State of the Art: Precision Nutrition in Preterm Infants

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Presented by
Christoph Fusch, MD, PhD

Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

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Mead Johnson Nutrition.

Faculty Presenter

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Faculty Disclosures

Christoph Fusch, MD, PhD	
Research Support	Fresenius, Milupa, Prolacta
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Speakers Bureau	Abbott, Baxter, Fresenius, Hamilton Medical, Heinen & Loewenstein, HiPP, Humana, Ikaria, Medela, Mead Johnson Nutrition, Milupa (Danone), Nestlé, Nutricia, Prolacta

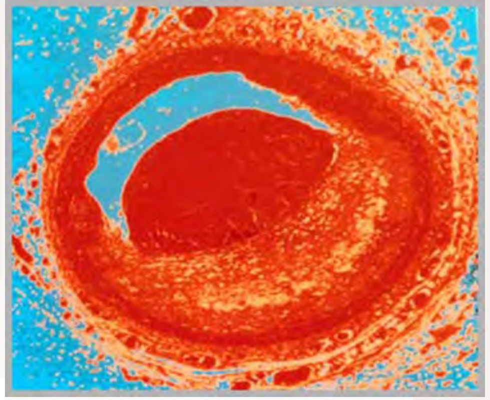
For complete disclosures see course CE statement

Learning Objectives

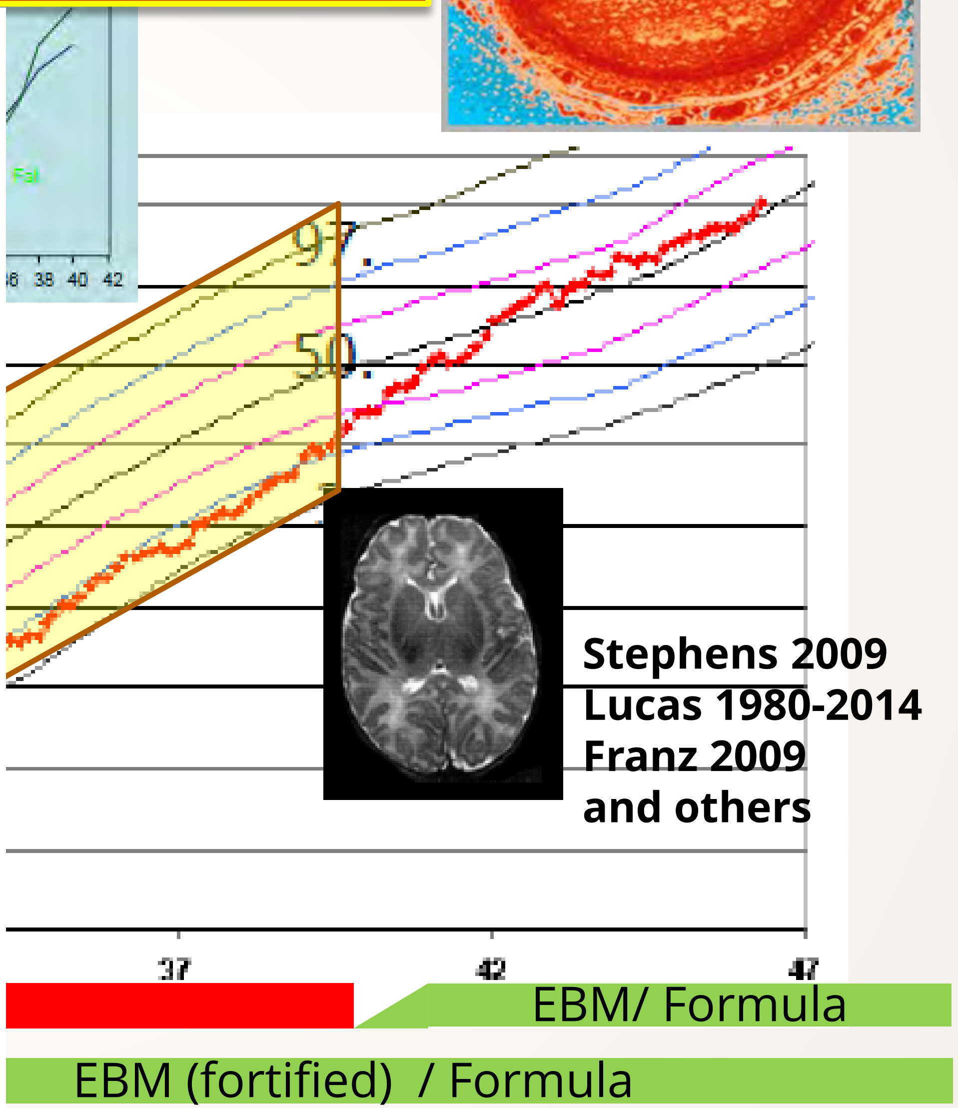
- Explain how nutritional needs vary among preterm and term infants
- Describe the clinical outcomes from nutrient research studies in preterm infants
- Develop individualized postnatal trajectories for preterm infants to reduce the risk of postnatal growth retardation
- Apply current recommendations based on nutrient research studies for the clinical management of preterm infants

POSTNATAL GROWTH, NUTRITION, AND LATER OUTCOME

Aim of postnatal growth: imitate/ensure/facilitate in-utero development

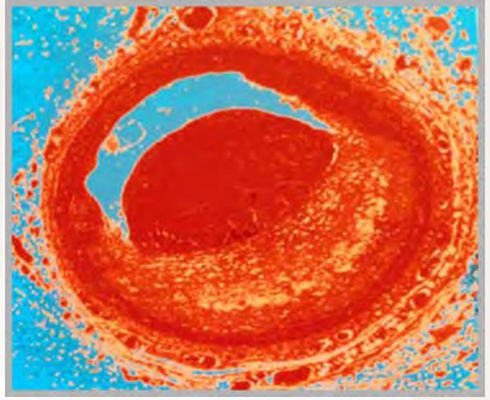


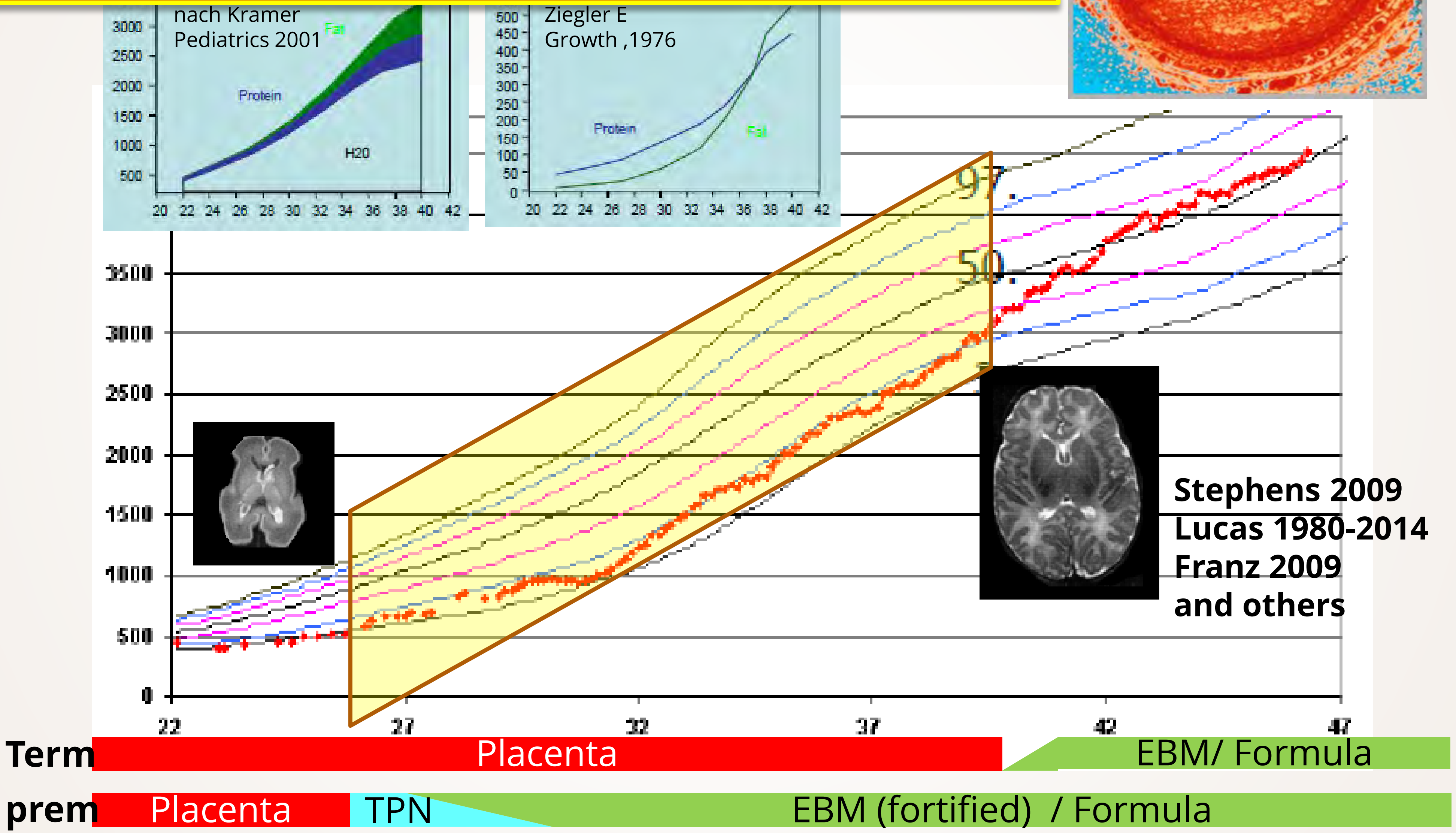
American Academy of Pediatrics (AAP) recommends that preterm infants achieve "…rates of growth and composition of weight gain for a normal fetus of the same postmenstrual age and to maintain normal concentrations of blood and tissue nutrients…"



Aim of postnatal growth: imitate/ensure/facilitate in-utero development

Weight—organ differentiation (brain)—body composition—%fat mass





Postnatal Preterm Growth Patterns

- Growth patterns are under the control of neonatal staff, who modify the infants' nutrient intake
  - Unlike term babies, preterm infant feedings are not self-regulated
  - Feeding volume is determined by neonatal staff
  - Feeding and nutrient intake occur according to timed scheduled
  - Baby has to metabolize nutrition "being filled into its body"

"Term babies cry when they are hungry and stop sucking when nutrient intake is sufficient."—C. Fusch

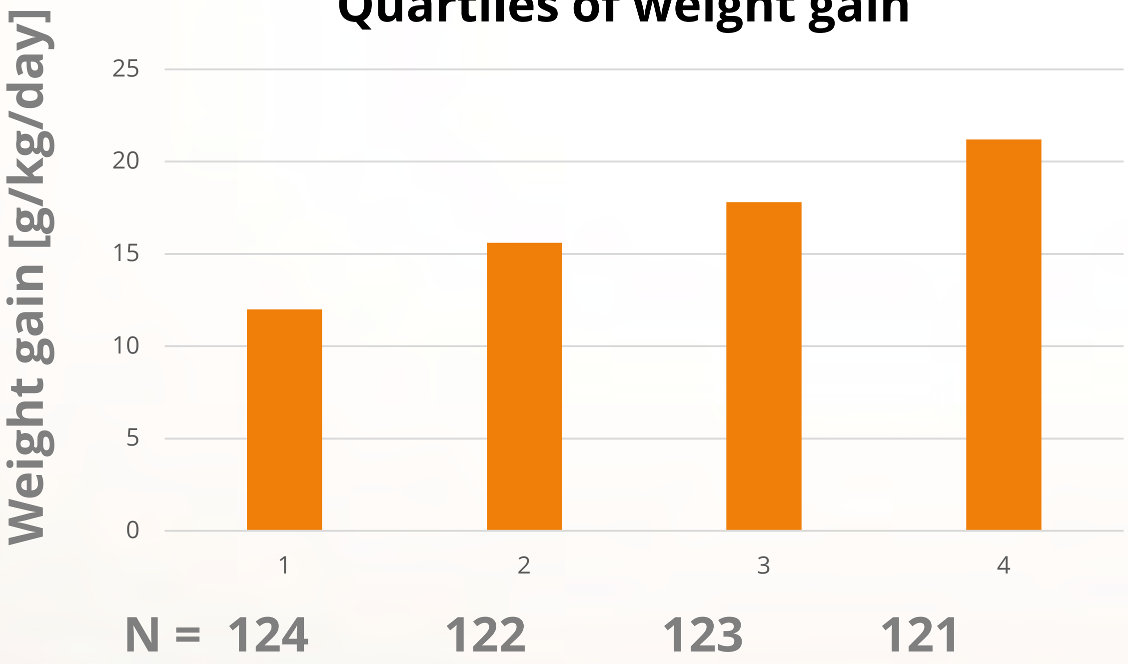
Rochow N, et al. *Pediatr Res.* 2016;79:870-9.

Landmark Study: Assessment of the Relationship of Growth and Neurodevelopmental Outcomes

Growth in Neonatal Intensive Care Unit Influences Neurodevelopmental and Growth Outcomes in Extremely Low Birth Weight Infants

Ehrenkranz RA, et al. *Pediatrics*. 2006.

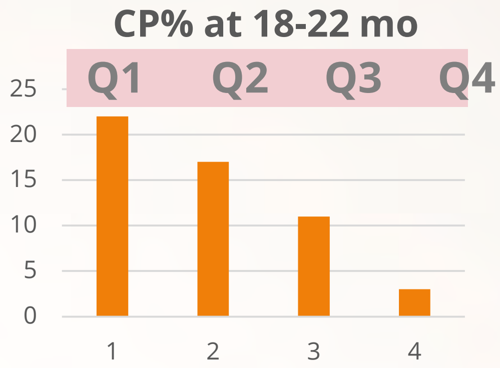
Quartiles of weight gain

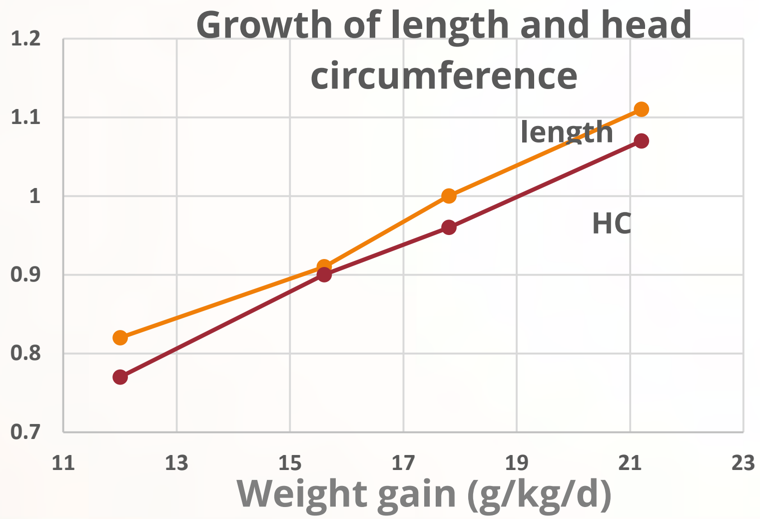


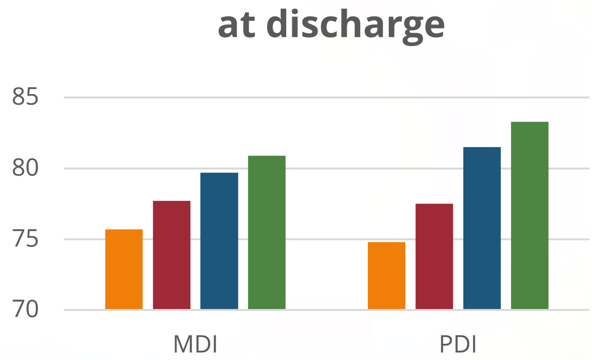
Multicenter cohort
Retrospective analysis
Birth weight <1000 g

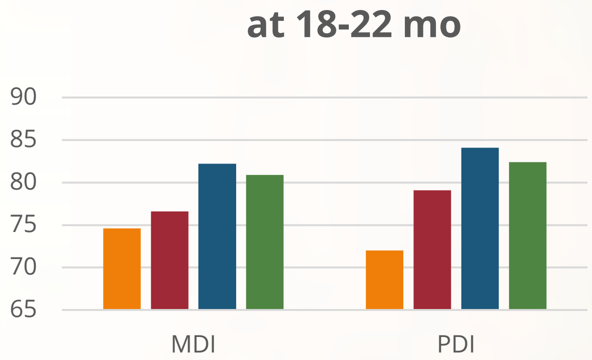
NDI at discharge & 18–22 months

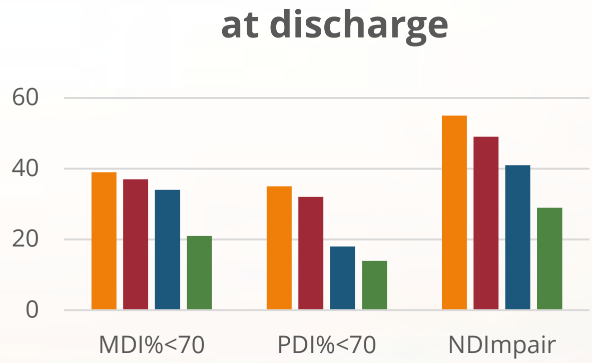
NDI and Growth Are Related at Discharge, But also at 1.5–2 Years of Life

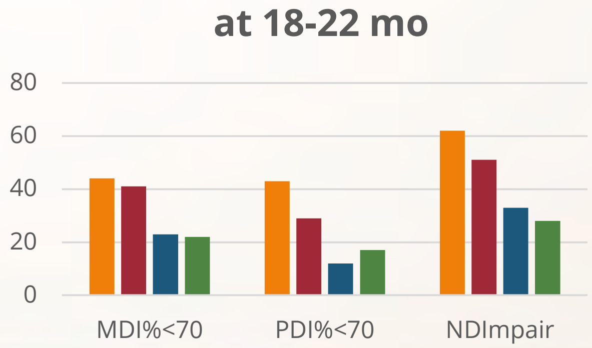












Neurodevelopment of ELBW Infants Correlates with the Nutritional Intake

- N=124 ELBW infants
- Mean birth weight 787 ±133 g
- Mean gestational age was 25.9 ±1.6 weeks

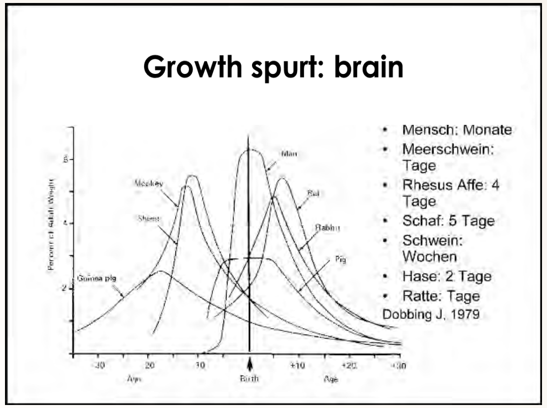


TABLE 3 Regression Analysis Week-1 Energy Intake and 18-Month MDI

Variable	b (SE)	*P*	Partial R^2
Birth weight	0.03 (0.01)	.0244	0.06
Male gender	−8.23 (2.90)	.0055	0.09
IVH	−1.51 (6.15)	.8063	0.01
CLD	0.38 (3.14)	.9046	0.00
NEC	−1.99 (3.94)	.6143	0.01
Maternal education, college graduate	4.77 (2.90)	.1036	0.01
Energy, 4.2 kJ (1 kcal)/kg per day	0.46 (0.18)	.0134	0.05

$R^2 = 0.23$. Adjusted $R^2 = 0.18$. b (SE) indicates effect size (SE).

TABLE 4 Regression Analysis Week 1 Protein Intake and 18 month MDI

Variable	b (SE)	*P*	Partial R^2
Birth weight	0.03 (0.01)	.0227	0.06
Male gender	−8.72 (2.90)	.0033	0.09
IVH	−2.41 (6.14)	.6948	0.01
CLD	−0.06 (3.14)	.9838	0.00
NEC	−3.17 (3.93)	.4210	0.01
Maternal education, college graduate	4.32 (2.90)	.1397	0.01
Protein, g/kg per day	8.21 (3.67)	.0274	0.04

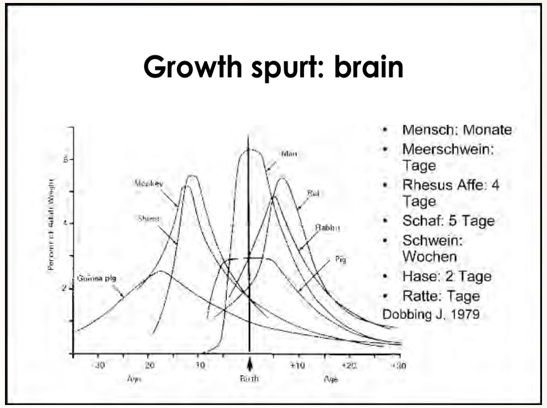
$R^2 = 0.22$. Adjusted $R^2 = 0.17$. b (SE) = effect size (SE).

Each **kcal/kg/d** increases **MDI** by **0.46 points**

Each **g protein/kg/d** increases **Bayley MDI** by **8.2 points**

Stephens BE, et al. *Pediatrics*. 2009.

Neurodevelopment of ELBW Infants Correlates with the Nutritional Intake



- N=124 ELBW infants
- Mean birth weight 787 ±133 g
- Mean gestational age was 25.9 ±1.6 weeks

Effect size of nutritional intervention probably in the same range as those of classical procedures and strategies applied during the "intensive" intensive care period

IVH	−1.51 (6.15)	.8063	0.01
CLD	0.38 (3.14)	.9046	0.00
NEC	−1.99 (3.94)	.6143	0.01
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Stephens BE, et al. *Pediatrics*. 2009.

Trajectories of Growth among Children Who Have Coronary Events as Adults

Barker DJ, et al. *N Engl J Med*. 2005; 353(17):1802-9.

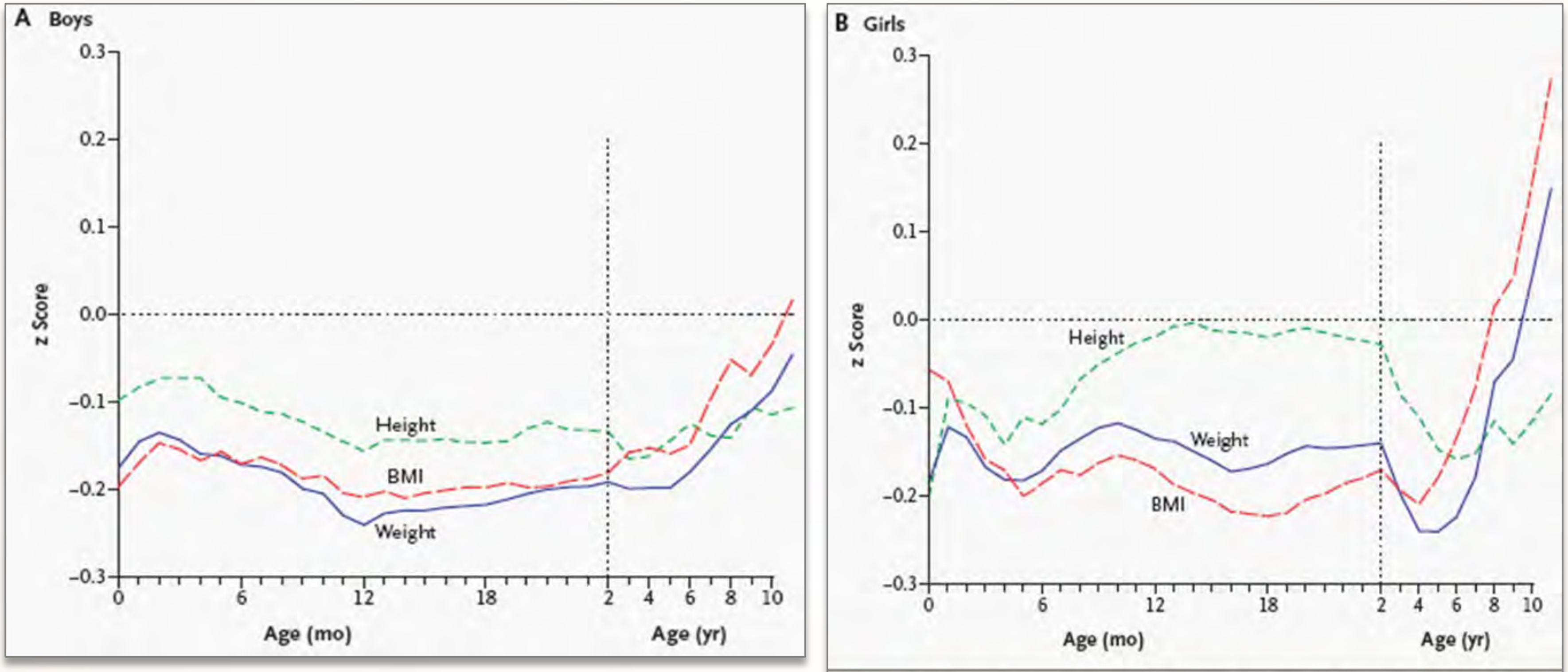


Figure 1. Mean z Scores for Height, Weight, and Body-Mass Index in the First 11 Years after Birth among Boys and Girls Who Had Coronary Heart Disease as Adults.

The mean values for all boys and all girls are set at zero, with deviations from the mean expressed as standard deviations (z scores).

Preterm Infants Show Growth Trajectories Making Them Vulnerable for DOHaD

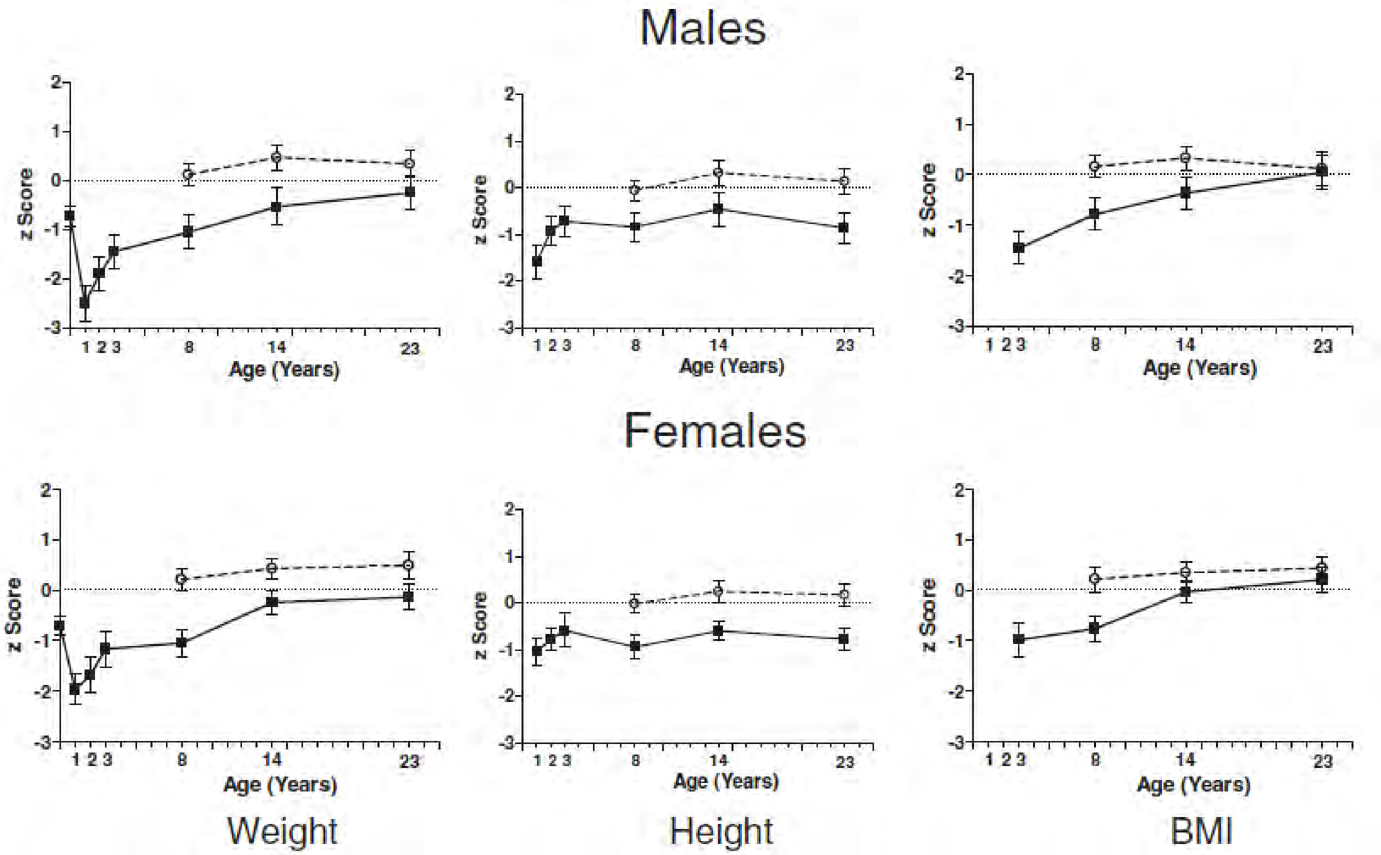
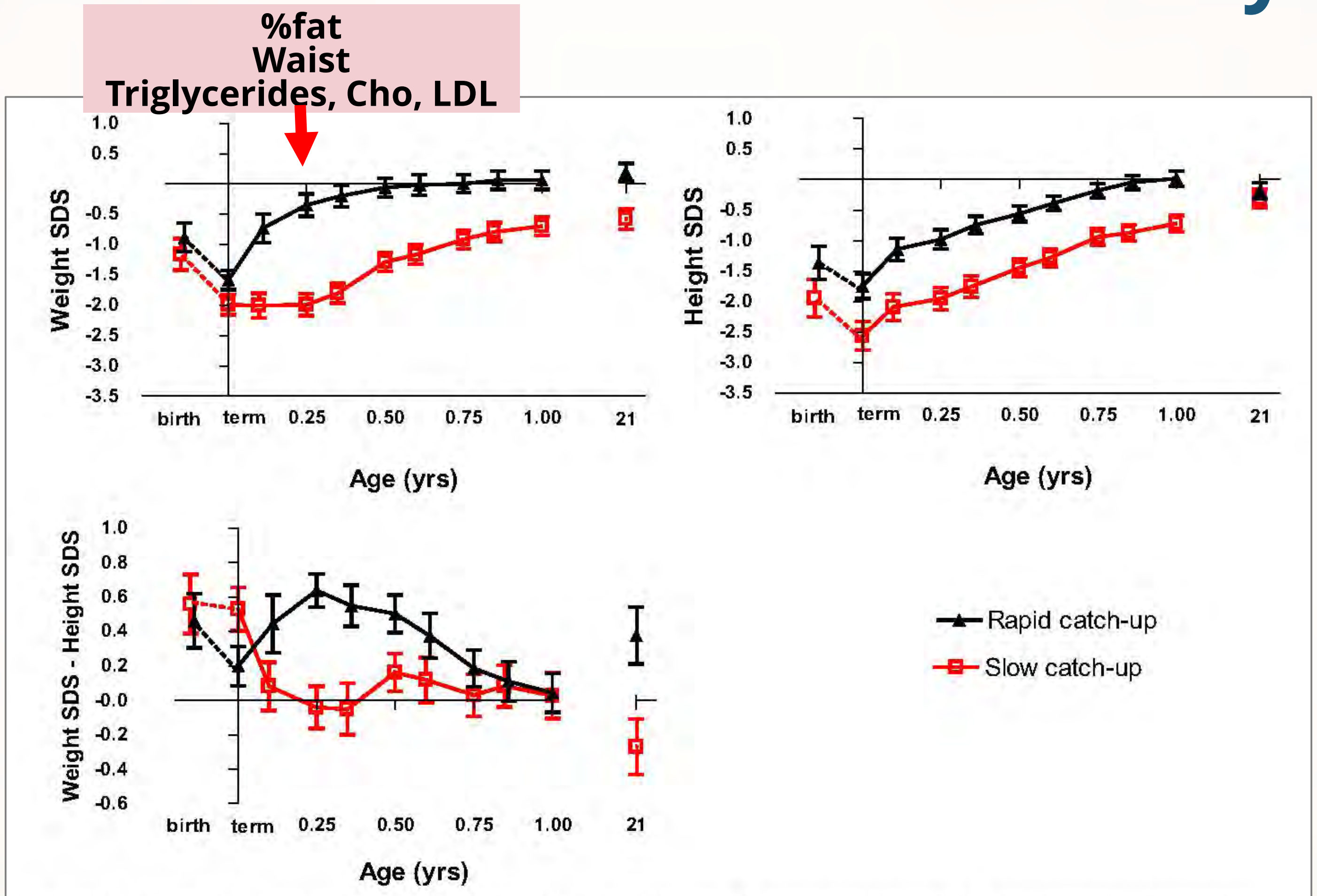


Figure 1. Mean height, weight, and BMI z-scores and 95% CI for ELBW (■) and NBW (○) subjects, from birth to adulthood.

n = 147 ELBW & 131 NBW

Saigal S. *Pediatr Res*. 2006.

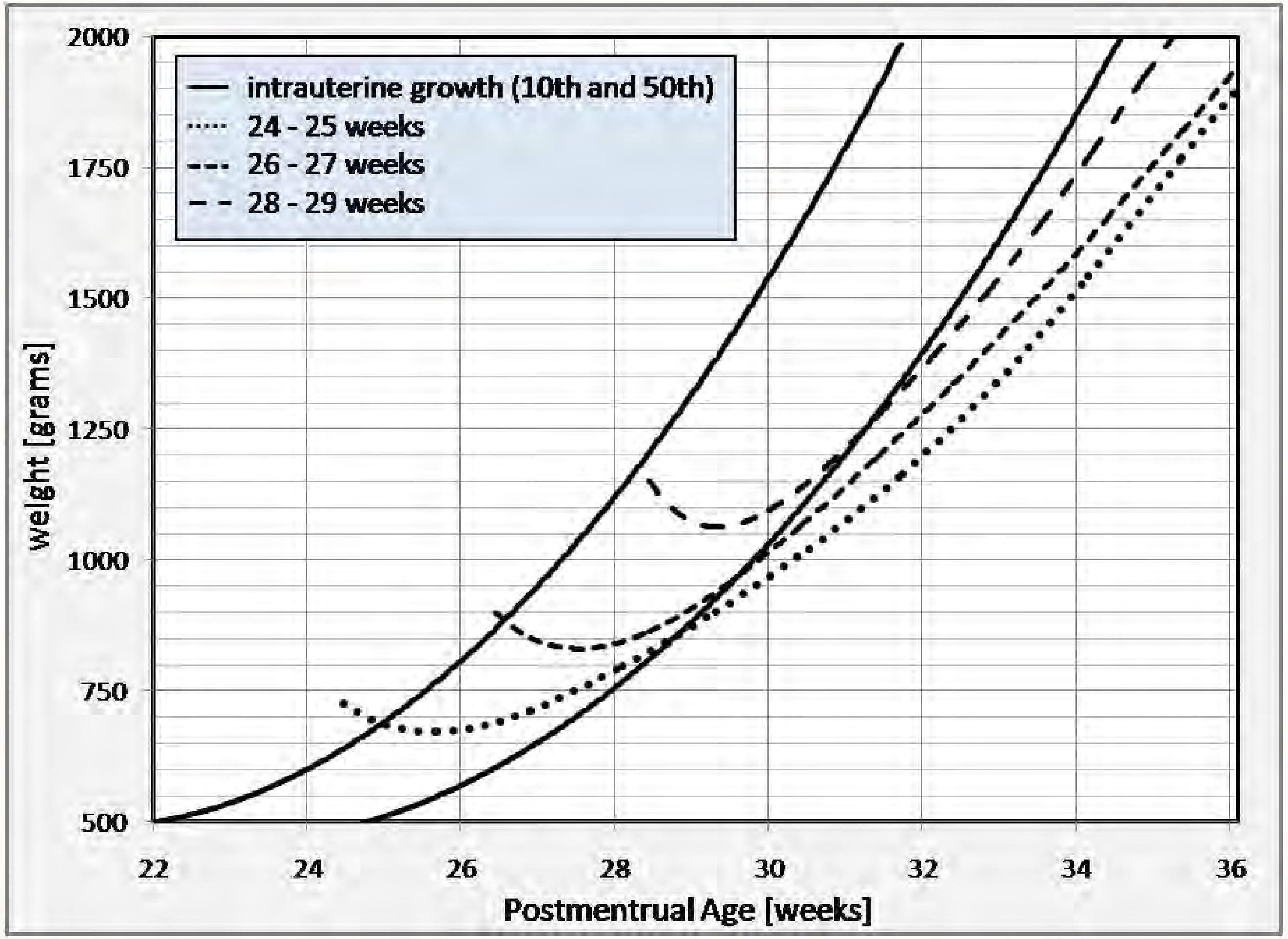
Rapid Weight Gain After Weight Loss Until Term Is Correlated With Metabolic Outcome in Early Adulthood



Weight SDS, height SDS, and weight SDS relative to height SDS in the first year after term age and in early adulthood in subjects born preterm with slow and rapid catch-up growth.

POSTNATAL GROWTH RETARDATION

Postnatal Growth Restriction and Cumulative Energy Deficits– A Universal Problem in VLBW infants?



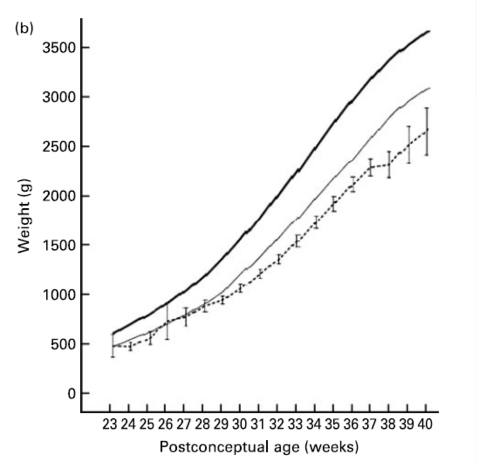
Ehrenkranz RA, et al. *Pediatrics.* 1999;104; 280-9. Embleton NE, et al. *Pediatrics.* 2001;107(2):270-3.
Cooke RJ, et al, *Arch Dis Child Fetal Neonatal Ed.* 2000;83(3):F215-8. Cooke RJ, et al. *Arch Dis Child Fetal Neonatal Ed.* 2004;89(5):F428-30.

Extra-uterine growth restriction at discharge observed in 58% of VLBW infants fed predominantly standard fortified breast milk (Henriksen

Growth and nutrient intake among very-low-birth-weight infants fed fortified human milk during hospitalisation

Christine Henriksen[1]*, Ane C. Westerberg[1], Arild Rønnestad[2], Britt Nakstad[3], Marit B. Veierød[1,4], Christian A. Drevon[1] and Per O. Iversen[1,5]

British Journal of Nutrition (2009), **102**, 1179–1186



127 VLBW infants
part of an interventional trial assessing PUFA supplementation on neuro-outcome

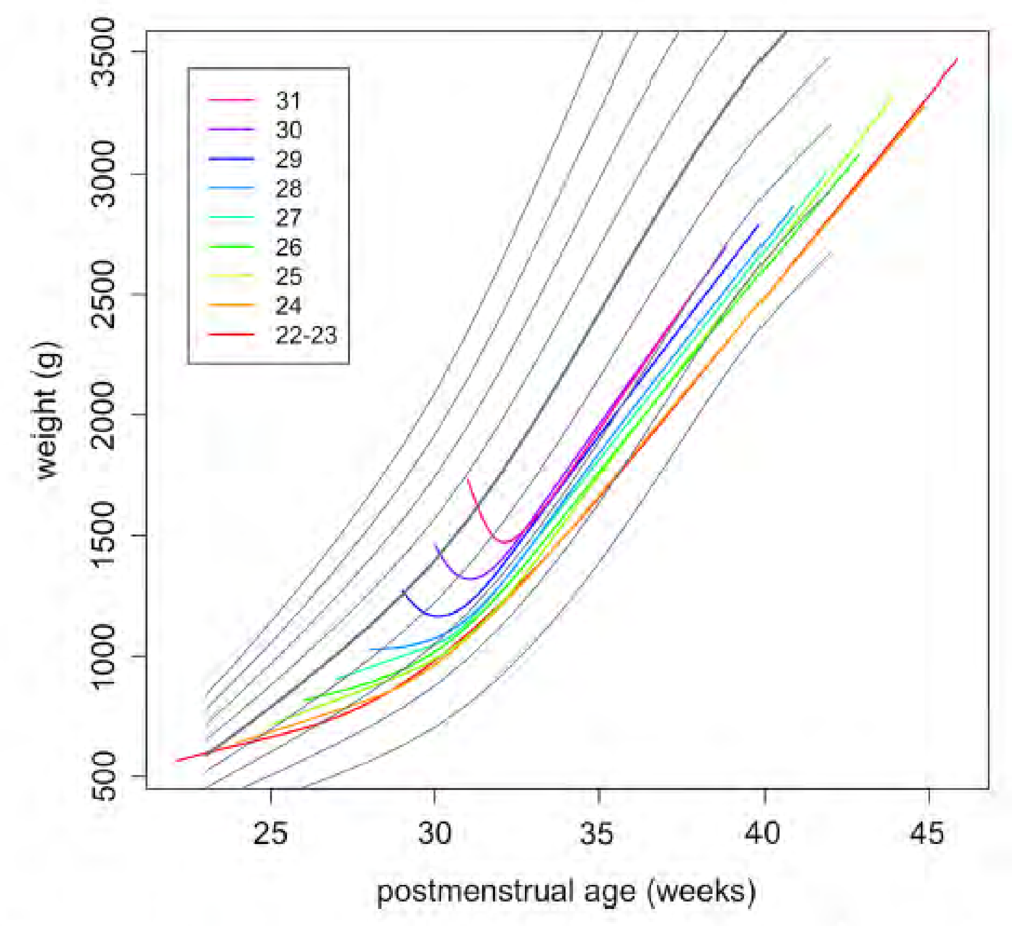
All infants on fortified BM , either own mothers (76%) or donor milk (24%),
fortified once
EI > 120 ml/kg/d

Extra-uterine growth restriction is common in VLBW infants fed fortified human milk. Recommended energy intakes for growing preterm infants were not met in the present study. We observed a significant positive association between energy intake and reduced risk of growth restriction at discharge. The present study shows that preterm infants have

	All (*n* 127)		Growth restricted at discharge (*n* 72)		Adequate weight at discharge (*n* 55)		
	Mean	SD	Mean	SD	Mean	SD	*P*
Maternal characteristics							
Age (years)	31	5	31	5	31	5	0·62
Non-smokers (%)	78		82		72		0·21
Infant characteristics							
SGA at birth (%)	33		63		11		< 0·001
Birth weight (g)	1066	285	1055	296	1082	271	0·59
Initial weight loss (g)	169	200	233	184	110	175	0·73
Time to regain birth weight (d)	9·8	4	10·2	4	9·5	4	0·37
Gestational age at birth (weeks)	28·8	2·7	29·6	3	27·8	2	< 0·001
Length at birth (cm)*	35·3	4·2	34·9	4·5	35·9	3·5	0·29
Head circumference at birth (cm)	26·5	2·5	26·5	2·8	26·4	2·2	0·78
Weight at discharge (g)	2683	656	2417	601	3055	541	< 0·001
Length at discharge (cm)*	44·6	4·6	44·1	4·8	45·5	4·4	0·19
Head circumference at discharge (cm)	34·4	2·6	34·0	2·7	34·9	2·4	0·10

Birth weight and longitudinal growth in infants born below 32 weeks' gestation: a UK population study

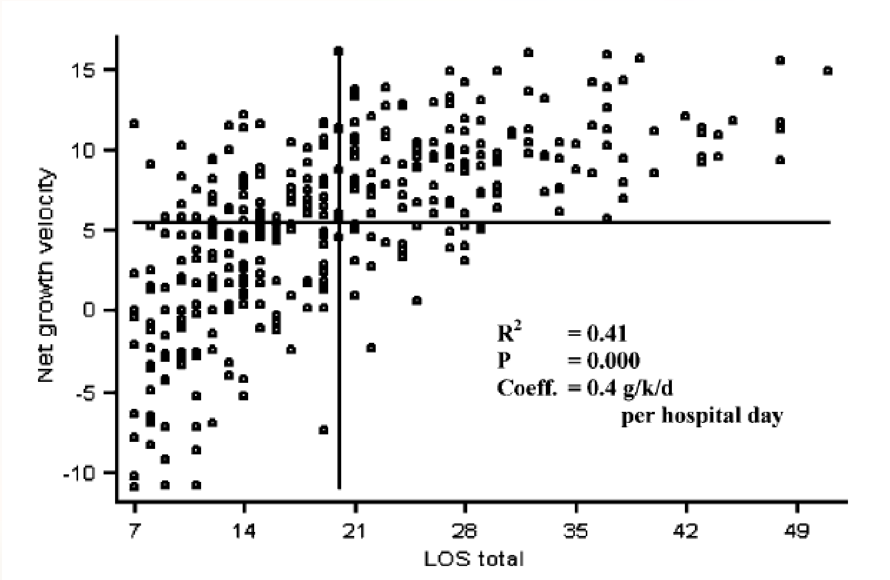
Cole TJ, et al. *Arch Dis Child Fetal Neonatal Ed*. 2014;99:F34-F40..

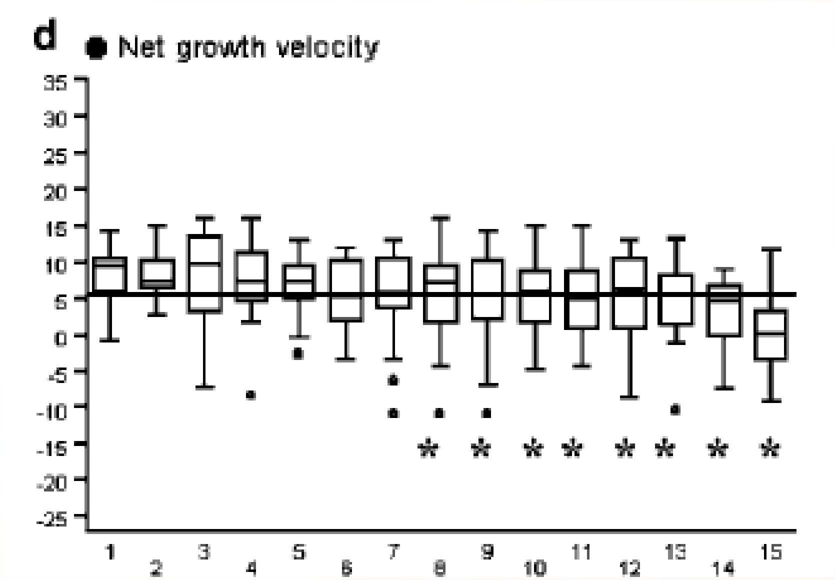


Mean growth curves of weight by postmenstrual age and week of gestation, superimposed on the British 1990 birth weight reference.

Significant Variation of Growth Rates and Nutritional Strategies Amongst NICU's Evidence for Operator-dependent Peformance

n = 450, 30 $^{0}/_{7}$ – 34 $^{6}/_{7}$ gestational weeks



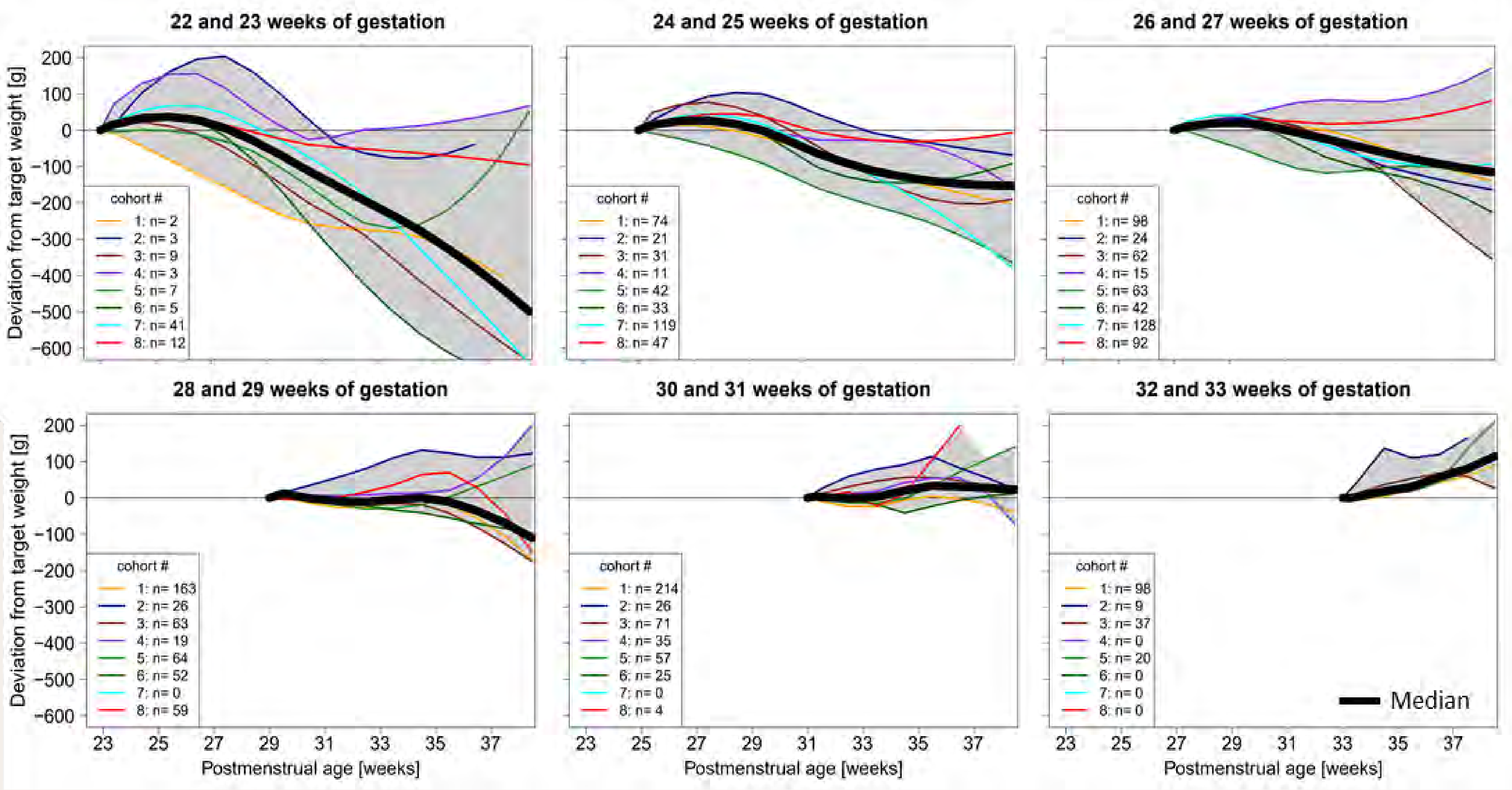


Interneonatal Intensive Care Unit Variation in Growth Rates and Feeding Practices in Healthy Moderately Premature Infants

Journal of Perinatology 2005; 25:478–485

Results: Postnatal Age and Deviation from the Target Weight (ΔW)

Centers 1-8

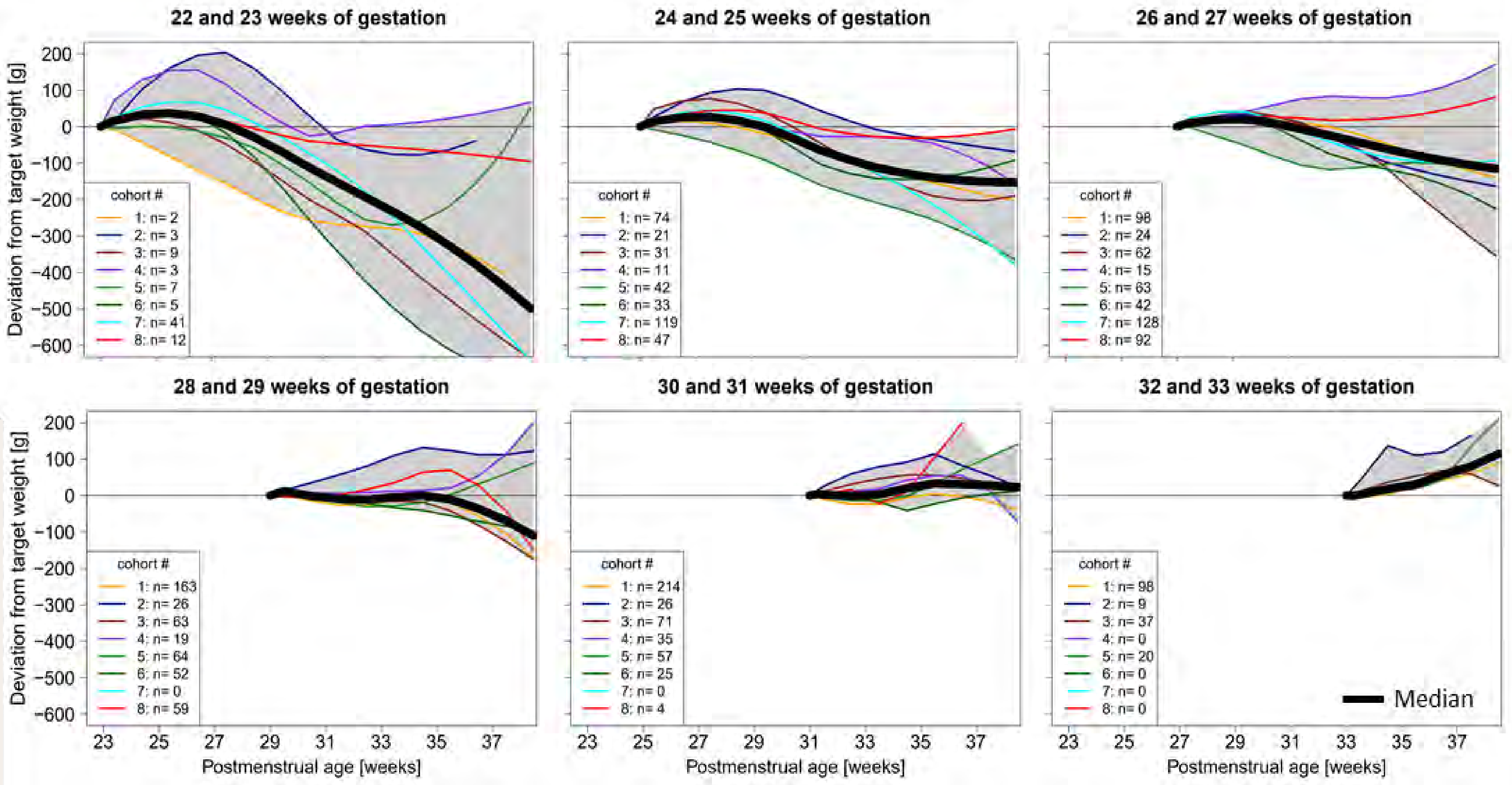


- There is a large variation in postnatal growth
- More immature infants have a larger deviation from the target trajectory.
- There is a large deviation in growth trajectories by center.
- Some centers achieve growth close to the target trajectory.

Individualized growth trajectories for preterm infants
Associations with short-term outcomes

N. Rochow, P. Kosmann, HY. So, E. Rochow, E. Landau-Crangle, D. Wackernagel, C. Collins, Z. Khan, D. Moya, D. Kontantelos, W. Göpel, C. Härtel, M. Belfort, M. Blennow, M. Makrides, B. Urlesberger, F. Moya, M. Rüdiger, C. Fusch

[1]McMaster Univ., Hamilton, CA, [2]Paracelsus Medical Univ., Nuremberg, GER, [3]Univ. of Waterloo, CA, [4]Independent scientist, Strasburg, GER, [5]Queen's Univ., Kingston, CA, [6]Karolinksa Univ., Stockholm, SN, [7]South Australian Health & Medical Research Institute, Adelaide, [8]Univ. of Veterinary and Animal Sciences, Lahore, PK, [9]Betty Cameron Children's Hospital, Wilmington, USA, [10]Univ. Hospital Carl Gustav Carus, Dresden, GER, [11]Univ. of Lübeck, GER [12]Brigham and Women's Hospital, Boston, USA, [13]Medical Univ. of Graz, A



variation in postnatal growth

- More immature infants have a larger deviation from the target trajectory.
- There is a large deviation in growth trajectories by center.
- Some centers achieve growth close to the target trajectory.

Nutritional Intake Factors

- Factors that can aggravate nutritional intake:
  - Delayed nutritional support
  - Slow postnatal enteral feeding advancement
  - Prolonged use of parenteral nutrition
  - Repeated bouts of feeding intolerance
  - Providing nutrition that does not offer optimal composition and nutrients needed for high growth rates in preterm infants
  - Lack of proper postnatal reference trajectories

Rochow N, et al. *Pediatr Res.* 2016;79:870-9.

nutrients MDPI

Nutrients. 2015 Jan; 7(1): 423–442.
Published online 2015 Jan 8. doi: 10.3390/nu7010423
PMCID: PMC4303848
PMID: 25580815

Guidelines for Feeding Very Low Birth Weight Infants

Sourabh Dutta,* Balpreet Singh, Lorraine Chessell, Jennifer Wilson, Marianne Janes, Kimberley McDonald, Shaneela Shahid, Victoria A. Gardner, Aune Hjartarson, Margaret Purcha, Jennifer Watson, Chris de Boer, Barbara Gaal, and Christoph Fusch

Working grp on feeding guidelines for VLBW infants constituted in McMaster University, Canada

VLBW Infants Weight	
First choice Mother's own breastmilk	
<1000 g at birth 1000–1500 g at birth	full feeds by ~2 weeks of age full feeds by ~1 week of age
>1250 g	3-hrly feeding regimen introduced
Trophic feeds (10–15 mL/kg/day)	start within 24 h of life; caution in extremely preterm, ELBW, or growth restricted infants
≥1 kg at birth	start nutritional feeds at 30 mL/kg/day; increase by 30 mL/kg/day

ELBW, extremely low birth weight;
VLBW, Very Low Birth Weight

Dutta S, et al. *Nutrients.* 2015;7(1):423-42.

Optimizing Postnatal Growth—Just need to do it!

A nutritional program to improve outcome of very low birth weight infants.
Rochow N, et al. *Clin Nutr.* 2012.

	Enteral Intake	Parenteral Nutrition (amino acids and lipids)
Start	Earlier, at 6 hrs of life	Higher 1.5 vs 1.0 g/kg/d
Increments	19 vs. 12 days	DOL 2 vs DOL 4
Max intake	-200 vs -160 ml/kg/d	3.5 vs 2.5 g/kg/d

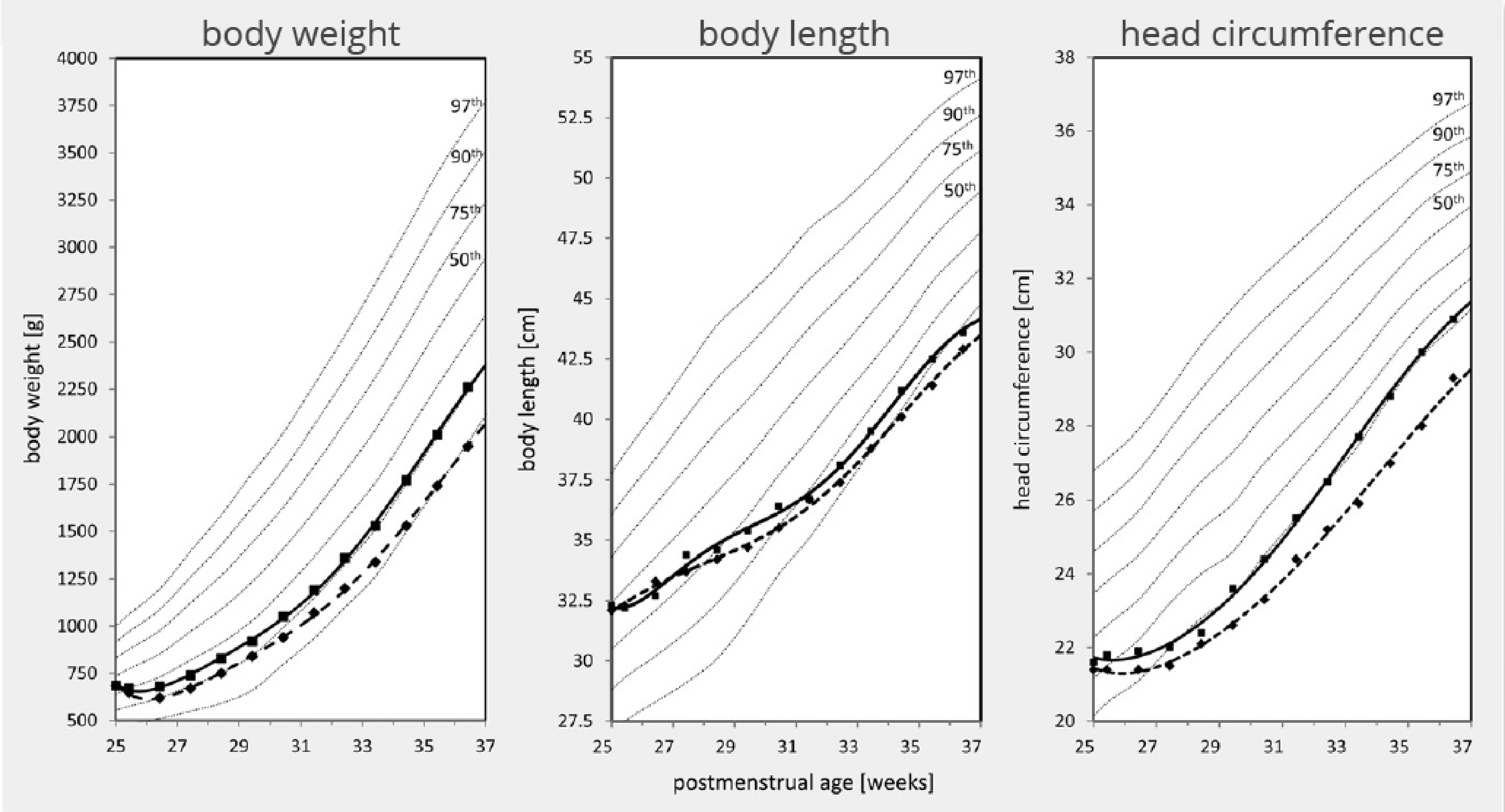
- Intervention study, VLBW (<1500 g birth weight), n=243
- Modification of the standard nutritional schedule can impact postnatal growth

DOL, days of life; VLBW, very low birth weight

Rochow N, et al. *Clin Nutr.* 2012;31:124-31.

Optimizing Postnatal Growth—Just need to do it!

Improvement of weight gain, length, and head circumference



Trajectories for growth of all infants with PMA of ≤ 25 weeks

Full line: Study group, S-GR; Dotted line: Control group, C-Gr. PMA, postmenstrual age.

Improvement of Growth Follows Favorable Body Composition

- Two longitudinal studies analyzed
- n=159 (87 boys; 72 girls) healthy term and preterm neonates
- GA 38.4 weeks

Not due to inappropriate gain of fat mass (i.e., %FM=const)

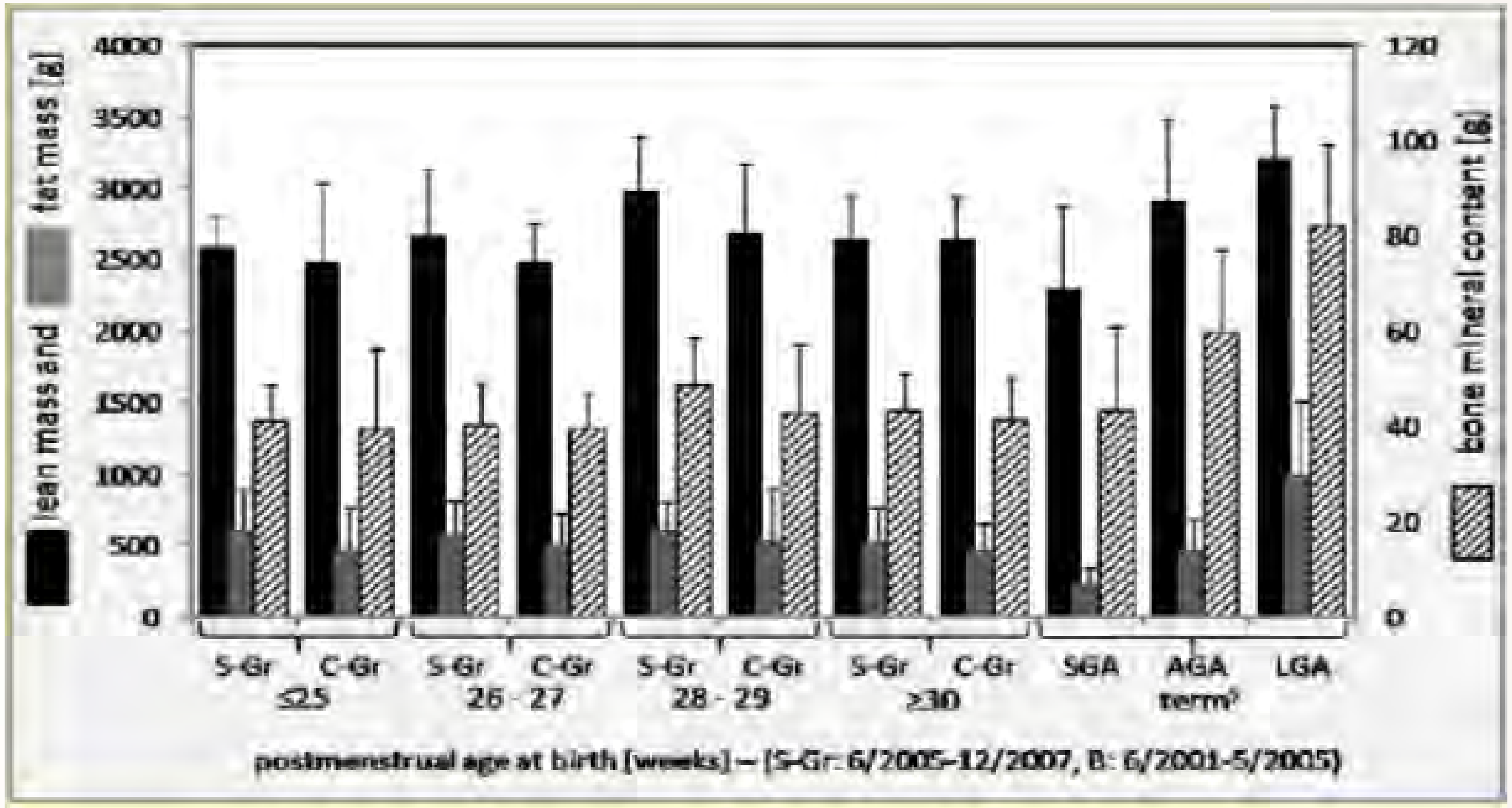


Figure shows body composition (DXA) at discharge, term-born infants reference data Schmelzle et al 2007.

DXA, dual-energy X-ray absorptiometry; GA, gestational age

Schmelzle HR, et al. *Eur J Pediatr.* 2007 ;166:161-7.

Nutrition Guidelines Improve Growth… (Montreal experience)

ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Pædiatrica ISSN 0803-5253

REGULAR ARTICLE

Preventing postnatal growth restriction in infants with birthweight less than 1300 g

M Lapointe[1], KJ Barrington[1,2], M Savaria[1], A Janvier (annie.janvier.hsj@ssss.gouv.qc.ca)[1,2,3]
1.Division of Neonatology, Sainte-Justine Hospital, Montreal, QC, Canada
2.Department of Pediatrics, Sainte-Justine Hospital Research Center, University of Montreal, Montréal, QC, Canada
3.Clinical Ethics University of Montreal and Hôpital Sainte-Justine, Montréal, QC, Canada

fortification in case of inadequate growth (failure to follow postnatal growth curves, or persistently under 20 g/kg/day) to 26 or occasionally 28 kcal/oz was used after increasing enteral feeding volume to 160–170 mL/kg/day (if higher volumes were tolerated without regurgitation or excessive abdominal distension). Our standard enteral intake there-

Table 4 Growth outcomes of the 2 cohorts

	Cohort 1 (n = 128)	Cohort 2 (n = 99)	Statistical significance (p)
Average PMA at final measurements (discharge), weeks (SD)	37.4 (4.1)	37.9 (4.8)	NS
Weight at discharge, g (SD)	2525 (746)	2888 (763)	<0.001
Length at discharge, cm (SD)	44.7 (5.4)	46.3 (3.5)	<0.01
Change in body weight *z*-score between admission and discharge	−1.03 (0.76)	−0.39 (0.79)	<0.001
Change in head circumference *z*-score	−0.6 (1.3)	−0.1 (1.2)	<0.001
Change in length *z*-score	−1.7 (1.1)	−1.5 (1.4)	<0.01

PMA = Postmenstrual age.

Growing Body of Evidence about Prevention of Postnatal Growth Restriction—Single-center Experience

OPEN ACCESS Freely available online PLOS ONE

Implementation of Nutritional Strategies Decreases Postnatal Growth Restriction in Preterm Infants

Paola Roggero[1*], Maria L. Gianni[1], Anna Orsi[1], Orsola Amato[1], Pasqua Piemontese[1], Nadia Liotto[1], Laura Morlacchi[1], Francesca Taroni[1], Elisa Garavaglia[1], Beatrice Bracco[1], Massimo Agosti[1,2], Fabio Mosca[1]

1 Neonatal Intensive Care Unit (NICU), Department of Clinical Science and Comunity Health, Fondazione IRCCS "Ca' Granda" Ospedale Maggiore Policlinico, University of Milan, Milan, Italy, 2 Maternal and Child Health Department, Del Ponte Hospital, A.O. Di Circolo Fondazione Macchi, Varese, Italy

Journal of Perinatology (2015) 35, 642–649

www.nature.com/jp

ORIGINAL ARTICLE

Prevention of postnatal growth restriction by the implementation of an evidence-based premature infant feeding bundle

PD Graziano[1], KA Tauber[2], J Cummings[2], E Graffunder[3] and MJ Horgan[2]

The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: http://www.tandfonline.com/loi/ijmf20

Optimising enteral nutrition in growth restricted extremely preterm neonates – a difficult proposition

P. Shah, E. Nathan, D. Doherty & S. Patole

Review

Avoiding postnatal undernutrition of VLBW infants during neonatal intensive care: evidence and personal view in the absence of evidence

Christoph Maas, Christian F Poets, Axel R Franz

OPEN ACCESS Freely available online PLOS ONE

Brief Parenteral Nutrition Accelerates Weight Gain, Head Growth Even in Healthy VLBWs

Naho Morisaki[1,2*], Mandy B. Belfort[3,4], Marie C. McCormick[5,6], Rintaro Mori[1], Hisashi Noma[1,7], Satoshi Kusuda[8], Masanori Fujimura[9], the Neonatal Research Network of Japan

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ELSEVIER

Very low birth weight infant care: adherence to a new nutrition protocol improves growth outcomes and reduces infectious risk

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PHYSIOLOGY OF POSTNATAL ADAPTATION AND GROWTH

Development of individualized postnatal trajectories

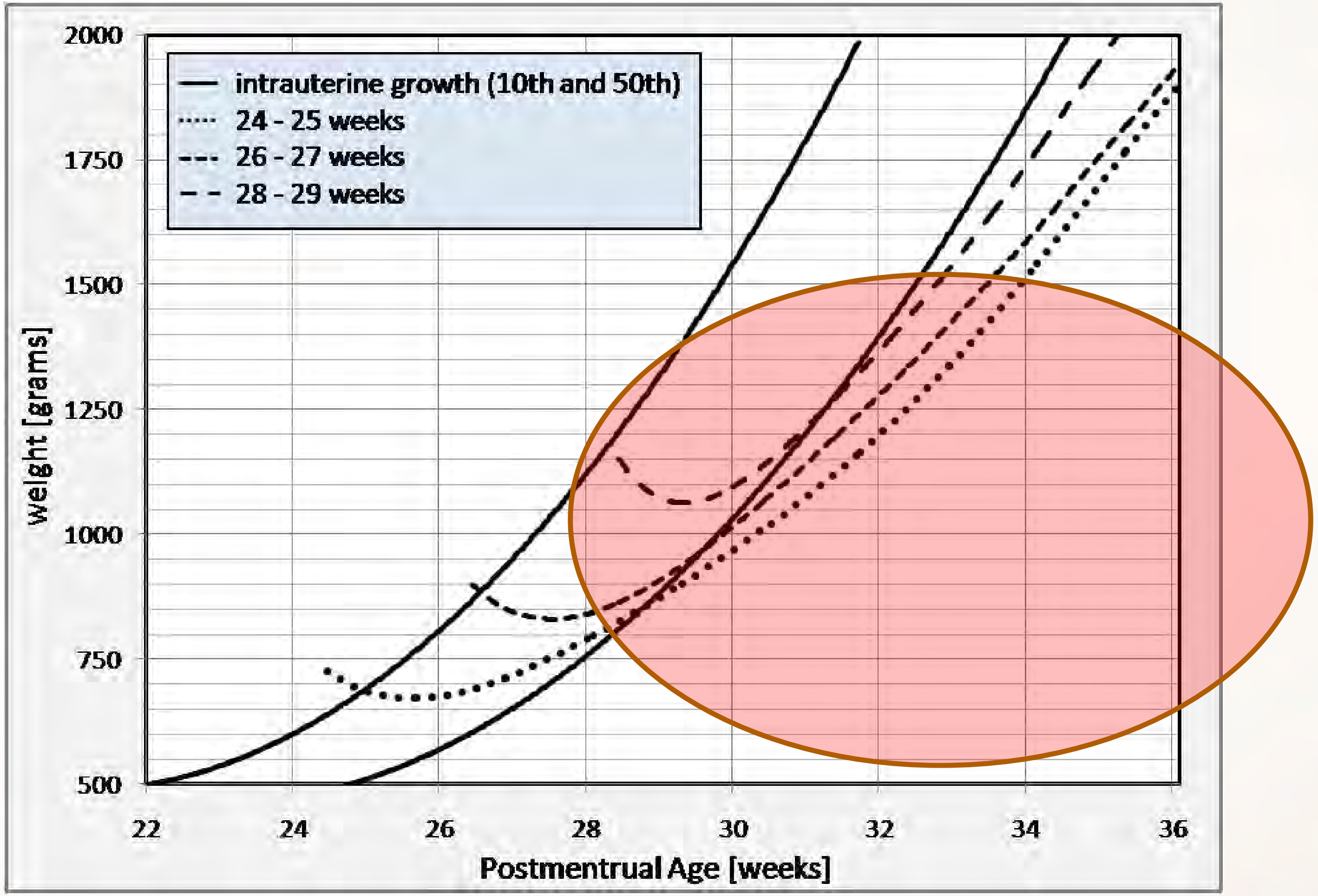
Individualized Precision Nutrition

- Precision nutrition starts with a growth goal that can be assessed

- Tools available to monitor accuracy of growth trajectories
  - Charts and Individualized trajectories (see next slides)

Factors Contributing to PNGR

- Nutrition
- Know-how
- The journey through “no man’s land“/ ”nowhere land“



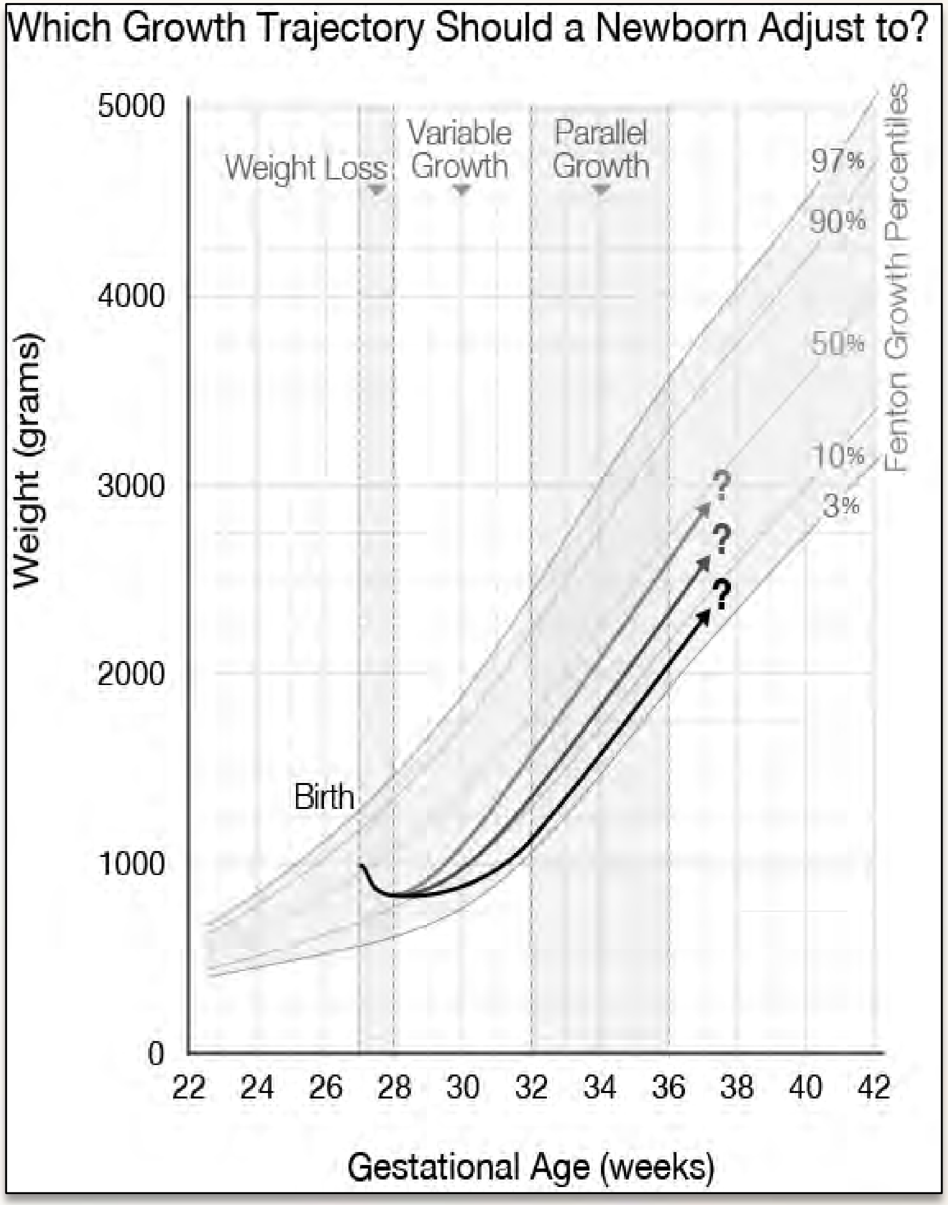
Ehrenkranz RA, et al. *Pediatrics.* 1999;104; 280-9. Embleton NE, et al. *Pediatrics.* 2001;107(2):270-3.
Cooke RJ, et al, *Arch Dis Child Fetal Neonatal Ed.* 2000;83(3):F215-8. Cooke RJ, et al. *Arch Dis Child Fetal Neonatal Ed.* 2004;89(5):F428-30.

Goal for Extrauterine Growth

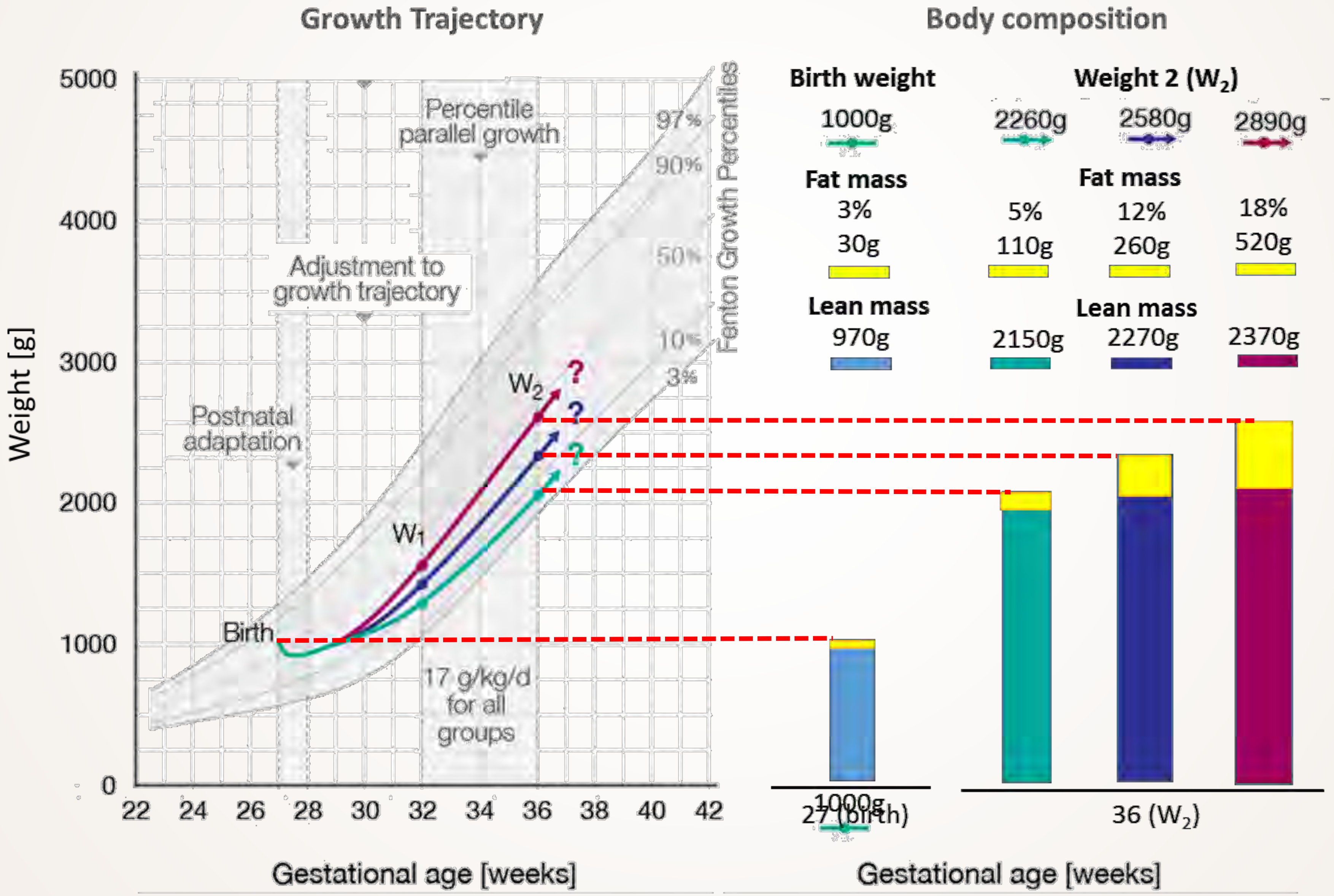
Question:

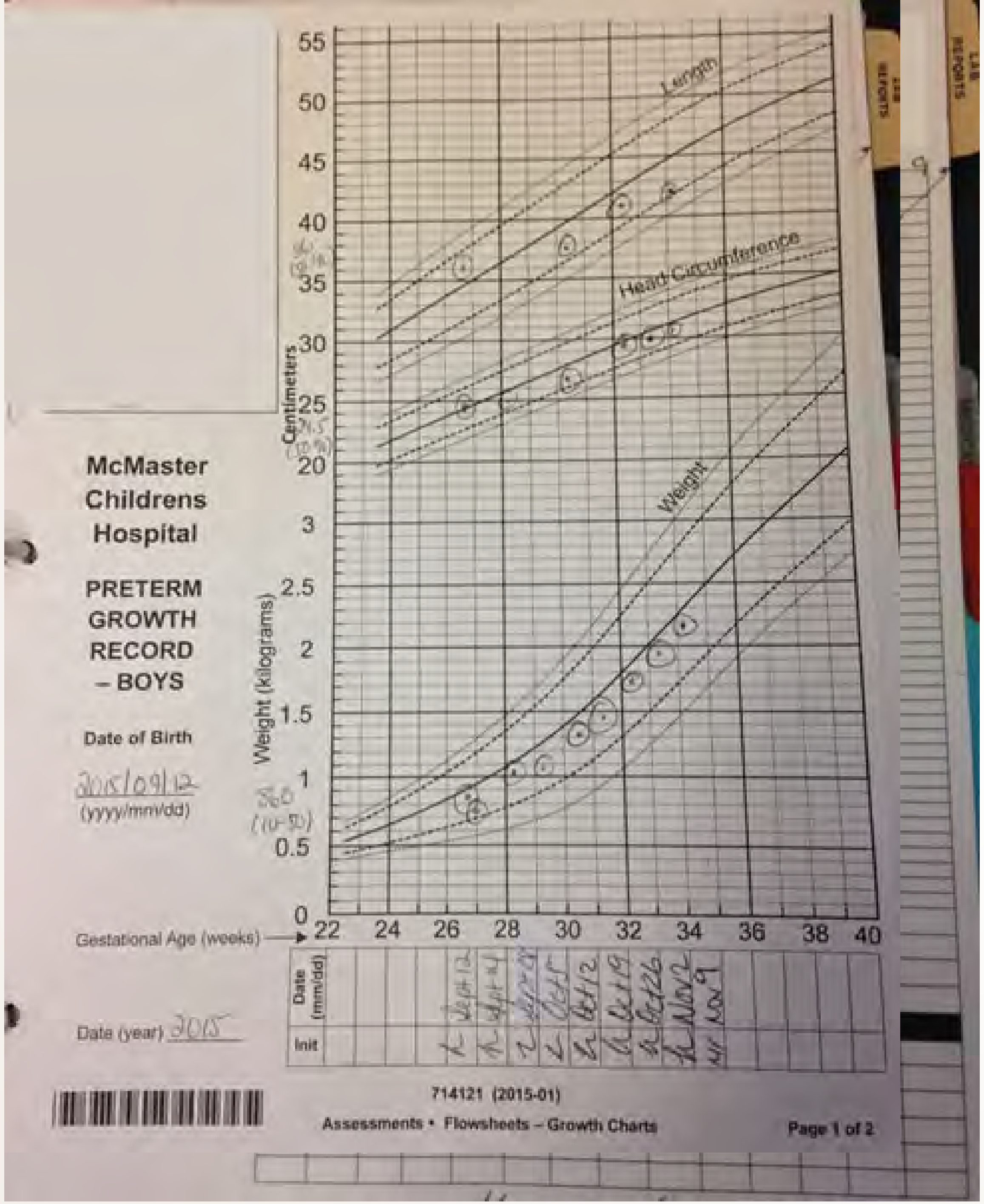
Which birth-weight percentile should preterm infants adjust to following completed postnatal adaptation?

BTW: Growth rates are all the same—same slope



Postnatal Trajectory Determines Body Composition and Risk for Early Onset of Adult Diseases (DOHaD—Barker Hypothesis)





Ways to monitor growth
Weight gain

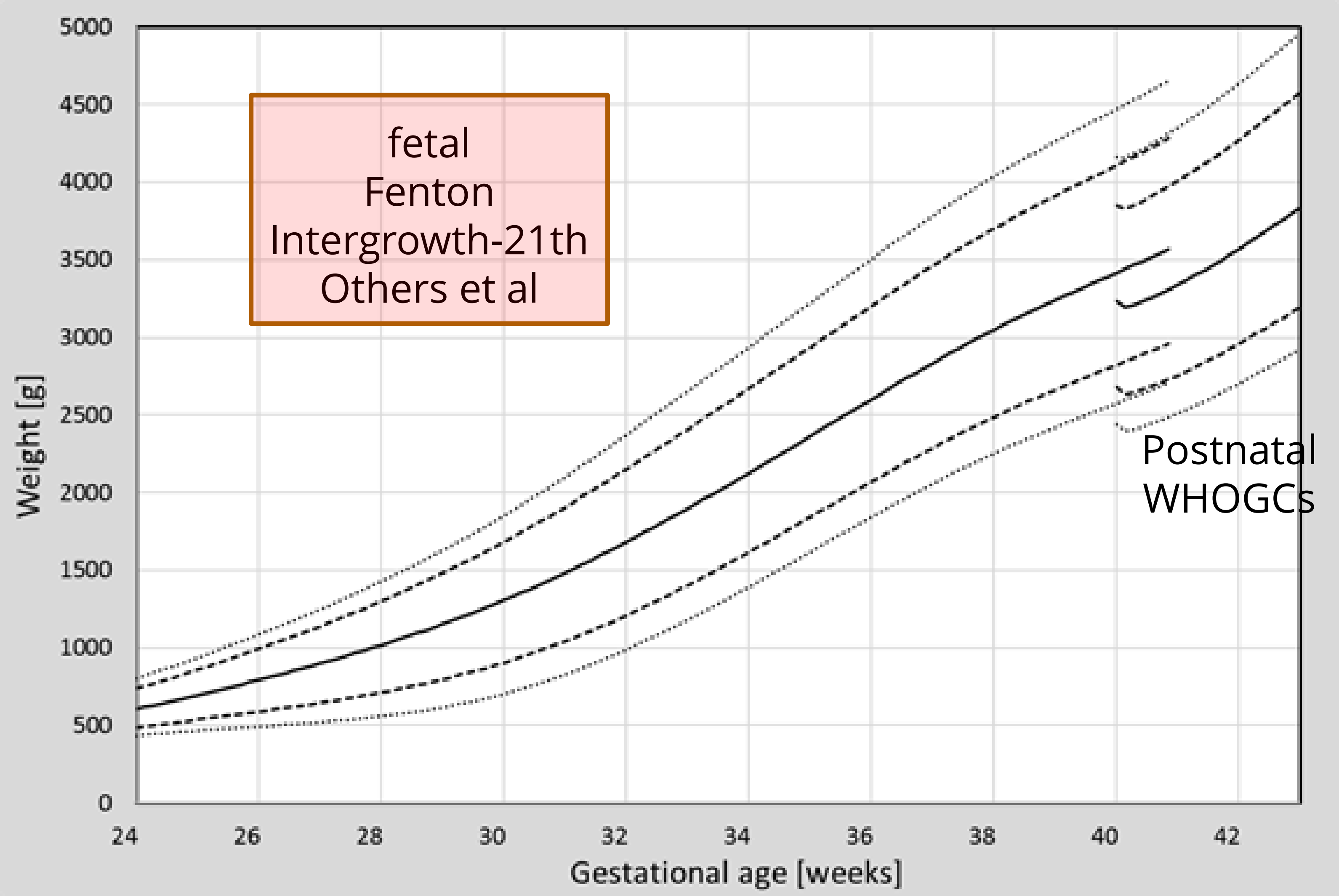
X-Y scatter plot

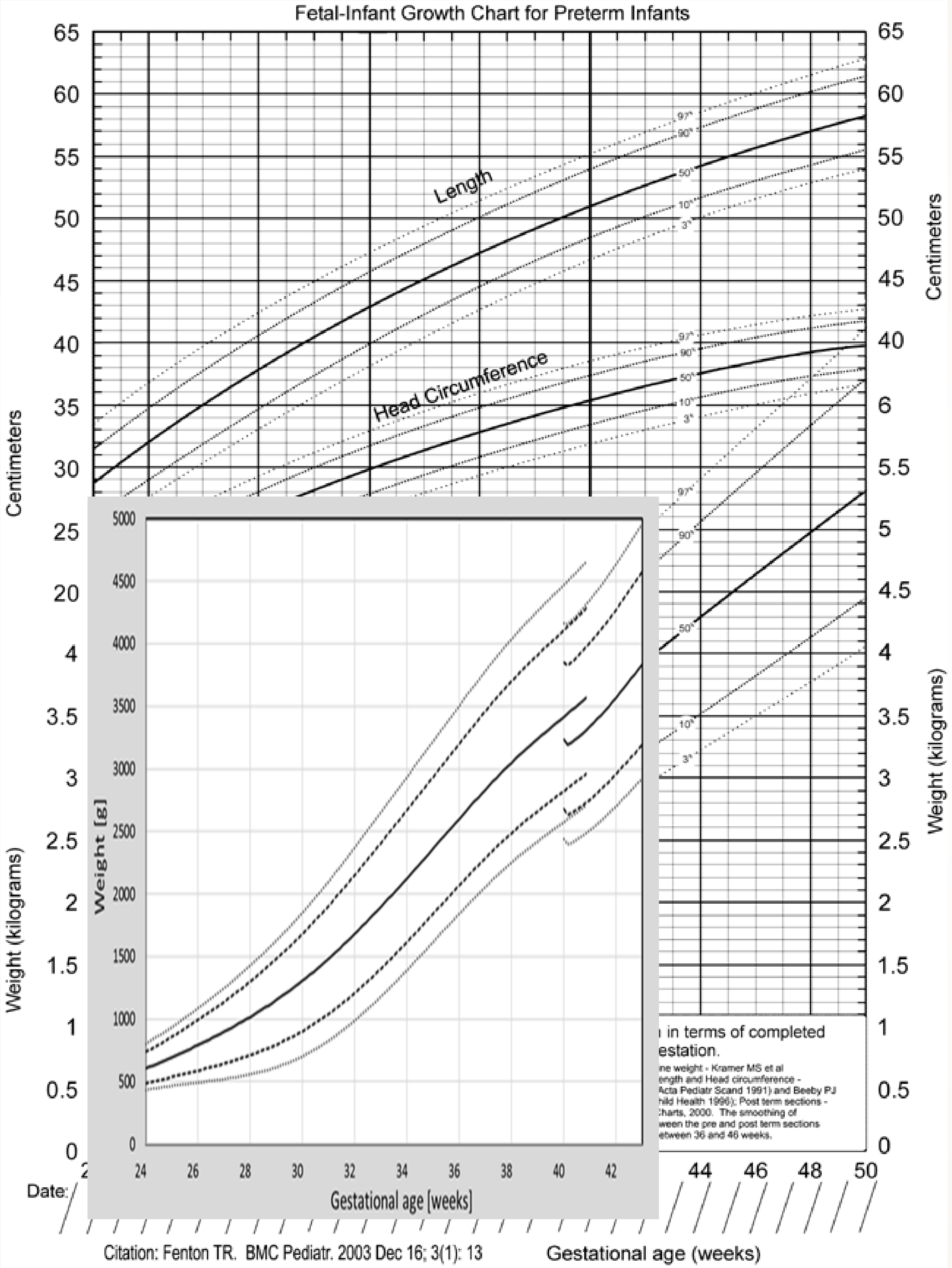
- No reference data
- Calculation of growth rates

Fetal growth charts

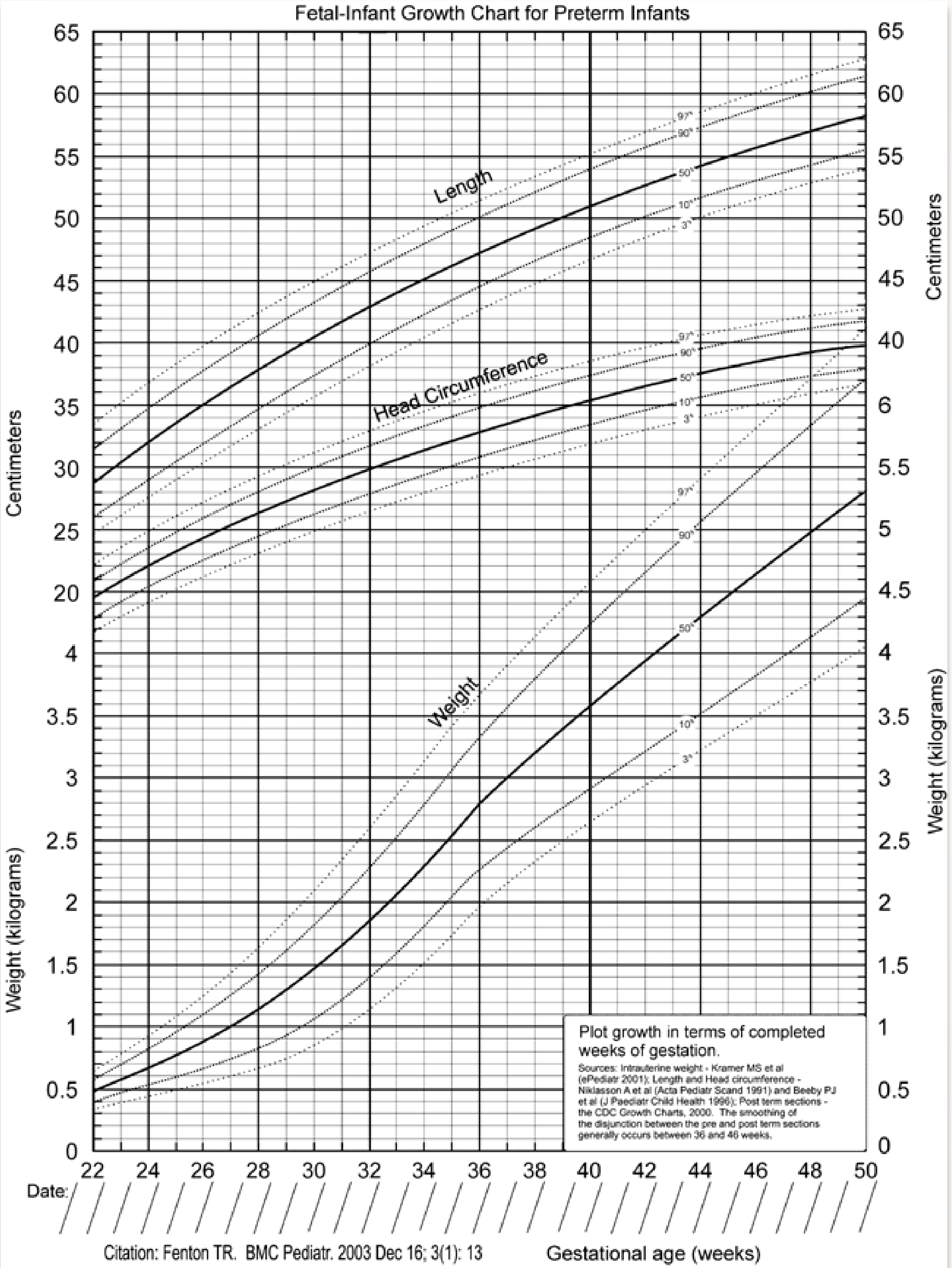
- Reference data
  (appropriate?)
- Where to grow?

Gap of fetal and post-term growth charts due to effects of postnatal adaptation





Combined intrauterine and WHOGS

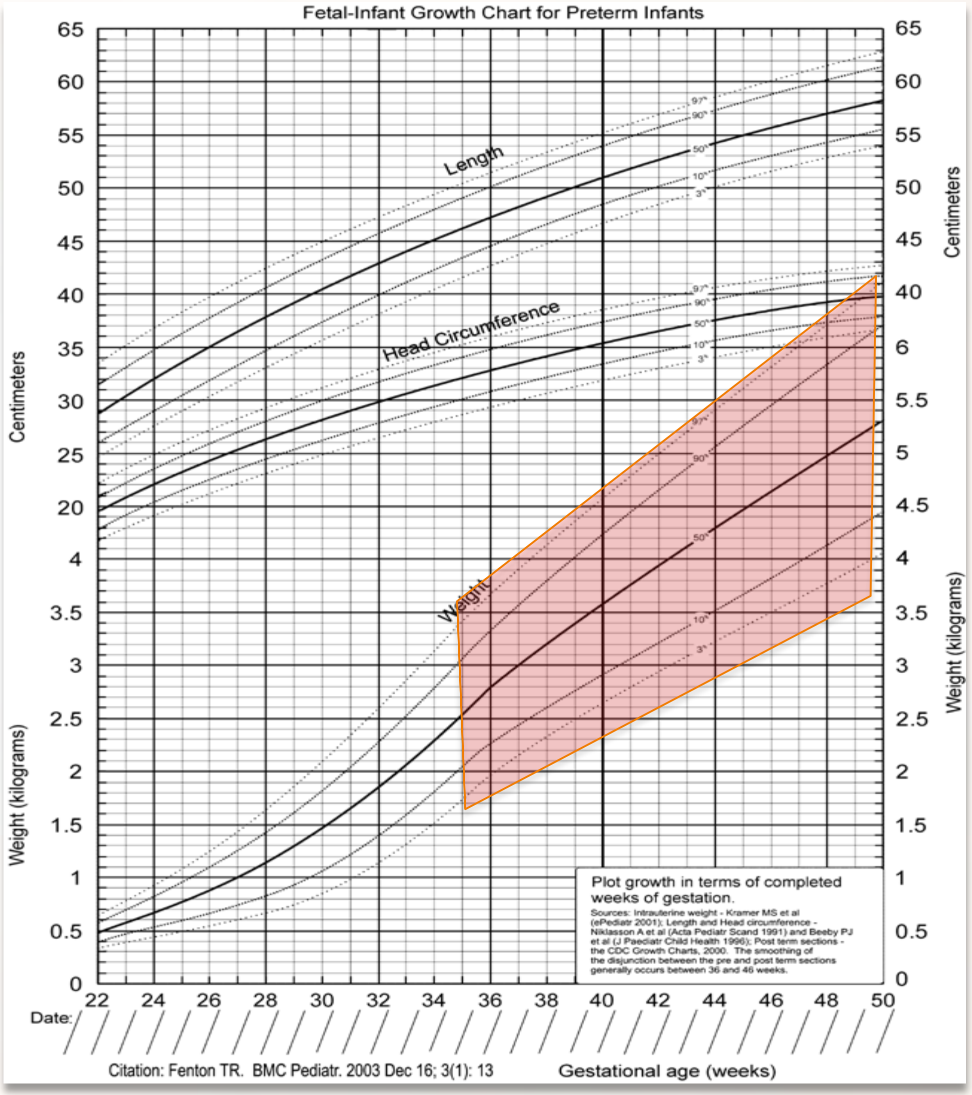


Combined intrauterine and WHOGS charts

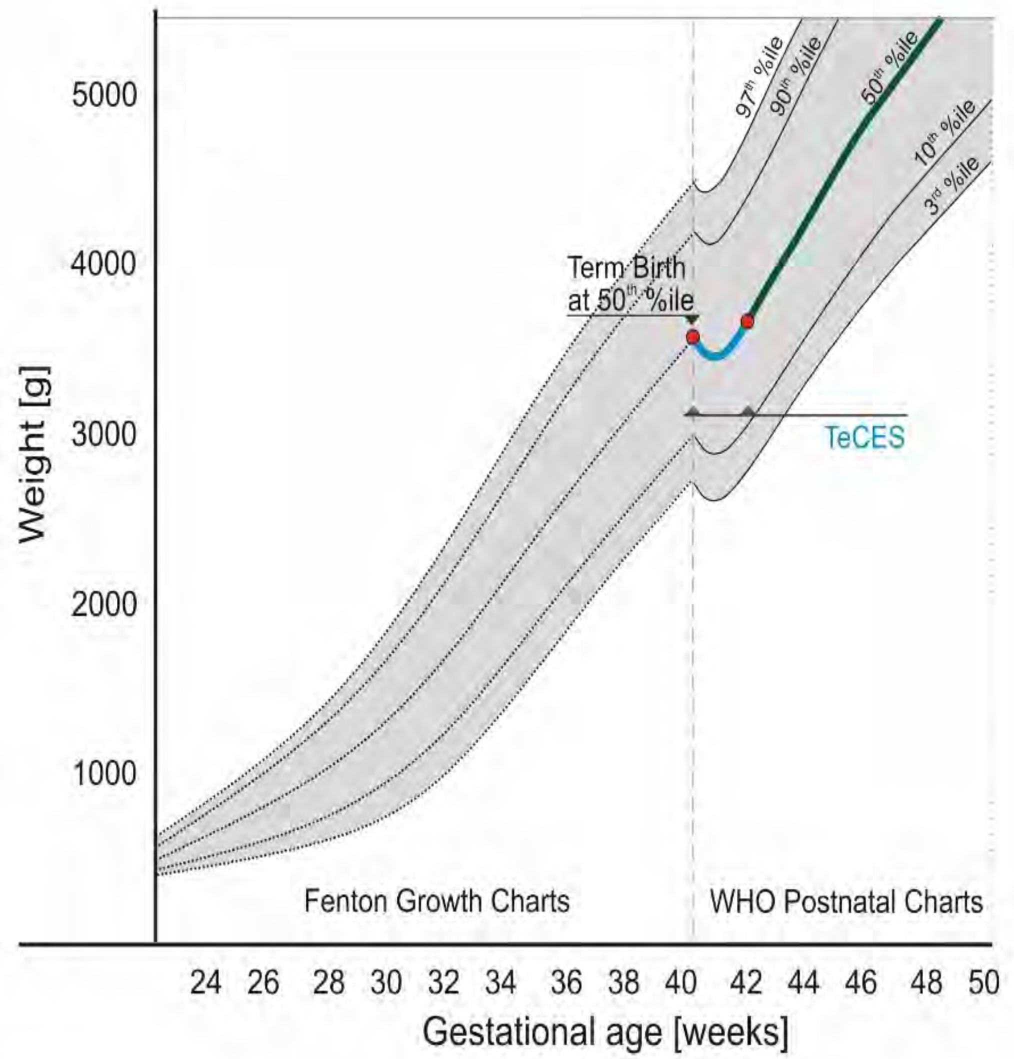
Smoothed around term (34–50 weeks) by Fenton

Current Growth Monitoring

- Charts developed from cross-sectional birth
- Weight data from infants with known gestational ages
- Smoothed from 35–50 weeks with WHO
- Great to monitor the transition from preterm period to infancy



Trajectories for Extrauterine Growth

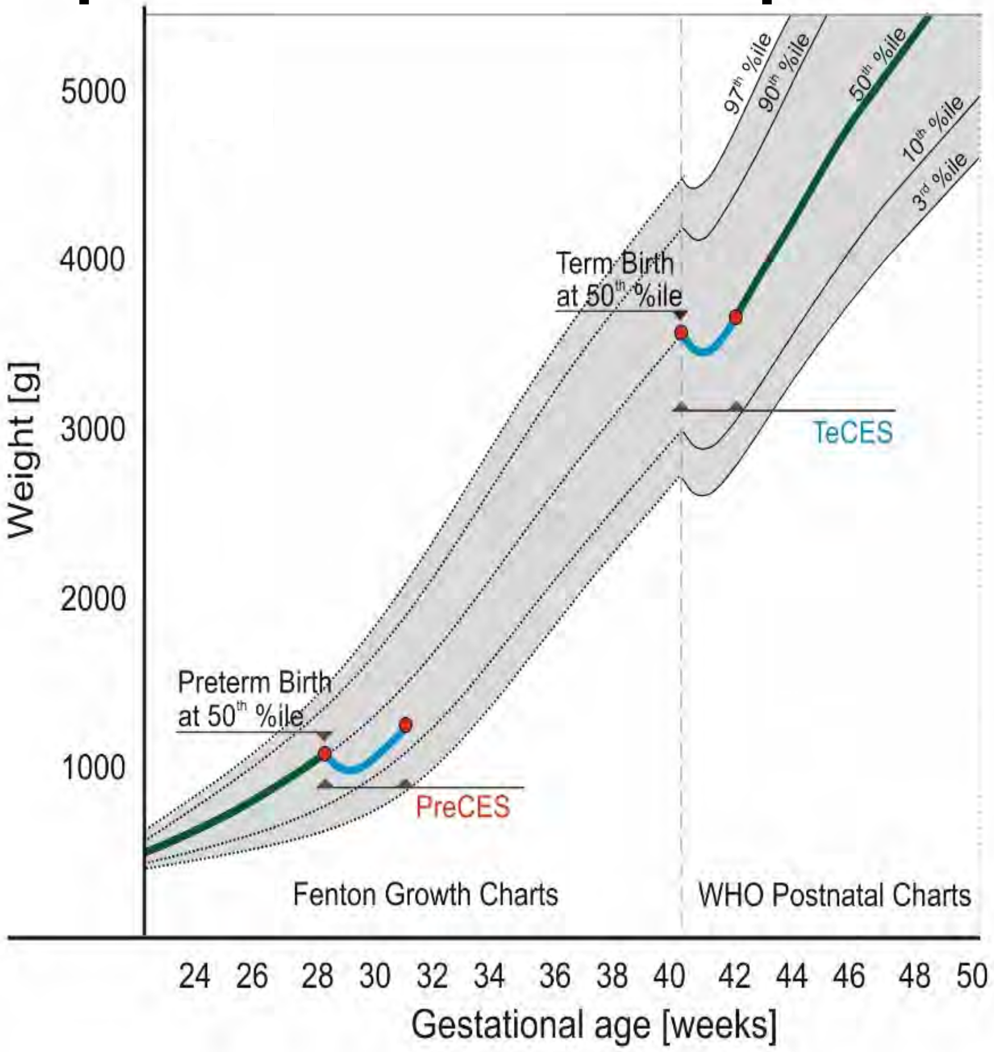


- The gold standard reference for term infants are the
  WHO Growth Standards
- Postnatal adaptation and weight loss is reflected in the WHO Growth Standards in the first two weeks

TeCES: **T**erm **C**ontraction of **E**xtracellular **S**paces

Trajectories for Extrauterine Growth

Premature rearrangement of water spaces due to premature birth
Implications for shift of postnatal growth trajectories

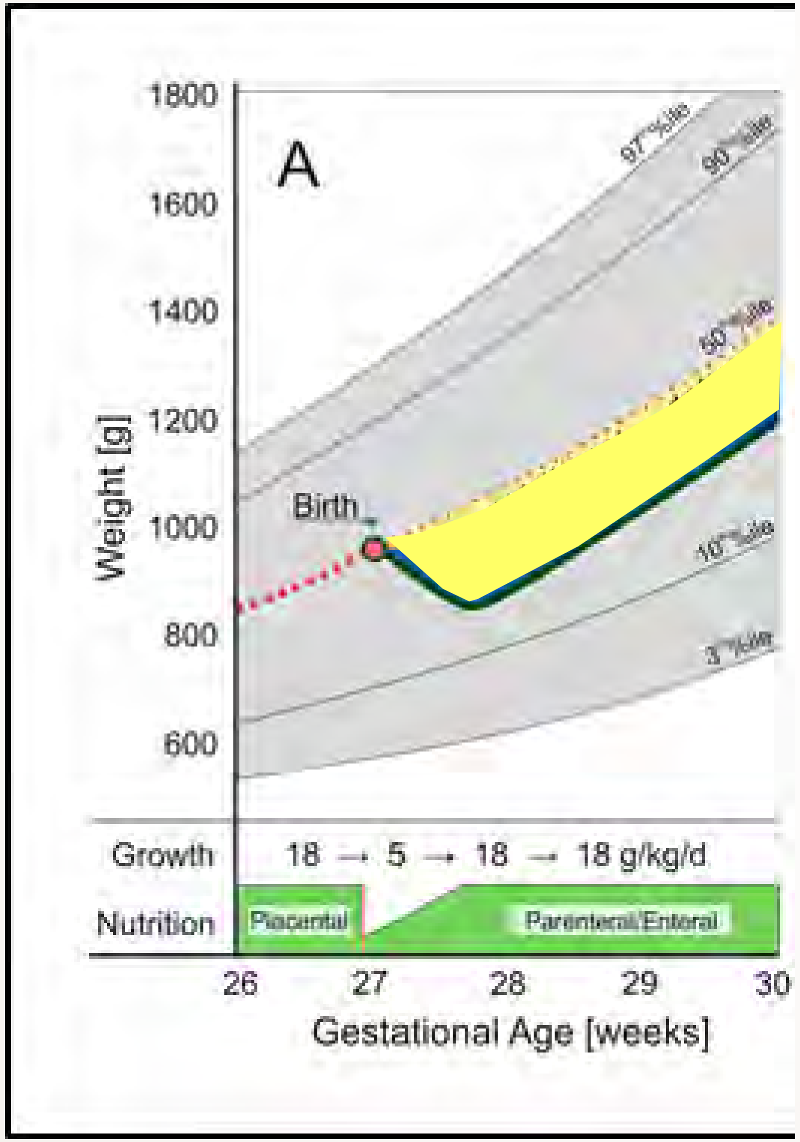


- Preterm infants also experience postnatal weight loss and therefore show an offset of growth trajectories
- Physiological postnatal growth curves for preterm infants are missing

PreCES: Preterm **C**ontraction of **E**xtracellular **S**paces

TeCES: Term **C**ontraction of **E**xtracellular **S**paces

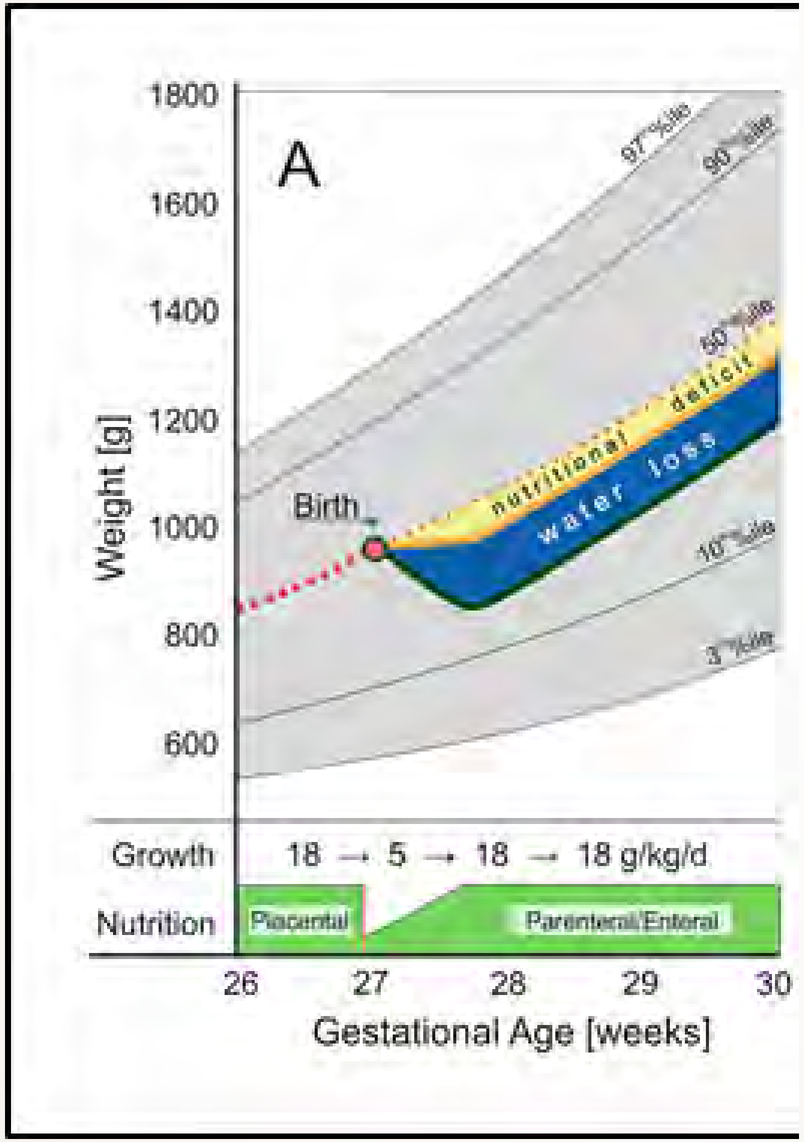
Postnatal Dynamics of Growth and Weight Gain: common understanding



"…All babies show a drop in body weight after birth, therefore they need some time until they restart to grow…"

Right?

Postnatal Dynamics of Growth and Weight Gain: common beliefs



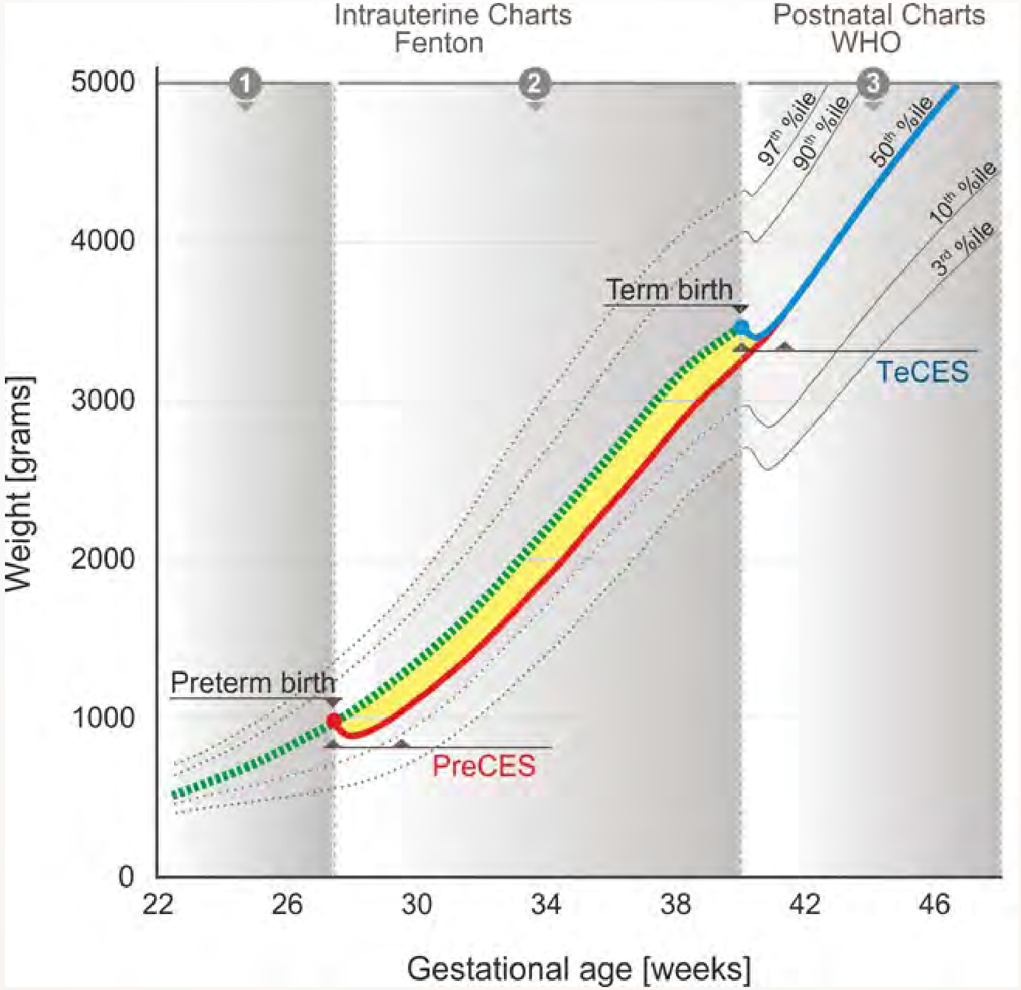
However:

TECES and PRECES:
This is a one-time, irreversible process.

In a preterm infants, ideally growth should slow down only for a short period of time—until nutrient intake meets the needs for continued growth

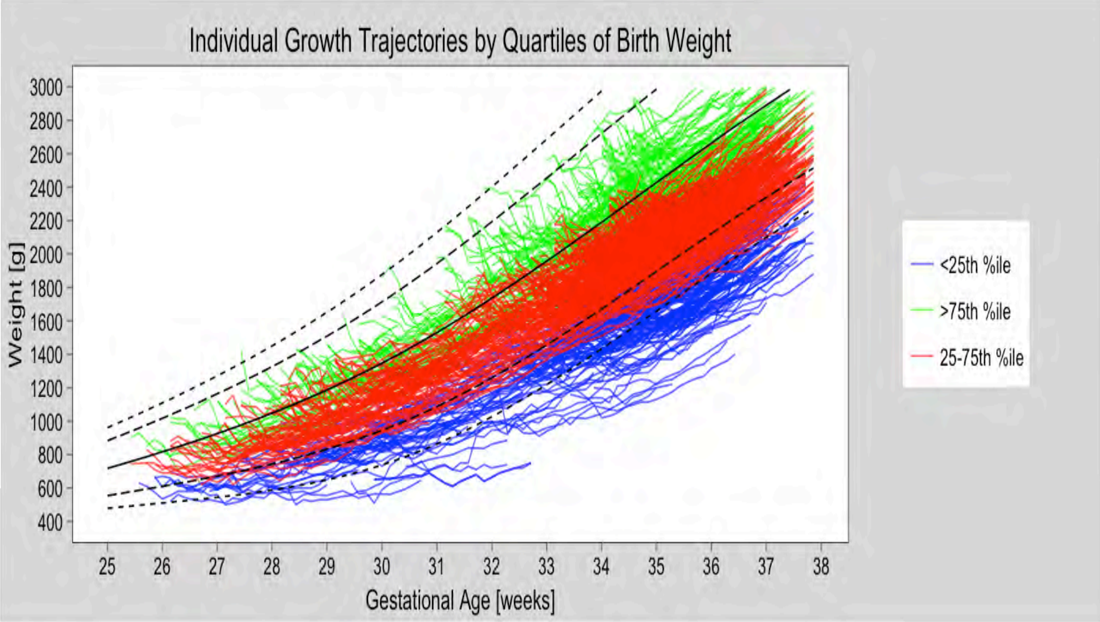
Premature rearrangement of water spaces due to premature birth
Implications for shift of postnatal growth trajectories

Individual fetuses in general grow on “their” intra-uterine percentile and transition to the corresponding postnatal one (Mei et al 2004)

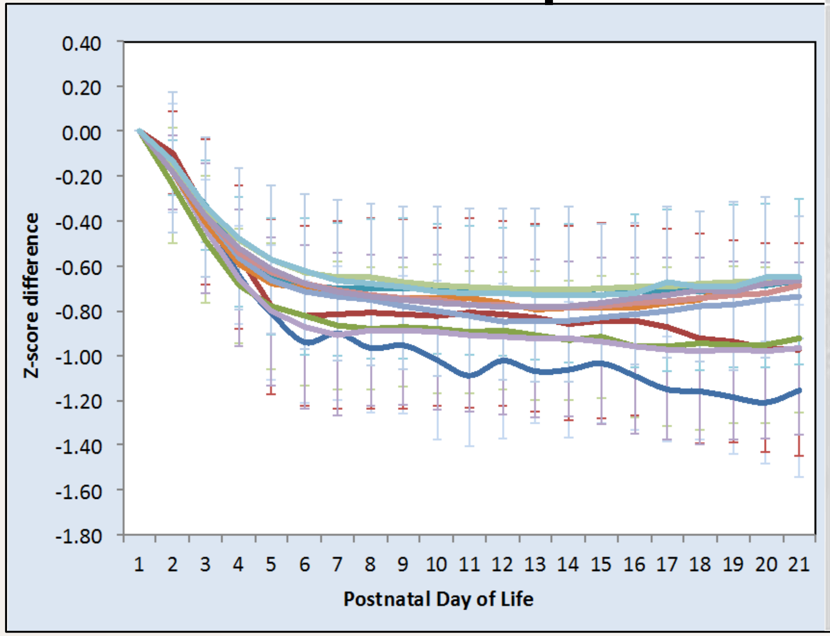


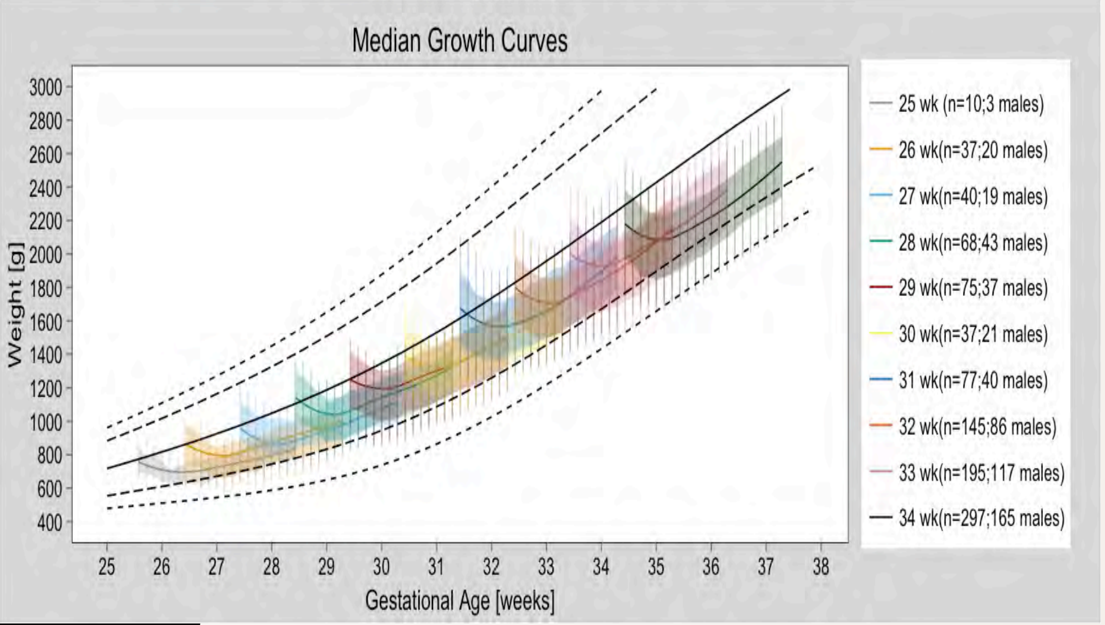
Changes in body weight of healthy non-IUGR preterm infants from birth during the first two

Center	GA	MUMC CDN	UHH GER	UHG GER	SMH CDN	SJH CDN	total
		Level III			Level II		
Screened	total	1,633	888	449	403	330	3,703
	25-29	461	194	137			792
	30-34	1,172	694	312	403	330	2,911
Include & analyze	total	185	344	100	140	212	981
	25-29	107	58	65			230
	30-34	78	286	35	140	212	751



The new percentile seems to be 0.8 Z-scores below the birth percentile





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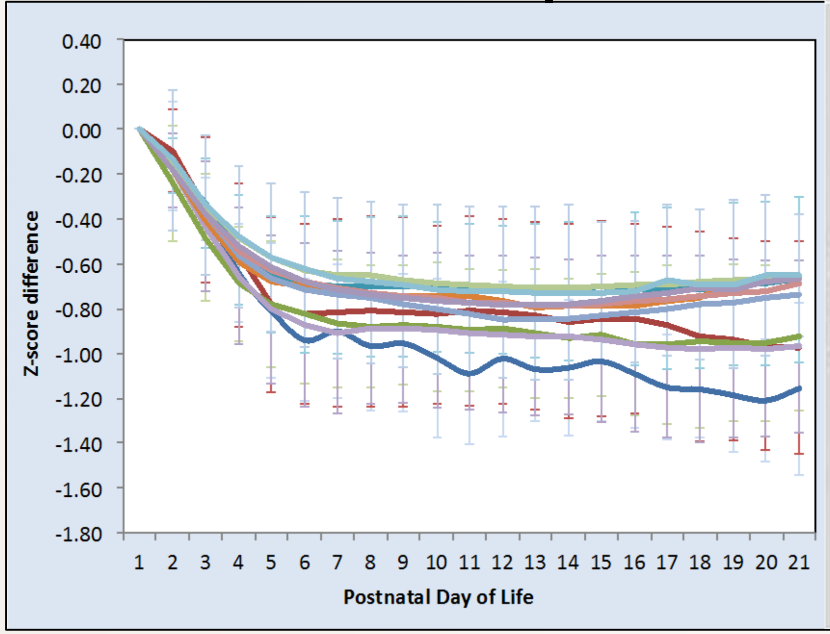
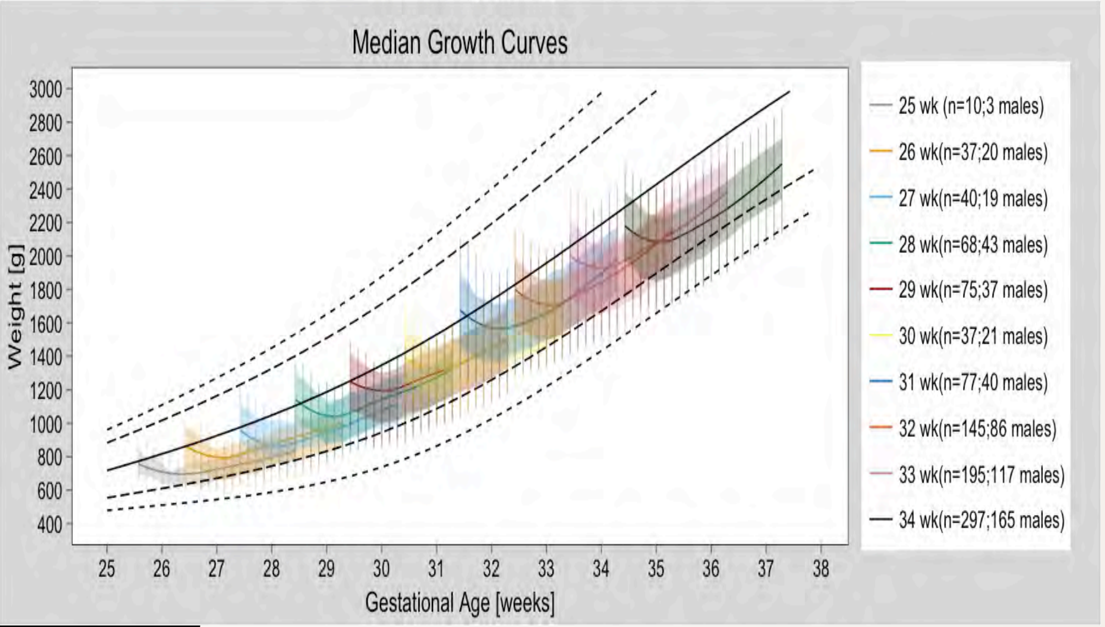
Include & analyze	total	185	344	100	140	212	981
	25-29	107	58	65			230
	30-34	78	286	35	140	212	751

No difference between NICUs despite moderate differences in fluid and nutritional protocols

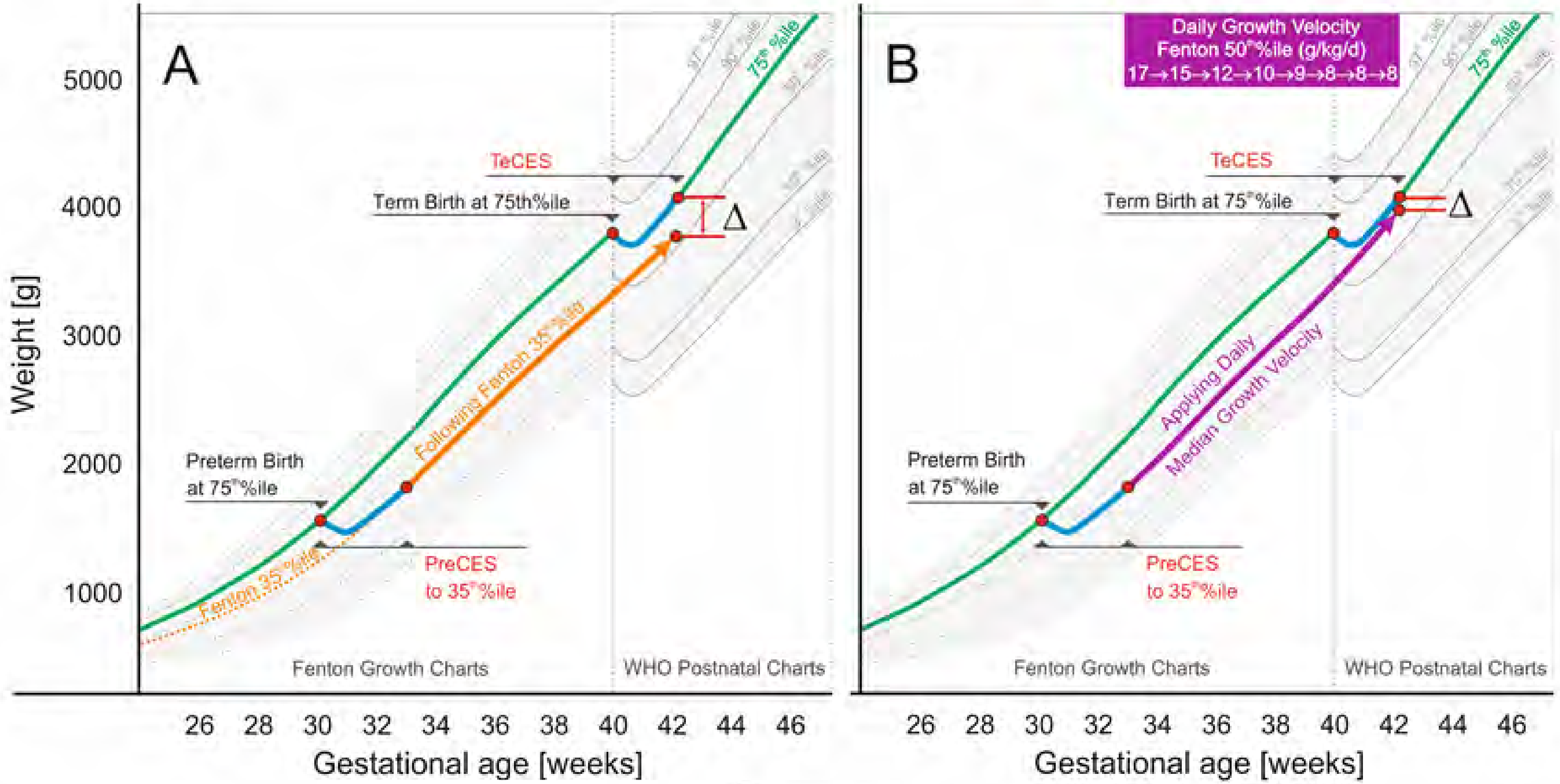
The new percentile seems to be 0.8 Z-scores below the birth percentile





Hypothesis to test: prediction of weight at 42 weeks by applying different concepts of postnatal growth

Postnatal percentile approach **Growth velocity approach**



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Individualized Postnatal Growth Trajectories for Preterm Infants

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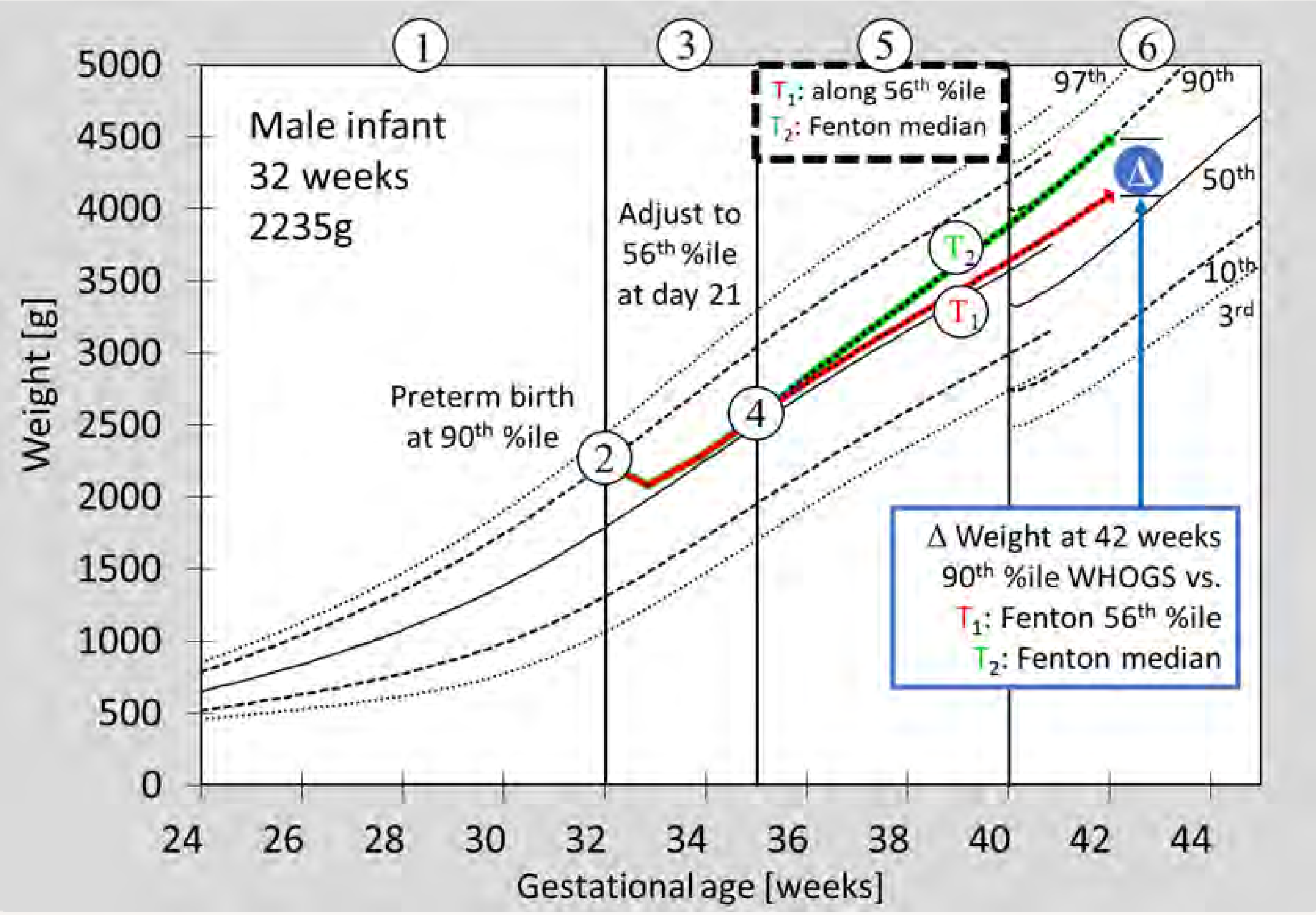
Concept of dynamic growth trajectories combining 5 principles

1. Fetal growth charts (Fenton),
2. Postnatal growth charts (WHOGS)
3. Theorem: a healthy fetus follows its intrauterine percentile and adapts to the corresponding postnatal percentile (Mei)
4. 21-day adaptation (Rochow/Fusch)
5. Median daily growth rates (Fenton)

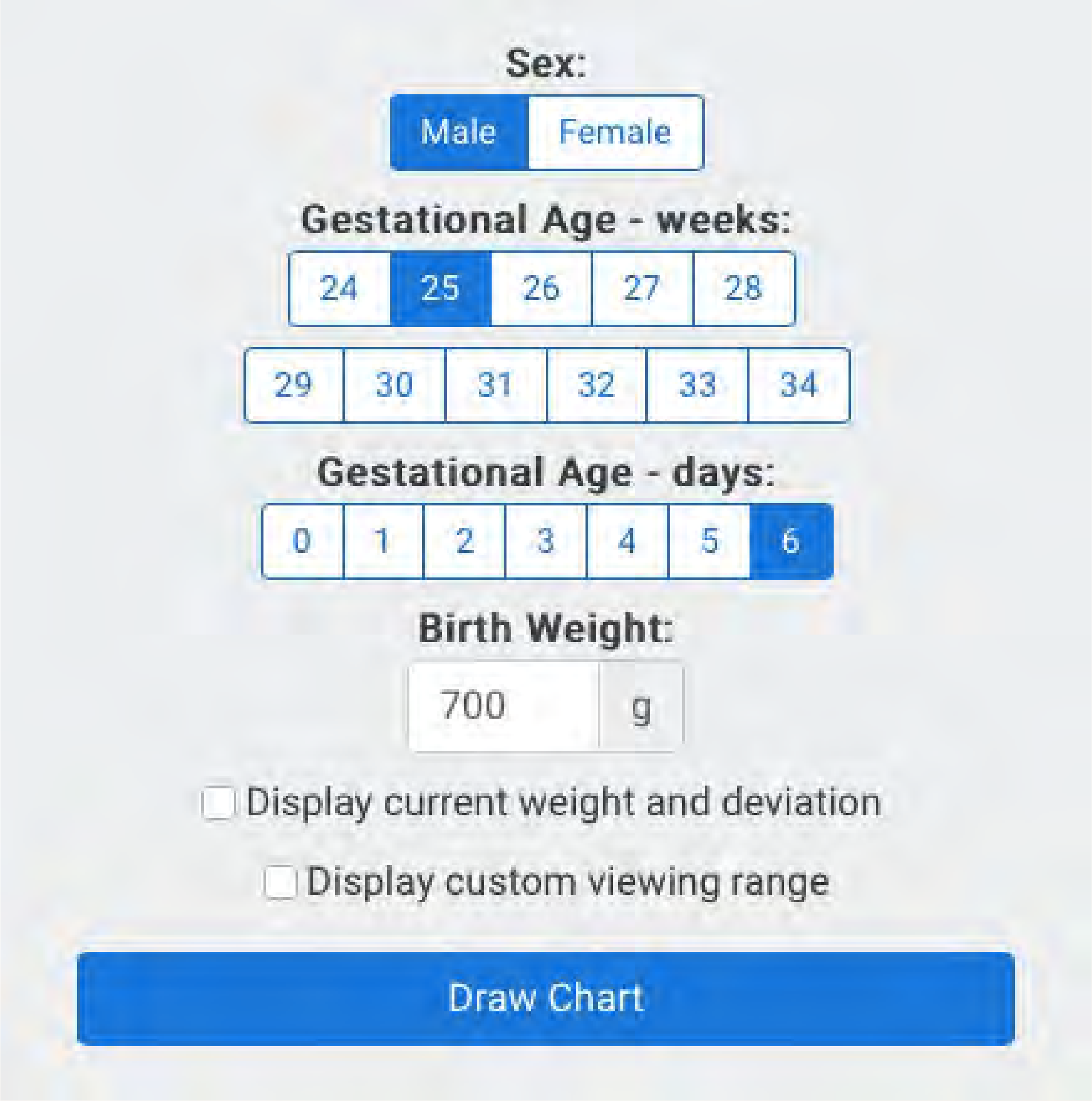


Growth model:(1) intrauterine growth on Fenton chart; (2) preterm birth (3) postnatal adjustment of growth trajectory during first 21 days; (4) day of life 21 (5) period of stable growth: T1-percentile-course approach or T2-growth-velocity-approach; (6)weight differences at 42 weeks between WHOGS and individual growth trajectory using T1 or T2 in post-term period

Growth Trajectory Calculator

Web-based **growth trajectory calculator** for preterm infants for gestational ages between 24- and 34-weeks PMA and all birth weights:

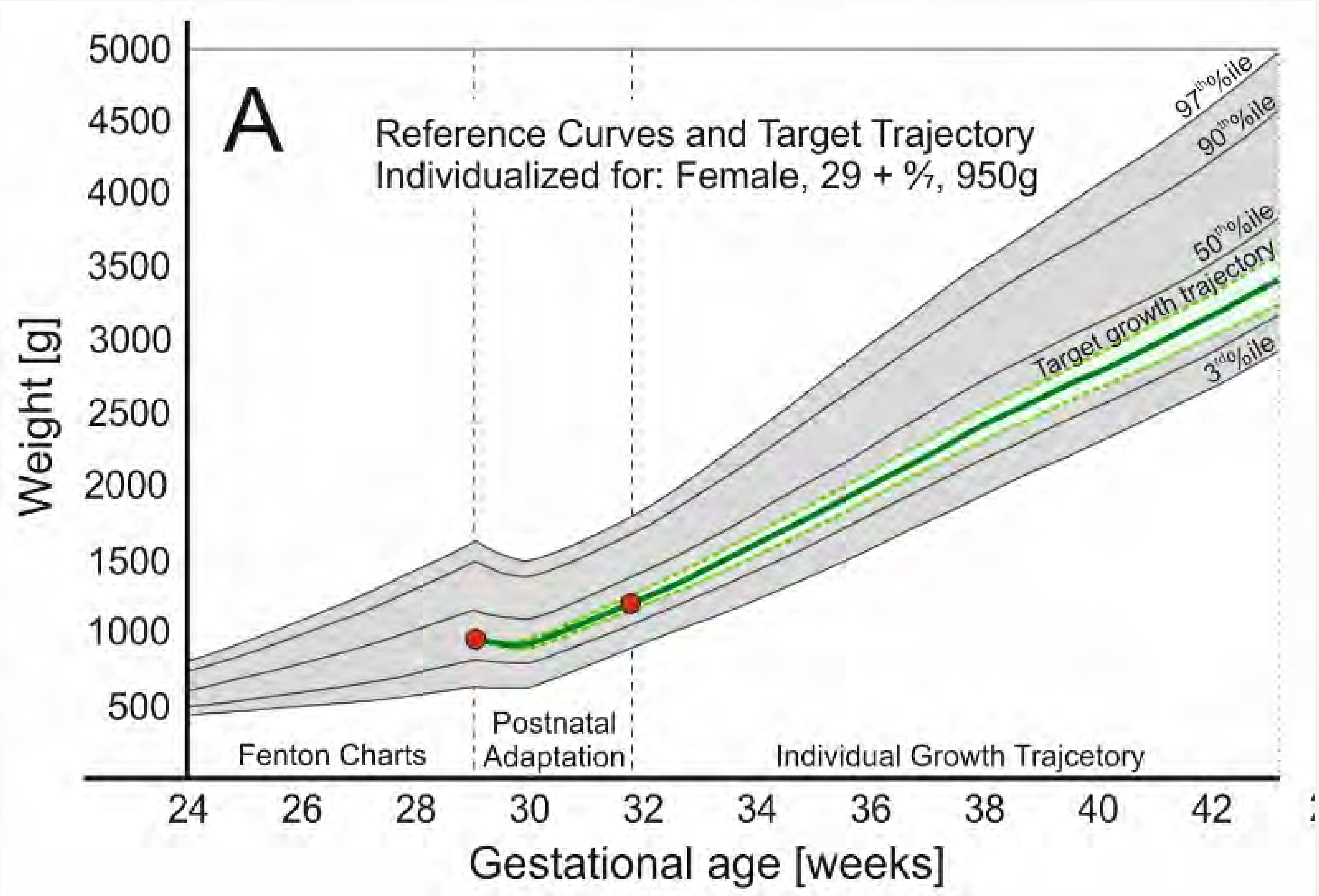
http://www.growthcalculator.org/



PMA, postmenstrual age.

Rochow N, et al. Online Calculator. 2016; http://www.growthcalculator.org/.

Individualized Growth Trajectory Concept:



Postnatal growth rates are about 10% higher compared to intrauterine growth rates.

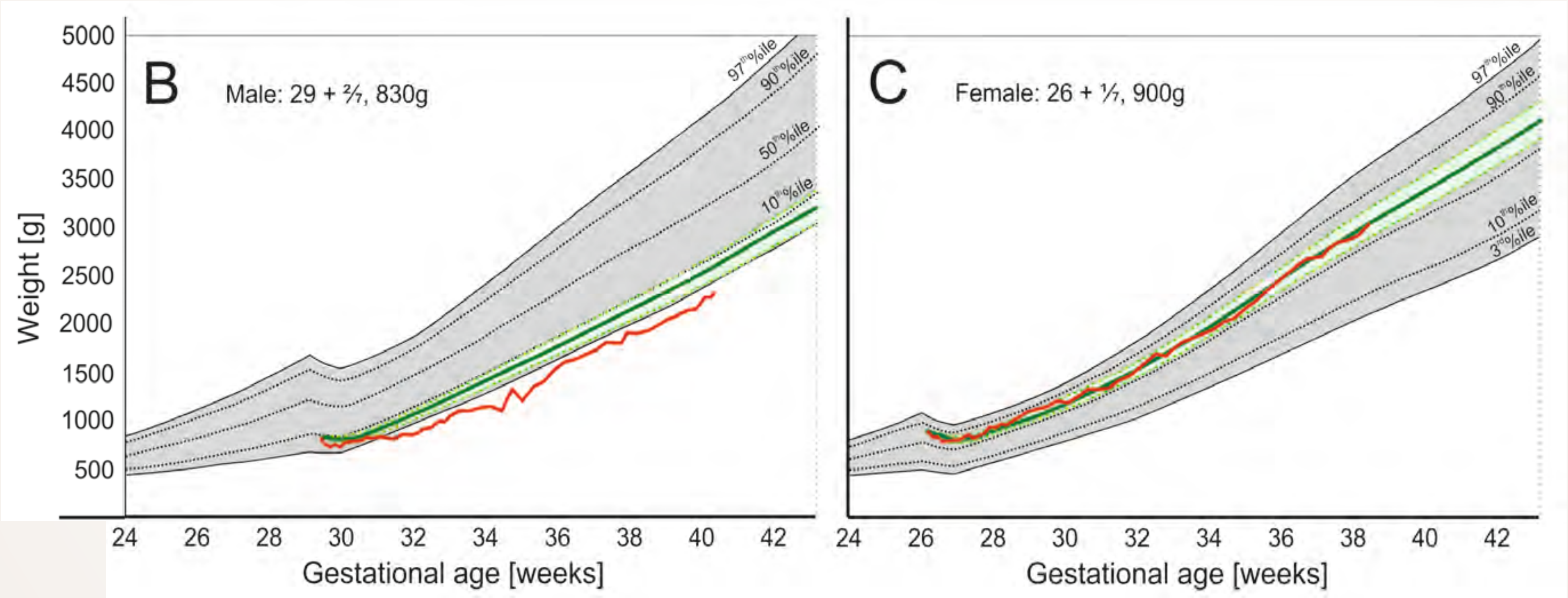
Growth Charts under

www.growthcalculator.org

New definition of PGR?

Two different real infants' weights plotted (red)

Deviation by 1 or 2 confidence intervals

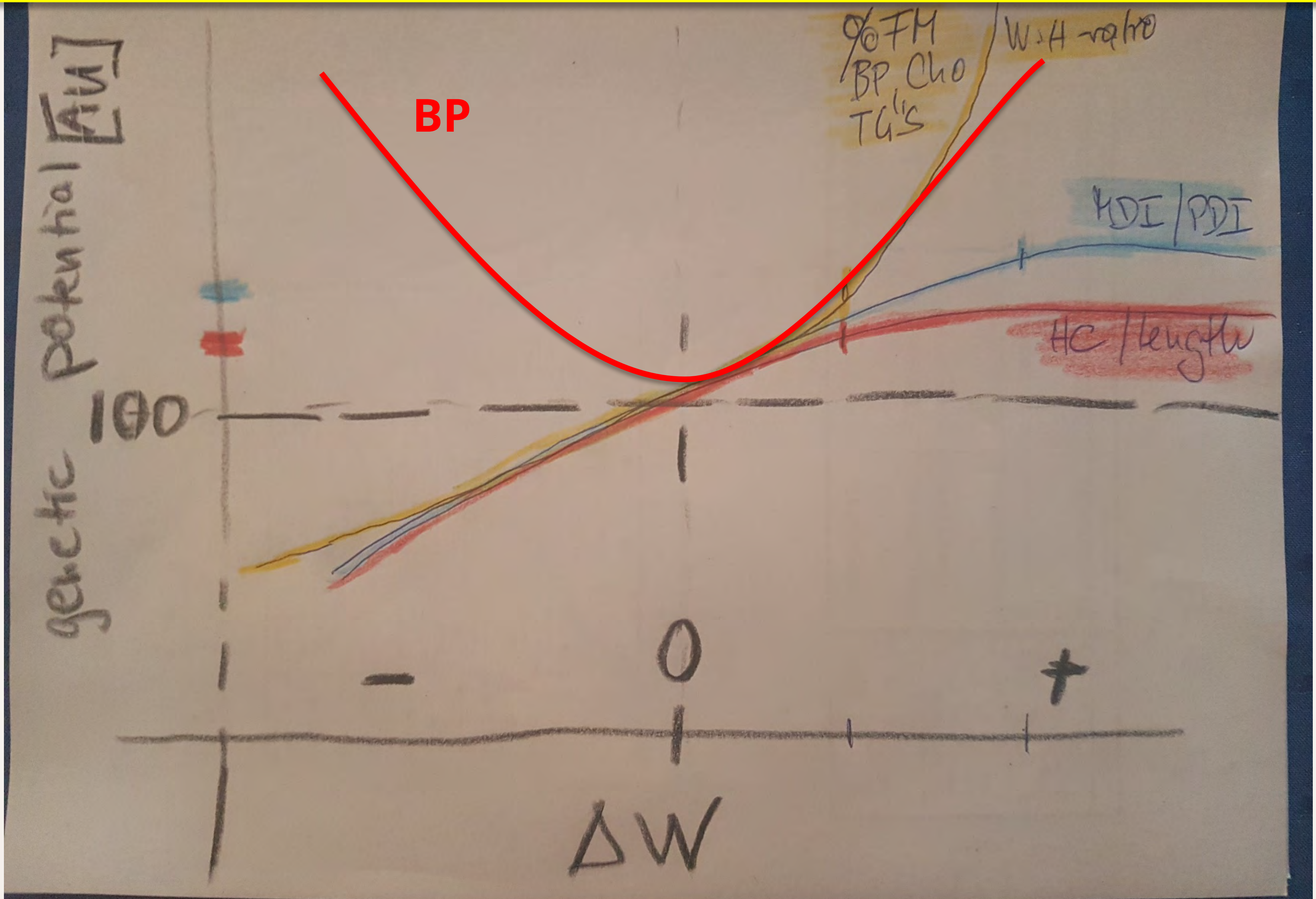


Current Research

Validation of growth calculator

- With a larger sample size of infants (n = 14.000) from databases in Canada (McMaster), Germany (Nuernberg, Rostock, Dresden, GNN), Australia (Adelaide GINO study), Sweden (Stockholm) and US (Wilmington, Boston)
- Against outcome based data
- Using weight, body composition, neurodevelopment (Bayley III), cardiovascular data
- Correlate with deviation from target trajectory to assess appropriateness of the model in relation to disease risk

Deviation from optimal growth trajectory and impact on outcome variables



Individualized growth trajectories for preterm infants
Associations with short-term outcomes

N. Rochow, P. Kosmann, HY. So, E. Rochow, E. Landau-Crangle, D. Wackernagel, C. Collins, Z. Khan, D. Moya, D. Kontantelos, W. Göpel, C. Härtel, M. Belfort, M. Blennow, M. Makrides, B. Urlesberger, F. Moya, M. Rüdiger, C. Fusch

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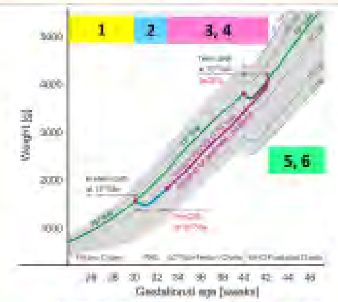
INTRODUCTION

- Individualized postnatal growth trajectories (GTC) for preterm infants based on 6 physiological principles were developed (Fig.1).
- These provide daily reference weights from birth to 42 weeks of postmenstrual age (PMA).



Principles:

1. fetal growth charts (Fenton)
2. 21-day adaptation (Rochow/Fusch)
3. median daily growth rates (Fenton)
4. correct growth rates by ~10%
5. postnatal growth charts (WHOGS)
6. theorem: a healthy fetus follows its intrauterine percentile and adapts to the corresponding postnatal percentile (Mei)

www.growthcalculator.org

Fig.1: Principles of the GTC trajectories

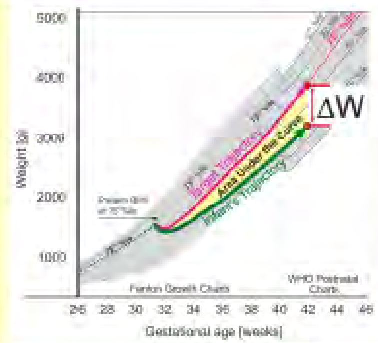
OBJECTIVE

- 1) to compare observed deviations of weight (ΔW) from the GTC trajectory between cohorts.
- 2) to analyze relationships between ΔW and short-term outcomes.

METHODS

- International multicohort study, including infants with a gestational age (GA) from 22 to 33 weeks with weekly or daily weight data
  - from eight local cohorts (Austria, Germany, Sweden, Australia, Canada, USA)
  - and the German Neonatal Network (birth weight (BW), 35 weeks PMA, discharge) during 2001 to 2017.
- The relationship of ΔW with head circumference, length, lean mass, fat mass, and blood pressure at discharge, adjusting for major NICU morbidities were analyzed.
- The relationship of ΔW-AUC with outcomes was assessed for 2-week periods from birth to discharge using a sequential multinomial logistic regression. Level of significance was $p<0.05$.

METHODS



- *For each infant, the GTC trajectory was calculated based* on GA, BW, and sex. The difference between the GTC trajectory and
  → 1) individual weights at various single time points (ΔW), and
  → 2) deviations integrated over the NICU stay (ΔW-AUC) were determined.

Fig. 2: ΔW from GTC

RESULTS

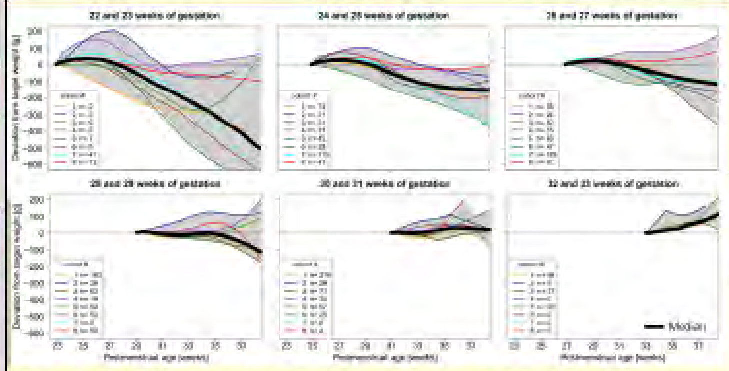


Fig. 3: Median deviation from target weight for different gestational ages for all subjects (black line) and single cohorts (coloured lines).

- Results: In this study, 2,027 infants from 8 cohorts (998 <28 weeks) and 15,971 infants from the German Neonatal Network (6,558 <28 weeks) were included.
- At 36 weeks, preterm infants showed a significantly different ΔW for GA and cohort (Fig. 3).

RESULTS

- Below 28 wks, median ΔW was large with cohort-specific variations (Fig. 3).
- However, some centers achieved growth, even for very low gestational age infants, which matched with the GTC trajectory.

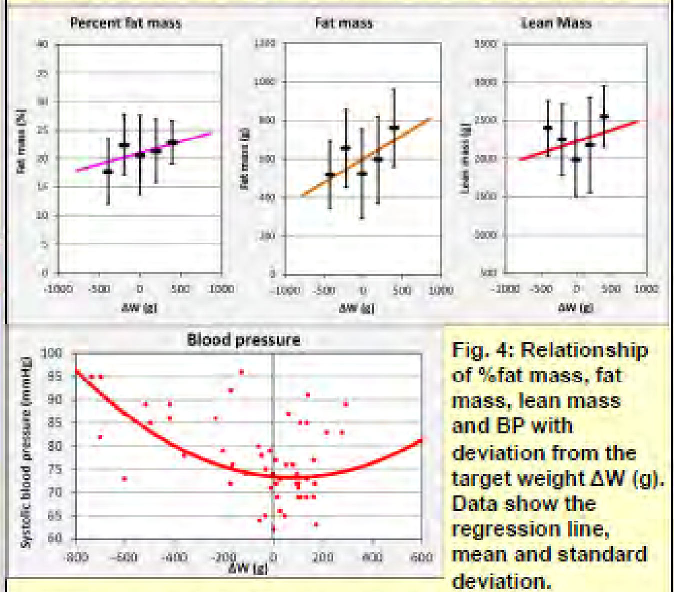


Fig. 4: Relationship of %fat mass, fat mass, lean mass and BP with deviation from the target weight ΔW (g). Data show the regression line, mean and standard deviation.

- At discharge, HC, length, fat mass (absolute and %), and lean mass were significantly related to ΔW ($p<0.05$) (Fig. 4).
- Blood pressure before discharge tended to be higher with high ΔW.
- Converging towards GTC trajectory seemed to improve outcomes while diverging was related to unfavorable outcomes.

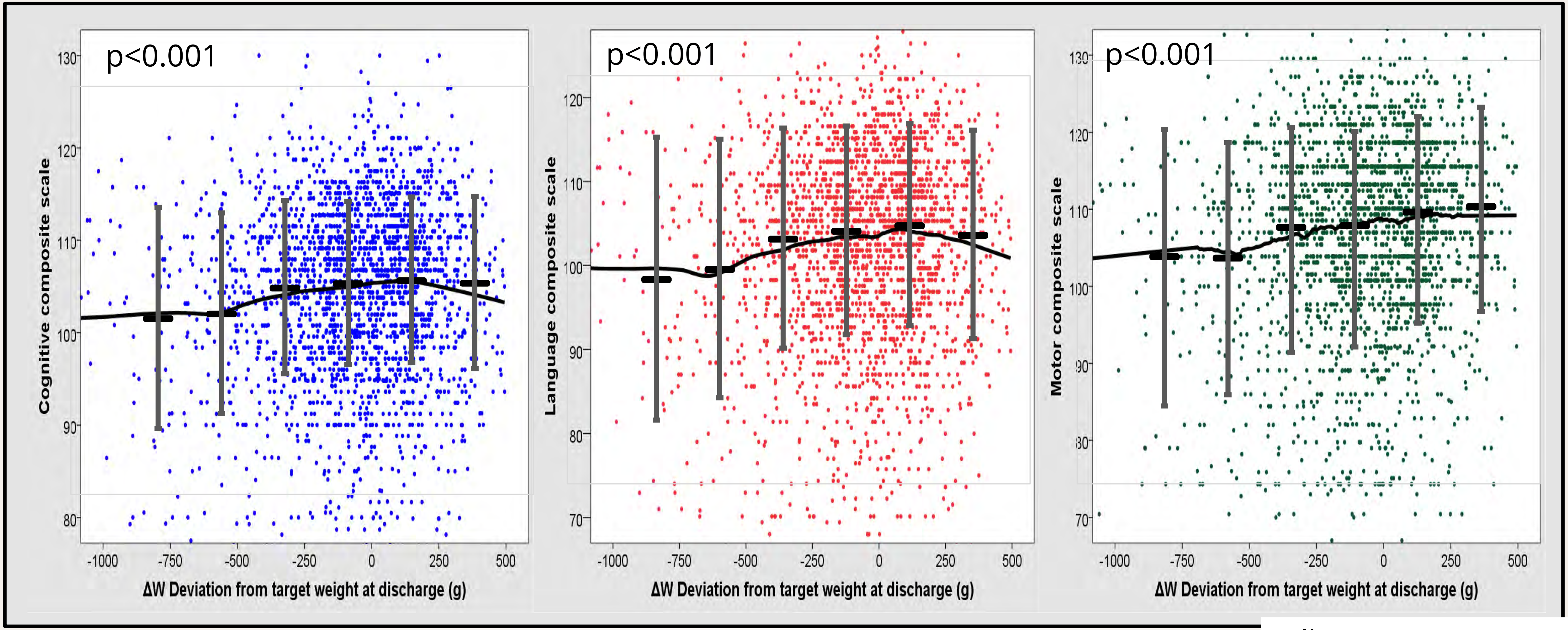
CONCLUSION

- This is the first study to analyze actual growth of preterm infants by comparing them to individual GTC.
- Outcomes were independently related to growth pattern.

Dr. Christoph Fusch, MD, PhD, Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada, e-mail: fusch@mcmaster.ca - www.growthcalculator.org

Results: Neurodevelopment at 18–24 months Assessed by Bayley Scale was Related to ΔW (n= 3152)

Cognitive Composite Scale | Language Composite Scale | Motor Composite Scale

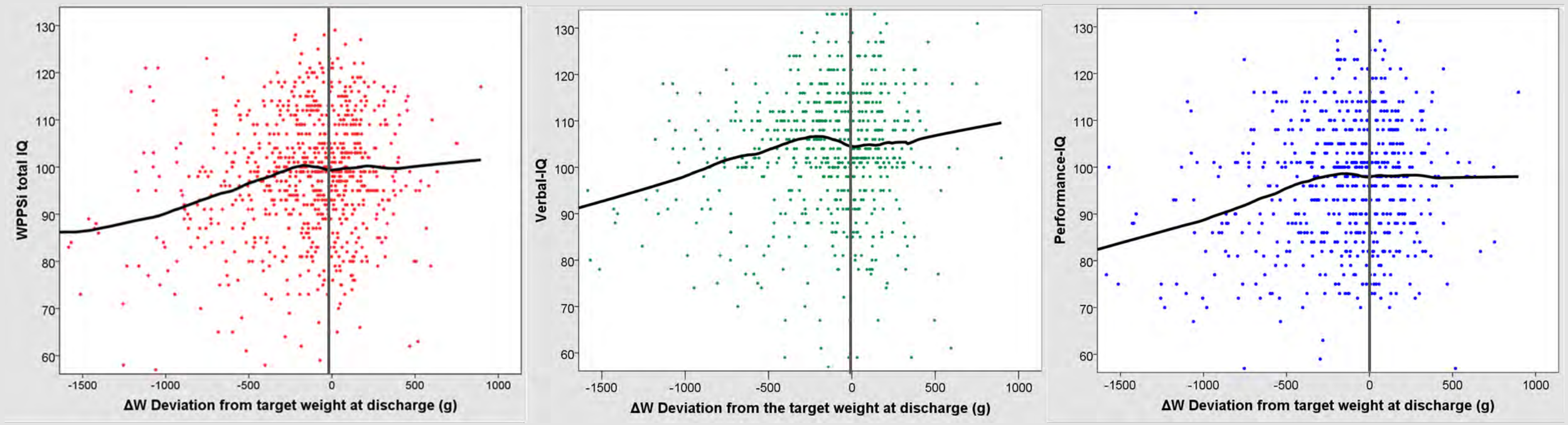


On average, 1 point increase per 10% weight difference for all 3 indices

(all centers except 5)

Results: Relation between Neurodevelopment and ΔW at 5 years

- At 5 years, the total IQ and verbal IQ WPPSI scores were significantly related to ΔW (N= 1511, $p<0.05$)
- For deviations from the target trajectory less than -250g, there was a positive relationship between higher growth and better neurodevelopment outcomes
- Above 250g deviation from the target trajectory, there was no significant relationship with neurodevelopment



Clinical Validation of Individualized Growth Trajectories

- California Quality perinatal org using ‘our curves’ to assess growth

- Portugal also using these curves

NUTRITION PHYSIOLOGY FOR GROWTH

Optimal, Individual Nutritional Management

Physiology: How Babies Should Grow

- Term vs preterm postnatal growth
- Critical to understand how preterm infants *should* grow
- A balanced diet is needed for optimal growth
- DOHaD concept suggests suboptimal growth of a fetus or a newborn infant can impact early onset of adult metabolic and cardiovascular diseases
- How can we meet preterm postnatal growth strategy?

DOHaD, Developmental Origins of Health and Disease.

Rochow N, et al. Pediatr Res. 2016;79:870-9.

In utero Growth

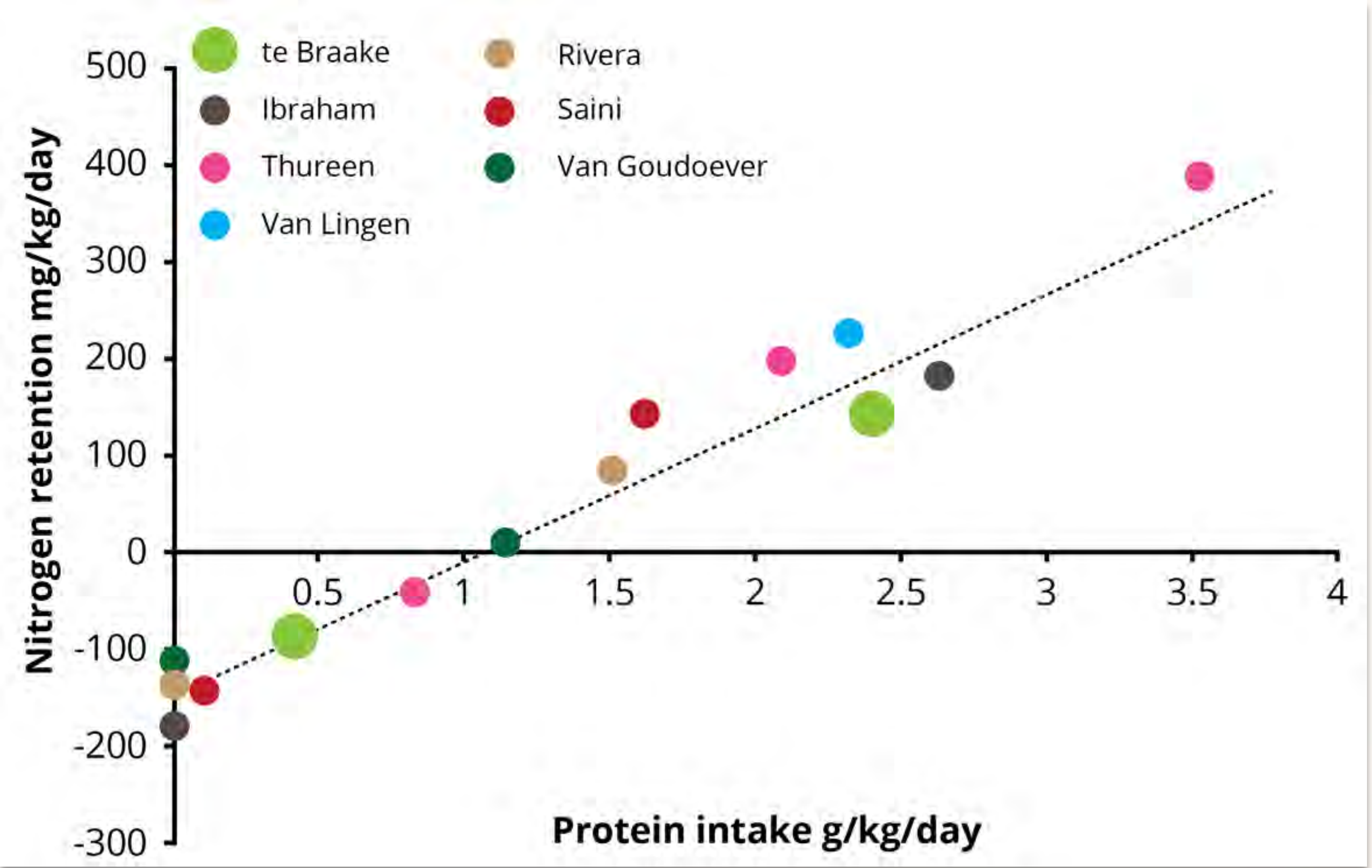
Growth rate of a fetus is determined by its genetic potential and modified by 'environmental' factors, such as:

- Maternal nutrition
- Body composition
- Pathologies

Rochow N, et al. *Pediatr Res.* 2016;79:870-9.

Amino Acids and N2 Retention in First Days of Life

Protein intake determines growth rates;
strong relationship;
Ventilator settings and BGA, only slower kinetics

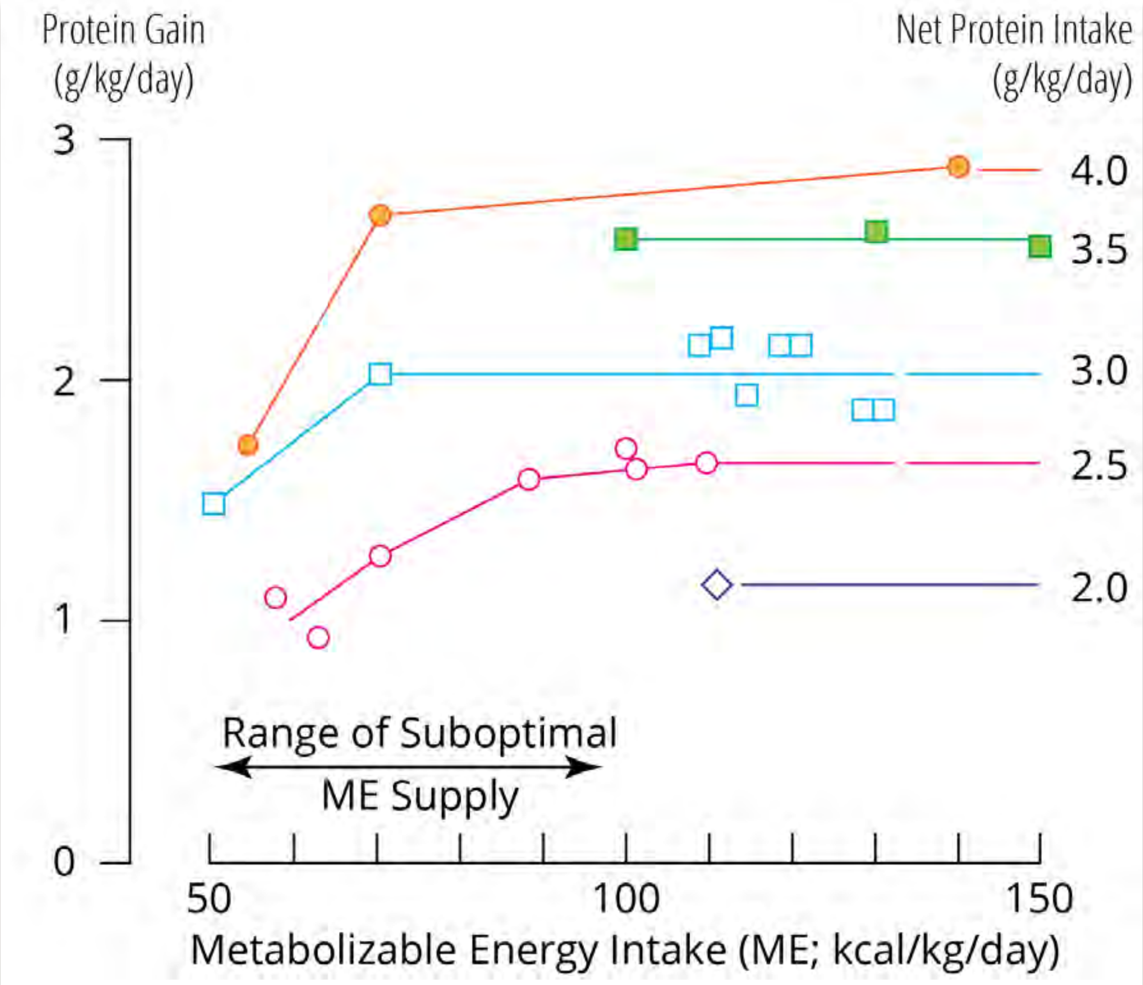


200mg of N2 retention equals 10g of growth

Protein Intake is the Limiting Factor for Growth

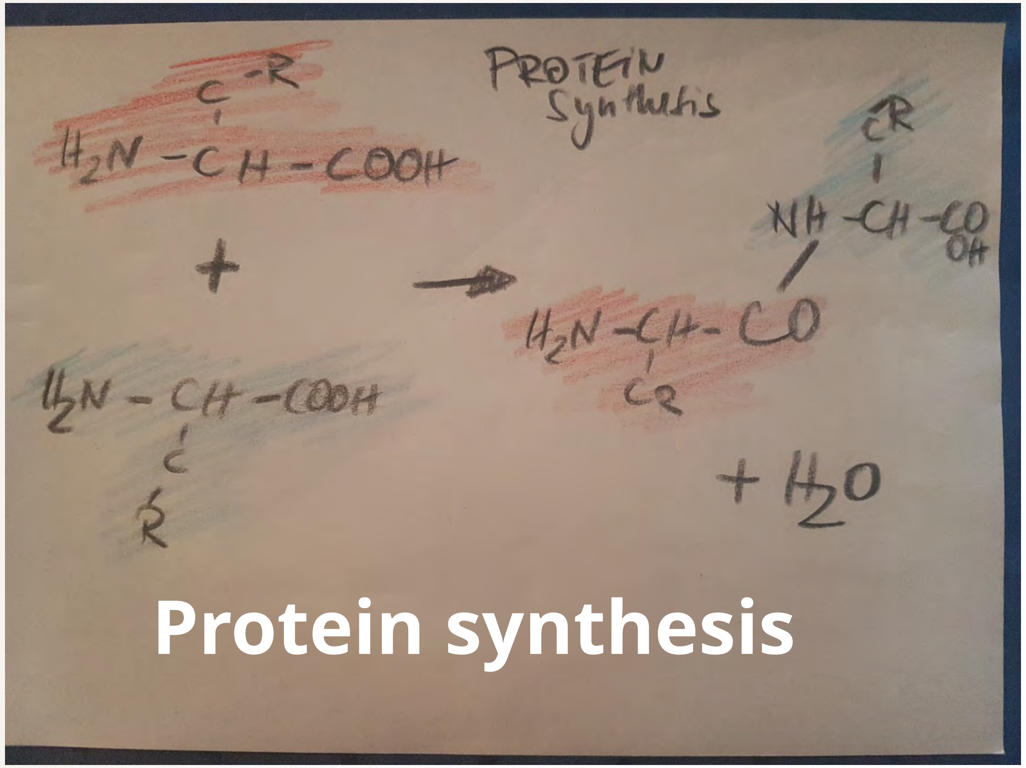
...and so is energy.

Protein : Energy ratio needs to be balanced

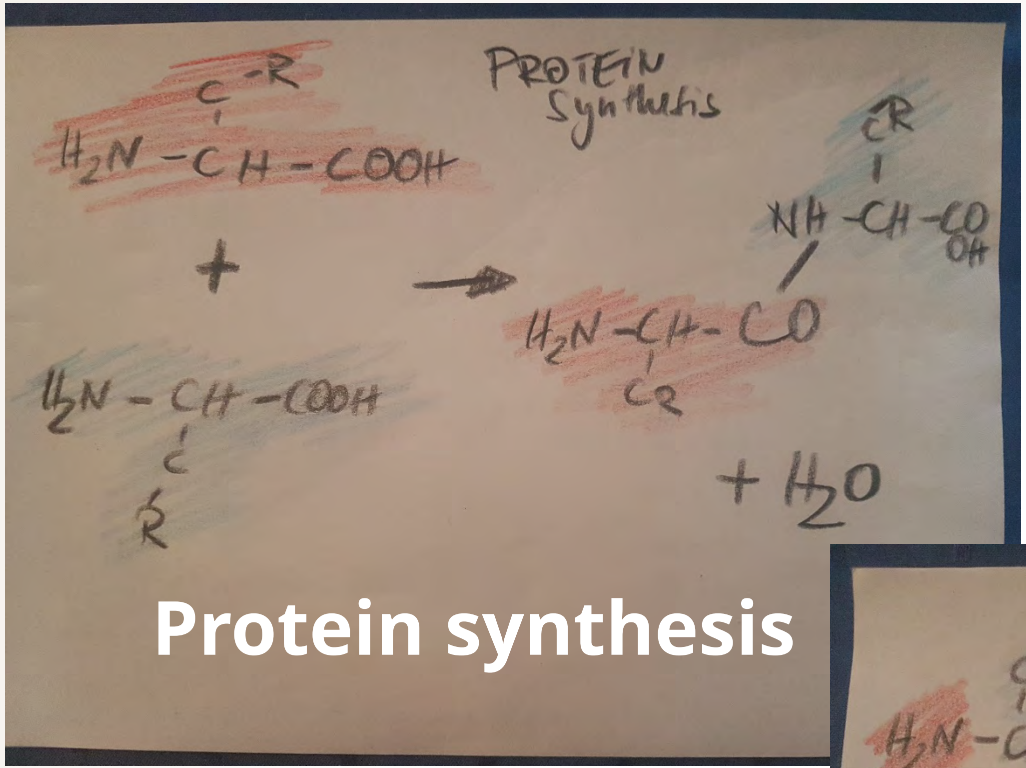


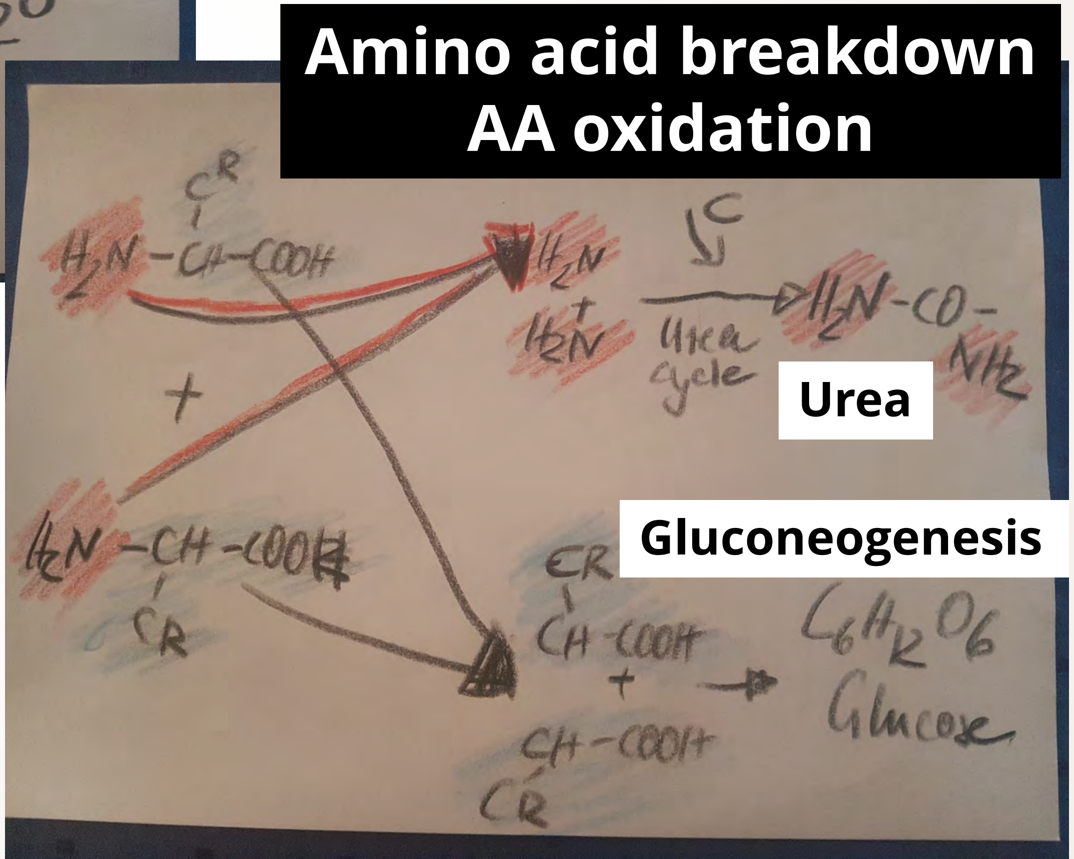
Micheli et al. Protein, pp 29–46 in Tsang RC, et al. Nutritional needs of the preterm infant. Williams & Wilkins. 1992)

Metabolic pathways of amino acids



Metabolic pathways of amino acids

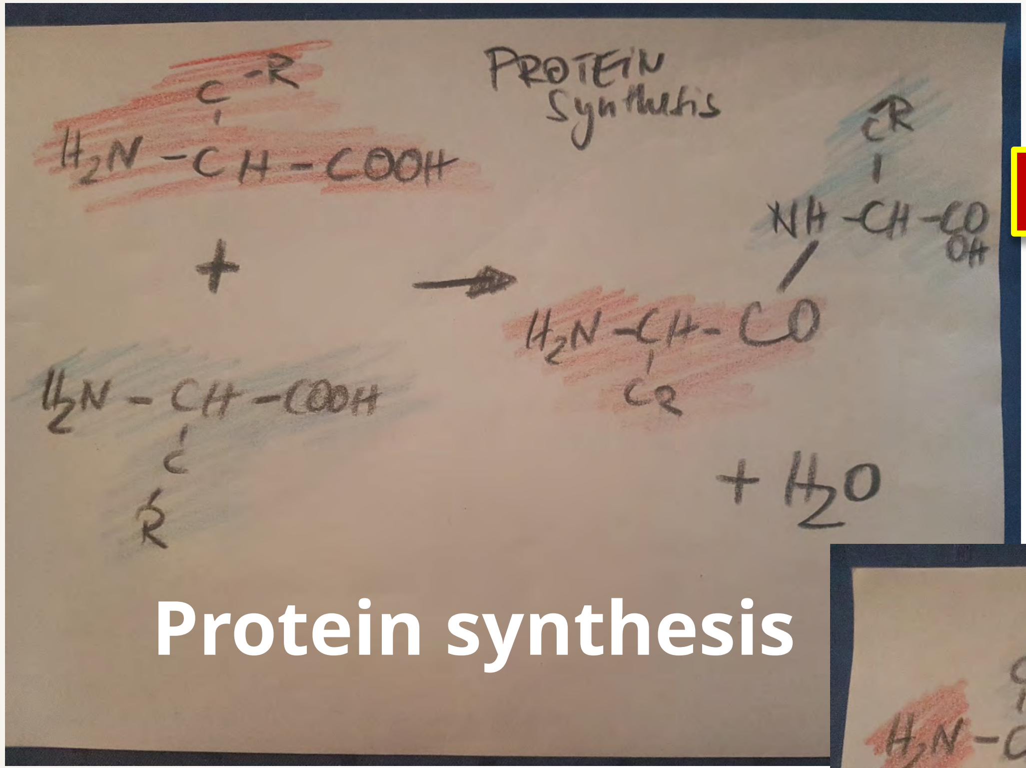




Process
energy consuming
water consuming
strong osmolyte

Metabolic pathways of amino acids

Balanced ratio of protein : energy



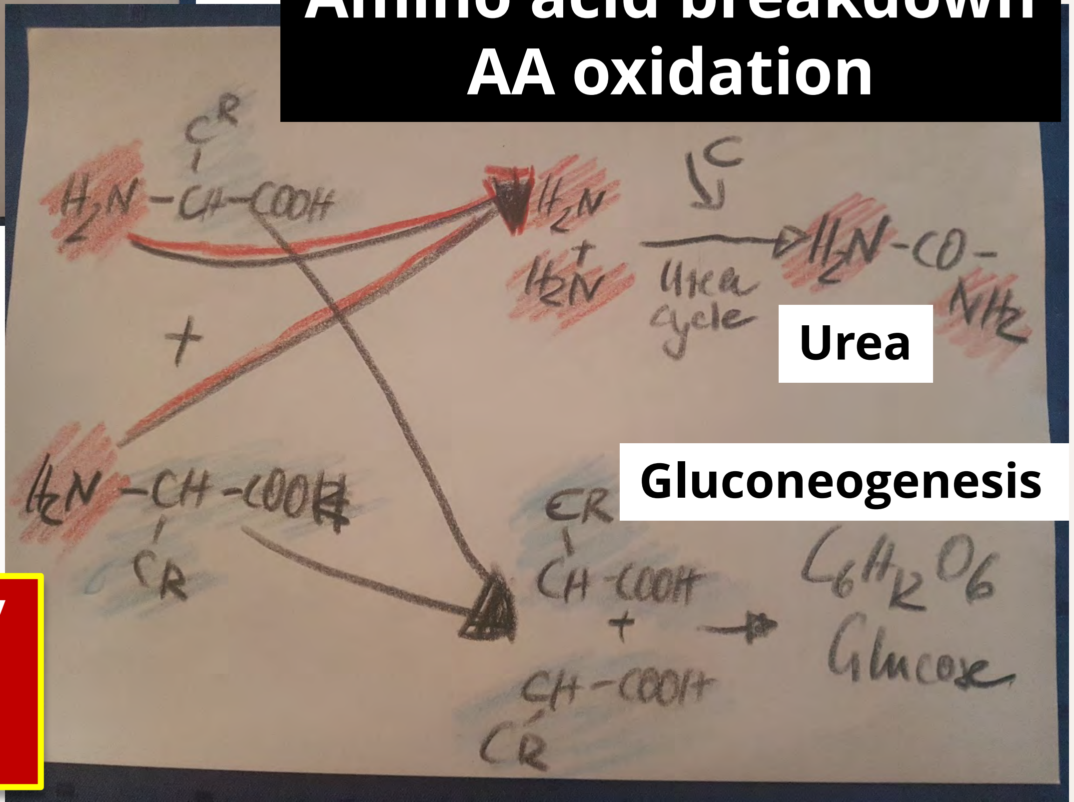
Protein synthesis

Process
energy consuming
water consuming
strong osmolyte

Unbalanced ratio of protein : energy

Protein too high
Energy too low

Amino acid breakdown
AA oxidation



Urea

Gluconeogenesis

CHO-to-Fat Ratio Influences Rate and Quality of Growth in Preterm Infants

		Group 1	Control	Group 2
Protein & Calories		4.0 g/kg/d and 130 kcal/kg/d		
CHO		35%	50%	65%
Δ Weight	[g/kg/d	20.2 ±1.8	21.4 ± 2.3	23.2 ± 2.9
Δ HC	[cm/wk]	1.19 ± 0.29	1.20 ± 0.11	1.24 ± 0.15
Δ Skinfold SC	[mm/wk]	0.89 ± 0.30	0.96 ± 0.35	1.00 ± 0.24
Fat Stored	[g/kg/d]	3.9 ± 0.7	4.1 ± 0.9	4.5 ± 0.6
Protein stored	[g/kg/d]	2.6 ± 0.1	2.7 ± 0.2	2.8 ± 0.1
Lean Mass Stored* **	[g/kg/d]	15.6 ± 3.0	15.8 ± 0.78	16.8 ± 0.84
Protein:Fat	[g/g]	0.70 ± 0.14	0.68 ± 0.15	0.63 ± 0.1
Protein Oxidation		1.05 ± 0.22	0.90 ± 0.12	0.85 ± 0.13

***"Lean mass stored" was calculated from "Protein Stored" assuming a protein content of 17% for lean mass.

Same calories, same protein intake: given preferentially as CHO (65 vs. 35%) lead to

Better growth,
weight gain,
head circumference
more lean mass

Less **protein oxidation**
fat mass

Effects of quality of energy on substrate oxidation in enterally fed, low-birth-weight infants[1,2]

Sudha Kashyap, Helen M Towers, Rakesh Sahni, Kiyoko Ohira-Kist, Kirsten Abildskov, and Karl F Schulze
Am J Clin Nutr 2001;74:374–80.

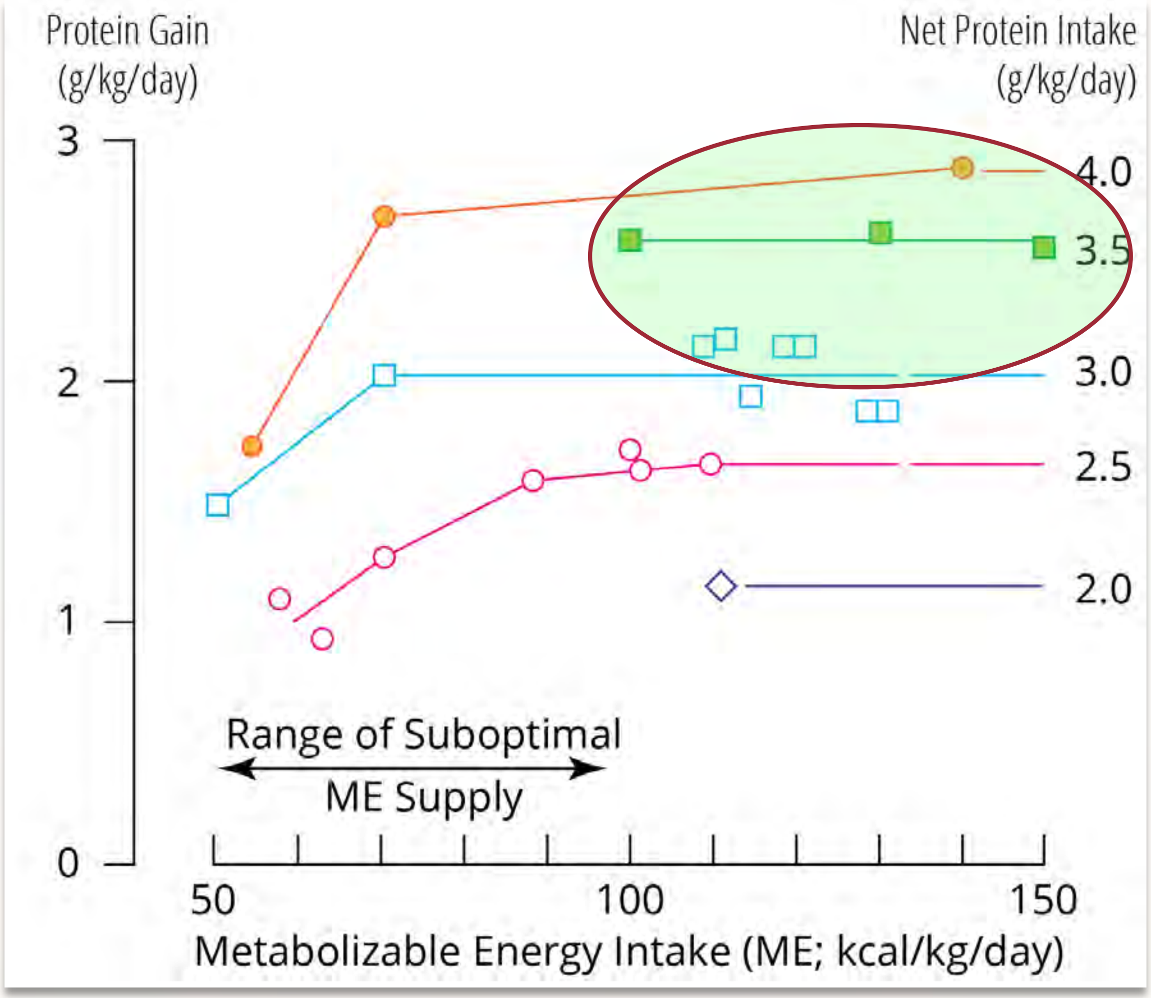
0031-3998/01/5003-0390
PEDIATRIC RESEARCH
Copyright © 2001 International Pediatric Research Foundation, Inc
Vol. 50, No. 3, 2001
Printed in U.S.A.

Effects of Quality of Energy Intake on Growth and Metabolic Response of Enterally Fed Low-Birth-Weight Infants

SUDHA KASHYAP, KIYOKO OHIRA-KIST, KIRSTEN ABILDSKOV, HELEN M. TOWERS, RAKESH SAHNI, RAJASEKHAR RAMAKRISHNAN, AND KARL SCHULZE

Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Babies and Children's Hospital of New York, College of Physicians and Surgeons, Columbia University, New York, New York 10032, U.S.A.

Impact of Nutritional Composition on Growth

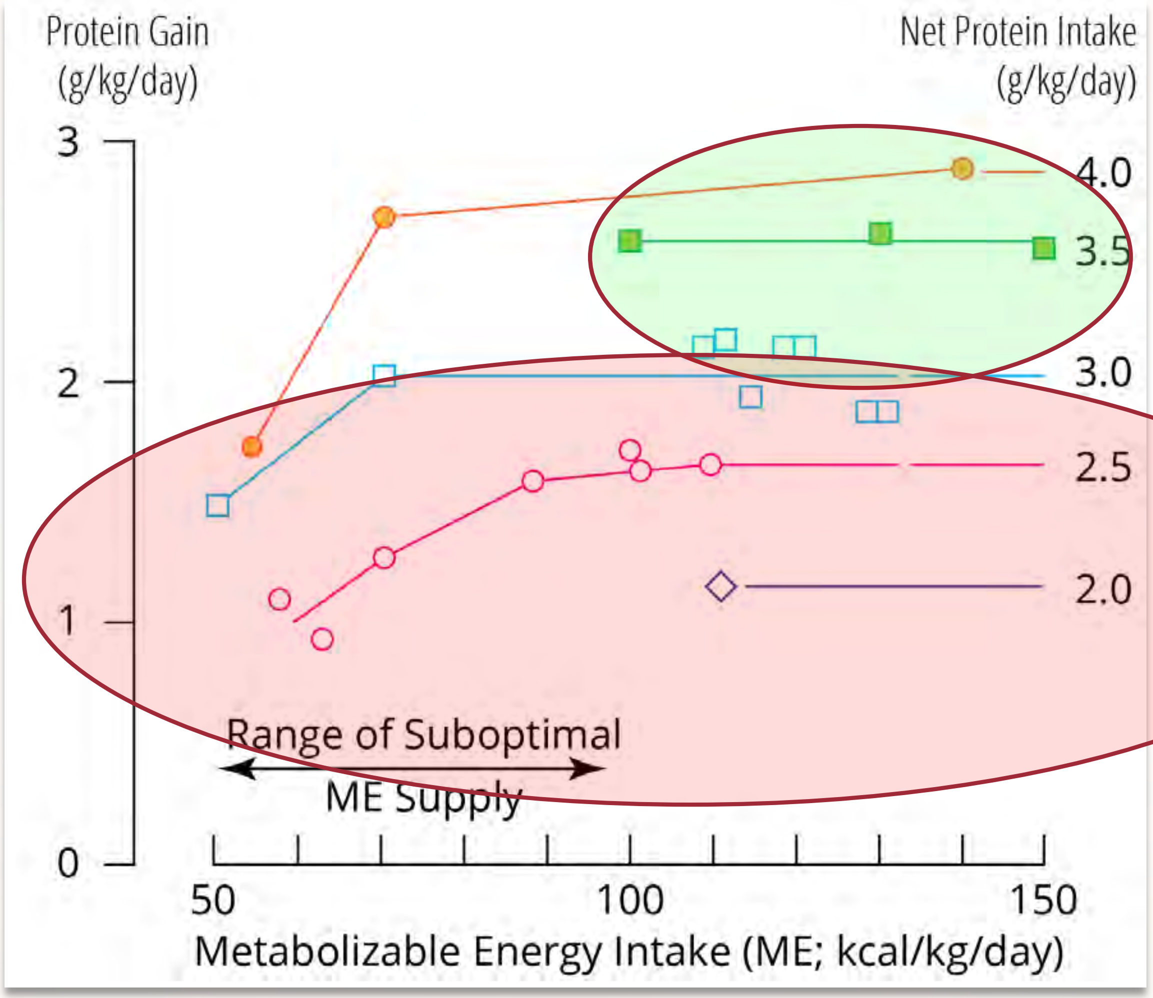


Optimum accretion of lean mass

Micheli et al. Protein, pp 29–46 in Tsang RC, et al. Nutritional needs of the preterm infant. Williams & Wilkins. 1992)

Impact of Nutritional Composition on Growth

Proportionate growth
FM : Lean ok



Optimum accretion of lean mass

Protein intake too low
Inappropriate Growth
< genetic potential

Micheli et al. Protein, pp 29–46 in Tsang RC, et al. Nutritional needs of the preterm infant. Williams & Wilkins. 1992)

Impact of Nutritional Composition on Growth

Energy intake too low
Inappropriate growth
< genetic potential
FM : Lean ↓↓
BUN ↑↑
Edema ↑↑

Area of optimum growth

Proportionate growth
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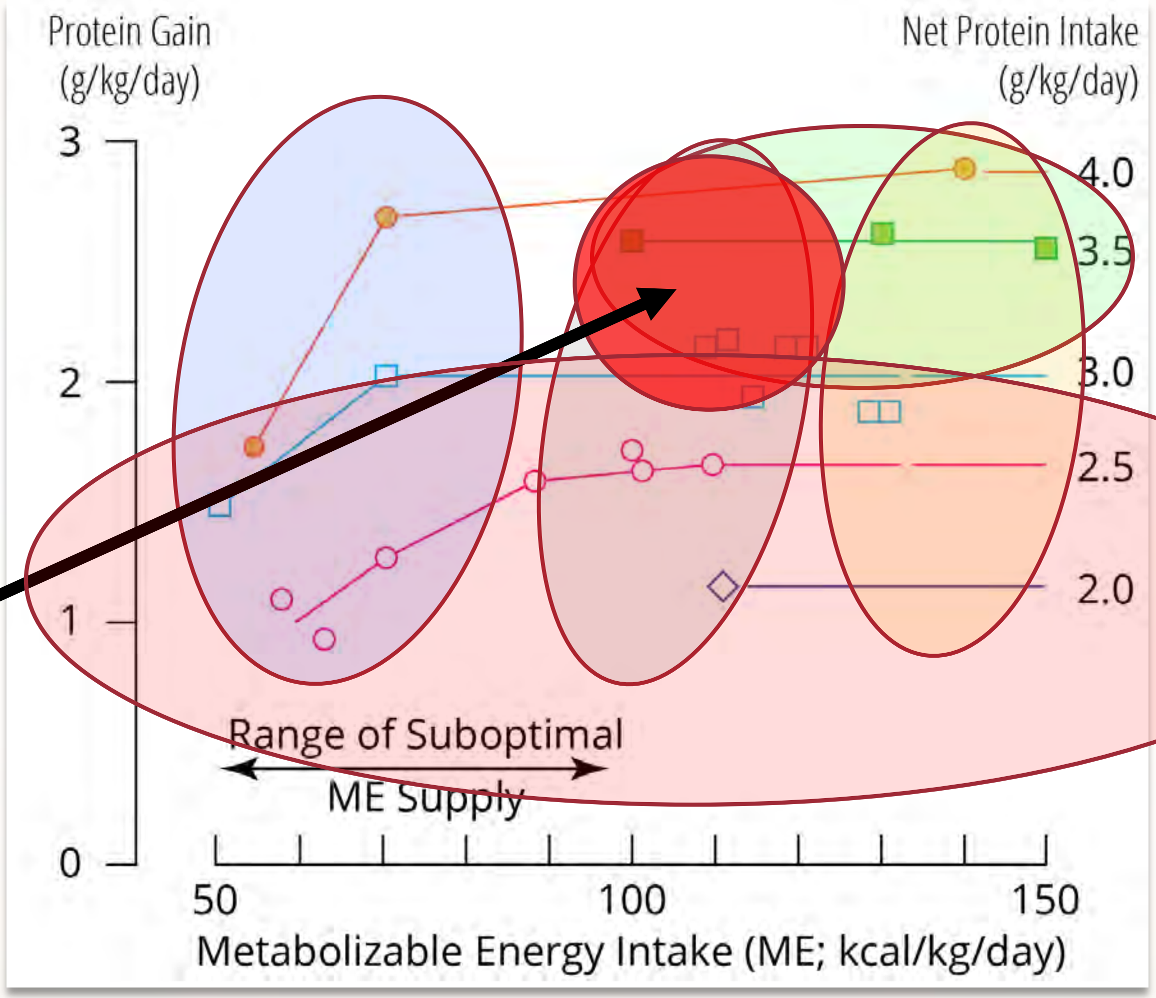

Optimum accretion of lean mass

Energy intake too high
Disproportionate growth
Excess FM
TG and Glc ↑↑

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Micheli et al. Protein, pp 29–46 in Tsang RC, et al. Nutritional needs of the preterm infant. Williams & Wilkins. 1992)

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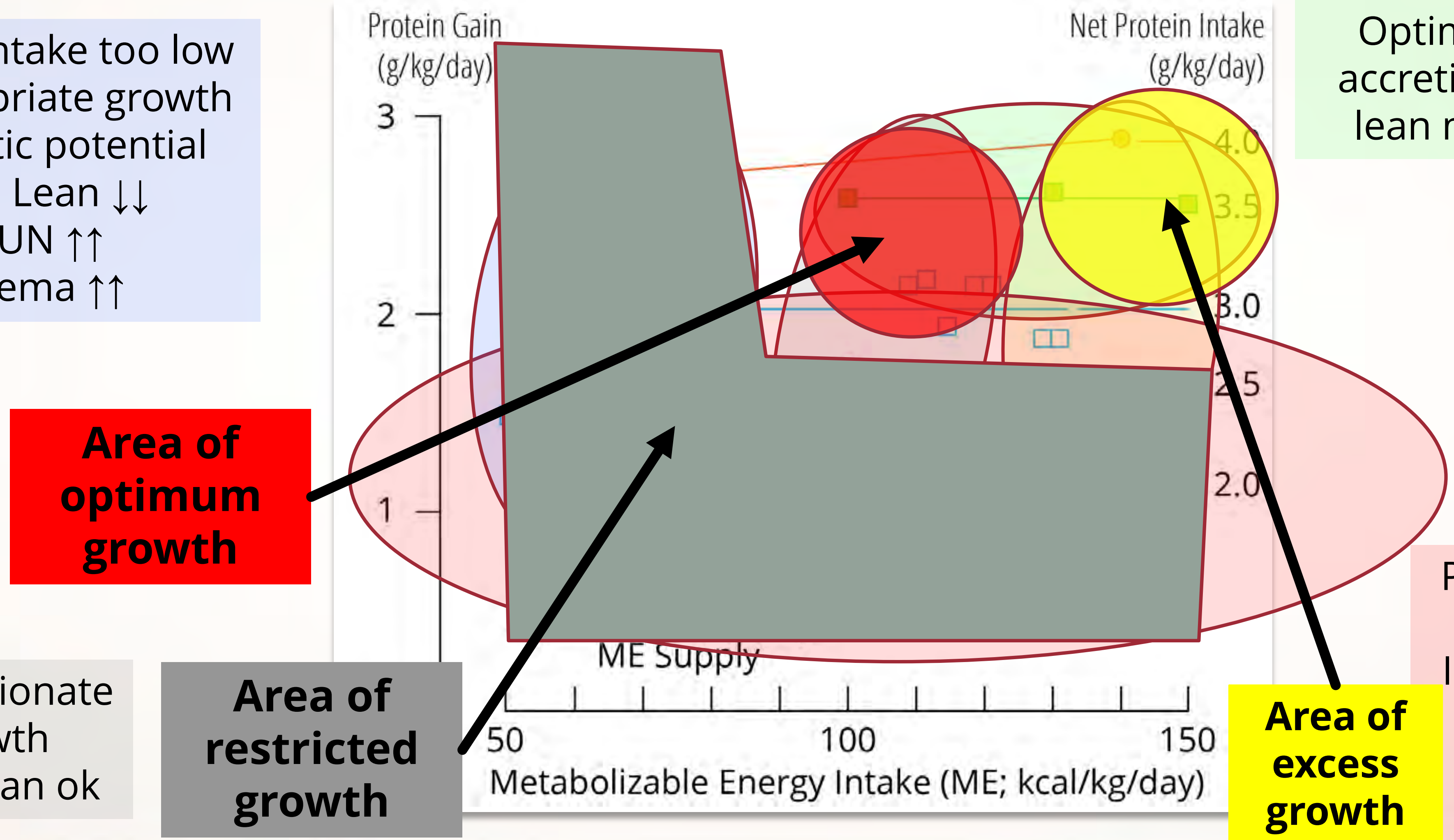

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Micheli et al. Protein, pp 29–46 in Tsang RC, et al. Nutritional needs of the preterm infant. Williams & Wilkins. 1992)

HOW NUTRITIONAL NEEDS VARY AMONG PRETERM AND TERM INFANTS

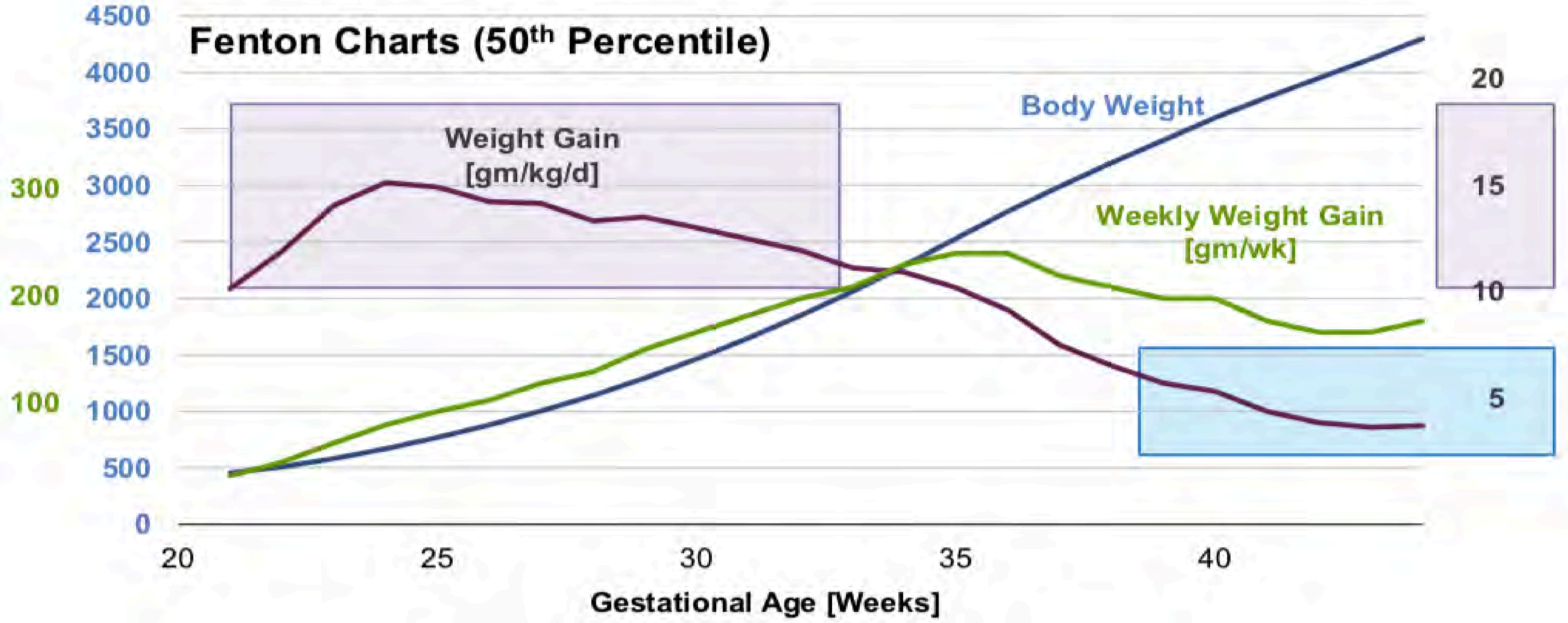
Mother's Breastmilk

Pros

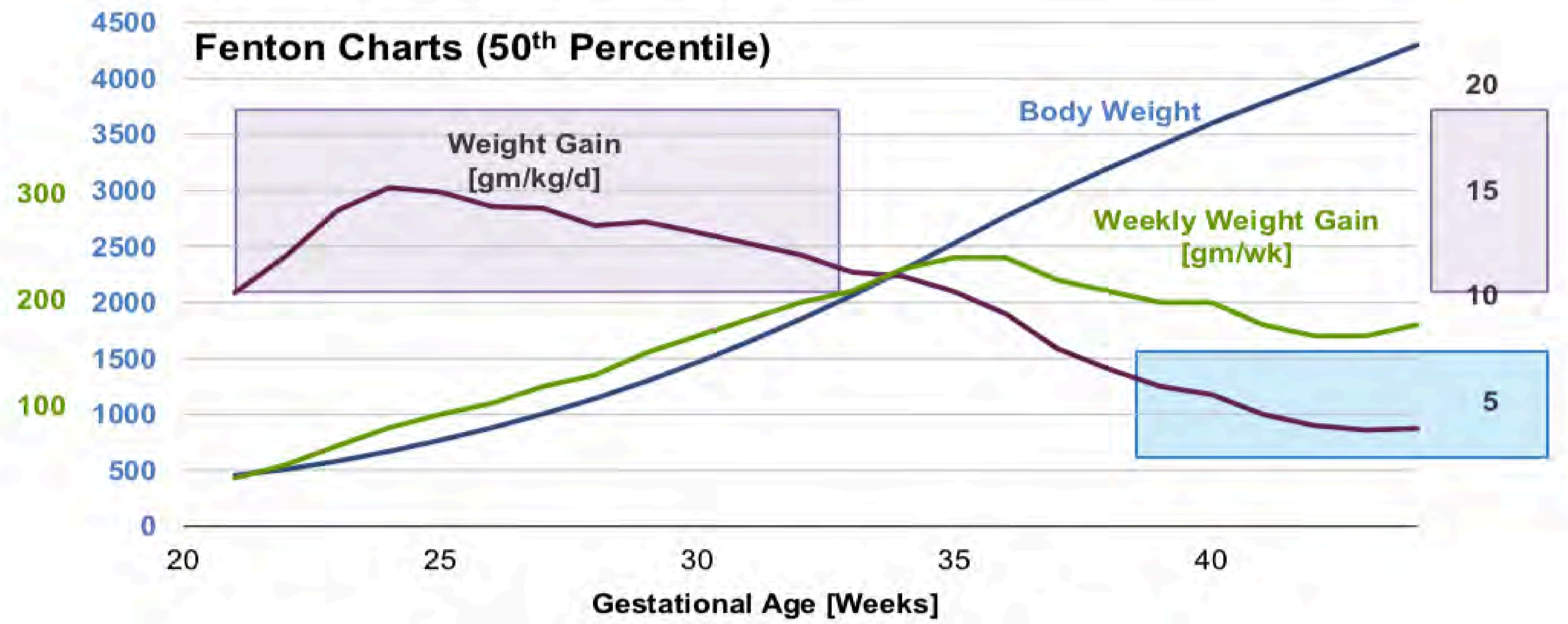
- Contains many natural substances
  - Oligosaccharides
    - Microbiome
  - Human proteins lead to better tolerance
  - Lower sepsis and NEC rates
  - Costs are low

Cons

- Variable macronutrient composition; not balanced
- Macronutrient content can be too low for preterm infants
- Protein content decreases with postnatal age and varies between mothers



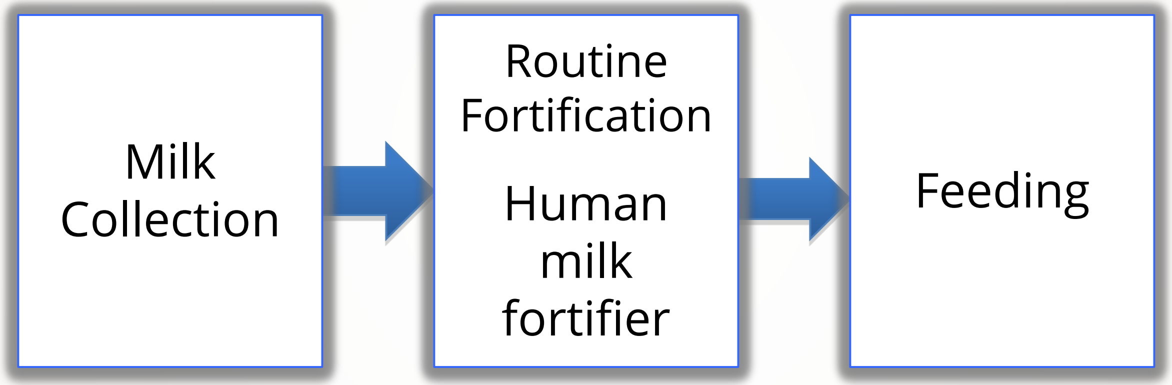
	Growth Velocity [g/kg/day]	Protein Intake [g/kg/day]	Protein Content of Milk [g/100 ml]
Preterm infants 24–32 weeks	(12–) 18	3–4.5	2–2.9
Term infants	(3–) 8	1.5–2	1–1.3



	Growth Velocity [g/kg/day]	Protein Intake [g/kg/day]	Protein Content of Milk [g/100 ml]
Preterm infants 24–32 weeks	(12–) 18	3–4.5	2–2.9
Term infants	(3–) 8	1.5–2	1–1.3

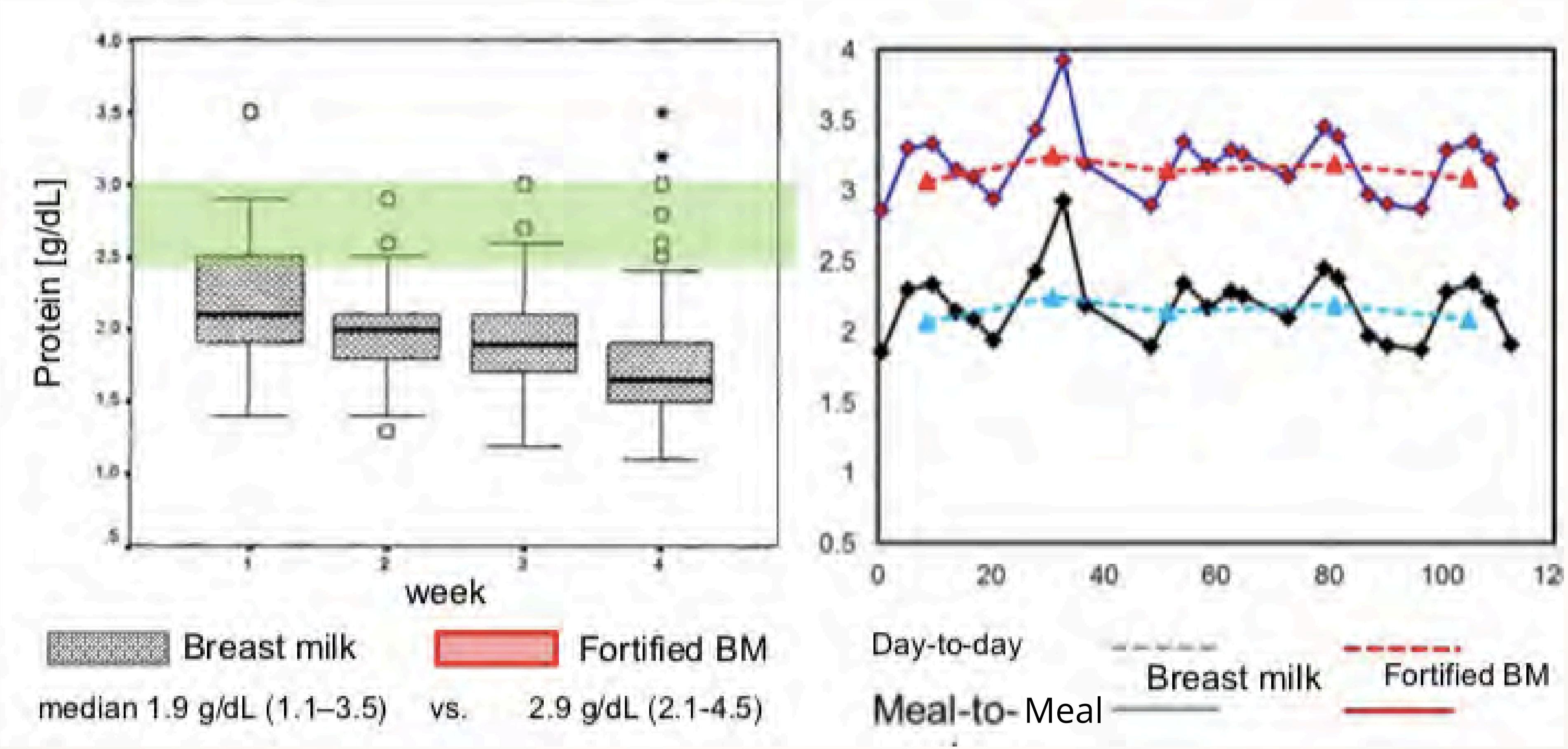
How to fortify breast milk?

- Current approach: Routine fortification
- Addition of a fixed dosage of fortifier to breast milk



Henriksen C, et al. 2009
Corvaglia, et al. 2010

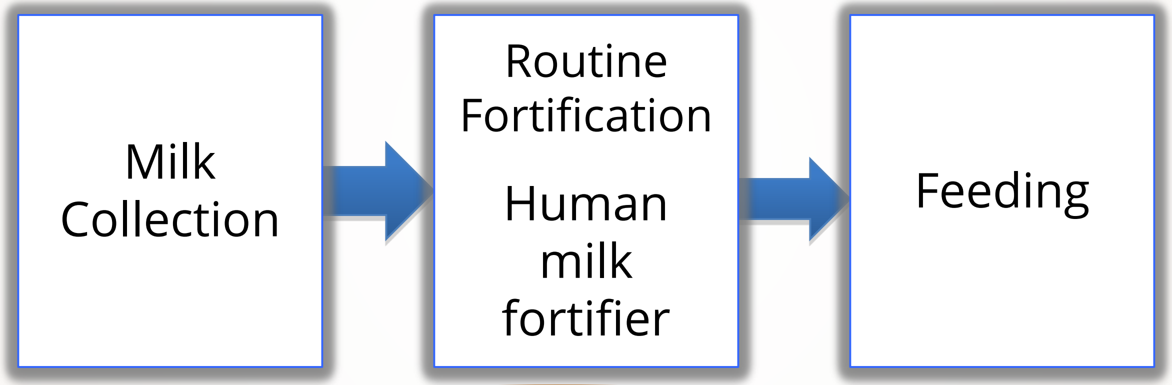
Variation of Protein Content in Breast Milk



Weber A, et al. *Acta Paediatr.* 2001;90:772-5; Polberger S. *Nestle Nutr Workshop.* 2009;63:195-204.

How to fortify breast milk?

- Current approach: Routine fortification
- Addition of <u>a fixed dosage of fortifier</u> to breast milk



Extra-uterine growth restriction at discharge observed in 58% of VLBW infants fed predominantly standard fortified breast milk

Henriksen C, et al. 2009
Corvaglia, et al. 2010

How to fortify breast milk?

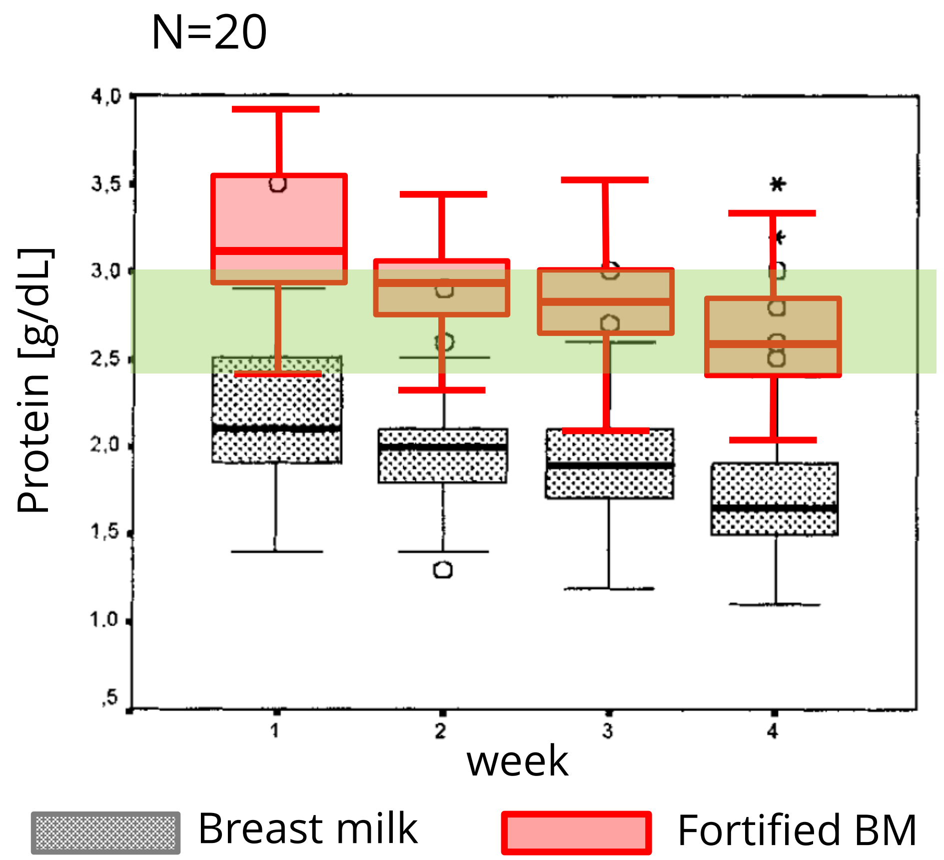
- Current approach: Routine fortification
- Addition of a fixed dosage of fortifier to breast milk

All based on the major assumption of an average composition of breast milk, which is not correct for all preterm infants and can lead to significant over and under nutrition. This effect is also frequently not taken into account in the design and interpretation of clinical studies as well as conclusions drawn from such results.

Extra-uterine growth restriction at discharge observed in 58% of VLBW infants fed predominantly standard fortified breast milk

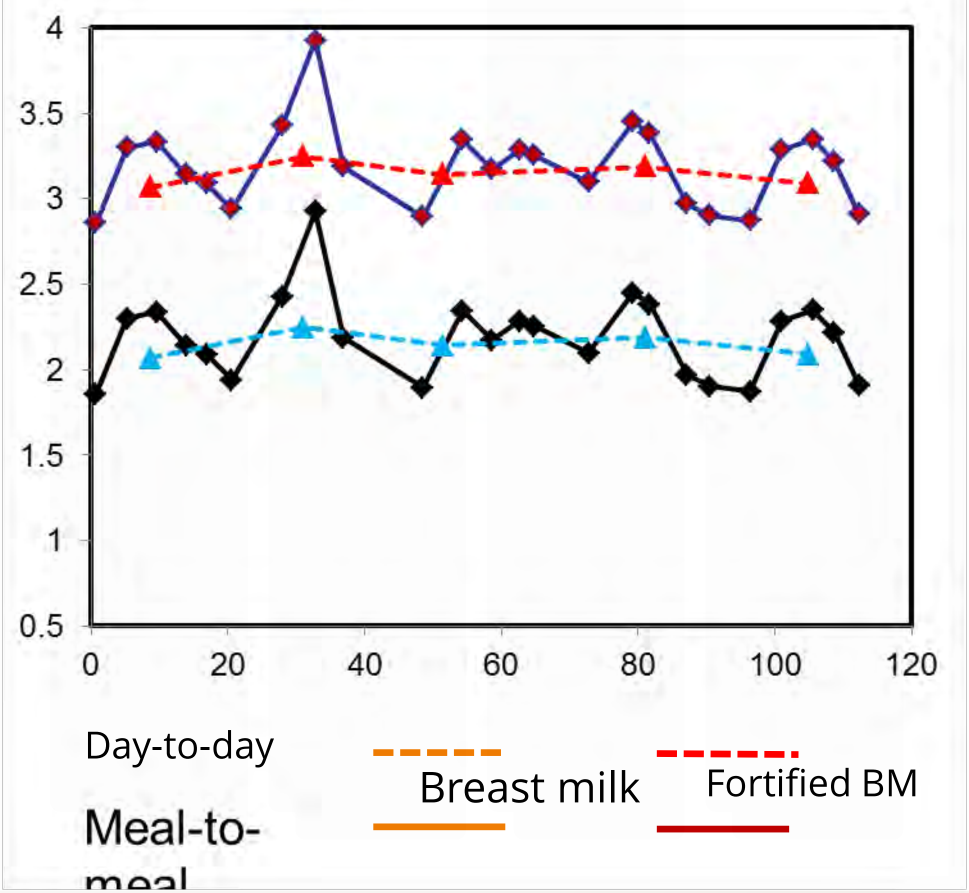
Henriksen C, et al. 2009
Corvaglia, et al. 2010

Variation of Protein Content in Breast Milk and Fortified Breast Milk vs. ESPGHAN Recommendations



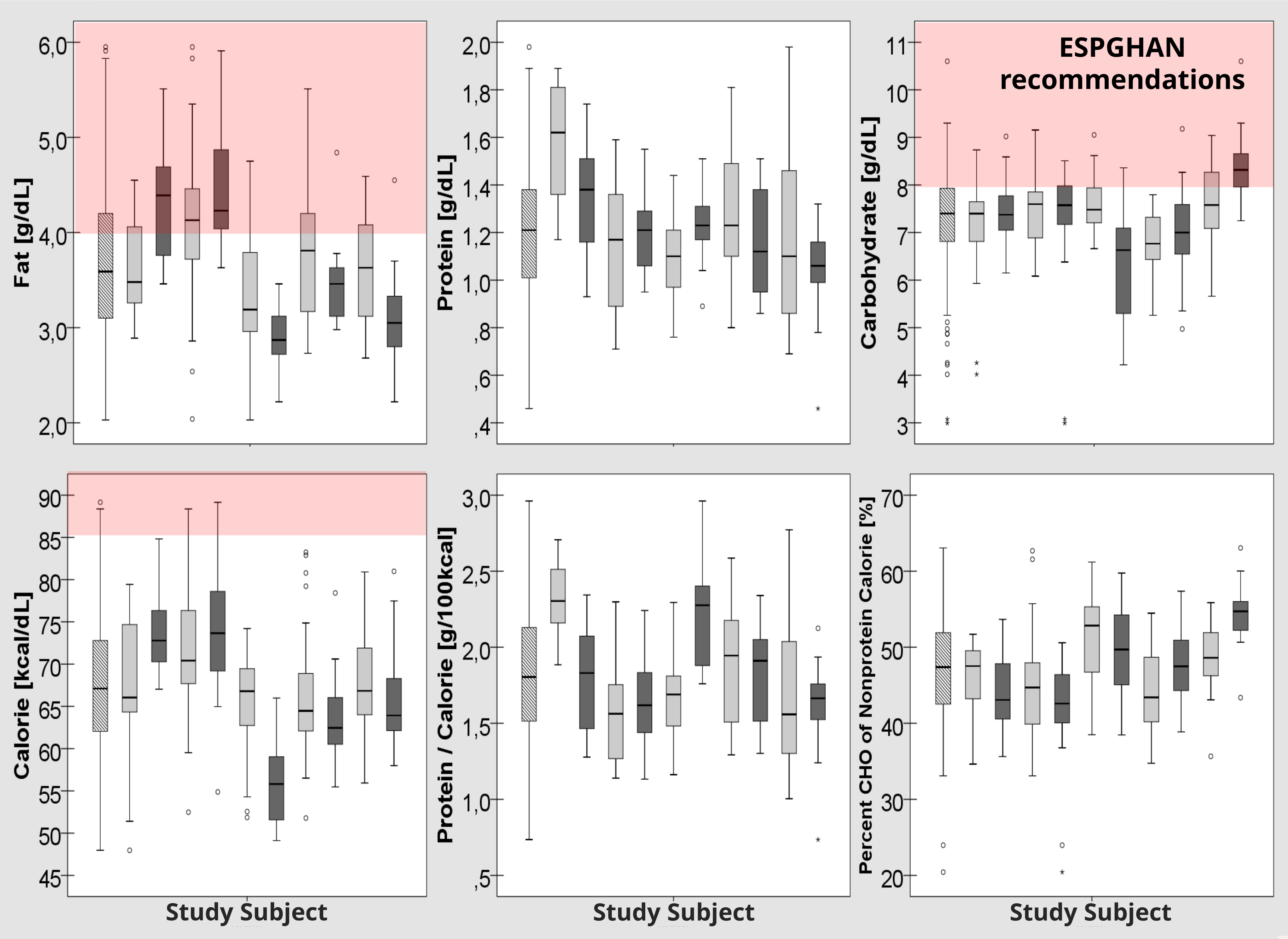
median 1.9 g/dL (1.1–3.5) vs. 2.9 g/dL (2.1-4.5)

Weber A, et al. *Acta Paediatr.* 2001;90:772-5.

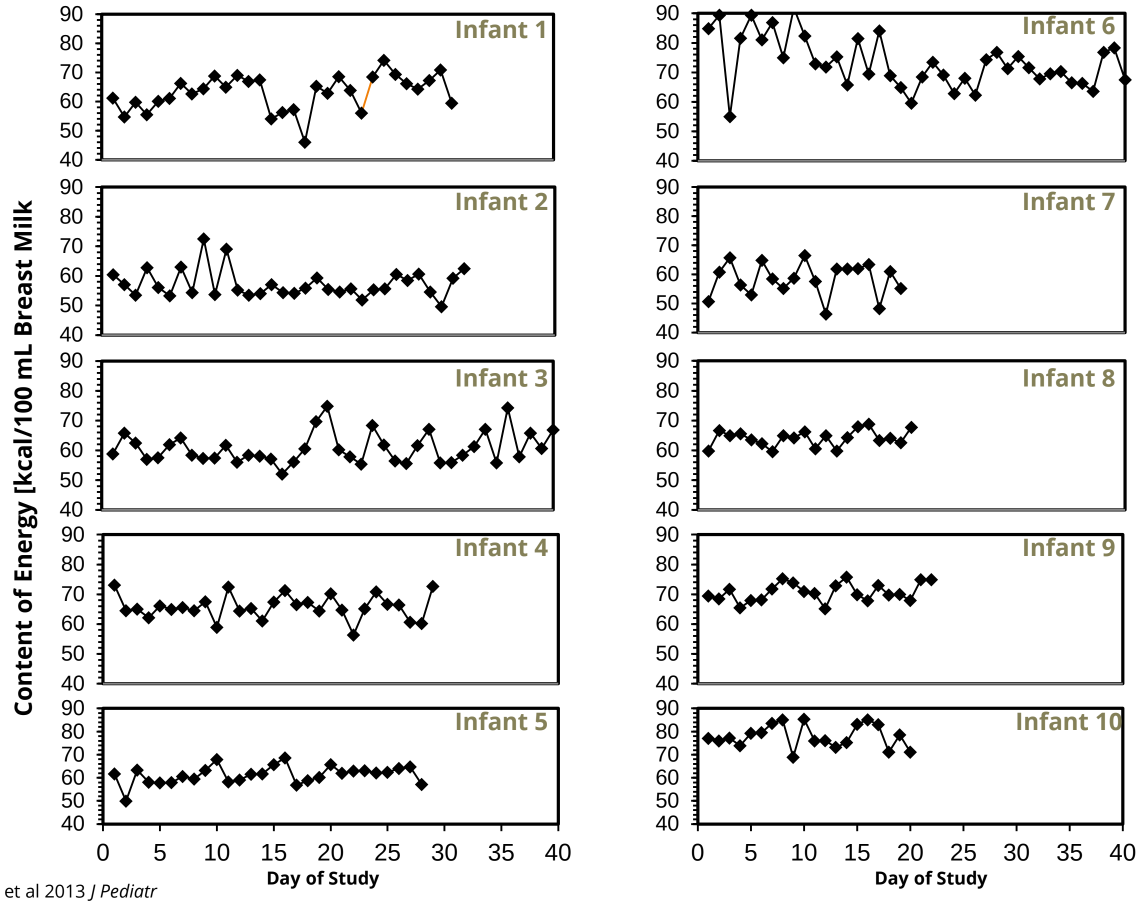


Polberger S. *Nestle Nutr Workshop Ser Pediatr Program.* 2009;63:195-204

Inter- and Intra-individual Variation of Breast Milk Composition in Unfortified 12h Batches



Variation between individuals, from day-to-day and between lactation periods is considerable



Rochow et al 2013 *J Pediatr*

No Correlation Between Macronutrient Levels (Wet Lab Chemistry)

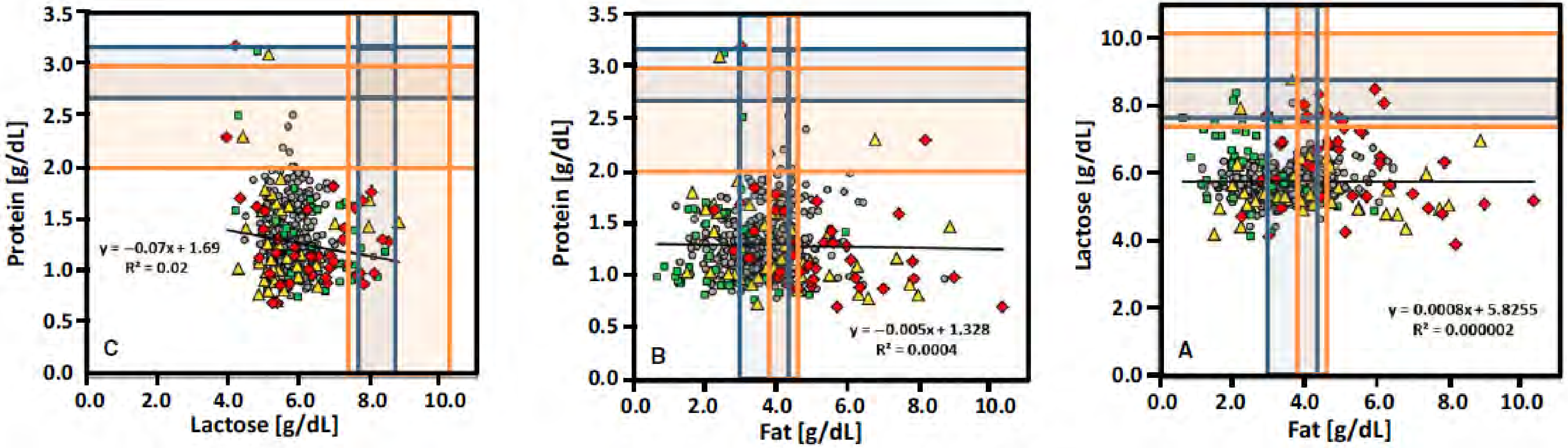
Colour: 40 mothers of term and preterm infants
fore, mid and hind milk (n = 3 x 40; 120)

Grey: 10 mothers of preterm infants; on average 85 batches used for feeding (n = 850)

Green: fore milk
Yellow: mid milk
Red: hind milk

Grey: batches

ESPGHAN guideline
commercially available formula: **Enfamil premature, Similac Advance, Preemie SMA 24, Beba, Prematil, Humana 0-VLB**



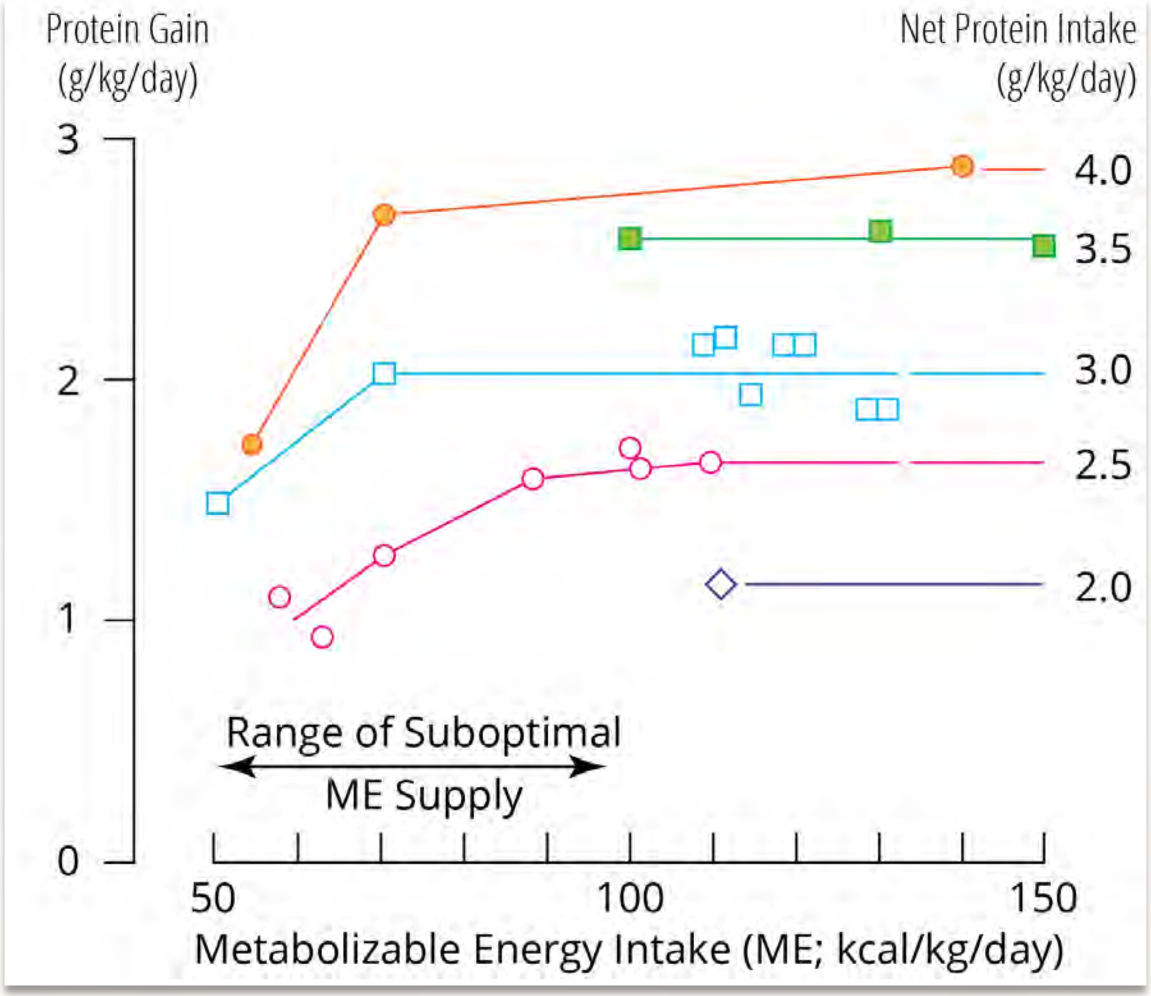
REGULAR ARTICLE

Target fortification of breast milk: levels of fat, protein or lactose are not related

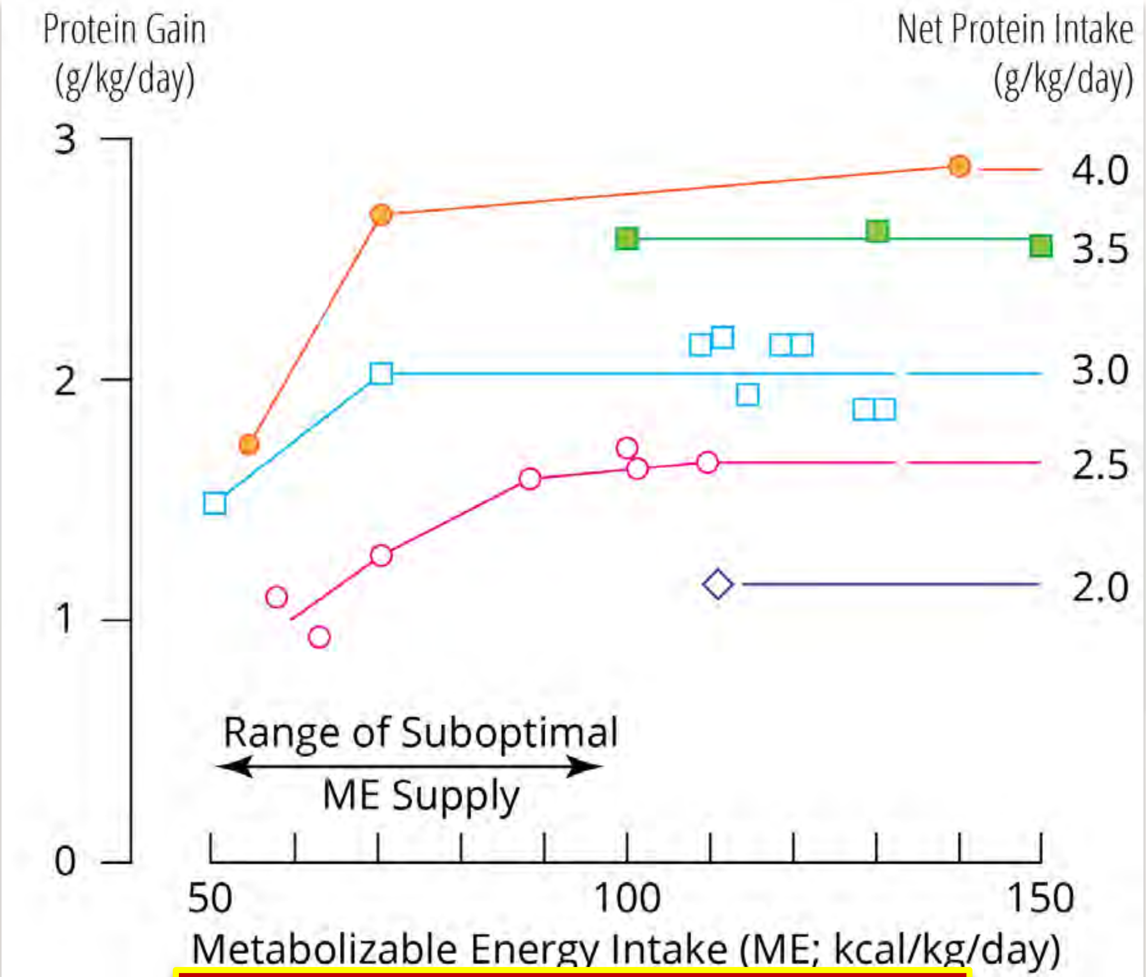
Gerhard Fusch, Souvik Mitra, Niels Rochow, Christoph Fusch (fusch@mcmaster.ca)

Fusch G, et al. Acta Paediatrica, 2015 ;104:38-42.

Protein Intake is the Limiting Factor for Growth



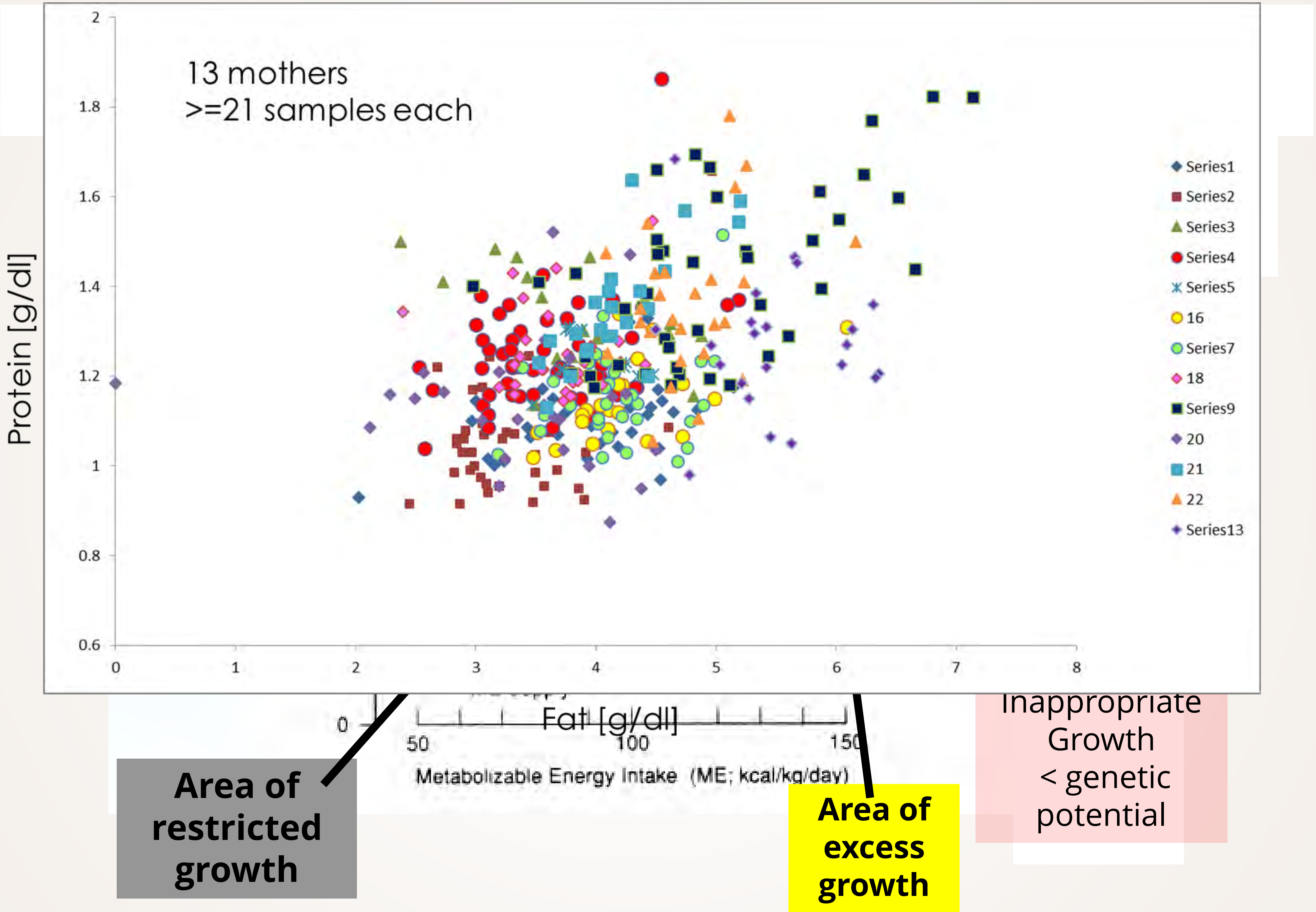
Protein Intake is the Limiting Factor for Growth



Protein intake

Fat is the main determinant

Micheli et al. Protein, pp 29–46 in Tsang RC, et al. Nutritional needs of the preterm infant. Williams & Wilkins. 1992.

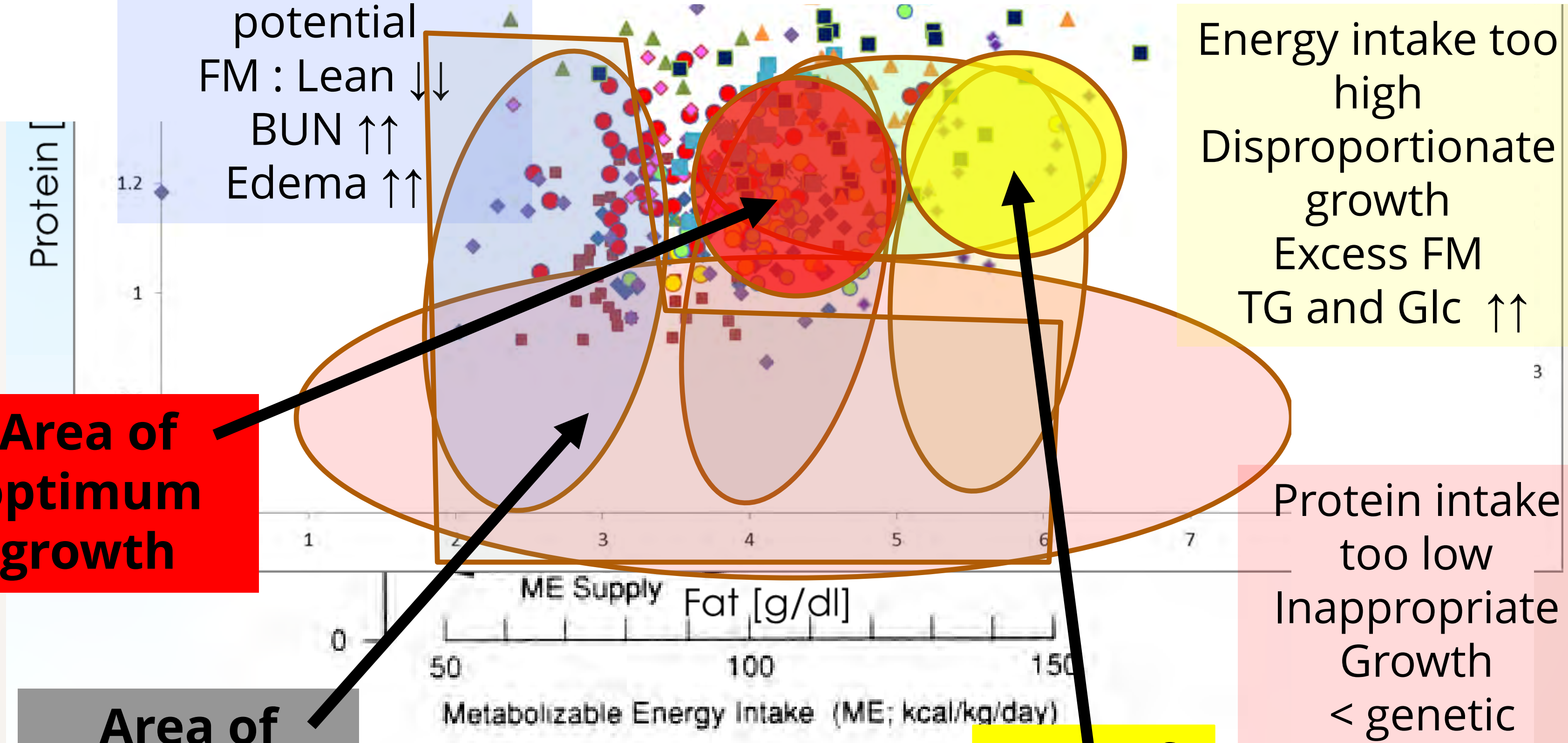

13 mothers
>=21 samples each
Protein [g/dl]
Fat [g/dl]
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0
1
2
3
4
5
6
7
8
Series1
Series2
Series3
Series4
Series5
16
Series7
18
Series9
20
21
22
Series13
0
50
100
150
Metabolizable Energy Intake (ME; kcal/kg/day)
Area of restricted growth
Area of excess growth
Inappropriate Growth
< genetic potential

Impact of nutritional composition on growth

Energy intake too low
Inappropriate growth < genetic potential
FM : Lean ↓↓
BUN ↑↑
Edema ↑↑

Proportionate growth
FM : Lean ok

Optimum accretion of lean mass



Energy intake too high
Disproportionate growth
Excess FM
TG and Glc ↑↑

Area of optimum growth

Area of restricted growth

Area of excess growth

Protein intake too low
Inappropriate Growth
< genetic potential

Impact of nutritional composition on growth

Energy intake too

Proportionate

Optimum accretion of

Preterm infants have no self regulation—different than term infants

Metabolizable Energy Intake (ME; kcal/kg/day)

Area of excess growth

< genetic potential

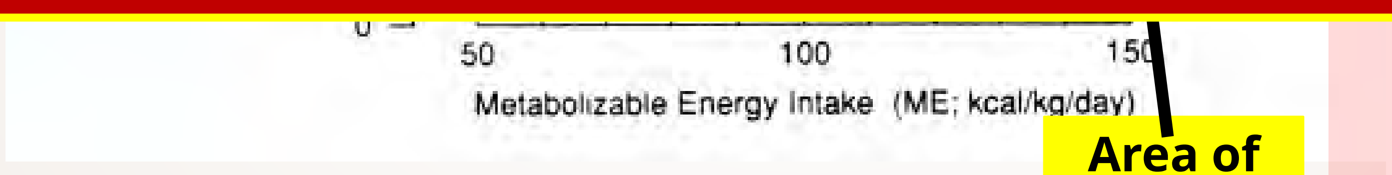
Impact of nutritional composition on growth

Energy intake too low

Proportionate

Optimum accretion of

Just adding more of an unbalanced diet does not help fix the problem



Area of excess growth

Growth < genetic potential

PRINCIPLES OF ADJUSTED FORTIFICATION
“PRECISION MEDICINE”

Adjustable fortification of breast milk improves growth, but not for all subjects

Inclusion criteria

BW 600–1750 g
GA 24–34 weeks
Healthy infants (no NEC, sepsis, IVH)
no ventilator support on day 21

Randomization stratified according to BW
<1250 g
<1500 g
<1750 g

Results

Table 5 Weight, length and head circumference gains during the study period

Outcome variable	STD	ADJ	P-*value*
Weight gain (g/day)	24.8±4.8	30.1±5.8	<0.01
(g/kg/day)	14.4±2.7	17.5±3.2	<0.01
Length gain (mm/day)	1.1±0.4	1.3±0.5	>0.05
Head circumference gain (mm/dy)	1.0±0.3	1.4±0.3	<0.05

Values are mean±s.d.

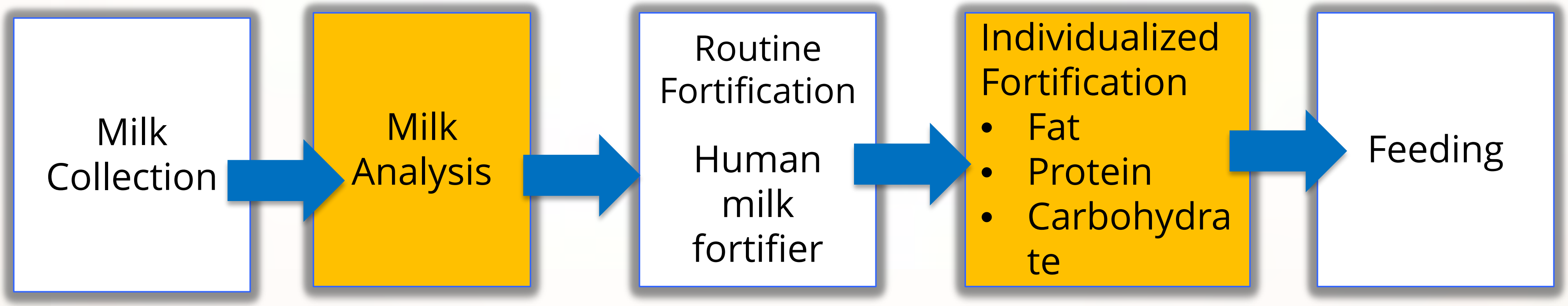
Table 2 Amount of HMF and protein at the various fortification levels

Fortification level	*Amount added (g/100 ml milk)*
3	HMF 6.25+prot 0.8
2	HMF 6.25+prot 0.4
1	HMF 6.25
0	HMF 5
−1	HMF 3.75
−2	HMF 2.5

Arslanoglu S, et al. *J Perinatol.* 2006 ;26:614-21.

How to Fortify Breast Milk

- **New individualized approach**
- Analyzing breast milk, and individually fortifying it to reach recommended macronutrient amounts



Goal: Standardized intake for preterm infants

Comparison of point-of-care milk analysers vs micro-methods

Sample volume 1 ml; measurement time 1–3 min

Unity
Spectrastar
Near Infrared

Miris
Mid Infrared

Originally developed for use in dairy industry

Correlation of Reference Method vs. Unity/MIRIS Data (non-corrected)

n = 978 !!


Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

ELSEVIER

Original article

Rapid measurement of macronutrients in breast milk: How reliable are infrared milk analyzers?*

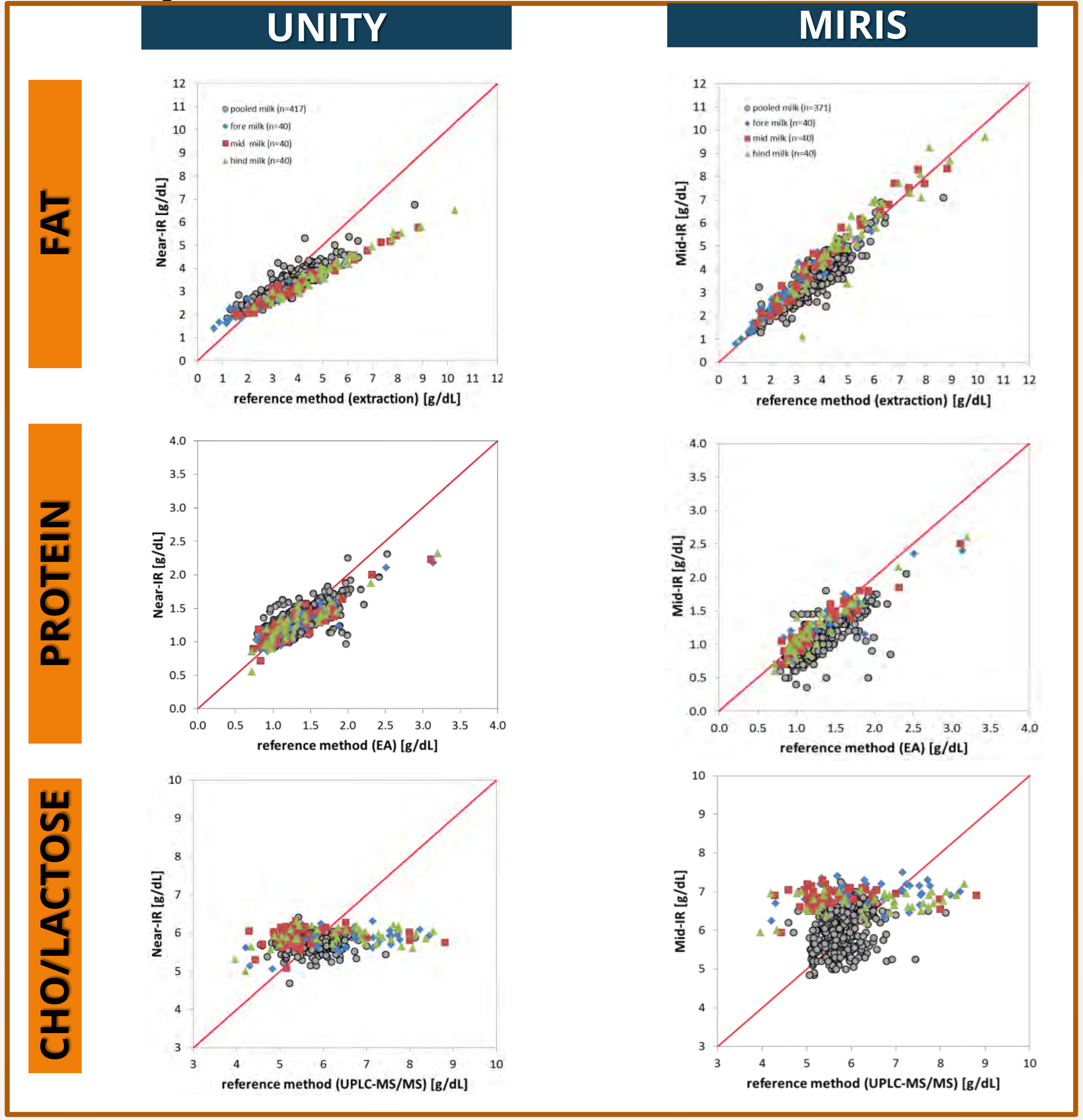
Gerhard Fusch, Niels Rochow, Arum Choi, Stephanie Fusch, Susanna Poeschl, Adelaide Obianuju Ubah, Sau-Young Lee, Preeya Raja, Christoph Fusch*

Division of Neonatology, Department of Pediatrics, McMaster University, Hamilton, ON, Canada

Fusch, G, et al.
Clin Nutr, 2014.

Fusch G et al
J Chromat , 2011

Choi A
Matern Child Nutr ,2013



MAMAS Study Protocol

Milk analysis using milk analyser study

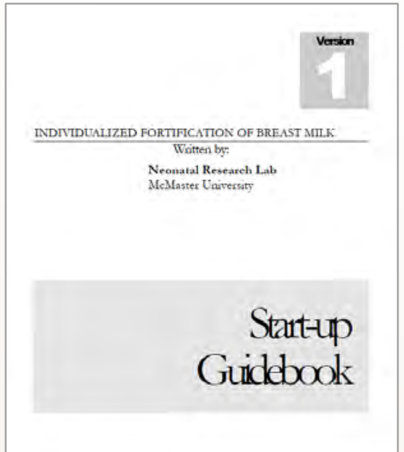
Part 1: Initial assessment of device performance

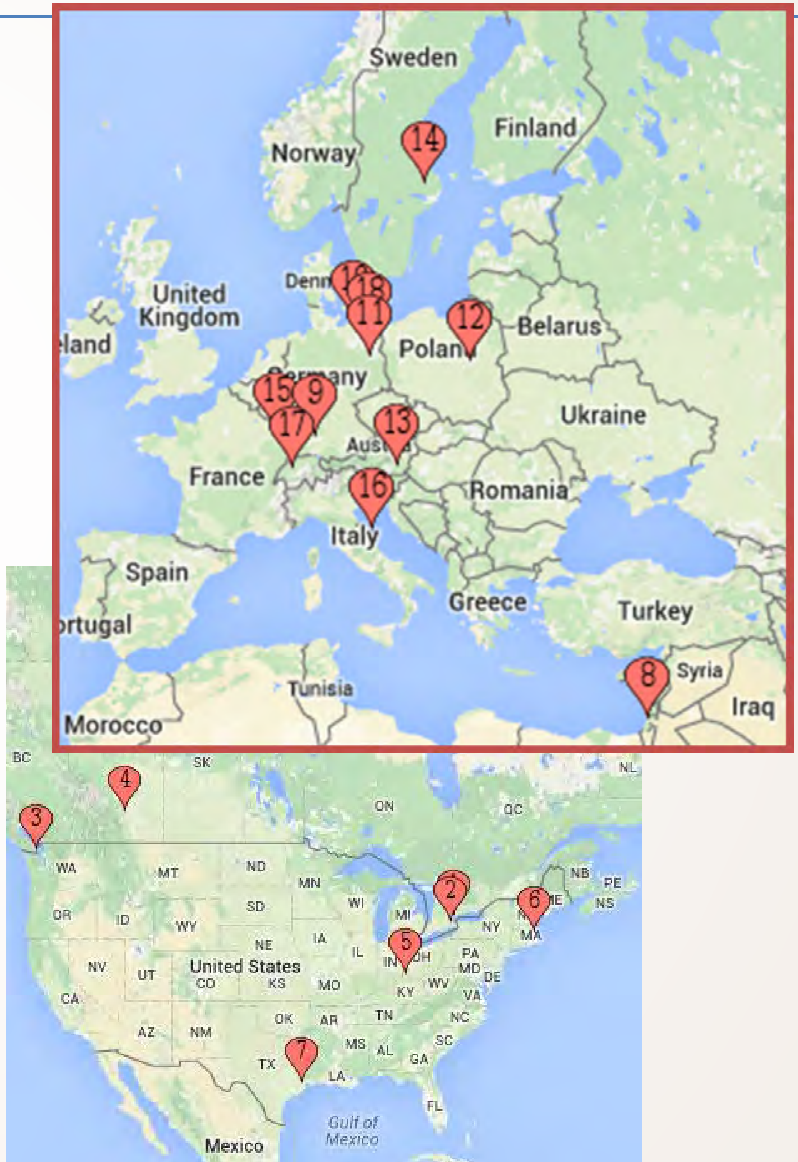
Part 2: Long term stability & quality control

Part 3: Ring trial

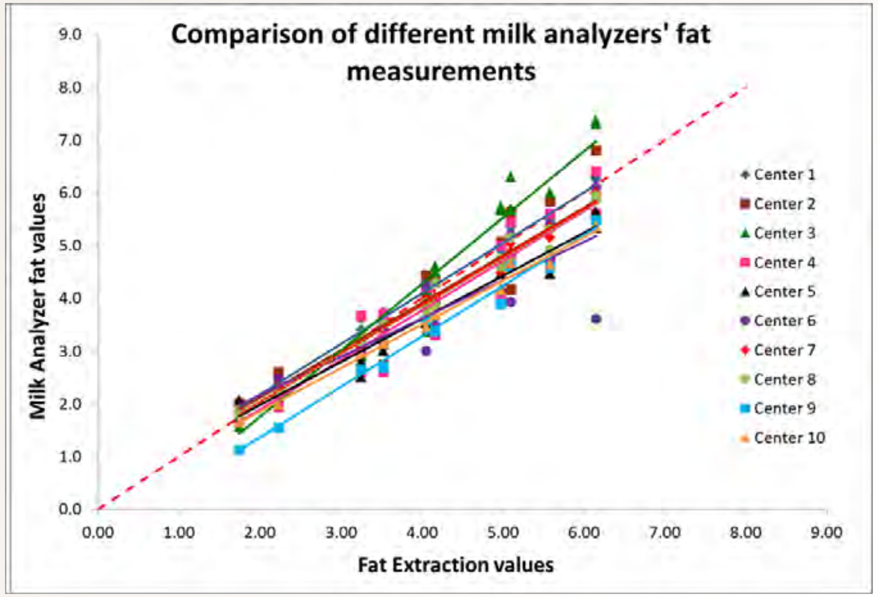
N = 18 centers

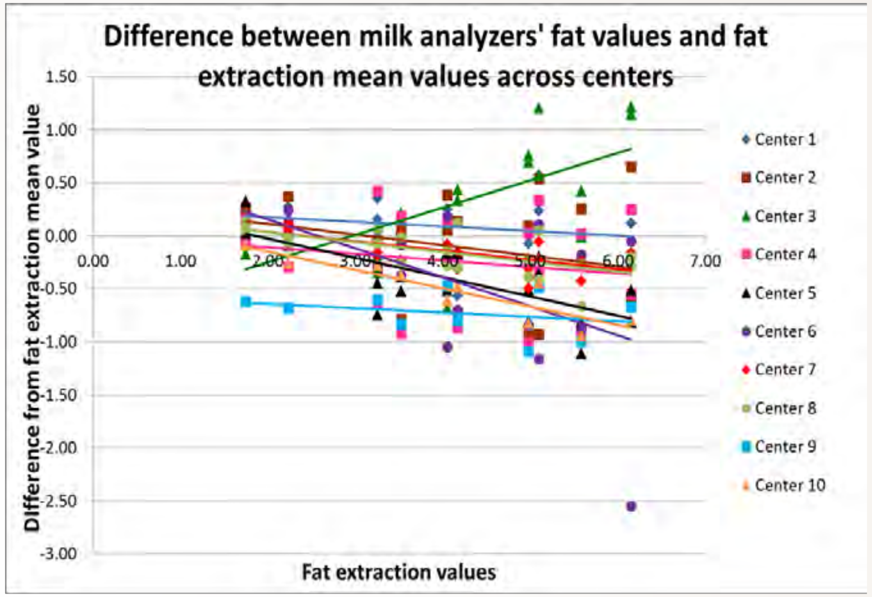
“Handbook of Target Fortification”
125 pages, 56.

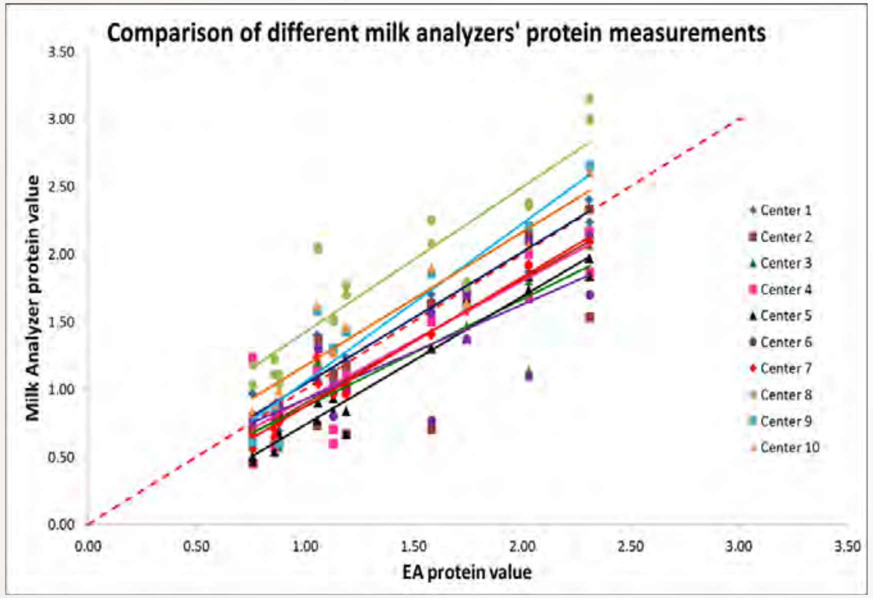


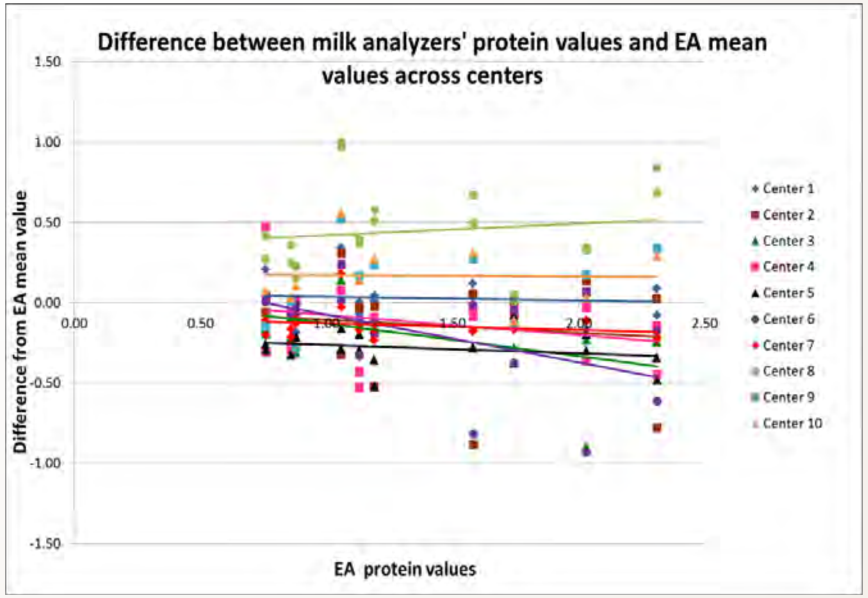


MAMAS Study Protocol

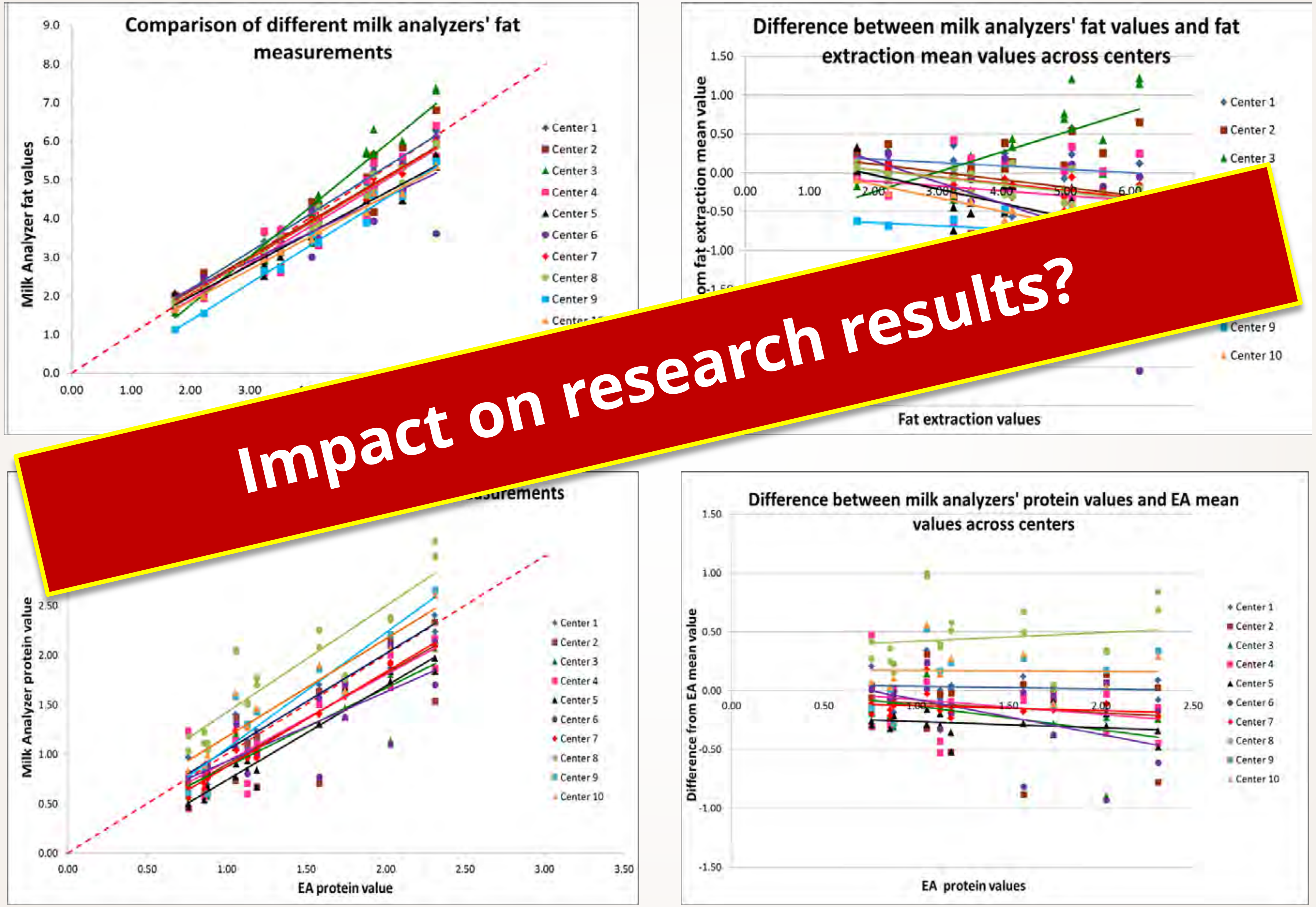




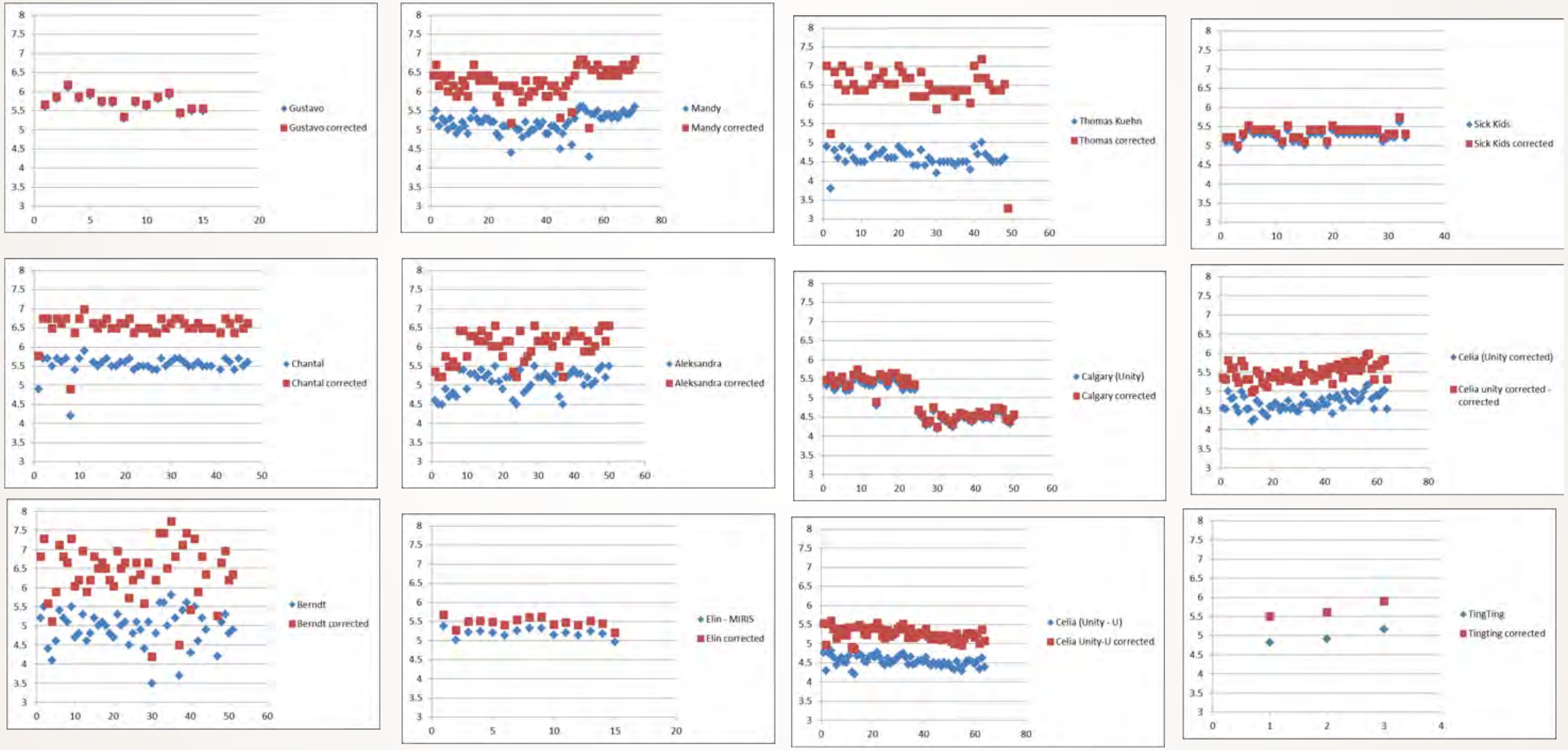




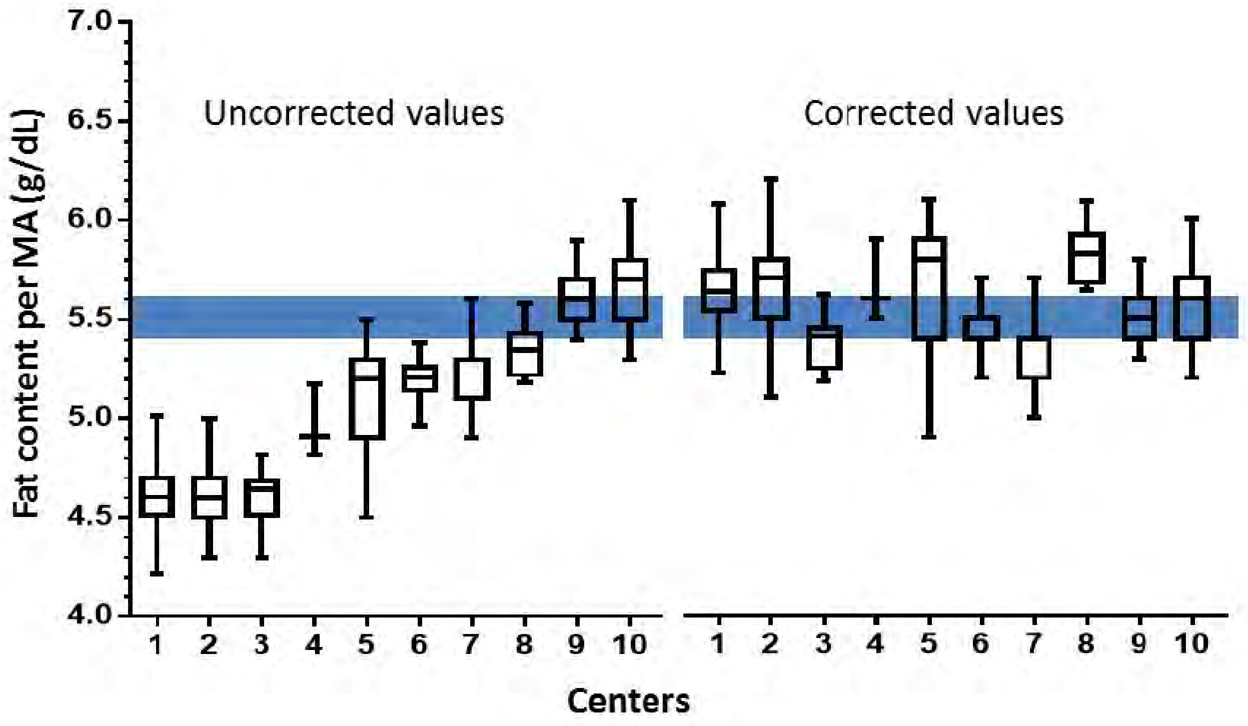
MAMAS Study Protocol



Comparison of all centers for high QC fat



Performance of bedside milk analysers can be improved by applying principles of good laboratory practice (GLCP)



Kwan C Clin Nutr 2019

Figure 2: Mean LQC fat values measured by MA from 10 centers, before correction (left) and after correction (right). The shaded area represents the target fat value of 5.5±0.1 g/dL.

CLINICAL OUTCOMES FROM NUTRIENT RESEARCH STUDIES

Nutrient enrichment by lyophilisation increases the nutrient content, but does not eliminate the variability of composition

PLOS | ONE

RESEARCH ARTICLE

Human milk enriched with human milk lyophilisate for feeding very low birth weight preterm infants: A preclinical experimental study focusing on fatty acid profile

Vanessa S. Bomfim[1], Alceu A. Jordão, Junior[2], Larissa G. Alves[3], Francisco E. Martinez[4], José Simon Camelo, Jr[4]*

1 Department of Pediatrics, Children´s Hospital, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil, 2 Department of Internal Medicine, Nutrition Laboratory, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil, 3 Human Milk Bank, Clinics Hospital, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil, 4 Department of Pediatrics, Neonatology, Children´s Hospital, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil

* jscamelo@fmrp.usp.br

Check for updates

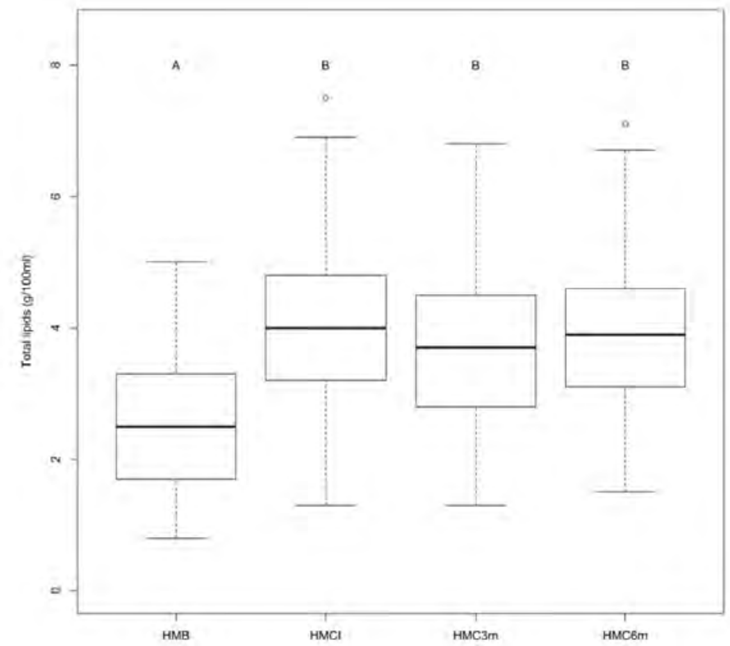


Fig 1. Box plot of total lipid values at HMB, HMCI, HMC3m and HMC6m. A x B: Mean values were significantly different (p<0.05).

Table 2. Macronutrient levels and osmolality of human milk and milk concentrates. Macronutrients have been analyzed using the Miris Human Milk Analyzer® by infrared transmission spectroscopy. Results expressed as mean ± standard deviation.

	HMB	HMCI	HMC3m	HMC6m
Protein (g/100ml)	0.90 ± 0.48	1.47 ± 0.58	1.39 ± 0.60	1.46 ± 0.54
Carbohydrate (g/100ml)	7.08 ± 0.67	9.17 ± 0.68	9.20 ± 0.63	9.18 ± 0.64
Total solids (g/100ml)	14.29 ± 17.30	14.76 ± 1.71	14.47 ± 1.77	14.53 ± 1.71
Energy (kcal/100ml)	56.30 ± 10.50	79.96 ± 13.74	76.98 ± 13.91	77.30 ± 13.77
True protein (g/100ml)	0.75 ± 0.39	1.20 ± 0.47	1.13 ± 0.49	1.19 ± 0.43
Osmolality (mOsm/Kg)	289.48 ± 43.64	452.12 ± 59.79	456.16 ± 56.57	458.14 ± 55.66

HMB—Human Milk Baseline; HMCI: Concentrate with Human Milk Lyophilisate in the immediate period; HMC3m: Concentrate with Human Milk Lyophilisate in the 3 months period; HMC6m: Concentrate with Human Milk Lyophilisate in the 3 months period.

British Journal of Nutrition (2016), **115**, 431–439
doi:10.1017/S0007114515004614

Comparing different methods of human breast milk fortification using measured *v.* assumed macronutrient composition to target reference growth: a randomised controlled trial

Gemma McLeod[1]*, Jill Sherriff[2], Peter E. Hartmann[3], Elizabeth Nathan[4], Donna Geddes[3] and Karen Simmer[1]

[1]*School of Paediatrics and Child Health, Centre for Neonatal Research and Education, The University of Western Australia, Perth, WA 6009, Australia*

[2]*Nutrition and Dietetics, School of Public Health, Curtin Health Innovation Research Institute, Curtin University, Perth, WA 6845, Australia*

[3]*School of Chemistry and Biochemistry, The University of Western Australia, Perth, WA 6009, Australia*

[4]*Women and Infants' Research Foundation, Carson House, King Edward Memorial Hospital, Perth, WA 6008, Australia*

(Submitted 15 December 2014 – Final revision received 6 October 2015 – Accepted 22 October 2015 – First published online 2 December 2015)

Does target fortification work?

Study done in 2009, published in 2016

	Igp (*n* 20)		RPgp (*n* 20)		
	n	%	*n*	%	*P*
Gestational age (weeks)					
Mean	27·0		27·1		0·781
SD	1·9		2·0		
Birth weight (g)					
Mean	1014·8		1009·2		0·953
SD	269·3		313·1		
Full enteral feeds achieved (d)					
Median	17		17		0·654
Range	8–27		9–29		
Days from birth when feeds were fortified					
Median	20		20		0·903
Range	10–39		10–36		
Weight at start of fortification (g)					
Median	1032		1155		0·925
Range	700–1998		505–1885		

No difference in growth…

Table 4. Growth data of infants at discharge
(Mean values and standard deviations)

	Igp (*n* 20)		RPgp control (*n* 20)		
	Mean	SD	Mean	SD	*P*
Growth at discharge					
Age (weeks)	37·7	2·5	37·8	2·2	0·762
Fat mass (g)	318	111	348	149	0·469
Body fat (%) (without correction for length)	13·7	3·6	13·6	3·5	0·984
Discharge weight (kg)	2294	356	2464	528	0·243
Discharge length (cm)	43·8	2·6	44·6	2·8	0·343
Discharge head circumference (cm)	32·4	1·6	33·1	1·8	0·184
Weight gain velocity from birth (g/kg per d)	11·4	1·4	12·1	1·6	0·135
Weight gain velocity after birth weight regained (g/kg per d)	13·4	1·9	14·3	1·6	0·139

Igp, intervention group; RPgp, routine practice group.

??

??

No difference in growth…

Table 4. Growth data of infants at discharge
(Mean values and standard deviations)

	Igp (*n* 20)		RPgp control (*n* 20)		
	Mean	SD	Mean	SD	*P*
Growth at discharge					
Age (weeks)	37·7	2·5	37·8	2·2	0·762
Fat mass (g)	318	111	348	149	0·469
Body fat (%) (without correction for length)	13·7	3·6	13·6	3·5	0·984
Discharge weight (kg)	2294	356	2464	528	0·243
Discharge length (cm)	43·8	2·6	44·6	2·8	0·343
Discharge head circumference (cm)	32·4	1·6	33·1	1·8	0·184
Weight gain velocity from birth (g/kg per d)	11·4	1·4	12·1	1·6	0·135
Weight gain velocity after birth weight regained (g/kg per d)	13·4	1·9	14·3	1·6	0·139

Igp, intervention group; RPgp, routine practice group.

??

??

Calculated nutritional intakes after milk was fortified on measured composition

	Igp (*n* 20)		RPgp (*n* 20)		
	Mean	SD	Mean	SD	
Fluid (ml)	158	14	153	9	0·256
Energy (kJ)	524	44	538	47	0·336
Protein (g)	3·3	0·4	3·4	0·5	0·673
PER	2·6	0·3	2·7	0·3	0·751
Lipid (g)	6·8	0·9	6·8	1·0	0·702
CHO (g)	12·9	1·1	13·5	0·9	0·640

??

??

But also no difference in intake… and P:E ratio low

Individualized fortification is superior to standard fortification: "Target" better "Adjusted"

BREASTFEEDING MEDICINE
Volume 14, Number 1, 2019

DOI: 10.1089/bfm.2018.0093

Comparison of the Effect of Three Different Fortification Methods on Growth of Very Low Birth Weight Infants

Gülsüm Kadıoğlu Şimşek, Evrim Alyamaç Dizdar, Sema Arayıcı, Fuat Emre Canpolat, Fatma Nur Sarı, Nurdan Uraş, and Serife Suna Oguz

TABLE 1. GENERAL CHARACTERISTICS OF STUDY POPULATIONS

	SF (n = 20)	*AF* (n = 20)	*TF* (n = 20)	p
Gestational age, weeks, median (range)	29 (28–30)	29 (28–31)	30 (27–31)	0.60
Birth weight, g, median (range)	1,090 (880–1,215)	1,080 (905–1,250)	980 (855–1,105)	0.35
Age at randomization, median (range)	11 (9–13)	10 (8–14)	10 (8–11)	0.48
Head circumference, cm, median (range)	26 (25–27)	26 (25–28)	26 (25–28)	0.92
Length, cm, median (range)	35 (33–36)	35 (34–38)	36 (35–37)	0.16
Gender (male), *n* (%)	12 (60)	8 (40)	8 (40)	0.34
Cesarean, *n* (%)	16 (80)	16 (80)	19 (95)	0.30
RDS, *n* (%)	15 (75)	13 (65)	16 (80)	0.55
PDA, *n* (%)	9 (45)	6 (30)	6 (30)	0.51
Clinical sepsis, *n* (%)	9 (45)	14 (70)	12 (60)	0.27
NEC, *n* (%)	1 (5)	1 (5)	2 (10)	0.76
ROP, *n* (%)	7 (35)	4 (20)	7 (35)	0.49
Osteopenia, *n* (%)	7 (35)	6 (30)	6 (30)	0.92
BPD, *n* (%)	5 (25)	6 (30)	6 (30)	0.92

AF, adjustable fortification; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; SF, standard fortification; TF, targeted fortification.

TABLE 2. GROWTH CHARACTERISTICS OF THE INFANTS

	SF (n = 20)	*AF* (n = 20)	*TF* (n = 20)	p
Daily weight gain [g/(kg · d)]	12 (9–17)	24 (22–26)	25.5 (21–28)	<0.001
HC rate (mm/day)	0.875 (0.5–1)	1.25 (1–1.5)	1 (1–1.25)	<0.001
Length rate (mm/day)	1 (0.75–1.1)	2 (1.5–2)	1.75 (1.5–1.88)	<0.001

Data shown as median (interquartile range).
HC, head circumference.

Nutrition in Clinical Practice
Volume 0 Number 0
xxx 2019 1–9

DOI: 10.1002/ncp.10307
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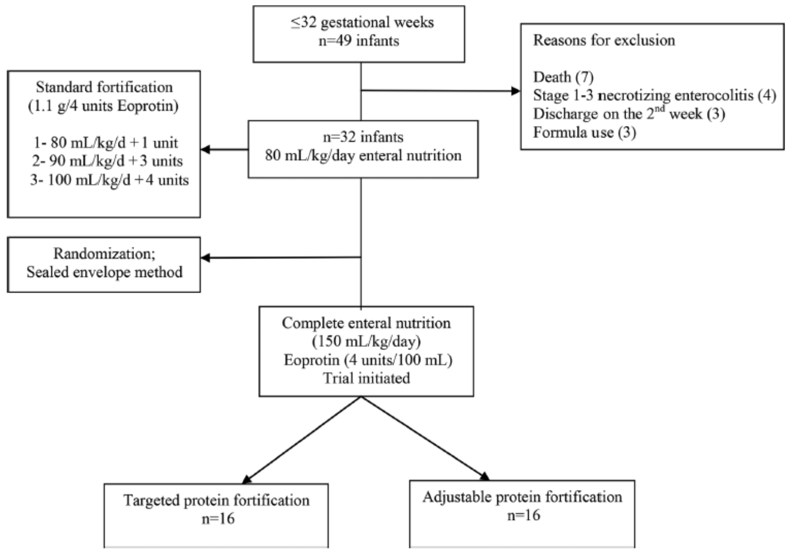
Effects of Targeted Versus Adjustable Protein Fortification of Breast Milk on Early Growth in Very Low-Birth-Weight Preterm Infants: A Randomized Clinical Trial

Ozgul Bulut, MD; Asuman Coban; Ozan Uzunhan, MD; and Zeynep Ince



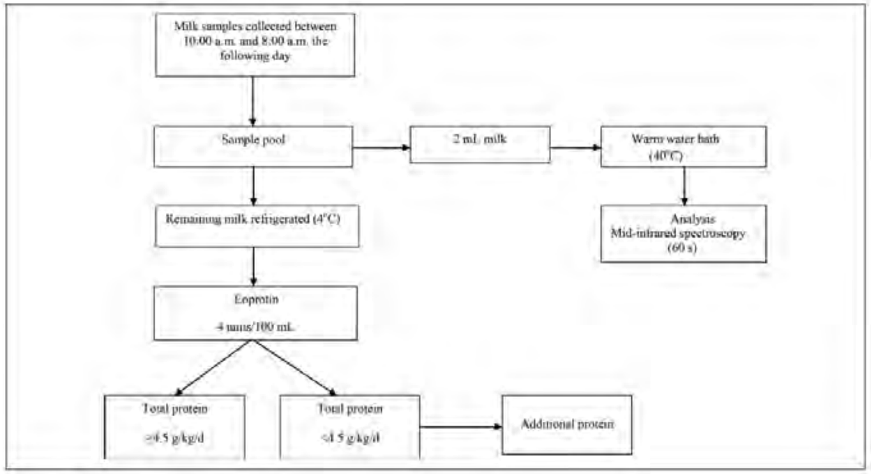


Figure 2. Targeted fortification protocol.

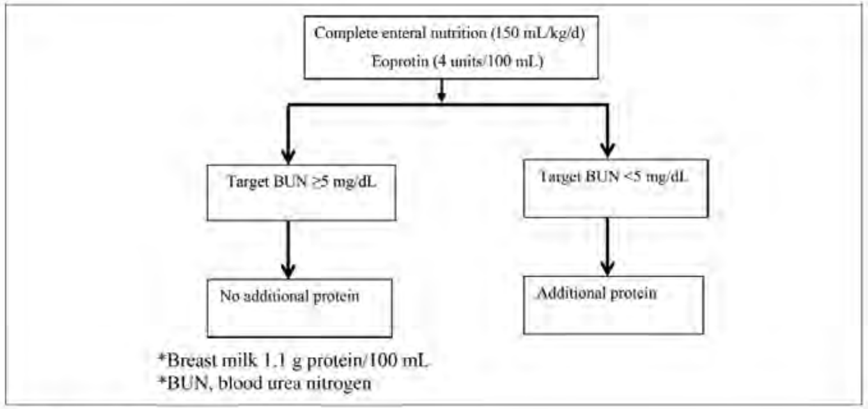


Figure 3. Adjustable fortification protocol.

Table 2. Mean Nutrition Contents Before and During the Study.

Nutrient	TF Group	AF Group	*P*-Value[a]
Cumulative nutrition contents delivered before the study period			
Protein, g	48.9 ± 8.6	46.2 ± 20.9	0.792
Energy, kcal	1224.2 ± 451.2	1102.4 ± 411.8	0.624
Fat, g	43.4 ± 20.3	33.6 ± 18.04	0.163
Carbohydrate, g	135.2 ± 48.8	239.7 ± 326.2	0.407
Breast milk contents during the study period			
Protein, g	1.1 ± 0.2	1.2 ± 0.1	0.147
Fat, g	4.0 ± 0.4	4.1 ± 0.6	0.865
Energy, kcal	73.1 ± 3.5	74.1 ± 5.7	0.880
Carbohydrate, g	7.0 ± 0.2	7.1 ± 0.2	0.940
Daily nutrition intake during the study period			
Protein, g/kg/d	4.5 ± 0.04	4.01 ± 0.3	0.001
Calories, kcal/kg/d	145.02 ± 5.4	144.3 ± 10.3	0.706
Carbohydrate, g/kg/d	11.5 ± 0.6	11.5 ± 0.5	0.851
Fat, g/kg/d	6.6 ± 0.6	6.6 ± 1.0	0.678
Protein/energy ratio	3.2 ± 0.1	2.8 ± 0.2	0.001

Values are presented as mean ± SD.
AF, adjustable fortification; TF, targeted fortification.
[a]Mann-Whitney *U*-test.

Table 3. Growth Data on Both Groups Obtained During the Study Period.

Growth Indices	TF Group	AF Group	*P*-Value[a]
Weight, g/d	25.7 ± 3.9	22.2 ± 6.4	0.048*
Weight, g/kg/d	23.1 ± 4.3	18.7 ± 4.3	0.014*
Length, mm/wk	10.4 ± 1.7	9.3 ± 2.1	0.168
Head circumference, mm/wk	9.8 ± 1.5	8.4 ± 2.1	0.040*

Values are presented as mean ± SD.
AF, adjustable fortification; TF, targeted fortification.
[a]Mann-Whitney *U*-test.
[b]$P < 0.05$.

McMaster Study: Target Fortification Improves Protein and Carbohydrate Intake

Study design

- Double-blinded, single-center, randomized control trial
- 3-weeks intervention period
- Primary outcomes—weight at 36 weeks
- n=100 preterm infants

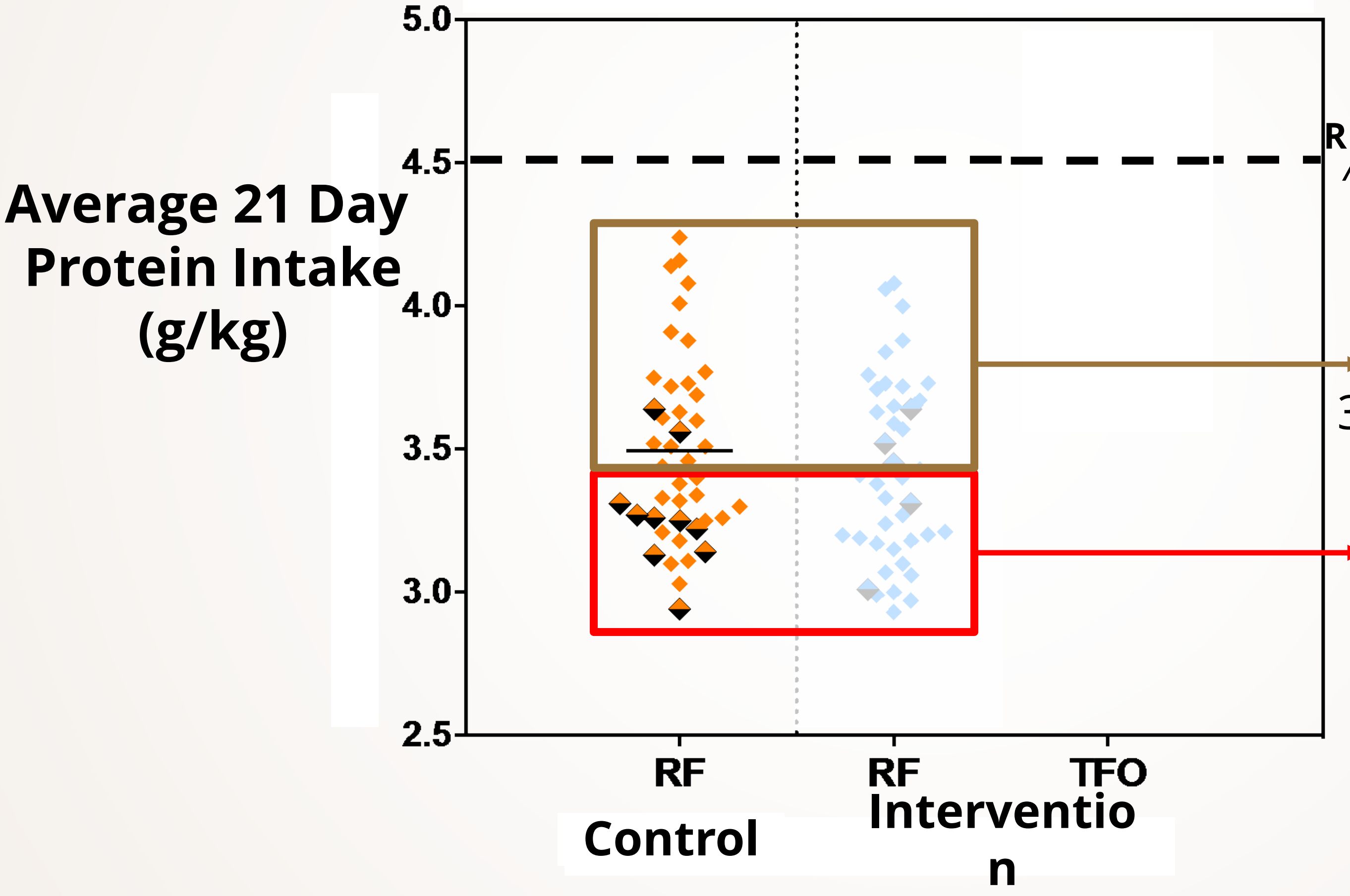
Baseline Demographics

	Control (n=43)	Intervention (n=42)	*P* value
Birth weight (g)	970 ± 260	960 ± 210	0.97
GA at birth (weeks)	27.0 ± 1.8	27.2 ± 1.2	0.44
GA at start (weeks)	30.4 ± 1.6	30.4 ± 1.1	0.85
DOL at start	22 ± 7	22 ± 6	0.31
Male (n)	24	22	0.75

Fusch G, et al. *Acta Paediatr.* 2015;104:38-42.

McMaster Children's Hospital
NEONATAL NURSERIES

TFO improves intake of Protein



ESPGHAN RECCOMENDATION
Agostini et al. 2010

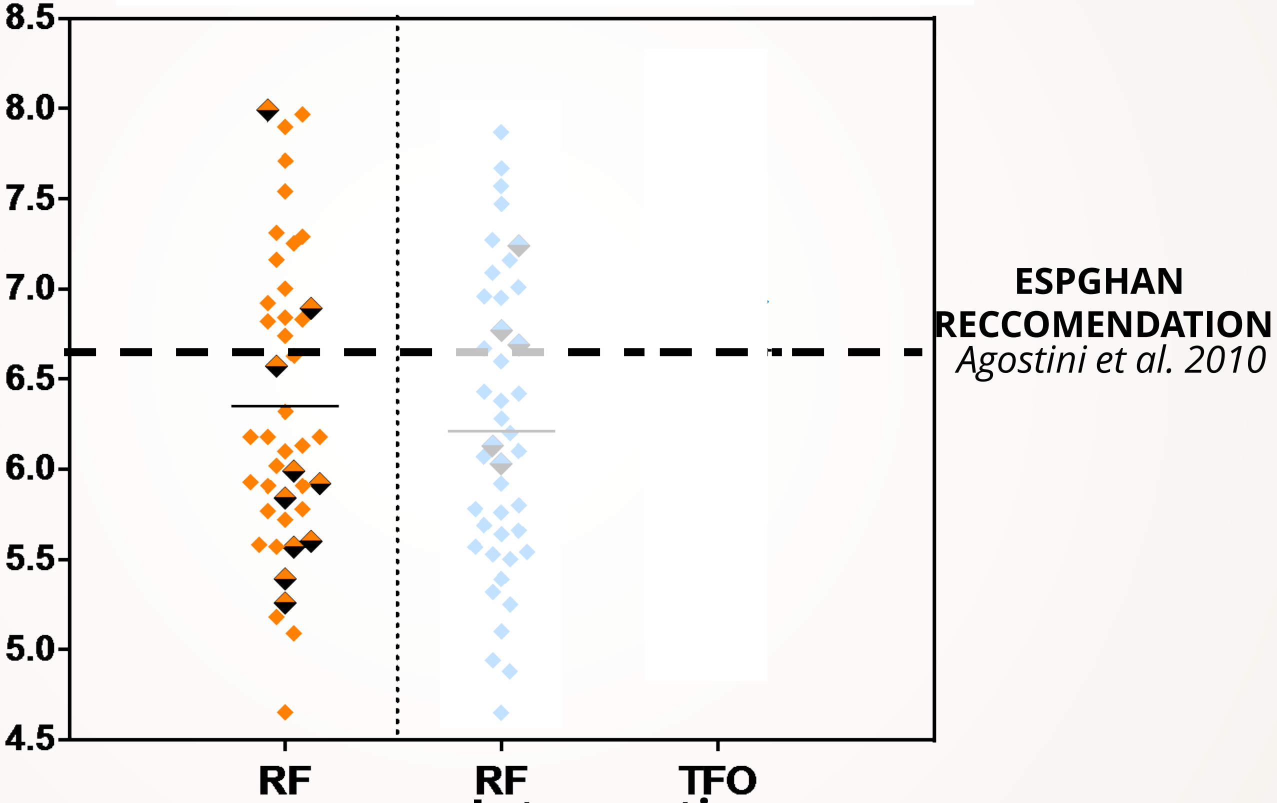
High Protein Group
Intake > Median of 3.41 g/kg/day after RF

Low Protein Group
Intake < Median of 3.41 g/kg/day after RF

Infants on Donor Milk

TFO improves intake of Fat

Average 21 Day Fat Intake (g/kg)

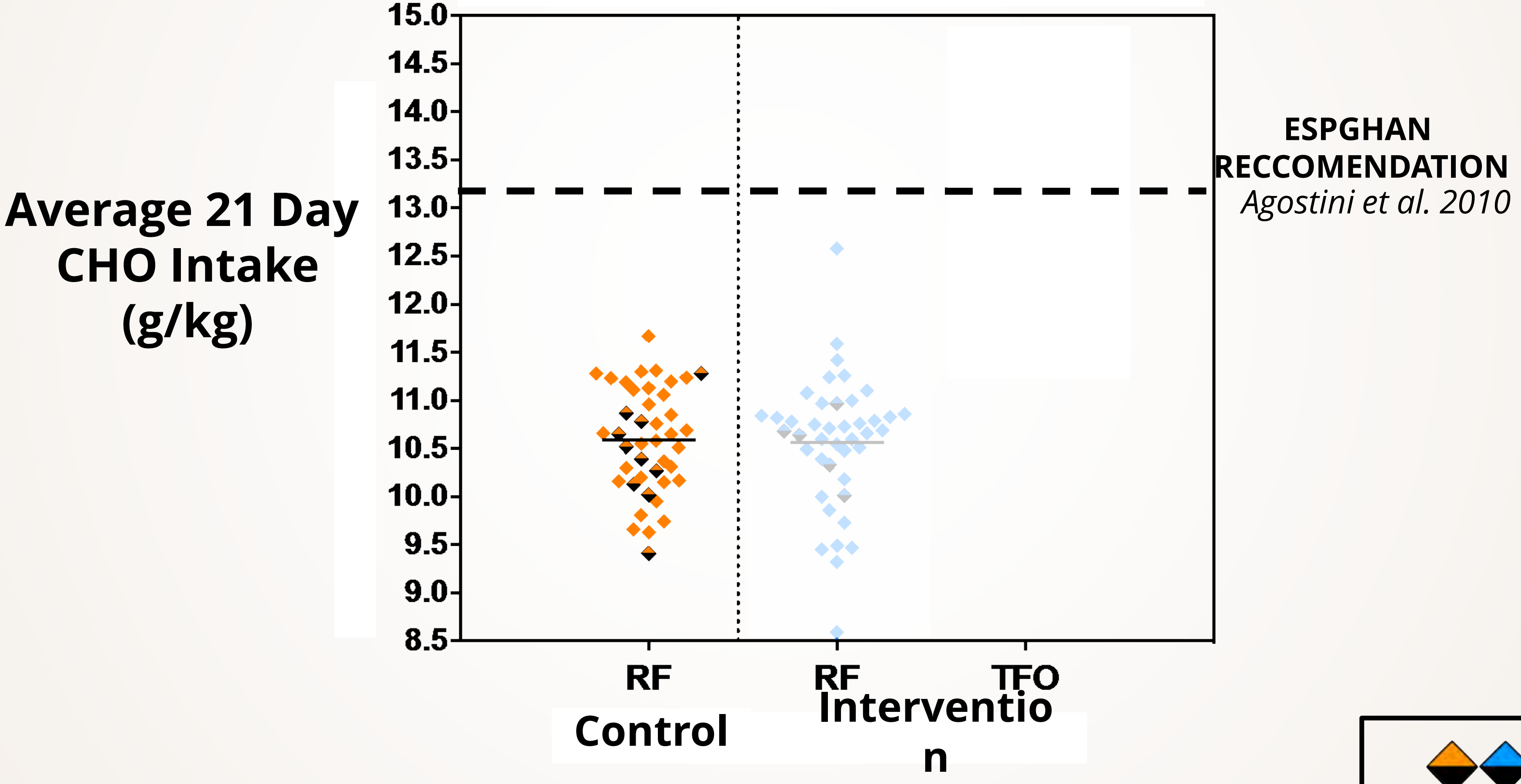


Control

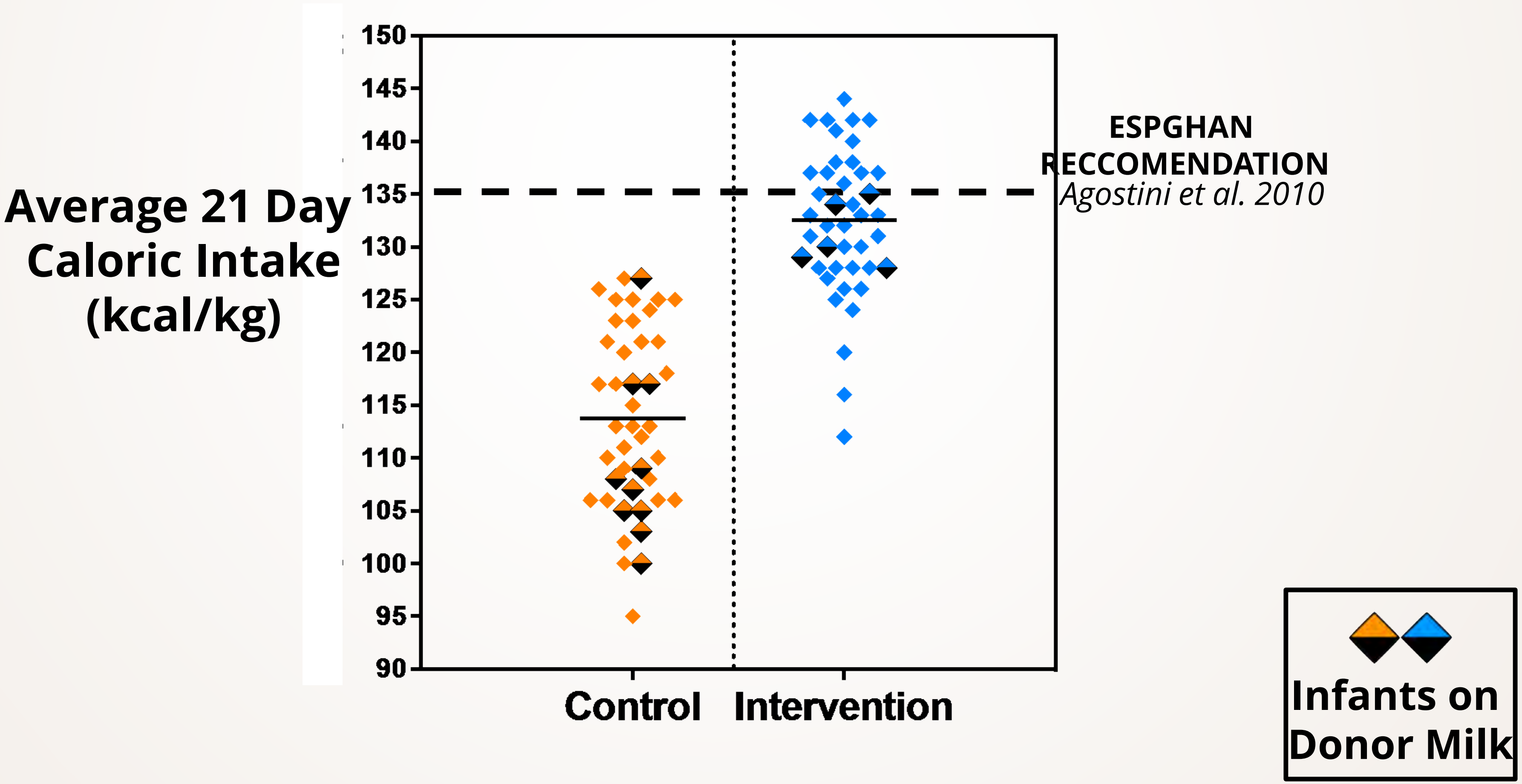
Interventio
n

Infants on Donor Milk

TFO improves intake of Carbohydrates



TFO increases caloric intake to provide more energy for preterm growth



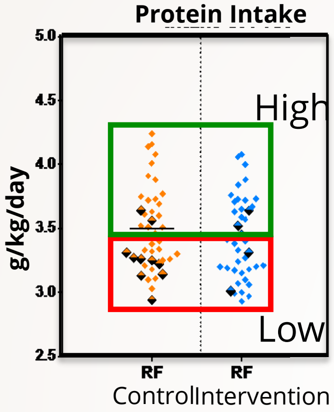
McMaster Study: Target Fortification Improves Growth Outcomes

	Control (n=43)	Intervention (n=42)	*P* value
Weight (g)	2280 ± 340	2510 ± 290	0.01
Growth velocity (g/kg/d)	19.4 ± 2.3	21.2 ± 2.3	<0.001
Nutritive efficiency (g/dL)	12.6 ± 1.6	13.9 ± 1.7	<0.001
TFI (mL/kg/d)	155 ± 4	153 ± 4	0.008

$$\text{Nutritive Efficiency} = \frac{\textit{Growth velocity}}{\textit{TFI}}$$

Fusch G, et al. *Acta Paediatr.* 2015;104:38-42.

Improved growth outcomes in Low Protein Group



	High Protein			Low Protein		
	Control (n=22)	**Intervention (n=21)**	**p-value**	**Control (n=21)**	**Intervention (n=21)**	**p-value**
Weight (g)	2400 ± 331	2480 ± 265	0.35	2170 ± 316	2540 ± 312	<0.001
Growth Velocity (g/kg/d)	19.7 ± 2.0	21.3 ± 2.0	0.011	19.2 ± 2.7	21.0 ± 2.6	0.030
Nutritive Efficiency (g/dL)	12.7 ± 1.4	14.0 ± 1.6	0.009	12.4 ± 1.9	13.8 ± 1.8	0.019
TFI (mL/kg/d)	155 ± 4	153 ± 3	0.087	155 ± 3	153 ± 4	0.044

Intake after RF > Median of 3.41 g/kg/day

Intake after RF < Median of 3.41 g/kg/day

Target fortification is not a superfortification. It just identifies babies from mothers with low content of macronutrients to provide them with an appropriate nutrition to reach ESPGHAN guidelines.

Perinatal Characteristics and NICU Outcomes

	Control Group		TFO Group	
	Randomized	Completed	Randomized	Completed
N -	89	51	90	52
Maternal Diabetes	6 (7)	3 (6)	7 (8)	6 (12)
Hypertension/Preeclampsia	16 (18)	12 (24)	25 (28)	17 (33)
Suspected Chorioamnionitis	32 (36)	15 (29)	25 (28)	13 (25)
Antenatal Corticosteroids	84 (94)	49 (96)	78 (87)	47 (90)
Died	5 (6)	2 (4)	0 (0)	0 (0)
NEC all cases	5 (6)	2 (4)	2 (2)	0 (0)
NEC Bell stage 3	3 (3)	1 (2)	0 (0)	0 (0)
Sepsis clinical	41 (46)	19 (37)	30 (33)	14 (27)
Sepsis culture positve	17 (19)	7 (14)	22 (24)	10 (19)
PDA	57 (64)	30 (59)	51 (57)	29 (56)
PDA treated	35 (39)	21 (41)	31 (34)	14 (27)
BPD mild	22 (25)	17 (33)	20 (22)	15 (29)
BPD moderate/severe	32 (36)	18 (35)	29 (32)	16 (31)
feeding intolerance		14 (27)		8 (15)**

- No difference in perinatal characteristics and demographics
- Trend towards better NICU outcomes
- Better tolerance of enteral nutrition (more balanced intake??)

Clinical Chemistry

	All		High protein group		Low protein group	
Outcome	Control Group	TFO Group	Control Group	TFO Group	Control Group	TFO Group
Glucose Day 14	4.1 ± 0.8	4.6 ± 0.9*	4.3 ± 0.9	4.6 ± 1.1	4.0 ± 0.8	4.5 ± 0.7*
Glucose Day 21	4.6 ± 2.3	4.3 ± 1.1	4.8 ± 3	4.3 ± 1.2	4.3 ± 0.9	4.2 ± 1
BUN Day 14	2.5 ± 1.1	4.2 ± 1.5***	2.8 ± 0.9	4.1 ± 1.6**	2.3 ± 1.2	4.2 ± 1.4***
BUN Day 21	2.5 ± 1.1	4.7 ± 1.5***	2.8 ± 1.2	4.8 ± 1.1***	2.3 ± 0.8	4.6 ± 1.8***
TG Day 14	0.9 ± 0.4	0.7 ± 0.2	0.8 ± 0.3	0.7 ± 0.2	0.9 ± 0.6	0.7 ± 0.2
TG Day 21	0.8 ± 0.5	0.7 ± 0.3	0.8 ± 0.3	0.7 ± 0.3	0.9 ± 0.7	0.7 ± 0.2

Mild increase in glucose and BUN levels without clinical significance
Drop in triglyceride levels

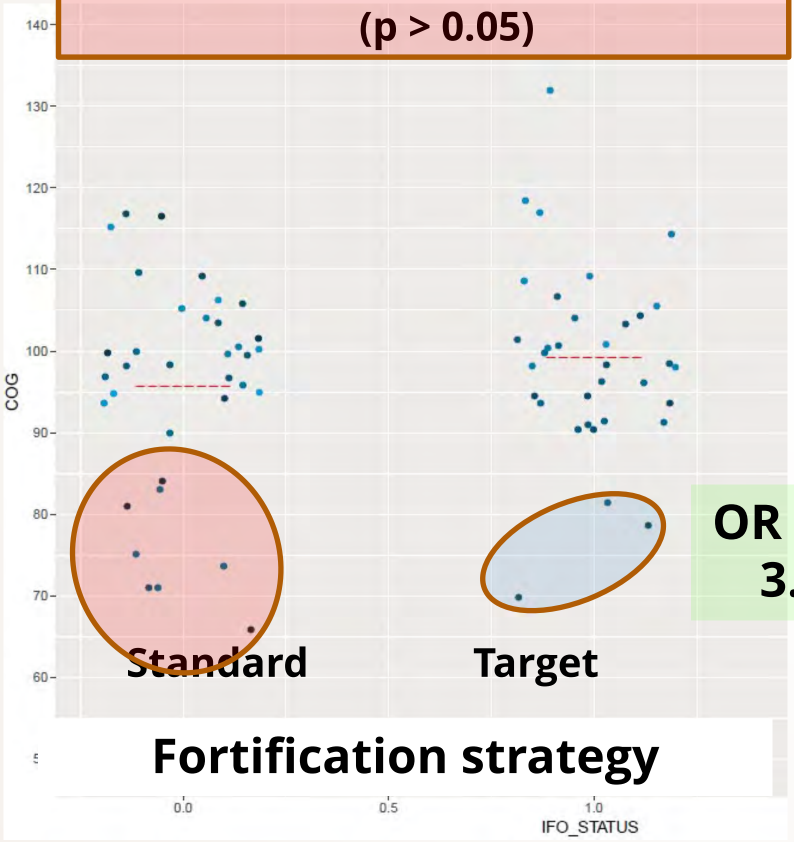
Body Composition Outcomes

	All		High protein group		Low protein group	
Outcome	Control Group (n=43)	TFO Group (n=43)	Control Group (n=21)	TFO Group (n=18)	Control Group (n=22)	TFO Group (n=25)
PMA [weeks]	39.5 ± 2.9	40.7 ± 2.9	39.3 ± 3	40.8 ± 3	39.7 ± 2.9	40.7 ± 2.9
Total Body Mass [g]	3030 ± 760	3470 ± 760*	3090 ± 910	3260 ± 910	2970 ± 610	3620 ± 610
FM [g]	590 ± 280	820 ± 280**	590 ± 300	770 ± 300	590 ± 260	850 ± 260
FFM [g]	2430 ± 530	2670 ± 530*	2500 ± 630	2620 ± 630	2360 ± 420	2710 ± 420
FM %	18.8 ± 5.4	22.8 ± 5.4**	18.1 ± 4.4	22.2 ± 4.4*	19.5 ± 6.2	23.2 ± 6.2
FFM %	81.2 ± 5.4	77.2 ± 5.4**	81.9 ± 4.4	77.8 ± 4.4*	80.6 ± 6.2	76.8 ± 6.2
FM Index [kg/m^2]	2.6 ± 1	3.4 ± 1**	2.5 ± 1	3.2 ± 1*	2.7 ± 1	3.5 ± 1

Increased lean mass (FFM) and increased fat mass (FM): potential effect, inherent due to the composition of standard fortifier because their high amount of fat can lead to excess fat intake in preterm infants receiving breast milk with high native fat content, which cannot be reduced.

Fortification and Neurodevelopment
Cognition—per protocol analysis
Subjects on target fortification do better

95.7 mean 99.3
13.0 SD 11.6
($p > 0.05$)

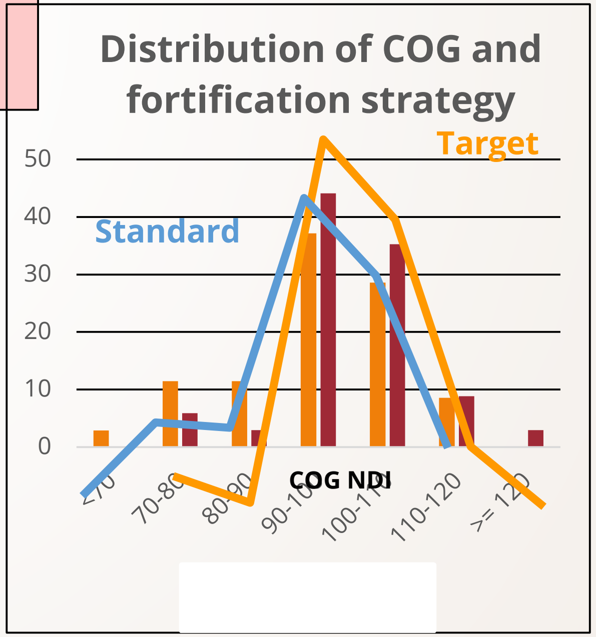


Sample size for
alpha 0.05
beta 0.80
delta ~3–4
SD ~12

n = 180–240
250–300 to
Recruit for ND-F/U

higher mean (average)
Lower OR for COG<85
Right shift of population

OR for COG < 85
3.1 ($p>0.05$)



JAMA | Original Investigation

Effect of Supplemental Donor Human Milk Compared With Preterm Formula on Neurodevelopment of Very Low-Birth-Weight Infar[...]
A Randomized Clinical Trial

DoMINO Trial

Lower NEC rates, but no improvement in neurodevelopment outcome

- No difference in BSID III scores
- Increased risk of cog <85
- No difference in risk of cog <70

Table 2. Neurodevelopment at 18 Months' Corrected Age Assessed by the Bayley Scales of Infant and Toddler Development, Third Edition[a]

Characteristic	Adjusted Mean (95% CI)[b] Donor Milk (n = 151)	Adjusted Mean (95% CI)[b] Preterm Formula (n = 148)	Adjusted: Model 1[c] Effect (95% CI)	Adjusted: Model 1[c] P Value	Adjusted: Model 2[d,e] Effect (95% CI)	Adjusted: Model 2[d,e] P Value
Composite scores[c]						
Cognitive-primary outcome	92.9 (89.8 to 95.9)	94.5 (91.4 to 97.5)	−1.6 (−5.5 to 2.2)	.41	−2.0 (−5.8 to 1.8)	.31
Language	87.3 (83.8 to 90.8)	90.3 (86.7 to 93.9)	−3.0 (−7.5 to 1.5)	.19	−3.1 (−7.5 to 1.3)	.17
Motor	91.8 (88.8 to 94.9)	94.0 (91.0 to 97.0)	−2.2 (−6.0 to 1.7)	.27	−3.7 (−7.4 to 0.09)	.06
	Donor Milk, No./Total (%)	Preterm Formula, No./Total (%)	Adjusted Risk Difference, % (95% CI)	P Value		
Neuroimpairment score <85						
Cognitive	41/151 (27.2)	24/148 (16.2)	10.6 (1.5 to 19.6)	.02		
Language	70/150 (46.7)	54/145 (37.2)	9.3 (−1.8 to 20.3)	.10		
Motor	38/149 (25.5)	30/147 (20.4)	3.7 (−5.2 to 12.6)	.41		
Disability score <70						
Cognitive	14/151 (9.3)	12/148 (8.1)	−1.2 (−8.4 to 6.1)	.75		
Language	29/150 (19.3)	22/145 (15.2)	1.6 (−7.0 to 10.2)	.72		
Motor	18/149 (12.1)	13/147 (8.8)	2.2 (−3.8 to 8.3)	.47		

[a] Standarized mean is 100 (SD, 15). Continuous variables were analyzed by analysis of covariance, with adjustment as indicated. All models were tested for treatment interactions, and except where indicated none were found to be statistically significant. Analyses were rerun without nonstatistically significant interactions in the models. Categorical variables were analyzed by logistic regression analysis with adjustment as indicated.

[b] Adjusted using covariates from model 1.

[c] Adjusted for recruitment center and birth weight group (<1000 g, 1000-1499 g).

[d] Adjusted for recruitment center, birth weight group, maternal education (high school or less, college or vocational diploma, baccalaureate degree, postbaccalaureate degree), and percentage of total enteral feeds for each infant consumed as mother's milk. For the motor composite score, a statistically significant interaction was found with maternal education (P = .01), and this interaction was retained in the model.

[e] Logistic regression analyses of the proportion of participants with scores indicative of neuroimpairment or disability were not performed using model 2 adjustments because of insufficient sample size.

BSID III, Bayley Scales of Infant and Toddler Development; Cog, cognition

O'Connor DL, et al. *JAMA.* 2016;316:1897-1905.

DoMINO Trial

- Double-blind, randomized trial
- VLBW infants, from 4 neonatal units in Canada, within 96 hours of birth
- n=363, randomized; fed for 90 days, or to discharge, when mother's milk was unavailable
  - 181 donor milk
  - 182 preterm formula
- No statistically significant differences in mean Bayley-III cognitive composite score (92.9 in donor milk group vs 94.5 in formula group)
- Significance of DoMINO trial
  - Babies on supplemental donor milk had reduced NEC rate
  - Neurodevelopmental outcome did not improve [at 18 months]

DoMINO, donor milk for improved neurodevelopmental outcomes; NEC, necrotizing enterocolitis; VLBW, very low birth weight.

O'Connor DL, et al. *JAMA.* 2016;316:1897-1905.

Protein content of breast milk: Term vs Preterm Effect on donor milk (Fenton systematic review)

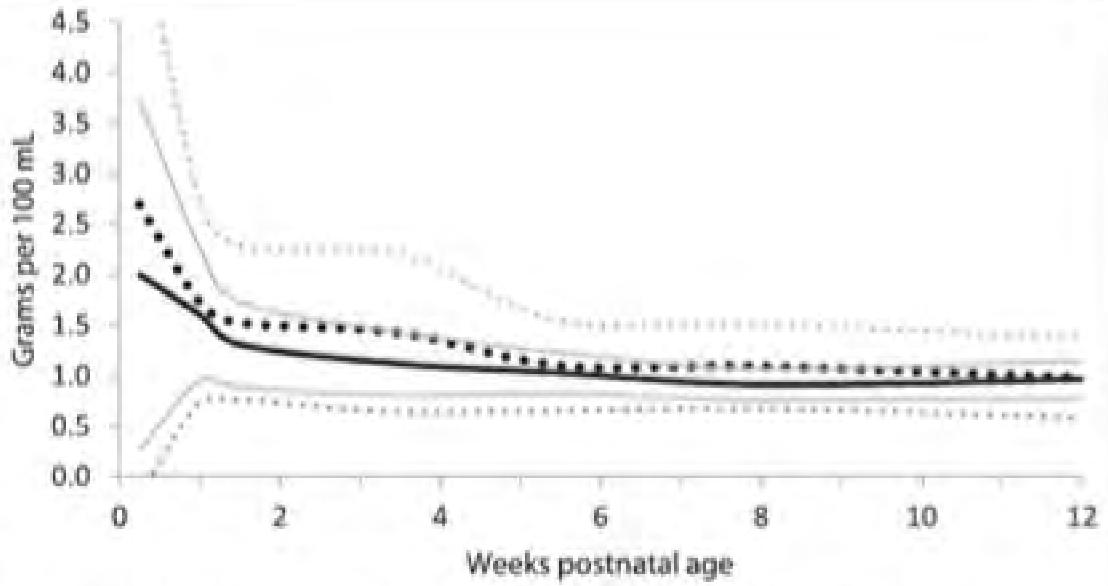
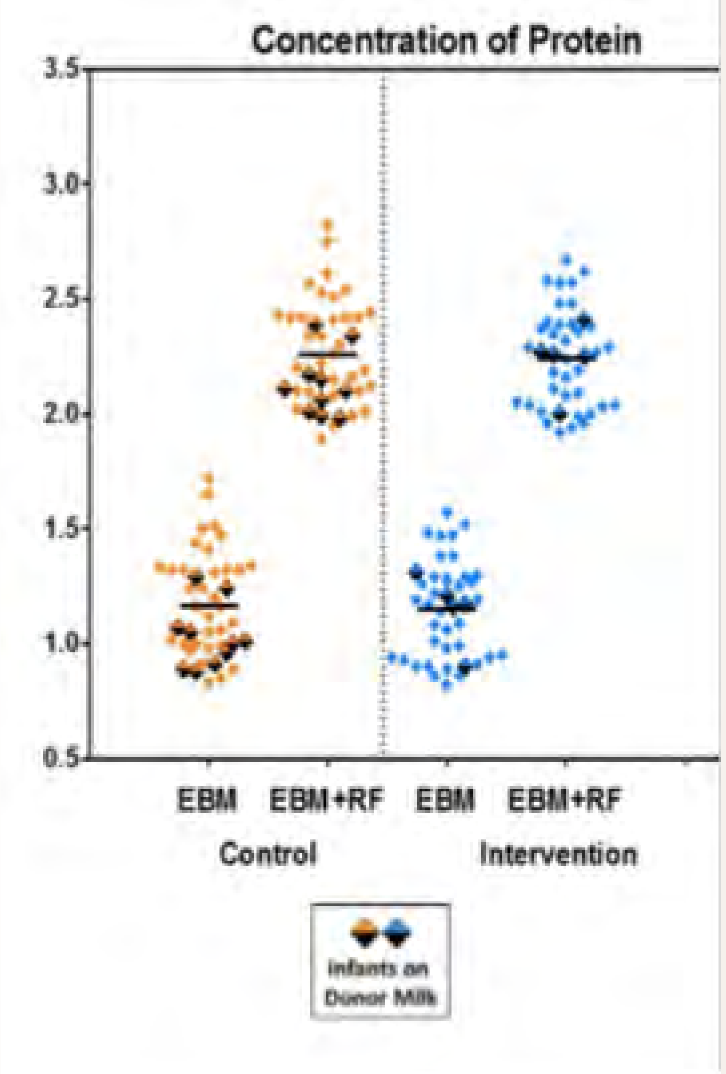
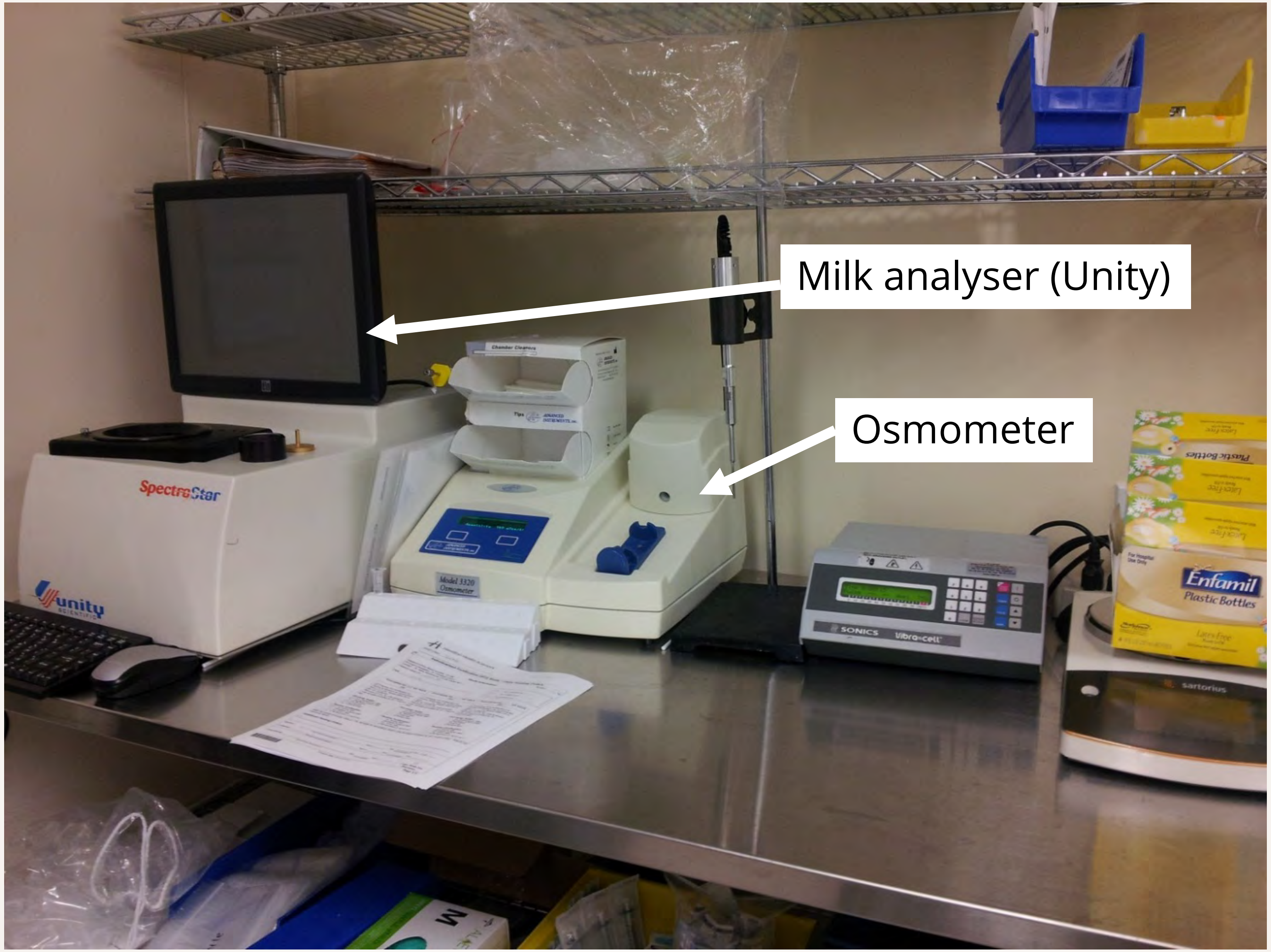


Figure 4 True Protein content distribution of preterm and term breast milk in by postnatal age over the first 12 weeks of lactation, weighted mean and 95% reference interval. Preterm milk ···· Term milk —— : mean +/- 2 standard deviations.

Own data: Target Fortification Study



IFO Analysis at McMaster Children's NICU



Always as a point-of-care solution?

- Does not need to be at the bedside
- Can be managed by the central lab
- Also more robust in terms of QC and GCLP


- Dr. Dirk Olbertz,
  Suedstadtklinikum, Rostock, Germany

Nuernberg practice and real life data

- Space needed: 50 cm footprint, standard bench
- Time needed: 2–3 minutes
- Calculation of target amount: 2 minutes
  can also be done using an excel based tool—"APP"

Klinik für Neugeborene, Kinder und Jugendliche

Klinikum Nürnberg

Target-Fortifizierung bei Früh- und Neugeborenen bei Ernährung mit Humaner Muttermilch und MM-Fortifier

Rechengewicht: ___________ g   Menge: ___________ ml/kg/d

Datum und Uhrzeit der Muttermilchmessung

Nährstoff	MM-Messung (g/100ml)	Anteil MM an der Gesamtmenge in ____% in g/100ml	Aktueller Fortifier +____ g/100ml Gesamtmenge	Σ MM und Fortfier in g/100ml	Empfehlung (g/100ml)	Differenz (g/100ml)	*Neuer* Fortifier +____ g/100ml	Anteil MM an der Gesamtmenge in ____% in g/100ml	Σ MM und Fortfier in g/100ml	Alternativ Duocal 4 Mßl/100ml	Alternativ Ceres-Öl g/100ml (1ml Öl = 0,09g Fett = 0,74kcal)	Σ MM und Fortifier +____ in g/100ml	Σ MM und Fortifier +____ in g/kg/d
KH (4,1kcal/g)					8,0					3,5			
Protein (4,1kcal/g)					3,0					%			
Fett (9,3kcal/g)					4,4					0,7			
Summe kcal					86					23,5			

Anordungen fürTageskurve (Öl in ml/d und ED):

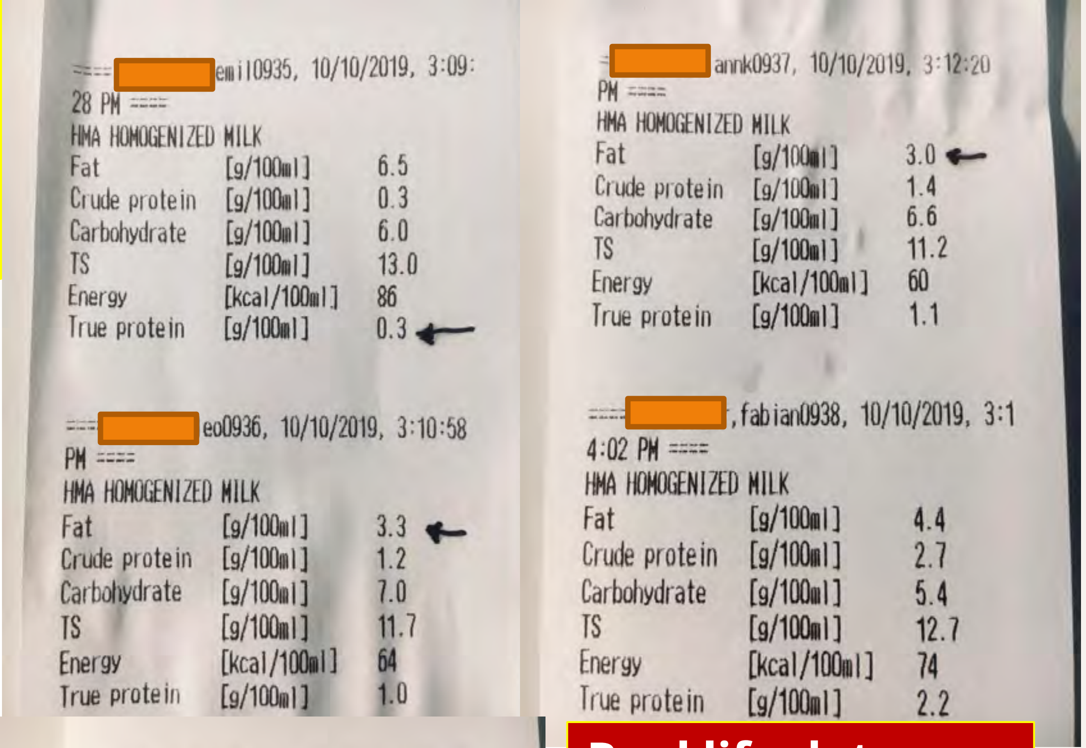
Requirements and benefits of target fortification

- Space needed: 50 cm footprint, standard bench
- Time needed: 2–3 minutes
- Calculation of target amount: 2 minutes can also be done using an excel based tool—“APP”

- Benefit
- Better tolerance
- Avoidance of postnatal growth retardation
- More constant weight gain, better growth
- Better body composition
- Better thermo control
- Shorter length of stay

Effects when you start to measure and when you care about BM content

- Staff develops interest in growth because they understand the nutritional physiology and expected growth patterns/trajectories
- Growth and nutritional assessment becomes an issue in the unit as part of daily routine, not only once per week
- Staff gets excited when they see the results of macronutrient contents and together with the knowledge stated in #1 call for action
- It is comparable to BGA, and if you see a pCO2 of 32mmHg (4.3 kPsc); you adjust your ventilator settings before you see cystic lesions in US weeks later



====[redacted]emil0935, 10/10/2019, 3:09:28 PM ====
HMA HOMOGENIZED MILK

Fat	[g/100ml]	6.5
Crude protein	[g/100ml]	0.3
Carbohydrate	[g/100ml]	6.0
TS	[g/100ml]	13.0
Energy	[kcal/100ml]	86
True protein	[g/100ml]	0.3

====[redacted]ann k0937, 10/10/2019, 3:12:20 PM ====
HMA HOMOGENIZED MILK

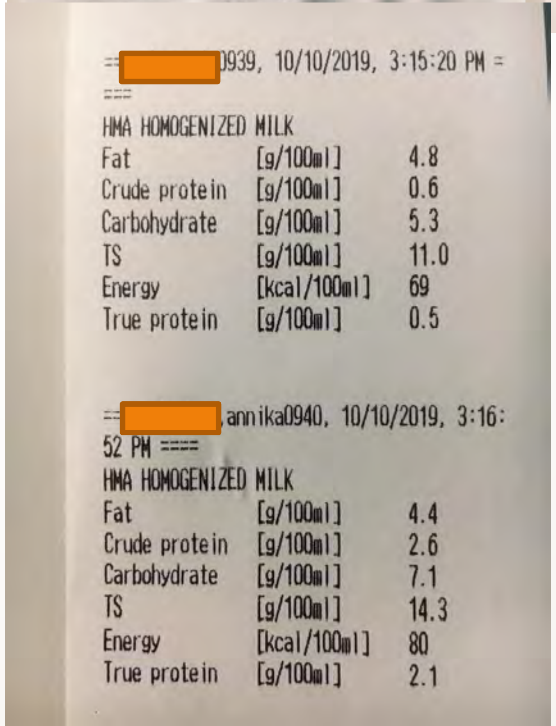
Fat	[g/100ml]	3.0
Crude protein	[g/100ml]	1.4
Carbohydrate	[g/100ml]	6.6
TS	[g/100ml]	11.2
Energy	[kcal/100ml]	60
True protein	[g/100ml]	1.1

====[redacted]eo0936, 10/10/2019, 3:10:58 PM ====
HMA HOMOGENIZED MILK

Fat	[g/100ml]	3.3
Crude protein	[g/100ml]	1.2
Carbohydrate	[g/100ml]	7.0
TS	[g/100ml]	11.7
Energy	[kcal/100ml]	64
True protein	[g/100ml]	1.0

====[redacted],fabian0938, 10/10/2019, 3:14:02 PM ====
HMA HOMOGENIZED MILK

Fat	[g/100ml]	4.4
Crude protein	[g/100ml]	2.7
Carbohydrate	[g/100ml]	5.4
TS	[g/100ml]	12.7
Energy	[kcal/100ml]	74
True protein	[g/100ml]	2.2



==[redacted]0939, 10/10/2019, 3:15:20 PM ====
HMA HOMOGENIZED MILK

Fat	[g/100ml]	4.8
Crude protein	[g/100ml]	0.6
Carbohydrate	[g/100ml]	5.3
TS	[g/100ml]	11.0
Energy	[kcal/100ml]	69
True protein	[g/100ml]	0.5

==[redacted]annika0940, 10/10/2019, 3:16:52 PM ====
HMA HOMOGENIZED MILK

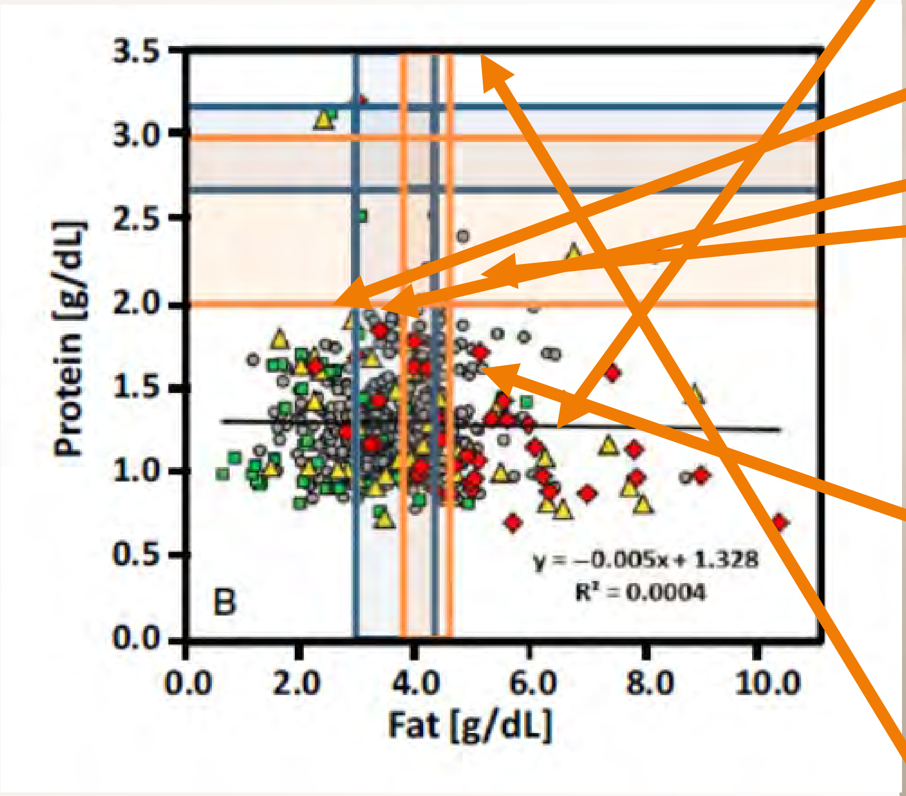
Fat	[g/100ml]	4.4
Crude protein	[g/100ml]	2.6
Carbohydrate	[g/100ml]	7.1
TS	[g/100ml]	14.3
Energy	[kcal/100ml]	80
True protein	[g/100ml]	2.1

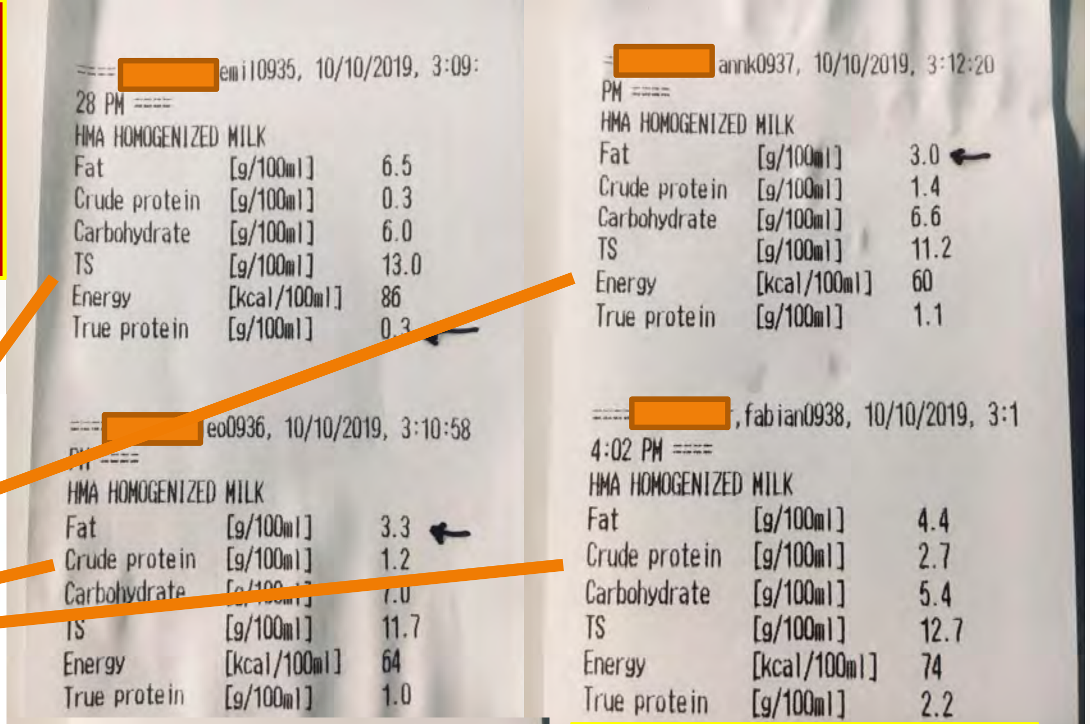
Real life data from Oct 10th analysis

Dysbalanced intake

See also time needed
7 minutes for 6 measurements

Effects when you start to measure and when you care about BM content





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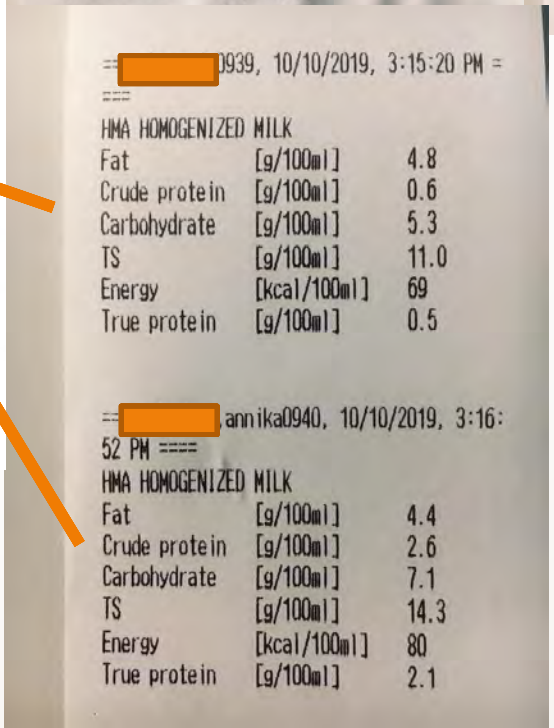

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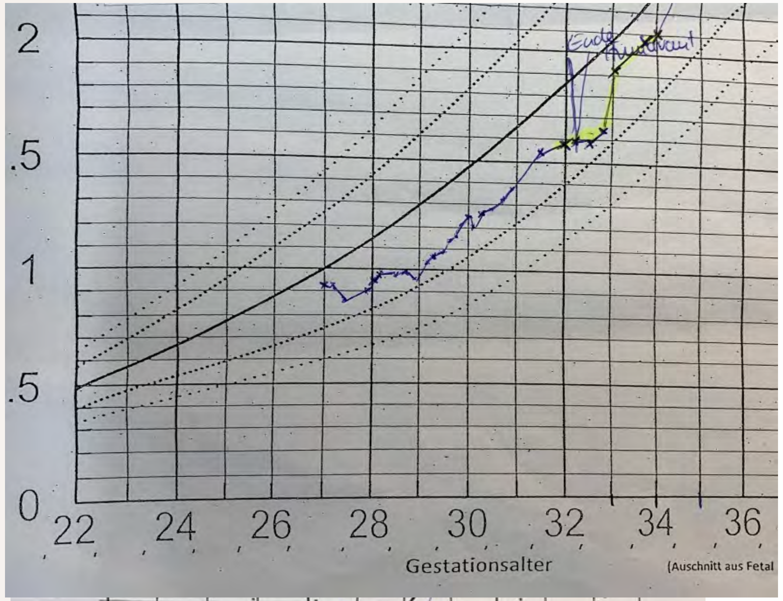
True protein	[g/100ml]	2.1

Real life data from Oct 10th analysis

Dysbalanced intake

See also time needed
7 minutes for 6 measurements

Growth achieved with target fortification



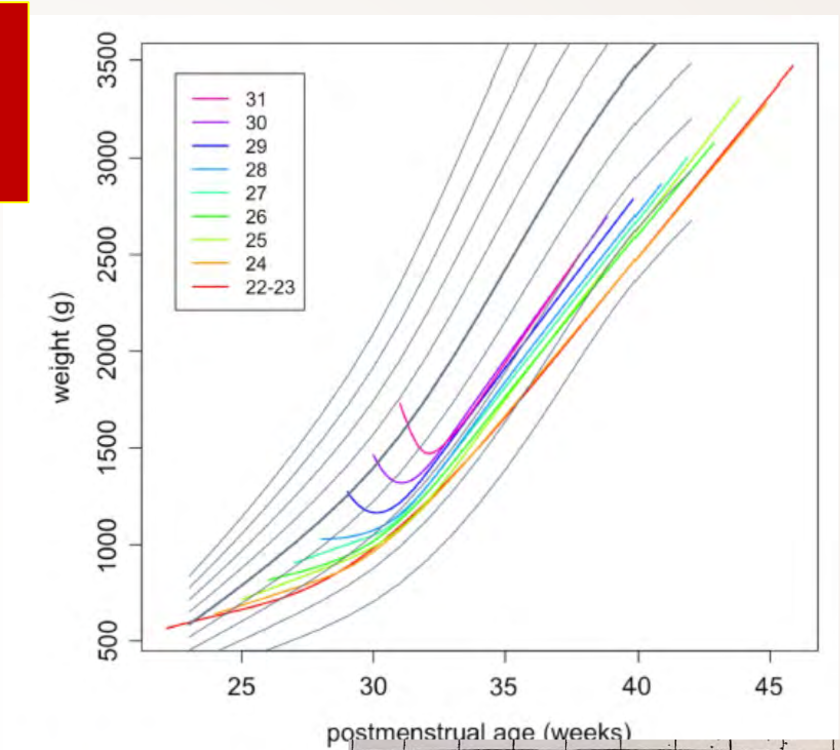
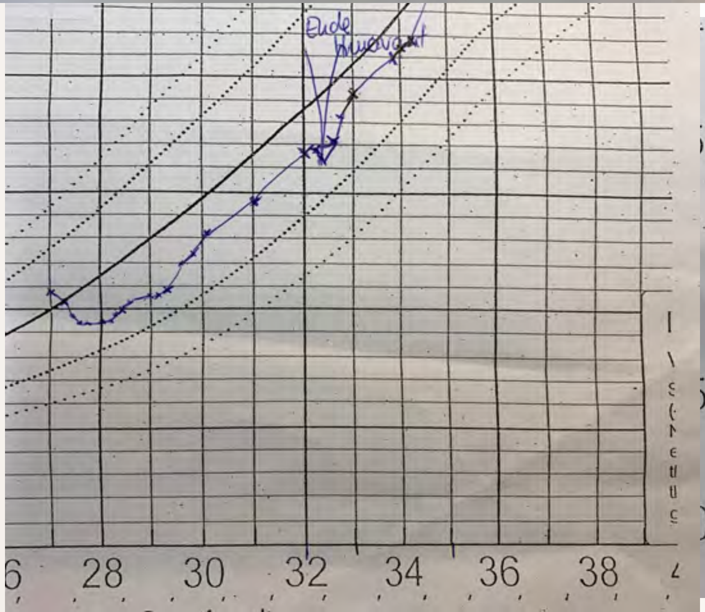
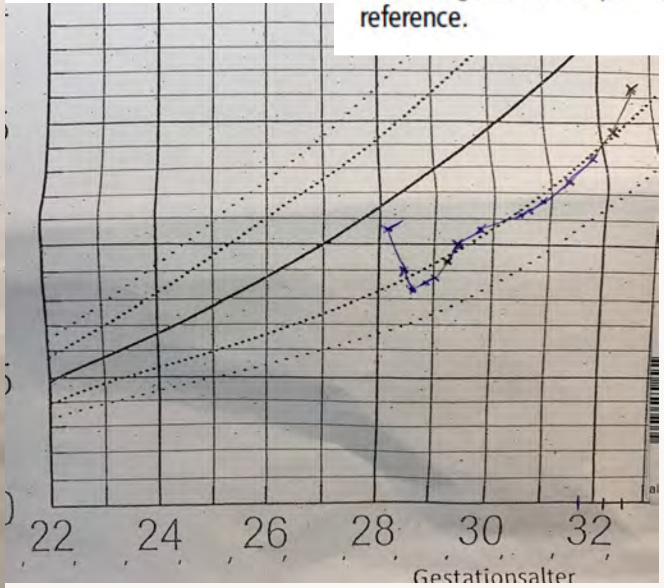
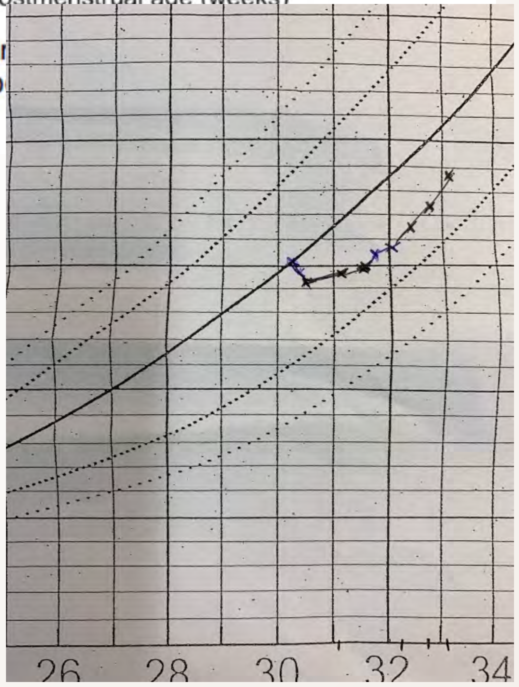


Figure 5 Mean growth cur
week of gestation, superimp
reference.







The Future:
FAT-MEN
Fully automated target macronutrient enhancer

Summary (1 of 7)

- Postnatal nutrition and growth patterns of preterm infants have an impact on later somatic and neurodevelopmental outcome.
- Postnatal growth patterns are related to nutritional intake provided by neonatal staff.
- All staff involved in neonatal care should have an understanding of the basic physiology of growth and how nutrition is related to it.

Summary (2 of 7)

- Individualized postnatal growth trajectories can be predicted, may provide a new reference point and support clinicians to guide growth of an individual infants ('Precision Medicine').
- Preliminary validation results appear reasonable.
- Postnatal weight gain [per kg/day] seems to be higher, by 10% compared to fetal weight gain.

Summary (3 of 7)

- The current concept of human milk fortification is based on the assumption of an average composition of breast milk.
- Composition of breast milk is highly variable.
- This can lead to clinical conditions with insufficient or unproportionate intake of one or more macronutrients thus compromising growth and later outcome.

Summary (4 of 7)

- Individualized fortification is feasible (‘Precision Medicine’).
- Adjusted fortification may help to improve growth, but is not efficient in all preterm infants. Data about NDI are not available.
- Target fortification reduces the risk of postnatal growth restriction.

Summary (5 of 7)

- **Important**: Target fortification is not providing “super” fortification. It identifies babies with mothers who “produce” BM with insufficient MN composition and provides them with intake according to ESPGHAN guidelines
- To measure solely protein content might not be sufficient. Fat content is highly variable, as the lactose content.
- Modern fortifiers should contain more protein (ca. 0.5–0.7 g/kg/d) and a more balanced mixture of fat and CHO (Rochow, Fusch, 2016)

Rochow N, et al. Pediatr Res. 2016;79:870-9.

Summary (6 of 7)

- Donor milk can be reliably measured. Pasteurization does not distort the analysis.
- For donor milk, additional supplementation using 0.3–0.5 g protein/100ml seems to be reasonable. (Simmer 2015)
- The optimum components for target fortification need to be developed. The fat-based concept of fortifiers available in NA to provide the extra calories needed should be reviewed.

Summary (7 of 7)

- For both "high-end" fortification strategies modern modular components need to be developed to conserve the NEC protective effect of breast milk (cow's milk protein free) and minimize the pro-inflammatory potential (omega 3 : 6, limited MCT).

- Concept should be proven in a blinded multicenter RCT including body composition measurements and neurodevelopment outcome.

ANY
Questions?