A Quantitative Analysis of Prenatal Intake of n-3 Polyunsaturated Fatty Acids and Cognitive Development

Joshua T. Cohen, PhD, David C. Bellinger, PhD, William E. Connor, MD, Bennett A. Shaywitz, MD

Abstract: Although a rich source of n-3 polyunsaturated fatty acids (PUFAs) that may confer multiple health benefits, some fish also contain methyl mercury (MeHg), which may harm the developing fetus. U.S. government recommendations for women of childbearing age are to modify consumption of high-MeHg fish to reduce MeHg exposure, while recommendations encourage fish consumption among the general population because of the nutritional benefits. The Harvard Center for Risk Analysis convened an expert panel (see acknowledgments) to quantify the net impact of resulting hypothetical changes in fish consumption across the population. This paper estimates the impact of prenatal n-3 intake on cognitive development. Other papers quantify the negative impact of prenatal exposure to MeHg on cognitive development, and the extent to which fish consumption protects against coronary heart disease mortality and stroke in adults.

This paper aggregates eight randomized controlled trials (RCTs) comparing cognitive development in controls and in children who had received n-3 PUFAs supplementation (seven studies of formula supplementation and one study of maternal dietary supplementation). Our analysis assigns study weights accounting for statistical precision, relevance of three endpoint domains (general intelligence, verbal ability, and motor skills) to prediction of IQ, and age at evaluation. The study estimates that increasing maternal docosahexaenoic acid (DHA) intake by 100 mg/day increases child IQ by 0.13 points. The paper notes that findings were inconsistent across the RCTs evaluated (although our findings were relatively robust to changes in the weighting scheme used). Also, for seven of the eight studies reviewed, effects are extrapolated from formula supplementation to maternal dietary intake.

Introduction

Because of evidence that prenatal exposure to methyl mercury (MeHg) in fish may adversely affect cognitive development, the U.S. Food and Drug Administration (FDA) and the U.S. Environmental Protection Agency issued a joint advisory in March 2004 recommending that pregnant women modify their fish consumption.1 However, fish is a rich source of n-3 polyunsaturated fatty acids (PUFAs). The n-3 PUFAs may confer protection against coronary heart disease (CHD) and stroke in adults, and may benefit cognitive development of the fetus during pregnancy.

Depending on how they are implemented, interventions to decrease exposure to MeHg may decrease overall fish consumption. For example, Oken et al.2 reported a 17% decrease in fish consumption among pregnant women following the release of the FDA’s 2001 MeHg advisory. Moreover, other members of the population could decrease their fish consumption as an unintended consequence of risk management actions targeting MeHg exposure among women of childbearing age.

In order to understand the possible public health ramifications of alternative risk management actions, it is necessary to quantify potential health benefits and risks associated with plausible changes in population fish-consumption patterns. This paper reviews the literature on the cognitive benefits of increasing n-3 intake in infants as a starting point for quantifying the benefits of maternal n-3 intake during pregnancy, since there is limited direct information on the relationship between maternal n-3 intake during pregnancy and cognitive development of the fetus. These benefits can then be compared to the risks associated with mercury exposure associated with fish consumption. This paper
quantifies the cognitive benefits of n-3 consumption in terms of changes in cognitive ability as measured by IQ. In particular, this analysis quantifies the permanent change in child IQ score per gram per day increase in maternal n-3 PUFA intake. Developing this estimate involves the aggregation of results across studies using different test instruments, extrapolation of impacts from early in childhood to later in life, and extrapolation of findings from studies investigating supplementation of baby formula with n-3 PUFAs to maternal intake of n-3 PUFAs during pregnancy.

Three other papers in this issue of the American Journal of Preventive Medicine develop dose–response relationships between prenatal MeHg exposure and IQ, and between adult fish consumption and both stroke incidence and CHD mortality. A fifth paper, also in this issue, combines these results to estimate the aggregate health effects of hypothetical changes in fish consumption on public health.

There have been at least two efforts to systematically review the literature on cognitive function and infant intake of n-3 PUFAs. However, those reviews are not sufficient for our purposes for two reasons. First, although they summarize the findings of different studies, these reviews do not quantitatively aggregate the findings so that they can be expressed in terms of a common metric (IQ points gained per gram per day of n-3 PUFA intake). Second, these reviews do not consider several recent studies that were not available at the time of their publication.

The remainder of this paper has three parts. The next section describes the methodology for aggregating information across studies that have measured this effect to quantify this relationship. The Results section reports the results in terms of the change in IQ associated with supplement intake. Finally, the findings are discussed and the dose–response relationship between IQ and maternal n-3 PUFA intake (IQ points per gram per day of n-3 maternal intake) is quantified.

Development of a Dose–Response Relationship for n-3 Intake and Cognitive Effects

Our methodology consists of three steps: identifying studies for inclusion in this analysis; aggregating the results and re-expressing them in terms of a change in IQ; and estimating the prenatal maternal intake of docosahexaenoic acid 22:6 n-3 (DHA) that produces an equivalent DHA internal dose to the child. Combining these results yields an estimate of the relationship between prenatal maternal DHA intake and the change in child’s IQ.

Literature Included in Analysis

The theory that different types of lipids may be critical to health in general and to early development in particular can be traced back to the 1920s. Because animals cannot synthesize n-3 PUFA, humans depend on their diet for this nutrient. Marine animals contain a relatively high concentration of n-3 PUFA because aquatic plants synthesize these molecules.

The n-3 PUFA molecule plays a crucial role in the brain, accounting for one third of the PUFA content of ethanolamine and serine phosphoglycerides in the brains of humans, monkeys, and rats. Studies have found that completely removing n-3 PUFA from the diet can adversely affect the nervous system in animals. For example, monkeys deprived of n-3 PUFA during the prenatal period suffer visual disturbances.

In human neonates, the debate over the essentiality of n-3 PUFA has often been argued in the context of whether infants fed breast milk are healthier than formula-fed infants (because breast milk contains n-3 PUFA), and in the context of whether infant formula should be supplemented with n-3 PUFA. Although some investigators have concluded that maternal diet influences the supply of n-3 PUFA to fetuses in utero, only one study was found that investigated the potential association between maternal n-3 PUFA intake during pregnancy and later cognitive development in offspring.

This review therefore also includes randomized trials of formula supplements for two reasons. First, as described below, there have been a substantial number of randomized trials that have investigated the association between n-3 PUFA intake during infancy and later cognitive development. Second, there is evidence that maternal n-3 PUFA intake influences n-3 PUFA concentrations in breast milk, and hence influences neonatal n-3 PUFA intake.

This investigation omits from consideration the two studies identified that have investigated the impact of formula supplementation on cognitive development in preterm infants. Studies of preterm infants are not directly comparable with studies of term infants because the benefits conferred by formula supplements may be greater for preterm infants than they are for term infants. For example, Fawcett et al. observed a statistically significant improvement in developmental test scores among preterm infants administered formula supplements (gestation <30 months), but not among infants with longer gestations. N-3 PUFA supplements may especially benefit preterm infants because they are deprived of the typical n-3 PUFA supply available in utero during the critical third trimester.

This analysis also limits attention to randomized trials, which make up the majority of the studies investigating this issue, and avoids the uncertainty due to confounding that is typically a much greater problem in observational studies. In particular, omitted...
Aggregation of Results Across Postnatal Development Studies

Development of a single estimate of an association between dietary supplements and cognitive function requires aggregation of scores both within and across studies. To accomplish this aggregation, each test used is first assigned to one of three domains: (1) general intelligence (Bayley Scales of Infant Development [BSID] Mental Development Index [MDI], Brunet-Lezine Developmental Quotient [DQ], problem solving, Knobloch Passamanik and Sherrards Developmental Screening Inventory [KPDS]), Fagan Test of Infant Intelligence [FTII], Kaufman Assessment Battery for Children [K-ABC], and Stanford–Binet IQ); (2) verbal ability (MacArthur Communicative Development Inventories, Peabody Picture Vocabulary Test-Revised [PPVT-R], mean length utterance); and (3) motor skills (BSID Psychomotor Development Index [PDI], and the Beery Visual-Motor Index test). We realize that many of the assessment tools classified here as measures of general intelligence are more appropriately described as tests of development (e.g., the BSID MDI). However, our classification reflects the finding that they are predictive of IQ performance at later ages.

Within each test domain, this analysis uses at most one set of results for each treatment group. In each case, the results recorded at the latest age are used. For example, Auestad et al.34 tested children at age 9 months using the FTII, and then at 12 months using the BSID MDI. Because both of these tests fall into the general intelligence category, the FTII results are omitted in favor of the BSID MDI scores, which were recorded at a later age. The FTII results are omitted in an effort to avoid “double counting” the results from the Auestad et al.34 study. The two studies that administered tests from the vocabulary domain16,35 reported two sets of scores—one for comprehension and one for expression. In these two cases, the analysis first normalizes the scores (see next paragraph) and uses the resulting average.

To combine results across studies within each test domain, the analysis first normalizes the difference between the supplement group scores and the control group scores so that they are expressed in terms of test-score standard deviations (SDs). For example, because the IQ test has a population SD of 15 points, a difference of 1.5 IQ points corresponds to a difference of 0.10 SDs. If population norm characteristics are not available, the distribution reported for the study sample is used to estimate the population SD.

Second, for studies that evaluated multiple formulas, both treatment groups are included. Typically, for example, one treatment group receives formula supplemented with fish oil, which contains DHA, while the other receives formula supplemented with egg-derived triglyceride (DTG), which contains both arachidonic acid (AA) and DHA.

Third, a weight is assigned to each result that is the product of its statistical precision (inverse of the normalized standard error [SE] squared), and an estimate of its correlation with IQ scores later in life. In a review of the literature, McCall40 concluded that the correlation between tests administered early in life (before age 30 months) and IQ tests administered later in life depended on the age at which the tests were administered. In general, the greater the difference in ages, the weaker the correlation. Moreover, McCall40 concluded that “[t]he first and strongest effect is that the correlations increase linearly with the age at which the infant test is administered.” Regressing the marginal median correlations that McCall40 identified (0.12, 0.26, 0.39, and 0.49) against the midpoint of the corresponding age ranges (1 to 6, 7 to 12, 13 to 18, and 19 to 30 months) suggests that the correlation with later IQ scores increases by 0.0176 per month (R²=96%). This linear relationship is used to assign weights to test results. For example, the weight assigned to a test result at age 24 months is twice the weight assigned to a test result at age 12 months.

The study conducted by Gibson et al.28 is eliminated from consideration because the investigators reported results only in terms of a correlation coefficient (between various DHA-level measures and BSID scores), and did not quantify the impact of DHA supplementation on BSID performance in terms of the points lost or gained for infants in the supplement group, compared to infants in the control group.

Finally, the domain averages are combined by assigning each domain a weight. Although attention could be limited to the “general intelligence” domain, or even to studies that used the IQ test in particular, doing so would omit consideration of data that probably provide some indication of how supplements might affect cognitive performance. The analysis therefore assigns some positive weight to the verbal ability domain and the...
 Ideally, the weights assigned to these other domains would correspond to the extent to which they are correlated with general intelligence. A search of the ERIC database (keywords “IQ” and “correlation” contained in any text field) did not yield any useful results. Based on our own subjective judgment, a weight of 0.6 was assigned to the verbal ability domain, and a weight of 0.2 to the motor domain.

In summary, the weighted average score change for domain k ($\Delta_k$) was computed as

### Table 1. Treatments and outcomes for studies considered

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Treatments</th>
<th>Outcome</th>
</tr>
</thead>
</table>
Treatment - Formula supplemented with AA (0.44%) and DHA (0.30%) | Age 4 mo. and 2 yr - Brunet-Lezine Developmental Quotient (DQ) |
| Gibson (1997)28 | Maternal diet supplements from day 5 through week 12 post partum.  
Five groups (0, 0.2, 0.4, 0.9, 1.3 g/day DHA)  
Maternal breast milk DHA concentrations: 0.1%–1.7% | Age 1 yr and 2 yr - Bayley Scales of Infant Development (BSID)  
Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) |
| Willatts (1998)29,30 | Controls - Standard formula  
Treatment - Formula supplemented with AA (0.3%–0.4%) and DHA (0.15%–0.25%) | Age 9 mo and 10 mo - Problem solving ability |
| Lucas (1999)31 | Controls - Standard formula  
Treatment - Formula supplemented with AA (0.30%) and DHA (0.32%) | Age 9 mo - Knobloch Passamanik and Sherrards Developmental Screening Inventory (KPSDSI)  
Age 18 mo - BSID MDI and PDI |
| Makrides (2000)32 | Controls - Standard formula  
Treatment 1 - Tuna oil formula supplement with DHA (0.35%)  
Treatment 2 - egg phospholipids formula supplement with AA (0.34%) and DHA (0.34%) | Age 2 yr - BSID MDI and PDI |
| Birch (2000)33 | Controls - Standard formula  
Treatment 1 - Formula supplement with DHA (0.35%)  
Treatment 2 - Formula supplement with DHA (0.36%) and AA (0.72%) | Age 18 mo - BSID MDI, PDI, and Behavior Rating Scale (BRS) |
| Auestad (2001)34 | Controls - Standard formula  
Treatment 1 - Egg derived triglycerides supplement with DHA (0.14%) and AA (0.45%)  
Treatment 2 - Fish oil and fungal oil supplement with DHA (0.13%) and AA (0.46%) | Age 6 mo - Fagan Test of Infant Intelligence (FTII), BSID MDI, PDI, Infant Behavior Questionnaire (IBQ)  
Age 9 mo - FTII, MacArthur Communicative Development Inventories (MCDI)  
Age 12 mo - BSID MID, PDI, IBQ  
Age 14 mo - MCDI |
| Helland (2003)16 | Controls - Maternal diet supplemented with 10 mL corn oil/day  
Treatment - Maternal diet supplemented with 10 mL cod liver oil/day  
Supplements administered from wk 18 of pregnancy through 3 mo postpartum | Age 4 yr - Kaufman Assessment Battery for Children (K-ABC) |
Treatment 1 - Fish oil supplement with DHA (0.25%)  
Treatment 2 - Supplement with DHA (0.12%) and AA (0.43%) | Age 12 mo - BSID MDI, PDI  
Age 14 mo - MCDI  
Age 39 mo - Stanford Binet IQ, Peabody Picture Vocabulary Test (PPVT-R), Beery Visual Motor Index, Mean length of utterance from 15–30 mins. of speech |

AA, arachidonic acid; DHA, docosahexaenoic acid; mo, month(s); wk, week(s); yr, year(s).
where $\delta_i$ is the standardized difference between the supplement group average score and the control group average score (positive value indicates superior performance among the supplement group subjects), $SE_i$ is the SE of $\delta_i$, and $Age_i$ is the age at which the subjects were assessed. The overall standardized impact on IQ was then calculated as

$$\frac{1}{1.8} \left(1.0\Delta_{GI} + 0.6\Delta_V + 0.2\Delta_M\right),$$

where the subscripts GI, M, and V refer to general intelligence, verbal ability, and motor ability, respectively.

### Extrapolation of Results to Prenatal Intake

The studies described above estimated the impact of n-3 intake on cognitive development in terms of the level of DHA supplementation in formula. As described in the technical appendix (located at www.ajpm-online.net), this analysis estimates that the impact on child IQ of a 1-g/day increase in maternal DHA intake during pregnancy is 18% to 39% of the IQ impact associated with a 1% increase in the DHA phospholipid fraction in either breast milk or formula. The appendix explains that to make this extrapolation, this analysis uses the child DHA phospholipid fraction in plasma (or, alternatively, in red blood cells [RBCs]) as a proxy for the biologically effective dose. In particular, it is assumed here that prenatal maternal DHA intake increasing the child plasma (RBC) DHA phospholipid fraction by 1% has the same impact on cognitive development as formula DHA supplementation that increases the child’s plasma (RBC) DHA phospholipid fraction by 1%.

### Results

#### Aggregate IQ-Equivalent Impact Observed in Reviewed Studies

Table 2 summarizes the study results used to estimate the aggregate impact of infant n-3 PUFA intake on cognitive function later in life. The weighted average changes for the three domains are 0.09 SDs (general intelligence), 0.08 SDs (verbal), and 0.05 SDs (motor). Assuming that these impacts correspond to a change in IQ, they amount to 1.3 IQ points (general intelligence), 1.2 points (verbal), and 0.8 points (motor). Combining the results across test domains yields a weighted average increase in test scores of 0.08 SDs, which corresponds to 1.2 IQ points.

#### IQ Points per 1% Increase in Formula or Breast Milk DHA Lipid Fraction

To estimate $\gamma$ (change in IQ per 1% increase in breast milk or formula DHA phospholipids fraction), this analysis assumes that the aggregate increase of 1.2 IQ points corresponds to the average level of DHA supplementation in the studies used here. All but one of the 12 supplement groups (Helland et al.16) listed in Table 1 that were used to develop this estimate reported DHA supplement concentrations. For these 11 groups, the average DHA fraction was 0.26% with an SE of 0.03%. Hence, $\gamma=1.2/0.26=4.6$.

#### IQ Points per Gram per Day Increase Maternal DHA Intake During Pregnancy

Our methodology implies that the impact on IQ of a 1-g/day increase in maternal DHA intake during pregnancy is equal to $\gamma$ multiplied by 18% to 39%. Hence, a 1-g/day increase in DHA intake during pregnancy will increase the child’s IQ by 0.8 to 1.8 points. For the purpose of this analysis, it is assumed that the arithmetic mean of these values (1.3 IQ points) represents the central estimate.

#### Sensitivity Analysis—Accounting for Age in Study Weights

As illustrated in Figure 1, the central estimate of 1.3 IQ points per gram per day of DHA intake during pregnancy is only modestly sensitive to the weighting scheme used. Each of the four pairs of bars represents one of the three test domains (general intelligence, verbal, and motor) and the weighted average of these domains. Within each pair, the white bar represents the estimate produced when the weight assigned to each study result reflects both the result’s statistical precision and the age at which cognitive development was evaluated. The gray bar represents the estimate produced when age is omitted from the weight. Although not illustrated in Figure 1, note that if all study results were assigned equal weight, the estimated aggregate impact on IQ would increase from 1.3 to 1.8 points per microgram of DHA intake per day. This result is omitted from further consideration because it does not make sense to disregard the statistical precision of the individual study results.

#### Sensitivity Analysis—Test Domain Weights

Figure 1 also indicates that the verbal and general intelligence domain values are similar to the weighted average, suggesting that only by substantially increasing the weight placed on the motor domain would the results change substantially. However, it is implausible that the motor domain would contribute a great deal of information to the estimation of IQ relative to the
verbal and general intelligence domains, so this alternative is omitted from consideration. Omitting age from consideration decreases the aggregate weighted estimate by less than 10%.

### Sensitivity Analysis—All Factors Considered

Finally, this analysis develops a range of values reflecting multiple sources of uncertainty. Factors considered

<table>
<thead>
<tr>
<th>Study (year)ref</th>
<th>Endpoint</th>
<th>Age (months)</th>
<th>Test standard deviationa</th>
<th>Pointsb</th>
<th>Normalizedc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General intelligence</strong></td>
<td>Brunet–Lezine DQ</td>
<td>24</td>
<td>8.7</td>
<td>1.0±2.4</td>
<td>0.11±0.27</td>
</tr>
<tr>
<td>Agostoni (1997)26</td>
<td>Problem solving</td>
<td>10</td>
<td>3.2d</td>
<td>2.5±1.0</td>
<td>0.77±0.31</td>
</tr>
<tr>
<td>Willatts (1998)30</td>
<td>BSID–MDI</td>
<td>18</td>
<td>15</td>
<td>1.0±1.7</td>
<td>0.07±0.11</td>
</tr>
<tr>
<td>Lucas (1999)31</td>
<td>BSID–MDI</td>
<td>24</td>
<td>15</td>
<td>4.0±5.0</td>
<td>0.27±0.33</td>
</tr>
<tr>
<td>Makrides (2000)32 (tuna oil group)</td>
<td>BSID–MDI</td>
<td>24</td>
<td>15</td>
<td>−2.0±6.1</td>
<td>−0.15±0.40</td>
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<tr>
<td>Makrides (2000)32 (egg group)</td>
<td>BSID–MDI</td>
<td>18</td>
<td>15</td>
<td>4.1±2.6</td>
<td>0.27±0.18</td>
</tr>
<tr>
<td>Birch (2000)33 (tuna oil group)</td>
<td>BSID–MDI</td>
<td>18</td>
<td>15</td>
<td>7.3±3.3</td>
<td>0.49±0.22</td>
</tr>
<tr>
<td>Birch (2000)33 (egg group)</td>
<td>BSID–MDI</td>
<td>12</td>
<td>15</td>
<td>−2.1±1.8</td>
<td>−0.14±0.12</td>
</tr>
<tr>
<td>Auestad (2001)34 (egg DTG group)</td>
<td>BSID–MDI</td>
<td>12</td>
<td>15</td>
<td>0.0±1.6</td>
<td>0.0±0.11</td>
</tr>
<tr>
<td>Auestad (2001)34 (fish/fungal group)</td>
<td>Kaufman–ABC</td>
<td>48</td>
<td>15</td>
<td>4.1±2.2</td>
<td>0.27±0.14</td>
</tr>
<tr>
<td>Auestad (2003)36 (fish oil)</td>
<td>Stanford–Binet IQ</td>
<td>39</td>
<td>15</td>
<td>−4.0±3.3</td>
<td>−0.27±0.22</td>
</tr>
<tr>
<td>Auestad (2003)36 (egg)</td>
<td>Stanford–Binet IQ</td>
<td>39</td>
<td>15</td>
<td>−2.0±3.4</td>
<td>−0.13±0.23</td>
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<tr>
<td><strong>Verbal</strong></td>
<td>MacArthur Test</td>
<td>12</td>
<td>12.2 (comp)</td>
<td>0.0±2.6 (comp)</td>
<td>−0.10±0.21</td>
</tr>
<tr>
<td>Auestad (2001)34 (egg DTG group)</td>
<td>MacArthur Test</td>
<td>12</td>
<td>15.6 (exp)</td>
<td>−3.0±3.2 (exp)</td>
<td>0.30±0.21</td>
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<tr>
<td>Auestad (2001)34 (fish/fungal group)</td>
<td>MacArthur Test</td>
<td>12</td>
<td>14.7 (comp)</td>
<td>3.0±3.0 (comp)</td>
<td>0.04±0.25</td>
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<tr>
<td>Auestad (2003)36 (fish oil)</td>
<td>PPVT–R (comp) and MLU morphemes (exp)</td>
<td>39</td>
<td>15.0 (comp)</td>
<td>−2.2±3.3 (comp)</td>
<td>0.12±0.24</td>
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<tr>
<td>Auestad (2003)36 (egg)</td>
<td>PPVT–R (comp) and MLU morphemes (exp)</td>
<td>39</td>
<td>0.87 (exp)</td>
<td>0.33±0.20 (exp)</td>
<td>0.18±0.16</td>
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<tr>
<td><strong>Motor</strong></td>
<td>BSID–PDI</td>
<td>18</td>
<td>15</td>
<td>0.5±1.2</td>
<td>0.03±0.08</td>
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<tr>
<td>Lucas (1999)31</td>
<td>BSID–PDI</td>
<td>24</td>
<td>15</td>
<td>7.0±5.5</td>
<td>0.47±0.36</td>
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<tr>
<td>Makrides (2000)32 (tuna oil group)</td>
<td>BSID–PDI</td>
<td>24</td>
<td>15</td>
<td>−1.0±5.9</td>
<td>−0.07±0.39</td>
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<tr>
<td>Makrides (2000)32 (egg phospholipids group)</td>
<td>BSID–PDI</td>
<td>18</td>
<td>15</td>
<td>0.8±1.7</td>
<td>0.05±0.11</td>
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<tr>
<td>Birch (2000)33 (tuna group)</td>
<td>BSID–PDI</td>
<td>18</td>
<td>15</td>
<td>3.1±1.5</td>
<td>0.21±0.10</td>
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<tr>
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<td>18</td>
<td>15</td>
<td>1.0±2.5</td>
<td>0.09±0.17</td>
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<tr>
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<td>12</td>
<td>15</td>
<td>−2.7±2.5</td>
<td>−0.18±0.16</td>
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<tr>
<td>Auestad (2001)34 (fish/fungal group)</td>
<td>BSID–PDI</td>
<td>12</td>
<td>15</td>
<td>−2.7±2.5</td>
<td>−0.18±0.16</td>
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<tr>
<td>Auestad (2003)36 (fish oil)</td>
<td>Visual Motor Index</td>
<td>39</td>
<td>1.2</td>
<td>−0.27±0.30</td>
<td>0.22±0.25</td>
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<tr>
<td>Auestad (2003)36 (egg)</td>
<td>Visual Motor Index</td>
<td>39</td>
<td>1.3</td>
<td>0.05±0.33</td>
<td>0.04±0.25</td>
</tr>
</tbody>
</table>

**Notes:**

- The population standard deviation was assumed to be 15 for the BSID, Kaufman–ABC, and Stanford–Binet IQ tests. For other tests, the population standard deviation was computed as \( \sqrt{\frac{(n_x+\bar{x}_n)^2}{n_x+n_n}} \), where \( n_x \) and \( n_n \) are the number of control group subjects and supplement group subjects, respectively, and \( \bar{x}_n \) and \( \bar{x}_n \) are the control group standard deviation and supplement group standard deviation, respectively.
- The standard error of the difference between the control group and supplement group scores is computed as \( \sqrt{(\frac{\bar{x}_n}{n_x})+(\frac{\bar{x}_n}{n_n})} \), where \( n_x \) and \( n_n \) are the number of control group subjects and supplement group subjects, respectively, and \( \bar{x}_n \) and \( \bar{x}_n \) are the control group standard deviation and supplement group standard deviation, respectively.
- The normalized values equal the results expressed in points (second column from right) divided by the test standard deviation (third column from right).
- The standard error is computed by assuming that the interquartile range reported by Willatts et al.29,30 represents ±1.35 standard deviations, and that the test scores are normally distributed.
- The result used is the precision-weighted average of the normalized comprehension (comp) and expression (exp) scores. The standard error (computed using the approach outlined in footnote b) amounted to around 0.21 for the MacArthur test results, and 0.24 for the set of tests used by Auestad et al.36

ABC, assessment battery for children; BSID, Bayley Scales of Infant Development; comp, comprehension; DQ, development quotient; exp, expression; MDI, mental development index; MLU, mean length of utterance; PPVT-R, Peabody Picture Vocabulary Test-Revised; SE, standard error.
include (1) the use of plasma DHA lipid fraction versus DHA lipid fraction (in RBCs) as dose proxy; (2) the value of weights assigned to the three test domains; and (3) consideration or omission of age at testing in the assignment of weights to results within each test domain. As noted above, the second of these factors has virtually no impact unless an implausible assumption is made (assignment of substantial weight to the motor domain, relative to the verbal and general intelligence domain for the purpose of estimating IQ effects). This factor is therefore omitted from consideration. Combining results from the other two factors produces IQ impacts ranging from 0.8 to 1.8 points per gram per day of DHA intake during pregnancy.

Discussion

Estimating the magnitude of this effect in the case of DHA is complicated by the disparity in the findings of the studies described in the Literature section. The disparities are particularly surprising given the fact that all of these studies were conducted as randomized clinical trials. Auestad et al. identified several potential explanations for the different findings, including: (1) differences in formula composition (amounts and ratios of different PUFAs); (2) the source of the DHA and AA supplements (e.g., egg phospholipids vs fish oil); (3) the age at which the tests were administered; and (4) differences in the types of tests used to evaluate cognitive function. To this list, this paper adds: (5) how and when the supplements were administered; and (6) random chance. Because there have been only seven clinical trials of formula supplements (representing 12 supplement groups) (Tables 1 and 2), it is not possible to evaluate definitively the role that any of these factors might play. (For the purpose of comparing results, this analysis omits from consideration one study by Helland et al. because it involved administration of cod liver supplements to the mothers during and after pregnancy, rather than direct supplementation of formulas administered to infants after birth. Although the findings reported by these authors are certainly relevant to the overall question of whether n-3 PUFA intake improves cognitive performance in children, the potential differences between this study and those investigating formula supplements complicates direct comparison of their findings.)

Formula Composition and AA/DHA Source

Restricting attention to the general intelligence findings (because a limited subset of studies evaluated motor and verbal performance), this analysis found no statistical difference between the impacts for groups receiving egg-derived n-3 PUFAs \((n=7, 0.15\pm SE 0.13 SDs)\) and the impacts for groups receiving supplements from animal tissue \((n=4, 0.07\pm SE 0.13 SDs)\). None of the PUFA concentration measures (percent AA, percent DHA, AA-to-DHA ratio) was significantly associated with test score impact reported in an analysis of variance that included these three quantities.

Age at Testing

In a second regression analysis, there was a significant association \((p<0.05)\) between test score impact and age at which supplementation was terminated, although the direction of this association was the reverse of what would be expected (i.e., increasing the duration of formula supplement administration was associated with a smaller impact on test scores). In a third regression analysis, the age at testing was marginally associated with the test score impact \((p=0.07)\), with the association becoming smaller at later ages. The direction of this association is plausible, but given the small sample size, it must be interpreted with caution.

Differences in Tests Used

This analysis has attempted to address this issue by grouping tests by domain and using subjective weights to account for the degree to which these domains inform estimation of the impact on IQ. As noted in the Results section, assumptions regarding these domain weights do not seem to have an important impact on the aggregate estimate. It is worth noting that this methodology does not account for differences among specific tests (e.g., differences in their reliability). However, because test domain relevance (a gross characteristic) appears to have limited influence on the aggregate findings, it seems unlikely that factors related to the characteristics of individual tests would be very important.

Extrapolation from Postnatal to Prenatal Intake

This paper assumes that prenatal and postnatal intakes having the same impact on a child’s DHA lipid fraction in
either plasma or RBCs will have the same impact on IQ. The plausibility of this assumption is bolstered by findings that n-3 PUFA supplementation has its most unambiguous impact on the neurologic function of preterm infants, as discussed in the introduction to this paper. Moreover, maternal PUFA status during pregnancy has an important impact on PUFA levels in newborns. For these reasons, it seems unlikely that prenatal n-3 intake would be less important than postnatal intake.

Random Chance

The strength of this analysis is that it reflects the results from a series of randomized control trials. These studies are generally less susceptible to systematic bias that can affect observational studies due to the difficulty of controlling for confounders. While the small sample size of some of the studies included here raises the possibility of chance confounding, it is important to keep in mind that this methodology places less weight on small studies (because their statistical precision is less than the statistical precision of larger studies).

Conclusion

This analysis finds that an increase in maternal intake of DHA during pregnancy of 1 g/day will increase child IQ by 0.8 to 1.8 points (central estimate of 1.3 points). Because typical DHA intake associated with fish consumption is well under 1 g/day, changes in fish consumption will result in IQ effects amounting to a fraction of a point. These differences are not clinically detectable. However, as with changes associated with exposure to neurotoxins like lead, which are also typically undetectable at the level of the individual, these changes can result in important impacts when aggregated over a population.

In interpreting this result, the factors complicating comparisons across studies mentioned earlier in this section must also be kept in mind, as well as the problems introduced by extrapolating these results (which predominantly reflect formula supplement studies) to the issue of maternal n-3 PUFA intake during pregnancy. Finally, these results reflect the extrapolation of results from a variety of test instruments administered very early in life to estimates of permanent changes in IQ later on. Nonetheless, the estimates developed here serve as a useful starting point for the purpose of quantitatively evaluating the cognitive benefits of maternal fish consumption, so that these benefits can be compared to the attendant risks resulting from prenatal exposure to mercury. That trade-off analysis is detailed in the final paper written as part of this project.

The expert panel convened by the Harvard Center for Risk Analysis for this project was chaired by Steven M. Teutsch, MD (Department of Outcomes Research and Management, Merck & Co., Inc., West Point PA). In addition to David Bellenger, William Connor, and Bennett Shaywitz, who are co-authors on this paper, the panel consisted of Penny M. Kris-Etherton, PhD (Department of Nutritional Sciences, Pennsylvania State University, University Park PA), Robert S. Lawrence, MD (Department of Health Policy and Management, Bloomberg School of Public Health, Johns Hopkins University, Baltimore MD), and David A. Savitz, PhD (Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill NC). This work was supported by a grant from the National Food Processors Association Research Foundation (NFPA-RF) and the Fisheries Scholarship Fund. Member companies of the NFPA-RF may be affected by the findings of research that funded my participation on the panel that wrote this paper.

References

A Quantitative Analysis of Prenatal Intake of n-3 Polyunsaturated Fatty Acids and Cognitive Development

Joshua T. Cohen, PhD, David C. Bellinger, PhD, William E. Connor, MD, Bennett A. Shaywitz, MD

Technical Appendix

The results section in the main text describes estimation of $\gamma$ in the equation

$$\Delta IQ = \gamma \times \Delta MilkDHA$$

where $\Delta IQ$ is the change in IQ in points, and $\Delta MilkDHA$ is the incremental DHA (decosahexanoic acid 22:6 n-3) fraction in formula or breast milk (in percent).

The goal is to estimate $\gamma^*$ in the equation

$$\Delta IQ = \gamma^* \times \Delta MomDHAIntake$$

where $\Delta MomDHAIntake$ is maternal prenatal incremental DHA intake (g/day). Setting the right side of these two equations for $\Delta IQ$ equal to each other and solving yields

$$\gamma^* = \gamma \frac{\Delta MilkDHA}{\Delta MomDHAIntake}$$

The equation for $\gamma^*$ can be solved by developing an expression for $\Delta MomDHAIntake$ in terms of $\Delta MilkDHA$. Here, it is assumed that a change in these two exposure measures yielding the same change in the child’s plasma or red blood cell DHA fraction are biologically equivalent. In particular, let us assume that $\Delta DHAFraction = \beta \times \Delta MilkDHA$ and that

$$\Delta DHAFraction = \beta^* \times \Delta MomDHAIntake$$

where $\Delta DHAFraction$ is the total DHA fraction in either plasma or red blood cells. Setting the right side of these two equations equal to each other yields

$$\Delta MomDHAIntake = \frac{\beta}{\beta^*} \Delta MilkDHA$$

Substituting this expression into the equation for $\gamma^*$

$$\gamma^* = \gamma \frac{\beta^*}{\beta}$$

yields $\gamma^* = \gamma \times \frac{\beta^*}{\beta}$. The remainder of this section estimates $\beta$ and $\beta^*$. The Results section reports the value of $\gamma$.

Data from Gibson et al.¹ are used to estimate $\beta$. Gibson et al.¹ measured the DHA plasma and erythrocyte fraction in breast-fed children whose mothers received DHA dietary supplements during the first 12 weeks post-partum. Appendix Table 1 summarizes their results. Regressing
the DHA fraction in plasma or erythrocytes against the DHA fraction in breast milk (SAS version 9.1 for Windows, procedure GLM, weighted by the standard error of the response variable, SAS Institute, Cary NC, 2004) yields $\beta = 4.68$ for plasma ($p<0.01$) and $\beta = 4.52$ for erythrocytes ($p<0.05$).

Data from Connor et al.$^2$ are used to estimate $\beta^*$. Connor followed women who received diets supplemented with either sardines or fish oil capsules during pregnancy. Subjects were enrolled between weeks 24 and 30 of pregnancy and continued to receive supplements through delivery. Total DHA intake averaged 59.4 g over the supplement period, which averaged 56 days. Taking the quotient of these two averages as an estimate of the daily supplement level yields approximately 1.1 g/day DHA. The authors reported that compared to the children of untreated women, the DHA fraction in plasma at delivery in the children of women who received supplements was 0.88% greater (2.35 ± 0.69 percent vs. 1.47 ± 0.29 percent, $p<0.01$). The corresponding value for the DHA fraction in red blood cells was a difference of 1.89% (5.97 ± 1.19 percent vs. 4.08 ± 1.13 percent, $p<0.01$). These results imply a value for $\beta^*$ of 0.83 (plasma) or 1.78 (red blood cells).

Table 1. Relationship between breast milk DHA levels and age 12-week total n-3 fraction$^a$

<table>
<thead>
<tr>
<th>Maternal DHA supplement (g/day)</th>
<th>Number of subjects</th>
<th>Total fatty acid fraction (percent) ± SD</th>
<th>Breast milk DHA</th>
<th>Plasma DHA</th>
<th>Erythrocyte DHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12</td>
<td>0.21 ± 0.07</td>
<td>4.7 ± 0.7</td>
<td>5.8 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>10</td>
<td>0.35 ± 0.04</td>
<td>6.3 ± 0.9</td>
<td>7.2 ± 0.8</td>
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</tr>
<tr>
<td>0.4</td>
<td>12</td>
<td>0.46 ± 0.16</td>
<td>6.9 ± 1.4</td>
<td>7.7 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>0.9</td>
<td>10</td>
<td>0.86 ± 0.24</td>
<td>8.1 ± 1.9</td>
<td>9.0 ± 1.5</td>
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</tr>
<tr>
<td>1.3</td>
<td>8</td>
<td>1.13 ± 0.33</td>
<td>9.1 ± 1.0</td>
<td>9.8 ± 1.2</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Source: Gibson et al.$^1$

All plasma DHA and erythrocyte DHA concentrations differed significantly at the $p<0.05$ level.
References
