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Symposium on 'Adipose tissue development and the programming of adult obesity'

Obesity epidemic in India: intrauterine origins?

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The epidemic of 'obesity' in India is not appreciated because BMI underestimates the adiposity of Indians. Specific adiposity measurements are necessary for recognition of the adiposity of 'thin' Indians. The origin of this adiposity is only beginning to be understood. In addition to a possible genetic predisposition, intrauterine 'programming' might be responsible, although in the 'thrifty phenotype' hypothesis the adiposity of the 'thin' fetus has not been appreciated. Dutch men who faced 'winter hunger' during the first trimester of their *in utero* life have become more obese as adults. Low birth weight predicts central obesity in some studies, including studies in urban children. It has also been shown that small and thin Indian newborns (weight 2·7 kg and ponderal index 2·4 kg/m^3) have poor muscle and visceral mass but higher adiposity for a given weight compared with white Caucasian babies. This body composition is influenced by maternal adiposity before pregnancy and by aspects of maternal nutritional intake and circulating nutrient concentrations during pregnancy. There are no strong paternal determinants of adiposity at birth. Adiposity may be an integral part of the orchestrated adjustments made to support 'brain preservation' during intrauterine growth, because brain tissue is predominantly fat. Increased nutrition in the face of a genetic predisposition or multigenerational undernutrition increases maternal insulin resistance in late pregnancy and promotes fetal adiposity even in absence of marked hyperglycaemia. Further research is necessary to define the role of specific nutrients and metabolites in the intrauterine processes promoting adiposity before maternal interventions to curtail the epidemic of obesity and diabetes are planned.

Obesity epidemic: Developing countries: Central adiposity: Intrauterine influence: Fetal body composition: Brain preservation

Obesity epidemic in the developing countries

There is a rapidly escalating epidemic of obesity all over the world (Prentice, 2001). In the developed countries the epidemic attracts much attention, but there is little realization of a similar and perhaps more serious epidemic in the developing countries. Countries like India have controlled the problem of severe undernutrition to a substantial extent, but are now facing a rising epidemic of obesity (Table 1). This epidemic is assuming serious proportions in cities and is affecting young adults and children.

Causes of the epidemic

The strongest risk factor for obesity is urbanization (Fall, 2001). Obesity is at least three times more common in cities than in villages, although it is increasing rapidly even in villages because traditional villages are also becoming urbanized in their habits (urbanization *in situ*, also termed *rubanization*). Another related risk factor is higher socio-economic status. This situation is opposite to that in developed countries where lower socio-economic groups are more affected ('reversal' of socio-economic gradient). In simple mechanistic terms weight gain occurs

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Table 1. Obesity and central obesity in Indian adults and obesity in Indian children

Reference	Place	Population	Obesity criteria	Obesity prevalence (%)	Males	Females
Obesity in adults						
Gopalan (1998)	New Delhi, middle class, slums	20–65 years Men 564 Women 443	>25*	High middle class Mid middle class Low middle class Slums	32 16 7 1	50 30 28 4
Desai *et al.* (2000)	Baroda, industrial employees	20–60 years Men 520 Women 317	Not mentioned	Overweight Obese	41 6	44 12
Misra *et al.* (2001)	New Delhi, slum	18–50 years Men 170 Women 362	>25*		13	16
Ramachandran *et al.* (2001)	Six Indian cities: Chennai, Bangalore, Hyderabad, Calcutta, Mumbai, New Delhi	>20 years Men 5288 Women 5928	≥25*	Normal glucose tolerance Impaired glucose tolerance Diabetes Overall		26 36 47 31
Reddy *et al.* (2002)	New Delhi	35–64 years Urban: Men 1594 Women 1456 Rural: Men 1417 Women 1070	>25*	Urban Rural	35 8	48 40
Shukla *et al.* (2002)	Mumbai	>35 years Men 40 071 Women 59 527	≥25*		19	30
Central obesity in adults						
Gopalan (1998)	New Delhi, middle class, slums	20–65 years Men 564 Women 443	Men >1·0† Women >0·85†	High middle class Mid middle class Low middle class Slums	39 29 16 4	50 49 50 6
Misra *et al.* (2001)	New Delhi, slum	18–50 years Men 170 Women 362	Men >0·95† Women >0·80†		9	51
Ramachandran *et al.* (2001)	Six Indian cities: Chennai, Bangalore, Hyderabad, Calcutta, Mumbai, New Delhi	>20 years Men 5288 Women 5928	Men >0·90† Women >0·85†	Normal glucose tolerance Impaired glucose tolerance Diabetes Overall		47 52 65 50
Reddy *et al.* (2002)	New Delhi	35–64 years Urban: Men 1594 Women 1456 Rural: Men 1417 Women 1070	Men ≥0·95† Women ≥0·80†	Urban Rural	72 45	40 36
Obesity in children						
Gupta & Ahmad (1990)	New Delhi, school	5–15 years Boys 2340 Girls 1521	>2·26‡		8	7
Kapil *et al.* (2002)	New Delhi, affluent school	10–16 years Boys 563 Girls 307	30·0–34·9*		8	6
Ramachandran *et al.* (2002)	Low-, Middle-, High-income schools	13–18 years Boys 2382 Girls 2318	>30·0*		4	3

* BMI (kg/m^2).
† Waist:hip ratio.
‡ Ponderal index (kg/m^3).

when energy intake by an individual exceeds energy expenditure over a period of time. Changing patterns of food intake (both in quality and quantity) and physical activity contribute to the positive energy balance. Genetic as well as non-genetic determinants affect an individual's response to energy intake as well as physical activity, and

therefore influence the balance between the two factors (Prentice, 2001).

It is possible that a 'thrifty genotype' may have helped man survive famine conditions by successfully depositing fat. However, in the current situation of excess food and reduced activity this genotype may lead to obesity. Like most other polygenic conditions, the contribution of genetic factors to obesity is not clear at the population level. However, a number of rare syndromes of extreme obesity have been related to specific mutations in genes (Barsh *et al*. 2000). Studies in twins also favour a role for genetic factors in the aetiology of obesity (Bouchard *et al*. 1990; Sims, 1990). It is possible that like other chronic polygenic disorders (diabetes and hypertension), the expression of obesity is influenced by environmental conditions.

Recent interest has focused on the possible role of early-life environment in the pathogenesis of obesity.

Definitions of obesity and applicability of international criteria to Indian and other Asian populations

World Health Organization (2000) recommendations for the diagnosis of obesity are based on BMI cut-offs. These cut-offs have been derived from data on increasing mortality and morbidity from diabetes, CHD and stroke in developed countries (kg/m^2): overweight ≥25·00, pre-obese 25·00–29·99, obese class I 30·00–34·99, obese class II 35·00–39·99, obese class III ≥40·00.

In the last few decades there has been an increasing realization that the distribution of fat is also an important determinant of morbidity and mortality, and that 'central' obesity may be more pathological than generalized obesity (measured as BMI). There are two recommendations for the diagnosis of central obesity for men and women respectively: World Health Organization (2000): waist : hip ratio >1·0, >0·85; waist circumference (mm) moderate risk ≥940, ≥800; waist circumference (mm) severe risk ≥1020, ≥880; National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults (2001): waist circumference (mm) ≥1020, ≥880.

Given the small body frame of Indians and other Asians, both the current BMI and waist circumference criteria may be inappropriate. Prospective data of appropriate outcomes for a large number of individuals are necessary to resolve these issues. Such data are now becoming available, and the World Health Organization Expert Consultation (2004) has taken these data into account in reducing the 'obesity-related action point' in Asians to 23 kg/m^2.

Modern techniques (bioimpedance, ^2H-labelled water enrichment and dual-energy X-ray absorptiometry) allow separation of body weight into its subcompartments (fat, lean and bone mineral). It is possible, therefore, to talk in terms of 'adiposity' and 'thinness' in relation to specific components rather than weight adjusted for height. Modern imaging techniques (computed axial tomography and magnetic resonance imaging) allow the separation of 'central obesity' into visceral and subcutaneous components. These new approaches have improved the understanding of the components of adiposity and their specific risks. These data will influence the choice of obesity measures used in future epidemiological studies.

Fat cells are recognized to be metabolically and hormonally active. Indeed, adipocytes are now referred to as the largest endocrine and paracrine organ in the body. They secrete a range of molecules that affect metabolism, vascular function, appetite and the immune and haemostatic systems (Mohamed-Ali *et al*. 1998; Gema *et al*. 2001). Results so far have suggested that deranged adipocyte function may be involved in the pathogenesis of insulin resistance syndrome, type 2 diabetes and atherosclerosis (Gema *et al*. 2001). These new findings will improve the ability to make more relevant measurements in studying the risks for obesity in different populations.

The thin–fat Indian

It is now clear that the metabolic and vascular risks for 'obesity' are manifest at a lower BMI in populations in developing countries compared with those in developed countries. This position is highlighted by data from India and other Asian countries (Gopalan, 1998; Reddy, 1998; Yajnik, 1998, 2001*a*, 2002; Dudeja *et al*. 2001; Deurenberg-Yap *et al*. 2002; Li *et al*. 2002). Indians (and other Asians) have a small body frame; thus, the BMI classification of obesity based on large-framed Europid populations may be inappropriate (James *et al*. 2002). For a given BMI Indians have a higher percentage body fat than white Caucasians and African Americans (Chowdhury *et al*. 1996; Banerji *et al*. 1999; Chandalia *et al*. 1999). This relationship has been conceptualized, based on an anthropometric comparison of patients with type 2 diabetes from India and from the UK (Fig. 1). Clinical studies in India (Shelgikar *et al*. 1991; Ramachandran *et al*. 1992, 2001; Misra *et al*. 2001; Snehalatha *et al*. 2003) and the UK (McKeigue *et al*. 1991) and computed axial tomography

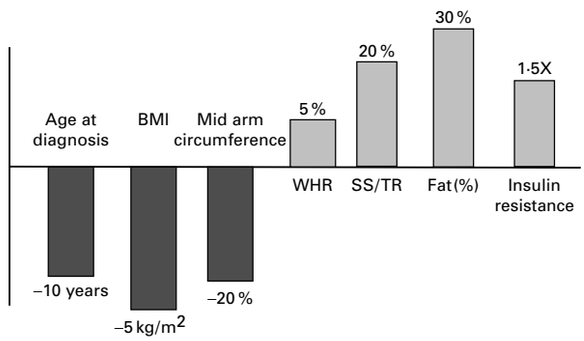

Fig. 1. Comparison of patients with type 2 diabetes from India and UK. Body composition and insulin resistance of newly-diagnosed patients are compared, with UK white as the reference. Indian patients are diagnosed at younger age, have less generalized obesity and thinner limbs, but have a higher adiposity, with a higher central adiposity, and are more insulin resistant (measured by the homeostasis model from fasting plasma glucose and insulin concentrations, HOMA-R; Matthews *et al.* 1985) than patients from the UK. WHR, waist : hip ratio; SS/TR, subscapular : triceps skinfold thickness. (From Yajnik, 2001.)

studies in India (Snehalatha *et al*. 1997), the UK (Forouhi *et al*. 1999) and the USA (Banerji *et al*. 1999; Chandalia *et al*. 1999; Raji *et al*. 2001) have demonstrated that Indians have a higher visceral fat mass than white Caucasians and African Americans. The visceral adiposity in Indians is accompanied by higher central subcutaneous adiposity (i.e. higher subscapular : triceps skinfold thickness as well as higher posterior subcutaneous fat thickness), shown by magnetic resonance imaging (Chandalia *et al*. 1999). The metabolic consequences of central obesity are usually assumed to be a result of visceral fat. The metabolic effects of subcutaneous adiposity need to be studied further.

Higher risk of incident diabetes and impairment of glucose tolerance at lower BMI in Indians has been highlighted in a small prospective study. The 10-year risk of developing impairment of glucose tolerance or diabetes in normal glucose-tolerant middle-aged men and women (*n* 191) is 2·4 times higher (95 % CI 1·1, 5·3) in subjects with a BMI of >23 kg/m^2 compared with those with a lower BMI (Yajnik *et al*. 2003*c*). In a large (approximately 10 000) cross-sectional study of glucose tolerance in six cities in India (National Urban Diabetes Survey), a BMI of >23 kg/m^2 has been shown to be associated with increased risk of diabetes (Snehalatha *et al*. 2003).

There have only been a few studies of body fat measurement (adiposity) by specific techniques in Indians in India. Bioimpedance analysis and ^{2}H-labelled water enrichment (two-compartment model) and dual-energy X-ray absorptiometry (three-compartment model) have been used to measure body fat in a community-based study of middle-aged men and women (Coronary Risk of Insulin Sensitivity in Indian Subjects (CRISIS)). Preliminary analysis of bioimpedance measurements has shown that BMI substantially underestimates adiposity in Indian men (Lubree *et al*. 2002; Joglekar *et al*. 2003). Thus, in rural men with a mean BMI of 21 kg/m^2 one-third are adipose (body fat >25 %), while 80 % of the urban middle-class men are adipose at a mean BMI of 24·1 kg/m^2. Only 7 % of these urban men would be classified as obese by the World Health Organization (2000) criteria (BMI >30 kg/m^2). This study has confirmed, using appropriate methods, what has been suspected from clinical measurements, that Indians are considerably adipose at a relatively lower BMI. Findings in northern India are similar (Misra *et al*. 2001). Such data have also influenced the decision of a World Health Organization Expert Consultation (2004) to reduce the 'obesity-related action point' in the Asians to 23 kg/m^2.

Origins of adiposity in India

Obesity is now reported in young Indian adults and even in children. The crucial questions are: what are the predisposing causes; how much of it is genetic; is it acquired *in utero*, during childhood or later? Prevention of obesity and, therefore, of the diabetes epidemic will be influenced by answers to these important questions. It is still unclear what role genetic factors play in the obesity epidemic. The possible role of intrauterine factors in the pathogenesis of adiposity, especially in Indians, will be discussed.

Intrauterine origins of adult obesity?

Hales & Barker (1992) and Barker (1998) have suggested that the current epidemic of type 2 diabetes and CHD originates in maternal and fetal undernutrition. The 'fetal origins' concept is based on the finding that there is an inverse relationship between birth weight (or ponderal index, as a measure of 'thinness') and prevalence of diabetes, insulin resistance syndrome and CHD in later life. The concept of (maternal and fetal) undernutrition is based on smaller size at birth rather than any measurements of food intake or circulating nutrients in the mother. Also, there are many non-nutritional determinants of size at birth, and the fetal supply line is long and has many non-nutritional regulators (Harding, 2001). It may thus be inappropriate to assume that small size at birth is a reliable reflection of maternal undernutrition. The relationship between size and body composition (which has a strong influence on subsequent morbidity and mortality) varies in different populations. Some caution is therefore necessary in the interpretation of these epidemiological studies. In addition, the relevance of retrospective studies in Europid populations born in the earlier part of the twentieth century to the contemporary populations in the developing world needs to be carefully assessed.

Apart from such difficulties, the concept of 'fetal origins' is an attractive one and in some ways states 'obvious truth'. Of an estimated average of fifty divisions of cells in an individual's lifetime at least forty are completed before birth (Milner, 1989). Thus, a large part of human development is over before birth. A human newborn is in many ways a miniature adult. This situation suggests that the intrauterine environment could have a profound and permanent effect on the structure and function of the developing organism ('programming'), which will determine the state of health in later life.

Studies relating intrauterine experiences to obesity in later life

The first report linking 'intrauterine undernutrition' with later obesity was based on the follow up of offspring born to mothers who experienced the Dutch famine in pregnancy (Ravelli *et al*. 1976). The risk of obesity was found to have increased in 19-year-old boys whose mothers had faced famine in the first trimester, and reduced if they had been exposed in the third trimester. The intrauterine origins of obesity have been reviewed recently (Martorell *et al*. 2001; Oken & Gillman, 2003; Rogers, 2003).

The majority of reports have used birth weight as a surrogate for intrauterine nutrition. The biological relationship between birth size and later outcomes appears to be 'U' shaped; however, this relationship may be modified in different populations (Fig. 2). The relationship between later obesity and larger birth weight could partly reflect an effect of maternal diabetes, but not necessarily so. Reasons for the association between lower birth weight and later obesity are not clear and could include contributions from altered body composition, appetite and physical activity pattern, and as yet unidentified changes in energy metabolism.

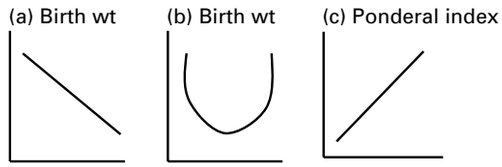

Fig. 2. Fetal origins of adult disease. There are three possible relationships between birth size and adult diabetes: (a), described in many European studies and interpreted to show an association with fetal undernutrition; (b), in Pima Indians, interpreted to show a relationship with both fetal under- and overnutrition; (c), described in Mysore, India and may be interpreted as fetal overnutrition. The true biological relationship is probably of type b. The other two may be seen as a result of characteristics of the population studied (sampling error) or differences in the body composition of the population (for further discussion, see p. 390).

Studies in India

Pune Childrens' Study

The first study of 'fetal origins' in Pune (Yajnik *et al*. 1995; Yajnik *et al*. 2003*b*) tested the hypothesis that low birth weight is an independent predictor of insulin resistance in childhood. Anthropometric, glucose tolerance and insulin resistance variables were measured in 4- and 8-year-old urban children born in the King Edward Memorial Hospital, Pune. Birth weight was available from the labour room records. It was found that circulating glucose and insulin concentrations are strongly related to the child's current size; there is an inverse relationship between circulating glucose and insulin concentrations and birth weight only when adjusted for the current size. Those children who are born the lightest but have grown to be the heaviest are the most insulin resistant (measured by the homeostasis model from fasting plasma glucose and insulin concentrations, HOMA-R; Matthews *et al*. 1985). Other insulin resistance variables (triacylglycerols, systolic blood pressure) and plasma cholesterol concentration show similar relationships.

Specific measures of adiposity were not available in this study, but BMI and the calculated fat mass (from skinfold thicknesses) were used. Central adiposity was assessed as subscapular:triceps skinfold thickness. It was found that BMI in childhood is inversely related to birth weight only when adjusted for current weight. Adiposity (percentage body fat) and central adiposity are related to age of the child, and are inversely related to birth weight. Surprisingly, taller children are more adipose (Fig. 3). Thus, children who are born lighter but grow heavier in childhood life are more adipose, more centrally adipose and are more insulin resistant, as well as having higher levels of other cardiovascular risk factors. Some of these findings may be a result of an earlier 'adiposity rebound' but serial growth measurements were not available for these children. There were no measurements at birth other than weight. Also, there was no information on nutritional and other determinants of size at birth or during childhood. The socio-economic status of parents is not predictive of birth weight but is a strong predictor of childhood size.

There is a debate about the relative contribution of small size at birth and subsequent accelerated growth to later

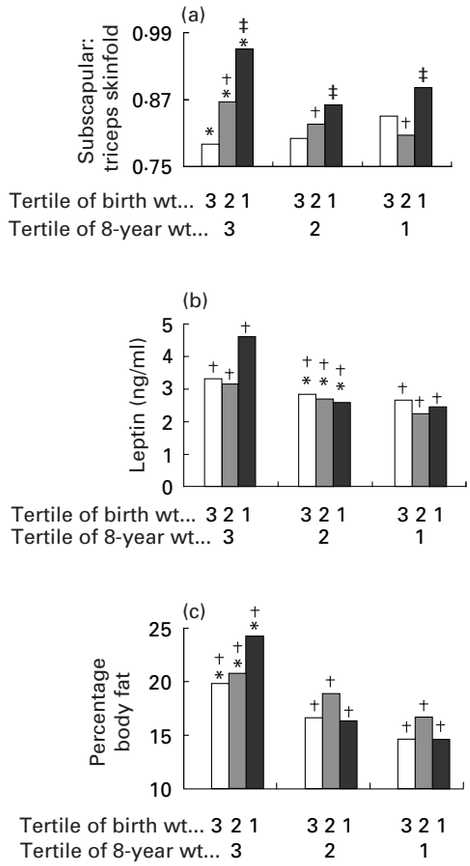

Fig. 3. Birth weight, current size and adiposity. Mean subscapular:triceps skinfold thickness (a), mean leptin levels (b) and percentage body fat (c) at 8 years of age by tertiles of birth weight and 8-year weight. When adjusted for age and sex the trend within tertiles of 8-year weight was significant: $^{*}P < 0{\cdot}05$. When adjusted for age and sex the trend within tertiles of birth weight was significant: †$P<0{\cdot}05$, ‡$P<0{\cdot}01$.

disease (Lucas *et al*. 1999). Barker and colleagues (Hales & Barker, 1992; Barker, 1998) favour an aetiological role for the small size at birth and attribute it to fetal and maternal undernutrition. There is little direct evidence for the role of maternal undernutrition in disease in the offspring. Lucas *et al*. (1999) favour a role for rapid postnatal change in size ('catch up' growth) rather than the small size at birth. A strong relationship has been found between growth velocity in childhood (4–8 years) and insulin resistance at 8 years of age (Yajnik, 2000). It is not easy to disentangle the contribution of small size at birth and growth velocity in childhood because they may be interrelated. Thus, the need for rapid postnatal growth may be stronger in those individuals who are growth restricted *in utero*. In either case, this pattern of growth (small to big) is accompanied by poor muscle mass and excess adiposity. These results raise the question: should low-birth-weight children be specially targetted to prevent obesity. This question is particularly relevant because the parents and the doctors looking after low-birth-weight babies make special efforts to increase their weight. In the Finnish study (Eriksson *et al*. 2002) resting metabolic rate

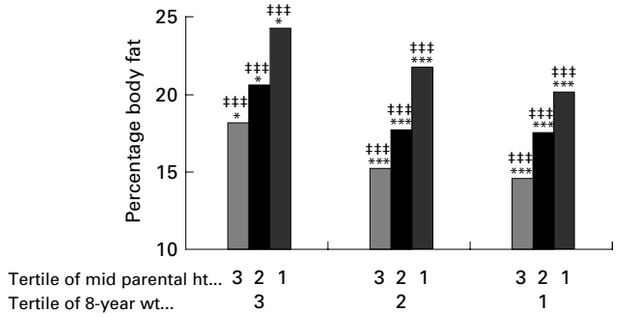

Fig. 4. Parental height, childhood growth and adiposity. Mean percentage body fat at 8 years of age by tertiles of mid parental height and 8-year height. When adjusted for age and sex the trend within tertiles of 8-year weight was significant: *$P<0{\cdot}05$, ***$P<0{\cdot}001$. When adjusted for age and sex the trend within tertiles of mid parental height was significant ‡‡‡$P<0{\cdot}001$.

was found to be higher in the low-birth-weight babies during their adult life than in those born with a normal weight, which should protect them from obesity. Thus, low-birth-weight children will need a substantial positive energy balance to become obese. This area of research could be fruitful from the viewpoint of preventing obesity in these children.

Parental size and adiposity in children. In the Pune Childrens' Study, children born to short parents were found to have higher adiposity. Maternal and paternal heights are independent predictors of this adiposity. Children who are taller in relation to mid-parental height have the highest adiposity (Fig. 4), thus explaining the similar relationship with insulin resistance. Parents' height may be regarded as a composite indicator of their own childhood growth (and possibly nutrition) and genetic determinants.

Mysore studies

Dr Caroline Fall and colleagues (Fall *et al*. 1998) have studied middle-aged men and women born in the Holdsworth Hospital, Mysore, where birth records have been preserved for >50 years. They have shown that higher birth weight predicts higher BMI, higher waist circumference, higher waist:hip ratio and higher skinfold thicknesses in middle age. Obesity is a strong predictor of diabetes. There is no relationship between birth weight and diabetes, but short length and higher ponderal index at birth predict increased risk of diabetes. This association contrasts with that reported in Europids (Phillips *et al*. 1994) and may indicate that intrauterine 'overnutrition' predicts diabetes in Indians. Another explanation may be related to differences in body composition; newborn Indian babies are more adipose at each ponderal index than white Caucasian babies (Yajnik *et al*. 2003*c*).

Pune Maternal Nutrition Study

The relationship between the birth size of the offspring and maternal size, nutrition and metabolism during pregnancy has been investigated in six villages near Pune (Fall *et al*. 1999; Rao *et al*. 2001, 2003; Yajnik *et al*. 2003*a*). This area is drought prone and the majority of the families live by subsistence farming. Between 1993 and 1996 >800 pregnancies were studied. Detailed anthropometric measurements of the mothers were made before and during pregnancy. Maternal food intake was assessed by 24 h recall and food-frequency questionnaire. Circulating nutrients (folate, vitamin C and ferritin) and metabolites (insulin, glucose, triacylglycerols and cholesterol) were measured twice during pregnancy (18 and 28 weeks gestation). Babies were measured in detail at birth.

The mothers were on average 21 years old, weighed 42 kg and were 1·5 m tall (BMI 18 kg/m^2). They consumed approximately 7400 kJ (1800 kcal), 45 g protein and 35 g fat per d. Gestational diabetes and hypertension were rare and none of the mothers smoked. The babies weighed 2·7 kg and were 475 mm long (ponderal index 24·1 kg/m^3). These babies are reputedly the smallest in the world and may be described as thin. However, when the anthropometric measurements of these babies are compared with those born in Southampton, UK, there are striking peculiarities in the body proportions of the Indian babies. Indian babies are approximately 800 g lighter, 30 mm shorter and 3 kg/m^3 thinner. These measurements however, do not reveal interesting aspects of the body composition of the babies. The smallest measurements in the Indian babies are abdominal circumference (a surrogate for visceral size) and mid-arm circumference (a surrogate for muscle mass). Head circumference is relatively preserved but the most preserved measurements are the skinfold thicknesses (subscapular more than triceps). A strikingly thin but fat baby! It would appear that the Indian baby has poor growth of protein-rich tissues but has a relatively preserved fat tissue and brain size.

To answer a number of methodological objections to such a comparison, two nutritionists from Pune measured Indian babies born in King Edward Memorial Hospital, Pune and white babies born in Whittington Hospital, London using the same instruments. The findings were identical to those in the Pune *v*. Southampton comparison. In addition, no differences were found in the cord blood leptin concentrations for the two groups of babies, suggesting that the two groups of babies have similar fat masses. Thus, Indian babies are in fact more adipose (higher percentage body fat; Figs. 5 and 6).

The Indian baby's birth size is predicted by the mother's size before pregnancy and there is an extent of 'mirror imaging' between the mother and the baby. The baby's skinfold thicknesses are predicted by maternal skinfold thicknesses and head circumference. The fattest babies are born to mothers who are short and fat and gain more weight in pregnancy. Maternal intake of energy and proteins during pregnancy does not predict the baby's size and adiposity. Higher maternal intake of fats ($P<0{\cdot}05$) and green leafy vegetables ($P<0{\cdot}01$) predict larger offspring skinfolds. These relationships are independent of socio-economic status. Higher maternal circulating glucose, cholesterol and triacylglycerol concentrations also predict larger skinfolds in the baby. On the other hand, maternal physical activity and circulating concentrations of ferritin and folate are inversely related to baby's skinfold thicknesses.

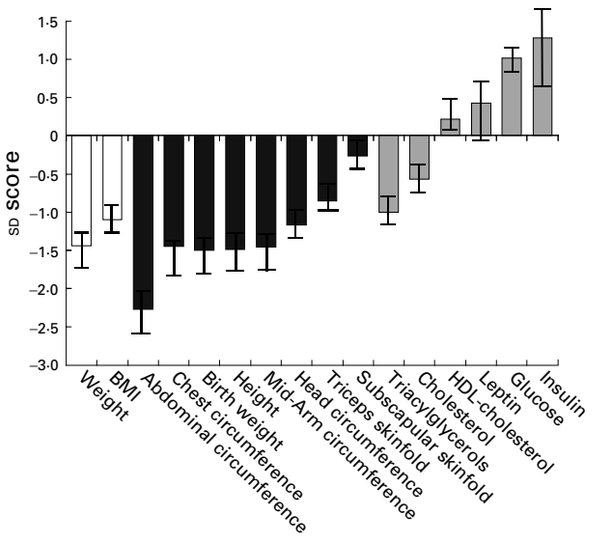

Fig. 5. A comparison of babies born in Pune, India and London, UK. UK measurements are used as a reference (zero). The values represent the difference in mean SD score for each measurement for Indian mothers (□) and newborn babies (■). (▨), Cord blood variables. Values are means and 95% CI represented by vertical bars. The measurements for the mothers have been shown for comparison. Indian babies are smaller than the white British babies in all measurements of size except the subscapular skinfold thickness, which is similar. Cord plasma leptin concentration is similar and cord plasma glucose and insulin concentrations are higher in Indian babies. (From Yajnik *et al.* 2002.)

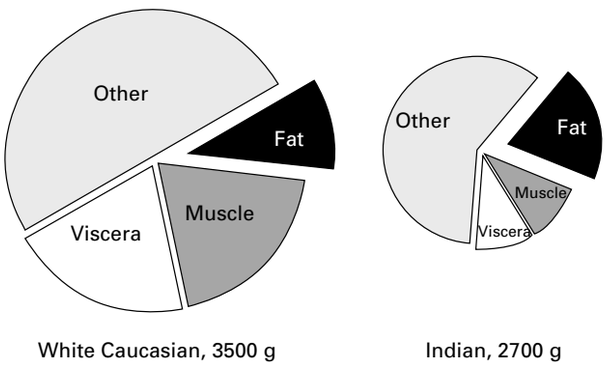

Fig. 6. A schematic diagram to compare the body composition of Indian and white Caucasian UK newborn babies. The Indian babies are approximately 800 g lighter, have less muscle but higher adiposity than the white babies.

Maternal insulin resistance, gestational diabetes and offspring adiposity

Increased maternal insulin resistance in the second half of pregnancy facilitates transfer of nutrients to the baby by reducing the mother's own utilization (Catalano *et al.* 1998). The mother's pre-gestational insulin resistance, as well as that acquired during pregnancy, determines the extent of insulin resistance in pregnancy. The pre-gestational insulin resistance reflects genetic and other determinants (adiposity) and the insulin resistance acquired during pregnancy is largely determined by the metabolic action of placental hormones (human placental lactogen, placental growth hormone, progesterone etc.). Thus, the growing fetus might control maternal metabolism. Mothers who fail to increase their insulin secretion to appropriate levels become hyperglycaemic. Clinical maternal diabetes (pre-gestational and gestational) is a well-known risk factor for fetal 'macrosomia'. Studies in Pima Indians (Pettitt *et al.* 1983, 1988) and in Chicago, IL, USA (Silverman *et al.* 1995) have shown that maternal diabetes is a risk factor for both obesity and type 2 diabetes in the offspring. Maternal diabetes contributes approximately 70% to diabetes in young Pima Indians (Dabelea *et al.* 1998).

A number of studies have shown a direct relationship between maternal circulating glucose concentrations in the 'normal' range and offspring size, suggesting that maternal diabetes is only an extreme example of normal physiology. Even more interesting is the relationship between maternal circulating triacylglycerol concentrations and the size of the offspring (Knopp *et al.* 1986), particularly the skinfold thicknesses and head circumference (reflecting brain growth; Yajnik *et al.* 2003*b*). Further investigation is needed to understand the implications of these findings in relation to the body composition and metabolism of the offspring.

Is brain preservation the drive for fat preservation?

During intrauterine life brain growth seems to have a priority over the growth of other organs. This 'brain-preservation' is apparent in fetuses that have suffered intrauterine growth retardation. The brain growth is promoted by increased blood flow to pre-ductal vessels (which supply the brain) at the cost of the post-ductal circuit (which supplies the viscera (including heart, liver, kidneys and pancreas) and bulk of the muscle in the lower limbs; Widdowson & McCance, 1960; Garrow *et al.* 1965; Winick *et al.* 1970). It is intriguing that these structures play a crucial role in the genesis of insulin resistance syndrome and type 2 diabetes (Fig. 7).

In the brain lipids comprise 700 g/kg dry weight, and brain growth is most rapid in late pregnancy and postnatal life. Teleologically, it makes sense for the fetus to make provisions for this demand and deposit lipids in the adipose tissue, which also acts as an insulator. Adipose tissue is also a store of energy and it signals reproductive fitness in girls before and after puberty. Thus, such a 'fat-preserving' fetus may be at an advantage both during intrauterine and subsequent life. There is little information on the regulators of nutrient allocation in a developing fetus. It is perhaps relevant that the uptake of nutrients by the brain is 'insulin-independent'. In the Pune Maternal Nutrition Study significant associations were found between maternal circulating concentrations of glucose, triacylglycerols and cholesterol and neonatal skinfold thicknesses and head circumference ($P<0{\cdot}05$ in all cases; Yajnik, 2001*b*). Thus, maternal metabolism, which is one of the major components of the intrauterine environment, may have profound implications for body composition and metabolism of the offspring. It could be a target for the prevention of obesity as well as type 2 diabetes in the offspring.

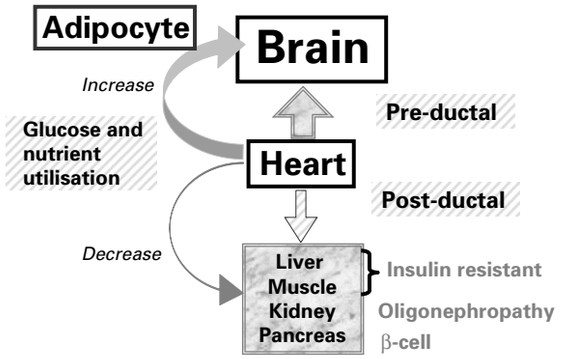

Fig. 7. The concept of 'brain-sparing' during fetal growth. 'Brain-sparing' is achieved by the diversion of blood flow to the pre-ductal circuit and by increased concentrations of nutrients in the blood (glucose, lipids, amino acids). Lipids constitute a large proportion of the brain, and lipid stores in the adipose tissue support rapid growth of the brain in the last trimester of pregnancy and in the postnatal period. The nutrition of the post-ductal structures suffers and their development is affected, which increases their susceptibility to later disease. Intrauterine origins of adiposity may thus be driven by the need for 'brain-sparing'.

Risk of birth weight for later obesity

Birth weight is usually directly related to later weight and BMI. Thus, high-birth-weight babies are expected to be more obese. Although this relationship is valid, it only partly explains obesity in a population (Martorell *et al*. 2001; Oken & Gillman, 2003; Rogers, 2003).

Birth weight is a poor indicator of the adiposity of the fetus. In the Europid population birth weight appears to be more strongly related to lean mass than fat mass. On the other hand, lower-birth-weight Indian babies are 'thin' but relatively adipose compared with white Caucasian babies. Indian babies are more adipose than white Caucasian babies at every ponderal index, and even the smallest (small-for-gestational age) Indian babies retain the tendency to adiposity. This pattern seems to be continued in later life, and both low- and high-birth-weight babies in India will have a correspondingly higher risk of adiposity. Indirect support for this outcome has come from the demonstration of increased risk of adiposity and metabolic syndrome in mothers of 'high'-birth-weight babies in Pune Children's Study (Yajnik *et al*. 2003*b*). The variable relationship in different populations between weight and adiposity should warn against generalizations based on studies in one population.

Thus, it would appear that in developing populations both the lower and higher birth weights hide an extent of adiposity that might herald risk of future adiposity and associated conditions. The contribution of genetic factors and intrauterine environment to these differences needs to be carefully studied. These ideas were discussed >20 years ago in the 'fuel-mediated teratogenesis' hypothesis (Freinkel, 1980). These facts should warn against the simplistic idea that increasing the birth weight of babies in the developing world would remove the problem of obesity, diabetes and heart disease.

Summary

The biology of the current epidemic of obesity is only beginning to be understood. In addition to the much-discussed role of lifestyle factors and genes, the new exciting candidate is the intrauterine environment. A fetus 'compromised' by relative lack of nutrients deposits more adipose tissue than lean tissue, and this action may be driven by the need for 'brain preservation'. Such mechanisms seem to operate prominently in developing countries like India. Increasing affluence and better nutrition of mothers may further exaggerate this tendency, possibly because of intergenerational influences. These factors are still poorly understood. Studies in urban Indians and those who have migrated abroad will provide important information on the fate of the 'thin-adipose' Indian phenotype after better nutrition. Better understanding of the biology of 'adipogenesis' *in utero* may be vital in preventing the epidemic of obesity.

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