The Korea Herald 헤럴드경제 HERALD EDU HERALD ARTDAY Busan Global Village WK HYP HERALD YOUTH PLANET

Jiho Lee
August 10, 2022

Associations Between Adverse Childhood Experiences and Increased Risk of Cancer.

Abstract

Context – The relationship between Adverse Childhood Experiences (ACEs) and increased risk of cancer.

Objective – This study summarizes how epigenetic modifications after exposure to violence as a child lead to increased risks of cancer.

Methods – The research gathered secondary quantitative data from past studies uploaded to the National Library of Medicine (NLM) and the National Center for Biotechnology Information (NCBI).

Results – Continuous exposure to violence as a child leads to increased toxic stress, which can dysfunction the stress response system. After exposure to chronic toxic stress, the stress-response hormone, cortisol, malfunctions the inflammatory response in the body, which increases the risk of tumor cell proliferation, which can turn into cancer. Also, cortisol alters the hypothalamic pituitary adrenal (HPA) axis - the main central stress response, which increases the risk of other adverse health outcomes – infections, illnesses, etc.

Conclusions – The findings suggest that Adverse Childhood Experiences can destroy a person by increasing the risk of lifelong disease – cancer, due to epigenetic modifications. Further study is needed to acknowledge the significance of recognizing the problem of child abuse in our daily lives to save future leaders for a better world.

Introduction

Exposure to violence always has negative impacts on children, but they experience violence in diverse environments such as home, school, neighborhood, or online, in many forms, such as domestic violence, bullying, harassment, maltreatment, or neglect. All of these sum up as “Adverse Childhood Experiences,” also known as ACEs, and they can seriously affect children’s emotional, physical, and psychological development (National Institute of Justice, “Children Exposed to Violence”). Adverse Childhood Experiences include three big types: abuse, neglect, and household dysfunction, and each type consist of specific examples (Fig. 1). The exposure to these experiences increases the risks of life-long consequences, such as sexually transmitted diseases, delayed brain development,

and cancer, which can not only impact the victim but his or her surroundings (Fortson, B. L., Klevens, J., Merrick, M. T., Gilbert, L. K., & Alexander, S. P.). And as children are exposed to constant violence, modifications in their epigenetics occur, which means that there are changes in how genes are expressed and used after exposure to abuse. These epigenetic changes can be inherited to the offspring, which proves why ACEs are life-changing problems, which not only impact the person who has gone through the situation but his or her children, too (Child Welfare Information Gateway). Therefore, this paper will focus on how epigenetic modifications lead to cancer, one of the life-long consequences of adverse childhood experiences.

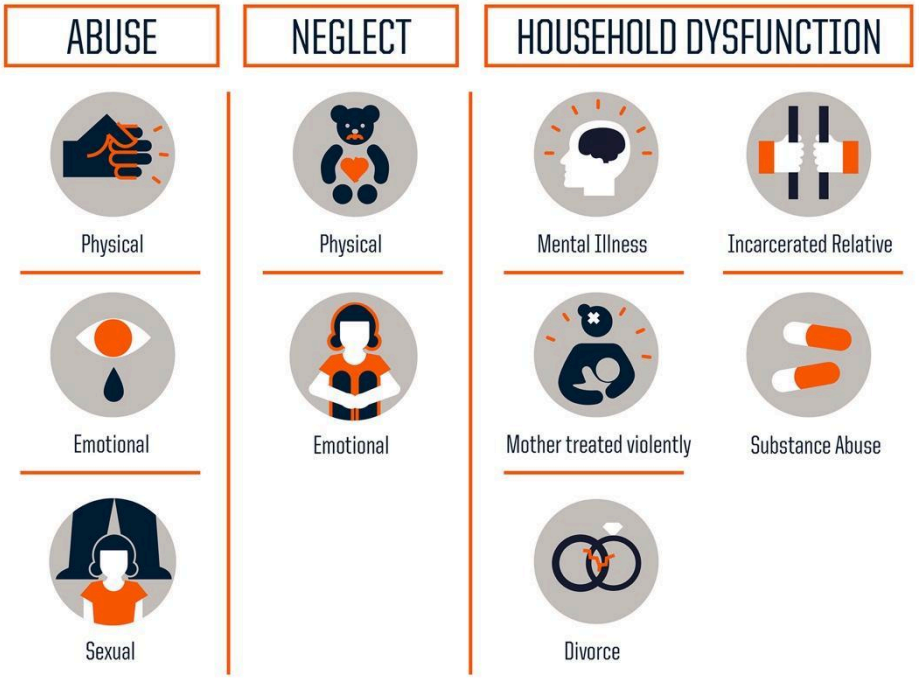

Fig. 1.
Diagram showing three big categories of adverse childhood experiences (ACEs) and specific examples for each type of ACE (Starecheski).

Background

Internationally, it is estimated that around 1 billion children have experienced some form of violence in the past year, and one in 11 people have experienced six or more ACEs out of ten in their childhood ("Violence against Children."). The ten types of ACE are emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, parents divorced or separated, mother victim of domestic violence, living with a substance abuser, a household member is mentally ill or attempted suicide, and household member is incarcerated (Fig. 2).

Type of Adverse Childhood Experience	%	
ACE 1: Emotional abuse	30.5	
ACE 2: Physical abuse	16.3	
ACE 3: Sexual abuse	20.5	
ACE 4: Emotional neglect	26.1	
ACE 5: Physical neglect	6.6	
ACE 6: Parents divorced or separated	32.5	
ACE 7: Mother victim of domestic violence	9.8	
ACE 8: Lived with substance abuser	30.9	
ACE 9: Household member mentally ill or attempted suicide	36.2	
ACE 10: Household member incarcerated	4.9	
Total ACE score: *M* (*SD*)		2.1 (2.2)
Total ACE score: Median		1.0

Note. ACE = adverse childhood experience.

Fig. 2.
Types of Adverse Childhood Experiences and the higher the score, the more serious ACE is. The data is gathered from surveying 5,540 social workers in the United States, and this study found that 24% of the surveyors reported experiencing more than four adverse childhood experiences, which is a high risk of toxic stress (Steen, Jeffrey T. et al.).

There are scores assigned, based on the number of experiences an individual has gone through the ACEs and this is known as the ACE score or ACE summary score, which assesses the seriousness of the risks of the abuses experienced. So, the people who have experienced six of the ACE categories would have an ACE score of 6, and an ACE score of 6 represents that the person is 4,600% more likely to have illnesses in the future, and 5,000% more likely to commit/attempt suicide than those who have not experienced one (Big Think, and Vincent Felitti). According to ACEs Aware, the first organization to screen patients for ACEs, a score of 4 or more is at high risk of toxic stress, meaning that the stress response can be turned off (Fig. 3). This can seriously harm one's body and brain, which will lead to life-long diseases, like cancer.

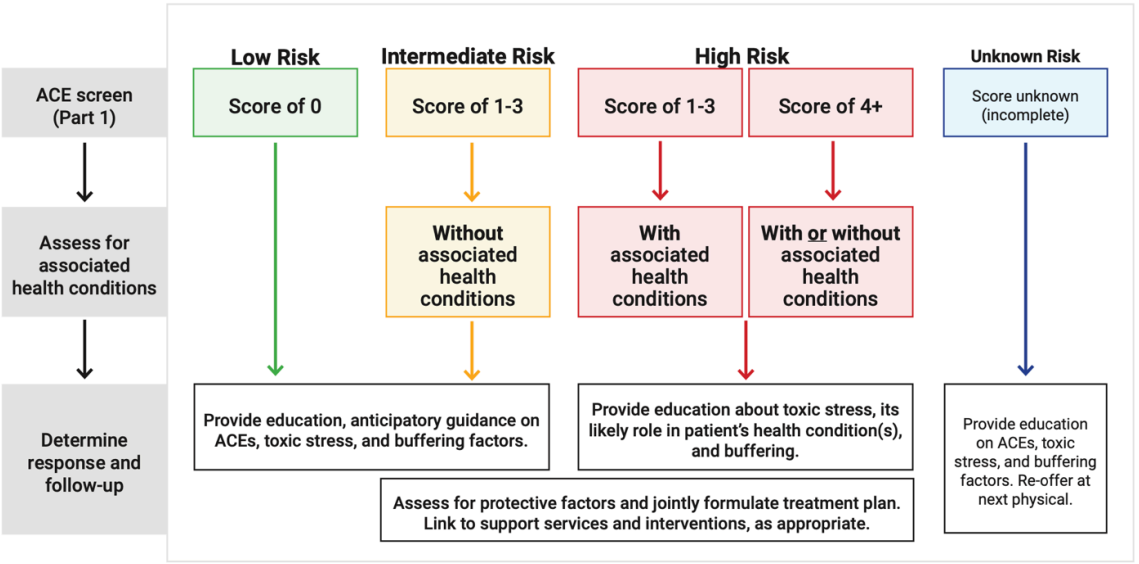

Fig. 3.
The figure describes the level of risks of ACE score: a score of 0 indicates low risk of toxic stress, a score of 1-3 without serious health conditions indicates intermediate risk for toxic stress, and a score of 1-3 with at least one adverse childhood experience related health issue or a score of 4 or more indicates that the patient is at a high risk of toxic stress, which can dysfunction toxic stress responses (Aces Aware).

When the risk of toxic stress reaches its maximum, there is a possibility of malfunction of the stress response, and one of the main stress response hormones in our body is cortisol (*University of Toronto. "Childhood Physical Abuse Linked To Cancer."*). Because cortisol is a stress response hormone, it controls our mood, motivation, and fear, as we are living in this world, and controls the inflammation of cells (Cassoobhoy). Inflammation is the body's response to damaged tissues in our body, which can be caused by types of traumas; normally, the inflammatory and immune responses repair the damaged tissue and cellular proliferation, but if the toxic stress turns chronic, cell mutations and tumor cell proliferation can occur, which will eventually develop cancer in our body due to the growth of tumor cells (Singh, Nitin, et al.). Because of this, dysfunction in cortisol will lead to an increased risk of inflammation, causing a higher chance of cancers spreading in our body.

Methodology

The research was to identify a cause-and-effect relationship between how adverse childhood experiences lead to epigenetic modification and increase the risk of cancer. The information gathered was secondary quantitative data from past research from the National Library of Medicine (NLM) and 21 other studies conducted by the World Health Organization, Centers for Disease Control and Prevention, ACEs Aware, and universities such as the University of Toronto, and the University of Michigan. The data sample that I used was an anonymous survey of 5,540 middle-class workers about the types of ACEs

that they experienced as a child, and this was held by three PhDs in New York. Other data were collected from the National Center for Biotechnology Information (NCBI), one of the most trustworthy sources for scientific studies. To analyze the data collected, I referenced the goals and outcomes stated in each journal and study because it might lead to a false analysis of the data that was held for certain reasons. The reason I held this research by gathering studies from different geneticists and cancer biologists is that they have conducted trustworthy research for people like me (students) to understand and recognize the new ideas that can arise upon the topic, without any charges. However, a limitation was that because of the heterogeneity of the studies and data, it was hard to come up with one exact conclusion, so I used the most recent information if there were different data for the same information, in this paper.

Result

Deoxyribonucleic acid, more commonly known as DNA, is composed of four different nitrogen nucleotides, or bases, of A, C, G, and T (A = adenine, C = cytosine, G = guanine, T = thymine). These bases form sequences that encode genetic information from the parents and pass it to the next generation, and during this process, a technique called “transcription” occurs. Transcription is the process of copying genetic sequences (nucleotides) from DNA to RNA (mRNA) and for transcription to work, several enzymes are needed so that areas of DNA can be transformed (Jiang, Shui, et al.). Firstly, RNA polymerase, which transcribes DNA, binds to the DNA. They bind to the DNA with the help of the promoter region in DNA, which contains a specific sequence that connects with RNA polymerase. Secondly, the transcription factors unwind the DNA and only allow the RNA polymerase to copy one strand of the DNA into mRNA since RNA is a single-stranded molecule. During this process, the nucleotide thymine (T), converts into uracil (U). Lastly, as the RNA polymerase reaches a certain sequence called, the terminator sequence, it releases the mRNA and detaches itself from the DNA (Bailey). At this point, the DNA has been transformed into pre-mRNA, and for this to be fully turned into an mRNA, areas of DNA must change through RNA splicing, During the RNA splicing, the introns, the noncoding area of DNA, which do not encode proteins during the translation process, are spliced out, and the exons, the coding area of DNA, are joined together and converted into mRNAs (“Transcription/translation - Exons and introns”). After the transcription and RNA splicing, mRNA goes through translation, in which the bases are identified into codons. Codon is a combination of three nucleotides of the mRNA sequence that encodes for a specific amino acid in a polypeptide chain(“Codon”).

The created codons help determine the “gene expression” and these processes are complicated but powerful for the body to function efficiently. Therefore, because of the body’s complexity, various regulators control these processes, and one of them is “epigenetic modification”. The term “epigenetic” means “outside the conventional genetics”, which focuses on turning on and off the gene without affecting the DNA sequence (Jiang, Shui et al.). As the definition, “outside the conventional genetics” reveals, epigenetics is affected by the environment you are going through, and the environmental factors change how the genes work (“What Is Epigenetics?”). So, under normal circumstances, in this case, without going through ACEs, the cells in our body will usually

share the same copy of DNA. However, multiple different environmental factors like exposure to violence as a child can lead to epigenetic regulations. This means that changes in the human genome have occurred, and they are usually linked to multiple diseases, such as diabetes, immune disorders, or cancer. These happen because, in the early ages, the brain is malleable, which allows for fast development. Thus, negative impacts during childhood will affect the brain, which will lead to mental problems such as trauma and depression, and later cause epigenetic modification of the cells (Jiang, Shui et al.).

So how does childhood trauma impact the increased risk of cancer? One of the main causes is “toxic stress”. As the background states, stress can be identified into three categories: low risk (good stress), intermediate risk (bearable stress), and high risk (toxic stress). Having some good stress will develop our mental and physical systems, and bearable stress can be a great source of stress under correct interventions, whereas toxic stress can induce long-term change and damage not only our brain but the whole body. A study proved that chronic stress impacts our body in many negative ways, such as increasing the heart rate and blood pressure. When threat signals are recognized due to long-term stress, the central nervous system (CNS) will be activated. The hypothalamus is one of the main CNS in our body that activates the stress response and with the help of neurotransmitters, neuropeptides, like the stress-induced corticotropin-releasing hormone (CRH) will be released (Jiang, Shui, et al.). As CRH is triggered, the type-1 CRF Receptor that is located on the anterior pituitary – located at the base of the brain, is activated and this functions only when the body is involved in stress, addiction, or psychological disorders such as trauma and depression (Slater, Paula G., et al.). Next, the type-1 CRF Receptor emits adrenocorticotropic hormone (ACTH), which mainly works on releasing stress-related hormones: glucocorticoids (cortisol) and mineralocorticoids (aldosterone) (Fig. 4). The stress-related hormones mediate the stress factors that occur in our body: increased heart rate, blood pressure, etc. Cortisol works on controlling the inflammation of the cells, too. Malfunction of cortisol, due to toxic stress, can cause cell mutations and tumor cell proliferation, since the inflammatory response should repair the damaged cellular proliferation under normal conditions, but exposure to ACE and toxic stress can lead to dysfunction of the system that will increase the risk of cancer (Jian, Shui, et al.). Cortisol can also stop the hypothalamic pituitary adrenal (HPA) axis - the central stress response system, which balances the effects of stressors by regulating immune responses and nervous systems, under toxic stress. If the HPA axis is suppressed, the body will not be able to regulate stress and energy levels in our brain, which can cause serious problems in the body (Sheng, Julietta A., et al.). Because in the end, ACEs alter the HPA axis, its outcome will be an increased risk of adverse health outcomes, such as infections, illness, hospitalization, etc., and because of the increased possibilities of malfunction in stress-response hormones – cortisol, under chronic stress, it can cause a higher risk of cancer.

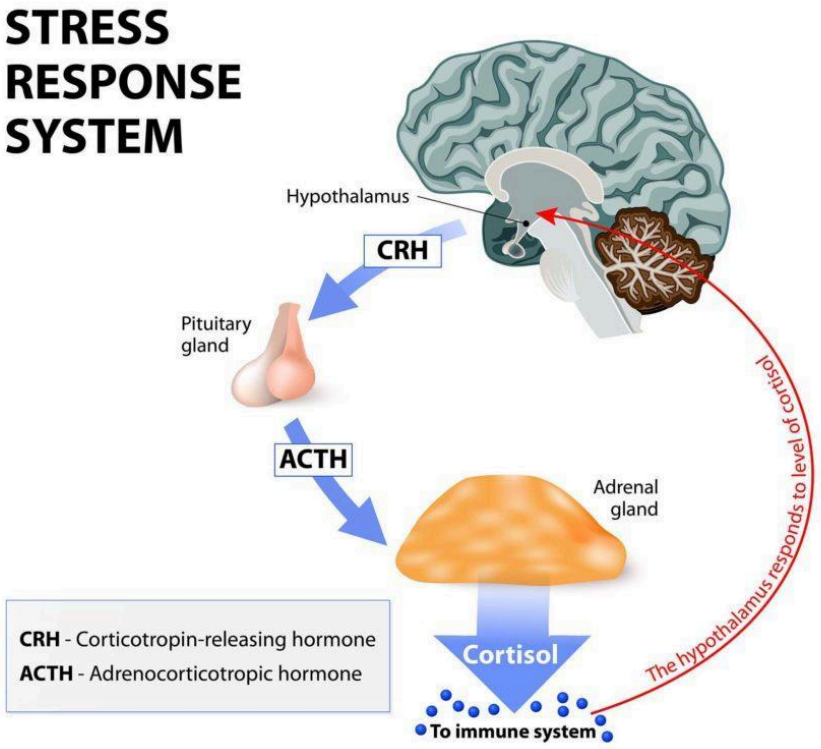

Fig. 4
Diagram of the process of how the stress response system works: Hypothalamus - Stress-Induced Corticotropin-Releasing Hormone (CRH) - Adrenocorticotropic Hormone (ACTH) - Glucocorticoids (cortisol) (Aiello).

Conclusion

Half of the children around the globe experience violence in their daily lives, and these experiences lead to increased risks of cancer due to epigenetic modifications. Exposure to violence as a child builds up stress in the body, and as the stress turns chronic, it affects the stress response system in the body, which causes increased possibilities of cancer due to suppression of the HPA axis and malfunction in cortisol, one of the main stress-response hormones. It is still undiscovered how specific background environments increase the risk of cancer, so the most important thing is to prevent the incidents first. The ideal solution to child abuse is prevention, and some of the effective methods are providing parenting skills with the help of organizations and governmental interventions, and informing the possible ending that might arise as their children are constantly exposed to violence. Despite this fact, the most effective and fundamental solution that is possible is for all the readers of this paper to pay attention to the surroundings, have an interest in child abuse, and have the will to provide a safer environment for our future leaders and a better world. Therefore, additional projects can be held to identify how people think about adverse childhood experiences and acknowledge how exposure to violence as a child can change our future and the world.

Abbreviations

- ACEs – Adverse Childhood Experiences
- NLM – National Library of Medicine
- NCBI – National Center for Biotechnology Information
- HPA – Hypothalamic Pituitary Adrenal
- DNA – Deoxyribonucleic Acid
- RNA – Ribonucleic Acid
- mRNA – Messenger Ribonucleic Acid
- CNS – Central Nervous System
- CRH – Corticotropin-Releasing Hormone
- CRF – Corticotropin-Releasing Factor
- ACTH – Adrenocorticotropic Hormone

Works Cited Page

Aces Aware. “ACE Screening Clinical Workflows, ACEs and Toxic Stress Risk Assessment Algorithm, and ACE-Associated Health Conditions: For Pediatrics and Adults.” Aces Aware, 2020, pp. 1–7, www.acesaware.org/wp-content/uploads/2019/12/ACE-Clinical-Workflows-Algorithms-and-ACE-Associated-Health-Conditions.pdf.

Aiello, Kelly. “Cortisol: What It Is and Natural Ways to Lower It.” HappiHuman by Kelly Aiello Nutrition Coach & Brain Health, Happihuman, 8 Apr. 2020, happihuman.com/blog/cortisol-what-it-is-and-natural-ways-to-lower-it.

American Psychological Association. (2009). Effective strategies to support positive parenting in community health centers: Report of the Working Group on Child Maltreatment Prevention in Community Health Centers: Washington, DC: Author.

Bailey, Regina. "An Introduction to DNA Transcription." ThoughtCo, Dec. 10, 2021, thoughtco.com/dna-transcription-373398.

Big Think, and Vincent Felitti. “How Childhood Trauma Can Make You A Sick Adult | Big Think.” *YouTube*, uploaded by Big Think, 11 Oct. 2015, www.youtube.com/watch?v=y3cCAcGeG8E.

Cassoobhoy, Arefa. “What Is Cortisol?” WebMD, WebMD, 6 Feb. 2017, www.webmd.com/a-to-z-guides/what-is-cortisol.

Centers for Disease Control and Prevention. “Preventing Child Abuse and Neglect.” Centers for Disease Control and Prevention, 2022, pp. 1–2, www.cdc.gov/violenceprevention/pdf/can/CAN-factsheet_2022.pdf.

Child Welfare Information Gateway. (2019). Long-term consequences of child abuse and neglect. Washington, DC: U.S. Department of Health and Human Services, Administration for Children and Families, Children's Bureau

"Codon." *Genome.gov*, 2022, www.genome.gov/genetics-glossary/Codon#:~:text=A%20codon%20is%20a%20DNA,are%20used%20as%20stop%20signals.

"Difference between Exons and Introns - Comparison Chart." *BYJUS*, BYJU'S, 7 Jan. 2019, byjus.com/biology/difference-between-exons-and-introns/.

Fortson, B. L., Klevens, J., Merrick, M. T., Gilbert, L. K., & Alexander, S. P. (2016). Preventing child abuse and neglect: A technical package for policy, norm, and programmatic activities. Atlanta, GA: National Center for Injury Prevention and Control, Centers for Disease Control and Prevention.

Fox Chase Cancer Center, Temple Health. "Chronic Inflammation and Cancer: What's the Connection?" Fox Chase Cancer Center - Philadelphia, PA, Temple University Health System, 14 Nov. 2019, www.foxchase.org/blog/chronic-inflammation-and-cancer-what%E2%80%99s-connection.

Heid, Markham. "How Stress Affects Cancer Risk." MD Anderson Cancer Center, The University of Texas MD Anderson Cancer Center, 13 Nov. 2014, www.mdanderson.org/publications/focused-on-health/how-stress-affects-cancer-risk.h21-1589046.html#:%7E:text=Stress%20hormones%20can%20inhibit%20a,of%20cancerous%20tumors%2C%20he%20adds.

Holman, Dawn M et al. “The Association Between Adverse Childhood Experiences and Risk of Cancer in Adulthood: A Systematic Review of the Literature.” Pediatrics vol. 138,Suppl 1 (2016): S81-S91. doi:10.1542/peds.2015-4268L

Jiang, Shui et al. “Epigenetic Modifications in Stress Response Genes Associated With Childhood Trauma.” Frontiers in psychiatry vol. 10 808. 8 Nov. 2019, doi:10.3389/fpsyt.2019.00808

National Cancer Institute. “NCI Dictionary of Cancer Terms.” National Cancer Institute, National Institutes of Health, www.cancer.gov/publications/dictionaries/cancer-terms/def/methylation. Accessed 12 Aug. 2022.

National Institute of Justice, "Children Exposed to Violence," September 21, 2016, nij.ojp.gov: https://nij.ojp.gov/topics/articles/children-exposed-violence.

Office of the Associate Director for Communication. “Preventing Adverse Childhood Experiences.” Centers for Disease Control and Prevention, 23 Aug. 2021, www.cdc.gov/vitalsigns/aces/index.html.

Pereznieto, Paola, et al. “The Costs and Economic Impact of Violence against Children.” ChildFund Alliance, Overseas Development, Sept. 2014, childfundalliance.org/wp-content/uploads/2014/10/ODI-Policy-Brief.-The-cost-and-economic-impact-of-violence-against-children.pdf.

Rogel Cancer Center, University of Michigan. “Adrenal Tumors and Cancer.” Rogel Cancer Center | University of Michigan, The Regents of the University of Michigan, 1 Nov. 2021, www.rogelcancercenter.org/adrenal-cancer/learn-about-adrenal-cancer.

Sheng, Julietta A., et al. “The Hypothalamic-Pituitary-Adrenal Axis: Development, Programming

Actions of Hormones, and Maternal-Fetal Interactions." *Frontiers in Behavioral Neuroscience*, vol. 14, Jan. 2021, https://doi.org/10.3389/fnbeh.2020.601939.

Singh, Nitin et al. "Inflammation and cancer." Annals of African medicine vol. 18,3 (2019): 121-126. doi:10.4103/aam.aam_56_18

Slater, Paula G., et al. "Corticotropin-Releasing Factor Receptors and Their Interacting Proteins: Functional Consequences." *Molecular Pharmacology*, vol. 90, no. 5, Sept. 2016, pp. 627–32, https://doi.org/10.1124/mol.116.104927.

Starecheski, Laura. "Take The ACE Quiz — And Learn What It Does And Doesn't Mean." Npr, 2 Mar. 2015, www.npr.org/sections/health-shots/2015/03/02/387007941/take-the-ace-quiz-and-learn-what-it-does-and-doesnt-mean.

Steen, Jeffrey T. et al. "Adverse Childhood Experiences Among Licensed Social Workers." Families in Society: The Journal of Contemporary Social Services 102 (2020): 182 - 193.

"Transcription/Translation - Exons and Introns:: CSHL DNA Learning Center." *Cshl.edu*, 2020, dnalc.cshl.edu/view/15549-Transcription-translation-Exons-and-introns.html#:~:text=In%20most%20eukaryotic%20genes%2C%20coding,form%20a%20contiguous%20coding%20sequence..

University of Toronto. "Childhood Physical Abuse Linked To Cancer." ScienceDaily. ScienceDaily, 25 June 2009. <www.sciencedaily.com/releases/2009/06/090625111425.htm>.

"Violence against Children." World Health Organization, 8 June 2020, www.who.int/news-room/fact-sheets/detail/violence-against-children.

Wang, Yun-He et al. "Depression and anxiety in relation to cancer incidence and mortality: a systematic review and meta-analysis of cohort studies." Molecular psychiatry vol. 25,7 (2020): 1487-1499. doi:10.1038/s41380-019-0595-x.\

"What Is Epigenetics?" *Centers for Disease Control and Prevention*, 18 May 2022, www.cdc.gov/genomics/disease/epigenetics.htm.

"What Is Toxic Stress?" Aces Aware, 2018, pp. 1–2, www.acesaware.org/wp-content/uploads/2019/12/2-What-is-Toxic-Stress-English.pdf.

World Health Organization. "Child Maltreatment." World Health Organization, 8 June 2020, www.who.int/news-room/fact-sheets/detail/child-maltreatment.