SYNESIS
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Epigenetic transgenerational inheritance: Should obesity- prevention policies be reconsidered?

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Abstract

Studies have shown that the nutrition of one generation can alter the epigenetics of DNA in subsequent generations. The increase in the obesity epidemic, especially in the US requires significant health care-related expenditures and negatively impacts the quality of life for many Americans. Obesity is influenced by genetic and immediate environmental factors, and also by epigenetic mechanisms that alter the expression of genes involved in various metabolic functions. This type of imprinting occurs in utero and early postnatal life, and is affected by parental diet and environment. Therefore, further complexity is added to the already complicated etiology of obesity, indicating the intricate individual and multi-generational variables that contribute to health, and the need to revise paradigms of obesity prevention and treatment. In addition, transgenerational inheritance and the acquisition of epigenetic traits are new variables that should be considered by health industry stakeholders when analyzing and projecting the economic attributes of health care. Based on the most current understanding of epigenetics, health policy makers should ensure that prevention programs would include a long-term component addressing transgenerational inheritance and its role in the expansion of obesity

Key words: epigenetics, transgenerational inheritance, obesity, prevention, policy, healthcare

Introduction

Obesity is among the leading causes of death in the US and Western Europe, with over 110,000 and over 270,000 deaths per year in US and EU countries, respectively, attributed to excess adiposity (1, 2). US medical expenses associated with overweight and obesity-associated diseases, accounted for $147 billion in 2008 dollars (3). The US is expected to spend $344 billion on health care costs attributable to obesity by 2018, if the actual rates of obesity increase are maintained (4, 5). Not only does obesity trigger the onset of a broad array of chronic illnesses (cardiovascular diseases, type II diabetes, cancer, renal failure, chronic pulmonary diseases, etc.), but younger generations are also increasingly becoming overweight and obese. The most recent available data (2007-2008) indicated that 31.7% of US children and adolescents were overweight or obese, with 16.9% in the obese category (6). When categorized by ethnic groups, the highest prevalence of childhood obesity was identified among Hispanic individuals (20.9%) (6). Table I summarizes the identified risk factors associated with childhood obesity (7).

Table I: Risk factors associated with childhood obesity

Risk factor	Details
Eating habits	• Solid food before age of 3 months • Fewer portions of fruit per day • Skip breakfast • Eat at irregular times
Sedentary behavior	• Watching television • Indoor activities (reading, art, etc.)
Family behavior	• Exposure to tobacco smoke
Socioeconomic factors	• Lower income levels • Lower education levels
Birth weight	• Babies large at birth

A simplified presentation of risk factors associated with childhood obesity, as identified using the Millennium Cohort study.

However, research during the last two decades has revealed new mechanisms that are partially responsible for the way we respond to environmental challenges, and which allow us to continuously adapt our phenotype accordingly. One of the strongest environmental triggers for such modifications is nutrition. This paper will 1) present scientific evidence that nutrition plays a role in the transgenerational amplification of the obesity epidemic, and 2) advocate for a change in the paradigms of obesity prevention used at the present.

Epigenetics in nutrition

In 1809, Jean-Baptiste Lamarck argued that individual characteristics acquired during life as a result of exposure to various environmental influences (soft inheritance) can be transmitted to offspring. Although largely disregarded, in light of Darwin's theory of evolution, one component of Lamarck's theory of soft inheritance has been recently resurrected (inheritance of acquired traits), due to scientific progress that has enabled understanding of mechanisms of DNA alteration by environmental factors, including nutrition (8). While not all Lamarckian theory has been accredited by modern science (i.e., the use and disuse component), modern research has established that environment is a potent trigger for phenotypic changes not only in the exposed individuals, but also in subsequent, unexposed, generations (9). Nutrition is a potent trigger for metabolic and phenotypic changes. Some of these characteristics can be further transmitted to subsequent generations, even when such exposures are absent from the life of subsequent generations of offspring (10). Human and animal studies have revealed that such changes can be initiated as a result of practically any type of environmental change (maternal and paternal nutrition, gestational exposure to endocrine disrupting chemicals, ionizing radiation, etc.) (11, 12).

The term *epigenetics* includes the study of heritable changes that are transmitted by mechanisms other than modification(s) in the DNA sequence (recently reviewed in (13)). The main three molecular substrates that are involved in this process are DNA, proteins that form the core around which DNA wraps (histones), and a specific form of RNA molecules (non-coding RNA). For the purpose of this essay, only DNA changes will be discussed, as such alterations have proven to have the clearest role in the transgenerational inheritance of acquired characteristics.

The biologic roles of DNA methylation

One of the extant misconceptions of the general public is that DNA acts as simply a passive carrier of genetic information. From this concept, certain theories (within sociological, psychological, economic, and philosophical fields) have promoted the idea that the physiological features of individuals are attributed (sometimes almost exclusively) only to genetic information, in combination with immediate environmental conditions.

Currently, it is clear that DNA is not merely a passive carrier of genetic information, but its chemical structure can be altered in ways other than changes in the genetic code. The most frequent type of change involves DNA methylation. The DNA methylation status of a gene is heritable, but also modifiable by nutrition, and this plays a major role in regulating genetic ("off" and "on") activities, and thus allows genetic repression or expression (Figure 1) (14). The sum of DNA methylation changes throughout the genome is referred to as the epigenetic pattern (profile). Each type of cell has a distinct epigenetic pattern that confers its unique physiologic properties. For instance, the reason why a liver cell differs from a skin cell is because many of their genes have specifically distinct epigenetic profiles. This engages differing patterns of gene and protein expression, which are confined within limits imposed by epigenetic status.

Children inherit some of these epigenetic patterns from their parents, as the parental DNA in sperm and ovum has specific methylation patterns, which are parental-specific (i.e., conferring epigenetic inheritance in a parent-of-origin manner). During embryonic and fetal development, some of these inherited patterns are maintained (imprinted genes), while others are changed. Therefore, the prenatal period of development is especially vulnerable to epigenetic changes induced by various environmental triggers that can influence not only the maternal organism, but also the fetus (15, 16). As a result of established epigenetic patterns, various genes will have specific activation states and, consequently, their DNA methylation will affect a variety of regulatory mechanisms, including the amount of protein that is produced by each gene (Figure 1).

Nutrition induces epigenetic changes

Animal and human studies have demonstrated that nutritional status in one generation can alter epigenetic profiles

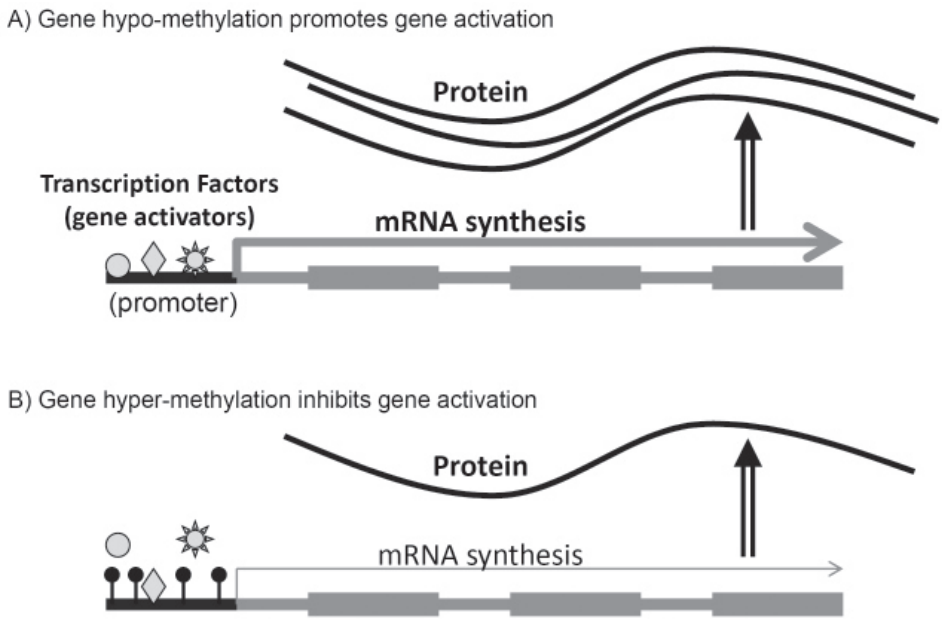

Figure 1. DNA methylation regulates gene expression. A simplified model indicating how DNA methylation controls the expression of genes. A) A gene is activated by the binding of gene activators (transcription factors) to its promoter (a DNA sequence ahead of the coding sequence). Promoter activation is followed by the synthesis of messenger RNA (mRNA), which carries the same coding information as the one stored by DNA. Further, the mRNA serves as a template for protein synthesis. The more a gene is activated, the more mRNA it will synthesize and, by consequence, a higher amount of same protein. B) The DNA methylation of a gene at its promoter (black circles represent each a methyl group, -CH_3, attached to a cytosine nucleotide that is followed by a guanine base) renders the promoter less accessible to gene activators. Therefore, the more a gene promoter is methylated, the less a gene will be active. The consequence is that less mRNA is synthesized and, consequently, less protein. Please note the inverse relationship between DNA methylation and gene activation: the more a gene is methylated, the less active it is.

in subsequent generations, having a clear impact upon the health of children and, possibly, upon their aging processes (reviewed in (13)). Nutrients such as folate, choline, niacin, flavonoids, or selenium are but a few examples (13). Moreover, high-fat diets and maternal protein restriction have a negative impact upon the epigenetic regulation of genes by altering their DNA methylation status (13).

The importance of obesogenic diets in shaping phenotypes was underscored by a study of identical twins, in which Bouchard and colleagues reported that overfeeding induced remarkable differences between siblings, despite their identical genotype (17). Other studies indicated that weight status (as an indicator of food intake) altered the risk of disease in subsequent generations (18-22). In humans, nutrient availability altered epigenetic profiles (23), which can be inherited by subsequent generations (18, 24). Similarly, animal models have revealed the molecular mechanisms responsible for such epigenetic changes. In primates, an obesity-promoting, calorie-dense maternal diet epigenetically altered fetal chromatin structure via covalent modifications of histones (25). In rodents, certain diets have been shown to differentially alter the epigenetic status (reviewed in (26)). Mice exposed to different diets in the post-weaning period exhibited epigenetic alterations that are associated with phenotypic changes (27).

Recent human studies indicated that food availability is not only important for the obesogenetic trajectory of directly-exposed generation, but also for their children and grandchildren. Data collected from the Dutch famine cohort suggested that maternal food restriction during pregnancy changed the DNA methylation of genes in the subsequent generation. Some of these genes are involved in the pathogenesis of obesity (and diabetes) (24); Kaati, et al. indicated that mortality rates due to cardiovascular events and diabetes of grandchildren were associated with the nutritional status of their grandparents, in a gender-specific manner (grandfather to grandsons, and grandmothers to granddaughters, respectively) (18).

All of these studies demonstrated several interesting points that have been largely disregarded by current US public health policies, notably that:

- Disease risk (i.e., diabetes, cardiovascular diseases, obesity) can be exacerbated by the nutrition status in/ of past generations;
- Nutritionally-driven changes are passed down to subsequent generations via epigenetic mechanisms (e.g., DNA methylation);
- Nutritionally-driven acquired epigenetic changes may, in some cases, be gender specific, and therefore, generating a gender-specific array of consequences upon the health status of subsequent generations;
- Epigenetic changes occur during the periods when the re-shaping of the epigenetic profiles is at peak (i.e., pregnancy, and perhaps even the late stage of sperm cell maturation in boys – prepuberal period).

Developmental plasticity: a short-term adaptation mechanism to nutrient availability

— The mismatch theory

Realization that epigenetic inheritance of acquired traits has an important role in our survival arose as a logical consequence of the observed role of nutrition in epigenetics. At present, nutrition-driven epigenetic changes are considered to be an important factor in developmental plasticity, allowing individuals to cope with predicted circumstances (28). In other words, by passing information acquired in one generation to the next, epigenetic mechanisms may increase a degree of environmental fitness to the next generation(s). In this light, it can be understood that any change in nutrient availability of one generation would "signal" the next generation to make certain physiological adjustments, in order for any offspring to be as fit as possible to accommodate and survive that specific change. Simply put, the next generation is "instructed" that certain changes in nutrient availability have occurred, and therefore, offspring should seek the most available types of foods (i.e., those which have been consumed by the parents).

Developmental plasticity may have allowed the human species (and other mammalian species) to better survive in continuously changing and, for the most part, hostile environments (i.e., deprivation of specific nutrients or food types), and to re-orient food choices toward those resources that were most available at a given time. The advantages of epigenetic inheritance of generationally acquired traits appear to be obvious. However, as humans re-shaped the environment(s) in which they live, developmental plasticity became something of a double-edged sword. In developed countries, increased food availability (and consumption) can be associated with increased burden of certain types of disease (i.e., mainly obesity, cancer, and the metabolic syndrome). Obesogenic diets (high-fat and calorie-dense foods) unfortunately, have become the most consumed diet types for US population. Thus, it may be that developmental plasticity - the ability for predictive adaptation, that was so useful in humankind's evolutionary past — has established the conditions for early-life origin of the aforementioned diseases (28). This mismatch occurs because of the collision of two forces: 1) the evolutionary force that, in a largely hostile environment, fosters physiological drives to consume foods that are the most available (but still scarce); and 2) the contemporary socio-economic force(s) that establish that such obesogenic foods are most available, and in abundance, and can therefore be over-consumed (Figure 2).

As a consequence, by eating an obesogenic diet, one generation prepares the next generation to seek and consume the "most available" diet in as large a quantity as the environment allows. Combined with behavioral factors as presented in Table I, our group hypothesized a "the perfect storm" scenario, which established conditions for the next generation to increase their obesity rates, and promote the deleterious consequences as expressed today. Figure 3 depicts the increasing mismatch induced by the pervasive presence of obesogenic diets throughout multiple generations, where each generation increasingly accumulates and further transmits its own acquired epigenetic modifications.

Rethinking obesity prevention policies

Individually tailored nutritional interventions are considered, today, as one of the most important factors in preventing or reversing the obesity epidemic. Recently, the need for individualized nutrition was officially recognized by the Institute of Medicine, emphasizing that it is essential to identify genetic and epigenetic mechanisms in order to fill fundamental gaps in the knowledge of nutrient-gene interactions (29).

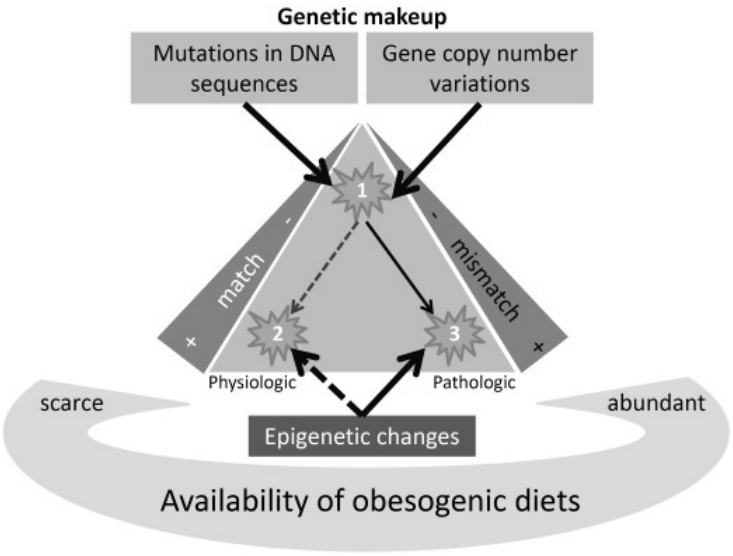

Figure 2. Developmental plasticity and the mismatch theory. The human genetic makeup is largely identical in all individuals. However, the genome of each individual is also unique, due to mutations in the DNA sequences, as well as, in many cases, to the existence of a different number of copies for a given gene (copy number variations). Outside of external influences, a specific genetic makeup should lead always to the same phenotype (phenotype 1). However, developmental plasticity, using various mechanisms that include epigenetic modifications, allows an individual to quickly adapt during fetal development to a predicted outside environment, based on the maternal signals received. In a largely assumed hostile environment (represented by food scarcity), epigenetic changes will increase the chances for the newborn to match his or her metabolic needs to the most available resources offered by the environment (phenotype 2). Such epigenetic changes will optimize the potential offered by the genetic makeup. However, if the presumption of food scarcity is not met (modern and developed countries), the same epigenetic optimization leads instead to mismatch between the predicted conditions (food scarcity) and the actual conditions (food abundance). Phenotype 3, in this case, has an increased risk for the onset of chronic disease (i.e., obesity and associated conditions).

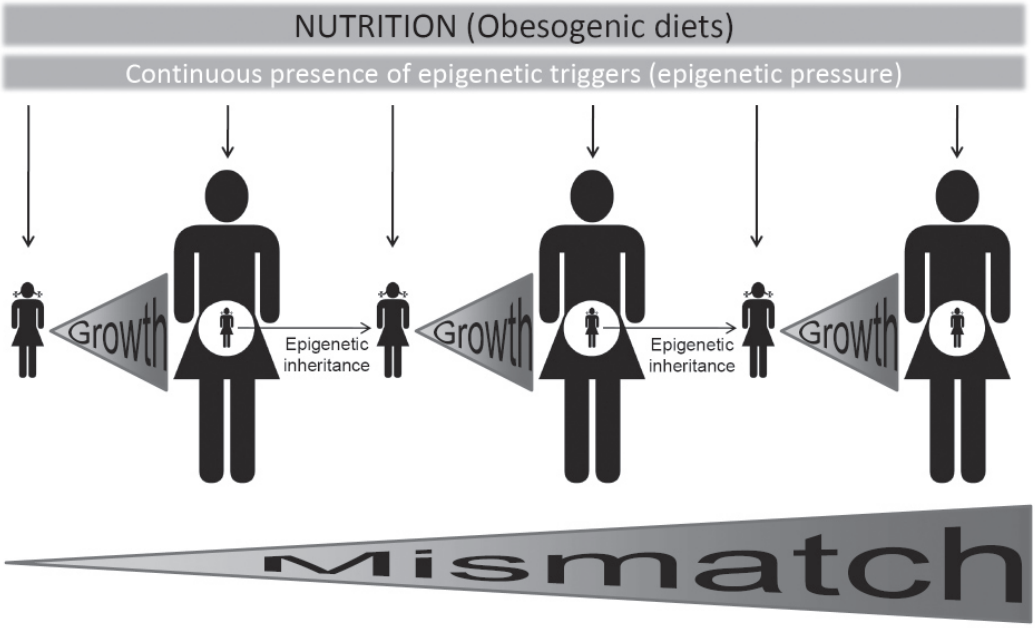

Figure 3. Transgenerational epigenetic pressure increases the existing mismatch. Since some of the epigenetic changes are inherited by the next generation, corresponding acquired characteristics will be also passed on. At the same time, the next generation, as long as it is exposed to the same epigenetic triggers (i.e., obesogenic diets), will continue to acquire epigenetic changes that could add up to those inherited. Therefore, as long as the epigenetic pressure is maintained throughout multiple generations, the epigenetic changes could either be maintained or increased from one generation to another. This can lead to an increased degree of mismatch, with an increased risk for disease from one generation to the next.

Pragmatic aspects of present policies

Combating obesity is clearly a priority of many stakeholders involved in shaping health care policies at state and federal levels (30). However, as indicated in a position statement by the Obesity Society, some of the measures implemented place an unfair burden exclusively on the affected individuals, without taking into account the environmental influences that drive, in part, individual behaviors (31). Two examples may be telling for the challenging ethical aspects discussed: First is Alabama's passing regulation on state employees, that imposed a surcharge on those employees who have a body mass index (BMI) over 30 kg/m2, and second is North Carolina's plan to deny employee access to the best insurance coverage option(s) if the employees' BMI exceed an imposed limit (cited in (31)).

These examples reflect— and emphasize— the incomplete understanding of the long-term mechanisms of obesity. As both animal and human studies have indicated, individual behaviors leading to obesity are also shaped by similar behaviors of past generations. Without minimizing the individual responsibility, scientific research has repeatedly shown that regulation of food intake is a complex process involving genetic background, epigenetics, acquired hormonal imbalances, parental behavior, and other social and economical factors (32, 33). Many of these are beyond the control of individuals. Far from saying that individual responsibility is minimal, it must be acknowledged that not all aspects incumbent to the control of food intake are completely manageable by individual assertions of free will.

Additionally, it is important to assess and address the role that epigenetic inheritance has in shaping decisions regarding food intake. As discussed, developmental plasticity is a strong trigger for developing certain eating patterns, in accordance with epigenetic signals during gestation, as well as epigenetic patterns inherited from generational predecessors. Therefore, any public health or health care measures should take into account the entirety of scientific evidence that indicates the complex mechanisms of generational and epigenetic variables in food intake regulation.

The need for a comprehensive long-term plan

When approaching the challenges that lay ahead in addressing and controlling public health and individual clinical aspects of obesity (as well as the interventions that are in place) several factors must have be analyzed and considered:

1. Long-lasting outcomes cannot be achieved by applying short-term solutions, or a succession of solutions that are not longitudinally implemented in a logical manner;
2. Pervasive causes of obesity, which are ubiquitously present at national level, require a unified approach, that can be specifically tailored to local conditions;
3. Scientific findings regarding the underlying causes of obesity, must form a basis for any/all programs of obesity prevention and treatment;
4. Efficient solutions to the existing forces that drive food over-consumption and consumption of foods with low-nutritional values must be feasible and acceptable to all involved parties (including food industry).
5. Solutions to be implemented must be ethically sound and acceptable to the involved individuals, in accordance with existing socio-cultural values;

Furthermore, it is posited that obesity prevention programs should specifically address the underlying biological- as well as psycho-socio-economic variables and dynamics of obesity. Thus, long-term solutions are needed for offsetting burdens incurred by the increased mismatch between epigenetic changes (developmental plasticity) and the increased availability and consumption of obesogenic diets. Since some epigenetic changes are heritable, multigenerational policies should be established, rather than establishing mainly short term objectives over a single generation.

At least two aspects should be considered regarding the need of a unified approach: 1) Because the causes of obesity are *pervasive* in the American society, and 2) because of the *high mobility* of the US workforce, it is imperative that prevention programs must be designed such that they would longitudinally and specifically "follow" the individuals. These programs should transcend state boundaries, and facilitate the conditions (legislation, health insurance, and health care accessibility) that would be necessary to sustain such an approach to prevention and care.

Although the role of transgenerational inheritance in health and disease is currently well-established, further research is needed to better define the roles and extent of epigenetic changes in obesity. Without wide scientific agreement, the chances of success for any prevention programs would be jeopardized by myriad proposed approaches that could

interfere with a more comprehensive view and assessment of the problem and its potential resolution(s).

Of course, it is essential that ethical aspects to be observed, especially when shaping legislation needed to support any such programs at state or federal levels. As previously discussed, there is a real danger that, in the interest of a legitimate interest to decrease the obesity burden, legislation would not take into account the intricate roles of epigenetic mechanisms in regulating human behaviors that may be contributing to obesogenesis. Any and all solutions should be acceptable to the individuals to whom the legislation is addressed and directed.

Towards such ends, an honest debate, with participation of all stakeholders involved in the obesity problem, is necessary. Any major changes in this direction would incur issues likely to affect the food industry, health insurance providers, and health care providers. The economic issues that would arise must be addressed, and adequate solution paths must be developed that meet the ethical and practical obligations of an obesity-prevention effort. Educating the young generation, and their parents, is clearly an important, major objective to be achieved in enacting such goals. Although education regarding deleterious effects of obesity is present in many schools, a more finely-grained approach is required in order to achieve the stated objectives, and to overcome the strong influences of advertising, sedentary life-styles in the family, and the short-term economical attractiveness of obesogenic foods.

Conclusions

In 2008 health care costs in US were over $2.3 trillion (16.2% of the nation's Gross Domestic Product), with spending per resident accounting for $7,681 (34). Interestingly, the same source projected a continuous increase in health care spending, even in the context of the Affordable Care Act implementation, reaching an estimated $4.3 trillion for 2018 (34). According to the Centers for Disease Control and Prevention (CDC), 75% of the health care costs account for chronic disease treatment - including obesity (discussed in (35)).

Is obesity a threat to national security? Obviously, the prevalent obesity limits the pool of personnel fit for recruitment and duty (36). However, obesity should be perceived as a national security threat beyond this perspective. The multiple aspects of this burden impact not only military recruitment potential, but, at least equally important, on nation's ability to ensure the well-being of its citizens. By incurring an enormous economic burden, loss of work time, and loss of life quality, obesity and its array of related diseases threaten the health and well-being of both for the present and forthcoming generations. In a world of increasing global competitiveness, excessive health care costs, lost productivity, and loss in the quality of life associated with obesity, have — and will continue to — become a liability.

As previously discussed, nutrition can alter the DNA methylation of genes, and this pattern can be inherited by next generation (at least to some extent). Transgenerational inheritance represents a first step influencing offspring, and can also render an increased or decreased risk of disease to subsequent generations. While epigenetic inheritance, in itself, may not be sufficient for the onset of disease, it certainly primes such risk. Even if definitive human studies are lacking, epidemiological studies have revealed that maternal obesity is associated with metabolic imbalances, and a variety of cognitive and behavioral disorders in children and eating disorders in adolescence (37).

Additional research is needed in epigenetics and nutrient-gene interactions in order to more precisely determine the involvement of transgenerational inheritance in obesity. Nevertheless, pragmatic presentation and analysis of all currently recognized factors contributing to obesity (including epigenetics and transgenerational inheritance) should be considered and regarded when establishing long-term obesity-prevention policies. Clearly, obesity is a complex disorder and its prevention and treatment requires a complex and comprehensive approach.

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Competing interests

The author declares he has no competing interests.

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