

*Review Article***Nutrition in Fetal Life and Childhood and Its Linkage with Adult Non-Communicable Disease: Lessons from Birth Cohort Studies in India**

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(Received on 18 June 2018; Accepted on 26 June 2018)

India is facing high and rising rates of mid- and late-life chronic non-communicable diseases (NCDs) such as hypertension, type 2 diabetes and coronary heart disease (CHD). Indian cohort studies have made a major contribution to the global evidence that disease risk is influenced by the nutritional environment experienced during fetal and childhood development. Adults who had a lower birth weight are more likely to develop diabetes and CHD, and children of lower birth weight have higher blood pressure, glucose concentrations, insulin resistance, and cholesterol concentrations. NCD risk is also related to childhood weight gain or body mass index (BMI) gain; upward crossing of BMI centiles is associated with an increased risk of adult type 2 diabetes, hypertension, dyslipidaemia, elevated pro-inflammatory factors and metabolic syndrome. Among people who had a low birth weight, or were underweight in infancy, risk is increased even by relatively modest levels of childhood BMI gain. Cohort studies have identified modifiable factors associated with low birth or infant weight and later NCD risk markers in children, including maternal diets poor in micronutrient-source foods and specific micronutrient deficiencies (eg. vitamins D and B12). In addition, maternal gestational diabetes has been identified as a common and important risk factor for excess adiposity, glucose intolerance and abnormal cardiovascular stress responses in the children. Nutritional interventions aimed at improving maternal health and nutrition before and during pregnancy, and optimising fetal and infant development in order to reduce NCD risk, are currently being tested in India.

Keywords: Nutrition; Fetal Life; Obesity; Diabetes;**Introduction*****The Problem of NCDs in India***

Cardiovascular disease (CVD) is the leading cause of death in India, in both urban and rural areas (Prabhakaran 2016), responsible for a quarter of all deaths, much higher than the global average. This situation has arisen recently; since 1960, the prevalence of coronary heart disease is thought to have risen 5-7-fold in urban India, and 3-fold in rural areas. Compared with Europeans, CVD affects Indians ten years earlier and predominantly during the working years; 52% of CVD deaths occur before the age of 70 years compared with 23% in western countries. Classical CVD risk factors such as hypertension (urban prevalence 34%, rural 28%), type 2 diabetes (T2DM; urban 17%, rural 9%) and

dyslipidaemia are common. Lifestyle and environmental risk factors are also high, including tobacco smoking, air pollution, low fruit and vegetable intakes and physical inactivity. Predictions are that 200 million men and women in India will be hypertensive, and 100 million diabetic, by 2030 (Prabhakaran 2016).

Obesity is a strong risk factor for CVD and T2DM ('cardio-metabolic disease') in all populations, including India. Mean body mass index (BMI) is rising in India, as elsewhere, although the overall prevalence of obesity remains relatively low, and cardio-metabolic disease develops at a lower BMI than in western populations. Yajnik and others have documented the 'thin-fat' phenotype of Indians (a low muscle and lean mass, masking a high fat mass, much of it stored intra-abdominally) which is thought to partially explain their

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high disease risk (Yajnik 2018). The cause of this phenotype is unknown.

Early-life Origins of NCDs

The concept that nutrition during early development (in the embryo, fetus and child) plays a role in the aetiology of adult CVD and diabetes was controversially put forward by David Barker in the 1980's (Barker 1993). He showed that areas of the UK with the highest infant mortality at the beginning of the 20th century were those with the highest CVD mortality in the 1970's, and that individuals who had a lower birth or infant weight (markers of under-nutrition) had a higher risk of developing adult hypertension, T2DM and coronary heart disease. He proposed that CVD has its origins in maternal under-nutrition and ill-health, through impaired fetal and infant development. At about the same time, fetal physiologists showed in animal models that inducing fetal under-nutrition, often subtly and transiently, permanently altered ('programmed') not only the structural development and function of metabolically important organs and tissues such as the pancreas, liver, kidneys, adipose tissue and muscle, but also reset the sensitivity to and/or secretion of hormones such as insulin and corticosteroids, leading to adult disease (Warner 2010). 'Barker's Hypothesis' became the 'fetal programming hypothesis' and inspired the multi-disciplinary field of science known as DOHaD (developmental origins of health and disease). Indian researchers were early to see the relevance of these ideas to India's NCD epidemic, and to start testing them.

Birth Cohort Studies: Maternal and Fetal Nutrition

One of the first DOHaD studies in India was carried out at the KEM Hospital, Pune by Pandit and Yajnik. It investigated children whose birth weights were recorded in labour ward records (Bavdekar 1999). Lower birth weight was associated with higher blood pressure, plasma glucose and cholesterol concentrations, insulin resistance and central adiposity. The highest risk markers were in children of low birth weight who had 'caught up', becoming heavier than average at 8 years. We coined the phrase 'small becoming big' as a risk factor for later cardio-metabolic disease. These findings were consistent with UK studies, which showed the highest CVD risk factors

in adults who started life with a low birth weight but had a high adult BMI. Importantly, the Pune study showed similar findings in a different ethnic population, with a different range of birth weight, and suggested that too much weight gain even during childhood increased CVD risk. Associations between low birth weight and CVD risk markers in children showed that researchers would not have to wait until mid-late life in order to study programming, and offered the potential of developing childhood biomarkers for the early detection of those at greatest risk of disease. Recent follow-up of the Pune children at the age of 21 years has shown that the low birth weight + high adult BMI combination remains associated with an adverse metabolic profile, and that CVD risk markers 'track' (correlate) between 8 and 21 years of age (Joshi 2014).

Another early cohort study was in Mysore, and resulted from a targeted search for old obstetric records. Several long-established Indian hospitals had such records, but those at the CSI Holdsworth Memorial Hospital (HMH) in Mysore stood out for several reasons. Records were available for every baby born in the hospital since 1934, documenting birth weight, length and head circumference, and maternal weight and pelvic diameters. The stability of the Mysore population meant that it was feasible to trace the babies (now adults) by a house-to-house survey of the city (Krishna 2015).

Initially, 500 men and women aged 40-60 years were traced and had blood pressure, lipids and glucose tolerance measured. Coronary heart disease (CHD) was assessed using electro-cardiographic changes, symptomatic and surgical criteria. Lower maternal weight and smaller size at birth were associated with a higher prevalence of CHD (Stein 1996). While this was consistent with western cohorts, the findings for T2DM were different. The Mysore men and women were more likely to have T2DM if they had been fatter (had a higher ponderal index) at birth, and if their mothers had higher body weight and external pelvic diameters (Fall 1998). These results were puzzling at the time, but reports were starting to emerge showing that offspring of mothers who developed gestational diabetes (born macrosomic) were at increased risk of developing later T2DM. We speculated that this could explain the findings in Mysore, and that fetal programming by exposure to

gestational diabetes (GDM) could be an important factor leading to increasing T2DM in India.

The Pune and Mysore studies provided enough evidence to justify taking the DOHaD research programme further, but clearly, better data than that available from routine obstetric records were needed: better characterisation of fetal growth, neonatal phenotype, maternal health and nutrition, and post-natal growth. New prospective cohorts were therefore established to understand maternal influences on fetal development and longitudinally study the evolution of NCDs. The first of these, the Pune Maternal Nutrition Study (PMNS), was started in 1994 by Yajnik and Rao in six poor and drought-prone rural villages (Rao 2001). Women of reproductive age were recruited (N=2,466); over three years 797 of them became pregnant and their babies became the cohort. In pregnancy, women's dietary intakes, blood micronutrient levels and glucose tolerance, as well as fetal growth and newborn body composition, were assessed. Since then the cohort has been followed continuously, with detailed CVD risk marker assessments at 6, 12 and 18 years of age.

The mothers in this rural farming population were young, short and thin (mean age 21.4 years; height 1.52 m; BMI 18 kg/m²) and their babies were small (mean birth weight 2648 g). The incidence of GDM was low (<0.5%). Ultrasound revealed that fetal growth and placental size fell away from western norms as early as 15-18 weeks' gestation. Maternal factors associated with smaller new born size included smaller body size (pre-pregnant height, BMI, skin folds and arm circumference) (Yajnik 2003), a heavier physical workload (Rao 2003), low intakes of micronutrient-rich food such as green leafy vegetables, dairy products and fruit (Rao 2001), lower blood levels of vitamin C and folate, and higher levels of homocysteine (indicative of vitamin B12 deficiency, present in 70% of mothers) (Rao 2001, Yajnik 2005). Compared with UK newborns, the babies were small in all dimensions, and there was a 'thin-fat' pattern to their smallness, with a marked deficit in non-fat soft tissues while sub-cutaneous fat was relatively preserved (Yajnik 2003). This thin-fat phenotype was accentuated in the smallest new borns and persisted through childhood.

The PMNS findings led directly to an intervention study (the Mumbai Maternal Nutrition Study or "Project SARAS", see below). In the PMNS itself, subsequent research focused on the striking vitamin B12/folate/homocysteine results. Low B12 concentrations were found to be common in other Indian populations, while folate deficiency was relatively rare. Yajnik showed that the main cause is low dietary B12 intakes (main sources: meat, fish, eggs and dairy products) and not mal-absorption. Continuing follow-up showed associations of lower maternal B12 concentrations and/or higher folate concentrations in pregnancy with greater adiposity and insulin resistance in the children (Yajnik 2008). These findings, and corroborating evidence from studies elsewhere, led to the decision in 2010 to convert PMNS into a vitamin B12 intervention study ("PRIYA"), still ongoing, in which the adolescent cohort members, both boys and girls, receive vitamin B12 with or without multiple micronutrients and protein (milk powder) or standard care (Kumaran 2017). The primary outcome will be in the next generation: newborn (cord blood) vitamin B12 levels of their offspring, and later cardio-metabolic outcomes. The rationale for supplementing both boys and girls is to examine direct effects of B12 supplementation on health, and the potential effects of paternal as well as maternal nutrition on fetal programming, through epigenetic effects.

The second prospective cohort was the Parthenon Birth Cohort, set up in urban Mysore in 1998 (Krishnaveni 2015a). Its focus is gestational diabetes and its consequences for the children. Women were recruited from the HMH antenatal clinic (N=785) and had an oral glucose tolerance test at 28-32 weeks. The babies have been followed up every 6-12 months through childhood, with detailed CVD risk marker measurements at ages 5, 9 and 13 years.

Six percent of the Mysore mothers developed GDM. This figure seemed high at the time but has been dwarfed by recent GDM prevalence figures of up to 20% among urban Indian women. As expected, newborns of GDM mothers were more adipose than those of non-GDM women. Low vitamin B12 concentrations (41% of mothers) were associated with an increased risk of GDM (Krishnaveni 2009). Follow-up has shown greater adiposity and insulin resistance (Fig. 1), higher glucose concentrations and

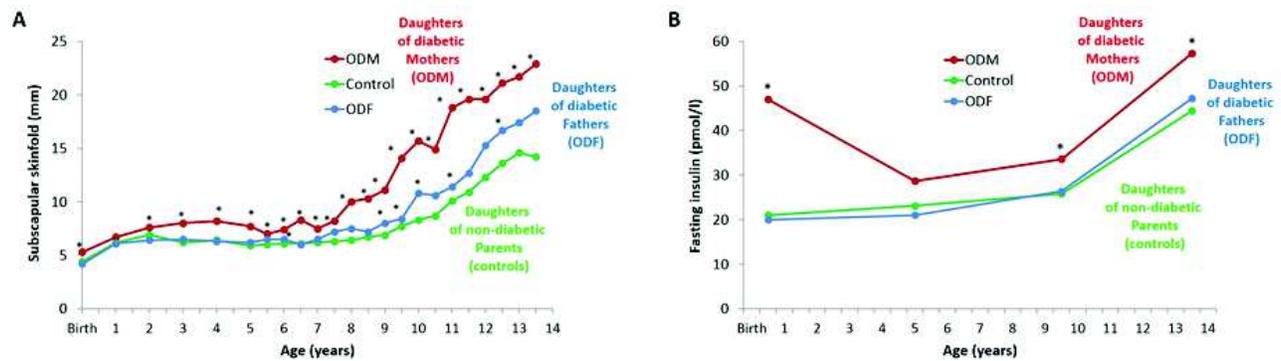


Fig. 1: Mysore Parthenon Birth Cohort: Mean subscapular skinfold thickness (a) and plasma fasting insulin concentrations (b) among daughters of mothers who had GDM (red), diabetic fathers (in blue) or (controls) non-diabetic parents (green). Asterisks indicate a significant difference ($p < 0.05$) from the control group

blood pressure, and increased cardiovascular reactivity to stress (Krishnaveni 2010a, Krishnaveni 2015b) in children of GDM mothers. In summary, these children are showing increased risk for future obesity, CVD and T2DM.

Maternal glucose is a normal fetal fuel, but as mothers get heavier and more adipose, fetuses will be exposed to unprecedented glucose concentrations. It is now certain that a rising prevalence of GDM globally will fuel the rise in child and adult obesity and diabetes in the next generation, and that this is a major problem for India. There is a need to find interventions to prevent GDM in Indian women.

While focusing on GDM exposure, the Parthenon study has provided other insights into early-life nutritional effects on later health. It has corroborated the ‘thin-fat’ new born and childhood phenotype seen in the PMNS, and small size at birth combined with rapid childhood adiposity gain (‘small becoming big’) as a risk factor for higher cardio-metabolic risk markers in childhood (Krishnaveni 2010b). The study has replicated associations of maternal B12/folate/homocysteine status with fetal growth and later cardio-metabolic risk in the children (Krishnaveni 2014). In addition, maternal vitamin D insufficiency (31% of mothers) was associated with smaller muscle size and higher insulin resistance in the children (Krishnaveni 2011). The cohort is currently in its 19-20 year follow-up.

Birth Cohort Studies: Post-natal Growth

The ‘small becoming big’ phenomenon has been

studied in greater depth in two large Indian birth cohorts, the New Delhi and Vellore birth cohorts (NDBC: Bhargava 2018; VBC: Antonisamy 2009). Both cohorts were established in 1969-1973, long before the DOHaD concept, to study the determinants of low birth weight, pre-term birth and infant mortality. In the NDBC the study population was a mainly middle-class sector of South Delhi; the VBC included 25 rural villages and selected areas of Vellore town representing varying socio-economic status. Around 20,000 women were recruited in each study and those who became pregnant were followed up. Measurements of newborn weight, length and head circumference (NDBC: N~8,000; VBC: N~11,000) were repeated throughout childhood. The investigators faced enormous challenges to maintain follow-up over this extended period, including intermittent funding, losses due to clearance of unauthorised housing, and increasing out-migration. Nevertheless, by 1998, at a mean cohort age of 29 years and when the emerging DOHaD research stimulated new interest in the cohorts, it was possible to re-trace more than 2,000 adults from each cohort.

In the NDBC, 4% and 11% were found to have T2DM and pre-diabetes (impaired glucose tolerance, IGT) respectively. The equivalent figures in Vellore were also strikingly high: diabetes 4% and IGT 19% in the urban members of the cohort, and 2% and 14% in the villages (Bhargava 2018, Raghupathy 2010). Figure 2 shows the pattern of post-natal BMI growth associated with adult glucose intolerance. The graphs contrast the childhood BMI of those who had IGT/T2DM at age 29 years relative to the rest of the

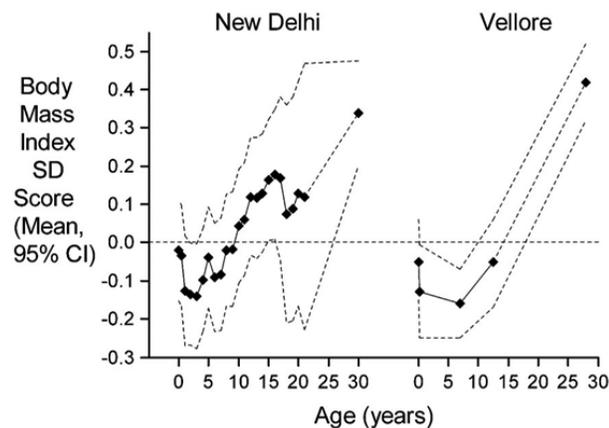


Fig. 2: New Delhi and Vellore birth cohorts: mean within-cohort BMI Z-scores from birth to adulthood of participants who developed T2DM/IGT at age 29 years compared with the rest of the cohort (indicated by the horizontal zero line; dashed lines indicate 95% confidence intervals)

cohort. They were lighter at birth, and significantly *thinner* than the rest of the cohort in infancy and early childhood, but after mid-childhood gained BMI faster, reaching the same mean BMI as the rest of the cohort in adolescence, and overtaking it to become significantly heavier at 29 years. Similar data from the Finnish Helsinki cohort, have shown an identical pattern (Eriksson 2003).

The data are shown in a different way in Figure 3, in which data from the New Delhi and Helsinki birth cohorts are shown on the same scale, as BMI Z-scores according to the CDC growth reference. The plots are remarkably similar in shape in both cohorts, even though the Finnish population had a much higher BMI at all ages. In both populations, the BMI of individuals who developed IGT/T2DM and those who did not differed significantly from each other at the beginning (2-5 years, when the IGT/T2DM group were thinner than the rest of the cohort) and the end (29 years, when the IGT/T2DM group were heavier). Between these ages, the lines cross over in both cohorts – the future IGT/T2DM group gained BMI slightly more rapidly than the healthy group. The point is that the children who went on to develop IGT/T2DM in Delhi were not obese; they were thin by international standards. There are large numbers of people in India (and other low- and middle-income countries) who are developing disease with no history

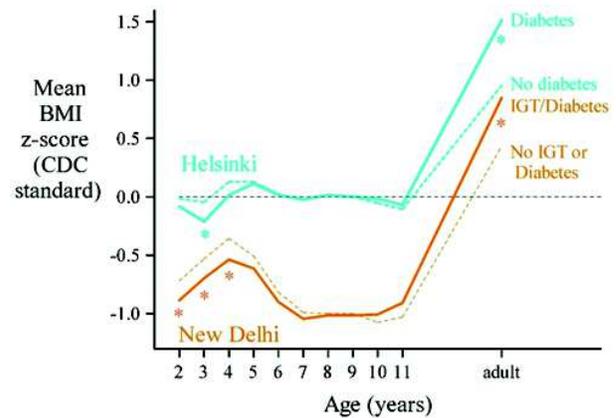


Fig. 3: New Delhi (orange) and Helsinki (blue) birth cohorts: mean BMI Z-scores of participants who did and did not develop adult IGT/T2DM, according to the CDC growth reference. Helsinki data presented with the kind permission of Johan Eriksson

of childhood obesity. The key childhood indicators of IGT/T2DM risk were: 1) a low BMI in infancy and early childhood, followed by 2) a subtle rise in BMI which started in mid-childhood but which was not visible as frank obesity.

It is undoubtedly important to prevent and treat childhood obesity. But this alone will not prevent the majority of future cases of T2DM in India, because many Indian children have the above growth pattern. The challenges are to recognise that newborn and infant *under-weight* is a risk factor for later diabetes, and to detect children crossing BMI centile lines upwards in childhood ('becoming obese relative to themselves'). The NDBC group has published centile charts to detect this growth pattern (Sachdev 2009). It is important to understand why pre-natal and early post-natal under-weight creates vulnerability to later diabetes (DOHaD theory suggests that under-nutrition impairs the early development, and therefore the later function, of key metabolic tissues). We do not know if the upward BMI trend after mid-childhood simply reflects economic transition or whether it indicates advanced maturation resulting from fetal under-nutrition. Should the early life under-nutrition or the childhood BMI gain (or both) be targeted for intervention? This question is being explored through intervention studies.

Interpretation of the Cohort Data and Move to Intervention Studies

Figure 4 brings together the findings from the Indian birth cohort studies to explain, from a DOHaD perspective, how transition could be inducing NCDs in populations with a recent and inter-generational history of under-nutrition (Yajnik 2014). The left-hand circle represents the situation in under-nourished communities in India; low birth weight and failure to thrive in infancy are common and are associated with childhood stunting, impaired neuro-development, and hence reduced adult human capital. These children are programmed for later CVD and T2DM, because their metabolic tissues have also been hit by under-nutrition, but in the absence of catch-up weight gain in childhood this does not result in NCDs. If the same levels of poverty and under-nutrition persist, the cycle goes round again, but transition to some degree is happening everywhere, and enables better childhood nutrition, and an increase in adiposity. On a background of fetal programming, this relative over-nutrition leads to increased insulin resistance, hypertension, other metabolic CVD risk markers, and the emergence of NCDs (left to right arrows between the two circles). In India, perhaps because of the severity of fetal undernutrition, it appears to take very little transition, and only a subtle increase in childhood adiposity to produce these metabolic changes and NCDs. This in turn leads to problems in the next generation (right-hand circle). Among women, the combination of early life undernutrition and later adiposity increases the risk of gestational diabetes, which exposes the fetus to excess glucose and other fuels, leading to fetal

hyperinsulinaemia, macrosomia, and increased insulin resistance and diabetes in later life (dashed line).

Attempts could be made to break these cycles at several points, for example by improving maternal nutrition, fetal development and infant nutrition (to avoid adverse metabolic programming and reduce vulnerability to later NCDs) or by preventing childhood BMI gain (to avoid placing excessive strain on individuals programmed to have impaired metabolic capacity). High-quality intervention studies in Indian children have shown that it is not easy to prevent BMI gain (Bhave 2016). Moreover, preventing BMI gain among children who were under-nourished in utero, and whose BMI remains well below international norms, is not a desirable option. In such populations, our subsequent work has therefore focused on improving maternal and fetal nutrition by intervening in pregnancy.

Nutritional Intervention Studies Before and During Pregnancy

Most nutritional interventions in pregnancy have tended to start in the mid- or late first trimester, thus missing fetal organogenesis (and thereby the opportunity to enhance the development of key metabolic tissues), placental development (and thereby the opportunity to enhance fetal nutrition throughout pregnancy), and peri-conceptual epigenetic changes, which are thought to play a mediating role in fetal programming (Fleming 2018, James 2018). Within a DOHaD perspective, pre-conceptual interventions, though more challenging, seem the logical way forward.

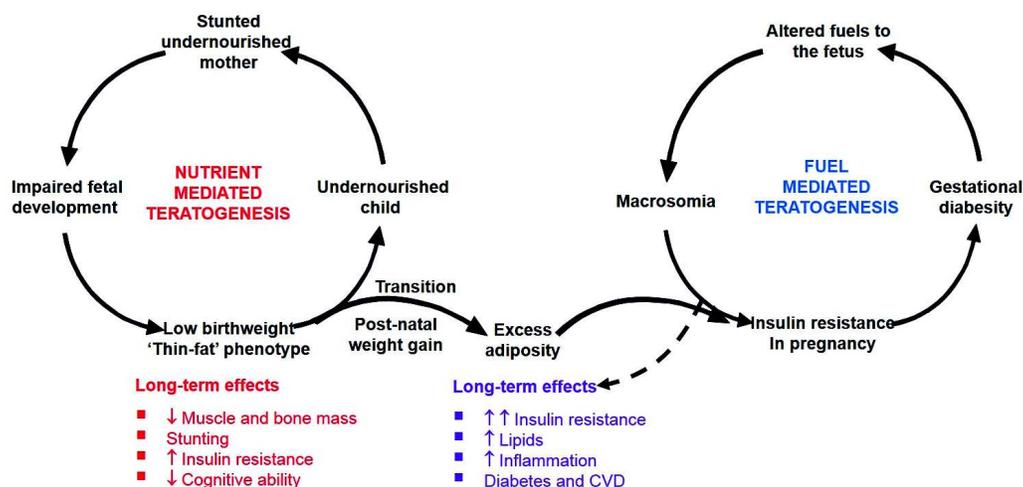


Fig. 4: Nutritional transitions leading to rising NCD risk

There are currently three ongoing pre-conceptional intervention studies in India, set up with the aim of preventing NCDs in the next generation. The Mumbai Maternal Nutrition Project (MMNP, or “Project SARAS”) was a food-based intervention among women living in slums in Mumbai (Potdar 2014). The aim was to improve maternal *diet quality* by supplementing the normal diet with locally-available micronutrient-rich foods (green leafy vegetables, milk and fruit). These were in the form of ‘snacks’ (e.g., samosas) prepared daily in a special kitchen. Among women who started supplementation before conception, there was a mean 48g increase in birth weight, and a reduction in LBW of 24%; the effect was greatest among women of normal pre-pregnant BMI (Fig. 5). The prevalence of GDM was almost halved (Sahariah 2016). The SARAS children are currently being studied at the age of 5-7 years to assess the effect of this intervention on the children’s CVD risk markers. The second intervention study, using vitamin B12, in Pune, has already been highlighted above. The third study (“EINSTEIN” Early Interventions to Support Trajectories for Healthy Life in India) will start in 2018 as part of the multi-country HeLTI family of studies (Healthy Life Trajectories Initiative) and will include multi-faceted interventions (nutrition, sanitation and hygiene, environmental and mental health interventions) in a rural South Indian population.

Conclusions

Birth cohort research in India over the past two decades has provided strong evidence that exposure during fetal life to maternal under-nutrition and/or gestational diabetes, sub-optimal nutrition in early childhood, and (sometimes small) increases in child/adolescent adiposity, all contribute to the Indian population’s high risk of CVD and type 2 diabetes. The exact cause of the ‘thin-fat’ Indian phenotype, present at birth and linked to a high NCD risk, remains elusive, but cohort studies have shown a clear progression from nutritional markers in mothers during pregnancy, through new born size and CVD risk markers in childhood, to adult disease. Modifiable maternal nutritional factors related to impaired fetal

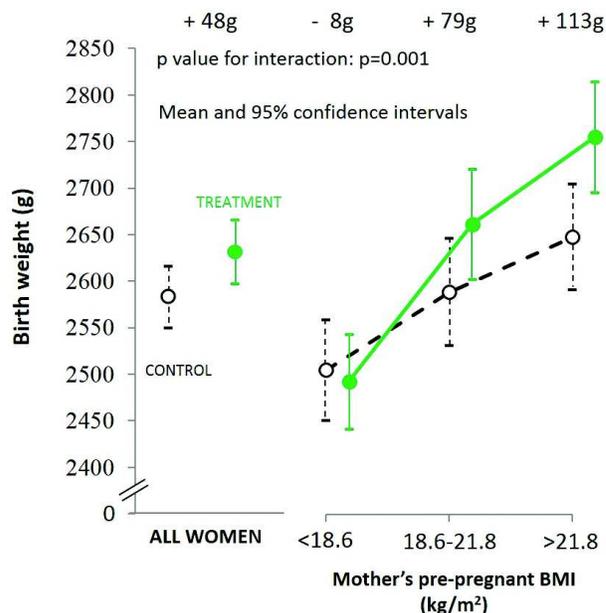


Fig. 5: Project SARAS, Mumbai: mean birth weight in the intervention and control groups according to maternal pre-pregnancy BMI

development and NCD risk markers have been identified and are currently being targeted in intervention studies, starting pre-conceptionally. These trials will be the ultimate test of the DOHaD concept and, we hope, will provide support for including measures to improve the health of girls and women in the public health strategy to prevent NCDs. Birth cohort studies continue to deliver fresh insights into the inter-generational effects of a rapidly changing nutritional landscape, other early-life exposures (eg pre-eclampsia), and paternal as well as maternal nutrition, on NCDs, other health outcomes and human capital development.

Acknowledgements

I thank my many colleagues and collaborators in India, and the Indian Council of Medical Research, Department of Biotechnology, Medical Research Council (UK), Department for International Development (UK), Wellcome Trust (UK), British Heart Foundation and Parthenon Trust (Switzerland) for funding our work.

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