Nutrition in the First 1,000 Days: DHA

Overview

Professor of Nutrition, **Susan E. Carlson, PhD**, emphasizes the importance of providing the essential fatty acids, DHA and ARA, for brain development and cognition. Sufficient dietary consumption of long-chain polyunsaturated fatty acids is vital throughout the first 1,000 days, especially during pregnancy and breastfeeding. Prenatal and postnatal DHA affects cortical visual acuity, sustained attention, problem solving ability, as well as brain structure and function. Dr. Carlson reviews the dietary recommended DHA intake for mothers and infants and outlines a balanced diet after infancy with foods that contain DHA.

Target Audience

This activity was developed for pediatric physicians, nurses, nurse practitioners, dietitians, and other healthcare providers who have an interest in newborns, infants and toddlers.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Associate DHA in the first 1,000 days with long-term cognitive outcomes
- Provide proper DHA dietary recommendations to mothers and infants in the first 1,000 days.

Faculty

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Faculty

Susan E. Carlson, PhD
Speakers Bureau: Mead Johnson Nutrition, Pharmavite

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The following have no significant relationship to disclose:
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This activity is supported by an independent educational grant from **Mead Johnson Nutrition**.

This activity is an online enduring material. It has been edited to meet requirements for online learning. Successful completion is achieved by reading and/or viewing the materials, reflecting on its implications in your practice, and completing the assessment component.

The estimated time to complete the activity is 1.0 hour.

This activity was released on December 23, 2020 and is eligible for credit through December 23, 2022.

Contact Information

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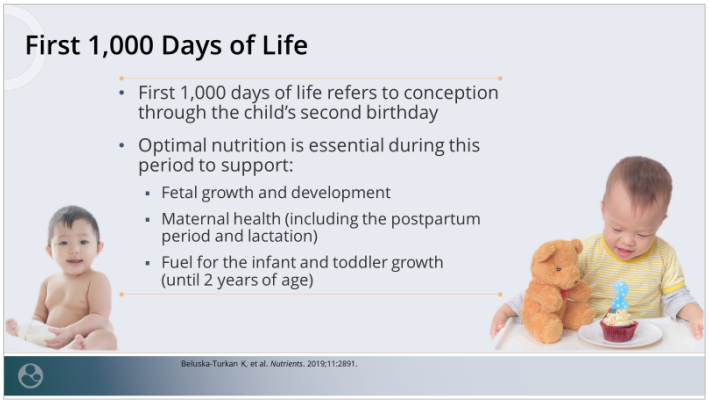
Editor's Note: This is a transcript of an audio webcast presented on December 9, 2020. It has been edited and condensed for clarity.

DHA and Cognitive Outcomes

Susan E. Carlson, PhD: I'm looking forward to sharing some of our data with you. Just talking about the first 1,000 days of life, which I know you're all aware, [is] that time from conception to about the second birthday of a child. That's the period of time I will be talking about today. Of course, optimal nutrition is essential during this period for fetal growth and development. But also, we're starting to be more aware that nutrition is having an impact on maternal health, including in the postpartum period and during lactation.

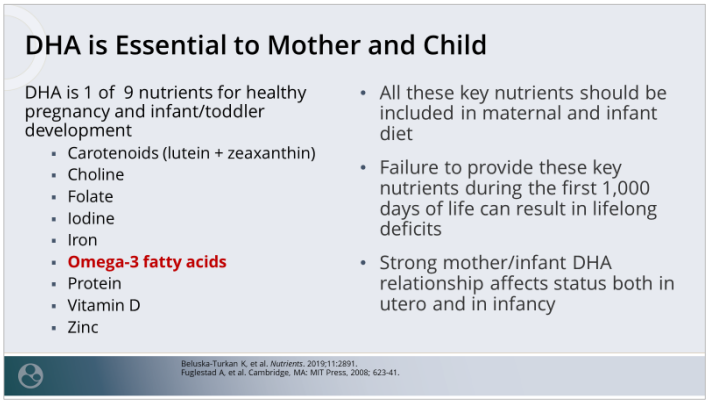


Slide 1 – First 1,000 Days of Life

Of course, nutrition is the fuel for the infant and their toddler growth until 2 years of age. We've focused for many years on growth almost exclusively, but now, and what we're going to be talking about today, is more about brain development. DHA [docosahexaenoic acid] is essential to mother and child. I've listed here [9] essential nutrients for healthy pregnancy and infant toddler development that are getting increasing attention these days, and of course omega-3 fatty acids are the ones we're focusing on today.[1,2]

They're getting attention because, and you'll hear me mention at the end of the slides, that choline and iodine, vitamin D... perhaps in the question and answer session... but these are all nutrients that we're increasingly aware may not be adequate in many pregnancies.

Of course, all essential nutrients, and there are many more than these [9], are essential to include in the maternal and infant diet. Failure to provide these during the first 1,000 days can result in lifelong deficit in brain function and also some of those long-term health issues, the chronic illnesses that occur in middle age.



Slide 2 – DHA is Essential to Mother and Child

Essential Micronutrients

We're aware that it's hard to do that in 1 study, but the data are increasingly coming out that these early years are setting people up for a lifetime of health, or maybe not such a healthy life. There's a strong mother-infant DHA relationship that affects the status both in utero and infancy, and we'll talk about that.

The first 1,000 days of life, DHA, iron, vitamin D are micronutrient essentials. These should be included in prenatal supplements. They are really important building blocks, in addition to some of the other nutrients I showed you on the previous slide [Slide 2]. As I said before, we're going to focus today on DHA, specifically on DHA and cognitive development. What I want to talk about is why

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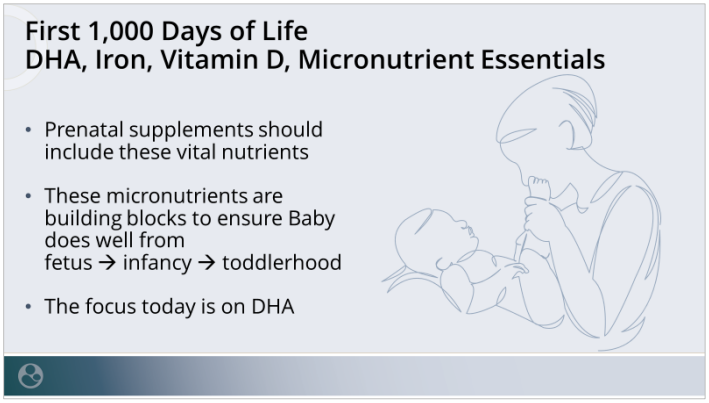
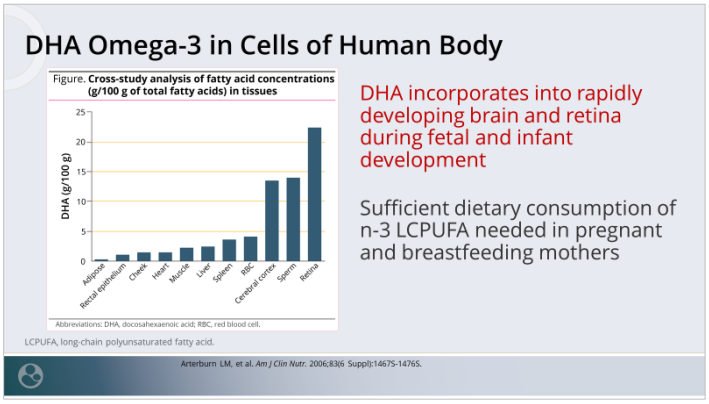
might DHA be important for fetal and infant development.



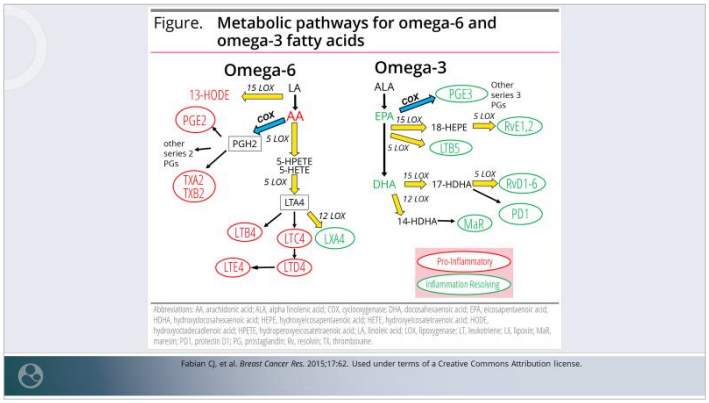
Slide 3 – First 1,000 Days of Life – DHA, Iron, Vitamin D, Micronutrient Essentials

Many of you may be aware that every cell in the body has a different level of DHA that tends to accumulate there, although there's a range related to the nutritional status of the person around this nutrient. As you can see on the slide [Slide 4], in the cerebral cortex and in the retina, those are 2 tissues that are particularly concentrating in terms of DHA concentration. We know that DHA incorporates rapidly in the developing brain and in the retina during fetal and infant development.[3] We're going to talk in a minute about what are the factors that influence that accumulation.



Slide 4 – DHA Omega-3 in Cells of Human Body

I want to just show you this very busy slide, and really if you'll just focus on LA [linolenic acid] and ALA [alpha linolenic acid], the 2 black fatty acids, the parent of the omega-6 and omega-3 families. These are converted to arachidonic acid (ARA), which is also an important fatty acid in the brain—although one we're not talking about today. The ALA, or alpha linolenic acid, is converted to EPA, and then onto DHA.[4] While I'm focusing more on the structural components of these fatty acids in membranes of different cell types in the body, you can see that there are many metabolites that are formed from them, and one of my interests is in how DHA reduces early preterm birth. I'll come back to that at the end.



Slide 5 – Metabolic pathways for omega-6 and omega-3 fatty acids

Many of these metabolites that come from DHA, including immune-modulating things that shut down inflammation, are actually of great interest to our group at the moment because we are very interested in why DHA might reduce early preterm birth. We know it does. But let's go back to the brain. One of the reasons I wanted to show you that pathway is we have it, but ALA is very poorly converted to DHA. Even with 1000 mg of ALA, a gram per day, only about 20–40 mg can be converted to DHA. As you will see, as we begin to talk about amounts here, 20–40 mg is a very small amount of DHA, lower than probably what is needed and certainly what we think is needed in pregnancy.

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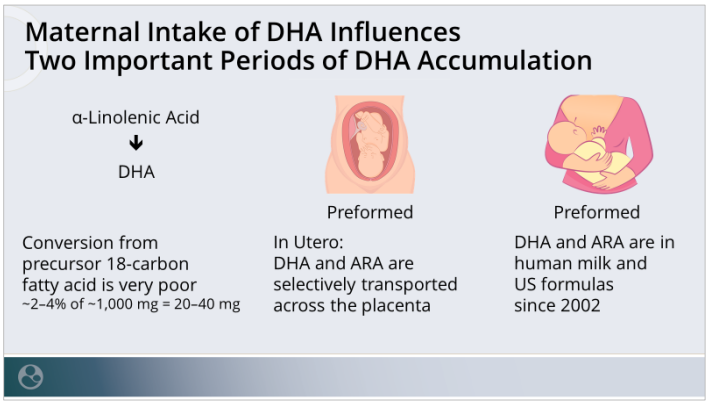
The 2 important periods for maternal DHA status to influence the fetus are the in utero period. We know that DHA and arachidonic acid are selectively transported across the placenta. That means they're selectively and preferentially... there's a very important mechanism to enhance the transfer of those fatty acids. We do know that some things can influence that, like smoking, for example, and maybe diabetes, maybe obesity. But for the most part, the placenta wants to get those to the fetus.

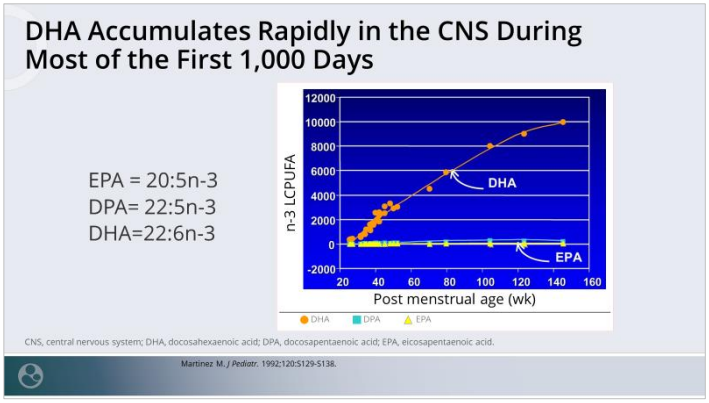
Subsequent to birth, we know that human milk provides DHA and arachidonic acid. In fact, all human milk has DHA and arachidonic acid. The difference there is that the mother's diet, or her DHA intake, is very critical in how much DHA will be in her milk.



Slide 6 – Maternal Intake of DHA Influences Two Important Periods of DHA Accumulation

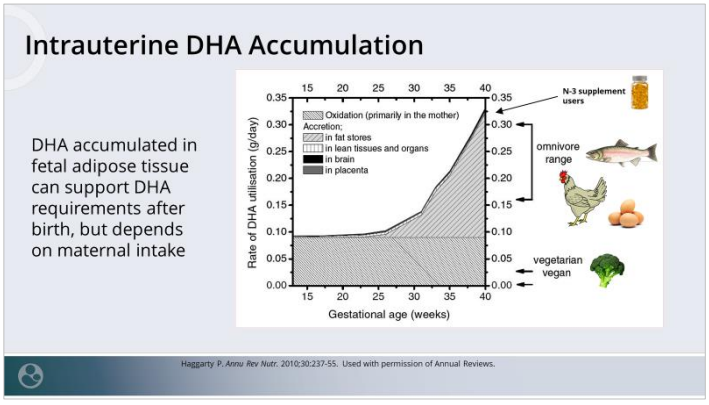
Since around 2002, we began to add DHA and arachidonic acid to US infant formulas. Currently that is the standard for formulas in the United States, although there are differences in concentration in some of the formulas. We'll be talking again about those levels.

In a healthy pregnancy, and this was data from Manuela Martinez's work that she did in Spain many years ago in infants who died of accident after term birth, or some of these were in utero, as well.[5] This is starting about 23 weeks gestation all the way through about 2 years of life, and she's showing how DHA accumulates in the brain as opposed to the other omega-3 or n-3 fatty acids that are on that pathway to DHA.



Slide 7 – DHA Accumulates Rapidly in the CNS During Most of the First 1,000 Days

It's important to understand (and we're not talking about the preterm infant today), but if you look at the bottom on the x-axis [Slide 8], the gestational age in weeks, and on the y-axis, the amount of DHA that's being consumed by the mother. In US women, we've done this in several studies, consume on average from their diet about 60 mg of DHA per day, which puts them below that line that would suggest much accumulation is going to the fetus. But what you can see is that if an infant is born between 20 and 25 weeks gestation, they have almost no accumulation of DHA, and that's not just the brain. The flash lines in the figure show the adipose tissue accumulation of DHA.[6]



Slide 8 – Intrauterine DHA Accumulation

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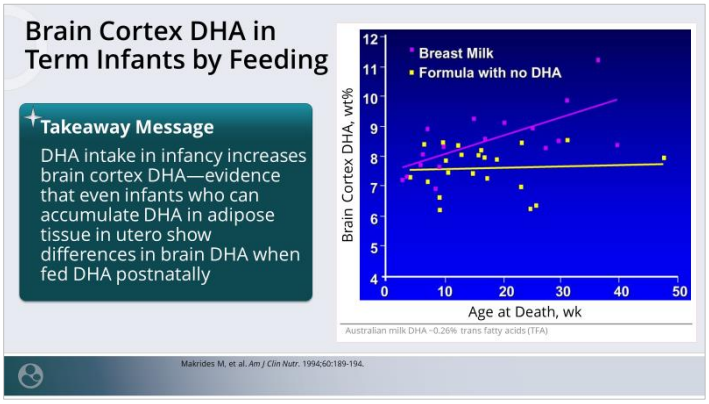
It's assumed that if a mother has a good intake—and what's shown here is maybe between 150 and 300 mg of DHA per day per infant—will accumulate DHA stores in utero in the adipose tissue. But we do know that, and this is data from Maria Makrides many years ago, a study done in Australia, of an infant born at term and dying, again they died accidentally.[7] (Those were the kinds of deaths.) You can see [Slide 9, figure] the yellow dots represent DHA accumulation in the brain of infants who were fed formula. At that time infant formulas did not contain DHA as opposed to human milk, which **all human milk, as I said before, does include DHA.**



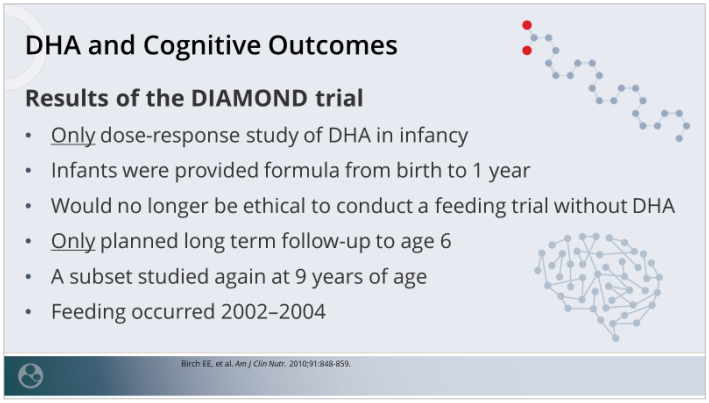
Slide 9 – Brain Cortex DHA in Terms Infants by Feeding

The takeaway message from this slide is that **DHA intake in infancy increases brain cortex DHA**. Evidence that even infants who can accumulate DHA in adipose tissue in utero do show differences in brain DHA when fed DHA postnatally.

Visual and Cognitive Outcomes

I want to spend some time talking about a trial we did a number of years ago. We've been publishing on this trial over all that time because the children reached 9 years of age several years back. We did some additional analysis with them.

Looking at DHA and cognitive outcomes and the results of the DIAMOND trial. The DIAMOND [DHA Intake And Measurement Of Neural Development] trial is the only dose response study of DHA in infancy.[8] It was supported by Mead Johnson nutrition, who is the sponsor of this program.



Slide 10 – DHA and Cognitive Outcomes

Infants were provided formula from birth to 1 year. I want to point out, it would no longer be ethical to conduct this feeding trial without DHA, but this trial began in 2002 just as the infant formula companies in the US were beginning to add DHA to their formulas, and it's the only planned long-term follow-up to age 6. We've studied, again, a subset at 9 years of age, but the main feeding study occurred between 2002 and 2004.

In the trial, **the primary reason for conducting this trial was to look at visual acuity**. It was done at 2 sites: Dallas, Texas, with Eileen Birch, and I was the PI [principal investigator] at the Kansas City site. There were 343 exclusively formula-fed infants in that trial. We measured visual acuity out to a year. The primary outcome was cortical visual acuity, which means what the brain is seeing, not what the eyeball is seeing.

A secondary outcome was cognitive development, which we negotiated as part of our consideration to participate in the trial. We said we wanted to enroll enough infants in Kansas City to look at their long-term cognitive development.

There were 4 levels of DHA. One formula had no DHA, and I'll talk about that formula as the control formula in the subsequent slides. And then there

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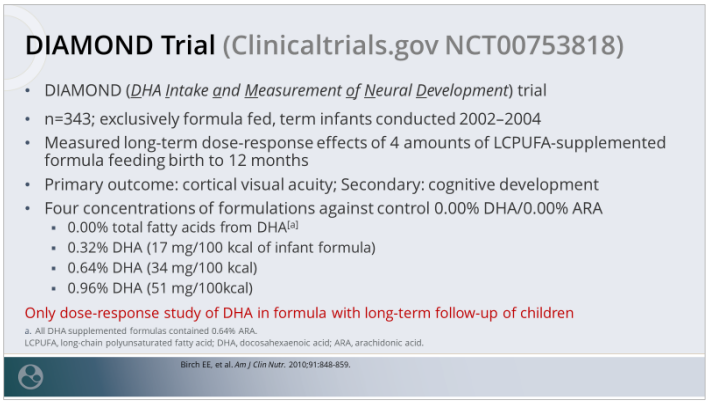
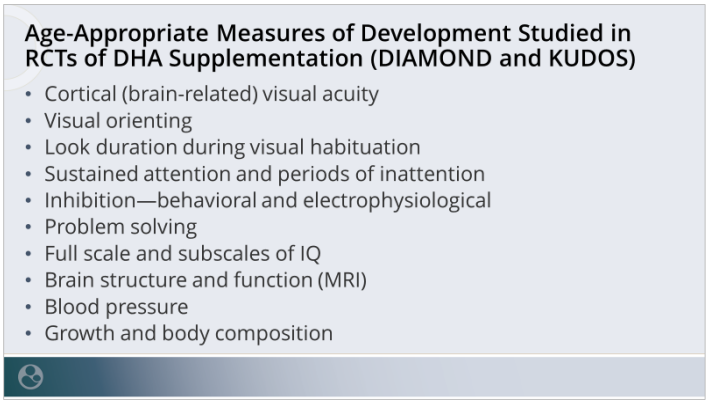
were 3 levels of DHA: 0.32, 0.64, and 0.96. You should know that in the US currently, 0.32 would be the desired level to have in an infant formula. But this was a study designed to see if we needed to add more DHA in the infant formula than was currently in it.



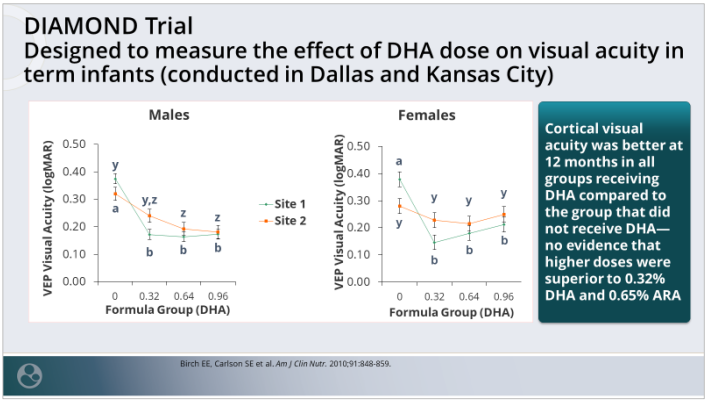
Slide 11 – DIAMOND Trial

We did some age-appropriate measures of development that were studied in the DIAMOND trial. I'm going to talk a little bit about another trial we did with prenatal DHA supplementation to Mom's, the KUDOS [Kansas University DHA Outcomes Study] trial that began in 2006. In those trials we looked at the cortical visual acuity, visual orienting look duration during visual habituation.[8]



Slide 12 – Age-Appropriate Measures of Development Studied in RCTs of DHA Supplementation

These are all cognitive tests. Sustained attention, periods of inattention, inhibition, both behavioral and electrophysiological. We looked at problem solving, full scale and sub scales of IQ, brain structure and function, MRI only with the DIAMOND trial, blood pressure, growth, and body composition.



Slide 13 – DIAMOND Trial – Designed to measure the effect of DHA dose on visual acuity in term infants

What we found on the visual acuity—and that was published some years ago—these are shown [Slide 13] with different colors because of the 2 sites, but the bottom line in this trial was that **visual acuity looked better at 12 months in all of the groups that received DHA compared to the group that did not receive DHA**. Just to make sure you understand, the lower logMAR means higher visual acuity. This goes in the opposite direction of what you might expect. The 3 formulas that contain DHA, those infants all had higher visual acuity than the infants in the formula without DHA.

Age-Relevant Assessments

We went on to do some of these cognitive assessments I mentioned a moment ago. This just shows you [Slide 14] the ages at which we conducted those assessments in infancy. We looked at visual habituation. These are specific and age relevant time points, I should point out. We looked at the Bayley scales of infant development at 18 months. We looked at tests of inhibition called Stroop [tasks],[8] and another called the dimensional change card sort, which I'll talk about in a moment.

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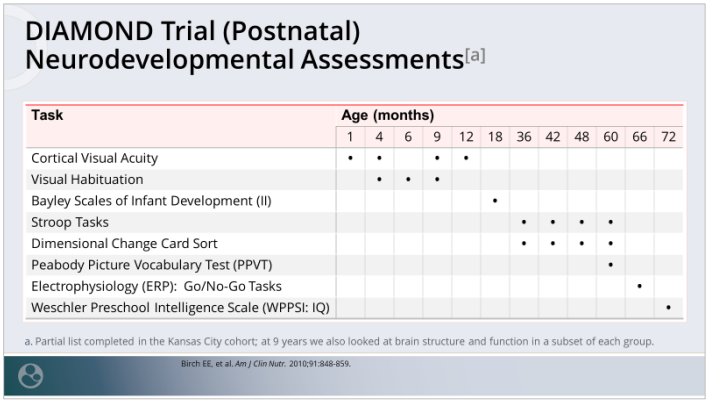
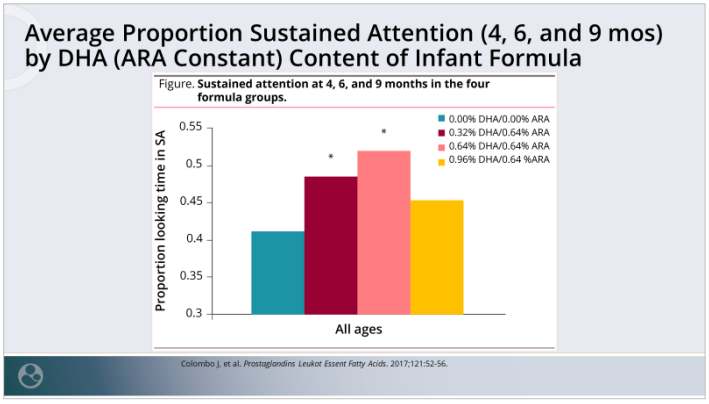


Slide 14 – DIAMOND Trial (Postnatal) Neurodevelopmental Assessments

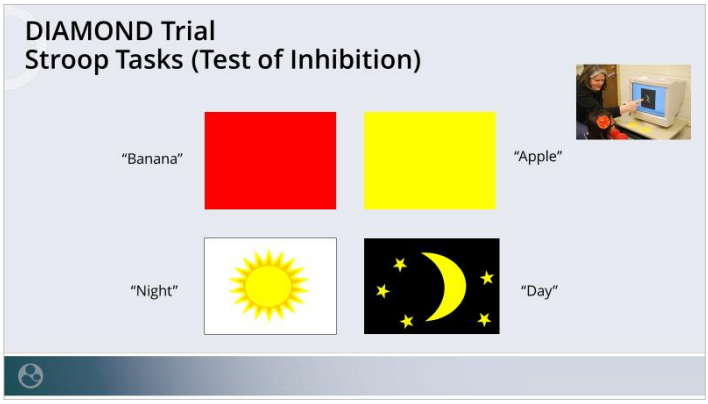
Then at 5 years of age and 6 years of age, we looked at verbal IQ, and later at 5 we were looking at electrophysiology at 5½. We did the full scale WPPSI [Wechsler Preschool and Primary Scale of Intelligence] at 6 years of age. This is just a partial list of some of the things we looked at, in addition, as I mentioned before, we brought back about half of the infants at 9 years to look at brain structure and function.



Slide 15 – Average Proportion Sustained Attention by DHA Content of Infant Formula

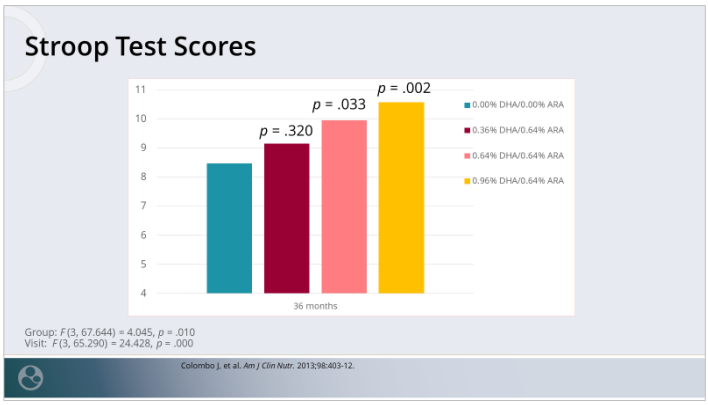
Attention Predictor

In infancy, attention is one of the things that you can measure that is actually a predictor of long-term cognitive function. As you can see from this, all 3 of the DHA supplemented groups did better than the control group. Only 2 of them reached statistical significance but they were all better, higher. And when the children were 3, we did a test of inhibition that involves the child understanding that the sun would be associated with day and the stars with night, or the yellow would be associated with banana and the red with apple. When they are pointed to on the screen, if they see the stars and the moon, they're supposed to say "Day." They're supposed to inhibit what they have already learned.



Slide 16 – DIAMOND Trial Stroop Tasks (Test of Inhibition)

On that test, again, we saw superior performance with all 3 of the DHA supplemented groups compared to the control group.



Slide 17 – Stroop Test Scores

Neurodevelopment Assessment

A more sophisticated test of inhibition is one where you teach the child a learning rule, and then you change the rule, and then they have to inhibit what

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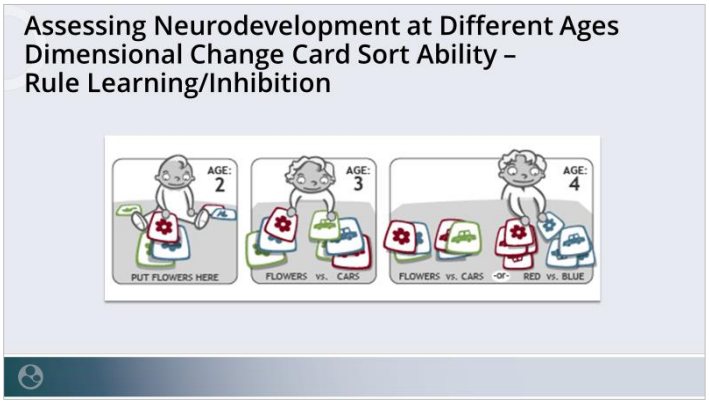
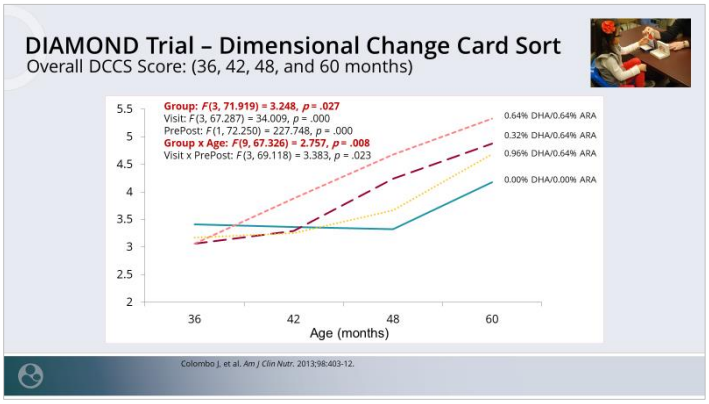
they've learned just then and make the other choice. For example, if you have a bunch of cards with flowers and cars, you can ask the child to put the flowers in 1 pile when they're 2 [in pairs], and they can probably do that pretty well. By the time they're 3, they should be able to sort flowers from the cars, and by the time they're 4, they should be able to learn 1 rule to sort it by flowers and cars and then switch over to the color, for example.



Slide 18 – Assessing Neurodevelopment at Different Ages Dimensional Change Card Sort Ability – Rule Learning/Inhibition

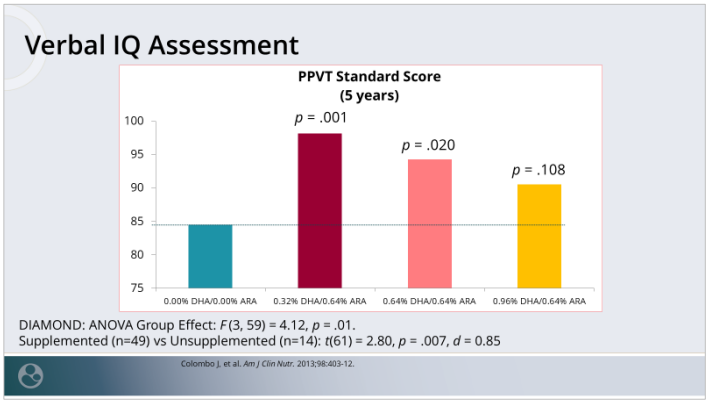
And again, what we found was the blue line shown here [Slide 19], which is the control group that didn't receive DHA, you can see they were not performing as well as any of the 3 groups that received DHA. Some of these were doing far better than we would have expected. The 0.64 group actually was pulling away from the other groups as early as 3½ years of age.[9]



Slide 19 – DIAMOND Trial - Dimensional Change Card Sort

Verbal IQ Assessment

Then, at 5 years of age we looked at verbal IQs. And you can see again [Slide 20], all 3 of the DHA-supplemented groups are superior to the group in blue. I want to point out one thing that might make this even more startling to you, and that is the mothers were performing like the blue group, and the mothers in all 4 groups were performing. This was a low SES [socioeconomic status] group of mothers who had chosen formula feeding. Basically, their verbal IQ was not as good as maybe a middle-class or upper-middle-class population.



Slide 20 – Verbal IQ Assessment

And then at 6 years, we did the WPPSI, or the Weschler Preschool Primacy Scale of Intelligence.[9] Again, the blue is the combined supplements group here [Slide 21] because we put different scales across the bottom in the verbal IQ and full-scale IQ at the end. What we found was the supplemented group were performing, again, on verbal IQ and on full-scale IQ.

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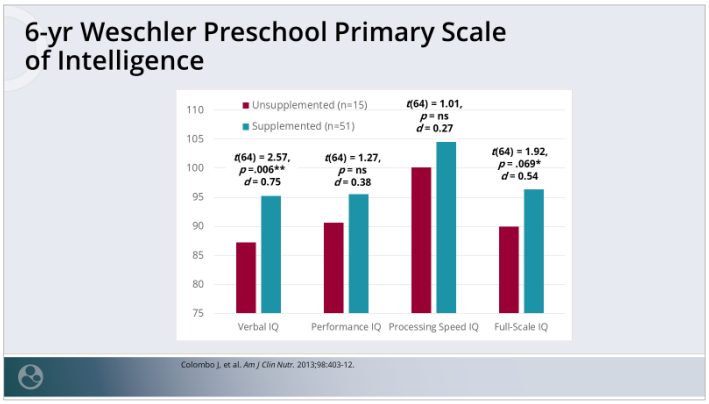
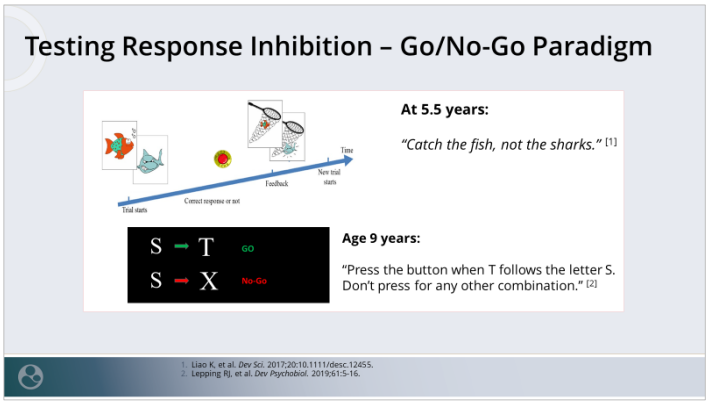


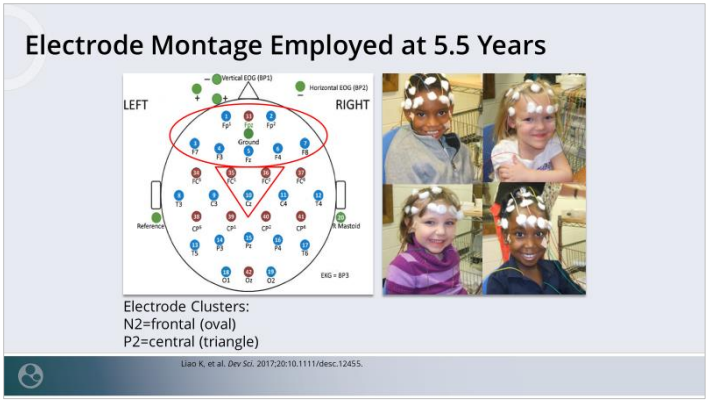
Slide 21 – 6-yr Weschler Preschool Primary Scale of Intelligence



Slide 23 – Testing Response Inhibition – Go/No-Go Paradigm

Reaction Time

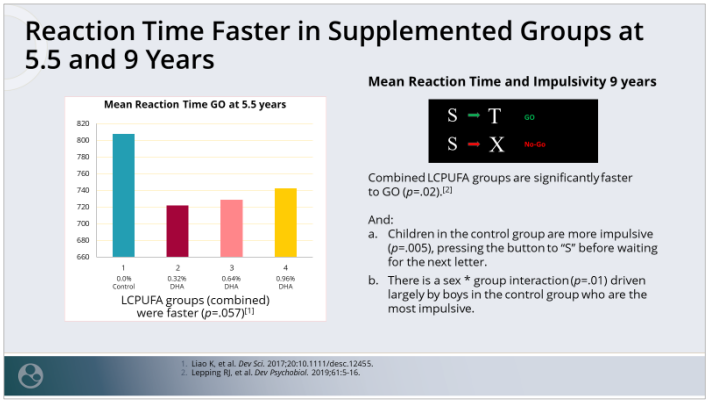
One of the other things we've been very interested in is it's not just looking at behavioral tests but also looking at how is the brain responding to various stimuli. Again, we can do tests of inhibition using things like a Go/No-Go task, which I'll show you in a moment. But with the electrode montage, this diamond in the middle is the central response. When a child looks at a visual stimulus, they're trying to decide what's going on. The action part is this frontal part that's shown in the oval.[10]



Slide 22 – Electrode Montage Employed at 5.5 Years

We've done a response of inhibition task that involves a fish and a shark, and a button press. The child is told to inhibit pressing the button if they see a shark, but to press that button if they see the fish.

We've done something similar, and I'll talk about this as well, at 9 years of age in the MRI. We did another Go/No-Go paradigm, which was press the button when T follows the S, but don't press it if you see an X or a G or a W or some other letter come up besides the T. These are different paradigms we've used on these same children at 5½ and 9 years of age. One of the things we found was that the reaction time in the supplemented group was faster, both at 5½ and 9 years of age. These are for the children who get the right answer. These are children who do the task correctly.



Slide 24 – Reaction Time Faster in Supplemented Groups at 5.5 and 9 Years

But we also found that children in the control group are more impulsive. They press the button to the S before waiting for the next letter. There was a sex group interaction on that given largely by boys in

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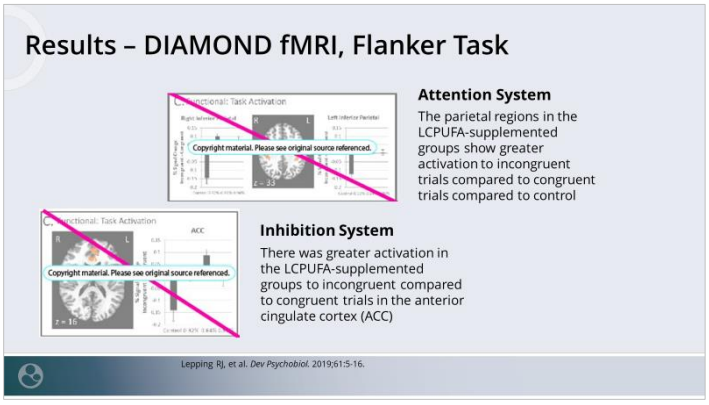
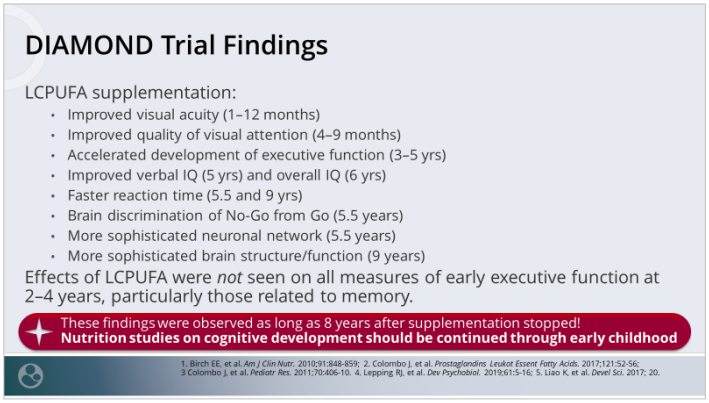
the control group who are the most impulsive pressing the button before the letter shows up.

We also, at 9 years of age, with the fMRI, we've done a Flanker task, which looks at the attention system and the inhibition system in terms of showing incongruent and congruent trials. Again, we find that the brain is operating differently in those 3 groups that received DHA compared to the 1 that you see in the first line here [Slide 25] that did not get DHA.[11]



Slide 25 – Results – DIAMOND fMRI, Flanker Task

The DIAMOND trial findings I mentioned improved visual acuity, but what we've done in Kansas City, we've found improved quality of visual attention in the first year, accelerated development of executive function in 3–5 years mostly around these tasks of inhibition, improved verbal IQ and overall IQ at 5 and 6 years, faster reaction times at 5½ and 9 years. I haven't shown you this baby yet, but the brain discrimination of No Go from Go at 5½ years and more sophisticated neuronal network at 5½ years, and more sophisticated brain structure function at 9 years.[8–11,12,13]



Slide 26 – DIAMOND Trial Findings

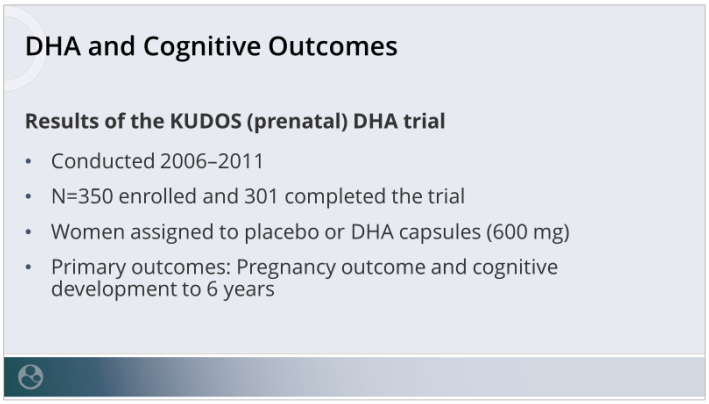
The effects of LCPUFA [long-chain polyunsaturated fatty acids], I want to point out, were not seen on all the measures of early executive function that we did, particularly around memory. We didn't find a lot that suggested DHA was affecting memory. It's more affecting those behaviors surrounding inhibition and attention. The take home here, that these findings were observed as long as 8 years after supplementation stopped.

Nutrition studies on cognitive development really should be continued through early childhood, but we have very few of those, and certainly none that have so consistently brought children back every 4–6 months to actually do an outcome task.

KUDOS Trial

I want to turn from this and talk about the results of the KUDOS trial, which was a prenatal DHA trial. I want to point out it was conducted between 2006 and 2011. You will note that this was some years after we began to provide DHA to infants postnatally, either through formula or through human milk. There were 350 women in this trial and 301 completed the trial. They were randomly assigned to either a placebo oil that had no DHA or DHA capsules that contained 600 mg.

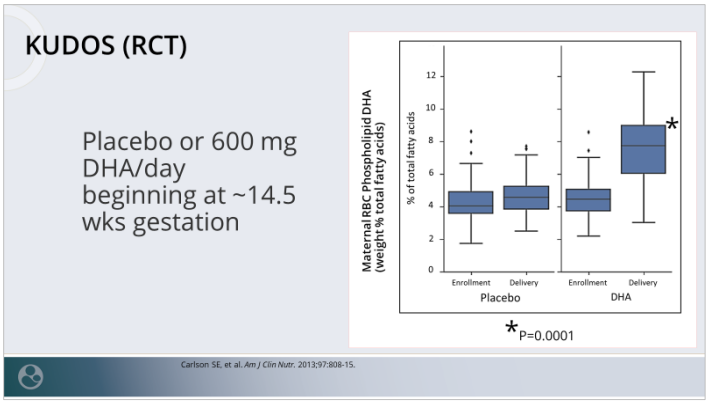
Nutrition in the First 1,000 Days: DHA



Slide 27 – DHA and Cognitive Outcomes

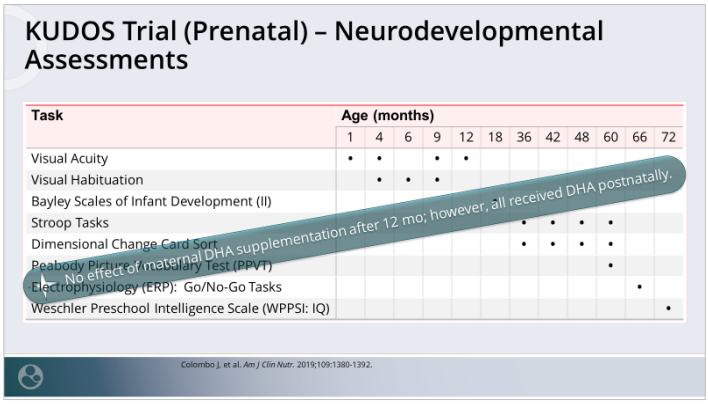
The primary outcomes were pregnancy outcomes. We were looking at things like gestation duration, weight/length at birth, early preterm birth, etc, and cognitive development to 6 years of age.

We did the same battery of tests, basically, that we did in the DIAMOND trial in these children. This [Slide 28] is to show you where women's status was in the placebo group and where they ended, which was somewhere around 4.3%–4.5% DHA in the red blood cells.[14] That's where the DHA group started, but they of course finished much higher because they were supplemented with DHA.



Slide 28 – KUDOS (RCT)

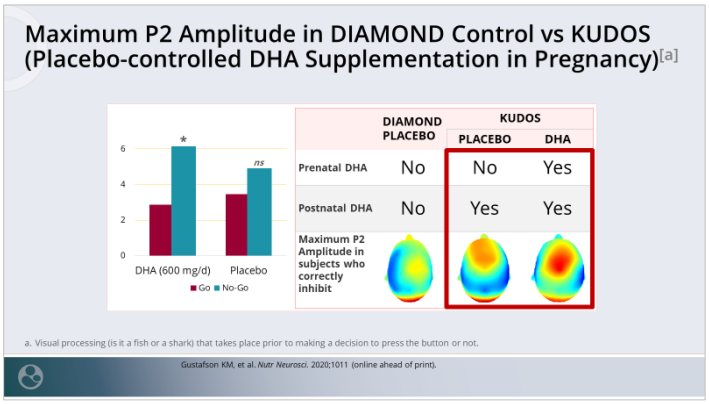
A disappointing thing of this trial was that we didn't find an effective maternal DHA supplementation after 12 months. We did find some signals in the first 12 months, but we don't know really what this means other than all of the infants received DHA postnatally, so it could be that they got adequate DHA accumulation from that postnatal supplementation. However, we find some differences in the brain. I want to show those to you because the way the brain was responding was different.



Slide 29 – KUDOS Trial (Prenatal) – Neurodevelopmental Assessments

I'll walk you through this slide. If you look over where the bars are [Slide 30, left], you can see that the children in that task I showed you with the button press, this is all visual processing in the maximum P2 amplitude. It's the visual processing. Is it a fish or is it a shark that takes place prior to making a decision to press the button or not? It's well prior to pressing. What we saw was that the children of the mothers who were given the DHA (shown in blue) had a much higher amplitude, a different amplitude than the control on the No-Go than to the Go. They're supposed to be seeing that there's something they have to inhibit, and we expect a higher amplitude when they have to inhibit. That is indeed what we found in the DHA group. In the placebo group, this difference was not significant.[15]

Nutrition in the First 1,000 Days: DHA



Slide 30 – Maximum P2 Amplitude in DIAMOND Control vs KUDOS

Now, if I take you over to the red box on the right, I've put this in terms of the KUDOS trial [the Kansas University DHA Outcomes Study]. Of course, prenatally the placebo did not get DHA in this trial but there was a DHA supplemented group. Both of these groups receive postnatal DHA, but you can see there's a greater intensity—the orange color in the visualization of what's going on in this contrast between Go and No-Go.

Then I take you outside of the box to the DIAMOND placebo group, and you can see that these infants who didn't get prenatal DHA and did not get postnatal DHA looked very, very different from either of the groups in the KUDOS trial. This is one of the reasons we speculate that there may be an advantage to getting postnatal DHA, and maybe why we didn't see such a big difference behaviorally between the placebo and DHA in the KUDOS trial.

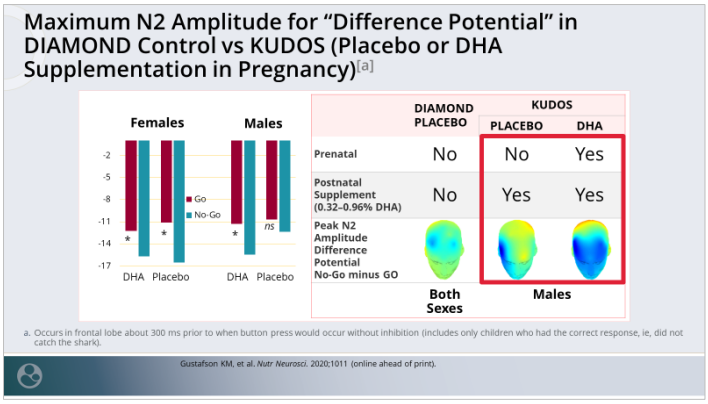
Difference Potential

The N2 is the different potential in the amplitude during the time the child is determining… this is occurring in the frontal about 300 milliseconds instead of about 700 milliseconds prior to the button press. This is the data [Slide 31] from only the children who had the correct response, that is they did not catch the shark.

Here we found something very interesting with the sex of the child. The female children had this difference potential, whether their mothers got DHA or whether they got the placebo. If you're looking over here at the bars on the left. Among the males though, if the mother got DHA, they showed the expected difference potential. But if the mothers got the placebo, they did not show that difference. It was not significant.

Over here in the red box, again, it's the same comparison I showed you in the previous slide but without the females included because, obviously, they were good responders. They looked like this DHA supplemented males. Again, you can see prenatal supplementation made a difference in the males' brain connection there.

Again, I take you to the outside of the box the DIAMOND placebo. This is both sexes from the DIAMOND trial where there was no prenatal and no postnatal supplementation. So, no obvious differences in cognition, but it seems we've built a better functioning brain.



Slide 31 – Maximum N2 Amplitude for "Difference Potential" in DIAMOND Control vs KUDOS

One of the other things that came out of the KUDOS [trial], which I want to mention, is that early preterm birth was dramatically reduced in the group who got the 600 mg of DHA compared to the placebo.[14]

You can see 4.8% vs 0.6%. There was 1 early preterm birth in the DHA group. This got us pretty excited—enough to write an NIH trial we just completed in

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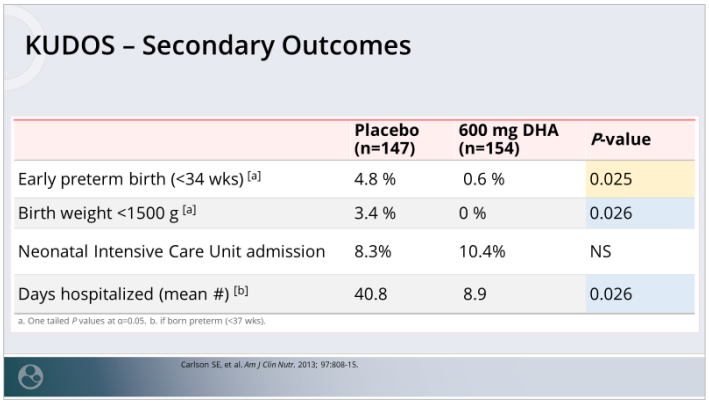
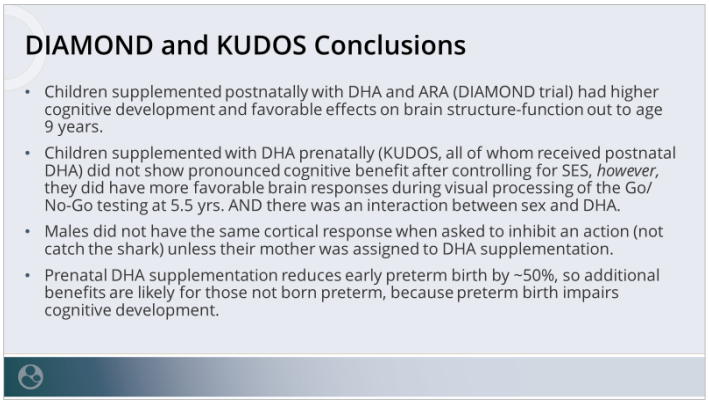
the past month, with 1100 women assigned to 200 or 1000 mg of DHA to look at the effective dose on preterm birth. Those data will be coming out soon, but I could tell you they are supporting the Cochrane review that came out in the fall of 2018, which shows at least the 42% reduction in birth before 34 weeks in women who receive a DHA supplement of a significant amount say in the range of 500–1000 mg.[16]



Slide 32 – KUDOS – Secondary Outcomes

Conclusions from DIAMOND and KUDOS Trials

Children supplemented postnatally with DHA and arachidonic acid, which is the DIAMOND trial, had higher cognitive development and favorable effects on brain structure function out to age 9.[8]

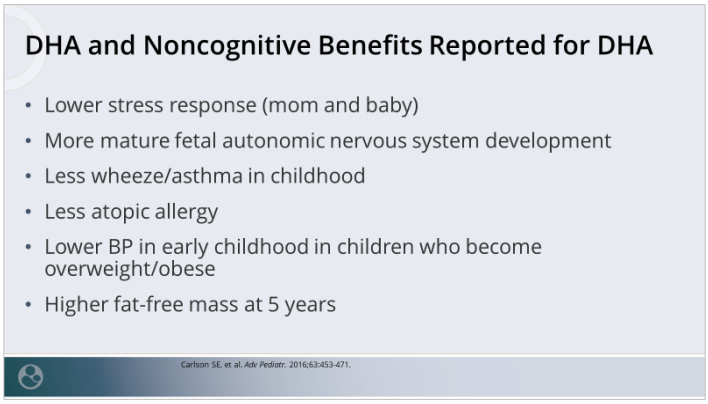


Slide 33 – DIAMOND and KUDOS Conclusions

Children supplemented with DHA prenatally in the KUDOS—all of whom received postnatal DHA—did not show pronounced cognitive benefit after we controlled for SES (socioeconomic status).[14] I did not mention this, but before we controlled for SES, we did see a relationship between higher DHA and cognition on those measures I showed you. But one of the things we learned is that some of our higher SES moms were better at taking their supplements than our lower SES moms. After we controlled for SES, we couldn't determine if it was DHA or SES. As you know, SES includes maternal education and probably a lot of stimulation for the child. We know that mothers who are more educated, their children perform better on cognitive tests. It was completely confounded in that way. However, we did find even after controlling for these, we did find more favorable brain responses during visual processing on the Go/No-Go testing at 5½ years.

We did find an interaction between sex and DHA suggesting that males were having more trouble with this inhibition in terms of seeing the difference between the Go and the No-Go.

Prenatal DHA supplementation reduces early preterm birth by about 50%. Additional benefits are likely for those not born preterm because preterm birth impairs cognitive development, and that's well known.



Slide 34 – DHA and Noncognitive Benefits Reported for DHA

DHA and Non-Cognitive Benefits

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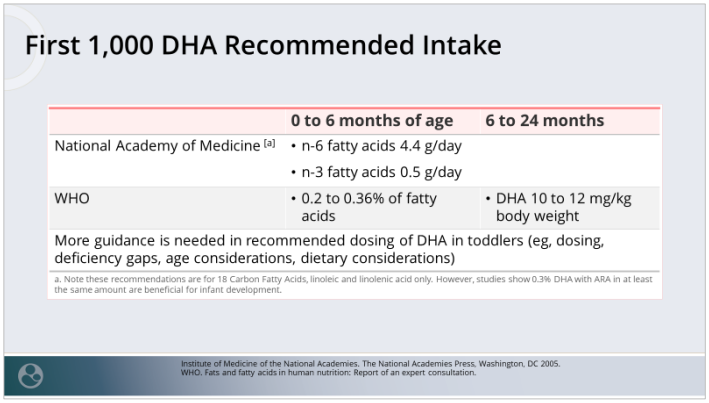
I didn't talk about some of the other things that have been reported around DHA and some of the noncognitive benefits reported for DHA. These we've talked about in a review article that's referenced here.[17] There are various degrees of evidence around all of these, but they all suggest there's a benefit of DHA for other aspects of physiology for mom and/or baby. One of those is lower stress response done by my friend, who is a psychologist at University of Chicago, Kate Keenan, [PhD]. She has been interested in DHA and whether that can reduce stress in mom and baby.

More mature fetal autonomic nervous system development, which is work that's been carried out by my collaborator, Dr. Kathleen Gustafson here in Kansas City, doing a number of assessments on the fetal development: autonomic nervous system development, less wheeze/asthma in childhood has been reported, less atopic allergy, lower blood pressure in early childhood in children who become overweight or obese from the KUDOS trial, and higher fat-free mass at 5 years of age.

Best Practices

There's some report throughout all of these topics, but not enough yet that people consider them strong evidence. The best practice guidelines to ensure maternal and infant DHA intake… the National Academy of Medicine, as many of you know—certainly the dietitians, if they're listening to this will know—that our National Academy of Medicine makes recommendations on N-6 and N-3 fatty acids,[18] but these are strictly around linoleic acid and alpha linolenic acid, both 18-carbon precursors of arachidonic acid and DHA, which we know conversion is very low.

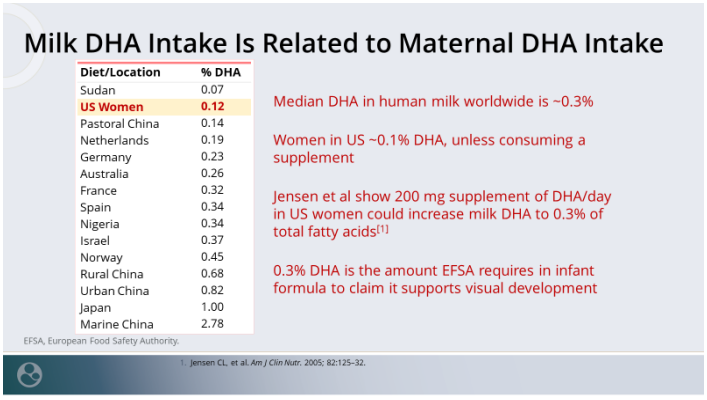


Slide 35 – First 1,000 DHA Recommended Intake

There are a number of us now working hard to try to get some recommendations for the actual long chain polyunsaturated fatty acids that are produced from these precursors. The WHO does make a recommendation around DHA of 10–12 mg/kg body weight for infants who are 6–24 months.[19]

DHA In Human Milk

Milk DHA intake is related to maternal DHA intake. I mentioned at the beginning that US women have a low DHA content in their milk unless they're consuming DHA. You can see that's in the range of pastoral China or Sudan, places where people are not eating a lot of fish or even any kind of good animal protein. But in the US, it's due to the low fish intake.



Slide 36 – Milk DHA Intake Is Related to Maternal DHA Intake

The median DHA in human milk worldwide is 0.3%. This is why infant formulas were developed around

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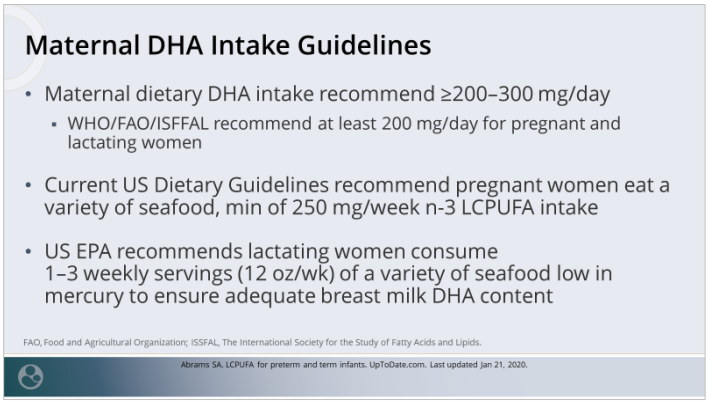
this level of 0.3%–0.32%. Craig Jensen showed some years ago that women who consume a supplement of 200 mg of DHA per day can increase their milk DHA up to that 0.3% or so.[20] That would be a recommendation, certainly, for a woman who was trying to lactate, that she be consuming a supplement of a couple of hundred milligrams of DHA per day unless she's willing to eat seafood. And we'll talk a little bit about that in a minute.

The 0.3% DHA, interestingly, is the amount that the European food safety folks require in infant formula to make a claim that the formula supports visual development.

Maternal DHA Intake Recommendations

Maternal DHA intake, again, these recommendations exist that maternal dietary DHA intake should be between 200–300 mg per day. We are maybe going to be challenging that after the results of the trial we just finished and the ORIP trial that was just finished in Australia about a year ago.[21] But WHO, FAO [UN Food and Agriculture Organization], and ISFFAL, which is the International Society for the Study of Fatty Acids and Lipids recommend at least 200 mg per day for pregnant and lactating women. We think that's a start.

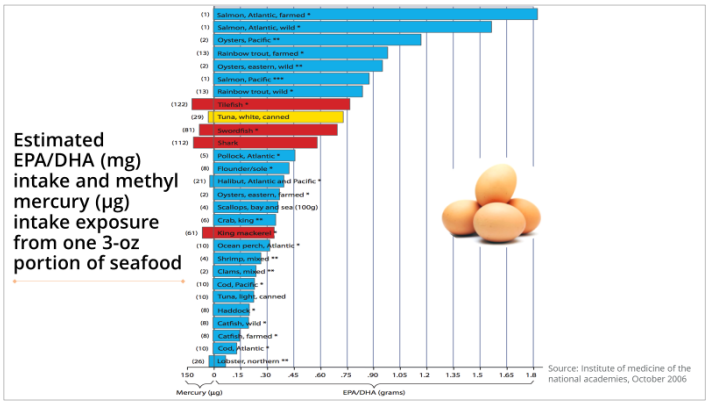


Slide 37 – Maternal DHA Intake Guidelines

Seafood Dietary Guidelines

Current US dietary guidelines recommend pregnant women eat a variety of seafood with a minimum of 250 mg of n-3 LCPUFA in the serving. Maybe I should say this differently. If they follow the US dietary guidelines, and have the servings of seafood recommended, they would achieve about 250 mg per day over the average of that week. The EPA recommends lactating women consume 1–3 weekly servings of a variety of seafood low in mercury to ensure adequate breast milk DHA content. You notice these recommendations are mostly around food.

This is something from a National Academy of Medicine conference that I participated in a number of years ago where we looked at seafood balancing benefits and risks. You see in red the fish that the EPA and DHA have recommended that women not consume during pregnancy and lactation.[22]



Slide 38 – Estimated EPA/DHA (mg) intake and methyl mercury (µg) intake exposure from one 3-oz portion of seafood

The x-axis shows the EPA/DHA content of the fish and you can see near the top: salmon, oysters, rainbow trout, etc, going on down to lobster and cod, which are pretty low in omega-3 fatty acids, but also the mercury, which is going out here. The highlighted ones are the ones that are high in mercury because those are very large fish, and they're recommended not to be consumed during pregnancy and lactation.

I put eggs on here because eggs are actually the main source of DHA in the US diet overall. This may be surprising to people, but we have a lot of people

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in the Midwest who are not big seafood eaters like people on the Coast, [who] may eat more. But the average egg in the US has somewhere around 50 to 60 mg of DHA, and we'll talk about that a little bit as it may be a source for feeding infants the egg yolk.

Key Takeaways

Providing DHA and ARA to term infants in amounts comparable to the median level of DHA and ARA in human milk worldwide builds a more functional brain. The effects are found long after DHA supplementation stopped, which is what we call developmental programming.

Infants need milk from a mother consuming approximately 200 mg of DHA per day from either food or supplements, or infant formula with at least 0.3 mg of DHA, and at least as much ARA. After infancy, the diet should include foods containing DHA or possibly supplemental DHA. Maternal DHA intakes should increase during pregnancy and lactation by a combination of diet and supplements. The optimal amount is not yet determined, but we think 200–300 mg is certainly a good start.

Question & Answer

Editor's Note: This is a transcript of audience questions together with presenter responses from the December 9, 2020 audio webcast.

Did the researchers in the DIAMOND trial giving the tests know which group each child had been assigned to?

Carlson: No, that's a wonderful question because, of course, in clinical trials and whenever we're doing outcomes, you're not allowed to know what the child was receiving. In the DIAMOND trial, we actually kept that trial blinded, which means nobody knew what the assignment was until every child had reached 6 years of age. Of course, by 9 years we had broken the code, but only the PIs knew what assignment. None of the psychologist who were doing testing were told that. We didn't tell the families either. We kept that even from them. So, it was really double blinded.

Can you repeat how the study was controlled for SES?

We collect a lot of information on our families. We have mother's education. We have income by zip code, which we use instead of actual income of the family, because it turns out the neighborhood you live in is actually a better predictor of your socioeconomic group than your actual income, but the income of the neighborhood you live in. We had the age of the mother, her education. I think I mentioned that, yes, so, a number of those factors. We use those to control for SES.

In the DIAMOND trial, were supplemented formula-fed infants compared to breastfed infants?

We did not include breastfed infants in the DIAMOND trial. I think one of the rationales for that is that there have been a number… Of course, human milk studies where infants are breastfed are not directly comparable to formula anyway because there are many, many different things in human milk that are not in formula. But there have been certainly a number of studies over the years that have compared breastfed [infants] and looked at cognitive development. In the case of the DIAMOND trial, we were asking about a specific nutrient. How is that affecting behavior? We didn't want to have a lot of other variables in that equation.

Would you recommend supplementation for all breastfed infants until what age and then how much?

I would certainly recommend supplementation of the mother because that's the easiest way to provide DHA to the baby that's being breastfed or fed human milk in general. I think we all know that a lot of moms do mixed feeding. If they're doing mixed feeding with an infant formula for the first

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year, then there shouldn't be any need to provide additional DHA. They're getting their DHA from either mom's milk or the formula. After weaning, then I think the rule should be that—and this is the way we think about this with our advice on diet, the dietary guidelines to Americans—is that children should begin to be eating from the table with the family, and the family should be having a couple of fish meals a week. That would be 1 way to provide DHA after weaning.

I also think egg yolk could be used as a weaning food very nicely because it's a good source of not only DHA but also choline, which is one of those nutrients of interest at the moment that we're not sure that either mothers or babies are getting enough of.

How do you recognize a child's diet is deficient in DHA and how do you manage it?

We always do 24-hour recalls every time we see an infant. If you do a 24-hour recall or you ask what is a typical diet? I would be looking for are they getting any fish? What kind of fish are they getting? Is it cod or are they getting some salmon every couple of weeks? Are they getting egg yolk? Those are the main sources of DHA.

If a child's not getting eggs, and they're not getting any seafood, they're probably not getting much DHA. We did a toddler study a few years back and the mean was about 20 mg per day for toddlers. Actually, there were many toddlers that... the median was even lower than 20. Most of the toddlers were not getting any significant DHA.

What amount of DHA per day then would you recommend a child consume that is older than 12 months and typically no longer receiving breast milk or DHA-fortified formula?

Again, one of the things that I would point out is that DHA is a fat. It's a lipid. So, you don't need to eat it all every day. This was pertinent to the comment I made earlier about seafood. A woman who has 3 oz of salmon twice a week is probably going to get the equivalent of the DHA that we recommend. She doesn't have to eat salmon every day. Children wouldn't have to eat it every day. I think if it averaged out around 100 mg per day, that would be a reasonable amount. That's the equivalent of 1 egg yolk or maybe a couple servings of seafood during the week.

There's also a lot of products out there on the market for supplementing toddlers. I looked at those a little while ago on my phone. They're accumulating every day. There's milk with DHA added, etc. I think some parents purchase those products, as well, if they don't want to serve fish or eggs to their child.

How would you recommend guiding mothers for choosing an appropriate DHA supplement to minimize risk of mercury?

Well, I don't think there's any supplement that's an issue with mercury. Of course, some of those foods that I highlighted in red, I could put that back up here again [Slide 38]. I don't think tilefish, swordfish, shark, and King Mackerel are commonly consumed in the US, but I certainly wouldn't feed those to a child. Other than that, I don't think we need to be concerned about mercury from supplemented foods or from eggs, from salmon and so on. Actually, I did a calculation a while ago, because about an ounce of salmon, which would be a reasonable serving for a 1–3-year-old, provides anywhere from 350–550 mg of DHA. Even consuming that amount of salmon once a week would get pretty close to the 100 mg that I was talking about.

I also do want to make it clear that these are best guidelines. These are the kinds of things that I would tell my daughter or my son. There's not a lot of science around these numbers. People, they could be concerned about giving too much. I did see some

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supplements when I was looking, drops that some of the vitamin companies make, that provide 500 mg. I don't think I'd want to give that amount to a child every day without some kind of evidence that it was desired. I think there is potential concern there.

Does adjusting a lactating mother's diet to include seafood benefit the infant through breast milk more than it would through supplements?

Well, as a nutritionist, even though I've used supplements in most of my studies instead of food, I do recommend food. I think, yes, because seafood provides a lot of good nutrients besides DHA. For example, it provides vitamin D. It provides iodine, some choline. Those are good nutrients. The mother needs those nutrients as much as the baby. I think there's not a lot of studies showing what the mother's intake affects the choline concentration of the milk, but certainly I would expect it would be higher if her status was higher. I would prefer to see that but it's not necessarily going to happen. Then the supplements can be the backup.

When the mother is taking the necessary prenatal vitamins to achieve appropriate levels of DHA, are there circumstances when infants do not accumulate DHA in adipose tissue in utero and are born at deficient levels?

There is not that I'm aware of, and I would be very surprised to find that would be the case. There are some studies in lactation. Women who have a certain genetic phenotype don't tend to put DHA into their milk during lactation, but that's a very rare finding. But crossing the placenta, there's not any evidence that I'm aware of that that would be a problem.

What does the NHANES data indicate regarding DHA and dietary intake for toddlers?

I have not seen that data recently, but I think it's very similar to what we found. We have a pretty large study in toddlers here. I think it's less than 20 mg per day. It may be increasing now with some of the supplemental foods that are out there that contain DHA. But those are often pricey products that all parents can't afford to purchase.

How often should a 1- to 2-year-old have omega-3 enriched eggs?

This is not scientifically based, but I would see no problem with a child eating an egg yolk every day if they like them. This used to be one of the weaning foods that parents commonly used, certainly while I was feeding my children who are in their 40s now. We gave them egg yolk every morning. I don't think there's any downside to that.

Can you share more detail on the impact of a DHA-enriched diet to the risk of a child developing an allergic or atopic disease?

This is not really my area. There are 2 formula studies that suggest benefits, actually found benefits. There's not very much data after infancy, trials where children were fed DHA and anybody looked at allergy or atopy. My understanding of this is that these are early development. This would be affected more by DHA early in development say in pregnancy and early postnatal life rather than giving DHA to a 6-year-old, say, and expecting to get a reduction. I'm not saying it couldn't happen, but I'm not aware of any data that says it would.

Does DHA and ARA in formulas for preterm help them catch up in weight to term breastfed infants?

There's not really much data on this. This is not the reason I would give DHA to a preterm baby. I would make sure they got it because their stores are going to be so low when they're born. And there is

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evidence that they require a higher level of DHA than in current term formulas, for sure. More [than] 1% DHA in the formula instead of 0.3 might be beneficial to a preterm baby. But that wouldn't be for increased weight. It would be for their brain.

Abbreviations

ALA	alpha linolenic acid	**LA**	linolenic acid
ARA	arachidonic acid	**LCPUFA**	long-chain polyunsaturated fatty acids
DHA	docosahexaenoic acid	**LogMAR**	Logarithm of the Minimum Angle of Resolution
DIAMOND trial	DHA Intake And Measurement Of Neural Development	**MRI**	magnetic resonance imaging
EPA	eicosapentaenoic acid	**PI**	Principal Investigator
FAO	UN Food and Agriculture Organization	**SES**	socioeconomic status
fMRI	functional MRI	**WHO**	World Health Organization
ISFFAL	International Society for the Study of Fatty Acids and Lipids	**WPPSI**	Wechsler Preschool and Primary Scale of Intelligence
KUDOS	Kansas University DHA Outcomes Study		

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