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Ann Hum Biol. Author manuscript; available in PMC 2012 August 28.

Published in final edited form as:
Ann Hum Biol. 2011 July ; 38(4): 410–428. doi:10.3109/03014460.2011.592513.

Evidence for the intra-uterine programming of adiposity in later life

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Abstract

Research in animals has shown that altering fetal nutrition by under-nourishing or over-nourishing the mother or rendering her diabetic, or fetal exposure to glucocorticoids and toxins, can programme obesity in later life. The increased adiposity is mediated by permanent changes in appetite, food choices, physical activity and energy metabolism. In humans, increased adiposity has been shown in people who experienced fetal under-nutrition due to maternal famine, or over-nutrition due to maternal diabetes. Lower birth weight (a proxy for fetal under-nutrition) is associated with a reduced adult lean mass and increased intra-abdominal fat. Higher birthweight caused by maternal diabetes is associated with increased total fat mass and obesity in later life. There is growing evidence that maternal obesity, without diabetes, is also a risk factor for obesity in the child, due to fetal over-nutrition effects. Maternal smoking is associated with an increased risk of obesity in the children, though a causal link has not been proven. Other fetal exposures associated with increased adiposity in animals include glucocorticoids and endocrine disruptors. Reversing the current obesity epidemic will require greater attention to, and better understanding of, these inter-generational (mother-offspring) factors that programme body composition during early development.

Introduction

In 1989, Barker and Osmond linked together for the first time birth weight data (collected by health visitors in the UK from 1911-1930) with information on causes of death in later life (from death certificates) and discovered that men and women who had a lower birth weight were at increased risk of death from cardiovascular disease (Barker et al. 1989, Osmond et al. 1993). Their controversial conclusion was that “processes linked to growth and acting in prenatal or early postnatal life strongly influence the risk of developing ischaemic heart disease”. Subsequent studies showed that lower birth weight also predicts an increased risk of later hypertension and type 2 diabetes (Huxley et al. 2000, Whincup et al. 2008). Research in animals had already shown that transient environmental conditions in early-life can permanently change or “programme” the body’s structure and physiology (Lucas 1991). Subsequent work in animal models has shown that fetal under-nutrition, achieved either by under-nourishing the mother during pregnancy or by impairing the fetal nutritional supply line (uterine artery ligation or placental reduction) produces hypertension and diabetes in later life (Gardner et al. 1998, Vickers et al. 2007, Taylor and Poston 2007, Warner and Ozanne 2010). These observations suggest that non-genetic inter-generational (mother-offspring) mechanisms influence adult non-communicable disease risk, and have led to the rapidly growing field of science known as the Developmental Origins of Health and Disease (DOHaD) (Barker 1998, Newnham and Ross 2009).

In animal models of fetal under-nutrition, the development of adult diabetes is associated with well-characterised permanent changes at tissue level (eg. reduced pancreatic beta cell mass), cellular level (eg. altered mitochondrial numbers) and molecular level (eg. altered

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expression of genes regulating the insulin signalling pathway) (Warner and Ozanne 2010). These changes may occur in response to under-nutrition during fetal development simply because of inadequate nutrients or 'building blocks' for the growth of specific tissues, or as orchestrated adaptations to reduce demand and thus enable immediate fetal survival (Figure 1). It has also been suggested that they could be 'predictive adaptive responses' by which the fetus interprets its current nutritional environment as a harbinger of its post-natal nutritional environment and tailors its metabolism appropriately (Gluckman et al. 2007). It is thought that the effects are permanent because they occur during windows of plasticity that are finite for most tissues, during early development.

Feeding rat mothers a moderately protein restricted diet (Jackson 1996) or a severe 'globally' restricted diet (Vickers et al. 2007) from conception until the end of pregnancy or lactation results in increased adult fat deposition in the adult offspring (Figure 2). In both models, the offspring demonstrate features comparable with human cardio-metabolic disease (increased adiposity, insulin resistance, glucose intolerance, dyslipidaemia, endothelial dysfunction and hypertension). In addition to maternal and/or fetal under-nutrition, other exposures during fetal life, including maternal obesity, diabetes, over-feeding, and exposure to stress or glucocorticoids, and to nicotine or other toxins, programme long-term metabolism and disease risk (Gardner et al. 1998, Vickers et al. 2007, Taylor and Poston 2007, Warner and Ozanne 2010) (Figure 3). All have been shown to increase adiposity or reduce lean body mass, or both, in the offspring.

Evidence for programming of adiposity by fetal under-nutrition in humans

Hypertension and type 2 diabetes are obesity-related disorders. An early and consistent finding in human studies was that at any level of adult body mass index (BMI), men and women of lower birthweight had a higher risk of disease, or higher risk markers, such as insulin resistance (Fall et al. 1995). In other words, people of lower birth weight behave as if they are more obese than their adult BMI would indicate. There has thus been considerable interest in whether low birth weight is associated with a more adipose adult body composition (Oken and Gillman 2003, Rogers et al. 2003, Wells et al. 2007, Taylor and Poston 2007).

Some populations are at particularly high risk of both low birth weight and adult obesity-related disease. For example, Indians and other South Asians have a low mean birth weight, thought to be due to poor maternal nutritional status and small maternal size. They also have a high risk of type 2 diabetes, which develops at a younger age, and lower mean BMI, than in white Caucasian populations. Their high risk has been partly attributed to a characteristic adult Indian phenotype of low muscle mass, increased percentage body fat and central adiposity (Yajnik 2004). It is now known that this phenotype is present in Indian newborns at birth (Yajnik et al. 2003) (Figure 4) and tracks through childhood (Krishnaveni 2005). African-Americans, another high-risk group for low birth weight and adult chronic disease, have a similar 'fat preserving' newborn phenotype (Singh et al. 2010).

Some of the earliest evidence for the intra-uterine programming of adiposity by fetal under-nutrition came from the Dutch Famine ('Hunger Winter') of 1944-45. Among 300,000 19-year old men entering military service, those whose mothers lived in famine-affected areas of the Netherlands during early pregnancy, had an increased risk of obesity compared to men whose mothers lived in non-famine areas (2.7% versus 1.5%) (Ravelli et al. 1976, Figure 5). Obesity was defined as a body weight for height 120% or more greater than the WHO reference standard. Men whose mothers were exposed to famine in late pregnancy or in the early post-natal period had lower rates of obesity. A more recent study of 700 Dutch adults showed that women whose mothers were exposed to the Famine in early gestation

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had an increased mean BMI (7.4% higher [95% CI 0.7%, 14.5%]) and waist circumference (5.7 cm [95% CI 1.1 cm, 10.3 cm]) compared with controls born before or conceived after the Famine (Ravelli et al. 1999). A study of men and women who were in utero during the much more prolonged famine that accompanied the Siege of Leningrad in 1941-44 showed no effects on BMI or waist measurements, though there was an increase in the subscapular/triceps skinfold ratio in women (Stanner et al. 1997).

Such 'experiments of history' are rare, and although recent studies have started to investigate body composition in children of women who took part in RCTs of nutritional interventions in pregnancy (see below), most studies investigating the programming of body composition in humans have been observational, and have used birth weight as a proxy for fetal nutrition.

Birth weight and later body mass index

Many studies have examined the association between birth weight and later BMI (Rogers et al. 2003), and have shown a small but consistently *positive* relationship (r=0.1-0.2; β=0.2-0.7 kg/m^2 per kg increase in birth weight) (Figure 6). Although some studies, especially in larger cohorts, have shown a slightly J-shaped relationship, with an upturn in mean adult BMI in the lowest birth weight categories (Curhan et al. 1996, Parsons et al. 2001), this is a small effect. In summary, it is clear that lower birth weight individuals do not develop more hypertension and diabetes because they are more obese, as defined by BMI.

Birth weight and lean and fat mass

BMI is used to define obesity because it is easy to measure, but it has the major disadvantage that it does not distinguish between fat and fat-free mass, tissues that have very different effects on health. Recent studies have therefore attempted to examine the relationship of birth weight to fat and fat-free or lean mass (Table 1). The variety of methods used, and differences in the age of the subjects, sample size, and statistical approaches, makes comparison between studies difficult. However, almost all have found a positive association between birth weight and fat-free or lean mass in childhood or adult life. Studies that have adjusted for height show that this association does not simply result from the strong positive relationship of birth weight to later height. In contrast, these studies show inconsistent relationships between birth weight and later body fat. There was a positive association in 6 out of 18 studies that measured fat mass (Table 1), no association in 11, and an inverse association in only one study. After adjusting for current BMI or weight, one of these 18 studies and one additional study showed an inverse association between birth weight and fat mass, suggesting that at any current body weight, lower birth weight individuals had a higher fat mass. However, percentage body fat or the ratio of fat to lean mass showed no association with birth weight in 9 out of 11 studies with this outcome. It can be concluded from these studies that lower birth weight individuals tend to be 'thinner' in terms of overall body mass, and to have a lower lean body mass, but do not have an increased fat mass or percentage body fat.

Birth weight and central adiposity

Increased central (or abdominal) fat deposition carries a particularly high cardio-metabolic risk. Studies relating birth weight to anthropometric measurements of central adiposity, such as waist circumference, waist/hip ratio or truncal/peripheral skinfold ratios, initially suggested that lower birthweight was associated with greater abdominal and/or truncal adiposity in later life (Law et al. 1992, Barker et al. 1997, Okosun et al. 2000, Byberg et al. 2000). With the accumulation of more studies, the evidence for this from anthropometric data was not impressive (Table 1). Birth weight was either positively related or unrelated to later waist circumference and waist hip ratio in most studies. After adjusting for current BMI

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or weight, some studies showed that lower birth weight, especially in women, was associated with higher waist/hip ratio. More consistently, several showed a higher subscapular/triceps skinfold (SS/TR) ratio in people of lower birth weight (Table 1). However, the relevance of a high SS/TR for disease risk is unclear.

Recent studies have used better methods to assess abdominal adiposity, including ultrasound, CT, DXA and MRI (Table 1). For example, Rasmussen *et al.* compared body composition between low birth weight (LBW, <10th percentile) and normal birth weight men (50th-90th percentile) in a small selected sample (N=74) of Danish men aged 19-23 years, using DXA (Rasmussen et al. 2005). Trunk and abdominal fat were examined separately. Abdominal fat mass was higher, abdominal lean mass lower, and the ratio of abdominal to total body fat higher, in the LBW group. A contrasting study, the largest to use imaging to assess body fat, was a DXA study of over 6000 UK children aged 9-10 years, from the population-based ALSPAC cohort (Rogers et al. 2006). Birth weight was positively related to total body lean mass index and fat mass index, but not their ratio, and positively related to trunk fat. There was no association between birth weight and the ratio of trunk to total body fat. Differences between this study and the Danish study above were the sample size and selection, and the age of the subjects. The UK study did not separate abdominal fat from the rest of the trunk fat, and all the analyses were adjusted for the children's height.

Out of 12 studies of truncal or abdominal adiposity using scan methods (5 in adults and 7 in children, Table 1), 4 showed an inverse association between birth weight and truncal or abdominal fat mass, and one more showed an inverse association after adjusting for current BMI. One of these, and three additional studies, showed that lower birth weight was associated with a higher ratio of trunk fat to total body fat. Of the remaining 4 studies, 3 showed no associations between birth weight and truncal fat, and 1 (the largest, Rogers 2006) showed a positive association. Overall, therefore, there is evidence in some populations that lower birth weight individuals have more abdominal fat, and/or more abdominal fat relative to total body fat. There is a need for more and larger studies, and for studies in different populations (all but one of the 12 studies were in white Caucasians and high income settings).

Maternal under-nutrition and adiposity

As already described, the Dutch famine studies showed that acute maternal under-nutrition in early pregnancy was associated with an increased risk of obesity in the offspring as young adults. Maternal under-nutrition in rodent experiments is also associated with increased adiposity in the offspring. Few of the animal studies have examined the effect of restoring nutrition to these under-nourished mothers. Several long-term follow-up studies of children born to under-nourished mothers taking part in randomised trials of nutritional interventions in pregnancy have recently been published. If maternal under-nutrition during pregnancy is a cause of increased adiposity in the offspring, we might expect to find evidence of 'better' body composition (more lean mass and less fat) among children born to mothers in the intervention groups than to control mothers.

Two trials were of protein-energy supplementation. In the Gambia, women received a daily high energy biscuit (energy 4250 KJ, protein 22 g) either from 20 weeks of pregnancy (intervention group) or during lactation (controls). The intervention influenced fetal nutrition, increasing birthweight by 136 g, reducing the incidence of low birthweight by 40%, and halving perinatal mortality. However, there were no differences in BMI, or in total and trunk body fat percentage (measured using bio-impedance) in the children at 11-17 years of age (Hawkesworth et al. 2008). Among adolescents in India, whose pregnant mothers received food-based energy and protein supplements as part of a package of public health interventions, insulin resistance and arterial stiffness were reduced compared to

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controls, but there was no difference in adiposity (skinfolds) compared with children of unsupplemented mothers (Kinra et al. 2008).

In animal models, maternal micronutrient deficiency, including deficiencies of iron, zinc, calcium and magnesium, has been associated with increased adiposity in the offspring (reviewed in Christian and Stewart 2010). Three recent studies have reported body composition outcomes in children born during trials of maternal micronutrient supplementation. Two of these, in Nepal, used multiple micronutrients and both showed an increase in birth weight in the intervention group (Vaidya et al. 2008, Stewart et al. 2009). Vaidya et al. followed up children at the age of 2 years whose mothers received either multiple micronutrient supplements (intervention group) or routine iron and folic acid tablets (controls) during the second and third trimesters of pregnancy (Vaidya et al. 2008). Children of women in the intervention group had larger head (2·4 mm [95% CI 0·6–4·3]) and mid-upper arm circumferences (2·4 mm [1·1– 3·7]) and larger triceps skinfold thickness (2·0 mm [0·0–0·4]) at 2 years, but lower systolic blood pressure (2·5 mm Hg [0·5–4·6]). In the other trial, women were randomised into 4 groups: 1) vitamin A alone (controls), and vitamin A plus 2) iron and folic acid, 3) iron, folic acid and zinc, and 4) multiple micronutrients including iron, folic acid and zinc. At 6-8 years of age, the children of mothers who received vitamin A, iron, folic acid and zinc were taller and less adipose (had thinner skinfolds) than children of control mothers (Stewart 2009, Figure 7). There were no differences in waist circumference or BMI, and there were no effects on adiposity in the other supplementation groups. In the third trial, infants of mothers who were supplemented with iron, folic acid and zinc were heavier and had larger calf muscle area than those of women who received iron and folic acid without zinc (Iannotti et al. 2008). There were no differences in adiposity, measured using skinfolds.

These studies provide some early evidence that altering the micronutrient intake of under-nourished human mothers during pregnancy affects growth and body composition in the children. It is noteworthy that all these trials took place in low- or middle-income countries, where rates of obesity, though rising, are relatively low and where the opportunity for accumulating adipose tissue is low, compared with high-income settings. This would tend to reduce any differences in adiposity between children from intervention and control groups. Also, these trials started supplementation after the diagnosis of pregnancy, and usually during the second trimester. If early pregnancy is a critical time for nutritional programming of adiposity (as suggested by the Dutch Famine studies) effects may be limited. However, longer follow-up of these trials would be helpful, and data are required from studies in other populations and of other interventions.

Programming of adiposity by fetal over-nutrition

Recent evidence, initially from studying offspring of mothers who were diabetic during pregnancy, suggests that fetal over-nutrition is a risk factor for later obesity.

Maternal diabetes

Maternal diabetes, including gestational diabetes (GDM, diabetes occurring for the first time during pregnancy), exposes the fetus to an excess of nutrients. Diabetic mothers are not only hyperglycaemic, but also have elevated circulating lipids and amino acids. These cross the placenta, in the case of glucose by free diffusion. The fetal pancreas and liver are stimulated to secrete increased insulin and insulin-like growth factors, both of which are growth-promoting hormones in the fetus. This results in the well-described large (“macrosomic”) infant of the diabetic mother. Freinkel coined the term “fuel mediated teratogenesis” to propose that the fetal effects of maternal diabetes could cause obesity and diabetes in later life (Freinkel 1980).

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In the same year, Vohr et al. reported early-onset obesity in the offspring of diabetic mothers; in a small study 24% of children (N=34) born to diabetic mothers were obese compared with 6% of age- and race-matched children of non-diabetic mothers (Vohr et al. 1980). This report was followed by similar findings among the Pima Indians (Pettit et al. 1987); a comparison of siblings born before and after the onset of maternal diabetes showed that BMI was higher in the latter (mean difference 2.5 kg/m2 [95% CI 0.9, 4.3]) (Dabelea et al. 2000). There was no difference between siblings born before and after the onset of diabetes in the father, suggesting that the effect of maternal diabetes was due to intra-uterine exposure, rather than to shared genes or post-natal lifestyle. In one of the largest studies of offspring of diabetic mothers, 465 US children aged 9-14 years, 9.7% were overweight (>95th percentile; OR 1.4 [95% CI 1.1, 2.0]) compared with 6.6% of children of non-diabetic mothers (Gillman et al. 2003). The phenomenon is present in every population examined. In South India, children born to mothers who developed GDM were larger in all body measurements, including skinfolds, at birth than children of non-diabetic mothers (Hill et al. 2005). Annual follow-up of the children showed that the difference in adiposity diminished during infancy, but widened increasingly through childhood (Krishnaveni 2010) (Figure 8).

As mothers become heavier in almost all populations, the incidence of diabetes in pregnancy is increasing, and this is likely to exacerbate and make an ever increasing contribution to the burden of obesity and diabetes in the next generation. Improved management of diabetes in pregnancy reduces macrosomia and other adverse pregnancy outcomes (Crowther et al. 2005) but there are limited data on whether this prevents overweight and obesity in the children. Follow-up of 4-5 year old children of mothers with ‘mild’ GDM, who participated in a randomised controlled trial of improved diabetes management showed no difference in mean BMI or risk of overweight between the intervention and control groups (Gillman et al. 2010).

There is debate as to whether lesser degrees of maternal glucose intolerance predict increased adiposity in the children. Birth weight and newborn adiposity increase linearly with maternal glucose concentrations, even in the sub-diabetic range (Metzger et al. 2009). Linear associations between glucose concentrations in the ‘normal’ range and other adverse pregnancy outcomes have led to recommendations that the glucose threshold for diagnosing diabetes in pregnancy be lowered (Coustan et al. 2010). However, data on longer term outcomes are limited. In a US study of 9439 women routinely screened for GDM using oral glucose tolerance tests, there was a positive association, even in the non-diabetic group, between maternal glucose concentrations and prevalence of overweight in the children at 5-7 years of age (Hillier et al. 2007). Among US women with normal or impaired glucose tolerance in pregnancy, higher insulin resistance was associated with greater adiposity in the children at one year, independently of maternal BMI and glucose concentrations (Hamilton et al. 2009). Maternal insulin resistance and glycaemia form part of the normal process of fetal nutrition, and we do not yet know the optimal levels of glucose and other fuels and nutrients in the mother.

Maternal obesity

Maternal glycaemia and insulin resistance are intricately linked to maternal adiposity, and there is now increasing interest in whether maternal obesity, through an effect on fetal nutrition, also programmes obesity in the children. Like the diabetic mother, an obese mother has altered lipid and glucose metabolism, increased insulin resistance and circulating pro-inflammatory factors (Huda et al. 2010), and potentially exposes the fetus to ‘fuel-mediated teratogenesis’. Newborns of obese women have more body fat (Catalano et al. 2009, Sewell et al. 2006) and there is clear evidence linking higher maternal BMI and/or maternal obesity during pregnancy with higher BMI and a greater risk of overweight and

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obesity in the children (reviewed by Oken 2009). The great debate currently is whether or not these associations indicate programming of obesity by intra-uterine exposure to fetal over-nutrition. As with glucose intolerance in pregnancy, this would have huge implications for public health because of the potential for upward trends in maternal weight to accelerate the obesity epidemic across generations. It would also highlight young women as key targets within strategies to prevent obesity. However, there are alternative explanations for the correlation between the BMI of mothers and their children, which would suggest different preventive approaches. The correlations could reflect shared genes and/or shared environments, diet and activity patterns post-natally (Figure 9). It could also reflect infant feeding practices; breast-feeding is thought to protect children from later obesity (Owen et al. 2005) and in some populations overweight women are less likely to breast-feed their infants (Baker et al. 2007).

Various approaches have been used in human studies to try and disentangle these factors. If shared genes explain the correlation between maternal and child BMI, similar correlations would be expected between paternal and child BMI. Studies have indeed shown remarkably similar effects from both parents (Safer et al. 2001, Kivimaki et al. 2007, Davey Smith et al. 2007, Li et al. 2009, Labayen et al. 2010, Whitaker et al. 2010) (Figure 10). Although several have reported significantly stronger mother-child than father-child correlations, the differences are small (Danielzik et al. 2002, Lawlor et al. 2007, Moschonis et al. 2008, Whitaker et al. 2010). Few of these studies measured BMI in mothers before pregnancy, or in mothers and fathers at the same time. They often relied upon self-reported values, especially for fathers, possibly weakening the father-offspring effect. In the UK ALSPAC cohort, maternal pre-pregnant BMI had a stronger effect on offspring fat mass measured by DXA at 9-11 years (0.24 SD [0.22-0.26] per SD BMI) than paternal BMI recorded at the onset of pregnancy (0.13 [0.11-0.15]), which supports a fetal over-nutrition effect. However, maternal FTO genotype, which influences maternal BMI completely independently of socio-economic factors or lifestyle choices, was unrelated to offspring fat mass (Lawlor et al. 2008), which goes against a fetal over-nutrition effect.

Another ingenious approach has been to study siblings with discordant intra-uterine exposures to maternal obesity. Kral et al. found that among 45 children born to obese mothers before they underwent biliopancreatic bypass surgery, the prevalence of obesity was 60%, compared with only 35% among 172 children (some of whom were siblings) born after maternal surgery (Kral et al. 2006) (Figure 11). The results were confirmed in a follow-up study limited to a comparison of siblings born before and after maternal surgery (Smith et al. 2009). Although these are small studies, they suggest a strong intra-uterine effect of extreme maternal obesity (mean BMI 48 kg/m^2) on obesity risk in the children.

Further supporting evidence comes from studies showing that children whose mothers gain more weight during pregnancy become heavier and have a greater risk of overweight and obesity. In the ALSPAC cohort, above recommended maternal weight gain during pregnancy was associated with higher BMI in the children (0.74 [95% CI 0.42, 1.38] kg/m^2), and below recommended weight gain with a lower BMI (− 0.33 [95% CI −0.50, −0.15] kg/m^2), compared with children whose mothers gained weight within the recommended range (Fraser 2010). In the UK Southampton Women's Survey, children whose mothers gained more weight had higher fat mass at birth and 4 and 6 years (Crozier et al. 2010). The important point about these and other similar studies (Oken et al. 2007, Oken et al. 2008a, Wrotniak et al. 2008, Reynolds et al. 2010a) is that the effects were independent of pre-pregnant weight or BMI. This supports an intra-uterine cause rather than genetic or shared lifestyle explanations.

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Once again, animal experiments provide 'proof of principle' that maternal obesity can cause obesity in the offspring purely through an intra-uterine effect. In one experiment, female rats were rendered obese by a 3-week period of intra-gastric over-feeding, mated, and fed normally during pregnancy (Shankar et al. 2008). The pups were cross-fostered at birth onto non-obese normally-fed dams. They became more obese as adults than controls. In addition, a number of rodent studies have shown that offspring of mothers fed high-energy, high-fat or 'junk food' diets pre-conceptionally and/or during pregnancy and lactation have increased obesity and abdominal fat deposition (Samuelsson et al. 2008, Bayol et al. 2008). Interestingly, some of these over-feeding studies have shown a negative effect on offspring muscle mass and/or muscle fibre number and size (Bayol et al. 2005, Samuelsson et al. 2008).

Programming of adiposity by other fetal exposures

Maternal smoking

There is consistent evidence that maternal smoking during pregnancy is a risk factor for overweight and obesity in the children (Huang et al. 2007, Oken et al. 2008b, Ino et al. 2010, Koshy et al. 2010, Syme et al. 2010). Based on data from >80,000 children in 14 observational studies from Australia, Europe and the USA, Oken et al. concluded that children whose mothers smoked had a higher mean BMI and were more likely to be overweight or obese than children whose mothers had either never smoked or were former smokers who abstained during pregnancy (pooled OR 1.50, 95% CI 1.36, 1.65) (Oken et al. 2008b) (Figure 12). Mothers who smoked differed from non-smokers in several ways that could predict an increased obesity risk in the children. They had a higher BMI and lower income, were less educated, more sedentary, and less likely to breast-feed. However, adjustment for these factors made little change to the estimate of risk, supporting a causal effect of maternal smoking on offspring obesity. Among seven studies that quantified maternal smoking, all found evidence for a dose-response effect, and some (though not all) studies with the relevant information showed that smoking throughout pregnancy carried a higher risk than smoking in early pregnancy alone. A recent study has shown that adolescents exposed to prenatal maternal smoking had more subcutaneous and intra-abdominal fat, measured by MRI, in late puberty than unexposed controls (Syme et al. 2010).

It is not known whether these associations represent a biological effect of intra-uterine exposure to cigarette smoke or residual confounding. However, animal studies have shown that administration of nicotine to pregnant mothers results in increased body fat in the pups at birth or in the early post-natal period (reviewed in Oken et al. 2008b). The mechanisms are unknown, but could be related to nicotine (which crosses the placenta) or other chemical constituents of smoke, and/or to altered fetal nutrition due to effects on maternal or fetal vascular function. There is limited information from intervention studies in humans; the Oken review reported data from two randomised controlled trials of smoking cessation programmes during pregnancy. There were no differences in body weight at age 3 or 9 years between children of mothers assigned to the intervention and control groups. This is clearly an important area for further research.

Exposure to glucocorticoids

Glucocorticoids are steroid hormones produced by the adrenal gland. In the fetus, they play a major role in the maturation of the fetus in late gestation. Post-natally, glucocorticoids are important in the regulation of body composition. The fetus is protected from maternal glucocorticoids by a placental enzyme, 11β-hydroxysteroid dehydrogenase-2 (11β-HSD2). Animal studies have shown that fetal exposure to excess glucocorticoids leads to increased

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intra-abdominal fat, hypertension, glucose intolerance and hyperinsulinaemia (reviewed in Reynolds 2010b). The long-term metabolic effects may be mediated by programmed changes in hypothalamo-pituitary-adrenal (HPA) axis activity. Affected offspring have increased glucocorticoid secretion; decreased glucocorticoid receptor (GR) expression in regions of the brain responsible for negative feedback; increased GR expression in insulin-sensitive tissues such as liver and muscle; and increased expression of enzymes favouring glucose production (Reynolds 2010b). In animal models, fetal glucocorticoid exposure is also increased in maternal undernutrition and placental insufficiency (Reynolds 2010b). Thus glucocorticoid exposure and effects on HPA axis function may be a mechanism linking maternal under-nutrition and low birth weight to later body composition, metabolism and disease (Edwards et al. 1993, Phillips 2007). Lower birthweight is associated with increased early morning cortisol concentrations (Philips 2007, van Montfoort et al. 2005) and with exaggerated cortisol responses to ACTH and stress in adults (Reynolds et al. 2001) and children (Jones et al. 2006).

In humans, short courses of glucocorticoids given to pregnant women to prevent preterm labour are not associated with increased obesity in the offspring (Dalziel et al. 2005). However, endogenous maternal cortisol concentrations during pregnancy, which are sensitive to diet and stress (as is placental 11β-HSD2 activity and thus fetal exposure to maternal glucocorticoids), and their relationship to outcomes in the children, have not been extensively investigated. Low cortisol concentrations have been described in infants of mothers who experienced the attack on the New York World Trade Centre in September 2001 during pregnancy, and developed post-traumatic stress disorder (Yehuda et al. 2005). This suggests that there may be long-term effects of maternal stress on HPA activity in children. It is not known whether these are associated with changes in body composition or risk of obesity.

Exposure to endocrine disrupting environmental pollutants

Prenatal exposure to common environmental pollutants that have endocrine activity (‘endocrine disruptors’) has been shown in animal studies to result in increased adiposity in later life (review by Heindel 2003 and Newbold 2010). Chemicals shown to have this effect include oestrogenic compounds such as diethylstilboestrol (DES, used in the past to prevent miscarriage), bisphenol A (BPA, a weak oestrogenic component of polycarbonate plastics used in food containers), polychlorinated biphenyls (PCBs, used in electrical equipment), dichlorodiphenyl dichloroethene (DDE, a breakdown product of the pesticide DDT) and phytoestrogens (derived from soya products). There are few human studies, but prenatal exposure to PCBs and or DDE was associated with increased weight for height in US adolescents (Gladen et al. 2000).

Mechanisms by which adiposity is programmed in utero

Intra-uterine effects on later adiposity are likely to include changes in one of more of the following processes: the development of adipose tissue depots and their capacity to expand or contract in later life; appetite and choices of foods; physical activity levels and energy metabolism. There is evidence from animal research that all of these can be programmed by intra-uterine exposures.

Development of adipocytes

Adipogenesis, the formation of new fat cells from stem cell progenitors is thought to occur mainly during fetal and early post-natal life in humans, and is sensitive to available nutrients, and hormones including insulin, insulin-like growth factors and glucucorticoids (Muhlhausler and Smith 2008). The number of fat cells is probably fixed by young

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adulthood, after which expansion occurs chiefly by hypertrophy of existing adipocytes. Studies in a variety of animal species suggest that fetal exposure to increased substrate, for example in maternal diabetes, is associated with a permanent increase in the capacity of adipocytes to store lipid (Muhlhausler and Smith 2008). Inadequate fetal nutrition is thought to result in reduced numbers of adipocytes and/or a reduced storage capacity of adipocytes, which may favour visceral fat deposition in the presence of a positive energy balance post-natally (Danforth 2000).

Programming of hypothalamic appetite control and feeding behaviour

The hypothalamus is the main brain centre regulating appetite and feeding behaviour. It monitors and responds to an array of signals about nutritional state (the presence of food in the gut, circulating fuels, stored fat and glycogen) (Berthoud and Morrison 2008). Leptin, secreted from adipocytes, and insulin, are two of these (many) signals. One population of leptin- and insulin-sensitive cells in the arcuate nucleus of the hypothalamus expresses neuropeptide Y (NPY) and agouti-related protein (AgRP) which are orexigenic (stimulate food intake); another expresses pro-opiomelanocortin (POMC) and cocaine and amphetamine regulated transcript (CART), which suppress food intake (Figure 13). These cells also receive signals from other areas of the brain, from gut hormones (ghrelin, glucagon-like peptide (GLP) and peptide YY (PYY)), and from circulating glucose, fatty acids and amino acids. They have extensive projections to other hypothalamic nuclei and directly and indirectly to other brain areas, and thus alter feeding behaviour.

There is considerable evidence from research in animals that this balanced system, especially the stages of cell proliferation, migration, differentiation, growth and apoptosis required to make the above connections, can be altered by the environment during fetal and early post-natal brain development (Bouret 2010). Excessive appetite can be induced by both maternal under-nutrition and high-fat diet during pregnancy (Bouret 2010, Taylor and Poston 2007). Food choices can also be influenced by pre-natal nutrition; for example offspring of mothers fed on a ‘junk food’ diet preferred junk food themselves after weaning (Bayol et al. 2008). Leptin and insulin are thought to be key regulators of hypothalamic development; for example leptin promotes neuronal growth from the arcuate nucleus to the paraventricular nucleus. In rodents, maternal under-nutrition and high fat feeding lead to hypothalamic leptin insensitivity (Bouret 2010, Taylor and Poston 2007). There are no data on hypothalamic effects of fetal nutrition in humans, but leptin and insulin are both increased in obese mothers and their babies (Ramsay et al. 2002, Catalano et al. 2009), which could theoretically re-set hypothalamic pathways.

Programming of physical activity

In animal studies, both maternal undernutrition and maternal high-fat feeding have been shown to reduce physical activity in the offspring (Vickers et al. 2007, Taylor and Poston 2008). The reasons are not clear, but in the severe global diet restriction rat model, it results partly from increased anxiety and reduced exploratory behaviour in the offspring (Vickers et al. 2007). Another reason could be impaired muscle development. As already described, both maternal dietary restriction in animals, and lower birth weight in humans, are associated with reduced lean body mass, including muscle mass. Lower birth weight is also associated with reduced muscle strength in children (Barr et al. 2010) and adults (Inskip et al. 2007). However, physical activity in later life in relation to fetal development has been little studied in humans.

Mitochondrial dysfunction

Mitochondria are double-membraned organelles that perform multiple intracellular functions, most notably the production of ATP as an energy source, and the generation of

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reactive oxygen species (Patti et al. 2010). It has been proposed that fetal under-nutrition leads to increased oxidative stress and/or a dysfunctional fuel supply in mitochondria, and that this leads to fatty acid accumulation, incomplete oxidation of fuels, further oxidative stress and mitochondrial damage, and thus creates a vicious cycle of metabolic abnormalities including insulin resistance and impaired insulin secretion (Patti et al. 2010). Muscle, hepatic and pancreatic β-cell mitochondrial function is impaired in rats with intra-uterine growth restriction induced by uterine artery ligation, and associated with adult diabetes and obesity (Simmons et al. 2008).

Epigenetic changes

Any of the above mechanisms would have to be effected through changes in the expression of genes. Gene expression is regulated by a variety of modifiable molecular structures or 'epigenetic marks' attached to DNA, including methyl groups and histones. The pattern of these marks differs among tissues, forming a mechanism by which cells with the same genetic code differentiate into a variety of functional phenotypes. Patterns of DNA methylation are largely established during embryogenesis, fetal development and early postnatal life, and are known to be sensitive to the nutritional environment (Burdge et al. 2007). For example, maternal protein restriction during pregnancy, which causes increased adiposity in the offspring, appears to act, at least partially, through altered methylation and expression of specific genes involved in energy and lipid metabolism (reviewed in Lillycrop and Burdge 2010). Both the altered methylation and the metabolic abnormalities can be prevented by supplementing the maternal diet with folic acid, an important component of the biochemical pathways involved in the generation of methyl groups (Lillycrop et al. 2005). Other experimental animal models have shown effects of methyl-donor nutrients in the mother, like folic acid and vitamin B12, on gene methylation and the development of obesity, insulin resistance and diabetes in the offspring (Waterland et al. 2003, Sinclair et al. 2007).

The science of epigenetics is in its infancy, and there are currently few data available from humans. However, epigenetic changes in the IGF-2 gene have been demonstrated in the offspring of women exposed to the Dutch famine (Heijmans et al. 2008), and epigenetic variation in umbilical cord tissue, has been related to childhood adiposity (Godfrey et al. 2010). Epigenetic phenomena are exciting because of their potential to explain the link between the pre-natal environment and a propensity to develop obesity and metabolic disease in later life. Epigenetic patterns can be inherited from one generation to the next (Waterland 2003, Drake and Walker 2004, Lillycrop and Burdge 2010). They could therefore also explain the observation, in both animals and humans, that transient pre-natal alterations in nutrition or glucocorticoid exposure can alter body composition and metabolic parameters across more than one generation (Waterland et al. 2003, Drake and Walker 2004, Painter et al. 2008, Reynolds 2010b).

Conclusions

There is strong evidence from animal research that nutritional and other exposures during pre-natal development have lifelong effects on the pathways that regulate food intake and energy expenditure, and thus on adult body composition, adiposity and the risk of obesity. In animal models, maternal under-nutrition and over-nutrition (obesity), diabetes, tobacco and chemical toxin exposure, and fetal gluco-corticoid exposure, have all been shown to cause increased adiposity in the offspring. These are examples of 'programming', whereby transient exposures occurring during critical periods of early development, permanently alter gene expression and the lifelong structural and metabolic phenotype. They represent non-genetic mechanisms for inter-generational (mother-offspring) pathways of disease risk.

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Evidence for such effects in humans, though much less direct, is sufficient to conclude that pre-natal exposures are important in people too. The evidence is particularly strong for maternal diabetes, obesity and smoking. The current epidemic of obesity shows that there is a great deal of unexplained variability in the degree to which different children and adults respond to obesogenic factors in the modern environment. A better understanding of the role of pre-natal factors is likely to be important in controlling this epidemic. Although this review specifically covers the pre-natal environment, there is also evidence that nutrition and growth during infancy, childhood and adolescence play a role in the development of adult body composition and obesity risk. For example, weight gain during infancy (the first 1-2 post-natal years) is more strongly associated with adult lean mass than with adult fat mass, while the opposite is true for weight gain later in childhood and during adolescence (Sachdev et al. 2005). The evidence that breast-feeding during infancy is protective against obesity has already been mentioned (Owen et al. 2005). Thus, to ignore the environment during the crucial early stages of human development as a potential target for interventions would be to miss important opportunities for prevention.

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Further research to advance understanding in this area would include

- Larger studies, in different populations, to examine associations between birth size and later body composition, using gold-standard methods of measuring total and regional fat and lean mass.
- High quality measurements of body composition in children and adults born to women who have taken part in randomised intervention trials before and during pregnancy, in different populations. Some trials of nutritional interventions have already initiated follow-up in the children; additional studies should include interventions to improve diet quality, control body weight and prevent smoking in pregnant/pre-pregnant women, with follow-up of body composition in the children.
- Studies examining the spectrum of maternal adiposity, insulin resistance and glycaemia. Maternal fat stores, insulin resistance and glycaemia form part of the normal processes of fetal nutrition, but more research is required to understand optimal levels of these parameters.
- Studies to determine ways of measuring maternal stress, and its impact on fetal glucocorticoid exposure and later body composition in the children.
- Studies of appetite, food choices, physical activity and energy metabolism in humans, in relation to maternal and other early-life exposures.
- Research in animal models to examine the tissue-level, cellular-level and molecular-level (including epigenetic) effects of materno-fetal exposures, and effects of exposures acting at different stages of development. It would be helpful to have animal models that are more comparable with human situations (for example, many existing animal models are based on extreme nutritional interventions that are unlikely to occur in human populations).
- Research into raising public awareness of the importance of maternal health and nutrition, and other environmental cues/toxins, during early development, and into ways of helping women to both adopt healthy behaviours during the peri-conceptional and pregnancy periods, and to pass these on to their children.

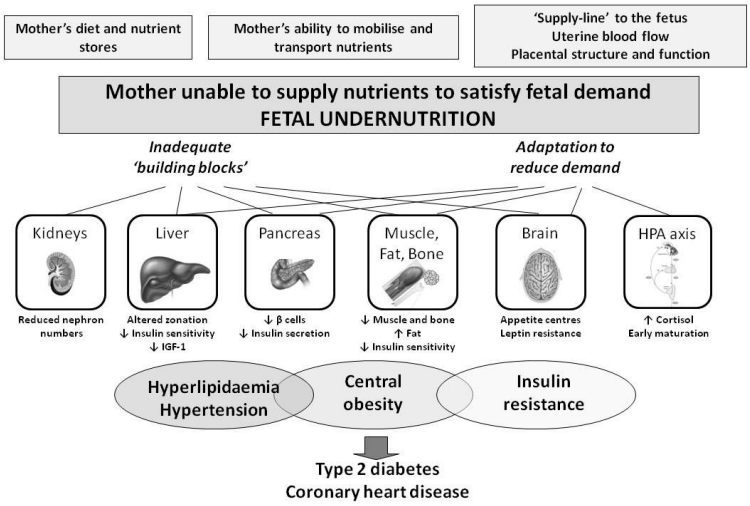

Figure 1. The fetal programming hypothesis; adult chronic disease resulting from the effects of fetal under-nutrition on the development of different tissues

Fetal under-nutrition can occur because of an inadequate maternal diet, inability of the mother to mobilise and transport sufficient nutrients, or an impaired vascular and placental supply line to the fetus. It can also occur if there is high fetal demand, for example because of faster growth. Changes in fetal structure and physiology occur because of a simple lack of the nutrients or building blocks required to construct high-quality organs and tissues, or because of adaptations to reduce nutrient demand eg by slowing fetal growth or prioritising essential organs. Endocrine systems (especially for hormones that regulate fetal growth and maturation) are re-set, and tissues are supported or sacrificed differentially. It is hypothesised that the resulting metabolic changes persist and increase the risk of developing diabetes and cardiovascular disease, especially if additional stressors are acquired in later life (such as obesity and physical inactivity).

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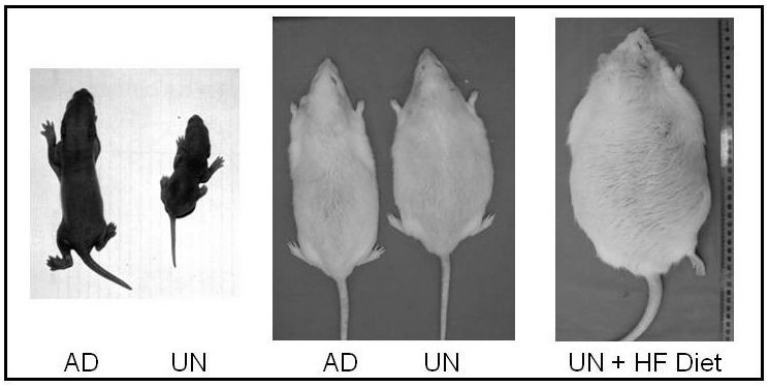

Figure 2. Increased adiposity in adult offspring of dams fed on a globally restricted diet during pregnancy

Offspring from undernourished (UN) mothers are shorter and lighter at birth than those born from ad-libitum (AD) fed mothers. UN animals remain shorter as adults but exhibit increased fat mass compared to AD animals. The increased adiposity is amplified in the presence of a postnatal high fat (HF) diet. Reproduced with permission from Bentham Science Publishers Ltd: Vickers MH et al. Current Drug Targets 2007; 8: 923-34.

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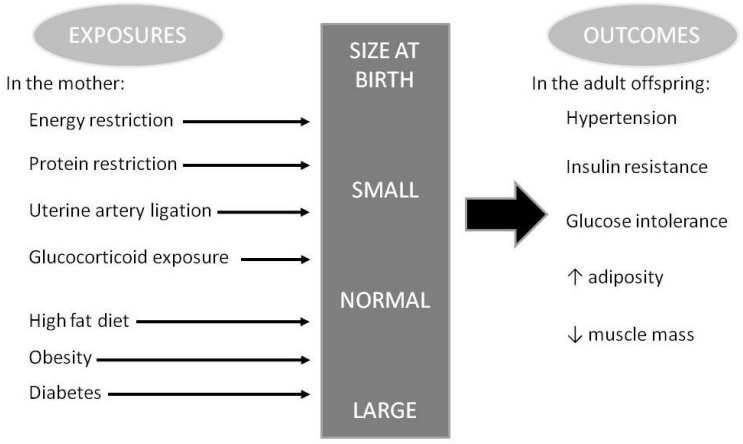

Figure 3. Animal models showing fetal programming of body composition and cardio-metabolic outcomes

There is an extensive literature on research in animal models showing that a variety of maternal exposures during pregnancy influence body composition and metabolism in the adult offspring. The maternal exposures include both under-nutrition and over-nutrition, and may or may not be associated with changes in birth weight (Gardner et al. 1998, Vickers et al. 2007, Taylor and Poston 2007, Warner and Ozanne 2010).

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Figure 4. The muscle-thin but adipose ('thin-fat') Indian newborn

Newborns in India are lighter than white Caucasian babies born in the UK (mean birth weight 2.7-2.9 kg v 3.5 kg) and have a reduced abdominal circumference (suggesting smaller viscera) and arm circumference (less muscle) but similar skinfold thickness. They are thus muscle-thin but relatively adipose. These features are also present in Indian children and adults, and contribute to an increased risk of insulin resistance and diabetes (Yajnik et al. 2003; Krishnaveni et al. 2005).

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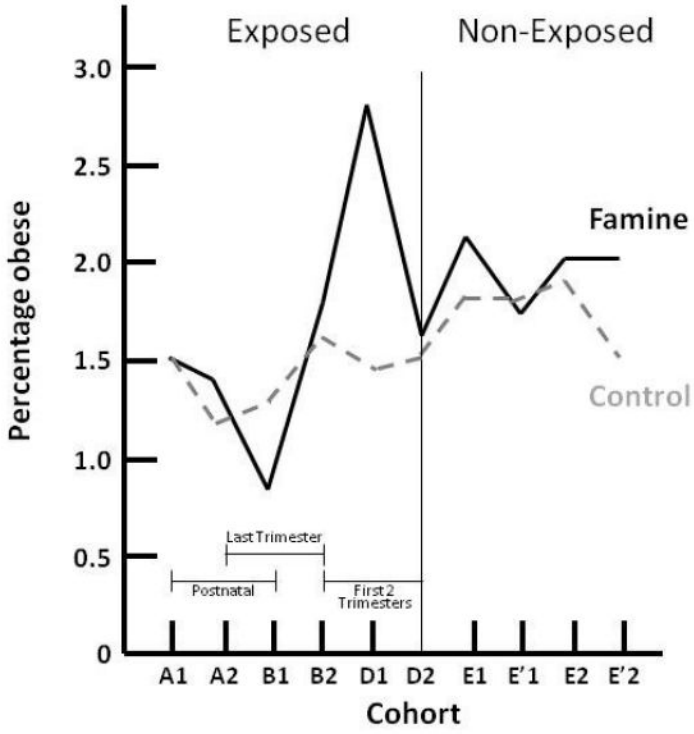

Figure 5. The prevalence of obesity among young Dutch men whose mothers were exposed or unexposed to famine during pregnancy

Men whose mothers lived in famine-affected areas during early pregnancy had an increased risk of obesity compared with controls whose mothers lived outside the famine areas or whose mothers were exposed to famine before pregnancy. Maternal exposure during late pregnancy or the early post-natal period was associated with a lower risk of obesity. Obesity was defined by a weight for height 120% or more above the (then) WHO standard. Reproduced with permission from the Massachusetts Medical Society (MMS): Ravelli et al. NEJM 1976;295:349-353

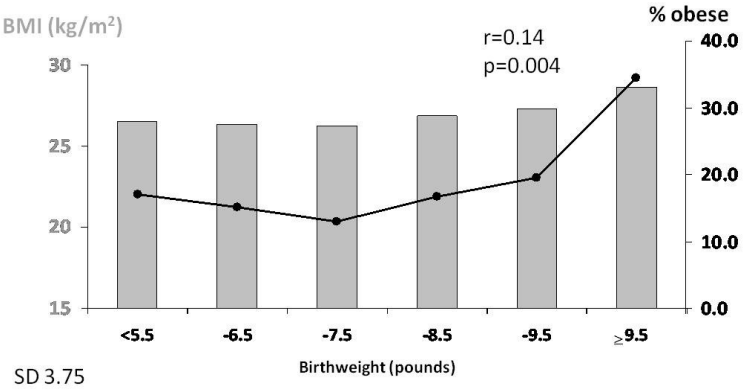

Figure 6. Adult body mass index according to categories of birth weight among Hertfordshire men aged 60-70 (n=845)

Adult body mass index and the prevalence of obesity increase with increasing birth weight. There is a small increase in BMI in the lowest birth weight categories.

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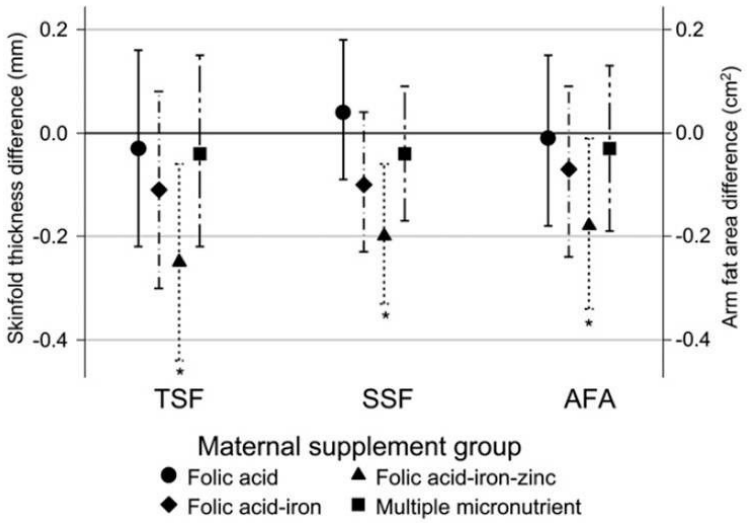

Figure 7. Differences in triceps skinfold thickness (TSF), subscapular skinfold thickness (SSF) and arm fat area (AFA) among Nepali children aged 6-8 y whose mothers received supplements containing vitamin A and other micronutrients in pregnancy compared with the control group (vitamin A alone)

Children of mothers who were randomised to receive vitamin A, iron, folic acid and zinc during pregnancy had thinner skinfolds and smaller arm fat area at age 6-8 years than children of control mothers (vitamin A alone, represented by the zero line). Reproduced with permission from Stewart CP et al. Am J Clin Nutr 2009;90:132-40.

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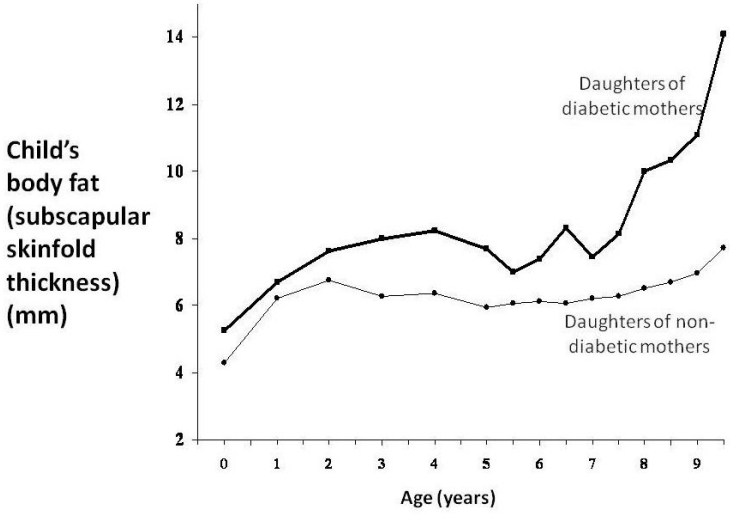

Figure 8. Subscapular skinfold thickness from birth to age 9 years among the daughters of South Indian mothers who developed gestational diabetes compared with controls

Children of GDM mothers were more adipose at birth than children born to non-diabetic mothers. The difference in adiposity diminished between birth and the age of one year, but increased again, and progressively widened after 2 years. Copyright 2003 American Diabetes Association. From Krishnaveni et al. Diabetes Care, Vol 33:402-4. Reproduced by permission of The American Diabetes Association.

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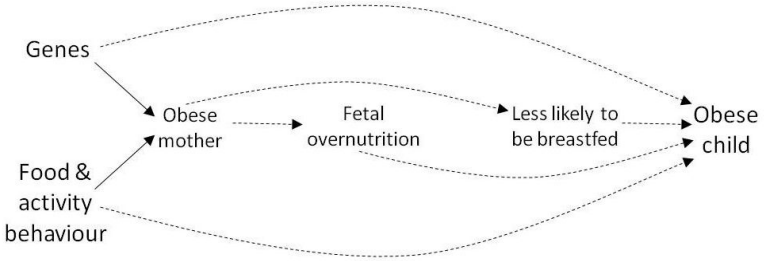

Figure 9. Maternal obesity and offspring obesity

Maternal adiposity and obesity could be linked to child adiposity and obesity by a number of mechanisms.

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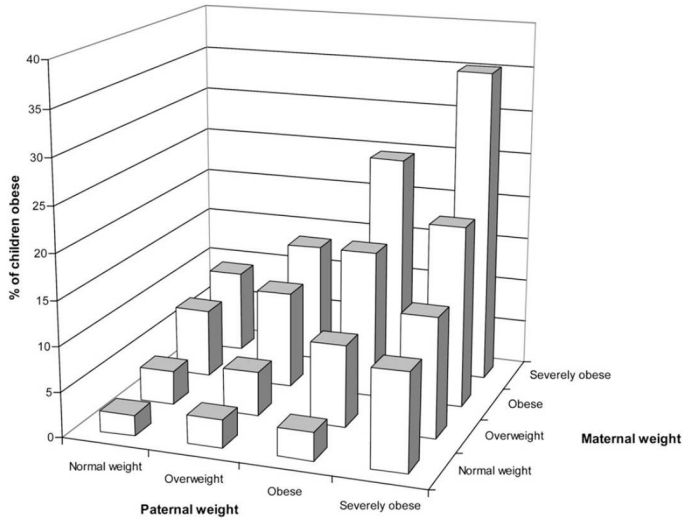

Figure 10. The prevalence of childhood obesity according to weight categories of mothers and fathers

Studies comparing mother-child and father-child BMI associations show similar effects from both parents. Reproduced with permission from Whitaker 2010 KL et al. Am J Clin Nutr 2010;91:1560-7.

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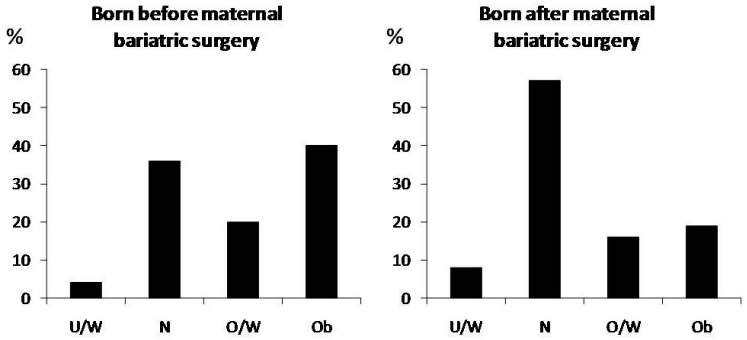

Figure 11. Prevalence of overweight and obesity among children born before and after maternal bariatric surgery

The prevalence of overweight and obesity is higher among children born to obese mothers before they underwent bariatric surgery than among children born after surgery. Reproduced with permission from Kral JG et al. Pediatrics 2006;118:e1644-9.

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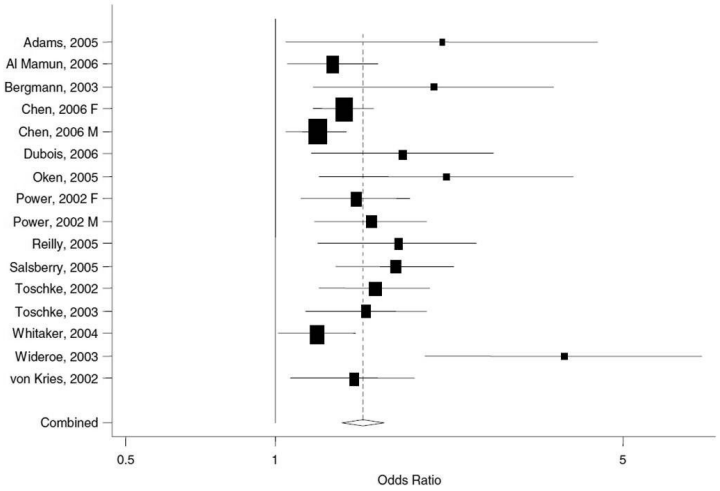

Figure 12. Meta-analysis of studies linking maternal smoking and child overweight

The risk of overweight and obesity is increased in children of mothers who smoked during pregnancy. Reproduced by permission from Macmillan Publishers Ltd: Oken E et al. Int J Obes 2008;32:201-10.

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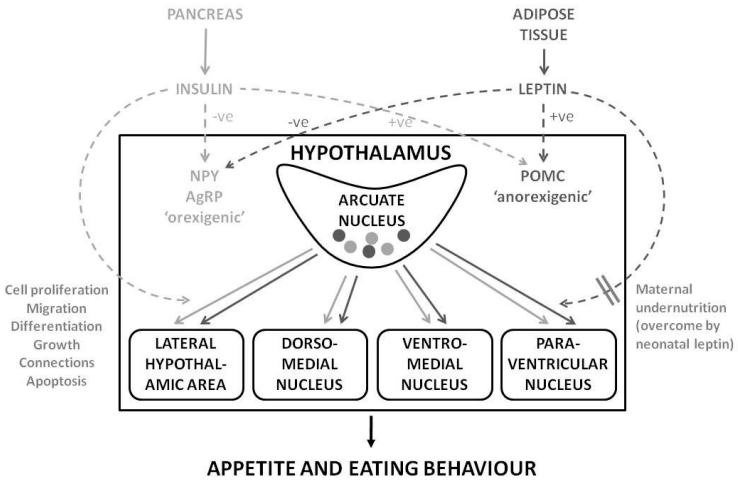

Figure 13. Hypothalamic pathways regulating appetite and feeding behaviour

Appetite and feeding behaviour are regulated by the arcuate nucleus and other hypothalamic nuclei, which respond to leptin, insulin and other incoming signals of the individual's nutritional status. During intra-uterine life, fetal leptin and insulin play a role in the development of these nuclei and their connections. Research in animal models has shown altered hypothalamic structure and function in offspring according to nutritional exposures in the mother.

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Ann Hum Biol. Author manuscript; available in PMC 2012 August 28.

Table 1

Studies relating birth weight to later body composition in a) adults and b) children

Papers Author, year, Men/women; location, sample size, age	BMI or wt for ht	WC	WC (BMI or wt adj)	WHR	WHR (BMI or wt adj)	TR	TR (BMI or wt adj)	SS	SS (BMI or wt adj)	SS/TR	SS/TR (BMIor wt adj)	LM/ FFM/ limb muscle area	LM index or ht adj	LM/ FFM (BMI or wt adj)	FM or limb fat area	FM index or ht adj	FM (BMI or wt adj)	Fat % or fat/lean	Fat % (BMI adj)	Trunk or abdo fat	Trunk or abdo fat/total fat	Trunk/abdo fat (BMI or wt adj)
(a) Adults																						
Kuh 2002 UK; 3200; 43 y	♀+ ♂O	♀+ ♂O	♀O ♂O	♀O ♂−																		
Gonzalez 2010 Brazil; 856; 24 y		+			O																	
Law 1992 Men UK; 845&239 51&64 y					−																	
Tian 2006 China; 973; 46 y	U	U																				
McCarthy 2007 UK; 679: 25 y	O	O			O																	
Yarbrough 1998 Women USA; 303; 50-84 y	O	+		O																		
Fall 1995 UK; 297; 60-71 y				+	O																	
Gunnarsdottir 2004 Iceland; 3707: 33-65 y	+					O	O	O	♀− ♂O	♀− ♂O	♀− ♂O											
Byberg 2000 Men Sweden;1268/734;50/70 y	+	+	O	O	−	+	O	O	−	−	−											
Valdez 1994 USA; 564:25-64 y	O			O						−												
Sachdev 2005 India; 1526; 26-32 y	♀+ ♂O			O						−	+a											
Aihie Sayer 2004 Men UK; 737; 64 y	+	+		O		O		O			+a			+a			Oa					
Euser 2005 Netherlands; 403; 19 y	+	+		O							+a	+a		+a	Oa							
Te Velde 2003 Netherlands; 329; 27-36 y	O	O	♀− ♂O	O	♀O ♂−				O	♀− ♂O		Oa			Oa							
Kahn 2000 USA; 192; 17-22 y	+	+										+a			Oa							
Meas 2008 Spain; 1308; 30 y		O		O														_Dia				
Yliharsila 2007 Finland; 2077; 56-70 y	+	+	O									+Dia		+Dia	+Dia		ODia	ODia	_Dia			
Leunissen 2009 Netherlands; 312; 18-24 y												Odxa	+dxa		Odxa	_Dia						
Weyer 2000 USA; 272; 18-49 y	O											+u/d			Ou/d							
Gale 2001 UK; 143; 70-75 y												+dxa			Odxa							
Rolfe 2010 UK; 1092; 30-55 y	+	O	O												Oaxa		_axa			Oaxa		_axa
McNeely 2007 USA; 91; 34-56 y																				Oct		Oct
Rasmussen 2005 * Men Denmark; 74; 19-23 y				O																_dxa	_dxa	

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Papers Author, year, Men/women; location, sample size, age	BMI or wt for ht	WC	WC (BMI or wt adj)	WHR	WHR (BMI or wt adj)	TR	TR (BMI or wt adj)	SS	SS (BMI or wt adj)	SS/TR	SS/TR (BMIor wt adj)	LM/ FFM/ limb muscle area	LM index or ht adj	LM/ FFM (BMI or wt adj)	FM or limb fat area	FM index or ht adj	FM (BMI or wt adj)	Fat % or fat/lean	Fat % (BMI adj)	Trunk or abdo fat	Trunk or abdo fat/total fat	Trunk/abdo fat (BMI or wt adj)
Kensara 2005 Men * UK; 32; 64-72 y														+dxa			−dxa		−dxa		−dxa	
Choi 2000 Men Korea; 22; 23 y																				−ct		
(b) Children Duran-Tauleria 1995 UK; 8374; 5-11 y	+					+		+														
Okosun 2000 USA; 2488; 5-11 y							O		−		−											
Koziel 2002 Poland; 2016; 14 y	♀O ♂+				♀− ♂O																	
Bavdekar 1999 India; 477; 8 y	+			O	O					−	−											
Boyne 2010 Jamaica; 296; 11 y		+																				
Malina 1996 Belgium; 237; 7-12 y	O										−											
Barker 1997 Girls UK; 216; 14-16 y	+					O	O	O	−	O	−											
Matthes 1996 UK; 164; 16 y						O		O														
Labayen 2008 Spain; 1223; 13-18 y	+	+								O		+a	Oa		+a	+a		Oa				
Eriksson 2008 Sweden; 2453; 15 y	+	+											+bia			+bia		Obia				
Walker 2002 Jamaica; 306; 7-11 y	+					O		O		O								Obia				
Murphy 2006 UK; 234; 6 y												+bia										
Wells 2005 Boys Brazil; 172; 9 y	+												+bia					Obia				
Joglekar 2007 India; 698; 6 y												+dxa			+dxa							
Singhal 2003 UK; 86; 7 y	+											Odxa	+dxa		Odxa	Odxa						
Elia 2007 UK; 85; 6-9 y												+4c	+4c	+4c	−4c	O4c	O4c	−4c	−4c			
Singhal 2003 UK; 78; 13-16 y	O											+bia	+bia		Oa	Oa						
Rogers 2006 UK; 6086; 9-10 y													+dxa			+dxa		Odxa		+dxa	Odxa	
Chomtho 2008 UK; 391: 4-20 y	♀O ♂+	♀O ♂O											♀O4c ♂+			♀O4c ♂O		♀O4c ♂O		♀O4c ♂O		
Labayen 2009 Spain; 284; 15 y		O		O				−												−dxa		
Durmus 2010 Netherlands; 471; 2 y																						Ous
Garnett 2001 Australia; 255; 7-8 y																		Odxa	−dxa		−dxa	−dxa
Dolan 2007 USA; 101; 13 y																	+dxa		+dxa		−dxa	Odxa
Ibanez 2008 * Spain; 64; 6 y												Odxa			Odxa					−mri		

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Studies were selected if they were of singleton births, and included measures of adiposity other than BMI alone. The table is arranged with studies of anthropometric measures of adiposity first (waist measurements and then skinfolds), then measures of lean or fat-free mass and fat mass (anthropometry, then bio-impedance, then other methods) and finally studies that examined truncal or abdominal fat. Within each of these sections, studies are ordered by sample size.

BMI=body mass index; OW=overweight; OB=obese; WC=waist circumference; WHR=waist/hip ratio; TR=triceps skinfold; SS=subscapular skinfold; SS/TR=triceps/subscapular ratio or other peripheral/central skinfold ratio; LM=lean mass; FFM=fat-free mass; FM=fat mass.

+ indicates a statistically significant positive association of the body composition measure with birth weight

− indicates an inverse association; U indicates a U-shaped association; and O indicates no association. ♂=males; ♀=females.

Methods used for assessing body composition: a=anthropometry; bia=bio-impedance; dxa=dual X-ray absorptiometry; ct=computed tomography; mri=magnetic resonance imaging; u/d=underwater weighing or DXA; 4c=four compartment model involving multiple methods (anthropometry, air displacement plethysmography (BodPod), DXA and deuterium dilution); us=ultrasound.

* Comparison of low birth weight (LBW) with normal (NBW), or small-for-gestational age (SGA) with appropriate for gestational age (AGA) babies, rather than analysis of birth weight as a continuous variable.