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Fish consumption, methylmercury and child neurodevelopment

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Abstract

Purpose of review—To summarize recent evidence regarding associations of early life exposure to mercury from maternal fish consumption during pregnancy, thimerosal in vaccines and dental amalgam with child neurodevelopment.

Recent findings—Recent publications have built upon previous evidence demonstrating mild detrimental neurocognitive effects from prenatal methylmercury exposure from maternal fish consumption during pregnancy. New studies examining the effects of prenatal fish consumption as well as methylmercury suggest there are benefits from prenatal fish consumption, but also that consumption of fish high in mercury should be avoided. Future studies incorporating information on both the methylmercury and the docosahexaenoic acid contained within fish will help to refine recommendations to optimize outcomes for mothers and children. Additional recent studies have supported the safety of vaccines containing thimerosal and of dental amalgam for repair of dental caries in children.

Summary—Exposure to mercury may harm child development. Interventions intended to reduce exposure to low levels of mercury in early life must, however, be carefully evaluated in consideration of the potential attendant harm from resultant behavior changes, such as reduced docosahexaenoic acid exposure from lower seafood intake, reduced uptake of childhood vaccinations and suboptimal dental care.

Keywords

child development; dental amalgam; fishes; mercury; *n*-3 fatty acids; pregnancy; thimerosal

Background

Mercury is a ubiquitous heavy metal with both natural and anthropogenic sources. The neurotoxic effects of exposure to high-dose mercury are well documented [1]. Although mercury can affect the central nervous system at any developmental stage, unfortunate episodes of community-wide poisoning in Japan and Iraq revealed the particular sensitivity of the fetus to the toxic effects from mercury exposure [2,3]. In these communities, exposed pregnant women who themselves had no or minimal symptoms had babies with devastating neurological handicaps, including delayed attainment of developmental milestones, blindness, deafness and cerebral palsy. Whereas adult mercury exposure causes localized damage to discrete areas of the brain, exposure in fetal life causes diffuse and widespread neurological damage [4].

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More recent research has examined whether lower levels of mercury exposure in early life result in appreciable harm for child cognitive development. In the following sections, we review current evidence regarding implications for child health from exposure to methylmercury from maternal fish consumption during pregnancy, ethylmercury contained within the vaccine preservative thimerosal and the metallic mercury in dental amalgams.

Fish consumption and methylmercury

The primary source of nonoccupational mercury exposure is consumption of fish and other seafood. Elemental or ionic mercury is released into the environment from natural processes such as volcanic eruptions, and from human activities such as burning of coal for energy and disposal of medical and other waste containing mercury. This inorganic mercury may ultimately make its way to the watershed, where it is organified through the process of methylation by phytoplankton in marine environments and by sulfate-reducing bacteria in freshwater sediments [5]. Once organified, methylmercury is readily absorbed by marine life, and bioaccumulates and biomagnifies as it ascends the aquatic food chain. As a result, the highest tissue concentrations are found in animals at the highest trophic levels, including long-lived predatory species such as sharks, swordfish and tuna. Methylmercury levels can also be high in marine mammals such as whales and in other animals that feed on marine life.

Older cohort studies of prenatal mercury exposure in high-fish-eating populations

Longitudinal prospective studies in island populations were established in the 1970s and 1980s to evaluate the effects of moderate methylmercury exposure from frequent fish consumption during pregnancy. Most notably, results from cohorts in New Zealand and in the Faroe Islands, but not in the Seychelle Islands, suggested that higher prenatal methylmercury exposure from seafood consumption was associated with decrements in attention, language verbal memory, motor speed and visuospatial function [6-9].

Integrative analysis of the overall effect of prenatal mercury exposure on intelligence

The apparent discrepancies in the findings of the New Zealand, Seychelles Islands and Faroe Islands studies have posed challenges to scientists trying to understand the effects of prenatal methylmercury. Recent analyses suggest that, although the findings of the three cohort studies appear to differ if compared solely on the basis of *P*-values associated with the dose–effect relationships, the inverse slopes of the relationships were very similar across studies. In an integrative analysis, Axelrad *et al.* [10•] estimated that each microgram per gram increase in maternal hair mercury was associated with a decrement of 0.18 child intelligence quotient (IQ) points. In another quantitative analysis also using data from the same three studies, Cohen *et al.* [11] estimated that prenatal methylmercury exposure sufficient to increase the concentration of mercury in maternal hair by 1 μg/g decreases child IQ by 0.7 points.

Advice from regulatory agencies regarding methylmercury exposure

Different regulatory agencies have made different choices regarding intake limits for methylmercury. In 2001 the US Environmental Protection Agency (EPA) relied primarily on the Faroe Islands study in deriving its reference dose (RfD) of 0.1 μg methylmercury/kg body weight/day, although the findings of the New Zealand study and, to a lesser extent, the Seychelles Islands study provided supporting evidence [12]. The US Agency for Toxic Substances and Disease Registry opted to use the Seychelle Islands study to derive its Minimal Risk Level of 0.3 μg methylmercury/kg body weight/day, expressing concern that some of the apparent adverse effects attributed to methylmercury in the Faroe Islands study might be the result of residual confounding by coexposures to persistent organic contaminants in the pilot whale blubber also frequently consumed in the Faroes [13]. More recently, in 2003, the Joint Expert Committee on Food Additives and Contaminants (JECFA), a committee of the WHO and Food and Agriculture Organization, did not consider the New Zealand study in its risk assessment due to concerns about the inordinate influence on the results of one observation that was more than four times higher than the next highest level in the study sample. The JECFA derived the provisional tolerable weekly intake of 1.6 μg methylmercury/kg body weight/week (or 0.23 μg/kg body weight/day) on the basis of the Faroe Islands and Seychelle Islands studies [14]. Another factor contributing to differences in the intake limits derived by the different regulatory groups is differences in the underlying assumptions, most notably in the uncertainty factors applied.

Fish is the primary dietary source of docosahexaenoic acid, an *n*-3 fatty acid that may benefit early brain development

A factor complicating any risk estimation regarding prenatal methylmercury exposure is that seafood also delivers beneficial nutrients such as the *n*-3 fatty acid docosahexaenoic acid (DHA). DHA is a necessary structural component of the brain and eye. In a recent review, Hadders-Algra *et al.* [15•] concluded that infant formula supplemented with DHA confers a mild benefit for infant neurodevelopment among term infants and that no clear evidence exists for a benefit among preterm infants, although data do not yet exist to determine whether supplementation in formula affects neurodevelopmental outcomes at later ages.

As the most rapid uptake of DHA into the brain occurs in late pregnancy, it is possible that prenatal exposure is even more important. Only a few studies have addressed whether maternal *n*-3 fatty acid supplementation or intake might benefit offspring cognition. Three randomized trials of prenatal *n*-3 supplementation suggest improvements in child outcomes in infancy and early childhood [16-19]. Some observational studies have also found that umbilical cord tissue or blood levels of DHA were associated with better development in infants [15•]. All these studies are small, and thus additional studies with larger samples and longer follow-up will be required to establish the magnitude of the benefits associated with prenatal DHA intake. On the basis of the limited data available, a European expert panel recently recommended an average daily intake of at least 200 mg/day of DHA during pregnancy [20]. Most pregnant women do not consume this amount [21].

US federal mercury advisories

In 2001, the US EPA and Food and Drug Administration (FDA) issued a joint consumer advisory based on the EPA RfD recommending that pregnant women avoid consuming fish types high in mercury and limit their total fish intake to no more than two 6-ounce servings per week [22]. In a time-series analysis, Oken *et al.* studied fish consumption in cohort of pregnant women, some surveyed before January 2001 and others surveyed afterwards. Women were not questioned regarding their awareness of the advisory. Average total fish intake decreased after publication of the advisory by about 1.4 monthly servings [23]. Women surveyed after the advisory ate fewer servings not only of the dark meat fish likely to have higher mercury contamination, but also of fish types not specifically named in the advisory, such as canned tuna fish and white meat fish. Similarly, an advisory in the Faroe Islands that focused on whale meat consumption succeeded in reducing hair mercury levels among women of childbearing age [24]. However, administration of a fish consumption advisory to women in France resulted in reduced consumption of tuna fish, but no change in intake of the most highly contaminated fish [25]. Therefore, care needs to be taken to ensure advisories effect the desired behavior change.

In 2004, a revised federal advisory did not alter the recommended 12-ounce weekly limit, but included advice encouraging women to eat a variety of fish types up to two weekly servings and provided more specific advice on different forms of tuna, one of the most frequently consumed fish ([26]; this website contains the current US federal recommendations regarding fish consumption during pregnancy, lactation and early childhood).

Recent studies examining overall effects of fish consumption

Whether the beneficial effects of *n*-3 fatty acids on child neurocognitive development might counteract or outweigh those of methylmercury is not known. Recent studies have attempted to understand the trade-offs that might result when fish intake is changed.

In a series of papers, Cohen *et al.* examined the risks and benefits of fish consumption, including methylmercury exposure and child cognitive development [11], prenatal n-3 polyunsaturated fatty acid intake and cognitive development [27], and adult fish consumption and risk for stroke and coronary heart disease [28,29], and combined these outcomes according to their estimated effects on quality adjusted life years for the population as a whole [30]. The effects of changes in fish consumption varied depending upon the hypothesized scenario. If women continued to eat fish at the same levels but switched to fish lower in mercury, there would be a net benefit for population health; if women reduced their overall fish intake including low mercury fish, the overall effect would be harmful. If all segments of the population including those who are not targeted in current federal advisories such as adult men and nonpregnant women reduced their fish intake, there would be an even greater net harm for population health, whereas if the entire population increased their fish intake, there would be a net benefit for the health of the population. These findings reinforce the need for effective risk communication. If people do not interpret the messages correctly, unintended harms may result.

Oken *et al.* [31] used data from a prospective prebirth cohort study called Project Viva to examine associations of maternal prenatal fish intake, maternal hair mercury and infant cognition at 6 months. In this analysis of data from 135 mother–child pairs, as anticipated, mothers who consumed more fish during the second trimester of pregnancy had higher hair mercury levels at birth, supporting evidence that fish consumption is the primary source of nonoccupational mercury exposure. Overall, greater maternal fish consumption was associated with higher infant scores on the visual recognition memory test – an assessment of visual memory that is correlated with later IQ. Additional adjustment for mercury levels strengthened the beneficial association of fish consumption with infant cognition, suggesting that, in the absence of mercury contamination, the benefits of prenatal fish consumption might be even greater. Higher maternal mercury levels were, however, associated with somewhat lower infant test scores. The highest test scores were among infants whose mothers consumed more than two weekly fish servings but had hair mercury levels below 1.2 μg/g, whereas the lowest scores were among those whose mothers consumed two or fewer weekly fish servings but had higher hair mercury levels. Investigators concluded that women should continue to consume fish during pregnancy, but should avoid fish most highly contaminated with mercury to gain the greatest possible benefit; however, the small sample size and young age at outcome limited strong conclusions from these findings.

A recent publication supported these findings with similar results among a much larger population. Hibbeln *et al.* [32•] studied prenatal fish consumption and neurodevelopmental outcomes among 11 875 mothers and children from the UK. Mothers reported their consumption of three categories of seafood on a food frequency questionnaire administered at 32 weeks' gestation. Study investigators assessed child developmental milestones from 6 to 42 months of age, measured behaviors at age 7 years and tested intelligence at age 8 years. Compared with mothers who ate more than 340 g (12 ounces) of seafood per week, those who ate less seafood had a higher risk of having children with suboptimal scores on measures of verbal IQ, prosocial behavior, fine motor skills and social development. For other outcomes, fish intake above 340 g/week was not predictive of better performance, but also was not associated with worse performance. No measure of mercury exposure in this study was available, so these analyses pertain mainly to the benefit side of the trade-off. However, mercury intake was estimated. As in the study of Oken *et al.* [31], simultaneous adjustment for fish intake and methylmercury strengthened the estimate of the benefits associated with fish and also revealed an inverse association between verbal IQ and methylmercury [33].

Also recently, investigators from the Faroe Islands reanalyzed their data using structural equation modeling to better estimate the independent effects of seafood intake and mercury exposure [34•]. In this analysis, maternal seafood intake was associated with higher scores of motor and spatial function in children at age 14 years. Associations with other measured outcomes such as attention, verbal performance and memory were not statistically significant, but were in a positive direction as well. Conversely, the effect of mercury was negative, with stronger estimates evident after adjustment for fish intake. These investigators concluded that consumers should include seafood and fish in their diet, but choose types low in contaminants.

In 2006, the US Institute of Medicine issued a report on *Seafood Choices: Balancing Risks and Benefits* [35••]. The committee concluded that seafood is a component of a healthy diet, particularly as it can displace other protein sources higher in saturated fat, but that consumers should make selections that reduce exposure to seafood-borne contaminants such as methylmercury. Other expert bodies including the American Dietetic Association and Dietitians of Canada recently reinforced the importance of a food-based approach for meeting dietary fatty acid recommendations [36].

Dental amalgam

Dental amalgam, used to restore carious lesions in teeth, is approximately 50% metallic mercury. Small amounts of mercury vapor liberated by chewing are inhaled and result in measurable levels of mercury in the body. Concern has existed that exposure to mercury vapor from dental amalgams may produce neurotoxicity in children. Resolving this question is important, because resin-based composite, the primary alternative to amalgam, is not as durable and may therefore require future replacement or repair. In addition, composite materials may leach estrogen-like molecules such as bisphenol-A that also have been associated with adverse childhood outcomes [37].

Dental amalgam in children

In a randomized trial, Bellinger *et al.* [38,39] studied neuropsychological function of children aged 6–10 years without prior exposure to dental amalgam, whose caries were repaired using either dental amalgam or mercuryfree composite. Children were evaluated at baseline and yearly for 5 years using tests of intelligence, achievement, language, memory, learning, visual-spatial skills, verbal fluency, fine motor function, problem solving, attention and executive function. As expected, urinary mercury levels were greater in the children in the amalgam group than in the composite group. Few differences were found between the test scores of children in the two groups, however, and directions of the associations were not consistent in finding that mercury exposure was detrimental. Of over 30 individual outcomes, one showed a greater improvement in test scores for the amalgam group, whereas one showed greater improvement in test scores for the composite group. Continuous measures of mercury exposure, including urinary mercury excretion and the number of surface-years of amalgam exposure, were also not associated with child test scores [40]. These findings, along with those of another trial that reached similar conclusions [41], suggest that dental amalgam is safe and without adverse neurocognitive effects in children, although it is possible that exposure at younger ages, or follow-up for longer duration, might reveal some evidence for harm.

Dental amalgam during pregnancy

The number of dental amalgams in a mother is correlated with mercury levels in cord blood, and thus presumably with fetal brain exposure [42]. However, in an analysis of data from the Avon Longitudinal Study of Parents and Children cohort, maternal dental care during pregnancy, including amalgam fillings, was not associated with birth outcomes such as preterm delivery and low birth weight, or with child development at age 15 months, among over 7000 British children [43]. In a case–control study, Hujoel *et al.* [44] found that having had a dental amalgam filling was not a risk factor for low birth weight, even among women who had up to 11 amalgam fillings placed during the course of pregnancy.

Vaccines and ethylmercury

Thimerosal, which contains approximately 50% ethylmercury, was widely used in the US as a preservative in multiuse vials of vaccines, until it was removed from most childhood vaccines by 2001 as a precautionary measure, since the dose of mercury infants receive over the first few years of life could exceed the recommended exposure threshold for methylmercury. For several reasons, however, exposure thresholds for thimerosal in vaccines might differ from those for prenatal methylmercury, including the much shorter half-life of ethylmercury and the fact that exposure is episodic rather than persistent [45].

Thimerosal and child development

A previous comprehensive review examined studies published from 1966 to 2004 for evidence of an association between thimerosal-containing vaccines and autism spectrum disorders in children [45]. These authors identified 12 original studies, of which the four studies that found evidence for a detrimental association were published by the same authors, used overlapping data sets, and contained critical methodologic flaws (e.g. [46]). Other studies of higher quality did not support any association between thimerosal exposure and autism spectrum disorders.

Since publication of that review, an additional study also did not support an association of thimerosal in vaccines with autism spectrum disorders. In a large survey of children in Montreal, Canada, Fombonne *et al.* [47] found no evidence that trends in exposure to ethylmercury accounted for the increasing trend in pervasive developmental disorder.

In addition, investigators [48•] in the Vaccine Safety Datalink study recently evaluated 42 neuropsychological outcomes among children aged 7–10 years in relation to their early life vaccine exposure. In this study of over 1000 children, there was no overall association of exposure to mercury from thimerosal-containing vaccines during pregnancy or in infancy with adverse neuropsychological functioning. Overall, the highest-quality data available do not support conjectures that thimerosal may account for the recent increase in autism spectrum disorders or other adverse neurodevelopmental outcomes in children.

Conclusion

Recent publications have extended earlier findings that prenatal methylmercury exposure from maternal seafood consumption is associated with mild but measurable decrements in child neurocognitive outcomes to detect effects at even lower exposure levels. Greater prenatal exposure to DHA is, however, beneficial for early childhood development and many pregnant women do not achieve recommended levels of intake. Studies evaluating the overall effect of maternal prenatal fish consumption suggest that there is on balance no harm, and perhaps some benefit, from greater maternal fish consumption. These studies also suggest that the benefits of increased maternal fish consumption would be greater if a woman chose seafood low in methylmercury. Additional recent studies have found no evidence for harm from vaccines containing thimerosal or from dental amalgam for repair of dental caries. Interventions intended to reduce exposure to low levels of mercury in early life must be carefully evaluated in consideration of the potential attendant harm from resultant behavior changes.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 226).

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