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Fetal programming: Maternal nutrition and role of one-carbon metabolism

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Abstract India is world's capital for low birth weight (LBW), which is ascribed to intrauterine growth restriction (IUGR) rather than prematurity. An average Indian mother is short and thin and gives birth to a light and thin baby. Maternal undernutrition is thought to be a major factor in the aetiology of IUGR, and the undernutrition is usually thought to be a low *macronutrient* intake. The Pune Maternal Nutrition Study (PMNS) showed that the Indian babies were thin but fat (more adipose) compared to European babies, and that maternal intake of *micronutrient*-rich foods was a strong determinant of fetal size. Two thirds of the mothers had low vitamin B_{12} concentrations, folate deficiency was rare, and high circulating concentrations of homocysteine predicted IUGR. Follow up of these children revealed that higher maternal folate in pregnancy predicted higher adiposity and insulin resistance at 6 years of age. The most insulin resistant children were born to mothers who were vitamin B_{12} deficient and had high folate concentrations. Thus, PMNS suggests an important role for maternal one-carbon (1C) metabolism in fetal growth and programming of diabetes risk. This could be due to the role of 1C metabolism in synthesis of nucleic acids, genomic stability and the epigenetic regulation of gene function. In addition, methionine has important role in protein synthesis. These ideas are supported by animal studies. The next logical step in India will be to improve 1C metabolism in adolescents to effect intergenerational prevention of adiposity, diabetes and other related conditions.

Keywords Maternal nutrition · One-carbon metabolism · Programming · Diabetes · Vitamin B_{12} · Folate

1 Introduction

India is considered world's capital of low birth weight babies, contributing 40% to the world burden every year [1]. At the same time India is also considered the world's diabetes capital. This paradoxical situation should have suggested a link between the two. This was recognised only recently after the pioneering studies by David Barker and his group in the UK where they showed that low birth weight (LBW) is a risk factor for future diabetes [2, 3]. Size at birth is a surrogate for a multitude of exposures during intrauterine life, and is also determined by genetic factors. The relative importance of heredity and environment in determining the birth size and subsequent risk of diabetes and related disorders has been a subject of research for last two decades.

LBW is endemic in the developing world which contributes 96% of the world's burden. This suggests a strong role for poor socio-economic conditions, where women are undernourished and more susceptible to repeated infections. Seventy-two per cent of LBW infants in developing countries are born in Asia where most births also take place, and 22% are born in Africa [1]. While Indian babies are born an average of 1 week earlier than the European babies, the predominant contribution to LBW is from intrauterine growth restriction (IUGR). IUGR carries both short- and

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long-term disadvantages for the offspring, viz. an increased risk of death in foetal, neonatal and infant life, impaired postnatal growth, defective immune function and defective intellectual development [1]. However, it is to be remembered that the association between birth weight and poor outcomes is a continuous one, and any cut-point is therefore arbitrary.

The link between birth weight and chronic non-communicable diseases (NCD) such as hypertension, type 2 diabetes and cardiovascular disease (CVD) has been extensively studied. A new area of medicine, named Developmental Origins of Health and Disease (DOHaD) has now evolved. There is an international DOHaD society (http://www.mrc.soton.ac.uk/dohad/), the 7th meeting of which was held in Portland, US in September 2011. This research has focussed attention on the health of young girls to reduce the risk of NCD in the next generation. Given the subtle nature of intrauterine exposures and the long latency period before the outcomes become manifest, these ideas have been long debated. But, animal work has provided crucial evidence [4] and genetic markers are helping in establishing causalities (Mendelian Randomisation) [5, 6].

2 Fetal growth, size at birth, and developmental origins of chronic disease

Though a number of genetic markers have been associated with birth size, fetal growth is mainly related to its nutrient supply. The nutritional status of the mother is an important determinant of fetal growth, as shown in animal models and human research. McCance in 1962 summed it very nicely when he said, "the size attained *in utero* depends upon the services which the mother is able to supply: these are mainly food and accommodation" [7]. He was referring to placental transfer of nutrients and maternal pelvic size, as the major determinants of offspring birth size. Walton and Hammond are famous for their mating experiment between a Shire horse and a Shetland pony, where the size of the young at birth closely resembled the mother rather than the father [8].

Epidemiological research during second half of last century has stressed on the long-lasting effects of intrauterine environment on the offspring health. Follow up of the Dutch children, who were *in utero* at the time of the Winter Hunger, have shown a tendency to obesity and increased risk of metabolic and cardiovascular disorders [9]. Animal and human research by Pedersen in Denmark [10] and Freinkel in the US [11] showed a substantial effect of maternal diabetes not only on fetal growth and offspring size at birth but on future risk of obesity and diabetes, starting at a relatively young age. Studies in Pima Indians confirmed these findings [12]. On this background, Hales and Barker's paper in early 1990s reported LBW as a strong risk factor for CVD and diabetes, and they suggested that fetal undernutrition leading to LBW was an important factor [2, 3]. Hales and Barker's idea caused a major upheaval in the medical world which was till then weaned on the idea that NCD was a result of genetic susceptibility and adult lifestyle. Further research from all over the world, especially from the low and middle income developing countries has provided support for this idea [13–16]. A recent demonstration that famine in China increased risk of diabetes in individuals who were *in utero* at the time of famine has lent even more credibility to the idea of 'intra-uterine origins' of type 2 diabetes [16].

Soon it was apparent that birth weight was not the major issue, and that both low and high birth weights were predictive of later diabetes (U shaped relationship) [17]. Influence of intrauterine environment on the health of the fetus is explained by the concept of 'fetal programming'. Alan Lucas defined it as 'permanent change in structure and function of a developing organism in response to an environmental factor' [18]. Maternal size, body composition, and her nutrition and metabolism are major programming stimuli. The fetus senses the intrauterine environment and adapts its structure and function to survive and grow in that environment. If postnatal environment is similar, the *in-utero* adaptations help it to live well. If postnatal environment is substantially different, the fetal 'programs' are unable to cope, resulting in disease. Given that the intrauterine growth and development is a very organized process, stimuli at different times affect development and programming of different systems and functions. Our knowledge about different stimuli is also improving. Different dietary components including macro- and micro-nutrients, environmental toxins and other stimuli are now shown to be involved in programming. The growing knowledge will provide a better appreciation of the 'windows of opportunity' for intervention in future studies.

3 Maternal nutrition and intrauterine growth

We joined David Barker and Caroline Fall in 1991, in the 'fetal origins' research. The first collaborative research (Pune Children Study) confirmed that LBW was associated with insulin resistance as early as 4 years of age [19], and that children who were born small but grew big in childhood had the highest level of risk factors for diabetes and cardiovascular disease [20]. These findings convinced that intrauterine nutrition could be an important contributor to the risk of adult disease.

The Pune Maternal Nutrition Study (PMNS) was then established in 1993 to investigate the influence of maternal nutrition during pregnancy on fetal growth and subsequent risk of chronic diseases [21]. Over 800 pregnancies from six

villages in Pune district were studied. The children are visited every 6 months for anthropometric measurements, and parents and children are investigated every 6 years for a detailed assessment of body composition, cardio-metabolic risk factors and neurocognitive development. Our observations in PMNS have contributed to a better understanding of fetal growth determinants in India.

The average mother in the PMNS was 21 years, weighed 42 kg (BMI 18.1 kg/m^2), and ate ≈1,700 kcal and 45 g proteins per day during pregnancy. The newborns weighed on average 2,700 g and 28% were LBW (<2,500 g) [22].

Babies of heavier mothers were larger in all aspects, and babies of taller mothers were longer. Maternal fat measurements influenced baby's weight and skin-folds. It is interesting that paternal size predominantly influenced skeletal measurements (length), while baby's adiposity was predominantly determined by maternal factors. Short and fat mothers gave birth to the most adipose babies, suggesting an intergenerational influence of maternal early life 'growth retardation' on body composition of the growing fetus [22]. One more interesting finding was that babies born to multiparous women had higher skin-fold thickness and abdominal circumference than those born to primiparous women [23].

Maternal weight gain during first 18 weeks and placental volume measurements at 18 weeks influenced all neonatal measurements, indicating that maternal-fetal nutrition during early weeks is an important determinant of birth size, and placenta plays an important role in fetal growth (Fig. 1) [22, 24].

We also found that Indian babies, though small, short and thin at birth, had comparable sub-scapular skin-fold thickness to white Caucasian babies born in the UK. This suggested that the ('thin-fat') body composition which is characteristic of adult Indians is established at birth [25].

In PMNS we measured maternal macro- and micronutrient intake and its association with fetal growth and birth size. Maternal energy and protein (macronutrient) intake was not associated with birth size, whereas fat intake was weakly associated. On the other hand, intake of micronutrient-rich foods (green leafy vegetables, milk and fruits) had a substantial effect on fetal growth [21]. This made us focus on maternal micronutrient status as a determinant of offspring growth and development.

4 Maternal one-carbon metabolism and offspring health

Cellular one-carbon (1C) metabolism is crucial for cell growth, differentiation and development. It is a network of interrelated biochemical reactions that involve the transfer of one-carbon groups from one compound to another. The coenzymes necessary for several of these reactions include the B-vitamins: folate, vitamin B_{12}, B_6 and B_2. Disturbances in the nutrition of one or more of these vitamins reflect in higher circulating concentrations of homocysteine (tHcy), while deficiency of vitamin B_{12} results in higher circulating methylmalonic acid (MMA). Recent research has indicated that insufficiency or an imbalance of these micronutrients, of a degree insufficient to cause well known deficiency syndromes, can still contribute to metabolic and degenerative conditions [26].

Seventy percent of the women in the PMNS had a low vitamin B_{12} status (plasma vitamin B_{12} <150 pmol/L) but none were folate deficient (red cell folate <283 nmol/L). Ninety percent of these women had high MMA (>0.26 μmol/l), and 30% had raised tHcy concentrations (>10 μmol/l) [27].

4.1 Fetal growth

We investigated the relationship between maternal circulating concentrations of tHcy, vitamin B_{12} and folate and offspring size at birth. Mothers of full term small for gestation age babies (SGA, gestation and sex specific birth weight <10th centile) and mothers of appropriate for

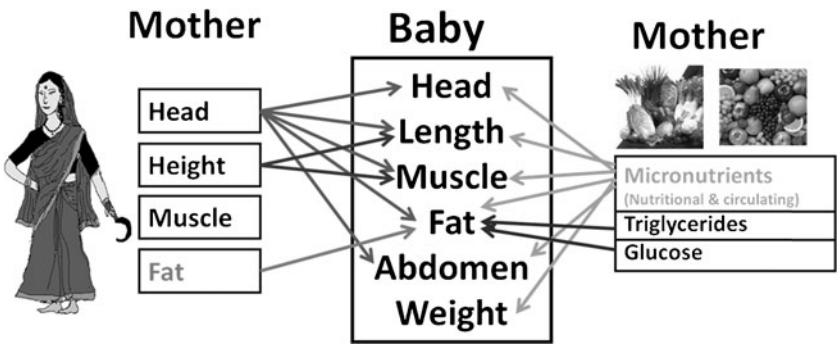

Fig. 1 Maternal size and nutrition influence baby's size and body composition. [Observations from the Pune Maternal Nutrition Study: maternal head circumference (a surrogate for early life growth and nutrition) is related to neonatal size; her height is related to neonatal length and muscle, and fat to neonatal fat. Maternal dietary and circulating micronutrients (folate and vitamin C) influence neonatal size, circulating glucose and triglycerides are predominantly related to neonatal fat] [adapted from references [21, 22]

gestational age babies (AGA, >10th centile) were compared for their body size, plasma tHcy, vitamin B_{12} and red cell folate concentration at 28 week gestation. Mothers of SGA babies were lighter and shorter than those of AGA babies and had higher plasma tHcy concentration ($P<0.01$). Homocysteine concentrations were inversely related to plasma vitamin B_{12} and red cell folate concentrations ($P<0.01$, both). The association of maternal plasma tHcy concentration with lower offspring birth weight was independent of maternal height, weight, gestation at delivery and baby's gender [28].

These results were substantiated by a cohort study in Bengaluru, India in 2006, where 486 women were studied during pregnancy for sociodemographic, anthropometric, dietary and micronutrient status in order to determine the association of these parameters with IUGR. Women in the lowest tertile for serum vitamin B_{12} concentration during each of the three trimesters of pregnancy had significantly higher risk of IUGR (AOR: 5.98, 9.28 and 2.81, p 0.006, <0.001 and 0.059, for 1st, 2nd and 3rd trimester respectively) [29].

4.2 Risk of diabetes, cardiovascular disease

In the PMNS, children are followed up every 6 months for growth (anthropometry), and every 6 years for detailed growth, body composition, and metabolic parameters. At 6 years of age children's adiposity and insulin resistance was significantly related to maternal B_{12} and folate levels in pregnancy. Higher maternal folate concentrations predicted higher adiposity, and children born to mothers with low vitamin B_{12} concentrations but high folate concentrations were the most insulin resistant (Fig. 2) [27].

4.3 Neurocognitive development

Vitamin B_{12} is important for nervous system development. In the PMNS we also investigated the relationship between maternal plasma vitamin B_{12} status during pregnancy and the child's cognitive function at 9 years of age. Children of mothers with low plasma vitamin B_{12} (lowest decile,<77 pM) concentration at 28 weeks of gestation performed lower on tests of sustained attention and short term memory as compared to the children of mothers with high plasma vitamin B_{12} (highest decile, >224 pM) [30].

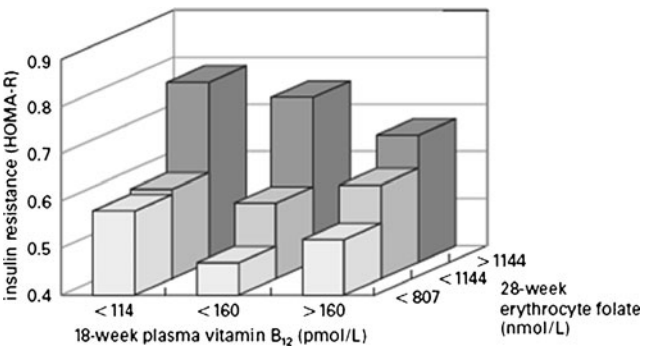

Fig. 2 Pune Maternal Nutrition Study: Insulin resistance (HOMA-R) in the children at 6 y in relation to maternal vitamin B_{12} (18 wk) and erythrocyte folate (28 wk) [27]

Thus the Indian Studies have demonstrated a relationship between maternal 1C metabolism in pregnancy and programming of body composition, neuro-cognitive function and cardio-metabolic risk in the offspring.

4.4 Neural tube defects

Prevention of neural tube defects (NTD) by periconceptional folic acid supplementation is considered a major achievement in modern medicine. Recently, we investigated the role of maternal nutritional and genetic markers related to 1C metabolism in the etiology of NTD in India. We measured maternal folate, vitamin B_{12}, tHcy and holo-transcobalamin (holo-TC) levels, and polymorphisms in methylenetetrahydrofolate reductase (MTHFR, 677C>T) and transcobalamin (TCN2, 776C>G) genes, in 318 cases and 702 controls in a multicenter case–control study.

Mothers of NTD foetuses had higher plasma tHcy and lower holo-TC concentrations ($p=0.003$) but similar folate and vitamin B_{12} concentrations as those in the mothers who delivered normal babies. The commonly associated maternal polymorphism 677C>T in the MTHFR gene did not predict risk of NTD in the offspring, but 776C>G polymorphism in TCN2 was strongly predictive of NTD in the offspring ($p=0.006$). This study has demonstrated for the first time, a possible role for maternal vitamin B_{12} deficiency in the etiology of NTD in India over and above the well-established role of folate deficiency [31].

4.5 Maternal 1C metabolism and gestational diabetes

Another evidence for role of vitamin B_{12} insufficiency in adiposity and insulin resistance came from a study in Mysore, India [32]. In a cohort of 785 women attending an antenatal clinic in Mysore, low plasma vitamin B_{12} concentrations (<150 pmol/l) were observed in 43% of women and low plasma folate concentrations (<7 nmol/l) in 4%. Vitamin B_{12}- deficient women had higher BMI, sum of skinfold thicknesses ($p<0.01$), and insulin resistance ($p=0.02$); and a higher incidence of GDM (8.7% vs. 4.6%; OR 2.1, $p=0.02$) compared to vitamin B_{12}- sufficient women. Among vitamin B_{12}-deficient women, the incidence of GDM increased with increasing folate concentration (5.4%, 10.5%, 10.9% from lowest to highest tertile, $p=0.04$). Vitamin B_{12} deficiency during pregnancy predicted higher insulin resistance ($p<0.05$) and higher prevalence of

diabetes at 5 year follow-up (p=0.009; p=0.008 after adjusting for BMI). This suggested that maternal vitamin B_{12} deficiency may be an important factor underlying the high risk of 'diabesity' in Asian Indian women.

5 Genetics and fetal growth

Fetal growth and size at birth, like all human characteristics, are influenced by both genetic factors and environmental influences. With advances in genetic techniques (genome-wide association study, GWAS) and formation of consortia to include large numbers, genetic influences on birth weight are being explored.

A recent GWAS identified variants in CCNL1/LEKR1 (rs900400) and ADCY5 (rs9883204) genes to be associated with birth weight [6, 33]. A study in Australian and Dutch birth cohorts (n=3,090) suggested that the genetic variant rs900400 is associated with symmetric growth restriction (early pregnancy influence), whereas the genetic variant rs9883204 is associated with asymmetric growth restriction (third trimester influence) [33]. These genetic studies support the 'genetic fetal insulin hypothesis' [34] because CCNL is also associated with type 2 diabetes. These studies will also provide important information on metabolic pathways influencing fetal growth and body composition.

5.1 Use of genetic markers to establish causality (Mendelian Randomization)

Proving causality from observational research is not easy. Conventionally this is done by interventional research which is difficult to execute, takes long time and is expensive. A recently proposed alternative method is the use of relevant genetic markers which are reliably related to the nutritional exposure of interest. Because the genetic polymorphisms are randomly distributed at conception they are not confounded by subsequent exposures or lifestyle. Therefore demonstrating a significant association between a genetic marker and the outcome of interest suggests causality [5].

We investigated the effect of genetic polymorphisms affecting the 1C metabolism on birth weight. Maternal *MTHFR* genotype (677C-T, 1298A-C) was tested in two Indian birth cohorts (PMNS, n=702 and Mysore Parthenon Study, n=526). Maternal *MTHFR 677TT* predicted high plasma tHcy concentrations and lower birth weight, independent of maternal BMI, socioeconomic status, gestational age and offspring MTHFR genotype. Higher maternal folate concentrations overcame the effect of maternal *MTHFR 677TT* genotype on birth weight. This suggests that maternal 1C metabolism influences birth weight and improving the balance of maternal vitamin B_{12} and folate status may help reduce IUGR and its long-term consequences (manuscript submitted).

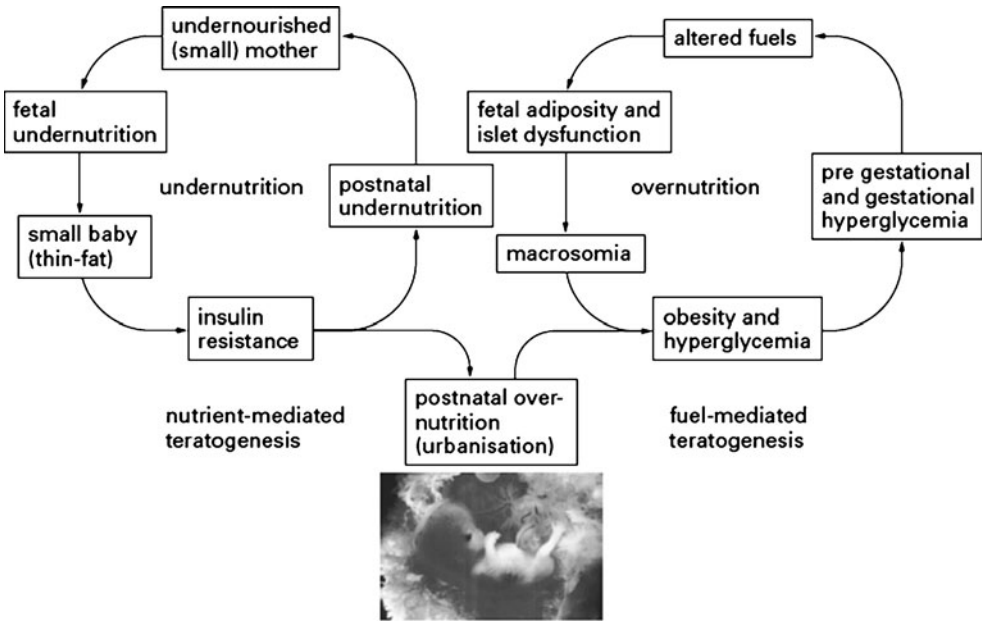

Fig. 3 The figure shows interrelationship of two major maternal factors (under-nutrition and over-nutrition) in fetal programming. An undernourished mother produces a small (thin-fat) insulin resistant baby. If this baby remains undernourished in postnatal life, the cycle is propagated. If the thin-fat insulin resistant baby is over-nourished it becomes obese and hyperglycemic. An obese and hyperglycemic mother produces a 'macrosomic' baby at 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 under-nutrition to over-nutrition, and contributes to escalation of the diabetes epidemic. Improving health of a girl child is of paramount importance in controlling the diabetes epidemic [41]

6 Epigenetics and possible role for 1C metabolism in fetal programming

Fetal growth and development are influenced by an interaction between genetic factors and the intrauterine environment. The size of the newborn is influenced not only by inheritance of genes but also by maternal size, nutrition and her metabolism. Hattersley et al. showed this through the interaction between glucokinase gene and maternal hyperglycemia [34].

It is increasingly appreciated that epigenetic changes, which refer to heritable modifications in the genome not associated with a change in the base sequence [35], are at the centre of programming. These changes may be mediated by methylation of DNA, acetylation of histones and through the role of micro RNAs, all of which modify gene expression. These could potentially result in production of different phenotypes from the same genotype by altering gene expression and increasing or decreasing the amount of encoded protein [36].

6.1 Evidence from animal models

Role of DNA methylation in influencing the phenotype of a growing fetus has been well demonstrated in animal models. Waterland and Jirtle fed genetically obese Agouti mice with a 'methylating cocktail' (B_{12}, folic acid, choline and betaine) and showed that the offspring had a different coat color and were less obese, despite inheriting the Agouti mutation [37]. This was related to methylation status of the promoter region of the Agouti gene. Lillycrop and colleagues demonstrated that the folate rescue in the rat model of maternal protein deficiency was related to methylation in some of the genetic sequences [38]. Sinclair and colleagues produced methionine deficiency in female sheep (by dietary restriction of methionine, B_{12} and folate) [39]. Ova from these sheep were fertilized *in vitro*, and the blastocysts were transferred to surrogate mothers with normal methionine status. The offspring, especially males, were obese and insulin resistant, and demonstrated differential methylation at number of sites in the genome. These models highlight the importance of periconceptional 1C (methyl) metabolism in fetal programming.

7 Conclusions

In Indians hyperhomocysteinemia and vitamin B_{12} deficiency are common. Unlike in Europeans, hyperhomocysteinemia in Indians is predominantly contributed by vitamin B_{12} deficiency rather than folate deficiency. Vitamin B_{12} deficiency is related to vegetarian food habits which originated over 2,000 years ago, and are strongly supported by religious beliefs. The ultimate source of vitamin B_{12} in nature is microbes, and this perhaps explains why vitamin B_{12} deficiency is associated with higher income and better hygiene [40]. Our finding of a disturbance in 1C metabolism in the undernourished (vitamin B_{12} and protein deficient) as well as in the urban glucose intolerant mothers (vitamin B_{12} deficiency associated with obesity and hyperglycemia) provides a unique explanation and an opportunity to tackle this dual teratogenesis: fetal growth restriction (nutrient-mediated teratogenesis) and fetal macrosomia (fuel-mediated teratogenesis) (Fig. 3) [41].

8 Key unanswered questions and the way ahead

Figures from the current Diabetes Atlas indicate diabetes as disease pandemic, with the major proportion of the diabetes burden borne by low- and middle-income countries, and disproportionately affecting lower socioeconomic groups [42]. The DOHaD theory offers a unique explanation for this. Our concept of 'dual teratogenesis' [41] needs to be further investigated and acted upon, both by further genetic and epigenetic research as well as by appropriate interventions to improve 1C metabolism in young girls from before conception. Improving early life environment may be more cost-effective in preventing the NCD epidemic than controlling only the lifestyle factors in later life.

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