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Adverse Childhood Experiences and their Connection to Autoimmune Disease in Adulthood

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ABSTRACT

Everyday in the United States, a child experiences a traumatic event. Autoimmune disease is one of the top two leading causes of death in the United States. Can these two horrifying events be connected? Autoimmune diseases currently affect millions of Americans and are considered an epidemic because of their prevalence within the adult population. Even with a high number of cases, this possible connection has been largely ignored and under researched for the history of modern medicine. However, two studies have begun to make the connection between adverse childhood experiences and how that affects the onset of autoimmune diseases in adulthood. This field of medicine is under-researched even though it may be the key to understanding the physiological or physical cause of suffering for millions of Americans. Childhood trauma may be the missing key to understanding the cause of adulthood autoimmune disease. With the prevalence of childhood traumatic experiences and autoimmune diseases, the reason for this lack of research is unexplainable, however it opens to door to future studies regarding the possible affect of childhood trauma on autoimmune disease development.

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LIST OF ABBREVIATIONS

ACE	Adverse Childhood Experience
CDC	Centers for Disease Control
MS	Multiple Sclerosis
SLE	Systemic Lupus Erythematous
RA	Rheumatoid arthritis
SpA	Spondyloarthritis
SSc	Scleroderma
CLUES	California Lupus Epidemiology Study
Th1	T helper cell 1
Th2	T helper cell 2
PCE	Positive Childhood Experience

INTRODUCTION

Autoimmune diseases are an epidemic in the United States. With a rising number of cases and almost no knowledge of a possible cause, there seems to be little in the way of stopping the onslaught of new diagnosis. Conversely, adverse childhood experiences are a public health crisis, affecting children across the country. The long term consequences of traumatic experiences during the developmental years of childhood are unknown. As we see a rise in both of these events, it is imperative to discover their connection. Do adverse childhood experiences affect the onset of autoimmune diseases in adulthood?

By defining what adverse childhood experiences are and who is affected, it is possible to then look into the known consequences of the trauma from before birth to adulthood. From there, defining and acknowledging the past research on autoimmune disorders is needed to fully understand the consequences of this lack in research. Two studies have found a positive association between adverse childhood experiences and autoimmune diseases that serve as the starting point for further research. Understanding the cause of autoimmune diseases and the consequences of adverse childhood experiences is imperative to saving lives now and for decades to come.

Chapter I: Adverse Childhood Experiences

Adverse Childhood Experiences, or ACEs, are categorized as potentially traumatic or stressful events that occur during childhood, between 0 and 17 years of age. These experiences can range from anything that has caused harm to a child either mentally, physically, or emotionally, to things that may have been stressful for a child's psyche. The largest study of Adverse Childhood Experiences and their potential harm was conducted by the Centers for Disease Control and Prevention (CDC) and the US health maintenance organization Kaiser Permanente from 1995 to 1997 (Felitti et al., 1998). From this study, the CDC broke down ACEs into three different categories. These categories are abuse, neglect, and household challenges. Each is then broken down into smaller sections, however the overarching three categories stay consistent.

Categories of Adverse Childhood Experiences

The first category of Adverse Childhood Experiences is abuse. The abuse category is broken down into three specific sections. The first being emotional abuse. This can include, but is not limited to, a parent/stepparent/adult that is living in the home: swearing, insulting, or acting in a way that made a child fear for their physical safety (Felitti et al., 1998). Emotional abuse is sometimes referred to as mental abuse, as this is typically abuse that comes in the form of words without physical attack. Emotional abuse can cause harm to the child's mental and emotional health.

The second type of abuse is physical abuse. This abuse can be done by any adult that is living within the home of a child. It can include anything that causes physical harm to a child, resulting in either marks or injuries. This can be done by pushing, grabbing, slapping, throwing objects, or hitting (Felitti et al., 1998). This is not a complete list but a good idea of the range that physical abuse can cover. Physical abuse can harm not only a child's physical health, but their mental and emotional security within the home as well.

The third type of abuse categorized in the ACE study preformed by the CDC, is sexual abuse. While emotional abuse and physical abuse have definitions that are not fully encompassing, there are more set guidelines for sexual abuse. The ACE study defines sexual abuse as:

> "An adult, relative, family friend, or stranger who was at least five years older than you ever touched or fondled your body in a sexual way, made you touch his/her body in a sexual way, attempted to have any type of sexual intercourse with you." (Felitti et al., 1998)

While this does not include everything and leaves room for personal and professional interpretation, this is a guideline for how someone can define sexual abuse in a child.

The second category is not as well known as abuse. While abuse is typically at the forefront of adverse childhood experience conversations, the second category can be just as harmful. The second category of Adverse Childhood Experiences that the CDC has outlined is household challenges. These are things that may not have directly impacted the child at the time of occurrence. Household challenges are things that the child may have witnessed during their formative years. The first type of challenge that the CDC has outlined is a parent being treated violently. This can include physical violence, threats, and the utilization of weapons. Typically, the CDC refers to this as a mother being treated violently by the father, stepfather, or boyfriend. While this is not always the case, during the creation of the ACE study, this was the most common type of violence that a child may witness within a home.

Another household challenge that a child may witness is substance abuse within the home. This can be any household member that has a problem with alcohol or drugs. This person may be an alcoholic or addict. Seeing any type of substance abuse within the home is defined as an ACE for every child living in the home. Seeing mental illness in

the home is also categorized as an ACE. Seeing an household member that is depressed, mentally ill, or suffers from any mental disorder can be harmful for a child. Seeing a in-house member attempt or complete suicide will cause trauma and stress within a child and therefore is an ACE.

A commonly overlooked adverse childhood experience within the household challenges section is parental separation or divorce. The rates that children are going through this are rising, however that does not negate the traumatic effects that it may have. A child that experiences that separation between parents will have undue stress because of it. This includes children that continue to have contact with both parents. The final household challenge that may cause an ACE is an incarcerated household member. This causes trauma as the child essentially loses that member of the family for an extended amount of time which can cause a lot of stress within the child.

The final category of Adverse Childhood Experiences, as defined by the CDC, is neglect. Broken down into two sections, neglect can be defined as either emotional or physical. Emotional neglect is when a childhood feels unimportant, not loved, and far from emotional connection with their family. They can not lean on their family as a source of support or emotional strength leading to an emotional neglect ACE.

The second is physical neglect. This can be a lack of care, protection, food, or other basic necessities. If a guardian is under the influence and is unable to care for a child, it is considered physical neglect. If the child did not have proper nutrition or

doctor's care, it is physical neglect. Anything that harms or is less than what is adequate to physically care for a child's needs is defined by the CDC as physical neglect.

Each of these categories has a range in the number of children that may endure them. In a study published in 2009, conducted on a group of 15,357 adults in San Diego, California, they were able to break down the percentage of people who experienced each grouping (Dube et al., 2009). While this varies from state to state, and even between cities, it is a valuable indication of what may be the most common experience ACE for a child living in the United States. Below is a chart breaking down the findings by the subcategories of ACES: emotional abuse, physical abuse, sexual abuse, substance abuse, mental illness, seeing violence, incarceration, and separation. This study's scoring ran on a scale on 0-8 as they did not account for physical and emotion neglect. Each category also lists the questions they used to ask the adults for further clarity.

Table 1

Definition and Baseline Prevalence of Categories of Adverse Childhood Experiences

Adverse Childhood Experiences (ACEs)	Women, % (*n* = 8293)	Men, % (*n* = 7064)	Total, % (*n* = 15,357)
Emotional abuse	12.8	7.4	10.3
Did a parent or other adult in the household …			
1) Often or very often swear at you, insult you, or put you down?			
2) Sometimes, often, or very often act in a way that made you that you might be physically hurt?			
Physical abuse	26.7	29.7	28.0
Did a parent or other adult in the household …			
1) Often or very often push, grab, slap, or throw something at you?			
2) Ever hit you so hard that you had marks or were injured?			
Sexual abuse	24.3	16.0	20.5
Did an adult or person at least 5 years older ever …			
1) Touch or fondle you in a sexual way?			
2) Have you touch their body in a sexual way?			
3) Attempt oral, anal, or vaginal intercourse with you?			
4) Actually have oral, anal, or vaginal intercourse with you?			
Substance abuse in household	29.2	23.6	26.7
1) Live with anyone who was a problem drinker or alcoholic?			
2) Live with anyone who used street drugs?			
Mental illness in household	22.8	14.4	19.0
1) Was a household member depressed or mentally ill?			

2) Did a household member attempt suicide?			
Mother treated violently	13.5	11.5	12.6
Was your mother or stepmother …			
1) Sometimes, often, or very often pushed, grabbed, slapped, or had something thrown at her?			
2) Sometimes, often, or very often kicked, bitten, hit with a fist, or hit with something hard?			
3) Ever repeatedly hit over at least a few minutes?			
4) Ever threatened with or hurt by a knife or gun?			
Incarcerated household member	5.0	3.9	4.5
1) Did a household member go to prison?			
Parental separation or divorce	23.8	21.6	22.8
1) Were your parents ever separated or divorced?			
ACE Score			
0	34.8	38.3	36.4
1	24.7	28.0	26.2
2	25.8	24.6	25.2
≥3	14.7	9.1	12.1

(Dube et al., 2009)

ACE Scoring

All three categories of adverse childhood experiences can undermine the security, bonding, or physical wellbeing of a child. Any neglect, household challenge, or abuse will cause the child to have stress and trauma relating to the incident. While these events are often repeating occurrences within a child's life, they do not need to be repetitive to be considered an ACE. Any event, even if it only occurs once in a child's life is an adverse experience. This is included in how ACE scoring works.

Adverse childhood experiences are typically scored on a scale of 1-10. Each subcategory that has happened to a child is considered one point. For example, any emotional abuse is one point. Any substance abuse that is witnessed is one point. Regardless of how often the event may have happened during the first 18 years of a child's life, it is counted as one point. This allows for ease in testing and defining the effects of ACEs. The test has questions regarding each of the types of adverse experiences and each yes is counted as one point. The higher the score, the more types of adverse experiences a child went through.

Typically, when examining ACE scores, scores are broken down into five groups. There are groups for children that experienced zero, one, two or three ACE events. The final group is typically defined as four or more ACE categories (CDC, 2015). This is how the CDC and Kasier ACE study was broken down and that same trend follows in many

other studies about ACE's. The group that has four or more ACEs typically have linked subgroups and repeated offenses.

There is evidence that indicates there is a stronger prevalence of higher ACE scores based on income and race. These studies have shown that while adverse childhood experiences are common across all race or ethnicity groups there is a higher rate among Black children (Bethell et al., 2017). While there may be some connection between black children being exposed to poverty, and therefore a higher risk of ACEs, there is still the data that indicates that black children account for 17.4% of all children in the United States with ACEs. The following chart displays the percentage of children that have experienced an adverse childhood experience. It is broken down by race/ethnicity, with the NH meaning non-hispanic.

Table 2

Prevalence of ACEs by Race/Ethnicity

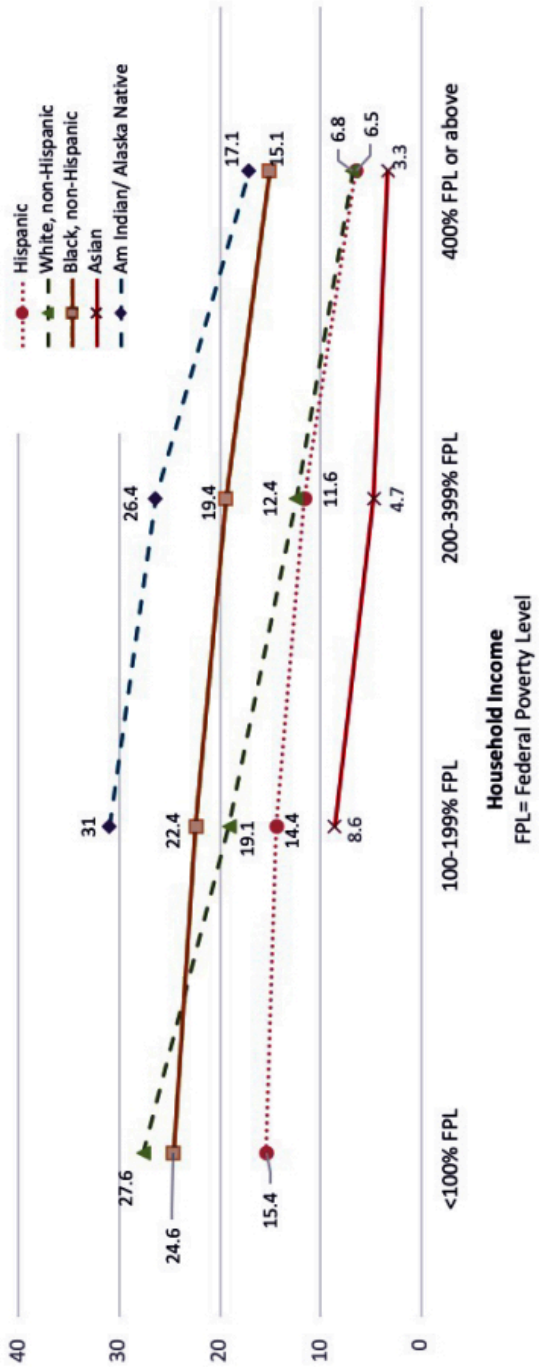
	All Children	White, NH*	Hispanic	Black, NH*	Asian, NH*	Other, NH*
% of all US children		51.9%	24.5%	12.7%	4.5%	6.3%
% 1+ ACEs	46.3%	40.9%	51.4%	63.7%	25%	51.5%
% 2+ ACEs	21.7%	19.2%	21.9%	33.8%	6.4%	28.3%
& Break -down of children with 1+ ACEs		46%	27%	17.4%	2.4%	7.1%

(Bethell et al., 2017)

Another prevalence factor to take into account is poverty. Poverty has been linked to higher ACE scores in children. The farther that a child gets from the poverty line, the average ACE score drops (NSCH, 2020). This is important to take into account with race or ethnicity as they are often linked together and the sets of data are more helpful when examined together. This following chart from the NSCH Data Brief June 2020, displays the dropping of ACE scores with the increase in distance to the poverty line.

Chart 1

(NSCH, 2020)



There are some negative aspects to consider about how the ACE scoring is preformed relating to how the total is summed. The test only speaks about negative experiences that a child experienced within their home. The test does not include trauma that may have happened outside the home, including in religious groups, schools, or groups the child may be apart of. There was only recently a correlating score for any positive aspects of a child's life. This is referred to as a positive childhood experience or PCEs. These positive experiences can help build resistance for a child against the stress of negative experiences. Positive experiences can also protect or negate the effects of ACEs in later life. Positive experiences could be having a teacher at school that provides emotional support, instead of the parents, or a grandparent that provides for the physical needs of a child when a parent is unable to care for them. These positive experiences should be taken into account alongside the negative experiences as they play an almost beneficial role in negating the adverse experiences that a child has endured.

Chapter II: Known Risks and Consequences

Any event that happens during childhood that causes stress will have negative consequences on the physical, emotional, and mental health for the child in their adult life. Some consequences of adverse childhood experiences have been well documented and researched. Hearing the phrase ‘vicious cycle’ can be used to describe some of the possible effects. The first known consequence that can occur from a child experiencing ACEs is repeating the same actions that caused that ACE in their childhood. For instance, if a child sees a parent having substance abuse problems, they are more likely to follow that chain of behavior in their adult life. Similar to how pre-birth challenges are something that happens to the parent and it is passed on to the child. This repetition of behavior can then impact their children and leading them to have ACEs and so on. This is the generational cycle that is involved when there are ACEs present for a child. This chapter is broken down into age brackets and their associated risks and consequences, starting with pre-birth to adult.

Pre-Birth Risks

Predicting what child may experience one or multiple adverse childhood experiences may seem to be an impossible challenge. While there is a certain element that researchers may never fully understand, and therefore limits the ability to accurately be able to tell what children are at risk, there are some known associations. In a study conducted for the Official Journal of the American Academy of Pediatrics called the Pre-birth Household Challenges, there was a link found between certain pre-birth challenges and the accumulation of ACEs that a child may experience (Rittman et al., 2020).

This study observed a number of pre-birth household challenges that could affect if a child had any ACEs during their life. The study observed household challenges such as financial struggles, a parent being in jail, substance abuse, divorce, and being treated for mental illness. All of these would be considered adverse childhood experiences if a child witnessed them during their formative years. However, when examining the adults that experience these events, the researchers were able to gauge what the possible scores of their children would be. If the event was occurring before birth, such as substance abuse, and it continued on after the child was born, then it would be consider an ACE for the child.

The Pre-birth Household Challenges Study collected data for one year before a child's birth. They recorded the number of household challenges during this time and then returned after three years to gather the ACE score of the child. The study found:

> On average, reporting 4+ pre-birth household challenges was associated with an ACEs score 4.1 times that of those reporting 0 challenges. Homelessness was associated with the greatest increase in ACEs score (relative rate ratio = 3.0) (Rittman et al., 2020).

These findings show that research is starting to make associations between the pre-birth and post-birth connections for a child that may experience an ACE. This connection demonstrates that household challenges that happen pre-birth can follow a child after birth.

Childhood Risks

The different types of adverse childhood experiences can all have a different effect on a child while they are happening. The easier ones to see within a child are the physical affects of abuse and neglect. Perhaps the child has injuries or bruises. The neglect can be exhibited by malnutrition or dirty clothing. Both of these are physical signs of an ACE happening within the home and can be seen by bystanders.

Mental Childhood Risks

The mental affects of ACEs for a child, can start showing in childhood. A child that has not experienced love and care within the home, may not know how to show that at school or with peers. The relationship building that many children learn at home may not be taught to a child that is surrounded by emotionally or physically absent parents. While there is evidence that peer groups and other children are essential to emotional learning during childhood, there is still the socialization that a child first receives from the parent. Even from birth, if a parent is absent or has a substance abuse problem that prevents them from being emotionally present, the child may not receive the socialization and emotional learning that they typically would.

Physical Childhood Risks

Other effects that can start showing during childhood and teenage years are repeat behaviors that they learned from their parents or guardians within the home. Revisiting the introduction to this chapter, there is a vicious cycle that perpetuates within homes that produce adverse childhood experiences. A child or teenager may start having substance abuse issues because they may have seen their parent using drugs or alcohol. There is also a risk of increased risk-taking behaviors. This can include: unprotected sexual activity, tobacco use, illegal substance abuse, trespassing, vandalism, fighting, unhealthy

dietary behaviors, inadequate physical activity, and truancy. This is not a comprehensive list but provides an indication idea of what the signs are of a child that is engaging in risky behavior.

These behaviors are generally learned behavior. The behaviors may have been taught by the parents or people living within the childhood home. Children often copy what they see adults around them doing. This is the same idea. The child is copying what they saw throughout their childhood and are now risking their health and safety because they never learned, or learned the incorrect, way to care for themselves. The decision making process for a child or teenager is never simple and even those who grow up without any ACEs may participate in some risky behaviors. However, the extent at with a child with ACEs participates in risky behavior is different from a teenager who is 'experimenting'. Teenage interest in thrill-seeking activites typically peaks at 15-16 years old and then starts to trail off (Risky Behavior in Teenagers, n.d.).

Engaging in these risky behaviors can be dangerous for the mental, physical, and developmental health of an adolescent. The physical effects of risky behavior can include any unintentional or intentional injuries that result from the behaviors. It can also include unwanted pregnancies or sexually transmitted diseases. The unhealthy eating habits can include binge eating, anorexia nervosa, and malnutrition, all of which can cause physical harm. The utilization of illegal substances such as alcohol, drugs, and tobacco can have immediate physical effects on the adolescent. There is a substantially higher risk of a drug overdose and alcohol poisoning for adolescents that engage and participate in risky

behaviors such as binge drinking. All of the risking behaviors that a teenager may participate in after experiencing ACEs, can have immediate physical effects. The danger does not start and end in childhood.

Developmental Childhood Risks

The developmental effects of ACEs for teenagers is not as studied as the physical effects. Research indicates that drinking and drug use during adolescence can have dramatic affects on the brain and can impair development, however the extent is not well known. The Smoke Free program by the US government mentions that e-cigarettes are a common teenage nicotine device (Know the Risks Smoke-free Teen, n.d.). The nicotine in these e-cigarette devices can have the same effect as nicotine elsewhere and can harm brain development (Know the Risks Smoke-free Teen, n.d.). Using drugs and tobacco during adolescence can have also potential effects on lung growth (Tobacco Use among Children and Teens, n.d.). All of these risk taking behaviors can have negative affects on the physical and mental development of a child or teenager. These developmental issues can affect the health of these children as they grow into adulthood.

Adverse childhood experiences can have a range of effects for a child before they even graduate high school. Often, the research about ACEs is focused on the effects during childhood or later in life. However, there is a large margin of time that can be affected by ACEs and then can cause even more negative effects in conjunction with the ACEs in later life. Acknowledging the effects that ACEs can have on a teenager is

important as the teenage years can be the difference between intervention and prevention of later effects or an ACE having prominent negative effects in adulthood.

Adulthood Risks

I have chosen to break down already know adult consequences into three categories. These categories are physical, mental, and developmental. These are three categories of potential harm later in life for a child with ACEs that have been previously researched. Each of these categories have numerous possible outcomes, such as diseases or disorders, or problems such as trauma responses and trouble connecting. However, these categories are vastly intertwined as one may affect another and they are often found together in the same individual.

Mental Adulthood Risks

Mental adulthood risks for children that experienced adverse childhood experiences can include changes to brain structure and function along with possible mental illnesses (Anda et al., 2006). This begs the question about the two types of mental risks and illness that a person may face: mental illnesses such as anxiety, depression, and PTSD can cause changes in brain structure and chemical levels within the brain. In a

study conducted by the Centers for Disease Control and Prevention (CDC), they found that individuals that had experienced adverse childhood experiences had a higher rate of exposure to stress during their childhood which resulted in impairment in multiple brain structures and functions (Anda et al., 2006). The main chemicals within the brain, grouped together into the monoamine neurotransmitter systems, are norepinephrine, dopamine and serotonin. In humans, when these chemicals are unbalanced there is a hypothesis that it can cause a group of neuropsychiatric disorders (Anda et al., 2006). This can include alcoholism, substance abuse, and aggressive/violent behaviors. Several studies have shown that this imbalance can be due to a childhood experiences (Bellis et al., 1999). The effect that adverse childhood experiences can have on the chemical composition of the brain is great, and this can have a tremendous effect on the respective adults.

Adverse childhood experiences also have a direct impact on the rate of mental illnesses in adults. There are a few theories on why this may occur, including the theory of unbalanced neurotransmitters. Another theory hypothesized that the trauma in childhood leads to a "heightened attention toward treating stimuli, heighten experience of loneliness, as well as social cognitive function and social interactions" (Herzog & Schmahl, 2018). These factors may influence the rate of mental illness in adults. The threat is highest for depression, followed by post-traumatic stress disorder, borderline personality disorder and substance abuse.

Numerous studies have shown that there is a connection between early abuse survivors, such as ACE survivors, and multiple psychiatric disorders (Kessler et al., 1995). These psychiatric disorders can range from: depression, PTSD, borderline personality disorder, dissociative disorders, and substance abuse. Having multiple of these psychiatric disorders is often described as 'comorbidity'. This term however, usually implies that there is different, unique disorders with different symptoms. This is not completely accurate in speaking of comorbidity of mental disorders because there is often overlapping symptoms. This is often seen in patients that have disorders such as anxiety and depression. However, it is important to keep in mind that the main point of the research indicates that there is a connection between psychiatric disorders and adverse childhood experiences.

Developmental Adulthood Risks

Another area that may be affected in adults that experienced childhood trauma is developmental issues. This can be broken down into emotional development and physical development. Currently, there is clear evidence that adverse childhood experiences are associated with longterm effects on the structure and function of the brain. There are multiple studies that have shown that adults that have experienced maltreatment as children, have a reduced volume in their hippocampus (Herzog & Schmahl, 2018). This is an important theory as underdevelopment in the brain can lead to changes in the stress

sensitivity within the adult (Herzog & Schmahl, 2018). This stress sensitivity alteration may be a possible cause of why mental illnesses are higher in adults that have survived childhood trauma.

Developmental issues can also be physical in the case of underdevelopment of bones and muscles. Typically, this is in response to an adverse childhood experience such as physical neglect or a situation where a child is inadequately provided for. The lack of nutrition in early childhood can lead to a decrease in bone density, muscle growth, and overall physical health (Widom et al., 2012). In a study of completed in 2012, they found there were numerous developmental issues in regard to childhood trauma. Physical abuse showed higher levels of malnutrition, whereas neglect showed poor airflow, oral and vision problems (Widom et al., 2012). Trauma and adverse experiences in childhood can have a direct impact on the physical development of a child. This can lead to many physical health issues in adulthood, along with physical health problems during childhood.

Physical Adulthood Risks

The physical risks of childhood trauma survivors is a complex research topic. Finding exactly one reason for a disease or disorder to appear in an adult is often impossible since there can be so many compounding or unknown causes. However, there is evidence that advise childhood experiences can affect the general stress level of

individuals (Herzog & Schmahl, 2018). Often, this stress level is initially heightened during childhood either during the traumatic experience or generally if the abuse/neglect/ trauma is ongoing (Herzog & Schmahl, 2018). The heightened stress can then continue into adulthood. This higher level of stress can play a role in increasing the likelihood of diseases and disorders in adults.

All types of child abuse are associated with having a physical condition, most commonly obesity (Afifi et al., 2016). Obesity on its own can be a precursor to a number of other health issues, including but not limited to: early death, high blood pressure (hypertension), type 2 diabetes, coronary heart disease, stroke, and osteoarthritis (CDC, 2021). These are all tremendously serious conditions that can have detrimental affects on a person's health. An adult that experienced ACEs are then at risk for the harmful effects that obesity can have on the body.

Abuse in childhood has been associated with higher rates of back problems, arthritis, hypertension, chronic bronchitis, cancer, stroke, and bowel disease (Afifi et al., 2016). These disorders were found to be higher in adults after ACEs even after smoking, obesity, and sociodemographic conditions were eliminated (Afifi et al., 2016). After further adjusting for co-morbid conditions the rates of back problems, migraine headaches, and bowel disease were still significantly higher than those that had not expressed childhood trauma. This data was found from a study of 23,395 Canadians from the 2012 Canadian Community Health Survey (Afifi et al., 2016). This study was

conducted as a survey so it also brings up the idea that there may be a decrease in self-perceived health in adults that have experienced ACEs.

In a study that matched children with documented cases of physical/sexual abuse and neglect with non-maltreated children and then interviewed both groups 30 years later, the findings again showed long-term health risks (Widom et al., 2012). The study found that after adjusting for age, gender, and race, the children that experienced ACEs were more likely to have health problems in their adult lives. The health problems that were documented were: poor airflow, vision problems, malnutrition, oral and vision health. These were also found in conjunction with irregular hemoglobin levels and low albumin levels. The study also coincided with previous studies when they found higher levels of diabetes and lung disease. The childhood abuse and neglect that these adults endured affected their long-term health, even after adjusting for other factors. (Widom et al., 2012)

Previously, many studies could only find that ACEs were associated with certain adulthood outcomes such as pain, diabetes, heart disease, and obesity, among others (Widom et al., 2012). These studies commonly relied upon retrospective self-reporting of the adults participating in the study. This can cause problems such as memory loss, reconstruction of memories, and inconsistencies. These factors led to many studies only being able to drawn associations between adverse childhood experiences and outcomes in adulthood. The 30 year study however, was the first prospective study that was able to take documented cases of childhood trauma and match them to medical examinations in

adulthood. This allowed for no potential problems with retrospective reports and allowed for the study to examine health in middle adulthood instead of the common adolescence and young adulthood of previous studies. The tests were also done in measurable techniques which made it possible to draw from data that is comparable and measurable instead of more self-reporting. This study allows for a more in-depth examination into the causations and correlations that ACEs can have on adulthood physical health. (Widom et al., 2012)

Chapter III: Autoimmune Disease

Autoimmune diseases are the product of immune system malfunctions where the immune system mistakenly attacks otherwise healthy organs, tissues, and cells or it may cause abnormally low immune activity (Dube et al., 2009). These mistaken attacks can affect any component of the body and can impair normal bodily function along with being possibly life-threatening. There are currently 70-80 known autoimmune diseases that affect approximately 3%-8% of the United States population, about 14.7 to 23.5 million people (Dube et al., 2009). While some are well documented, including multiple sclerosis, lupus, type I diabetes, and rheumatoid arthritis, there are a long list of other less common autoimmune diseases. These can be rare and often tremendously difficult to diagnose. Patients often suffer for years before being diagnosed and receiving the proper treatment. Almost all of these autoimmune disorders have no cure and awfully modest knowledge about what may be the cause. The rates of autoimmune diseases are increasing among the population , and with no cure and little knowledge about causes, these diseases are becoming an epidemic (Dube et al., 2009).

Living with an Autoimmune Disease (symptoms and severity)

When a person develops an autoimmune disease, it can often take over a large part of their life. Medical needs often become first priority and figuring out how to live with a new diagnosis can often be mentally and emotionally taxing, not to forget the physical symptoms that develop due to the disease. The physical symptoms can vary widely based on the diagnosis. Each autoimmune disease has a variety of different symptoms as the diseases can affect any part of the body. Commonly, the early symptoms of many autoimmune diseases can present in an extremely similar way and can include: fatigue, achy muscles, swelling, fever, hair loss, rashes, and numbness (Stacy Sampson, 2019). Going over a few of the most common diagnosed autoimmune diseases will give a good indicator of the generality of symptoms.

Multiple Sclerosis (MS)

Multiple sclerosis (MS) is a debilitating autoimmune disease that attacks the brain and spinal cord, also known as the central nervous system (Love, 2006). This disease specifically attacks the myelin, or the protective sheath, that covers the nerve fibers. This

myelin can be compared to the insulation coating that surrounds wires. When this is damaged, much like the insulation coating on wires, the signals are not able to properly function or be transmitted. This can then cause communication problems between the brain and the rest of the body. Exposing the nerve, by discarding the myelin, can cause permanent and irreversible deterioration of the nerves. This is what makes MS an autoimmune disease as the immune system views the myelin as harmful, and therefore attacks it similar to how it should attack harmful bacteria.

Symptoms of MS include: numbness or weakness in limbs, tremors, loss of vision, slurred speech, fatigue and dizziness (Love, 2006). MS can present differently in each patient. Each patient may show some of the symptoms listed above, while others may show even more symptoms. Being able to discern what symptoms are a result of MS or other common co-morbid diseases is often challenging. There is no complete and accurate list of symptoms for autoimmune diseases (Love, 2006).

Multiple sclerosis is a progressive disease. The disease course is often relapsing-remitting disease which means that there are periods where new symptoms, often called relapses, develop over days or weeks. The symptoms are often worse during these periods and then improve either partially or return to baseline for remission periods that can last days, months, or years. Often, the trigger for a relapse is unknown. As the disease progresses, often the relapse periods last longer and the remissions last shorter periods of time. Over the course of the disease, there is also a steady progression of symptoms. This causes relapses and remissions to have more severe symptoms. Multiple sclerosis has a

variety of symptoms and courses. While there is a thread of common symptoms, the exact course of the disease and symptoms is unknown. The cause of MS is unknown (Love, 2006).

Lupus

Lupus is another commonly known autoimmune disease. There are four main types, but the most prevalent is systemic lupus erythematous (SLE). This is what lupus is typically referring to when not specified. Similar to how multiple sclerosis is a disease that attacks the myelin on the nerves, lupus attacks organs and tissues within the body. A common part of lupus is the serve inflammation within the body. This inflammation can impact any part of the body including: joints, kidneys, skin, heart, lungs and brain. Just like other autoimmune diseases, lupus is often hard to diagnose because of the unclear symptoms. Often symptoms can mimic other ailments and each person with lupus displays different symptoms. These two factors often makes diagnosing the disease difficult and in-turn, research about the possible causes. (Maidhof & Hilas, 2012)

Each case of lupus is different in both the progression and symptoms that may develop. Unlike multiple sclerosis, lupus does not have a common trajectory of disease progress. Symptoms may come on rapidly or slowly, can be mild or severe. There is a common factor between the two diseases where symptoms can appear in episodes. MS has relapses and lupus has episodes or flares. This is where, similar to relapses,

symptoms of the disease get worse for a period of time and then improve or completely disappear for another period of time. Symptoms during these flares can be: fatigue, fever, joint pain, rash, skin lesions, chest pain, and deoxygenated fingers during stressful or cold periods. All of these, plus more, are possible for each patient with lupus with some only appearing for one flare, causing lupus to raise more questions than it answers. (Maidhof & Hilas, 2012)

There is often a complex combination of symptoms that can make it challenging to diagnose autoimmune disorders. Often, the diagnoses come later in life and after years of suffering from the patient. It is not commonly the first diagnosis, and with symptoms that can be explained by other diseases, it is not commonly the second or third choice either. However, with rising numbers of autoimmune diseases in developed countries, the need to understand the cause and signs of these diseases are critical. With more knowledge about what autoimmune diseases can present as, such as common symptoms and disease progression paths, more patients can be helped. Conversely, with an increase in knowledge about autoimmune diseases, there may be an increase in the knowledge about the possible causations. Knowing more about the people who suffer from an autoimmune disease will increase the ability for research to be conducted on the causations and correlations for autoimmune diseases.

Possible Causations of Autoimmune Disease

There is no certain cause for autoimmune diseases, but there is some debate on some possible factors and associations. There is some evidence that multiple sclerosis is present in family members. There is not currently evidence that people with MS will have children will MS, but instead that their children may be more prone to developing a type of autoimmune disorder (Stacy Sampson, 2019). First degree relatives of someone with lupus also appear to be more likely to develop SLE, or lupus, then the rest of the population (Maidhof & Hilas, 2012).

This concept is called familial autoimmune disease. This is where one autoimmune disease tends to affect more than one family member, even seeming to jump generation to generation. Another less studied topic, but with more supporting evidence is 'familial autoimmunity'. The idea of familial autoimmunity is that if there is a history of a family member having one autoimmune disease, the other close relatives will have a higher rate of suffering from an autoimmune disease. This is not familial autoimmune disease where members of a family suffer from the same autoimmune disease but instead a higher rate of aggregation of a diverse range of autoimmune diseases. This connection has been found in analysis of previous studies of autoimmune patients and their family medical history, which stresses the need for continued study of autoimmune diseases (Cárdenas-Roldán et al., 2013). In an analysis of 44 studies, all studies showed familial autoimmunity was present (Cárdenas-Roldán et al., 2013). The exact path that

autoimmune diseases follow in a family line is undetermined, such as if it is maternal or paternal, however there is evidence that autoimmune diseases aggregated within families. (Cárdenas-Roldán et al., 2013)

A large portion of autoimmune diseases are found more prevalently in women (Quintero et al., 2012). The reason for this female dominance of autoimmune diseases has not been fully explained. There are some theories regarding the difference in hormones that may cause a change in the rate of women that develop autoimmune diseases (Quintero et al., 2012). This may lead to an increased rate of autoimmune diagnosis during pregnancy and puberty, however the research on if this may be due to other factors has been not be conclusive and therefore remains as only a theory. There is also current research being conducted on if the X chromosome has any effect on the rate of autoimmune diseases, but no conclusive evidence has been seen.

As autoimmune disease typically displays itself or develops between the ages of 18 to 55, which is the reason behind the theory that the changing hormone levels in women may play a role in the onset of symptoms (Amador-Patarroyo et al., 2011). While each autoimmune disease has a different onset age, they typically appear in early to middle adulthood (Amador-Patarroyo et al., 2011). Children may be diagnosed with an autoimmune disease, however this has not been proven to be universally worse for the patient. For diseases such as SLE and type 1 diabetes, there is a worse onset of symptoms and typically when children are diagnosed it can mean the worst progression of symptoms (Amador-Patarroyo et al., 2011). However, for diseases such as rheumatoid

arthritis and MS, there is no conclusive evidence that indicates the age of diagnoses worsens symptoms.

There is also some emerging evidence that autoimmune diseases, such as lupus, are more prevalent in African Americans, Hispanics, and Asian Americans (Maidhof & Hilas, 2012). This prevalence has been shown through a variety of studies. One study that examined the medical records of 52 million individuals and found that autoimmune disease rates were significantly higher for African Americans than for Caucasians (Roberts & Erdei, 2020). This follows for Native Americans and multiracial rates as well. While there is no known cause for why this is true, there is an association between different minorities and rates of autoimmune diseases. There was a regional variation that was noted within this study.

Another theory that emerged in 2015 was the “hygiene hypothesis," which observed the chemical exposure rate of present day Western countries (Stiemsma et al., 2015). The hygiene hypothesis proposed that the increase of immune dysregulation in developed countries is due to the increased efforts to eliminate microbes from early childhood. Due to an increase in vaccinations, cleaning products, and medications, there is a decrease in the amount of micro-organisms that children are being exposed to in early life. The hygiene hypothesis seeks to understand the connection between lower bacterial rates in developed countries and higher level of immune dysregulation. There is evidence that there is a connection between the human immune development and the commensal microbial organisms that co-evolve. While the hypothesis speaks about a number of

different illness, the main idea is that increased manipulation and disposal of microbial organisms may be a reason for the increased rate of autoimmune disease. (Stiemsma et al., 2015)

The most common theory of what triggers an autoimmune disease is that there is a number of genes throughout the body that makes people more prone to developing an autoimmune disorder. These genes cluster are then triggered by something, it is unknown if this is bacteria or possibly drugs. At least 50% of all autoimmune disorders have been attributed to an unknown trigger (Stojanovich & Marisavljevich, 2008). The drugs or microorganisms may confuse the immune system causing it to misfire and then attack parts of the body. This also may be why, even in families that have a member with an autoimmune disorder, it is not passed on to every child. The theory revolves around both of these things happening, first having the genes and then the new substance being introduced to trigger the autoimmune response. (Autoimmune Disorders, n.d.)

This theory is a way to explain the unknown etiology of autoimmune disease that has multiple possible factors such as: genetics, environment, hormonal, and immunological. However, recent studies have begin to show that stress may play a considerable component in developing an autoimmune disease. Retrospective studies have found that up to 80% of patients reported uncommon emotional stress right before disease onset (Stojanovich & Marisavljevich, 2008). This study has proven that a majority of patients with autoimmune disorders had experienced a large stress before the diagnosis of any autoimmune disease. This could be because of numerous reasons such as

the stress altering the brain chemistry and therefore weakening the immune system or the stress acting as the trigger for those that already have predisposed autoimmune disease genes as previously thought (Stojanovich & Marisavljevich, 2008).

All of these theories are just possible reasons for someone to be diagnosed with an autoimmune disease. Each one proposes a different trigger and cause of the disease. While we have rates for those who are typically more affected, such as women and multiracial individuals, we do not understand the cause of autoimmune disease and therefore do not know why these individuals are affected at higher rates. Each theory does have the common idea of needing a trigger for disease onset and the question of what this trigger could be is varied. These factors fit into four different categories with the first being genetic, for the gene that causes someone to be more prone to autoimmune disease onset. Environmental, such as microorganisms or drugs. Possibly hormonal triggers during pregnancy or puberty and immunological factors such as stress. Understanding autoimmune disease and the causes behind it are tremendously important in prevention and curing the illness of rising numbers of autoimmune disease cases.

Chapter IV: Connection Between Autoimmune Diseases and ACEs

After reviewing the current research that is available about the causes for autoimmune diseases, there appears to be a clear lack of understanding about how past experiences may affect autoimmune rates. While most research agrees that there is a gene cluster required and a trigger of some sort, most studies do not examine the impact that early life stress can have as a pre-trigger. I propose that adverse childhood experiences may have an effect on the likelihood of autoimmune diseases later in life, generally during adulthood. Adverse childhood experiences can have multiple traumatic effects on the mental, physical, and emotional health of an individual, all of which have been proven to have an affect on the onset of autoimmune diseases. The possible factors including environmental, immunological, and hormonal may all be explained by adverse childhood experiences, along with the trauma and increased stress that corresponds with ACEs.

Previous Research

There is currently substantial research regarding adverse childhood experiences and the possible negative effects. There is research regarding the negative effects during childhood, even going as far as before birth (as mentioned in Chapter I). There is also evidence of how adverse childhood experiences affect adulthood health. These range from increased stress levels, mental health issues, to physical health. These studies include autoimmune disease as one of the physical health conditions found but usually group it along with all other poor health conditions an adult might face. These studies only found associations, such as an adult may have both experienced an ACE and an autoimmune disease, but no conclusive connection has been researched.

A 2019 study examined the relationship between adverse childhood experiences and systemic lupus erythematous (SLE). This study used data from the California Lupus Epidemiology Study (CLUES) which was a sample of adults that suffer from SLE. They found that there is an association between higher ACE scores and higher levels of patient-reported SLE activity (DeQuattro et al., 2020). This activity ranged from depression and health status to disease symptoms. While not providing evidence that adverse childhood experiences can increase the likelihood of developing an autoimmune disorder, it is a promising glance at how ACEs may affect the severity of autoimmune diseases.

A study published in the *Clinical Rheumatology Journal,* examined the connection between ACEs and four adult diseases: systemic lupus erythematous (SLE),

spondyloarthritis (SpA), scleroderma (SSc), and rheumatoid arthritis (RA) (Luiz et al., 2018). They found no association between these four disease and adverse childhood experiences. They used a scoring of 0-9 ACEs, instead of the typical 0-10. With a small study group of 315 and focusing only on rheumatic disease, all of which are not definitively autoimmune diseases, the data is not enough to be sure of the research answer.

There is currently research being completed by the World Health Organization in collaboration with the CDC to build a framework of how adverse childhood experiences are affecting health through the world. This research started in May 2009 aims to advance understanding of the effects of ACEs. Currently, there is no published work on this research. (Anda et al., 2010)

Link between ACE and Autoimmune Diseases

There are currently two published works that have found a connection between adverse childhood experiences and autoimmune diseases. The first study, published in 2009 in *Psychosom Med,* found that childhood traumatic stress or adverse childhood experiences increase the likelihood of having a diagnosed autoimmune disease decades later (Dube et al., 2009). The second work, published in 2019 in *Molecular Neurobiology,* found that adverse childhood experiences are significantly associated with the development of autoimmune diseases in adulthood (Morris et al., 2019). These two studies are integral to understanding the connection between adverse childhood experiences and autoimmune disease. While the research on this topic is slim, understanding what these studies found will be beneficial in conducting more research on this connection.

Cumulative Childhood Stress and Autoimmune Disease in Adults Study (2009)

The first study conducted 2009, used a retrospective study of 15,357 adults to research if childhood traumatic stress increased the risk of developing an autoimmune disease later in life (Dube et al., 2009). While retrospective studies have their weak points and we need to consider that there is some error in retrospective reporting, as a first study

in this connection, it made some remarkably interesting observations. A weakness in retrospective reporting is that adults that experienced childhood trauma tend to underestimate the actual occurrence of the trauma when interviewed in adult. Accounting for this may actually lead to the relationships being stronger as those that may have reported a low or zero score may actually fit the criteria for an ACE. The scoring ran on a scale of 0-8 (Table 1) because this study did not account for physical or emotional neglect as per the CDC's scoring technique of 0-10.

The study did not account for all 70-80 autoimmune diseases but instead focused on about 25. These were grouped into four immunopathology groups of Th1, Th2, Th2 rheumatic and a mix of Th1/Th2 (Dube et al., 2009). These groups refer to the helper cells, Th1 or Th2, that are commonly the aggressors in different autoimmune diseases. Th1 diseases are typically organ-based diseases as this is where Th1 cells are found, such as the brain or stomach (Ishida et al., 1997). Th2 cells are found throughout the body and are involved with systemic autoimmune diseases (Ishida et al., 1997).While these factors of limiting the diseases studied and retrospective questioning does not allow for the study to be completely all encompassing, it is a admirable start.

The results from this study found that the number of hospital visits for the 25 autoimmune diseases, increased with increased ACE scores (Dube et al., 2009). This means that adults with no adverse childhood experiences are less likely to be hospitalized with an autoimmune disease in their life. The statistics that they found were large enough to show a significant difference between adults that had experienced childhood trauma

and those who did not. Compared to an adult that experienced no childhood trauma, a person with an ACE score of ≥2 were at a 70% increased risk of Th1 diseases (Dube et al., 2009). Some examples of Th1 diseases are: multiple sclerosis, type 1 diabetes, Hashimoto's, Crohn's, and Celiac disease (Ishida et al., 1997).

These numbers keep increasing with the different immunopathology groups. A person with an ACE score of ≥2 are at a 80% increased risk for Th2 diseases (Dube et al., 2009). Some examples of Th2 diseases are: lupus, scleroderma, asthma, and ulcerative colitis (Ishida et al., 1997). The final result that they found was that an adult that had experienced two or more adverse childhood experiences were at a 100% increased risk for rheumatic diseases such as rheumatoid arthritis (Dube et al., 2009). Rheumatic diseases are inflammatory diseases that produce tissue damage, and can include any autoimmune disease that attacks the joints, muscles, tendons, ligaments, and bones (Dube et al., 2009) (Nancy Garrick, 2017). These connections between adverse childhood experiences and autoimmune disease development are staggering.

This study's findings found that early life stress has an effect on later life health. The study proposed that perhaps this was due to the inflammatory response that comes with trauma, however, this was not proven within the study (Dube et al., 2009). This would be consistent with previous studies regarding nervous, endocrine, and immune functions are interconnected. Previous studies have shown that chronic stress affects the hormone and chemical makeup within the body and therefore can affect other bodily functions. Previous works have also shown that ACEs can have negative effects on a

person (Chapter II), but have yet to connect the effects of ACEs on autoimmune disorders. This study was the first, within mine and the studies knowledge, to demonstrate the relationship between childhood trauma and autoimmune diseases in adulthood. This is groundbreaking research and provides preliminary evidence of a topic that can shed light on the cause of one of the most mysterious diagnosis in present day.

Adverse Childhood Experiences and Medical Disorders in Adulthood (2019)

The second study to report on this connection was published in 2019, ten years after the initial findings. This study reviewed the medical research that has been published regarding inflammatory responses to adverse childhood experiences and how that may affect onset of adult illnesses. There is plentiful data regarding this response to early life trauma but the connection for how this may affect disease is still small, therefore the study aimed to show how these inflammatory response have an effect on adults.

The study found that there is strong evidence that adverse childhood experiences are associated with the development of adult autoimmune diseases (Morris et al., 2019). This study used evidence surrounding the change in chemical and endocrine imbalance that occurs from chronic stress. Stress and inflammation are what they found to be the cause of these associations. The change in chemical makeup within the brain changes the neuropathological responses that occur and can then possibly play as a cause for

autoimmune disease during adulthood. They hypothesized that mitochondria may play a part in this connection. This mitochondria may change the DNA sequence and in turn their expression. Their expression may be what causes the immune system cells, such as Th1 and Th2, to misfire causing the development of an autoimmune disease. Until there is confirmation of this with more peer-reviewed studies, I consider this still a hypothesis but it is a new way to consider how childhood trauma may affect autoimmune disease onset.

This conclusion is in line with the previous study from 2009. Both found that ACEs increase the risk or affect the development of autoimmune diseases. This study found it through the inflammation that is commonly found with chronic stress, and the first hypothesized the same thing. With both studies finding a positive connection between the two, it is important that this research continues as there appears to be more knowledge to be discovered regarding the connection between ACEs and autoimmune disease.

Future Research

Looking towards the future of medicine, there is always another theory to be researched. There is always going to be unknown relationships and causes of disease, however we are sitting on what appears to be a connection that could explain the cause of one of our most pressing epidemics. Autoimmune disease cases continue to rise within the United States and will continue to rise until research is done to find the cause. With it, we will be able to find therapeutic and medicinal interventions that may slow or even stop disease progression. This could be a life changing connection for the millions of Americans that currently suffer with a mostly unknown disease. Future research can begin to expand on the connections made from these two studies and make progress regarding the association between ACEs and autoimmune diseases. Future research is the key to understanding this relationship and in turn helping the millions of people currently suffering and the people that will start to see disease onset in the coming decades. These two studies are only the beginning of the wealth of knowledge that can be learned from researching the connection between autoimmune disease and adverse childhood experiences.

CONCLUSION

Finding the cause of autoimmune diseases, and concurrently the reason for rising causes, is imperative to finding a cure. This cause may lie in the understanding of effects of adverse childhood experiences. Documenting the known effects of adverse childhood experiences is crucial and comparing it to the known symptoms of autoimmune diseases is key to understanding the connection. Through the studies of 2009 and 2019, this connection has been discovered; adverse childhood experiences affect the onset and disease progression of autoimmune diseases. This is a stepping stone on which future research can begin. Researching what part of the trauma may trigger autoimmune disease onset is of upmost importance in finding a cure. This thesis serves to show the lack of research in this connection and provoke the want for future research. Autoimmune diseases and adverse childhood experiences are not decreasing in rate and the time to act is now. Understanding the connection between the two is a matter of life or death for millions of Americans.

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