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How Exposure to Adverse Childhood Experiences While in the Foster Care System Leads to Epigenetic Mutations and Reduced Life Spans

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Introduction

For decades, studies have surveyed the health outcomes of children who have spent time in the United States foster care system. Scientists identified connections between adult obesity, crime, and mental health disorders and how time spent in the foster care system. Furthermore, in the 1990s, social workers and scientists used the term "ACEs" (adverse childhood experiences) to study how various traumatic experiences shape adult decisions. The term "ACEs" was coined in 1995 during a study by the Center for Disease Control (CDC) and Kaiser-Permanente, which examined how adverse childhood experiences influence adult decisions and health outcomes. These experiences were grouped into ten categories: sexual, physical, and emotional abuse; physical or emotional neglect; parental mental illness, substance dependence, and incarceration; parental separation or divorce; and exposure to domestic violence, either witnessed or experienced (Harris, 2014). The ACEs survey determined that children in the foster care system had a higher exposure rate to ACEs than children in the general population. In the 21st century, it was then found that exposure to ACEs and health risks in adulthood are directly related; the higher the number scored on the ACEs survey (one point for exposure to each of the ten categories defined above), the more likely a person was to develop a wide array of physical and mental disorders later in life. This phenomenon is due to a chemical reaction in the body termed toxic stress. Unlike positive and tolerable stress, toxic stress is the continuous activation of the body's stress response over an elongated stretch of time (Franke, 2014). When the body is forced to maintain a high level of immune responsiveness, it leads to the malfunction of various body systems, such as the functioning of the Hypothalamic-pituitary-adrenal (HPA) axis and the sympatho-adrenomedullary (SAM) axis (Bucci et al., 2016) both of which regulate cortisol.

A newly developed scientific field, epigenetics, works to provide a combined social and biological outlook on how toxic stress experienced in childhood relates to health challenges in adulthood. While studies are still working to solidify the fact that children in the foster care system experience epigenetic mutations due to high amounts of toxic stress, it is a confirmed fact that toxic stress leads to maladaptive mutations that increase the likelihood of various health risks such as cardiovascular problems and mental health disorders (Johnson et al., 2013). Brain plasticity is highest in childhood, so both negative and positive influences are highly defining of later life outcomes, thus making this an important developmental period. This paper works to identify how children in the foster care system, more so than children in the general population, face adult health challenges due to epigenetic mutations caused by the toxic stress factors that they are exposed to during childhood. Throughout this literature review, an exploratory analysis will be explained using a theoretical model and pre-existing research to support that hypothesis.

Foster Care, ACEs, and the Connection to Health Risks

In the United States, over 391,000 children are in the foster care system with roughly 50,000 children in the California foster care system alone (U.S. Department of Health and Human Services, 2023). Although the numbers are difficult to record with 100% accuracy, the government categorizes a foster child as a minor (ages 0 -18) taken into state custody and placed with a state-licensed adult who cares for the child in place of their parent or guardian (Cornell Law School, n.d.). Foster children enter the system due to unsafe circumstances in their home, usually due to abuse or parental negligence. Furthermore, these children lack stable housing conditions and access to health services, which increases their likelihood of exposure to an

Adverse Childhood Experience (ACE). An ACE is a traumatic event occurring in childhood that leaves a person with lasting trauma (Center for Disease Control, 2023) and can influence the outcome of their adult lives. Although people in all ranges of society can be exposed to ACEs, children in the foster care system are at a higher risk of being in a toxic environment and facing exposure to ACEs, specifically substance abuse, sexual abuse, and parental mental illness (Felitti, 1998). This risk is, in part, due to the definition of what being a foster child entails because unstable home conditions must be present for a child to be placed into the system. Housing conditions range in severity but can include adolescent abuse, neglect, parental mental illness/substance dependence that interferes with adequate parenting, and exposure to domestic violence. In this way, most foster children are exposed to ACEs before their entrance into the foster care system. Moreover, children who face ACEs are at a higher risk of adulthood health risks: persons who scored a seven or higher on the exposure test for ACEs are 12 times more likely to be suicidal than the general population and are more likely to face challenges like obesity and alcoholism (Felitti, 1998; Harris, 2014). More severely, people who report exposure to six or more ACEs in their lifetime are shown to have a reduced lifespan of almost 20 years – 60.6 years vs. 79.1 years at the time of death (Bucci et al., 2016).

Toxic Stress and Epigenetics and Their Intersection with Health Risks

Stress is a human emotion felt in response to emotionally charged situations, commonly experienced by people as a part of everyday life. Stress can express itself in an array of emotions (e.g., sadness or anger) and typically subsides within a day. Although uncomfortable, experiencing stress is an essential part of maintaining a healthy emotional balance and can have positive side effects (e.g. teaching perseverance). When dealt with in small doses, this type of

stress is referred to as positive stress or eustress. *Tolerable stress*, a longer-lasting form of stress, occurs when there is a temporary upheaval of one's environment and requires a greater degree of bodily intervention to mitigate than eustress (Bucci et al., 2016). Unlike positive stress, tolerable stress is categorized as a *distress* caused by a major life stressor (e.g., a natural disaster). Stress can also become negative when a person is forced to live in a state of elongated immune responsiveness while experiencing trauma, a phenomenon referred to as *toxic stress* (See Figure 1). Toxic stress is a severe form of distress and occurs when the body is forced to sustain activation of the body's stress response – fight-or-flight mode – leading to the malfunctioning of various body systems e.g., the functioning of the Hypothalamic-pituitary-adrenal (HPA) axis and the sympatho-adrenomedullary (SAM) axis (Franke, 2014). When these axes stop working properly, the body either remains in an inflammatory state for too long, or deactivates the stress response too early, putting the body in a vulnerable position and making it more susceptible to infections and diseases such as various cancers (Griffins, 2012).

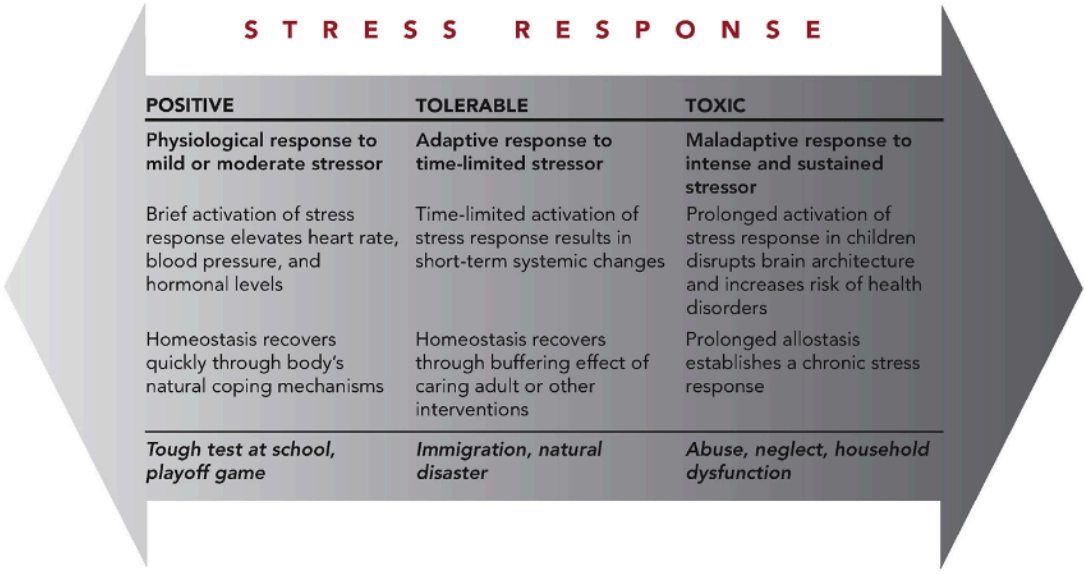

Figure 1.

Stress response spectrum: positive, tolerable, and toxic.

Figure 1. Reprinted from Toxic Stress in Children and Adolescents by Bucci et al., 2016, *Advancing Pediatrics,* 63(1):403-28. doi: 10.1016/j.yapd.2016.04.002. PMID: 27426909.

ACEs

As previously stated, an ACE is a harmful occurrence or exposure experienced during childhood that can affect the functioning of various body systems. ACEs, more so than trauma experienced later in life, are exceedingly harmful as the brain retains the most plasticity during adolescence (Shonkoff et al., 2012). During childhood, the brain responds to positive and negative stimuli, learning from positive experiences while being damaged by negative, harmful, or toxic experiences. Studies have shown that those exposed to ACEs have a greater risk of exposure to toxic stress because neglect, abuse, extreme poverty, family violence, substance abuse, and parental mental illness are all risk factors directly related to toxic stress (Johnson et al., 2013). People who have experienced or lived in one of the aforementioned risk factors are likely to experience epigenetic mutations, leading to a higher risk of developing cardiovascular problems, depression, processing disorders, and other mental and physical illnesses (Shonkoff et al., 2012). Each of these illnesses decreases a person's quality of life and, if severe enough, can result in death (CDC, 2021). The pathway from ACEs exposure to repeated childhood trauma to possible early death is illustrated in the figure below (See Figure 2).

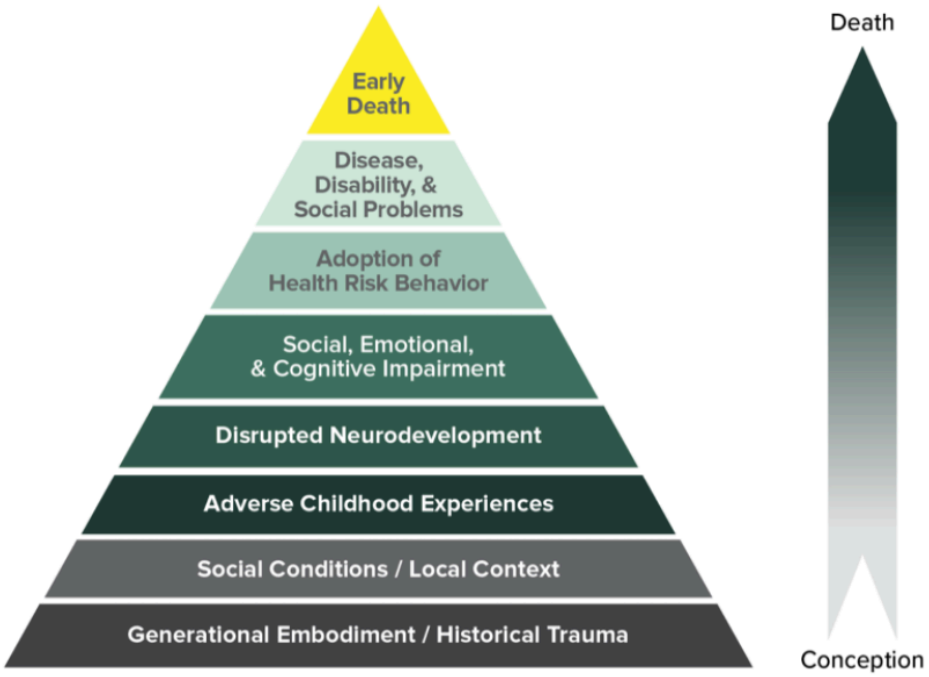

Figure 2.
A pyramid depicting how Adverse Childhood Experiences influence long-term health
Figure 2. Reprinted from Centers for Disease Control and Prevention. (2023, September 5). *Fast Facts: Preventing Adverse Childhood Experiences.* https://www.cdc.gov/violenceprevention/aces/fastfact.html

Epigenetics and Health Risks

Epigenetic mutations can affect various parts of the human body and can lead to various outcomes, but their basic function remains the same. *Epigenetics* (*Epi* - meaning on top of - and *genetics* - in relation to genes) are codes of instructions that sit on top of chromatin in cells and change how cell DNA is read by either activating or silencing certain genes (Griffins, 2012). Due to variations in genetic code, epigenetic alterations affect the body's stress response as the HPA axis, SAM axis, and central nervous system (CNS) undergo mutations. One of the most significant impacts of an epigenetic mutation is that the body's process of allostasis is permanently altered. During allostasis, a glucocorticoid is bound to the glucocorticoid receptor (GR) gene and regulates the body's stress response at both an epigenetic and genetic level. When

a person cannot properly return to a state of homeostasis, they are at an increased chance for various cardiovascular and immune diseases. Accordingly, exposure to childhood trauma and elongated periods of distress alters the methylation status and expression of the GR gene, hindering its ability to return the body to homeostasis (Jiang et al., 2019).

The HPA axis is one of the systems mediating allostasis and can face multiple types of epigenetic mutations based on the type of trauma endured. Generally, the HPA and SAM axes can face long-term dysregulation after the body undergoes an elongated stress response (Jiang et al., 2019). The SAM axis, which controls the body's sympathetic response to a stressor, undergoes mutations when exposed to toxic stress because it is forced to keep the body's heart rate and blood pressure elevated for unhealthy amounts of time instead of undergoing allostasis to return the body to homeostasis. The HPA axis, which handles the distribution of cortisol during the sympathetic and parasympathetic response to a stressor, becomes disrupted when exposed to toxic stress as the cycle for distributing cortisol never fully reaches the parasympathetic stage. Chronic dysregulation of the HPA axis affects the immune and inflammatory response systems, leading to harmful effects in adulthood; when the HPA axis cannot properly regulate cortisol amounts and too much cortisol is released, the immune system is suppressed, and a person's chance of infection increases. On the other hand, when too little cortisol is released, the inflammatory response persists after it is needed, delaying the body's return to homeostasis and causing adults who faced ACEs to have elevated inflammatory markers, making them more susceptible to infections and cancers than the general population (Johnson et al., 2013).

Toxic stress has also been shown to cause mutations in certain genes and parts of the brain (See Table 1). Similar to HPA dysregulation, childhood trauma is one cause of global DNA

hypomethylation, an epigenetic mutation that increases a person's risk of developing cancer because it leads to chromosomal instability (Jiang et al., 2019). Epigenetic mutations have also been shown to silence the tumor suppressor gene, which slows down cell division and tells cells when to die so that tumors, both benign and cancerous, do not form. When this gene is silenced, or an epigenetic mutation is "placed on top of it," one is at increased risk of developing tumors and cancers. Additionally, exposure to ACEs has been shown to mutate the rsl1360780 risk allele, increasing a person's probability of psychiatric disorders. In foster children, on top of situational causes, the chance of mental illness is exacerbated by toxic stress. Toxic stress causes a faster serotonin turnover in the brain, and heightens serotonin to levels associated with neurotoxicity, depression, and substance dependence (Jiang et al., 2019). Exposure to early adversity also affects the nucleus accumbens, the pleasure center of the brain, which increases the likelihood of substance dependence. Subjection to ACEs also inhibits the prefrontal cortex, which manages impulse control and executive functioning, and alters the amygdala, the part of the brain that controls emotion regulation, furthering the likelihood that psychiatric illnesses are developed (Harris, 2014). With all this being said, it is important to note that toxic stress, even when caused by the same stressors, affects people in different ways. Identifiers such as gender, genetic code, and pre-existing illnesses affect how people both biologically and emotionally react to toxic stress and epigenetic mutations.

Genetic and Hormonal Mutations

Mutations	Physical Manifestation
NR3C1 (GR gene) - encodes glucocorticoid receptors (GR) and mediates the stress effects of cortisol. Chronically high amounts of basal cortisol make the body more susceptible to immune suppression and reduced synaptic plasticity and cause impaired regulation of the HPA axis.	**NR3C1 (GR gene) -** Dysregulated cortisol is associated with trauma and psychiatric disorders such as post-traumatic stress disorder (PTSD), MDD, anxiety, and personality disorders.
FKBP5 (GR gene) - mutations reduce the negative feedback loop and create "glucocorticoid resistance." Epigenetic disinhibition can increase FKBP5 levels, altering cellular and circuit functions. Lower methylation levels cause functional alterations to the interior orbital gyrus.	**FKBP5 (GR gene) -** FKBP5 circuit malfunctions increase a person's chances of psychiatric disorders, notably major depressive disorder and (PTSD), along with structural alterations in the inferior frontal orbital gyrus.
SLC6A4 (5-HTT) - Responsible for serotonin reuptake. Hypermethylation of SLC6A4 is caused by trauma, notably childhood trauma and sexual assault.	**SLC6A4 (5-HTT) -** Hypermethylation increases the severity of major depressive disorder (MDD) and antisocial behavior.
BDNF (brain-derived neurotrophic factor) - Directly regulates the HPA axis and is associated with the neuroplastic and structural changes seen in the brain after trauma. Mutations cause decreased levels on BDNF in the amygdala, infralimbic cortex, and hippocampus.	**BDNF -** Decreased levels of BDNF increase the possibility of developing many neuropsychiatric diseases such as eating disorders, MDD, addiction, and diabetes.

Table 1: Data collected from Epigenetic Modifications in Stress Response Genes Associated With Childhood Trauma by Jiang et al., (2016) Frontiers in Psychiatry / Frontiers Research Foundation, 10, 808. https://doi.org/10.3389/fpsyt.2019.00808 and "Child Maltreatment and the Developing HPA Axis" by Tarullo et al., (2006) *Hormones and Behavior*, vol. 50, no. 4, Nov. 2006, pp. 632–39, https://doi.org/10.1016/j.yhbeh.2006.06.010.

Discussion

Depending on the type of trauma a person experiences (e.g. toxic vs tolerable stress), their body acts in various ways to try and return to homeostasis and a state of mental stability. In Table 1, four of the most common epigenetically mutated genes resulting from childhood toxic stress and their manifestations are shown. NR3C1 and FKBP5 are glucocorticoid receptors (GRs) which target and work to mediate cortisol. When a person is introduced to high stress levels, the NR3C1 gene begins to produce chronically high amounts of basal cortisol, the primary stress hormone that mediates glucose production. Although cortisol is needed for the body to function, chronically high amounts of it make the body more susceptible to immune suppression and reduced synaptic plasticity. Additionally, high levels of basal cortisol can cause impaired regulation of the HPA axis and increase a person's chances of developing psychiatric disorders such as post-traumatic stress disorder (PTSD), Major Depressive Disorder (MDD), anxiety, and other personality disorders. Like NR3C1, FKBP5 encodes the GR gene. It also functions as a tumor suppressor gene. FKBP5 is responsible for cell growth and regulation, ensuring that sick and damaged cells do not reproduce (Cooper, 2000). FKBP5 is also one of the most common genes affected by epigenetic mutations because it can be turned "on" and "off" in terms of its ability to regulate cells. Additionally, FKBP5 serves to regulate the activity of glucocorticoid receptors, and, when mutated, has a reduced capacity for regulation, creating a reduced negative feedback loop and more glucocorticoid resistance. Lower methylation levels of FKBP5 also cause functional alterations to the anterior orbital gyrus which increases a person's chances of psychiatric disorders, notably MDD and PTSD. Because the orbital gyrus is part of the frontal lobe, the part of the brain that controls emotional and intellectual intelligence, people with FKBP5 mutations have a higher chance of adapting health risk behavior, such as alcohol

and drug addictions. SLC6A4, another of the most commonly mutated genes, is slightly different from NR3C1 or FKBP5 because it does not connect with the GR gene or its receptors. SLC6A4 is responsible for serotonin reuptake, the process in which serotonin is absorbed into nerve cells. When exposed to toxic stress, specifically through childhood trauma and sexual assault, the body begins to hypermethylate SLC6A4. Unfortunately, instead of returning the body to mental homeostasis, this hypermethylation increases the severity of the physical manifestations of MDD and overarching antisocial behavior.

The final mutated strain mentioned in Table 1 is the brain-derived neurotrophic factor (BDNF). Despite its categorization alongside the other genetic mutations in the table, BDNF is actually a protein hormone encoded by the BDNF gene. BDNF lives in the brain and other bodily tissues, and is responsible for neuron growth and neuronal plasticity, two essential components of learning and memory. When young children are exposed to childhood trauma and toxic stress, the high levels of plasticity in their brains are altered by negative stimuli. Specifically, BDNF mutations result in altered neuroplastic and structural alterations in the brain post-trauma. Mutations such as these cause decreased levels of BDNF in the amygdala, infralimbic cortex, and hippocampus. BDNF also directly regulates the HPA axis, meaning when the hippocampus and amygdala are altered, the hypothalamus is as well, resulting in alterations to the functionality of the HPA axis. Decreased levels of BDNF also increase the possibility of developing many neuropsychiatric diseases such as eating disorders, addiction, and diabetes as the brain struggles with regulating cravings and dangerous habits. The combination of the above genetic and hormonal mutations partnered with psychiatric trauma and other, less common epigenetic mutations hinders a person's quality of life. Thus, it is extremely important to address possible mitigation and prevention strategies regarding childhood trauma and toxic stress. There

should also be a considerable focus on vulnerable populations such as children in foster care who experience less stability and more trauma than the general population.

Future Directions and Limitations

The challenge faced by doctors and social workers when trying to prevent foster children from experiencing negative health effects later in life is determining who to hold accountable for the prevention, detection, and elimination of ACEs. The foster care system is largely underfunded and understaffed, so trying to put the responsibility of trauma exposure onto overloaded social workers is not a feasible plan. While Child Protective Services (CPS) is supposed to respond when a child is in a dangerous housing situation, in practice, it can take days for a CPS worker to visit a house or living facility. Additionally, there is no promise that a child can/will be removed from the dangerous living conditions in which they currently reside. Although social workers can be screen-trained to recognize signs of acute trauma and serve as proxy CPS workers, their overwhelming caseload and low wages makes the possibility of implementing screen-training unlikely. Foster parents can also be screen-trained in signs of acute trauma, but foster parents and the environment they create are often what foster children are trying to escape. Therefore, it is hard to place the burden of reporting ACEs on foster care parents or the heads of group homes. The third, and most commonly proposed, prevention strategy is the possibility of pediatric intervention. This would include training doctors on the signs and detection methods of ACEs, childhood trauma, and toxic stress (Johnson 2013, Schilling et al., 2015). For the general population, pediatricians are often the people who ask children about their physical, sexual, and emotional safety, and are privy to seeing the most

vulnerable parts of a child. Therefore, pediatricians would be one of the first to diagnose ACEs exposure to ACEs in children. However, due to the underfunding of foster care and the instability of their placements, most foster children rarely visit the pediatrician in a timely fashion. Moreover, when they do visit the doctor, it is often at a free clinic run by under-paid, overworked doctors.

Although future, more feasible, solutions are being discussed to better foster children's health outcomes, the field of epigenetics is a newly evolving field. There are minimal studies available on how specific types of trauma result in specific gene mutations. Additionally, only a limited number of studies have been conducted on people as many labs are still limited to testing their theories on rats. Moreover, the foster care system is a niche that presents a challenge when finding accurate and precise data as children are constantly moving into, out of, and within the system.

Conclusion

As seen above, epigenetic mutations are closely associated with ACEs when determining the health risks caused and amplified by time spent in foster care. For a long time, health risks such as substance dependence and obesity were associated with psychological or emotional terms and causes. It was generally accepted that the causes of depression, anxiety, and obesity experienced by ex-foster children stemmed from psychological insecurities and their childhood traumas. However, the evolving field of epigenetics has demonstrated that these illnesses have a biological basis rooted in DNA mutations. The research connecting ACEs to early death also allows social workers and scientists alike to confront one of the root causes of the mental,

physical, and emotional illnesses experienced by ex-foster children instead of just treating the secondary symptoms such as psychiatric conditions.

Exposure to Adverse Childhood Experiences triggers stress in children, potentially leading to the development of epigenetic mutations. While in the foster care system, children are often exposed to elongated periods of stress due to their changing environments and toxic households. As children live in the foster care system, their exposure to toxic stress increases their likelihood of developing maladaptive epigenetic mutations, which can shorten their lifespan by up to two decades. With new research linking ACEs, toxic stress, and epigenetic mutations, it is an important time to advocate for systematic changes to prevent adverse experiences and minimize the effects of toxic stress. The most commonly proposed way to combat ACE exposure is pediatric intervention, where pediatricians can evaluate if a child has been exposed to trauma and if they live in unsafe environments where they may be predisposed to further adverse experiences (Schilling et al., 2015). Foster children also rarely receive reliable and timely pediatric care, making pediatric intervention even more necessary. Moreover, if experienced before excessive exposure to toxic stress, nurture and healthy love can reverse the effects of toxic stress and undo or prevent the spread of epigenetic mutations (Griffins, 2012). Overall, scientists must draw distinct, concrete connections between ACES experienced in the foster care system and the biological effects they cause, which alter not only a person's physical health but also their emotional and mental stability.

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