

Impact of DHA on Pregnancy and Child Outcome

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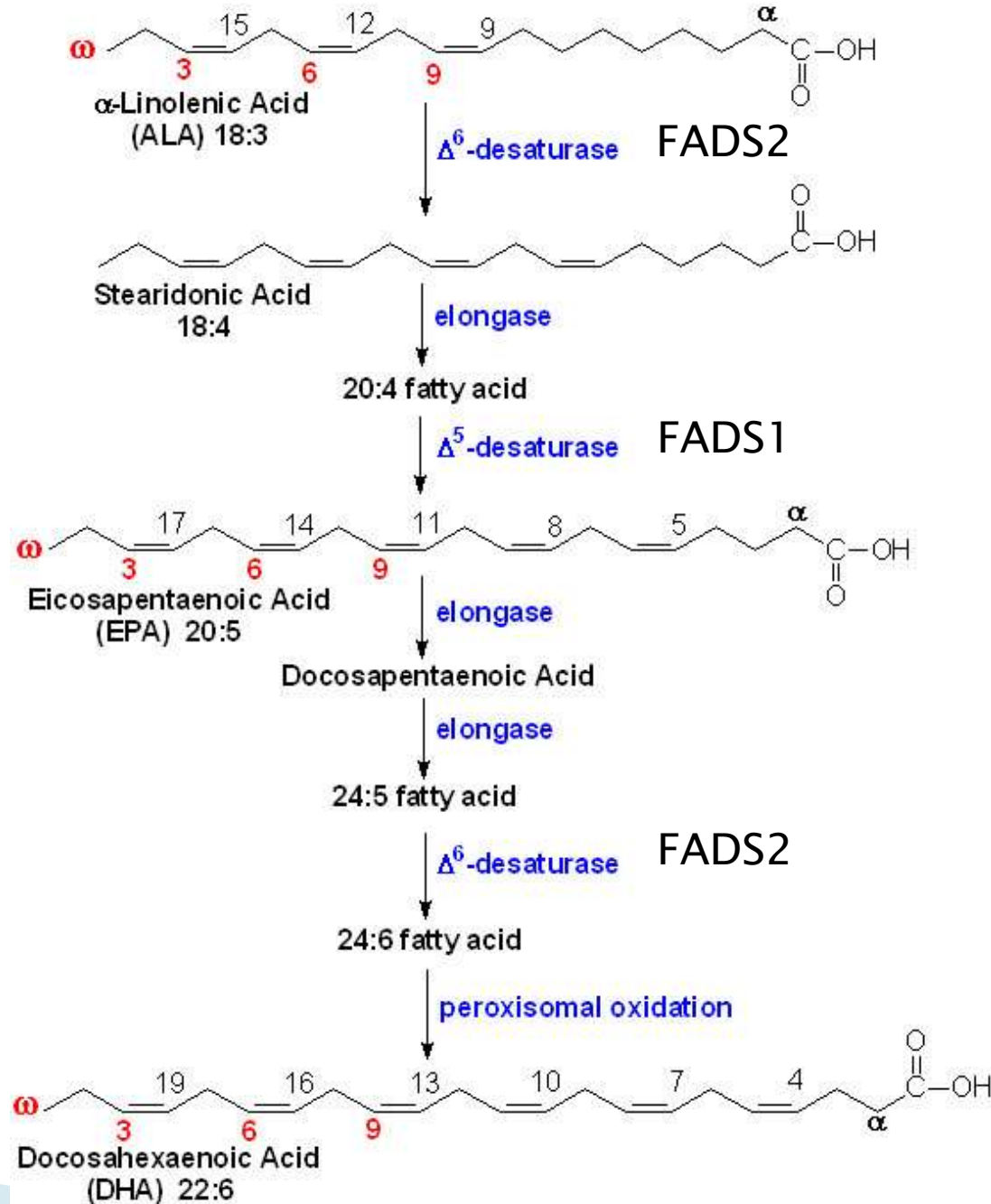
What is DHA?

22 carbon, 6 double bond omega-3 (or n-3) fatty acid

Can be obtained from the diet (seafood and eggs) and supplements (e.g., fish oil or **algal oil**)

Can be synthesized from another dietary fatty acid, ALA, found in plants and plant oils

US adults consume ~1 g ALA and ~0.07 g DHA daily



DIAMOND STUDY: Randomized Trial of Postnatal DHA Supplementation*

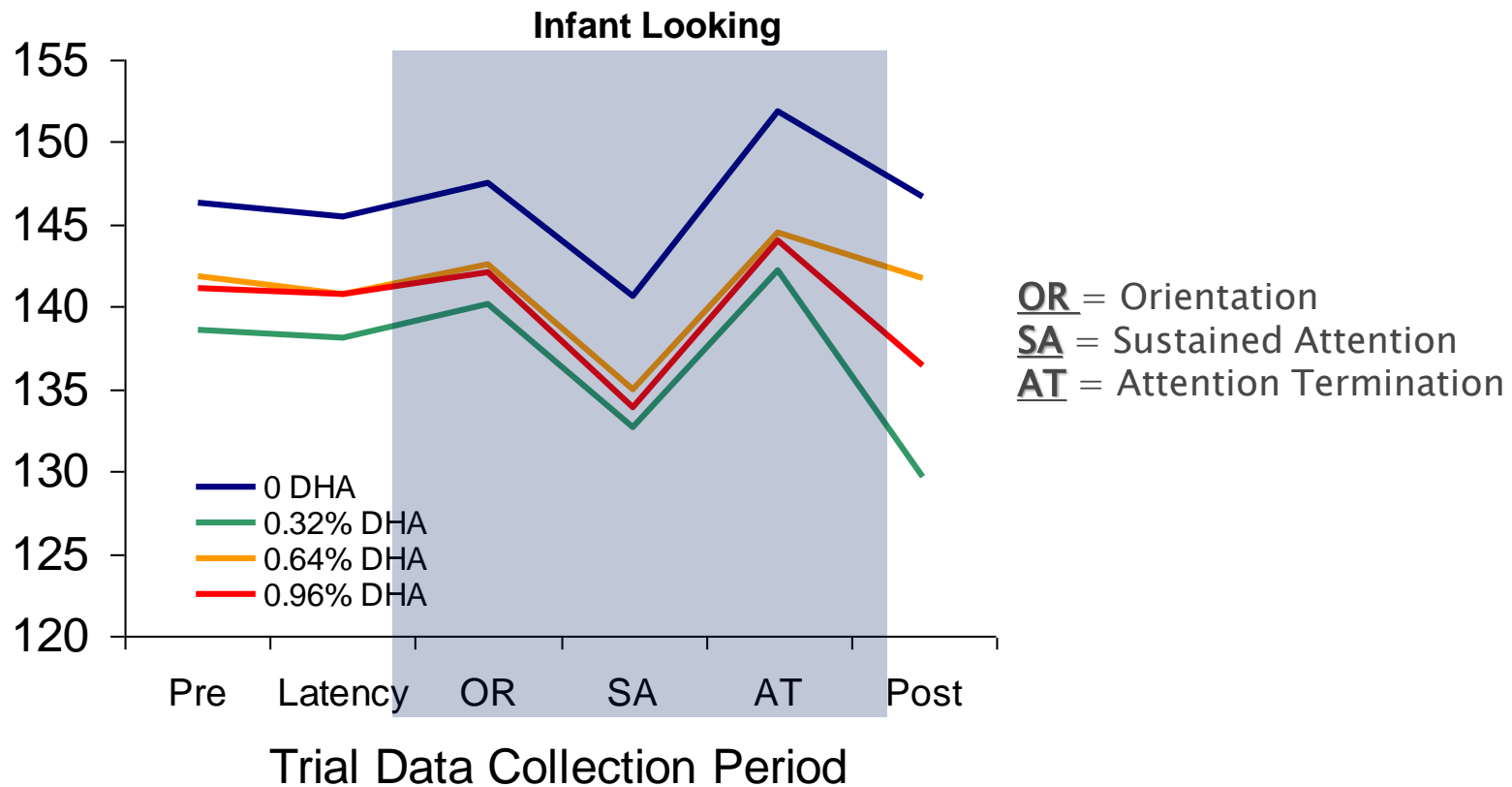
- ▶ DHA Intake And Measurement Of Neural Development
- ▶ Algal DHA supplementation in infant formula fed first 12 mo on visual acuity and cognitive development to 6 years
- ▶ Four concentrations of formula DHA**
 - 0.0% DHA
 - 0.32% DHA
 - 0.64% DHA
 - 0.96% DHA

In most analyses we combine these groups and compare them to the control as they yielded similar results

*All DHA supplemented formulas contained 0.64% ARA

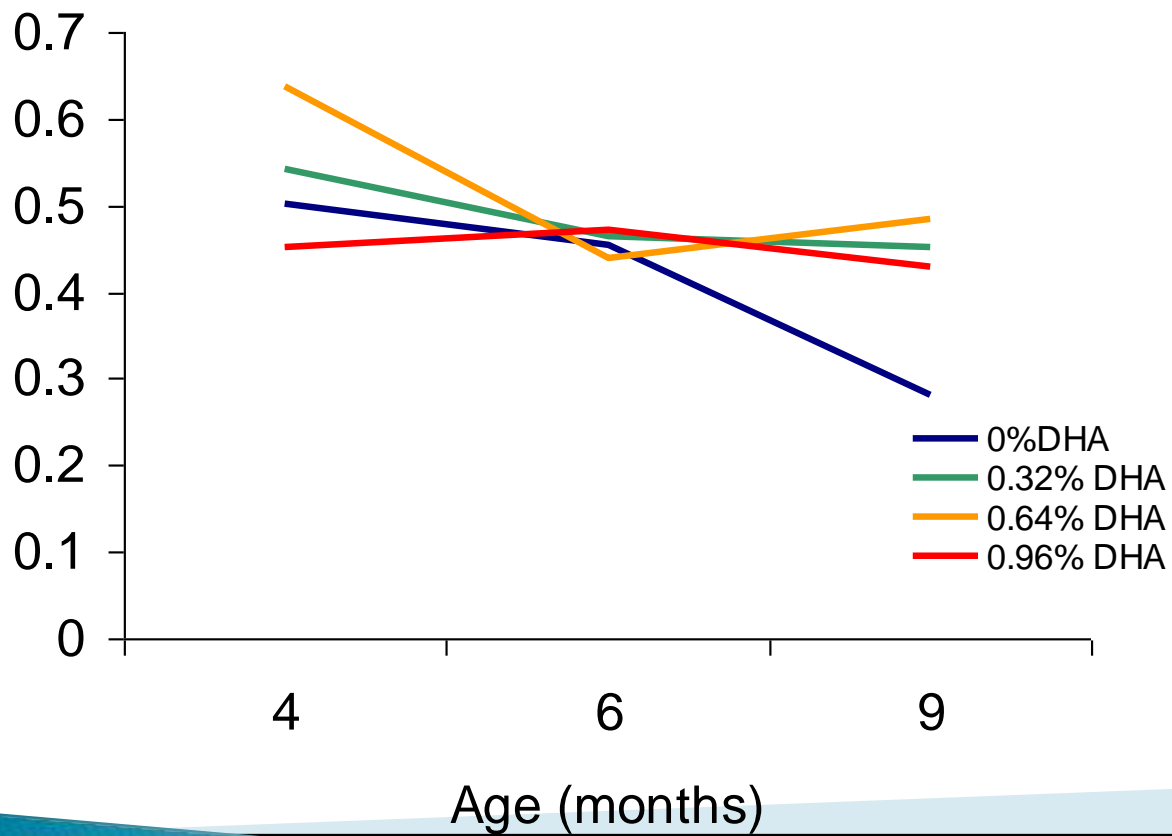
**0, 17, 34 or 51 mg DHA/100 kcal of infant formula

DIAMOND STUDY: At 6 months of age, infants consuming DHA (and ARA) had lower heart rate (bpm) in all phases of an attention task



Colombo et al., Pediatr Res 2011

DIAMOND STUDY: Dietary DHA and ARA increases infant sustained attention (an early measure of cognition) at 9 mo



Colombo et al., Pediatr Res 2011

Age X Group Mixed Model Analysis
Age: $F(2,168.864) = 7.94, p=.001$
Group: $F(3,265.235) = 3.16, p=.025$
Age X Group: $F(6,171.332) = 2.04, p=.068$

DIAMOND TRIAL: Stroop Test Scores

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

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

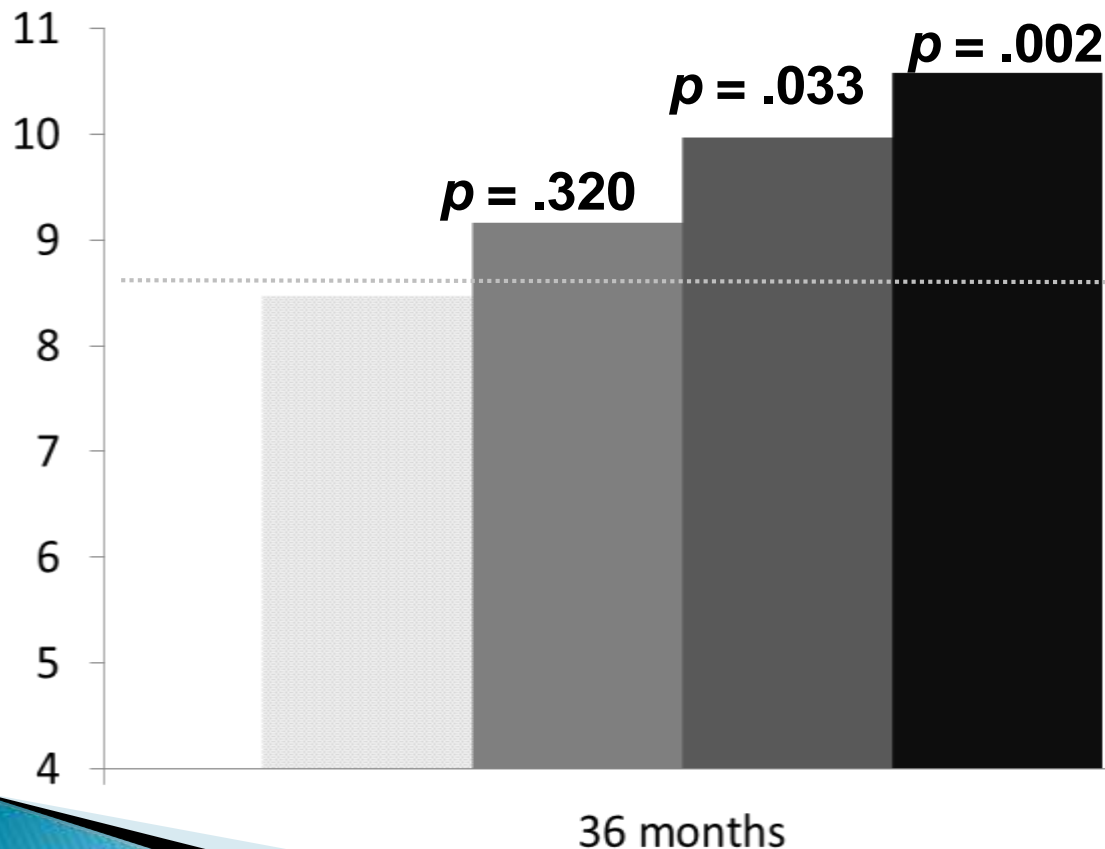
Group X Visit: $F(9, 76.162) = 1.265, p = ns$

■ 0.00% DHA/0.00% ARA

■ 0.36% DHA/0.64% ARA

■ 0.64% DHA/0.64% ARA

■ 0.96% DHA/0.64% ARA



Children required to Follow a rule counter To an automatic response: for example, point to the color red when shown a banana or the color yellow when shown an apple

DIAMOND TRIAL RESULTS: DCCS Score (36, 42, 48, and 60 months)

Visit: $F(3, 69.621) = 15.138, p = .000$

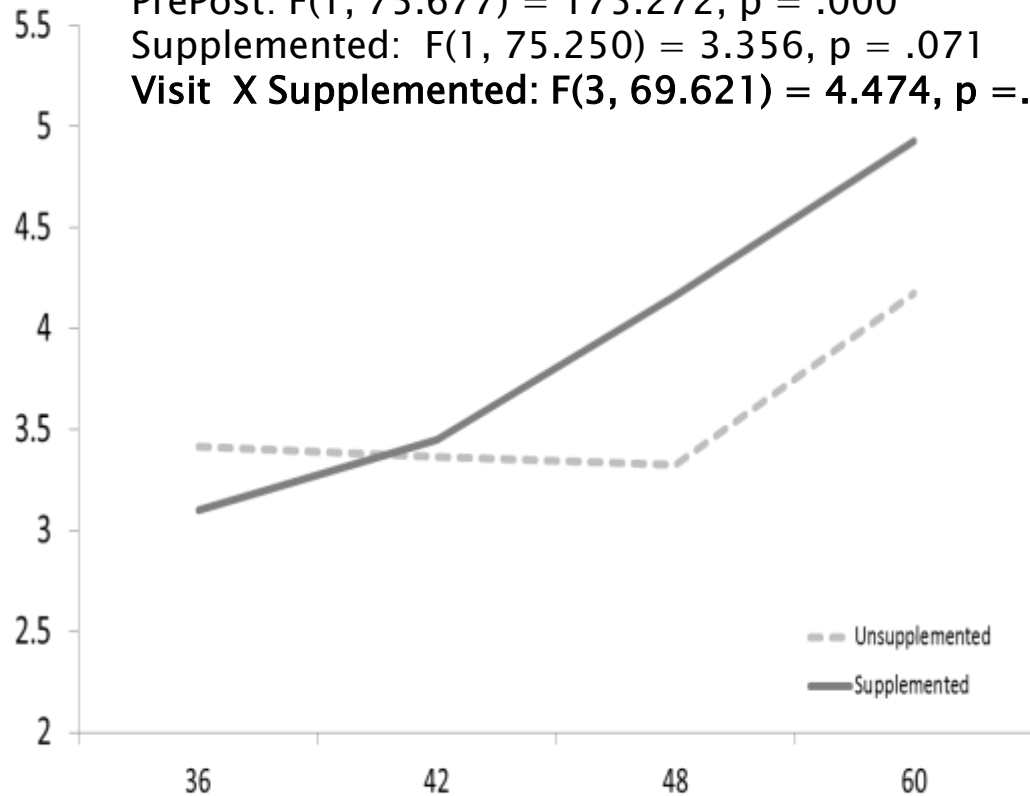
PrePost: $F(1, 75.677) = 175.272, p = .000$

Supplemented: $F(1, 75.250) = 3.356, p = .071$

Visit X Supplemented: $F(3, 69.621) = 4.474, p = .006$

The Dimensional Change Card Sort (DCCS) is based on classic discrimination learning and is administered according to a standard protocol.

It provides data on rule learning and the ability to inhibit use of an old rule when a new one is introduced.



Age (months)

Adapted from Colombo et al., AJCN 2013

DIAMOND TRIAL RESULTS

The Peabody Picture Vocabulary Test, 3rd edition (PPVT-III) is a well-standardized and widely used measure of vocabulary for individuals from 2.5 to 90 y of age. It is used in some cases as an indicator of verbal intelligence quotient (IQ) or as a surrogate for overall IQ.

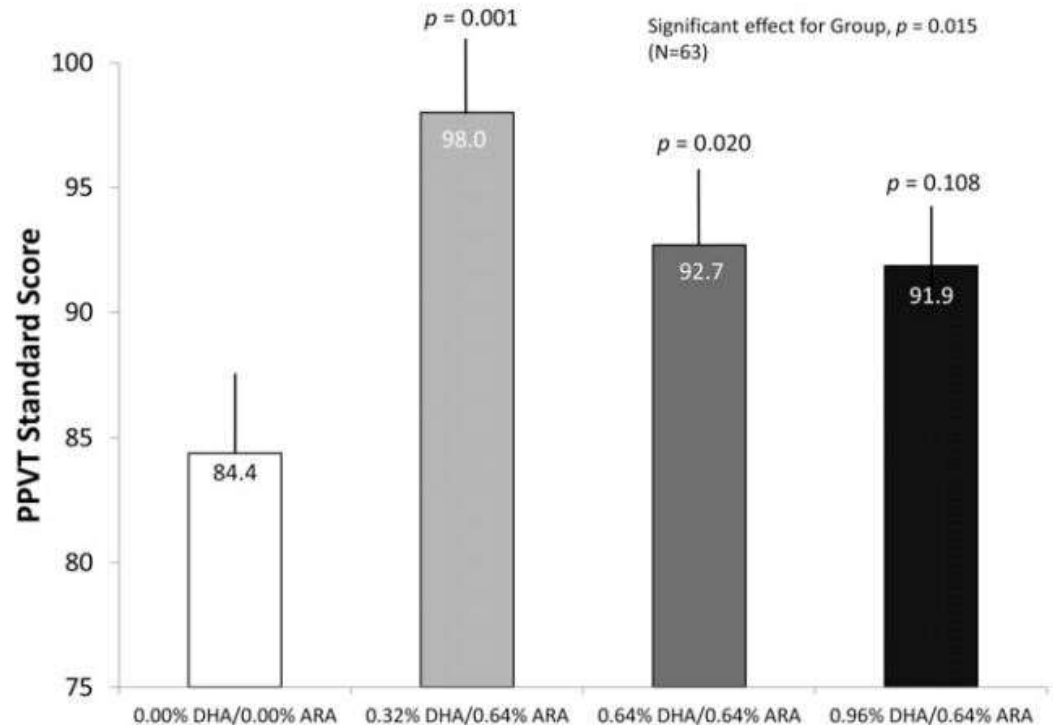


FIGURE 5. Mean (\pm SE) PPVT-III standard scores, adjusted for covariates, at age 5 y as a function of group assignment. Both one-factor ANOVA and ANCOVA analyses showed that infants who received the long-chain PUFA formula performed better on the PPVT-III. The effects were most evident in the 0.32% DHA and 0.64% DHA groups; the *P* values represent statistical test results against control group values; the numbers within the bars are means. ARA, arachidonic acid; PPVT-III, Peabody Picture Vocabulary Test, 3rd edition.

DIAMOND TRIAL RESULTS

The WPPSI-III is among the most widely used and best-standardized tests of early intelligence available. At this age, there are 8 core subtests (information, vocabulary, word reasoning, block design, matrix reasoning, picture concepts, symbol search and coding) which are combined in various configurations to provide

- Verbal IQ
- Performance IQ
- Full-Scale IQ Score
- Processing Speed Quotient

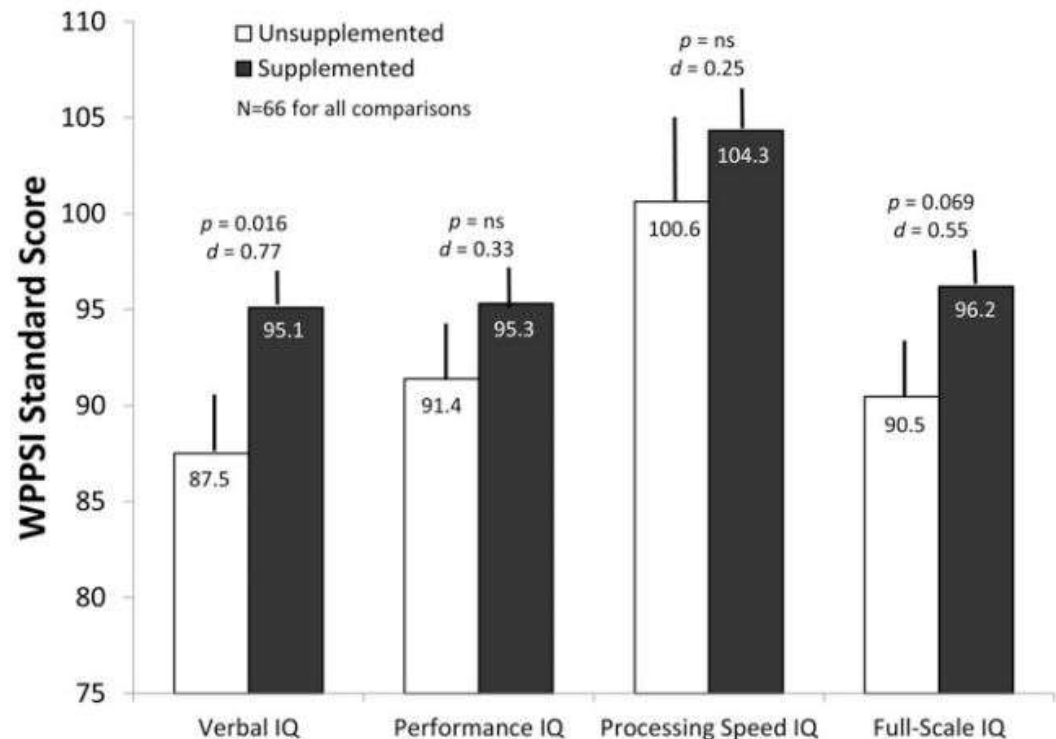
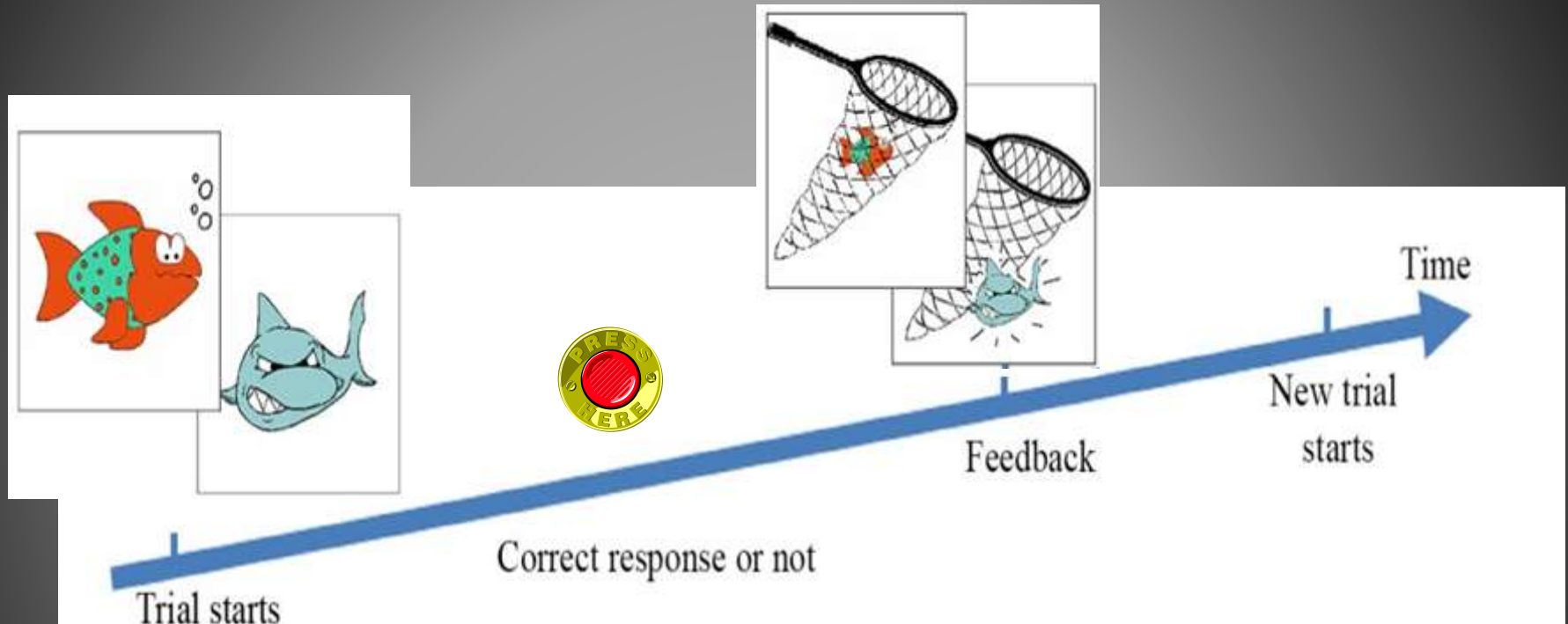


FIGURE 6. Mean (\pm SE) WPPSI-III standard scores, adjusted for covariates, at age 6 y as a function of assignment to LCPUFA or control formula. Both ANOVA and ANCOVA analyses showed that infants who received the LCPUFA formula performed significantly better on the Verbal IQ subscale, and the differences were nearly significant for Full-Scale IQ. The numbers within the bars are means. The *P* values represent the results of ANCOVAs that compared values from the 3 LCPUFA groups (collapsed) with the control group; the *d* values represent the effect size for each comparison and were adjusted for covariates. IQ, intelligence quotient; LCPUFA, long-chain PUFA; WPPSI-III, Weschler Primary Preschool Scale of Intelligence, 3rd edition.

Go vs. No-Go



Go trials (catch a fish) = 74% of trials n=51

No-Go trials (do NOT catch the shark) = 26% of trials
n=18

DIAMOND Trial: Evoked Response Potentials (ERPs) at 5.5 Years of Age

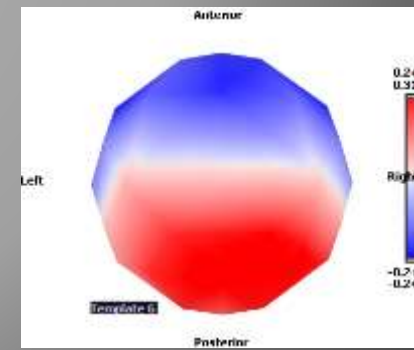
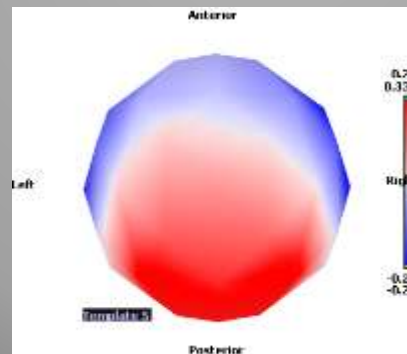
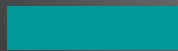
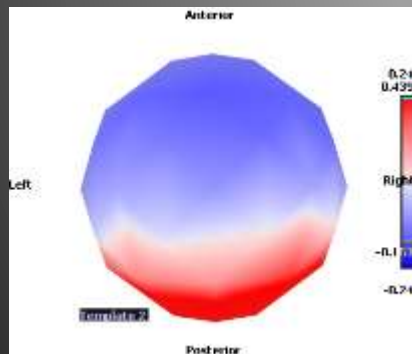
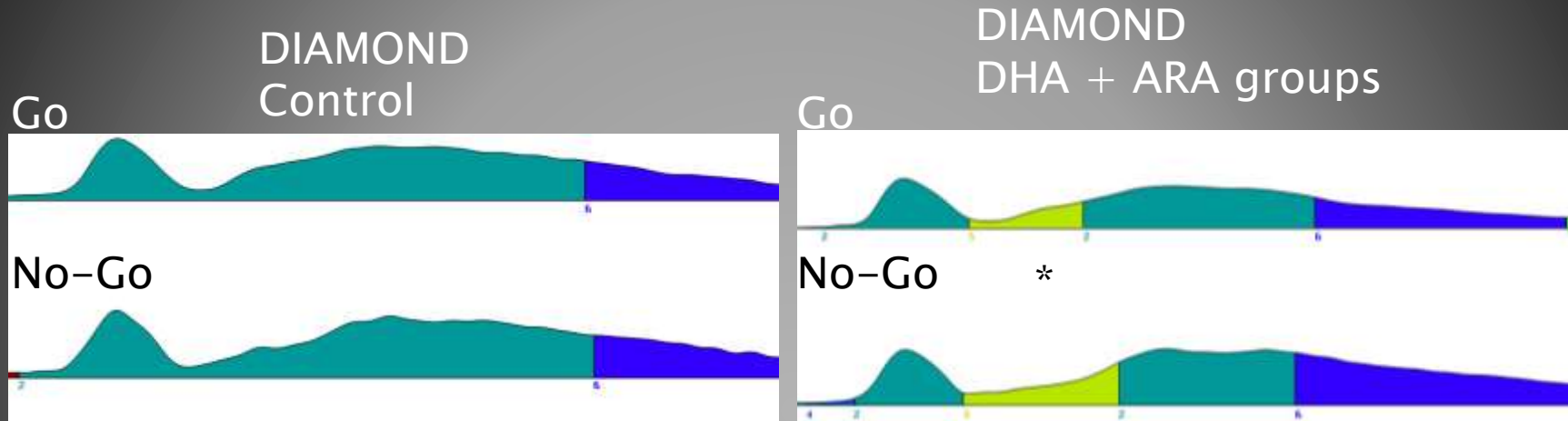


Using GO-No GO Paradigm:
Child is told to catch the fish
But not the sharks

DHA supplemented children
show a distinct brain
electrophysiological
difference between No GO
(Sharks) and Go (fishes);
unsupplemented children
did not

Confirms our published
behavioral results showing
better ability to inhibit

Brain Electrical Interconnectivity Microstates at 5.5 Years of Age



*Unique microstate in supplemented children; significantly different between Go and NoGo

DHA IN INFANCY HAS LONG TERM (PROGRAMMING) EFFECTS ON BRAIN DEVELOPMENT

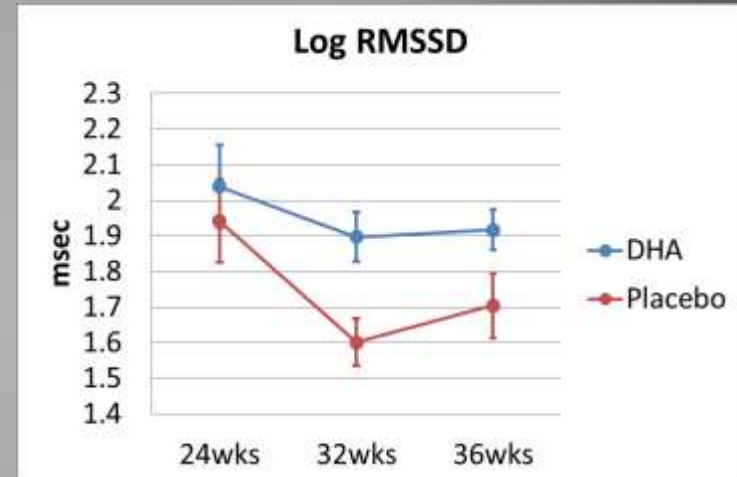
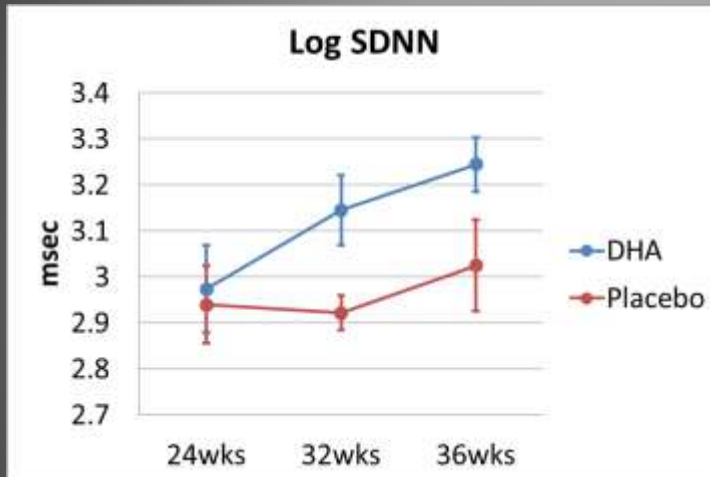
In general we find positive effects of DHA and ARA supplementation in infancy on

- ▶ Attention; e.g., more mature looking or sustained attention that are evidence of lower distractibility
- ▶ Processing speeds
- ▶ Vocabulary and verbal IQ
- ▶ Ability to inhibit actions; e.g., learn a new rule or inhibit an automatic response
- ▶ Response inhibition on a Go-No Go task
- ▶ Brain interconnectivity during response inhibition
- ▶ Evidence with 0.64% DHA and ARA, that children realize their mistake

Prenatal DHA Supplementation

- ❖ **KUDOS trial** → Phase III RCT provided 600 mg algal DHA/d or placebo beginning at a mean of 14.4 wks gestation until birth. Primary aims: Pregnancy outcomes and offspring cognitive function to 6 yrs
- ❖ All children received DHA and ARA postnatally either from human milk or LCPUFA supplemented formula

HOPE trial: Fetal HRV from 24 – 36 weeks GA



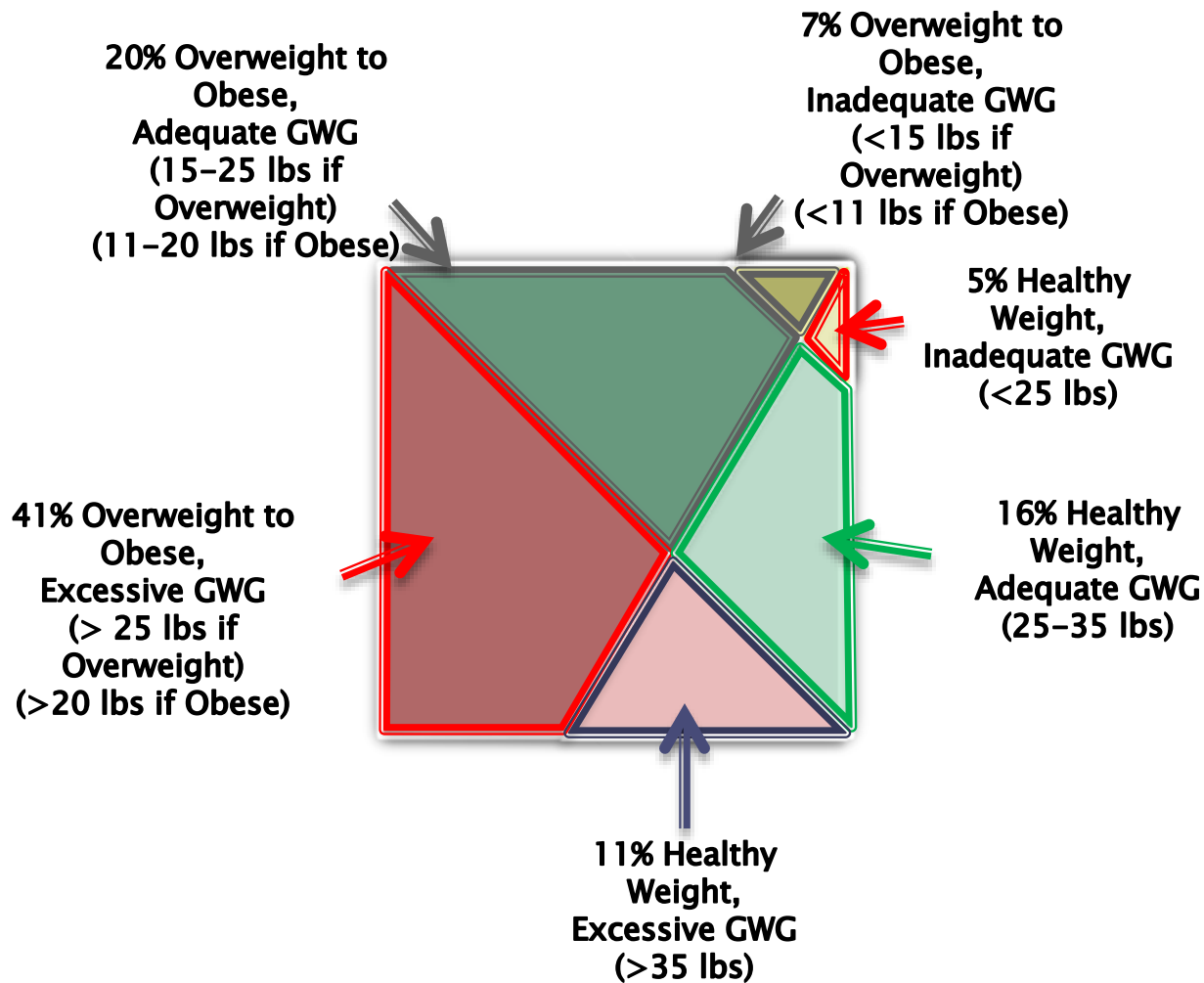
Fetal overall HRV (log SDNN) and short-term HRV (log RMSSD)

Population Demographics

	Placebo	DHA
Maternal age (yrs)	25.1	25.6
White/black (%)	56/44%	64/34%
Pre-pregnancy BMI	24.9	25.8
Normal wt/overwt/obese (%)*	42/32/26%	36/32/31%
History of smoking	44%	41%
Smoked during pregnancy**	37%	30%

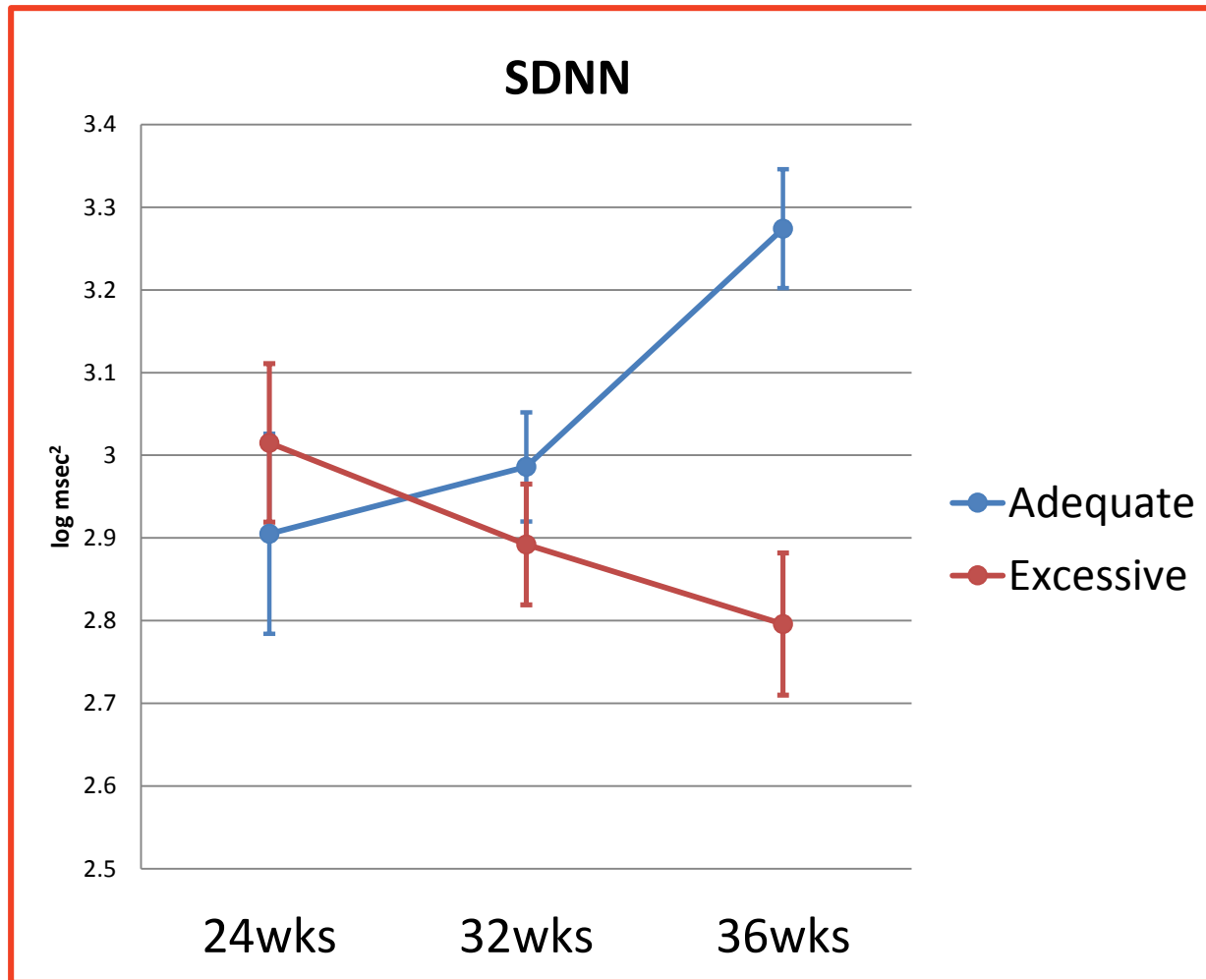
*Similar to US statistics for overweight and obesity during pregnancy

**Smoking during pregnancy higher than US in general~16%



Known risk factors for mother and child: Inadequate or excessive gestational weight gain (GWG); entering pregnancy overweight or Obese: 84% of US pregnant women. Only 16% healthy wt and best GWG

Effect of excessive gestational weight gain on fetal overall HRV



KUDOS Results (USA)

	Placebo N= 147	DHA N=154	P-value
GA (d)	272.7	275.6	0.041
Birth weight (g)	3187	3359	0.004
Birth length (cm)	49.0	49.7	0.022
Birth head circumference (cm)	33.7	34.2	0.012
Low birth wt (<2500g) (%)	9.0	3.9	Trend (0.059)
Preterm birth (%)	8.8	7.8	NS
Pre-eclampsia (%)	1.3	1.3	NS
GDM (%)	4.1	5.6	NS
C-section (%)	29.9	29.9	NS
Labor on own (%)	60.0%	56.5%	NS

Carlson et al., AJCN 2013

What About VLBW and Hospitalization?

	Placebo	DHA	P-value
Birth wt <1500 g*	3.4 %	0 %	P=0.026
Early preterm birth (<34 wks)*	4.8 %	0.6 %	P=0.025
Neonatal Intensive Care Unit admission (n/%)	12 (8.3)	16 (10.4)	NS
Days hospitalized (mean #)**	40.8	8.9	P=0.026

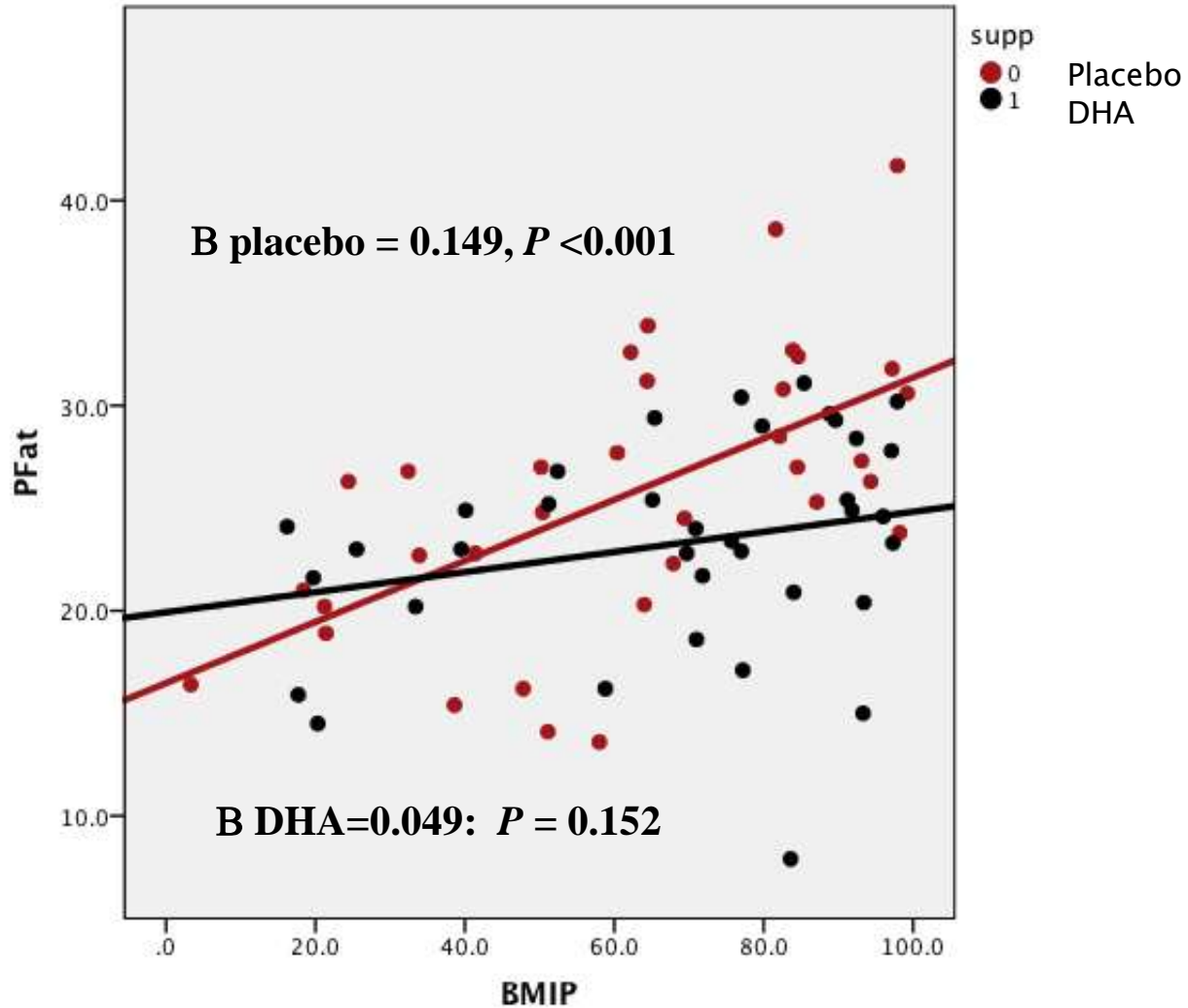
*One tailed *P* values at $\alpha=0.05$ were considered significant;
**if born <37 wks.

BOD POD

- 2 compartment model: fat mass and fat free mass
- Air displacement plethysmography

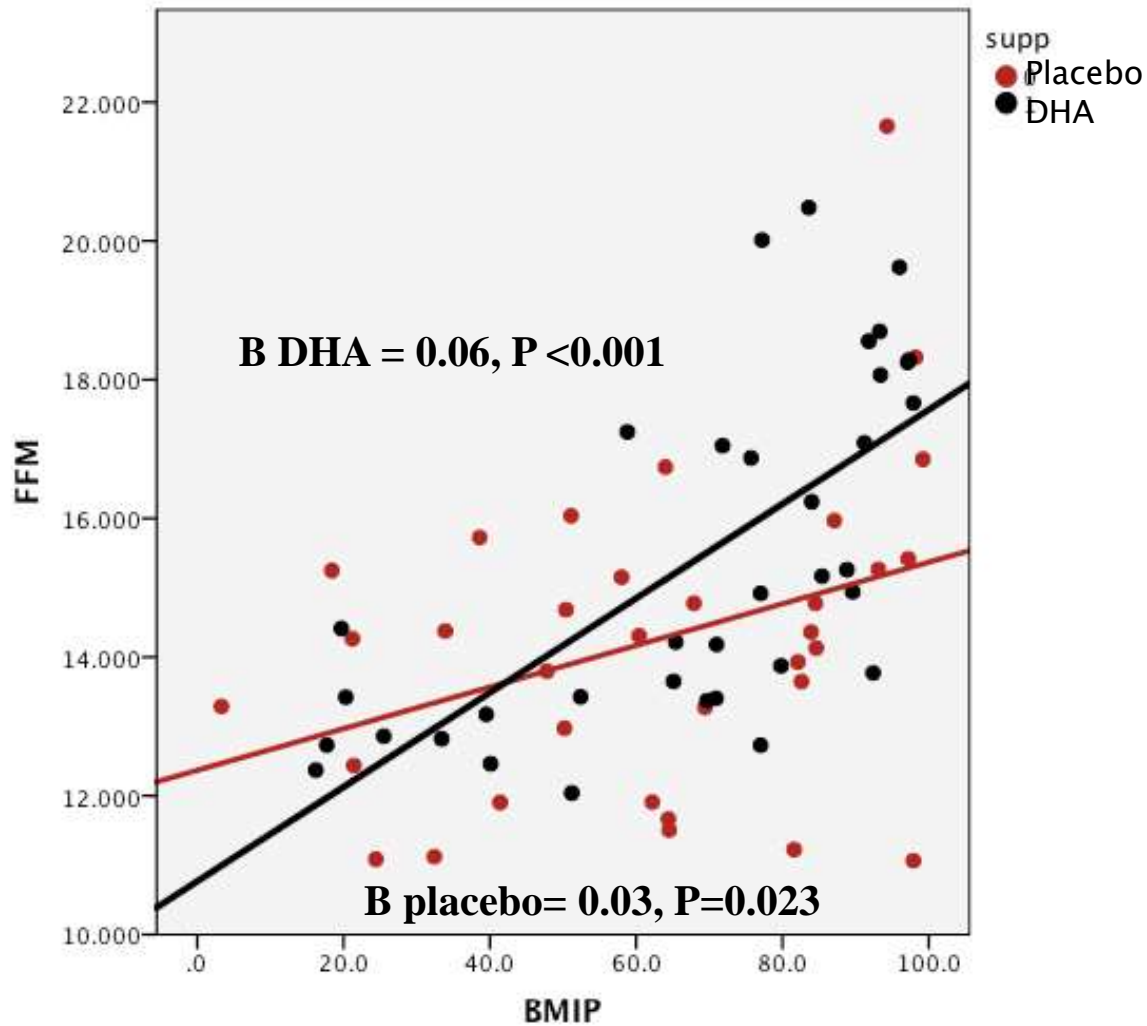


Percent Fat



Placebo vs. DHA, $P = 0.041$

FFM (kg)




Placebo vs DHA, $p=0.041$

SUMMARY

- DIAMOND (postnatal supplementation): Intervention: Formula with DHA and ARA in the first year of life vs. control formula:
 1. Enhanced targeted tests of early (9 mo) and later (to age 6 yrs) cognitive function
 2. Behavioral results are supported by new ERP data and fMRI
 3. Documented allergy was significantly reduced in infancy and early childhood (being written up).
 4. Increased linear and stature achievement from birth – 6 yrs (in review)

- KUDOS (prenatal supplementation): Intervention: 600 mg DHA from ~14.4 wks gestation to birth vs placebo:
 1. Increased gestation duration and infant size at birth
 2. <34 wk gestation deliveries and births less than 1500 g were significantly decreased
 3. Longer Sustained Attention in Infancy
 4. Maternal DHA supplementation increases fat free mass at age 5 yr and those children do not show an increase in body fat percent as BMI increases

CONCLUSION

- ▶ The effects of postnatal DHA and ARA supplementation (DIAMOND results) suggest favorable programming of cognitive but also immunological and growth outcomes in data I have not shown.
 - ▶ Why programming? Because algal DHA (and ARA) were provided only to 12 mo of age but favorable effects of supplementation on cognition, immunity and growth are observed many years later.
 - ▶ The KUDOS results are still being analyzed
 - ▶ So far we find less early PT birth and favorable effects on early child cognition and body composition if women are supplemented with significant amounts of DHA.
 - ▶ These are being observed despite the fact that all children in the study received DHA and ARA from birth to 12 months of age.
 - ▶ As with the DIAMOND study (prenatal algal DHA), they suggest favorable programming.
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FUNDING SOURCES AND COLLABORATORS

- ▶ NIH (R01 HD047315)
- ▶ Office of Dietary Supplements
- ▶ NIH (R21 HD059019) – Gustafson
- ▶ Mead Johnson Nutrition
- ▶ DSM (formerly Martek Bioscience)
- ▶ Core support: KIDDRC (P30 HD02528)
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