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# The role of low birthweight in the aetiology of type 2 diabetes

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## SUMMARY

**The aetiology of type 2 diabetes is still poorly understood. Although it is clear that obesity is a risk factor for the disease, obesity leads to diabetes only in susceptible individuals. Both genetic and environmental factors determine this susceptibility. This review describes the emerging evidence that low birthweight caused by malnutrition or a genetic predisposition increases the risk of type 2 diabetes.**

## Evidence for a link between low birthweight and type 2 diabetes

All of the epidemiological studies conducted to date show an association between low birthweight and the risk of diabetes or impaired glucose tolerance (IGT). Some of the earliest work, done by Hales and colleagues in 1991, showed a three-fold difference in the prevalence of impaired glucose tolerance and diabetes between men with the lowest and highest infant body weights (1). Two years later, Phipps et al. showed similar findings in women (2). Since then, others have confirmed that low birthweight is associated with an approximately two- to three-fold increased risk of type 2 diabetes (3-8). A smaller number of studies have shown that low birthweight is associated with impaired glucose tolerance (9-13). Most of these studies have been conducted on adults born in the first half of the twentieth century using retrospective data collection, but several recent studies of children show similar relationships (9,14-16). For example, anthropometrical measurements made in school children from Papua New Guinea have shown a lower mean birthweight in children from a community with a very high prevalence of type 2 diabetes than in children from low prevalence communities (17).

Many studies report continuous relationships between birthweight and diabetes and between birthweight and glucose intolerance from a birthweight below 2.5 kg up to a birthweight of approximately 4.5 kg (1,5,8,10,18). In addition, several studies report an increased diabetes prevalence in those with birthweights over 4.5 kg (3,6,8). Therefore both low and high birthweights predispose individuals to subsequently develop diabetes. Interestingly, not just the weight of the baby but also unusual patterns of fetal growth predict diabetes. For example, babies who are thin or short in relation to their head circumference, or have a disproportionately large placenta, or have abnormal thinness indicated by a low ponderal index (weight/length$^3$) are at greater risk of developing diabetes (2,14,19-22).

## Why is there a link between birthweight and type 2 diabetes?

The link between low birthweight and type 2 diabetes is independent of gestational age indicating that the association is not due to prematurity (2). It is also independent of confounding variables acting in later life, such as low socioeconomic status. Influences that act after birth do, however, add to the effects of low birthweight; for example, the increased risk of type 2 diabetes associated with small size at birth is exacerbated in those subjects who become obese. Several studies have shown that children (15,16) and adults (12,23) who were thin at birth but had grown heavy (or tall) appear to be more resistant to insulin and hence susceptible to type 2 diabetes. Childhood obesity predicts insulin resistance in

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adulthood with an odds ratio of 4.4 (24). Some studies show that the diabetogenic effects of obesity add to that of birthweight (1), while others show that the effect of low birthweight interacts with that of adult obesity so that the diabetogenic effect of obesity is more marked among people of low birthweight than among those of high birthweight (19).

Infants who show greatest catch-up growth during the first 1-2 years of postnatal life are smaller and thinner at birth but larger and fatter than other children at 5 years (25). Interestingly, the association between low birthweight and IGT/type 2 diabetes is more evident in subjects who show catch-up growth from birth to one year of age than those who follow their genetic growth trajectory (26). This suggests that factors that signal and regulate postnatal catch-up growth may contribute to the pathogenic link between early growth and diabetes (21). Why catch-up growth is detrimental is not known, but could be because fetal growth restriction leads to reduced cell numbers and catch-up growth is achieved by overgrowth of a limited cell mass.

However, many individuals who are born with low birthweight do not show catch-up growth (27) and do not develop obesity later in life. Unlike the clear association between birthweight and diabetes outlined above, the association between birthweight and obesity is more controversial (28) with some studies reporting an association between low birthweight and increased risk of obesity and dyslipidaemia (12,29) while others do not (4,30,31).

**Is insulin resistance the link between low birthweight and type 2 diabetes?**

A large number of studies have reported an association of low birthweight with an increase in insulin, either fasting or after an oral glucose tolerance test (OGTT) (10-12,14-16,18,19,32,33). Four studies have reported a decrease in insulin sensitivity in subjects that had low birthweights (15,19,29,34).

Therefore, it appears that the diabetogenic effect of low birthweight is at least partly due to a decrease in insulin sensitivity. It is less clear whether impaired insulin secretion also contributes to the diabetogenic effect of low birthweight. Most studies that have looked for associations between low birthweight and defective insulin secretion have reported negative findings (15,19,34-36) or suggestive findings only (36-38). Prospective studies with measurements of both insulin secretion and insulin resistance are needed to determine the role of each in the diabetogenic effect of low birthweight.

The studies that have examined an association between low birthweight and features of type 2 diabetes are summarized in Table 1.

**Low birthweight and the metabolic syndrome**

There is substantial evidence that low birthweight is associated with several features of the metabolic syndrome (or syndrome X), which is characterized by obesity, glucose intolerance, raised blood pressure and dyslipidaemia, and is known to be associated with insulin resistance (10,15,18,20,23, 29,31,34,39). For example, in 1993, Barker and colleagues showed that 22% of 64-year-old men whose birthweight was 2.9 kg or less had the metabolic syndrome. Their risk of developing this syndrome was more than 10 times greater than that of men whose birthweight was more than 4.3 kg, leading the authors to suggest that the metabolic syndrome should perhaps be renamed 'the small-baby syndrome' (20). Many others have shown similar associations, although the risks reported are lower than those reported by Barker et al. For example, compared with women in the highest birthweight tertile (~4.2 kg), those in the lowest birthweight tertile (~2.5 kg) had 2.4 times the risk of developing the metabolic syndrome (23). There are, however, some conflicting data that have not shown an association between birthweight and the subsequent development of the metabolic syndrome, in a Finnish population of 712 subjects (24) and in a Danish population of 620 subjects (13). As described above, a significant number of studies have also failed to show an association between low birthweight and the high triglyceride, low HDL cholesterol levels, and/or abdominal obesity that is typically a component of the metabolic

**TABLE 1**

STUDIES THAT HAVE EXAMINED AN ASSOCIATION BETWEEN LOW BIRTHWEIGHT AND FEATURES OF TYPE 2 DIABETES

| Reference | Location | Age and Sex | N | Association | Independent of |
|---|---|---|---|---|---|
| Hales et al. (1) | UK | Men, 59-70 years | 370 (66 of these had IGT, 27 had diabetes) | Small babies were 3 times more likely to develop diabetes or IGT than large babies. | Gestational age, social class |
| Phipps et al. (2) | UK | Men and women, 50 years | 140 men, 126 women | Prevalence of IGT or diabetes fell from 27% in subjects who weighed 2.5 kg or less at birth to 6% in subjects who weighed more than 3.41 kg. | BMI, gestational age |
| McCance et al. (3) | USA | American Indians | 1179 | Prevalence of type 2 diabetes was greatest in those with the lowest and highest birthweights. Odds ratio for diabetes in subjects with birthweight <2.5 kg was 3.81 compared to normal weight babies. | Age, sex, BMI, maternal diabetes during pregnancy, birth year |
| Lithell et al. (19) | Sweden | Men, 50-60 years | 1333 | Inverse relations of birthweight with diabetes and positive associations with insulin sensitivity. | BMI |
| Curhan et al. (4) | USA | Men, 48-83 years | 22,846 (4.9% of these had birthweight <2.3 kg) | Compared to men with a birthweight between 3.2 and 3.8 kg, the odds ratio of diabetes was 1.9 for men with a birthweight below 2.3 kg. | Age, BMI, parental history of diabetes, smoking, physical activity |
| Rich-Edwards et al. (5) | USA | Women, 46-71 years | 69,526 including 2123 cases of type 2 diabetes | An inverse association across the entire range of birthweight with risk of type 2 diabetes. Compared to the reference group, relative risk was 1.8 for birthweight less than 2.3 kg. Association was strongest for women whose mothers had no history of diabetes. | Age, adult BMI, maternal history of diabetes, ethnicity, childhood SES, adult lifestyle factors |

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| Williams et al. (6) | USA | Women of child-bearing age | 21,528 non-Hispanic white, 6359 African American, 7456 Native American and 6496 Hispanic women (~3% had gestational diabetes) | In all groups, women with a birthweight less that 2 kg were 2- to 3-fold more likely to have a pregnancy complicated by gestational diabetes than those with a birthweight between 3 and 4 kg. | Maternal age, parity, cigarette smoking, a history of hypertension |
| Carlsson et al. (7) | Sweden | Men, 35-56 years | 2237 (50% had a family history of diabetes) | In subjects without a family history of diabetes, the odds ratio for diabetes was 2.3 for birthweights less than 3.0 kg. In subjects with a family history, this value was 5.4. The combination of low birthweight and family history increased the odds ratio to 10.9. | Age, BMI |
| Egeland et al. (8) | Norway | Women, 15-32 years | 138,714 (196 with gestational diabetes) | Low birthweight or low weight for gestational age or having a mother who was diabetic during pregnancy increases the risk of gestational diabetes. Women with birthweight less than 2.5 kg had an 80% increased risk of gestational diabetes. | Age, parity, mother's diabetic status |
| Valdez et al. (18) | USA | Mexican Americans and non-Hispanic whites | 564 | Normotensive, nondiabetic subjects whose birthweight was in the lowest tertile had higher fasting insulin. | Sex, ethnicity, current SES |
| Law et al. (9) | UK | Children, 7 years | 250 | Plasma glucose after an OGTT rose by 0.07 mmol/l for every unit fall in ponderal index (ie increasing thinness) | Gestation, sex, social class, current weight |
| Fall et al. (12) | UK | Women, 60-71 years | 297 | Fasting glucose, insulin and 32-33 split proinsulin, and glucose and insulin after an OGTT, fell with increasing birthweight. Blood pressure, waist:hip ratio and serum TG also fell with increasing birthweight while HDL cholesterol rose. | BMI |
| Vestbo et al. (13) | Denmark | Offspring of diabetic and nondiabetic subjects, 41-54 years | 620 | Birthweight was negatively correlated with fasting glucose but birthweight was not a major risk factor for the development of hypertension and cardiovascular disease. | Age, BMI, sex, sex of affected parent, diabetic status of parents |

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| Leger et al. (32) | France | 20-year-old adults | 236 small for gestational age and 281 normal birthweight | SGA subjects had higher glucose, insulin and proinsulin levels after an OGTT. Lipid and blood pressure levels were not different. | Sex, BMI |
| Whincup et al. (14) | UK | Children, 10-11 years | 591 (fasting) and 547 (OGTT) | For each kg increase in birthweight, fasting insulin fell by 16.9% and post-OGTT-load insulin by 11.6%. No relationship with glucose levels. | Childhood height and ponderal index |
| Crowther et al. (16) | South Africa | Black children, 7 years | 152 | Lower birthweights were associated with higher glucose and insulin levels during the first 30 minutes of an OGTT. Higher insulin values were seen in those children who had low birthweight but high weight at 7 years. | |
| Bavdekar et al. (15) | India | Children, 8 years | 477 | Lower birthweight was associated with higher blood pressure, fasting plasma insulin, 32-33 split proinsulin, glucose and insulin levels 30 min post-OGTT, subscapular/triceps skinfold ratio, total and LDL cholesterol, and increased calculated insulin resistance but not β-cell function. | Current weight, age, sex |
| Dabelea et al. (11) | USA | Pima Indians, 5-29 years | 3061 (2272 were nondiabetic) | 2-hour glucose concentrations after an OGTT showed a U-shaped relationship with birthweight in subjects >10 years of age. In nondiabetic subjects, fasting and 2-hour insulin levels negatively correlated with birthweight (independent of weight and height). | Current body size |
| Flanagan et al. (33) | Australia | Adults, 20 years | 163 | Men who were lighter or shorter at birth were less insulin sensitive and had higher insulin secretion but were not glucose intolerant. No relationships were seen in women. | BMI |
| Mi et al. (10) | China | Adults, 45 years | 627 | Low birthweight was associated with elevated plasma glucose and insulin levels. For every 1 kg increase in birthweight, the 2-hour plasma glucose level after an OGTT decreased by 5%. Low maternal BMI during pregnancy was also associated with impaired glucose tolerance in adult offspring. | Sex, current BMI |

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| Serne et al. (29) | Netherlands | Healthy subjects | 30 | Birthweight was significantly associated with insulin sensitivity. | Age, sex and BMI |
| Choi et al. (34) | Korea | Young nondiabetic adults | 22 | Birthweight correlated significantly with insulin sensitivity. | |

IGT = impaired glucose tolerance
BMI = body mass index
SES = socioeconomic status
OGTT = oral glucose tolerance test
TG = triglycerides
HDL = high-density lipoprotein
SGA = small for gestational age
LDL = low-density lipoprotein

syndrome (4,18,19,30-34). This suggests that the association of low birthweight with insulin resistance is not mediated by dyslipidaemia or abdominal obesity. It is possible that truncal obesity rather than abdominal obesity may be a more common consequence of low birthweight (18,31).

It is not surprising then that many studies have shown that the association between low birthweight and insulin resistance exists independent of current body weight or body mass index (15,19,33). For example, low birthweight Pima Indians are thinner at ages 5-29 years, yet they are more insulin resistant relative to their body size than those of normal body weight (11).

**Frequency of low birthweight**

Maternal size, maternal nutrition during pregnancy and placental efficiency are important determinants of birthweight (40). The proportion of births that can be classified as low birthweights (ie below 2.5 kg) varies enormously between different ethnic groups in different environmental circumstances (41). For example, less than 10% of the general population in the USA are born with low birthweight (30), whereas 30% of American Indian children are born with a birthweight below 2.5 kg (3). In Papua New Guinea, the reported percentage of babies born with a low birthweight varies, with some studies showing incidence rates as low at 7% (42,43) while others report rates of 20% to 40% (44,45). Indian babies are characteristically smaller and thinner than caucasian babies with a mean birthweight of only 2.6-2.7 kg (15). They do, however, have preserved subcutaneous fat (40). The thinness of Indian babies is due to poor muscle and small abdominal viscera.

In countries undergoing rapid modernization, such as Papua New Guinea, there is clear evidence of a trend in increasing mean birthweight and a decline in the proportion of infants born with a low birthweight (<2.5 kg) over the past 30 years (46). This is likely to be a consequence of improvements in maternal diet and increased maternal body size. In malarious areas of Papua New Guinea, exposure to malaria has an impact upon birthweight with up to 40% of low birthweight in babies attributable to malarial infection (47). Other identified risk factors for low birthweight in Papua New Guinea include maternal age (<22 years or >35 years) and maternal size, past delivery of a low birthweight infant, lack of antenatal care and smoking during pregnancy (42,48,49).

Most diabetes occurs in subjects with intermediate birthweights (2.5 – 4.5 kg) (3) which means that even though the prevalence rate of diabetes is higher in individuals with low birthweight, these subjects only account for a minority of diabetes cases in the population (50). Low birthweight is therefore likely to be a component factor rather than a sufficient cause or a necessary factor for the development of diabetes. This is why mean birthweights are not significantly different between groups of diabetic and nondiabetic subjects (35,51,52). In contemporary children, obesity is a stronger determinant of insulin level and insulin resistance than size at birth (53). However, suboptimal fetal growth may be widespread in the population (and may not necessarily manifest as an absolute low birthweight) and may contribute to an increased risk of diabetes later in life.

**Does an insulin-resistant genotype contribute to low birthweight?**

The risk of diabetes associated with low birthweight is strongly related to the development of paternal diabetes, suggesting a genetic link between lower birthweight and later diabetes (54). It is possible that low birthweight, measures of insulin resistance, glucose intolerance and diabetes are all phenotypes of the same insulin-resistant genotype (55). In other words, a genetically determined defect in insulin action could manifest itself in utero as reduced growth and later in life as impairment of insulin-stimulated uptake of glucose: a ‘thrifty genotype’. This is consistent with observations in mice in which the gene for insulin receptor substrate-1 has been deleted: compared with their normal littermates these mice are lighter at birth and resistant to insulin-stimulated uptake of glucose as adults (56). The genes that predispose to insulin resistance and diabetes may enable a fetus to survive undernutrition in utero by preserving growth of certain organs, such as the brain, at the expense of others, such as the viscera: this is the 'surviving small baby hypothesis' proposed by McCance et al. (3,57). A search for these genes is actively underway. An association between the maternal G protein beta3 subunit 825T allele and low birthweight has been recently reported in babies born to women without other risks for reduced fetal growth (58). An association between the insertion/deletion polymorphism of the angiotensin I-converting enzyme gene (ACE I/D) and plasma insulin has also been reported, with increased plasma insulin levels observed in the presence of the ACE I allele (59). In adults who were born small for gestational age, this allele confers a relative insulin resistance that is attenuated by the presence of the ACE D allele. In contrast, the ACE gene polymorphism is not associated with plasma insulin levels in adults born with an appropriate birthweight for gestational age. Associations have also been reported between the insulin gene (INS) VNTR (variable number of tandem repeats) and both size at birth (60) and IGT/type 2 diabetes (26) which were amplified in subjects who did not show early catch-up growth and were independent of the maternal restraint on fetal growth. Others have shown that maternal restraint on fetal growth may also be, in part, genetically determined, with the mitochondrial 16189 variant related to both thinness at birth and IGT/type 2 diabetes in subjects who show greater early postnatal catch-up growth (61). Negative findings have also been reported. For example, the coding regions of insulin-like growth factor (IGF-1) and the IGF-1 receptor (62), and polymorphisms in the promoter of the TNF$\alpha$ (tumor necrosis factor alpha) gene (63) do not associate with reduced birthweight, insulin sensitivity index or type 2 diabetes in a Danish population.

### Does insulin deficiency in utero lead to low birthweight?

There is some evidence for this in human subjects where inheritance of a glucokinase mutation by the fetus results in a mean reduction of birthweight of 533 g (64). In sibpairs discordant for the presence of a glucokinase mutation, the child with the mutation had a 521 g lower birthweight. Studies in family members from a MODY2 kindred caused by glucokinase mutations also show that birthweight was reduced in the presence of a fetal glucokinase mutation (65). Mice that have no glucokinase in their pancreatic beta-cells have reduced birthweights, providing direct evidence for a link between insulin and fetal growth (66). Thus, glucokinase mutations in beta-cells may impair insulin response to glucose and alter intrauterine growth as well as glucose metabolism after birth.

### Do adaptations to adverse environmental conditions contribute to low birthweight?

Another explanation for the association between insulin resistance and reduced fetal growth is that inadequate nutrition causes adaptations which program the fetus to develop resistance to insulin-stimulated uptake of glucose in later life: the 'thrifty phenotype' or 'fetal origins hypothesis'. These adaptations may be cardiovascular, metabolic or endocrine and they may permanently change the structure and function of the body (22).

Several studies suggest that the maternal environment rather than genetic factors have a dominant influence on birth size. For example, ovum donation studies have shown that the birthweights of the babies were strongly related to the weight of the recipient mother, not to the weights of the women who donated the eggs (67). In addition, there is a higher correlation between the birthweights of half-siblings who share the same mother than among half-siblings who share a father (68). In an analysis of 14 pairs of monozygous twins discordant for type 2 diabetes, twins with diabetes or IGT had significantly lower birthweights than did their nondiabetic genetically identical co-twins suggesting that the association between low birthweight and diabetes is at least partly independent of genetic factors and may be due to intrauterine malnutrition (69). Bo and colleagues have found identical results in a group of 13 monozygotic twins discordant for IGT and/or hyperinsulinaemia (70). The within-pair birthweight difference was a significant predictor of abnormal responses to an OGTT.

Fetal undernutrition could cause insulin resistance by directly influencing the growth and differentiation of insulin-sensitive tissues, although studies that have addressed this in human muscle have shown no evidence of structural changes (71,72). It is possible that fetal undernutrition causes other features of the metabolic syndrome, such as high blood pressure, by directly influencing the growth and differentiation of the kidney. Low birthweight is associated with postpartum anatomical and functional alterations in the kidney (21,73) although low kidney weight and few and/or small glomeruli have not been shown to be associated with low birthweight in Danish subjects with and without type 2 diabetes (51). Impaired endothelial function – believed to be crucial in the development of the chronic vascular complications of diabetes – appears to be a feature of fit young adults if they had low birthweight (<2.5 kg) (74,75), as is reduced capillary recruitment and acetylcholine-mediated vasodilation (29), impaired microvascular vasodilatory function (76) and renal disease (77,78).

In addition, there is evidence that low birthweight may be associated with changes in the neuroendocrine development of the fetus by permanently resetting major hormonal axes that control growth and metabolism (79). This could result in altered setpoints of several major hormonal axes, including an increase in the activity of the hypothalamic-pituitary-adrenal (HPA) axis. This axis is known to be reset by fetal growth retardation in animals (80,81), and there is evidence in humans of an association between raised HPA activity and the insulin resistance syndrome (82,83). It is therefore of interest that increased adrenal glucocorticoid secretion is associated with low birthweight. Some data in animals suggest that fetal overexposure to endogenous glucocorticoids (eg via prenatal stress) reduces birthweight and produces permanent alterations of the HPA axis (53). Subjects who have low birthweight have higher plasma cortisol concentrations, independent of age and body mass index (BMI) (83,84), enhanced responses of plasma cortisol to ACTH-(1-24) stimulation and increased total urinary cortisol metabolite excretion, but no difference in plasma cortisol after dexamethasone (82). In disadvantaged urbanized South Africans, cortisol axis activation appears to be an early feature in the process linking low birthweight with adult glucose intolerance and is not dependent upon adult obesity or full catch-up growth (85). Therefore programmed increases in the activity of the HPA axis and consequent elevated circulating cortisol concentrations could

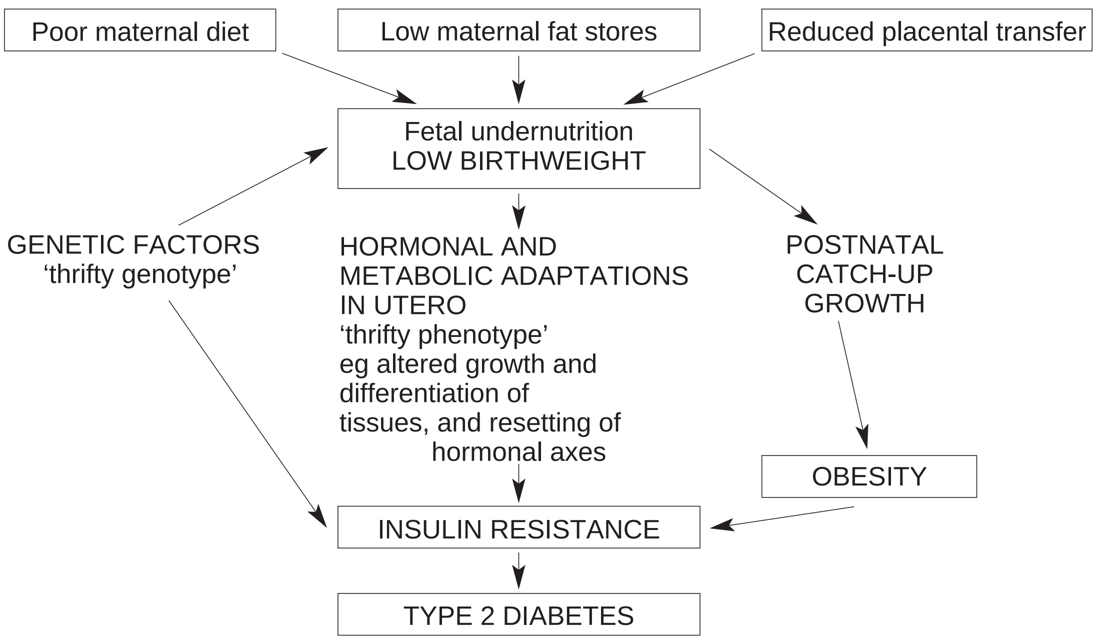


Figure 1. Mechanisms by which fetal undernutrition may predispose individuals to insulin resistance and type 2 diabetes.

contribute to the pathogenesis of the insulin resistance syndrome.

## Conclusion

Most cases of type 2 diabetes cannot be explained by low birthweight; however, individuals born with body weight less than 2.5 kg have a substantially increased risk of developing type 2 diabetes later in life. For this reason, populations that have a high incidence of babies born with low birthweight due to poor maternal nutrition should attempt to address this problem with maternal education and improved antenatal care.

Low birthweight may predispose individuals to type 2 diabetes by inducing insulin resistance and, in some individuals, promoting the accumulation of excess body fat. There is evidence that genetic factors influence both birthweight and insulin resistance (the 'thrifty genotype' hypothesis); but there is also equally convincing evidence that low birthweight can cause phenotypic adaptations which reset hormonal axes and tissue growth to promote insulin resistance (the 'thrifty phenotype' hypothesis) (Figure 1). Either or both these mechanisms may be responsible for the development of type 2 diabetes in many individuals who are born with a low birthweight.

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