The Liggins Institute
An Institute of The University of Auckland

The Long Term Legacy of Early Life Nutrition

Changing the way we think about public health interventions for non-communicable diseases

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Gravida
NATIONAL CENTRE FOR GROWTH AND DEVELOPMENT

Lakes DHB

Outline

- Early life nutrition
  - What does nutrition mean to the developing embryo and fetus?
  - Maternal nutrition during critical periods of gestation
  - Postnatal nutrition and growth

What does this have to do with later health?

Background

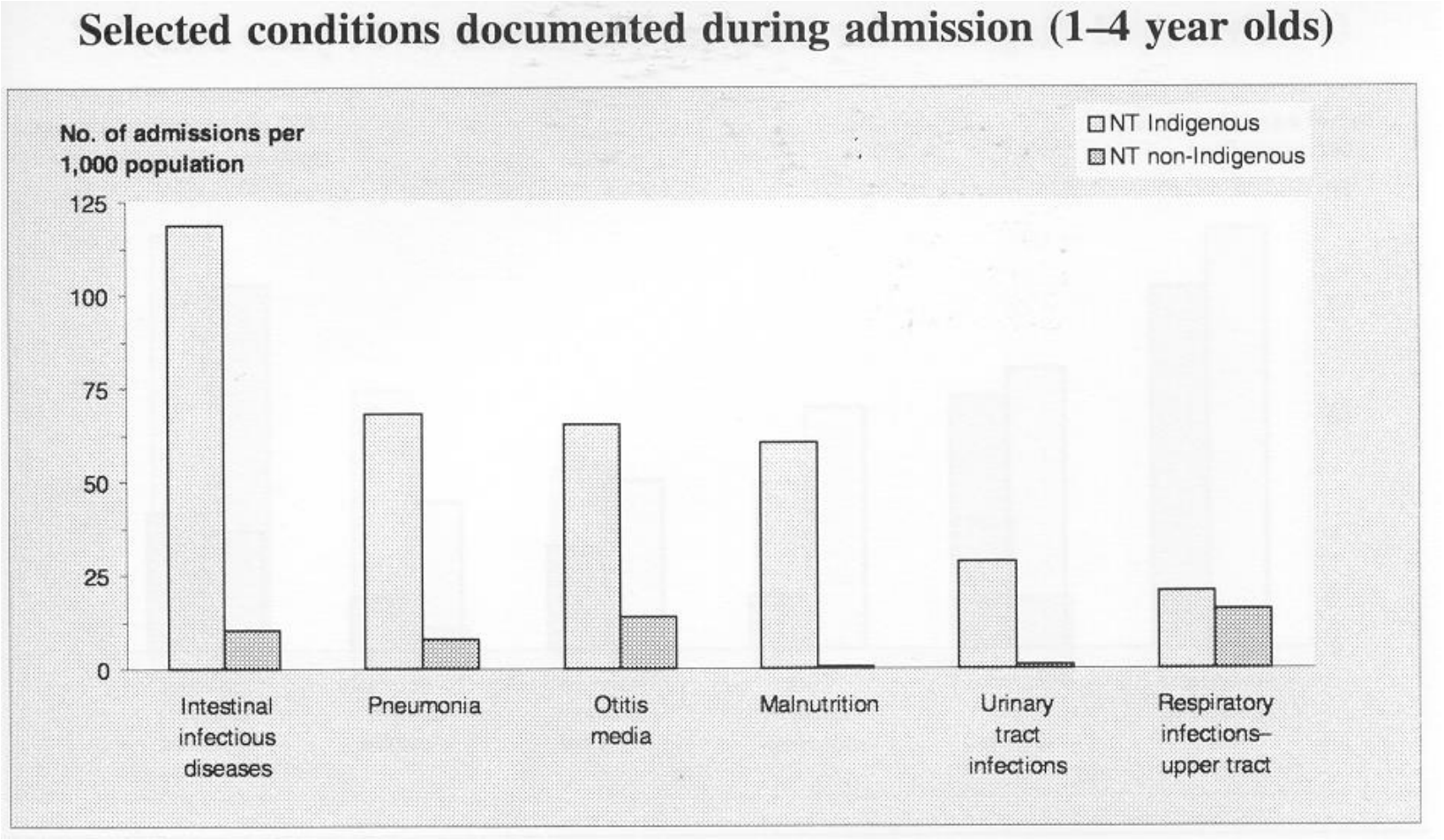
- 1980s – Barker ‘Fetal origins hypothesis’
  - association between low weight at birth and adverse later health outcomes (mostly metabolic and CV)
  - gender differences in outcomes
  - worse health outcomes if low birth weight was followed by rapid weight gain in later childhood

- Nutritional insult during different periods of gestation can affect fetal and postnatal physiology, and later disease risk, independently of birth size.

- ‘Developmental origins of health and disease’ (DOHaD)

Background

Malnutrition in hospitalised children aged 1-4 years



Maternal anaemia during pregnancy

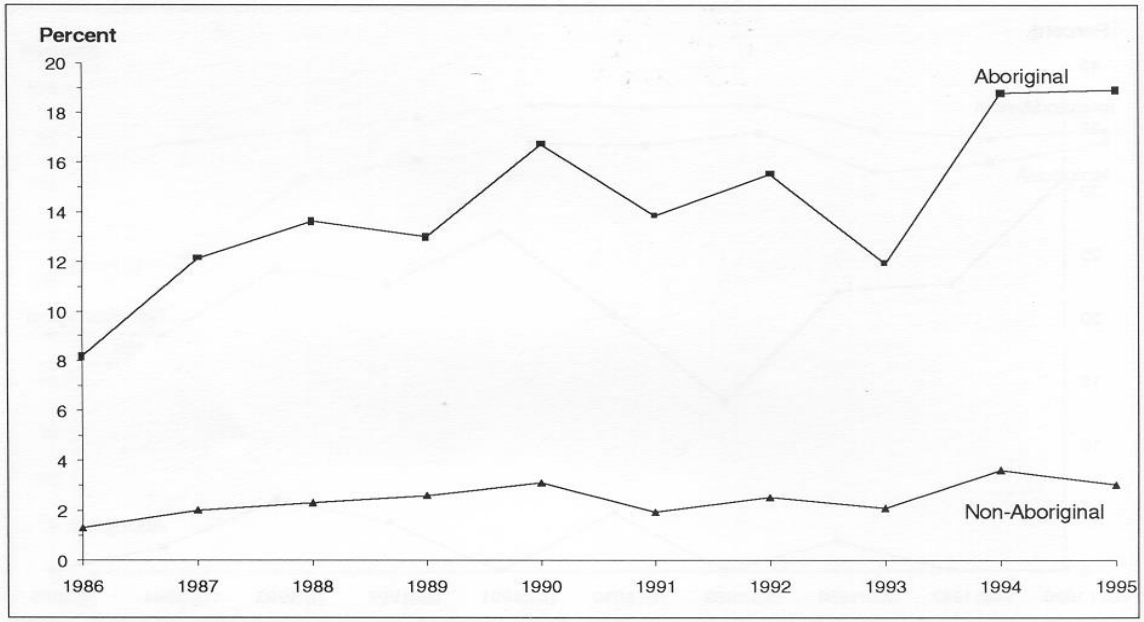
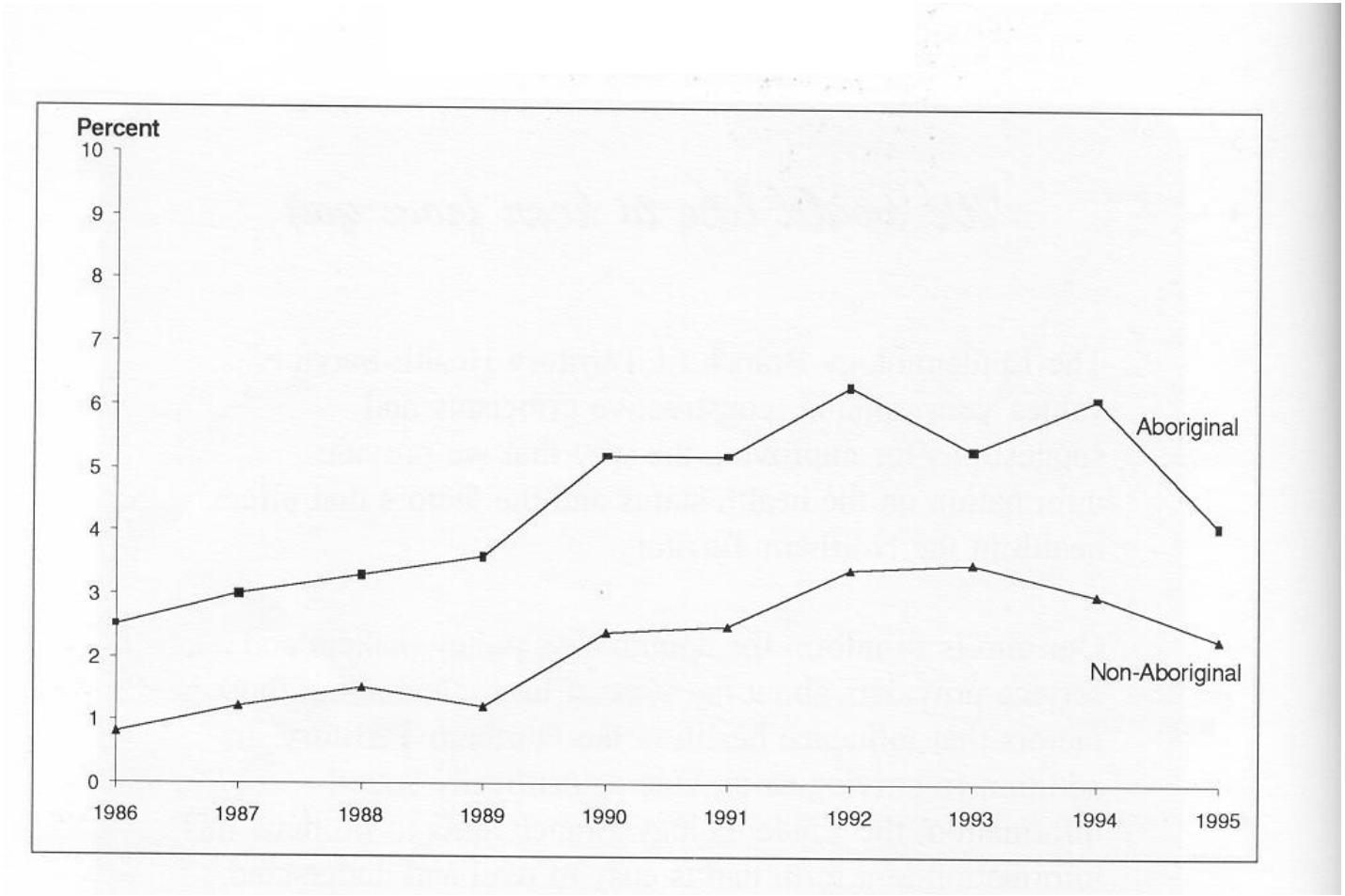


Table 13: Proportion of mothers who were diagnosed with anaemia during their pregnancy, NT, 1986–95

	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995
					Percent					
Aboriginal	8.2	12.1	13.6	13.0	16.7	13.8	15.5	11.9	18.8	18.9
Non-Aboriginal	1.3	2.0	2.3	2.6	3.1	1.9	2.5	2.1	3.6	3.0
Total	3.6	5.6	6.6	6.8	7.7	5.9	6.9	5.4	8.7	8.3

Gestational diabetes in women < 30years



Birth weight<2500g

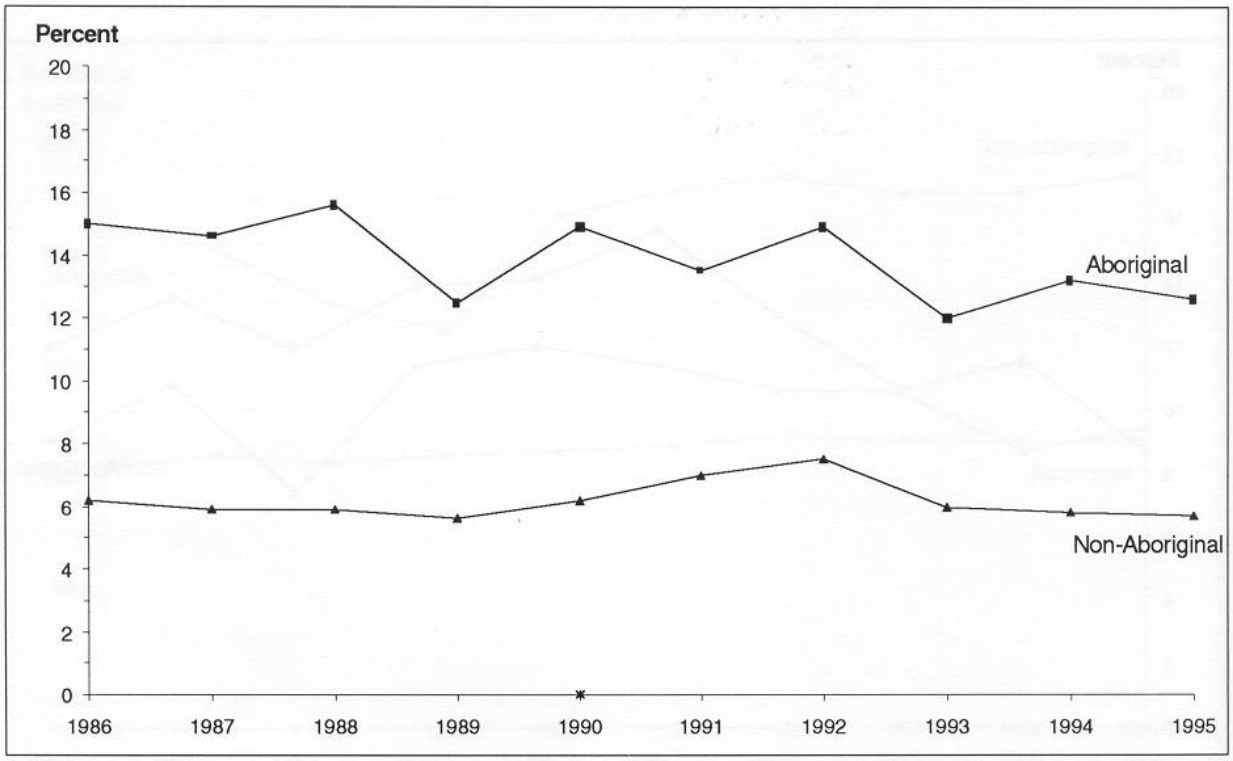


Table 27: Proportion of livebirths with birthweight of less than 2,500 grams, NT, 1986–95

Impact of nutrition

- Maternal nutritional deficiency
- Intrauterine growth retardation (IUGR), low birth weight
- Faltering growth in infancy and childhood
- Chronic disease in (young) adulthood
- Maternal diabetes, renal disease, CV disease

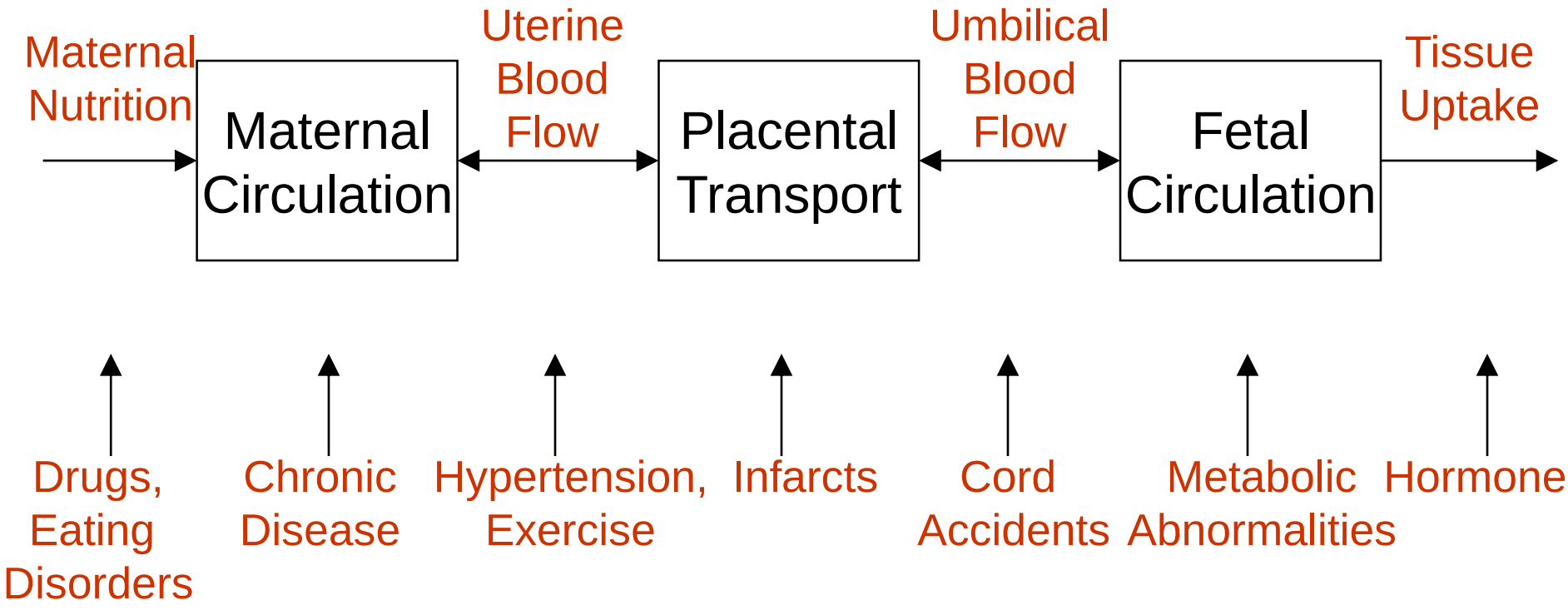
Outline

- The effect of intrauterine and early postnatal nutrition on later health
  - What does nutrition mean to the developing embryo and fetus?
    - Role of nutrition in development (and growth)
  - Maternal nutrition during critical periods of gestation
    - Periconceptional undernutrition
  - Postnatal nutrition and growth
    - Relationship between intake, growth and metabolism

What do we mean by intrauterine nutrition?

- (Ovum – exposed to maternal nutritional influences before fertilisation)
- Intrauterine nutrition is dependent on maternal nutrition
- Embryo – bathed in nutrient and hormone rich fluid
  - both cell division (growth) and cell differentiation (organ development and function) must be supported
  - The nutrients the embryo ‘sees’ determine both these functions
- Fetus – amniotic fluid plus nutrient supply via placenta to fetal circulation

‘Fetal supply line’



JEH

Fetal nutrition

- Glucose is a key nutrient for fetal growth
- Amino acids (aa) important in
  - physiological maturation of fetal organ systems - brain, liver, pancreas
  - protein accretion (building lean mass) and regulation of protein turnover

- Hormones and growth factors regulate nutrient use
  - IGF2 - embryonic growth; IGF1 - fetal growth

- *The nutrients themselves regulate the hormones and the genes that code for them – for example, both IGF 1 & 2 are regulated by glucose supply, and genes involving amino acid synthesis induced by aa depletion*

Nutrition is a powerful moderator of epigenetic modifications

- Early life is a period of developmental ‘plasticity’
- Nutrients are affecting nutrient use by regulation of hormones and their receptors
- This is achieved by altering the expression of genes involved in organ growth and function
- ‘setting up ‘ phase – developmental changes in response to the nutritional environment will continue to occur throughout development into postnatal life and beyond

Nutrition is a powerful modulator of epigenetic processes

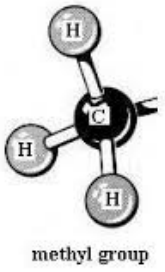
Epigenetic control of fetal gene expression:

Each differentiated cell type has its own epigenetic signature, which reflects its genotype, developmental history, and environmental influences, and is ultimately reflected in the phenotype of the cell and organism.

Nafee TM, et al

Folate in DNA synthesis and epigenetics

- Folate essential cofactor in enzyme reactions involved in DNA synthesis and methylation (‘methyl donor’)

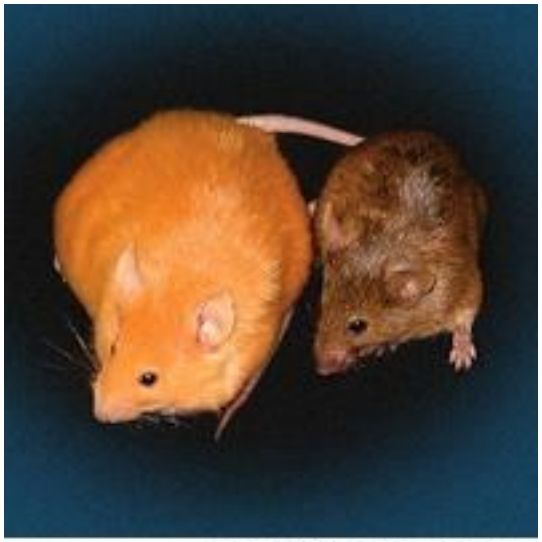


- Methylation one way in which genes are switched on and off, thereby altering gene expression (even though DNA remains the same)

Agouti mouse model

- The agouti mouse model provides a demonstration of the importance of methyl donors, including folate, in DNA methylation and embryonic development

- Dietary supplementation with methyl donors of agouti dams during pregnancy causes the agouti gene to be silenced by methylation, altering the coat colour of the offspring.



Randy Jirtle/Duke University

Maternal undernutrition

Outcomes of maternal undernutrition

- Pregravid weight and 3rd trimester weight gain have independent and cumulative effects on gestation length and pregnancy outcome (Siega-Riz et al)

- Dutch hunger winter
  - Early pregnancy – Early onset coronary heart disease (Painter), atherogenic lipid profiles (Roseboom), increased adiposity (Jackson), decreased insulin secretion (de Rooij)
  - Mid-late gestation – decreased glucose tolerance (Ravelli, 2000)

Why is the periconceptional period important?

- Is there any evidence that nutritional manipulations around the time of conception and in very early pregnancy make any difference to long term outcomes?

- IVF media
  - Altering nutrients resulted in different childhood growth
- Human observational studies
  - Hyperemesis
  - Gambia ‘hungry season’
  - Dutch hunger winter

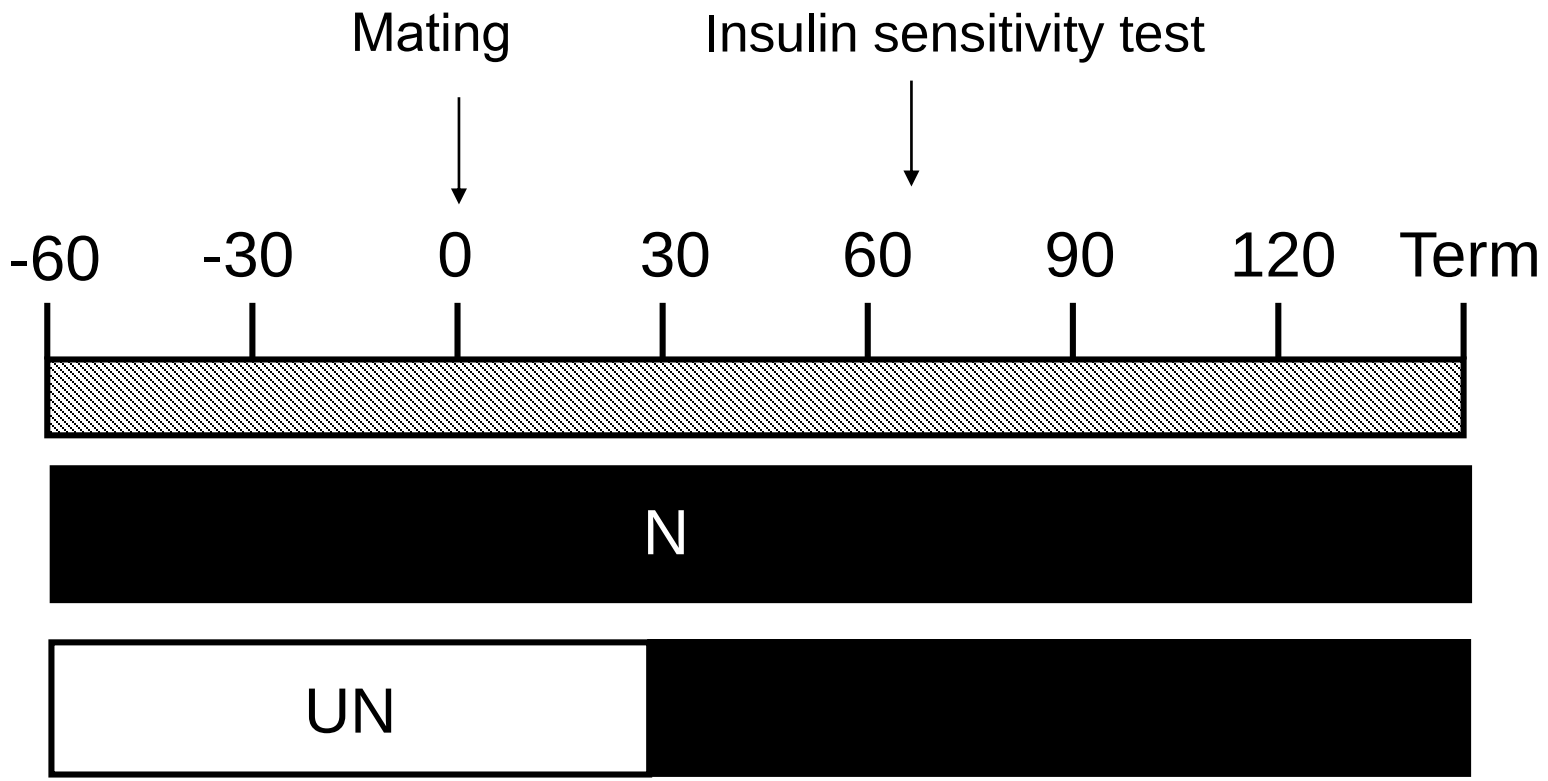
- Animal studies (experiments)

How does maternal undernutrition affect outcome?

- Disrupted maternal adaptation to pregnancy resulting in abnormal fetal environment beyond the period of undernutrition

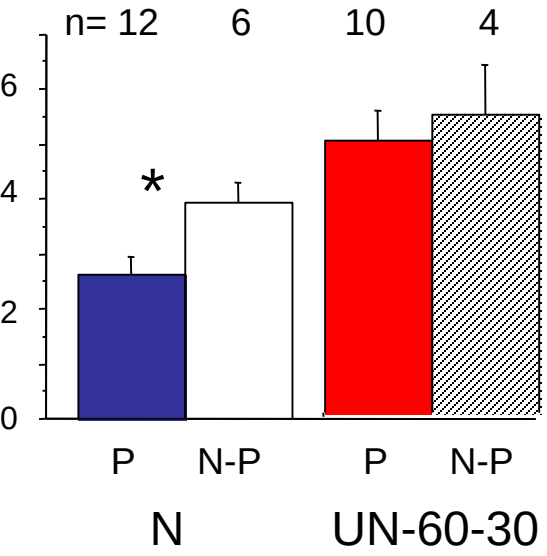
- Direct effect of maternal nutritional environment on oocyte, embryo and placental development

Maternal adaptation to pregnancy
Periconceptional undernutrition of ewes

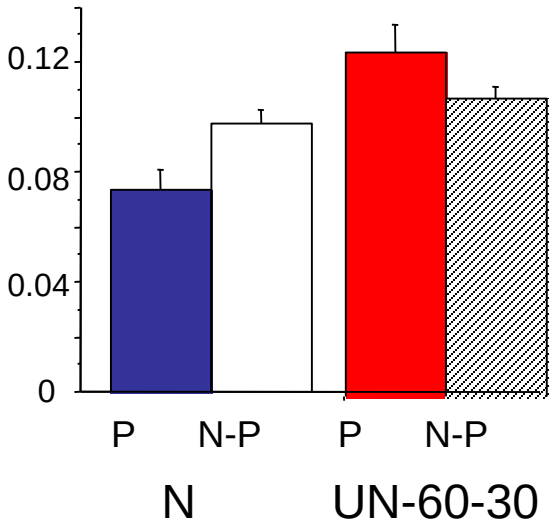


Insulin sensitivity (S_I) in pregnant and non-pregnant N and UN-60-30 ewes at 65d

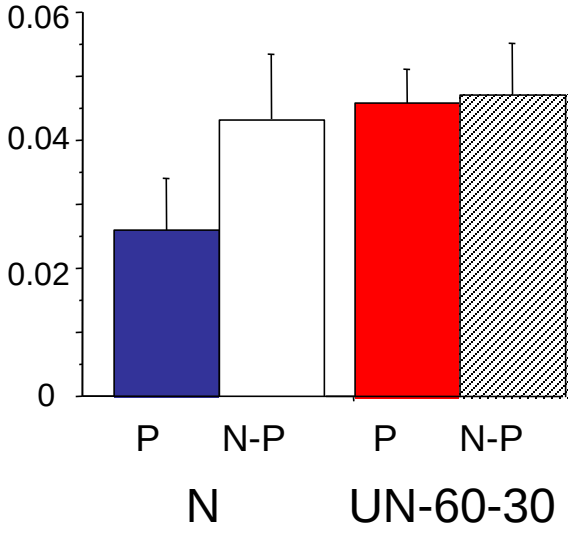
S_I glucose
$mg.l.\mu U^{-1}.kg^{-1}.min^{-1}$



S_I fat
$\%\Delta FFA.mUinsulin^{-1}.l^{-1}$

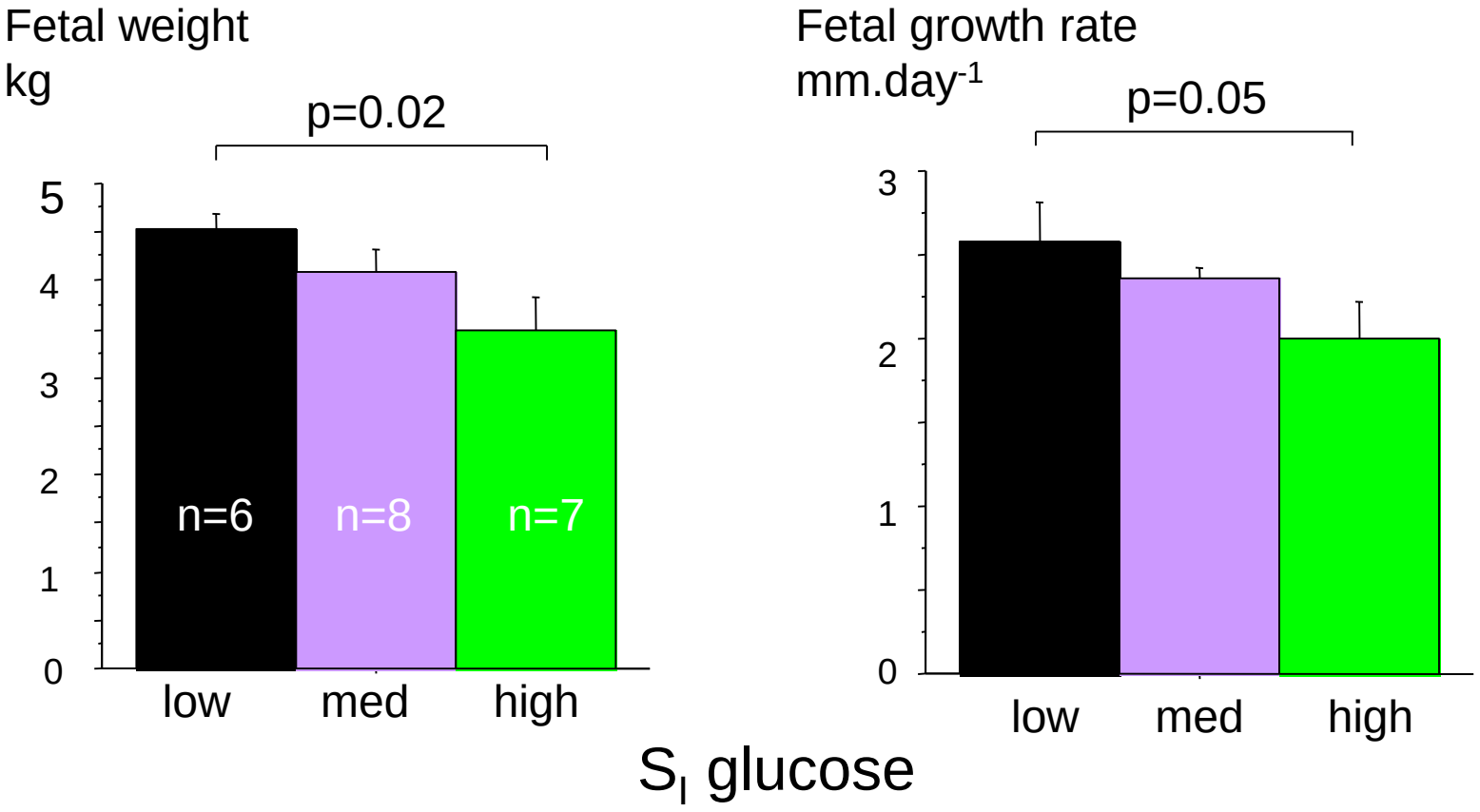


S_I amino acids
$\%\Delta AA.mUinsulin\text{-}1.l^{-1}$



*p=0.02

Effect of maternal insulin sensitivity to glucose on fetal growth



Maternal and fetal outcomes after PCUN

- Altered adaptation to pregnancy
- Altered fetal growth trajectory
- Accelerated maturation of HPA axis and pancreas
- Decreased length of gestation

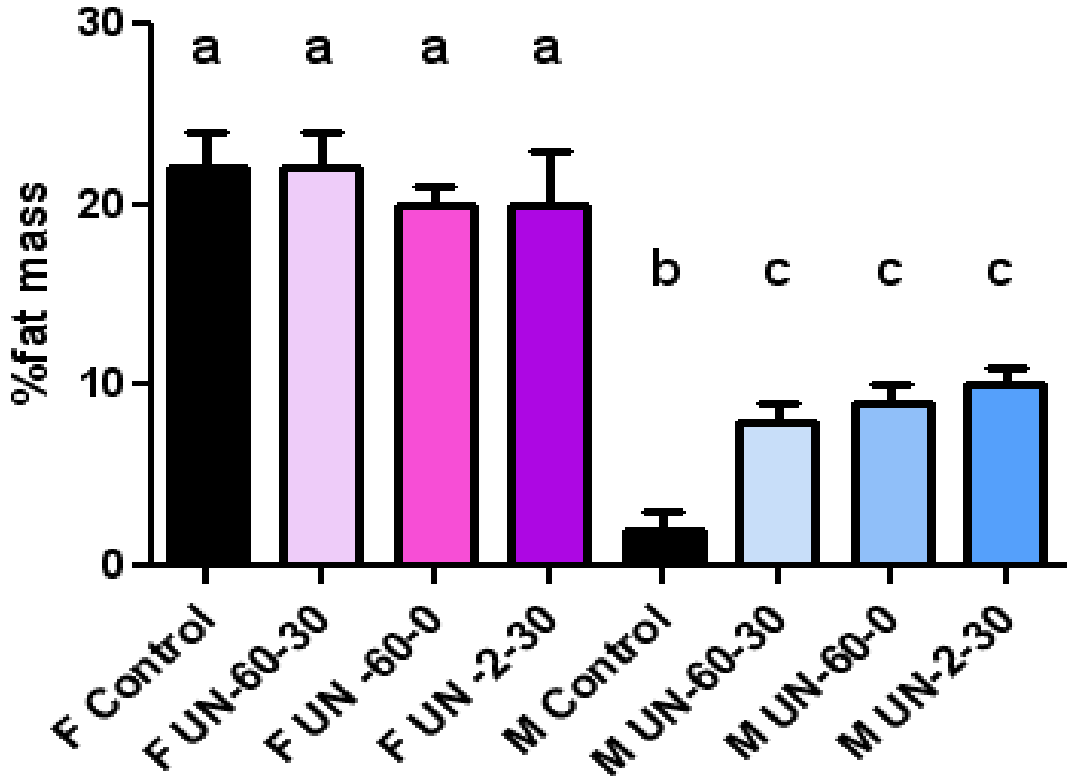
Are there long term effects on the health of the offspring?

- If so, what are the underlying mechanisms?

Juvenile and Adult Outcomes

- Altered postnatal growth regulation
- Increasing glucose intolerance with age due to decreased insulin secretion.
  - Effect greater in females; UN after mating greatest effect
- HPA axis suppression, increasing with age
  - UN before mating greater effect.
- Decreased spontaneous exercise (males especially)
- Increased % fat mass in males

Body composition after PCUN



Summary – maternal periconceptional undernutrition

- Maternal nutritional health before and during pregnancy affects both pregnancy outcome and the later health of the offspring in animals and humans
- Offspring have altered endocrine and metabolic function, likely mediated by epigenetic change in key physiological pathways
- Effects different in male and female offspring

Neonatal nutrition and growth –an opportunity for intervention?

- The neonatal period is still a time of ‘developmental plasticity’
- Can we intervene postnatally to prevent long term outcomes associated with poor nutrition *in utero*?

The magic of breast feeding

Prebiotics and probiotics

- Prebiotics: Substrates that promote the growth of beneficial gut microflora
  - Oligosaccharides in breast milk pass undigested to the colon, fermented by bifidobacteria to create an acidic environment
  - These promote growth of bifidobacteria and prevent adhesion of pathogens to gut wall and host cell receptors

- Probiotics: Live micro-organisms used to promote healthy gut colonisation
  - Lactobacilli and bifidobacteria
  - Usually ingested in breast milk
  - Early colonisation of infant gut

Hormones in breast milk

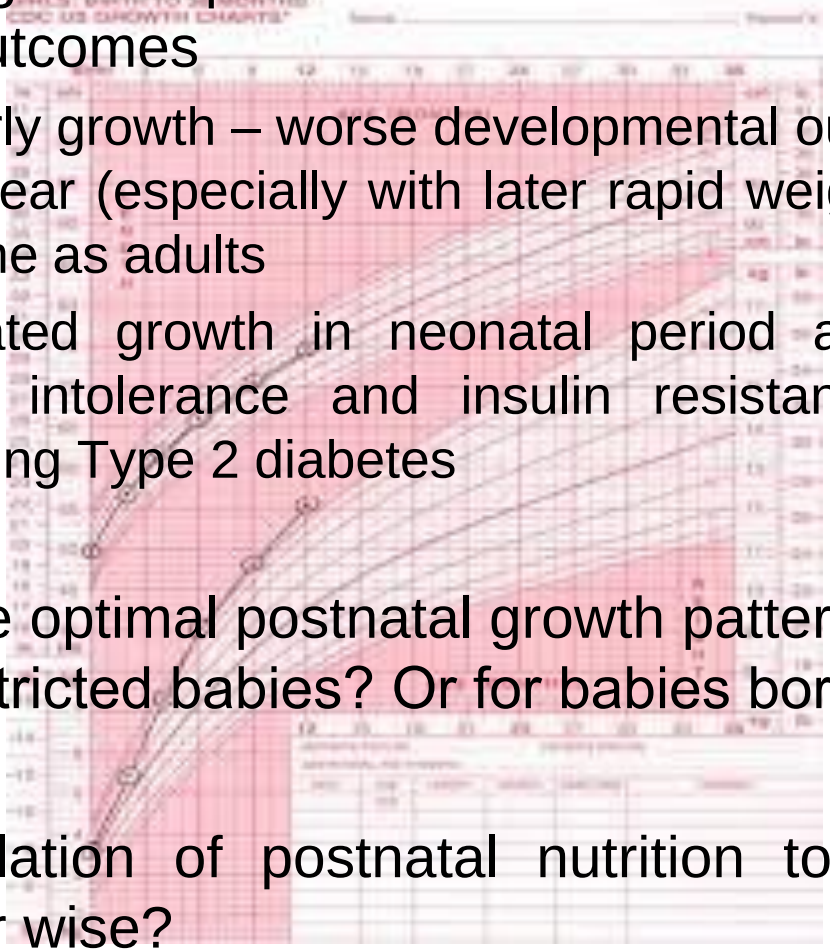
- Leptin, adiponectin, IGF-1, ghrelin and others
- Involved in food intake regulation, energy balance

What is the effect of hormones in breast milk on later metabolic health and appetite regulation?

- Infant formula
  - More rapid weight gain observed in formula fed than breast fed babies
  - Is this due to ‘overfeeding’? To high protein content?
  - Due to lack of exposure to the satiety factors in breast milk?
  - Due to alterations in the microbiome?

- ? Co-ordination of hunger, feed, changing milk composition during feed and satiety factor intake disrupted

Postnatal growth and later health



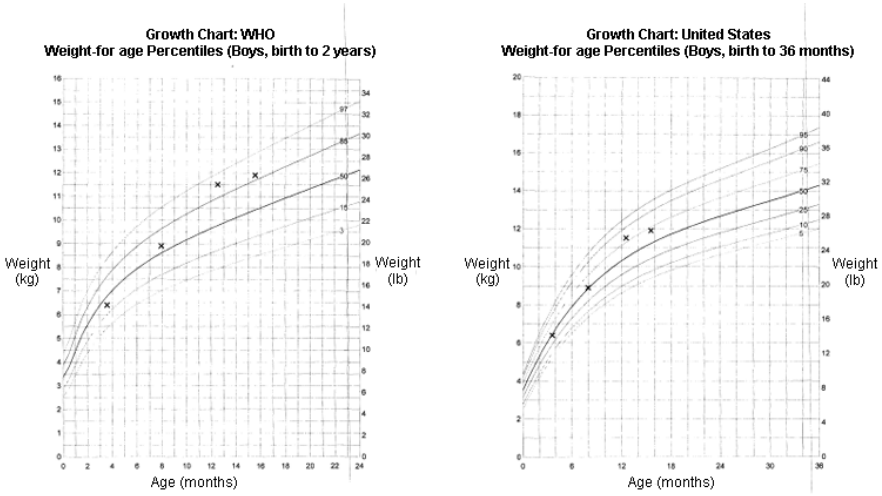
- Different growth patterns after birth are associated with adverse outcomes
  - poor early growth – worse developmental outcomes; poor growth in first year (especially with later rapid weight gain) – metabolic syndrome as adults
  - accelerated growth in neonatal period associated with later glucose intolerance and insulin resistance, risk factors for developing Type 2 diabetes
- What is the optimal postnatal growth pattern for preterm and growth restricted babies? Or for babies born ‘fat’?
- Is manipulation of postnatal nutrition to alter growth rate effective or wise?

Accelerated growth

- Does accelerated postnatal growth affect later health independently, or are both growth pattern and later health risk determined by what happened *in utero*?

- Animal study

'Long term consequences of rapid postnatal growth after term and preterm birth in lambs'



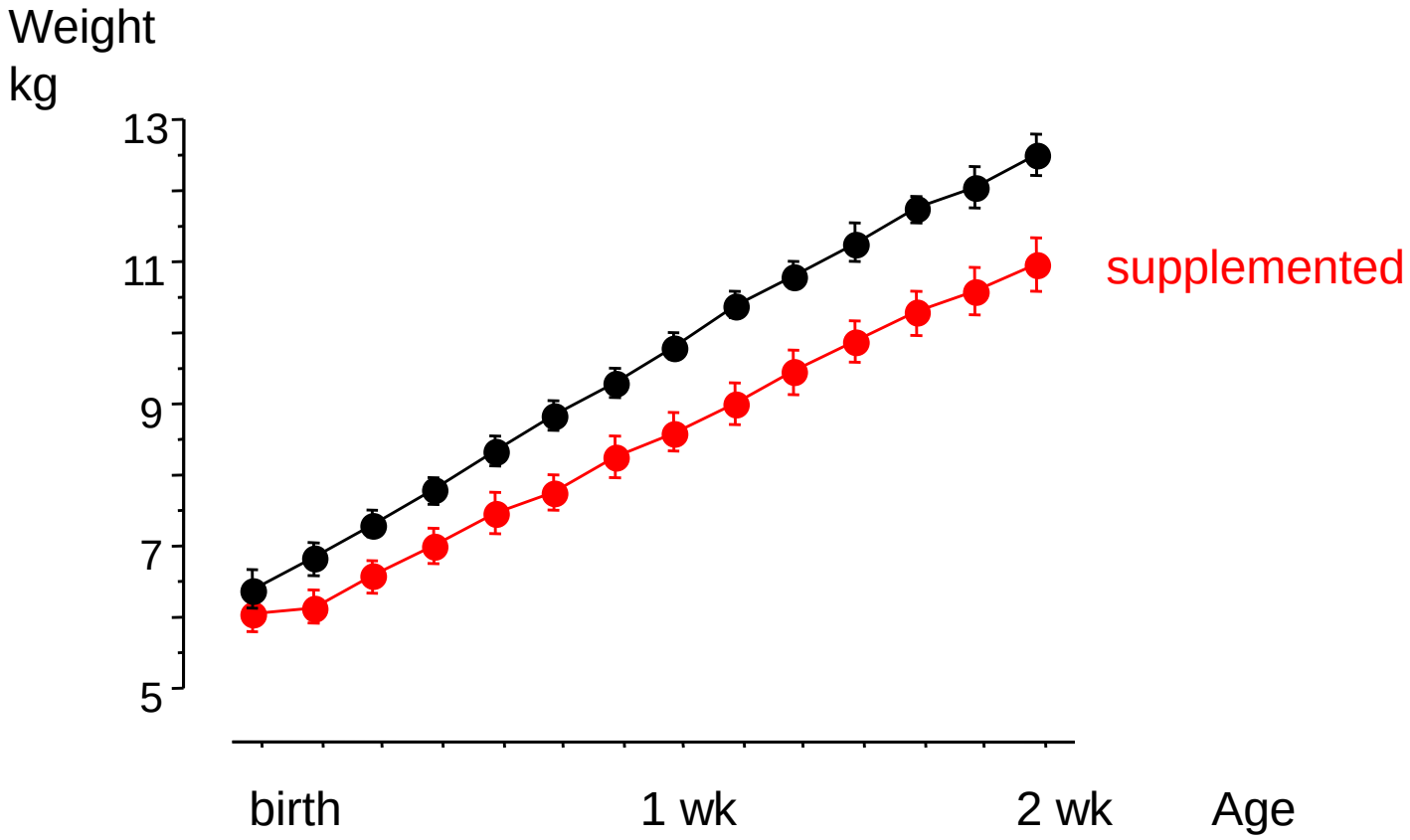
Weight measurements of the same child plotted using the WHO chart (left) and CDC (right). Note that the child's weight plots above the 85th% according to the WHO chart and below the 75th% according the the CDC chart.

Pilot study design

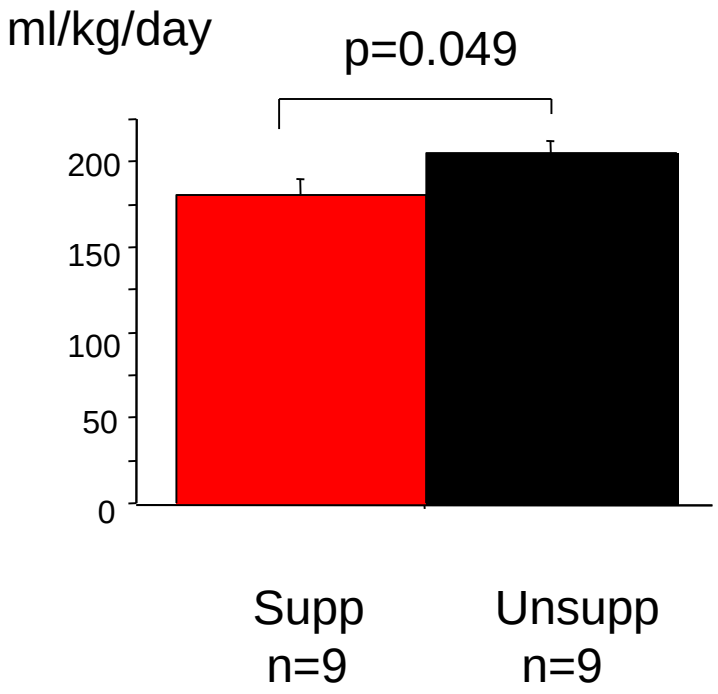
- Term (147 days) and preterm (136 days) lambs
- Growth was accelerated by giving nutritional supplements in the first 2 weeks after birth similar to breast milk fortifier, based on ewe milk composition
- Outcome measures
  - growth rate
  - milk intake
  - glucose / insulin metabolism

  at 4 months of age

Neonatal growth in supplemented and unsupplemented term lambs



Milk intake

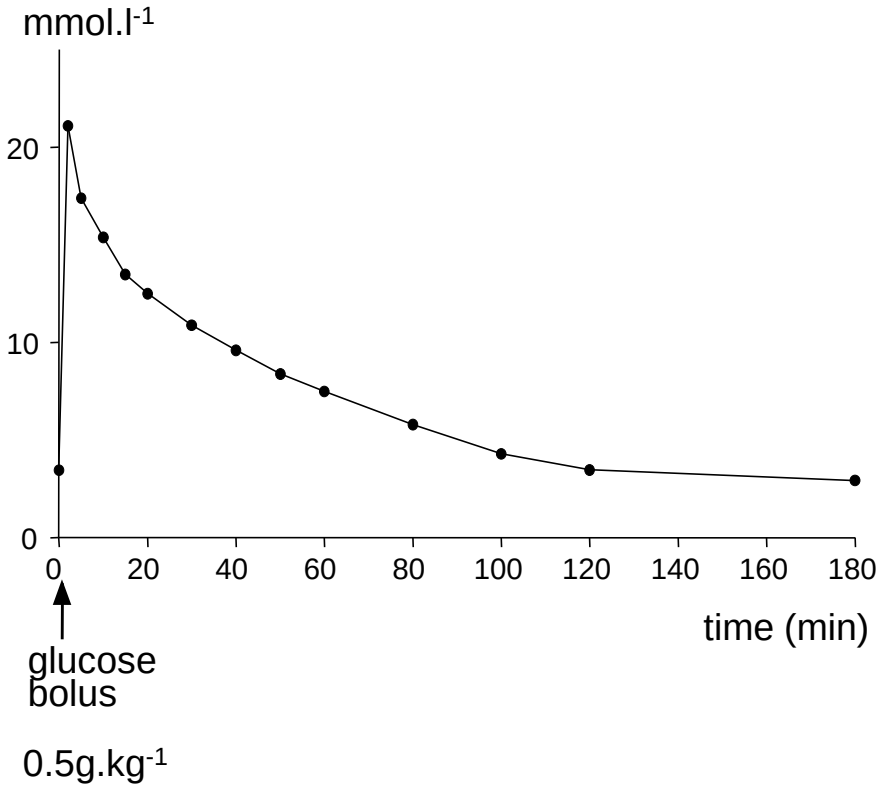


Summary – dietary supplementation

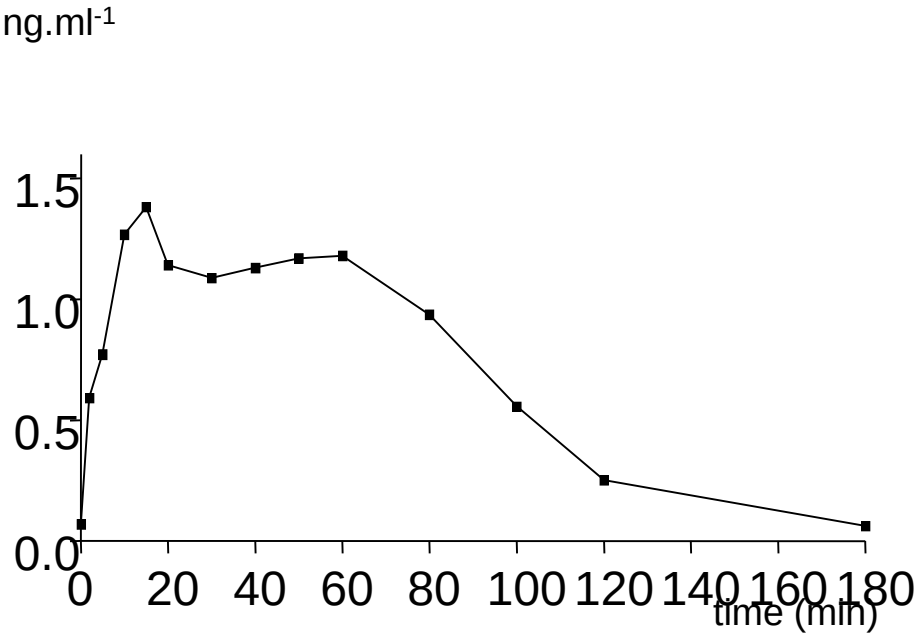
- In healthy term lambs, a high protein & CHO supplement did not accelerate growth
- Possible explanations include altered satiety signals and increased metabolic cost of a high protein diet
- Caloric intake ≠ growth
- Manipulation of neonatal growth may not be as easy as it sounds

Intravenous Glucose tolerance test (IVGTT)

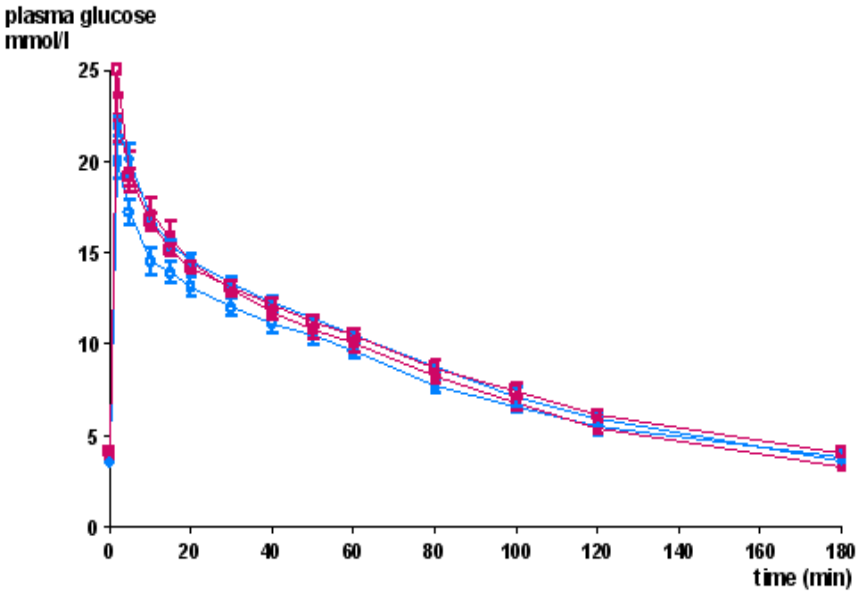
plasma glucose

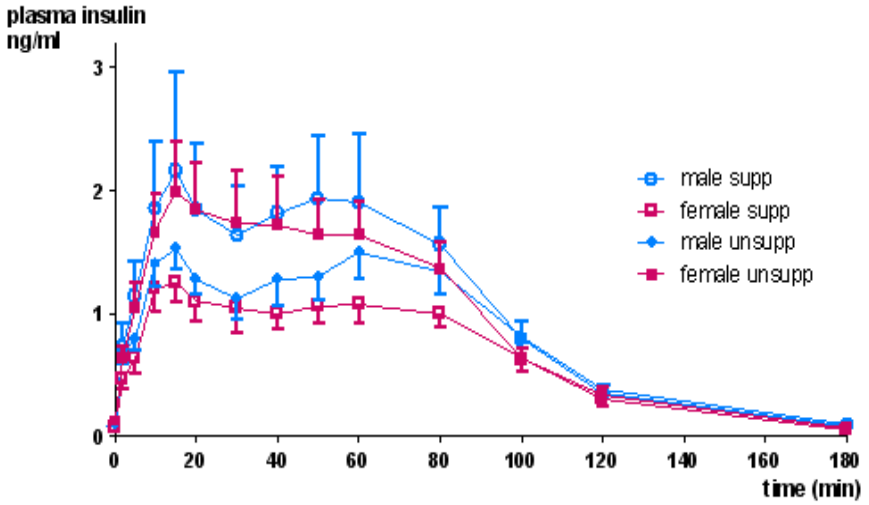


plasma insulin



Glucose tolerance tests in supplemented and unsupplemented single lambs at 4 months of age





Insulin Secretion from Pancreatic β-cell

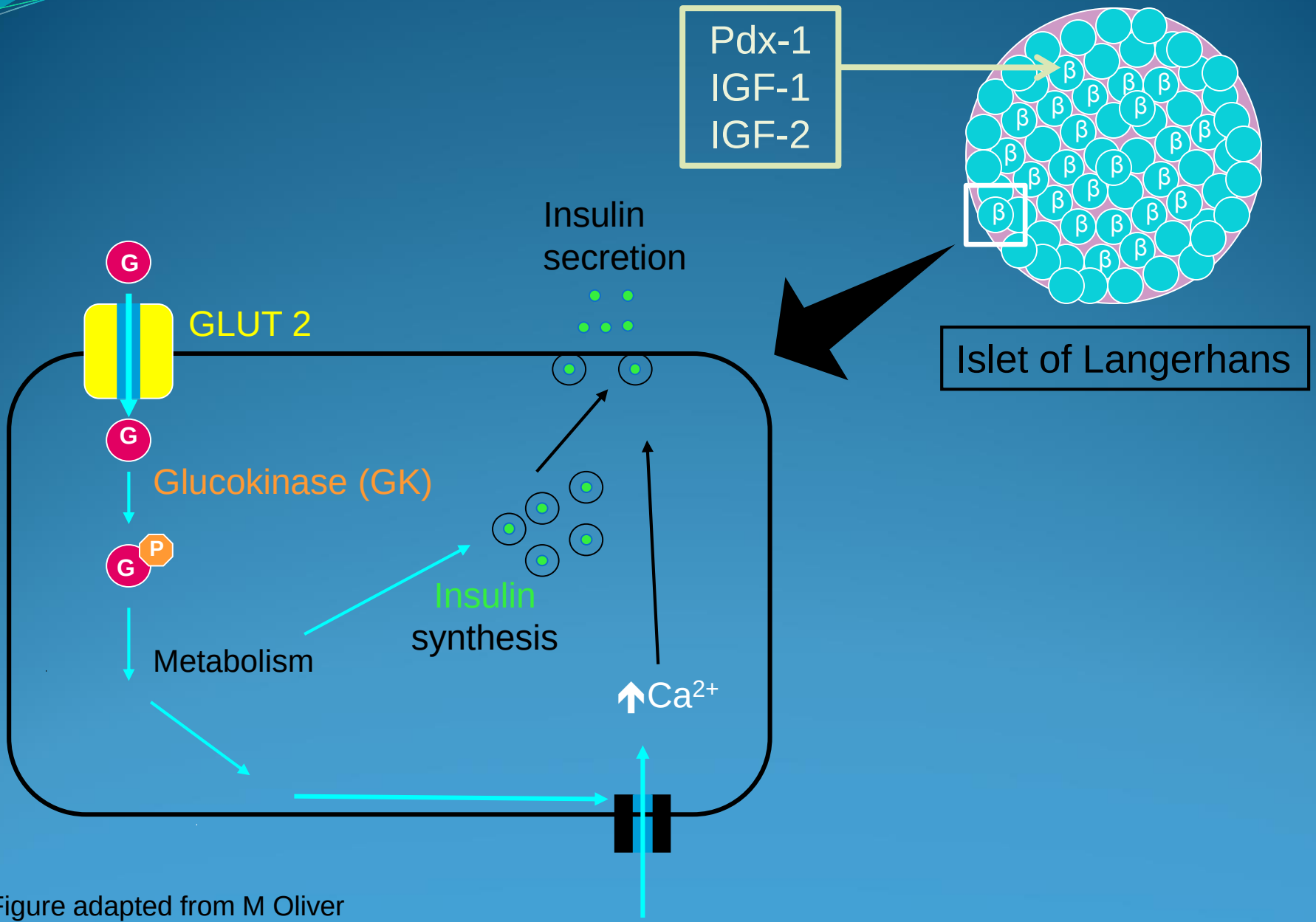
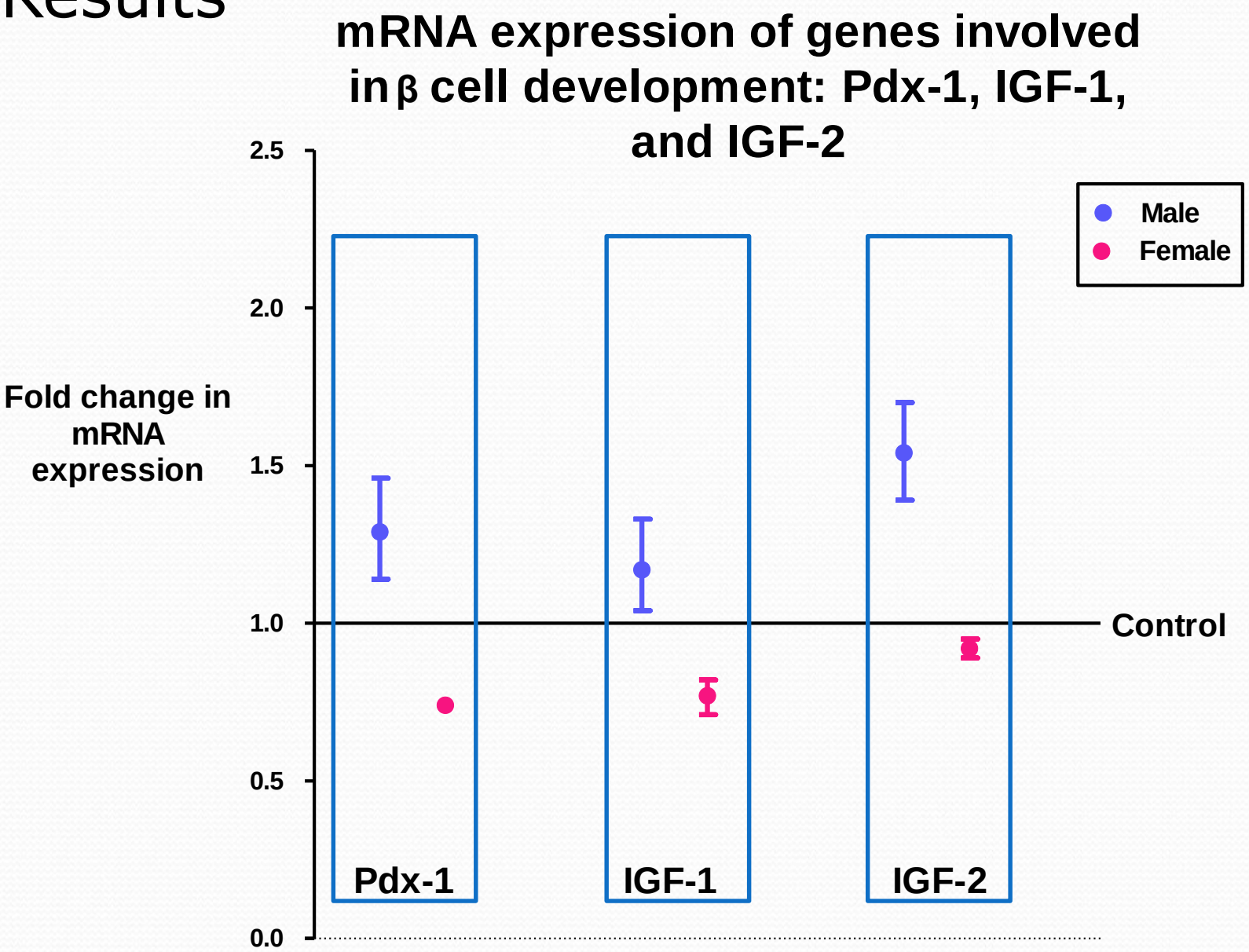
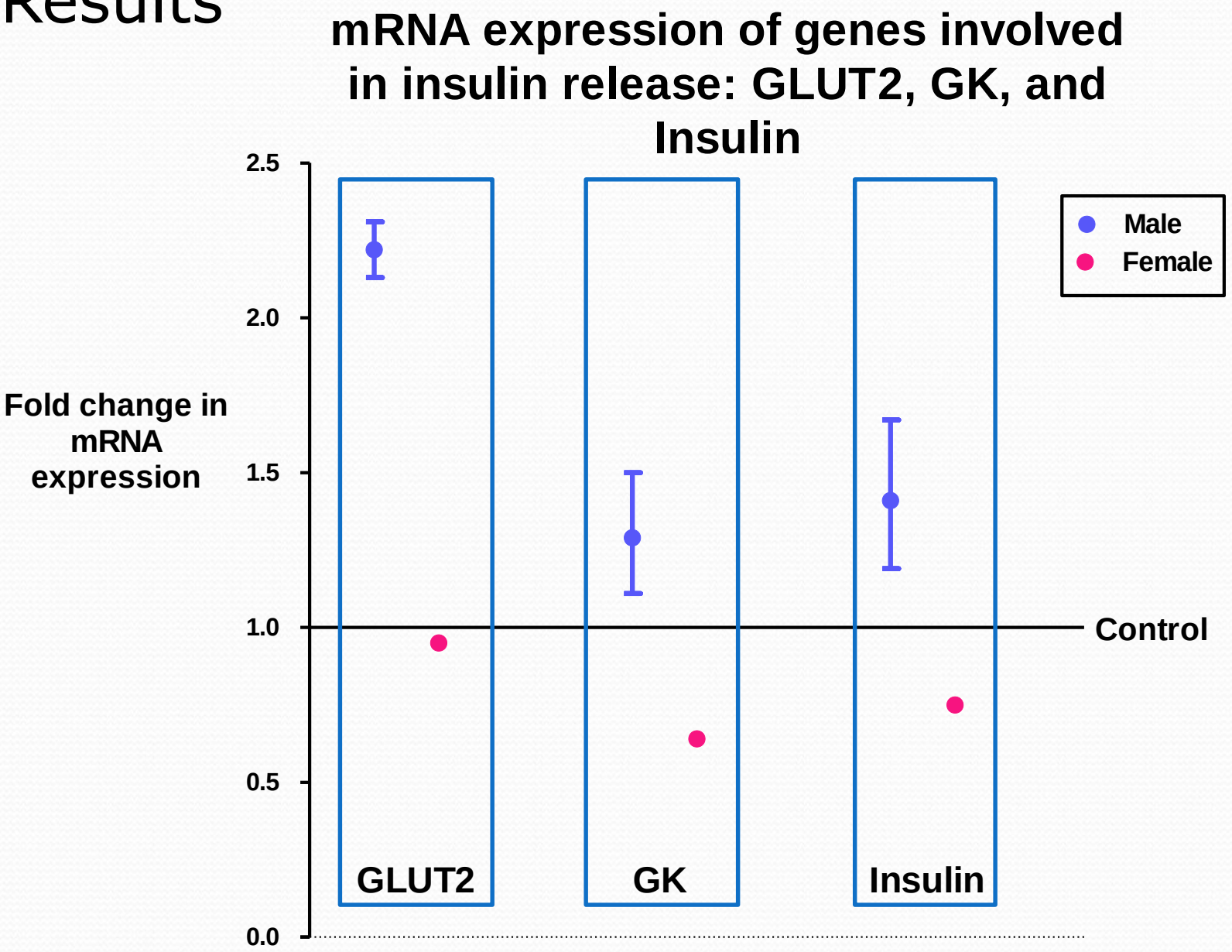


Figure adapted from M Oliver

Results


mRNA expression of genes involved in β cell development: Pdx-1, IGF-1, and IGF-2
Fold change in mRNA expression
2.5
2.0
1.5
1.0
0.5
0.0
Male
Female
Control
Pdx-1
IGF-1
IGF-2

Results


mRNA expression of genes involved in insulin release: GLUT2, GK, and Insulin
Fold change in mRNA expression
2.5
2.0
1.5
1.0
0.5
0.0
Male
Female
Control
GLUT2
GK
Insulin

Summary
Postnatal nutrition and growth

- Not a simple relationship
- Postnatal growth regulation and appetite are influenced by events *in utero*
- Macronutrient balance in the neonatal period may alter growth, pancreatic development and later metabolism
- Rapid postnatal growth – benefits and risks
- Real opportunities for intervention – but first do no harm

Postnatal nutrition - future directions

- Well planned animal studies are needed on which to base clinical trials
- Better understanding of neonatal appetite regulation
- We need to better define ‘optimal’ growth patterns – ‘one size fits all’ is unlikely to be true or effective
- There may be differences between sexes in response to nutritional manipulation

Summary

- Nutrition is a powerful modulator of epigenetic change in the fetus and neonate
- Key nutrients are important for organ development and function, not just for growth
- Maternal undernutrition around the time of conception affects her own adaptation to pregnancy and the long term health of her offspring
- Postnatal nutrition is a potential time for intervention but the effects of nutritional manipulation need more study

What does this mean for public health interventions?

- Investment in early life for long term health
- Education for maternal and child health sector
- The importance of nutritional health at the time around conception needs recognition
  - Teenagers; Interpregnancy interval
  - Not just in lower SE groups
- Nutritional interventions in the postnatal period after intrauterine compromise may be beneficial for long term health, but this needs to be explored more fully, including sex-specific effects

Acknowledgements

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