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The Developmental Origins of Modern Disease - Are We Programmed to Develop Disease in the Womb?

OAND November 13-15, 2009
Toronto, ON

Dr. Nigel Plummer

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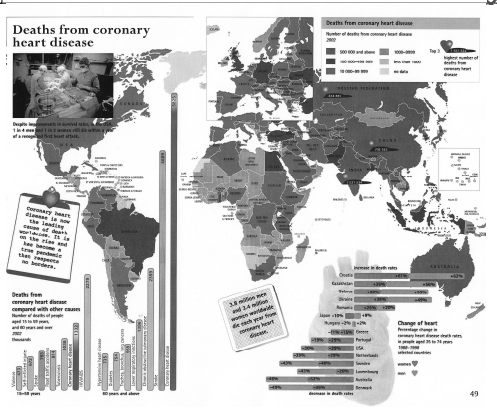

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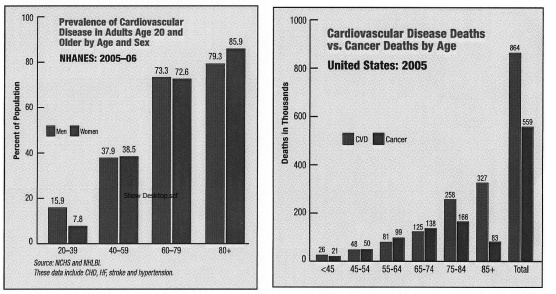
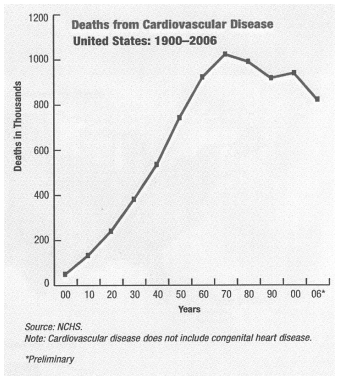
Cardiovascular Disease – Still Our Most Common Chronic Disease.

- **Number of U.S. adults* with CVD = 80 million (36.3%)**
- **Mortality = 865,000/year**
- **35% of mortality is before 75 years of age**
- **15% of mortality is before 65 years of age**
- **Total cholesterol above 240mg/dl = 15.7% of population**
- **Little difference in figures for male and female.**

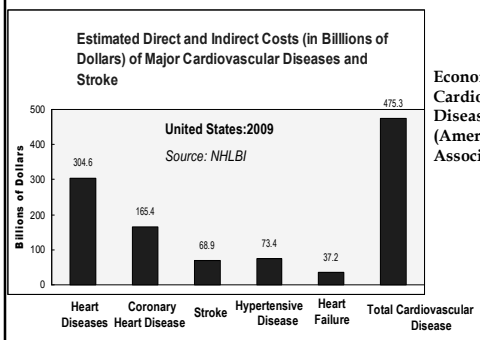
*Above 20 years of age (American Heart Association 2009)



(American Heart Association 2009)



(American Heart Association 2009)



Economic Cost of Cardiovascular Diseases (American Heart Association 2009)

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Some Interesting Facts

- Currently accepted etiology of CVD as resulting from a combination of genetic inheritance – approximately 5% and unhealthy lifestyles – approximately 95%
- However this leaves some inexplicable gaps, such as changing incidence and why some people with similar risk factors develop disease and others do not.
- It is recognised that people in the lowest risk groups for cigarette smoking, cholesterol level, and blood pressure the most common cause of death is…..heart disease.
- Are we missing something?
- In the U.K., regions with the highest rates of low birth weight babies and infant mortality also have the highest rates of cardiovascular disease decades later.

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Early Indications of Another Potential Factor.

- Kermak et al in 1930's showed that over previous 200 years increased survival and health of infants correlated with increase age of death. They concluded: '*… these results are consistent with the hypothesis that he important factor from the point of view of health of the individual during his whole life is the environment up to the age of say 15 years, and that improved conditions in later ages have little direct effect*' **Kermak et al Int J Epidem 1935**
- Rose in 1960's found that siblings of patients with CHD had still birth and infant mortality rates twice that of individuals with healthy siblings leading them to conclude '…**CHD tends to occur in in individuals who come from a constitutionally weaker stock.**' **Rose D Br J Prev Soc Med 1964**
- Forsdahl in 1970's geographical correlation between between CHD in the 1960's and high infant mortality rates 70 years earlier and concluded that a poor childhood environment caused permanent damage which left people vulnerable to aspects of a sedentary adult lifestyle **Forsdahl A Br J Prev Soc Med 1977**
- In 1974 Gunter Dorner was the first to postulate the concept of 'epigenetic' perinatal programming of the lifetime functioning of fundamental regulatory systems.
- Finally David Barker in 1992 found that the U.K., regions with the highest rates of low birthweight babies and infant mortality also have the highest rates of cardiovascular disease 6-7 decades later.

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Developmental origins of Coronary Heart Disease

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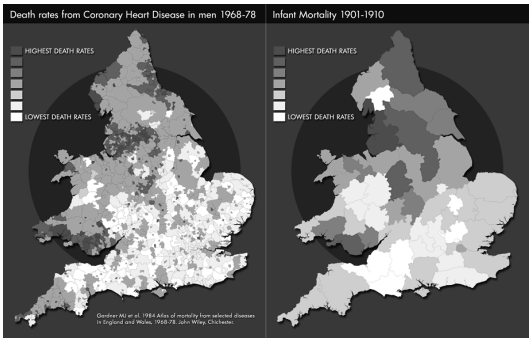

From The Barker Foundation

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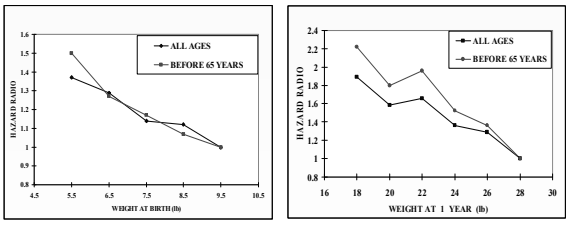
Hazard Ratio of Death From Coronary heart Disease at 65 Years and All Ages to Weight at Birth and 1 Year



Data from 10 636 men born in Hertfordshire U.K between 1911 and 1930 *(Barker 2007 J. Internal Medicine)*

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Summary of large trial evidence for CHD

(Studies with over 10,000 subjects)

No. of subjects	LBW	Follow up age	Risk per 1kg increase
14,611 (m +f)	<2.5kg	65-80	**0.77(m) 0.83(f)** Leon et al BMJ 1998 317:241
13,517 (m+f)	<2.5kg	53-73	**0.8 (average)** Barker et al Int J. Epidemiol. 2002 31:1235
10,803 (m+f)	<2.5kg	40-45	**0.62 (average)** Lawlor et al Circulation 2005: 112: 1414
66,111 (f)	<2.5kg	35-79	**0.77** Rich-Edwards et al BMJ 2005: 330: 1115

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Summary of Large Trial Evidence for Stroke (> 10,000 subjects)

Number of subjects	LBW	Follow up age	Risk per 1kg increase IS	HS	AS
14,611 (m +f)	<2.5kg	65-80	0.89(av)	0.61(av)	---
10,803 (m+f)	<2.5kg	40-45	---	---	0.38
66,111 (f)	<2.5kg	35-79	0.83	0.86	---

Morley R Fetal and Neonatal Med 2006

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Summary of Evidence for hypertension - the most common cardiovascular disease

Number subjects	LBW	Ref BW	Age of measure	Odds
276,000 males	<2.5kg	>2.5kg Lundgren et al 2001 J Hypetension 19:1533	17-24 yrs	1.65
22,846 males	<2.5kg	3.2-3.8kg Curhan et al Circulation 1996	40-75 yrs	1.26
164,000 female	<2.4kg	3.18- 3.86 Curhan et al Circulation 1996	30-35yrs	1.39-1.43

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The Fetal Link to Heart Disease - Compelling Evidence

- 15 out of 16 epidemiological studies over 14 different countries have reported inverse relationships between birth weight and cardiovascular events.
- This correlates overall to a 20% lowered risk of CVD with every 1kg of higher birth weight.
- The risk factors for CVD such as hypertension, metabolic syndrome, type 2 diabetes and obesity are now also known to be linked to low birth weight and more particularly malnutrition in the in-utero and neonatal periods

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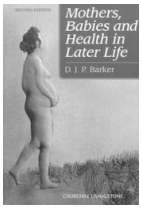
The Developmental Origins of Chronic Diseases:
Barker Hypothesis



'Adverse influences early in development and particularly during intrauterine life can result in permanent changes in physiology and metabolism which result in increased risk of disease in adulthood'

from David Barker

"The way a baby grows in the womb affects its adult life"

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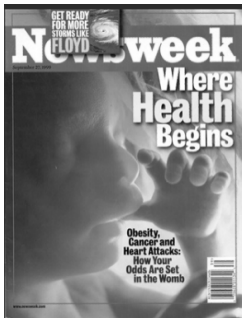

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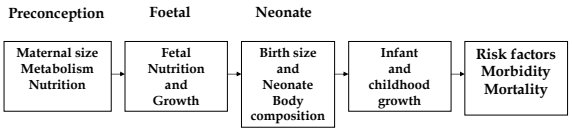
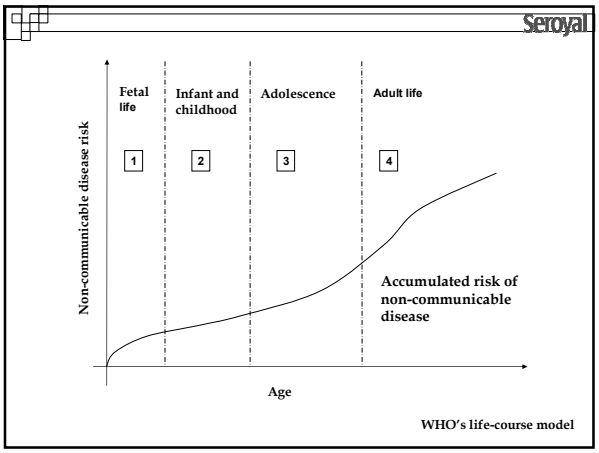
Developmental Origins concept



(Yajnik 2008, Rev Endocr Metab Disord)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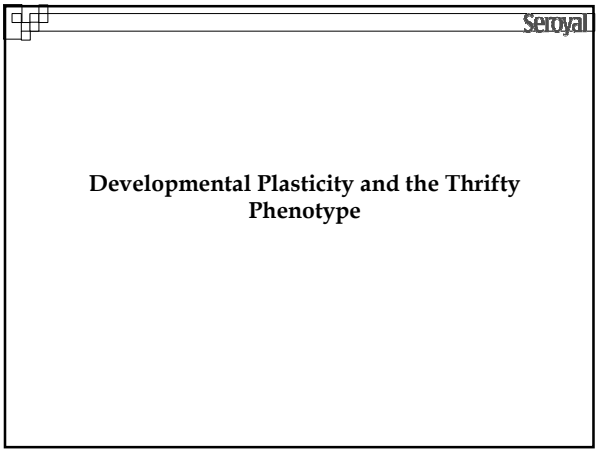
Fetal life
Infant and childhood
Adolescence
Adult life
1
2
3
4
Non-communicable disease risk
Accumulated risk of non-communicable disease
Age
WHO's life-course model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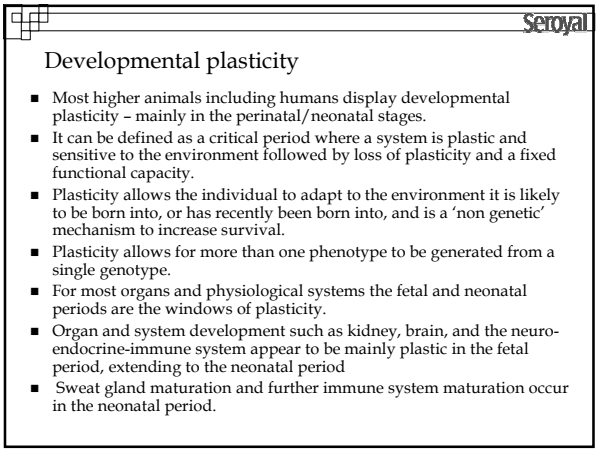
Developmental Plasticity and the Thrifty Phenotype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Developmental plasticity
Most higher animals including humans display developmental plasticity – mainly in the perinatal/neonatal stages.
It can be defined as a critical period where a system is plastic and sensitive to the environment followed by loss of plasticity and a fixed functional capacity.
Plasticity allows the individual to adapt to the environment it is likely to be born into, or has recently been born into, and is a 'non genetic' mechanism to increase survival.
Plasticity allows for more than one phenotype to be generated from a single genotype.
For most organs and physiological systems the fetal and neonatal periods are the windows of plasticity.
Organ and system development such as kidney, brain, and the neuro-endocrine-immune system appear to be mainly plastic in the fetal period, extending to the neonatal period
Sweat gland maturation and further immune system maturation occur in the neonatal period.

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The Thrifty Phenotype

- To explain the link between low birth weight and adult cardiovascular disease, Barker developed the concept of the 'thrifty phenotype.
- Low birth weight simply reflects an under or malnutrition of the fetus, in the case of early studies, caused by macro undernutrition during the foetal stages.
- As there is no reason to believe that the environment may be different following birth the foetus prepares itself by laying down 'set points' in metabolic pathways, which will enable survival in a thrifty environment.
- In this case, limited maternal – fetal glucose flow leads to reduced fetal insulin level , and underdevelopment of pancreatic beta cells.
- Limitation of glucose leads to preferential re-direction to the brain and relative under-supply to peripheral organs and muscular tissue.
- To assist this these tissues become more resistant to insulin so directing more blood to the developing brain. This tendency to insulin resistance then becomes 'programmed'.
- The abundant nutrient availability in post-natal life and adult life is opposite to the programmed pancreatic cell deficiency and inherent 'nutrient limited' insulin 'status' (resistance) of peripheral tissues laid down in the thrifty phenotype.
- The thrifty phenotype is unsuited to this environment, and hence the pathophysiological outcomes of glucose intolerance, overt insulin resistance and obesity ensue.

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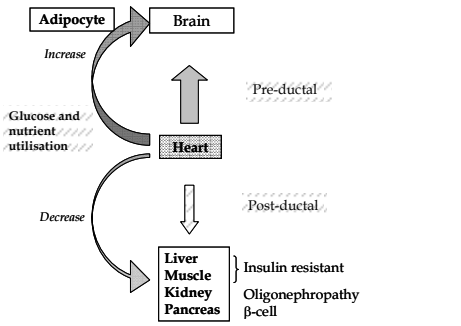
'Brain-sparing' during fetal growth



(Yajnik, Proc Nutr Soc 2004)

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Birth weight and later body mass and composition

- In the absence of insult – humans grow to their individual growth potential
- There is a positive relationship between birth weight and childhood and adult BMI.
- However the relationship for birth weight and BMI is stronger in some studies for lean mass rather than fat – other studies show the association with lean and fat.
- Low birth weight leads to adults with less lean mass and hence less metabolic activity and a predisposition to set down abdominal fat if presented with an energy dense diet. Druet and Ong 2008 Best Prac and Res Clin. End and Met
- Hence many trials have shown that the relationship between birthweight and BMI is J-U shaped – low birth weight subjects (babies born in the Dutch Famine) are more likely to be obese as adults Litonjua and Golg Clin Rev All and Immun 2008

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Growth Potential and Insult

- The 'supply chain' model of uterine growth is now considered most accurate… 'disease risk is most profound in those who fail to reach their growth potential in utero i.e foetal demand outstrips supply'
- In response to insult the individual demonstrates growth faltering. The severity depends upon the potency and duration of the insult.
- In response to the alleviation of the insult, the individual shows accelerated catch-up growth which normally returns pattern to the original trajectory.
- It appears that rapid 'catch-up' growth particularly in the first year of life comes at a cost.
- 95% of SGA babies are born in developing countries – catch up growth occurs. India and now have soaring rates of abdominal obesity and type 2 diabetes and Africa soaring rates of hypertension **Adair and Prentice 2004**
- It is possible that adolescent growth spurt includes catch up growth for numerous minor insults during previous years.

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Low Birth Weight and Catch-Up Growth – An Accumulating Problem

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SGA or Catch Up Growth – Which is worse?

- **Most babies born either at the small end of normal weight range, premature, or SGA will catch up to the average within 2 years – this is termed catch-up growth. It appears that rapid 'catch-up' growth particularly in the first year of life comes at a cost.**
- **Rapid catch up growth (i.e crossing more than one centile) in this period is associated with significantly increased risk (typically 2-3 fold) of obesity, hypertension and insulin resistance, type 2 diabetes and CVD later in life.** Williamson et al Clin End 2007
- **Catch up growth in the childhood and adolescence rather than the infant stage is less associated with obesity, and appears to have no association with increased risk of metabolic syndrome** Ekelund et al 2007 J Clin End and Met
- **The window for 'safe' early catch up growth if it exists appears narrow.**
- **For SGA babies who remain small and short during infancy, using growth hormone to catch up seems not to carry the disadvantages of metabolic and disease risk increase associated with spontaneous nutritional catch up** Hokken-Koelega et al 2004 Horm Res.

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Catch-up growth early in life

- Catch up growth is characterised by a disproportionately higher rate of fat gain relative to lean tissue gain. Thrifty 'catch-up fat' phenotype cross-links with insulin and leptin resistance .
- Experimentation has proven that over-feeding in the neonatal period leads to hyperinsulinism, increased lifelong hyperleptinism and risk of hypercortisolism. The SGA 'thrifty' baby is most susceptible to this.
- Once catch-up growth in terms of lean mass has occurred and stops, accumulation of fat continues.
- 95% of SGA babies are born in developing countries – catch up growth occurs. India and now have soaring rates of abdominal obesity and type 2 diabetes and Africa soaring rates of hypertension Adair and Prentice 2000

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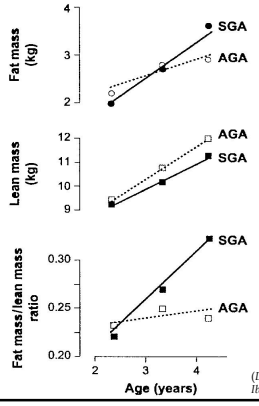
Preferential catch –up fat in infants born small for gestational age



- By 4 years SGA children had
  - greater total fat
  - greater abdominal fat
  - higher insulin resistance

Compared to AGA infants

(*Dulloo AG 2008, Ibanez L et al 2006*)

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The Causes of Intrauterine Growth Restriction and LBW

Experimental models

- Protein deprivation
- Vitamin A deficiency
- Antibiotic administration
- Corticosteroid administration
- Insulin resistance
- Genetics

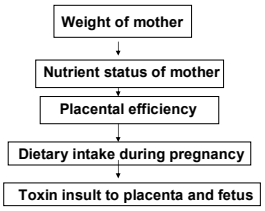
Human evidence

- Malnutrition during pregnancy (and before) Low glycemic index diet can reduce birthweights by average of approx. 200g
- Maternal weight below 50kg
- Gestation weight gain less than 7kg
- Chronic infections
- LBW of mother
- Diabetes (2) /metabolic syndrome during pregnancy
- Smoking/alcohol abuse
- Genetics
- Social - adolescent pregnancy
  - family dysfunction

Scholl Nestle Nut Work 2008

The Fetal Supply Chain

- The supply of nutrients to the fetus and it's environment are the main influences of fetal growth.
- Fetal growth depends upon a series of steps known as the 'fetal supply line' This supply line is vulnerable to insult at all points and this will inevitably result in growth restriction.
- Low birth weight is simply one blunt expression of malnutrition. Other types of malnutrition may be more subtle, not result in low birth weight, but result in programmed effects in later life e.g vitamin D



Many Diseases Now Linked with Birth Weight

- **Widely accepted association with small birth weight**

Hypertension
Coronary artery disease
Type 2 diabetes
Stroke
Dislipidaemia
Impaired neurodevelopment

- **Less widely accepted association with low birth weight**

Chronic lung disease
Depression
Schizophrenia
Behavioural problems
Fingerprint patterns and left-handedness
Precocious puberty and menarche

- **Association with high birth weight**

Polycystic ovary disease
Breast cancer
Prostate cancer
Testicular cancer
Childhood leukaemia.

Developmental origins of Diabetes

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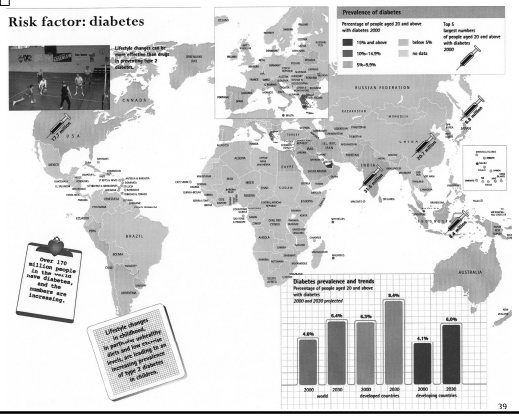
Risk factor: diabetes



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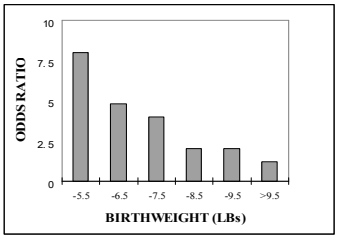
Original Observations Made By Barker and Colleagues On Association Between Birthweight and Type 2 Diabetes in 68 Yr Old Men

Hales and Barker 2001, Br Med Bull)



Odds ratio for impaired glucose tolerance or type 2 diabetes according to birth weight among 370 men aged 64 years born in Hertfordshire (adjusted for adult body mass index)

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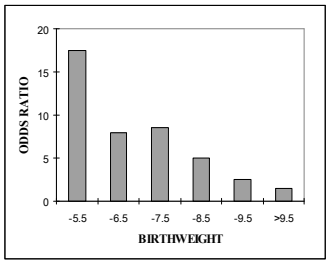
Initial Observations Made by Barker on Association of Metabolic Syndrome and Birthweight in 68 Yr Old Men



Odds ratio for the metabolic syndrome according to birth weight among 407 men born in Hertfordshire (adjusted for adult body mass index).

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Odds ratio for Type 2 diabetes by birth weight Meta-analysis (1966-2005)

Birth weight (g)	No. of estimates*	Odds ratio	95% confidence interval
≤2,000	5	1.00	0.84, 1.19
2,001-2,500	6	0.82	0.69, 0.98
2,501-3,000	10	0.82	0.61, 1.08
3,001-3,500	11	0.72	0.59, 0.89
3,501-4,000	8	0.55	0.48, 0.62
4,001-4,500	7	0.60	0.51, 0.70
>4,500	7	0.92	0.63, 1.34

* Number of estimates from single studies.

Harder et al 2007, Am J Epidemiol

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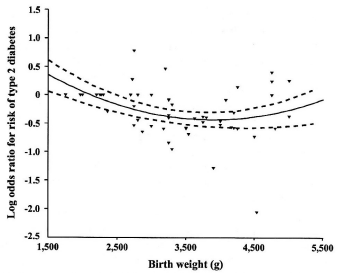
U-shaped relation between birth weight and Type 2 diabetes risk



Harder et al 2007, Am J Epidemiol

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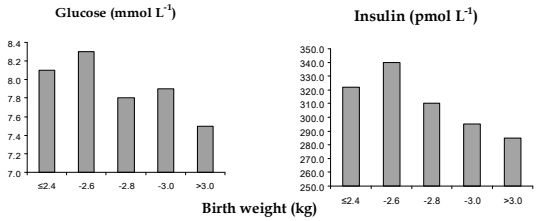
Pre-Diabetes in 4 yr olds related to birth weight



Plot shows plasma glucose and insulin levels 30 mins after oral glucose load

- **Low birth weight associated with tendency to hyperglyceamia and hyperinsulinemia**

(Yajnik et al, Rev Endocr Metab Disord 2008)

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- Published literature- a meta-analysis of 40 studies shows inverse relationships of birth weight and later glucose and insulin metabolism
  -fasting plasma concentrations of glucose and insulin
  -plasma glucose concentration 2 h after a glucose load,
  - the prevalence of Type 2 DM and insulin resistance.
  (Newsome et al 2003, Diabet Med)
- These relationships are similar for males and females.
- However ……..

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It is well recognised that obese and diabetic women give have a high risk of giving birth to large babies with a high risk of developing diabetes……..

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Insulin and Foetal Growth

- **Insulin is the key controller of foetal growth in early foetal life – growth hormone takes over later in foetal life.**

The Barker Hypothesis – small babies have high risk of diabetes

- A major responsibility for insulin is to provide energy for cell division and growth of muscle tissue. If there is under nutrition in mid gestation, then muscle and other peripheral tissues become resistant to insulin allowing nutrients to be diverted to the brain. In effect the growth of these tissues is sacrificed to allow brain growth, leading to a low birthweight baby.
- The important point is that resistance to insulin is then programmed into the foetal physiology.
- This is then expressed as a susceptibility to development of insulin resistance and type 2 diabetes in childhood and as a adult.

The Pedersen Hypothesis – prediabetic and diabetic mothers give birth to large babies with high risk of diabetes.

- Maternal hyperglyceamia causes fetal hyperglyceamia by direct trans-placental imprinting. This leads to excessive fetal insulin secretion (hyperinsulinemia) which facilitates excess foetal growth particularly of fat component. However, insulin resistance then develops.

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Hyperinsulinism In The Fetus

- Offspring exposed to maternal diabetes are at increased risk of developing obesity and diabetes.
- This association is largely independent of genetic background, and appears to relate directly to fetal hyperinsulinism resulting from maternal hyperinsulinism.
- High circulating fetal insulin leads to high insulin concentrations in developing organs such as the brain, hypothalamus,(blood brain barrier not developed) and pancreas at critical windows of 'set point' imprinting.
- This leads to hyperinsulinism, and lifelong high risk of obesity, diabetes and CVD in the offspring. This process has been entirely proven in animal experiments and is highly likely to also occur in humans.

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- Interestingly, this acquired predisposition for diabetic risk in animal experiments results in spontaneous gestational diabetes in the offsprings own progeny leading to diabetes in the third generation. This strongly indicates epigenetic transfer from one generation to the next, mediated by maternal diabetes. **Plagemann 2005**
- The important point is that this intergenerational hyperinsulinism, and diabetes cycle appears ENTIRELY preventable if maternal hyperinsulinism is treated.
- In addition hyperinsulinism caused by overfeeding (catch-up growth) can be prevented by not overfeeding.

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Transgenerational diabetes related to maternal and fetal nutritional status

Barker	**Pederson**
Maternal undernutrition	**Fetal overnutrition**
('Marasmus-like')	('Kwashiorkor-like')
Small baby	Large baby
Fat wasted	Fat retention

Insulin resistance
Metabolic syndrome
Prediabetes
Diabetes

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Other Phenotypes May be Programmed

- The structure of a metabolic pathway is genetically determined, but the set points which guide the activity of the pathway are laid down in the fetal and neonatal stages based upon the environmental conditions experienced by the fetus.
- Hence, in a pregnant type 2 diabetic mother the insulin set points will reflect this environment and will predispose the child to be hyperinsulemic and types 2 diabetic either in childhood or adulthood. (In one long term follow-up trial of infants of diabetic mothers:
  - 50% newborns had birthweights above 90% percentile
  - At 8 years of age 55% of children were clinically obese with significantly higher levels of glucose intolerance than controls
  - This correlated with both pre-pregnancy maternal weight independently with fetal insulin levels at 32-38wks gestation (*Silverman et al 1991, Diabetes)*
- Adverse outcomes may have a correlation which is U-shaped

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Renal and Vascular Origin of Hypertension

- **Under nutrition of the foetus leads to impairment of development of kidneys leading to lower nephron number.**
- **In clinical hypertension in humans there is a direct relationship of risk with lowered nephron number** Franco et al Cardiovascular research 2003
- **Several studies have now shown a strong link between low birth weight and impaired endothelial function in both children and adults. The impairment is particularly associated with reduced capacity for endothelial relaxation , leading to pre-disposition to hypertension.** Goodfellow et al 1998; leeson et al 2001

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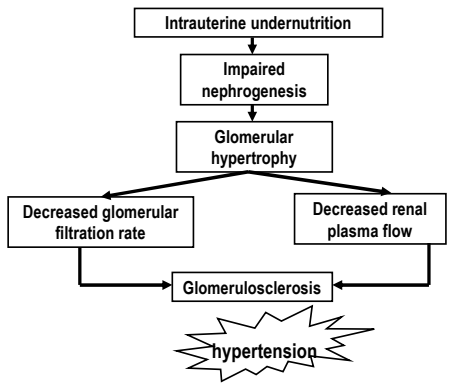

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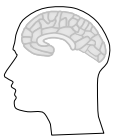
Birthweight and Mental Health



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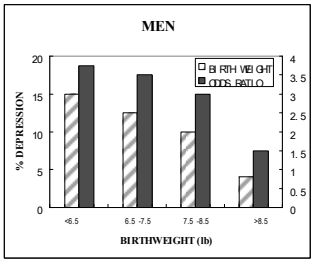
Birth weight, fetus under nutrition and depressive disorder

In a trial of 882 individuals born in the 1920's (birth record available) depression is measured at 68 years using the geriatric mental state examination.

These results were corrected for the following risk factors in later life

- Current social class
- Social class at birth
- Bereavement in past year
- Living alone
- Low social contact
- Illness causing pain
- Illness preventing activity



These trends persist for weight at 12 months

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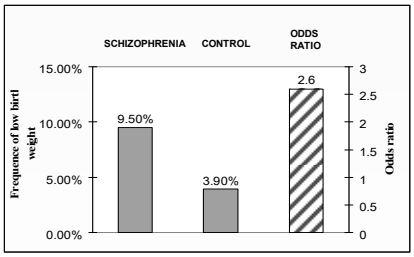
Human Fetal Undernutrion and Schizophrenia

Below is pooled analysis of 7 studies measuring schizophrenia and birth weight (<2500g)



Total 747 schizophrenic subjects

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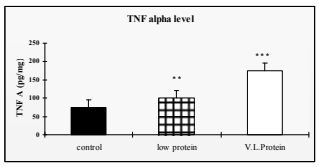
Pre Natal Under-nutrition, Pro-inflammatory Factors and Implications for Schizophrenia

Fetal placenta



- **Animal study where feeding a low protein (-20%) and very low protein (-50%) diet to pregnant rats had effect of increasing inflammatory markers and disturbed schizophrenic behaviour in offspring.**

Shen et al 2008 Shizophrenia Res

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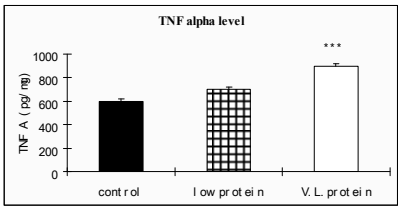
Pro-inflammatory factors, prenatal undernutrition and implications for schizophrenia (con't)

Fetal liver



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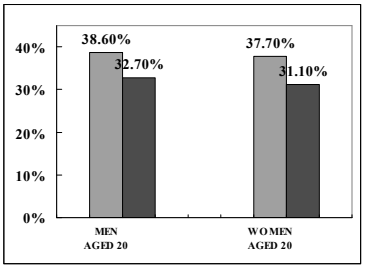
Fetal Programming, Psychopathology and ADHD

Level of measured behavioural problems associated with low birth weight babies.



Behavioural parameters

- **Anxious /depression Withdrawn**
- **Thought problems**
- **Attention problems**
- **Intrusive**
- **Aggressive**
- **Delinquent**
- **Internalism**
- **Externalism**

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Perinatal Programming of the HPA Axis

- Over stimulation of the HPA axis of the fetus either from administration of glucocorticoids or from maternal stress, leads to a lasting hyperactivity of the HPA following birth and in later life. **Plagemann Physiol and Behav 2005**
- The consequences of this may be lifetime hyperactivity of the HPA axis leading to risk of impaired glucose regulation hypertension or depression, or development of adrenal fatigue and hypocortisolism leading to risk of CFS, fibromyalgia etc. **Kajante et al J Clin End Metab 2007**

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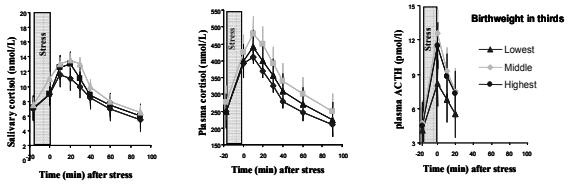
Birthweight predicts hypothalamic-pituitary-adrenal axis response to psychosocial stress in late adulthood



300 subjects of different birth weights aged between 60-70 were subjected to the Trier Social Stress test.

- Response showed an inverse U shaped relationship between stress response and birth weight with low birthwight showing the lowest response levels.

- Results suggest that hypo and possibly hypercortisolism may be programmed to some extent in –utero **Kajante et al 2007 J Clin End Metab**

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- **Response showed an inverse U shaped relationship between stress response and birth weight with low birthweight showing the lowest response levels.**
- **Results suggest that hypo and possibly hypercortisolism may be programmed to some extent in –utero.**

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Fetal Undernutrition and Rapid Progression Through Puberty

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Foetal Under-nutrition and Rapid Progression Through Puberty

Reduced pre-natal growth cause rapid progression through puberty and reduced final height in girls compared to those with unaffected prenatal growth.

	<2.5kg	>2.5kg
BIRTH WEIGHT		
ONSET OF PUBERTY	8.6 years	8.6 years
MENARCHE	11.3 years	12.9 years
FINAL HEIGHT	153cms	158.3cms

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Fingerprint association with CVD and fetal programming

- Fingerprints formed in-utero in first 19 weeks and pattern depends upon quality of blood flow in the fetus.
- Disturbed blood flow, particularly restriction during foetal growth retardation cause specific pattern types with increased fingertip 'whorls' predicting increased risk of low birth weight and subsequent development of CVD esp hypertension in childhood and adulthood.
- In a study of 35-42 year olds low birth weight babies had an average of 4 whorls on their right hand, which correlated with mean systolic blood pressure increase of 8mmHg. Average SBP increased 2mm with each additional whorl.
- This disturbed blood flow and fingerprint pattern type is also associated with increasing abdominal adiposity in mother and with risk of CVD in adult.
- Worst combination in pregnant woman is high central adiposity with low tricep and bicep skinfolds.
- Insulin resistance occurs in growth retardation, and limits growth and development of peripheral tissues including skin fingerprint patterns
- Could this be used as a predictor of CVD, type 2 diabetes and metabolic syndrome later in life?

Wheeler et al B.J Ob and Gyn 1998
Godfrey et al BMJ 1993

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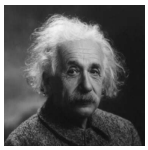




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Influence of Birth Weight and Fetal Under-nutrition on Left Handedness

- Left handedness appears to be associated with lower life expectancy.
  (James 2001, J Theo biol)
- Left handedness is associated with low birth weight.
  (Saigal et.al 1992, Dev Med Child Neurol)
- Left handedness probably due to asymmetry / restriction of blood flow in fetus.

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- Normal blood flow to fetal arms is asymmetrical with greater flow to right arm and left side of brain particularly in conditions of no nutritional constriction. This leads to different fingerprint on left and right hand.
- Deficient nutrition to fetus leads to alteration of blood flow to brain. Domination of left side is balanced- with greater relative flow to right hand side of brain - increase in left handedness (right side of brain).

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- Autoimmune disorder ,IBD, allergies, asthma, diabetes are more common in left-hand subjects?

  (McMANUS et.al ,The LANCET 1993)

- Is left handedness a weak sign of fetal undernutrition?

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Conditions Associated with High Birth Weight

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Statistics

Leading Sites of New Cancer Cases and Deaths – 2008 Estimates

Estimated New Cases*		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 186,320 (25%)	Breast 182,460 (26%)	Lung & bronchus 90,810 (31%)	Lung & bronchus 71,030 (26%)
Lung & bronchus 114,690 (15%)	Lung & bronchus 100,330 (14%)	Prostate 28,660 (10%)	Breast 40,480 (15%)
Colon & rectum 77,250 (10%)	Colon & rectum 71,560 (10%)	Colon & rectum 24,260 (8%)	Colon & rectum 25,700 (9%)
Urinary bladder 51,230 (7%)	Uterine corpus 40,100 (6%)	Pancreas 17,500 (6%)	Pancreas 16,790 (6%)
Non-Hodgkin lymphoma 35,450 (5%)	Non-Hodgkin lymphoma 30,670 (4%)	Liver & intrahepatic bile duct 12,570 (4%)	Ovary 15,520 (6%)
Melanoma of the skin 34,950 (5%)	Thyroid 28,410 (4%)	Leukemia 12,460 (4%)	Non-Hodgkin lymphoma 9,370 (3%)
Kidney & renal pelvis 33,130 (4%)	Melanoma of the skin 27,530 (4%)	Esophagus 11,250 (4%)	Leukemia 9,250 (3%)
Oral cavity & pharynx 25,310 (3%)	Ovary 21,650 (3%)	Urinary bladder 9,950 (3%)	Uterine corpus 7,470 (3%)
Leukemia 25,180 (3%)	Kidney & renal pelvis 21,260 (3%)	Non-Hodgkin lymphoma 9,790 (3%)	Liver & intrahepatic bile duct 5,840 (2%)
Pancreas 18,770 (3%)	Leukemia 19,090 (3%)	Kidney & renal pelvis 8,100 (3%)	Brain & other nervous system 5,650 (2%)
All sites 745,180 (100%)	All sites 692,000 (100%)	All sites 294,120 (100%)	All sites 271,530 (100%)

*Excludes basal and squamous cell skin cancers and in situ carcinoma except urinary bladder.

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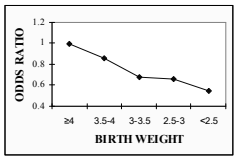
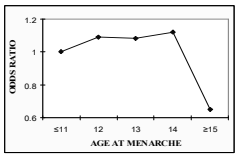
Perinatal nutrition and risk of breast cancer

- Human breast cancer probably originates in-utero.
- Evidence is that Japanese migration to NA takes several generations for breast cancer rates to converge cf- colorectal cancer which converge in single generation. This indicates epigenetic origin, ie modification of expression of genome in-utero, over several generations – this is not a genetic hereditary trait however.
- Etiology is probably multifactorial But high oestrogen exposure in-utero is highly implicated.

(Michels et al 1996, The Lancet)





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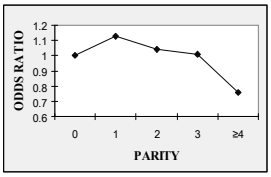

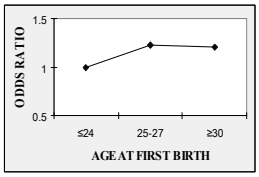

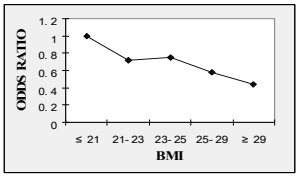

BMI data for pre-menopausal women; post menopausal women have raised BMI associated with increased risk

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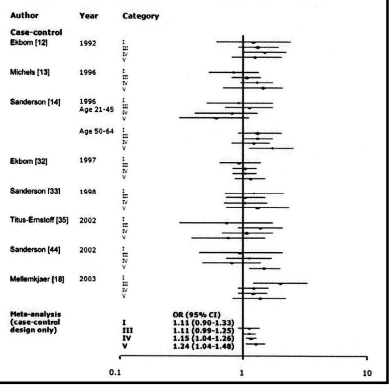
Meta analysis of breast cancer studies 1966 -2007

(Park et al 2008, Breast Cancer Research)

1 = <2500g
2 = reference = 2500-3000g
3 = 3000-3500g
4 = 3500-4000g
5 = 4000g



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Meta analysis of breast cancer studies 1966 -2007

(Park et al 2008, Breast Cancer Research)

- Higher birth weights are associated with increased breast cancer risk.
- There was no association between birth order, prematurity, or maternal smoking and breast cancer risk.
- Higher birth weights have been attributed to higher maternal estrogens levels through epigenetic modification of breast stem cells, increasing risk for development of breast cancer in adulthood.
- The same high estrogen levels and other risk factors which increase risk in utero appear to decrease risk if they are experienced at puberty. Hence high estrogen level at puberty appears protective by producing a decrease in the number of TEB's (terminal duc lobular units in humans)
- Always remember – susceptibility still always requires trigger factor to produce disease!

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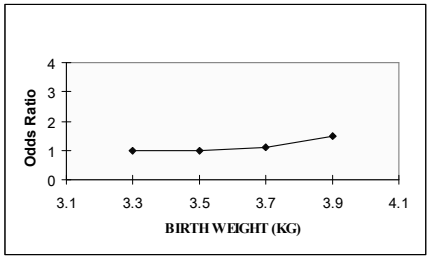
Metastatic prostate cancer



The records of 19,000 men born in Norway between 1920 and 1958 were analysed for birth weight related to prostate cancer later in life. Risk factor found to be 1.5 for birth weight above 3.5 kg.

(*Nilsen et al 2005 Int.J.Cancer*)

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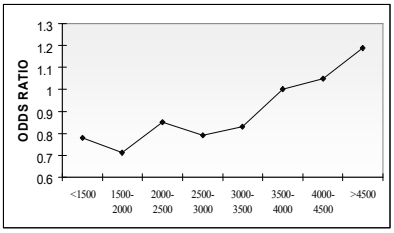
Relationship between high birthweight and childhood acute lymphoblastic leukaemia

A meta analysis of over 10,000 leukaemia patients concluded that high birth weight (kg) was a risk factor for childhood leukaemia.



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Mother's hip size – a possible risk factor for cancer?

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BBC NEWS

Hip size 'gives cancer risk clue'

Women whose mothers have big hips may be more likely to develop breast cancer, research suggests.

Mail Online

How your mother's hips can raise the risk of cancer

By FIONA MACRAE
Last updated at 12:01 09 October 2007

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Breast Cancer

- Helsinki Birth Cohort – 6,370 women born from 1934 to 1944 and whose mothers' pelvic bones were measured.

  (Barker et at, Am J Hum Biol 2008)
- All admissions for breast cancer or deaths during 1971-2003 were recorded.
- Breast cancer had been diagnosed in 300 women (48 died from the disease).

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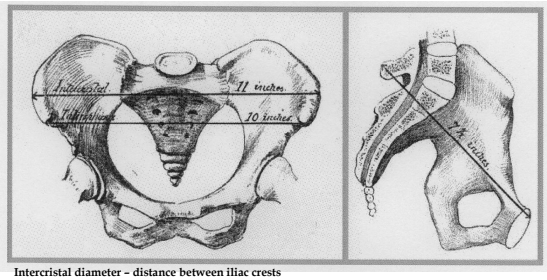
The Intercristal, interspinous and external conjugate diameters of the bony pelvis



- Intercristal diameter – distance between iliac crests
- Interspinous - distance between iliac spines
- External conjugates – distance from pelvic bone to and the fifth lumbar vertebra

(Barker et al 2008, Berkley 1941)

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Hazard ratios for breast cancer according to mothers' pelvic diameters and the length of gestation

	Length of gestation (completed weeks)			
	<40		≥40	
Maternal pelvic measurement	Hazard Ratio per Cm increase	*P*-value	Hazard Ratio Per cm increase	*P*-Value
Intercristal	0.92	0.27	1.34	<0.0001
Interspinous	0.84	0.01	1.18	0.01
External conjugate	0.80	0.04	1.25	0.01

(Barker et at, Am J Hum Biol 2008)

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Breast Cancer - conclusion

- Higher risk of breast cancer in the daughters of mothers whose hips had large intercristal widths and round iliac crests
- Suggestion – hip size and shape are markers of high mother's sex hormones. High hormone concentrations cause genetic instability in differentiating breast cells in their daughters in utero

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Ovarian Cancer

- Helsinki Birth Cohort – 6,370 women born from 1934 to 1944 and whose mothers' pelvic bones were measured.

(Barker et at, Am J Hum Biol 2008)

- All admissions for ovarian cancer or deaths during 1971-2003 were recorded.
- Ovarian cancer had been diagnosed in 55 women (14 died from the disease).

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Ovarian cancer according to mothers' pelvic diameters and age at menarche

	Menarche at age 14 years or less	*Menarche at age 15 years or more*
	Hazard ratio	**Hazard ratio**
Intercristal diameter (cm)		
≤27.5	**1.0**	**1.0**
27.6-28.5	**4.8**	**0.4**
28.6-29.5	**4.9**	**0.6**
>29.5	**7.3**	**0.4**
Interspinous diameter (cm)		
≤25.0	**1.0**	**1.0**
25.1-26.0	**2.1**	**0.8**
26.1-27.0	**2.8**	**0.3**
>27.0	**9.5**	**1.5**

(Barker et at, Am J Hum Biol 2008)

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Ovarian Cancer- conclusion

- Daughters of women with a large distance between the crests were at increase risk of ovarian cancer
- Although this work needs repeating, early menarche, together with short height and wide hips are greatest predictors of daughters ovarian cancer.
- Ovarian cancer is initiated by exposure of fetal ovary to maternal sex hormones.
- Maternal sex hormone profile – product of poor nutrition and growth in early childhood followed by catch-up pre-pubertal growth.

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Developmental Origins and Role of Nutrition

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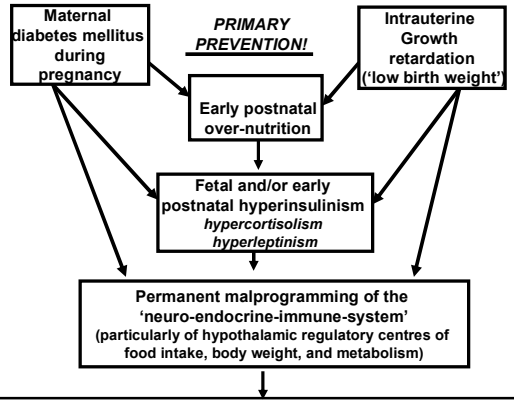

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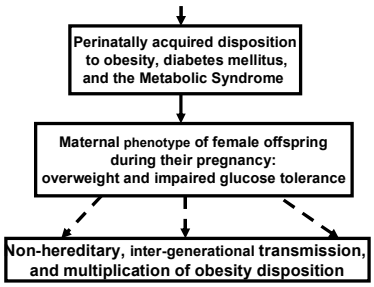

General concept of 'functional teratogenesis' and possible primary prevention of materno-fetal transmission of perinatally acquired obesity disposition, which may pass on epigenetically to succeeding generations of the maternal descendents, leading to a snowball effect, intergenerative multiplication, and thereby considerable contribution to obesity epidemics.

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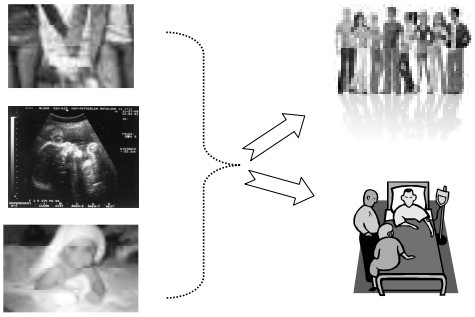
Role of nutrition in early programming



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Preconception and Foetal Nutrition

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The Importance of Folic acid – not just for NTD

- It is estimated that at least 5% of babies are born with some serious congenital abnormality and that by ensuring folic acid sufficiency in the preconceptual and early fetal periods can reduce this by half. Hall 2000 CMAJ; Eichholzer 2007 The Lancet.
- The case for folate and NTD is proven with Canadian rates of NTD falling from 1/1000 births in 1991 to 0.58/1000 births in 1999. This is due in part to increased testing and subsequent termination, but the main supporting reason is the use of folate in supplements and food fortification. Wilson 2007 JOGC
- Folic acid in combination with multivitamin supplemntation has been shown to reduce the risk of congenital:
  - NTD (Odds ratio: 0.67-0.2)
  - CV defects (Odds ratio: 0.78-0.61)
  - Limb defects (Odds ratio: 0.48-0.57)
  - Cleft palate (odds ratio 0.76-0.42)
  - Urinary tract anomolies (Odds ratio 0.48-0.68)
- There is a possible link of increased risk of neoplasia and **exaccerbation of pre-existing cancer** with increased supplementation levels of folate, but this needs confirmation.

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FOLIC ACID

- Epidemiological study of 38,000 pregnant women in USA.
- Folic acid taken for one year 100-400mcg/day prior to pregnancy reduced risk of premature delivery by 70% for early prematurity(20-28 weeks) and by 50% in weeks 28-32.
- Above data is in addition to benefits of folate effects on neural tube development. **US SOC Fetal-Maternal Medicine 2008**
- Note the neural tube relationship with folate is only relevant for the first 4 weeks from conception when the neural tube closes – preconception folate levels are more important than foetal stage folate.
- 33% of babies born before 28 weeks die with a further 30-40% facing lifelong disability of varying severity.
- Only 25-30% of females take folic acid supplements prior to and during pregnancy.
- Folic acid compulsory to women for 12 months before IVF?

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Pre Conception Multivitamin use and Risk of preterm and SGA Birth

Analysis of 1800 women divided into those who had taken a multivitamin daily for minimum of 6 months prior to notification (9 weeks after conception), showed the following:

- 1.2% of daily multivitamin users had pre-term births <34 weeks compared to 3.5% of non vitamin users. Adjusted odds ratio 0.29 (see graph)
- 3.6% of daily vitamin users had SGA (<2500kg) compared to 5.9% of non vitamin users. Adjusted odds ratio 0.64.

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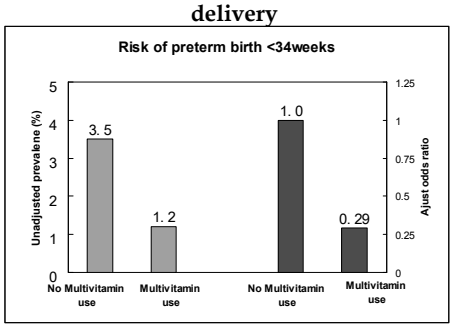
Periconceptional vitamin use and risk of preterm delivery



(Catov et al , Am J Epidemiol 2007)

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Vitamin status and conception, early pregnancy loss and the risk of preterm delivery

- Maternal suboptimal vitamin B_6 status and elevated plasma homocysteine (a marker of poor folate or vitamin B_{12} status) were associated with increased risk of clinical spontaneous abortion. Odds ratio 1.4
- Poor preconception vitamin B_6 status (<30nmol/l) was associated with increased risk of early pregnancy loss and reduced probabilities of conception in a prospective cohort of young Chinese women. Odds ratio 0.7 for loss when B6 was in upper quartile, and hazard ratio of 1.6 for conception.

(Ronnenberg et al, Am J Epidemiol 2007)

- Vitamin C deficiency may lead to premature rupture of the membranes.
- Women with a low vitamin C intake preconceptionally had the elevated risk of preterm premature rupture of membranes (R=2.2, 95% CI; 1.1-4.5)

(Siega-Riz et al 2003, Am J Obstet Gynecol)

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Birthweight and prenatal vitamin/mineral intake

- Vitamin D status has been positively shown to improve birth weight with each additional ug of vitamin D intake associated with an average of 11g increase in birth weight. **Mannion et al CMAJ 2006**
- In Camden NJ, it was found that plasma concentration of α-tocopherol is positively associated with increased fetal growth and reduced risk of small for gestation births. Average gain of 200g birthweight from lowest to highest quintile. Depending on dietary intake – highest quintile equal to supplementation 50-100mg/day

(Scholl et al, Am J Clin Nutr 2006)

- Iron deficiency anemia early in pregnancy was associated with more than 2-fold increase in the risks of low birthweight and preterm delivery.

(Scholl et al, Am J Clin Nutr 1994)

- In another study, supplementation with iron (30mg/day as ferrous sulphate) in early pregnancy (<20wks) increased infant birthweight and lower risk of preterm delivery.

(Siega-Riz et al, Am J Obstet Gynecol 2006)

- Maternal iodine supplements in deficient areas significantly increase birthweight by 157g.

(Mahomed et al, Cochrane Database Syst Rev 1997)

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Periconceptional vitamin and leukemia risk in children with Down Syndrome

- Children with DS experience nearly a 20-fold increased risk of developing leukemia compared with children without DS.
- Children's Oncology Group reported findings on periconceptional vitamin use and leukemia risk in children with Down syndrome. *(Ross et al, Cancer 2005)*
- The study showed a 63% reduction of risk of leukemia with vitamin supplementation in the periconceptional period. Multivitamin use was assessed as frequent or daily compared with no use in preconception (6 months) and throughout gestation period.
- Further when stratified by leukemia type, the significantly reduced risk was observed for acute lymphoblastic leukemia, but not for acute myeloid leukemia.

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You Are What Your Mother Eats!

- Frequency of male births has been steadily decreasing in developed nations.
- Compared with lowest energy level intake at time of conception, those mothers with highest energy intake had a 25% increased chance of having a boy. The effect rose to 40% if this energy increase was associated with having breakfast.
- Rationale, is that male selection in the thrifty genotype is related to times of 'feast', as male births are evolutionary costly.

Matthews et al 2008 Proc. R. Soc B

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The Importance of Maternal/Foetal Vitamin D

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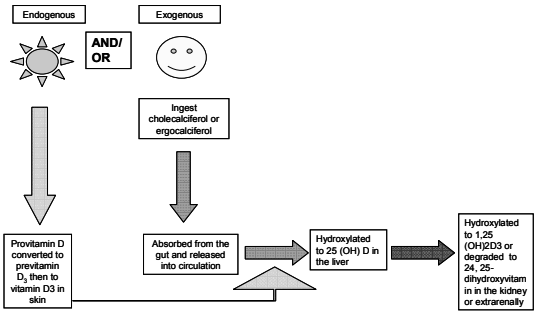
Pathway for Vitamin D synthesis



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Early Programming and Vitamin D

- Vitamin D deficiency in fetal/neonatal stages may effect organ/ physiology development which then has implications in later life and may also alter 'set points' for 'invisible' health risks such as pre-eclampsia in the offspring.
- Metabolic syndrome in cohort of British 45 yr olds now strongly linked with low vitamin D status in the fetal/neonatal period.
- Also association of frequency of multiple sclerosis in northern hemishpere and winter season may have cause in low vitamin D status in fetal/neonatal period. *(Hypponnen et al 2008)*
- Vitamin D deficiency in the perinatal period may lead to programming of susceptibility in tissues which is exaccerbated by later deficiency in vitamin D. This is supported by evidence of cellular responsivity and organ differentiation in early deficiency of vitamin D. This may predispose to the greater risk of various types of cancer now known to be associated with vitamin d insufficiency.
- What else may be 'invisibly' programmed??

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Vitamin D Deficiency, Pre-eclampsia, and Neonatal Imprinting

- 29% of pregnant black and 5% pregnant white women in north eastern USA are vitamin D deficient (serum 25-hydroxyvitamin D 25(OH)D < 37.5nmol/litre)
- 54% of black and 47% of white women have insufficiency of vitamin D (25(OH)D at 37.5-80.0nmol/litre.
- These deficiencies are caused by:
  - too little sunlight
  - higher demand for vitamin D during pregnancy
  - too low intake – including supplements providing 400iu
- Vitamin D deficiency during pregnancy has been linked with short and long term problems in the offspring:
  - impaired growth
  - skeletal problems
  - type 1 diabetes
  - asthma
  - schizophrenia
- Low maternal vitamin D status means neonate is born deficient in vitamin D

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Vitamin D and Pre-eclampsia

- Case controlled study of 2200 pregnant women found:
  - 4.9% incidence (59 cases) of pre-eclampsia
  - Mothers who developed pre-eclampsia had an average of 15% lower vitamin D status than controls 45nmol/litre vs 54nmol/litre.
  - Vitamin D status of < 37.5nmol/litre associated with 5-fold increase in pre-eclampsia risk.
  - There is a dose response relationship of decreased pre-eclampsia risk with increased serum level of vitamin D up to levels of 200nmol/litre (Bodnar et al 2007, J.Clin.Endocrin Metab)

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Vitamin D and risk of pre-eclampsia

(Hyppönen et al, Eur J Clin Nutr 2007)

- Northern Finland Birth Cohort 1966 (2969 women)
- Vitamin D recommendation was 2000IU/day
- Risk of pre-eclampsia **was halved** among women who had received Vitamin D supplementation regularly during the first year of life compared to irregular/none users (2.1% vs 3.8%).
- Vitamin D intake (large doses) in infancy may affect long-term programming of the immune response pattern.

Proposed mechanism is to shift Th1 dominance prevalent in pre-eclamptic women to be more balanced with Th2

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Maternal vitamin D and calcium and musculoskeletal health

- Literature suggests that the risk of osteoporosis and fragility fractures in adulthood might be programmed by environmental influences during gestation.
- Data from Australia and UK suggests that maternal vitamin D status in pregnancy affects intrauterine skeletal mineralisation and bone matrix turnover "set points" which are then expressed in adulthood.
  (Pasco et al, Medical Hypotheses 2008)
- Vitamin D is necessary for the bones to absorb calcium, which plays a crucial role in bone health. The fetus accumulates about 30 g of calcium in utero from its mother – 80% of this transfer occurs in the last trimester.
  (Prentice, Annual Rev Nutr 2000)

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Vitamin D and brain development

- Eyles et al (2003) found that gestational Vitamin D_3 deficiency has profound effects on the developing brain including changes in volume, shape, cell proliferation and growth factor expression in study on rats.
- The neuropathological findings of enlarged lateral ventricles and reduced cortical thickness are frequently reported in patients with schizophrenia and bipolar disorders.
- The pattern of brain structure difference reported with schizophrenia and depressive disorders is consistent with that found in vitamin D deficiency.

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Maternal Vitamin D intake during pregnancy and risk of wheezing in early childhood

Aberdeen, Scotland Study *(Devereux G et al. Am J Clin Nutr 2007)*

- Low maternal Vitamin D intake during pregnancy is associated with increased wheezing symptoms in children at the age of 5 years.
- These associations were independent of maternal smoking status and maternal intakes of vitamin E, zinc, calcium and vitamin D by the 5 years old children.
- The Vitamin D intake range from 46 to 751 IU/d.
- Higher intake of vitamin D was associated with odds ratio of 0.33 ofpresence of persistent wheeze in at 5 years.
- In addition, lower maternal total Vitamin D intakes in pregnancy are associated with decreased bronchodilator response (p=0.04).
- No associations between maternal Vitamin D intakes and spirometry or exhaled nitric oxide concentrations.

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Maternal Vitamin D intake during pregnancy and risk of recurrent wheeze in early childhood

Project Viva, Massachusetts *(Camargo et al. Am J Clin Nutr 2007)*

- A prospective pre-birth cohort study with 1194 mothers participated
- A higher maternal intake of vitamin D during pregnancy was associated with lower risk of recurrent wheeze in children 3 years of age ($p < 0.001$).
- In addition, among children conceived in the winter months, the inverse association between maternal intake of Vitamin D and risk of recurrent wheeze was stronger.
- The vitamin D intake range from 60 to 1145 IU
- In 19% of women, maternal intake of vitamin D during pregnancy was < 400 IU/day.
- Previous studies showed that higher Vitamin D intake by pregnant mothers reduces asthma risk by as much as 40% in 3 to 5 years old children.

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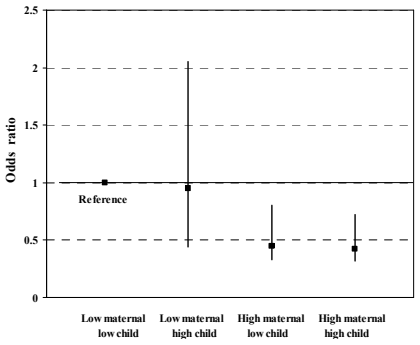
Vitamin D intake and risk of recurrent wheeze (con't)



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Antioxidants and risk for wheezing and asthma

- In study from Scotland, low maternal vitamin E intake was associated with an increased risks for wheezing and asthma in 1253 children at 2 and 5 years of age. Also low maternal zinc intake during pregnancy was associated with and increased risk of asthma and eczema outcomes in children at 5 years of age.

  (Devereux et al, Am J Respir Crit Care Med 2006)
- In Project Viva, similarly maternal intakes of vitamin E and zinc were negatively associated with any wheeze and recurrent wheeze in 1290 children at the age of 2 years.

  (Litonjua et al, Am J Clin Nutr 2006)
- The UK ALSPAC study reported low umbilical cord selenium concentrations associated with an increased likelihood of persistent wheeze in 2044 children between ages 0-6 months and 30-42 months and cord blood iron was negatively associated with late-onset wheeze (30-42 months) and eczema at 18-30 months.

  (Shaheen et al, Eur Respir J 2004)

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Maternal Vitamin and Mineral Supplementation in the Foetal period

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Multivitamin Supplementation and Childhood Cancer

- About 10,000 children under 15 develop cancer in the USA each year.
- The most prevalent forms are: leukeamia, malignant brain and spinal cord tumours and neuroblastoma.
- In a review of 61 publications, 7 studies met the inclusion criteria for daily or frequent use of multivitamins during pregnancy

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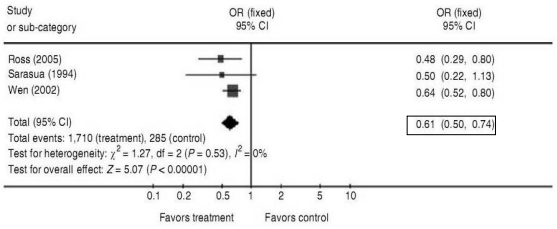
Maternal Multivitamin intake and Childhood Cancer

(Goh et al, Clin Pharm Ther 2007)



Acute lymphocystic leukemia

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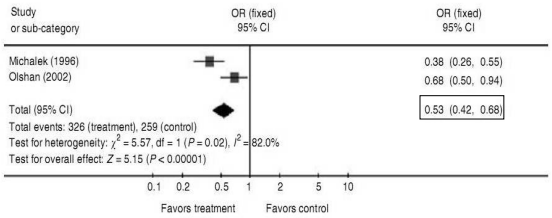
Maternal Vitamin intake and Childhood Cancer (con't)



Neuroblastoma

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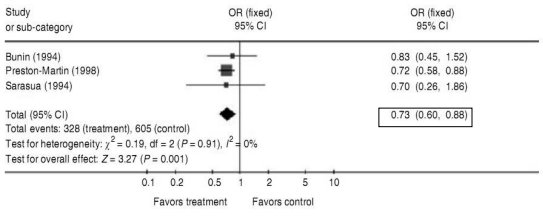
Maternal Vitamin intake and Childhood Cancer (con't)



Brain tumor

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Accumulation of Fatty Acids in Infant Brain

- 60% by weight of brain at birth is lipid
- 18% of total fatty acids (11% brain weight) is DHA
- 12% of total fatty acids (8% brain weight) is AA
- Brain cell division, brain growth and fatty acid deposition occurs substantially in third trimester of pregnancy (400 - 500% growth)
- From birth to 3 months of age, DHA and AA accumulation continues at same level. This is time of maximum neural development with synaptic development, myelination and cell growth (but not division) in brain stem and spinal cord.
- DHA continues to accumulate in brain and neural tissue up to 2 years of age, and then at a much slower rate into adulthood. *Martinez 1999 Carlson 2001*
- In pregnancy, DHA and AA must be obtained from maternal bloodflow. The placenta preferentially selects AA and DHA
- If DHA is deficient, AA and then docosapentaenoic acid (DPA) is laid down

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Summary of Benefits of DHA and AA

Many studies on the effects of increased levels of DHA and AA have been performed over the past 30 years. Analysis of the whole data strongly suggests the following benefits:

- Improved cognitive function (benefits lifelong)
- Improved visual acuity (probably by improvement of brain translation of visual information)
- Increases in gestation time and birth weight
- Improvements in neonate growth rate
- Reduction in severity of neonatal allergy

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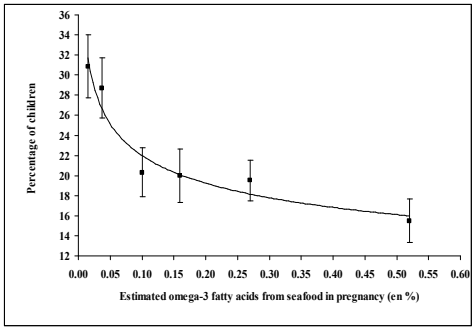
Seafood Consumption In Pregnancy and Neurodevelopmental Outcomes

Prevalence of children with low verbal IQ according to mothers omega-3 fatty acid intake from seafood consumption. ALSPAC – Avon Longitudinal Study of Parents and Children



(Hibbeln et al, Lancet 2007)

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Can Omega 3 Fatty Acids Protect Against Perinatal Depression?

- Pregnant women receiving the omega 3 –PUFA (3.4 g/d) or placebo for period of last 8 weeks were assessed for depressive symptoms. Women taking the omega 3 –PUFA had significantly lower scores of standardised ratings of depression and significantly higher response rate (62% vs 27%). *(Su et al, J Clin Psych 2008)*

- A study published last month compared fatty acid blood levels between depressed and non-depressed women in the final third trimester. Women with high DHA , high total omega 3 and low omega 6:3 ratio were associated with significantly reduced risk of depression. Authors concluded that women with lower omega 3 - PUFA levels are 6 times more likely to be depressed antenatally compared to women with higher omega 3 PUFA levels.
(Rees et al, Psychiatry Research 2009)

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Fetal period

- Encourage lifestyle modifications away from those predisposing to metabolic syndrome – reducing severity e.g level of hyperinsulineamia and hypercholesteroleamia will be helpful to the fetus/offspring.
- Ensure protein intake at least 80g/day
- Ensure high intake of fruit and vegetables (8-10 portions/day)
- Stop smoking, and preferably eliminate alcohol.
- Provide following supplementation/diet
  - Supply a good quality multivitamin and mineral.
  - Provide additional folic acid to each 600-800mcg/day, and vitamin B12 to 20ug-50ug/day
  - Provide vitamin D supplementation at minimum of 25ug/day level
  - Provide vitamins C and E to daily levels of minimum 200mg and 50mg
  - Increase DHA and to lesser extent EPA status with supplementation of fish oil – approximate minimum 1000mg DHA/day
  - Increase calcium and magnesium intake to ensure 1200mg elemental calcium and 300mg elemental magnesium.
  - Provide probiotic (and prebiotic) to mother minimum level 8 billion/day

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Neonatal and Infant Period and Nutrition

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Nutrition and risk of type 1 Diabetes

- Type 1 diabetes one of the most prevalent chronic diseases with onset in childhood.
- Type 1 diabetes (insulin-dependent) is an autoimmune disease caused be progressive destruction of insulin-producing β-cells of the pancreas.
- Result of interactions between genetic susceptibility and environmental exposures.

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Vitamin D and risk of type 1 diabetes mellitus (EURODIAB study)

- Seven European countries participated in this multinational case-control study
- Combined data from 820 patients and 2335 controls were analysed
- **Vitamin D supplementation in first year of infancy was associated with a 33% reduction in the risk of developing type 1 diabetes before the age of 15**
  (combined OR =0.67, 95%CI: 0.53, 0.86, p<0.001).

Diabetologia 1999

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Vitamin D and risk of type 1 diabetes (Finnish Study)

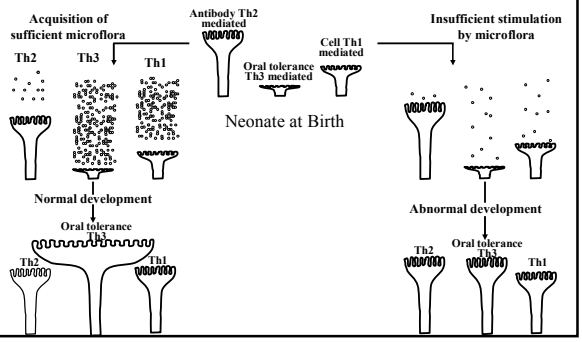
- Retrospective study with a 1966 North Finland birth cohort of 10 366 children
- 81 children were diagnosed with type 1 diabetes before 1998
- Vitamin D supplementation during the first year of children was associated with decreased frequency of type 1 diabetes by age 31 years (regular/irregular vs no supplementation)
- In children who received vitamin D supplementation regularly the **risk of type 1 diabetes was reduced by about 80%. In other words children with no supplementation had an 8 –fold risk diabetes.** if the recommended dose was given (2000 IU/day)
- Infants suspected of having had rickets during the first year of life had a threefold risk of developing type 1 diabetes compared with others.

Hyppönen E et al. Lancet 2001

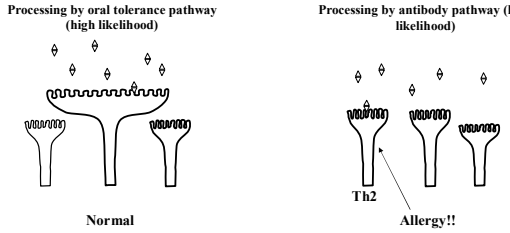
Neonatal Programming of the Immune System

- The neonatal immune system is substantially underdeveloped at birth with bias towards Th2.
- There then follows a period of profound plasticity which allows the immune system to be driven in different directions.
- A major factor in normal development during this period is the acquisition of normal flora, which drives the development of Th1 and tolerance.
- If this does not occur in first 0-6 months then immune system remains Th2 dominant and the plasticity hardens leading to predisposition to allergy which can affect the individual lifelong.

Maturation of the Human Neonate Immune System by Acquisition of Normal Flora



Different Likelihood of Response to First Experience of New Antigen (Allergen)



Probiotic Studies on Prevention of Allergic Diseases

Reference	No. of Subjects	Study design and population	Treatment and dose	Prenatal duration of treatment	Postnatal duration of treatment	Effect
Kalliomaki 2001 Kalliomaki 2003 Kalliomaki 2007	At 2 years: 132 At 4 years: 107 At 7 years: 115	DBPC At least one first-degree relative with allergic disease	*L. rhamnosus* at $1x10^{10}$ cfu/day	Pregnant women 2-4 wk before delivery	6 months	At 2 years: Significant reduction (50% in infant eczema at 2 years (p=0.008). At 4 years follow up: Atopic eczema was diagnosed in 26% of children in probiotic group compared with 42% in placebo. At 7 years follow up: Significantly lower cumulative risk for developing eczema in probiotic group than in placebo.
Rautava 2002	62	DBPC Pregnant women with family history of atopy and breastfeeding	*L. rhamnosus* (ATCC 53103) at $2x10^{10}$ cfu/day	Pregnant women 4 wk before delivery	12 months	Maternal intake of probiotic associated with significant reduction in infant eczema at 2 years (p=0.03).

Probiotic Studies on Treatment of Allergic Diseases

Reference	No. of Subjects	Study design and population	Treatment and dose	Duration of treatment	Effect
Weston 2005	53	DBPC Moderate of severe atopic dermatitis at 6-18 months	*L. fermentum* VRI-003 PCC at $2x10^9$ cfu/day	8 weeks	Significant reduction in SCORAD in probiotic group (p=0.03) at week 16, but not in placebo group.
Viljanen 2005	230	DBPC Atopic eczema/dermatitis syndrome± suspected Cow's milk allergy in infants	Group 1: *L. rhamnosus* at $1x10^{10}$ cfu/day Group 2: *L. rhamnosus* *L. rhamnosus* *B. breve* *P.Freudenreichii ssp. Shermanii JS* at $2.44x10^{10}$ cfu/day	4 weeks	No significant differences in SCORAD reduction between the probiotic groups and placebo group. Significant reduction in SCORAD in LGG group in IgE-sensitized infants compared to placebo (p=0.04).
Isolauri 2000	27	DBPC Atopic eczema (during exclusive breastfeeding)	*L. rhamnosus* GG (ATCC 53103) at $3x10^8$ cfu/g formula or*B. lactis* Bb-12 at $1x10^9$ cfu/g formula	8 weeks	Significant reduction in SCORAD in probiotic groups compared to placebo at 8 weeks (p=0.002).

Neonatal period

- Do not overfeed – particularly if baby is low birthweight, try not to accelerate 'catch-up'
- Breast feed for a minimum of 3 months and thereafter continue with reducing reliance for up to 1 year.
- Most neonatal nutrition is reflected by quality of the breast milk.

- **For breast feeding mother:**
- **Ensure protein intake at least 80g/day**
- **Ensure high intake of fruit and vegetables (8-10 portions/day)**
- **Stop smoking, and limit alcohol to 1 glass per day**
- **Provide following supplementation/diet**
  - **Supply a good quality multivitamin and mineral.**
  - **Provide additional folic acid to each 600-800mcg/day, and vitamin B12 to 20µg/day**
  - **Provide vitamin D supplementation at 25µg/day level**
  - **Provide vitamins C and E to daily levels of minimum 200mg and 50mg**
  - **Increase DHA and to lesser extent EPA status with supplementation of fish oil – approximate minimum 1000mg DHA/day**
  - **Increase calcium and magnesium intake to ensure 1200mg elemental calcium and 300mg elemental magnesium.**
- **Provide probiotic and prebiotic at levels of minimum 8 billion per day.**
- **Provide probiotic to neonate at minimum 2 billion per day**

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For formula feeding mother:

- **Provide increased levels of vitamin D_3(10mcg) over and above amount in formula.**
- **Provide high DHA fish oil or vegetarian DHA to provide minimum of 200mg DHA but not more than 500mg.**
- **Provide probiotic at minimum 2 billion per day.**

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Summary

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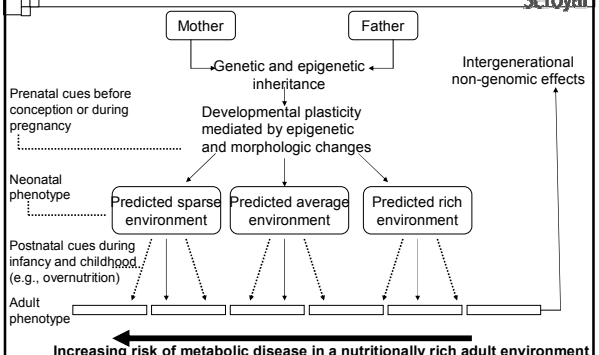

Environmental Cues during Development, Developmental Plasticity, and Determination of the Adult Phenotype.

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- Preconceptual, fetal and neonatal health is just now being recognised as having profound direct implications on adult health and risk of major chronic disease. Most authorities now agree that of the accumulating factors which affect our risk of chronic adult disease HALF are acquired during the perinatal period.
- As such perinatal programming offers a new paradigm to add to the genetic, and adult environment as determinants of chronic disease.
- The relationship with birthweight is likely a blunt instrument of measure of malnutrition or other insult at the perinatal period. Hence the liklihood of U shaped curves for risk with some diseases when related to birthweight.
- The relationship is complex throughout the perinatal period, with different developmental stages having greater or lesser importance.
- The fetal programming, can be as a result of organ development or sub-optimal set point fixing in any part of the neuro-immuno-endocrine system.
- Foetal programming increases risk but does not obviate beneficial modifications due to diet and lifestyle later in life. Indeed, it increases the importance of these in individuals who are at increased risk

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- **Science is only at the beginning of the process of unravelling this concept, but the implications are enormous.**
- **Elucidation of the impact of preconceptual and perinatal nutrition will be the most exciting and most valuable research area for nutritional medicine in the next 25-50 years, with proof of effect being felt by our grand and great grandchildren long after we've gone!**