

Nutritional requirements in late and moderately preterm newborn infants

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Dr Nicholas Embleton

Professor of Neonatal Medicine, Newcastle, UK

Conflicts of interest



- Research funding
 - National Institutes for Health Research (NIHR)
 - Action Medical Research, Tiny Lives charity
 - Danone Early Life Nutrition, Prolacta Bioscience
- Professional associations, committees etc.
 - ESPGHAN Committee of Nutrition
 - UK Neonatal Nutrition Network (N3)



NEONATAL RESEARCH

- HOME
- GREAT NORTH NEONATAL BIOBANK
- RESEARCH STUDIES
- TALKS & PRESENTATIONS
- BUTTERFLY PROJECT



Newcastle Neonatal Research Team

We are a multi-disciplinary, clinically focused, neonatal research team based in the UK, Europe and USA. Our main areas of research focus on neonatal studies include large scale collaborative trials of feeding and nutrition (I-GUT microbiome and metabolome (INDIGO & MAGPIE). Team members from Newcastle University, Northumbria University and Newcastle University.

We have a separate website for our qualitative research that has led to professional and higher education, and for parents www.neonatalbutts.com

Partners

We work closely with parent-led organisations, advocacy groups and charities. We are indebted to the hundreds of parents of sick babies who have supported us and without whom we would not have succeeded. We also gratefully acknowledge all the organisations who have supported us, but there are many others.

- Late Moderate Preterm
- Teaching links
- Executive function in preterm infants
- Energy ESPGHAN guidelines
- Gut health
- Butterfly project
- Post-discharge nutrition
- Growth of preterm infant
- Early Nutrition Later Outcomes
- How to study Microbiome
- Nutrition & brain high risk
- Breast milk fortification
- Feeding Strategies
- Gut & immune function
- Personalised nutrition China
- Donor milk trials
- ELFIN trial background
- Ethics & Butterfly
- Should we use in-utero growth charts
- Late Moderately Preterm

11 collaborators across the enterocolitis (NEC). Our research studies focusing on the hospitals NHS Foundation

resources, free resources for health

advise on our projects. We are grateful to them none of our projects or projects. Some of these are

Newcastle NICU



- Population region: ~3million
 - 3 NICUs
 - 35,000 births/year
- Newcastle – referral NICU
 - Surgery (NEC), congenital etc.
 - 7,500 inborn + 300 transfers
 - 175 infants <1500g p.a.
 - 60 infants <1000g p.a.

I am fortunate to work with some amazing nurses and doctors



Saturday 18th May 20.14hrs - Whatsapp message from Attending consultant 24 week **QUINTUPLETS** emergency C-section NOW!!

Berrington mobile, Jenny, Nav...

All go just now (with no notice!!) for us so if anyone free to come in NOW it'd be great thanks

20.14hrs 16:14

Berrington mobile Janet
On my way

16:15

Richard Hearn
Me toi

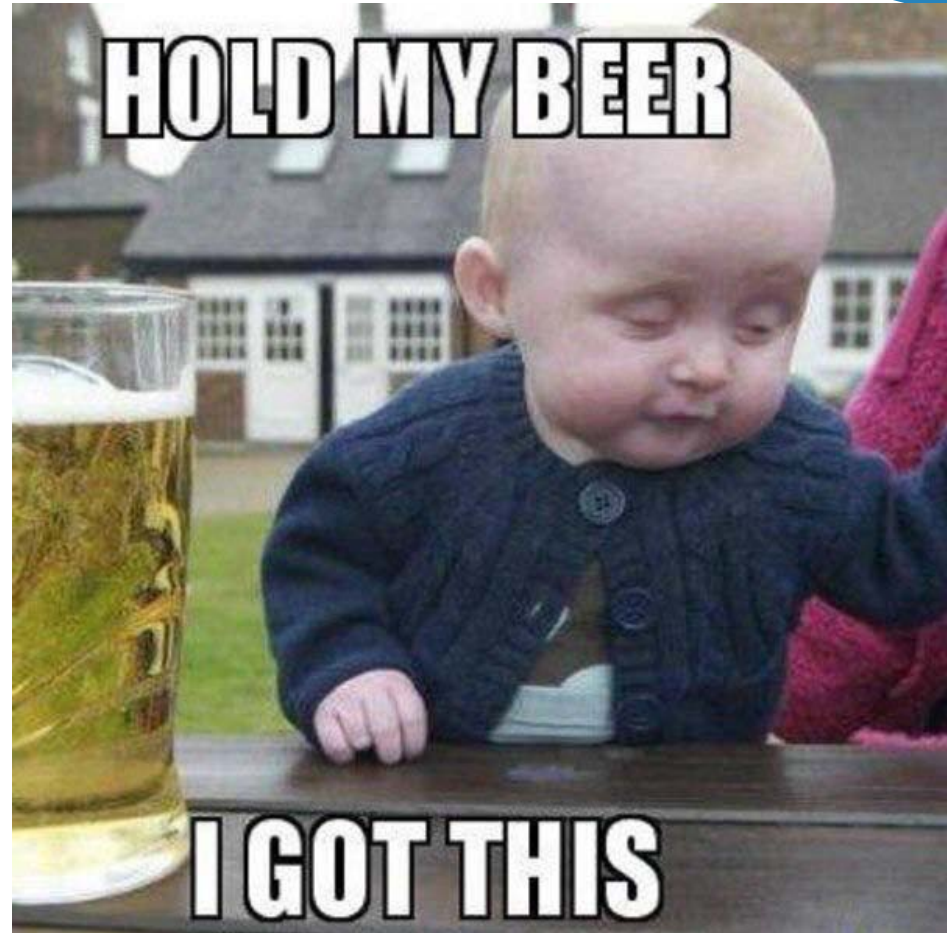
16:15

Robert Tinnion
Ta.

16:19

And me

16:27 ✓✓

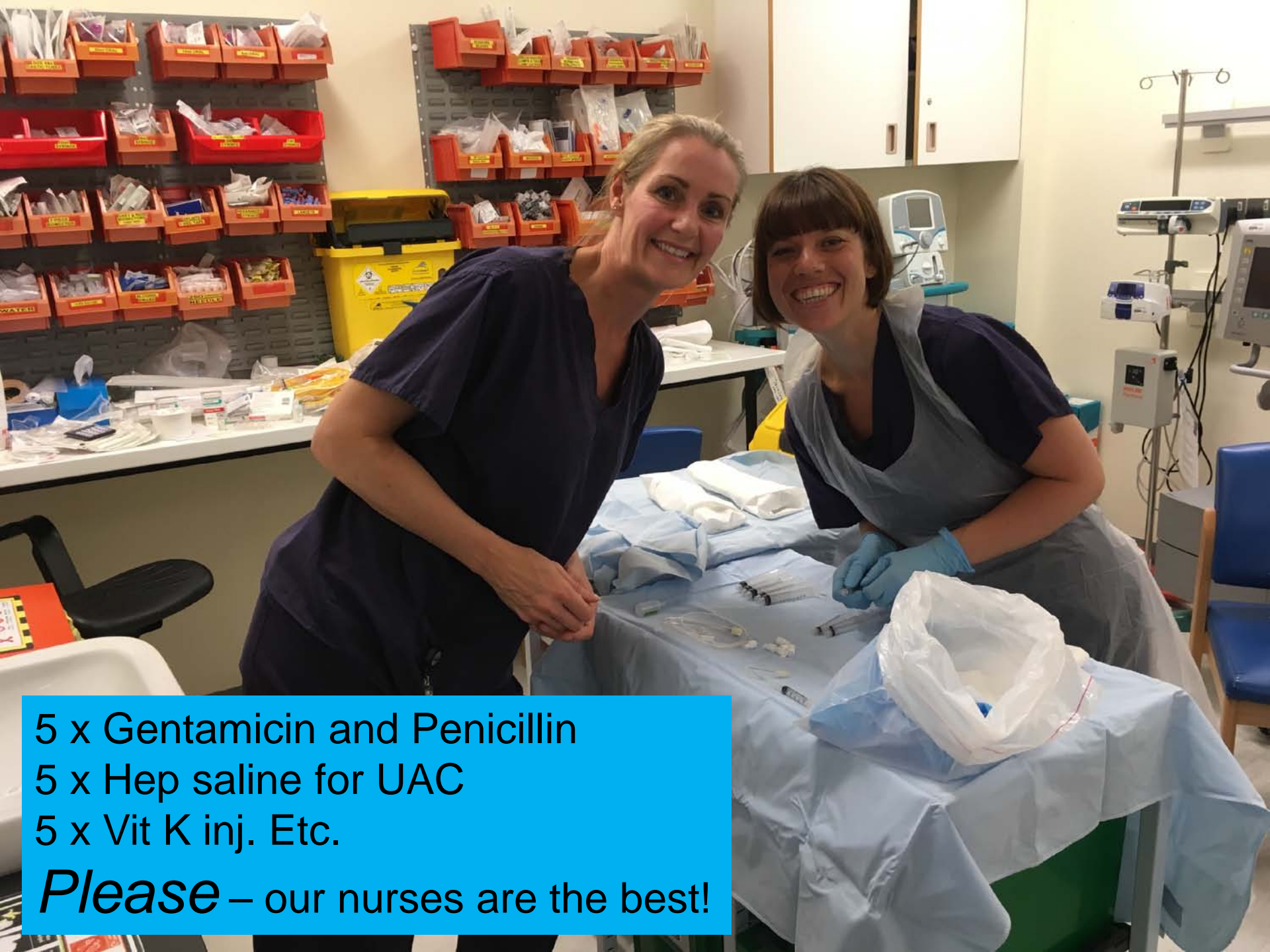




WARD 35
NICU

UAC/UVC
INSERTION BOX





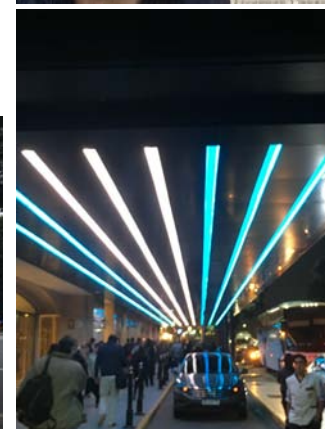
5 x Gentamicin and Penicillin
5 x Hep saline for UAC
5 x Vit K inj. Etc.

Please – our nurses are the best!



12 hours later – kids, let's go the beach!
Newcastle is a lovely City – please come visit me

I need to finish my
powerpoint slides
for Argentina!





Late and Moderately Preterm (LMPT)

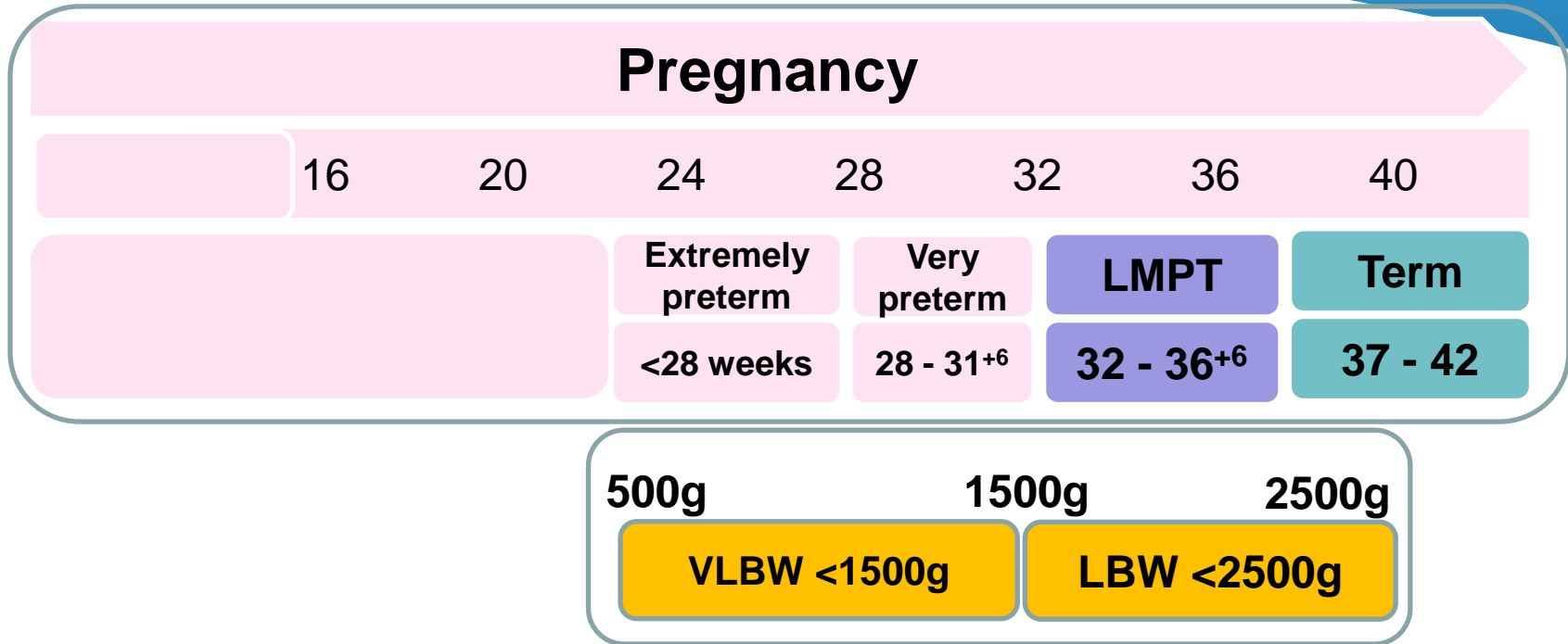
Key messages of talk

1. LMPT infant prevalence >> very preterm (<32w)
 - Important global context
2. LMPT associated with worse outcomes over life-course
 - **Healthcare** costs
 - Short and long-term **cognitive** outcomes
 - Long-term **behavioral** problems e.g. eating & autism
 - **Metabolic** outcomes in adulthood
3. LMPT infants: nutritional management inadequate

Improved breastfeeding: potential to reduce costs & improve outcomes

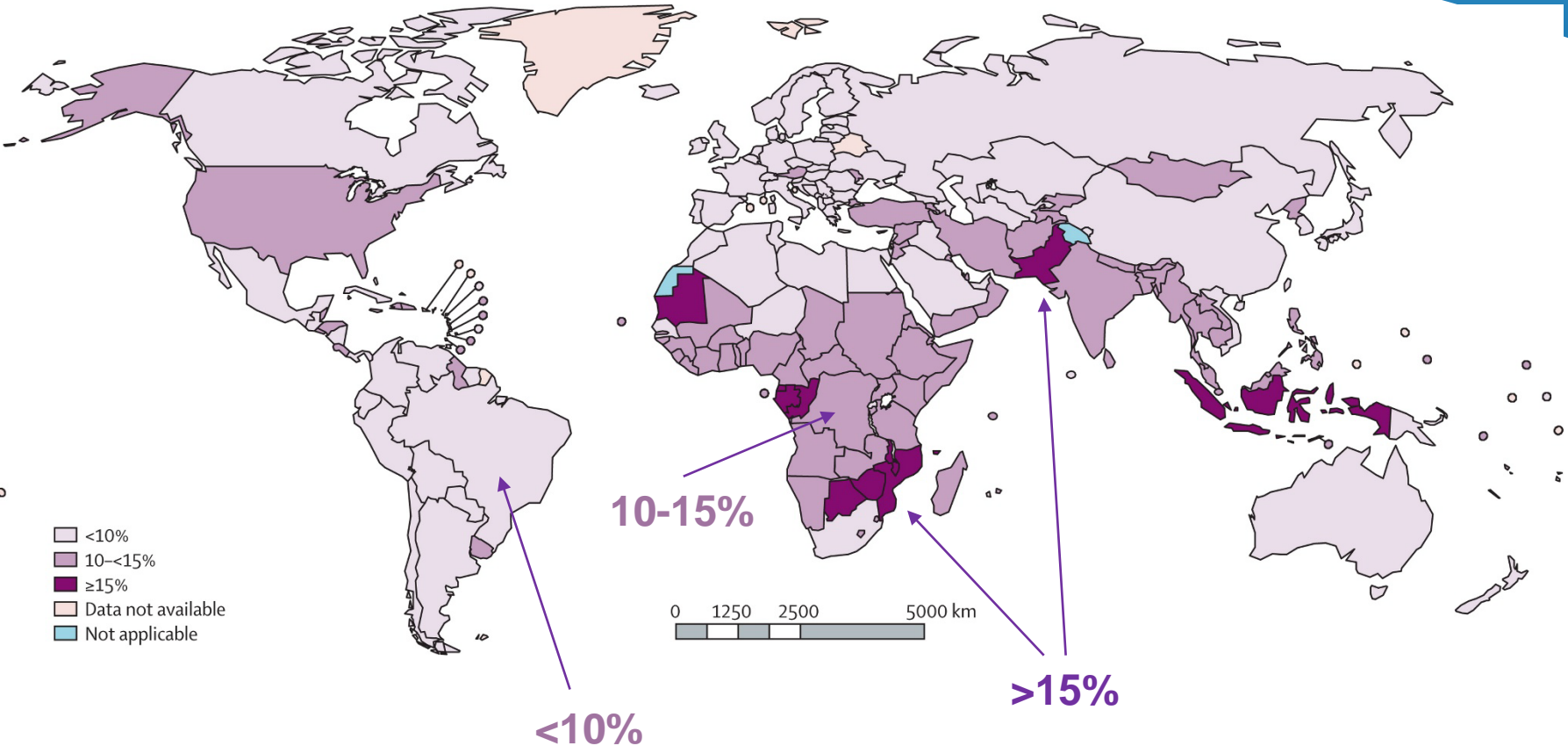


Definitions: LMPT 32-36⁺⁶ weeks

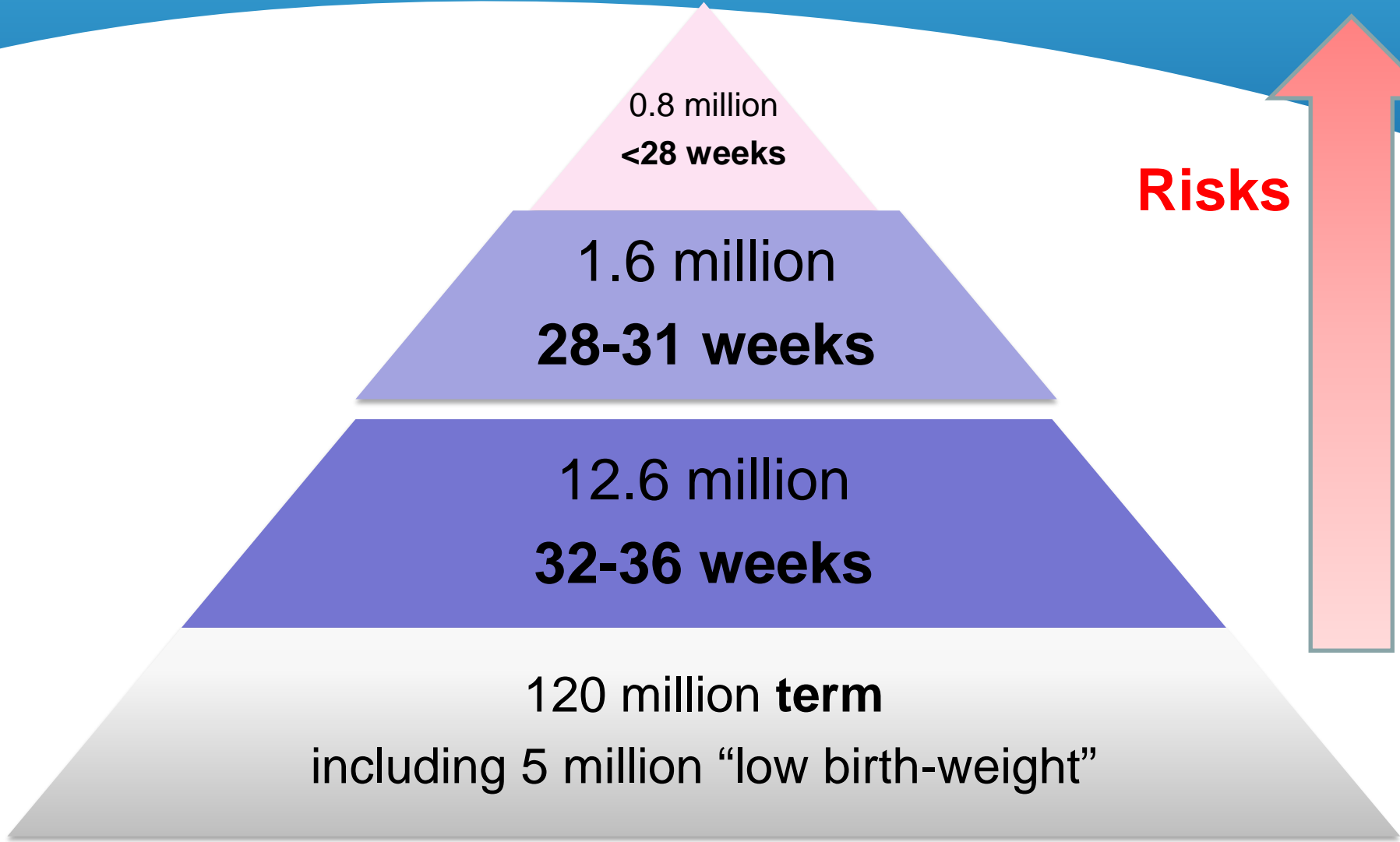


Low birthweight (LBW) does not equal LMPT

Global prevalence of preterm birth

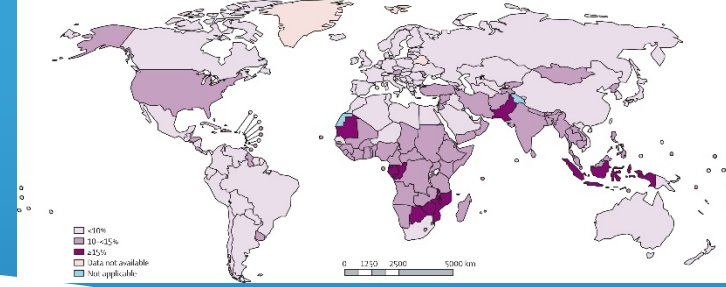


Global prevalence



Based on Lee et al. 2013 & Lawn et al. 2015

Prevalence of LMPT birth

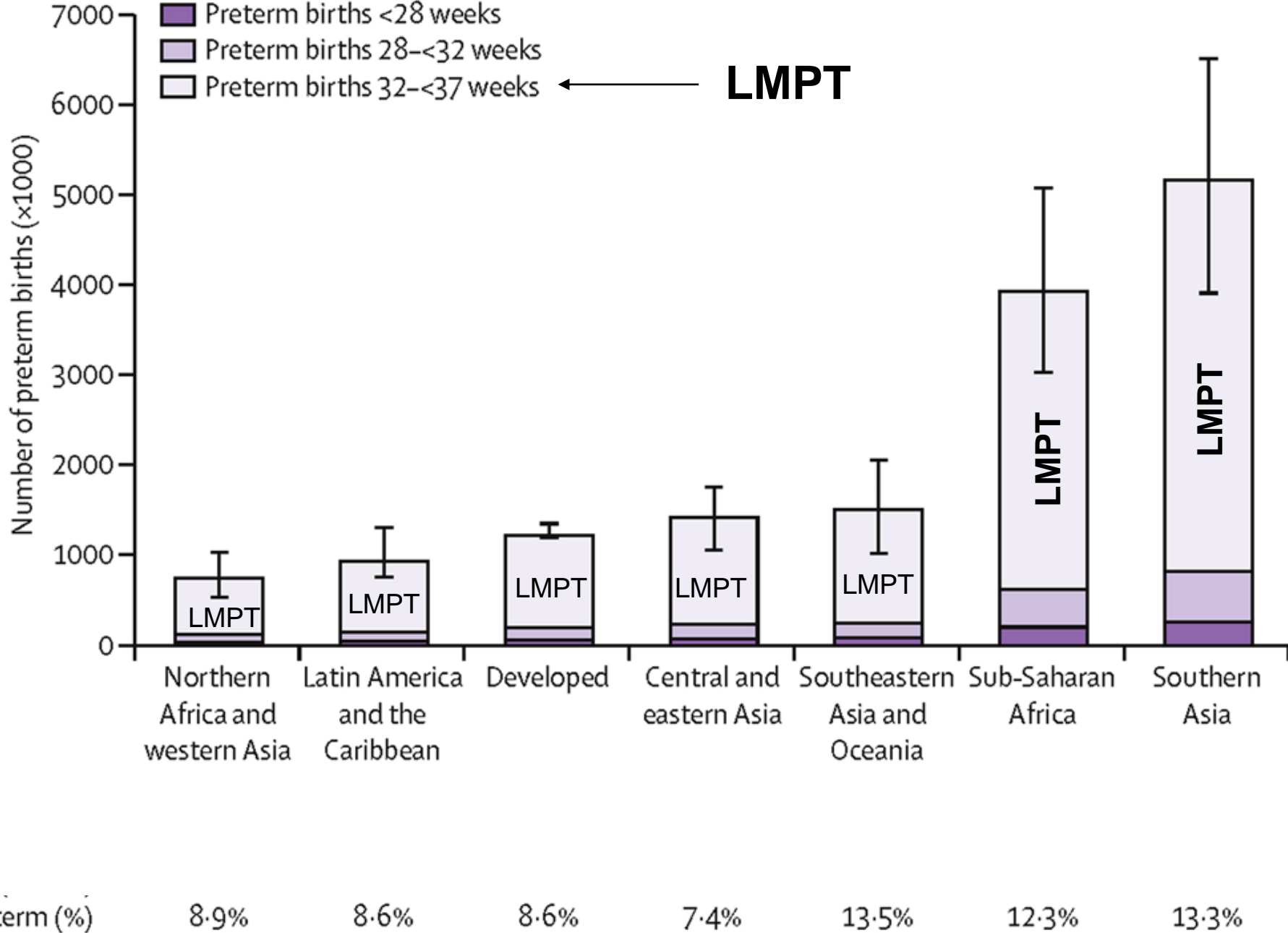


- >80% of all **preterm** births are LMPT
- ~6-7% of **all births** are LMPT
- Inter-country variations reflect
 - Population resource (income / wealth)
 - maternal illness, health, choices etc.
 - antenatal practices, ultrasound, induced early delivery
 - data collection: dating scans, accuracy (LMPT v LBW)

LMPT & LBW: needs may be similar but risks differ

SGA ≠ LBW ≠ IUGR ≠ LMPT



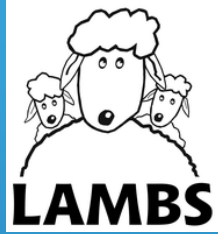




Late & Moderately Preterm (LMPT)

- Massive global challenge >12 million infants per year
- What are the economic costs?
- What are the risks of LMPT
 - short-term
 - longer term

Economic costs associated with LMPT birth



- Population based cohort using health records
- Length of hospital stay & care level
 - National Health Service (NHS) reference costs
 - Costs of inter-hospital transfer
 - Delivery & maternal postnatal costs
 - Postnatal costs for infant (questionnaires)
 - Hospital stay, clinics, drugs, special equipment etc.

Complex regression modeling & sensitivity analyses



Economic costs (Khan et al. 2015)

Cost per infant over first 2 years

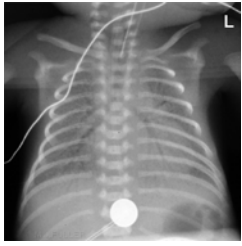
- | | | |
|-----------------------------|---------|------------|
| • Moderate preterm (32-33w) | £12,037 | US\$15,000 |
| • Late preterm (34-36w) | £5,823 | US\$7,500 |
| • Term | £2,056 | US\$2,500 |

Multivariable modeling

- LMPT costs were **\$9,000 (moderate)** and **\$2,500 (late)** higher than term born infants



LMPT increased risks: multiple morbidities



RDS / TTN



CPAP



Hypothermia



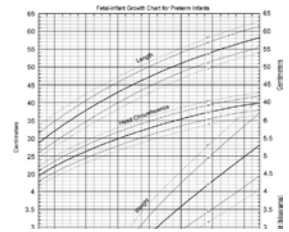
Hypoglycemia



Feeding difficulties



**Weight loss
Poor growth after discharge**



Infections

NEONATAL JAUNDICE		
	PHYSIOLOGICAL	PATHOLOGICAL
STARTS @	After 4 days	1 st or 2 nd Day
BILIRUBIN	< 20mg/dl	> 20mg/dl
KERNICTERUS	Rare	Common
RESOLVES	Early	Late

Jaundice

- ↑ Hospital readmissions
- ↑ Respiratory problems in infancy
- ↑ Mortality

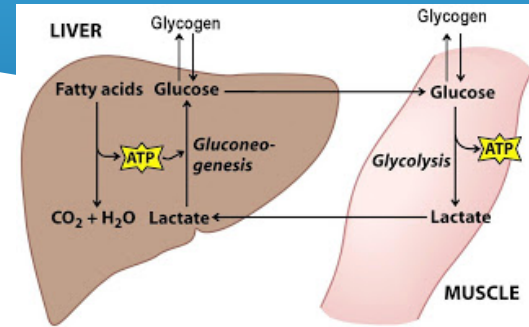


Acute energy supply for LMPT: hypoglycemia risk is higher

- Immature counter-regulatory mechanisms
- Lower hepatic glycogen stores
- Lower adipose tissue stores

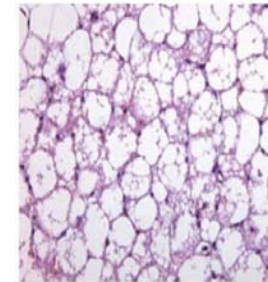
Contributory factors

- Delayed feeding, low volume feeds
- Low use/availability of mother's milk

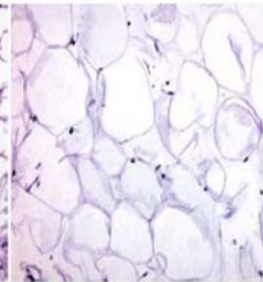


Principles of Biochemistry, 4th
© 2004 Pearson Prentice Hall, Inc.

Brown Fat (or BAT)



White Fat





Neonatal outcomes

	Moderate PT	Late PT	Term
Resuscitation at birth	37%	14%	7%
Endotracheal intubation	9%	2.4%	0.8%
Admitted to NICU ↑	100%	36%	4%
Length of stay (days) ↑	16 (4-78)	4 (1-49)	2 (0-25)
Ventilated or respiratory support ↑	34%	8%	1%
Parenteral nutrition ↑	12%	2%	0.3%
Any breastmilk	66%	64%	74%
Breastmilk at discharge ↓	53%	59%	72%
Exclusive breastmilk at discharge ↓	34%	40%	65%

Significant inter-unit variations



Boyle et al. 2015

www.neonatalresearch.net
Improving outcomes



The Newcastle upon Tyne Hospitals
NHS Foundation Trust





Feeding difficulties are more common

- Cardiorespiratory instability
- Metabolic / glucose control: supplements & NG tubes
- Oro-motor function
- Uncoordinated suck & swallow
- Immature peristalsis: reflux, possetting etc.

Do feeding difficulties persist in later infancy?





Eating difficulties in children born LMPT at 2 years

- Population-based cohort: recruited at birth
- 651 LMPT and 771 term infants at 2 years
- Questionnaire for eating behaviors in 4 domains:
 1. refusal/'picky' or 'fussy' eating
 2. oral motor problems
 3. oral hypersensitivity
 4. eating behavior problems
- PARCA-R (Parent reported outcomes ~ BSID III), emotional assessment score (BITSEA)





Eating difficulties in children born LMPT at 2 years

- LMPT infants
 - increased refusal/picky eating (RR: 1.5)
 - oral motor problems (RR: 1.6)
- Independent associations of difficulties
 - **prolonged NG > 2 weeks (RR: 1.8)**
 - **behavior problems (RR: 2.9)**
 - **delayed social competence (RR: 2.2)**
- Feeding difficulties: due to neurodevelopmental problems rather than premature delivery





LMPT & feeding difficulties

- Co-occurrence with behavioral problems
 - “Eating difficulty” may indicate neurological problem
- Oro-motor difficulties also prevalent in VLBW
 - Underlying neurological/maturation problem

32% required NG feeding

- NG tube >2 weeks was strong risk factor
- brief use not associated with later problems
- LMPT infants 2x as likely to have anti-reflux Rx





LMPT at risk for cognitive & eating problems: other behavioural concerns?

- Good data show very preterm infants: higher risks of behavioural problems including autism
- Social-communication difficult to assess in early infancy
- **M-CHAT**: Modified Checklist for Autism in Toddlers
 - Parent questionnaire



Infants born LMPT at increase risk for autism screen at 2 years

- M-CHAT questionnaire at 2 years
- Telephone discussion with parents
 - **2.4% LMPT v 0.5% term (RR 4.52)**
 - Non-significant trend to be associated with
 - Maternal age >35years
 - Poor mental health
 - Not receiving breast-milk at discharge



Guy et al. 2015

www.neonatalresearch.net
Improving outcomes



The Newcastle upon Tyne Hospitals
NHS Foundation Trust





Neurodevelopmental outcomes after LMPT: population-based study

- 1130 LMPT & 1255 term-born controls
- **2 years corrected age questionnaire**
 - neurosensory (vision, hearing, motor) impairments
 - PARCA-R (validated against BSID)
- **Neurosensory impairment**
 - **LMPT 1.6% v Term 0.3% (RR 4.89)**
- **Cognitive impairment**
 - **LMPT 6.3% v Term 2.4% (RR 2.09)**
- Independent risk factors for cognitive impairment in LMPT
 - **Male, socio-economic, preeclampsia**
 - **Not receiving breastmilk at discharge**

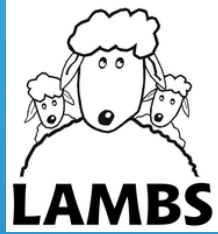


Neurodevelopmental outcomes

	Moderate preterm (n=87)	Late preterm (n=551)	All LMPT (n=638)	Term (n=765)	Adjusted RR	p
Non-verbal cognition	27.1	27.6	27.5	28.0	-0.49	0.04
Expressive language	58.9	61.7	61.3	66.4	-3.96	0.03
Total parent composite (PRC)	86.0	89.3	88.9	94.5	-4.49	0.02
Cognitive impairment	4.7%	6.6%	6.3%	2.4%	2.09	0.01
ND disability	4.7%	7.3%	6.9%	2.5%	2.19	0.004



Neuro-developmental outcomes



- Cognitive/language score deficit
 - 2.3 points deficit in “IQ”
 - Small for individual; large for society
- LMPT: **boys 7x** risk of girls
- Associated with **breast-milk** at discharge
 - Multiple potential mechanisms





Inadequate breast-milk associated with worse outcomes: possible mechanisms?

- **Nutrient profiles**
 - fatty acids, proteins, hormones etc.
- **Growth** trajectories
- **Psychosocial/bonding**
- **Sensory** – taste & smell and later eating (Bloomfield et al.)
- **Functional** aspects
 - **Anti-infective**
 - **Microbiota: direct** (in milk) and **indirect** (HMOs etc.)



Why are breast-feeding rates low in Late and Moderate Preterm?

1. Early use of formula
2. NICU admissions – interrupted skin:skin etc.
3. Sensory experiences: taste, smell, NG tubes
4. Maternal illness – diabetes, obesity etc.
5. Difficulties in establishing breast-feeding
6. Delayed lactogenesis
7. Socio-economic factors
8. Etc.

No high quality RCTs and few qualitative studies



Late preterm birth and outcomes at age 6 years

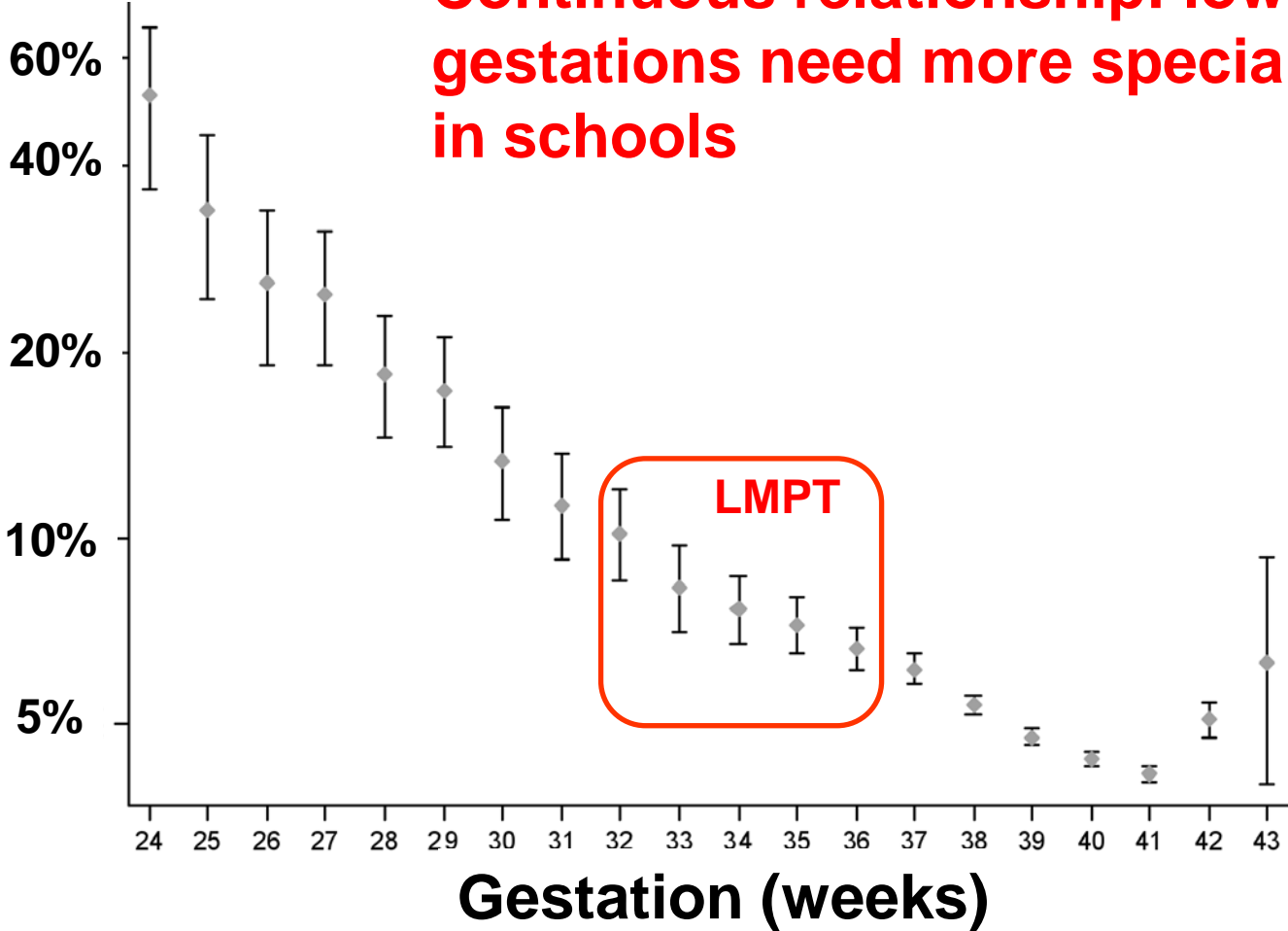
Late-preterm birth 34-36w

- Study years 1983-85: IQ & behaviour at 6 years
 - **Full scale IQ < 85: OR 2.35**
 - **Performance OR 2.04**
- Higher levels of internalizing & attention problems
 - Adjusted for maternal IQ and SES factors

Talge et al. 2010

Gestational age and needing special educational support

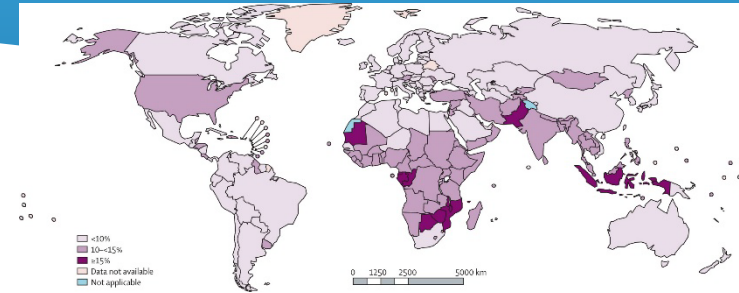
Proportion with Educational Needs



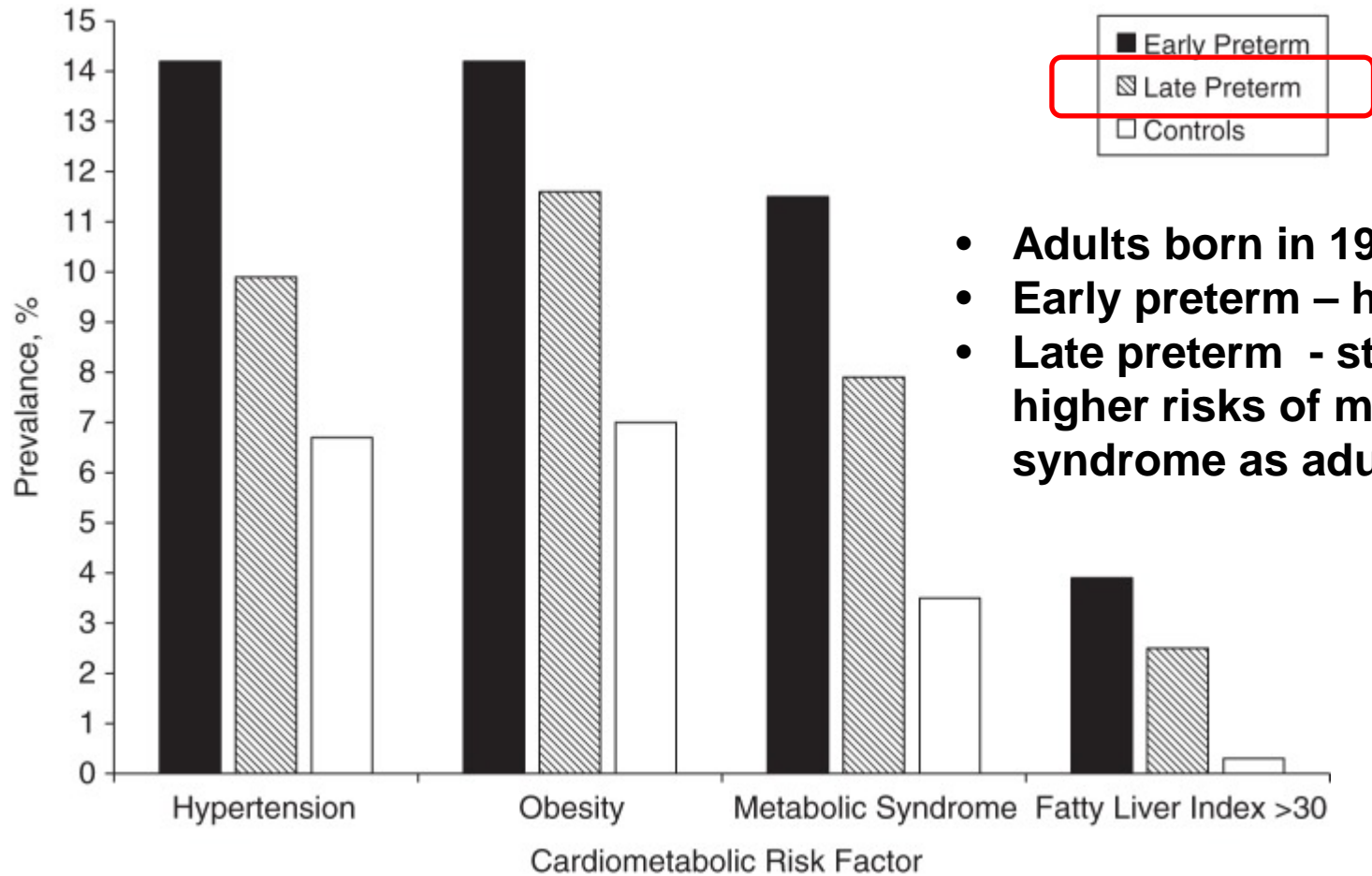


LMPT - Growth outcomes: multiple studies, varying populations

- Brazil – Santos et al. (2009)
 - 34-36w v term controls **at 2 years**
 - **Underweight OR 3.3 ; Stunted OR 2.3**
- US - Goyal et al. (2012)
 - 34-36w ‘late’ preterm
 - **OR 2.1 for underweight** at 12m
 - but not at 18m
- India - Gupta et al. (2017)
 - **OR 4.1 for underweight** at 12m



Prevalence of abnormal metabolic phenotype in adulthood

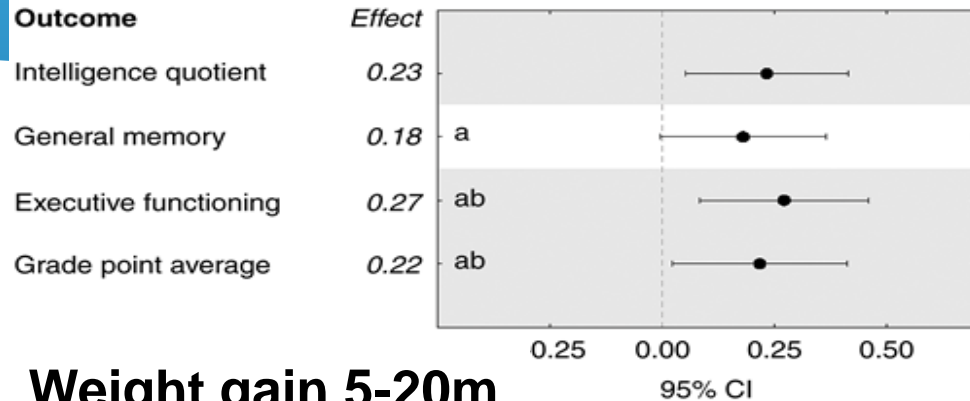


- Adults born in 1985
- Early preterm – highest risk
- Late preterm - still have higher risks of metabolic syndrome as adults

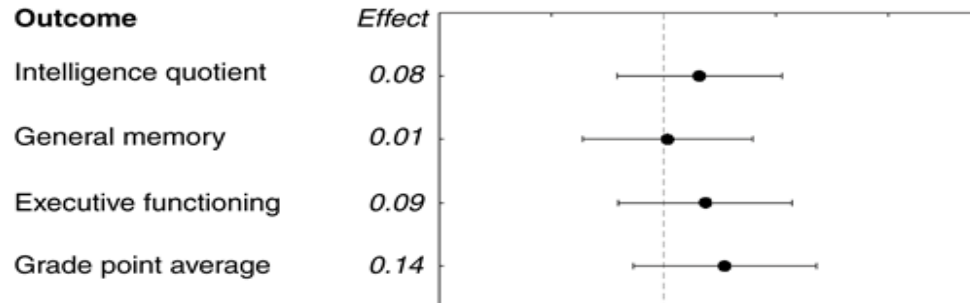
Late preterm infants - is early growth important?

- Finland
- 34 - 36⁺⁶wks
- n=108
- Detailed testing
- Multiple adjustments

Weight gain birth – 5m



Weight gain 5-20m



Faster growth birth to 5 months associated with

- Higher IQ
- Better executive functioning
- Higher grade point average
- Lower odds of receiving special education





LMPT have worse 'brain' outcomes over the life-course

- Very strong observational evidence
- Multi-factorial aetiology
- **Lack of breast-feeding is independent risk factor**
 - Is this a marker for other maternal behaviours?
 - Is this due to biological mechanisms?

Why do LMPT have adverse long-term outcomes: possible mechanisms

EXPOSURES

**Pre-
conception**

Maternal disease
Drugs (Rx & rec.)
Lifestyle

In-utero

Pre-eclampsia
Placental nutrients
Drugs

Postnatal

Hypoglycemia
Inadequate early AA etc.
Sensory/environmental

MECHANISMS

Toxic

Nutritional

Interrupted brain development

Epigenetic



Adverse effects: are they due to poor nutrition?

Prenatal, postnatal & post-discharge

- Inadequate early nutrient supply
- Abnormal sensory & environmental exposures
 - NICU environment, NG feeding, taste & smell
- Inadequate macronutrients for normal growth?
- Inadequate micronutrients
 - **Especially iron**
 - Vitamin D, DHA, Choline, Zinc, Iodine etc.?

Nutritional philosophy & practice

Mother's Own Milk (MOM)

Very preterm

LMPT

Term

Prevent NEC & sepsis
"One brain for life"
Avoid malnutrition

'Normal & natural'
Breastfeeding
Avoid rapid growth

Protein +++, Energy ++
Parenteral nutrition
Daily review

?

Low protein

Human milk has lowest protein density of all mammals except for Orangutan monkeys!

Nutritional philosophy & practice

Mother's Own Milk (MOM)

LMPT

Prevent NEC & sepsis
"One brain for life"
Avoid slow growth

Normal & natural
Breastfeeding
Avoid rapid growth

High protein
Parenteral nutrition?
Daily review

Low protein
Iron, Vitamin D etc.



What can we do?

We need

- **High quality RCTs**
 - To provide evidence for optimal management
- **Longer term observational studies**
 - To understand what LMPT means in later life
- Better data on **nutritional aspects**
- **Qualitative studies**
 - to understand why breast-feeding rates are low

THINK about the infants more than we do at present



Potential methods to improve breast-feeding rates in LMPT

1. Education – staff & parents
 2. More emphasis: early colostrum & continued expression
 3. ‘Aim/focus’: breast-milk intake rather than weight gain
- Alternative energy sources to Rx or prevent hypoglycemia
 - dextrose gel (Harding et al. 2016)
 - donor milk ; ‘other’ milks ??
 - Remuneration or incentives (Relton et al. 2017)?
 - Earlier discharge with NG support ?

Need testing in high-quality RCTs



Nutritional strategies to improve brain or metabolic outcomes

- Give more Mother's own breastmilk!
- Give more or less macronutrients
 - Specialised formula, use fortifiers etc.
- Make growth faster or slower in first few weeks
- Earlier/later or more/less iron supplements
- Use supplements – lactoferrin, probiotics, MFGM etc.
- Etc.

Need testing in high-quality RCTs



How can we make a difference?

1. **Support mother's** & advocate for breastfeeding
2. Be aware of potential **conflicts** – formula milk
3. Remember need for **supplements** – iron, Vit D
4. **Educate** - staff, families, society, government
5. **Audit** – are your outcomes as good as they can be
6. **Collaborate** in clinical networks – share good ideas
7. **Evidence** – collaborate on pragmatic research studies
8. **Recognise your UNIQUE role** to make this better



Summary

- LMPT infants are an important group
 - Many more babies than extremely preterm
 - Lifetime risks of worse health outcomes
- Often ‘ignored’ by neonatal physicians
- Nutrition has the potential to improve outcomes
 - Brain development & cognition
 - Metabolic outcomes – hypertension, obesity etc.
 - Behavioural / family – breastfeeding, eating
- ***Do not forget the post-discharge period***
 - Follow up; breastfeeding support, supplements etc.

Leche materna! Remember – Late and Moderate Preterm

- YOU have the opportunity to improve outcomes of all your babies with better nutrition
- YOU can make a difference – if you want to ...
- YOU may determine their health outcomes until they are 70 years old!

Muchas gracias!
www.neonatalresearch.net

