

Nutrition in the First 1,000 Days: DHA

Presented by
Susan E. Carlson, PhD



Thriving in
1,000



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This activity is supported by an educational grant from
Mead Johnson Nutrition.

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Faculty Disclosures

Susan E. Carlson, PhD

Speaking Fee Mead Johnson Nutrition, Pharmavite

Donation of DHA DSM



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





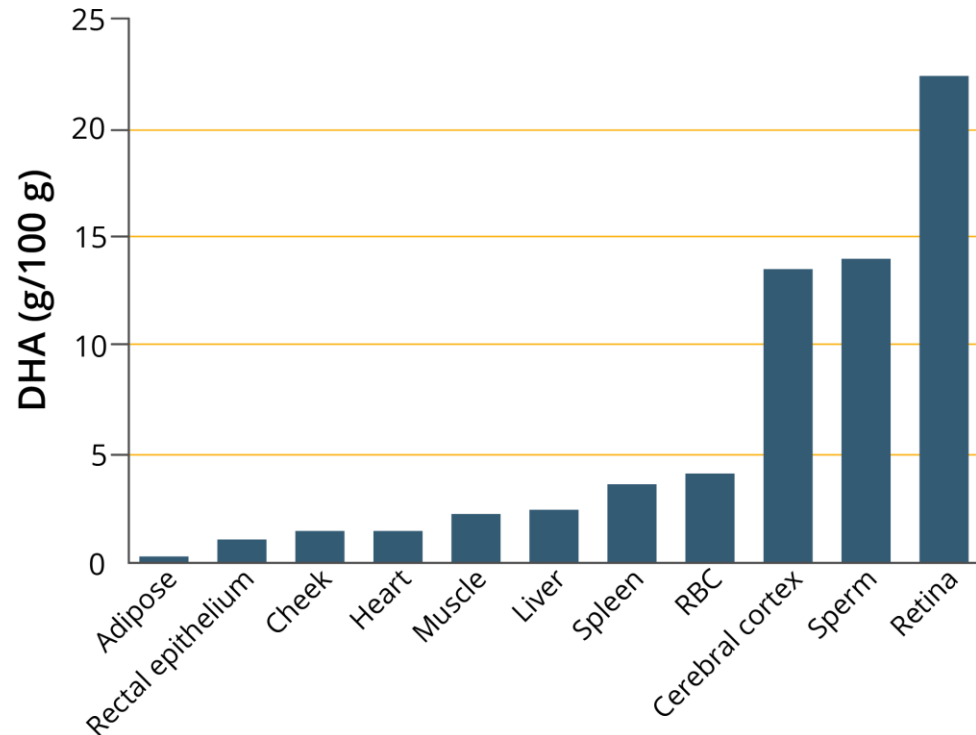
DHA and Cognitive Outcomes

Why might DHA be important for fetal and infant development?



DHA Omega-3 in Cells of Human Body

Figure. Cross-study analysis of fatty acid concentrations (g/100 g of total fatty acids) in tissues



Abbreviations: DHA, docosahexaenoic acid; RBC, red blood cell.

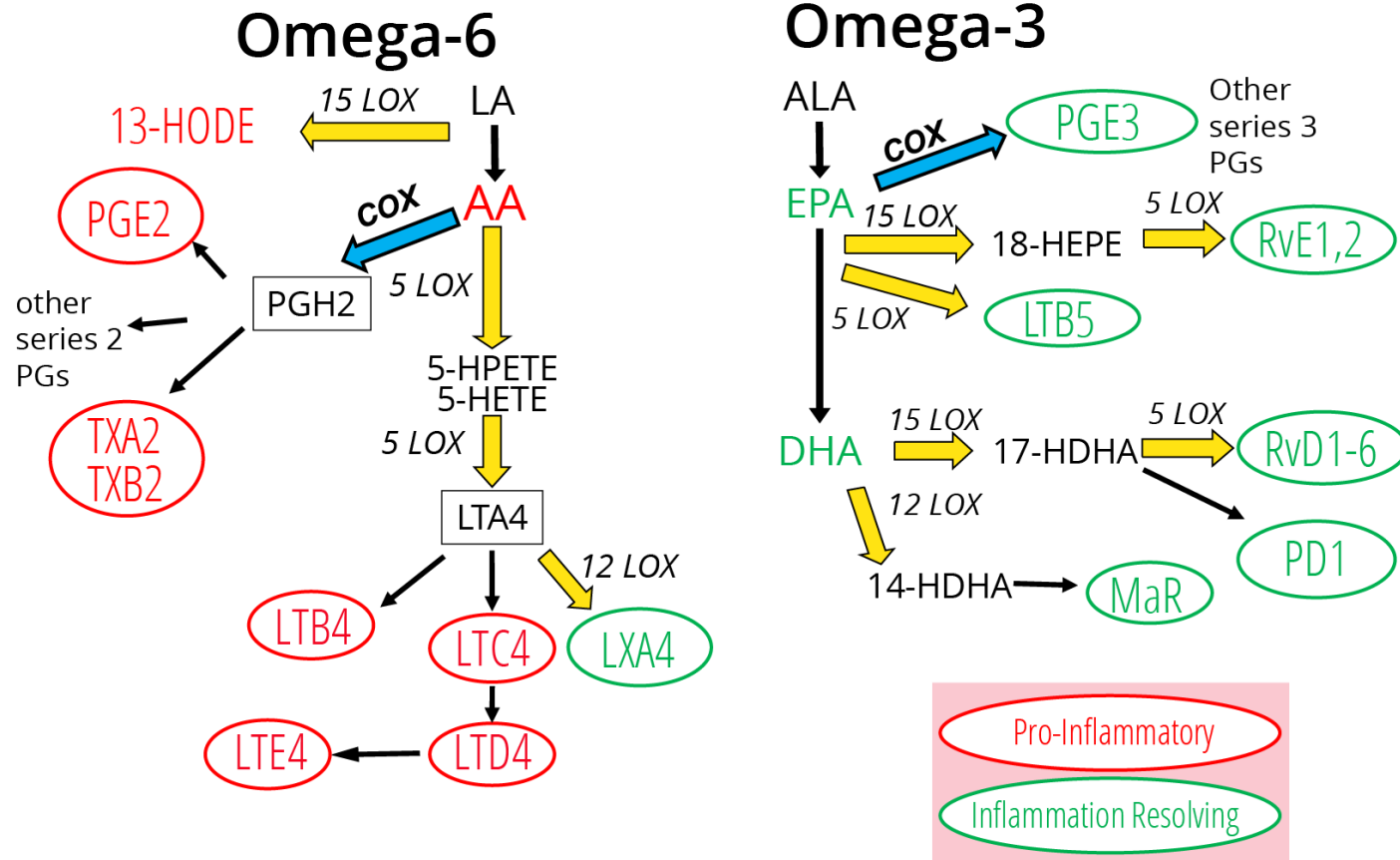
DHA incorporates into rapidly developing brain and retina during fetal and infant development

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

LCPUFA, long-chain polyunsaturated fatty acid.



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



Abbreviations: AA, arachidonic acid; ALA, alpha linolenic acid; COX, cyclooxygenase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDHA, hydroxydocosahexaenoic acid; HEPE, hydroxyeicosapentaenoic 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, resolvin; TX, thromboxane.



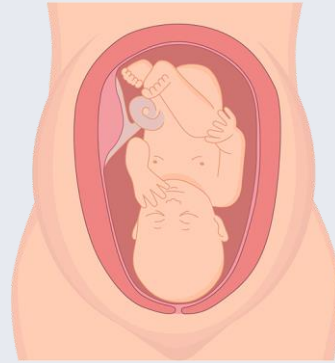
Maternal Intake of DHA Influences Two Important Periods of DHA Accumulation

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



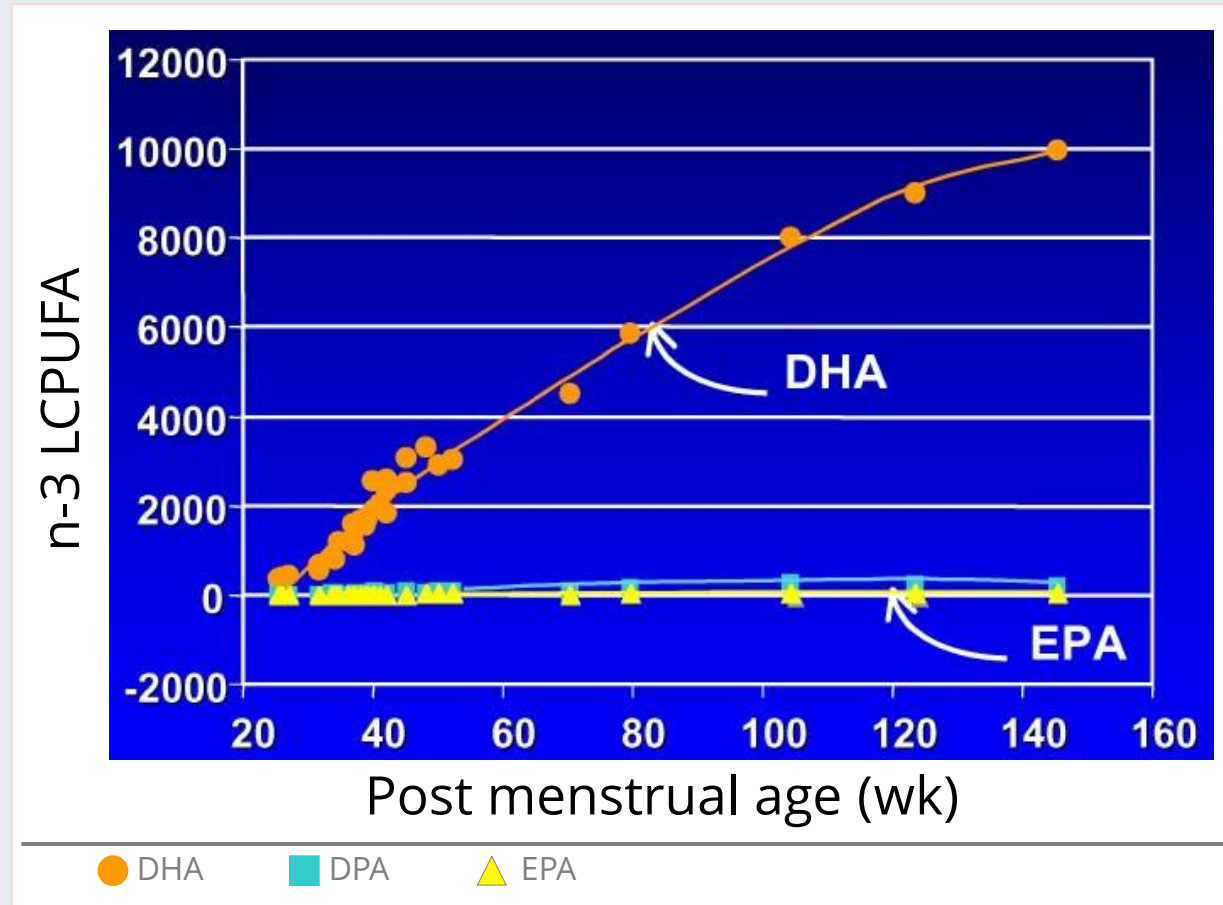
Preformed

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



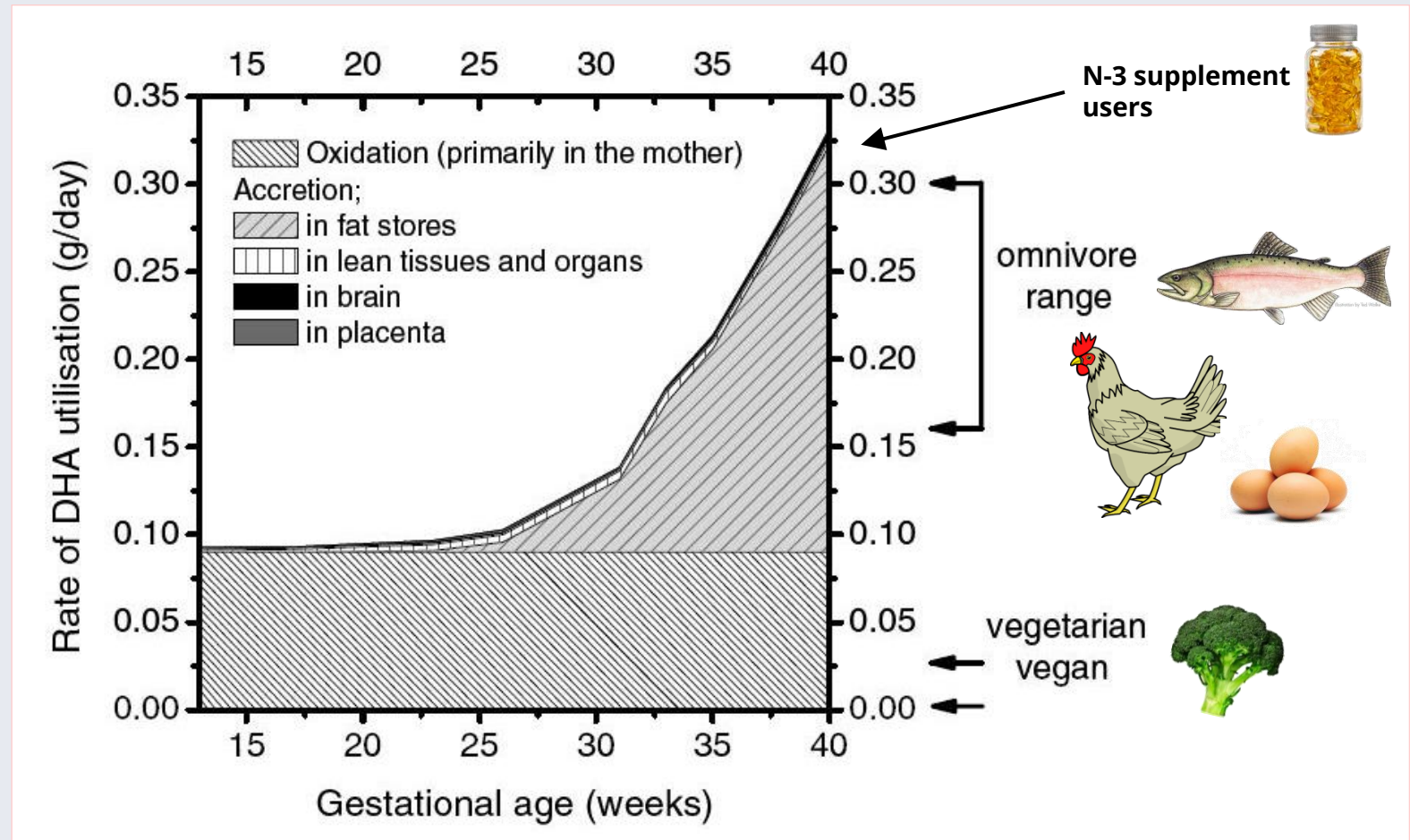
CNS, central nervous system; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid.

Martinez M. *J Pediatr.* 1992;120:S129-S138.



Intrauterine DHA Accumulation

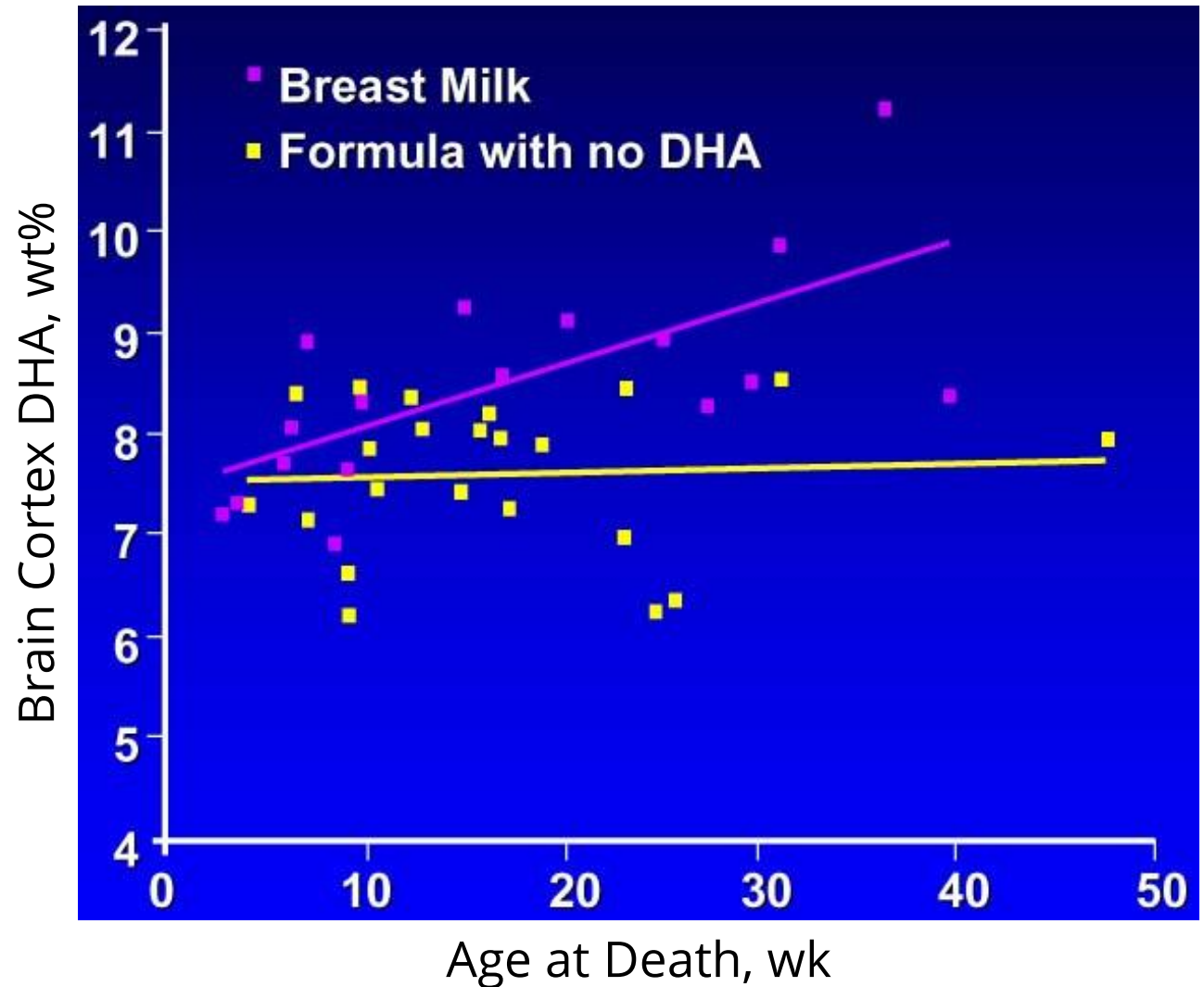
DHA accumulated in fetal adipose tissue can support DHA requirements after birth, but depends on maternal intake



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



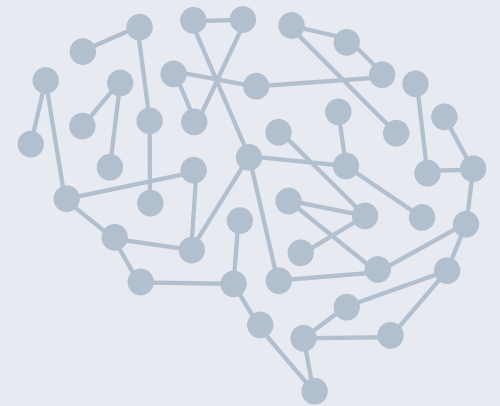
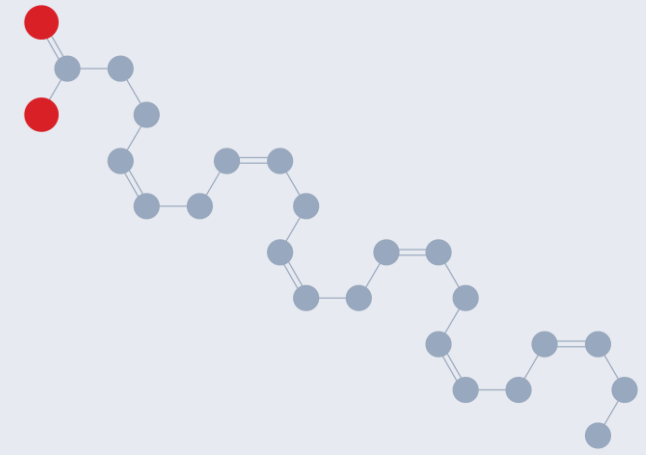
Australian milk DHA ~0.26% trans fatty acids (TFA)



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/100kcal)

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.



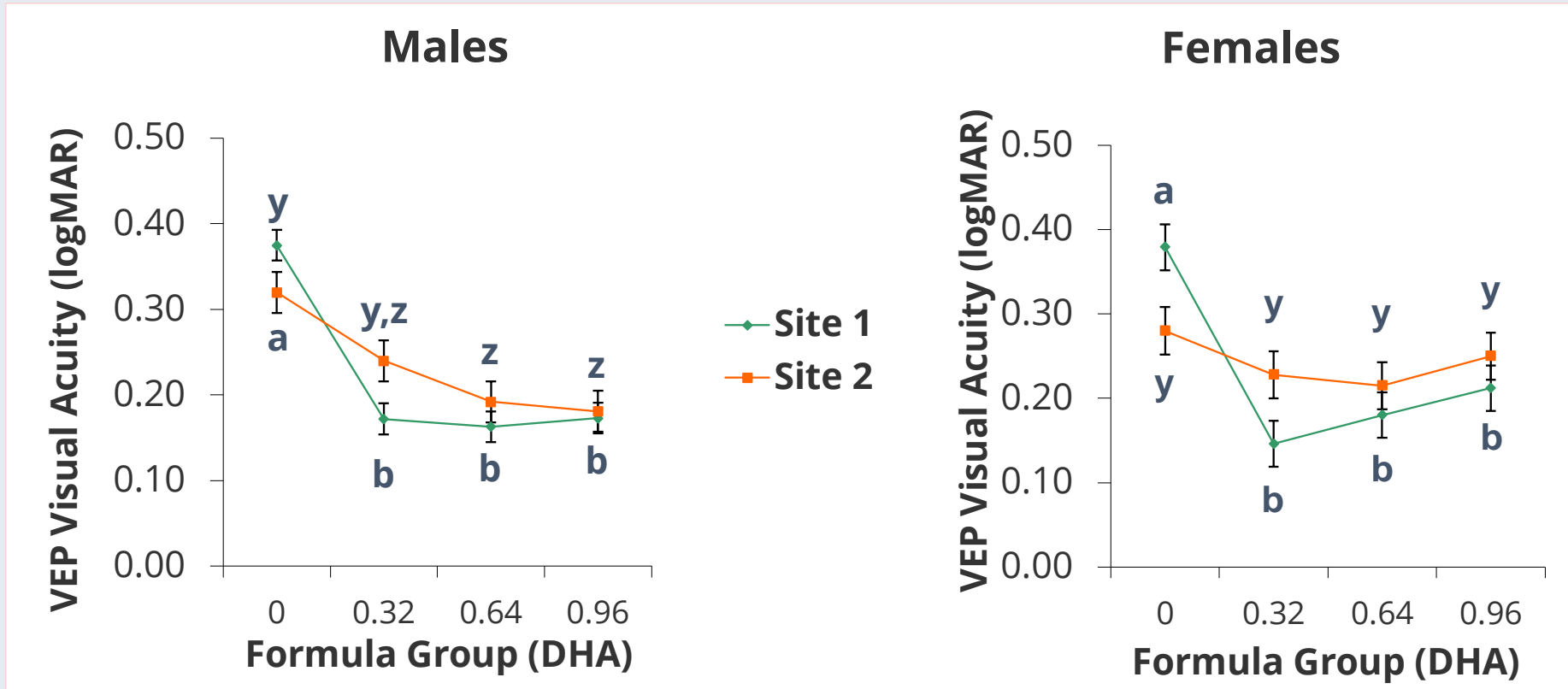
Age-Appropriate Measures of Development Studied in RCTs of DHA Supplementation (DIAMOND and KUDOS)

- 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^[a]

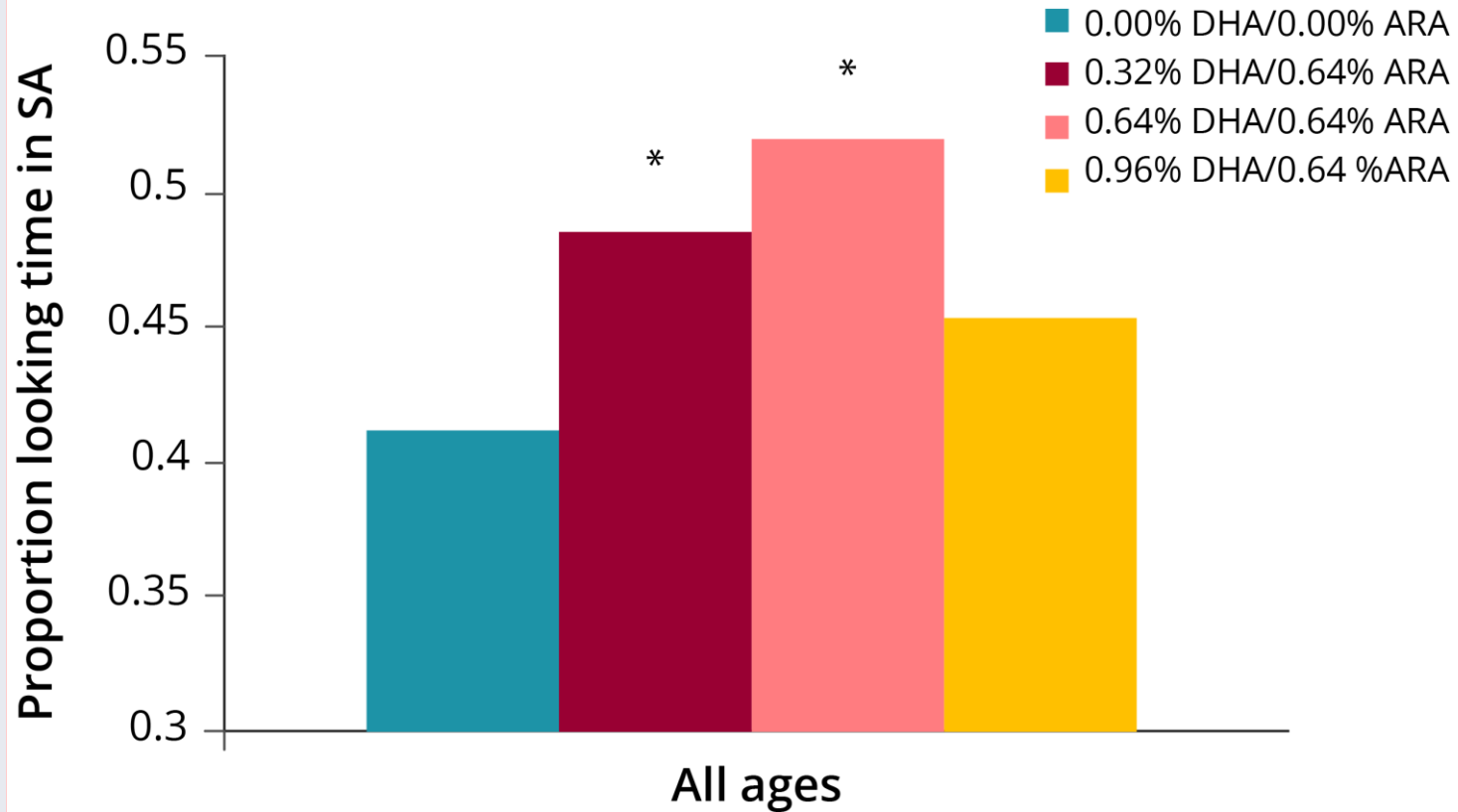
Task	Age (months)											
	1	4	6	9	12	18	36	42	48	60	66	72
Cortical Visual Acuity	•	•		•	•							
Visual Habituation		•	•	•								
Bayley Scales of Infant Development (II)						•						
Stroop Tasks							•	•	•	•		
Dimensional Change Card Sort							•	•	•	•		
Peabody Picture Vocabulary Test (PPVT)										•		
Electrophysiology (ERP): Go/No-Go Tasks											•	
Weschler Preschool Intelligence Scale (WPPSI: IQ)												•

a. 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

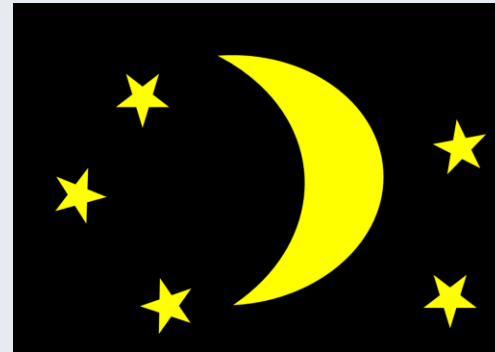
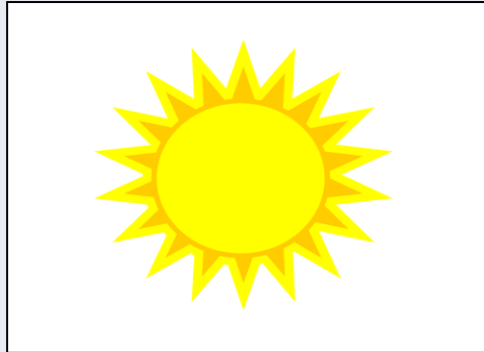
Stroop Tasks (Test of Inhibition)

"Banana"



"Apple"

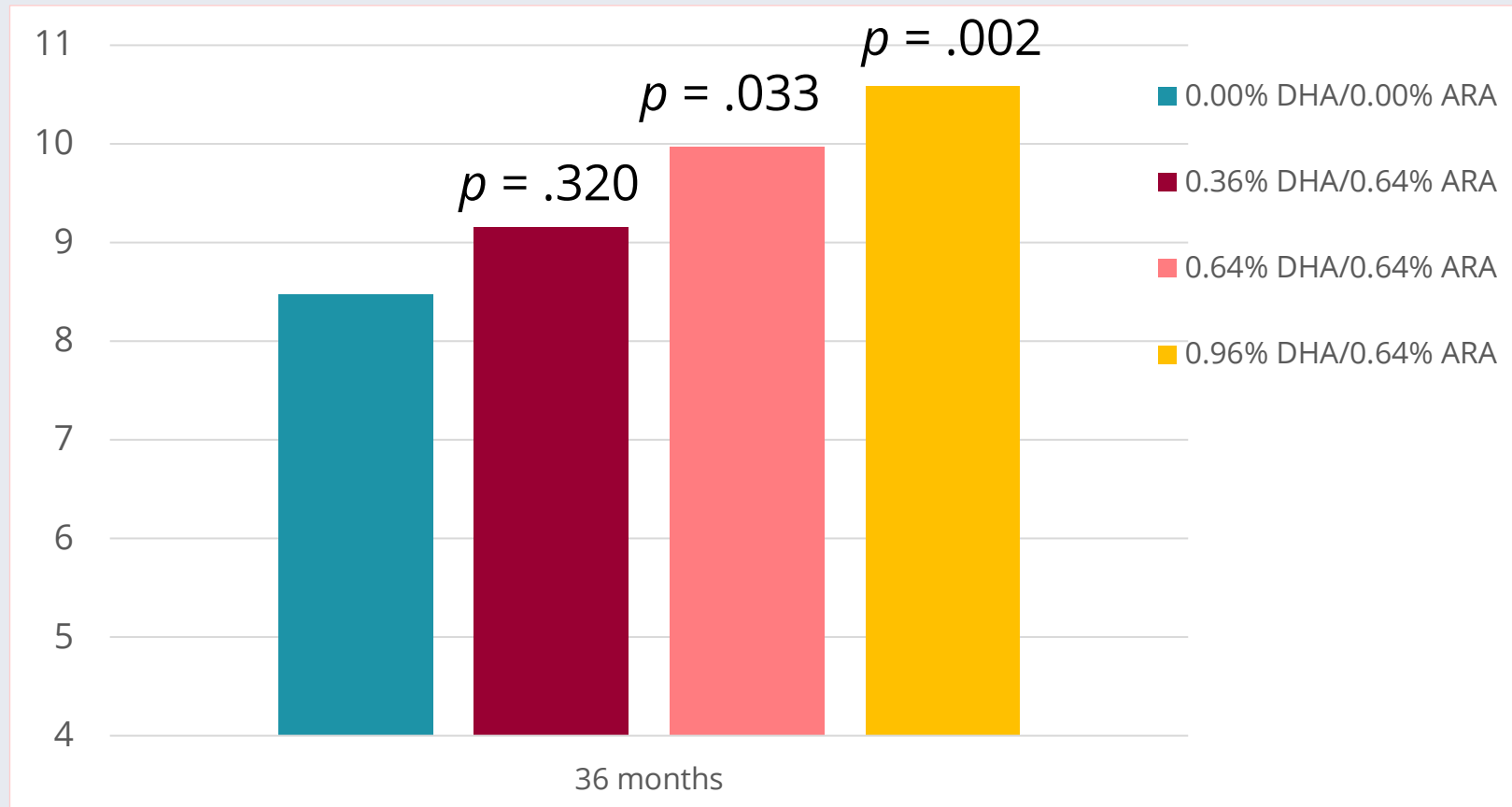
"Night"



"Day"



Stroop Test Scores



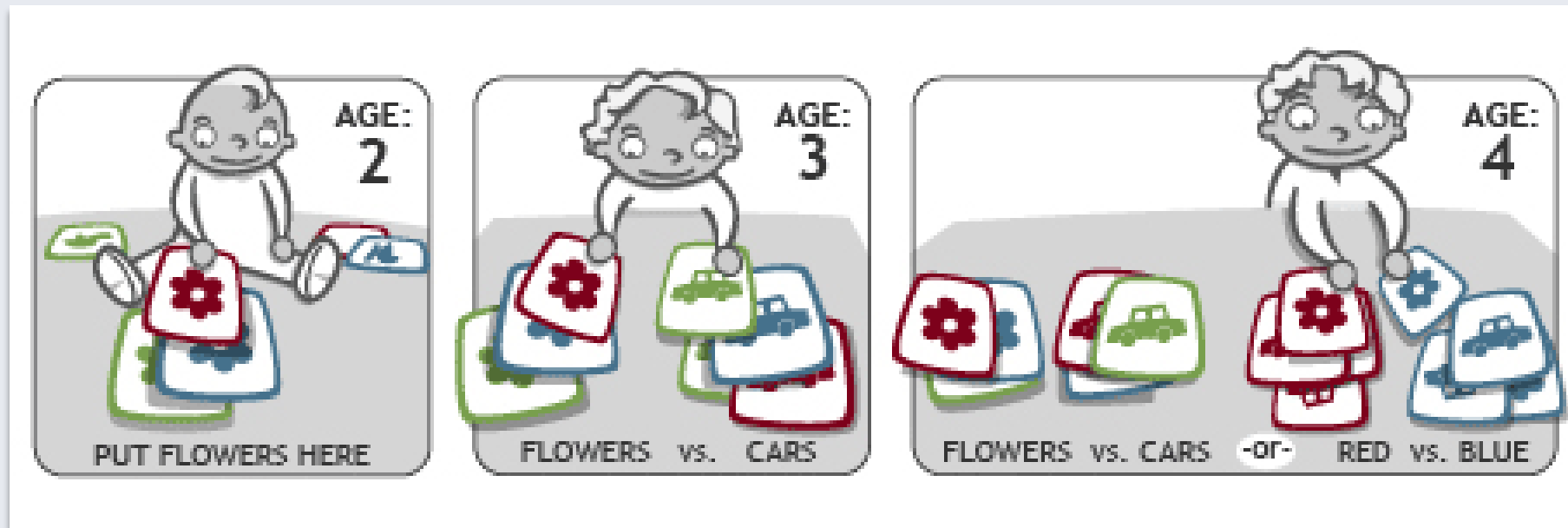
Group: $F(3, 67.644) = 4.045, p = .010$

Visit: $F(3, 65.290) = 24.428, p = .000$



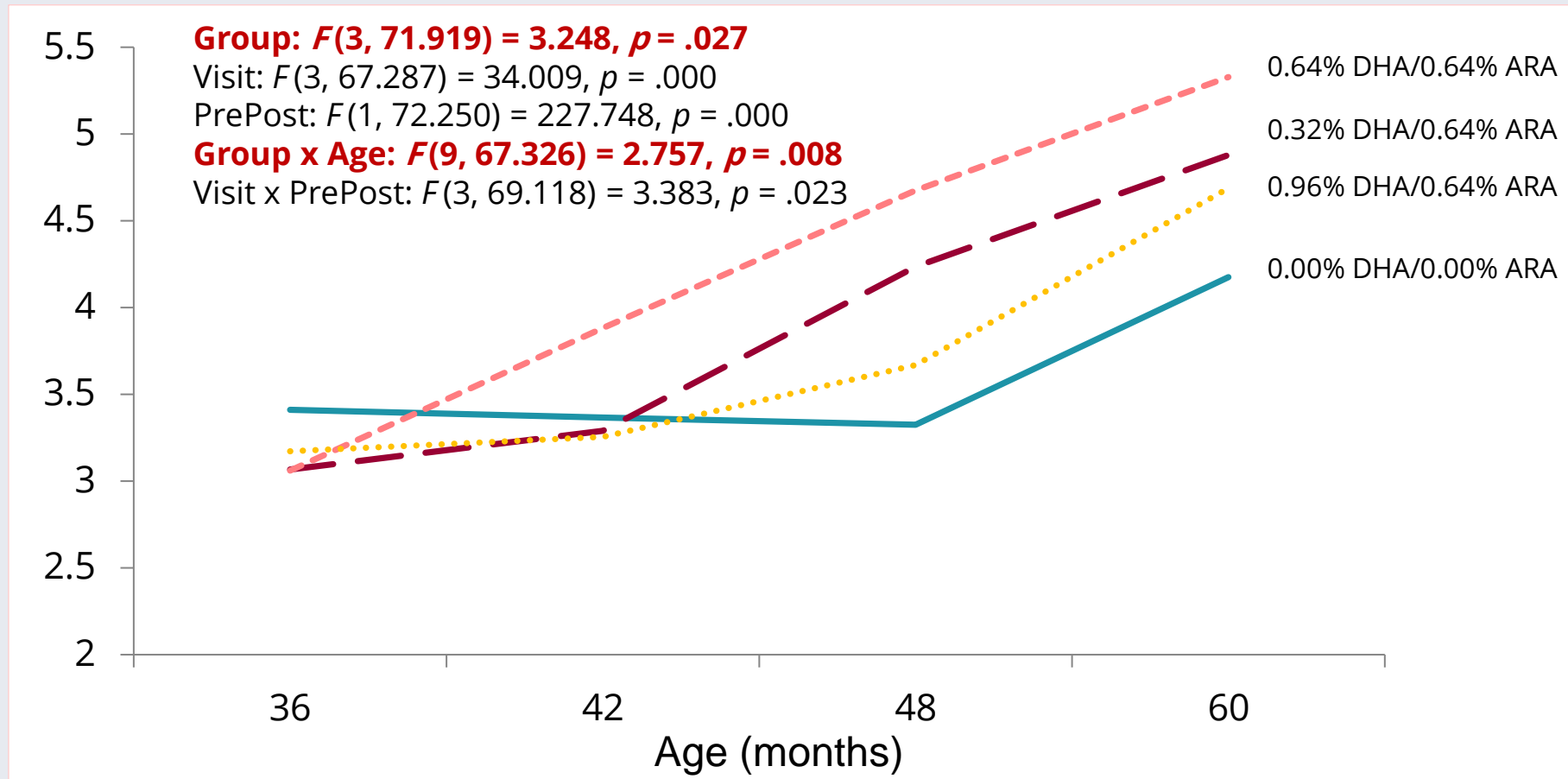
Assessing Neurodevelopment at Different Ages

Dimensional Change Card Sort Ability - Rule Learning/Inhibition

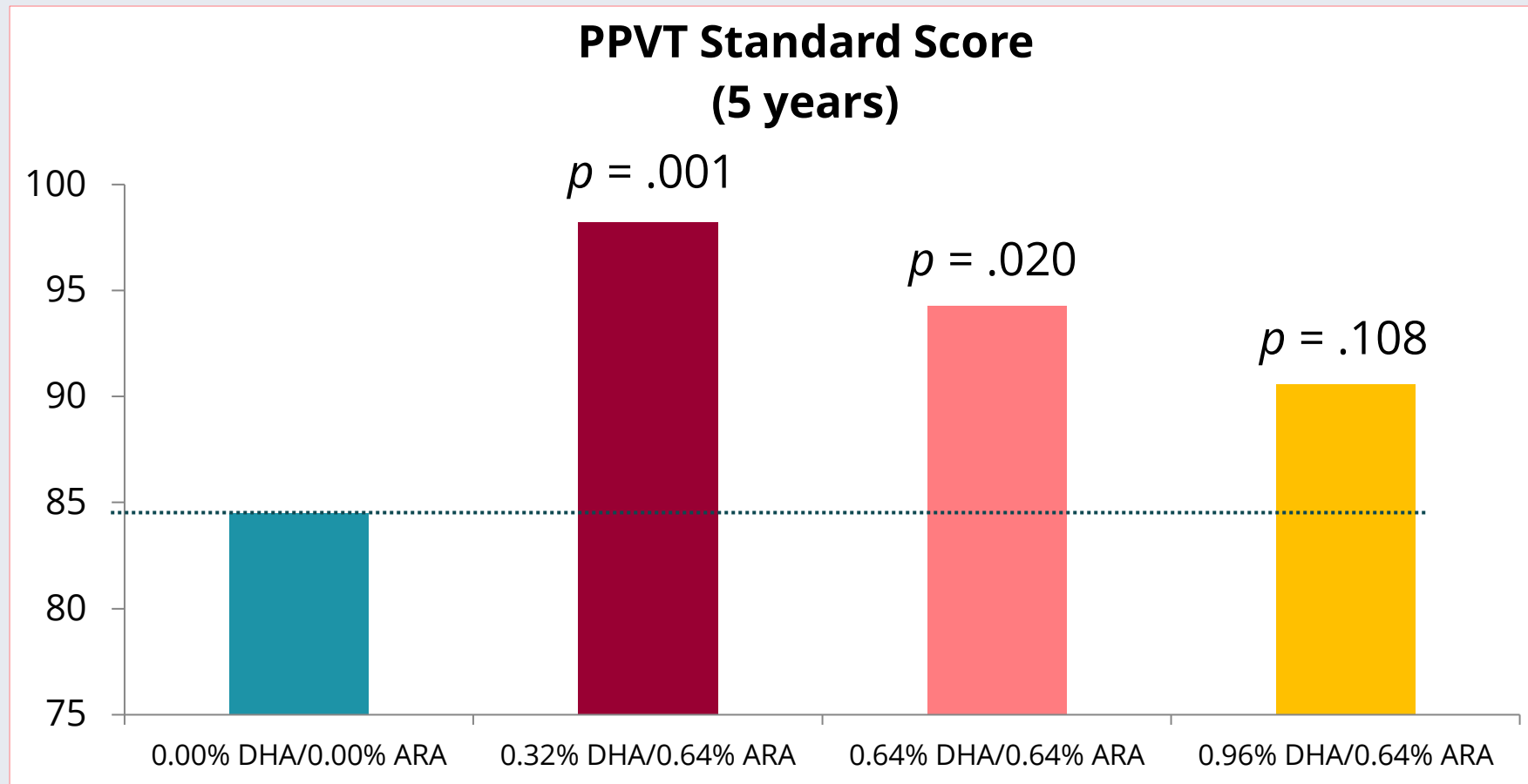


DIAMOND Trial – Dimensional Change Card Sort

Overall DCCS Score: (36, 42, 48, and 60 months)



Verbal IQ Assessment

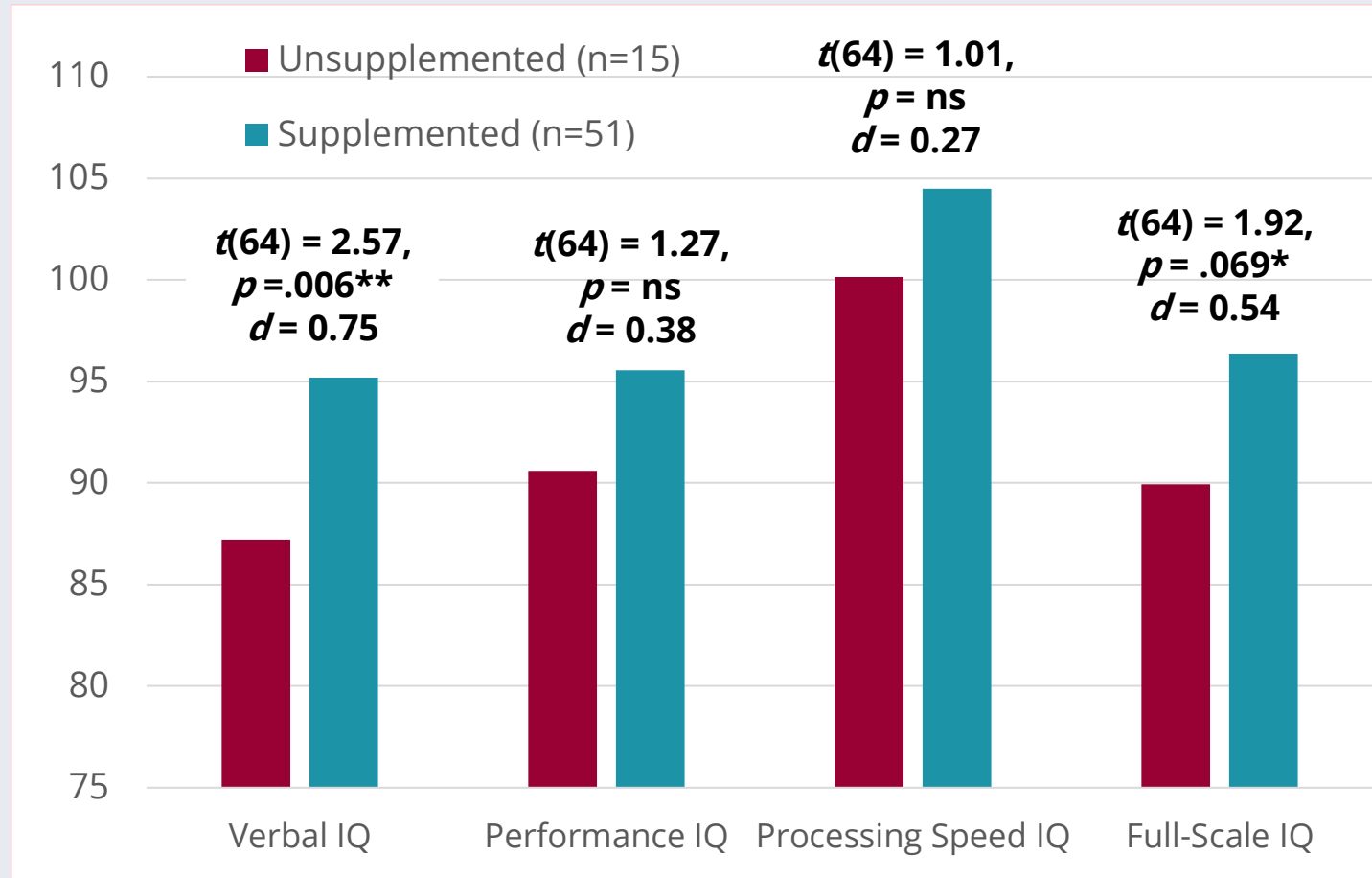


DIAMOND: ANOVA Group Effect: $F(3, 59) = 4.12, p = .01$.

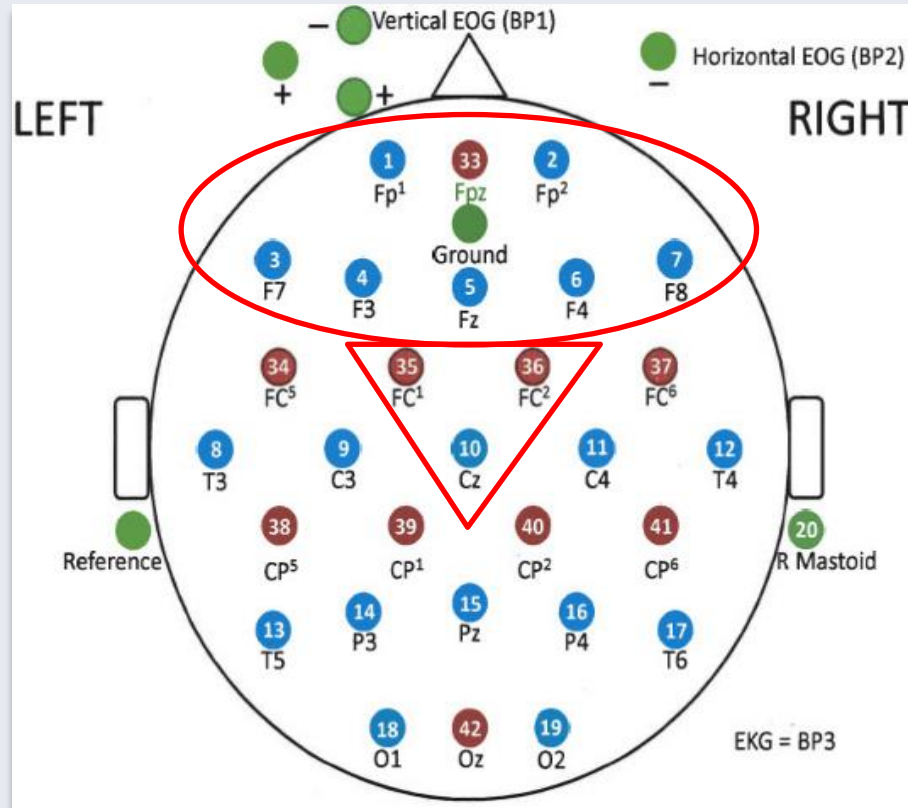
Supplemented (n=49) vs Unsupplemented (n=14): $t(61) = 2.80, p = .007, d = 0.85$



6-yr Weschler Preschool Primary Scale of Intelligence



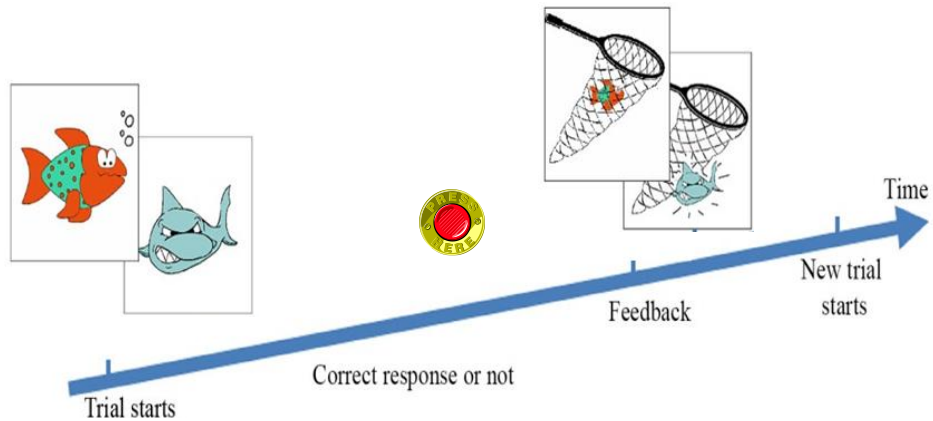
Electrode Montage Employed at 5.5 Years



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

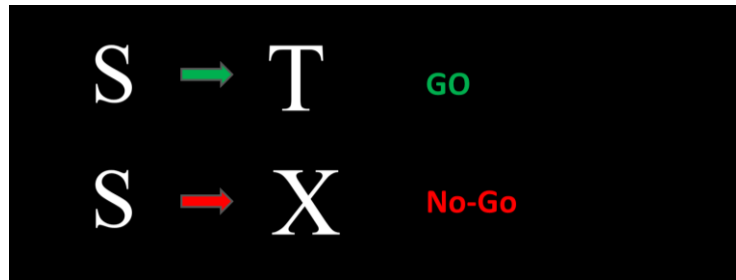


Testing Response Inhibition – Go/No-Go Paradigm



At 5.5 years:

“Catch the fish, not the sharks.” [1]



Age 9 years:

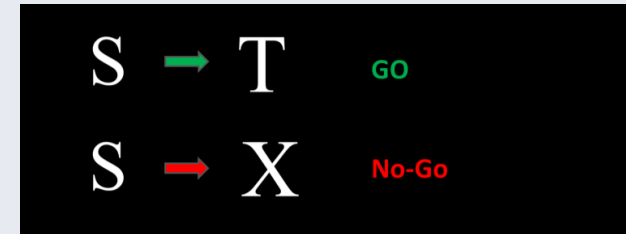
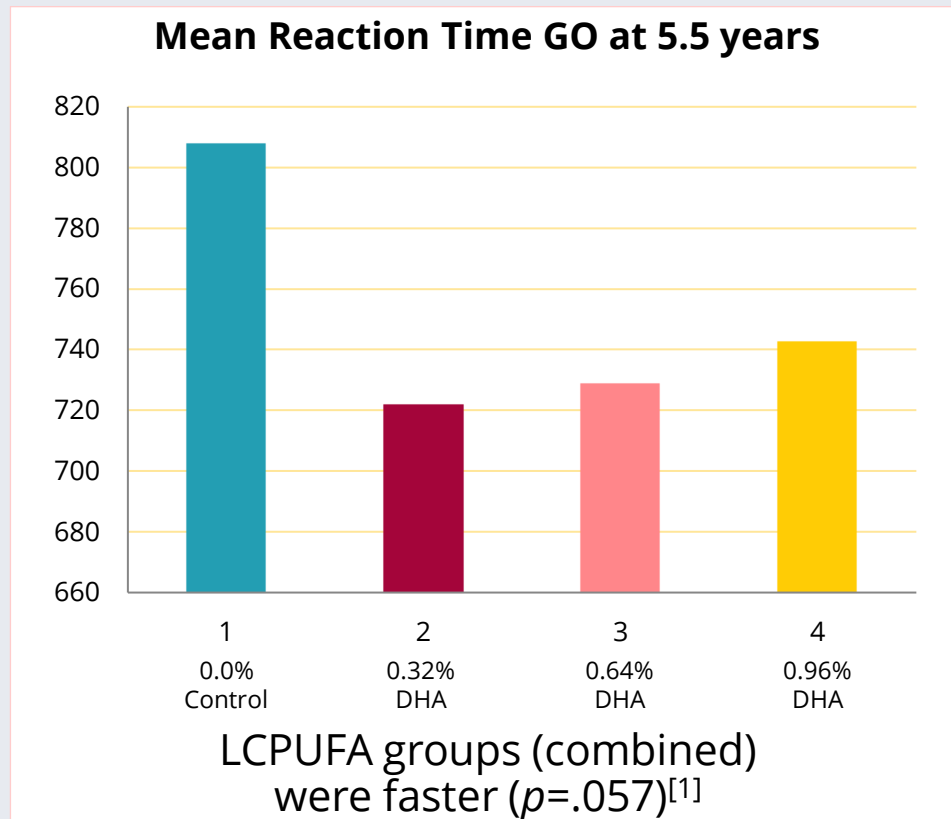
“Press the button when T follows the letter S. Don’t press for any other combination.” [2]

1. Liao K, et al. *Dev Sci.* 2017;20:10.1111/desc.12455.
2. Lepping RJ, et al. *Dev Psychobiol.* 2019;61:5-16.



Reaction Time Faster in Supplemented Groups at 5.5 and 9 Years

Mean Reaction Time and Impulsivity 9 years



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

And:

- Children in the control group are more impulsive ($p=.005$), pressing the button to "S" before waiting for the next letter.
- There is a sex * group interaction ($p=.01$) driven largely by boys in the control group who are the most impulsive.

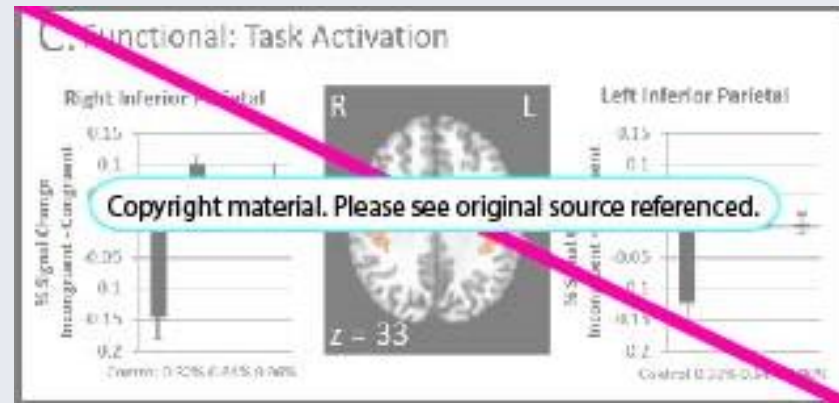
1. Liao K, et al. *Dev Sci.* 2017;20:10.1111/desc.12455.
2. Lepping RJ, et al. *Dev Psychobiol.* 2019;61:5-16.



Results – DIAMOND fMRI, Flanker Task

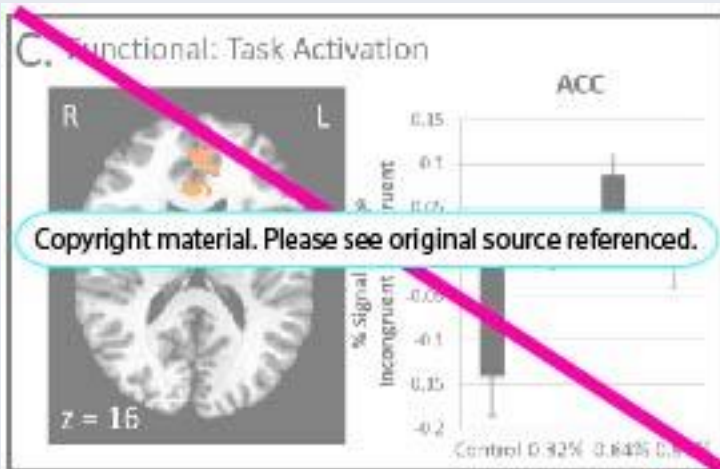
Attention System

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



DHA and Cognitive Outcomes

Results of the KUDOS (prenatal) DHA trial

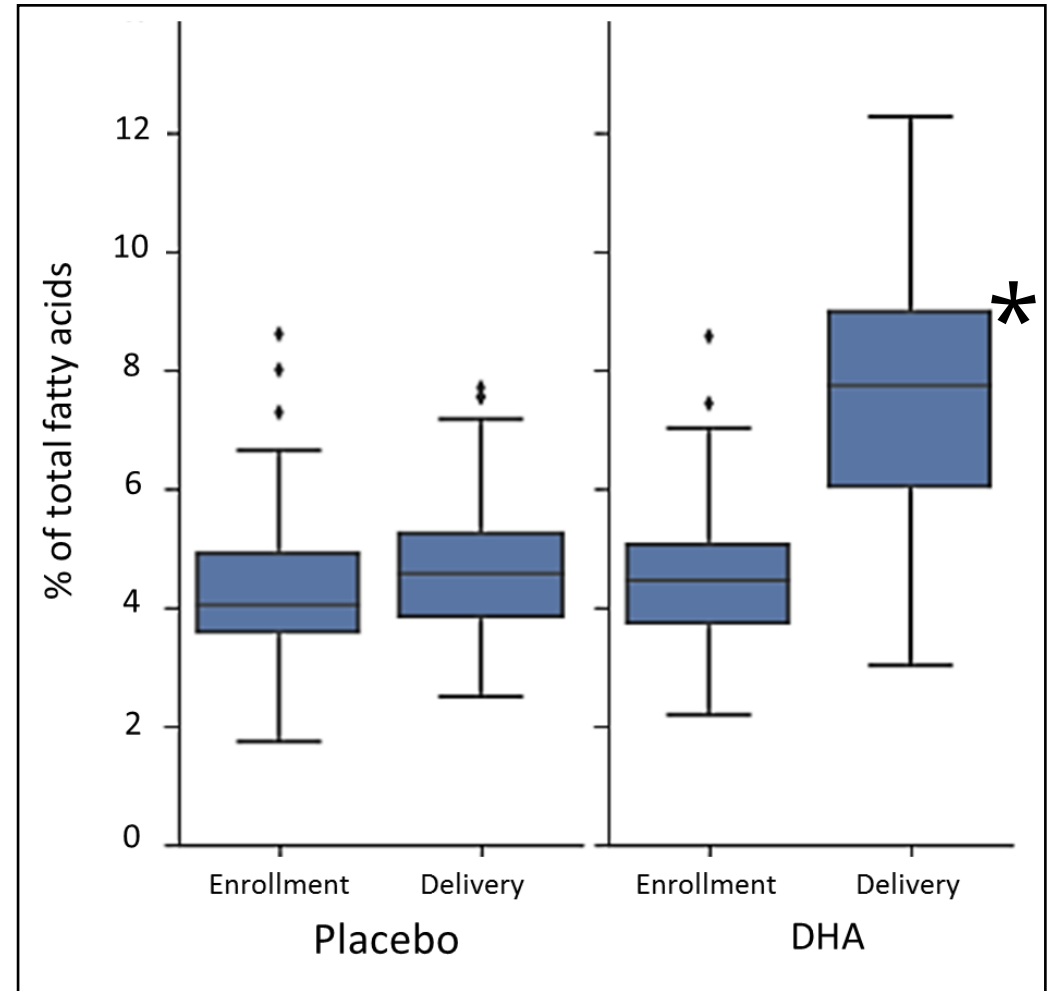
- Conducted 2006–2011
- N=350 enrolled and 301 completed the trial
- Women assigned to placebo or DHA capsules (600 mg)
- Primary outcomes: Pregnancy outcome and cognitive development to 6 years



KUDOS (RCT)

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

Maternal RBC Phospholipid DHA (weight % total fatty acids)



* P=0.0001



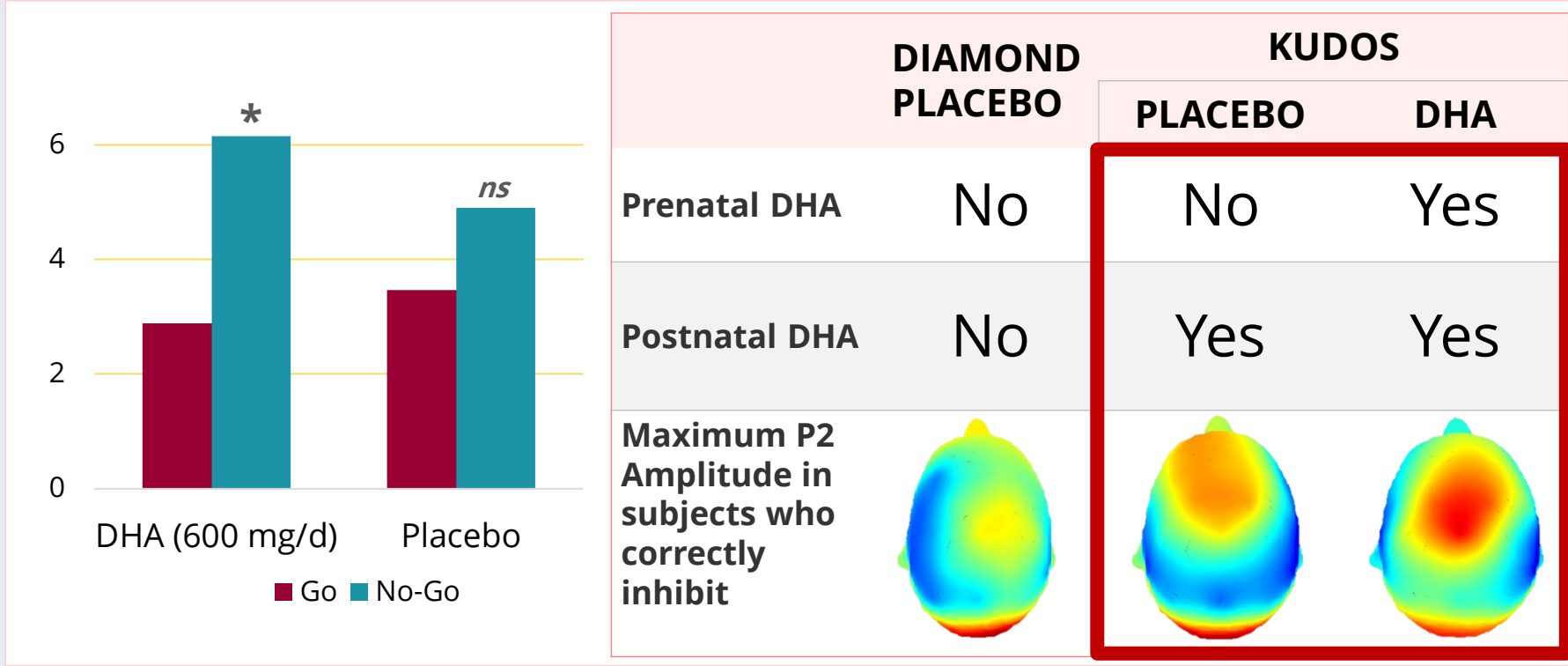
KUDOS Trial (Prenatal) – Neurodevelopmental Assessments

Task	Age (months)												
	1	4	6	9	12	18	36	42	48	60	66	72	
Visual Acuity	•	•		•	•								
Visual Habituation		•	•	•									
Bayley Scales of Infant Development (II)													
Stroop Tasks									•	•	•	•	
Dimensional Change Card Sort									•	•	•	•	
Peabody Picture Vocabulary Test (PPVT)											•		
Electrophysiology (ERP): Go/No-Go Tasks												•	
Weschler Preschool Intelligence Scale (WPPSI: IQ)													•

No effect of maternal DHA supplementation after 12 mo; however, all received DHA postnatally.



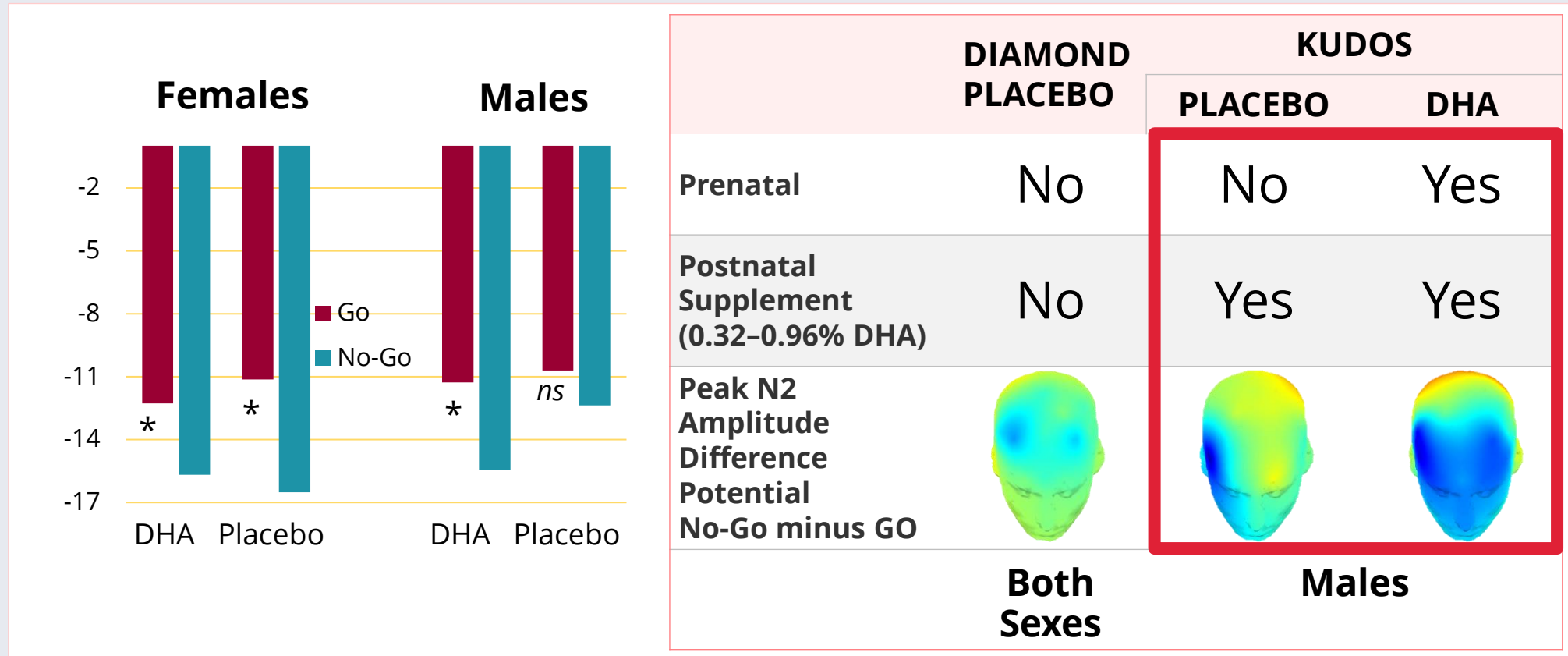
Maximum P2 Amplitude in DIAMOND Control vs KUDOS (Placebo-controlled DHA Supplementation in Pregnancy)^[a]



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)^[a]



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

	Placebo (n=147)	600 mg DHA (n=154)	P-value
Early preterm birth (<34 wks) ^[a]	4.8 %	0.6 %	0.025
Birth weight <1500 g ^[a]	3.4 %	0 %	0.026
Neonatal Intensive Care Unit admission	8.3%	10.4%	NS
Days hospitalized (mean #) ^[b]	40.8	8.9	0.026

a. One tailed *P* values at $\alpha=0.05$. 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

	0 to 6 months of age	6 to 24 months
National Academy of Medicine ^[a]	<ul style="list-style-type: none">• n-6 fatty acids 4.4 g/day• n-3 fatty acids 0.5 g/day	
WHO	<ul style="list-style-type: none">• 0.2 to 0.36% of fatty acids	<ul style="list-style-type: none">• DHA 10 to 12 mg/kg body weight

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

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

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

EFSA, European Food Safety Authority.

1. Jensen CL, et al. *Am J Clin Nutr.* 2005; 82:125–32.



Maternal DHA Intake Guidelines

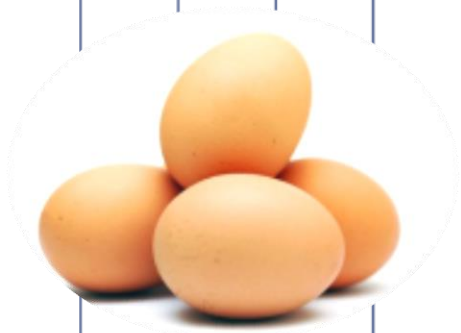
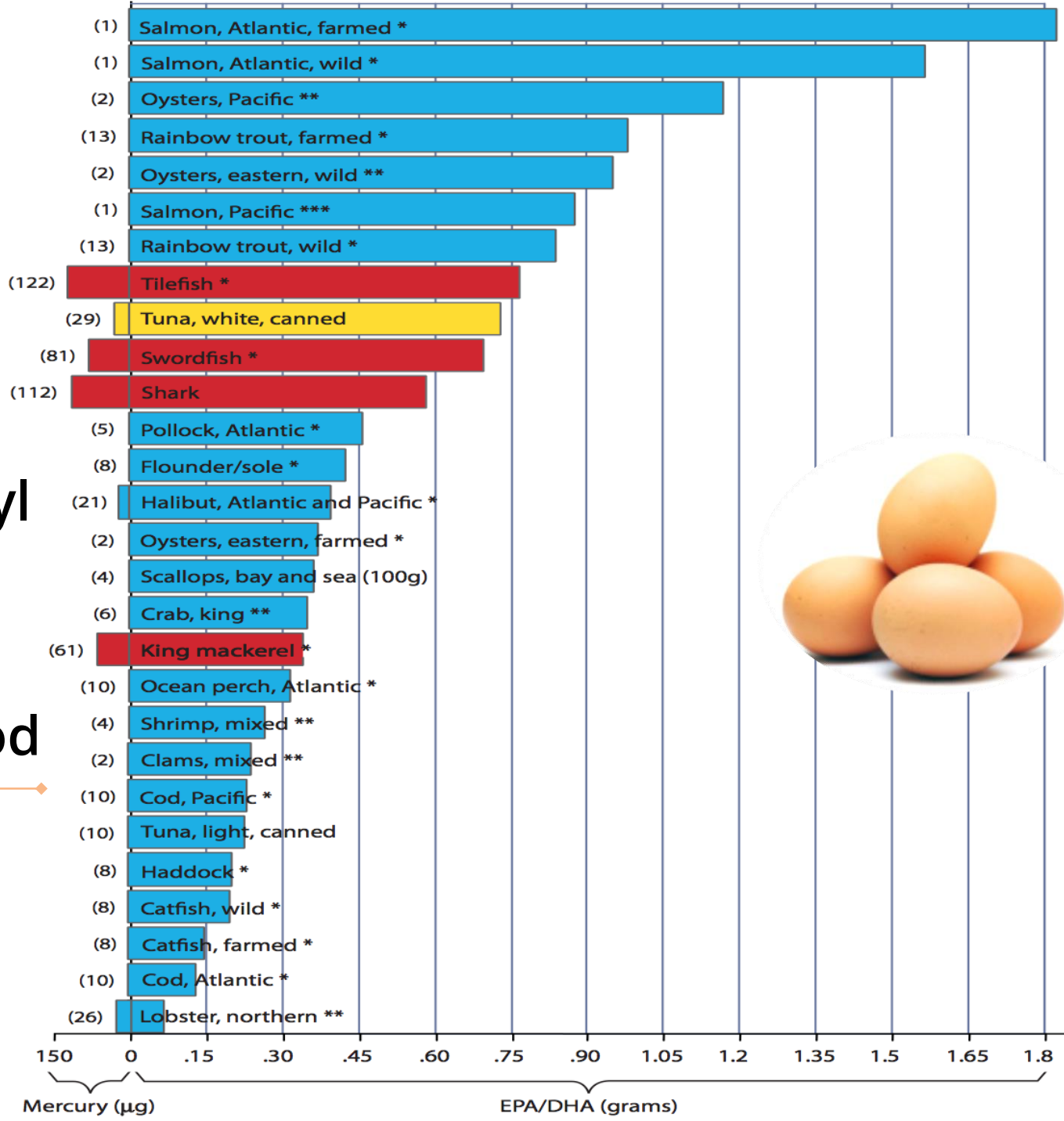
- Maternal dietary DHA intake recommend ≥ 200 –300 mg/day
 - WHO/FAO/ISSFAL recommend at least 200 mg/day for pregnant and lactating women
- Current US Dietary Guidelines recommend pregnant women eat a variety of seafood, min of 250 mg/week n-3 LCPUFA intake
- US EPA recommends lactating women consume 1–3 weekly servings (12 oz/wk) of a variety of seafood low in mercury to ensure adequate breast milk DHA content

FAO, Food and Agricultural Organization; ISSFAL, The International Society for the Study of Fatty Acids and Lipids.

Abrams SA. LCPUFA for preterm and term infants. UpToDate.com. Last updated Jan 21, 2020.



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

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.



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

pnce.org/Thriving-1000

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

Common Seafood Varieties	DHA+EPA ¹ mg/4 ounces	Mercury mcg/4 ounces
Salmon [†] : Atlantic*, Chinook*, Coho*	1,200–2,400	2
Anchovies ^{††} and Herring ^{††}	2,300–2,400	5–7
Mackerel: Atlantic and Pacific	1,350–2,100	8–13
Oysters: Pacific	1,550	2
Trout: Freshwater	1,000–1,100	11
Tuna: White (Albacore) canned	1,000	40
Salmon [†] : Pink* and Sockeye*	700–900	2
Crab: Blue [†] , King ^{††} , Snow [†] , Queen*, and Dungeness*	200–550	9
Flounder ^{††} and Sole ^{††}	350	7
Clams	200–300	0
Tuna: Light canned	150–300	13
Catfish	100–250	7
Cod [†] : Atlantic* and Pacific*	200	14
Scallops [†] : Bay* and Sea*	200	8
Shrimp	100	0
Seafood varieties that should <i>not</i> be consumed by women who are pregnant or breastfeeding.		
Shark	1,250	151
Tilefish [†] : Gulf of Mexico [†]	1,000	219
Swordfish	1,000	147
Mackerel: King	450	110

Source: Adapted from USDA, Feb 2012

