

Preventing the Projected Epidemic of Non-Communicable Diseases in Emerging Nations

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Imperative of Preventive Measures Addressing the Life-Cycle

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Abstract



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Introduction

The world is facing an unprecedented epidemic of type 2 diabetes (T2D) and other chronic non-communicable diseases (NCDs). The rise in the prevalence of T2D in the last few decades has been phenomenal, perhaps unmatched by any other chronic condition. The pattern of affliction is rapidly changing; the poor and the young are increasingly affected. In 2007, there were an estimated 246 million diabetic patients in the world, of which 165 million (80%) were in the developing world [1, 2]. A substantial number are diagnosed before 40 years of age, and it is increasingly common to see T2D in children. Current trials of diabetes prevention have concentrated on modifying lifestyle in middle-aged people with advanced risk factors (obese and impaired glucose tolerant). Such attempts are unlikely to curtail the epidemic, fuelled by the increasing incidence in the young.

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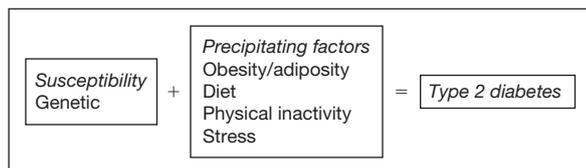


Fig. 1. The conventional model for the origin of type 2 diabetes. The current diabetes prevention trials are based on the conventional model.

Over last three decades there has been growing recognition that early life factors have a major influence on the risk of T2D. Studies in Pima Indians showed that maternal hyperglycemia in pregnancy increased the risk of obesity and diabetes in the offspring [3]. On the other hand studies in the UK showed that low birthweight (LBW) was a risk factor for T2D diabetes in the offspring [4]. These studies focused attention on intrauterine environment as an important determinant of subsequent risk of T2D. Subsequent studies demonstrated that rapid childhood growth was also a strong risk factor for obesity and T2D. Thus, factors influencing intrauterine and childhood growth seem to affect the risk of T2D. These new developments have challenged the rather limited idea of controlling the diabetes epidemic by intervening in the middle-aged population with advanced risk factors.

Here we will review some of these new ideas and discuss the imperative for a life-course approach to the prevention of chronic NCD, with focus on T2D.

Conventional Model of Pathogenesis of Type 2 Diabetes and Prevention Strategies

The classic view of the etiology of T2D suggests that aging and modern-day lifestyle factors (dietary excess and physical inactivity) cause hyperglycemia in those genetically predisposed (fig. 1). The lifestyle factors act to promote obesity, which is an integral part of this process ('diabesity') and thought to act by causing insulin resistance (IR). The contribution of genetics is less clear. Recent genome-wide association studies have shown that variations in more than 10 regions in the human genome increase the risk of T2D, the majority of these seem to affect pancreatic β -cell function [5]. In the absence of any methods to tackle genetic susceptibility, the preventive approach has so far focused on the control of lifestyle factors in those at high risk (middle-aged, those with a family history of diabetes, obese and impaired glucose tolerance). A number of studies across the world demonstrated that dietary modifications and promotion of physical activity (sometimes with a pharmacological agent) improved glycemia in individuals with impaired glucose tolerance (IGT) [6]. This has been interpreted to mean 'prevention' of diabetes,

which may be a bit naïve. Obesity and IGT are both ‘end-stage’ conditions with arbitrary cutoff points (which have changed substantially over last 2 decades). Trying to treat only such ‘high risk’ individuals is unlikely to curtail the burgeoning epidemic of obesity and diabetes, which is rapidly spreading to involve the younger and the poorer. Controlling obesity and metabolism in post-reproductive years will not benefit the offspring, a major limitation to our efforts at curtailing the epidemic.

Changing Epidemiology of Obesity and Type 2 Diabetes

A few decades ago T2D was considered a disease of the affluent (‘what gout was to the royalty in the UK’). However the scene has rapidly changed. There are more diabetic patients in developing countries than in developed countries. Moreover, in many developed countries and in some developing countries, the prevalence of obesity and diabetes is higher in the lower socio-economic groups compared to the affluent (‘reversal’ of the socioeconomic gradient). While part of this change could be ascribed to the healthy behavior of the affluent and the educated, other biological factors seem to operate.

Some striking features of diabetes epidemiology in developing countries (like India) include: (1) younger age at diagnosis; (2) lower body mass index; (3) higher adiposity (body fat percent) and central adiposity (waist-hip ratio and visceral fat, ‘thin and fat’), and (4) higher IR [7]. Over the last few decades, age at diagnosis of T2D has fallen by many years in India. Children are increasingly affected with obesity and T2D, especially in the urban affluent. Clearly the diabetogenic influences are operating at a much younger age and at lower threshold of body size. We know that hyperglycemia is usually present for many years before clinical diagnosis [8] and that the risk factors are present for a long time before glucose concentrations start rising [9, 10]. It is increasingly clear that preventive strategies will have to start very early in life.

Early Life Factors and Risk of Diabetes

Maternal Diabetes and Offspring Obesity and Diabetes

Pettitt et al. [3] and Dabelea et al. [11] made a very interesting observation in Pima Indians. Taking advantage of a prospective serial database in the Pima Indian community, they analyzed the contribution of genetics and intrauterine environment to the risk of obesity and diabetes in the offspring. The risk of diabetes was many times higher if the mother had diabetes during pregnancy (‘intrauterine exposure’) compared to the risk in the children whose mothers developed diabetes after pregnancy (‘genetic risk’). They suggested that intrauterine hyperglycemia is more important in intergenerational

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propagation of diabetes compared to genetic factors. Diabetes in young girls is thus a major factor in the escalating epidemic of diabetes. A subsequent analysis showed that 70% of diabetes in young Pima Indians could be ascribed to maternal diabetes.

Maternal Nutrition and Offspring Diabetes

Barker [12] proposed a novel model for the etiology of T2D and cardiovascular disease (CVD) when they demonstrated that LBW was a risk factor for these conditions. In addition to LBW, other measures of small size at birth (length, ponderal index, etc.) also predicted future T2D or its two pathogenic mechanisms, i.e. IR and impaired β -cell function. It was proposed that intrauterine growth restriction (IUGR) consequent upon maternal undernutrition contributed to this association. In the original form this was called the 'thrifty phenotype' hypothesis and other terms like 'fetal origins' and 'small baby syndrome' were also used. Many studies across different populations confirmed the association between small size at birth and later diabetes [13].

Size at birth is only a surrogate for events during intrauterine life. It is useful to remember that it is an intermediate phenotype between the intrauterine exposures and the final outcome. It is also a nonspecific and insensitive marker for nutritional exposures, and does not provide a clue to the nutrient or the time of exposure. Another point of relevance is that the association between birthweight and T2D is U-shaped (as shown in Pima Indians [14]), thus both LBW and large birth weight (contributed by maternal diabetes) increase risk of T2D. Target for intervention is thus the intrauterine environment rather than birthweight.

Fetal Programming

The associations between size at birth and later disease have been explained by the concept of 'fetal programming'. It refers to a permanent change in the structure and function of a developing organism in response to an environmental factor [15]. The intrauterine environment thus assumes a great significance in determining the future prospects for the fetus. Programming is thought to be a 'predictive' adaptation [16]. The programmed fetus will do well in a similar postnatal environment, but if the environment is substantially different, the fetal 'programs' are unable to cope and result in disease.

I will review briefly some of the findings of the studies in Pune, which have helped the thinking in this field.

Pune Children's Study

In 1991 Prof. David Barker visited us and discussed the idea of 'intrauterine origins'. With his help we started a study of over 400 children whose birthweights were available from the labor room records at King Edward Memorial Hospital in Pune. We studied their anthropometry, glucose

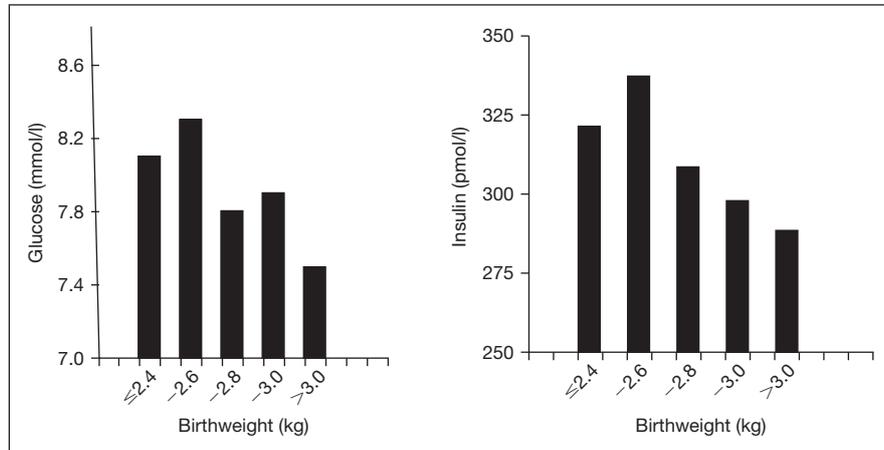


Fig. 2. Plasma glucose and insulin concentrations after an oral glucose load in 4-year-old Indian children. Significance of the trend is corrected for age, gender and current bodyweight. The results show that low birthweight is associated with higher glucose and insulin concentrations [17].

tolerance and circulating insulin concentrations. Plasma glucose and insulin concentrations 30 min after the glucose load were inversely related to birthweight (fig. 2). [17] This provided the first proof for Barker's hypothesis in a developing country. Given the fact that almost a third of the babies born India are small by international standards, this could have enormous implications for the diabetes epidemic.

We studied these children again at 8 years of age, and confirmed the association of LBW with higher IR [18]. In addition, we found that the levels of the risk factors for diabetes and CVD (glucose, IR, lipids, blood pressure, leptin concentrations, etc.) were highest in children who were born lightest but were heaviest by 8 years of age (fig. 3). This finding focused attention on rapid childhood growth as a risk factor for T2D. We also found that children born to short parents were more insulin resistant, and those who had grown taller in relation to parental height were the most insulin resistant, suggesting an intergenerational influence of poor parental growth on the metabolic risk of the offspring. A discordance in size (presumably due to nutritional factors) in one's lifetime (LBW and later overweight) as well as across generations (short parents and tall children) predicts a higher metabolic risk.

A study in Delhi provided further proof that rapid childhood growth predisposes to T2D [19]. Over 1,500 men and women, for whom growth data were available from birth, were studied at 28 years of age. The diabetic subjects were born lighter, grew more slowly during infancy but progressively faster from 3 years of age compared to those who were normal glucose tolerant (fig. 4). They had an earlier adiposity rebound.

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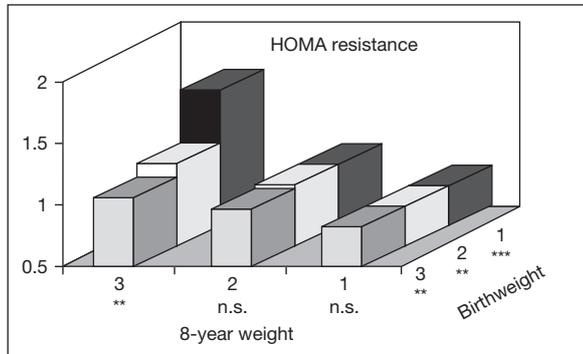


Fig. 3. The mean levels of insulin resistance (HOMA) in 8-year-old children by tertiles of birthweight and 8-year weight. Those born the lightest but having grown heaviest are the most insulin-resistant. The effect of the 'rapid transition' in one's lifetime is highlighted, and the effect of the double burden (early life undernutrition and subsequent overnutrition) in an individual is depicted. n.s. = Not significant. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ [18].

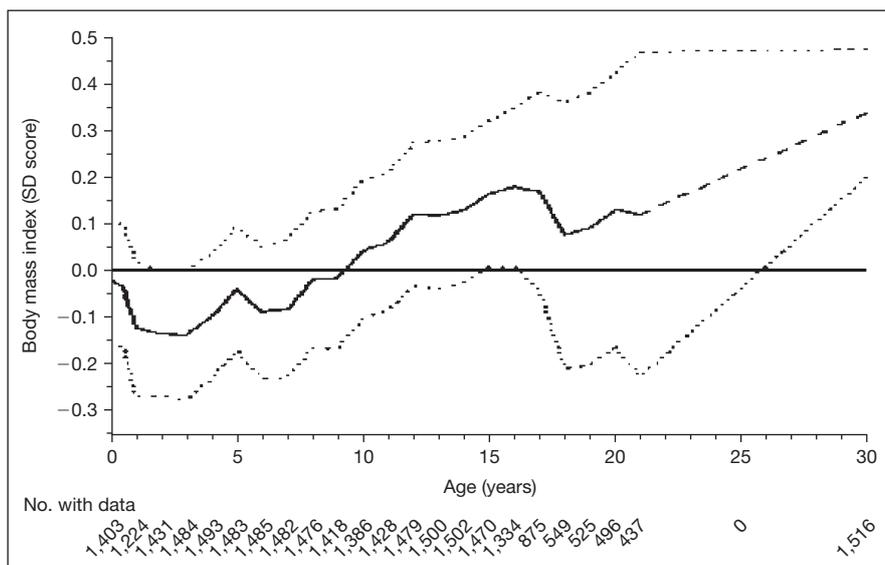


Fig. 4. Mean sex-specific unadjusted SD scores for body mass index, according to age, for subjects in whom impaired glucose tolerance or diabetes developed. The mean SD scores (solid lines) are obtained by linear interpolation of yearly means, with one additional observation at 6 months. The dotted lines represent 95% confidence intervals. The dashed portions of the lines indicate years in which there was no follow-up. The SD score for the cohort is set at zero (solid horizontal line) [19].

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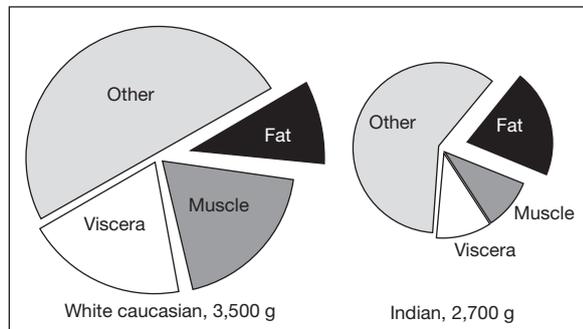


Fig. 5. A schematic diagram to compare the body composition of Indian and White Caucasian (UK) newborn babies. The Indian babies are approximately 800 g lighter, have less muscle but higher adiposity than the White babies.

In all these studies only size measurements were available at birth and later. The possible role of nutrition in these associations is speculative. We therefore set up a prospective, community-based study of maternal nutrition and fetal growth, with a view to follow the children until adult life for the risk of NCD.

Pune Maternal Nutrition Study

The Pune Maternal Nutrition Study (PMNS) was started in 1992 in 6 villages near Pune. Over 2,500 eligible nonpregnant women were followed up regularly, of whom over 800 women became pregnant during the study. We measured their nutrition, physical activity, biochemistry and fetal growth. Newborn babies were measured in detail at birth and every 6 months thereafter. Every 6 years we do a detailed assessment of body composition, IR and a range of other cardiovascular risk factors. Over 700 children are being followed up currently at 12 years of age.

We made an interesting observation that Indian babies, though small, short and thin, had comparable subscapular skin-fold-thickness measurements compared to White Caucasian babies born in the UK [20]. In other words they were 'thin but fat' very similar to our previous description of Indian adults. This suggests that body composition is established at birth (fig. 5). In a subsequent study we compared cord blood measurements, and showed that Indian babies have higher concentrations of insulin and leptin but lower concentrations of adiponectin, compared with those in White Caucasian babies in the UK, again suggesting that the high risk Indian phenotype for T2D is established at birth [21]. If we were to think of a real preventive intervention, it will have to start in utero, and improving the health of young girls will be a very important aspect of such an approach. This must represent a paradigm shift in thinking about the prevention of the T2D epidemic.

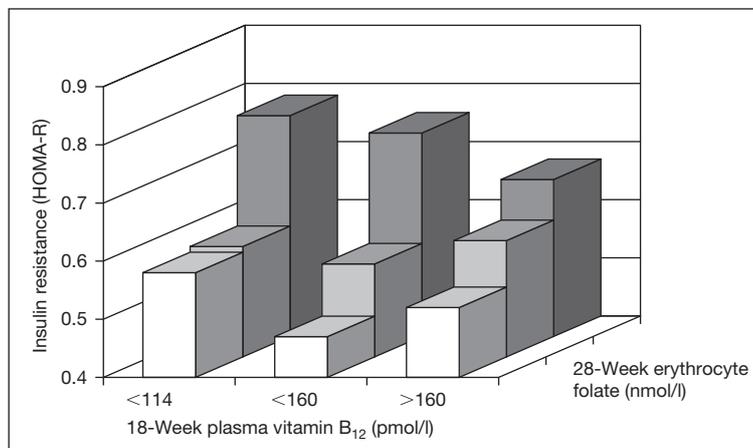


Fig. 6. Insulin resistance (HOMA-R) in children at 6 years in relation to maternal vitamin B₁₂ (18 weeks) and erythrocyte folate (28 weeks) [24].

Another important observation in the PMNS was that maternal micronutrient nutrition was an important determinant of fetal growth in this population. Maternal intake of calories, proteins and fats did not have a significant effect on fetal growth but the frequency of consumption of green leafy vegetables, milk and fruits had a major effect [22]. Additionally we found that higher maternal circulating concentrations of homocysteine predicted IUGR [23]. Over two thirds of mothers had low vitamin B₁₂ concentrations, while only one woman had folate deficiency. Low vitamin B₁₂ status in this population was ascribable to low dietary intake, predominantly due to vegetarianism. Even more interestingly, at 6 years of age the children's adiposity and IR were significantly related to maternal B₁₂ and folate levels in pregnancy [24]. Children born to mothers with low B₁₂ concentrations but high folate concentrations were the most insulin resistant (fig. 6). This is the first demonstration in a prospective study of a relationship between maternal nutrition in pregnancy and offspring risk of T2D.

Thus, a deficiency as well as an imbalance between these two related vitamins which affect one-carbon (methyl) metabolism may be responsible for structural and functional programming. Maternal nutritional disturbance of these two vitamins disturbs fetal growth and development, which may manifest as early abortions, congenital anomalies (neural tube defects and cardiovascular anomalies), IUGR or a change in neurocognitive function, body composition and metabolism. To include such a spectrum of effects we propose a new term, 'nutrient-mediated teratogenesis' analogous to Freinkel's [25] concept of 'fuel-mediated teratogenesis' in a diabetic pregnancy.

Experimental Models and the Concept of Epigenetics

Animal models of maternal undernutrition and fetal programming have provided crucial information on these phenomena. A review is outside the scope of this article and readers are referred to work from Hoet and Hanson [26] and Hales et al. [27].

Animal models have provided exciting information on the role of methyl groups in fetal programming. Waterland and Jirtle [28] fed genetically obese Agouti mice with a 'methylating cocktail' (B₁₂, folic acid, choline and betaine) and showed that the offspring had a different coat color and were less obese, despite inheriting the Agouti mutation. This was related to the methylation status of the promoter region of the Agouti gene. Lillycrop et al. [29] demonstrated that folate rescue in the rat model of maternal protein deficiency was related to methylation in some of the genetic sequences. Sinclair et al. [30] produced methionine deficiency in female sheep (by dietary restriction of methionine, B₁₂ and folate). Ova from these sheep were fertilized in vitro, and the blastocysts were transferred to surrogate mothers with normal methionine status. The offspring were obese and insulin resistant, especially males. They demonstrated a differential methylation at number of sites in the genome of these animals. This model highlights the importance of periconceptual one-carbon (methyl) metabolism in fetal programming.

These phenomena are included under the concept of 'epigenetics' which refers to heritable modifications in the genome not associated with a change in the base sequence [31]. Periconceptual, embryonic and fetal life are considered the most opportune times for epigenetic manipulation, though it may continue postnatally. Many of these changes are organ-specific and contribute to differentiation and development. Methylation of cytosine residues in the CpG dinucleotide regions of DNA and acetylation of lysine residues of the histones are two known mechanisms that affect gene expression and function.

Fetal Programming in Rapid Transition

In countries undergoing rapid transition there is a double burden of disease: the rapidly emerging T2D and CVD along with the unconquered nutritional and infective disorders. This is evident in the morbidity and mortality statistics of rural and urban populations in India. The rural populations predominantly suffer from undernutrition and infections while urban populations are increasingly affected by overnutrition-related NCD (T2D and CVD). Often the two coexist, for example urban women have the double burden of micronutrient deficiencies and gestational diabetes with potentially grave consequences for fetal programming. Such a combination of factors could be at the heart of the rapidly escalating epidemic of T2D.

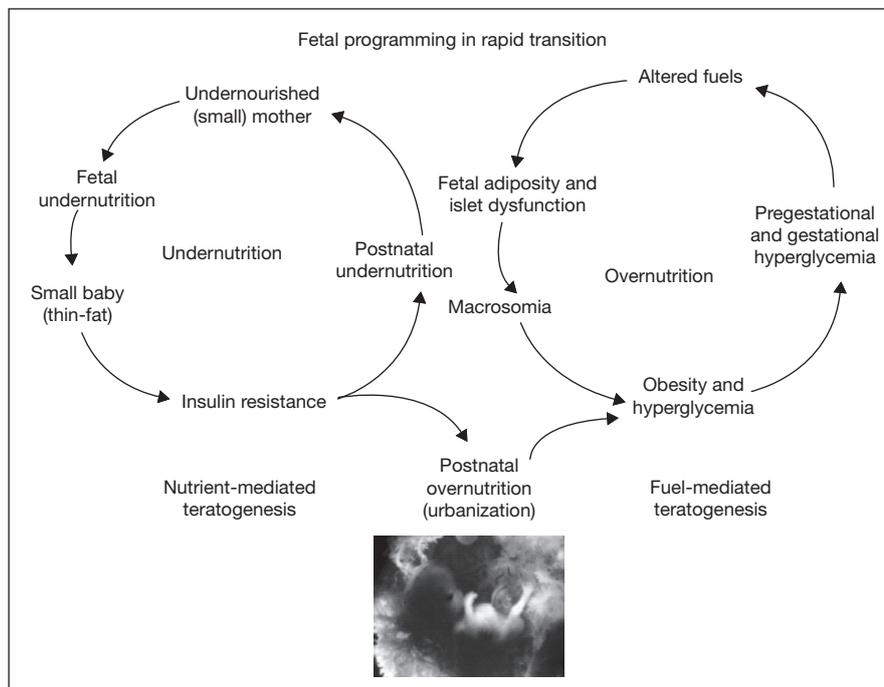


Fig. 7. The interrelationship of two major maternal factors (undernutrition and overnutrition) in fetal programming is shown. An undernourished mother produces a small (thin-fat) insulin-resistant baby. If this baby remains undernourished in postnatal life, the cycle is propagated. If the thin-fat insulin-resistant baby is overnourished, it becomes obese and hyperglycemic. An obese and hyperglycemic mother produces a 'macrosomic' baby at a higher risk of obesity and hyperglycemia. Thus the intergenerational insulin resistance–diabetes cycle is propagated through a girl child. Rapid transition shifts the balance from undernutrition to overnutrition, and contributes to escalation of the diabetes epidemic. Improving the health of a girl child is of paramount importance in controlling the diabetes epidemic [32].

We have conceptualized this complex interplay in a model based on data from our own and other research. It proposes that the two cycles of fetal programming (related to 'undernutrition' and obesity-diabetes related 'overnutrition') operate separately, overlap or combine to produce a spectrum of NCD that are influenced by postnatal nutrition. Thus, 'nutrient-mediated teratogenesis' and 'fuel-mediated teratogenesis' are two operational faces of the same coin (fig. 7) [32]. The undernutrition 'track' produces 'small, thin and fat' babies who are insulin resistant and remain so if postnatal nutrition is not excessive. They have low rates of NCD. When postnatal nutrition is relatively plentiful, it promotes obesity and hyperglycemia, many times without correction of the micronutrient imbalance. In a female such

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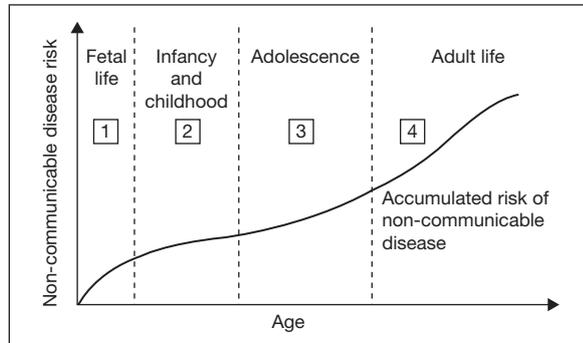


Fig. 8. The World Health Organization's life-course model of non-communicable disease. The model suggests that non-communicable diseases have their origins in early life. The risk progressively accumulates throughout the life course and the disease becomes manifest in later life [34].

a situation exposes her fetus to multiple adverse programming influences, resulting in a complex phenotype that includes exaggerated adiposity ('macrosomia') and pancreatic islet dysfunction with a tendency to develop diabetes, CVD and other disorders at a young age. The nutritional history of a population thus becomes an important determinant of the health of the present generation.

The Life-Course Model and DOHaD

Kuh and Ben-Shlomo [33] synthesized such ideas into a 'life-course' model for NCD which stresses that risk of these conditions is not attributable solely to either early life or adult experiences but instead they operate cumulatively throughout life. A WHO committee adopted these ideas to include many disorders (fig. 8) [34]. To accommodate the new evidence since the coining of the original term 'fetal origins of adult disease', the international council of 'early life origins' also adopted a new term 'developmental origins of health and disease' (DOHaD) [35]. All these terms represent the growing recognition of the importance of environmental factors acting on the genotype throughout the life cycle of an individual to progressively modify its phenotype (fig. 9). Clearly there are 'windows' of time in the lifecycle when the susceptibility of the genome to such an influence is very high. The periconceptual and intrauterine period seems to be the most crucial time, when a small change in environment could have a large effect on the phenotype. The need is to define these periods and the environmental exposures of importance. Research in this area has a lot to contribute to our understanding of the determinants of health and disease in populations.

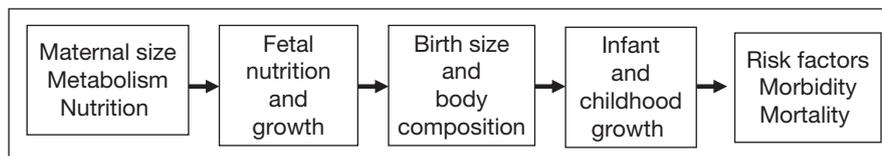


Fig. 9. Current concept of the Developmental Origins of Health and Disease (DOHaD). The influence of early life factors (including maternal factors and childhood growth) on the burden of type 2 diabetes and other non-communicable disease is shown.

The Imperative of Life-Cycle Prevention

I hope, the above discussion has highlighted the need to start early in life to prevent NCD. Current teaching and medical practice revolve around the idea of ‘fixing’ the end-stage conditions, which is difficult, expensive and unaffordable for the majority. The lack of appreciation of the life-course evolution of these conditions has resulted in prevention trials that concentrate on high-risk adults. Such an approach leaves the larger and more important issue of ‘susceptibility’ unanswered, and has no benefits for the offspring who are at an even higher risk. Recognition that intergenerational environmental influences (‘epigenetic’ rather than ‘genetic’) might be important has opened new avenues for research and intervention in NCD. Maternal nutrition and metabolism appear crucial to the risk of the offspring. Thus, improving early life environment may be more beneficial and cost-effective than only concentrating on the lifestyle factors in later life and devising newer treatments for the end-stage conditions. The health of young girls and women is of paramount importance, as highlighted in the Millennium Development Goals [36]. A recent meeting captured this well in its slogan: ‘Woman’s health is nation’s wealth’ [32]. It is time to capitalize on the new exciting ideas in this field and promote translation research.

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Discussion

Dr. Wharton: So far we have done a lot on the coexistence of these two conditions and I did hope that for the rest of the conference we could be discussing whether there was interaction. I think throughout there has been an underlying assumption, which we just heard about in detail very elegantly, that a period of malnutrition primes, programs or predisposes, whichever word you wish to use, to later obesity. We have heard quite a lot about secular changes in the amount of obesity and then we haven't heard anything about secular changes in birthweight in any of these countries, and I think we would need to do that if we were developing that theme; some on the reduction in childhood malnutrition; perhaps not very much on the growth patterns whether there is a secular change in growth patterns in the first few months of life to fit in with the fetal or early catch-up growth hypothesis, whichever one you support, we would need to know about. I just have a slightly uncomfortable feeling about taking on the idea that early undernutrition leads to later obesity because if we look at so many countries we find that childhood malnutrition is going down but adult obesity is going up. China is probably the best one to quote because of such extensive figures on this. Of course the cohort studies seem to leave no doubt, but they don't seem to account for the temporal changes we are seeing in societies because there is less childhood malnutrition in many but their obesity is going up. The same applies to other ideas about adult obesity. We are getting more breastfeeding in communities throughout the world but obesity is going up. The amount of protein that we give to the very young is going down mainly because we rely less on whole cow's milk and yet obesity is going up. So those overall population observations don't seem to fit in very well with the results that you conclude from the cohort studies. Now I can't fault the cohort studies but I do see a sort of mismatch of conclusions in the cohort studies, but does it explain these big population changes that we are seeing throughout the world?

Dr. Yajnik: Sachdev [1] wrote a systematic review a few years ago about birthweight in India and showed the magnitude of an increase in birthweight of about 52–126 g over a period of 25 years. Studies in Indian immigrants in the UK have not shown much change in birthweight [2, 3]. The question you ask is, 'Is the increasing obesity in adults matched by increasing birthweight?' The transfer of nutrients to the fetus is complex and if the fetus grew bigger compared to the mother's pelvis there would be a disaster. Christian and Osrin [4] analyzed the outcomes of maternal intervention in Nepal and Bangladesh where a multi-nutrient supplementation to the underweight women increased birthweight but also increased the perinatal and infant mortality.

Dr. Wharton: What I am saying is that there has been a 200-gram increase in birthweight, which is an amazing change in population terms on average birthweight. The conclusions we draw from cohort studies, shouldn't that increase in birthweight being

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accompanied by a reduction in obesity and yet you are seeing actually increases in obesity?

Dr. Yajnik: Birthweight is one aspect, ponderal index is the next complexity and body composition the next. Indian babies put on more fat when they put on weight. So increasing birthweight in Indian babies because of their adipose composition might increase the problem.

Dr. Shahkhalili: The increase in average birthweight is also due to a continuous increase in the number and weight of large babies, especially among obese/overweight mothers with gestational diabetes. Thus an increase in average birthweight does not reflect a birthweight improvement among small babies.

Dr. Popkin: I think we are completely mixing concepts related to averages vs. distributions. We are talking about the proportion of children with a certain ponderal index and a certain fetal environment and what comes later. Even in a country like China average birthweight is going up and low birthweight is going down, so we still have a subset of children who still suffer the kinds of problems that we have with the DOHAD group. You must be careful not to extrapolate too much from trends in income, etc., without studying the proportion poor.

Dr. Sawaya: I don't think birthweight is a good measurement or a good marker; I would say lean body mass. You need to know if lean body mass is increasing or not because just an increase in birthweight means an increase in body fat in many Western countries. I would like you to help me to understand your data in comparison to our data about the increase in height. You mentioned that in short parents there was an increase in the height of the baby and this was related to an increase in insulin resistance.

Dr. Yajnik: No, what I said was children who had grown more than what we would expect from the parental height had the highest insulin resistance. But this is an observational cross-sectional study.

Dr. Sawaya: As I showed you yesterday we had the normalization of height and in this case we had the normalization of insulin resistance as well. So that is not different to what you are showing.

Dr. Yajnik: It would be interesting to intervene and see if we are able to achieve this.

Dr. Sawaya: Among adults we showed that a BMI of <21.5 decreased productivity in Brazil in sugarcane workers. You are saying that a BMI of 18.1 is good enough in Indian terms to label capacity. I would like you to comment on these differences. Why do you think it is happening?

Dr. Yajnik: Basically we have described the average village woman. I am not saying that lower BMI does not compromise work activity because at a BMI of 20 she might have done better. But the WHO idea that at a BMI of <18.5 you are severely incapacitated is just not true because that one woman's activity in 1 day is more than my activity in a week.

Dr. Prentice: I have a question, but first I would quickly like to make a comment because the results of this discussion are going to appear in the book and I feel that there may be a misunderstanding. To my knowledge, and I have done quite a considerable amount of reading and analysis of this, there is actually no indication that low birthweight predisposes to obesity. We constantly quote the Ravelli study [5] in which there was in 19-year-olds a significant increase in a very small component of the population. The other Ravelli study [6] suggests that there is an association, but if you read it clearly there is no significant association. Meta-analyses have been done on this and in fact it is big babies that become obese, not small babies. There is a little bit of information to suggest that body fat pattern may be altered, a higher waist-hip ratio in small babies but even there the effects are extremely small. So I think we need

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to be careful not to make any implication that small babies lead to obesity, there are different patterns that are going on and it is, as Dr. Yajnik has so elegantly shown, the disharmony of growth between what the child is programmed to do and what he actually does that causes the metabolic damage. If I could quickly ask a question, and again I congratulate you on your fantastic presentation and for leaving such novel thoughts in this field, the question is about extrapolatability. You have got a very heavily vegetarian population there, would you be able to extrapolate to African populations to some extent, and could you quickly comment on the conflicts and the paradoxes that your data reveal in relation to folate recommendations? And the final point is, what are the key markers? You have looked at homocysteine in terms of your pilot intervention but from your mechanistic model in your latest paper it may be that homocysteine is actually not the best thing to be measured.

Dr. Yajnik: The first question about extrapolation. When I started presenting these results, everyone told me that there is no B₁₂ deficiency in India, so it took us 6 years to publish that. The reason was a paper from Vellore which was published 30 years ago and said that drinking 1.5 liters of water from a well provided enough B₁₂ to the population. They were referring to microbial contamination. It was predicted that with better hygiene and a piped water supply, people will have B₁₂ deficiency. We surveyed the literature from 1954, and a series of papers has been published about B₁₂ deficiency in India, in migrant Indians in the UK, US and Singapore. We have analyzed samples from Delhi and South Indian and from Exeter in the UK. We found that Indians everywhere seem to have much lower B₁₂ concentrations starting from cord blood to adult life [7]. Muthayya et al. [8] measured this in Bangalore and showed that low maternal B₁₂ was a strong risk factor for intrauterine growth retardation. In Mysore and Exeter we have now found that low B₁₂ is associated with obesity. So I think there is a basic biological association in this which needs investigation. Probably we should take Dr. Kalhan's advise on what we should measure, and probably use his help to do isotope studies to look at different pathways. In addition we plan to measure nonesterified fatty acids and 3-hydroxybutyrate. The ratio of 3-hydroxybutyrate to any fatty acid might give us an indication whether B₁₂ deficiency blocks ketogenesis. This takes me back 25 years when my first few papers were actually on ketosis resistance in Indians. We seem to have one full circle. About folate supplementation there is a controversy. More than 50 countries have already introduced folic acid fortification in some form or other; in many countries it is mandatory; Australia has recently come on board; the UK I think is just now discussing the final stages, and there have been discussions in India on how to fortify flour with folic acid. My take on this is that both the vitamin B₁₂ status of the population and the amount of folic acid need to be carefully considered. There is concern about an increase in dementia in the elderly and an increase in different forms of cancer. Smith et al. [9] wrote a review article on this subject. In India we should consider B₁₂ supplementation along with folic acid. Otherwise we are likely to create a bigger imbalance and might open Pandora's box.

Dr. Haschke: My comment is also related to the potential imbalance between folic acid and vitamin B₁₂ intake in the study population. The Nestlé Nutrition Institute recently conducted a survey among Indian obstetricians asking which supplements are important during pregnancy. Folic acid supplementation is generally accepted, but multivitamin supplements (including B₁₂) is seen by many obstetricians as a gimmick promoted by the industry. There seems to be a consensus during this discussion, however, that the vegetarian population in India has an increased risk of vitamin B₁₂ deficiency.

Dr. Yajnik: There is another question of supplementing folic acid in already folate-replete populations because folic acid is different from folate. There are a number of chemical differences, a number of possible toxicities or unmetabolized folic acid.

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Smith et al. [9] have beautifully reviewed this, and recently there was a paper from Selhub et al. [10] showing that in B₁₂-deficient people increasing folate concentrations are associated with increasing homocysteine levels.

Dr. Kalhan: I just want to add that B₁₂-folate interaction is so important. If a large amount of folate is given to a B₁₂-deficient subject, folate is not going to work. We used to call that the folate trap and it should be kept in mind.

Dr. Vaidya: The presentation concerns clinical neonatology and pediatrics. All these data show the profound implications of rapid growth in later life. In neonatology today we are still making IUGR babies grow faster. We give them parenteral amino acids; we don't have the best formulas so we give them additional fortifications with fat. There is tremendous confusion as to what is the real benchmark for catch-up growth. How much should we make our babies grow? So far everybody is focusing on making IUGR babies grow and making them catch up faster. From these data we are very confused about the extent to which we make them catch up or do not make them catch up at all. What would you recommend; how should we neonatologists and pediatricians approach this problem in the community practice?

Dr. Yajnik: My first response is these are observational studies, not intervention studies. Our observation is that children who are born small but become big later tend to have trouble. This is not to say that you don't do anything, I just don't know what to do. Barker faced this criticism and therefore he went back to the Finnish cohort where many measurements were made in the first 2 years of life. What he showed is that poor growth in the first 2 years of life, what they call infant growth, predisposed to problems and it is the rapid growth after that period. We have now analyzed some of the data in the Pune Maternal Nutrition Study and found that insulin resistance at 6 years was associated with poor growth in the first 6 months, but after that they caught up. I think this needs to be investigated in very properly conducted trials.

Dr. Al Waili: In our country we have a program of folate supplementation and flour is fortified with folate. We rarely look at vitamin B₁₂ although there is anemia, but we don't know if it is because of iron or vitamin B₁₂ deficiency. Do you think the children in your studies have adiposity because the mothers consume more than 70% carbohydrates which convert to esterified fatty acid? What is the role of breastfeeding? We advise the mothers to exclusively breastfeed their children up to 6 months and we know that it will prevent adiposity, and it will also prevent diabetes later in life.

Dr. Yajnik: The micronutrient content of the diet did not relate to fetal growth in our study. That is not to say that it is not important; many people have suggested that a high carbohydrate content could be responsible for adiposity. I don't have a definite answer to that. We found an association between maternal intake of micronutrients and inflammatory markers (CRP) at 6 years. About breastfeeding in villages, almost every child was exclusively breastfed for a minimum of 6 months and yes, we advise breastfeeding.

Dr. Ajayi: As nutritionists we have been advising mothers to feed their children very well knowing that the intergenerational problems will not affect them. At what age does insulin resistance increase? In developing countries the majority of mothers give birth at home (70%), so we have no idea about the birthweight. What advice do we give the mothers, because the message has been feed your child to grow well? What role do fathers play in this life cycle? When you talk of the parents is the father included or is it only the mother?

Dr. Yajnik: About the role of the father, we were the first to include the father's measurements in the PMNS. The Exeter team has also written a number of papers showing that maternal factors influence the soft tissues and adiposity in the baby, while paternal factors affect skeletal growth more. There are complexities within this scheme so that we are thinking of two things: one is the parent of origin effect and

second the gender specificity because it seems that the effects may be different for boys and girls. We have discussed this issue in an editorial on fetal programming [11].

Dr. Singhal: The issue of promoting catch-up growth in small babies is very controversial but I think the important thing to remember is that the effect is different in various populations. Going back to the question about neonates, there is no doubt that promotion of growth in preterm babies or babies who are vulnerable is important for brain function and for the survival of the baby. In that population we would advocate that you should be promoting growth because of the favorable risk/benefit balance. I think the same applies to babies who are born in a vulnerable environment where it has been shown that promotion of growth helps survival. But I think faster growth promotion in small full-term babies from richer countries could have the opposite effect. There are roughly 27 studies showing that babies who grow faster in infancy are at increased risk of later obesity [12]. In the UK we don't advocate the promotion of growth in the healthy SGA baby [13]. So I think it is more complicated than applying a policy for all babies.

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