

Helpdesk Report: 55. Fetal Health and NCDs

Date: 14 June 2011

Query: What is the evidence about the relationship between gestational nutrition, maternal nutrition and preterm delivery on the one hand and disposal to NCDs in the adult life of the child? Please consider the Barker hypothesis, the lifecourse approach and any other models advanced recently in addition to any other evidence available.

Enquirer: DFID UK

Content

1. Overview
2. The programming of chronic disease by impaired fetal nutrition, WHO
3. The Barker Hypothesis
4. Barker papers
5. Diabetes and more on heart disease
6. Cancer risk
7. Lung disease
8. More on fetal/maternal nutrition and health implications
9. Additional information

1. Overview

The WHO document outlined in section 2 gives a good overview of the evidence about the relationship between gestational and nutrition, and disposal to NCDs. It notes that smaller size at birth appears to be more related to chronic disease when due to intrauterine growth rather than premature birth. Maternal and fetal nutrition are related to size at birth. They are very closely related to each other but not entirely synonymous, fetal health can be related to factors outside the mothers' influence.

Little information on a link between premature birth and disease later in life was found within the scope of this report. One explanation may be that survival of preterm babies is a relatively recent phenomenon so long-term studies are limited. Crump et al. (2011) found preterm birth associated with a modestly increased risk of diabetes. De Boo & Harding (2006) find some studies that suggest prematurity increases the risk of several diseases, although the relative contributions of fetal growth and gestational age remain uncertain. Godfrey and Barker (2000) found evidence that cardiovascular disease is linked to fetal growth restriction rather than to premature birth.

Many studies found evidence which confirmed the link between fetal nutrition and disease in the adult life of the child. A few find the evidence is not clear. Most commonly discussed is the link with heart disease and then associated with this, diabetes. Information is also found on the link with cancer and lung disease. These were the four main NCDs identified in helpdesk report 46. A link with cancer was found but is generally weak. Stronger studies show that restricted fetal growth can alter lung development. This problem may be

exacerbated in developing country cities where pollution levels are high. There seems to be a clearer link between being born premature and impaired lung function.

Most information in this report was found in medical journals where only abstracts are available without a subscription so details are not always given. The studies found were mostly conducted in more developed countries but there is some evidence from India.

The Barker Hypothesis is commonly referred to and states that undernutrition *in utero* permanently changes the body's structure, physiology, and metabolism which leads to higher susceptibility to disease in later life, particularly heart disease, stroke, diabetes and hypertension. This is also sometimes referred to as fetal programming of chronic disease.

The lifecourse approach looks at childhood, adolescence and the life cycle beyond as well as looking at fetal influences. It should be noted that many factors later in life influence the incidence of disease as well as maternal and gestational nutrition.

Some information found suggests that maternal nutrition before pregnancy is as important or more important than nutrition during pregnancy.

2. The programming of chronic disease by impaired fetal nutrition, WHO

Programming of Chronic Disease by Impaired Fetal Nutrition, Evidence and Implications for Policy and Intervention Strategies

Delisle H, WHO, 2002

http://whqlibdoc.who.int/hq/2002/WHO_NHD_02.3.pdf

Undernutrition and micronutrient deficiency diseases continue to affect mothers and children in developing countries, and remain the major focus of nutrition intervention efforts. Low birth weight (LBW) associated with retarded fetal growth is at least twice as common in developing countries, and it reflects poor maternal nutrition, although maternal smoking may also emerge as an important factor in some societies.

This WHO document reports on a number of epidemiological studies linking small size or disproportions at birth and chronic diseases. Some findings include:

- Smaller size at birth appears to be more closely related to chronic disease when due to intrauterine growth impairment rather than premature birth.
- Evidence of the link between fetal nutrition and chronic disease is provided by several studies in twins and observations in populations exposed to famines, although there are some conflicting findings.
- Observational and cohort studies first found an association between LBW and later disease rates in England and Scandinavia. Many studies have since confirmed the link, including in the USA and India.
- Based on the findings of some 80 studies around the world, the inverse association of birth weight and systolic blood pressure was consistently observed.
- In the British cohorts, impaired glucose tolerance and type 2 diabetes showed a three-fold decline with increasing birth weight. These observations were confirmed in many other studies, including in Sweden and India.
- The large body of data on people exposed to the Dutch Famine (1944-45) while *in utero* support the hypothesis of chronic disease programming by intrauterine undernutrition, and highlight differences in long-term effects according to the timing of the insult.

The report discusses fetal programming of chronic disease. The notion implies that during critical periods of prenatal growth, changes in nutritional and hormonal milieu of the

conceptus may alter the full expression of the fetal genome, leading to permanent effects on a range of physiological functions and structures.

The report finds that genes and nutrition interact *in utero*, but short nutrient and oxygen supply, combined or not with maternal constraints, appear to be predominant factors of impaired fetal growth. Fetal malnutrition is not synonymous with maternal nutrition, however. An inadequate supply of nutrients (or oxygen) to the fetus may also be due to maternal disease, abnormal utero-placental blood supply, or to placental insufficiency.

Poor nutritional status and poor food intake of mothers is recognised as a major factor of fetal growth impairment in developing countries and poorer population groups. Maternal nutritional status at the onset of pregnancy appears to be more critical than nutritional adequacy during pregnancy for fetal growth, but it is not known whether this is also the case for chronic disease programming.

Early or chronic fetal undernutrition appears to be linked with higher risk of hypertension, obesity and CHD. In contrast, impaired fetal nutrition in late pregnancy exposes to insulin resistance and type 2 diabetes.

Other findings on maternal nutrition include:

- Maternal diet quality rather than quantity was found to be related to the natal phenotype in India.
- Micronutrients believed to have a programming role include iron, folate, zinc, magnesium, calcium, and vitamin C.
- It is likely that nutrition helps prevent, but not reverse, impaired fetal growth.

The report notes that there are clearly cumulative influences on chronic disease risk throughout the life cycle, and links between fetal growth and chronic diseases have to take this into account. Also, epidemiological associations do not prove a cause-and-effect relationship. Rather, it is possible that LBWs and higher rates of diseases are both related to a common cause. Poverty is seen as a common determinant, and according to some researchers, socioeconomic status can hardly be fully accounted for. In only a few studies, including one on heart disease in South India, the inverse association of size at birth and chronic disease was no longer significant when adjusting for socioeconomic status. This association was little affected in most studies, nonetheless low socioeconomic status may predispose to suboptimal fetal growth and to lifestyles later that increase disease risk, such as smoking, lack of physical activity, and “anthrogenic” diets which is not so relevant in developing countries. Genetic factors are also suspected of being responsible for both impaired fetal growth and disease.

The report concludes that though there are still controversial areas and information gaps, there is accumulating evidence for an inverse association between size at birth and chronic diseases. Fetal programming likely represents one more risk factor for chronic diseases, in addition to genetic and environmental factors. The development of chronic disease should be conceived as resulting from cumulative risks throughout the course of life, an approach that may easily reconcile apparently conflicting theories based on genetic susceptibility, fetal programming, or lifestyle risk factors.

It is estimated that intrauterine programming affects 30 million children annually, of whom 75% are in Asia and 20% in Africa.

3. The Barker Hypothesis

The Barker Theory, New Insights into Ending Chronic Disease

The Barker Foundation
<http://www.thebarkertheory.org/>

Dr. David Barker is a physician and researcher. In 1989, with colleagues at the MRC Unit, University of Southampton, he discovered the relationship between birth weight and the lifetime risk for coronary heart disease. He showed that the lower the weight of a baby at birth and during infancy, the higher the risk for coronary heart disease in later life.

The theory is that undernutrition *in utero* permanently changes the body's structure, physiology, and metabolism. This then programmes chronic diseases in later life, including coronary heart disease and related disorders, such as stroke, diabetes and hypertension.

This website includes an overview of the hypothesis and the science. It has sections on links between birth weight and:

- coronary heart disease
- high blood pressure
- stroke
- type 2 diabetes
- osteoporosis
- ageing
- breast and ovary cancer

A publications section lists academic publications, refereed papers and book chapters but does not include web links.

Early Origin of Coronary Heart Disease (the “Barker hypothesis”), Editorial

Paneth N & Susser M, *BMJ* 310(6977), 1995
<http://www.bmj.com/content/310/6977/411.full>

The hypothesis of Professor David Barker and colleagues working in Southampton is that “a baby's nourishment before birth and during infancy,” as manifest in patterns of fetal and infant growth, “programmes” the development of risk factors such as raised blood pressure, fibrinogen concentration, and factor VIII concentration and glucose intolerance and hence these are key determinants of coronary heart disease.

Since 1987 the group has elaborated this hypothesis in at least 40 papers (many of them in the *BMJ*) and two books. Although some evidence comes from comparisons among populations, the most recent approach has been to seek places where infant anthropometric measures were systematically recorded many years ago (Hertfordshire and Preston). Middle aged and elderly survivors have then been searched out for study. This idea is in line with a body of research of the past 50 years on the deferred effects of fetal exposure to viral infections, the atomic bomb, undernutrition and famine, hormonal treatment in pregnancy, and smoking.

None of the Southampton studies provides an actual measure of nutritional intake in mothers or babies. Early nutrition is inferred indirectly from fetal and infant growth, and fetal growth especially is a doubtful surrogate measure. Thus, even if we take the findings as valid, we still must ask whether nutrition or some other effect is being measured. In addition, inconsistencies in the data, with many findings failing to support the “baby's nourishment” hypothesis, have not gone unnoticed, and evidence contrary to the early experience hypothesis has been published.

This edition of the journal contains four relevant studies. One paper is a further contribution from the Hertfordshire cohort (another paper from this cohort was published last month), whereas the three other papers cast doubt on some aspects of the early nutrition thesis.

Strachan et al. find mixed evidence about whether the health of migrants in England relates to where they came from or where they went to. Although for coronary heart disease, initial and current place of residence contribute equally to the risk of death, for stroke, current place of residence contributes more, particularly if it is London. This kind of analysis, limited to place of origin (which is not necessarily place of birth) rather than to individual exposures in early life, strongly suggests the potential for confounding by migration in the Southampton studies but does not constitute a direct test of the hypothesis.

The two papers from Southampton support the hypothesis inconsistently. Although in men, weight at age 1 predicts cardiovascular disease in their 60s, birth weight does not. On the other hand, it seems at first glance that in women of the same age, birth weight, but not infant weight, is significantly associated with some risk factors for coronary heart disease (low/high density lipoprotein cholesterol concentration and most measures of glucose intolerance), although not with others (blood pressure and concentrations of total cholesterol, fibrinogen, and factor VIII).

The significant associations with birth weight are suspect because they are controlled for current body mass index; from inspection of the raw data we guess that without this adjustment many would not hold up. Body mass index may well be an intervening variable; to adjust for such a variable is to overcontrol and, usually, to misinterpret.

Body mass index is a much more powerful predictor of insulin concentrations than is birth weight (see tables III and IV) and is positively related to birth weight. So to control for current body mass index when assessing the effect of birth weight is to cancel out the positive effect of birth weight on body mass index and thence on risk of glucose intolerance. This allows the effect of birth weight in the direction favoured by the authors to remain unopposed. The baby's nourishment hypothesis is not easily reconciled with the finding in this paper that plasma insulin concentration relates to current body mass index much more strongly than to birth weight.

A paradox inherent in the scientific method is that, attached though we are to the hypotheses we formulate, we must subject them to assault and search for circumstances that really test their resilience. Hypotheses, as Silverman has written, citing Galileo, must be "subjected to an ordeal." The results of the ordeal may prove consistent with the hypothesis or inconsistent with it, forcing its reformulation. When a hypothesis is clearly focused, reformulation is possible; when it is broad and fuzzy, no reformulation is necessary as much of the evidence can be incorporated into it. Thus the inconsistency in the results from Southampton is linked to the failure to specify hypotheses more tightly focused than "a baby's nourishment ... influences the diseases it will experience in later life."

With so broad a hypothesis, researchers are free to test the relation between a whole range of possible markers of a baby's nourishment and any diseases it will experience and to pronounce important those relations that are confirmed. In this work, researchers faced with findings that fail to support the hypothesis seem not to be treating them as threats to the integrity of the hypothesis.

The notion of induction, that knowledge is gained by the summarising of facts and experiences, has fallen on hard times as a credible approach to research. Indeed, it is easy to see the barrage of papers from Barker's group as an inductionist's delight. Example is piled on example, each somewhat consistent with the hypothesis but none seriously testing it. Francis Bacon, the founding father of the inductionist approach, advocated something else: "The induction which is to be available for the discovery and demonstration of sciences and arts must analyse nature by proper rejections and exclusions, and then after a sufficient number of negatives, come to a conclusion on the affirmative instances." What is missing in this work so far is the rigorous testing by rejections and exclusions—that is, by deliberate attempts at refutation.

Two papers in this issue suggest some ordeals to which the baby's nourishment hypothesis might be subjected, and we add some more:

- Twins have greatly restricted fetal growth in the third trimester. But Christensen et al. report that the mortality among surviving twins differs little from that among the general population. Given that cardiovascular disease is the leading cause of death in older adults, an effect of growth retardation would be expected. The Southampton group has not provided any information about twins.
- One of the strongest associations uncovered by the Southampton group is the relation between a high ratio of placental weight to birth weight and subsequent risk factors for coronary heart disease. But what exactly influences placental weight? The Southampton group suggests anaemia (thus bringing in nutrition). But maternal diabetes, maternal smoking, and gestational age may influence the relation of birth weight to placental weight. Perry et al. raise the possibility that maternal obesity may as well. No account has yet been taken of these variables by the Southampton group.
- Much of the support for the early nutrition hypothesis comes from observations of subjects who constitute a very small proportion of the birth cohort from which they arose. Selection bias is likely to be operating. Attrition by death, migration, and simple "untraceability" is virtually never distributed equally across groups at risk. What would the results look like if access were available to a cohort in whom the losses were not so extreme?
- Smoking by the mother is a key determinant of both birth weight and smoking in offspring and hence of coronary heart disease in them. What would the results look like if smoking in the mother was an additional factor in the equation?
- Social class exerts its noxious effects on health in many ways. Would the findings still hold if we truly knew the social status of the subjects throughout their lifetime, as well as that of their parents? In neither of the two most recent papers from Southampton did the measure of social class at birth—occupation of the father—correlate with either birth weight or weight at age 1 in England in the 1920s. The absence of these highly consistent and well recognised associations points to weak measures and misclassification of either the social background or the growth of the child, or both, if not to biased sampling of the population.
- Most importantly, infant anthropometry is taken as a proxy for fetal and infant nutrition, although many other factors can affect these measures. What would the results look like if the exposure were nutritional intake itself? The best available evidence indicates, firstly, that only below a famine threshold does nutritional deprivation cause more than minor retardation of fetal growth and, secondly, that only in the third trimester are the effects substantial.

The Developmental Origins of Adult Disease (Barker) Hypothesis

De Boo HA & Harding JE, *Australian and New Zealand Journal of Obstetrics and Gynaecology* 46(1), 2006

Abstract <http://onlinelibrary.wiley.com/doi/10.1111/j.1479-828X.2006.00506.x/full>

Many studies have provided evidence for the hypothesis that size at birth is related to the risk of developing disease in later life. In particular, links are well established between reduced birthweight and increased risk of coronary heart disease, diabetes, hypertension and stroke in adulthood. These relationships are modified by patterns of postnatal growth. The most widely accepted mechanisms thought to underlie these relationships are those of fetal programming by nutritional stimuli or excess fetal glucocorticoid exposure. It is suggested that the fetus makes physiological adaptations in response to changes in its environment to prepare itself for postnatal life. These changes may include epigenetic modification of gene expression. Less clear at this time are the relevance of fetal programming phenomena to

twins and preterm babies, and whether any of these effects can be reversed after birth. Much current active research in this field will be of direct relevance to future obstetric practice.

An important but as yet unanswered question is to what extent the associations with low birthweight may be influenced by gestation length rather than fetal growth. Many of the early epidemiological studies had quite limited data on gestational age of the subjects, and survival of large numbers of preterm babies is a relatively recent phenomenon so that long-term outcome studies are extremely limited. Furthermore, most of the experimental work has focused on impaired fetal growth, largely because of the lack of suitable animal models of prematurity. Nevertheless, there are now a number of studies suggesting that prematurity itself may increase the risk of several of the diseases of interest, although the relative contributions of fetal growth and gestational age remain uncertain. Blood pressure is elevated in some cohorts of young adults born preterm and is reported to be inversely related to gestational age in some larger population studies. Insulin resistance, elevated fasting insulin levels, and elevated plasma cortisol levels have also been reported in young adults born preterm. If a relationship between adult disease risk and gestation length is confirmed, then this may provide some interesting new challenges for obstetric practice, since elective early delivery, even close to term, may have implications for life-long health of the baby.

4. Barker papers

Fetal Nutrition and Cardiovascular Disease in Adult Life

Barker DJP et al., *The Lancet* 341 (8850), 1993

Abstract <http://www.sciencedirect.com/science/article/pii/014067369391224A>

Babies who are small at birth or during infancy have increased rates of cardiovascular disease and non-insulin-dependent diabetes as adults. Some of these babies have low birthweights, some are small in relation to the size of their placentas, some are thin at birth, and some are short at birth and fail to gain weight in infancy. This paper shows how fetal undernutrition at different stages of gestation can be linked to these patterns of early growth. The fetuses' adaptations to undernutrition are associated with changes in the concentrations of fetal and placental hormones. Persisting changes in the levels of hormone secretion, and in the sensitivity of tissues to them, may link fetal undernutrition with abnormal structure, function, and disease in adult life.

Maternal Nutrition, Fetal Nutrition, and Disease in Later Life

Barker DJP, *Nutrition* 13(9), 1998

<http://www.sciencedirect.com/science/article/pii/S0899900797001937>

Recent findings suggest that many human fetuses have to adapt to a limited supply of nutrients and in doing so they permanently change their physiology and metabolism. These "programmed" changes may be the origins of a number of diseases in later life, including coronary heart disease and the related disorders stroke, diabetes, and hypertension.

Fetal Nutrition and Adult Disease

Godfrey KM & Barker DJP *American Journal of Clinical Nutrition* 71(5), 2000

<http://www.ajcn.org/content/71/5/1344S.full>

Recent research suggests that several of the major diseases of later life, including coronary heart disease, hypertension, and type 2 diabetes, originate in impaired intrauterine growth and development. These diseases may be consequences of "programming," whereby a stimulus or insult at a critical, sensitive period of early life has permanent effects on structure, physiology, and metabolism.

Evidence that coronary heart disease, hypertension, and diabetes are programmed came from longitudinal studies of 25,000 UK men and women in which size at birth was related to the occurrence of the disease in middle age. People who were small or disproportionate (thin or short) at birth had high rates of coronary heart disease, high blood pressure, high cholesterol concentrations, and abnormal glucose-insulin metabolism. These relations were independent of the length of gestation, suggesting that cardiovascular disease is linked to fetal growth restriction rather than to premature birth.

Replication of the UK findings has led to wide acceptance that low rates of fetal growth are associated with cardiovascular disease in later life. Impaired growth and development in utero seem to be widespread in the population, affecting many babies whose birth weights are within the normal range. Although the influences that impair fetal development and program adult cardiovascular disease remain to be defined, there are strong pointers to the importance of the fetal adaptations invoked when the maternoplacental nutrient supply fails to match the fetal nutrient demand.

Fetal Origins of Coronary Heart Disease

Barker DJP, *BMJ* 311(171), 1995

Abstract <http://www.bmj.com/content/311/6998/171.extract>

The fetal origins hypothesis states that fetal undernutrition in middle to late gestation, which leads to disproportionate fetal growth, programmes later coronary heart disease. Animal studies have shown that undernutrition before birth programmes persisting changes in a range of metabolic, physiological, and structural parameters. Studies in humans have shown that men and women whose birth weights were at the lower end of the normal range, who were thin or short at birth, or who were small in relation to placental size have increased rates of coronary heart disease. We are beginning to understand something of the mechanisms underlying these associations. The programming of blood pressure, insulin responses to glucose, cholesterol metabolism, blood coagulation, and hormonal settings are all areas of active research. A *BMJ* editorial on the fetal origins hypothesis published prior to this article stated that it rests only on the "very general" proposition that fetal undernutrition causes coronary heart disease. This is incorrect. The hypothesis states that coronary heart disease is associated with specific patterns of disproportionate fetal growth that result from fetal undernutrition in middle to late gestation.

The Relation of Small Head Circumference and Thinness at Birth to Death from Cardiovascular Disease in Adult Life

Barker DJ et al., *BMJ* 306(6875), 1993

Abstract <http://www.bmj.com/content/306/6875/422.abstract>

This was a study of men born during 1907-24 whose birth weights, head circumferences, and other body measurements were recorded at birth. Death from cardiovascular disease was measured.

Standardised mortality ratios for cardiovascular disease fell from 119 in men who weighed 5.5 pounds (2495 g) or less at birth to 74 in men who weighed more than 8.5 pounds (3856 g). The fall was significant for premature cardiovascular deaths up to 65 years of age (chi 2 = 5.0, p = 0.02). Standardised mortality ratios also fell with increasing head circumference (chi 2 = 4.6, p = 0.03) and increasing ponderal index (weight/length³) (chi 2 = 3.8, p = 0.05; for premature deaths chi 2 = 6.0, p = 0.01). They were not related to the duration of gestation. Among men for whom the ratio of placental weight to birth weight was in the highest fifths the standardised mortality ratio was 137.

These findings show that reduced fetal growth is followed by increased mortality from cardiovascular disease. They suggest that reduction in growth begins early in gestation. They are further evidence that cardiovascular disease originates through programming of the body's structure, physiology, and metabolism by the environment during fetal life. Maternal nutrition may have an important influence on programming.

5. Diabetes and more on heart disease

Maternal Nutrition: Effects on Health in the Next Generation

Fall C, *The Indian Journal of Medical Research* 130(5), 2009

Abstract <http://www.ncbi.nlm.nih.gov/pubmed/20090113>

Nearly 20 years ago, it was discovered that low birthweight was associated with an increased risk of adult diabetes and cardiovascular disease (CVD). This led to the hypothesis that exposure to undernutrition in early life increases an individual's vulnerability to these disorders, by 'programming' permanent metabolic changes. Implicit in the programming hypothesis is that improving the nutrition of girls and women could prevent common chronic diseases in future generations.

Research in India has shown that low birthweight children have increased CVD risk factors, and a unique birth cohort in Delhi has shown that low infant weight, and rapid childhood weight gain, increase the risk of type 2 diabetes. Progress has been made in understanding the role of specific nutrients in the maternal diet. In the Pune Maternal Nutrition Study, low maternal vitamin B12 status predicted increased adiposity and insulin resistance in the children, especially if the mother was folate replete. It is not only maternal undernutrition that causes problems; gestational diabetes, a form of foetal overnutrition (glucose excess), is associated with increased adiposity and insulin resistance in the children, highlighting the adverse effects of the 'double burden' of malnutrition in developing countries, where undernutrition and overnutrition co-exist.

Recent intervention studies in several developing countries have shown that CVD risk factors in the offspring can be improved by supplementing undernourished mothers during pregnancy. Results differ according to the population, the intervention and the post-natal environment. Ongoing studies in India and elsewhere seek to understand the long-term effects of nutrition in early life, and how best to translate this knowledge into policies to improve health in future generations.

Vitamin B₁₂ and Folate Concentrations During Pregnancy and Insulin Resistance in the Offspring: the Pune Maternal Nutrition Study

Yajnik CS et al. *Diabetologica* 51(1), 2011

<http://www.springerlink.com/content/b436104175k10x08/>

Aims/hypothesis:

Raised maternal plasma total homocysteine (tHcy) concentrations predict small size at birth, which is a risk factor for type 2 diabetes mellitus. We studied the association between maternal vitamin B₁₂, folate and tHcy status during pregnancy, and offspring adiposity and insulin resistance at 6 years.

Methods:

In the Pune Maternal Nutrition Study we studied 700 consecutive eligible pregnant women in six villages. We measured maternal nutritional intake and circulating concentrations of folate, vitamin B₁₂, tHcy and methylmalonic acid (MMA) at 18 and 28 weeks of gestation. These were correlated with offspring anthropometry, body composition (dual-energy X-ray

absorptiometry scan) and insulin resistance (homeostatic model assessment of insulin resistance [HOMA-R]) at 6 years.

Results:

Two-thirds of mothers had low vitamin B₁₂ (<150 pmol/l), 90% had high MMA (>0.26 µmol/l) and 30% had raised tHcy concentrations (>10 µmol/l); only one had a low erythrocyte folate concentration. Although short and thin (BMI), the 6-year-old children were relatively adipose compared with the UK standards (skinfold thicknesses). Higher maternal erythrocyte folate concentrations at 28 weeks predicted higher offspring adiposity and higher HOMA-R (both $p < 0.01$). Low maternal vitamin B₁₂ (18 weeks; $p = 0.03$) predicted higher HOMA-R in the children. The offspring of mothers with a combination of high folate and low vitamin B₁₂ concentrations were the most insulin resistant.

Conclusions/interpretation:

Low maternal vitamin B₁₂ and high folate status may contribute to the epidemic of adiposity and type 2 diabetes in India.

The Lifecycle Effects of Nutrition and Body Size on Adult Adiposity, Diabetes and Cardiovascular Disease

Yajnik C, *Obesity Reviews* 3(3), 2002

Abstract <http://onlinelibrary.wiley.com/doi/10.1046/j.1467-789X.2002.00072.x/full>

This study was undertaken to review the links between maternal nutrition, offspring's birth weight and the propensity to early insulin resistance and high diabetes rates in Indian adults. Studies included a comparison of maternal size and nutrition with birth weights in Pune, India, and Southampton, UK.

In Pune, the growth, insulin resistance and blood pressure of four-year-old children were assessed. Adults >40 years of age, who were resident in rural areas, were compared with adults living in urban areas for size, glucose handling, lipid status and blood pressure. Newly diagnosed diabetic adults living in urban areas were also monitored. Height, weight, head, waist and hip circumferences, skin-fold measurements and blood pressure were routinely measured. Fasting glucose, insulin, total and high-density lipoprotein cholesterol and triglycerides were linked to the glucose and insulin responses during glucose tolerance tests. Cytokine levels were measured in plasma samples of urban and rural adults.

Indian babies were lighter, thinner, shorter and had a relatively lower lean tissue mass than the Caucasian babies. However, the subcutaneous fat measurements of these babies were comparable to those of the white Caucasian babies. The Indian mothers were small, but relatively fat mothers produced larger babies. Maternal intake of green vegetables, fruit and milk, and their circulating folate and vitamin C levels, predicted larger fetal size. Rapid childhood growth promoted insulin resistance and higher blood pressure. Rural adults were thin, with a 4% prevalence of diabetes and a 14% prevalence of hypertension, but the risks increased within the normal body mass index (BMI) range.

Type 2 diabetes was common in urban adults younger than 35 years of age. Although the average BMI was 23.9 kg m⁻², central obesity and thin limbs were noteworthy. Levels of interleukin-6 and tumour necrosis factor- α were markedly increased in urban dwellers. Hence, there is evidence of a remarkably powerful, intergenerational effect on body size and total and central adiposity. Indians are highly susceptible to insulin resistance and cardiovascular risks, with babies being born small but relatively fat. Insulin resistance is amplified by rapid childhood growth. Dietary factors seem to have profound long-term metabolic influences in pregnancy. Overcrowding with infections and central obesity may amplify cytokine-induced insulin resistance and early diabetes in Indian adults with a low BMI.

Risk of Diabetes Among Young Adults Born Preterm in Sweden

Crump C et al, *Diabetes Care*, 2011

<http://care.diabetesjournals.org/content/early/2011/03/13/dc10-2108.short?rss=1>

Objective:

Previous studies have suggested that preterm birth is associated with diabetes later in life. These studies have shown inconsistent results for late preterm births and have had various limitations, including the inability to evaluate diabetic outpatients or to estimate risk across the full range of gestational ages. Our objective was to determine whether preterm birth is associated with diabetes medication prescription in a national cohort of young adults.

Research design and methods:

This was a national cohort study of 630,090 infants born in Sweden from 1973 through 1979 (including 27,953 born preterm, gestational age <37 weeks), followed for diabetes medication prescription in 2005–2009 (ages 25.5–37.0 years). Medication data were obtained from all outpatient and inpatient pharmacies throughout Sweden.

Results:

Individuals born preterm, including those born late preterm (gestational age 35–36 weeks), had modestly increased odds ratios (ORs) for diabetes medication prescription relative to those born full term, after adjusting for fetal growth and other potential confounders. Insulin and/or oral diabetes medications were prescribed to 1.5% of individuals born preterm compared with 1.2% of those born full term (adjusted OR 1.13 [95% CI 1.02–1.26]). Insulin without oral diabetes medications was prescribed to 1.0% of individuals born preterm compared with 0.8% of those born full term (1.22 [1.08–1.39]).

Conclusions:

Preterm birth, including late preterm birth, is associated with a modestly increased risk of diabetes in young Swedish adults. These findings have important public health implications given the increasing number of preterm births and the large disease burden of diabetes, particularly when diagnosed in young adulthood.

Impact of Maternal Undernutrition on Diabetes and Cardiovascular Disease Risk in Adult Offspring

Le Clair C, *Canadian Journal of Physiology and Cardiology* 87(3), 2009

Abstract <http://www.ncbi.nlm.nih.gov/pubmed/19295658>

Epidemiological, clinical, and experimental observations have led to the hypothesis that the risk of developing chronic diseases in adulthood is influenced not only by genetic and adult lifestyle factors, but also by environmental factors during early life. Low birth weight, a marker of intrauterine stress, has been linked to predisposition to cardiovascular disease (CVD) and diabetes. The compelling animal evidence and significant human data to support this conclusion are reviewed. Specifically, the review discusses the role of maternal nutrition before and during pregnancy, placental insufficiencies and epigenetic changes in the increased predisposition to diabetes and CVD in adult life. The impact of low birth weight and catch-up growth as they pertain to risk of disease in adult life is also discussed. In addition, adult disease risk in the overnourished fetus is also mentioned. Reference is made to some of the mechanisms of the induction of diabetes and CVD phenotype. It is proposed that fetal nutrition, growth and development through efficient maternal nutrition before and during pregnancy could constitute the basis for nutritional strategies for the primary prevention of diabetes and CVD.

Fetal Nutrition and Adult Hypertension, Diabetes, Obesity, and Coronary Artery Disease

Thompson JN, *Neonatal Network* 26(4), 2007

Abstract <http://www.ncbi.nlm.nih.gov/pubmed/17710957>

The fetal-origins-of-adult-disease hypothesis describes an adaptive phenomenon of in utero reprogramming of the undernourished fetus that predisposes the infant to increased morbidity as an adult. Studies have identified a positive association between indicators of fetal undernutrition such as low birth weight and chronic adult diseases like hypertension, diabetes, obesity, and coronary artery disease. Current research is focusing on determining other factors that may contribute to these chronic adult diseases.

Early Life Experience and Adult Cardiovascular Disease: Longitudinal and Case-Control Studies

Elford J, Whincup P & Shaper AG, *International Journal of Epidemiology* 20(4), 1991

http://ije.oxfordjournals.org/content/20/4/833.abstract?ijkey=8aab692ba9da84b4891b61efa8820dd81b7e643e&keytype=tf_ipsecsha

It has been postulated that experiences early in life influence cardiovascular risk in later adult life. This article considers 15 longitudinal and four case-control studies which, directly or indirectly, have examined the hypothesis concerning the prenatal and childhood origins of adult cardiovascular disease. Criteria laid down by Bradford Hill were used to assess whether these epidemiological studies provided sufficient evidence for a causal relation between experiences early in life and subsequent cardiovascular risk.

No consistent dose-response relationship was found between the index of early life experience and adult cardiovascular disease. The relationships were usually non-specific with the index of early life experience being correlated with several causes of death, not only cardiovascular disease. The formulation of the hypothesis varied between the studies. Most reports dealt inadequately with the fact that the relation between adult cardiovascular risk and early life experience was confounded by persisting social and economic disadvantage.

Overall these studies do not provide strong support for the hypothesis that experiences early in life determine the subsequent risk of cardiovascular disease. While future epidemiological studies may resolve this issue, the very nature of the hypothesis presents methodological problems that may prove to be insurmountable. Further progress in this field urgently requires the formulation of a clear and specific hypothesis.

Fetal and infant growth and cardiovascular risk factors in women

Fall CHD et al, *BMJ* 310(428), 1995

http://www.bmj.com/content/310/6977/428.abstract?ijkey=33efc8d1c23bc4dfd7fa1681b53c5885e24dc4b6&keytype=tf_ipsecsha

This study found that in women, as in men, reduced fetal growth leads to insulin resistance and the associated disorders: raised blood pressure and high serum triglyceride and low serum high density lipoprotein cholesterol concentrations. The highest values of these coronary risk factors occur in people who were small at birth and become obese. In contrast with men, low rates of infant growth did not predict levels of risk factors in women.

6. Cancer risk

Birth Weight and Risk of Renal Cell Cancer

Bergström A, Lindblad P & Wolk A, *Kidney International* 57, 2001
<http://www.nature.com/ki/journal/v59/n3/full/4492127a.html>

Background:

The prenatal period has been suggested to be important for future cancer risk. Conditions in utero are also important for the development of the kidney, and birth weight, a marker of fetal nutrition and growth, is linearly correlated with the number of nephrons and the structural and functional unit of the kidney. An association between birth weight and renal cell cancer, the major form of kidney cancer, is biologically plausible, but has never been studied.

Methods:

This research conducted a population-based, case-controlled study in Sweden of men and women aged 20 to 79 years. Self-reported information was collected on categories of birth weight from 648 patients with newly diagnosed renal cell cancer and from 900 frequency-matched control subjects. Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) as estimates of the relative risks.

Results:

An increased risk of renal cell cancer was observed among men with a birth weight of ≥ 3500 g (adjusted OR = 1.3, 95% CI, 1.0 to 1.8) compared with men with a birth weight between 3000 and 3499 g, especially in the subgroup without hypertension or diabetes (adjusted OR = 1.8, 95% CI, 1.2 to 2.6). No clear association among men with a birth weight < 3000 g or among women was found.

Conclusions:

This study shows that conditions in utero, reflected by birth weight, might affect the risk of renal cell cancer in adulthood. It is unclear why no association was found among women. Further studies, based on weight from birth certificates, are needed to clarify this relationship.

Maternal Dietary Risk Factors in Childhood Acute Lymphoblastic Leukemia (United States)

Jensen CD et al., *Cancer Causes and Control* 15(6), 2004

<http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.61.4998&rep=rep1&type=pdf>

Objective:

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, and the second most common cause of mortality in children aged 1-14 years. Recent research has established that the disease can originate in utero, and thus maternal diet may be an important risk factor for ALL.

Methods:

The Northern California Childhood Leukemia Study is a population-based case-control study of risk factors for childhood leukemia, including maternal diet. Cases (n = 138) and controls (n = 138) were matched on sex, date of birth, mother's race, Hispanicity, and county of residence at birth. Maternal dietary intake in the 12 months prior to pregnancy was obtained by a 76-item food frequency questionnaire.

Results:

Consumption of the vegetables (OR = 0.53; 95% CI, 0.33-0.85; p = 0.008), protein sources (OR = 0.40; 95% CI, 0.18-0.90, p = 0.03), and fruits (OR = 0.71; 95% CI, 0.49-1.04; p = 0.08) food groups were inversely associated with ALL. Among nutrients, consumption of provitamin A carotenoids (OR = 0.65, 95% CI, 0.42-1.01; p = 0.05), and the antioxidant glutathione (OR = 0.42; 95% CI, 0.16-1.10; p = 0.08) were inversely associated with ALL.

Conclusion:

Maternal dietary factors, specifically the consumption of vegetables, fruits, protein sources and related nutrients, may play a role in the etiology of ALL. Dietary carotenoids and glutathione appear to be important contributors to this effect.

Maternal Folate Supplementation in Pregnancy and Protection Against Acute Lymphoblastic Leukaemia in Childhood: a Case-Control Study

Thompson JR et al., *The Lancet* 358(9297), 2001

Abstract <http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2801%2906959-8/fulltext>

Background:

Acute lymphoblastic leukaemia is the most common childhood cancer in more-developed countries but it has few recognised risk factors or preventive measures. We aimed to determine and assess the risk factors associated with this disease.

Methods:

From 1984 to 1992, we investigated known and suspected risk factors for common acute lymphoblastic leukaemia diagnosed in a population-based case-control study of children aged 0—14 years in Western Australia. 83 children in the study group came from the sole referral centre for paediatric cancer in the state and 166 controls matched for age and sex were recruited through a postal survey of people randomly selected from the state electoral roll. We interviewed mothers of 83 study and 166 control children (82% and 74%, respectively, of those eligible). Fathers completed a self-administered questionnaire.

Findings:

We recorded a protective association between iron or folate supplementation in pregnancy and risk of common acute lymphoblastic leukaemia in the child (odds ratio 0.37 [95% CI 0.21—0.65]; $p=0.001$). For iron alone, the odds ratio was 0.75 (0.37—1.51); only one mother took folate without iron. Further analyses of folate use with or without iron (0.40; 0.21—0.73) showed that the protective effect varies little by time of first use of supplements or for how long they were taken. The association was not weakened by adjustment for potentially confounding variables.

Interpretation:

Our results, though unexpected, suggest that folate supplementation in pregnancy reduces the risk of common acute lymphoblastic leukaemia in the child.

The Influence of Maternal Diet on Breast Cancer Risk Among Female Offspring

Hilakivi-Clarke L, Clarke R & Lippman M, *Nutrition* 15(5), 1999

Abstract <http://www.nutritionjrn.com/article/S0899-9007%2899%2900029-5/abstract>

The induction of breast cancer is a long process, containing a series of biological events that drive a normal mammary cell towards malignant growth. However, it is not known when the initiation of breast cancer occurs. One hypothesis is that a high estrogenic environment during the perinatal period increases subsequent breast cancer risk. There are many sources of exogenous estrogens, particularly in the diet.

The purpose of this paper is to review the evidence that a high maternal intake of dietary fats increases serum estrogens during pregnancy and increases breast cancer risk in daughters. Our animal studies show that a high maternal consumption of corn oil consisting mainly of linoleic acid (ω -6 polyunsaturated fatty acid, PUFA), increases both circulating estradiol (E2) levels during pregnancy and the risk of developing carcinogen-induced mammary tumors among the female rat offspring. A similar increase in breast cancer risk occurs in female offspring exposed to injections of E2 through their pregnant mother.

Data suggest that the mechanisms by which an early exposure to dietary fat and/or estrogens increases breast cancer risk is related to reduced differentiation of the mammary epithelial tree and increased number of mammary epithelial cell structures that are known to be the sites of neoplastic transformation. These findings may reflect our data of the reduced estrogen receptor protein levels and protein kinase C activity in the developing mammary glands of female rats exposed to a high-fat diet in utero. In summary, a high dietary linoleic acid intake can elevate pregnancy estrogen levels and this, possibly by altering mammary gland morphology and expression of fat- and/or estrogen-regulated genes, can increase breast cancer risk in the offspring. If true for women, breast cancer prevention in daughters may include modulating the mother's pregnancy intake of some dietary fats.

7. Lung disease

Early Developmental Origins of Impaired Lung Structure and Function

Maritz GS, Morley CJ & Harding R, *Early Human Development* 81(9), 2005

Abstract <http://www.earlyhumandevelopment.com/article/S0378-3782%2805%2900134-9/abstract>

Epidemiological studies show that exposure to factors that restrict fetal growth or lead to low birthweight can alter lung development and have later adverse effects on lung function and respiratory health. The major causal factors include reduced nutrient and oxygen availability, nicotine exposure via maternal tobacco smoking and preterm birth, each of which can affect critical stages of lung development. Experimental studies show that these environmental insults can permanently alter lung structure and hence lung function, increasing the risk of respiratory illness and accelerating the rate of lung aging.

Further studies are required that address the molecular and cellular mechanisms by which these factors adversely affect lung development and whether such effects can be blocked or reversed. Ultimately however, a major goal should be to prevent prenatal compromises through clinical monitoring, and in the case of smoking through education, thereby ensuring that each fetus has the best possible environment in which to develop.

Family Medicine Certification Review

Lipsky MS et al., Lippincott Williams & Wilkins, 2007

Google books preview <http://bit.ly/ioMF8R>

In the developing world, environmental pollutants are important causes of chronic obstructive pulmonary disease. Because poor *fetal nutrition* causes small lungs, low birth weight is also a risk factor for chronic obstructive pulmonary disease.

“Ethnic” Variation in Childhood Lung Function may Relate to Preventable Nutritional Deficiency

Mukhopadhyay S et al. *Acta Paediatrica* 90(11), 2001

Abstract <http://onlinelibrary.wiley.com/doi/10.1111/j.1651-2227.2001.tb01579.x/abstract>

This study aimed to define the differences in lung function between British Caucasian and rural eastern Indian children, and to test the hypothesis that nutrition could account for such “ethnic” variation. To exclude confounders, a rural Indian setting was identified and children were screened for respiratory illness before lung function and nutritional characteristics were measured. Regression equations for this population have already been published. In this study, the lung function differences between rural eastern Indian ($n= 391$) and mean

predicted lung function for Caucasian children were characterised, matched for height and sex. In addition, stepwise multiple regression models were fitted to investigate the relative associations of lung function differences with body mass index (BMI), occipitofrontal circumference and age.

Although the largest differences in the forced expiratory volume in 1 s (FEV₁) [girls 28.7 (27.3-30.1), boys 23.4 (22.2-24.6)] and forced vital capacity [girls 27.9 (26.4-29.4), boys 30.7 (29.6-31.9)] [values as mean difference in % predicted (95% confidence intervals)] ever reported between two populations were observed, differences in peak expiratory flow rate (PEFR) were small. BMI was strongly associated with inter-racial differences for FEV₁ for both sexes (boys β =-0.227, girls β =-0.353, $p \leq 0.001$) and PEFR for girls (β =-0.200, $p \leq 0.05$) (β = standardised coefficient).

Conclusion:

Preventable nutritional factors may play a causal role in determining the FEV₁ differences between rural Indian and Caucasian children. As peak FEV₁ in youth influences respiratory morbidity in later life, it is important to define specific nutrient deficiencies that may relate to poor FEV₁ growth in these children

Randomised Trial of Erythromycin on the Development of Chronic Lung Disease in Preterm Infants

Lyon A, *Archives of Disease in Childhood: Fetal and Neonatal* 78(1), 1998

Abstract <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1720741/>

Nine infants (13%) were positive for *U urealyticum*. The inflammatory cytokines in the lungs increased over the first 5 days of life in all babies, but no association was found between their concentrations and the development of CLD. Those treated with erythromycin showed no significant differences from the non-treated group in the differential cell counts or concentrations of the cytokines. The two groups had a similar incidence of CLD. Babies infected with *U urealyticum* did not have a more pronounced cytokine response than those without infection. Chorioamnionitis was associated with significantly higher concentrations of IL-1 β and IL-8 on admission: these babies had less severe acute lung disease and developed significantly less CLD.

The study concludes that *U urealyticum* in the trachea was not associated with an increased inflammatory response in preterm infants. Erythromycin did not reduce the incidence or severity of CLD.

Children's lung disease

British Lung Foundation

<http://www.lunguk.org/you-and-your-lungs/conditions-and-diseases/childrens-lung-disease#4>

Premature babies' lungs are not as developed as babies born at full term – they haven't had enough time to develop.

Premature lungs often don't have enough 'surfactant', a substance that lines the lungs and stops the air sacs from collapsing.

Complications can also play a part; such as womb infections, which may lead to premature birth.

Some children born prematurely need life support machines. The high oxygen level they breathe helps their undeveloped lungs cope with breathing by themselves. But it also stops the air sacs from developing properly - this can also lead to breathing difficulties.

8. More on fetal/maternal nutrition and health implications

Fetal Nutrition and Future Health

Henriksen T et al, *Tidsskrift for Den Norske Lægeforening* 125(4), 2005

Abstract <http://www.ncbi.nlm.nih.gov/pubmed/15742018>

Fetal nutrition may permanently affect physiological properties of the new individual and hence the risk of future disease. Epidemiological studies indicate that fetal nutrition may significantly influence the risk of diabetes, cardiovascular disease, and cancer. Controlled animal studies show that even properties traditionally considered as exclusively genetic, like fur colour, may be modified by altered maternal nutrition.

The expression "fetal programming" has been introduced to describe permanent effects of environmental conditions in fetal life. An important mechanism of fetal programming seems to be epigenetic regulation. One example of epigenetic regulation is methylation of the DNA base cytosine in promoter regions of some genes. DNA methylation will lead to decreased gene expression.

Over the last two decades, marked changes in dietary habits and other life style features have taken place among young Norwegian women. This is particularly reflected in the increasing prevalence of obesity. Maternal weight and metabolic status is closely associated with the growth and development of the fetus. Thus, diet and physical activity become particularly important aspects of the health of young women.

Maternal Nutrition, Fetal Weight, Body Composition and Disease in Later Life

Zadik Z, *Journal of Endocrinological Investigation* 26(9), 2003

Abstract <http://www.ncbi.nlm.nih.gov/pubmed/14964450>

Nutritional and hormonal milieu *in utero* affect fetal growth. Both parties involved have an independent chance, for the occurrence of a developmental error at any stage of their constant developing system. Studies suggest that pregnancy outcome is associated with fetal demand for nutrients and the materno-placental capacity to meet that demand.

Failure of the materno-placental supply line to satisfy fetal nutrient requirements results in a range of fetal adaptations and developmental changes, and may lead to permanent alterations in the body's structure and metabolism, and thereby to cardiovascular and metabolic disease in adult life. Changes in the in-utero homeostasis may lead to programming of endocrine and metabolic systems so that feedback systems and reactions are permanently changed. At the present stage, short- and long-term hazards of intra-uterine growth retardation (IUGR) have been identified, but preventive strategies are still lacking. It is unlikely that a single factor will reduce a multi-causal outcome like IUGR. Appropriate population-specific interventions should be a priority.

Maternal Nutrition and Fetal Development

Wu G et al., *The Journal of Nutrition* 134(2), 2004

<http://jn.nutrition.org/content/134/9/2169.full>

Nutrition is the major intrauterine environmental factor that alters expression of the fetal genome and may have lifelong consequences. This phenomenon, termed "fetal programming," has led to the recent theory of "fetal origins of adult disease." Namely, alterations in fetal nutrition and endocrine status may result in developmental adaptations that

permanently change the structure, physiology, and metabolism of the offspring, thereby predisposing individuals to metabolic, endocrine, and cardiovascular diseases in adult life.

Animal studies show that both maternal undernutrition and overnutrition reduce placental-fetal blood flows and stunt fetal growth. Impaired placental syntheses of nitric oxide (a major vasodilator and angiogenesis factor) and polyamines (key regulators of DNA and protein synthesis) may provide a unified explanation for intrauterine growth retardation in response to the two extremes of nutritional problems with the same pregnancy outcome.

There is growing evidence that maternal nutritional status can alter the epigenetic state (stable alterations of gene expression through DNA methylation and histone modifications) of the fetal genome. This may provide a molecular mechanism for the impact of maternal nutrition on both fetal programming and genomic imprinting. Promoting optimal nutrition will not only ensure optimal fetal development, but will also reduce the risk of chronic diseases in adults.

Does Fetal Under-Nutrition Predispose Disease in Adult Offspring?

Tomkins CC, *University of Alberta Health Sciences Journal* 4(1), 2007

<http://www.uahsj.ualberta.ca/files/Issues/4-1/pdf/16.pdf>

Normal fetal growth is the result of an equilibrated interplay between maternal nutrition, placental transport, and fetal growth factors. Any imbalance in maternal nutrient intake has the potential to cause profound changes in maternal and fetal metabolism. A nutritional insult to the fetus during development may not only affect fetal survival and organ growth, but also disturb the finely tuned homeostatic mechanisms necessary for proper fetal growth and metabolism.

A number of theories have been proposed to attempt to explain how the insult of under-nutrition in the womb may potentially have deleterious effects on adult health. The thrifty genotype hypothesis and the 'fetal origins of adult disease' theories combined provide a conceptual basis for the understanding of the physiological mechanisms by which maternal under-nutrition may eventually lead to diseases such as hypertension and type 2 diabetes in adult offspring. It appears that adult disease results from an inability of the fetus to adapt to the postnatal environment.

With advancing research in gestational nutrition and fetal physiology, it is possible that we may begin to understand how maternal and fetal nutrition affect not only the growth of the fetus while in the womb, but also the subsequent adaptation of the body to its environment and reaction to the adult diet. This understanding could be of paramount importance when considering the current health issues surrounding diseases such as obesity, hypertension, and diabetes.

Early life influences on later health: the role of nutrition

Moor V & Davies M, *Asia Pacific Clinical Nutrition* 10(2), 2001

Abstract <http://www.ncbi.nlm.nih.gov/pubmed/11710349>

Individuals who were small at birth have an increased risk of cardiovascular disease in later life. Barker has put forward a hypothesis to explain this and other associations, known as the 'fetal origins theory of adult disease'. It is proposed that chronic disease is the long-term outcome of physiological adaptations the unborn baby makes when it is undernourished, a process referred to as 'programming'. Maternal nutrition is thought to be a major influence on programming, and growth in childhood as well as obesity in later life may modulate the propensity for disease acquired in the womb. While robust evidence to support specific nutritional interventions during pregnancy is currently lacking, the theory in general affirms

broader public health nutritional strategies and policies to improve the social and economic status of women.

Influence of Maternal Nutrition on Outcome of Pregnancy: Prospective Cohort Study

Mathews F, Yudkin P & Neil A, *BMJ* 319 (7206), 1999

Abstract <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC28185/>

The objective of this study was to investigate the relations of maternal diet and smoking during pregnancy to placental and birth weights at term.

Results showed placental and birth weights were unrelated to the intake of any macronutrient. Early in pregnancy, vitamin C was the only micronutrient independently associated with birth weight after adjustment for maternal height and smoking. Each 1n mg increase in vitamin C was associated with a 50.8 g (95% confidence interval 4.6 g to 97.0 g) increase in birth weight. Vitamin C, vitamin E, and folate were each associated with placental weight after adjustment for maternal characteristics. In simultaneous regression, however, vitamin C was the only nutrient predictive of placental weight: each 1n mg increase in vitamin C was associated with a 3.2% (0.4 to 6.1) rise in placental weight. No nutrient late in pregnancy was associated with either placental or birth weight.

The research concludes that concern over the impact of maternal nutrition on the health of the infant has been premature. Maternal nutrition, at least in industrialised populations, seems to have only a small effect on placental and birth weights. Other possible determinants of fetal and placental growth should be investigated.

Key messages:

- Placental and infant birth weights were not associated with the intake of any macronutrient early or later in pregnancy
- After adjustment for the effects of maternal height and smoking, only vitamin C independently predicted birth weight. The expected mean difference in birth weight for infants with mothers in the upper and lower thirds of intake was about 70 g
- Vitamin C was the only nutrient that independently predicted placental weight, but again this relation was of doubtful clinical significance
- Among relatively well nourished women in industrialised countries, maternal nutrition seems to have only a marginal impact on infant and placental size. Other causes of variation in the size of clinically normal infants should now be investigated.

Intake of Micronutrient-Rich Foods in Rural Indian Mothers Is Associated with the Size of Their Babies at Birth: Pune Maternal Nutrition Study

Rao S et al, *Journal of Nutrition* 131, 2001

<http://jn.nutrition.org/content/131/4/1217.full>

One third of Indian babies are of low birth weight (<2.5 kg), and this is attributed to maternal undernutrition. This study therefore examined the relationship between maternal nutrition and birth size in a prospective study of 797 rural Indian women, focusing on macronutrient intakes, dietary quality and micronutrient status.

Maternal intakes (24-h recall and food frequency questionnaire) and erythrocyte folate, serum ferritin and vitamin C concentrations were measured at 18 ± 2 and 28 ± 2 wk gestation. Mothers were short (151.9 ± 5.1 cm) and underweight (41.7 ± 5.1 kg) and had low energy and protein intakes at 18 wk (7.4 ± 2.1 MJ and 45.4 ± 14.1 g) and 28 wk (7.0 ± 2.0 MJ and 43.5 ± 13.5 g) of gestation. Mean birth weight and length of term babies were also low (2665 ± 358 g and 47.8 ± 2.0 cm, respectively).

Energy and protein intakes were not associated with birth size, but higher fat intake at wk 18 was associated with neonatal length ($P < 0.001$), birth weight ($P < 0.05$) and triceps skinfold thickness ($P < 0.05$) when adjusted for sex, parity and gestation. However, birth size was strongly associated with the consumption of milk at wk 18 ($P < 0.05$) and of green leafy vegetables ($P < 0.001$) and fruits ($P < 0.01$) at wk 28 of gestation even after adjustment for potentially confounding variables.

Erythrocyte folate at 28 wk gestation was positively associated with birth weight ($P < 0.001$). The lack of association between size at birth and maternal energy and protein intake but strong associations with folate status and with intakes of foods rich in micronutrients suggest that micronutrients may be important limiting factors for fetal growth in this undernourished community.

Nutritional Update: Relevance to Maternal and Child Health in East Africa

Duggan MB, *African Health Science* 3(3), 2003

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2141604/pdf/AFHS0303-0136.pdf>

Nutritional and hormonal factors in pregnancy influence, not only immediate foetal outcome, but also morbidity and mortality in later life. Analysis of the health of cohorts of British adults, born at different birth weights and sizes, indicate an association between underweight and low weight for height at birth and later adult disease. Specifically, intra-uterine growth retardation IUGR is linked with a greater risk of cardiovascular disease, hypertension, and diabetes mellitus in later life. The process whereby a foetal insult provokes late effects is known as foetal programming.

Detrimental foetal programming may be implicated in the rising incidence in Africa of the 'diseases of affluence', commonly attributed to the urban transition towards a high fat diet, which echoes Western dietary and health trends in the early 20th century. The survival of Gambian adults known to have been born in the 'hungry' season was significantly shorter than those born in post harvest season, therefore less prone to low birth weight. Differences in survival, were not due to childhood death, but became apparent in early adulthood.

A Life Course Approach to Chronic Disease Epidemiology

Lynch J & Smith GD, *Annual Review of Public Health* 26, 2005

Abstract

<http://www.annualreviews.org/doi/abs/10.1146/annurev.publhealth.26.021304.144505>

A life course approach to chronic disease epidemiology uses a multidisciplinary framework to understand the importance of time and timing in associations between exposures and outcomes at the individual and population levels. Such an approach to chronic diseases is enriched by specification of the particular way that time and timing in relation to physical growth, reproduction, infection, social mobility, and behavioural transitions, etc., influence various adult chronic diseases in different ways, and more ambitiously, by how these temporal processes are interconnected and manifested in population-level disease trends. This review discusses some historical background to life course epidemiology and theoretical models of life course processes, and reviews some of the empirical evidence linking life course processes to coronary heart disease, hemorrhagic stroke, type II diabetes, breast cancer, and chronic obstructive pulmonary disease. The review also underscores that a life course approach offers a way to conceptualize how underlying socio-environmental determinants of health, experienced at different life course stages, can differentially influence the development of chronic diseases, as mediated through proximal specific biological processes.

9. Additional information

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