FETAL ORIGINS OF ADULT DISEASE: WHERE DO WE STAND?

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Abstract:

The 'fetal origins' hypothesis would predict that the rising epidemic of diabetes and CHD in India would be due to poor intrauterine growth of the India babies. While this explanation may be valid to an extent, the higher prevalence of these disorders in urban compared with rural India (where birth weights are lower) would suggest a significant role for postnatal factors. In a cohort of 477 children born in the King Edward Memorial Hospital, Pune, we found that at eight years of age, current obesity strongly predicted insulin resistance. When this effect was allowed for, low birth weight was significantly associated with insulin-resistance variables and other cardiovascular risk factors. Children who were born small but had grown heavy (or tall), were the most insulin resistant and had the highest levels of cardiovascular risk factors. Accelerated growth in relation to mid parental height was similarly predictive. Poor intrauterine growth also predicted higher central adiposity at eight years of age. We have also studied maternal nutrition and fetal growth in six villages near Pune. A newborn Indian baby is small (2650g, SD score (SDS)- 1.6 compared with an average white Caucasian baby born in the UK) and 'thin' (ponderal index 2.45 kg/m^3, SDS-1.2), but has preserved its subcutaneous fat (subscapular skinfold thickness SDS-0.6). The thinness of the Indian babies is due to poor muscle and small abdominal viscera. We have proposed this composition as the 'thrifty phenotype' of Indian babies. Maternal size and intake of certain food groups during pregnancy were important determinants of the baby's phenotype. Thus, the small Indian babies are programmed to deposit fat from their intrauterine life. Exaggeration of this tendency in later life is associated with Insulin resistance syndrome. Control of the insulin-resistance epidemic in India might depend on improved intrauterine development and prevention of childhood obesity.

Key words : Insulin Resistance: Type 2 diabetes: Coronary heart disease: Intrauterine growth retardation: Childhood obesity: Indian babies

CHANGING SCENE OF DEGENERATIVE DISEASES:

The traditional view of the nutritional risk for chronic degenerative diseases (diabetes, hypertension and coronary heart disease [CHD]) consists of the relationship of increased prevalence of these disorders with obesity, excess dietary intake of energy, fats and salt and reduced physical activity. Not long ago these degenerative diseases were considered diseases of affluence and over nutrition. Over last few decades, some developed countries have shown a decline in the prevalence of CHD; in some, the prevalence has shown a reversal of socioeconomic gradient (i.e. more affection of the poor rather than the rich). At the same time many of the developing countries (previously thought to be protected) are facing a rapidly rising epidemic of diabetes and CHD.

GENES AND ENVIRONMENT

Occurrence of diabetes and other related disorders is traditionally linked to a 'thrifty genotype' which it is proposed enhanced survival in subsistence conditions in the past, but becomes detrimental in a modern context of plentiful food and reduced physical activity (1). The most obvious phenotypic expression of the thrifty genotype is obesity. Though teleologically a useful concept, no specific gene markers have yet been described. A recently proposed alternative explanation is the 'fetal origins' (2) or the 'thrifty phenotype' hypothesis (3). Prof Barker noticed a strong geographical association between mortality from CHD in adults and infant mortality around the time these people were born (4). Thus, CHD mortality was high in the relatively poor areas in Britain where infant mortality was high. He reasoned that high infant mortality reflected intrauterine malnutrition in these communities. In a series of brilliant epidemiological studies, he demonstrated in different places in the UK, a strong association between poor intrauterine growth (measured as low birth weight, short length, thinness, smaller head circumference etc) and adult cardiovascular disease and type 2 diabetes (5,6). Soon it became clear that the strongest relation of poor intrauterine growth was with the prevalence of the so called 'insulin resistance syndrome' (IRS, also called 'syndrome X': glucose intolerance, high circulating triglyceride and low HDL-cholesterol concentrations, hypertension and CHD).Initially received with skepticism, the relationship of poor

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intrauterine growth with adult IRS has been demonstrated in different populations of the world (7). 'Barkerology' is now an accepted phenomenon.

FETAL PROGRAMMING

Though the concept of 'fetal origins' is now well established the mechanisms involved are not clear. It has been suggested that a growing fetus faced with adverse conditions, responds with endocrine, metabolic and vascular or other structural adaptations (2,5,8). The commonest adversity for the fetus may be 'malnutrition'. The first priority for a developing fetus is survival, and during the 'lean' periods this is achieved by reduced rate of growth (intrauterine growth retardation, IUGR). The time during intrauterine life when this occurs determines the systems affected. The 'fetal origins' hypothesis suggests that these adjustments are 'imprinted', affecting the response of the system in future life ('programming'). Insulin resistance seems to be one such survival mechanism in response to fetal malnutrition. Poor maternal nutrition may be the most common cause of fetal malnutrition, though this has not been proved beyond doubt. Maternal 'nutrition' might thus determine the future risk of type 2 diabetes and cardiovascular disease in the offspring. If proved correct, this hypothesis may have profound implications for prevention of these disorders.

ENVIRONMENT: EARLY LIFE, LATER LIFE OR BOTH?

The relationship of poor intrauterine growth (mostly represented by low birth weight) with IRS and cardiovascular disease was obvious only when the effect of current (adult) obesity was adjusted for in the statistical analysis (9). For some time, attention was focussed only on intrauterine environment which was the new exciting discovery. However, the worst sufferers of the IRS were always those who were born small but had grown big in later life.

THE THIRD WORLD SCENCE

Majority of research in the 'fetal origins' area has been done in the UK and other developed countries, where birth records of individuals born in early part of this century were available. The largest burden of intrauterine malnutrition is, of course, in the developing world. In India, mothers suffer from chronic malnutrition and one third of the babies are born low birth weight (<2.5 kg) predominantly due to an asymmetric growth retardation (10). There has been an explosion of diabetes and CHD during last few decades especially in the urban cities (11,12). There is thus, a priori reason to believe that 'fetal origins' could contribute to this epidemic. However, there is an obvious paradox in the Indian scenario. Maternal malnutrition is more widespread and birthweights are lower in rural India (~2700g) than those in the cities (~2900g). This would predict a higher prevalence of diabetes and CHD in rural India if 'fetal origins' were the sole explanation. The situation is exactly opposite; diabetes and CHD are at least four times more common in the cities than in the villages. The explanation for this 'paradox' is found in the adult body size. The mean BMI of the adult rural Indians is 19.0 kg/m^2 while that of the urban adults is 23 kg/m^2. Thus, the urban adults overgrow their rural counterparts by 130% while they were only 109% larger at birth. Factors related to postnatal growth clearly influence the cardiovascular risk, probably on the background of intrauterine programming.

STUDIES IN INDIAN CHILDREN

Risk of being small

In collaboration with Prof Barker and Dr Caroline Fall we investigated the relationship between birth weight and glucose and insulin metabolism in four year old children, born in the King Edward Memorial Hospital, Pune. Birth weights were available in the labour room register. We traced over 200 children whose birth weight was >2.0 kg at term and who had not required any special postnatal care. Standard oral glucose tolerance test (1.75g/kg anhydrous glucose load) was performed, and circulating concentrations of glucose, insulins, IGF-1, lipids (total and HDL-cholesterol and triglycerides) and blood pressure were measured. Growth was assessed by detailed anthropometry (13).

Plasma glucose and insulin concentrations were strongly related to current weight and body fat measures (skinfold thicknesses). When this strong influence of current body size was adjusted in statistical analysis, plasma glucose and insulin concentrations 30 mins after glucose load were inversely related to birth weight (Figure 1 and 2). There was an interaction between birth weight and subsequent growth. children who were born small and grown big at four years of age had the highest plasma glucose and insulin concentrations 30 mins after oral glucose. Higher glucose with higher insulin concentrations are indicative of insensitivity of the peripheral tissues to metabolic actions of insulin, particularly in the muscle and the adipose tissue. We also noticed an inverse relationship

between head circumference at four years of age and 30 min plasma glucose and insulin concentrations. A substantial part of the head circumference (2/3 rd of the adult size) is attained at birth and thus four year measurement is a surrogate measure, at least in part, of the intrauterine growth. We thus interpreted this finding as confirming the relationship between poor intrauterine nutrition and subsequent development of insulin resistance. Birth weight was inversely related to blood pressure but not related to fasting and 120 min plasma glucose and insulin concentrations, and was inconsistently related to circulating lipid concentrations.

Figure 1: Plasma glucose and insulin concentrations 30 minutes after oral glucose in 4 year old children by categories of birth weight. Significance of the trend corrected for age, sex and current body weight.

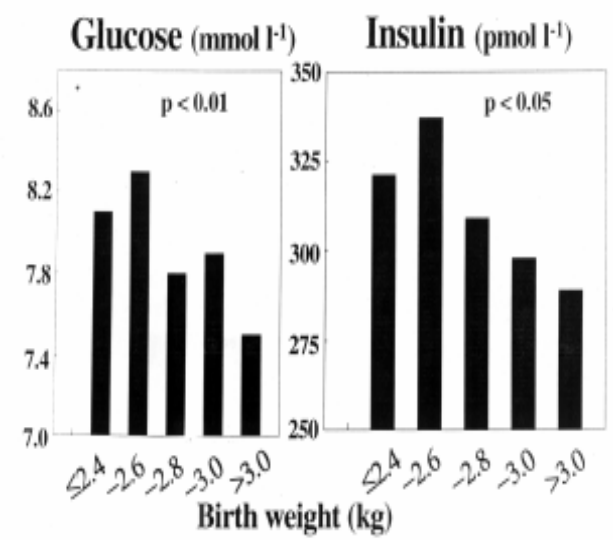
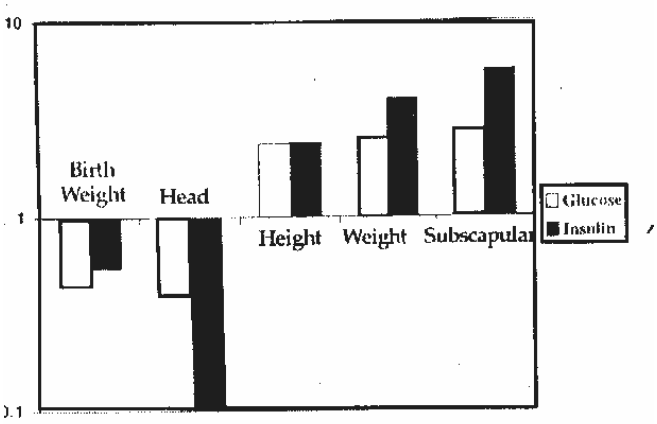


Figure 2: Relative risk of belonging to the highest quartile of plasma glucose and insulin concentrations 30 minutes after oral glucose between extreme quartiles of birth weight and anthropometric measurements at 4 years of age.



We studied these children again at eight years of age. Additional children were included in the study to expand the range of birth weights. A total of 477 children (Table 1), and their parents (Table 2) were studied. Plan of the study was similar to that at four years of age (14). The findings have improved our understanding of the interaction between intrauterine and post natal growth in relation to subsequent development of IRS and the cardiovascular risk.

Table 1 : Anthropometric measurements in eight year old children. Note low birth weights and lack of obesity at eight years of age.

	Girls (n=221)	Boys (n=256)
Birthweight (kg)	2.7	2.8*
Weight (kg)	21.3	22.0
Height (cm)	124.7	125.4
MUAC (cm)	16.3	16.2
Head (cm)	49.9	50.4*
Triceps (mm)^g	8.1	6.7***
Subscapular (mm)^g	6.5	5.5***

Figures represent mean values, g = geometric mean
MUAC= Mid Upper Arm Circumference, Head = Head Circumference Triceps and Subscapular are skinfold thicknesses
*p<0.05, ***p<0.001 refer to the significance of difference between boys and girls

Table 2 : Anthropometric measurements in parents of eight year old children. Less number of fathers participated the study .

	Fathers (n=395)	Mothers (n=459)
Age (yrs)	38	32
Weight (kg)	63.3	52.4
Height (cm)	166.0	153.1
BMI (kg/m^2)	22.9	22.3

Figures represent mean values
BMI= Body Mass Index

Risks of being born small and growing big

We confirmed the strong and direct relationship between current indices of 'obesity' (weight, body mass index [BMI] and calculated fat mass) and components of the IRS (plasma glucose, insulin, triglyceride and HDL-cholesterol concentrations, a calculated index of insulin resistance [HOMA-R] (15) and systolic blood pressure) and also found a relation with plasma total cholesterol and

Table 3 : Correlations of cardiovascular risk factors at 4 years and 8 years of age with birthweight and concomitant anthropometric measures.

	4 Years					8 years					
	Birth weight	weight	Height	Head	Subscapular skinfold	Mid arm	Birth weight	weight	Height	Head	Subscapular skinfold	Mid arm
HOMA R	-0.06	0.25***	0.17**	-0.06	0.13*	0.26***	-0.16***	0.41***	0.26***	0.14**	0.41***	0.39***
Cholesterol	0.11*	0.12*	0.11*	0.03	0.04	0.12*	-0.30***	0.22***	0.15**	0.04	0.19***	0.20***
HDL	-0.13*	0. 09	0.06	0.03	-0.09	0.02	0.39***	0.07	0.10*	0.14**	0.01	0.08
Triglycerides	-0.44***	-0.03	-0.10*	-0.01	0.09	0.07	-0.27***	0.17***	0.03	0.012	0.17***	0.15**
Systolic BP	-0.23***	0.21***	0.17**	0.09	0.01	0.15**	-0.43***	0.13**	0.05	-0.004	0.14**	0.13**

Head and Mid arm refer to circumference, HOMA-R= Calculated insulin resistance variable. Cholesterol, HDL-Cholesterol and Triglycerides refer to plasma concentrations, BP= Blood pressure.

Figures represent Correlation Coefficients, *p<0.05, **p<0.01, ***p<0.001 (adjusted for age and sex)

Correlation coefficients for birthweight are adjusted for age, sex and weight at 4 and 8 years respectively.

LDL-cholesterol concentration (Table 3). At eight years of age, after adjusting for current obesity indices, birth weight was inversely related to a range of cardiovascular risk factors including many IRS variables. Highest levels of insulin resistance (Figure 3) and other cardiovascular risk factors were found in children who were born small and had grown 'big' . Insulin resistance (HOMA-R) and plasma cholesterol concentration were related not only to indices of obesity at eight years of age but also to the height of the child. (Table 3). Such a relationship has previously not been described in children. Intriguingly, insulin resistance in children was inversely related to midparental height. In other words children born to shorter parents were more insulin resistant than those born to taller parents. Both maternal and paternal height contributed independently to this relationship. Even more interestingly, children who had grown fatter, and taller in relation to midparental height were the most insulin resistant (Figure 4).

Figure 3 :

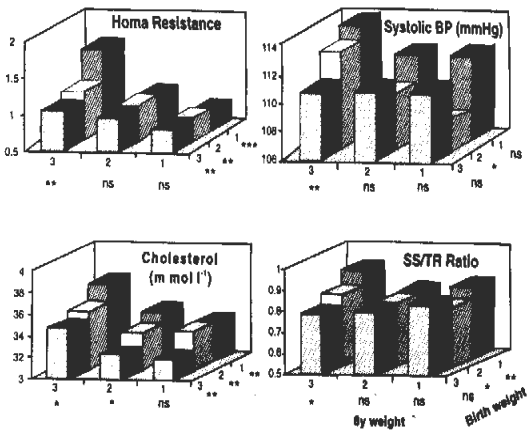


Figure shows mean levels of insulin resistance variable (HOMA-R), systolic blood pressure, serum cholesterol concentration and subscapular-triceps skinfold ratio (SS/TR) at 8 years of age by tertiles (1,2,3) of birth weight (rows) and 8 year weight (columns). Significance level for the trend in each row and column (adjusted for age and sex) is shown at the end (ns = not significant, *p<0.05, **p<0.01,***p<0.001).

Figure 4 :

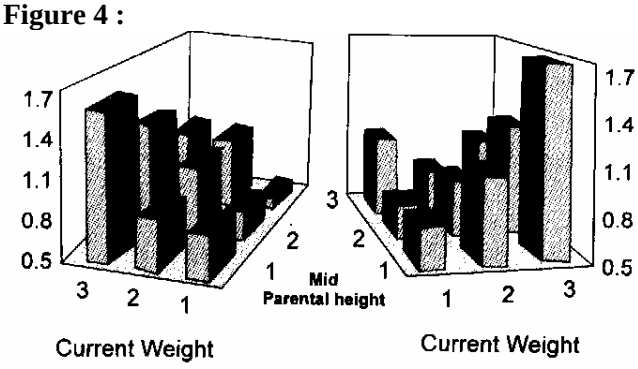


Figure shows mean levels of insulin resistance variable (HOMA-R) at 8 years of age by tertiles (1,2,3) of 8 year weight or height (columns) and midparental height (rows). Children born to short parents but heavier or taller at 8 years of age were the most insulin resistant.

We investigated the characteristics of children who possesed more than one IRS variable. Increasing expression of the IRS was associated with increasing current obesity (weight and fat mass), increasing central adiposity (subscapular-triceps ratio, STR) and increasing height but decreasing birth weight (Table 4). Thus, the IRS expressed progressively more severely in low birth weight children who grew progressively more 'fat' or 'tall' during childhood. 'Catch up' growth thus appears to be associated with an adverse profile of IRS and cardiovascular risk. Growth velocity of each component of growth between four and eight years of age (weight, fat mass, height, head circumference and muscle) was even more strongly associated with insulin resistance than the individual measures at eight years of age (Table 5).

Table 4 : Clustering of insulin resistance variables, birthweight and anthropometric measures at eight years of age.

	n	Birth Weight (kg)	8 year Weight (kg)	8 year Height (cm)	8 year Fatmass (kg)	8 year SS/TR	F-Insulin (pmol l^{-1})
Non Resistant	364	2.78	20.4	124.2	3.21	0.81	20.0
HOMA-R	83	2.72	23.3	127.6	4.03	0.81	40.3
HOMA-R+BP	16	2.46	23.3	129.1	3.89	1.24	44.7
HOMA-R+ BP + TG	11	2.75	27.5	130.9	6.52	1.04	63.7
HOMA-R+ BP+TG+HDL	3	2.36	30.7	129.6	6.85	0.97	63.0
p		***	***	***	***	*	***

SS/TR = Subscapular / Triceps skinfolds ratio, F= Fasting, BP= Systolic blood pressure, TG=Triglycerides, HDL = High Density Lipoprotein Cholesterol.
Figures represent mean values except n (number)

p represents significance for trend adjusted for age and sex, the birth weight is also adjusted for 8year weight.

Insulin resistance was calculated by HOMA model, childrenbelonging to the uppermost quartile were labeled resistant (HOMA-R) , other children are called Non Resistant. Insulin resistant children who also belong to the uppermost quartile of systolic blood pressure, plasma triglycerides concentration and to lowest quartile of plasma HDL concentration were progressively larger at 8 years in all body measurements, and had progressively lower birth weight (adjusted for 8 year weight)

Table 5 : Correlations between growth velocity and Insulin Resistance (HOMA-R)*

Growth Velocity	Correlation Coefficient	p**
Birth to 4 years		
Weight	0.18	< 0.05
4 years to 8 years		
Weight	0.50	< 0.001
Height	0.36	< 0.01
Head circumference	0.24	< 0.01
Subscapular skinfold	0.42	< 0.01
Triceps skinfold	0.37	< 0.01
Mid-arm circumference	0.41	< 0.01

* n=190
** P values adjusted for age and sex

We have thus noticed a very interesting interaction between intrauterine growth, and post natal growth as well as growth velocity in relation to the insulin resistance syndrome in childhood. Our children are relatively small and thin by international standards (Table 1) and therefore, an imbalance or discordance between intrauterine and post natal growth seems more strongly associated with insulin resistance, than poor intrauterine growth or childhood 'obesity' alone. An 'upward' movement on the trajectory of growth started in utero ('centile crossing') is associated with higher insulin resistance.

Our findings support and expand on the observations made in two previous studies in children. Whincup and colleagues studied over 1000 children at a mean age of ten years (16). They showed that childhood growth was a much stronger determinant of glucose tolerance and insulin resistance (fasting plasma insulin concentration and HOMA) than birth size. There was an interaction between intrauterine growth (low birth weight and ponderal index) and subsequent growth such that those who were born small but subsequently 'caught up' were the most insulin resistant (Figure 5). Crowther et al reported on black children from South Africa (Table 6)(17). Low birth weight was associated with higher 30 min glucose concentration during an oral glucose tolerance test at age of seven years. Relationships of current obesity were much stronger and with a wider range of glucose and insulin parameters. Growth velocity for weight was a strong predictor of insulin resistance at seven years of age. Authors concluded that intrauterine growth retardation coupled with increased growth velocity during post natal life was related to insulin resistance.

Figure 5

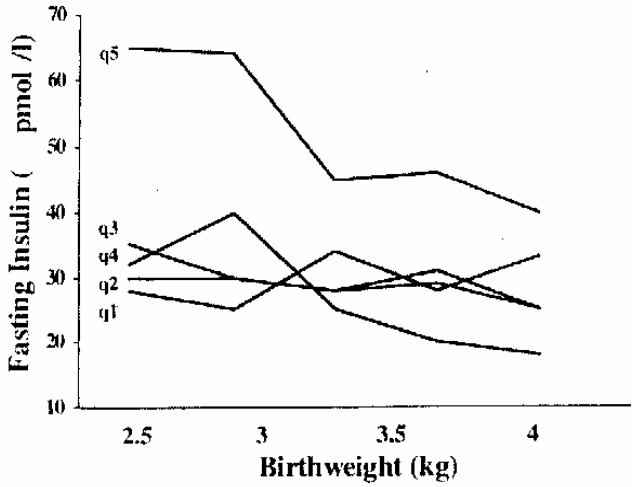


Figure shows fasting plasma insulin concentrations in 591 white Caucasian 10 year old children by categories of their birthweight and quintiles of ponderal index at 10 years of are (q1 to q5 (16).

Table 6

	30 min Glucose	30 min Insulin	120 min Insulin	HOMA R
Birthweight	(-) 0.20*	-	-	-
Height 1 year	(-) 0.19	-	-	-
Subscapular 5 years	0.19*	0.23**	-	-
Triceps 5 years	0.21*	0.22*	0.19*	-
Height 7 year	(-) 0.22*	-	-	-
BMI 7 year	-	0.40***	0.27**	0.24*
Weight Velocity (Birth - 7 year)	-	0.36**	0.30**	0.18*

Subscapular and triceps are skinfolds.

Figures represent correlation coefficients, *p<0.05, **p<0.01, ***p<0.001.

Correlation of birthweight and postnatal growth parameters with circulating glucose and insulin concentrations (30 minutes and 120 minutes, during an oral glucose tolerance test) and calculated insulin resistance variable (HOMA-R) at 7 years of age in 152 black South African children (17).

Studies in adult populations have also shown the interaction between small birth size and adult obesity (BMI) in relation to insulin resistance syndrome outcomes (diabetes and CHD). For example, diabetes and impaired glucose tolerance were more common in people who had small birth weight but had grown more obese at 65 years of age (9). Similarly syndrome X was most prevalent in those born small but grown most obese as adults (6). A recent study in Finland was able to trace not only the birth records but also the childhood growth in a large cohort of people (18). Mortality from CHD was higher in those who had low birth weight and were thin at birth (low Ponderal Index). Cardiovascular mortality was even higher in those who were born small but became obese as children. The childhood growth curve (BMI) of people who died of cardiovascular disease was persistently above the median for the whole population. In a study of people born in Mysore (India) , the highest prevalence of CHD at 45 years of age was found in individuals who had lower weight, height or head circumference at birth, but who had 'normal' weight as adults (19). Thus, poor intrauterine growth reduces the threshold of risk of adult obesity because the 'normal' adult weight represents an 'upward' movement during postnatal growth in the small babies. In populations with low birth weight this would mean that the risk of IRS will be much higher at relatively lower adult BMI compared to the well nourished populations. This is dramatically obvious in rural Indian adults. We studied adults >40 years of age (n= 321, mean age 55 years) in the village of Pimpale Jagtap, near Pune City. The mean BMI was 19 kg/m^2. The relative risk for men in the highest quartile of BMI (mean 23.5 kg/m^2) compared to those in the lowest quartile (mean 16.5 kg/m^2) was 2.04 for glucose intolerance (impaired glucose tolerance + diabetes, WHO criteria), 4.51 for hypertension (blood pressure >140/90) and 1.54 for CHD (Rose-WHO questionnaire and Minnesota coded resting electrocardiogram) (20). Clearly, there is a need to reconsider the BMI criteria of obesity in the developing world.

Intrauterine malnutrition and subsequent obesity

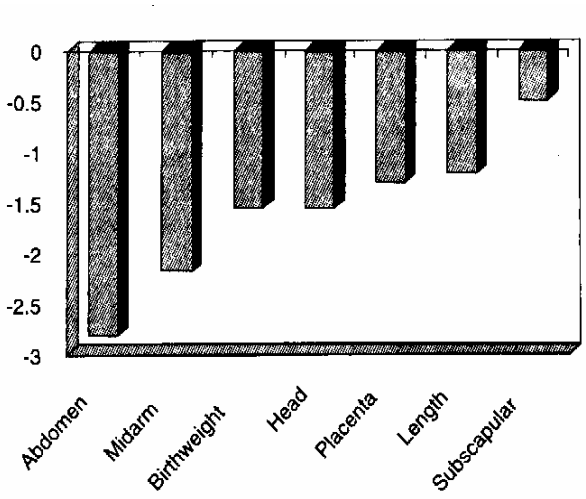
Young Dutch adults born to mothers who faced famine conditions during early gestation, showed an excess risk of obesity (21). The association between poor intrauterine growth and later obesity (BMI) has been reviewed (22, 23). It is now clear that central (predominantly visceral) fat distribution is an even more powerful risk factor for the IRS than the total body fat. In our study of eight year old children, we noticed a significant relationship between low birth weight and high STR, which is thought to be a better indicator of central fat deposition in children than the waist/hip ratio (WHR). Low birth weight has been shown to be associated with higher WHR (24) and higher STR (28) in adults, and with higher STR in children (14,26) and adolescents (27). It would appear that malnourished fetus preferentially deposits fat in the truncal region during postnatal life.

INTRAUTERINE GROWTH OF INDIAN BABIES: A THRIFTY PHENOTYPE

We had a unique opportunity to study fetal growth and body composition in relation to maternal nutrition in six villages near Pune (Pune Maternal Nutrition Study, PMNS) (28).We studied over 800 pregnancies in mothers whose anthropometry was measured serially from before the time they became pregnant. Maternal food intake, physical activity, biochemical parameters and the fetal growth (ultrasound) were studied during pregnancy. Babies were measured in detail at birth. Mothers were small and thin (mean weight 42 kg, height 1.52 m and BMI 18.0 kg/m^2) and gave birth to small and thin babies (full term babies mean birth weight 2.65 kg, ponderal index 24.5 gm/cm^3). There were striking peculiarities of the body composition of Indian babies when compared with white Caucasian babies

(mean birth weight 3.45 kg, ponderal index 27.3 gm/cm^3). Indian babies were small in all respects but there was a scheme in their smallness. Birth weight, head circumference and height were smaller to a similar extent, whereas soft tissues were differentially affected. Protein rich soft tissues (skeletal muscle and abdominal viscera) were the most affected, while subcutaneous fat was the most preserved body component (Figure 6). In other words, the small and thin, growth retarded Indian baby, is thin in muscle and viscera, but is relatively fat! We consider this as the 'Indian thrifty phenotype' which is remarkably similar to the 'thin and fat' adult Indian who is insulinresistant and is experiencing an epidemic of insulin resistance syndrome in the last few decades. When we compared our newborns with those born in the Netherlands, where both subscapular and triceps skinfolds were measured, it was obvious that in the Indian babies subscapular, rather than triceps fat, is deposited more prominently, suggesting that the propensity of the Indians for central obesity is programmed in utero.

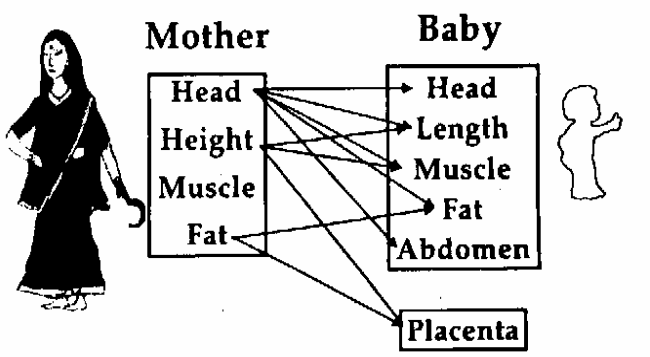
Figure 6 : Mean SD scores for birth measurements in Pune babies compared with Southampton babies. The Southampton mean is represented by 0.



Maternal determinants of fetal growth

In our study, maternal intake of energy and proteins was not related to fetal growth, maternal intake of fat was weakly related to birth weight. Frequency of consumption of dairy products, green leafy vegetables and fruits was associated with larger birth size (29). Maternal prepregnant body size was the most important determinant of fetal growth. Of maternal body components, head circumference (a surrogate of mother's own early life growth and nutrition) was a significant determinant of all aspects of fetal growth, maternal height determined neonatal length, and maternal fat mass determined neonatal fat (Figure 7). The fattest babies were born to mothers who were short and fat (poor growth in early life, energy excess in later years). Thus, maternal 'nutritional history' (as evident in different body measurements) reflected in different body compartments of the fetus. We interpret our findings to indicate that a 'proportionate' improvement in fetal growth would require improved maternal nutrition throughout her life rather than nutritional supplementation after she becomes pregnant. Nutritional supplementation in late pregnancy (typical of all intervention programmes) might make babies more fat, without much affecting brain (head) and skeletal (length) growth. Such phenotype may have improve neonatal survival but could prove detrimental for the long term cardiovascular risk.

Figure 7



Relationship between maternal anthropometric measurements before pregnancy and neonatal measurements at birth. Note that maternal head circumference (a surrogate for early life growth and nutrition) is significantly related to all of the neonatal measurements except placental weight. Maternal height is related to neonatal height, muscle and maternal fat (fat mass calculated from 4 skinfold thicknesses) to neonatal fat (subscapular and triceps skinfolds). Maternal midarm circumference is not related to any of the neonatal anthropometry. Placental weight was related to maternal height and fat.

ORIGINS OF INSULIN RESISTANCE SYNDROME : THE BIOLOGY OF TRANSITION?

Thus, in our studies, we have been able to define a pattern of intrauterine growth in Indian babies, which is organ and muscle depleted but fat preserving. The mechanisms linking these growth perturbations with insulin resistance syndrome and increased cardiovascular risk are only beginning to be understood. The central issue seems to be the

fundamental biological drive in a developing fetus to preserve the brain (head) growth. This is achieved by preferential diversion of blood flow to the head and by making other tissues insensitive to action of insulin and related growth hormones. These adaptations allow diversion of nutrients from the developing peripheral tissues to the brain. At cellular and molecular level, this probably expresses as alterations in the structure of membranes as well as altered intracellular metabolic pathways. We speculate that the endocrine and metabolic adaptations which allow the best use of available nutrients for survival in utero, programme the pathways of nutrient utilisation in later life. In situations of positive energy balance this leads to excess fat deposition, especially in 'central' depots, which aggravates insulin resistance. There is recent exciting data to show that an adipocyte may influence insulin sensitivity and endothelial function not only by excess release of non-esterified fatty acids, but also by release of a number of other molecules, including leptin and other proinflammatory cytokines (31). Urban environment makes the matters worse by providing a backdrop of pollutedand infective environment (32). Thus, babies born in countries undergoing a rapid transition would face malnutrition in their intrauterine life and a state of relative over nutrition in later life, which provides opportunities for 'catch up'. Babies which 'catch up' in body weight, fat and height are more insulin resistant as children . We need to investigate factors which determine which babies are able to catch up. The role of post natal nutritional supplementation in low birth weight babies needs to be carefully assessed in view of the long term effects of insulin resistant state on development of diabetes and CHD (33). It may be more rewarding to avoid 'obesity' in those who were small at birth. Given the strong association of socioeconomic growth with increasing obesity, there may be some inevitability to the occurrence of IRS in the developing populations. It is fascinating that the Indian saint Tukaram
(1590 AD - 1630 AD) from Pune advised

zoivalao AnaMto tOsaocaI rhavao
ica%tI Asaao Vavao samaaQaana.

Live as God wished you to, be satisfied with what he has given you.

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