Early Origins of Obesity

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The global epidemic of childhood obesity is a major public health issue. Although a positive energy balance is likely to be a final common pathway for obesity, the determinants of this imbalance are much debated. Secular changes in eating behavior and genetic susceptibility are factors that have received a considerable amount of attention recently. However, programming—the process by which factors acting during early life may have a longer-term effect on health—has been suggested as a further potentially important mechanism that could contribute to the development of obesity (1). For instance, adults born during the Dutch famine whose mothers were exposed to poor nutrition in the first and second trimesters were more likely to be obese (and those exposed in the last trimester, leaner) than their unexposed peers (2,3). The greater propensity to obesity in later life seen in children heavier at birth, and an increase in central fat distribution in those with low birth weight, also suggest that fetal life is a critical window for programming later body fatness (4).

The contribution of the early postnatal environment, and particularly early nutrition, to the programming of obesity, however, has received relatively little attention. An effect of nutrition is suggested by an association between greater weight gain in infancy and a slightly greater risk of obesity as adults (5), and by the finding that breast-feeding is associated with a lower risk of later obesity (6,7). However, although consistent with the hypothesis that nutrition in infancy may influence the later propensity to obesity, these previous studies have rarely followed subjects beyond the age of 7 years (4), and such observational data could be confounded by factors influencing both early diet and later adiposity (4). Nevertheless, experimental data from animal models support this underlying hypothesis: Rats food-restricted before weaning were permanently lighter, regardless of how much food was available after weaning (8), whereas baboons overfed before weaning developed obesity in adolescence and adult life (9).

Despite the strong epidemiologic data, in humans a causal association between early factors such as poor fetal growth or infant nutrition and later risk of fatness has not been established. Paradoxically, recent evidence suggests that intrauterine growth retardation may program lower lean mass rather than greater body fatness (10–12). Also, the mechanisms that link early factors to later obesity have been inadequately researched, although programming of the hypothalamic–pituitary axis,
insulin-like growth factor 1 (IGF-1) concentrations, and, recently, leptin has been suggested to play an important role. In this review we consider the evidence that intrauterine and early postnatal factors influence body composition in later life, discuss the possible mechanisms involved, and suggest possible experimental studies that could help establish a causal association between early factors such as nutrition and later obesity.

FETAL PROGRAMMING OF OBESITY

Fetal Growth

A recent systematic review of the childhood predictors of adult obesity identified 20 reports that suggested an association between greater fetal growth as measured by birth weight and a later index of obesity such as a high body mass index (BMI) (4). More recent reports have confirmed the association between birth weight and BMI (13,14), and this association has now been seen in adults and children, in both developing and developed countries, and appears to be independent of gestation (4).

Birth weight, however, is related to various other factors, such as maternal size, which could explain any association between greater size at birth and later obesity. Studies that attempted to adjust for maternal size have shown inconsistent findings. For example, BMI increased with birth weight only for offspring of mothers with a medium rather than a thin or heavy build (4); and in another study, birth weight of more than 3.5 kg was associated with obesity only in children whose mothers were in the first and second (but not the third or fourth) quartiles for BMI (4). Despite this inconsistency, several studies have now reported an association of birth weight with later BMI that is independent of maternal size. However, as both birth weight and later BMI are likely to share genetic determinants, the critical influence of genetic make-up on the association between birth weight and later obesity remains unresolved.

Socioeconomic status is another factor that could influence both fetal growth and the susceptibility to obesity. Low socioeconomic status is associated with a higher risk of obesity (particularly in women) but with a low rather than high birth weight. Socioeconomic factors could therefore be expected to confound the association between birth weight and later obesity, although several studies have shown this association to remain positive after adjusting for these factors (4). For example, in 17-year-old adolescents, birth weight was associated with a greater risk of later obesity (odds ratio of 2.2 for BMI of more than the 90th centile) after controlling for maternal age, education level, and social class as measured by area of residence (4).

Although most studies have consistently shown a positive association between birth weight and BMI, relatively few have assessed the influence of birth weight on direct measures of adiposity such as skinfold thickness. Compared with these direct measures of fatness, body mass index may not identify obese subjects accurately because at any given BMI there is a large range of percentage body fat. Methods to determine body composition are available, but these techniques have rarely been used to assess the influence of fetal growth on later obesity. Nevertheless, a high birth
weight has been associated with an increase in the sum of triceps, subscapular, and suprailiac skinfolds or of triceps and subscapular skinfolds in children below 5 years of age (4). By contrast, in older subjects and after adjustment for BMI, Barker et al. showed a negative association between birth weight and later skinfold thickness, which would oppose the view that a high birth weight programs a greater risk of later obesity (15). Similarly, Okosun et al., using data from the third US National Health and Nutrition Examination Survey, found that birth weight was negatively associated with subscapular skinfold thickness in white, black, and Hispanic American children (16). In the same study, birth weight was also negatively related to suprailiac skinfold thickness in blacks and Hispanics, and to the sum of four skinfolds (subscapular, suprailiac, triceps, and biceps) in blacks only (16). These observations, which appear to contradict the hypothesis that a high birth weight programs greater adiposity in later life, have been explained by ethnic differences in the association of birth weight and later fat distribution, or by the possibility that poor fetal growth programs more truncal fat. Consistent with this hypothesis, several studies have shown an association between low birth weight and a high subscapular to triceps skinfold ratio in later life (a measure of truncal fat distribution) in both children and adults (4). The mechanisms underlying these associations are unknown but, as high glucocorticoid concentrations are associated with a truncal fat distribution, programming of a greater sensitivity to glucocorticoids by low birth weight has been suggested as one possibility.

Data on the influence of intrauterine factors on visceral fat mass (an established risk factor for insulin resistance and cardiovascular disease), rather than truncal fat, are less consistent. Significant correlations between birth weight and waist-to-hip ratio have been reported in some but not most populations (4). In one study the association between low birth weight and greater waist-to-hip ratio was a consequence of low birth weight predicting a smaller hip circumference rather than a greater waist circumference (13). Furthermore, in the only study to measure visceral fat directly, using computerized tomography, there was no significant association between birth weight and later visceral obesity (17). These recent observations do not, therefore, support the hypothesis that associations between low birth weight and later cardiovascular risk are mediated by programming of greater visceral adiposity.

**Programming of Lean Tissue**

The concept that a greater birth weight may program a high BMI, an established cardiovascular risk factor, contradicts the considerable evidence that a high birth weight is associated with a reduced rather than an increased susceptibility to cardiovascular disease and its risk factors (18) (Fig. 1). One explanation for this apparent discrepancy could be the possibility that low birth weight programs greater visceral fat mass (which would increase the metabolic risk of cardiovascular disease), although the evidence for this hypothesis is inconclusive. Alternatively, as BMI correlates strongly with both total lean and total fat mass, positive associations between birth weight and later BMI could represent programming of lean rather than fat tissue. Consequently,
as muscle is an important site for glucose uptake in response to insulin, a high birth weight could program increased muscle mass and therefore improved insulin sensitivity and a reduced risk of cardiovascular disease.

Recently, several studies have suggested that a favorable intrauterine environment, as determined by greater fetal growth and birth weight, programs greater lean rather than fat mass (10–12). For example, Hediger et al. compared muscle mass (mid-upper-arm circumference and mid-upper-arm muscle area) in children from the third National Health and Nutrition Survey who were born small, appropriate, or large for gestation (11). Children born small for gestation tended to remain smaller throughout childhood, with the discrepancy in weight attributable to differences in lean body mass rather than fat mass. Similarly, adults with low birth weight had lower weight and muscle mass (measured by urinary excretion of creatinine) (10), and birth weight was positively related to thigh muscle and bone area in a study of 192 men aged 17 to 22 years (12). However, although consistent with the hypothesis that a high birth weight programs greater lean mass, these studies were based on regional measures of lean mass (such as the composition of the upper arm or thigh) and not on whole-body composition.

Relatively little is known about the mechanisms underlying the association between birth weight and lean body mass in later life. Barker et al. have suggested that fetal muscle growth may be sacrificed as a consequence of intrauterine stress in order to favor brain development (18). An inadequate nutrient supply in utero would predispose to fetal hypoglycemia and so limit insulin secretion and subsequently increase protein breakdown and decrease protein accretion. Alternatively, genetic factors that predispose to insulin resistance in the fetus could explain associations between low birth weight and insulin resistance (19), and so possibly between low birth weight and lower lean tissue mass in later life. Genetically determined insulin resistance could result in low insulin-mediated fetal growth and therefore a small, thin baby (19). The same genetic factors could lead to insulin resistance in later life and an increased susceptibility to obesity as a consequence of the lower metabolic activity associated with less lean tissue.
In summary, although there is a consistent and positive association between birth weight and later BMI, the concept that fetal growth programs later propensity to obesity rather than body size or lean body mass remains unproven. Genetic factors have a major influence on BMI, and separating these influences from the intrauterine environment has proved difficult up to now. There is some evidence that low birth weight may predispose to a truncal fat distribution, but the evidence suggesting programming of visceral obesity is inconclusive.

Maternal Factors
Associations between several maternal factors known to change the fetal environment and the later propensity to obesity are consistent with the "fetal programming" of obesity hypothesis. As reviewed recently, maternal obesity, diabetes, and pregnancy weight gain have all been linked to an increased susceptibility to obesity in the offspring (20). However, these studies have not been able to isolate the influence of the uterine environment from transmitted genetic factors, which are also likely to have a marked effect on the propensity to obesity.

Suggestive evidence that the intrauterine environment is a critical window for the programming of obesity comes from the Dutch Famine study. Conscripts (aged 19 years) exposed in utero to the famine of 1944–45 during the first half of gestation had a prevalence of obesity of 2.8% (defined as body weight for height in excess of 120%), compared with 0.8% in those exposed in the last trimester and 1.8% in non-exposed men (2). At the later follow-up at the age of 50 years, the BMI of women exposed to famine in early gestation was 7.4% greater than in those who were not exposed, but in men the BMI was unaffected by exposure to famine at any stage of gestation (3). Waist circumference was also greater in women exposed to famine, which suggested that these women tended to deposit fat intraabdominally. Interestingly, there were no differences in birth weight between those exposed or not exposed to famine in early pregnancy, which suggests that intrauterine factors other than those affecting fetal growth contributed to the programming of obesity (3).

As discussed previously (20), several factors prevent a causal interpretation of the link between maternal nutritional deprivation and the later risk of obesity identified by the Dutch Famine study. For example, babies exposed to famine who were less prone to obesity may have had a higher mortality. Also, women who conceived during the famine may have been a selected group (although the association of famine exposure and BMI at age 50 years was unaffected by adjustment for maternal characteristics likely to influence fertility) (3). Furthermore, the role of maternal undernutrition in the programming of obesity has not been confirmed in subjects exposed to famine in utero during the German siege of Leningrad in 1941–44, or from comparable levels of maternal undernutrition from studies in developing countries (20).

Maternal factors known to influence the fetal environment that are less extreme than famine also support the fetal programming of obesity hypothesis. For instance, maternal diabetes during pregnancy has been associated with a greater risk of obesity in the offspring. This association has been shown in at least 11 studies and appears to
be independent of maternal weight or birth weight (20), which is therefore consistent with the hypothesis that the intrauterine environment alters the propensity to obesity independent of genetic factors. The mechanism whereby this occurs remains speculative, but one hypothesis is that chronic hyperinsulinemia or hyperglycemia in the fetus may down-regulate insulin receptors or postinsulin receptor signaling, thereby increasing insulin resistance in the fetus. However, despite these strong associations, a causal link between the intrauterine environment in diabetic mothers and the later risk of obesity in the offspring has not been established. Correcting for maternal weight does not exclude the influence of genes that could affect both the risk of diabetes in the mother and the susceptibility to obesity in the offspring.

Further support for the fetal programming of obesity has emerged from the intriguing association between early cold exposure and an increased susceptibility to obesity (14). Adults who were born in the first half of the year (and therefore exposed to cold in utero) had a greater prevalence of obesity (BMI > 30 kg/m²). The relation between birth weight and adult obesity was also stronger in those born in the first 6 months of the year or following cold winters than in those born in the last 6 months of the year or following mild winters. These observations are consistent with evidence from animal studies indicating that exposure to lower environmental temperatures before or soon after birth promotes the development of obesity in the newborn. The physiologic links between climate and obesity in later life are conjectural, but factors that are sensitive to both temperature and season, such as nutrition, are postulated to be involved.

EARLY DIET AND LATER OBESITY

The hypothesis that diet in infancy (and particularly overfeeding) can program the later risk of obesity has often been considered, but as discussed recently, few studies have addressed the influence of early diet on obesity beyond childhood (4). In one such report, Charney et al. showed that 36% of those whose weight exceeded the 90th centile as infants were overweight as adults, compared with 14% of the average and light weight infants (5). The association between a vigorous breast-feeding pattern, which was associated with a higher energy intake, and greater obesity in later life also supports a role for “overfeeding” in infancy and the later susceptibility to obesity (21). Nonetheless, the role of early energy or nutrient intake on the later susceptibility to obesity remains unproven (4).

Research on the programming of body composition by early diet has focused mainly on whether breast-feeding reduces the risk of adult obesity. Formula-fed infants are larger than breast-fed infants, but whether this contributes to obesity in later life is debated. Although comparatively small studies have not shown any association between breast-feeding and the later risk of obesity (4), several larger cohorts have found that breast-fed infants are less predisposed to obesity in later life. For instance, a protective effect of breast-feeding against obesity was shown in cross-sectional studies of adolescents born in the late 1960s (6) and in a recent cohort of over 134,000 children aged 5 and 6 years from Germany (7). In both studies the protective
effect of breast-feeding appeared to be independent of confounding factors such as social class, which suggested that properties of breast milk rather than lifestyle factors associated with breast-feeding programmed the lower later risk of obesity. Consistent with this hypothesis, a longer duration of breast-feeding was associated with lower subsequent fatness, even after adjustment for socioeconomic status (6). How breast milk intake protects against subsequent fatness is debated, but one hypothesis is that higher insulin concentrations in infants who are formula-fed could stimulate fetal fat deposition and the early development of adipocytes.

MECHANISMS

Proposed mechanisms for the programming of obesity fall into two broad categories: (a) the influence of genes on the relations between early factors and later risk of obesity, which is strongly supported by data from twins (22), and (b) the effects of the fetal and early postnatal environment. As reviewed previously (23), it has been suggested that environmental influences on the programming of obesity act either at the level of the fat cell or as a consequence of abnormalities of hypothalamic function (3,23).

The fat cell theory, which proposes that overnutrition in late gestation and early postnatal life (e.g., as a consequence of maternal overweight or fetal hyperinsulinemia in the offspring of diabetic mothers) affects either adipose cell number or metabolism, is supported by an extensive animal literature (20,23). As comprehensively reviewed (24), adipose cell development in utero is regulated by a complex interaction of maternal endocrine and paracrine influences that could affect the tendency for later obesity. For example, the offspring of pigs with experimentally induced diabetes have been shown to have an increased number and size of lipid-containing adipocytes and a 40-fold increase in fetal adipose tissue lipogenesis. There are, however, few data to support the in utero programming of adipocyte number or function in humans (24).

By contrast, there is some preliminary evidence that the intrauterine environment could program hypothalamic function in humans. Fetal undernutrition has been suggested to program higher growth hormone or IGF-1 concentrations in later life (18). This programming of the hypothalamic–pituitary axis could then affect adipocyte cell function. Further, Ravelli et al. have proposed that maternal energy deprivation could affect fetal hypothalamic development and impair later appetite regulation (3). Leptin, a key regulator of appetite and body fatness, has been suggested as a potential candidate for this hormonal programming (25).

Programming of Leptin Concentrations

Obesity in humans is associated with a high leptin concentration relative to fat mass, leading to the concept that resistance to the actions of leptin could impair appetite regulation and so predispose to obesity. Associations between low birth weight and higher leptin concentrations relative to fat mass are consistent with the hypothesis
that programming of leptin physiology, and specifically greater leptin resistance, is one mechanism for the early origins of obesity (25). Studies in rats that showed that a hypercaloric diet early in postnatal life programmed greater leptin resistance (26), support this hypothesis and suggest that the critical window for the programming of leptin physiology may extend beyond the fetal period.

As being overweight in infancy might increase the later risk of obesity, we tested the hypothesis that a higher nutrient intake in infancy programs greater leptin concentrations relative to fat mass in humans (Singhal A, et al., in press). Also, as breastfeeding rather than formula feeding is associated with a lower susceptibility to obesity, we explored the hypothesis that breast milk consumption is associated with lower leptin concentrations relative to fat mass in adolescence. A cohort of children randomized at birth to a nutrient-enriched or standard diet provided a unique opportunity to test our hypothesis in an experimental study with prospective follow-up (27).

The participants were born preterm in the early 1980s and had been randomized at birth in two trials to a nutrient-enriched preterm formula versus banked donated breast milk, or preterm formula versus standard formula (27) (Fig. 2). A representative subgroup of 216 children was followed up at age 13 to 16 years to assess the impact of early nutrition on cardiovascular risk factors, obesity, and leptin concentrations. Serum leptin concentrations were measured by a radioimmunoassay, and fat mass was estimated by bioelectric impedance analysis (N = 197).

Combining trials 1 and 2, as originally planned, we found the ratio of leptin to fat mass was significantly greater in children randomized to nutrient-enriched preterm formula at birth (geometric mean 0.84 μg/l/kg) than in those randomized to standard formula or banked breast milk (0.62 μg/l/kg), the mean difference being 30.8% (95% confidence interval [CI] for difference, 8.4% to 53.2%; p = 0.007). Similar observations were obtained for the ratio of leptin to percentage fat mass. The difference between randomized dietary groups remained significant after adjustment for age, sex, Tanner stage, social class, and fat mass. Human milk intake was associated with lower leptin concentrations relative to fat mass in adolescence (regression coefficient, −0.3% change per 100 ml increase in human milk intake; 95% CI, −0.6 to −0.04%; p = 0.023) (Fig. 3), independent of potential confounding factors. There were, however, no differences in total fat mass between randomized groups.

Given the experimental design, our observations strongly supported an influence of early diet on later leptin concentrations. Leptin concentration relative to fat mass was 30% greater in children randomized to a nutrient-enriched preterm formula at birth than in those randomized to one of the two standard diets, and this difference was independent of population differences at birth or in adolescence. However, unlike previous studies in children born at term, low birth weight in our preterm cohort was not related to relative hyperleptinemia in adolescence, possibly because the programming of leptin concentrations by antenatal factors such as obesity differs according to the timing of the in utero insult. Alternatively, the association between birth weight and later leptin concentrations may be disturbed by relative hyperleptinemia in adolescence, which could also explain the higher leptin concentrations relative to fat mass in our study compared with data from adults.
FIG. 2. Follow-up at age 13 to 16 years of children randomized at births to different diets. A: Trial 1 banked breast milk versus preterm formula. B: Trial 2 term formula versus preterm formula. A, Subjects receiving assigned milk as sole diet; B, Subjects receiving assigned milk as a supplement to mother’s expressed breast milk.
FIG. 3. Geometric mean (95% confidence interval) of leptin concentration relative to fat mass according to thirds of percentage human milk intake (from lowest to highest, 1–3).

We postulate that programming of leptin physiology could be one mechanism that links early nutrition with a later propensity to overweight or obesity. Although adolescents previously fed the nutrient-enriched diet were not fatter at 13 to 16 years of age, the tendency for excess weight gain in some nonobese populations with high leptin concentrations at baseline (25) suggests that they are at higher risk of becoming obese in adult life. Whether they will become so is a key aspect for further follow-up. Nonetheless, it seems likely that factors acting in childhood may promote obesity in early adulthood (4). We postulate that insensitivity to leptin in individuals who received a nutrient-enriched diet could program the commonest onset of obesity, which is that seen in early adult life. Lower leptin resistance in infants fed human milk could also provide one potential mechanism for the long-term benefit of breast-feeding on adiposity.

Possible Mechanisms

We postulate that higher leptin levels associated with greater body fatness early in postnatal life program the leptin-dependent feedback loop, such that the regulation of body fat is less sensitive to leptin in later life. The physiologic mechanisms for this could involve down-regulation of hypothalamic leptin receptors or postreceptor effector mechanisms—analogous in animal studies to the up-regulation of hypothalamic leptin receptors when there is a lack of functioning leptin (28), or to the greater expression of receptors within the hypothalamus of feed-restricted versus well-fed ewes (probably caused by down-regulation of leptin receptors in well-fed ewes) (29). Therefore if exposed to an environment favoring a positive energy balance, these individuals will be more susceptible to greater body fatness, particularly when there is physiologic leptin insensitivity and an increase in body fat, such as at puberty.
FUTURE STUDIES

The Need for Experimental Studies

Previous studies of the early origins of obesity have been based on retrospective and observational data and so could suffer from the problems of confounding and selection bias. These studies have also relied on measures of body size (e.g., BMI) rather than direct measures of fat mass. There is a clear need therefore for interventional studies that use an experimental design to control for potential confounding factors, and for studies that use sophisticated measures of body composition (e.g., the four-component model of body composition). Also, different compartments within the whole-body fat mass should be better identified, (e.g., by using magnetic resonance imaging to measure visceral adiposity directly). Finally, as programming effects may amplify with age and be most marked after puberty, subjects should be followed beyond childhood (4). For instance, in one of the few experimental studies of the programming of obesity, Morley and Lucas found no significant difference in skinfold thicknesses or body mass index in children randomized to a nutrient-enriched or a standard diet (27). However, the lack of any influence of early diet on obesity at age 7 to 8 years in that study is consistent with both animal data (9) and our own data for blood pressure in the same cohort, which suggest that programming effects may not emerge until after puberty.

Studies in Twins

The observation that the BMI of monozygous twins raised apart is strongly correlated despite their markedly different postnatal environments suggests a large genetic component to the development of obesity. Genetic factors are likely therefore to be the major confounder of data that support the early origins of obesity hypothesis. Studies in twins discordant for birth weight could, however, provide a unique approach to test the influence of the fetal environment on later adiposity that is independent of genetic and postnatal environmental factors. In one such study, in monozygous twins discordant for birth weight, the between-pair differences in birth weight correlated with between-pair differences in adult height but not with adult BMI (30). This study therefore did not support the intrauterine environment as critical to the programming of later whole-body adiposity, although programming of specific fat compartments such as visceral fat, which may be relevant to the development of cardiovascular disease, could not be excluded. On the other hand, this study was consistent with the hypothesis that factors acting in utero may program lean body mass in later life. Further studies in twins could therefore help elucidate the influence of fetal factors on later body composition.

CONCLUSIONS

Much preliminary evidence suggests that factors acting in utero and early in postnatal life program the later susceptibility to obesity. However, a causal association
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between early factors and later susceptibility to obesity has not been established owing to a lack of experimental data in humans. The influence of early factors on whole-body composition, rather than just BMI, and the relative contribution of environmental and genetic factors to the early origins of obesity also remain unknown.

At present, the contrasting associations between birth weight and the later risk of obesity compared with other cardiovascular risk factors (such as insulin resistance), and our lack of understanding of the physiology of programming of obesity, prevents the implementation of soundly based intervention strategies. However, given the growing evidence that the association between low birth weight and an increased propensity to cardiovascular disease may be most marked in those who become obese (18), further research on the early origins of obesity is now of the highest priority.

REFERENCES


DISCUSSION

Dr. Dietz: You referred to intraterine exposure of infants to cold being associated with a higher prevalence of later obesity. My interpretation of those same studies is the opposite, that it is the postnatal exposure to cold that is associated with a greater likelihood of leanness. That would make more sense from a physiologic point of view because of the potential role of programming brown fat in early childhood. In fact, at one point Danforth in the USA was arguing that all infants should be exposed to cold for a week, and if we did that, we would reduce the prevalence of obesity!

Dr. Singhal: The data I was referring to were published by Phillips et al. in the International Journal of Obesity (1). They showed that children born in the first half of the year—whose mothers were therefore exposed to the cold of the winter—had a higher risk of obesity in later life. They also showed that children who were born heavier in the first half of the year after a cold winter had a stronger association between birth weight and an increased risk of obesity. Thus the effect seemed to be related to cold exposure in pregnancy rather than postnatally.

Dr. Dietz: I also have a comment relating to the earlier discussion about the effects of low birth weight. We need to determine the potential role of reduced birth weight in the complications of obesity at lower BMIs. We must investigate the prevalence of those complications and adjust for birth weight in the target populations, or else exclude individuals with low birth weights from the analyses, so that we can compare the effects of birth weight or subsequent weight gain in normal-birth-weight populations on the risk of later complications of obesity. This is an area where we need much more sophistication so that we can begin to separate the prenatal and postnatal influences.

Dr. Singhal: I completely agree. One thing that’s often forgotten about the fetal origins of adult disease hypothesis is that it’s not just low birth weight that is associated with an increased risk of cardiovascular disease—it’s the interaction between low birth weight and “Western” factors, Western diet, increased obesity, and so on. It is the combination of the two that is
important. This is a factor that discriminates between the data from developing countries and those from developed countries. Up to now the developing countries have not been much exposed to Western-type adult risk factors.

Dr. Endres: I always have problems with the term imprinting. Could you explain it?

Dr. Singhal: I can try. Three terms have been proposed: imprinting, entrainment, and programming. There has been active debate about which of these is the most appropriate. From my experience as a user rather than a creator of terminology, I don’t have a preference. All three mean the same thing to me: what they imply is that factors acting during critical windows may have a long-term influence, and there may be a period when an influence of these factors is not evident.

Dr. Koletzko: Your data on leptin resistance were fascinating. It appeared to me that in the two graphs you showed, the relative effect was about similar between the highest and lowest tertile of human milk consumption and what you called standard diet and high-nutrient diet. Do you have any indication about whether this is primarily an effect of nutrient intake—in other words, high or low energy, protein, and so on—or do you think it is an effect of human milk per se. So if you compare the human milk group to the term formula group, do you see a difference?

Dr. Singhal: The means for human milk and term formula were very similar, but the individuals who received the most human milk on an epidemiologic basis had lower leptin concentrations. It is hard to say whether the effect is related to protein, energy, or some other nutrient because the preterm formula was mainly enriched with protein, but it also had extra energy.

Dr. Koletzko: The different diets would be associated with different rates of growth early on and different times of discharge from hospital. Is it conceivable that those factors could be the primary cause?

Dr. Singhal: We looked at differences in growth and they did not explain the findings. In fact, when we used a regression model to correct for growth, the data stayed quite robust.

Dr. Dulloo: There appears to be some controversy about the effects of low and high birth weight on later obesity. I’m sure it must have crossed your mind that there may be a U-shaped relation between birth weight and later obesity, with two quite different mechanisms. The metabolic complications are certainly quite different, depending on whether obesity was associated with high or low birth weight. What is your opinion on that?

Dr. Singhal: The programming-of-obesity hypothesis is in its really early days. We don’t have good data on fat mass as opposed to BMI, which is a real problem. I personally don’t believe in a U-shaped distribution effect because the association between low birth weight and an increased risk of central obesity occurs all across the spectrum and does not change between the lowest and highest birth weights. Similarly, the associations between high birth weight and later high BMI have been seen in 20 populations and are always there. One possible explanation for this, though I don’t have any data to back it up, is that you are programming lean tissue rather than adipose tissue. That may seem a controversial statement, but fat mass and lean tissue correlate so strongly with each other that you may not actually be programming obesity.

Dr. Dulloo: I’m glad that you mentioned the need for mechanistic studies, and we certainly need mechanistic theories. When we talk about low birth weight and later obesity, there is a big element of catch-up growth in between—catch-up fat growth basically. Widdowson showed that if you restrict food for a short period in normal-birth-weight animals there was not much tendency to develop obesity later, but if you restrict intake for longer periods, then you do see a higher body fat later. It seems that earlier (intrauterine) malnutrition simply exacerbates the catch-up fat growth.
Dr. Singhal: I don’t agree with your interpretation of the McCance and Widdowson data. It was not the duration of nutrition restriction that was important, it was the timing (2). If you restrict food intake before weaning, these animals will stay small, however much nutrition you give them afterward. But if you reduce food intake at any time after weaning, then they will catch up when refed. Their data had nothing to do with birth weight or with the duration of restriction; it was the timing of the restriction that introduced the concept of critical windows. However, I do agree that it is important to investigate catch-up fat growth.

Dr. Cai: Where a baby is born with a high birth weight, is there any evidence that prolonged breast-feeding could reduce the risk of a high BMI in later life?

Dr. Singhal: I don’t know of any evidence that breast-feeding for a prolonged period can influence the later risk of obesity. There is a well-known hypothesis that breast-fed babies regulate their diet better than bottle-fed babies, because of the cultural tendency to insist that a baby finishes the bottle, or because bottles are given whenever the baby cries. To what extent that contributes to long-term BMI I can’t say. I’m a strong advocate of breast-feeding irrespective of the obesity data, but could not say whether long-term breast-feeding would reduce later risk of obesity.

Dr. Srivastava: Babies of low birth weight are not a homogeneous group. There are many different causes of low birth weight. Do such babies behave in a uniform way in terms of later risk? In particular, is there a difference between babies born prematurely to normal mothers and those born small because of maternal malnutrition, which is much more common in developing countries?

Dr. Singhal: I think this is a controversy that continues to run in the fetal programming and adult disease hypothesis. Is it low birth weight per se that’s important, or is it low birth weight relative to gestation? There have been letters going to and fro in Lancet, with people arguing both stances. I personally believe the low birth weight for gestation situation is much more important—in other words, it is the growth-retarded baby who is at increased risk of later cardiovascular disease and complications. That is my personal opinion, and I have data to support that view (3).

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