Growth

Sabita Uthaya
Consultant and Honorary Senior Lecturer in Neonatal Medicine

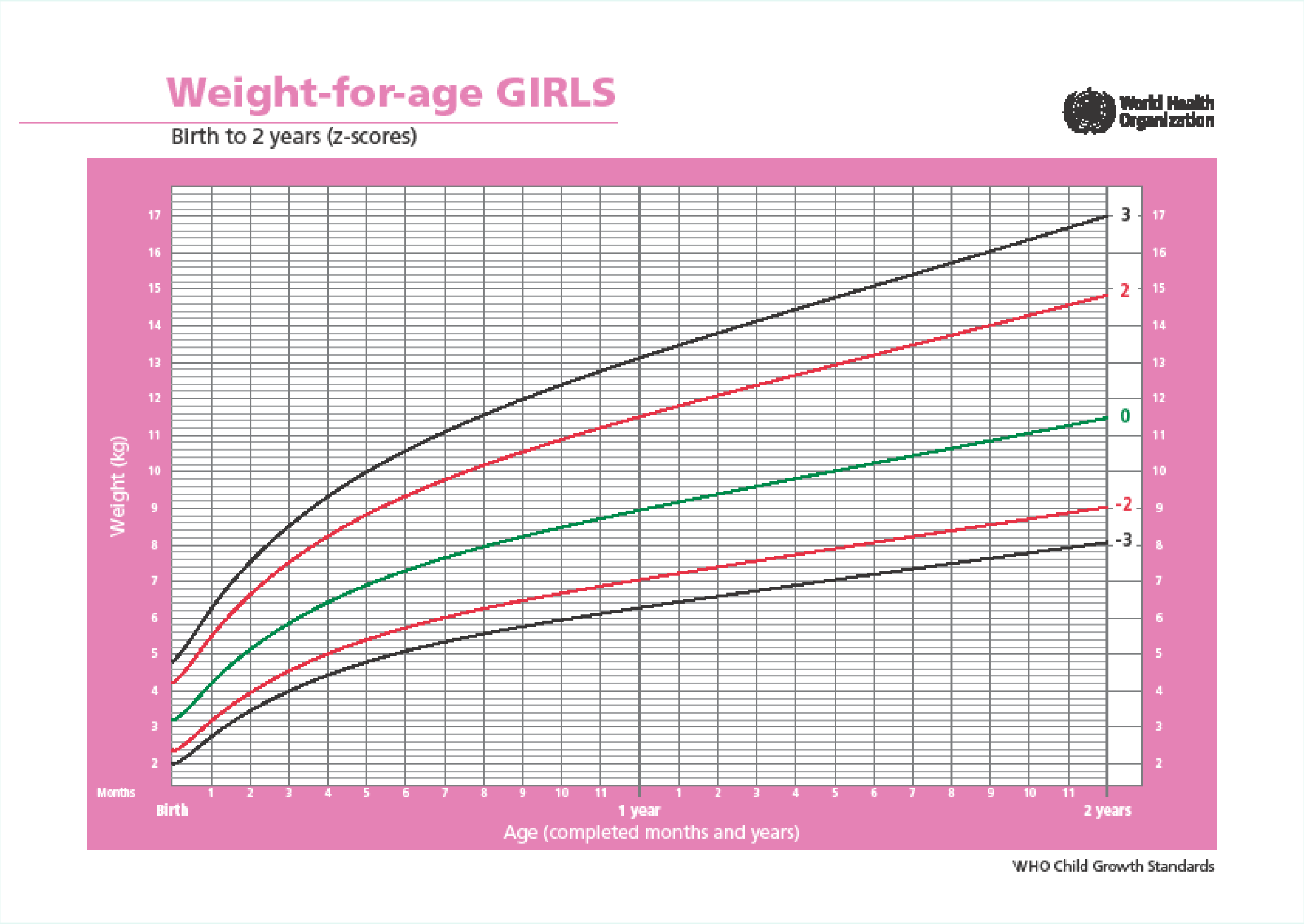
Outline

- Measurement of growth
- Patterns of growth and consequences
  - Consequences of poor growth in utero
  - Consequences of poor growth ex utero
  - Consequences of rapid growth
- Growth outcomes of preterm infants
- Limitations of using growth as outcome
- Current research

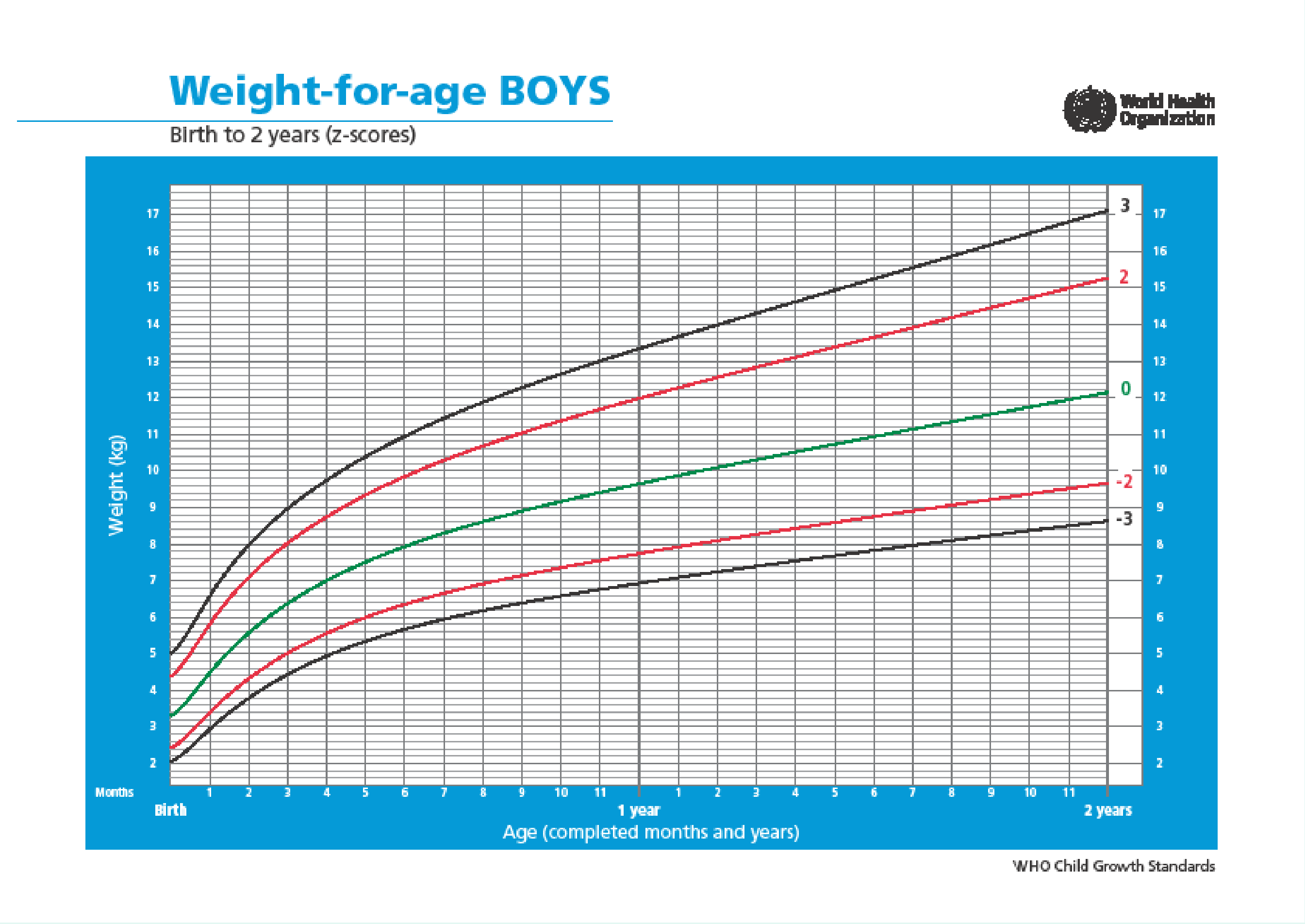
Measurement of growth

- Anthropometry
- Growth charts
  - Child Growth Foundation
  - WHO Growth standards (WHO Multi-centre growth study)
- Preterm growth charts and their limitations
- Fetal growth charts – customised growth charts (www.gestation.net)

WHO growth standard



WHO growth standard



Consequences of poor growth in utero

Barker

- Adult disease has fetal origins
- Size in early life is related to later health outcomes
- Impaired intrauterine growth and development result in coronary heart disease, hypertension and type 2 diabetes in later life so-called “metabolic syndrome”

Barker

- Evidence from longitudinal studies of 25,000 U.K men and women in which size at birth was related to occurrence of disease in middle age
- Small or disproportionate (thin or short) at birth had high cholesterol concentrations and abnormal glucose-insulin metabolism

Programming

- The process whereby a stimulus or insult at a sensitive or critical period of development has long term effects

Thrifty phenotype

- During critical period of fetal life exposure to adverse environment
- Compensatory survival responses develop that become permanent
- In the subsequent absence of adverse environment the responses become maladaptive leading to disease

IUGR in humans

- Cognitive / neurodevelopmental outcome
- Behavioural problems
- Cerebral palsy
- Imaging studies

Cognitive and neurodevelopmental outcomes after IUGR

- IUGR infants at 7 years, poor neurodevelopmental outcome associated with poor antenatal head growth. Strauss RS, J Pediatr. 1998 Jul;133(1):67-72
- Higher incidence of school failure, inattentiveness, low verbal IQ compared to AGA controls. Hollo O, Arch Pediatr Adolesc Med. 2002 Feb;156(2):179-87
- Perinatal complications better indicators than size at birth. Gutbrod T, Arch Dis Child Fetal Neonatal Ed. 2000 May;82(3):F208-14
- Low developmental scores and behavioural problems more likely earlier the slowing of head growth antenatally. Parkinson CE, Dev Med Child Neurol. 1981 Feb;23(1):41-50

IUGR and behavioural outcome

- Increased incidence of ADHD in SGA. Hawdon, Dev Med Child Neurol. 1990 Nov;32(11):943-53
- Increased incidence of developmental and behavioural problems. Kjellmer I, Acta Paediatr Suppl. 1997 Jul;422:83-4 (animal work)

IUGR and neuropsychological outcomes

- Prospective study
- Evaluated at 9 years, compared with AGA children matched for gestational age and multiple socioeconomic factors
- IUGR children had lower intelligence quotient and difficulties in creative problem solving, attention and executive functions (frontal lobe functions)
  - Geva R, Pediatrics. 2006 Jul;118(1):91-100

IUGR and Cerebral Palsy

- Prospective study, increase in spastic diplegia in SGA compared with AGA. Ellenberg JH, Am J Dis Child. 1979 Oct;133(10):1044-8
- Retrospective study, odds ratio for CP 6.48 if birth weight <3rd centile and 3.81 if < 10th centile. Blair, Am J Obstet Gynecol. 1990 Jan;162(1): 229-37
- In preterm infants effects of prematurity overwhelm those of IUGR. Drummond PM, Paediatr Perinat Epidemiol. 2002 Apr;16(2): 172-80

Imaging studies – IUGR and preterm

- Volumetric MRI
  - Reduction in cerebral cortical grey matter at two weeks and at term.
- Diffusion Weighted Imaging
  - Diffusion tensor analysis to assess effect on microstructural development of brain
- Metabolic: Proton MRS
  - Energy supply mechanisms altered in brain.

Sizonenko, Mol Cell Endocrinol. 2006 Jul 25;254-255:163-71

Small for gestational age infant

- Abnormal metabolism detected shortly after birth
- Decreased insulin sensitivity in early childhood
- Those infants who show catch up growth more insulin resistant than those who do not

Consequences of poor growth ex utero

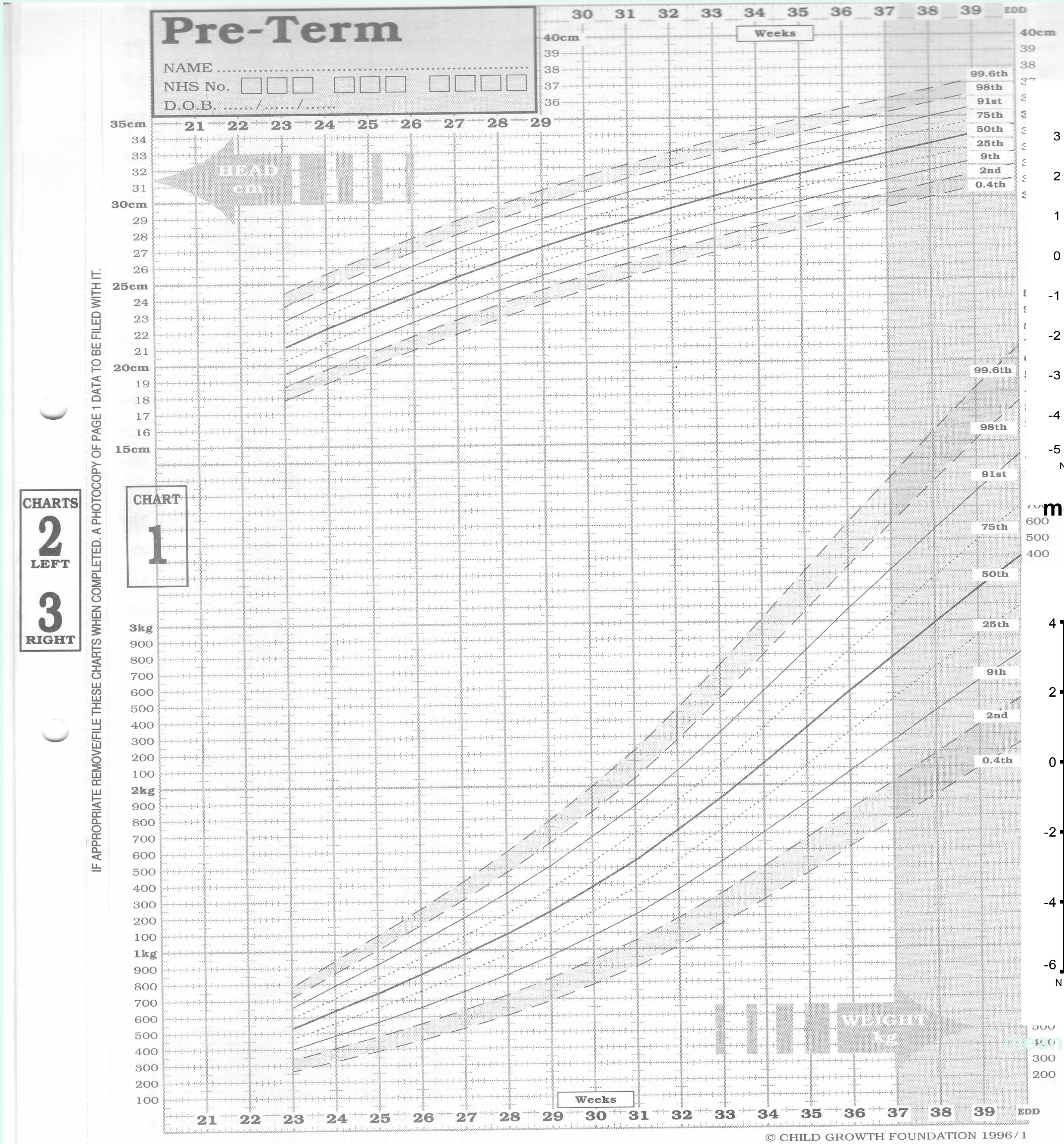
Consequences of poor growth

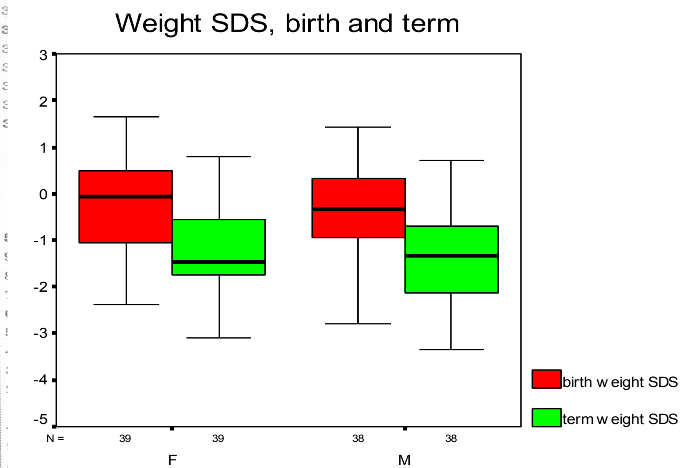
- Preterm infants who grow poorly have adverse neurodevelopmental outcomes
- At 2 years infants who remained below the 10th centile for weight had poorest neurodevelepmental outcomes (Latal-Hajnal)
- SGA infants who showed catch up growth had better outcomes than those who did not

Consequences of poor growth

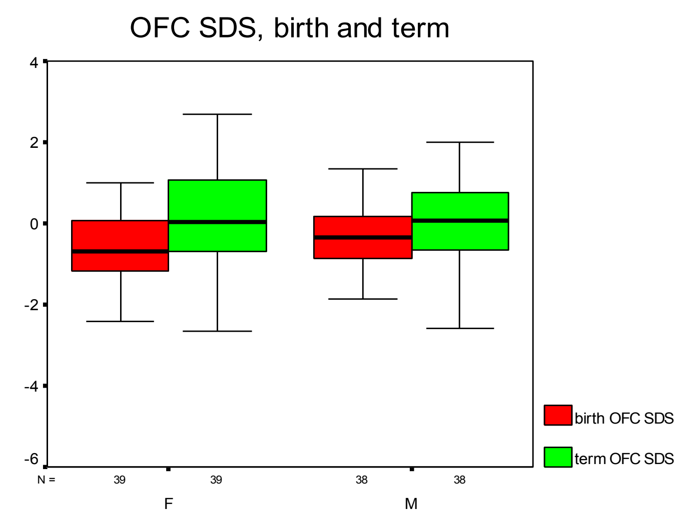
- Higher rate of cerebral palsy in infants with poor growth (Latal-Hajnal, Astbury)
- At 7 years of age boys with short stature associated with poor motor and cognitive performance (Cooke)

Present experience





mean difference 1.01, 95% CI 0.76, 1.27, p<0.001



mean difference -0.49, 95% CI -0.81, -0.18, p=0.003

Cockerill, Uthaya, Doré, Modi
Arch Dis Child 2006

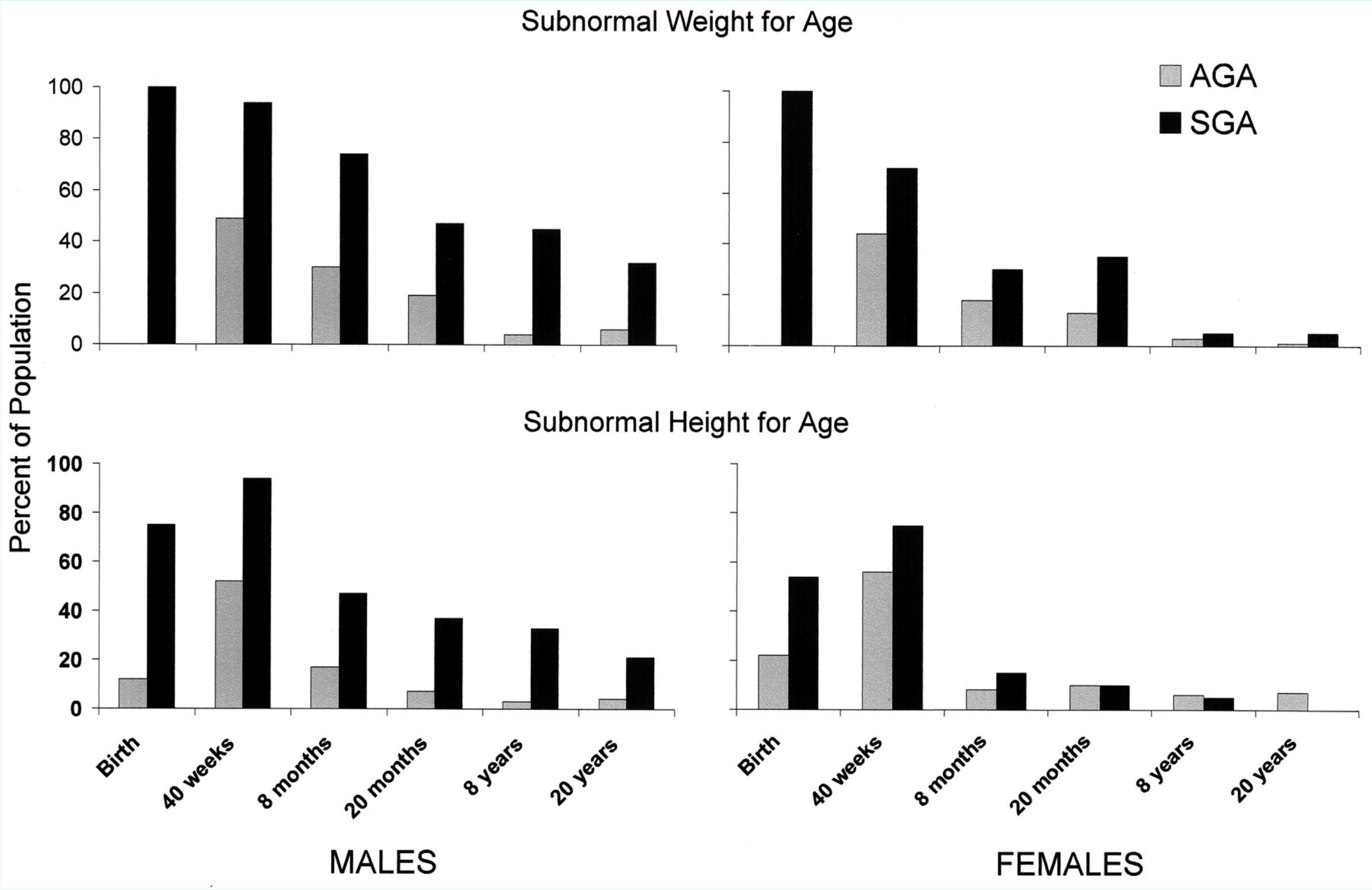
Early growth outcomes in preterm infants

- Preterm infants show growth failure postnatally (Ehrenkranz, O’Shea, Wood, Finnstrom, Bucher, O’Callaghan, Daily)
- Some catch up between discharge and 2 years

Long term growth outcomes in preterm infants

- Catch up in adolescence and later (Lucas, Niklasson, Cooke, Hirata, Doyle, Saigal)
- Tendency of weight catch up over height catch up

Fig 2. Percentage of VLBW infants born AGA or SGA (less than -2 SD) with subnormal (less than -2 SD) weight or height for age at birth, 40 weeks, 8 months, 20 months, and 8 years corrected age and at 20 years postnatal age



Hack, M. et al. Pediatrics 2003;112:e30-e38

PEDIATRICS

Consequences of rapid growth

Accelerated growth

- Insulin resistance
- Hypertension
- Obesity
- Coronary vascular disease
- Reduced longevity
- Dyslipidaemia

Consequences of rapid growth

- Animal studies demonstrate abnormal glucose tolerance, high blood pressure and reduced longevity following rapid growth during critical periods

Table 1 **Dietary factors and lifespan of male mice**

Group	*Pregnancy diet (% protein)*	*Lactation diet (% protein)*	*Weaning diet*	*Average age at death (days)*
Normal chow	20	20	Chow	765 ± 22
Normal cafeteria	20	20	Cafeteria	715 ± 21
Catch-up chow	8	20	Chow	568 ± 36
Catch-up cafeteria	8	20	Cafeteria	517 ± 35
Postnatal low-protein chow	20	8	Chow	814 ± 25
Postnatal low-protein cafeteria	20	8	Cafeteria	807 ± 28

The different dietary regimes are summarized in the first three columns ($n = 24$ mice per group). Lifespans are expressed as mean ± standard error and were analysed by two-way analysis of variance followed by Duncan's post-hoc testing where appropriate. Effect of early diet: $P < 0.001$; effect of obesity, $P < 0.01$.

Ozanne & Hales, Nature 2004; 427:411-2

Consequences of rapid growth

- Finnish cohort – highest death rates from coronary artery disease in boys who were thin at birth but showed rapid catch up in weight (Erikkson)
- British cohort – rapid increase in weight between birth and 5 years associated with high blood pressure in adulthood (Law)

OPEN ACCESS

Systematic review and meta-analyses of risk factors for childhood overweight identifiable during infancy

Stephen Franklin Weng,[1] Sarah A Redsell,[2] Judy A Swift,[3] Min Yang,[4] Cristine P Glazebrook[5]

▸ Additional appendices are published online only. To view these files please visit the journal online (http://dx.doi.org/10.1136/archdischild-2012-302263).

[1]Division of Epidemiology and Public Health, School of Community Health Sciences, University of Nottingham, Nottingham, UK
[2]School of Nursing, Midwifery and Physiotherapy, University of Nottingham, Queen's Medical Centre, Nottingham, UK
[3]Division of Nutritional Sciences, University of Nottingham, Sutton Bonington Campus, Loughborough, UK
[4]Nottingham Clinical Trials Unit, Nottingham Health Science Partners, Queen's Medical Centre, Nottingham, UK
[5]Division of Psychiatry, Institute of Mental Health, University of Nottingham Innovation Park, Nottingham, UK

Correspondence to
Professor Cris Glazebrook, Division of Psychiatry, Institute of Mental Health, University of Nottingham Innovation Park, Nottingham NG7 2TU, UK; Cris.Glazebrook@nottingham.ac.uk

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ABSTRACT

Objective To determine risk factors for childhood overweight that can be identified during the first year of life to facilitate early identification and targeted intervention.

Design Systematic review and meta-analysis.

Search strategy Electronic database search of MEDLINE, EMBASE, PubMed and CAB Abstracts.

Eligibility criteria Prospective observational studies following up children from birth for at least 2 years.

Results Thirty prospective studies were identified. Significant and strong independent associations with childhood overweight were identified for maternal pre-pregnancy overweight, high infant birth weight and rapid weight gain during the first year of life. Meta-analysis comparing breastfed with non-breastfed infants found a 15% decrease (95% CI 0.74 to 0.99; I^2=73.3%; n=10) in the odds of childhood overweight. For children of mothers smoking during pregnancy there was a 47% increase (95% CI 1.26 to 1.73; I^2=47.5%; n=7) in the odds of childhood overweight. There was some evidence associating early introduction of solid foods and childhood overweight. There was conflicting evidence for duration of breastfeeding, socioeconomic status at birth, parity and maternal marital status at birth. No association with childhood overweight was found for maternal age or education at birth, maternal depression or infant ethnicity. There was inconclusive evidence for delivery type, gestational weight gain, maternal postpartum weight loss and 'fussy' infant temperament due to the limited number of studies.

Conclusions Several risk factors for both overweight and obesity in childhood are identifiable during infancy. Future research needs to focus on whether it is clinically feasible for healthcare professionals to identify infants at greatest risk.

What is already known on this topic

- There is evidence that overweight or obesity during childhood increases the risk of adult obesity.
- Previous reviews have identified rapid weight gain, high birth weight and maternal smoking in pregnancy as important risk factors for childhood obesity.

What this study adds

- Early rapid weight gain, high birth weight, maternal pre-pregnancy overweight and maternal smoking in pregnancy increase the likelihood of childhood obesity and overweight.
- Breastfeeding and the late introduction of solid foods is moderately protective against childhood overweight.
- Other maternal and infant factors were not associated with childhood overweight.

INTRODUCTION

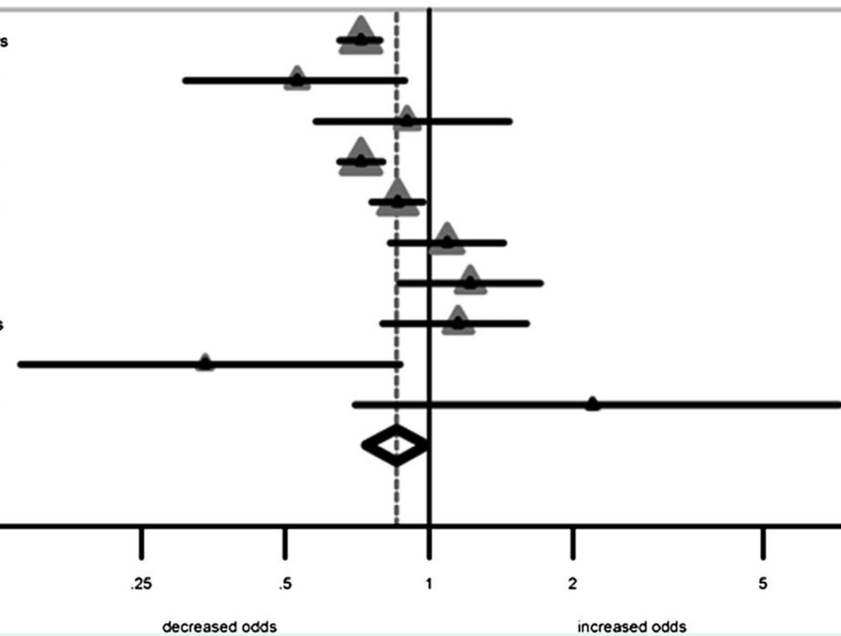
In the UK in 2008, 31% of boys and 29% of girls

obesity[6] and to date interventions have focused on nutritional modification through supporting parents regarding, for example, healthy eating and breastfeeding.[7–10] Both the Canadian Paediatric Society[11] and the American Academy of Pediatrics[12] advocate that all typically developing children aged 2 years and older should have their growth monitored to screen for under-development, wasting, overweight and obesity. However, in many countries, early life intervention is not routine clinical practice. Although in the USA, the Institute of Medicine has recently introduced early childhood

Pooled adjusted OR for childhood overweight from random effects meta-analysis of 10 studies:26 27 33 36 39 46 52–55: ever breastfed compared with never breastfed.

Author	PubYr	Country	Sex	N	Follow-up	ES (95% CI)	% Weight
Armstrong et al.	2003	Scotland	Both	32,200	3.5 yrs	0.72 (0.65 to 0.79)	18.17
Bergmann et al.	2006	Germany	Both	480	6 yrs	0.53 (0.31 to 0.89)	5.52
Burke et al.	2005	Australia	Both	1,430	8 yrs	0.90 (0.58 to 1.47)	6.58
Grummer-Strawn and Mei	2004	USA	Both	12,587	4 yrs	0.72 (0.65 to 0.80)	17.97
Hawkins et al.	2009	UK	Both	13,172	3 yrs	0.86 (0.76 to 0.97)	17.37
Kwok et al.	2009	Hong Kong	Both	7,026	7 yrs	1.09 (0.83 to 1.43)	11.72
Reilly et al.	2005	UK	Both	6,651	7 yr	1.22 (0.87 to 1.71)	9.60
Shields et al.	2006	Australia	Both	3,698	14 yrs	1.15 (0.80 to 1.60)	9.35
Taveras et al.	2006	USA	Both	988	3 yrs	0.34 (0.14 to 0.87)	2.26
Weyermann et al.	2006	Germany	Both	855	2 yrs	2.20 (0.70 to 7.20)	1.45
Overall (I-squared = 73.0%, p = 0.000)						0.85 (0.74 to 0.99)	100.00

NOTE: Weights are from random effects analysis



Weng S F et al. Arch Dis Child 2012;97:1019-1026

Difference between intrauterine (fetal) and neonatal weights

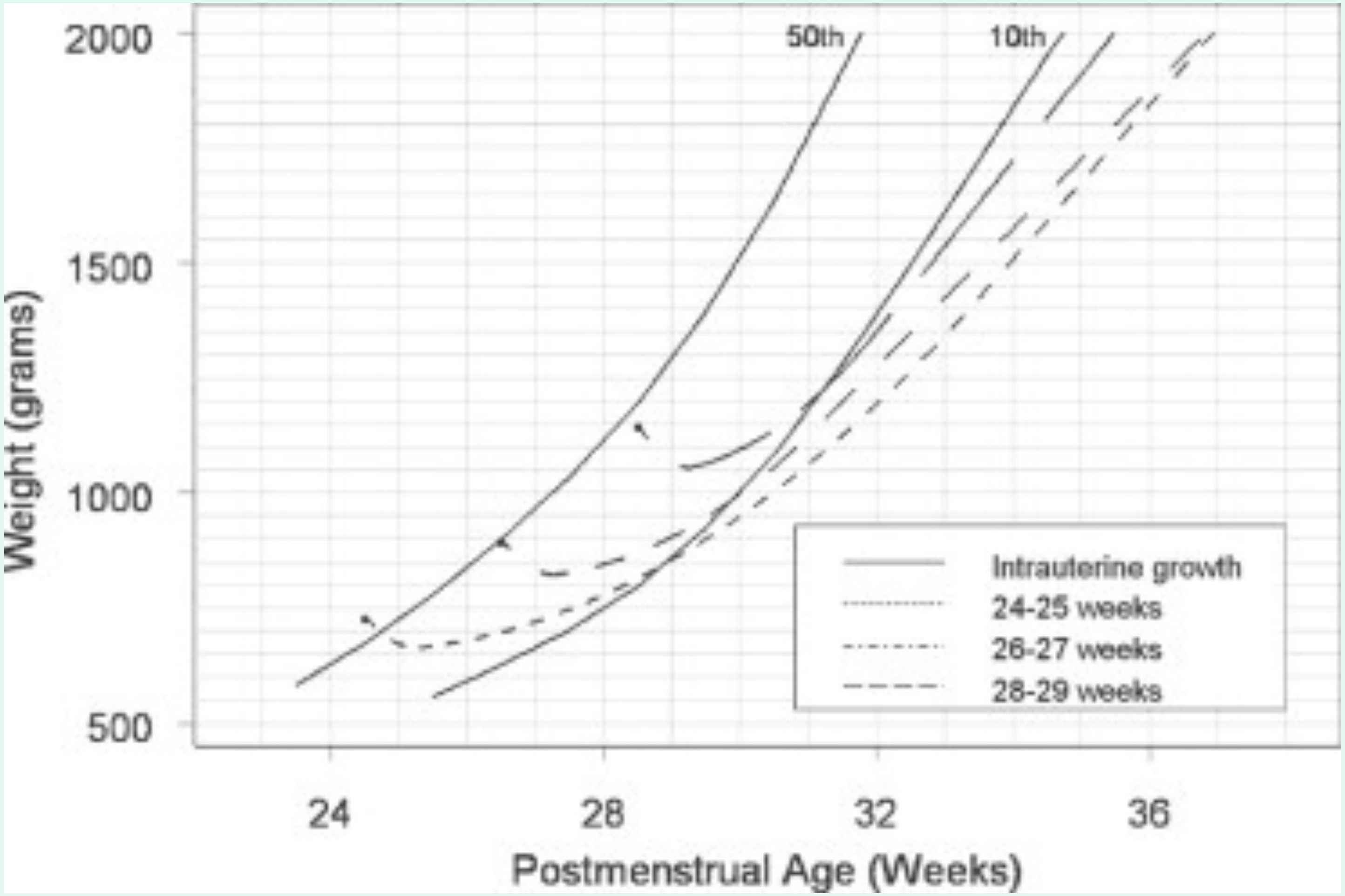
Table I. Birth weight 3rd and 10th percentiles and differences between fetal (Hadlock et al[13]) and neonatal (Arbuckle et al[8]) standards

	Birth weight (g)									
	3rd Percentile					*10th Percentile*				
	Neonatal standard			*Difference between fetal and neonatal standards*		*Neonatal standard*			*Difference between fetal and neonatal standards*	
Gestational age (wk)	*Female*	*Male*	*Fetal standard*	*Female*	*Male*	*Female*	*Male*	*Fetal standard*	*Female*	*Male*
25	500	500	589	89	89	600	620	652	52	32
26	540	570	685	145	115	650	710	758	108	48
27	580	650	791	211	141	750	790	876	126	86
28	680	680	908	228	228	800	880	1004	204	124
29	730	850	1034	304	184	910	1000	1145	235	145
30	840	960	1169	329	209	1030	1150	1294	264	144
31	970	1020	1313	343	293	1180	1250	1453	273	203
32	1100	1220	1465	365	245	1350	1460	1621	271	161
33	1300	1360	1622	322	262	1560	1630	1794	234	164
34	1440	1550	1783	343	233	1770	1850	1973	203	123
35	1670	1790	1946	276	156	1970	2070	2154	184	84
36	1930	2010	2110	180	100	2210	2300	2335	125	35
37	2150	2240	2271	121	31	2430	2530	2513	83	–17
38	2380	2490	2427	47	–63	2640	2750	2686	46	–64
39	2550	2650	2576	26	–74	2790	2910	2851	61	–59
40	2660	2770	2714	54	–56	2910	3030	3004	94	–26

A significant proportion of fetuses destined to deliver preterm do not reach their individual growth potential compared with those delivered at term

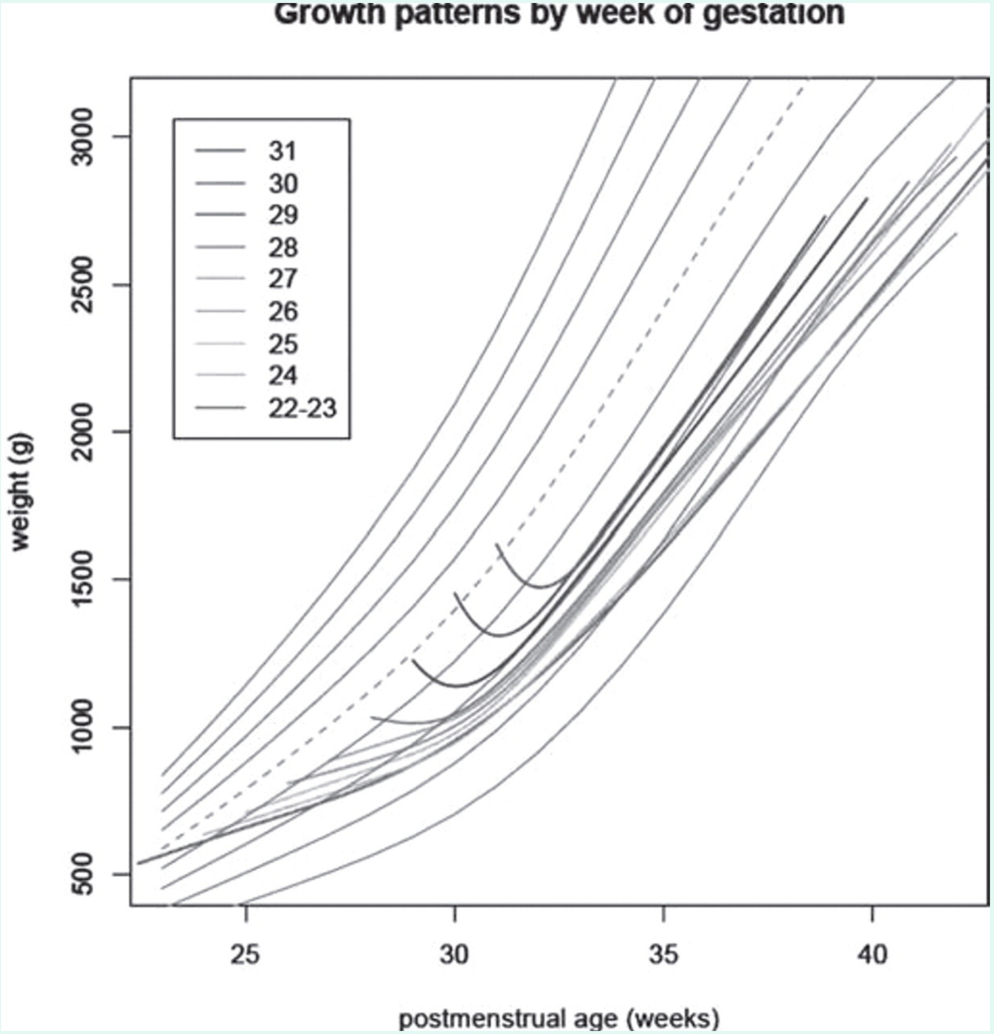
Bukowski et al, Am J Obs Gynecol 2001; 185:463-467

Not always!



Average body weight versus postmenstrual age in weeks for infants 24 to 29 weeks gestational age plotted with smoothed 10th and 50th percentile reference intrauterine growth curves. The infants are stratified by gestational age: 24 to 25 weeks (short dashes), 26 to 27 weeks (medium dashes), and 28 to 29 weeks (long dashes). Ehrenkranz et al.

Pattern of postnatal weight gain by week of gestation.



Cole T J et al. Arch Dis Child 2011;96:A3-A4

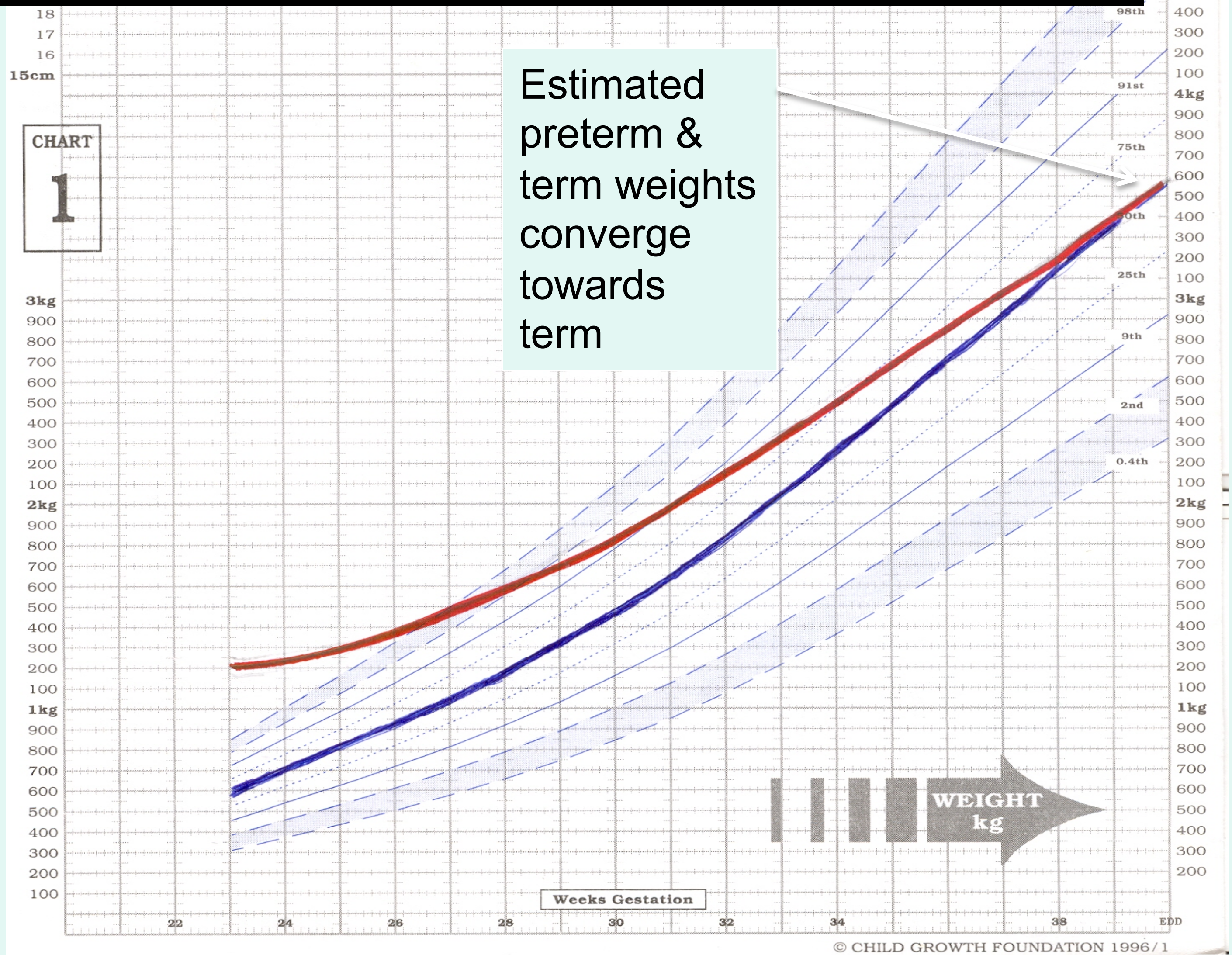
What growth rate should we aim for?

- As a group preterm infants more likely to be born <50th centile of normal predicted fetal growth
  - *Zeitlin et al Br J Obs Gyn 2000*
  - *Lackman et al Am J Obs Gyn 2001*
  - *Bukowski et al Am J Obs Gyn 2001*
  - *Bertino et al ADC F&N 2007*
- Approaching term, estimated preterm and term birth weights converge.

Growth in-utero

Fetal growth of a baby delivered at term = (red line)

baby destined to deliver preterm = (blue line)



Limitations of using growth as an outcome of nutrition


Sc 5
TSE/M
SI 11
H
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Sc 5
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SI 12
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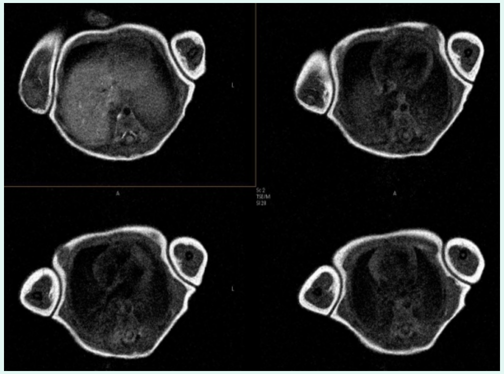
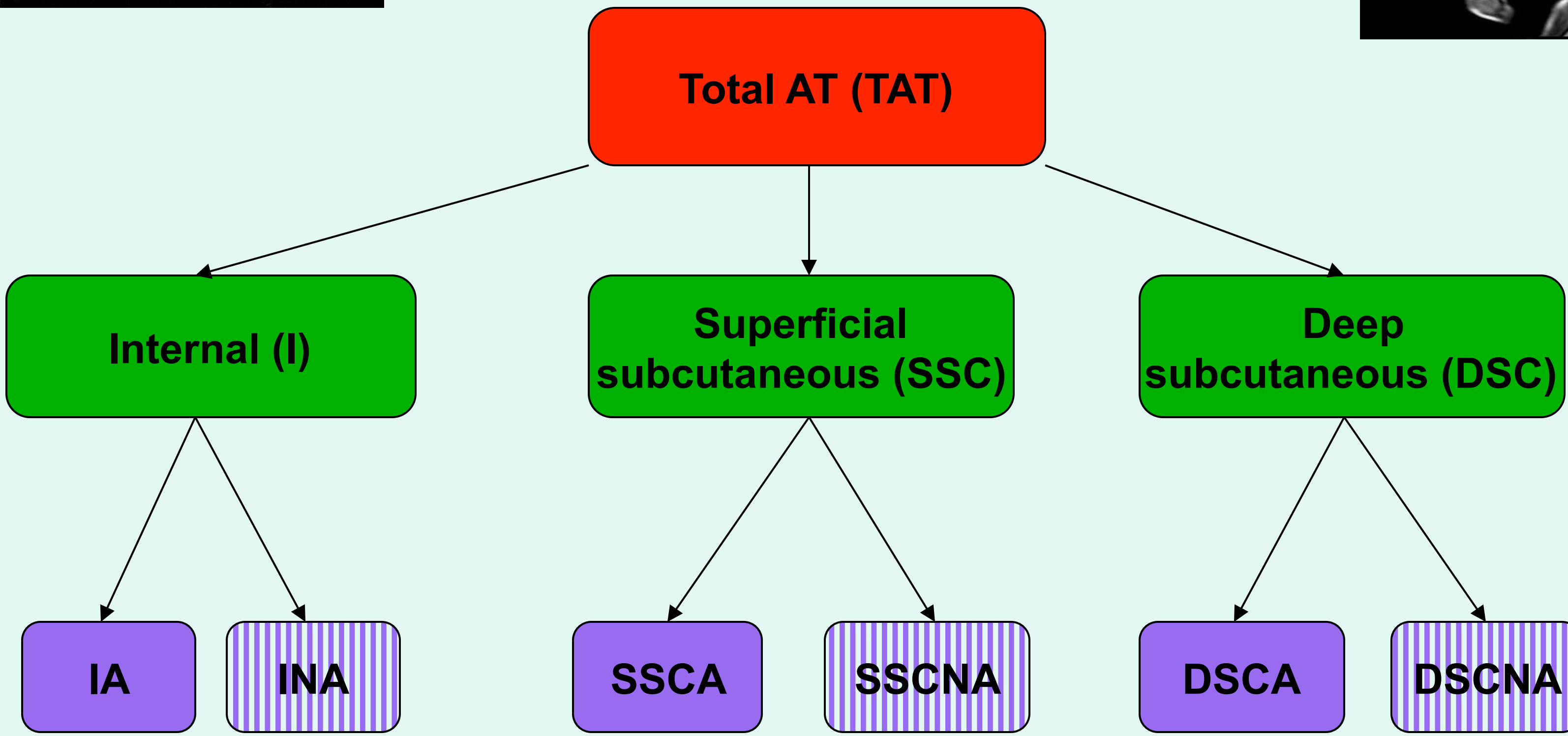
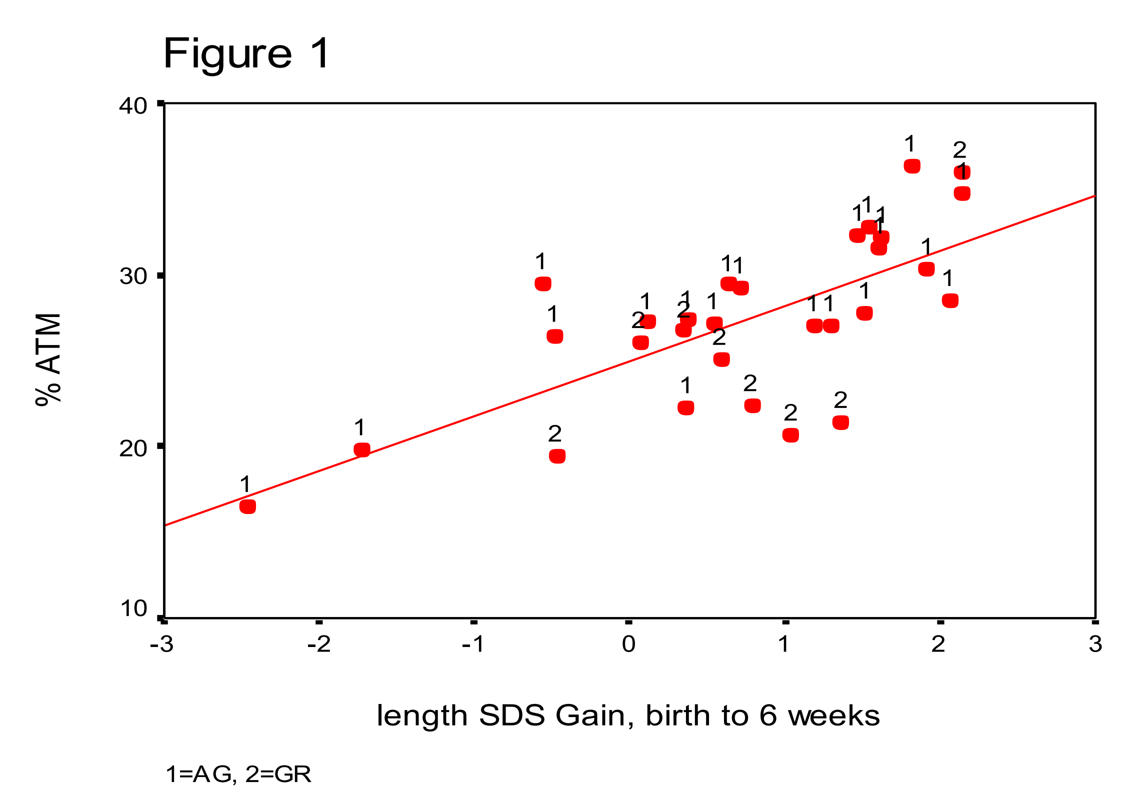


WHOLE BODY MRI CLASSIFICATION OF ADIPOSE TISSUE DEPOTS





r = 0.71

adjusted R2 = 0.49

p<0.001

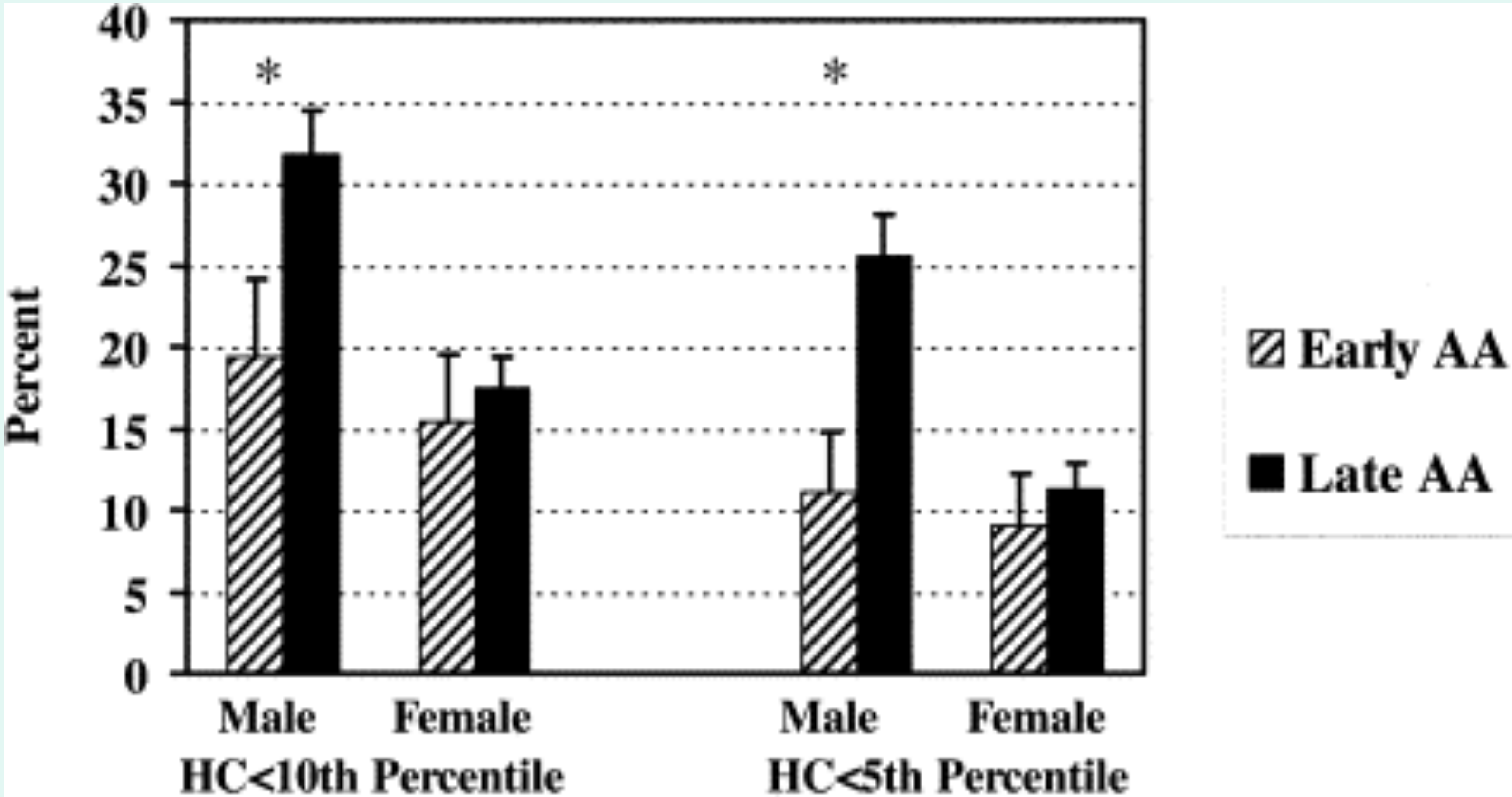
Accelerated growth alters body composition and increases whole body adiposity

Modi et al, Pediatr Res. 2006; 60:345-8

Early provision of parenteral amino acids in extremely low birth weight infants: relation to growth and neurodevelopmental outcome

Poindexter et al, J Pediatr 2006

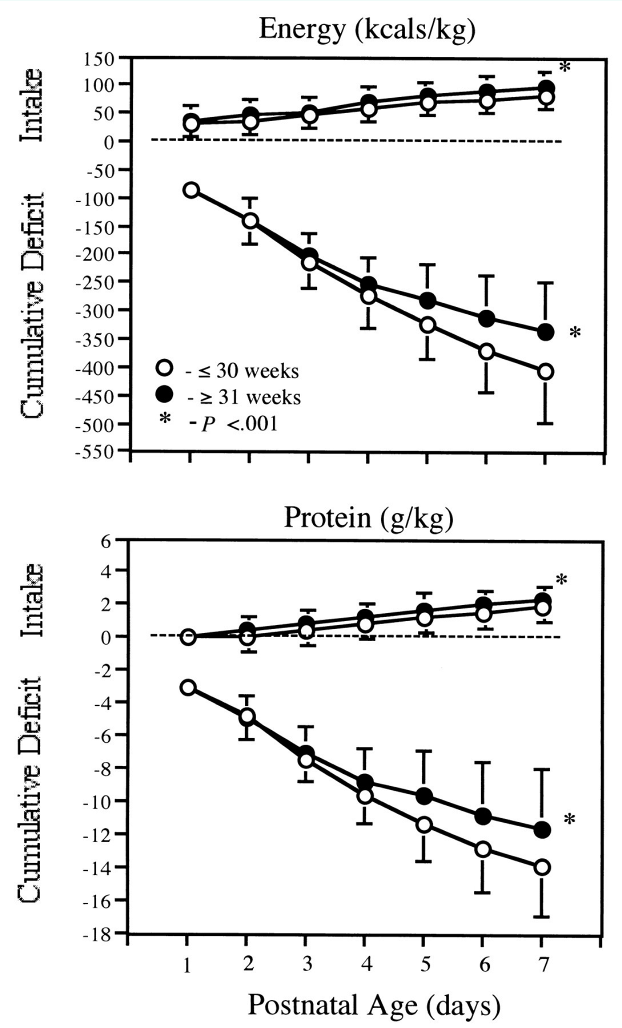
- Secondary analysis of 1018 infants enrolled in a randomized, clinical trial of glutamine supplementation
- Determined if early provision of parenteral amino acids is associated with better growth and neurodevelopmental outcomes
- Infants were stratified by whether they were provided ≥3 g/kg per day of AA at ≤5 days of life (early; n = 182) or not (late; n = 836).



Comparison of head circumference at 18 months' CA according to sex and study group; *$P < .05$.

Poindexter et al, J Pediatr 2006; 148:300-

Nutrient intake and cumulative nutrient deficit during the first weeks of life.



Embleton N E et al. Pediatrics 2001;107:270-273

Amino acid regimen and intravenous lipid composition in preterm parenteral nutrition: a randomised double blind controlled trial.

Nutritional **E**valuation and **O**ptimisation in **N**eonates

NEON

Background

- Current nutritional management results in substantial cumulative protein / energy deficits
- Current parenteral nutrition practices are variable and do not meet the recommended nutritional intake for macronurients
- Embleton has shown that by end of the first week cumulative energy and protein deficits in infants < 30 weeks gestational age are 400 kCal/kg and 14 g/kg

Background

Preterm infants:

- are predisposed to long term metabolic ill health
- added cardiovascular risk factors when they reach adulthood.

This may be mediated by early diet

Background

- We have shown aberrant adipose tissue partitioning, increased intrahepatocellular lipid content, **reduced** insulin sensitivity and higher blood pressure in preterm infants by the age of term compared to healthy term infants
- Our data suggest that even as early as term equivalent preterm infants demonstrate the manifestations of cardiovascular risk factors.

Aims

To confirm the safety and demonstrate the efficacy of immediate introduction of RDI of amino acids and SMOF lipid to decrease the deficit in lean body mass and IHCL respectively, and to improve total and regional brain growth in preterm infants at term age.

IHCL: Intrahepatocellular lipid

SMOF: Soy bean, Medium chain triglycerides, Olive oil, Fish oil

Study design

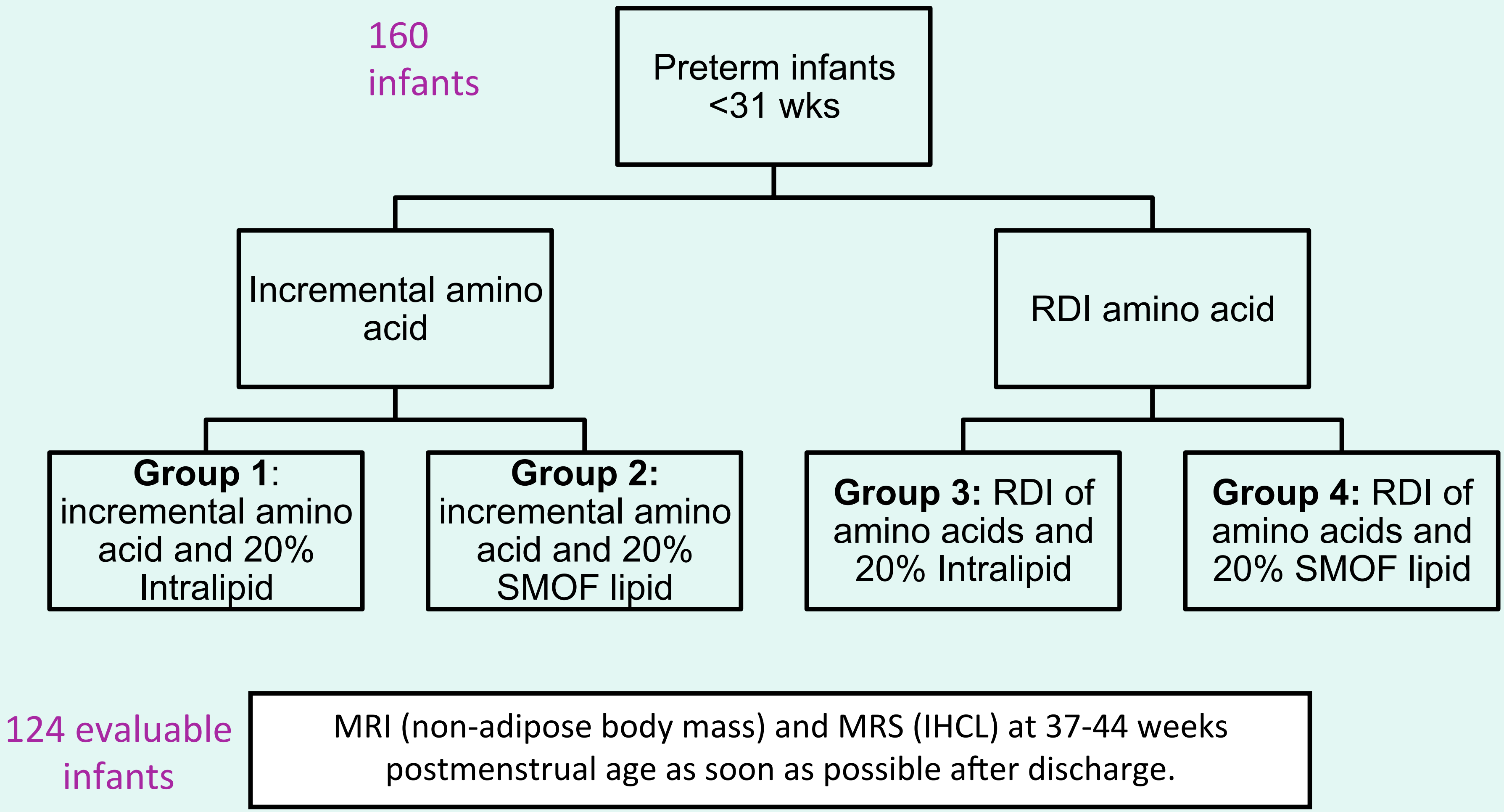
Design

- Randomised controlled
- Double-blind
- Multicentre: 3-6 London centres
- 160 patients

Randomisation

- 2x2 factorial
- Stratified by gestational age, weight (<500g, 500-1000g, >1000g), (23-26 wks and 27-31 wks) and centre
- Telephone randomisation by Interactive Voice Recognition System

Study flow chart



Primary outcomes

- Non-adipose body mass by whole body Magnetic Resonance Imaging
- Intrahepatocellular lipid content (IHCL) by hepatic Magnetic Resonance Spectroscopy
  - MR scans will be carried out at the Robert Steiner MR unit at the Hammersmith Hospital in a dedicated research scanner

Secondary outcomes

- Quantity and distribution of adipose tissue measured using whole body MRI
- Anthropometry
- Brain MRI (total and regional brain volumes)
- Metabolic index of insulin sensitivity at term or near term age equivalent (QUICKI) using fasting serum glucose and insulin
- Serum lipids

Optimal growth rate unknown

Evaluation of body composition in relation to nutritional regimens

Rigorous follow-up assessing long-term outcomes

The Seven Ages of Woman

(Hans Baldung Grien Leipzig Museum der Bildenden Künste)