

# A Critical Evaluation of the Fetal Origins Hypothesis and Its Implications for Developing Countries

## Early Life Origins of Insulin Resistance and Type 2 Diabetes in India and Other Asian Countries<sup>1</sup>

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**ABSTRACT** There is a rapidly increasing epidemic of type 2 diabetes in India and other Asian countries. The *thrifty genotype* and the *thrifty phenotype* are two nonexclusive explanations. People in the Indian subcontinent have faced undernutrition for many generations, and Indian babies are among the smallest in the world. However, the diabetes epidemic is of recent origin, and diabetes is more common among urban than rural Indians despite the higher birth weight of urban babies. This suggests that postnatal factors must also contribute. Thus, a life-course model of evolution of insulin resistance and type 2 diabetes, incorporating fetal, postnatal and adult components, seems most appropriate. For a given BMI, Indians have a higher percentage of body fat and more visceral fat than members of other populations. This *thin-fat phenotype* is present at birth. Neonatal size and body composition are influenced by parental size, maternal food intake, physical activity and circulating concentrations of nutrients and metabolites (folate, glucose, triglycerides, cholesterol etc.). Maternal insulin resistance promotes transfer of nutrients to the fetus. Accelerated childhood growth is another risk factor for adiposity and insulin resistance, especially in children born small. Childhood growth seems to be more influenced by paternal genetic factors, whereas intrauterine growth is more influenced by maternal factors (intrauterine environment). Urban lifestyles, including poor diet and sedentary habits, promote further obesity, insulin resistance and type 2 diabetes. These factors may be amenable to correction. Prevention of type 2 diabetes must begin in utero and continue throughout the life course. J. Nutr. 134: 205–210, 2004.

**KEY WORDS:** • type 2 diabetes • birth weight • fetal programming • Asians

India and other countries in Asia are experiencing rapidly escalating epidemics of diabetes and cardiovascular disease. The prevalence of type 2 diabetes in urban Indian adults has increased from < 3% in the 1970s to > 12% in 2000 (1). Similar numbers of adults have impaired glucose tolerance (IGT).<sup>3</sup> India has the highest number of diabetic patients of any country. Over the past 25 y, the prevalence of coronary heart disease (CHD) in Indian adults has increased from < 2% to ~10% (2). It is predicted that by 2025 India will have >60 million diabetic patients and that CHD will be the leading cause of death in adults (3,4). In other words, one in five

diabetic patients in the world will be Indian, and three out of four will be from developing countries (4). This phenomenal rise in diabetes and CHD has been ascribed to rapid changes in demographic, nutritional and socioeconomic factors, the so-called epidemiologic, nutritional and economic transition. It is customary to ascribe the susceptibility to diabetes to the evolutionary enrichment of *thrifty genes*, which enhanced the chances of survival in the past when food supplies were scarce and intermittent, but have become detrimental in contemporary conditions of plentiful food and sedentary lifestyles (5). An alternative explanation is the recently proposed *thrifty phenotype* hypothesis (subsequently generalized as *fetal origins*) which ascribes the epidemic to an unfavorable intrauterine environment (6,7). This thinking is based on the observation of an inverse relationship between birth weight and risk of diabetes and metabolic syndrome in elderly populations. The two explanations are not necessarily exclusive and may compliment each other. Indeed, the *fetal insulin* hypothesis envisages that the association between low birth weight and diabetes could have common genetic determinants but highlights the suggestion that the intrauterine environment may influence this relationship (8).

### *Fetal origins hypothesis in the developing countries of Asia*

Hales and Barker proposed that undernutrition at critical periods in intrauterine development causes permanent changes in the structure and/or function of the developing

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<sup>3</sup> Abbreviations used: CHD, coronary heart disease; CVD, cardiovascular disease; IGF-1, insulin growth factor-1; IGT, impaired glucose tolerance; LBW, low birth weight; HOMA, homeostatic model assessment; NEFA, nonesterified fatty acid.

systems of the fetus (9,10). This increases susceptibility to disease in later life. Of the many possible insults during the intrauterine life, Hales and Barker favored undernutrition as the most likely cause, though many factors could operate in a similar manner. The original hypothesis (6) overlooked the classic association among maternal diabetes, fetal macrosomia and increased risk of diabetes for the offspring. A recent version of the thrifty phenotype hypothesis allows for this (11). However, the relationships among maternal nutrition, fetal nutrition, neonatal size and later diabetes appear to be more complicated than originally proposed (12). This may have important implications for preventive strategies.

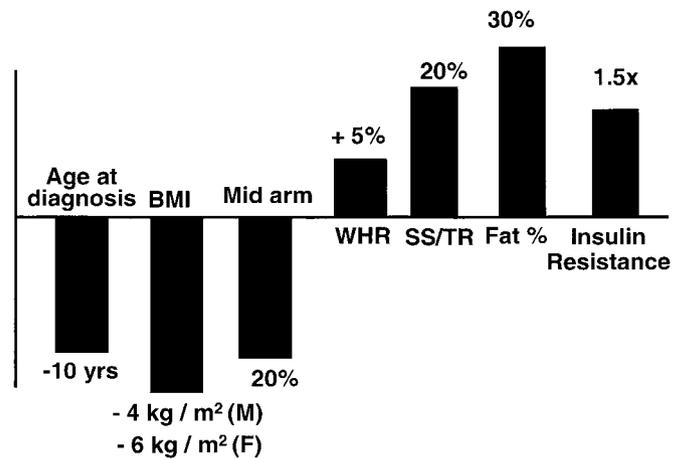
The crucial importance of the intrauterine period in determining health and disease is not difficult to understand if one appreciates that humans begin life as a single cell and that more than three quarters of total cell divisions occur in utero. Substantial growth and development is completed before birth. Intrauterine growth and development involves orchestrated gene expression regulated by the environment of the fetus, which is of course largely regulated by the mother.

How do these concepts apply to the situation in the Indian subcontinent and other countries in Asia? Asians as a group have small body size. Mothers (especially in rural India) are small and thought to be chronically undernourished because of their low BMI. Iron and other nutrient deficiencies are common. Indian babies are the smallest in the world. One-third of Indian babies are born with low birth weight (LBW; <2.5 kg) as are half of those born in Bangladesh. Thus, more than half of the LBW babies in the world are born in Southeast Asia (13). It is thus possible that maternal and fetal undernutrition contribute to the diabetes epidemic in the Asian countries.

However, many observations point toward a more complex situation and suggest that fetal undernutrition is unlikely to be the sole explanation for the epidemics of type 2 diabetes and CHD in India. Small size at birth and LBW have been present for many centuries, whereas the diabetes epidemic is recent. Urban Indian babies are heavier (i.e., better nourished) than rural babies (mean weight ~ 2.9 and ~2.6 kg, respectively) but have >5× higher susceptibility to diabetes.

Temporally, the diabetes epidemic is associated with a rapid epidemiologic and nutritional transition rather than smaller size at birth. In the past 50 y, food and milk production have substantially increased (the “green” and “white” revolutions) and per capita food consumption has also increased. Mean birth weight has increased by 0.1 kg; infant mortality has declined; deaths from starvation have almost disappeared, and those from infectious diseases are on the decline. Rural to urban migration is increasing. Among urban residents, “junk food” consumption has soared and physical activity has dramatically declined. As a consequence, obesity is rapidly increasing. Life expectancy has increased from 42 to 62 y. All these factors have contributed to the rising epidemic of diabetes. It is obvious that the insulin resistance syndrome evolves continuously over an individual’s lifetime, thereby calling for a life-course model for its management.

At the Diabetes Unit, King Edward Memorial Hospital, Pune, we investigated aspects of body size and composition in rural and urban Indians in relation to their metabolic and endocrine characteristics (14). We also studied the relationship between intrauterine and childhood growth and the insulin resistance syndrome. **Figure 1** shows the characteristic body composition of Indian type 2 diabetes patients. We compared demographic, anthropometric and metabolic-endocrine characteristics of newly diagnosed type 2 diabetes patients in urban Pune with those of newly diagnosed type 2



**FIGURE 1** Comparison of characteristics of newly diagnosed Type 2 diabetes patients in India with those in the United Kingdom (not drawn to scale). Bars above the line indicate higher levels in Indian patients. Insulin resistance was calculated from the homeostatic model assessment (HOMA) model. Abbreviations and labels used: mid-arm, midarm circumference; SS/TR, subcapsular-triceps skinfold ratio; WHR, waist-hip ratio. Adapted from Yajnik (14).

diabetes patients in the United Kingdom. There are striking differences in the physical characteristics of these two populations, which are reflected in different patterns of diabetes. Indian diabetes patients are diagnosed a decade earlier and are considerably thinner than their U.K. counterparts (BMI = 23.9 and 28.5 kg/m<sup>2</sup>, respectively). Indians have thinner limbs, suggestive of smaller muscle mass. Despite their thinness they are centrally obese, with a higher waist-hip ratio and higher subscapular-triceps skinfold ratio than their U.K. counterparts (14). Many studies show that Indians have more body fat at each BMI compared with Caucasians and black Africans (15,16). Indians also have higher levels of central obesity (measured as waist circumference, waist-hip ratio, visceral fat mass and posterior subcutaneous abdominal fat) compared with these populations. This is reflected in higher plasma nonesterified fatty acid (NEFA) and triglyceride concentrations, hyperinsulinemia in fasting as well as postglucose challenge, and higher insulin resistance (17). Thus, Indians have an unusual *thin-fat* body composition associated with the insulin resistance syndrome. Migrant Indians also have greater insulin resistance than native local populations (18,19), which relates to central obesity (measured as waist-hip ratio, level of visceral fat, central subcutaneous fat or body fat percentage).

#### **Rural-urban migration, increasing adiposity, insulin resistance and type 2 diabetes**

Recently we studied body fat and insulin resistance in middle-aged males in villages, urban slums and urban middle-class residences in and around Pune (Table 1). Urban slum residents are mostly first-generation migrants from villages, whereas middle-class residents have settled in cities for many generations. Despite low BMI, a considerable proportion of these men were adipose: at a mean BMI of 21, 34% of rural subjects had >25% body fat (the currently accepted definition of obesity; measured by bioimpedance (Multiscan 5000, Bodystat, Isle of Man, UK) calibrated against the deuterated water method); at a mean BMI of 22, 45% of slum residents had >25% body fat; and at a mean BMI of 24, 84% of middle-class residents had >25% body fat. There was a graded increase in

TABLE 1

Body size and cardiovascular risk factors in Indians<sup>1</sup>

	Rural (n = 149)	Urban slums (n = 142)	Urban (n = 150)
Age, y	38	39	40
BMI, kg/m <sup>2</sup>	21.2	22.3	24.3
Percent body fat (bioimpedance)	21.6	24.1	29.6
>25% body fat, %	34	45	84
Diabetes, %	0	4	10
IGT, %	9	12	20
Hypertension, %	2	4	10
Cholesterol, mg/dl	145	155	166
Triglycerides, mg/dl	83	93	119
Metabolic syndrome, %	8	22	32

<sup>1</sup> Adapted from Food and Nutrition Bulletin (2002) 23(3): 146–49.

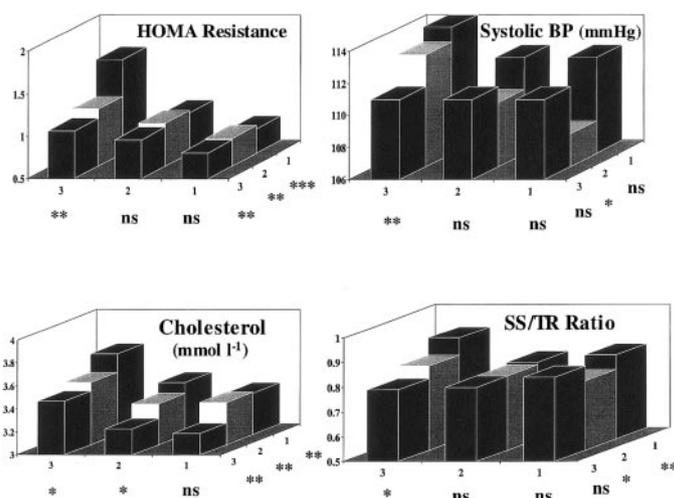
insulin resistance, type 2 diabetes and other cardiovascular disease (CVD) risk factors from rural to urban middle-class (20). During 10 years of follow-up of middle-aged male and female subjects with normal glucose tolerance, incident IGT and diabetes were predicted most strongly by initial insulin resistance and weight gain (21). A BMI > 23 increased the risk of incident hyperglycemia 2.4×. In a large cross-sectional study in middle aged Indians, a BMI > 23 was associated with increased risk for type 2 diabetes (22). Appreciating these facts, the WHO has recently reduced the action-point BMI for obesity-related interventions in Asians to 23 (23). Clearly, body fat rather than BMI should be measured as a risk factor in studies of type 2 diabetes and CHD in Indians, and the international BMI cutoff of 25 is inappropriate to define the increased risk in Indians.

### Susceptibility of Indians to type 2 diabetes

As discussed, susceptibility to type 2 diabetes could be due to genetic factors, intrauterine “programming,” accelerated childhood growth and lifestyle factors (14,24,25). These should not be viewed as mutually exclusive but can be easily incorporated to construct a life-course approach. Some of the relevant findings from our studies are presented below.

### Studies with urban Indian children

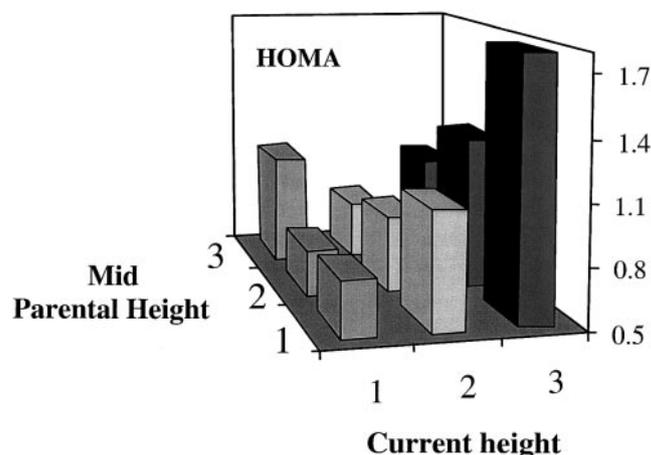
We studied body size, glucose tolerance and insulin resistance variables in children born in the King Edward Memorial Hospital in Pune. Birth weight was available from the labor room register. At 4 y of age, blood plasma glucose and insulin concentrations (30 min after 1.75 g/kg oral glucose load) and fasting IGF-1 concentrations were strongly related to current body size (weight and skinfold thicknesses). When the effect of current size was allowed for, glucose, insulin and insulin-like growth factor-1 (IGF-1) concentrations were inversely related to birth weight (26,27). At 8 y of age (n = 477, including 190 children studied at 4 y of age) homeostatic model assessment (HOMA) insulin resistance and other cardiovascular risk factors (blood triglyceride and cholesterol concentrations, systolic blood pressure and central obesity measured as subscapular-triceps skinfold ratio) were highest in children who had the lowest birth weight but had grown the biggest (Fig. 2) (28). The definition of “bigness” at 8 y included not only weight and fat mass but also height. Growth velocity (for height, weight and other measurements) from 4 to 8 y of age was a stronger predictor of insulin resistance and CVD risk



**FIGURE 2** Mean levels of insulin resistance variable homeostatic model assessment (HOMA), systolic blood pressure, serum cholesterol concentration and subscapular-triceps skinfold ratio (SS/TR) at 8 y of age by tertiles (1,2,3) of birth weight (rows) and weight at 8 y (columns). Significance level for the trend in each row and column (adjusted for age and sex) is shown at the end (ns = not significant; \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ ). Adapted from Bavdekar et al. (28).

factors than the measurements at 8 y of age (24). These results suggest that rapid childhood growth exaggerates risk in those born small. Rapid childhood growth in those born small could be considered catch-up growth, which may depend on the adequacy of nutrition in childhood. This may have important implications for populations undergoing economic and nutritional transitions, among which opportunities for overnutrition are substantial.

The unexpected finding in our study was the higher cardiovascular risk in taller children, especially if born to shorter parents (as measured by midparental height or independently by paternal and maternal height; Fig. 3). Thus, accelerated growth in childhood increases the risk for diabetes and CVD



**FIGURE 3** Mean levels of homeostatic model assessment (HOMA) resistance variable at 8y of age by tertiles (1,2,3) of child's height at 8 y of age and midparental height. Midparental height was calculated as the average of the parental heights + 7 cm for males and the average of the parental heights – 7 cm for females. Adapted from Yajnik (14).

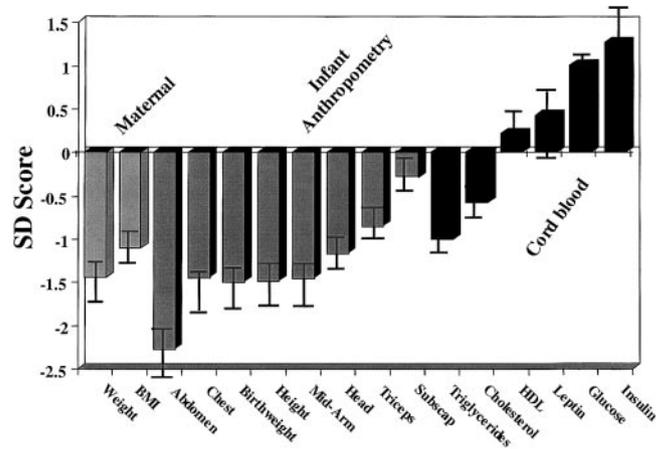
among children who have lower birth weight or are born to shorter parents. It will be interesting to see whether these fast-growing children develop into shorter adults due to earlier fusion of bones, as reported in France (29). Few of these children were obese by conventional BMI criteria. We do not have formal measurements of body fat in these children but only estimated fat mass data calculated from anthropometric measurements. Rapidly growing children who had lower birth weight or were born to shorter parents were the most adipose, and adiposity explains a substantial proportion of the increased insulin resistance and CVD risk in these children.

We also analyzed the risks of high birth weight. Higher-birth-weight children had higher BMI in childhood and had correspondingly higher insulin resistance. Unlike populations in the United Kingdom and Europe, in which lower birth weight in children was associated with an increased parental risk of insulin resistance, diabetes and CVD, in our population higher birth weight in urban children was associated with an increased risk of adiposity in both parents and increased risk of metabolic syndrome in the mother 8 y after the birth of the child (30).

Our findings thus suggest an association of small and large size at birth with later insulin resistance. This is exaggerated by rapid postnatal growth. Small and large size may be surrogates for adiposity (body fat percentage), a major determinant of insulin resistance. Being born to shorter parents seems to aggravate this risk, suggesting an intergenerational connection, which may be genetic as well as nutritional. Knowledge of the factors that regulate fetal body composition and childhood growth may help to elucidate the origins of diabetes. We therefore set up a maternal nutrition study in 6 villages near Pune to investigate these questions.

#### **The thin-fat Indian baby: A thrifty phenotype? (Pune Maternal Nutrition Study)**

We followed >2500 young nonpregnant women in 6 villages near Pune, recording their menstrual dates and detailed anthropometric data. Of these subjects, 770 women delivered babies within the study timeframe (31,32). The babies had a mean birth weight of 2.614 kg, and 28% had LBW. The birth measurements of 633 full-term babies were compared with those of 521 full-term babies born in Southampton, U.K., recorded using a comparable technique. The Indian babies were lighter (2.665 vs. 3.450 kg), shorter (47.3 vs. 50.2 cm) and thinner (ponderal index of 24.1 vs. 27.3 kg/cm<sup>3</sup>) compared with the British babies (Fig. 4). However, the subscapular skinfold was substantially preserved (4.2 mm, vs. 4.8 mm in the U.K. babies). The thinness of the Indian babies was predominantly because of the paucity of nonfat soft tissue (i.e., abdominal viscera and skeletal muscle, both protein-rich tissue). Thus, the thin Indian babies were relatively fat. A similar finding from the carcass analysis of Indian babies was reported many years ago (33). In a subsequent study we repeated such measurements with urban children born at the King Edward Memorial Hospital, Pune, and white Caucasian children born at the Whittington Hospital, London, U.K. (34). The same two nutritionists measured the babies in both hospitals using the same instruments, and cord blood measurements were conducted in the same laboratory. This study confirmed our original anthropometric findings. In addition, we found that cord leptin concentrations (a measure of fat mass) were similar in the two populations despite a difference in birth weight of 0.800 kg, suggesting higher adiposity in the Indian babies.



**FIGURE 4** Mean SD scores for maternal prepregnancy weight and height and for birth measurements and cord blood concentrations of babies born in Pune, India, compared with those of babies born in London, U.K. The London group mean is represented by 0 and the mean difference for each measurement is shown. All SD scores are negative, suggesting that the Indian babies are smaller than the British babies. *Abdomen, mid-arm and head* are circumference measurements. Adapted from Yajnik et al. (34).

#### **Maternal nutrition and offspring size**

Rural Indian mothers were considerably smaller (42 kg, 1.52 m and 18.0 kg/m<sup>2</sup>) than the British mothers (63 kg, 1.63 m and 23.5 kg/m<sup>2</sup>) and had much lower daily intakes of energy and protein (~7.53 MJ and 45 g, compared with 10.04 MJ and 90g, respectively). Carbohydrates provided a considerably higher proportion of total energy intake in the Indian maternal diet (72%, vs. 50% for the U.K. group). Of the macronutrients, only maternal fat intake at 18 wk of gestation was positively related to fetal size; energy and protein intake were not related to fetal size. The strongest determinants of fetal size were the frequency of intake of micronutrient-rich foods (i.e., green leafy vegetables, fruits and milk) and blood levels of folate and ascorbic acid (35). The child's skinfold thickness was related to the frequency of maternal consumption of green leafy vegetables but not to that of fruits and milk. Our data highlight the important influence of maternal prepregnancy body size, maternal nutrition during pregnancy and maternal metabolic milieu on fetal growth and body composition.

#### **Relationship between birth size and diabetes in Asian populations**

Data are available from two studies, conducted in India and China, respectively. In the Mysore (South India) study, birth weight was not related to IGT and type 2 diabetes at age 45, but shorter body length and higher ponderal index at birth were. Individuals born to heavier mothers were particularly susceptible. Low birth weight predicted insulin resistance only in males, whereas higher ponderal index at birth predicted a smaller insulin increment during an oral glucose tolerance test (36). In the China study, conversely, lower birth weight individuals born to lighter mothers had a higher incidence of diabetes (37).

#### **Adipose tissue: An important player in insulin resistance syndrome**

Traditionally, the increased risk of disease associated with excess body fat is ascribed to the liberation of excess amounts

of NEFA, which causes metabolic problems (e.g., through the glucose fatty acid cycle) (38). Moreover, NEFA are also vasculotoxic (39). Visceral fat is thought to be more problematic because it pours its NEFA into the portal system that bathes the liver (contributing to steatosis) and alters the liver's metabolic settings. This causes widespread effects on metabolic pathways (40), including those of insulin action and the synthesis of lipids, coagulation factors and inflammatory substances. The recent demonstration that adipose tissue is involved in the synthesis and release of cytokines and similar molecules (TNF- $\alpha$ , interleukin-6 and leptin) has opened new possibilities for understanding the pathogenesis of cardiovascular risk due to obesity (41).

Intrauterine regulation of adipogenesis may be an important mechanism of the fetal origins of diabetes and CHD. Differences in body composition among different ethnic groups imply that we might see different relationships between birth weight and later disease. Body fat rather than body weight may be the more relevant measurement to assess such relationships.

### *Origins of insulin resistance syndrome in the Indian population*

In our studies we defined a pattern of intrauterine growth and body composition in Indian babies that suggests a paucity of visceral and muscle tissue but preservation of adipose tissue (especially central but also total). This pattern may result partly from genetic and partly from nutritional influences. The fundamental biological drive in the developing fetus is to preserve brain growth. This is achieved by the preferential diversion of blood flow to the growing brain (42) and may be helped by rendering other tissues insensitive to the action of insulin and related growth hormones. This allows the diversion of nutrients from the peripheral tissues to the brain. We postulate an additional fat-preserving compulsion, at least in the studied Indian populations, but also demonstrated in growth-restricted fetuses in other populations (43). This adipose tissue acts as a ready source of lipids for the fast-developing brain during the intrauterine and immediate postdelivery periods. Positive energy balance in later life exaggerates adiposity, especially in the central depots. The urban environment provides many opportunities for such a sequence of events. The backdrop of a polluted and infective environment may stimulate the fat cells to secrete molecules that promote insulin resistance, endothelial dysfunction, coagulation disturbances and a proinflammatory state, leading to type 2 diabetes and CHD.

If this scheme of events is true, the prevention of obesity, type 2 diabetes and CHD in the Indian population requires improving aspects of fetal growth, reducing overnutrition in later life and controlling environmental factors that stimulate adipocytes. Prevention should begin much before the stage of IGT, as is the currently fashionable misconception. The specific nutrients that influence intrauterine growth as well as catch-up growth must be identified.

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