Review

Epigenetic Consequences of Famine: Lessons Learned and Future Research Directions

Hasan Khatib *, Elijah Ellsworth , Norisha Badhwar

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Article

Epigenetic Consequences of Famine: Lessons Learned and Future Research Directions

Hasan Khatib *, Elijah Ellsworth and Norisha Badhwar

Department of Animal and Dairy Sciences, The University of Wisconsin-Madison, 1675 Observatory Dr., Madison, Wisconsin, 53706, USA

* Correspondence: hkhatib@wisc.edu

Abstract

The recent rise in global food insecurity has renewed scientific interest in understanding the long-term health consequences of early-life nutritional deprivation. This study critically evaluates the experimental designs and methodological approaches of key publications examining the epigenetic and phenotypic effects of the Dutch and Chinese famines. Specifically, these studies were assessed for sample size, control group selection, relevance of tissue sampling, timing of famine exposure, and the quality of statistical reporting. Research on both famines has centered on prenatal exposure and subsequent health outcomes, providing important insights into how in utero nutritional deprivation may lead to long-lasting epigenetic modifications. These changes have been linked to elevated risks for metabolic, cardiovascular, and neuropsychiatric disorders. Despite these contributions, many studies exhibited notable limitations, including small sample sizes, questionable accuracy in reporting health outcomes, and issues with the selection of control groups. Such methodological shortcomings may have led to misinterpretation of some findings. Ongoing and recent famines in regions such as Sudan, Somalia, and Gaza—driven by conflict and environmental disasters, including droughts and floods—represent some of the most pressing humanitarian crises of our time. Lessons learned from studies of the 20th century Dutch and Chinese famines can inform the design of future research on the biological and intergenerational consequences of famine and trauma. Improved study designs will enhance the ability to generate reliable evidence and guide global health strategies for populations at risk of transgenerational effects from nutritional deprivation.

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1. Introduction

Environmental exposures, including nutritional constraints, stress, chemicals, and toxicants, are known to modify the epigenome, consequently influencing disease susceptibility and other phenotypic outcomes across subsequent generations in humans and experimental animals [1]. Several groundbreaking studies have demonstrated that environmental factors, including maternal diet and exposure to endocrine disruptors during pregnancy, can induce phenotypic and epigenetic changes in offspring [2–5]. Environmental epigenetics studies indicate that the effects of parents' experiences, including undernutrition or stress, can be passed to their offspring through intergenerational or transgenerational epigenetic inheritance mechanisms.

According to the United Nations World Food Program, the world is facing an ongoing global food crisis driven by four main factors: conflict, climate change, economic instability, and displacement (https://www.wfp.org). Among these, conflict is the leading cause, as it destroys infrastructure, displaces populations, fuels inflation, and restricts access to markets, ultimately resulting in widespread hunger and food insecurity. In turn, hunger can fuel social unrest, as communities protest about rising food prices or compete for limited resources.

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At the same time, extreme weather events are becoming more frequent and severe, disrupting agriculture and significantly affecting both local and global food systems. In 2021, climate-related disasters were the leading cause of severe hunger in eight African countries, pushing 23.5 million people into critical levels of food insecurity (https://www.wfpusa.org).

According to the 2023 Global Report on Food Crises (GRFC), nearly 282 million people across 59 countries and territories faced severe acute hunger, representing an increase of 24 million from the previous year. This rise is attributed to both expanded reporting and a worsening food security situation, particularly in regions such as the Gaza Strip and Sudan (https://www.wfpusa.org). Global food demand is projected to rise by more than 50% by 2050; however, climate change is expected to reduce agricultural yields of major crops over the same period (https://www.csis.org). This imbalance could lead to sharp increases in food prices, heightened food insecurity, social unrest, and political instability—conditions that may escalate into conflict and trigger famine-like scenarios (https://2021-2025.state.gov). To better anticipate the potential consequences of such crises, it is crucial to study historical famines that highlight the impacts of nutritional deprivation. Two of the most frequently examined cases are the Dutch Famine of 1944 and the Chinese Famine of 1959.

The Dutch Famine, commonly known as the 'Hunger Winter' (Hongerwinter), occurred between November 1944 and April 1945 during the final stages of World War II. It severely impacted the western region of the Netherlands, particularly major cities such as Amsterdam, Rotterdam, and Hague [6]. The immediate cause of the famine was a German blockade, imposed in retaliation for a railway strike organized by the Dutch resistance in support of the advancing Allied forces. The blockade cut off food and fuel supplies to the affected regions, further straining an already fragile wartime economy [7]. As a result, the population experienced severe malnutrition, with daily caloric intake dropping to as low as 400–800 calories [8]. An estimated 20,000 people died, and approximately 4.5 million were affected by the direct and indirect consequences of the famine [9]. The famine had lasting demographic and health effects, particularly among individuals exposed in utero or during adolescence. The famine officially ended in May 1945 with the liberation of the Netherlands by Allied forces [10]. However, its legacy persists, as subsequent generations continue to experience consequences linked to parental exposure, effects associated with epigenetic modifications.

The Dutch famine presented a unique opportunity to examine David Barker's fetal origins hypothesis and the multigenerational effects of hunger on subsequent generations. Prenatal exposure to famine during early gestation correlated with hypertension, elevated blood pressure, and a notable rise in coronary heart disease later in adulthood, thereby substantiating the Barker hypothesis [11]. Moreover, women who experienced famine during pregnancy gave birth to offspring with increased neonatal adiposity and compromised health, indicating the potential transgenerational transmission of maternal undernutrition effects [11]. To investigate whether prenatal exposure to the Dutch famine resulted in epigenetic alterations, DNA methylation levels of insulin-like growth factor II (*IGF2*) were evaluated in individuals conceived during the famine six decades earlier, with unexposed same-sex siblings serving as controls [12]. The exposed individuals showed lower methylation levels. The Dutch famine studies illustrate that maternal undernutrition during both the early and late stages of pregnancy can influence the health of offspring.

The Great Chinese Famine has been largely attributed to policies implemented by the Chinese Government during the “Great Leap Forward” in the mid-20th century. This campaign introduced unproven agricultural techniques and prioritized rapid industrialization, diverting labor from farming and severely disrupting food production. As a result, grain output declined sharply—by more than 25% at its peak, equivalent to a reduction of 53 million tons—triggering widespread famine across China [13]. The death toll is estimated to have exceeded 30 million people by 1961 [14], and the famine caused a dramatic decline of more than 20% in the birth rate over the following five years [15]. Beyond the death toll, the famine had profound effects on physical and mental health, cognition, and other severe consequences for both those who experienced it and their offspring. Exposure to famine between the ages of 3 and 5 was linked to mental health issues, resulting in approximately 8

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million additional cases of depression in adulthood [16]. Furthermore, fathers who were affected by malnutrition during the famine had children with impaired cognitive abilities [17]. Interestingly, exposure to poor nutrition in utero and during early adulthood during the Chinese famine was associated with reduced height in two successive generations [18].

Research on the epigenetic effects of the Dutch and Chinese famines has primarily focused on increased health risks associated with prenatal exposure to famine. While numerous studies have explored these outcomes, our objective is to critically evaluate the experimental designs underpinning these studies. Specifically, we assessed whether Chinese and Dutch famine studies employed appropriate controls, had sufficient sample sizes, defined clear famine exposure windows, and collected accurate phenotypic measurements, all of which are essential for ensuring the validity and interpretability of their conclusions. This analysis is significant in identifying the methodological strengths and limitations of existing famine research, thereby guiding future studies toward more rigorous and informative designs. Ultimately, improved methodologies will enhance our understanding of how prenatal famine exposure affects long-term disease risk, with significant implications for public health planning and policy development in the context of future nutritional crises.

2. Methods

The studies included in this analysis were primarily identified through PubMed using search terms such as “famine epigenetics,” “famine methylation,” and “prenatal famine exposure,” applied to both the Dutch and Chinese major famines of the 20th century. A total of 15 representative papers were selected based on their examination of the effects of famine exposure on subsequent generations, with an emphasis on studies investigating epigenetic mechanisms, particularly DNA methylation. However, due to the limited number of available studies, all relevant papers addressing intergenerational effects of famine were included, regardless of their specific epigenetic focus. This inclusive and systematic approach ensured a robust foundation for evaluating the long-term biological consequences of famine exposure.

3. Results and Discussion

The analysis of the Dutch and Chinese famine studies involved several critical considerations, including epigenetic analysis to detect associations between famine outcomes and epigenetic marks, tissue selection for epigenetic and metabolic analyses, sample size, and the timing of exposure to famine.

3.1. Epigenetic Analysis

Wang et al. [13] investigated the impact of the Chinese famine exposure on the insulin receptor (INSR) gene by comparing three distinct birth cohorts defined by their timing of famine exposure. The pre-famine-exposure group consisted of individuals born in 1958 (n = 82), while the post-famine-exposure group included those born between October 1, 1962, and September 30, 1964 (n = 78). The main famine exposure group was composed of individuals born between October 1, 1959, and September 30, 1961, during the height of the famine (n = 75). Epigenetic analysis of blood samples focused on DNA methylation levels in the INSR gene. Phenotypic measures included body mass index (BMI), waist circumference, fasting plasma glucose levels, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and diastolic and systolic blood pressure. This study found a link between early-life nutritional deprivation and subsequent epigenetic changes that are associated with metabolic health in adulthood. Individuals exposed to the Chinese famine during the prenatal period displayed higher waist circumference compared to non-exposed individuals (P = 0.029). Specifically, the fetal-exposure group showed significantly higher DNA methylation levels (+3.3%) in INSR (P = 0.003). Additionally, the DNA methylation level of INSR was associated with increased triglyceride concentrations and decreased

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HDL-C levels. However, this study and similar undernutrition studies have several limitations, some of which have been acknowledged by the authors. A major limitation is the methylation level difference (3.3%) between famine-exposed and non-exposed groups. There is no evidence that such a small methylation difference would affect gene expression and hence phenotypes. Other limitations discussed by the authors include that the DNA methylation analysis was conducted 50 years after fetal exposure to famine, the differing environmental exposures of the exposed and non-exposed groups following the exposure, and the distinct genetic backgrounds of the exposed and non-exposed groups. These limitations need to be considered in future famine or undernutrition studies.

In a different study, the effects of prenatal famine on DNA methylation in the serotonin signaling pathway were examined in 184 individuals born during the famine (January 1, 1959, to December 31, 1961) and 105 unexposed controls born after the famine (January 1, 1963, to December 31, 1964) [19]. This study provided insight into how prenatal famine exposure may affect the epigenetic regulation of genes involved in neurotransmission pathways, potentially influencing long-term health outcomes. Reduced methylation of the 5-hydroxytryptamine receptor 2C gene (HTR2C), which is associated with serotonin signaling, was observed in females ($P = 0.014$), but no significant methylation differences were detected in males. The authors did not provide the absolute methylation level differences between groups, limiting the ability to assess biological relevance. A major limitation of the study is the reliance on DNA methylation data derived from blood, which may not accurately reflect methylation patterns in brain regions associated with neuropsychiatric disorders. Without validating whether methylation patterns in blood correspond to those in relevant brain tissues, conclusions drawn about the impact of famine exposure on brain-related outcomes remain speculative. Additionally, while the study's control group consisted of individuals born after the famine, their parents' germ cells were likely exposed to the same famine conditions. This compromises the distinction between exposed and non-exposed groups, limiting the ability to attribute observed differences solely to in utero famine exposure.

Similarly, epigenetic effects of prenatal famine were examined in 25 individuals exposed to the Chinese famine during the first three months in utero and 54 controls from the same population [20]. In addition, the authors analyzed the DNA methylation of fibroblasts obtained from skin samples of five healthy Dutch individuals, cultured under conditions similar to those of famine. Genome-wide methylation analysis was conducted in blood cells of the 79 individuals and the sample of fibroblast cells, followed by pathway enrichment analysis. However, this analysis has not revealed any significant methylation differences between the two groups. Instead, the authors reported an overlap of three DMRs between blood and cell culture samples. These DMRs were assigned to genes involved in nervous system development and neurogenesis, including ENO2, ZNF226, CCDC51, and TMA7. One key limitation of the study investigating the effects of the Chinese Famine on individuals exposed in utero is the use of blood cells for DNA methylation analysis, which the authors acknowledge as suboptimal for capturing relevant epigenetic changes. Additionally, the study suffers from an unbalanced sample size, with 54 control individuals compared to only 25 famine-exposed individuals, reducing the statistical power of the analysis. This limitation, combined with an overall lack of power, hindered the ability to detect DMRs with confidence. Furthermore, the comparison of DMRs from famine-exposed individuals with those from fibroblasts of healthy Dutch individuals is methodologically inappropriate, given the differences in tissue type and population background. Finally, the absence of phenotypic data from the famine-exposed individuals limits the ability to interpret the functional relevance of any observed epigenetic differences.

The Genomic Research of the Chinese Famine (GRECF) study examined the impact of famine exposure on DNA methylation of the insulin-like growth factor 2 (IGF2) gene and blood lipid levels in adulthood. The study included individuals who experienced famine as fetuses, infants, or those who were born after the famine [21]. Blood samples from 180 participants were collected approximately 50 years after the famine and analyzed for DNA methylation. The participants were assigned to moderate or severe famine groups based on their residence in provinces with varying rates of starvation and death. Analysis of eight CpG sites revealed only one CpG that was associated

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with severe famine exposure, with a 7% increase in methylation at the CpG1 site of IGF2 observed in the during-famine cohort. The methylation level of this CpG was associated with elevated cholesterol levels in adulthood. This study has several notable limitations. The observed differences in DNA methylation (7%) were minimal, with only one out of eight examined CpG sites reaching statistical significance. Moreover, the analysis was conducted in blood cells, which the authors acknowledged may not accurately reflect methylation patterns in relevant tissues. Additionally, the study's limited sample size further reduced its statistical power, compromising the reliability of the findings.

Other epigenetic studies have reported methylation differences using percentages or P values, which may be statistically significant but fail to convey the biological relevance of the findings [22]. To enhance interpretability, future studies should incorporate measures that combine statistical significance with biologically meaningful metrics. For example, reporting absolute and relative methylation differences, effect sizes, or fold changes would provide deeper insights into the functional implications of prenatal famine exposure.

3.2. Exposure to Famine

A crucial consideration in famine studies, particularly regarding prenatal exposure, is the timing of exposure during specific periods of gestation. Several Dutch studies define famine exposure according to early, mid, or late stages of pregnancy. For instance, Roseboom et al. [23], in their analysis of lipid profiles, categorized individuals into three gestational exposure groups: early (born August 19–December 8, 1945), mid (born April 29–August 18, 1945), and late gestation (born January 7–April 28, 1945). Similarly, Ravelli et al. [24], focusing on glucose metabolism, used the same three 16-week intervals to classify late (January 7–April 28), mid (April 29–August 18), and early gestation (August 19–December 8) exposure. Research on cognitive function has also followed this gestational categorization [25], reinforcing the importance of developmental timing in assessing the long-term effects of prenatal famine exposure.

Most Chinese famine studies utilized a cohort-based design to compare individuals born during the famine period (1959–1961) with those born post-famine (1962–1964). Although these comparisons may provide useful information for contrasting famine and post-famine cohorts, some control groups [19,26] included individuals born soon after famine recovery, thereby increasing the risk of residual maternal nutritional stress and reducing the ability to detect biologically meaningful differences between groups. Control groups, such as those used in Wang et al. [13] and Shen et al. [21] included pre-famine cohorts (1956–1958), which may be more informative as a baseline for comparison of permanent environmental and epigenetic effects.

In the Dutch Famine studies, some control groups included individuals conceived after the famine, an approach that may introduce confounding factors related to post-famine recovery and environmental changes [12,22–24,27,28]. However, the use of controls conceived after famine introduces the possibility that observed epigenetic changes may reflect modifications present in the oocyte before fertilization. This raises the potential for confounding due to maternal germline exposure, complicating the interpretation of results attributed solely to famine effects on the fetus.

In contrast, some studies lacked a well-defined measure of famine exposure, which may have introduced bias into their findings. For example, the study by Hughes et al. [29] examined the impact of famine exposure on colorectal cancer risk in the Dutch population. They found that energy restriction during adolescence and early adulthood was associated with a reduced risk of developing tumors marked by promoter methylation in five specific genes. However, the criteria used to define famine exposure—such as the father's place of residence during the famine, the individual's residence during World War II, and employment status—could have introduced bias. As the authors acknowledged, these proxy indicators may have led to misclassification of exposure. In a separate study, Franzek et al. [28] examined the association between prenatal famine exposure and addiction later in life among individuals in Rotterdam, the Netherlands. They reported that exposure to famine during the first trimester was associated with an increased risk of addiction in adulthood. However, a significant limitation of the study was the uncertainty regarding whether the patients and controls

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were actually born in the Rotterdam area, making it unclear if they had been exposed to the famine. Additionally, the authors acknowledged the lack of information on the health status of the control group, which further limited their ability to rule out potential bias in the results.

3.3. Tissue Selection

Selecting the appropriate tissue for analysis is crucial in famine research, as it enables an accurate assessment of intergenerational changes and more precise predictions of genotype-to-phenotype relationships, given the variability in gene expression patterns and functional roles across different tissues. Tissue selection varied across the studies, impacting the interpretation of the famine effects on epigenetic modifications.

Blood samples were the primary medium for DNA methylation analysis [13,19–21]. Indeed, most authors acknowledge that the use of peripheral blood cells decades after the famine may not reflect the actual DNA methylation patterns in the relevant tissues. For example, it would be a challenge to interpret the association between DNA methylation profiles and brain disorders using blood DNA methylation in the absence of knowledge about the shared gene expression between blood and brain. He et al. [20] simulated famine conditions using fibroblast cell cultures derived from skin biopsies obtained from healthy Dutch individuals. They analyzed these cell lines for DNA methylation and compared the results with those obtained from DNA methylation profiles of Chinese individuals with a famine history. Three DMRs located in genes involved in nervous system development were common between fibroblasts and blood cells. A major limitation of this study is the selection of fibroblasts and blood cells for DNA methylation analysis, as these tissues, as acknowledged by the authors, may not represent the DNA methylation patterns in the brain. In addition, the comparison between DNA methylation patterns obtained from fibroblast cell culture and blood samples taken 50 years after the famine exposure raises questions about the validity of the results. In contrast, Boks et al. [30] incorporated both blood and postmortem prefrontal cortex samples to investigate the effects of famine on the DNA methylation levels of the DUSP22 gene in individuals with schizophrenia and controls. They reported higher methylation levels of this gene in schizophrenia patients exposed to famine compared to healthy famine-exposed controls and healthy non-exposed controls. The authors also used fibroblast cell lines nutritionally deprived to mimic famine conditions.

Blood samples have also been used in metabolic and cardiovascular research [12,22], offering insight into systemic changes in gene regulation. However, blood may not fully capture tissue-specific epigenetic effects, as its heterogeneous cell composition (e.g., lymphocytes, neutrophils) can obscure or confound methylation signals. Moreover, DNA methylation changes detected in blood cells may not accurately reflect the epigenetic consequences of prenatal famine exposure in relevant target tissues. The reliance on blood or fibroblast cell lines may, therefore, limit the interpretability and biological relevance of these studies.

3.4. Selection of Controls

The selection of case and control groups is critical for understanding the effects of prenatal famine exposure. Most studies employed a cohort-based design, comparing individuals exposed to famine in utero with those conceived before or after the famine. Interestingly, one particular study examining prenatal exposure for colorectal cancer risk did not utilize a control group [29], weakening the validity of the study and undermining its ability to draw solid conclusions. Another relevant study is that by Franzek et al. [28], which investigated the relationship between prenatal famine exposure and later-life addiction. The study may have misclassified some individuals with addiction as controls, potentially underestimating the true association. Additionally, the authors acknowledged their inability to verify whether all participants, both cases and controls, were born in the Rotterdam area during the famine. This uncertainty raises concerns about exposure misclassification, particularly for individuals born outside the famine-affected zone, which could introduce further bias into the results. In contrast, some studies employed same-sex sibling controls who were conceived

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after exposure of maternal oocytes [12,22,31]. This approach enhanced the reliability of findings by reducing genetic and environmental variability. However, residual maternal stress remained a potential confounding factor and limitation.

Difficulties in recruiting participants for famine-related research have led to considerable variation in sample sizes across studies, which affects the statistical robustness of the findings. Large-scale epidemiological research, such as that by Wang et al. [32] (n = 17,023), investigated the effects of the famine on individuals born before the famine, those born during the famine, and those born after the famine. They identified strong population-level associations between prenatal famine exposure and an increased risk of short stature and overweight. These findings suggest that exposure to famine during early development has long-term consequences for metabolic health. In contrast, He et al. [20] acknowledged that the small sample size used in the DNA methylation analysis (25 famine-exposed individuals versus 54 unexposed individuals) lacked the statistical power to identify genetic markers associated with famine exposure. However, other factors could limit power, such as the use of blood samples from decades after the famine and the lack of additional phenotypes collected for the examined population, except for exposure status to the famine. Similarly, Shen et al. [21] also acknowledged that the small sample size used in their analysis could have limited the generalizability of their results.

Another important consideration across famine studies is the variation in sample sizes, which influences both statistical power and the generalizability of findings. For example, Heijmans et al. [12] examined DNA methylation in the IGF2 gene in 60 individuals prenatally exposed to famine and 60 same-sex sibling controls. In contrast, Hulshoff Pol et al. [33] investigated the association between prenatal famine exposure and schizophrenia using a smaller cohort of 36 patients and matched controls. On the other hand, De Groot et al. [27] conducted a larger study assessing cognitive function in 951 exposed individuals compared to 890 controls at the age of 59. Larger sample sizes, such as those in Roseboom et al. [23] (n = 704), provided greater statistical power to detect associations, including a significantly higher LDL: HDL ratio in individuals exposed during early gestation. Similarly, De Groot et al. [27] reported significantly lower General Cognitive Index (CGI) scores in individuals exposed during early gestation, suggesting potential long-term cognitive impacts of famine-related exposure.

4. Lessons Learned and Future Directions

The Dutch and Chinese famines have offered valuable insights into the long-term health consequences of in utero nutritional deprivation. These studies support the hypothesis that early-life famine exposure can result in lasting epigenetic modifications, contributing to an increased risk of metabolic, cardiovascular, and neuropsychiatric disorders. However, this body of research faces several important limitations, including technical challenges in data collection, limited accuracy of historical information, and suboptimal experimental designs. Many studies were conducted decades after the exposure period and, in some cases, lacked precise or well-defined phenotypic data. Inadequate selection of control groups, particularly when individuals were born shortly after the famine ended, raises concerns about residual maternal stress exposure. Moreover, variation in tissue types, small sample sizes, and inconsistent phenotypic measures further reduce statistical power and hinder meaningful comparisons across studies.

Current and recent famines in Sudan, Somalia, and Gaza in Palestine, caused by wars and environmental factors such as droughts and floods, are among the most serious humanitarian crises in recent history. In 2011–12, Somalia experienced the most severe famine of the twenty-first century, resulting in an estimated 258,000 deaths. This devastating famine was caused by a combination of extreme drought, major agricultural failures, a global surge in food prices that sharply diminished purchasing power, and ongoing conflict [34]. At present, approximately 18 million people in Sudan are suffering from acute hunger, with five million facing emergency levels (www.wfp.org). Furthermore, Sudan is grappling with the worst displacement crisis globally, where over nine million

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people have been displaced due to conflict, and more than two million have sought refuge in neighboring countries (www.wfp.org).

Multiple United Nations (U.N.) agencies have reported that since October 2023, the Palestinian population in Gaza has been facing hunger, stress, trauma, and a scarcity of healthcare services. According to the U.N. World Food Program (WFP) USA, the displacement of over 90% of Gaza's population, the destruction of food production and farmland, and restrictions on food imports have resulted in profound food insecurity across the entire population of 2.2 million people, elevating the risk of famine (www.wfpusa.org). According to the Integrated Food Security Phase Classification (IPC) report, approximately 50% of Gaza's population is currently classified as being in the emergency phase, facing acute malnutrition, while around 25% of the population is experiencing extreme food scarcity (www.wfpusa.org). The IPC serves as the principal framework utilized by the international community to assess the severity and scale of hunger crises based on established scientific criteria. The widespread food insecurity in Gaza's entire population poses differential risks to individuals depending on developmental stage, with fetuses and their germ cells bearing the potential for lifelong detriment deriving from a nutrient-deficient in-utero environment. Other critical periods of early development are also highly vulnerable to environmental stressors that may influence disease susceptibility, such as pre-puberty [35]. Consequently, hunger and other factors may have a more profound impact on children in Gaza, with the additional potential for detrimental effects on their future offspring.

Alongside shortages in food, clean water, medicines, and access to adequate healthcare, children in Gaza have endured significant traumatic events, such as repeated displacements, bombings, and parental separation. The United Nations Children's Fund (UNICEF) approximates that at least 17,000 children have been separated from their parents, with nearly all children in Gaza requiring mental health and psychological support (www.unicefusa.org). These children exhibit symptoms including increased anxiety levels, loss of appetite, sleep disturbances, and panic attacks (www.unicefusa.org). Yehuda and colleagues explored intergenerational transmission of epigenetic markers in response to Holocaust trauma [36]. Exposure to the Holocaust—whether through detention in a concentration camp or witnessing or experiencing torture—was linked to elevated methylation levels in the FK506 binding protein 5 (*FKBP5*) gene [36]. Additionally, alterations in DNA methylation within *FKBP5* were noted in the children of Holocaust survivors [36]. While this study has certain limitations, including a small sample size, the use of blood cells for methylation analysis, and a limited number of genes, its findings reveal notable epigenetic effects in the offspring of Holocaust survivors. Indeed, to thoroughly investigate transgenerational epigenetic inheritance, it is essential to determine whether sperm or egg cells carry the epigenetic marks altered in response to environmental stimuli. The question of whether offspring can inherit effects of parental experiences was explored in mice [37]. The researchers exposed F0 mice to odor fear conditioning before mating and observed that subsequently conceived F1 and F2 generations displayed heightened behavioral sensitivity to the F0-conditioned odor. Notably, the inheritance of this behavior was concomitant with the transmission of DNA methylation alterations in the Olfr151 odorant receptor gene, which were detected in the sperm of both the conditioned F0 and F1 generations [37].

Human and animal studies offer substantial evidence supporting the concept that parental experiences, including trauma and behavior, can be transmitted to subsequent generations, potentially mediated by epigenetic mechanisms. Therefore, it is imperative to investigate the phenotypic and epigenetic impacts of undernutrition, trauma, and stress in the vulnerable population of Gaza, Sudan, and Somalia, particularly among children and pregnant women. Unlike the investigations of the epigenetic effects of the Dutch and Chinese famines, which occurred several decades later, initiating the study of these effects earlier could yield more reliable data with fewer confounding factors. Conducting studies earlier may offer several advantages, including more precise definitions of famine or trauma exposure, access to a broader range of tissue samples, larger sample sizes, and better-defined control groups. Additionally, earlier studies could contribute to identifying potential interventions for affected individuals later in life, as well as for their offspring.

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Epigenetic research has the potential to identify both resilience-promoting factors and vulnerability factors in response to trauma and famine. Understanding these factors can inform interventions aimed at enhancing resilience and alleviating the adverse effects of trauma on children's health and development. Furthermore, studying epigenetic effects can offer insights into the biological mechanisms through which trauma and famine impact individuals, leading to more targeted and effective interventions for children who have endured the stress of war. Ultimately, such research can shed light on how trauma and undernutrition experienced during conflict can have enduring effects on health and well-being.

In conclusion, future post-famine research should prioritize more rigorous experimental designs to enhance reliability and minimize bias. This includes selecting truly unexposed control groups born before the onset of famine, precisely defining exposure timing, using tissues relevant to the studied phenotype, and incorporating both molecular and physiological outcome measures. Studies should also report relevant methylation changes and validate their biological impact through gene expression or functional assays. Larger, multi-cohort analyses and longitudinal designs would enhance statistical power and allow for examination of transgenerational effects. By establishing these standards, future work can better clarify the role of early nutritional deprivation in shaping lifelong health and contribute more directly to evidence-based public health interventions. More accurate research outcomes can help inform public policy and interventions, such as nutritional supplementation for pregnant women in food-insecure or famine-affected regions.

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