

Programming of lean body mass: a link between birth weight, obesity, and cardiovascular disease?¹⁻³

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ABSTRACT

Background: A high birth weight has been suggested to increase the later risk of obesity, as measured by body mass index, but, paradoxically, to decrease the later propensity to cardiovascular disease. Programming of more lean tissue rather than fat mass by a high birth weight might explain this paradox and also explain the association of birth weight with later body mass index. This concept has been inadequately tested.

Objective: The objective was to test the hypothesis that a high birth weight programs a greater proportion of lean mass in children and adolescents.

Design: Body fat mass and fat-free mass were assessed by both skinfold-thickness measurement and bioelectrical impedance analysis in adolescents aged 13–16 y ($n = 78$) who were part of a study that investigated the early origins of cardiovascular disease. Body composition was assessed by dual-energy X-ray absorptiometry in a separate group of younger children.

Results: An increase in birth weight of 1 SD was significantly associated with a 0.9–1.4-kg (2–3%) increase in fat-free mass in adolescents but not with an increase in fat mass. This association was independent of age, sex, height, pubertal stage, socioeconomic status, and physical activity. Similar observations were made in younger children.

Conclusions: Our data support the hypothesis that fetal growth, measured by birth weight, programs lean mass later in life. Our observations may therefore explain the association of birth weight with body mass index and have implications for the early origins of both obesity and cardiovascular disease. *Am J Clin Nutr* 2003;77:726–30.

KEY WORDS Fat-free mass, lean mass, obesity, programming, birth weight, cardiovascular disease

INTRODUCTION

The idea that factors act during early critical windows such as intrauterine or early postnatal life to influence or “program” long-term health is now a major public health concern (1). For instance, a high birth weight has been suggested to program an increased risk of later obesity, as measured by body mass index (BMI; in kg/m^2) (2, 3). The association between birth weight and BMI, however, contradicts considerable evidence that a high birth weight programs less susceptibility rather than greater susceptibility to cardiovascular disease (CVD) risk factors (4, 5). One hypothesis that could partially explain this paradox is that low birth weight is associated with programming of greater abdominal or truncal fat

mass (6–8), which would increase the metabolic risk of CVD, although the evidence for this is inconclusive (9). Another possibility is that, because BMI correlates strongly with both total lean mass and fat mass (10), positive associations between birth weight and later BMI represent an association of birth weight with lean rather than fat tissue.

The hypothesis that poor fetal growth, as measured by low birth weight, programs a smaller proportion of lean mass later in life is now supported by several studies (11–13). Compared with children born at an appropriate size or large for gestational age, children born small for gestational age tended to remain smaller throughout childhood, and the discrepancy in weight was attributable to differences in lean rather than fat mass (12). Similarly, adults with low birth weight had less muscle mass (11) and, in another study, less thigh muscle area (13). The influence of birth weight on later lean mass has not been adequately investigated, however, because previous studies were often based on regional measures of lean tissue such as muscle mass or the composition of limbs. We therefore tested the hypothesis that fetal growth programs whole-body lean mass later in life in 2 populations. We studied adolescents because they were old enough for the amplification of programming effects but not so old as to incur a large contribution of lifestyle factors, which cumulatively may strongly influence the body composition of older subjects. We also studied younger children whose lean mass was assessed by dual-energy X-ray absorptiometry (DXA).

SUBJECTS AND METHODS

Subjects

Adolescents aged 13–16 y were recruited from schools in 5 communities in the United Kingdom (Norwich, Cambridge, Sheffield, Ipswich, and King’s Lynn) as part of a study that investigated the early influences on later risk factors for CVD (14). All subjects who were clinically well, born at term, and willing to

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TABLE 1
Characteristics of the subjects

	Adolescents (<i>n</i> = 78)	Children (<i>n</i> = 86)
Males [<i>n</i> (%)]	41 (53)	41 (48)
Age (y)	14.8 ± 0.9 ¹	7.4 ± 1.9
Birth weight (kg)	3.3 ± 0.7	3.4 ± 0.6
(<i>z</i> score)	-0.38 ± 1.1	-0.02 ± 1.0
Gestation (wk)	39.7 ± 1.8	39.7 ± 1.8
Weight (kg)	58.6 ± 13.2	25.3 ± 6.7
Height (cm)	164.9 ± 9.5	123.6 ± 11.4
BMI (kg/m ²)	21.5 ± 4.2	16.3 ± 2.0
Tanner stage		
Pubic hair	4.0 ± 0.8	1.0 ± 0.1
Genitalia or breast development	4.0 ± 0.9	1.0 ± 0.1
Body composition (kg) ²		
Fat-free mass (kg)		
Houtkooper et al (21)	46.2 ± 8.7	—
Schaefer et al (20)	43.3 ± 7.5	—
Slaughter et al (23)	43.7 ± 7.4	20.7 ± 4.8
Deurenberg et al (22)	46.2 ± 9.2	20.7 ± 4.7
DXA	—	19.8 ± 4.4
Fat mass (kg) ³		
Houtkooper et al (21)	10.3 ± 0.7	—
Schaefer et al (20)	12.5 ± 0.7	—
Slaughter et al (23)	12.2 ± 0.6	4.1 ± 0.4
Deurenberg et al (22)	11.4 ± 0.4	4.2 ± 0.4
DXA	—	4.3 ± 0.5

¹ $\bar{x} \pm$ SD; a slight loss of *n* for some variables.

²Calculated from skinfold-thickness measurements or bioelectrical impedance analysis by the use of 4 predictive equations or by dual-energy X-ray absorptiometry (DXA).

³SD given as log_e.

attend a clinical center set up in each of the 5 communities (*n* = 78) were included. Written informed consent was obtained from each parent and subject, and the study was approved by national and local research ethics committees.

A group of younger children from one community (Cambridge) was also studied. These children had participated in a study of bone mineralization, in which their whole-body fat and lean masses and bone mineral content were assessed by DXA (15). The children were recruited from 4 schools that provided a population representative of the Cambridge area (15). They were given a letter to take home to their parents, and one-half of the parents agreed to allow their child to participate in the study. For the purpose of analysis, all children for whom birth weight, length of gestation, anthropometric measures, and body composition were available (86 of 95) were included.

Anthropometric measures, socioeconomic status, and physical activity

Height was measured with a portable stadiometer accurate to 1 mm (Holtain Instruments Ltd, Crymych, United Kingdom), and weight with electronic scales accurate to 0.1 kg (Seca, Hamburg, Germany). Triceps, biceps, subscapular, and suprailiac skinfold thicknesses were measured in duplicate with skinfold calipers (Holtain Instruments), and the mean value was obtained. Measurements were made by 1 of 2 observers trained in the techniques involved, and measurers were blind to each subject's birth weight or length of gestation. Equipment was calibrated before each

field-site visit, and the measuring technique of the observers was monitored throughout. Tanner staging was performed in private by self-assessment with the use of standard Tanner stage photographs (16). Birth weight and gestational age at birth were obtained by maternal recall and verified through parental records or other medical records where available.

Birth weight was expressed as the SD from expected weight (*z* score), calculated with the use of appropriate birth centiles (17). Socioeconomic status (SES) was expressed as an index of overcrowding based on the number of persons per room of the home. Physical activity was assessed by a simple rating relative to peers. The question "compared with others of your age and sex, how much physical activity do you get?" was answered on a 5-point scale ranging from "much less active" to "much more active." This index was validated in children previously (18) and in the populations assessed in the present study (19). Data on SES were not available in the younger study population.

Body composition

For the adolescent population, fat-free mass (FFM) was determined with the use of bioelectrical impedance analysis (BIA; EZ Comp 1500; Fitness Concepts Inc, Park City, UT) after the subjects had fasted overnight and had lain supine for 15–20 min. Electrodes were attached in 2 pairs to the right hand and foot in a tetrapolar arrangement in accordance with the manufacturer's instructions. The impedance value obtained was used to calculate FFM according to the equations of Schaefer et al (20) and Houtkooper et al (21), which are suitable for use in studies of children and adolescents. Fat mass was obtained from body weight. Skinfold-thickness measurements were also used to estimate fat mass (and hence FFM) by using the equations of Deurenberg et al (22) or Slaughter et al (23), which are also suitable for use in studies of children and adolescents.

In the younger study population, body composition (fat mass and FFM) was assessed by skinfold-thickness measurement (as above), and fat mass and lean mass were obtained by DXA scanning (QDR1000 W; Hologic, Inc, Waltham, MA; 15). Whole-body DXA scans were conducted while the participants were wearing light clothing (usually shorts and a T-shirt), and most were performed by one observer (MF). Analyses were performed with enhanced whole-body V5.61 software (Hologic). Quality-control scans were performed daily on each machine by using the Hologic spine phantom.

Statistical analysis

Outcome measures were FFM (lean) and fat mass (calculated according to equations of Schaefer et al (20), Houtkooper et al (21), Deurenberg et al (22), or Slaughter et al (23) or obtained from DXA). Regression analysis was used to assess associations between FFM or fat mass and the *z* score for birth weight, and multiple regression analysis was used to adjust for age, sex, Tanner stage, SES, and physical activity level. The associations between birth weight *z* score and both FFM and fat mass were also adjusted for variation in body size by adjusting for height. This was achieved by raising height to the power of 2, as advocated by Van Itallie et al (24). Log-log regression analyses were conducted to confirm the validity of this approach. Fat mass was log_e transformed and significance was *P* < 0.05 for all analyses.

RESULTS

Some characteristics of the 2 study populations are shown in **Table 1**. Both study groups were representative of the national

TABLE 2
Regression analyses of body composition with birth weight *z* score¹

	Unadjusted			Adjusted for age, sex, SES, Tanner stage, and physical activity			Adjusted for age, sex, SES, Tanner stage, physical activity, and height squared		
	β^2	SE	<i>P</i>	β^2	SE	<i>P</i>	β^2	SE	<i>P</i>
Adolescents (<i>n</i> = 78) ³									
Fat-free mass (kg)									
Houtkooper et al (21)	2.4	0.8	0.005	2.3	0.9	0.011	1.3	0.6	0.044
Schaefer et al (20)	1.9	0.7	0.010	1.7	0.7	0.012	0.9	0.5	0.044
Slaughter et al (23)	2.2	0.7	0.002	2.2	0.8	0.006	1.4	0.6	0.022
Deurenberg et al (22)	2.3	0.9	0.011	2.3	0.9	0.015	1.4	0.7	0.067
Fat mass (kg) ⁴									
Houtkooper et al (21)	0.01	0.07	0.84	0.06	0.04	0.14	0.04	0.07	0.52
Schaefer et al (20)	0.06	0.07	0.33	0.12	0.07	0.11	0.08	0.08	0.24
Slaughter et al (23)	0.04	0.06	0.46	0.07	0.06	0.24	0.05	0.06	0.41
Deurenberg et al (22)	0.03	0.04	0.44	0.05	0.04	0.30	0.05	0.04	0.30
BMI (kg/m ²)	-0.6	0.4	0.21	0.7	0.4	0.07	0.8	0.4	0.08
Children (<i>n</i> = 86) ^{3,5}									
Fat-free mass (kg)									
DXA	0.5	0.4	0.29	0.5	0.2	0.039	0.3	0.1	0.039
Slaughter et al (23)	0.5	0.5	0.26	0.6	0.3	0.022	0.4	0.2	0.026
Deurenberg et al (22)	0.6	0.5	0.22	0.6	0.3	0.017	0.4	0.2	0.022
Fat mass (kg) ³									
DXA	0.07	0.05	0.18	0.06	0.04	0.13	0.04	0.04	0.24
Slaughter et al (23)	0.05	0.04	0.25	0.05	0.03	0.10	0.04	0.03	0.21
Deurenberg et al (22)	0.04	0.04	0.32	0.05	0.03	0.13	0.03	0.03	0.26
BMI	0.4	0.2	0.07	0.4	0.2	0.039	0.4	0.2	0.06

¹SES, socioeconomic status; DXA, dual-energy X-ray absorptiometry.

²Regression coefficients (β) represent change in body-composition measure per *z* score increase in birth weight.

³Some loss of *n* in some models.

⁴Log_e transformed.

⁵SES not available for children.

population in terms of their birth weight for length of gestation. FFM in the adolescent study group (but not fat mass, age, sex distribution, height, weight, or Tanner stage) was significantly greater in the top half than in the bottom half of the population for birth weight *z* score (data not shown). FFM in adolescents measured by BIA or skinfold-thickness measurement was significantly associated with birth weight *z* score (Table 2). These associations remained significant after adjustment for age, sex, Tanner stage, SES, and physical activity (Table 2). After adjustment for height, the associations between birth weight *z* score and FFM calculated by the equations of Schaefer et al (20), Houtkooper et al (21), and Slaughter et al (23), but not Deurenberg et al (22), remained significant. However, the increase in FFM per *z* score increase in birth weight was similar for all 4 FFM measures (ranging from 0.9 to 1.4 kg; *P* > 0.2 for all comparisons between regression coefficients). There was no significant interaction between birth weight *z* score and sex with regard to later FFM (*P* = 0.3–0.7 for the 4 different measures of FFM).

BMI in adolescence was not significantly associated with birth weight *z* score, and this association remained nonsignificant after adjustment for potential confounding factors (Table 2). Similarly, fat mass, estimated by the 4 different predictive equations, was not significantly related to birth weight *z* score.

In the younger study population, lean mass assessed by DXA (or FFM assessed by skinfold-thickness measurement) was significantly associated with birth weight *z* score independent of age, sex, pubertal stage, physical activity, or height (Table 2). There was no significant interaction between birth weight *z* score and

sex with regard to later lean mass (*P* = 0.9). Measures of fat mass or BMI were not significantly related to birth weight *z* score, except for BMI in one regression model, as shown in Table 2.

DISCUSSION

The present study showed that a higher birth weight was associated with greater FFM, but not with greater fat mass, in children and adolescents. This association was independent of age, sex, pubertal stage, SES, physical activity, and height and was observed for FFM measured by skinfold-thickness measurement, BIA, or DXA scanning. Our observations suggest, therefore, that poor fetal growth, as measured by low birth weight, programs a smaller proportion of lean mass later in life.

Earlier studies have shown inconsistent associations between birth weight and later body composition. A high birth weight, although usually related to greater BMI later in life, has also been associated with less body fatness assessed by skinfold-thickness measurement (25). Furthermore, a study in twins discordant for birth weight showed interpair differences in height, but not BMI, which contradicts an influence of fetal growth on later body fatness (26). These discrepant data could be explained in part by the use of surrogate measures of obesity (eg, BMI), rather than of body composition, in most previous studies. Alternatively, the association of birth weight with later BMI could in fact relate to programming of greater lean tissue rather than of fat mass (13). Our observation that an increase in birth weight of 1 SD was associated with an increase of ≤ 1.4 kg (3%) in FFM in adolescence

was consistent with this hypothesis. However, we found that birth weight was related to whole-body lean mass later in life rather than to markers of lean tissue such as muscle mass (11) or the composition of limbs (12, 13). The association of birth weight with lean body mass was independent of height, which suggests that a high birth weight programs body composition rather than simply predisposing to greater body size. Therefore, our observations were consistent with the association of birth weight with lean mass in twins (27), but it is important that our study now confirms these findings in 2 singleton populations.

Our findings in adolescents were confirmed in a second population, which suggests that the influence of fetal growth on later FFM is likely to apply to the general population. The smaller effect of fetal growth on lean tissue in younger children than in adolescents was not unexpected, as programming of body composition tends to amplify with age and, as in animal models, may be most marked after puberty (28). A determination of whether our data apply to older populations requires further study. However, we chose to confine our study to children and adolescents to reduce the relatively large contribution of lifestyle factors that, cumulatively, may strongly influence the body composition of older subjects.

Several plausible hypotheses might explain the association between birth weight for gestational age and lean mass later in life. For example, genetically determined insulin resistance could result in impaired insulin-mediated growth of fetal muscle, and the continuation of this pattern of body composition would lead to less muscle mass later in life (29). However, in utero differences in the birth weights of monozygotic twins are associated with differences in lean mass later in life, which suggests that intrauterine factors could program later body composition independent of maternal and genetic influences (27). As previously suggested (4, 5), fetal muscle growth may be sacrificed, as a consequence of intrauterine stress, in favor of brain development. Suboptimal nutrition in utero would predispose to fetal hypoglycemia and so would limit insulin secretion and, consequently, increase protein breakdown and decrease protein accretion. Similarly, poor fetal nutrition could lower the concentrations of insulin-like growth factor 1, which could compromise intrauterine muscle growth (4, 30). Intrauterine growth retardation may therefore be associated with a relatively greater deficit in lean mass than in fat mass, which is a hypothesis supported by recent data (31, 32). Continuation of this pattern of body composition established at or near birth could then predispose to a smaller proportion of lean mass later in life in babies born small for their gestational age.

The programming of less lean mass by suboptimal fetal growth is supported by theoretical evolutionary considerations. In an evolutionary approach, early postnatal growth can be modeled as an investment by the mother in her offspring. A greater proportion of lean mass in adulthood is associated with increased reproductive success in both sexes, though for different reasons (33, 34). In a good-quality environment, the mother is therefore predicted to maximize her own reproductive success by investing in offspring lean mass. In a poor-quality environment, however, the long-term benefits of lean mass are offset by the more immediate benefits of fatness for survival in the weaning period (35). Therefore, in poorer environments, with scarce resources for investment, lean mass deposition is reduced, and fat mass deposition is enhanced, which leads to the "fat-thin" phenotype of the growth-retarded infant (31, 32). Thus, our findings of a relation between birth

weight and later lean mass, but not fat mass, are consistent with evolutionary principles, indicating that greater early-life investment by the mother manifests as a greater proportion of lean tissue than of fat tissue in her offspring.

Potential limitations

By necessity, we used relatively inaccurate field techniques to measure body composition in one of our study populations. However, our observations were consistent with the programming of FFM estimated with the use of both skinfold-thickness measurements and BIA and calculated by 4 different predictive equations. After adjustment for height, birth weight *z* score was significantly associated with later FFM in adolescents, as calculated with 3 out of 4 equations, and the calculations by the equation of Deurenberg et al (22) just failed to reach statistical significance. Furthermore, our observations were consistent with the findings of a recent study that, like ours, used BIA to measure FFM and fat mass (27).


Implications for cardiovascular disease

Our observations could have important implications for the early origins of adult disease hypothesis. Because muscle is an important site for glucose uptake in response to insulin, programming of a smaller proportion of lean tissue by low birth weight could adversely affect later insulin sensitivity, and this could be one mechanism that partially links low birth weight with increased risk of later CVD. Although muscle mass was not linked to abnormalities of glucose and insulin metabolism in subjects aged ≈ 50 y (11), the influence of other contributors to insulin resistance at that age could have potentially overwhelmed and obscured a small beneficial effect of greater muscle mass. Such a beneficial effect on insulin sensitivity, if present from childhood, would make a strong and cumulative contribution to the development of CVD later in life.

Implications for obesity

Programming of lean mass is likely to have several implications for the early origins of obesity. First, programming of lean tissue, rather than of fat mass, could explain associations between birth weight and later BMI. Therefore, future research into the early origins of obesity requires more accurate measures of body composition. Second, the association of low birth weight with a smaller proportion of lean mass, and therefore lower metabolic activity, in adolescents could, in the presence of an energy-dense diet, predispose to greater adiposity later in life. This hypothesis could then partly explain observations of greater percentage body fat in adults of low birth weight.

Conclusion

Our observations suggest that low birth weight programs a smaller proportion of lean mass later in life. Because body composition is a critical factor in the development of CVD, further investigation of the programming of body composition could shed light on the early origins of adult disease. 

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expertise; and AL helped with the study design. All authors contributed to the study design, statistical analysis, and writing of the final manuscript. There were no conflicts of interest for any author.

REFERENCES

- Lucas A. Programming by early nutrition in man. In: Bock GR, Whelan J, eds. The childhood environment and adult disease. Ciba Found Symp 1991;156:38–55.
- Dietz WH. Critical periods in childhood for the development of obesity. *Am J Clin Nutr* 1994;59:955–9.
- Parsons TJ, Power C, Logan S, Summerbell CD. Childhood predictors of adult obesity: a systematic review. *Int J Obes Relat Metab Disord* 1999;23:S1–107.
- Barker DJP, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. *Lancet* 1993;341:938–41.
- Barker DJP. Fetal origins of coronary heart disease. *BMJ* 1995; 311:171–4.
- Law CM, Barker DJP, Osmond C, Fall CHD, Simmonds SJ. Early growth and abdominal fatness in adult life. *J Epidemiol Community Health* 1992;46:184–6.
- Barker M, Robinson S, Osmond C, Barker DJP. Birth weight and body fat distribution in adolescent girls. *Arch Dis Child* 1997;77:381–3.
- Malina RM, Katzmarzyk PT, Beunen G. Birth weight and its relationship to size attained and relative fat distribution at 7 to 12 years of age. *Obes Res* 1996;4:385–90.
- Choi CS, Kim CH, Lee WJ, et al. Association between birth weight and insulin sensitivity in healthy young men in Korea: role of visceral adiposity. *Diabetes Res* 2000;49:53–9.
- Wells JC. A Hattori chart analysis of body mass index in infants and children. *Int J Obes Relat Metab Disord* 2000;24:325–9.
- Phillips DIW. Relation of fetal growth to adult muscle mass and glucose tolerance. *Diabet Med* 1995;12:686–90.
- Hediger ML, Overpeck MD, Kuczmarski RJ, McGlynn A, Maurer KR, Davis WW. Muscularity and fatness of infants and young children born small or large for gestational age. *Pediatrics* 1998;102: e60.
- Kahn HS, Narayan KMV, Williamson DF, Valdez R. Relation of birth weight to lean and fat thigh tissue in young men. *Int J Obes Relat Metab Disord* 2000;24:667–72.
- Singhal A, Kattenhorn M, Cole TJ, Deanfield J, Lucas A. Preterm birth, vascular function and risk factors for atherosclerosis. *Lancet* 2001;358:1159–60.
- Fewtrell MS, Prentice A, Jones SC, et al. Bone mineralization and turnover in preterm infants at 8–12 years of age: the effect of early diet. *J Bone Miner Res* 1999;14:810–20.
- Duke PM, Litt IF, Gross RT. Adolescents' self-assessment of sexual maturation. *Pediatrics* 1980;66:918–20.
- Freeman JV, Cole TJ, Chinn S, Jones PRM, White EM, Preece MA. Cross-sectional stature and weight reference curves for the UK, 1990. *Arch Dis Child* 1995;73:17–24.
- Sallis JF, Patterson TL, Buono MJ, Nader PR. Relation of cardiovascular fitness and physical activity to cardiovascular disease risk factors in children and adults. *Am J Epidemiol* 1988;127:933–41.
- Stafford M, Wells JC, Fewtrell M. Television watching and fatness in children. *JAMA* 1998;280:1231–2.
- Schaefer F, Georgi M, Zieger A, Scharer K. Usefulness of bioelectric impedance and skinfold measurements in predicting fat-free mass derived from total body potassium in children. *Pediatr Res* 1994;35: 617–24.
- Houtkooper LB, Lohman TG, Going SB, Hall MC. Validity of bioelectric impedance for body composition assessment in children. *J Appl Physiol* 1989;66:814–21.
- Deurenberg P, Pieters JLL, Hautvast JGAJ. The assessment of the body fat percentage by skinfold thickness measurement in childhood and young adolescence. *Br J Nutr* 1990;63:293–303.
- Slaughter MH, Lohman TG, Boileau RA, et al. Skinfold equations for estimation of body fatness in children and youth. *Hum Biol* 1988; 60:709–23.
- Van Itallie TB, Yang M, Heymsfield SB, Funk RC, Boileau RA. Height-normalized indices of the body's fat-free and fat mass: potentially useful indicators of nutritional status. *Am J Clin Nutr* 1990; 52:953–9.
- Okosun IS, Liao Y, Rotimi CN, Dever GEA, Cooper RS. Impact of birth weight on ethnic variations in subcutaneous and central adiposity in American children aged 5–11 years. A study from the third National Health and Nutrition Examination Survey. *Int J Obes Relat Metab Disord* 2000;24:479–84.
- Allison DB, Paulre F, Heymsfield SB, Pi-Sunyer FX. Is the intra-uterine period really a critical period for the development of adiposity? *Int J Obes Relat Metab Disord* 1995;19:397–402.
- Loos RJJ, Beunen G, Fagard R, Derom C, Vlietinck R. Birth weight and body composition in young adult men—a prospective twin study. *Int J Obes Relat Metab Disord* 2001;25:1537–45.
- Lewis DS, Bertrand HA, McMahan CA, McGill HC, Carey KD, Masoro EJ. Prewaning food intake influences the adiposity of young adult baboons. *J Clin Invest* 1986;78:899–905.
- Hattersley AT, Tooke JE. The fetal insulin hypothesis: an alternative explanation of the association of low birth weight with diabetes and vascular disease. *Lancet* 1999;353:1789–92.
- Gluckman PD, Harding JE. Fetal growth retardation: underlying endocrine mechanisms and postnatal consequences. *Acta Paediatr Suppl* 1997;422:69–72.
- Yajnik CS. Fetal origins of adult disease: where do we stand? *Int J Diab Dev Countries* 2001;21:42–9.
- Lapillonne A, Braillon P, Claris O, Chatelain PG, Delmas PD, Salle BL. Body composition in appropriate and in small for gestational age infants. *Acta Paediatr* 1997;86:196–200.
- Trivers RL, Willard DE. Natural selection of parental ability to vary the sex ratio of offspring. *Science* 1973;179:90–2.
- Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. *Bull World Health Organ* 1987;65: 663–737.
- Kuzawa CW. Adipose tissue in human infancy and childhood: an evolutionary perspective. *Am J Phys Anthropol* 1998;27:177–209.