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The lifecycle effects of nutrition and body size on adult adiposity, diabetes and cardiovascular disease

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Summary

This study was undertaken to review the links between maternal nutrition, offspring's birth weight and the propensity to early insulin resistance and high diabetes rates in Indian adults. Studies included a comparison of maternal size and nutrition with birth weights in Pune, India, and Southampton, UK. In Pune, the growth, insulin resistance and blood pressure of four-year-old children were assessed. Adults >40 years of age, who were resident in rural areas, were compared with adults living in urban areas for size, glucose handling, lipid status and blood pressure. Newly diagnosed diabetic adults living in urban areas were also monitored. Height, weight, head, waist and hip circumferences, skin-fold measurements and blood pressure were routinely measured. Fasting glucose, insulin, total and high-density lipoprotein cholesterol and triglycerides were linked to the glucose and insulin responses during glucose tolerance tests. Cytokine levels were measured in plasma samples of urban and rural adults. Indian babies were lighter, thinner, shorter and had a relatively lower lean tissue mass than the Caucasian babies. However, the subcutaneous fat measurements of these babies were comparable to those of the white Caucasian babies. The Indian mothers were small, but relatively fat mothers produced larger babies. Maternal intake of green vegetables, fruit and milk, and their circulating folate and vitamin C levels, predicted larger fetal size. Rapid childhood growth promoted insulin resistance and higher blood pressure. Rural adults were thin, with a 4% prevalence of diabetes and a 14% prevalence of hypertension, but the risks increased within the normal body mass index (BMI) range. Type 2 diabetes was common in urban adults younger than 35 years of age. Although the average BMI was 23.9 $kg\,m^{-2}$, central obesity and thin limbs were noteworthy. Levels of interleukin-6 and tumour necrosis factor-α were markedly increased in urban dwellers. Hence, there is evidence of a remarkably powerful, intergenerational effect on body size and total and central adiposity. Indians are highly susceptible to insulin resistance and cardiovascular risks, with babies being born small but relatively fat. Insulin resistance is amplified by rapid childhood growth. Dietary factors seem to have profound long-term metabolic influences in pregnancy. Overcrowding with infections and central obesity may amplify cytokine-induced insulin resistance and early diabetes in Indian adults with a low BMI.

Keywords: Abdominal obesity, cardiovascular risk, diabetes, fetal programming.

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Background

There is an epidemic of type 2 diabetes and coronary heart disease (CHD) in Indians, both in India and abroad (1,2). Between 1988 and 2000 there was a 70% increase in the prevalence of diabetes in the city of Chennai (Madras), reaching a prevalence of 13% in adults over 20 years of age (3). India has the highest number of diabetic patients

in a single country and the number will rise to 57 million by the year 2025; CHD will then be the leading cause of premature death in India. There is a striking excess in the prevalence of these conditions in urban compared with rural Indians (4,5) and in Indian migrants compared with indigenous populations, viz. white Caucasians in the UK (6–9). These observations imply a future risk of a major public health crisis with continuing rural-to-urban migration and progressive ageing of the population as a result of increasing life expectancy.

The cause of this 'epidemic' is not clear but rapid lifestyle changes in a population with high genetic susceptibility ('thrifty genotype') (10), or programmed by early life growth retardation ('thrifty phenotype') (11), are two not necessarily mutually exclusive possibilities. Yet, the rapid changes in incidence of these conditions with migration from rural to urban areas imply additional powerful environmental influences on risks operating in adult life. The main environmental determinant of both diabetes and CHD in Indians is obesity, particularly when centrally distributed (4,8,12,13). Obesity results from an imbalance between energy intake and expenditure consequent upon inappropriate changes in diet and lifestyle. This obesity increases insulin resistance, which is associated with the future risk of both type 2 diabetes and CHD (14–16).

At the KEM Hospital Diabetes Unit in Pune, India, we have been actively involved in studying the determinants of insulin resistance in Indians, especially the phenotype and body composition that might predispose to the insulin resistance syndrome (IRS). Over the last 15 years we have collected data on diabetic patients in our clinic and community-based data on rural and urban subjects, and started a number of prospective studies to investigate the role of intrauterine growth and subsequent events on the risk of diabetes and CHD. We have made several relevant observations in newborns, young children and adults, which give important clues to explain the high prevalence of IRS and its possible aetiology in Indians.

Body composition of newborn Indian babies: intrauterine origins of a 'thrifty' (thin fat) phenotype

In a study of maternal nutrition and fetal growth (17) in six villages near the city of Pune, in Maharashtra, we found that the mean birth weight of babies was 2614 g, with 28% of all babies being of low birth weight (LBW) (i.e. <2500 g); this prevalence is very similar to the Indian national statistics. Comparing the full-term babies born in our study with those born in Southampton, UK (Fig. 1) who were measured using comparable techniques, we found that Indian babies are lighter (2665 g vs. 3450 g), shorter (47.3 cm vs. 50.2 cm) and thinner (ponderal index 24.1 vs. 27.3 kg cm^{-3}). However, the subscapular skin-fold measurements were more comparable to those of the western babies. The thinness of the Indian babies is predominantly because of a paucity of non-fat ('protein-rich') soft tissues (i.e. abdominal viscera and skeletal muscle). A thin Indian baby is thus relatively 'fat'!

The rural Indian mothers are considerably smaller [weight, 42 kg; height, 1.52 m; and body mass index (BMI) 18.0 kg m^{-2}] compared with the western mothers (weight 63 kg; height, 1.62 m; BMI, 23.5 kg m^{-2}). Different body measurements in the mother were reflected in neonatal measurements. Maternal anthropometric measurements could be interpreted as reflecting her own 'nutritional history' (18). Thus, maternal growth in her early life (intrauterine and early childhood), reflected in her own head circumference, proved to be the most consistent predictor of different aspects of her child's intrauterine growth. The relationships between maternal and neonatal characteristics are displayed in Fig. 2. Mothers who were short and

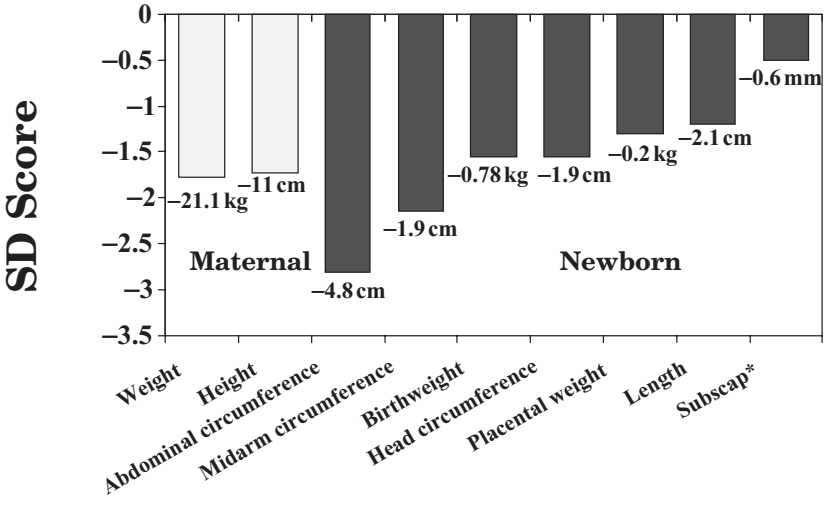

Figure 1 The Indian Thrifty Phenotype at birth (adapted from refs 18 and 48). Mean standard deviation (SD) scores are shown for prepregnant maternal weight and height and for certain measurements in babies born in Pune compared with babies born in Southampton. The Southampton mean is represented by 0 for calculating the Indian SD score; the absolute mean differences are also given. *Subscap refers to the subscapular skin-fold thickness.

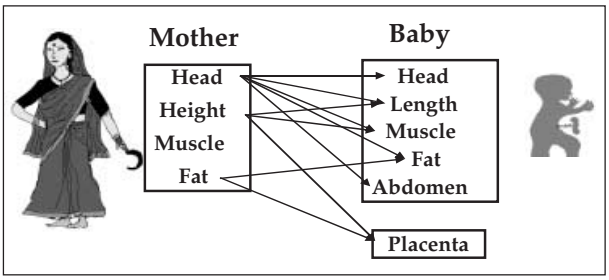

Figure 2 Relationship between maternal anthropometric measurements before pregnancy and neonatal measurements at birth (adapted from ref. 18). Note that maternal head circumference (a surrogate for early life growth and nutrition) is significantly related to all of the neonatal measurements except placental weight. Maternal height is related to neonatal length, muscle and maternal fat (fat mass calculated from four skin-fold thicknesses) to neonatal fat (subscapular and triceps skin-folds). Maternal midarm circumference is not related to any of the neonatal anthropometry. Placental weight was related to both maternal height and maternal fat content.

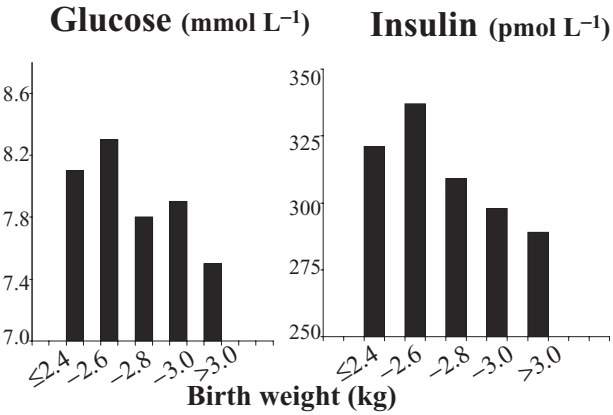

Figure 3 The glucose and insulin responsiveness in childhood in relation to birth weight (adapted from ref. 21). Plasma glucose and insulin concentrations are shown 30 min after administration of oral glucose to 4-year-old-children in different categories of birth weight. Significance of the trend is corrected for age, gender and current body weight.

fat (reflecting poor growth in early life but positive energy balance in later years) gave birth to the fattest babies, suggesting indirectly the influence of nutritional transition on neonatal 'obesity'. Indian mothers ate fewer calories and less protein compared with western mothers (~1800 cals d^{-1} and 45 g of proteins d^{-1} compared with 2400 cals d^{-1} and 90 g of proteins d^{-1}, respectively) but still expended a considerable amount of energy in household work and farming. Of the macronutrients, only fat intake of the mother was related to fetal growth (positive); the intake of calories and proteins was not related. The frequency of intake of green leafy vegetables, fruit and milk was a strong determinant of fetal growth (19). In this rural population maternal diabetes and hypertension were conspicuous by their absence, but maternal fasting plasma glucose (within the normal range) and triglyceride (TG) concentrations were strong predictors of fetal size. Circulating folate and ascorbic acid levels in the mother were, similarly, related to fetal growth. Our data highlights the influence of maternal prepregnant size, her food intake during pregnancy and her metabolic milieu, on fetal growth and body composition.

We also studied the relationship between paternal size and fetal growth. We found that father's size and paternal insulin resistance were independent determinants of fetal growth, suggesting that genetic mechanisms influencing size and insulin resistance might also influence fetal growth and body composition (20).

Cardiovascular risk of low birth weight and later weight gain

In 4-year-old-urban children born in our hospital, plasma glucose and insulin concentrations, 30 min after an oral glucose load, were related strongly to their body weights at four years of age and to their skin-fold thicknesses, but were inversely related to birth weight when the effect of current size was allowed for (21) (Fig. 3). When studied again at eight years of age, the levels of cardiovascular risk factors (HOMA-insulin-resistance variable, circulating TG and cholesterol concentrations and systolic blood pressure) were highest in children who were born small but had then grown large (in weight, fat mass and height) (22) (see Fig. 4). Even though causality cannot be ascertained in an observational study such as ours, it supports the idea that the risk of excess energy intake is accentuated in those born small [energy adaptation maladaptation syndrome (ENAMAS)] (23,24). It is important to note that few of these children at eight years of age were 'obese' by international standards. The interactions between birth weight and body size at eight years of age on the risk factors are shown in Fig. 4.

The unexpected finding was the higher levels of cardiovascular risk factors in children who were taller, especially in relation to their birth weight. Children born to shorter parents had higher levels of cardiovascular risk factors and the risk was higher the taller the child was in relation to its midparental height. These findings raise important questions about the role of 'catch-up' growth in influencing the cardiovascular risk. This would have important implications for populations in economic and nutritional transition which provide opportunities for an imbalance between nutrition in early life and diet and physical activity in later life.

The considerably higher prevalence of diabetes and CHD in urban communities compared with the pattern in rural India is contrary to the expectations of the original Barker's

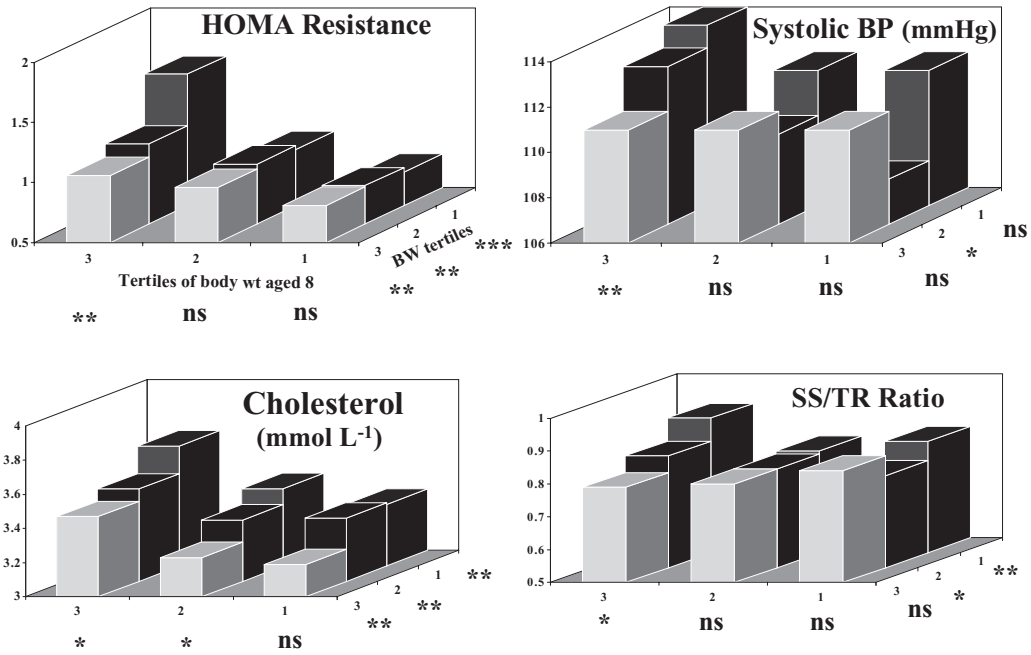

Figure 4 The interactions of birth weight and the body weight of 8-year-old children (in tertiles) in relation to insulin resistance, blood pressure, serum cholesterol and fat distribution (adapted from ref. 22). The mean levels of the insulin resistance variable (HOMA-R), systolic blood pressure, serum cholesterol concentration and of subscapular-triceps skin-fold ratio (SS/TR) at 8 years of age by tertiles (1, 2 and 3) of birth weight are shown in the rows, with the 8-year weight shown as columns. The significance level for the trend in each row and column (adjusted for age and gender) is shown (ns = not significant, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$).

hypothesis. The birth weights of rural babies (mean ~2650 g) were lower than those of the urban babies (mean ~2900 g). The explanation for this paradox may be found in the differences in adult body size. The mean BMI of adult rural Indians is 19.0 kg m^{-2}, whilst that of the urban adults is 23.5 kg m^{-2}. Therefore, the urban adults outweigh their rural counterparts by 130% but their babies are only 109% larger. Alternatively, the 'heavier' birth weight of urban Indian babies may reflect a much greater fat content at birth and this 'fat phenotype' may predispose to problems in later life. An important fact to remember is that the birth weight of Indian babies has been low for centuries and the cardiovascular epidemic is only a recent phenomenon. These facts point towards the crucial role of postnatal environment in the aetiology of the cardiovascular and diabetes epidemic. The overwhelming association of the epidemic with urbanization could reflect changes in nutrition (food intake and physical activity), psychosocial stress and many other environmental factors that could be toxic to vital tissues.

Studies in adults

Rural

We studied cardiovascular risk factors in 321 rural adults above the age of 40 years (84% of the eligible population) in a village ~50 km from the city of Pune. These adults were thin (BMI 19.4 ± 2.8 kg m^{-2} in men and 19.7 ± 3.8 kg m^{-2} in women) but otherwise fit (Table 1). Approximately 4% showed an impaired glucose tolerance (IGT) and ≈€4% were diabetic [according to the World Health Organization (WHO) 1985 criteria]; ≈€14% were hypertensive (blood pressure ≥140/90, or on antihypertensive treatment).

The 2-h plasma glucose was related to age ($P < 0.05$), gender (higher in women, $P < 0.05$), larger waist : hip ration (WHR) ($P < 0.05$) and to smaller head circumference ($P < 0.05$). Despite their thinness, the level of cardiovascular risk factors was related to measures of obesity. The highest BMI quartile vs. the lowest had a 3.8-times [confidence interval (CI) 0.8–16.0] increased risk of hyperglycaemia, i.e. glucose intolerance (IGT) and diabetes mellitus, and a 6.5-times (CI 1.5–27.0) increased risk of hypertension in both men and women. Similarly, the highest waist circumference quartile had an 8.0-times (CI 1.05–82.0) increased risk of hyperglycaemia in both men and women, and a 6.5-times (CI 1.6–27.0) higher risk of hypertension in men and a 2.7-times (CI 0.8–9.3) higher of hypertension in women (25).

We repeated our assessment of these rural adults five years later. Twenty-one had died. The causes of death included diabetes and cardiovascular ($n = 5$) cancer ($n = 3$), accidents ($n = 2$) and other causes ($n = 11$). As expected, older individuals had died but when the effect of age was

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Table 1 Anthropometric characteristics and cardiovascular risk factors in a rural population of adults over 40 years of age in Pimple Jagtap near Pune (adapted from ref. 25)

Characteristics	Men (n = 159)	Women (n = 162)
Age (years)	58.60 (±10.6)	53.08 (±10.5)
Height (m)	1.63 (±0.06)	1.49 (±0.05)
Weight (kg)	51.90 (±8.3)	44.50 (±9.3)
BMI (kg m^{-2})	19.40 (±2.8)	19.70 (±3.8)
General obesity (kg m^{-2})	>27 kg m^{-2}, 1.8%	>25 kg m^{-2}, 9.8%
Waist (cm)	74.50 (±9.5)	67.10 (±10.0)
Central obesity (waist cm)	>95 cm 4.4%	>85 cm, 4.3%
Hip (cm)	84.90 (±5.3)	85.70 (±8.4)
WHR	0.87 (±0.07)	0.78 (±0.07)
Head (cm)	53.60 (±1.6)	52.90 (±1.5)
IGT*	3.1%	4.9%
Diabetes*	4.4%	4.3%
Hypertension >140/90 mmHg	14.5%	13.0%
Cholesterol >240 mg%	Nil	0.6%
Triglycerides >150 mg%	11.3%	14.8%
HDL cholesterol ≤mg%	28.3%	19.8%

HDL, high-density lipoprotein; IGT, impaired glucose tolerance; WHR, waist : hip ratio.
Data are expressed as mean value (±SD).
*75-g oral glucose tolerance test.
2-h plasma glucose 140–199 mg% = impaired glucose tolerance.
2-h plasma glucose ≥200 mg% = diabetes

allowed for, the dead men were shorter and had a smaller head circumference, while the dead women were also shorter, had a smaller head circumference and were more centrally obese. Therefore, small head circumference (an indication of poor growth in very early life and childhood) and stunting (a marker of poor growth in early life and during puberty) are significant predictors of early death in both men and women. Energy excess in later life, reflected in larger waist circumferences and WHRs, was an additional risk factor for death in women. Poor growth in early life and 'over nutrition' in later life seem to be a unfavourable combination for the health of Indian adults. It is important to note that these individuals are quite thin by international standards.

Clinical studies of type 2 diabetic and coronary heart disease in an Indian urban clinic

More than one-third of urban patients with type 2 diabetes in our clinic are diagnosed before they reach 35 years of age. They are not obese by BMI criteria (mean BMI 23.9 kg m^{-2}; see Table 1) but are centrally obese as judged by their high WHR and the elevated ratios of subscapular to triceps skin-fold thicknesses (12). The different charac-

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Table 2 Characteristics of newly diagnosed hyperglycaemic patients in an urban diabetic clinic in Pune, India. (Adapted from refs 12, 26 and 27)

Patient's characteristics	Non-diabetic (n = 133)	IGT (n = 79)	Diabetic (n = 189)
Male/female	57%/43%	56%/44%	65%/35%
Age (years)	40	47	43
BMI (kg m^{-2})			
Men	23.3	25.5	23.9
Women	23.6	26.6	24.9
Obesity			
Men (BMI >27 kg m^{-2})	15%	30%	22%
Women (BMI >25 kg m^{-2})	40%	71%	47%
WHR			
Men	0.88	0.93	0.92
Women	0.77	0.79	0.80
2-h plasma glucose (mg%)	82.5	148.0	335.5
Fasting plasma IRI (mU L^{-1})	7.5	11.0	16.0
Blood pressure (systolic/diastolic, mmHg)	121/83	129/85	129/87
Hypertensive (>140/90 mmHg)	18%	34%	33%
Plasma cholesterol (mg dL^{-1})	163	180	167
Cholesterol (>240 mg dL^{-1})	5%	5%	6%
Plasma triglyceride (mg dL^{-1})	79	104	136
Triglyceride (>150 mg dL^{-1})	15%	28%	38%
Plasma NEFA (mmol L^{-1})	0.81	1.02	1.02
Ischaemic ECG*			
Men	3%	16%	11%
Women	12%	18%	23%

Mean values are shown.
BMI, body mass index; IGT, impaired glucose tolerance; NEFA, non-esterified fatty acids; IRI, immunoreactive insulin; WHR, waist : hip ratio.
*Electrocardiogram (ECG) classified as ischaemic using the Minnesota code system.

teristics and risk factors between non-diabetic adults and those with diabetes and glucose intolerance are shown in Table 2. They also have thin limbs (smaller midarm circumferences), suggestive of a small muscle mass. Belying the expectation that relatively thin type 2 diabetic patients will be insulin deficient, Indian type 2 diabetic patients are relatively hyperinsulinaemic and insulin resistant. They have high levels of circulating non-esterified fatty acids (NEFA) and TG concentrations, which are positively related to fasting plasma insulin concentration (26). Plasma insulin concentrations are also related to blood pressure (27). Thus, the Indian type 2 diabetic patient represents a classic example of the IRS (28). Ramachandran *et al.* showed that higher obesity (BMI) and central obesity (WHR) in urban compared to rural Indians was reflected in a higher prevalence of diabetes in urban Indians (4). McKeigue *et al.* also showed that a higher WHR in Indians explained the higher risk of IRS in migrant Indians compared to local white Caucasians in the UK (8,13). A representative Indian patient with CHD has features which are very similar to those of an Indian diabetic patient (29)

Why are Indians at higher risk of the insulin resistance syndrome at lower body mass index values?

The exaggerated risk of the IRS in Indians at a relatively lower BMI is very probably the result of excess total body fat in comparison with that in the white Caucasians. This has been reported in small studies in migrant Indians in Sweden and the USA (30,31). Moreover, an ethnic comparison study in the UK showed that truncal skin-fold thicknesses in South Asian men were significantly greater, despite similar skin-fold thicknesses on the limbs, at comparable BMI values (8). A recent comparative study in the US confirmed that Indians have a higher body fat percentage, higher central visceral fat and higher posterior subcutaneous abdominal fat than those reported in white Caucasians and that this was associated with a higher insulin resistance in Indians (32).

Adipose signals for insulin resistance and vascular disease: a role for cytokines?

Traditionally, the metabolic problems owing to excess body fat are ascribed to the liberation of NEFA from adipose tissue (and the effects of the glucose/fatty acid cycle) (33). The free fatty acids are also vasculotoxic (34). The recent demonstration that adipose tissue is involved in the synthesis and release of cytokines and similar molecules [tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6) and leptin] has opened up new possibilities for the pathogenesis of the cardiovascular risk of obesity. Yudkin and his colleagues have recently shown that both the IRS and markers of endothelial damage are related to circulating concentrations of the acute-phase reactant C-reactive protein and of the proinflammatory cytokines, TNF-α and IL-6 (35). Both cytokines have powerful effects on the regulation of activities of lipolytic and lipogenic enzymes (36) and on the expression of endothelial proteins (37). TNF-α has been shown to inhibit insulin-receptor signalling (38), an action that it may share with IL-6. Both IL-6 and TNF-α are expressed in adipose tissue (39), and up to one-third of circulating IL-6 in healthy subjects may originate from adipose tissue (40), potentially providing a novel mechanism for the association between obesity and vascular risk. The concentrations of cytokines were related to the measures of overall obesity with a correlation to BMI of $r = 0.3$ ($P < 0.001$) and particularly to central obesity (WHR $r = 0.5$, $P < 0.0001$).

Table 3 Levels of interleukin-6, tumour necrosis factor-α and obesity in three Indian populations (adapted from ref. 41)

	Urban middle class ($n = 40$)	Urban slum-dwellers ($n = 28$)	Rural ($n = 43$)
BMI ($kg\,m^{-2}$)	23.5 (3.9)	22.2 (3.1)	18.9 (2.4)
WHR	0.85 (0.08)	0.85 (0.10)	0.83 (0.07)
Leptin ($ng\,mL^{-1}$)	7.10 (2.28)	8.11 (2.12)	2.20 (2.09)
IL-6 ($pg\,mL^{-1}$)	7.52 (2,51)	13.6 (2.34)	3.50 (3.31)
TNF-α ($pg\,mL^{-1}$)	17.9 (2.74)	2.13 (2.44)	2.54 (2.84)

BMI, body mass index; IL-6, interleukin-6; TNF-α, tumour necrosis factor-α; WHR, waist : hip ratio.

In a small pilot study, we measured circulating levels of leptin, IL-6 and TNF-α in subjects from three geographical locations in and near the city of Pune, India (Table 3). The circulating levels of leptin and cytokines in the rural subjects were comparable to those in the white Caucasians, but were elevated many fold in the urban subjects, being highest in the urban slum-dwellers (41).

These findings suggest a novel hypothesis for the epidemic increase in the risk of diabetes and CHD in Indians, i.e. adipose tissue-derived cytokines may mediate insulin resistance. The higher adipose tissue mass in urban dwellers may contribute substantially to these, possibly stimulated by the infected and polluted environment, especially in the overcrowded slums. Two more pieces of recent data are intriguing. Magnetic resonance imaging (MRI) measurements of abdominal fat revealed that insulin resistance was more tightly related to posterior subcutaneous, and not to intraperitoneal, fat mass (42,43). It is interesting that the skin-fold thickness which is best maintained, or even increased in thickness, in thin Indian adults and neonates is on the posterior trunk wall (subscapular region). It is possible that both abdominal subcutaneous and visceral fat might have metabolic roles hitherto unsuspected.

In conclusion, we propose that the excess risk of diabetes and CHD in Indians is associated with a body composition that includes excess fat, especially in the central areas (both visceral and posterior subcutaneous), and poor skeletal muscle. We have evidence that this phenotype is present from birth and could be influenced by both genetic and environmental factors, especially maternal health before and during pregnancy. Catch-up growth in childhood is associated with increased levels of cardiovascular risk factors, including the components of the IRS. Excess body fat might be detrimental, not only because of the metabolic implications but because the adipose tissue seems to be active in the synthesis and release of cytokine-like molecules that may influence insulin action, endothelial function and inflammatory responses. Urbanization in India offers many opportunities to increase body fat, and cytokine release may also be stimulated by atmospheric pollutants and infective agents. Fat-soluble pollutants may be particularly relevant. Elevated circulating levels of inflammatory markers (44–46) and antibodies to common infective agents (such as *Helicobacter pylori* and *Chlamydia pneumoniae*) (47) have been shown to predict the development of diabetes and CHD. Gastrointestinal and respiratory infections are very common in Indians, especially in cities, and antibodies to the microbes responsible for such infections are present in a substantial proportion of population. This aspect merits further investigation. Our data suggest that improvement in the nutrition of an individual who is malnourished in early life promotes excess fat deposition, expression of proinflammatory and IRS markers, and increases the risk of both diabetes and cardiovascular disease. Hence, the control of the epidemic of diabetes and cardiovascular disease in India will require lifelong improvements in both nutrition and the environment.

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