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Eating fish for two

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Summary

This article is based on the British Nutrition Foundation's Annual Lecture, which focused on maternal fish consumption and the effects of methylmercury (MeHg) on fetal development, with respect to current guidance and policy on fish consumption during pregnancy. Fish makes a valuable contribution to nutrient intakes across the globe and is the primary protein source for many individuals, particularly those in the developing world. Populations with a high fish consumption, such as in the Republic of the Seychelles, have a greater exposure to MeHg, which is present in varying amounts in all fish. Methylmercury is a toxic pollutant, which is known to impair neurodevelopment. The dose of MeHg from fish consumption, however, needed to impair neurodevelopment is unknown. Current UK and US guidance on fish consumption during pregnancy tend to focus more on avoiding risks rather than highlighting the benefits which can be obtained from eating fish. Such recommendations have been mainly based on data arising from epidemiological studies in the Faroe Islands, where methylmercury exposure was largely from pilot whale consumption. Although small adverse effects on child development have been reported in data from the Faroe Islands, data from the on-going Seychelles Child Development Studies have shown no adverse effects of prenatal methylmercury exposure from high maternal fish consumption (9–12 meals containing fish per week) on developmental outcomes. Instead these data suggest that nutrients, including long chain polyunsaturated fatty acids (LC-PUFAs), provided by fish may offer a beneficial effect and attenuate or modify any effects of MeHg on developmental outcomes. Recent expert consultations have concluded that the health benefits of fish consumption outweigh the risks posed by MeHg exposure and have argued the need for improved education and guidance to highlight the importance of consuming nutrients, including LC-PUFAs, from fish for optimal child development and to encourage fish consumption during pregnancy.

Keywords

methylmercury; fish consumption; child development; risks and benefits; nutrition; Seychelles Child Development Studies

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Conflict of interest

The author has no conflict of interest to disclose.

Introduction

Fish is an important component of a healthy, balanced diet and provides a number of key nutrients, including protein, long chain polyunsaturated fatty acids (LC-PUFAs), iodine, selenium and vitamin D (Weichselbaum *et al.* 2013). Consumption rates vary across the globe and fish consumption in the UK is relatively low compared to other countries. Data from the most recent *National Diet and Nutrition Survey* show that mean consumption of white fish (not coated or fried), shellfish, fish dishes and canned tuna in adults aged 19–64 years was 19g/day (133g/week), while mean oily fish consumption was 11g/day (equivalent to 77g/week) (Bates *et al.* 2012). These fish intakes are considerably lower than in Japan, where the average consumption rate is 72kg per person per year, equivalent to 197g per day (Myers *et al.* 2007). Although fish consumption has increased in the UK in the last decade, the current level of consumption still falls short of the recommendations (for all ages) to consume, per week, at least two portions (a portion being 140g cooked weight) of fish ; one portion of which should be oily (e.g. salmon, mackerel, herring or sardines). Oily fish provide LC-PUFAs, which are essential for the development of the brain and central nervous system during early life and, therefore, it might be prudent to consume oily fish during pregnancy. Evidence also suggests that fish consumption offers a protective effect against cardiovascular disease, as well as a reduced risk of mortality from coronary heart disease (He *et al.* 2004).

Contamination of fish and implications for neurodevelopment

Oceans and rivers are known to contain contaminants, which are subsequently incorporated into aquatic organisms as they feed and, therefore, into the food chain. The pollutants typically present in fish include dioxins, polychlorinated biphenyls (PCBs) and mercury; excessive exposure to these compounds can be detrimental to human health. For example, mercury is mainly present in the organic form methylmercury (MeHg), and can have neurotoxic effects if consumed in sufficient amounts. Mercury occurs naturally in the environment and is also released into the atmosphere as a by-product of industrial pollution. In water, MeHg is produced from inorganic mercury by bacteria and is then incorporated into small organisms as they feed and accumulates up the food chain. The further up the food chain, the greater the increase in the accumulation of MeHg and so the highest amounts are found in large predatory fish and mammals at the top of the food chain. For example, a report by the US Food and Drug Administration (FDA) found that shark and swordfish can contain up to 1ppm of mercury, whereas most other oceanic fish contain much lower amounts (less than 0.1ppm) (FDA, 2013). However,, MeHg is a potent neurotoxin which is known to impair neurodevelopment in infants. Therefore, it has been suggested that mothers who have high fish consumption during pregnancy may receive exposure to MeHg, which may adversely affect fetal brain development. Assessment of the level of exposure can be achieved by measuring the mercury concentration of hair or blood. Prenatal MeHg exposure is usually assessed by measuring maternal hair grown during pregnancy.

Man-made disasters

The effects of MeHg first became apparent following two major incidents of mass mercury poisoning. The first case occurred in Minamata in Japan in the 1950s following consumption of fish and shellfish contaminated with mercuric compounds, particularly MeHg, that had leaked into seawater from an industrial waste plant. Nearly 3000 individuals were affected and presented with a variety of symptoms including numbness of limbs, tremors, difficulty walking and impaired vision (later termed Minamata disease). Babies and fetuses were more severely affected and presented with mental retardation, gnarled limbs, deafness and blindness (Harada, 1995). The second major case of MeHg poisoning occurred in Iraq in the early 1970s following consumption of imported, from America and Mexico, barley and wheat that had been treated with MeHg as an antifungal agent. Originally, the grain was not intended for human consumption and was dyed pink to ensure this did not happen; however, problems with labelling and various miscommunications meant that the grain was inadvertently consumed by Iraqi residents. The aftermath of this error meant that more than 6000 individuals were admitted to hospital following exposure to MeHg. This poisoning resulted in symptoms including numbness of skin in extremities, lack of co-ordination of muscle movements and loss of vision that manifested 16–28 days after ingestion (Skerfving and Copplestone, 1976).

Both of these cases sparked huge concern among public health authorities regarding the detrimental effects of MeHg poisoning on the central nervous system, particularly of unborn children, where the symptoms were much more severe. Therefore, the findings have prompted further investigation to assess the impact of MeHg exposure on fetal neurodevelopment during pregnancy.

The effect of prenatal methylmercury exposure on subsequent child development

To date, several epidemiological studies have been carried out to assess whether prenatal MeHg exposure from fish consumption affects child neurodevelopment. Three major mother-child studies have measured prenatal methylmercury exposure within different populations consuming high amounts of fish and seafood and have reported different findings. The first study, carried out in New Zealand, investigated maternal MeHg exposure that came primarily from the consumption of shark meat. Findings, which were equivocal as they depended on whether outliers were included, showed a reduction in IQ as measured by the Wechsler Intelligence Scale-Revised (WIS-R) among children ($n=237$) aged between 4 and 6 years born to mothers who had mercury hair concentrations $>6\text{ppm}$ (Kjellstrom *et al.* 1986; 1989). The second study, conducted in the Faroe Islands, comprised a cohort of 1022 consecutive singleton births during a 21-month period in 1986–87. Mercury exposure in this population primarily occurs from the consumption of pilot whale meat and blubber, which can contain higher concentrations of MeHg and PCBs than ocean fish. Mercury exposure was assessed by measuring the concentrations of MeHg in cord blood and maternal hair (mean MeHg exposure at enrolment was 4ppm) and a range of neurobehavioural examinations were carried out in the children at seven years of age. The results showed evidence of neurophysiological dysfunction across a number of domains, particularly

language, attention and memory, following MeHg exposure in the children (Grandjean *et al.* 1997). The third study was carried out in the Republic of the Seychelles, where exposure to MeHg occurs on a daily basis owing to high levels of ocean fish consumption (12 meals per week on average). For this study, 779 mother-child pairs were initially enrolled to participate. Prenatal mercury exposure was measured in maternal hair growth during pregnancy (mean prenatal exposure was 6.9ppm) and numerous assessments of cognitive function were carried out in their offspring at various ages. Although this study was similar to the Faroe Islands study, the authors concluded that the data suggested that prenatal MeHg exposure from ocean fish consumption alone does not pose a risk to neurodevelopment in the fetus (Myers *et al.* 2003). Subsequent follow-up of this cohort continue to find no adverse effects of prenatal exposure of MeHg on development up to 19 years of age (van Wijngaarden *et al.* 2013).

Policy on maternal fish consumption

Much of the guidance to date surrounding fish consumption in the UK has focused on the avoidance of risks and limiting exposure to pollutants, as opposed to the benefits that can be obtained from consuming fish. Current advice from the Foods Standards Agency (UK) states that pregnant women should avoid eating shark, marlin and swordfish and should limit tuna consumption to no more than two tuna steaks (140g cooked weight or 170g raw) or four medium-size cans of tuna per week (FSA, 2002) because of the high levels of mercury present in these fish, and which could affect development of the nervous system of the fetus. Similarly, the Food and Drug Administration (FDA) in the US advises that pregnant women should not consume shark, swordfish, king mackerel or tilefish. Furthermore, pregnant women are advised to consume a maximum of 12oz (2 average meals) per week of fish and shellfish that contain lower levels of mercury, such as salmon, canned light tuna, pollock, shrimp and catfish. Because commonly eaten fish in the US known as albacore or “white” tuna has more mercury than canned light tuna, consumers are advised to eat no more than 6oz (one average meal) of this type of tuna per week (FDA, 2004). With the risk of exposure in mind, it is important that health organisations are particularly mindful to communicate messages regarding exposure carefully; otherwise, fish intake is likely to be avoided during pregnancy.

Epigenetic programming

The risks of MeHg exposure and fetal health provide a clear illustration of how environmental influences can affect our development. During early life development the fetus is extremely vulnerable, and as such any changes to the environment, such as nutrient deficiency or exposure to teratogens (substances or environmental agents that cause abnormalities during fetal growth), during this time can alter the developmental process. Previously, experts accepted that response to changes in the environment happened very slowly and was caused by changes to the DNA sequence and over a long period of time changes to the genome based on genetic mutations may offer certain advantages with respect to the changed environment. More recently, however, it has been acknowledged that an organism can respond to a different environment quite quickly by small changes in the genome without changing the DNA sequence. These small changes turn gene expression on

and off and are known as epigenetics. There are numerous epigenetic mechanisms which can modify the genome, and these include DNA methylation, histone modifications and RNA and DNA editing. Such epigenetic marks are established in the germ line and are maintained throughout the process of cell division. Epigenetic mechanisms can also influence genetic imprinting. This is the process whereby the expression of a copy of a gene is determined according to the parent of origin. Normally, both the maternal and paternal copies of a gene (alleles) are expressed within cells, but a small number of genes (approximately 100) are only expressed depending on whether they are passed down from the mother or father. Gene expression that occurs in this way is termed monoallelic expression, an example of which can be seen with the insulin-like growth factor 2 (*Igf-2*) gene, which is only expressed from the paternal allele (DeChiara *et al.* 1991). Epigenetic mechanisms, and subsequently gene expression, can be altered by environmental stimuli, including nutrition, and there is accumulating evidence to suggest that these epigenetic mechanisms can be inherited and may influence disease risk (Godfrey *et al.* 2007; Gluckman *et al.* 2009).

Several cohort studies have investigated the concept of epigenetic programming and suggested that adverse environmental conditions experienced during early life (e.g. maternal undernutrition because of famine) may influence the developmental outcomes of the child and grandchild, including their disease risk in adult life. Within the last century there have been several incidences of famine that have demonstrated such an effect. For example, children who were exposed to famine during early gestation in the Dutch Hunger Winter were more likely to have increased body fatness, and to experience coronary heart disease, diabetes and schizophrenia in adulthood compared to those who did not experience famine or who were exposed during the latter part of gestation (Susser and Lin 1992; Ravelli *et al.* 1999). In addition, individuals exposed to the famine during the early stages of development had less DNA methylation of *Igf-2* over 60 years later compared to their same-sex siblings who were unexposed. No association was found following exposure during late gestation; suggesting that epigenetic marks are made very early on during the developmental process (Heijmans *et al.* 2008). These findings suggest that dietary restriction may alter epigenetic marks in the mother and that such changes are then inherited by the child, and thus lead to the observed health effects. Similar findings were observed in adults whose mothers experienced maternal nutrient restriction during the famine in the Nigerian civil war. These individuals were more likely to be overweight, have hypertension and diabetes, compared to those who were born after the famine (Hult *et al.* 2010); suggesting that the timing of the exposure is an important determinant for the programming of disease risk. More recently, the *Southampton Women's Study* has shown that appropriate weight gain during pregnancy is associated with a lower amount of body fat in children, thereby indicating that women should avoid excessive weight gain during pregnancy (Crozier *et al.* 2010). Together these studies illustrate how certain exposures during early life development can affect long term health outcomes. Epigenetic modifications can alter gene expression across multiple generations and may alter an individual's susceptibility to disease. Therefore, it can be seen that a complex interplay of a number of factors, including genetics, epigenetics, imprinting and social factors, may be involved in 'programming' our development and disease risk.

Studies from the Seychelles

Given that intrauterine exposures can alter long-term development, it is important to ascertain the degree of exposure that can elicit detrimental effects, and when such effects may become visible (i.e. prior to/at birth or at a later stage of development). Therefore, with fish consumption and mercury exposure in mind, numerous studies are currently being carried out in the Republic of the Seychelles to assess the effect of MeHg exposure from maternal fish consumption on child developmental outcomes. The Seychelles offers many advantages as a study population, mainly owing to the high level of fish consumption (i.e. they consume on average 8 or more fish or fish-containing meals per week), a pristine environment and the necessary infrastructure to undertake such studies. The Seychelles Child Development Study (SCDS) is an on-going research project involving the Ministries of Health and Education in the Seychelles, the University of Ulster in Northern Ireland, and the University of Rochester in the United States. The study, which originally began in the 1980s, has two main objectives: to study child development in the Seychelles and, to ascertain if mercury exposure from fish consumption during pregnancy affects child development (University of Rochester Medical Center, 2014). A total of 779 mother-child pairs initially enrolled in the SCDS when it first commenced in 1989 has since led to the study of a variety of cohorts to establish the effects of pre- and post-natal exposure from fish consumption on developmental outcomes at various stages of childhood. To date, the study has not revealed any association between prenatal MeHg exposure and abnormal development in children. However, research is still on-going to assess whether any effects are apparent in later life or if other dietary factors may be counteracting or masking the effects of mercury exposure.

More recent findings from the main cohort of the SCDS show no adverse effects of prenatal MeHg exposure from fish consumption (mean prenatal Hg exposure 6.9ppm) on cognitive and behavioural outcomes in children at 17 years of age as assessed by a test battery (Davidson *et al.* 2011). Similar results have also been observed from a smaller cohort study (n=229 mother-child pairs) which had pre-natal nutrition data as well as MeHg exposures and again no adverse effects of prenatal MeHg consumption (5.7ppm) on developmental outcomes were seen. Blood samples taken at 28 weeks gestation and 1 day after delivery were analysed for various nutritional status biomarkers alongside a test battery of mental and psychomotor developmental tests taken at ages 5,9,25 and 30 months. Findings showed that maternal status of omega-3 fatty acids from the fish could be modifying the toxicity of MeHg and therefore counteracting any detrimental effects of MeHg on the nervous system (Strain *et al.* 2008). More recently, a second cohort was recruited by the Seychelles Government to further analyse how LC-PUFAs modulate the toxicity of MeHg and to assess the effects of other nutrients in the fish (specifically selenium and vitamin E) on child development. About 1500 mother-child pairs were recruited to this second cohort and serum concentration of vitamin E, selenium and LC-PUFA in maternal blood at 28 weeks gestation is being measured along with the assessment of infant cognition at 20 months. As with the other cohorts, this study is funded by the US National Institute of Environmental Health. It will also entail a more comprehensive analysis to include genotyping for genetic polymorphisms involved in the metabolism of mercury and LC-PUFAS. Initial results are

anticipated in 2014. Findings from the SCDS have helped to inform the joint Food and Agriculture Organisation of the United Nations and the World Health Organization (FAO/WHO) expert consultation, which involved a comparison of the health risks and health benefits of fish consumption based on the levels of nutrients (specifically LC-PUFAs) and contaminants present. Following a thorough review of the evidence, the panel concluded that maternal exposure to MeHg and other contaminants at a level below the provisional tolerable monthly intake of 70pg/kg body weight posed a negligible risk to neurodevelopment in infants (FAO/WHO, 2011). Furthermore, the expert consultation concluded that maternal fish consumption may lower the risk of suboptimal development compared to women who do not consume any fish. The group recommended that member states should emphasise the benefits of consuming fish and the risks of avoiding fish in relation to neurodevelopment of the offspring to women of childbearing age. The report calls for an update to dietary guidelines across the world.

Current evidence – where does that leave us?

Based on the most recent evidence from cohort studies, it seems that the health benefits that can be obtained from consuming fish outweigh the risks from contaminants. The research in the Seychelles has consistently reported no risk of maternal fish consumption on subsequent neurodevelopment and some benefits with respect to child development have been identified in those women who consumed the most fish during pregnancy compared to those women who consumed fewer fish. Fish should be acknowledged as a rich source of protein, omega-3 fatty acids, iodine, selenium and vitamin D. Although LC-PUFAs are required for optimal fetal development, current research regarding fish oil supplementation of pregnant women and infant health outcomes is inconsistent and therefore fish oil supplementation during pregnancy is not currently advised. However, fish consumption during pregnancy should be encouraged and improved communication strategies may be required to promote these benefits to all expectant mothers. This approach may require a change in policy and or educational strategies to ensure that mothers-to-be are fully aware of the benefits that can be obtained from fish consumption and that any information regarding how to maximise these benefits, while also minimising the risks, is communicated in a clear and consistent manner to avoid confusion amongst the general public.

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