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Current controversies in preterm enteral nutrition and implications for clinical practice

Neena Modi
Professor of Neonatal Medicine
Imperial College London

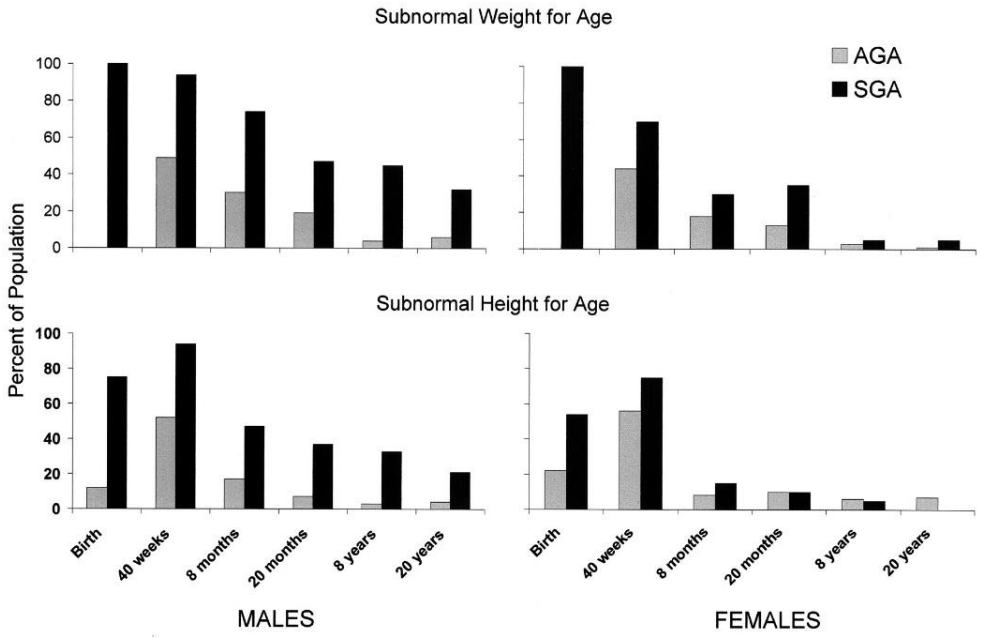
President
UK Royal College of Paediatrics and Child Health

Chelsea and Westminster Hospital NHS
NHS Foundation Trust

Uncertainty 1
What is the goal of preterm nutrition?

- To sustain growth?
- To reduce short-term problems?
- To enhance neurodevelopment?
- To promote optimum life-long health?

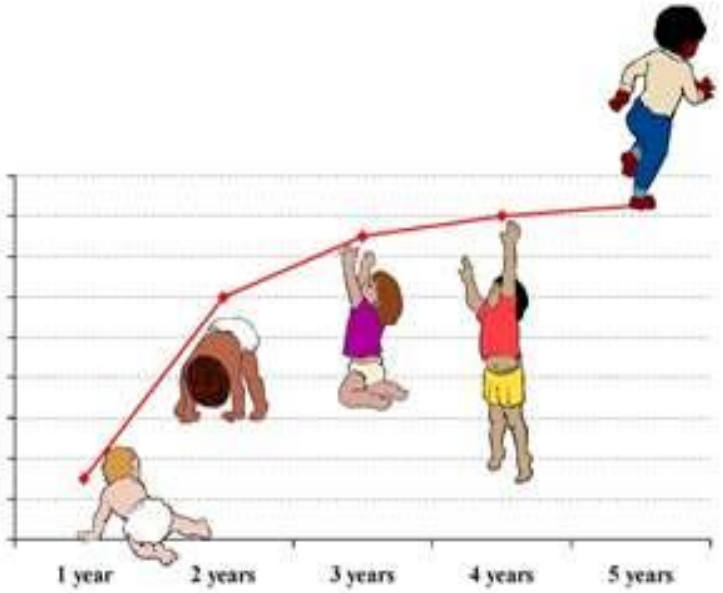
An unhelpful preoccupation with growth



Adult height and weight of preterm infants (Hack et al, Pediatrics 2003)

The WHO Multicentre Growth Reference Study

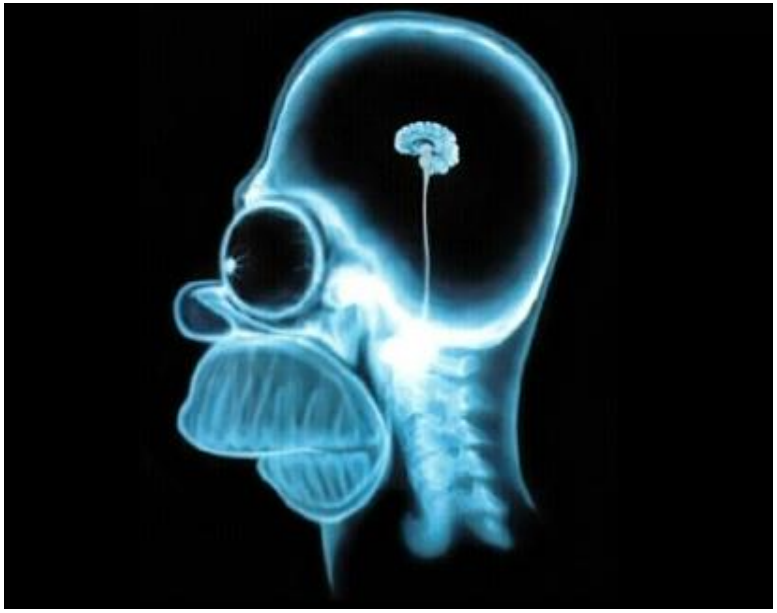
- Undertaken 1997 - 2003
- Analysed data from around 8500 breast fed children born at term to healthy mothers from Brazil, Ghana, India, Norway, Oman and the USA
- Provides a single international standard for all children from birth to five years
- Establishes the breastfed infant as the normative model for growth



Growth velocity is slower in breast-fed compared with formula fed babies

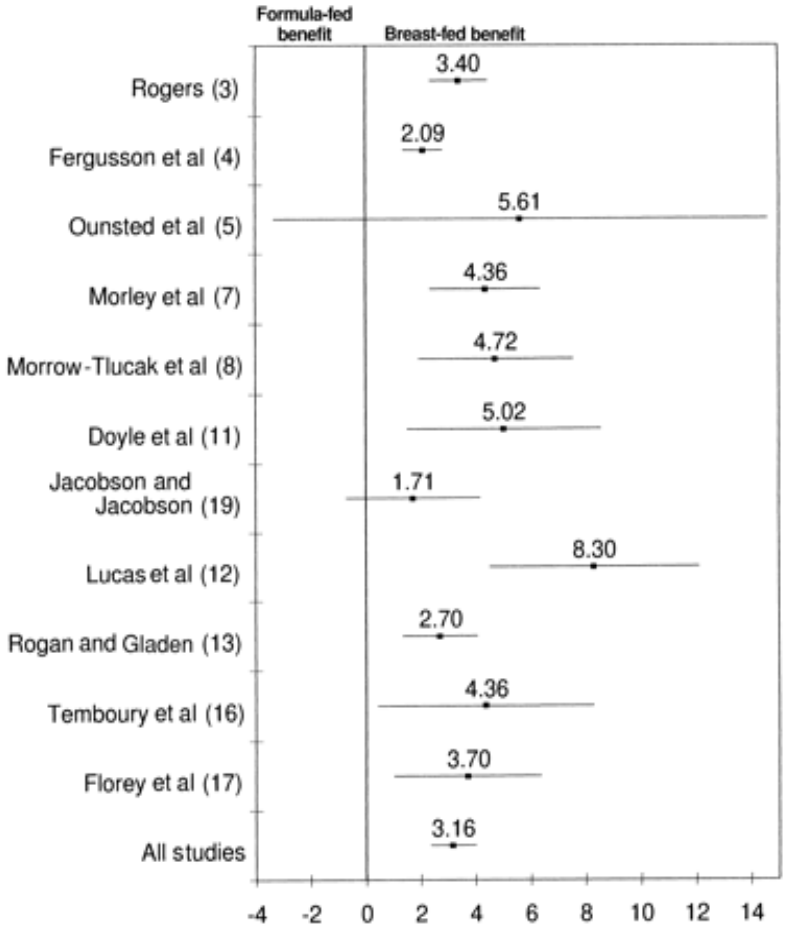
Neurodevelopment and "aggressive" nutrition

- Slower growth is ***associated*** with more adverse neurodevelopment
- Breast feeding is ***associated*** with slower growth velocity but improved neurodevelopment
- No randomised controlled trial in preterm babies to date, targeting faster growth, has resulted in improved neurodevelopment or other functional clinical outcomes



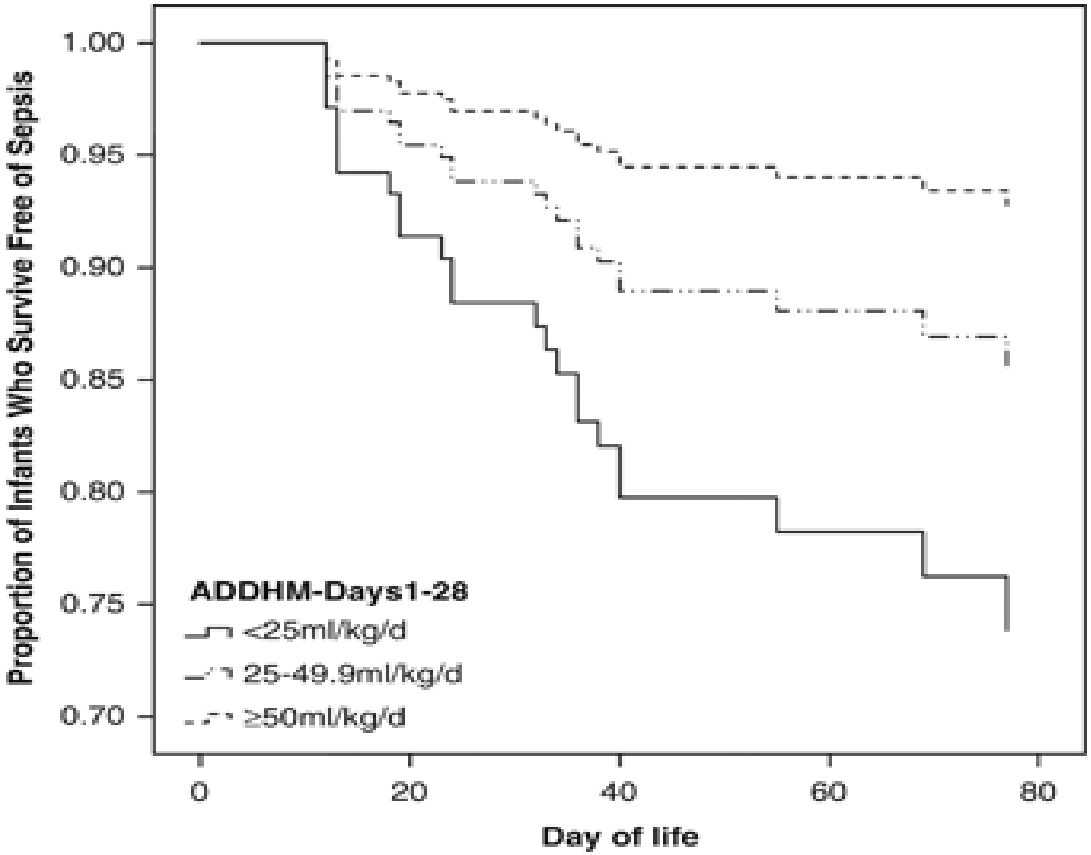
- **Bigger is not necessarily brighter!**
- **Faster growth is not necessarily better growth**
- **Association is not causation**

Breast feeding and cognitive outcome (Anderson et al 1999)



- Breast feeding associated with cognitive benefit (3.16 points; 95% CI: 2.35, 3.98)
- Benefit is greater in low birth weight infants (5.18 points; 95% CI: 3.59, 6.77) than normal-birth-weight infants (2.66 points; 95% CI: 2.15, 3.17)
- Cognitive benefits increased with duration of breast-feeding

Impact of early human milk on sepsis (Patel et al, Meier, 2013)



Dose-response relationship between average daily dose of human milk Days 1-28 and a reduction in the odds of sepsis after controlling for propensity score;

for every dose increase of 10 ml kg^{-1} day^{-1} human milk the odds of sepsis decreased by 19%

PRACTICE POINTS

- The optimal growth velocity of the preterm baby is unknown
- Growth is a poor outcome measure for evaluating preterm nutrition
- Functional outcome measures should be used to assess nutritional adequacy

Uncertainty 2
How should maternal breast feeding best be promoted?

- Close contact
- Accommodation for mothers
- Facilities for supporting mothers to express breast milk
- A positive approach by all neonatal staff
- Parental leave
- Facilitatory national policies

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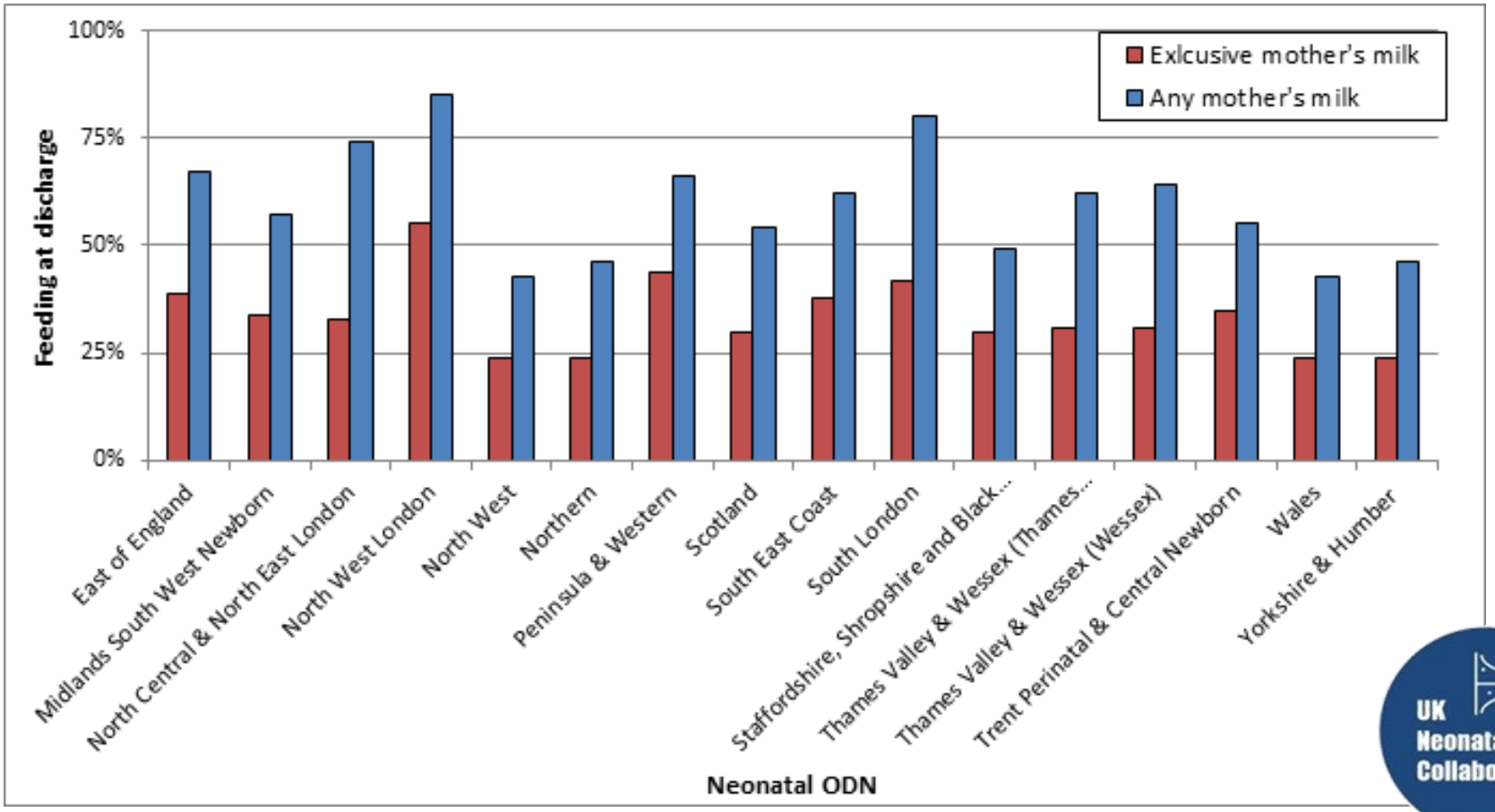
NATIONAL AUDIT

Mother's milk at discharge, England and Wales, babies <30 weeks gestation, 2015 (Neonatal Data Analysis Unit)



UK Neonatal Collaborative

PRACTICE POINT

Audit performance

Uncertainty 3

How quickly should milk feeds be commenced and advanced?

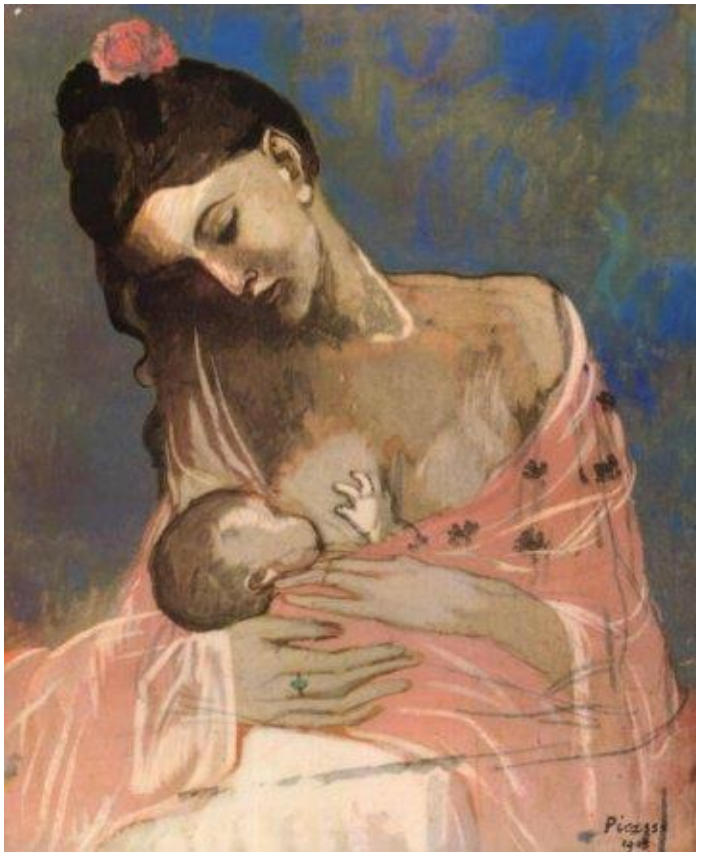
Commencing and advancing milk feeds

- Leaf et al, Pediatrics 2012, ADEPT trial, early or delayed enteral feeding for preterm growth-restricted infants
- McGuire & Bombell, Cochrane Database 2008, 3 trials, 396 infants
- Raban et al, Modi, ADC 2015, 200 infants ≤1000g in low income setting randomised to low or high initiation volume, and slow or rapid advancement
- Dorling et al, SIFT trial,30 ml/kg/day versus 18 ml/kg/day

No differences in NEC or other outcomes

Colostrum and maternal breast milk: more than nutrition

- Composition of colostrum unique to each mother
- Rich source of lactoferrin, IgA, and a host of immunologically active molecules
- Prebiotic oligosaccharides
- Probiotic species
- Long-chain polyunsaturated fatty acid content influenced by maternal diet
- Trophic factors (insulin-like growth factor-1, epidermal growth factor, transforming growth factor-a)
- Bile salt-stimulated lipase
- Hormones (eg leptin, ghrelin, insulin, obestatin, resistin)



Picasso, 1900

PRACTICE POINT

Providing colostrum as soon as possible after birth and advancing enteral feeds to around 30ml/kg/day appears safe and effective

Uncertainty 4
What if there is insufficient Maternal Milk (MM); is pasteurised Human Donor Milk (HDM) preferable to Preterm Formula (PTF)?

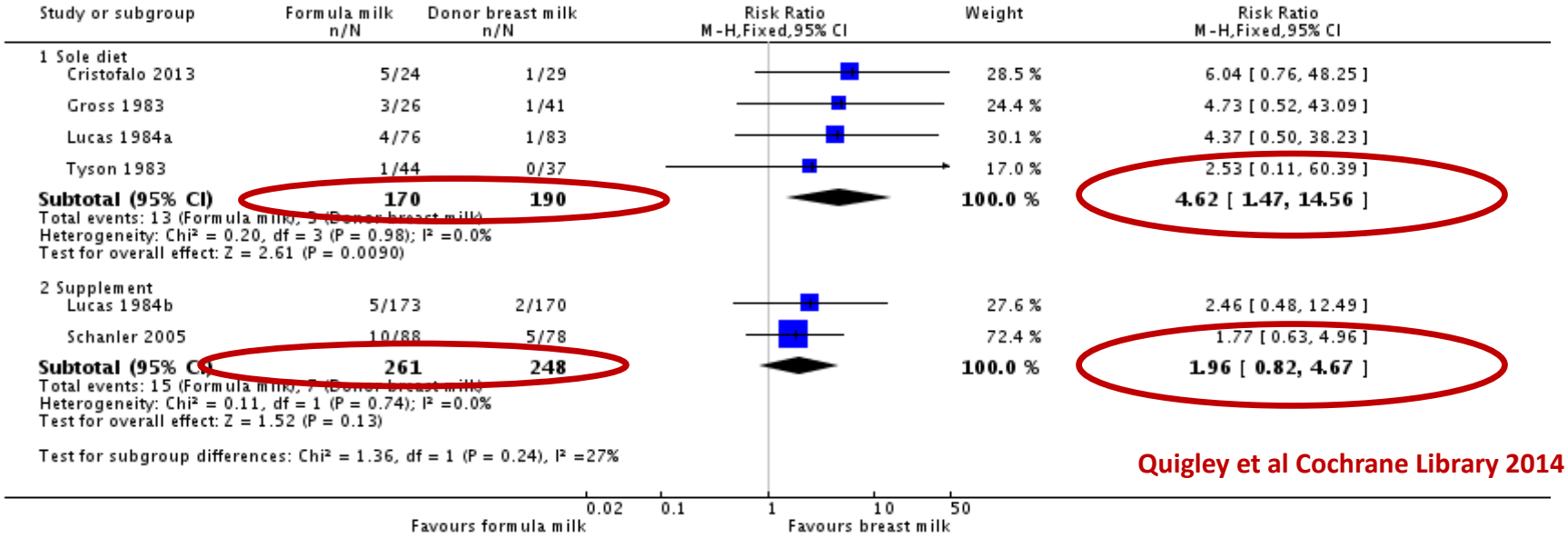
- Pasteurisation reduces immunological benefits and eliminates probiotic species
- Composition, hormones, immune factors, and prebiotic and probiotic content unique to each mother
- Nutrient and non-nutrient composition affected by maternal health, disease, diet and environmental exposures (e.g. leptin, cytokines, long chain polyunsaturated fatty acids, trans-fers, toxins)
- Nutrient content of mature milk lower than milk from mothers delivering preterm

Pasteurised HDM not equivalent to MM; HDM may or may not be be superior to PTF; we just don't know!

Formula versus donor breast milk for preterm infants: necrotising enterocolitis

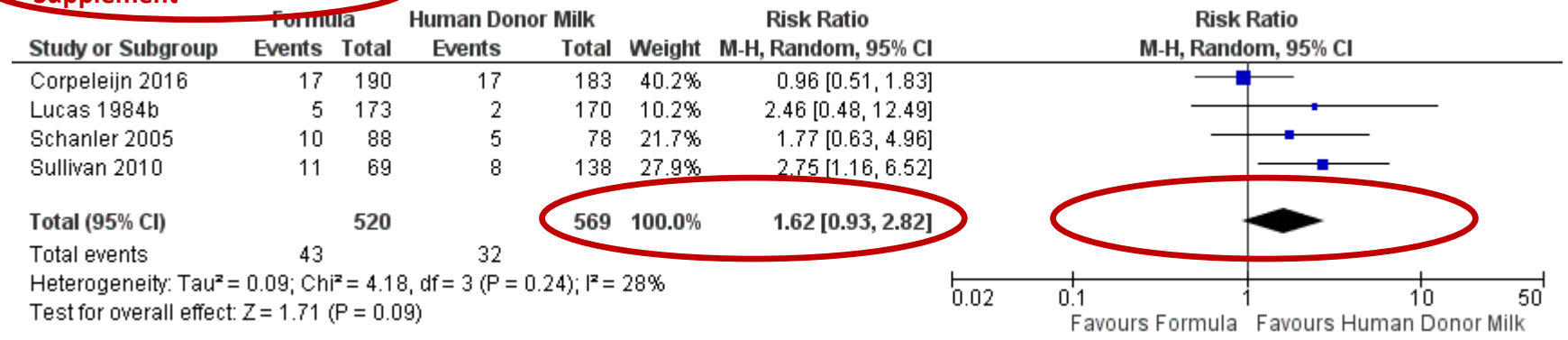
Sole diet

Review: Formula versus donor breast milk for feeding preterm or low birth weight infants
Comparison: 2 Subgroup analysis: Formula (preterm) versus donor breast milk given as (i) sole diet or (ii) a supplement to maternal expressed breast milk
Outcome: 17 Necrotising enterocolitis



Quigley et al Cochrane Library 2014

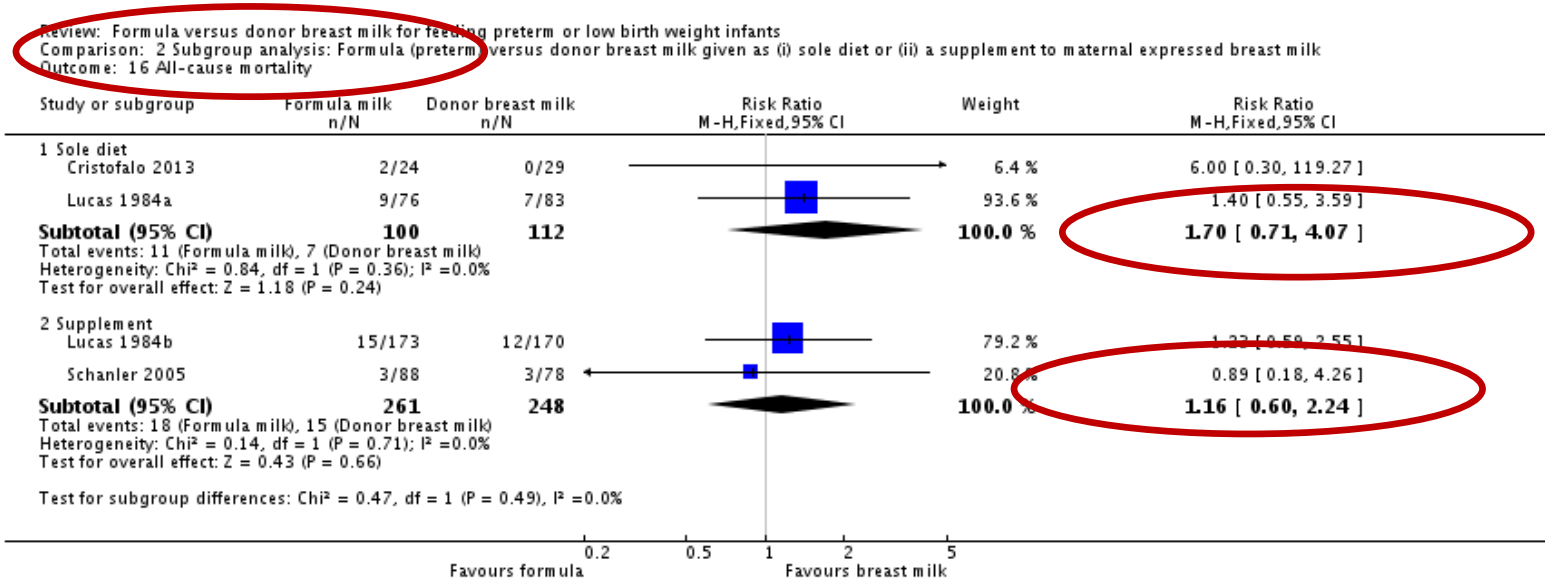
Supplement



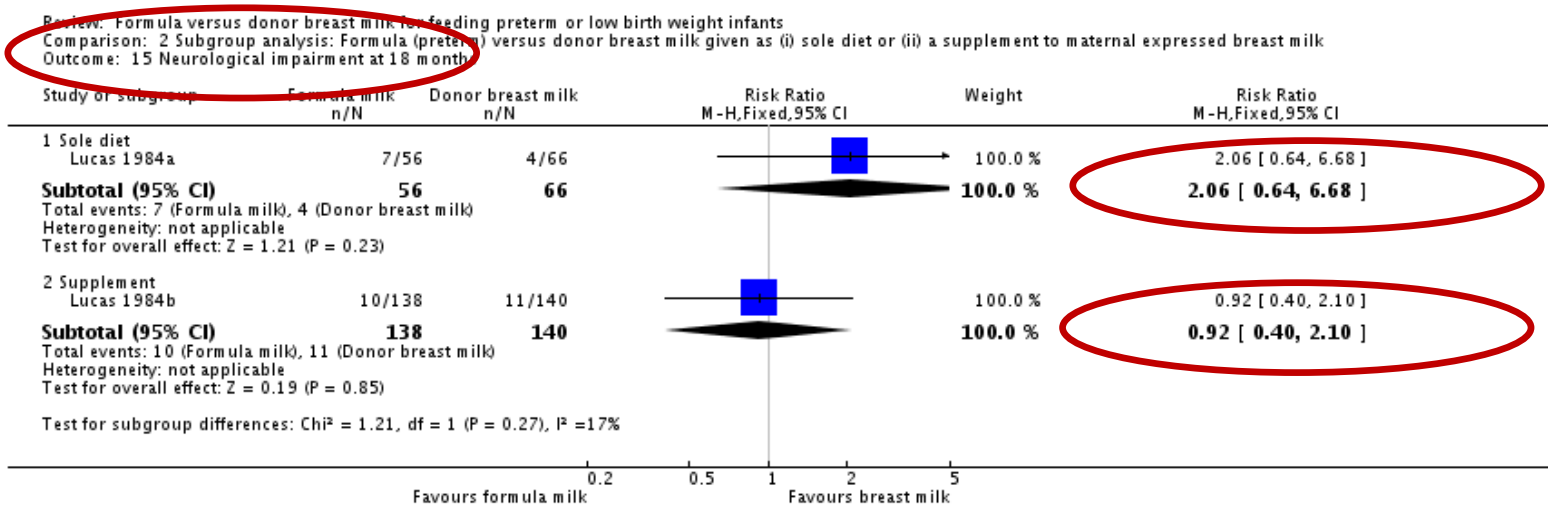
Hyde and Modi, updated, 2016

Formula versus donor breast milk for preterm infants: all-cause mortality and neurodevelopment

Mortality



Neurodevelopment



Cochrane Database of Systematic Reviews
22 APR 2014 DOI: 10.1002/14651858.CD002971.pub3
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002971.pub3/full#CD002971-fig-00216

Adverse impact of marketing breast-milk substitutes

Brady J, Arch Dis Child 2012

Table 2

Summary of the Articles of the WHO International Code of Marketing Breast Milk Substitutes*

No advertising to the public
No free samples or gifts to mothers
No promotion of products in healthcare facilities
No contact of mothers by company representatives
No gifts or samples to health workers
No baby pictures idealising formula
No unsuitable products such as sweetened condensed milk to be promoted for babies
Information to health workers to be scientific
All information to be objective and to explain the benefits and superiority of breastfeeding
Health professionals to disclose to their institution any fellowships, research grants, or conferences provided by baby food manufacturers
Manufacturers and distributors to comply with above even if country has not implemented the Code
Professional groups, non-governmental organisations and individuals to inform manufacturers, distributors and governments of activities violating the Code

- The WHO International Code of Marketing Breast Milk Substitutes was passed in 1981 by 118 votes to 1
- The Code arose out of concern that the increase in mortality in infants in the developing world was associated with aggressive marketing of formula
- The Code prohibited any advertising of baby formula, bottles or teats and gifts to mothers or health workers

Might a Human Donor Milk industry be harmful?

"For profit" milk industries reduce maternal breastfeeding if inappropriately promoted

Costs

- Human Donor Milk (from a UK Human Milk Bank)
  ~ £175/litre
- Commercial Preterm Formula
  ~ £12/litre
- Commercial Human Donor Milk
  ~ £1700/litre
- Commercial Human Donor Milk
  ~ £140/litre

Five reasons to question use of human donor milk

Inadequate evidence of

- efficacy
- effectiveness
- safety
- cost benefit

and

- danger of creating a “human-milk” industry

Recent evidence

Incidence of severe neonatal necrotising enterocolitis across neonatal networks in England and enteral feed antecedents, 2012-13: a whole-population surveillance study

Battersby C, Longford N, Mandalia S, Costeloe K, Mod Ni, on behalf of the UK Neonatal Collaborative Necrotising Enterocolitis study group In press Lancet Gastroenterology and Hepatology

- Propensity score analysis of 11,939 infants <32w GA and 220 cases of severe NEC (death and/or surgery)
- Commencing any Own Mothers Milk within 7 postnatal days resulted in an Absolute Risk Difference of -0·88% (95% CI -1·15, -0·61), Relative Risk 0·69 (95% CI 0·60, 0·78), and Number Needed to Treat 114 (95% CI 87, 136)
- Commencing Own Mothers Milk early may reduce NEC but absolute risk reductions appear small
- The rarity of severe NEC requires national and international collaboration for adequately powered preventive trials

PRACTICE POINTS

- Own mothers milk is the optimal feed for the preterm baby
- The place of pasteurized human donor milk is uncertain

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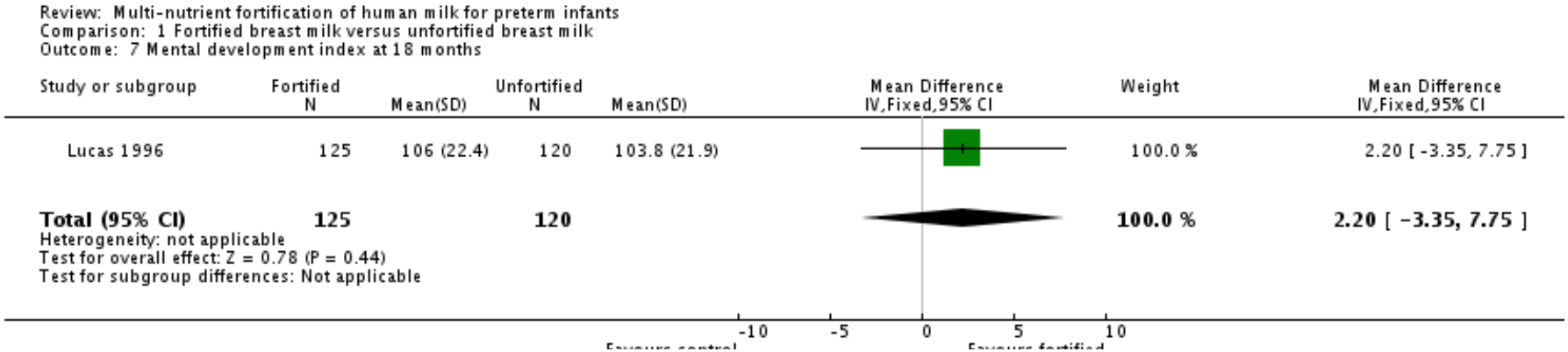
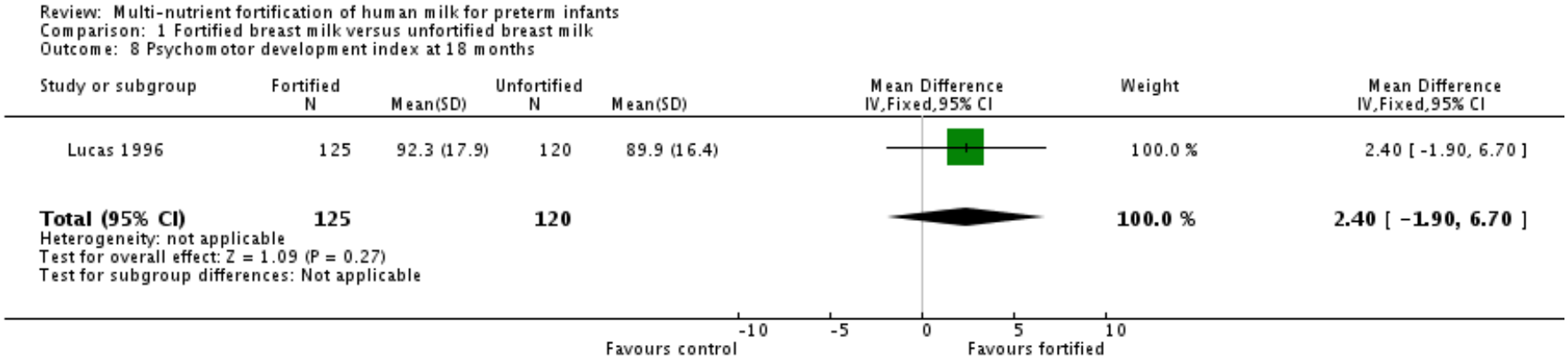
Uncertainty 5
Should human milk be fortified with protein and carbohydrate routinely?

Neurodevelopment and necrotising enterocolitis (Brown et al, Cochrane Database Syst Rev 2016)





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Nutritional Evaluation and Optimisation in Neonates: a randomized, double-blind controlled trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition[1,2]

Sabita Uthaya,[3,4] Xinxue Liu,[5] Daphne Babalis,[5,7] Caroline J Doré,[8] Jane Warwick,[9] Jimmy Bell,[5,10] Louise Thomas,[6,10] Deborah Ashby,[5] Giuliana Durighel,[6] Ash Ederies,[6] Monica Yanez-Lopez,[6] and Neena Modi[3,4]*

Comparison of immediate delivery of Recommended Daily Intake of amino acids and SMOF (*Soy bean, Medium chain triglycerides, Olive oil, Fish oil)* lipid in comparison with incremental introduction of amino acids, and Intralipid, on lean body mass and hepatic lipid respectively, and brain growth in preterm infants

- No difference in primary outcomes (body composition and liver lipid at term)
- Immediate delivery of recommended daily intake poorly tolerated and head circumference smaller
- Total protein intake exceeding 3.5g/kg/day may be harmful

PRACTICE POINTS

- Theoretical justification to fortify maternal milk with protein supplements but experimental evidence is lacking
- The optimal protein intake for the preterm baby is unknown
- Protein intakes exceeding 3.5g/kg/day should only be used in the context of randomized controlled trials

Recommended

- Immediate colostrum
- Fresh own mothers milk as soon as available
- Parenteral nutrition for as short a time as possible
- Phosphate and vitamin supplements
- Increase in enteral intake in increments as tolerated to at least 200ml/kg.day
- Transition to suck feeds at the breast as soon as possible

Uncertain

- Optimum growth velocity
- How best to support breast feeding
- Advantage of pasteurised Human Donor Milk over preterm formula when maternal milk is unavailable or insufficient
- Benefit from routine multicomponent fortification of maternal milk
- Optimum protein intake

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Department of Health

British Heart Foundation

Bliss for babies born too soon, too small, too sick

Chelsea and Westminster Health Charity

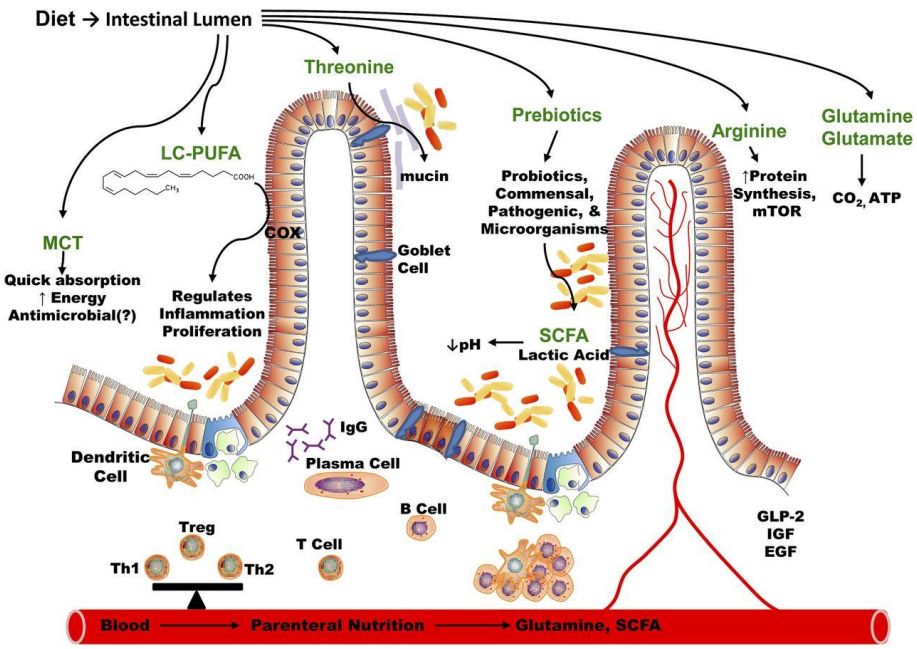
…. and the babies, their parents, and our collaborators

Sucking, swallowing, and enteral substrate

- By term, the fetus swallows about 150 cc/kg/day of amniotic fluid; this contains nutrients, immunoglobulins and growth factors, and plays an important role in the development of gastrointestinal function

- Enteral substrate is needed for gut peptide release, enterocyte turnover and nutrient transport, bile acid secretion, resistance to infection through intestinal epithelium barrier function by, and colonization by normal commensal flora

- For fat digestion, the newborn depends in part on lingual lipase, which is stimulated by sucking and swallowing and by nutrients in the stomach



Sucking, swallowing and enteral substrate promote intestinal growth, digestion and the establishment of the microbiome

Jacobi and Odle Adv Nutr 2012;3:687-696

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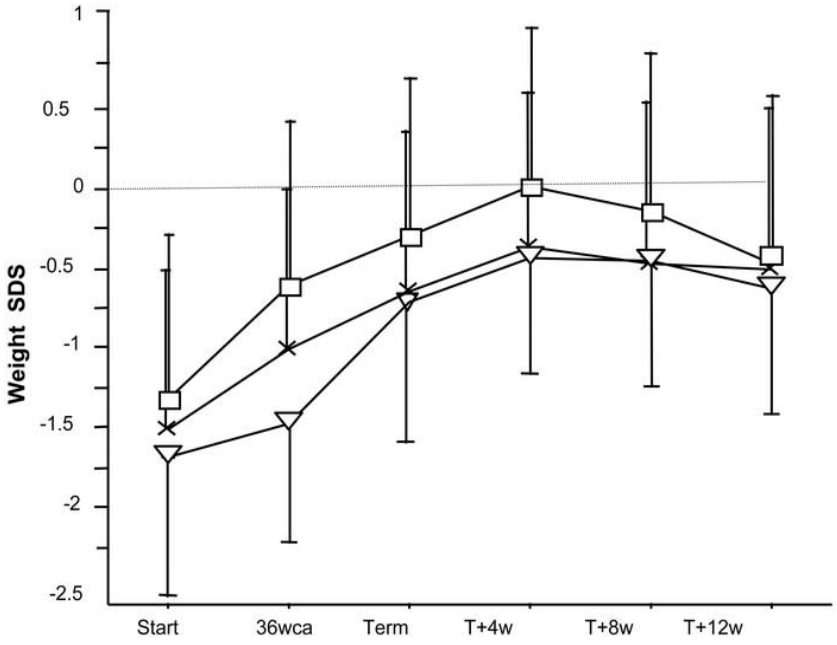
Transitioning to self regulated suck feeds



Preterm infants fed isocaloric diets delivering 3 protein intakes (A=3.3g, B=3.0g, C=2.7 g/100 kcal) from 150 ml/kg/d until Term plus 12 w; no differences in body composition at Term + 12 weeks (Embleton and Cooke 2005)

Transition to suckled feeds at the breast as soon as possible!

Encourage suckling and transition to self-regulated breast-feeds as soon as possible