Global Guidelines for the *Nutritional Care of Preterm Infants*

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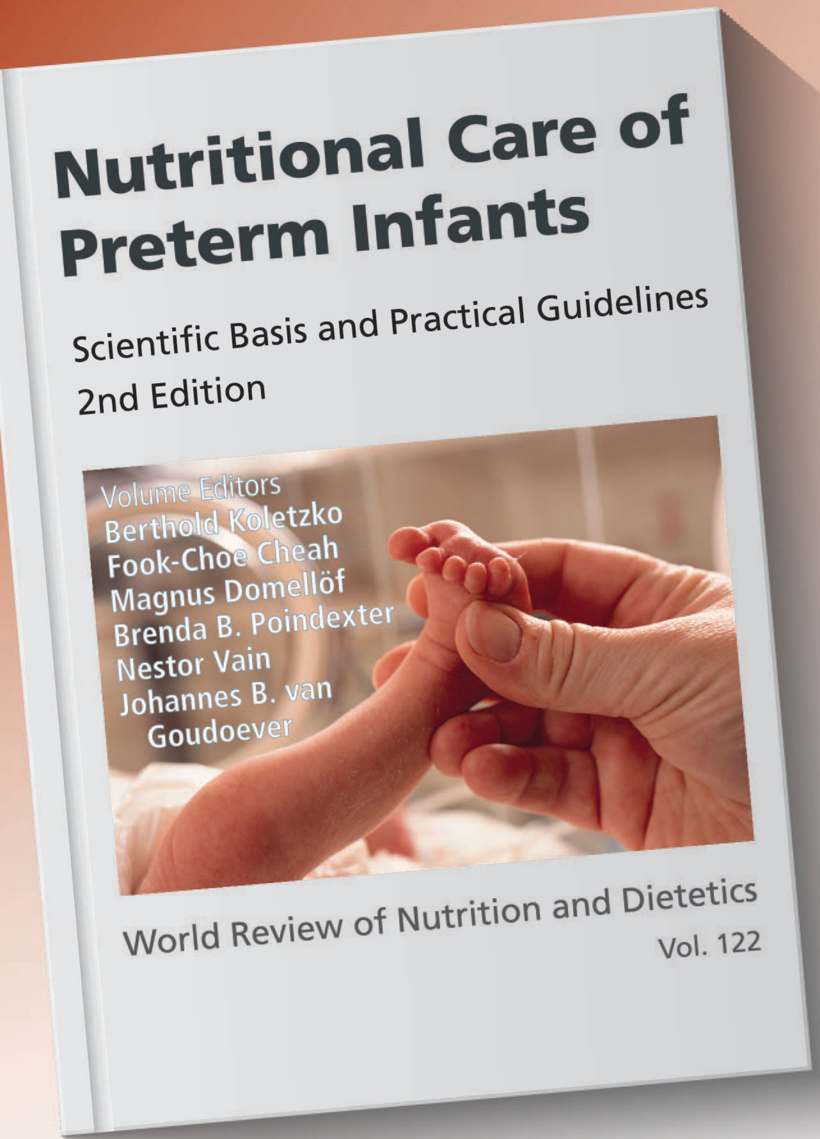

Global Guidelines for the *Nutritional Care of Preterm Infants*

Presented by

Berthold Koletzko, MD, PhD
Brenda B. Poindexter, MD, MS

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Learning Objectives

- Apply expert nutrition recommendations for very low-birth-weight infants in your clinical practice based on 2021 preterm infant nutritional guidelines.
- Identify areas in your clinical practice that will benefit from the latest preterm infant nutritional guidelines for enteral nutrition in very low-birth-weight infants.
- Identify research opportunities to advance nutritional care of preterm infants.

Outline

1. Nutritional needs and recommended intakes for preterm infants
2. New protein requirements of preterm infants
3. New lipid intake recommendations for preterm infants
4. What’s new in iron and vitamins
5. Human milk (donor vs mom’s own) and fortifiers
6. Enteral nutrition in very low and extremely low-birth-weight infants
7. Multidisciplinary approach and audit nutrition in preterms
8. Feeding after discharge

Nutritional needs and recommended intakes for preterm infants

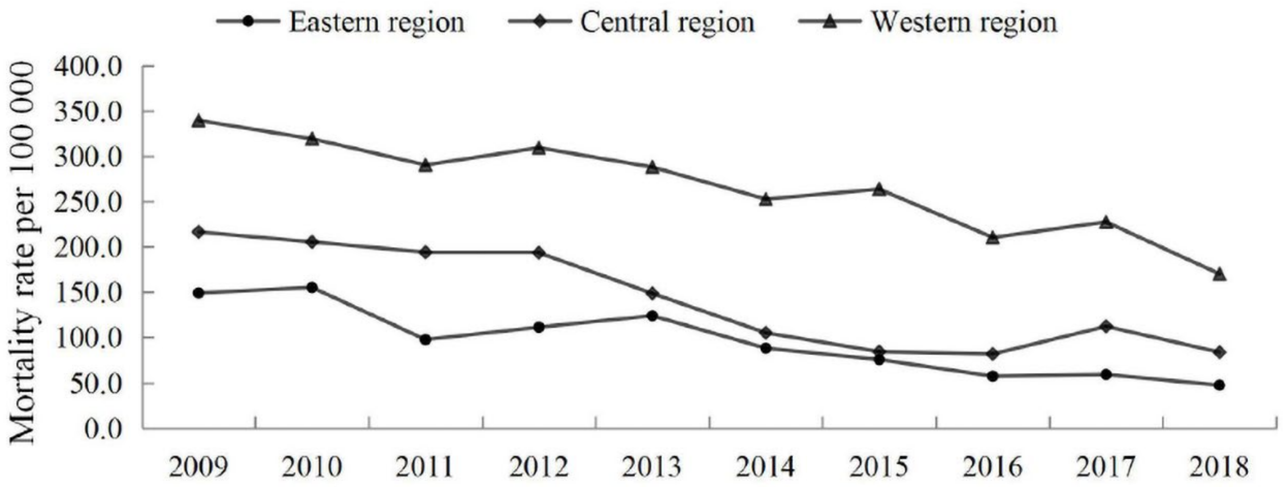
Increased attention to preterm nutritional care

- **Improved survival** of preterms globally *(partic. very/extremely preterms)*

➔ **Long-term outcome** gets greater attention

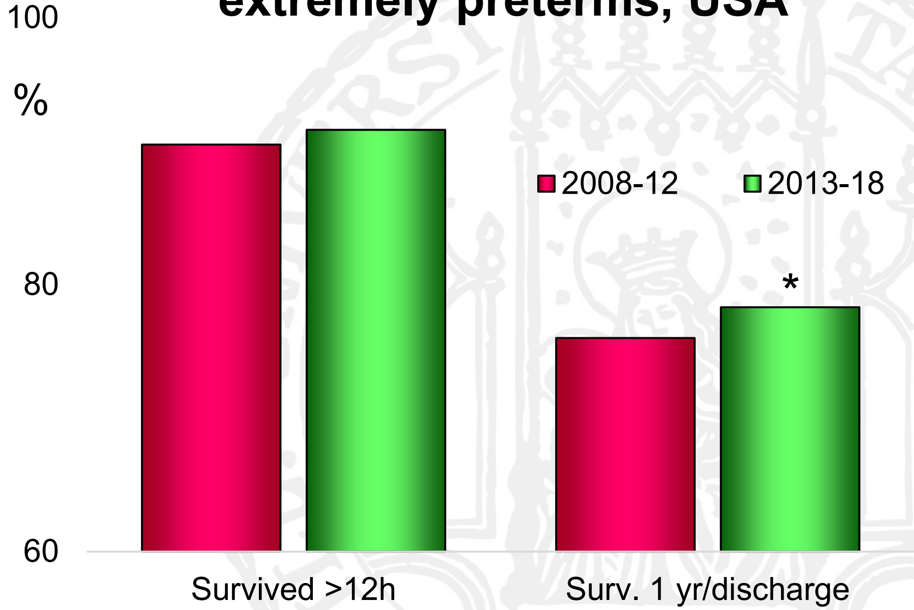
➔ **Greater focus on nutritional care** *which markedly affects outcome*

Preterm mortality declines, China

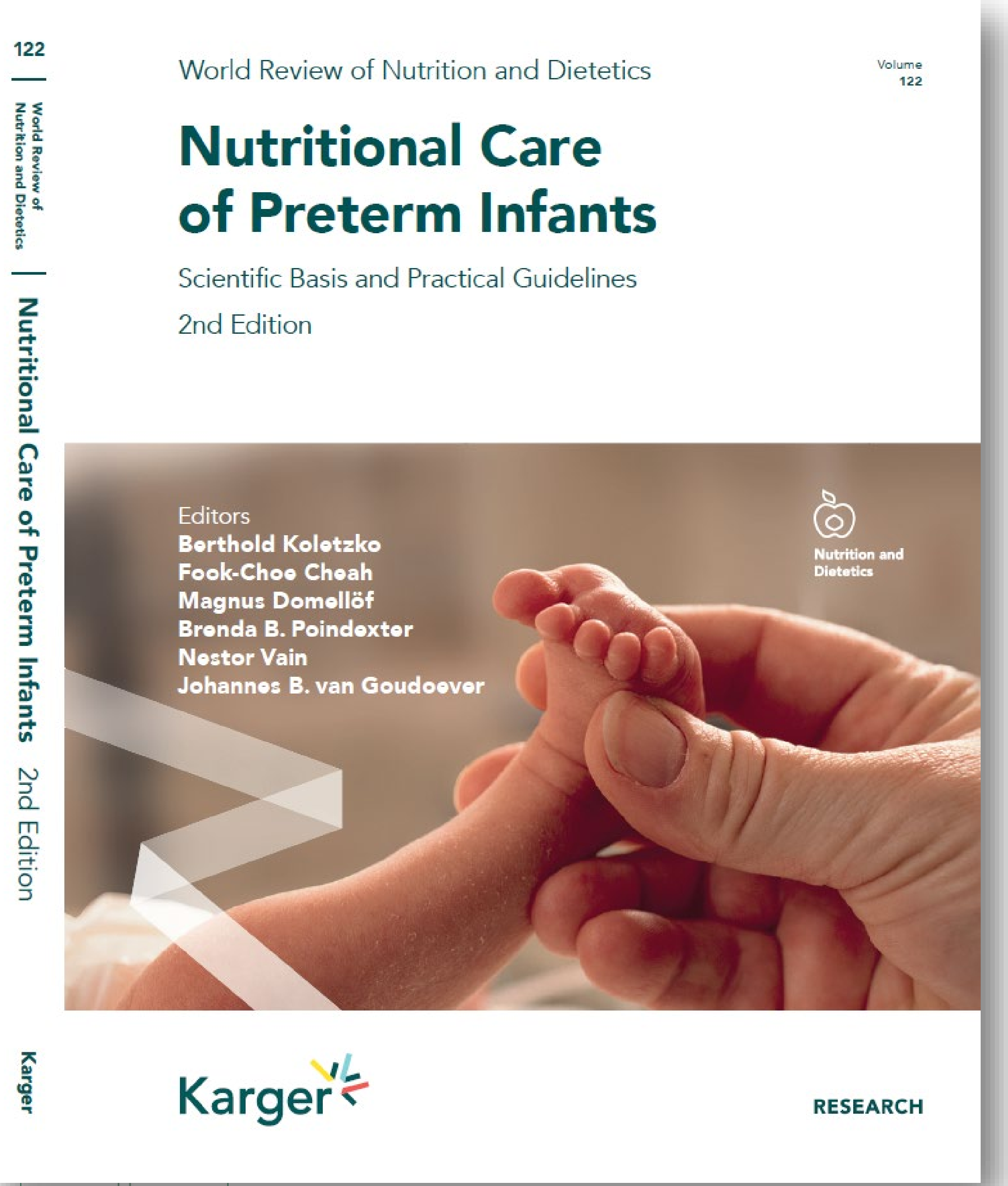


Yu X et al, PLoS One 2021;16(12):e0260611.

Increased survival of extremely preterms, USA

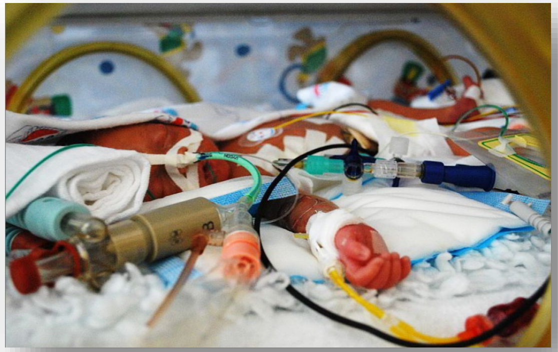


Bell EG et al, JAMA 2022;327(3):248-63.



- New global recommendations 2021
- Compiled by leading experts from around the world
- Chapters critically peer reviewed *(2 external reviewers + 2 editors)* & carefully revised
- Formal consensus process for recommendations *(3 consensus conferences with authors and editors)*

New / revised recommendations, e.g.



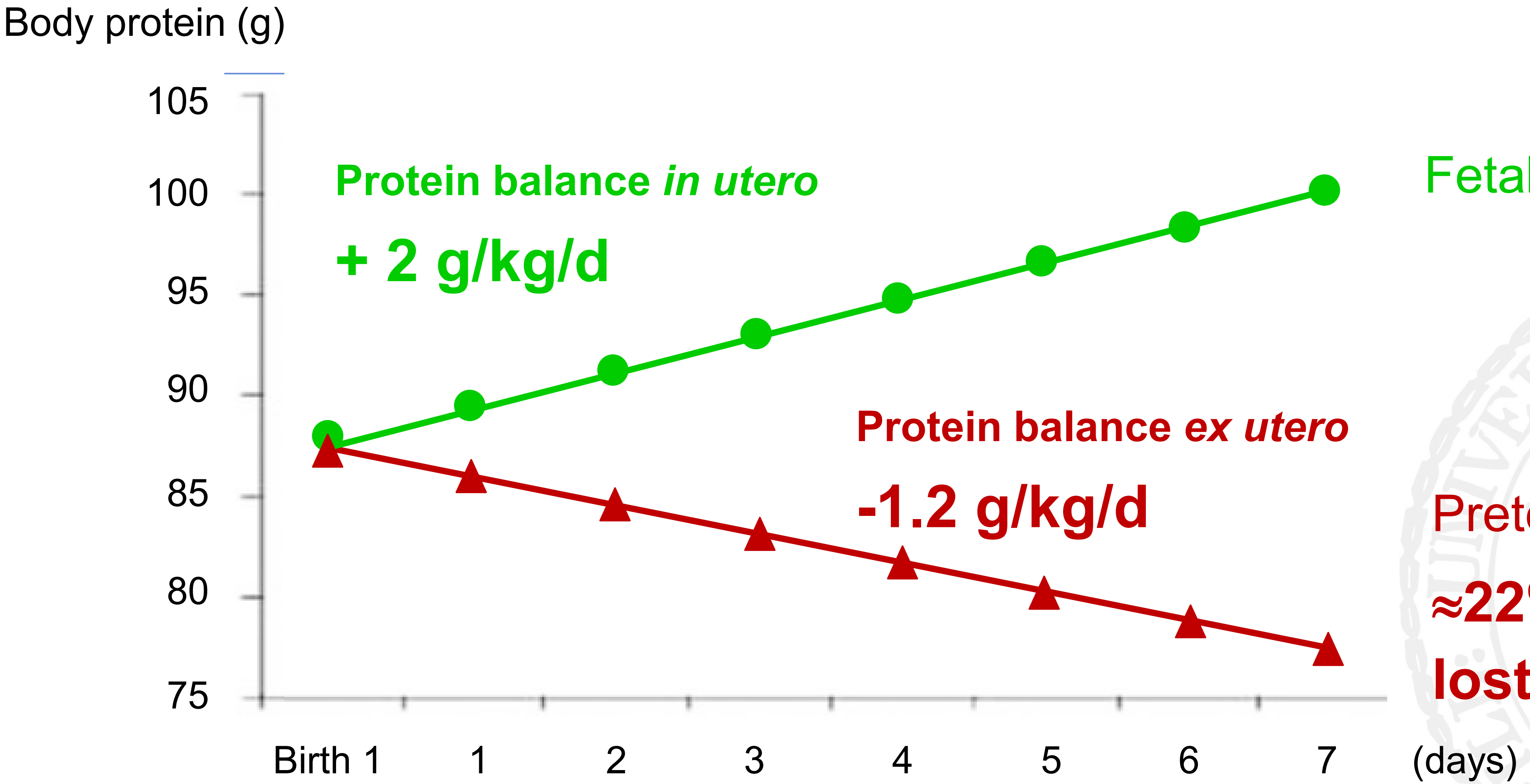
- Practice of parenteral nutrition from day 1
- More amino acids/protein & phosphorus
- Early lipid emulsion / higher supply of long chain PUFA
- More emphasis of meeting protein needs
- Prioritize own mother‘s milk with fortification
- More attention to feeding after discharge, and more ….

Margarita: a nutritional emergency

- Born preterm, 28 wks, 1000 g birthweight
- Her body consists of:
  - Water 850 g
  - Protein 100 g
  - Lipid 20 g *(structural lipid, no subcutanous fat)*
  - Glycogen absent
- No utilizable energy stores ⇨ without immediate feeding
  ⇨ high loss of body protein for energy production
  ⇨ nutritional emergency

Importance of early supply

Fetal amino acid supply via the placenta ≈3.5-4.0 g/kg/d



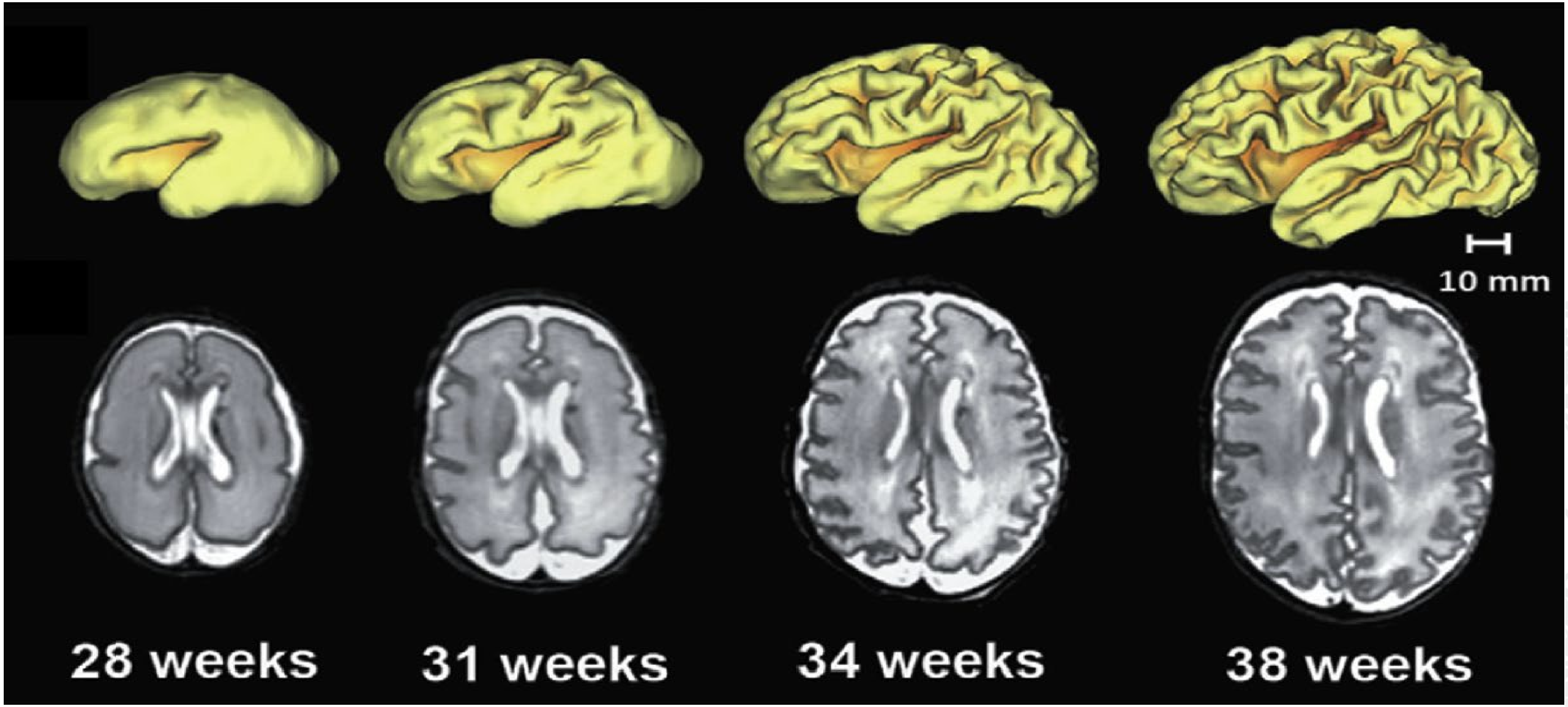
Fetal accretion, wk 26

Preterm, glucose i.v. :

≈22% body protein lost in 1 week

Denne SC & Poindexter BB, Sem Perinat 2007; Embleton ND & v d Akker CHP, Sem Perinat 2019.

Brain growth needs substrates incl. amino acids



28 wks ≈140 g

term birth ≈400 g

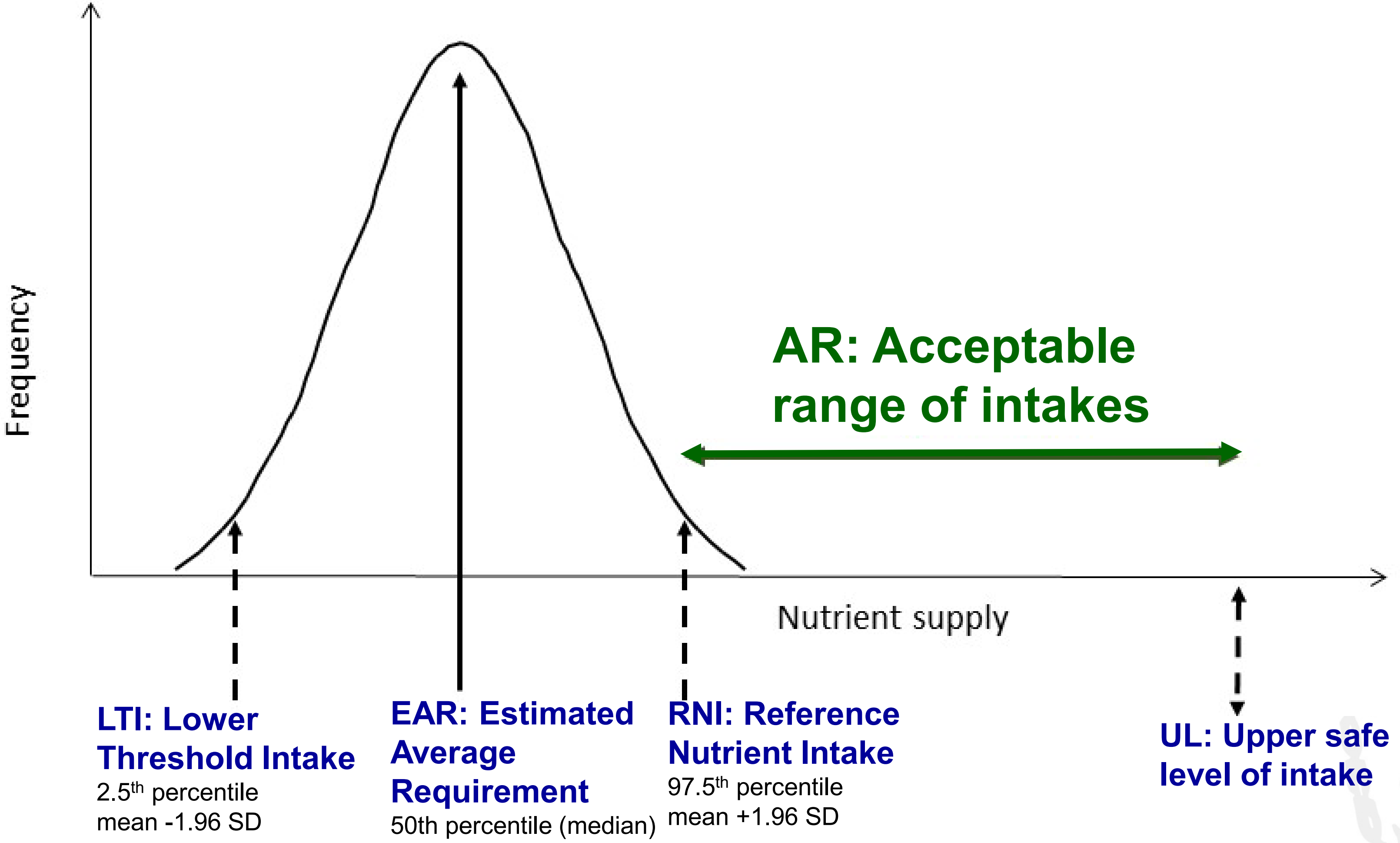
Defining recommended nutrient intakes

- Goal: meet physiological requirements to maintain normal growth, health and development
- Systematic review of scientific evidence: for several nutrients lack of conclusive studies ⇨ considerable uncertainties on adequate intakes
- For several nutrients, needs are related to weight gain velocity

Body weight	Desired weight gain (g/kg/d)
< 1500 g	17-21
1500-2000 g	14-17
2000-2500 g	12-14
2500-3000 g	10-13

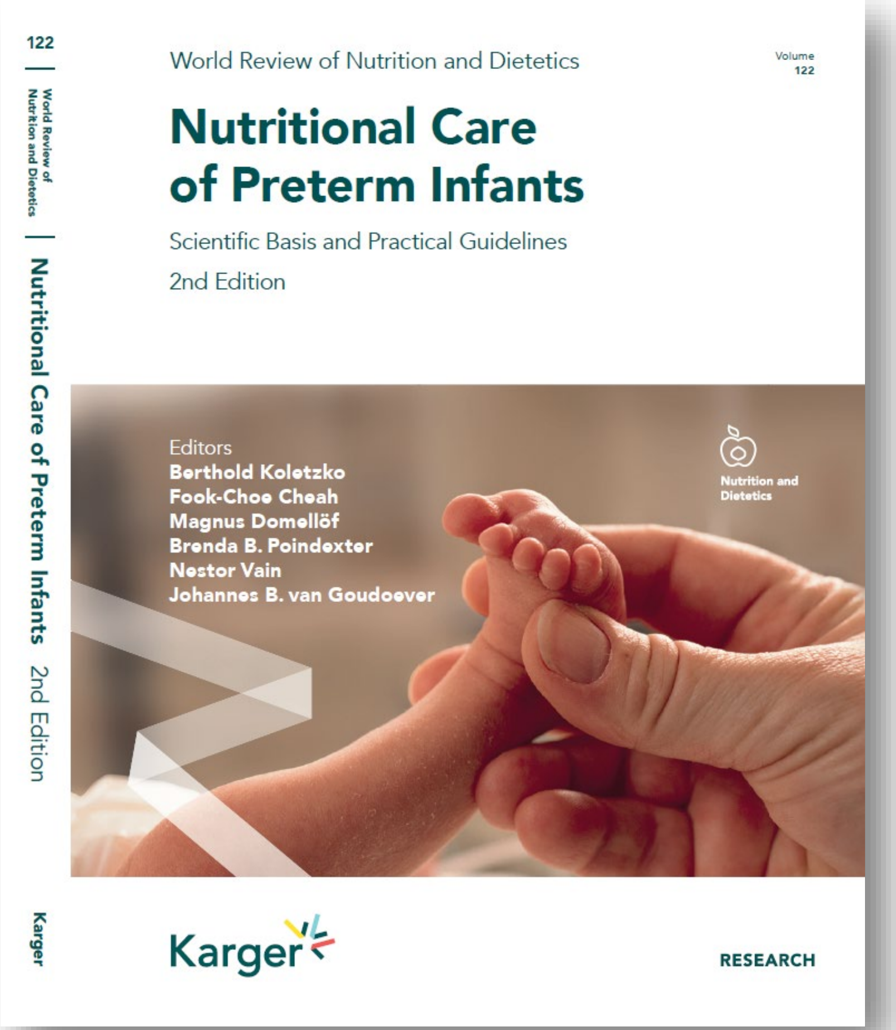
Koletzko B et al, Defining nutritional needs of preterm infants. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants, Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

Nutrient intake recommendations refer to preterm populations, not individuals



Koletzko B et al, Defining nutritional needs of preterm infants. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

Defining recommended nutrient intakes



Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

- Leading experts reviewed evidence and drafted text and recommendations
- Critical peer review *(2 external reviewers + 2 editors)* & careful revision
- Formal consensus process *(3 consensus conferences with authors and editors)*

Level of consensus	**Support** (% votes)
Strong consensus	>95 %
Consensus	>75-95 %
Majority support	>50-75 %
No consensus	<50 %

Take-home messages: RNI

- Reference nutrient intakes (RNI) refer to stable growing preterm infant populations according to current body weight categories
- For most nutrients, needs are proportional to growth rate *(few exceptions e.g. water, fat)*
- Nutrient intakes below RNI may be appropriate during the early postnatal phase prior to full feeding, and during critical illness
- Needs of an individual preterm infant may markedly deviate from population reference intakes

Koletzko B et al, Defining nutritional needs of preterm infants. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

Research opportunities: RNI

- Great opportunities to reduce the knowledge gap on nutrient needs in different subgroups of preterm infants

- Application of current methods and technologies can limit the burden on infants participating in such studies

- Neonatologists, researchers and funding agencies should invest in studies to advance solid knowledge on optimal nutrition of preterms, to support their optimal health and development

Koletzko B et al, Defining nutritional needs of preterm infants. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

Protein Requirements of Preterm Infants

Protein Requirements of Preterm Infants

Current body weight	g/kg/d
500–1000 g	3.5–4.5 (max 3.5 parenteral)
1000–1500 g	3.5–4.5 (max 3.5 parenteral)
1500–2000 g	3.0–4.0 (max 3.0 parenteral)
2000–2500 g	2.5–3.5 (max 2.5 parenteral)

v d Akker, CHP, et al. Proteins and Amino Acids. In: Koletzko B et al (eds). *Nutritional Care of Preterm Infants.* Karger. 2021. Table from appendix, modified by Annenberg Center for clarity.

Protein Quality

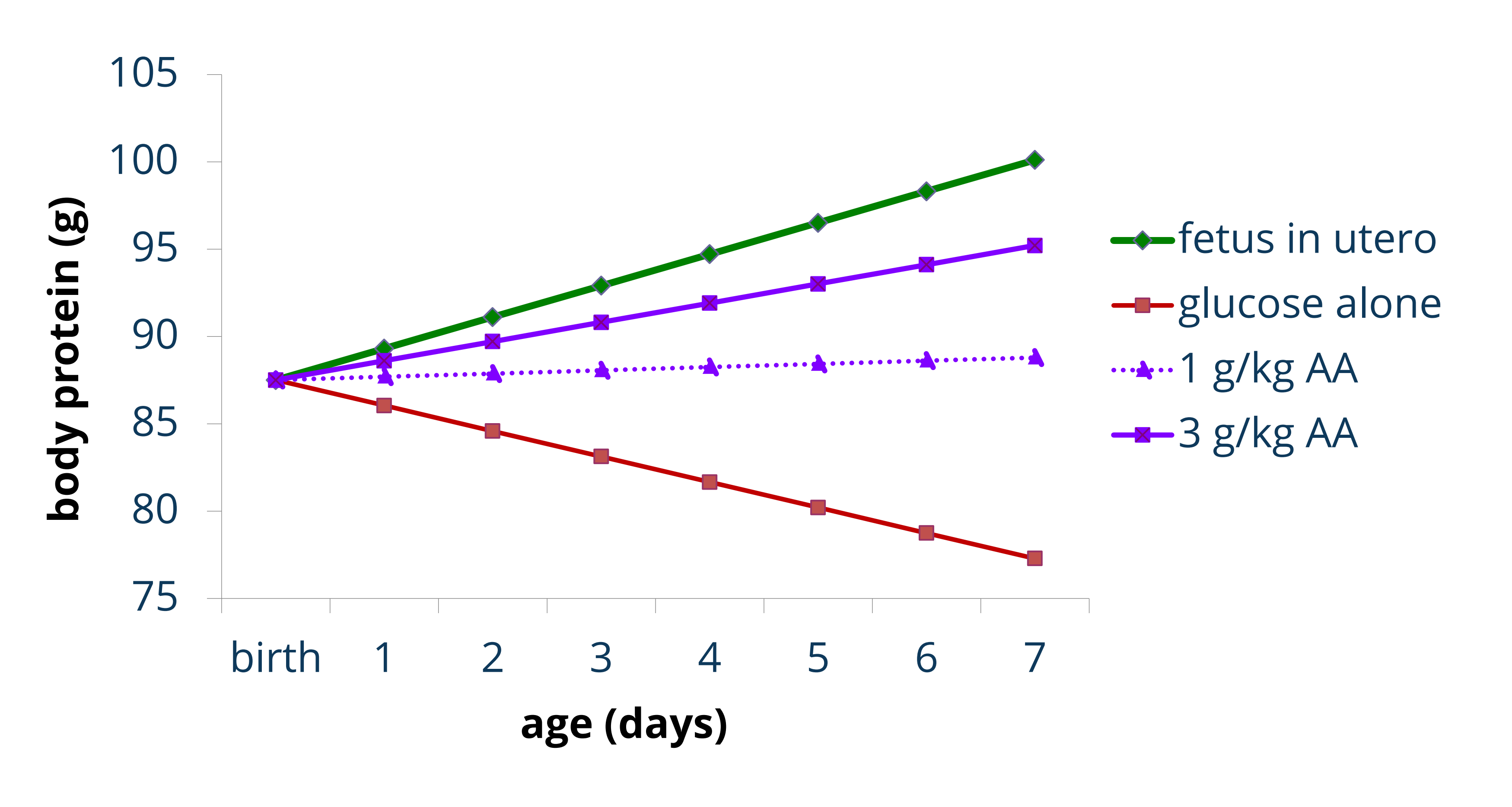
Essential	Semi-essential	Non-essential
Histidine	Arginine	Alanine
Isoleucine	Cysteine	Asparagine
Leucine	Glutamine	Aspartic acid
Lysine	Glycine	Glutamic acid
Methionine	Proline	Ornithine [a]
Phenylalanine	Taurine [a]	Serine
Threonine	Tyrosine	
Tryptophan		
Valine		

a. Not an α-amino acid (not incorporated into proteins)

✦ **No currently available amino acid solutions designed for the ELBW infant!**

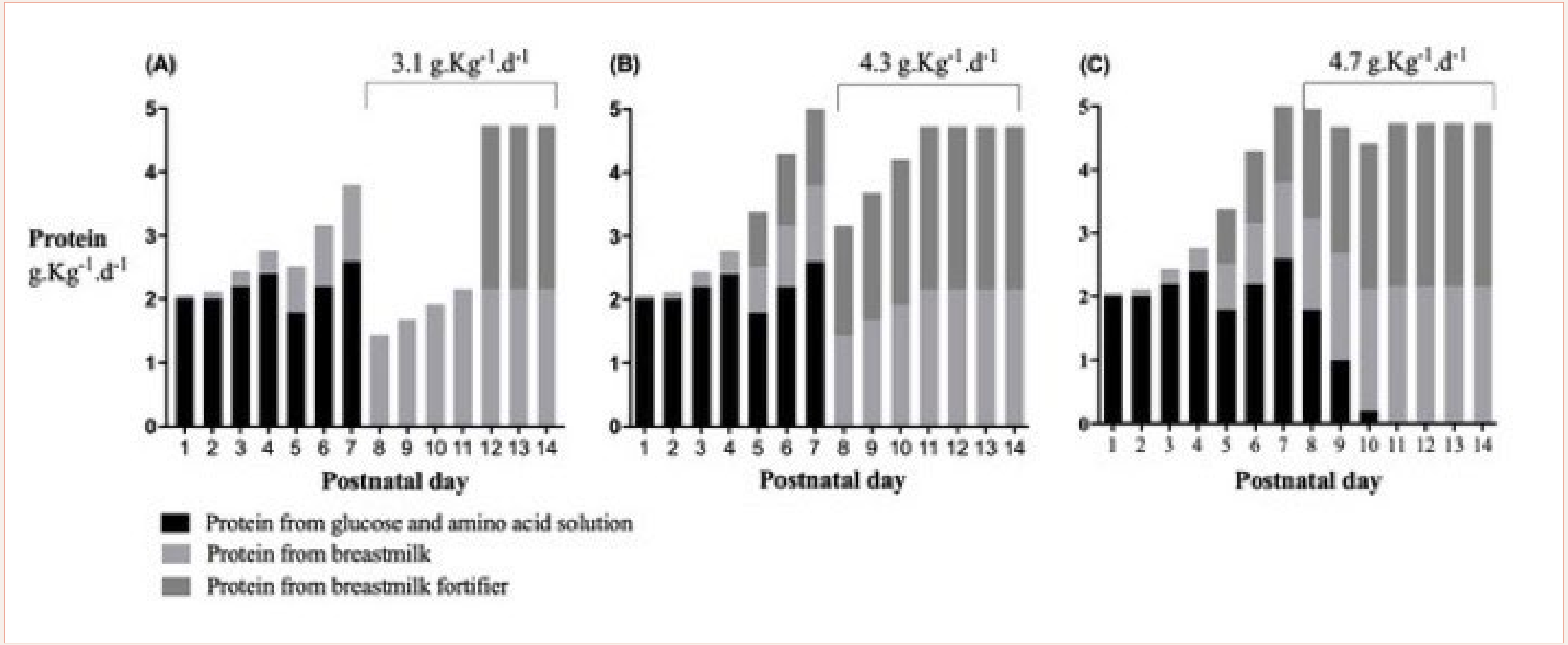
v d Akker, CHP, et al. Proteins and Amino Acids. In: Koletzko B et al (eds). *Nutritional Care of Preterm Infants.* Karger. 2021. Table 1 modified by Annenberg Center for clarity.

Rationale for Early Amino Acids



1. Denne SC, et al. *J Clin Invest.* 1996;97(3)L748-754.
2. Denne SC, and Poindexter BB. *Semin Perinatol.* 2007;31:56-60. Original figure; figure 5 in print.
3. Poindexter, *Am J Physiol.* 2001;281:E472-E478.

Transition from Parenteral to Enteral Intake



✦ Do not taper off parenteral nutrition too soon while enteral intake increases!

Individual Amino Acid Requirements

- Glutamine
  - 12 RCTs with glutamine supplementation
  - No consistent evidence of benefit for outcomes including mortality, sepsis, NEC, and time to reach full enteral feeding
- Arginine
  - 3 small RCTS (n=285) suggest decrease in risk of NEC and mortality
- Taurine
  - Most abundant free amino acid in breast milk
  - Important role in intestinal fat absorption (but not effect on weight gain), hepatic function, and auditory and visual development in preterm/LBW infant

LBW, low birth weight; NEC, necrotizing enterocolitis; RCT, randomized controlled trial.

Key Messages

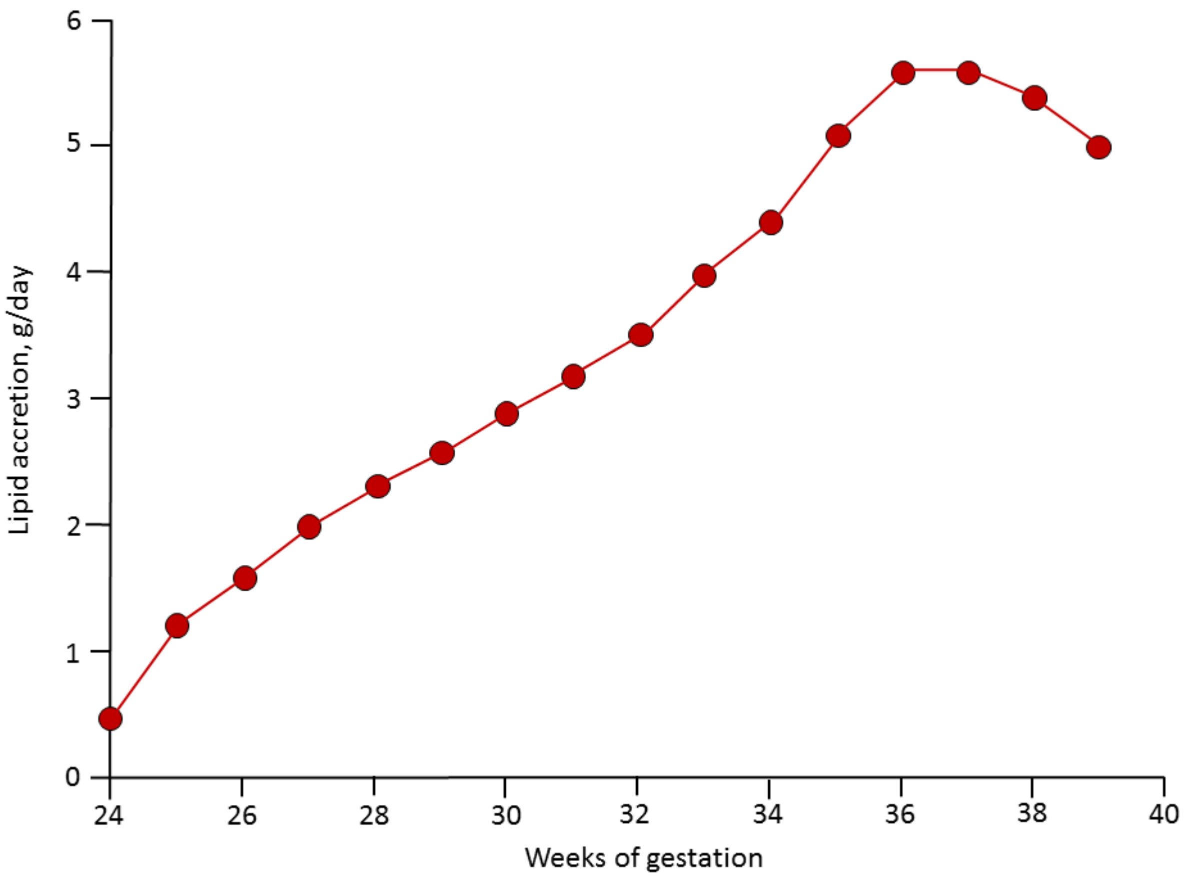
- Parenteral amino acid supply for very preterm infants can start immediately after birth at a rate of 1.5–2.5 g/kg/day safely and can be increased to 3.5 g/kg/day in the next few days.
- Enterally fed very preterm infants should receive at least 3.5–4.0 g protein/kg/day (together with sufficient other macro- and micronutrients).
- Protein intake may be further increased up to 4.5 g/kg/day in case of growth faltering provided protein quality is good, concomitant energy and other macronutrient intakes are optimal, and there are no other causes for suboptimal growth.
- Parenteral amino acid intake should not be tapered before an enteral intake of at least 75 mL/kg/day has been reached.

Research Priorities

- Defining individual amino acid requirements will allow the development of a high-quality parenteral amino acid solution and may provide a scientific base for eventually lowering total protein intakes.
- Arginine supplementation to reduce the incidence of necrotizing enterocolitis requires large, well-designed randomized clinical trials.

New lipid intake recommendations for preterm infants

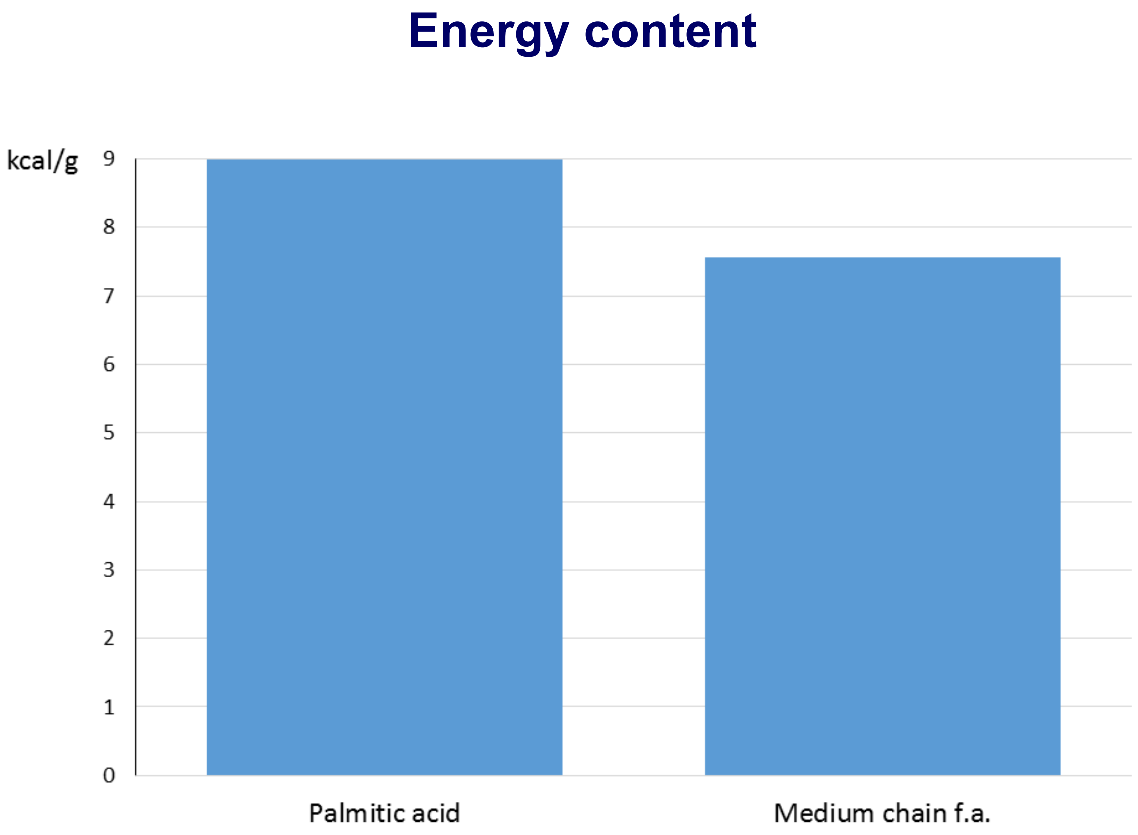
High total lipid intake (≈37-67 E%)



- Lipids: high energy density *(≈9 kcal/g)*, no high osmotic load
- *De novo* lipogenesis from glucose consumes ≈25% of energy, provides only non-essential fatty acids
- High intake beneficial to meet energy needs and to match fetal lipid accretion
- Intake similar to human milk supply

Koletzko B, Lapillonne A. Lipid requirements of preterm infants. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

MCT (Medium chain triglycerides)

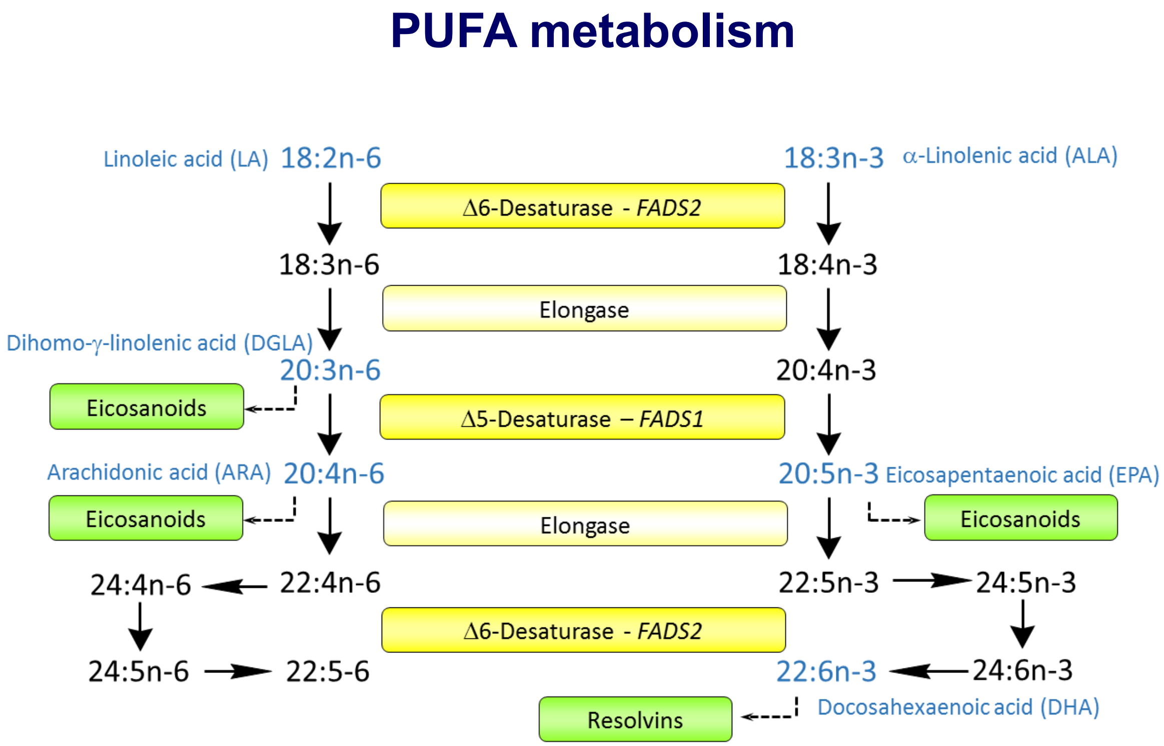


- MCT: better absorbed but less energy content than LCT
- No benefit for energy balance/growth
- Rapid oxidation
- Improved calcium absorption
- If used (not required) ≤40% of fat

Koletzko B, Lapillonne A. Lipid requirements of preterm infants. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

Which one of the following is correct for long-chain polyunsaturated fatty acids?

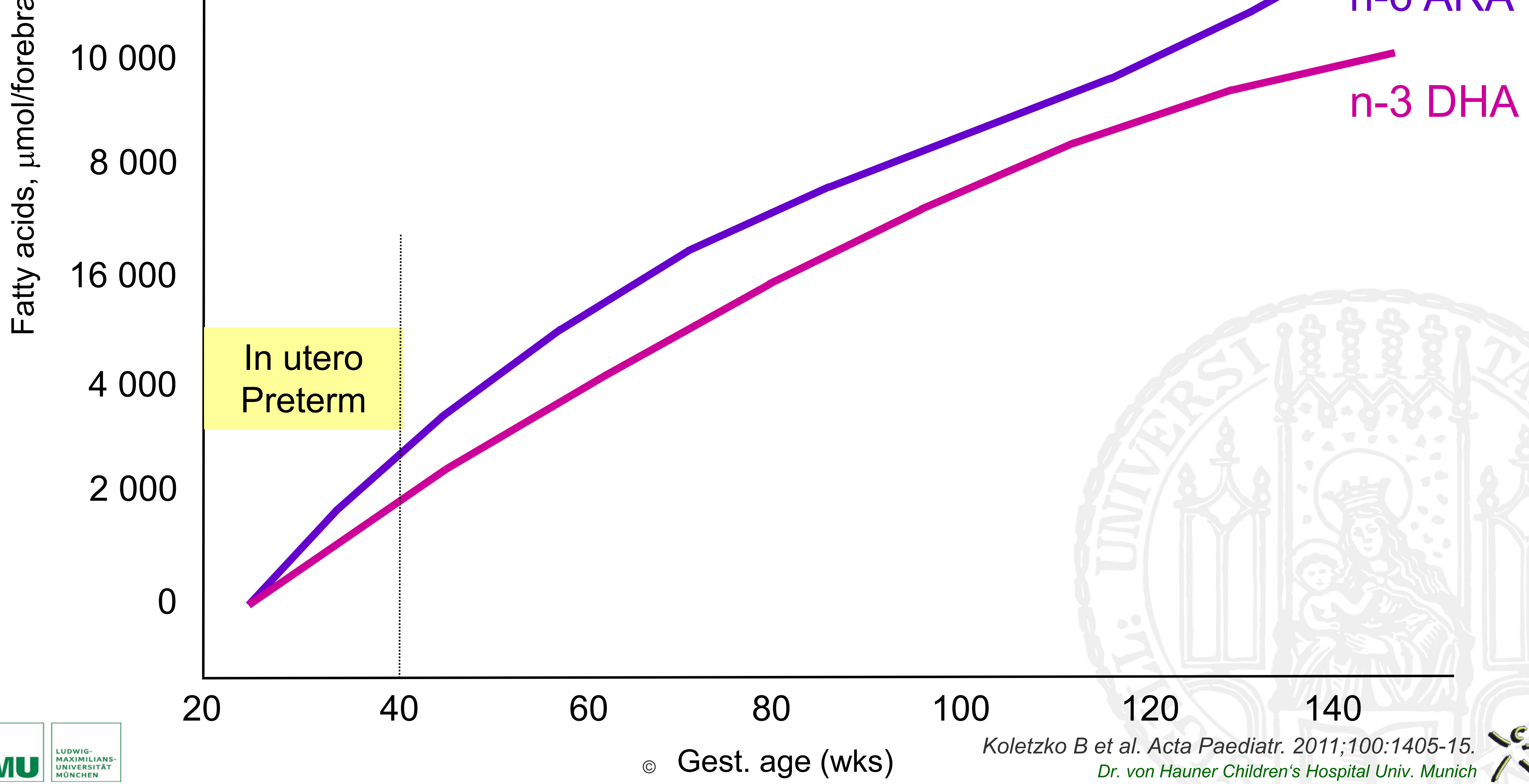
PUFA essential, LC-PUFA conditionally essential



- ω-6 linoleic acid and ω-3 α-linolenic acids = essential nutrients
- Very preterms synthesize less ω-6 and ω-3 LC-PUFA (ARA, DHA) than needed for growth
- DHA intakes ≈1% of fatty acids with ARA is similar to fetal accretion
- RCTs: some report benefits for visual & mental development, and ↓ ROP

Koletzko B, Lapillonne A. Lipid requirements of preterm infants. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

ARA & DHA brain accretion



Koletzko B et al. Acta Paediatr. 2011;100:1405-15.

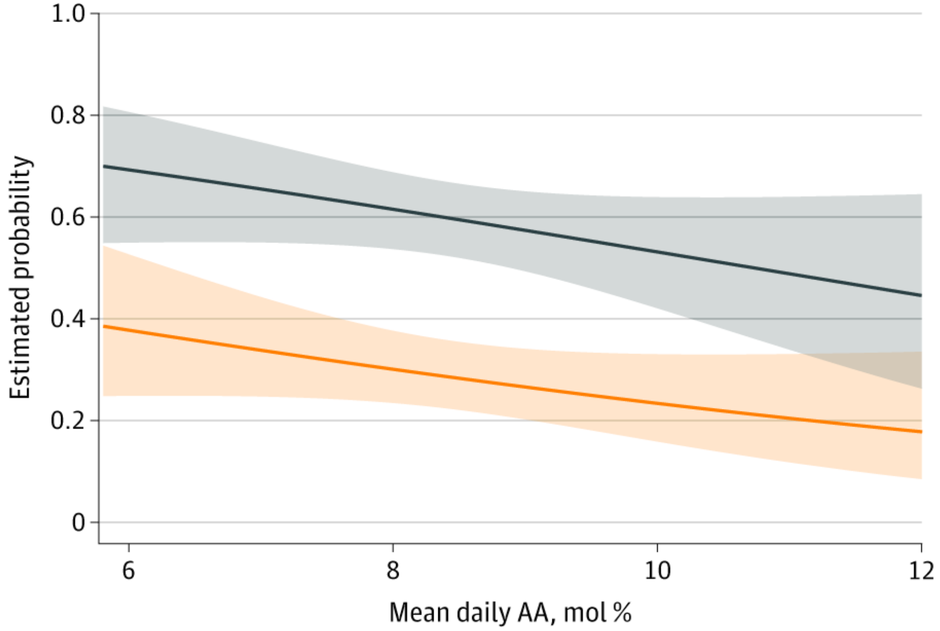
Dr. von Hauner Children's Hospital Univ. Munich

LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

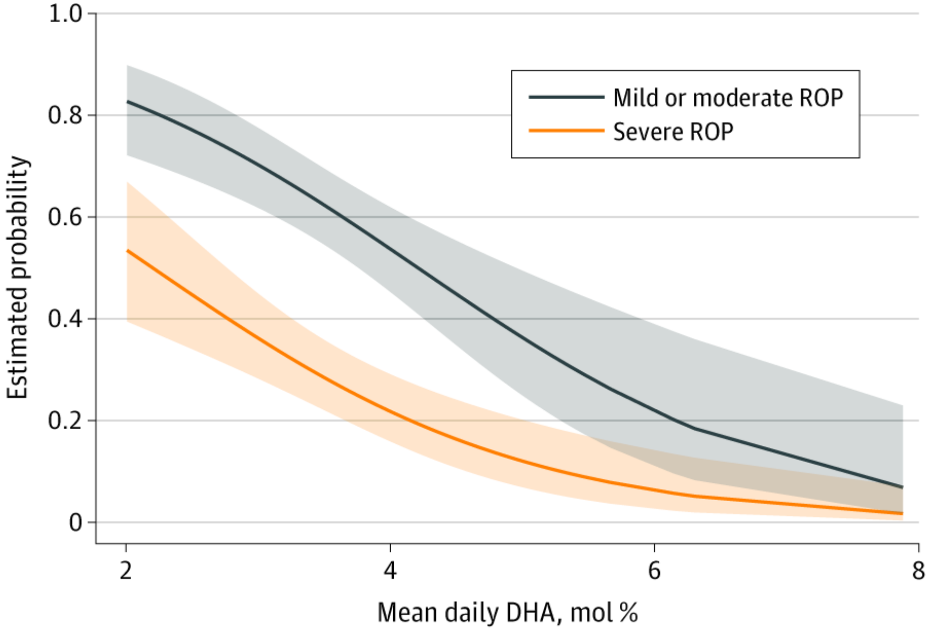
RCT: DHA + ARA supply reduces ROP risk

Treatment with enteral ARA (100 mg/kg/d) + DHA (50 mg/kg/d) **reduced severe ROP** *(adj. RR **0.50**, 95%CI 0.28-0.91, P=0.02)*

Serum ARA



Serum DHA



175 preterms
<28 gest weeks

Hellström A, JAMA Netw Open 2021;4(10):e2128771. doi: 10.1001/jamanetworkopen.2021.28771.

Human milk always provides ARA & DHA

Auguste Renoir: Woman breastfeeding her child.
Oil on canvas, 1886, after the birth of first son Pierre

Human milk worldwide:

- **ω-6 ARA: 0.47**±0.13% (CV 29%) %wt, M±SD, range 0.24-1.0%
- **ω-3 DHA: 0.32**±0.22% (CV 69%) range: 0.06-1.4%

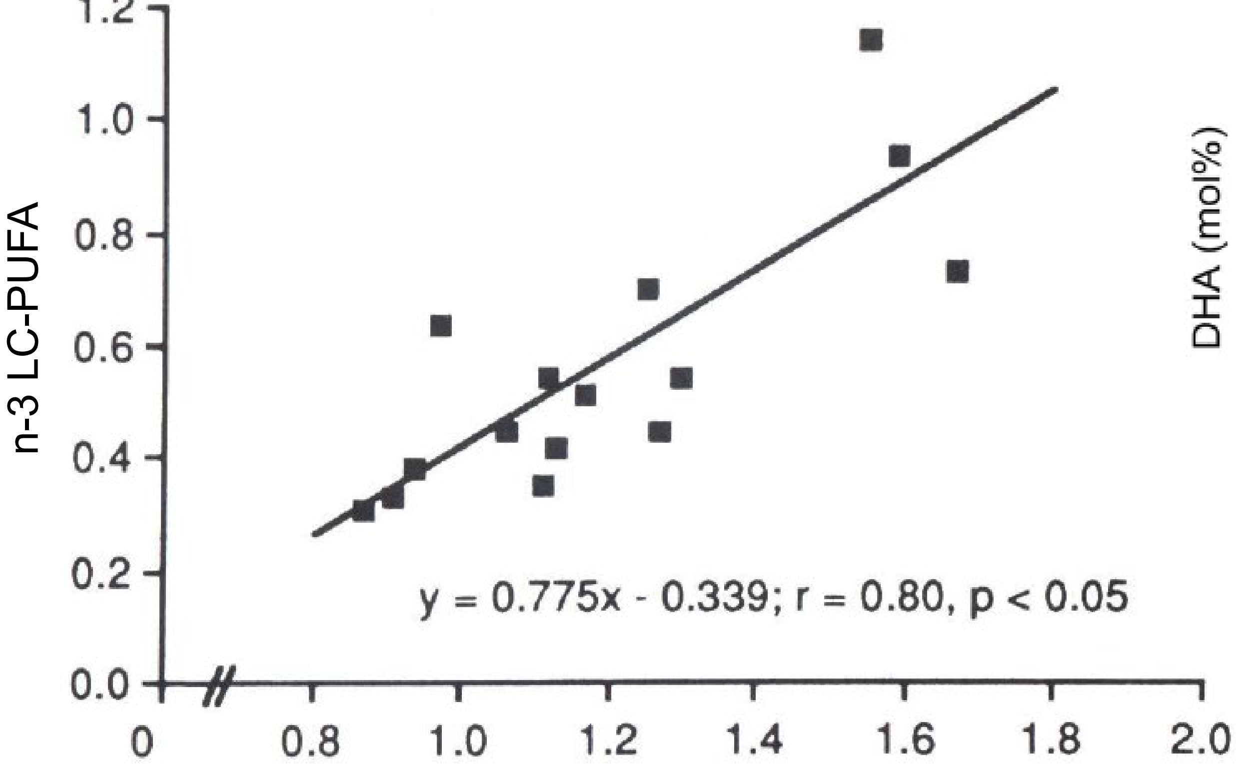
65 studies worldwide, 2474 women. Milk DHA related to marine food intake, highest in coastal populations.

Brenna JT et al. Am J Clin Nutr. 2007 Jun;85(6):1457-64.

ARA & DHA in human milk are correlated

Milk for term infants
Germany

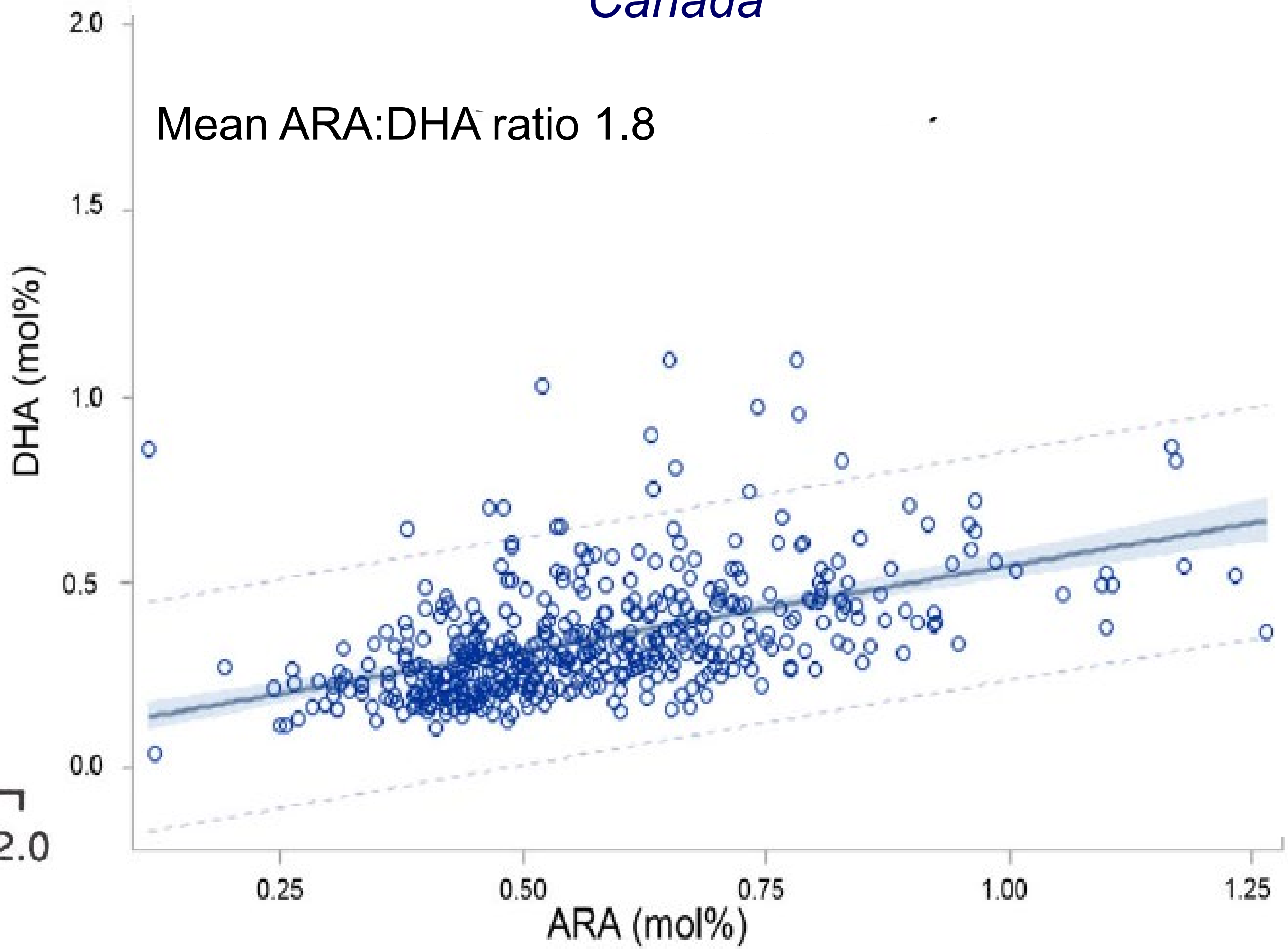
Mean ARA:DHA ratio 1.8



n-6 LC-PUFA

Milk for preterm infants
Canada

Mean ARA:DHA ratio 1.8



Koletzko B et al, Am J Clin Nutr 1988;47:954-9.

Hopperton KE et al, Lipids. 2022. doi: 10.1002/lipd.12338.

Human milk provides LC-PUFA (DHA & ARA)

- Preterm infants deposit much DHA & ARA in brain and other tissues, with functional importance. Fetal accretion >> term infants
  ⇨ preterms need ≈30-65 mg DHA/kg & 50-130 mg ARA/kg/day

- Mothers providing breast milk: to enhance milk DHA **eat oily fish**, take **DHA supplements** *(e.g. ≈1 g/d)*

- Preterm formula should provide 0.5-1 % of fat as **DHA**, with **ARA ≥ DHA** (ARA:DHA ratio = 1-2)

Koletzko B, Lapillonne A. Lipid requirements of preterm infants. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

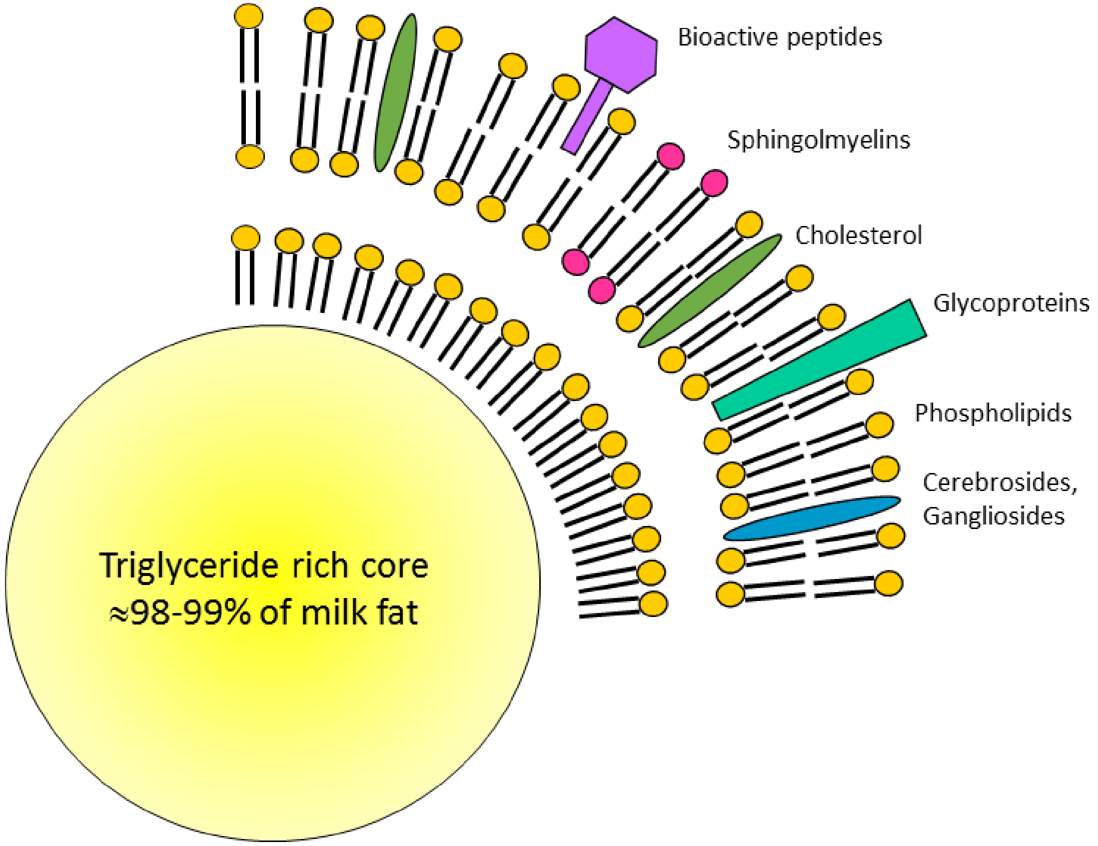
Lipid supply to preterm infants

Substrate	Advisable supply
Total fat	4.1-7.4 g/100 kcal *(≈37-67 E%)*
Medium chain triglyc. *(MCT)*	$\leq$40 % of fat
ω-6 Linoleic acid	350-1400 mg/100 kcal
ω-3 α-linolenic acid	>50 mg/100 kcal
ω-3 DHA	0.5-1 % of fatty acids
ω-3 DHA:ω-6 ARA-ratio	0.5 to 1
Total choline *(free & bound)*	$\geq$30 mg/100 kcal
L-carnitine	$\geq$1.5 mg/100 kcal

Koletzko B, Lapillonne A. Lipid requirements of preterm infants. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

Research opportunities: Lipids

Human milk fat globule



- More quality studies to elucidate optimal intakes of PUFA, such as linoleic and arachidonic acids
- Characterize metabolism, biological effects and optimal intakes of complex lipids and other components of human milk fat globule membranes

Koletzko B, Lapillonne A. Lipid requirements of preterm infants. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

What’s new in iron and vitamins

What's New in Iron, Microminerals and Vitamins

- No new studies to suggest a change of recommendations for iron supplementation from the previous edition of the book.
- Breast milk will not meet the vitamin requirements of preterm infants—therefore fortification of human milk is needed.

Domellöff M, Embleton N. *World Rev Nutr Diet.* 2021;122:167-179.
Gerasimidis K, Haiden, N. *World Rev Nutr Diet.* 2021;122:149-166.

Iron Requirements of Preterm Infants

Birth Weight	mg/kg/d	Start (wks)	End (months)
<1500 g	2-3	2	6-12
1500-2000 g	2	2-4	6-12
2000-2500 g	1-2	4-6	6

- Preterm infants especially vulnerable to excessive iron intakes (immature antioxidant systems) and ROP and BPD have been associated with increased oxidative stress
- Iron supplementation lowers risk of iron-deficiency anemia but paucity of studies evaluating neurodevelopmental outcomes
- No benefit in exceeding standard doses of iron
- Iron not routinely provided in parenteral nutrition

BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity.

Mills JM, Davies, MW. *Cochrane Database Syst Rev.* 2012 Mar 14;(3):CD005095.
McCarthy EK, et al. *Nutr Rev.* 2019;77(12):865-877.

Monitoring Ferritin

- Repeated measurements of serum ferritin recommended:
  - If <35–70 μg/L, consider increasing iron dose to 3–4 mg/kg/d during a limited period
  - If >300 μg/L, hold iron supplementation until serum ferritin falls below this level

Zinc Requirements of Preterm Infants

Current Weight	Growth velocity, g/kg/d	Minimum dietary Zn requirement, µg/kg/d
<1000 g	20	2.7–2
1000-1500 g	18	2.4–2.7
1500-2500 g	15	2-2–25

- Zinc deficiency is associated with poor growth, increased risk of infections, skin rash, and possibly poor neurodevelopment
- Small RCT of zinc supplementation (6.6 vs 0.9 mg/kg/day) with higher NEC and mortality in placebo group; no effect on growth
- Recommend an enteral zinc intake of 2–3 mg/kg/d (400–500 µg/kg/d in PN)

Terrin G, et al. *Am J Clin Nutr.* 2013;98(6):1468-74.

Dietary Recommendations for Vitamins

- Vitamin dosage from supplementation studies demonstrating improvement of clinical outcomes in preterm infants.
- Vitamin intakes from preterm infants who do not manifest deficiency symptoms.
- Recommendations for term infants based on concentration of vitamins in mature human milk (may underestimate increased requirements of rapidly growing or sick preterm infants).
- Human milk fortifiers contain vitamins and should be used to meet the vitamin requirements of preterm infants.

Vitamin A

- Daily enteral intake of 1,332–3,330 IU/kg/day in preterm infants
- Human milk contains only 1,767 IU/L of vitamin A
  - HMFs provide an additional 700–1,100 IU/100 mL vitamin A
- Low vitamin A concentrations associated with BPD, respiratory tract infections and ROP
  - Cochrane review of additional vitamin A supplementation had small benefit of reducing risk of death or oxygen requirement at 1 month of age and risk of BPD at 36 wks PMA (NNT = 15)

BPD, bronchopulmonary dysplasia; HMF; human milk fortifier; NNT, number needed to treat; PMA, postmenstrual age; ROP, retinopathy of prematurity.

Darlow BA, et al. *Cochrane Database Syst Rev.* 2016;2016(8):CD000501.

Key Messages

- An adequate supply of iron is required for optimal brain development of preterm infants.
- Follow serum ferritin to adjust iron supplements for preterm infants who undergo repeated blood samplings and/or receive blood transfusions. Monitor zinc status in patients with high gastrointestinal fluid output (eg, ileostomy losses).
- Preterm infants are born with low levels and reduced stores of fat-soluble vitamins.

Research Priorities

- Further studies needed to ensure that high-dose zinc supplementation >3 mg/kg/day is safe and effective.
- Adequately powered trials, with clinically relevant outcomes, are needed to determine optimal intakes of microminerals and vitamins.
- Further research is required to understand optimal doses and routes of administration of fat-soluble vitamins, and the impact on the prevention of morbidity and mortality with special focus on vitamin A.

Human milk (donor vs mom’s own) and fortifiers

Feeding human milk reduces NEC risk

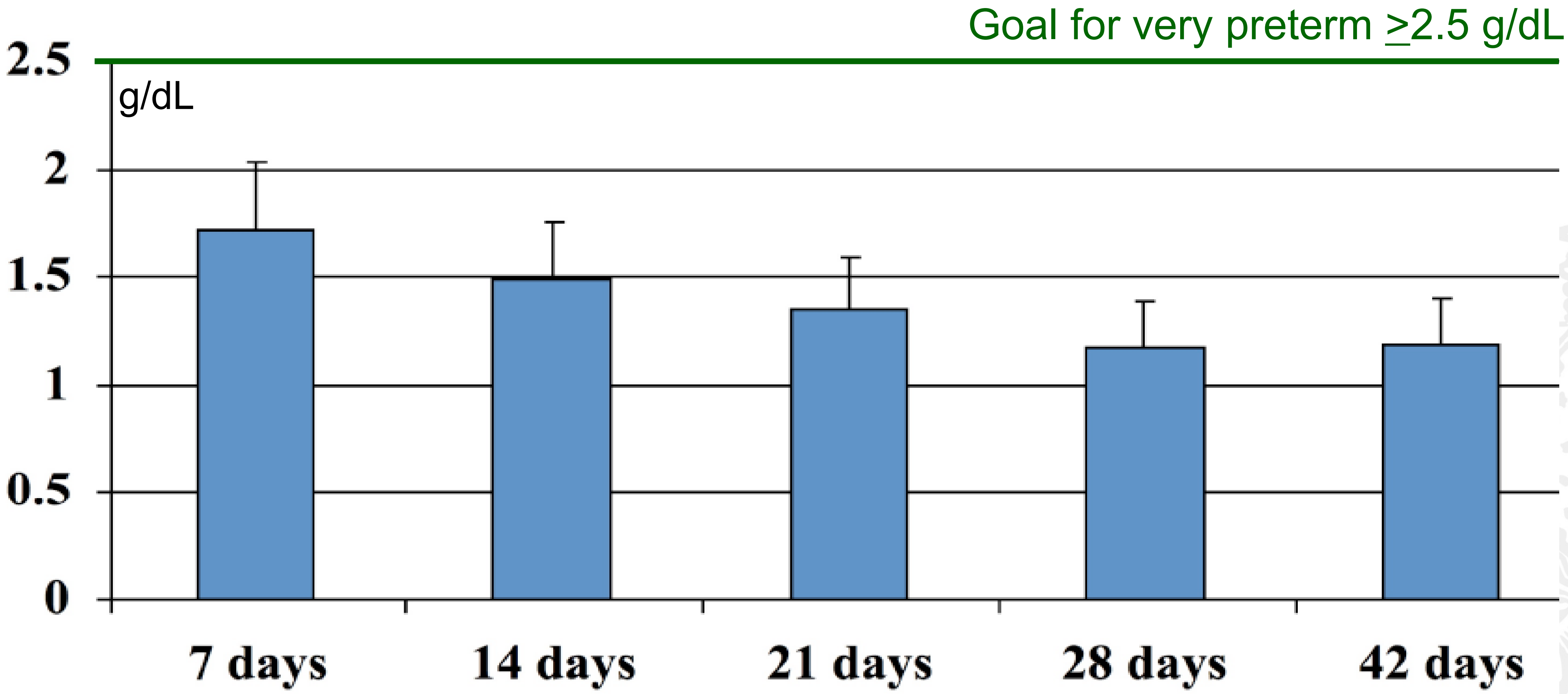
- 12 RCTs or quasi-RCTs comparing feeding with formula versus donor breast milk in 1879 preterm or LBW infants
- Formula feeding (vs. human milk):

RR NEC: 1.87 *(95% CI 1.23 to 2.85)*

NNT for 1 NEC case: 33 *(95% CI 20 to 100)*

Quigley M et al, Cochrane Database of Systematic Reviews 2019.

Protein in preterm own mothers' milk too low ➔ add fortifier *@reaching 50-100 ml/kg/d*



from Ziegler E, based on data by Lemons et al 1982
in Koletzko B et al (eds.): Nutritional Care of the Premature Infant, 1st. ed. 2014

Protein fortification of human milk improves growth in preterm infants

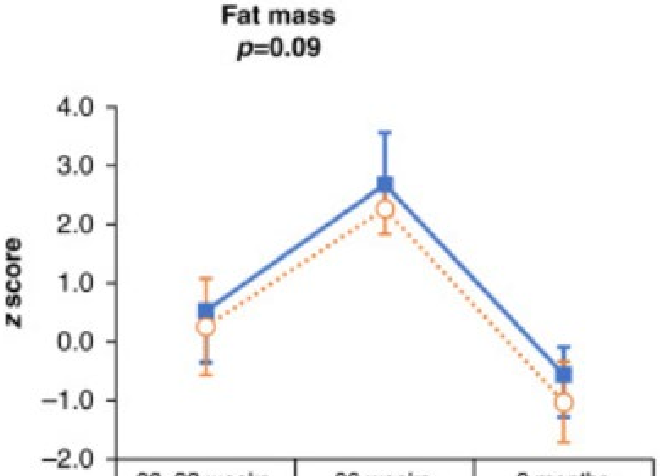
Protein fortification of human milk (6 RCTs, 204 preterms):

- Improved gain of **weight** (Δ 3.82 g/kg/day, 95% CI 2.94-4.7), **length** (Δ 0.12 cm/wk, 95% CI 0.07- 0.17), and **head circumference** (Δ 0.06 cm/wk, 95% CI 0.01-0.12)
- No NEC increase (RR 1.11, CI 0.07-17.12)

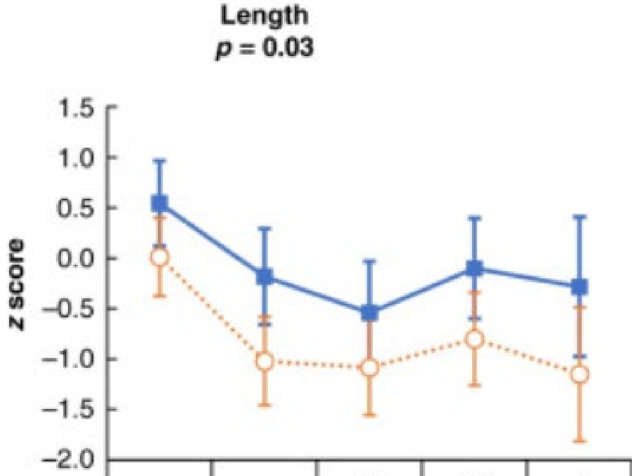
Amissah EA et al, Cochrane Database Syst Rev 2018.

RCT: adding extra protein to fortified human milk improves growth & body composition in ELBWI

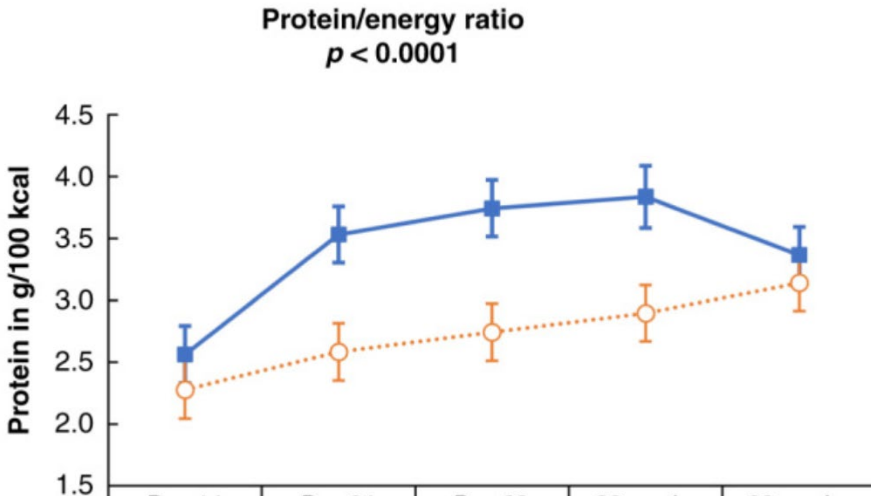
56 preterm infants, 25–28 wks GA, followed to 3 mon CA



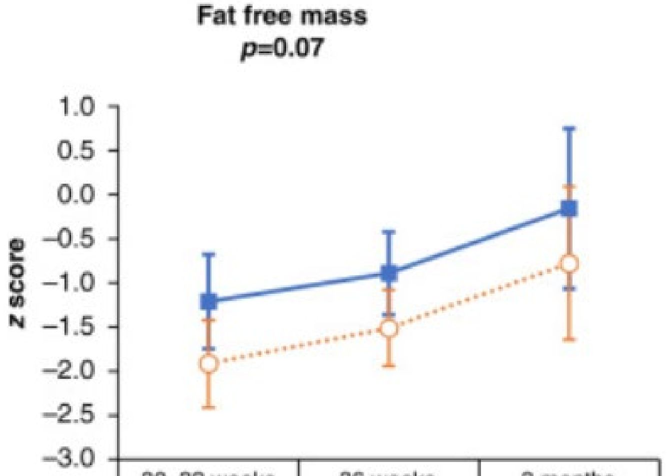
	30–32 weeks PMA	36 weeks PMA	3 months CA
High	0.5	2.7	−0.6
Standard	0.3	2.3	−1.0



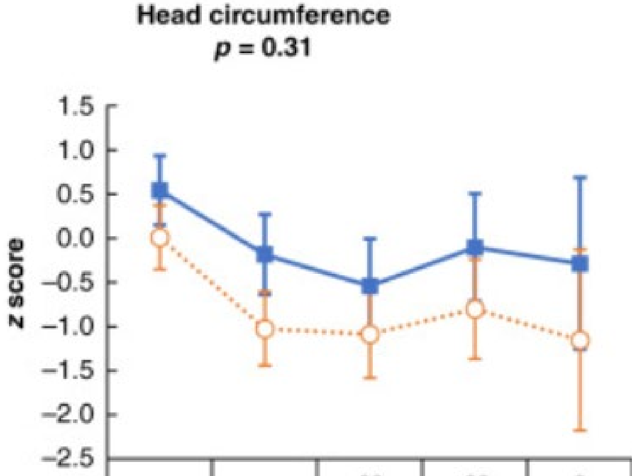
	Birth	Day 28	32 weeks	36 weeks	3 months
High	0.5	−0.2	−0.5	−0.1	−0.3
Standard	0.0	−1.0	−1.1	−0.8	−1.2



	Day 14	Day 21	Day 28	32 weeks	36 weeks
High	2.6	3.5	3.7	3.8	3.4
Standard	2.3	2.6	2.7	2.9	3.1



	30–32 weeks PMA	36 weeks PMA	3 months CA
High	−1.2	−0.9	−0.2
Standard	−1.9	−1.5	−0.8



	Birth	Day 28	32 weeks	36 weeks	3 months
High	0.5	−0.2	−0.5	−0.1	−0.3
Standard	0.0	−1.0	−1.1	−0.8	−1.2

*Salas AA et al, Ped Res . 2021 Jun 28;1-7.
doi: 10.1038/s41390-021-01628-x.*

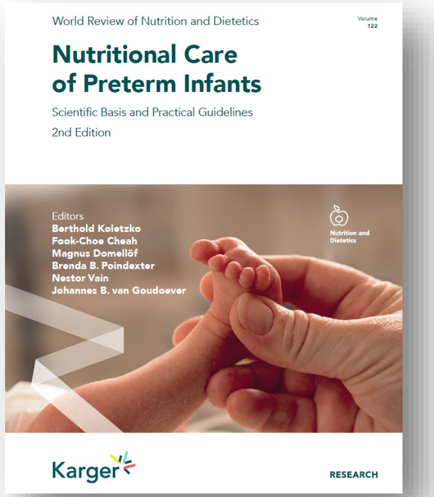
No evidence for benefit of HM-based fortifiers

- No conclusive evidence for benefit of human milk- vs. bovine milk-derived fortifier in exclusively breast milk-fed preterm infants

- Low-certainty evidence from 1 study in exclusively breast milk-fed preterm infants suggests that human milk-derived fortifiers may not change the risk of NEC, mortality, feeding intolerance, infection, or growth

Premkumar MH et al, Cochrane Database of Systematic Reviews 2019.

Fortification of human milk



- Always fortify human milk for preterms <1800 g
- Start full strength fortification when 50-100 ml/kg/d enteral feeding is well tolerated
- Bovine protein multicomponent fortifiers recommended
- No evidence for greater benefit of human milk-based fortifiers
- Aim at protein intakes >3g/kg/day

If fortifiers are unavailable/unaffordable, formula powders have been used

Pichaud JC et al, in: Koletzko B et al, Nutritional Care of Preterm Infants, 2nd. ed. 2021, World Rev Nutr Diet 122.

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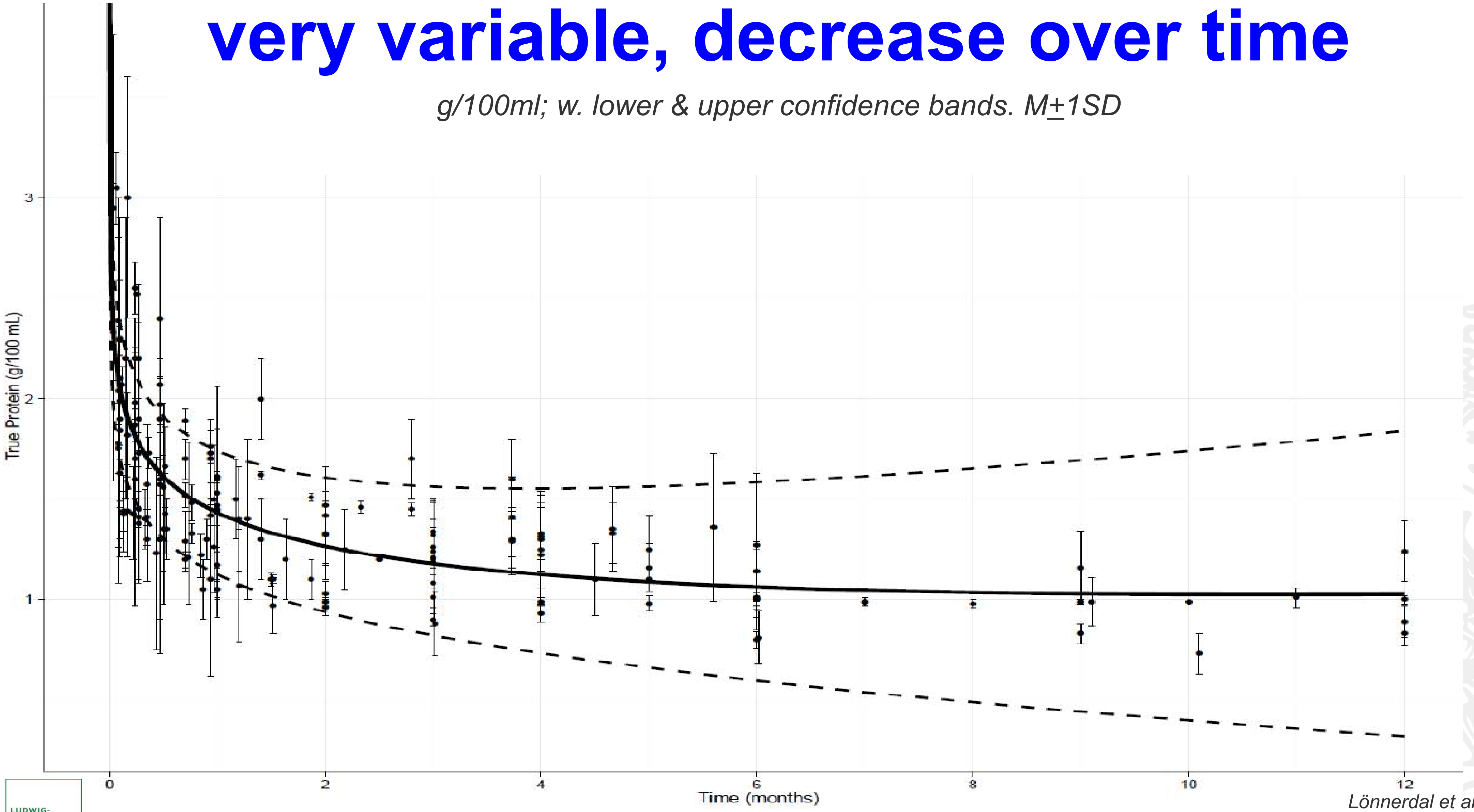
Human milk protein too low for preterms, very variable, decrease over time

g/100ml; w. lower & upper confidence bands. M±1SD



Lönnerdal et al. 2016.

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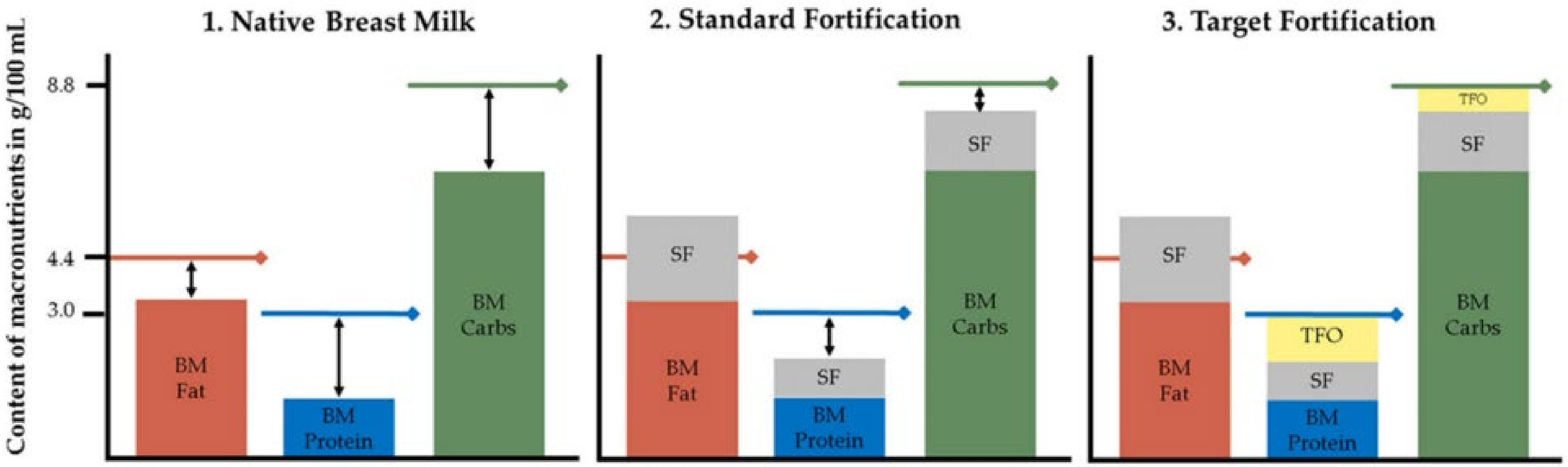
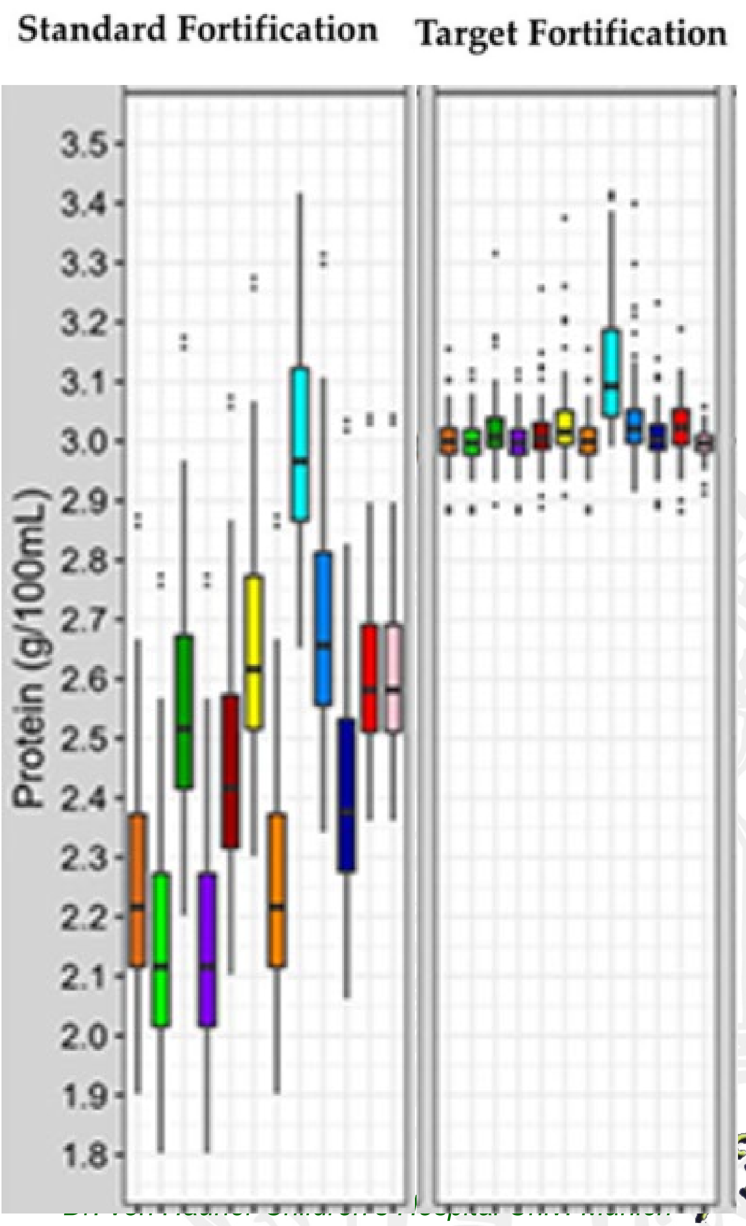
Targeted fortification based on HM analysis improves intake





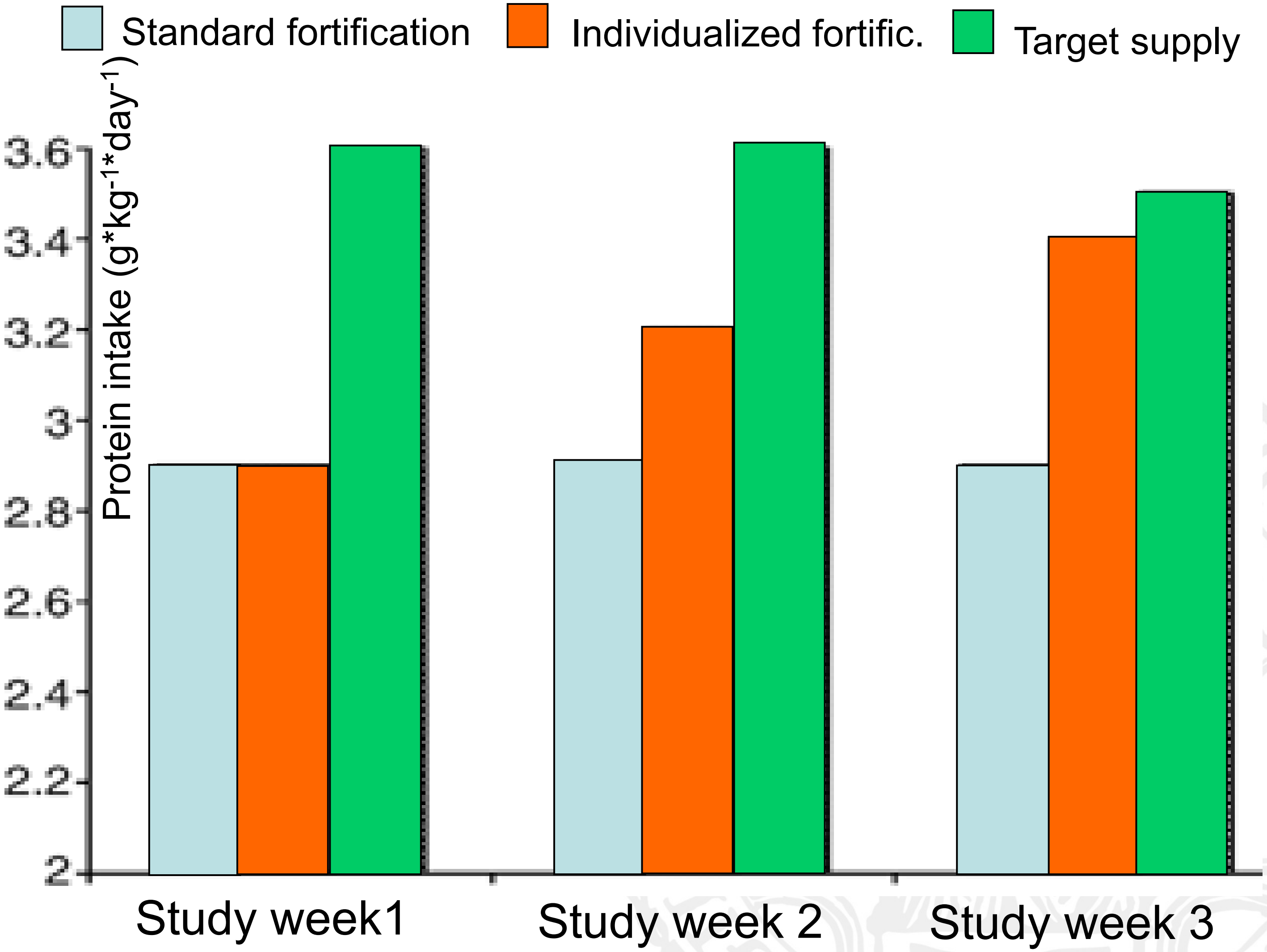
Fusch S et al, Front Nutr.. 2021 Sep 21;8:652641. doi: 10.3389/fnut.2021.652641.

Adjusted fortification: enhanced supply

Start standard fortification, 2x/wk blood urea nitrogen (BUN)

BUN mg/dL	BUN mmol/L	Adjustment
9-14	3.2-5	None
<9	<3.2	+1 Level
>14	>5	-1 Level

Fortification	g HMF/100 ml
3	6.25 + 0.8 prot
2	6.25 + 0.4 prot
1	6.25
0	5
-1	3.75
-2	2.5



Arslanoglu et al, J Perinatol 2006.

Adjusted fortification: enhanced growth

Start standard fortification, 2x/wk blood urea nitrogen (BUN)

BUN mg/dL	BUN mmol/L	Adjustment
9-14	3.2-5	None
<9	<3.2	+1 Level
>14	>5	-1 Level

Fortification	g HMF/100 ml
3	6.25 + 0.8 prot
2	6.25 + 0.4 prot
1	6.25
0	5
-1	3.75
-2	2.5

Gain	Standard	Adjusted	P
Weight (g/d)	24.8	30.1	<0.01
Length (mm/d)	1.1	1.3	n.s.
HC (mm/d)	1.0	1.4	<0.05

Arslanoglu et al, J Perinatol 2006.

Donor milk ≠ mother's own milk

Preterms 22-36 wks PCA before (n=139) vs. after (183) donor human milk bank

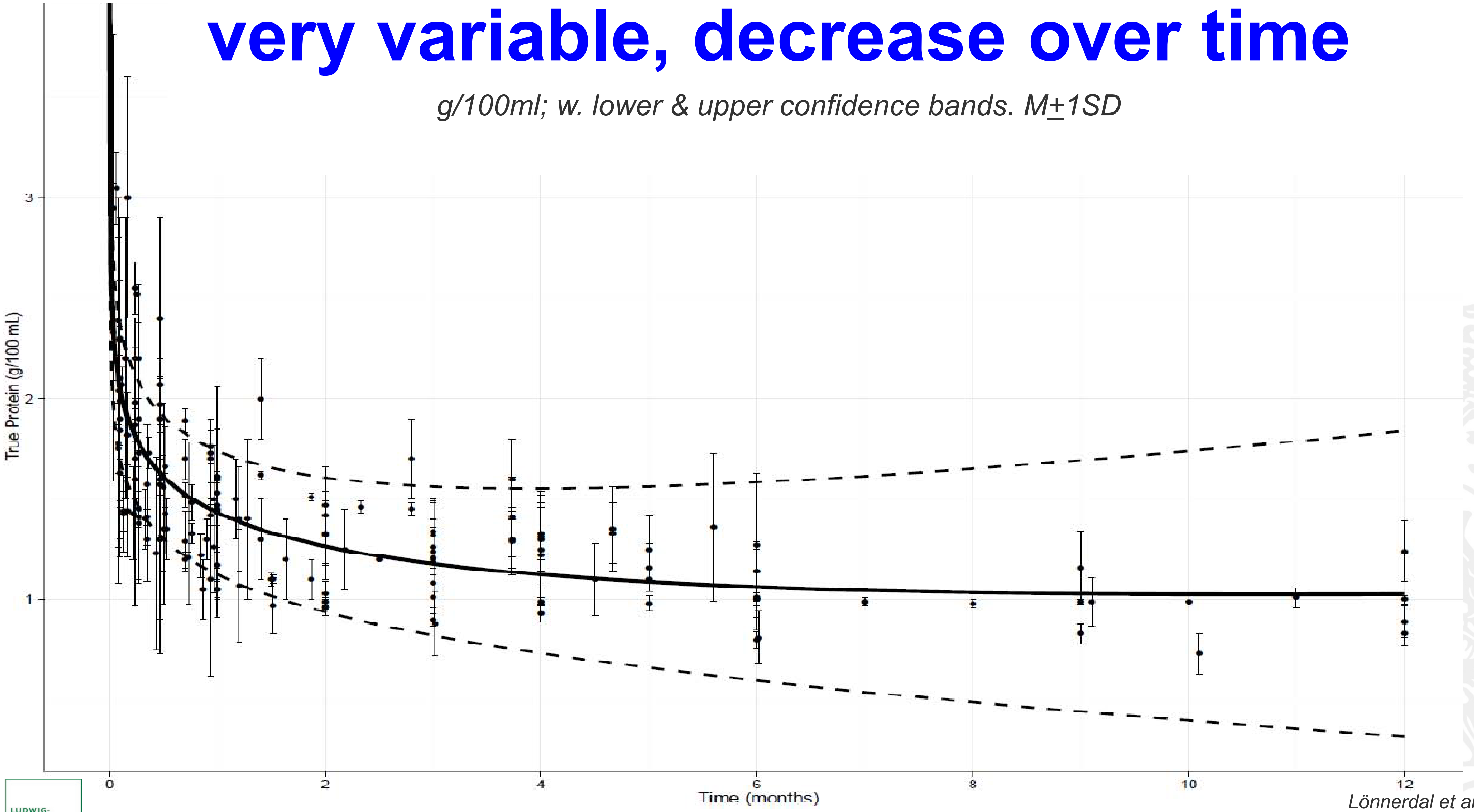
	No donor milk	Donor milk	P
Feed advance, ml/kg/d	7.4±3.5	9.9±4.5	<0.001
Time to full enteral feeds, d	21.0 (14.5–31.0)	20.0 (14.0–28.0)	n.s.
Time to regain bw, d	11.0 (8.0–14.0)	8.0 (3.0–11.0)	<0.001
SDS weight, 37 wks/discharge	−1.5 ± 0.8	−1.9 ± 0.7	<0.001

Donor milk ⇨ **lower weight gain**

Wu T et al, Matern Child Nutr. 2022, 18 Jan. DOI: 10.1111/mcn.13319.

Human milk protein too low for preterms, very variable, decrease over time

g/100ml; w. lower & upper confidence bands. M±1SD



Lönnerdal et al. 2016.

Own mother's vs. donor milk: growth differs

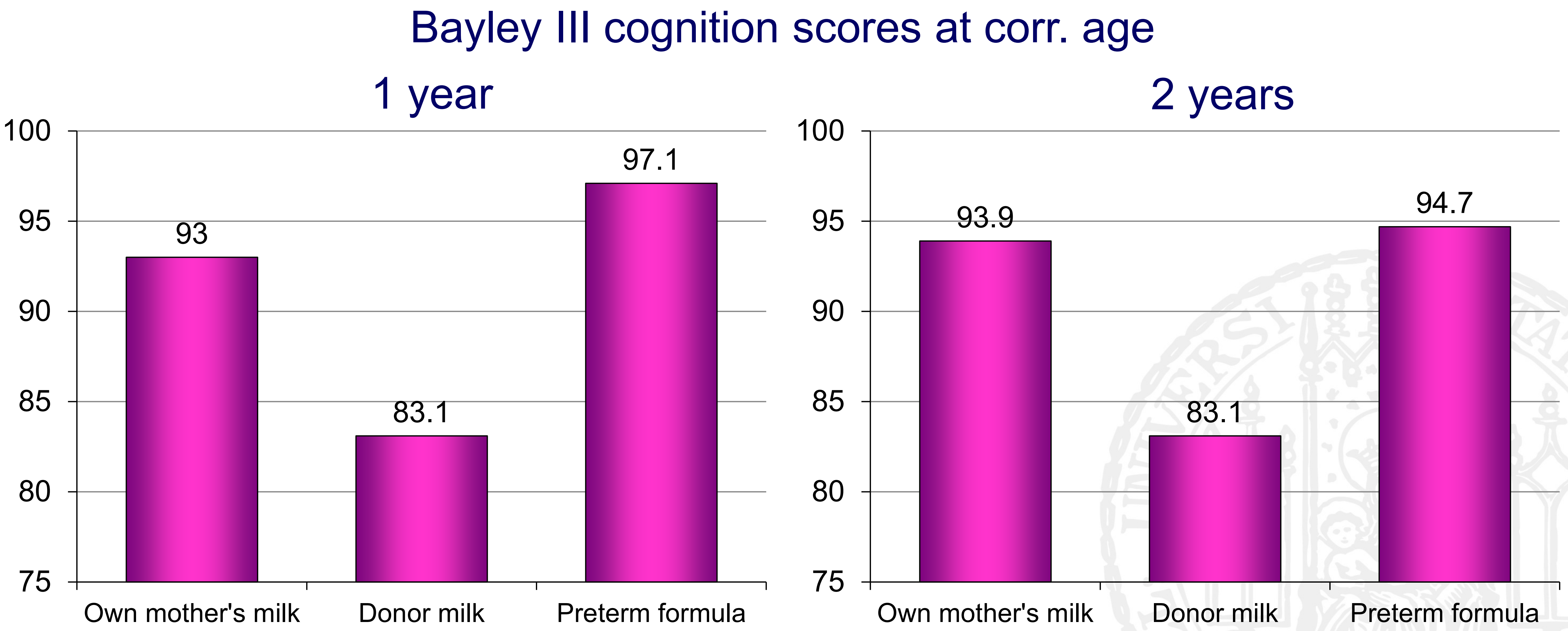
- Single-center retrospective study, 314 infants ≤32 wks GA or ≤1800 g with NICU stay ≥7 days fed fortified human milk

- Per **+10% more donor human milk** vs. own mothers' milk **-0.17 g/kg&d weight gain** to 36 weeks GA or NICU discharge

- Per **+10% more donor human milk** vs. own mothers' milk **-0.01 cm/wk** adjusted **head circumference**

Brownell et al, JPGN 2018;67:90-6. doi: 10.1097/MPG.0000000000001959.

Cognition: donor vs. own mother's milk differ



81 preterms, GA 27,1 wks, Tufts Med Center Boston. Donor milk from Mother's Milk Bank of New England

Madore et al, Clin Ther 2017.

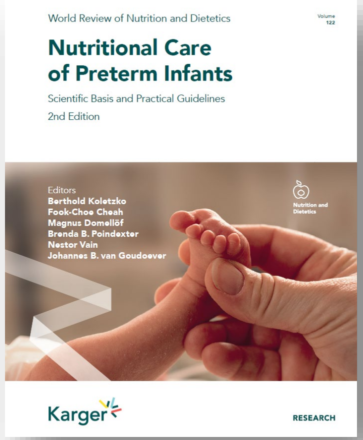
Mother's own milk = preferred choice

- **Fortified mother's own milk** (MOM) = **best option** for preterms
- Donor human milk from a milk bank with established safety standards is the second-best choice, but not the same as MOM
- Key benefit: risk reduction for necrotizing enterocolitis (NEC)

Koletzko B, Cheah F-C, Domellöf M, Poindexter BB, Vain N, van Goudoever JB (eds): Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines. World Rev Nutr Diet. Basel, Karger, 2021, vol 122, pp 212–224 (DOI: 10.1159/000514733)

Mother's Own Milk and Donor Milk

Regina Valverde[a] Nestor Alejandro Dinerstein[b] Nestor Vain[c]



American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Promoting Human Milk and Breastfeeding for the Very Low Birth Weight Infant

Margaret G. Parker, MD, MPH,[a] Lisa M. Stellwagen, MD,[b,c] Lawrence Noble, MD,[d,e] Jae H. Kim, MD, PhD,[f] Brenda B. Poindexter, MD,[g] Karen M. Puopolo, MD, PhD,[h] SECTION ON BREASTFEEDING, COMMITTEE ON NUTRITION, COMMITTEE ON FETUS AND NEWBORN

Valverde R et al, In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.
American Academy of Pediatrics. Peds. 2021148:e2021054272.

Mother's own milk = preferred choice

- Initiate milk expression soon after birth
  (RCT, 180 mothers: no diff. with first expression at 1, 1-6 or 3-6 h after birth)

- Frequent milk expression *(≥4-7 times/day)*
  ⇨ longer duration of milk production, greater milk volumes

- Discourage informal milk sharing
  (risk of contamination with infectious agents, drugs; suboptimal handling/storage)

- Establish NICU protocols and parent education on milk pump handling/cleaning, milk storage, handling & transport

Parker MD, et al. Pediatrics. 2021;148(5):e2021054272.

Fortification of human milk: research needs

- Multi-nutrient human milk fortification improves in-hospital preterm growth, but lacking data on later neurodevelopment
- More evidence needed on timing of introducing fortifier, routine fortification of feeds post-discharge, routine use of fortifiers made from human vs. bovine milk

Beggs MR et al, Acta Paediatr. 2022 Feb 10. doi: 10.1111/apa.16283.

Enteral nutrition in very low and extremely low-birth-weight infants

Practice of Enteral Nutrition

- Enteral nutrition and postnatal growth of preterm infants linked with outcomes but few intervention studies to promote growth in NICU have provided information on later outcomes.
- Standardized feeding protocols improve outcomes of preterm infants and simply having a feeding protocol is more important than the individual components of the protocol.
- Will review current evidence to guide enteral feeding among very preterm infants.

Bozzetti V, Martin CR. *World Rev Nutr Diet.* 2021;122:265-280.
Kaplan HC, Poindexter BB. *World Rev Nutr Diet.* 2021;122:289-300.

Timing of Initiation of Enteral Feedings

- Benefits of early minimal enteral feeding/trophic feeding (<25 mL/kg/d) well-established
- Early introduction of human milk reduces need for PN and risk of late-onset sepsis
- Cochrane comparing early vs late introduction of feedings found that introduction of feedings beyond 4 days after birth did not reduce risk of developing NEC
  - Caution given limited number of ELBW infants included
- Presence of umbilical catheters or inotropes no longer contraindications to initiate enteral feeding

Morgan J, et al. *Cochrane Database Syst Rev.* 2013(5):CD001970.
Morgan J, et al. *Cochrane Database Syst Rev.* 2014(12):CD001970.

Early Progressive Feeding in ELBW Infants

P: Extremely preterm infants ≤ 28 wks

I: Early progressive feeding without trophic feeding

C: 4-day course of trophic feeding

O: Number of full enteral feeding days in first month

T: 36 wks PMA outcomes including death, NEC, culture-proven sepsis, growth

✦ Early progressive feeding increases the number of full enteral feeding days in the first month and reduced days on PN without an increase in NEC

Salas-Huetos A, et al. *Am J Clin Nutr.* 2018;108(5):953-962.

You are developing a standardized feeding guideline for your unit for VLBW infants. What rate of enteral feeding advancement would you incorporate into your guideline?

Speed of Advancing Enteral Feeding Volumes

- Slow (up to 24 mL/kg) vs faster (30–40 mL/kg) rates of advancing enteral feeds on incidence of NEC
- 10 RCTs included in analysis; n=3753 (2804 infants in 1 large trial)
  - Infants who had slow rates of feeding advancement took longer to establish full enteral feedings (1 to 5 days)
  - No statistically significant effect on risk of NEC or mortality
- Faster rates of advancement (30 mL/kg) of enteral feeding does not affect risk of survival without moderate or severe neurodevelopmental impairment (Dorling, *NEJM* 2019)

Oddie SJ, et al. *Cochrane Database Syst Rev.* 2017;8(8):CD001241.
Dorling J, et al. *N Engl J Med.* 2019;381(15):1434-1443.

Feeding Modality

- Limited evidence re OG vs NG
- Observational studies of transpyloric feeding associated with less frequent apnea/bradycardia and lower risk of death or BPD
- Transpyloric feeding is not physiologic and fortified/high-osmolarity nutrition can induce bloating/dumping

◈ Evaluation of transpyloric feeding in setting of modern neonatal practice is clearly an opportunity for further studies

NG, nasogastric tubes; OG, orogastric tube.

Checking Gastric Residuals—Not Recommended

- Common practice in many NICUs despite paucity of evidence to support utility in the diagnosis of feeding intolerance or NEC
- No evidence to support discontinuation of enteral feeds based only on gastric residuals
- RCT of 61 infants found infants without routine gastric residual evaluation reached full enteral feedings 6 days earlier and had fewer CVL days than infants randomized to routine gastric residual measurements (Torrazza and Neu, *J Perinatol* 2015)
- Not checking residuals can be incorporated into standardized feeding guidelines

CVL, central venous line.

Torrazza RM, et al. *J Perinatol.* 2015;35:57-60.

Key Messages

- The primary objective of enteral nutrition is to meet nutrient needs, support adequate growth, and limit duration of parenteral nutrition.
- The timing of introduction and the rate of advancement of enteral feedings for very preterm or VLBW infants influence growth and later outcomes.
- It is important to balance the negative effect of withdrawing EN because of suspected feeding intolerance with the risk of undernutrition and impairment of gastrointestinal physiological, endocrine, and metabolic maturity.

EN, enteral; VLBW, very low birth weight.

Research Priorities

- Further RCTs could provide more precise estimates of the effects of different nutritional delivery strategies (intragastric vs transpyloric, bolus vs continuous) on important clinical outcomes.
- More studies including ELBW and IUGR infants are needed.

ELBW, extremely low birth weight; IUGR, intrauterine growth restriction.

Multidisciplinary approach and audit nutrition in preterms

Impact of Multidisciplinary Approach to the Implementation and Audit of Nutrition

- Nutrition is the cornerstone for improving neonatal outcomes.
- Multidisciplinary approach to focus clinical practice on:
  - Macro- and micronutrient intake guidelines
  - Technical aspects
  - Sensory and behavioral aspects
- NICUs must implement policies, procedures and guidelines that help to ensure safe and effective nutrition and conduct regular audits in order to ensure high-quality practice.

Kaplan HC, Poindexter BB. *World Rev Nutr Diet.* 2021;122:289-300.
Embleton N, Granger C. *World Rev Nutr Diet.* 2021;122:301-311.

Multidisciplinary Teams

Role	Roles within team
Parents	Provide MOM, understand need for supplements/fortifiers, determine outcomes that matter most
Nurses	Help mothers express breast milk, conduct growth measurements
Pharmacist	Compounding/delivery of PN, compatibility issues for coinfusion of PN and medications
Dietitian	Review intake, growth, and advise on use of supplements, fortifiers, specialized formula
Speech	Transition to oral feedings, safety of swallowing, support for infants unable to establish oral feeding
OT/PT	NICU environment, positioning to promote neurodevelopment
Lactation	Assist with milk expression, support for mothers/nursing staff

MOM, mother's own milk; PN, parenteral nutrition.

Embleton N, Granger C. *World Rev Nutr Diet.* 2021;122:301-311.

Evidence for Multidisciplinary Teams

- Implementation of nutrition MDT can improve nutrient intake and growth, reduce duration of PN and reduce length of NICU stay (Johnson, *BMJ* 2017).
- MDTs that develop standardized feeding protocols and audit successful implementation may reduce rates of NEC ($400–500K per case) (Nathan, *J Perinatol* 2018).
- Standards of Care: European Foundation for Care of the Newborn Infant, AAP Guidelines for Perinatal Care

MDT, multidisciplinary team; PN, parenteral nutrition.

Johnson MJ, et al. *BMJ Open.* 2017;7:e017727.
Nathan AT, et al. *J Perinatol.* 2018;38:742-750.

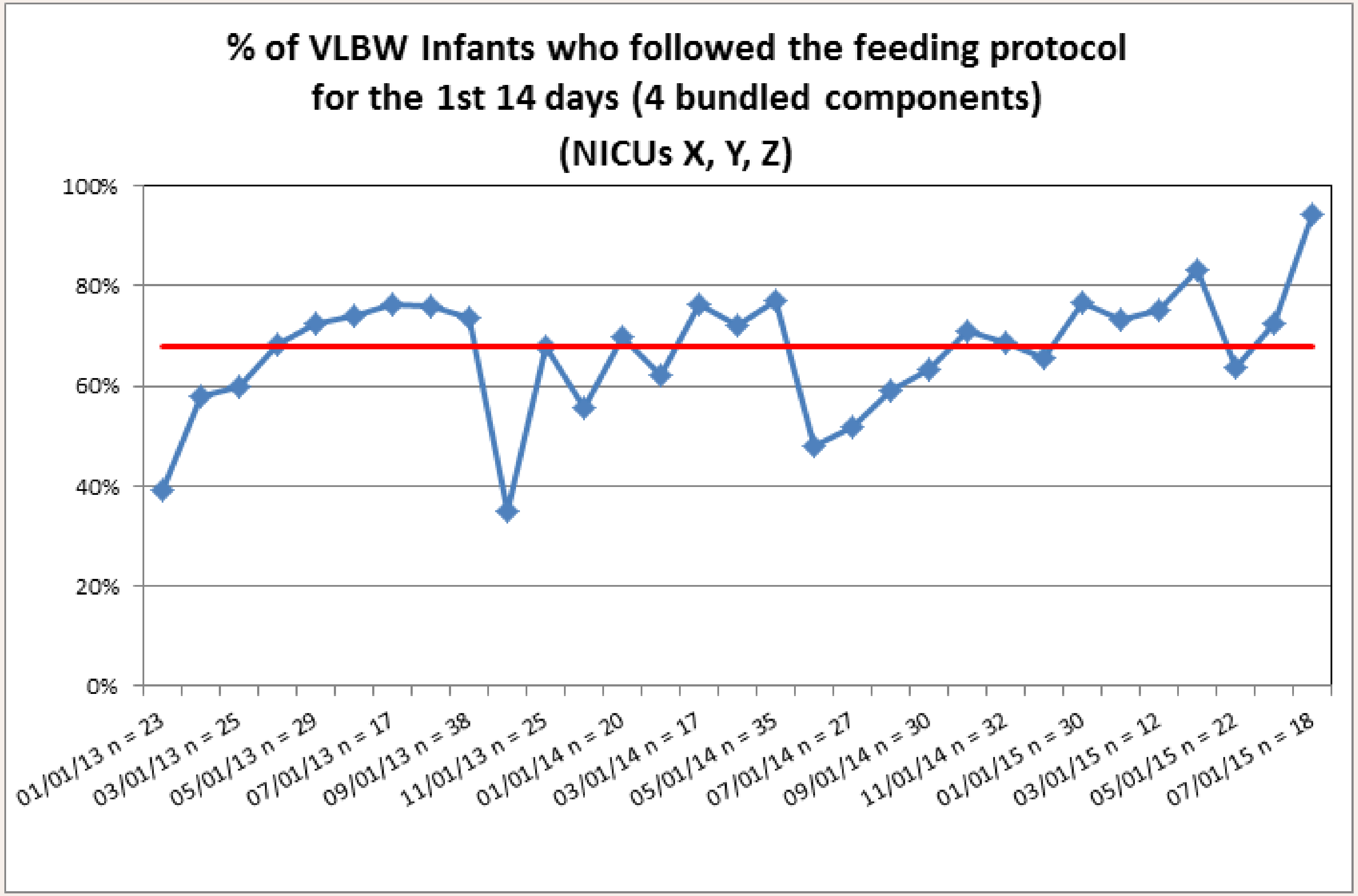
Auditing Guidelines

Standard	Target and Source
All mothers receive written information on benefits of HM within 48 hrs of admission	100%; survey mothers or notes in chart
Preterm receive oral colostrum within the 48 hrs	>90%; some mothers with delayed lactation or ill; nursing or medical records
Enteral feedings are increased by 20-30 mL/kg/d until full feedings are achieved	Infant records; Pareto chart to understand reasons for deviation from guideline
Use of donor milk when insufficient MOM	Infant record
Support and advice for continued breast milk expression	100%; can track maternal milk supply at milk depot

SMART aims: Specific, Measurable, Assignable, Realistic, Time-related

HM, human milk; MOM, mother's own milk.

Measuring and Monitoring the Process



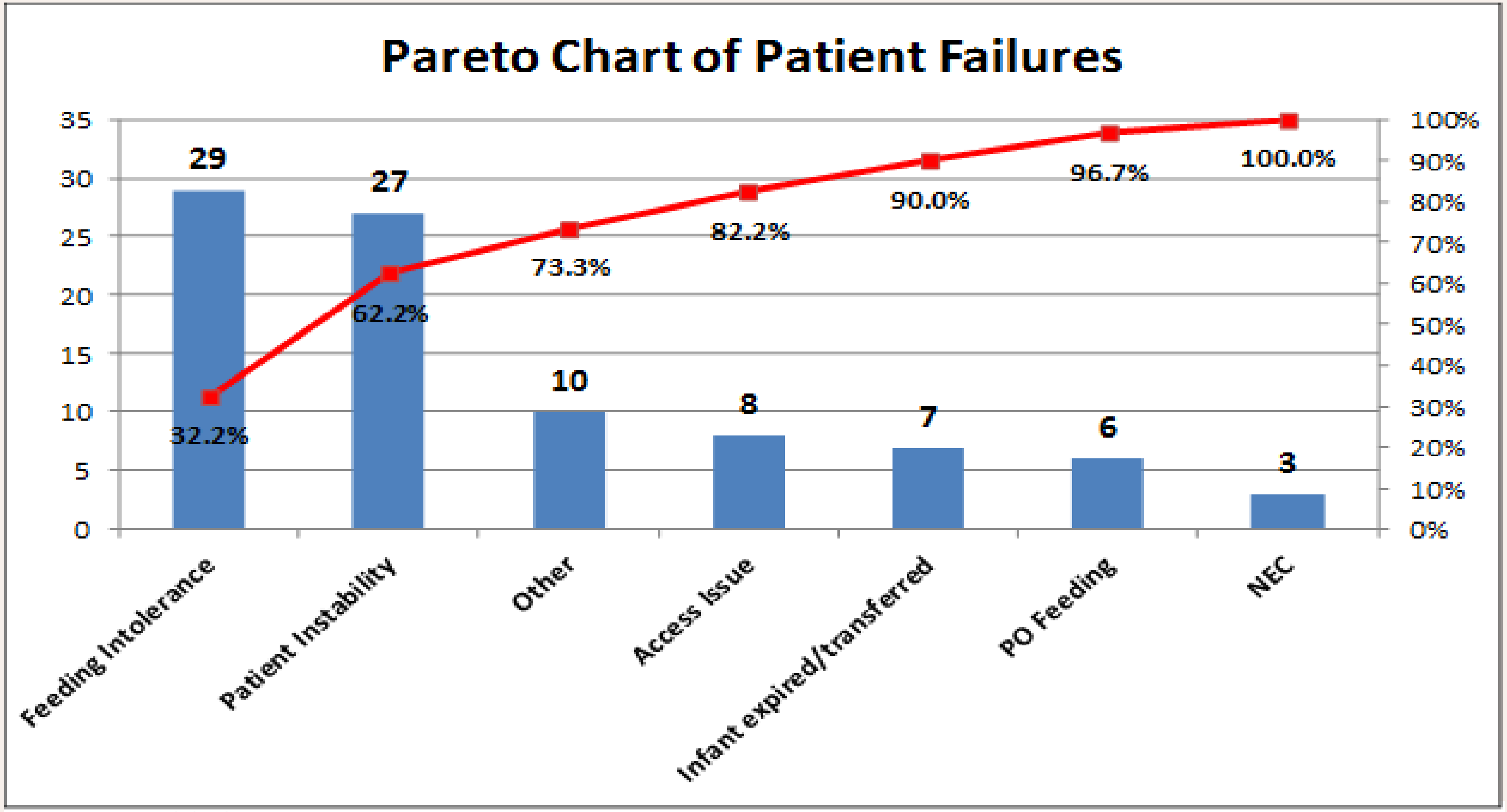
Kaplan HC, Poindexter BB. *World Rev Nutr Diet.* 2021;122:289-300.

Understanding Failures

- Failures are an opportunity to learn… compliance failures may reflect:
  - Appropriate customization for a particular patient's characteristics or value—some patients require customized care!
  - Important considerations that were missed when developing the standardized protocol (may lead to revisions in guideline)
  - Lack of buy-in among providers
  - Barriers to use of the standardized protocol
  - Lack of awareness among providers
- Use a Pareto chart to examine your failures and how they change over time

Kaplan HC, Poindexter BB. *World Rev Nutr Diet.* 2021;122:289-300.

Audit Failures over Time



- Staff failures (compliance issues)
- Patient failures (clinical symptoms or situations)

Kaplan HC, Poindexter BB. *World Rev Nutr Diet.* 2021;122:289-300.

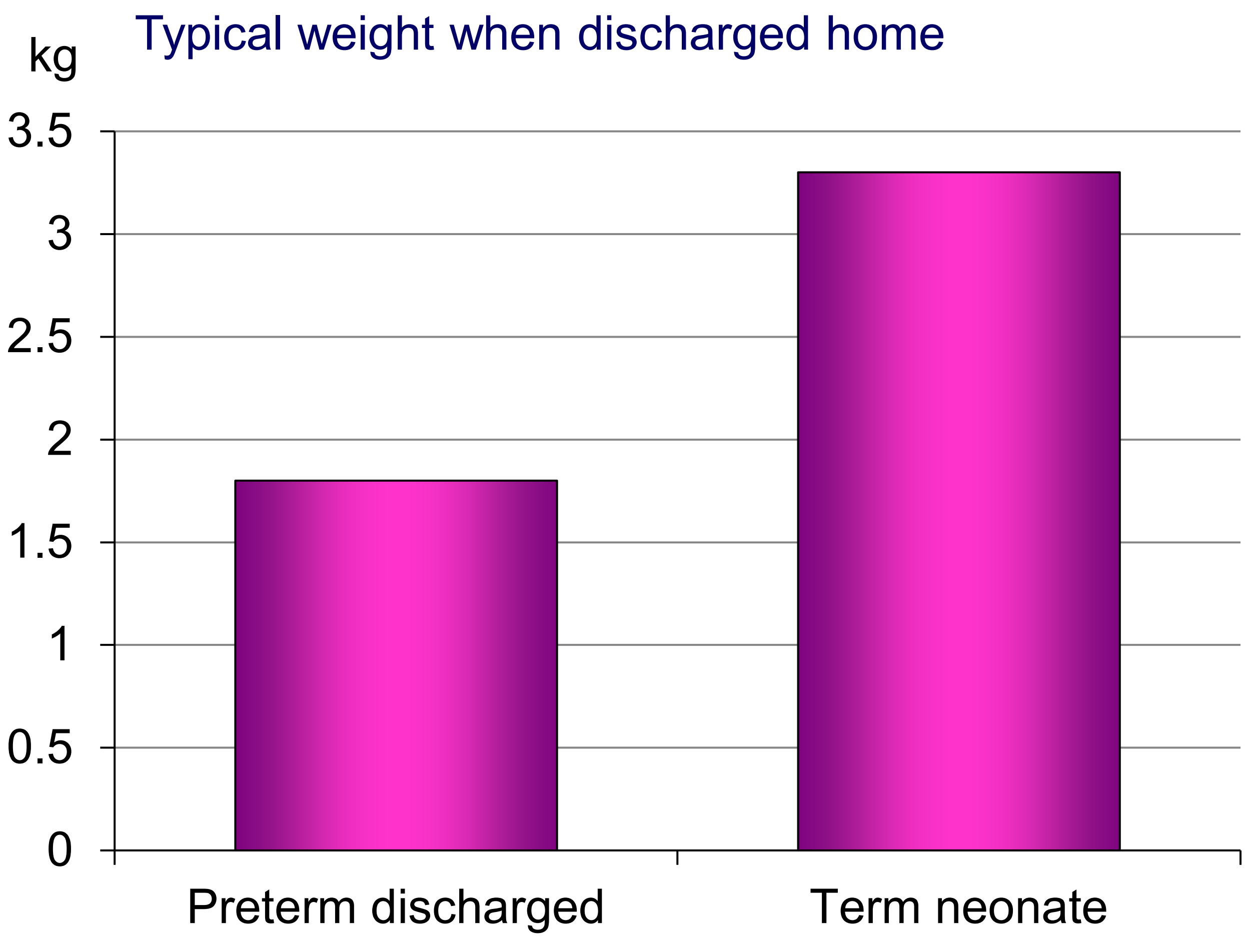
Key Messages

- The implementation of a nutrition multidisciplinary team within the NICU is key to improving key outcomes for preterm infants.
- The design, implementation, and maintenance of a standardized feeding protocol requires broad, multidisciplinary effort with engagement of all stakeholders including medical providers, dietitians, lactation consultants and parents.
- Multidisciplinary teams must promote a holistic approach to the assessment of nutritional status.
- Regular audit of practice against standards of care ensures that outcomes are optimized, and key areas for improvement are identified.

Embleton N, Granger C. *World Rev Nutr Diet.* 2021;122:301-311.

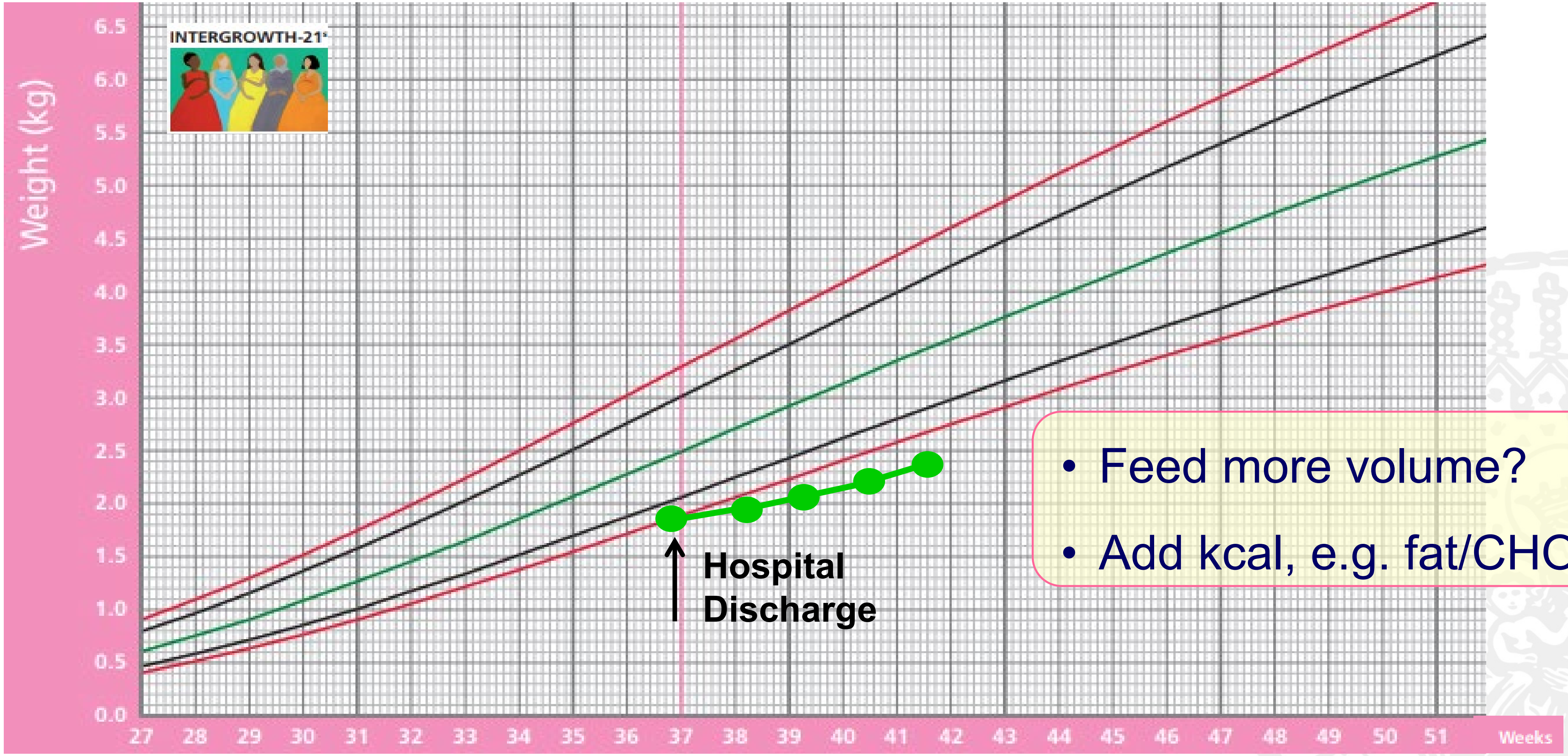
Feeding after discharge

How to feed after discharge?



- Preterms at discharge: ≈55% of term baby's weight
- Lower nutrient stores & higher needs than term infants
  e.g. protein, iron, other micronutrients, LC-PUFA
- Unfortified breastfeeding / standard infant formula meet needs of term infants, but not optimal for preterms

Growth faltering after hospital discharge



- Feed more volume?
- Add kcal, e.g. fat/CHO?

Growth after discharge: no excessive fatness

- Weight gain through excessive fat accretion not desirable
- Avoid overfeeding empty calories that support fat deposition *(sugar, starch, fat)*

Photo: © Berthold Koletzko

Koletzko B, Li Z. Feeding after discharge. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

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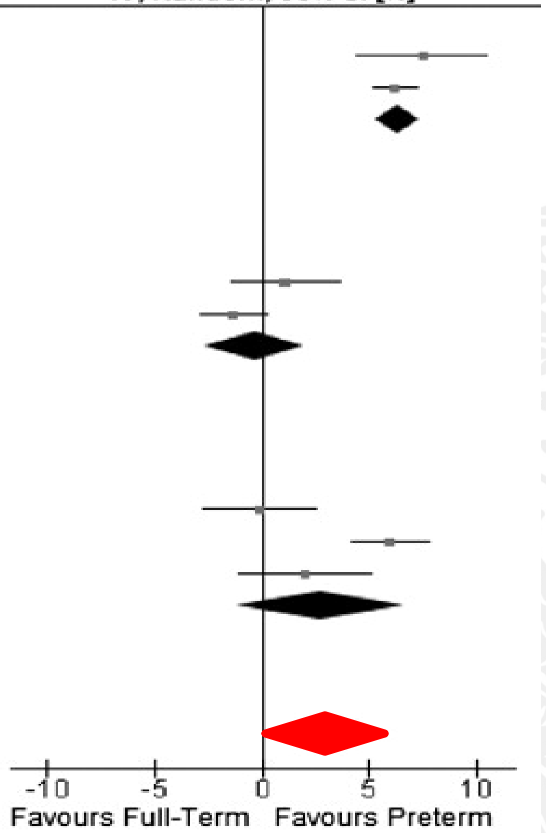
Higher body fat% at term in preterm than term infants: systematic review

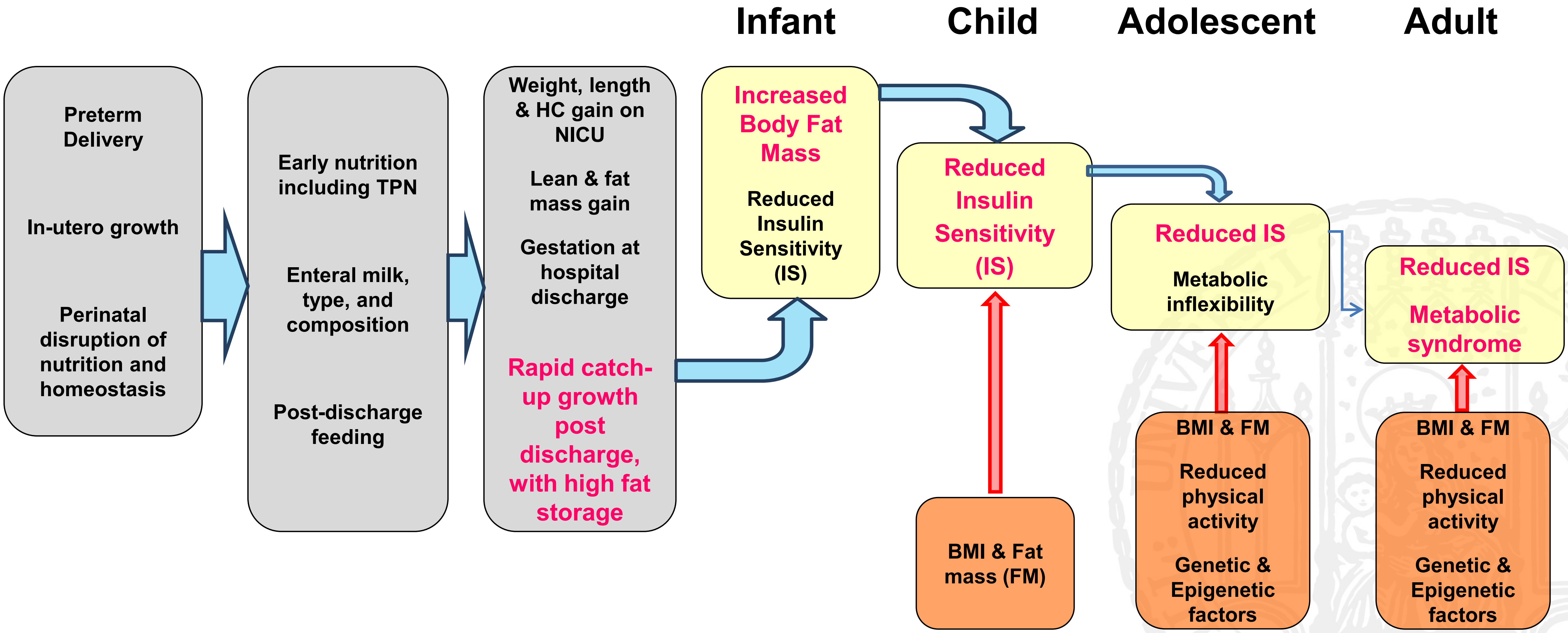
Study or Subgroup	Preterm Mean [%]	Preterm SD [%]	Preterm Total	Term Mean [%]	Term SD [%]	Term Total	Weight	Mean Difference IV, Random, 95% CI [%]
ADP								
Mcleod 2009	17	2.5	20	9.5	5.4	14	13.4%	7.50 [4.47, 10.53]
Roggero 2009	14.8	4.4	159	8.6	3.7	87	15.5%	6.20 [5.16, 7.24]
Subtotal (95% CI)			**179**			**101**	**28.8%**	**6.34 [5.36, 7.32]**
Heterogeneity: I² = 0%								
Test for overall effect: Z = 12.67 (P < 0.00001)								
MRI								
Olhager 2003	18.1	1.4	8	17	3.6	9	14.0%	1.10 [-1.44, 3.64]
Uthaya 2005	17	4	38	18.3	2.5	29	15.1%	-1.30 [-2.86, 0.26]
Subtotal (95% CI)			**46**			**38**	**29.1%**	**-0.32 [-2.63, 1.99]**
Heterogeneity: I² = 60%								
Test for overall effect: Z = 0.27 (P = 0.79)								
DXA								
Ahmad 2010	11.1	5.2	20	11.2	4.1	39	13.9%	-0.10 [-2.72, 2.52]
Atkinson 1994	22	6	69	16	5	87	14.9%	6.00 [4.24, 7.76]
Fusch 1999	18	8	52	16	7	41	13.3%	2.00 [-1.05, 5.05]
Subtotal (95% CI)			**141**			**167**	**42.1%**	**2.74 [-1.23, 6.70]**
Heterogeneity: I² = 87%								
Test for overall effect: Z = 1.35 (P = 0.18)								
Total (95% CI)			**366**			**306**	**100.0%**	**3.06 [0.25, 5.88]**
Heterogeneity: I² = 93%								
Test for overall effect: Z = 2.13 (P = 0.03)								

Mean Difference IV, Random, 95% CI [%]



Johnson et al. Pediatrics 2012;130:e640-e649.

Rapid growth with excessive body fat ⇨ risk for later metabolic disease



Modified after Tinnion R et al. Arch Dis Child. 2014;99:362ff.

Growth after discharge: no excessive fatness

- Weight gain through excessive fat accretion not desirable
- Avoid overfeeding empty calories that support fat deposition *(sugar, starch, fat)*
- Low protein:energy ratio ⇨ body fatness
- High dietary density of protein & other essential nutrients

Photo: © Berthold Koletzko

Koletzko B, Li Z. Feeding after discharge. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

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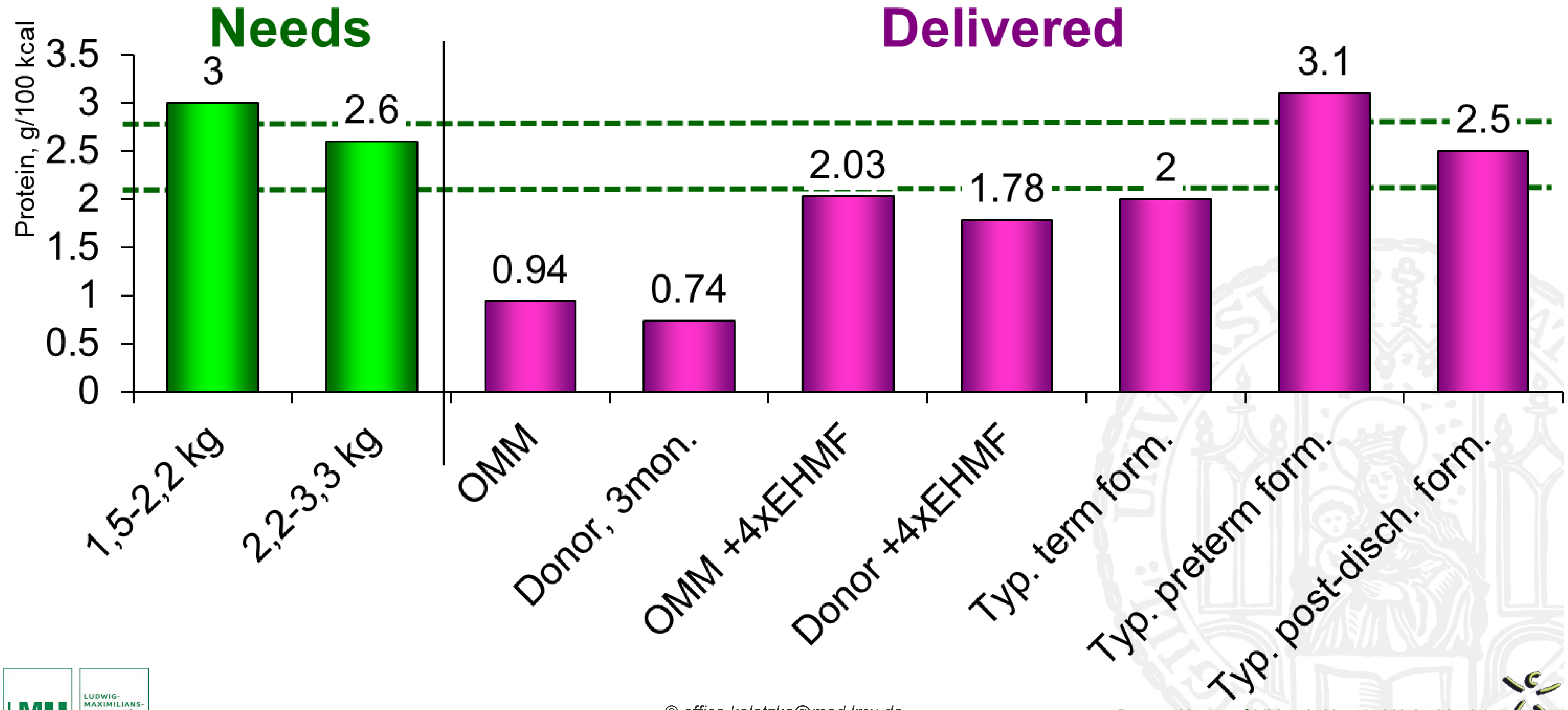
Protein & energy supply to match fetal growth

Weight (g)	500-1000	1000-1500	1500-2200	2200-3000
Fetal wt gain (g/kg/d)	19.0	17.4	16.4	13.4
Protein (g/kg/d)	**4.0**	**3.9**	**3.7**	**3.4**
Energy (kcal/kg/d)	106	115	123	130
Protein/100kcal (g/100 kcal)	**3.8**	**3.4**	**3.0**	**2.6**

Ziegler, World Rev Nutr Diet. 2014.

Protein/energy ratio after discharge



Nutrient-enriched formula for preterm infants after hospital discharge

- 16 trials with 1251 preterms on nutrient-enriched formula (post-discharge or preterm formula) vs. standard formula
- No consistent evidence on growth effects to 12-18 mon. with "post-discharge formula" (≈74 kcal/dl) vs standard (≈67 kcal/dl)
- Higher growth rates with **"preterm formula" (≈80 kcal/dl)** vs standard: weighted mean differences at 12-18 mon. corr. age **≈500 g, 5-10 mm length, 5 mm head circumference**
- Few trials on neurodevelopment, no sign. differences @18 mon. CA

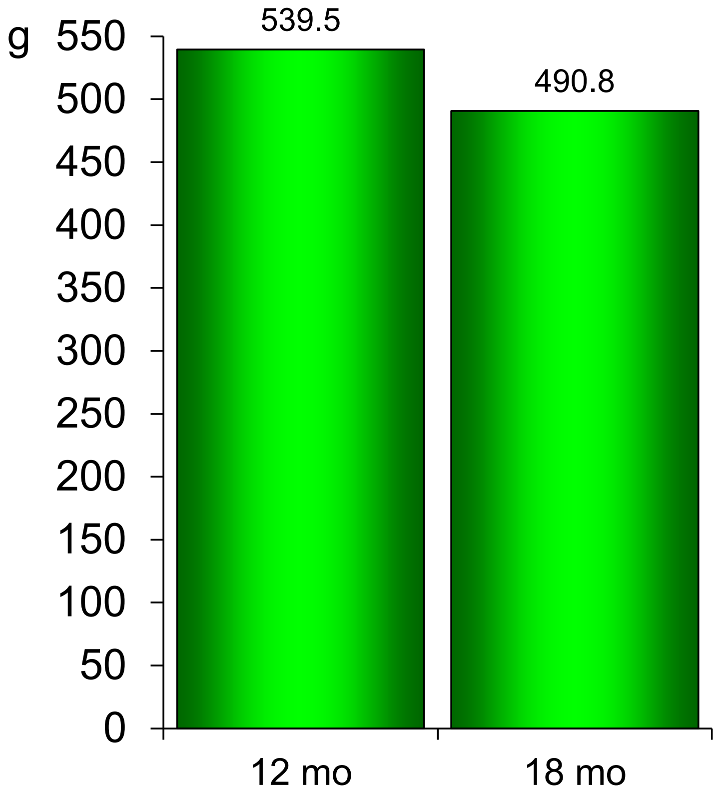
Young et al, Cochrane Database Syst Rev 2016.

Nutrient-rich formula post discharge & growth

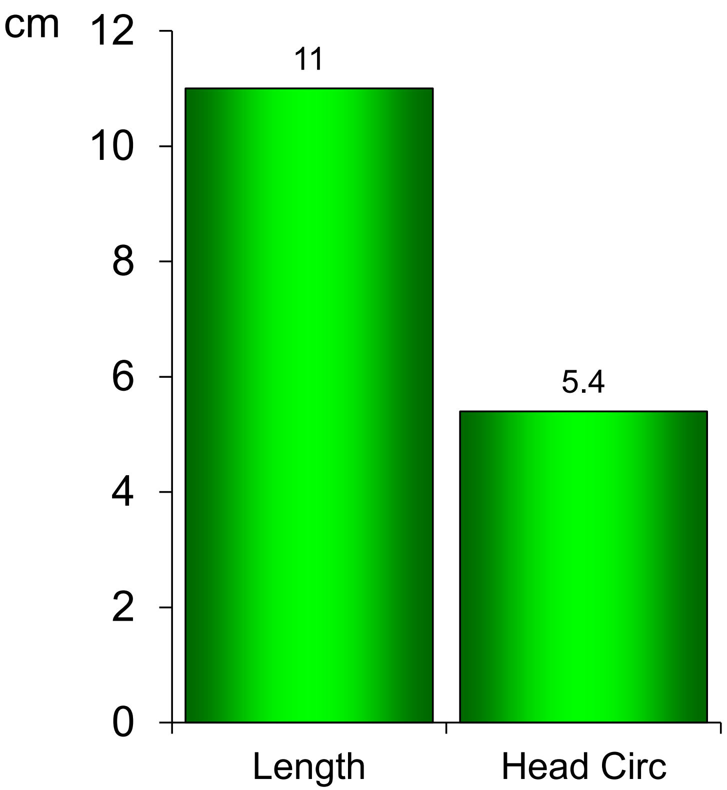
Cochrane review: 16 trials, 1251 preterms: preterm or post-discharge vs. standard formula

Preterm vs. Term Formula

Weight benefit
at 12 &18 mon

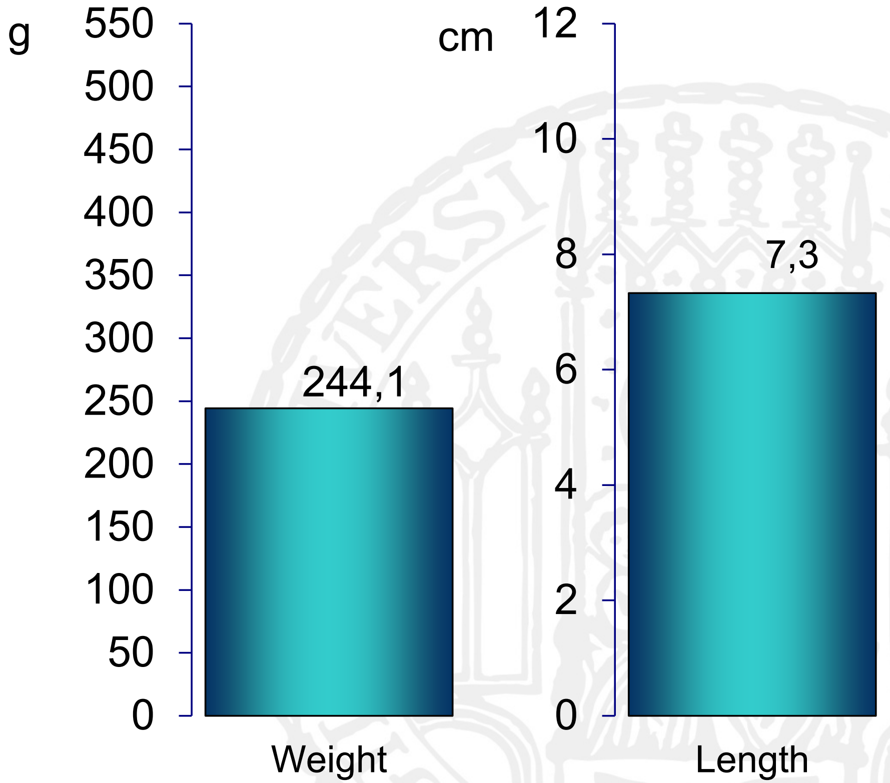


Length & HC benefit
at 18 mon



Post-Discharge vs Term F.

Weight & Length Benefit
at 9 mon



Young et al, Cochrane Database Syst Rev 2016.

Macronutrient intake and body composition

- 50 preterms, 28±1.7 wks, 1175±296 g. Body composition @ 34-37weeks PMA (PEA POD)
- **Protein:carbohydrate ratio** ⇨ strongest nutrient predictor of **lean body mass** *(adj. for birthweight, birthweight z-score & PMA)*

Protein:Carboh. ratio	Lean mass effect	R *overall model*	P
Days 1-3	**102 g/0.1**	0.869	0.006
Days 1-7	**137 g/0.1**	0.863	0.015
Day1-Week34	**318 g/0.1**	0.866	0.009

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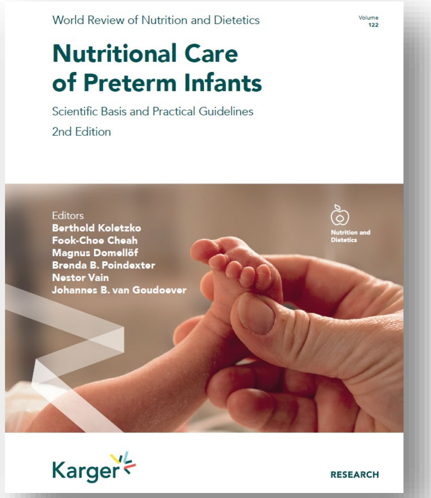
Lingwood BE et al, Bnit J Nutr 2020;123:800-6.

Protein Supply



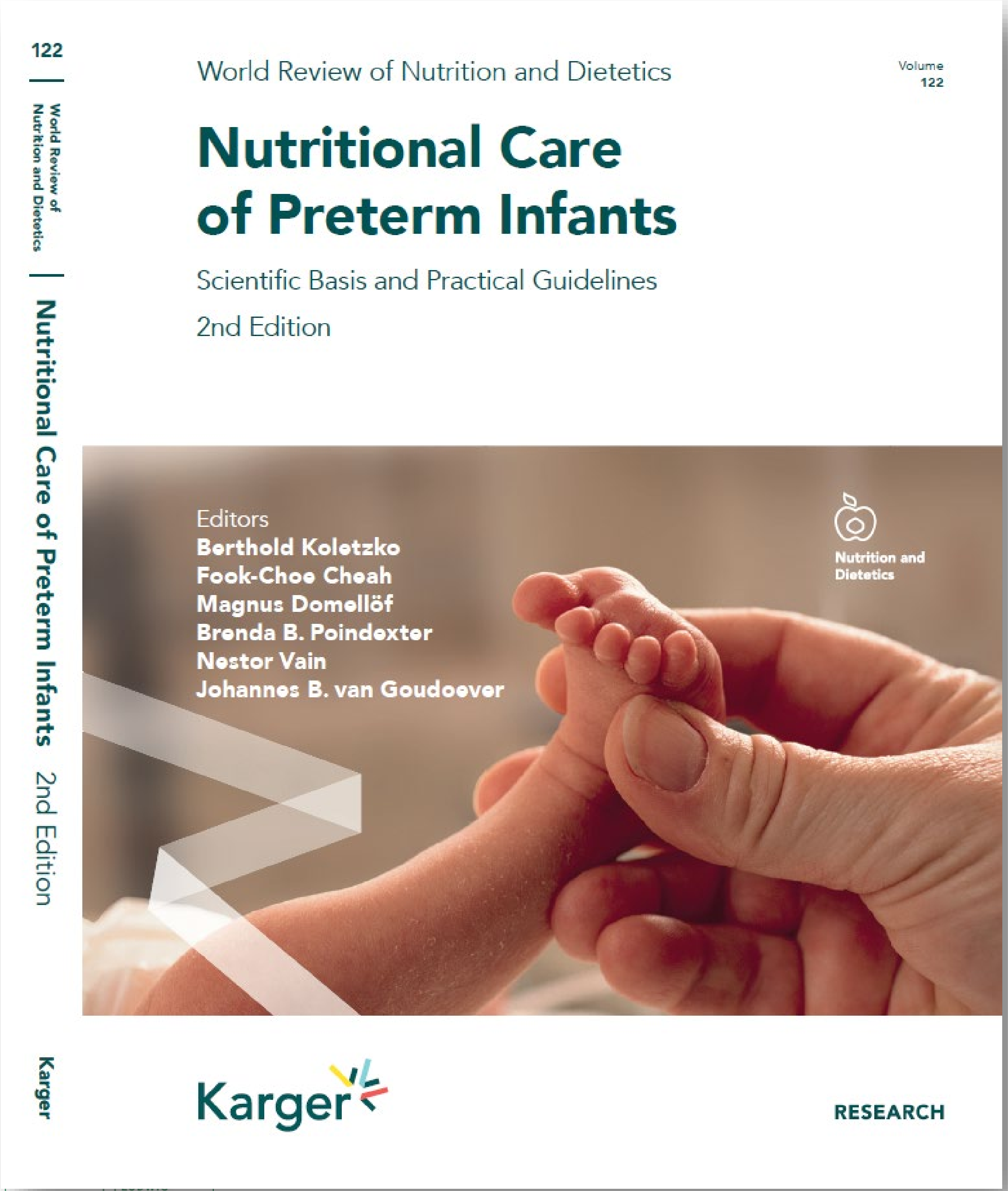
- In the hospital: >3 g protein/kg/d
- After discharge:
  ≈1.5 - 2 kg bw.: ≈3 g protein/100 kcal
  ≈2 - 2.5 kg bw.: ≈2.5 g protein/100 kcal

Koletzko B, Li Z. Feeding after discharge. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

Feeding after discharge: research needs

- Define optimal nutrient supply for growth and development for subgroups of preterm infants after discharge
- Define optimal fortification strategies of breastfed preterm infants after discharge
- Define optimal strategies for timing and choices of complementary feeding for subgroups of preterm infants

Koletzko B, Li Z. Feeding after discharge. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.



- New global recommendations
- Available as printed and e-book
- Every neonatal unit and their patients can benefit from considering recommendations
- Sincere thanks to a wonderful team of global contributors!