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Intrauterine Growth and Adult Diseases from Theory to Practices

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Early childhood have a critical importance for brain development and for setting in place the structures that will shape future cognitive, social, emotional, and health outcomes. This review tries to shade the light on the origin of adult disease during fetal life. Searching on the internet using the Google search engine was the main source of data as well as books was the method to explore this interaction. Changing the body composition and diets of young women, more instantaneous profit may be obtained from preventing imbalances between parental and postnatal growth among children.

Keywords: Fetal; origin; adult; chronic; disease; obesity.

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ABBREVIATIONS

CHD : Chronic Heart Diseases
FOAD : Fetal Origin of Adult Disease
IUGR : Intra-uterine growth retardation
NIDDM : Non insulin dependent diabetes
HT : Hypertension
IGFs : Insulin-like growth factors
CVD : Cardiovascular Diseases
HPA : Hypothalamo- pituitary- adrenal
SAG : Small-for- gestational-age
BMI : Body mass index

1. INTRODUCTION

Normal fetal growth is the end stage of an balanced interaction between maternal nutritional status, placental transport, and fetal factors [1]. Growth is characterized by a series of critical step, including times of intense development where cells rapidly divide and differentiate in order to synthesize the various tissues and organs that will eventually environment, and thus depend on maternal nutrition and metabolism [2,3]. Maternal inadequate nutrient intake has the strong effects in both fetal and maternal metabolism [4]. Thus a nutritional status during pregnancy affect both fetal survival and growth, as well as disturb the finely homeostatic mechanisms that are essential for fetal growth and metabolisms [5]. Fetal growth restriction has been defined as a pattern of intrauterine growth constrained by internal or environmental factor [nutrition], where the constraints are sever enough that the fetus must limit growth in order to ensure survival at birth, and subsequent postnatal life [6]. All of these factor reflect adaptations made by the fetus to ensure survival in the face of a compromised intrauterine environment [3] infancy anthropometric measurements at birth, such as birth-weight, placental weight, body proportion, and length are strongly associated with later disease incidence such heart disease mortality, non insulin dependent diabetes and risk factor for those mentioned diseases [7-11]. This paper aims to review all theories behind the roots of adult diseases during infancy and or childhood and the scenarios behind this connection.

2. METHODOLOGY

Searching on the internet using the Google search engine was the main source of data. The keywords include fetal, origin, adult, chronic, disease, obesity. The search has generated about 88 sources, of which 63 sources have actually been used. These 63 articles were considered relevant because they answered the aim and objectives of the review. The library database was also used during the study. All included articles and books were written in English. The study period has extended from March to end of January 2017.

3. HUMAN EPIDEMIOLOGICAL STUDIES

Evidence from historical cohorts retrospective studies has shown clear association between retarded fetal growth [as evidenced by small size at birth] and risk of CHD, diabetes stork [12]. A number of studies, mostly in developing countries, have suggested that intrauterine growth retardation and low birth weight are associated with subsequent development of insulin resistance [13]. There is considerable evidence, mostly from developed countries, that IUGR[intra-uterine growth restardation] is associated with an increased risk of coronary heart disease[CHD], stroke, and diabetes [14]. Original reports linking disease to fetal growth restriction as marketed by low birth weight came from a long history of retrospective cohort studies established by baker et al. [15,16] from archival data in Hertfordshire , England between 1911 and 1930. These data of men born in Sheffieled and Hertfordshire showed increased incidence of cardiovascular disease to be associated with low birth weight, as well as a strong relationship between death from coronary heart disease and head circumference or ponderal index. The developmental origins of adult disease [17]. The Hertfordshire study also demonstrated that low birth weight was associated with insulin resistance syndrome [syndrome X] occurring in adult life, characterized by glucose intolerance, hypertension, and altered lipoprotein metabolism. Similar studies by Hales et al. [1], as well as six international studies from the US, Sweden and India, [1] confirmed these finding. These results have been repeated in other studies from many different countries, as well as in women [The developmental origins of adult disease], [17]. During the Dutch Famine 1944-1945, some 4.5 million were affected. About 22,000 died because of the famine [18]. The famine had a strong effect on the general health of the population, in Amsterdam, the mortality rate in 1945 was more than doubled compared with 1939, and it is likely that most of this increase in mortality was attributable to malnutrition. But even during this disastrous famine, women conceived and gave birth to

babies, and it is in these babies that the effects of maternal malnutrition during different periods of gestation on health in adult life can be studied. Of the 2414 infants who were included, 307 were exposed in late gestation, 297 exposed in mid gestation and 217 in early gestation. People conceived after the famine had the lowest mortality up to age 50 [7.2%]. Mortality was higher in offspring exposed to famine during early gestation [11.5%] and mid gestation [11.2%]. Mortality was highest in those exposed to famine in late gestation [14.6%] and those born before the famine [15.2%] [19]. Furthermore studies examining the Dutch famine showed that under-nutrition during the first trimester was associated with adult obesity, while under-nutrition later in pregnancy predisposed individuals to low birth weight, GI and NIDDM [16]. There is also a wealth of data showing that poor intrauterine and infant growth and nutrition are associated with reduced capacity in adult life, including reduced stature, lower physical work capacity, impaired cognitive function and educational attainment, and [for women] an increased risk of low birth weight in the next generation [20]. Over the last decade, there have been increasing reports linking small size at birth to HT,NIDDM, and GI in adults. Systematic literature reviews dating back to the 1970 in Australia, China, India, and Japan have shown an association between increase in infant weight and reduction in blood pressure. Both HT and NIDDM in adults have been associated with small size at birth, low birth weight, shortness and low ponderal index, in both retrospective and prospective human epidemiological studies. The association being made between fetal growth restriction and adult disease are in fact independent of adult lifestyle and socio-economic status. However, there is no doubt that these factor play a role in exacerbating disease which have their roots in the prenatal period [3]. Studies in Preston showed that babies whose placentas are disproportionately large in relation to their own weight tend to have raised blood pressure [21]. Association between low birth weight and later disease have been widely replicated in studies in Europe and the USA. The association between low birth weight and coronary artery disease has been confirmed in studies of men in Sweden, Helsinki, Finland, and South Wales, and among 80.000 women in the American nurses study. The fetal origins theory is of greatest relevance to the developing world, and the implications of this work for global health are enormous. Studies in southern India have shown that babies who are short and fat tend to become insulin deficient and have high rates of non-insulin dependent diabetes. These finding were similar to those seen in Pima Indians and also with observations in Sheffieled that showed an association between abdominal circumference at birth rate and mortality from coronary heart disease. Shortness and fatness are thought to be the result of maternal hyper glycaemia, with consequent imbalance in the supply of glucose and other nutrients to the fetus. Studies in Preston showed that babies whose placentas are disproportionately large in relation to their own weight tend to have raised blood pressure [21,22].

Experimental studies: Experimental studies in animals have concluded that maternal nutrition can have strong effects on the offspring disease. Feeding pregnant rats a low protein food results in causes increase of blood pressure in the offspring [21]. Prospective investigation using animal models are now providing substantial experimental evidence to support the "fetal programming, hypothesis [3]. A number of studies using growth- restricted rats have demonstrated the long- term effects of under-nutrition in the womb on adult offspring. It has been shown that fetal growth restriction is associated with HT, obesity, hyper insulinemia, and a decreased responsiveness of insulin to glucose in adult rats specifically, maternal low protein diets [23] or sever caloric restriction of mother rats [24] were associated with HT in adult offspring. Sheep have also been used extensively as models of fetal growth restriction. Under-nutrition in pregnant sheep has been shown in some cases to increase placental size, an adaptation that occurs in order to increase nutrient extraction from the mother, but also related to increased blood pressure in offspring [6]. Conversely in other studies, under-nourished fetal sheep with restricted placental function have demonstrated diminished overall growth, with the exception of the brain [6]. Brain function maintenance appears to be at the expense of other organs, including the spleen and thymus. Growth restricted sheep also exhibited decreased levels of fetal anabolic hormones[insulin, IGFs, thyroid hormones], as well as increased stress hormone concentration [cortisol and catecholamine's] [25]. Similar results were obtained in guinea pig studies where mild to moderate dietary restriction resulted in GI and HT in adults offspring [25]. Many of these adaptations have been linked to onset of HT and NIDDM in adults. It is apparent through the examination of animal studies, that in fact,

maternal under-nutrition can be associated with major changes in fetal development that may be carried over to adult life. The hypothesis is supported by examples in experimental animals of permanent structural and metabolic changes resulting from transient nutritional insults in utero [16]. In rats, maternal protein restriction in pregnancy leads to higher blood pressure, impaired glucose tolerance, insulin resistance and altered hepatic architecture and function in the adult offspring. There are number of possible reasons why weight and height gain in childhood, on a background of fetal restriction, might be associated with disease. Low birth weight babies undergo compensatory post-natal growth, the rapidity of which may simply indicate the severity of the growth retardation. Alternatively rapid weight gain may be disadvantageous in itself, for example because of excess demand on tissues which are not capable of compensatory hyperplasia such as the pancreas, or through body composition [26].

Fetal origin of adult disease "Theories behind": A number of theories have been proposed to attempt to understand the relationship between under nutrition in the womb and deleterious effects on the adult health. The thrifty genotype hypothesis [27,28] intrauterine programming [6] and the "fetal origins of adult disease"[15] theories combined provide a conceptual basis for the understanding of the physiological mechanisms by which maternal under-nutrition may be associated with adult disease, such as hypertension[HT] and type II diabetes [non-insulin dependent diabetes mellitus, NIDDM] in offspring. A number of adaptive metabolic and endocrine mechanisms occur within the fetal-placental-maternal axis that ensure fetal survival in the face of under-nutrition [16], including changes to fetal metabolism, hormonal milieu, and resetting of developmental processes [29]. So that by which fetus adapts to unfavorable intrauterine environments. The thrifty phenotype hypothesis was originally proposed in 1962 in attempts to explain the high incidence of NIDDM in recently westernized, previously under-nourished cultures. The hypothesis has recently been refined to include the following premises [3]: 1- the growth of the fetus is altered by its nutritional environment. 2- changes in fetal growth occur in order to select growth rates for different tissues, and alter organ function to create a "thrifty" offspring adapted to survive in undernourished environments: nutrition are diverted to the brain at the expense of other organs such as the pancreas, liver and muscle [15]. 3- adverse consequences of these fetal adaptations may result if the offspring experiences abundant nutrition in later life. 4- poor insulin secretion, insulin resistance[IR], glucose intolerance[GI], HT, and NIDDM may be manifested in adult life as a result of these fetal adaptations [3]. Thus, according to the thrifty genotype hypothesis, fetal adaptation that occur subsequent to maternal under-nutrition may persist in to adult life. A number theory proposed by Barker et al. [6] has been termed the "fetal origins of adult disease" this hypothesis proposes that "adverse condition in the womb can give rise to restricted fetal growth, and result in the resetting of physiological system, thereby predisposing the individual to chronic disease later in life". Many researchers now support this theory of "programming" where "memories" of under-nutrition from fetal life are reflected in altered physiological systems and function in the adult [9]. In short, the intrauterine environment may partially determine the propensity of the adult for the acquisition of certain disease. memories of under-nutrition such as change in cell type distribution, hormonal feedback loops, metabolic activities and organ structure, may be later translated in to disease pathology [15]. This association between birth phenotype and adult disease may extend across the range of normal birth weight, suggesting that even subtle nutritional insults are sufficient to program a predisposition to adult disease.[the fetal origins hypothesis proposes that alterations in fetal nutrition and endocrine status result in developmental adaptations that permanently change structure, physiology, and metabolism, thereby predisposing individuals to cardiovascular, metabolic and endocrine disease in adult life. The process whereby a stimulus or insult at a sensitive or critical period of development has long-term effects is termed programming. In evolutionary terms, the phenomenon is likely to reflect the benefits of plasticity during early development. Consistent with this, it is thought that coronary heart disease may be a consequence of fetal adaptations to under nutrition that are beneficial for short-term survival, even though they are detrimental to health in post reproductive life. In other words, and according to Baker's hypothesis; association between small size at birth or during infancy and later CVD reflect permanent effects of fetal under nutrition. The fetus is dependent on the nutrient from the mother and adapts to an inadequate nutrient supply in a number of ways: prioritization of brain growth at the expense of other tissue such as the abdominal viscera, reduced

secretion of sensitivity to the fetal growth hormones insulin and IGF-I, and up regulation of the hypothalamo- pituitary- adrenal [HPA] axis. The FOAD hypothesis proposes that although occurring in response to a transient phenomenon [fetal under-nutrition] these adaptation become permanent or "programmed" because they occur during critical periods of early development [15]. Initially, these theories linking maternal under-nutrition to adult disease pathology in offspring were met with considerable skepticism. Recently, and accumulating body of epidemiological evidence and experimental animal studies have led to increasing acceptance of such association [9]. In fact, the link between in utero experience and later metabolic\ cardiovascular disease pathology is thought to be one of the most important advances in epidemiological research of recent years [9].

The Fetal Origins Hypothesis the role of Nutrition: Neonatal size is strongly related to maternal BMI, height, head circumference and even birth weight. This probably has both genetic and environmental components, but strongly suggests that the nutrition of the female throughout her life [during her own fetal life and childhood] as well as during pregnancy, influences the growth of her fetus. Nutritional effects on fetal growth are also shown by the drop in birth weight observed during famines. There is some evidence that improvement in the micronutrient quality of mother diet leads to an increase in fetal growth [15]. Among men and women born during the Dutch famine of 1944-45, late gestation exposure to famine was associated with glucose intolerance, insulin resistance, and a[small] increase in type 2 diabetes. Early gestation exposure was associated with higher LDL\HDL cholesterol concentration and [in women] higher BMI and waist circumference. Three recent studies suggested that the balance of maternal protein and carbohydrate intakes during pregnancy is related to blood pressure in the offspring. Several studies have found that women 58. Following diets composed of low glycaemic index [GI] foods were more likely to have infants who were small for gestational age [SGA]x and of lower birth weight [31]. This may reflect the energy density of different GI diets and thus total energy intake, and subsequent effects on maternal weight gain and infant birth weight. A dietary intervention study found that infants of women assigned to food of moderate to high GI were heavier than those eating food of low GI. Infants in the former group had a higher ponderal index [PI] too. Other studies have reported inverse associations between carbohydrate intake and birth weight [30] and "total sugar" intake it and birth weight [SGA]. Small-for-gestational-age [SAG] is defined as a newborn whose weight falls below a given threshold[most commonly $<10^{th}$ percentile] on a specified birth weight reference. The single study that has been able to distinguish between these effects, finds that, among Swedish young men, higher blood pressure was associated with both reduced growth for gestational age and reduced gestational age-I.E, the highest blood pressure occurred among those who grew less well in utero and were delivered early [31].

Onset of under-nutrition and fetal growth: There is a consensus between human and animal studies regarding the relative timing of maternal under-nutrition, and the overall impact on fetal growth. It appears that nutritional insults occurring early in pregnancy result in a small, but normally proportioned fetuses, where growth restriction is symmetrical [31]. Infants who have been under nourished in later pregnancy stages are more likely to be of normal weight, with disproportionate organ size due to asymmetrical growth [6]. Fetal nutrient demand depends on fetal size, and the pre-determined growth trajectory. Fetal nutrition on the other hand is determined by a combination of maternal diet, nutrient stores, nutrient delivery to the placenta, and placental transport capabilities [6]. Generally, discrete developmental effects of single nutrient deficiency are not common in human pregnancy. Under-nutrition is more likely to be global in nature, where more than one major nutritional component [macronutrients, vitamin and minerals] is deficient. In the face of a fetal nutritional demand in excess of the maternal-placental supply, the fetus will adapt in a number of different ways. it appears that the acute response to under-nutrition is increased catabolism. A prolonged insult on the other hand, will cause fetal growth to be restricted and slowed through an effect on fetal cells, and indirectly via a change in growth factors and hormones [6,32,3]. The mechanisms of fetal adaptation to under-nutrition generally fall in to the following categories: 1-Altered body composition and organ growth due to a redistribution of nutrients by the fetus. 2-Altered endocrine mechanisms. 3-Fetal cardiovascular changes. It is through these fetal adaptive mechanisms that imprints and permanent functional changes occur, which may eventually predispose individuals to adult disease as HT and NIDDM [3].

4. PROGRAMMING OF CHRONIC DISEASE THROUGH LIFE

Hypertension: Hypertension id defined as a mean systolic blood pressure of 140mm HG, mean diastolic blood pressure of 90mm HG [33]. The relationship between birth weight and adult blood pressure were reported by law& shiell. In their meta-analysis study, in which 66,000 individuals from 25 cohort studies, 4 case-control or comparative studies and 5 longitudinal; the result showed that nearly all studies reported an inverse association, with a few exception in adolescents and newborns. Roughly half of the studies reported multiple regression analyses, controlling for current size, which was the most important potential confounder. Blood pressure was typically 2-3 mmHg lower per Kg increase in birth weight [34]. The association between low birth weight and raised blood pressure in later life has now been reported in more than 50 published studies of men, women, and children. It has been shown to result from retarded fetal growth rather than premature birth [33]. There is also another study carried on adolescent in Israel, in this study only female subjects a positive correlation between birth weight and blood pressure was found. When blood pressure was measured during the first four days of life, the relationship with birth weight was consistently positive. The longitudinal studies with reported measures during infancy and childhood [one was done in adult] suggested that after being positive in the first few months of life, systolic blood pressure is negatively associated with birth weight. One study described a U-shaped relationship in 4-year olds, with higher blood pressure both in children who were smaller and those who were bigger at birth. In a systematic review update by Huxley and Shiell, in which 46 studies on birth weight and blood pressure were examined, representing with the previous review more than 444,000 male and female subjects of all races and ages. Other measures at birth and the role of postnatal catch-up growth were also considered in the later review of 37 cohort studies and 9 longitudinal studies. The conclusion of the above mentioned studies were brought about the inverse association of birth weight and systolic blood pressure with a decrease of around 2 mmHg per Kg increase in birth weight [34]. Furthermore, in law and Hulex [35], s two systematic reviews on the association between birth weight and subsequent blood pressure, there were 55 eligible studies [ie, individual cohorts, or subsets analyzed separately] that had reported regression coefficients of systolic blood pressure on birth weight and a further 48 studies that did not report regression coefficients but did indicate the direction of this association. Interpretation claims of a strong inverse association between birth weight and subsequent blood pressure may chiefly reflect the impact of random error, selective emphasis of particular result, and inappropriate adjustment for current weight and for confounding factors. These finding suggest that birth weight is of little relevance to blood pressure levels in later life [34]. The relationship between head circumstance and blood pressure was also studied and found an inverse relation with blood pressure. There is less consistency in the reported association between blood pressure and other measurements at birth. Hypertension was not found to relate to the mothers height or weight, but there were reported rise in hypertension incidence with increasing maternal BMI. The incidence of hypertension was unrelated to parity but rose with increasing maternal age. This association with age became non significant in a simultaneous regression analysis with mother's BMI [33]. Maternal under-nutrition has the potential to program a number of physiological systems involved in the control of blood pressure. Numerous studies have shown that growth restricted animals tend to develop HT in adult life [36]. It has been suggested that even a modest fetal overexposure to glucocorticoids, as a result of nutritional insult or stress can slow intra-uterine growth, and have permanent function of the fetal hypothalamic- pituitary-adrenal [HPA] axis, as well as the rennin-angiotensin system. Both of these system are essential in the regulation of blood pressure, and therefore any changes in development could lead to impairment in adult stress response, and consequently, the development of diseases such HT [37]. Thus, prenatal stress may alter the HPA axis, resulting in increased responsiveness to stress and higher steroid levels postnatally.

Diabetes mellitus: Diabetes influences more than 180 million people worldwide and this number is most likely to double by 2030. Type II diabetes, a major prevalent from of diabetes, is suggested to have its origin during fetal development. Maternal nutrition during all the stage of gestation and lactation plays an important role in the control of type II diabetes risk. Although type 1 diabetes has been suggested to also have its origin in the fetal period as well, most epidemiological studies have confirmed the association between low

birth weight and adult impairment of glucose metabolism and increased predisposition to type II diabetes in adult life. Low birth weight is associated with increased rates of type 2 diabetes in later life early adiposity rebound in childhood and risk of type 2 diabetes in adult life [20]. People who were small at birth remain biologically different from people who were larger, and these differences include an increased susceptibility to type 2 diabetes. This disorder is associated with the same general pattern of growth as coronary heart disease. In both sexes risk of disease falls with increasing birth weight and rises with rapid weight gain in early childhood [31]. In a study carried out by Phipps [30], he and coo leagues recruited 140 men and 126 women age 50 who were born in Preston, England between 1935 and 1943 for whom record of birth size was recorded. Subjects that were found to have abnormal glucose tolerance or type II diabetes at age 50 had a lower birth weight, a smaller head circumference and were thinner at birth. Longitudinal studies in to the effects of famine on the risk of disease in adult life have provided compelling evidence. The Dutch Famine Birth Cohort Study showed that children of Dutch mothers who were pregnant during the "Hunger Winter" of 1944, suffered higher rates of obesity, diabetes and cardiovascular disease in adult life than those born a year or two earlier .observations from the Chinese famine, and more recently Cambodia have confirmed this phenomenon. Records of low birth weight in China, America, Europe and the Middle East have also been linked to higher incidence of diabetes, but recent research has shown perinatal influences can act across the whole birth weight range [38]. Another meta-analysis also observed an association between low birth weight[<2500g] and increased risk of type 2 diabetes in adult. In this study a similar increase in risk was attributable to birth weight exceeding 4000g compared with birth weight<4000g. Thus overall a U-shaped relationship was identified. The relationship between type1 diabetes and birth weight has been less frequently studied though a meta-analytic review identified increased risk among those of higher birth weight. This observation was questioned on grounds of reported publication bias, unsatisfactory adjustment for confounders and inclusion of duplicate cases. The strongest association between birth weight and chronic disease is probably seen with the features of the insulin resistance syndrome [or syndrome X, or metabolic disease] which combines high blood pressure, hypertriglyceridemia, and often obesity, with insulin resistance or diabetes [28]. Intrauterine growth retardation [IUGR] or clinically abnormal thinness at birth strongly predicts the subsequent occurrence of hypertension, hyperlipidemia, insulin resistance, type2 diabetes and ischemic heart disease. However, there are conflicting results, such as the absence of association between birth weight and any marker of metabolic risk around age 30 in a longitudinal study of 137 African Americans [39]. In Beijing, birth weight of term offspring was negatively associated not only with blood pressure, but also with 2-h serum glucose and insulin, and with triacylglycerol concentration, in a cross-sectional sample of over 600 men and women aged 45. Current weight and sex were controlled for. There was also a positive association of birth weight with HDL cholesterol levels, but not LDL-cholesterol. Insulin resistance in children and adults has been found to be associated with thinness [low PI] at birth [34]. Not only low birth weight but also but rapid weight gain in childhood that is thought to associate with adult disease risk for many aspects of metabolic syndrome appears greatest in those born small who subsequently gain the most weight. The early life growth patterns of individuals in this cohort who later developed coronary heart disease[CHD] resembled the growth patterns preceding type 2 diabetes. Both groups showed lower birth weight and thinness at 1 year of age, followed by the attainment of higher body mass index later in childhood. Most subjects who developed type2 diabetes in this cohort were not obese during childhood. This is thought to reflect persistence of the changes in glucose and insulin metabolism which accompany slow growth in utero. Because type 2 diabetes is strongly associated with obesity in adult life, its association with the tempo of weight gain at different stages in childhood needs to be investigated. After the age of 2 years the degree of obesity of young children as measured by BMI decreases to a minimum around 6 years of age before increasing again, i.e. the so-called adiposity rebound [40,41]. In a support of this obesity rebound and adult disease theory; in a study of more than 300 young Danish adult, insulin sensitivity index was significantly, but only weakly, related to birth weight and there was no significant association with ponderal index [42]. Concurrent BMI and waist hip ratio were much more strongly related to insulin sensitivity than birth parameters. In Finland, longitudinal study of subjects born after World War II only showed an association of lower birth weight with higher risk

of metabolic syndrome among those who were in the upper BMI quarter in early school years programming of chronic disease [35]. In appears that the risk for developing NIDDM is U-shaped, where infants on the low and high ends of birth weight are at increased risk. Does Fetal Under-nutrition predispose disease in adult Offspring? [30] The difference in risk holds true for siblings born before and after the onset of maternal diabetes and is not seen among off springs of diabetic fathers. Gestational diabetes produces a U-shaped or J-shaped relationship between birth weight and adult type2 diabetes [15]. As explained in FOADS theory, the mother, in effect, gives the fetus a 'forecast' of the nutrition it can expect at birth. The fetus is then 'programmed', largely due to epigenetic changes, to match that environment. If the nutritional environment in childhood and adult life differ sharply from that experienced within the womb, obesity and diabetes can result. The risk of future disease is further increased if there is a mismatch between the fetal and adult environment [43]. Along with inadequate fetal nutrient supply, other explanations, including the operation of genetic factors and programming of certain endocrine axes, have also been put forward to explain the origin of these non-communicable diseases and the epidemiological associations. In relation to insulin action and diabetes, Hales and Barker have described this phenomenon as the "thrifty phenotype" . the basic premise of the thrifty gene hypothesis is that certain populations may have genes that determine increased fat storage, which in times of famine represent a survival advantage, but in a modern environment, result in obesity and type2 diabetes. Phipps and his colleagues recruited suggests association diabetes between low birth weight and diabetes reflects the long term effects of reduced growth of found in his study. The endocrine pancreas and other tissues in utero, as a consequence of maternal under nutrition. In an effort to establish a relationship between size at birth and type II diabetes, Lithell et al. [34] observed the incidence of glucose intolerance amongst a cohort of 2322 men born during 1920-4 in Uppsala , Sweden, Results of this study indicated an association between reduced fetal growth and an increased risk of diabetes. This association was especially strong when the infant was thin at birth. The combination of thinness at birth and overweight in adult life was associated with higher insulin concentrations at 1 hour after intravenous glucose, suggesting an effect on insulin resistance rather than impairment in beta cell function. There is also possible suggestion the 'thrifty phenotype hypothesis', NIDDM may result from the developmental interaction between inadequate nutrition prenatally, and abundant nutrition later in life. Basically, the metabolic system of the fetus prepares itself for under-nutrition and, in the face of nutritional excess the metabolism of the offspring is not prepared. Thus, NIDDM ensues. There are number of physiological mechanisms by which this phenomenon could occur. Abnormalities in pancreatic growth and fetal metabolism have been implicated in programming the fetus for potential NIDM later in life, including a decrease in pancreatic beta cell mass, and subsequent decreased insulin production. In addition, permanent changes to numerous metabolic enzymes, including GLUT-4[glucose transporter], p13 kinase and insulin-like growth factors [IGFs] have been implicated in predisposing undernourished fetuses to adult diabetes.

Fetal insulin hypothesis: Hattersley proposed that the relationship between small size at birth and impaired glucose tolerance in adulthood could be explained by inherited deficits in insulin secretion or action. Since insulin is an important regulator of fetal growth, affected individuals with impaired insulin secretion would have impaired growth before birth, and would also go on to have impaired glucose tolerance in adulthood. Isolated genetic polymorphisms have been described that clearly support this hypothesis. However, these relatively rare changes seem unlikely to explain the very widespread relationships between birth size and later glucose tolerance described in many different populations and across the range of normal birth weights. Intriguingly, two recent studies have reported lower birth weight in the offspring of diabetic fathers. Furthermore, fathers of low birth weight infants, who were not diabetic at the time of the birth of their child, had a nearly two fold increases in the risk of developing diabetes later in life [9].

Impaired glucose tolerance and insulin resistance: Whether exposed to protein deficiency only during uterine life or also during lactation, offspring have worse glucose tolerance than controls by 15 months and this can be worsened by a high fat diet. Although frank diabetes has not been produced of many features of insulin resistance syndrome have providing much information on potential mechanism for these effects. In rat fetuses of low protein mothers, it was found that the islets,

while showing no difference in basal insulin secretion, had a reduced secretory response to both leucine and arginine. Similarly, glucose-induced insulin secretion was impaired. As reviewed by Ozanne [29], livers of protein-deprived offspring are resistant to glucagon in that they show an altered ability to stimulate hepatic glucose output, and they also have an altered response to insulin, somewhat similar to what is observed in subject with type-2 diabetes, and in young aborigines, a population highly exposed to developing diabetes [9].

Cardiovascular Disease [CVD]: The first evidence was described following Hertfordshire study, in which men with lower weight at the age of one year had increased CVD mortality. In this study, there was an approximate doubling of CVD mortality from the highest to the lowest extremes of birth weight, similar in men and women. It is restricted fetal growth rather than pre-term delivery which carries the risk of CVD. The effects were described as linear, graded across the whole range of birth weight and independent of adult socio-economic status [9]. Subsequent work has shown that lower birth weight and other measures of small size at birth are also associated with higher levels of some 'classical' CVD risk factors. Cardiovascular function: Arterial intimae media thickness and carotid stenosis, examined using ultrasound, are increased in lower birth weight men and women and flow-mediated dilatation, a measure of endothelial function, is reduced in young adults and children of lower birth-weight [44,45].

Obesity: Result of several studies have shown that people who were heavier at birth tend to become 'fatter' adults as measured by body mass index. However, this may reflect increased lean mass rather than adiposity. There is no evidence that low birth weight leads to increased total body fat, but leptin concentrations were increased in low birth weight men and women in one study and central obesity has linked to small size at birth. The sub scapular\triceps ration is consistently higher in adults and children of lower birth weight [46-48]. Unlike weight gain during infancy, accelerated childhood weight gain is associated with an increased risk of high blood pressure in young adults. In order determine to whether it is birth size or weight gain later in life that contribute to the occurrence of chronic diseases, it became necessary to elucidate the independent association of birth size with these diseases risk factors. However, this raises the issue of whether a given parameter such as current body size is really a confounder or whether it is a mediator of the effect. Adjustment for current body size may not be appropriate. As conceptualized by Waterland & Garza [49], correcting for current body weight or BMI in order to determine the magnitude of the birth weight effect on chronic disease risk would require that the variance of BMI be partitioned into two components, one related to birth weight, and an unrelated one. Since this partition cannot be estimated, it is suggested to report associations adjusted and non-adjusted for current BMI [49]. The complex relationship of birth weight with BMI indeed complicates the studies reporting associations between birth weight and adult outcomes associated with BMI. In quite a few studies reporting both uncorrected and corrected association, the findings and conclusions were not affected by the adjustment, which suggests that there is no spurious link between birth weight and CVD because of the birth weight-BMI relationship. What can also be suggested is to test the interactions of birth weight with BMI in the multivariate models with CVD or other outcomes as dependent variables. More detailed measures of size and proportions at birth such as PI and length are unrelated to BMI in adult life [48]. And therefore, as pointed out by Leon et al. [50], adjustment for current BMI is less of an issue. Lucas, Fewtrell & cole contributed an interesting discussion on this issue of adjusting for current size and the statistical implications. Adjusting for current body weight or size has usually been justified on the grounds that birth weight[or size] is positively related to later size, and that current weight [or fatness] is also correlated with the outcome of interest, be it blood pressure or insulin resistance. Omitting to adjust for current size would therefore obscure the relationship of birth weight with the outcome variable. However, several alternatives have to be considered. If adjustment attenuates or suppresses the effect of early size, then it may be that later size is more relevant than size at birth in the causal pathway. In contrast, if the outcome is amplified with adjustment, Lucas, fewtrell & Cole consider that the determinant factor may be the magnitude of size change with age, that is, the magnitude of centile crossing during postnatal growth [51].

Cancer: There are a number of cancers that have been found to originate early in life. Childhood leukemia and brain cancer may have environmental components in their development as pesticides. It has been postulated that breast cancer may originate in utero. It is however in the

opposite direction of that of CVD, with higher birth weights associated with higher odds ratio for breast cancer current evidence for perinatal influences on breast cancer risk is less consistent than the evidence for perinatal influences on CVD [52-54]. The hypothesis of early life modulation of breast cancer risk is supported by immigrant studies. A case-control study in Western Australia observed a 60% reduced risk of acute lymphocytic leukaemia [ALL] in the offspring of mothers who took iron and folate supplements in pregnancy. Births between 1984 and 1992 were studied, including 83 children with acute lymphocytic leukaemia, and 166 controls of matched background [subjects were aged 0 to 14 years] [55]. The reduced risk appeared principally attributable to folate intake since consumption of iron supplements alone was associated with a reduced risk of only 25%. [56]. High birth weight has been associated with increased risk of childhood leukaemia. A meta-analysis identified 18 studies [15 case-control; 'case-referent' and 1 cohort study] including 10,282 children with leukaemia. The most recent meta-analysis of the relationship between birth weight, size at birth and breast cancer [including 32 studies from developed countries and a total 22,508 breast cancer cases, both pre and postmenopausal] found moderate positive associations in studies based on birth records. The risk of breast cancer rose with increasing birth weight, length and head circumference. A 0.5Kg increment in birth weight was associated with a significant increase in risk. Women who were >51 cm long at birth showed a 17% greater risk of developing breast cancer relative to those in the baseline category for length [49.0-49.9cm], whilst those who had a head circumference at birth of >35 cm had an 11% increase in risk relative to those in the baseline category for head circumference [33.0-33.9cm]. these effects were not confounded by known breast cancer risk factors[including maternal age, maternal parity and maternal birth size] nor moderated by age or menopausal status.[56]. The World Cancer Research fund systematic review identified 6 cohort studies and 4 case control studies, concluding that greater birth weight 'probably' increases risk of premenopausal breast cancer. Meta-analysis of the cohort data showed an 8 percent increase in risk per kilogram of birth weight [26]. No association was found between birth weight and postmenopausal breast cancer. A prospective cohort study in Sweden of individuals born preterm and \or small for gestational age between 1925 and 1949 [n=3364], showed a 7 fold increase in risk of oesophageal adenocarcinoma in the cohort compared with a control group born after 35 weeks of gestation having a birth weight of >2000g.those with a birth weight <2000g regardless of gestation were at greatest risk, though there were few cases. It was postulated that the increased prevalence of infantile gastro-esophageal reflux in preterm infants may be an explanation [56]. However, there is insufficient evidence to support an association between birth weight and oesophageal or gastric cancers. Another prospective study of 1,080 Swedish women observed a statistically significant positive association between birth weight and length and all cancers. When risk for combined hormone-related cancers [104 cases] or breast cancer alone [62cases] were analyzed separately, the association with birth weight was not statistically significant. There was a doubling in risk of non-hormonal cancers [158 cases] at the highest quintile of birth weight compared to the lowest quintile [56].

Immune system programming: The development of immune system, including the development of the repertoire of reactive lymphocytes that will exist in postnatal life, begins prenatally. Alteration of the fetal immune environment might pre programmed the highly sensitive fetal immune system for aberrant immune regulation, leading to loss of tolerance to self-antigens and resulting in a increased risk for autoimmune disease. These changes might manifest in adult life and perhaps only after a second exposure to related environmental chemicals. There is evidence in humans and experimental animals that prenatal exposure to immunosuppressive drugs can lead to a higher risk of autoimmune disease in the later life [15].

FOAD and urbanization: The linear and graded trends in CVD mortality with birth weight suggest that majority of the world's population experience sub-optimal fetal growth being highest in developing countries. In India the mean full-term birth weight is 2.6-2.7Kg, almost 1 Kg lower than in Western Europe [57]. A high proportion of infants and children in India are still undernourished, but with economic progress, childhood and adult obesity is an emerging problem, especially in cities. It is estimated that 20% of women and 16% of men in India will be overweight [BMI>25Kg\m2] by the tear 2020 [58]. Furthermore, there is evidence that any level of BMI, south Asian is & women have a higher fat mass, more centrally distributed fat, and a higher

risk of obesity associated disease than white Caucasians [59]. According to the FOAD hypothesis, increasing child and adult obesity in combination with persistently poor fetal growth creates a high risk for adult CVD and diabetes more so because of undergoing rapid economic development and modernization. In India mortality from cardiovascular disease is expected to rise by about 60% and over take deaths from infectious disease, by 2015-20. "That the prevalence of type 2 diabetes will rise by 30% worldwide, from 4.0% to 5.4% by 2025, and that the proportional rise will be greatest in developing countries [48%], especially China [68%] and India [59%]. India will have more people with diabetes [57 million] than any other country, with the 209 greatest numbers in the 45-64 year age group with likelihood increase in type 2 diabetes in children" [15].

5. CONCLUSION

Early childhood have a critical importance for brain development and for setting in place the structures that will shape future cognitive, social, emotional, and health outcomes. Research findings have important public health implications. More instantaneous profit may be obtained from preventing imbalances between parental and postnatal growth among children. Future studies should focus on measuring the amount of effect needed at prenatal level to obtain the optimum adult prevention measures.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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