

EARLY LIFE ORIGINS OF ADULT CHRONIC DISEASES: A SOUTH AFRICAN PERSPECTIVE

Naomi S Levitt,^a Estelle V Lambert,^b Shane A Norris^c

INTRODUCTION

Over the past 20 years substantial epidemiological evidence has accumulated indicating that low birth weight is associated with an increased risk of adult-onset chronic diseases, such as hypertension, glucose intolerance, ischaemic heart disease and, more recently, osteoporosis. These studies have largely emanated from industrialised societies where birth records have been preserved for many decades and there is access to detailed growth data and health outcomes, in many instances through a sophisticated informatics network. Some have questioned the relevance of these observations to industrialised societies where low birth weight is becoming less common, but not to developing countries where the vast majority of low birth weight babies are born and which are currently experiencing a steep rise in the prevalence of obesity, diabetes and cardiovascular disease. However, countries with emerging economies have also contributed to the body of epidemiological data associating low birth weight with adult onset chronic disease, in particular studies from India, China, the Caribbean and South Africa.

This report will review evidence linking early life origins and adult, chronic diseases of lifestyle, with specific reference to South African studies. Furthermore, this report will consider the putative mechanisms for these associations, and, finally, attempt to highlight areas of research priority based on current national and global health concerns.

Intra-uterine and early life influences on obesity

Numerous previous reports have found an association between birth weight, subsequent growth and development, and attained body mass index (BMI). These relationships have generally been shown in children, but there are also reports in adults, with most studies showing a direct association, i.e. higher birth weight being associated with higher BMI, and, conversely, low birth weight associated with increased body fat content, because of reduced lean tissue mass, and increased central adiposity.¹⁻⁴ Other studies have found that the relationship between birth weight and subsequent BMI is J- or U-shaped.⁴ However, the timing of the intra-uterine insult may also influence the nature of the relationship between birth weight and subsequent adiposity. Ravelli *et al.*⁵ described the impact of intra-uterine undernutrition in a "natural experiment" which occurred in offspring born during the Dutch 'Hunger Winter' of the Second World War. In this instance, individuals who were exposed to the famine while in utero during the first and second trimesters were nearly three times more likely to become obese, compared to those who were not exposed. In recent reviews, this association between low birth weight and later obesity, as well as visceral fat accumulation, is corroborated.¹⁻³

However, the association is not consistent in all settings, and in particular, in developing countries, the progression to obesity and associated morbidity appears to be usually dependent on the interaction between birth weight and subsequent growth during critical, developmental windows.^{4,6,7} This has been described as a "thrifty phenotype".⁸ Further to this is the potential for early life experiences, maternal nutrition and post-natal nutrition and timing of catch-up growth to modulate the expression of so-called intra-uterine programming for obesity.^{4,9-11}

^a MD; Endocrine Unit, Department of Medicine, and

^b MS, PhD; UCT/MRC Research Unit for Exercise Science and Sports Medicine, Department of Human Biology, Faculty of Health Science, University of Cape Town

^c MRC Mineral Metabolism Research Unit, University of the Witwatersrand, South Africa

SOUTH AFRICAN STUDIES

Data from South Africa concerning early life “programming” and subsequent obesity are rather limited. One such study involves a small longitudinal cohort of children (n=162), resident in rural villages in the central region of the Limpopo province, followed from birth.¹² In this group, a high prevalence of stunting (48%), overweight (22%) and obesity (24%) were found at three years, while 31 (19%) of the children were both stunted and overweight. Being underweight at birth and rapid weight gain within the first year of life increased the risk of being overweight at three years six-fold. Demographic associations with being overweight at this age included: having a mother younger than 20 years old, having the mother as the main caregiver and having a working mother.¹²

In another example, researchers in the Birth-to-Ten study, a prospective cohort study of the determinants of growth, development and health in children born in the metropolitan area of Soweto and Johannesburg between April and June 1990, have published two reports assessing the relationship between birth weight, weight gain in infancy and subsequent adiposity. In 193 children with normal birth weights and anthropometry collected at age 2 and 9 years, children with rapid weight gain were significantly lighter at birth, but heavier, taller and had more subcutaneous total body and abdominal fat at equivalent BMIs.¹³ Similarly, Crowther *et al.*¹⁴ found that in 7-8-year-old children from the Birth-to-Ten cohort, weight gain velocity was associated with increased adiposity, measured by skinfold thickness.

Conversely, in another South African birth cohort, Levitt *et al.*¹⁵ were unable to demonstrate an association between birth weight and adult obesity or adipose tissue distribution. This failure to show an association may be a consequence of the fact that the group were generally similarly socio-economically disadvantaged at birth, and that the sample size was relatively small. They were, however, able to distinguish that the attributes of the chronic disease phenotype in those with low birth weight was prominent and significant only in those who were currently above the median for BMI, fatness or centralisation of body fat stores.¹⁶ Similarly, in the Birth-to-Ten cohort, those who had a low birth weight, but who were above the median weight for age when studied, also presented with increased blood pressure (BP) at age 5 years,¹⁷ and a greater insulin response to oral glucose tolerance testing at age 7.¹⁴

Furthermore, South African studies, provide a consistent case for the role of early life exposures on later obesity. In the recent national Household Food Consumption Survey, nearly 20% of the more than 2800 children studied were stunted, while 17% were considered overweight. However, it was found that stunting itself conferred an increased risk for overweight in children (OR 1.8; 95% CI 1.48, 2.20).¹⁸ Similarly, in another study of nearly 500, 10-15-year-old school girls from the Northwest province, stunting was also associated with increased deposition of subcutaneous fat, as well as centralisation of body fat stores, compared to non-stunted counterparts.¹⁹

Thus, South African studies of large and representative samples of children and pre-adolescents have demonstrated the association between adverse early life exposures and propensity to obesity. Further, the presentation of attributes of the chronic disease phenotype associated with early life programming has been more consistently demonstrated in those children or adults, whose current weight places them above the median for the sample population.

EARLY LIFE INFLUENCES ON THE CHRONIC DISEASE PHENOTYPE: FEATURES OF THE METABOLIC SYNDROME: BLOOD PRESSURE, GLUCOSE TOLERANCE, DYSLIPIDAEMIA, INSULIN RESISTANCE

As mentioned previously, an adverse intra-uterine environment, as determined primarily by low birth weight, is strongly associated with an increased risk of deleterious metabolic sequelae in adult life, including elevated BP, glucose intolerance/insulin resistance, dyslipidaemia and increased mortality from cardiovascular disease.²⁰⁻²⁵ This has led to the hypothesis that events occurring before birth may ‘programme’ physiological responses which lead to cardiovascular and metabolic disorders in later life. Furthermore, the extent of metabolic dysregulation, including the degree of BP elevation, glucose intolerance and insulin resistance, is greater when low birth weight at term has been associated with adult obesity,²⁶⁻²⁸ thereby suggesting an interaction between intra-uterine events and later environmental influences.

SOUTH AFRICAN STUDIES

These relationships have been explored in various South African cohorts, in children and adults at various ages, and stages of development. One such cohort is the Birth-to-Ten cohort, originally designed to examine determinants of growth, development, and health in children born in the metropolitan area of Soweto and Johannesburg between April and June 1990;²⁹ it has been extended for a further ten

years. The first report examined the relationship between BP and birth weight in 818 children from this cohort at age 5 years. Systolic BP was inversely associated with birth weight, independent of current weight, height, gestational age, maternal age, or current socio-economic status. Indeed, for every 1000 g increase in birth weight, systolic BP was 3.4 mmHg lower (95% CI 1.4, 5.3 mmHg). Further, the highest BP was noted in children who fell into the lowest quartile for birth weight (<2 800 g) and the highest quartile for current weight – suggesting that the birth-weight effect on BP may be amplified by early childhood events and subsequent growth.¹⁷

Metabolic studies, using an oral glucose tolerance test, were undertaken in a smaller representative subgroup of the Birth-to-Ten children (n=152) at age 7 years. In these children, an inverse association was found between birth weight and the 30-min plasma glucose concentration ($r=-0.20$, $p=0.02$), as well as the amount of insulin secreted within the first 30 min ($r=-0.19$, $p=0.04$) and the last 90 min of the oral glucose tolerance test (OGTT) ($r=-0.19$, $p=0.04$). These data confirm the relationship between poor foetal growth as measured by birth weight, and both glucose tolerance and insulin resistance.¹⁴

The effect of postnatal and early childhood weight accumulation on these relationships was assessed by separating the low birth weight children by current median weight. The group who were above the current median for weight (low-high), had greater 120-min insulin concentrations ($p < 0.05$) than those who were below the current median weight (low-low), suggesting that post-natal and childhood growth patterns modulate the development of insulin resistance. Surprisingly, the low-high group demonstrated more insulin sensitivity as assessed by greater suppression of non-esterified fatty acids postprandially, a measurement of the antilipolytic action of insulin, than the low-low group.³⁰ This finding may suggest tissue-specific down regulation of the insulin receptor or the insulin-signalling pathways.

The effect of birth weight and subsequent growth was examined on insulin secretory capacity in the same children. The low-high children had similar glucose responses to the OGTT but a greater beta cell response measured by the Δ insulin₃₀/glucose₃₀ ratio ($p < 0.05$), total des-31,32 proinsulin, total proinsulin concentrations and higher 120 min insulin level as mentioned above, compared to the low-low children.³⁰

A second South African cohort of full-term offspring of primiparous women of mixed ancestral origin who gave birth in the Groote Schuur maternity centre, Cape Town, in 1975 and 1976, were sampled at the age of 20 years (n=137). The sample was divided into those who were low birth weight (< 10th centile UFA) and those of normal birth weight (25th - 75th centiles AFA) for their gestational age, and these subjects were recalled for studies examining the association between birth weight and adult onset chronic diseases. The UFA group was still smaller and lighter, with a lower BMI, yet this group had significantly higher systolic and diastolic BPs than the AFA group ($p=0.007$) and diastolic ($p=0.02$) BPs, after covarying for current weight and gender.¹⁶

The low birth weight group also had higher fasting plasma glucose levels ($p=0.047$), and a greater proportion demonstrated glucose intolerance (11.9% vs. 0%, $p < 0.01$) compared to the normal birth weight group. Interestingly, the low birth weight or UFA group, had mothers who were smaller, weighed less and attained a lower level of education than did the mothers of the AFA group. Whether this implies a relationship between low maternal socio-economic status and the observed low birth weights observed, an intergenerational effect independent of socio-economic hardship or genetic influences that could play a role in the association between low maternal weight, low birth weight, and subsequent adult glucose intolerance, is uncertain.¹⁶

A later analysis examined whether the association between low birth weight and this chronic disease phenotype depended upon birth weight alone or upon an interaction between birth weight and the subsequent accrual of weight for height, the accumulation of fat generally, abdominally or attained height in this cohort.¹⁵ This was assessed by dividing the two birth weight groups by the current median for each anthropometric measure. Subjects who were low birth weight (UFA), but above the median at 20 years for BMI, body fat or waist circumference had significantly higher levels of systolic BP (and for fatness, diastolic BP), plasma lipids (triglycerides, total cholesterol or low-density lipoprotein cholesterol) and insulin resistance which was measured by either fasting insulin or HOMA IR, than subjects who were UFA but below the median for the respective anthropometric measures.

However, none of these metabolic and BP effects were replicated when the interaction between low birth weight and current size was determined by height. Additionally, although the levels of current BMI, body fat and waist were similar in the respective above the median groups, those who were UFA had higher systolic BP and triglycerides (BMI and waist) and both systolic and diastolic BP (body fat) than the AFA group. On the other hand, the metabolic and BP levels were similar in the groups below the median, for all of the anthropometric measures, regardless of their birth weight.

A further study was conducted in preterm neonates. In this, the glucose and insulin responses to a meal test of milk were examined at 19.6 ± 12.2 days after birth. The neonates, who were small for gestational age and had the greatest postnatal gain in weight, had the greatest insulin resistance. These findings were notable for the extension of the association between low birth weight and insulin resistance from full to preterm children and the evidence that these abnormalities were already evident in the first few weeks of life.³¹

PUTATIVE UNDERLYING MECHANISMS FOR THE METABOLIC SEQUELAE ASSOCIATED WITH ADVERSE EARLY LIFE EXPOSURES

The explanation advanced for the so-called foetal origins of adult disease proposed by Hales and Barker⁸ in the early 1990s was the thrifty phenotype hypothesis, initially relating specifically to type 2 diabetes. Their concept was that an adverse intra-uterine environment relating to poor foetal nutrition imposed mechanisms that programmed fetal metabolism for subsequent nutritional thrift. Should this state of nutritional hardship persist, the physiological adaptation would be appropriate. In contrast, should the individual subsequently be exposed to good or over-abundant nutrition, there would be a state of physiological maladaptation and disease, e.g. glucose intolerance would occur. An alternative theory, that of the thrifty genotype, had already been invoked by Neel³² in 1962, to explain the profound rise in diabetes prevalence among traditional populations, such as the Pima Indians and Naurians, as their lifestyles changed from active hunter gatherers and farmers to more westernised ones.³³ The Naurians being typified by sedentary occupations and profound dietary changes. This theory proposed that genes, in this case diabetogenic genes, persisted in a population as they somehow provided a survival advantage in states of deprivation or famine. In states of plenty, on the other hand, these genes proved to be detrimental.

Notwithstanding, the extensive epidemiological and animal data associating low birth weight with adult chronic disease, and the assumption that low birth weight was a proxy for intra-uterine or foetal undernutrition, this is not necessarily the case. Many factors impact upon birth weight, such as birth order, gestational age, maternal age, maternal size, weight gain in pregnancy, maternal diabetes, maternal hypertension, maternal smoking, alcohol and drug use, stress and infection. Furthermore, while an adverse intra-uterine environment may have major long-term consequences, it may not always result in low birth weight. Experimental evidence to date clearly indicates that programming during gestation does occur. The mechanisms underpinning the programming are largely unknown, but include variation in organ structure, programming or imprinting of which, would of necessity occur during the phase of organogenesis. This might result in alterations in vascular supply, neural innervation or in the physical arrangement of cell types, as well as alteration in cell number, cellular proliferation or metabolic differentiation. The last is the process through which cells acquire a stable pattern of gene expression and refers to enzymes, hormones, transmembrane transporters, and hormone receptors that are additional potential mechanisms.³⁴ The period during which programming may occur is not simply limited to the time of gestation, the periconception period in addition to the early postnatal period also seem to be subject to these processes.

EARLY LIFE INFLUENCES ON BONE METABOLISM, FRACTURE RISK AND OSTEOPOROSIS

Bone mass of an individual in later life depends upon the peak bone mass obtained during skeletal growth, and the subsequent rate of bone loss in adulthood (Fig. 1).³⁵ Consequently, strategies to prevent osteoporosis may be aimed at either increasing bone mass acquisition during childhood and adolescence, or reducing the rates of bone loss during adulthood. The majority of variance in peak bone mass is accounted for by genetic factors, but it is likely that the interplay between environmental factors (exercise, nutrition) and the genome establishes the functional level of a variety of metabolic processes involved in skeletal growth.³⁶

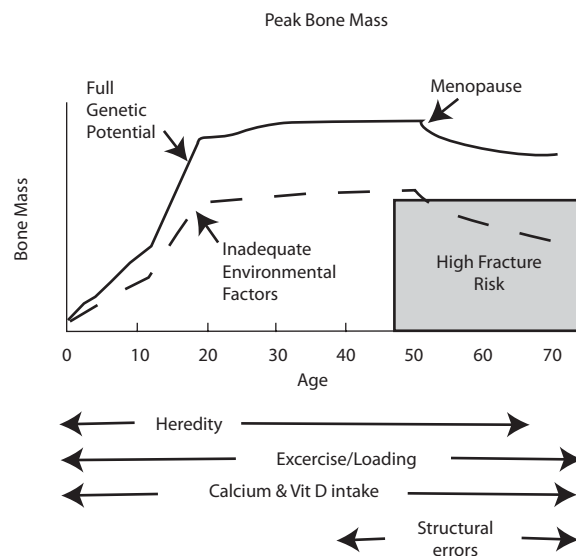


Figure 1. Schematic representation of determinants of peak bone mass. Derived from Heaney *et al*⁴ with permission

Supportive evidence has accumulated suggesting that intra-uterine programming can contribute to the risk of osteoporosis in later life. Such evidence includes: (a) bone mineral measurements undertaken in cohorts of adults, whose detailed birth and/or childhood records have been preserved;^{37,38} (b) physiological studies exploring the relationship between candidate endocrine systems that may be programmed (GH/IGF-I; hypothalamic-pituitary adrenal, gonadal steroid) and age-related bone loss;^{39,40} (c) studies characterising the nutrition, body composition and lifestyle of pregnant women and relating these factors to the bone mass of their newborn babies;⁴¹ and (d) studies relating childhood growth rates to the later risk of hip fracture.³⁷

SOUTH AFRICAN STUDIES

In developed countries, emphasis is placed on the importance of optimising bone mass during childhood and adolescence to reduce the prevalence of postmenopausal osteoporosis. In South Africa, little is known of the factors which influence bone mass in the different racial groups with very different environmental factors. Although osteoporosis and minimal trauma fractures are thought to be uncommon in postmenopausal black women in South Africa, changes in lifestyle and dietary patterns associated with urbanisation and the move to a more westernised lifestyle pattern may predispose black females, who have spent most of their lives in an urban environment, to suboptimal peak bone mass and a greater risk of postmenopausal fractures than previously. Furthermore, the role intra-uterine programming, birth weight, and early growth and nutrition have on bone mass acquisition and fracture risk within a South African population has not been thoroughly explored. Currently, only two paediatric studies have explored the association between birth weight and bone mass.

The first study in a Johannesburg-Soweto-based birth cohort investigated associations between birth weight, weight and length at one year, and bone mass in a group of 10-year-old black and white girls and boys. Bone area (BA) and bone mineral content (BMC) measurements were made of the whole body, femoral neck, and lumbar spine using dual energy x-ray absorptiometry (DXA). Birth weight (BW), weight (WT1) and length (LT1) at one year were positively and significantly correlated with BMC of the whole body (both $p < 0.0001$), femoral neck (both $p < 0.0001$) and lumbar spine (BMC: BW & WT1: $p < 0.0001$; LT1: $p < 0.05$), in 10-year-old children. However, after correcting bone mass for confounders (ethnicity, gender, and body size (height and weight)), body size at one year, more so than birth weight, remained a significant predictor of BMC of the whole body (WT1: $p < 0.01$; LT1: $p < 0.05$) and of the femoral neck (WT1: $p < 0.05$; LT1: $p < 0.05$). The results suggest that small size at one year is associated with less bone mass of the whole body and femoral neck independent of body size effects. Consequently, growth and development both intra-uterine and up until one year of age, which are measures of genetic, intra-uterine and postnatal environmental factors, have consequences on the pre-pubertal skeleton.⁴²

The second study, a birth cohort of mixed ancestral origin from a working class community in Cape Town, explored associations between birth weight and DXA-derived BMC of the whole body, femoral neck, and lumbar spine when the children were 7-8 years old. The study results showed a significant association between birth weight and the femoral neck BMC ($p < 0.005$). However, after correcting for current body size this association disappeared (Micklesfield *et al*, unpublished data).

In summary, further studies in South Africa are needed to conclusively determine the independent effect intra-uterine and early growth programming have on bone mass acquisition during childhood and adolescence, and the adult risk of fracture and osteoporosis. The same is not true for the metabolic and cardiovascular sequelae of these early events. The public health challenge in South Africa is however clear, i.e. prevention of stunting and subsequent rebound adiposity.

CONCLUSION

There is clearly evidence, both at a global level and in nationally representative studies, for the substantial impact of adverse, early life events on early growth, subsequent adiposity and metabolic sequelae and, finally, adult chronic disease morbidity. This is possibly predominantly the effect of programming of the various neuro-endocrine axes, and thereby altering, for example, appetite, sympathetic activation, insulin, growth hormone and cortisol metabolism. There is ample evidence for 1) various susceptible genotypes, and 2) the critical role of perinatal and subsequent growth trajectory, nutritional and physical activity exposures and even socio-economic status and education, on the final presentation of the chronic disease phenotype in response to the early life insults. These studies, and the respective gaps which remain unfilled, nevertheless highlight the importance of adopting a life-course approach to the prevention of chronic disease. This may be particularly important in developing countries, which are currently undergoing epidemiological transition.

REFERENCES

- 1 Oken E, Gillman MW. Fetal origins of obesity. *Obes Res* 2003;11:496-506.
- 2 Ong KK, Dunger DB. Perinatal growth failure: the road to obesity, insulin resistance and cardiovascular disease in adults. *Best Practice & Res Clin Endocrinol and Metab* 2002;16:191-207.
- 3 Rogers I and EURO-BLCS Study Group. The influence of birthweight and intrauterine environment on adiposity and fat distribution in later life. *Int J Obes* 2003;27:755-777.
- 4 Yajnik CS. Obesity epidemic in India: intrauterine origins. *Proc Nutr Soc* 2004;63:387-396.
- 5 Ravelli GP, Stein ZA, Susser MW. Obesity in young men after famine exposure in utero and early infancy. *N Engl J Med* 1976;295:349-353.
- 6 Cameron N, Demerath EW. Critical periods in human growth and their relationship to diseases of aging. *Yearbook of Physical Anthropology* 2002;45:159-184.
- 7 Monteiro POA, Victora CG, Barros FC, Monteiro LMA. Birth size, early childhood growth, and adolescent obesity in a Brazilian birth cohort. *Int J Obes* 2003;27:1274-1282.
- 8 Hales CN, Barker DJP. Type 2 (non-insulin dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 1992;35:595-601.
- 9 Moore V, Davies M. Nutrition before birth, programming and perpetuation of social inequities in health. *Asia Pacific J Clin Nutr* 2002;11(Suppl):S529-536.
- 10 Power C, Li L, Manor O, Davey Smith G. Combination of low birth weight and high adult body mass index: at what age is it established and what are its determinants? *J Epidemiol Community Health* 2003;57:969-973.
- 11 Sayer AA, Syddall HE, Dennison EM, Gilbody HJ, Duggleby SL, Cooper C, *et al*. Birth weight, weight at 1 y of age, and body composition in older men: findings from the Hertfordshire Cohort Study. *Am J Clin Nutr* 2004;80:199-203.
- 12 Mamabolo RL, Alberts M, Steyn NP, Delemarre-van de Waal HA, Levitt NS. Prevalence and determinants of stunting and overweight in 3-year-old black South African children residing in the Central Region of Limpopo Province, South Africa. *Public Health Nutr* 2005;8:501-508.
- 13 Cameron N, Pettifor J, De Wet T, Norris S. The relationship of rapid weight gain in infancy to obesity and skeletal maturity in childhood. *Obes Res* 2003;11:457-460.
- 14 Crowther NJ, Cameron N, Trusler J, Gray IP. Association between poor glucose tolerance and rapid postnatal weight gain in seven-year-old children. *Diabetologia* 1998;41:1163-1167.
- 15 Levitt, N.S., Lambert, E.V., Woods, D., Seckl, J.R., Hales CN. Adult BMI and fat distribution but not height amplify the effect of low birth weight on insulin resistance and increased BP in 20-year-old South Africans. *Diabetologia* 2005;48:1118-1125.
- 16 Levitt NS, Lambert EV, Woods D, Hales CN, Andrew R, Seckl JR. Impaired glucose tolerance and elevated BP in low birth weight, non-obese, young South African adults: early programming of cortisol axis *J Clin Endocrin Metab* 2000;85:4611-4618.
- 17 Levitt NS, Steyn K, De Wet T, Morell C. An inverse relationship between BP and birth weight among five year old children from Soweto, South Africa. *J Epidemiol Commun Health* 1999;53:264-268.

- 18 Steyn NP, Labadarios D, Maunder E, Nel J, Lombard C. Directors of the National Food Consumption Survey. Secondary anthropometric data analysis of the National Food Consumption Survey in South Africa: the double burden. *Nutrition* 2005;21:4-13.
- 19 Mukkuddem-Petersen J, Kruger HS. Association between stunting and overweight among 10-15 y-old children in the North West Province of South Africa: the THUSA BANA Study. *Int J Obese Relat Metab Disord* 2004;28:842-851.
- 20 Barker DJP, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, BP in childhood and adult life and mortality from cardiovascular disease. *BMJ* 1989;298:564-567.
- 21 Hales CN, Barker DJP, Clark PMS, Cox LJ, Fall C, Osmond C *et al*. Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 1991;303:1019-1022.
- 22 Barker DJP. Fetal origins of Coronary Heart Disease. *BMJ* 1995;311:171-174.
- 23 Barker DJP, Hales CN, Fall CHD, Osmond C, Phipps K, Clark PMS. Type 2 (non-insulin dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X: relation to reduced fetal growth.) *Diabetologia* 1993;36:62-67.
- 24 Law CM, Shiell AW. Is BP inversely related to birth weight? The strength of evidence from a systematic review of the literature. *J Hypertension* 1996;14:935-941.
- 25 Rich-Edwards JW, Stampfer MJ, Manson JE, Rosner B, Hankinson SE, Colditz GA, *et al*. Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. *BMJ* 1997;315:396-400.
- 26 Valdez R, Athens MA, Thompson GH, Bradshaw BS, Stern MP. Birthweight and adult health outcomes in a biethnic population in the USA. *Diabetologia* 1994;37:624-631.
- 27 Leon DA, Koupilova I, Lithell HO, Berglund L, Mohsen R, Vagero D, *et al*. Failure to realise growth potential in utero and adult obesity in relation to BP in 50 year old Swedish men. *BMJ* 1996;312:401-406.
- 28 McKeigue PN, Lithell HO, Leon DA. Glucose tolerance and resistance to insulin stimulated glucose uptake in men aged 70 years in relation to size at birth. *Diabetologia* 1998;41:1133-1138.
- 29 Yach D, Cameron N, Padayachee N, Wagstaff L, Richter L, Fonn S. 'Birth to Ten': Child health in South Africa in the 1990s. Rationale and methods of a birth cohort study. *Paediatr Perinat Epidemiol* 1991;5:211-233.
- 30 Crowther NJ, Trusler J, Cameron N, Toman M, Gray IP. Relation between weight gain and beta-cell secretory activity and non-esterified fatty acid production in 7-year-old African children: results from the Birth to Ten Study. *Diabetologia* 2000;43:978-985.
- 31 Gray IP, Cooper PA, Cory BJ, Toman M, Crowther NJ. The intrauterine environment is a strong determinant of glucose tolerance during the neonatal period, even in prematurity. *J Clin Endo Metab* 2002;87:4252-4256.
- 32 Neel JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? *Am J Hum Genet* 1962;14:353-362.
- 33 Neel JV, Weder AB, Julius S. Type II diabetes, essential hypertension, and obesity as „ syndromes of impaired genetic homeostasis“: the "thrifty genotype" hypothesis enters the 21st century. *Perspect Biol Med* 1998;42(1):44-74.
- 34 Waterland RA, Garza C. Potential mechanisms of metabolic imprinting that lead to chronic disease. *Am J Clin Nutr* 1999;69:179-197.
- 35 Heaney RP, Abrams S, Dawson-Hughes B, Looker A, Marcus R, Matkovic V, Weaver C. Peak bone mass. *Osteoporosis Int* 2000;11:985-1009.
- 36 Ralston SH. Do genetic markers aid in risk assessment? *Osteoporosis Int* 1998;8(Suppl 1):S37-42.
- 37 Cooper C, Cawley M, Bhalla A, Egger P, Ring F, Morton L, *et al*. Childhood growth, physical activity, and peak bone mass in women. *J Bone Miner Res* 1995;10:940-947.
- 38 Cooper C, Westlake S, Harvey N, Javaid K, Dennison E, Hanson M. Review: developmental origins of osteoporotic fracture. *Osteoporosis Int* 2005; (Epub ahead of print).
- 39 Dennison EM, Syddall HE, Sayer AA, Gilbody HJ, Cooper C. Birthweight and weight at 1 year are independent determinants of bone mass in seventh decade: the Hertfordshire cohort study. *Pediatr Res* 2005;57:582-586.
- 40 Fall C, Hindmarsh P, Dennison E, Kellingray S, Barker D, Cooper C. Programming of growth hormone secretion and bone mineral density in elderly men: a hypothesis. *J Clin Endo Metab* 1998;83:135-139.
- 41 Godfrey K, Walker-Bone K, Robinson S, Taylor P, Shore S, Wheeler T, Cooper C. Neonatal bone mass: influence of parental birthweight, maternal smoking, body composition, and activity during pregnancy. *J Bone Miner Res* 2001;16:1694-1703.
- 42 Vidulich I, Norris SA, Cameron N, Pettifor JM. Differences in bone size and bone mass between black and white 10-year-old South African children. *Osteoporosis Int* 2005;14:1-8.