

# Size and Body Composition at Birth and Risk of Type-2 Diabetes

## A Critical Evaluation of ‘Fetal Origins’ Hypothesis for Developing Countries

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India and other developing countries are experiencing a rapidly escalating epidemic of diabetes and cardiovascular disease. Over the past 25 years there has been a 5-fold increase in the prevalence of type-2 diabetes and coronary heart disease (CHD) [1, 2]. It is predicted that by 2025 India will have more than 60 million diabetic patients and that CHD will be the leading cause of death in adults. This phenomenal rise in diabetes and CHD has been ascribed to the so-called epidemiologic, nutritional and economic transition.

It is customary to ascribe diabetes susceptibility to the evolutionary enrichment of thrifty genes [3]. An alternative explanation is the recently proposed thrifty phenotype hypothesis which ascribes it to an unfavorable intrauterine environment [4, 5]. The two explanations are not necessarily exclusive. The fetal insulin hypothesis envisages that the association between birth weight and diabetes could have common genetic determinants but acknowledges the role of intrauterine environment in modifying this relationship [6].

Hales and Barker [4, 5] proposed that undernutrition in utero increased the susceptibility to diabetes in later life. This was based on an inverse association between birth weight and later risk of diabetes in elderly men and women in the UK. It was suggested that an improvement in maternal and therefore fetal nutrition would reduce the risk of diabetes. However, there is growing recognition that the relationship between maternal nutrition, fetal nutrition, neonatal size and later diabetes is more complex. The simplistic assumption that improvement in maternal nutrition will reduce the risk of these disorders is unlikely to be true [7].

How do these concepts apply to the situation in the Indian subcontinent? Indians as a group have small body size, mothers (especially rural) are short and thin. This is traditionally ascribed to 'chronic undernutrition'. A third of Indian babies are born with low birth weight (<2.5 kg). It is thus possible that maternal and fetal undernutrition contribute to the diabetes epidemic in India. However, small size at birth and low birth weight have been present for many centuries whereas the diabetes epidemic is recent. Urban Indians have a five times higher risk of diabetes than rural Indians despite the larger size of mothers and their babies ('better nourished'). Temporally, the epidemic is associated with a rapid epidemiologic and nutritional transition which may be associated with increasing fetal nutrition rather than undernutrition.

The Diabetes Unit, King Edward Memorial Hospital, Pune, has contributed a number of observations on the evolution of the insulin resistance syndrome during the life course. Specifically we have studied the relationships between size, body composition and nutrition both in mothers and offspring.

### **Size at Birth, Body Composition and Future Risk of Diabetes**

Studies in Europe showed an inverse relationship between birth weight and type-2 diabetes in elderly individuals [8]. Such 'retrospective' studies are a marvelous achievement in epidemiology but there are difficulties in their interpretation. Large-scale attrition due to death and migration and convenience sampling probably introduce a substantial bias. Migration is an important determinant of diabetes. There are reasons to doubt the applicability of these results to (future) populations in developing countries.

There is little information about which component of birth weight is the most relevant to future risk of diabetes. Weight at birth is the sum total of fetal experiences in utero but does not indicate the timing or the type of 'insults' nor does it tell us about body composition. It is usually assumed that low weight is a surrogate only for poor muscle mass. Weight for length indices (for example, the ponderal index,  $\text{kg/m}^3$ ) are used as a 'body composition' measurement and a low ponderal index (thinness) is thought to represent poor muscle mass. Studies in European populations showed an inverse association between the ponderal index at birth and later diabetes [9]. The 'thinness' at birth was interpreted to represent 'undernutrition' in utero. The ponderal index tells us about weight for a given height but not the composition of that weight. There is little appreciation that 'thinness' (poor lean mass) is necessarily associated with 'adiposity' (higher fat percent). This could lead to misinterpretation about the etiology of the associations. Given the marked differences in body composition of different populations, a relation between birth weight and later morbidity may have a very different meaning. The metabolically most relevant component of weight at

birth may be adiposity. The relationship of 'thinness' at birth with later diabetes could be due to the 'adiposity' of these babies. The implications of such a misinterpretation for possible intervention are obvious. There is a need to measure relevant body composition and the factors that regulate these to elucidate the relationship between size at birth and later risk of diabetes.

### *Gender*

A related issue in the interpretation of these studies is the effect of offspring gender. Girls have lower weight and higher body fat percent than boys, i.e. they are thinner but adipose. The usual practice is to analyze them together, 'adjusting' for gender. It is advisable to analyze the results separately for boys and girls. Generalizations based on combined analysis may be misleading.

### *Size and Growth*

Another common practice is to equate size at birth with intrauterine 'growth' and assert that 'low' birth weight in a full-term baby is due to intrauterine growth retardation. A small baby of a small mother may not be growth-retarded. Thus neonatal size needs to be interpreted in relation to parental size to be more meaningful.

### *Genetics*

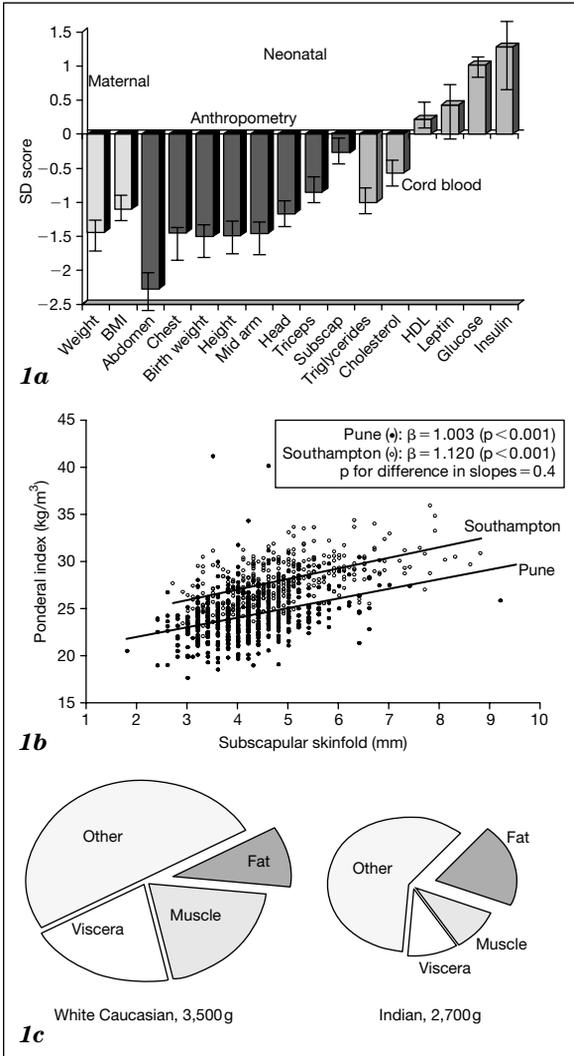
Finally, the father's (genetic) contribution in such relationships is usually forgotten. The paternal influence on the size at birth is predominantly skeletal [10]. Adiposity at birth is determined predominantly by maternal body composition and her metabolism and food intake during pregnancy. During childhood paternal size is an equally if not more important determinant of offspring adiposity [11]. In the absence of paternal measurements, asserting an etiological role to maternal measurements alone may confuse the issue.

### *The Pune Maternal Nutrition Study*

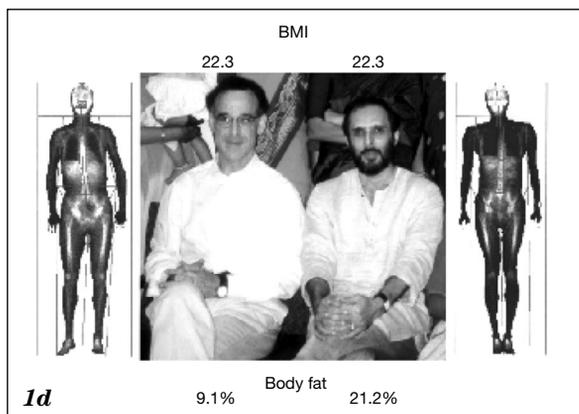
This is one of the few studies where detailed measurements are available. These include: maternal and paternal size; maternal nutrition and metabolism during pregnancy, and detailed anthropometric measurements of newborns in 6 villages near Pune, India. Mothers weighed 42 kg and were 1.52 m tall; babies weighed 2.7 kg and were 47.5 cm long with a ponderal index  $24.5 \text{ kg/m}^3$ .

Comparison of Indian babies' measurements with those of white Caucasian babies born in the UK was revealing [12]. Indian babies were 800 g lighter and  $3 \text{ kg/m}^3$  thinner. They had smaller mid-arm circumference (small muscle) and smaller abdominal circumference (smaller viscera). The head circumference (brain size) was better preserved but the best preserved measurement in the Indian babies was skinfold thickness, subscapular more than the triceps

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**Fig. 1. a** Comparison of babies born in Pune, India and UK. UK measurements are used as a reference (0 line). The bars represent the mean SD score for each measurement in Indians. Measurements of 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 almost similar. Cord plasma leptin concentration is similar and cord plasma glucose and insulin concentrations are higher in Indian babies. **b** For each ponderal index Indian babies had higher subscapular skinfold thickness compared to the white Caucasian babies. **c** Body composition of newborns. A schematic diagram to compare the body composition of Indian babies and white British babies. Indian babies were ~800 g lighter, muscle thin but more adipose compared to the white babies. **d** The Y–Y paradox [16].



(fig. 1a). For each ponderal index Indian babies had higher subscapular skinfold measurement than the white Caucasian babies (fig. 1b). In another study we showed that the cord blood leptin concentration was comparable in the 2 groups of babies despite the size difference [13]. These findings suggest that the Indian babies are thin but fat (adipose). A similar finding was reported many years ago from carcass analysis of Indian babies [14]. The thin-fat phenotype of Indians persists in childhood and adult age [15, 16] and adiposity is the strongest predictor of insulin resistance and diabetes in Indians [17]. These facts help us understand the differences in relationships between birth size and later risk of diabetes in Indians compared to those in white Europeans, and warn us against hasty decisions to intervene.

### **Correction for Current Size in the Fetal Origins Studies**

Many times the relationship between smaller birth size and diabetes is apparent only after adjusting for current obesity. Such an adjustment will reduce the effect of larger birth weight (birth weight and later size are directly related) and there is debate about the relative etiological importance of size at birth and change in size. Those born small but grown big usually have the highest rates of diabetes.

### **Birth Size and Later Diabetes**

Majority of studies in European populations have reported an inverse relationship between birth weight and later diabetes (table 1). In published reports from developing populations this is not always so. For example, in Pima Indians the relationship between birth weight and later diabetes is

**Table 1.** Birth size and later risk of diabetes in adults

Reference	Subjects	Relationship of birth size with diabetes
<b><i>Developing populations</i></b>		
McCance et al. [18], 1994	Arizona, US (Pima Indians) 1,179 (men + women) 20–39 years	Birth weight, U-shaped with diabetes
Fall et al. [19], 1998	Mysore, India 506 (men + women) 47 years	Ponderal index, direct with diabetes Length, inverse with diabetes
Mi et al. [21], 2000	Beijing, China 627 (men + women) 45 years	Birth weight, inverse with glucose and insulin
Levitt et al. [25], 2000	Cape Town, South Africa 137 (men + women) 20 years	Birth weight, inverse with impaired glucose tolerance
Dyck et al. [24], 2001	Canada (Indians, non-Indians) 3,992 (men + women) 32 years	High birth weight, direct with diabetes
Wei et al. [22], 2003	Taiwan 978 (boys + girls) 6–18 years	Birth weight, U-shaped with diabetes
Bhargava et al. [20], 2004	Delhi, India 1,492 (men + women) 26–32 years	Birth weight, nil with impaired glucose tolerance and diabetes and inverse with glucose and insulin
<b><i>Developed populations</i></b>		
Hales et al. [8], 1991	East Hertfordshire, UK 370 (men) 64 years	Birth weight, inverse with diabetes

U-shaped [18]. In Mysore, South India, there was no relationship between birth weight and later diabetes, but short length at birth and larger ponderal index were predictive [19]. The latter relation is the opposite of the findings in Europeans. These ‘fat’ babies were born to heavier mothers. In a recent report from Delhi, India, birth weight was not predictive of diabetes or impaired glucose tolerance in young adults, though there was an inverse association between birth weight and later glycemia [20]. In China low birth weight (as well as shorter length and smaller head circumference) predicted insulin resistance variables in middle-aged men and women while in Taiwan both low and high birth weight predicted type-2 diabetes in children [21, 22]. In Guatemala, birth weight was not related to glucose tolerance in young people [23]. In Canadian Indians high birth weight

**Table 2.** Maternal weight, birth weight and insulin resistance at 8 years in the offspring (Pune Children Study)

Birth weight, kg	Maternal weight, kg			p
	<46.5	<57	≥57	
≤2.5	0.86	0.91	1.19	0.002
-3.0	1.06	1.09	0.94	0.06
>3.0	0.82	1.03	1.03	0.19
p	0.46	0.32	0.56	

Geometric means. Insulin resistance measured from fasting plasma glucose and insulin concentrations using the HOMA model.

(macrosomia) predicted diabetes, there was no relation with low birth weight [24].

Thus, it appears that, unlike the reports in the Europid populations, there is frequently a U-shaped or direct relationship between size at birth and later diabetes in the developing populations. One possible explanation for this difference is the difference in body composition in these populations. In Europeans weight appears to represent lean mass more than the fat mass while in Indians and other developing populations the relation is other way round. If relevant body compartment (adiposity) is measured with appropriate technique, the relationship would probably be a direct one. This could seriously challenge the conventional interpretation of a low birth weight association. Unfortunately there are few attempts to perform good quality prospective studies, we continue to base our ideas on relationships of surrogate measurements in ‘retrospectively’ assembled cohorts.

### **Parental Size and Nutrition, and Offspring Birth Weight**

Since the publication of ‘thrifty phenotype’ hypothesis, there has been a widespread belief that small babies born to small (‘undernourished’) mothers are at increased risk of diabetes. It is also tacitly assumed that improving maternal ‘nutrition’ and offspring size will reduce this risk. Where information is available on maternal size, smaller babies born to larger mothers were at increased risk [26, 27]. In the Pune Children’s Study, small birth weight babies born to the heaviest mothers were the most insulin-resistant at 8 years of age (table 2). In Mysore, fatter babies born to heavier mothers were at the highest risk of diabetes. Improving the nutrition of mothers in chronically undernourished populations may increase the risk for mothers as well as the offspring. Increasing maternal nutrition (pre-pregnant size and weight gain in pregnancy) increases the risk of gestational diabetes which increases the risk

of obesity and diabetes in the offspring [28–31]. Gestational diabetes is a major concern in urban Indian women. We also found that larger birth weight babies increased the maternal risk of metabolic syndrome 8 years later [32]. A large offspring in a small mother will increase the risk of cephalo-pelvic disproportion, interventional deliveries and will increase the threat to the mother's life. Injuries to the maternal birth canal and adjacent organs may cause life-long disability (e.g. urogenital fistulas in African women). In a large study of multiple micronutrient supplementation in pregnant women in Nepal, infant mortality increased despite increased birth size [33].

### **Maternal Nutrition and Offspring Risk**

There are few studies which describe the offspring risk of diabetes in relation to maternal nutrition in pregnancy. In the Dutch winter hunger study, in utero exposure of the fetus to famine during mid and late gestation was associated with a higher plasma glucose concentration in middle age [34]. The Leningrad study failed to show any such relationship [35]. A study in Scotland showed that a high maternal intake of proteins, fats and carbohydrate during pregnancy was predictive of insulin resistance and hyperglycemia in the offspring [36]. There are no prospective studies to show that poor maternal nutrition in pregnancy is associated with an increased risk of type-2 diabetes in children.

The Pune Maternal Nutrition Study will provide crucial information on these relationships. Mothers in the Pune Maternal Nutrition Study had much lower daily intakes of energy and protein compared to UK white women (7.53 MJ and 45 g, compared with 10.04 MJ and 90 g, respectively). Of the macronutrients, only maternal fat intake at 18 weeks of gestation was positively related to fetal size; energy and protein intake were not related. The strongest determinant of fetal size was the frequency of intake of micronutrient-rich foods (i.e. green leafy vegetables, fruits and milk) and blood levels of folate and ascorbic acid [37]. 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 pre-pregnancy body size, maternal nutrition during pregnancy and maternal metabolic milieu on fetal growth and body composition. The preliminary analysis of cardiovascular risk in the offspring at 6 years of age has shown intriguing and unexpected results.

### **Conclusions**

The 'fetal origins' hypothesis has helped focus attention on the importance of intrauterine life in population health and disease. However, the idea that fetal undernutrition is a causative factor for offspring diabetes seems over simplistic. Ideas based on routinely measured parameters of size at birth need

to be reassessed in view of major differences in body composition in different populations. In addition, there could be major differences in the relationships between fetal nutrition and later diabetes in the developing and developed populations. It may be misleading to extrapolate results of retrospective cohort studies in Europeans to populations in the developing world. It seems possible that increasing fetal nutrition could be responsible for the current epidemic of diabetes in developing countries. Prospective studies with well-defined exposures and outcomes are necessary to answer these questions.

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## Discussion

*Dr. Kramer:* At the beginning of your talk you said that it is time to think about prevention. So I have two questions for you. First, for a long time there have been

preventive efforts from the WHO and the World Bank to increase the size of babies in South Asia [1]. I wonder if you could comment on the likely benefits and risks of those efforts? Second, there are some specific trials current in the field. Dr. Fall (unpublished), for example, is selectively increasing the intake of green leafy vegetables as a way of increasing birth weight. What are your comments about that? If you think that these two kinds of preventive efforts are misguided, what would you recommend for prevention other than converting Indians from vegetarians to meat eaters?

*Dr. Yajnik:* The first one about the international efforts to increase the size of Indian babies: as I already mentioned I think we need a better appreciation of what is small for the Indian subcontinent and what are the risks. Currently everyone relates birth weight with perinatal risk. In the current thinking there are hardly any ideas of future risk of diabetes or heart disease. Now what I can tell you is that, within the last 20–30 years, the perinatal mortality has been substantially reduced in India without much change in birth weight. I think low birth weight is to a large extent a surrogate for a whole lot of conditions which increase the bad outcome for the pregnancy. If you educate the mothers, improve hygiene, improve the safety of delivery, then we are going to have better perinatal statistics than just concentrating on birth weight. In urban India birth weight has increased by 40 to 90 g within the last 50 years, so has the prevalence of diabetes. I suspect that the increase in birth weight might actually be related to future problems, partly because Indians are very likely to increase their birth weight by depositing more fat. This brings us to the next point: rather than concentrating on birth weight we would like to produce babies who will have a larger lean mass rather than fat the so-called ‘good’ birth weight. That also is slightly tricky because in the adult study that we did [2] the story is a bit more complicated. At a given fat mass we found that increasing fat free mass does not protect against insulin resistance. People ask me again and again: is this genetic? If there is an additional genetic predisposition which is expressed just by being larger either for the total size or for fat mass or for fat-free mass then again we are in trouble by just increasing size. I think we need more basic studies to understand what all these things mean before we jump into intervention. In the meanwhile we could concentrate on interventions which might actually improve perinatal outcome without changing birth size. The second question was about Fall’s intervention study [3]. I did not join it because of our results. It was a conscious decision. At that time I had a suspicion, now I have some proof that vitamin B<sub>12</sub> deficiency modified the response to green leafy vegetables and folate. Therefore I have strongly recommended vitamin B<sub>12</sub> supplementation in addition. They have gone up and down, first they said they will include B<sub>12</sub> later they said they don’t want to. So my stand is that I would not like to intervene with green leafy vegetables until we have improved the B<sub>12</sub> status of this population. As to the third question: I think it is impossible to influence hardcore Indian vegetarians to eat non-vegetarian food. Therefore we have to look at B<sub>12</sub> sources which are more acceptable to them. Vitamin B<sub>12</sub> comes from microbes, plants don’t make it, animals also get it from microbes. Therefore we have to think more about items like milk, which is acceptable to the vegetarians, and foods fermented by B<sub>12</sub> producing microbes.

*Dr. Patel:* In terms of protein intake that you mentioned: do you have any information about protein coming from milk products versus legumes so that we might be able to see what kind of B<sub>12</sub> intake might be coming from animal products such as milk, and whether the milk intake during pregnancy might be beneficial not so much for the protein but for vitamin B<sub>12</sub> that it may provide?

*Dr. Yajnik:* That is a very good point. I reanalyzed our data, correcting for milk intake, animal protein intake and total protein intake, and the relationship between B<sub>12</sub> and folate in predicting birth size and insulin resistance at 6 years holds. Your point

is well taken that if we improve the intake of animal protein it should also bring more B<sub>12</sub> with it I think we should seriously think about it.

*Dr. Uauy:* One concern I have when you talk about under- and overnutrition: we get the concept that this is poverty and the other is affluence. So I would warn that we should talk about an imbalance of energy versus nutrients because otherwise we are talking about a dichotomy which in fact does not truly exist because they coexist. You actually have focused on the micronutrients. How about energy, the micronutrient quality namely carbohydrate versus fat, type of carbohydrate in fat, because one possibility is that this is genetic and the other is that it is perhaps a combination of genetics plus diet, but interacting in ways that we can't actually measure, which is hormonal responses to food. So in a way some of what you are hinting about insulin resistance may have to do with the combination of micronutrients and hormonal responses to food. Have you examined micronutrient composition, type of fat, simple carbohydrate, in this threshold analysis with the beautiful dietary data that you have?

*Dr. Yajnik:* Not really, we have restricted ourselves just macronutrient contribution to energy percentage but I should go back to our data and analyze the quality of carbohydrates and the quality of fats. We are now in the process of setting up a new study where we will be able to prospectively collect this on a relatively smaller number.

*Dr. Uauy:* One of the issues of the Indian diet to consider is of course the trans fats that are both in the fat that is used for cooking and some of your hydrogenated fats which are excessively consumed. Of course they are hard to measure, but in terms of the biological effect of trans, in terms of metabolism, some of what we may be seeing here may be related to trans fatty acids.

*Dr. Yajnik:* I agree with you, I really didn't know trans fatty acids could be measured in blood samples, all these days I thought it was only intake data. So we have these samples in the freezer and we are collecting new samples so perhaps with your help we can set it up.

*Dr. Rosenquist:* In your presentation you showed some data about hyperhomocysteinemia in a very high rate. This obviously is typically related to the complex interaction among B<sub>12</sub> and folic acid and other nutrients. I wonder if you have looked at any potential genetic influence of the methyltetrahydrofolic reductase gene that has a substitution at C677T? A substitution has been found in a large percentage of people who have been tested in the US and Holland (25%). It predicts high homocysteine even in the presence of folate repletion as you have shown. I wonder if you have done any testing for this?

*Dr. Yajnik:* All these samples have been tested for MTHFR C677T and the allele frequency is less than 3%. Other Indian studies have also shown an allele frequency of less than 5% [4]. Thus, this allele frequency is very low in Indians. We haven't looked at the other A1298C polymorphism. In collaboration with Dr. Miller at UC Davis, we are investigating polymorphisms in B<sub>12</sub>-transporting proteins. Thus we are preparing to look at the genetics of folate and B<sub>12</sub> metabolism.

*Dr. Rosenquist:* Your large population presents an exciting possibility to survey for polymorphisms of various kinds.

*Dr. Yajnik:* Yes, we now collaborate with Prof. Hattersley and the Center for Cellular and Molecular Biology (CCMB), Hyderabad, India. Within the next few years we will be able to tell you a whole lot about different polymorphisms in relation to this.

*Dr. Rosenquist:* I am looking forward to that.

*Dr. Pencharz:* I would like to go back to your point about improving lean mass, because I looked at your intake data and protein is certainly very low and people in India are known to have a low protein intake in part because of the vegetarian diet. So that is an issue. In fact the question that came up is, are there differences between Indians and people in Boston, at least as far as lysine requirements per unit of body

weight or unit of lean body mass, and the answer is no. So I really think that if you are willing to work forward you are going to worry about protein intake in these women. My question is, you have very elegant dietary data, but I find that I don't even tell myself the truth about what I eat. Do you have an external validation of those energy intakes of 1,700 cal, have you actually got double-labeled water to know what the expenditure is so you know that these intakes relate to expenditure?

*Dr. Yajnik:* I take your point of protein intake. We plan to collaborate with Dr Kurpad to seriously look into protein metabolism. At one time we thought that vitamin B<sub>12</sub> concentration may be a surrogate for low protein intake but this does not appear so. Your second point was about external validation. We did not have double-labeled water that time because of world shortage, but we are going to do it some time. Therefore we did the two validations about food intake. I would say that in this village community there is unlikely to be any underreporting because women were interested in helping us. To improve the reliability of the data we employed girls belonging to the local community and they were given responsibility for 20 households. They visited these women the day before and stayed with them for the whole day. They weighed every single food item that was cooked, and part of it was put in bags and analyzed in a laboratory for macronutrient content. The next day when we asked them for recall, these girls helped them with the recall. In a limited number we validated the intake by collecting 25% food sample of the total intake for laboratory estimation. This was as good as we could do. There may be some underestimation. However, we applied WHO BMR guidelines [5] and found that 150 women had inappropriately low intakes (<1.2 times of BMR).

*Dr. Hornstra:* I congratulate you on this talk. I think you presented fascinating data and a lot of food for thought, that is for sure. There is one thing though I would like to discuss with you. If we relate outcome to maternal values I see your point because that is where you can intervene. On the other hand why not relate it to infant values because that is where the action is. To give you an example, I told you yesterday about the relationships between neonatal  $\gamma$ -linolenic acid and insulin resistance at age 7 years. We did not find those relationships when we looked into the  $\gamma$ -linoleic acid status of the mothers during pregnancy. So I am a little bit in conflict with myself and with your data. Should we look to the mother because we are intervening in the mother, or should we look to the infant where the action is?

*Dr. Yajnik:* I think we should look at both. In this study unfortunately we did not have cord bloods, because these women delivered at home. In the last 10 years the practice has changed and today 2 out of 3 deliveries happen in an institute. From May 1, 2004, we are doing a new study in which we are going to study all the women delivering in institutes in the villages, with collection of cord blood and placenta. We are going to look at maternal B<sub>12</sub> status at 3 times during pregnancy, their food intake and a number of other parameters which have been suggested just now. I think the Indian situation is that we have actually a PIH outcome in baby without PIH in the mother, and therefore placental histology will be interesting.

*Dr. Hornstra:* I was somewhat disturbed to see that there is a negative relationship with the intake of green leafy vegetables, and I was wondering whether this is some kind of surrogate for prosperity perhaps? Which brings me to the question, did you correct for socioeconomic status?

*Dr. Yajnik:* We did correct for socio-economic status. I accept it is not easy to measure. We now measure it in the best way possible, the National Family Health Survey method (NFHS-II). This is based on the information about housing, education, family size, possessions etc. The statistical relationship between GLV and birth size is independent of these measurements.

*Dr. Hornstra:* Can it be that this negative relationship exists because of low B<sub>12</sub>?

*Dr. Yajnik:* Probably yes, we are working on this.

*Dr. Waller:* First question: there is a high prevalence of diabetes in your country, is there a birth defect monitoring system there and do you have any idea whether the rate of birth defects is elevated in your country due to diabetes? Second question: did I hear correctly that you think there may be a relationship between maternal levels of folate or B<sub>12</sub> and the development of insulin resistance in the offspring?

*Dr. Yajnik:* First question: we don't have a birth defect monitoring, and second is yes. I feel that high folate in the mother in the presence of low B<sub>12</sub> is associated with insulin resistance in the offspring. Whether this is causal we can't say because this is an observational study. I have been reading more about biochemistry of folate and B<sub>12</sub>, and there are very interesting pathways which are opened up when there is B<sub>12</sub> deficiency and folate sufficiency. If you give a lot of folate to a B<sub>12</sub>-deficient patient then you suppress the hematological manifestations but you worsen the neurological manifestations. The neurological manifestations are because myelin synthesis is affected, and myelin is largely lipids. We are in the process of analyzing the fatty acid patterns in adults who have B<sub>12</sub> deficiency and high folate. Thus 'B<sub>12</sub>-deficient folate-replete' status alters fat metabolism in some way, which might promote adiposity on one hand and insulin resistance on the other hand. Such pathology could also affect  $\beta$ -cells and alter its function.

*Dr. Waller:* So if they were B<sub>12</sub>-deficient the increased folate might be disadvantageous.

*Dr. Yajnik:* That's it, yes.

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