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Early-Life Exposure to Abuse Increases the Risk of Developing Diseases

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ABSTRACT

This present thesis explores researchers' views on the role different epigenetic mechanisms play in contributing to health-related outcomes arising from child abuse exposure, and the management of subsequent psychosomatic diseases linked to child abuse. The current study analyzes three main themes: epigenetics, child abuse, and the medical management of diseases in a series of three interdependent steps. First, a systematic review of published literature examines whether epigenetics and child abuse are interrelated, defines key concepts, and presents evidence supporting the thesis questions. Second, this paper presents results from a semi-structured interview with researchers and health professionals of diverse expertise. This step focuses on gathering data from individuals that have worked with child abuse survivors and individuals that are actively studying child abuse from a biological perspective. Third, researchers' subjective views and implications for future research are discussed. This discussion summarizes the actual understanding of epigenetics, child abuse, and diseases and shares recommendations for future management. The data show that evolutionary perspectives can help understand epigenetic modifications. In addition, increased telomere erosion rates worsen the outcomes for child abuse, therefore more accurate screening tests can help improve abuse-related trauma management. This study will contribute to the overall literature by sharing insights on why epigenetics matter when managing patients that have survived childhood maltreatment. It will also bring new insights into the necessity to develop specialized clinical practice and drugs that can help reverse harmful effects and promote beneficial effects in post-trauma therapy.

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Chapter 1

Literature Review

Epigenetics shows how childhood experiences and environment can have lifelong impacts. Early childhood is a more sensitive period to childhood adversity (Erin et al., 2019). Childhood adversity is associated with epigenetic alterations (Labonté et al., 2012). Adverse Childhood Experiences (ACE) are associated with chronic health conditions, obesity, depression, suicide, smoking, heavy drinking, and certain socio-economic challenges (Merrick et al., 2019). Given that early and specialized medical intervention is needed to prevent and manage the bad outcome of childhood trauma, the science community examines biological issues arising from child abuse. This thesis shares health professionals' insights on why epigenetics matters in the understanding of Adverse Child Abuse experiences health's.

Child abuse, Adverse Childhood Experiences (ACEs)

Adverse childhood experiences are a series of cumulative and recurring events with variable frequency and severity, originating from familial and socio-environmental circumstances, and causing distress and harm to children (Kalmakis & Chandler, 2013). The social environment encompasses immediate physical surroundings, social relationships, and the cultural milieu with which the individual interacts (National Institutes of Health, 2000). From 1995 to 1997, the Center of Diseases Control and Prevention and the Kaiser Permanente San Diego conducted the first study on ACE which they classified into three main categories: childhood abuse, neglect, and household challenges (*Adverse Childhood Experiences Resources*,

2021). The most common adverse event, child abuse can be subdivided into physically, sexually, and emotional abuse (Kalmakis & Chandler, 2013). ACE and poor health outcome is supported by long-term consequences that a child witnessing violence and familial conflict or cold relationships in a non-supportive environment had poorer health outcome (Cannon et al. 2010). Stress generated upon traumatic experiences can be classified into: “positive stress’’, “tolerable stress’’ and “toxic stress’’ based on how the stress response system impacts the body (Center on the developing child, 2020). ACEs led to harm whether they are caused by intentional negative experiences or a lack of positive experiences (Kalmakis & Chandler, 2013). Positive stress shortly activates the stress response system which briefly increases in heart rate and cortisol levels of an individual; ‘’tolerable stress’’ occurs during a long-lasting difficulty and may disrupt brain structure which will then recover; and ‘’toxic stress’’ keeps the stress response system activated and on high alert occur, for example, when a child is experiencing prolonged and/or frequent adversity (Center on the developing child, 2020).

From 2015 to 2017, 15.6% of adults in a study population reported four or more types of ACEs, and higher odds of having chronic health conditions ranging from overweight or obesity to chronic obstructive pulmonary disease, and depression were associated with the highest incidence of ACE (Merrick, 2019). Since ACE affects children regardless of their race, ethnicity, gender, and citizenship, many scientists have reported ACEs around the world. For instance, in South Africa, a group of researchers demonstrated how the prevalence of ACE increases the risk of women acquiring HIV and Herpes simplex virus (Jewkes et al, 2010). In the United States, about 61% of adults surveyed across 25 states reported at least one type of ACE, and nearly 1 in 6 reported they had experienced four or more types of ACEs (Preventing Adverse Childhood

Experiences, 2022). Overall half of the world's children experience violence which constitutes an economic and societal cost for families and societies (*Child Protection,* 2018).

Epigenetic Modifications

Epigenetic modifications are important regulators of gene expression that occur at the chromatin level (Gilbert,2000). These modifications require the action of different types of proteins, namely readers, writers, and erasers. Random epigenetic drift (gradual increases or decreases of allele frequencies at a specific locus due to chance) might inactivate a gene without any environmental cues (Gilbert, 2000). On the other hand, more selectable epigenetic variation induced by environmental agents might affect both somatic and germline DNA (Gilbert, 2000). A variant of chromatin structure, part of an epigenetic system can be transmitted from one generation to another – a phenomenon called epigenetic inheritance (Gilbert, 2000). While these changes in gene expression have occurred for many generations through the natural selection process, epigenetic changes that occur at the individual level can maximize survival but also have a detrimental impact (Gilbert, 2000). Because the gene sequence does not tell the whole story, studying epigenetic mechanisms can help researchers better understand the impact of the environment on genes.

Relevance of Epigenetics to Understand Child Abuse

Telomere erosion

Telomeres, the TTAGGG sequence at the end of linear chromosomes, have been used to predict longevity and as biomarkers of stress (Epel, 2009). Studies have shown that telomeres can lengthen and/or shorten in response to sociobiological signals during stressful periods (Epel, 2009). In fact, In the past few years, there has been evidence that behaviors and many other features of the environment such as stress may influence how genes are expressed. For instance, studies have demonstrated that chronic stress can impact telomerase activities which would lead to shorter telomeres in adulthood (Epel, 2009). Based on these findings, scientists have conducted another study that assessed bullying victimization and physical maltreatment in children and simultaneously measured the length of their telomeres (Shalev, 2013). Their results indicated that children who experienced more ACE had more telomere erosion between ages 5 and 10 (Shalev, 2013). If telomere erosion is associated with stress, there might also be a relation between telomere erosion and life-long health.

DNA methylation

DNA methylation is a biochemical process by which methyl groups (CH3-) are added to the DNA. This process often occurs at a region of a promoter sequence of DNA, regions that control transcription initiation, called CpG islands. These islands are regions where cytosine (C) pairs with guanine (G), hence the CpG, in double-stranded DNA (Gilbert, 2000). High CpG-content promoters (HCPs) are unmethylated, actively repressed by histones methylation, and are

usually ON (Gilbert, 2000). Being ON means that they are in an active state, ready to synthesize transcription factors or other protein regulatory proteins. Low CpG-content promoters (LCPs) have methylated CpG sites and are usually OFF (Gilbert, 2000). They are less likely to synthesize transcription factors. However, LCPs can become activated by transcription factors. Having methylated promoters is an important feature of LCP regulation. In summary, DNA methylation can be a Switch to turn ON or OFF a gene. Childhood adversity has been associated with diverse epigenetic mechanisms. A ‘’two-stage structured life course modeling approach’’ has shown that early childhood is a more sensitive period to childhood adversity since it can predict the accumulation of DNA methylation (Erin et al, 2019).

Highly methylated gene promoter associated with childhood trauma

A comparison of brain tissue between individuals that were classified as suicide-abused, and a control group indicated that the DNA promoter region of the tissues in the first group was hypermethylated (McGowan et al., 2008). The DNA promoter hypermethylation was associated with a decrease in rRNA (ribosomal RNA) expression. The increase of promoter-wide DNA methylation was associated with the decrease of rRNA gene expression in suicide brains. Early childhood adversity altered the epigenetics of the genome which impacts neural function and contributes to certain risk differences in vulnerability to certain health diseases among individuals.

Another comparison of brain tissue between individuals that were classified as suicide abused and a control group indicated that cytosine methylation of the glucocorticoid receptor (NR3C1) was correlated to a decreased level of the 1F variant of the NR3C1 in humans (McGowan et al.,

2009). Findings show that early life adversities such as childhood trauma were strongly associated with epigenetic changes that occur in the promoter of the NR3C1 gene. The findings bring questions about the relationship between cytosine methylation, transcription factor binding, and gene expression. The result of this study indicated that epigenetics modifications led to lower expression of receptors which increased vulnerability to chronic illness and psychopathology.

Furthermore, a comparison of brain tissue between individuals that were classified as suicide abused and a control group indicated that 326 promoters were studied, 248 promoters were hypermethylated, and 114 promoters were hypomethylated (Labonte et al., 2012). A comparison of brain tissue between individuals that were classified as suicide abused and a control group showed that DNA methylation was associated with decreased expression of 1B, 1C, and 1H variants of NR3C1. In addition, it was observed that the expression of several variants of the human glucocorticoid receptor (hGR) decreased was correlated with a decrease in transcriptional activity in specific sites of hGR promoter (B) and (1C), hGR1(H) in individuals with abuse histories compared to individuals with non-abuse histories and controls. These studies showed that ACE altered the expression of several hGR variants by constant activation of the hypothalamic-pituitary-adrenal (HPA) activity, where cortisol is secreted. The increase in cortisol secretion was correlated with an increase in DNA methylation which is inversely correlated with gene expression. The author concluded that childhood adversity is associated with epigenetic alterations. DNA methylation on the promoter of hGR of an individual that had ACE impacted the function of HPA (Labonte et al., 2012).

Table 1:An analysis of the hippocampal tissue in suicide brain of childhood trauma abused individuals in specific CpG loci data

Sample size	**The technique used to detect DNA methylation on promoters**	**Region of the genome analyzed**	**DNA methylation phenotype associated with SA**	**References**
41 (25 SA /16 CTRL)*	DNA immunoprecipitation and microarray hybridization	Genome-wide: 362 specific promoters; follow up an experiment on ALS2 gene	Hypermethylation on 248 promoters (ALS2 methylated significantly) and hypomethylation on 114 promoters	Labonté & al., 2012 [1]
56 (21 SA, 21 SNA, 14 CTRL)*	Sodium Bisulfite and Luciferase Assay	Exons 1B, 1C, 1H of NR3C1	DNA methylation is associated with decreased expression of 1B, 1C, and 1H variants of NR3C1	Labonté & al., 2012 [2]
36 (12 SA, 12 SNA, 12 CTRL)*	qRT-PCR Sodium bisulfite mapping chromatin immunoprecipitation assays	The promoter of exon 1F of NR3C1	DNA methylation is associated with decreased expression of the 1F variant of NR3C1	McGowan & al., 2009 [3]
24 (13 SA, 11 CTRL)*	Bisulfite mapping and qRT-PCR	rRNA promoter	rRNA promoter hypermethylation is associated with a decrease in rRNA expression	McGowman & al., 2008 [4]

*__SA__: abused suicide individual __CTRL__: control subjects __SNA__: non-abused suicide Individuals

Chapter 2

Methods

Overview

A semi-structured interview methodology was used to better understand how epigenetics is associated with childhood trauma and with management of related health issues. Interviews are an appropriate methodology to seek out data-driven connections and experts' opinions about current events and predictions of future developments in qualitative research (Pickard, 2017). The semi-structured approach with open-ended questions was asked of various researchers who study evolution, molecular biology, stress or abuse-related disorders or mechanisms, and clinicians with a subspeciality in managing child abuse.

Participants Recruitment

Potential individuals were identified through websites such as the Penn State Elsevier by searching key terms like "epigenetics'' and "trauma''. Professionals were also identified based on previous papers published, and/ or their research interests publicly available on their websites. Professionals contacted suggested other researchers or health professionals who may fit the inclusion criteria. Participants were recruited through email after receiving IRB approval in Fall 2021 under protocol number 00017996. Personally identifiable information or sensitive information was not collected nor reported in the results section of the thesis. Out of 136 researchers contacted, 6 were interviewed.

Inclusion Criteria

Individuals were contacted if they met the following criteria:

- Research professionals that have studied or currently are studying trauma, and/or epigenetic changes linked to the trauma studied
- Health professionals that interacted with traumatized patients

Exclusion Criteria

- Individuals who are not qualified as professional researchers or health professionals
- Individuals who are less than 18 years old
- Participants from which implied or verbal consent was not obtained

Early Withdrawal of Subjects

Participants who did not consent to participate were immediately excluded from the study. Participants could also choose to withdraw from the study at any time. Withdrawal from the study and/or Withdrawal of Authorization was without penalty.

Data collection

Professionals who consented to participate in the study were asked to schedule a time for the semi-structured interview via Zoom for 30 minutes. The progression of questions per each interview was based on the interviewee's responses. This choice is supported by the fact that

most interviewees have different backgrounds and have interacted with abuse survivors or have studied their samples in different contexts. The interview was developed and validated based on their previous research findings or what other professionals have witnessed within medical settings in relation to abuse survivors' patients. I stopped reaching out to researchers until no new information emerged from the interviews – the point of saturation. Table 2 shows the key themes of the questions. For more details, the list of questions that were submitted to the IRB is in the Appendix. In addition, the interviewees learned about what their colleagues have said regarding the same subject and shared their points of view. With participant's agreement, Note-taking was the main method used during discussions to collect data.

Table 2 Themes of interview questions

About Epigenetics	**About Trauma**	**About Health Management**
• Analysis of epigenetic changes • Unexpected findings • Epigenetic changes observed	• Type of trauma studied • Trauma link to epigenetics • Trauma linked to diseases	• Trauma impact on diseases • Screening process of ACE • Behavioral therapies

Data Analysis

This study used a qualitative methodology. The analysis of data from interviews started with summaries of key take away of each interview and categorized them into categories. Narrative analysis was the method used to see an important link between child abuse,

epigenetics, and diseases. To do so, I grouped them based on similarities in response and looked for continuity and connections.

Chapter 3

Results

Epigenetic changes evolve to other forms of epigenetic modifications with time

Interviewee 1 has an MD/Ph.D. degree with expertise in pharmacology, biochemistry, and molecular biology from the Cancer Institute, Next-Generation Therapies at Penn State Cancer Institute. The focus of the interview was on whether DNA methylation can be reversed, and how? According to interviewee 1, certain epigenetic modification happens later and lasts longer when compared to other epigenetic modification which can happen initially. In the case of stress exposure, creating parameters helps better assess individuals' stress. To do so, a control group can help determine if an environmental trade-off trend causes the differences observed. The main challenge facing this approach is that research participants have different backgrounds, and they have acquired different characteristics which overlap with targeted trends, thus making the results unclear. Analysis of a large population reveals similarities and differences in how likely someone is to develop diseases once the change in epigenetics is observed. For instance, the stress levels of a person who has lived in a specific place for 5 years might be different from that of a person who has lived in the same place for 20 years. The interviewee thinks that a higher level of some epigenetic modification is harder to treat than others making them easier targets for drugs. In addition, a change in epigenetic markers can happen over time even without the use of drugs. However, the usage of specific treatment approaches will be required for any

given epigenetic changes observed. In the case of epigenetic modification inhibitors, for instance, can be metabolized differently among individuals.

Evolution can help understand why epigenetic modification occurs

Interviewee 2 has a Ph.D. with expertise in ecology & evolutionary biology. The focus of the interview was on understanding the evolutionary perspectives of epigenetic mechanisms. According to interviewee 2, studying traits' evolution can help explain why epigenetic modifications occur. And thus, knowing why a certain aspect of the phenotype is sensitive to certain environmental cues and others can help understand diseases occurring at a later stage in life. Interviewee 3 suggests that natural selection's effect on regulatory pathways and adaptive plasticity explains why environmental cues, such as a stressful environment, affect genes through epigenetics.

Box 1. Do epigenetic changes always lead to a negative outcome?

This case study is fictional and inspired by interview 3 to help provide context to the evolution of epigenetic changes.

Sandra grew up in a poor neighborhood and has struggled with food insecurity for most years of her life. Her body has adapted and developed changes that could give her a better chance of being able to reproduce in this risky environment. Her firstborn Emma has developed a phenotype that makes her ready for starvation conditions. Fortunately, Emma was born and raised with high access to food; unfortunately, her body does not react well because of this mismatched phenotype, and she has been diagnosed with an eating disorder. It does not

make sense that she has inherited epigenetic changes that hurt her rather than helped her. Analyzing Emma's mother's story, these changes must have been beneficial at some level, otherwise, she would not have had them. Although these adaptation processes have increased Emma's mom's fitness in an environment of high uncertainty, they have also increased Emma's chance of developing an eating disorder.

Emma's dad has worked in a high-stress environment for more than 40 years. After an accident in the workplace, Emma's dad and 8 workers went to the hospital, and all had a low level of iron in their blood. The health professionals gave the workers iron supplements, thinking that the low level of iron was not good. All the workers developed infections once they started taking the medications. The low blood iron level was an adaptive response to prolonged stress and had helped prevent infections. When somebody receives low-quality environmental signals due to stress environment, the body adapts even if that would lead to poor health outcomes in the long term. In the case of Emma's dad, was it worth it to change parameters without knowing that it was an adaptive response to prolonged stress? From an evolutionary perspective, the advantage of these epigenetic changes to individuals, but to genes.

Telomere Erosion and Child Abuse

Interviewee 3 has a Ph.D. with expertise in neurobiology. His work focuses on the effects of stress in early childhood on changes in telomere length. The interview goal was to understand the consequences of change in telomere length as a biomarker for physical and mental health problems in response to childhood trauma. Interviewee 3 shared that an increased shortening rate

of telomere after child abuse exposure may put children at risk to develop diseases later in life. Although telomeres naturally get shorter with age independently of stress, interviewee 3 acknowledges that people that have shorter telomeres have a greater risk of dying prematurely. And thus, if an individual starts with shorter telomeres when compared to the average individual at the same age during childhood, at 20 years old this difference will persist. In addition, researcher 4 analysis of other epigenetic changes happening at the same time as telomere shortening to quantify biological age, showed evidence of epigenetic changes in relation to childhood trauma. To better established this relation, interviewee 4 has tracked information on epigenetics and telomeres at a young age and following up with the individuals over time is key to determining the evolution of diseases.

Management of Child Abuse in the Emergency Department

Interviewee 4 is an M.D. and currently works as an emergency medicine pediatric child abuse specialist at the emergency medicine department of Penn State Health. Interviewee 4 has witnessed that children who have adverse childhood experiences have an increased risk of infection. For instance, as the rate of ACE increases, children are more likely to have chronic obstructive pulmonary diseases (COPD) even if they have not been exposed to smoking, although the biggest risk factor for the development of COPD is smoking. And so, ACE increases individuals' risk of the worst health outcomes. And thus, ACE negatively impacts society as it increases the cost of healthcare for the population in general. The interviewee was aware of clinical trends that help health professionals identify or start investigating whether the injury is abuse-related. For example, a child abuse pediatrician would know that a gonococcal

infection among infants and children is most likely an ocular manifestation of child abuse causing an eye infection of Sexually Transmitted Infection (STI) (gonorrhea) instead of accidental infection. According to the interviewee, from a symptomatology standpoint, disease outcomes that arise from child abuse are managed in the same fashion as if they did not occur in response to an adverse childhood experience. However, the long-term outcome of a given accidental trauma when compared to the same abuse-related non-accidental trauma differs. Furthermore, interviewee 4 witnessed that ACE increases the risk that a clinical condition becomes more severe although the way doctors approach a child with an accidental head injury and abuse-related head injury is the same: a sexually abused child with an STI would receive the same medications as an individual who has STI after consensual sexual activities. According to interviewee 4, there are no specific drugs that target specific biochemical mechanisms in the diagnosis of abuse-related trauma: “a psychiatrist might use the same medication that they would use for someone who is experiencing a great loss”. Whether infants fail to thrive because of excess vomits or because of a cardiac disease that requires high energy expenditure is easier to treat than infants who lose weight because they are not being fed. In fact, from a long-term perspective, changes in gene expression in response to stress are harder to revert and might explain why trauma survivors have an increased risk of having diseases later in life.

Comorbidity overlap between ACE and diseases

Interviewee 5 is a pediatric psychologist with expertise in feeding and eating disorders. The Interviewee’s research interest is understanding fear and anxiety and improving cognitive-behavioral therapy (CBT) for eating disorders. My interview goal was to understand the co-

morbidity overlap between childhood trauma and eating disorders. Although ACE, such as being bullied at a young age, increases the risk of having eating disorders, results from ACE self-report questionnaires are not often relevant to assess the origin of the eating disorder. Restriction in the diet is for many children a way to cope with trauma. However, using CBT or exposure therapy to treat eating disorders only targets either trauma or the eating disorder, but not both.

ACE Screening tools do not always lead to accurate results

Interviewee 6 is the founder and director of the Pediatric Brain Injury Research Network, a board-certified Child Abuse Pediatrician at Penn State Health Children's Hospital, and a Professor of Pediatrics at Penn State College of Medicine. Our interview focused on evaluating whether ACE is addressed in medical practice and the long-term outcome of abuse survivors observed. According to interviewee 6, not having a standard definition of ACE in clinical practice often leads health professionals to misdiagnosis of child abuse. Interviewee 6 witnessed that attention deficit, learning disabilities, developmental delays, and self-harming behavior such as overeating or suicide and/or developmental delays are often observed in patients that have experienced ACE. Screening tools of child maltreatment using the ACE score have helped raise awareness about abuse. By preventing underdiagnosis and/or overdiagnosis of ACE, evidence-based medical screening tools indirectly decrease implicit bias of health professionals by helping physicians make better diagnoses and protect children from further abuse. However, ACE scores might lead to false-positive cases and may fail to predict abuse probability. For those reasons, health professionals often refuse recommendation of ACE screening tools.

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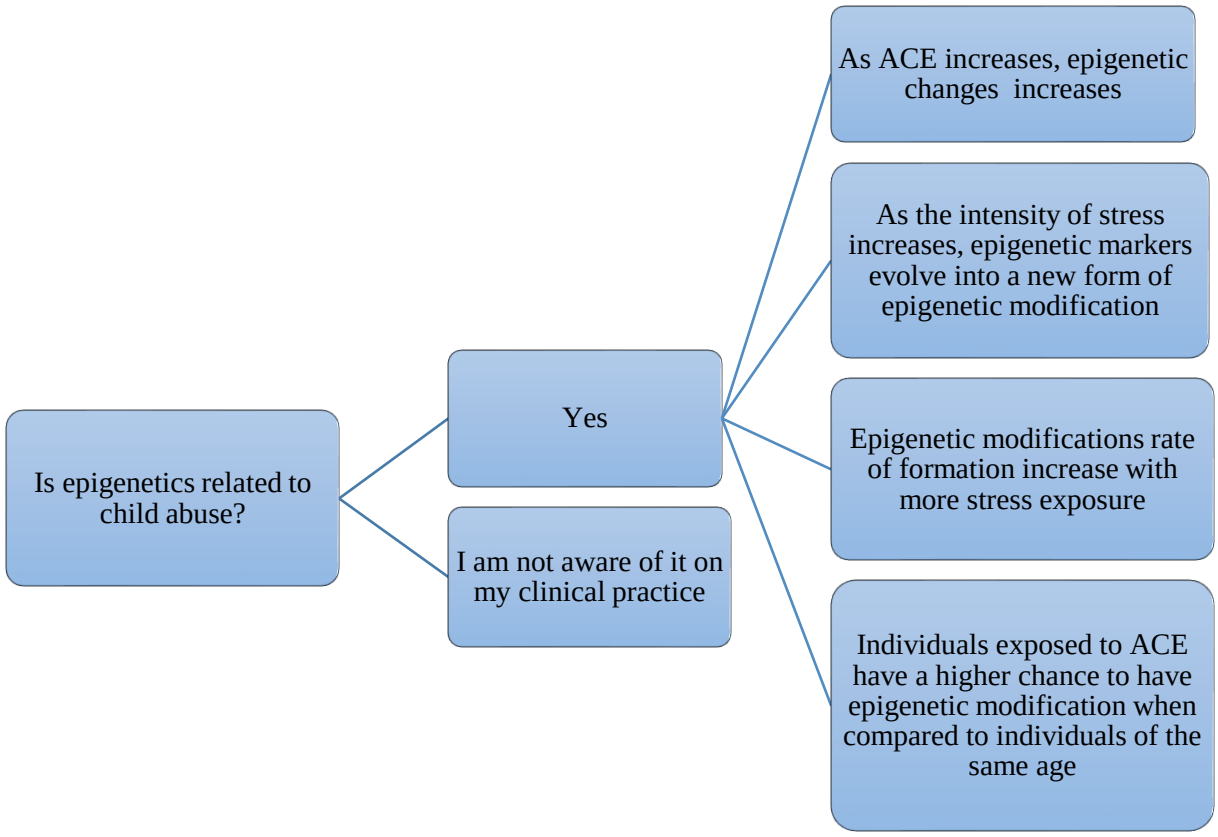
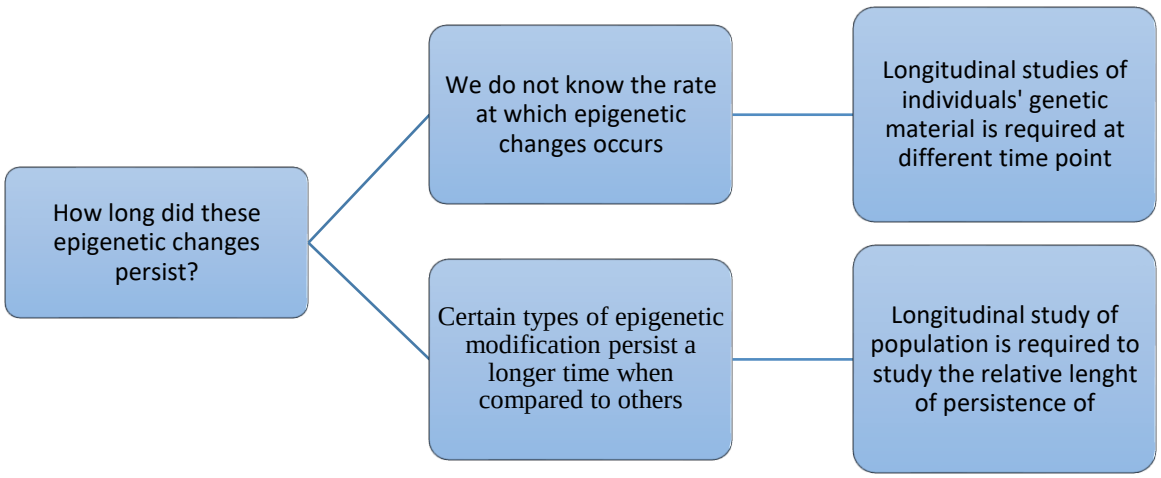
Figure 1 How ACE, epigenetics, and diseases are interrelated interviews take away

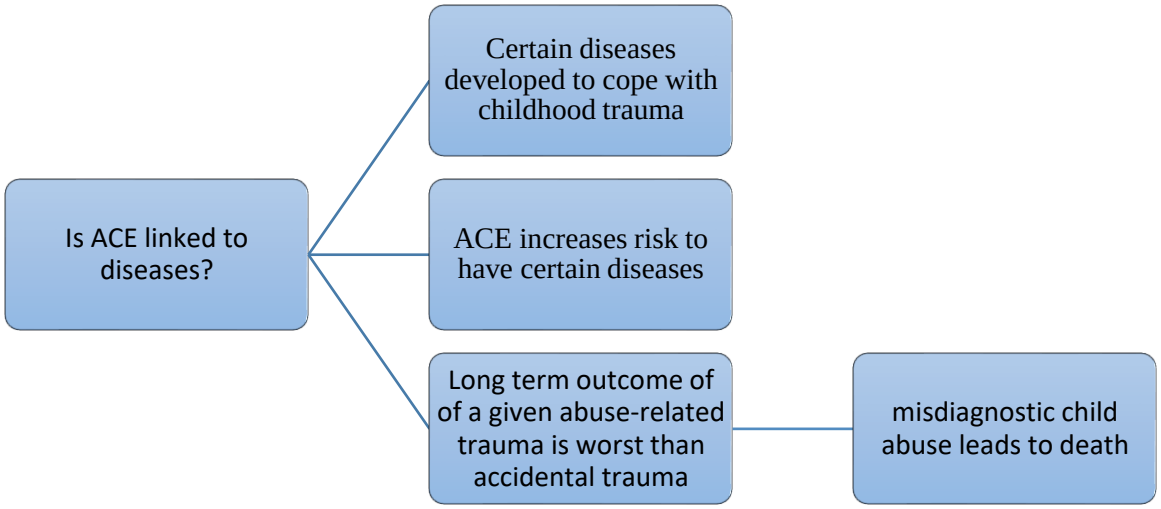
Panel A. Epigenetics linked to child abuse



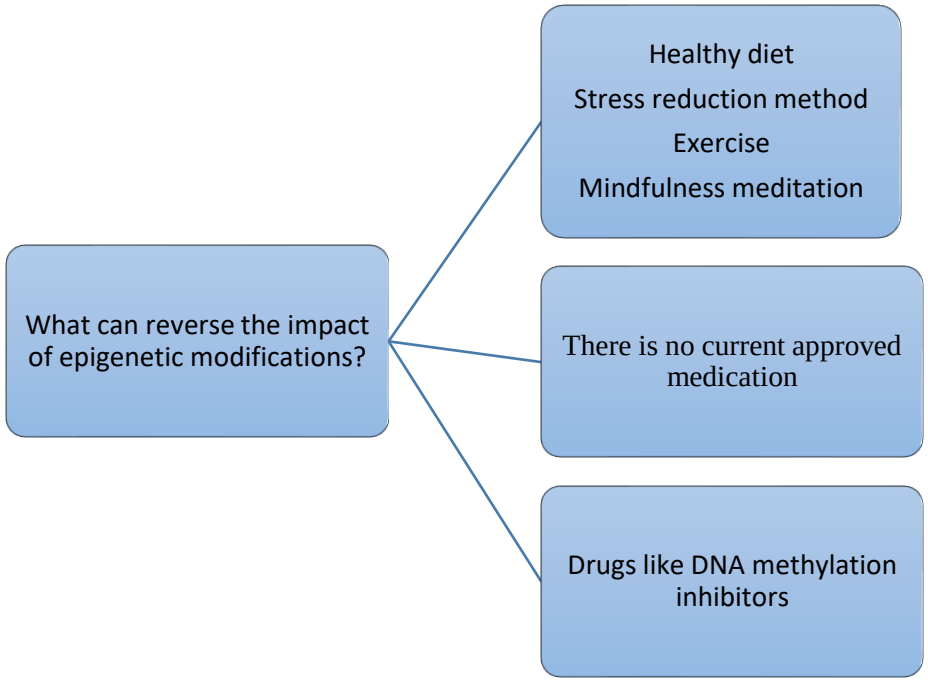
Panel B. Epigenetic changes persistence



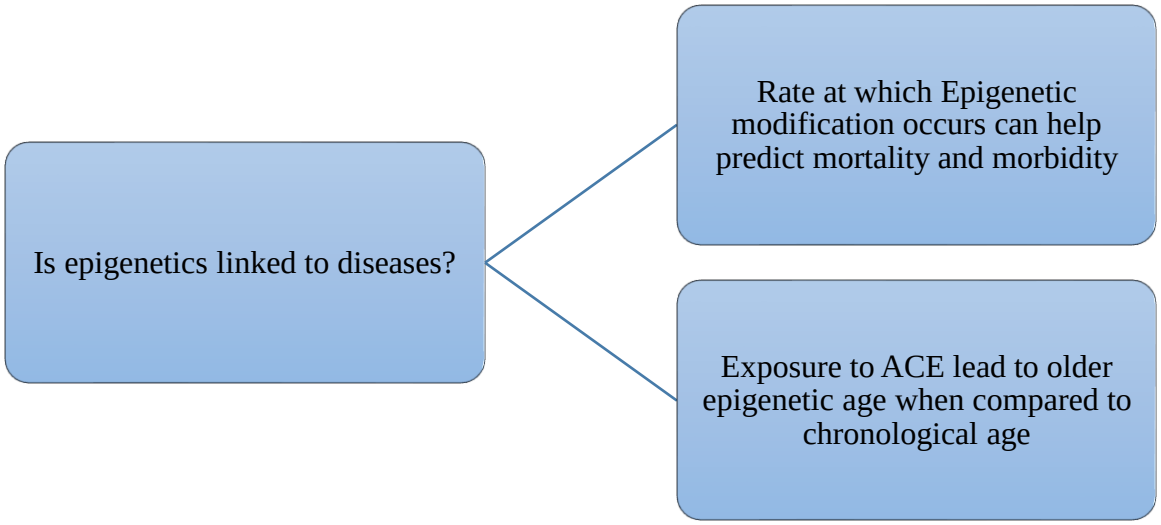
Panel C. ACE link to diseases



Panel D. Epigenetic modifications are reversible



Panel E. Epigenetic linked to diseases



Chapter 4
Discussion

This thesis explores researchers' views on the role child abuse plays in contributing to epigenetic modification and diseases. The data suggest that many health professionals are unaware of epigenetics linked to child abuse. In addition, researchers support that as ACE increases, epigenetic modification changes happen, leading to a different epigenetic profile. Furthermore, some interviewees think that diseases can result from the physical adaptation to trauma; as ACE increases, so does the risk of certain diseases. Likewise, from a long-term health perspective, abuse-related trauma leads to the worst outcome when compared to accidental trauma. In both cases, the null hypothesis suggesting that epigenetics is not related to ACE and ACE is not related to diseases has been rejected. The results support that epigenetics is related to child abuse and, in turn, child abuse is related to diseases.

The developmental plasticity field helps us understand why genetically similar genetically individuals produce offspring that are different in phenotype by interacting with diverse environmental conditions during early life (Lea, 2018). Because developmental plasticity involves producing different phenotypes from the same genotype, it necessarily involves epigenetic mechanisms (Lafuente & Beldade, 2019). To better understand the influence of the environment on trait evolution, two types of models have been proposed to describe how living organisms adapt when facing environmental challenges and how we can outline conditions that can maximize health (Lea, 2018). The developmental constraints model suggests that organisms that face limited resources make trade-offs to protect their function and increase their chance of survival (Lea, 2018). Consistent with my findings, these studies reported that trade-offs in early life can reduce the long-term health quality of adults (Lea, 2018). In addition, the predictive

model suggests that environmental cues in early life can help predict the adult environment (Lea, 2018). One explanation would be that because we have changed our environment, genes characteristic that used to serve our ancestors are now maladaptive. And thus, to better understand how the environment impacts phenotype expression, it is important to acknowledge how early-life environment affects gene expression. Furthermore, another study suggests that knowledge of early life environment can help understand what types of environmental stimuli are atypical to human evolutionary history and what kinds of exposures perturb regulatory programs, thus leading to poor health outcomes (Lafuente& Beldade, 2019). Knowing when ACE occurs, and the timing, the stability of epigenetic changes could help predict health outcomes. Future work should focus on evaluating the impact early life conditions have on gene expression, and whether environmental induced effects on physiology and metabolism are reversible.

Previous studies suggested that DNA methylation-predicted age increased when compared to chronological age is associated with cancer (Durso et al., 2017), and cardiovascular diseases (Roetker et al., 2018). A population-based cohort study comparing DNA methylation age between children that have been exposed to four or more ACE and children that have been exposed to zero ACE reveals that ACE was associated with DNA age acceleration in girls not in boys (Tang et al., 2020). These studies support our finding stating that ACE leads to older epigenetic age when compared to chronological age which explains that epigenetics relates to diseases that occur after ACE exposure in a long term. Whereas another meta-analysis study using Childhood Trauma Questionnaire did not find a correlation between the association of trauma exposure with DNA methylation aging (Wolf et al., 2018). Results from interviews reveal

that ACE questionnaires are not always relevant in explaining the origin of certain abuse-related diseases. These differences in findings can be explained by the tools used to measure trauma exposure. Using retrospective self-administered questionnaires relies on one-time points while other tools can measure ACE by relying on multiple time points.

The present analysis includes exploring the opinions and experiences of experts from diverse backgrounds to better understand how ACE, epigenetics, and child abuse are interrelated from both clinicians' and researchers' perspectives. A limitation of this study is the small sample size. Another possible limitation would be the interviewees' different social and lifestyle factors which might cause research bias and influence the results. For this reason, I limit drawing broad conclusions from the data collected. Finally, given that research questions needed to be addressed and re-reviewed as the interview progressed, it would be difficult to reproduce the same research. The results of this study should be interpreted cautiously and require further data collection with a larger sample.

To better understand how ACE can influence adults and children, future research should measure child and parents of trauma survivors' epigenetic modifications at different time points to track the impact of early life events on genes and health over time. In addition, the integration of bioinformaticians in research teams to analyze the effect of length of time exposure on our genes at a population level can help establish a target for epigenetic drugs. Further research needs to be done to evaluate what type of traits are sensitive to environmental changes such as ACE to understand which specific type of abuse accelerates epigenetic modification more than another.

Chapter 5

Conclusion

Epigenetic modifications and telomere erosion have been shown in past studies to be excellent biomarkers of ACE. It appears they result from adaptation processes of our body coping with stress or other changes in the environment. Based on a life-span approach, an increased level of ACE might have influenced epigenetic mechanisms, leading to a different epigenetic profile, and increasing the risk of certain diseases. Although abuse-related trauma often leads to the worst outcomes, the way health professionals manage abuse-related trauma and accidental trauma is very similar as ACE screening tools are not always accurate. This thesis has shared researchers' thoughts on the fact that epigenetics, child abuse, and diseases might be interrelated. Future research needs to evaluate epigenetic changes' persistence and impact on the overall epigenome, how epigenetic modifications can be integrated into screening tools for ACE, and what type of ACE might increase the susceptibility of specific diseases in childhood trauma survivors.

Appendix

List of questions that were asked during the semi-structured interview:

About Epigenetics

a) How did you analyze epigenetic changes? (Specify any techniques or methods used)

b) What results did you obtain regarding the epigenetic changes?

c) How long did these epigenetic changes persist?

About Trauma

d) What type of trauma did you study?

e) Was the trauma linked to the epigenetics changes that you studied?

f) Was the trauma experienced linked to other diseases? If so, how?

About the professional's research

g) How did your research contribute to the field?

h) Did your results fulfill your predictions? Were there any unexpected findings?

I) What is your next step?

j) Are there any drugs or targets that can reverse the impact of epigenetic modification? If so, how might they be used?

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ACADEMIC VITA

Mélissa Césaire

EDUCATION

May 2022 Bachelor of Science in Developmental Biology/Genetic, Penn State Harrisburg

CLINICAL EXPOSURE

2021-Present Shadowing a GI doctor at Carlino Family IBD Center, Penn State Health
Fall 2021 Shadowed ER doctor at Penn State Health Emergency Medicine Department
Summer 2021 Assisted Medical meetings at Children's Hospital of Philadelphia

RESEARCH EXPERIENCE

2021- Present Undergraduate Researcher (thesis), Penn State Harrisburg
- Epigenetic Modifications Worsen Outcome in Child Abuse-Related Trauma
- Qualitative research, semi-structured interviews

Summer 2021 Summer Intern, Laboratory of Dr. Diva D. De León-Crutchlow, NIDDK, NIH
- Characterization of an ABCC8 inactivating mutation in the zebrafish Model
- Genotyping, Microinjection, blood Collection, Insulin Elisa, ImageJ
- Euthanasia, setting up mating pairs, Fin clipping, collecting embryos, Bleaching eggs

2020-2021 Clinical Research Assistant, Laboratory of Dr. Jamal Essayli, Penn State Hershey
- Wrote Human Research Protocol, consent form, and recruiting emails
- Mastered Excel, Power Chart, and Redcap software

2019-2020 Student Researcher, State University of Haiti
- Qualitative study analyzing how Haitian professionals understand the definition of Health given by WHO
- Qualitative research using semi-structured interviews as a method to collect data

HONORS AND AWARDS

2021-2022 NIH Undergraduate Scholarship Program (UGSP)
2020-2022 Dean's List
2020-2021 Dandrea Trustee Scholarship, Academic Merit Scholarship
2020-2021 Penn State Harrisburg Board of Advisers Scholarship, Academic Merit Scholarship
2020-2022 Schreyer Honors College
2021 Student Engagement Network, Grant

LEADERSHIP & COMMUNITY SERVICE

2021- Present Volunteer Interpreter, Respond Crisis Translation
2021- Present Volunteer ESL-aid instructor, Immigration & Refugee Services

TUTORING & MENTORING EXPERIENCE

2021-Present Professional Tutor, Varsity Tutoring
2020-2021 Peer Tutor, Learning Center, Penn State Harrisburg
2021-Present Peer Mentor, Global Lions Mentor, Penn State Harrisburg
2019-Present Peer Mentor, Education Haiti

POSTER/ORAL PRESENTATIONS

2021 Zebrafish as a Model for Examining the Pathophysiology of Hyperinsulinism.

STEP-UP/ Virtual. *Oral*

2021 Zebrafish as a Model for Examining the Pathophysiology of Hyperinsulinism. ABRCMS/ Virtual. *Oral and Poster*

PUBLICATIONS

Camille P. J., Césaire M., Chéry M. O. et al. A qualitative study analyzing How Haitian professionals understand the definition of Health given by WHO.(2020). *INFO-CHIR-RHCA: La Revue Haitienne de Chirurgie et d'Anestesiologie, 5*(30), 29-35. https://info-chir.org/rhca/Info-CHIR_No_30.pdf

Manuscript: How Epigenetics, Child abuse, and Diseases are interrelated, *unpublished*

CERTIFICATES

2020 Certificate on Protection of Human Research Subjects - Biomedical

2020 Certificate on GCP for Clinical Trials with Investigational Drugs and Medical Devices