Nutrition in the First 1,000 Days: DHA

Presented by
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Thriving in 1,000
Presenter

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Director, PhD Program in Medical Nutrition Science
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Kansas City, Kansas
### Faculty Disclosures

**Susan E. Carlson,** PhD

<table>
<thead>
<tr>
<th>Speaking Fee</th>
<th>Mead Johnson Nutrition, Pharmavite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donation of DHA</td>
<td>DSM</td>
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</tbody>
</table>
Learning Objectives

Nutrition in the First 1,000 Days: DHA

- Associate DHA in the first 1,000 days with long-term cognitive outcomes
- Provide recommendations for DHA intake to mothers and infants in the first 1,000 days
First 1,000 Days of Life

• First 1,000 days of life refers to conception through the child’s second birthday

• Optimal nutrition is essential during this period to support:
  ▪ Fetal growth and development
  ▪ Maternal health (including the postpartum period and lactation)
  ▪ Fuel for the infant and toddler growth (until 2 years of age)

DHA is Essential to Mother and Child

DHA is 1 of 9 nutrients for healthy pregnancy and infant/toddler development
- Carotenoids (lutein + zeaxanthin)
- Choline
- Folate
- Iodine
- Iron
- **Omega-3 fatty acids**
- Protein
- Vitamin D
- Zinc

- All these key nutrients should be included in maternal and infant diet
- Failure to provide these key nutrients during the first 1,000 days of life can result in lifelong deficits
- Strong mother/infant DHA relationship affects status both in utero and in infancy

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

• Prenatal supplements should include these vital nutrients

• These micronutrients are building blocks to ensure Baby does well from fetus → infancy → toddlerhood

• The focus today is on DHA
DHA and Cognitive Outcomes

Why might DHA be important for fetal and infant development?
DHA Omega-3 in Cells of Human Body

DHA incorporates into rapidly developing brain and retina during fetal and infant development

Sufficient dietary consumption of n-3 LCPUFA needed in pregnant and breastfeeding mothers

Figure. Metabolic pathways for omega-6 and omega-3 fatty acids

**Omega-6**

13-HODE → PGE2 → TXA2, TXB2

15 LOX → 15-HETE → PGH2

5-HETE → 5-HPETE → LA → AA

COX → 5 LOX → PGH2 → LT4, LTE4, LTD4

LTA4 → LTB4

**Omega-3**

ALA → EPA → DHA

COX → 5 LOX → PGH2 → PGE2, PGF2α

15 LOX → 15-HETE, 5-HETE

18-HEPE → 5-LOX → LTB5, RvD1-6, RvE1, 2

17-HDHA → MaR, PD1

14-HDHA → MaR

Abbreviations: AA, arachidonic acid; ALA, alpha linolenic acid; COX, cyclooxygenase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDHA, hydroxydocosahexaenoic acid; HEPE, hydroperoxyeicosatetraenoic acid; HETE, hydroxyeicosatetraenoic acid; HODE, hydroxyoctadecadienoic acid; HPETE, hydroperoxyeicosatetraenoic acid; LA, linoleic acid; LOX, lipoxygenase; LT, leukotriene; LX, lipoxin; MaR, maresin; PD1, protectin D1; PG, prostaglandin; Rv, resolvins; TX, thromboxane.
Maternal Intake of DHA Influences Two Important Periods of DHA Accumulation

α-Linolenic Acid

↓

DHA

Conversion from precursor 18-carbon fatty acid is very poor

~2–4% of ~1,000 mg = 20–40 mg

Preformed

In Utero:
DHA and ARA are selectively transported across the placenta

Preformed

DHA and ARA are in human milk and US formulas since 2002
DHA Accumulates Rapidly in the CNS During Most of the First 1,000 Days

EPA = 20:5n-3
DPA= 22:5n-3
DHA=22:6n-3

CNS, central nervous system; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid.

Intrauterine DHA Accumulation

DHA accumulated in fetal adipose tissue can support DHA requirements after birth, but depends on maternal intake.

Brain Cortex DHA in Term Infants by Feeding

**Takeaway Message**

DHA intake in infancy increases brain cortex DHA—evidence that even infants who can accumulate DHA in adipose tissue in utero show differences in brain DHA when fed DHA postnatally.


![Graph showing brain cortex DHA percentage vs. age at death for breast milk and formula with no DHA.](image-url)

*Australian milk DHA ~0.26% trans fatty acids (TFA)*
DHA and Cognitive Outcomes

Results of the DIAMOND trial

- **Only** dose-response study of DHA in infancy
- Infants were provided formula from birth to 1 year
- Would no longer be ethical to conduct a feeding trial without DHA
- **Only** planned long term follow-up to age 6
- A subset studied again at 9 years of age
- Feeding occurred 2002–2004

DIAMOND Trial (Clinicaltrials.gov NCT00753818)

- DIAMOND (*DHA Intake and Measurement of Neural Development*) trial
- n=343; exclusively formula fed, term infants conducted 2002–2004
- Measured long-term dose-response effects of 4 amounts of LCPUFA-supplemented formula feeding birth to 12 months
- Primary outcome: cortical visual acuity; Secondary: cognitive development
- Four concentrations of formulations against control 0.00% DHA/0.00% ARA
  - 0.00% total fatty acids from DHA\[a\]
  - 0.32% DHA (17 mg/100 kcal of infant formula)
  - 0.64% DHA (34 mg/100 kcal)
  - 0.96% DHA (51 mg/100 kcal)

Only dose-response study of DHA in formula with long-term follow-up of children

*a.* All DHA supplemented formulas contained 0.64% ARA.

LCPUFA, long-chain polyunsaturated fatty acid; DHA, docosahexaenoic acid; ARA, arachidonic acid.

Age-Appropriate Measures of Development Studied in RCTs of DHA Supplementation (DIAMOND and KUDOS)

- Cortical (brain-related) visual acuity
- Visual orienting
- Look duration during visual habituation
- Sustained attention and periods of inattention
- Inhibition—behavioral and electrophysiological
- Problem solving
- Full scale and subscales of IQ
- Brain structure and function (MRI)
- Blood pressure
- Growth and body composition
DIAMOND Trial
Designed to measure the effect of DHA dose on visual acuity in term infants (conducted in Dallas and Kansas City)

Cortical visual acuity was better at 12 months in all groups receiving DHA compared to the group that did not receive DHA—no evidence that higher doses were superior to 0.32% DHA and 0.65% ARA

### DIAMOND Trial (Postnatal) Neurodevelopmental Assessments

<table>
<thead>
<tr>
<th>Task</th>
<th>Age (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Cortical Visual Acuity</td>
<td>😎</td>
</tr>
<tr>
<td>Visual Habituation</td>
<td>🍀</td>
</tr>
<tr>
<td>Bayley Scales of Infant Development (II)</td>
<td>🍀</td>
</tr>
<tr>
<td>Stroop Tasks</td>
<td>🍀</td>
</tr>
<tr>
<td>Dimensional Change Card Sort</td>
<td>🍀</td>
</tr>
<tr>
<td>Peabody Picture Vocabulary Test (PPVT)</td>
<td>🌿</td>
</tr>
<tr>
<td>Electrophysiology (ERP): Go/No-Go Tasks</td>
<td>🌿</td>
</tr>
<tr>
<td>Weschler Preschool Intelligence Scale (WPPSI: IQ)</td>
<td>🌿</td>
</tr>
</tbody>
</table>

* 😎: Partial list completed in the Kansas City cohort; at 9 years we also looked at brain structure and function in a subset of each group.

Average Proportion Sustained Attention (4, 6, and 9 mos) by DHA (ARA Constant) Content of Infant Formula

Figure. Sustained attention at 4, 6, and 9 months in the four formula groups.

DIAMOND Trial
Stroop Tasks (Test of Inhibition)

“Banana”

“Apple”

“Night”

“Day”
Stroop Test Scores

Group: $F(3, 67.644) = 4.045, p = .010$
Visit: $F(3, 65.290) = 24.428, p = .000$

Assessing Neurodevelopment at Different Ages
Dimensional Change Card Sort Ability –
Rule Learning/Inhibition
DIAMOND Trial – Dimensional Change Card Sort
Overall DCCS Score: (36, 42, 48, and 60 months)

Group: $F(3, 71.919) = 3.248, p = .027$
Visit: $F(3, 67.287) = 34.009, p = .000$
PrePost: $F(1, 72.250) = 227.748, p = .000$
Group x Age: $F(9, 67.326) = 2.757, p = .008$
Visit x PrePost: $F(3, 69.118) = 3.383, p = .023$

Verbal IQ Assessment

DIAMOND: ANOVA Group Effect: $F(3, 59) = 4.12, p = .01$.
Supplemented (n=49) vs Unsupplemented (n=14): $t(61) = 2.80, p = .007, d = 0.85$

6-yr Weschler Preschool Primary Scale of Intelligence

Electrode Montage Employed at 5.5 Years

Electrode Clusters:
N2=frontal (oval)
P2=central (triangle)

Testing Response Inhibition – Go/No-Go Paradigm

At 5.5 years:

“Catch the fish, not the sharks.” [1]

Age 9 years:

“Press the button when T follows the letter S. Don’t press for any other combination.” [2]

Combined LCPUFA groups are significantly faster to GO ($p=.02$).\[2\]

And:

a. Children in the control group are more impulsive ($p=.005$), pressing the button to “S” before waiting for the next letter.

b. There is a sex * group interaction ($p=.01$) driven largely by boys in the control group who are the most impulsive.

---

Results – DIAMOND fMRI, Flanker Task

**Attention System**

The parietal regions in the LCPUFA-supplemented groups show greater activation to incongruent trials compared to congruent trials compared to control.

**Inhibition System**

There was greater activation in the LCPUFA-supplemented groups to incongruent compared to congruent trials in the anterior cingulate cortex (ACC).
**DIAMOND Trial Findings**

**LCPUFA supplementation:**
- Improved visual acuity (1–12 months)
- Improved quality of visual attention (4–9 months)
- Accelerated development of executive function (3–5 yrs)
- Improved verbal IQ (5 yrs) and overall IQ (6 yrs)
- Faster reaction time (5.5 and 9 yrs)
- Brain discrimination of No-Go from Go (5.5 years)
- More sophisticated neuronal network (5.5 years)
- More sophisticated brain structure/function (9 years)

Effects of LCPUFA were *not* seen on all measures of early executive function at 2–4 years, particularly those related to memory.

*These findings were observed as long as 8 years after supplementation stopped!*  
*Nutrition studies on cognitive development should be continued through early childhood*

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DHA and Cognitive Outcomes

Results of the KUDOS (prenatal) DHA trial

- Conducted 2006–2011
- N=350 enrolled and 301 completed the trial
- Women assigned to placebo or DHA capsules (600 mg)
- Primary outcomes: Pregnancy outcome and cognitive development to 6 years
KUDOS (RCT)

Placebo or 600 mg DHA/day beginning at ~14.5 wks gestation

Maternal RBC Phospholipid DHA (weight % total fatty acids)

![Box plot showing maternal RBC phospholipid DHA](image)

*P=0.0001

# KUDOS Trial (Prenatal) – Neurodevelopmental Assessments

<table>
<thead>
<tr>
<th>Task</th>
<th>Age (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Visual Acuity</td>
<td></td>
</tr>
<tr>
<td>Visual Habituation</td>
<td></td>
</tr>
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<td>Bayley Scales of Infant Development (II)</td>
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### Maximum P2 Amplitude in DIAMOND Control vs KUDOS (Placebo-controlled DHA Supplementation in Pregnancy)\[a\]

<table>
<thead>
<tr>
<th></th>
<th>DIAMOND PLACEBO</th>
<th>KUDOS</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PLACEBO</td>
<td>DHA</td>
<td>PLACEBO</td>
<td>DHA</td>
</tr>
<tr>
<td>Prenatal DHA</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Postnatal DHA</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Maximum P2 Amplitude in subjects who correctly inhibit</td>
<td>[Image]</td>
<td>[Image]</td>
<td>[Image]</td>
<td>[Image]</td>
</tr>
</tbody>
</table>

\[a\] Visual processing (is it a fish or a shark) that takes place prior to making a decision to press the button or not.

Maximum N2 Amplitude for “Difference Potential” in DIAMOND Control vs KUDOS (Placebo or DHA Supplementation in Pregnancy)\textsuperscript{[a]}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{Graph showing the maximum N2 amplitude for “Difference Potential” in DIAMOND Control vs KUDOS (Placebo or DHA Supplementation in Pregnancy).}
\end{figure}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
 & \textbf{DIAMOND PLACEBO} & & \textbf{KUDOS} & \\
 & \textbf{PLACEBO} & \textbf{DHA} & & \\
\hline
\textbf{Prenatal} & No & No & Yes & \\
\textbf{Postnatal} & No & Yes & Yes & \\
\textbf{Supplement} & & & & \\
\textbf{(0.32–0.96% DHA)} & & & & \\
\hline
\textbf{Peak N2 Amplitude} & & & & \\
\textbf{Difference Potential} & & & & \\
\textbf{No-Go minus GO} & & & & \\
\hline
\end{tabular}
\end{table}

\textsuperscript{[a]} Occurs in frontal lobe about 300 ms prior to when button press would occur without inhibition (includes only children who had the correct response, ie, did not catch the shark).

## KUDOS – Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=147)</th>
<th>600 mg DHA (n=154)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early preterm birth (&lt;34 wks)</td>
<td>4.8 %</td>
<td>0.6 %</td>
<td>0.025</td>
</tr>
<tr>
<td>Birth weight &lt;1500 g</td>
<td>3.4 %</td>
<td>0 %</td>
<td>0.026</td>
</tr>
<tr>
<td>Neonatal Intensive Care Unit admission</td>
<td>8.3%</td>
<td>10.4%</td>
<td>NS</td>
</tr>
<tr>
<td>Days hospitalized (mean #)</td>
<td>40.8</td>
<td>8.9</td>
<td>0.026</td>
</tr>
</tbody>
</table>

a. One tailed P values at α=0.05. b. if born preterm (<37 wks).

DIAMOND and KUDOS Conclusions

• Children supplemented postnatally with DHA and ARA (DIAMOND trial) had higher cognitive development and favorable effects on brain structure-function out to age 9 years.

• Children supplemented with DHA prenatally (KUDOS, all of whom received postnatal DHA) did not show pronounced cognitive benefit after controlling for SES, however, they did have more favorable brain responses during visual processing of the Go/No-Go testing at 5.5 yrs. AND there was an interaction between sex and DHA.

• Males did not have the same cortical response when asked to inhibit an action (not catch the shark) unless their mother was assigned to DHA supplementation.

• Prenatal DHA supplementation reduces early preterm birth by ~50%, so additional benefits are likely for those not born preterm, because preterm birth impairs cognitive development.
DHA and Noncognitive Benefits Reported for DHA

• Lower stress response (mom and baby)
• More mature fetal autonomic nervous system development
• Less wheeze/asthma in childhood
• Less atopic allergy
• Lower BP in early childhood in children who become overweight/obese
• Higher fat-free mass at 5 years
Best Practice Guidelines to Ensure Maternal and Infant DHA Intake
First 1,000 DHA Recommended Intake

<table>
<thead>
<tr>
<th></th>
<th>0 to 6 months of age</th>
<th>6 to 24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Academy of Medicine [a]</td>
<td>• n-6 fatty acids 4.4 g/day</td>
<td>• DHA 10 to 12 mg/kg body weight</td>
</tr>
<tr>
<td></td>
<td>• n-3 fatty acids 0.5 g/day</td>
<td></td>
</tr>
<tr>
<td>WHO</td>
<td>• 0.2 to 0.36% of fatty acids</td>
<td></td>
</tr>
</tbody>
</table>

More guidance is needed in recommended dosing of DHA in toddlers (eg, dosing, deficiency gaps, age considerations, dietary considerations)

---

\[a\] Note these recommendations are for 18 Carbon Fatty Acids, linoleic and linolenic acid only. However, studies show 0.3% DHA with ARA in at least the same amount are beneficial for infant development.

Milk DHA Intake Is Related to Maternal DHA Intake

<table>
<thead>
<tr>
<th>Diet/Location</th>
<th>% DHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudan</td>
<td>0.07</td>
</tr>
<tr>
<td>US Women</td>
<td><strong>0.12</strong></td>
</tr>
<tr>
<td>Pastoral China</td>
<td>0.14</td>
</tr>
<tr>
<td>Netherlands</td>
<td>0.19</td>
</tr>
<tr>
<td>Germany</td>
<td>0.23</td>
</tr>
<tr>
<td>Australia</td>
<td>0.26</td>
</tr>
<tr>
<td>France</td>
<td>0.32</td>
</tr>
<tr>
<td>Spain</td>
<td>0.34</td>
</tr>
<tr>
<td>Nigeria</td>
<td>0.34</td>
</tr>
<tr>
<td>Israel</td>
<td>0.37</td>
</tr>
<tr>
<td>Norway</td>
<td>0.45</td>
</tr>
<tr>
<td>Rural China</td>
<td>0.68</td>
</tr>
<tr>
<td>Urban China</td>
<td>0.82</td>
</tr>
<tr>
<td>Japan</td>
<td>1.00</td>
</tr>
<tr>
<td>Marine China</td>
<td>2.78</td>
</tr>
</tbody>
</table>

Median DHA in human milk worldwide is ~0.3%

Women in US ~0.1% DHA, unless consuming a supplement

Jensen et al show 200 mg supplement of DHA/day in US women could increase milk DHA to 0.3% of total fatty acids[1]

0.3% DHA is the amount EFSA requires in infant formula to claim it supports visual development

---

Maternal DHA Intake Guidelines

- Maternal dietary DHA intake recommend ≥200–300 mg/day
  - WHO/FAO/ISFFAL recommend at least 200 mg/day for pregnant and lactating women

- Current US Dietary Guidelines recommend pregnant women eat a variety of seafood, min of 250 mg/week n-3 LCPUFA intake

- US EPA recommends lactating women consume 1–3 weekly servings (12 oz/wk) of a variety of seafood low in mercury to ensure adequate breast milk DHA content


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

Source: Institute of medicine of the national academies, October 2006
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.

Effects are found long after DHA supplementation is stopped, includes developmental programming.

Infants need milk from a mother consuming ~200 mg DHA/day or infant formula with at least 0.3% DHA, and at least as much ARA.
Key Takeaways

After infancy, diet should include foods containing DHA or (possibly) supplemental DHA.

Maternal DHA intake should increase during pregnancy and lactation by a combination of diet and supplements— the optimal amount is not determined.
ANY Questions?
Please type your question into the *Ask a Question* box and hit send.
Nutrition in the First 1,000 Days—Driving Early Development

Vitamin D
Presented by Carol L. Wagner, MD

- DHA
Presented by Susan E. Carlson, PhD

Iron
Presented by Michael K. Georgieff, MD
# DHA and EPA and Mercury Content in 4 Ounces of Selected Seafood Varieties

<table>
<thead>
<tr>
<th>Common Seafood Varieties</th>
<th>DHA+EPA mg/4 ounces</th>
<th>Mercury mcg/4 ounces</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmon*: Atlantic*, Chinook*, Coho*</td>
<td>1,200–2,400</td>
<td>2</td>
</tr>
<tr>
<td>Anchovies**: Alaskan, Pink*, and Sockeye*</td>
<td>2,300–2,400</td>
<td>5–7</td>
</tr>
<tr>
<td>Mackerel: Atlantic and Pacific</td>
<td>1,350–2,100</td>
<td>8–13</td>
</tr>
<tr>
<td>Oysters: Pacific</td>
<td>1,550</td>
<td>2</td>
</tr>
<tr>
<td>Trout: Freshwater</td>
<td>1,000–1,100</td>
<td>11</td>
</tr>
<tr>
<td>Tuna: White (Albacore) canned</td>
<td>1,000</td>
<td>40</td>
</tr>
<tr>
<td>Salmon*: Pink* and Sockeye*</td>
<td>700–900</td>
<td>2</td>
</tr>
<tr>
<td>Crab: Bluet*, King**, Snow*, Queen*, and Dungeness*</td>
<td>200–550</td>
<td>9</td>
</tr>
<tr>
<td>Flounder**: Atlantic* and Sole**</td>
<td>350</td>
<td>7</td>
</tr>
<tr>
<td>Clams</td>
<td>200–300</td>
<td>0</td>
</tr>
<tr>
<td>Tuna: Light canned</td>
<td>150–300</td>
<td>13</td>
</tr>
<tr>
<td>Catfish</td>
<td>100–250</td>
<td>7</td>
</tr>
<tr>
<td>Cod*: Atlantic* and Pacific*</td>
<td>200</td>
<td>14</td>
</tr>
<tr>
<td>Scallop*: Bay* and Sea*</td>
<td>200</td>
<td>8</td>
</tr>
<tr>
<td>Shrimp</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

**Seafood varieties that should not be consumed by women who are pregnant or breastfeeding.**

<table>
<thead>
<tr>
<th>Seafood Varieties</th>
<th>DHA+EPA mg/4 ounces</th>
<th>Mercury mcg/4 ounces</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shark</td>
<td>1,250</td>
<td>151</td>
</tr>
<tr>
<td>Tilefish*: Gulf of Mexico**</td>
<td>1,000</td>
<td>219</td>
</tr>
<tr>
<td>Swordfish</td>
<td>1,000</td>
<td>147</td>
</tr>
<tr>
<td>Mackerel: King</td>
<td>450</td>
<td>110</td>
</tr>
</tbody>
</table>

*Source: Adapted from USDA, Feb 2012*