PLOS ONE

RESEARCH ARTICLE

Contributions of a Child's Built, Natural, and Social Environments to Their General Cognitive Ability: A Systematic Scoping Review

Jazmin Del Carmen Ruiz[1,2]*, James J. Quackenboss[3], Nicolle S. Tulve[2]

1 Oak Ridge Institute for Science and Education, Research Participation Program, Oak Ridge, TN, United States of America, **2** Human Exposure and Atmospheric Sciences Division, National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, Durham, NC, United States of America, **3** Human Exposure and Atmospheric Sciences Division, National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Las Vegas, NV, United States of America

* jaz13ruiz@gmail.com; ruiz.jazmin@epa.gov

OPEN ACCESS

Citation: Ruiz JDC, Quackenboss JJ, Tulve NS (2016) Contributions of a Child's Built, Natural, and Social Environments to Their General Cognitive Ability: A Systematic Scoping Review. PLoS ONE 11 (2): e0147741. doi:10.1371/journal.pone.0147741

Editor: David O. Carpenter, Institute for Health & the Environment, UNITED STATES

Received: September 29, 2015

Accepted: December 9, 2015

Published: February 3, 2016

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: The authors have no support or funding to report.

Competing Interests: The authors have declared that no competing interests exist.

Abstract

The etiology of a child's cognitive ability is complex, with research suggesting that it is not attributed to a single determinant or even a defined period of exposure. Rather, cognitive development is the product of cumulative interactions with the environment, both negative and positive, over the life course. The aim of this systematic scoping review was to collate evidence associated with children's cognitive health, including inherent factors as well as chemical and non-chemical stressors from the built, natural, and social environments. Three databases were used to identify recent epidemiological studies (2003–2013) that examined exposure factors associated with general cognitive ability in children. Over 100 factors were evaluated from 258 eligible studies. We found that recent literature mainly assessed the hypothesized negative effects of either inherent factors or chemical exposures present in the physical environment. Prenatal growth, sleep health, lead and water pollutants showed consistent negative effects. Of the few studies that examined social stressors, results consistently showed cognitive development to be influenced by both positive and negative social interactions at home, in school or the community. Among behavioral factors related to diet and lifestyle choices of the mother, breastfeeding was the most studied, showing consistent positive associations with cognitive ability. There were mostly inconsistent results for both chemical and non-chemical stressors. The majority of studies utilized traditional exposure assessments, evaluating chemical and non-chemical stressors separately. Collective evidence from a limited number of studies revealed that cumulative exposure assessment that incorporates multiple chemical and non-chemical stressors over the life course may unravel the variability in effect on cognitive development and help explain the inconsistencies across studies. Future research examining the interactions of multiple stressors within a child's total environment, depicting a more real-world exposure, will aid in understanding the cumulative effects associated with a child's ability to learn.

Introduction

Despite progress over the past decades in improving children's cognitive outcomes in the U.S. with lead poison prevention [1] and early childhood development programs [2], disparities in cognitive development in the U.S. persist. Successive waves of studies repeatedly show children from low-income families and minority races/ethnic groups continue to be at greatest risk [3–6]. This growing disparity has driven children's research to shift towards a transdisciplinary approach [7] to considering the impact of cumulative toxic stress from chemical and non-chemical (e.g., economic, prenatal stress, parent child interaction) stressors within the total environment (i.e., built, natural and social environments).

Cognitive development during childhood is a ladder of successive stages with a network of interactions within and between stages that culminates from the continuous experiences with the environment [8]. There is, however, a critical period of time (i.e., 3–6 years old) when a child is primed to develop specific cognitive skills essential for later learning provided the right environmental variables are present [9, 10]. While peak influence on developing skills is during these defined critical periods, research in animal models does suggest that the plasticity of the brain may allow for influence beyond the critical period allowing for later intervention [11]; holding promise for similar changes in children.

Because of its dynamic nature, there is no single factor or single window of exposure which determines a child's potential cognitive ability; rather, it is a result of real-world exposure over time to a mixture of factors with cumulative or interactive effects beginning with maternal exposures prior to conception. The U.S. Environmental Protection Agency (EPA) recognizes that children are more vulnerable to both chemical and non-chemical stressors, positive and negative, in their homes, schools and where they play, as compared to adults. As part of its commitment to protecting children's health and well-being, EPA's strategy includes equipping communities with tools and models that forecast the impact of real-world exposures to chemical and non-chemical stressors in the total environment.

The purpose of this manuscript is to provide a systematic scoping review of positive and negative stressors associated with children's general cognitive ability that are linked to a child's total environment; thus serving as a source of evidence for tailoring existing tools or models used by communities that consider cognitive development a critical area of concern. Previous reviews of child development have considered exposures within their respective discipline (i.e., social or physical; chemical or non-chemical) [12–17], with the exception of one review focused on children from developing countries [18]. This review aims to identify both protective and risk factors of general cognitive ability using a more encompassing model of environmental exposure and review the state-of-the-science in addressing the complex and interactive effects of these factors.

Methods

Data Source

To identify studies eligible for inclusion in the review, a search of the peer-reviewed literature was conducted using the following databases: PubMed, Web of Science, PsycINFO. A combination of words associated with cognitive health (e.g., neurodevelopment or cognitive development) OR ((cognition or learning) AND association) AND children were used to form search strings and applied in the literature search. Filters were used to limit the search to studies published within the past 10 years (2003–2013), available in English, and conducted in children from birth to 18 years of age.

Study Selection

The publications found using the search strings and limitations went through three rounds of screening. In the first round, titles were screened and selected based on their relevance to the research question. In the second round, abstracts of the selected titles were reviewed based on whether they met the inclusion criteria. Finally, full text articles of the selected abstracts were retrieved for further assessment of relevance to the research question. The top ten PubMed related citations of the articles that met the inclusion criteria were also reviewed.

Inclusion Criteria. The following criteria were used to determine whether a study was eligible to be included in this review.

- Observational studies, randomized control trials, review or meta-analysis;
- Time of exposure to a determinant or stressor occurred at or before health outcome was assessed;
- Health outcome was measured in children under 18 years old;
- General cognitive outcome was measured using current and earlier versions of evidence-based assessments of cognitive functioning classified as well established [19] and expressed as a continuous variable or categorized as below average or significant cognitive delay (i.e., >1 or >2 standard deviations (SD) below the mean).
- Study included a measure of association and statistical significance;
- Majority of study participants were healthy children without any existing developmental disabilities, neonatal morbidities, pathologies associated with cognitive deficits, or rare disorders.

Data Extraction and Synthesis

Information extracted from the eligible studies included: author(s) and year of publication, name of study (if available) or the country in which the study was conducted, number of children evaluated, exposure factors and cognitive health outcome measured, the average age(s) at which these measures were assessed, covariates used in the analysis and study results (i.e., means and SD, regression or (B or β) Pearson correlation (r) coefficients, odds ratios (OR)) and indicators of statistical significance (i.e., 95% CI, p-values). Study results include those from univariate (univ) and multivariate analyses for the exposure of interest (EOI) and all possible independent predictors (IP). Factors were categorized into three broad domains: 1) individual determinants; 2) social environment, and 3) built and natural environments A narrative review is provided for each factor assessed in two or more studies either as the EOI or an IP included in the multivariate analysis with consistent results. Results were reported as point differences or B when comparing studies with similar cognitive score SD (i.e., mean = 100, SD = 15–16) and similar exposure measures; otherwise, differences in SD of the cognitive score, β or r are used.

Results

A total of 133 observational studies and 13 cohorts nested within randomized controlled trial studies conducted in 38 countries met the inclusion criteria. Four studies included in this review were pooled data or meta-analysis studies, two of which included cohorts from nine of the observational studies. The most common reasons for exclusion was not reporting results for general cognitive outcome or not using one of the specified tools to measure the outcome.

A summary of characteristics of these studies are presented in Table 1. S1 Table provides a summary of the 258 publications [20–281], grouped by study, included in this review. Over 100 unique factors were examined across the studies. A flowchart of the selection process is illustrated in Fig 1. Table 2 lists a summary of results for all determinants/stressors presented in two or more studies. S2 Table lists the factors that were examined in only one study.

Individual Determinants

Individual determinants of health and well-being include inherent biological (e.g., health, genetics) and social demographic characteristics of the child and parent. Individual determinants also include behaviors or activities of the child (e.g., physical activity, diet) and the parent (e.g., diet, smoking, drugs). However, it is important to note that levels of exposure to such behaviors and activities are factors that may be influenced by lifestyle choices and modelling by parents or other elements of the social environment. Determinants at this level may also impact the extent of exposure and vulnerability to stressors within the social, built and natural environments; making it necessary to examine the embedded heterogeneous effects of both inherent and behavioral stressors of cognitive outcome with reference to exogenous environmental contexts.

Household Demographics. Eleven U.S. studies and one UK study included maternal race/ethnicity in their analyses (IP n = 11). In general, minority or non-white children when lumped into one group had lower cognitive scores than white children ($P_{univ}(s)<0.05$) [20, 21].

Table 1. Summary of Characteristics of the Included Studies.

Type of Study		*n*
Pooled Analysis		3
Meta-analysis		1
Cohort Studies		
	Prospective	105
	Retrospective	3
	Cross-Sectional	38
Average Sample Size		
	<100	27
	100-<1000	103
	1000-<10000	14
	≥10000	2
First Year of Recruitment		
	<1990	19
	1990–1999	53
	≥2000	41
	Not Reported	33
Location of Study		
	U.S, Canada	61
	Latin America	8
	Europe	40
	Australia	13
	Asia	19
	Africa	2
	International	3

doi:10.1371/journal.pone.0147741.t001

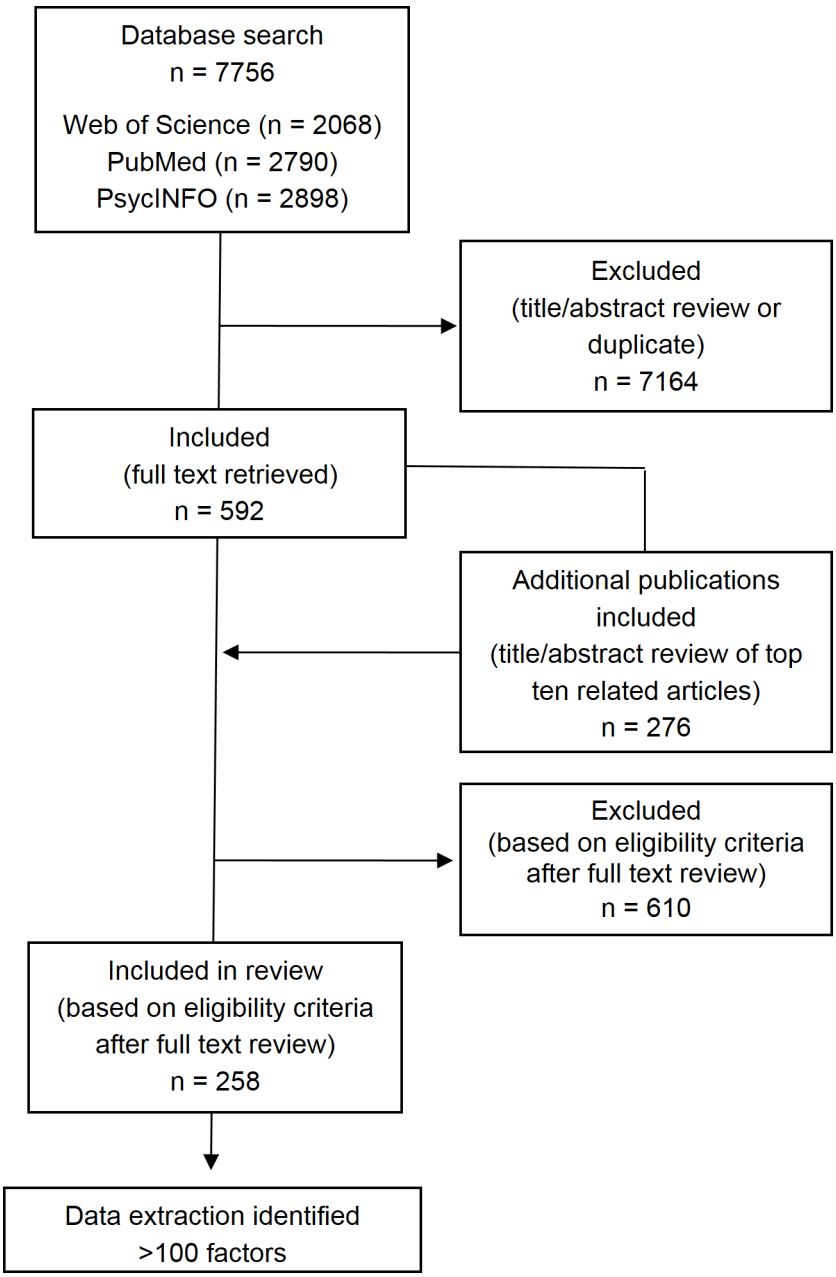

Fig 1. Flowchart of selection process for review.

doi:10.1371/journal.pone.0147741.g001

Differences in effect were found in studies that separated minorities into multiple groups. The cognitive scores of black children measured as early as one year old were two to ten points lower than white children in eight studies in which the effects of race were independent of EOIs (i.e., illicit drug or lead (Pb) exposure, choline, child care, maternal employment, parenting quality, and cognitive stimulation) (B(s) = -9.9 to -1.7, $P(s)<0.05$) [22–29]. Similar differences in cognitive scores were noted in a U.S. cohort of Pb-exposed children (>20 μg/dL) when black children were compared to non-black children (B = -3.0, $P<0.05$) [30].

In comparisons of Hispanic versus white children, the negative association was weaker after adjusting for similar exposures ($P<0.05$ [27]; $P(s)>0.05$ [23, 24, 26]). The disadvantage may be

Table 2. Factors Examined in Multiple Studies as EOI or IP of General Cognitive Ability.

Factor	Number of Studies	Total *n*	Results Across Studies			Overall Trend of Association (% of studies)
			Positive	Negative	Null	
Demographics						
Age (Maternal) [22,23,27,41,43,49,56–60,75,78,82–84, 86,100,127]	19	10187	4	1	14	No trend (74)
Ethnicity/Race						
All minorities vs white [20,21]	2	8138	0	1	1	Inconsistent
Non-Hispanic black vs non-Hispanic white or non-black [22–25,27–30]	8	5694	0	8	0	Negative (100)
Hispanic vs non-Hispanic white [23,24,27]	3	3393	0	1	2	No trend (67)
Other Minorities (Asian, Native American, mixed, other) vs non-Hispanic white [22,24,26]	3	1504	0	0	3	No trend (100)
Non-Hispanic black versus Hispanic [32,35]	2	293	2	0	0	Positive (100)
Education						
Maternal [23,27,29,37–49,56–66]	27	10716	17*	1	9	Positive (63)
Paternal [41,58,61,63,67]	5	1622	3	0	2	Positive (60)
Employed [27,30,46,61,75]	5	3548	1	0	4	No trend (80)
Income						
Household [20,23,27,41,46,57,58,66,249]	9	12379	4	0	5	Inconsistent
Low income [22,27,36,272]	4	4462	1	1	2	Inconsistent
Resources						
Household assets [65,70,71]	3	2734	3*	0	0	Positive (100)
Lack of resources, material hardship [22,31,42,84,126]	5	1550	2*	0	3	Inconsistent
Additional Socioeconomic Status (SES) Factors						
Occupational class [20,48,63,72,74,75]	6	10676	5*	1	0	Positive (83)
Hollingshead four factor index [80,82,84,94,128,170]	6	1202	3*	0	3	Inconsistent
Other SES index/composite [22,24,26,47,61,85,88,157,224]	9	6509	5	0	4	Positive (56)
Language (English is dominant language) [22,23,30,35]	4	3226	0	0	4	No trend (100)
Parent Origin (Immigrant) [58,75]	2	2288	0	0	2	No trend (100)
Inherent Factors-Child						
Gender (female vs male) [22,23,27,29,30,37,38,40,41,43,48, 54,56,58,62,63,66,70,71,75–77,80–89]	32	17465	20	2	10	Positive (63)
Anthropometry						
Birthweight (BW) [20,24,41–43,48,58,73,79,82,84,85, 102,141,171]	15	23395	7*	1	7	Inconsistent
Low BW [23,70,71,75,90, 91, 93–97]	11	5871	0	10	1	Negative (91)
Current body mass index (BMI) [60,80,101] or weight [98]	4	884	0	2*	2	Inconsistent
Below average BMI or weight [66,219]	2	811	0	1	1	Inconsistent
Current height [39,47,64,65,98,101]	6	1324	5	0	1	Positive (83)
Current head circumference [64,65,100,101]	4	1262	4	0	0	Positive (100)
Growth over time [49,102,103]	3	12922	3	0	0	Positive (100)
Poor growth over time [55,251]	2	5935	0	1	1	Inconsistent
Birth Outcomes and Neonatal Health						
Gestation (weeks) [20,31,40,48,75,83,127,128,170]	9	10415	3	1	5	No trend (56)
Preterm (<37 weeks) [58,60,104,105]	4	1021	0	2	2	Inconsistent
Moderate to late preterm (32-<37 weeks) [106–108]	3	12785	0	1	2	No trend (67)
Extremely preterm (<32 weeks) [109–111]	3	3020	0	3	0	Negative (100)
Neonatal ICU [58,267]	2	903	0	1	1	Inconsistent
Neonatal medical risk [86,97]	2	354	0	1	1	Inconsistent

(*Continued*)

Table 2. (*Continued*)

Factor	Number of Studies	Total *n*	Results Across Studies			Overall Trend of Association (% of studies)
			Positive	Negative	Null	
Resuscitation [221,263]	2	6075	0	1	1	Inconsistent
Sleep Behavior and Health						
Sleep disordered breathing (SDB) [112–119]	8	2180	0	7*	1	Negative (88)
SDB symptom (snoring) [114,116,117,120]	4	356	0	4	0	Negative (100)
Daytime sleepiness [121,122]	2	674	0	2*	0	Negative (100)
Sleep wake problems [80,122]	2	205	0	0	2	No trend (100)
Duration [80,118,122,234]	4	1100	2	1	1	Positive (50)
Childhood Health						
Health history [28,84,88]	3	5509	0	1	2	No trend (67)
Atopic disease [74,252]	2	691	0	1	1	Inconsistent
Eczema [243,252]	2	614	0	1	1	Inconsistent
Thyroid biomarkers (TSH level) [217,229,241,258]	4	1363	0	2	2	Inconsistent
Inherent Factors-Parents						
Maternal IQ [20,23,24,27–30,37,60,61,64,65,72,79,81–87,89,100,123–126,128]	28	18768	24	0	4	Positive (86)
Physical Health (prenatal)						
Multiple gestation [20,58,83,97]	4	8477	0	3	1	Negative (75)
Parity [20,22,26,54,57,62,63,74,78,83,124, 127]	12	11640	0	5	7	No trend (58)
Body Mass Index or weight (pre-pregnancy) [20,60,75,133]	4	16418	0	4	0	Negative (100)
Thyroid dysfunction (low T4) [129–132]	4	2224	0	3	1	Negative (75)
Thyroid dysfunction (TPOAb) [83,129]	2	183	0	1	1	Inconsistent
Thyroid dysfunction (high TSH) [83,129,130,258]	4	2431	0	1	3	No trend (75)
Thyroid biomarkers (TSH level) [222,241,258]	3	1065	0	0	3	No trend (100)
Thyroid biomarkers (T4 level) [222,241,258]	3	1065	0	0	3	No trend (100)
Dental amalgam [82,277]	2	828	1	0	1	Inconsistent
Hypertension [128,278]	2	1497	0	0	2	No trend (100)
Maternal Mental Health						
Anti-depressants (prenatal) [125,232]	2	281	0	0	2	No trend (100)
Prenatal depression (high risk) [125,134,135]	3	7198	0	1	2	No trend (67)
Prenatal depression (symptom score) [125,135]	2	463	0	0	2	No trend (100)
Postpartum depression(high risk) [134–136]	3	7565	0	2*	1	Negative (67)
Postpartum depression (symptom score) [27,57,135]	3	1900	0	2*	1	Negative (67)
Postnatal depression (high risk) [46,83,134]	3	5215	0	1	2	No trend (67)
Postnatal depression(symptom score) [27,28,57,125]	4	2318	0	1	3	No trend (75)
Prenatal stress [43,137,138]	3	825	0	3*	0	Negative (100)
Postnatal stress [43,83,138]	3	877	0	0	3	No trend (100)
Prenatal anxiety [43,135,139]	3	473	0	1	2	No trend (67)
Prenatal cortisol [43,137,139]	3	335	0	3	0	Negative (100)
Diet						
Breastfeeding						
Ever breastfed [56,141,154]	3	1623	3	0	0	Positive (100)
Breastfeeding duration [20,48,52,60,61,63,74,83,142,146, 147]	11	10191	8*	0	3	Positive (73)
Exclusively breastfed [54,148,150]	3	2375	3*	0	0	Positive (100)
Breastfeeding intensity [148,149]	2	7601	2*	0	0	Positive (100)
Total n-3 long chain-polyunsaturated fatty acid (LC-PUFA) [82,148]	2	745	1	0	1	Inconsistent

(*Continued*)

Table 2. (*Continued*)

Factor	Number of Studies	Total *n*	Results Across Studies			Overall Trend of Association (% of studies)
			Positive	Negative	Null	
Docosahexaenoic acid (DHA) [48,148,151–153]	5	1018	3	0	2	Positive (60)
Total n-6 LC-PUFA [82,148]	2	745	0	0	2	No trend (100)
Arachidonic acid (AA) [48,148,151,153]	4	938	1	1	2	Inconsistent
Linolenic acid [48,148]	2	577	0	0	2	No trend (100)
DHA/AA ratio [48,148,152]	3	653	2	0	1	Positive (67)
α-linolenic acid [48,148]	2	577	0	0	2	No trend (100)
Eicosapentaenoic acid [48,148]	2	577	0	0	2	No trend (100)
Child's Diet						
Infant diet pattern, recommended/healthy [149,155]	2	7338	2	0	0	Positive (100)
Infant diet pattern, not recommended, processed [149,155]	2	7338	0	1	1	Inconsistent
All fish [71,144]	2	226	0	1	1	Inconsistent
Canned fish [71,144]	2	226	1	0	1	Inconsistent
Dietary iron [38,40,47,87,100,157]	6	1292	4	0	2	Positive (67)
Prenatal Diet						
Any seafood [237,247,253,258]	4	10082	2	0	2	Inconsistent
Fish [71,75,233,253]	4	2431	2	0	2	Inconsistent
Choline [29,281]	2	486	1	0	1	Inconsistent
Folate supplementation [159,160]	2	973	0	0	2	No trend (100)
Folate deficiency [127,158]	2	508	1	0	1	Inconsistent
Iodine supplementation or intake [258,265]	2	2201	0	0	2	No trend (100)
Lifestyle Factors						
Alcohol (pre-conception) [161,239]	2	412	0	1	1	Inconsistent
Alcohol (prenatal, any exposure) [20,25,42,43,78,84,86]	7	9438	0	1	6	No trend (86)
Alcohol (prenatal, frequency) [161,164,216, 240,280]	6	19516	0	2	4	No trend (67)
Low alcohol intake (prenatal) [162,163,165]	3	9020	0	0	0	No trend (67)
Moderate to high alcohol intake (prenatal) [161–163,165]	4	9095	1	3	0	Negative (75)
Binge drinking (prenatal) [164,165,216,262]	4	18567	0	1	3	No trend (75)
Alcohol (father, frequency) [169,216]	2	24549	1*	1	0	Inconsistent
Alcohol related dependence (father) [28,166]	2	680	0	2	0	Negative (100)
Maternal smoking (prenatal, any) [41,56,60,63,71,78,83,242]	8	2526	0	1	7	No trend (88)
Maternal smoking (prenatal, frequency) [42,43,86,216, 226,242]	6	16345	0	1	5	No trend (83)
Maternal smoking (postnatal, any) [61,242]	2	584	0	0	2	No trend (100)
Maternal smoking (postnatal, frequency) [42,242]	2	590	0	0	2	No trend (100)
Environmental tobacco smoke (ETS) (prenatal, any) [31,50,62,126,242]	5	1372	0	2	3	No trend (60)
ETS (prenatal, frequency) [44,216,242]	3	14314	0	1	2	No trend (67)
ETS (postnatal, any) [41,52,62]	3	972	0	0	3	No trend (100)
Cocaine (prenatal) [25,42,77,86,124,248,254,257,268]	9	3322	0	3	5	No trend (63)
Marijuana (prenatal) [28,42,86]	3	1049	1	0	2	No trend (67)
Social Environment						
Family Structure						
Marital status [20,27,30,31,124,126,127,169]	8	22484	4*	0	4	Inconsistent
Live with both parents [23,82]	2	2330	1	0	1	Inconsistent
Primary caregiver is mother [42,75]	2	1853	1	0	1	Inconsistent
Foster or institutional care [167,168]	2	420	0	2	0	Negative (100)

(*Continued*)

Table 2. (*Continued*)

Factor	Number of Studies	Total *n*	Results Across Studies			Overall Trend of Association (% of studies)
			Positive	Negative	Null	
Siblings [20,25,27,58,61]	5	9595	0	4*	1	Negative (80)
Changes in family structure [22,169]	2	11956	0	2	0	Negative (100)
Parent Interactions						
Cognitive stimulation–activities [26,88]	2	4920	2	0	0	Positive (100)
Cognitive stimulation-HOME [20,27,37,59,64,70,72,76,81,84,87,89,124,141,170]	15	12490	15****	0	0	Positive (100)
Cognitive stimulation–HSQ [28,29,63,136]	4	1632	3	1	0	Positive (75)
Cognitive stimulation–PROCESS [25,82]	2	500	2	0	0	Positive (100)
Cognitive stimulation—other tool [22,84,86]	3	1287	2	0	1	Positive (67)
Quality of maternal interaction [23,35,88,170]	4	6366	4	0	0	Positive (100)
Sensitivity [22,27,67,69,97,171]	6	1611	3	0	3	Inconsistent
Supportive behavior [26,88,170,171]	4	5036	3	0	1	Positive (75)
Discipline [22,88,170]	3	4557	0	0	3	No trend (100)
Social support for the mother [28,138]	2	1171	2	0	0	Positive (100)
Childcare/School						
School attendance [64,100]	2	595	2	0	0	Positive (100)
Child care attendance [27,46]	2	974	0	0	2	No trend (100)
Type of child care (center or group) [22,27]	2	1260	2	0	0	Positive (100)
Quality of care [22,27,69]	3	1323	3	0	0	Positive (100)
Additional Psychosocial Factors						
Witnessed domestic violence [66,245]	2	2384	0	1	1	Inconsistent
Neglect or abuse [68,224]	2	662	0	0	2	No trend (100)
Stress/anxiety [48,68,83,224]	4	832	0	1	3	No trend (75)
Built and Natural Environments						
Metals and Other Elements						
Arsenic (As) (current) [47,64,65,100,173,175,176]	7	3725	1*	5	1	Negative (71)
As (prenatal) [175,176]	2	2149	0	1*	1	Inconsistent
Cadmium [186,190]	2	1297	0	0	2	No trend (100)
Fluoride (current) [47,174,178–180]	5	1475	0	5	0	Negative (100)
Lead (Pb) (current, sample restricted to ≤10 μg/dL) [24,41,79,157,184,185]	6	1588	0	5	1	Negative (83)
Pb (current, no restriction) [38,47,85,87,182,183, 185,187–189]	10	2316	0	8*	2	Negative (80)
Pb (prenatal) [31,52,59,85,98,127,190]	7	2111	0	5	2	Negative (71)
Pb (lifetime) [59,85,183,187]	4	1120	0	3	1	Negative (75)
Pb (postnatal) [85,183,187,188]	4	1481	0	1	3	No trend (75)
Manganese (postnatal) [38–41,64,99,100,188,192]	8	1906	1	6*	1	Negative (75)
Mercury (Hg) (prenatal) [51,71,75,218,223,247,271]	7	4436	0	4*	3	Positive (57)
Hg (postnatal) [30,71,84,144]	4	1664	1	1	2	Inconsistent
Air Pollutants						
Nitrogen dioxide (NO2) (indoor) [74,193]	2	2305	0	2	0	Negative (100)
NO2 (outdoor) [230,236]	2	2099	0	1	1	Inconsistent
Polyaromatic hydrocarbons (prenatal) [37,50,126]	3	561	0	3	0	Negative (100)
Endocrine Disruptors						
Total polybrominated diphenyl ether (PBDE) (prenatal) [194,195]	2	267	0	2*	0	Negative (100)
Total PBDE (postnatal) [194,196,197]	3	608	0	1	2	No trend (67)
PBDE 47 (prenatal) [195,198,199]	3	254	0	1	2	No trend (67)

(*Continued*)

Table 2. (*Continued*)

Factor	Number of Studies	Total *n*	Results Across Studies			Overall Trend of Association (% of studies)
			Positive	Negative	Null	
PBDE 47 (postnatal) [196,198,199]	3	600	0	0	3	No trend (100)
PBDE 99 (prenatal) [95,198]	2	176	0	2	0	Negative (100)
PBDE 99 (postnatal) [196,197]	2	360	0	1*	1	Inconsistent
PBDE 100 (prenatal) [195,198]	2	176	0	1	1	Inconsistent
PBDE 100 (postnatal) [196,197]	2	360	0	0	2	No trend (100)
PBDE 153 (prenatal) [195,198]	2	133	0	1	1	Inconsistent
PBDE 153 (postnatal) [196,197]	2	360	0	0	2	No trend (100)
PBDE 154, 183 (postnatal) [196,197]	2	360	0	0	2	No trend (100)
PBDE 209 (postnatal) [196,197]	2	360	0	2	0	Negative (100)
Phthalate [200–202]	3	1145	0	2	1	Negative (67)
Total PCBs (polychlorinated biphenyl) (prenatal) [89,212,227,250,260,271]	6	2845	0	2	4	No trend (67)
PCB 118 (prenatal) [89,227,260,270]	4	1381	0	1	3	No trend (75)
PCB 138 (prenatal) [89,212,227,270]	4	2638	0	1*	3	No trend (75)
PCB 153 (prenatal) [89,212,227,250,270]	5	2670	0	2*	3	No trend (60)
PCB 153 (postnatal) [227,250]	2	306	0	0	2	No trend (100)
PCB 156 (prenatal) [89,260]	2	894	0	1	1	Inconsistent
PCB 170 (prenatal) [89,260]	2	894	0	0	2	No trend (100)
PCB 180 (prenatal) [89,212,227,260,270]	5	2772	0	1*	4	No trend (80)
PCBs+dioxins (prenatal) [260,279]	2	284	0	0	2	No trend (100)
Pesticides						
Mirex (prenatal) [203,204]	2	262	0	0	2	No trend (100)
Chlorpyrifos (prenatal) [205,206]	2	635	0	1	1	Inconsistent
Dichlorodiphenyltrichloroethane (DDT) (prenatal) [204,209–212]	5	2528	0	3	2	Positive (60)
Hexachlorobenzene (prenatal) [204,212]	2	1549	0	1	1	Inconsistent
Dialkylphosphates (DAP) (prenatal) [205,208,214]	3	599	0	2	1	Negative (67)
DAP (postnatal) [205,208]	2	450	1	0	1	Inconsistent
House quality [65,174,206]	3	2481	1	1	1	Inconsistent

* indicates number of studies that were significant after stratified analysis

doi:10.1371/journal.pone.0147741.t002

stronger in Hispanic children living in urban cities as evidenced in two U.S. studies evaluating cognitive development. Hispanic children had lower scores assessed at earlier ages as compared to non-Hispanic black children (i.e., 4–6 points) independent of EOIs (i.e., parent child interactions, pesticide exposure and air pollution) ($P(s)<0.05$) [31–35]. However, the effect diminished with age; whereas, the effects of air pollution and pesticide exposure persisted ($P(s)>0.05$) [36, 37].

Maternal education (i.e., years or level of attainment) was included in 27 studies as a possible predictor of cognitive ability (EOI n = 2; IP n = 25). Maternal education was measured in years in sixteen studies (EOI n = 1; IP n = 15). In a low-income U.S. cohort, years of education continued to be a positive predictor of early cognitive development even after accounting for other significant positive predictors (i.e., economic resources and parenting) (B = 0.11; $P<0.05$) [23]. Maternal education can have a protective influence in children exposed to manganese (Mn) as evidenced in four studies where cognitive scores increased 0.7–1.0 point per year of education ($P(s)<0.05$ [38–40]; $P = 0.08$ [41]). In fact, the benefit associated with

maternal education was strongest in Korean children with high Mn levels (>14 μg/dL) (B = 1.72, $P<0.05$) [41]. In one U.S. study that used several models to evaluate the effects of choline, level of education was a consistent positive predictor of cognitive ability (B(s) = 0.9; $P(s)<0.05$) [29]. Years of education was also a positive predictor in six studies independent of their EOIs (i.e., employment, stress, cocaine, Pb, pesticide and indoor mold) ((+) $P(s)<0.05$ [27, 36, 42–45]; (-) $P<0.05$ [46]; $P(s)>0.05$ [47–49]).

Thirteen studies included level of educational attainment as a predictor of cognitive ability (EOI n = 1; IP n = 12). Three longitudinal cohort studies of children from the U.S. [31, 32, 34, 36, 37], Poland [44, 50–54] and the UK [20, 55, 56] consistently found level of education to be a positive predictor of cognitive development over time regardless of the EOI. Seven studies suggested that completion of secondary education (at a minimum) benefitted cognitive development for children from higher income countries independent of EOI (B(s) = 1.3–7.5; $P(s)<0.05$ [37, 54, 56–60]; $P(s)>0.05$ [61–63]). In children from low income countries any education above the primary level (vs. no education or illiteracy) may positively influence cognitive ability, as suggested by two studies examining the effects of water contamination on cognitive development in Bangladeshi children (SD(s) = 0.26 and 0.42, $P(s)<0.07$ [64, 65]; $P>0.05$ [66]). Additional studies suggest that the cognitive benefits of education are not specifically related to the mother, rather education attained by either parent can be a positive predictor ($P(s)<0.05$ [30, 41, 67, 68]; $P<0.10$ [69]; $P_{univ}<0.05$ [58]; $P(s)>0.10$ [61, 63]).

Family assets (e.g., car, real estate, household items) assessed in three studies (IP n = 3) were associated with higher cognitive scores by as much as 0.25–0.85 SD. Household items, such as televisions, positively influenced cognitive ability in two Bangladeshi cohorts independent of the effects of the EOI (i.e., low birth weight or water contaminants ($P<0.05$ [70]; $P<0.10$ [65]). Homeownership was also a positive predictor of cognitive ability in Italian school children, independent of mercury (Hg) exposure ($P = 0.04$) [71].

Occupational social class (or job prestige) was assessed in six studies (EOI n = 1; IP n = 5). A father's job prestige was a positive indicator of cognitive ability in two Australian cohorts (i.e., 1.2–2.0 points per point change in prestige score) [63, 72, 73]. This association remained significant for cognitive scores measured at four and seven years old independent of effects associated with cognitive stimulation at home and maternal intelligence ($P(s)<0.05$) [72]. In a second Australian cohort, paternal job prestige was a positive predictor independent of breastfeeding (P = 0.08) [63]. Better parent job prestige predicted higher cognitive scores in three of four studies independent of their EOIs (i.e., atopy, diet, Hg) (unskilled vs. professional—B(s) = -11.0 to -1.8; $P(s)<0.05$ [20, 74, 75]; $P>0.05$ [48]).

Inherent Factors–Child. The majority of studies that included gender as an IP (n = 32) found that girls scored 2–5 points higher than boys independent of the effects associated with the EOI (i.e., socio-demographic determinants, metals, parent-child interactions, prenatal diet, air pollutants, breastfeeding, synthetic chemicals, sleep duration, and drugs) ($P(s)<0.05$ [22, 23, 26, 27, 29, 40, 48, 51, 53, 54, 56, 58, 63, 70, 75–84]; $P(s)>0.05$ [30, 38, 41, 43, 62, 66, 71, 85–87]). The opposite was true in two studies after accounting for the effects of the EOI (i.e., health and demographic risks, thyroid health) ($P(s)<0.05$) [88, 89]. Multiple analyses for one U.S. cohort investigating the effects of pesticides, air pollutants and material hardship provided mixed results [31–34, 36, 37].

Eleven studies evaluated the association between low birth weight (LBW) status (i.e., <2500 g) or extremes of LBW (i.e., <1500 g or very and <1000 g or extremely LBW) and cognitive development (EOI n = 7; IP n = 4). LBW status adversely affected cognitive development as early as infancy as evidenced in ten month old Bangladeshi infants (not LBW–B = 2.7, $P<0.05$) [70]. In a cohort of Indian schoolchildren, children born with LBW were at risk of below average scores or cognitive delay (OR(s) = 1.76, 4.46, $P_{univ}(s) = 0.10, 0.02$) with risk of

cognitive delay heightened for children born VLBW (OR = 5.27, P_{univ} = 0.01) [90]. The six studies that examined very or extremely LBW as the EOI also found that these BWs were associated with lower cognitive scores (i.e., 7.6–16.2 points) as compared to those born full term among cohorts of children ranging in age from 1.5 to eight years old ($P<0.05$ [91]; $P_{univ}(s)<0.05$ [92–96]). Effects of LBW status were also detrimental in three studies independent of EOIs (i.e., dietary Hg [71, 75] or economic indicators and parenting quality [23]).

LBW as a result of intrauterine growth restriction during multiple gestation was also a negative predictor of cognitive score at two years old in an Israeli cohort of triplets [97]. The cognitive scores of triplets with a discordant birth weight (i.e., 15% lower than the heaviest triplet) was six points lower than their siblings ($P<0.05$) [97].

The impact of current height and/or head circumference on cognitive development was assessed in seven studies (EOI n = 1; IP n = 6). Height was positively associated with cognitive scores in a cohort of Mexican toddlers independent of prenatal Pb exposure (Z-score B = 2.87, $P = 0.05$) [98]. In three Bangladeshi cohorts of school children height and/or head circumference were positive predictors of cognitive ability independent of the effects of water contaminants (i.e., arsenic (As), Mn) (per centimeter—height SD(s) = 0.04–0.07; head circumference SD(s) = 0.08–0.30; $P(s)<0.05$ [64, 65, 99, 100]). In two cross-sectional studies, height was not associated with cognitive scores after accounting for effects associated with the same contaminants ($P(s)>0.05$) [39, 47]. In a UK cohort assessing different growth parameters (e.g., height, head circumference, weight, BMI), these measures were correlated with better cognitive scores at seven years old only in those born very preterm ($P_{univ}(s)<0.05$); whereas there was no correlation in full term children [101].

Three studies examined the impact of physical growth over time on cognitive development as the EOI. Growth (i.e., weight and height) during the first year of life and subsequent growth until five years old was associated with increased cognitive scores at six years old in a Belarusian cohort (difference in weight and height Z-score–B(s) = 0.29–0.77 and 0.57–0.84, $P(s)<0.05$) [102]. One UK cohort evaluated gains in height, weight and head circumference in multiple analyses. Head growth during the first year of life was positively associated with cognitive ability at four and eight years old, independent of later growth (Z-score difference B(s) = 1.56–1.97, $P(s)<0.05$) [103]. Increases in cognitive score were seen at eight years old with weight gain specifically between birth and two months (per SD difference in weight–B = 0.84, $P<0.05$) [55].

Fetal growth (i.e., head diameter, chest circumference and leg length) and its influence on cognitive ability was evaluated in a Scandinavian cohort as the EOI [49]. Fetal size at each trimester was a positive predictor of cognitive ability at 13 months old (Z-score difference per trimester B(s) = 1.35, 1.93 and 2.12, $P(s)<0.05$).

Ten studies evaluated the effect of preterm birth on cognitive development (EOI n = 8; IP n = 2). In general, results associated with any preterm birth (i.e., less than 37 weeks gestation) were inconsistent ($P<0.05$ [104], $P_{univ}<0.05$ [105]; $P(s)>0.05$ [58, 60]. Any negative effects associated with preterm birth became evident when the severity of preterm birth was examined.

Moderate to late preterm birth (i.e., 32 to < 37 weeks) was a negative predictor of cognitive ability in seven year old Dutch children (B = 2.7, $P = 0.03$) [106]. However, the adverse effects may be restricted to girls in the Dutch cohort as suggested after stratified analysis [106]. In a U.S. cohort, preterm birth at this stage increased the risk of receiving a below average score at two years old as compared to full term birth (OR = 2.26, $P_{univ}<0.001$) [107]. On the other hand, in a UK cohort, births in the moderate to late preterm stage were not associated with cognitive ability measured at eight years old even before adjusting for covariates ($P_{univ} = 0.14$) [108].

The negative effects associated with preterm birth were more consistent in studies that excluded children born late preterm (34 to <37 weeks). One study showed that five year old children born very or extremely preterm (≤32 weeks) were at risk of significant cognitive delay (OR = 3.78, P_{univ}<0.001) [109]. Risk of cognitive delay was enhanced as gestation time decreased in this cohort, as well as in two other studies that evaluated extreme preterm birth (≤ 28 weeks) (OR(s) = 32, 23, $P_{univ}(s)$<0.001) [110, 111]).

Severity of sleep disordered breathing (SDB) and/or symptoms (i.e., ranging from loud, frequent snoring to obstructive sleep apnea) in children between three and twelve years old was evaluated as the EOI in nine studies. Severity of SDB or symptoms observed in sleep studies or reported by parents was negatively associated with cognitive measures in the majority of studies ($P(s)$<0.05 [112, 113]; P = 0.06 [114]; $P_{univ}(s)$<0.05 [115–117]; P>0.05 [118]; P_{univ}>0.05 [119]). Frequent snoring symptoms in SDB diagnosed children regardless of SDB severity was also an indicator of lower cognitive scores ($P_{univ}(s)$<0.05 [114, 116, 117, 120]). Two additional studies evaluating sleep-related patterns as the EOI found that daytime sleepiness was also a negative predictor of cognitive scores (P<0.05 [121];P_{univ}<0.05 [122]).

Inherent Factors–Parents. Maternal IQ was included in the analyses of 28 studies evaluating cognitive development (EOI n = 2; IP n = 26). IQ was a positive predictor of cognitive development in Australian children assessed from two to 11–13 years of age independent of the effects of cognitive stimulation at home and occupational social class (per 10 IQ points—B (s) = 0.29–0.48, $P(s)$<0.05) [72]. In a Spanish cohort, higher maternal intelligence (i.e., tertile 3 vs. 1) appeared to impart a protective effect on early cognitive development only for children with mothers belonging to a lower occupational class after accounting for the effects of maternal mental health (B = 7.9, interaction P<0.05) [123]. No difference in association was seen based on maternal education [123]. In a second Spanish cohort, both maternal and paternal IQ were positive predictors of early cognitive development independent of each other and breastfeeding (per maternal IQ—B(s) = 0.02; $P(s)$<0.05) [61]. IQ was a positive predictor of children's cognitive ability in 20 studies independent of the EOI (i.e., synthetic chemicals, drugs, socioeconomic determinants, genetics, parent-child interaction, maternal health, metals, diet, water and air pollutants, and pesticides) ($P(s)$<0.05 [20, 23, 24, 26–30, 37, 60, 64, 78, 79, 81, 84–86, 89, 100, 124–128]; $P(s)$>0.05 [65, 82, 83, 87]).

Signs of thyroid dysfunction during pregnancy associated with low free or total thyroxine (FT4 orTT4) in women without thyroid disease were evaluated in four studies (EOI n = 4). Low TT4 levels (i.e., <2.5th percentile) assessed at 16–20 weeks gestation were negative predictors of early cognitive development in a cohort from China (B = -9.3, OR (cognitive score<100) = 12.98, $P(s)$<0.05) [129]. Two studies found that low FT4 levels (i.e., <10th percentile) during early pregnancy (i.e., ≤20 weeks gestation) were predictive of lower cognitive scores measured in Spanish and Dutch toddlers (B(s) = -2.2 and -8, $P(s)$<0.05) [130, 131]. Conversely, a U.S. study found that low levels of FT4 (i.e., <3rd percentile) specifically during the second trimester were not associated with cognitive ability in children of similar age [132].

Pre-pregnancy BMI was examined in four studies (EOI n = 1; IP n = 3). In a U.S. cohort, children born to underweight or severely obese mothers were at increased risk of below average scores as compared to those born to women with healthy weights (RR(s) = 1.36 and 1.38; P<0.05) [133]. In a Dutch cohort, the effect of pre-pregnancy BMI on cognitive ability at seven years old remained significant after accounting for the effects of the child's BMI at 4 years old (per kg/m^2- B_{univ} = -0.66, B = -0.62) [60]. This significance did not hold when BMI at 7 years old was included in the regression model [60]. Adverse effects were also associated with higher BMIs in two studies independent of prenatal Hg exposure in Spanish toddlers [75] and diet patterns in eight year old UK children [20].

Four studies included multiple gestation in their analysis of cognitive development (EOI n = 1; IP n = 3). Twin gestation was associated with lower cognitive scores independent of socio-demographic determinants in Greek toddlers [58] and independent of diet in UK school-children [20] (B = -7.82 and -2.47, respectively; $P(s)<0.05$). Multiple gestation, in general, adversely affected cognitive development by two years of age in an Israeli cohort (β = -0.22, $P<0.05$) [97]. In fact, the cognitive scores of triplets at multiple assessments were lower than both that of twins and singletons (vs. singleton and twins–B(s) = -7.3 to -4.1 and -6.0 to -2.5, $P(s)<0.05$) [97]. Multiple gestation was not a significant predictor in a Scottish study evaluating the effects of thyroid health on cognitive scores by 5.5 years old [83].

Prenatal depression was evaluated in three studies (EOI n = 2; IP n = 1), one of which also evaluated the cumulative effect of maternal depression from pregnancy through childhood [134]. Exposure to mothers at high risk of prenatal depression adversely affected cognitive development as seen in three studies which noted a decrease in cognitive scores in Greek toddlers (B = -5.45, $P<0.05$) [135] and Canadian preschoolers (B = -5.1, $P_{univ}<0.05$) [125]. High risk of prenatal depression was not a significant predictor of cognitive scores in eight year old UK children after adjusting for any postnatal depression [134]. A score of cumulative depressive symptoms, on the other hand, was not predictive of early cognitive development in the Canadian or Greek cohorts ($P>0.05$ [135]; $P_{univ}(s)>0.05$ [125]).

Post-partum depression during infancy was evaluated in five studies (EOI n = 4; IP n = 1). Children born to mothers at higher risk for post-partum depression had lower cognitive scores as measured in the Greek cohort (B = -5.64, $P<0.05$) [135] and the UK cohort (B = -2.4, $P_{univ}<0.05$) [134]. A third study found no association between risk of depression during this period and cognitive ability in an Australian cohort [136]. A score for cumulative symptoms of postnatal depression assessed two months after birth was also negatively associated with cognitive development in the Greek cohort (B = -0.33, $P<0.05$) [135] and in two year old French children (B = -0.85, $P = 0.07$) [57]. Conversely, depressive symptom scores did not appear to be associated with cognitive development in a U.S. cohort after accounting for the effects of mother-child interactions ($P>0.05$) [27].

Four studies suggest that high levels of prenatal stress assessed using an assessment tool and/or measuring cortisol levels, a biomarker of stress, may be predictive of lower cognitive scores (EOI n = 4). An increased risk of lower cognitive scores ($\leq 25^{th}$ percentile) was noted in Dutch infants whose mothers experienced high stress due to everyday problems, specifically during early pregnancy, independent of postnatal stress and depression (OR = 1.1, $P<0.05$) [137]. Adverse effects on cognitive scores due to high stress levels were also found in a New Zealand cohort of pre-school children (B = -3.4, $P<0.01$) [138]. Similar results were presented in a third study of UK toddlers in which prenatal stress was a negative predictor independent of cortisol and postnatal stress (index score—B = -2.60, $P<0.001$) [43].

The effects of prenatal cortisol were evaluated in the Dutch and UK cohorts, as well as in a U.S. study. The studies yielded inconsistent results possibly due to timing of exposure. For the UK cohort, cortisol measures only during the first half of pregnancy were negatively associated with cognitive development between 1 and 2 years old (ln (nmol/L)—B = -9.45, $P<0.05$) [43]. In Dutch infants, the period of sensitivity to the negative effects of cortisol exposure occurred during late pregnancy (tertile 3 vs. 1 –B = 5.0, $P<0.05$) [137]. The U.S study revealed a difference in effect across pregnancy where cortisol levels during early pregnancy had an adverse effect (per μg/dL–β = -0.23) and levels during late pregnancy enhanced early cognitive development (β = 0.17; $P(s)<0.05$) [139].

Breastfeeding. Exposure to breastfeeding was examined in eleven studies (EOI n = 9; IP n = 2). The association between breastfeeding and cognitive ability was explored using three different types of measures (i.e., ever-exposed, duration and intensity of exposure).

Two studies evaluated ever being breastfed as an IP of cognitive development. Breastfeeding seemed to be associated with higher cognitive scores among a Mexican cohort in which scores were measured periodically over the child's first year of life. The beneficial effects associated with breastfeeding were not apparent as early as the first month of life (P_{univ}>0.05) [140]. However, breastfeeding over a child's first year of life was a positive predictor of cognitive development from one to twelve months old independent of prenatal pesticide exposure (B = 1.14, P = 0.03) [141]. These effects were also evident in a UK study examining the association between physical growth and cognitive scores measured at four years old (B = 3.4, P< 0.01) [56]).

Duration of breastfeeding was included in eight independent studies and one multi-cohort study (EOI n = 5; IP n = 4). Together, these studies suggest that a minimum of four to six months of breastfeeding may benefit cognitive development. Two distinct Spanish cohorts included in a multi-cohort study examined the impact of breastfeeding duration on cognitive ability. Four to five months of breastfeeding (versus 2 weeks) was associated with a 10.7 point increase in cognitive ability at one year old in the first cohort [142]. In the second cohort, each month of breastfeeding was associated with a 0.56 point increase in cognitive score at four years old after adjusting for effects associated with atopy (P = 0.052) [74]. In an analysis that included both cohorts, a minimum of five months of breastfeeding was associated with a 7.7 point increase at four years old as compared to those children breastfed for less than one month (P<0.05), with a stronger protective effect seen in children prenatally exposed to high levels of DDT (>20 ng/mL, B = 13.04, P<0.05); thus counteracting any adverse effects associated with DDT [143]). Similar durations of breastfeeding (i.e., four to six months) were positively associated with children from four additional cohorts from this study (P_{univ}<0.05 [75], P_{univ}>0.05 [144]). Similarly, a second Spanish study found that a minimum of four months of breastfeeding (versus >0–4 months) was associated with increases in cognitive scores at 18 [145] and 24 months old [61] (B(s) = 4.6 and 4.3, $P(s)$<0.05). In a Polish cohort, breastfeeding for a minimum of 6 months was beneficial in regards to cognitive development even with inclusion of childhood exposure to mold (B = 4.0, P<0.05) [44]. Duration of breastfeeding was a positive predictor in one of two studies evaluating cognitive development in preschool children (per week–B = 0.29, P<0.05 [48], P>0.05 [63]). Preliminary analysis from both studies found that a minimum of five to six months of exposure was positively associated with cognitive scores ($P_{univ}(s)$<0.05) [48, 63]. Breastfeeding duration was a significant predictor in one study after accounting for the effects of the child's BMI (per month—B = 0.93, P<0.05) [60]; unlike, in studies evaluating thyroid health or pesticides [83, 146].

A pooled analysis study suggested that economic measures at the national level may influence the effect of breastfeeding (heterogeneity P = 0.09) [147]. The study showed duration of breastfeeding (i.e., 0-<1, 1-<3, 3-<6 and 6 months) having a stronger effect on cognitive ability in four year old Brazilian children (B = 1.97) as compared to eight year old UK children (B = 0.97, $P(s)$<0.001), with significant increases in cognitive scores associated with a minimum of three months duration for both groups ($P(s)$<0.05) [147]. In a second analysis of the UK cohort, the beneficial effects of breastfeeding by one month were also independent of later childhood diet ($P(s)$≤0.051) [20].

The UK, Spanish multi-cohort, Polish studies, and an Italian study also evaluated the effect of exclusivity or intensity of breastfeeding (EOI n = 4). Two studies found that a higher proportion of breastfeeding in a child's diet during the first year of a child's life can significantly improve cognitive scores as early as fourteen months old as seen in the Spanish cohort [148] and as late as eight years old as seen in the UK cohort [149] ($P(s)$<0.05). In fact, the beneficial effects of exclusive breastfeeding for six months or longer superseded those of complementary feeding in the Polish and Spanish cohorts (B(s) = 2.5–3.5, $P(s)$<0.05) [54, 148] and duration of

exclusivity in an Italian cohort (per week, B = 0.04, $P = 0.09$) [150] may account for variations in the beneficial effects of breastfeeding.

Long Chain Polyunsaturated Fatty Acids (LC-PUFAs)—The benefits of breastfeeding may be associated with essential nutrients present in breast milk as suggested by the Spanish cohort study [148]. Maternal sources of 11 LC-PUFAs and their association with cognitive development were examined in five studies (EOI n = 4; IP n = 1). LC-PUFAs obtained through childhood diet were also examined in two studies (EOI n = 2).

The effect of total and/or individual omega-3 and omega-6 LC-PUFAs was examined in six studies (EOI n = 5; IP n = 1). Spanish toddlers exclusively breastfed for longer duration (i.e., >4 months) benefitted from higher levels of omega-3 LC-PUFAs as measured in the mother's first milk (B = 4.85, $P<0.05$) as compared to those infants never exclusively breastfed and exposed to lower LC-PUFA levels [148]. Total omega-3 LC-PUFAs were not predictive of cognitive ability in Seychelles toddlers after accounting for the effects of Hg vapor exposure [82].

Docosahexaenoic acid (DHA), an omega-3 LC-PUFA, was a positive predictor in three of five studies. Two studies found that DHA (per μg/mL) measured from postnatal sources (i.e., breast milk [48] or child's diet [151]) was positively associated with cognitive ability in Swedish (B = 0.92, $P< 0.01$) [48] and Egyptian children (B = 0.52, $P_{univ}<0.05$) [151]. Additionally, a study of Inuit infants found that prenatal DHA levels were associated with higher cognitive scores (per μg/mL-B = 0.6, $P<0.05$) [152]. DHA was not associated with cognitive development in Dutch school children [153] or Spanish toddlers [148] ($P(s)>0.05$).

The beneficial effects of LC-PUFAs and breastfeeding may be attributed to mechanisms known to regulate LC-PUFA metabolism, as suggested by additional analyses in a Swedish study [48]. An analysis of the Spanish multi-cohort that included a cohort of toddlers and a cohort of four year olds assessed fatty acid desaturases (FADS), elongase-2 (ELOVL2) and ELOVL5 genes [154]. Variants in ELOVL and FADS in both the mother and child were identified as being associated with cognitive development ($P(s)<0.05$). In fact, the beneficial effects of ever being breastfed were only seen in children with specific polymorphisms for these enzymes resulting in higher cognitive scores by as much as five to nine points ($P(s)<0.05$) [154].

Other Dietary/Nutrition Factors. Two UK studies examined the effect of dietary patterns on cognitive development (EOI n = 2). Early dietary patterns for infants/toddlers consisting of higher amounts of fruits and vegetables, homemade foods and breast milk were positively associated with cognitive scores for both cohorts ($P(s)<0.01$) [149, 155]. Early diets that included processed foods and snacks were negative predictors of cognitive ability in the older cohort ($P<0.05$ [20, 149]; $P>0.05$ [155]). The effects of diet patterns after toddlerhood (i.e., 3, 4, 7 and 8 years old) on cognitive scores varied in this cohort ($P(s)<0.05$) [156].

Six studies assessed the impact of childhood iron levels through the measurement of different biomarkers (i.e., ferritin, transferrin, hemoglobin) (EOI n = 1; IP n = 5). Early Fe deficiency in children adversely affected cognitive scores measured at four years old Fe levels independent of any effects associated with prenatal drug use and Pb (B = -8.1, $P<0.05$) [87]. Childhood Fe levels were a positive predictor in studies primarily evaluating the effect of environmental contaminants (i.e., As, Mn, Pb) on cognitive development ($P(s)<0.05$ [38, 100, 157]; $P(s)>0.05$ [40, 47].

Prenatal folate intake and/or methylenetetrahydrofolate (MTHFR) genotype were evaluated in four studies as the EOI(s). MTHFR polymorphisms (e.g., 677, 1298) are associated with reduced enzymatic activity resulting in slower folate metabolism. Deficient folate intake through diet posed a risk for children whose mothers carried the homozygous variant of MTHFR 677 (i.e., TT) (B = -1.8, $P<0.05$) [158]. In a second Mexican cohort, maternal MTHFR 677TT was associated with lower cognitive scores (B = -3.52, $P = 0.004$) after

accounting for the effects of low folate intake, which was not a significant predictor ($P>0.05$) [127]. Haplotype analysis of maternal MTHFR 677 and 1298 polymorphisms showed that only children of mothers with both variants have lower scores as compared to mothers with neither variant ($P<0.05$). No associations were seen with fetal MTHFR in this cohort. Alternatively, for mothers whose diets already provide high folate levels (e.g., Mediterranean), additional folate supplementation had no added benefit to early cognitive ability in Greek [159] or Spanish [160] cohorts ($P(s)>0.05$).

Lifestyle Behaviors. Prenatal alcohol exposure was examined in fourteen studies (EOI n = 7; IP n = 7). Most studies found no association with cognitive development. However, four studies that examined level of prenatal alcohol consumption (i.e., low, moderate, heavy) consistently found that moderate (0.5 to ≤1 drink/day) to higher exposures adversely affected cognitive development in school-aged children. A U.S. study showed a negative association between moderate to high amounts of alcohol exposure and cognitive ability in preschool-aged black children (at risk vs. < at risk-levels—β = -0.24, $P<0.01$) [161]. No difference in cognitive scores was seen in eight year old UK children whose mothers reported moderate to high consumption of alcohol during pregnancy as compared to no alcohol exposure [20]. However, further analysis indicated that some children were vulnerable to the effects of prenatal alcohol exposure at this level depending on the alcohol metabolism enzyme genotypes of the mother and child (per allele—B(s) = -1.27,-1.95, $P(s)<0.05$) [162]. The negative effects on cognitive ability were limited to higher or more frequent drinking behaviors in a Dutch study, which found a risk of significant cognitive delay associated with greater than eight drinks per week as compared to no exposure (OR = 4.6, $P<0.05$) [163, 164]. In contrast, the effects of moderate to high alcohol consumption had no significant effect on cognitive scores in an adolescent cohort from Australia [165].

Fathers or male figures in the household with alcohol-related problems or dependence was a negative predictor in two cohorts (EOI n = 1; IP n = 1). A father diagnosed with alcohol dependence was associated with lower cognitive scores in school children from India (B = -9.0, $P_{uandj}<0.05$) [166]. A U.S. study found that in addition to the negative effects associated with prenatal marijuana exposure, children living with a male with alcohol-related problems scored 3.2 points lower than those without this exposure *(P<0.05)* [28].

Social Environment

Both direct and indirect interactions within the social environment can foster cognitive development. These include not only stressors within the home, but more distal stressors within the school and the greater community, which may have a similar or even an additive impact on children's health. Interactions which stimulate cognitive development can serve as a protective measure against other exposures which may be negatively associated with child development. Alternatively, negative social interactions may exert a negative influence itself or enhance the adverse effects of other variables. Elements within the postnatal social environment have psychosocial implications which can impact their performance at the time of cognitive assessment. The social environment of the mother during pregnancy has a direct psychosocial impact on the mother, but an overwhelmingly biological impact on the fetus. Because of this, this section only includes factors related to a child's postnatal social environment.

Family Structure. Two studies assessed how alternative care for children can affect cognitive development (EOI n = 2). Preliminary analyses for both studies found children currently [167] or previously [168] in foster or long-term institutional care had significantly lower cognitive scores as compared to children never fostered or adopted (foster care d(s) = -0.72 [167] and -0.53 [168]; institutional care d = -1.08 [168]) ($P_{univ}(s)<0.05$).

The association between siblings and cognitive development was evaluated in five studies (EOI n = 1; IP n = 4). In a Greek cohort, toddlers with older siblings scored 2.9 points lower than children without siblings after accounting for effects associated with demographic and biological measures ($P<0.05$) [58]. The number of older siblings was a negative predictor of early cognitive ability in two U.S. cohorts after accounting for the effects of maternal employment (B = -2.06) [27] or prenatal cocaine exposure (B = -1.48) [25] ($P(s)<0.05$). One of two studies found that having more than one sibling was a negative predictor of cognitive ability independent of the EOI (i.e., childhood diet, B = -1.93, $P = 0.07$ [20]; breastfeeding, $P>0.10$ [61]).

Two studies accounted for the influence that changes in family structure can have on cognitive development (EOI n = 1; IP n = 1). In a UK study, mothers with a history of unstable relationships with partners was a negative predictor in a study primarily examining the effects of early child care in toddlers (B = -6.6, $P<0.05$) [22]. Preliminary analysis in a second study showed no significant differences in cognitive scores among children who lived in single parent or stable two parent households in a study of Belarusian children ($P_{univ}>0.05$) [169]. However, introduction to new family members (i.e., step-family) did negatively impact cognitive ability in this cohort (B = -1.3, $P_{univ}<0.05$) [169].

Parenting Behaviors. Cognitive stimulation from parents (i.e., different tasks including book reading, singing and/or playing) was evaluated in two U.S. studies (EOI n = 1; IP n = 1). In a cohort representative of children across the U.S., frequency of a mother reading to a child daily over time (i.e., 14–36 months) was associated with better cognitive scores at two and three years old (B = 3.4, $P<0.05$) [26]. Either parent engaging their child in play was another form of stimulation that was positively correlated with cognitive scores at three years old ($P_{univ}(s)<0.01$) [67]. The benefits of paternal cognitive stimulation through activities including book reading significantly benefitted early cognitive development in a cohort of low income children ($\beta = 0.14$, $P< 0.001$) [88].

Opportunity for cognitive stimulation present within the child's home rather than specific tasks was included in 23 studies (EOI n = 2; IP n = 21). The home observation measurement environment (HOME) inventory was the most common tool used to measure both the quality and quantity of opportunities for cognitive stimulation within the home. In an analysis that included breastfeeding and socioeconomic status (SES), cognitive stimulation was the strongest predictor of cognitive ability in a four year old Australian cohort (per SD in Home Screening Questionnaire score- B = 1.8, $P<0.05$) [63]. The beneficial effects of cognitive stimulation at home were seen as early as six months old in a Mexican-American cohort, in which this variable was a stronger predictor of cognitive ability as compared to other parenting behaviors assessed in the same analysis (HOME score—B = 0.8, $P = 0.10$) [170]. A second Australian study evaluating cognitive development from two to 11–13 years of age suggested that early cognitive stimulation at home may also be predictive of later cognitive measures. This exposure measured at three years old had a stronger influence on cognitive scores at all ages of assessment as compared to other significant predictors in the same analysis (i.e., SES, maternal intelligence) (HOME score—B(s) = 0.4–0.9, $P(s)<0.05$) [72]. Cognitive stimulation at home was also a positive predictor in UK toddlers independent of any cognitive stimulation received at child care (higher HOME score—B = 3.4, $P<0.01$) [22]. Multiple analyses of a U.S. cohort consistently showed that cognitive stimulation was a positive predictor of cognitive development over time (i.e., one to five years old) regardless of the EOI (i.e., air pollutants, pesticides) (HOME score—B(s) = 0.33–0.59, $P(s)<0.03$ [32–34, 37]), with the exception of one study which measured cognitive ability at seven years old ($P>0.05$) [36]. Similar results were found in studies independent of the EOI (i.e., prenatal exposure to drugs, pesticides, synthetic

chemicals, Pb, As, Hg, LBW, depression, employment and diet) ($P(s)<0.05$ [25, 27–29, 64, 70, 76, 81, 82, 84, 86, 89, 124, 136, 141]; $P(s)<0.10$ [20, 59, 87]).

The overall quality of the interactions between a mother and child (e.g., sensitivity, responsiveness) was the EOI in four U.S. studies. Early measures of parenting quality were a positive predictor of cognitive development in three cohorts of toddlers independent of the effects of a child's own persistence (β = 0.30, $P<0.05$) [35], other parent behaviors (β = 0.0.06, $P<0.05$) [88], or economic indicators (β = 0.17, $P<0.05$) [23]. Current measures of quality of interaction were not associated with cognitive development in the first cohort [35] or in a cohort of Mexican-American infants after adjusting for HOME [170] ($P(s)>0.05$).

Supportive behavior (e.g., warmth, nurturing, and positive regard) were assessed in four U. S. studies (EOI n = 4). Early displays of support by mothers and fathers were positively associated with early cognitive ability independent of other behaviors (β(s) = 0.20–0.29, $P(s)<0.05$) [26, 88]. Maternal nurturing (r = 0.36) [170], communication (β = 0.43) [171], and positive regard from both parents (r(s) = 0.14–0.29) [67] were also positive correlates of early cognitive development ($P<0.05$, $P_{univ}(s)<0.05$).

Social Support. Two studies evaluated the association between social support from family and friends and cognitive development (EOI n = 1; IP n = 1). An Australian study found that low levels of social support during pregnancy were negatively associated with cognitive scores for 3–4 year old children (1^{st} vs. 4^{th} quartile—B = -3.1, $P = 0.03$) [138]. Social support at the time of cognitive assessment also imparted a protective effect in children born to mothers with high levels of stress (B = -0.6, $P>0.05$) as compared to those with lower levels of support (B = -4.1, $P = 0.08$) [138]. The level of social support was also a positive predictor of cognitive scores for a U.S. cohort of six year old children independent of the effects associated with prenatal marijuana exposure (B = 0.94, $P<0.001$) [28].

Child Care or School. Type of care (e.g., group or center, individual care) was assessed in two studies (EOI n = 1; IP n = 1). Child care at a center or group setting imparted a slight, yet significant, benefit to cognitive development in a UK cohort of toddlers independent of the quality of child care (B = 0.17, $P<0.01$); while individual child care had no effect [22]. Similarly, in a U.S. study evaluating the effect of maternal work schedules, center care was the only type (i.e., center, family daycare, relative, non-relative) of child care positively associated with cognitive scores measured at two years old (B = 0.81, $P<0.01$) [27].

A composite measure of child care quality (i.e., stimulation, sensitivity, adult child ratio) was assessed in two studies (EOI n = 1; IP n = 1). Better quality child care was associated with an average increase of 3.3 points in cognitive scores in a UK cohort of toddlers (β = 0.19, $P<0.01$) [22]. Increases in cognitive scores were also seen in a U.S. cohort of toddlers enrolled in child care rated as above average (β = 0.09, $P<0.01$) [27]. A second UK study found that when qualities were treated as individual predictors within the same analyses, only cognitive stimulation provided the most benefit for infants (β = 0.38, $P<0.05$) [69]. However, the effect associated with cognitive stimulation was strongest if it was provided by caregivers rated higher for sensitivity (interaction $P = 0.055$) [69].

School attendance was an IP in two Bangladeshi studies examining the effects of water contaminants on cognitive development. Attendance rate (i.e., days/week or total months) was a positive predictor of cognitive scores even after adjusting for the effects of As and/or Mn (β(s) = 0.11 and 0.5, $P(s)<0.05$) [64, 100].

Built and Natural Environments. The physical environment is made up of both natural and built characteristics which may have an effect on child development. Chemicals of concern present in the physical environment (i.e., soil, air, water) come from both natural and man-made sources. Regulations have been established for some, but not all, chemicals of concern due to adverse human health effects including those related to cognitive development. Non-

chemical aspects of the natural and built environments garner attention because they can introduce or modify non-chemical and chemical stressors, thus, altering a child's exposure.

Arsenic (As). Seven studies examined the association between As exposure and cognitive ability in school children (EOI n = 7). Children in these studies were from countries with drinking waters known to have high As levels far exceeding the recommended U.S. standards (i.e., 10 μg/L [172]). Results from cohort studies of Bangladeshi, Chinese and Mexican children with co-exposures to other elements such as fluoride and Mn suggested that concurrent As levels in drinking water were a negative predictor of cognitive ability (0.05–0.41 per log(μg/L), $P(s)<0.05$ [47, 64, 65]; with cognitive scores dropping by as much as 0.30 to 0.54 SD in children exposed to levels greater than 176 μg/L (vs. <10)($P(s)<0.05$ [65], $P_{univ}<0.05$ [173]). As measured in urine or blood was also predictive of cognitive scores ($P(s)<0.05$ [100]; $P(s)<0.10$ [47, 65]). Evidence from a separate cohort of Bangladeshi children suggested that both prenatal and postnatal As levels adversely affected cognitive development measured at five years old [174, 175]. The effects associated with cognitive scores at five years old were strongest for girls and specific to As exposures during late pregnancy and at the age of cognitive assessment (0.15–0.21 SD's per log(μg/L), interaction $P(s)\leq0.06$) and late pregnancy (interaction $P = 0.06$) [175]. Conversely, one study found that neither period of As exposure was predictive of cognitive scores measured in Indian children ranging in age from 5–15 years old ($P(s)>0.05$) [176].

Fluoride (F). Five cross-sectional studies of school-aged children (i.e., 6–12 years old) from countries (e.g., India, Iran, Mexico and China) with elevated fluoride levels in groundwater (i.e., >4 mg/L per U.S. recommendations [177]) suggest that fluoride adversely affects cognitive development (EOI n = 5). Levels greater than 4 mg/L were associated with cognitive scores 0.3–0.6 SDs lower than those exposed to levels below 1–2 μg/L [173, 178]. In fact, even levels below the recommended maximum level were found to be associated with lower cognitive scores or risk of below average scores in the Iran cohort (>1 mg/L, OR = 1.75) [178] and an Indian cohort (≥1.5 mg/L) [179] ($P_{univ}(s)<0.05$). Fluorosis, an indicator of high fluoride exposure, was also associated with low cognitive scores (<80) in a second Indian cohort (OR = 2.91, $P_{univ}<0.002$) with stronger effects in girls ($P_{univ} = 0.003$) [180]. Fluoride also remained a predictor of cognitive development in Mexican children in a study examining co-exposure to As (0.68 SD per log (mg/L), $P<0.001$) [47].

Lead (Pb). Seventeen studies evaluated the effect of Pb on cognitive development (EOI n = 13; IP n = 4). Ten studies restricted their cohort samples to children with blood Pb (BPb) levels less than or equal to 10 μg/dL to understand the effects associated with lower exposure levels. Historically, research has focused on the effect of Pb on cognitive function with moderate to high doses of Pb [181].

Thirteen studies assessed childhood Pb exposure (EOI n = 10; IP n = 3). One additional study assessed gene-environment interactions associated with Pb. A study of black U.S. children found differences in cognitive scores at seven years old between children with BPb levels above and below 5 μg/dL ($P<0.05$) and suggested the possibility of adverse effects with levels as low as 3 μg/dL ($P< 0.10$) [182]. A second study restricted to U.S. school children with BPb levels under 10 μg/dL also found differences in effect on cognitive ability associated with 5–10 μg/dL BPb (B = -6.04, $P = 0.01$) as compared to 1–2 μg/dL BPb (B = -0.12, $P = 0.94$) [24]. Similar results were yielded in a U.S. cohort that found declines in cognitive scores in six year olds with BPb levels under 10 μg/dL (5–10 μg/dL vs. <5 μg/dL -B = -3.7, $P = 0.10$ [183]; per μg/dL–B = -1.58, $P<0.05$ [184]). In two U.S. cohorts that included children with prenatal drug exposure, Pb exposure adversely influenced cognitive ability at four years old ($P(s)<0.05$) [87, 185], but this association did not hold true when one cohort was restricted to children with BPb levels under 10 μg/dL ($P_{univ} = 0.23$) [185]. In a U.S. cohort with initial BPb levels greater than 20 μg/dL at two years old, concurrent Pb levels were a negative predictor of cognitive development

measured until seven years of age independent of effects associated with previous Pb, Hg and Mn exposures (per μg/dL B(s) = -0.4 to -0.2, $P(s)<0.05$) [30, 186, 187].

These effects were not restricted to U.S. cohort studies as evidenced by a pooled analysis of cohorts from multiple countries (including [73, 85, 183]) [45] and a Mexican cohort of two year olds [79], which revealed steeper declines in cognitive scores with increasing Pb exposure in children with concurrent BPb levels under 7.5–10 μg/dL as compared to those with greater exposure ($P<0.05$). BPb levels were also predictors independent of the effects associated with Mn exposure as evidenced in this cohort of Mexican toddlers [188], as well as in older children from Italy [157] and Korea [41] ($P(s)<0.05$). Conversely, in a study primarily investigating the effects of Mn exposure in a second cohort of Mexican children, concurrent Pb exposure greater than 6 μg/dL was not associated with their cognitive ability [38]; with similar findings in two additional Mexican cohorts ($P(s)>0.05$) [47, 85]. However, further stratification of children by Mn exposure may show that those with higher Mn exposure may be more vulnerable to Pb toxicity as evidenced in two of the previous cohorts co-exposed to Pb and Mn ($P(s)<0.05$) [41, 188]. Similar vulnerabilities to concurrent Pb levels were also evident in Polish school children with specific polymorphisms (i.e., δ-aminolevulinic acid dehydratase (ALAD) and Vitamin D receptor (VDR)) whose products may modify Pb availability and toxicity (interaction $P(s)\leq 0.02$) [189]. There was no direct association between variants of ALAD or VDR and cognitive ability.

Evidence from seven studies suggested that prenatal exposure may adversely affect cognitive development possibly more so than concurrent postnatal exposure (EOI n = 5; IP n = 2). However, the exact timing of exposure in which the child is most susceptible during pregnancy is unclear. One study of Polish children with umbilical cord (fetal) BPb levels under 5 μg/dL suggested that fetal exposure to low BPb levels may adversely affect early cognitive development (per log(μg/dL)–B = -6.7, $P = 0.02$), with effects being more prominent in boys (interaction $P<0.05$) [53] and in those born to mothers without any college education ($P_{univ}<0.05$) [52]. In a Mexican cohort of two year olds, fetal Pb exposure was negatively associated with cognitive scores even after accounting for effects associated with maternal and child MTHFR genotypes (per μg/dL–B(s) = 0.7, $P(s)<0.05$) [127]. Fetal Pb levels were not predictive of cognitive development in a U.S. cohort of two year old children after accounting for the effects of other contaminants and material hardship [31].

Studies which measured Pb in maternal blood gave more insight into the exact timing in which cognitive development is most sensitive to Pb toxicity. Maternal BPb levels during late pregnancy negatively influenced cognitive development in Mexican school children (per ln(μg/dL)–B = -4.1, $P<0.01$) [85]. Umbilical cord, early pregnancy and postnatal measures were not associated with cognitive ability at this age [85]. Results from a study of Korean infants suggested that cognitive development by as early as six months may also be sensitive to low maternal BPb levels (<10 μg/dL) during late pregnancy ($P = 0.02$), with children co-exposed to higher Cd levels (>1.51 μg/L) during this period being most vulnerable to these adverse effects (per log(μg/dL)–B = -12.1, $P<0.01$) [190].

Contrary to this, maternal BPb levels during late pregnancy did not influence cognitive development in two other studies which measured Pb exposures at multiple time points. Analyses of a Mexican cohort found that decreases in cognitive scores measured at two years old were specific to prenatal (i.e., first trimester) (per $\log_e$ (μg/dL)-B = -3.5) and postnatal (i.e., birth, 1, 2 years old) Pb exposure ($P(s)<0.05$) [98]. Stratification analysis for this cohort revealed that early postnatal Pb exposure (per μg/dL) may influence early cognitive development (i.e., 1 to 3 years old) specifically for children with BPb levels under 10 μg/dL (B = -1.04) [79], those born to mothers with low self-esteem (B = -0.31) [78], or those co-exposed to high Mn levels (B = -1.3) [188] ($P(s)<0.05$). In a Taiwanese cohort with BPb levels below 10 μg/dL,

third trimester BPb was not associated with any period of cognitive development (i.e., 2–3, 5–6, or 8–9 years old) ($P(s)>0.05$) [59]. However, earlier postnatal measures rather than concurrent exposures were associated with cognitive measures at 5–6 and 8–9 years old (per ln (μg/dL)-B = -6.0, $P<0.05$) [59]. In a U.S. cohort of children with BPb levels over 20 μg/dL at baseline, both cumulative and concurrent postnatal measures were significant predictors ($P(s)<0.05$) [187]. In a second U.S. study, all postnatal exposure measures (i.e., early postnatal, concurrent, cumulative) were predictive of cognitive scores ($P(s)<0.05$) [183, 184].

Manganese (Mn). Results from eight studies (EOI n = 7; IP n = 1) found that concurrent Mn levels measured in water, blood or hair negatively influenced cognitive development of school children from areas with exposure levels that exceeded the recommended U.S. guidelines (i.e., 50 μg/L in water or 5 mg/m^3 in air [191]) ($P(s)<0.05$ [38, 39, 41, 65, 99, 192]; $P<0.10$ [100]; $P>0.10$ [64]). Studies have suggested that some groups may be more vulnerable to the effects of Mn. Within a Mexican cohort of school children, girls and younger children were more sensitive to the adverse effects associated with Mn (interaction $P(s) = 0.06$) [38].

Deficits in Mn exposure may also have an adverse effect on cognitive development over time as evidenced in a second cohort of Mexican children [40]. Children with Mn levels below 20.2 μg/L and above 28 μg/L had significantly lower cognitive scores between one and two years old as compared to those with moderate Mn exposure ($P<0.05$).

Three studies that examined co-exposures to Mn and other elements revealed how effects associated with Mn may be modified by another contaminant or vice versa. In co-exposure models for As and Mn measured in Bangladeshi children, As appeared to preclude any effects on cognitive scores associated with Mn ($P(s)>0.05$) [64, 65, 100]. Similar to Cd, elevated Mn levels may also enhance Pb toxicity as suggested in two studies examining cognitive ability in Korean infants and children from Mexico City with co-exposures to Pb and Mn [41, 188].

Indoor Nitrogen Dioxide (NO2). Indoor NO_2 was evaluated in two cohorts from the Spanish multi-cohort study (EOI n = 1; IP n = 1). Indoor NO_2 had a negative effect on cognitive scores in a four year old cohort independent of any effects associated with atopy [74]. Among these children, those carrying the glutathione S transferase P1 (GSTP1) Ile105Val minor allele had less detoxification enzyme activity or efficiency and, as a result, were more susceptible to these effects (B = -3.36 per 10 μg/m^3, interaction $P = 0.04$).

Similarly, use of domestic gas cookers, a source of indoor NO_2, negatively influenced early cognitive development in a younger Spanish cohort (B = -2.5, $P<0.05$) [193]. Children with non-smoking mothers or in smoke-free homes were more vulnerable to these effects. However, older homes, urban neighborhoods and higher outdoor NO_2 levels also enhanced these effects. Similar to the previous study [74], children carrying a minor allele(s) for GSTP1 Ile105Val were also more susceptible to the effects associated with gas cooking (B = -6.5, $P<0.05$). Whereas, higher prenatal fish and vegetable/fruit consumption and breast feeding greater than six months seemed to impart a protective effect.

Polycyclic Aromatic Hydrocarbons (PAHs). Three studies evaluated the impact of prenatal PAH exposure on cognitive development (EOI n = 3). A longitudinal U.S. cohort study found that exposure to higher levels of PAHs (>2.26–4.16 ng/m^3) resulted in a 5.7 point decrease by age three years ($P = 0.02$) [33] and a 4.3 point decrease at age five ($P<0.01$) [37] as compared to lower levels of exposure. In fact, there was a 2.89 times greater risk of below average scores at three years old with higher levels of PAH exposure ($P<0.05$) [33]. However, this association was no longer significant for the same cohort when additional pollutants and economic disparities were considered [31, 36]. The effects of prenatal PAH exposure were also associated with lower scores at five years old in a Polish cohort of children exposed to higher levels of PAHs (>17.96 ng/m^3, B = -1.4, $P = 0.04$) [50]. A combined analysis of both cohorts to evaluate gene environment interactions found significant modification of PAH effect on

cognitive score by selected variants in cytochrome P450 and GST genes with most of these interactions being unique to a specific race or ethnicity (i.e., Polish, Dominican or black) [21]. The negative effects of PAHs were confirmed in a third study where PAH exposure was estimated by measuring umbilical cord blood DNA adducts [126]. However, this negative effect was restricted to children whose mothers were exposed to ETS while pregnant ($P = 0.02$).

Polybrominated Diphenyl Ethers (PBDEs). Three studies evaluated the sum effect of up to 14 different PBDEs (∑PBDE) either in blood or breast milk (EOI n = 3). Total PBDE exposure measured in blood were yielded adverse effects on cognitive score in two studies. Childhood and prenatal $\sum PBDE_4$ exposure were associated with declines in cognitive scores (i.e., 4–5 points per log(ng/g)) at seven years old in a cohort of Mexican-American children (postnatal median = 84.4 ng/g lipid, $P<0.05$; prenatal median = 24.9, $P<0.10$) [194]. Risk of below average cognitive scores associated with prenatal $\sum PBDE_{11}$ measured in cord blood may occur as early as infancy as shown in a Taiwanese cohort (>median (4.63 ng/g lipid), OR = 1.13, $P<0.05$) [195].

Conversely, no significant correlation was seen in the Taiwanese infant cohort with PBDE exposure through breast milk ($\sum PBDE_{14}$ median = 2.92) ($P_{univ}>0.05$) [196]. Any potential negative association for PBDE exposure through breast milk in a cohort of Spanish toddlers was no longer apparent after adjustment for organochlorine pollutants ($\sum PBDE_7$ median = 3.50 ng/g lipid, $P = 0.21$) [197]. However, PBDE-209 was a negative predictor in both studies. There was evidence that PBDE-209 in breast milk, one of the main congeners present in the highest concentrations in both cohorts, potentially affected cognitive development as seen in the Taiwanese cohort ($P<0.05$) [196]. Duration and timing of PBDE-209 exposure may be an important factor to consider, as seen in the Spanish cohort in which a stronger association was seen in children breastfed longer than four months even after adjusting for additional pollutants (per log (ng/g) ->4 months, B = -3.48 $P<0.05$; ≤4 months, B = -1.07, $P>0.05$) [197].

Three additional studies examined the effects of individual PBDE congeners (EOI n = 3). Effects seen with prenatal ∑PBDE exposure may be specific to individual congeners including PBDE-15, -47, -85, -99, -100, -157 ($P(s)<0.05$) [195, 198]. Postnatal PBDE-47 exposure was also evaluated in an older Spanish cohort in which no associations were seen with cognitive scores measured at four years old ($P>0.05$) [199].

Phthalates. Three studies evaluated the association between phthalate exposure and cognitive development (EOI n = 3). Effects associated with prenatal phthalate exposure may be gender specific as suggested by one study evaluating early cognitive development in Korean infants [200]. Decrements in cognitive scores at six months old with increasing dibutyl and di-2-ethylhexyl phthalate (DBP and DEHP) exposure were greater for boys (per ln(μg/g creatinine) males-B(s) = -1.6 to -0.9, $P(s)<0.05$) as compared to girls ($P(s)>0.05$) [200]. However, the differential effects seen may be dependent on the metabolite measured. In a U.S. cohort, girls were more susceptible to any negative effects associated with mono-n-butyl phthalate, a metabolite of DBP, on cognitive development by three years old ($P<0.01$, interaction $P = 0.054$) [201]. Postnatal exposure to DEHP was negatively associated with cognitive scores in Korean school children (per ln (μg/g creatinine—B = -2.3, $P<0.01$) [202]. Adjustment for maternal intelligence weakened this association ($P>0.55$).

Pesticides. Studies examining the effects of pesticides (i.e., mirex [203, 204], chlorpyrifos [32, 36, 205, 206], dialkyl phosphate (DAP) [205, 207, 208], dichlorodiphenyltrichloroethane (DDT) [74, 141, 143, 146, 199, 209–211], hexachlorobenzene [204, 212]) as the EOI consistently found no association with cognitive development (S2 Table) with the exception of three studies that considered gene-environment interactions. Variants of paraoxonase-1 (PON1) and glutathione S transferases (GSTs) are detoxification enzymes known to detoxify organophosphate (OP) pesticides. The moderating effects of PON1 were examined in Mexican-American and urban U.S. cohorts. Mexican-American children homozygous for the minor allele

PON1 R192Q, which is associated with reduced enzyme activity, and those with one or more minor alleles for PON1 C108T, which are associated with decreased enzyme levels, were more susceptible to the adverse effects of prenatal DAP on cognitive development at two years old (per $\log_{10}$(nmol/L)-B(s) = -7.4 to -3.4, $P(s)<0.10$) [213]. Conversely, in an urban cohort where both black and Hispanic infants were susceptible to DAP, those born to mothers with one or more major allele for PON1 R192Q were more susceptible to the effects of OP pesticides on cognitive scores at one year old (per $\log_{10}$(μmol/L)-B(s) = -4.9 to -4.5, $P(s)<0.05$) [214]. In a third study examining cognitive scores in a four year old Spanish cohort, children heterozygous for the minor allele, GSTP1 I105V, were more susceptible to the adverse effects of prenatal DDT exposure (per ng/mL -B = -9.4, $P = 0.04$, interaction p = 0.05) [215].

Discussion

Summary of Findings

This review summarizes the myriad factors that can influence general cognitive outcomes during childhood. In summary, 150 studies investigated 110 possible stressors of general cognitive ability. This number does not include factors which were included as IPs in multivariate analyses. An overview of the potential stressors grouped into four broad domains–inherent determinants, behaviors, social environment and physical environment—shows that the body of literature included in this review is largely focused on negatively associated inherent factors of the mother or child or chemical exposures present in the child's physical environment (Figs 2 and 3). Of the 33 individual or grouped factors, only three were investigated in a large number of studies (i.e., ≥10)—Pb, Hg and breastfeeding (Fig 3).

Factors with evidence of an association with general cognitive ability (i.e., consistent associations, ≥60% consensus) were not limited to already well-recognized factors, including cognitive stimulation and supportive behavior from parents, which impart beneficial effects, and childhood Pb exposure, low birth weight and early preterm birth, which impart negative effects. A consistent, positive effect was also seen with social support provided to the mothers during pregnancy, the type and quality of child care, maternal occupational class, maternal intelligence, and duration and exclusivity of breastfeeding. Evidence of a negative association also included potential indoor NO_2 exposure, prenatal PAH exposure, postnatal fluoride or Mn exposure, belonging to a minority racial/ethnic group, multiple gestation, pre-pregnancy BMI, prenatal stress, and having siblings. It is important to note that these conclusions are only indicative of the degree of consensus of the direction of association, and not on the strength of association, which would require a meta-analysis for each stressor.

These results suggest that the positive impacts on measured cognitive ability are largely attributed to non-chemical stressors related to the mother and child's social environment and personal decisions and inherent factors of the mother. On the other hand, declines in cognitive score are attributed to both chemical and non-chemical stressors within a child's total environment. This review suggests that it may be a combination of stressors over a child's lifecourse that can impact his/her cognitive development or explain the true etiology in disparities in cognitive outcomes defined by race or income.

There is general agreement between agencies, organizations and academia that there is a need to examine the cumulative impacts of exposure to both chemical and non-chemical stressors over a lifecourse to better understand variations in health outcomes and disparities [283–285]. However, the translation of this theory into research, as in the case of this review, has largely had an interdisciplinary approach, where multiple stressors are being evaluated but within their respective domains–social or physical environment, chemical or non-chemical. Recent studies indicate that non-chemical stressors can interact with or modify vulnerability to

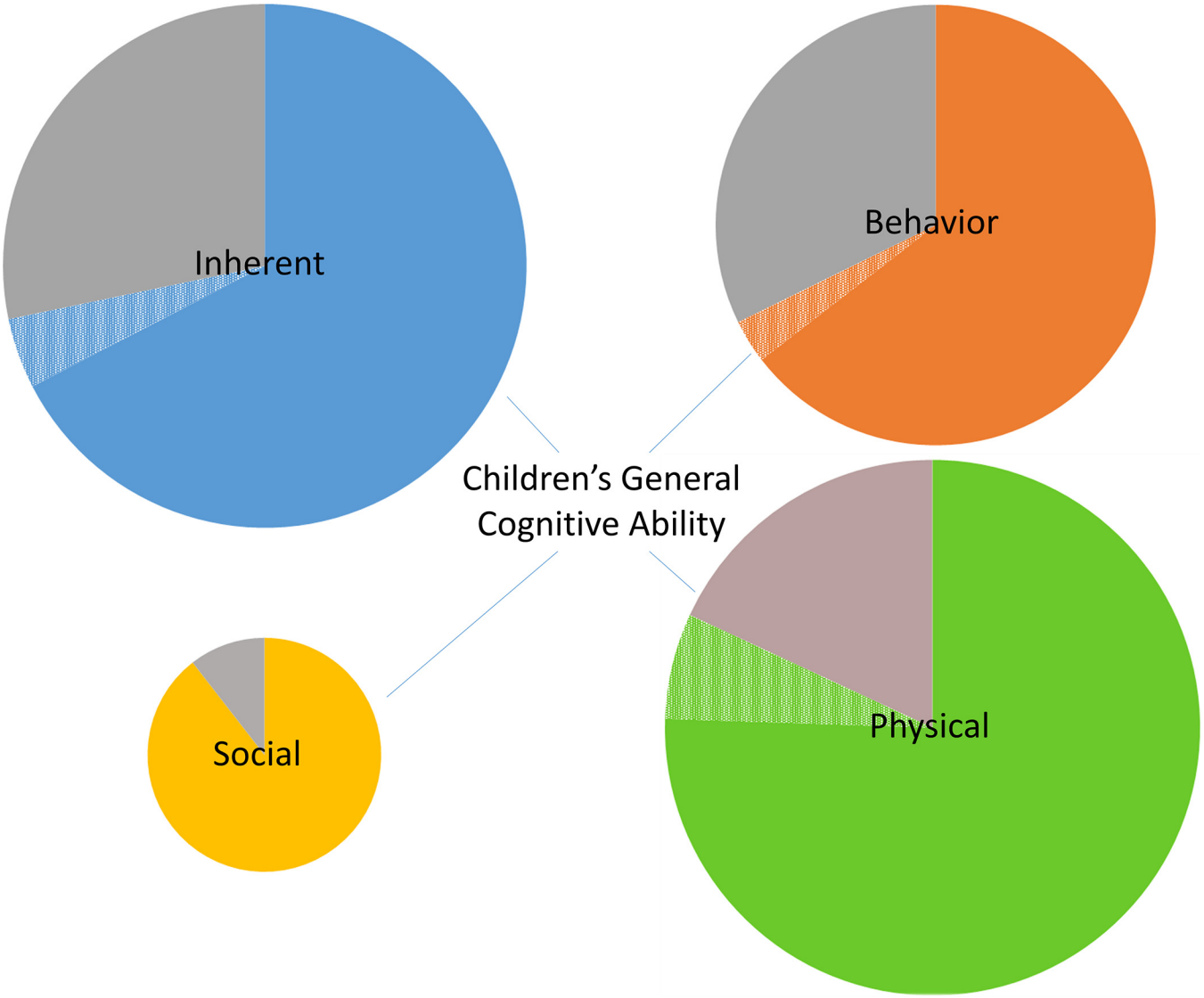

Fig 2. Factors Associated With General Cognitive Ability Grouped Into Four Domains: Inherent, Behavioral, Social Environment and Physical Environment. The size of the circles are in proportion to the total number of studies. The colored section in each circle represents the proportion of studies within each category that found a statistically significant association with general cognitive score (solid color–$P<0.05$; pattern – $0.05<P<0.10$). This graphic is adapted from Strina et al. [282].

doi:10.1371/journal.pone.0147741.g002

neurotoxicants; thus affecting healthy brain development [286–291]. There are ongoing prospective studies included in this review that lend support to this type of research approach focused on children's cognitive ability. However, the non-chemical moderators of interest in this review were largely inherent or behavioral determinants, with the exception of three studies which looked at social and chemical stressors together [31, 78, 206]. Additionally, the broader definition of cumulative and environmental exposures (e.g., inclusion of community level psychosocial stressors and a range of chemical stressors) and their combined impact on children's cognitive ability need to be considered in understanding children's cognitive health.

An overview of the most common covariates used in this study (Table 3) reveals that current research is largely accounting for individual determinants and behaviors (e.g., demographics, maternal intelligence, birth outcomes, prenatal smoking or alcohol, and breastfeeding) in ten

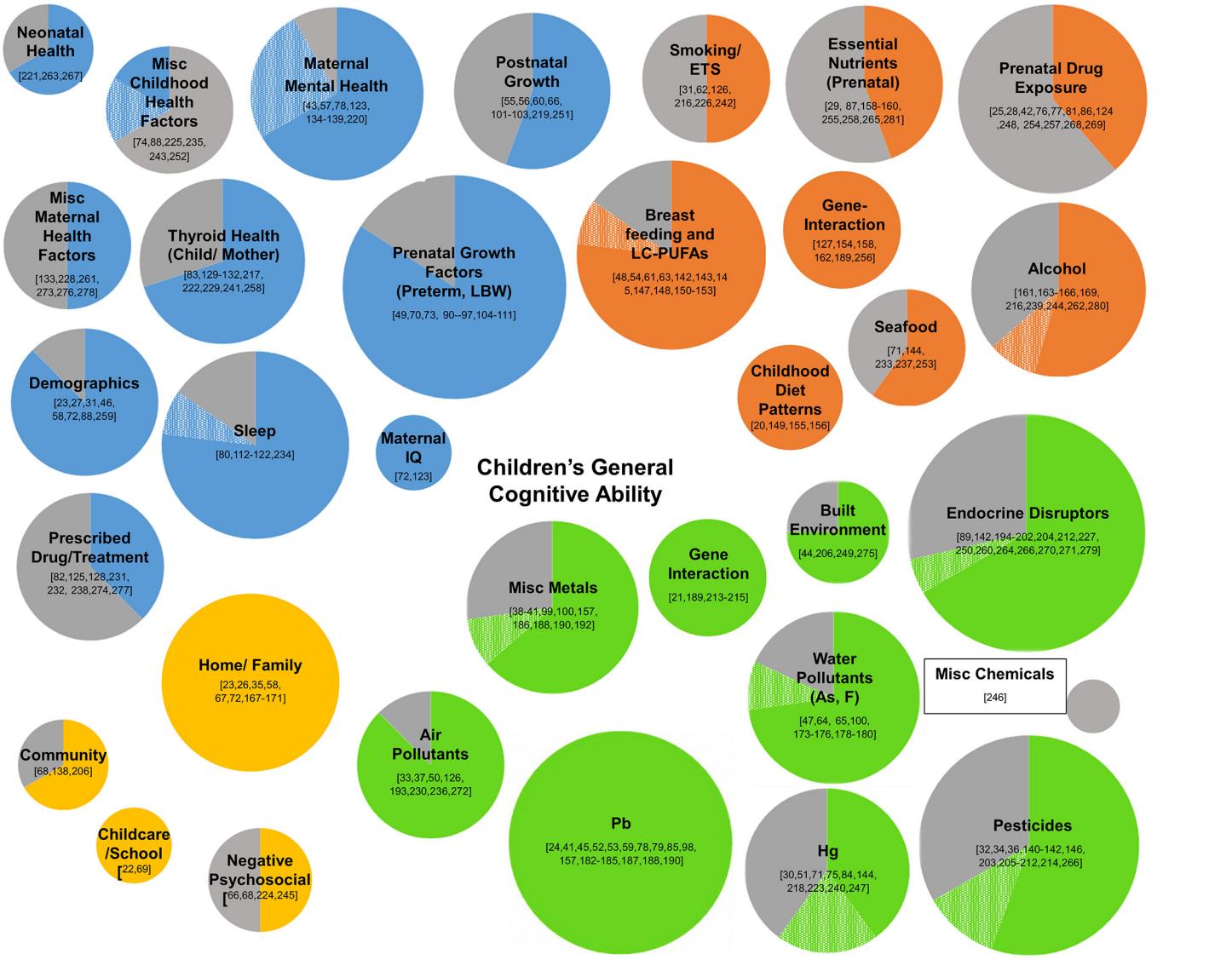

Fig 3. Factors Associated With General Cognitive Ability Further Divided Into Sub-categories. The color of the circles corresponds to the larger categories in which these sub-categories are grouped (inherent: blue; behavioral: orange; social environment: yellow and physical environment: green). The size of the circles is in proportion to the total number of publications included in the review (n = 258). The colored section in each circle represents the proportion of publications within each category that found a statistically significant association with general cognitive score (solid color–$P<0.05$; pattern – $0.05<P<0.10$). This graphic is adapted from Strina et al. [282].

doi:10.1371/journal.pone.0147741.g003

percent or more of the studies included in this review. The inclusion of inherent factors and behaviors, such as parent intelligence and education, are not only crucial to controlling for their influence on the level of exposure, but also serve as a safeguard for researchers to avoid over-shadowing of inheritable vulnerabilities to environmental stressors. Typically, environmental stressors included as covariates were described as confounders, rather than co-exposures, and used to focus on the variations in the effect of the exposure of interest, rather than the variation in outcome. The focus on the effect of a single stressor can stray attention away from the unknowns such as additivity, antagonism and synergism of a mixture of stressors and predispositions. Additionally, the lack of use of negative social stressors or other chemical stressors as modifying factors/covariates in multivariate regression may garner decisions

Table 3. Covariates Used Across Publications Included in the Review.

Rank	Covariate	Frequency of Use (%)
1	Gender	56.2
2	maternal education	51.2
3	maternal intelligence	31.8
4	social/occupational class	29.8
5	maternal age at birth	28.3
6	cognitive stimulation	25.6
7	exact age at cognitive assessment	23.6
8	parity/birth order	21.7
9	birthweight, prenatal smoking	21.3
10	gestational age	20.2
11	breastfeeding	19.4
12	race/ ethnicity	15.9
13	marital/relationship status	15.5
14	prenatal alcohol	13.2
15	psychologist/evaluator	12.8
16	geographical location	9.7
17	paternal education, parent anthropometry	9.3
18	prenatal environmental tobacco smoke (ETS)	8.9
19	Income	8.5
20	child's physical health, postnatal ETS	6.6
21	birth length, parent employment, child's diet	5.4
22	maternal physical health	5.0
23	siblings, fetal/infant health, preterm/low birth weight, postnatal lead, language, resources/adverse living	4.7

doi:10.1371/journal.pone.0147741.t003

relevant to blanket policies/interventions that may not be sufficient to protect children additionally facing a socially/economically disadvantaged environment which may make them more vulnerable to the stressor of interest.

Limitations of the Study

The main limitation of this study is the considerable heterogeneity across studies due to different methodological approaches (i.e., timing of exposure and outcome, variety of cognitive assessment tools, statistical methods) that were allowed in the inclusion criteria. This limitation allowed for inconsistent results in a large number of determinants explored (Table 2), as well as difficulty in identifying critical windows of exposure for any specific stressor. The diversity in statistical methodologies alone (e.g., measurement units, data transformation) proved to be a limiting factor in making qualitative comparisons across studies for a single factor in this review; possibly hindering the ability to derive summary effects for each factor and further comparisons of effect size between factors using more formal statistical analyses.

A second limitation in this study was that only published data was used, subjecting the results to publication bias. Any effort to identify the real world effect of any stressor, with consideration of the total environment, is limited by the available data and the assumptions made by each researcher. In general, little or no data are ever published when investigations of possible stressors produce non-significant associations; thereby limiting new research from fully understanding potential moderating effects of stressors and possibly inflating summary results for each stressor in this review. This bias may have also made it challenging to identify or rule

out factors that were sparsely considered. However, the approach used in this study provides the best overview of evidence that is available to describe the current state-of-the-science.

Another limitation in this study was the small number of social stressors identified in this review as compared to inherent factors, behaviors and chemical stressors which may have resulted from omission of searchable databases that may have been a better source of psychological or child development publications than PSYCInfo. The cutoff point for inclusion of studies published within the last ten years and exclusion of non-observational studies may have also limited the number of social stressors associated with this specific endpoint.

Lastly, the use of general cognitive scores as the end point in this review may not allow for identification of every single stressor or even the most important stressor because it is an average of cognitive performance over multiple domains. Certain factors that target a specific domain as opposed to having a blanketed effect over all the domains, which may help to explain inconsistencies and null effects across studies and may overlook stressors that selectively impair a specific domain. Therefore, it is important to note that the relative importance of a stressor in this study may differ for other endpoints. However, this endpoint was the one most consistently reported across studies and allowed for a greater number of factors and studies to be examined in a comparative analysis.

Challenges and Future Direction

A major challenge in children's research, and particularly neurodevelopment, is defining vulnerability and susceptibility so that the research community may move forward effectively in addressing the challenge of children's exposures to chemical and non-chemical stressors and the impact on health and well-being. Childhood is defined as a sequence of unique stages described by distinct anatomical, physiological and behavioral characteristics that create variations in vulnerabilities to the environment [292]. During childhood, the brain itself is resilient and malleable, making it difficult to pinpoint an effect from a single exposure, as this may not determine the final outcome. This literature review suggests that the difficulty in identifying clear determinants of cognitive development is likely a result of the complexity with defining a child's total environmental exposures.

This review highlights the current body of research from exposure and social sciences that have identified several factors associated with cognitive ability, with the exception of non-chemical characteristics of neighborhoods (e.g., noise, crime, social capital) and physical features of the built and natural environments (e.g., green space, food deserts, design and integrity of homes, schools and neighborhoods). Only three studies evaluated non-chemical stressor characteristics at the neighborhood level, non-chemical stressors or of the broader physical environment [44, 68, 206]. The limited research in this area may be due to the lack of quantifiable and consistent measures for neighborhood level determinants that have not been normally explored in exposure science. Additionally, non-chemical features of the physical environment are commonly considered a source of either stressors or protective factors for child development with differences in exposure being linked to social aspects of the environment (i.e., income, social class) [13, 293], rather than a determinant of health itself. A better understanding of the direct and indirect influences of the broader context of children's environments that includes both school and neighborhood settings, as well as the built and natural environments, may be important for understanding cognitive development and associated disparities [14, 294].

Conclusions

Cognitive development is a dynamic process, constantly changing in response to interactions with the total environment. This scoping review identified several determinants of general

cognitive ability including inherent factors, behaviors, chemical stressors and family-related social stressors. Areas with limited data included distal sources of psychosocial stressors beyond those within the family and non-chemical stressors in the natural and built environment. Within this review, researchers have tackled looking at cumulative exposure by looking at multiple chemical stressors within a defined group and the interactive effects between individual determinants and chemical stressors. Few studies examined psychosocial and chemical stressors together. Given the complexity of cognitive development, the pathway(s) leading to this outcome may be as difficult to understand, considering the ubiquitous stressors children are faced with, especially those in disparate environments. A holistic approach that considers the interplay between chemical and non-chemical stressors in the built, natural, and social environments over a lifecourse can help to elucidate the true effects of key stressors that shape cognitive development.

Supporting Information

S1 PRISMA Checklist. PRISMA Checklist.
(DOC)

S1 Table. Summary of Publications that Met Review Criteria. Publications are grouped by study and country.
(XLSX)

S2 Table. Factors Examined in Only One Study and Their Reported Association with General Cognitive Ability.
(XLSX)

Acknowledgments

This project was supported by an appointment to the Internship/Research Participation Program at the U.S. Environmental Protection Agency, Office of Research and Development, National Exposure Research Laboratory, Human Exposure and Atmospheric Sciences Division, Exposure Measurements and Analysis Branch, administered by the Oak Ridge Institute for Science and Education (ORISE) through an interagency agreement between the U.S. Department of Energy and EPA. It has been subjected to Agency administrative review and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Author Contributions

Conceived and designed the experiments: JDCR JJQ NST. Performed the experiments: JDCR. Analyzed the data: JDCR. Wrote the paper: JDCR JJQ NST.

References

1. Grosse SD, Matte TD, Schwartz J, Jackson RJ. Economic gains resulting from the reduction in children's exposure to lead in the United States. Environ Health Perspect. 2002; 110:563–9. PMID: 12055046
2. Chambers B, Cheung A, Slavin R, Smith D, Laurenzano M. Effective early childhood education programs: a systematic review. Baltimore: Johns Hopkins University, Center for Research and Reform in Education. 2010.
3. Aratani Y, Wight V, Cooper J. Racial gaps in early childhood: socio-emotional health, developmental and educational outcomes among African-American boys. New York: Columbia University, National Center for Children in Poverty. 2011.

4. Reardon S. The widening academic achievement gap between rich and poor: new evidence and possible explanations. In: Duncan GJ, Murnane RJ, editors. Whither opportunity? Rising inequality, schools, and children's life chances. New York: Russel Sage Foundation; 2011; p. 91–115.
5. Hillemeier MM, Morgan PL, Farkas G, Maczuga SA. Perinatal and socioeconomic risk factors for variable and persistent cognitive delay at 24 and 48 months of age in a national sample. Matern Child Health J. 2010; 15:1001–10.
6. Lacour M, Tissington L. The effects of poverty on academic achievement. Educational Research and Reviews. 2011; 6(7):522–7.
7. Wright RJ. Moving towards making social toxins mainstream in children's environmental health. Curr Opin Pediatr 2009; 21:222–9. doi: 10.1097/MOP.0b013e3283292629 PMID: 19300262
8. Piaget J, Inhelder B. The psychology of the child. New York: The Perseus Books Group; 1972.
9. Doherty G. Zero to six: the basis for school readiness. Quebec: Human Resources Development Canada. 1997.
10. Hensch TK. Critical period plasticity in local cortical circuits. Nat Rev Neurosci. 2005; 6:877–88. PMID: 16261181
11. Hensch TK, Fagiolini M, Mataga N, Stryker MP, Baekkeskov S, Kash SF. Local GABA circuit control of experience-dependent plasticity in developing visual cortex. Science. 1998; 282:1504–8. PMID: 9822384
12. Engle PL, Castle S, Menon P. Child development: vulnerability and resilience. Soc Sci Med. 1996; 43:621–35. PMID: 8870128
13. Evans GW. Child development and the physical environment. Annu Rev Psychol. 2006; 57:423–51. PMID: 16318602
14. Ferguson KT, Cassells RC, MacAllister JW, Evans GW. The physical environment and child development: an international review. Int J Psychol. 2013; 48(4):437–68. doi: 10.1080/00207594.2013.804190 PMID: 23808797
15. Gordon N. Some influences on cognition in early life: a short review of recent opinions. Eur J Paediatr Neurol. 1998; 2(1):1–5. PMID: 10726840
16. Jurewicz J, Polanska K, Hanke W. Chemical exposure early in life and the neurodevelopment of children—an overview of current epidemiological evidence. Ann Agric Environ Med. 2013; 20:465–86. PMID: 24069851
17. Liu J, Lewis G. Environmental toxicity and poor cognitive outcomes in children and adults. J Environ Health. 2014; 76(6):130–8. PMID: 24645424
18. Walker SP, Wachs TD, Grantham-McGregor S, Black MM, Nelson CA, Huffman SL, et al. Inequality in early childhood: risk and protective factors for early child development. The Lancet. 2011; 378 (9799):1325–38.
19. Campbell JM, Brown RT, Cavanagh SE, Vess SF, Segall MJ. Evidence-based assessment of cognitive functioning in pediatric psychology. J Pediatr Psychol. 2008; 33(9):999–1020. doi: 10.1093/jpepsy/jsm138 PMID: 18194973
20. Smithers LG, Golley RK, Mittinty MN, Brazionis L, Northstone K, Emmett P, et al. Do dietary trajectories between infancy and toddlerhood influence IQ in childhood and adolescence? Results from a prospective birth cohort study. PLoS One. 2013; 8(3):e58904. doi: 10.1371/journal.pone.0058904 PMID: 23516574
21. Wang S, Chanock S, Tang D, Li Z, Edwards S, Jedrychowski W, et al. Effect of gene-environment Interactions on mental development in African American, Dominican, and Caucasian mothers and newborns. Ann Hum Genet. 2010; 74(1):46–56. doi: 10.1111/j.1469-1809.2009.00550.x PMID: 19860743
22. Sylva K, Stein A, Leach P, Barnes J, Malmberg LE. Effects of early child-care on cognition, language, and task-related behaviours at 18 months: an English study. Br J Dev Psychol. 2011; 29(1):18–45.
23. Lugo-Gil J, Tamis-LeMonda CS. Family resources and parenting quality: links to children's cognitive development across the first 3 years. Child Dev. 2008; 79(4):1065–85. doi: 10.1111/j.1467-8624.2008.01176.x PMID: 18717907
24. Surkan PJ, Zhang A, Trachtenberg F, Daniel DB, McKinlay S, Bellinger DC. Neuropsychological function in children with blood lead levels <10 microg/dL. Neurotoxicology. 2007; 28(6):1170–7. PMID: 17868887
25. Richardson GA, Goldschmidt L, Willford J. The effects of prenatal cocaine use on infant development. Neurotoxicol Teratol. 2008; 30(2):96–106. doi: 10.1016/j.ntt.2007.12.006 PMID: 18243651

26. Raikes H, Pan BA, Luze G, Tamis-LeMonda CS, Brooks-Gunn J, Constantine J, et al. Mother-child bookreading in low-income families: correlates and outcomes during the first three years of life. Child Dev. 2006; 77(4):924–53. PMID: 16942498

27. Han WJ. Maternal nonstandard work schedules and child cognitive outcomes. Child Dev. 2005; 76 (1):137–54. PMID: 15693763

28. Goldschmidt L, Richardson GA, Willford J, Day NL. Prenatal marijuana exposure and intelligence test performance at age 6. J Am Acad Child Adolesc Psychiatry. 2008; 47(3):254–63. doi: 10.1097/CHI.0b013e318160b3f0 PMID: 18216735

29. Signore C, Ueland PM, Troendle J, Mills JL. Choline concentrations in human maternal and cord blood and intelligence at 5 y of age. Am J Clin Nutr. 2008; 87(4):896–902. PMID: 18400712

30. Cao Y, Chen A, Jones RL, Radcliffe J, Caldwell KL, Dietrich KN, et al. Does background postnatal methyl mercury exposure in toddlers affect cognition and behavior? Neurotoxicology. 2010; 31(1):1–9. doi: 10.1016/j.neuro.2009.10.017 PMID: 19969021

31. Rauh VA, Whyatt RM, Garfinkel R, Andrews H, Hoepner L, Reyes A, et al. Developmental effects of exposure to environmental tobacco smoke and material hardship among inner-city children. Neurotoxicol Teratol. 2004; 26(3):373–85. PMID: 15113599

32. Rauh VA, Garfinkel R, Perera FP, Andrews HF, Hoepner L, Barr DB, et al. Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. Pediatrics. 2006; 118(6):e1845–59. PMID: 17116700

33. Perera FP, Rauh V, Whyatt RM, Tsai WY, Tang D, Diaz D, et al. Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. Environ Health Perspect. 2006; 114(8):1287–92. PMID: 16882541

34. Horton MK, Rundle A, Camann DE, Boyd Barr D, Rauh VA, Whyatt RM. Impact of prenatal exposure to piperonyl butoxide and permethrin on 36-month neurodevelopment. Pediatrics. 2011; 127(3): e699–706. doi: 10.1542/peds.2010-0133 PMID: 21300677

35. Banerjee PN, Tamis-LeMonda CS. Infants' persistence and mothers' teaching as predictors of toddlers' cognitive development. Infant Behav Dev. 2007; 30(3):479–91. PMID: 17683756

36. Rauh V, Arunajadai S, Horton M, Perera F, Hoepner L, Barr DB, et al. Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. Environ Health Perspect. 2011; 119(8):1196–1201. doi: 10.1289/ehp.1003160 PMID: 21507777

37. Perera FP, Li Z, Whyatt R, Hoepner L, Wang S, Camann D, et al. Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. Pediatrics. 2009; 124(2):e195–202. doi: 10.1542/peds.2008-3506 PMID: 19620194

38. Riojas-Rodriguez H, Solis-Vivanco R, Schilmann A, Montes S, Rodriguez S, Rios C, et al. Intellectual function in Mexican children living in a mining area and environmentally exposed to manganese. Environ Health Perspect. 2010; 118(10):1465–70. PMID: 20936744

39. Menezes-Filho JA, Novaes Cde O, Moreira JC, Sarcinelli PN, Mergler D. Elevated manganese and cognitive performance in school-aged children and their mothers. Environ Res. 2011; 111(1):156–63. doi: 10.1016/j.envres.2010.09.006 PMID: 20943219

40. Claus Henn B, Ettinger AS, Schwartz J, Tellez-Rojo MM, Lamadrid-Figueroa H, Hernandez-Avila M, et al. Early postnatal blood manganese levels and children's neurodevelopment. Epidemiology. 2010; 21(4):433–9. PMID: 20549838

41. Kim Y, Kim BN, Hong YC, Shin MS, Yoo HJ, Kim JW, et al. Co-exposure to environmental lead and manganese affects the intelligence of school-aged children. Neurotoxicology. 2009; 30(4):564–71. doi: 10.1016/j.neuro.2009.03.012 PMID: 19635390

42. Frank DA, Rose-Jacobs R, Beeghly M, Wilbur M, Bellinger D, Cabral H. Level of prenatal cocaine exposure and 48-month IQ: importance of preschool enrichment. Neurotoxicol Teratol 2005; 27 (1):15–28. PMID: 15681118

43. Bergman K, Sarkar P, Glover V, O'Connor TG. Maternal prenatal cortisol and infant cognitive development: moderation by infant–mother attachment. Biol Psychiatry. 2010; 67(11):1026–32. doi: 10.1016/j.biopsych.2010.01.002 PMID: 20188350

44. Jedrychowski W, Maugeri U, Perera F, Stigter L, Jankowski J, Butscher M, et al. Cognitive function of 6-year old children exposed to mold-contaminated homes in early postnatal period. Prospective birth cohort study in Poland. Physiol Behav. 2011; 104(5):989–95. doi: 10.1016/j.physbeh.2011.06.019 PMID: 21763705

45. Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, et al. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ Health Perspect. 2005; 113(7):894–9. PMID: 16002379

46. Williamson DL, Salkie FJ, Letourneau N. Welfare reforms and the cognitive development of young children. Can J Public Health. 2005; 96(1):13–7. PMID: 15682687

47. Rocha-Amador D, Navarro ME, Carrizales L, Morales R, Calderon J. Decreased intelligence in children and exposure to fluoride and arsenic in drinking water. Cad Saude Publica. 2007; 23(S4):S579–87.

48. Gustafsson PA, Duchen K, Birberg U, Karlsson T. Breastfeeding, very long polyunsaturated fatty acids (PUFA) and IQ at 6 1/2 years of age. Acta Paediatr. 2004; 93(10):1280–7. PMID: 15499945

49. von Ehrenstein OS, Mikolajczyk RT, Zhang J. Timing and trajectories of fetal growth related to cognitive development in childhood. Am J Epidemiol. 2009; 170(11):1388–95. doi: 10.1093/aje/kwp296 PMID: 19889710

50. Edwards SC, Jedrychowski W, Butscher M, Camann D, Kieltyka A, Mroz E, et al. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and children's intelligence at 5 years of age in a prospective cohort study in Poland. Environ Health Perspect, 2010; 118(9):1326–31. doi: 10.1289/ehp.0901070 PMID: 20406721

51. Jedrychowski W, Perera F, Jankowski J, Rauh V, Flak E, Caldwell KL, et al. Fish consumption in pregnancy, cord blood mercury level and cognitive and psychomotor development of infants followed over the first three years of life: Krakow epidemiologic study. Environ Int. 2007; 33(8):1057–62. PMID: 17643489

52. Jedrychowski W, Perera F, Jankowski J, Mrozek-Budzyn D, Mroz E, Flak E, et al. Gender specific differences in neurodevelopmental effects of prenatal exposure to very low-lead levels: the prospective cohort study in three-year olds. Early Hum Dev. 2009; 85(8):503–10. doi: 10.1016/j.earlhumdev.2009.04.006 PMID: 19450938

53. Jedrychowski W, Perera FP, Jankowski J, Mrozek-Budzyn D, Mroz E, Flak E, et al. Very low prenatal exposure to lead and mental development of children in infancy and early childhood: Krakow prospective cohort study. Neuroepidemiology. 2009; 32(4):270–8. doi: 10.1159/000203075 PMID: 19223686

54. Jedrychowski W, Perera F, Jankowski J, Butscher M, Mroz E, Flak E, et al. Effect of exclusive breastfeeding on the development of children's cognitive function in the Krakow prospective birth cohort study. Eur J Pediatr. 2012; 171(1):151–8. doi: 10.1007/s00431-011-1507-5 PMID: 21660433

55. Emond AM, Blair PS, Emmett PM, Drewett RF. Weight faltering in infancy and IQ levels at 8 years in the Avon Longitudinal Study of Parents and Children. Pediatrics. 2007; 120(4):e1051–8. PMID: 17908725

56. Beyerlein A, Ness AR, Streuling I, Hadders-Algra M, von Kries R. Early rapid growth: no association with later cognitive functions in children born not small for gestational age. Am J Clin Nutr. 2010; 92(3):585–93. doi: 10.3945/ajcn.2009.29116 PMID: 20592132

57. Sutter-Dallay AL, Murray L, Dequae-Merchadou L, Glatigny-Dallay E, Bourgeois ML, Verdoux H. A prospective longitudinal study of the impact of early postnatal vs. chronic maternal depressive symptoms on child development. Eur Psychiatry. 2011; 26(8):484–9. doi: 10.1016/j.eurpsy.2010.05.004 PMID: 20621453

58. Koutra K, Chatzi L, Roumeliotaki T, Vassilaki M, Giannakopoulou E, Batsos C, Koutis A, Kogevinas M. Socio-demographic determinants of infant neurodevelopment at 18 months of age: mother-child cohort (Rhea Study) in Crete, Greece. Infant Behav Dev. 2012; 35(1):48–59. doi: 10.1016/j.infbeh.2011.09.005 PMID: 22018719

59. Huang PC, Su PH, Chen HY, Huang HB, Tsai JL, Huang HI, et al. Childhood blood lead levels and intellectual development after ban of leaded gasoline in Taiwan: a 9-year prospective study. Environ Int. 2012; 40:88–96. doi: 10.1016/j.envint.2011.10.011 PMID: 22280932

60. Veldwijk J, Scholtens S, Hornstra G, Bemelmans WJ. Body mass index and cognitive ability of young children. Obes Facts. 2011; 4(4):264–9. doi: 10.1159/000331015 PMID: 21921648

61. Gomez-Sanchiz M, Canete R, Rodero I, Baeza JE, Gonzalez JA. Influence of breast-feeding and parental intelligence on cognitive development in the 24-month-old child. Clin Pediatr (Phila). 2004; 43(8):753–61.

62. Lee BE, Hong YC, Park H, Ha M, Kim JH, Chang N, et al. Secondhand smoke exposure during pregnancy and infantile neurodevelopment. Environ Res. 2011; 111(4):539–44. doi: 10.1016/j.envres.2011.02.014 PMID: 21397902

63. Zhou SJ, Baghurst P, Gibson RA, Makrides M. Home environment, not duration of breast-feeding, predicts intelligence quotient of children at four years. Nutrition. 2007; 23(3):236–41. PMID: 17320351

64. Wasserman GA, Liu X, Parvez F, Ahsan H, Factor-Litvak P, Kline J, et al. Water arsenic exposure and intellectual function in 6-year-old children in Araihazar, Bangladesh. Environ Health Perspect. 2007; 115(2):285–9. PMID: 17384779

65. Wasserman GA, Liu X, Parvez F, Ahsan H, Factor-Litvak P, van Geen A, et al. Water arsenic exposure and children's intellectual function in Araihazar, Bangladesh. Environ Health Perspect. 2004; 112 (13):1329–33. PMID: 15345348

66. Silva Rde C, Assis AM, Hasselmann MH, dos Santos LM, Pinto Ede J, Rodrigues LC. Influence of domestic violence on the association between malnutrition and low cognitive development. J Pediatr (Rio J). 2012; 88(2):149–54.

67. Tamis-LeMonda CS, Shannon JD, Cabrera NJ, Lamb ME. Fathers and mothers at play with their 2- and 3-year-olds: contributions to language and cognitive development. Child Dev. 2004; 75(6):1806–20. PMID: 15566381

68. Fishbein D, Warner T, Krebs C, Trevarthen N, Flannery B, Hammond J. Differential relationships between personal and community stressors and children's neurocognitive functioning. Child Maltreat. 2009; 14(4):299–315. doi: 10.1177/1077559508326355 PMID: 18971345

69. Albers EM, Riksen-Walraven JM, de Weerth C. Developmental stimulation in child care centers contributes to young infants' cognitive development. Infant Behav Dev. 2010; 33(4):401–8. doi: 10.1016/j.infbeh.2010.04.004 PMID: 20493531

70. Tofail F, Hamadani JD, Ahmed AZ, Mehrin F, Hakim M, Huda SN. The mental development and behavior of low-birth-weight Bangladeshi infants from an urban low-income community. Eur J Clin Nutr. 2012; 66(2):237–43. doi: 10.1038/ejcn.2011.165 PMID: 21952697

71. Deroma L, Parpinel M, Tognin V, Channoufi L, Tratnik J, Horvat M, et al. Neuropsychological assessment at school-age and prenatal low-level exposure to mercury through fish consumption in an Italian birth cohort living near a contaminated site. Int J Hyg Environ Health. 2013; 216(4):486–93. doi: 10.1016/j.ijheh.2013.02.004 PMID: 23523155

72. Tong S, Baghurst P, Vimpani G, McMichael A. Socioeconomic position, maternal IQ, home environment, and cognitive development. Journal Pediatr. 2007; 151(3):284–8.

73. Tong S, Baghurst P, McMichael A. Birthweight and cognitive development during childhood. J Paediatr Child Health. 2006; 42(3):98–103. PMID: 16509907

74. Sunyer J, Basagana X, Gonzalez JR, Julvez J, Guerra S, Bustamante M, et al. Early life environment, neurodevelopment and the interrelation with atopy. Environ Res. 2010; 110(7):733–8. doi: 10.1016/j.envres.2010.07.005 PMID: 20701904

75. Llop S, Guxens M, Murcia M, Lertxundi A, Ramon R, Riano I, et al. Prenatal exposure to mercury and infant neurodevelopment in a multicenter cohort in Spain: study of potential modifiers. Am J Epidemiol. 2012; 175(5):451–65. doi: 10.1093/aje/kwr328 PMID: 22287639

76. Singer LT, Moore DG, Min MO, Goodwin J, Turner JJ, Fulton S, et al. One-year outcomes of prenatal exposure to MDMA and other recreational drugs. Pediatrics. 2012; 130(3):407–13. doi: 10.1542/peds.2012-0666 PMID: 22908109

77. Nair P, Black MM, Ackerman JP, Schuler ME, Keane VA. Children's cognitive-behavioral functioning at age 6 and 7: prenatal drug exposure and caregiving environment. Ambul Pediatr. 2008; 8(3):154–62. doi: 10.1016/j.ambp.2008.02.002 PMID: 18501861

78. Surkan PJ, Schnaas L, Wright RJ, Tellez-Rojo MM, Lamadrid-Figueroa H, Hu H, et al. Maternal self-esteem, exposure to lead, and child neurodevelopment. Neurotoxicology. 2008; 29(2):278–85. doi: 10.1016/j.neuro.2007.11.006 PMID: 18261800

79. Tellez-Rojo MM, Bellinger DC, Arroyo-Quiroz C, Lamadrid-Figueroa H, Mercado-Garcia A, Schnaas-Arrieta L, et al. Longitudinal associations between blood lead concentrations lower than 10 microg/dL and neurobehavioral development in environmentally exposed children in Mexico City. Pediatrics. 2006; 118(2):e323–30. PMID: 16882776

80. Gruber R, Laviolette R, Deluca P, Monson E, Cornish K, Carrier J. Short sleep duration is associated with poor performance on IQ measures in healthy school-age children. Sleep Med 2010, 11(3):289–294. doi: 10.1016/j.sleep.2009.09.007 PMID: 20156702

81. Smith LM, LaGasse LL, Derauf C, Newman E, Shah R, Haning W, et al. Motor and cognitive outcomes through three years of age in children exposed to prenatal methamphetamine. Neurotoxicol Teratol. 2011; 33(1):176–84. doi: 10.1016/j.ntt.2010.10.004 PMID: 21256431

82. Watson GE, Evans K, Thurston SW, van Wijngaarden E, Wallace JM, McSorley EM, et al. Prenatal exposure to dental amalgam in the Seychelles Child Development Nutrition Study: associations with neurodevelopmental outcomes at 9 and 30 months. Neurotoxicology. 2012; 33(6):1511–7. doi: 10.1016/j.neuro.2012.10.001 PMID: 23064204

83. Williams FL, Watson J, Ogston SA, Visser TJ, Hume R, Willatts P. Maternal and umbilical cord levels of T4, FT4, TSH, TPOAb, and TgAb in term infants and neurodevelopmental outcome at 5.5 years. J Clin Endocrinol Metab. 2013; 98(2):829–38. doi: 10.1210/jc.2012-3572 PMID: 23322817

84. Davidson PW, Myers GJ, Cox C, Wilding GE, Shamlaye CF, Huang LS, et al. Methylmercury and neurodevelopment: longitudinal analysis of the Seychelles child development cohort. Neurotoxicol Teratol. 2006; 28(5):529–35. PMID: 16904865

85. Schnaas L, Rothenberg SJ, Flores MF, Martinez S, Hernandez C, Osorio E, et al. Reduced intellectual development in children with prenatal lead exposure. Environ Health Perspect. 2006; 114(5):791–7. PMID: 16675439

86. Bennett DS, Bendersky M, Lewis M. Children's cognitive ability from 4 to 9 years old as a function of prenatal cocaine exposure, environmental risk, and maternal verbal intelligence. Dev Psychol. 2008; 44(4):919–28. doi: 10.1037/0012-1649.44.4.919 PMID: 18605824

87. Nelson S, Lerner E, Needlman R, Salvator A, Singer LT. Cocaine, anemia, and neurodevelopmental outcomes in children: a longitudinal study. J Dev Behav Pediatr. 2004; 25(1):1–9. PMID: 14767350

88. Cabrera NJ, Fagan J, Wight V, Schadler C. Influence of mother, father, and child risk on parenting and children's cognitive and social behaviors. Child Dev. 2011; 82(6):1985–2005. doi: 10.1111/j.1467-8624.2011.01667.x PMID: 22026516

89. Park HY, Hertz-Picciotto I, Sovcikova E, Kocan A, Drobna B, Trnovec T. Neurodevelopmental toxicity of prenatal polychlorinated biphenyls (PCBs) by chemical structure and activity: a birth cohort study. Environ Health. 2010; 9:51. doi: 10.1186/1476-069X-9-51 PMID: 20731829

90. Chaudhari S, Otiv M, Chitale A, Pandit A, Hoge M. Pune low birth weight study—cognitive abilities and educational performance at twelve years. Indian Pediatr. 2004; 41(2):121–8. PMID: 15004297

91. Orchinik LJ, Taylor HG, Espy KA, Minich N, Klein N, Sheffield T, et al. Cognitive outcomes for extremely preterm/extremely low birth weight children in kindergarten. J Int Neuropsychol Soc. 2011; 17(6):1067–79. doi: 10.1017/S135561771100107X PMID: 21923973

92. Munck P, Haataja L, Maunu J, Parkkola R, Rikalainen H, Lapinleimu H, et al. Cognitive outcome at 2 years of age in Finnish infants with very low birth weight born between 2001 and 2006. Acta Paediatr. 2010; 99(3):359–66. doi: 10.1111/j.1651-2227.2009.01589.x PMID: 19912142

93. Munck P, Niemi P, Lapinleimu H, Lehtonen L, Haataja L. Stability of cognitive outcome from 2 to 5 years of age in very low birth weight children. Pediatrics. 2012; 129(3):503–8. doi: 10.1542/peds.2011-1566 PMID: 22371467

94. Kilbride HW, Thorstad K, Daily DK. Preschool outcome of less than 801-gram preterm infants compared with full-term siblings. Pediatrics. 2004; 113(4):742–7. PMID: 15060222

95. Anderson P, Doyle LW, Victorian Infant Collaborative Study Group. Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990s. JAMA. 2003; 289 (24):3264–72. PMID: 12824207

96. Short EJ, Klein NK, Lewis BA, Fulton S, Eisengart S, Kercsmar C, et al. Cognitive and academic consequences of bronchopulmonary dysplasia and very low birth weight: 8-year-old outcomes. Pediatrics. 2003; 112(5):e359. PMID: 14595077

97. Feldman R, Eidelman AI. Does a triplet birth pose a special risk for infant development? Assessing cognitive development in relation to intrauterine growth and mother-infant interaction across the first 2 years. Pediatrics. 2005; 115(2):443–52. PMID: 15687454

98. Hu H, Tellez-Rojo MM, Bellinger D, Smith D, Ettinger AS, Lamadrid-Figueroa H, et al. Fetal lead exposure at each stage of pregnancy as a predictor of infant mental development. Environ Health Perspect. 2006; 114(11):1730–5. PMID: 17107860

99. Wasserman GA, Liu X, Parvez F, Ahsan H, Levy D, Factor-Litvak P, et al. Water manganese exposure and children's intellectual function in Araihazar, Bangladesh. Environ Health Perspect. 2006; 114 (1):124–9. PMID: 16393669

100. Wasserman GA, Liu X, Parvez F, Factor-Litvak P, Ahsan H, Levy D, et al. Arsenic and manganese exposure and children's intellectual function. Neurotoxicology. 2011; 32(4):450–7. doi: 10.1016/j.neuro.2011.03.009 PMID: 21453724

101. Cooke RW, Foulder-Hughes L. Growth impairment in the very preterm and cognitive and motor performance at 7 years. Arch Dis Child. 2003; 88(6):482–7. PMID: 12765911

102. Yang S, Tilling K, Martin R, Davies N, Ben-Shlomo Y, Kramer MS. Pre-natal and post-natal growth trajectories and childhood cognitive ability and mental health. Int J Epidemiol. 2011; 40(5):1215–26. doi: 10.1093/ije/dyr094 PMID: 21764769

103. Gale CR, O'Callaghan FJ, Bredow M, Martyn CN. The influence of head growth in fetal life, infancy, and childhood on intelligence at the ages of 4 and 8 years. Pediatrics. 2006; 118(4):1486–92. PMID: 17015539

104. Begega A, Mendez-Lopez MJ, Cuesta-Izquierdo M, Solis G, Fernandez-Colomer B, Alvarez L, et al. Assessment of the global intelligence and selective cognitive capacities in pre-term 8-year-old children. Psicothema. 2010; 22(4):648–53. PMID: 21044492

105. Soria-Pastor S, Padilla N, Zubiaurre-Elorza L, Ibarretxe-Bilbao N, Botet F, Costas-Moragas C, et al. Decreased regional brain volume and cognitive impairment in preterm children at low risk. Pediatrics. 2009; 124(6):e1161–70. doi: 10.1542/peds.2009-0244 PMID: 19948618

106. Cserjesi R, Van Braeckel KN, Butcher PR, Kerstjens JM, Reijneveld SA, Bouma A, et al. Functioning of 7-year-old children born at 32 to 35 weeks' gestational age. Pediatrics. 2012; 130(4):e838–46. doi: 10.1542/peds.2011-2079 PMID: 22945414

107. Nepomnyaschy L, Hegyi T, Ostfeld BM, Reichman NE. Developmental outcomes of late-preterm infants at 2 and 4 years. Matern Child Health J. 2012,; 6(8):1612–24.

108. Odd DE, Emond A, Whitelaw A. Long-term cognitive outcomes of infants born moderately and late preterm. Dev Med Child Neurol. 2012; 54(8):704–9. doi: 10.1111/j.1469-8749.2012.04315.x PMID: 22616920

109. Larroque B, Ancel PY, Marret S, Marchand L, Andre M, Arnaud C, et al. Neurodevelopmental disabilities and special care of 5-year-old children born before 33 weeks of gestation (the EPIPAGE study): a longitudinal cohort study. Lancet. 2008; 371(9615):813–20. doi: 10.1016/S0140-6736(08)60380-3 PMID: 18328928

110. Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med. 2005; 352(1):9–19. PMID: 15635108

111. Serenius F, Kallen K, Blennow M, Ewald U, Fellman V, Holmstrom G, et al. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden. JAMA. 2013; 309(17):1810–20. doi: 10.1001/jama.2013.3786 PMID: 23632725

112. Kennedy JD, Blunden S, Hirte C, Parsons DW, Martin AJ, Crowe E, et al. Reduced neurocognition in children who snore. Pediatr Pulmonol. 2004; 37(4):330–7. PMID: 15022130

113. Gottlieb DJ, Chase C, Vezina RM, Heeren TC, Corwin MJ, Auerbach SH, et al. Sleep-disordered breathing symptoms are associated with poorer cognitive function in 5-year-old children. J Pediatr. 2004; 145(4):458–64. PMID: 15480367

114. Jackman AR, Biggs SN, Walter LM, Embuldeniya US, Davey MJ, Nixon GM, et al. Sleep-disordered breathing in preschool children is associated with behavioral, but not cognitive, impairments. Sleep Med. 2012; 13(6):621–31. doi: 10.1016/j.sleep.2012.01.013 PMID: 22503657

115. Kaemingk KL, Pasvogel AE, Goodwin JL, Mulvaney SA, Martinez F, Enright PL, et al. Learning in children and sleep disordered breathing: findings of the Tucson Children's Assessment of Sleep Apnea (tuCASA) prospective cohort study. J Int Neuropsychol Soc. 2003; 9(7):1016–26. PMID: 14738283

116. Bourke R, Anderson V, Yang JS, Jackman AR, Killedar A, Nixon GM, et al. Cognitive and academic functions are impaired in children with all severities of sleep-disordered breathing. Sleep Med. 2011; 12(5):489–96. doi: 10.1016/j.sleep.2010.11.010 PMID: 21493135

117. Miano S, Paolino MC, Urbano A, Parisi P, Massolo AC, Castaldo R, et al. Neurocognitive assessment and sleep analysis in children with sleep-disordered breathing. Clin Neurophysiol. 2011; 122(2):311–9. doi: 10.1016/j.clinph.2010.06.019 PMID: 20637692

118. Emancipator JL, Storfer-Isser A, Taylor HG, Rosen CL, Kirchner HL, Johnson NL, et al. Variation of cognition and achievement with sleep-disordered breathing in full-term and preterm children. Arch Pediatr Adolesc Med. 2006; 160(2):203–10. PMID: 16461879

119. Calhoun SL, Mayes SD, Vgontzas AN, Tsaoussoglou M, Shifflett LJ, Bixler EO. No relationship between neurocognitive functioning and mild sleep disordered breathing in a community sample of children. J Clin Sleep Med. 2009; 5(3):228–34. PMID: 19960643

120. Kohler MJ, Lushington K, van den Heuvel CJ, Martin J, Pamula Y, Kennedy D. Adenotonsillectomy and neurocognitive deficits in children with Sleep Disordered Breathing. PLoS One. 2009; 4(10): e7343. doi: 10.1371/journal.pone.0007343 PMID: 19806214

121. Calhoun SL, Fernandez-Mendoza J, Vgontzas AN, Mayes SD, Tsaoussoglou M, Rodriguez-Munoz A, et al. Learning, attention/hyperactivity, and conduct problems as sequelae of excessive daytime sleepiness in a general population study of young children. Sleep. 2012; 35(5):627–32. doi: 10.5665/sleep.1818 PMID: 22547888

122. Buckhalt JA, El-Sheikh M, Keller P. Children's sleep and cognitive functioning: race and socioeconomic status as moderators of effects. Child Dev. 2007; 78(1):213–31. PMID: 17328701

123. Forns J, Julvez J, Garcia-Esteban R, Guxens M, Ferrer M, Grellier J, et al. Maternal intelligence-mental health and child neuropsychological development at age 14 months. Gac Sanit. 2012; 26(5):397–404. doi: 10.1016/j.gaceta.2011.10.011 PMID: 22284911

124. Arendt R, Short E, Minnes S, Hewitt J, Flynn S, Carlson L, et al. Children prenatally exposed to cocaine: developmental outcomes and environmental risks at seven years of age. J Dev Behav Pediatr. 2004; 25(2):83–90. PMID: 15083129

125. Nulman I, Koren G, Rovet J, Barrera M, Pulver A, Streiner D, et al. Neurodevelopment of children following prenatal exposure to venlafaxine, selective serotonin reuptake inhibitors, or untreated maternal depression. Am J Psychiatry. 2012; 169(11):1165–74. doi: 10.1176/appi.ajp.2012.11111721 PMID: 23128923

126. Perera FP, Tang D, Rauh V, Tu YH, Tsai WY, Becker M, et al. Relationship between polycyclic aromatic hydrocarbon-DNA adducts, environmental tobacco smoke, and child development in the World Trade Center cohort. Environ Health Perspect. 2007; 115(10):1497–1502. PMID: 17938742

127. Pilsner JR, Hu H, Wright RO, Kordas K, Ettinger AS, Sanchez BN, et al. Maternal MTHFR genotype and haplotype predict deficits in early cognitive development in a lead-exposed birth cohort in Mexico City. Am J Clin Nutr. 2010; 92(1):226–34. doi: 10.3945/ajcn.2009.28839 PMID: 20504979

128. Chan WS, Koren G, Barrera M, Rezvani M, Knittel-Keren D, Nulman I. Neurocognitive development of children following in-utero exposure to labetalol for maternal hypertension: a cohort study using a prospectively collected database. Hypertens Pregnancy. 2010; 29(3):271–83. doi: 10.3109/10641950902777705 PMID: 20670152

129. Li Y, Shan Z, Teng W, Yu X, Fan C, Teng X, et al. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25–30 months. Clin Endocrinol (Oxf). 2010; 72(6):825–9.

130. Julvez J, Alvarez-Pedrerol M, Rebagliato M, Murcia M, Forns J, Garcia-Esteban R, et al. Thyroxine levels during pregnancy in healthy women and early child neurodevelopment. Epidemiology. 2013; 24(1):150–7. doi: 10.1097/EDE.0b013e318276ccd3 PMID: 23232616

131. Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol (Oxf). 2003; 59(3):282–8.

132. Craig WY, Allan WC, Kloza EM, Pulkkinen AJ, Waisbren S, Spratt DI, et al. Mid-gestational maternal free thyroxine concentration and offspring neurocognitive development at age two years. J Clin Endocrinol Metab. 2012; 97(1):E22–8. doi: 10.1210/jc.2011-1772 PMID: 22031521

133. Hinkle SN, Schieve LA, Stein AD, Swan DW, Ramakrishnan U, Sharma AJ. Associations between maternal prepregnancy body mass index and child neurodevelopment at 2 years of age. Int J Obes. 2012; 36(10):1312–9.

134. Evans J, Melotti R, Heron J, Ramchandani P, Wiles N, Murray L, et al. The timing of maternal depressive symptoms and child cognitive development: a longitudinal study. J Child Psychol Psychiatry. 2012; 53(6):632–40. doi: 10.1111/j.1469-7610.2011.02513.x PMID: 22211468

135. Koutra K, Chatzi L, Bagkeris M, Vassilaki M, Bitsios P, Kogevinas M. Antenatal and postnatal maternal mental health as determinants of infant neurodevelopment at 18 months of age in a mother-child cohort (Rhea Study) in Crete, Greece. Soc Psychiatry Psychiatr Epidemiol. 2013; 48(8):1335–45. doi: 10.1007/s00127-012-0636-0 PMID: 23248031

136. Piteo AM, Yelland LN, Makrides M. Does maternal depression predict developmental outcome in 18 month old infants? Early Hum Dev. 2012; 88(8):651–5. doi: 10.1016/j.earlhumdev.2012.01.013 PMID: 22361258

137. Huizink AC, Robles de Medina PG, Mulder EJ, Visser GH, Buitelaar JK. Stress during pregnancy is associated with developmental outcome in infancy. J Child Psychol Psychiatry. 2003; 44(6):810–8. PMID: 12959490

138. Slykerman RF, Thompson JM, Pryor JE, Becroft DM, Robinson E, Clark PM, et al. Maternal stress, social support and preschool children's intelligence. Early Hum Dev. 2005; 81(10):815–21. PMID: 16019165

139. Davis EP, Sandman CA. The timing of prenatal exposure to maternal cortisol and psychosocial stress is associated with human infant cognitive development. Child Dev. 2010; 81(1):131–48. doi: 10.1111/j.1467-8624.2009.01385.x PMID: 20331658

140. Bahena-Medina LA, Torres-Sanchez L, Schnaas L, Cebrian ME, Chavez CH, Osorio-Valencia E, et al. Neonatal neurodevelopment and prenatal exposure to dichlorodiphenyldichloroethylene (DDE): a cohort study in Mexico. J Expo Sci Environ Epidemiol. 2011; 21(6):609–14. doi: 10.1038/jes.2011.25 PMID: 21750576

141. Torres-Sanchez L, Rothenberg SJ, Schnaas L, Cebrian ME, Osorio E, Del Carmen Hernandez M, et al. In utero p,p'-DDE exposure and infant neurodevelopment: a perinatal cohort in Mexico. Environ Health Perspect. 2007; 115(3):435–9. PMID: 17431495

142. Ribas-Fito N, Cardo E, Sala M, Eulalia de Muga M, Mazon C, Verdu A, et al. Breastfeeding, exposure to organochlorine compounds, and neurodevelopment in infants. Pediatrics. 2003; 111(5 Pt 1):e580–5. PMID: 12728113

143. Ribas-Fito N, Julvez J, Torrent M, Grimalt JO, Sunyer J. Beneficial effects of breastfeeding on cognition regardless of DDT concentrations at birth. Am J Epidemiol. 2007; 166(10):1198–1202. PMID: 17890756

144. Freire C, Ramos R, Lopez-Espinosa MJ, Diez S, Vioque J, Ballester F, et al. Hair mercury levels, fish consumption, and cognitive development in preschool children from Granada, Spain. Environ Res. 2010; 110(1):96–104. doi: 10.1016/j.envres.2009.10.005 PMID: 19909946

145. Gomez-Sanchiz M, Canete R, Rodero I, Baeza JE, Avila O. Influence of breast-feeding on mental and psychomotor development. Clin Pediatr (Phila) 2003; 42(1):35–42.

146. Torres-Sanchez L, Schnaas L, Cebrian ME, Hernandez Mdel C, Valencia EO, Garcia Hernandez RM, et al. Prenatal dichlorodiphenyldichloroethylene (DDE) exposure and neurodevelopment: a follow-up from 12 to 30 months of age. Neurotoxicology. 2009; 30(6):1162–5. doi: 10.1016/j.neuro.2009.08.010 PMID: 19733589

147. Brion MJ, Lawlor DA, Matijasevich A, Horta B, Anselmi L, Araujo CL, et al. What are the causal effects of breastfeeding on IQ, obesity and blood pressure? Evidence from comparing high-income with middle-income cohorts. Int J Epidemiol. 2011; 40(3):670–80. doi: 10.1093/ije/dyr020 PMID: 21349903

148. Guxens M, Mendez MA, Molto-Puigmarti C, Julvez J, Garcia-Esteban R, Forns J, et al. Breastfeeding, long-chain polyunsaturated fatty acids in colostrum, and infant mental development. Pediatrics. 2011; 128(4):e880–9. doi: 10.1542/peds.2010-1633 PMID: 21930546

149. Smithers LG, Golley RK, Mittinty MN, Brazionis L, Northstone K, Emmett P, et al. Dietary patterns at 6, 15 and 24 months of age are associated with IQ at 8 years of age. Eur J Epidemiol. 2012; 27 (7):525–35. doi: 10.1007/s10654-012-9715-5 PMID: 22810299

150. Tozzi AE, Bisiacchi P, Tarantino V, Chiarotti F, D'Elia L, De Mei B, et al. Effect of duration of breastfeeding on neuropsychological development at 10 to 12 years of age in a cohort of healthy children. Dev Med Child Neurol. 2012; 54(9):843–8. doi: 10.1111/j.1469-8749.2012.04319.x PMID: 22590982

151. El-khayat H, Shaaban S, Emam EK, Elwakkad A. Cognitive functions in protein-energy malnutrition: in relation to long chain-polyunsaturated fatty acids. Pak J Biol Sci. 2007; 10(11):1773–81. PMID: 19086537

152. Jacobson JL, Jacobson SW, Muckle G, Kaplan-Estrin M, Ayotte P, Dewailly E. Beneficial effects of a polyunsaturated fatty acid on infant development: evidence from the Inuit of arctic Quebec. J Pediatr. 2008; 152(3):356–64. doi: 10.1016/j.jpeds.2007.07.008 PMID: 18280840

153. Bakker EC, Ghys AJA, Kester ADM, Vles JSH, Dubas JS, Blanco CE, et al. Long-chain polyunsaturated fatty acids at birth and cognitive function at 7 years of age. Eur J Clin Nutr. 2003; 57(1):89–95. PMID: 12548302

154. Morales E, Bustamante M, Gonzalez JR, Guxens M, Torrent M, Mendez M, et al. Genetic variants of the FADS gene cluster and ELOVL gene family, colostrums LC-PUFA levels, breastfeeding, and child cognition. PLoS One. 2011; 6(2):e17181. doi: 10.1371/journal.pone.0017181 PMID: 21383846

155. Gale CR, Martyn CN, Marriott LD, Limond J, Crozier S, Inskip HM, et al. Dietary patterns in infancy and cognitive and neuropsychological function in childhood. J Child Psychol Psychiatry. 2009; 50 (7):816–23. doi: 10.1111/j.1469-7610.2008.02029.x PMID: 19236526

156. Northstone K, Joinson C, Emmett P, Ness A, Paus T. Are dietary patterns in childhood associated with IQ at 8 years of age? A population-based cohort study. J Epidemiol Community Health. 2012; 66 (7):624–8. doi: 10.1136/jech.2010.111955 PMID: 21300993

157. Lucchini RG, Zoni S, Guazzetti S, Bontempi E, Micheletti S, Broberg K, et al. Inverse association of intellectual function with very low blood lead but not with manganese exposure in Italian adolescents. Environ Res. 2012; 118:65–71. doi: 10.1016/j.envres.2012.08.003 PMID: 22925625

158. del Rio Garcia C, Torres-Sanchez L, Chen J, Schnaas L, Hernandez C, Osorio E, et al. Maternal MTHFR 677C>T genotype and dietary intake of folate and vitamin B(12): their impact on child neurodevelopment. Nutr Neurosci. 2009; 12(1):13–20. doi: 10.1179/147683009X388913 PMID: 19178787

159. Chatzi L, Papadopoulou E, Koutra K, Roumeliotaki T, Georgiou V, Stratakis N, et al. Effect of high doses of folic acid supplementation in early pregnancy on child neurodevelopment at 18 months of age: the mother-child cohort 'Rhea' study in Crete, Greece. Public Health Nutr. 2012; 15(9):1728–36. doi: 10.1017/S1368980012000067 PMID: 22314109

160. Julvez J, Fortuny J, Mendez M, Torrent M, Ribas-Fito N, Sunyer J. Maternal use of folic acid supplements during pregnancy and four-year-old neurodevelopment in a population-based birth cohort. Paediatr Perinat Epidemiol. 2009; 23(3):199–206. doi: 10.1111/j.1365-3016.2009.01032.x PMID: 19775381

161. Chiodo LM, Janisse J, Delaney-Black V, Sokol RJ, Hannigan JH. A metric of maternal prenatal risk drinking predicts neurobehavioral outcomes in preschool children. Alcohol Clin Exp Res. 2009; 33 (4):634–44. doi: 10.1111/j.1530-0277.2008.00878.x PMID: 19183137

162. Lewis SJ, Zuccolo L, Davey Smith G, Macleod J, Rodriguez S, Draper ES, et al. Fetal alcohol exposure and IQ at age 8: evidence from a population-based birth-cohort study. PLoS One. 2012; 7(11): e49407. doi: 10.1371/journal.pone.0049407 PMID: 23166662

163. Falgreen Eriksen HL, Mortensen EL, Kilburn T, Underbjerg M, Bertrand J, Stovring H, et al. The effects of low to moderate prenatal alcohol exposure in early pregnancy on IQ in 5-year-old children. BJOG. 2012; 119(10):1191–1200. doi: 10.1111/j.1471-0528.2012.03394.x PMID: 22712749

164. Kesmodel US, Bertrand J, Stovring H, Skarpness B, Denny CH, Mortensen EL. The effect of different alcohol drinking patterns in early to mid pregnancy on the child's intelligence, attention, and executive function. BJOG. 2012; 119(10):1180–90. doi: 10.1111/j.1471-0528.2012.03393.x PMID: 22712700

165. O'Callaghan FV, O'Callaghan M, Najman JM, Williams GM, Bor W. Prenatal alcohol exposure and attention, learning and intellectual ability at 14 years: a prospective longitudinal study. Early Hum Dev. 2007; 83(2):115–23. PMID: 16842939

166. Raman V, Prasad S, Appaya MP. Children of men with alcohol dependence: Psychopathology, neurodevelopment and family environment. Indian J Psychiatry. 2010; 52(4):360–6. doi: 10.4103/0019-5545.74313 PMID: 21267372

167. Pears K, Fisher PA. Developmental, cognitive, and neuropsychological functioning in preschool-aged foster children: associations with prior maltreatment and placement history. J Dev Behav Pediatr. 2005; 26(2):112–22. PMID: 15827462

168. Loman MM, Wiik KL, Frenn KA, Pollak SD, Gunnar MR. Postinstitutionalized children's development: growth, cognitive, and language outcomes. J Dev Behav Pediatr. 2009; 30(5):426–34. doi: 10.1097/DBP.0b013e3181b1fd08 PMID: 19692931

169. Yang S, Kramer MS. Paternal alcohol consumption, family transition and child development in a former Soviet country. Int J Epidemiol. 2012; 41(4):1086–96. doi: 10.1093/ije/dys071 PMID: 22586132

170. Kolobe TH. Childrearing practices and developmental expectations for Mexican-American mothers and the developmental status of their infants. Phys Ther. 2004; 84(5):439–53. PMID: 15113277

171. Lowe J, Erickson SJ, MacLean P. Cognitive correlates in toddlers born very low birth weight and full-term. Infant Behav Dev. 2010; 33(4):629–34. doi: 10.1016/j.infbeh.2010.07.016 PMID: 20708803

172. Agency for Toxic Substances Disease Registry. Toxicological profile for arsenic. Atlanta: US Department of Health and Human Services, Public Health Service. 2007.

173. Wang SX, Wang ZH, Cheng XT, Li J, Sang ZP, Zhang XD, et al. Arsenic and fluoride exposure in drinking water: children's IQ and growth in Shanyin county, Shanxi province, China. Environ Health Perspect. 2007; 115(4):643–7. PMID: 17450237

174. Hamadani JD, Grantham-McGregor SM, Tofail F, Nermell B, Fangstrom B, Huda SN, et al. Pre- and postnatal arsenic exposure and child development at 18 months of age: a cohort study in rural Bangladesh. Int J Epidemiol. 2010; 39(5):1206–16. doi: 10.1093/ije/dyp369 PMID: 20085967

175. Hamadani JD, Tofail F, Nermell B, Gardner R, Shiraji S, Bottai M, et al. Critical windows of exposure for arsenic-associated impairment of cognitive function in pre-school girls and boys: a population-based cohort study. Int J Epidemiol. 2011; 40(6):1593–1604. doi: 10.1093/ije/dyr176 PMID: 22158669

176. von Ehrenstein OS, Poddar S, Yuan Y, Mazumder DG, Eskenazi B, Basu A, et al. Children's intellectual function in relation to arsenic exposure. Epidemiology. 2007; 18(1):44–51. PMID: 17149142

177. Agency for Toxic Substances Registry. Toxicological profile for fluorides, hydrogen fluoride and fluorine (update). Atlanta: US Department of Health and Human Services Public Health Service. 2003.

178. Saxena S, Sahay A, Goel P. Effect of fluoride exposure on the intelligence of school children in Madhya Pradesh, India. J Neurosci Rural Pract. 2012; 3(2):144–9. doi: 10.4103/0976-3147.98213 PMID: 22865964

179. Seraj B, Shahrabi M, Shadfar M, Ahmadi R, Fallahzadeh M, Eslamlu HF, et al. Effect of high water fluoride concentration on the intellectual development of children in Makoo/Iran. J Dent (Tehran). 2012; 9(3):221–9.

180. Shivaprakash PK, Ohri K, Noorani H. Relation between dental fluorosis and intelligence quotient in school children of Bagalkot district. J Indian Soc Pedod Prev Dent. 2011; 29(2):117–20. doi: 10.4103/0970-4388.84683 PMID: 21911949

181. Koller K, Brown T, Spurgeon A, Levy L. Recent developments in low-level lead exposure and intellectual impairment in children. Environ Health Perspect. 2004; 112(9):987–94. PMID: 15198918

182. Chiodo LM, Jacobson SW, Jacobson JL. Neurodevelopmental effects of postnatal lead exposure at very low levels. Neurotoxicol Teratol. 2004; 26(3):359–71. PMID: 15113598

183. Jusko TA, Henderson CR, Lanphear BP, Cory-Slechta DA, Parsons PJ, Canfield RL. Blood lead concentrations < 10 microg/dL and child intelligence at 6 years of age. Environ Health Perspect. 2008; 116(2):243–8. doi: 10.1289/ehp.10424 PMID: 18288325

184. Canfield RL, Henderson CR Jr., Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. Intellectual impairment in children with blood lead concentrations below 10 microg per deciliter. N Engl J Med. 2003; 348(16):1517–26. PMID: 12700371

185. Min MO, Singer LT, Kirchner HL, Minnes S, Short E, Hussain Z, et al. Cognitive development and low-level lead exposure in poly-drug exposed children. Neurotoxicol Teratol. 2009; 31(4):225–31. doi: 10.1016/j.ntt.2009.03.002 PMID: 19345261

186. Cao Y, Chen A, Radcliffe J, Dietrich KN, Jones RL, Caldwell K, et al. Postnatal cadmium exposure, neurodevelopment, and blood pressure in children at 2, 5, and 7 years of age. Environ Health Perspect. 2009; 117(10):1580–6. doi: 10.1289/ehp.0900765 PMID: 20019909

187. Chen A, Dietrich KN, Ware JH, Radcliffe J, Rogan WJ. IQ and blood lead from 2 to 7 years of age: are the effects in older children the residual of high blood lead concentrations in 2-year-olds? Environ Health Perspect. 2005; 113(5):597–601. PMID: 15866769

188. Claus Henn B, Schnaas L, Ettinger AS, Schwartz J, Lamadrid-Figueroa H, Hernandez-Avila M, et al. Associations of early childhood manganese and lead coexposure with neurodevelopment. Environ Health Perspect. 2012; 120(1):126–31. doi: 10.1289/ehp.1003300 PMID: 21885384

189. Pawlas N, Broberg K, Olewinska E, Prokopowicz A, Skerfving S, Pawlas K. Modification by the genes ALAD and VDR of lead-induced cognitive effects in children. Neurotoxicology. 2012; 33(1):37–43. doi: 10.1016/j.neuro.2011.10.012 PMID: 22101007

190. Kim Y, Ha EH, Park H, Ha M, Hong YC, Kim EJ, et al. Prenatal lead and cadmium co-exposure and infant neurodevelopment at 6 months of age: the Mothers and Children's Environmental Health (MOCEH) study. Neurotoxicology. 2013; 35:15–22. doi: 10.1016/j.neuro.2012.11.006 PMID: 23220728

191. Agency for Toxic Substances Registry. Toxicological profile for manganese. Atlanta: US Department of Health and Human Services Public Health Service. 2012.

192. Bouchard MF, Sauve S, Barbeau B, Legrand M, Brodeur ME, Bouffard T, et al. Intellectual impairment in school-age children exposed to manganese from drinking water. Environ Health Perspect. 2011; 119(1):138–43. doi: 10.1289/ehp.1002321 PMID: 20855239

193. Vrijheid M, Martinez D, Aguilera I, Bustamante M, Ballester F, Estarlich M, et al. Indoor air pollution from gas cooking and infant neurodevelopment. Epidemiology. 2012; 23(1):23–32. doi: 10.1097/EDE.0b013e31823a4023 PMID: 22082993

194. Eskenazi B, Chevrier J, Rauch SA, Kogut K, Harley KG, Johnson C, et al. In utero and childhood polybrominated diphenyl ether (PBDE) exposures and neurodevelopment in the CHAMACOS study. Environ Health Perspect. 2013; 121(2):257–62. doi: 10.1289/ehp.1205597 PMID: 23154064

195. Shy CG, Huang HL, Chang-Chien GP, Chao HR, Tsou TC. Neurodevelopment of infants with prenatal exposure to polybrominated diphenyl ethers. Bull Environ Contam Toxicol. 2011; 87(6):643–648. doi: 10.1007/s00128-011-0422-9 PMID: 21953308

196. Chao HR, Tsou TC, Huang HL, Chang-Chien GP. Levels of breast milk PBDEs from southern Taiwan and their potential impact on neurodevelopment. Pediatr Res. 2011; 70(6):596–600. doi: 10.1203/PDR.0b013e3182320b9b PMID: 21857391

197. Gascon M, Fort M, Martinez D, Carsin AE, Forns J, Grimalt JO, et al. Polybrominated diphenyl ethers (PBDEs) in breast milk and neuropsychological development in infants. Environ Health Perspect. 2012; 120(12):1760–5. doi: 10.1289/ehp.1205266 PMID: 23052368

198. Herbstman JB, Sjodin A, Kurzon M, Lederman SA, Jones RS, Rauh V, et al. Prenatal exposure to PBDEs and neurodevelopment. Environ Health Perspect. 2010; 118(5):712–9. doi: 10.1289/ehp.0901340 PMID: 20056561

199. Gascon M, Vrijheid M, Martinez D, Forns J, Grimalt JO, Torrent M, et al. Effects of pre and postnatal exposure to low levels of polybromodiphenyl ethers on neurodevelopment and thyroid hormone levels at 4 years of age. Environ Int. 2011; 37(3):605–11. doi: 10.1016/j.envint.2010.12.005 PMID: 21237513

200. Kim Y, Ha EH, Kim EJ, Park H, Ha M, Kim JH, et al. Prenatal exposure to phthalates and infant development at 6 months: prospective Mothers and Children's Environmental Health (MOCEH) study. Environ Health Perspect. 2011; 119(10):1495–1500. doi: 10.1289/ehp.1003178 PMID: 21737372

201. Whyatt RM, Liu X, Rauh VA, Calafat AM, Just AC, Hoepner L, et al. Maternal prenatal urinary phthalate metabolite concentrations and child mental, psychomotor, and behavioral development at 3 years of age. Environ Health Perspect. 2012; 120(2):290–5. doi: 10.1289/ehp.1103705 PMID: 21893441

202. Cho SC, Bhang SY, Hong YC, Shin MS, Kim BN, Kim JW, et al. Relationship between environmental phthalate exposure and the intelligence of school-age children. Environ Health Perspect. 2010; 118(7):1027–32. doi: 10.1289/ehp.0901376 PMID: 20194078

203. Puertas R, Lopez-Espinosa MJ, Cruz F, Ramos R, Freire C, Perez-Garcia M, et al. Prenatal exposure to mirex impairs neurodevelopment at age of 4 years. Neurotoxicology. 2010; 31(1):154–60. doi: 10.1016/j.neuro.2009.09.009 PMID: 19818364

204. Stewart PW, Reihman J, Lonky E, Pagano J. Issues in the interpretation of associations of PCBs and IQ. Neurotoxicol Teratol. 2012; 34(1):96–107. doi: 10.1016/j.ntt.2011.11.003 PMID: 22146557

205. Eskenazi B, Marks AR, Bradman A, Harley K, Barr DB, Johnson C, et al. Organophosphate pesticide exposure and neurodevelopment in young Mexican-American children. Environ Health Perspect. 2007; 115(5):792–8. PMID: 17520070

206. Lovasi GS, Quinn JW, Rauh VA, Perera FP, Andrews HF, Garfinkel R, et al. Chlorpyrifos exposure and urban residential environment characteristics as determinants of early childhood neurodevelopment. Am J Public Health. 2011; 101(1):63–70. doi: 10.2105/AJPH.2009.168419 PMID: 20299657

207. Bouchard MF, Chevrier J, Harley KG, Kogut K, Vedar M, Calderon N, et al. Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. Environ Health Perspect. 2011; 119 (8):1189–95. doi: 10.1289/ehp.1003185 PMID: 21507776

208. Harari R, Julvez J, Murata K, Barr D, Bellinger DC, Debes F, et al. Neurobehavioral deficits and increased blood pressure in school-age children prenatally exposed to pesticides. Environ Health Perspect. 2010; 118(6):890–6. doi: 10.1289/ehp.0901582 PMID: 20185383

209. Eskenazi B, Marks AR, Bradman A, Fenster L, Johnson C, Barr DB, et al. In utero exposure to dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) and neurodevelopment among young Mexican American children. Pediatrics. 2006; 118(1):233–41. PMID: 16818570

210. Ribas-Fito N, Torrent M, Carrizo D, Munoz-Ortiz L, Julvez J, Grimalt JO, et al. In utero exposure to background concentrations of DDT and cognitive functioning among preschoolers. Am J Epidemiol. 2006; 164(10):955–62. PMID: 16968864

211. Torres-Sanchez L, Schnaas L, Rothenberg SJ, Cebrian ME, Osorio-Valencia E, Hernandez Mdel C, et al. Prenatal p,p -DDE exposure and neurodevelopment among children 3.5–5 years of age. Environ Health Perspect. 2013; 121(2):263–8. doi: 10.1289/ehp.1205034 PMID: 23151722

212. Forns J, Lertxundi N, Aranbarri A, Murcia M, Gascon M, Martinez D, et al. Prenatal exposure to organochlorine compounds and neuropsychological development up to two years of life. Environ Int. 2012; 45:72–7. doi: 10.1016/j.envint.2012.04.009 PMID: 22575806

213. Eskenazi B, Huen K, Marks A, Harley KG, Bradman A, Barr DB, et al. PON1 and neurodevelopment in children from the CHAMACOS study exposed to organophosphate pesticides in utero. Environ Health Perspect. 2010; 118(12):1775–81. doi: 10.1289/ehp.1002234 PMID: 21126941

214. Engel SM, Wetmur J, Chen J, Zhu C, Barr DB, Canfield RL, et al. Prenatal exposure to organophosphates, paraoxonase 1, and cognitive development in childhood. Environ Health Perspect. 2011; 119 (8):1182–8. doi: 10.1289/ehp.1003183 PMID: 21507778

215. Morales E, Sunyer J, Castro-Giner F, Estivill X, Julvez J, Ribas-Fito N, et al. Influence of glutathione S-transferase polymorphisms on cognitive functioning effects induced by p,p'-DDT among preschoolers. Environ Health Perspect. 2008; 116(11):1581–5. doi: 10.1289/ehp.11303 PMID: 19057715

216. Alati R, MacLeod J, Hickman M, Sayal K, May M, Smith GD, et al. Intrauterine exposure to alcohol and tobacco use and childhood iq: findings from a parental-offspring comparison within the avon longitudinal study of parents and children. Pediatr Res. 2008; 64(6):659–66. doi: 10.1203/PDR.0b013e318187cc31 PMID: 18670372

217. Álvarez-Pedrerol M, Ribas-Fitó N, Torrent M, Julvez J, Ferrer C, Sunyer J. TSH concentration within the normal range is associated with cognitive function and ADHD symptoms in healthy preschoolers. Clin Endocrinol (Oxf). 2007; 66(6):890–8.

218. Axelrad DA, Bellinger DC, Ryan LM, Woodruff TJ. Dose-response relationship of prenatal mercury exposure and iq: an integrative analysis of epidemiologic data. Environ Health Perspect. 2007; 115 (4):609–15. PMID: 17450232

219. Barrigas C, Fragoso I. Obesity, academic performance and reasoning ability in Portuguese students between 6 and 12 years old. J Biosoc Sci. 2012; 44(02):165–79.

220. Busch AL, Lieberman AF. Mothers' Adult Attachment Interview ratings predict preschool children's IQ following domestic violence exposure. Attach Hum Dev. 2010; 12(6):505–27. doi: 10.1080/14616734.2010.504542 PMID: 20931412

221. Carlo WA, Goudar SS, Pasha O, Chomba E, McClure EM, Biasini FJ, et al. Neurodevelopmental outcomes in infants requiring resuscitation in developing countries. J Pediatr. 2012; 160(5):781–5. doi: 10.1016/j.jpeds.2011.10.007 PMID: 22099522

222. Chevrier J, Harley KG, Kogut K, Holland N, Johnson C, Eskenazi B. Maternal thyroid function during the second half of pregnancy and child neurodevelopment at 6, 12, 24, and 60 months of age. J Thyroid Res. 2011; 2011:426427. doi: 10.4061/2011/426427 PMID: 22132346

223. Davidson PW, Strain JJ, Myers GJ, Thurston SW, Bonham MP, Shamlaye CF, et al. Neurodevelopmental effects of maternal nutritional status and exposure to methylmercury from eating fish during pregnancy. Neurotoxicology. 2008; 29(5):767–75. doi: 10.1016/j.neuro.2008.06.001 PMID: 18590763

224. DePrince AP, Weinzierl KM, Combs MD. Executive function performance and trauma exposure in a community sample of children. Child Abuse Negl. 2009; 33(6):353–61. doi: 10.1016/j.chiabu.2008.08.002 PMID: 19477515

225. Escobar GJ, Liljestrand P, Hudes ES, Ferriero DM, Wu YW, Jeremy RJ, et al. Five-year neurodevelopmental outcome of neonatal dehydration. J Pediatr. 2007; 151(2):127–133. PMID: 17643761

226. Falgreen Eriksen HL, Kesmodel US, Wimberley T, Underbjerg M, Kilburn TR, Mortensen EL. Effects of tobacco smoking in pregnancy on offspring intelligence at the age of 5. J Pregnancy. 2012; 2012:945196. doi: 10.1155/2012/945196 PMID: 23316364

227. Forns J, Torrent M, Garcia-Esteban R, Grellier J, Gascon M, Julvez J, et al. Prenatal exposure to polychlorinated biphenyls and child neuropsychological development in 4-year-olds: an analysis per congener and specific cognitive domain. Sci Total Environ. 2012; 432:338–43. doi: 10.1016/j.scitotenv.2012.06.012 PMID: 22750179

228. Fraser A, Nelson SM, Macdonald-Wallis C, Lawlor DA. Associations of existing diabetes, gestational diabetes, and glycosuria with offspring IQ and educational attainment: the Avon Longitudinal Study of Parents and Children. Exp Diabetes Res. 2012; 2012:963735. doi: 10.1155/2012/963735 PMID: 22927834

229. Freire C, Ramos R, Amaya E, Fernandez MF, Santiago-Fernandez P, Lopez-Espinosa MJ, et al. Newborn TSH concentration and its association with cognitive development in healthy boys. Eur J Endocrinol. 2010; 163(6):901–9. doi: 10.1530/EJE-10-0495 PMID: 20829366

230. Freire C, Ramos R, Puertas R, Lopez-Espinosa MJ, Julvez J, Aguilera I, et al. Association of traffic-related air pollution with cognitive development in children. J Epidemiol Community Health. 2010; 64 (3):223–8. doi: 10.1136/jech.2008.084574 PMID: 19679705

231. Gaily E, Kantola-Sorsa E, Hiilesmaa V, Isoaho M, Matila R, Kotila M, et al. Normal intelligence in children with prenatal exposure to carbamazepine. Neurology. 2004; 62(1):28–32. PMID: 14718692

232. Galbally M, Lewis AJ, Buist A. Developmental outcomes of children exposed to antidepressants in pregnancy. Aust N Z J Psychiatry. 2011; 45(5):393–9. doi: 10.3109/00048674.2010.549995 PMID: 21314237

233. Gale CR, Robinson SM, Godfrey KM, Law CM, Schlotz W, O'Callaghan FJ. Oily fish intake during pregnancy—association with lower hyperactivity but not with higher full-scale IQ in offspring. J Child Psychol Psychiatry. 2008; 49(10):1061–8. doi: 10.1111/j.1469-7610.2008.01908.x PMID: 18422546

234. Geiger A, Achermann P, Jenni OG. Association between sleep duration and intelligence scores in healthy children. Dev Psychol. 2010; 46(4):949–54. doi: 10.1037/a0019679 PMID: 20604614

235. Gunnell D, Miller LL, Rogers I, Holly JM. Association of insulin-like growth factor I and insulin-like growth factor-binding protein-3 with intelligence quotient among 8- to 9-year-old children in the Avon Longitudinal Study of Parents and Children. Pediatrics. 2005; 116(5):e681–6. PMID: 16263982

236. Guxens M, Aguilera I, Ballester F, Estarlich M, Fernandez-Somoano A, Lertxundi A, et al. Prenatal exposure to residential air pollution and infant mental development: modulation by antioxidants and detoxification factors. Environ Health Perspect. 2012; 120(1):144–9. doi: 10.1289/ehp.1103469 PMID: 21868304

237. Hibbeln JR, Davis JM, Steer C, Emmett P, Rogers I, Williams C, et al. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. Lancet. 2007; 369(9561):578–85. PMID: 17307104

238. Ing C, DiMaggio C, Whitehouse A, Hegarty MK, Brady J, von Ungern-Sternberg BS, et al. Long-term differences in language and cognitive function after childhood exposure to anesthesia. Pediatrics. 2012; 130(3):e476–85. doi: 10.1542/peds.2011-3822 PMID: 22908104

239. Jacobson SW, Jacobson JL, Sokol RJ, Chiodo LM, Corobana R. Maternal age, alcohol abuse history, and quality of parenting as moderators of the effects of prenatal alcohol exposure on 7.5-year intellectual function. Alcohol Clin Exp Res. 2004; 28(11):1732–45. PMID: 15547461

240. Jedrychowski W, Jankowski J, Flak E, Skarupa A, Mroz E, Sochacka-Tatara E, et al. Effects of prenatal exposure to mercury on cognitive and psychomotor function in one-year-old infants: epidemiologic cohort study in Poland. Ann Epidemiol. 2006; 16(6):439–47. PMID: 16275013

241. Julvez J, Debes F, Weihe P, Choi AL, Grandjean P. Thyroid dysfunction as a mediator of organochlorine neurotoxicity in preschool children. Environ Health Perspect. 2011; 119(10):1429–35. doi: 10.1289/ehp.1003172 PMID: 21719373

242. Julvez J, Ribas-Fito N, Torrent M, Forns M, Garcia-Esteban R, Sunyer J. Maternal smoking habits and cognitive development of children at age 4 years in a population-based birth cohort. Int J Epidemiol. 2007; 36(4):825–32. PMID: 17550944

243. Julvez J, Torrent M, Guxens M, Anto JM, Guerra S, Sunyer J. Neuropsychologic status at the age 4 years and atopy in a population-based birth cohort. Allergy. 2009; 64(9):1279–85. doi: 10.1111/j.1398-9995.2009.01987.x PMID: 19236318

244. Kesmodel US, Eriksen HL, Underbjerg M, Kilburn TR, Stovring H, Wimberley T, et al. The effect of alcohol binge drinking in early pregnancy on general intelligence in children. BJOG. 2012; 119 (10):1222–31. doi: 10.1111/j.1471-0528.2012.03395.x PMID: 22712770

245. Koenen KC, Moffitt TE, Caspi A, Taylor A, Purcell S. Domestic violence is associated with environmental suppression of IQ in young children. Dev Psychopathol. 2003; 15(2):297–311. PMID: 12931829

246. Laslo-Baker D, Barrera M, Knittel-Keren D, Kozer E, Wolpin J, Khattak S, et al. Child neurodevelopmental outcome and maternal occupational exposure to solvents. Arch Pediatr Adolesc Med. 2004; 158(10):956–61. PMID: 15466682

247. Lederman SA, Jones RL, Caldwell KL, Rauh V, Sheets SE, Tang D, et al. Relation between cord blood mercury levels and early child development in a World Trade Center cohort. Environ Health Perspect. 2008; 116(8):1085–91. doi: 10.1289/ehp.10831 PMID: 18709170

248. Lewis MW, Misra S, Johnson HL, Rosen TS. Neurological and developmental outcomes of prenatally cocaine-exposed offspring from 12 to 36 months. Am J Drug Alcohol Abuse. 2004; 30(2):299–320. PMID: 15230078

249. Li X, Atkins MS. Early childhood computer experience and cognitive and motor development. Pediatrics. 2004; 113(6):1715–22. PMID: 15173496

250. Lynch CD, Jackson LW, Kostyniak PJ, McGuinness BM, Buck Louis GM. The effect of prenatal and postnatal exposure to polychlorinated biphenyls and child neurodevelopment at age twenty four months. Reprod Toxicol. 2012; 34(3):451–6. doi: 10.1016/j.reprotox.2012.04.013 PMID: 22569275

251. Mackner LM, Black MM, Starr RH Jr. Cognitive development of children in poverty with failure to thrive: a prospective study through age 6. J Child Psychol Psychiatry. 2003; 44(5):743–51. PMID: 12831118

252. Meldrum SJ, D'Vaz N, Dunstan JA, Mori TA, Hird K, Simmer K, et al. Allergic disease in the first year of life is associated with differences in subsequent neurodevelopment and behaviour. Early Hum Dev. 2012; 88(7):567–73. doi: 10.1016/j.earlhumdev.2011.12.032 PMID: 22284984

253. Mendez MA, Torrent M, Julvez J, Ribas-Fito N, Kogevinas M, Sunyer J. Maternal fish and other seafood intakes during pregnancy and child neurodevelopment at age 4 years. Public Health Nutr. 2009; 12(10):1702–10. doi: 10.1017/S1368980008003947 PMID: 19026093

254. Messinger DS, Bauer CR, Das A, et al. The maternal lifestyle study: cognitive, motor, and behavioral outcomes of cocaine-exposed and opiate-exposed infants through three years of age. Pediatrics. 2004; 113(6):1677–85. PMID: 15173491

255. Morales E, Guxens M, Llop S, Rodriguez-Bernal CL, Tardon A, Riano I, et al. Circulating 25-hydroxyvitamin D3 in pregnancy and infant neuropsychological development. Pediatrics. 2012; 130(4):e913–20. doi: 10.1542/peds.2011-3289 PMID: 22987876

256. Morales E, Sunyer J, Julvez J, Castro-Giner F, Estivill X, Torrent M, et al. GSTM1 polymorphisms modify the effect of maternal smoking during pregnancy on cognitive functioning in preschoolers. Int J Epidemiol. 2009; 38(3):690–7. doi: 10.1093/ije/dyp141 PMID: 19244254

257. Morrow CE, Culbertson JL, Accornero VH, Xue L, Anthony JC, Bandstra ES. Learning disabilities and intellectual functioning in school-aged children with prenatal cocaine exposure. Dev Neuropsychol. 2006; 30(3):905–31. PMID: 17083299

258. Murcia M, Rebagliato M, Iniguez C, Lopez-Espinosa MJ, Estarlich M, Plaza B, et al. Effect of iodine supplementation during pregnancy on infant neurodevelopment at 1 year of age. Am J Epidemiol. 2011; 173(7):804–12. doi: 10.1093/aje/kwq424 PMID: 21385833

259. Najman JM, Hayatbakhsh MR, Heron MA, Bor W, O'Callaghan MJ, Williams GM. The impact of episodic and chronic poverty on child cognitive development. J Pediatr. 2009; 154(2):284–9. doi: 10.1016/j.jpeds.2008.08.052 PMID: 19038402

260. Nakajima S, Saijo Y, Kato S, Sasaki S, Uno A, Kanagami N, et al. Effects of prenatal exposure to polychlorinated biphenyls and dioxins on mental and motor development in Japanese children at 6 months of age. Environ Health Perspect. 2006; 114(5):773–8. PMID: 16675436

261. Nulman I, Rovet J, Barrera M, Knittel-Keren D, Feldman BM, Koren G. Long-term neurodevelopment of children exposed to maternal nausea and vomiting of pregnancy and diclectin. J Pediatr. 2009; 155 (1):45–50. doi: 10.1016/j.jpeds.2009.02.005 PMID: 19394042

262. Nulman I, Rovet J, Kennedy D, Wasson C, Gladstone J, Fried S, et al. Binge alcohol consumption by non-alcohol-dependent women during pregnancy affects child behaviour, but not general intellectual functioning; a prospective controlled study. Arch Womens Ment Health. 2004; 7(3):173–81. PMID: 15241663

263. Odd DE, Lewis G, Whitelaw A, Gunnell D. Resuscitation at birth and cognition at 8 years of age: a cohort study. Lancet. 2009; 373(9675):1615–22. doi: 10.1016/S0140-6736(09)60244-0 PMID: 19386357

264. Park HY, Park JS, Sovcikova E, Kocan A, Linderholm L, Bergman A, et al. Exposure to hydroxylated polychlorinated biphenyls (OH-PCBs) in the prenatal period and subsequent neurodevelopment in eastern Slovakia. Environ Health Perspect. 2009; 117(10):1600–6. doi: 10.1289/ehp.0900611 PMID: 20019912

265. Rebagliato M, Murcia M, Alvarez-Pedrerol M, Espada M, Fernandez-Somoano A, Lertxundi N, et al. Iodine supplementation during pregnancy and infant neuropsychological development: INMA mother and child cohort study. Am J Epidemiol. 2013; 177(9):944–53. doi: 10.1093/aje/kws333 PMID: 23548753

266. Roze E, Meijer L, Bakker A, Van Braeckel KN, Sauer PJ, Bos AF. Prenatal exposure to organohalogens, including brominated flame retardants, influences motor, cognitive, and behavioral performance at school age. Environ Health Perspect. 2009; 117(12):1953–8. doi: 10.1289/ehp.0901015 PMID: 20049217

267. Schermann L, Sedin G. Cognitive function at 10 years of age in children who have required neonatal intensive care. Acta Paediatr. 2004; 93(12):1619–29. PMID: 15841771

268. Singer LT, Minnes S, Short E, Arendt R, Farkas K, Lewis B, et al. Cognitive outcomes of preschool children with prenatal cocaine exposure. JAMA. 2004; 291(20):2448–56. PMID: 15161895

269. Singer LT, Moore DG, Fulton S, Goodwin J, Turner JJ, Min MO, et al. Neurobehavioral outcomes of infants exposed to MDMA (Ecstasy) and other recreational drugs during pregnancy. Neurotoxicol Teratol. 2012; 34(3):303–10. doi: 10.1016/j.ntt.2012.02.001 PMID: 22387807

270. Stewart PW, Lonky E, Reihman J, Pagano J, Gump BB, Darvill T. The relationship between prenatal PCB exposure and intelligence (IQ) in 9-year old children. Environ Health Perspect. 2008; 116 (10):1416–1422. doi: 10.1289/ehp.11058 PMID: 18941588

271. Stewart PW, Reihman J, Lonky EI, Darvill TJ, Pagano J. Cognitive development in preschool children prenatally exposed to PCBs and MeHg. Neurotoxicol Teratol. 2003; 25(1):11–22. PMID: 12633733

272. Suglia SF, Gryparis A, Wright RO, Schwartz J, Wright RJ. Association of black carbon with cognition among children in a prospective birth cohort study. Am J Epidemiol. 2008; 167(3):280–6. PMID: 18006900

273. Thomas SV, Sukumaran S, Lukose N, George A, Sarma PS. Intellectual and language functions in children of mothers with epilepsy. Epilepsia. 2007; 48(12):2234–40. PMID: 17941847

274. Thompson WW, Price C, Goodson B, Shay DK, Benson P, Hinrichsen VL, et al. Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years. N Engl J Med. 2007; 357(13):1281–92. PMID: 17898097

275. Vrijheid M, Martinez D, Forns J, Guxens M, Julvez J, Ferrer M, et al. Prenatal exposure to cell phone use and neurodevelopment at 14 months. Epidemiology. 2010; 21(2):259–62. doi: 10.1097/EDE.0b013e3181cb41e0 PMID: 20087192

276. Waisbren SE, Azen C. Cognitive and behavioral development in maternal phenylketonuria offspring. Pediatrics. 2003; 112(6 Pt 2):1544–7. PMID: 14654662

277. Watson GE, Lynch M, Myers GJ, Shamlaye CF, Thurston SW, Zareba G, et al. Prenatal exposure to dental amalgam: evidence from the Seychelles Child Development Study main cohort. J Am Dent Assoc. 2011; 142(11):1283–94. PMID: 22041415

278. Whitehouse AJ, Robinson M, Newnham JP, Pennell CE. Do hypertensive diseases of pregnancy disrupt neurocognitive development in offspring? Paediatr Perinat Epidemiol. 2012; 26(2):101–8. doi: 10.1111/j.1365-3016.2011.01257.x PMID: 22324495

279. Wilhelm M, Wittsiepe J, Lemm F, Ranft U, Kramer U, Furst P, et al. The Duisburg birth cohort study: influence of the prenatal exposure to PCDD/Fs and dioxin-like PCBs on thyroid hormone status in newborns and neurodevelopment of infants until the age of 24 months. Mutat Res. 2008; 659(1–2):83–92. PMID: 18093869

280. Willford J, Leech S, Day N. Moderate prenatal alcohol exposure and cognitive status of children at age 10. Alcohol Clin Exp Res. 2006; 30(6):1051–9. PMID: 16737465

281. Wu BT, Dyer RA, King DJ, Richardson KJ, Innis SM. Early second trimester maternal plasma choline and betaine are related to measures of early cognitive development in term infants. PLoS One. 2012; 7(8):e43448. doi: 10.1371/journal.pone.0043448 PMID: 22916264

282. Strina A, Barreto M, Cooper P, Rodrigues L. Risk factors for non-atopic asthma/wheeze in children and adolescents: a systematic review. Emerg Themes in Epidemiol. 2014; 11(1):5.

283. Lewis AS, Sax SN, Wason SC, Campleman SL. Non-chemical stressors and cumulative risk assessment: an overview of current initiatives and potential air pollutant interactions. Int J Environ Res Public Health. 2011; 8(6):2020–73. doi: 10.3390/ijerph8062020 PMID: 21776216

284. Sexton K, Linder SH. Cumulative risk assessment for combined health effects from chemical and nonchemical stressors. Am J Public Health. 2011; 101(S1):S81–8.

285. Juarez PD, Matthews-Juarez P, Hood DB, Im W, Levine RS, Kilbourne BJ, et al. The public health exposome: a population-based, exposure science approach to health disparities research. Int J Environ Res Public Health. 2014; 11(12):12866–95.

286. Cory-Slechta DA, Stern S, Weston D, Allen JL, Liu S. Enhanced learning deficits in female rats following lifetime pb exposure combined with prenatal stress. Toxicol Sci. 2010; 117(2):427–38. doi: 10.1093/toxsci/kfq221 PMID: 20639260

287. Solon O, Riddell TJ, Quimbo SA, Butrick E, Aylward GP, Lou Bacate M, et al. Associations between cognitive function, blood lead concentration, and nutrition among children in the central Philippines. J Pediatr. 2008; 152:237–43. doi: 10.1016/j.jpeds.2007.09.008 PMID: 18206696

288. Horton MK, Kahn LG, Perera F, Barr DB, Rauh V. Does the home environment and the sex of the child modify the adverse effects of prenatal exposure to chlorpyrifos on child working memory? Neurotoxicol Teratol. 2012; 34(5):534–41. doi: 10.1016/j.ntt.2012.07.004 PMID: 22824009

289. Perera FP, Wang S, Rauh V, Zhou H, Stigter L, Camann D, et al. Prenatal exposure to air pollution, maternal psychological distress, and child behavior. Pediatrics. 2013; 132(5):e1284–94. doi: 10.1542/peds.2012-3844 PMID: 24101766

290. Yumoto C, Jacobson SW, Jacobson JL. Fetal substance exposure and cumulative environmental risk in an African American cohort. Child Dev. 2008; 79(6):1761–76. doi: 10.1111/j.1467-8624.2008.01224.x PMID: 19037948

291. Virgolini MB, Rossi-George A, Lisek R, Weston DD, Thiruchelvam M, Cory-Slechta DA. CNS effects of developmental Pb exposure are enhanced by combined maternal and offspring stress. Neurotoxicology. 2008; 29(5):812–27. doi: 10.1016/j.neuro.2008.03.003 PMID: 18440644

292. United States Environmental Protection Agency. A framework for assessing health risk of environmental exposures to children. Washington, DC. 2006.

293. Cummins SK, Jackson RJ. The built environment and children's health. Pediatr Clin North Am. 2001; 48(5):1241–52. PMID: 11579672

294. Gee GC, Payne-Sturges DC. Environmental health disparities: a framework integrating psychosocial and environmental concepts. Environ Health Perspect. 2004; 112(17):1645–53. PMID: 15579407