

Session II :
Early Origins of Obesity

Fetal origins of obesity

The epidemic of obesity as observed globally and the increasing interest in the fetal origins of adult disease has led to numerous studies examining the role of fetal factors in the development of subsequent obesity.

Most studies show a direct relationship between birth weight and obesity, with higher birth weight associated with higher mean body mass index (BMI) and higher rates of obesity among children and adults. There appears to be an approximately 0.5-0.7 kg/m² increase in mean BMI for each 1 kg increase in birth weight. Child obesity is also associated with parental obesity, though the association between birth weight and BMI is only partly explained by a higher maternal BMI. Another factor associated with child and adult obesity is exposure to hyperglycemia in utero (i.e., maternal diabetes mellitus). Although many studies show a direct relationship between birth weight and obesity, several studies also show that low birth weight is associated with higher rates of central obesity. Recent studies show that infants born preterm and small-for-gestational age are particularly at risk for a larger waist circumference and a higher BMI.

Various explanations have been offered to explain these associations. The association between birth weight and obesity may be explained by genes that have effects on both birth weight and obesity. The association between parental and child obesity can be explained by similar prenatal and postnatal eating habits. Finally, it is possible that fat cell size/number is determined in utero.

Research Needs:

1. What are the trends in low birth weight, preterm birth and SGA in India?
2. What are health vs unhealthy trajectories of growth e.g., will preterm SGA infants who have a healthy diet and adequate physical activity have central obesity?
3. Does the pathway between low birth weight and poor cardiovascular health flow through obesity?



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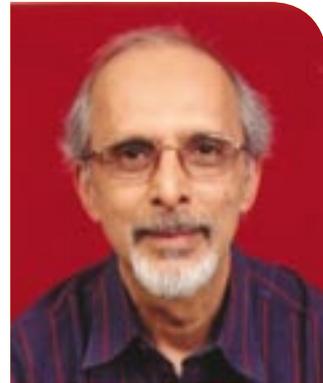
Suggested reading

1. Oken E, Gillman MW. Fetal origins of obesity. *Obes Res* 2003;11:496-506.
2. Evensen KA, Steinshamn S, Tjønnhaug AE, et al. Effects of preterm birth and fetal growth retardation on cardiovascular risk factors in young adulthood. *Early Hum Dev* 2008 Nov 12.

Childhood obesity & maternal influences

The epidemic of Obesity is becoming prominent in low-middle income countries. Recent research findings of adiposity being programmed in the intrauterine life, and the role of genetic and epigenetic factors offer a unique opportunity for its early prevention.

Current definitions and cut offs for defining limit comparisons across populations as well as assessment of adiposity. The higher body fat percent (adiposity) in Indians for any given BMI compared to Europeans, leads to higher risk of metabolic and vascular problems at lower BMI. This has led to the concept of 'thin fat' Indians. Using some of the anthropometry and imaging techniques, Indian newborns are shown to be 'thin and fat' as compared to European babies. Fetal programming influences future health and susceptibility to disease, and Maternal nutrition and metabolism are two prominent stimuli for it. These influences interact with fetal genome and modify gene expression without any change in base sequence of DNA (Epigenetics). Methyl donors like folate and vitamin B12 play a pivotal role in epigenetic changes. Another possible mechanism of epigenetic change is through maternal metabolism, highlighted in studies of diabetic pregnancy. Norbert Fienkel developed the concept of 'fuel-mediated teratogenesis' to describe a spectrum of fetal outcomes in diabetic pregnancy (early fetal wastage, birth defects, affection of brain function and adiposity and risk of diabetes). We have extended this thinking to the spectrum of affection by 1-C (methyl) metabolism and called it 'nutrient-mediated teratogenesis'. Both are associated with changes in body composition (adiposity) and metabolic programming which predisposes to insulin resistance, B-cell dysfunction and type 2 diabetes. The Pune Maternal Nutrition Study has shown that maternal vitamin B12 deficiency coupled with folate excess is associated with offspring adiposity and insulin resistance. If the epigenetically affected offspring is female, then she transmits the susceptibility to her children (transgenerational amplification of obesity and diabetes). In India, rapid transition seems to have combined the nutrient-mediated and fuel-mediated teratogenesis to cause a rapid rise in prevalence of adiposity and



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diabetes in the young, including children. Rapid childhood growth in Intra Uterine Growth Retarded (IUGR) babies is associated with increased adiposity and insulin resistance and increased levels of cardiovascular risk factors. This finding is counterintuitive to current practice of rehabilitation of low birth weight children by feeding them to achieve 'normal' growth and needs to be further investigated.

Research Needs:

1. Need for a life-cycle based approach to health and disease prevention. This should begin very early in the life-cycle and many will have effect only intergenerationally.
2. Investigate the needs and methods of supplementing protein and micronutrients
3. Rationalisation of growth charts with adult outcomes in mind.
4. Nutritional rehabilitation of IUGR children

Suggested reading :

1. Yajnik CS, Fall CHD, Coyaji KJ, etal. Neonatal anthropometry: The thin-fat Indian baby, The Pune Maternal Nutrition Study. *International Journal of Obesity* 2003; 26:173-180.
2. Yajnik CS, Deshpande SS, Jackson AA, etal. Vitamin B12 and folate concentrations during pregnancy and insulin resistance in the offspring: The Pune Maternal Nutrition Study. *Diabetologia* 2008; 51:29-38
3. Yajnik CS. Nutrient-mediated teratogenesis and fuel-mediated teratogenesis: Two pathways of intrauterine programming of diabetes. *Int J Gynaecol Obstet.* 2009 Jan 17.

Role of infant feeding in the obesity epidemic

The main controversies in this area concern the effects of early growth (especially weight gain) and breastfeeding.

Infant feeding is a potent determinant of the growth rate in the early weeks and months of life. IGF-I, the principal hormone affecting growth in infancy, is responsive to both the energy and protein concentration of the diet. Lucas, Singhal, and colleagues from the U.K. argue from both animal studies and their own follow-up studies of children, that rapid early infant weight (especially in the first 3 months) increases the risk of obesity and insulin resistance in later childhood and adulthood. Barker, Ericsson, et al from Finland, however, have reported that low, rather than high, weight gain in the first 2 years of life is associated with future risk. Cohort studies from both Pune and Delhi suggest that rapid weight gain in later childhood is associated with these risks.

Although infants who receive prolonged and exclusive breastfeeding have been reported to grow more slowly than those who are formula-fed or who are weaned early, the causal nature of this association remains controversial. A meta-analysis based on individual patient data suggests that breastfeeding affords little or no long-term protection against obesity, an inference also supported by the cluster-randomized PROBIT trial from Belarus.

Research Needs:

1. RCTs of energy and/or protein supplementation of breastfed SGA infants
2. RCTs of high-energy, low-bulk complementary foods in poor rural settings
3. Epigenetic effects of breast- vs formula feeding

Suggested reading:

1. Chomtho S, Wells JCK, Williams JE, et al. Infant growth and later body composition: evidence from the 4-component model. *Am J Clin Nutr* 2008;87:1776-1784.



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2. Owen CG, Martin RM, Whincup PH, et al. The effect of breastfeeding on mean body mass index throughout life: a quantitative review of published and unpublished observational evidence. *Am J Clin Nutr* 2005;82:1298-1307.
3. Kramer MS, Matush L, Vanilovich I, et al. Effects of prolonged and exclusive breastfeeding on child height, weight, adiposity, and blood pressure at age 6.5 years: New evidence from a large randomized trial. *Am J Clin Nutr* 2007;86:1717-1721.

Infant nutrition and later obesity: An Indian perspective

Recently, four systematic reviews from observational studies have summarized information on the association between infant feeding and later obesity. These studies were primarily from developed countries, evaluated children, adolescents or adults and usually compared breast versus formula feeding. Information was invariably incomplete with respect to infant feeding exclusivity, duration and introduction of semi-solids. Confounder adjustment was infrequent and the most common evaluated outcome was body mass index (BMI) rather than firmer measures of adiposity like skinfold thickness, bio-impedance or DEXA.

The reviews suggested a protective effect of breastfeeding for later obesity; ~20% for exclusively breast-fed versus formula fed infants. There was some evidence of a “dose response effect” – longer duration of breast-feeding had greater effect (4% lower risk per month of breast-feeding) but there was no relation with mean BMI. Confounder adjustment attenuated all relationships. A study documented an inverse association of breast-feeding with fat mass (DEXA) at 9-10 years age. There was virtually no information on: (i) Effects of different formulas; (ii) Age of starting solids; (iii) Type and quality of complementary feeds; and iv) Micronutrient supplements.

A similar analysis was done on the New Delhi Birth cohort when subjects were between the ages of 28 and 32 years. During infancy, over 99% of them received breast-feed while the exact duration of breast-feeding was not recorded. Delayed introduction of semi-solids (beginning from 7-9 months was associated with a significantly lower (confounder adjusted) adult waist circumference, BMI and overweight but not fat percentage or skinfold thickness. However, there was no significant relationship with blood pressure, hypertension, impaired glucose tolerance or diabetes. Accelerated growth in the first 2 years of life was more correlated with adult lean tissue mass rather than sum of skin-folds.

Research needs :

(i) Relating the childhood cohort study data to adult DEXA measures



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- (ii) Conducting similar analyses on recent observational trials of growth with detailed infant feeding information and on randomized controlled trials of infant feeding and single micronutrient interventions
- (iii) Relating early infant growth to adult adiposity measures. Efforts should be directed towards extraction of meticulous feeding definitions, firmer measures of adiposity and adult metabolic disease markers.
- (iv) Evaluating potential hormonal mechanisms.

Animal models to understand the obesity epidemic Neonatal ghrelin and sensitivity to high fat diet in adulthood

Animal studies are an integral part of obesity research. Identification of new genes promoting weight excess or protecting against it and testing of novel hypotheses related to gene-nutrient interactions are two of many opportunities offered by animal models. A brief summary of one animal model used at the Child and Family Research Institute in Vancouver is discussed as a potential offered by laboratory research in general and animal studies in particular for scientific collaboration between India and Canada.

The objective of our research program is to investigate in rodents the role of ghrelin, a 28-amino acid peptide secreted primarily by the pancreas in the fetus and the neonate (and by the fundus of the stomach in adult animals) in the development of obesity. We hypothesize that administration of acylated ghrelin prior to weaning (during the 2nd postnatal week) will affect the sensitivity of the adult animal to the obesogenic effects of high fat diet. Ghrelin circulates as acylated and desacyl forms. Acylation of Ser3 by n-octanoic acid is required for binding of ghrelin to the growth hormone secretagogue receptor (GHS-R). Exogenous administration of acylated [but not desacyl] ghrelin stimulates GH secretion, inhibits insulin secretion and increases appetite through binding to GHS-R. Both acylated and desacyl ghrelin decrease adipogenesis through GHSR-independent pathways. Animal knock-out models of ghrelin (*ghrl*^{-/-}) are resistant to the development of obesogenic effects of high fat diet if the high fat diet is started at weaning, which may suggest developmental issues. After investigating the characteristics of ghrelin metabolism in mice during the perinatal period, we will compare the effects of acylated ghrelin, desacyl ghrelin and a ghrelin antagonist, administered during a critical period of brain development (2nd postnatal week) on the effects of a high fat diet (started at weaning) on weight, body composition, energy expenditure and hormonal profile.



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Research Needs:

The use of animal models for the study of obesity poses challenges and offers opportunities for collaborative projects at several levels:

1. Type of intervention
 - Genetic, nutritional, hormonal, behavioural or others
2. Timing of intervention
 - Prenatal factors; maternal undernutrition, maternal high-fat diet feeding, maternal stress during gestation
 - Postnatal factors; changes in the composition or amount of maternal milk, maternal-pup behavioural interactions
3. Mechanisms of action; eg. increased maternal milk intake
4. Its relevance to human conditions?

Suggested reading:

1. P Walia, A Asadi, J Johnson, T Kieffer and JP Chanoine. Ontogeny of Ghrelin, Obestatin, Preproghrelin and Prohormone Convertases in Rat Pancreas and Stomach. *Pediatr Res.* 2009 Jan;65(1):39-44
2. JP Chanoine. Ghrelin in growth and development. *Horm Res.* 2005;63:129-38 (Review)
3. JP Chanoine and ACK Wong. Ghrelin gene expression is markedly higher in fetal pancreas compared with fetal stomach: effect of maternal fasting. *Endocrinology.* 2004;145:3813-20

Animal models to understand the obesity epidemic

Overweight and obesity are problems of global importance. Among its several aetiological various factors, altered developmental programming due to maternal under-nutrition is of particular relevance to India considering the widespread under-nutrition [specially of micronutrients (MNs)] among adolescent Indian girls, pregnant and lactating mothers. Assessing the importance of maternal MN deficiency in modulating developmental programming for obesity in later life of the human offspring is difficult. Therefore appropriate animal models have been in use for this purpose. The effects of maternal MN deficiency (Hidden hunger - widely prevalent in India) on developmental programming for obesity and associated diseases in later life are little understood.

We investigated in the Wistar / NIN rat model, whether or not maternal MN deficiencies modulate body composition (adiposity and lean body mass) in the offspring which could predispose them to adult onset diseases. Our initial studies showed that maternal vitamin or mineral restriction increased body fat %, decreased lean body mass (LBM), fat free mass (FFM) and impaired the offspring's capacity to secrete insulin to a glucose challenge. Similar changes were seen in the offspring of Mg, Cr, Zn, folic acid and / or vit B12 restricted rat dams. Although maternal Mn restriction altered only body fat % and plasma lipid profile in offspring, it increased their susceptibility to impaired glucose metabolism on feeding high fat diet in later life. In general, increased body fat % was associated with increased central adiposity, altered lipid profile and expression of adipokines. Decreased LBM % and FFM % were associated with altered myogenic gene expression and glucose uptake by muscle indicating altered muscle development and function. Alterations seen in fasting plasma insulin and insulin secretion to a glucose challenge probably suggest alterations in carbohydrate metabolism. Considering that the phenotypic changes in offspring were mostly irreversible by rehabilitation from as early as birth (in line with Barker's hypothesis), our studies demonstrate the utility of ani-



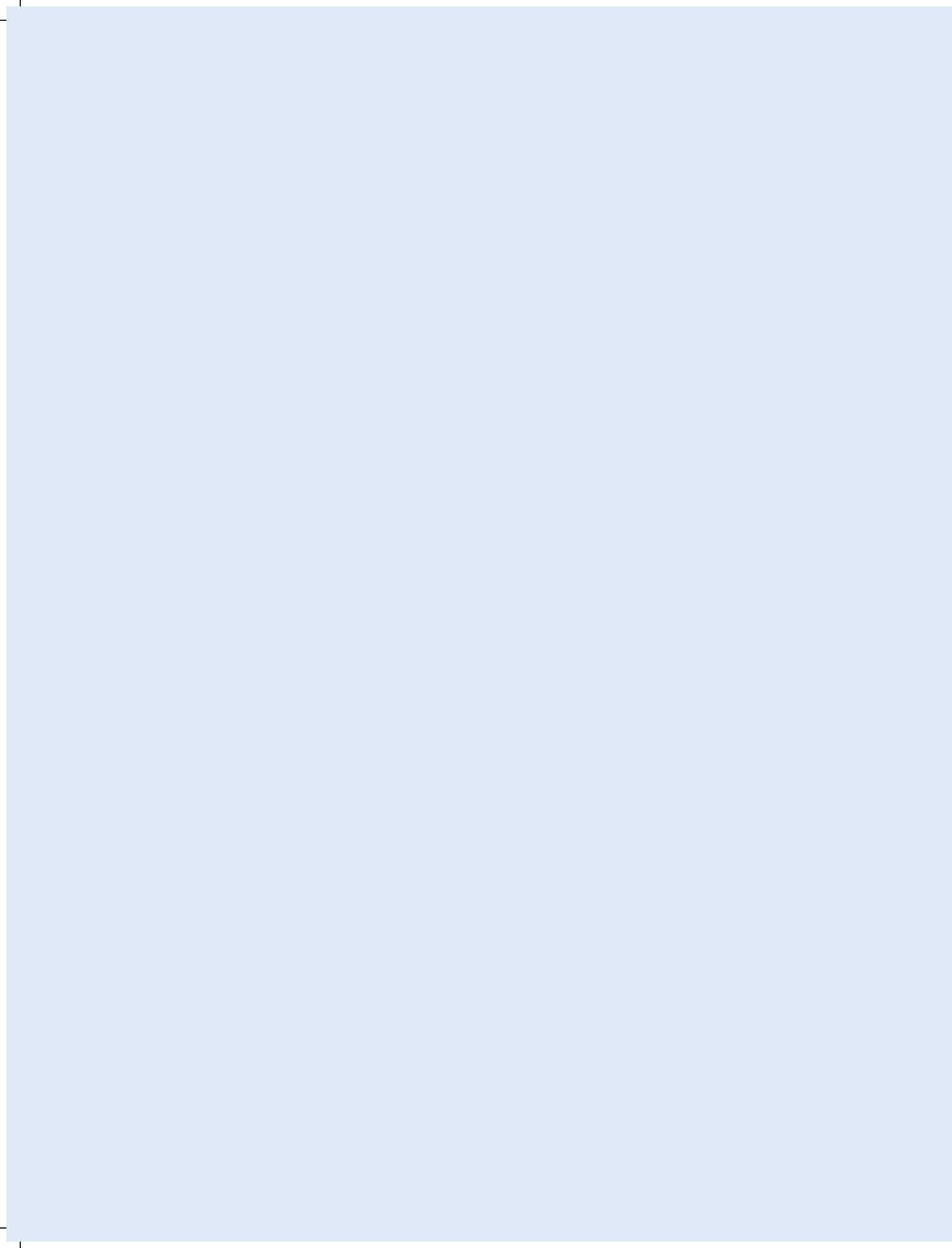
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mal models in deciphering the role of maternal micronutrient deficiencies on childhood obesity.

Research Needs:

1. To study the importance of experimental animal models in evaluating the effects of maternal micronutrient deficiency in the aetiology of obesity and associated diseases in the offspring.



Session II :

Early Origins of Obesity

WORKING GROUP
REPORTS

1. Working Group - I

Fetal and infant origins of obesity

The group discussed the healthy and unhealthy child growth trajectories, longitudinal evaluation of body composition, Preterm/term, SGA/AGA, Indian/European, rural/urban differences, Cohort studies by socio-economic groups, role of micronutrient deficiency including Vitamin D, infant feeding and biomarkers of health in children at 2, 4 6 years of age, innovative markers of malnutrition in childhood and the need (outcome-based) for ethnic-specific fetal and infant growth standards?

Recommendations:

1. Investigate the maternal attitudes towards infant (esp. LBW) feeding, more vs less fortification for Small for Gestational Age infants
2. Influences of Preconception health on fetal/infant outcomes
3. Investigate role of physical activity in maternal and pre-school settings so as to influence the 'Indian phenotype'



2. Working Group - II

Genetics, epigenetics and animal models of obesity

The genetic and epi-genetic studies could investigate different populations in a different environment (eg. how environment affects epigenetic characteristics), similar populations/different environment (Indians in India and Canadian immigrants); different populations/similar environment (Indians and Canadians in Canada) and how does environment affect epigenetic characteristics in subsequent siblings from the same family (born in 2 different countries)

Recommendations:

1. Strengthen Technical collaboration for exchange of technology/expertise (incl. animal models), student training, synergies to decrease cost of doing research, development of common methodology to facilitate phenotyping of individuals for genetic/epigenetic studies
2. Harmonization of Bio-Banking (including development of methodology for “non-blood” samples such as saliva)
3. Development of replication cohorts of subjects to confirm genome-wide studies performed in one population

