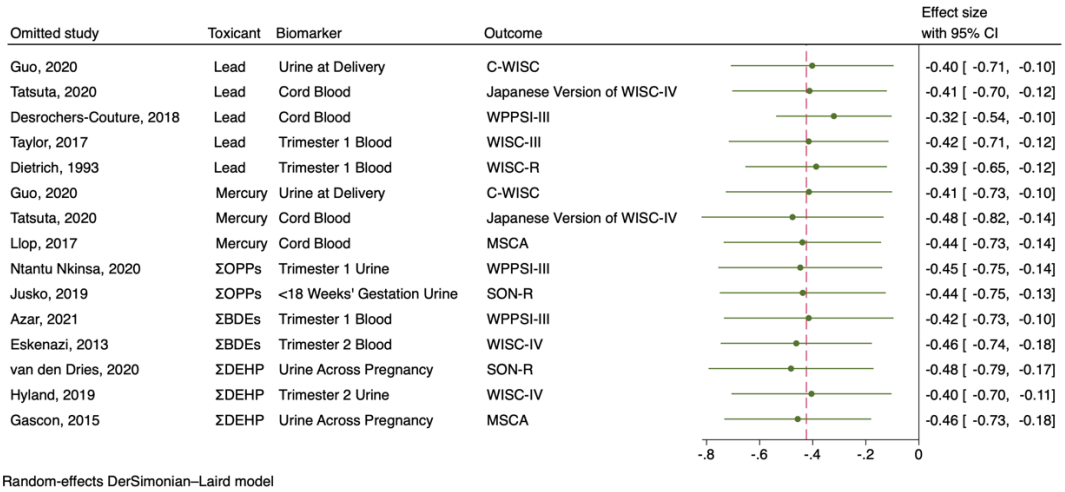


Figure 24. Leave One Out - Nonverbal Intelligence in Males

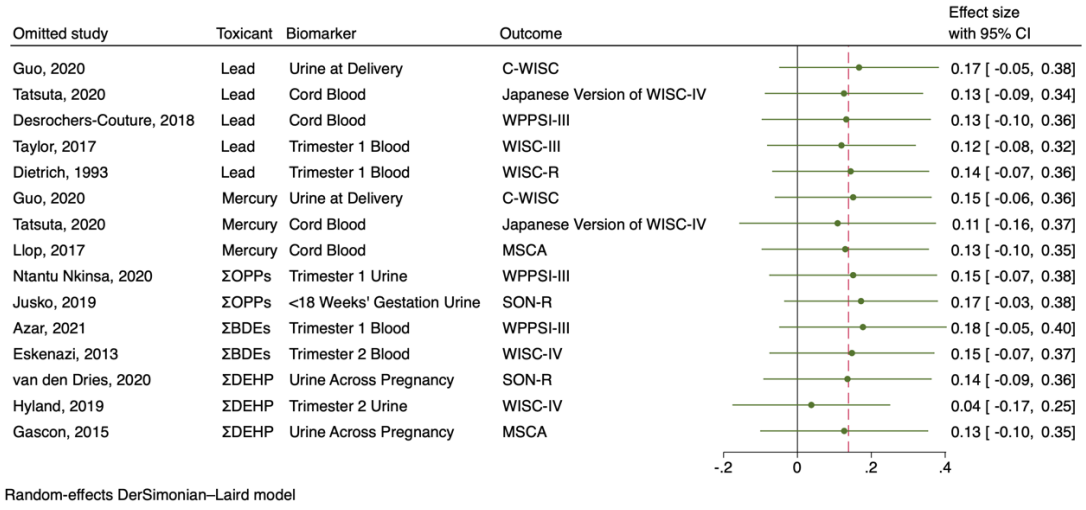


Figure 25. Leave One Out - Nonverbal Intelligence in Females

Prenatal Exposures and Verbal Intelligence. In males, the overall effect size varies from -0.12 to 0.00 depending on the study excluded (see Figure 26). Omitting Llop (2017) has a larger influence than other studies on the overall effect size; omitting this study causes the overall effect to increase from -0.02 to -0.12. In females, the overall effect size varies from 0.11 to 0.29 (see Figure 27). Omitting Guo (2020) has a larger influence than other studies on the overall effect size. Specifically, omitting Guo (2020) causes the overall effect to increase from 0.19 to 0.29.

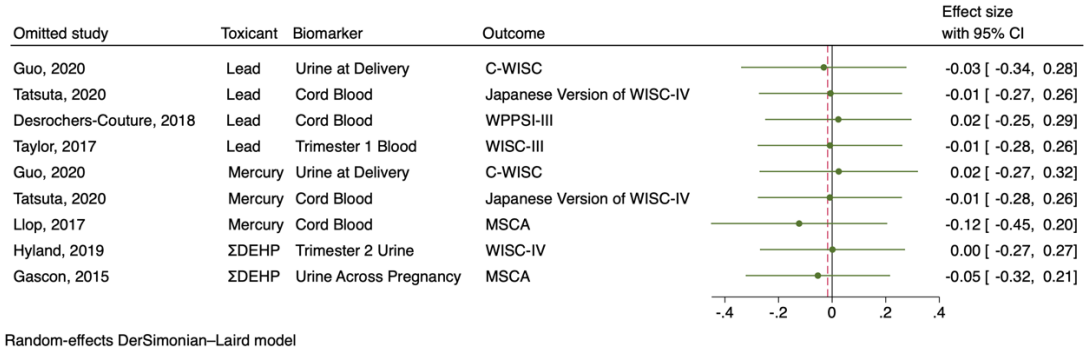


Figure 26. Leave One Out - Verbal Intelligence in Males

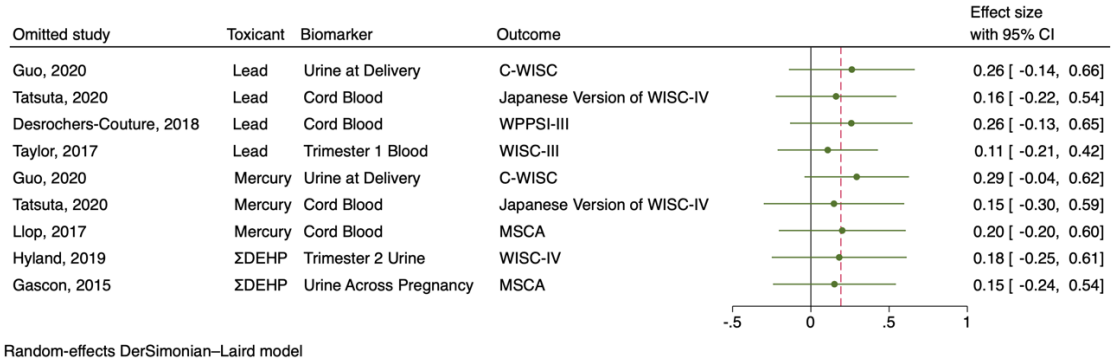


Figure 27. Leave One Out - Verbal Intelligence in Females

Prenatal Phthalate Exposure and General Intelligence. In both males and females, the overall effect size does not vary substantially regardless of the study excluded (see Figure 28 and Figure 29).

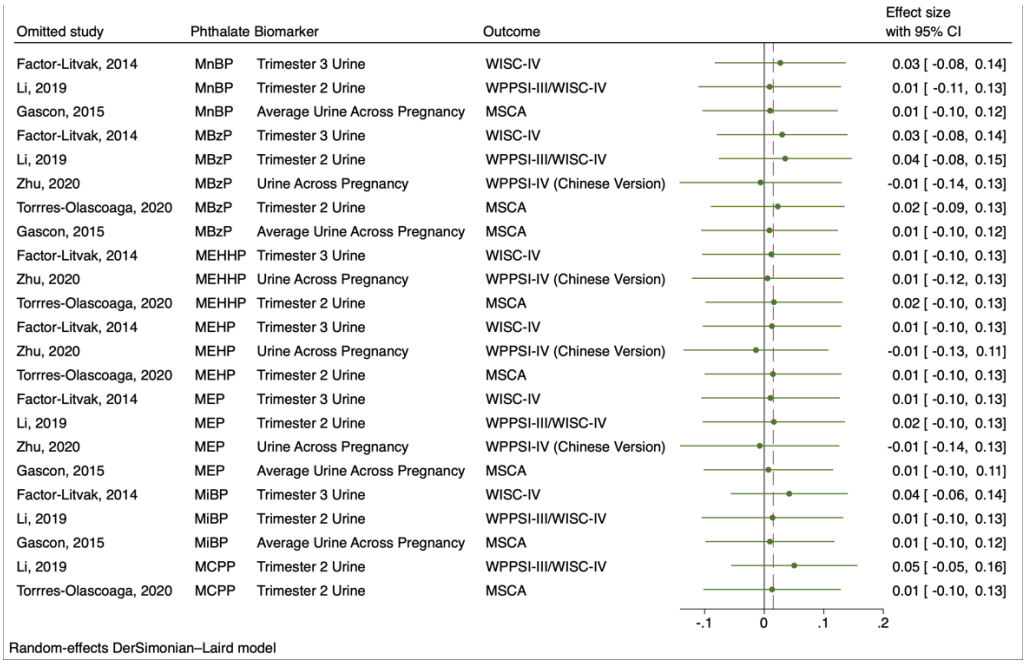


Figure 28. Leave One Out - Phthalates and General Intelligence in Males

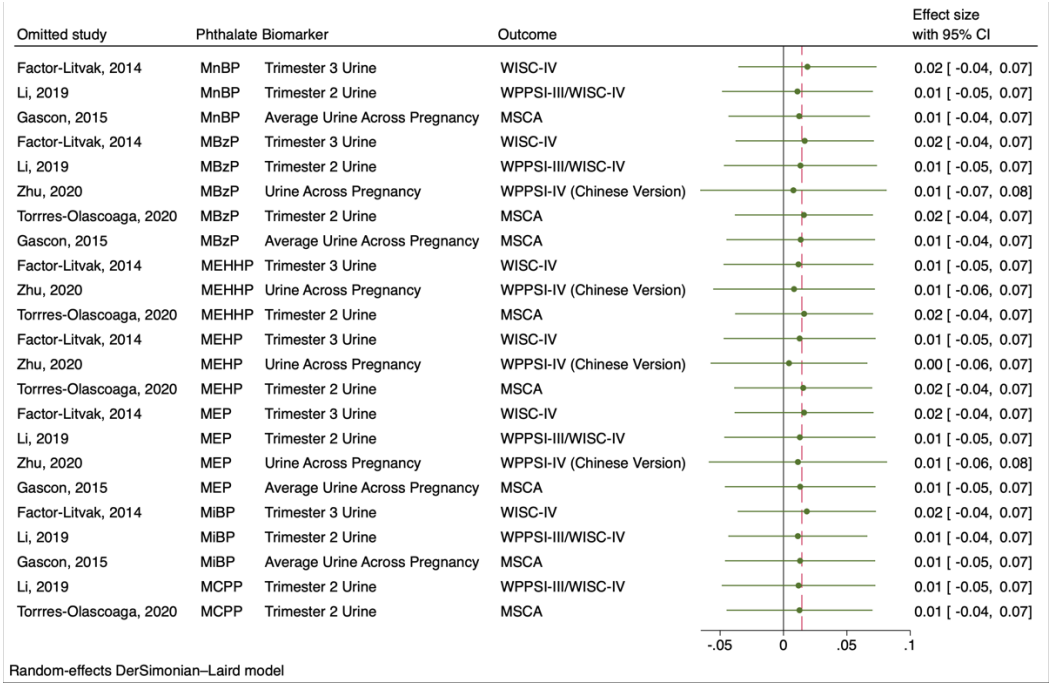


Figure 29. Leave One Out - Phthalates and General Intelligence in Females

Postnatal Lead Exposure and General Intelligence. In males, the overall effect size varies from -0.78 to -1.65 depending on the study excluded (see Figure 30). Similarly, in females, the overall effect size varies greatly from 0.15 to -1.34 (see Figure 31).

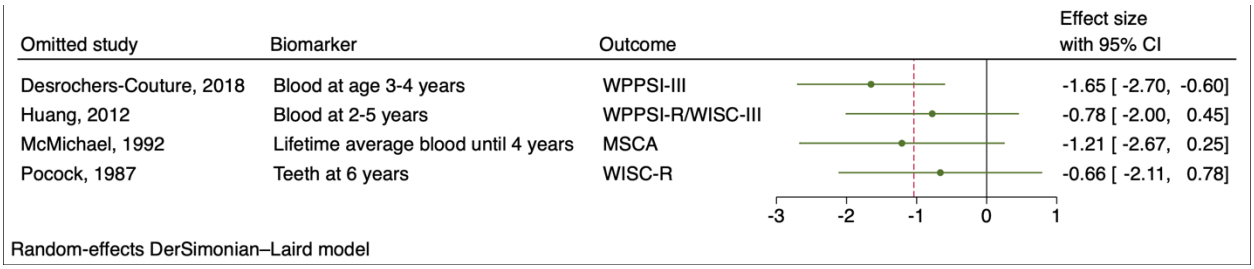


Figure 30. Leave One Out - Postnatal Lead and General Intelligence in Males

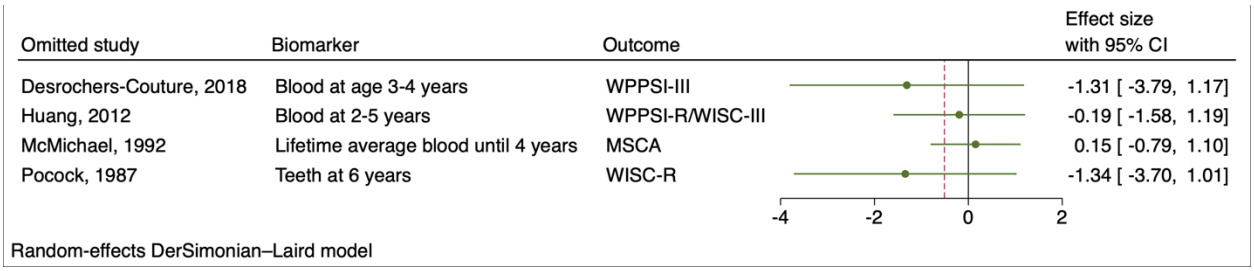


Figure 31. Leave One Out - Postnatal Lead and General Intelligence in Females

Meta-Analysis with only Low Risk of Bias Studies

The overall pooled effects of neurotoxicants on general and nonverbal intelligence in males and females did not change appreciably when only low risk of bias studies were included (see Figures 32, 33, 34, 35). However, the overall pooled effect for verbal intelligence became more negative (-0.02 to -0.57; but remained nonsignificant) in males, and became more positive (0.19 to 0.28; but remained nonsignificant) in females (See Figures 36 and 37).

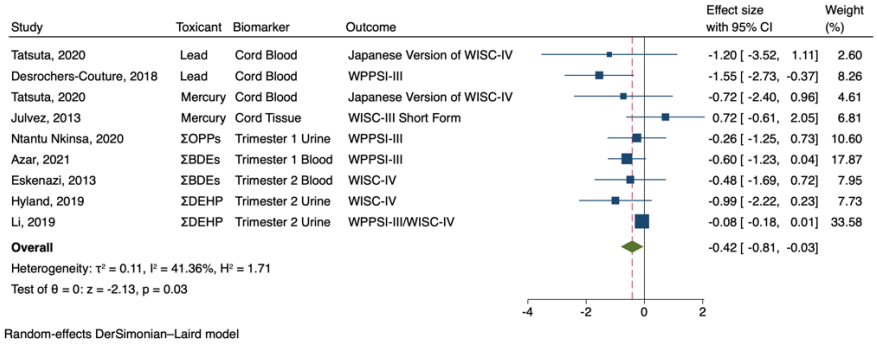


Figure 32. Low Risk of Bias - General Intelligence in Males

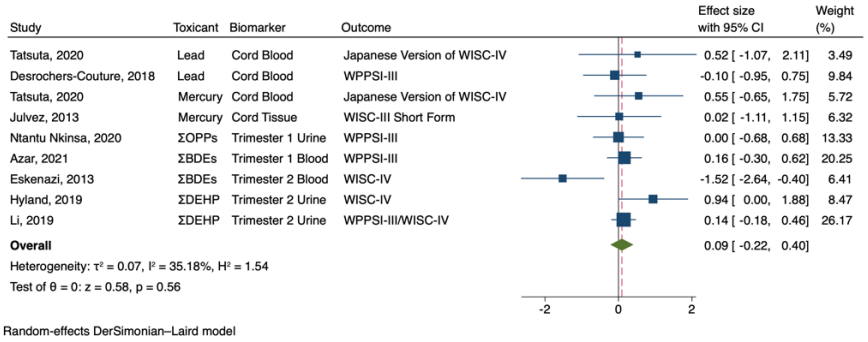


Figure 33. Low Risk of Bias - General Intelligence in Females

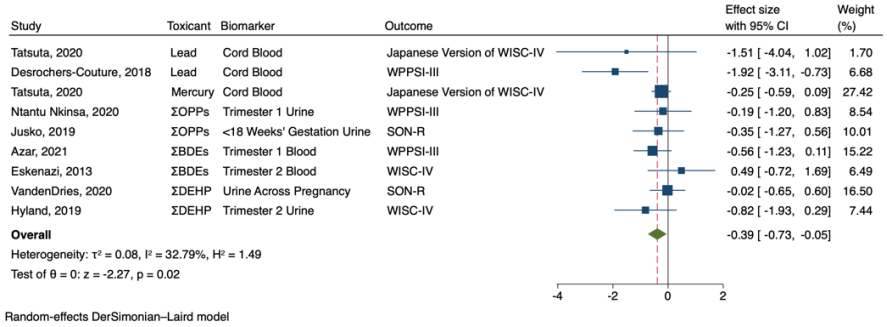


Figure 34. Low Risk of Bias - Nonverbal Intelligence in Males

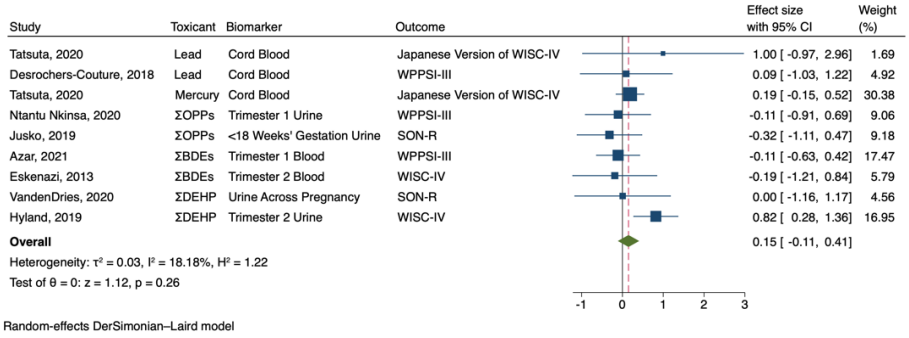


Figure 35. Low Risk of Bias - Nonverbal Intelligence in Females

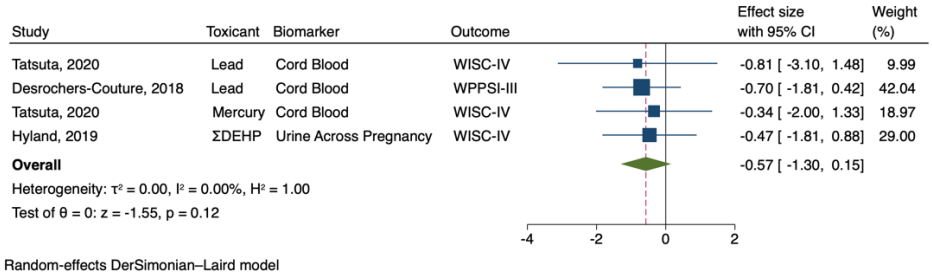


Figure 36. Low Risk of Bias - Verbal Intelligence in Males

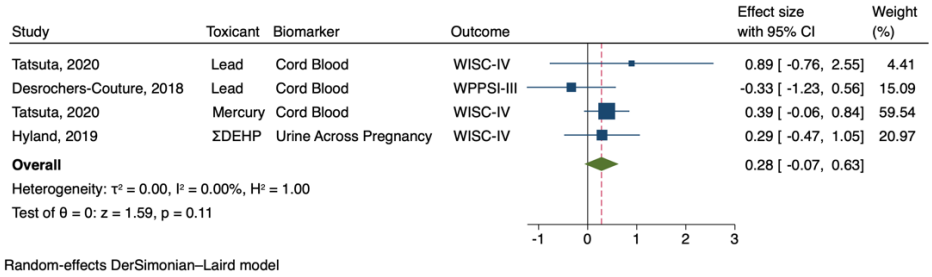


Figure 37. Low Risk of Bias - Verbal Intelligence in Females

Qualitative Results

Systematic-Review Study Characteristics

Table 2 provides a detailed overview of the studies included in the systematic review but excluded from the meta-analysis. Studies were published from 1982 to 2021 and involved between 35 and 2128 participants from 21 different cohorts around the world. Ten studies were conducted in North America, seven from Africa, six in Europe, three from Asia, and four in Australia. Ten studies pertained to lead, nine to mercury, three to PBDEs, two to OPPs, two to phthalates, and five to PCBs. Most of these studies measured neurotoxicant exposure in blood (n = 16), followed by hair (n = 7), urine (n = 4), teeth (n =2), and the placenta (n =1). Fourteen studies measured toxicant exposure during the prenatal period, seven studies measured toxicant exposure during the postnatal period, and seven measured toxicant exposure during both the prenatal and postnatal period. Intelligence was assessed using a variety of measures, including the Kaufman Assessment Battery for Children (K-ABC; n = 2), MSCA (n = 10), Peabody Picture

Vocabulary Test (PPVT; *n* = 1), Stanford-Binet- 5 (SB5; *n* = 1), WISC (*n* = 1), WISC-III (*n* = 6), WISC-III-NL (*n* = 1), WISC-IV (*n* = 5), WISC-R (*n* = 4), Wide Range Achievement Test (WRAT-III; *n* = 1), WPPSI (*n* = 1), WPPSI-III (*n* = 2), and WPPSI-R (*n* = 2).

Table 4 depicts the risk of bias ratings for the studies included in the systematic review but excluded from the meta-analysis. Nine studies were rated as "low" or "probably low" risk of bias across all the domains, whereas 22 studies were rated a "high" or probably high" risk of bias in one or more domain. Studies rated as "high" or "probably high" risk of bias were mostly rated as such in the domains of selection bias, confounding, and incomplete outcome data. Of the nine low risk of bias studies, eight found no significant difference between the sexes [95,100,120,124,126,127,133,137], and one found that the negative association between 9CBs and the mental processing scale was stronger in males[129].

Table 2. Systematic Review Study Characteristics

Lead Author, Year	Country (Cohort)	N (%males)	Neuro-toxicant	Compound	Biomarker	Median of Exposure (ppb)	Outcome Measure	Interpretation	Reason Excluded from Meta-Analysis
Baghurst, 1992	Australia (Port Pirie Cohort Study)	494 (N/A)	Lead	N/A	Lifetime average blood up to 3 years	122.0-282.0*[a]	FSIQ on WISC-R at 7 years	The negative association between lead exposure and FSIQ was more pronounced in females.	No standard error or p-value to calculate effect size.
Berghuis, 2018	Netherlands (DACE Study)	35-40 (~54.5)	PCB PBDE	ΣOH-PCBs[c] BDE-47	2nd/3rd trimester serum 2nd/3rd trimester serum	0.4 0.9	FSIQ, PRI, and VCI on WISC-III-NL at 13-15 years	Positive association between ΣOH-PCBs and VCI and FSIQ in females. Negative association between BDE-47 and FSIQ in females.	No other combinable study of OH-PCBs or BDE-47 (only data for females)
Castorina, 2017	USA (CHAMACOS)	248-275 (~54.8)	OPP OPP OPP	BDCIPP DPHP ip-PPP	2nd trimester urine 2nd trimester urine 2nd trimester urine	0.4 0.9 0.3	FSIQ, PRI, PSI, VCI on WISC-IV at 7 years	No significant differences between the sexes.	No data available
Chen, 2014	USA (HOME)	190 (44.0)	PBDE	BDE-47	2nd trimester blood	18.9	FSIQ on WPPSI-III at 5 years	No significant differences between the sexes.	Not enough combinable date to meta-analyze BDE-47
Choi, 2021	Norway (MoBA, Preschool ADHD Sub-Study)	310 (56.9)	Phthalate Phthalate Phthalate Phthalate Phthalate Phthalate	MBzP, MiBP, MnBP, MEP, ∑DEHP[d] ∑DiNP[e]	2nd trimester urine 2nd trimester urine 2nd trimester urine 2nd trimester urine 2nd trimester urine 2nd trimester urine	5.45[b] 19.64[b] 21.70[b] 129.71[b] 0.30[b] 0.02[b]	Verbal and non-verbal WM on SB5 at 3.5 years	The negative association between MiBP, MnBP, and MEP and non-verbal WM was more pronounced in females.	Non-combinable outcome measure (i.e., verbal, and nonverbal WM)
Damm, 1993	Denmark (N/A)	141-162 (45.4-46.9)	Lead	N/A	Shed deciduous teeth at 6 years	Low: <5,000 High: >18,700	FSIQ, PIQ, VIQ on the Danish version of the WISC at 8 and 15 years	Females were better at coping with lead-related deficits in PIQ compared to males.	No data available

Davidson, 2006	Republic of Seychelles (SCDS)	711 (N/A)	Mercury Mercury Mercury	N/A	Maternal hair Hair at 5.5 years	6800.0[a] 6500.0[a] 6100.0[a]	GCI on MSCA at 5.5 years and FSIQ on WISC-III at 8.9 years	Positive association between postnatal mercury exposure and global cognition in males	No data available for prenatal exposure. Not enough combinable data to meta-analyze postnatal exposure.
Davidson, 2004	Republic of Seychelles (SCDS)	711 (N/A)	Mercury	N/A	Maternal hair	5900.0	GCI on MSCA at 5.5 years	No significant differences between the sexes.	No data available
Davidson, 1998	Republic of Seychelles (SCDS)	711 (N/A)	Mercury Mercury	N/A	Maternal hair Hair at 5.5 years	6800.0[a] 6500.0[a]	GCI on MSCA at 5.5 years	No significant differences between the sexes.	No data available
Ernhart, 1989	USA (N/A)	146-169 (N/A)	Lead Lead	N/A	Cord blood Maternal blood at delivery	58.9[a] 65.0[a]	FSIQ, PIQ, and VIQ on WPPSI at 4 years 10 months	No significant differences between the sexes.	No data available
Freire, 2018	Spain (INMA)	302 (71.5)	Lead Mercury	N/A	Placenta at birth Placenta at birth	<6.5 0.025	GCI on MSCA at 4-5 years	The negative association between mercury and GCI is more pronounced in males.	Same cohort, exposure, and outcome as Llop, 2017
Furlong, 2017	USA (The Mount Sinai Children's Environmental Health Center)	141 (51.0)	OPP OPP	∑DEP[f] ∑DMP[g]	2nd/3rd trimester urine 2nd/3rd trimester urine	2.5 4.7	FSIQ, VIQ and PIQ on the WPPSI-III at 6 years and FSIQ, PRI, PSI, VCI, WMI on the WISC-IV between 7-9 years	No significant differences between the sexes.	No data available
Golding, 2017	UK (ALSPAC)	1758-1759 (49.9)	Mercury	N/A	1st trimester blood	1.86	FSIQ, PIQ, and VIQ on WISC-III at 8 years	No significant differences between the sexes.	Non-linear regression techniques (logistic regression)

Huang, 2015	Taiwan (TMICS)	73-100 (N/A)	Phthalate Phthalate Phthalate Phthalate Phthalate	MMP MEP MBP MBzP ΣMEHP[h]	3rd trimester urine, urine at 2-3, and urine at 5-6 years	49,840[b] 66,610[b] 77,870[b] 17,430[b] 58,690[b]	FSIQ on WPPSI-R at 5 years, WISC-III at 8 years and WISC-IV at 11 years	No significant differences between the sexes.	No data available
Huang, 2007	Republic of Seychelles (SCDS)	643 (N/A)	Mercury	N/A	Maternal hair	5,990 – 8,790[a]	FSIQ on WISC-III at 9 years	No significant differences between the sexes.	No data available
Ikeno, 2018	Japan (N/A)	141 (46.8)	PCBs PCBs PCBs	Non-Ortho Mono-Ortho Coplanar	2nd trimester blood 2nd trimester blood 2nd trimester blood	0.059 8.029 8.101	MPS and AS on the K-ABC at 3.5 years	Strong negative association for total non-ortho PCBs and MPS in males. Strong positive association for total mono-ortho, as well as total coplanar PCBs and AS in females.	No other combinable study of PCBs
Jacobson, 2002	USA (N/A)	124-158 (N/A)	PCBs PCBs PCBs	Total PCBs Total PCBs Total PCBs	Cord blood Maternal blood at birth Maternal milk at 0.5-4.5 months	2.6[a] 5.7[a] 829.7[a]	GCI, VS, PPS, QS, MS, MoS on MSCA at 4 years and FSIQ, FRI, VCI, PRI, on WISC-R at 11 years	At 11 years, the negative effects of PCBs on FSIQ and PRI were more pronounced among males.	No standard-error or exact p-value to calculate effect size
Kyriklaki, 2016	Greece (Rhea Study)	695 (51.6)	PCBs	Total PCBs	1st trimester blood	0.32	GCI on MSCA at 4 years	No significant differences between the sexes.	No data available
McBride, 1982	Australia (N/A)	84-88 (N/A)	Lead	N/A	Blood at 4-5 years	2629.4[b]	VIQ on the PPVT at 4-5 years	No interpretation made.	Non-linear regression technique (mean scores)

McMichael, 1994	Australia (Port Pirie Cohort Study)	262 (43.3)	Lead	N/A	Incisor teeth at 6 years	8600[b]	FSIQ, PIQ, and VIQ on WISC-R at 7 years	No significant differences between the sexes.	No data available
McMichael, 1988	Australia (Port Pirie Cohort Study)	474-534 (NA)	Lead Lead Lead Lead Lead Lead Lead	N/A	1st trimester blood Cord blood Blood at 6 months Blood at 15 months Blood at 2 years Blood at 3 years Blood at 4 years	91.00[b] 95.00[b] 144.7[b] 208.9 [b] 213.0 [b] 194.4 [b] 163.3 [b]	GCI, MS, and PPS, on MSCA at 4 years	No significant differences between the sexes.	No data available
Min, 2009	USA (N/A)	273-278 (~48)	Lead	N/A	Blood at 4 years	61.0	FSIQ, PIQ and VIQ, on WPPSI-R at 4 years and FSIQ, PRI, PSI, VCI, and WMI, on WISC-IV at 9 and 11 years	No significant differences between the sexes.	No data available
Myers, 2003	Republic of Seychelles (SCDS)	643 (N/A)	Mercury	N/A	Maternal hair	6900.0[a]	FSIQ on WISC-III at 9 years	No significant differences between the sexes.	No data available
Myers, 1995	Republic of Seychelles (SCDS)	217 (N/A)	Mercury	N/A	Maternal hair	7100.0	GCI, PPS, MS, MoS on MSCA at 5.5 years	No significant differences between the sexes.	No data available
Palumbo, 2000	Republic of Seychelles (SCDS)	708-711 (N/A)	Mercury Mercury	N/A	Maternal hair Hair at 5.5 years	6800.0[a] 6500.0[a]	MS, MoS, PPS, QS, VS on MSCA at 5.5 years	No significant differences between the sexes.	No data available
Rauh, 2011	USA (CCCEH)	265 (44.2)	OPP	CPF	Cord blood	0.003[a]	FSIQ, PRI, PSI, VCI, WMI on WISC-IV at 7 years	No significant differences between the sexes.	No data available

Ris, 2004	USA (Cincinnati Lead Study)	195 (53.6)	Lead	N/A	Maternal blood Blood samples up to 5 years	Range: 50.0-270.0	Learning/IQ factor derived from WRAT-3 and WISC-III at 15-17 years	No significant differences between the sexes.	No data available
Schnaas, 2000	Mexico (Mexico City Prospective Lead Study)	112 (47.3)	Lead	N/A	Blood at 6-18 months Blood at 24-36 months Blood at 42-54 months	101[b] 97[b] 84[b]	GCI on MSCA at 3, 3.5, 4, 4.5 and 5 years	No significant differences between the sexes.	No data available
Tatsuta, 2014	Japan (TSCD)	387 (52.2)	PCBs	9CBs	Cord blood	0.22	MPS on K-ABC at 3.5 years	The negative association between the MPS and 9CBs was more pronounced in males.	No other combinable study of 9CBs
Vuong, 2017	USA (HOME)	208 (44.7)	PBDE	∑PBDEs[i]	Blood at 1 year Blood at 2 years Blood at 3 years Blood at 5 years	118.1[b] 127.7[b] 100.5[b] 64.6[b]	FSIQ on WISC-IV at 8 years	No significant differences between the sexes.	No other combinable study of postnatal PBDEs

[*] Mean low to mean high quartiles

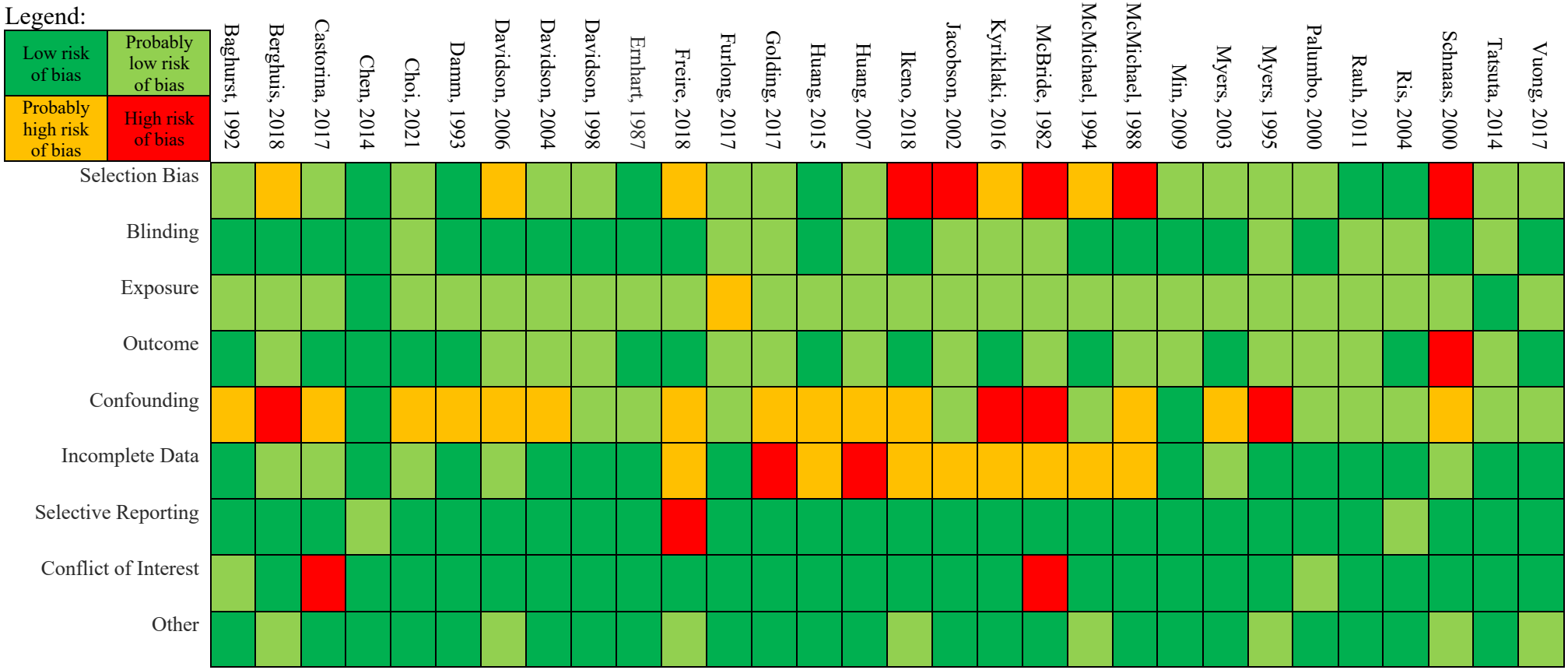
[a]Arithmetic mean, [b]geometric mean

[c]ΣOH-PCBs = 4-OH-PCB-107 + 4-OH-PCB-146 + 4-OH-PCB-187 + 3-OH-PCB-153 + 3′-OH-PCB-138 + 4′-OH-PCB-172; [d]∑DEHP = MEHHP + MEHP + MEOHP + MECPP + MMCHP; [e]∑DiNP = cx-MiNP + oxo-MiNP + OH-MiNP; [f]∑DEP = DEP + DETP + DEDTP; [g]∑DMP = DMP + DMTP + DMDTP; [h] ΣMEHP = MEHP+MEHHP+MEOHP; [i]∑PBDE = BDE-28 + BDE-47 + BDE-99 + BDE-100 + BDE-153;

Abbreviations: ADHD = Attention-Deficit/Hyperactivity Disorder; ALSPAC = Avon Longitudinal Study of Parents and Children; AS = Achievement Score; BDCIPP = Bis(1,3-dichloro-2-propyl) Phosphate; BDE = Brominated Diphenyl Ethers; BDE-47 = Tetrabromodiphenyl Ether; CCCEH = Columbia Center for Children's Environmental Health; CHAMACOS = Center for the Health Assessment of Mothers and Children of Salinas; CPF = Chlorpyrifos; cx-MiNP = Mono-4-methyl-7-carboxyheptyl phthalate; DACE= Development at Adolescence and Chemical Exposure; DAP = Dialkyl Phosphates; DEDTP = Diethyl Dithiophosphate; DEHP = Bis(2-ethylhexyl) Phthalate ; DEP = Diethyl phosphate; DETP = Diethyl Thiophosphate; DiNP = Diisononyl Phthalate; DMDTP = Dimethyl Dithiophosphate; DMP = Dimethyl Phosphate; DMTP = Dimethyl Thiophosphate; DPHP = Di(2-propylheptyl) Phthalate; FRI = Fluid Reasoning Index; FSIQ = Full-Scale IQ; GCI = General Cognitive Index; HOME = Health Outcomes and Measures of the Environment; INMA = INfancia y Medio Ambiente (Environment and Childhood) Project; ip-PPP= 2-((isopropyl) phenyl) Phenyl Hydrogen Phosphate; IQ = Intelligence Quotient; K-ABC = Kaufman Assessment Battery for Children; MBP = Monobutyl Phthalate ; MBzP = Monobenzyl Phthalate; MECPP = Mono(2-ethyl-5-carboxypentyl) Phthalate ; MEHHP = Mono(2-ethyl-5-hydroxyhexyl) Phthalate; MEHP = Mono(2-ethylhexyl) Phthalate; MEOHP = Mono-(2-ethyl-5-oxohexyl) Phthalate; MEP = Mono-ethyl Phthalate; MiBP = Mono-isobutyl Phthalate ; MMP = Mono-methyl Phthalate; MMCHP = Mono-2-methylcarboxyhexyl phthalate; MnBP = Mono-n-butyl Phthalate; MoBA = The Norwegian Mother & Child Cohort Study (den norske Mor & barn-undersøkelsen); MoS = Motor Scale; MPS = Mental Processing Scale; MS = Memory Scale; MSCA = McCarthy Scales of Children's Abilities ; OH-MiNP = Mono-4-methyl-7-hydroxyoctyl phthalate; OH-PCB = Hydroxylated Polychlorinated Biphenyl; OPP = Organophosphate Pesticides; oxo-MiNP = Mono-4-methyl-7oxooctyl phthalate; PBDE = Polybrominated Diphenyl Ethers; PCB = Polychlorinated Biphenyls; PIQ = Performance Intelligence; PPS = Perceptual Performance Scale; PPVT = Peabody Picture Vocabulary Test; PRI = Perceptual Reasoning Index; PSI = Processing Speed Index; QS= Quantitative Scale; SB5 = Standford Binet 5; SCDS = Seychelles Child Development Study; SON-R = Snijders-Oomen Nonverbal Intelligence Test; TMICS = Taiwan Maternal and Infant Cohort Study; TSCD = Tohoku Study

of Child Development ; UK = United Kingdom; USA = United States of America; VCI = Verbal Comprehension Index; VIQ = Verbal Intelligence; VS= Verbal Scale; VSI = Visual Spatial Index; WISC-III = Wechsler Intelligence Scale for Children, Third Edition; WISC-IV= Wechsler Intelligence Scale for Children, Fourth Edition; WISC-III-NL = Wechsler Intelligence Scale for Children, Third Edition, Netherlands Version; WISC-R = Wechsler Intelligence Scale for Children, Revised; WM = Working Memory; WMI = Working Memory Index; WPPSI-III = Wechsler Preschool & Primary Scale of Intelligence, Third Edition; WPPSI-R = Wechsler Preschool & Primary Scale of Intelligence, Revised; WRAT-III= Wide Range Achievement Test, Third Edition

Table 3. Risk of Bias Ratings for Studies Included in the Systematic Review



Discussion

We conducted a systematic review and set of meta-analyses to examine sex-specific differences in vulnerability to pre- and post-natal exposure to six neurotoxicants on the development of intellectual abilities. While there have been several systematic reviews examining the sex-specific neurodevelopmental impacts from heavy metals[7,9,60] and developmental neurotoxicants[8], none have quantitatively examined the strength of the evidence while looking at timing of exposure and IQ as the specific outcome measure. Combining data from individual studies using meta-analytic techniques allows for a more precise and objective estimate of the underlying effects on males' and females' intelligence.

Through our meta-analysis of 22 studies, we found that prenatal exposure to developmental neurotoxicants (i.e., lead, mercury, phthalates, PBDEs, and OPPs) was associated with a decrement in general and nonverbal intelligence, but only among males. Specifically, the pooled effect demonstrated that a 50% difference in exposure level was associated with a 0.38 and 0.42 decrease in general and nonverbal intelligence, respectively, among males. Further, the largest effects on general and nonverbal intelligence in males and the largest differences between males and females were consistently found for prenatal lead exposure.

Prenatal Exposure

Theories and Mechanisms Underlying a Male Vulnerability to Prenatal Exposures

Various studies have documented sex-specific effects of neurotoxicant exposure on a variety of cellular, hormonal, and molecular endpoints, providing potential mechanisms to explain the male vulnerability of prenatal exposure to lead on intellectual abilities.

The sex-specific impact of prenatal exposure to developmental neurotoxicants on intelligence is consistent with research demonstrating a protective placental female effect in

response to maternal perturbations[138]. To buffer the fetus from environmental insults, the placenta must detect subtle changes and adapt to the changing maternal milieu[139]. A large amount of research has demonstrated that males and females utilize different strategies in the womb to adapt to environmental perturbations[138]. For example, the male placenta responds to adverse maternal environments with fewer genes and proteins[140,141], and instead invests resources in growth[142]. In contrast, the female fetus conserves resources and adjusts to the maternal milieu through a greater expression of genes and proteins[141]. Specifically, female placentas have greater expression of genes associated with transport, immune regulation, growth, and development than male placentas[140,141]. As a result, the male fetus has a limited ability to adjust to adversity and is at greater risk for subsequent morbidity and mortality. This pattern is consistently seen in response to exposure to prenatal stress[64].

A similar pattern can be seen in relation to exposure to developmental neurotoxicants. While the placenta plays an essential role in the regulation of the fetal environment and in the communication and transportation of nutrients to the developing fetus, it is also implicated in fetal exposure to toxic chemicals[139]. Thus, the greater expression of genes in female fetuses may then better equip them to respond to and buffer against neurotoxicants. For example, neurotoxicants (e.g., lead, phthalates) are known to impact intrauterine inflammation[143,144] and several studies demonstrate that females are resilient to maternal immune perturbations while males are at increased risk[145]. Specifically, intrauterine inflammation has been found to induce a neuroinflammatory response (e.g., up-regulation of pro-inflammatory cytokines in the brain and greater macrophage activation) only in males[146–148].

Similarly, prenatal exposure to developmental neurotoxicants (e.g., lead, mercury, PCBs, and pesticides) can impact one or more steps in oxidative phosphorylation, resulting in an

increase in oxidative stress, a general degradation of mitochondria, and ultimately a decrease in energy production[149]. One study examined twins exposed to the same environmental insult during fetal development and found that male infants at birth had higher levels of oxidative stress than females, suggesting that the male fetus may be more susceptible to maternal oxidative stress than the female fetus[150], consistent with research on differences in placental adaptation. Neuroinflammation and oxidative stress in offspring can alter fetal developmental trajectories, which can have detrimental downstream effects on the development of cognitive abilities and ultimately the pathogenesis of intellectual disability[147,151–153]

Moreover, estradiol and progesterone, the two main circulating female sex hormones, have been found to have neuro-protective and neuro-reparative properties during brain development[154–156]. For example, they can enhance cell proliferation, synaptic plasticity, axonal growth, and remyelination, as well as decrease oxidative stress and neuroinflammation[154,156]. Males typically have fewer estrogen receptors throughout their central nervous system than females[50]. Thus, differing levels of sex hormones offer another reason that females may be more protected from adverse neurological effects from prenatal exposure to neurotoxicants.

There is also evidence that male and female fetuses differ in the rate of neural maturation in-utero. Specifically, using fetal heart rate responses to vibroacoustic stimulation (VAS) as a proxy for fetal nervous system development and functioning, studies have found that male fetuses recover more slowly to VAS at 31 weeks' gestation than 37 weeks' gestation. In contrast, female fetuses exhibit a mature response at 31 weeks' gestation[157]. Similarly, using fetal habituation as an indicator of neural functioning, another study found that a greater proportion of female fetus' habituate at 35 weeks' gestation compared with male fetuses habituation response maturation[158]. Taken together, these findings suggest that male fetal nervous system functioning

matures at a slower rate than that of females. This difference in maturation may reflect a greater sensitive time-window in which males' brains are more vulnerable to the impact of toxic chemicals.

More recently, sex differences in epigenetic transmission have been proposed as another mechanism to explain prenatal sex differential vulnerability[159]. Epigenetic mechanisms are non-genetic influences that effect gene expression and activity[160]. While epigenetic changes can occur across the lifespan, the prenatal period is particularly vulnerable to epigenetic disruption[160]. Fetal development is a period of extensive epigenetic programming whereby stable and long-lasting alterations to cell- and tissue-specific gene expression occur[160]. Certain epigenetic mechanisms, such as DNA methylation, are known to impact neurodevelopment[161] and some studies have found that neurotoxicants can impact DNA methylation differently in males and females[159]. For example, in one study, perinatal exposure to lead resulted in the hypomethylation of a gene in the hippocampal methylome associated with learning and memory, but only in males[162]. In humans, prenatal mercury levels were associated with cord blood DNA methylation changes at the Paraoxonase 1 (*PON1*) gene in males but not females[163]. Further, cord blood DNA methylation changes at the PON1 gene ultimately predicted lower cognitive test scores during early childhood[163].

Domain-Specific Effects

We found that prenatal exposure to developmental neurotoxicants was negatively associated with boy's general and nonverbal intelligence rather than verbal intelligence. Nonverbal intelligence encompasses an individual's visuospatial abilities, which is their ability to perceive, process, and manipulate information using visual and spatial reasoning. A male advantage in mental rotation, and spatial orientation and perception is well-documented in the

literature[164,165]. Thus, why we found visual-spatial abilities to be more vulnerable in males but not females is of particular interest.

This domain- and sex-specific effect may be explained by the vulnerability hypothesis based on evolutionary and sexual selection theory[166]. According to this theory, sexually selected cognitive advantages are supported by elaborated brain networks (i.e., more neural tissue and more intermodular connections) that are highly energy dependent[166]. Thus, more elaborated traits are more vulnerable to disruptions in energy production and responding to oxidative stress, as they require more energy to build, maintain, and express[166]. Furthermore, cognitive vulnerabilities are likely to be greatest during trait development and under conditions that require maximum trait expression[166].

The male advantage in visuospatial abilities is a sexually selected trait, as it supports aspects of male-male competition[167]. For example, males with better navigational abilities find mates more efficiently[168]. In line with the vulnerability hypothesis, males have larger volumes and higher tissue density in the hippocampi than females[169], an area involved in higher-order visual-spatial perception[170]. Given that the visual system develops early in the prenatal period and that by the third trimester of pregnancy the human fetus has the capacity to process perceptual information[171], visual-spatial abilities in males should be susceptible to energy disruptions during prenatal development. It is known that neurotoxicants can induce oxidative stress in males and that males may be more vulnerable to the effects of it[149,150]. Thus, the combination of sex and developmental neurotoxicity in fetal life may act synergistically as a double-hit model to disrupt energy production and ultimately affect visual spatial abilities in males.

Overall, our results suggest that the relative magnitude of the adverse effects of prenatal exposure to developmental neurotoxicants on general and nonverbal intelligence is greater in males in females; this finding could be due to differences in placental functioning, hormonal responses, epigenetics, brain maturation, and evolutionary reactions. Although females may demonstrate adaptive flexibility in response to maternal exposures during gestation with respect to the development of their general intellectual and nonverbal abilities, this adaptability does not preclude the possibility that developmental neurotoxicants influence the development of females in some other way. Females may exhibit greater vulnerability during different periods of exposure or to other outcomes, such as social and psychological deficits[138,166]

Subgroup Effects

Lead

Although the effect sizes did not significantly vary by neurotoxicant in males, in subgroup analyses the strongest and most consistent effects on general and nonverbal intelligence in males were for prenatal lead exposure. Specifically, the pooled effect demonstrated that every 50% difference in prenatal lead levels was associated with a 1.07-point and 1.18-point decrease in general and nonverbal intelligence, respectively, in males, whereas the pooled effect among females was 0.45 and 0.15 for general and nonverbal intelligence, respectively. This result is not surprising given that the global number of disabilities-adjusted life years of idiopathic developmental intellectual disability in 2019 was 4.39 million, of which 61.90% was attributable to lead exposure[172]. Further, despite global efforts to reduce lead exposure, and research demonstrating that there is no safe level of exposure, around 1 in 3 children – up to approximately 800 million globally – have blood lead levels at or above 5 micrograms per deciliter (μg/dL)[173].

Moreover, relative to other neurotoxicants, lead may induce greater negative effects in males due to the interaction between lead and stress, as mothers with exposure to chronic stress (e.g., those with low socioeconomic status or resource deprivation) are more likely to be exposed to higher levels of lead, indicating the potential for a multiple stressor model[75,174,175]. Prenatal lead exposure and stress have shared biological substrates, as they both disrupt the programming of the hypothalamic-pituitary-adrenal axis[175]. Further, combined exposure to prenatal lead and stress has been found to alter epigenetic profiles in the brain in sex-specific manner[176–178]. For example, combined exposure to lead and stress increases the expression of methyl CpG binding protein 2 (MECP2) in the frontal cortex of male rats and decreases the expression of MECP2 in the hippocampus of female rats[177]. Overexpression of MECP2 can impede on proper neuronal development and increase risk of severe neurological deficits[179]. In another study, male rats exposed to both prenatal lead and stress showed more dramatic increases in global post-translational histone modifications levels (associated with intellectual disability and neuropsychiatric disorders[180,181]) in the hippocampus compared to females[178]. Further, combined exposure to lead and stress can produce transgenerational effects on brain and behaviour in a sex-specific manner[176]. Most research done on combined exposure to lead and stress has been experimental; more epidemiological research is needed to better characterize the effects of exposure to both risk factors in humans.

Mercury

The subgroup effect of mercury on general intelligence in males had a moderate to high degree of heterogeneity across studies with some studies showing positive effects and others negative effects. This variability is expected and may be due to differences in exposure levels, the confound of fish intake, or the underlying genetic composition of the populations. For

example, the mean or median of exposure ranged from 0.4 to 26.0 ppb across the studies[88,89,111,115]. Lower levels of exposure may be indicative of lower consumption of fish. Fish contains essential fatty acids and nutrients such as n-3 polyunsaturated fatty acids, iodine, selenium, vitamin D and B12 that are crucial for the development of the fetal brain[182]; thus lower consumption could also adversely impact neurodevelopment. In fact, Llop and colleagues (2017) found that mercury concentration was only associated with lower scores among children whose mothers consumed fewer than three weekly servings of fish during pregnancy[115]. Moreover, in Julvez et al. (2013), the presence of a specific genetic polymorphism was associated with greater mercury neurotoxicity[111]. The differences across the studies and even within studies demonstrates the complexity of isolating effects of exposure on IQ by sex without considering other environmental and genetic factors.

Phthalates

We found that the sum of DEHPs was significantly positively associated with nonverbal intelligence in females. Despite this, the pooled effect of developmental neurotoxicants on nonverbal intelligence in females was non-significant and effects did not significantly differ by neurotoxicant. However, generally, effect sizes for the sum of DEHPs were near zero or positive in females. The possible protective or positive effect in females is intriguing. Phthalates are endocrine disrupters and one study found that exposure to phthalates later in pregnancy was associated with increased estrogens in women carrying female fetuses[183]. In contrast, exposure to phthalates earlier in pregnancy was associated with decreased estrogen (albeit not significantly) in women carrying male fetuses[183]. While the increased estrogen may confer a benefit to females with respect to the neurotoxic effects of phthalates due to its neuro-protective properties[154], it may also put females at increased risk for other adverse health outcomes, such as endometriosis,

earlier onset of puberty, polycystic ovarian syndrome, breast cancer, or metabolic disorders[184]. Given the relative inconsistency in results of phthalates in females across outcomes (i.e., null for general and verbal intelligence, versus positive for nonverbal intelligence) and the potential for publication bias, more research is needed.

OPPs and BDEs

We found that the effect sizes for OPPs and BDEs in males were generally negative for general intelligence, consistent with the findings overall and for lead. Similarly, we found that the effect sizes for OPPs and BDEs in females were generally negative for general intelligence; however, there were moderate to high degrees of heterogeneity across studies. For nonverbal intelligence, we found that the effects sizes were generally closer to zero. It is important to note that there were only two studies available for each of these neurotoxicants and there was a high degree of heterogeneity for females, suggesting that more research is needed.

Postnatal Exposure

We did not find a significant pooled effect of postnatal lead exposure on either males or females general intelligence; however, the effect size in males was negative, as was seen with prenatal exposures. Nevertheless, we were limited by the small number of estimates, most of the studies included were considered higher risk of bias, there was indication of publication bias, and there were discrepancies in the pooled effect sizes when individual studies were excluded. Further, we were unable to assess the effect of postnatal exposure to other chemicals or on other domains of intelligence which could have been more sensitive to sex-specific effects. Since infancy is a critical period for the development of language[185] and since females have advantages in language competence, females may be more vulnerable to energy disruptions to verbal abilities during the early postnatal period, consistent with the vulnerability hypothesis[166]. More

research on the sex-specific effects of postnatal neurotoxicant exposure is needed, with consideration of domains of intelligence.

Qualitative Findings

Most studies that were not included in the meta-analysis concluded that there were no differences between the sexes. Nonetheless, many of these studies did not report separate estimates for males and females, and therefore we were unable to determine the general trends of the individual effects. Further, studies of smaller sample sizes may have had inadequate power to detect sex differences through an interaction effect, which highlights the need for studies to report individual effect estimates for males and females to allow for inclusion in a meta-analysis.

Moreover, few studies published to date have evaluated the sex-specific impact of PCB exposure on intellectual abilities. Of the studies that did evaluate the sex-specific impact of PCB exposure on intellectual abilities, the methods were too heterogenous (i.e., different congeners of PCBs or outcomes), thus limiting our ability to include PCB-related effects in the meta-analysis. However, consistent with our meta-analytic findings, four out of the five studies of prenatal PCB exposure found stronger negative associations in males or more positive associations in females[86,110,113,129].

Limitations and Future Directions

There are several limitations of the present study and directions for future research. First, there were only 22 studies included in this meta-analysis. Given the limited number of estimates available, we included studies from the same cohort with the same methodology if they had data on different neurotoxicants; doing so artificially reduced the standard error of our estimates.

Second, this review focused on prenatal and early postnatal exposure. Exposure during early adolescence may represent another critical window where sex-specific effects occur.

Adolescence is characterized by substantial structural and functional brain changes, particularly in regions associated with higher-level cognitive processing[186]. Further, there is evidence for sexually dimorphic trajectories of these brain changes[187]. For example, frontal gray matter peaks at an earlier age in females (~10.5 years) than males (~11.5 years). Different behaviours and body weight between genders may also result in differences in exposure levels[53]. Future research should explore early adolescence as a critical window of exposure and take special consideration of sex-specific effects during this time.

Third, while intellectual abilities are the most common neurodevelopmental outcome studied, as previously mentioned, neurodevelopment can also encompass other outcomes such as attention, motor skills, social skills, reading ability, and memory. Given the sex bias of ADHD and ASD, future research should explore the potential sex-specific effects related to neurotoxicant exposure on outcomes related to these disorders. Further, research should explore the sex-specific effects related to neurotoxicant exposure on other outcomes such as social and psychological outcomes, given the greater prevalence of internalizing disorders in females[188].

Fourth, the impact of environmental chemicals on intellectual abilities is a global issue[189]. Yet, most of the studies on the sex-specific effects of pre- and post-natal exposure to developmental neurotoxicants were conducted in developed countries. The effect of lead on IQ has been found to be stronger in underdeveloped and developing countries[190], however this has not been investigated with respect to sex differences. The results of this meta-analysis may lack generalizability to low-income countries. Future research in developing countries evaluating the impact of neurotoxicants on IQ should consider incorporating analyses examining the sex-specific effects.

Lastly, this review focused on the effects of exposure to a single developmental neurotoxicant on children's neurodevelopment, as that is what is most commonly reported in the literature[191]. Yet, developmental toxicants often co-occur – particularly among at-risk populations[191]. Exposure to cumulative risk factors – both chemical and nonchemical – can produce additive or synergistic effects that may initiate a developmental cascade, as shown with the example of lead and prenatal stress[191]. Thus, the effect in males' is likely an underestimate of the true nature of the problem. Additional studies are needed examining the sex-specific effects of cumulative exposure to environmental stressors especially in human epidemiological cohorts.

Conclusions

This is the first study to quantitatively synthesize the sex-specific effects of pre- and post-natal exposure to developmental neurotoxicants on intelligence. Overall, this meta-analysis demonstrated that males' general and nonverbal intelligence are more impacted by prenatal exposure to developmental neurotoxicants than females, and especially from lead exposure. This study highlights the necessity to include sex as a fundamental variable when examining the effects of developmental neurotoxicants on intellectual abilities.

Unfortunately, the impacts of developmental neurotoxicants are often dismissed because the effects are subtle. Yet, subtle shifts in intellectual abilities can cause a downward shift in the population mean IQ, ultimately increasing the number of children with intellectual disability[4]. Importantly, compared with the general population, individuals with intellectual disabilities (ID) have increased risk of health problems (e.g., epilepsy, cerebral palsy, sensory disorders, and metabolic and nutritional disorders), are more likely to face problems with equal access to effective healthcare, and are more likely to die prematurely[192]. Further, even mild IQ deficits can have major academic, occupational, and psychological consequences[72]. In addition to the

individual impacts, the economic impact is enormous. In fact, from 2001 to 2016, exposure to lead, mercury, PBDEs, and OPPs cost over $6 trillion in the US alone due to IQ point loss[193.] The results of this meta-analysis provide much needed insight into one of the influential factors in the sex bias of IDs and highlights the possibility for early identification and prevention.

Appendices

Appendix A: PRISMA Guidelines

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Cover page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	iii
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	8
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	8
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	9
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	9
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	9
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	9
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	9-10
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	9
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	9-10
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	10
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	11-15
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	11-15
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	12

	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	13-14
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	13-14
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	14-15
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	15
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	14-15
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	17
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	17
Study characteristics	17	Cite each included study and present its characteristics.	18-21 + 43-49
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	22 + 50
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	23-36
Results of syntheses	20a	For each synthesis, briefly summaries the characteristics and risk of bias among contributing studies.	21 + 43
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	23-43
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	23-36
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	36-43
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	23-36
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	51
	23b	Discuss any limitations of the evidence included in the review.	60-61
	23c	Discuss any limitations of the review processes used.	60-61
	23d	Discuss implications of the results for practice, policy, and future research.	61
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	17

	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	17
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	N/A
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

Appendix B: Instructions for Making Risk of Bias Determinations

Please answer LOW RISK, PROBABLY LOW RISK, PROBABLY HIGH RISK, or HIGH RISK.

These questions are adapted from those used in the Navigation Guide systematic review of PBDEs and neurodevelopmental effects[20].

An answer of "Yes" aligns with a rating of "Low risk of bias," "Probably Yes" aligns with a rating of "Probably low risk of bias," "Probably No" aligns with a rating of "Probably high risk of bias", and "No" aligns with a rating of "High risk of bias."

1. Did the study sample adequately represent their source population such that the risk of selection effects was minimal?

Criteria for a judgment of LOW risk of bias (i.e., answer: "Yes"):

EITHER:

a) The descriptions of the source population, inclusion/exclusion criteria, recruitment and enrollment procedures, participation and follow-up rates were sufficiently detailed, and adequate data were supplied on the distribution of relevant study sample and population characteristics to support the assertion that risk of selection effects was minimal.

OR

b) Although the descriptions and/or data as indicated in "a" above suggested the potential for selection effects, adequate support was given indicating that potential selection effects were *not* differential across both exposure and outcome.

OR

c) Although the descriptions and/or data as indicated in "a" above suggested the potential for selection effects and there was no support indicating that potential selection effects were *not* differential across both exposure and outcome, selection factors appeared to be well-understood, were measured in the data set, and appropriate adjustment post hoc techniques were used to control for selection bias.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably Yes"):

There is insufficient information about participant selection to permit a judgment of low risk of bias, but there is indirect evidence which suggests that inclusion/exclusion criteria, recruitment and enrollment procedures, and participation and follow-up rates were consistent across groups as described by the criteria for a judgment of low risk of bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably No"):

There is insufficient information about participant selection to permit a judgment of high risk of bias, but there is indirect evidence which suggests that inclusion/exclusion criteria,

recruitment and enrollment procedures, and participation and follow-up rates were inconsistent across groups, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: “No”):

a) There were indications from descriptions of the source population, inclusion/exclusion criteria, recruitment and enrollment procedures, participation and follow-up rates, or data on the distribution of relevant study sample and population characteristics that risk of selection effects were substantial; and
b) There was no support to indicate that potential selection effects were *not* differential across both exposure and outcome; and
c) Adjustment post hoc techniques were not used to control for selection bias.

2. Was knowledge of the exposure or outcome adequately prevented (i.e., blinded or masked) during the study?

Criteria for a judgment of LOW risk of bias (i.e., answer: “Yes”):

Any of the following:

- Blinding of key study personnel was ensured, and it is unlikely that the blinding could have been broken; or

- Some key study personnel were not blinded, but exposure and outcome assessment were blinded and the non-blinding of others is unlikely to introduce bias.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: “Probably Yes”):

There is insufficient information about blinding to permit a judgment of low risk of bias, but there is indirect evidence which suggests the study was adequately blinded, as described by the criteria for a judgment of low risk of bias. Or the review authors judge that the outcome measures as well as the exposure measures are not likely to be influenced by lack of blinding. For example, if the exposure was measured by a separate entity and the outcome was obtained from a hospital record.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: “Probably No”):

There is insufficient information about blinding to permit a judgment of high risk of bias, but there is indirect evidence which suggests the study was not adequately blinded, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: “No”):

Any of the following:

- No blinding or incomplete blinding, and the outcome measures or exposure measures is likely to be influenced by lack of blinding (i.e., differential outcome or exposure assessment); or
- Blinding of key study personnel attempted, but likely that the blinding could have been broken so as to introduce bias; or
- Some key study personnel were not blinded, and the non-blinding of others was likely to introduce bias.

3. Is there high confidence in the accuracy of the exposure assessment methods?

Criteria for a judgment of LOW risk of bias (i.e., answer: "Yes"):

The reviewers judge that there is low risk of exposure misclassification, i.e.,:

- There is high confidence in the accuracy of the exposure assessment methods, such as methods that have been tested for validity and reliability in measuring the targeted exposure;
    - Lead – measured in whole blood, taking the mean of serial measurements, or in circumpulpal dentin[194]
    - Mercury – measured in hair or whole blood for acute exposure[195]
    - PCBs – measured in serum or breastmilk shortly after birth and lipid adjusted [196,197]
    - PBDEs – measured in serum or plasma for prenatal exposure, or in breastmilk for postnatal exposure and lipid adjusted[198,199]
    - OP Pesticides – measured in urine and adjusted for urinary dilution or in blood with multiple measurements[200]

    - Phthalates – measured in multiple urine spot samples and adjusted for urinary dilution through specific gravity[201].

- or
- Less-established or less direct exposure measurements are validated against well-established or direct methods

AND

- Appropriate QA/QC for methods are described and are satisfactory, with at least three of the following items reported, or at least two of the following items reported plus evidence of satisfactory performance in a high-quality inter-laboratory comparison:
    - Limit of detection (LoD) or quantification (with fewer than 10% of the observations being below the LoD)[202]
    - standards recovery;
    - measure of repeatability;
    - investigation and prevention of blanks contamination.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: “Probably Yes”):

- There may be insufficient information about the exposure assessment methods to permit a judgement of low risk of bias but there is indirect evidence, which suggests that methods were robust, as described by the criteria for a judgement of low risk of bias. For example, studies reporting that the QA/QC items above were satisfactory but not reporting all the actual numbers may receive a judgement of “probably low risk of bias”.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: “Probably No”):

- There is insufficient information about the exposure assessment methods to permit a judgment of high risk of bias, but there is indirect evidence which suggests that methods were not robust, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: "No"):

The reviewers judge that there is high risk of exposure misclassification and any one of the following:

- There is low confidence in the accuracy of the exposure assessment methods; or
- Less established or less direct exposure measurements were not validated and are suspected to introduce bias that impacts the outcome assessment (example: participants are asked to report exposure status retrospectively, subject to recall bias)
- Uncertain how exposure information was obtained

4. Is there high confidence in the accuracy of the outcome assessment methods?

Criteria for a judgment of LOW risk of bias (i.e., answer: "Yes"):

The reviewers judge that there is low risk of outcome misclassification, i.e.:

- Outcomes were assessed and defined consistently across all study participants, using valid and reliable measures of intelligence; or
    - For example, assessed via the McCarthy Scales of Children's Abilities (MCSA), the Wechsler Preschool and Primary Scale of Intelligence

(WPPSI), the Wechsler Intelligence Scale for Children (WISC), or the Kaufman Assessment Battery for Children (K-ABC).

- Less established or less direct outcome measurements are validated against well-established or direct methods; or
- Appropriate sensitivity analyses were conducted that suggest the influence of outcome misclassification would be minimal
- AND, if applicable, appropriate QA/QC for methods is described and is satisfactory.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: “Probably Yes”):

There is insufficient information about the outcome assessment methods to permit a judgment of low risk of bias, but there is indirect evidence which suggests that methods were robust, as described by the criteria for a judgment of low risk of bias. Appropriate QA/QC for methods are not described but the review authors judge that the outcome and the outcome assessment are objective and uniform across all study participants.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: “Probably No”):

There is insufficient information about the outcome assessment methods to permit a judgment of high risk of bias, but there is indirect evidence which suggests that methods were not robust, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: “No”):

The reviewers judge that there is high risk of outcome misclassification and any one of the following:

- There is low confidence in the accuracy of the outcome assessment methods; or
- Less established or less direct outcome measurements are not validated and are suspected to introduce bias that impacts the outcome assessment
- Uncertain how outcome information was obtained

5. Were potential confounders adequately considered?

List of important potential confounders, collectively generated by review authors prior to the initiation of screening for studies based on expert opinion and knowledge gathered from the literature:

Tier I: Important confounders

- maternal IQ/education
- SES-based measure (e.g., socioeconomic status, parental occupation/employment, household income, or income-to-needs ratio, poverty-to-income ratio,)
- Home Observation for Measure of the Environment (HOME) score (Caldwell & Bradley, 1984); or Family Assessment Measure (FAM; Skinner, Steinhauer, & Santa-Barbara, 1983); or another acceptable measure of HOME environment
- Race/ethnicity
- Centre/city if it's multi-site study

- Fish intake if the exposure is mercury

Tier II: Other potentially important confounders:

- Exposure to at least one other neurotoxic agents (e.g., pesticides, mercury, lead, air pollutants)
- Exposure to tobacco smoke during pregnancy
- Maternal age
- Marital status
- Maternal alcohol intake
- Maternal depression or stress/mood disorder/psychopathology

Other variables for consideration – could be exclusions or confounders:

- Low birth weight, preterm birth, or other birth complications
- Parental drug use
- Serious head injury (exclusion)

Criteria for a judgment of LOW risk of bias (i.e., answer: "Yes"):

The study appropriately assessed and considered or accounted for all important confounders[2] (Tier I), or reported that important confounders were evaluated and omitted because inclusion did not substantially affect the results.

AND the study appropriately assessed and considered or accounted for most but not necessarily all other potentially important confounders relevant (Tier II), or reported that these confounders were evaluated and omitted because inclusion did not substantially affect the results,

AND the important potential confounders were measured consistently across study groups using valid and reliable methods, or the influence of covariate measurement error was determined, through sensitivity analysis, to be minimal.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: “Probably Yes”):

The study appropriately assessed and considered or accounted for most but not all the important confounders (Tier I),

AND this is not expected to introduce substantial bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: “Probably No”):

The study evaluated some but not all the important confounders (Tier I),

AND some but not all the other potentially important confounders relevant (Tier II),

AND this is expected to introduce substantial bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: “No”):

The study did not account for or evaluate multiple important confounders (Tier I),

AND did not account for or evaluate multiple other potentially important confounders relevant (Tier II),

OR the important potential confounders were inappropriately measured and/or inappropriately analyzed across study groups.

6. Were incomplete outcome data adequately addressed?

Criteria for a judgment of LOW risk of bias (i.e., answer: "Yes"):

Participants were followed long enough to obtain outcome measurements
OR any one of the following:

- No missing outcome data; or
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias); or
- Attrition or missing outcome data balanced in numbers across exposure groups, with similar reasons for missing data across groups; or

- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a relevant impact on the exposure effect estimate; or
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a relevant impact on the observed effect size; or
- Missing data have been imputed using appropriate methods

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: “Probably Yes”):

There is insufficient information about incomplete outcome data to permit a judgment of low risk of bias, but there is indirect evidence which suggests incomplete outcome data was adequately addressed, as described by the criteria for a judgment of low risk of bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: “Probably No”):

There is insufficient information about incomplete outcome data to permit a judgment of high risk of bias, but there is indirect evidence which suggests incomplete outcome data was not adequately addressed, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: “No”):

Participants were not followed long enough to obtain outcome measurements

OR any one of the following:

- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across exposure groups; or
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce biologically relevant bias in intervention effect estimate; or
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce biologically relevant bias in observed effect size; or
- Potentially inappropriate application of imputation.

7. Is the study report free from selective outcome reporting?

Criteria for a judgment of LOW risk of bias (i.e., answer: "Yes"):

All the study's pre-specified (primary and secondary) outcomes outlined in the protocol, methods, abstract, and/or introduction that are of interest in the review have been reported in the pre-specified way.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably Yes"):

There is insufficient information about selective outcome reporting to permit a judgment of low risk of bias, but there is indirect evidence which suggests the study was free of selective reporting, as described by the criteria for a judgment of low risk of bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: “Probably No”):

There is insufficient information about selective outcome reporting to permit a judgment of high risk of bias, but there is indirect evidence which suggests the study was not free of selective reporting, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: “No”):

Any one of the following:

- Not all the study’s pre-specified primary outcomes (as outlined in the protocol, methods, abstract, and/or introduction) have been reported; or
- One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; or
- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected effect); or
- One or more outcomes of interest are reported incompletely

8. Is the study free of a financial conflict of interest as in did the study not receive any support from a company, study author, or other entity having a financial interest in any of

the exposures studied?

Criteria for a judgment of LOW risk of bias (i.e., answer: “yes”):

The study did not receive support from a company, study author, or other entity having a financial interest in the outcome of the study. Examples include the following:

- Funding source is limited to government, non-profit organizations, or academic grants funded by government, foundations and/or non-profit organizations;
- Chemicals or other treatment used in study were purchased from a supplier;
- Company affiliated staff are not mentioned in the acknowledgements section;
- Authors were not employees of a company with a financial interest in the outcome of the study;
- Company with a financial interest in the outcome of the study was not involved in the design, conduct, analysis, or reporting of the study and authors had complete access to the data;
- Study authors make a claim denying conflicts of interest;
- Study authors are unaffiliated with companies with financial interest, and there is no reason to believe a conflict of interest exists;
- All study authors are affiliated with a government agency (are prohibited from involvement in projects for which there is a conflict of interest or an appearance of conflict of interest).

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: “Probably Yes”):

There is insufficient information to permit a judgment of low risk of bias, but there is indirect evidence which suggests the study was free of support from a company, study author, or other entity having a financial interest in the outcome of the study, as described by the criteria for a judgment of low risk of bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: “Probably No”):

There is insufficient information to permit a judgment of high risk of bias, but there is indirect evidence which suggests the study was not free of support from a company, study author, or other entity having a financial interest in the outcome of the study, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: “No”):

The study received support from a company, study author, or other entity having a financial interest in the outcome of the study. Examples of support include:

- Research funds;
- Chemicals, equipment or testing provided at no cost;
- Writing services;
- Author/staff from study was employee or otherwise affiliated with company with financial interest;

- Company limited author access to the data;
- Company was involved in the design, conduct, analysis, or reporting of the study;
- Study authors claim a conflict of interest

9. Does the study appear to be free from other problems that could put it at a risk of bias?

Criteria for a judgment of LOW risk of bias (i.e., answer: “Yes”):

The study appears to be free of other sources of bias.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: “Probably Yes”):

There is insufficient information to permit a judgment of low risk of bias, but there is indirect evidence which suggests the study was free of other threats to validity.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: “Probably No”):

There is insufficient information to permit a judgment of high risk of bias, but there is indirect evidence which suggests the study was not free of other threats to validity, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: “No”):

There is at least one important risk of bias. For example, the study:

- Had a potential source of bias related to the specific study design used; or
- Stopped early due to some data-dependent process (including a formal-stopping rule); or
- The conduct of the study is affected by interim results (e.g. recruiting additional participants from a subgroup showing greater or lesser effect); or
- Has been claimed to have been fraudulent; or
- Had some other problem (i.e., statistical assumptions were violated, sensitivity analyses show significant changes, no sensitivity analyses)

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