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Scientific foundations of fish-consumption advice for pregnant women: Epidemiological evidence, benefit-risk modeling, and an integrated approach

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A B S T R A C T

Background: Pregnant women need fish consumption advice that increases seafood intake and simultaneously reduces methylmercury (MeHg) exposure. Two disciplines, epidemiology and benefit-risk modeling, can support such advice. Some current models suggest that fish consumption during pregnancy has only net beneficial effects. In contrast, many recent epidemiological studies have associated adverse effects on cognitive development with ordinary fish intake and MeHg doses routinely encountered by up to one in six US women of childbearing age. Proposed federal fish-consumption advice is based solely on a benefit-risk model. A more complete assessment integrating both types of evidence is needed.

Objectives and methods: The goal of this paper is to use a model to rank seafood items by their relative benefits and risks, producing consumer seafood choice recommendations that are also consistent with epidemiological observations. Recent epidemiological studies and benefit-risk models are reviewed, and model results are compared with one another and with epidemiological observations to identify commonalities that support inter-calibration.

Results and conclusions: Both approaches quantify MeHg doses at which harm slightly exceeds benefit. A model from the US Food and Drug Administration (FDA) predicts adverse effects at fish intakes containing, on average, more than 16 times the the US Reference Dose (RfD) for MeHg. Epidemiological results indicate that the RfD itself approximates a minimal adverse dose. This conceptual similarity allows FDA's model to be calibrated with the epidemiological results to generate fish intake recommendations that both the model and the epidemiology suggest should have substantially positive public health impacts.

1. Introduction

Fish consumption by women of childbearing age, especially during pregnancy, is a matter of substantial public health concern. (In this paper the terms “fish” and “seafood” are used interchangeably to encompass marine and freshwater finfish and shellfish.) Seafood is the principal dietary source of the omega-3 (n-3) polyunsaturated fatty acids (PUFAs), primarily Docosahexaenoic Acid (DHA) and Eicosapentaenoic Acid (EPA), essential for prenatal nervous system development (Hibbeln et al., 2007). But fish is also a source of methylmercury (MeHg), formed in the environment from inorganic mercury (Hg) emitted by natural and anthropogenic sources, and accumulated in aquatic food webs. MeHg is neurotoxic, and even mildly elevated exposure during gestation can damage the developing brain (Karagas et al., 2012).

Fish consumption during pregnancy thus poses significant benefit-risk tradeoffs for prenatal brain development. While nutritional guidelines urge 2–3 seafood meals (about 8-12 ounces) per week (DGA, 2015), the average American woman of childbearing age currently eats less than half that amount (FDA, 2014a). Concerns about MeHg appear to be one factor discouraging greater consumption (Lando and Lo, 2014).

An analysis of data from the National Health and Nutrition Examination Survey (NHANES) from 1999 through 2010 found that seafood intake among women of childbearing age remained stable, while blood Hg levels decreased moderately (Birch et al., 2014), which suggests that recent fish consumption advice has helped American women reduce MeHg exposure. On the other hand, the possible methylmercury exposure consequences of efforts to increase seafood consumption need careful assessment.

While advice simply to eat *more* seafood is important, *which types* of seafood women choose to eat also can affect health outcomes (Mahaffey et al., 2011). As Table 1 illustrates, popular fish

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Table 1
Omega-3 and mercury content of selected popular fish and shellfish varieties.[a]

Seafood Item	n-3 s, mg/100 g	Hg, μg/100 g
Sardines	1190	2
Salmon	1180	2
Herring, Anchovies	2020	5
Shrimp	350	1
Pollock	530	4
Clams	200	2
Tilapia	90	1
Flounder, Sole	300	8
Tuna, Canned Albacore	860	35
Tuna, Canned Light	270	13
Cod	160	9
Lobster	200	11
Swordfish	900	100
Shark	690	98
Orange Roughy	30	57

[a] Source of data, US FDA (2014a, Table V-8).

and shellfish types vary widely in both n-3 and MeHg content. In practical terms, a woman who doubles her fish intake without changing her seafood selections will double her doses of both beneficial n-3 s and potentially harmful MeHg. But a woman who switches from eating, for example, 100 g/week each of cod and canned light tuna to 100 g/week each of salmon and shrimp would almost quadruple her n-3 intake, from 430 to 1530 mg. She would also reduce her MeHg dose from 22 to 3 μg, and substantially increase the benefit-risk ratio of her seafood meals. Fish consumption advice can thus improve health outcomes most effectively not only by persuading women to eat fish more often but also by guiding them to choose varieties with more n-3 s and less MeHg, and to avoid or limit consumption of varieties with the opposite profile.

Advice for pregnant women on how much seafood of which varieties to eat should rest on scientific understanding of the comparative benefits and risks of consuming different seafood choices. Two types of evidence can support such recommendations: epidemiological studies of benefits and risks of fish consumption during pregnancy, and benefit-risk models.

Each type of evidence has advantages, disadvantages and limitations. Epidemiology deals only with associations between environmental exposures (e.g., to n-3 s and MeHg) and outcomes, and repeated concordant findings from similar studies are generally required to establish and quantify any particular relationship. Studies of neurodevelopmental effects of fish consumption during pregnancy are subject to mutual negative confounding; i.e., beneficial and harmful effects tend to offset or obscure each other, making it more difficult to measure outcomes in either direction (Budtz-Jørgensen et al., 2007). Further, it is not feasible in an epidemiological study to record in detail what fish varieties women ate at various points during a pregnancy, or to associate positive or negative developmental outcomes with any particular seafood choices.

Models, on the other hand, incorporate some epidemiological data and use assumptions and data about seafood constituents and intakes to estimate the benefits, harm and net effects of different fish consumption choices. They can be powerful tools for comparing and contrasting relative benefits and risks of consuming different fish varieties in different scenarios. However, a model is only as good as the data and assumptions fed into it by the modelers, decisions that are quite subjective and often arbitrary. While policymakers may be tempted to overlook the uncertain nature of model results, practitioners of the discipline are certainly aware of its limitations. The statistician George Box, an early modeler, famously quipped, “All models are wrong, but some models are also useful” (see Box and Draper, 1987).

Ideally, epidemiological evidence and benefit-risk modeling would be used complementarily to provide the fullest and most balanced evidentiary basis for fish consumption advice, but that has not been the case. Simply stated, the different approaches have led to different conclusions, and advice based on the two disciplines has also varied markedly.

For example, two prominent recent models (FAO/WHO, 2011; FDA, 2014a) both suggest that eating any amount of any fish during pregnancy almost always has only net beneficial effects on neurodevelopment. Fish consumption advice for pregnant women recently proposed by four US agencies is based only on results of these models; the proposed advice stresses increasing fish intake and downplays the need to manage MeHg exposure (DGAC, 2015; FDA, 2014b).

In contrast, more than a dozen epidemiological studies published since 2005 (enumerated in the next section) indicate that for a substantial minority of children, adverse neurodevelopmental effects of prenatal MeHg exposure can outweigh beneficial nutritional effects of maternal fish consumption. The same evidence suggests that even for children with net benefits, the beneficial effect is significantly larger when MeHg exposure is minimized. Consequently, many research teams have urged pregnant women to eat more fish, but have also stressed the importance of choosing low-Hg varieties (e.g., Ginsberg and Toal, 2009; Karagas et al., 2012; Lederman et al., 2008; Oken et al., 2005, 2008a; Orenstein et al., 2014; Sagiv et al., 2012).

In short, results of population studies and prominent models have differed; epidemiological evidence contradicts the models, and advice based on the different approaches has diverged. To ground fish consumption advice more soundly on science, it is essential to resolve this conflict between modeling and epidemiology, to weigh both types of evidence in a balanced and integrated way.

2. Methods

A review of evidence from both disciplines was conducted to identify commonalities that support a synthesis. A crucial concept in both approaches is the “minimal adverse dose” (MAD) of methylmercury. In epidemiology, the MAD is the exposure level above which adverse effects are first observed. One model, the FDA's, predicts an intake for each seafood variety (and thus, the MeHg dose it contains) above which adverse effects just begin to outweigh beneficial effects, i.e., a model-derived MAD. By comparing results of both approaches quantitatively, the model can then be re-calibrated with MAD estimates from epidemiology.

FDA's model also identifies weekly intakes of each seafood variety above which net adverse effects first occur; these can be taken as maximum permissible intakes for each fish type. After recalibrating the model with an epidemiologically-derived MAD, new maximum weekly intakes were calculated for each seafood item. Those results were then arrayed in a seafood-choice chart for pregnant women, sorting varieties in terms of permissible weekly servings.

The step-by-step analysis leading to that end point is presented in the sections that follow. The epidemiological evidence is first reviewed and summarized. Four benefit-risk models are then reviewed and compared with each other and with the epidemiological data. The quantitative re-calibration of the FDA model by comparing its MADs with those from epidemiology is then carried out to produce the consumer choice chart. Finally, results of this analysis are discussed and compared with other seafood-choice advice based only on risk-benefit models.