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Impact of dietary mercury intake during pregnancy on the health of neonates and children: a systematic review

Steven Saavedra, Ángeles Fernández-Recamales, Ana Sayago, Antonio Cervera-Barajas, Raúl González-Domínguez, and Juan D. Gonzalez-Sanz

Affiliation: *S. Saavedra and J.D. Gonzalez-Sanz* are with the Department of Nursing, University of Huelva, Huelva, Spain. *Á. Fernández-Recamales*, *A. Sayago*, and *R. González-Domínguez* are with the AgriFood Laboratory, Department of Experimental Sciences, University of Huelva, Huelva, Spain; and the Agrifood Campus of International Excellence (ceiA3), University of Huelva, Huelva, Spain. *A. Cervera-Barajas* is with the Department of Nursing, University of Seville, Seville, Spain.

Correspondence: *J.D. Gonzalez-Sanz*, Department of Nursing, Nursing Faculty, University of Huelva, 21007 Huelva, Spain. Email: juan.gonzalez@denf.uhu.es.

Abstract

Context: ~~Influence~~ Growing evidence suggests that prenatal exposure to methyl mercury through the maternal diet could have great influence on the neurological and physical development of neonates and young children. **Objective:** The aim of this review was to evaluate the clinical repercussions of maternal exposure to methyl mercury during pregnancy on the health of fetuses, neonates, and children up to 8 years of age. **Data Sources:** The Web of Science, PubMed, CINAHL, Scopus, and Dialnet Plus databases were searched for articles published in English or Spanish from 1990 to 2020. **Study Selection**. To select the studies for detailed review, we considered original articles published in English or Spanish from 1990 to 2020. All study designs were eligible for inclusion, whereas animal studies were excluded. The study selection was accomplished by two independent reviewers by means of double-screening. Out of the 971 initial records, 19 studies were finally included in the systematic review. **Data Extraction:** This systematic review adhered to the PRISMA guidelines. Outcomes extracted included maternal dietary exposure to methyl mercury during pregnancy, possible health repercussions in offspring up to 8 years of age, and quantitative measurement of mercury in a biological sample. All studies included in this review complied with the requirements established by López de Argumedo et al. for assessing both study quality and risk of bias. **Results**: Prenatal exposure to mercury has been consistently associated with a lower weight of the neonate at birth, but only one study reported a negative association with the newborn length. Higher mercury levels have also been related to lower scores in various neuropsychological and developmental tests. **Conclusion:** The literature shows clear evidence of the adverse effects of maternal methyl mercury exposure on anthropometric variables and cognitive or physical development in children. It is noteworthy, however, that mercury toxicity may sometimes be masked by other essential nutrients in the maternal diet, such as polyunsaturated fatty acids.

Keywords: fish, mercury, newborn health, pregnancy, polyunsaturated fatty acids.

INTRODUCTION

The Barker hypothesis, also known as the intrauterine programming effect, was a pioneering theory that proposed the possible fetal origin of coronary heart disease.[1] Several studies based on this theory have since revealed the prominent role of intrauterine life in the onset of numerous chronic diseases in the adulthood.[2] Today, the vital importance of diet during pregnancy for fetal development and infant health is well recognized. Thus, the evaluation of eating practices in pregnant women is highly advisable to detect deleterious dietary habits in the early stages of pregnancy, to ensure proper nutritional status in the mother and the fetus/newborn, and to avoid malnutrition that could favor the development of future chronic diseases in the offspring.[3] In particular, some vitamins, minerals, and other nutrients such as essential fatty acids (eg, long-chain n-3 and n-6 polyunsaturated fatty acids) have been shown to play a critical role during pregnancy.[4,5] Accordingly, personalized dietary recommendations regarding supplementation or avoidance of certain foods or nutrients are imperative to minimize risks to the fetus. Such recommendations should include consideration of genetic factors as well as intakes of total energy and the different macro- and micronutrients.[6]

Mercury is the most common heavy metal found in food sources. It normally accumulates as methyl mercury in aquatic species found in higher positions of the food chain, a consequence of the biomagnification phenomenon.[7] It is not possible to reduce the concentration of mercury in fish meat through preparation or cooking methods. As a result, fish consumption constitutes the main source of this heavy metal in humans. Not unexpectedly, the highest levels of mercury exposure are observed in populations in which fish is the main source of animal protein in the diet.[8–10] Almost 95% of methyl mercury is absorbed in the gastrointestinal tract and then passes into the bloodstream, where it has a relatively long half-life within the range of 44 to 80 days. Subsequently, methyl mercury is distributed throughout all tissues, easily crossing both the blood–brain and the placental barriers, thereby potentially affecting neonatal development from an early gestational age.[11]

Mercury poisoning is an important health problem worldwide, highlighted by several critical pollution episodes that occurred over the last 50 years (eg, Minamata Bay in Japan,[12,13] and Iraq[14]). Considerable research has been conducted worldwide to investigate the relationship between prenatal exposure to mercury and its impact on the neurological and physical development of neonates.[15–17] The consumption of fish typically found to contain high levels of mercury (eg, tuna, swordfish, shark) is usually reduced during pregnancy, not only because pregnant women are often aware of the risks of mercury-containing fish but also because they are advised by their healthcare providers to avoid these types of fish. A recent review found that dietary guidelines are usually based on the mercury content of fish, with far less consideration given to other factors.[18] However, some authors recommend that each country/region should consider its own pattern of fish consumption, in terms of both quantity and type of fish consumed, with the aim of carefully assessing the risk of exceeding the tolerable intake of methyl mercury while also considering the positive beneficial effects of the nutrients provided by fish.[19–21]

Limiting the consumption of fish/seafood, however, may compromise the intake of other essential nutrients (eg, n-3 fatty acids).[22,23] Therefore, increasingly more authors have emphasized the need to improve the dietary recommendations for fish consumption by pregnant women.[18,24–26]

The objective of this review is to evaluate the effect of maternal exposure to mercury via the diet during pregnancy on the health of fetuses, newborns, and children up to 8 years of age (ie, early childhood).

METHODS

This systematic review is based on a qualitative synthesis of the literature (not a meta-analysis) and was conducted according to guidelines established by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[27] Table 1 shows the PICOS (Participants, Intervention, Comparison, Outcomes, Study design) criteria used for inclusion of studies.

Eligibility criteria

Original studies published in English or Spanish from 1990 to 2020 were eligible for inclusion. Studies published in English or Spanish were included to minimize language bias. The following eligibility criteria were applied: (1) participants comprised pregnant women and their offspring; (2)_studies examined prenatal maternal exposure to mercury through the diet and evaluated possible effects on the health of offspring up to 8 years of age; and (3) quantitative measurement of mercury in a biological sample (eg, maternal hair, umbilical cord blood) was performed. All study designs were eligible for inclusion. Animal studies were excluded. All studies included in this review complied with the requirements established by López de Argumedo et al[28] for assessing both study quality and risk of bias.

Search strategy

A search for peer-reviewed literature published between January 1990 and March 2020 was conducted using library electronic resources available at the University of Huelva. The following databases were searched: Web of Science, PubMed, CINAHL, Scopus, and Dialnet Plus. Keywords used included “nutrition,” “diet,” “pregnancy,” “pregnant,” “heavy metals,” “nursing mothers,” “health consequences,” and “mercury.” The corresponding keywords in Spanish were “nutrición,” “dieta,” “embarazo,” “embarazada,” “metales pesados,” “madres lactantes,” “consecuencias salud,” and “mercurio.” The Boolean operators “and” and “or” were used to search combinations of the different terms. Additional hand searches of reference lists were performed to identify other eligible studies.

Selection of studies

Figure 1 shows the process used to search the literature and select studies for inclusion in the review. The search strategy yielded a total of 971 records

(PubMed, n = 584; Web of Science, n = 129; CINAHL, n = 79; Scopus, n = 157; Dialnet Plus, n = 12; additional hand searching, n = 10). A total of 164 duplicate studies were eliminated. The remaining 807 records were screened on the basis of title and abstract to remove studies that did not fulfill the inclusion criteria and articles for which the full text was not available (n = 684). The remaining full-text articles (n = 123) were read and evaluated for inclusion in the review. Studies that did not meet all of the inclusion criteria (n = 33), did not correspond to the objective of this review (n = 63), or focused on the study of substances other than mercury (n = 8) were excluded, resulting in 19 studies included in the systematic review.

RESULTS

Table 2[29–39,41–48] summarizes the most relevant information from the 19 studies included in the systematic review. The studies reviewed were published over a time period of 28 years (1990–2018). Eight studies were carried out in Europe, 4 in Asia, 3 in Africa, 3 in North America, and 1 in South America. All studies were observational cohort studies conducted in pregnant women and their children, with sample sizes ranging from 135 to 1869, for a total of 14 616 participants in the 19 studies. All studies also used the amount of mercury measured in pregnant women to determine the prenatal load of mercury as a risk factor. Mercury concentrations were measured in cord blood or maternal venous blood or both in 7 studies, in maternal hair in 5 studies, and in both umbilical cord blood and maternal hair in 6 studies; other study used only umbilical cord tissue. Mercury concentrations shown in Table 2 were converted to the same unit: micrograms per gram (µg/g) for hair samples and umbilical cord tissue and micrograms per liter (µgL) for blood samples. In 15 studies, the health outcome evaluated was the cognitive or physical development of children, whereas 4 studies investigated anthropometric data such as weight or length at birth. The age at assessment of the effect of mercury on these health outcomes ranged from birth to 7 years. Attending with Spiller et al,[49] information on the quantity and type of fish/seafood consumption and other sources of exposure to methyl mercury from the included studies is shown in Table 3.[29–39,41–48]

DISCUSSION

Mercury levels and anthropometric data

Four studies evaluate the association between anthropometric variables and prenatal exposure to mercury.[29–32] All of these studies were performed in neonates at the time of birth, and the health outcomes evaluated were either solely the weight of the neonate[29] or both the weight and the length of the neonate.[30–32] Three studies used umbilical cord blood as the biological sample for measurement of mercury concentrations,[30–32] and one used maternal hair.[29] Interestingly, all of these studies used tolerable umbilical cord blood mercury levels that exceeded the recommendations of the Environmental Protection Agency and the European Food Safety Authority (5.8 µg/L and 10.8 µg/L, respectively) when evaluating outcomes.[11] Pregnant women enrolled in these cohorts had large total mercury loads during pregnancy. These loads, in turn, were positively correlated with total fish intake. Despite this, the mercury loads varied widely between cohorts, depending on the type of fish consumed, and therefore the extent of fetal mercury exposure resulting from transplacental transport of mercury varied as well. Of these four studies, in the one carried out in areas of the Madeira river basin (Amazonia, Brazil)[29] significant differences in the birth weight between the different population groups were found, but the regression analysis showed that only family income and gestational age had a significant impact on birth weight. The other three studies found a strong association between maternal total mercury concentrations and weight of the neonate at birth (ie, the higher the level of mercury, the lower the birth weight).[29–32] However, some authors highlighted that certain confounding factors, such as smoking or intake of n-3 fatty acids, could have a considerable impact on these results by counteracting or potentiating these associations. With regard to length of the neonate at birth, the findings were more heterogeneous. ~~Foldspang~~ In contrast, with regard to the length of the neonate at birth, only Ramón et al[31] reported that the length of newborns markedly decreased when maternal total mercury levels increased during pregnancy. They also noted an increased risk for newborns of mothers with higher mercury levels to be classified as small for gestational age.

Mercury levels and cognitive or physical development

The most consistent findings related to neurological toxicity elicited by prenatal exposure to mercury were observed in 2 complementary studies carried out in the Faroe Islands.[33,34] Mercury levels in umbilical cord blood and maternal hair were considerably elevated in both studies, significantly exceeding the tolerable levels recommended by the Environmental Protection Agency and the European Food Safety Authority.[11] In one of the studies, mercury concentrations in umbilical cord blood showed a negative association with neurological optimization scores.[34] Similarly, Grandjean et al[33] reported that various domains of brain function were affected by prenatal exposure to methyl mercury, especially those related to language. Regression coefficients showed that doubling in mercury exposure can cause a developmental delay of approximately 2 months for various functions. In contrast, other studies performed within the framework of the Seychelles Child Development Nutrition Study did not show any negative impact of mercury exposure through maternal fish intake during pregnancy on the offspring.[35–37] Only when maternal levels of polyunsaturated fatty acids (PUFAs) were considered in the analyses were significant interactions found between methyl mercury and scores on the Psychomotor Developmental Index, with an inverse association observed among mothers with higher n-6/n-3 PUFA ratios and a positive association found among mothers with higher n-3 PUFA levels.[37] These results support the idea that the beneficial influence of other nutrients derived from fish (eg, PUFAs) may act as a confounding factor in the detection of significant associations between prenatal exposure to methyl mercury and child development. Similarly, 2 other studies from the Viva Project performed in the United States demonstrated that higher fish consumption during pregnancy was associated with better infant cognition, but higher mercury levels were associated with lower cognition, thus suggesting that the consumption of certain types of fish may have greater benefits than negative consequences.[38,39] These findings are consistent with the results of a large systematic review by Hibbeln et al.[40]

Other studies have shown that the impact of maternal dietary mercury intake on offspring varies greatly according to the maternal mercury load. Daniels et al[41] reported that increased maternal fish consumption during pregnancy was associated with higher developmental scores on the language, understanding, and social activity components of the MacArthur-Bates Communicative Development Inventory at 15 months of age as well as higher scores on the Denver Developmental Screening Test at 18 months of age. However, total mercury concentrations were low in this cohort and were not associated with neurodevelopment, in line with findings of other studies.[42] Conversely, other authors suggested that exposure to low levels of mercury in pregnant women may have adverse effects on offspring, including the appearance of late psychomotor development in children during the first year of life[43] and impaired neuropsychological development as measured by the McCarthy Scales of Children's Abilities.[44] Noteworthy, the latter study also demonstrated that the relationship between total mercury concentrations in cord blood and infant neuropsychological development was influenced by maternal nutritional factors, such as the consumption of fish and PUFAs, which were able to mask the toxic effects of mercury, although further research is needed.[44]

Finally, the sex and age have been also identified as important confounders when determining the effects of prenatal exposure to mercury. Gao et al[45] found that prenatal exposure to mercury significantly influenced neonatal neurological development at birth, but only among male newborns, in agreement with another work by Jeong et al,[46] published later. Moreover, 2 studies in cohorts from the Korean Mothers and Children's Environmental Health Study investigated the effects of maternal exposure to mercury on the neurocognitive development of offspring during the first 5 years of life.[46,47] The results suggested that prenatal exposure to mercury during early pregnancy was inversely associated with neurocognitive development only at age 6 months, whereas it was negatively associated with IQ.[48]

Factors influencing the impact of maternal mercury exposure on offspring health

Although the 19 studies reviewed here point to a significant impact of maternal exposure to mercury on the physical and neurological development of children (Table 2), the wide heterogeneity between these studies is also noteworthy. Marked differences were observed in terms of the maternal and fetal body burden of methyl mercury. For instance, concentrations of methyl mercury in umbilical cord blood ranged from around 20 μg/L in studies conducted in Greenland and the Faroe Islands to levels below 10 μg/L in European populations. This variability was also remarkable in studies that used maternal hair as the biological sample to assess mercury exposure (0.53–12.12 μg/g), which is sometimes preferred over blood because it can be collected noninvasively and because methyl mercury levels in hair have been shown to reflect circulating blood concentrations.[50] Interestingly, this variability mirrored a lack of consistent association between mercury exposure levels and anthropometric, cognitive, or physical development variables across the 19 studies. Thus, it is possible that multiple factors could contribute to the heterogeneity of the findings reported here, including differences in fish/seafood consumption, exposure to other pollutants, and genetic factors, as recently reviewed.[40,49]

The patterns of seafood consumption, with regard to both quantity and type of seafood, were significantly different across the studies reviewed (Table 3), which could have caused much of the variability in the results, since fish consumption is the primary source of mercury exposure. From a quantitative point of view, fish intake varied from 1 to 2 meals per week in most continental populations (eg, Spain, Italy, United States)[32,35,36,51,52] to 8 to 12 meals per week in the studies conducted in Seychelles.[51,53,54] Curiously, no significant adverse associations between prenatal maternal fish consumption and child development were found in the studies that reported higher fish intakes.[51,53,54] In contrast, in populations with moderate seafood consumption (1–3 servings per week), authors have reported inverse associations between levels of total mercury in the mother and variables related to the physical or cognitive health of the neonate.[32,35–37,51,52] Therefore, this could indicate that the effect of maternal exposure to mercury on neonatal health depends not only on the total amount of fish consumed, but also on other factors.

In view of this, the type of seafood stands out as a major determinant of the adverse effects of maternal consumption of mercury-containing fish on anthropometric variables and the physical or cognitive status of the offspring. In particular, across the 19 studies included in this review, the strongest negative associations between methyl mercury levels and health outcomes were observed in populations that consumed whale meat in Greenland and the Faroe Islands.[30,33,34] Other studies of nonconsumers of whale meat, however, did not report significant differences according to the type of fish. On the other hand, Oken et al[38,39] found that, among women consuming varied seafood products during pregnancy (bluefish/whitefish and shellfish, 1.5 meals per week), higher seafood intake was associated with increased health benefits for young children, whereas higher levels of methyl mercury were correlated with adverse effects. Altogether, these results suggest that the type of fish consumed, and not the quantity, is the most important factor influencing the impact of maternal fish intake on health outcomes of the child.

Besides exposure to mercury through dietary components, co-exposure to other sources of mercury could be also responsible, at least in part, for the variability in outcomes observed across populations. Most of the studies listed in Table 2 considered smoking as a potential confounding covariate, and some studies also took into account the exposure to dental amalgam (Table 3), but neither of these factors showed a significant impact on the results. Marques et al[29] reported significantly higher mercury levels among tin mining settlers compared with volunteers from riverside, urban, and rural locations. However, other investigators found no significant differences according to the place of residence for other populations.[30–33,47]

Finally, genetic predisposition is another crucial factor that may explain the wide interindividual variability in response to mercury exposure, since certain genetic variants have been demonstrated to increase the susceptibility to methyl mercury toxicity during pregnancy and to affect cognition in childhood. In recent years, genetic and epigenetic factors that may influence mercury toxicokinetics have been documented, although only a few studies have been published, most of which were conducted in adult populations.[53] To date, several genes have been demonstrated to play an important role in mercury homeostasis. These include L-type amino acid transporters (*LAT1* and *LAT2*) and anionic transporters (*OAT1* and *OAT3*), which are involved in mercury uptake; glutathione-related enzymes, which participate in biotransformation processes; metallothioneins, which play a role in mercury distribution; and ATP-binding cassette (ABC) family transporters (*MRP1*, *MRP2*, and *MDR1*), which are involved in mercury removal.[53] For example, Llop et al[52] reported that some polymorphisms in ABC genes found in 2 Mediterranean birth cohorts were associated with an accumulation of mercury in the fetus as a result of increased transfer across the placenta. Furthermore, these polymorphisms had a modifiable effect on the associations between fish intake during pregnancy and mercury concentrations in umbilical cord blood.

Other studies have evaluated whether genetic susceptibility modifies the effect of prenatal exposure to methyl mercury on the cognitive development of children. Ng et al[54] studied apolipoprotein E (*APOE*) gene polymorphisms to assess genetic susceptibility to the effects of mercury toxicity and to determine the relationship between cord blood mercury concentrations and neurodevelopment in 2-year-old children. The results showed that a polymorphism in *APOE* could modify mercury toxicity, since children carrying the ε4 allele, which is associated with impaired neural repair function, scored worst on neuropsychological tests. In another study that investigated the effect of gene–mercury interactions on neurodevelopment in children from the Avon Longitudinal Study of Parents and Children, conducted in the United Kingdom, the authors identified 4 single-nucleotide polymorphisms in, respectively, brain-derived neurotrophic factor (*BDNF*), paraoxonase 1 (*PON1*), transferrin (*TF*), and progesterone receptor (*PGR*) genes, where the presence of the minor allele was associated with greater methyl mercury–related cognitive deficits at low background exposure.[51]

CONCLUSION

The evidence from this systematic review suggests that maternal dietary exposure to mercury has a significant impact on the physical and neurological development of children. This, in turn, may be associated with the onset of chronic diseases in adulthood within the framework of the intrauterine programming effect. The deleterious effects of mercury, however, can be masked or limited by other nutrients from fish, such as polyunsaturated fatty acids. For these reasons, current recommendations to avoid the ingestion of mercury-containing fish during pregnancy should be revised to encourage the consumption of fish species with beneficial levels of PUFAs but low levels of mercury.

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Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Appendix S1 PRISMA checklist.

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Figure 1 **Flow diagram of the literature search process.**

Table 1 **PICOS criteria for inclusion of studies**

Parameter	Criterion
Participants	Pregnant women, fetuses, newborns, and young children
Intervention	Not described
Comparison	Pregnant women who ingested mercury-containing seafood during pregnancy and those who did not
Outcomes	Clinical repercussions in offspring up to 8 years of age
Study design	All study types

Table 2 **Characteristics and summary of the 19 studies included in the systematic review**

Reference	Country	Study design	Sample size	Biological sample and mercury concentration	Health outcomes evaluated	Age of child at assessment	Key results	Study quality[28]
Foldspang & Hansen (1990)[30]	Greenland	Cohort	376	Maternal venous blood (14.9 µg/L) and umbilical cord blood (21 µg/L)	Gestational length and weight	At birth	High MeHg content in maternal and offspring blood was associated with low birth weight, but not with gestational length	High
Grandjean et al (1997)[33]	Faroe Islands (Denmark)	Prospective cohort	917	Umbilical cord blood (22.9 µg/L) and maternal hair (4.27 µg/g)	Scores on neuropsychological tests[a]	At 7 y	Various domains of brain function, especially those related to language, may be affected by prenatal exposure to MeHg	Medium
Davidson et al (1998)[35]	Seychelles	Longitudinal prospective cohort (SCDNS)	711	Maternal hair (6.8 µg/g) and infant hair (6.5 µg/g)	Scores on neurodevelopmental tests[b]	At 66 mo	No significant effects of maternal prenatal consumption of fish on offspring was found at 66 mo of age	High
Steuerwald et al (2000)[34]	Faroe Islands (Denmark)	Prospective cohort	182	Maternal hair (4.08 µg/g), umbilical cord blood (20.4 µg/L), and serum (2.54 µg/L)	Results of neurological examination (Prechtl assessment)	At birth	Negative association found between neonatal neurological function and MeHg concentration in umbilical cord blood	High
Daniels et al (2004)[41]	United Kingdom	Avon Longitudinal Study of Parents and Children	1054	Umbilical cord tissue (0.01 µg/g)	Scores on MCDI and DDST	At 15 mo and 18 mo	Fish intake was associated with higher scores for MCDI components (language, comprehension, and social activity) at 15 mo and higher DDST scores at 18 mo	High
Oken et al (2005)[38]	United States	Prospective cohort (Viva Project)	135	Maternal hair (0.55 µg/g)	Scores on a visual recognition memory test	At 6 mo	Higher fish consumption in pregnancy was associated with better infant cognition, but	High

							higher mercury levels were associated with lower cognition	
Jedrychowski et al (2006)[43]	Poland	Prospective cohort	233	Umbilical cord blood (0.88 µg/L) and maternal blood (0.55 µg/L)	Scores on BSID-II, leading to the MDI	At 1 y	Maternal mercury levels were associated with late psychomotor development of children in the first year of life	Medium
Gao et al (2007)[45]	China	Cohort	408	Maternal hair (1.25 µg/g) and umbilical cord blood (5.58 µg/L)	Scores on Neonatal Behavioral Assessment Scale	At birth	Prenatal exposure to mercury affects the behavioral ability of newborns only among males	High
Oken et al (2008)[39]	United States	Prospective cohort (Viva Project)	341	Red blood cells (3.8 µg/L) and maternal hair (0.53 µg/g)	Scores on Peabody Picture Vocabulary Test and Wide Range Assessment of Motor Visual Abilities	At 3 y	Higher fish intake was associated with better performance on infant cognition tests, but higher mercury levels were associated with poorer test scores	High
Davidson et al (2008)[36]	Seychelles	Longitudinal prospective cohort (SCDNS)	300	Maternal hair (5.7 µg/g)	Scores on BSID-II, MDI, and PDI	At 5 mo, 9 mo, 25 mo, and 30 mo	Adverse association between MeHg and the PDI score at 30 mo	Medium
Ramón et al (2009)[31]	Spain	Prospective cohort (INMA)	554	Umbilical cord blood (9.4 µg/L)	Anthropometric measurements (weight, length, and gestational age)	At birth	Length and weight at birth decreased with increased exposure to MeHg	High
Marques et al (2013)[29]	Brazil	Cohort	1433 (riverside = 396, urban = 676, rural = 67, tin mining settlers = 294)	Maternal hair (12.12 µg/g, 5.36 µg/g, 7.82 µg/g, and 4.45 µg/g, respectively)	Weight	At birth	No negative association of MeHg with birth weight of newborns	Medium
Valent et al (2013)[42]	Italy	Cohort	606	Maternal hair (1.069 µg/g) and umbilical cord blood (5.54 µg/L)	Scores on BSID-III	At 18 mo	No significant adverse effects of maternal fish consumption	High
Strain et al (2015)[37]	Seychelles	Longitudinal prospective cohort (SCDNS[a])	1265	Maternal hair (3.69 µg/g)	Scores on BSID-II, MCDI, and revised CBQ	At 20 mo	No adverse associations of maternal fish consumption with child development	High

Murcia et al (2016)[32]	Spain	Prospective cohort (INMA)	1869	Umbilical cord blood (8.2 µg/L)	Anthropometric measurements (weight, length, and head circumference), placental weight, and gestational length	At birth	Total mercury was inversely associated with placental weight and marginally associated with anthropometric measurements at birth	High
Llop et al (2017)[44]	Spain	Prospective cohort (INMA)	1362	Umbilical cord blood (8.8 µg/L)	Scores on MSCA	At 4–5 y	Inverse association of MeHg with MSCA scores (only among children whose mothers consumed < 3 servings of fish per week during pregnancy) and with scores on the motor scale (in children with an n-6/n-3 PUFA ratio above the median)	High
Tatsuta et al (2017)[48]	Japan	Cohort (TSCD)	566	Umbilical cord blood (15.7 µg/L) and maternal hair (2.5 µg/g)	Scores on BSID-II and Kyoto Scale of Psychological Development	At 18 mo	Exposure to mercury was negatively associated with PDI only among boys	Medium
Jeong et al (2017)[46]	Korea	Prospective cohort (MOCEH)	553	Maternal venous blood (3.14 µg/L)	Scores on Korean version of the WPPSI-R (verbal and performance IQ)	At 5 y	Maternal blood mercury during pregnancy was inversely associated with the children IQ	Medium
Kim et al (2018)[47]	Korea	Prospective cohort (MOCEH)	1751	Maternal venous blood in early pregnancy (3.3 µg/L) and late pregnancy (3 µg/L), and cord blood (5.1 µg/L)	Scores on BSID-II, MDI, and PDI	At 6 mo, 12 mo, 24 mo, and 36 mo	Prenatal exposure to mercury during early pregnancy was inversely associated with BSID-II on neurocognitive development only at 6 mo	High

[a] Finger tapping, hand-eye coordination, reaction time of the Continuous Performance Test, Wechsler's Intelligence Scale for Children–Revised (digit span, similarities, and block design, Bender Visual-Motor Gestalt Test, Boston Naming Test, and California Verbal Learning Test–Children's Version.

[b] Six neurodevelopmental tests: McCarthy Scales of Children's Abilities, Preschool Language Scale, applied problems of the Woodcock-Johnson Test, achievement tests for letters/word recognition, the Bender Visual-Motor Gestalt Test, and Child Behavior Checklist.

Abbreviations: BSID-II, Bayley Scales of Infant Development–II; BSID-III, Bayley Scales of Infant Development–III; CBQ, Children's Behavior Questionnaire; DDST, Denver Development Screening Test; INMA, INfancia y Medio Ambiente (Childhood and Environment Project); MCDI, MacArthur Communicative Development Inventory; MDI, Mental Development Index; MeHg, methyl mercury; MOCEH, Mothers and Children's Environmental Health Study; MSCA, McCarthy Scales of Children's Abilities; PDI, Psychomotor Development Index; SCDNS, Seychelles Child Development Nutrition Study; TSCD, Tohoku Study of Child Development; WPPSI-R, Wechsler Preschool and Primary Intelligence Scale–Revised.

Table 3 **Quantity and type of fish/seafood consumption in the 19 studies included in the systematic review**

Reference	Country	Amount of fish/seafood consumed	Type of fish/seafood	Other factors studied
Foldspang & Hansen (1990)[30]	Greenland	Not reported	Whale meat and organs	Maternal smoking during pregnancy; residence (Godthaab/Thule)
Grandjean et al (1997)[33]	Faroe Islands (Denmark)	Not reported	Seafood and whale meat	Maternal smoking and alcohol intake during pregnancy; current residence (Faroe Islands, Denmark)
Davidson et al (1998)[35]	Seychelles	12 meals/wk	Yellowfin tuna, mackerel, grouper, bonito, bludger, and emperor	Maternal smoking and alcohol intake during pregnancy
Steuerwald et al (2000)[34]	Faroe Islands (Denmark)	50.6% ate 3 fish meals/wk	Seafood and whale meat	Maternal smoking and alcohol intake during pregnancy
Daniels et al (2004)[41]	United Kingdom	80% ate fish at least 1 time/wk, 40% ate white fish 1–3 times/wk, and 34% ate oily fish 1–3 times/wk	Whitefish (cod, haddock and plaice) and oily fish (sardines, tuna, mackerel, herring, trout, and salmon)	Maternal smoking and alcohol intake during pregnancy; whether dental treatment was received during pregnancy
Oken et al (2005)[38]	United States	1.2 meals/wk	Canned tuna, bluefish (salmon, mackerel, swordfish), white fish (cod, halibut), and seafood (lobster, scallops, clams)	Maternal smoking, alcohol intake, and illicit drug use during pregnancy
Jedrychowski et al (2006)[43]	Poland	Not reported	Not reported	Only nonsmoking women. Smoking practices of others present in the home
Gao et al. (2007)[45]	China	40% ate 3–4 meals/wk, and 30.4% ate > 5 meals/wk	Marine fish (species not reported)	Parental smoking habits (including passive smoking). Maternal alcohol consumption, hair treatments (including bleaching, permanent wave, and coloring), use of skin-lightening makeup, and dental amalgam treatment
Oken et al (2008)[39]	United States	1.5 meals/wk	Canned tuna, bluefish (salmon, mackerel, swordfish), white fish (cod, halibut), and seafood (lobster, scallops, clams)	Maternal smoking and alcohol intake during pregnancy
Davidson et al (2008)[36]	Seychelles	9 meals/wk	Tuna, karang, cobbler, mackerel, and barracuda	Not reported
Ramón et al (2009)[31]	Spain	1–2 meals/wk	Mainly whitefish (hake, sole, and sea bream), and, to a lesser extent, canned tuna and bluefish (swordfish, bonito, and tuna)	Maternal smoking during pregnancy; residence (rural/urban)
Marques et al (2013)[29]	Brazil	5 meals/wk in river areas, and 1–3 meals/wk in rural or urban areas	Not reported	Mining vs nonmining environment
Valent et al (2013)[42]	Italy	1.69 meals/wk	Tuna, sea bass, sea bream, shad, cod, trout, plaice, sole, and mackerel	Maternal smoking and alcohol intake during pregnancy. Children's exposure to environmental tobacco smoke at home
Strain et al (2015)[37]	Seychelles	8.5 meals/wk	Not reported	Not reported
Murcia et al (2016)[32]	Spain	1.65 meals/wk	Whitefish, bluefish, canned tuna, and seafood (type not specified)	Maternal smoking during pregnancy; residence subcohort (Asturias/Gipuzkoa/Sabadell/Valencia)

Llop et al (2017)[44]	Spain	39.8% ate 5–8 meals/wk, and 34.1% ate > 8 meals/wk	Whitefish, bluefish, canned tuna and seafood (type not specified)	Maternal and paternal smoking
Tatsuta et al (2017)[48]	Japan	Not reported	Not reported	Maternal smoking and alcohol intake during pregnancy
Jeong et al (2017)[46]	Korea	1–2 meals/wk	Not reported	Maternal alcohol consumption, nutritional habits, exposure to second-hand smoke in the home, and exposure to occupational hazards
Kim et al (2018)[47]	Korea	64.7% ate 1–2 meals/wk	Not reported	Maternal passive smoking status; residential area