Birth weight is a reflection of growth during the fetal period. Disruption in the normal pattern of fetal growth may result in birth of neonates who are low birth weight or small-for-gestational age or had experienced intrauterine growth restriction. Fetal life is of great significance as numerous key developmental processes such as the growth and development of organs occur during this period. Certain processes particularly, the growth and development of the brain is also continued in the early postnatal life too. Thus, both fetal and postnatal growth are crucial.

This review throws light on the influence of birth weight on the body composition and metabolic risk factors during various stages of life. Further, it also discusses about the influence of early nutrition on the growth of brain and the further implication on cognition.

2.1 Fetal Growth and Birth Weight

In utero growth and development of the fetus determines its weight at birth. The growth is slow during the embryonic stage i.e. during the initial eight weeks. Thereafter, during the fetal stage i.e. from eight week onwards, the rate of growth accelerates. Maximum growth is achieved from 16 to 32 weeks. Most of the fetal weight is gained from 20th week till term. The growth rate increases from 5 g/d at 15 weeks to 15 – 20 g/d at 20 weeks reaching 30 – 35 g/d by 34 weeks of gestation. At the cellular level, growth is described as hypertrophy and hyperplasia. The fetus undergoes a predominant phase of hyperplasia from conception to 20 weeks with an increase in the DNA and protein content of the cell. This is followed by a period of simultaneous hypertrophy and hyperplasia from 20 to 28 weeks. Thereafter, growth mainly occurs in the form of hypertrophy with increase in the accumulation of fat, muscle and connective tissue (Blackburn, 2007).
Certain hormonal factors are also known to regulate fetal growth. Insulin is one of the main anabolic hormones essential for fetal growth. It is required for the cellular uptake of glucose and amino acids thus, promotes tissue accretion. The actions of insulin are mediated via insulin-like growth factor – 1 (IGF-1) and insulin-like growth factor – 2 (IGF-2) (Oliver et al, 1996). During the embryonic phase, IGF-2 has been reported to be the primary growth factor (Le Roith et al, 2001), while, IGF-1 is thought to be the dominant fetal growth stimulator in the late gestation. Further, the fetal IGF-1 system is also sensitive to maternal nutrition. Short-term maternal undernutrition has been associated with reduced fetal IGF-1 levels causing cessation of fetal growth (Gluckman and Pinal, 2003). The IGFs regulate the cell cycle, cell differentiation and cell proliferation in accordance with the nutritional and the endocrine conditions. In addition, they are also involved in regulation and development of the nutrient transfer capacity of the placenta (Fowden & Forhead, 2013).

Glucocorticoids have a growth inhibitory role in utero. Nevertheless, they are essential for tissue differentiation in the preparation for delivery. The deficiency of glucocorticoids during late gestation promotes increased fetal weight gain while overexposure to cortisol results in growth retardation (Gluckman and Pinal, 2003). Hormonal levels are closely associated with the nutritional status of the growing fetus. Thus, hormonal alterations are bound to happen if the growing fetus’s nutritional status is compromised.

Besides hormones, many other factors govern the in utero growth of the fetus. These include – chromosomal and genetic disorders as well as environmental influences. Environmental influences take in to account a wide spectrum of factors such as – maternal nutrition, smoking, alcohol consumption and socioeconomic status. However, maternal nutrition is one of the chief factors driving the growth of the fetus. For instance, poor maternal diet throughout pregnancy results in fetal growth retardation. Maternal protein restriction is seen to be detrimental to both fetal and placental growth causing lower birth weight (Blackburn, 2007).
2.2 Low Birth Weight (LBW) or Small-for-Gestational Age (SGA) or Intrauterine Growth Restriction (IUGR)

Lately, much of the literature focusses on low birth weight (LBW) and small-for-gestational age (SGA) and intrauterine growth restriction (IUGR) infants. These terms though have different implication but at times, are used interchangeable. Low birth weight is a term used for infants with an absolute birth weight < 2500g irrespective of the gestational age. On the other hand, small for gestational age (SGA) refers to infants who weigh < the 10th percentile for their gestational age at birth (Norwitz and Schorge, 2010). The term SGA is often used interchangeably with intrauterine growth restriction (IUGR). But, there is a slight difference in the definition of the two terms. SGA is a statistical definition whereas IUGR is a clinical definition that includes neonates with clinical evidence of malnutrition as detected by ultrasound (Deorari et al, 2001). All SGA infants would have experienced intrauterine growth restriction. However, not all IUGR infants may be SGA; some may be appropriate for gestational age (AGA).

Fetal undernutrition results in growth restriction which is manifested in the form of LBW and/or SGA and/or IUGR. During fetal growth restriction, the fetus adapts to the undernutrition in certain specific ways. The immediate response to undernutrition is catabolism. If the period of nutritional insult is prolonged, there is a decline in the metabolic rate of the fetus. This reduces the use of substrates and thereby slows down growth. Besides the duration of undernutrition, the period at which undernutrition sets in also has an influence. For instance, when IUGR occurs early in gestation, the weight, length and head circumference of the neonate are equally affected. This is known as symmetric IUGR. However, when the insult occurs late in gestation, there is relative head growth sparing, resulting in asymmetric body size known as asymmetric IUGR (Deorari et al, 2007). Along with this, certain endocrine changes do occur which bear an immediate benefit by promoting survival of the growing fetus. However, the same metabolic alterations may prove to be detrimental later in life.
2.3 Metabolic Consequences of Fetal Growth Restriction

As mentioned earlier, being LBW or SGA or IUGR poses a risk for future metabolic complications. The findings of a number of studies carried out by Barker and coworkers during 1980s and 1990s on the association of birth weight and mortality from coronary heart disease (CHD) have led to the development of ‘Barker’s hypothesis’ or ‘Fetal Origins of Adulthood Diseases’. This hypothesis proposes that the fetus adapts to an adverse intrauterine milieu by optimizing the use of reduced nutrient supply to ensure the development of certain organs (brain) at the expense of the other developing tissues thus, promoting survival (Hales and Barker, 1992). These intrauterine events ‘programme’ the metabolism of the fetus in such a way that it increases the vulnerability of the child to various metabolic events in later life. ‘Programming’ is a phenomenon where a relatively brief stimulus (fetal growth restriction) induces long-term and irreversible alterations in the structure or metabolism of the organs of the body (WHO, 2002). The most significant of these events are – alterations in the structure of the kidney, increase in systolic blood pressure, impaired glucose tolerance, reduction in pancreatic insulin content as also the β-cell mass and metabolic alterations in the liver. Many mechanisms have been proposed which attempt to explain the relationship between fetal growth restriction and metabolic outcome. These include -

2.3.1 Resetting of the hypothalamus-pituitary-adrenal (HPA) axis

Maternal nutrition restriction (especially protein) and excess of glucocorticoid may result in higher blood pressure and hyperglycemia. In utero, the fetal glucocorticoid levels may increase owing to fetal stress (undernutrition) or due to lack of placental barrier function which protects the fetus from receiving excessive glucocorticoids from the mother.

The fetus usually has lower levels of glucocorticoid levels than the mother. This is mainly because of the rapid conversion of 11 β-hydroxysteroid (cortisol) to 11-oxysteroid (cortisone) by placental 11 β-hydroxysteroid dehydrogenase. Thus the placental barrier
protects the fetus from overexposure. This enzyme is usually maintained till the end of human gestation. Normally, glucocorticoid levels rise before term as a signal for tissue maturation. However, in cases of fetal growth restriction, the enzyme levels could be attenuated. As a result, there are increased levels of cortisol in growth retarded fetuses (Gluckman & Pinal, 2003).

Excessive fetal exposure to glucocorticoids stimulates gluconeogenesis and increases the availability glucose and free fatty acids thus, facilitating the immediate survival of the fetus. Chronic fetal exposure to high levels of cortisol stimulates tissue differentiation and accelerates the rate of organ maturation, especially of the heart, lungs and the immune system. Thus, early increase in glucocorticoid levels induces an early shift from cell proliferation to differentiation which is an inappropriate pattern of growth (Gluckman & Pinal, 2003).

In the bargain of this short-term benefit, the overexposure to the hormone, results in stimulation of gluconeogenesis in both, the liver and kidney leading to increased glucose production. Insulin-stimulated glucosal disposal in the skeletal muscles may also be altered. Glucocorticoids also regulate insulin, growth factors their receptors and binding proteins (Delisle, 2002). Increased fetal exposure to glucocorticoids causes hyperactivity of the HPA axis resulting in increased blood pressure and hyperglycemia. Experiments conducted in fetal sheep during late gestation revealed that high levels of glucocorticoids induced the activation of the renin, angiotensinogen and angiotensin II (Forhead et al, 2000). Animal studies have also suggested impairment in the development of blood vasculature (Langley-Evans et al, 1999). Evidence from studies on low birth weight infants also suggests an activation of sympathetic nervous system (Phillips & Barker, 1997). All these events programme a sustained increase in the blood pressure. These events may predispose individuals to hyperglycemia and insulin resistance early in adulthood.
2.3.2 Thrifty phenotype hypothesis

This hypothesis was proposed by Hales and Barker (1992). According to this hypothesis, there is resetting of the metabolism in such a manner that the metabolism becomes ‘thrifty’ when the nutrient supply to the fetus is poor.

Endocrine alterations such as insulin resistance aid in redirecting the glucose away from the skeletal muscle towards vital organs such as – brain and placenta. Evidence from animal studies shows decreased levels of glucose transporter (GLUT 4) in the skeletal muscles of IUGR fetuses while their concentration remained normal in the brain (Simmons et al, 1993). However, evidence presented by Ozanne et al (1998) suggests that resistance to insulin’s action of glucose transport is not accompanied by resistance to it’s anabolic actions. Thus, there appears to be ‘selective insulin resistance’ which benefits the survival of the fetus in a nutritionally deprived state.

Nevertheless, these adaptations tend to increase the risk of type 2 diabetes mellitus in the later life. Increased peripheral insulin resistance stimulates the β-cells to produce larger amounts of insulin to maintain normal blood glucose levels (Simmons et al, 1993). This gives rise to hyperinsulinemia and over a period of time results in pancreatic exhaustion precipitating in the development of type 2 diabetes mellitus. Thus, these metabolic adaptations that aid the immediate survival of the fetus tend to become a liability in situations of nutritional abundance.

2.3.3 Resetting IGF system

IGFs are major mediators of prenatal and postnatal growth in humans. IGFs bind to the insulin receptor with lesser affinity than insulin. Both the IGFs (1 and 2) play a vital role in the embryonic development while only IGF-1 appears to have a role in the fetal development (Gluckman & Pinal, 2003).
The primary axis regulating the fetal growth is the glucose-insulin-IGF-1 axis. The IGF-1 is under acute nutritional regulation. Fetal IGF-1 is secreted in response to fetal insulin levels. Fetal insulin in turn depends on the placental glucose transfer. Fetal insulin primarily acts as a adipogenic factor. Its effect on lean body mass (LBM) is said to be mediated via IGF-1. Growth hormone (GH) appears to have a small effect on fetal growth probably through the regulation of IGF-1 (Gluckman & Pinal, 2003).

Low IGF-1 and Insulin-like growth factor binding protein – 3 (IGFBP-3) levels at birth are said to be indicative of fetal malnutrition in humans. According to the catch-up growth hypothesis, tissues are depleted of insulin and IGF-1 in the fetal life under circumstances of nutritional deprivation. After birth, when there is adequate nutrient supply, there is increased activation of IGF system to promote growth. At the same time, insulin resistance develops as a defense mechanism to shield the growing infant from hypoglycemia (Cianfarani et al, 1999). Thus, on one hand the overactivation of IGF system ensure CUG while on the other hand, it induces insulin resistance as a metabolic adaptation making way for future detrimental consequences.

### 2.3.4 Tissue remodelling

Normal development of tissues and organs depends on key processes – proliferation and differentiation. Proliferation of cells is followed by differentiation. Some organs are formed early during the gestation such as the heart while some grow in the late gestation like the kidneys.

As mentioned earlier, during undernutrition, the fetus redirects the blood supply to the brain. This affects the processes of proliferation or differentiation of other vital organs. Disruption in either of the processes induces characteristic changes in tissue formation. Adverse condition during proliferation would not influence the process of differentiation within the tissue. However, the affected organ would have lower number of cells resulting in reduced size of the organ with normal profile of the cells. On the other hand,
if adverse events occur during differentiation, the affected organ will be normal in size but would have altered profile of the cell types and potentially fewer functional units (Langley-Evans, 2009).

**Kidneys** – According to animal studies, maternal undernutrition did not affect the size of the kidneys. But, 30 to 40% reduction was noted in the number of nephrons. The number of nephrons correlated strongly with the size at birth. Further, animals subjected to global undernutrition experienced a decline in the process of nephrogenesis (Delisle, 2002).

**Pancreas** – Experimental studies have used different animal models to study the influence of growth restriction on the pancreas – calorie restriction, global nutrient restriction and low protein diet. Studies have mainly concentrated on impact on β-cell function. Calorie restriction in rats throughout the gestation affected the β-cell differentiation. On the other hand, global nutrient and oxygen restriction had an impact on the β-cell maturation and proliferation. Feeding low protein isocaloric diets to dams throughout the gestation led to lower pancreatic weight, poor β-cell mass and islet size but, did not affect the β-cell differentiation. All these models resulted in reduced β-cell mass which might reflect vascular deficiencies and/or poor growth factor concentrations (Green et al, 2010). In addition to this, global nutrient restriction and low protein diet disturbed the β-cell metabolism by decreasing the insulin secretion responsiveness. Similarly, in fetal sheep models, effects of maternal undernutrition were seen on β-cell function including insulin storage, proliferation and glucose metabolism (Green et al, 2010; Rinaudo and Wang, 2012).

**Liver** – Changes that occur due to hepatic reprogramming are unsuppressed endogenous hepatic glucose production owing to increased gluconeogenesis and hepatic insulin resistance. Evidence from studies on IUGR male rats suggested presence of hypertriglyceridemia, increased hepatic free fatty acid synthesis and decreased β-oxidation. Livers of protein-restricted rats had fewer but larger lobules. Also, there was
considerable decrease in the mitochondrial ATP production and NADH availability. Thus, both these factors appear to restrict the growth of the fetus (Rinaudo & Wang, 2012).

*Skeletal Muscles* – Offspring of the protein-restricted rats showed reduced mass of fast-twitch type and slow-twitch type of muscle fibres (Desai et al, 1996). Muscles of IUGR rats showed lower glycogen content and insulin-stimulated 2-deoxyglucose uptake, indicating presence of insulin resistance. Evidence also supports the presence of decreased pyruvate oxidation and ATP production in the muscle mitochondria leading to reduced translocation of insulin-stimulated GLUT 4 on to the cell surface (Selak et al, 2003).

*Adipose Tissue* – In the adipose tissue of the protein-restricted offspring, evidence indicates decrease in the insulin-stimulated glucose uptake and insulin-stimulated lipolysis, a sign of insulin resistance. Maternal undernutrition has been shown to increase the retroperitoneal fat and the proportion of large fat cells in the visceral adipose tissue of the offspring (Ozanne et al, 2001; Rinaudo and Wang, 2012).

All these mechanisms collectively promote the immediate survival of the fetus but, increase the likelihood of obesity, insulin resistance and hypertension early in life. Studies carried out in different cohorts of birth weight further confirm this association between poor fetal growth and metabolic diseases as discussed in the next section.

### 2.4 Relationship of Birth Weight with Body Composition and Metabolic Consequences in Individuals born IUGR/SGA/LBW

The relationship between birth weight and adverse metabolic outcome was first explored by Barker and his colleagues in late 1980s. This was followed by studies in Sweden and Finland (Forsen et al, 1997; Leon et al, 1998). In India, Stein et al (1996) studied 517
men and women born between 1934 – 54 in Mysore. Findings of this work revealed that low birth weight, short birth length and small head circumference at birth were associated with higher prevalence of CHD. Further, thinness at birth was related to insulin resistance and type 2 diabetes mellitus in adult life (Hales, et al., 1991; Curhan, et al., 1996; Lithell, McKeigue et al, 1996; Phillips, 1996). These findings have led to the development of fetal origins hypothesis. Thereafter, a number of studies have explored similar issues.

Studies establishing the relationship of birth weight with body composition and metabolic complications have been conducted in varying settings and across age groups. For a clear understanding of the findings, studies discussed below have been categorized on the basis of ethnic setting and age group of the subjects.

2.4.1 Birth Weight and Body Composition in Infants/Children/Adolescents/Adults

Yajnik et al (2003) compared the body measurements and body fat of neonates born in rural areas near Pune with Caucasian neonates born in Southampton, UK. Indian babies were lighter than their Caucasian counterparts (mean birth weight 2.7 kg v 3.4 kg). Further, the Indian babies had lower measurements for most of the anthropometric parameters - weight, abdominal circumference and mid arm circumference. Similar observations were also noted when Krishnaveni et al (2005) compared the neonates born in Mysore to those born in Southampton, UK. In both these studies, in spite of the lower anthropometric measurements, the Indian neonates tended to preserve their subscapular skinfold thickness as compared to the Caucasian neonates. Subscapular fat is a well acknowledged depot of central fat which increases the risk of insulin resistance and cardiovascular diseases (McKeigue et al, 1991; Shelgikar et al, 1991).

The Indian neonates also had lower abdominal circumference and mid arm circumference. Abdominal circumference indicates the visceral size whereas the mid arm circumference reflects the muscle mass. (Yajnik, et al., 2003; Krishnaveni, et al., 2005). This suggests that in underweight Indian neonates fat deposition occurred at the expense
of their abdominal viscera and muscle mass. The fat preserving tendency of the smallest of the Indian babies (< 10\textsuperscript{th} percentile) superseded their normal weight Caucasian counterparts (10\textsuperscript{th} to 90\textsuperscript{th} percentile) thus, increasing the risk of future obesity and adverse metabolic outcomes (Yajnik, et al., 2003).

Similar observations were noted by Krishnaveni et al (2005) in four year old children in Mysore when they were compared with their UK counterparts. Joglekar et al (2007) found that higher weight, length and MUAC at birth were associated with higher lean mass and body fat at 6 months, one year, from 2 to 5 years and at 6 years of age in Pune children. The ‘thin-fat phenotype’ (negative birth weight with positive skinfold measurements at birth) was positively associated with both lean mass and fat mass at 6 years of age (standardized $\beta = 0.11$, $P < 0.001$ for fat mass and $\beta = 0.09$, $P < 0.001$ for lean mass). Bavdekar et al (1999) noted that after adjusting for current weight, age and sex, lower birth weight was associated with higher subscapular:triceps ratio in eight year old children ($p = 0.002$)

With respect to older children, Kelly et al (2008) examined the association between birth weight and body composition in 242 overweight (BMI > 85\textsuperscript{th} percentile) Latino children with mean age of 11.1 ± 1.7 years. Birth weight was positively related to total fat mass and lean body mass at 11 years of age. Birth weight was inversely associated with truncal fat and BMI. The children were followed up for six years. As the children progressed into adolescence, no significant associations were seen between birth weight and adiposity-related variables.

Labayen et al (2008) assessed a similar association in 1223 adolescents aged 13 to 18.5 years from five Spanish cities. Birth weight Z score was positively associated with body fat (%) in boys ($p = 0.018$) but not in girls ($p = 0.105$). On controlling for the age, pubertal age, socioeconomic status, physical activity, height and gestational age, this association strengthened in boys and remained non significant in girls. On the other hand,
birth weight Z score was seen to be negatively associated with central adiposity measured by subscapular thicknesses in both boys and girls (p = 0.026) after controlling for the confounding variables. Birth weight Z score was significantly associated with fat free mass (FFM) in both boys and girls (p = 0.001; p < 0.001). However, after controlling for the confounding variables, the association was significant only for girls (p < 0.001). This suggests that gender could have an influence on programming effect of birth weight on body fat and FFM during adolescence.

Gender differences were also noted by Labayen et al (2011). They studied the body composition of 247 children (9-15 years) and 162 adolescents (15-21 years) of Swedish origin over a period of six years. At baseline, among children, significant relation was displayed between birth weight and both, BMI and FFM (p < 0.05). Over a period of six years, in the girls from the children cohort, significant inverse associations were seen between birth weight and change in BMI (β = −0.736, P = 0.002) and sum of skinfolds (β = −6.381, P = 0.009). Negative correlation was also seen between birth weight and central adiposity in girls (p < 0.05). In boys, birth weight was only significantly associated with change in FFM (p < 0.05). No such associations were seen among adolescents. This lack of any association seen in adolescents could be due to environmental factors. The authors did not control for the confounding factors such as consumption of energy dense foods and sedentary lifestyle which can potentially influence the results.

Further, Jaquet et al. (2000) carried out a case-control study among 26 IUGR-born young adults and control subjects. At the age of 25 years, IUGR adults had significantly higher percent body fat than the controls (27.2 ± 7.6 v 22.0 ± 7.3%; p = 0.02). Fagerberg et al. (2004) examined the influence of birth weight and weight at 18 years on risk factors of metabolic syndrome among 396 men aged 58 years. The ratio of weight at 18 years of age to birth weight correlated with BMI (r = 0.24, P < 0.001) and waist to hip ratio (WHR) (r = 0.24, P < 0.001). That means, those who weighed higher at 18 years but had
lower birth weight had greater probability of having a higher BMI and WHR. Meas et al. (2008) compared the anthropometric measurements of full-term SGA-born and AGA-born adults at 22 and 30 years of age. During the 8-year follow-up period, significant larger differences were seen in the SGA-born individuals than the others in terms of BMI (p = 0.03) and waist circumference (WC) (p = 0.04). Also, the proportion of individuals with obesity increased significantly in the SGA group than the AGA (12.1 v 6.5%, p = 0.02). At 30 years of age, the SGA group had significantly higher percent body fat than their AGA counterparts (23.5 ± 8.7 vs. 21.9 ± 8.0%; P < 0.01). Similar observations were made for waist circumference too.

In one study, Gale et al. (2001) studied the association of birth weight and adult body composition among a cohort of 143 men and women aged 70 -75 years in Sheffield, United Kingdom. Birth weight was weakly associated with body fat (r = 0.19, p = 0.06). But strong associations were observed between birth weight and lean body (p < 0.005) as also bone mass (p < 0.005). Thus, lower birth weight was associated with lower lean body mass and bone mass. Similarly, in India, Sachdev et al (2005) found that birth weight was associated with adult lean mass (p < 0.001) in 1526 men and women aged 26 – 32 years residing in New Delhi. Birth weight was positively related to adiposity in women (p = 0.006) but was not associated with central adiposity in both men and women.

Much of the evidence in India comes from two cohorts namely – the Pune Maternal Nutrition Study and the Mysore Parthenon Birth Cohort. Both have studied infants and children. These studies revealed that birth weight was positively correlated with total body fat and FFM; but negatively related to central adiposity in infancy and childhood. Joglekar et al (2007) found that many of the children in their study could be classified as underweight according to WHO standards but had higher body fat in relation to their body weight (thin-fat phenotype). Indian studies are yet to study the relationship of birth weight and body fat in adolescents and adults.
Indian and Western studies clearly show inverse relation between birth weight and central adiposity in children although conflicting reports are seen in adolescents with respect to this relationship in boys and girls. Clear trends were observed between birth weight and body fat in adults born with IUGR and SGA. This tendency of increased central adiposity can potentially increase the risk for adverse metabolic outcomes.

2.4.2 Birth Weight and Metabolic Outcomes in Infants/Children/Adolescents/Adults

Higher body fat has been implicated as one of the underlying factors leading to adverse metabolic outcomes. In view of this, a number of studies have investigated the relationship between birth weight and different metabolic risk factors. Soto et al (2003) studied 86 SGA infants and 23 AGA infants born in Chile. At 48 hours after birth, the SGA neonates had similar fasting glucose concentration as the AGA but lower fasting insulin and C-peptide concentration. At the age of one year, no differences were noted in the glucose and insulin levels of the two groups. Similar observations were made by Meriq et al (2005) in a longitudinal study, wherein changes in insulin concentration from birth to three years of SGA and AGA children were studied. Though the SGA infants had lower fasting insulin 48 hours post birth but at three years, they had higher fasting insulin levels (p = 0.005) and HOMA IR (p = 0.007) than the AGA children. This was attributed to be influenced by the rapid postnatal weight gain in the SGA children.

Besides fasting insulin, Wang et al (2006) noted that SGA neonates had higher insulin to glucose ratio 72 hours after their birth (n = 516). Further, SGA group had higher triglyceride levels, total cholesterol and LDL-cholesterol levels as compared to the AGA neonates. Similar observations were made by Soto et al (2003) despite the SGA group having lower weight, BMI and leptin concentration than their AGA counterparts.

In India, Bavdekar et al (1999) studied the association between birth weight and cardiovascular risk factors including insulin resistance syndrome (IRS) in 477 children aged 8 years who were born in KEM Hospital, Pune. After adjusting for current weight,
age and sex, lower birth weight was associated with higher insulin concentration 30 mins post glucose load \((p = 0.02)\) and insulin resistance (HOMA-IR) \((p = 0.03)\). It was noted that the highest level of IRS variables and cholesterol were observed in children with low birth weight and having high fat mass at 8 years of age. Similarly, Joglekar et al (2007) reported that thinner subscapular skinfold was associated with higher 120-min glucose concentration. Faster growth in weight, height by 6 months and one year of age were associated with higher HOMA-IR at 6 years. Further, Krishnaveni et al (2010) studied the Mysore cohort and found that lower birth weight, length and MUAC were significantly associated with higher fasting glucose levels at 9.5 years \((p < 0.01)\) of age.

Parallel to these findings, Bavdekar et al (1999) reported that lower birth weight was associated with higher systolic blood pressure \((p = 0.008)\) at 8 years of age. Further, Joglekar et al (2007) observed that lower birth weight, faster growth in weight and height by 6 months and one year of age were associated with higher systolic blood pressure at 6 years of age. Likewise, Krishnaveni et al (2010) showed that after adjusting for the weight at 9.5 years, birth weight was inversely associated with systolic BP and diastolic BP \((p < 0.05)\). Similar trends were seen with lipid parameters. Bavdekar et al (1999) noticed a strong association between lower birth weight and high total and LDL cholesterol \((p = 0.002; 0.001)\). Krishnaveni et al (2010) also reported similar association with fasting triglycerides \((p < 0.05)\).

In congruence with the Indian studies, evidence from the developed nations also supports the early advent of insulin resistance in young children. Challa et al (2009) studied the levels of markers of insulin resistance in 57 SGA and AGA children aged between 4 to 10 years in Greece. SGA children were already insulin resistant at this young age \((p < 0.05)\). Also, they had lower IGF-1 and IGFBP-3 levels than the AGA children. Further, in the SGA group, the adiponectin levels were negatively correlated with body weight, height, waist circumference and BMI. Lemos et al (2010) studied 506 children aged between 5 to 8 years in Brazil. Results revealed that HOMA index was negatively
associated with birth weight (p < 0.001), SGA (p = 0.027) and positively associated with waist circumference (p < 0.001). Likewise, Hill et al (2013) also displayed that insulin resistance and fasting plasma insulin were inversely associated with birth weight. Obese adolescents were more likely to have higher fasting plasma insulin levels and insulin resistance if they were SGA.

In adults, Jaquet et al. (2000) observed that insulin-stimulated glucose uptake was significantly lower in IUGR adults than the controls (6.7 ± 2.9 v 8.0 ± 1.9 mg/kg fat-free mass.min; p = 0.05). Further, fasting triglyceride concentration was positively associated with fasting insulin (r = 0.42, p = 0.03) and inversely related to insulin-stimulated glucose uptake (r = -0.5, p = 0.009). Also, the decrease in free fatty acid (FFA) concentration during insulin stimulation was positively related to insulin-stimulated glucose uptake (r = 0.48, p = 0.02) and marginally and inversely related with fasting insulin (r = -0.39; p = 0.07). These associations were not seen in the control group. This association between relative decrease in FFA during insulin stimulation and insulin-stimulated glucose uptake in IUGR was regarded as an indirect evidence of insulin resistance in adipose tissue.

Fagerberg et al. (2004) noted that the ratio of weight at 18 years of age to birth weight correlated with a number of risk factors for metabolic syndrome - diastolic blood pressure (r = 0.13, P < 0.05), triglycerides (r = 0.10, P < 0.05), HDL cholesterol (r = -0.13, P < 0.01) and LDL particle size (r = -0.17, P < 0.05). High BP, high TG, low HDL-c and smaller LDL particle size are considered to be atherogenic in nature, thus increasing the risk for cardiovascular events.

Contrary to the other studies, Wilkin et al (2002) found that insulin resistance was not related to birth weight but, the current weight. This study was conducted among 300 children aged five years in Britain. The lack of association could be owing to the fact that the incidence of low birth weight in United Kingdom is quite low (1.4%). Interestingly, the fetal origins hypothesis was also developed based on observations seen in the birth
cohort of UK during 1911 – 1930. In those days, the incidence of LBW was much higher (10%).

Thus, studies conducted across the ages and ethnic groups suggest that lower birth weight increases the risk of insulin resistance, dyslipidemia and high blood pressure. Evidence also indicates that Indian children display adverse metabolic outcomes as early as 6 to 9 years of age. Besides, lower birth weight, the ‘thin-fat phenotype’ is also likely to play a crucial role in elevating the risk of chronic lifestyle diseases. In addition to birth weight, a number of studies indicate that weight gain during infancy, childhood and adolescence may also increase the metabolic risk. During growth, physiological changes occur in the body. These children are exposed to a number of environmental factors through their childhood and adolescence which may further accelerate the occurrence of diabetes mellitus and cardiovascular diseases.

2.5 High Birth Weight

Like neonates born LBW pose a risk for future metabolic consequences, even those born on the other extreme end of the spectrum are seen to be at-risk. Neonates born with a birth weight above the 90th percentile for a given gestational age and gender are referred to as large-for-gestational age (LGA) (Ahmad et al, 2006). Many studies use the term ‘high birth weight’ (HBW) which usually corresponds to a birth weight of above four kilos unless otherwise specified. The incidence of LGA to normal healthy mothers in Thailand was 10.8% (Luengmettakul et al, 2007). In a recent study, the prevalence of LGA newborns to mothers with gestational diabetes mellitus (GDM) was highest in African American women (25.1%), lowest in Asians (13.9%), and intermediate among Hispanic (17.3%), white (16.4%), and Filipina women (15.3%) (Sridhar et al, 2013). Therefore, it appears that the prevalence of LGA is largely dependent on the ethnic background of the mothers.
2.5.1 HBW and Obesity, Metabolic Outcomes

Maternal obesity, excessive weight gain during pregnancy and diabetes or impaired glucose tolerance during pregnancy increase the risk of LGA neonate (Ahmad et al, 2006; Ng et al, 2010; Pornprasertsuk et al, 2010). According to Pedersen’s hypothesis, rise in the maternal glucose concentration increases the nutrient transfer to the fetus across the placenta. This is believed to accelerate the fetal growth resulting in LGA neonate. This hypothesis was mainly put forth to explain macrosomia among babies born to mothers with diabetes. A similar scenario occurs in women with modestly elevated blood glucose but below the diagnostic criteria for GDM (Norman & Reynolds, 2011).

These maternal factors which increase the risk of macrosomia also programme the fetal metabolism increasing the risk of metabolic outcomes in the postnatal life.

(i) Increase in nutrient transfer, especially glucose may result in fetal hyperinsulinemia. Hyperinsulinemia facilitates the increase uptake of glucose and it’s subsequent conversion to FFA. This is postulated to occur via two ways. Firstly, there is an increase in the glucose uptake via a rise in GLUT 4 translocation. Secondly, there is elevation in the de novo fatty acid synthesis owing to increased expression of rate limiting enzymes fatty acid synthase and acetyl CoA carboxylase (Catalano & Hauguel-De Maouzon, 2011).

(ii) In addition to hyperinsulinemia, inflammation also plays a crucial role in programming the fetal metabolism. Both, maternal obesity and GDM present a low to moderate inflammatory status. Maternal cytokines are however, not transferred across the placenta to the fetus. Nevertheless, it is hypothesized that this low to moderate inflammatory status results in excess glucose and lipid availability which aids fetal lipogenesis (Catalano & Hauguel-De Maouzon, 2011).
Thus, maternal obesity and/or impaired glucose tolerance during pregnancy creates an obesogenic environment for the growing fetus by increasing the fetal adipose tissue accretion. This fetal programming not only results in a higher birth weight but also, paves way for obesity and other metabolic complications early in life.

2.5.2 Studies on HBW and Body Composition

As compared to studies conducted on LBW, fewer researchers have investigated the relation of high birth weight (HBW) with metabolic outcomes.

Singhal et al (2003) carried out a study among 78 adolescents (mean age 14.8 ± 0.9 years) and 48 children (mean age 7.4 ± 1.9 years) in UK to test the hypothesis whether higher birth weight programmes higher lean body mass in children and adolescents. FFM was measured using skinfold thicknesses, bioelectric impedance and dual X-ray absorptiometry (DEXA). The mean birth weight of adolescents and children was 3.3 ± 0.7 kg and 3.4 ± 0.6 kg respectively. The findings showed that higher birth weight was associated with higher FFM and not fat mass in children. This association was independent of sex, age, pubertal stage, socioeconomic status and physical activity. With every one unit increase in SD of the birth weight, the lean body mass increased by 0.9 to 1.4 kg. Likewise, Gunnarsdottir et al (2004) examined the relation between high birth weight, truncal fat and obesity in adulthood in a group of 1833 women and 1874 men in Iceland. High birth weight was associated with high BMI in adult life without being a risk factor for adult obesity (BMI ≥ 30 kg/m²). In the highest birth weight quartile (> 4000g), the odds for being above 90th percentile of truncal fat was 0.7 (0.6 – 1.0; p = 0.021) for men and 0.4 for women (0.3 – 0.8; p = 0.002) as compared to the lowest quartile (< 3250 g). Thus, high birth weight was seen to be protective against high truncal fat in both the genders.

Contrary to these reports, Danielzik et al (2004) found that high birth weight and parental overweight were the chief independent predictors of overweight and obesity in 5 to 7 year
old German children. This study however, did not measure body composition. Similarly, Loaiza & Atalah (2013) found a strong relationship between large-for-gestational age neonates and obesity at adolescence (p < 0.01) in high school students in Chile.

Literature does suggest a link between high birth weight and obesity. However, the mechanisms that explain this association are mainly related to maternal obesity and/or GDM as explained earlier. The findings of Danielzik et al (2004) are very much in congruence with this. In the other studies, the cause for high birth weight remains unknown. Thus, one possibility is that high birth weight owing to maternal characteristics results in fetal programming which translates into obesity later in life.

2.6 LBW, HBW and Obesity/Metabolic Outcomes: Is there a U-shaped Relationship?

Both, LBW and HBW appear to have high risk for obesity and other metabolic diseases in the later life. Some researchers have studied the relationship between a wide range of birth weights and metabolic outcomes.

Wei et al (2003) studied 6 to 10 year old Taiwanese school children to ascertain the relationship between birth weight and type 2 diabetes mellitus. The odds ratio (OR) for type 2 DM after adjusting for sex, BMI, family history, GDM and socioeconomic status for the HBW group (> 4.0 kg) was 1.64 (0.91 – 2.96) as compared to the referent group (birth weight: 3.0 – 3.4 kg). Similarly, the OR after adjustment for the given confounding variables for the LBW was 2.87 (1.19-6.92). Further, Oldroyd et al (2011) studied 4367 children aged 4 to 5 years in Australia. Contrary to the results reported by Wei et al (2003) these workers found that LBW was associated with lower risk of overweight/obesity among girls (OR- 0.5; 95% CI: 0.32 – 0.77). However, no such association was seen for LBW boys. On the other hand, in the HBW group, a higher odds
of being overweight/obese was reported for girls (2.42; 95% CI: 2.06 – 2.86) than boys (1.76; 95% CI: 1.12 – 2.78).

Azadbakht et al (2014) studied 5528 adolescents aged 10 – 18 years in Iran. When compared to LBW adolescents, HBW were at higher risk for elevated diastolic blood pressure (p < 0.05), low levels of HDL-c (p < 0.05) and lower risk of generalized obesity (p < 0.05). The LBW adolescents were seen to have high risk of low HDL-c (p < 0.01) and low risk of overweight/obesity (p < 0.01) and high diastolic blood pressure (p < 0.05) as compared to normal birth weight adolescents.

It may be too early to comment on the U-shaped relationship between birth weight and metabolic risk. Well-designed cohort studies are required to ascertain such a relationship. This is mainly important owing to the varying prevalence rates of LBW and HBW across the ethnic groups. In addition to this, the different confounding variables that influence this relationship should be adequately controlled. Nevertheless, at this juncture, it would not be incorrect to say that both the extremes of birth weight appear to increase the risk for adiposity and adverse metabolic outcomes.

2.7 Factors Influencing the relationship of Early Growth with Adult Body Composition and Chronic Disease Risk

Early growth depends on several factors such as – catch-up/ catch-down growth, breastfeeding, dietary components and socioeconomic status. All these factors can potentially modify the relationship of birth weight with body composition and metabolic outcomes in later life.

2.7.1 Catch-up Growth

Infants born after fetal growth restriction experience catch-up growth (CUG) in the immediate postnatal period. CUG is a phenomenon by which rapid growth occurs
following a period of growth restriction (undernutrition or illness) thus, allowing the child to return to their genetic growth trajectory. This may result in accelerated growth in terms of weight or height or both. CUG typically occurs in the first two years after birth among children born with growth restriction. CUG occurs in almost 85-90% of children born with IUGR. However, in children born prematurely this catch-up growth may be completed by four years of age. Technically, an increase in 0.67 SD in weight or height or both is considered as clinically significant catch-up growth (Ong et al, 2000). Several researchers have studied the pattern and impact of catch-up growth both, in animal models and humans.

*Catch-up Growth, BMI and Body Composition* - Literature on relationship of catch-up with BMI and body composition in later life have studied the association independent of birth weight and considering the influence of birth weight. Ong et al (2000) studied the birth cohort from the Avon Longitudinal Study of Pregnancy and Childhood (ALSPC). Children with complete anthropometric measurements at birth, 2 years and 5 years were selected (n=846). In all, 30.7% and 24.6% infants showed catch-up growth in weight and height respectively from birth till two years of age. The children who documented catch-up growth in weight in the first two years of life were found to be heavier, had greater BMI, total fat mass and waist circumference at five years of age than other children independent of the birth weight. Similar findings were noted when children who attained catch-up growth in terms of height were analyzed. Likewise, Ong, et al. (2004) examined the relation between early postnatal growth and risk of obesity and insulin resistance among 841 children from the ALSPC cohort. Children who showed rapid postnatal weight gain (> 0.67 SD) between 0 to 3 years had larger BMI and waist circumference at eight years of age. Also, the insulin sensitivity at eight years decreased significantly with higher current weight, BMI and waist circumference (r = - 0.33, p < 0.0005). Ay et al. (2009) studied postnatal catch-up growth and body composition at six months of age in 252 infants. Birth weight and weight at six weeks positively correlated with percent fat
mass at six months. Those infants who demonstrated catch-up growth had much higher percentage of fat mass than the others. Much of this fat mass was observed to be in the truncal area. All these effects were seen to be the strongest when the catch-up occurred within the first six weeks of life. Baird et al. (2005) reviewed 24 published papers to study the relation between growth during infancy and chances for obesity later in life. Evidence suggested that infants who were at the highest end of the distribution of weight or those who grew rapidly (in terms of weight gain) during infancy were more likely to be at risk of subsequent obesity.

Further, Beltrand et al. (2009) studied the body composition and metabolic changes of 94 infants who exhibited fetal growth restriction at one year of age. At four months of age, infants with fetal growth restriction (FGR+) were shorter and lighter than those without fetal growth restriction (FGR-). Despite this, there was no difference in the BMI Z scores and the sum of skinfolds of FGR+ and FGR- groups. However, FGR+ showed a two-fold increase in the BMI Z scores from birth till four months of age. Further, at 12 months of age, all measurements – weight, height, BMI and sum of skinfolds were similar in both the groups. The main determinants of sum of skinfolds at 12 months of age were – fetal growth velocity and early changes in the BMI z scores, accounting for 41% of the variance.

Iba´nez et al (2006) studied the postnatal weight gain pattern from birth to four years of age in 29 children born SGA with 22 children born AGA. From birth to two years of age, children born SGA showed greater increase in the weight than their AGA counterparts (SD change in weight: 2.02 ± 0.04; p < 0.0001). However, the mean height, weight and BMI did not differ at the ages of 2, 3 and 4 years. Nevertheless, SGA children had greater abdominal fat mass than the AGA children at four years of age (SGA: 1.17 ± 0.1 kg; AGA: 0.80 ± 0.04 kg; P < 0.0003). Also, SGA children had significantly lower lean body mass at age 4 year than the others (SGA: 11.16 ± 0.33 kg; AGA: 12.36 ± 0.28 kg; P < 0.02). Abdominal fat mass at four years showed strong correlation with weight gain.
between 0 to 2 years and much weaker correlation with weight gain between 2 to 4 years of age. In another study, Iba`nez et al (2008a) observed that at age 6, SGA children had significantly greater total fat mass (P < 0.0001) and visceral adipose tissue than AGA children (VAT - SGA: 30 ± 3, AGA: 19 ±1; P< 0.005). Interestingly, in another study, non-overweight SGA children had significantly higher visceral fat mass and ratio of visceral to subcutaneous fat mass without any difference in the total fat mass as compared to their non-overweight AGA counterparts (Iba`nez et al., 2008b). Thus, fetal growth restriction followed by early postnatal weight gain (0 to 2 years) promoted gain in fat mass and particularly abdominal fat mass. These changes in the body composition are accompanied by a couple of hormonal alterations.

*Catch-up Growth and Hormonal Alterations* - Catch-up growth (refeeding) after a period of starvation or undernutrition leads to a numerous alterations in the hormonal profile. These changes in the hormonal levels appear to be interlinked with the changes in the body composition discussed earlier. Beltrand et al. (2009) studied the metabolic changes post fetal growth restriction (FGR) among 94 infants at one year of age. At birth, the FGR+ had lower levels of insulin (p < 0.01), IGF-1 (p < 0.01) and IGFBP-3 (p < 0.05) in the cord blood. Insulin sensitivity was markedly higher in FGR+ at birth (p < 0.05). However, there was no difference in these parameters at 12 months. Cord blood leptin levels were lower in FGR+ (p < 0.05) than the controls. But, serum leptin levels at 12 months was higher in FGR+ (p < 0.05) despite similar fat mass in the control group. Further analysis revealed that, leptin levels at 12 months negatively correlated with fetal growth velocity (β = -0.04; p = 0.05) and positively correlated to change in the BMI from birth to four months of age (β = 0.12; p = 0.008). Higher leptin levels at 12 months possibly reflect the positive energy balance in children with fetal growth restriction. Early catch-up was believed to be related to the fetal growth pattern and was not associated with adverse metabolic profile at 12 months of age.
Ong et al. (2004) examined the relation between early postnatal growth and insulin resistance among 841 children from the ALSPC cohort. Children who showed rapid postnatal weight gain (> 0.67 SD) between 0 to 3 years had lower insulin sensitivity at 8 years of age (p < 0.005). Lower birth weight was associated with reduced insulin sensitivity only in highest BMI tertile at 8 years (r = 0.17; p = 0.006). Also, lower insulin secretion was related to small size at birth (p < 0.01), independent of postnatal growth and insulin sensitivity.

Ibañez et al. (2006) found that at two years of age, SGA children who had similar body weight and BMI as the AGA, had lower serum insulin, HOMA-IR scores, serum IGF-1 and neutrophil:lymphocyte ratio than their AGA counterparts. However, from two to four years of age, the IGF-1 concentration increased in both SGA and AGA children reaching similar values at four years. The fasting serum insulin levels remained unchanged in the AGA children but rose in the SGA ones. Similar rise was also seen in total neutrophil count and neutrophil:lymphocyte ratio. In another study, Ibañez et al (2008a) examined the visceral adipose tissue (VAT), insulin and IGF-1 among SGA and AGA children with similar weight and height. The SGA children documented significant elevation in serum insulin, serum IGF-1 and neutrophil:lymphocyte ratio than their AGA counterparts at 6 years of age (p < 0.0001). These children showed rising levels of IGF-1 despite lower lean body mass. This is possibly indicative of relative IGF-1 resistance. Also, the increase in neutrophil:lymphocyte ratio is suggestive of inflammatory state.

Further, Ibañez et al (2008b) also studied 32 matched pairs (matched for weight, height and BMI) of non-overweight SGA and AGA children at the age of six years. SGA children showed significantly higher serum insulin, serum IGF-1 and leptin levels. Another interesting finding was that SGA children had lower serum high molecular weight adiponectin levels than the AGA ones (p < 0.0001). Moreover, body fat, visceral fat and serum IGF-1, leptin and adiponectin levels were higher among SGA girls than boys. Multiple stepwise regression showed that serum IGF-1 and leptin levels explained
29 and 10% of the variance respectively in body fat. Similarly, serum insulin and serum IGF-1 were able to explain 28 and 10% of the variance respectively in the visceral fat mass. Thus, defects in insulin and/or IGF-1 signalling in the muscle may divert the nutrients towards fat accumulation (Ibañez et al, 2006).

Absence of Catch-up Growth - Ibañez et al (2009) also investigated the levels of insulin, IGF-1 and adiponectin in the absence of catch-up growth in SGA children. The study included 24 short SGA (< -3 SD), 32 AGA and 32 SGA children who had completed catch-up growth. Findings revealed that short SGA children had low fasting serum insulin, low IGF-1 with better insulin sensisity (p < 0.0001) as compared to the AGA and SGA children who had completed catch-up growth. Also, the short SGA children reported normal or elevated levels of high molecular weight adiponectin than others.

CUG appears to be pivotal in programming the risk of adverse metabolic outcomes early in life. Rapid CUG in the first year of life increases the risk of adiposity as early as two years of age. Moreover, both, overweight and non-overweight SGA who had completed CUG were found to be insulin resistant, had lower levels of leptin, adiponectin and neutrophil:lymphocyte ratio. This, may translate in to higher food intake and increased inflammation. However, more work needs to be carried out in this area.

2.7.2 Breastfeeding

Breastfeeding has been suggested to have protective role in preventing obesity and other non-communicable disease (NCDs) risk during adulthood. A systematic review of 19 studies conducted in affluent population revealed that breastfeeding for nine months resulted in 400 grams lower weight at one year of age as compared to formula-fed infants. Further, infants breastfed for 12 months weighed as much as 600 to 650 grams less than their formula-fed counterparts (Dewey, 1998). The duration of breastfeeding is of crucial importance. Studies show that longer the duration of breastfeeding, lower was the prevalence of obesity (von Kries et al, 1999).
O'Tierney et al (2009) studied the Helinski Birth Cohort comprising of 13,345 men and women born in Helsinki, Finland between 1934 to 1944. Of all the subjects, only those who had been breastfed and had another sibling in the same cohort were selected. When these sibling pairs were analyzed, it was seen that at the age of one year, with the increasing duration of breastfeeding, the BMI progressively declined (p < 0.05). However, this association disappeared by the age of 7 years. At the age of 62 years, individuals breastfed for 5 to 7 months had the lowest BMI although, this was not statistically significant. Further, a U-shaped relationship was found between duration of breastfeeding and that of BMI and body fat. Those who were breastfed for the shortest duration (< 2 months) and those breastfed for longest duration (> 8 months) had the highest BMI. In another study, Yin et al (2012) found that breastfeeding for more than 25 days was negatively associated with body fat in adolescence. Gunther, et al (2013) observed that longer duration of breastfeeding (> 4 months) was negatively associated with fat mass index only in young adult women and not men. Moreover, women who were breastfed for longer duration had higher values of IGFBP-2 (p = 0.02) and lower HOMA-IR (p = 0.003). No such association was found among men.

One proposed mechanism that links longer duration of breastfeeding and lower risk of obesity is the programming of insulin metabolism and GH-IGF-axis. The GH-IGF-axis, IGF-I and the binding proteins regulate the human growth and glucose metabolism. Breastfed infants have low levels of insulin and IGF-I. This may favourably influence the body composition and yield long-term metabolic adaptation (Gunther, et al., 2013).

Experiments in rats have revealed that early weaning modifies the glucagon-like peptide-1 (GLP-1) levels which may contribute to development of obesity. GLP-1 is a gut-derived peptide which reportedly improves insulin resistance and promotes preadipocyte differentiation. Experimental rats were weaned after day 3 and sacrificed at either day 21 or 180. At day 21, these rats had higher serum GLP-1 and lower gut GLP-1 levels. Also, the GLP-1 receptor levels were lower in the gut but higher in the adipose tissue. Lower
gut levels contributed to lower insulin secretion. On the other hand, higher levels in the adipocyte, signalled preadipocyte differentiation and reduced apoptosis. This programmed hyperplasia resulted in hypertrophy of the adipocytes along with alteration in glucose homeostasis and insulin resistance. These results were evident when the rats weaned early were sacrificed at day 180. The rats were overweight and had higher visceral adipocyte area and tissue (Oliveira et al, 2013).

2.7.3 Dietary Composition

Nutrient composition of the diet during early life appears to play a significant role in determining the body composition in later life. Infants who were formula fed were reported to have higher prevalence of overweight and obesity during childhood, adolescence and adulthood (von Kries et al, 1999). Several components in the diet may be responsible for this -

Proteins - Infant formula differ in the content of nutritive and non-nutritive components. Infant formulas have higher energy density causing 10 – 18% greater energy intake by infants. In addition, infant formulas increase the protein intake by as much as 55 – 80%. Mayol et al (2013) showed that protein intake at 18 months of age (1.24; 95% CI: 1.02 – 1.50) was associated with the risk of being overweight at the age of 20 – 22 years. Protein consumption in excess of the metabolic requirement resulted in increased secretion of insulin and IGF-I. Similar observations have been made in infants who were fed cow’s milk instead of breastmilk. Higher levels of insulin and IGF-I stimulate adipocyte differentiation and adipogenic activity (Hauner et al, 1989). Besides, both insulin and IGF-I result in a fall in the growth hormone concentration which eventually leads to decrease in lipolysis. Thus, the net result is an increase in adipocyte proliferation and lipogenesis. Epidemiological studies indicate that higher protein intake early in life and not energy or carbohydrates or fats, is predictive of early occurrence of adiposity rebound.
and higher BMI in childhood. This effect of higher dietary protein in the initial years of life is popularly known as ‘the early protein hypothesis’ (Koletzko, et al., 2009).

*Fatty acids* - Likewise, Mayol et al (2013) showed that fat intake at 24 months (1.28; 95% CI: 1.06 -1.51) were associated with the risk of being overweight at the age of 20 – 22 years. Also, fat intake at 24 months was significantly associated with waist circumference (β = 0.57; 95% CI: 0.11 – 1.04) and percent body fat (β = 0.41; 95% CI: 0.09 – 0.72) in adulthood.

Most of the studies that have examined the effect of fat on adiposity have been conducted in animal models. Studies have evaluated the effect of long chain poly unsaturated fatty acids (LC PUFA) i.e. linoleic acid (LA) and α-linolenic acid (ALA) separately. In a study, keeping the energy intake constant, rats aged 4 weeks were given LA-rich diets for six months and were compared with those who received saturated fatty acid (SFA) rich diet. The group that received LA-rich diets exhibited higher body weight, retroperitoneal fat pad weight and adipocyte number as compared to the SFA-rich group (Okuno et al, 1997). In another study 10 day old piglets received arachidonic acid (AA) supplementation for two weeks. At the end of two weeks, the body weight of the piglets rose by 27% mainly due to the increase in the fat mass. In a study carried out among infants who were fed formula milk containing varying amounts of LA from 1.4% to 43.1%, the LA content of the subcutaneous fat rose in accordance with their levels in the infant formula (Weiler, 2000).

Among all the long chain fatty acids, AA is known to be highly adipogenic in nature. Arachidonic acid is a potent activator of adipogenesis. It acts as activator/ligand of peroxisome proliferator-activated receptor-α (PPAR-α). Arachidonic acid acts through the prostacyclin synthesis and triggers cAMP production and activates protein kinase A pathway (Massie´ra, et al., 2003).
Conversely, when ALA content of the diet was increased, there was lower adiposity. In a trial, five week old mice were either kept on high LA-low ALA diet or low LA-high ALA diet. At the end of the trial, it was noted that the group on high LA-low ALA had highest, while the group that received low LA-high ALA had lowest proportion of body fat (Ailhaud et al, 2008). A study was conducted on full term infants who received a formula containing 16% LA and 0.4% ALA. On increasing the ALA content to 3.2%, there was 13% lower body weight gain and also a fall in the serum AA and rise in the serum docosahexaenoic acid (DHA) levels (Jensen et al, 1997).

DHA inhibits adipogenesis. There are several mechanisms through which it acts. Firstly, DHA inhibits the prostaglandin – 2 (PG-2) series which arises from AA metabolism. Certain n-3 PUFAs directly inhibit the activity of cyclooxygenase-2 (COX-2). Both COX-2 and COX-1 are expressed in the preadipocytes. DHA decreases the expression of COX-2 mRNA and COX-2 protein by blocking NF-κB-mediated transcription of COX-2 through multiple signalling pathways. n-3 PUFA also inhibits the cAMP production (Kim, Della-Ferra, Lin, & Baile, 2006).

Thus, diets high in protein, linoleic acid and low in ALA are seen to promote adiposity in children. In IUGR, LBW and SGA children, catch-up growth is imperative. However, it is the quality of diet provided which will modulate the body composition of the growing children.

### 2.7.4 Thrifty Phenotype and Thrifty Genotype

According to the ‘thrifty phenotype hypothesis’, the nutritional deprivation during the prenatal life increases the risk for chronic lifestyle diseases when the individual is exposed to nutritional abundance in the postnatal life. The fetus adapts to survive in a state of nutritional deprivation by bringing about certain metabolic alterations. However, this ability becomes a burden and tends to predispose the individual to future risk of chronic diseases. This hypothesis was formed on the basis of observations made in
affluent nations like the United Kingdom (Barker et al, 1989; Barker et al, 1993; Barker, 1995).

There is a derth of such evidences from the resource poor or developing countries. This is mainly because of scarcity of data on birth weight to carry out retrospective studies. However, it is vital to realize that the prevalence of low birth weight is highest among these developing nations. In view of this, infants born in these nations would have a higher risk of the detrimental effects of fetal programming.

Another factor which may increase the risk is ‘thrifty genotype hypothesis’. In 1962, James Neel put forth ‘thrifty genotype hypothesis’ to explain the high incidence of type 2 diabetes mellitus in previous centuries. According to this hypothesis, our predecessors survived the difficult times of famine and food scarcity only because they could efficiently store excess energy and utilize it such times. This modified their metabolic profile by altering the regulation of insulin release and glucose storage. However, in the modern times, this genotype poses a threat to the descendents of these individuals. In the modern age of plentiful food supply, this genetic disposition has led to increased energy storage and higher insulin levels giving rise to obesity and insulin resistance.

A combination of ‘thrifty phenotype’ and ‘thrifty genotype’ is believed to amplify the predisposition of population in developing nations as well as among those who have migrated from poor countries to wealthy ones. Developing nations are currently undergoing a rapid economic and nutrition transition thus, increasing the availability of processed energy-dense foods (Prentice & Moore, 2005). Though scanty but, some evidence for this comes from India and Africa. Studies from rural areas of Pune, India suggested early genesis of insulin resistance in Indian infants. Also, as compared to their Caucasian counterparts, these infants had lower anthropometric measurements except the fat mass. This indicates the presence of a ‘thin-fat phenotype’ (Yajnik, et al., 2003). Similarly, African population is seen to have a higher prevalence of obesity and salt
sensitivity that predisposes them to hypertension (Forrester, 2004). Thus, populations from such nations are likely to suffer greater effects of early programming owing to both, genetic disposition and fetal programming.

Thus, the relationship between birth weight and adiposity during later life is likely to be influenced by catch-up growth, breastfeeding, dietary composition and combination of thrifty phenotype and genotype.

2.8 Early Growth and Brain

Fetal growth restriction not only poses a threat to obesity and metabolic complications but also affects the cognitive functions. Undernutrition during critical periods of growth and development of the brain can potentially hamper many of the cognitive functions. Much of the growth and development of the brain happens in utero and during the first two years of the postnatal life.

2.8.1 Growth and Development of the Brain

The growth and development of the brain begins in utero. Human gestation is divided into two stages namely, the embryonic stage (conception till eighth week) and fetal stage (ninth week till term). The brain begins to develop in the embryonic stage i.e. from third week post conception. By the end of the embryonic stage, the main structures – brain, spinal cord and peripheral nervous system (PNS) are established (Huttenlocher, 2002; Dowling, 2004; Kliegman et al., 2007). The embryonic stage is followed by fetal stage which is a critical period for the development of the neocortex, the outer layer of the cerebral hemispheres. The fetal stage is marked by extensive neurogenesis, migration of neurons, formation of neuronal processes (axons and dendrites), aborization (dense population of dendritic branches in and around each cell) and synaptogenesis (Rice and Barone, 2000; Huttenlocher, 2002; Stiles and Jemigan, 2010).
Brain development begins prenatally but continues in the postnatal life too. In the postnatal period, major development occurs from birth up to first two years of life. At birth the infant’s brain is approximately 400 grams i.e. 25% of the adult brain by weight (Keenan and Evans, 2009). The total brain volume increases by 101% in the first year followed by 15% rise in the second year of life. Likewise, the volume of cerebral hemispheres increases by 88% during infancy and by 15% in the second year of life. Amongst the various brain structures, maximum increase during the first year is seen in the cerebellum (i.e. by 240%) (Knickmeyer et al, 2008). By the age of two, the brain reaches almost 80-90% of the adult size (Pfefferbaum et al, 1994).

Neurogenesis that begins in the prenatal period continues after birth although the pace is slower than during prenatal period (Stiles and Jernigan, 2010). The highlight of the postnatal brain development is the proliferation and differentiation of glial cells which proceeds rapidly after birth and continues even in the adult brain. Glial cells support and insulate the neurons by creating the myelin sheath. The main function of myelin is to accelerate the conductivity of impulses along the axon (Rice and Barone, 2000; Huttenlocher, 2002; Stiles and Jernigan, 2010). The general pattern of adult myelination develops by the end of two years (Sampaio and Truwit, 2001).

There is an exuberant rise in the number of synapses both prenatally and during the initial two years of life (Huttenlocher and Dabholkar, 1997). In congruence with this growth, there is systematic elimination of some of synapses through a process called synaptic pruning or sculpting. In simple words, it is the ‘use it or lose it’ process. This depends heavily on the levels of presynaptic activity. For instance, with minimal activity/stimulation, synaptic connections get diluted. On the other hand, release of neurotrophic factors helps the presynaptic and postsynaptic interconnections to grow more tightly (Perry, 2002; Dowling, 2004). Sculpting continues throughout the lifecycle but the rate decreases with age. This activity-dependent process appears to be the basis of learning and memory and hence, essential for neurodevelopment (Huttenlocher, 2002).
2.9 Theories of Cognitive Development

Prenatal and postnatal brain growth and development are crucial for the development of perception, cognition and emotion. Cognition is defined as ‘the study of thought processes or mental activity by which knowledge is acquired and used’ (Keenan and Evans, 2009). Cognition is the process by which the individual gets acquainted with the world, the objects in it including himself. Cognitive development results in increased application of information and experiences that have been abstracted and stored in the memory (Keenan and Evans, 2009). Human cognitive development can be explained with the help of three main theories – Piaget’s cognitive development theory, Vygotsky’s sociocultural development theory and the information processing theory.

2.9.1 Piaget’s Cognitive Development Theory

Jean Piaget’s theory of cognitive development is based on evolutionary biology. He believed that children actively explore their world and construct cognitive structures or schemas. A schema is an interrelated set of actions, thoughts, memories or strategies employed to predict and understand the environment. As children grow, they further develop and refine the schemas. He suggested that with time, children begin to link the schemes together and organize them to create complex cognitive structures that help further interaction with the environment. In addition to the concepts of schemes and organization, Piaget also emphasized on ‘adaptation’. Adaptation aids in adjusting the schemes to better fit with the demands of the environment (Keenan and Evans, 2009).

Piaget viewed children’s cognitive development as a process consisting of four stages –

1. Sensorimotor stage (0 to 2 years) – The infant thinks about the world through symbols. This stage is characterized by the development of object permanence.
2. Preoperational stage (2 to 7 years) – is marked by growth of representational abilities. The characteristic features of this stage are egocentrism (thinking from
only one’s perspective), animistic thinking (attributing life-like qualities to inanimate things) and centration (focus on a single aspect of a problem).

3. Concrete operational stage (7 to 12 years) – is marked by the ability to use mental operations such as conservation, classification and transitive inference.

4. Formal operational stage (above 12 years) – is marked by the development of reasoning in propositional, abstract and hypothetical ways.

Thus, Piaget believed that children actively explore their world and develop their thinking from their actions on the world.

2.9.2 Vygotsky’s Sociocultural Development Theory

Lev Vygotsky believed that the child’s social and cultural environment played a major role in his/her cognitive development. According to Vygotsky, every child has certain innate abilities which develop to a limited extent without intervention from other members of the child’s community. These abilities which the child was naturally endowed such as – memory, attention and perception were referred as elemental mental functions. He suggested that these functions can be transformed into higher mental functions by social interactions with other more experienced members of the culture. He also suggested that the development of higher mental functions was mediated by the use of symbolic tools like language, numbers, art and other culturally derived products. Later on some other researchers introduced the term ‘scaffolding’. Scaffolding is an interactive process in which adults adjust the amount and type of support they offer to a child. In addition, development also occurs through intersubjectivity i.e. interaction between two participants with varying level of understanding (Keenan and Evans, 2009).

2.9.3 Information Processing Theory

The information processing approach to cognitive development is based on the analogy between the computer and the human mind. Much like the computer, the human mind
encodes information received from the environment, moulds it in a symbolic form which the mind can process using various operations and yield an output like a solution to a problem. Information processing theories are based on three assumptions. Firstly, any thought process such as remembering or perceiving involves processing of information. Secondly, theorists emphasize on the need to study how development proceeds from one level to the next. Thirdly, information processing system is driven by self-modification i.e. earlier knowledge and strategies can modify thinking to a higher level of development (Keenan and Evans, 2009).

Thus, Piaget, Vygotsky and the information processing theory view cognitive development through different perspectives. All these three theories aid in the understanding of the development of different cognitive functions.

2.10 Development of Cognitive Functions

Cognition is a broad term that encompasses various processes or functions such as – perception, spatial cognition, concept formation, language development, reasoning, problem solving, attention and memory. These functions develop at different stages in a child’s life. Development of each of these functions is closely associated with the growth and development of brain. Also, the above discussed theories contribute to better understanding of these functions.

2.10.1 Perceptual Development

A newborn baby begins to explore his/her environment by the use of his/her sensory attributes such as – seeing, touching, smelling and hearing. The infant is able to explore and gather meaningful knowledge about the physical environment through ‘perceptual development’. Perceptual development is a psychological process that connects the infant with the environment, allows an interface with the physical reality and aids in
understanding the surroundings which the growing infant is expected to adapt soon in order to survive. Thus, perceptual development forms a fundamental base for the development of cognition (Rosser, 1994).

Human infants are born with operational visual system however it is not as mature as that of adults. Over the initial few months, the cerebral cortex and the neuron layers within the visual system mature. The cells in the fovea (a shallow depression in the retina that contains many photoreceptors) experience cell migration leading to changes in cell density during the first 18 months (Youdelis and Hendrickson, 1986). The changes in the fovea are closely related to higher spatial resolution. Visual perception enables to look at structures such as – surfaces, objects, forms and patterns. Knowledge of the structure facilitates adaptation to the environment. Along with this, movement perception also develops in early infancy. Infants are able to track moving objects and show preferences for movement (Rosser, 1994).

With age, visual perception undergoes refinement. This is attributed to synaptogenesis and synaptic pruning which occur in the early postnatal life (Rosser, 1994)

2.10.2 Spatial Development

Infants perceive the spatial layout, visually process information about spatial features and adapt to the visual-spatial environment. However, as the infants grow older, they are able to use ‘spatial representation’. Spatial representation is a cognitive act which transpires in the absence of sensory contact. Spatial perception requires sensory contact with the space. But in spatial representation, the contents of the space are cognitive contents in the form of symbols and/or mental models which can be manipulated and transformed. These cognitive contents are used to draw inferences (Rosser, 1994).

According to Piaget, spatial development occurs along with nonspatial development. Nonspatial development refers to the knowledge derived from physical and exploratory
actions on environmental objects. Thus, an important prerequisite of mental representation of space is mental representation of objects. ‘Object concept’ originates through physical interactions (touching, grasping, holding in the mouth, observing) between the infant and the objects. The presence of this concept is the first indication of mental representation of symbols. The object concept develops between 18 to 24 months of age. Piaget described six stages of object-knowledge attainment (stages of search) which are summarized in Table 2.1. The change in the cognitive state across the stages is gradual and is generated by the co-ordination of sensorimotor schemes (Rosser, 1994).

As seen in Table 2.1, researchers have observed age-related differences across the children in development of the object concept. The maturation of object concept coincides with the neurological maturation (the maturation of neurons, synaptogenesis and synaptic pruning) which mainly occurs in the postnatal life. The areas of the brain which are believed to be involved in spatial cognition are – medial temporal lobe, parietal lobe, retrosplenic cortex, parietal-occipital sulcus and hippocampus (Burgess, 2008).

Thus, object concept, knowledge that the object exists and moves in space without any sensory contact the infant or the young child is the main accomplishment in spatial cognition. In addition to neuronal maturation, hippocampal development is crucial for ‘learning’ activity and to use distal cues to search the invisible object.
Table 2.1: Stages of Object-knowledge Attainment

<table>
<thead>
<tr>
<th>Stage</th>
<th>Situation</th>
<th>Piagetian Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I and II</td>
<td>If the infant looks at an object and it disappears/ moves out of the view/ is hidden by a occlude, the infant does not look around for it or request for the object again</td>
<td>At this age, the object’s existence depends on it’s perception. As the perception ceases (due to the disappearance), so does the existence.</td>
</tr>
<tr>
<td>Age: 0 to 4 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>If the object is occluded or disappears then, the infant looks in the direction from where the object was removed in anticipation of the object’s return.</td>
<td>Infants have motor skills to carry out successful retrieval. However, they do not search. Objects are still not permanent.</td>
</tr>
<tr>
<td>Age: 4 to 8 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>If the infant observes an object being hidden and he observes the hiding place then, he will retrieve it.</td>
<td>Infants exhibit true search. They have the concept of ‘object permanence’. For eg, after retrieving the object from the hidden place ‘A’, if it is hid at ‘B’ then, the infant may still search at ‘A’. This is called preservation error. Thus, object permanence is incomplete.</td>
</tr>
<tr>
<td>Age: 8 to 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage V</td>
<td>Infant is able to retrieve the object from ‘B’. The object is put in a container and the container is moved to numerous locations. The object is left on the path and the container is empty.</td>
<td>If the empty container triggers a systematic search, Piaget considers it as a mature response</td>
</tr>
<tr>
<td>Age: 12 to 18 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage VI</td>
<td></td>
<td>Until this age, children do not conduct systematic search because they are unable to represent the action and transposition of the object though they can represent it’s entity.</td>
</tr>
<tr>
<td>Age: 18 to 24 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.10.3 Conceptual Development

The ability of children to organize or to form categories and concepts is yet another cognitive ability. ‘Concepts’ are mental representations that can be expressed in a single word such as – flower or fruit. It can represent a set of ideas like – red flower or fruit basket. Further, it can describe a whole idea like – Newton’s law of motion. Formation of concepts is central to understanding the models of reality as also the complex and abstract representation (Zirbel, 2005). They support cognitive activities such as – categorizing, classifying and scaling.

According to Piaget, children in the concrete-operational stage internalize a system of quasi-mathematical rules. This helps them make logical inferences about the working of the world. Children in the pre-operational stage are yet to achieve this. Therefore their thought process is less logical, less internally consistent, less rule-governed and more contextual and perceptual in nature.

2.10.4 Planning

Planning is a cognitive process that is a part of a broader cognitive function known as executive functions. Executive functions are those which are involved in complex cognitive processes such as – solving novel problems, modifying behavior in the light of new information and generating strategies. Executive functions are also viewed as ‘a product of the co-ordinated operations of various processes to accomplish a goal in a flexible manner.’ Thus, co-ordination, control and goal orientation are an integral part of executive functions (Elliot, 2003).

The prefrontal cortex is believed to play a crucial role in planning behavior. The frontal lobe constitutes more than 30% of all the cortical cells. The prefrontal cortex receives input from other neocortical areas (parietal and inferotemporal lobes), hippocampus, cingulate cortex, substantia nigra and the thalamus. The prefrontal cortex is thus highly
interconnected with other cortical and subcortical areas (Unterrainer and Owen, 2006). Thus, planning is a complex process that requires co-ordination from various structures of the brain.

2.10.5 Memory

The act of remembering or memory is associated with most of the cognitive tasks. The brain’s structures (neurons and synapses) undergo changes in response to different experiences. This results in a behavioural change. This adaptive capacity in response to experiences reflects the ability of the brain to learn and remember. Learning is a process of acquiring new information while memory is retrieving the learnt information or knowledge at a later time. In other words, memory can be said to be a expected consequence of learning (Rosser, 1994).

Atkinson and Shiffrin (1968) developed a model of memory consisting of three separate stores – sensory register, short-term store and long-term store. Sensory register receives information from the environment through the senses. Information is stored in the sensory register for a brief period of time before being lost. If the information is relevant, it is selectively copied to the short-term store. Information can be lost from the short-term store if it is not rehearsed within 30 seconds. If the information is needed on a more permanent basis then it is copied to the long-term store. It is also believed that if necessary, information can be copied from long-term to short-term store.

The long-term store is also known as long-term memory. It is further categorized as explicit memory and implicit memory. Explicit memory pertains to memory of facts and events. Further, there are two types of explicit memory – semantic and episodic memory. Semantic memory refers to the memory of the knowledge of the world; for example it is known that monsoon usually begins in June in Mumbai. On the other hand, episodic memory pertains to specific events such as the first job interview an individual faced.
Contrary to this, implicit memory refers to learning without being aware that one is learning.

Short-term store or memory can be explained with the help of the working memory model proposed by Baddeley and Hitch (1974). This model explains the temporary storage system and how it is put to work. The model was divided into – phonological loop, visuo-spatial sketchpad and a central executive. The phonological loop stores information in a ‘speech-based’ form. The visuo-spatial sketchpad on the other hand, stores information based on visual characteristics and relative position in space. The central executive was believed to control and co-ordinate mental activities like reasoning in order to use the information stored in the separate short-term systems. Further, it was suggested that the central executive had limited resources which could be used for either storage or other processes, as was required according to the individual’s priority.

Recall and recognition are two ways of retrieving the memory. Recall is creation of mental representation of stimuli that are no longer present. The ability to recall is present at an early age of one year. Infants are capable of finding hidden objects and imitating the actions and facial expressions of others after a couple of hours of seeing them. However, ability of infants and young children to recall is limited and usually requires some cues. For instance, a two year old child can recall one or two pieces of information while a four year can recall three to four pieces. Recognition is a more basic form of memory retrieval. It involves identifying that a stimulus is identical or similar to a previously experienced stimulus. Unlike recall, young infants are able to recognize information (Keenan and Evans, 2009). The ability to recall and recognize depends on the multiple connections between various regions of the brain.

The structures of the brain that are related to memory are – cerebellum, hippocampus, amygdala and the cerebral cortex. Cerebellum has been implicated in the performance of skilled movements, motor learning and classical conditioning (Thompson, 1986).
Hippocampus is associated with spatial mapping. Lesions in the hippocampus have been associated with profound effect on working memory, temporal memory and spatial memory. On the other hand, combined lesions on hippocampus and amygdala, affects the global memory. Cerebral cortex contains the neural systems that are responsible for perception, analysis, information processing and storage. Among these, the role of the hippocampus is considered to be of prime importance from the developmental perspective. This is because in most areas of the brain, neurogenesis occurs in the prenatal life. However, the generation of the granule cells in the hippocampus occurs postnatally. Neuronal proliferation is believed to continue postnatally till six months. By 24 months of age, the hippocampus approximately reaches the adult level of functioning (Rosser, 1994).

Structural growth of the brain begins during prenatal life and continues during early postnatal life. Undernutrition during this period can bear a strong impact on the brain growth. The following section discusses the normal growth pattern of the brain and the influence of undernutrition.

2.11 Critical Period of Brain Growth

As early as 1968, Winick analyzed brains of 31 dead foetuses and/or infants ranging from 13 weeks gestational age to 13 months postnatal age. The DNA content of the brain was seen to increase linearly in the prenatal period, which tapered down at around birth and again peaked at about one year of age. Similarly, Dobbing and Sands (1970) demonstrated that the rate of cell division in the human brain peaked twice. The first phase when it peaked was during 15 to 20 weeks of gestation. This period coincided with the phase of neuronal proliferation. The second phase of peak in cell division occurred from 25 weeks of gestation until birth during which there was glial proliferation.
This growth spurt of the brain is said to be a transient period of rapid brain growth that can be seen in all species. In anatomical terms, it begins when the adult neuronal number has been largely achieved with an exception for cerebellar neurons (Dobbing and Sands, 1973). In humans, the period of brain spurt or ‘the vulnerable period’ or ‘critical period’ is said to begin in the third trimester and extends to almost two years of age. Thus the period of growth spurt excludes the phase of neuronal proliferation. This does not mean that the phase of neuronal proliferation is unimportant or less critical. In humans, neuronal growth occurs under a highly protected environment and hence it is not included in the brain spurt. Therefore, many do not recognize neuronal proliferation as a ‘vulnerable period’.

Literature suggests that undernutrition during critical periods of brain growth (prenatal and postnatal) can adversely affect various structural facets of the brain (Ahmad and Rahman, 1975). This may bear an impact on the development of cognitive functions.

2.12 Early Undernutrition and the Brain

Undernutrition during periods of fetal and postnatal growth has varying effects on the growth and development of the brain.

2.12.1 Effect of Prenatal Growth Restriction on the Brain

Animals and not humans have been used as models for experiments to study growth and development of the brain. This is simply because of the ethical and practical concerns. Therefore, findings of the animal studies have been used to understand the human brain development.

Studies have been undertaken to examine the effect of prenatal undernutrition on brain development and structure in animal models of IUGR and maternal protein restriction.
Cha et al (1987) studied the effect of mild and severe IUGR on brain growth at birth in rats. On the first day of life, the brain weight of control and mild IUGR was similar. But, the weight of the brain of severe IUGR rats was significantly lower than that of controls. Moreover, the DNA, protein and lipid content of brain of IUGR rats were significantly lower than that of controls. Mallard et al (2000) induced IUGR at 30 days gestational age in guinea-pigs. At one week of age, the number of CA1 pyramidal neurons in hippocampus and Purkinje neurons in cerebellum was determined. As compared to the control group, the IUGR-induced animals showed 16% reduction in total brain weight \( (p < 0.01) \). In the hippocampal region, there was a significant decrease in CA1 pyramidal neurons \( (4.19\pm0.43\times10^5 \text{ v } 5.20\pm0.44\times10^5, p < 0.01) \) and 21% drop in the volume of stratum oriens layer above CA1 region which contains apical dendrites. In the cerebellum, there was significant decrease in the number of Purkinje neurons, internal granular layer and the volume of cerebellar white matter.

In another study on rats, Gressens et al (1997) found a significant effect of prenatal undernutrition on the brain structure. They studied the effect of early maternal protein restriction on the postnatal brain development. The rats were fed either 5% or 20% casein diet at conception and during first two weeks of the gestation period. In the first two weeks after birth, the animals showed delayed astrocytogenesis, abnormal neuronal differentiation, abnormal synaptogenesis and delayed apoptosis.

Thus, when models of prenatal protein restriction as well as IUGR were immediately analyzed after birth (day 1 or within a week), they showed reduction in brain weight, decreased neuronal number and alterations in the structure of dendrites in the hippocampus region. Thus, prenatal undernutrition has a detrimental influence on the brain.
2.12.2 Effect of Undernutrition during the Critical Period on the Brain

Animal Studies – In all animals, the rate of cell proliferation and DNA synthesis drastically increases at a specific time period. This period is known as ‘vulnerable’ or ‘critical’ period for growth. In rats, under normal and healthy circumstances, it is expected that the DNA content and the protein: DNA ratio (i.e. the protein content in each cell) increases in the postnatal period up till 21 days after which it tapers off. The vulnerable period of brain development in rats is said to be from day 10 to day 21 approximately. Within this period, the cell number rises in the cerebrum, cerebellum and hippocampus (Fish and Winick, 1969). Considering this, the brains of the experimental animals were structurally analyzed at varying postnatal ages to study the effect of undernutrition.

Normally, during the suckling period (i.e. up till day 21), the number of cells in the brain increases most rapidly. This is observed earliest in the cerebellum followed by cerebrum and hippocampus. The protein/DNA content also increases in the cerebrum followed by the brainstem. Fish and Winick (1969) restricted the food intake of newly born rats who were later sacrificed by day 21. The increase in the cell number was curtailed in the areas of cerebellum, cerebrum and hippocampus. In addition, the normally occuring increase in the protein/DNA content was hindered in the brainstem.

Ahmad and Rahman (1975) studied the effect of moderate and severe undernutrition during suckling on rats born to normally fed and undernourished mothers. When rats born to normally fed mothers were subjected to moderate undernutrition during suckling, no significant difference was seen in the brain weight, nucleic acid content and phospholipid levels. Thus, the pups appeared to be resistant to mild nutritional deprivation imposed during suckling period as it did not alter the brain composition. However, in response to severe undernutrition during suckling period, significant reduction were seen in the body weight, brain weight, nucleic acid content and phospholipid levels of the brain. But, these
significant reductions were not corrected with nutritional rehabilitation during the weaning period.

Similar pattern of changes were also seen when rats born to malnourished mothers were subjected to moderate or severe undernutrition during suckling by increasing the litter size. Also, rats born to and nursed by undernourished mothers in litters of 12 pups per dam had significantly lower brain weight, DNA, RNA content than those nursed in litters of 6 pups per dam (Ahmad and Rahman, 1975). Likewise, Cha et al (1987) observed that when mild IUGR pups were under fed for the first two weeks of life, their brain weights were similar to normally fed control pups with higher DNA content and lower protein:DNA content. However, under fed severe IUGR pups had lower brain weight than normally fed control pups with higher DNA content, lower protein and lower protein:DNA content. This emphasizes on the impact of undernutrition during the critical period of suckling. Thus, severe undernutrition during the critical period of suckling altered the brain composition in both groups of the pups, those who were undernourished and adequately nourished during gestation.

Diaz-Cintra et al (1994) studied the hippocampus of rats born to undernourished mothers who were fed on 6% casein diet. These rats after birth were fed by well nourished mothers who received 25% casein diet up till day 15. Rats were sacrificed by day 15. They observed a drop in the number of neurons, somal size and length of the apical dendrites in the CA3 pyramidal cells of the hippocampus. It is important to note that the pups in this study were nursed by well nourished mothers till day 15. However, as discussed earlier, the critical period of growth lasts from day 10 to 21. This means that the pups did not receive optimum nutrition throughout this vulnerable period and were sacrificed early during this period. This could have influenced the findings of the study.
In simple words, when undernutrition occurs during suckling or if it is continued from the prenatal period in to the immediate postnatal period, it adversely affects the brain growth. Thus, undernutrition during suckling can hamper the brain growth and chemistry.

*Human Studies* - Human studies conducted in late 1960s and early 1970s suggest that severe malnutrition during infancy resulted in reduction in the number of cells in the cerebrum, cerebellum and brain stem (Winick and Rosso, 1969; Winick, 1970). Further, infants with severe malnutrition who died in the first year had reduced amount of total lipid content, cholesterol and phospholipid in the cells (Rosso et al, 1970).

In the previous decade, studies were undertaken to examine the structural abnormalities of brain in infants or children with IUGR and/or those who had VLBW. However all these studies have been done on children who were born preterm. Tolsa et al (2004) studied the brains of prematurely born infants with IUGR and placental insufficiency using MRI. The IUGR infants at birth showed significant reduction in cortical gray matter (CGM) and intracranial volume (ICV) as compared to the controls. In a similar study conducted by Lodygensky et al (2008), it was seen that the total hippocampal volume was significantly reduced in the IUGR group. Hippocampal volume also showed a significant correlation with birth weight \(r=0.507; \ p=0.008\). Furthermore, the head circumference correlated with ICV \(r=0.86; \ p<0.01\) and CGM \(r=0.76; \ p<0.01\) (Tolsa et al, 2004). In the above discussed studies, the participants were born at a gestational age of < 32 weeks. Thus, prematurity and IUGR appears to have a significant impact on the brain development. In contrast to this, Fearon et al (2004) found no significant difference in the whole brain volume, cortical gray matter and hippocampal volume of VLBW adults with the control group. This study however, did not specify if the subjects were born preterm or at term. This probably suggests that preterm babies are more likely to have a sustained structural deficit than the term infants. This implies that the final trimester of gestation is indeed crucial for structural development of the brain.
2.12.3 Effect of IUGR/VLBW/SGA/LBW on Cognitive Functions in Humans

Several prospective studies on cognition have been conducted among children born with IUGR, VLBW, SGA and LBW.

Tolsa et al (2004) and Lodygensky et al (2008) assessed the neurodevelopmental outcomes of the infants at-term using Assessment of Preterm Infant Behaviour (APIB). IUGR infants recorded lower scores than controls in attention-interaction. CGM at term significantly correlated with the attention-interaction capacity ($r=0.45; p<0.05$) (Tolsa et al, 2004). The total hippocampal volume significantly correlated with mental developmental index (MDI) at 24 months corrected age ($r=0.516; p=0.034$) (Lodygensky et al, 2008). Geva et al (2006) found that IUGR born children at nine years had significantly lower digit span ($p < 0.001$), immediate recall ($p = 0.024$) and delayed recall ($p < 0.002$), lower in certain executive functions – visual attention ($p < 0.001$), form fluency ($p < 0.001$) and Tower of London ($p < 0.014$) than the controls at nine years of age.

Aarnoundre-Moons et al (2009) carried out a meta-analysis which highlighted that preterm and VLBW children (< 1.5 kg at birth) had poorer executive functions than the control. In another meta-analysis, Geldof et al (2012) found that children born VLBW had deficits in visuo-spatial abilities and visuo-motor integration. Isaac et al (2000) found that VLBW adolescents at 13.5 years had significantly decreased hippocampal volume than the full term normal birth weight controls. As a result, the adolescents born preterm VLBW had deficits in everyday memory when compared with the controls. Thus, structural deficits that occur in the brain can bear long-term effects on the certain functions of the brain. Lohangen et al (2010) showed that at 19 years of age, 53% of the VLBW and 15% of the normal birth weight participants had low IQ i.e. 1 SD below the mean (OR: 6.4, 95% CI: 2.8 -14.4; $p < 0.001$).
Theodore et al (2009) found marginal decrease in the IQ scores at the age 7 years of SGA children compared to AGA ones \((p = 0.07)\). Ostgard et al (2014) found that SGA-born adolescents had significantly lower visuo-motor and visuo-spatial functions \((p < 0.01)\), lower auditory immediate memory scale \((p < 0.01)\), lower executive functions than the non-SGA participants at 19 – 20 years of age \((p < 0.01)\). Chaudari et al (2012) studied adolescents at the age of 18 years who were born with a weight of < 2 kgs. Preterm SGA children had the lowest IQ than the full term SGA and AGA, though it was within the normal range.

Ittyerah and Mangapalli (2009) reported that LBW infants lagged behind their normal weight counterparts in the domains of – auditory preference, imitation of task and object concept at the age of 4 – 8 months. Lira et al (2009) observed that normal birth weight children scored higher in full scale IQ and performance IQ than the LBW children \((p = 0.05\) and \(p = 0.04\) respectively).

Besides children with lower birth weight or fetal growth restriction, studies have also examined the influence of early stunting (< 2 years of age) on cognitive functions. Crookston et al (2010) studied the longitudinal data of 1674 Peruvian children of the Young Lives study. The children were classified on the basis of their height-for-age Z (HAZ) score as – not stunted, stunted in infancy but not in childhood, stunted in childhood and stunted in infancy as well as childhood. The cognitive functions were assessed at 4.5 to 6 years of age. It was seen that the verbal vocabulary and quantitative score of the not stunted group was significantly higher than the children stunted in childhood \((\beta = -6.21\) and \(-0.91\) respectively) and those who were persistently stunted \((\beta = -10.03\) and \(-0.86\) respectively). Further, Crookston et al (2013) analysed the complete data of 8062 children of Young Lives study (Peru, Ehtopia, Vietnam and India). The schooling and cognitive achievement of the children were assessed at 8 years of age. As compared to those who were never stunted, the Maths scores of the persistently stunted and recovered groups were significantly lower (effect sizes: \(0.22 – 0.48\) and \(0.12 – 0.21\))
respectively). Also, the children who were stunted in childhood and those who were persistently stunted had significantly lower reading comprehension scores (effect sizes: 0.24 – 0.38 and 0.05 – 0.37 respectively).

Overall, children born with IUGR, VLBW and SGA scored lower than the normal birth weight controls in several cognitive function. Some studies indicate that these deficits may last even during adolescence and later. In addition, children who were chronically undernourished (stunted) also had lower cognitive scores and poor academic performance as compared to those who were never stunted. Thus, undernutrition in fetal and early postnatal life i.e. during the critical period were vulnerable to poor cognitive outcomes. Other factors also influence brain structure and function in the postnatal life which include nutritional status and environmental stimulation.

2.12.4 Effect of Undernutrition after the Critical Period on the Brain: Evidence from Animal Studies

Ahmad and Rahman (1975) observed that when the in pups born to and nursed by malnourished mothers in large litters were deprived of protein after the weaning period (postnatal day 21), they had significantly lower brain weight, DNA and RNA content than the controls. On the other hand, post weaning undernutrition in pups born to and nursed by normally nourished mothers, had a fall in the cholesterol content of brain but not the levels of phospholipids. The accretion of sphingomyelin is believed to occur from 10 to 70 days and that of ethanolamine happens till 100 days. The total process of myelination continues throughout the adult life. As a result, absence of nutrition hampered the lipid content of the brain. Furthermore, significant reductions were seen in the RNA content of the brain. It was suggested that the decrease in the RNA content led to reduction in the cell size and resulted in lower brain weight. However, no significant difference was observed in the DNA content as compared to the controls. The lack of difference in the DNA content can be attributed to the fact that cell division in pups in
completed by day 21. Undernutrition induced after this critical period bears no influence on the cell number (i.e. DNA content). Thus, undernutrition post weaning resulted in a decrease in the lipid content and the cell size (RNA content) but not the cell number (DNA content).

Similar effects of post-weaning malnutrition were seen in the pups born to malnourished mothers and suckled by normally-fed mothers. The pups born to malnourished mothers had recovered from the early insult when they were nursed by normally-fed mothers. This suggests that the effects of prenatal malnutrition disappeared with rehabilitation during the suckling period. The brain thus, appears to positively respond to rehabilitation immediately after birth. The suckling period i.e up till day 21 is refered to as the critical period of brain growth in rats. The process of cell division is almost complete by this time and hence no difference was noted in the cell number (i.e DNA content). Thus, post-weaning undernutrition in previously well nourished rats only negatively influenced the cell size and not the cell number.

### 2.12.5 Effect of Nutritional Rehabilitation on Brain Development: Evidence from Animal Studies

Some studies have examined the effect of nutrition supplementation on the brain growth in undernourished rats. The brain being heterogeneous in nature, different regions may be affected differently. It all depends on the cellular events that occur when the stimulus (undernutrition) was active. Ahmad & Rahman (1975) found that rats born to protein malnourished mothers and nursed by well nourished mothers had similar brain weight as compared to controls. Also, there was no difference in the levels of DNA, RNA and phospholipids in their brains as compared to the controls. Cha et al (1987) compared the effect of underfeeding and nutrition rehabilitation up till day 14 from the time of birth in three groups - control, mild IUGR and severe IUGR rats. The brain weight of the adequately fed mild and severe IUGR rats did not differ from that of the control normally
fed rats. This was mainly owing to the increase in DNA and lipid content in the brain cells of IUGR rats. Adequately fed mild IUGR and severe IUGR rats had significantly higher brain DNA content than the control adequately fed group (p < 0.05). Likewise, the lipid content of the brain was significantly higher in the adequately fed mild and severe IUGR rats than their control counterparts. Other indices such as protein content and protein/DNA ratio of cells were significantly lower in the adequately fed IUGR groups than the control. Thus, rehabilitation during the suckling period resulted in catch-up growth in both, mild and severe IUGR rats. This is evident from the fact that their brain weights were similar to the control group. Catch-up growth was mainly manifested in terms of increase in the cell number (DNA content) in mild and severe IUGR though not in cell size.

Bedi (1991) studied the impact of nutritional rehabilitation on rats who were undernourished between 16th day of gestation and 30 postnatal days of age. Nutritional rehabilitation was initiated after 30 days of birth. By 212 days of age, the control group (adequately nourished) had significantly higher number granule cells in the dentate gyrus than the undernourished group. Undernutrition was induced in the prenatal period and lasted through the suckling period (till postnatal day 21) i.e. the vulnerable period. The critical timing of the insult thus resulted in long-term deficit in the total number of dentate gyrus granule cells. In another study, Diaz-Cintra et al (1994) fed female rats with either 6% or 25% casein diet five weeks before conception. After delivery, the pups were randomly cross-fostered to 25% casein-receiving dams. At day 90 and 220, there were significant reductions in the length of the apical dendrites, basal dendritic branching and dendritic spine density in the hippocampus in the pups born to malnourished dams. At the same time, there was significant increase in apical dendritic branching. In this case undernutrition began in the prenatal period and was followed by nutritional rehabilitation. In spite of the rehabilitation, significant structural reductions were noted in certain parameters. This indicates that prenatal malnutrition can have long-term effects on the
developing brain. Nutritional rehabilitation did show positive effects in the branching of apical dendrites. This suggests that the rate of cell division and the pattern of growth is region specific and cannot be generalized (Fish & Winick, 1969).

In another study, previously undernourished rats were nutritionally rehabilitated between 150 to 250 days of age. The number of synapses in the dorsal lip of dentate gyrus was estimated. Findings showed that up to 75 days of age (i.e. prior to rehabilitation) the control group had significantly higher number of synapses than the undernourished group. By the end of the study period, the previously undernourished rats who received nutritional rehabilitation showed significantly higher number of synapses and synapse:neuron ratio than the controls (Ahmed et al, 1987). This suggests that previously malnourished rats were capable of some ‘catch-up’ in the ratio of synapse: neurons post nutritional rehabilitation.

Gressens, et al (1997) studied the effect of early prenatal undernutrition (5% casein diet) imposed during conception and first two weeks of gestation. At the end of the period of malnutrition, the fetal body weight and brain cortical thicknesses were lower than the control. At birth, body weight and brain weight had normalised. Moreover, it was observed that in the prenatally protein-restricted adult animals, all the features of brain growth and development - astrocytogenesis, neuronal differentiation, synaptogenesis and apoptosis had normalized. Thus, it was seen that prenatal protein restriction may induce transient period of multiple alteration in brain size and development. But in spite of this early insult, all the alterations observed early in the fetal life were seen to normalize in the adulthood. This suggests that the brain is capable of enormous plasticity in the postnatal life after an early insult.

2.12.6 Lessons from the Animal Studies

Malnutrition causes a decline in the availability of nucleotides and the enzymes required for DNA synthesis. This therefore, leads to impaired cell division and lowered protein
synthesis (Winick et al., 1972). Animal studies indicate that when malnutrition occurs early i.e. during the period of cell division, it disrupts the process of cell division. In rats, this corresponds to the suckling period. If rats were rehabilitated during this phase, catch-up was evident in certain areas especially cell number and lipid content. However, when malnutrition occurs during this vulnerable period, it can have long-lasting effects. Severe malnutrition during suckling may not be reversed with feeding after weaning. Thus, malnutrition during the critical period can result in irreparable damage to the developing brain. If rehabilitation is initiated after the period of cell division, recovery does not take place. However, if the period of cell division has ended and undernutrition happens later then, there is no effect on the cell number or DNA content of cell. The change that occurs is a decrease in the protein: DNA ratio. But, this change can be reversed on subsequent refeeding (Fish and Winick, 1969). Thus, the brain appears to be responsive to nutritional rehabilitation immediately after birth. So, prenatal undernutrition if corrected in the immediate postnatal period i.e. during the critical period, can result in compensatory brain growth. Therefore, this critical period should be used as a window of opportunity to compensate the previous growth deficits.

2.12.7 Impact of Catch-Up Growth on the Cognitive Functions in Humans

Cognitive deficits pertaining to IQ were seen to be attenuated when the IUGR infants achieved complete catch-up growth (Geva et al., 2006). Geva et al. (2006) observed that academic achievements were much lower in IUGR children who failed to document catch-up growth by the third year of life. Moreover, children whose either height or weight or head circumference caught up but the catch-up growth was not evident in all the parameters (i.e. weight, height and head circumference) performed worse than the children who documented catch-up in all the three parameters at the age of 9 years. Martorell, et al. (2010) analyzed the data on birth weights and weight gain during the first two years vis-à-vis schooling outcomes in five cohorts – Brazil, Guatemala, Philippines, South Africa and India. Stunting at the age of 2 years was associated with reduction in
schooling by 0.9 years and by 16% increased risk of failing in at least one grade in school.

Crookston et al (2013) studied the Young Lives cohort which included 8062 children from Ethiopia, Peru, Vietnam and India. HAZ was calculated at age one and eight years of age. Those who were persistently stunted till 8 years of age and the children who had normal HAZ during infancy but were stunted at 8 years had lower scores in reading-comprehension and receptive vocabulary than those who were never stunted, however no difference was noted in Maths scores of the children.

On the other hand, Crookston et al (2010) found no difference in the in the IQ scores of stunted and non-stunted children at 4.5 to 6 years after adjustment for maternal age, education, preschool attendance, wealth index, number of siblings and area of residence. Sokolovic et al (2014) studied the effect of government subsidized lunch of 300 grams of cooked rice and lentil for a period of six months on children aged 6 – 12 years. At baseline, significant differences were seen in short-term memory (p = 0.023), retrieval ability (p = 0.026), visuospatial ability (p = 0.028) and overall cognitive score (p = 0.006) in the stunted and the non-stunted children. However, no difference was seen in the magnitude of change between the two groups in any of the domains.

In all the studies discussed above, stunting has been used as a measure of nutritional status. This is mainly because stunting is an indicator of chronic undernutrition. It examines the impact of long-term undernutrition on the brain. Most of the studies do support that stunting for extended periods in the postnatal life particularly, beyond the critical period is detrimental for the brain. The critical period of growth for humans begins in the third trimester of pregnancy and continues till two years of life. The deficit in growth if not corrected during this period can adversely affect the brain growth and functions. However, Crookston et al (2010) and Sokolovic et al (2014) failed to document any difference in the stunted and the non-stunted groups. This could be
because along with nutrition, factors such as environmental stimulation also play a pivotal role in shaping up the cognitive functions of the young child.

2.12.8 Impact of ‘Nutritional Supplementation Alone’ on Cognition

Earlier, the relationship between undernutrition and cognitive development was believed to be linear. Researchers assumed that undernutrition in early life caused structural damage to the brain leading to poor cognition. Levitsky and Barnes (1972) conducted experiments on rodents to study the effect of nutrition and environmental interactions on behavioural development. They observed that the malnourished rodents lacked energy, withdrew from the peers and other objects. Mothers of these rodents cuddled them thus preventing further growth and independence.

Based on these observations Pollitt and colleagues (1993) designed a longitudinal study in rural areas of Guatemala, Central America. Pregnant women and children under the age of seven participated in the study received either ‘Atole’ (11.5 g protein; 163 kcals) or ‘Fresco’ (59 kcals) from 1969 – 77. As compared to the infants born to the Fresco group, infants born to the Atole consuming group showed a 69% drop in the infant mortality. Furthermore, growth rates of children under three improved with Atole. These children were again followed up during 1988 – 89 to examine the effects of nutritional supplementation during pregnancy on intellectual development in the long-term. Children who received Fresco grew slowly, experienced gradual recovery from infection as compared to Atole group. In addition, their motor development (for eg. crawling, walking and so on) was hindered resulting in limitations in exploring their physical and social environment. This delayed the acquisition of cognitive skills. Contrary to this, the Atole consuming group grew faster, had low incidence of malnutrition, received more challenges from the physical and social environment which in turn promoted social and cognitive skills. In spite of this, when compared with the children of the middle-income households of the same area, the Atole group did not perform as well as them. The
participants of this study resided under extreme conditions of poverty. Thus, nutritional supplementation alone could not completely compensate for the negative effects of poverty on cognition.

2.13 Role of Environmental Enrichment on the Cognition

The brain is considered to be malleable during infancy and early childhood than later in life. This malleability of the young and immature brain enhances the ability and capacity to learn and overcome the earlier deficits in brain functioning. This is also known as plasticity of the brain (Huttenlocher, 2002). Plasticity is defined as the adjustment of the brain to internal and external milieu. Plasticity has been seen in many neural systems but, is most evident in the immature cerebral cortex. In the cerebral cortex, neural plasticity is more prominent in regions related to higher-mental-processes such as – language, mathematical ability, music and executive functions. On the other hand, areas concerning voluntary motor movements, visual and auditory information processing are said to be less malleable (Huttenlocher, 2002).

In a study, Derrington et al (2003) reported that rats in the ‘enriched environment’ had an increase in the total cortical thickness and length of the cortex as compared to those in the standard condition. The increase in the cortical thickness was attributed to the increase in the nerve cell size, number of cells, dendritic aborization, length of the dendrites, size and number of synapses and length of postsynaptic thickening (Diamond, 2001; Sale et al, 2008). These changes have been observed in the occipital cortex and the visual cortex. There was increase in the hippocampal neurogenesis and decrease in the apoptotic cell death. In addition to this, there was increase in spine densities in hippocampal CA1 pyramidal cells in hippocampus (Diamond, 2001).
Researchers have studied the impact of environmental enrichment (EE) provided up to two years of age on the cognition of children with severe malnutrition (Grantham-McGregor et al, 1980; Grantham-McGregor et al, 1994; Walker et al, 2005; Walker et al, 2010). Stimulation showed marked improvements in the cognition of malnourished children. Follow-up studies evaluated the benefits of providing stimulation at a young age and its effect on IQ, educational attainment during childhood (Walker et al, 2010), middle (Grantham-McGregor et al, 1994) and late adolescence (Walker et al, 2005). Significant improvements were seen in verbal scores, performance IQ and school performance of the malnourished children. Also, these children had fewer behaviour difficulties than the groups that did not receive stimulation (Walker et al, 2010). Similar improvements have been documented when such interventions were used in poorly resourced areas (Eickmann et al, 2003) and when mothers of undernourished babies received the intervention (Powell et al, 2004). Thus, it is clearly evident that early psychological stimulation positively influences and bears long-lasting impact on the cognitive function in malnourished children.

2.14 Gaps in the Literature

The available literature suggests that birth weight and body fat are positively associated while birth weight bears an inverse relation with central adiposity. Strong evidence also exists to confirm the association between birth weight and IRS and CV risk factors. However, much of this association appears to be mediated by postnatal growth which includes both, catch-up growth and catch-down growth.

India not only has a high prevalence of LBW but also of malnutrition in children under five years of age especially in the lower socioeconomic strata. So, it is possible that children born with normal birth weight may become undernourished and those born with low birth weight may continue to remain undernourished during their childhood. Most of
the studies carried out in India have explored the association between birth weight and adiposity and/or metabolic outcomes. They have not really looked at the nutritional status, catch-up growth and catch-down growth of the children in relation to adiposity. These factors may possibly influence their body composition.

Along with LBW, India also has high prevalence of stunting (< 5 years of age). Both, LBW and stunting seem to influence cognitive functions of children. However, not much literature is available about the cognitive functions of LBW children who recover in the postnatal life and normal birth weight children who might experience growth faltering in early postnatal life. Considering the high rates of chronic undernutrition in India, exploring these influences would be worthwhile.