HUMAN MILK FOR PRETERM INFANTS: ONE SIZE FITS ALL?

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Disclosures

- Consultant: Nestle
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Objectives

- Scope of the problem
- Rationale for aggressive nutrition
- Benefits of human milk
- Limitations of human milk
- Fortification of human milk
- Outcomes of interest

Introduction

- Rate of prematurity still high in the United States
- Increasing survival of very low birth weight infants
- Overriding attention to cardio-respiratory problems
- “Adjunctive” needs often not addressed: nutrition

CDC Data, NCHS 2014

• Infants born less than 2500g:	318,847
• Percent LBW:	8.00
• Percent VLBW:	1.40
• Percent preterm:	9.57

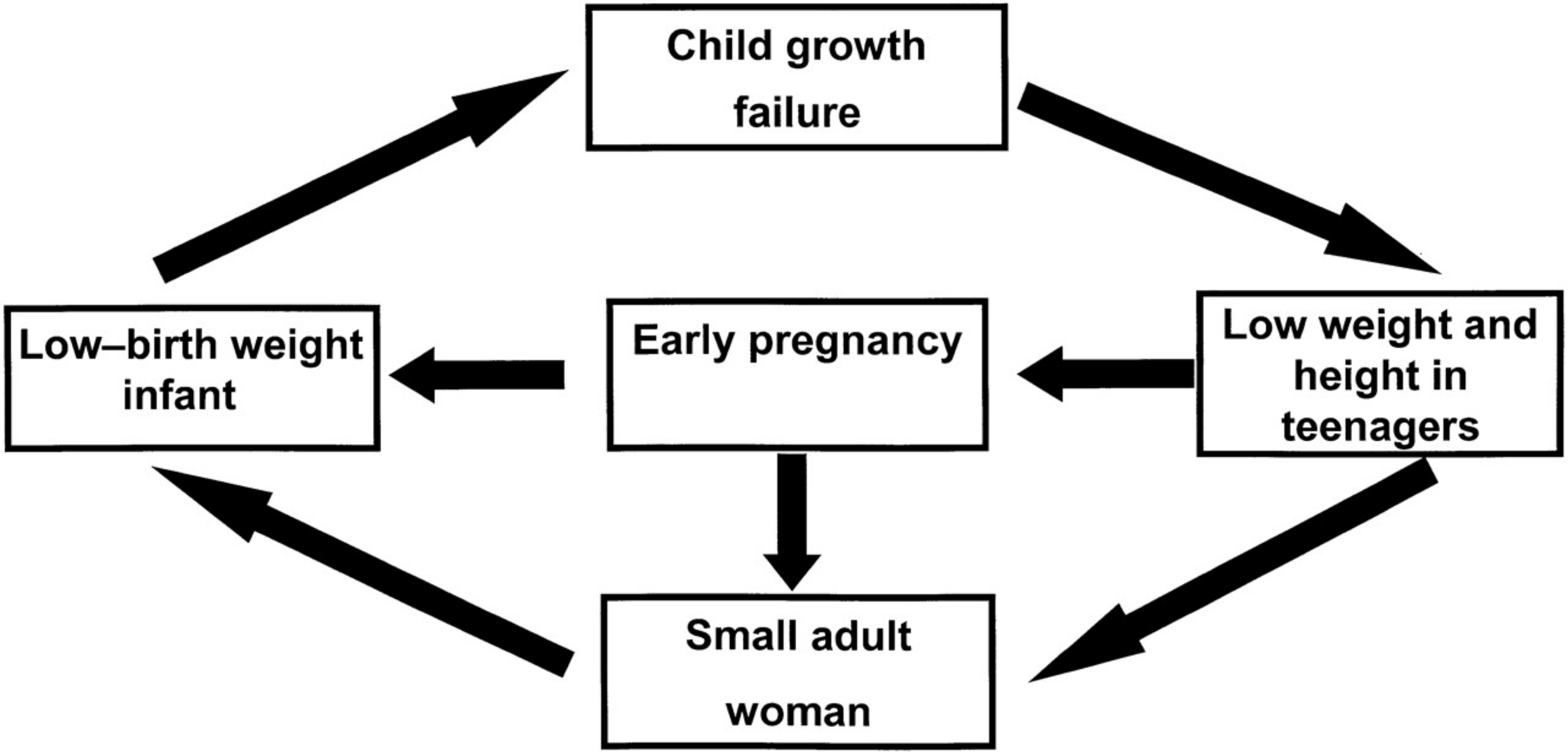
Low Birthweight

- Important public health indicator
- Not a proxy for maternal or perinatal health outcomes
- Globally, it is measure of long-term maternal malnutrition, ill health, poor pregnancy health care
- Low birth weight may not be the best indicator and a broader definition of the outcome of pregnancy outcome is needed
- Cut-off of 2500g may not be appropriate in all settings: for e.g., in some countries with a high incidence of low birth weight do not have high mortality rates [Sri Lanka]

Pathmanathan et al., Health, Nutrition, and Population Series, World Bank, Washington, DC 2003

ACN/SCN,WHO: IFPRI, 1992

Intergenerational cycle of growth failure



Ramakrishnan U Am J Clin Nutr 2004;79:17-21

Goals and Requirements

- Optimal nutritional goal is to duplicate normal in utero fetal growth rates
- *Should have no negative impact on growth and development*
- *Achieve maximal appropriate growth without adverse effects*
- In reality, extrauterine growth restriction is almost universal in small premature infants
- Growth restriction or failure associated with adverse outcomes: neurocognitive effects and chronic lung disease
- Accelerated growth associated with insulin resistance, cardiovascular disease

AAP 2008; Ehrenkranz et al., 1999; Morley et al., 1999; Singhal et al., 2003;
Singhal, Cole and Lucas 2001; Singhal et al., 2004

Bhatia, J. Ann Nutr Metab 2013;62(suppl 3):8–14 DOI: 10.1159/000351537

Rationale for aggressive nutrition

Last Trimester → Active amino acid transport

Calcium, Phosphorus, Magnesium, Iron,
Lipid transfer present; DHA transported

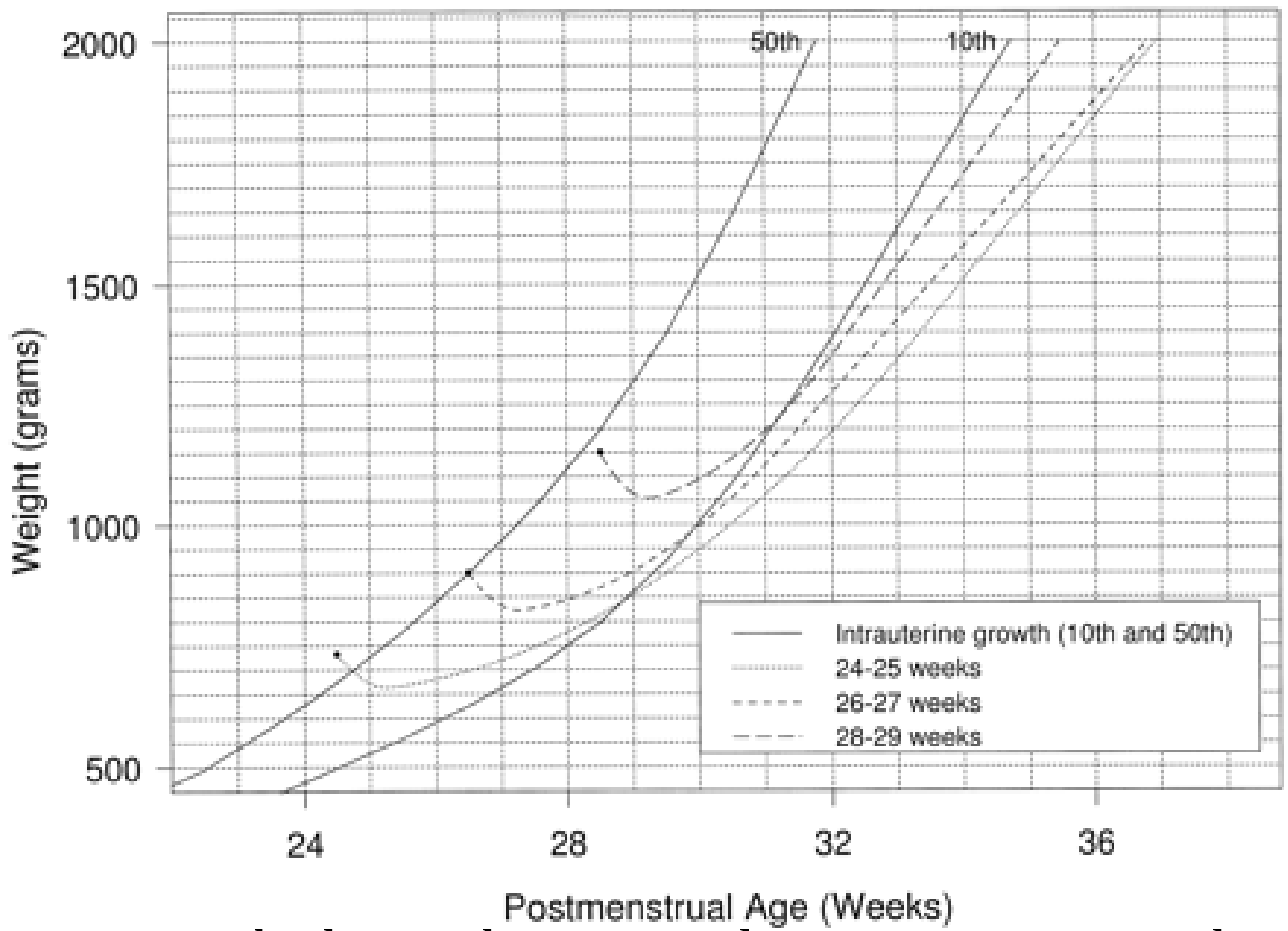
Glucose, facilitated diffusion

Delivery of premature infant → *Higher* energy expenditure
Inadequate protein and energy intake

Lipid and glucose *exceed* in utero
Amino acid *lower* than in utero

Negative Nitrogen Balance

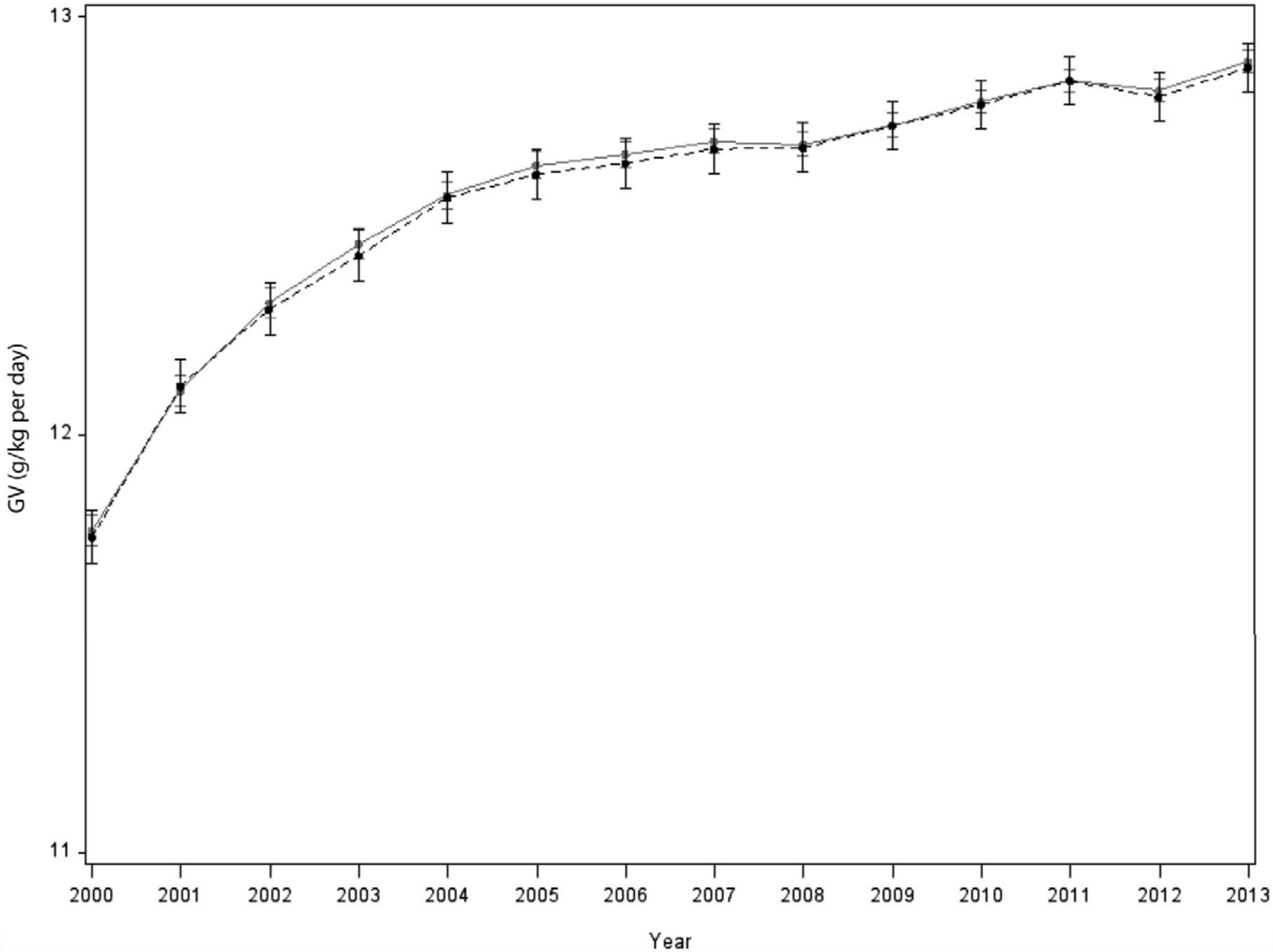
Extremely Low Birth Weight Infants Grow Poorly



Average body weight compared to intrauterine growth

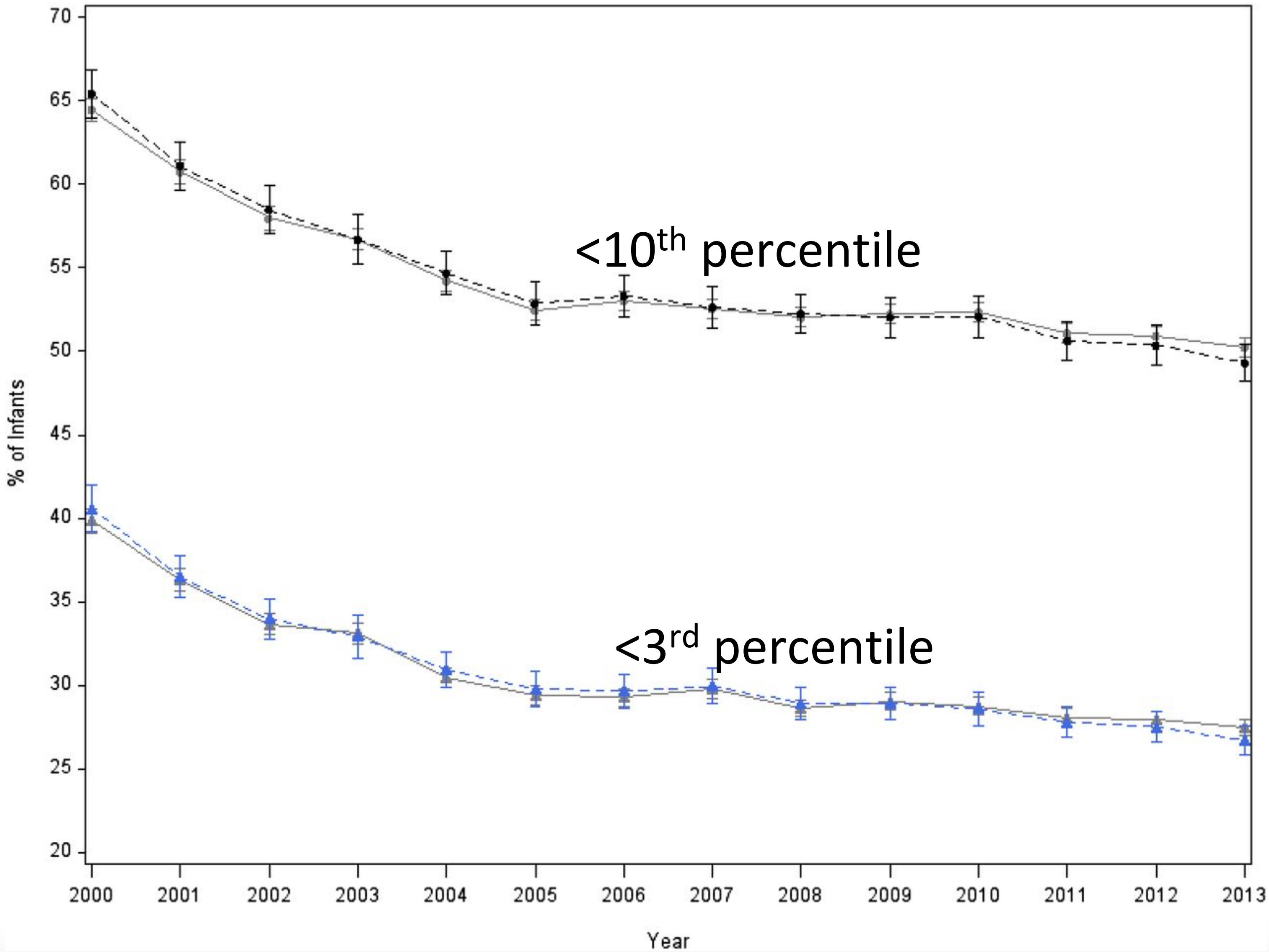
Ehrenkranz, Pediatrics, 1999

Average GV for infants weighing 501 to 1500 g, 2000 to 2013.



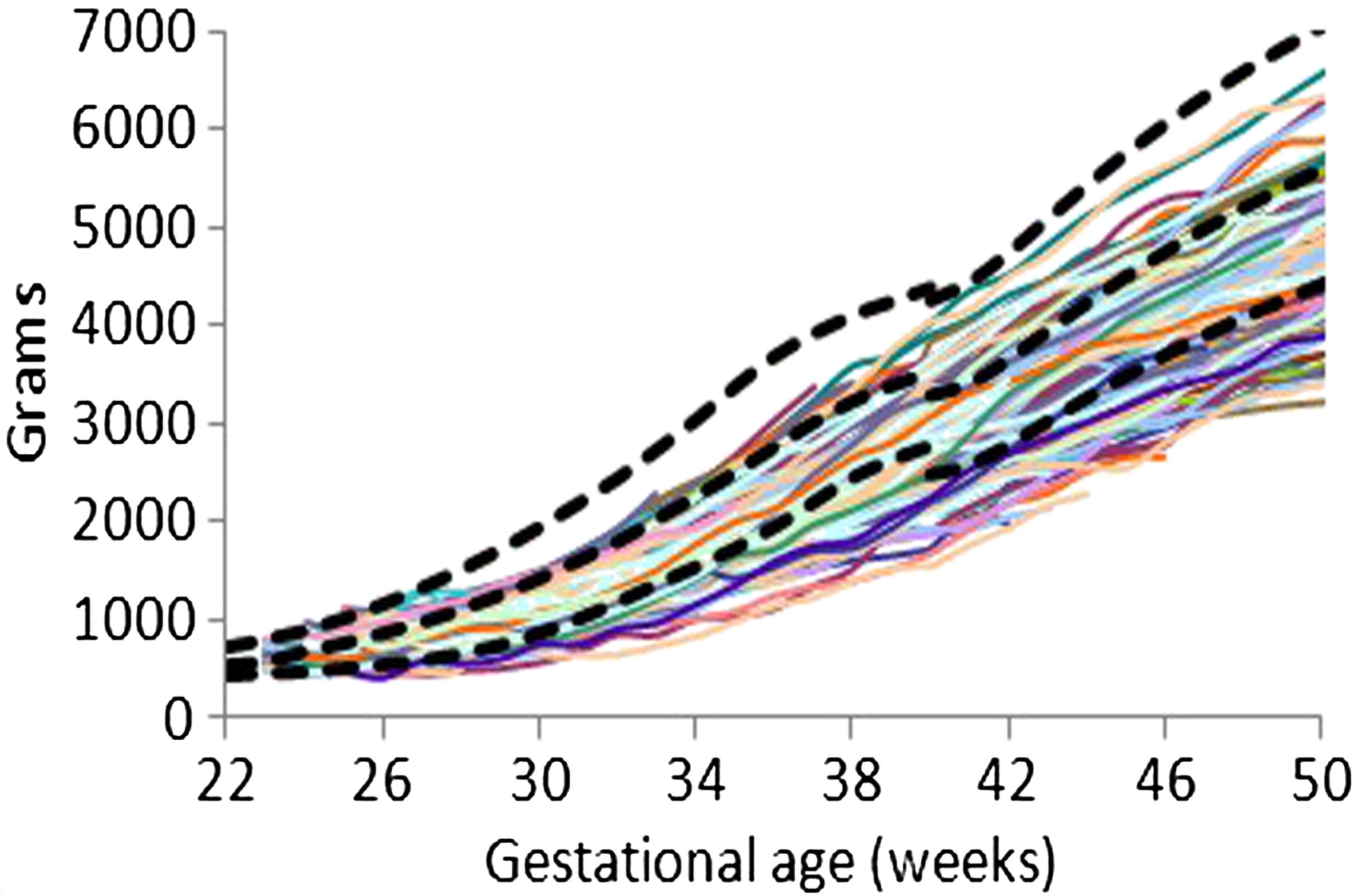
Jeffrey D. Horbar et al. Pediatrics 2015;136:e84-e92

Percentage of infants weighing 501 to 1500 g who were discharged below the third or 10th percentiles of the Fenton growth chart, 2000 to 2013.



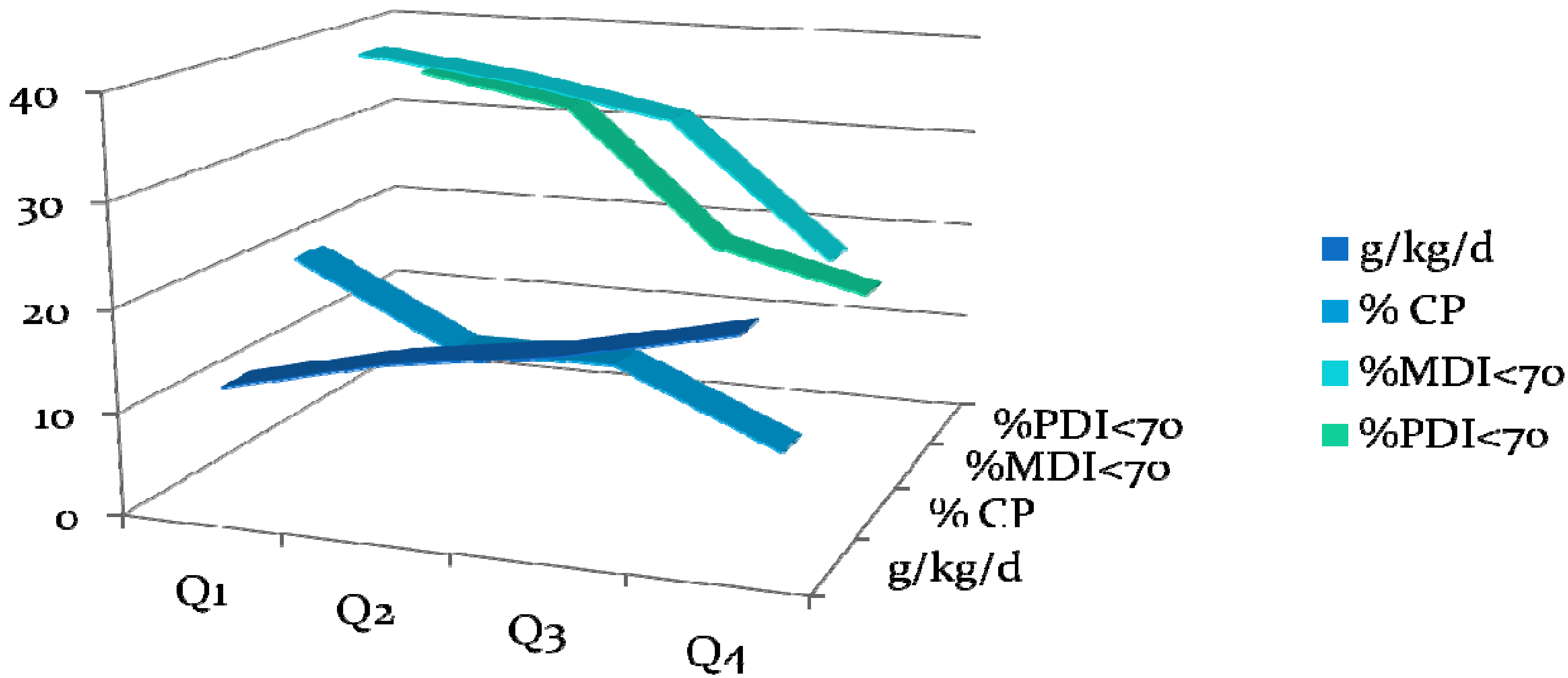
Jeffrey D. Horbar et al. Pediatrics 2015;136:e84-e92

Weight gain patterns 23-25 weeks



Fenton et al., BMC Pediatrics 2013, 13:92

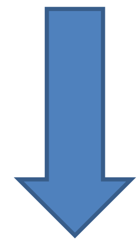
Growth Quartiles and Outcomes



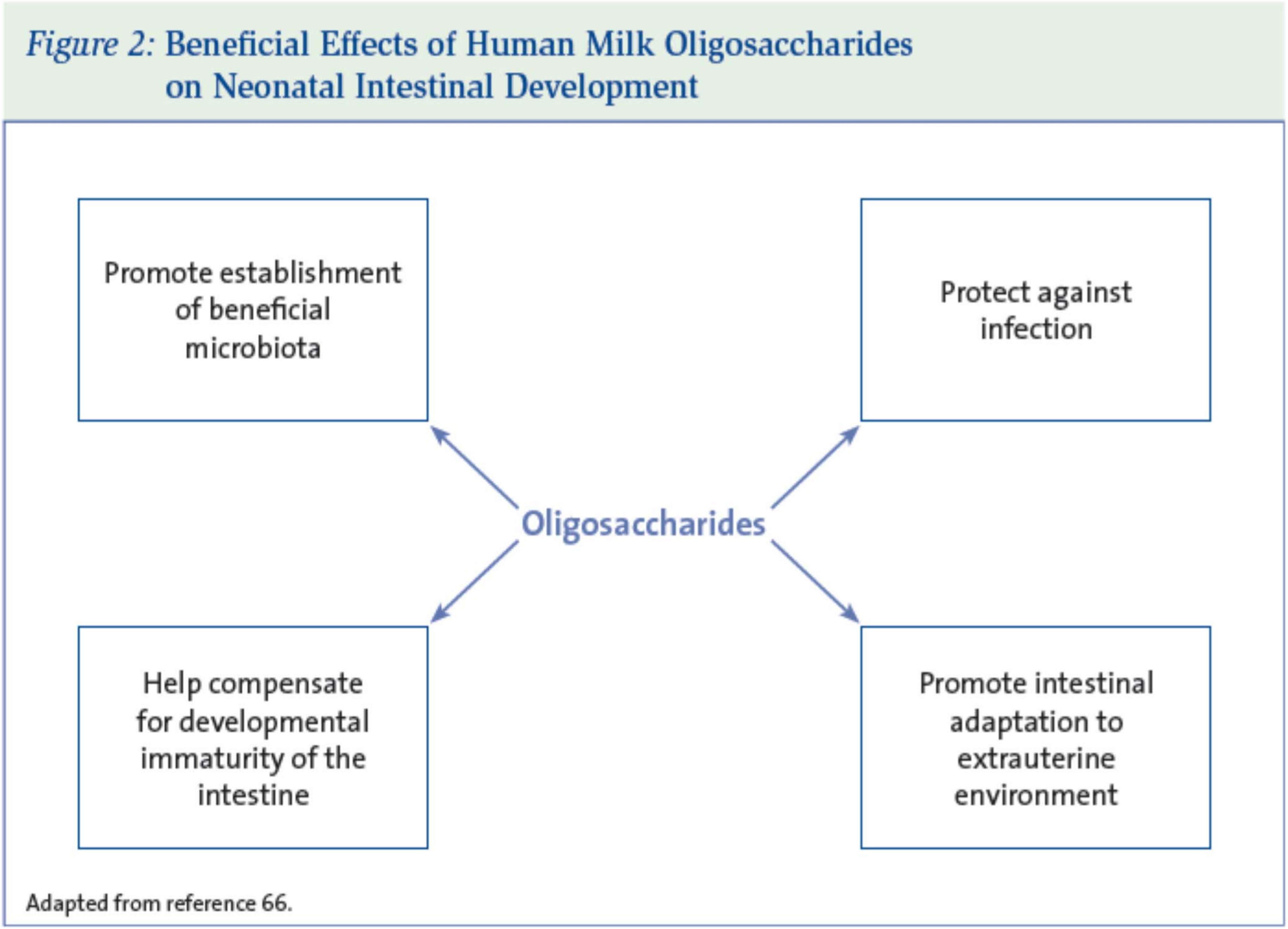
Ehrenkranz et al., Pediatrics 2006

Human Milk and the Premature Infant

- Late onset sepsis
- Necrotizing enterocolitis
- Neurocognitive adverse outcomes
  - ?VLBW infants
- Retinopathy of Prematurity
- ?Bronchopulmonary dysplasia
- Feeding intolerance
- Metabolic syndrome
- Insulin resistance
- Lower blood pressure and lower low-density lipoproteins



Arch Dis Child Fetal Neonatal Ed 2007; Cochrane Database Syst Rev 2007; Pediatrics 2012; JPGN 2003; Pediatrics 2005; Cohrane Database Syst Rev 2007; J Maternal Fetal Neonatal Med 2010; Nutr J 2014



From: Prebiotics in Infant Nutrition, Donovan, Gibson, Newburg; meadjohnson.com/pediatrics/US../LB2329 [Donovan, J Pediatrics, 2006]

Limitations of Human Milk

- Nutrients
  - Protein, energy, calcium, phosphorus, iron, vitamins, sodium, zinc
- Supply
  - Reduced supply, maternal stress, biological
- Delivery
  - Restriction of volumes
  - Inappropriate fortification [donor or mothers own milk]

Nutrient Recommendations

Nutrient	Koletzko[1]	ESPGHAN[2]
Fluid, mL/kg/day	135-200	135-200
Energy, Kcal/kg/day	110-135	110-135
Protein, g/kg/day	3.5 -4.5	4-4.5 (<1 kg) 3.5-4 (1-1.8 kg)
Lipids, g/kg/day	4.8-6.6	4.8-6.6 (<40% MCT)
Calcium, mg/kg/day	120-200	120-140
Phosphate, mg/kg/day	60-140	60-90
Vitamin D, IU/day	400-1000	800-1000

MCT=medium-chain triglyceride.

1. Koletzko B, et al. *World Rev Nutr Diet.* Basel: Karger. 2014;110:297-299.
2. Agostoni C, et al. *J Pediatr Gastroenterol Nutr*. 2010;50:85-91.

Growth Expectations

	500-700g	700-900g	900-1200g	1200-1500g
g/kg/d, fetal	21	20	19	18
g/kg/d, protein intake	4.0	4.0	4.0	3.9
Kcal/kg/d, energy intake	105	118	119	127

Ziegler 2011

Macronutrient Composition

	Protein, g/dL (mean)	Energy, kcal/dL (mean)
Term milk	0.9-1.5 (1.2)	57-83 (70)
Donor milk	0.6-1.4 (0.9)	50-115 (67)
Preterm milk, <29 wks	1.3-3.3 (2.2)	61-94 (78)
Preterm milk, 32-33 wks	1.3-2.5 (1.9)	64-89 (77)
Preterm, donor milk	0.8-1.9 (1.4)	53-87 (70)

Ballard O, Morrow AL. *Pediatr Clin North Am.* 2013;60:49-74.

Feeding Practices

- Colostrum swabbing
- Human Milk, mother's preferred
- Donor human milk
- Fortify
- Caution in abrupt cessation of amino acids
- Ideal fortification would be analysis + modular fortification

Fortification

- Protein content of human milk declines with duration of lactation
- Routine fortification and a low protein intake from human milk is the main cause of postnatal growth restriction
- Problem is worsened with donor human milk
- Strategies to improve nutritional status
  - Measure protein concentration and target fortification
  - Fortify based on BUN [in the absence of renal dysfunction, BUN is a sensitive indicator of protein sufficiency]
  - Blind fortification

Fortifiers Available

- Powder human milk fortifiers
- Liquid human milk fortifiers
  - Casein hydrolysate
  - Whey hydrolysate
- Human milk-based fortifiers
- Human milk cream
  - 25% fat, 2.5 kcal/mL

Comparison of 3 Fortifiers

Nutrient	Nutrient Intake Guidelines	Acidified Liquid Human Milk Fortifier (HMF 1)	Human Milk Fortifier Extensively Hydrolyzed Protein Concentrated Liquid (HMF 2)	Human Milk Fortifier (HMF 3)
(Amount in parenthesis is what is provided with goal feeds of 150 ml/kg/day. Compare to recommended levels)				
Kcal/oz.	115-130 kcal/kg	24	24	24
Protein, g/100 calories	**4-4.5 g/kg***	**4 *(4.8)**	**3.58 **(4)**	**2.8*** (3.4)**
Calcium, mg/100 calories	120-200 mg/kg	145 (174)	152 (182)	150 (180)
Phosphorus, mg/100 calories	60-140 mg/kg	80 (96)	85 (102)	78 (94)
Iron, mg/100 calories	4-6 mg/kg	1.9 (2.3)	0.6 (0.7)	0.2 (0.3)
Vitamin D, IU/100 calories	**800-1000 IU/day**	**210 (126-453)**	**150 (90-270)**	**34 (20-61)**
mOsm/kg H2O	450	326	450	N/A

*Assumes 1.6 g/100 calories
**Assumes 2.1 g/100 mL
***Assumes 2.1 g/100 mL

HMF=human milk fortifier.

Amy Gates, RD, CSP, LD and Jatinder Bhatia

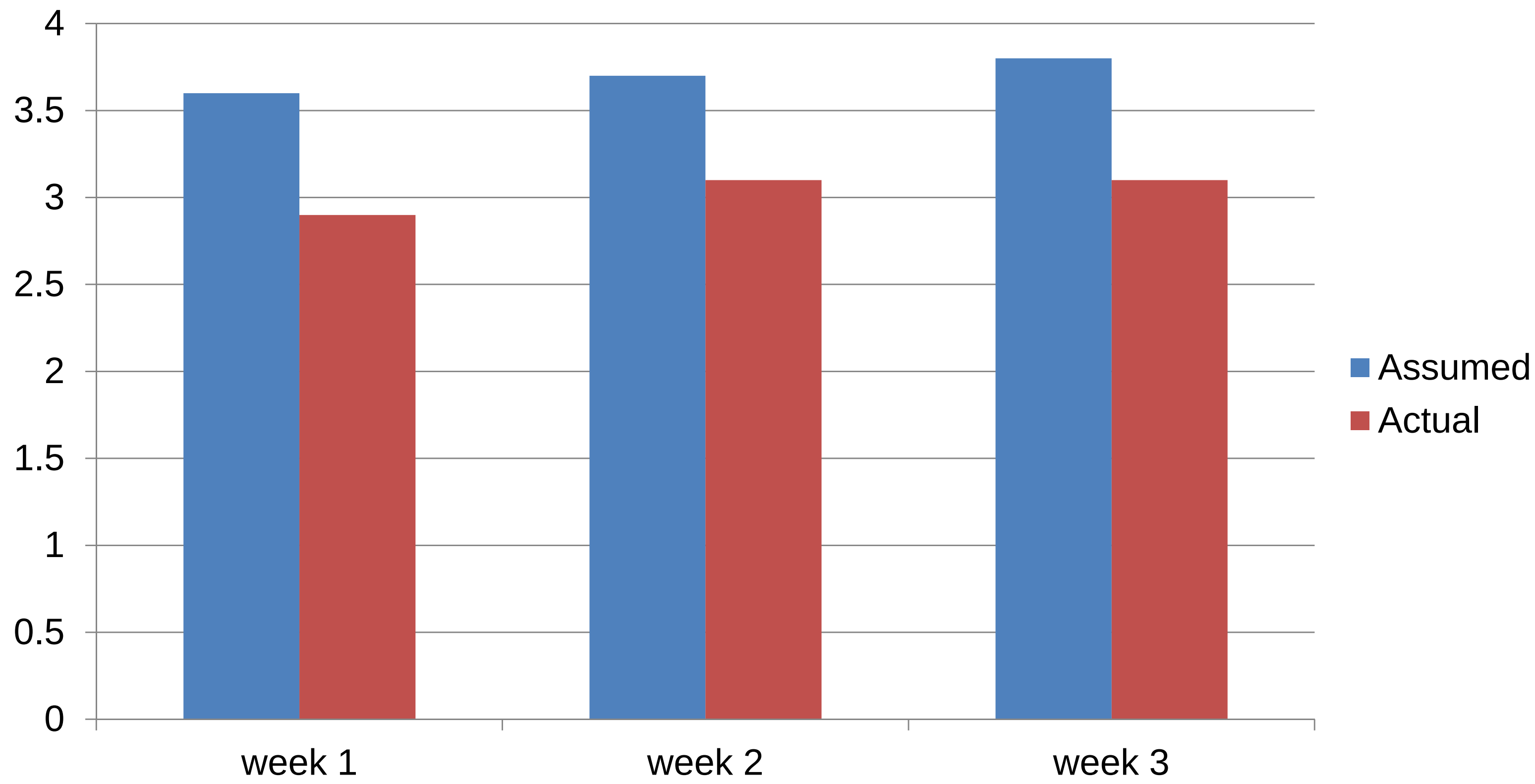
Calories and Protein Provided by LHMFs

	Human Milk, Mature/Term	Preterm Human Milk, <29 weeks EGA	Donor Human Milk
Calories/ounce	**19-21**	**20-26**	**15-20**
LHMF 1, 4 vials + 100 mL	23-25	24-29	19-24
LHMF 2, 4 packets + 100 mL	23-25	24-29	19-24
LHMF 3, 20 mL + 100 mL	23-25	24-29	19-24
Protein, g/100 mL	**0.9-1.5**	**2.2-3.3**	**0.8-1.4**
LHMF 1, 4 vials + 100 mL	3.1-3.7	4.4-5.5	**3-3.6**
LHMF 2, 4 packets + 100 mL	2.9-3.5	4.2-5.3	**2.8-3.4**
LHMF 3, 20 mL + 100 mL	2.1-2.7	3.4	**2-2.6**

Amy Gates, RD, CSP, LD and Jatinder Bhatia, 2016

LHMF=liquid human milk fortifier.

Protein Intake, g/kg/d with fortification



Arslanoglu, Moro and Ziegler, J Perinatol 2009

Growth

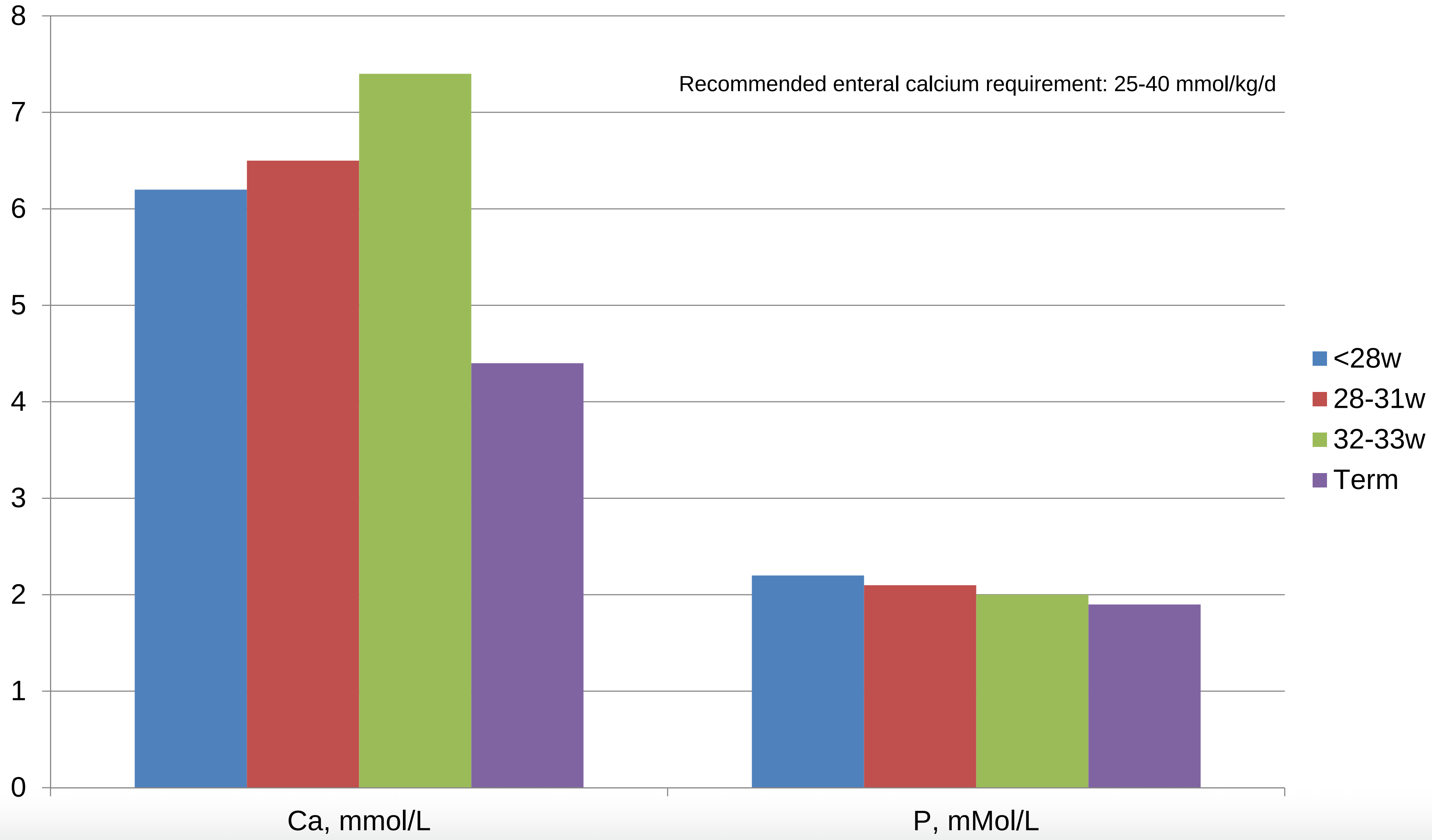
- Premature infants fed fortified human milk experience better weight and length gain than those fed unfortified human milk
- No differences in long-term growth parameters
- However, infants fed fortified human milk [MOM or donor] receive less protein than assumed, grow slower

Schanler at al., 1999; Kuschel, Harding 2004; Schanler and Abrams 1995; Lucas et al., 1996; Miller et al., 2012;Arslanoglu et al., 2009; Bier et al., 2002; Carlson and Ziegler 1998., 2010

Calcium and Phosphorus

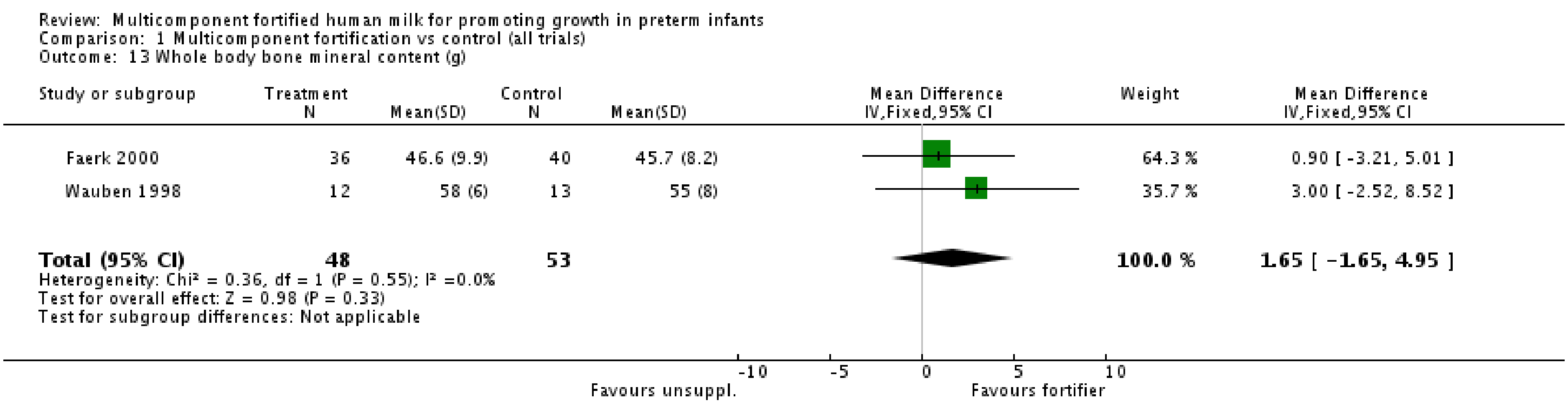
- Content in human milk is insufficient to achieve intrauterine accretion rates or normal bone mineralization
- Additional calcium and phosphorus is recommended after enteral feeds are established
- Impossible to meet requirements on parenteral nutrition

Calcium and Phosphate in Human Milk



Growth

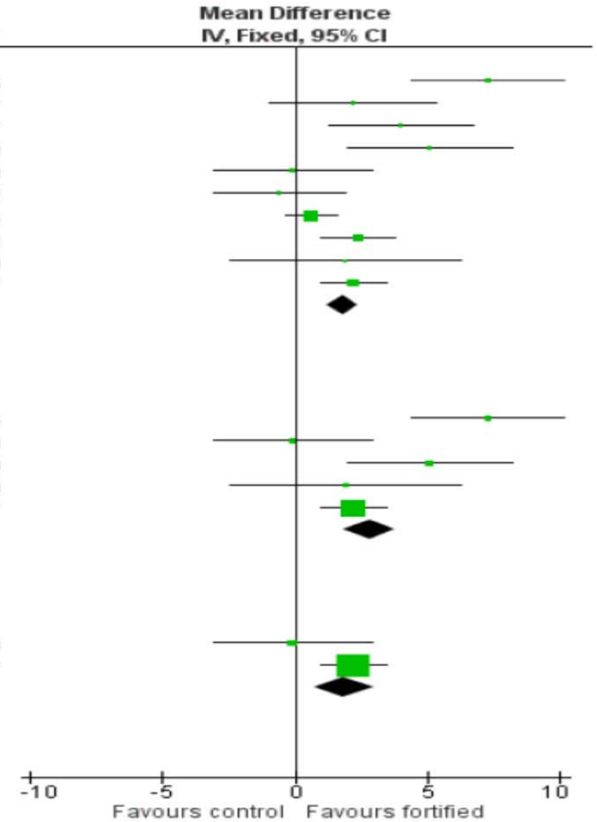
- Better nutrient retention, increased bone mineralization
- Use of fortified milk approaches the net nutrient intrauterine rates of accretion
- Prevents a decrease in linear growth



Greer, McCormick 1988; Schanler, Abrams 1995; Schanler, Garza, Smith 1985; Horsman et al., 1989; Schanler, Garza 1988; Abrams et al., 1989

Figure 3. Forest plot of comparison: 1 Fortified breast milk versus unfortified breast milk, outcome: 1.1 Weight gain (g/kg/d).

Study or Subgroup	Fortified Mean	Fortified SD	Fortified Total	Unfortified Mean	Unfortified SD	Unfortified Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
1.1.1 All trials									
Modanlou 1986	26.7	3.4	8	19.4	2.7	10	4.0%	7.30 [4.41, 10.19]	1986
Gross 1987 (1)	19.9	2.5	10	17.7	4.4	10	3.4%	2.20 [-0.94, 5.34]	1987
Gross 1987 (2)	21.5	3.5	17	17.5	3.3	9	4.6%	4.00 [1.28, 6.72]	1987
Polberger 1989	20.4	2.8	7	15.3	3.2	7	3.4%	5.10 [1.95, 8.25]	1989
Pettifor 1989	16.7	5	29	16.8	6.4	28	3.8%	-0.10 [-3.09, 2.89]	1989
Porcelli 1992	11.4	2.7	10	12	3	10	5.4%	-0.60 [-3.10, 1.90]	1992
Lucas 1996	15.6	4.7	137	15	3.5	138	35.2%	0.60 [-0.38, 1.58]	1996
Wauben 1998	16.6	1.6	12	14.2	2	13	16.9%	2.40 [0.99, 3.81]	1998
Nicholl 1999	15.1	3.3	13	13.2	6.4	10	1.8%	1.90 [-2.45, 6.25]	1999
Mukhopadhyay 2007	15.1	4	82	12.9	4	75	21.5%	2.20 [0.95, 3.45]	2007
Subtotal (95% CI)			**325**			**310**	**100.0%**	**1.81 [1.23, 2.40]**	
Heterogeneity: Chi² = 32.63, df = 9 (P = 0.0002); I² = 72%									
Test for overall effect: Z = 6.12 (P < 0.00001)									
1.1.2 Trials recruiting only very preterm or VLBW infants									
Modanlou 1986	26.7	3.4	8	19.4	2.7	10	11.7%	7.30 [4.41, 10.19]	1986
Pettifor 1989	16.7	5	29	16.8	6.4	28	10.9%	-0.10 [-3.09, 2.89]	1989
Polberger 1989	20.4	2.8	7	15.3	3.2	7	9.9%	5.10 [1.95, 8.25]	1989
Nicholl 1999	15.1	3.3	13	13.2	6.4	10	5.2%	1.90 [-2.45, 6.25]	1999
Mukhopadhyay 2007	15.1	4	82	12.9	4	75	62.3%	2.20 [0.95, 3.45]	2007
Subtotal (95% CI)			**139**			**130**	**100.0%**	**2.82 [1.83, 3.80]**	
Heterogeneity: Chi² = 16.02, df = 4 (P = 0.003); I² = 75%									
Test for overall effect: Z = 5.58 (P < 0.00001)									
1.1.3 Trials conducted in low- or middle-income countries									
Pettifor 1989	16.7	5	29	16.8	6.4	28	14.9%	-0.10 [-3.09, 2.89]	1989
Mukhopadhyay 2007	15.1	4	82	12.9	4	75	85.1%	2.20 [0.95, 3.45]	2007
Subtotal (95% CI)			**111**			**103**	**100.0%**	**1.86 [0.70, 3.01]**	
Heterogeneity: Chi² = 1.94, df = 1 (P = 0.16); I² = 48%									
Test for overall effect: Z = 3.15 (P = 0.002)									

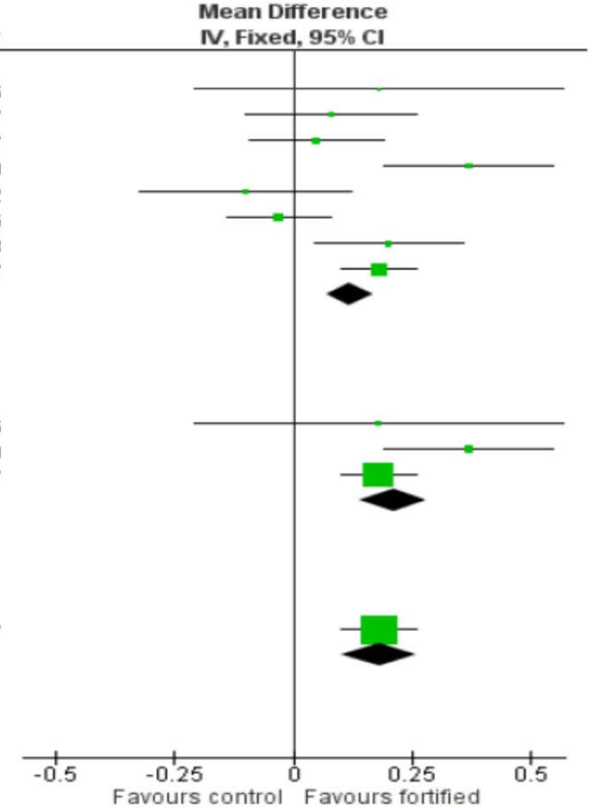


Test for subgroup differences: Chi² = 3.04, df = 2 (P = 0.22), I² = 34.2%

Brown et al., Cochrane Database Syst Rev,
DOI:10.1002/14651858, 2016

Figure 4. Forest plot of comparison: 1 Fortified breast milk versus unfortified breast milk, outcome: 1.2 Length gain (cm/wk).

Study or Subgroup	Fortified Mean	Fortified SD	Fortified Total	Unfortified Mean	Unfortified SD	Unfortified Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
1.2.1 All trials									
Modanlou 1986	0.99	0.4	8	0.81	0.44	10	1.6%	0.18 [-0.21, 0.57]	1986
Gross 1987 (1)	0.89	0.19	10	0.81	0.22	10	7.3%	0.08 [-0.10, 0.26]	1987
Gross 1987 (2)	0.84	0.25	17	0.79	0.12	9	11.8%	0.05 [-0.09, 0.19]	1987
Polberger 1989	1.2	0.17	7	0.83	0.17	7	7.5%	0.37 [0.19, 0.55]	1989
Porcelli 1992	0.6	0.2	10	0.7	0.3	10	4.8%	-0.10 [-0.32, 0.12]	1992
Lucas 1996	0.93	0.47	137	0.96	0.47	138	19.3%	-0.03 [-0.14, 0.08]	1996
Wauben 1998	1.1	0.2	12	0.9	0.2	13	9.7%	0.20 [0.04, 0.36]	1998
Mukhopadhyay 2007	1.04	0.3	82	0.86	0.2	75	38.0%	0.18 [0.10, 0.26]	2007
Subtotal (95% CI)			**283**			**272**	**100.0%**	**0.12 [0.07, 0.17]**	
Heterogeneity: $Chi^2 = 22.71$, df = 7 (P = 0.002); $I^2 = 69\%$									
Test for overall effect: Z = 4.80 (P < 0.00001)									
1.2.2 Trials recruiting only very preterm or VLBW infants									
Modanlou 1986	0.99	0.4	8	0.81	0.44	10	3.3%	0.18 [-0.21, 0.57]	1986
Polberger 1989	1.2	0.17	7	0.83	0.17	7	15.9%	0.37 [0.19, 0.55]	1989
Mukhopadhyay 2007	1.04	0.3	82	0.86	0.2	75	80.7%	0.18 [0.10, 0.26]	2007
Subtotal (95% CI)			**97**			**92**	**100.0%**	**0.21 [0.14, 0.28]**	
Heterogeneity: $Chi^2 = 3.67$, df = 2 (P = 0.16); $I^2 = 46\%$									
Test for overall effect: Z = 5.80 (P < 0.00001)									
1.2.3 Trials conducted in low- or middle-income countries									
Mukhopadhyay 2007	1.04	0.3	82	0.86	0.2	75	100.0%	0.18 [0.10, 0.26]	2007
Subtotal (95% CI)			**82**			**75**	**100.0%**	**0.18 [0.10, 0.26]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 4.46 (P < 0.00001)									



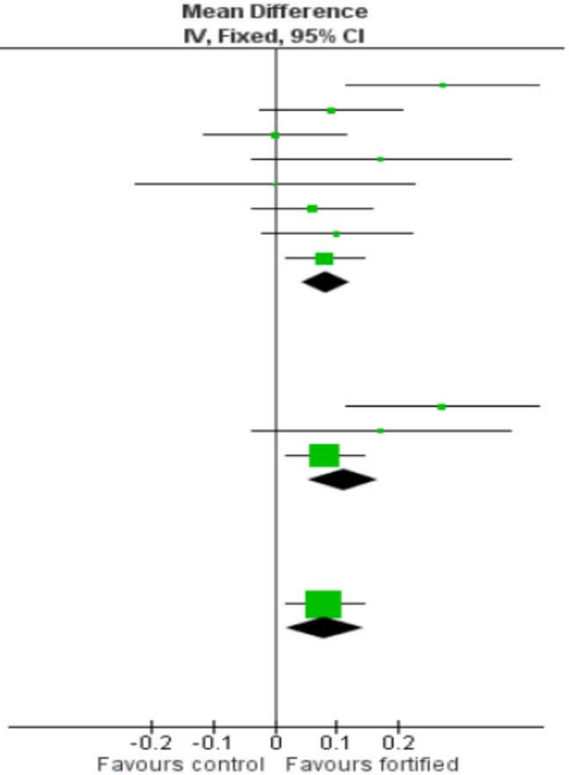
Test for subgroup differences: $Chi^2 = 4.72$, df = 2 (P = 0.09), $I^2 = 57.6\%$

Brown et al., Cochrane Database Syst Rev DOI:10.1002/14651858, 2016

Figure 5. Forest plot of comparison: 1 Fortified breast milk versus unfortified breast milk, outcome: 1.3 Head growth (cm/wk).

Study or Subgroup	Fortified Mean	Fortified SD	Fortified Total	Unfortified Mean	Unfortified SD	Unfortified Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
1.3.1 All trials									
Modanlou 1986	1.09	0.07	8	0.82	0.24	10	6.2%	0.27 [0.11, 0.43]	1986
Gross 1987 (1)	0.92	0.09	10	0.83	0.16	10	11.7%	0.09 [-0.02, 0.20]	1987
Gross 1987 (2)	0.84	0.21	17	0.84	0.09	9	11.3%	0.00 [-0.12, 0.12]	1987
Polberger 1989	1.11	0.13	7	0.94	0.25	7	3.5%	0.17 [-0.04, 0.38]	1989
Porcelli 1992	0.7	0.3	10	0.7	0.2	10	3.0%	0.00 [-0.22, 0.22]	1992
Lucas 1996	1.01	0.47	137	0.95	0.35	138	15.7%	0.06 [-0.04, 0.16]	1996
Wauben 1998	1	0.1	12	0.9	0.2	13	10.1%	0.10 [-0.02, 0.22]	1998
Mukhopadhyay 2007	0.83	0.2	82	0.75	0.2	75	38.6%	0.08 [0.02, 0.14]	2007
Subtotal (95% CI)			**283**			**272**	**100.0%**	**0.08 [0.04, 0.12]**	
Heterogeneity: Chi² = 8.96, df = 7 (P = 0.26); I² = 22%									
Test for overall effect: Z = 4.21 (P < 0.0001)									
1.3.2 Trials recruiting only very preterm or VLBW infants									
Modanlou 1986	1.09	0.07	8	0.82	0.24	10	12.8%	0.27 [0.11, 0.43]	1986
Polberger 1989	1.11	0.13	7	0.94	0.25	7	7.2%	0.17 [-0.04, 0.38]	1989
Mukhopadhyay 2007	0.83	0.2	82	0.75	0.2	75	80.0%	0.08 [0.02, 0.14]	2007
Subtotal (95% CI)			**97**			**92**	**100.0%**	**0.11 [0.05, 0.17]**	
Heterogeneity: Chi² = 5.22, df = 2 (P = 0.07); I² = 62%									
Test for overall effect: Z = 3.88 (P = 0.0001)									
1.3.3 Trials conducted in low- or middle-income countries									
Mukhopadhyay 2007	0.83	0.2	82	0.75	0.2	75	100.0%	0.08 [0.02, 0.14]	2007
Subtotal (95% CI)			**82**			**75**	**100.0%**	**0.08 [0.02, 0.14]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.50 (P = 0.01)									

Test for subgroup differences: Chi² = 0.74, df = 2 (P = 0.69), I² = 0%



Brown et al., Cochrane Database Syst Rev DOI:10.1002/14651858, 2016

Multi-nutrient fortification of Human Milk

Outcomes	Risk with fortified breast milk	Relative effect	N	Quality of Evidence [GRADE]
g/kg/d	1.81 g/kg/d more [1.23-2.4]	-	635	Low
L, cm/wk	0.12 cm/wk, [0.07-0.17]	-	555	Low
HC, cm/wk	0.08 cm/wk, [0.04-0.12]	-	555	Moderate
MDI @ 18 m	2.2 [-3.35- +7.75]	-	245	Moderate
PDI @ 18 m	2.4 [-1.9- +6.7]	-	245	Moderate
NEC	40/1000 [19-82]	RR 1.57 [0.76-3.23]	882	Low

Brown et al, Cochrane Database of systematic reviews,
DOI:10.1002/14651858.CD000343.pub3, 2016

Individualized Fortification and Fortifiers

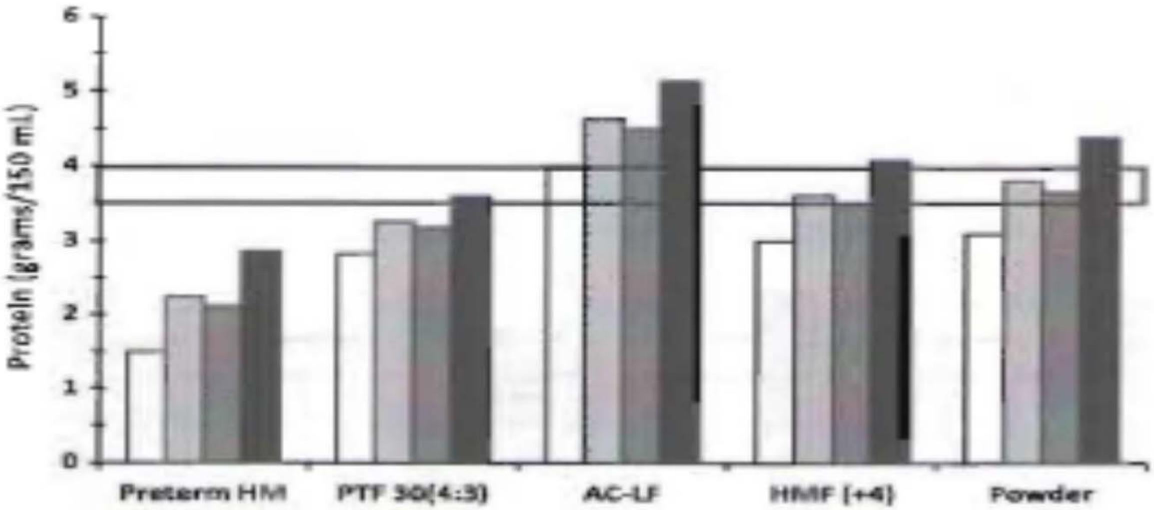


Fig. 1. Preterm human milk (HM) protein (g) achieved with four different fortifier strategies* when fed at 150 mL and compared to estimated goals. Low P □; Expected P ▨; Expected P ■; High P ■. *Fortifier strategies: PTF: Preterm formula (Similac Special Care 30®, Abbott Nutrition, Columbus, OH); AC-LF: Acidified liquid fortifier (Mead Johnson Nutritionals, Evansville, IN); HMF +4: Prolacta Bioscience (Monrovia, CA); Powder: Enfamil Human Milk Fortifier (Mead Johnson Nutritionals, Evansville, IN).

Radmacher, Lewis, Adamkin J Neonatal Perinatal Medicine 6:319-323, 2013

Protein, Carbohydrate, fat and energy after target fortification

	ESPGHAN	BM		FIXED + BM	Target
Protein, g/dL	2.7-3.0	1.2 ± 0.3		2.3 ± 0.3	2.9 ± 0.3
Carb, g/dL	7.7-8.8	7.3 ± 1.1		7.7 ± 1.1	8.6 ± 1.2
Fat, g/dL	3.2-4.4	3.7 ± 0.8		4.7 ± 0.8	4.8 ± 0.8
Energy, kcal/dL	73-90	67 ± 9		82 ± 9	89 ± 8

Day-to-day variations in macronutrient intake would differ if breast milk is not analyzed daily

76/210 milk batches with fixed fortification required extra fortification with fat

Minimum 2 days a week need to be analyzed

adapted from Rochow et al., Nutrients 2015, 7:2297-2310

Human Milk Cream vs Standard Fortification

- Prospective, noninferiority, randomized, unblinded study
- 750-1250g, n=78
- Control group: mother's own milk or donor HM fortified with human milk fortifier
- Cream group: as above + cream if HM < 20 kcal/oz
- Cream supplement is 25% lipids, 2.5 kcal/mL
- Assumption that HM was 20 kcal/oz

J Pediatr 2014

Human Milk Cream

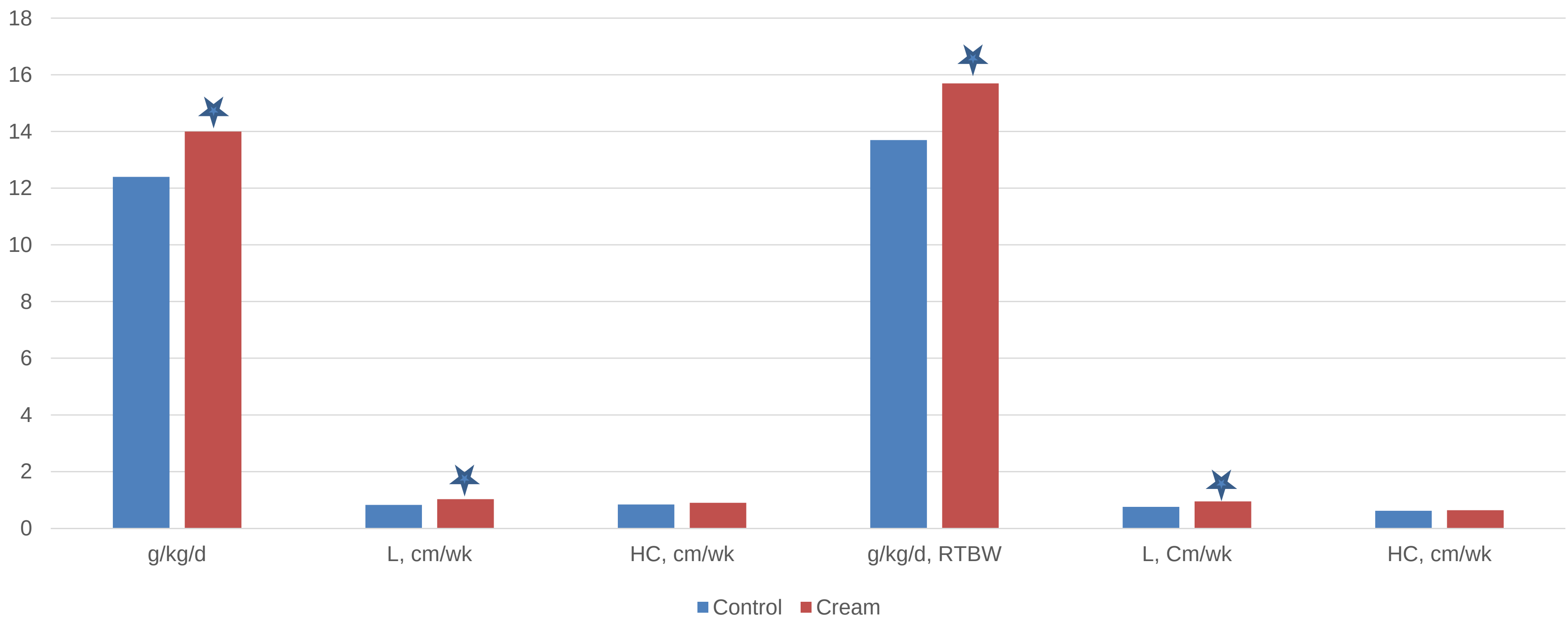
	Control	Cream
g/kg/d	12.4 [3.9]*	14.0 [2.5]
L, cm/week	0.83 [0.41]*	1.03 [0.33]
RTBW g/kg/d	13.7 [4.0]*	15.7 [2.5]

Exclusive Human Milk Fortification

- Preterm infants <37 weeks gestation [27.6 ± 2.0]
- BW <1250g [913 ± 182]
- Exclusive human milk-based diet
- Achievement of full feeds by 4 weeks of age
- Mother's own milk supplemented with pasteurized donor milk [HMBA]
- Fortification began at 60 mL/kg/d [HMF60] with an additional 4 kcal/30 mL
- Additional 6kcal/30 mL at 100-120 mL/kg/d
- If weight gain less than 15g/kg/d within a week, 8kcal/30 mL fortification
- Assumed HM to be 0.67kcal/g, 0.9g/dL protein

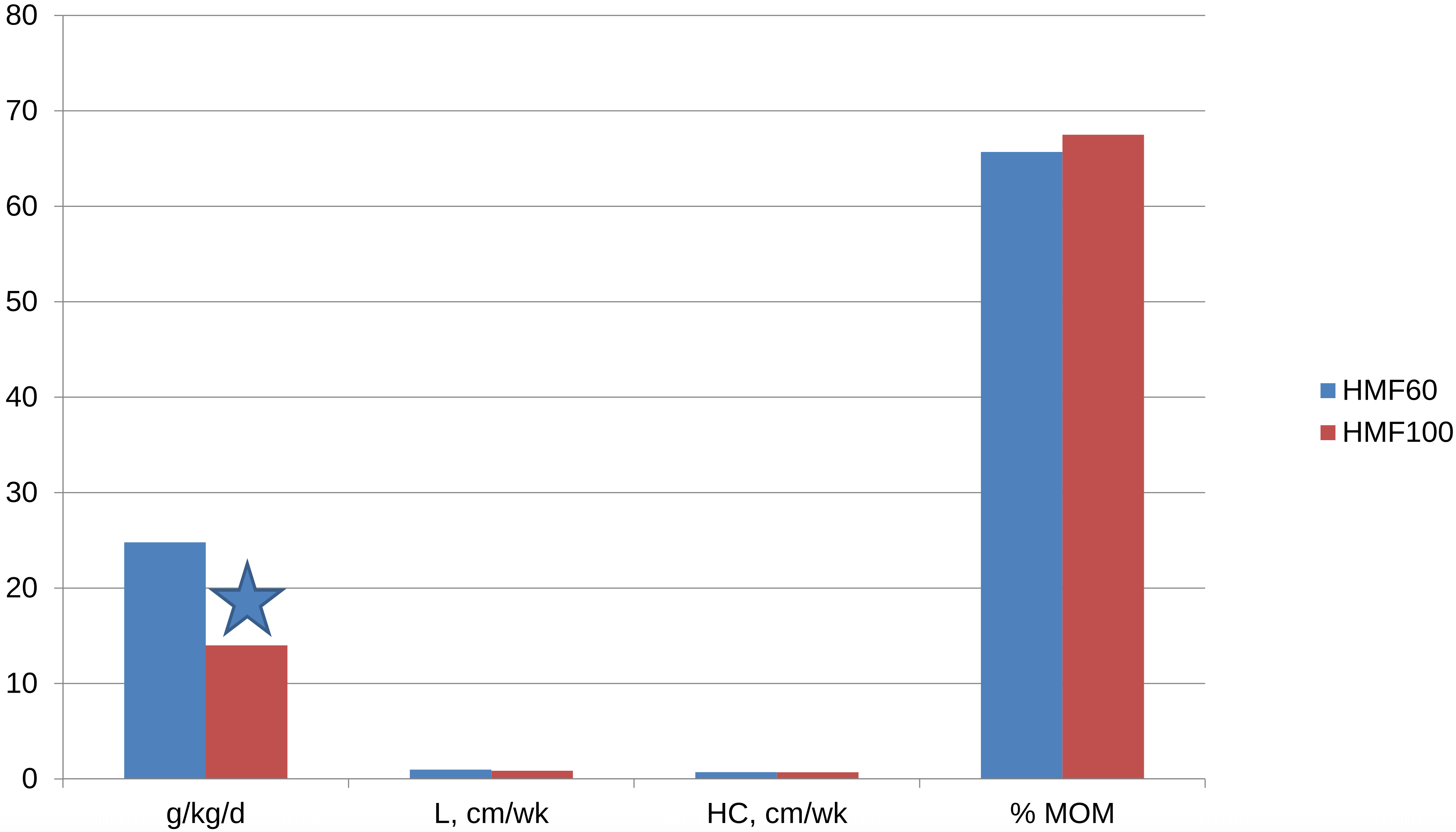
Hair et al., bmcresnotes.biomedcentral.com/articles/10.1186/1756-0500-6-459, 2013

Human Milk Cream and Exclusive Human Milk-Based Diet



Hair et al., J Pediatr 2014;165:915-920

Exclusive Human Milk Fortification

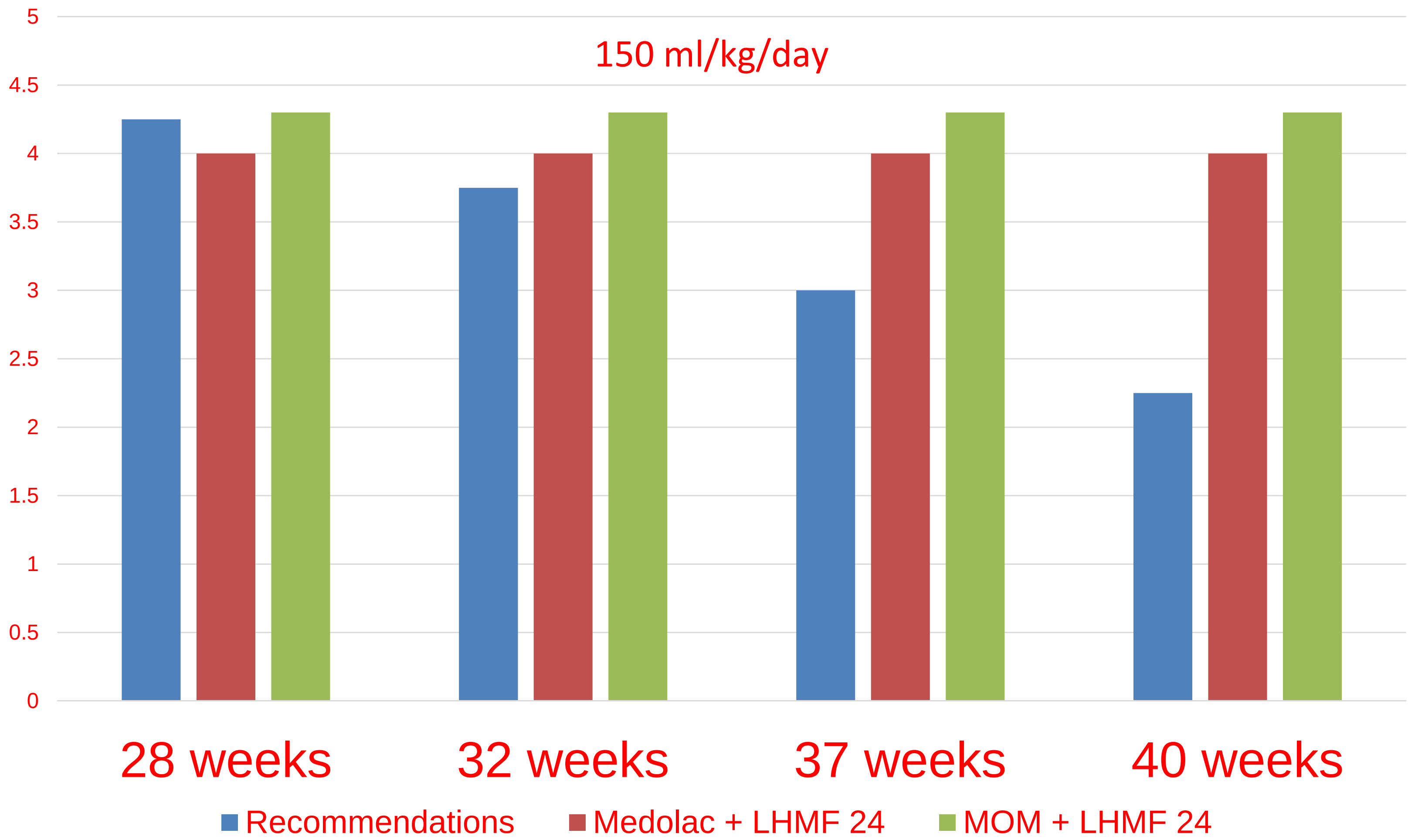


* Sullivan et al; J Pediatr 2010

Exclusive Human Milk Fortification

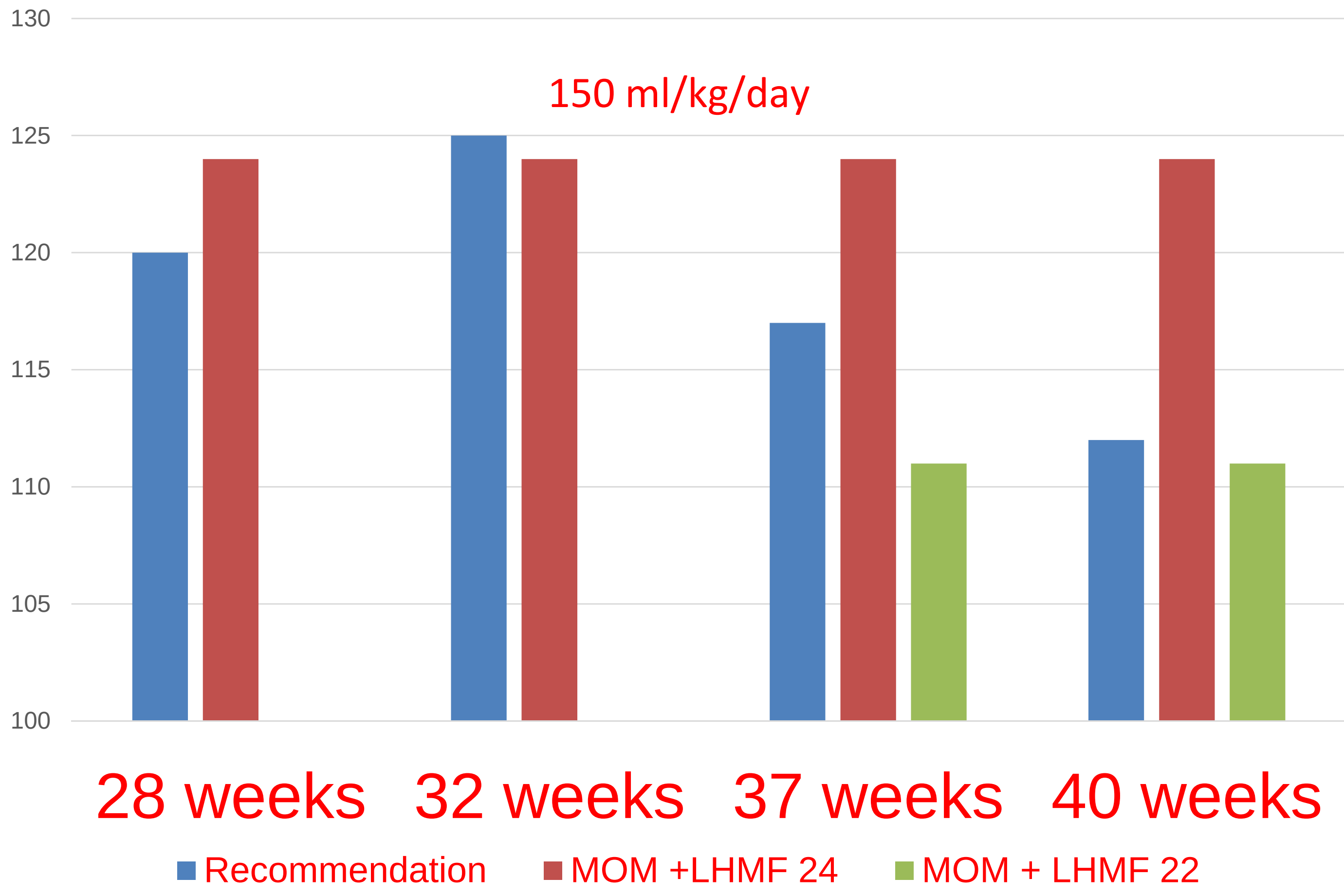
- A more rapid fortification strategy [n=104]
- Exact intakes assumed as MOM + donor milk + fortifier was given
- SGA at birth 21%
- SGA at DC 43%

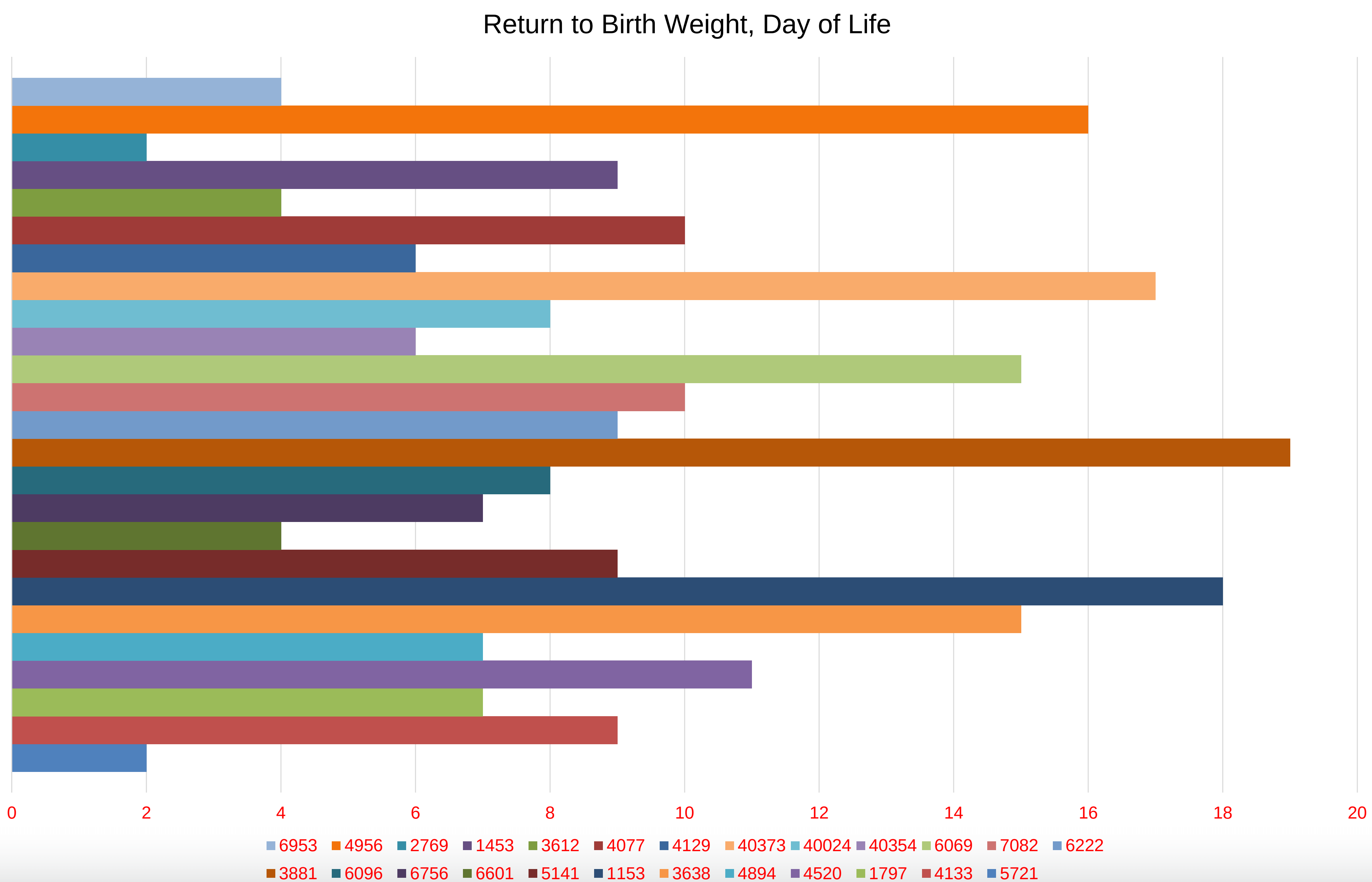
Protein Recommendations vs Estimated Intake: Donor and MOM



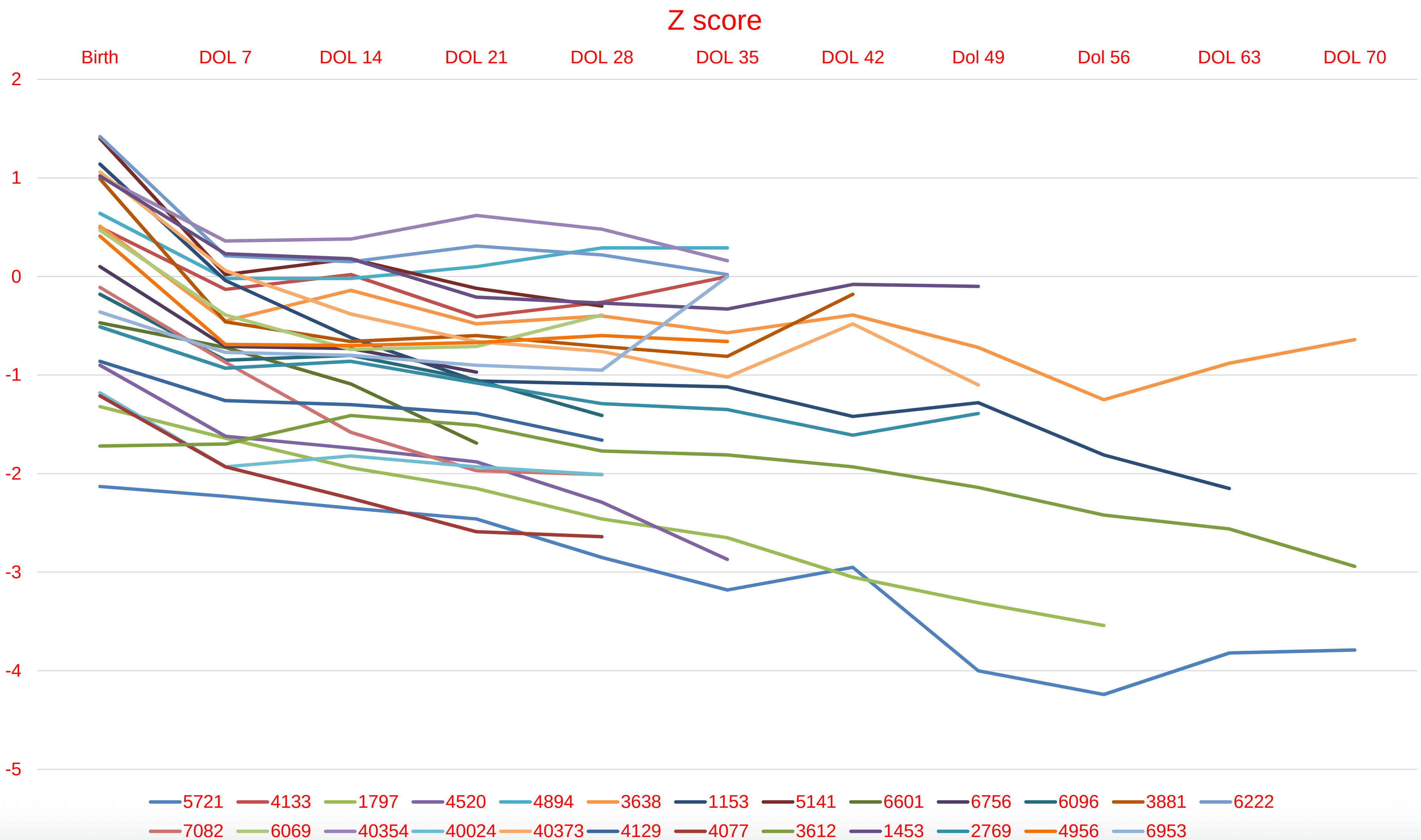
Protein intake estimation based on manufacturer's estimations

Energy Recommendations vs Estimated Intake




Return to Birth Weight, Day of Life
0
2
4
6
8
10
12
14
16
18
20
6953 4956 2769 1453 3612 4077 4129 40373 40024 40354 6069 7082 6222
3881 6096 6756 6601 5141 1153 3638 4894 4520 1797 4133 5721

-- 1.0 to -1.99 At risk
-2 to -2.99 Moderate
<-3 Severe



Increased enteral protein intake in human milk-fed preterm infants

- <32 weeks gestation
- <1500g
- Enteral intake of at least 100 mL/kg/d by day 7
- Randomized 2:1:1
  - Lower protein [standard fortification, 5g/100 mL, FM85, Nestle]
  - Higher-protein
    - Higher protein supplementation using an investigational multicomponent fortifier
    - Individually adjusted fortification on top of standard fortification

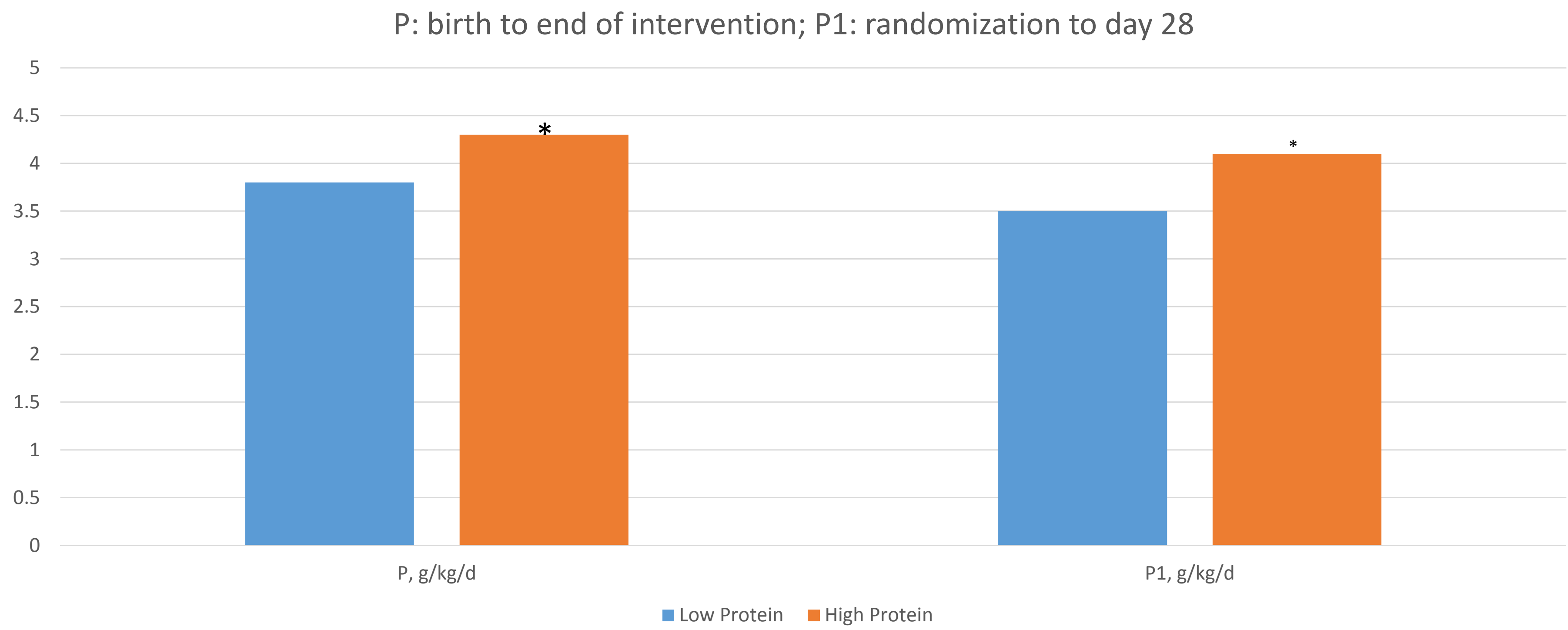
Maas C et al., JAMA Pediatr 2017:171(1)16-22

Methods [continued]

- Lower protein: overall supply 3.5g/kg/d, assuming 1.3 g/100 mL in HM and fed at 150 mL/kg/d
- Higher protein aimed at 4.5g/kg/d
- Investigational fortifier: 1.8g bovine protein/5g fortifier [10.01.DE.INF; Nestle Nutrition]

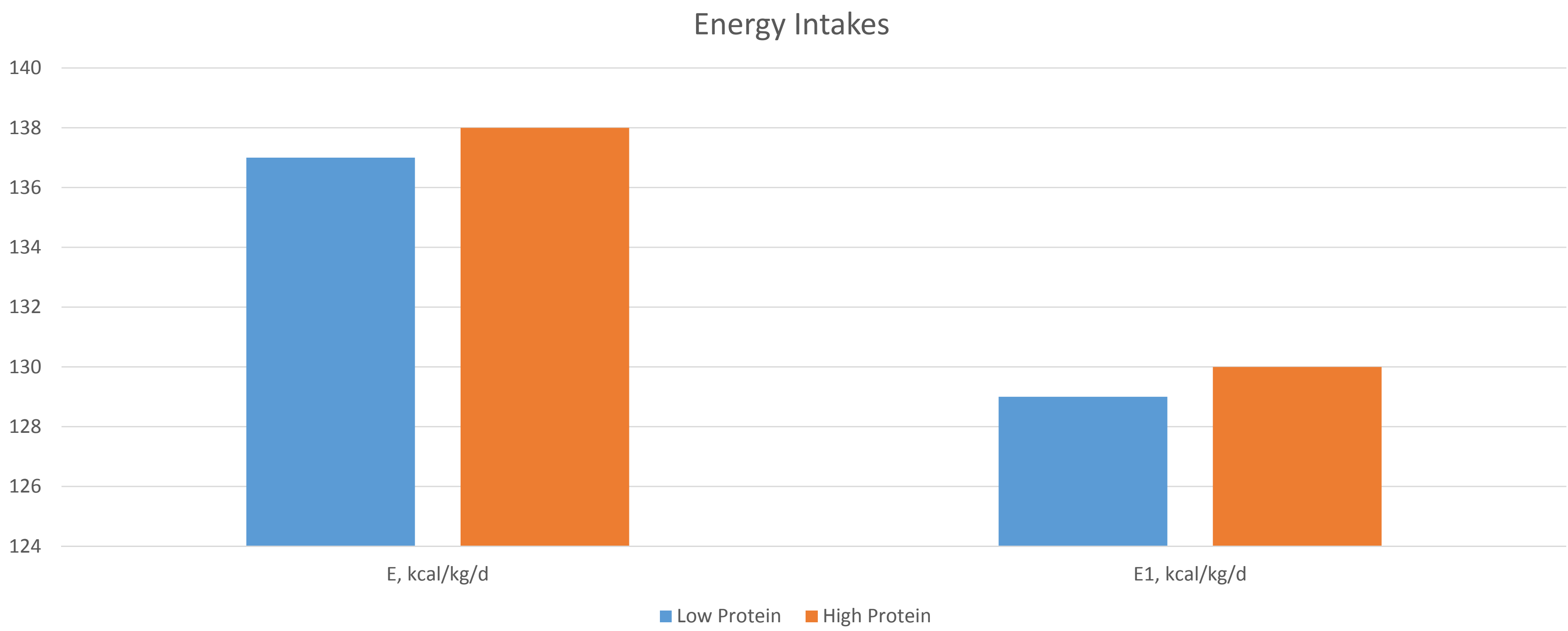
- All three groups had fixed dose fortification of 2.5g/100 mL [100-149 mL/kg/d] and 5g/100 mL [150 mL/kg/d and thereafter]
- Group 2b: bovine protein added according to weight as well as MCT

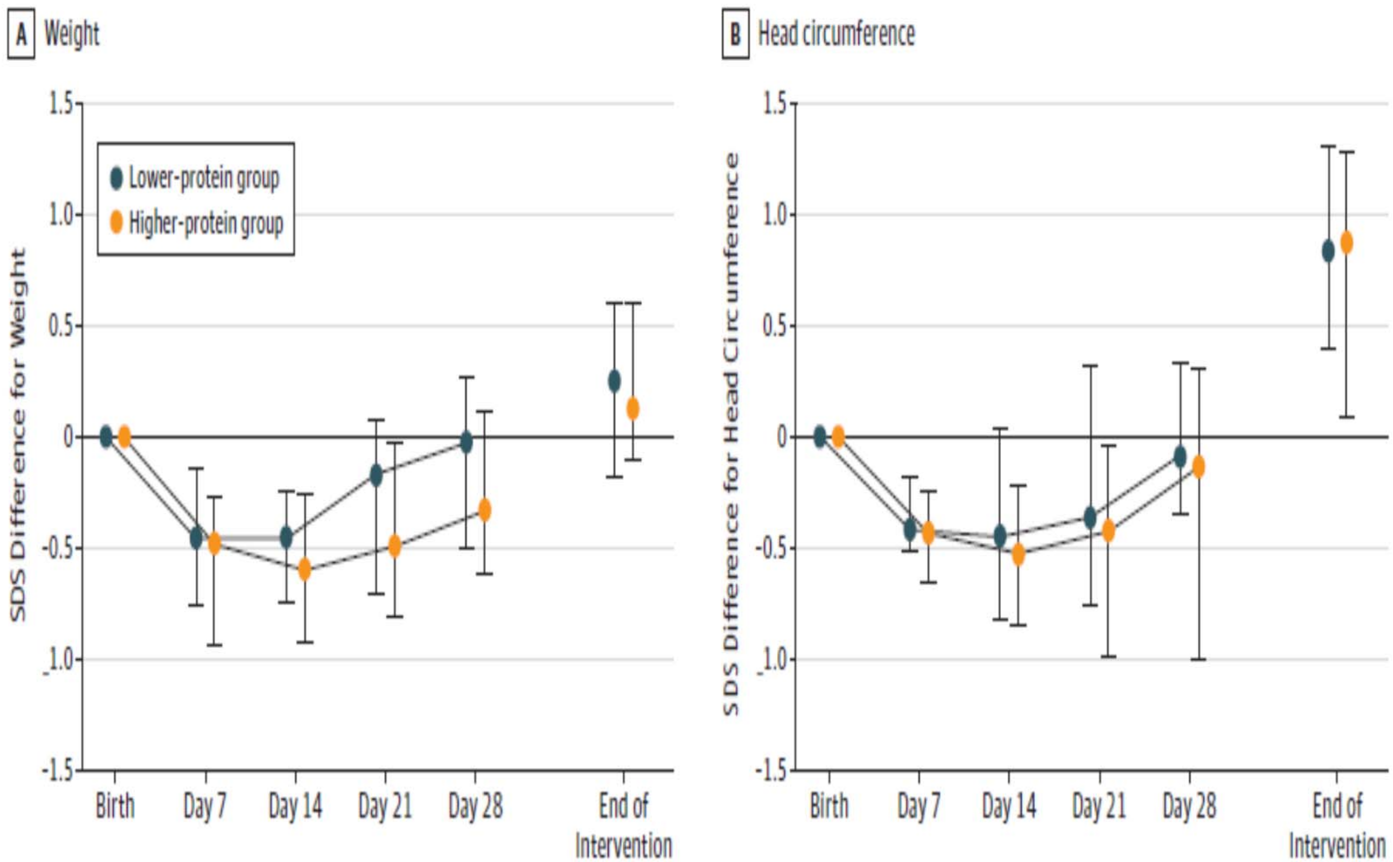
Results I



P: birth to end of intervention; P1: randomization to day 28
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
*
*
P, g/kg/d
P1, g/kg/d
Low Protein
High Protein

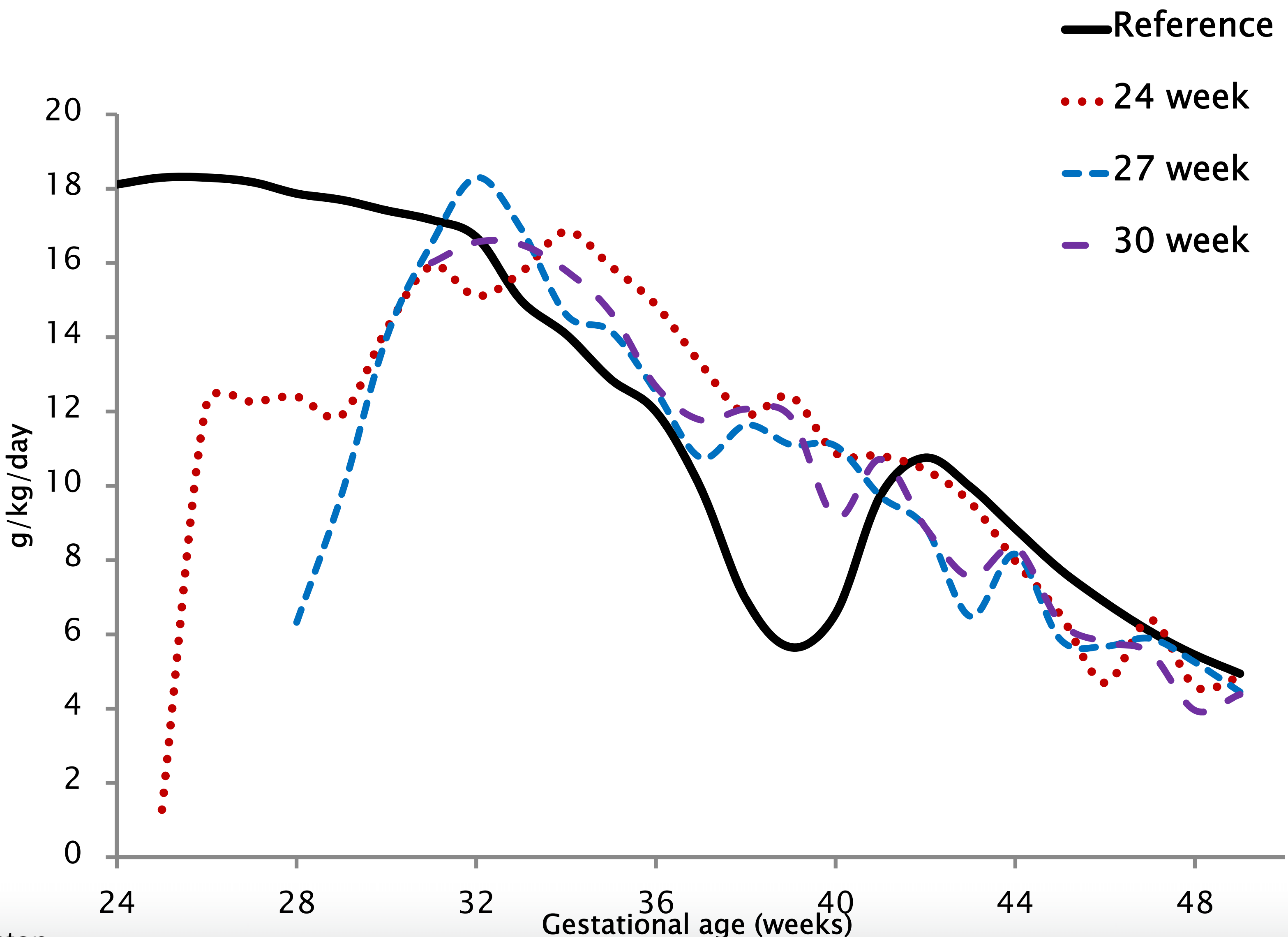
Results II


Energy Intakes
140
138
136
134
132
130
128
126
124
E, kcal/kg/d
E1, kcal/kg/d
Low Protein
High Protein



Plots for data points in time are separated only to enhance clarity of data presentation. Each data point represents the median value; error bars, interquartile range. Study interventions were continued for a median (interquartile range) of 41 (30-57) days and until definite discharge planning.

Weight gain velocity of preterm infants with the reference fetus and infant



Courtesy Fenton

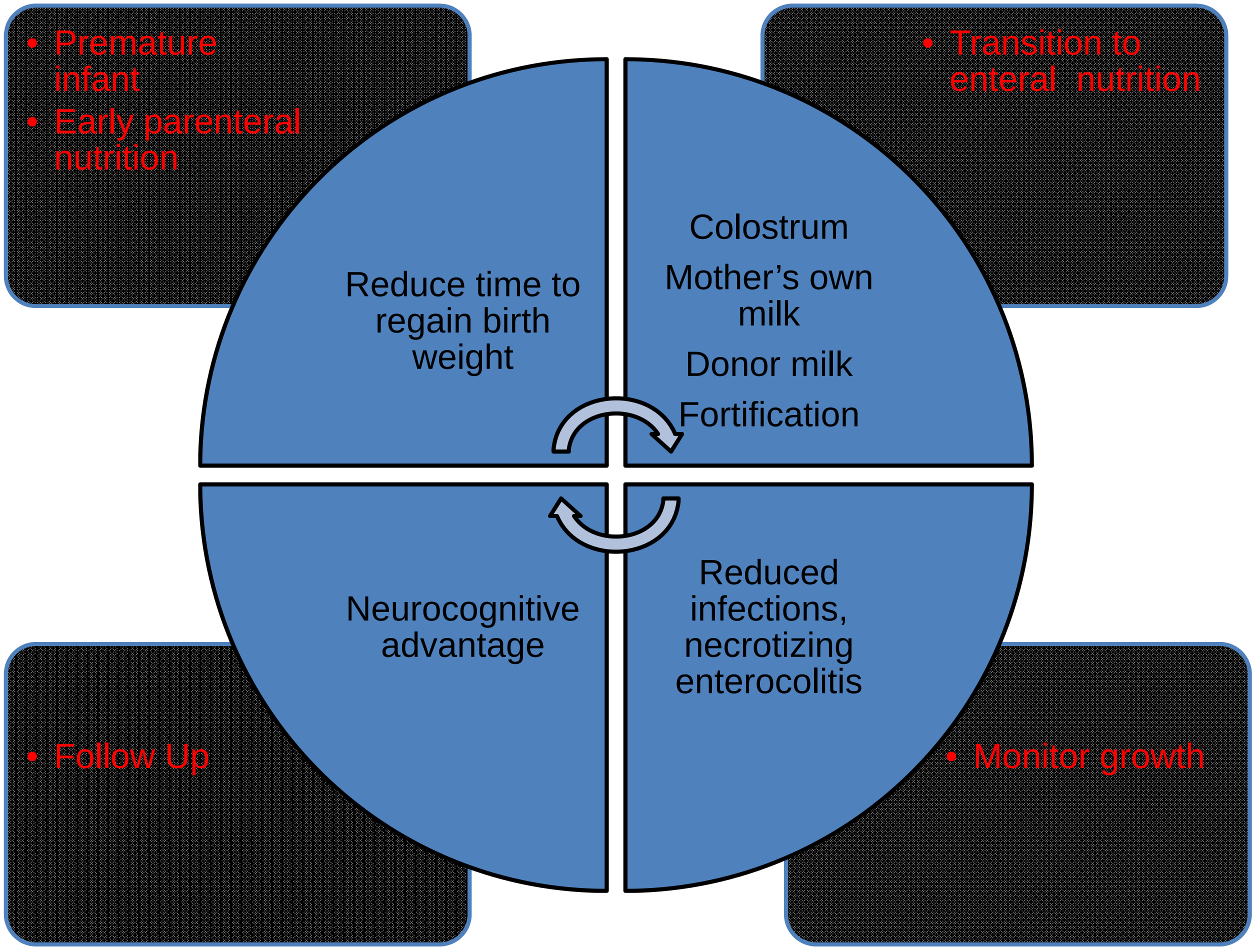
Summary of Fortification

- Adjustable fortification using BUN and growth appears to be a safe and suitable strategy
- When milk analyzers are made available [US], target fortification may be practiced
- Bedside analyzers currently in use over estimate human milk protein content by ~17% [Ziegler 2014]
- Day to day variation in human milk composition makes target fortification a labor intensive task
- More attention needs to be paid when using donor human milk

Feeding Premature and LBW Infants

- Balance the risk of under and over feeding particularly LBW infants who are small for gestational age
- Global epidemic of metabolic syndrome especially in countries where growth restriction rates are high
- For premature infants
  - Early aggressive parenteral nutrition
  - Early trophic feeds, colostrum swabbing
  - Human milk feeds with appropriate fortification
  - Monitor weight, length, head circumference

  - *Accepted goal is to achieve postnatal growth similar to that of a normal fetus*


• Premature infant
• Early parenteral nutrition
• Transition to enteral nutrition
Reduce time to regain birth weight
Colostrum
Mother's own milk
Donor milk
Fortification
Neurocognitive advantage
Reduced infections, necrotizing enterocolitis
• Follow Up
• Monitor growth

Bhatia 2013

Summary

- Nutrition in premature and LBW infants is a continuum from birth through discharge and after
- Particular attention is needed during parenteral nutrition, human milk feedings
- Growth restriction still a problem: Nutrition or predisposition?
- Fortification strategies need to be improved
- Vitamin D and Iron supplementation
- Current recommendations need to be followed as most of the deficiency states are preventable
- ONE SIZE DOES NOT FIT ALL!!

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