Review

The impact of prenatal mercury exposure related to fish intake on child developmental outcomes (2015-2019)

Alexandra Bandier and Leslie Hope Wills
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Department of Nutrition, Children's Hospital Los Angeles, Los Angeles, California, USA

Abstract

Purpose of review: Results of prior studies report mixed evidence on the impact of prenatal mercury (Hg) exposure related to fish intake on child developmental outcomes. Six reviews were conducted with inconclusive results from 2000-2015. This review aims to build upon prior evidence to better inform policy decisions by assessing the research from January 2015 to January 2019.

Methods: Pubmed and Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched using combinations of keywords and phrases. 1307 studies were assessed for inclusion eligibility. Of those studies, 13 were included for final review.

Summary: While the current evidence is not conclusive, this review suggests that the beneficial impact of prenatal fish intake on developmental outcomes outweighs the associated Hg exposure. Further research is warranted using consistent Hg collection and developmental outcome measures before any policy changes regarding fish consumption during pregnancy are made.

Introduction

Mercury (Hg) is considered a developmental neurotoxicant (Llop, Ballester, Murcia, Forns, & Sunyer, 2017). During pregnancy, the fetus is susceptible to Hg exposure because Hg can pass through the blood-brain barrier and the placenta (Kim et al., 2018). The primary source of non-occupational Hg exposure is the consumption of fish and seafood, especially predatory species (ex: tuna, swordfish, shark, bass, king mackerel, and tilefish) (Barbone et al., 2019). As such, it is important to understand the impact on offspring developmental outcomes from Hg exposure related to prenatal fish intake.

Public perception is that mercury exposure from fish intake during pregnancy is harmful to offspring development. Government organizations have supported this perception by placing limits on fish intake during pregnancy. The U.S. Food and Drug Administration (FDA) recommends that pregnant and breastfeeding women limit fish intake to 12 oz per week, only choosing fish that are lower in mercury (FDA, 2010). The Joint Food and Agriculture

Organization / World Health Organization Expert Committee on Food Additives (JECFA) fixed a maximum acceptable intake for Hg of 1.6 ug/kg body weight per week for pregnant women to protect the fetus from neurotoxic effects (Barbone et al., 2019). Following these recommendations, the reported intake of fish during pregnancy decreased (Kim et al., 2018). Given the beneficial nutrients contained in fish, including polyunsaturated fatty acids, iron, vitamins, minerals, and protein, it is crucial to understand if the evidence supports the current restrictions on fish intake during pregnancy. This uncertainty about the safety of fish intake represents an important public health issue.

Despite public perception and government guidelines, the results of prior studies report mixed evidence on the impact of prenatal mercury exposure related to fish intake on child developmental outcomes. Six reviews were conducted with inconclusive results from 2000-2015 (Dzwilewski & Schantz, 2015; Jurewicz, Polańska, & Hanke, 2013; Myers & Davidson, 2000; Oken & Bellinger, 2008; Solan & Lindow, 2014; Starling, Charlton, McMahon, & Lucas, 2015). The most recent review conducted by Starling et al. in 2015 concluded that the existing evidence is currently insufficient to inform advice regarding fish intake during pregnancy and that further studies are required that assess maternal fish consumption during pregnancy and neurodevelopmental outcomes in offspring while considering the contribution of mercury from fish containing diets (Starling et al., 2015). This review aims to close the gap to better inform policy decisions by assessing the research from January 2015 to January 2019.

Methodology

Search Strategy

Pubmed and Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched using the following combination of terms and keywords: Maternal mercury exposure and child developmental outcomes; Maternal mercury exposure, fish, developmental outcomes; Prenatal mercury exposure and developmental outcomes; Pregnancy mercury exposure developmental outcomes; Review mercury maternal child outcomes; Review prenatal mercury child outcomes; Prenatal mercury exposure neurodevelopment; Prenatal mercury exposure school achievement; Prenatal mercury exposure mental health; Prenatal mercury exposure behavioral problems; Prenatal mercury exposure cognitive development; Prenatal mercury exposure IQ; Prenatal mercury exposure intellectual disability; Maternal exposure, mercury; Prenatal exposure delayed effects.

Eligibility Criteria

Articles published between January 2015 and January 2019 were included in this review. Eligible studies included those that focused on mercury exposure from fish intake during pregnancy and the resulting developmental outcomes in offspring. Studies that investigated mercury exposure due to contaminants or other sources aside from fish were excluded. Animal studies were also excluded.

Search Results

The database search resulted in 1307 studies, which were assessed for inclusion eligibility. 13 studies were included for final review as seen in Figure 1.

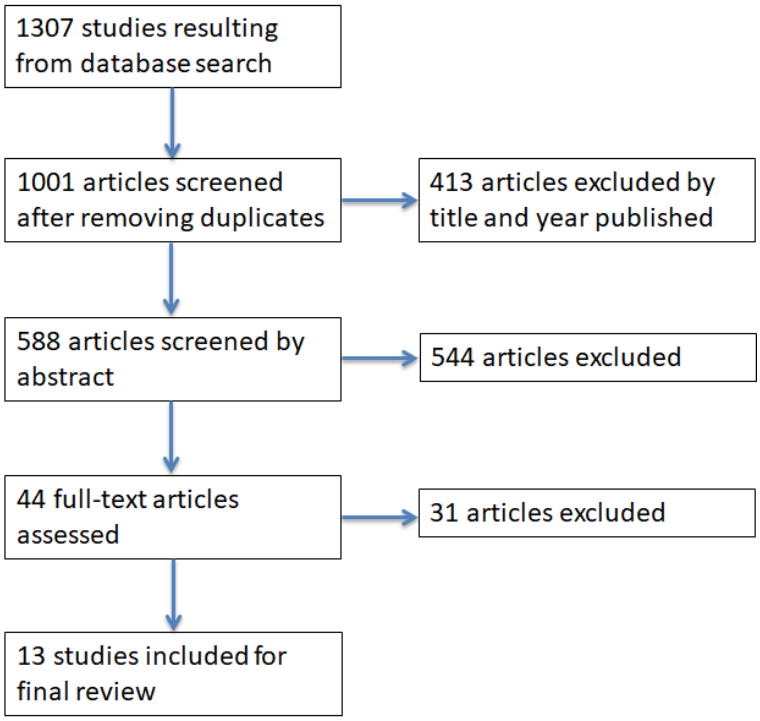

Figure 1: Flow diagram for inclusion of journal articles

Abstraction of Information

The 13 studies included in this review were analyzed and data were extracted into table format. The quality of the studies was ranked according to the Academy of Nutrition and Dietetics Evidence Analysis Library Quality Criteria Checklist (Academy of Nutrition and Dietetics, 2019). A summary of the articles and their associated outcomes are presented in Table 1.

Table 1: Summary of reviewed articles

Study Number	First author, Year	Title	Quality Rating (EAL)	Country	Study Design	Study Purpose	Study Sample (age, race, # of the sample)	Setting	Main exposure/intervention	How is outcome measured? (methods/tools)	Conclusion
1	Xu, 2106	Low-level gestational exposure to mercury and maternal fish consumption: Associations with neurobehavior in early infancy.	Neutral	USA	Prospective cohort	Examine the effects of low-level gestational methylmercury exposure from fish consumption on neurobehavioral outcomes in early infancy	Utilized participants in the Health Outcomes and Measures of Environment (HOME) study. 389 women, at least 18 years old, living in homes built before 1978. Mostly non-Hispanic white, middle class income, married, employed, some college education 344 infants at 5-weeks. Mostly term with normal birth weight	Cincinnati, Ohio	Gestational mercury exposure was measured as whole blood total mercury (WBTHg) in maternal and cord blood. Fish consumption information and PUFA intake was collected via food frequency questionnaires at 16 weeks gestation and 5 weeks post-partum	Infant neurobehavior was assessed at 5-weeks of age at a home visit, using the NICU Network Neurobehavioral Scale (NNNS)	In current study of a cohort with low fish consumption and mercury exposure representative of US women (WBTHg of .64ug/L or hair concentration of .16ppm), results found minimal evidence of mercury associated detrimental effects on neurobehavioral outcomes during early infancy, as evaluated with the NNNS. - Only potential detrimental effect: increased asymmetry among girls with higher mercury exposure as measured by maternal WBTHg and cord WBTHg. But this was no longer significant when fish was included in the model. - Higher fish consumption and higher estimated PUFA intake were significantly associated with less need for special handling - Mothers in this study consumed fish on average 13 times during pregnancy or 2 oz/week (assuming 6oz/meal). This is lower than recommended 12 oz/week by the fish consumption advisory - Fish consumed by mothers in the study were mostly tuna, shellfish and salmon (lower mercury content) - Observed better attention and less need for special handling with increases in WBTHg, but this was not significant. Not a beneficial effect of MeHg exposure (which is neurotoxic), but rather the beneficial effects of fish consumption, primarily through PUFA, on neurodevelopment - In this cohort, fish consumption was the main source of mercury exposure so any detrimental effects of mercury exposure may have been outweighed by the beneficial effects of fish nutrition
2	Iles-Caven, 2016	Data relating to early child development in the Avon Longitudinal Study of Parents and Children (ALSPAC), their relationship with prenatal blood mercury and stratification by fish consumption.	Neutral	UK	Prospective cohort study (ALSPAC)	Relationship with data from ALSPAC study on child development with prenatal blood mercury and stratification by fish consumption	- Analyzing data from the Avon Longitudinal Study of Parents and Children (ALSPAC) - ALSPAC aimed to study all births to women born between 4/1/1991 and 12/31/1992	UK. Centered around Bristol	- Whole blood samples were collected as early as possibly in pregnancy - Fish intake was reported via FFQ at 32 weeks gestation	- Measures of early child development were collected using hands-on expert assessment by trained psychologists using the Griffiths Mental Development Scales and from detailed questionnaires completed by the study mothers using assessments based on the Denver Developmental Screening Test (four categories: social skills, fine motor skills, communication, gross motor skills)	- There were no negative associations of prenatal blood mercury with the total development scores after adjustment using the continuous scales of each measurement
3	Oken, 2016	Maternal prenatal fish consumption and cognition in mid childhood: Mercury, fatty acids, and selenium.	Neutral	USA	Longitudinal cohort	Examine associations of maternal prenatal fish intake with child neurodevelopment accounting for biomarkers of exposure to mercury, long-chain n-3 fatty acids, and selenium, which are hypothesized to mediate associations with child neurodevelopment.	Study participants were from Project Viva, a prospective longitudinal cohort study designed to examine prenatal diet and other health factors in relation to pregnancy and child health outcomes. - 1068 pairs of moms and children (872 with mid-pregnancy blood) - Cohort with blood samples: 72% white, 32.4 years, 64% annual income above $70,000, 93% married	Boston, MA. Enrollment from 8 obstetrical offices of Atrius Harvard Vanguard Medical Associates	At 27.9 weeks gestation, maternal fish intake was estimated with FFQs and collected blood. Erythrocytes were assayed for total mercury and selenium, and plasma for fatty acids.	In mid-childhood (7.7 years), cognitive tests were administered including the Kauffman Brief Intelligence Test (KBIT).	In this population with average fish consumption of 1.5 weekly servings, there was no evidence for an association of maternal prenatal fish intake or of mercury, DHA+EPA, or selenium status, with verbal or non-verbal intelligence, visual motor function or visual memory at median 7.7 years of age.
4	Llop, 2017	Prenatal exposure to mercury and neuropsychological development in young children: the role of fish consumption.	Neutral	Spain	Prospective Cohort	Evaluate the association between prenatal exposure to mercury and child neuropsychological development in high-fish-intake areas	1362 children, participants in the INMA (Environment and Childhood) birth study cohort - Mothers were at least 16 years old, 10-13 weeks gestation - Children enrolled since birth and monitored until 4-5 yrs old - Final population 1362 mother-child pairs in whom both mercury concentrations and neuropsychological test scores were available - 44.5% of women were between 30-34 yrs old	Spain. Enrollment from four regions: Valencia, Sabadell, Gipuzkoa, Asturias	- Cord blood total mercury (CB-Hg) and cord polyunsaturated fatty acids (PUFA) concentrations were analyzed in samples collected between 2004-2008. - Fish intake was collected using a validated semi-quantitative FFQ during 1st trimester	- Child neuropsychological development was assessed at age 4-5 years by the McCarthy Scales of Children's Abilities (MSCA) - Women completed 2 questionnaires (1st trimester, 3rd trimester) to obtain socio-demographic, environmental and lifestyle information	- Increased mercury levels were associated with higher scores in most of the MSCA scales (not significant), but this association was influenced by maternal fish consumption. - Higher mercury concentration in cord blood was associated with lower scores only among children whose mothers consumed fewer than 3 weekly servings of fish during pregnancy. - Scores on motor scale decreased with increasing mercury exposure among children with lower n-3 PUFA concentrations or higher n-6/n-3 PUFA ratio - General lack of a negative effect of mercury and, in contrast, the interaction between CB-Hg and fish intake or n6/n3 PUFA ratio could be indicating that CB-Hg concentrations possibly acted as a proxy of part of the fish intake variability that is beneficial for brain development

Study Number	First author, Year	Title	Quality Rating (EAL)	Country	Study Design	Study Purpose	Study Sample (age, race, # of the sample)	Setting	Main exposure/intervention	How is outcome measured? (methods/tools)	Conclusion
5	Kim, 2018	Prenatal mercury exposure, fish intake and neurocognitive development during first three years of life: Prospective cohort Mothers and Children's Environmental Health (MOCEH) study.	Positive	Korea	Prospective cohort	Assess the effect of prenatal Hg exposure on neurocognitive development during the first 3 years of life	- During 2006-2010, 1751 participants were recruited from the Mothers and Children's Environmental Health (MOCEH) study - Pregnancy women (>18 years) were living in Seoul, Cheonan and Ulsan and were in early pregnancy (earlier than 20 weeks)	Korea - Seoul, Cheonan, Ulsan	- Maternal blood levels of Hg were assessed during pregnancy (12-20 weeks and again at 28-42 weeks) and in cord blood at birth - Maternal fish intake was assessed by interviewing the weekly frequency of fish intake during pregnancy - Maternal n-3 and n-6 fatty acid intake was estimated based on 24h recall food intake interview	- The mental (MDI) and psychomotor (PDI) development index scores were assessed using the Bayley Scores of Infant Development at 6, 12, 24, 36 months of age '- Characteristics of the study subjects with respect to Hg levels were analyzed using x2 tests for categorical variables and t-tests for continuous variables - General linear models (GLM) were modeled with a development index (MDI or PDI) score as the outcome variable and prenatal maternal blood Hg levels as the predictor variables. Further adjustments were made for weekly frequency of fish intake and also n-3 and n-5 fatty acid intake	- Prenatal Hg exposure during early pregnancy adversely associated with early neurodevelopment during infancy (Bayley MDI and PDI scores), after adjusting for fish and n-3 and n-6 fatty acid (PUFA) intake - These results replicate other prior studies - Inverse association between prenatal Hg exposure and cognitive development at 6 mo became apparent only after adjustment with prenatal fish intake, and became stronger after further - Prenatal fish consumption and n-3 and n-6 fatty acid intake modulate the inverse association between Hg during early pregnancy and infant neurocognitive development - Consuming fish high in fatty acids and low in Hg during pregnancy may be important to neurocognitive development at early infancy
6	Hibbeln, 2018	Total mercury exposure in early pregnancy has no adverse association with scholastic ability of the offspring particularly if the mother eats fish.	Neutral	UK	Prospective cohort study (ALSPAC)	Examine whether prenatal exposure to total mercury is associated with the child's scholastic abilities in reading, spelling, phoneme awareness, mathematics and science	- Analyzing data from the Avon Longitudinal Study of Parents and Children (ALSPAC) - ALSPAC aimed to study all births to women born between 4/1/1991 and 12/31/1992 - 14,541 women were recruited	Avon, UK	- Blood samples collected in acid-washed vacutainers by midwives. Analyzed 19 years later by CDC for whole blood mercury - 93% of samples were collected at <18 weeks gestation, median value of 11 weeks - Fish consumption collected using FFQ at 32 weeks gestation	- 15 different scholastic tests were used covering spelling, reading, phoneme, understanding, math and science - Multiple regression was used to assess relationships between prenatal total blood mercury concentrations and 16 different test results - In parallel, logistic regression was used to determine associations with the risk of the child being in the lowest 15% of each score. Analyses were repeated stratifying for fish consumption and sex of the child	- Unable to demonstrate any adverse scholastic test results with increasing prenatal total mercury levels - No evidence of harm associated with the level of total mercury, provided the mother ate fish during pregnancy. Particularly true of mathematics and science - Suggestion that children whose mothers denied eating fish were less likely to do well in math and science reasoning with increasing exposure to mercury than the child whose mother had eaten fish in pregnancy - Women should be confident that eating fish in pregnancy is beneficial for their unborn child - Recommendation to eat at least 2 portions of fish per week should be supported
7	Golding, 2017	Maternal prenatal blood mercury is not adversely associated with offspring IQ at 8 years provided the mother eats fish: A British prebirth cohort study.	Positive	UK	Prospective cohort study (ALSPAC)	Investigate the relationship between mercury (Hg) and offspring cognition if the mother eats fish	- Analyzing data from the Avon Longitudinal Study of Parents and Children (ALSPAC) - ALSPAC aimed to study all births to women born between 4/1/1991 and 12/31/1992 - 2,062 offspring were included in this analysis	Avon, UK	- Blood samples collected in acid-washed vacutainers by midwives. Analyzed 19 years later by CDC for whole blood mercury - 93% of samples were collected at <18 weeks gestation, median value of 11 weeks - Fish consumption collected using FFQ at 32 weeks gestation	- Verbal, performance and total IQ of offspring were measured at age 8 using the Wechsler Scale - Analysis treated IQ as continuous and the lowest 25% of distribution. Multiple and logistic regression analyses took account of social and demographic variables. Stratification considered children of fish eaters separately	- The relationship between intrauterine exposure to mercury and offspring IQ appears to be benign provided the mother consumes fish, but there may be an adverse effect if the mother eats no fish - Comparing offspring of mothers who ate fish vs. no fish: there was a significant negative relationship bt the prenatal mercury level and offspring IQ in the non-fish eaters but a significant positive association among the offspring of the fish-eaters - Offspring of mothers who ate fish had higher mean IQs and lower risk of suboptimal IQ level with increasing blood Hg levels, but offspring of mothers who did not eat fish had worse outcomes related to prenatal mercury exposure
8	Jacobson, 2015	Relation of Prenatal Methylmercury Exposure from Environmental Sources To Childhood IQ	Positive	Canada	Prospective Cohort	Determine the degree to which co-exposure to PCBs may account for the adverse effects of methylmercury and the degree to which co-exposure to DHB may obscure these effects in children	- 282 school age children from 14 Inuit villages in Artic Quebec	Artic Quebec, Canada	- Mercury in cord blood and maternal hair were obtained - Samples were analyzed for mercury and other environmental exposures - Cholesterol and triglycerides were analyzed, and DHA was determined using gas-liquid chromatography	- Each child was assessed on seven subtests comprising 3 of the 4 index scores from the Wechsler Intelligence Scales for Children, and 2 tests of verbal proficiency adapted for Inuit culture - The relation of each of the contaminant exposures to IQ was examined using a series of nested multivariable regression models	- Significant association with prenatal mercury exposure with poorer performance on school-age assessment of IQ - Confirms associations of prenatal mercury exposure with poorer cognitive function in school-age children reported in Faroe Islands - DHA partially obscured the association of prenatal mercury with lower IQ - Prenatal methylmercury exposure from environmental sources in teratogenic, and it is associated with clinically meaningful impairment in overall cognitive function at levels of exposure within the range found in the general US population

Study Number	First author, Year	Title	Quality Rating (EAL)	Country	Study Design	Study Purpose	Study Sample (age, race, # of the sample)	Setting	Main exposure/intervention	How is outcome measured? (methods/tools)	Conclusion
9	Barbone, 2018	Prenatal mercury exposure and child neurodevelopmental outcomes at 18 months: Results from the Mediterranean PHIME cohort.	Negative	Mediterranean (Italy, Slovenia, Croatia, and Greece)	Cohort study	Use international comparisons of Hg concentrations in mother-child biological samples and neurodevelopmental scores embedded in birth cohort studies to evaluate the effect of prenatal exposure to low Hg levels on child neurodevelopment and the question about “safety” of fish-eating during pregnancy	The Mediterranean (Italy, Slovenia, Croatia, and Greece) cohort study included 1308 mother-child pairs enrolled in the Public Health Impact of long-term, low-level, Mixed Element exposure in a susceptible population EU Sixth Framework Programme (PHIME).	Recruitment from - Institute for Maternal and Child Health IRCCS Burlo Garofolo in Trieste, Italy - Maternity Hospital of the University Medical Centre of Ljubljana, Slovenia - University Hospital of Rijeka, Croatia - General regional hospitals of Mytilini (Lesvos), Chios, Samos, and Leros in Greece	- Maternal hair and venous blood, cord blood and breast milk samples were collected, and total Hg (THg) levels were measured. - Demographic and socioeconomic information, lifestyles and nutritional habits were collected through questionnaires at different phases of follow-up.	- Children at 18 months of age underwent neurodevelopmental testing using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). - Multivariate linear and logistic regressions were performed, for each country, to assess the association between THg and BSID-III scores, obtaining adjusted β coefficients and odds ratios (ORs). - These values were used to conduct a meta-analysis, to explore possible heterogeneity among countries and to obtain combined estimates of the association between THg exposure and BSID-III scores.	This study showed an inverse relation between THg levels and developmental motor scores at 18 months, - These results, which describe both fine and gross motor development and were measured in different biological samples and in four Mediterranean populations, have only partial internal and external consistency and should be confirmed by further testing conducted at an older age. - Evidence was weak and partially internally and externally inconsistent - No evidence of detrimental effects of THg was found for cognitive and language outcomes at these concentrations and age
10	Van Wijngaarden, 2017	Methyl mercury exposure and neurodevelopmental outcomes in the Seychelles Child Development Study Main cohort at age 22 and 24 years.	Positive	Republic of Seychelles	Prospective Cohort Study OR observational? (Seychelles)	To report on associations with neurodevelopmental outcomes obtained at 22 and 24 years of age from the Seychelles Study. In 1989-1990, the Main Cohort of the Seychelles Child Development Study was recruited to assess the potential developmental effects of prenatal MeHg exposure.	Recruited participants in the Main Cohort of the Seychelles Child Development Study in 1989-1990 to study the potential developmental effects of prenatal MeHg exposure, and have evaluated them 10 times during 24 years of follow up. In 1989-1990, the Main cohort of 779 mother and their children were enrolled at 6 months (+/- 2 weeks) postpartum from among the women who had, during or after their pregnancy, agreed to give a hair sample. Participants were excluded if there was inadequate maternal hair to recapitulate prenatal MeHg exposure, were twins, or had illnesses or injuries known to adversely affect neurodevelopment. There were 740 children eligible for further study. Cohort children were previously evaluated at 19, 29, 66, and 107 months of age, and at 10.5, 17, and 19 years of age	Seychelles Study data	Prenatal exposure to MeHg was determined by measuring total maternal hair Hg in the sample that best recapitulated growth during pregnancy using cold vapor atomic absorption spectroscopy with previously-described quality control procedures - Recent postnatal MeHg exposure at 22 and 24 years of age was measured using the same approach in a 1 cm length of each participant’s hair closest to the scalp taken at the time of testing. - Confidential healthy behaviors (HB) questionnaire was adapted specifically for the Seychellois culture with items from the WHO global school-based student health survey and the US Centers for Disease Control and Prevention Youth Risk Behavior Survey	- Neurodevelopmental tests at 22 years included the Boston Naming Test, Cambridge Neuropsychological Test Automated Battery (CANTAB), and the Profile of Mood States. - At 24 years, administered the Stroop Word-Color Test, the Barkley Adult ADHD Rating Scale, the Test of Variables of Attention, and the Finger Tapping test. - Primary analyses examined covariate-adjusted associations in multiple linear regression models with prenatal MeHg exposure. - In secondary analyses examined associations with recent postnatal MeHg exposure.	After 24 years of follow up of the SCDS Main cohort, findings show that prenatal MeHg exposure from fish consumption during pregnancy is not adversely associated with neurobehavioral outcomes in offspring. These results are consistent with those reported after each of the previous eight evaluations, and the probability that there are missed adverse associations in this cohort appear to be increasingly small. - Findings suggest that prenatal and recent postnatal MeHg exposure from ocean fish consumption is not adversely associated with neurobehavioral development at levels that are about ten times higher than typical U.S. exposures. - Studies in the Republic of Seychelles (Davidson et al., 1998; van Wijngaarden et al., 2013b) and those of others in the UK and Spain (Daniels et al., 2004; Llop et al., 2012) have found no consistent evidence of adverse consequences on children’s development associated with prenatal MeHg exposure.
11	Strain, 2015	Prenatal exposure to methyl mercury from fish consumption and polyunsaturated fatty acids: associations with child development at 20 mo of age in an observational study in the Republic of Seychelles.	Positive	Republic of Seychelles	Prospective Cohort Study OR observational? (Seychelles)	To investigate the associations of prenatal MeHg exposure and maternal PUFA status with child development at 20 mo of age.	Observational study in the Republic of Seychelles, a highfish-eating population. Mothers were enrolled during pregnancy and their children evaluated at 20 mo of age. - Recruited a total of 1535 mother-child pairs and conducted primary analyses on 1265 with complete covariate data after exclusions and a measure of at least one outcome	Seychelles Study data	At delivery, maternal hair samples were collected to determine prenatal MeHg exposure. - Total mercury was measured by the standard technique of atomic absorption spectroscopy at the University of Rochester in the longest hair segment available to reflect exposure throughout pregnancy. Hair was assumed to grow at a rate of 1.1 cm/mo - Mercury deposited in hair is 80% MeHg and is known to correlate with mercury deposited in the infant brain - Therefore, refer to this measurement as the prenatal MeHg exposure.	- Development was measured using Bayley Scales of Infant Development II (BSID-II), the MacArthur Bates Communicative Development Inventories (CDI), and the Infant Behavior Questionnaire–Revised.	Found no overall adverse association between prenatal MeHg exposure and neurodevelopmental outcomes. - However, maternal PUFA status as a putative marker of the inflammatory milieu appeared to modify the associations of prenatal MeHg exposure with the PDI. - Increasing DHA status was positively associated with language development yet negatively associated with the MDI. - These findings may indicate the existence of an optimal DHA balance with respect to arachidonic acid for different aspects of neurodevelopment.

Study Number	First author, Year	Title	Quality Rating (EAL)	Country	Study Design	Study Purpose	Study Sample (age, race, # of the sample)	Setting	Main exposure/intervention	How is outcome measured? (methods/tools)	Conclusion
12	Marques, 2015	Traditional living in the Amazon: Extended breastfeeding, fish consumption, mercury exposure and neurodevelopment	Neutral	Amazon Basin	Cohort study	To study neurodevelopment in 690 children in relation to prolonged breastfeeding and mercury exposure since features of traditional living in the Amazon Basin (high fish consumption and long breastfeeding) are likely to expose children to Mercury (Hg).	Identified mother–infant pairs that showed at least 6 months of exclusive breastfeeding. - All mother–infant pairs were residents of rural and periurban areas in the state of Rondonia. These families are mostly riverines, rural and urban dwellers sharing a preference for fish, manioc and regional foods. - For reference, there were 258 pairs (with 6 months of breastfeeding), group two was made up of 288 mothers that breastfed from 7–12 months and a third group comprised 144 mothers that breastfed up to 24 months	Western Amazon	For each household, obtained information related to socioeconomic data and the feeding status of the child from birth to the time of the visit, using questionnaires. Frequency of fish consumption information was obtained during the interview. - Mercury exposure was assessed from Thimerosal-containing vaccines and fish consumption from hair Hg (HHg).	- Neurodevelopment was assessed as age of walking, age of talking and the Bayley Scales of Infant Development–BSID.	- Frequency of maternal fish consumption and education had a positive association with BSID scores; it is speculated that maternal education and nutrients in fish have an opposing effect on Hg exposure. - A conclusive link between Hg (derived from fish, breastfeeding and TCVs) and neurodevelopmental delays is challenging to establish, but this study indicates that a prolonged lactation could attenuate worsening of BSID scores.
13	McKean, 2015	Prenatal mercury exposure, autism, and developmental delay, using pharmacokinetic combination of newborn blood concentrations and questionnaire data: a case control study	Negative	USA	Case Control Study	- The goal of this paper was to develop a toxicokinetic model that incorporates both biomarker and questionnaire data to estimate the cumulative exposure to MeHg through seafood consumption using data collected from the Childhood Autism Risks from Genetics and the Environment (CHARGE) study. - CHARGE is an ongoing large-scale case–control study focusing on several genetic and environmental exposures as underlying causes of autism	The CHARGE study was initiated in 2002 and is an ongoing population-based case–control study with participants from three strata: (1) children with autism spectrum disorder (ASD); (2) children with developmental delay but not autism (DD); (3) children selected from the general population without regard to developmental characteristics (GP). - Eligible children met the following criteria: (a) between the ages of 24 and 60 months; (b) living with at least one biological parent; (c) has a parent who speaks English or Spanish; (d) born in California; (e) resides in the study catchment areas of California, including more than 20 counties within a 2-h drive from the MIND Institute clinic located at UC Davis	California	Utilized a discrete-time model that estimates blood MeHg concentration given a piecewise-constant ingestion rate and single-compartment pharmacokinetics. - Measured newborn bloodspot Hg concentrations and obtained information pertaining to maternal fish consumption using a questionnaire. - Using MeHg concentration estimates from the toxicokinetic model, cumulative MeHg exposure was estimated in children with autism, children with developmental delay, and typically developing children	- Median estimated cumulative MeHg was compared among diagnostic groups using the Kruskal-Wallis Test. - Multinomial logistic regression models were constructed to assess the association between cumulative MeHg concentration and the risk of autism and developmental delay (vs. typical development).	- Overall, cumulative MeHg exposure does not appear to detectably elevate the risk of autism or developmental delay.

Results and Discussion

The 13 studies from Table 1 were reviewed to analyze whether or not patterns existed between the studies. Each study was given a study corresponding number for ease of classification which are listed in Table 1. The following Figures will refer to the studies by their numbers.

The studies were stratified based on methods of Hg collection, dietary assessment, and developmental outcomes. Hg collection method was divided between gestational serum Hg or hair and/or cord blood Hg. Dietary assessment of maternal fish consumption was divided between using a validated food frequency questionnaire (FFQ) or dietary recall/questionnaire. Developmental outcomes were measured using a variety of tools including the Bayley Scales of Infant and Toddler Development (BSID), Denver Developmental Screening Test (DDST), Griffiths Mental Development Extended Scales (GMDS), Kauffman Brief Intelligence Test (KBIT), NICU Network Neurobehavioral Scale (NNNS), McCarthy Scales of Children's Abilities (MSCA), and Wechsler Intelligence Scales for Children (WISC). This is illustrated in Figure 2.

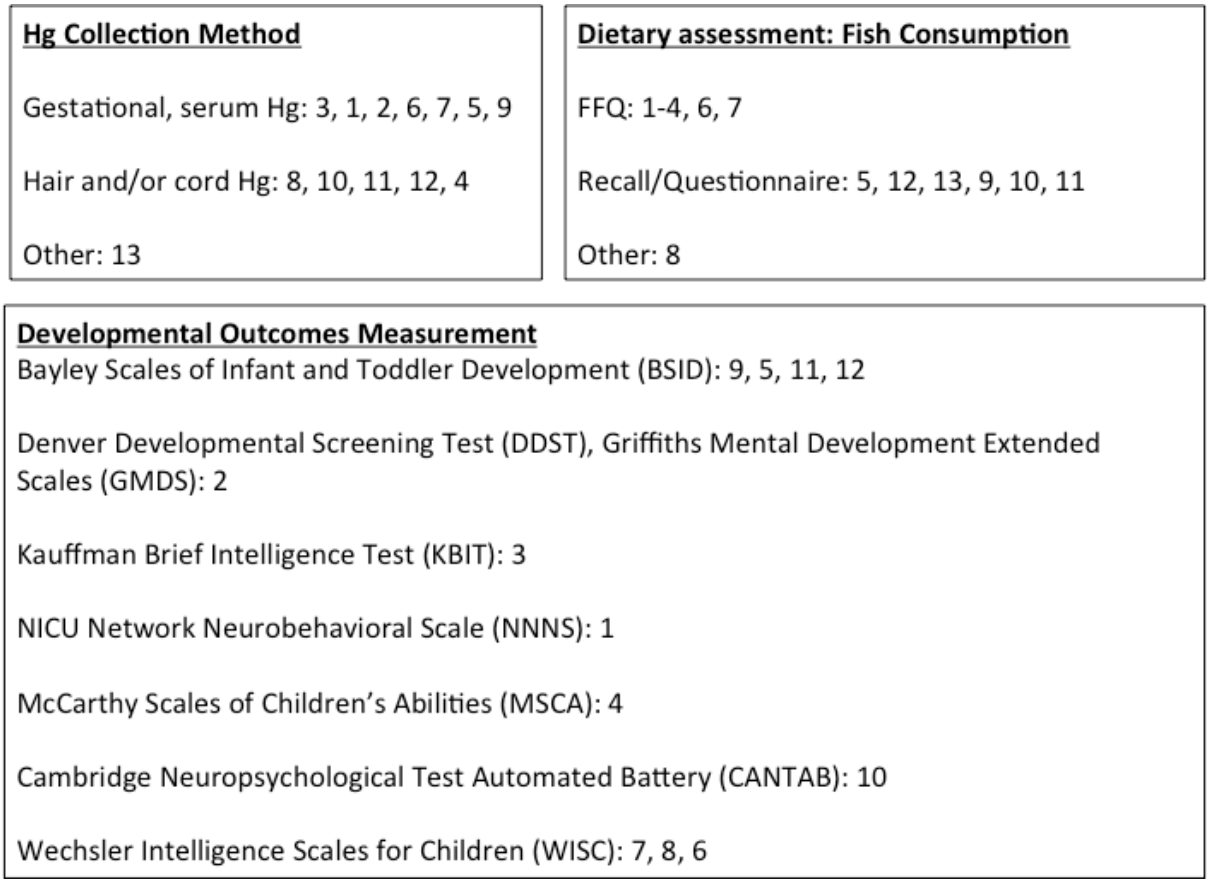

Figure 2: Organization of studies according to methodology

The outcomes of each study were then included alongside the methodology, as seen in Figure 3. The outcomes varied between four main themes: the benefits of prenatal fish intake on developmental outcomes outweighed the associated Hg exposure (Fish > Hg), no negative association of prenatal fish intake and Hg exposure on developmental outcomes, a negative

association between Hg from prenatal fish intake and developmental outcomes, and mixed/inconclusive results. Study 13 was not stratified given the Hg collection method used was neither serum Hg or hair/cord blood Hg. It was noted if outcomes measured early exposure (EE) or late exposure (LE). The corresponding age at measurement is recorded as well.

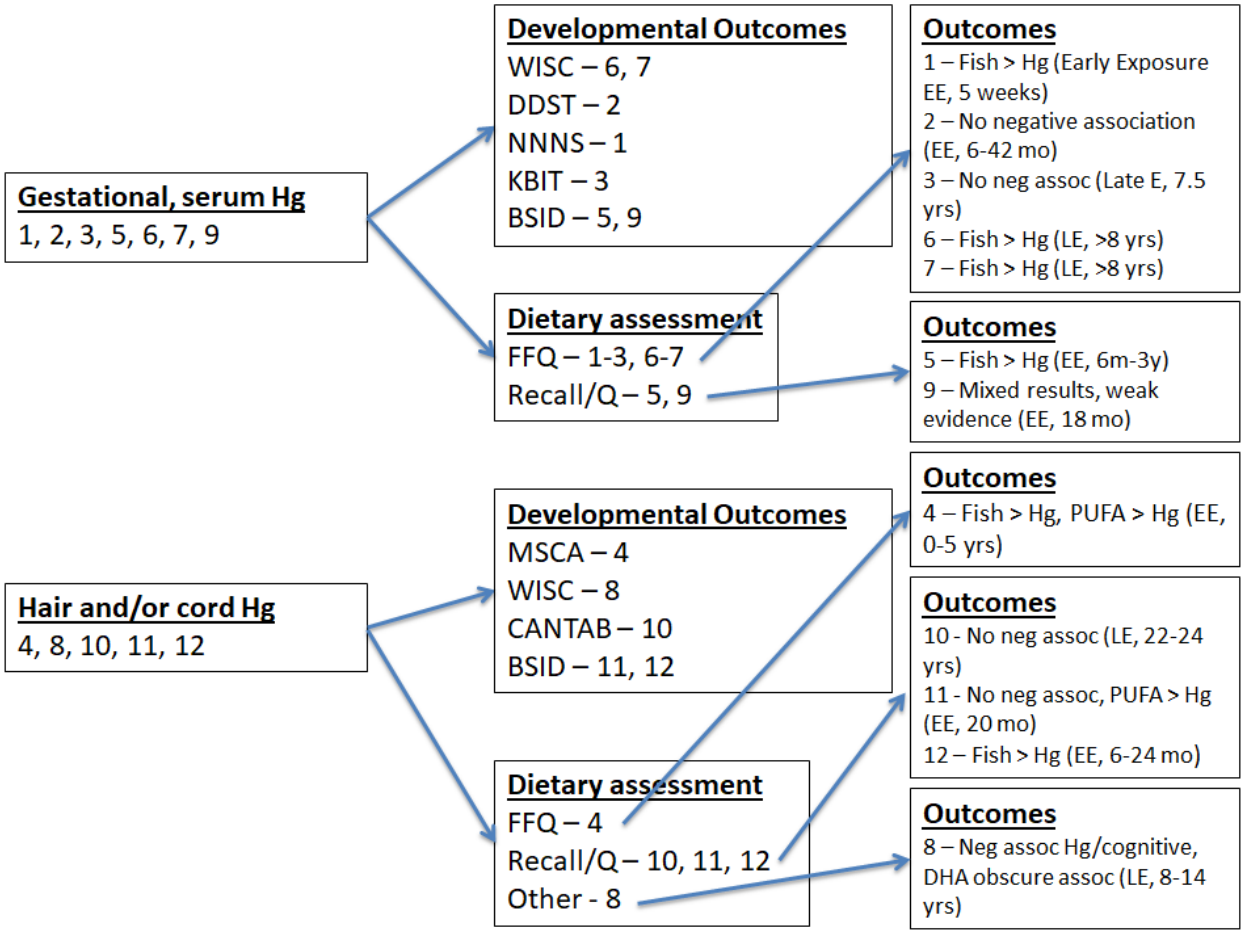

Figure 3: Stratification of studies with associated outcomes

There were 6 studies that had a similar conclusion that the beneficial nutritional effects of prenatal fish consumption on developmental outcomes outweighs Hg exposure (Fish > Hg). 4 studies found no negative association, 1 study found a negative association, and 1 study had a mixed result.

In study 1 by Xu et al., the researchers examined the effects of low-level gestational mercury exposure from fish consumption on neurobehavioral outcomes in early infancy (Xu et al., 2016). The results showed that there was minimal evidence of mercury associated detrimental effects on neurobehavioral outcomes during early infancy, and infants with higher prenatal mercury exposure and those whose mothers consumed more fish had better attention and needed less special handling, which likely reflects the beneficial nutritional effects of fish consumption (Xu et al., 2016). Beneficial effects were also found in study 6 by Hibbeln et al. who examined whether

prenatal exposure to total mercury is associated with the child's scholastic abilities in reading, spelling, phoneme awareness, mathematics and science (Hibbeln et al., 2018). Results showed that there was no evidence of harm and no adverse scholastic test results associated with the level of total mercury, provided the mother ate fish during pregnancy. They also suggested that children whose mothers denied eating fish were less likely to do well in math and science reasoning with increasing exposure to mercury than the child whose mother had eaten fish in pregnancy. The authors recommended that women eat 2 portions of fish per week and that women should feel confident that eating fish in pregnancy is beneficial for their unborn child (Hibbeln et al., 2018). In study 7 by Golding et al., researchers investigated the relationship between Hg and offspring cognition if the mother eats fish (Golding et al., 2017). Results showed that the relationship between intrauterine exposure to mercury and offspring IQ appears to be benign provided the mother consumes fish, but there may be an adverse effect if the mother eats no fish. When comparing offspring of mothers who ate fish versus no fish, there was a significant negative relationship between the prenatal mercury level and offspring IQ in the non-fish eaters but a significant positive association among the offspring of the fish-eaters (Golding et al., 2017). Study 5 by Kim et al. assessed the effect of prenatal Hg exposure on neurocognitive development during the first 3 years of life (Kim et al., 2018). The researchers found that prenatal fish consumption and n-3 and n-6 fatty acid intake modulate the inverse association between Hg during early pregnancy and infant neurocognitive development, so consuming fish high in fatty acids and low in Hg during pregnancy may be important to neurocognitive development at early infancy (Kim et al., 2018). In study 4 by Llop et al., researchers evaluated the association between prenatal exposure to mercury and child neuropsychological development in high-fish-intake areas (Llop et al., 2017). The results showed that there was a general lack of a negative effect of mercury and, in contrast, the interaction between cord blood Hg and fish intake or n-6/n-3 polyunsaturated fatty acid ratio could be indicating that cord blood Hg concentrations possibly acted as a proxy of part of the fish intake variability that is beneficial for brain development (Llop et al., 2017). Lastly, in study 12 by Marques et al. researchers studied neurodevelopment in children in relation to prolonged breastfeeding and mercury exposure finding that frequency of maternal fish consumption and education had a positive association with BSID scores; it is speculated that maternal education and nutrients in fish have an opposing effect on Hg exposure (Marques et al., 2016).

Of the 6 studies that found fish intake to be beneficial, 4 of those studies measured Hg during pregnancy exposure, while only 2 studies measured Hg hair and/or cord blood Hg. Developmental outcomes were measured using various tools with the studies measuring both early and late exposure. This information is summarized in Figure 4.

Outcome: Fish > Hg
6 studies total
1, 6, 7, 5, 4, 12

Of those 6 studies:
Hg Collection Method
4 studies measured serum Hg during pregnancy exposure
1, 6, 7, 5

2 studies measured Hair Hg or cord blood Hg
4, 12

Developmental Outcomes Measurement
4 studies, early exposure
- 2 studies Bayley, similar age range 6-24 months (5, 12)
- 1 study McCarty, age 0-3 years (4)
- 1 study NNNS, age 5 weeks (1)

2 studies, late exposure
- 2 studies WISC, age >8 years (6, 7)

Figure 4: Study outcomes for Fish > Hg

Strengths and weaknesses of the studies were assessed for each of the four general findings and summarized in Figure 5 below. While there were both strengths and weaknesses for each category, the strengths for Fish > Hg outweighed the weaknesses found within those studies. This is unlike the other finding categories in which the weaknesses were far greater and important than the strengths.

For the study outcomes that found the beneficial impact of prenatal fish intake on developmental outcomes outweighs the associated Hg exposure, strengths included that 4 of the 6 studies used an FFQ to measure maternal fish consumption versus recall or a non-validated questionnaire. An FFQ is a validated tool that is known to have high accuracy and validity measuring food intake. These majority of these studies (4/6) also used serum Hg measured during pregnancy versus hair or cord blood Hg. Cord blood Hg levels associated with maternal dietary intake are less sensitive (Solan & Lindow, 2014). The studies were mixed in terms of measuring early exposure (4/6) and late exposure (2/6), but since the outcomes were similar for age ranges 0-3 years and for older than 8 years, this suggests that the results are consistent. The weaknesses of this category included using different developmental outcome tools and differeng Hg collection methods.

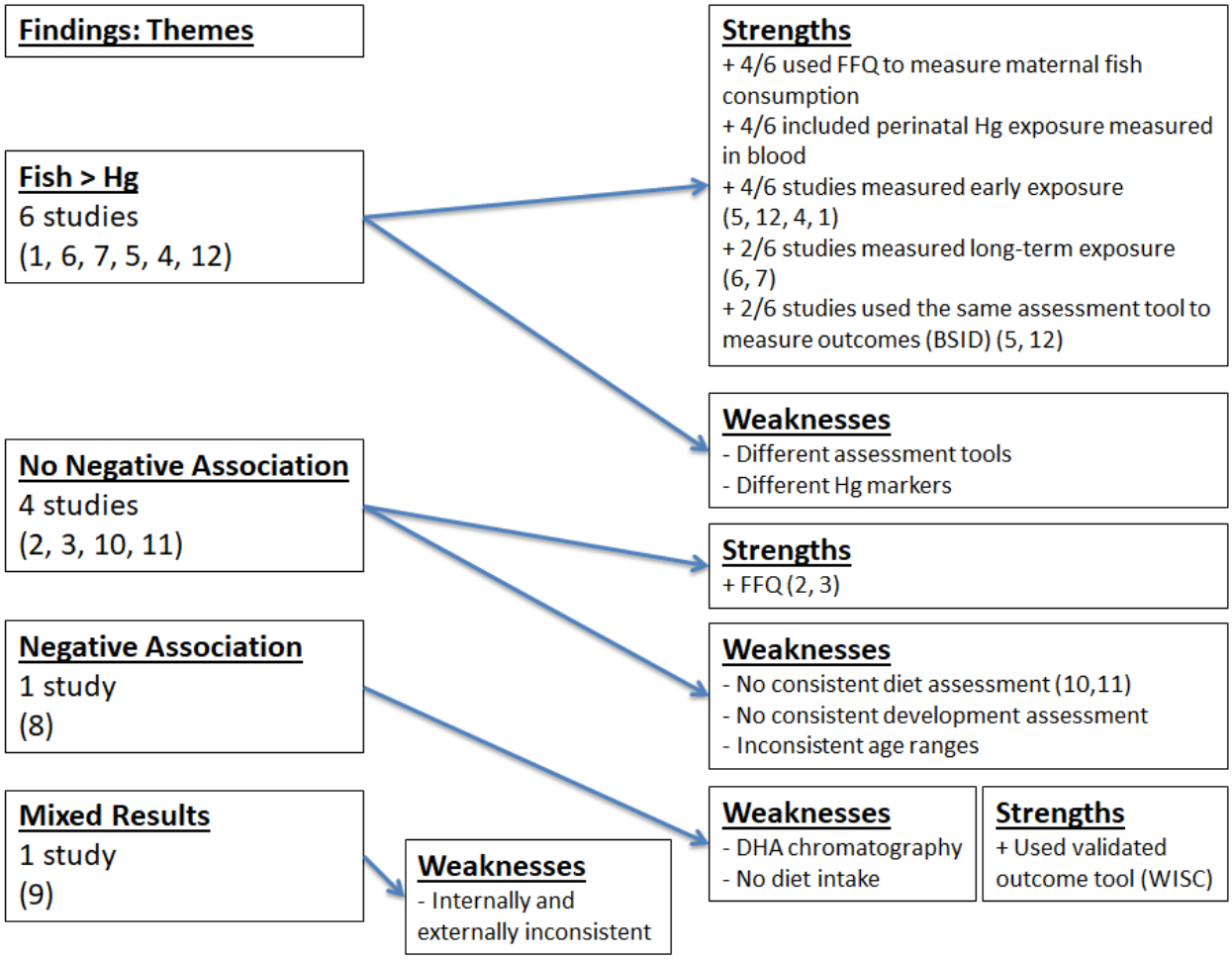

Figure 5: Strengths and weaknesses associated with each finding category

Conclusions

This review assessed the impact of prenatal mercury exposure related to fish intake on child developmental outcomes (2015-2019). The goal of the review was to incorporate new evidence to build upon previous inconclusive reviews conducted from 2000-2015. While the current evidence is not conclusive, this review suggests that the beneficial impact of prenatal fish intake on developmental outcomes outweighs the associated Hg exposure. This finding was the most prevalent one in our review with the strongest methodology and developmental outcome assessment. Further research is warranted using consistent Hg collection and developmental outcome measures before any policy changes regarding fish consumption during pregnancy are made.

Conflicts of Interest

The authors declare no conflicts of interest.

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