Chapter 17
Perinatal and Infant Determinants of Obesity

Debbie A. Lawlor, George Davey Smith, and Richard Martin

Introduction

Both professionals and the public view obesity as one of, if not *the*, most important public health problem of our times and concerns are increasingly focused on childhood obesity. Obesity has been included in the international classification of diseases since 1948, since when we have seen an epidemic develop internationally affecting all age groups, including children and adolescents (Kipping et al. 2008). Whilst, repeat cross-sectional surveys such as the Health Survey for England in the UK and the USA National Health and Nutrition Examination Survey show year on year increases in the prevalence of overweight and obesity in children aged 2–15 for at least the last 2–3 decades, it is unclear whether these represent period or cohort effects (Kipping et al. 2008). A recent study comparing two birth cohorts from the UK (one born in 1946 and the other in 1958) found that mean birth weight and body mass index (BMI) from childhood to age 20 years were similar, but that by mid-adulthood the cohort born in 1958 had on average a greater BMI (1–2 kg/m^2 greater), waist circumference (6–7 cm) and hip circumference (5 cm) and also a higher prevalence of obesity (25 vs. 11%) than those born in 1946 (Li et al. 2008). The obesity epidemic in the UK began around the late 1970s to early 1980s and the separation of obesity prevalence in the 1958 birth cohort compared to those born in 1946 from their early 20s corresponds to a period effect – starting to affect both cohorts in the late 70s/early 80s when they were aged mid-20s (1958 cohort) and mid-30s (1946 cohort) respectively. The large difference in obesity prevalence for these cohorts born just 12 years apart illustrates the likely effect on contemporary children who will have higher prevalences of obesity from earlier in childhood and potentially more marked differences in adulthood.

Obese children often become obese adults. Childhood obesity increased the risk of adult obesity fourfold in men, and 3.2-fold in women in the British 1958 birth cohort, although child to adult BMI correlations across the range were modest (Power et al. 1997). Among contemporary children and adolescents, obesity is associated with elevated blood pressure, dyslipidemia, glucose intolerance, hyperinsulinemia and greater left ventricular mass (Berenson et al. 1998; Forrester et al. 1996; Law et al. 1995; Lawlor et al. 2004; Owen et al. 2003). In a recent large prospective study greater BMI, waist circumference and DXA determined fat mass assessed at age 9–12 were all found to be associated

D.A. Lawlor (✉) and G.D. Smith
MRC Centre for Causal Analyses in Translational Epidemiology, Department of Social Medicine, University of Bristol, Oakfield House, Oakfield Grove, BS8 2BN, Bristol, UK
e-mail: d.a.lawlor@bristol.ac.uk

R. Martin
Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, Bristol BS8 2PR, UK

L.A. Moreno et al. (eds.), *Epidemiology of Obesity in Children and Adolescents*,
Springer Series on Epidemiology and Public Health 2, DOI 10.1007/978-1-4419-6039-9_17,

with adverse cardiovascular risk factors at age 15–16, with the magnitudes of association for these three measurements of adiposity being very similar. These results suggest that in childhood BMI is as good a measure of adiposity related future adverse cardiovascular risk factors as is total fat mass or a measure of centrally distributed fat (waist circumference) (Lawlor et al. 2010a). Type 2 diabetes, which just 10 years ago was believed to be a disease of adults only (hence its previous name of "adult onset diabetes") is now increasingly diagnosed in obese children and adolescents (Ehtisham et al. 2000; Fagot-Campagna et al. 2000). Furthermore, higher BMI in childhood and adolescence, from age 7–10 years and above, is associated with increased future risk of all-cause mortality, cardiovascular disease, respiratory disease and some cancers (Baker et al. 2007; Bjorge et al. 2008; Owen et al. 2007). Given the evidence that obesity in childhood and adolescence is already associated with adverse metabolic and vascular risk factors and is associated with future cardiovascular risk and other adverse outcomes, understanding the determinants of childhood obesity is essential to future prevention of these diseases.

This chapter explores current evidence for prenatal and infant determinants of childhood obesity. Specifically, we examine the evidence for risk factors that have been proposed to act only or to a greater extent during intrauterine development or infancy (defined as the first year of life).

Prenatal Risk Factors for Obesity

Gestational Diabetes or Hyperglycemia and Offspring Obesity Risk

The Diabetic and Hyperglycemic Intrauterine Environment and Infant Adiposity

Maternal diabetes (either existing type 1 or 2 diabetes or gestational diabetes) during pregnancy is associated with higher birth weight and greater fetal adiposity (Catalano et al. 2003; Jovanovic and Pettitt 2001; Kjos and Buchanan 1999). The effects of maternal hyperglycemia on fetal growth and adiposity are not limited to women with diagnosed diabetes. Among non-diabetic mothers there is a linear or "J" shaped association between fasting and post-challenge glucose levels during pregnancy and greater birth size and other adverse perinatal outcomes (Metzger et al. 2008; Scholl et al. 2001; Sermer et al. 1995). For example, the recent Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study with more than 20,000 mothers and babies noted a strong, continuous association of maternal glucose levels below those diagnostic of diabetes with increased birth weight and cord-blood serum C-peptide (a marker of insulin resistance) (Metzger et al. 2008). However, whether these more subtle changes in maternal glycemia (at levels lower than those seen for diagnosed gestational diabetes) are associated with increased offspring obesity risk in later life remains unclear.

The Diabetic and Hyperglycemic Intrauterine Environment and Later Obesity Risk

In addition to the association with greater adiposity at birth, there is increasing evidence that the offspring of women with pregnancy diabetes are at increased risk of obesity (Dabelea 2007; Kostalova et al. 2001; Pettitt et al. 1983, 1987, 1993; Pribylova and Dvorakova 1996; Silverman et al. 1991), impaired glucose tolerance (Dabelea 2007; Dabelea and Pettitt 2001; Kostalova et al. 2001; Pettitt et al. 1993; Pribylova and Dvorakova 1996; Silverman et al. 1995), hyperinsulinemia (Pribylova and Dvorakova 1996), dyslipidemia (Manderson et al. 2002) and high blood pressure (Pribylova and Dvorakova 1996) in later life. However, a recent review of the long-term effects of exposure to an intrauterine diabetes environment on offspring obesity and glucose metabolism concluded that the strongest evidence (largest and most consistent studies) for these associations comes from studies of Pima Indians, a population in whom obesity and type 2 diabetes risk is particularly high (Dabelea 2007). Further studies in general populations that are not at particularly high risk for

these outcomes are needed to understand the likely impact of maternal pregnancy diabetes on future offspring obesity risk.

Several mechanisms that are not mutually exclusive may explain the associations of maternal diabetes during pregnancy with obesity and related outcomes in offspring later in life. These include genetic predisposition, shared familial socioeconomic and lifestyle factors, as well as specific intrauterine effects. Work from the Pima Indian population suggests that the effect of maternal pregnancy diabetes on offspring obesity risk is not fully explained by genetic and shared familial lifestyle factors. In studies amongst Pima Indians a marked excess in the risk of obesity was found in offspring (assessed up to age 20 years) born to mothers who had diabetes during their pregnancy compared to either the offspring of mothers who developed diabetes later in their lives (but were non-diabetic in pregnancy) or those who never developed diabetes (risk of offspring obesity was similar in these two latter groups) (Pettitt et al. 1983, 1987). In a nuclear family study (52 families, 182 siblings), also conducted in the Pima Indian population, obesity was greater among offspring born after the mother had been diagnosed with diabetes (i.e. exposure to increased intrauterine glucose levels) than in their sibs born before their mother's diagnosis (i.e. exposed to lower intrauterine glucose levels) (Dabelea et al. 2000). These siblings will have experienced similar familial socioeconomic position and behaviors and on average 50% of their genetic variation, making these characteristics unlikely to fully explain the differences. Furthermore, the offspring of fathers with type 2 diabetes, but whose mothers are free of diabetes, in the Pima Indian population are no more at risk of future obesity than those whose fathers did not have diabetes, whereas for genetic variation to explain the maternal-offspring associations one would also expect a paternal-offspring association (Pettitt and Knowler 1998). Thus, these studies provide some evidence for an intrauterine mechanism, at least in the specific population of Pima Indians.

In a small French study the offspring of mothers with type 1 diabetes during pregnancy ($N=15$) were compared to a control group of offspring of fathers with type 1 diabetes ($N=16$) (Sobngwi et al. 2003). The group whose mothers had type 1 diabetes during pregnancy (offspring exposed to intrauterine diabetic environment) had similar mean BMI, waist-to-hip ratio, total fat mass and truncal fat mass to those whose father's had type 1 diabetes (and hence were exposed to genetically increased risk but not an intrauterine exposure) (Sobngwi et al. 2003). Most parameters from an oral glucose tolerance test conducted in the offspring in later life were also similar, though early insulin secretion was lower and 120 min mean glucose levels were higher in those whose mothers had had type 1 diabetes during their pregnancy than the control group of offspring of fathers with type 1 diabetes. The small sample size and multiple comparisons in this study make firm conclusions difficult. In a more recent study of Danish individuals four groups were compared: (a) offspring of women with a genetic predisposition to type 2 diabetes (defined on the basis of existing risk factors such as family history) and with oral glucose tolerance test diagnosed and diet treated gestational diabetes – i.e. defined as genetic and intrauterine risk ($N=168$); (b) offspring of women with a genetic predisposition to type 2 diabetes and with a normal oral glucose tolerance test during pregnancy – i.e. genetic but no intrauterine risk ($N=141$); (c) offspring of women with no genetic predisposition to type 2 diabetes and with oral glucose tolerance test diagnosed and diet treated gestational diabetes – i.e. no genetic but positive intrauterine risk ($N=160$) and (d) offspring of women with no genetic predisposition to type 2 diabetes and a normal pregnancy oral glucose tolerance test – i.e. no genetic or intrauterine risk ($N=128$) (Clausen et al. 2008). In a large UK prospective study gestational diabetes and glycosuria in pregnancy were associated with increased BMI, waist circumference and DXA determined fat mass at age 9–12 in offspring (Lawlor et al. 2010b). Furthermore, in a recent very large sibling study, which used a similar approach to that used previously in the Pima Indians but which included over 130,000 siblings, offspring of mothers who were exposed to diabetes during pregnancy had greater mean BMI at mean age 18 years than their older siblings born before their mother was diagnosed with diabetes (Lawlor et al. 2010c). This suggests that in Western populations, as with the Pima, that intrauterine mechanisms explain at least some of the association of pregnancy diabetes with later offspring adiposity. Mean BMI, fasting and 2-h postload glucose were all higher in groups (a)–(c) compared to individuals in

group (e), leading the authors to conclude that both genetic predisposition to type 2 diabetes and intrauterine exposure to gestational diabetes increase the risk of future obesity and glucose intolerance (Clausen et al. 2008).

The long-term follow-up of the offspring of mothers who have been involved in randomized trials of the effectiveness of strict glycemic control during pregnancy will provide particularly valuable insights into the potential of intervening during this period to improve obesity risk and related outcomes in the offspring. In the short term, improved perinatal outcomes have been observed amongst those women with gestational diabetes randomized to intensive glycemic control vs. those on standard care (Crowther et al. 2005). There were fewer large for gestational age infants amongst those in the intervention group (13 vs. 22%, $P<0.001$) and fewer infants with macrosomia (10 vs. 21%, $P<0.001$). However, these differences may have been largely driven by the shorter period of gestation among the intensively treated group, due mainly to the greater rate of inductions of labor in that group (Crowther et al. 2005). Nevertheless, long-term follow-up of these infants to determine whether a brief intervention during the intrauterine period has long-term beneficial effects on the offspring in terms of the development of obesity and its associated diseases is important for testing the developmental overnutrition hypothesis (see below) and determining whether a brief intervention during the intrauterine period among this high risk group has a lasting effect.

Developmental Overnutrition

The developmental overnutrition hypothesis (also known as fetal teratogenesis) provides a possible intrauterine mechanism for the association of maternal pregnancy diabetes/hyperglycemia with offspring adiposity (Dabelea 2007). This hypothesis was first proposed in the 1950s by Pederson to explain the association between maternal diabetes in pregnancy and excessive growth in the developing fetus (Pederson 1954). According to this hypothesis the greater delivery of glucose to the fetus in the diabetic pregnancy results in fetal hyperinsulinemia (a necessary response to prevent fetal hyperglycemia) and as a consequence increased insulin-mediated fetal growth. In the 1980s this hypothesis was broadened to include the possibility that other fuels, in addition to glucose but also related to maternal hyperglycemia/diabetes, such as free fatty acids, ketone bodies and amino acids also contributed to fetal hyperinsulinemia and increased fetal growth (Freinkel 1980). The original hypothesis was specific to intrauterine growth. However, birth weight is positively correlated with later weight and BMI, and a further expansion of the original hypothesis has been the suggestion that developmental overnutrition resulting from a diabetic intrauterine environment may program offspring to life-long increased adiposity (Whitaker and Dietz 1998).

In support of the developmental overnutrition hypothesis, high concentrations of maternal glucose among those with gestational diabetes has been shown to increase nutrient (glucose, amino acids, free fatty acids) transfer to the fetus and result in fetal hyperinsulinemia and increased fetal growth (Freinkel 1980; Pederson 1954). In studies of humans, fetal hyperinsulinemia has been detected in the offspring of diabetic mothers both in utero (assessed in samples of amniotic fluid) (Persson et al. 1982; Silverman et al. 1993, 1995; Weiss et al. 2000) and immediately after birth (assessed in samples of cord blood) (Dornhorst et al. 1994). Furthermore, this hyperinsulinemia is associated, not just with increased fetal growth, but with later obesity and glucose intolerance in the offspring (Metzger et al. 1990; Silverman et al. 1993, 1995; Weiss et al. 2000). Offspring of female rats with diet-induced obesity during pregnancy have been found to be heavier than the offspring of rats with the same genotype, but without the diet-induced maternal obesity (Levin and Govek 1998). In vitro, animal and human studies have also demonstrated that fetal pancreatic development and fat stores are influenced by the availability of fetal fuels – in particular glucose, lipids and amino-acids – which are in turn determined by maternal adiposity, insulin secretion and responsiveness, plasma levels of glucose, free fatty acids and inflammatory signals (Dahlgren et al. 2001; Freinkel and

Metzger 1979; Ramsay et al. 2002). As noted above, evidence from sibling studies in Pima Indians and a European population, support an intrauterine mechanism for the association of pregnancy diabetes with later offspring greater adiposity.

Maternal Adiposity During Pregnancy and Future Offspring Obesity Risk

Obesity is a major risk factor for diabetes and several studies have shown an independent (of pregnancy diabetes) association of maternal obesity with excessive fetal growth and adiposity (Baeten et al. 2001; Guillaume et al. 1995; Okun et al. 1997; Sebire et al. 2001). Thus, there is increasing interest in the hypothesis that maternal obesity, and also "excessive" weight gain during pregnancy, in healthy non-diabetic women, are associated with life long obesity and related metabolic and vascular abnormalities in offspring (Ebbeling et al. 2002; Freinkel and Metzger 1979; Whitaker and Dietz 1998). It has been suggested that the consequences of this hypothesis, if true, are formidable: "the obesity epidemic could accelerate through successive generations independent of further genetic or environmental factors" (Catalano 2003; Ebbeling et al. 2002). In this respect the developmental overnutrition hypothesis has been expanded to include not only hyperglycemia/diabetes in pregnancy but also greater maternal adiposity during pregnancy as a key risk factor for future offspring obesity risk.

Epidemiological support for this hypothesis is provided by studies finding a positive association between maternal pre-pregnancy or early pregnancy BMI and offspring BMI or obesity in later life (Laitinen et al. 2001; Li et al. 2005; Parsons et al. 2001; Stettler et al. 2000; Whitaker 2004). For example, a record linkage study of families in the Special Supplemental Nutrition Program for Women, Infants, and Children in Ohio, which included over 5,000 children, found strong and linear associations between maternal BMI in the first trimester of pregnancy and the risk of childhood obesity up to age 4 years: the adjusted odds ratio of obesity at age 4 comparing the highest fifth of maternal BMI to the lowest fifth was 4.31 (95% confidence interval (CI): 3.17, 5.87) (Whitaker 2004). This association was independent of a range of covariables including birth weight, socioeconomic position, maternal smoking in pregnancy and weight gain during pregnancy. However, an association between maternal BMI and offspring obesity may be explained by shared genetic risk factors or familial lifestyle characteristics for obesity.

One proposed mechanism for distinguishing intrauterine mechanisms is to compare the association of maternal BMI, assessed pre-pregnancy or in early pregnancy, with offspring adiposity to the association of paternal BMI assessed at the same time with offspring adiposity, the assumption being that a stronger maternal-offspring, than paternal-offspring association would support specific maternal effects, of which intrauterine mechanisms would be a candidate. By contrast a similar maternal-offspring to paternal-offspring association would support shared genetic, socioeconomic or lifestyle characteristics which would be likely to be similar for both parents. Several studies have made such comparisons with varying results that may be explained by chance, differences in how parental BMI was obtained and different measurements of offspring adiposity (Davey Smith et al. 2007; Kivimaki et al. 2007; Lake et al. 1997; Lawlor et al. 2007).

In the Avon Longitudinal Study of Parents and Children (ALSPAC) the associations of maternal and paternal pre-pregnancy BMI with offspring DXA determined fat mass measured at 9 and 11 (4,091 parent-offspring trios) were compared. Both maternal and paternal BMI were positively associated with offspring fat mass, but the size of the maternal association was larger than that of the paternal association in all models: mean difference in offspring sex- and age-standardized fat mass *z*-score per 1 standard deviation (SD) BMI were 0.24 (95% CI: 0.22, 0.26) for maternal BMI vs. 0.13 (95% CI: 0.11, 0.15) for paternal BMI (*P*-value for difference in effect <0.001) (Lawlor et al. 2008b). The stronger maternal association was robust to sensitivity analyses assuming levels of non-paternity up to 20%. A plausible explanation for the stronger maternal association is provided by the developmental

overnutrition hypothesis. However, in the same study, maternal *FTO* genotype, controlling for offspring *FTO*, was used as an instrument for maternal adiposity, and these analyses did not provide strong support for the developmental overnutrition hypothesis (Lawlor et al. 2008b).

An instrumental variable is one that is associated with the exposure/risk factor of interest (in this case maternal BMI) but is not associated with the outcome (here offspring fat mass) of interest by any mechanism other than through its association with the exposure of interest (Lawlor et al. 2008a). If these assumptions hold, the instrumental variable can be used to provide an estimate of the causal association of exposure with outcome that will not be biased by confounding or reverse causality (Lawlor et al. 2008a). It has been suggested that a genetic variant that is robustly associated with an exposure of interest provides a powerful instrumental variable for that exposure (Davey Smith and Ebrahim 2003). This is because the random allocation of genetic variants from parents to offspring results in them rarely being associated with any of the environmental and lifestyle characteristics that commonly confound conventional epidemiological associations (Davey Smith and Ebrahim 2003; Davey Smith et al. 2008). Furthermore, genetic variation is determined at conception and cannot be influenced by later outcomes and hence associations of genetic variants with outcomes cannot be explained by reverse causation.

Variation in *FTO* predisposes to greater BMI and fat mass (Frayling et al. 2007; see also Chapters 14 and 15). Mothers with one or two A alleles of *FTO* will on average have greater fat mass than those with two T alleles. This association with adiposity will be present throughout life, including during pregnancy. When maternal *FTO*, controlling for offspring *FTO*, was used as an instrumental variable to determine the causal association of maternal adiposity with offspring adiposity it was found that the mean difference in offspring fat mass *z*-score per 1 SD maternal BMI was −0.08 (95% CI: −0.56, 0.41) (Lawlor et al. 2008b). The point estimate (−0.08 SD) for this instrumental variable analysis suggests that greater maternal adiposity during pregnancy does not result in greater fat mass in later life in her offspring. However, the confidence interval is wide and statistically this finding is not different from that found for the parental comparison. Thus, these analyses cannot rule out a small intrauterine effect of greater maternal adiposity on offspring future risk of greater adiposity.

One of the strongest pieces of evidence for an effect of maternal obesity during pregnancy on future obesity risk comes from a study of obesity surgery (Kral et al. 2006). In that study the prevalence of obesity was compared between 172 children (aged 2–18 years) born to 113 women who had been morbidly obese (mean BMI 48 kg/m^2) and who had experienced substantial weight loss following biliopancreatic bypass surgery prior to their pregnancy with 45 of their siblings who were born prior to their mother's surgery (i.e. exposed to extreme maternal obesity during pregnancy) and were assessed at a similar age to their younger siblings. Compared to their siblings born prior to their mothers' surgery-related weight loss, those conceived after mother's surgery had a reduced prevalence of obesity (relative reduction 52%) and severe obesity (relative reduction 45%) (Kral et al. 2006). This study suggests that extreme obesity during pregnancy is causally (and through intrauterine mechanisms) related to future offspring obesity risk, but whether less extremes of maternal overweight or obesity that do not warrant surgical intervention are associated with future offspring obesity are unclear. If the effect of maternal obesity is only seen at these extreme levels then it will have limited public health impact and will not have been a major driver of the obesity epidemic.

Maternal Weight Gain During Pregnancy

A number of studies have also examined the association between maternal weight gain during pregnancy (as opposed to BMI at the start of pregnancy) and later BMI or obesity in offspring, with all but one of these (Whitaker 2004), finding an association between greater weight gain during pregnancy

and greater mean BMI or increased risk of obesity in offspring (Fisch et al. 1975; Mamun et al. 2009; Moreira et al. 2007; Okens et al. 2005; Schack-Nielsen et al. 2005; Sharma et al. 2005; Seidman et al. 1996). This association appears to be robust to adjustment for indicators of socioeconomic position, maternal pre-pregnancy or early pregnancy BMI and infant birth size. In a recent study from Australia the association remained up to age 21 years in the offspring and was also associated with an increase in systolic blood pressure of the magnitude predicted by the association of maternal pregnancy weight gain with offspring BMI at age 21 and the association of offspring BMI with their systolic blood pressure (Mamun et al. 2009). In a second large study (N=5154) greater gestational weight gain up to 36 weeks gestation was associated with greater offspring BMI, waist circumference, fat mass and a wide range of adverse cardiovascular risk factors at age 9–10 years (Fraser et al. 2010).

Maternal Diet During Pregnancy

The developmental overnutrition hypothesis might imply that high fat and high energy diets during pregnancy will be associated with future offspring obesity risk. Results from a study of mice presented at the Society for Neuroscience's 38th annual conference support this assertion (naturenews 2009; http://www.nature.com/news/2008/081120/full/news.2008.1240.html). The offspring of mice fed a high-fat diet throughout their pregnancies and suckling were more obese than the offspring of mice fed a normal diet during pregnancy and sucking. Furthermore, the greater risk of obesity was transmitted into the next generation (the original experimented upon mother's grand-children), without any further manipulation of their mother's diet. However, whether these findings would translate into similar results in humans is unclear. Parental-offspring association comparisons, suggest that mother's diet during pregnancy is more strongly associated with offspring diet than in father's diet, which may represent an intrauterine effect or the greater impact of mothers on family diet in general (Brion et al. 2010a). Randomized controlled trials of different dietary intakes in pregnancy with long-term follow-up would be expensive and potentially difficult to undertake, as pregnant women are unlikely to be happy to be randomized to different dietary intake. In the future it may be possible to use genetic variants that have been shown to be robustly associated with clear differences in dietary intake as instrumental variables to assess these associations (Davey Smith and Ebrahim 2003; Lawlor et al. 2008a).

Maternal Smoking During Pregnancy

Several studies have found an association of maternal smoking during pregnancy with greater offspring BMI or obesity risk in later life (Mamun et al. 2006; Power and Jefferis 2002; Toschke et al. 2003; von Kries et al. 2002). It has been suggested that exposing the developing fetus to nicotine might adversely affect development of hypothalamic function and through this mechanism impact appetite control over the life course and hence increase the risk of future obesity (Kane et al. 2000; Slotkin 1998). However, there are many confounding factors that could generate non-causal links between maternal smoking and the later offspring adiposity. As noted above, one approach to this issue is to compare the strength of associations between an exposure among mothers and offspring outcomes and the same exposure among fathers and the offspring outcomes. If there were a direct biological effect of intrauterine exposure to maternal smoking on offspring obesity, then the link with offspring obesity should be much stronger for exposure among mothers

than for exposure among fathers (Davey Smith 2008). This can be illustrated with respect to birth weight where there is strong evidence of a causal influence of maternal smoking during pregnancy. Figure 17.1 demonstrates that, in ALSPAC, maternal smoking during pregnancy is associated with lower offspring birth weight (with a magnitude, 162 g lower weight in those whose mothers smoked during pregnancy compared to those who did not, consistent with other studies), whereas partner smoking during pregnancy is only weakly associated with birth weight (Davey Smith 2008). When both maternal and partner smoking during pregnancy are taken into account in the same multivariable statistical model, the former shows a robust association that is little attenuated, whereas the latter association is essentially abolished. These results suggest that the weak association of paternal smoking with offspring birth weight is explained by the association of paternal smoking with maternal smoking and provides very little evidence of any effect of second hand smoking on birth weight.

If we now apply the same logic to offspring adiposity in later life the results are notably different to those seen for birth weight. In ALSPAC, data show that the average BMI at age 7 of children whose mothers smoked during pregnancy is raised compared to those whose mothers did not smoke, with the magnitude of this effect being similar to findings of previous epidemiological studies (Leary et al. 2006). However a similar sized association is seen with partner smoking, and including both maternal and partner smoking behavior in the same model leaves residual effects of similar magnitude (Leary et al. 2006). Furthermore, when a more direct measure of adiposity – DXA scan determined fat mass – was used as the outcome the findings were similar (Fig. 17.2) (Leary et al. 2006). These results suggest that in the case of offspring adiposity, maternal smoking during pregnancy does not have a direct intrauterine effect, rather confounding factors associated with parental smoking and offspring adiposity generate an association between both maternal and paternal smoking and greater offspring adiposity. Similar findings are seen with respect to parental smoking and offspring blood pressure (Brion et al. 2007).

The analyses are restricted to singleton births and all results are adjusted for infant sex and gestational age; the results on the right are additionally mutually adjusted for mother's and partner's smoking status during pregnancy. Partner's were described as being biological fathers by the mothers

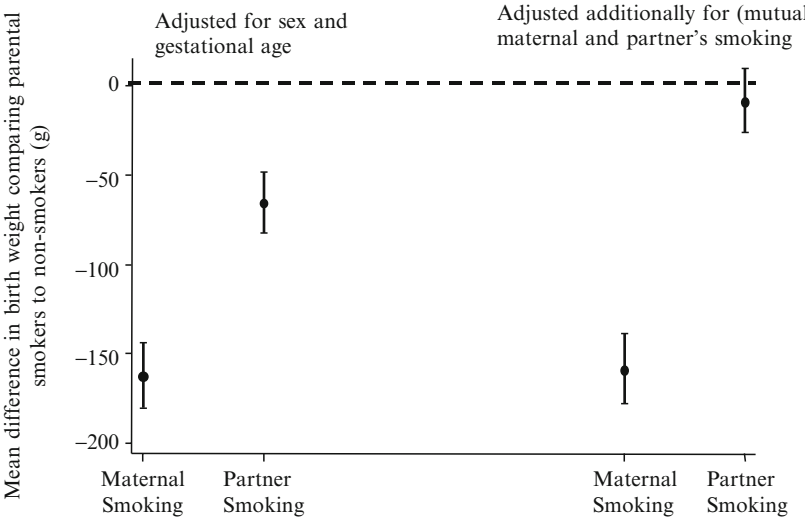

Fig. 17.1 Mean difference in birth weight by mother's and partner's smoking status during pregnancy

The analyses are restricted to singleton births and all results are adjusted for sex, age, height and height squared; the results on the right are additionally mutually adjusted for mother's and partner's smoking status during pregnancy. Fat mass was determined by DXA scan at mean age 9.9 years

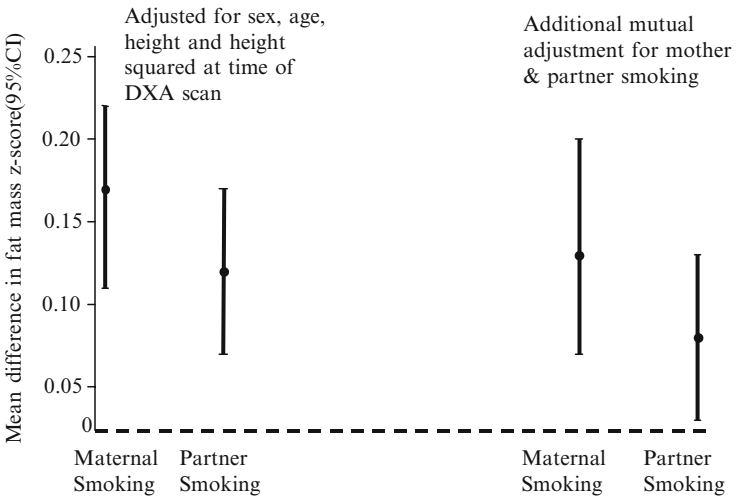

Fig. 17.2 Mean difference in total fat mass *z*-score at 9.9 years by mother's and partner's smoking status during pregnancy

Intrauterine Growth and Later Risk of Obesity

A large number of studies have demonstrated inverse associations (sometimes "reverse-J" shaped) between birth size (most commonly birth weight or birth weight standardized for gestational age) and coronary heart disease (Barker 1995; Huxley et al. 2007), type 2 diabetes (Whincup et al. 2008) and a wide-range of cardiovascular risk factors that are all thought to be influenced by obesity, including blood pressure (Whincup et al. 2004), fasting glucose (Forouhi et al. 2004), insulin (Forouhi et al. 2004), total cholesterol and triglycerides (Gluckman and Hanson 2004; Owen et al. 2003). Low levels of high density lipoprotein cholesterol (HDLc) is associated with increased risk of cardiovascular disease and is more commonly seen in obese compared with lean individuals and for this risk factor birth weight is positively associated with HDLc (i.e. lower birth weight is associated with lower HDLc which is an adverse cardiovascular risk factor and consequence of obesity) (Gluckman and Hanson 1995). Despite these associations with adverse consequences of obesity, birth weight and ponderal index (birth weight relative to height) have been found to be positively associated with mean infant, childhood and adulthood BMI and overweight/obesity in a large number of studies (Binkin et al. 1988; Duran-Tauleria et al. 1995; Fisch et al. 1975; Hediger et al. 1999; Kramer et al. 1985; Pietilainen et al. 2001; Rasmussen and Johansson 1998; Seidman et al. 1991; Strauss 1997).

Despite the positive associations of childhood BMI with cardiovascular risk factors in childhood (Berenson et al. 1998; Forrester et al. 1996; Law et al. 1995; Lawlor et al. 2004; Owen et al. 2003; Lawlor et al. 2010a) and with adult cardiovascular mortality (Baker et al. 2007; Bjorge et al. 2008; Owen et al. 2007), investigators have criticized the examination of birth size with BMI or overweight/obesity based on BMI suggesting that birth size may be differentially associated with fat and lean mass, and with fat distribution, and that these differential associations may mediate the association between lower birth weight and higher later cardiovascular disease risk. That is to say, it is suggested that individuals with lower birth weight (a marker for poorer intrauterine nutrition) will be programmed to greater fat mass and in particular greater central/visceral fat in later life and that this will increase their risk of adverse cardiovascular and metabolic outcomes (Law et al. 1992).

Studies examining the associations of birth size with fat mass and fat distribution have reported inconsistent conclusions. In by far the largest study to date ($N=6,086$) birth weight was positively associated with both DXA determined lean and fat mass in males and females, with a 1 SD greater birth weight being associated with a 4.3% greater fat mass at age 9–10 years in models that adjusted for height, age, sex, pubertal stage, gestational age, family socioeconomic position, maternal parity, age and smoking during pregnancy (Rogers et al. 2006). Ponderal index in that study was also positively associated with DXA determined fat and lean mass (Rogers et al. 2006). In a smaller study of 78 adolescents (mean age 15 years) and 86 children (mean age 7 years) birth weight was positively associated with fat-free (lean) mass, but there was no association with fat mass (Singhal et al. 2003a, b). The latter may reflect a type 2 error given the small study size. In a third small study ($N=32$), 16 men aged 64–72 years at time of assessment, whose birth weight was below the 25th centile (mean birth weight 2.76 kg) had a higher DXA assessed fat mass than 16 age matched men whose birth weight was above the 75th percentile (mean 4.23 kg): 29.3 vs. 25.3%, $P=0.03$ after adjustment for BMI (Kensara et al. 2005). A smaller difference was found without adjustment for BMI (28.7 vs. 26.0%, $P=0.15$) and the very small sample size of this study make it difficult to make valid inferences.

Inverse associations of birth weight with measurements of central adiposity (based on subscapular skinfold thickness, subscapular to triceps skinfold ratio, waist circumference or waist-to-hip ratio) in children, adolescents and adults have been reported (Labayen et al. 2006; Law et al. 1992; te Velde et al. 2003; Walker et al. 2002). However, most studies to date have had small sample sizes (three with fewer than 250 participants and one with 1,084). The largest study, to date, relied on adjustment for BMI to unmask associations with central adiposity (Law et al. 1992) and two of the three small studies reported sex differences that were inconsistent between studies. Thus, in one there was an inverse association of birth weight with central adiposity in boys only (Labayen et al. 2006) and in the other an inverse association only in females (te Velde et al. 2003). Thus, evidence to date suggests that birth weight is positively associated with BMI and total fat and lean mass, but whether there is an inverse association with central adiposity remains unclear due to a paucity of large well-conducted studies of this association.

Infant Risk Factors of Obesity

Accelerated Infant Growth

Amongst preterm infants in a UK study rapid weight gain in very early infancy (first 2 weeks after birth) has been shown to be associated with greater insulin resistance (Singhal et al. 2003a, b) and this has led to the suggestion that rapid weight gain in early infancy might predispose to obesity and cardiovascular disease risk (Singhal and Lucas 2004). However, results from preterm infants may not be generalizable to the majority of the population born at term. Three general population cohort studies, two from the UK (McCarthy et al. 2007; Ong et al. 2009; Howe et al. 2010) and one from Delhi in India (Sachdev et al. 2005), have examined detailed growth trajectories from birth to childhood and their relationship to later obesity. One of the UK studies, based on a cohort of men only from Wales ($N=679$) found positive associations between weight velocity (rate of weight gain) in the immediate infancy period (between birth and 5 months) and greater BMI and waist-to-hip ratio in early adulthood (mean age 25 years) (McCarthy et al. 2007). This association was independent of a range of potential confounding factors and weight velocity in childhood (rate of weight gain between 1.75 and 5 years), though the latter was more strongly associated with adult BMI and waist-to-hip ratio than weight velocity in infancy. The second UK study, based on

a cohort of girls only from South West England ($N = 2{,}715$) found that faster weight gain between the three time points with measurements – 0–2; 2–9 and 9–19 months – were all positively associated with BMI at 9–10 years (Ong et al. 2009). However, only faster early infancy weight gain (0–2 and 2–9 months) were positively associated with DXA determined fat mass, with later faster growth (9–19 months) being positively associated with fat free mass, but not fat mass at age 9–10 years. However, a more detailed assessment in that same study, with longer follow-up, found that later childhood rapid BMI gain (more so that gain in infancy) was more strongly associated with fat mass and adverse cardiovascular risk factors at age 15–16 years, with no evidence that infancy was a particularly sensitive period (Howe et al. 2010). By contrast, in the Delhi study, where many participants were stunted and underweight in infancy, weight velocity in infancy was associated with adult lean mass, with little association with general or central adiposity (Sachdev et al. 2005). Taken together these findings suggest that the impact of rate of weight gain in early infancy on later risk of adiposity and its associated adverse cardiovascular and metabolic outcomes may vary depending upon the underlying nutritional status of the infants being studied. The UK studies also suggest that rate of weight gain in later childhood is more important than that in infancy with respect to later adiposity and associated cardiovascular risk factors (McCarthy et al. 2007; Howe et al. 2010).

Infant Nutrition

During the last two decades there have been numerous and rapidly increasing claims about potential long-term beneficial effects of having been breastfed, including papers suggesting protection against the development of obesity in childhood and adulthood. Breastfeeding is known to be associated with multiple social, behavioral and biological exposures that are themselves correlated with obesity. The evidence-base, however, for long-term protective effects of breastfeeding on obesity is largely observational and not experimental (i.e. randomized controlled trials). A major challenge, therefore, in understanding the current epidemiological literature is that it is difficult to disentangle breastfeeding effects from the influence of factors correlated with maternal choice to breastfed.

Owen et al. published a systematic review of breastfeeding and mean levels of BMI in 2005 (Owen et al. 2005b). The meta-analysis was based on a systematic search that identified 36 individual effect-estimates. Those who were breastfed had a BMI that was, on average, 0.04 kg/m^2 less (95% CI: −0.05, −0.02) than those who were bottle-fed. This was conventionally "statistically significant," but is a very small effect. For example, a reduction of 2 kg/m^2 (a 50-fold greater effect than the observed effect of breastfeeding) is needed to reduce the incidence of coronary heart disease and type 2 diabetes by 10%. Arguing against causality for the association of breastfeeding and BMI in this systematic review, were the observations that the difference in BMI by type of infant feeding was less in those studies that defined breastfeeding as exclusive, the absence of any association in the pooled estimate of the 11 studies that controlled for maternal smoking, social class and parental BMI, and that there was convincing evidence of small study bias, suggesting the possibility of publication bias.

It has been suggested that the lack of any important association with mean BMI is because breastfeeding only affects the upper and lower tails of the distribution. There have been at least three quantitative systematic reviews of the effect of breastfeeding on risk of obesity, defined in most studies by cut-offs at the 95th or 97th percentile (Arenz et al. 2004; Harder et al. 2005; Owen et al. 2005a). The largest and most recent meta-analysis included 28 studies with almost 300,000 participants (Owen et al. 2005a). Breastfeeding was associated with a reduction in risk of obesity of 13% compared to formula-feeding (pooled odds ratio (OR) = 0.87; 95% CI: 0.85, 0.89) and the effect was greater in studies that defined breastfeeding as exclusive (OR = 0.76; 95% CI: 0.70,

0.83) or those breastfed for 2 months or more (OR = 0.81; 95% CI: 0.77, 0.84). However, the association was strongest amongst the smallest studies indicating possible publication bias, i.e. small studies being more likely to be published if they showed a large effect (pooled OR in studies of <500 participants = 0.43; OR in studies of >2,500 participants = 0.88). The effect of adjustment for potentially important confounders could only be examined in six studies. In these six studies, the pooled odds ratio before adjustment was 0.86, but after controlling for parental obesity, maternal smoking and social class, this was reduced to 0.93. Thus, as with the systematic review of mean BMI, this review does not provide strong evidence for a causal protective effect of breastfeeding on future obesity risk.

Kramer et al. have illustrated that reverse causality is a major concern in observational studies of the association of breastfeeding duration with adiposity (Kramer et al. 2002). It may be that breast milk output is sufficient for slower-growing infants, destined to remain relatively thin; such infants are satisfied by continued exclusive breastfeeding. In contrast, faster growing infants, destined to become obese, may be switched to formula to meet their higher energy demands and satisfy more frequent hunger. An association of exclusive or prolonged duration of breastfeeding compared with lesser degrees of breastfeeding with adiposity may reflect the fact that the faster-growing infant "causes" supplementation with formula feeding, rather than the formula feeding causing the faster growth.

Well conducted randomized controlled trials remove problems of confounding, reverse causality and selection bias that afflict observational studies, but randomization to breast- vs. formula-feeding is not feasible and may be unethical. However, randomization to a breastfeeding promotion intervention is ethical and feasible, particularly if mothers who intend to breastfeed are randomized to an intervention that promotes breastfeeding duration and exclusivity. A large randomized controlled trial of an intervention to promote breastfeeding exclusivity and duration, with analysis by "intention to treat" has been conducted, involving over 17,000 term and normal weight children in the Republic of Belarus who are now aged 11.5 years (Promotion of Breastfeeding Intervention Trial, PROBIT) (Kramer et al. 2001). Infants from the intervention sites were 7 times more likely to be exclusively breastfed at 3 months (43.3 vs. 6.4%) and 13 times more likely at 6 months (7.9 vs. 0.6%), and were breastfed to any degree at higher rates throughout infancy. Thus, the PROBIT trial resulted in two cohorts that differed substantially in the exclusivity and duration of breastfeeding. These cohorts were created by randomization, not the choice of the mother, enabling strong causal inferences with respect to breastfeeding effects on long-term outcomes. Despite the fact that the breastfeeding promotion intervention resulted in considerable increases in the duration and exclusivity of breastfeeding, it did not reduce measures of adiposity at age 6.5 years (Table 17.1) (Kramer et al. 2007). Neither was any important effect of the experimental intervention observed on the risk of overweight or obesity defined, respectively, by the BMI ≥ 85th percentile (cluster-adjusted OR = 1.1; 95% CI: 0.8, 1.4) or ≥95th percentile [cluster-adjusted OR = 1.2 (0.8, 1.6)] (Kramer et al. 2007). These findings are also supported by a recent cross cohort comparison study in which breast feeding was not found to be associated with offspring BMI in a cohort from Brazil where socioeconomic position (a likely key confounder in the association) is not related to breast feeding (Brion et al. 2010b).

Table 17.1 Cluster-adjusted differences in adiposity comparing the breastfeeding promotion intervention (experimental) arm with the control arm of PROBIT

Outcome	Experimental	Control	Difference (95% CI)
BMI (kg/m^2)	15.6	15.6	+0.1 (−0.2, 0.3)
Waist circumference (cm)	54.6	54.2	+0.3 (−0.8, 1.4)
Triceps skinfold (mm)	9.9	10.0	−0.4 (−1.8, 1.0)
Subscapular skinfolds (mm)	5.9	5.8	0.0 (−0.4, 0.5)

Adapted from Kramer et al. (2007)

Conclusions

Evidence to date suggests an association between maternal hyperglycemia/diabetes during pregnancy and future risk of greater offspring adiposity, with some evidence that this is at least in part explained by intrauterine mechanisms that are consistent with developmental overnutrition. Evidence for an effect of greater maternal BMI or weight gain during pregnancy is less clear. Extreme obesity during pregnancy (even in the absence of diagnosed diabetes) might, via an intrauterine mechanism, result in increased offspring obesity, but further research is required to determine whether less extreme levels of maternal overweight/obesity and weight gain during pregnancy are causally related to future offspring obesity risk. Comparisons of maternal and paternal associations suggest that exposure to maternal tobacco smoking during pregnancy is not causally (via intrauterine mechanisms) associated with future offspring obesity, although the clear adverse health consequences of smoking during pregnancy on the developing fetus (intrauterine growth retardation) and on the mother's own health warrant advice and interventions to reduce smoking in women of reproductive age.

Recent systematic reviews of observational studies, and the PROBIT randomized controlled trial of breast feeding promotion, suggest that previous reports of protective effects of breastfeeding against the later development of obesity may reflect uncontrolled confounding and bias. The continued follow-up of PROBIT will help unpick whether any effects emerge later in life as adiposity rates increase.

The exact mechanisms underlying prenatal and infant exposures that do appear to be causal are unclear. Epigenetic effects are frequently invoked as potentially important mechanisms for associations of prenatal risk factors with a range of later life outcomes. However, as yet there is insufficient research in humans to make clear conclusions about the nature and importance of these effects. Whilst there is strong evidence for causal effects of some prenatal and infant exposures (maternal hyperglycemia and extreme obesity during pregnancy and rapid weight gain in early infancy), there is no clear evidence that interventions during this period of the life course are effective at reducing childhood or later life obesity.

References

Arenz, S., Ruckerl, R.., Koletzko, B., & von Kries, R. (2004). Breast-feeding and childhood obesity – a systematic review. *International Journal of Obesity and Related Metabolic Disorders*, *28*, 1247–1256.

Baeten, J.M., Bukusi, E.A., & Lambe, M. (2001). Pregnancy complications and outcomes among overweight and obese nulliparous women. *American Journal of Public Health*, *91*, 436–440.

Baker, J.L., Olsen, L.W., & Sorensen T.I. (2007). Childhood body-mass index and the risk of coronary heart disease in adulthood. *New England Journal of Medicine, 357*, 2329–2337.

Barker, D.J. (1995). Fetal origins of coronary heart disease. *British Medical Journal, 311*, 171–174.

Berenson, G.S., Srinivasan, S.R., & Nicola, N.A. (1998). Atherosclerosis: a nutritional disease of childhood. *The American Journal of Cardiology, 82*, 22–29.

Binkin, N.J., Yip, R., Fleshood, L., & Trowbridge, F.L. (1988). Birth weight and childhood growth. *Pediatrics, 82*, 828–834.

Bjorge, T., Engeland, A., Tverdal, A., & Smith, G.D. (2008). Body mass index in adolescence in relation to cause-specific mortality: a follow-up of 230,000 Norwegian adolescents. *American Journal of Epidemiology, 168,* 30–37.

Brion, M.J., Leary, S.D., Davey Smith, G., & Ness, A.R. (2007). Similar associations of parental prenatal smoking suggest child blood pressure is not influenced by intrauterine effects. *Hypertension, 49,* 1422–1428.

Brion, M.-J.A., Ness, A.R., Rogers, I., Emmett, P., Cribb, V., Davey Smith, G., & Lawlor, D.A. (2009). Maternal diet in pregnancy and offspring diet at ten years: exploring parental comparisons and prenatal effects, submitted.

Brion, M.-J.A., Ness, A.R., Rogers, I., Emmett, P., Cribb, V., Davey Smith, G., & Lawlor, D.A. (2010a). Maternal macronutrient and energy intake in pregnancy and offspring intake at 10 years: exploring parental comparisons and prenatal effects. *American Journal of Clinical Nutrition*, 91:748–756.

Brion, M.-J. A., Lawlor, D.A., Matijasevich, A., Horta, B., Anselmi, L., Araújo, C.L., Menezes, A.M.B., Victora, C.G., & Davey, Smith, G. (2010b). What are the causal effects of breastfeeding on IQ, obesity and blood pressure? Evidence from comparing high-income and middle-income cohorts. International Journal of Epidemiology, in press (accepted November 2010).

Catalano, P.M. (2003). Obesity and pregnancy – the propagation of a viscous cycle? *The Journal of Clinical Endocrinology and Metabolism, 88*, 3505–3506.

Catalano, P.M., Thomas, A., Huston-Presley, L., & Amini, S.B. (2003). Increased fetal adiposity: a very sensitive marker of abnormal in utero development. *American Journal of Obstetrics and Gynecology, 189*, 1698–1704.

Clausen, T.D., Mathiesen, E.R., Hansen, T., Pedersen, O., Jensen, D.M., Lauenborg, J., & Damm, P. (2008). High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. *Diabetes Care, 31*, 340–346.

Crowther, C.A., Hiller, J.E., Moss, J.R., McPhee, A.J., Jeffries, W.S., & Robinson, J.S. (2005). Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *New England Journal of Medicine, 352*, 2477–2486.

Dabelea, D. (2007). The predisposition to obesity and diabetes in offspring of diabetic mothers. *Diabetes Care, 30*, 169–174.

Dabelea, D., & Pettitt, D.J. (2001). Intrauterine diabetic environment confers risks for type 2 diabetes mellitus and obesity in the offspring, in addition to genetic susceptibility. *Journal of Pediatric Endocrinology & Metabolism, 14*, 1085–1091.

Dabelea, D., Hanson, R.L., Lindsay, R.S., Pettitt, D.J., Imperatore, G., Gabir, M.M., Roumain, J., Bennett, P.H., & Knowler, W.C. (2000). Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes, 49*, 2208–2211.

Dahlgren, J., Nilsson, C., Jennische, E., Ho, H.P., Eriksson, E., Niklasson, A., Björntorp, P., Wikland, K.A., & Holmäng, A. (2001). Prenatal cytokine exposure results in obesity and gender-specific programming. *American Journal of Physiology, Endocrinology and Metabolism, 281*, 326–334.

Davey Smith, G. (2008). Assessing intrauterine influences on offspring health outcomes: can epidemiological studies yield robust findings? *Basic & Clinical Pharmacology & Toxicology, 102*, 245–256.

Davey Smith, G., & Ebrahim, S. (2003). "Mendelian randomisation": can genetic epidemiology contribute to understanding environmental determinants of disease? *International Journal of Epidemiology, 32*, 1–22.

Davey Smith, G., Steer, C., Leary, S., & Ness, A. (2007). Is there an intra-uterine influence on obesity? Evidence from parent-child associations in the Avon Longitudinal Study of Parents and Children (ALSPAC). *Archives of Disease in Childhood, 92*, 876–880.

Davey Smith, G., Lawlor, D.A., Harbord, R., Timpson, N., Day, I.N.M., & Ebrahim, S. (2008). Clustered environments and randomized genes: a fundamental distinction between conventional and genetic epidemiology. *PLoS Medicine, 4*, e352.

Dornhorst, A., Nicholls, J.S., Ali, K., Andres, C., Adamson, D.L., Kelly, L.F., Niththyananthan, R., Beard, R.W., & Gray, I.P. (1994). Fetal proinsulin and birth weight. *Diabetic Medicine: A Journal of the British Diabetic Association, 11*, 177–181.

Duran-Tauleria, E., Rona, R.J., & Chinn, S. (1995). Factors associated with weight for height and skinfold thickness in British children. *Journal of Epidemiology and Community Health, 49*, 466–473.

Ebbeling, C.B., Pawlak, D.B., & Ludwig, D.S. (2002). Childhood obesity: public-health crisis, common sense cure. *Lancet, 360*, 473–481.

Ehtisham, S., Barrett, T.G., & Shaw, N.J. (2000). Type 2 diabetes mellitus in UK children – an emerging problem. *Diabetic Medicine: A Journal of the British Diabetic Association, 17*, 867–871.

Fagot-Campagna, A., Pettitt, D.J., Engelgau, M.M., Burrows, N.R., Geiss, L.S., Valdez, R., Beckles, G.L., Saaddine, J., Gregg, E.W., Williamson, D.F., & Narayan, K.M. (2000). Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. *The Journal of Pediatrics, 136*, 664–672.

Fisch, R.O., Bilek, M.K., & Ulstrom, R. (1975). Obesity and leanness at birth and their relationship to body habitus in later childhood. *Pediatrics, 56*, 521–528.

Forouhi, N., Hall, E., & McKeigue, P. (2004). A life course approach to diabetes. In D. Kuh & Y. Ben-Shlomo (Eds.), *A life course approach to chronic disease epidemiology* (pp. 165–188). Second ed. Oxford: University Press.

Forrester, T.E., Wilks, R.J., Bennett, F.I., Simeon, D., Osmond, C., & Allen, M. (1996). Fetal growth and cardiovascular risk factors in Jamaican school children. *British Medical Journal, 312*, 156–160.

Fraser, A., Tilling, K., Macdonald-Wallis, C., Sattar, N., Brion, M.-J., Benfield, L., Ness, A., Deanfield, J., Hingorani, A., Nelson, S.M., Davey Smith, G., & Lawlor, D.A. (2010). Association of maternal weight gain in pregnancy with offspring obesity and metabolic and vascular traits in childhood. *Circulation*, 121:2557–2564.

Frayling, T.M., Timpson, N.J., Weedon, M.N., Zeggini, E., Freathy, R.M., Lindgren, C.M., Perry, J.R.B., Eilliot, K.S., Lango, H., Rayner, N.W., Sheilds, B., Harries, L.W., Barrett, J.C., Ellard, S., Groves, C.J., Knight, B., Patch, A.-M., Ness, A.R., Ebrahim, S., Lawlor, D.A., Ring, S.M., Ben-Shlomo, Y., Javelin, M.-R., Sovio, U., Bennett, A.J., Meltzer, D., Ferrucci, L., Loos, R.J.F., Wareham, N.J., Karpe, F., Owen, K.R., Cardon, L.R., Walker, M., Hitman, G.A., Palmer, C.N.A., Doney, A.S.F., Morris, A.D., Davey Smith, G., The Wellcome Trust Case Control

Consortium, Hattersley, A.T., & McCarthy, M.I. (2007). A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science*, *316*, 889–894.

Freinkel, N. (1980). Of pregnancy and progeny. *Diabetes, 29*, 1023–1035.

Freinkel, N., & Metzger, B.E. (1979). Pregnancy as a tissue culture experience, the critical implications of maternal metabolism for fetal development. In Ciba Foundation (Eds.), *Pregnancy metabolism, diabetes and the fetus (Ciba Foundation Symposium No. 63)* (pp. 3–23). Amsterdam: Excerpta Medica.

Gluckman, P.D., & Hanson, M.A. (2004). The developmental origins of the metabolic syndrome. *Trends in Endocrinol Metab*, *15*, 183–187.

Guillaume, M., Lapidus, L., Beckers, F., Lambert, A., & Bjorntorp, P. (1995). Familial trends of obesity through three generations: the Belgian-Luxembourg child study. *International Journal of Obesity and Related Metabolic Disorders, 19, Suppl 3*, 5–9.

Harder, T., Bergmann, R., Kallischnigg, G., & Plagemann, A. (2005). Duration of breastfeeding and risk of overweight: a meta-analysis. *American Journal of Epidemiology, 162*, 397–403.

Hediger, M.L., Overpeck, M.D., McGlynn, A., Kuczmarski, R.J., Maurer, K.R., & Davis, W.W. (1999). Growth and fatness at three to six years of age of children born small- or large-for-gestational age. *Pediatrics, 104*, e33.

Howe, L.D., Tilling, K., Benfield, L., Sattar, N., Ness, A.R., Davey Smith, G., & Lawlor, D.A. (2010). Changes in ponderal index and body mass index across childhood and their association with fat mass and cardiovascular risk factors at age 15. PLoS One, (accepted October 2010)

Huxley, R., Owen, C.G., Whincup, P.H., Cook, D.G., Rich-Edwards, J., & Davey Smith, G. (2007). Is birth weight a risk factor for ischemic heart disease in later life? *American Journal of Clinical Nutrition, 85*, 1244–1250.

Jovanovic, L., & Pettitt, D.J. (2001). Gestational diabetes mellitus. *Journal of the American Medical Association, 286*, 2516–2518.

Kane, J.K., Parker, S.L., Matta, S.G., Fu, Y., Sharp, B.M., & Li, M.D. (2000). Nicotine up-regulates expression of orexin and its receptors in rat brain. *Endocrinology, 141*, 3623–3629.

Kensara, O.A., Wootton, S.A., Phillips, D.I., Patel, M., Jackson, A.A., Elia, M., & Hertfordshire Study Group (2005). Fetal programming of body composition: relation between birth weight and body composition measured with dual-energy X-ray absorptiometry and anthropometric methods in older Englishmen. *American Journal of Clinical Nutrition, 82*, 980–987.

Kipping, R.R., Jago, R., & Lawlor, D.A. (2008). Obesity in children. Part 1: epidemiology, measurement, risk factors, and screening. *British Medical Journal, 337*, a1824.

Kivimaki, M., Lawlor, D.A., Smith, G.D., Elovainio, M., Jokela, M., Keltikangas-Jarvinen, L., Viikari, J.S., & Raitakari, O.T. (2007). Substantial intergenerational increases in body mass index are not explained by the fetal overnutrition hypothesis: the Cardiovascular Risk in Young Finns Study. *American Journal of Clinical Nutrition, 86*, 1509–1514.

Kjos, S.L., & Buchanan, T.A. (1999). Gestational diabetes mellitus. *New England Journal of Medicine, 341*, 1749–1756.

Kostalova, L., Leskova, L., Kapellerova, A., & Strbak, V. (2001). Body mass, plasma leptin, glucose, insulin and C-peptide in offspring of diabetic and non-diabetic mothers. *European Journal of Endocrinology, 145*, 53–58.

Kral, J.G., Biron, S., Simard, S., Hould, F.S., Lebel, S., Marceau, S., & Marceau, P. (2006). Large maternal weight loss from obesity surgery prevents transmission of obesity to children who were followed for 2 to 18 years. *Pediatrics, 118*, 1644–1649.

Kramer, M.S., Barr, R.G., Leduc, D.G., Boisjoly, C., McVey-White, L., & Pless, I.B. (1985). Determinants of weight and adiposity in the first year of life. *The Journal of Pediatrics, 106*, 10–14.

Kramer, M.S., Chalmers, B., Hodnett, E.D., Sevkovskaya, Z., Dzikovich, I., Shapiro, S., Collet, J.P., Vanilovich, I., Mezen, I., Ducruet, T., Shishko, G., Zubovich, V., Mknuik, D., Gluchanina, E., Dombrovskiy, V., Ustinovitch, A., Kot, T., Bogdanovich, N., Ovchinikova, L., Helsing, E., & PROBIT Study Group (Promotion of Breastfeeding Intervention Trial) (2001). Promotion of Breastfeeding Intervention Trial (PROBIT): a randomized trial in the Republic of Belarus. *Journal of the American Medical Association, 285*, 413–420.

Kramer, M.S., Guo, T., Platt, R.W., Shapiro, S., Collet, J.P., Chalmers, B., Hodnett, E., Sevkovskaya, Z., Dzikovich, I., Vanilovich, I., & PROBIT Study Group (2002). Breastfeeding and infant growth: biology or bias? *Pediatrics, 110*, 343–347.

Kramer, M.S., Matush, L., Vanilovich, I., Platt, R., Bogdanovich, N., Sevkosvkaya, Z., Dzikovich, I., Shishko, G., Collet, J.P., Martin, R.M., Davey Smith, G., Gillman, M.W., Chalmers, B., Hodnett, E., Shapiro, S., & Promotion of Breastfeeding Intervention Trial (PROBIT) Study Group (2007). Effects of prolonged and exclusive breastfeeding on child height, weight, adiposity, and blood pressure at age 6.5y: evidence from a large randomized trial. *American Journal of Clinical Nutrition, 86*, 1717–1721.

Labayen, I., Moreno, L.A., Blay, M.G., Blay, V.A., Mesana, M.I., Gonzalez-Gross, M., Bueno, G., Sarria, A., & Bueno, M. (2006). Early programming of body composition and fat distribution in adolescents. *Journal of Nutrition, 136*, 147–152.

Laitinen, J., Power, C., & Jarvelin, M.R. (2001). Family social class, maternal body mass index, childhood body mass index, and age at menarche as predictors of adult obesity. *American Journal of Clinical Nutrition, 74*, 287–294.

Lake, J.K., Power, C., & Cole, T.J. (1997). Child to adult body mass index in the 1958 British birth cohort: associations with parental obesity. *Archives of Disease in Childhood, 77*, 376–381.

Law, C.M., Barker, D.J., Osmond, C., Fall, C.H., & Simmonds, S.J. (1992). Early growth and abdominal fatness in adult life. *Journal of Epidemiology and Community Health, 46*, 184–186.

Law, C.M., Gordon, G.S., Shiell, A.W., Barker, D.J., & Hales, C.N. (1995). Thinness at birth and glucose tolerance in seven-year-old children. *Diabetic Medicine, 12*, 24–29.

Lawlor, D.A., Riddoch, C.J., Page, A.S., Anderssen, S.A., Froberg, K., & Harro, M. (2004). The association of birth weight and contemporary size with insulin resistance among children from Estonia and Denmark: findings from the European Heart Study. *Diabetic Medicine, 22*, 921–930.

Lawlor, D.A., Davey Smith, G., O'Callaghan, M., Alati, R., Mamun, A.A., Williams, G.M., & Najman, J.M. (2007). Epidemiologic evidence for the fetal overnutrition hypothesis: findings from the mater-university study of pregnancy and its outcomes. *American Journal of Epidemiology, 165*, 418–424.

Lawlor, D.A., Harbord, R.M., Sterne, J.A.C., Timpson, N.J., & Davey Smith, G. (2008a). Mendelian randomization and instrumental variables. *Statistics in Medicine, 27*, 1133–1163.

Lawlor, D.A., Timpson, N., Harbord, R., Leary, S., Ness, A., McCarthy, M.I., Frayling, T.M., Hattersley, A.T., & Davey Smith, G. (2008b). Exploring the developmental overnutrition hypothesis using parental-offspring associations and the *FTO* gene as an instrumental variable for maternal adiposity: findings from the Avon Longitudinal Study of Parents and Children (ALSPAC). *PLoS Medicine, 5*, e33.

Lawlor, D.A., Benfield, L., Logue, J., Tilling, K., Howe, L.D., Fraser, A., Cherry, L., Watt, P., Ness, A.R., Davey Smith, G., & Sattar, N. (2010a). The association of general and central adiposity, and change in these with cardiovascular risk factors in adolescence: A prospective cohort study. *BMJ*, in press (accepted September 2010)

Lawlor, D.A., Fraser, A., Lindsay, R.S., Ness, A., Dabelea, D., Catalano, P., Davey Smith, G., Sattar, N., & Nelson, S.M. (2010b). The association of existing diabetes, gestational diabetes and glycosuria in pregnancy with macrosomia and offspring body mass index, waist and fat mass in later childhood: findings from a prospective pregnancy cohort. *Diabetologia*, *53*, 89–97

Lawlor, D.A., Lichtenstein, P., & Långström, N. (2010c). Maternal diabetes in pregnancy programmes greater offspring adiposity into early adulthood: Sibling study in a prospective cohort of 280,866 men from 248,293 families. *Circulation*, in press (accepted October 2010)

Leary, S.D., Davey Smith, G., Rogers, I.S., Reilly, J.J., Wells, J.C., & Ness, A.R. (2006). Smoking during pregnancy and offspring fat and lean mass in childhood. *Obesity, 14*, 2284–2293.

Levin, B.E., & Govek, E. (1998). Gestational obesity accentuates obesity in obesity-prone progeny. *American Journal of Physiology, 275*, 1374–1379.

Li, C., Kaur, H., Choi, W.S., Huang, T.T., Lee, R.E., & Ahluwalia, J.S. (2005). Additive interactions of maternal prepregnancy BMI and breast-feeding on childhood overweight. *Obesity Research, 13*, 362–371.

Li, L., Hardy, R., Kuh, D., Lo, C.R., & Power, C. (2008). Child-to-adult body mass index and height trajectories: a comparison of 2 British birth cohorts. *American Journal of Epidemiology, 168*, 1008–1015.

Mamun, A.A., Lawlor, D.A., Alati, R., O'Callaghan, M.J., Williams, G.M., & Najman, J.M. (2006). Does maternal smoking during pregnancy have a direct effect on future offspring obesity? Evidence from a prospective birth cohort study. *American Journal of Epidemiology, 164*, 317–325.

Mamun, A.A., O'Callaghan, M., Callaway, L., Williams, G., Najman, J., & Lawlor, D.A. (2009). Associations of gestational weight gains with offspring body mass index and blood pressure at 21 years: evidence from a birth cohort study. *Circulation*, *119*, 1720–1727.

Manderson, J.G., Mullan, B., Patterson, C.C., Hadden, D.R., Traub, A.I., & McCance, D.R. (2002). Cardiovascular and metabolic abnormalities in the offspring of diabetic pregnancy. *Diabetologia, 45*, 991–996.

McCarthy, A., Hughes, R., Tilling, K., Davies, D., Davey Smith, G., & Ben-Shlomo, Y. (2007). Birth weight; postnatal, infant, and childhood growth; and obesity in young adulthood: evidence from the Barry Caerphilly Growth Study. *American Journal of Clinical Nutrition, 86*, 907–913.

Metzger, B.E., Silverman, B.L., Freinkel, N., Dooley, S.L., Ogata, E.S., & Green, O.C. (1990). Amniotic fluid insulin concentration as a predictor of obesity. *Archives of Disease in Childhood, 65*, 1050–1052.

Metzger, B.E., Lowe, L.P., Dyer, A.R., Trimble, E.R., Chaovarindr, U., Coustanm, D.R., Hadden, D.R., McCance, D.R., Hod, M., McIntyre, H.D., Oats, J.J.N., Persson, B., Rogers, M.S., & Sacks, D.A. (2008). Hyperglycemia and adverse pregnancy outcomes. *New England Journal of Medicine, 358*, 1991–2002.

Moreira, P., Padez, C., Mourao-Carvalhal, I., & Rosado, V. (2007). Maternal weight gain during pregnancy and overweight in Portuguese children. *International Journal of Obesity (London), 31*, 608–614.

Naturenews. (2009). http://www.nature.com/news/2008/081120/full/news.2008.1240.html, accessed on April 14, 2009.

Okens, K., Taveras, E.M., Kleinman, K.P., Rich-Edwards, J.W., & Gillman, M.W. (2005). Maternal weight gain during pregnancy and child adiposity at age 3 years. *Pediatric Research, 58*, 1127.

Okun, N., Verma, A., Mitchell, B.F., & Flowerdew, G. (1997). Relative importance of maternal constitutional factors and glucose intolerance of pregnancy in the development of newborn macrosomia. *The Journal of Maternal-Fetal Medicine, 6*, 285–290.

Ong, K.K., Emmett, P., Northstone, K., Golding, J., Rogers, I., Ness, A.R., Wells, J.C., & Dunger, D.B. (2009). Infancy weight gain predicts childhood body fat and age at menarche in girls. *Journal of Clinical Endocrinology and Metabolism*, doi:10.1210/jc.2008-2489.

Owen, C.G., Whincup, P.H., Odoki, K., Gilg, J.A., & Cook, D.G. (2003). Birth weight and blood cholesterol level: a study in adolescents and systematic review. *Pediatrics, 111*, 1081–1089.

Owen, C.G., Martin, R.M., Whincup, P.H., Davey Smith, G., & Cook, D.G. (2005a). Effect of infant feeding on the risk of obesity across the life course: a quantitative review of published evidence. *Pediatrics, 115*, 1367–1377.

Owen, C.G., Martin, R.M., Whincup, P.H., Davey Smith, G., Gillman, M.W., & Cook, D.G. (2005b). The effect of breast feeding on mean body mass index throughout the lifecourse; a quantitative review of published and unpublished observational evidence. *American Journal of Clinical Nutrition, 82*, 1298–1307.

Owen, C.G., Whincup, P.H., Orfei, L., Chou, Q., Eriksson, J., & Osmond, C. (2007). Body mass index and risk of coronary heart disease: a lifecourse approach. *Early Human Development, 83*, 78.

Parsons, T.J., Power, C., & Manor, O. (2001). Fetal and early life growth and body mass index from birth to early adulthood in 1958 British cohort: longitudinal study. *British Medical Journal, 323*, 1331–1335.

Pederson, J. (1954). Weight and length at birth of infants of diabetic mothers. *Acta Endocrinologica, 16*, 330–342.

Persson, B., Heding, L.G., Lunell, N.O., Pschera, H., Stangenberg, M., & Wager, J. (1982). Fetal beta cell function in diabetic pregnancy. Amniotic fluid concentrations of proinsulin, insulin, and C-peptide during the last trimester of pregnancy. *American Journal of Obstetrics and Gynecology, 144*, 455–459.

Pettitt, D.J., & Knowler, W.C. (1998). Long-term effects of the intrauterine environment, birthweight, and breastfeeding in Pima Indians. *Diabetes Care, 21*, 138–141.

Pettitt, D.J., Baird, H.R., Aleck, K.A., Bennett, P.H., & Knowler, W.C. (1983). Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. *New England Journal of Medicine, 308*, 242–245.

Pettitt, D.J., Knowler, W.C., Bennett, P.H., Aleck, K.A., & Baird, H.R. (1987). Obesity in offspring of diabetic Pima Indian women despite normal birth weight. *Diabetes Care, 10*, 76–80.

Pettitt, D.J., Nelson, R.G., Saad, M.F., Bennett, P.H., & Knowler, W.C. (1993). Diabetes and obesity in the offspring of Pima Indian women with diabetes during pregnancy. *Diabetes Care, 16*, 310–314.

Pietilainen, K.H., Kaprio, J., Rasanen, M., Winter, T., Rissanen, A., & Rose, R.J. (2001). Tracking of body size from birth to late adolescence: contributions of birth length, birth weight, duration of gestation, parents' body size and twinship. *American Journal of Epidemiology, 154*, 21–29.

Power, C., & Jefferis, B.J. (2002). Fetal environment and subsequent obesity: a study of maternal smoking. *International Journal of Epidemiology, 31*, 413–419.

Power, C., Lake, J.K., & Cole, T.J. (1997). Body mass index and height from childhood to adulthood in the 1958 British born cohort. *American Journal of Clinical Nutrition, 66*, 1094–1101.

Pribylova, H., & Dvorakova, L. (1996). Long-term prognosis of infants of diabetic mothers. Relationship between metabolic disorders in newborns and adult offspring. *Acta Diabetologica, 33*, 30–34.

Ramsay, J.E., Ferrell, W.R., Crawford, L., Wallace, A.M., Greer, I.A., & Sattar, N. (2002). Maternal obesity is associated with dysregulation of metabolic, vascular, and inflammatory pathways. *The Journal of Clinical Endocrinology and Metabolism, 87*, 4231–4237.

Rasmussen, F., & Johansson, M. (1998). The relation of weight, length and ponderal index at birth to body mass index and overweight among 18-year-old males in Sweden. *European Journal of Epidemiology, 14*, 373–380.

Rogers, I.S., Ness, A.R., Steer, C.D., Wells, J.C.K., Emmett, P.M., Reilly, J.R., Tobias, J., & Davey Smith, G. (2006). Associations of size at birth and dual-energy X-rat absorptiometry measures of lean and fat mass at 9 to 10 years of age. *American Journal of Clinical Nutrition, 84*, 739–747.

Sachdev, H.S., Fall, C.H, Osmond, C., Lakshmy, R., Dey Biswas, S.K., Leary, S.D., Reddy, K.S., Barker, D.J.P., & Bhargava, S.K. (2005). Anthropometric indicators of body composition in young adults: relation to size at birth and serial measurements of body mass index in childhood in the New Delhi birth cohort. *American Journal of Clinical Nutrition, 82*, 456–466.

Schack-Nielsen, L., Mortensen, E.L., Michaelsen, K.F., & Ti, S. (2005). High maternal pregnancy weight gain is associated with an increased risk of obesity in childhood and adulthood independent of maternal BMI. *Pediatric Research, 58*, 1020.

Scholl, T.O., Sowers, M., Chen, X., & Lenders, C. (2001). Maternal glucose concentration influences fetal growth, gestation, and pregnancy complications. *American Journal of Epidemiology, 154*, 514–520.

Sebire, N.J., Jolly, M., Harris, J.P., Wadsworth, J., Joffe, M., Beard, R.W., Regan, L., & Robinson, S. (2001). Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London. *International Journal of Obesity and Related Metabolic Disorders, 25*, 1175–1182.

Seidman, D.S., Laor, A., Gale, R., Stevenson, D.K., & Danon, Y.L. (1991). A longitudinal study of birth weight and being overweight in late adolescence. *American Journal of Diseases in Children, 145*, 782–785.

Seidman, D.S., Laor, A., Shemer, J., Gale, R., & Stevenson, D.K. (1996). Excessive maternal weight gain during pregnancy and being overweight at 17 years of age. *Pediatric Research, 39*, 112A.

Sermer, M., Naylor, C.D., Gare, D.J., Kenshole, A.B., Ritchie, J.W., Farine, D., Cohen, H.R., McArthur, K., Holzapfel, S., Biringer, A., Chen, E., & Toronto Tri-Hospital Gestational Diabetes Investigators (1995). Impact of increasing carbohydrate intolerance on maternal-fetal outcomes in 3637 women without gestational diabetes. The Toronto Tri-Hospital Gestational Diabetes Project. *American Journal of Obstetrics and Gynecology, 173*, 146–156.

Sharma, A.J., Cogswell, M.E., & Grummer-Strawn, L.M. (2005). The association between pregnancy weight gain and childhood overweight is modified by mother's pre-pregnancy BMI. *Pediatric Research, 58*, 1038.

Silverman, B.L., Rizzo, T., Green, O.C., Cho, N.H., Winter, R.J., Ogata, E.S., Richards, G.E., & Metzger, B.E. (1991). Long-term prospective evaluation of offspring of diabetic mothers. *Diabetes, 40, Suppl 2*, 121–125.

Silverman, B.L., Landsberg, L., & Metzger, B.E. (1993). Fetal hyperinsulinism in offspring of diabetic mothers. Association with the subsequent development of childhood obesity. *Annals of the New York Academy of Sciences, 699*, 36–45.

Silverman, B.L., Metzger, B.E., Cho, N.H., & Loeb, C.A. (1995). Impaired glucose tolerance in adolescent offspring of diabetic mothers. Relationship to fetal hyperinsulinism. *Diabetes Care, 18*, 611–617.

Singhal, A., & Lucas, A. (2004). Early origins of cardiovascular disease: is there a unifying hypothesis? *Lancet, 363*, 1642–1645.

Singhal, A., Fewtrell, M., Cole, T.J., & Lucas, A. (2003a). Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. *Lancet, 361*, 1089–1097.

Singhal, A., Wells, J., Cole, T.J., Fewtrell, M., & Lucas, A. (2003b). Programming of lean body mass: a link between birth weight, obesity and cardiovascular disease? *American Journal of Clinical Nutrition, 77*, 726–730.

Slotkin, T.A. (1998). Fetal nicotine or cocaine exposure: which one is worse? *The Journal of Pharmacology and Experimental Therapeutics, 285*, 931–945.

Sobngwi, E., Boudou, P., Mauvais-Jarvis, F., Leblanc, H., Velho, G., Vexiau, P., Porcher, R., Hadjadj, S., Pratley, R., Tataranni, P.A., Calvo, F., & Gautier, J.F. (2003). Effect of a diabetic environment in utero on predisposition to type 2 diabetes. *Lancet, 361*, 1861–1865.

Stettler, N., Tershakovec, A.M., Zemel, B.S., Leonard, M.B., Boston, R.C., Katz, S.H., & Stallings, V.A. (2000). Early risk factors for increased adiposity: a cohort study of African American subjects followed from birth to young adulthood. *American Journal of Clinical Nutrition, 72*, 378–383.

Strauss, R.S. (1997). Effects of the intrauterine environment on childhood growth. *British Medical Bulletin*, *53*, 81–95.

Te Velde, S.J., Twisk, J.W.E., Van Mechelan, W., & Kemper, H.C.G. (2003). Birth weight, adult body composition, and subcutaneous fat distribution. *Obesity Research, 11*, 202–208.

Toschke, A.M., Montgomery, S.M., Pfeiffer, U., & von Kries, R. (2003). Early intrauterine exposure to tobacco-inhaled products and obesity. *American Journal of Epidemiology, 158*, 1068–1074.

Von Kries, R., Toschke, A.M., Koletzko, B., & Slikker, W., Jr. (2002). Maternal smoking during pregnancy and childhood obesity. *American Journal of Epidemiology, 156*, 954–961.

Walker, S.P., Gaskin, P.S., Powell, C.A., & Bennett, F.I. (2002). The effects of birth weight and postnatal linear growth retardation on body mass index, fatness and fat distribution in mid and late childhood. *Public Health Nutrition, 5*, 391–396.

Weiss, P.A., Scholz, H.S., Haas, J., Tamussino, K.F., Seissler, J., & Borkenstein, M.H. (2000). Long-term follow-up of infants of mothers with type 1 diabetes: evidence for hereditary and nonhereditary transmission of diabetes and precursors. *Diabetes Care, 23*, 905–911.

Whincup, P.H., Cook, D.G., & Geleijnse, J.M. (2004). A life course approach to blood pressure. In D. Kuh & Y. Ben-Shlomo (Eds.), *A life course approach to chronic disease epidemiology* (pp. 218–239). Second ed. Oxford: University Press.

Whincup, P.H., Kaye, S.J., Owen, C.G., Huxley, R., Cook, D.G., Anazawa, S., Barrett-Connor, E., Bhargava, S.K., Birgisdottir, B., Carlsson, S., De Rooij, S., Dyck, R., Eriksson, J.G., Falkner, B., Fall, C., Forsen, T., Grill, V., Gudnason, V., Hulman, S., Hypponen, E., Jeffreys, M., Lawlor, D.A., Leon, D.A., Mi, J., Minami, J., Mishra, G., Osmond, C., Power, C., Rich-Edwards, J., Roseboom, T.J., Sachdev, H.P.S., Suzuki, T., Syddall, H., Thorsdottir, I., Vanhala, M., Wadsworth, M., & Yarbrough, D.E. (2008). Birthweight and risk of type 2 diabetes: a quantitative systematic review of published evidence. *Journal of the American Medical Association, 300*, 2886–2897.

Whitaker, R.C. (2004). Predicting preschooler obesity at birth: the role of maternal obesity in early pregnancy. *Pediatrics, 114*, 29–36.

Whitaker, R.C., & Dietz, W.H. (1998). Role of the prenatal environment in the development of obesity. *The Journal of Pediatrics, 132*, 768–776.