Human Milk and Brain Development in the Preterm Infant

MatNeoSIP 14th December 2022

Nick Embleton, Newcastle upon Tyne, UK

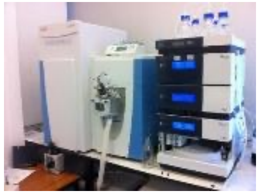
The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust
Newcastle University

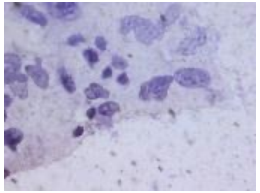
Newcastle Biomedicine

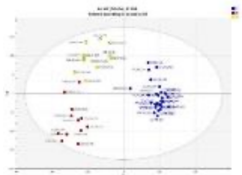
Newcastle Neonatal Nutrition & NEC research

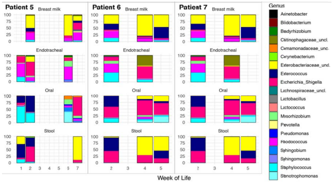
- Collaborative RCTs nutrition & feeding
- Microbiome, probiotics
- Breastmilk: IgA, bacteriophage, HMOs
- NEC, immunology, enteroids
- Donor human milk, fortifiers
- Long-term metabolic outcome

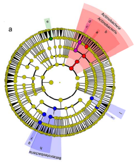
www.neonatalresearch.net











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NEONATAL RESEARCH

HOME BIOBANK RESEARCH TALKS/TEACHING BUTTERFLY PROJECT NEONATAL NUTRITION NETWORK

N4 Newcastle Neonatal Nutrition & NEC Research | Stewart Lab | GNNB Great North Neonatal Biobank

Newcastle Neonatal Research Team

We are a multi-disciplinary, world-leading, clinically focused, neonatal research team based in Newcastle, UK with collaborators across the UK, Europe and USA. **Our research is built on a legacy (click here) of over 100 years neonatal research in Newcastle** in the areas of nutrition, social determinants of health over the life-course, metabolism and infectious disease. Current research focuses on neonatal nutrition in preterm infants, necrotising enterocolitis (NEC), growth, lung function and long-term outcome, as well as exploring parental experiences of baby loss.

Our studies include large scale collaborative trials of feeding and nutrition, mechanistic studies focusing on the gut microbiome and metabolome, development of gut enteroid models, immune development, motor function, and long-term metabolic outcome using longitudinal cohort studies.

Team members are based at Newcastle Hospitals NHS Foundation Trust, Northumbria University and Newcastle University. Our research programme is coordinated by Janet Berrington and Nick Embleton. You can read about post-graduate (doctoral) student projects here and follow us on twitter here @NeoResearch_Net and here @neonatalbiobank

Recent research highlights

- Caffeine for the care of preterm infants in sub-Saharan Africa: a missed opportunity? (Nabwera et al. BMJ Global Health 2022)
- Secretory immunoglobulin A in preterm infants: normal values in breast milk and stool (Granger et al. Pediatr Res 2022)
- Evaluation of effectiveness of incentive strategy on response rate (Juszczak et al. Trials 2021)
- Time of Onset of Necrotizing Enterocolitis and Focal Perforation in Preterm Infants (Berrington et al. Front Pediatr 2021)

NEONATAL RESEARCH

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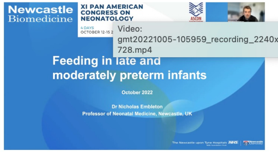
Feeding in late and moderately preterm infants 2022.



Bionutrients in milk 2022

Human milk & neurodevelopment 2022 (30 minutes)

Standardised v individualised parental nutrition 2022

Nutritional interventions to improve brain outcomes

The Butterfly project: caring for parents after twin loss.

Overview

- Nutrition is more than nutrients
- Preterm infants are nutritionally vulnerable
- Mechanisms linking nutrition to brain development
- Evidence from macronutrients, DHA etc.
- Evidence for the benefits of human milk (MRI)

Nutrient requirements are very high
Risk of poor brain development is very high

Tour de France
7000Kcal/day
100kcal/kg/day

↑ 20- 30%

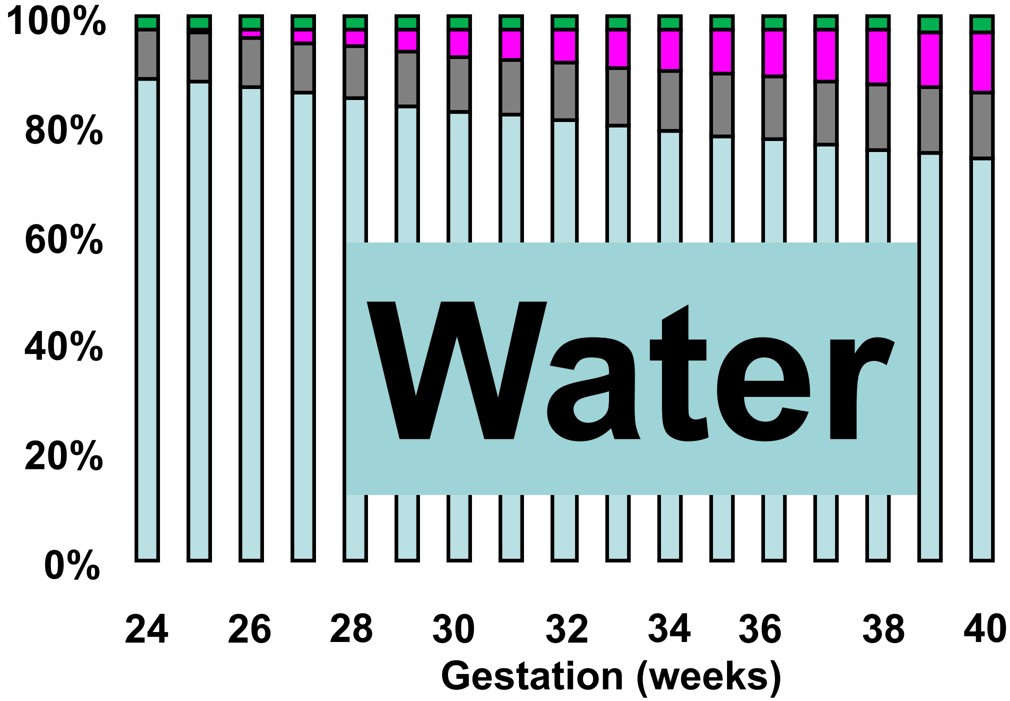
NICU

120-130kcal/kg/day

Significant energy expenditure is the brain

Egan Bernal

Body composition of reference fetus



Minerals	1 - 2%
Lipid	1 - 15%
Protein	10 - 12%

24 weeks gestation:
90%Water

Birthweight 500g = only 50g of solid matter

Zeigler & others 1976

This baby must survive ex-utero with less than 40g of lean tissue

50g of non-hydrated tissue: all natural, no artificial flavours or preservatives

Weight	50g	51g
Total energy	250kcal	261Kcal
Available energy	50kcal?	

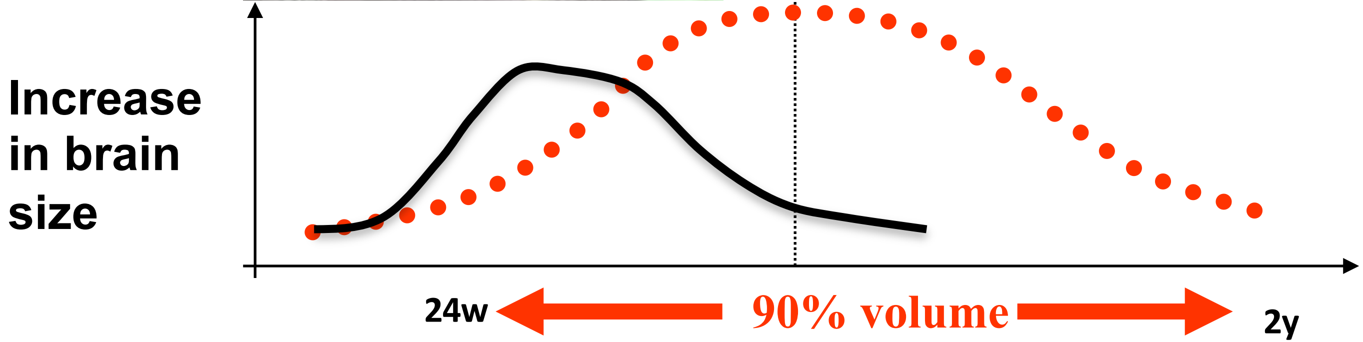
Preterm infant is one bite of a chocolate bar from death due to malnutrition

NUTRITION is more than 'nutrients'

NUTRITION

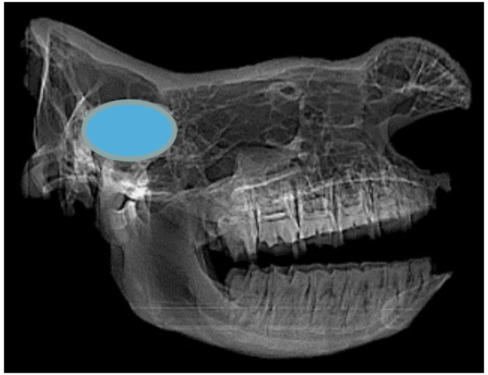
NUTRIENTS *Proteins, fats, micronutrients etc.*	**FUNCTIONAL COMPONENTS** *HMOs, growth factors, enzymes etc.*
MICROBES *Breastmilk, environment, probiotics etc.*	**'TECHNICAL' & SOCIO-BEHAVIORAL** *Bolus, skin:skin, breastfeeding, taste, belief, behaviour etc.*

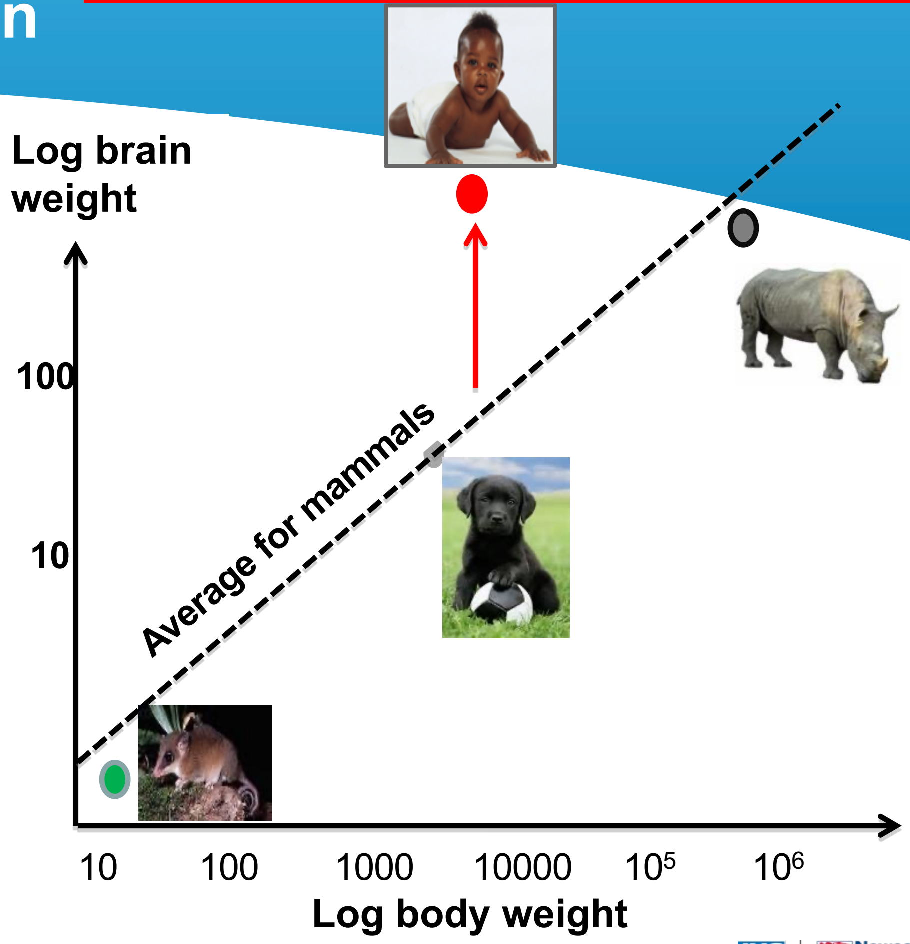
Brain growth in early life is rapid



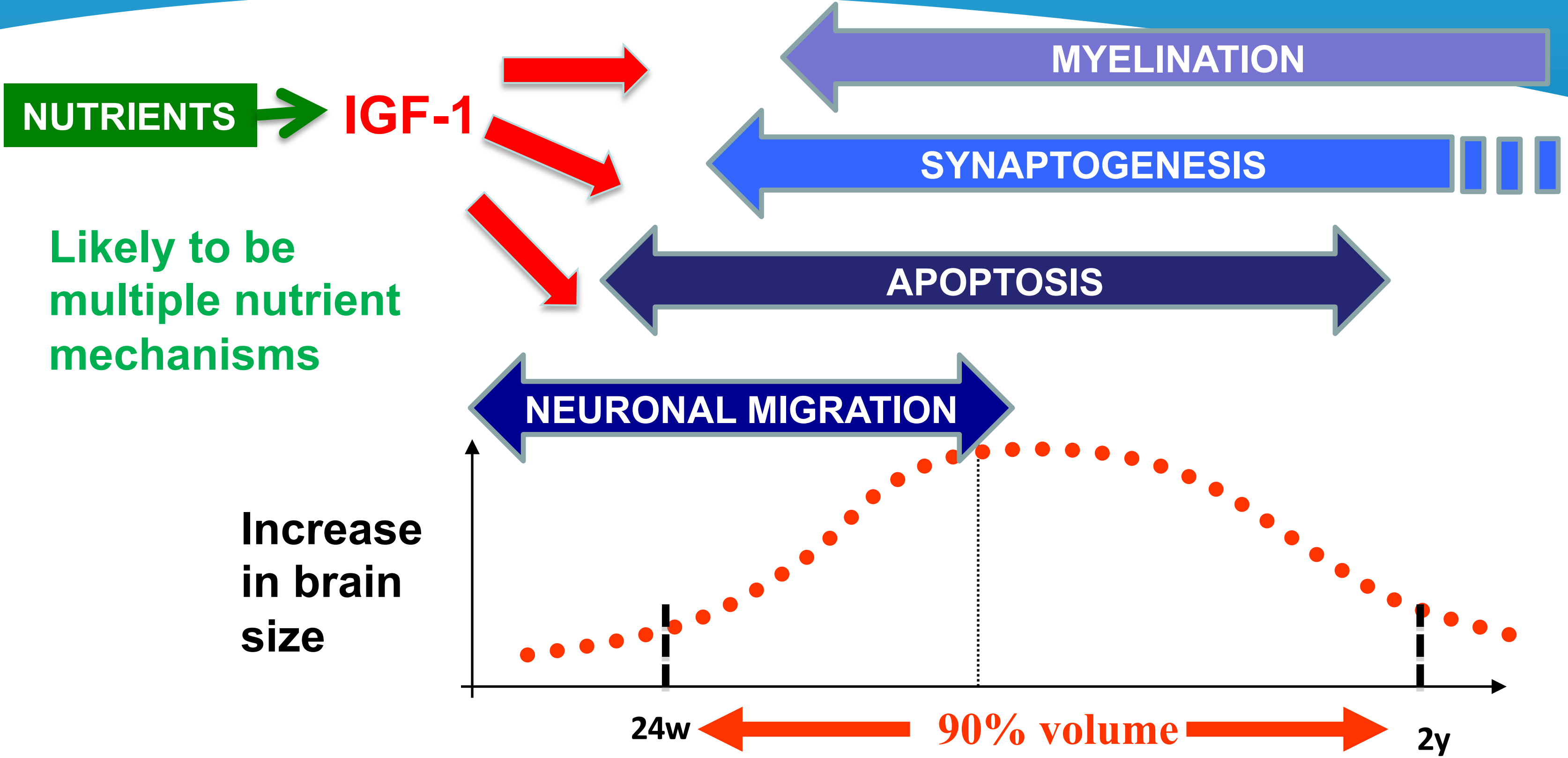
Humans: it’s all about the brain

Human brain 10-20x other mammals





Neuronal processes: growth factors, signaling molecules & gene expression

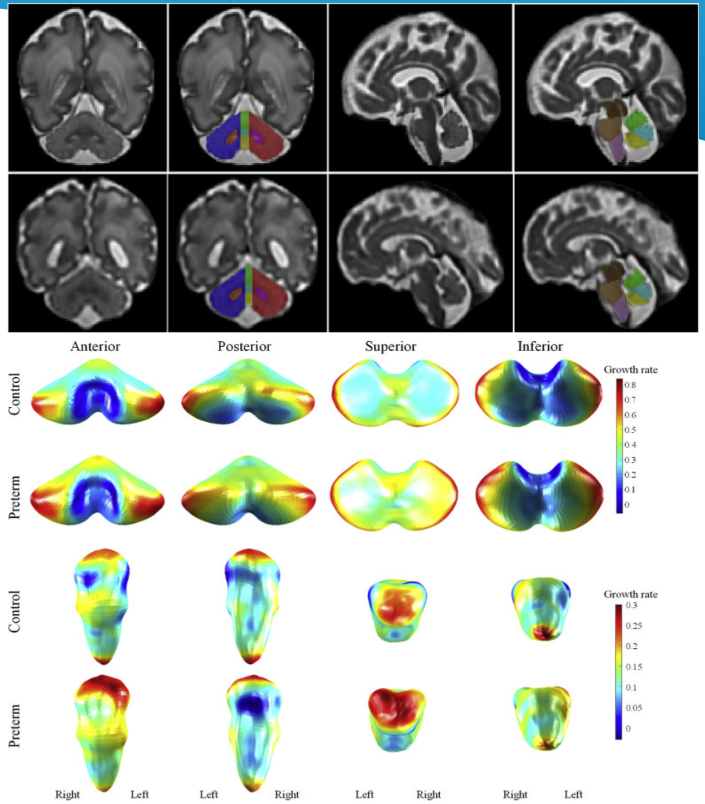


Biology explains preterm brain vulnerability to sub-optimal nutrient supply

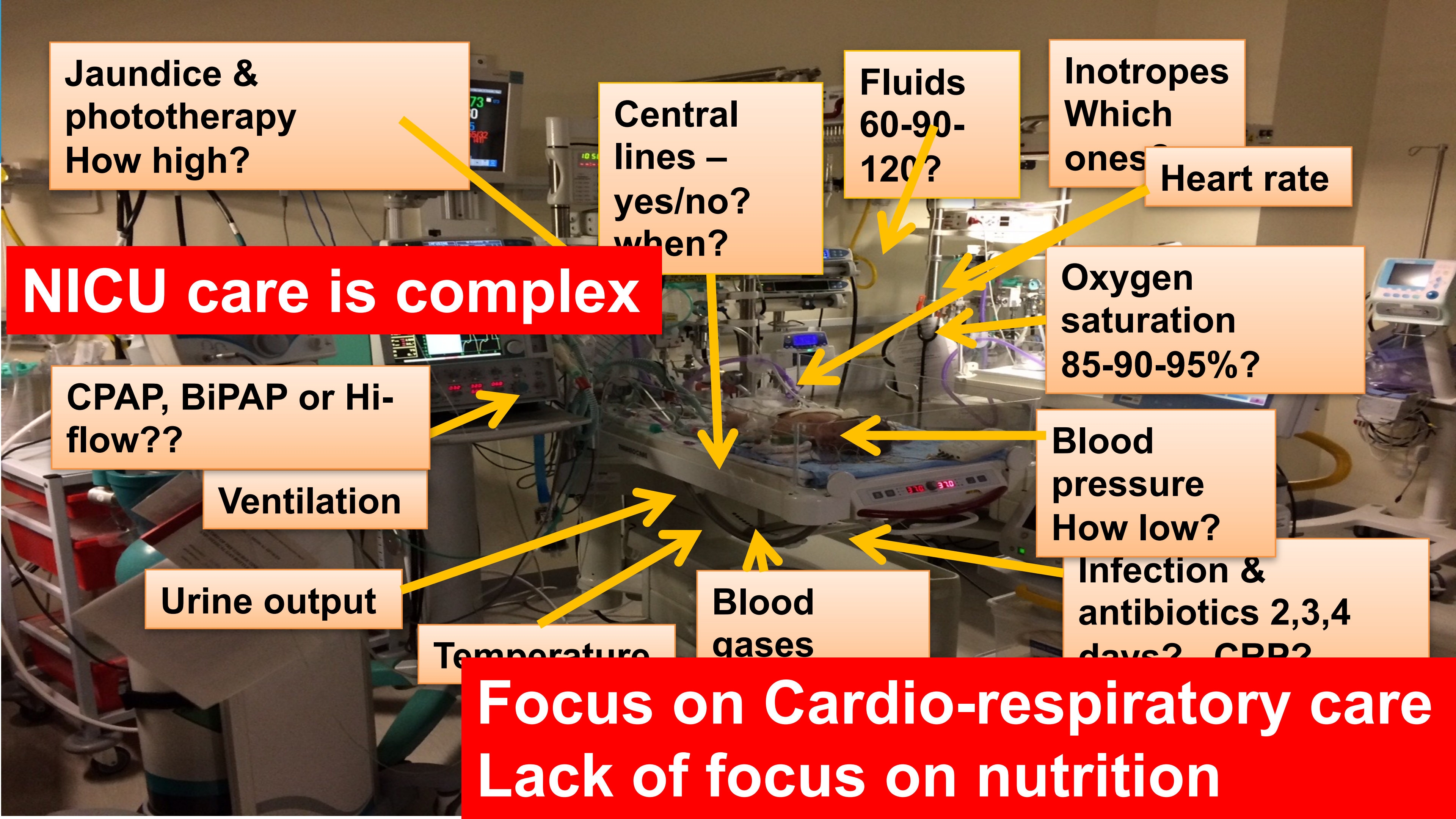
- Damage is common: cystic PVL, haemorrhage
  - Tissue 'repair' requires higher intakes
  - Substrate & energy

- Large brain + very high demands
  - easy to malnourish

- Cerebellum – more rapid growth than cortex
  - Altered cerebellar & brainstem shape
  - Altered development even if MRI 'normal'



Wu et al. Neuroimage 2020



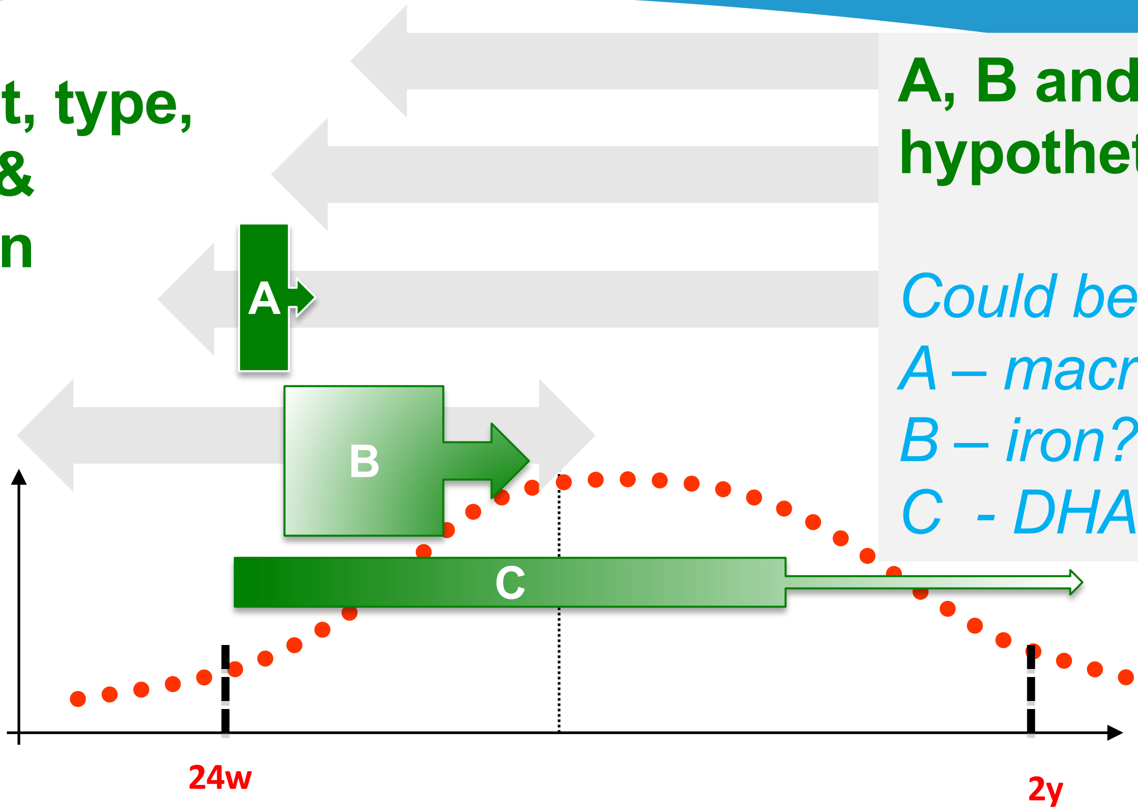
Jaundice & phototherapy How high?
Central lines – yes/no? when?
Fluids 60-90-120?
Inotropes Which ones
Heart rate
NICU care is complex
Oxygen saturation 85-90-95%?
CPAP, BiPAP or Hi-flow??
Ventilation
Blood pressure How low?
Urine output
Temperature
Blood gases
Infection & antibiotics 2,3,4 days?.. CRP?
Focus on Cardio-respiratory care
Lack of focus on nutrition

Malnutrition is invisible

If only we had a machine that beeps when nutrition is sub-optimal

What does nutrient deficiency do to the preterm brain?

Amount, type, timing & duration



A, B and C are hypothetical nutrients

Could be….
A – macronutrients??
B – iron??
C - DHA ??

What does nutrient deficiency do to the preterm brain?

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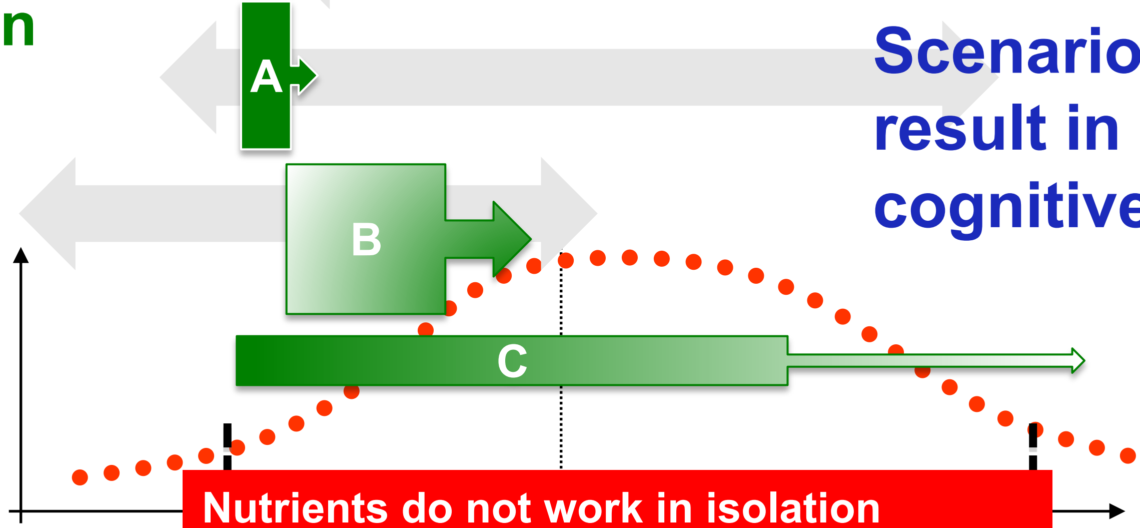
- Multiple nutrients
- Changing diet (PN / EN)
- Multiple mechanisms

Amount, type, timing & duration



Scenarios A, B and C result in different neuro-cognitive phenotypes

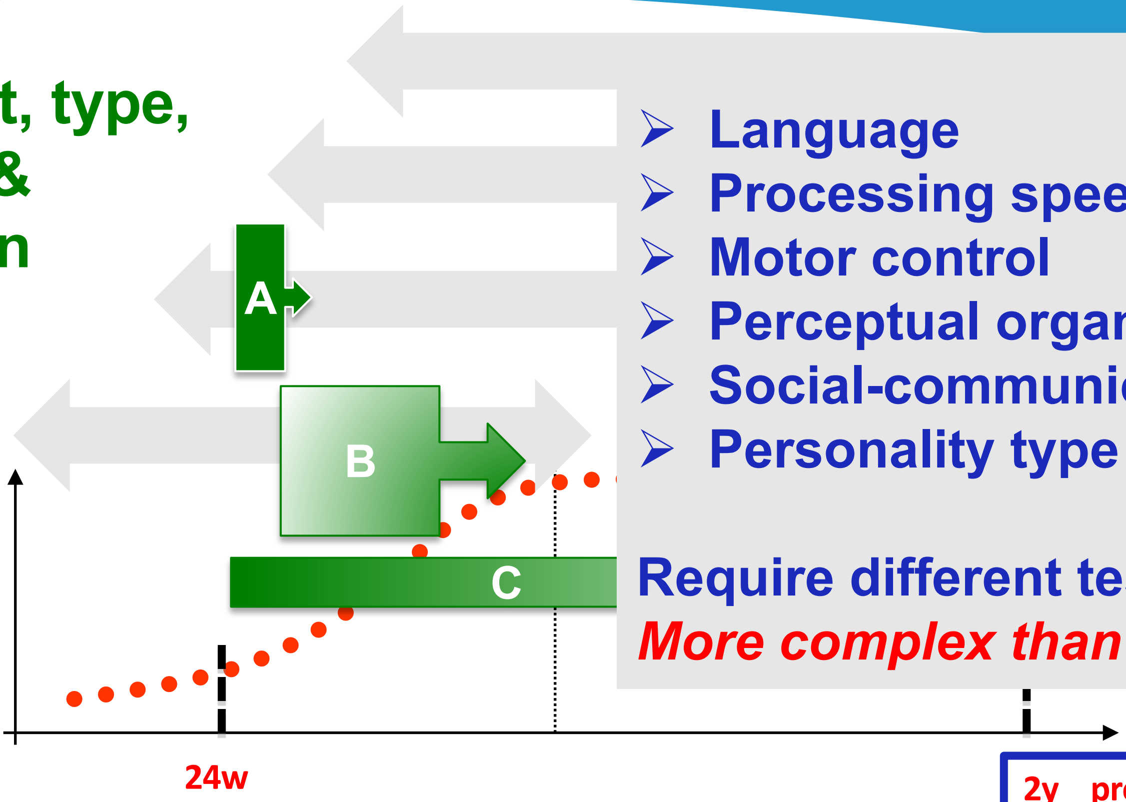
Nutrients do not work in isolation

- Co-factors, enzymes, energy etc.

Healthy brain needs every nutrient

Sub-optimal nutrition results in differing neuro-cognitive phenotypes in later infancy, childhood, adulthood

Amount, type, timing & duration



- Language
- Processing speed
- Motor control
- Perceptual organisation
- Social-communication
- Personality type

Require different test / tools

More complex than "BSID"

2y pre-school – school – teen – adult

Nutrition impacts on brain development: multiple mechanisms

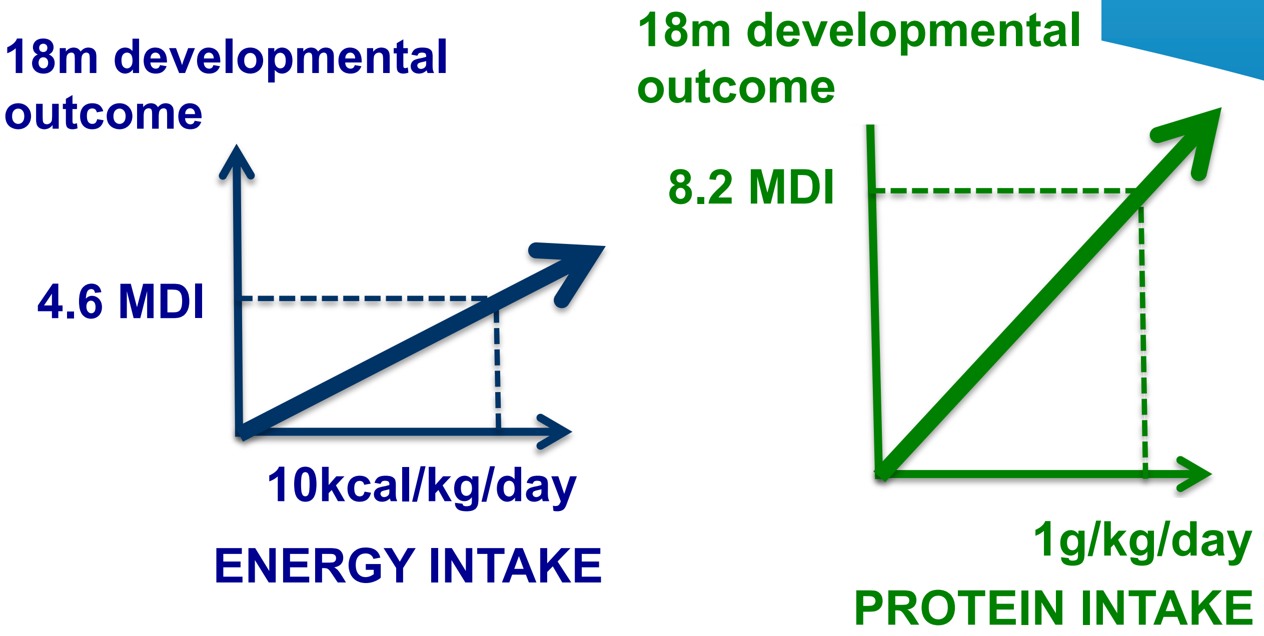
Nutrients for tissue substrate	Macro- and micronutrients
Energy to drive the system	Carbohydrate, lipids & ...protein
Signalling & growth factors	mTOR, MFGM (SM, PLs), IGF-1, EGF etc.
Gene expression	Folate, B12, iron, DHA, choline etc.
Gut microbes & metabolites	Prebiotics, HMOs, lactoferrin, probiotics
Prevention of disease	Breastmilk: ↓ NEC, sepsis, ROP, BPD

What is evidence that macro & micronutrients matter?

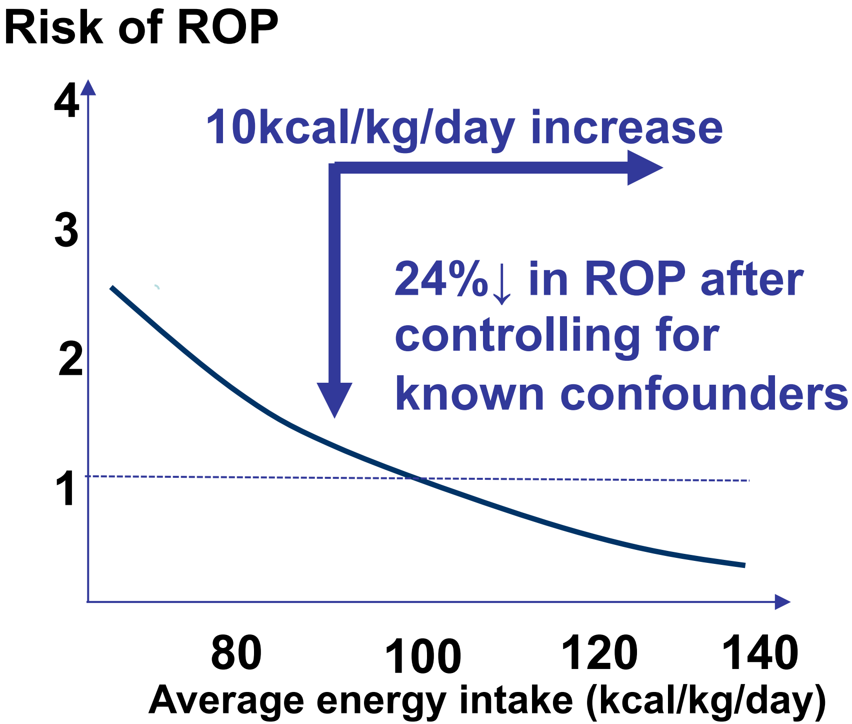
1. First week macronutrient intakes: BSID outcome at 18 months
2. Energy intakes in first 4 weeks: ROP
3. Protein & energy: MRI at discharge
4. Macronutrients: IQ at 16 years age
5. DHA & ROP

First week protein & energy intakes associated with 18m outcomes

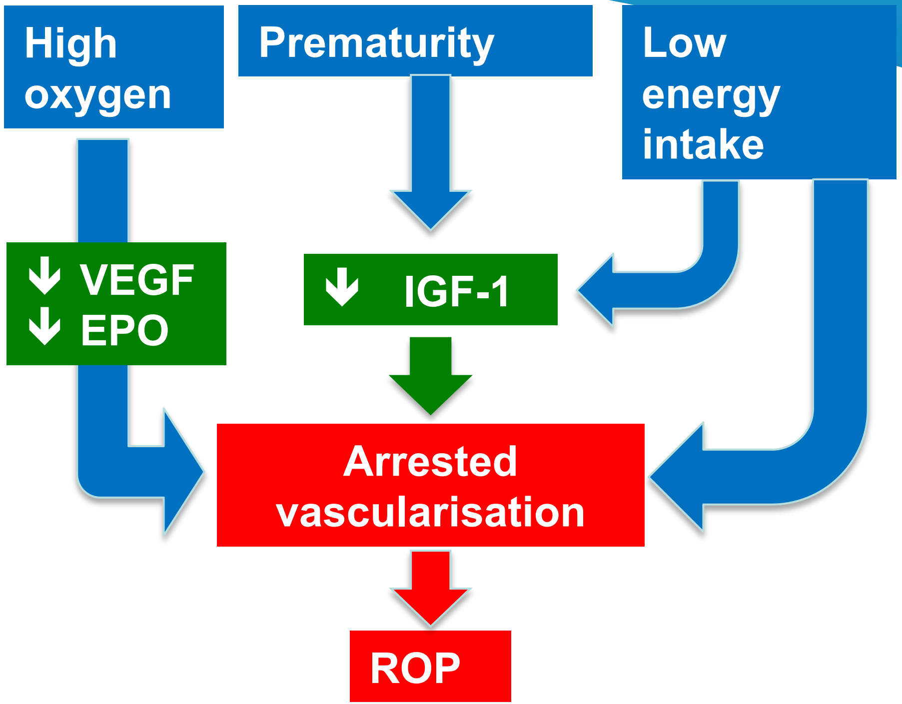
- 124 infants ≤1000g
- Early PN, slow increments
- Multiple regressions to adjust data for likely confounders



Low energy intake during first 4 weeks of life increases risk for severe ROP



Parenteral and enteral

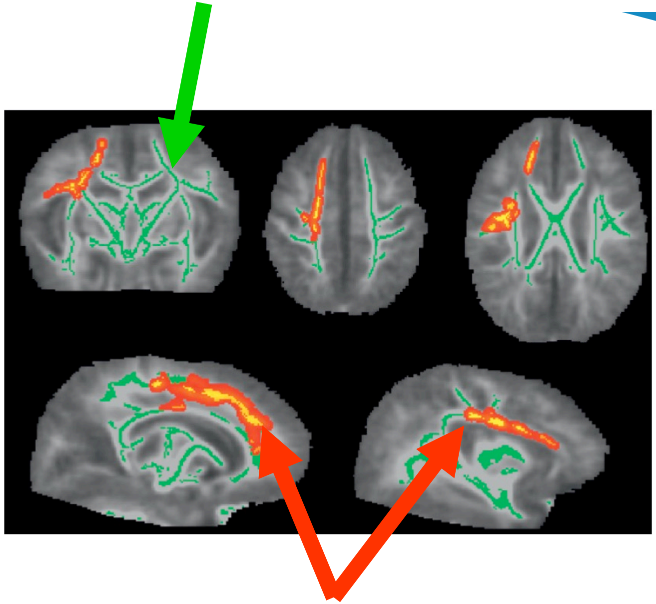


Stolz Sjostrom et al. 2015

Enhanced nutrient supply to VLBW infants associated with improved white matter maturation & head growth

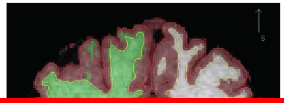
- RCT n=44
- Postnatal nutrient enhancement (parenteral & enteral)
  - ↑ AA, lipid, enteral protein, DHA etc.
  - MRI diffusion tensor imaging (DTI) at term

- Weight gain **16.5** v **13.8g/kg/day** (p=0.01)
- Head SDS **0.24** v **-0.12** (p=0.15)
- Lower mean diffusion in WM tracts on MRI
  - Superior longitudinal fasciculi: motor, perception, language



Strommen & Moltu et al. 2015

The effect of early diet on caudate volumes and IQ



- n=76 (subset of Lucas et al.)
- Standard nutrient diet group
  - term formula or donor milk
- High nutrient group
  - Preterm formula

- Neurologically normal at 8 years

- Weschler (WISC III)
- MRI brain volume

Significant effects size - 16 year old children who were on high nutrient diets as preterm infants have 8 point higher VERBAL IQ than those on standard diet

	Standard	High	*p*
Verbal IQ	94	102	<0.01
Performance IQ	96	98	ns
Brain volume	1300	1318	ns
Cortical gray	660	666	ns
Left caudate	3648	3989	<0.05
Right caudate	3855	4221	<0.04

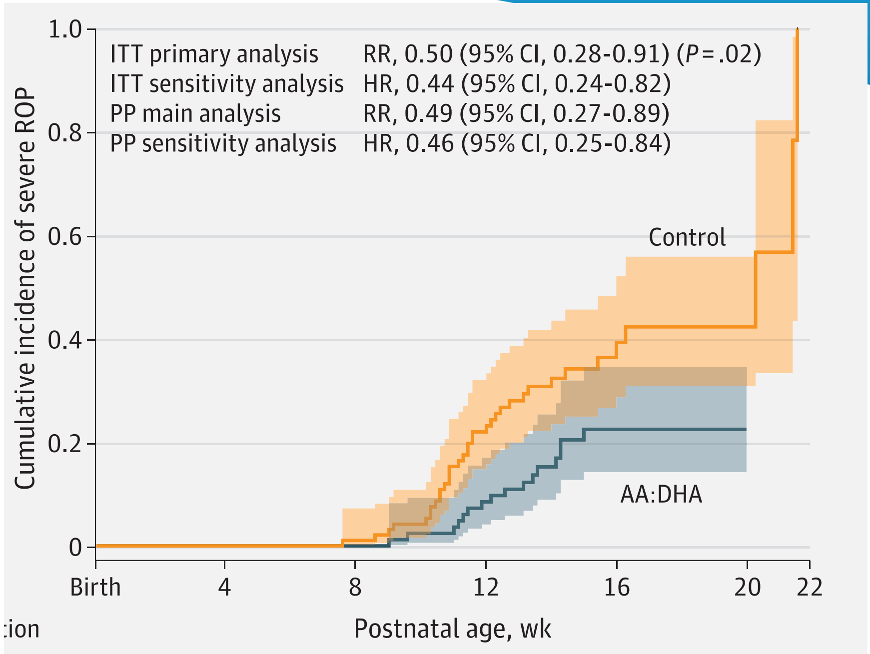
No effect on total brain volume, but significant differences in size of caudate

Isaacs et al. 2008

Effect of Enteral Lipid Supplement on Severe ROP (Hellstrom et al. JAMA 2021)

- P n=207 <27 weeks gestation
- I AA + DHA from day 3 – term corrected
- C none
- O Severe ROP 15.8% vs 33.3% (adj RR 0.5)

- Higher AA/DHA in serum phospholipids



Nutrients matter – multiple studies

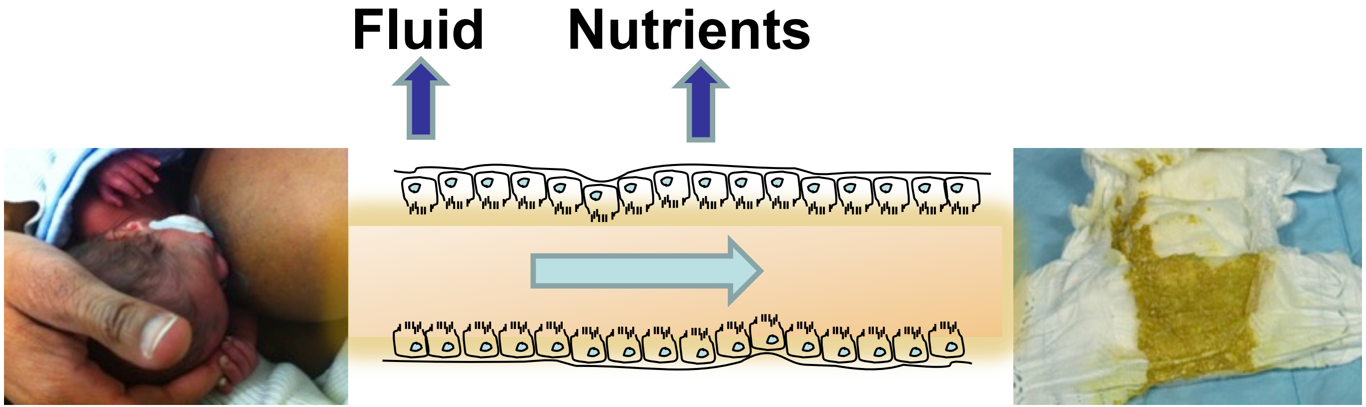
1. Greater first week macronutrient intakes
   - Improved BSID outcome at 18 months
2. Higher energy intakes in first 4 weeks
   - Less ROP
3. Greater nutrient intakes on NICU
   - Greater white matter on MRI at discharge
4. More macronutrients in first 4 weeks
   - Greater IQ at 16 years age
5. DHA supplementation until term
   - Halving in risk of ROP

What is the role of human milk in promoting brain development?

Nutrition impacts on brain development: HUMAN BREASTMILK

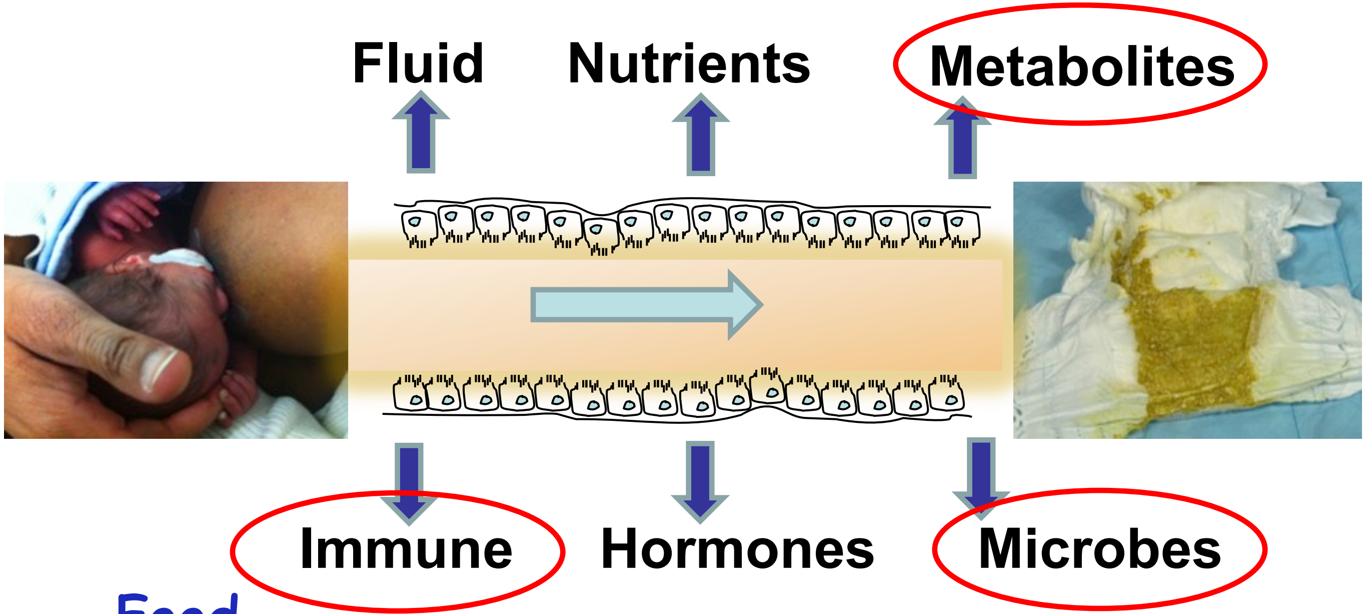
Nutrients for tissue substrate	Macro- and micronutrients
Energy to drive the system	Carbohydrate, lipids & ...protein
Signalling & growth factors	MFGM (SM, PLs), IGF-1, EGF etc.
Gene expression	Folate, B12, iron, DHA, choline etc.
Gut microbes & metabolites	Prebiotics, HMOs, lactoferrin, probiotics
Prevention of disease	Breastmilk reduces NEC & sepsis

Why is human milk so amazing?
Drink milk → absorb nutrients → make stool?



Food → Waste

Breast milk: developmentally regulated maternal-infant biochemical signalling pathway



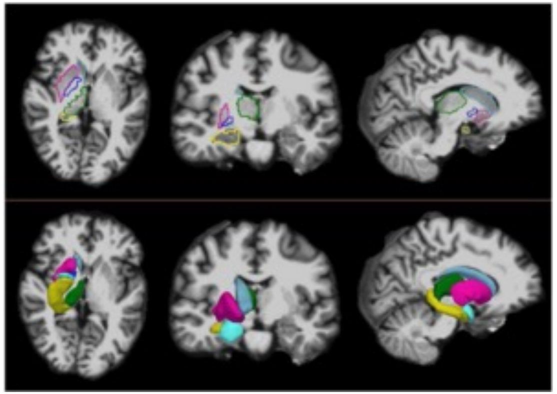
~~Food~~

NUTRITION is more than NUTRIENTS

BREASTMILK is more than FOOD

Impact of breast milk on IQ, brain size, and white matter development

- Adolescents born preterm; 15 years age
- Neurologically normal
- Cognitive assessment and brain MRI
- **Largest predictors of later IQ: Social class & breastmilk**
- Amount of breastmilk associated ***15 years later with***
  - Verbal & Full Scale IQ
  - White matter volume on MRI
  - Dose response effects

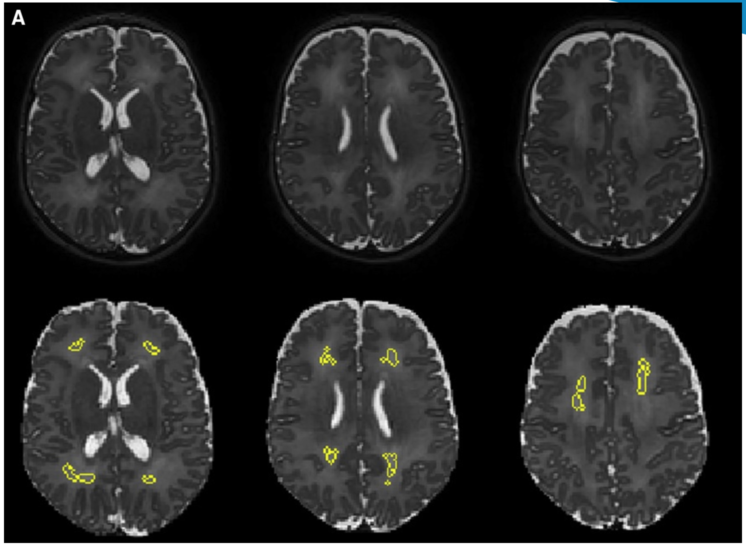


Isaacs et al. 2008,2009

....evidence from more recent MRI studies

Perinatal Risk & Protective Factors in Development of Diffuse White Matter Abnormality (DWMA) on MRI at term age. Parikh et al. *J Peds* 2021

- N=392 <32 weeks gestation 2016-2019 (Cincinnati)
- MRI at 39-45 weeks evaluate DWMA volume
- Key associations with ***increase*** DWMA volume
  - pneumothorax (P = .027)
  - severe BPD (P = .009)
  - severe ROP (P < .001)
  - male sex (P = .041)
- **Protective factor**
  - **Exclusive maternal milk diet at NICU discharge (P = .049).**



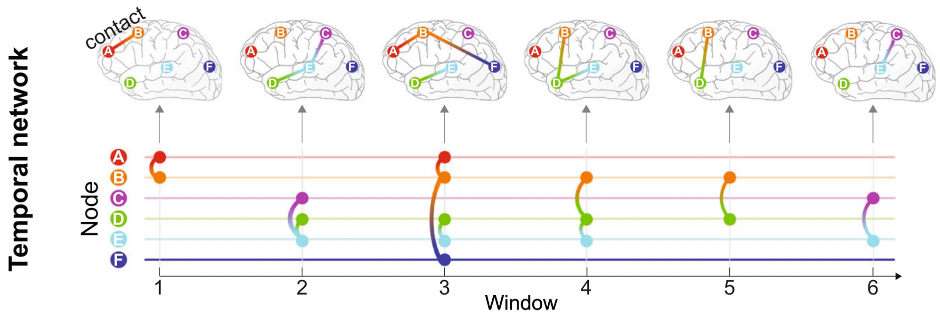
WM lesions – brighter on T2 – small vessel or microstructural abnormal myelination

Human Milk and Preterm Infant Brain Development: A Narrative Review
Belfort et al. *Clinical Therapeutics* 2022

Breastfeeding improves dynamic reorganization of functional connectivity in preterm infants: temporal brain network study. Niu et al. 2020

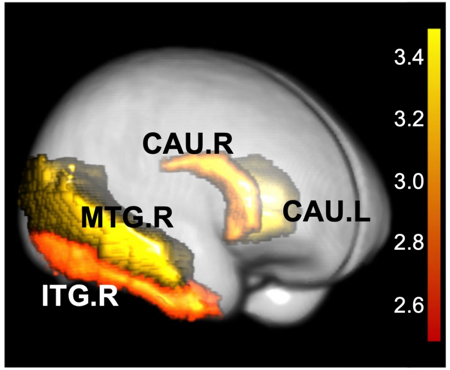
Newcastle Biomedicine

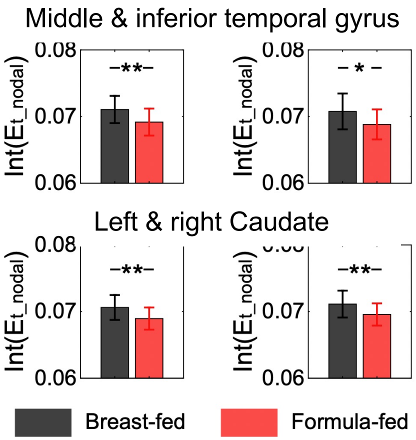
- N=50 29-33weeks gestation
  - 30 breast fed, 20 formula
- Resting-state **functional MRI** at term
- 3D spatiotemporal architecture of the temporal brain networks



- ***Dynamic functional connectivity*** -> efficient information transfer over time at both local and global levels

- **Breastfed exhibited greater temporal global efficiency**



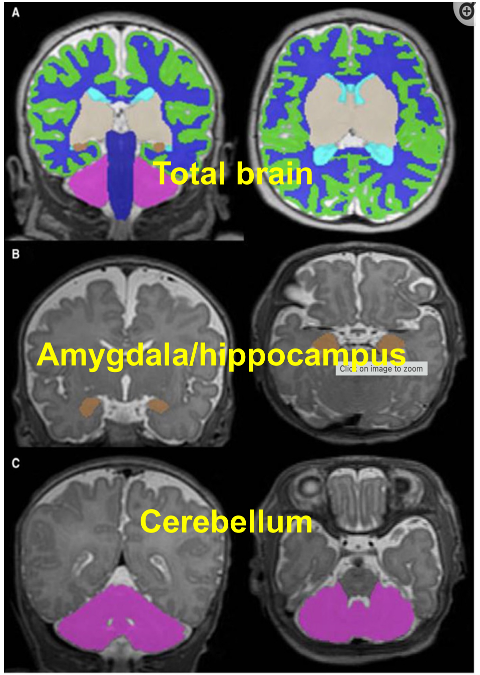


Improved brain growth and microstructural development in breast milk–fed VLBW. Ottolini et al. *Acta Ped* 2020

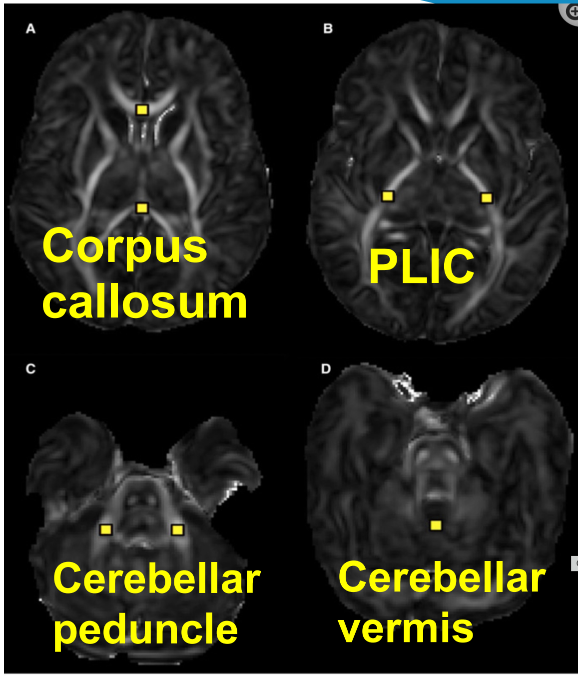
- n=68 <32w or <1500g
  - 44 breastmilk, 24 formula
- MRI at term: volumetric segmentation & diffusion tensor imaging (DTI)
- **Breast milk - higher**
  - total brain volumes ($P = .04$)
  - amygdala-hippocampus & cerebellum ($P < .01$)
  - white matter microstructural organisation in corpus callosum, posterior limb of internal capsule & cerebellum ($P < .01$ to $.03$)

DTI is similar to diffusion-weighted imaging (DWI) & determines white matter connectivity

Segmentation

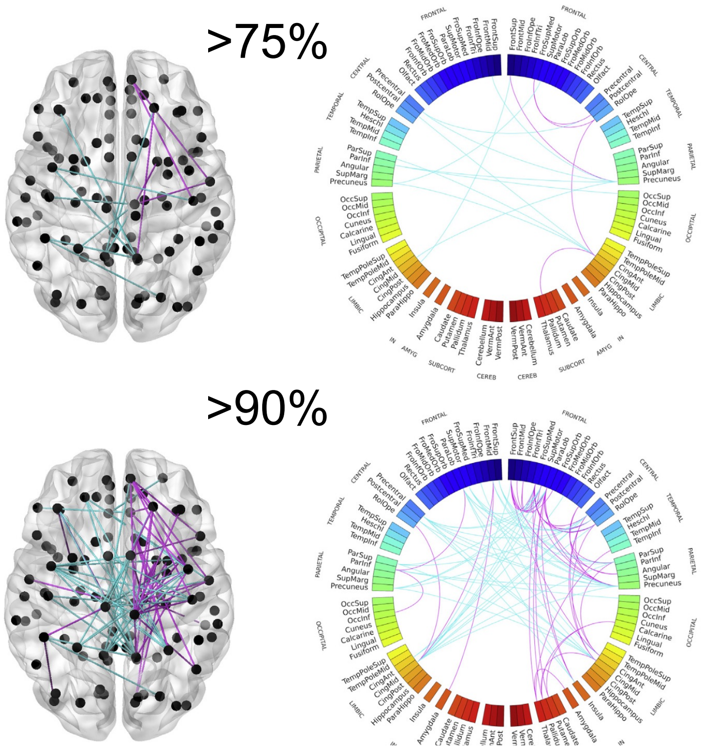


DTI



Early breast milk exposure modifies brain connectivity in preterm infants. Blesa et al. *Neuroimage* 2019

- N=47 Preterm 23-33w & brain MRI at term
- Network- & Tract-Based Spatial Statistics & volumetric analyses
- N=27 received **exclusive breastmilk for >75% days**
  - higher connectivity in fractional anisotropy (FA)-weighted connectome
  - higher FA within the corpus callosum, cingulate gyri, corticospinal tracts, PLICs
  - adjusted for gestation, BPD etc.
  - No group differences in brain volumes.
- **Breast milk exposure associated with improved structural connectivity**



Greater connectivity with higher breastmilk intakes

Breast Milk Feeding, Brain Development, & Neurocognitive Outcomes: 7 year outcomes <30w gestation (Belfort et al. 2016 J Peds)

- N=180 infants >30w or <1250g Victorian study (Australia) 2001-2003
- Days when breastmilk >50% milk intakes between 0-28 days
- MRI (term) & 7 years – cognitive (IQ, read, maths, attention, memory, language, visual perception) and motor
- Adjusted for age, sex, social risk, & neonatal illness
- **Results** - Days when breast milk >50% associated
  - MRI: greater deep nuclear gray matter (term) but not at 7y
  - better performance IQ, working memory & motor at 7y

- IQ **0.5 points higher per additional day** that breast milk intake >50%

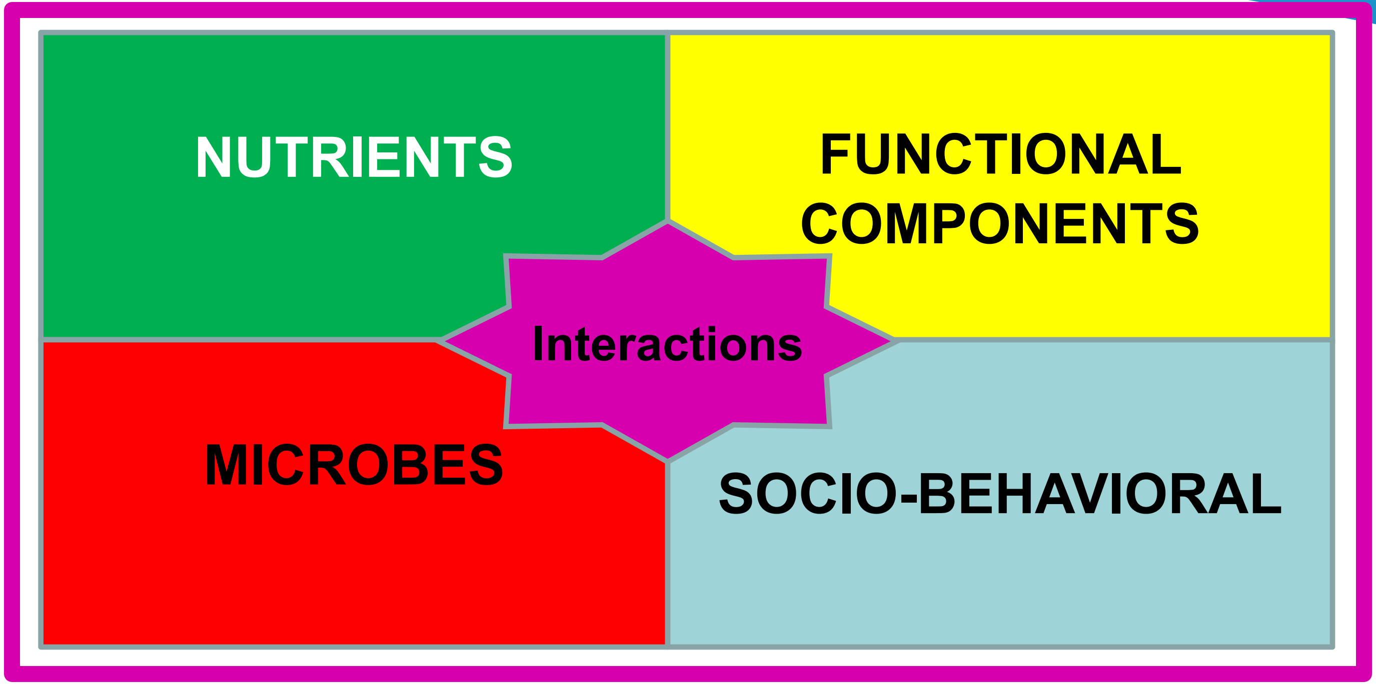
Human milk & neurodevelopmental outcomes

- Strong evidence from multiple studies showing benefits of human milk
- Large RCT comparing DHM v formula (O'Connor et al. 2016)
  - no neuro-developmental advantage to using donated human milk
  - Perhaps pasteurisation partially 'inactivates' functional components
- Benefits appear to be due to mother's own milk
  - Better infant neurodevelopment & childhood cognition
  - Greater brain volumes on MRI
  - Improved **network connectivity** of fMRI

Which aspects or component/s of breastmilk are most important?

Which component matters most?

Human milk



Human milk benefits – might be microbial?

Amino acids

Lactoferrin

HMOs
Human milk oligosacharides

Fatty acids

Gut microbial metabolism

Short chain fatty acids e.g. butyrate

Amino acids & peptides

Bile acids

Choline, Vit B & K

Signalling molecules

Anti- or pro-inflammatory

Human milk benefits – nutrient structure

- Human milk differs from bovine milk
  - **Protein structures** – whey v casein
  - **Fat structures** – Palmitic acid in human TGs is sn2 position
  - Variations in amounts and **proportions of lipids**
    - ALA, LA, DHA etc.
  - **Milk fat globule membrane**
    - TG tri-membrane layer
    - MFGM absent in most formula
  - **HMOs**
    - Most oligosaccharides in humans are fucosylated; sialylated HMOs might be especially important in brain development

Human milk superior – does it matter why? Do the mechanisms matter in clinical practice?

- **Maybe not!!**
- Strong evidence **mother's own milk** is superior to formula & DHM
- Multiple mechanisms
  - **complex**
  - Individually each mechanism may only exert small effect
  - May **differ** between individuals; nutrients **interactions**
  - Some associations might be **confounded**
- Understanding the broad mechanisms
  - Helps us promote/support ; educate staff etc
  - Keeps clinicians interested!

Water

Trypsin
Taurine
L-Carnitine
Soy Lecithin

Fats

Xanthine oxidase
Antiproteases
a-1-antitrypsin
a-1-antichymotrypsin

C.cohnii oil (Algal ARA)
Minerals
Potassium citrate

Leukocytes
Phagocytes
Basophils
Neutrophils
Eoisinophils
Macrophages
Lymphocytes
B lymphocytes
T lymphocytes
sIgA
IgA2 , IgG , IgD , IgM ,
IgE

Complement
Glycoproteins
Mucins
Lactadherin
Alpha-lactoglobulin
Alpha-2 macroglobulin
Lewis antigens
Ribonuclease

Phospholipids
Phosphatidylcholine
Phosphatidylethanolamine
Phosphatidylinositol
Lysophosphatidylcholine
Lysophosphatidylethanolamine
Plasmalogens
Sphingolipids
Sphingomyelin
Gangliosides : GM1 ,
GM2 , GM3 , Glucosylceramide

Lactoferrin
Choline
Lactoperoxidase
Fibronectin
>200 HMOs
Growth Factors
Cytokines
IL-1β; IL-2 ; IL-4 ; **IL-6; IL-8;** IL-10

Lactose
Carboxylic acid , Alpha hydroxy acid
Lactic acid,
Alpha-lactalbumin
HAMLET
Lactoferrin
Casein
Serum albumin
Creatine , Creatinine
Urea , Uric acid

Amino Acids: Alanine, Arginine, Aspartate, Glycine, Cystine, Glutamate, Histidine, Isoleucine, Leucine, Methionine, Phenylalanine, Proline, Serine, Taurine, Theronine, Tryptophan, Tyrosine, Valine
Carnitine

Leukotrienes
Thromboxane
Prostacyclin
Amylase
Arysulfatase
Catalase
Histaminase
Lipase
Lysozyme
PAF-acetylhydrolase
Phosphatase

Insulin
Corticosterone
Thrombopoietin
GnRH
GRH
Leptin
Ghrelin
Adiponectin
Eicosanoids
Prostaglandins

Triglycerides
Long-chain PUFA: DHA, AHA, Linoleic acid , ALA, EPA
Conjugated linoleic acid
Free Fatty Acids
Monounsaturated FA: Oleic, Palmitoleic, Heptadecenoic acids Saturated fatty acids: Stearic , Palmitic, Lauric, Myristic acid

Sphingolipids
Galactosylceramide
Lactosylceramide
Globotriaosylceramide (GB3)
Globoside (GB4)
Sterols
Squalene
Lanosterol
Dimethylsterol
Methosterol
Lathosterol
Desmosterol
Triacylglycerol

β-defensin-1
Calcitonin
Gastrin & Motilin
Bombesin, Neurotensin
Somatostatin,
Cortisol
T3, T4, TSH
TRH
Prolactin
Oxytocin

Cholesterol
7-dehydrocholesterol
Stigma-and campesterol
7-ketocholesterol
Sitosterol
β-lathosterol
Vitamin D metabolites
Steroid hormones
Vitamin A
Beta carotene
Vitamin B6, Vitamin B8 (Inositol)
Vitamin B12, Vitamin C, Vitamin D , Vitamin E

Nucleotides
Cytidine 5-MP
Disodium uridine 5-MP
Adenosine 5-MP
Disodium guanosine 5-MP
5'-Adenosine monophosphate (5"-AMP)
3':5'-Cyclic adenosine monophosphate (3':5'-cyclic AMP) , 5'-CMP; CDP, 3'-UMP), 5'-UMP, UDP, UDPH , UDPAH , UDPGA

a-Tocopherol
Vitamin K , Thiamine , Riboflavin ,Niacin , Vitamin D3
Vitamin B12
Folic acid
Pantothenic acid
Biotin
Calcium , Sodium , Potassium

Copper , Manganese, Iodine,, Selenium, Sulpher , Chromium , Cobalt , Fluorine , Nickel, Molybdenum, Iron, Zinc , Chloride , Phosphorus , Magnesium

IGF-II
Nerve growth factor (NGF)
Erythropoietin
Peptides
HMGF I, II & III (Human growth factor)
Cholecystokinin (CCK)
β-endorphins
Parathyroid hormone (PTH)
Parathyroid hormone-related peptide (PTHrP)

Granulocyte-colony stimulating factor (G-CSF)
Macrophage-colony stimulating factor (M-CSF)
Platelet derived growth factors (PDGF)
VEGF
Hepatocyte growth factors
TNF-α
Interferon-γ
Epithelial growth factor (EGF)
TGF-α
TGF β1
TGF-β2
IGF-I

Water

Trypsin
Taurine
L-Carnitine
Soy Lecithin

Fats

Xanthine oxidase
Antiproteases
a-1-antitrypsin
a-1-antichymotrypsin

C.cohnii oil (Algal ARA)
Minerals
Potassium citrate

Leukocytes

IgA2 , IgG , IgD , IgM , IgE

Complement
Glycoproteins
Mucins
Lactadherin
Alpha-lactoglobulin
Alpha-2 macroglobulin
Lewis antigens
Ribonuclease

Phospholipids
Phosphatidylcholine
Phosphatidylethanolamine
Phosphatidylinositol
Lysophosphatidylcholine
Lysophosphatidylethanolamine
Plasmalogens
Sphingolipids
Sphingomyelin
Gangliosides : GM1 , GM2 , GM3 , Glucosylceramide

Lactoferrin
Choline
Lactoperoxidase
Fibronectin

Thank you!

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Casein
Serum albumin
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Urea , Uric acid

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TGF β1
TGF-β2
IGF-I

Key take home messages

- Macronutrients & mother's own milk (MOM): key interventions
- Human milk
  - **Reduced disease** (ROP, BPD, NEC etc.) = less inflammation
  - **Better metabolic** outcomes over the life-course
  - **Better brain** & cognitive outcomes (MRI & functional studies)
- Donor milk does **not** have the same advantages
- To further improve outcomes:
  - improve **support & education** for mother's own milk
  - Guidelines, audit, QI etc. – **macronutrients (PN, EN) & MOM**
  - MOM = most **cost-effective** intervention in neonatal medicine

Human milk to improve brain outcomes is a team effort!

GREAT NORTH NEONATAL BIOBANK

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www.neonatalresearch.net

Newcastle University

NHS The Newcastle upon Tyne Hospitals NHS Foundation Trust

DOLFIN

MAGPIE

eLFIN

SIFT Speed of increasing milk feeds

tiny lives SPECIAL CARE BABIES

Northumbria University NEWCASTLE

N4 Newcastle Neonatal Nutrition & NEC research

MRC Medical Research Council

NHS NIHR

NIH National Institutes of Health

Stewart Lab