

Disparities in Toxic Chemical Exposures and Associated Neurodevelopmental Outcomes: A Scoping Review and Systematic Evidence Map of the Epidemiological Literature

Devon C. Payne-Sturges,^{1*} Tanya Khemet Taiwo,^{2*} Kristie Ellickson,^{3,4} Haley Mullen,⁵ Nedelina Tchangalova,⁶ Laura Anderko,⁷ Aimin Chen,⁸ and Maureen Swanson⁹

¹University of Maryland School of Public Health, College Park, Maryland, USA

²University of California, Davis, Davis, California, USA

³Minnesota Pollution Control Agency, St. Paul, Minnesota, USA

⁴Union of Concerned Scientists, Cambridge, Massachusetts, USA

⁵Department of Geographical Sciences, University of Maryland, College Park, Maryland, USA

⁶University of Maryland Libraries, College Park, Maryland, USA

⁷M. Fitzpatrick College of Nursing, Villanova University, Villanova, Pennsylvania, USA

⁸Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

⁹The Arc, Washington, DC, USA

BACKGROUND: Children are routinely exposed to chemicals known or suspected of harming brain development. Targeting Environmental Neuro-Development Risks (Project TENDR), an alliance of >50 leading scientists, health professionals, and advocates, is working to protect children from these toxic chemicals and pollutants, especially the disproportionate exposures experienced by children from families with low incomes and families of color.

OBJECTIVE: This scoping review was initiated to map existing literature on disparities in neurodevelopmental outcomes for U.S. children from population groups who have been historically economically/socially marginalized and exposed to seven exemplar neurotoxins: combustion-related air pollution (AP), lead (Pb), mercury (Hg), organophosphate pesticides (OPs), phthalates (Phth), polybrominated diphenyl ethers (PBDEs), and polychlorinated biphenyls (PCBs).

METHODS: Systematic literature searches for the seven exemplar chemicals, informed by the Population, Exposure, Comparator, Outcome (PECO) framework, were conducted through 18 November 2022, using PubMed, CINAHL Plus (EBSCO), GreenFILE (EBSCO), and Web of Science sources. We examined these studies regarding authors' conceptualization and operationalization of race, ethnicity, and other indicators of sociodemographic and socioeconomic disadvantage; whether studies presented data on exposure and outcome disparities and the patterns of those disparities; and the evidence of effect modification by or interaction with race and ethnicity.

RESULTS: Two hundred twelve individual studies met the search criteria and were reviewed, resulting in 218 studies or investigations being included in this review. AP and Pb were the most commonly studied exposures. The most frequently identified neurodevelopmental outcomes were cognitive and behavioral/psychological. Approximately a third (74 studies) reported investigations of interactions or effect modification with 69% (51 of 74 studies) reporting the presence of interactions or effect modification. However, less than half of the studies presented data on disparities in the outcome or the exposure, and fewer conducted formal tests of heterogeneity. Ninety-two percent of the 165 articles that examined race and ethnicity did not provide an explanation of their constructs for these variables, creating an incomplete picture.

DISCUSSION: As a whole, the studies we reviewed indicated a complex story about how racial and ethnic minority and low-income children may be disproportionately harmed by exposures to neurotoxins, and this has implications for targeting interventions, policy change, and other necessary investments to eliminate these health disparities. We provide recommendations on improving environmental epidemiological studies on environmental health disparities. To achieve environmental justice and health equity, we recommend concomitant strategies to eradicate both neurotoxic chemical exposures and systems that perpetuate social inequities. <https://doi.org/10.1289/EHP11750>

Introduction

Evidence of disparities in pollutant and chemical exposures and disproportionate impacts of environmental hazards in communities of color and low-income communities is long standing and mounting.^{1–5} Scholars on race, racism, and environmental justice have linked these disproportionate exposures to racist and

discriminatory policies and processes such as racial residential segregation,⁶ disproportionate citing of polluting sources in communities of color,^{1,6,7} and government-backed policies to dispossess Native Americans of their lands and cultures.^{8–12} These environmental injustices contribute to disparities in harmful exposures and the erosion of the health of Indigenous communities and communities of color across all age groups.^{13–16} However, as noted by science writer Harriet Washington, environmental assaults on the developing brain are particularly pernicious because the effects can have lifelong implications.¹⁷

Neurodevelopmental disorders in children have increased substantially over the last few decades.¹⁸ As reported by Zablotsky et al. in 2019, one in six children in the United States has a developmental disability, including learning disabilities, intellectual impairment, attention deficit and hyperactivity disorder (ADHD), and autism.¹⁸ The rate is even higher among African American children and those from low-income families or living in rural areas.^{18–20} For example, in 2016–2018, non-Hispanic Black children (16.9%) were more likely than non-Hispanic White (14.7%) or Hispanic (11.9%) children to be diagnosed with either ADHD or a learning disability compared with 13.8% of children 3–17 years of age overall.¹⁹ Widely used chemicals are known or suspected neurodevelopmental toxicants associated with serious learning

*These authors are joint first senior authors.

Address correspondence to Devon C. Payne-Sturges, Maryland Institute for Applied Environmental Health, University of Maryland School of Public Health, 2234 L SPH, 255 Valley Dr., College Park, MD 20742 USA. Telephone: (301) 405-2025. Email: dps1@umd.edu

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disabilities and loss of intelligence, poor impulse control, developmental delays, hearing impairment, ADHD, and autism, any of which can affect a child's potential with long-term consequences for mental and behavioral health in adulthood.^{21–23} Further, mounting evidence shows that social conditions can modify associations between environmental contaminant exposures and neurodevelopment.²³ For example, poverty, maternal material hardship, and poor diet have been shown to heighten the toxic effects of air pollutants and other chemical exposures on cognitive functioning of children.^{24–30} The cumulative impacts of exposures to these chemicals and social inequities present dangers not only for today's children but also for future generations.

Despite growing concerns about cumulative environmental health risks/impacts and the relationship with health disparities, to our knowledge only three previous reviews have examined how neurodevelopmental outcomes in children are impacted by exposures to environmental contaminants and social disadvantage. In a 2016 systematic review, Appleton et al. examined the interplay between environmental and social stressor exposures in relation to several commonly assessed childhood health outcomes, including cognition and behavior.³⁰ The researchers found evidence supporting the conclusion that social and environmental risks operate jointly to affect child health. In addition, they observed that air pollution (AP) was the most commonly studied environmental exposure, whereas socioeconomic status (SES) was the most commonly studied social exposure.³⁰ In a 2016 review, Ruiz et al.³¹ identified a wide range of social and environmental exposures associated with children's cognitive health. In 2019, Barrett and Padula reported on epidemiological literature (published since 2015) regarding joint impact of chemical and nonchemical stressors on pregnancy and child development outcomes. Although they excluded studies of AP and heavy metals, these authors concluded that stronger associations with adverse health outcomes occur when chemical and nonchemical stressors are combined.³² However, no systematic or scoping reviews have been conducted specifically on children living in the United States to examine both exposure disparities and the joint effects of combined exposures of environmental neurotoxins and social disadvantage as they relate to disparities in neurodevelopmental outcomes.

Targeting Environmental Neuro-Development Risks (Project TENDR) is an alliance of >50 leading scientists, health professionals, and advocates focused on preventing exposures of children and pregnant women to toxic substances that are harmful to brain development and eliminating disproportionate exposures among children of color and children from low-income families.²² To achieve these goals, Project TENDR combines scientific evidence with advocacy to inform and empower decision-makers to create policies that ensure no child is exposed to chemicals that are toxic to the developing brain. Project TENDR formed a Health Disparities Workgroup that included 13 experts from academic, governmental, and nonprofit advocacy organizations to conduct a scoping review of the scientific literature regarding social disparities in neurodevelopmental health outcomes for children living in the United States in relation to seven exemplar neurotoxic chemicals and pollutants: combustion-related AP, lead (Pb), mercury (Hg), organophosphate pesticides (OPs), phthalates (Phth), polybrominated diphenyl ethers (PBDEs), and polychlorinated biphenyls (PCBs).^{22,33,34}

To carry out this review, we adapted the Healthy People 2020 definition of health disparity as “a particular type of health difference that is explicitly linked with social, economic, or environmental disadvantage.”³⁵ Thus we defined [neurodevelopmental] health disparities as health differences that are avoidable, unnecessary, unfair, and unjust,³⁶ impacting population groups that have

been historically economically/socially marginalized or made vulnerable.³⁷ As articulated by Ward et al., meaningful assessment of disparities in health should include examination of the distribution of the outcomes and exposures across racial/ethnic minority groups as “critical companions to assessment of interaction and stratum-specific effects.”³⁸ In addition, to better address health disparities, it is also important to understand how social differences are conceptualized and measured in epidemiological studies. For example, scholars have noted that race is notoriously poorly measured.^{39–41} In recent years there have been renewed calls for environmental epidemiological (and epidemiology in general) research to rigorously report and measure race/ethnicity, and by extension other constructs of difference, as is typically done for reporting environmental exposure measurement.^{42–44} Thus, our scoping review on neurodevelopmental outcome disparities related to environmental exposures aimed to address the following questions:

1. What proportion of studies provide a conceptualization (i.e., definition) of race/ethnicity and other indicators of sociodemographic and socioeconomic disadvantage?
2. How are race/ethnicity, sociodemographic, and socioeconomic disadvantage data operationalized (i.e., measured and coded)?
3. Do the studies present data on exposure and outcome disparities by race/ethnicity and other indicators of sociodemographic and socioeconomic disadvantage, and what are the patterns of those disparities?
4. Did included studies investigate effect modification by or interaction with race/ethnicity and other indicators of sociodemographic and socioeconomic disadvantage?

Methods

This review follows guidance for undertaking scoping reviews,^{45–48} and reports findings based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist.⁴⁹ “Scoping reviews seek to develop a comprehensive overview of the evidence rather than a quantitative or qualitative synthesis of data”⁴⁸ and have been used in a variety of fields, including finance, health care service delivery, and occupational health. Thus, scoping reviews help to identify gaps in the literature, which fits with Project TENDR's mission to encourage the scientific community to work in collaboration with impacted communities and populations to build a more complete picture of the challenges and possible solutions for disparities in exposures and neurodevelopmental outcomes. We used this approach to broadly map, report, and discuss key concepts from a wide array of studies on disparities in neurodevelopmental health outcomes resulting from exposures to the seven exemplar neurotoxic chemicals and pollutants.

Inclusion/Exclusion Criteria

To inform our inclusion/exclusion criteria and search strategy, we used the Population, Exposure, Comparator, Outcome (PECO) framework (Table S1) and the following question: Are 0- to 18-year-old children living in the United States who are members of population groups that have been historically economically/socially marginalized (i.e., P) and who are exposed (pre- and/or postnatally) to the seven exemplar environmental neurotoxins (AP, Pb, Hg, OP, Phth, PBDE, and PCB) (i.e., E) at greater risk of neurodevelopmental disability or delay when compared with children who are not exposed to the neurotoxins or social disadvantage (i.e., C)? Studies were considered eligible if they were published in English; conducted in the United States and its territories only; involved 0- to 18-y-old children and adolescents and/or pregnant women exposed to one or more of the seven

exemplar neurotoxicants; and included explicit group comparisons by indicators of social disadvantage (e.g., low vs. high SES) or focused on populations of special interest for health disparities (e.g., racial and ethnic minority populations). No restriction was placed on publication year. During the initial screen for eligibility, we included all studies with PEC components regardless of outcome. Articles identifying neurodevelopmental outcomes were tagged after PEC screening. We decided to take this approach to ensure we would not miss any relevant study based on how the health outcome was described or named by authors. Neurodevelopmental outcomes cover a variety of outcomes and can be assessed by a wide array of protocols. Comprehensiveness of the results was assessed by checking against articles identified through other means (e.g., checking against studies included in the prior review articles cited above) to ensure inclusion of the majority of *a priori* known publications. Our initial and final inclusion and exclusion criteria are detailed in Table S2. Our process for finalizing our criteria is explained below.

Information Sources

Public health librarian (N.T.) and graduate assistant (K. Hirabayashi) searched four databases. Dates for the literature searches were from inception of the databases—PubMed, CINAHL Plus (EBSCO), GreenFILE (EBSCO), and Web of Science—through 18 November 2022.

Search Strategy

Search terms were identified from the authors' prior knowledge, in relevant articles found from preliminary searches, and in published similar systematic reviews. In addition, keywords, synonyms, and controlled vocabulary terms representing the PECO components were combined using the Boolean operators AND, OR, and NOT. Searches were refined to ensure inclusion of the majority of articles from previous reviews. Additional hedges and filters were employed to exclude non-English studies, studies conducted outside of the United States, animal studies, and non-observational studies. The search strategies for all databases searched are available in Table S3.

Selection of Sources of Evidence

Records from databases were imported into CADIMA (<https://www.cadima.info/>), a free web tool that allows for an automated duplicate removal and blinded review of records by several reviewers. Authors D.C.P.S. and K.E. and graduate assistant K. Hirabayashi conducted consistency checks reviewing titles and abstracts on 5% of the studies in CADIMA to assess interrater reliability and refine study inclusion and exclusion criteria. Reviewers were required to attain at least 80% agreement. As a result of the consistency checks, we added more detailed descriptions for the criteria under each of the PECO components. For example, in addition to screening for studies of “*in utero* development,” we included studies “on pregnant women” and excluded studies that did not make specific reference to our target population (e.g., children, adolescents, *in utero* development, pregnant women). Our finalized inclusion and exclusion criteria are also detailed in Table S2. After updating inclusion/exclusion criteria, one reviewer (K. Hirabayashi) used the inclusion and exclusion criteria to perform the preliminary screening of all titles and abstracts. The other two reviewers (K.E. and D.C.P.S.) each independently rated 12% of the titles and abstracts.

Three reviewers (D.C.P.S., K.E., and graduate assistant K. Hirabayashi) conducted full-text screening. All discrepancies were identified and resolved through discussion and consensus among the three reviewers. Studies found to be of the wrong study type, population, exposure, comparator, and/or outcomes

were removed. Studies included after full-text screening were categorized based on the PECO components. Studies examining neurodevelopmental outcomes were identified and tagged by outcome subcategory (birth defects; other relevant physical outcomes measured at birth; cognitive, behavioral/psychological, motor or sensory outcomes⁵⁰; or other neurological outcomes), population, exposure, and comparator terms.

Data Extraction

For the included studies, we extracted basic information regarding study design (case-control; ecologic; longitudinal; cross-sectional), location (U.S. state), sample size, age of study subjects (infancy: neonatal to 12 months; early: 1–6 y old; mid: 6–12 y old; adolescence: 12–18 y old), exposure assessment method (direct exposure, such as biomonitoring, or indirect exposure, such as ambient environmental measurements), neurodevelopmental outcome (as defined above), covariates, main disparity comparator employed (e.g., race; ethnicity; socioeconomic indicator; geography), description of primary results, and evidence of effect modification or interaction, if conducted. In addition, we noted for each article if authors provided a working definition of the comparator terms (yes/no; if yes, verbatim definitions were recorded) to examine whether study authors had an *a priori* conceptualization of race/ethnicity and other sociodemographic and socioeconomic variables used and how these comparator terms were coded following the approach by Martinez et al.⁵¹ and according to Conway et al.⁵² We developed a set of measurement definitions for each social comparator (Table S4) and extracted this information from the articles. All extracted information was exported into Microsoft Excel and subsequently visualized using Tableau Desktop Professional Edition (version 2021.4.3; Tableau).

Disparity Assessment

Following the recommendations by Ward et al.,³⁸ we examined whether the studies reported disparities in exposure and outcomes, as well as evidence for effect modification or interaction by race/ethnicity and other indicators of social disadvantage. Among studies that assessed heterogeneity in effects by these comparators, we documented whether the investigators reported either *a*) stratum-specific estimates (yes/no effect modification), or *b*) the interaction term between exposure and the comparator (yes/no interaction), scale used (additive, multiplicative, or not reported) and whether authors conducted a formal statistical test for heterogeneity, like a Cochran's *Q* (yes/no). When reporting on race and ethnicity, we maintained the terminology used by the authors of the studies. In addition, we relied on the authors' statements/conclusions about evidence of associations between the exposures and neurodevelopmental outcomes (effect sizes and statistical significance). We did not conduct a meta-analysis of quantitative results or risk bias because of the heterogeneity of study designs, exposures, and outcomes assessed.

Community Stakeholder Engagement

During the early stages of our scoping review, Project TENDR Health Disparities Workgroup members conducted a workshop with 16 community and environmental justice leaders in December 2020 and January 2021. The purpose was to identify possible areas of collaboration and opportunities for Project TENDR to support the work of the environmental justice organizations. One recommendation from the stakeholders regarding the scoping review was that we not just focus on the seven exemplar pollutants individually but also highlight studies that address concurrent exposures to multiple chemicals or pollutants. Information on cumulative risks/impacts is of high interest to impacted communities. In response to

this guidance, we created an eighth category for studies examining the effects of multi-neurotoxicant exposures.

Results

After screening over 14,000 titles and abstracts and 1,728 full-texts, 212 individual articles met our criteria for inclusion in the review, including one piece of gray literature, resulting in 218 studies or investigations (several articles reported separate analyses of different pollutants). The complete process of selecting relevant papers for this scoping review is provided in [Figure 1](#) (PRISMA figure). Information on these articles can be found in Excel Tables S1–S9.

Overview of Study Characteristics

Publication dates ranged from 1974 to 2022, with studies of Pb exposure having the longest history (Table S5). Fifty-seven percent of all articles (120 of 212 articles) were published between 2010 and 2019. We mapped study locations by state (Figure S1), and several regions of the United States were not represented. The most frequently analyzed data sets (Table S6) included the Columbia Center for Children’s Environmental Health (CCCEH) cohort; the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort; the Mount Sinai Children’s Environmental Health Study; the Cincinnati Lead Study (CLS); the National Health and Nutrition Examination Survey (NHANES); and the Childhood Autism Risks from Genetics and the Environment (CHARGE) study. Among the

seven exemplar neurotoxicants, the most frequently studied exposures were Pb (63 of 218 studies or 28%) and ambient AP (52 of 218 or 24%), followed by OPs (41 of 218 or 19%), Phth (12 of 218 or 6%), PCBs (7 of 218 or 3%), Hg (6 of 218 or 3%), and PBDEs (3 of 218 or 1%), with exposures to chemical mixtures or concurrent exposures to multiple contaminants examined in 17 studies (of 218 or 8%) ([Figure 2](#)).

The most frequently identified neurodevelopmental outcomes were cognitive and behavioral/psychological (203 of 218 or 93%) using a wide variety of assessment protocols and measures (Table S7). Thirty-two studies of 218 or 15% evaluated motor, sensory, and other neurological outcomes, whereas 12 (or 6%) examined outcomes at birth, including head circumference and birth anomalies. Most of the studies were longitudinal analyses (135 of 218 or 62%) and examined effects during early childhood (0–6 years of age) (78 of 218 or 36%). A majority of studies reported adverse neurodevelopmental outcomes associated with exposures to the exemplar pollutants/environmental contaminants (203 of 218 or 93%). Articles often examined multiple pollutants and types of outcomes, and thus counts are not mutually exclusive.

Conceptualization and Operationalization of Race/Ethnicity and Other Indicators of Sociodemographic and Socioeconomic Disadvantage

Study authors used a variety of comparator variables in their analyses, either as covariates, confounders, effect modifiers, or for interaction terms. These comparators included race, ethnicity,

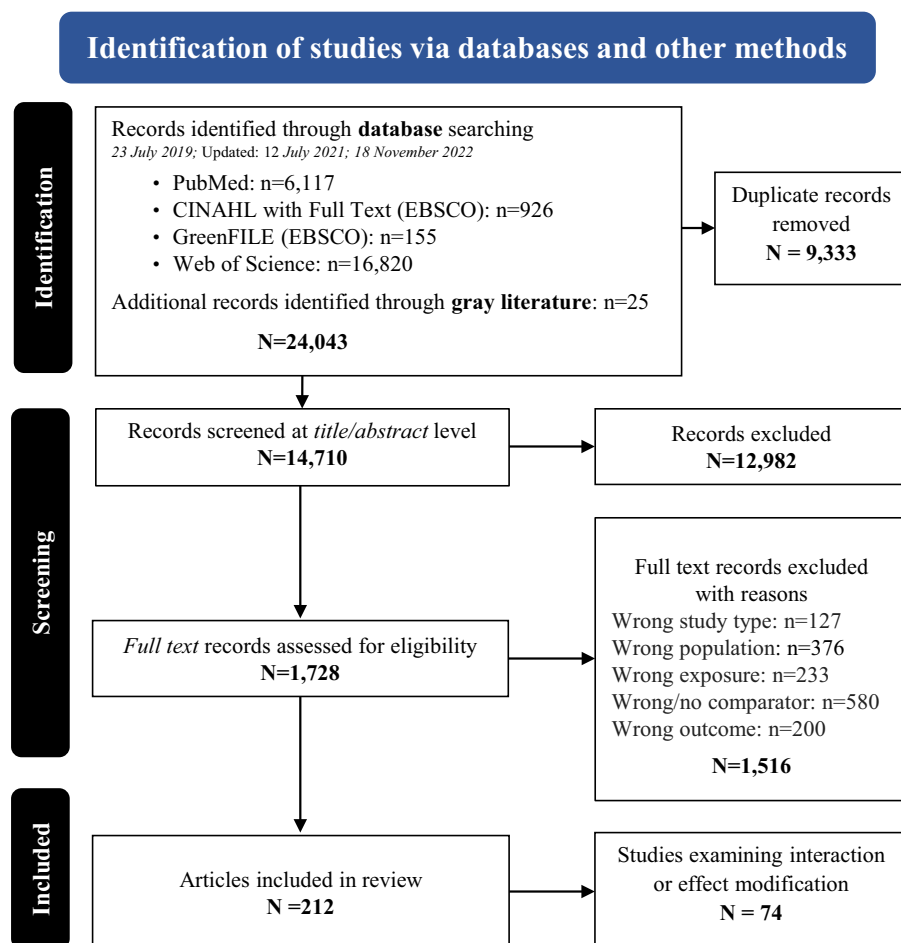


Figure 1. PRISMA flowchart of study inclusion (included articles: $n = 212$). Note: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

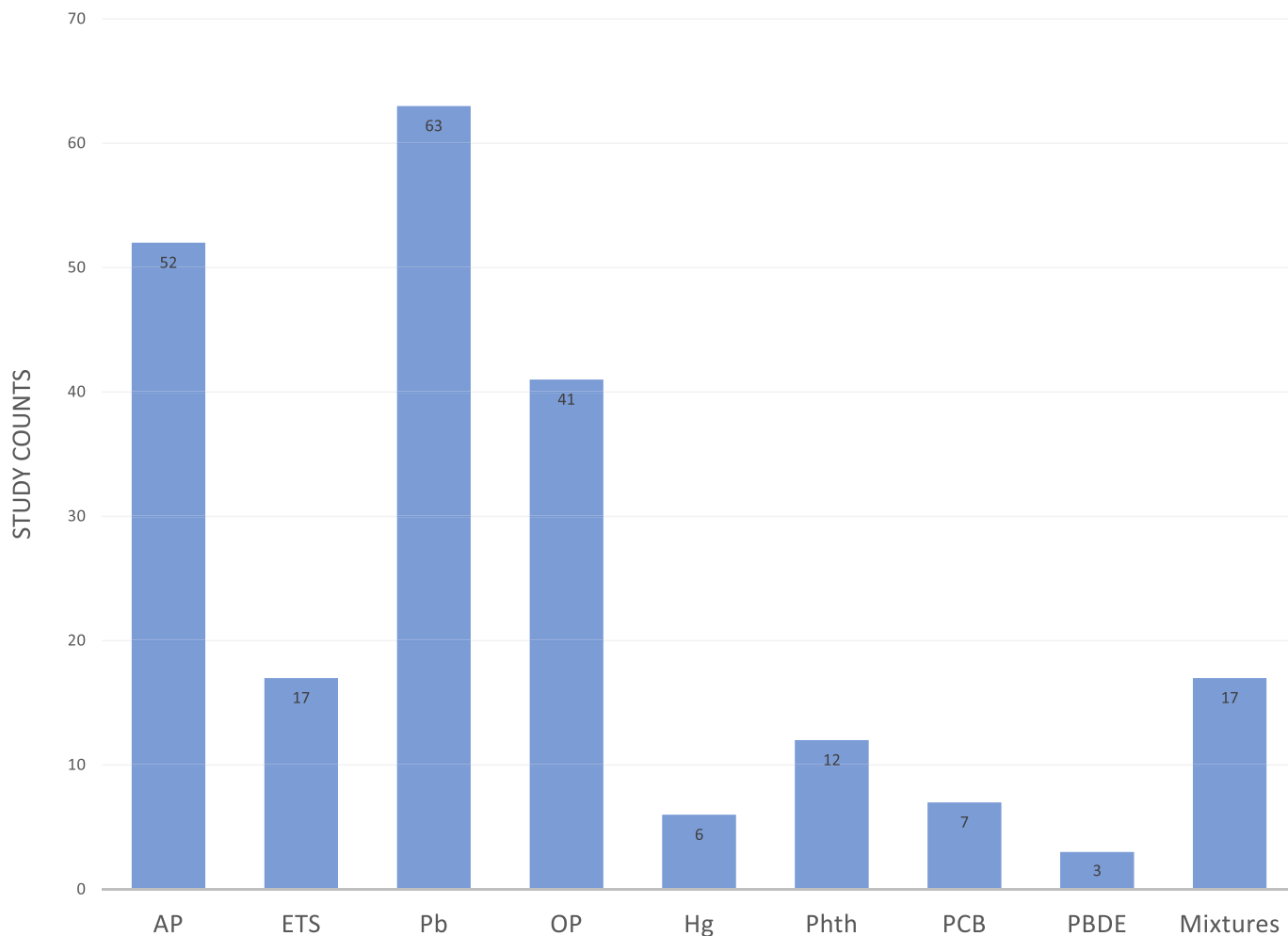


Figure 2. Frequencies of TENDR exemplar contaminants examined by the studies. Some studies are counted more than once if they examined multiple exemplar neurotoxicants separately. Note: AP, air pollution; ETS, environmental tobacco smoke; Hg, mercury; mixtures, chemical mixtures; OP, organophosphate pesticides; Pb, lead; PBDE, polybrominated diphenyl ethers; PCB, polychlorinated biphenyls; Phth, phthalates; TENDR, Targeting Environmental Neuro-Development Risks.

geography, SES, social adversity indices, language, and Home Observation for Measurement of the Environment (HOME) Inventory^{53,54} scores. One or more SES variable was used in every study. As shown in Figure 3 (and in Excel Table S10), the proportion of articles with participants' race designated was somewhat constant, between 1970 and 2009, at ~72% on average per decade (of an average of 18 articles per decade), then reached a peak of 85% (99 of 117 articles) during the period 2010–2019 before declining. Conversely, the use of ethnicity increased from 33% (1 of 3 articles) in the 1970s to a peak of 81% (95 of 117 articles) in the 2010s (similar to race) and then decreased recently (Figure 3). Meanwhile the use of social adversity indices and a language proficiency variable both increased from zero articles in the 1970s to 32% and 21%, respectively, of the 28 articles published recently (period of 2020–2023). Use of HOME scores peaked within the decade the measure was first published by the developers, Bradley and Caldwell, in the late 1980s.

Among the 165 articles that included race and/or ethnicity variables, a majority (151 of 165 articles or 92%) did not provide a definition or a conceptualization. Among the few that did, the reasons varied from “because other studies included race”⁵⁵ and race “as a distinct human type based on inherited physical characteristics”⁵⁶ to race as culture with influence on diet⁴⁹ and “behaviors and patterns of consumption.”⁵⁷ Race and ethnicity were sometimes conflated and together considered as indicators of culture.^{58–60} One

article explicitly considered race as a proxy for institutional racism and psychosocial stress⁶¹ and another stated that race was a marker for “diminished life chances.”⁶² SES variables were used in 100% of articles, yet only 4 of 212 articles or 2% defined constructs for SES as material hardship, economic stress, or household deprivation known to affect child development and well-being.^{63–66} Among the articles that used the predefined HOME index, two studies offered their own conceptualizations, inferring that low HOME scores denoted “less optimal parental intellectual stimulation”⁶⁷ or “[low] quality of intellectual stimulation provided by the mother.”⁶⁸

We captured the operationalization of the social comparator variables by tracking how authors measured these variables and their coding schemes for race and ethnicity. As shown in Table S8, similar proportions of publications did not provide details on how race (43% or 71 of 165 publications that used a race variable) or ethnicity (47% or 63 of 135 articles that included ethnicity) were ascertained (“unclear or not stated”) as the proportion stating that self-classification—assessment through a closed-ended question such as census questionnaire, birth records (although these might be completed by a third party)—was used (45% for race and 47% for ethnicity). SES was measured in a variety of ways (income, parental education, poverty status, insurance) at the individual, family, and area level. Papers often used more than one SES variable in their analyses. Measurement of SES variables was less likely to be

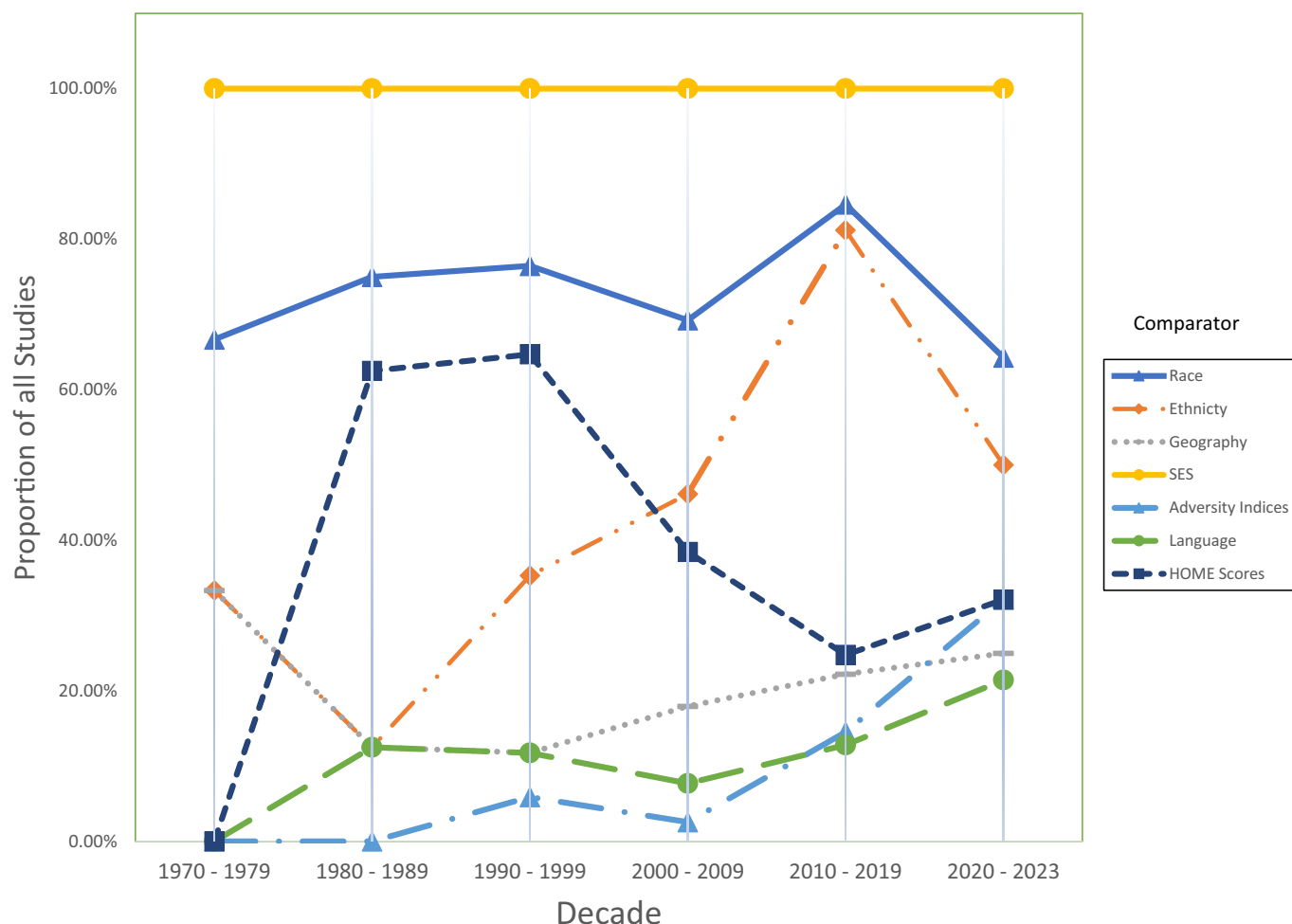


Figure 3. Proportion of studies that included social comparators by decade. Data for the graph can be found in Excel Table S10. Number of publications per decade = 3, 8, 17, 39, 117, and 28 for 1970–1979; 1980–1989; 1990–1999; 2000–2009; 2010–2019; and 2020–2023, respectively. Note: SES, socioeconomic status.

“unclear or not stated” as compared with race and ethnicity variables. Use of the other three comparator variables (HOME scores, adversity indices, and language) always had details on how they were measured.

We identified 179 coding schemes and nearly 29% were strictly racial, whereas the most frequently observed ethnic coding was Hispanic/Latino (Table 1). However, vastly more articles used ethnoracial coding schemes (110 of 179 coding schemes or 62%)—meaning combined or conflated racial and ethnic data—such as “Black, Hispanic/Latino, White, and other” or “Black, Dominican.” Recent articles were more likely to include Asian and Native American populations than articles published in the earlier decades. In addition, more recent articles (data not shown) were more likely to distinguish between Black and White non-Hispanic and Hispanic study participants and to include coding for participants who identified as more than one race. But these observations represent a small proportion of the coding schemes from the articles in this review. This suggests that certain population groups and communities may be understudied for harms associated with neurotoxicant exposures.

Exposure and Outcome Disparities

Thirty-nine percent of studies (84 of 218 studies) provided data on the distribution of pollutant exposure and 41% (90 of 218 studies) provided data on the health outcome disparity at baseline

(Table S9). Among studies that presented exposures by sociodemographic and socioeconomic comparators, greater Pb exposures were found among low-income and Black children^{64,69–78}; higher ambient AP was found in predominantly non-White and low-income communities^{56,79–88}; children in households with lower incomes, or of mothers who were non-White or with less than a high school education were more likely to have significantly higher PBDE levels^{57,89}; Phth metabolite concentrations were higher among non-White mothers^{61,90,91}; and Black and Hispanic children were exposed to higher levels of OPs.^{57,92–97}

Evidence of Effect Modification and/or Interaction

Seventy-four of 218 studies (or 34%) included evaluations of effect modification or interactions between the exemplar pollutants and sociodemographic or socioeconomic comparators (Tables 2–8). Fifty-three of the 74 studies (or 72%) reported heterogeneity in the effects. However only 18 studies of these 53 studies (or 34%) used formal tests of heterogeneity (e.g., Wald test, chi-square, Cochran’s *Q* or conducted regression analysis using interaction terms). Among the 43 studies that conducted assessment for interaction, only 5 presented results with scale (mostly multiplicative). For Pb exposures, significantly more studies examined interaction compared with effect modification (stratified analyses). This is distinct from the ambient AP and OP studies, which overwhelmingly examined effect modification

Table 1. Most common racial, ethnic, and ethnoracial coding schemes, 1974–2022.

Coding scheme (total publications with racial/ethnic coding, <i>N</i> = 179)	<i>n</i>	Percentage of total (%)
Racial	51	28.5
African American/Black	11	6.1
Black, White	17	9.5
Black, White, other	7	3.9
Ethnic	18	10.1
Hispanic/Latino	14	7.8
Ethnoracial	110	61.5
Black, Dominican	18	10.1
Black, Hispanic/Latino, other, White	15	8.4
Black, Hispanic/Latino, White	11	6.1
Hispanic-Latino, non-Hispanic black, non-Hispanic white, other	8	4.5

Note: Coding schemes that represent >3% of all coding schemes.

instead of interaction using regression and cross-product terms. Cognitive outcomes were the most frequently assessed outcomes for interaction or effect modification (47 studies) followed by behavioral/psychological (34 studies), birth anomalies (5 studies), motor (4 studies), and other physical outcome (1 study). SES was the most frequently used strata/comparator for effect modification or interaction (46 studies or 62%) followed by race (27 studies or 37%), ethnicity (16 studies or 22%), adversity indices (12 studies or 16%), geography (5 studies or 7%), HOME scores (3 studies or 4%), and language (3 studies or 4%). Many articles used more than one comparator/strata for effect modification or interaction analysis. A majority of studies that found heterogeneity by SES–income strata reported stronger associations between exposure and outcome for lower SES groups (25 of 31 studies, or 81%). For example, McGuinn et al. observed “suggestive evidence of a stronger association between PM_{2.5} (fine particulate matter; PM ≤ 2.5 μ m in aerodynamic diameter) exposure in the first year of life and autism spectrum disorder (ASD) for those living in more deprived neighborhoods.”¹⁰⁵ Some authors reported statistically significant heterogeneity among strata without explicitly noting which groups had higher vs. lower associations, and a few papers reported trends that were inconsistent with expected outcomes (e.g., “Besides differing from most other Pb study samples in terms of the prevalence of socioeconomically advantaged families, our sample also does not reflect, in the period between birth and 24 months, the inverse association usually noted between children’s Pb exposure and social class”¹¹⁸).

A majority of papers that used interaction or effect modification to examine race found heterogeneity by racial group (19 of 27 studies or 70%). Twelve of these 19 studies or 63% reported stronger associations between exposure and outcome for racially minoritized groups. For example, Evens et al. noted “[these] models also indicated significant interaction between race/ethnicity and blood Pb for non-Hispanic black children compared with non-Hispanic white children.”⁷⁰ Similar to analyses using SES, some authors reported statistically significant heterogeneity among strata without explicitly noting which groups had higher vs. lower associations, and a few papers reported trends that were inconsistent with expected outcomes (e.g., “Control of race by stratification demonstrated a lead effect within both black and white strata, and disclosed an increased effect size for lead in white subjects.”¹³⁰) There were other unexpected results where the direction of enhanced effects was reported among higher-income or White mothers.⁶¹ Some scholars have advanced the idea of “saturation”¹⁴⁹ among minority populations to explain such unexpected results. But as far as we can tell, this theory has not been rigorously tested, and, given the poor treatment of the race variable by epidemiology generally, we are not yet convinced.

Data Visualization

Characteristics and findings from the articles included in this scoping review are also available in an interactive format using Tableau. See https://public.tableau.com/app/profile/project.tendr/viz/HealthDisparitiesScopingReview/heatmap_dash?publish=yes and description in Figure S2. We created a data visualization tool to supplement the manuscript, allowing readers to interact with and quickly find articles included in the scoping review that align with their questions, interests, and areas of expertise. The Tableau tool provides links to all of the included articles in the scoping review. The data in the heat maps, the selectable article links, the exposure–outcome relationship descriptor, and the effect modification/interaction count visualization are automatically filtered by pollutant type using the selection buttons at the top. The counts in the heat map report the number of studies for the combination of outcome and disparity comparator based on any pollutant selections. The heat map cells may also be used to further narrow the exposure–outcome relationship counts, the effect modification and interaction counts, and the article links. Some articles included multiple pollutants, comparators, or outcomes, and so there may be multiple studies within some articles that are reflected in the counts. Links to pollutant-specific Tableau views are provided in each of the pollutant summary sections. All of the data that is reflected in the Tableau tool may be downloaded by clicking on the download icon on the upper righthand side of the tool.

Pollutant-Specific Results

Given the diversity in study design and outcomes measured, we summarize below the findings on neurodevelopmental disparities for each of the seven exemplar neurotoxic pollutants and the studies that addressed multiple pollutant exposures. We follow guidance by Ward et al. and report on group-specific differences in outcome prevalence, and exposure prevalence and whether the relationship between the exposure and outcome differ between groups for each pollutant category, to the extent possible.³⁸ Given that an overview of how studies conceptualized and operationalized comparator terms is provided earlier, we do not address this here under the pollutant-specific results.

Ambient AP. Overview. We found 69 investigations of AP exposures and neurodevelopment, including 52 (or 24% of 218 studies) on outdoor ambient AP and 17 (or 8% of 218 studies) of environmental tobacco smoke exposures (ETS) (Excel Tables S1 and S2 and the AP-specific view in Tableau at https://public.tableau.com/shared/J9K649DDQ?:display_count=n&:origin=viz_share_link). Twenty-six of the ambient air pollution-related articles (or 50%) reported adverse effects^{29,56,81,83–85,87,99,104,107–109,150–162}; 24 (or 46%) reported mixed results,^{26,65,79,82,86,88,98,100–103,105,106,110,112,163–171} and there were 2 (or 4%) with null findings.^{111,172} Traffic exposures were associated with neural tube defects (NTDs)¹⁰⁰ and ASD,¹⁶⁰ early life exposure to PM_{2.5} was associated with intelligence quotient (IQ) loss,⁷⁹ and polycyclic aromatic hydrocarbon (PAH) exposures were associated with lower cognitive test scores²⁹ and with psychiatric symptoms in school-age children.¹⁰⁸ Exposures to ambient PM_{2.5} among children was found to be associated with pediatric psychiatric emergency department (ED) utilization.⁹⁹ ETS exposure was associated with greater neurodevelopmental impairment in 10 studies,^{63,114–116,173–178} with mixed findings in 6 studies,^{24,117,179–182} and null associations observed in 1 study.¹⁸³

Disparities in exposures and outcomes. Twenty-one of the ambient AP studies (or 40% of 52) and 8 of the ETS studies (or 47% of 17) included comparison of exposures by sociodemographic and/or socioeconomic characteristics. Except for 1 study on PM ≤ 10 μ m in aerodynamic diameter (PM₁₀),¹⁰⁷ exposures

Table 2. Summary of ambient air pollution and environmental tobacco smoke studies with investigations for effect modification and interaction (*n* = 29).

Study	Effect modification (EM) or interaction?	Comparator	Description of exposure disparity	Description of outcome disparity at baseline	Assessed additive vs. multiplicative interaction		Formal test for heterogeneity in EM? (Y/N)	Statistical test for heterogeneity in EM (if used)	Description of EM or interaction results
					NA	Y			
Al-Hamdan et al. ⁹⁸	EM	Race, ethnicity	Did not present.	Did not present.	NA		N	NA	The OR of ASD due to the exposure to the unhealthy AQI was higher for Asian children (OR = 2.96; 95% CI: 1.11, 7.88) than that for Hispanic children (OR = 1.308; 95% CI: 0.607, 2.820), and it was higher for Black children (OR = 1.398; 95% CI: 0.827, 2.364) than that for White children (OR = 1.219; 95% CI: 0.760, 1.954). Authors concluded that adverse effects occurred only among Asian children.
Brokamp et al. ⁹⁹	EM	SES	Did not present.	Did not present.	NA		Y	Chi-square test	<i>p</i> -Values for modification of associations between PM _{2.5} and ED visits by community deprivation (high vs. low) were significant for at least 1 lag period for ED visits related to anxiety, adjustment disorder, and suicidality. Associations between a 10-μg ³ increase in PM _{2.5} and psychiatric ED visits were stronger for children living in high- vs. low-deprivation communities for anxiety-related ED visits on the same day and for ED visits related to suicidality on the same day.
Cowell et al. ¹⁰⁰	Both	Adversity Index	Did not present.	Boys with higher exposure to prenatal stress scored an average of 9.5 points lower on the Attention Concentration Index compared with boys with low prenatal BC exposure.	Unclear		N	NA	In adjusted models, we found that among boys with high exposure to prenatal stress, Attention Concentration Index scores were on average 9.5 points lower (95% CI: -18.5, -0.6) for those with high compared with low prenatal BC exposure.
Harris et al. ⁷⁹	EM	SES	Third trimester BC exposures were higher for non-White mothers, those with lower education, and lower household income.	Did not present.	NA		N	NA	In models examining the joint effect of BC, prenatal stress, and sex, we observed a significant 3-way interaction (3-way <i>P</i> _{interaction} = 0.04) between these variables for the Attention Concentration Index.
Lett et al. ⁸¹	EM	HOME	Children with high isophorone exposure were more likely to be Black or Hispanic, to have a language other than English as their primary language, have a lower SES, or residence in disadvantaged neighborhoods.	Children with lower HOME scores had math scores that were 1.20 points lower than children with better HOME scores.	NA		Y	Wald test	Impact of exposure to AP on cognitive outcomes was not found to be modified by household income (data were not shown). The potential for effect measure modification between the two exposures was investigated by adding an interaction term between isophorone exposure and HOME scores to the unadjusted and adjusted models. There were ~ 350 children (8.3%) who were exposed to both high isophorone concentrations and low-quality home learning environments. Our results suggest they experienced a decrement in math scale score beyond the additive effect of both exposures, although this effect was not statistically significant in our analysis.
Lofthus et al. ¹⁰¹	EM	Race, SES	Mothers with higher exposure to NO ₂ and busy road proximity were more likely to be African American, experience sociodemographic disadvantage, and use Medicaid insurance.	Did not present.	NA		Y	Wald test	Associations between PM ₁₀ and FSIQ were stronger among children whose mothers had lower plasma folate, and the test of interaction by quartiles of maternal folate was borderline significant. For the lowest folate quartile, FSIQ decreased 6.8 points per 5-unit increase in PM ₁₀ , over twice the magnitude of effect in the overall population. No association between PM ₁₀ and FSIQ was observed for those in the highest quartiles of folate exposure.

Table 2. (Continued.)

Study	Effect modification (EM) or interaction?	Comparator	Description of exposure disparity	Description of outcome disparity at baseline	Assessed additive vs. multiplicative interaction	Formal test for heterogeneity in EM? (Y/N)	Statistical test for heterogeneity in EM (if used)	Description of EM or interaction results
Lofthus et al. ¹⁰²	EM	Race, SES	Mothers with higher exposure were more likely African American, had lower levels of educational attainment, were less likely covered by private insurance, had lower reported incomes at enrollment and lived in census tracts with lower educational and social and economic opportunity scores.	Did not present.	NA	Y	Wald test	Associations between prenatal NO ₂ and externalizing behavior were stronger for those with Medicaid or no insurance at baseline compared with those with private insurance [12% increase (95% CI: 1%, 24%) vs. 1% increase (95% CI: -10%, 13%); $p_{\text{interaction}} = 0.09$]. Higher PM ₁₀ was associated with more externalizing behavioral problems in children from lower-income families but not those with higher incomes [11% increase (95% CI: 0%, 25%) vs. 10% decrease (95% CI: -1%, 19%) per 2 g/m ³ , $p_{\text{interaction}} = 0.01$].
Lovasi et al. ²⁹	EM	SES, language	Did not present.	Neighborhood limited English language proficiency was associated with lower WPPSI-R total, verbal, and PIQ scores. Low neighborhood-level educational attainment was associated with lower PIQ scores.	NA	Y	Wald test	In models examining effect modification, neighborhood associations were similar or diminished among the high PAH exposure group, as compared with the low PAH exposure group. Several of the associations between neighborhood characteristics and cognitive test scores were stronger within the low PAH exposure stratum. Neighborhood percentage low English proficiency was more strongly associated with worse WPPSI-R scores at 5 years of age among the low PAH exposure group than the high PAH exposure group. For example, low PAH total score: -3.23 (95% CI: -4.77, -1.69); high PAH total score: -1.69 (95% CI: -2.64, -0.73).
Lu et al. ¹⁰³	EM	Race, ethnicity, SES	Did not present.	Did not present.	NA	N	NA	The EMM by grades for the associations between test scores and all three pollutants were positive (less harmful at higher grades) except for the association between math and NO ₂ . The EMM by higher proportion of Black students was positive for the association between English language/arts (ELA) test scores and PM _{2.5} , and negative for the association between math and ozone. The EMM by higher proportion of Hispanic/Latino students were positive for the associations between math and all three pollutants.
Margolis et al. ¹⁰⁴	EM	SES	Did not present.	Did not present.	NA	N	NA	The EMMs by SES were negative for all six association pairs, suggesting that the association between AP and test scores were stronger for Geographic School Districts (GSDs) with higher SES. Among individuals with higher prenatal PAH exposure, greater stress was associated significantly with smaller hippocampal subfield volumes; among individuals with lower prenatal PAH exposure, stress and hippocampal subfield volumes were not significantly associated.
McGuinn et al. ¹⁰⁵	Both	SES	PM _{2.5} levels were higher among the highest deprivation group compared with less deprived.	Children with ASD were more likely to be born to non-White, lower-educated mothers.	Both	N	NA	There was suggestive modification by neighborhood deprivation for the association between PM _{2.5} during the first year of life and ASD on the additive (RERI = 0.81; 95% CI: -0.88, 2.47) and multiplicative ($p_{\text{interaction}} = 0.08$) scales when PM _{2.5} was dichotomized at 12.0 µg/m ³ . The association between PM _{2.5} exposure and ASD was strongest in regions of high deprivation (OR = 2.42; 95% CI: 1.20, 4.86) rather than moderate (OR = 1.21; 95% CI: 0.67, 2.17) or low (OR = 1.46; 95% CI: 0.80, 2.65) deprivation neighborhoods.

Table 2. (Continued.)

Study	Effect modification (EM) or interaction?	Comparator	Description of exposure disparity	Description of outcome disparity at baseline	Assessed additive vs. multiplicative interaction	Formal test for heterogeneity in EM? (Y/N)	Statistical test for heterogeneity in EM (if used)	Description of EM or interaction results
Padula et al. ¹⁰⁶	EM	SES	Pollutants were not strongly associated with the neighborhood factors. For instance, the correlations (as determined by Pearson coefficients) between PM ₁₀ and the neighborhood factors ranged from 0.02 (older housing) to 0.17 (home value <\$100,000). Poverty and PM ₁₀ had a correlation of 0.12. Did not present.	Higher rates of anencephaly among children born to mothers with <12 y of education compared with more-educated mothers.	NA	Y	Chi-square test	Increased odds of spina bifida comparing the highest to lowest quartile of PM ₁₀ among those living in a neighborhood with <i>a</i>) median household income of <\$30,000/y (OR = 5.1; 95% CI: 1.7, 15.3); <i>b</i>) >20% living below the federal poverty level (OR = 2.6; 95% CI: 1.1, 6.0); and <i>c</i>) >30% with less than or equal to a high school education (OR = 3.2; 95% CI: 1.4, 7.4).
Padula et al. ¹⁰⁷	EM	Geography, language, SES, Adversity Index	Did not present.	Neural tube disorder cases were slightly more likely to have mothers who were foreign-born, used multivitamins, and were exposed to passive smoke early in pregnancy.	NA	Y	Wald test	Increased odds of NTDs were observed for individuals who had high exposures to CO, NO, or NO ₂ and lived in neighborhoods that were more acculturated. When stratified by individual nativity (U.S.- vs. foreign-born), CO, NO, and NO ₂ were more strongly associated with NTDs among U.S.-born Hispanic mothers.
Pagliaccio et al. ¹⁰⁸	EM	SES	Did not present.	Did not present.	NA	Y	Chi-square test	We detected significant prenatal airborne PAH–postnatal early life stress (ELS) interaction effects that predicted CBCL Attention Problems T-scores and Thought Problems at 11 years of age. Children with higher prenatal PAH exposure showed stronger positive associations between postnatal ELS and CBCL Attention Problems and Thought Problems T-scores. The prenatal PAH–postnatal ELS–time interaction on Child Behavior Checklist (CBCL) Thought Problems T-scores was not significant.
Perera et al. ¹⁰⁹	Interaction	Ethnicity	There were significant differences between high- and low-exposure groups in the distributions of maternal high school degrees. Did not present.	There were significant differences between maternal high school degree and infant's verbal IQ and FSIQ but not PIQ.	Unclear	NA	NA	There were no significant ethnic differences in the relationship between PAH levels and IQ scores (FSIQ: <i>p</i> = 0.36; verbal IQ: <i>p</i> = 0.62; PIQ: <i>p</i> = 0.35).
Perera et al. ⁶⁵	Interaction	SES, Adversity Index	Did not present.	Did not present.	Multiplicative	NA	NA	Although the interactions between high PAH exposure and hardship experienced at either period ("persistent hardship" or "any" hardship) were not significant, we observed significant differences in the number of ADHD symptoms between children with high prenatal PAH exposure and either persistent hardship or any hardship compared with the others. These differences were most significant for combined high PAH and persistent hardship: ADHD Index (<i>p</i> < 0.008), DSM-IV Inattentive (<i>p</i> = 0.006), DSM-IV Hyperactive Impulsive problems (<i>p</i> = 0.033), and DSM-IV Index Total (<i>p</i> = 0.009).
Stingone et al. ⁸³	EM	Race	Children born in areas with high BTEX compounds were more likely to be born to mothers who were Latina. Their mothers were also more likely to have either less than a high school education or more than a college education than mothers of children with lower pollutant exposures.	Did not present.	NA	N	NA	Data were stratified by maternal race and child sex, and analyses were repeated to assess whether associations between BTEX and use of academic services were consistent across levels of these factors.

Table 2. (Continued.)

Study	Effect modification (EM) or interaction?	Comparator	Description of exposure disparity	Description of outcome disparity at baseline	Assessed additive vs. multiplicative interaction	Formal test for heterogeneity in EM? (Y/N)	Statistical test for heterogeneity in EM (if used)	Description of EM or interaction results
Stingone et al. ⁸²	EM	Geography	Examining communities with higher isophorone levels reveals that these communities are more likely to have greater proportions of residents who are Black, non-Hispanic, living in poverty, and renting, as opposed to owning, their housing.	Did not present.	NA	Y	Wald test	Within the full population, among children with exposure to higher levels of trichloroethylene, higher exposure to isophorone was associated with slightly more than a 1-point decrement on the math assessment. A similar magnitude of association was observed between isophorone and math scores in both the urban and highly populated urban populations. Among the children living in areas with lower isophorone levels, lower levels of other pollutants, such as ethyl acrylate and benzyl chloride, were also associated with lower than average math scores. Authors examined the effects of residential proximity to TRI sites on NTD risk by maternal age and race/ethnicity (White vs. Hispanic). Living within 1 mi of a TRI facility carried a slight risk (adjusted OR = 1.2; 95% CI: 1.0–1.5). The effect was highest among mothers ≥ 35 years of age (OR = 2.7; 95% CI: 1.4, 5.0) and among non-Hispanic white mothers (OR = 1.8; 95% CI: 1.1, 2.8).
Suarez et al. ¹¹⁰	EM	Race, ethnicity	Did not present.	IQ varied by race and ethnicity.	NA	Y	Unclear	Significant interactions were observed between high PAH-DNA cord adducts and prenatal hardship on working memory scores ($\beta = -8.07$; 95% CI: -14.48, -1.66) and between high cord adducts and recurrent material hardship ($\beta = -9.82$; 95% CI: -16.22, -3.42).
Vishnevsky et al. ²⁶	Interaction	SES	Did not present.	Reported high vs. low material hardship with IQ test markers.	Unclear	NA	NA	There was no evidence from Weighted Quantile Sum (WQS) regression of PAH mixtures on behavior scores not evidence for effect modification by child sex, breastfeeding, neighborhood social and economic or educational opportunity. Family SES significantly modified the association between PM _{2.5} and PIQ score ($p_{interaction} < 0.01$): 89% stronger in families with low SES ($\beta = -3.83$; 95% CI: -6.98, -0.69) than in families with high SES ($\beta = -2.03$; 95% CI: -6.12, 2.36).
Wallace et al. ¹¹¹	EM	Adversity Index	Did not present.	Did not present.	NA	N	NA	Children with lower levels of self-reported positive parent-to-child affect (PCA), denoting a poorer parent-to-child relationship as compared with their counterpart, had much stronger (3- to 5-fold) adverse PM _{2.5} effects, and most of these differences were statistically significant ($p < 0.05$; Table S7). The adverse PM _{2.5} effect was slightly greater in families with high (vs. low) levels of negative PCA (with a worse parent-child relationship assessed by either children or parents) and also strengthened by parental stress or maternal depressive symptoms.
Wang et al. ⁸⁵	EM	SES	Those with higher PM _{2.5} exposures were mostly Hispanic and Black, from lower SES neighborhoods, lower greenness, more negative perception of neighborhood quality, and perceived more stress.	IQ scores varied by race and ethnicity.	NA	Y	Wald test	For example, 1-yr PM _{2.5} exposure prior to baseline, Low maternal depression $\beta = 0.12$ (95% CI: -0.22, 0.46). High maternal depression $\beta = 0.55$ (95% CI: 0.18, 0.92); $p_{interaction} = 0.07$.
Younan et al. ⁸⁷	Both	Adversity Index	Racial/ethnic minority groups, from households of lower SES, living in urban areas, neighborhoods with unfavorable SES characteristics or perceiving poorer neighborhood quality, had higher levels of ambient PM _{2.5} .	More delinquent behavior was found in African Americans populations, lower SES household, families perceiving poorer neighborhood quality or those living with unfavorable nSES or limited greenspace, higher levels of parental stress, and maternal depressive symptoms.	NA	Y	Wald test	

Table 2. (Continued.)

Study	Effect modification (EM) or interaction?	Comparator	Description of exposure disparity	Description of outcome disparity at baseline	Assessed additive vs. multiplicative interaction	Formal test for heterogeneity in EM? (Y/N)	Statistical test for heterogeneity in EM (if used)	Description of EM or interaction results
Zhang et al. ¹¹²	EM	SES, geography	Did not present.	Did not present.	NA	Y	Following a similar method developed for birth weight (Rosa et al. ¹¹³) authors applied log-linear models to multilevel contingency tables to examine the between-site heterogeneity in the associations among PM _{2.5} exposure, cognition, and select covariates, which were disproportionately distributed among sites.	A complex analysis suggested that the association between prenatal PM _{2.5} exposure and cognitive functioning may have been modified by maternal education and urbanicity by looking at the pooled New York City and northern Virginia sites data.
Bandiera et al. ¹¹⁴	EM	Race, ethnicity	The researchers did not examine prevalence of ETS exposure by race/ethnicity or poverty income ratio, although they refer to "known variations in the prevalence, patterns of use, and outcomes of smoking across sex and race/ethnicity strata."	Did not present.	NA	N	NA	Associations with serum cotinine level were more apparent for boys and for participants of non-Hispanic white race/ethnicity.
Byrd et al. ¹¹⁵	Interaction	SES	Did not present.	Increased risk of grade retention was associated with poverty and low maternal education.	Multiplicative	NA	NA	Children's exposure to tobacco smoke in combination with either deafness or high maternal education is associated with a greater risk than that predicted by the multiplication of the risk associated with each of these two factors, although the main effect of smoking is less when considering these two interactions.
Kabir et al. ¹¹⁶	EM	SES	Children of Black race, non-English language spoken in the home, and whose parents had lower education levels, and higher poverty status had higher exposure to SHS.	Children living in English-speaking households, mothers' with more education had reduced odds of outcomes.	NA	N	NA	Researchers found that children exposed to SHS at home had a 50% increased odds of having ≥ 2 childhood neurobehavioral disorders compared with children who were not exposed to SHS. Boys had a significantly higher risk. Older children, especially those 9–11 years of age, and those living in households with the highest poverty levels were at greater risk. The interaction between ETS and material hardship was tested and found to be significant, such that the adverse impact of prenatal ETS exposure on child development was greater among children whose mothers reported greater material hardship ($p = 0.03$), resulting in a cognitive deficit of ~ 7 points. All tests of interactions with race were nonsignificant.
Rauh et al. ²⁴	EM	SES	ETS exposure did not differ between material hardship groups, and was higher among African American populations and those with lower income.	Total number of material hardships in the postpartum period was significantly associated with 24-month development.	NA	Y	Chi-square test	The interaction between ETS and material hardship was tested and found to be significant, such that the adverse impact of prenatal ETS exposure on child development was greater among children whose mothers reported greater material hardship ($p = 0.03$), resulting in a cognitive deficit of ~ 7 points. All tests of interactions with race were nonsignificant.
Xu et al. ¹¹⁷	Interaction	Race, ethnicity	Blood cotinine varied by race.	Did not present.	Unclear	NA	NA	A significant interaction between race and blood cotinine levels was found after adjustment for all selected covariates (Wald χ^2 13.7; $p < 0.03$).

Note: ADHD, attention deficit and hyperactivity disorder; AP, air pollution; AQI, air quality index; ASD, autism spectrum disorder; BC, black carbon; BTEX, benzene, toluene, ethylbenzene, and xylene; CI, confidence interval; CO, carbon monoxide; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th ed.; ED, emergency department; EMM, effect measure modification; ETS, environmental tobacco smoke exposure; FSIQ, full-scale intelligence quotient; HOME, Home Observation for Measurement of the Environment (Inventory); IQ, intelligence quotient; N, no; NA, not applicable; NO₂, nitrogen dioxide; nSES, neighborhood socioeconomic status; NTDs, neural tube defects; OR, odds ratio; PAH, polycyclic aromatic hydrocarbon; PIQ, Performance IQ; PM_{2.5}, particulate matter ≤ 2.5 μm in aerodynamic diameter; PM₁₀, particulate matter ≤ 10 μm in aerodynamic diameter; RERI, relative excess risk due to interaction; SES, socioeconomic status; SHS, secondhand smoke; TRI, Toxic Release Inventory (sites); WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence; Y, yes.

Table 3. Summary of lead studies with investigations for effect modification and interaction ($n = 22$).

Study	Effect modification (EM) or interaction?	Comparator	Description of exposure disparity	Description of outcome disparity at baseline	Assessed additive vs. multiplicative interaction	Formal test for heterogeneity in EM? (Y/N)	Statistical test for heterogeneity in EM (if used)	Description of EM or interaction results
Amato et al. ⁷⁸	EM	Race, ethnicity	Black and Hispanic children were more likely to have elevated BLLs than non-Hispanic white children.	African American students were approximately three times more likely to be suspended at least once than White students.	NA	Y	Chi-square test	The magnitude of the effect of Hispanic membership on suspension rates increased when Pb exposure was added to the model, with an OR of 0.48 (95% CI: 0.32, 0.74), suggesting that Hispanic students were roughly half as likely as White students to be suspended.
Bellinger et al. ¹¹⁸	Both	SES	Did not present.	Infants in the upper social class group tended to score higher than infants in the lower social class group.	Unclear	N	NA	Effect modification was evident despite adjustments in the regression analyses for several social class correlates. The apparent interaction between Pb and social class differs considerably from the examples of interaction described in epidemiologic textbooks.
Bellinger et al. ¹¹⁹	Interaction	SES	Did not present.	Among children with high PbB, means \pm SEs of Δz scores for Bayley MDI scores from 24 to 57 months of age: -0.37 ± 0.15 for low SES; 0.46 ± 0.12 for high SES.	Unclear	NA	NA	Although the associations between mean change in z-scores for MDI score from the Bayley Scales of Infant Development measured from 24 to 57 months of age and SES appear to depend on initial exposure status (i.e., cord PbB level), interaction terms constructed to assess the differences were not statistically significant. Regression results not presented.
Bravo et al. ¹²⁰	Interaction	Geography	In particular, racial residential segregation has, through the concentration of poverty and poor physical and social environments, resulted in distinctive environments that may underlie racial disparities in health outcomes.	In the United States, there are racial/ethnic disparities in academic performance and educational attainment, evidenced by lower high school and college graduation rates among some racial/ethnic groups, particularly Hispanic and non-Hispanic black (NHB) individuals.	Unclear	NA	NA	There was no evidence of an interactive effect between BLL and neighborhood racial isolation (RI) of the non-Hispanic black population (RINHB) at time of birth for either NHB or non-Hispanic white children. Authors observed evidence of an interaction between BLL and RINHB on reading test scores among NHB children.
Coscia et al. ¹²¹	Interaction	Race, SES	Did not present.	Did not present.	Unclear	NA	NA	The child's race, gender, and family SES were statistically significantly related to scores both as main effects and interaction effects with age.
Dietrich et al. ¹²²	Both	SES	Did not present.	Did not present.	Unclear	Y	Chi-square test	Two key perinatal risk factors appeared to be operative in modifying the effects of fetal exposure to Pb. Infants of lower social class families appeared to be more sensitive to the effects of fetal exposure as indexed by newborn (10 d) blood levels. Multiple regression analyses for infants with scores of less than the median SES score showed that each 1- μ g/dL increase in 10-d BLL was associated with a covariate-adjusted decrement of 0.73 MDI points ($p = 0.03$), or 16.1 MDI points across the range of 10-d PbB observed in the sample.
Dietrich et al. ¹²³	Interaction	SES	Higher prenatal PbB levels were significantly associated with lower maternal IQ scores, whereas higher postnatal PbB levels were significantly associated with lower social class, lower HOME scores and lower maternal IQ.	Did not present.	Unclear	NA	NA	There was a statistically significant Neonatal PbB–Social Class interaction which was retained in the final model. The covariate-adjusted regression coefficient for Neonatal PbB was -0.91 ($p = 0.003$) for children from the poorer families, whereas for children of families of relatively higher socioeconomic standing the adjusted Neonatal PbB regression coefficient was 0.06 ($p = 0.81$).

Table 3. (Continued.)

Study	Effect modification (EM) or interaction?	Comparator	Description of exposure disparity	Description of outcome disparity at baseline	Assessed additive vs. multiplicative interaction	Formal test for heterogeneity in EM? (Y/N)	Statistical test for heterogeneity in EM (if used)	Description of EM or interaction results
Evens et al. ⁷⁰	Both	Race, ethnicity	There were differences in mean PbB concentrations by race/ethnicity and SES.	Differences in proportions for reading and math failure were statistically significant for all characteristics (including race/ethnicity and SES) using chi-square tests.	Unclear	Y	Chi-square test	Interaction terms between BLL and race/ethnicity were added to the model to test for effect modification by race/ethnicity and were found to be significant for Black participants and Hispanic vs. White participants, but not significant for Black participants compared with Hispanic participants. These models also indicated significant interaction between race/ethnicity and BLL for NHB children compared with non-Hispanic white children. The interaction for Hispanic vs. White children was significant for reading, but not math failure.
Greene and Ernhart ⁷¹	Interaction	Race, SES	Pb levels are higher for low maternal IQ and education, lower HOME scores, and Black race.	Did not present.	Multiplicative	NA	NA	The possibility of pairwise interactions between the effect of Pb and each of the selected covariates [including the HOME scores based on preschool form of the inventory (ages 3 and 4–10 years), which were averaged to form a preschool index (PREHOME)] was assessed by individually adding product terms between the square root transformed of lead dentine levels (SPbD) and the respective covariates to the multiple regression of the FSQ. None of these multiplicative interactions approached statistical significance.
Ji et al. ¹²⁴	Both	SES	Did not present.	Did not present.	Unclear	N	NA	High maternal HDL levels and low maternal stress during pregnancy could partially counteract the increased odds of ADHD associated with early life Pb exposure in boys. Compared with girls with low Pb levels and adequate maternal HDL levels, boys with high Pb levels and lower maternal HDL levels had 10-fold increased odds of having any ADHD diagnosis. Among boys, the association was significantly stronger (OR = 2.49; 95% CI: 1.46, 4.26); in girls, the association was largely attenuated (sex–Pb interaction = 0.017).
Kim et al. ⁷³	EM	Geography	BLL concentrations were higher in children 5–8 years of age, African Americans, and children living inside the Lead Investigation Area (LIA) of a former Pb refinery in Omaha, Nebraska.	Did not present.	NA	N	NA	Authors stratified the analysis by residence to examine whether the associations remain both inside and outside of the LIA. Inside the LIA, the 27 cases had BLL GM = 1.89 µg/dL and the 41 controls had BLL GM = 1.51 µg/dL. Outside the LIA, the 44 cases had PbB GM = 1.02 µg/dL, whereas the 17 controls had PbB GM = 0.97 µg/dL.
Lu et al. ¹²⁵	EM	Race	Did not present.	Did not present.	NA	N	NA	An interaction term between this binary variable and water lead levels (WLL) was added to model 3 and the coefficient of this term is tested. The effect measure modification by grade is statistically significant for math (coefficient = $-0.0242 \pm SE$ of 0.0051, $p < 0.01$). For cohorts with <90% of White students, higher WLLs are associated with a larger reduction in standardized math test scores, compared with cohort years with >90% of White students.
Magzamen et al. ⁷⁴	Interaction	Race, SES	Higher BLLs were found in African American children and children with lower parental education.	Compared with White students, students whose parents or guardians designated race or ethnicity as African American/Black scored lower on each section of the examination.	Unclear	NA	NA	Interaction terms were entered into the model for a) race and Pb exposure, b) parent-rated child health and Pb exposure, and c) parent education and Pb exposure. No interaction terms reached statistical significance.

Table 3. (Continued.)

Study	Effect modification (EM) or interaction?	Comparator	Description of exposure disparity	Description of outcome disparity at baseline	Assessed additive vs. multiplicative interaction	Formal test for heterogeneity in EM? (Y/N)	Statistical test for heterogeneity in EM (if used)	Description of EM or interaction results
Magzamen et al. ²⁵	Interaction	Race, SES	Race, parent education, and SES are all significantly related to exposure status. More than two-thirds of the Black children in the sample were classified as Pb exposed, whereas over 75% of the White children had no record of an elevated BLL prior to 3 years of age.	The Wisconsin Knowledge and Concepts Exam (WKCE) scores varied by race/ethnicity and education of parent.	Unclear	NA	NA	Five interactions were tested: race and exposure, gender and exposure, parent education and exposure, enrollment in the federal free/reduced price lunch program (FRLP) and exposure, parent-rated health and exposure. The results showed an interaction of Pb exposure and parent education such that Pb exposure combined with low parental education was strongly associated with reduced reading test scores at lower quantiles, but had little interactive effect on other children. The largest covariate was Black race, which resulted in a mean 24.57 decrease in reading scores (95% CI: 31.38, 17.76) compared with White students.
Marshall et al. ²⁶	Interaction	SES	There were stronger negative associations of living in high-Pb risk census tracts in children from lower- vs. higher-income families.	Did not present.	Unclear	NA	NA	There was a significant family income–Pb risk interaction ($F(2,9.699) = 7.34, p = 0.001$). Specifically, the negative association between Pb risk and cognitive test scores was significant in the low-income group ($p < 0.001$), but not in the mid- or high-income groups ($p \geq 0.127$). No interactions were found between Pb and any other variable.
Mendelsohn et al. ¹²⁷	Interaction	SES	Did not present.	Did not present.	Unclear	NA	NA	No interactions were found between Pb and any other variable in predicting the dependent variable in multiple regression analyses.
Mendelsohn et al. ¹²⁸	Interaction	Race, ethnicity, SES, language, HOME	Did not present.	Did not present.	Unclear	NA	NA	No interactions were found between Pb and any other variable in predicting the dependent variable in multiple regression analyses.
Min et al. ⁷⁶	Interaction	Race, ethnicity	Higher Pb level was related to greater maternal parity, and lower HOME scores, and African American race.	Did not present.	Unclear	NA	NA	No interaction effects were found between the BLL and race, gender, prenatal alcohol, tobacco, marijuana, or cocaine exposure measures, or birth parameters (gestational age, birth weight or head circumference).
Miranda et al. ¹²⁹	Interaction	SES	Did not present.	Differences in 4th-grade average reading end of grade testing scores by Black/White race.	Unclear	NA	NA	We tested for interaction between BLLs and parental education or enrollment status in the free and reduced lunch program, but no significant interactions were found. We also tested for interaction between Pb exposure and the age indicators, and again, the results were not significant.
Needleman et al. ¹³⁰	Interaction	Race, SES, Adversity Index	White delinquents had higher bone Pb levels than African American delinquents, BLL highest in children involved in the criminal justice system.	Did not present.	Unclear	NA	NA	Two interaction terms were created on the basis of exploratory analyses employing variables in pairs. They were Pb–race and Pb–single parent. Adjusted delinquents were four times more likely to have bone Pb concentrations > 25 ppm than controls (OR = 4.0; 95% CI: 1.4, 11.1). A trend toward significance was found for the PbB–SES interaction for Learning/IQ ($p < 0.07$).
Ris et al. ¹³¹	Interaction	SES	Did not present.	Observed trend toward a significant interaction between Learning/IQ and SES.	Unclear	NA	NA	Multiplicative interactions between Pb and sex, and Pb and race were estimated across all equations. No significant interactions were detected.
Wright et al. ¹³²	Interaction	Race, ethnicity	Did not present.	Did not present.	Multiplicative	NA	NA	Multiplicative interactions between Pb and sex, and Pb and race were estimated across all equations. No significant interactions were detected.

Note: ADHD, attention deficit and hyperactivity disorder; BLL, blood lead level; CI, confidence interval; FSQ, full-scale IQ; GM, geometric mean; HDL, high-density lipoprotein; HOME, Home Observation for Measurement of the Environment (Inventory); IQ, intelligence quotient; MDI, Mental Development Index; N, no; NA, no applicable; NHB, non-Hispanic black; OR, odds ratio; Pb, lead; PbB, blood lead; SE, standard error; SES, socioeconomic status; Y, yes.

Table 4. Summary of mercury studies with investigations for effect modification and interaction (*n* = 2).

Study	Effect modification (EM) or interaction?	Comparator	Description of exposure disparity	Description of outcome disparity at baseline	Assessed additive vs. multiplicative interaction	Formal test for heterogeneity in EM? (Y/N)	Statistical test for heterogeneity in EM (if used)	Description of EM or interaction results
Brender et al. ¹³³	EM	SES	Did not present.	Case-women (women with children born with neural tube disorder) were poorer and less educated and more likely to have conceived in Mexico than control-women.	NA	N	NA	Authors reported they observed a strong association between urinary Hg levels and NTD risk among the highest socioeconomic group in the study. Among women with household incomes >\$25,000/y, case-women were nine times more likely than control-women to have a urinary Hg of ≥ 5.62 $\mu\text{g/L}$ the NHANES 95th percentile (95% CI: 1.4, 57); the ORs in the lower-income groups were close to unity, with an OR of 1.1 among women with a household income of <\$10,001 and an OR of 1.2 among women with a household income of between \$15,000 and \$25,000. CIs were not reported for these other income strata.
Orenstein et al. ¹³⁴	EM	SES	Did not present.	Non-Hispanic white children scored higher on the WRAML than children of other races or ethnicities.	Unclear	NA	NA	No significant interactions with the sociodemographic variables (maternal IQ, prenatal smoking, parental education, household income, breastfeeding) were observed with PCBs. Quantitative results were not presented.

Note: CI, confidence interval; Hg, mercury; IQ, intelligence quotient; N, no; NA, not applicable; NHANES, National Health and Nutrition Examination Survey; NTDs, neural tube defects; OR, odds ratio; PCBs, polychlorinated biphenyls; SES, socioeconomic status; WRAML, Wide Range Assessment of Memory and Learning; Y, yes.

were higher in study populations identified as low-income and predominantly racial and ethnic minority populations^{56,79–88}. For example, in Mohai et al., 44.4% of White schoolchildren in Michigan attended schools located in the highest 10th decile AP category, in comparison with 81.5% of African American and 62.1% of Hispanic schoolchildren.⁵⁶ Disparities in prenatal and child ETS exposure^{24,63,116,176,183} followed similar patterns as ambient AP.

Only 19 of the AP studies (or 37% of 52) also included a descriptive statistical analysis of disparities in outcomes. Most articles showed worse outcomes among low-income and minority children. Examples include increased risk of kindergarten grade retention and poverty¹¹⁵; higher NTDs and mothers who were Hispanic, had a lower education level, or had a lower household income⁸⁸; delinquent behavior and African American and lower SES households⁸⁷; higher absentee rates in households below the poverty line¹⁶⁹; lower grade point averages and qualifying for free or reduced lunch⁸⁴; and higher rate of adjudications per 10,000 and the number and percentage of African Americans in a population.⁸⁰ Seven of the ETS studies (or 41% of 17) presented data on the disparities in outcomes at baseline. For example, maternal material hardship was associated with worse neurodevelopmental outcomes.^{24,177}

Evidence of effect modification or interaction. Nineteen (or 37% of 52) of the ambient AP studies included an investigation of effect modification, 3 (or 6%) examined interaction and 3 studies (or 6%) presented results for both (Table 2). The impacts of AP exposures on juvenile delinquent behavior was stronger in families with psychosocial adversities,⁸⁷ associated with worse scores on the Wide Range Assessment of Memory and Learning, 2nd ed. assessment (WRAML2), among Hispanic and Black boys with exposure to high prenatal stress,¹⁰⁰ associated with more adverse Performance IQ scores among children from families with low SES,⁸⁵ and had stronger association with ASD for those living in high- rather than moderate- or low-deprivation neighborhoods.¹⁰⁵ Confidence in these associations were bolstered with statistically significant interaction terms reported by authors. Other studies that evaluated interactions between PAH exposures, as measured by cord PAH-DNA adducts, and comparator variables found that joint exposure with material hardship resulted in reduced IQ²⁶ and multiple ADHD symptom scores (more symptoms),⁶⁵ whereas there was no evidence of interaction between AP and ethnicity (defined by authors as Black and Dominican) impacting IQ.¹⁰⁹

Among the studies with analyses on effect modification, all but two reported significant differences in effects by race, ethnicity, or SES. One of the few studies that included Asian populations, Al-Hamdan et al., reported effect modification by race/ethnicity was significant only for Asian populations exposed to unhealthy air quality [as measured by air quality index (AQI)] for ASD outcomes [odds ratio (OR) = 2.96; 95% confidence interval (CI): 1.11, 7.88] as opposed to Hispanic populations (OR = 1.308; 95% CI: 0.607, 2.820), Black populations (OR = 1.398; 95% CI: 0.827, 2.364), and White populations (OR = 1.219; 95% CI: 0.760, 1.954).⁹⁸ Maternal age and race/ethnicity was a significant modifier for proximity to Toxic Release Inventory (TRI) sites with chemical emissions and NTDs, but was significant only for mothers >35 years of age and for non-Hispanic white mothers.¹¹⁰ SES status was a significant modifier for fine particle exposures and lower IQs, and this was stronger with the Performance IQ results.⁸⁵ However, formal tests of heterogeneity were not performed by these authors for any of these studies. Investigations of effect modification with formal tests included findings that neighborhood SES was a significant modifier for effects of exposures to criteria pollutants on NTD,¹⁰⁷ early life stress magnified the

Table 5. Summary of organophosphate pesticides studies with investigations for effect modification and interaction ($n = 14$).

Study	Effect modification (EM) or interaction?	Comparator	Description of exposure disparity	Description of outcome disparity at baseline	Assessed additive vs. multiplicative interaction	Formal test for heterogeneity in EM? (Y/N)	Statistical test for heterogeneity in EM (if used)	Description of EM or interaction results
Engel et al. ⁹²	Both	Race, ethnicity	GM Σ DAP and Σ DMP concentrations were substantially higher in the CHAMACOS cohort than in all other cohorts, whereas the Σ DEP exposure distributions were fairly similar across cohorts. CHAMACOS is mainly a Latino cohort from farmworker communities.	Interaction of race and OP on the MDI and PDI scores was found to be largely driven by Hispanic ethnicity and thus the CHAMACOS study site.	Unclear	Y	We considered all interactions to be significant at $p < 0.10$ using an F -test with 2 df. NA	There was significant heterogeneity in the Σ DAP and Σ DMP associations with the MDI by race/ethnicity ($p = 0.06$ and $p = 0.02$, respectively), with the strongest negative associations found among Hispanic participants for Σ DAP and Σ DMP (Σ DAP $\beta = -2.91$; 95% CI: -4.71 , -1.12 ; Σ DMP $\beta = -2.34$; 95% CI: -3.77 , -0.91). Across racial/ethnic groups, the overall pooled association was still negative (Σ DAP $\beta = -1.39$; 95% CI: -2.67 , -0.10), although this was to a large degree driven by the strong negative association among Hispanic participants. Race/ethnicity-OP interaction p -values: 24-month MDI: Log ₁₀ Σ DAP = 0.06; Log ₁₀ Σ DEP = 0.60; Log ₁₀ Σ DMP = 0.02. 24-month PDI: Log ₁₀ Σ DAP = 0.18; Log ₁₀ Σ DEP = 0.54; Log ₁₀ Σ DMP = 0.25. Prenatal OP biomarker levels and 12-month BSID-II MDI: OP Biomarker and tertile: Black/Hispanic study subjects adjusted mean (95% CI); White study subjects adjusted mean (95% CI), $P_{interaction}$: DAP Log ₁₀ $\beta = -3.29$ (95% CI: -5.88 , -0.70); 4.77 (95% CI: 0.69, 8.86), $P_{interaction} = 0.001$ DEP Log ₁₀ $\beta = -0.33$ (95% CI: -3.00 , 2.35); 0.86 (95% CI: -3.16 , 4.87), $P_{interaction} = 0.62$. DMP Log ₁₀ $\beta = -3.35$ (95% CI: -5.64 , -1.06); 4.45 (95% CI: 0.82, 8.08), $P_{interaction} = <0.001$. Note that higher exposures were associated with better MDI scores among White children. No heterogeneity was found in Σ DEP effect estimates according to race/ethnicity. Prenatal OP biomarker levels and 12-month BSID-II MDI: For PDI, no relationship between OP metabolites and the PDI at 12 months overall was found and no interaction with race/ethnicity for any of the metabolite groups. At the 24-month BSID-II, effect estimates were not heterogeneous by race/ethnicity (data not shown). Although authors reported no association between OPs and SRS scores, in multivariate adjusted models associations were heterogeneous by race and by sex. Among Black participants, each 10-fold increase in Σ DEP was associated with poorer social responsiveness. Σ DEP $P_{interaction} = 0.06$ for race and Σ DEP $P_{interaction} = 0.12$ for sex in multivariate adjusted models.
Furlong et al. ¹³⁵	Both	Race	Black participants had more variability in levels of sigma DEP, although mean levels for White and Black participants fell within 1 SD of each other.	Authors observed higher mean SRS scores in Black vs. White and Hispanic participants.	NA	N	NA	There was little evidence of interactions between prenatal residential proximity to pesticide use and childhood adversity assessed with ACEs on risk-taking and delinquent behaviors in young adulthood. Among those with high ACEs, malathion use was associated with higher rates of unique types of delinquent acts and frequency of delinquent acts. Conversely, authors observed elevated IRR with chlorpyrifos and glyphosate use only among those with low ACEs for both the number of unique types of delinquent acts respectively, and the frequency of delinquent acts respectively.
Gunier et al. ¹³⁶	EM	Adversity Index	Did not present.	Did not present.	NA	Y	Chi-square test	

Table 5. (Continued.)

Study	Effect modification (EM) or interaction?	Comparator	Description of exposure disparity	Description of outcome disparity at baseline	Assessed additive vs. multiplicative interaction	Formal test for heterogeneity in EM? (Y/N)	Statistical test for heterogeneity in EM (if used)	Description of EM or interaction results
Horton et al. ¹³⁷	Interaction	HOME	Did not present.	Did not present.	Unclear	NA	NA	Authors report they did not detect an interaction between prenatal exposure to chlorpyrifos and the quality of the home environment using either Total HOME score as a covariate or Parental Nurture, suggesting that the quality of the home environment does not modify the relationship between prenatal CPF exposure and working memory.
Hyland et al. ¹³⁸	EM	Adversity Index	Did not present.	Did not present.	NA	N	NA	We observed little evidence of modification of associations between agricultural pesticide use near maternal homes during pregnancy and maternal- and youth-reported behavioral and emotional problems during adolescence by ACEs. For internalizing problems, only associations with malnutrition were modified by ACEs; results were consistent across maternal- and youth-report.
Lovasi et al. ⁹³	Interaction	SES	Participants with high chlorpyrifos exposure, the highest tertile of detectable concentrations (greater than 6.17 pg/g), tended to live in areas with more poverty (mean difference 1.3%; = 0.06). Did not present.	Did not present.	Unclear	N	NA	Interaction terms Neighborhood poverty–chlorpyrifos exposure were not significant: PDI ($p = 0.4$) or MDI ($p = 0.2$) in this population. Authors concluded that neighborhood poverty did not significantly modify the association between chlorpyrifos and neurodevelopment.
Percy et al. ¹³⁹	EM	Race, SES, Adversity Index	Did not present.	Did not present.	NA	N	NA	Authors observed effect modification by race/ethnicity for the associations between urinary OPE metabolites and FSIQ, Verbal Comprehension, Perceptual Reasoning, and Working Memory. Children of mothers with the lowest level of education had a 1.75-point lower IQ score for each log-unit increase in urinary diphenyl-phosphate (DPPH) (95% CI: –2.86, –0.64). Urinary bis-2-chloroethyl-phosphate (BCEP) was also negatively associated with FSIQ in children of mothers with less education (β : –0.93; 95% CI: –1.77, –0.08). The Verbal Comprehension subscale was also significantly associated with all three urinary OPE metabolites in children of mothers with the lowest level of education (BCEP = β : –1.43; 95% CI: –2.35, –0.52; bis(1,3-dichloro-2-propyl)-phosphate (BDCIPP) = β : –1.48; 95% CI: –2.69, –0.28; DPPH = β : –1.89; 95% CI: –3.15, –0.64). An increase of \$100,000 of household income was associated with a further increased effect estimate for the association between DPPH and both FSIQ and Perceptual Reasoning. Authors also observed that an IQR increase in neighborhood deprivation is associated with the greatest effect modification of the relationships between BCEP and BDCIPP and Perceptual Reasoning.
Rauh et al. ⁹⁴	Both	Race, ethnicity, SES	There were significant race/ethnicity differences in the distribution of chlorpyrifos exposure, in that 24.2% of Black women and 14.9% of Dominican women had high exposure.	Children who lived in homes with higher HOME scores scored higher at 36 months of age. Black children scored Dominican children consistently.	Unclear	NA	NA	The adverse chlorpyrifos effect on PDI scores was significant at the 0.05 level in both race/ethnicity groups. Specifically, among Black children with high vs. low exposure, the deficit was ~7 points (97.07 points vs. 104.22 points). Among Dominican children with high vs. low exposure, the deficit was ~6 points (93.95 points vs. 99.13 points). The chlorpyrifos effect on MDI scores was significant ($p < 0.05$) for Black children, with a deficit of 6 points (88.47 points vs. 94.81 points), but was not significant for Dominican children, for whom the deficit was slightly <2 points (85.17 points vs. 86.87 points). ¹⁴⁰ In addition, the authors noted “the GLM analysis did indicate significant within-subject effects of both race ($p = 0.001$) and HOME scores ($p = 0.03$) on MDI scores, consistent with results at the individual time points. There was also a significant change over time in the effect of ethnicity, in that the difference between the mean PDI scores of the two groups increased over time, with Dominican children having lower mean scores regardless of exposure level.” ¹⁴¹ However when testing interaction terms between chlorpyrifos exposure with sociodemographic variables in the full model, none were significant.

Table 5. (Continued.)

Study	Effect modification (EM) or interaction?	Comparator	Description of exposure disparity	Description of outcome disparity at baseline	Assessed additive vs. multiplicative interaction	Formal test for heterogeneity in EM? (Y/N)	Statistical test for heterogeneity in EM (if used)	Description of EM or interaction results
Rauh et al. ¹⁴⁰	Interaction	Race, ethnicity, SES	Did not present.	Did not present.	Unclear	NA	NA	Authors found no significant interactions between CPF and any of the potential or final covariates, including the other chemical exposures measured during the prenatal period (ETS and PAH).
Rowe et al. ¹⁴¹	Both	SES	Proximal pesticide use is associated with neighborhood and household poverty.	Decreased FSQ scores measured in children living in a low vs. highest SES neighborhood at 10.5 years of age.	NA	N	NA	Authors created an interaction term for the ordinal quartiles of pesticide use and ordinal quartiles of neighborhood poverty while controlling for household poverty and other covariates. Authors reported that none of the interaction terms were statistically significant ($p > 0.2$), but still concluded that they observed statistically significant negative associations between living in the highest quartile of proximal pesticide use and FSQ ($\beta = -3.8$; 95% CI: $-7.0, -0.5$). Perceptual Reasoning ($\beta = -4.4$; 95% CI: $-8.7, -0.1$), and Working Memory ($\beta = -3.8$; 95% CI: $-7.2, -0.5$) among children in households at or below the poverty threshold but not in those in households above the poverty threshold.
Sagiv et al. ¹⁴²	Both	Adversity Index	No difference in OP exposure by high or low adversity score. Prenatal total DAP concentrations, were slightly higher among mothers who were younger, not born in the United States, more educated, and less impoverished.	Youth risky behaviors were found to be more common among those born to non-U.S.-born mothers who were living in the United States >5 y.	NA	Y	Wald test	There were no consistent differences in associations between OP pesticide exposure and risk behaviors by sex or childhood adversity. There was slightly higher risk for smoking/vaping nicotine in the past 30 d in association with DAP concentrations for those with high ACE scores (RR = 2.49; 95% CI: 0.95, 6.54) vs. those with low ACE scores (RR = 1.41; 95% CI: 0.55, 3.60), but CIs were wide and the difference was not statistically significant ($p_{interaction} = 0.43$). Differences were found for counts of police encounters, but were again imprecise (IRRhighACEs = 2.53; 95% CI: 1.07, 6.02 vs. IRRlowACEs = 1.39; 95% CI: 0.69, 2.83; $p_{interaction} = 0.30$). The only statistically significant difference associated with prenatal DAP concentrations was for counts of delinquency acts, although in the opposite direction than expected (IRRhighACEs = 0.72; 95% CI: 0.36, 1.45 vs. IRRlowACEs = 1.76; 95% CI: 1.06, 2.92; $p_{interaction} = 0.04$).
Stein et al. ¹⁴³	Both	Adversity Index	Did not present.	Did not present.	Unclear	N	NA	Considering boys and girls together, the relationship between maternal total DAPs and Verbal Comprehension is stronger among children whose mothers have experienced greater adversity ($\beta = -2.8$, $p = 0.13$), and among children with greater total adversity ($\beta = -3.6$, $p = 0.09$). The relationship between DAPs and Processing Speed is stronger among children with greater adversity in their learning environment ($\beta = -2.8$, $p = 0.15$), and with greater family dysfunction ($\beta = -2.7$, $p = 0.18$). Interaction between adversity in parent-child relationship, total DAP concentration, and child sex was significant for Perceptual Reasoning ($p_{interaction} = 0.10$) and FSQ ($p_{interaction} = 0.06$). The interaction between stressful life events, total DAP concentration, and child sex was significant for Verbal Comprehension ($p_{interaction} = 0.19$), Perceptual Reasoning ($p_{interaction} = 0.12$), and Working Memory ($p_{interaction} = 0.11$). The interaction between total adversity, total DAP concentration, and child sex was significant for FSQ ($p_{interaction} = 0.13$).
Taiwo ²¹²	EM	SES	Did not present.	Differences in ASD vs. typically developing cases among mothers with financial hardship.	NA	N	NA	Relationship between exposure to OP and ASD modified by maternal financial hardship. OR for residential proximity to OP application stratified by financial hardship, OR = 1.93 (95% CI: 1.35, 2.76) without and 3.01 (95% CI: 1.34, 6.75) with financial hardship in second trimester.

Note: ACEs, Adverse Childhood Experiences; ASD, autism spectrum disorder; BSID, Bayley Scales of Infant Development; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CI, confidence interval; DAP, dialkylphosphate; DEP, diethyl phthalate; df, degrees of freedom; DMP, dimethylphosphate; ETS, environmental tobacco smoke exposure; FSQ, full-scale intelligence quotient; GLM, generalized linear model; GM, geometric mean; HOME, Home Observation for Measurement of the Environment (Inventory); IQ, intelligence quotient; IQR, interquartile range; IRR, incidence rate ratio; MDI, Mental Development Index; N, no; NA, not applicable; OP, organophosphate pesticide; OPE, organophosphate ester; PAH, polycyclic aromatic hydrocarbon; PDI, Psychomotor Development Index; RR, relative risk; SD, standard deviation; SES, socioeconomic status; SRS, Social Responsiveness Scale; Σ DEP, total diethylphosphates; Y, yes.

Table 6. Summary of phthalates studies with investigations for effect modification and interaction (*n* = 1).

Study	Effect modification (EM) or interaction?	Comparator	Description of exposure disparity	Description of outcome disparity at baseline	Assessed additive vs. multiplicative interaction	Formal test for heterogeneity in EM? (Y/N)	Statistical test for heterogeneity in EM (if used)	Description of EM or interaction results
Bloom et al. ⁶¹	Interaction	Race	African American mothers had higher urinary concentrations of all Phth metabolites (<i>p</i> < 0.0001), except for DEHP metabolites, than White mothers. Quantitative results present in a main table in publication, but too long to present here.	Head circumference was bigger for White newborns (34.23 ± 1.07 cm) than African American newborns (33.24 ± 1.06 cm) with <i>p</i> < 0.0001. GM cephalization index was greater for African American newborns (0.011 ± 1.17 cm/g) compared with White newborns 0.010 ± 1.18 cm/g with <i>p</i> < 0.0001.	Unclear	NA	NA	Interactions for maternal race with urinary Phth, and head circumference for MBP (<i>p</i> _{interaction} = 0.03), MBZP (<i>p</i> _{interaction} = 0.01), MEHP (<i>p</i> _{interaction} = 0.05), MMP (<i>p</i> _{interaction} = 0.02), and ΣDBP (<i>p</i> _{interaction} = 0.05), in which reduced head circumference associations were stronger among White newborns than African American newborns.

Note: DBP, dibutyl phthalate; DEHP, di(2-ethylhexyl) phthalate; GM, geometric mean; MBP, monobutyl phthalate; MBZP, monobenzyl phthalate; MEHP, mono (2-ethylhexyl) phthalate; MMP, mono-methyl phthalate; N, no; NA, not applicable; Phth, phthalates; ΣDBP, total diethylphosphates; Y, yes.

psychiatric effects of PAH exposures,¹⁰⁸ and neighborhood low English proficiency worsened cognitive test scores within the low PAH exposure stratum.²⁹

Five of the 17 studies (29%) of ETS exposure investigated effect modification or interactions. All 5 studies reported interactions or effect modification between ETS and measures of health disparity, including poverty,¹¹⁶ race,^{114,117} and material hardship,^{24,184} on neurodevelopmental outcomes that included learning disabilities,¹¹⁶ cognitive deficits,^{24,184} and ADHD.^{114,117}

Pb exposure. Overview. Sixty-three studies examined the association between Pb exposure and child neurobehavioral development, and 43 studies or 68% reported cognitive or behavioral deficits associated with Pb exposure, mainly measured by blood Pb levels (BBLs), with the remaining having mixed (17 studies or 27%) or null findings (2 studies or 3%) (Excel Table S3 and the Pb exposure-specific view in Tableau at https://public.tableau.com/shared/6H7Q76Q7M?:display_count=n&origin=viz_share_link). Prenatal and postnatal exposure to Pb was related to reduced cognitive function,^{69,74,118,119,123,126,131,172,185–194,269} attention,^{73,124,190,195–197} verbal comprehension,¹²¹ vocabulary development,¹²¹ and academic achievement in reading and mathematics.^{70,75,120,187,198} Pb exposure in early life was also related to impaired executive function,¹⁹⁶ hyperactivity,¹⁹⁹ aggression and externalizing behavior,^{200–202} school suspension,⁷⁸ delinquency,^{130,201,203,204,268} and criminal behaviors.¹³² The deficits in cognitive function and behavior were observed at various BLLs, from Pb poisoning to levels below the most recent Centers for Disease Control and Prevention (CDC) reference level of 3.5 µg/dL.²⁰⁵ No threshold for Pb neurotoxicity in children has been identified. Two studies examined lifelong effects of early Pb exposure and found associations with firearm violence perpetration and victimization²⁰⁶ and criminal arrests¹³² in late adolescence and early adulthood.

Exposure and health outcome disparities. Factors including race and ethnicity, parental educational achievement, poverty, and parenting support were usually adjusted for in the investigation of developmental neurotoxicity of Pb exposure. Pb exposure disparities by these factors are well documented.^{70,144,207} Less than half of the Pb articles, 25 articles (40%), included comparison of Pb exposures by sociodemographic and/or socioeconomic characteristics, and a similar number included descriptive statistics on neurodevelopmental outcomes under study. When provided, data showed BBLs were highest in children who were Black,^{64,69–78} spoke languages other than English or Spanish,⁷¹ from low-income families and/or had other measures of lower SES (e.g., qualified for free/reduced lunch⁷²). In addition, exposure disparities were noted among children living in large families and in deteriorated and crowded housing.¹⁸⁶ Minority and poor children were more likely to have lower scores on cognitive⁶⁹ or educational assessments⁷⁰ and higher prevalence of adverse outcomes, such as ADHD diagnoses.¹⁹⁵ In one study, a record of high BBLs was related to school suspension by the fourth grade (OR = 2.66; 95% CI: 2.12, 3.32), which partially (23%) explained the difference of suspension percentage between African American and White school children.⁷⁸

Evidence of effect modification or interaction. Twenty-two of the 63 studies (or 35%) on Pb exposure and child neurobehavior and neurodevelopment examined effect modification or interactions between Pb exposure and disparity comparators including poverty, low parental education achievement, race, ethnicity, and parental stress (Table 3). A majority of the 22 studies examined SES (15 studies or 68%) and race (12 studies or 55%) effects. Six of the 22 investigations (or 27%) reported evidence of interaction; 3 studies (or 14%) reported effect modification (but did not provide test for

Table 7. Summary of polychlorinated biphenyls studies with investigations for effect modification and interaction ($n = 1$).

Study	Effect modification (EM) or interaction?	Comparator	Description of exposure disparity	Description of outcome disparity at baseline	Assessed additive vs. multiplicative interaction	Formal test for heterogeneity in EM? (Y/N)	Statistical test for heterogeneity in EM (if used)	Description of EM or interaction results
Orenstein et al. ¹³⁴	Interaction	SES	Did not present.	Non-Hispanic white children scored higher on the WRAML than children of other races or ethnicities.	Unclear	NA	NA	No significant interactions with the socio-demographic variables (maternal IQ, prenatal smoking, parental education, household income, breastfeeding) were observed with Hg. Quantitative results not provided.

Note: Hg, mercury; IQ, intelligence quotient; N, no; NA, not applicable; SES, socioeconomic status; WRAML, Wide Range Assessment of Memory and Learning; Y, yes.

heterogeneity); 4 studies (or 18%) reported evidence of interaction analyzing for both effect modification and testing interaction; and 9 (or 41%) reported no statistically significant interactions.

Nine studies revealed more adverse impact of Pb exposure in children from families with low SES. For example, in the Cincinnati Lead Study (CLS) with enrollment from 1979–1984, infant BBLs at 10 d of age (mean = 4.6 y, range: 1–22 µg/dL) had an interaction with SES ($p = 0.01$) on Bayley Mental Development Index (MDI), indicating a deficit of 16.1 points in MDI across this range of exposure in infants from families with below-median SES.¹²² This interaction remained at 4 years of age when the children were assessed by Kaufman Assessment Battery for Children (K-ABC). Neonatal BBLs were inversely associated with K-ABC Mental Processing Composite (MPC) in children from families with below-median SES but not in children from families with higher SES.¹²³ Subsequently, this research group's studies showed that BBLs at 78 months of age were associated with deficits in learning/IQ in mid-adolescence ($p < 0.07$) for children from families with low SES.¹³¹

Of the 11 studies that examined effect modification or interaction by race, 5 studies (or 45%) reported worse outcomes among racially minoritized children. Two of these studies found interactions between BBLs and race on school performance, using Pb screening data from early life and standardized test scores at school age. In Chicago Public School children, an interaction between race and BBLs was identified for reading and math test failure in the third grade. The OR of reading test failure per 5-µg/dL increase in BBLs was 1.28 (95% CI: 1.21, 1.35) in non-Hispanic black children, 1.47 (95% CI: 1.29, 1.66) in Hispanic children, and 1.93 (95% CI: 1.47, 2.54) in non-Hispanic white children.⁷⁰ However, because non-Hispanic Black children had the highest mean BBLs, the combined racial disparities for both exposure and outcome are greater than those ORs indicate. Lu et al. tested racial disparities in the effects of Pb in community drinking water supplies by adding an interaction term to their model and reported “effect measure modification by grade is statistically significant for math [$\beta = -0.0242$, standard error (SE) = 0.0051, $p < 0.01$].”¹²⁵ In other words, for student populations with a higher proportion of non-White students in Massachusetts school districts, “higher drinking water lead levels were associated with a larger reduction in standardized math test scores, compared with cohort years with more than 90% White students.”¹²⁵

Hg. Overview. Six studies investigating Hg exposures^{133,134,172,208–210} exclusively were screened into our study (Excel Table S4 and the Hg exposure-specific view in Tableau at https://public.tableau.com/shared/MY5X9H3PR?:display_count=n&origin=viz_share_link). Disparity comparators used included race, ethnicity, SES, and the CDC's Social

Vulnerability Index. Four of the six studies or 67% reported adverse effects and two studies or 29% found no associations.

Disparities in exposures and outcomes. Authors employed different methods for assessing Hg exposures, such as soil concentrations near residences of pregnant women, maternal hair and urinary Hg concentrations, fish tissue concentrations, and proximity to industrial emissions sources. Brender et al. compared their study participants' (who were all Mexican-American mothers) urinary Hg levels with those of Mexican-American women participants in the 1999–2000 NHANES, and ~28% of their study case-women and 18% of the control-women had urinary Hg levels at or above the 95th percentile from NHANES.¹³³

Four studies (67%) included a descriptive statistical analysis of disparities in the outcomes. McKean et al. investigated maternal fish consumption, newborn blood methyl Hg (MeHg) levels, and its association with autism or developmental delay.²⁰⁸ The developmental delay group had fewer mothers with a bachelor's or graduate/professional degree, more mothers born in Mexico, more Latino children, and a higher proportion of deliveries covered by public health insurance when compared with the ASD and typically developing groups.²⁰⁸ Similarly, Brender et al. found mothers (all Mexican-American) with children born with neural tube disorder were poorer and less educated and more likely to have been conceived in Mexico than control-women.¹³³ The remaining two studies noted that outcomes varied by race and ethnicity.^{134,209}

Evidence of effect modification or interaction. Only two investigations^{133,134} considered interactions by comparators (Table 4). Brender et al. reported that household income modified the association between urinary Hg and NTD,¹³³ whereas Orenstein et al. found no significant interactions with the socio-demographic variables.¹³⁴ Specifically, Brender et al. noted that among women with the highest income (>\$25,000), women with children born with neural tube disorder were nine times more likely (OR = 9.0; 95% CI: 1.4, 57) than control-women to have a urinary Hg level of ≥ 5.62 µg/L, a level that represented the 95th percentile for Mexican-American participants in the 1999–2000 NHANES.¹³³ Quantitative results were not provided by Orenstein et al.¹³⁴

OPs. Overview. Forty-one of the 218 studies included in our review (19%) considered OPs and of these (Excel Table S5 and the OP exposure-specific view in Tableau at https://public.tableau.com/shared/ZCGG8RJSJ?:display_count=n&origin=viz_share_link), 2 studies considered OPs in combination with other pollutants (discussed in mixtures section below). Most studies used prenatal maternal urinary OP metabolite concentrations or residential proximity to pesticide application for exposure assessment. A few

Table 8. Summary of multiple chemical exposures/mixtures studies with investigations for effect modification and interaction ($n = 5$).

Study	Effect modification (EM) or interaction?		Comparator	Description of exposure disparity	Description of outcome disparity at baseline	Assessed additive vs. multiplicative interaction	Formal test for heterogeneity in EM? (Y/N)	Statistical test for heterogeneity in EM (if used)	Description of EM or interaction results
	Both	EM							
Dellefante et al. ¹⁴⁵	Both		SES	Did not present.	Did not present.	Unclear	N	NA	The stratum-specific estimates [by material deprivation] showed only slight differences in the odds of ADHD-suggestive behavior. The assessment of effect measure modification between pollutant and material hardship exposures revealed that the interaction term was not statistically significant for the individual pollutant models or the combined BTEX variable. AOR for ADHD within stratum of high material hardship: 1.77 (95% CI: 0.70, 4.47); AOR within stratum of lower material hardship: 1.50 (95% CI: 1.09, 2.07), $p_{\text{interaction}} = 0.73$.
Dickerson et al. ¹⁴⁵	EM		SES	All ambient concentrations of metals of interest decreased for tracts with a greater percentage of White residents ($p < 0.01$), and median household income in the upper quartile (highest 25th percentile) compared with areas with incomes in the other quartiles ($p < 0.01$).	Association between prevalence of ASD and potentially confounding SES factors using multilevel negative binomial regression models.	NA	N	NA	Statistical significant elevated odds for combined metal exposure comparing 50–75th quartile exposure with <25th percentile stratified by poverty. Adjusted RR among the below poverty-level group: 1.36 (95% CI: 1.06, 1.74); adjusted RR among the above poverty-level group: 1.10 (95% CI: 0.57, 2.10).
Furlong et al. ¹⁴⁶	Interaction		Race, ethnicity	Did not present.	Did not present.	Unclear	N	NA	There were no interactions between sex, race/ethnicity, or PON1 and the ΣDMPs or ΣDEPs, for any factor. However, there was an interaction between race and ΣDMPs for the WISC-IV Working Memory Index. The positive association between ΣDMPs and the Working Memory Index was present only among Black children ($\beta = 0.34$; 95% CI: 0.15, 0.53), but not among Hispanic ($\beta = -0.09$; 95% CI: -0.27 , 0.08) or White children ($\beta = 0.16$; 95% CI: -0.16 , 0.49).
Persico and Venator. ¹⁴⁷	Interaction		Race, ethnicity, SES	Schools within 1 mi (1.6 km) of a TRI site are relatively less White, slightly more economically disadvantaged, and slightly smaller than schools between 1 and 2 mi (1.6 and 3.2 km).	Did not present.	Unclear	N	NA	The effects of TRI site exposure on test scores were quite similar for White, Black, and Hispanic students. Although they found that a TRI site opening is associated with a 2.9% of a SD decline in average Florida Comprehensive Assessment Test (FCAT) scores for Black students, compared with a 2.3% of a SD decline for White students. None of the results within a regression (e.g., race) were significantly different from each other at the $p < 0.1$ level.
Persico et al. ¹⁴⁸	EM		Race	Black children living in Florida are nearly three times more likely to live within 2 mi (3.2 km) of a Superfund site than White children.	Did not present.	NA	Unclear	NA	Results differed by income groups and tended to be stronger for children of low-income families (children who always received free and reduced-price lunch during their school years): likelihood \pm SE of repeating a grade was 0.046 ± 0.014 ; test scores -0.068 ± 0.024 . No differences by race were noted.

Note: ADHD, attention deficit and hyperactivity disorder; AOR, adjusted odds ratio; ASD, autism spectrum disorder; BTEX, benzene, toluene, ethylbenzene, and xylene; CI, confidence interval; DEP, diethyl phthalate; DMP, dimethylphosphate; N, no; NA, not applicable; PON1, paraoxonase 1 enzyme; RR, relative risk; SD, standard deviation; SE, standard error; SES, socioeconomic status; WISC, Wechsler Intelligence Scale for Children; Y, yes.

studies analyzed pesticides in dust and umbilical cord plasma. Most studies were conducted in California ($n = 24$) involving participants from the CHAMACOS cohort or in New York City ($n = 11$) and examined a variety of neurological health outcomes at different life stages. In terms of main effects, 25 of the 41 studies (or 61%) showed adverse effects of OP exposure on ASD,^{96,211–213} infant development,^{93,94,143,214} intelligence,^{140,215,216} neural dynamics and executive functioning,^{217,218} increases in abnormal reflexes,^{219,220} inattention and internalizing behavior,¹³⁸ and tremors in both arms.²²¹ There were mixed results in 13 studies (or 32%),^{92,97,135–137,139,222–229} Null findings were reported from 2 studies (or 5%),^{230,231} and 1 study reported protective effects²³¹ within a mostly White, educated population, with the highest levels detected among those eating the most vegetables.

Disparities in exposures and outcomes. Fourteen (of 41 or 34%) studies included comparison of OP exposures by sociodemographic and/or socioeconomic characteristics. Eleven (of 41 or 27%) studies also included a descriptive statistical analysis of disparities in the outcomes that were the focus of their studies. Although few studies reported disparities in exposures or outcomes, many were conducted in special populations, urban cohorts,^{93,135,137} and farmworker communities.^{141,143,215,227,232} A longitudinal study by Butler-Dawson et al. that conducted home visits with Latino agricultural and nonagricultural children at two time points ~ 1 y apart identified few differences between the two groups of children at both visits, but more deficits in learning from the first visit to the second visit, or less improvement, was found in agricultural children relative to nonagricultural children.⁹⁶ In addition, pesticide residues were detected in dust samples more frequently and in higher concentrations in agricultural homes.

Evidence of effect modification or interaction. Less than half of OP studies (14 of 41 or 34%) examined effect modification by or interactions with a variety of comparators, including race and ethnicity (although often these were combined), poverty measures, HOME scores, and adversity (Table 5). One study reported significant effect modification by financial hardship of the association between OP exposure and ASD.²¹² Two studies involving the CHAMACOS cohort reported little evidence of effect modification by childhood adversity [Adverse Childhood Experiences (ACEs) based on the survey instrument from the CDC] on associations between OP pesticide applications near maternal residences and risk-taking behavior in young adults at 18 years of age¹³⁶ or in youth-reported internalizing behaviors, hyperactivity, and attention problems at 16 and 18 years of age.¹³⁸ Authors noted that “adversity can be assessed using different methods other than ACEs,” suggesting their null results should not necessarily mean the absence of such effects.¹³⁶ Two studies found no significant interactions of prenatal chlorpyrifos exposure with neighborhood poverty⁹³ or HOME scores on neurodevelopment at 36 months of age or working memory at 7 years of age.¹³⁷ This result regarding HOME scores may indicate no remediating effect of a high-quality home environment (either parental nurturance or environmental stimulation) on the adverse effects of prenatal chlorpyrifos exposure on working memory.

Eight studies presented both stratified analyses and statistical tests for interactions. Although statistically significant interaction between proximity to pesticide use and neighborhood poverty was not observed, Rowe et al. noted that the results of the multivariable regression models stratified by household poverty suggest that 10-y-old children in poorer households may experience greater cognitive impacts in association with OP and carbamate exposures.¹⁴¹ Statistically significant associations were found between living in the highest quartile of proximal pesticide use and full-scale IQ (FSIQ; $\beta = -3.8$; 95% CI = $-7.0, -0.5$),

Perceptual Reasoning ($\beta = -4.4$; 95% CI = $-8.7, -0.1$), and Working Memory ($\beta = -3.8$; 95% CI = $-7.2, -0.5$) among children in households at or below the poverty threshold but not in those in households above the poverty threshold.¹⁴¹ In this same cohort, adverse associations between prenatal OP metabolite concentrations and IQ at 7 years of age were stronger in children experiencing greater adversity, and the association between prenatal OP exposure and FSIQ was higher among boys who experienced high adversity in the learning environment indicated by a significant three-way interaction between total dialkylphosphate (Σ DAP) concentration, adversity scores, and child sex.¹⁴³

In one study from the Mount Sinai Children’s Environmental Health Study, third trimester maternal urinary DAP metabolites were assessed for their association with scores on the Social Responsiveness Scale (SRS) for children 7–9 years of age.¹³⁵ Although there was no overall association, for Black children, each 10-fold increase in total diethylphosphates (Σ DEP) metabolites was associated with poorer social responsiveness ($\beta = 5.1$ points; 95% CI: 0.8, 9.4), as well as among boys in general ($\beta = 3.5$ points; 95% CI: 0.2, 6.8).¹³⁵ The association of Σ DEP metabolites with total SRS score was heterogeneous by race and by sex: Σ DEP $p_{\text{interaction}} = 0.06$ for race, and Σ DEP $p_{\text{interaction}} = 0.12$ for sex.¹³⁵ However, to perform this analysis, Furlong et al. had to combine White and Hispanic study participants for sample size concerns. In a pooled analysis across four cohorts (from California, New York, and Ohio), Engel et al. reported that there was significant heterogeneity in the Σ DAP and total dimethylphosphates (Σ DMP) associations with the MDI at 24 months of age by race and ethnicity ($p = 0.06$ and $p = 0.02$, respectively), with the strongest negative associations found among Hispanic participants for Σ DAP and Σ DMP (Σ DAP $\beta = -2.91$; 95% CI: $-4.71, -1.12$; Σ DMP $\beta = -2.34$; 95% CI: $-3.77, -0.91$).⁹² Authors reported that the overall pooled association was still negative (Σ DAP $\beta = -1.39$; 95% CI: $-2.67, -0.10$) and concluded this was to a large degree driven by the strong negative association among Hispanic participants, specifically from the CHAMACOS cohort in California which “accounted for approximately 70% of all Hispanics included in this pooled analysis.”

Phth. Overview. Twelve (6%)^{59–61,90,91,233–239} of the 218 studies examined Phth (Excel Table S6 and the Phth exposure-specific view in Tableau at https://public.tableau.com/shared/8T7SJ4GM9?display_count=n&origin=viz_share_link). Four employed data from the Mount Sinai Children’s Environmental Health Study,^{90,233,234,239} whereas 4 were included in the CCCEH study.^{59,60,91} Studies were conducted primarily in urban environments, with 9 studies located in New York City, 1 in the Charleston, South Carolina, metro area, and 1 in Alabama; most were longitudinal. Associations with adverse neurodevelopmental outcomes were found in 7 studies (or 58%),^{60,61,91,234–236,238} improved outcomes in 1,²⁴⁰ and mixed results in 4 studies (33%), with worse outcomes only in girls.^{59,90,233,239} Null findings were reported in a pilot study that compared concentration of Phth metabolites in serum or urine samples collected from children with and without ASD²³⁷ from communities along the Gulf of Mexico in Alabama, a state with 14 Superfund sites.

Disparities in exposures and outcomes. Notably, only a few studies assessed differences in Phth exposure by race. Doherty et al.⁹⁰ found that Phth concentrations among non-White mothers were 1.4–3.1 times the concentrations among White mothers. Study authors of the two studies using the CCCEH cohort noted that Phth concentrations in their African American and Dominican study populations were slightly higher but overlapped with those measured in U.S. women in general in NHANES.²⁴¹

Evidence of effect modification or interaction. Only one study (Table 6) assessed interaction. Bloom et al. used cross-

product terms for race \times Phth \times time in regression models and found reduced head circumference associations with prenatal Phth exposures were stronger among White mothers than among African American mothers.⁶¹ It was unclear if these interactions were on the additive or multiplicative scale.

PBDEs. Overview. Our review included only three studies on PBDEs (Excel Table S7 and the PBDE exposure-specific view in Tableau at https://public.tableau.com/shared/6TTJXK49X?:display_count=n&:origin=viz_share_link); two (or 67%) found mixed associations between PBDEs and cognitive outcomes (memory, reading ability).^{58,89} Liang et al. found associations between PBDE serum concentrations and worse reading scores at 5 and 8 years of age, but the associations were not statistically significant after covariate adjustment.⁸⁹ Cowell et al. found associations between prenatal PBDE exposure (cord blood) and poor working memory only among girls.⁵⁸ Attina et al. (2019) applied existing exposure-response relationships between PBDEs and IQ loss to national-scale PBDE exposure estimates to examine racial disparities in disease burden and associated costs.⁵⁷

Disparities in exposures and outcomes. All studies used either serum or plasma PBDE concentrations as the measure of exposures. Two studies included comparison of exposures by comparator and both found higher concentrations among racial and ethnic minority participants and among those from lower-income households.^{57,89} Two studies presented data showing disparities in outcome. Attina et al. reported associated disease burden and costs for IQ loss and intellectual disability due to PBDE exposure were higher in racial/ethnic minorities in proportion to their respective population.⁵⁷ In the study by Liang et al., children in households with lower incomes, of mothers with less than a high school education, and/or of non-White mothers were more likely to have lower reading scores.⁸⁹

Evidence of effect modification or interaction. Interactions between PBDE and indicators of social disadvantage were not assessed in any study. Therefore no results are presented.

PCBs. Overview Seven studies included in this review examined PCBs (Excel Table S8 and the PCB exposure-specific view in Tableau at https://public.tableau.com/shared/NGXY5BXNW?:display_count=n&:origin=viz_share_link), with exposure measured in a variety of ways, including environmental media (soil, fish tissue, and sediments), placental tissue, prenatal maternal serum, breast milk, and cord serum. Prenatal PCB exposure was significantly associated with reduced cognitive functioning in four of these seven studies (or 57%)^{67,68,242,243} and with psychomotor outcomes²⁴⁴ after controlling statistically for a broad range of potential confounding variables that included SES, education, and HOME characteristics. Although larger quantities of PCBs are transferred by lactation than *in utero*, there were no deleterious effects of PCBs associated with breastfeeding in either of the studies exploring this exposure.^{68,243} In fact, one study found the association of prenatal PCB exposure with cognitive outcomes to be stronger and statistically significant only among the non-breastfed children. One explanation offered is that certain nutrients in breast milk attenuate adverse neurological effects associated with prenatal PCB exposure. Almost all of the adverse associations between breastfeeding and cognitive outcome could be accounted for statistically by measures of quality of parental intellectual input.⁶⁸

Disparities in exposures and outcomes. None of the studies presented exposure data by comparators. Only one study (Orenstein et al.) described disparities in neurodevelopmental outcomes by sociodemographic and socioeconomic characteristics.¹³⁴ Children with higher household income and parental education, and who were non-Hispanic white, performed better on the WRAML.¹³⁴

Evidence of effect modification or interaction. Only one study assessed interaction (Table 7): Orenstein et al. found no significant interactions with PCBs and the sociodemographic variables (i.e., maternal IQ, prenatal smoking, parental education, household income, and breastfeeding).¹³⁴ Perhaps this is not surprising given that the authors did not find significant associations between prenatal PCB exposures and memory and learning skills as assessed by the WRAML or other learning outcomes.¹³⁴

Multiple chemical exposures/mixtures. Overview. Seventeen of 218 studies (8%) included in the review explicitly sought to examine the effects of multiple contaminant exposures on neurodevelopment (Excel Table S9 and the chemical mixtures exposure-specific view in Tableau at https://public.tableau.com/shared/DZRSQH9C5?:display_count=n&:origin=viz_share_link).^{55,62,66,80,145,147,148,209,245–253} These studies focused on multiple metals [e.g., Pb, Hg, cadmium, arsenic (As)], OPs in combination with other chemical exposures, and toxic air pollutants and PCBs in combination with other exposures. Outcomes assessed were wide ranging and included NTDs, cognitive and behavioral outcomes, ASD, and adjudicated juvenile felonies. Mixtures or combined exposures to multiple pollutants (by class or functional group) were found to be associated with neurodevelopmental outcomes. Ten of these 17 studies (59%) reported adverse effects, 5 (29%) reported mixed associations, and 3 (20%) were null studies.

Disparities in exposures and outcomes. Among these 17 studies that evaluated health outcomes in relationship to mixtures or combined effects of multiple pollutants, 7 (41%) reported sociodemographic, socioeconomic, or geographic disparities in these exposures.^{80,145,147,148,246,249,251} Pregnant women residing near mountaintop mining operations were more likely to have a lower level of education and births with congenital anomalies, “reflecting the chronically disadvantaged nature of mining-dependent economies and the associated burden of poor health for Appalachian residents in coal mining areas.”²⁴⁶ Haynes et al. reported in their main text that airborne metals and particulate matter emissions were positively correlated with county sociodemographic characteristics, including population size, population density, and number and percentage of African Americans and that poverty measures (median family income and percentage of families below the poverty level) were not related to air pollutant emissions.⁸⁰ Authors speculated these findings may be explained by elevated emission concentrations in metropolitan areas that contained a mix of high- and low-income populations⁸⁰; the correlation statistics were found only in their supplemental material (Appendix Table 1). Using univariate associations, Dickerson et al. found that ambient concentrations of metals of interest (Pb, Hg, As) decreased for tracts with a greater percentage of White residents ($p < 0.01$) and a median household income in the upper quartile (highest 25th percentile) compared with areas with incomes in the other quartiles ($p < 0.01$).¹⁴⁵ Tests for trend also indicated a negative (inverse) trend for proportion of White residents and ambient air concentrations of As, Hg, and summed metal concentrations ($p = 0.01$).¹⁴⁵ In their study on ASD prevalence and proximity to industrial facilities known to release Hg, Pb, or As, Dickerson et al. found counterintuitive results. U.S. Census tracts reporting a greater proportion of Black residents were significantly farther away from industrial facilities, whereas tracts with a greater proportion of White residents and Hispanic residents were closer in proximity to industrial facilities.²⁵¹ Conversely, Persico et al. found that Black families in Florida were much more likely to live near Superfund sites and that mothers with children living within 2 mi (3.2 km) of a Superfund site were less well educated compared with mothers of all Florida children.¹⁴⁸ In a later study, Persico et al. found that schools within 1 mi (1.6 km) of a TRI site were relatively less White and slightly more economically disadvantaged.¹⁴⁷

Disparities in target health outcomes at baseline were noted in 9 of the 17 studies (53%). Studies that examined ASD reported higher rates among White and better educated mothers,^{145,249,251} reflecting past trends in ASD prevalence. Rates of learning or intellectual disabilities and ADHD were found to be higher among poor and racial and ethnic minority children.^{245,248,250,252}

Evidence of effect modification or interaction. Five of the 17 mixtures studies (29%) assessed for effect modification by or interaction with sociodemographic or socioeconomic comparator variables (Table 8).^{66,145–148} Only Furlong et al. and Dickerson et al. found evidence of effect modification.^{145,146} For example, in census tracts below the poverty level and with combined metal concentrations (Pb, Hg, and As) in the 50th to the 75th percentile, adjusted relative risk (RR) for ASD prevalence was 1.36 (95% CI: 1.06, 1.74) compared with those in the lowest quartile of exposures.¹⁴⁵ Conversely, among tracts above the poverty level, the RR was 1.10 (95% CI: 0.57, 2.10) for the same exposure comparison.¹⁴⁵ When stratifying results by race, Furlong et al. noted that the association between the sum of dimethylphosphate metabolites (Σ DMPs) and decrements in the Working Memory Index differed by race/ethnicity, with a negative or inverse association among Black participants and no associations among White or Hispanic participants when accounting for other chemical exposures (9 Phth, 3 pyrethroid, and 5 phenol metabolites modeled as coexposures).¹⁴⁶ This is counterintuitive because it suggests that pesticide exposures lead to better neurodevelopmental outcomes among Black children. The authors stated that this association between Σ DMPs and executive functioning among Black participants, but not Hispanic or White participants, was unexpected and may reflect residual confounding by race-specific factors or may be a chance finding given the small sample size.¹⁴⁶ Neither Dickerson et al. or Furlong et al. mentioned a formal test of heterogeneity. In addition, Furlong et al. often used the terms effect modification and interaction interchangeably, and their “Methods” section did not provide enough information as to whether they also used interaction terms.

The studies by Dellefratte et al. and Persico et al. did not find a statistically significant difference in the exposure–effect relationships by poverty (air toxics and ADHD) or by race (proximity to TRI facilities and Superfund sites and cognitive outcomes) or statistically significant interaction terms.^{66,147} Although Persico et al. did not find differences in exposure–effect relationships by race (i.e., children from all backgrounds are harmed by proximity to Superfund sites before and during cleanup), these authors estimated that the racial disparities in exposures to environmental toxicants from Superfund sites alone accounted for ~2% of the Black–White cognitive test score gap in Florida during their study period.¹⁴⁸ However, Persico et al. reported that results differed by income groups and tended to be stronger for children of low-income families: the likelihood of repeating a grade $\beta = 0.046 \pm \text{SE of } 0.014$ and a reduction in scores on Florida Comprehensive Assessment Tests, $\beta = -0.068 \pm \text{SE of } 0.024$.¹⁴⁸

Discussion

In this scoping review, we examined the epidemiological literature published in 1974–2022 considering the relationships between exposures to seven exemplar neurotoxic chemicals and pollutants and disparities in neurodevelopmental health outcomes for children living in the United States. Our results indicate a complex story about how racial and ethnic minority and low-income children may be disproportionately harmed by exposures to neurotoxicants, and this has implications for targeting interventions, policy change, and other necessary investments to eliminate these health disparities. We took a unique approach and evaluated these environmental epidemiological studies for the authors’ conceptualization and

operationalization of the race and ethnicity variables, as well as for other variables traditionally used to denote social disadvantage, which may contribute to the ambiguous results reported in some cases, along with the qualitative assessment of study results typical of scoping reviews. We identified several key points: *a*) the need for better reporting on and the interpretation of effect modification and interaction, *b*) the importance of exposure disparities, *c*) the need for improving the use of race and other variables to denote social group difference in environmental epidemiology studies, and *d*) the need for more research examining impacts of neurotoxicant exposures into later childhood and adolescence.

Interpretation of Effect Modification and Interaction in the Context of Environmental Health Disparities

The traditional approach in environmental epidemiology for answering the question of “who is more harmed?” is to examine the statistical significance and magnitude of an interaction term between the chemical and social comparator (sometimes called social stressors) and/or to conduct analysis stratified by the social comparators of interest (or their proxy). The practice and reporting of these types of analyses has come under some criticism,²⁵⁴ especially with regard to research on health disparities by race and ethnicity.^{38,43,255,256} Kauffman and MacLehose noted that one of the most “egregious improprieties is to assert heterogeneity of the effect on the argument that the exposure has a ‘significant’ effect in one stratum of the baseline covariate, but not in another.”²⁵⁴ Therefore, we note that <9% of articles presented stratum-specific estimates and appropriate tests for interaction when asserting evidence of heterogeneity of effects.

In this review we also observed that many researchers use the terms effect modification and interaction interchangeably, and this complicates interpretation. Effect modification occurs when the magnitude of the effect of the primary exposure on an outcome differs depending on the level of a third variable. Many researchers interpret effect modification as evidence of susceptibility or vulnerability, whereas interaction refers to the joint effect of two or more exposures on a disease or outcome. These “exposures” are considered to be on the causal pathway, combining to affect a health outcome. We observed that although a majority of studies that reported heterogeneity by SES, racial, or ethnic group identified stronger associations in more disadvantaged groups, this trend is not entirely consistent across comparators. Approximately 80% of the papers that reported heterogeneity in outcomes by SES strata found the strongest associations in lower SES groups. Of the studies that found heterogeneity in outcomes by race or ethnicity, stronger associations in the more disadvantaged group were only reported in 63% (race) and 60% (ethnicity) of articles.

It is preferable to report results of interaction with scale—additive or multiplicative. However, this was rarely done among the studies in this review. Only five of the studies on interaction presented interaction results with scale, mostly multiplicative, suggesting that when scale of interaction is reported, authors find that the effects of having both exposure to a selected pollutant and a marginalized identity or socioeconomic disadvantage is greater than the product of their individual effects. Remedies to improve the reporting of effect modification and interaction results by study authors (e.g., formal tests of heterogeneity, scale for interaction) are readily available,^{254,257} which we support. Our results provide directions for which specific pollutant exposures and neurological outcomes to target next for closer examination of heterogeneity in effects and apply these recommend tools to improve the reporting where possible.

Evidence of effect modification hypothetically suggests one avenue for intervention and that is to focus on the primary exposure, whereas interaction (between two exposures) suggests both could

be targets for interventions to reduce those exposures. This raises a question about how to approach designing interventions if the effect modifier or the second “exposure” is considered fixed or unchangeable or static, such as how race and ethnicity are often treated in environmental epidemiological studies (more on this below). Hence, this is why environmental health researchers tend to interpret effect modification as evidence of susceptibility/vulnerability and advocate for the accounting of vulnerability in environmental regulatory policy, especially when the legal framework mandates protection of public health while “allowing an adequate margin of safety.”²⁵⁸ Promulgating environmental standards that are protective of vulnerable populations is needed. However, we are concerned about two dangers this interpretation creates: *a*) the assumption that populations defined by the modifying variable are inherently or uniformly more vulnerable than the comparison group (e.g., Black Americans as a racial group are inherently or uniformly more vulnerable than White Americans), and *b*) conditions or social policies creating the vulnerabilities in the first place remain unaddressed. Rather, environmental epidemiologists should work more toward “build[ing] the evidence on the features of the landscape that render different social groups differentially vulnerable to the health impacts of [environmental exposures]”⁴³ so that the policy targets are clearer. This means developing more rigorous frameworks and conceptualization on the meaning of race, ethnicity, and other social comparators than what is presented in the studies we reviewed.

Why Exposure Disparities Are Still Important in the Context of Health Disparities

Ward et al. cautioned against relying solely on evidence of effect modification or interaction to identify disparities in health outcomes as impetus for policy action. Health disparity may arise because of disparities in exposures or heterogeneity in effects by social group, or both. They further recommend that assessment of health disparities should also evaluate the underlying distribution of the outcome and exposure across racial/ethnic/social groups along with the assessment of interaction terms and stratum-specific effects.³⁸ The reason being that interventions based on evidence of effect modification or interaction alone may overlook other scenarios that lead to disparities. For example, there can be situations where race or ethnicity–exposure interaction is not present, but differences in exposure prevalence produce racial disparities in outcomes.¹⁴⁸ Thus, it is just as important to focus on population groups with demonstrated increased exposures to neurotoxicants and address the drivers of the higher/increase in harmful exposures. Among the few studies that provided this information (84 of 218 studies), we observed persistent greater Pb exposures among low-income and Black children, higher ambient AP and mixture exposures impacting non-White and low-income communities, higher Phth metabolite concentration among non-White mothers, and higher levels of prenatal and postnatal OPs among Black and Hispanic children. In addition, several articles that did not find effect modification presented compelling evidence about the benefits to the neurological health of minority children from policies and environmental programs aimed at cleaning up Superfund sites,¹⁴⁸ reducing TRI reporting facilities’ emissions,¹⁴⁷ and reevaluating acceptable soil metal concentrations.²⁵⁰ Being clear on how minority and low-income children are more harmed gives insight on where to focus action.

Improve the Rigor and Treatment of Race in Environmental Epidemiological Studies

In the spirit of being clearer on where to focus actions to address racial, ethnic, and SES disparities in neurodevelopmental and

neurological health associated with exposure to neurotoxicants, environmental epidemiology needs to look farther upstream and establish more comprehensive conceptual frameworks regarding the meaning and use of race and ethnicity in studies. We evaluated how authors operationalized race, ethnicity, SES, and other indicators of social disadvantage and captured the variety of ways authors measured these comparators, adapting the approach from Martinez et al.⁵¹ We found that detailed conceptualization and justification for the use of race and ethnicity were rarely provided, even among the more recently published articles. Nearly half of all studies did not provide description for how these variables were measured. The treatment of race and ethnicity in epidemiological studies deserves as much rigor as exposure and health outcome assessment. This is especially important for informing policy and intervention responses to research reporting effect modification and interaction. To start, racial categories must be recognized as social constructions whose meanings are not static⁴⁴ and are the result of racism and racialization, processes that allocate differential economic, political, social, and even psychological rewards to groups along racial lines²⁵⁹ and are maintained to preserve status differences.^{9,13} Scholars on race and health inequities offer a number of approaches that environmental epidemiologists can take to better reflect a more rigorous understanding of race, ethnicity, and other proxy variables for the processes of marginalization.^{13,14,43,44,260} For example, if minority race is meant to confer excess stress or adversity, it would be better to incorporate measures for these features directly into analytical models rather than or in addition to race. In our review, we observed a slight increase in the use of adversity indices by study authors over our study period, which is promising. In addition, conducting studies on entirely racial and ethnic minority populations allows researchers to explore variability within groups by geography, adversity, or education, for example, which may provide clues to the social features that create vulnerabilities to the health effects of neurotoxicant exposures (e.g., Perera et al.⁶⁵; Vishnevetsky et al.²⁶; Pagliaccio et al.¹⁰⁸; Brender et al.¹³³; Stein et al.¹⁴³; Engel et al.⁹²). After all, “race and ethnicity have different meanings in relation to health across place that is not simply related to markers of socioeconomic status.”⁴³

Although the vast majority of studies did not define race or ethnicity, a majority used ethnoracial construct (collapsing race and ethnicity) for coding their data. Martinez et al. observed that ethnoracial coding is the most common practice among general epidemiological studies and notes this is concerning given that “race (i.e., skin tone, bone structure), and ethnicity (i.e., language, religion) are distinct theoretical constructs having different embedded assumptions.”⁵¹ In our review, the most common ethnoracial coding schemes were “Black, Dominican” and “Black, Hispanic/Latino, other, White.” These schemes imply mutual exclusivity between groups and may mask health disparities of Black Hispanic populations. Further, these coding schemes leave out Asian, Native American, and Indigenous populations, among many others. In addition, our review highlights a conspicuous lack of studies involving Native American and Indigenous populations. This may reflect the absence of relevant studies that may be due to many systemic reasons, including the need for generalizability and adequate sample sizes to test hypotheses,²⁶¹ the funding mechanisms for research, the locations of Indigenous communities and research institutions, and a dearth of Indigenous researchers. These all contribute to a knowledge gap for disproportionately exposed and underprotected communities.²⁶²

Understanding the Impacts of Neurotoxicant Exposure in Later Ages

Very few studies (20 of 218 studies, or 9%) addressed health effects of neurotoxicant exposures in later childhood and adolescence.

Exceptional examples, however, include papers by Brokamp et al.,⁹⁹ Emer et al.,²⁰⁶ Marshall et al.,¹²⁶ Sagiv et al.,²¹⁸ and Wright et al.¹³² The implications are critical given that we lack an understanding of the long-term impacts of exposures to neurotoxins and their contribution to disparities over the life course. Impairment in brain development in one domain could alter the trajectory of development in other domains, leaving a child poorly equipped to make good, future-oriented decisions and who, because of poor academic success, faces restricted employment opportunities, material hardship, and other socioeconomic stresses. Changes in brain function occur throughout life, and some consequences of early damage may not even emerge until advanced age.²⁶³ Cohorts, such as the ongoing Adolescent Brain Cognitive Development study, the largest long-term study of brain development and child health in the United States ($N = 11,878$) generating structural and functional brain imaging along with environmental, neuropsychological, behavioral, and health assessments,²⁶⁴ may be uniquely positioned to fill these data gaps.^{126,265,266} In our view, linking neurodevelopmental outcomes across the life course would help policymakers better account for the burden of neurotoxicant exposures and associated costs to societal health and welfare.

Strengths and Limitations

This scoping review provides a broad overview of the existing literature assessing associations between seven exemplar environmental contaminants, a wide range of socioeconomic and sociodemographic disparities, and the resultant neurodevelopmental outcomes. Using explicit, systematic methods to select studies allowed us to map key concepts on the populations, exposures, health disparity comparators, and outcomes of interest. The broad overview provided by a scoping review also enabled us to identify major gaps in the literature. A unique strength of our review is characterizing the conceptualization and operationalization of race, ethnicity, and SES, for example, by study authors. This kind of assessment is rarely done in systematic reviews of environmental epidemiological studies investigating environmental health disparities. However, because we did not conduct a systematic review, we could not formally assess the quality of the included studies or conduct a quantitative meta-analysis.

It may be helpful to compare our findings to relevant previous reviews. Ruiz et al., examined >100 chemical and nonchemical stressors from the built, natural, and social environments on children's cognitive ability.³¹ Although the authors affirmed the adverse effects of Pb, they observed inconsistent results for most exposures, including AP [PAHs and nitrogen dioxide (NO_2)], PBDEs, Phth, and pesticides. In contrast, our present review found more studies showing evidence for adverse effects of these contaminants on cognitive outcomes than did Ruiz et al.³¹ This may be the result of differences in our search terminology and eligibility criteria. Ruiz et al. identified 258 eligible studies examining cognitive outcomes, whereas our review identified only 108 studies. We limited our search to observational studies of children in the United States, whereas Ruiz et al. identified observational studies, randomized controlled trials, reviews, and meta-analyses of children worldwide. The review by Ruiz et al.³¹ also spanned a shorter range of publication dates (2003–2013), whereas our review included studies published through 18 November 2022. Therefore, our review is more timely given that this is a burgeoning field, with a wealth of new publications on this topic. Last, we examined studies that included both exposures to the Project TENDR exemplar contaminants and race, ethnicity, and other indicators study authors used as proxies for social or economic disadvantage or marginalization, whereas Ruiz et al.³¹ identified studies only through a single exposure.

In another 2016 review examining joint contributions of social determinants and environmental exposures in a range of early

life outcomes, researchers identified 14 studies that investigated cognitive and behavioral outcomes, 12 of which examined effect modification. Synergistic associations were observed in 10 (83%) of these studies.³⁰ In contrast, our review observed a slightly lower percentage of articles reporting evidence for effect modification or interaction associations. However, our review included a much larger number of studies owing to its broader examination of environmental contaminants and factors related to socioeconomic and environmental disadvantage. In contrast to Appleton et al., we explicitly searched for PBDE, OP, Pb, Hg, Phth, and combustion-related AP and included additional factors related to race/ethnicity, language/immigration/nativity, geography, home environment, and neighborhood. Our review also identified a broader set of neurodevelopmental outcomes, including birth defects and psychological, motor, sensory and neurological outcomes. Thus, our review provides a useful map, not only of the literature on exposures to the seven exemplar neurotoxins and neurodevelopmental disparities, but also on gaps in the treatment of race and ethnicity in environmental epidemiology to inform a more targeted question and quantitative appraisal of the evidence and quality of studies as follow-up.

Given our exclusion criteria, we were unable to examine studies of pediatric populations outside of the United States or studies exclusively focused on documenting exposure disparities. This likely contributed to the small number of studies on Hg, Phth, PCB, and PBDE exposures or very specific sources of exposures (e.g., aviation fuel as source of Pb exposure, dental amalgam, child care centers) being included in our review. We acknowledge that the literature base on these chemicals may be larger than examined in this manuscript. In addition, numerous studies from Europe, Asia, and Australia have contributed to scientific understanding of the neurotoxicity of Hg, PCBs, and Phth but did not meet our review criteria. Comparisons with studies conducted outside of the United States may help provide valuable context, particularly considering populations possessing differing prevalence of social and environmental factors. We also excluded non-observational studies and animal studies, some of which may provide unique insights into associations of environmental exposures and health disparities with neurodevelopmental outcomes. Publication bias may also have affected the results of our review, given that published studies are more likely to report the presence of associations. The majority of included studies were obtained by searching databases for academic publications. We attempted to reduce publication bias by including gray literature; however, our gray literature search resulted in the inclusion of only one eligible article. Last, although we employed systematic strategies to identify and map literature for a broad range of neurodevelopmental outcomes, overall study quality was not assessed as would be done in a formal systematic review. However, future studies can take this evidence base that we mapped to evaluate the data/quality of the literature about specific exposure–outcome relationships and the contribution to health disparities. The review by Vesterinen et al.²⁶⁷ is one example of systematic review in environmental health sciences, although that review lacks critical appraisal of the use of the race and ethnicity variables.

Conclusions

Project TENDR initially launched this scoping review to understand the state of the science on neurodevelopmental outcomes for children in the United States who face racial, social, or economic disadvantage in addition to disproportionate exposures to seven exemplar neurotoxins²² and to more comprehensively inform our work of joining scientific evidence with advocacy to create policy recommendations to protect pregnant women and children from chemicals and pollutants known to harm brain development. Working to eliminate the causes of children's environmental health

disparities is a primary goal of Project TENDR. How we frame the question of who is more harmed by neurotoxic chemical exposures is critical for informing the design of policy interventions.

In this scoping review, we adopted a more comprehensive framework to assess disparities. We did not rely solely on evidence of interaction, but looked at the evidence within each study regarding underlying disparities in outcomes and chemical exposures. In addition, we examined the conceptualization and operationalization of comparator variables, such as race and ethnicity, to provide a critical assessment of the rigor by which environmental epidemiologists treat constructs of social disparities. This literature review of articles published in 1974–2022 both documents neurotoxic effects and identifies gaps in the data and interpretations to help build a more complete picture of the challenges and possible solutions. Our results indicate a complex story about how racial and ethnic minority and low-income children may be disproportionately harmed by exposures to neurotoxins, and this has implications for targeting interventions, policy change, and other necessary investments to eliminate these health disparities. Although researchers in this field look to evidence of effect modification or interaction by race, ethnicity, or SES as indicators of disproportionate harm, the interpretation is challenging because the meaning of these variables is rarely presented. For future epidemiological research, we recommend improving the rigor and treatment of race and ethnicity in environmental epidemiological studies; conducting studies on the social processes that create vulnerabilities, and not just accepting race, ethnicity, or SES as fixed markers; increasing the reporting of underlying disparities in exposures and outcomes along with more formal tests of heterogeneity to support interaction and effect modification results; and conducting more studies on the long-term impacts of prenatal and child exposures to neurodevelopmental toxicants among minority and low-income populations. Effective actions to address racial inequities in children's environmental health must be directed at the social mechanisms or racialization processes as the plausible explanations of environmental exposures and illnesses. Policymakers should not wait for further evidence to act, because this perpetuates harm. Overall, the studies in this review reported that children of color and those living in poverty were more highly exposed to seven exemplar neurotoxins and thus at greater risk of cognitive and behavior disorders. Decisive action grounded in authentic stakeholder engagement to reduce exposures and health inequities is needed now to protect disproportionately exposed children and communities.

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