Importance of Adequate DHA/ARA in Preterm Infants

ANNENBERG CENTER FOR HEALTH SCIENCES
AT EISENHOWER
Imparting knowledge. Improving patient care.

Presented by

Michael Caplan, MD
Clinical Professor of Pediatrics
University of Chicago Pritzker School of Medicine
Chairman of the Department of Pediatrics
NorthShore University HealthSystem

Camilia Martin, MD, MS
Associate Professor of Pediatrics
Harvard Medical School
Associate Director, NICU, Department of Neonatology
Director for Cross-Disciplinary Research Partnerships
Division of Translational Research
Beth Israel Deaconess Medical Center

Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

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

Presenters

Michael Caplan, MD

Chairman, Department of Pediatrics
Chief Scientific Officer
NorthShore University HealthSystem
Clinical Professor of Pediatrics
University of Chicago, Pritzker School of Medicine
Chicago, Illinois

Camilia Martin, MD, MS

Associate Professor of Pediatrics
Harvard Medical School
Associate Director
NICU Department of Neonatology
Director for Cross-Disciplinary Research Partnerships
Division of Translational Research
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Faculty Disclosures

Michael Caplan, MD

Research Support	Mead Johnson Nutrition
Consultant	Sigma Tau Pharmaceuticals
Speakers Bureau	Mead Johnson Nutrition

Camilia Martin, MD, MS

Research Support	Abbott Nutrition, Alcresta Therapeutics
Consultant	Fresenius Kabi, Mead Johnson Nutrition
Scientific Advisory Board	Laurent Pharmaceuticals, Prolacta Bioscience

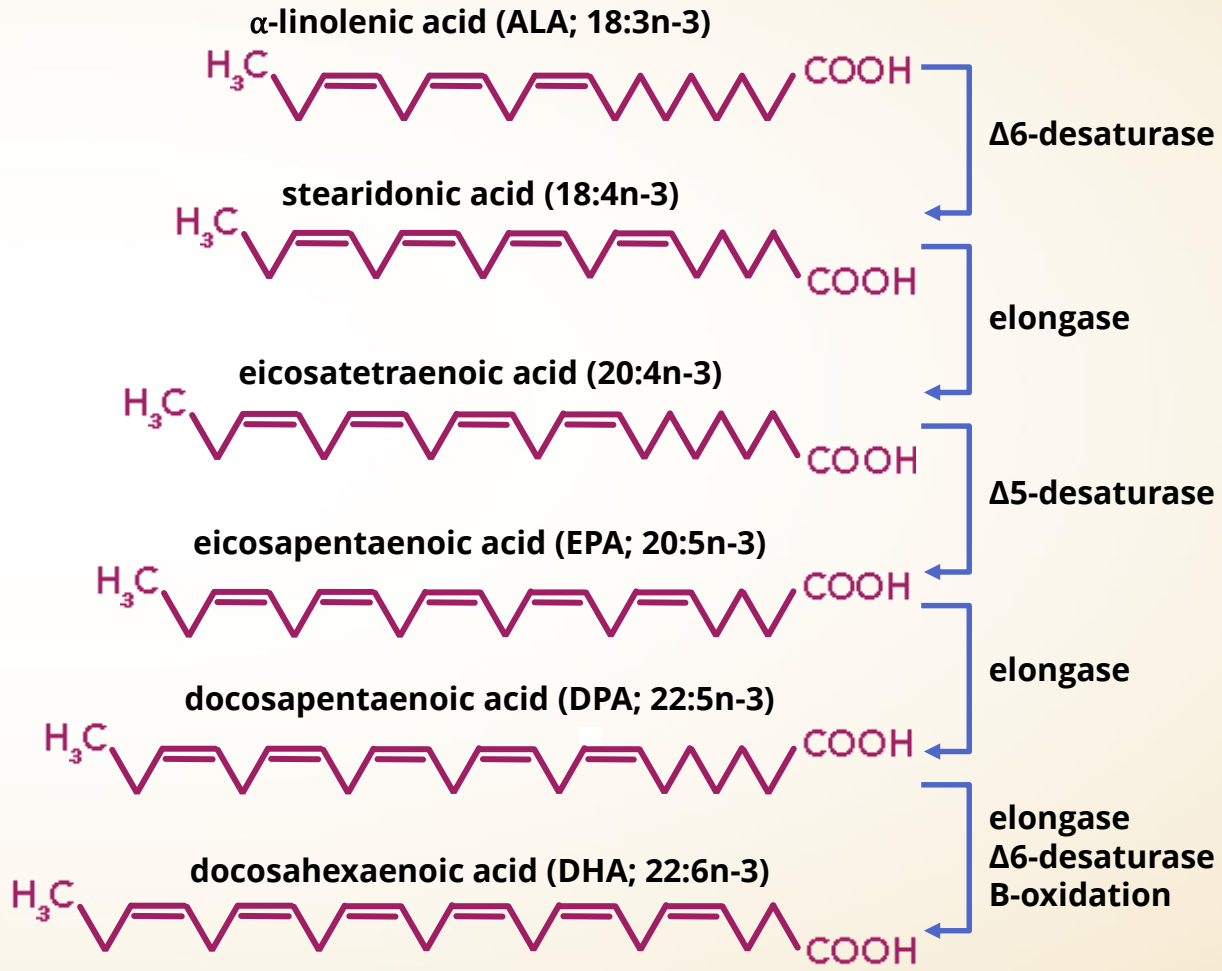
Learning Objectives

- Describe the role DHA/ARA plays in developing infants
- Recognize the importance of adequate DHA/ARA balance in preterm infants
- Associate current NICU practices with DHA/ARA accretion rates in preterm infants

THE ROLE OF DHA/ARA IN INFANT GROWTH

Overview of Docosahexaenoic Acid (DHA)

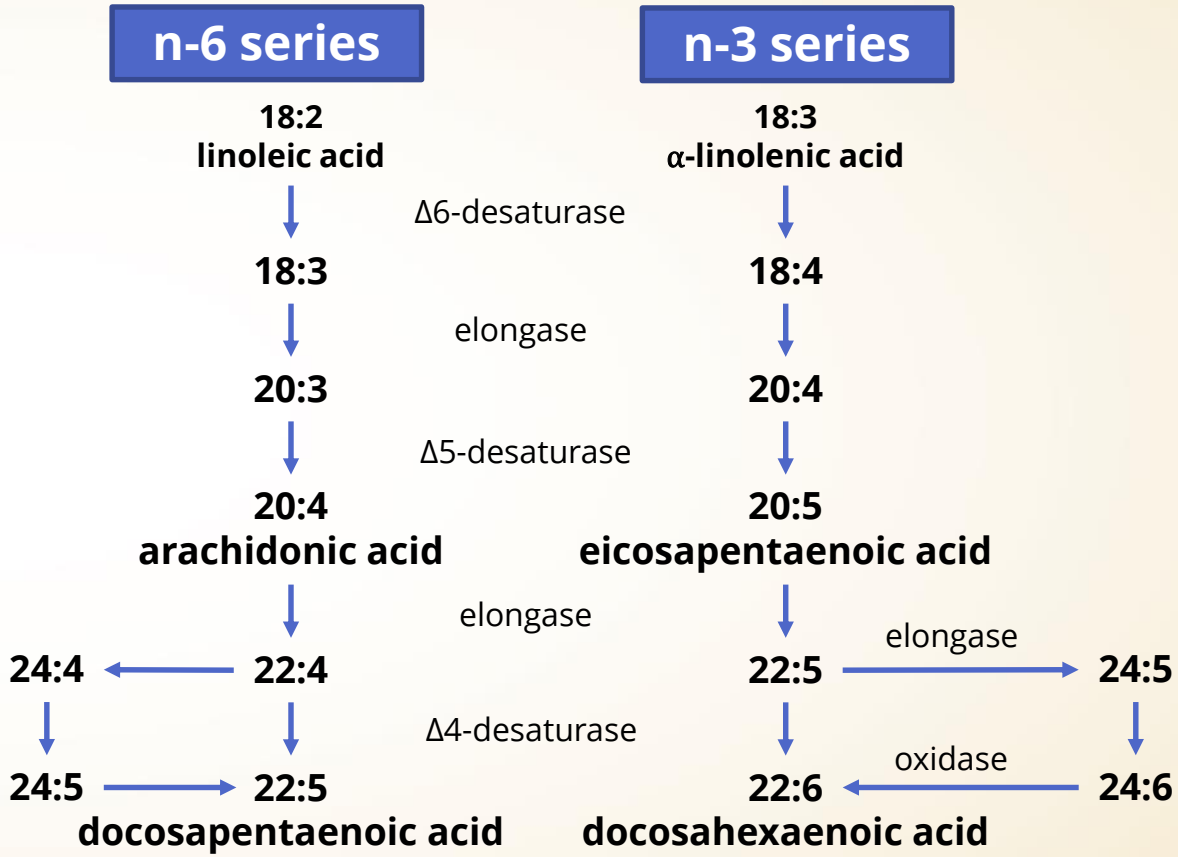
- Long-chain, highly unsaturated omega-3 fatty acid (22:6*n*-3)
- Metabolized from α-linolenic acid
- Found in seafood, especially fatty fish, and products derived from seafood



Calder PC. *Ann Nutr Metab*. 2016;69 Suppl 1:7-21.

Overview of Arachidonic Acid (ARA)

- Long-chain, highly unsaturated omega-6 fatty acid (20:4*n*-6)[1]
- Abundant in brain, muscles, and liver[1]
- Immediate precursor for adrenic acid[2]
  - Pathway for ARA utilization in infants to meet increase needed for neural tissue development



1. Hadley KB, et al. *Nutrients*. 2016;8(4):216. 2. Wijendran V, et al. *J Lipid Res*. 2002;43(5):762-767.

Functions of DHA/ARA

Structure and function of tissues

Retinal development

Brain development

Immune function

Martinez M. *J Pediatr*. 1992;120(4 Pt 2):S129-S138.

DHA/ARA: Important Building Blocks of the Growing Brain

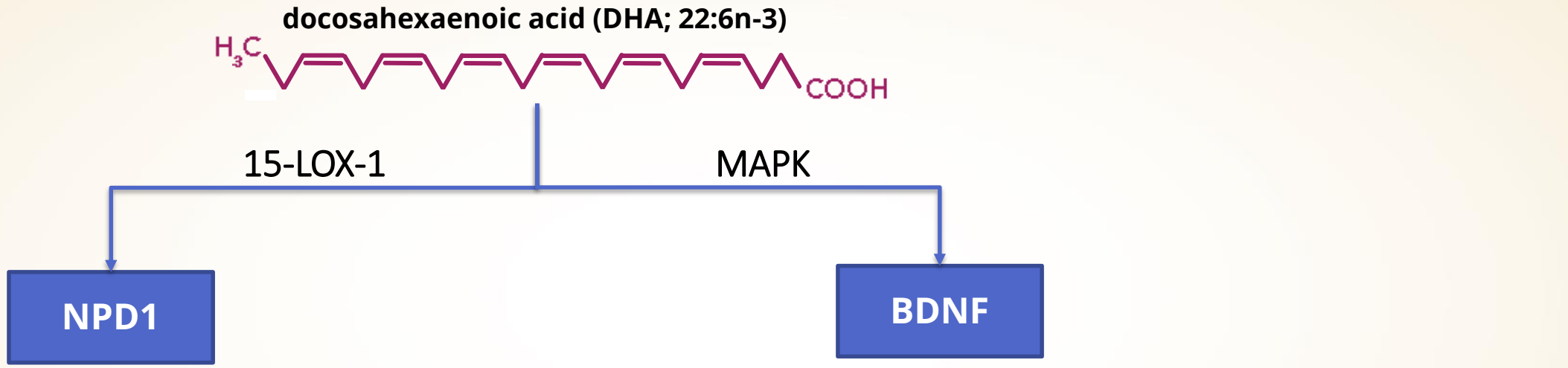
- DHA and ARA play an important role in neuronal cell division and signaling

- Mammalian brains are 60% fat
  - About **25% of the total fatty acid content of the brain** is made up of DHA or ARA

- DHA and ARA are primarily in the form of phospholipids
  - Found in **neural cell membranes**, providing structural support

Hadley KB, et al. *Nutrients*. 2016;8(4):216.

DHA Signaling: NPD1 and BDNF



Protective roles

- Inhibits retinal ganglion cell death
- Protects against oxidative stress
- Downregulates pro-inflammatory signaling
- Upregulates antiapoptotic proteins
- Downregulates proapoptotic proteins

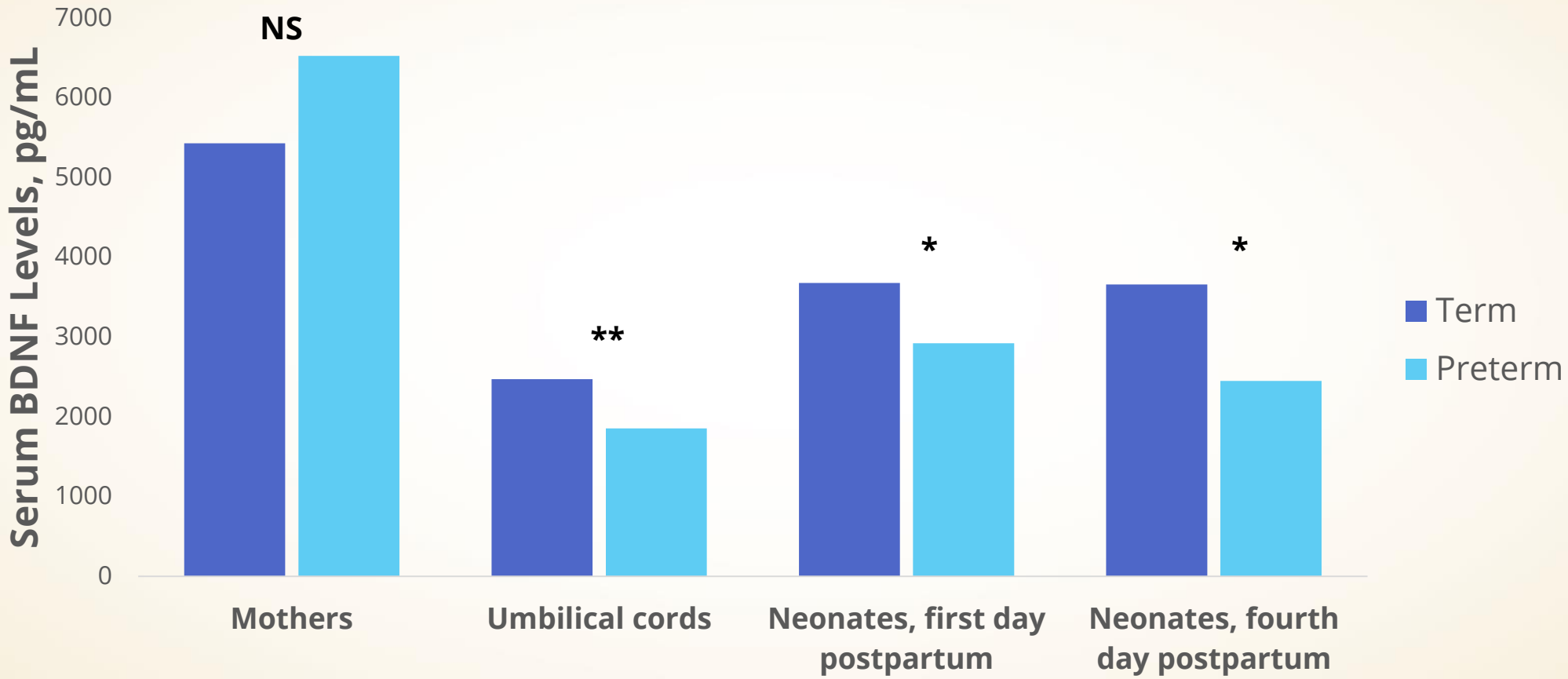
Protective roles

- Promotes neuronal survival
- Increases synaptic plasticity
- Plays a role in neurogenesis

BDNF, brain-derived neurotrophic factor; NPD1, neuroprotectin D1.

1. Niemoller TD, Bazan NG. *Prostaglandins Other Lipid Mediat*. 2010;91(3-4):85–89.

BDNF Levels Are Lower in Preterm Infants



BDNF, brain-derived neurotropic factor.
*P <.05; **P <.001.
Prospective study in 30 healthy term and 15 healthy preterm neonates. BDNF measured by enzyme immunoassay.

1. Malamitsi-Puchner A, et al. *Early Hum Dev*. 2004;76(1):17-22.

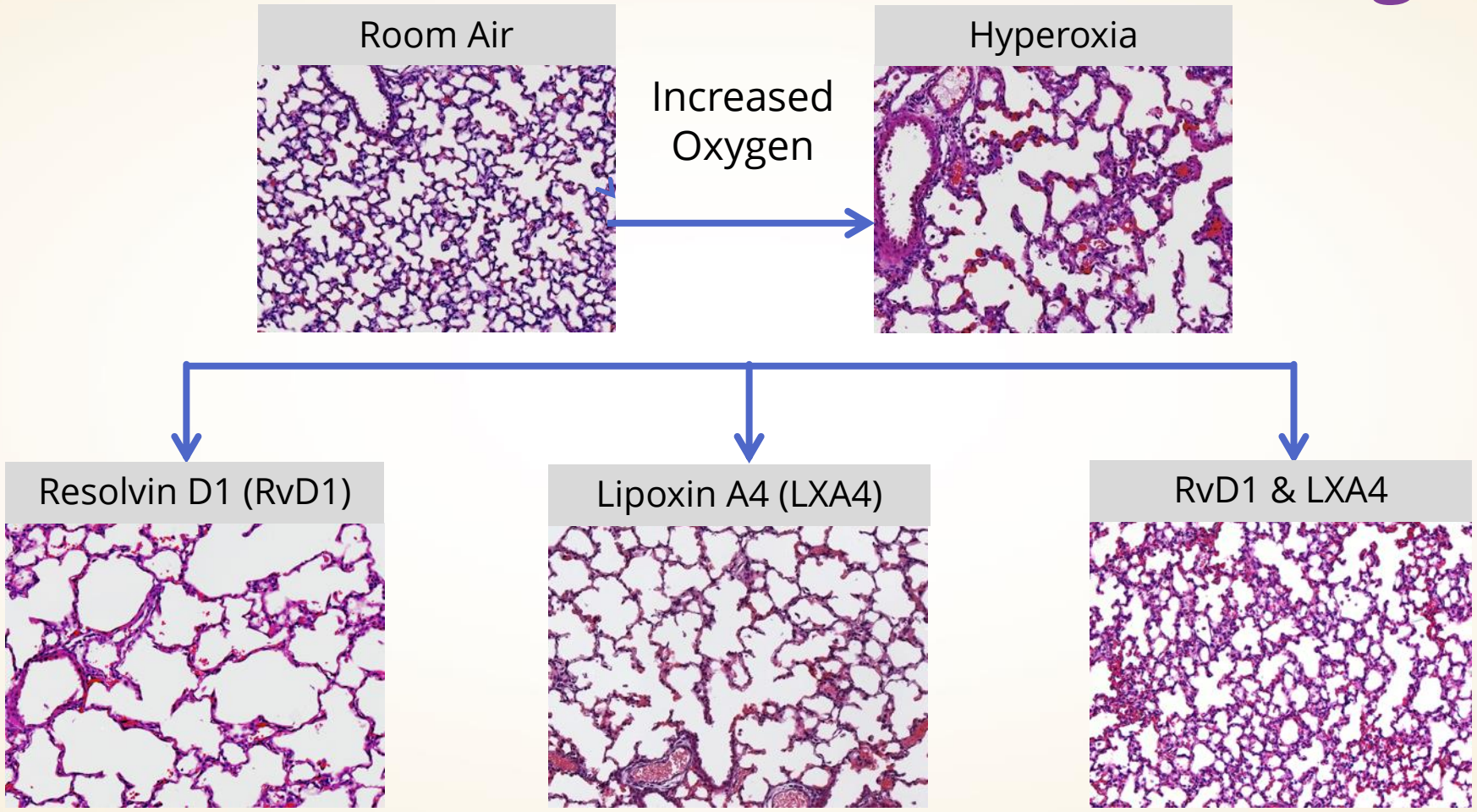
DHA/ARA in Infant Retinal Development

- DHA/ARA play a role in the maturation and survival of photoreceptor cells[1-3]
- Incorporation of DHA into phospholipids is important for retinal function[4]
- Animals raised on fatty acid–free diets develop abnormal electroretinograms[5]

Electroretinography (ERG) is an eye test that detects function of the retina by measuring electrical response of the light-sensitive cells in eyes.

1. Benolken RM, et al. *Science*. 1973;182:1253-1254. 2. Jastrzebska B, et al. *Prog Lipid Res*. 2011;50:267-277. 3. Jeffrey BG, et al. *Invest Ophthalmol Vis Sci*. 2009;50:4360-4367. 4. Shindou H, et al. *J Biol Chem*. 2017;292(29):12054-12064. 5. Neuringer M, et al. *J Clin Invest*. 1984;73:272-276.

DHA and ARA Metabolites Attenuate Lung Injury†

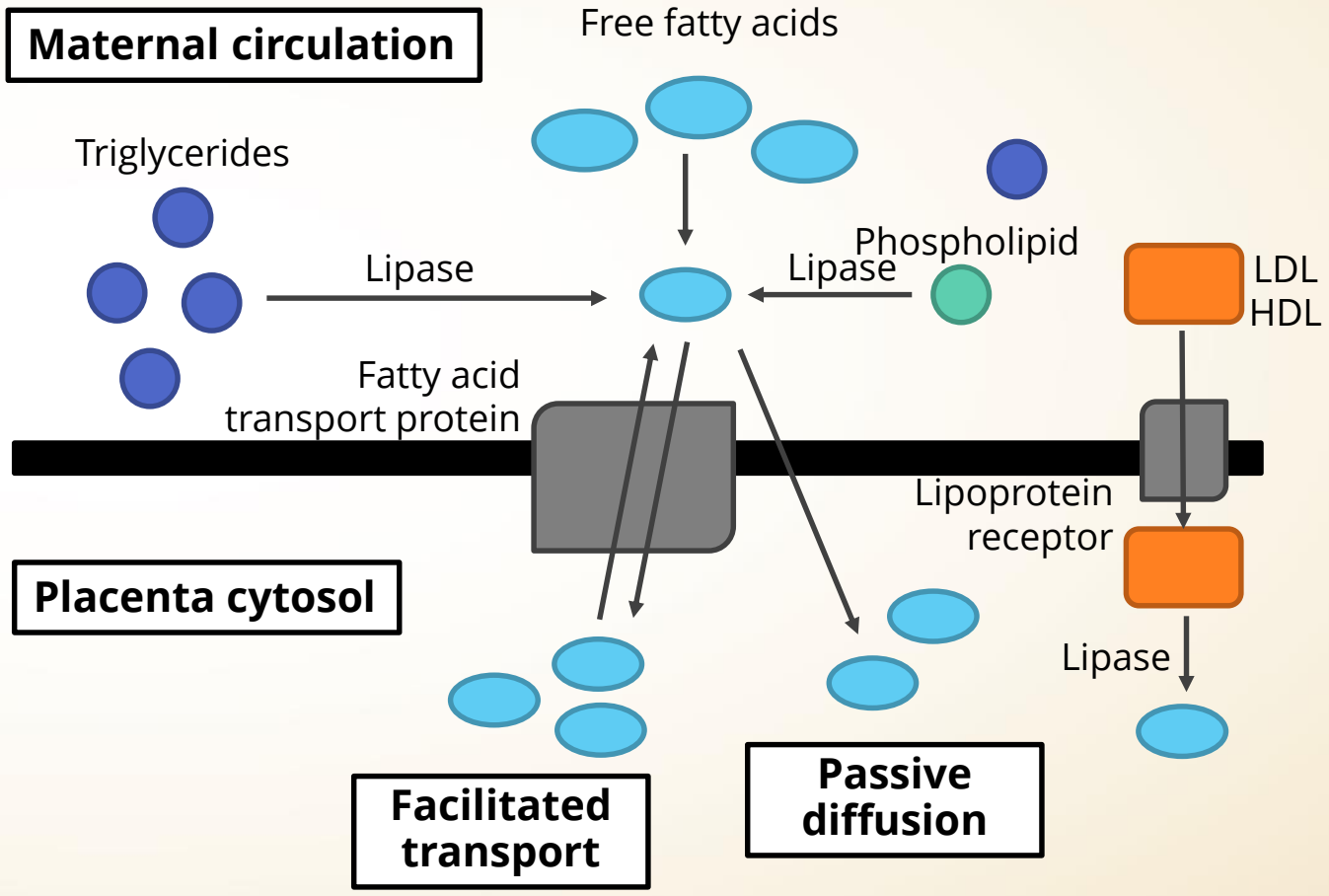


Histology (H&E): 200x.
†C57/BL6 pups were randomized at birth and treated IP on days 0, 3, 6, and 9. On day 10, mice were sacrificed and lungs were collected for morphometric analyses. Hyperoxia, >90% oxygen.

Martin CR, et al. *PLOS One*. 2014;9(6):e98773.

Mechanisms of Maternal-Fetal Fatty Acid Delivery

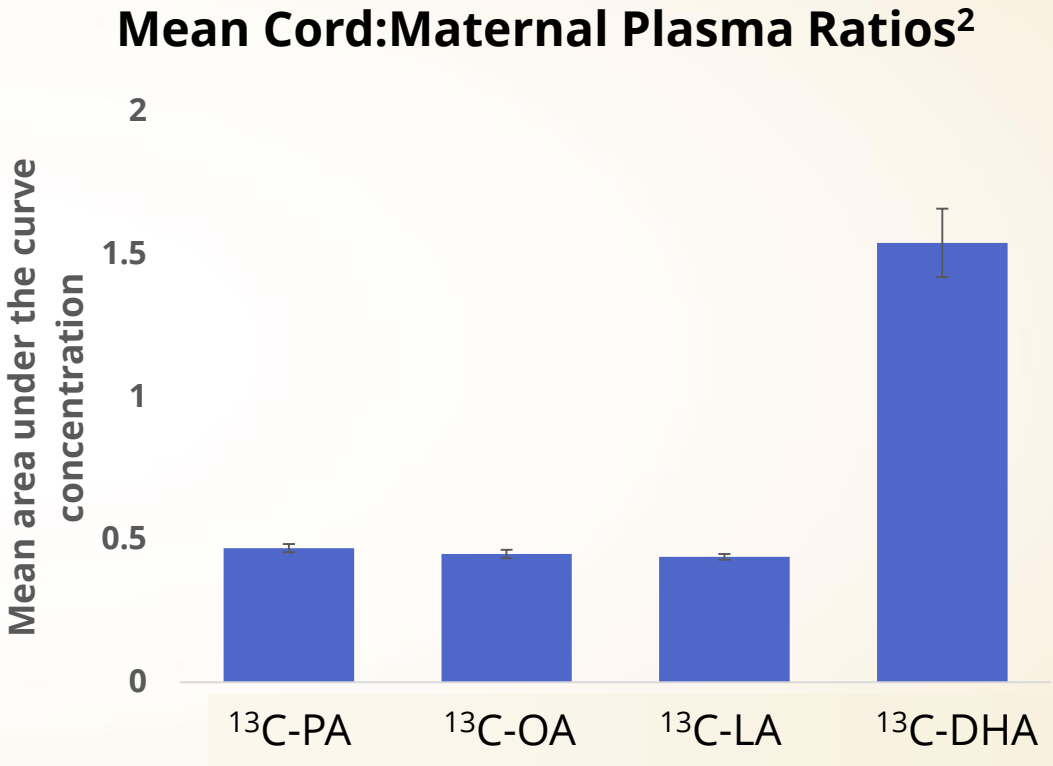
- Mechanisms involved in fatty acid transfer across placenta are poorly defined
- DHA may selectively accumulate in fetal tissue through higher placental uptake
- Fatty acid transfer can occur through passive diffusion or facilitated transfer



Larqué E, et al. *Am J Clin Nutr.* 2011;94(6 Suppl):1908S-1913S.

DHA Accumulates in the Placenta at a Higher Rate Than Other Fatty Acids[1,2]

- In a study of 11 pregnant women given radio-labeled fatty acids, the maternal-fetal distribution was evaluated
- Twelve hours after oral intake of fatty acids, an elective cesarean section was performed
- Mean ratios between cord and maternal plasma area under the curve (AUC) concentration of ^{13}C-fatty acids (expressed as percentages) are shown in the figure

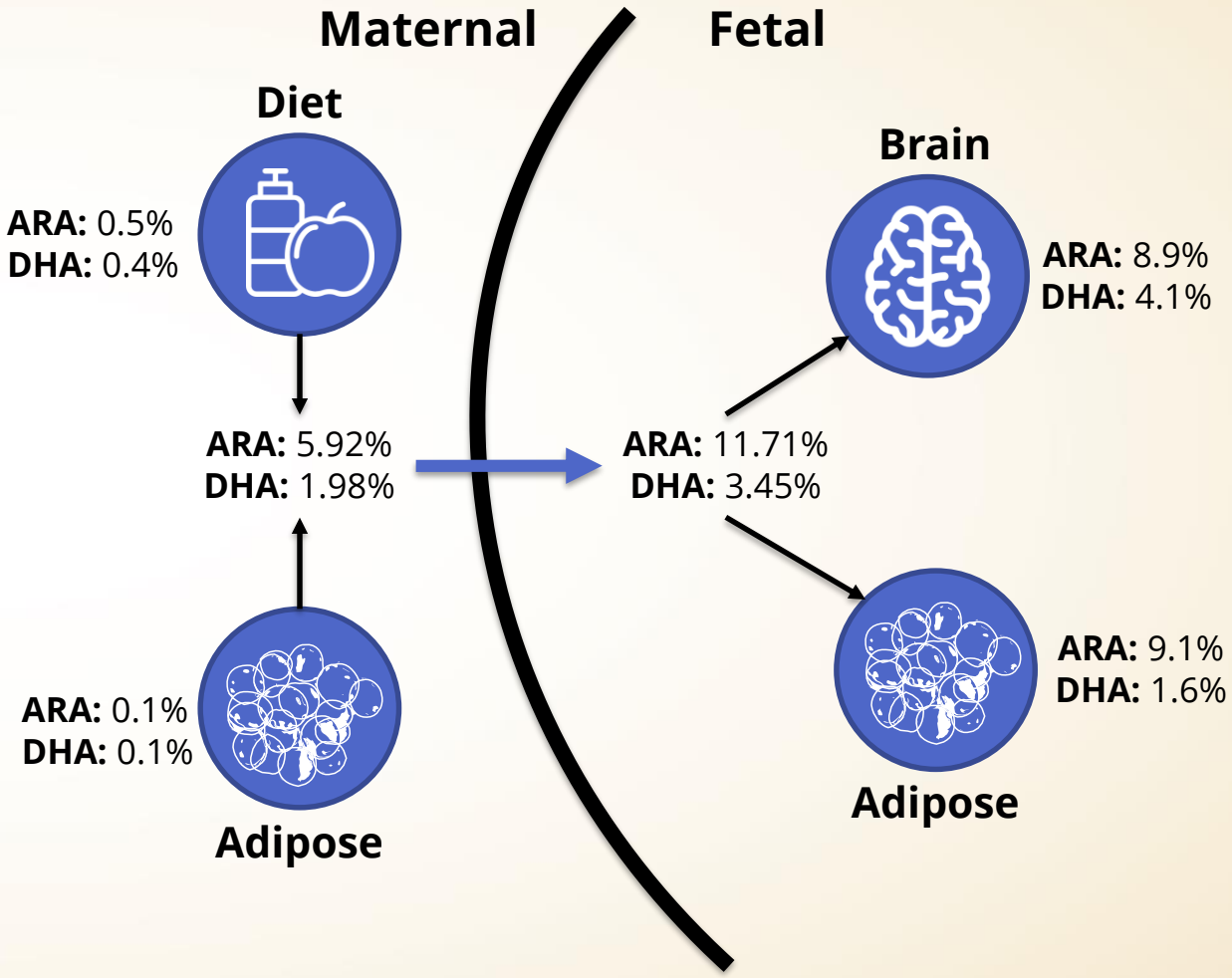


1. Hanebutt FL, et al. *Clin Nutr*. 2008;27(5):685-693. 2. Gil-Sanchez A, et al. *Am J Clin Nutr*. 2010;92(1):115-122.

Accumulation of DHA/ARA in Fetal Tissue at End of Pregnancy[1-5]

- During the final weeks of pregnancy, the DHA and ARA content in **fetal plasma is almost twice as high** as in the mother's blood[1-4]

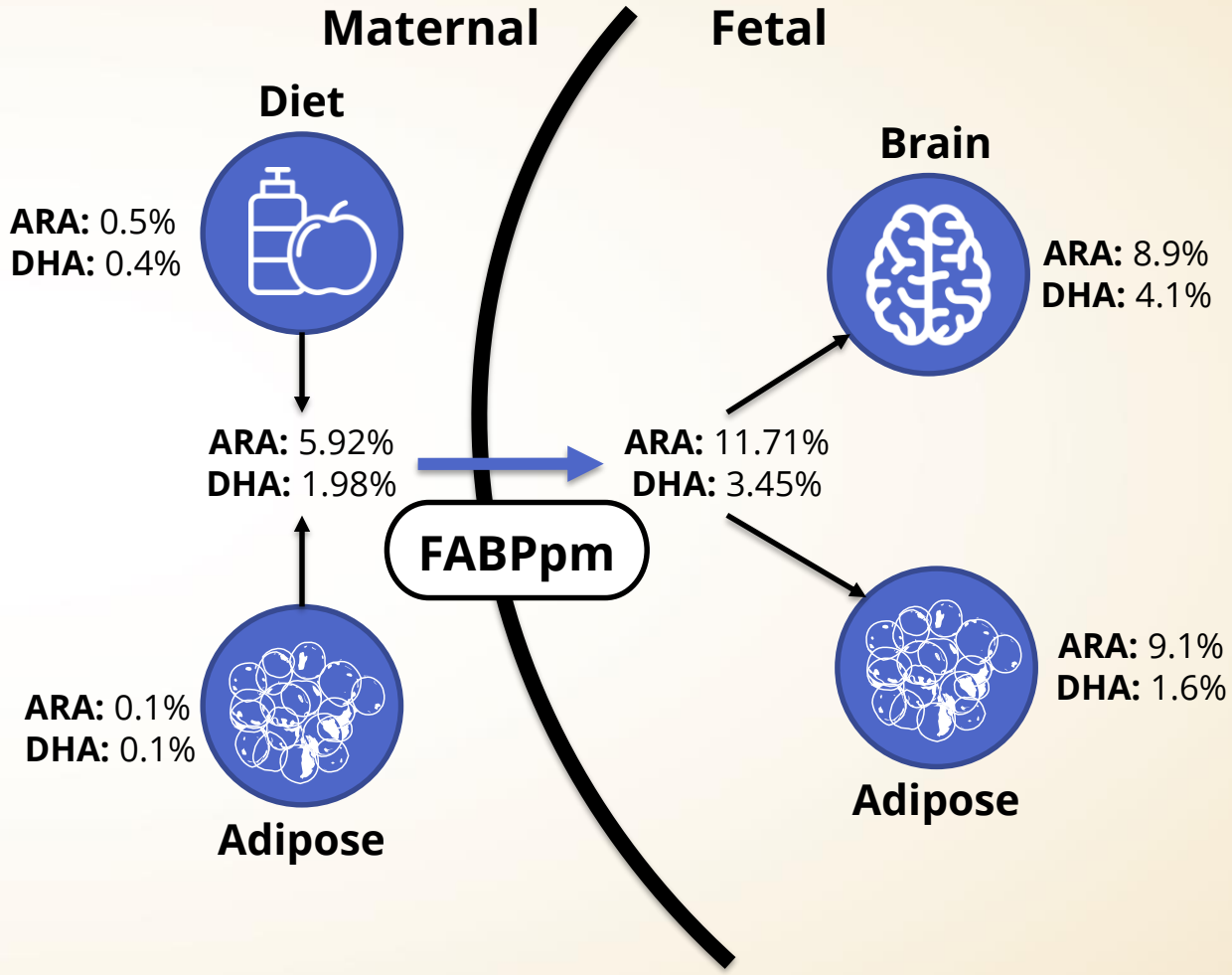
- Towards the end of the pregnancy, levels are **several times higher in fetal adipose tissue** than in the maternal adipose tissue:[1-4]
  - **DHA:** 16 times higher
  - **ARA:** 90 times higher



1. Haggarty P. *Placenta*. 2002;23 Suppl A:S28-S38. 2. Otto SJ, et al. *Eur J Clin Nutr*. 1997;51(4):232-242. 3. Lakin V, et al. *Prostaglandins Leukot Essent Fatty Acids*. 1998;59(3):209-220. 4. Clandinin MT, et al. *Early Hum Dev*. 1981;5(4):355-366. 5. Bobinski R, Mikulska M. *Acta Biiochim Pol*. 2015;62(3):499-507.

FABPpm Transports DHA Selectively Across the Placenta[1-4]

- **Membrane associated fatty acid binding protein (FABPpm)** is a peripheral membrane protein and fatty acid transporter
- FABPpm selectively binds LC-PUFA on the maternal side to transfer fatty acids to the placenta[1,2]
- FABPpm binds only 10% of total fatty acids, with a high affinity for DHA/ARA:
  - ARA: 98%
  - DHA: 87%
  - Smaller quantities of LA and OA (oleic acid)[3]



1. Kaufmann P, Scheffen I. In Fetal and Neonatal Physiology. 1998, pp 59–70. 2. Campbell FM, et al. *Life Sci*. 1998;63(4):235-240. 3. Schmitz G, et al. *Prog Lipid Res*. 2008;47(2):147-155. 4. Bobinski R, Mikulska M. *Acta Biochim Pol*. 2015;62(3):499-507.

Enteral Sources of DHA/ARA for Term Infants

- **Human milk:** DHA/ARA is always present[1]
  - Concentration of DHA/ARA is related to maternal diet
  - Breastfeeding is ideal, but the majority of infants receive some formula during the first year of life[2]

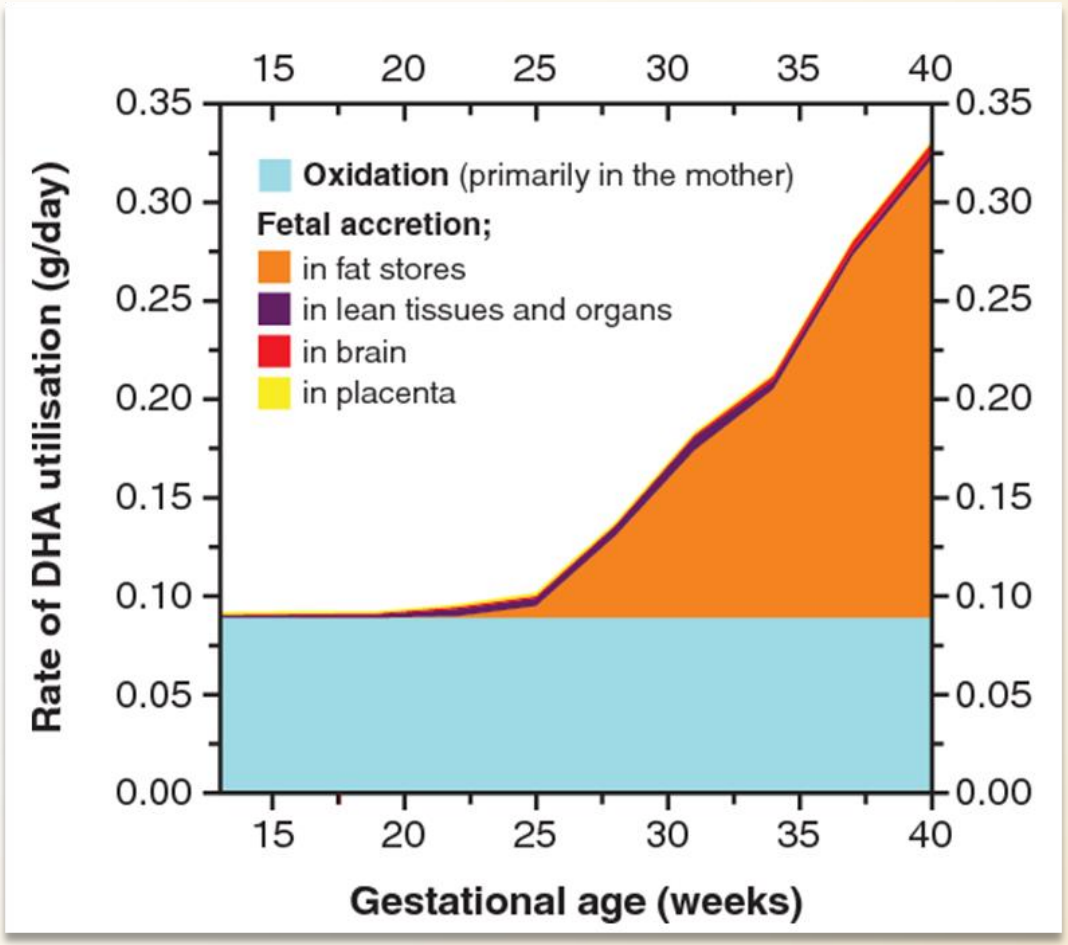
- **Formula:** DHA/ARA is added in the US since 2001 based on worldwide averages in human milk[3]
  - 0.2% to 0.4% DHA
  - 0.35% to 0.7% ARA

1. Hadley KB, et al. *Nutrients*. 2016;8(4):216. 2. http://www.cdc.gov/breastfeeding/data/reportcard.htm. Accessed October 28, 2019. 3. Brenna JT, et al. *Am J Clin Nutr*. 2007;85(6):1457-1464.

IMPORTANCE OF ADEQUATE DHA/ARA BALANCE IN PRETERM INFANTS

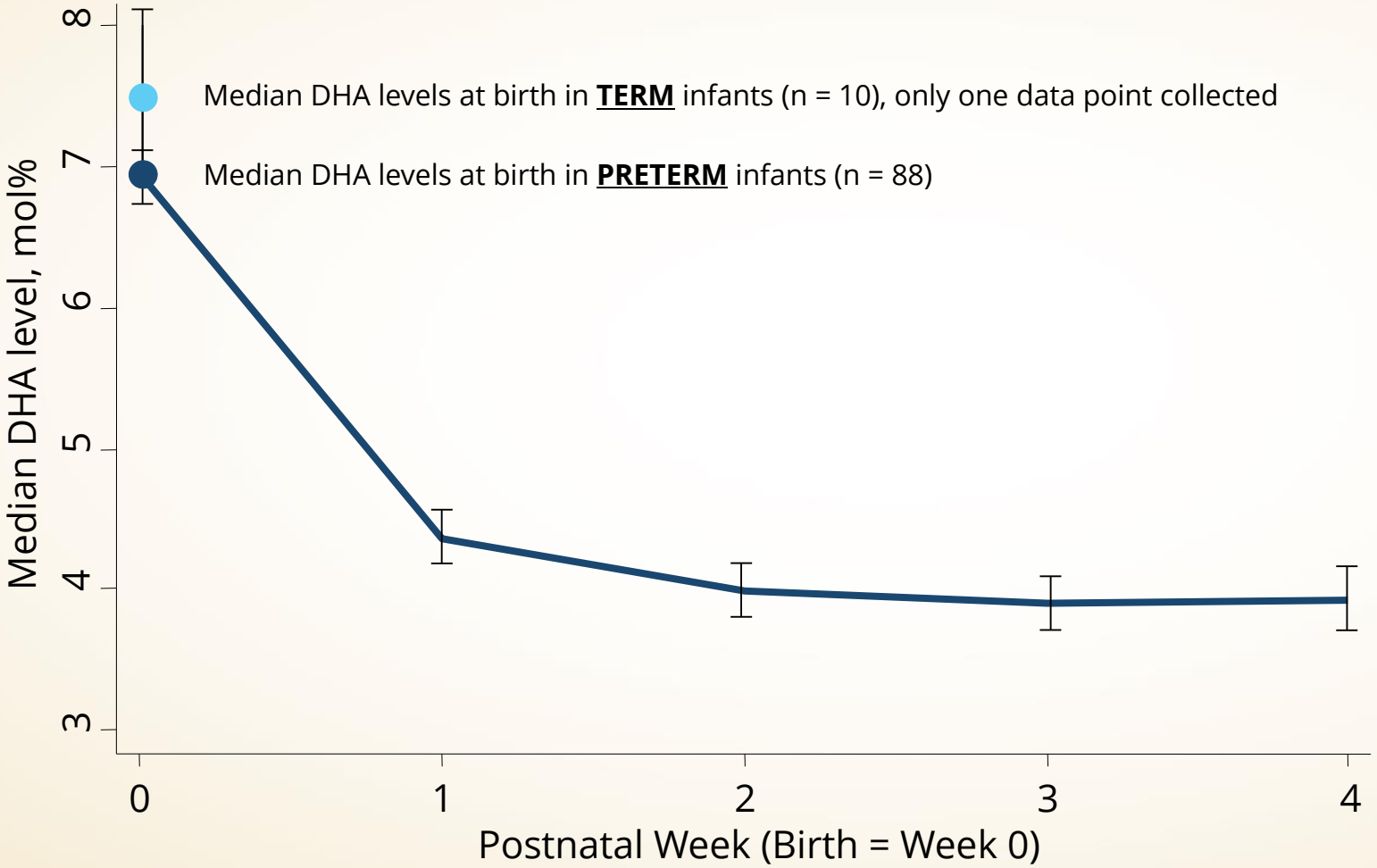
DHA/ARA Are Stored in the Brain and Adipose Tissue

- Since maternal diets may not always meet DHA/ARA needs, these fatty acids are stored in the adipose tissue for later use
- Storage in adipose tissue increases substantially in the final weeks of pregnancy
- Preterm infants may not have the same levels of DHA/ARA accretion as term infants



Haggarty P. *Annu Rev Nutr*. 2010;30:237-255.

DHA Levels Rapidly Decline in the First Postnatal Week

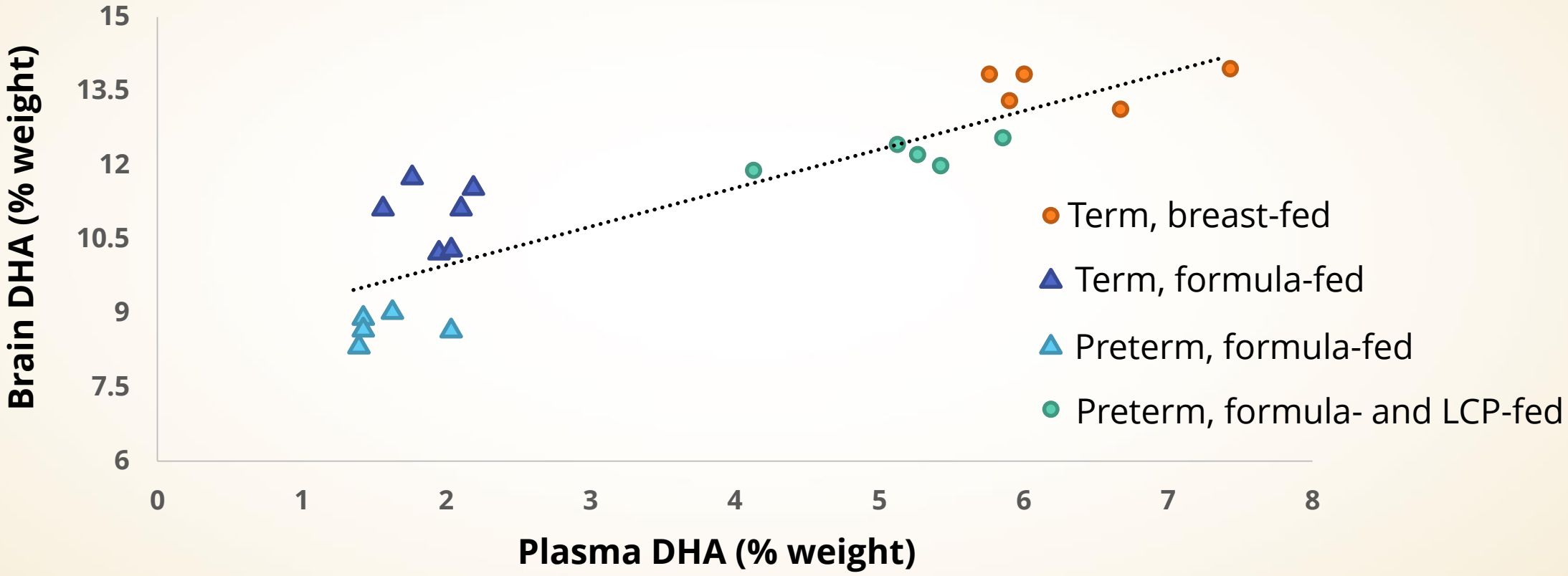


Median DHA levels at birth comparable across gestational age

Retrospective cohort study of 88 infants born at <30 weeks' gestation. Fatty acid profiles and infant outcomes were assessed during the first postnatal month.

Martin CR, et al. *J Pediatr*. 2011;159(5):743-749.e1-2.

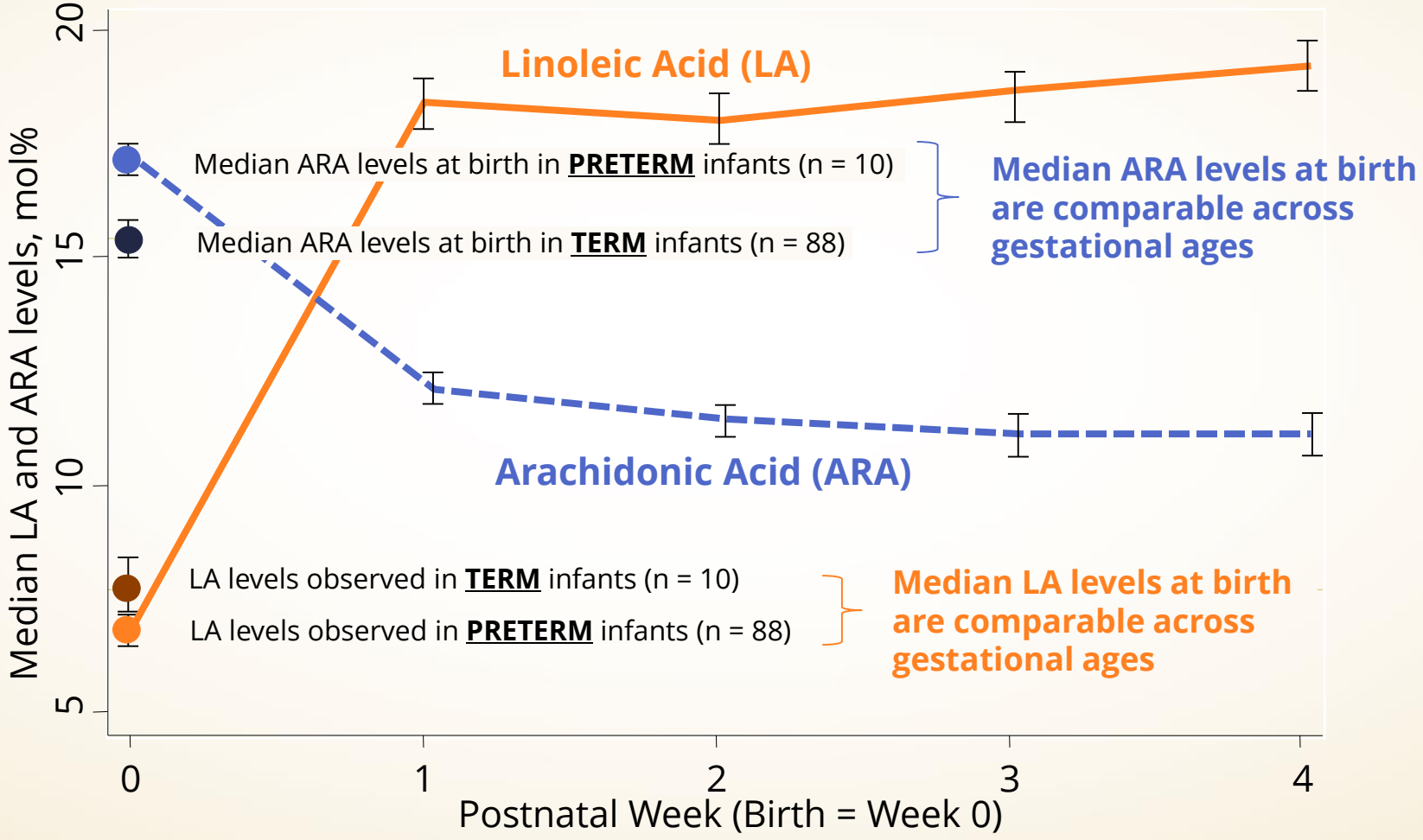
Plasma Levels of DHA Approximate Brain Levels†



†Study in 22 pregnant baboons/neonates randomized to term breast-fed, term formula-fed, preterm formula-fed, or preterm DHA/ARA-supplemented formula-fed

Sarkadi-Nagy E, et al. *Pediatr Res*. 2003;54(2):244-252.

ARA Levels Are Rapidly Altered in the First Postnatal Week



Retrospective cohort study of 88 infants born at <30 weeks' gestation. Fatty acid profiles and infant outcomes were assessed during the first postnatal month.

Martin CR, et al. *J Pediatr*. 2011;159(5):743-749.e1-2.

DHA/ARA Imbalance Associated With Disease in Preterm Infants

Suboptimal cognitive development

Retinopathy of prematurity

Chronic lung disease

Sepsis and infection

1. Martin CR, et al. *J Pediatr*. 2011;159(5):743-749.e1-2. 2. Martin CR, et al. *PLoS One*. 2014;9(6):e98773. 3. Lavoie JC, et al. *JPEN J Parenter Enteral Nutr*. 2018;42(8):1314-1321. 4. Löfqvist CA, et al. *JAMA Ophthalmol*. 2018;136(3):271-277.

DHA/ARA Levels Are Linked With Improved Neurodevelopment

- In a study of 60 preterm infants, red blood cell fatty acid composition was evaluated
- A 1% increase in DHA levels was associated with **4.3-fold reduced risk of intraventricular hemorrhage**
- Higher DHA and lower LA levels early after delivery were associated with **better developmental scores at a mean follow-up of 33 months**

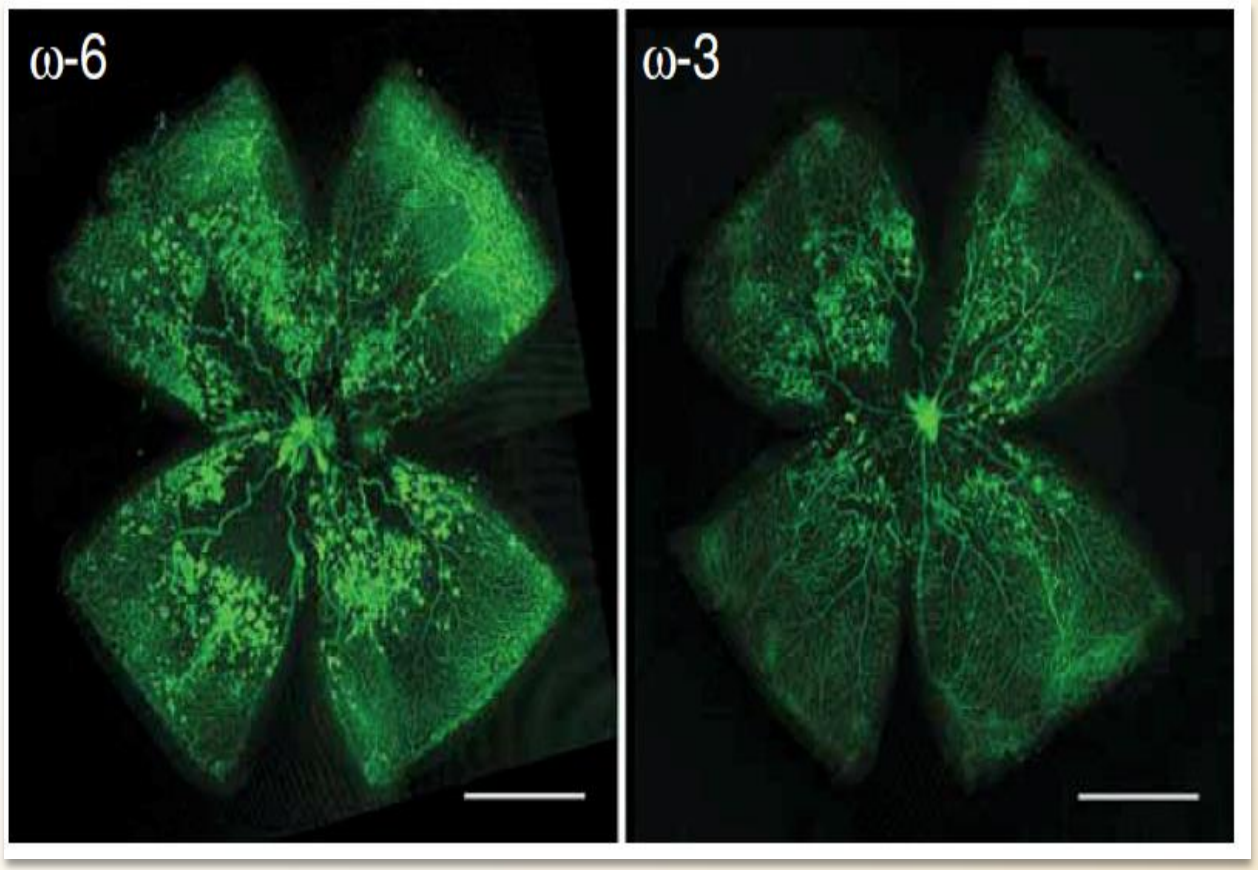
Tam EW, et al. *Pediatr Res.* 2016;79(5):723-30.

Omega-3 and Retinopathy of Prematurity†

- Mice receiving ω-6-PUFAs had a significantly greater vaso-obliterated/total retinal area of 21.5% vs 13.7% in those receiving ω-3-PUFAs
- Mice receiving ω-3-PUFAs were significantly protected from pathologic neovascularization (5.7% vs 9.0%)

Vaso-obliteration / Neovascularization:

21.5% / 9% **13.7% / 5.7%**

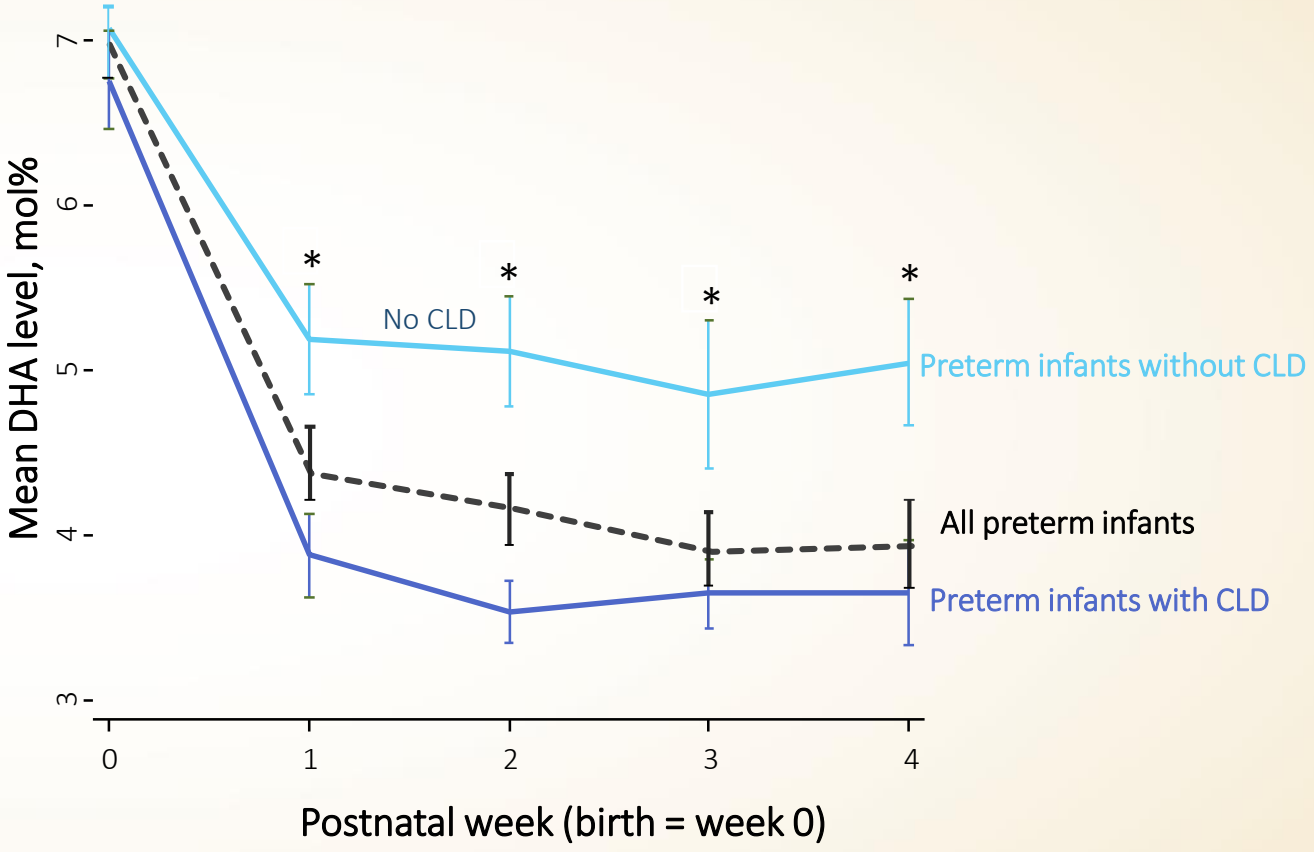


†Mouse pups exposed to 75% O_2 from P7-P12. Scale bar, 1 mm. P17 retinal vasculature stained with isolectin B4-FITC. Omega-6, n = 14; omega-3, n = 27.

Connor KM, et al. *Nat Med*. 2007;13(7):868-873.

Low DHA Levels Are Linked to the Development of Chronic Lung Disease

- In a retrospective cohort study of 88 preterm infants, fatty acid profiles were measured for the first 4 weeks
- Decreased levels of DHA were associated with a **2.5-fold increased risk of chronic lung disease (CLD)**
- Imbalanced DHA/LA levels were associated with an **8.6-fold increased risk of CLD**



Martin CR, et al. *J Pediatr*. 2011;159(5):743-749.e1-2.

Association With Increased Risk of Chronic Lung Disease and Late-onset Sepsis

- In the same study, fatty acid levels and imbalance were associated with late-onset sepsis
- Imbalanced LA:DHA was associated with a **4.6-fold increased risk** of late-onset sepsis

Chronic lung disease		
Fatty acid	**OR (95% CI)**	***P***
LA	0.9 (0.7, 1.1)	.4
ARA	0.9 (0.6, 1.3)	.6
DHA	2.5 (1.3, 5.0)	.001
LA: DHA	8.6 (1.4, 53.1)	.02
Late-onset sepsis		
Fatty acid	**Hazard ratio (95% CI)**	***P***
LA	0.8 (0.7, 0.96)	.02
ARA	1.4 (1.1, 1.7)	.02
DHA	1.4 (1.0, 2.0)	.08
LA: DHA	4.6 (1.5, 14.1)	.007

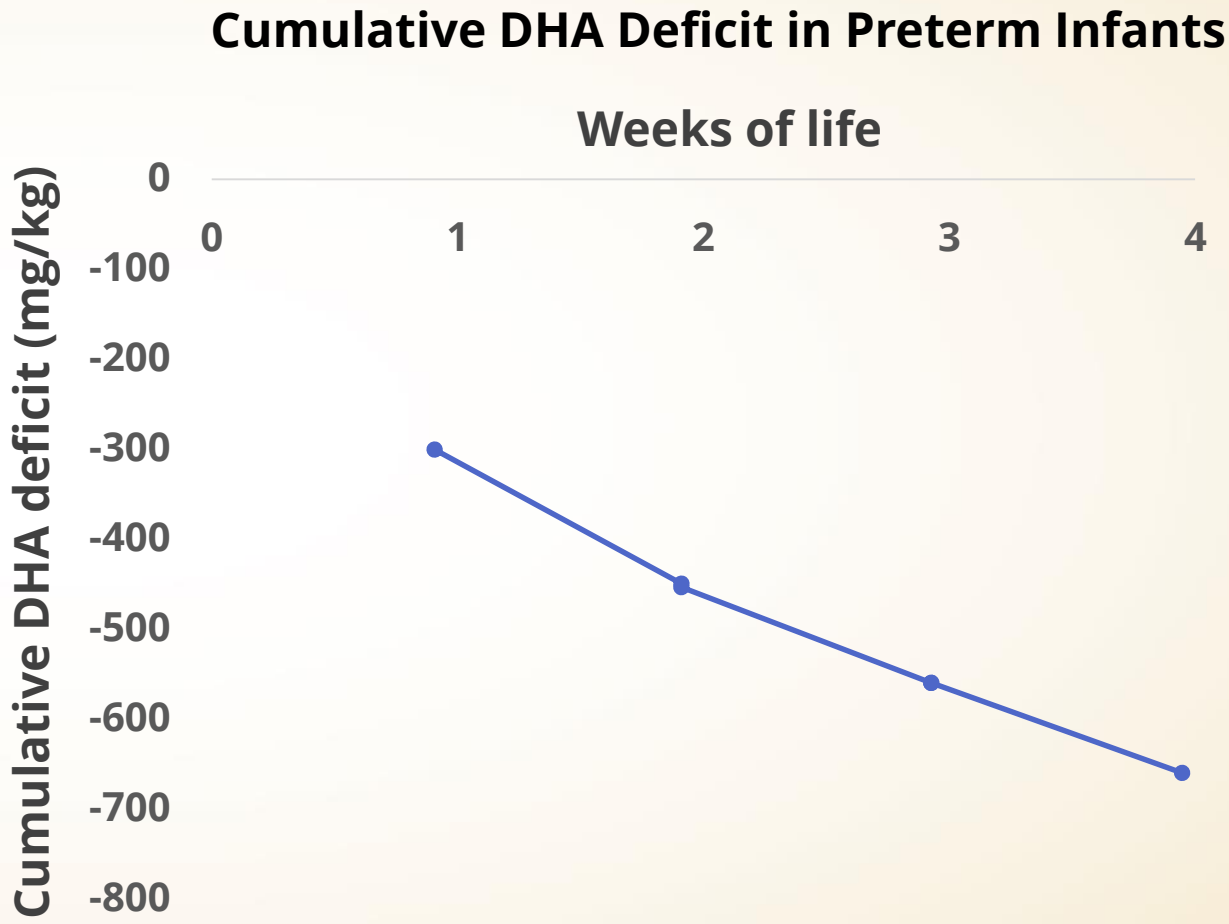
Models adjusted for gestational age, gender, growth restriction, severity of illness, total Intralipid intake.

Martin CR, et al. *J Pediatr*. 2011;159(5):743-749.e1-2.

DHA/ARA SUPPLEMENTATION IN PRETERM INFANTS

Current Nutritional Practices Are Inadequate to Maintain Optimal Levels of Fatty Acids in Preterm Infants†

- In a study of 40 preterm infants (≤28 weeks gestational age), nutritional data were collected for the first 4 weeks of life
- DHA deficit was greater for low-birth-weight infants
- In preterm infants, DHA accumulation is half that of term infants at 1 month of age



†Nutritional data were collected for the first 28 days of life in 40 preterm infants born with a gestational age ≤28 weeks at a single center.

Lapillonne A, et al. *Neonatology*. 2010;98(4):397-403.

Challenges in Achieving Adequate DHA/ARA Intake in Preterm Infants

- Delivery of DHA/ARA[1]
  - Breast milk and formulas provide DHA/ARA
  - Intravenous lipid emulsions available for routine use do not include DHA/ARA
  - Extremely premature infants may rely on intravenous lipid emulsion for the first weeks of life,[2] contributing to DHA/ARA deficiency

1. Robinson DT, et al. *J Pediatr*. 2013;162(1):56-61. 2. Ehrenkranz RA, et al. *Pediatrics*. 1999;104(2 Pt 1):280-289.

Challenges in Achieving Adequate DHA/ARA Intake in Preterm Infants

- Providing additional DHA is dependent on the infant's ability to tolerate full-volume enteral feedings
  - Variable among NICUs
  - Dependent on size, clinical status, and gestational age

Baack ML, et al. *Lipids*. 2016;51(4):423-433.

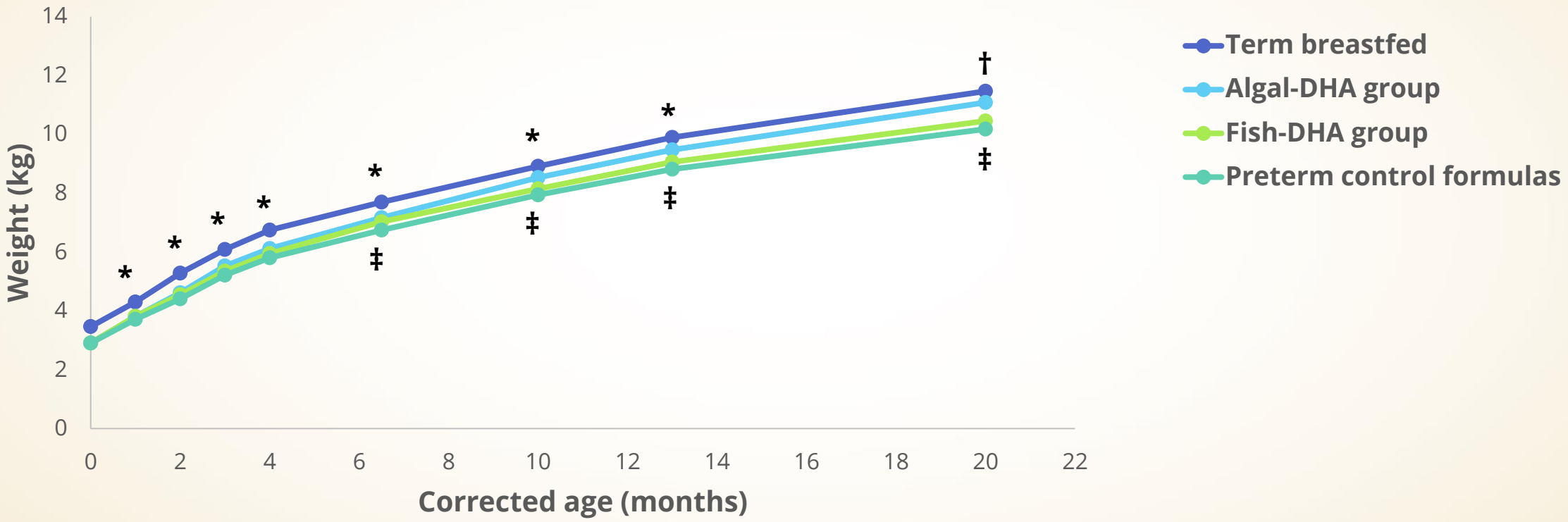
DHA Supplementation Alleviates DHA Deficiency in Preterm Infants†

	Baseline DHA, mol%	Full-Feedings, DHA mol%	Discharge, DHA mol%
Placebo preterm (n = 29)	2.91 (0.45)	2.83 (0.50)	2.87 (0.50)*
DHA preterm (n = 31)	2.88 (0.68)	3.03 (0.54)	3.55 (0.44)**
Term (n = 30)	4.31 (0.95)		

†Double-blind, randomized, controlled trial evaluating DHA supplementation (50 mg/day) for preterm infants (24-34 weeks gestational age) beginning in the first week of life.
Results expressed as mean (SD) mol%.
*Groups compared with term reference peers via ANOVA; $P < .001$.
**Placebo vs DHA comparison via linear mixed models; $P < .001$.

Baack ML, et al. *Lipids*. 2016;51(4):423-433.

Weight of Preterm Infants Fed DHA/ARA Formula Is Closer to Term Breast-fed Infants§

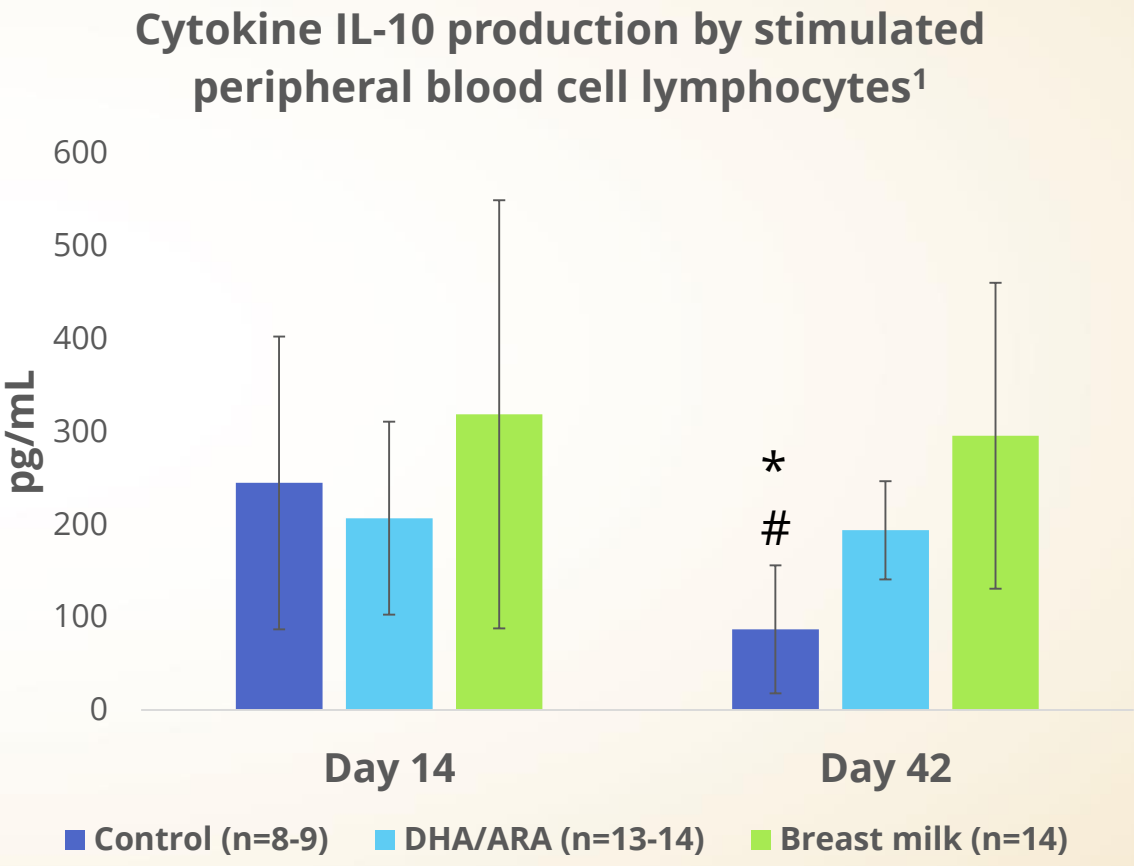


§Double-blinded study of 361 preterm infants fed until 92 weeks postmenstrual age, with follow-up to 118 weeks postmenstrual age
*Breast-fed term infants > all preterm groups ($P < .05$).
†Infant formulas not different from term breast milk, both > control and fish/fungal formulas.
‡Infant formulas > control formulas.

Clandinin MT, et al. *J Pediatr*. 2005;146(4):461-468.

Enhanced Immune Function With DHA/ARA Supplementation†

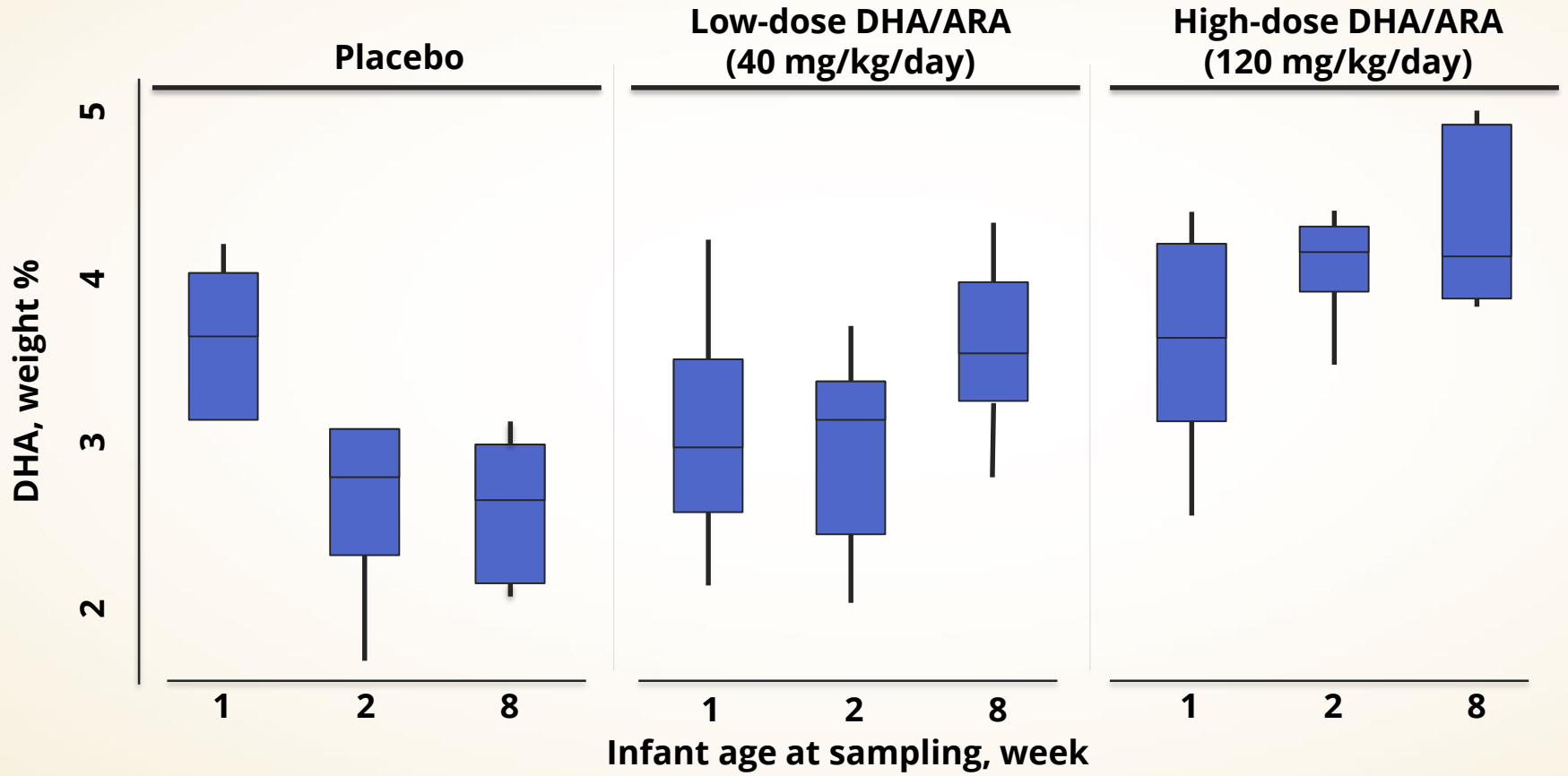
- Adding DHA/ARA to preterm formula resulted in immune function more consistent with breast milk-fed infants[1]
- In another study, infants supplemented with DHA had reduced levels of inflammatory cytokines believed to play a role in type 1 diabetes development[2]
- DHA/ARA supplementation may affect the ability of an infant to respond to immune challenges[1,2]



†Study of 44 preterm infants with gestational ages between 27 and 36 weeks receiving 100% enteral nutrition by day 14 of life.
*$P < .05$, compared with Day 14. #$P < .05$, compared with breast milk, Day 42.

1. Field CJ, et al. *J Pediatr Gastroenterol Nutr*. 2000;31(3):291-299. 2. Chase P, et al. American Diabetes Association Scientific Sessions 2010. Orlando, Florida: June 25-29. Abstract 1918-P.

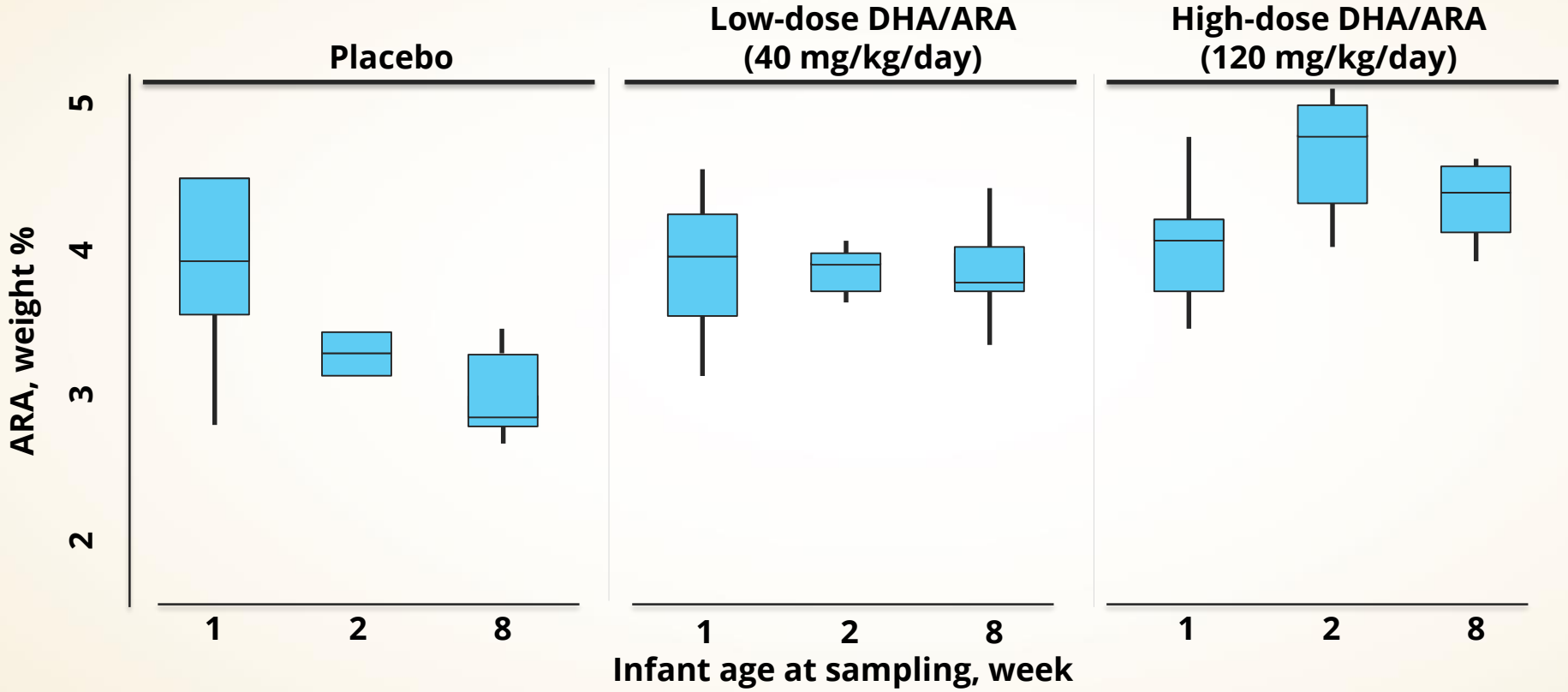
Effect of Emulsified DHA/ARA Enteral Supplementation on Serum DHA Levels in Preterm Infants



Randomized, double-blind, placebo-controlled trial of 30 very low-birth-weight infants given low dose or high dose PUFA via nasogastric tube. Dosing started within first 72 h of life and was given for 8 weeks or until discharge, whichever came first.

Frost B, et al. Pediatric Academic Societies Meeting. April 24 – May 1, 2019. Baltimore, MD.

Effect of Emulsified DHA/ARA Enteral Supplementation on Serum ARA Levels in Preterm Infants†



†Randomized, double-blind, placebo-controlled trial of 30 very low-birth-weight infants given low dose or high dose PUFA via nasogastric tube. Dosing started within first 72 h of life and was given for 8 weeks or until discharge, whichever came first.

DHA/ARA Supplementation and Neurodevelopment in Preterm Infant Neurodevelopment at 6 Months and 1 Year†

- In a double-blind study, preterm infants between gestational age of 30 and 37 weeks were randomly assigned to receive formula with or without DHA/ARA supplementation
- DHA/ARA supplementation for 6 months led to significantly increased measures of neurodevelopment in preterm infants

	Mean ± SD MDI score		Mean ± SD PDI score	
Age	**6 mo**	**1 y**	**6 mo**	**1 y**
+DHA/ARA (n = 16)	96.1±8.6	98.7±8.0	102.2±10.5	98.0±5.8
-DHA/ARA (n = 11)	91.7±10.4	90.5±6.9	95.4±13.2	86.7±11.1

†Double-blind, randomized study of preterm infants >2000 g body weight and >32 weeks of gestation in full feeding status who received formula with or without DHA/ARA for 6 months.
MDI, Mental Development Index; PDI, Psychomotor Development Index.

Fang PC, et al. *Chang Gung Med J*. 2005;28(10):708-715.

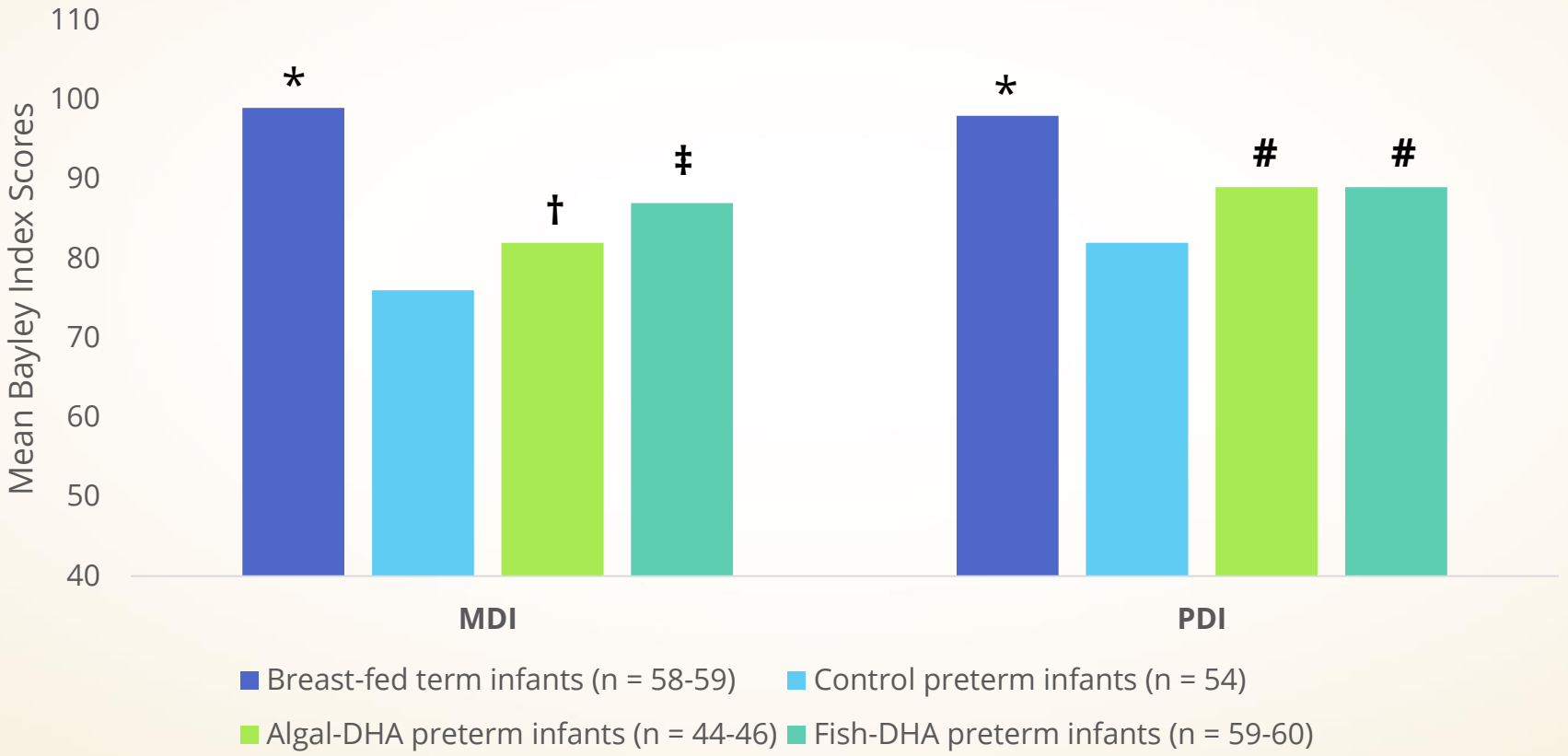
DHA/ARA Supplementation Improves Cognitive Development at 6 Months†

	Score, Mean (SD)	
	Control (n = 55)	**DHA/ARA supplementation (n = 50)**
Total score	215 (39)	221 (32)
Communication	46.6 (9.1)	45.4 (7.9)
Gross motor	30.9 (11.1)	33.3 (11.5)
Fine motor	45.8 (14.3)	45.2 (10.7)
Problem-solving	49.5 (9.5)	53.4 (7.0)*
Personal-social	42.2 (12.3)	43.2 (12.8)

†Randomized, double-blind, placebo-controlled study of 141 infants with birth weights <1500 g. Intervention = 32 mg DHA + 31 mg ARA per 100 mL human milk started 1 week after birth and continued through hospital discharge (mean, 9 weeks). Cognitive development assessed at 6 months of age using Ages and Stages Questionnaire.

Henriksen C, et al. *Pediatrics*. 2008;121(6):1137-1145.

DHA/ARA Supplementation Improves Bayley Scores at 118 Weeks Postmenstrual Age in a Double-Blind Study

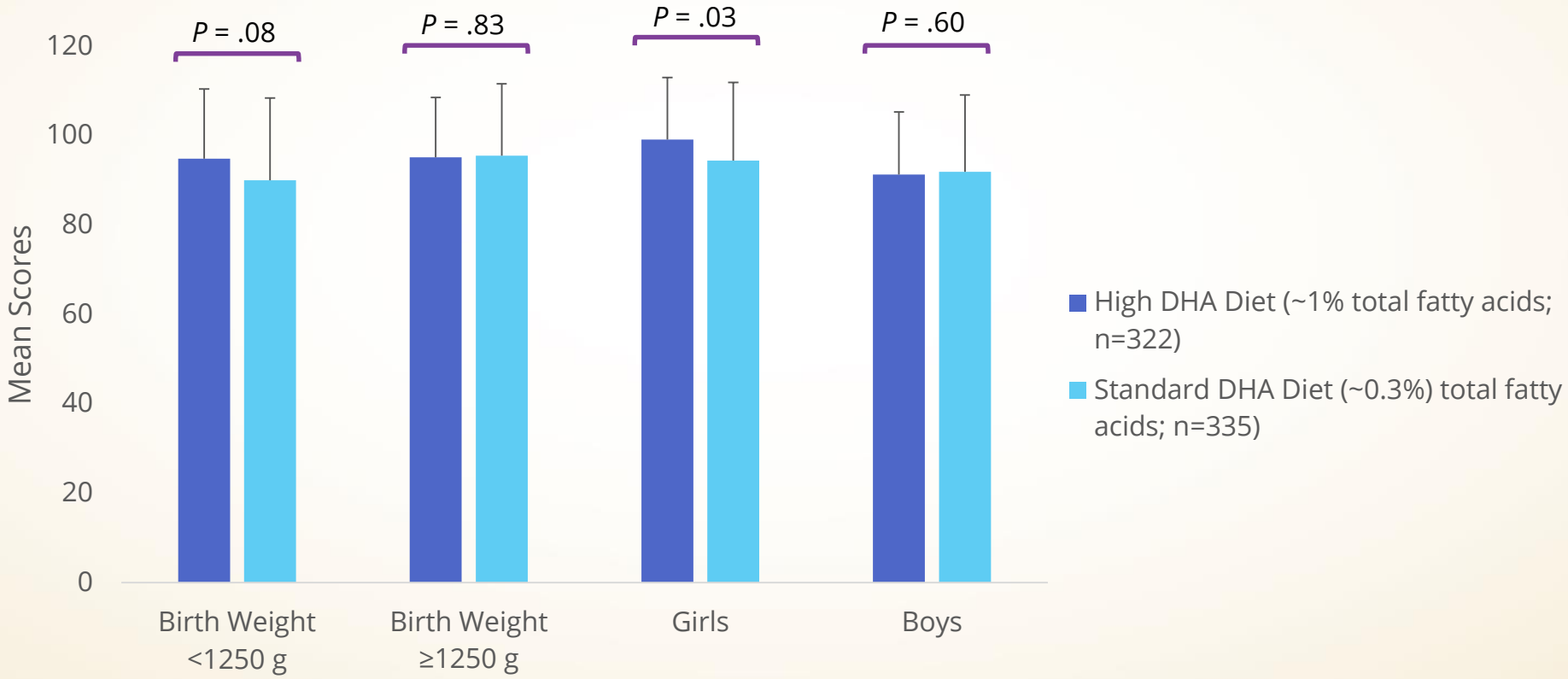


MDI, Mental Development Index; PDI, Psychomotor Development Index. *Breast-fed term > control, algal-DHA, fish-DHA ($P < .05$); †Algal-DHA > control ($P = .056$); ‡ Fish-DHA > control ($P < .05$); #Algal-DHA, fish-DHA > control ($P < .05$). Parentheses indicate number of infants per group.
Double-blinded study of 361 preterm infants. MDI and PDI assessed at 118 weeks postmenstrual age.

Clandinin MT, et al. *J Pediatr*. 2005;146(4):461-468.

Conflicting Results Regarding Benefit of DHA/ARA Supplementation in Preterm Infant Neurodevelopment: No Significant Difference†

Bayley MDI Scores at 18 Months' Corrected Age



†Randomized, double-blind controlled trial of 657 infants born at less than 33 weeks' gestation at 5 Australian tertiary hospitals with follow-up to 18 months. Standard-/high-DHA enteral feeds were given from day 2 to 4 of life until term corrected age

Makrides M, et al. *JAMA*. 2009;301(2):175-182.

Long-Chain PUFA Supplementation in Formula

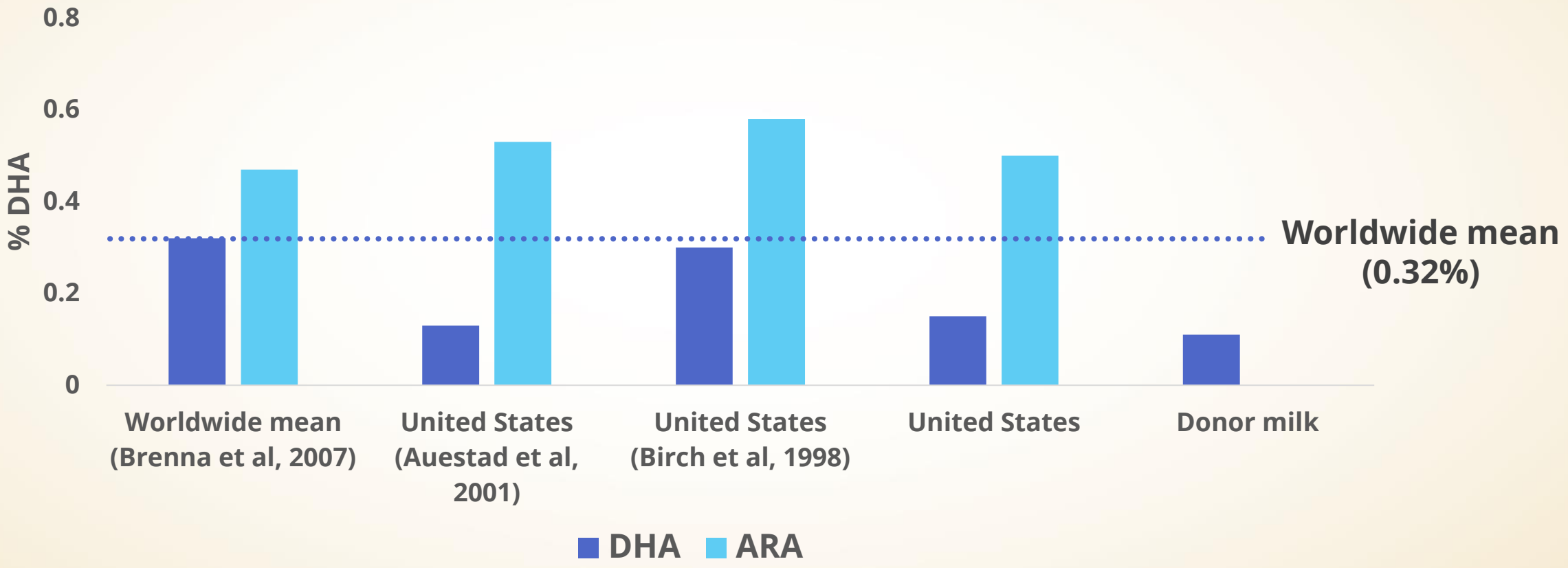
- Systematic review and meta-analysis of 17 randomized trials (13 classified as high quality) of formula supplemented with LCPUFA to assess safety and benefit to preterm infants
- Infants enrolled in the trials were relatively mature and healthy preterm infants
- Assessment schedule and methodology, dose and source of supplementation and fatty acid composition of the control formula varied between trials
- On pooling of results, **no clear long-term benefits or harms** were demonstrated for preterm infants receiving LCPUFA-supplemented formula

Schulzke SM, et al. *Cochrane Database Syst Rev*. 2011;(2):CD000375.

Enteral Strategies for Increasing DHA/ARA Intake in Preterm Infants

- Maternal supplementation
- Breast milk (mother's own)
- Structured lipids
- Pre-emulsified lipids
- Enzyme technologies

Donor Milk Levels of DHA Are Lower Than Mean Reported Levels[1†]



†Descriptive meta-analysis of 65 studies of human breast milk, including 2474 women.

1. Valentine C, et al. *J Pediatr*. 2010;157(6):906-910. 2. Auestad N, et al. *Pediatrics*. 2001;108(2):372-381. 3. Birch EE, et al. *Pediatr Res*. 1998;442:201-209. 4. Brenna JT, et al. *Am J Clin Nutr*. 2007;85(6):1457-1464.

Fatty Acid Replacement in Formula Is Challenging and Requires Standardization

- Defining target levels
- Determining dietary balance of n-3:n-6 fatty acids
- Ensuring optimal sn-position for absorption and incorporation into cellular phospholipids
- Optimizing digestion and absorption
- Achieving adequate levels at the tissue, cellular, and molecular levels

CURRENT NICU PRACTICES INVOLVING DHA/ARA IN PRETERM INFANTS

Current Practices

- Provide long chain PUFA in enteral feedings[1]
- DHA/ARA are available in breast milk and commercially available infant formula[1]
- Very premature infants do not reach full enteral feedings for several weeks[1]
  - Standard parenteral lipid emulsions do not provide DHA/ARA[1]
  - After reaching full enteral feedings, standard dietary DHA provision[2] is not adequate to alleviate deficiency of prematurity[3,4]

1. Baack ML, et al. *Lipids*. 2016;51(4):423-433. 2. Brenna JT, et al. *Am J Clin Nutr*. 2007;85(6):1457-1464. 3. Harris WS, et al. *J Perinatol*. 2015;35(1):1-7. 4. Lapillonne A, et al. *Neonatology*. 2010;98(4):397-403.

Current Parenteral Nutrition Practices†

Lipid emulsion ≤28 days (mean [SD])

	Birth (n = 17)	2 weeks (n = 14)	4 weeks (n = 17)	8 weeks (n = 17)
LA	3.6 (1.6)	8.7 (2.1)	8.8 (2.1)	7.9 (1.9)
ALA	0.03 (0.02)	0.08 (0.03)	0.07 (0.03)	0.07 (0.03)
DHA	5.3 (1.7)	3.6 (1.0)	3.7 (1.1)	4.2 (1.9)
ARA	14.8 (2.2)	12.0 (2.0)	12.7 (1.8)	11.5 (2.5)

Lipid emulsion >28 days (mean [SD])

	Birth (n = 17)	2 weeks (n = 14)	4 weeks (n = 17)	8 weeks (n = 17)
LA	3.6 (1.0)	10.1 (2.2)	11.3 (2.4)	10.1 (3.1)
ALA	0.03 (0.01)	0.09 (0.04)	0.12 (0.04)	0.12 (0.06)
DHA	5.5 (1.4)	3.0 (1.0)	3.1 (0.4)	2.7 (0.6)
ARA	15.7 (3.8)	11.7 (2.3)	11.4 (1.9)	9.4 (1.6)

- Infants showed a decline in DHA/ARA over time
- Longer exposure to intravenous lipid emulsion had a significantly greater decline in RBC DHA levels
- Infants who received intravenous lipid emulsion >28 days had longer time to start enteral feeds and reached full enteral nutrition 33 days later

†Prospective cohort study of 26 extremely low-birth-weight infants given intravenous lipid emulsion for ≤28 days or >28 days to assess change in LCPUFA
Levels reported as weight % (g/100 g).

Robinson DT, et al. *J Pediatr*. 2013;162(1):56-61.

Transition to Enteral Nutrition

Even after transitioning to full enteral feedings, premature infants cannot overcome the decline in whole blood DHA/ARA levels apparent after birth[1]

- Suggests limited activity of desaturase enzymes[2] or increased utilization of DHA/ARA due to disease or disease severity

1. Martin CR, et al. *J Pediatr*. 2011;159(5):743-749.e1-2. 2. Carnielli VP, et al. *Pediatr Res*. 1996;40(1):169-174.

The Role of Clinicians

- Help families navigate supplementation fads by sharing evidence from high-quality studies
  - Discuss problems with observational and cross-sectional findings used by companies to promote products that are not regulated directly to parents
- Consider better ways to supplement DHA/ARA in the highest risk patients

Cowden JD. *NEJM Journal Watch*. November 7, 2018. jwatch.org/na47834/2018/11/07/can-docosahexaenoic-acid-supplementation-help-toddlers.

The Role of Nurses and Dietitians

- Provide diet-related information to pregnant and lactating women to increase omega-3 fatty acid intake
- Collaborate with colleagues to determine what supplements/formulas would be appropriate to help ensure adequate DHA intake
- Continue to monitor supplement/formula developments

Brooks SL, et al. *MCN Am J Matern Child Nurs*. 2000;25(2):71-75.

The Role of Hospital Pharmacists

- Provide advice
  - Appropriate choice and correct use of formula
  - Appropriate choice of foods and drinks in weaned infants
  - Vitamin and fatty acid supplementation
- Collaborate with colleagues to ensure adequate information is provided throughout pregnancy to make informed choices about feeding
- Evaluate for and counsel on potential medication and supplement interactions

Mason P. *Pharmaceut J*. 2000;264(7089):471-475.

Future Considerations

- Define goals for fatty acid levels at specific, clinically relevant times
- Ongoing monitoring
  - Feeding advancement
  - Adverse events
  - Effects on other essential fatty acid levels
- DHA supplementation
  - Provide additional daily enteral DHA (start before full enteral feedings are reached and at a dose approximating in utero accretion rates)

Baack ML, et al. *Lipids*. 2016;51(4):423-433.

ANY Questions?