Impact of Human Milk on the Neurodevelopment of the Preterm Infant

Richard J. Schanler, MD, FAAP
Cohen Children's Medical Center
Zucker School of Medicine at Hofstra/Northwell
New Hyde Park, New York
November 17, 2018

AAP Recommendations on Breastfeeding Management for Preterm Infants

- All preterm infants **should** receive human milk.
  - Human milk should be fortified, with protein, minerals, and vitamins to ensure optimal nutrient intake for infants weighing <1500 g at birth. **34 weeks**
  - Pasteurized donor human milk, appropriately fortified, **should** be used if mother's own milk is unavailable or its use is contraindicated.

http://pediatrics.aappublications.org/content/early/2012/02/22/peds.2011-3552
Pediatrics 2012; 129 (3): e827-842

Objectives

- Why human milk for preterm infants?
- Review neurodevelopmental outcomes in preterm infants fed human milk.

Why Human Milk?

- Lower morbidity from infection-related events
  - Necrotizing enterocolitis
  - Sepsis
  - Urinary tract infection
- Benefits persist beyond NICU stay

Why Human Milk?

	OR	(CI 95%)
BPD		
Exclusive formula	2.59	(1.33-5.04)
Mixed feeding	1.61	(1.15-2.25)
NEC		
Exclusive formula	12.86	(2.84-58.29)
Mixed feeding	3.59	(1.68-7.63)
ROP		
Exclusive formula	1.80	(1.05-3.11)
Mixed feeding	1.34	(1.02-1.76)

Referent = Exclusive breastmilk feeding
Controlled for ethnicity, steroids, inborn, gender, multiples, gestational age, enteral feeding, weight z-score at birth and discharge

Spiegler, *J Pediatr* 2016;169: 76-80

Neurodevelopmental Outcomes

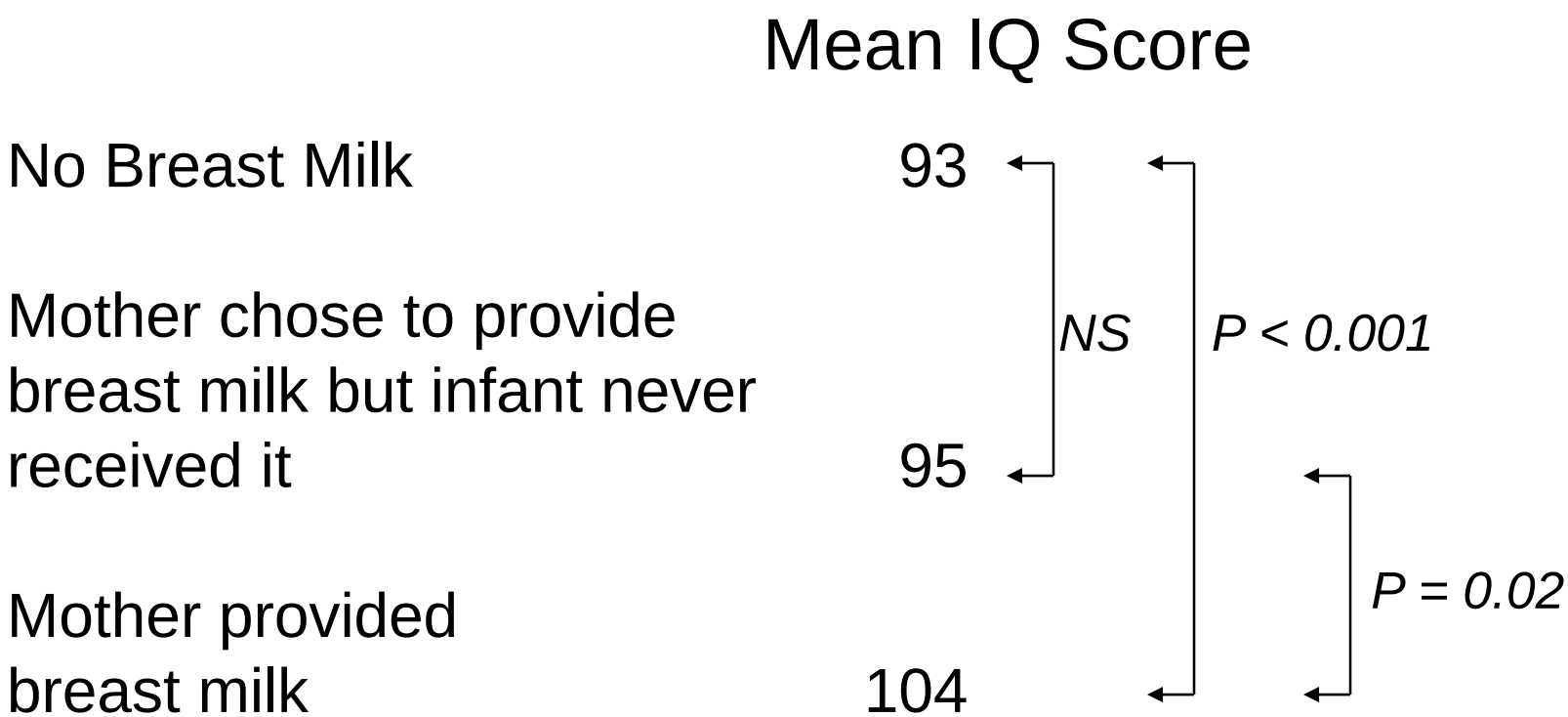
- Vision
- Mental Scales
- Motor Scales
- Behavior
- Hearing

Association between human milk diet and neurodevelopmental outcome in premature infants is complicated…

Considerations for Premature Infants

- Diet
  - Mother's own milk
  - Donor human milk (pasteurized)
  - Episodic use of formula
- Morbidity of premature infants
  - Chronic lung disease
  - Sepsis
  - Necrotizing enterocolitis
  - Retinopathy of prematurity
  - Co-morbidities
- Growth of premature infants
- Rapidity of brain growth
- Decision to provide human milk
- Maternal-infant interactions
  - bonding
  - attachment
- Non-homogeneity of human milk composition
- Taste, odor of human milk
- Unknown

Breast Milk and Subsequent Intellectual Performance in Premature Infants at 8 Y

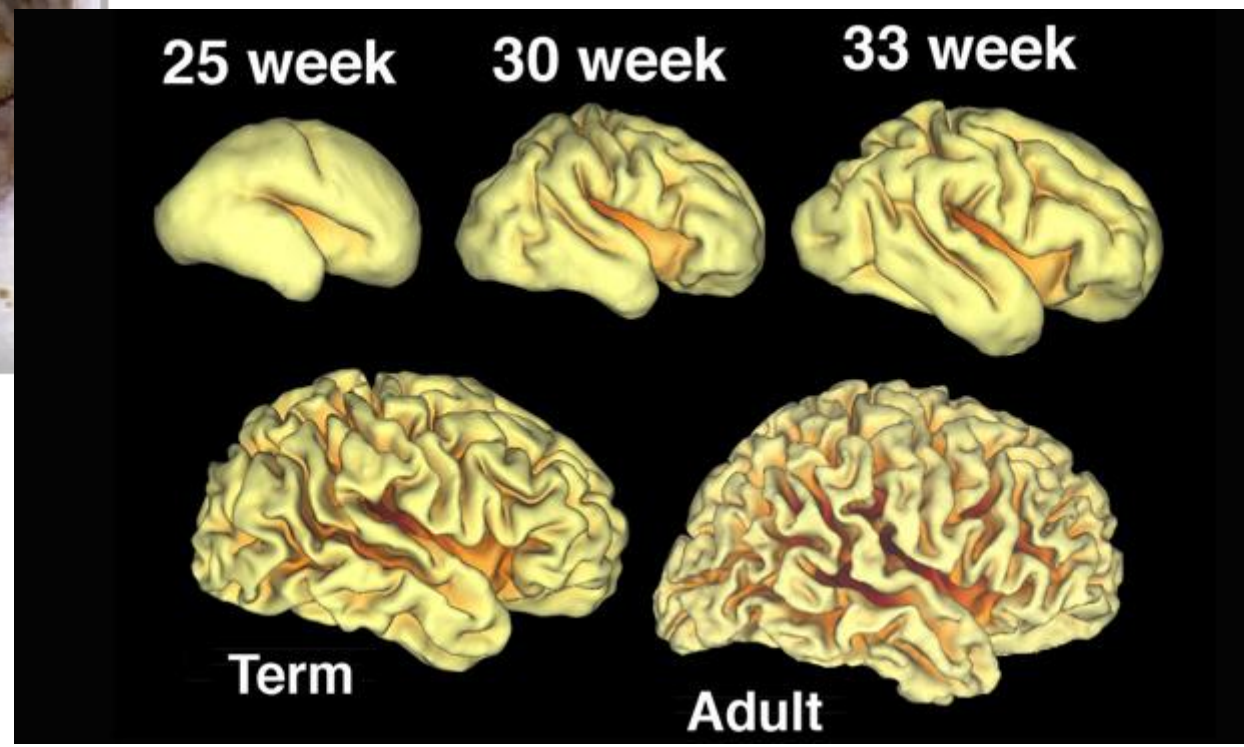


Lucas, Lancet 1992;339:261

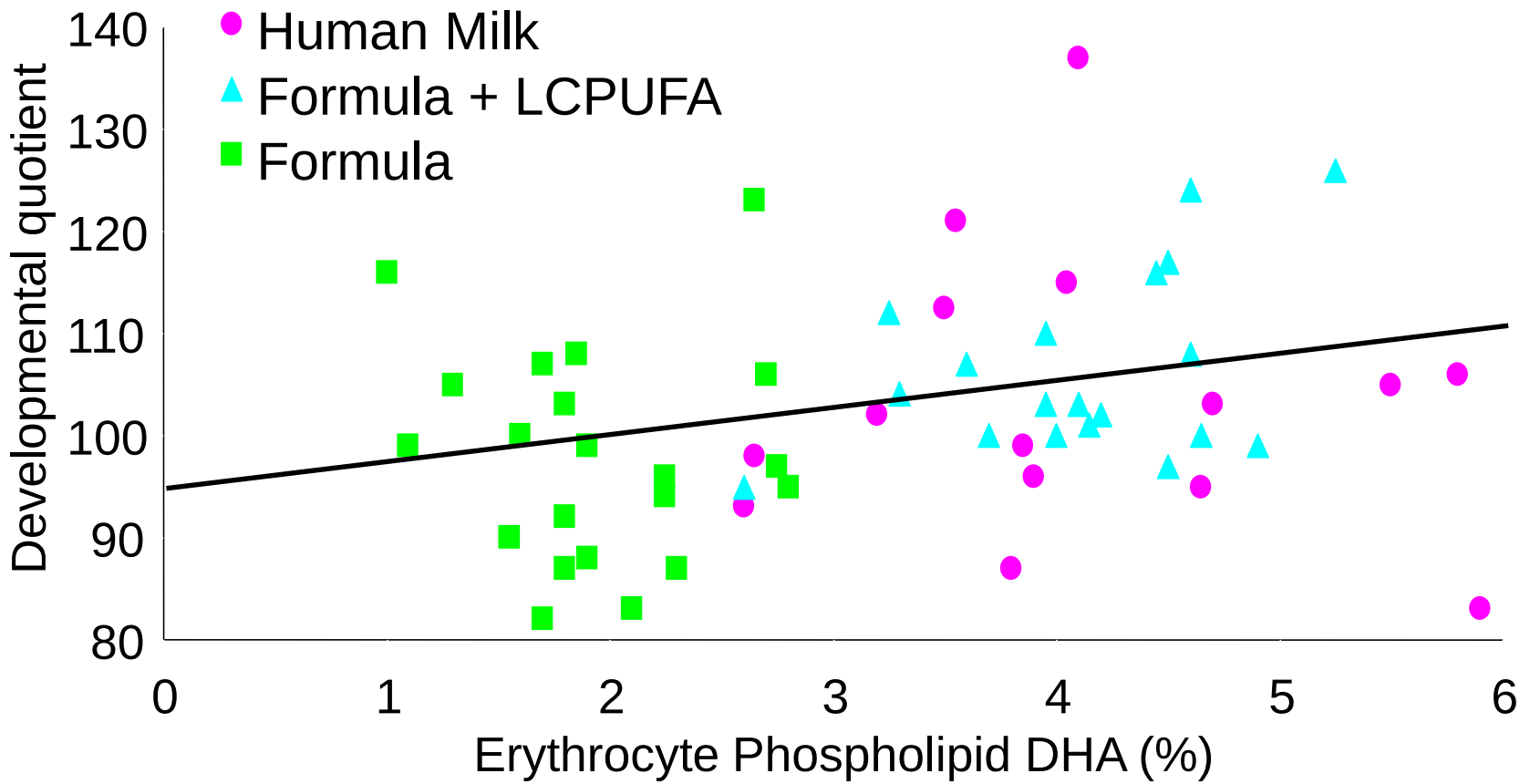
Nutrients/Factors with Effects on Brain

- Macronutrients
  - Protein
    - Protein quality
  - Energy
    - Fat (LC-PUFA: DHA)
    - Glucose
- Micronutrients
  - Zinc
  - Selenium
  - Iodine (Thyroid)
  - Iron
- Vitamins
  - B vitamins (B6, B12)
  - Vitamin A
  - Vitamin K
  - Folate
- Human milk components
  - Oligosaccharides
  - Microbiome
  - Cholesterol
  - Nucleotides
  - Antioxidants
  - Taurine
  - Choline
  - Growth factors

Ensure optimal somatic growth to effect brain growth and development



DHA and DQ @ 4 mo



Agostoni, Lancet 1995; 346:638

Early Nutrition Mediates the Influence of Severity of Illness

Energy Intake by Degree of Critical Illness

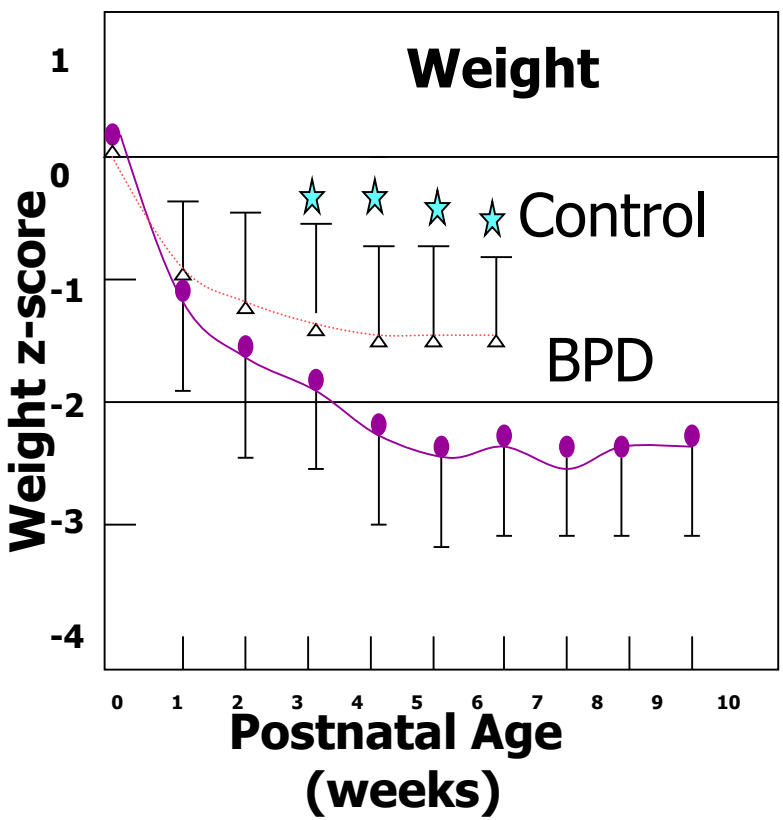
Energy Intake (kcal/kg/d) Days 1-7	Critically Ill (AGA Infants)		
	Less (MV < 7d) (n=499)	More (MV d1-7) (n=464)	p-value
Parenteral	46.1 (12.5)	41.1 (12.5)	<.0001
Enteral	3, 5.8 (8.1)	0, 1.6 (3.5)	< .0001
Total Energy	52.0 (13.8)	42.7 (13.1)	<.0001

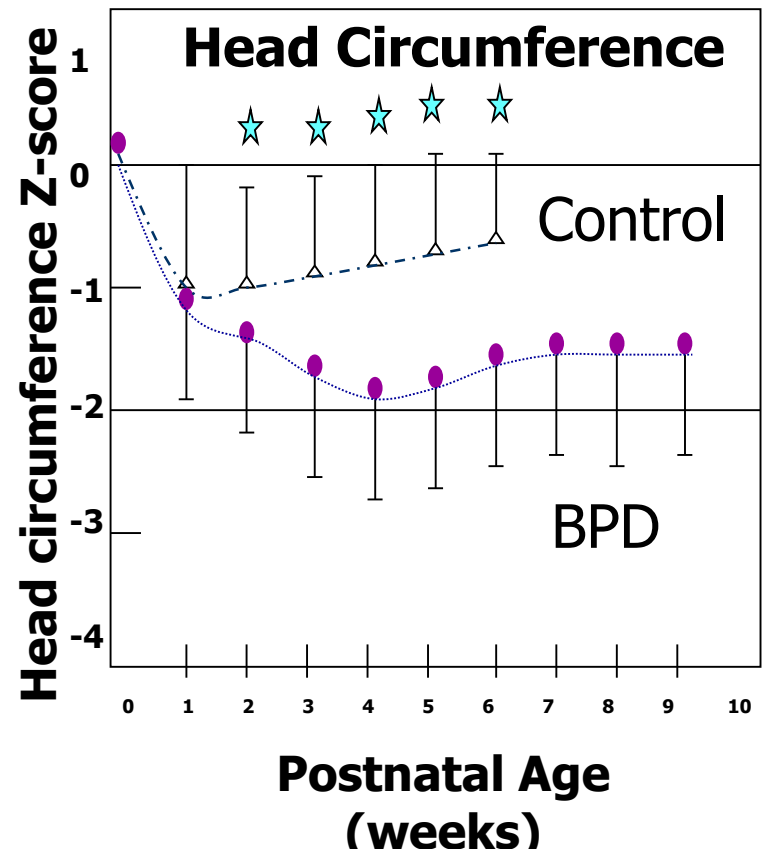
Outcome Variables by Degree of Critical Illness

Variable	Less Critically Ill	More Critically Ill	p-value
BPD [n(%)] Moderate Severe	 109 (23.1) 51 (10.8)	 210 (38.6) 170 (31.3)	<.0001
Duration of PPV (d)	13.5 (16.6)	40.9 (26.6)	<.0001
Duration of O_2 (d)	46.7 (33.1)	74.6 (34.5)	<.0001
PN Steroids [n(%)]	88 (17.6)	331 (51.2)	<.0001
Late onset-sepsis	187 (37.5)	306 (47.4)	.0008
Death [n(%)]	35 (7)	123 (19)	<.0001
Length of stay (d)	82.6 (34.9)	102.6 (57.9)	<.0001
Wt @ 36 wks PMA	1926 (312)	1781 (340)	<.0001
MDI < 70 [n(%)]	**83 (21.3)**	**180 (42.7)**	**<.0001**
PDI < 70 [n(%)]	**34 (8.9)**	**117 (27.9)**	**<.0001**
Mod/Sev CP [n(%)]	**12 (2.5)**	**41 (9.1)**	**0.0002**

Extremely preterm infants
Ehrenkranz Pediatr Res 2011

Effect of Bronchopulmonary Dysplasia (BPD) on Growth





deRegnier et al, 1996

IQ at School Age in Preterm Infants with and without BPD vs Term Infants

First Author and Publication Year	Preterm or VLBW with BPD	Preterm or VLBW Without BPD	Full-Term Controls
Vohr et al,[47] 1991	n = 13 93 ± 21	n = 15 94 ± 13	n = 15 108 ± 11
Robertson et al,[44] 1992	n = 21[a] 88 ± 21	n = 21 97 ± 20	n = 21 115 ± 10
Hughes et al,[45] 1999	n = 95 86 ± 18	n = 311 96 ± 18	n = 188 100 ± 17
Short et al,[41] 2003	n = 98 87 ± 20	n = 75 95 ± 16	n = 99 102 ± 15

[a] Born less than 32 weeks gestation with oxygen dependence at 36 weeks postmenstrual age.

Full scale IQ testing

Human Milk Reduces ROP

Descriptive studies suggest less retinopathy of prematurity (ROP) in human milk-fed premature infants

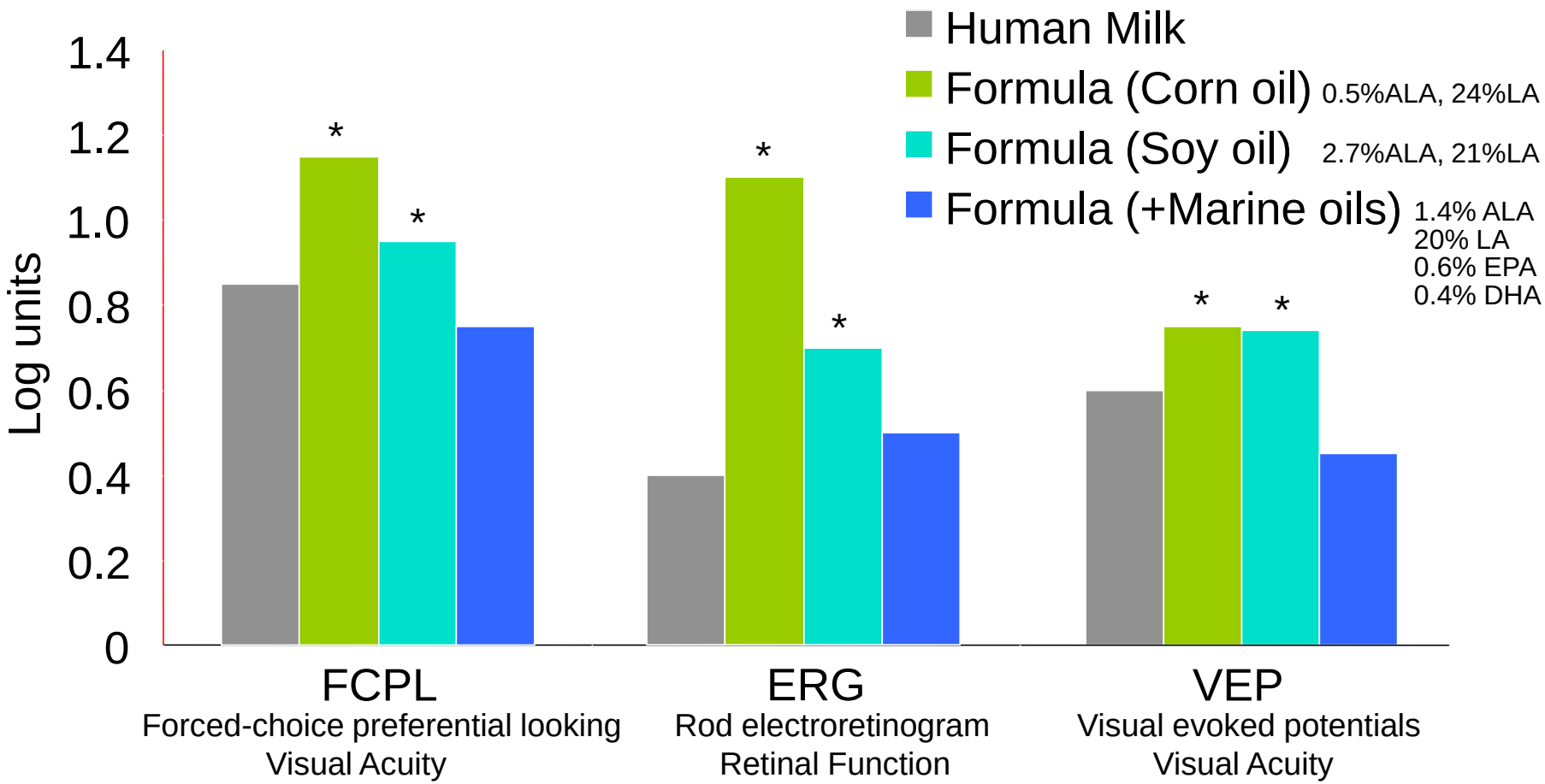
2 RCTs at 11 Italian NICUs: 314 infants exclusively HM feeding vs. 184 formula

- Overall ROP less (3.5% vs 15.8%)
- Threshold ROP (needing treatment) less (1.3% vs. 12.3%)

With multivariate regression, human milk was protective against ROP, $p < 0.01$

Hylander, J Perinatol 2001; Schanler Pediatrics 2005; Okamoto, Pediatr Int 2007, Manzoni, Early Human Devel 2013

Effect of Diet on Visual Function in Premature Infants



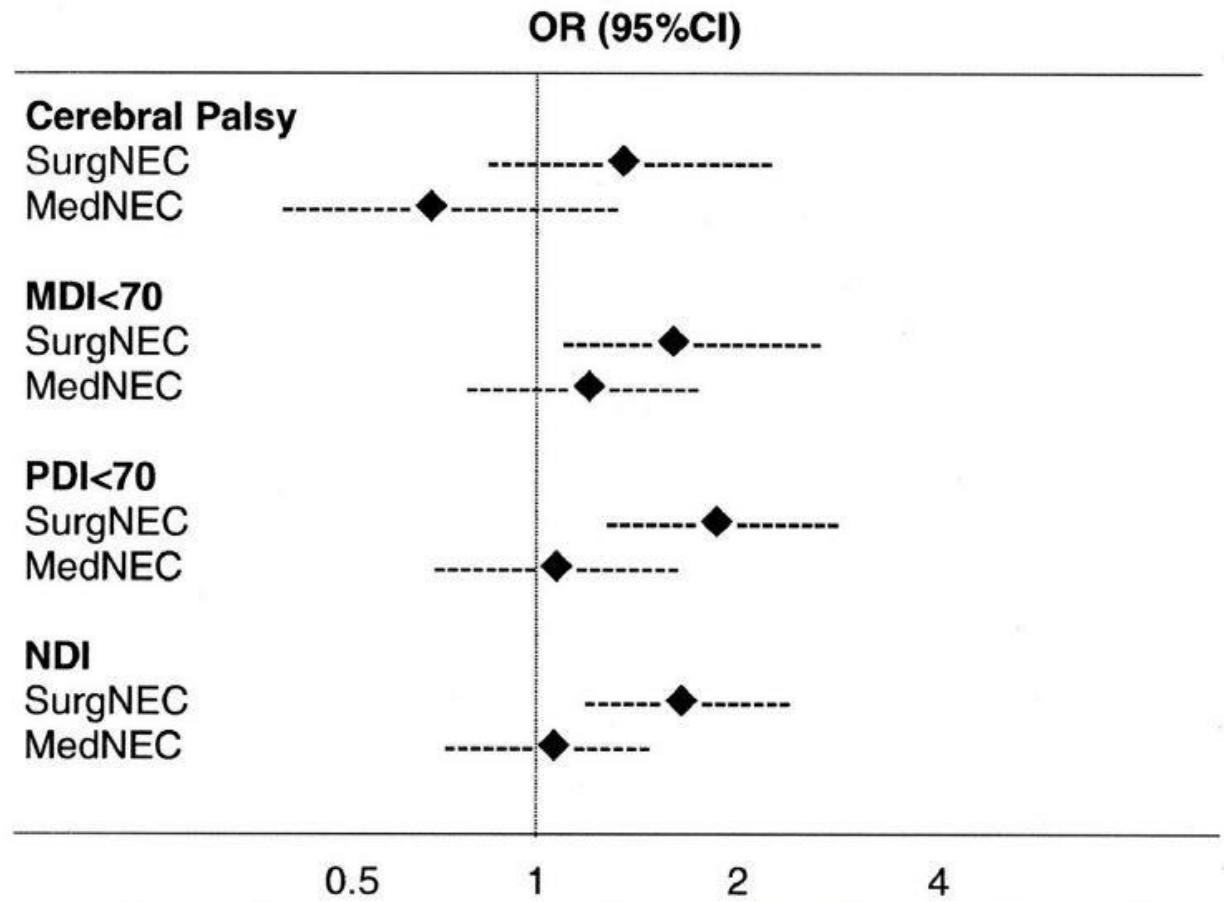
Uauy, 1997 n=85; BW 1000-1500 g, 28-32 wk) **Significantly different vs Human Milk*

Late Complications of NEC

- Gastrointestinal
  - Stricture
  - Short bowel syndrome
  - Cholestasis, liver cirrhosis and liver failure
- Postnatal growth delay
  - Surgical > Medical NEC
- Hospital costs
- **Neurodevelopmental disadvantages**

Hintz et al, Pediatrics 2005; 115:696
Shah et al, J Pediatr 2008; 153:170
Johnson et al, J Pediatr 2013: 162:243-9

Neurodevelopmental Outcomes in Premature Infants with NEC

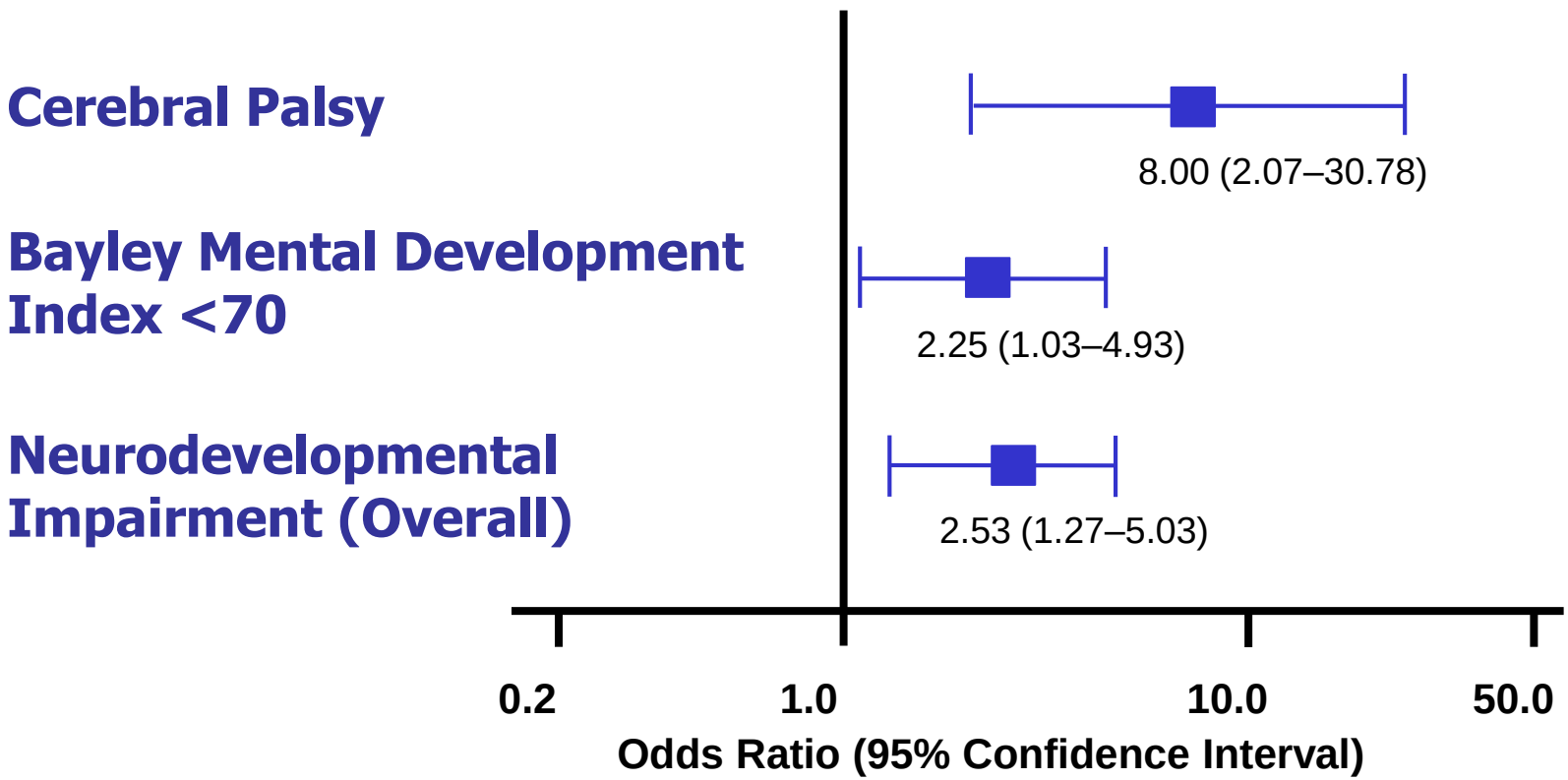


Adjusted odds ratios (ORs) for CP, MDI less than 70, PDI less than 70, and NDI in Surgical NEC and Medical NEC compared with No NEC infants. (*From* Hintz SR, Kendrick DE, Stoll BJ, et al. Neurodevelopmental and growth outcomes of extremely low birth weight infants after necrotizing enterocolitis. Pediatrics 2005;115(3):696–703.)

Body growth is a major predictor of neurodevelopmental outcome

Weight Gain Affects Outcome

In-hospital growth: **12.0** vs **21.2** g/kg/day



Ehrenkranz RA, et al. *Pediatrics* 2006;117:1253-61.

Human milk and neurodevelopmental outcomes

Predictors of Neurodevelopmental Outcome

Human milk feeding	**3.799**	**0.05**
IVH/PVL	-23.307	<0.001
NEC	-5.067	0.246
Sepsis	-1.124	0.667
Mechanical ventilation	-3.831	0.108
Gestational age	0.810	0.069
Small-for-gestational age	1.432	0.546
Extrauterine growth restriction	-1.408	0.453
Socioeconomic status	3.284	<0.001

24 month follow-up; n=316

PLOS ONE 10 (1): e0116552 1/13/2016 Giberton D, Corvaglia L, et al. Bologna, IT

Effects in Human Milk-Fed Children

- Greater white matter development
- Increased cortical thickness of parietal regions
- Higher scores for receptive language
- Higher scores for vision reception

Deoni, Neuroimage 2013: 82:77-86
Kafouri, Int J Epidemiol 2013; 42:150-9
Isaacs, Pediatr Res 2010; 67:357-62

Maternal-Infant Interaction

- N=86 <1750 g infants 1996-9

Feldman & Eidelman, 2003	86 infants <1750 g	1996–1999	At discharge and 6 mo	6m	Substantial	Intermediate	Minimal	*P*
				MDI	94.2 ± 9	91.7 ± 7	90.5 ± 8	<.05
				PDI	85.8 ± 11	78.6 ± 13	78.0 ± 12	<.01

- Substantial HM group:
- Maternal affectionate touch assoc with higher cognition
- Infants more alert

Slower Weight Gain but Higher MDI & PDI

RCT of formulas fed as supplements to Human Milk vs Formula only. Formula-fed (PFF) infants had greater weight gain.

Positive assoc between **HM duration** and MDI at 12 months after adjustment for HOME and maternal IQ (p = 0.03).

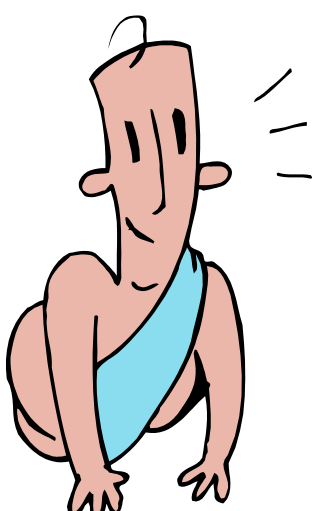
Infants with chronic lung disease fed > 50% HM had 11 point advantage in MDI at 12 months compared with PFF group.

N=463
750-1800 g 1996-8
O'Connor 2003

Human Milk and Subsequent IQ in Preterm Infants at 8 y

Significant factors affecting IQ

Social Class	- 3.5/class
Mother's Education	+ 2.0/group
Female Gender	+ 4.2
Mechanical Ventilation	- 2.6/week
Receipt of Human Milk	**+ 8.3 IQ points**



Lucas, Lancet 1992;339:261

Human Milk: IQ, Brain Size, White Matter Development

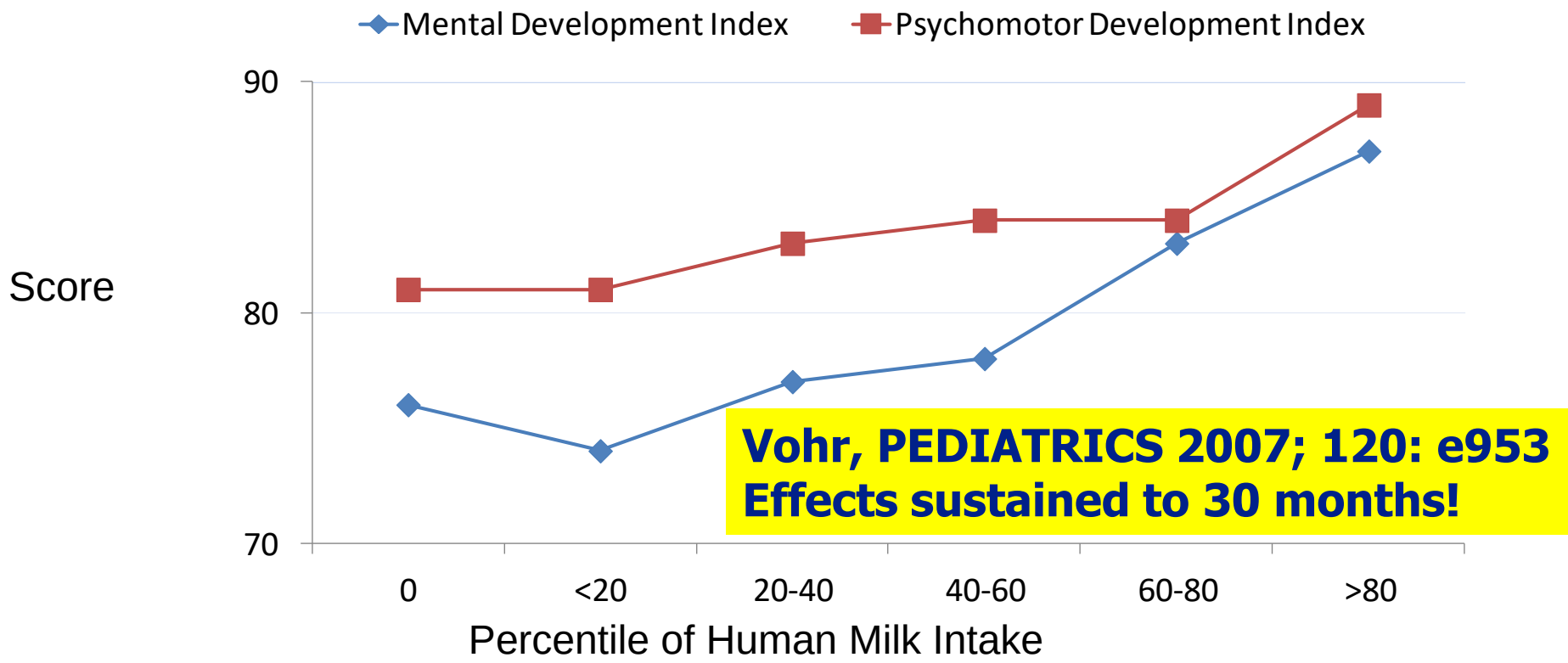
- Subset of 8 yo preterm study
- Follow-up to adolescence, 13-19 y
- Positive correlation:

  %Expressed Human Milk and .....

  - Verbal IQ $r = 0.3$, $p \leq 0.05$
  - White matter volume $r = 0.5 - 0.7$, $p < 0.001$

Covariates: maternal education, class, test age, gestational age
Isaacs, Pediatr Res 67:357-362, 2010

Dose of Human Milk in NICU & Outcomes at 18 mos



Vohr, PEDIATRICS 2006; 118: e115
Bayley Scales of Infant Development II
MDI, Mental Development Index
PDI, Psychomotor Development Index

N=775 Human milk (75%) 260 No Human milk (25%), = 1,035 infant
Birth weight 800 g Gestational age 27 wk
Pattern remains even after excluding any infant DC on human milk
Confounders included: maternal age, education, marital status, race/ethnicity

Dose of Human Milk in NICU & Outcomes at 18 mos

For every 10 mL/kg/d increase in HM ingestion:

- MDI increased by 0.53 points
- PDI increased by 0.63 points
- Behavior Rating Scale score increased by 0.82 points
- Likelihood of rehospitalization decreased by 6%

This small increase in scores reduces **economic burden** by decreasing the number of ELBW children who require special education services.

The **societal implications** of a five-point difference (one-third of an standard deviation) in IQ are substantial.

Vohr, PEDIATRICS 2006; 118: e115
Bayley Scales of Infant Development II
MDI, Mental Development Index
PDI, Psychomotor Development Index

N=775 Human milk (75%) 260 No Human milk (25%), = 1,035 infants
Birth weight 800 g Gestational age 27 wk

Neurodevelopment at 7 y

Predominant human milk diet for 28 days (>50% HM)

< 30 week gestation infants

Number of days infants received > 50% HM:

@ Term age: MRI showed greater deep gray matter volume

0.15 cc/day, 95% CI = 0.05 to 0.25 cc/day

@7 years: significant outcomes

IQ	0.5 points/day (0.2 to 0.8)
Math	0.5 points/day (0.1 to 0.9)
Working memory	0.5 points/day (0.1 to 0.9)
Motor function	0.1 points/day (0.0 to 0.2)

Belfort, J Pediatr 2016;177:133-9

Premature infants are already at high risk for neurodevelopmental delay and abnormalities, any intervention that has the potential to increase cognitive ability, even if the effect is small, is a significant tool.

Putative mechanisms

- Polyunsaturated fatty acids
- Direct stimulation of deep nuclear gray matter and hippocampus (working memory) and other areas
- Maternal – infant bonding
- Ghrelin and leptin re apetite regulation
- Antibodies and microbiome effects

Effects of Donor Human Milk

Bayley III score, mean (SD)	Mother's Own Milk	Preterm Formula	DBM	*P**	*P***
1-y corrected age	n = 15	n = 13	n = 18		
Cognition	93.0 (9.6)	97.1 (11.8)	**83.1 (11.6)**	0.003‡, §	0.005§
Language	86.1 (14.7)	91.1 (17.5)	**74.1 (8.8)**	0.02‡, §	0.04§
Motor	91.1 (9.9)	93.1 (7.8)	**82.4 (16.5)**	0.05	0.09
2-y corrected age	n = 18	n = 13	**n = 16**		
Cognition	93.9 (12.2)	94.7 (15.1)	**83.1 (13.9)**	0.04‡, §	0.03§
Language	91.9 (17.6)	88.7 (17.3)	**79.3 (9.2)**	0.06	0.09
Motor	89.0 (13.4)	92.4 (15.4)	**80.5 (12.5)**	0.06	0.16

*P*** based on 1-way ANCOVA adjusted for multiples, bronchopulmonary dysplasia, and social work involvement.
‡Post hoc pairwise comparisons of donor breastmilk vs mother's own milk; $P < 0.05$.
§ Post hoc pairwise comparisons of donor breastmilk vs preterm formula; $P < 0.05$.

Madore et al, Clin Therapeutics 2017; 39: 1210-20

Effects of Donor Human Milk

Pasteurized donor milk vs preterm formula used as supplements to fortified mother's own milk, n=363 infants, 27.7 wks, 996 g.

	DM	PF		
Necrotizing enterocolitis Stage $\geq$ II	1.7%	6.6%	-4.9 (-9.0 to -0.9)	*
Cognitive Neuroimpairment Score < 85	27.2%	16.2%	10.6 (1.5 to 19.6)	*

O'Connor JAMA 2016; 316:1897-1905

Albert Einstein was breastfed for 3 to 4 years!

Breastfeeding, Early Weight Gain, Neurodevelopment

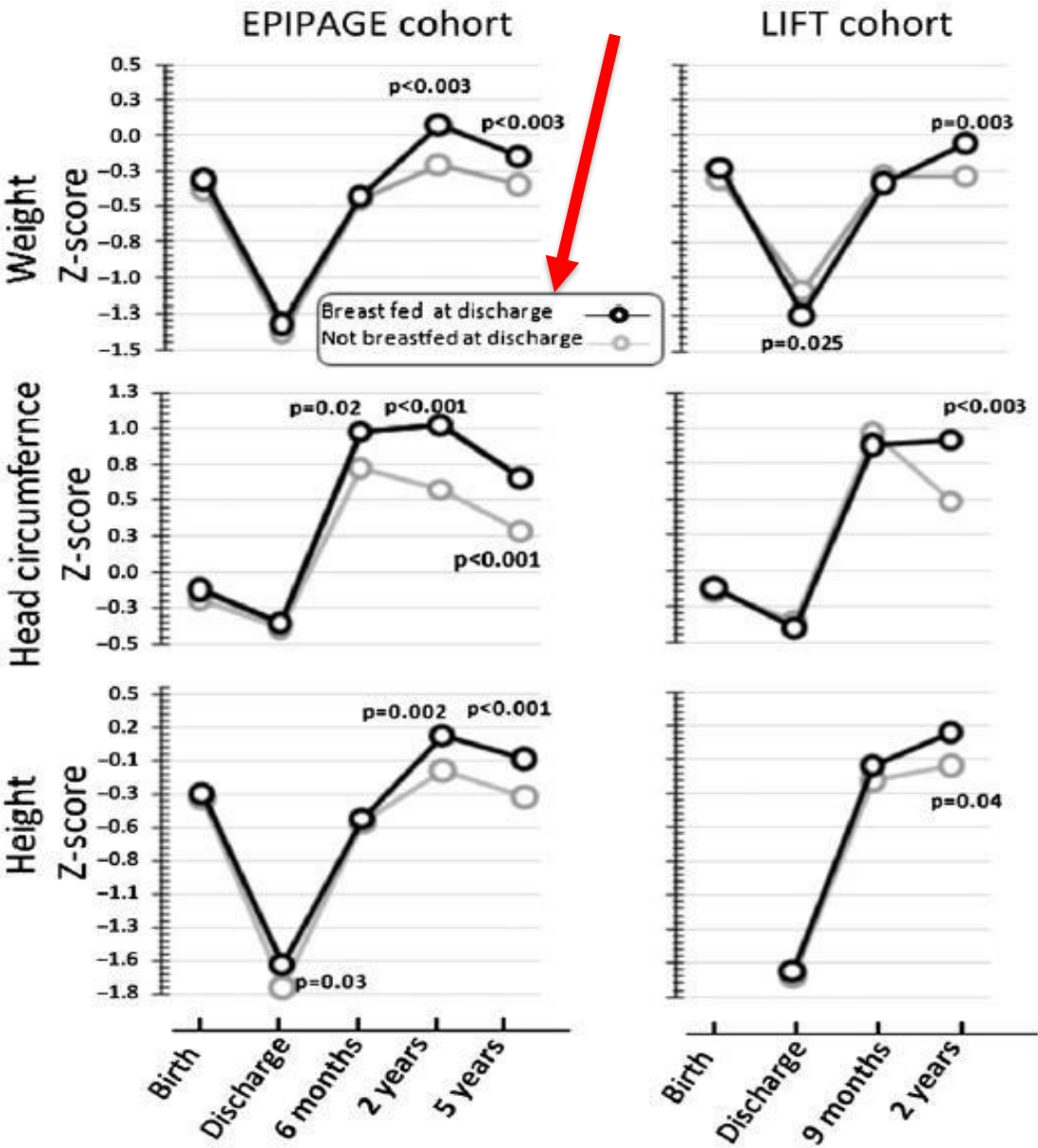
Follow-up studies of 2 French cohorts infants <32 weeks gestation

EPIPAGE 1997 (France): 19% BF at DC (n=1462)
LIFT 2003-8 (LOIRE Infant Follow-Up Team): 16% BF at DC (n=1463)

Propensity Score: maternal age + BMI + socioeconomic status + educational attainment + other kids + infant characteristics and morbidity.

Rozé J-C, Darmaun D, Boquien C-Y, Flamant C, Picaud J-C, Savagner C, Claris O, Lapillonne A, Mitanchez D, Branger B, Simeoni U, Kaminski M, Ancel P-Y.

BMJ Open 2012;2:e000834



Weight, head circumference and height Z-scores at discharge, 6, 9 mo and 2 y corrected age (EPIPAGE and LIFT cohorts) and at 5 y (EPIPAGE cohort).

At DC: BF slower NICU growth when adjusted for GA, gender, BW, propensity score

At Follow-Up:
BF at DC had greater growth measures

BMJ Open 2012;2:e000834

IMPROVED Neurodevelopmental Outcome at 2-5 y in Preterm Infants Breastfed at Discharge

- **NORMAL Neurodevelopment** (no adjustments)
  - EPIPAGE (n=1462) 2.3 x *p*=0.001
  - LIFT (n=1463) 1.9 x *p*=0.001

- Adjusted for gestation, birth weight, gender, propensity score
  - EPIPAGE (n=1462) 1.5 x *p*=0.008
  - LIFT (n=1463) 1.6 x *p*=0.005

~ < 32 wks survived to DC; EPIPAGE 1997 (France): 19% BF at DC;
LIFT 2003-8 (LOIRE Infant Follow-Up Team): 16% BF at DC
Propensity Score: sum of mom age, BMI, socioeconomic status, educational attainment, other kids, pregnancy; infant characteristics and morbidity. Roze et al. BMJ Open 2012;2:e000834

Confounding Factors Affect IQ

- **Maternal/paternal characteristics**
  - Age
  - Marital status
  - Race
  - Education
  - Socioeconomic status
  - Height
  - Intelligence
  - Attitude
  - Breadth of experience
  - Parenting skills
  - Interest in education
  - Working
  - Tobacco smoking
  - Choice of breastfeeding
- **Infant characteristics**
  - Duration of feeding
  - Feeding difficulties
  - Age at weaning
  - Bonding
  - Family size
  - "Constitutional difficulties"
  - Childhood experiences, ills
  - Birth weight
  - Gestational age
  - Birth rank
  - Gender
- Home environment
- Family size

Strategies

Effects of Human Milk Fortification

- > 600 infants; randomized*
- Growth — Weighted Mean Difference
  - Weight gain (g/kg/d) + 3.6 [2.7;4.6]
  - Length (cm/wk) + 0.12 [0.07; 0.18]
  - Head circumference (cm/wk) + 0.12 [0.07; 0.16]
- Bone mineral content (mg/cm) + 8.3 [3.8; 12.8]
- Nitrogen balance (mg/kg/d) + 66 [35; 97]
- BUN (mg/dL) + 16 [8; 24]
- Relative Risk — Relative Risk
  - Feeding intolerance 2.9 [0.6; 13] NS
  - Necrotizing enterocolitis 1.3 [0.7; 2.5] NS
  - Death 1.5 [0.7; 3.3] NS

Kuschel CA & Harding JE 2005 The Cochrane Library

*Some comparisons with partial supplements

Growth

- Ensure optimal intake ~160 ml/kg/day **fortified** human milk
- Variable composition of human milk
- Fortified **donor milk** needs proactive attention:
  - protein supplement (added protein ~1.3 g/day)
  - energy supplement (vegetable oil 1 ml bid = +16 kcal/day)
  - human milk-derived HMF with ability to increase protein and energy as well as minerals
- Follow **rate** of weight gain and **growth curve** to prevent drop < 10thile
- Increase supplementation as needed based on growth rate and percentiles
- Encourage human milk fortification after discharge:
  - at least "40 weeks" corrected age, or 12 weeks post-discharge

Conclusions

- Human milk diet is associated with improved neurodevelopmental outcomes
- Adjust diet to ensure growth and to meet nutrient needs::FORTIFIERS
- Milk components or their effects on disease accounts for enhanced outcomes
- Human milk diet is "Required" for premature infants