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Perspective

Molecular insights into trauma: A framework of epigenetic pathways to resilience through intervention

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SUMMARY

Experiences of complex trauma and adversity, especially for children, are ongoing global crises necessitating adaptation. Bioadaptability to adversity and its health consequences emphasizes the dynamism of adaptation to trauma and the potential for research to inform intervention strategies. Epigenetic variability, particularly DNA methylation, associates with chronic adversity while allowing for resilience and adaptability. Epigenetics, including age- and site-specific changes in DNA methylation, gene-environment interactions, pharmacological responses, and biomarker characterization and evaluation, may aid in understanding trauma responses and promoting well-being by facilitating psychological and biological adaptation. Understanding these molecular processes provides a foundation for a biologically adaptive framework to shift public health strategies from restorative to long-term adaptation and resilience. Psychological, cultural, and biological trauma must be addressed in innovative interventions for vulnerable populations, particularly children and adolescents. Understanding molecular changes may provide a biopsychosocial perspective for culturally sensitive, evidence-based interventions that promote resilience and thriving in new settings.

INTRODUCTION

The world is currently witnessing an unprecedented displacement of war refugees, and the humanitarian challenges associated with this crisis are multifaceted.[1,2] These displaced populations are not only forced to grapple with the immediate trauma of conflict and forced migration but also must confront the daunting task of adapting to entirely new environments, cultures, and social systems. Understanding the dynamic nature of adaptation to such trauma is essential for promoting the health and well-being of these vulnerable populations.

This article seeks to explore the concept of biological adaptability in response to trauma exposure and its implications for intervention strategies. We draw from empirical evidence in both animal and human studies to emphasize the dynamic nature of adaptive responses to traumatic circumstances with a focus on the potential of epigenetics. We then outline and contextualize the opportunities, challenges, and implications of implementing intervention strategies to support and investigate both the biological and psychological adaptations to new environments for those who experienced trauma through studying molecular plasticity, specifically through the lens of epigenetic modifications.

EXPERIENCES OF TRAUMA

The experience of trauma is a well-studied construct across multiple fields, including mental health and psychology, sociology, anthropology, and public health.[3] Trauma is commonly understood as an individual's response to an overwhelmingly distressing event or series of events, often involving tangible or perceived threat to life, self-concept, physical integrity, or the well-being of oneself or others.[4] The subjective nature of trauma underscores the deeply personal and context-dependent aspects of its definition, as what may be perceived as traumatic varies across individuals and cultures.[5] Traumatic experiences span a spectrum, ranging from acute incidents, such as accidents and assaults, to chronic exposures, such as poverty, apartheid, and displacement.[4] Furthermore, the impact of trauma extends beyond the immediate aftermath of an event, influencing cognitive, emotional, and physiological sequelae over time.[6,7] As an interplay between the external stressor and

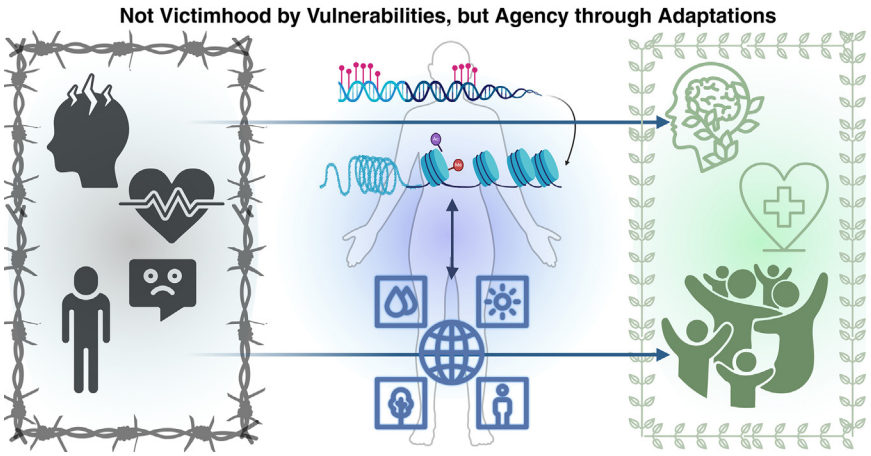

Figure 1. Representation of epigenetic adaptation to environmental contexts

This figure presents a tripartite diagram illustrating the interplay between psychological, physiological, and social-environmental factors that contribute to biological adaptation to promote overall well-being. The left image depicts the mental health challenges and stressors, such as psychological difficulties, emotional distress, and social issues, that may arise from biological adaptations to trauma in environments where these are maladaptive. However, through systemic biological change in response to intervention, such as through DNA methylation alterations, we may re-adapt to flourish within non-traumatic environmental contexts with benefits to mental, physical, and social health. Collectively, these elements emphasize the holistic approach necessary for understanding adaptable well-being over time, understanding that individual health is deeply interwoven with both internal physiological states and external social-environmental contexts. The figure was created with BioRender.com.

an individual's internal processing, the continuum of trauma defies a singular definition, necessitating a comprehensive examination of its diverse manifestations, cultural nuances, contextual and subjective meaning, and the complex interrelationships between environmental factors and individual resilience. Among these influences are the contextual and cultural factors that inform trauma as well as resilience and healing.[8] For example, different populations interpret and experience trauma in ways shaped by their cultural beliefs, values, and historical experiences, including the meanings ascribed to both suffering and healing and how communities construct narratives of resiliency and recovery.[9,10]

The response to experiences of trauma and profound stress requires a complex interaction between psychological resilience and biological adaptation.[11,12] In response to stress, the body undergoes physiological and molecular changes involving the hypothalamic-pituitary-adrenal (HPA) axis and immune system functioning, hormone concentrations (e.g., cortisol), and epigenetic processes (e.g., DNA methylation, histone modifications),[13,14] often acting in a synergistic manner. These biological adaptions can help individuals survive during a challenging time, but they also increase the likelihood of maladaptive behaviors when these adaptations are entrenched and environmental pressures persist beyond the immediate stressors.[15] However, the ability to adapt the function of certain genes pertaining to biological systems, such as immune and neural activity, confers, in part, the capacity for psychological resilience.[16] This resilience is not a biological process and is distinct from, yet interacts with, biological adaptation. Psychological resilience is the ability to recover emotionally and mentally after experiencing adversity and is facilitated by biological processes, such as stress reactivity and neuroplasticity, along with social support systems, emotional regulation mechanisms, and coping strategies.[11,16,17]

We possess an inherent capacity to adapt in the face of adversity, yet these changes are not positive or negative but simply an attempt to enhance survivability within a challenging context.[11,16] Biological adaptations to trauma can manifest in multiple forms, including hypervigilance to stress hormone alterations, by which the body attempts to maintain homeostasis in the face of adversity.[13,14,18] The biological processes involved in these adaptations are akin to physiological responses to any other challenge. These responses are adaptive survival strategies, attuned to the specifics of the event or environment—especially if exposure is prolonged—and the individual's biological, psychological, social, and cultural background.[11] For example, the impact of adversity on cognition in adolescents differed between the trauma of poverty and the trauma of war experiences for refugees.[19] As these biological responses do not discriminate between tangible and perceived threats,[13,16,20] the complex diversity of conceptualizations and operationalizations of trauma can be understood with this framework. Thus, a biologically adaptive framework for understanding the contextual response to trauma and opportunities for intervention supports the rejection of fatalistic, static, or deficit perspectives of life during and after trauma in favor of an agentic and optimistic one: from victimhood through vulnerability to agency through adaptation (Figure 1).

BIOLOGICAL ADAPTATIONS TO TRAUMA

Understanding these biological adaptations is critical, as they inform how to transform responses maladaptive in non-traumatic environments into constructive coping strategies through adaptation across new contexts (Figure 1). These biological changes can range from differences in genetic modifications to brain structure and neurochemistry to stress reactivity and alterations of hormone levels.[7,13] For example, a study of 12-year-old children revealed that exposure to bullying and early-life stress caused a significant decrease in cortisol levels, especially when these children were placed in unfamiliar, stressful situations.[21] This may act as a protective adaptation, as lower levels of cortisol in response to stressful situations decrease pain and stress and, in some cases, allow individuals to better cope. However, the trade-off is that elevated levels of cortisol for a prolonged period may foster adverse psychological and physical effects.[22] This is just one illustrative example of the many biological

adaptations to trauma and how they can shape individuals' responses to future health, contexts, and challenges.[3,7]

One of the intriguing aspects of these survival adaptations is their capacity for long-lasting effects on biology, typically by turning genes *on* or *off* in response to trauma through molecular mechanisms such as epigenetics,[23,24] which may be analogized as a "dimmer switch," regulating the onset and quantity of gene expression, thereby shaping the individual's response to trauma or stress. Epigenetic modifications are a crucial yet understudied avenue for understanding the enduring molecular effects of adverse experiences. The mitotic heritability, accessibility, persistence, and environmental responsiveness of epigenetic changes, particularly in DNA methylation—a chemical tag involving the attachment of a methyl group to the 5′ carbon of cytosine at a CpG dinucleotide[25]—make them an attractive focus for research on trauma-induced adaptation and future psychological resilience in humans.[12,16,25] DNA methylation can associate with gene transcription or act as a biomarker of transcriptional history.[25,26] DNA methylation is a mechanism by which environmental exposures can be translated into molecular change with long-term health outcomes. Extensive research has demonstrated that chronic stress can lead to distinct DNA methylation patterns, which are associated with changes in stress physiology, biological pathways of development, and health issues, including mental health disorders and cardiovascular diseases,[27–32] and may persist over time.[25] Therefore, DNA methylation provides a mechanism by which experiences, both traumatic and resilience-building, may become enduringly embedded at the molecular level. However, while many narratives of biological embedding of trauma and adversity through epigenetics can focus on the fatalism, "scarring," and enduring the nature of these experiences, it is crucial to emphasize, as we will throughout this manuscript, that these mechanisms are, by their nature, designed for change and adaptation and have the capacity to change throughout the lifespan.[25]

While DNA methylation is able to regulate gene expression under basal conditions, these modifications also regulate responses to environmental challenges, such as how genes respond to extreme stress and immune insults, thus affecting our capacity to adapt to changing environments and impact susceptibility or resistance to health conditions.[33,34] However, the extent of DNA methylation's impact on transcriptional regulation is limited by the underlying and immutable genetic context upon which it acts. DNA methylation is known to interact with the genome, especially at those sites affected by genetic variants known as methylation quantitative trait loci (mQTLs) that influence DNA methylation patterns.[35,36] These genetic contributions to DNA methylation are mostly stable across the lifespan, often in physical proximity, and known to act on almost half of the CpGs covered by available genomic microarray technologies.[36,37] However, while there is a robust link between DNA methylation and the genotypic variants we are born with, environment also acts on DNA methylations in multiple ways,[24] allowing for singular, additive, and interactive effects of genetics and environments. Thus, DNA methylation lies at the crux of gene-environment (GxE) interactions.[38] Limited perinatal studies in birth tissues have dissected the contribution of genetics and environment, both individually and additively, to explain DNA methylation variation in maternal conditions (e.g., depression, anxiety) and behaviors (e.g., smoking).[37,39] This biological characteristic of the methylome to crosstalk with the genome has enabled the discovery of mechanisms that may likely explain some of the observed individual variation underlining complex human phenotypes, such as in certain psychiatric and behavioral conditions that have a genetic predisposition. However, these studies have overwhelmingly discovered interactive effects of the environment and genome.[37,39] Most pertinently, a recent multi-cohort study reported the interaction between exposure to childhood trauma and underlying genotype to causally influence differences in DNA methylation.[38]

Within the genomic context, DNA methylation differences with the experiences of trauma have been found. Though most studies report associations, many of these are not consistently replicated or validated except for target candidate studies.[23] The main exception to this is exon 1F of the gene *NR3C1*, the gene encoding the glucocorticoid receptor, which has consistently replicated across experiences of adversity and tissue of origin in both human and animal studies.[23] Persistent DNA methylation changes in *NR3C1* can dysregulate the body's stress response system, predisposing individuals to heightened stress reactivity and emotional dysregulation. Such epigenetic modifications can either facilitate adaptation to a hostile environment by promoting hypervigilance or contribute to maladaptive outcomes like chronic anxiety or depression when the stressor is removed but the DNA methylation persists. A related gene important in the long-term sequelae of stress that has been less validated but also commonly associates with exposures to trauma and adversity is *FKBP5*.[40] *FKBP5* is a vital regulator of the HPA cortisol response to stress,[40] and prior exposure to stress and trauma during childhood has been found to be associated with DNA demethylation within *FKBP5* at the glucocorticoid receptor binding site (GREs).[41] For example, *FKBP5* DNA methylation in an epigenome-wide association study (EWAS) of blood, but not cheek swab, DNA methylation of children (6–11 years old) was found to associate with cumulative family adversity (consisting of maternal depressive symptoms, parenting stress, and financial stress) in a recent study.[42] Crucially, in candidate gene studies, DNA methylation in *FKBP5* appears to be sensitive to therapeutic intervention;[43,44] thus, epigenetic changes at the FKBP5 gene critical to understanding the concept of resilience in response to early-life exposure to stress and trauma. Specifically, the upregulation of *FKBP5* and DNA demethylation in response to stress can cause increased glucocorticoid receptor resistance and desensitization. This adaptive mechanism decreases the negative effects of stress and better equips individuals to deal with stress in the long term. Furthermore, this protects tissue such as the brain from the overactivation of the stress response.[45] Moreover, some papers suggest that this protective mechanism represents an evolutionary adaptive response that can anticipate future stressors and modulate the individual's stress response to prevent an overreaction to the stress.[40]

Also consistently replicated across studies of adversity, particularly in saliva and cheek swab DNA methylation studies, is not a commonly tested candidate but a family of genes: neural homeobox genes. These genes are critical developmental genes

that are regulators of brain development and neural differentiation, and their consistent discovery in EWAS of adversity may point to the adaptation of neural development and neural plasticity in response to environmental challenges.[46] Genes from this family have consistently been identified as differentially methylated in human studies of psychopathology,[47–50] maltreatment,[51,52] and child slavery.[53] However, there is a candidate gene, commonly tested and associated with the experiences of trauma, that is also functionally related to brain development and neural differentiations: brain-derived neurotrophic factor (*BDNF*).[23] This gene is highly expressed in the adult brain and is a key mediator of neuroplasticity, holding functional relevance in brain regions involving emotional and behavioral regulation.[54] In addition, peripheral BDNF is secreted by immune cells, including T cells, B cells, and monocytes,[55] and exhibits neuroprotective abilities.[54] Therefore, *BDNF* has been increasingly investigated by researchers to understand its effects at the molecular level, both on the transcriptome and epigenome in humans and animal and in the brain and peripheral blood, in the context of early-life adversity and psychiatric disorders.[56–61] While BDNF mRNA levels significantly decrease and DNA methylation levels at *BDNF*-associated CpGs increase in early-life and chronic-stress situations, only a few studies, in rodent models, have explored the regulation of *BDNF* gene transcription by DNA methylation in such stressful settings. Further, in a rodent model of infant maltreatment, it was demonstrated that changes in DNA methylation and gene expression patterns in adults owing to early-life adverse experiences were rescued by infusion with a DNA methylation inhibitor in the prefrontal cortex, supporting a possible avenue for interventions to explore the reversal of stress-associated molecular effects.[62] Notably, genetic variants at *BDNF* have been shown to modify the association of *BDNF* promoter DNA methylation with psychosis conditions, including depression[63] and anxiety.[64]

In humans, exploratory EWASs have reported DNA methylation associations with a wide range of responses to trauma, including alterations in stress response systems, cognitive functions, and immune system regulation.[23,65–67] In addition, the timing of trauma, specifically adversity experienced before 3 years of age, had the strongest associations with DNA methylation when compared with adversity experienced in early childhood (3–5 years), middle childhood (6–7 years), late childhood (8–11 years), and early adolescence (12–15 years).[68] This study directly tested the hypothesis that there are sensitive periods of the biological embedding of adversity through DNA methylation differences. By using DNA methylation from venous blood samples in the British longitudinal Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, researchers used the high-dimensional stratified linkage and correlation analysis method to compare competing hypotheses for at which developmental stage, if any, adversity has a disproportionally strong impact on DNA methylation.[68] Further, these finding align with the popular developmental origins of health and disease (DOHaD) hypothesis, which emphasizes that experiences and exposures within the first 1,000 days of life (<3 years) biologically embed or ''get under the skin'' of the developing fetus and the infant, consequently shaping health trajectories into adulthood via molecular processes such as epigenetics.[69] However, it must be noted that not all conceptualizations and operationalizations of trauma were present in the study, which was conducted in a large community cohort rather than empirically designed to investigate the timing of traumatic experiences on DNA methylation.[68] While biological pathways linked to stress and inflammation have been consistently reported in EWASs focused on trauma and their responses, reproducing DNA methylation changes at the specific CpG-site level has been challenging.[23] This is the result of several challenges with high-dimensional exploratory analyses of human experiences, including the importance of tissue, as one of the main biological functions of DNA methylation is defining cell identity; population, as both the variability in experience and underlying genetic structure can make statistical analyses challenging; appropriate control groups, given the need for similarity in genetic and environmental factors as well as both biological samples and deep phenotyping; understanding functional consequences, as many studies do not simultaneously measure transcript or protein changes and the complex association between DNA methylation and transcription is contextually dependent; and effect and sample sizes, as even a small 1% change in DNA methylation could be biologically meaningful but difficult to detect in the relatively small sample sizes available in EWASs due to the still-prohibitive research costs.[23,25,70,71]

As an alternative to EWASs, another promising avenue based on DNA methylation measures to inform on health and trauma are epigenetic clocks. These DNA methylation-based tools measure an individual's biological age (or epigenetic age), which is reliably estimated from the level of DNA methylation at certain CpG sites predictive of chronological age. Greater biological age estimations than chronological age may indicate health challenges, and, when in response to psychosocial stress, support the biological weathering hypothesis.[72] Biological weathering refers to the cumulative biological damage that occurs due to chronic stress and adverse environmental conditions that lead to DNA methylation changes that prematurely age cells, increasing the risk of age-related diseases and overall decline in physiological function.[73] Thus, these clocks are sensitive to social environments, including early-life adversity and psychologically protective factors,[74–76] and experiences of profound and chronic stress may result in epigenetic age acceleration and poor adolescent and adult health.[77–80] In adolescents, exposure to long-term stressors, such as adverse childhood events, was significantly associated with accelerated epigenetic aging.[81] Similarly, research has found that experiences of childhood maltreatment, discriminatory experiences, and risk of psychiatric problems were all associated with epigenetic age acceleration.[82–84] While epigenetic age acceleration is the most commonly assessed DNA methylation biomarker in both trauma and preventative and intervention sciences, the available biomarkers continue to be developed and evolve. A major benefit of employing biomarkers in DNA methylation research is that by using a summary score or proxy measure of a biological system derived from the methylome, the multiple testing burden, and thus the power to detect true effects, is greatly increased. Recently, DNA methylation proxies, developed in adult blood, have been applied and characterized in pediatric blood and saliva samples to estimate proxies of inflammation (e.g.,

interleukin-6,[85] C-reactive protein[86]) and glucocorticoid receptor activity (e.g., Epistress score[87]).[79,88–90] In theory, these scores, while only middlingly correlated with the serum measures they are trained to be proxies for, may be more reflective of chronic signatures of inflammation and stress exposure. Currently, the best empirical evidence for this is the significantly greater consistency over time and from sample to sample of the DNA methylation-derived scores over the measure serum biomarkers.[91] One recently published study found that participation in a parenting intervention reduced one of these DNA methylation-derived inflammation risk scores.[89] This indicates the possibility that such scores, especially as they continue to be developed and characterized, may allow for bioinformatically testing hypotheses of change in biological systems underlined by DNA methylation.

There is currently substantial evidence that DNA methylation, both accelerated epigenetic aging and CpG specific, is responsive to interventions in humans, especially nutrient supplementation,[92,93] dietary,[94,95] and lifestyle interventions[96] to improve health and pregnancy outcomes. In contrast, though the evidence of epigenetic changes to trauma and profound stress is robust, the evidence of their reactivity to intervention is limited yet promising. A significant limitation of the extant literature is the predominant focus on risk, with little attention devoted to understanding the role of psychosocial protective factors that impact DNA methylation. One study of predominately Latino children with developmental delay found that supporting families to enhance parenting practices (e.g., warmth, consistency) for those with the highest cumulative adversity, such as parental stress and financial strain, reduced epigenetic age acceleration[97] and an epigenetic chronic inflammation risk score.[89] Similarly, a dyadic psychosocial intervention was found to ameliorate accelerated biological aging in trauma-exposed children.[98] In adolescence, another study found that participation in a family-centered program that enhances parenting and family relationships buffered the detrimental effect of racial discrimination[100] and family risk on epigenetic aging a decade later.[48] A multimodal intervention addressing post-traumatic stress symptomology in adolescents who experienced multiple early-life adverse events found that participation in the program resulted in differential DNA methylation changes, especially in genes associated with previous studies of adversity.[100] In adulthood, several studies have found changes in the DNA methylation of candidate stress-related genes (e.g., *NR3C1*, *FKBP5*, *SLC6A4*) following response to psychotherapy treatment for internalizing disorders (e.g., anxiety, post-traumatic stress disorder [PTSD]).[43,44,101–104] Additionally, using epigenome-wide methods, Vinkers and colleagues found that adult PTSD psychotherapy treatment responders demonstrated significant changes in DNA methylation at 12 differentially methylated regions.[105] Overall, promising evidence is building for the positive, resilience-building impact of interventions on epigenetic modifications (see Schiele et al.[106] and Smeeth et al.[16] for comprehensive reviews).

Though analyses have not yet begun, DNA methylation change will be studied in a mindfulness study in high-stress adults,[107] a Mercy Corps resilience-building intervention (Advancing Adolescence) for Syrian refugee and non-displaced adolescents in Jordan,[108] and a socioemotional learning reading intervention with young Syrian refugee children (We Love Reading).[109] These in-progress analyses showcase the timeliness of this work and the necessity for a biological framework for intervention and resilience for these populations. The experience-based plasticity reflected in environmentally sensitive epigenetic modifications in these available data reveals molecular mechanisms that underlie an individual's capacity to adapt to both traumatic experiences and subsequent environmental changes.

OPPORTUNITIES AND CHALLENGES IN STUDYING MOLECULAR PLASTICITY IN INTERVENTION

The implications of a biologically adaptive framework for interventions, especially with a focus on molecular plasticity, are profound, providing a potential pathway for translating environmental exposures and contextual changes, such as stress attunement and behavioral modifications, into epigenetic modifications. These adaptations at the interplay of the genome and environment have predictive relevance for health outcomes, response to treatment, and promoting sustainable resilience.[24]

Several questions remain to fully understand and employ epigenetics, such as DNA methylation, in the context of intervention and resilience building for those who have experienced profound stress and trauma (Figure 2). First, the scope of epigenetic alterations achievable by intervention must be characterized, such as their location, degree, and functionality. Identifying the extent of epigenetic malleability to intervention and, importantly, which biological pathways are the most likely to be affected may elucidate the biological processes that underlie trauma's long-term effects, leading to more effective interventions targeting these mechanisms and highlighting the most influenceable health risks. For example, previous work identified differential DNA methylation in pathways of cardiovascular health with both experiences of trauma and psychosocial intervention.[100]

Describing differences in these epigenetic changes depending on the target and timing of interventions allows for the refinement of strategies to achieve the most effective and sustainable health outcomes. For instance, a study of parent-child interaction training found reduced epigenetic age acceleration only for those who had the highest cumulative adversity, especially with increases in positive parenting, which may indicate the potential to build resilience even in the most adverse situations.[97] Additionally, nutrition-based interventions[42–45] and environmental enrichment[110] have also shown early support for impacting epigenetic outcomes. For example, McCreay and colleagues found that environmental enrichment in a rodent model (e.g., enriched housing, including more space, enhanced bedding, and enrichment materials for activities) may be a powerful intervention for adverse transgenerational epigenetic programming. Further, Jönsson and colleagues found that a lifestyle intervention for pregnant women with obesity was associated with epigenetic changes in offspring.[111] These findings indicate that understanding both aspects of a range of environmental changes and the previous experiences of participating individuals could allow us to tailor interventions to be as biologically effective as possible in the future.

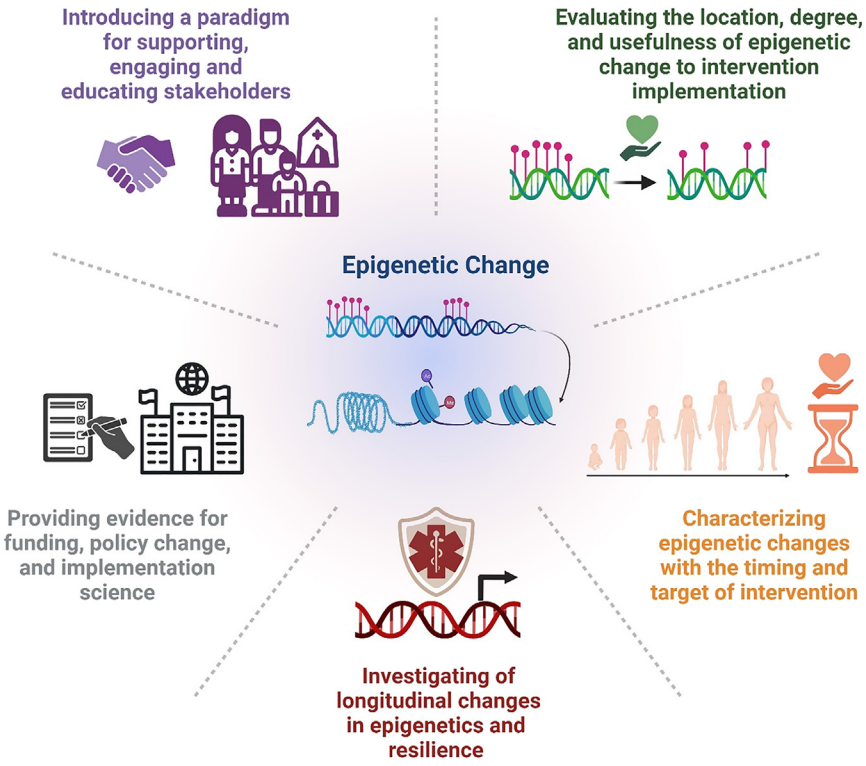

Figure 2. Opportunities in the intersection of epigenetics and psychosocial interventions for trauma

This figure highlights critical inquiries into the mechanisms, timing, and longevity of DNA methylation changes influenced by psychosocial interventions in trauma survivors, as well as the utility of this knowledge for implementation science, policy, and trauma survivor stakeholders. The figure was created with BioRender.com.

Regarding timing, DNA methylation has greater interindividual variability within the first five years of life,[112] with early-life adversity being the most reflected in later DNA methylation.[68] This implies that early-life intervention may be the most effective. However, emerging findings suggest that family-based psychotherapy can have a positive epigenetic impact in early childhood,[89,98] middle childhood,[113] and adolescence.[82,99] Further, health-focused interventions, even in middle-aged adults, have resulted in DNA methylation changes maintained over time,[94] indicating the potential for intervention to have effects at the molecular level even well into adulthood. Research on the effect of intervention on epigenetic alternations at different developmental stages throughout life is necessary to understand the window for potential change.

At the heart of this framework is the investigation of longitudinal changes in epigenetics as a potential measure of individual resilience (Figure 2).[16] These changes in response to intervention may not only be maintained over time but also provide a defense against future insults, as previously proposed in a conceptual model for epigenetic research into resilience.[12,16] While not an intervention focused on trauma, a still meaningful example of the potential longevity of DNA methylation changes in response to intervention is a recent USA study that found significant improvement in epigenetic age acceleration in response to a nutritional intervention employing a caloric restriction model.[94] These results were maintained over multiple years after the intervention ended and indicate resilience against future morbidity and mortality.[94,114] Thus, understanding the patterns of these epigenetic changes could offer insights into how molecular changes in response to interventions—and thus potentially resilience—can be built and sustained through public health strategies.

However, there are still challenges to overcome with applying epigenetics, specifically DNA methylation, to intervention. For example, causality has recently been explored using Mendelian randomization,[115,116] and future randomized controlled trial intervention designs will inevitably build upon this foundation to examine causal inference.[117] Similarly, it is unclear what aspects of DNA methylation are likely to be functionally significant, as recent research illuminated that DNA methylation's relation to transcription may depend on health and environmental contexts.[34] For example, in an *in vitro* experiment, cellular methylation-dependent regulatory activity was only detectable upon immune stimulation, consistent with the hypothesis that DNA methylation influences responsiveness to environmental stimuli,[33] and the extent of this molecular regulation to the environment may only be observable under specific challenges and pressures. Despite these extant challenges and persistent issues of sample size and tissue specificity in all epigenetics research,[25] this work could provide a foundation for a scalable precision medicine approach to intervention in the future. Together, these investigations will uncover what aspects of intervention implementation may be most likely to mitigate the effects of prolonged stress on biology, as well as identify pathways sensitive to intervention to aid in risk identification and prevention with the goal of reducing health disparities for diverse and vulnerable groups.[118]

While these investigations into the effects of psychosocial interventions alone are integral to the future of the field, one of the largest questions remaining is the use of medication to potentially enhance the effectiveness of interventions at the molecular level. There is currently no existing strategy to alter DNA methylation at the CpG-site level in human beings, but we can manipulate chromatin structure by adding modifications like methyl or acetyl groups to histones, like the addition of a methyl group to DNA. This, in turn, affects the way DNA is folded and therefore its level of accessibility for gene transcription. Additionally, these histone alterations interact with DNA methylation, which may act to "fix" changes in gene expression initially precipitated by histone modifications.[119] Histone deacetylase (HDAC) inhibitors, consisting of four main isoforms, obstruct

the deacetylation of histone proteins and enhance gene transcription, which may influence several biological pathways, including those related to mental health and trauma responses. In fact, HDAC inhibitors have substantial evidence from model organisms to promote longevity and healthy aging,[120] and some hypothesize they may also affect epigenetic age acceleration, an epigenetic biomarker linked to chronic stress and adverse health effects that is sensitive to psychosocial interventions in cases of trauma.[98,121] HDAC inhibitors may provide a therapeutic strategy to slow or perhaps reverse epigenetic age acceleration by modifying histone acetylation, especially in groups who have experienced considerable trauma. These potential benefits to human longevity and aging may be of pertinence to those most at risk for morbidities and mortality due to the health consequences of such adversity.[23,122]

Preclinical and animal model investigations have shown that HDAC inhibitors may modify DNA methylation patterns, especially in genes related to stress response, immunological function, and neural plasticity.[120] Specifically, HDAC inhibitors have enhanced transcription of genes critical for synaptic plasticity and long-term potentiation, such as *BDNF*, necessary for learning and memory consolidation.[123–125] In animal models, HDAC inhibitors have been found to ameliorate cognitive deficits and improve memory,[119,126,127] as well as re-open critical-period neuroplasticity in adult mice.[128] Meanwhile, in one human study, adult men unable to identify musical pitch any better than chance were given the HDAC inhibitor valproate in combination with music lessons. These men learned to identify pitch significantly better than those taking placebo, even though absolute pitch can only be acquired early in life, providing evidence that an HDAC inhibitor could facilitate critical-period learning in a mature human brain. Given the synaptic plasticity hypothesis of depression,[129] this evidence of increased synaptic plasticity—potentially to the level of early-life critical periods—may also elucidate the benefits of HDAC inhibition on the treatment of depression. The research, though primarily in mice, is promising for HDAC inhibitors in therapies for even treatment-resistant depression by stimulating synaptic plasticity, especially in the hippocampus and prefrontal cortex, and alleviating depression behaviors.[124,125,130–132] These findings indicate that the combination of HDAC inhibitors with psychosocial therapeutic interventions may improve their effectiveness by fostering molecular plasticity in critical biological pathways, especially when preventing or addressing co-morbid mental health difficulties as a result of childhood adversity.

However, the use of HDAC inhibitors in combination with psychosocial therapeutic interventions is not without challenges. These are not target pharmaceutical therapies—HDAC inhibitors have epigenome-wide effects that, currently, we are unable to restrict to only specific portions of the genome.[130] The lack of specificity for various HDAC isoforms and the possibility of off-target effects raise considerable concerns about their widespread use in clinical environments. Encouragingly, though, recent work in animal models illustrated the potential of manufacturing a novel class IV HDAC inhibitor (an isoform that is highly expressed in the brain) that targets microglial activation and reduces depression symptoms in mice.[125] Additionally, the potentially, and arguably ideally, enduring effects of HDAC inhibition on gene expression and chromatin dynamics, especially in developing populations like children and adolescents, need further investigation to comprehensively grasp the consequences of these treatments. Nonetheless, the potential of HDAC inhibitors to impact molecular plasticity, both by increasing synaptic plasticity and the potential interaction with DNA methylation to facilitate long-term change, and aid in trauma recovery is a significant avenue for future research, specifically when integrated with evidence-based psychosocial therapies designed to promote resilience and well-being. As our comprehension of the interaction between epigenetic mechanisms and environmental exposures advances, the significance of HDAC inhibitors in trauma intervention may gain future prominence in research and clinical approaches to alleviate the enduring impacts of trauma.

IMPLICATIONS OF A BIOLOGICALLY ADAPTIVE FRAMEWORK FOR PUBLIC HEALTH INTERVENTIONS

This burgeoning field of epigenetics offers a transformative lens through which public health interventions and policies can be re-evaluated and, potentially, restructured. Traditional approaches to trauma have often centered on a preventative or restorative framework for adversity.[133] However, including a biologically adaptive framework shifts focus toward promoting agency, learning, and re-adaptation among refugees and others who have experienced profound and prolonged stress (Figure 2). This approach empowers individuals to learn about, understand, and harness their own adaptive mechanisms, thereby enhancing their resilience and well-being in the face of adversity. This framework, and the subsequently informed research, introduces a paradigm shift in the conceptualization and implementation of therapeutic strategies, both in refining and personalizing interventions to improve long-lasting biological outcomes and providing stakeholders with an agentic and optimistic perspective on their own lived experiences.

Public health initiatives are most successful when they are participatory and when stakeholders are fully engaged in the process.[133] Thus, learning about biological adaptation to trauma and our continued malleability to our contexts, such as through epigenetics, would promote enthusiastic participation in available interventions by those who would perhaps not have fully availed themselves with a more fatalistic or even restorative perspective. Stakeholders may also be more likely to participate in anticipation of a precision intervention approach in the future with consideration of their biology and past experiences.[134] However, future research is necessary to discern if a biologically adaptive framework will increase participation in and completion of public health programs.

As refugees often encounter profound and sustained adversity, epigenetic modifications, especially DNA methylation, may provide insights into the enduring molecular imprints of trauma and how these may be re-adapted through intervention. Tailoring public health interventions to account for these biological adaptations allows for a more nuanced approach, addressing not only immediate psychological needs but also the underlying physiological consequences of trauma. Given the culturally agnostic nature of a biologically adaptive approach, this

framework also allows for its integration with other public health approaches, such as social-ecological models, that promote dignity and respect local traditions and wisdom of dealing with trauma, such as the work of the Palestinian trauma center in Gaza employing local traditions to address death and loss.[135–138] Moreover, recognizing the potential intergenerational effects of epigenetic modifications opens avenues for preventative strategies aimed at breaking the cycle of trauma within refugee communities,[12] though more work is necessary to establish mechanisms of inheritance, such as microRNA, given that epigenetic reprogramming makes the direct transfer of DNA methylation impossible.[139,140] Integrating a biologically adaptive perspective into public health interventions could enhance their precision, foster resilience, and promote the well-being of refugee populations affected by trauma.

Additionally, exploring the concept of biological adaptability in response to trauma exposure requires consideration of the perspective of the target communities on the epigenetics of their experiences—both traumatic and beneficial. As in all communities, there are differing opinions with a balance of both "epigenetic hope" and concern about reinforcing colonial narratives when biologizing trauma. In Australia, Indigenous groups historically refused the concept of genetic research due to its perceived propagation of social segregation based on claims of genetic inferiority.[141] However, the recent rise of epigenetic research in Australia, New Zealand, Canada, and the USA has been strongly embraced by some Indigenous and vulnerable communities, most specifically the bridge between social experiences and biological mechanisms that may lead to understanding intergenerational disadvantages or sequalae.[142] This can be exemplified by looking at the "First 1000 Days" organization in Australia, a name directly referencing the DOHaD hypothesis that posits the importance of early-life experiences to lifelong health outcomes.[141] This organization is internationally recognized as an Indigenous-led body that explicitly embraces historical trauma and epigenetics as mechanisms of making social justice, rights, equity, and multigenerational damage claims. There is also an appreciation of science and scientists who position epigenetics as a way of providing biological evidence of social harms and shifting responsibilities from individuals to broader structures to support these mechanisms.[142] Ultimately, the hope of vulnerable populations, scientists, and clinicians is to improve trauma-informed care and provide biological validation for the long-term effects of trauma—informing more tailored interventions.[143] The presence of such a thriving organization reflects that there are some communities being targeted by works such as this paper that are explicitly open to the epigenetic perception of their experiences, health, and history.

However, there is reasonable hesitancy and even fear around epigenetic research, even given the potential benefits to vulnerable communities. Paramount is the fear of misuse of epigenetic narratives to biologize trauma and resilience in a reductionist manner rather than a multifaceted and complementary one, shifting attention away from structural inequities and psychosocial supports.[141,143,144] This is a fear founded in historical precedent, as is the mishandling of genetic data and epigenetics of trauma in the public discourse.[145] Some Indigenous groups in Australia, for example, take a political stance of refusing epigenetics, as they do not want to be pathologized and reduced to biological markers but instead desire to situate their experiences, healing, and trauma in the context of decolonization, community restoration, and culture.[144] These perspectives are necessary not only for engaging ethically and mindfully with communities that may benefit from a biopsychosocial approach to intervention and prevention science but also for acknowledging and addressing realistic concerns in the foundational stages of this scientific work. These differences also highlight the importance of accounting for cultural contexts in intervention, especially when including epigenetic elements, including how communities construct narratives of resilience, recovery, and agency.[9]

Thus, public health efforts, especially interventions, should begin with the goal of promoting agency through adaptation rather than addressing deficit. This mindset shift is required among all stakeholders. Thus, robust biological evidence may also address a persistent hindrance in evidence-based intervention, especially for mental health: funding decisions and policy changes[146] (Figure 2). For example, a major barrier to policy change from research is policymakers' perception of evidence, which may be improved by having clear, potentially long-term biological changes that may reduce future healthcare costs.[147] Currently, health research funding bends toward the conservative, with a preference for biological changes in disease etiology.[148] By illustrating the systemic biological changes from even psychosocial interventions to improve mental health and community well-being, it is possible that more funding may be allocated to those most in need—especially as low-income countries make up only a fraction of the current health research funding.[148] Adequate funding for mental health interventions for the profoundly stressed, such as displaced refugees, is an issue of human rights and equity.[12,146]

While there remain ethical considerations for the implementation of epigenetics in a biologically adaptive framework, such as accessibility and equity of access to DNA methylation profiling in the future,[149] the perspective itself and knowledge to be gained from its study are still promising. Public health efforts that embrace this perspective can better address the unique needs of displaced individuals, both in implementation and resources, fostering their ability to thrive and adapt within new environments while honoring their inherent resilience, both individual and cultural.

The integration of epigenetic insights into public health policy and practice promises to enhance the precision and efficacy of interventions to improve health for those who have experienced profound stress. By adopting a multidisciplinary, biologically adaptive framework that encompasses stakeholder engagement, evidence-based policy, and targeted interventions, we can move toward a future where public health is precise and reactive. While the evidence for epigenetic modification in response to trauma-informed intervention is sparse, it is promising, and the framework it provides is a foundation to enrich our understanding of the etiology of health after adversity. This is relevant now more than ever, with people and communities experiencing displacement—due to both extreme climate change and prejudice, war, and violence around the globe. Children and adolescents are particularly sensitive to global

crises and world events, and the cumulative impacts of prolonged trauma during important developmental periods may result in long-term changes in stress reactivity, immunological function, and cognition. In particular, the genocide in Gaza[137,138,150,151] and undeniable systematic trauma experienced by those living there and in the region will have profound psychological, cultural, sociological, and physiological, likely epigenetic, consequences, necessitating the need for innovative multidisciplinary strategies for biologically adaptive interventions that promote resilience. These populations require interventions that are carefully tailored to address not only immediate psychological needs but also the long-term biological imprint of trauma, incorporating culturally sensitive approaches that honor community narratives while encouraging future adaptation and healing. It is imperative that we employ a framework of resilience through biological adaptation to improve intervention and prevention, influence policy and funding decisions, support and engage stakeholders, and work together to make this world a better place.

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AUTHOR CONTRIBUTIONS

Conceptualization, S.M.M. and R.D.; manuscript drafting, S.M.M., C.K., Z.F., and R.D.; manuscript editing, S.M.M., C.K., J.P., and R.D. Each author has approved the final version of the manuscript and agrees to be accountable for all aspects of the work.

DECLARATION OF INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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