Early life influences and type-2 diabetes – a review

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Early life factors encompassing parental, foetal and postnatal characteristics, have an important influence on individual disease risk. Of particular importance is the role of maternal lifetime nutrition and metabolic reserves, and the impact on offspring birth outcomes. Birth weight, in turn, affects disease risk in later life. Being born small and showing rapid weight gain during childhood are especially important risk determinants for impaired glucose tolerance, higher blood pressure, dyslipidaemia, overweight and obesity in later life. Postnatal growth patterns, socio-environmental factors and genetic influences thus act in concert to increase the predilection for chronic diseases, including type-2 diabetes.

Keywords: Birth weight, disease risk, maternal nutrition, type-2 diabetes.

Introduction

EPIDEMIOLOGICAL transitions over the last few decades have affected populations worldwide with current man-made or lifestyle disorders replacing the earlier burden of infectious diseases in most parts of the world[1]. Chronic non-communicable diseases (NCDs), including cardiovascular diseases, type-2 diabetes (T2D), chronic respiratory disorders, cancers, mental illness and injuries account for a huge burden of morbidity and mortality[2]. Diabetes has particularly debilitating consequences given its propensity to affect all populations, both genders, children and adults, with every organ system in the body eventually affected under uncontrolled glycaemic states[3].

In India and worldwide, the diabetes epidemic is a leading cause for morbidity, mortality and life-long disease burden, thereby causing health systems to face an increasing challenge in providing care. Population-based data from 751 studies in 146 countries showed the worldwide trends in diabetes in 4,372,000 subjects aged over 18 years from 1980 to 2014 (ref. 4). Age-standardized adult diabetes prevalence increased from 4.3% (95% CI 2.4–7.0) to 9.0% (7.2–11.1) in men and from 5% (2.9–7.9) to 7.9% (6.4–9.7) in women worldwide. In absolute numbers, adults with diabetes increased from 108 million in 1980 to 422 million in 2014, with East Asia and South Asia estimated to have had the largest increase and largest number of people with diabetes in 2014 – 106 million and 86 million respectively. Five countries accounted for half the diabetes in the world – China, India, USA, Brazil and Indonesia, with low and middle-income countries like Indonesia, Pakistan, Mexico and Egypt replacing European nations like Germany, Ukraine, Italy and the United Kingdom in the top 10 countries having most people with diabetes[4–8].

India till recently, was projected as the 'diabetes capital' of the world with nearly 69 million people suffering from the disease[8,9]. The projected burden is that it will be nearly 80 million by 2025 (ref. 8). The WHO Global Monitoring Framework endorsed by member states aims to establish action to achieve a 25% reduction in premature mortality from the four leading NCDs – diabetes, cardiovascular diseases, cancer and chronic lung diseases, and their risk factors[10]. Since these are conditions that share a number of common and modifiable risk factors, a coordinated multi-sectoral approach would be critical in combating the rising trends in NCDs and their risk factors. The present review aims to summarize the role of early life events in diabetes and related metabolic disorders as an important first step in planning appropriate programmes, interventions and policies to curb the rising levels of T2D across populations. But what constitutes early life events and influences? Figure 1 categorizes these as parental, foetal and post-natal factors, and a review of evidence of these concepts is presented here.

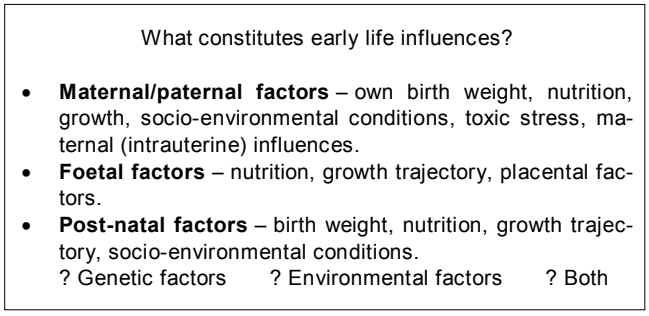

Figure 1. Early life influences.

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Pathogenesis of type-2 diabetes

Extensive epidemiological research has provided evidence of the association between early life factors and later metabolic diseases. Impaired glucose tolerance, high blood pressure and abnormal lipid levels leading to high rates of T2D and cardiovascular disease have been shown to originate early in life[11–14].

Early life growth and development

Foetal growth and development is a complex and dynamic process that is dependent on adequate maternal nutrition, placental function and the appropriate intrauterine milieu to foster healthy growth. Poor intrauterine growth affecting weight at birth has been linked to adverse outcomes later in life[15–20]. This 'developmental programming' hypothesis propounded by David Barker and colleagues posits that a stimulus or insult during a critical period of foetal growth and development that causes perturbations of the maternal–placental–foetal unit can cause permanent changes in metabolism, structure and function of foetal organs and systems[15,21]. These in turn can cause long-term effects in the affected individuals with increased susceptibility to later life diseases and their risk factors. According to the 'thrifty phenotype' hypothesis, the foetus learns to adapt itself to such metabolic disturbances caused by maternal malnutrition or placental insufficiency by developing trajectories of growth suited to survival[13]. These adaptive responses may be suited for immediate survival, thereby protecting vital organs like the brain while down-regulating overall growth of less vital muscular and skeletal tissues. However, the 'predictive adaptive responses' by the foetus may sometimes result in a 'mismatch', if the postnatal environment is different from that predicted by the foetus[22]. This mismatch can result in unhealthy patterns of postnatal growth, some of which can result in greater levels of risk factors for chronic diseases, including diabetes. Birth weight has been used as a proxy marker of intrauterine growth and in turn, lower weight at birth has been linked to increased propensity of adverse outcomes later in life[15,16,18]. This paradigm, at the centre of the 'developmental origins' hypothesis, has been the focus of research for nearly four decades, in assessing mechanistic pathways for metabolic and lifestyle disorders like T2D and cardiovascular disease[23–25].

Figure 2 depicts the maternal–placental-foetal unit and the metabolic perturbations with their resultant consequences.

Animal studies

Experimental studies in mice provided the earliest evidence of the impact of changes in maternal nutrition states on the foetus. Total caloric restriction of mothers to nearly 50% during late pregnancy was shown to affect pancreatic beta-cell mass in the offspring with consequent effects on insulin production and glycaemic states. Similarly, rats fed with high saturated fat diets delivered offspring with foetal insulin resistance, endothelial dysfunction and increased adiposity. Low-protein diets resulted in offspring with reduced birth weight and later age-dependent decline in glucose tolerance, possibly related to effects on beta-cell number and size[26–28]. Studies on global under-nutrition, high-fat and low-protein diets leading to metabolic disorders in the offspring have been corroborated by similar studies in guinea pigs, sheep, pigs, horses and primates[29,30]. These informative findings from animal models have served as useful hypothetical evidence for research on mechanistic pathways in humans.

Human studies

Research on the early life influences that predispose to disease risk in later life in humans has been conducted in both developed and developing country settings.

Prenatal nutrition

Nutritional adversities in earlier generations lead to poorer health outcomes in subsequent generations of humans as well. The vicious intergenerational cycle of maternal malnutrition affecting offspring growth and development has been studied in diverse settings.

A classic example of this comes from the Dutch Hunger Winter study where depending upon the timing of exposure of mothers to famine during gestation, there was increased susceptibility to glucose intolerance, coronary heart disease, atherogenic lipid profiles, obesity, disturbed blood coagulation and increased stress responsiveness in the next generation[31]. The Dutch Hunger Winter study was a natural experiment that examined the effects of poor calorie intake in the Nazi-occupied Netherlands during November 1944–May 1945. An embargo on food supplies reduced the caloric intake of the Dutch people to less than 1000 calories per day. All children ($n = 2414$) born in a single hospital, Wilhelmina Gasthius, between November 1943 and February 1947 were retraced between the ages of 52 and 58 years, and invited for a detailed clinic examination. This allowed assessment of adult outcomes in children born before and after the famine, in comparison to those exposed to the famine during different stages of gestation. All children born during the year 1945 ($n = 1380$) were considered as exposed. Exposure was measured as the average official daily rations provided for adults greater than 21 years in Amsterdam, and those who received less than 1000 calories during any 13-week period of gestation were considered

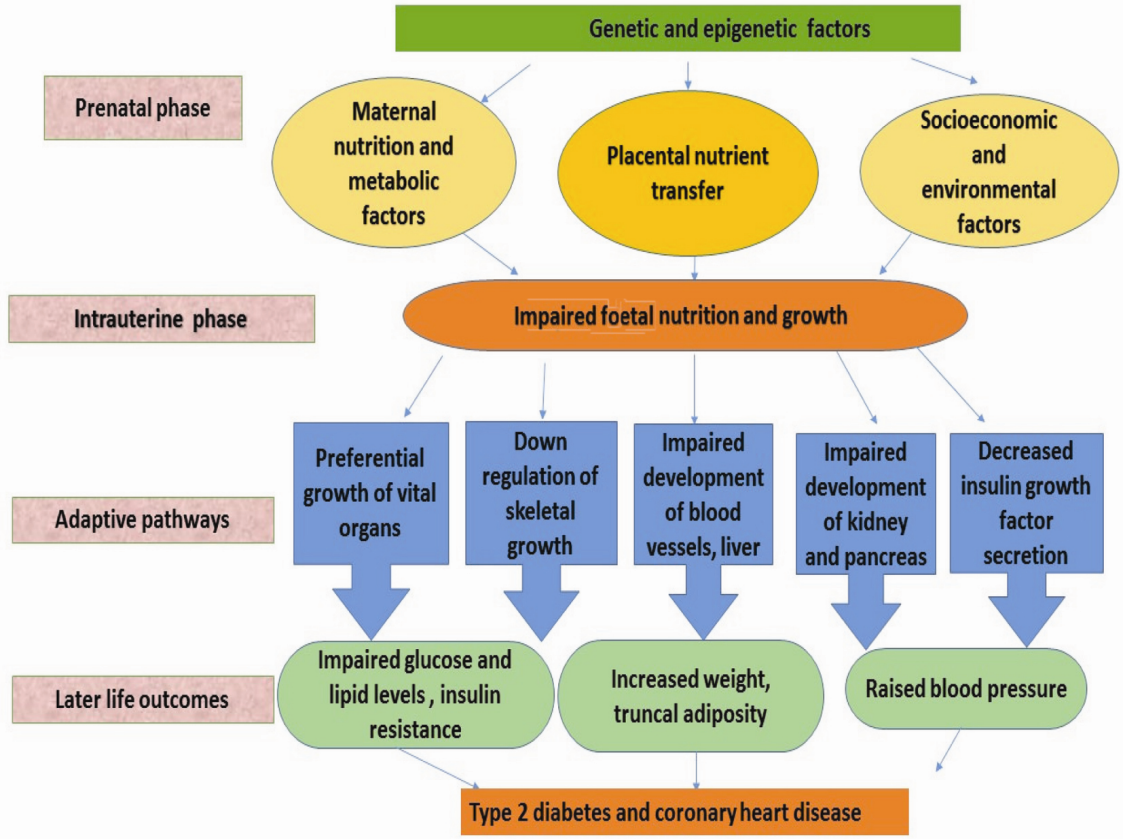

Figure 2. Maternal–placental–foetal unit and pathways to diseases.

exposed. Those exposed to the famine in early gestation ($n = 87$) were typically found to be more prone to coronary heart disease, obesity, atherogenic lipid profiles and breast cancer, mid-gestation ($n = 137$) to obstructive airways disease and micro albuminuria, while poor nutrition at any stage of gestation, including late stage ($n = 140$) was associated with glucose intolerance. The Dutch Hunger Winter was followed by a period of almost immediate food abundance with calorie intake reaching 2000 calories per day by the summer of 1945. The transition from a well-nourished population to a period of acute starvation during the famine, followed by nutritional abundance could be an explanation for metabolic conflict and disease in later life. The small sample sizes prevent generalisability of these findings, although they provide insightful views on long-term consequences of nutritional deprivation during pregnancy.

In contrast, the Leningrad (now St. Petersburg) Siege study which examined 169 individuals exposed to *in utero* undernutrition during 1941–1944, did not show any associations of poor nutrition during gestation or infancy with later risk factors for coronary heart disease and diabetes mellitus. There were no differences in glucose and insulin concentrations, lipid levels, blood pressure, obesity or coagulation factors in subjects exposed to under nutrition *in utero* or during infancy, compared to unexposed individuals born before the siege or during these same study periods in an area outside the siege[32]. The fact that subjects in the Leningrad area were not exposed to better nutrition after the period of acute starvation, unlike in the Dutch study, provides some clue to the possibility of the role of the 'thrifty phenotype' and rapid postnatal catchup growth in the Netherlands study. This suggests that in addition to intrauterine programming due to sub-optimal nutrition in foetal life, the mismatch imposed by later nutritional excess possibly affects long-term disease risk.

Several studies around the world have since assessed the critical role of maternal nutrition on offspring outcomes at birth and in later life[33–41]. In India too, studies on maternal pre-pregnancy nutrition have contributed to the developmental origins evidence base. Among the most extensive prospective maternal nutrition studies are those from Pune. In the early 1990s, about 800 pregnant women from a rural farming community were assessed for nutritional status, physical activity, metabolism and foetal growth by ultrasound studies. The women in this Pune Maternal Nutrition Study (PMNS) had an average weight of 42 kg, body mass index of 18.1 kg/m^2 (underweight by standard norms) and gave birth to babies with an average birth weight of 2.6 kg with an overall prevalence of 26% low birth weight (birth weight < 2.5 kg) in

the study population[42]. Amongst PMNS mothers, dietary quality and macro- and micronutrient intake were assessed. Women were short, underweight, with low protein and energy intake at 18 and 28 weeks, but these (low protein and energy intake) were not predictive of birth weight, though maternal fat intake was associated with birth weight, length and skinfold thickness, a measure of fatness or adiposity. Those who had a higher frequency of intake of green leafy vegetables, fruit and milk, however, had heavier offspring. Micronutrients were therefore implicated as greater determinants of offspring growth and development[16,43] Maternal levels of folate, vitamin B_{12}, total homocysteine and methylmalonic acid (MMA; a specific indicator of vitamin B_{12} deficiency) were measured at 18 and 28 weeks of gestation. The mothers had high levels of vitamin B_{12} deficiency (nearly 70%), with 90% of these women showing high MMA levels (≥0.26 μmol/l). These were correlated with offspring anthropometry, body composition and insulin resistance measures using HOMA-IR (homeostasis model assessment of insulin resistance) at 6 years. A combination of low maternal vitamin B_{12} and high folate concentration predicted offspring adiposity and insulin resistance at 6 years. The low B_{12} levels, rather than folate levels were associated with prevalence of high homocysteine levels (30%), and the higher maternal total homocysteine levels in turn predicted lower birth weight for gestational age[44]. The role of 1-carbon (1-C) metabolism that involves the donation and regeneration of 1-C groups, including the methyl group has since been widely debated[45]. Maternal nutrition should provide adequate supply of methyl donors such as folate, vitamin B_{12}, betaine, methionine and choline – all important nutrients essential for optimal foetal organogenesis, growth and development[46]. Whether the sub-optimal intrauterine nutrition affects pancreatic development and predisposes to beta-cell dysfunction in early life has not been extensively studied and is a potential area for future research in Indian settings.

Maternal hyperglycaemia

Maternal overnutrition can also affect offspring metabolic markers, including glucose, foetal size and growth in early infancy and childhood. The flow of nutrients across the maternal–placental–foetal axis suggests that maternal hyperglycaemic states should also trigger similar metabolic changes in the offspring. However, a recent review of the literature covering animal studies, observational human studies, clinical trials and systematic reviews showed that *in utero* exposure to maternal hyperglycaemia has minimal direct effect on T2D in the offspring[47]. Individual studies in India however have conflicting findings and have related foetal macrosomia to gestational diabetes, with a resultant *U*-shaped association of foetal size to later glycaemic states in the offspring. Amongst the Pima Indians, the prevalence of diabetes in infants born between 1940 and 1972 was assessed by a glucose tolerance test at 20–39 years. Both low and high birth weight were related to greater levels of T2D (30% and 32% respectively) and this was related to parental diabetes[48]. The Mysore Parthenon cohort, for example, detected a gestational diabetes mellitus (GDM) prevalence of 6.2% in a cohort of 785 women enrolled from a single maternity unit. Of the 663 babies born in this cohort, those born to women with GDM were heavier, with greater measures of fat, muscle and bone mass, when assessed at 5 and 9.5 years[49]. The 'fuel-mediated teratogenesis' hypothesis[38] is being studied in a more recent pre-pregnancy cohort study in Bengaluru. The glycaemic status of mothers during pregnancy is being assessed in relation to skinfold measures in infants at six weeks, third and ninth months. Hyperglycaemic status of mothers can lead to foetal hyperinsulinaemia, increase in fat cells and adiposity at early ages, which in turn can enhance the risk of diabetes in later life[50]. Thus, maternal undernutrition and over nutrition can both predispose to the diabetes epidemic through the *U*-shaped association with offspring birth weight.

Parental body size

The size of the mother throughout her life-course can affect her offspring birth size, growth and predilection for disease risk. Indian women are by nature shorter than peers elsewhere and the 'maternal constraint' imposed by physical stature (shorter height), pelvic size and lifetime reserves of metabolic substrates can impact the next generation through effects on offspring birth size, linear growth and future biomarkers for metabolic disease[22,51,52]. Pre-pregnancy maternal weight, weight gain during pregnancy and own birth weight of the parents are all shown to be positively associated with offspring birth weight, body composition and insulin resistance in childhood and later life[12,52–56].

Postnatal growth and development

Research into the developmental origins hypothesis in India has involved prospectively studied birth cohorts in New Delhi, Vellore, Mysore and Pune[16,57–61]. These studies have confirmed that people with lower birth measurements (weight/ponderal index) were more likely to develop chronic diseases[42,62,63] and such risk was particularly heightened for those who gained weight rapidly in childhood[57,60,64]. The children who were born small, remained small at age one or two, showed an early age of adiposity rebound (earliest age when body mass index (BMI) starts to rise in childhood), and generally became obese relative to themselves due to postnatal and childhood weight gain, overall had heightened risk for glucose

intolerance and T2D. The hyperglycaemic and insulin-resistant states are in turn associated with heightened risk of developing cardiovascular disease.

While the findings from developed countries show a largely consistent inverse association between birth weight and impaired glucose tolerance/diabetes mellitus (IGT/DM), this has not been clearly shown in the Indian setting. The New Delhi Birth Cohort (NDBC), established in 1969 with an initial sample of about 8000 children in South Delhi, examined serial anthropometric measurements (height and weight recorded every six months) from birth to young adulthood in 1492 subjects at 26–32 years in relation to cardiometabolic biomarkers, including glucose levels. This showed no association between impaired glucose tolerance or diabetes with birth size, but rather with a lower infant BMI and early age of adiposity rebound[57]. Across the range of birth weights, however, an inverse association was found between birth weight and 120 min plasma glucose[57]. The prevalence of adult dysglycaemia was inversely related to weight and BMI at one year; specifically, those who were in the lowest third of BMI at age 2 and highest third of BMI at age 12, reflecting rapid childhood weight gain, had the highest prevalence of IGT/DM as adults. A 1 SD (standard deviation) change in BMI between 2 and 12 years was associated with a greater odds (OR = 1.3) of IGT/DM as adults[57]. The comprehensive NDBC growth measures provided important childhood growth pattern assessments in relation to several outcomes in later life, including insulin resistance, high waist circumference, blood pressure and lipid levels[61].

Similarly, the Vellore birth cohort which comprised of 2218 men and women, followed from birth examined at a mean age of 28 years, also found no direct association between birth size and adult glucose intolerance, although an inverse association was apparent for birth weight and ponderal index with risk of IGT and DM, after adjusting for adult BMI. The highest risk for IGT/DM therefore was consistently seen in subjects in the lowest third of early (infant) BMI and highest third of adult BMI[58]. In the Parthenon Mysore cohort, established in the 80s to study gestational diabetes mellitus, 663 children were measured at birth and 6–12 monthly thereafter. Lower weight, smaller length and mid-arm circumference in the Mysore babies were associated with higher fasting glucose concentrations in children followed up at 9.5 years[60].

'Thin–fat' hypothesis

A unique finding amongst the 800 Pune babies compared to Caucasian babies born in Southampton, UK was their 'thinness', as measured by their ponderal index (weight in kg/length in cm^3). Indian Pune babies were lighter, thinner (ponderal index = 24.1 kg/cm^3 versus 28.2 kg/cm^3 in Caucasian babies) and shorter; however, although born small with proportionately smaller abdominal viscera and low muscle mass, these babies preserved their body fat and had greater measures of subcutaneous and visceral fat measured by MRI. This led to the 'thin–fat' hypothesis, which states that Indians have a propensity for greater fat accumulation, mostly truncal, at lower levels of BMI, compared to European counterparts[42]. This further corroborated earlier findings from Pune that showed Indian T2D individuals, at younger ages and lower BMI had greater waist–hip ratio and higher insulin resistance compared to European adults[65]. This pathway was therefore shown in the Pune studies to be set very early in life. In 1993, the Pune Children's Study was conducted to further evaluate the developmental origins hypothesis. Children who were small at birth but gained rapid postnatal weight gain were those at highest risk of developing cardiometabolic risk factors, including impaired glucose and insulin resistance, when assessed at 4 and 8 years[64]. A follow-up of the same children at 21 years showed a tendency for 'tracking' of cardiovascular risk factors, with all measurements at 8 years correlating positively with those at 21 years, except the 120 min glucose. Children in the highest risk category at 8 years were at highest risk at 21 years, especially for BMI and total cholesterol, with weaker associations for glucose, fasting insulin and blood pressure[66]. This phenomenon of 'tracking' where individuals remain in the same risk categories throughout the active growth period may be a critical and potential area for screening and appropriate intervention strategies.

Babies in the Parthenon Mysore cohort also displayed the 'thin–fat' phenotype with abdominal adiposity preserved (i.e. lower muscle bulk represented by lower mid-arm circumference but with greater measures of subscapular skinfold – a measure of truncal adiposity) at 1 and 4 years[60,67]. The 'tissue overflow hypothesis' by Sniderman *et al.*[68] has suggested that South Asians have a greater tendency to store visceral adipose tissue than to store their fat in the metabolically inert superficial compartments of the body. This truncal adiposity or fatness, imposed by visceral fat stores has been shown to predispose to dysglycaemia and dyslipidaemia[68].

The findings from all the Indian birth cohorts therefore established that being born small or normal weight, remaining small or faltering in growth in the first two years of life and thereafter gaining weight rapidly in childhood is detrimental to later life disease risk. Elsewhere too, a consortium of birth cohorts from five developing countries – Brazil, Cebu (the Philippines), Guatemala and South Africa, together with the NDBC from India, conducted pooled data analyses which reinforced these findings. The COHORTS (Consortium of Health Oriented Research in Transitioning Societies) established that lower birth weight and sub-optimal nutrition in early life predispose to higher glucose, blood pressure and lipid levels

in adult life, after accounting for current height and BMI. The evidence from these analyses too implicated rapid postnatal growth patterns as predictors of adverse health outcomes later life[69,70].

The entire period from birth through the first two years of life therefore seems to be critical from the point of view of optimal strategies to prevent adverse outcomes later in life. This fits into the dialogue of the 'first 1000 days concept', whereby pregnancy (270 days) + year 1 (365 days) + year 2 (365 days) have evolved as the 'critical window of opportunity' for nutritional and related interventions aimed at reducing later disease risk[71]. The importance therefore of monitoring growth patterns of children and enhancing awareness amongst parents and clinicians alike of the potential disease risk that can be curtailed by appropriate early life interventions cannot be understated.

Breastfeeding in infancy

Observational evidence generally points to a protective role of breastfeeding in infancy on later life disease. Breastfed infants, compared to formula-fed ones, have a lower risk of T2D; they have a lower blood glucose and insulin concentration in infancy with marginally lower insulin concentration as adults[72]. In the Indian setting, the Mysore cohort examined associations between breastfeeding duration and timing of introduction of complementary foods on glucose tolerance at 5 and 9.5 years. Longer duration of breastfeeding in this population had a protective effect, with children who were breastfed showing both lower levels of insulin and HOMA-IR. Similar analyses in the COHORTS data, however, did not show an association of breastfeeding duration or early complementary feeding on diabetes risk in later life[73]. The role of exclusive breastfeeding was not studied and may provide different insights.

Social and environmental factors

In the 1970s, Anders Forsdahl in Norway showed a significant correlation between middle-age chronic disease rates and infant mortality rates at the time and place of an individual's birth[74]. Based on this, he posited that early socio-economic adversities that affect physical and social environments in early childhood can lead to increased later life Coronary Heart Disease (CHD) risk[75]. The work by Barker and colleagues in the 1980s further reinforced the role of early life influences by using individual-level data from Hertfordshire medical ledgers linked to the UK National Health Service data for mortality outcomes. Low birth weight and weight at one year were linked to greater cardiovascular mortality among 15,000 men and women born between 1911 and 1930, assessed in 1992 (refs 15 and 76). This suggests that poor environmental conditions, in turn leading to poor birth and childhood outcomes can be related to adverse health outcomes in later life, including metabolic diseases like diabetes. Subsequent studies in Hertfordshire also assessed other health outcomes in smaller samples of men and women born between 1920 and 1930 (Hertfordshire cohort study), who underwent detailed physiological investigations in later life. Low birth weight and weight at one year were again associated with cardiovascular disease, T2D, metabolic syndrome and insulin resistance in adulthood[76,77]. These and several studies around the world have since elucidated the role of poor social and nutritional environments in early life as putative causes for metabolic dysfunction in adult stage.

Life-course studies

The epidemiological associations between poor foetal and infant growth and the subsequent development of T2D and the metabolic syndrome resulting from the effects of poor nutrition in early life, which causes changes in glucose–insulin metabolism, are significantly important but environmental influences in the postnatal period possibly have a modulating effect on these pathways. The relative contribution of genes and environment to these relationships, however, remains inconclusive. Lifestyle factors, like dietary habits from early life, including infancy, physical activity patterns throughout life, tobacco and alcohol consumption are all important determinants of individual disease risk. Studies that assess these determinants from birth, through childhood, adolescence and adulthood are called life-course studies and help understand the gene–environment interactions that predispose to developing T2D and other lifestyle disorders.

An exemplar of a life-course study in India comes from the Andhra Pradesh Children and Parents Study (APCAPS)[78]. An early study by the National Institute of Nutrition (NIN) in Hyderabad was built into part of the Government of India's flagship programmes in the 1980s. The Integrated Child Development Services (ICDS) scheme was launched on 2 October 1975 (ref. 79). While its central focus was the improvement of nutritional status of pregnant and lactating women and children less than 6 years of age, it also included complementary programmes for early childhood education, health, hygiene and nutrition education for the mothers and delivery of other national programmes (immunization, anaemia control and basic healthcare) from the ICDS centres, through the Anganwadis. As the programme saw stepwise expansion in the 1980s and 1990s, the NIN conducted an impact evaluation trial called the Hyderabad Nutrition Trial to study the effect of nutritional supplementation in pregnancy on the birth weight of the offspring. A controlled, cluster randomized trial of the nutrition supplementation of pregnant mothers was carried out between 1987 and

1990, with 15 intervention villages where the ICDS programme was in place and 14 control villages where it was yet to start, all located in the Rangareddy district of Andhra Pradesh near Hyderabad city. Mothers in the intervention sites received a locally prepared nutritional supplement made of corn–soya blend throughout pregnancy and lactation. All children born between 1 January 1987 and 31 December 1990 in the study villages ($N = 4338$) formed a birth cohort within the trial groups. Mean birth weight recorded within 48 h of delivery and available in 2964 (68%) newborns was higher in the intervention villages (2655 (SD 430) g) than that in control villages (2594 (SD 430) g); the mean difference was 61 g (95% CI 18–104; $P = 0.007$). Incidence of low birth weight was higher (34.3%) in control than in intervention villages (31.3%). It was lower (27%) in infants born to mothers who consumed supplements at least three days in a week compared to those who did so occasionally (36.3%)[80].

The small, yet significantly improved birth weights in the intervention group and their beneficial effects seemed to persist into adolescence when the children in this group appeared to have a better metabolic risk profile when assessed at adolescence[81]. Among 1165 adolescents (13–16 years of age) studied (78%), children in the intervention village were on average 14 mm taller (95% CI 4–23; $P = 0.007$), insulin resistance was 20% lower (HOMA-IR score) (95% CI 3–39%; $P = 0.02$) and arterial stiffness was 3.3% lower (95% CI 1–5.7%; $P = 0.008$). Body composition was similar in the two groups, but there were no significant differences in lipid levels and blood pressure[81]. A rapid socio-economic transition of this population in the ensuing decade, however, quickly nullified the early benefits of maternal nutritional intervention. The study showed that the adoption of later life unhealthy dietary and lifestyle behaviours with the rapid urbanization in these study villages made these same groups almost at equal, if not greater likelihood of adverse later life disease risk factors, including impaired glucose tolerance, overweight and adiposity[82–84]. Life-course studies like the APCAPS are insightful but logistically difficult to establish and conduct. Nevertheless, these findings suggest that apart from early life influences and strategies to modify them, interventions should have a holistic life-course approach encompassing the improvement of nutrition of the girl child and women, promoting appropriate dietary behaviour, increased physical activity and a move away from sedentary, mechanized lifestyles across life in order to curtail the diabetes and globesity epidemic in our region.

Genetics/epigenetics

Genetic influences, including the role of single nucleotide polymorphisms (SNPs) in the pathogenesis of T2D have been widely studied, including in genome wide association studies. SNPs involve a change in a specific position in the genome in the nucleotide. The *TCF7L2* gene association with T2D is well known, while *SLC30A8*, *DE-KIF11-HHEX* and *EXT2–ALX4* genes were discovered using high-density arrays that tested over 300,000 SNPs in a French case-control study[85].

Epigenetics, first defined by Waddington[86] is a newer science that assesses the role of environmental factors that cause changes in gene expression, thereby causing a change in phenotype, without any alteration in the DNA sequence. Such alterations in heritable changes in gene expression usually occur through processes involving histone modification or methylation of DNA, thereby providing an alternative explanation for the origin of diseases that cannot be explained by genetics alone. Agouti mice have specifically served as excellent animal models to study epigenetic processes[46,87,88]. The distinct coat colour in the Agouti viable yellow mice has been a useful model because of the visibility of the marker, specific methylation processes and their propensity to diseases like diabetes, cancer and obesity. The Agouti gene that causes expression of large quantities of the Agouti-related protein is responsible for the yellow colour of the fur, and is also associated with the animals being obese and hyperinsulinaemic. Genetic imprinting that involves the silencing of an allele of maternal or paternal origin occurs soon after fertilization and involves DNA methylation using methyl groups generally derived from the mother's diet during conception. If there is adequate supply of the methyl donors, methylation results in a different coat colour, lower risk of diabetes and cancer as well as a longer life. Genetic and epigenetic influences comprise important early life influences and the study of the gene–environment interactions is an important area for future research.

Conclusion

The early life influences encompassing parental, foetal and postnatal factors have important influences on the propensity of individual risk of developing T2D. While maternal nutrition, physical stature and lifetime metabolic reserves can affect offspring birth outcomes and postnatal growth patterns, paternal factors may have some influences through different pathways, likely epigenetic in origin. While genetic and shared household factors (social and behavioural) of both parents can also affect offspring disease risk, an additional risk through unique intrauterine pathways can be conferred by the mother. Early socio-economic environments too have strong associations with later life disease. Genetic influences are not amenable to modification, but potential modifiable factors, including maternal nutrition and appropriate dietary and lifestyle practices can form the focus of intervention

programmes and policies to control the burden of T2D. Epigenetic processes and gene–environment interactions are important areas for future research.

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