



## REVIEW ARTICLE

# Early-life nutrition and adult-life outcomes

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### KEYWORDS

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### Abstract

**Objectives:** To verify the association between early-life nutrition and chronic adult diseases.

**Data Sources:** Medline, Embase, Cochrane Database, and Lilacs.

**Summary of finds:** The Developmental Origins of Health and Disease (DOHaD) hypothesis postulates that a mismatch between early-life circumstances and later-life situations may have an impact on chronic diseases. In this review, the authors emphasize the research supporting the impact of early nutrition on the origins of adult height, obesity and metabolic syndrome, type 2 diabetes mellitus, cardiovascular diseases, and reproductive outcomes.

**Conclusion:** Even though this is a new topic and there are still many research questions to be answered, there is strong evidence that both deficiency and excess nutrition in early life can cause epigenetic changes that have effects that last a lifetime and contribute to the development of chronic diseases. Public health efforts to protect adults from getting chronic diseases should focus on nutrition in the first 1000 days of life, from conception to the end of the second year of life.

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## Introduction

Early nutrition has a well-known impact on a child's growth and development. Recent research, however, reveals that early-life nutrition has long-term consequences and may influence adult outcomes. In 1977, Forsdahl<sup>1</sup> first postulated the association between early-life nutrition and the future risk of chronic diseases in adulthood. He reported a positive association between infant mortality rate and an increased risk of cardiovascular diseases in adulthood. In a subsequent

study conducted by Barker et al. in 1989, it was discovered that there exists an inverse correlation between birth weight and the likelihood of mortality due to cardiovascular disorders.<sup>2</sup> The concept that diet during the early stages of life can have lasting phenotypic consequences was initially introduced by Barker in the 1990s, referred to as the "fetal programming hypothesis".<sup>3</sup> After two decades of extensive investigation, it has been widely acknowledged on a global scale.

Early-life nutrition, or the first 1000 days from conception to the age of two, can have a significant and lasting impact on the development of tissues and organs.<sup>4</sup> These effects, known as "programming," are a significant risk factor for

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developing chronic illnesses in adulthood. The hypothesis is that nutritional programming results from the altered expression of genes brought about by early-life nutritional and environmental disturbances.<sup>5</sup> The structure and function of remodeled tissue and organs improve the organism's ability to persist under adverse nutritional conditions. However, when confronted with proper nutritional conditions later in life, the body interprets the environment as obesogenic. The statement that features programmed by dietary exposures in childhood can be passed down to future generations adds to the evidence that heritable epigenetic changes dominate nutritional programming.<sup>6</sup>

Epidemiological studies have found links between early-life nutritional exposures and long-term health outcomes.<sup>1,5</sup> Breastfeeding for more than six months, for example, was linked to a decreased risk of diabetes and obesity.<sup>7,8</sup> Other studies have identified early gestation as a key period of development, and severe nutritional deficiency in childhood has been linked to a variety of long-term morbidities.<sup>1,3</sup> Adults who were severely malnourished as children and then exposed to an obesogenic environment are especially vulnerable to cardio-metabolic abnormalities. This cycle of childhood malnutrition and adult risk can predispose future generations to greater hazards.<sup>3</sup> In a world of aging populations and a growing burden of non-communicable diseases, particularly cardio-metabolic diseases, the authors deem it imperative and essential to investigate the potential of early-life nutrition investments in preventing chronic diseases. The authors will discuss several unfavorable adult outcomes that can be attributed to insufficient early nutrition.

### Adult-attained height

Adult-attained height has been associated with a variety of adult outcomes, including health and disease, cognitive abilities, and earning capacity. Also, although inconsistently, a correlation has been postulated between adult height and mortality. There is a correlation between short stature in mothers and obesity, hypertension, and stunted offspring.<sup>9</sup> Moreover, adult height appears to be an accurate indicator of early-life exposures and is frequently affected by early-life nutrition.<sup>4</sup>

The height achieved in adulthood is influenced by a combination of genetic and environmental variables, with particular emphasis on early nutrition throughout the time of early growth. Research has demonstrated that people with comparable genetic backgrounds, but exposed to varying dietary environments, may exhibit disparities in adult height. When exposed to inadequate nourishment during the early stages of life, the fetus and young newborns typically exhibit compromised growth in terms of length and weight, while placing a greater emphasis on the development of the brain.<sup>10</sup> Currently, some experts claim that body disproportionality rather than low stature is a more reliable sign of undernutrition in early life. Although some experts continue to point to the adolescent stage, it appears that the window for treatments that don't compromise height is formed in the first 1000 days of life.

According to certain research, early exposure to famine has a long-term effect on an adult's anthropometric

measurements. For both sexes, people who experienced the Dutch famine in 1944/45 and undernutrition from "gestation to age 1 or 2" had significantly reduced adult heights.<sup>11</sup> The Dutch famine, however, had no substantial impact on height achieved at any other age. The same outcomes were observed during the world's worst famine, which occurred in China between 1959 and 1961. Data from a cohort of 35,025 women born between 1957 and 1963 revealed that the height of the 1958 and 1959 cohorts decreased by 1.7 and 1.3 cm, respectively. This corresponded to exposures during late pregnancy and between 0 and 2.5 years for the 1959 cohort.<sup>12</sup> A study conducted on a cohort of 1384 individuals who endured the Ethiopian Great Famine between 1983 and 1985 revealed that when compared to non-exposed groups, the adult height of persons in the early life, prenatal, and post-natal exposed groups was found to be lower by 1.83 cm, 1.35 cm, and 2.07 cm, respectively.<sup>13</sup> According to a recent systematic review, it is established that individuals who experienced famine throughout their prenatal life and early childhood exhibited a notable reduction in adult height.<sup>14</sup> The available research consistently demonstrates a robust association between inadequate nutrition during early life and reduced adult height.

### Obesity and metabolic syndrome

Obesity is currently a significant public health concern. Adult obesity increases the risk of cardiovascular disease, type 2 diabetes, and certain cancers ([www.who.int](http://www.who.int)). Obesity is a primary pathophysiological mechanism in the development of metabolic syndrome (MetS), a cluster of cardiovascular disease (CVD) risk factors that include dyslipidemia, hypertension, and insulin resistance. According to NHANES data (2011–2016), 20% of 20–34-year-olds and 49% of those over 60 years old in the United States<sup>15</sup> have MetS. MetS doubles the risk for cardiovascular disease and multiplies the risk for type 2 diabetes by six. According to the Global Burden of Disease study, cardiovascular disease is responsible for 41% of fatalities and 34% of disability-adjusted life years caused by a high BMI.<sup>16</sup> More than 80% of adults with T2DM were overweight or obese, indicating that obesity is a major contributor to the prevalence of T2DM. Therefore, obesity and MetS are significant contributors to CVD and T2DM, two of the leading global causes of mortality and morbidity. Globally, the prevalence of childhood obesity has risen dramatically over the past two to three decades in all global regions, with the most devastating impact occurring in low- to middle-income countries where malnutrition and obesity coexist.

Obesity begins in childhood for most adults.<sup>17</sup> Childhood obesity often persists throughout adulthood. Thus, early obesity prevention is crucial. Several epigenetic, metabolic, and metagenomic mechanisms have recently been found to be able to predict the future risk of obesity within the first 1000 days of life.<sup>6</sup> Recent research has indicated that a healthy diet throughout infancy may be essential for preventing obesity.<sup>4</sup>

A substantial number of epidemiological research have found a link between birth weight and adult body mass index as a result of intrauterine growth restriction.<sup>18</sup> Several studies have also looked at the relationship between low and

high birth weight and indicators of later central obesity.<sup>19</sup> The precise mechanisms underlying these relationships have yet to be elucidated, however, it is plausible that they can manifest irrespective of a pre-existing genetic predisposition. Exposure to inadequate nutrition during intrauterine development can induce enduring alterations in gene expression, giving rise to a "thrifty phenotype" that prioritizes the preservation of life and the growth of the vital organ, the brain, in the face of inadequate nutritional conditions. However, this fetal rearrangement may result in permanent alterations to certain tissues and organs, particularly adipose tissue and hormone secretion. Another possibility is that long-term modifications in the activation of the hypothalamic-pituitary-adrenal axis mediate associations between birth weight and subsequent obesity and adipose tissue distribution.

Adipose tissue synthesizes and releases peptides, hormones, and adipokines, which have many roles. Under steady diets, intrauterine growth restriction favors fat deposition.<sup>20</sup> Fetal malnutrition during the later stages of gestation has been found to potentially increase the likelihood of developing central obesity and associated metabolic alterations. The association between central adiposity and visceral adipose tissue is of significant concern due to its strong relationship with the development of diabetes and cardiovascular disease. Moreover, an abundance of visceral adipose tissue and an uneven distribution thereof contribute to an elevated susceptibility to obesity and associated medical conditions.

Both a greater pre-pregnancy BMI and excessive mother gestational weight increase are linked to childhood overweight status.<sup>21</sup> The two most significant risk factors for obesity transmitted vertically have been identified as these two risk factors. Exclusive breastfeeding throughout postnatal and the first few years of life is crucial in preventing childhood obesity. On the other hand, formula-fed babies during the first six months of life should be taken into account as a risk of obesity in later life. Supplemental feeding may also be important, particularly for formula-fed infants, for whom the introduction of solid meals before the age of four months has been linked to rapid weight growth and juvenile obesity.<sup>22</sup>

Studies with societies that experienced famine outbreaks have unequivocally demonstrated the link between intrauterine malnutrition and adult obesity. Women who were younger than 3 years old during the 1959 Chinese famine were 1.5 times more likely to be overweight or obese than women who were born after the famine.<sup>12</sup> An analysis of a cohort of males who were born in Holland before, during, and after the famine that was enforced by the Nazis in 1945<sup>23</sup> revealed that men who were exposed to hunger during the first trimester of pregnancy were more likely to develop overweight or obesity than men who were exposed to the famine during the last trimester of pregnancy. Thus, maternal obesity or overweight and undernutrition both raise the risk of childhood obesity.

In summary, the dietary patterns of mothers and children during the initial 1000 days of life have the potential to influence the likelihood of developing overweight/obesity or metabolic syndrome in adulthood. The implementation of preventive strategies targeting obesity and metabolic

syndrome should commence during the period spanning from conception to the second year of life.

## Type 2 diabetes

Type 2 diabetes (T2DM) is considered a pandemic worldwide, and its prevalence is increasing at an alarming rate.<sup>24</sup> Diabetes affects or will affect one-tenth of the world's population, according to estimates. Diabetes was responsible for 6.7 million deaths worldwide in 2021, which equates to one diabetes fatality every 5 seconds (<https://www.diabetesatlas.org>). Obesity has been highlighted as a significant cause of the worldwide rise in type 2 diabetes prevalence. Obesity length and age of beginning (early obesity), according to new research, may provide additional insight into the contribution of obesity to T2DM risk.<sup>25</sup> Although the pathophysiology of diabetes is not fully understood, it is widely believed that genes and lifestyle are the key risk factors for diabetes. There is growing evidence that early life nutrition may play an important role in determining diabetes susceptibility in adulthood.<sup>26</sup> During dietary restriction, the growing fetus develops a variety of strategies to boost its chances of survival postnatally in comparable nutritionally deprived conditions. These adaptations include prioritizing brain growth over other body tissues like skeletal muscle and the endocrine pancreas.<sup>5</sup> Another adaptation is to train the metabolism in such a way that it promotes the storage of nutrients when they are available.<sup>27</sup> This phenomenon perturbs the established process of fetal fat distribution and contributes to an accumulation of visceral fat, which is linked to insulin resistance, heightened lipolytic activity, decreased levels of adiponectin, resistance to leptin, and elevated inflammatory cytokines. These factors collectively play a role in the pathophysiology of diabetes. Moreover, recent research has emphasized the significance of elevated liver fat in the development of type 2 diabetes (T2D) among individuals with low birth weight (LBW).<sup>26</sup> The many adaptations that occur within the uterus can provide benefits during fetal development but can have negative consequences when the newborn is exposed to situations that are different from those experienced during gestation.

The first study to establish a link between low birth weight and increased susceptibility to type 2 diabetes revealed that adults with the lowest birth weight were six times more likely to develop type 2 diabetes or impaired glucose tolerance than those with the highest birth weight.<sup>27</sup> These results have been confirmed in numerous populations and ethnic groupings around the world. High birth weight was linked to an increased risk of diabetes, according to other research. In a recent study, the association between low birth weight and type 2 diabetes was reinforced by accounting for cumulative obesity dose and included 17,634 participants from the 1958 National Child Development Study who were followed from birth to age 50.<sup>28</sup>

Nutrition during the first few months of life may also be related to the risk of type 2 diabetes in adults. Accelerated early development has been identified as a risk factor for diabetes, particularly in infants born prematurely. Children with a low birth weight are more likely to develop T2DM, particularly if they experience accelerated catch-up growth in early childhood.<sup>29</sup> Another benefit of breastfeeding is that

breastfed infants have a distinct growth pattern than formula-fed infants, who are more likely to experience rapid catch-up growth.

All this suggests that the risk for the development of diabetes consequent to early-life nutrition can be broken by improving nutrition during pregnancy and in early childhood. Support for public health programs aimed at intergenerational (primordial) prevention of diabetes is needed.

## Cardiovascular diseases

Globally, cardiovascular diseases (CVDs) constitute the primary cause of mortality, resulting in approximately 17.9 million deaths annually. CVDs are a group of disorders of the heart and blood vessels including mainly coronary heart disease and cerebrovascular disease. According to the WHO, more than four out of five CVD deaths are due to heart attacks and strokes. Besides, more than 30% of these deaths occur prematurely in persons under 70 years of age ([www.who.int](http://www.who.int)).

Atherosclerosis is the leading cause of CCVD, and numerous studies in recent decades have demonstrated that atherosclerosis begins in childhood.<sup>30</sup> The first evidence of the origins of CVD in childhood came from the studies of the epidemiologist David Barker in England in the late 80's, who described an association between low birth weight and CVD in adult life.<sup>3</sup> Currently, low birth weight, the reflex of restriction growth intrauterine, is recognized as an independent risk factor for cardiovascular in adulthood. LBW is associated with increased mortality from coronary heart disease and a higher risk of hypertension. Restriction growth intrauterine leads to LBW and these newborns usually undergo a rapid (catch-up) growth early in an attempt to compensate for the slow uterine development. Experimental studies in animals submitted to restriction growth intrauterine have identified the cardiovascular system as a major target of developing programming. These studies have also shown alterations in cardiomyocyte number and size. Overeating in pregnancy causing excess weight gain in the fetus is also associated with CVD in the future. A recent meta-analysis ( $n = 1220$  cases,  $n = 1997$  controls), reported the following factors associated with greater aortic intima-media thickness, i.e., atherosclerosis: small for gestational age status, intrauterine growth restriction, and large for gestational age status.<sup>31</sup>

The first postnatal feeding must be breastfeeding, sustained and exclusive because it has many benefits for health that last throughout life.<sup>32,33</sup> This includes the protective effect of CVD. Breastfeeding, regardless of duration or exclusivity, is associated with lower blood pressure at 3 years of age and this probably has repercussions in adult life.<sup>34</sup> The amount of sodium in the diet of an infant in the first 6 months of life may have an impact on cardiovascular health outcomes in later life and human milk may prevent these effects. Besides, there are some advantages also for the breastfeeding mother.<sup>35</sup> The risk of CVD significantly decreases.

Among the risk factors for CVD, an unhealthy diet is one of the most important. It is well known that dietary habits are established in childhood and that they are difficult to change throughout life. Diet is a modifiable risk factor and

has a large impact on the reduction of CVD morbidity and mortality. Recent studies have shown that the foods eaten by the mother during pregnancy influence her child's taste after birth.<sup>36</sup> The flavor of the food reaches the amniotic fluid, allowing the fetus to taste and smell the food. A classic study clearly showed this: mothers who had the habit of eating carrots during pregnancy had children who, at the time of weaning, accepted carrot baby food better, when compared to other babies whose mothers did not have the habit of eating this vegetable in pregnancy.<sup>37</sup> Therefore, the formation of healthy eating habits should begin with maternal nutrition during pregnancy. Another important phase in forming healthy eating habits in the first 1000 days of life is weaning. What is promoted to adults as a healthy diet should start here: fruits and vegetables daily, little salt and sugar, and avoiding processed foods.

In summary, there is strong evidence supporting the benefits of a healthy diet for pregnant women, exclusive and long breastfeeding, and weaning for long-term cardiovascular health.

## Reproductive outcomes

Early-life nutrition may have an impact on a person's ability to reproduce. Early stages of development are when primordial germ cells are created, and the fetal era is when follicle reserves are exclusively established. Women go through menopause when their follicular reserve runs out during the course of their lifetime. Early-life malnutrition has the potential to cause fetal developmental modifications, which can lead to changes in the development of the reproductive system and impairments in reproductive function. Fetal malnutrition may have an effect on ovarian capacity through its impact on follicle production, possibly causing a decrease in the initial follicle pool or an accelerated follicular loss later. Early malnutrition may affect epigenetic mechanisms, specifically the hypothalamus gene expression, which is essential for the development of reproductive function.<sup>38</sup> According to earlier investigations,<sup>5</sup> both animal and human infants that underwent fetal nutrition deficiency showed epigenomic changes, specifically in the form of DNA methylation. Early-life malnutrition can have an impact on the methylation pattern of peroxisome proliferator-activated receptors (PPARs), which are highly expressed in reproductive tissues and play a significant role in the transformation from embryo to fetus in developing mammals. These alterations have an impact on a number of reproductive processes, including oocyte maturation, ovulation, embryo implantation, placental development, and male fertility.<sup>39</sup> This could have generational-spanning consequences on the health of the reproductive system. The malfunctioning of the hypothalamic-pituitary-gonadal axis may also be influenced by early undernutrition. Girls with restricted intrauterine growth showed higher basal levels of gonadotropin-releasing hormone, follicle-stimulating hormone, luteinizing hormone, and estradiol than girls who were born healthy.

Studies have found indications that early exposure to starvation may damage females' ability to procreate later in life. One of the worst famines in recent memory, the Great Chinese Famine of 1959–1961 is thought to have killed



an additional 30 million people and caused 33 million miscarriages.<sup>40</sup> According to a population-based ecological study conducted with 58,601 girls born between 1959 and 1961, the Great Chinese Famine, early exposure to the famine was linked to an increased chance of stillbirth.<sup>41</sup> According to some reports, spontaneous abortion is more influenced by hereditary variables than stillbirth, which has been shown to be more responsive to environmental circumstances. The risk of future perinatal death was similarly elevated in women who were exposed to the great Chinese famine during the third trimester of pregnancy. After reviewing cohort studies from Brazil, Guatemala, India, the Philippines, and South Africa that involved long-term child monitoring, the Maternal and Child Undernutrition Study Group came to the conclusion that early-life nutritional deprivation was associated with lower birthweight in babies born to mothers who themselves had been stunted as children.<sup>42</sup> These studies imply that early life nutrition may be crucial for human reproduction and may have an impact on future generations.

Another effect of poor early nutrition appears to be an earlier menopause. Compared to women who were not exposed, women who were born during the Chinese famine (1956–1964) who were subjected to prenatal starvation had a greater incidence of early menopause.<sup>43</sup> Similar outcomes were noted in Dutch women who had been subjected to starvation during pregnancy.<sup>44</sup> Other research has found that early childhood undernutrition is connected with an earlier age of natural menopause. A systematic analysis evaluated whether poor early life factors result in menopause at a younger age.<sup>45</sup> The authors evaluated 11 studies and confirmed that fetal famine exposure was strongly related to a younger age at menopause. These findings support the thrifty phenotype theory of reproductive aging and contribute to a better understanding of the causes of early menopause.

## Conclusion

There is substantial evidence that early life nutrition influences several adult health outcomes. Rapid growth, development, and maturity of tissues and organs characterize the first 1000 days of life. Malnutritional (excess or failure) during this period might cause irreversible structural changes in developing tissues and organs. Although the precise mechanisms are still unknown, epigenetic processes have emerged as a possible involvement. Changes to these mechanisms can disrupt metabolism and fat storage.

These alterations have been reported as a significant risk factor for adult noncommunicable diseases, including adult-attained height, obesity and metabolic syndrome, type 2 diabetes, cardiovascular disease, and unfavorable reproductive outcomes. Interventions to avoid adult chronic diseases must prioritize nutrition in early life.

## Conflicts of interest

The authors declare no conflicts of interest.

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