Birth weight symposium

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Birth weight symposium

Nick Mann

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Introduction to the Birth weight symposium

What factors determine birth weight and do they have any biological significance for the future health and welfare of the individual? These are important questions for all paediatricians and four groups of experts have been approached to independently give their thoughts on key areas. The aim was for concise pithy comments and opinions, so the length of the articles was rigorously controlled. Firstly, are there genetic factors that contribute to birth weight, secondly does maternal nutrition determine size, then are there social influences on birth weight? Is birth weight of biological significance for the individual or the species? Patrick Cartlidge, Senior Lecturer in child health in Cardiff, kindly refereed this symposium. Please feedback your views and comments to the rapid response section of the journal website at www.archdischild.com.

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Author's affiliations
Nick Mann, Commissioning Editor

Birth weight symposium

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Genetic factors contributing to birth weight

L B Johnston, A J L Clark, M O Savage

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Epidemiological studies suggest that genetic factors account for 30-80% of birth weight variance

The genetic influence on birth size has been recognised for many years, but only recently have some of the specific genes and chromosomal loci involved been identified. This article outlines the evidence for a genetic influence on birth size and reviews our current understanding of the specific genetic factors involved.

WHAT IS THE EVIDENCE THAT GENES INFLUENCE BIRTH WEIGHT?

Epidemiological studies estimate that environmental influences account for about 25% birth weight variance and genetic influences account for 38–80% birth weight variance.[1–3] There is considerable variability in the estimates of the fetal and parental components of these genetic influences from 18 to 69.4% and from 3 to 20% variance of birth weight respectively. Overall there is strong evidence that genetic factors play a significant role in determining birth size.

> "Thus there is evidence of strong familial trends in birth size."

Familial trends in birth weight have also been observed. There is significant correlation between parental birth weights and birth weight in index cases using multiple regression analysis (mothers 0.19–0.20; fathers 0.12–0.16).[4 5] Maternal and paternal birth weights were significantly lower in families with two small for gestational age (SGA) births (index child below 10th centile) compared with families with no SGA births in the Scandinavian SGA study.[5] The odds ratio calculated for having an SGA mother and SGA father in families with two SGA births were 1.74 and 2.49. A mother born SGA is 2.5 (white) or 2.7 (African American) times more likely to have an SGA child than a mother of normal birth weight, and this increased to 10.2 and 10.1 if there was also a low birthweight sibling.[6] A study of cousins in which the correlation between birth weights was greater if the mothers were sisters ($r = 0.135$) than if the fathers were brothers ($r = 0.015$) suggests that there is greater influence of maternal than paternal birth size.[7] Thus there is evidence of strong familial trends in birth size.

WHICH GENETIC FACTORS INFLUENCE BIRTH WEIGHT?

Birth size is the result of fetal growth. The fetal experience is unique and influenced by parental, placental, and fetal factors. Furthermore, it is likely that there are complex interactions between genetic and environmental factors of parental, placental, and fetal origin.

Parental genes

Parental genetic influences are likely to be polygenic, but the exact genes involved and how they act is not fully understood. Glucokinase provides an elegant example of the effect of a parental genetic variant and also shows the interaction between parental and fetal genotypes. Mutations in this gene have been found to cause maturity onset diabetes of the young type 2.[8] Hattersley and colleagues investigated the influence of glucokinase gene defects on birth size in 58 offspring where one parent was known to be affected.[9] If a mother had a glucokinase mutation, the birth weight was increased by a mean 601 g as a result of maternal hyperglycaemia in pregnancy. If a fetus had inherited a glucokinase mutation, the birth weight was decreased by 533 g, equivalent to a fall from the 50th to the 25th birth weight centile. An affected mother resulted in a rise from the 50th to the 85th centile in an unaffected child, or the 25th to the 50th centile in an affected child.

Placental genes

The placenta is critically involved in transporting nutrition and acting as a barrier to infection and maternal corticosteroids. In most cases, it is genetically identical with the fetus, but in 1–2% of conceptuses confined placental mosaicism is observed, in which a cytogenetic abnormality is detected in the placenta and not the fetus.[10 11] Up to 20% of idiopathic SGA term deliveries have confined placental mosaicism.[11 12] How mosaicism affects fetal growth

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Abbreviations: IGF, insulin-like growth factor; SGA, small for gestational age dehydrogenase.

is not known, but presumably it is related to an alteration of placental function.

Fetal genes

Insight into the genes that may be involved in human fetal growth has been provided by studies on human and animal fetal physiology. In particular, mouse gene knockout studies have clearly shown that insulin-like growth factor (IGF)-I, IGF-II, IGF receptor type 1, insulin, insulin receptor, and insulin receptor substrate 1 are all critical for normal fetal growth.[13–16]

In humans, the first single gene defect in a short SGA subject was found in the IGF-I gene.[17] A homozygous deletion of exons 4 and 5 of the IGF-I gene resulted in undetectable levels of serum IGF-I, extreme intrauterine growth retardation, severe postnatal growth failure, deafness, and moderate learning difficulties. This case shows that, in man, an IGF-I gene defect can be compatible with life whereas there is high mortality in the knockout mice as a result of respiratory muscle weakness.[13 14]

Studies of the insulin gene in the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) subcohort of 758 term singletons found a significant association of the insulin variable number tandem repeat class III genotype and longer length, weight, and head circumference at birth in children who did not change weight centile from birth to 2 years.[18] Children homozygous for the class III allele showed a 200 g increase in birth weight. There was no association of genotype with birth size in the group as a whole, which the authors argued was due to the effect of environmental factors.

Detailed genetic studies have been performed in children with Silver-Russell syndrome, but no consistent cytogenetic abnormalities have been found. However, it has been shown that 10% of these children have inherited two copies of the maternal chromosome 7 and no paternal copy (uniparental disomy; mUPD7).[19–21] This suggests that there may be a recessive gene defect if there is isodisomy—that is, two copies of the same chromosome are inherited—or an imprinted paternally expressed gene if there is heterodisomy—that is, both maternal chromosomes 7 are inherited—in this region. There are several good candidate genes in the two regions of interest (7p12–13 and 7q32) that are homologous to imprinted regions in the mouse genome. Molecular studies have not yet found the causative defect(s).

CONCLUSIONS

Epidemiological studies have shown that genetic factors account for 38–80% birth weight variance. There is growing evidence supporting the roles of certain candidate genes in influencing size at birth. Many more genetic influences remain to be discovered. Furthermore, an understanding of how these factors interact will be necessary before this knowledge can be fully exploited.

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Birth weight symposium

Maternal nutrition as a determinant of birth weight

T Stephenson, M E Symonds

Maternal nutrition, encompassing maternal dietary intake, circulating concentrations, uteroplacental blood flow, and nutrient transfer across the placenta, influences birth weight

THE CONTRIBUTION OF MATERNAL NUTRITION TO BIRTH WEIGHT

Birth weight is correlated between half siblings of the same mother but not of the same father[1] because of the greater contribution of the maternal genotype and environment.[2] As summarised in table 1, the latter includes maternal nutrition.

MATERNAL NUTRITION AND CLINICALLY SIGNIFICANT INTRAUTERINE GROWTH RESTRICTION

In the narrow sense, "maternal nutrition" describes the pregnant woman's diet. The effects of severe macronutrient deficiency depend on the stage of gestation. During the Dutch famine of 1944–1945, a 50% reduction in energy intake during the first trimester was associated with increased placental weight but no change in birth weight.[4] Maternal undernutrition in late gestation was associated with reduced placental and fetal weights.

> "The effects of severe macronutrient deficiency depend on the stage of gestation."

Embryo transfer and litter reduction experiments similarly show that maternal environment predominantly influences later fetal growth.[5] Although macronutrient deficits in later pregnancy would be expected to exert greatest impact on birth weight (the human fetus weighs only 20% of term weight at 24 weeks[3]), catch up growth often occurs.[6][7] In contrast, the earlier in postnatal life that undernutrition occurs, the more likely it is to have permanent—that is, programming—effects.[8] In normal pregnancies of malnourished women, dietary supplementation during late pregnancy increases birth weight.[9]

MATERNAL NUTRITION AND VARIATION WITHIN THE NORM: THE BARKER HYPOTHESIS

In developed countries, dietary macronutrient or micronutrient deficiency are rarely thought to be responsible for clinically significant impaired fetal growth.[10] Lower birth weight is associated with lower social class, but although it is often assumed that this is nutritional, there are many confounders such as smoking and genetic factors. Recent human pregnancy studies do not confirm the dietary hypothesis,[11][12] but these studies have been criticised.[13] Contemporary studies in Australia, however, indicate that nearly 30% of women who deliver babies with a low birth weight (< 2500 g) suffer from eating disorders.[14] Experimentally increasing maternal nutrition in sheep enhances birth weight.[13]

Epidemiological studies have shown that size at birth and/or placental weight predict adult disease.[15][16] The hypothesis that variations in maternal diet within the normal range can lead to concomitant variations in birth weight and hence to later disease remains the subject of intense debate. These studies are criticised because of possible confounding factors. However, later blood pressure is independent of maternal blood pressure and smoking,[17] social class at birth, adult social class, later cigarette smoking, and obesity.[15] In the Hertfordshire cohort,[18] birth weight is unrelated to social class either at birth or currently.[15] Moreover, birth weight was not associated with lung cancer or deaths from non-cardiovascular causes, which may also be expected to be influenced by social class and lifestyle.

FETAL SUBSTRATE SUPPLY

So far, this review has focused on the mother's dietary intake. In the wider sense, maternal "nutrition" encompasses the complete supply line of maternal intake, circulating concentrations, uteroplacental blood flow, and nutrient transfer across the placenta.[3] Experimental reduction of the number of placentomes in sheep results in a smaller fetus,[19] as does reduction in uterine artery blood flow.[20] Maternal smoking[21] and pre-eclampsia are associated with lower birth weight.[22] Nutritional or vascular factors probably account for the association between lower birth weight and placental anomalies, twin-twin transfusion syndrome, and maternal diseases (respiratory, cardiac, renal, and collagen).[23] Nutrition is a dominant influence on insulin-like growth factor-I concentrations prenatally,[24] and the correlation between birth weight and insulin-like growth factor-I[25] is further evidence that nutrition, in this broader sense, is a determinant of birth weight.

However, most fetuses with clinical intrauterine growth restriction have a reduced placental to birth weight ratio, suggesting that the fetus adapts to improve placental transfer when the placenta is pathologically small. In contrast, in Barker's studies of predominantly healthy (and surviving) infants from 50 years ago, it was men with a high placental to birth weight ratio who had highest death rates from cardiovascular disease,[15] suggesting different mechanisms. The association between maternal anaemia and increased placental weight[26][27] could be linked by nutrition or oxygen delivery.

In the Dutch famine, dietary restriction during early gestation increased the placental to birth weight ratio and resulted in a much greater risk of adult coronary heart disease and obesity.[28] In a sheep model, maternal nutrient restriction between early to mid gestation resulted in increased placental weight but not fetal weight at term.[29]

HOW COULD MATERNAL NUTRITION PROGRAMME RISK IN LATER LIFE DESPITE A BIRTH WEIGHT IN THE NORMAL RANGE?

Small for gestational age does not necessarily equate with intrauterine growth

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Table 1	Genetic and environmental contributions (%) to birth weight variation (adapted from James & Stephenson[3])	
Genetic		
Maternal genotype		20
Fetal genotype		16
Fetal sex		2
Total genetic contribution		38
Environmental		
General maternal environment		18
Immediate maternal environment		6
Maternal age and parity		8
Unknown environmental influences		30
Total environmental contribution		62

Abbreviations: 11β-HSD, 11β-hydroxysteroid dehydrogenase.

restriction. Even if birth weight remains within the normal range, this may conceal a birth weight significantly below genetic potential because of sub-optimal maternal or fetal nutrition.[30] Nutritional deprivation redistributes maternal cardiac output away from the uterine vasculature,[31] and a chronic fetal "stress response" to this could permanently reprogramme steroid sensitivity. Fetal overexposure to maternal glucocorticoids may programme hypertension[32][33] In sheep, dexamethasone treatment during early pregnancy results in persistent hypertension in the offspring.[34]

Sensitivity to glucocorticoids is regulated by expression of the glucocorticoid receptor and 11β-hydroxysteroid dehydrogenase (11β-HSD). 11β-HSD1 catalyses the conversion of cortisone to the more potent cortisol,[35][36] and 11β-HSD2 does the opposite, "protecting" the fetus from adverse glucocorticoid exposure.[32][37] The renin-angiotensin system is also regulated by glucocorticoids[38] and is critical to the control of blood pressure during fetal and postnatal life.[39][40] Increased tissue exposure to cortisol could explain how early reduction in maternal nutrition affects fetal cardiovascular development while birth weight remains within the normal range.

In the sheep model with maternal nutrient restriction in early gestation and increased placental to fetal weight ratio at term,[29] both glucocorticoid and type 1 angiotensin II receptor mRNA expression are increased in the offsprings' adrenal and kidney.[41] Conversely, placental 11β-HSD2 mRNA expression is decreased, which could increase cortisol transfer across the placenta in the absence of any apparent change in maternal cortisol.[42][43]

CONCLUSIONS

In developing countries, maternal dietary intake can affect birth weight, and intervention helps. In developed countries, epidemiological studies and experiments using animals indicate that modest reductions in maternal food intake could affect survival at birth and longevity, in the absence of pathological changes in birth weight.[44][45] It appears to be earlier maternal nutrient restriction that increases placental size[29] and alters the expression of genes regulating the glucocorticoid and renin-angiotensin systems.[41]

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Birth weight symposium

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Social influences on birth weight

N Spencer, S Logan

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Risk factors for low birth weight are strongly influenced by the social environment

Birth weight, like growth, is determined by the complex interplay of genetic and environmental factors. The proportional contribution of these influences is unclear. However, birth weight varies within genetically similar populations,[1–3] suggesting that environmental factors play a significant role. Secular changes in birth weight[4] also suggest an environmental influence. Birth weight also shows a reverse social gradient such that increasing disadvantage is associated with decreasing birth weight.[1–3]

ENVIRONMENTAL FACTORS AFFECTING BIRTH WEIGHT

Environmental factors with a known association with birth weight are nutrition, smoking, maternal ill health, and genital infection. The association of other factors such as stress[5] and exposure to some types of work during pregnancy[6] remains unproven. Other risk factors for low birth weight such as maternal age, although not themselves environmental factors, are strongly influenced by the social environment.

Severe energy restriction during pregnancy, such as occurs in some developing countries[7] and was noted in the 1945 Dutch Hunger Winter,[8] reduces birth weight but, randomised controlled trials of nutritional interventions in the index pregnancy have failed to show convincing benefit.[9] Nutrition may exert its effect over a longer period through an effect on maternal growth in childhood[10] and possibly through an intergenerational effect.[11] Adult height has a known association with relative nutritional impairment in childhood,[12] and maternal height is an important determinant of birth weight.[13]

The association of smoking with a reduction in birth weight is well established.[13] Maternal ill health has been associated with reduced birth weight,[14] and genital infection exerts its

influence through increasing the risk of preterm delivery.[15]

Evidence for an independent effect of stress is slight, but one study does show stress exerting an effect through increased smoking.[16]

SOCIAL GRADIENT IN BIRTH WEIGHT

Given the importance of birth weight for infant, childhood, and adult health,[17] a 150–200 g social gradient in mean birth weight and 30% of births less than 2500 g attributable to social inequalities[1] is a key public health issue. Reductions in inequalities in infant mortality and many childhood and adult health inequalities, key government health targets,[18] are unlikely to be achieved without a narrowing of the social gradient in birth weight. Interventions to increase birth weight in disadvantaged groups have been largely unsuccessful,[19] and, although mean birth weight has increased,[20] the rate of change is slow and the gradient remains unchanged.

> "Reductions in inequalities in infant mortality and many childhood and adult health inequalities, key government health targets, are unlikely to be achieved without a narrowing of the social gradient in birth weight."

The failure of interventions to influence the social gradient is likely to result from a focus on modifying individual risk factors such as smoking, diet, and infection in the already established pregnancy with the intervention starting around 16 weeks at the earliest. The social gradient in birth weight probably arises as a result

of the accumulation and addition of risk and protective factors over time[21] and across generations[11] rather than resulting from risk exposures within the index pregnancy. Poor socioeconomic circumstances in early life may lead to biological vulnerability in later life,[22] and adult health behaviours seem to have socioeconomic roots early in life.[23] A woman whose parents were disadvantaged is more likely to have been low birth weight herself, to have experienced more childhood ill health, to have had a less nutritious diet with adverse effect on her growth, to have started smoking in adolescence and be less likely to quit in early pregnancy, and to come to pregnancy at an earlier age.

Although innovative approaches to smoking cessation and stress reduction may have some effect in the short term, reduction of the social gradient is likely to be a long term goal requiring attention to the nutritional and health status of young children. Of equal importance will be improving the overall social environment in which children grow up so that protective factors, such as maternal education, become more evenly distributed across social groups and risk factors are reduced in disadvantaged groups.

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Birth weight symposium

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Significance of birth weight for the future

C M Law

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Correct size at birth is associated with health later in life

"How much did he/she weigh?" is often the first question proud parents are asked after they have announced the sex of their newly delivered progeny. A big baby, according to common knowledge, is a healthy baby. What evidence lies behind this popular assumption?

Paediatricians have long been familiar with the increased risk of mortality and early morbidity of babies born very small or very early. These babies have a greater risk of dying throughout the first year of life.[1] In addition, they are more likely to have a range of morbidities, particularly neurological, respiratory, and gastrointestinal.[2][3]

In the last 20 years or so, there has been increasing evidence that size at birth is also associated with later health, particularly with the chronic degenerative diseases that are major causes of death in middle and later life. The best documented are the relations between smaller size at birth and higher death rates from coronary heart disease and stroke.[4–7] Smaller size at birth is also related to increased levels of cardiovascular risk factors such as hypertension,[8] type II diabetes mellitus,[9] and hyperlipidaemia.[10] However, high birth weight is also associated with long term health. People with high birth weight have higher death rates from prostate cancer[11] and possibly breast cancer.[12]

"In the last 20 years or so, there has been increasing evidence that size at birth is also associated with later health, particularly with the chronic degenerative diseases that are major causes of death in middle and later life."

They may also be at risk of obesity[13] and type II diabetes mellitus.[14][15]

Although these associations, particularly those of reduced birth weight with increased cardiovascular risk, are now widely recognised, there remains a debate about what they indicate. The most important issue is whether the associations are causal or whether birth weight is simply an indicator of some other factor in prenatal or postnatal life that causes the associations. It seems unlikely that the associations arise simply because of confounding variables in adult life, as they are demonstrable in children (there are over 30 published studies showing an association between lower birth weight and higher childhood blood pressure, for instance) and persist when allowance is made for adult lifestyle factors such as smoking habit or levels of obesity.[8] The failure to identify genes for cardiovascular disease and the evidence against the control of fetal growth being primarily genetic argue against pure genetic causes.

PROGRAMMING HYPOTHESIS

The programming hypothesis is a plausible explanation of the associations of birth weight with adult health. Programming occurs when an event in a critical early period of an organism's life permanently changes structure or function, and is well described in experimental biology.[16] Under a programming hypothesis, the fetus, which is highly plastic, adapts to adverse influences, such as undernutrition or hypoxia, in order to ensure its immediate survival. These adaptations are accompanied by reduced fetal growth. However, the adaptations may also lead to detrimental effects in postnatal health. For example, shunting of blood away from the fetal kidney in order to protect the fetal brain may result in a decreased number of nephrons and reduced renal reserve for postnatal challenges.[17] Modification of the structure of the large conduit arteries in order to maintain fetal circulation may lead to blood vessels that are less compliant in adult life.[18] In these scenarios, birth weight is an indicator of the prenatal cause, not the cause itself.

BIRTH WEIGHT AS AN INDICATOR OF RISK

Using birth weight as an indicator of risk at an individual level (for instance, to counsel the parents of a low birth weight baby) has three major problems. Firstly, risk of coronary heart disease, for example, is thought to be related to the extent of the reduction in fetal growth. However, we do not know how much a baby should have weighed, only what it actually weighs. A 3500 g baby who should have weighed 4000 g is just as growth retarded as a 2300 g baby who should

have weighed 2600 g. Furthermore a 3500 g baby may be perfectly grown, growth retarded, or even "overgrown", depending on its genetic potential. Secondly, the differences in risk factor levels between birth weight groups are relatively small—systolic blood pressure may be 1 or 2 mm Hg higher if birth weight is 500 g lower. However, whereas it may make little difference to an individual to reduce his or her blood pressure by such small amounts, if the population mean blood pressure decreased by about 6 mm Hg, then approximately 30% of all strokes would be prevented.[19] Thirdly, parents tend to be interested in risk in terms of longevity or quality of life, whereas the research perspective (and therefore the available evidence) has usually been focused on the prediction of specific diseases or risk factors. This points to the need for "consumers" to be involved in all parts of the research process.[20 21]

> "Promotion of infant growth and avoidance of childhood obesity are both goals with immediate as well as long term benefits and may be worth emphasising to parents."

Of particular interest to paediatricians are pathologically growth retarded babies. In theory, these infants may be at very high risk of cardiovascular disease in adult life. Currently, empirical evidence is lacking, as the subjects in most cohort studies of very low birthweight survivors have yet to reach adulthood and thus stable indicators of cardiovascular risk. In addition, some of these infants were also born prematurely. Although most studies have indicated that it is growth for gestational age rather than duration of gestation itself that is associated with adult health, few have had the statistical power to look at the separate effects. In the single study that has, raised blood pressure was associated with both reduced growth for gestational age and reduced gestation. So the highest blood pressures were found in those who grew less well in utero and were delivered early. However, the ranges of gestation studied were only from 35 to 44 weeks.[22] Thus the long term health risks of babies born very early or very small remain uncertain.

If part of the risk of adult disease is set before birth, what positive messages can paediatricians give to the parents of neonates who may be at high risk? Recent research has focused on the extent to which postnatal growth can modify or add to the risks established in utero. Both poor infant growth and excessive weight gain in childhood seem to be associated with increased cardiovascular risk.[4] Promotion of infant growth and avoidance of childhood obesity are both goals with immediate as well as long term benefits and may be worth emphasising to parents.

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