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Famine, Epigenetics, and Long-Term Health: Implications for Gaza

Dima Elzayat
dima.elzayat21@gmail.com

ABSTRACT

Prolonged periods of famine have been linked to a number of long-term physical health issues beyond those related to immediate malnutrition. The evidence of this has accumulated over several decades of study, showing that nutritional deficiencies during the critical periods of development can cause alterations in gene expression through changes in mechanisms of epigenetics (DNA methylation, histone modification, and non-coding RNA), which could be maintained across an individual's life span and may contribute to health problems in future generations. This literature review will examine the available evidence from major historical famine cohorts, including the Dutch Hunger Winter, the Chinese Great Famine, and the Leningrad Siege, as well as experimental studies utilizing animal models. Together, the results of all of these studies suggest that there is an association between early-life nutritional deprivations and altered regulation of genes responsible for growth, metabolism, and stress response, especially IGF2 and NR3C1. This review will also explore whether these results are relevant to current-day food shortages and maternal-child malnutrition occurring in Gaza. Gaza-related discussions within this manuscript are presented as a risk-based extrapolation of historical cohorts rather than a predictive model for expected outcomes due to the lack of Gaza population-specific epigenetic studies and the many confounders present, including but not limited to trauma exposure, infectious disease, displacement, and disrupted access to healthcare. While there is substantial evidence supporting the biological plausibility of maintaining epigenetic changes resulting from famine exposures, there are still a number of important limitations regarding making causative inferences about the exposure, measuring exposure, and how much of the epigenetic changes are transmitted between generations in humans. As such, this review will conclude that providing early nutritional and psychosocial interventions may offer some protection against long-term health risks and emphasize the necessity of continued research into the effects of famine and other forms of extreme hardship and trauma in conflict-affected areas.

INTRODUCTION

With more than a million people suffering from widespread famine, the Gaza Strip is experiencing one of the most severe humanitarian crises seen in the twenty-first century (UNICEF, 2024). This paper presents a narrative literature review that draws upon prior research that examined the association of famine exposure and subsequent long-term health consequences with regard to epigenetic regulation.

Intergenerational effects refer to effects observed in children who were directly exposed to famine during fetal development; however, transgenerational inheritance (i.e., effects observed in later generations without direct exposure) has been identified in animal studies, but the evidence supporting such an effect in humans has been indirect at best. Sources were chosen as relevant to famine exposure, epigenetic mechanisms, and long-term health outcomes, using established human cohort study data and some supporting animal model experiments. This was a narrative review; there were no systematic review inclusion or exclusion criteria used in selecting sources, and thus, the conclusions that can be drawn from this review are strictly limited to a synthesis and critical evaluation of the existing literature.

The population in Gaza is experiencing extreme levels of famine due to the total blockage of food and other essential living needs. This blockage results in the immediate physical symptoms associated with starvation, including acute malnutrition, stunted growth, extreme weight loss, and increased mortality rates. However, there are deeper biological effects caused by famine that affect the next generation and may be less noticeable or even unknown until it is too late. Recent studies have shown that famine may be associated with molecular changes in DNA and chromatin that may persist and could contribute to intergenerational outcomes (Bird, 2007; Jirtle & Skinner, 2007).

Research indicates that while famine exposure has been associated with changes in DNA regulation and chromatin function in the expression of genes and does not alter the actual DNA sequence, these changes may persist and are capable of passing from one generation to another (Bird, 2007; Jirtle & Skinner, 2007). As a result of this process, these individuals may develop the capacity to grow at a slower rate than those who were not affected by famine, as well as potentially have altered metabolic processes affecting nutrient absorption, exhibit reduced tolerance for environmental stressors, and develop chronic disease later in life. Furthermore, research has demonstrated that although an individual may never have been exposed to direct famine conditions themselves, the same nutritional deficits they experienced during their early life may produce negative health-related outcomes (Lumey et al., 2011). Past famines have similarly produced biologically significant relationships as well. The biological impacts of early life malnutrition due to the Great Famine in China (1959-1961), the Dutch Hunger Winter (1944-1945), and the Leningrad Siege (1941-1944) have been shown to persist into adult life (Lumey et al., 2011).
Studies on the Dutch Hunger Winter provide examples of the biological consequences of famine extending far beyond the time when it occurs. Researchers have identified epigenetic changes of the IGF2 gene that persisted for many years after the Dutch Hunger Winter (Heijmans et al., 2008). The IGF2 gene has an important role in regulating metabolism and growth, and the epigenetic changes are associated with hypomethylation of this gene. Years of conflict and blockage of food supply routes to Gaza have caused a significant disruption to maternal and early childhood nutrition.

Malnutrition rates in certain areas of Gaza have surpassed 25% and are higher than the international famine threshold as defined by UNICEF (UNICEF, 2024). The poor nutritional status of pregnant mothers, along with a lack of prenatal medical care for women during times when their fetus may be at an increased risk of harm, may increase the likelihood of the fetus having its DNA epigenetically altered. The alteration of DNA is made possible by the various processes that can cause changes to the epigenome, including but not limited to DNA methylation, histone modification, and the alteration of noncoding RNA sequences. These changes to the epigenome can have long-term effects on how the

offspring express their genes and potentially lead to the development of neuropsychiatric disorders, cardiovascular disease, and metabolic disorders in the offspring (Jirtle & Skinner, 2007; Meaney & Szyf, 2005; Feil & Fraga, 2012; Bird, 2007).

Understanding this process is crucial to assessing whether the biological effects of the current emergency in Gaza could be passed on through generations. Walker et al. (2017) define the "epigenetic memory" of famine as the potential for poor nutrition at specific points in fetal and early infant development to interfere with the body's regulation of metabolism and its stress responses. A critical point in fetal development is the first trimester, when DNA methylation is established (Langley-Evans, 2001). Typically, epigenetic changes are made to genes that regulate growth, brain development, and energy homeostasis (Waterland & Jirtle, 2003). Therefore, based on historical data, if the nutritional status of individuals in Gaza does not improve, it may be possible that they will experience similar long-term health risks.

As a result, these epigenetic changes typically occur in genes that regulate growth, brain development, and energy balance (Waterland & Jirtle, 2003). Historical data indicate that if the nutritional environment does not improve, similar long-term health risks may develop in Gaza. All sources were selected based on relevance to famine exposure and long-term health outcomes, with emphasis on well-established cohort studies and experimental models.

BIOLOGICAL MECHANISMS LINKING UNDERNUTRITION TO EPIGENETIC CHANGE

The body relies primarily on dietary glucose for energy under normal conditions. When there is no food available, blood sugar levels fall, and the liver and muscle stores of glycogen are mobilized to maintain metabolic function (Lillycrop & Burdge, 2011). At some point during starvation, the body will begin breaking down muscle and fat tissue to continue basic processes. The changes made through epigenetics will help a cell respond to nutrient availability by making genetic information accessible for gene expression without altering the DNA sequence (Bird, 2007).

DNA methylation is one of the most important ways that cells can regulate gene expression through epigenetics by adding methyl groups to cytosines, thereby typically suppressing gene expression (Waterland & Jirtle, 2003). There have been studies done that show how nutrients provided during development have changed methylation patterns of genes involved in growth and metabolism in such a way that these changes may be present throughout life (Waterland & Jirtle, 2003). Histones are modified, such as acetylated and/or methylated, which influence gene expression by changing the structure of chromatin to allow or prevent transcription machinery from accessing the DNA (Feil & Fraga, 2012). In addition to coding RNA, a wide variety of noncoding RNAs, which include miRNAs and lncRNA, also serve as post-transcriptional regulators of gene expression (Feil & Fraga, 2012).
Physiological responses to famine are tightly linked to the various epigenetic mechanisms. The most important area of study, however, relates to the effects of maternal undernutrition, as it occurs at a time

when organ systems are developing and establishing DNA methylation patterns (Langley-Evans, 2001). Maternal undernutrition occurring within the first two trimesters has been reported to have detrimental effects on both fetal organ development and the function of the hypothalamo-pituitary-adrenal (HPA) axis, along with its associated neuronal circuits (Langley-Evans, 2001). Further disruptions in these developmental trajectories can occur in early childhood due to postnatal starvation.

Studies using rodents have shown that maternal protein restriction results in changes in methylation of genes that regulate glucose metabolism in the pancreas and liver of the offspring, resulting in an increased risk for obesity and diabetes (Langley-Evans, 2001).

Starvation increases oxidative stress, increases cortisol levels, increases autophagy, and decreases insulin sensitivity (Walker et al., 2017). These stress signals may become embedded in epigenetic regulatory pathways over time and therefore alter the expression of metabolic and hormonal genes. As an example, prenatal undernutrition has been associated with changes in the methylation of IGF2, while genes associated with stress regulation (such as NR3C1) have had alterations in their expression, which have resulted in impaired stress response later in life (Heijmans et al., 2008; Meaney & Szyf, 2005).

EVIDENCE FROM HUMAN FAMINE COHORTS

Early nutritional deprivation affects the development of the human body and influences health over a lifetime by making a series of genetic changes. Research from the Dutch Hunger Winter of 1944–1945 is widely recognized for its investigation into how nutrition during the early stages of development influences the epigenetic process and an individual's future health. Research has demonstrated that people whose mothers were pregnant during the period of time that their babies were exposed to the Dutch famine of 1944–1945 had lower levels of DNA methylation at the IGF2 gene locus fifty years later than others who did not experience the famine. This evidence supports that nutrition during early life stages can influence how an individual's genes regulate themselves (Heijmans et al., 2008). Additionally, people who experienced famine while still in utero were more likely to develop conditions including cardiovascular disease, type II diabetes, and obesity than people who were not exposed to the famine (Roseboom et al., 2006).

The same patterns of how nutrition in early life affects an individual's epigenetics and future health have also been observed with children born to mothers who suffered from extreme malnutrition due to the Chinese Great Famine. Similar to the Dutch study, research suggests that the offspring of mothers who experienced the Great Famine showed altered methylation of genes that regulate metabolism and neuropsychiatry, but it is unclear if the observed alterations in methylation of these genes are associated with the increased risk of developing conditions such as depression, anxiety, or schizophrenia (Li et al., 2019).

Furthermore, in addition to detecting the metabolic changes in the offspring of the parents who were exposed to a period of famine, researchers found that there are changes in methylation in those genes involved in responding to stress. One example of this is that researchers detected changes in methylation of the NR3C1 gene, which is responsible for the regulation of the glucocorticoid receptor and has been

shown to be associated with impaired regulation of stress and an increased risk of developing anxiety or depression as a result of experiencing early life adversity (Meaney & Szyf, 2005). Generally speaking, in famine cohorts, research shows that nutritional deprivation experienced by children during their early developmental stages can lead to long-lasting biological consequences.

However, the magnitude and duration of the effects will be influenced by the population and the context in which the famine occurred.

EVIDENCE FROM MODEL ORGANISMS AND EXPERIMENTAL STUDIES

Experimental research conducted on model organisms can provide an understanding of biological processes that cannot be studied in humans. Starvation was demonstrated in C. elegans to alter the expression of small RNA molecules; this alteration continued across generations and influenced both stress tolerance and metabolic pathways (Rechavi et al., 2011). These results suggested that non-coding RNA molecules could act as environmental indicators to pass along information regarding nutrient availability to offspring.

Studies involving rodents provide evidence for maternal epigenetic programming as a result of maternal undernutrition. Reduced caloric intake or reduced maternal protein intake during pregnancy is associated with reduced DNA methylation in the liver, pancreas and hypothalamus of the offspring; this condition results in an inability of the offspring to maintain normal blood glucose levels and increases the likelihood of the offspring being obese (Lillycrop & Burdge, 2011) Similar effects were demonstrated in some instances in second-generation offspring, indicating a possible transgenerational effect.

Similar patterns of early life nutritional restriction have been observed across a range of vertebrates (for example, zebrafish and birds). Nutritional deficiencies during early development have produced epigenetic adaptations that influence both immune function, metabolic function, and behavior. Epigenetic adaptation to nutritional deficiency appears to be evolutionarily conserved; however, it is critical to be cautious when generalizing findings from animal studies to human populations.

KEY DEBATES AND LIMITATIONS IN THE LITERATURE

Although there has been substantial research linking famine exposure to later life health status, the studies that have been conducted contain many limitations in interpreting results from previous research. Since most human studies use either food availability in an individual's geographic location or a record of famine exposure (such as crop failure) as a proxy for the individual's nutritional status, these indicators of nutritional status do not always reflect the actual level of exposure experienced by the individual. Furthermore, since famine typically coincides with other stressful events such as high levels of infectious diseases, forced migration, psychological trauma, and reduced access to medical care, it is possible that

these stressful events could also independently affect the development and/or future health status of individuals exposed to a famine.

The second major area of contention regarding famine-related epigenetic changes is the question of whether observed epigenetic changes in response to famine represent a true form of transgenerational inheritance in humans. Animal studies indicate that epigenetic traits can be passed to subsequent generations provided specific environmental conditions exist during the time when the original epigenetic trait was established; however, human studies remain limited in number and indirect. Therefore, observed effects in offspring may be due to the mother experiencing physiological changes during pregnancy or to a shared post-natal environment (and not necessarily due to the transmission of epigenetic marks through the germline). Consequently, many of the observed effects are best characterized as intergenerational and not necessarily transgenerational.

A third major limitation to understanding the relationship between famine-related epigenetic changes and disease is the question of whether observed epigenetic changes are directly responsible for the disease process or if they serve as biomarkers for the adverse exposures experienced by the offspring. To better understand the causal relationship between famine-exposure-related epigenetic changes and disease status, longitudinal studies that include multiple measures of biological samples and improved measures of exposure to famine are necessary.

APPLICATION TO GAZA

Gaza's current famine conditions have many of the same attributes as other famine events throughout history, which include extended time frames of food insecurity and increased vulnerability to pregnant individuals and infants or young children. More than 1.2 million people are experiencing extreme food insecurity, and child malnutrition is estimated at over 25 percent in many locations (UNICEF, 2024; UNRWA, 2024), according to UNICEF and UNRWA. Given that the prior famine cohorts were found to have altered methylation in the aforementioned genes during critical development periods, there may also exist an elevated long-term risk for metabolic and stress-related disorders in the Gaza population. However, these inferences are all context dependent and should be interpreted cautiously: historical cohort findings do not establish the inevitability of disease, and outcomes in Gaza may differ due to environmental and medical factors as well as limited direct epigenetic evidence from the population.

There exists a high level of association between altered methylation of genes such as IGF2 and NR3C1 and changes in growth regulation, metabolic function, and stress responses. These issues may be further exacerbated by continued psychological trauma and limited availability of healthcare services in Gaza. There is a lack of epigenetic studies conducted in Gaza populations, and conclusions should be made as evidence-based risk assessments and not as final results.

POTENTIAL MITIGATION STRATEGIES

Early intervention has the potential to correct some of the long-term effects of genetic expression that occur due to the attachment of methyl groups to specific sections of DNA, and therefore, how many methyl groups attach to a particular piece of DNA, which can be reversed due to early exposure to famine. The use of nutritional supplementation during both pregnancy and early childhood, particularly with respect to essential fatty acids and necessary nutrients, may help establish an optimal environment for the maintenance of DNA methylation patterns in those genes that determine growth and control stress (Lillycrop & Burdge, 2011). In addition to providing a supportive environment, interventions that focus on addressing the psycho-social impacts of chronic stress may also benefit individuals who experienced early-life adversity. This is because chronic stress has a strong correlation to the manner in which genes express themselves through epigenetic mechanisms. Programs that provide young people with a sense of stability of thought, education, and social support may assist in mitigating the long-term health risks associated with early-life adversities. The possibility of using epigenetic biomarkers to identify children who are at a high risk of long-term health effects due to early-life adversities has been proposed; however, there are many issues that need to be addressed before this type of program could be implemented.

CONCLUSION

The body of evidence provided by historical cohorts exposed to extreme famine, laboratory studies, and studies examining epigenetic changes provides strong evidence that exposure to extreme undernutrition during critical developmental periods is associated with enduring changes to gene expression in relation to growth, metabolism, and response to stress. Food insecurity and child-maternal malnutrition experienced in Gaza may create similar opportunities for long-term negative impacts to occur in populations currently experiencing and will experience in the future as a result of their exposures.

While there are many unknowns concerning causation and the degree to which an individual's epigenetic profile is inherited, the available evidence clearly illustrates the necessity of providing both nutritional and psycho-social support early in life to mitigate negative outcomes. Drawing lessons from previous famines may allow for developing effective strategies to reduce long-term health burdens in response to humanitarian crises. These conclusions should be interpreted as evidence-based risk considerations rather than deterministic predictions, especially when applying historical findings to Gaza.

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