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REVIEW

Early-life nutritional programming of longevity

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Available data from both experimental and epidemiological studies suggest that inadequate diet in early life can permanently change the structure and function of specific organs or homoeostatic pathways, thereby 'programming' the individual's health status and longevity. Sufficient evidence has accumulated showing significant impact of epigenetic regulation mechanisms in nutritional programming phenomenon. The essential role of early-life diet in the development of aging-related chronic diseases is well established and described in many scientific publications. However, the programming effects on lifespan have not been extensively reviewed systematically. The aim of the review is to provide a summary of research findings and theoretical explanations that indicate that longevity can be influenced by early nutrition.

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Introduction

Traditionally, gerontological research has tended to focus on adult lifestyle as the main determinant of aging rate and longevity. However, available data from clinical, experimental and epidemiological studies suggest that aging-associated chronic diseases may have their origin during early life.[1–3] Evidence is growing that early nutrition is a key factor affecting adult health status. The inadequate diets during critical developmental periods was found to cause permanent structural and functional changes of several organs, and therefore it can lead to long-term consequences on individual's health.[4,5] Early-life nutritional programming of age-related pathological conditions was reviewed in many publications.[5–7] To date, however, there are only few reviews that have focused on demographic consequences of developmental programming, such as the impacts on mortality and life expectancy.[8,9] The aim of this review is to provide a summary of research findings and theoretical explanations that indicate that longevity can be influenced by early nutrition.

Current concepts and mechanisms of developmental metabolic programming

To date, a set of hypotheses and concepts were suggested to explain the link between early-life nutritional conditions and adult health status and longevity. According to the 'programming' concept,[10] adverse events during early developmental stages can permanently program structures and functions of the organism, and cause poor productivity and metabolic dysfunction throughout the organism's lifespan and even across generations.[11,12] Nowadays, the epigenetic mechanisms of developmental plasticity are mainly in focus.[13] In the following sections, a brief summary of modern concepts and proposed mechanisms linking early nutritional exposures to adult diseases are presented.

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'Thrifty phenotype' hypothesis

In 1962, James Neel proposed the 'thrifty genotype' hypothesis, according to which the same genes that helped our ancestors survive occasional famines are now being challenged by modern life conditions, in which food is plentiful.[14] In 1992, Hales and Barker introduced the 'thrifty phenotype' hypothesis,[15] suggesting that, if the fetus is undernourished, long-term hypoglycemia can lead to fetal glucose, conserving adaptation consisting of decreased insulin secretion and increased peripheral insulin resistance, thus redirecting more glucose to especially vital organs, such as the brain, and less to other organs, such as the endocrine pancreas. It results in long-term adaptive changes such as reduced insulin secretion and insulin resistance that may improve survival in conditions of postnatal nutritional deprivation. However, if dietary conditions predicted *in utero* and actual conditions experienced in subsequent life are mismatched, it may subsequently lead to different aspects of metabolic syndrome and ultimately shorten the lifespan.[16,17] Several studies clearly show that epigenetic regulation is a key mechanism linking nutritional insults in early life to type 2 diabetes (T2D) development.[18–20]

'Catch-up growth' hypothesis

More recently, a 'catch-up growth' hypothesis has been proposed, postulating that poor fetal growth followed by rapid postnatal catch-up growth is associated with some aspects of subsequent metabolic syndrome, such as insulin resistance, hypertension and dyslipidemia, and high risk for non-alcoholic fatty liver disease (NAFLD), T2D and cardiovascular disease (CVD) in adults.[21] For example, in a Finish cohort, men who

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had low birth weight, but whose weight caught up so that they had a standard or above standard body mass from the age of 7 years, had elevated death rates from CVD.[22] Catch-up growth is assumed to allow to survive till a reproductive age but has a negative effect on lifespan.[23]

Epigenetic (re)programming of metabolic status

The epigenetic mechanisms regulating gene activity are currently thought to play a central role in linking early-life events with adult health and disease. Epigenetic modifications including DNA methylation, histone modifications and non-coding RNA-based mechanisms are heritable but reversible changes that affect gene expression without altering the underlying DNA sequence. Aging process is known to be linked to increased stochastic deregulation of gene expression caused by errors in maintaining the established epigenetic patterns ('epimutations').[24] Evidence continues to accumulate that epimutations are crucially important as causal factors in aging-associated disease onset and progression.[25,26] However, most of the detectable epigenetic modifications are systematic, and DNA responds to environmental challenges by modifying its epigenetic status in an adaptive manner, to maintain a proper functionality.[27] The aging process is characterized by both genome-wide hypomethylation and promoter-specific hypermethylation.[28] Generally, DNA hypomethylation leads to genome instability, whereas promoter hypermethylation can suppress the expression of tumor-suppressor genes. Such age-related methylation changes can modify the normal gene responsiveness to environmental signals, in turn contributing to generalized failure of homeostasis.[29]

Epigenetic modifications occur throughout the whole individual's life course. It has been found that 'epigenetic drift' is genome-wide, suggesting a global epigenetic deregulation with age.[30] Twin studies have provided evidence that epigenetic patterns diverge in monozygotic twins as they become older. The epigenetic patterns diverge with age in all monozygotic twins studied; however, those who had divergent lifestyles were shown to be the most epigenetically dissimilar.[31] These results suggest that epigenetic divergences that occur throughout the lifetime are solely not because of stochastic epigenetic drift, but can be directed by environmental signals. There are, however, specific developmental stages when the epigenetic landscape is more labile than it is during adulthood.[32] Epigenetic marks are established early in development and stably maintained throughout the organism's life. In mammals, the predominant epigenetic modifications occur during gametogenesis and early embryogenesis.[33,34] In human beings, the period of epigenetic plasticity extends from preconception to early childhood.[35,36] Increasing evidence has accumulated, indicating that epigenetic marks influenced by early-life nutrition can determine the subsequent appearance, stress response, behavior and the organism's longevity.[36,37] The genes associated with energy utilization are likely candidate genes to maintain epigenetic memory of early dietary conditions. The gene encoding leptin, a hormone-regulating appetite and energy homeostasis, seems one of the best thrifty gene candidates.[20] A role of the leptin gene in epigenetic programming of metabolic dysfunction was shown in a study by Bouchard *et al.*,[38] which has demonstrated that the placental level of DNA methylation of this gene was correlated with the glucose level in women with impaired glucose tolerance. The authors hypothesized that maternal hyperglycemia can lead to DNA demethylation of fetal leptin gene and to higher leptin level in adulthood, thereby contributing to both leptin resistance and obesity development.

Intrauterine endocrine programming

The endocrine system is considered to be substantially contributed to developmental programming processes. Undernutrition, along with other fetal stresses, leads to intrauterine growth restriction (IUGR) and alters fetal concentrations of many hormones including insulin, growth hormone (GH), insulin-like growth factors (IGFs), glucocorticoids, leptin and thyroid hormones.[39] An accumulating body of animal and human studies suggest that IUGR can permanently change the GH/IGFs axis that plays a fundamental role in cell differentiation and somatic growth, as well as in the organism's metabolism and survival.[39] These processes are thought to involve complex interrelations among insulin, GH, IGFs and insulin-like growth factor-binding proteins (IGFBPs). Fetal insulin and IGFs play a crucial role in fetal growth, and the IGFs and IGFBPs are shown to be nutritionally regulated in the fetus.[40] For example, subjects born small for gestational age had lower serum IGF-1 and IGFBP-3 levels in adulthood than those born appropriate for gestational age.[41]

Insulin activates the signaling pathways affecting longevity, primarily by influencing cell proliferation and apoptosis. In addition, insulin resistance contributes to the formation of reactive oxygen species and proinflammatory conditions. Insulin resistance may also be related to the telomere shortening, another key regulator of longevity.[42] *In utero* programming of the GH/IGF axis has been suggested as a candidate mechanism to explain the association between birth weight and adult disease,[43] and IGF-1 signaling is likely an important pathway implicated in aging and longevity.[44,45] Higher levels of IGF-1 may increase risk of some cancers during adulthood, including breast, colorectal, lung and prostate tumors,[46] and reduce the risk for T2D and CVD.[47] Recent animal evidence indicates that IGF-1 decreases the atherosclerotic burden and increases stability of atherosclerotic plaques. Potential mechanisms include cell apoptosis, reduction in oxidative stress, proinflammatory signaling and endothelial dysfunctions induced by IGF-1.[48] Low birth weight infants have low levels of IGF-1,[49] high risk for insulin resistance and T2D,[50] ischemic heart disease,[51] cognitive decline[52] and osteoporosis[53] in adulthood. The low birth weight followed by accelerated catch-up growth during early childhood is associated with lower adult IGF-1 levels, and it may be an important pathway linking early growth to adult hypertension, insulin resistance and CVD.[54]

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Such pattern, on the contrary, can be associated with decreased risk for some cancers.[46]

Consistent evidence suggests that reduced IGF-1 levels in early life are associated with extended lifespan in rodents and invertebrates.[44,55] In humans, reduced IGF-1 levels are linked to higher adult morbidity owing to increased risk for CVD, T2D, neurodegenerative pathology and osteoporosis, and with decreased risk for cancers. Recently, the effect of reduced GH/IGF-1 activity on human longevity was also confirmed. In a study by Milman *et al.*,[56] it has been found that low IGF-1 levels can determine the life expectancy of nonagenarians.

Demographic and epidemiological evidence

Substantial epidemiological evidence supports the idea that inadequate nutrition early in life plays a role in risk for disease in adulthood. Early work in this field focused on the link between intrauterine undernutrition and risk for chronic degenerative diseases during adulthood. The 'fetal origins of adult disease' hypothesis proposed by David Barker in the 1990s was based on the observation that small size at birth is related to increased risk of CVD in adulthood.[4] Since then, it has been repeatedly demonstrated that catch-up growth, by which infants with low birth weight reach or exceed normal body weight in later life, is linked to different aspects of adult metabolic syndrome,[57] and the risk for death from CVD in adults.[22] Furthermore, the relationship between low birth weight and some other adult diseases such as osteoporosis[58] and depressive disorder[59] was also found.

While the 'fetal origins of adult disease' hypothesis has focused on fetal growth restriction, fetal overnutrition also results in a series of central and peripheral neuroendocrine responses that program fat cell development and appetite regulation, and large-for-gestational age infants are also at increased risk for T2D, obesity and CVD.[60]

On the basis of 'small baby syndrome' hypothesis, it was assumed that the relation between birth weight and T2D is inversely linear, implying that high birth weight causes decreased risk.[61] The relationship between low birth weight and T2D is, however, not linearly inverse but rather U-shaped, and high birth weight is associated with an increased risk of T2D to the same extent as low birth weight.[62] Evidence also showed that high birth weight is linked to an increased risk for breast cancer.[63] Intrauterine exposure to higher levels of growth factors was proposed as underlying mechanism, increasing both cell proliferation and birth weight and causing increased risk for cancer in later life. For example, in a Danish cohort, the association of birth weight with cancer increased linearly, whereas the association with CVD and all other causes was U-shaped, with increased risk for premature death in adults born with both the lowest and highest birth weights.[64] Thus, although birth weight is commonly used as an indicator of the early-life environment because of its relative simplicity, there is a growing recognition that birth weight alone may be 'a dreadful marker' of prenatal etiologic pathways.[65] Therefore, other indicators are necessary, and it can be assumed that more relevant evidence can be found in natural experiments, that is, naturally occurring circumstances in which different subpopulations have different levels of exposure to assumed causal factors.[66]

Early exposure to famine and late-life mortality

Early-life famine exposure has numerous desirable features for its use as a natural experiment. The cohort-based approach provides evidence of the effects of famine on long-term health outcomes. The best known research in this area is the Dutch famine ('Hunger Winter') study. The Dutch famine was a severe famine that affected the western Netherlands during the German occupation from November 1944 to May 1945.[67] Since the mid-1990s, it has been repeatedly shown that prenatal exposure to this famine is associated with various adult metabolic and mental disorders, including higher body mass index, elevated plasma lipids, and increased risks for obesity and CVD, which may be a sign of accelerated aging.[68,69] Consistent data were obtained in research on other famines, such as the Ukrainian famine of 1932–1933[70] and the Chinese famine of 1959–1961.[71]

Several demographic studies indicated inconsistent associations between early-life exposure to the famine and survival in later life. The women affected by the Dutch famine of 1944–1945 in early gestation had a higher overall, cardiovascular, cancer and breast cancer mortality risk compared with unaffected ones.[72] No effects were detected in men exposed to the famine in early gestation. An analysis of the Dutch Potato famine of 1846–1847 showed higher late-life mortality in cohorts born during the famine.[73] Men and women lost 4 and 2.5 years of life after the age of 50, respectively, after exposure to the famine at birth. However, other studies, including those on the Dutch famine of 1944–1945,[74] the Ukraine famine of 1932–1933,[75] the Finnish famine of 1866–1868[76] and the Chinese famine of 1959–1961,[77,78] have failed to find any effects of early-life famine on mortality in later life. In most cases, cohorts exposed to the famine during early life continued to exhibit a higher mortality compared with those not exposed to the famine not long after the end of the famine; hereafter, the differences in mortality between cohorts might return to a normal level or even become reversed over time. Such 'mortality crossover' pattern is usually considered as an evidence for both debilitation and selection effects.[78,79] The debilitation effect refers to the possibility that undernutrition along with other negative conditions such as disease, stress, etc. experienced in early life may influence the lifetime health and mortality in those individuals who survived the famine. The selection effect refers to the possibility that, as a consequence of the famine, weaker members of the famine-exposed cohort die, whereas famine survivors are stronger, and therefore have reduced mortality risk later in life. In addition, it is necessary to consider that, in a famine-exposed cohort, the conception rate may be reduced, and life-course survival, from prenatal stages through adulthood, may be affected.[80–82]

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Several studies used business cycles as an indicator of early-life economic adversities that are obviously associated with nutritional status. A significant negative effect of early-life economic conditions on mortality rate at older age was observed in the Danish population.[83] If the economic performance in the birth year exceeded the trend value (i.e. during the favorable business cycle), it lowered the mortality rate later in life. More recently, the significant negative effects of poor economic conditions around birth on the cardiovascular mortality rate at older age have been also found.[84]

The biological mechanisms underlying links between malnutrition during early life and adult health status may involve the persistent epigenetic changes.[67] Exposure to the Dutch famine during early gestation resulted in significant demethylation of the IGF-2, a gene that plays an important role in human development, than their controls.[85] More recently, this exposure was shown to be associated with methylation levels of six of the candidate loci implicated in growth, and metabolic and cardiovascular complications in later life.[86]

Early-life seasonal programming of longevity

The month of birth is a good instrument for the study on effects of early-life exposures on adult health outcome, independently of life-course factors. In the last few decades, there were significant nutritional differences between seasons. Such differences in access to quality food supply may likely influence fetal development, depending on the month of gestation. Over the past 20 years, seasonality of birth was shown for many aging-related pathological conditions, such as high systolic blood pressure,[87] obesity,[88] T2D,[89] coronary heart disease[90] and cancer.[91,92]

The dependence of human longevity on the month of birth was shown in different countries around the world.[93] Women from European aristocratic families born in May lived 3.61 years longer compared with those born in August.[94] In Austria and Denmark, autumn-born people live longer than those born in spring; in the Southern Hemisphere (Australia), the pattern was shifted by half a year: average age at death was minimal in autumn-born individuals, and peaked for spring-born.[95] Longevity was strongly linked to the season of birth in Ukraine.[96] The seasonal patterns were very similar in both men and women, with lowest values in subjects born in April–July, and highest in individuals born at the beginning and end of the year. Minimum and maximum values of age at death differed by 2.6 years in men and 2.3 years in women. For all major death causes, the individuals born in the fourth quarter had highest mean age at death. In Germany, individuals born in May–July had the lowest age at death, whereas those born in October–December had the highest, supporting earlier findings.[97] In Greece, significantly increased birth weight, gestational age and longevity in individuals born during the autumn and winter seasons were obtained.[98] Month of birth of centenarians born in the United States in 1880–1895 had strong effect on survival to age 100: siblings born in September–November had higher odds to become centenarians compared with siblings born in March.[99] The season-of-birth patterns for mortality rates after the age of 60 were shown for historical cohorts of French Canadian women born before 1750.[100] Among individuals born in 1800–1870 in Minorca Island (Spain), summer births had a lower risk for death after the age of 15.[101] Among the major US league baseball players, those born in November had the greatest longevity, whereas those born in June had the shortest lifespans.[102] Rural African people born during the annual nutritionally debilitating hungry season (July–December) in three Gambian villages were up to 10 times more likely to die prematurely in young adulthood.[103] In a nation-wide Swedish study (n = 6,194,745), the lowest mortality rates were observed in individuals born in November, and the highest rates in those born in the spring/summer, peaking in May for the mortality >30 years and in April for the mortality >50–80 years.[104]

Several plausible causal mechanisms were proposed to explain the phenomenon of the seasonal programming of human lifespan. Among them, the seasonal variation in nutrient intake likely plays the most prominent role,[105] although other factors such as environmental temperature,[98] sun exposure[106] and infections[107] during prenatal and early postnatal periods may also be involved.

Mechanistic insights from animal models

Given the difficulties linked to showing robust associations between early-life nutritional environment and late-life health and longevity, there is a need for carefully controlled studies that can establish the biological plausibility of developmental programming of life-shortening diseases. A broad array of animal models of both undernutrition and overnutrition during gestation has been developed, allowing direct evaluation of the capacity for early-life dietary factors to program the rate of aging and longevity, with full control over the dietary manipulations, as well as genetic factors and other confounders.

Metabolic programming: an impact on longevity

Post-weaning dietary restriction is well known to be linked to reduced age-related disease, slower aging and life extension in many simple model organisms and rodents.[108] However, the effects of pre-weaning dietary restriction have not been so well studied. In an attempt to understand the molecular mechanisms underlying the link between early growth restriction and later-life disease, a number of models were developed using controlled maternal calorie, protein or macronutrient deficiency. Most of these experiments demonstrated the development of conditions commonly associated with aging, such as obesity, insulin resistance, hypertension, T2D and CVD.[109] In the rodent models, obesity and metabolic disorders were induced in progeny by maternal undernutrition,[110] a low protein (LP) diet,[111] iron restriction[112] and maternal uterine artery ligation.[113] Data from the model of maternal high-fat feeding also showed

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that maternal overnutrition and obesity during pregnancy and/or lactation can be risk factors for metabolic disturbance in the offspring, including increased adiposity, glucose intolerance, elevated blood pressure and abnormal lipid profile in the offspring of high-fat-fed rodent dams.[114–116]

The maternal low protein (MLP) model of growth restriction is, to date, the most extensively used model to examine the mechanistic links between malnutrition during early development and later-life health outcomes. This model involves *ad libitum* feeding to pregnant dams a diet containing 5–9% protein, generally a little under half the protein content but equivalent in energy of a control diet containing 18–20% protein.[117] In rats exposed to LP diet throughout gestation, the programming effects on adult blood pressure and metabolic dysfunction were associated with a reduced 11-month survival rate[118] and shortened lifespan.[117,119] Low birth weights were associated with increased lifespan, whereas rapid postnatal growth had a detrimental effect.[120]

To get further information on the importance of intrauterine and/or lactation nutrition, Hales and co-workers used cross-fostering techniques, where newborn pups were separated from their genetic mothers and raised by unrelated dams.[121] In this study, offspring from LP dams were 15–20% lighter at birth than progeny of control-fed dams. Extending MLP diet to the lactation period increased this weight difference and permanently limited later growth. If offspring of MLP mothers were cross-fostered to dams fed a control (20%) diet during lactation, they showed rapid postnatal weight gain so that these offspring ('recuperated' animals) have similar body weights to control animals by weaning (21 days of age). Conversely, when control offspring were cross-fostered to LP dams, they grew slowly and were significantly smaller throughout life ('postnatal low protein', PLP animals).[122,123] The most remarkable observation of this study was the effect on male lifespan. The recuperated animals had a shorter lifespan than controls. On the contrary, PLP rats had a longer lifespan than controls. Consequently, the generally similar results were obtained in mice.[23] The PLP mice were shown to be protected from the lifespan-shortening effects of the excessive postnatal nutrition. Both control and recuperated mice had a significantly reduced lifespan if they were fed a highly palatable diet, whereas the PLP animals did not show this impairment.[23] In addition to reduced mean lifespan, *in utero* growth-restricted mice that grew rapidly throughout the lactation period have a reduced maximum lifespan.[124] Maximum lifespan of these mice was further reduced if they were weaned onto an obesity-inducing cafeteria diet. Female mice were more vulnerable to adverse health consequences of low birth weight than the male ones.[125] Male offspring from LP dams showed elevated food intake, hyperactivity and enhanced metabolic rate only when weaned to the high-fat diet, whereas female offspring showed increased food intake and were hypometabolic, regardless of post-weaning diet.

To investigate the molecular mechanisms underlying these associations, the expression of key proteins involved in antioxidant capacity and insulin sensitivity was evaluated.[126] In rat experiments, PLP animals had improved insulin sensitivity at weaning, as suggested by lower insulin levels required to maintain concentrations of glucose similar to those in the control group. These animals also had significantly elevated expression of Sirt1 (a member of the family of sirtuin proteins that are essential for gene silencing) and key antioxidant enzymes including CuZnSOD, catalase and glutathione peroxidase-1. In contrast, recuperated rats had significantly increased MnSOD expression and elevated fasting glucose concentration, whereas insulin level remained comparable to those of the control group, suggesting relative insulin resistance. Thus, it can be assumed that early-life nutrition may program the antioxidant capacity and insulin sensitivity, thereby influencing longevity. It was demonstrated that mitochondrial abnormalities and DNA damage occur in the kidney of offspring who die prematurely.[127] Nutritional disturbance in pregnant rats has been shown to cause reduction in the growth of the endocrine pancreas throughout organogenesis and increased rate of β-cell apoptosis, leading to impaired insulin secretion and hyperglycemia in adult offspring.[128] Animal longevity studies show that programmed phenotypes can change markedly with aging. The combined effects of prenatal undernutrition and aging were shown to lead to microalbuminuria, insulin resistance, hypertension, obesity and other features of metabolic syndrome. Therefore, rats exposed to MLP diet throughout intrauterine development demonstrated little evidence of metabolic abnormalities at 9 months of age; however, hepatic steatosis, raised plasma insulin (indicating insulin resistance), and profound hypertriglyceridemia and hypercholesterolemia were evident in these rats with increasing age, in the 18 months old age group.[129] Similar findings were observed in the study by Ozanne *et al.*,[130] where rats exposed to MLP diet during their fetal and suckling periods develop insulin resistance, resulting from insulin-signaling defects, but only in old age.[131] Together, these findings assume that protein restriction in early life can program insulin resistance in old rats.

Similar programming effects of LP diet were observed in mice. Changes in key insulin-signaling molecules have been shown at day 21 in the skeletal muscle in both the recuperated and PLP mice.[132] PLP animals that were protein restricted throughout lactation demonstrated lower fasting glucose and insulin levels, suggesting improved insulin sensitivity, and higher relative weights of the thymus and brain compared with controls, assuming that increased functional capacity of these two organs is beneficial to longevity. These mice also had elevated expression of insulin receptor substrate 1 and protein kinase Cζ; they expressed decreased levels of many insulin-signaling proteins that can predispose these animals to insulin resistance later in life. Sirt1 protein expression was reduced in recuperated offspring. The interaction of prenatal undernutrition with an atherogenic diet in a postnatal period resulted in significantly increased risk of atherosclerotic disease in the Apo E*3 Leiden mouse.[133] Ogawa *et al.*,[134] by examining the effect of LP diet on genome-wide changes in maternal and fetal

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mice liver transcriptomes, have revealed that, of the genes studied, 103 genes that were significantly upregulated in the mother were downregulated in the fetus, whereas 108 downregulated maternal genes were upregulated in the fetus; remarkably, these 211 genes are potential candidates associated with health and longevity.

Taken together, these findings assume that maternal protein restriction may affect major metabolic pathways implicated in longevity.[130] Protein restriction throughout suckling might act in a similar manner as caloric restriction in adulthood, by inducing a protective hormetic response.[135] The noteworthy aspect of the MLP model is the timing of protein restriction.[105] During lactation, it is a beneficial condition, but in gestation the same condition is detrimental. One plausible explanation is that unfulfilled energy demands can cause chronic stress in protein-restricted fetuses, resulting in a negative effect on longevity.[23,117]

Tissue remodeling

Many mammal organs have completed their development by the time of birth, and although the developmental window extends a short way into postnatal life, the great bulk of tissue growth and maturation is complete by parturition. If insults impact on cell proliferation or differentiation during periods of rapid growth, then it would be expected that the organs will mature at a smaller size and with a reduced functional capacity. Such impairment of structural and functional capacity of several organs or systems can be a consequence of an effort to selectively protect the most important organs, such as the brain, under conditions of decreased energy supply.[136]

Numerous examples of this are available from experimental models. In the pancreas of rats exposed to LP diets *in utero*, there are fewer islets, smaller islets and reduced islet vascularization.[137] The same maternal insults were also associated with altered size and neuronal densities in the hypothalamic center that regulate food intake,[138] with reduced vascularization of the brain cortex,[139] alterations to the bone growth plate[140] and differences in muscle fiber types.[141] MLP diet in mice has been shown to influence the thymic growth in early adult life.[142] PLP offspring demonstrated rapid thymic growth from 21 days to 12 weeks of age, although that was not detected in control or recuperated offspring. The mitotic activity was initially elevated in the thymus from both PLP and recuperated offspring, but persisted into adulthood only in the PLP mice.

Telomere shortening

The accelerated rate of aging at the cellular level might be another potential underlying mechanism of developmental nutritional programming. Studies using rodent MLP model suppose that telomere shortening, which serves as a marker of cellular senescence, can also play an important role in the early-life programming of lifespan.[143] The reduced lifespan was associated with telomere shortening in the kidney,[23] aorta,[144] islets[145] and cardiac tissue[146] in the recuperated rat offspring. Remarkably, many of the detrimental effects of nutritional programming on cardiac aging, including oxidative damage, telomere shortening and cellular senescence, were rescued by post-weaning dietary supplementation with coenzyme Q10, which is a key component of the electron transport chain and also has antioxidant effects.[147]

The rat findings were confirmed in the wild bird model showing that king penguin chicks entering the post-winter growth season at a smaller size showed catch-up growth accompanied by elevated levels of oxidative damage and shortened telomere lengths compared with chicks entering their growth phase at a larger size.[148] By analyzing these findings, Crespi[149] suggests that 'while catch-up growth allows smaller chicks to head off into the world on equal footing with chicks that hatched at a larger size, it likely comes at the cost of a shortened lifespan.' In general, it may be hypothesized that adverse intrauterine nutritional environment can lead to accelerated telomere shortening during the lifespan and, thereby, to premature cellular senescence and accelerated aging phenotypes.[150]

On the contrary, the maternal protein restriction during lactation led to increased longevity in the PLP rat offspring.[123,135] These rats also did not display substantial renal telomere shortening with age and had significantly longer telomeres at 12 months of age.[135] Such lack of age-related renal telomere shortening was associated with elevated level of antioxidant enzymes: glutathione reductase, glutathione peroxidase and manganese superoxide dismutase. These data suggest that beneficial effect of slow growth during lactation can be linked to prevention of age-associated telomere shortening and enhanced antioxidant capacity in the PLP animals.

Epigenetic modifications

Persistent epigenetic modification of genes linked to health and disease is considered to be a key mechanism for developmental programming of lifespan.[151] In rats, maternal dietary protein restriction was shown to result in alterations in methylation and expression levels of several genes in the liver and kidney of the offspring. The maternal protein restriction during gestation caused lower level of methylation and higher expression of hepatic peroxisomal proliferator-activated receptor (PPAR)-α gene, a key regulator of liver lipid metabolism, whereas the glucocorticoid receptor (GR) gene methylation was lower and expression higher compared with control.[152] These findings were confirmed in many subsequent studies.[153,154] Remarkably, such changes may be reversed if the LP diet was supplemented with folic acid.[152] In the adipose tissue, recuperated male offspring demonstrated enhanced levels of adipocyte proliferation and leptin mRNA at 28 days of age.[155] Guan *et al.*[156] using rat MLP model, in which dams were fed LP diet during pregnancy and lactation, observed a global upregulation of genes implicated in angiogenesis, adipocyte differentiation and remodeling of extracellular matrix, as well as in protein, carbohydrate and lipid metabolism in the visceral adipose tissue.

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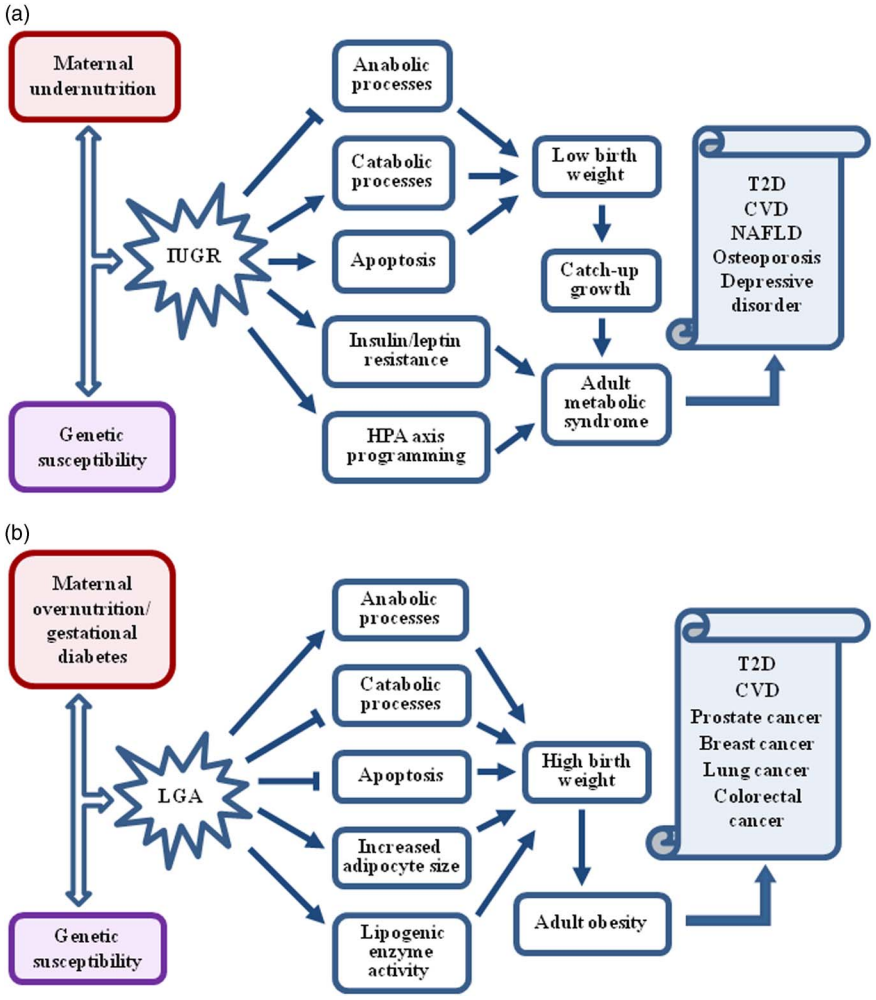


Fig. 1. Schematic models of hypothetical mechanisms linking maternal undernutrition and overnutrition with adverse adult outcomes. (*a*) IUGR conditions caused by maternal undernutrition are associated with decreased levels of anabolic hormones (sex steroids, insulin, GH and IGF-1) along with the increased concentrations of catabolic hormones, such as glucocorticoids, higher apoptosis rate, and reprogramming of the HPA axis and GH/IGF axis during the fetal development. Such changes in the intrauterine growth-restricted fetus lead to low birth weight (<2.5 kg) and subsequent rapid catch-up growth, followed by higher risk for metabolic complications, including glucose intolerance, insulin resistance, hypertension and dyslipidemia, as well as T2D, CVD, NAFLD, osteoporosis and depressive disorder in adulthood. (*b*) LGA conditions, which are the result of excessive fetal growth caused by maternal overnutrition or gestational diabetes, are accompanied by upregulation of adipogenic genes, increased anabolic and decreased catabolic hormone levels, enhanced cell proliferation, increased adipocyte cell size and high activity of lipogenic enzymes. These conditions result in high birth weight (⩾4.0 kg), impaired development of the central appetite regulatory system, and a range of health problems including hyperinsulinemia and obesity, as well as several cancers, CVD and T2D in adulthood. IUGR, intrauterine growth restriction; GH, growth hormone; IGF-1, insulin-like growth factor-1; HPA, hypothalamic–pituitary–adrenal axis; T2D, type 2 diabetes; CVD, cardiovascular disease; NAFLD, non-alcoholic fatty liver disease; LGA, large-for-gestational age.

Perinatal protein restriction also permanently changed the expression of genes regulating lipid metabolism, as well as insulin signaling and nutrient sensing in the rat hypothalamus.[157] In the above-cited study by Erhuma *et al.*,[129] the obtained phenotypic changes were accompanied by age-associated alterations in mRNA and protein expression of several transcription factors and their respective downstream target genes. The expression level of PPAR-α was significantly elevated in LP offspring aged 1 or 9 months, which is indicative of enhanced lipid oxidation. The downstream target of PPAR-α, medium-chain acyl-CoA dehydrogenase, was also overexpressed in these animals. Expression of the insulin-sensitive regulator of lipogenesis, sterol regulatory element-binding protein-1c (SREBP-1c), and its downstream targets fatty-acid synthase and acetyl-CoA carboxylase were significantly suppressed in LP-exposed animals at 1 and 9 months of age. Between 9 and 18 months of age, there was a switch in the expression of these genes, such that by 18 months the expression of PPAR-α was

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lower in LP-exposed animals, and PPAR-γ, SREBP-1c and the lipogenic pathways were all overexpressed. At this stage, the expression of IRS2 was also suppressed, indicating a defect of insulin signaling. Such changes in the expression of these genes and transcription factors, alongside the developing metabolic phenotype, suggest that they may play an important role in establishing a metabolic profile that is likely to be detrimental with advancing age. The protein restriction throughout gestation resulted in histone modifications at the glucose transporter 4 (GLUT4) promoter region along with induced GLUT4 expression in the skeletal muscle of female rat offspring.[158] The expression levels of GLUT4 and transcriptional coactivator, peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) were significantly reduced, and mean CpG island methylation in the PGC-1α promoter sequence was significantly increased in the skeletal muscle of 18-month-old MLP female rats. These epigenetic alterations were accompanied by impaired glucose tolerance and obesity in old age.[159] The gestational protein restriction followed by an accelerated postnatal growth influenced the expression of markers of cellular stress in rat pancreatic islets.[145] Specifically, the elevated expression of heme oxygenase-1, peroxiredoxin-1 and peroxiredoxin-3 under stress conditions was detected. The expression of MnSOD was significantly reduced in recuperated offspring, suggesting impairment of mitochondrial antioxidant defense. Markers of cellular senescence, p16 and p21, were markedly elevated in the recuperated group. It has been also shown that MLP diet enhances cholesterol in adult rat offspring through permanent repressive post-translational histone modifications at the promoter of Cyp7a1 gene.[160] These epigenetic modifications originated partly because of MLP-induced decreased expression of fetal hepatic histone H3 (K9) demethylase, JMJD2A.

Gene expression profiles of the kidneys from 21-day-old mice were differentially affected, depending on whether protein restriction was imposed during gestation or lactation.[143] The differentially expressed genes were implicated in different biological functions including cellular senescence, vitamin D synthesis, protein homoeostasis, cytoprotective functions and regulation of antioxidant enzymes. In contrast, SNF1-like kinase 2 and NUAK family were upregulated, and Cu/Zn SOD, LON peptidase 2, forkhead box O3a and sestrin 1 were downregulated in the kidneys of recuperated offspring, suggesting that resistance to oxidative stress and protein homoeostasis are compromised, leading to accelerated senescence in the shorter-lived mice.

Rats exposed to MLP diet throughout gestation and lactation showed reduced levels of transcription factor HNF4a involved in the etiology of T2D.[161] Such reduced levels of HNF4a expression were detected at a young age and persisted throughout life compared with normally fed controls. Malnutrition in early life led to epigenetic silencing at the enhancer region n, which weakened the P2 promoter–enhancer interaction and to a permanent decrease in HNF4a expression. The progressive age-related epigenetic silencing of the HNF4a locus in islets was more pronounced in rats exposed to poor maternal diet. The authors suggest that alterations in promoter–enhancer interactions may be a fundamental epigenetic mechanism by which early-life diet and aging influence lifelong health.[161,162]

In a study on mice, offspring of LP-fed males showed enhanced hepatic expression of many genes implicated in cholesterol and lipid biosynthesis and reduced levels of cholesterol esters, compared with control offspring.[163] Epigenetic profiling in the offspring livers indicated moderate (~20%) changes in DNA methylation, depending on paternal diet, including alterations in the methylation of an enhancer of the PPAR-α gene. These findings demonstrate that parental LP diet may influence lipid and cholesterol metabolism in the offspring.

In the sheep model, the maternal undernutrition influenced the fetal hypothalamic GR and appetite-regulating neuropeptides, including neuropeptide Y and proopiomelanocortin.[164] In this study, periconceptional undernutrition was linked to marked epigenetic changes in hypothalamic genes, which predispose offspring to altered regulation of food intake, glucose homeostasis and metabolism in later life.

Overall, these studies provide evidence that epigenetic mechanisms may significantly contribute to lifelong effects of early nutritional insults.[165] The research findings demonstrate that intrauterine malnutrition can epigenetically program development of a metabolic syndrome-like phenotype that commonly develops with aging. Hypothetical models of the relationships between both maternal undernutrition and overnutrition and adverse health outcomes influencing longevity are shown in Fig. 1a and 1b, respectively.

Conclusion

Relationship between early-life conditions and late-life health was found in a number of studies. It has highlighted the key role of epigenetic mechanisms in mediating the relationship between early-life environment and lifelong health outcomes, including the development of aging-associated diseases.[29] Nutrition significantly affect the epigenetic processes, and therefore offers great promise for health promotion and disease prevention.[166–169]

In contrast with relatively stable genetic information, epigenetic marks are highly dynamic, responsive to the environment and potentially reversible.[28] The possibility of reversing epigenetic marks can provide new targets for emerging preventive and therapeutic strategies. Such preventive approaches initiated in prenatal and early postnatal periods of human development seem to be particularly promising. If one could modify the incorrect or deleterious epigenetic patterns through specific nutritional interventions in early ontogeny, then it would be possible to correct the disrupted gene expression programs to treat age-related diseases and to achieve better health and longevity. These interventions may include improvement in the quality of diet for pregnant women, identification of individuals at risk for chronic disease based on the screening of maternal and perinatal characteristics, or

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administration of specific therapeutic agents in childhood.[107] There are already several findings supporting the usefulness of this kind of intervention in animal models. For example, it was found that the supplementation of LP diet during rat pregnancy with glycine[170] or folate[171] can offset the long-term adverse effects of the developmental protein restriction. Supplementation of LP diet in rat pregnancy with folic acid (the synthetic form of folate) can also ameliorate the adverse programming effects.[172] Aside from glycine and folate, other nutrients involved in one-carbon metabolism and affecting DNA methylation, such as vitamins B_6 and B_{12}, choline, betaine, methionine and riboflavin, along with several another bioactive food components (tea polyphenols, resveratrol, curcumin, retinoic acid, sulforaphane, etc.), which affect epigenetic patterns by changing the levels of S-adenosylhomocysteine and S-adenosylmethionine, or directing the enzymes catalyzing histone modifications and DNA methylation, may also be promising candidates for a range of biomedical applications.[173]

The idea that nutrition during critical windows of development can program age-related disease and lifespan may have important biological and public health implications. Optimizing the nutritional environment to which individuals are exposed during early development has the essential potential to extend the human health span. Future studies could provide the basis for identifying specific nutrition-based treatment strategies focusing on prevention of chronic adult diseases and lifespan extension.

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Conflicts of Interest

None.

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