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Hamazaki K, Matsumura K, Tsuchida A, Kasamatsu H, Tanaka T, Ito M, et al. Maternal dietary intake of fish and PUFAs and child neurodevelopment at 6 months and 1 year of age: a nationwide birth cohort—the Japan Environment and Children's Study (JECS). Am J Clin Nutr [Internet]. 2020 Nov 11;112(5):1295–303.

What We Know, Think We Know, or Are Starting to Know

We know that nutrition is an important determinant of successful pregnancies and healthy offspring. In the developed world, nutritional inadequacy of key nutritions - iron, iodine, selenium - remains common [1]. In the context of pre-natal and peri-natal nutrition, certain nutrient insufficiency risk factors are well-established, for example the 70% reduction in risk for neural tube defects from vitamin B9 [folic acid] supplementation in the 2-3 months pre-conception [2].

Other nutrients, in particular the long-chain omega-3 and omega-6 polyunsaturated fats, docosahexaenoic acid [DHA] and arachidonic acid [AA], are critical from around 20-24 weeks gestation into the third trimester and through the first 2-years of infancy to support a crucial developmental period, known as the "infant brain growth spurt" [3,4]. Data going back to the 1990's suggests that maternal diet, and the fatty acid composition of breastmilk, may have important influences on infant cognitive development [5].

However, there have also been suggestions in the literature that gestation, and therefore maternal diet, has a greater influence on cognitive development than breastfeeding. For example, in one study greater umbilical cord DHA levels, not breastmilk DHA levels, were associated with greater cognitive capacities at 11-months in full-term infants [6]. And although DHA receives much of the focus in the conversation about long-chain PUFA, there may also be critical roles for AA* and the balance of these respective omega-3 and omega-6 fatty acids. It has been suggested that the ratio of DHA to AA is important, with cognitive benefits from DHA observed with a 2:1 to 1:1 ratio of DHA:AA [7].

Generally, it is becoming more well-known that maternal fatty acid intake is an important factor, however, there are concerns about fish intake during pregnancy due to potential pollutants. In addition, it can be challenging to study cognitive development as it relates to maternal dietary intake, given the potential for factors like supplementation to come into play in family planning. Thus, prospective data remains of interest. The present study investigated the association between maternal fish intake during pregnancy and infant psychomotor development at age 6-months and 12-months.

*Geek Box: Arachidonic Acid

Poor arachidonic acid. This 20-carbon length long-chain fatty acid has the dubious distinction of having a final double-carbon bond 6th bonds from the end of the fatty acid, resulting in the ignominious "omega-6" moniker. Run for the hills! Omega-6 hysteria and poor chemistry sarcasm aside, AA is a critically important fatty acid for the human brain, particularly during developmental periods. Up to 60% of the brain's dry weight is fats, and of that up to 30% is comprised of polyunsaturated essential fatty acids [EFAs]. The omega-3 docosahexaenoic acid [DHA] comprises over 90% of omega-3 fatty acids in the brain, and AA is present in similar quantities. This ratio of nearly 1:1 in terms of brain fatty acid content may be important for the associated cognitive effects of these fatty acids. AA is crucial during the brain growth spurt period due to the rapid incorporation of AA [and DHA] into the brain. AA has a number of critical roles in the brain, including brain cell firing, signalling, and long-term potentiation, which is the strengthening of connections between brain cells associated with learning and memory. Levels of AA in the body are maintained at relatively constant levels. Mechanistically, the dietary essential omega-6 fat, linoleic acid [LA], may convert to AA, however we know that there is little conversion of LA to AA, even with massive levels of LA intake. Thus, most of the AA in the body is derived from maternal fat stores, and from triglyceride breakdown in the body. This means that the AA level of breastmilk may be maintained at constant levels without emphasising specific dietary intakes, while conversely DHA levels are much more variable and require dietary input to maintain sufficient levels. Interestingly, AA appears to be particularly critical for pre-term infants, and AA levels are a determinant of growth attainment in the first year of life in infants born pre-term with low birthweight. The balance of fatty acids for pre-term infants also appears to be important, with cognitive benefits of DHA observed when the percentage of fatty acids as DHA is half or equal to the value AA in infant formula, and attenuated where DHA exceeds AA. While DHA tends to receive the lions share of attention when it comes to fatty acids and brain health, the crucial role of AA in the early life stage should not be overlooked.

The Study

The Japan Environment and Children's Study [JECS] is a nationwide birth cohort [i.e., a group born during a defined period or even specific year and followed over the lifespan] in which pregnant women were recruited between 2011-2014. Mothers completed a 171 food item semi-quantitative food-frequency questionnaire at mid-late pregnancy and were asked to record intake for the period between confirmation of pregnancy and the second/third trimester. 21 food questionnaire items related to fish or shellfish. Daily intake of fish was calculated as grams per day, and Japanese food composition tables used to calculate the levels of omega-3 and omega-6 polyunsaturated fats [PUFA].

Infant psychomotor development was assessed using the Ages and Stages Questionnaire 3rd Edition [ASQ-3], which is a parent-completed screening tool to monitor infants for developmental delay. The ASQ-3 assesses 5 psychomotor domains:

1. communication;
2. personal social skills;
3. gross motor skills;
4. fine motor skills;
5. problem solving.

The assessment is scored on a 0-10 scale, with "yes" being a score of 10, "sometimes" = 5, and "not yet" = 0. Each domain contains 6 questions, and the threshold to pass screening is 2 standard deviations below the mean score [also known as a 'z-score', this is a population average and 2 SD either side of the mean would capture 95% of the population]. Thus, any score on or under 2SD below the mean would be a low score and indicate developmental delay.

if >2 questions in any domain were not answered, the participant was excluded from the analysis. The ASQ-3 was administered at 6-months [± 30-days] and again at 12-months [± 30-days]. Fish and PUFA intake was divided into quintiles [5 levels from lowest to highest], and compared to each domain of development in the ASQ-3. To set a threshold for low scores. Odds ratios* and 95% confidence intervals were calculated for the ASQ-3 scores according to quintile of fish/PUFA intake.

*Geek Box: Odds Ratios vs. Relative Risk & Hazard Ratios

In epidemiology, the outcome of interest is typically a categorical event, for example 'cerebrovascular stroke' which falls under the umbrella of 'cardiovascular disease'. In order to determine whether a particular exposure - for example fish intake - increases or decreases the risk of a particular categorical event occurring, statistical analysis is concerned with proportions, e.g., the proportion of events which occurred in a total sample of people. How this risk is expressed may differ based on the particular needs of the analysis, for example whether the timing of events is relevant or whether the outcome is rare. Risk may be expressed as a hazard ratio, relative risk, or odds ratio. Often these are conflated, and it is assumed that each are communicating the same quantification of risk. However, each are different in subtle but important ways. For example, hazard ratios are used to express risk of an event occurring at/after a specific time point in a study's follow-up period. Conversely, relative risk is concerned with the total number of events which occurred at the end of the study, and does not consider whether that risk was different at 5yrs or 10yrs. So, how does odds differ? The main distinction is that odds is the probability of an event occurring divided by the probability of an event <u>not occurring</u>, i.e., events vs. non-events. Risk on the other hand divides the number of events in an exposure group by the total number of participants in the exposure group. For example, let's say we have 100 participants in whom 30 had a stroke and 70 did not. The risk in this case would be 30/100 = 0.30; the odds would be 30/70 = 0.43. You can see these are different. To calculate relative risk here, we would calculate the risk in an exposed group [as we just did] and divide this by the risk in the comparison group. The 'relative risk' is therefore the ratio of risk in Group A vs. ratio of risk in Group B. Conversely, the odds ratio is the odds of an event in Group A vs. odds in Group B. The exact same data set would yield different values for relative risk and odds ratios. Generally, when an association between an exposure and outcome is positive [>1.0] or negative [<1.0], the odds ratio will be higher or lower than the RR, respectively. So why use odds ratio over relative risk? Primarily, odds ratio is preferable where the outcome event is rare, i.e., there are a low number of events in the comparison groups. If this is the case, then the odds ratio and relative risk will be similar. However, if not, the odds ratio will be higher or lower than the relative risk value, thus potentially being interpreted as a greater risk.

Results: Compared to low fish intake, women with high fish intakes tended to be older, have multiple children, higher education and income, be a current drinker, non-smoker, and more physically active. All of these potential confounding factors were adjusted for in the statistical analysis.

Fish:

- **6-months:** Women with the highest fish intake had a 12% lower odds of a low ASQ-3 score for problem-solving.
- **12-months:** Women with the highest fish intake had a 10% lower odds of a low ASQ-3 score for problem-solving, and 10% lower odds of a low ASQ-3 score for fine motor skills.

Omega-3 PUFA:

- **6-months:** Women with the highest omega-3 PUFA intake had a 16%, 13%, and 11% lower odds of a low ASQ-3 score for communication, fine motor skills, and problem-solving, respectively.
- **12-months:** Women with the highest omega-6 PUFA intake had a 14% and 21% lower odds of a low ASQ-3 score for fine motor skills and problem-solving, respectively.

Omega-6 PUFA

- **6-months:** Women with the highest omega-6 PUFA intake had a 17% and 16% lower odds of a low ASQ-3 score for communication and fine motor skills, respectively.
- **12-months:** Women with the highest omega-6 PUFA intake had a 9%, 11%, and 16% lower odds of a low ASQ-3 score for gross motor skills, fine motor skills, and problem-solving, respectively.

Omega-6:Omega-3 Ratio:

- **6-months:** Women with the highest ratio of omega-6:3 PUFA intake had a 14% higher odds of a low ASQ-3 score for problem solving.
- **12-months:** Women with the highest ratio of omega-6:3 PUFA intake had a 13% higher odds of a low ASQ-3 score for problem solving.

There were no significant differences in relation to other psychomotor domains relative to fish or PUFA intake.

The Critical Breakdown

Pros: Intakes of omega-3/6 were adjusted for total energy intake, which is important in epidemiological research as intake of nutrients correlates with total energy intake, i.e., adjusting for total energy yields a more direct association between the nutrient and outcome. There were participants in the cohort with no recorded fish intake, providing a wide contrast in exposure between the highest and lowest intake groups. Data was available for 81,697 mother-child pairs at 6-months, and 77,751 pairs at 12-months, thus this cohort contained a large sample size substantially greater than previous studies investigating the same relationships.

Cons: There was no data for specific omega-3 and omega-6 subclasses, i.e., DHA or AA. Given the positive associations for both omega-3 and omega-6 PUFA in isolation, but negative association for the omega-6:3 ratio, quantifying the actual levels fatty acids would have been helpful to try to reconcile these findings. In this regard, it could have been useful to have taken biomarkers of PUFA intake, although no study is perfect and this would have added additional expense. The psychomotor assessment, the ASQ-3, was parent-measured rather than researcher-measured, which introduces potential for bias.

Key Characteristic

The emphasis on fish as an exposure of interest provided an important addition to the literature, much of which is focused on maternal supplementation with specific fatty acids, e.g., DHA and/or AA. Public health advice for long-chain PUFA during pregnancy tends to recommend no more than 280g per week of low-mercury fish, with an additional 200-300mg/d DHA supplemented on top [8]. Mercury and other pollutants have been suggested to potentially impair cognition in offspring. In the present study, in a population noted for habitual fish consumption, the highest quintile of fish intake averaged 485g per week [69.3g/d], and there was no evidence of harm - indeed the opposite, with lower odds of poor scores in relation to communication, fine motor skills, and problem-solving in the highest quintile of fish consumption. At the other end of the lifespan, brain autopsy studies have also shown that although higher seafood intake correlates with higher brain mercury levels in healthy brains than brains of patients who died with Alzheimer's Disease, the healthy brains also exhibit lower neuropathology [9]. Taken together, there is research suggesting that the benefits of fish consumption may outweigh excluding fish due to concerns over potential pollutants.

Interesting Finding

The higher level of omega-6:omega-3 ratio was associated with increased odds of delay in problem solving skills. Digging into the data further, it is clear that there was a U-shaped curve evident: both the lowest omega-6:3 ratio and highest were associated with higher odds of delayed problem-solving, while the middle quintiles demonstrated a benefit. The authors highlight that this finding could in fact reflect pre-term infants, and this is a distinct possibility. Previous research has shown that a ratio of 2:1 or 1:1 of AA to DHA may be optimal for cognitive and psychomotor development, particularly in pre-term infants [(7,10)]. For example, an intervention in pre-term infants supplemented with infant formula fortified with either 2:1 or 1:1 AA to DHA found that the 2:1 formula resulted in greater psychomotor development during the first year of life, compared to the 1:1 formula [(10)]. Interestingly, however, there was no difference between the 2:1 and 1:1 groups in the plasma omega-6:3 ratio. It is important to remember that both the highest quintile of omega-6 and omega-3 intakes were each individually associated with significant benefit. It may be that this finding reflects pre-term infants not supplemented with the appropriate ratios of AA to DHA, but further research will be needed to tease this out.

Relevance

Family planning and birth control are much more widespread in the developed world, however unplanned pregnancies still happen and there is limited scope for pre-emptive or prophylactic nutrition intake at the individual level in this regard, i.e., it is prudent to consider dietary intake of key nutrients during reproductive years generally. The study demonstrates that higher levels of fish consumption than previously demonstrated in cohort studies are not associated with risk of harm, on the contrary high fish intake is associated with lower odds of poor psychomotor development over the first year of infancy.

In addition both omega-6 and omega-3 fats were individually associated with benefits, although we have no further detail on specific fatty acids within both of these PUFA types. The finding of an adverse effect of a high omega-6:3 ratio may not be a cause for concern in full-term infants, given that AA levels are maintained at a relatively constant level in the body. If the finding reflects pre-term infants, who are prone to developmental delays, then this may the fact that pre-term infants require specific formulations of AA to DHA to facilitate growth attainment and psychomotor development [(7,10)].

In the wider literature, it is evident that maternal DHA status is a vital determinant of infant cognitive development. The rapid accumulation of DHA and AA during the last trimester, and the fact that high DHA levels lead to longer gestation [(11)], are indicative of the importance high maternal DHA during this period. The rich source of preformed DHA that fish provides may explain the benefit to fish consumption in the peri-natal period, however, as no analysis of fatty acids was conducted with this study, we are left with inferences.

The present study confirms what is known on this topic, and converging lines of evidence support the role of PUFA in infant psychomotor development. What the present study adds is that higher levels than the recommended 280g/week may be safe for consumption during pregnancy, although advice to consume low-mercury fish remains valid and prudent.

Application to Practice

It is advisable to consume 2-3 servings (280-360g/week) of oily fish low in mercury per week, but additionally supplement with 200-300mg DHA/d through pregnancy and lactation [(8)]. This may also be preventative against preterm birth [(11)]. Where fish is excluded for individual considerations, supplementation with a direct source of 500-600mg/d DHA is preferable from 20-weeks gestation [fish oil or algae oil], either through maternal supplementation or infant formulas. Infant formulas are recommended to contain at least 0.2% and 0.35% DHA and AA, respectively [or 2:1 AA to DHA] [(11)].

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