Chapter

The Relationship of Adulthood Chronic Disease and Adverse Childhood Experiences (ACEs): Implications Regarding Prevention and Promotion in International Health

Jordan Holter, Christine Marchionni and Bankim Bhatt

Abstract

Several studies, including the innovative 1998 ACE Study by CDC-Kaiser Permanente, have assessed the association among adulthood chronic disease and the prevalence of maladaptive, health-harming behaviors including: excessive alcohol use, tobacco use, physical inactivity, psychiatric illness including suicidal ideation or attempts, promiscuous sexual behavior (>50 sex partners), history of STI/STD and severe obesity (obesity (BMI > 35 kg/m^2)), subsequent to an individual's exposure to adverse childhood experiences (ACEs). Individuals that have encountered numerous instances of ACEs are almost twice as likely to die before the age of 75, demonstrating a dose-dependent relationship between the instances of ACEs and an increased morbidity/mortality in regard to chronic disease. This excerpt examines the contribution of ACEs to chronic disease and the consequential maladaptive behavior to said adversity, the consequential physiologic and biomolecular changes explained by the Biological Embedding of Childhood Adversity Model in addition to the implications of recounted ACEs on international health security in regard to concepts like conflict, displacement and food insecurity. The apparent association among adulthood chronic disease and ACEs demand changes that promote preventative processes as a means to address the implications these interconnections have on international health.

Keywords: adverse childhood experiences, biological imbedding, childhood adversity, child abuse, child health, dysfunction, trauma, traumatogenic, inflammation, health-harming behavior, behavioral health, chronic disease, chronic illness, prevention, public health, psychiatry, international health, vulnerability

1. Introduction

Chronic disease as defined by the U.S. National Center for Health Statistics is a disease that is pervasive and persists 3 months or more. About 60% of adults in the United States possess a chronic disease meanwhile about 40% possess two or more

diagnoses indicative of chronic disease [1]. By 2030, it is predicted that the U.S. population, predominantly individuals age 65 years and older, could possess three or more chronic diseases [2]. Non-communicable chronic diseases such as: coronary artery disease, ischemic heart disease, asthma, COPD, chronic bronchitis, emphysema, Alzheimer's disease, stroke, hepatic disease, type 1 diabetes, type 2 diabetes, depression, PTSD and an assortment of cancers, possess significant implications pertaining to international health. Chronic disease is a predominant cause of premature death and disability.

In 2016, direct domestic costs related to the medical management of chronic disease approximated 6% of the GDP, including roughly $3.3 trillion in indirect costs like work loss, worker replacement and diminished economic productivity [3]. Direct costs average approximately $3300 per person and indirect costs average approximately $7901 per person [2]. Examples of the financial implications of chronic disease include $189.6 billion in care expenditures that comprise the management of diabetes and the $185.9 billion that comprise the management of Alzheimer's disease [3]. These totalities pose significant problems to the patient, the relatives of the patient, employers and the economy. The increase in the prevalence of chronic disease certainly will increase direct costs, indirect costs and expenditures in the U.S. healthcare system.

Several studies have attempted to ascertain the predisposition for chronic disease in particular individuals. The innovative and inventive 1998 CDC-Kaiser Permanente Adverse Childhood Experiences (ACE) study validates the interconnection of chronic disease states and health-harming behaviors subsequent to the exposure of adverse childhood experiences. This retrospective study surveyed 13,494 patients with 9508 respondents by use of their health history and a health appraisal questionnaire. The ACE study and successive similar studies acknowledge the importance of potential prevention of adverse childhood experiences because of their contribution to chronic disease through maladaptive adulthood behaviors that perpetuate pathologic conditions. Through early identification of these interconnections that predispose individuals to costly chronic disease, practitioners and medical organizations anticipate having the ability to address and advocate for the appropriate deterrence of adverse childhood experiences that contributes to the development of chronic disease in adulthood.

2. Methodology

Previous studies, such as the prominent Adverse Childhood Experiences (ACE) study by CDC-Kaiser Permanente that considers the correlation among chronic disease in adulthood and adverse childhood experiences, employed substantiated surveys. These substantiated surveys included an assortment of adverse exposures, categorized as abuse, neglect or adversity in the household. Said surveys were devised using pre-existing published surveys like the Behavioral Risk Factor Surveillance System (BRFSS) survey. Accordingly, several analogous studies, including prospective study of one's childhood and retrospective study that recalls one's childhood, arose that included use of similar substantiated surveys. Additionally, multivariable logistic regression models were used to adjust odds ratios (OR) and confidence intervals (CI) that assess for associations among ACEs and adulthood chronic disease.

A website search engine was used to assist in the selection of an assortment of studies. Scholarly sources such as the National Library of Medicine, particularly the National Center for Biotechnology Information including peer-reviewed literature catalogs like PubMed was used. Inclusion criteria included: sample sizes of at least

100 patients, a population of patients at least 18 years of age, the ability to assess for multiple ACEs, the ability to assess prevalence of ACEs among a diverse patient population pertaining to age, gender, race, ethnicity and education and statistical analysis of the correlation among the instances of ACEs and likelihood of chronic disease in adulthood.

3. What is an adverse childhood experience?

Adverse Childhood Experiences (ACEs) are defined as direct or indirect childhood abuse and domestic disruption before the age of 18, denoted by seven categories in the health appraisal questionnaire including: psychological abuse, physical abuse, sexual abuse, substance abuse, domestic violence, psychiatric illness including suicidal ideation or attempt and incarceration. Studies illustrate that individuals that have encountered ACEs are likelier to engage in maladaptive, high-risk, health-harming behaviors that typically commence at the age of adolescence. The maladaptive adulthood behaviors that contribute to chronic disease include: excessive alcohol use, tobacco use, physical inactivity, psychiatric illness including suicidal ideation or attempts, promiscuous sexual behavior (>50 sex partners), history of STI/STD and severe obesity (BMI > 35 kg/m^2), resulting from unhealthy diet.

4. Relationship among ACEs and chronic disease

Throughout the years, several studies, including the influential ACE study, have recognized the relationship among early exposure to ACEs and the prevalence of chronic disease. ACE exposure predisposes individuals to poorer physical and mental health in comparison to individuals that do not encounter ACEs because of a higher likelihood that said individuals partake in high-risk behavior that is detrimental to their health [4]. Fifty six percent of individuals that lack exposure to ACE possessed none of the high-risk behaviors that are linked to chronic disease, meanwhile merely 14% of individuals that encountered 4 or more ACEs possessed none of the high-risk behaviors [5]. An average of 54.5% of individuals who encountered one instance of ACE encountered multiple instances of ACEs throughout their childhood. Repeated exposures to ACEs exacerbate the high-risk, health-harming behaviors that increase the likelihood of an individual developing chronic disease in adulthood. Individuals that encountered 6 or more ACEs are 1.7 times more likely to die before the age of 75 [6]. This affirms a dose-dependent relationship among the number of ACEs encountered and the likelihood that an individual possesses the high-risk behavior that results in a higher morbidity and mortality in regard to their chronic disease (**Figure 1**).

Unfortunately, ACEs are common in the early years of development with the most prevalent being exposure to substance abuse (25.6%) while the least prevalent is exposure to criminal behavior including incarceration (3.4%). Several studies use an odds ratio (OR) in an attempt to assess the association among ACE exposure and consequent maladaptive behaviors that precipitate the development of chronic disease. To illustrate the association among exposure and outcome, recall that an OR greater than 1 means that there are greater odds of an association among exposure and outcome. A modest association for physical inactivity, severe obesity and diabetes (OR less than 2) is present in individuals encountering at least 4 ACEs. A moderate association (OR 2–3) is present for smoking, excessive alcohol use, tobacco use, cardiovascular disease, respiratory disease and cancer in addition to substandard self-reported health. Likewise, excessive alcohol and tobacco users are approximately six-times likelier to have encountered an ACE. A strong association

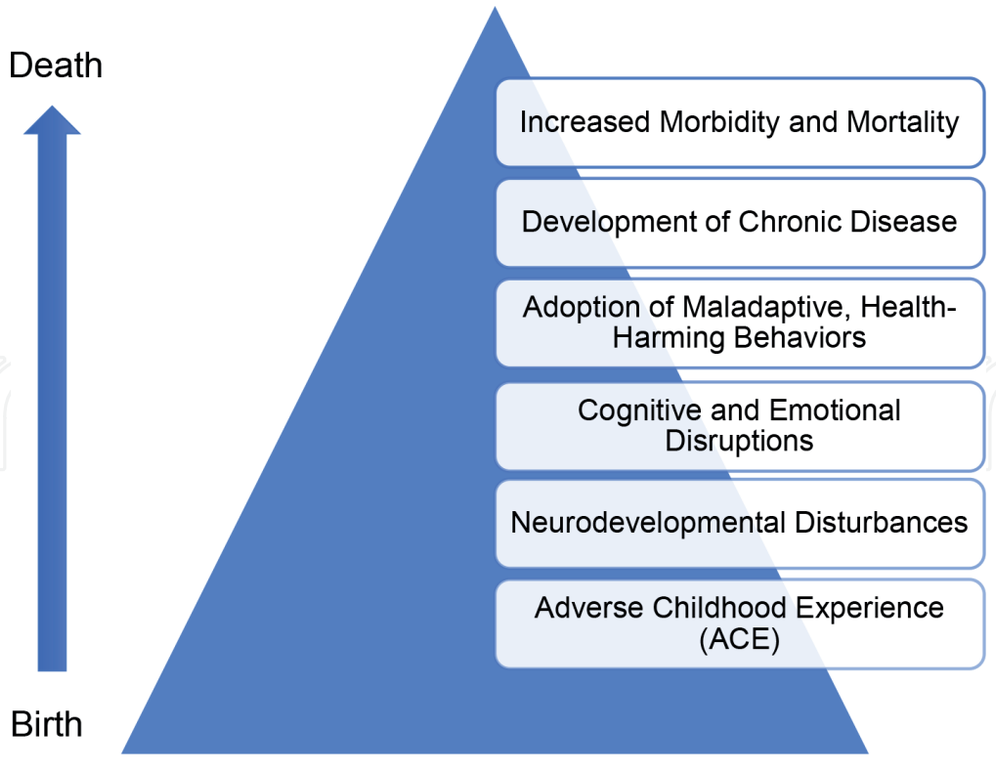

Figure 1.
ACEs effects on health and well-being as adapted from Felitti et al. [5].

(OR 3–6) is present for promiscuous sexual behavior, the presence of an STD/STI and mental illness including depression or PTSD. The strongest association (OR greater than 7) is present for substance abuse and suicidal ideation or attempt secondary to a diagnosis of mental illness like depression or PTSD. Notably, individuals that have a pre-existing diagnosis of PTSD possess twice the odds of coronary artery calcification, contributing to poor cardiovascular health and complications of chronic disease. In general, an OR for maladaptive, high-risk behavior and morbidities increased as ACE scores increased to 4 or more. This affirms that a strong dose-response relationship exists pertaining to the number of ACEs encountered and the likelihood that health-harming behavior contributes to premature death in individuals diagnosed as having a chronic disease [7].

Aside from studies that assess for a direct correlation among instances of ACE and the development of chronic disease, incidences of international health detriments like food insecurity, armed conflict and displacement are higher in populations that admit to one or more ACEs. In the United States, 19.5% of households with children reported food insecurity [7]. In comparison, the Central African Republic comprised of the countries: Burundi, Comoros, Democratic Republic of Congo, Eritrea, Libya, Papua New Guinea, Somalia, South Sudan and Syria, reported food insecurity in 46% of households, secondary to famine [7]. Individuals that encountered 4 or more ACEs were five times more likely to encounter food insecurity in their household versus individuals that denied encountering an ACE [8]. Also, individuals that endorse 4 or more ACEs in addition to depression are associated to an approximate 30-fold increase in food insecurity. This illustrates that ACEs are an important predictor for food insecurity, regardless of the presence or absence of depression. Displacement, a common consequence of armed conflict and violence, is an international concern. Internationally, more than 1 in 10 children are affected by armed conflict. The SABE-Columbia survey, comprised of 23,694 Columbian respondents, 60 years and older, illustrates that displacement throughout one's childhood correlates with at least one chronic illness

in approximately 68% of respondents [9]. A 2018 study surveying approximately 8000 children that encountered armed conflict or displacement exposed significant prevalence of PTSD (47%), depression (43%) and anxiety (27%) [10]. Several studies illustrate a predisposition and an increased risk of ill-health into adulthood as a result of an inappropriate activation of biological and behavioral mechanisms commonly identified in conditions like PTSD and the aforementioned mood disorders. Therefore, it is fundamental to recognize at-risk patient populations in regard to their exposure to international health detriments to mitigate their high risk of chronic disease development.

5. Proposed mechanisms

ACE exposure results in a higher likelihood of developing chronic disease as an adult because of proposed mechanisms that alter an individual's development. This is resultant of recurrent physiologic and biomolecular damage, termed allostatic load. A proposed mechanism pertaining to allostatic load, accepted by the ACE study, is the Biological Embedding of Childhood Adversity Model. This model states that as stress accumulates from abuse, maltreatment or abandonment, a threshold is attained [11]. Attainment of this threshold promotes pro-inflammatory cellular predispositions including a disproportionate cytokine response to the posed challenge that desensitizes the inhibition of hormone signals. Studies suggest that inflammation is the fundamental mediator that translates an adolescent's altered psychosocial influences into biological predisposition for chronic disease. Adults that incurred adverse childhood experiences encountered an elevation in inflammation biomarkers, exacerbated by concurrent mood disorders like depression at the time of assessment. The lack of hormone inhibition and resultant hormonal deregulation stimulates impaired self-regulation in an individual that is already likely to possess genetic predisposition to develop adulthood chronic disease. The Biological Embedding of Childhood Adversity Model explains the alteration of an individual's neural, endocrine, immune, metabolic axes through recurrent negative stressors in the stages of life that are susceptible to such insults. These changes mediate one's cognition and emotional wellbeing as an adult that pose complications in and of itself (**Figure 2**).

The brain and neural development in the first 2 years of life is crucial. The brain acquires 80–90% of gray and white matter throughout this time prior to adulthood advancement [12]. Aside from possible changes in the acquisition of gray and white matter, normal neurodevelopment of the brain enables environmental alterations to essentially inactivate neural synapses. This is referred to as "pruning." This illustrates the susceptibility that the young developing brain has regarding adverse experiences. ACEs are linked to pervasive and calculable changes in the structure and the function of the brain. Functional MRI has illustrated the structural and functional implications of ACE-mediated risk on psychopathologies including maladaptive adulthood behavior like substance use/abuse as depicted by changes in reward-related cognition including the prefrontal complex and mesolimbic systems. Brain anatomy including the prefrontal cortex, critical in regard to higher-level cognition, is diminished in individual's that experience ACEs as seen in functional MRI studies [12]. Additionally, the limbic system, i.e. the hippocampus and the amygdala, are instrumental in an individual's ability to recall, regulate emotion and learn. This is diminished as a result of adverse experiences, since the limbic system is deemed "stress sensitive" because of the overabundance of glucocorticoid receptors. The neurotoxicity hypothesis implies that early elevation in glucocorticoids in the anatomical regions of the brain that includes the pre-frontal cortex and limbic system, hinders the development of neurons through oxidative stress subsequent to

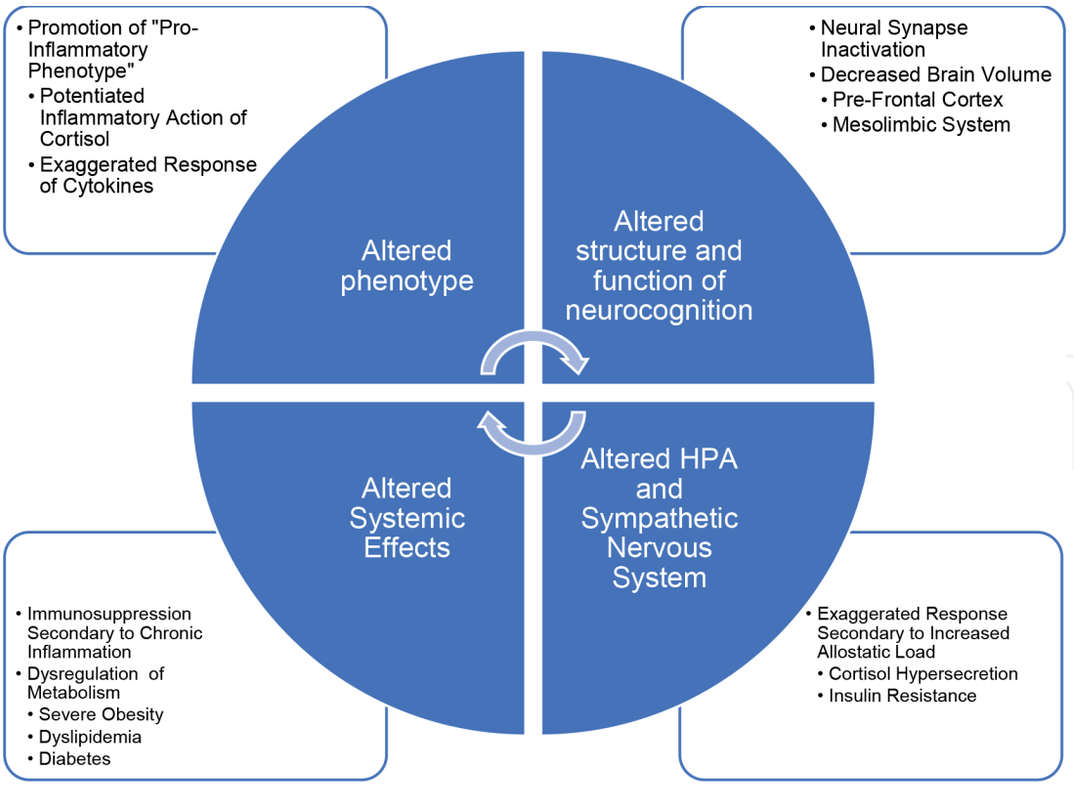

Figure 2.
The biological embedding of childhood adversity model resultant of early exposure psychosocial stressors as adapted from Berens [12].

elevated cortisol. An elevation in cortisol and the subsequent elevation in inflammatory cytokines and excitatory amino acids like glutamate potentiate this hindrance.

The Hypothalamic-Pituitary-Adrenal (HPA) axis and the autonomic axes, involving the sympathetic and parasympathetic nervous system, are fundamental in an individual's response to stressors through release of molecular mediators like corticotrophin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and glucocorticoids. An individual's exposure to ACEs promotes adulthood HPA deregulation through an exaggerated hyper- or hypoactive response secondary to an increased allostatic load. Increased allostatic load promotes physiologic and biomolecular changes related to the development of chronic disease [13]. Sympathetic activation by the brainstem induces adrenal-medullary epinephrine/norepinephrine output to organs like the heart, liver, pancreas. Conversely, parasympathetic activation significantly mitigates this response to stressors. Autonomic dysregulation and imbalance implies deleterious stress-sensitive alterations by an increased allostatic load which has the propensity to predispose individuals to chronic disease through a predictable response by stress-sensitive organ to the excess hormones. This results in cardiovascular and metabolic derangements. Detrimental metabolic changes include severe obesity, dyslipidemia and diabetes. These changes transpire through the dysregulation of catabolism and anabolism. The balance between catabolism and anabolism is achieved through the regulation of hormones, i.e. cortisol, glucagon, epinephrine/norepinephrine and insulin. Exposure to ACEs stimulates inflammation and the hypersecretion of cortisol, stimulating catabolism. This results in resistance of peripheral tissues to insulin and an ensuing increase in blood glucose levels.

The response to internal and external stimuli is mediated by innate and adaptive immune systems. Regularly, this response results in an appropriate elevation in inflammatory mediators that include tumor necrosis factor, nuclear factors and interleukins. Conversely, chronic elevation in inflammation results in a prevailing immunosuppressed state secondary to cytotoxic, oxidative stress. Studies affirm

that this state of immunosuppression, portrayed as a "pro-inflammatory phenotype," potentiates the anti-inflammatory action of cortisol through the resistance of downstream receptors [14]. The pro-inflammatory state that promotes immunosuppression has implications on predisposing individuals to chronic ailments related to the development of oncologic disease through the inability of the immune system to impede oncogenic viruses. This increases an individual's likelihood that a precursory, precancerous condition becomes malignant. Additionally, the role of a pro-inflammatory state is apparent in cardiovascular and metabolic diseases like coronary artery disease and diabetes [15].

6. Examples of inflammation and allosteric load in chronic disease

Chronic inflammation is a hallmark of cardiovascular disease. Initially, cardiovascular disease, specifically coronary artery disease, was deemed a cholesterol storage disorder described by the accumulation of cholesterol in the walls of the arteries. Nonetheless, studies have shown that the presence of an elevated serum inflammatory marker is a significant predictor of cardiovascular risk irrespective of an individual's lipid profile. Also, elevated inflammatory markers correlate to a recurrent risk of complications including myocardial infarction, peripheral artery disease and stroke in individuals diagnosed as having acute coronary syndrome. Common cardiovascular risk factors like hypertension, hyperglycemia and tobacco use promote a pro-inflammatory phenotype through vascular injury. The propagation of the pro-inflammatory state through recruitment of inflammatory mediators transpires through transformation of lipoproteins to fatty streaks. The accumulation of coagulation factors promotes the propagation of inflammation and destabilizes the plaque. This state promotes cardiac complications like myocardial infarction, peripheral artery disease and stroke. This cascade of chronic inflammation considerably worsens an individual's cardiovascular condition.

Several studies have illustrated the importance of inflammation in pathophysiology of type 1 (T1D) and type 2 diabetes (T2D). The pathophysiology of T1D is described as an autoimmune phenomenon caused by the inflammation of beta cells of the pancreas, referred to as insulitis. The predominance of inflammation is mediated through inflammatory mediators that increase in metabolic stress. A peri-islet inflammation cascade is triggered that subsequently destroys pancreatic beta cells causing type 1 diabetes. The pathophysiology of T2D is described as insulin resistance balanced by the hypersecretion of insulin by pancreatic beta cells. Unfortunately, throughout the disease process progression, the beta cells are unable to attain a balance, causing a pathologic state to be present. Inflammation of the pancreatic beta cells increases the number of dysfunctional beta cells. This is predominantly achieved through the activation of a pro-inflammatory state as opposed to anti-inflammatory state in the presence of mediators.

A 2000 study by A. A. Alonzo examined the addition of adverse experiences to an initially identified trauma as an example of the negative implications allosteric load has on chronic illness. Alonzo defines the term "cumulative adversity" as the propagation of physiologic changes like a pro-inflammatory state, more pronounced in increasing instances of adversity, through maladaptive behavior and an incapacity to cope. Additionally, increasing instances of adversities or ACEs predispose individuals to the triggering of PTSD. The prevalence of PTSD and exposure to trauma throughout one's childhood into adulthood is 40–75%, often occurring with other comorbid conditions [16]. Therefore, it is imperative to identify the role of ACEs and PTSD in the development of adulthood chronic illness in addition to the role chronic illness has itself as a traumatogenic burden that has the ability

to accumulate because of disease trajectory, intrusive or invasive procedures and administrative annoyances.

7. ACEs and implications on international health security

The challenges of chronic disease are evident and encountered not merely by the individual and their support system, but by the healthcare system. The increase in incidence of chronic disease increases direct and indirect healthcare costs that have significant implications on the economy and the ensuing measures to address this problem. It is apparent that adverse childhood experiences (ACEs) considerably contribute to the development of chronic disease as an adult through a higher likelihood of engaging in high-risk, health-harming behaviors, characteristically used as maladaptive coping mechanisms to contest traumatic experiences. It is approximated that 1 billion children, ages 2–17, are anticipated to have encountered an adverse childhood experience as previously described [17]. ACEs are avertible by creating safe and stable childhood settings that encourage less health-harming behaviors used as a strategy to cope with suicidal behavior, substance abuse, etc. [18]. Additionally, stable settings support academic achievement and the possibility to overcome poverty, recognized as a contributor to instances of ACE and perchance an ACE itself.

International health surveillance and initiatives that promote preventative measures on a practitioner level are paramount to address this destructive trend [19]. Said initiatives are beginning to appear in an attempt to address the important implications ACEs have on chronic disease as an adult. Primary and secondary prevention is essential in creating a nonviolent and encouraging environment for children. This includes a surveillance system that is comprehensive, cooperative and effective in identifying vulnerable individuals like a Behavioral Risk Factor Surveillance System (BRFSS). This system provides statistics on ACEs throughout a child's early years. Irrespective of the specific survey utilized, it is important to include trauma-informed practices that possess the empathy essential by primary care practitioners to initiate critical conversations and promote appropriate childhood practices, especially in children that have previously encountered an ACE [20]. It is imperative that individuals that are affected by ACEs be medically managed by clinicians accustomed to their particular health risks and resource for intervention. Initiatives like supplementary feeding programs and targeted food distribution may be initiated in regions where a demonstrated burden of food insecurity including micronutrient deficiency or acute malnutrition is present [21]. In conflict zones, disease prevention including vaccination campaigns, civil protection authorities including legal aid and academic training would be crucial in addressing the detriment of displacement. Tertiary prevention via rehabilitation programs that assist in diminishing high-risk, health-harming behaviors that propagate chronic disease like smoking cessation. Individuals with mental illness like depression, PTSD, etc. need access to appropriate psychiatric management. By enacting these preventative and promotional strategies on a state and national level, it is reasonable to reverse forthcoming projections pertaining to the negative implications of chronic disease on the patient population and healthcare system as an entity.

8. Conclusion

Unfortunately, ACEs are acknowledged to be prevalent and pervasive in society. Slightly under 50% of individuals under the age of 18 admit to an exposure to at

least 1 ACE. An increase in odds ratio for maladaptive, high-risk behavior and morbidities increased as ACE scores increased to 4 or more. Therefore, a strong dose-response relationship exists pertaining to the number of ACEs encountered and the likelihood that health-harming behavior contributes to premature death in individuals diagnosed as having a chronic disease, particularly maladaptive coping mechanisms such as substance abuse and suicidality. Additionally, exposures to ACEs in itself predisposes individuals to chronic disease in their adulthood through proposed mechanisms like the Biological Embedding of Childhood Adversity Model and the negative determents of chronic inflammation described as allosteric load [22]. Because of the prevalence and immense impact ACEs have on patient populations and international health including the censorious concepts like conflict, displacement and food insecurity, it is important to implement appropriate intervention and prevention to diminish the prevalence of ACEs in high-risk patient populations.

Author details

Jordan Holter[1], Christine Marchionni[1] and Bankim Bhatt[2*]

1 Department of Psychiatry, St. Luke's University Health Network, Easton, PA, USA

2 Division of Endocrinology and Metabolism, St Luke's University Health Network, Easton, PA, USA

*Address all correspondence to: bankim.bhatt@sluhn.org

References

[1] Bellis MA, Hughes K, Leckenby N, Hardcastle KA, Perkins C, Lowey H. Measuring mortality and the burden of adult disease associated with adverse childhood experiences in England: A national survey. Journal of Public Health. 2015;**37**(3):445-454. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4552010/

[2] Arredondo A, Aviles R. Costs and epidemiological changes of chronic diseases: implications and challenges for health systems. PLoS One. 2015;**10**(3):e0118611. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4364072/

[3] The Costs of Chronic Disease in the U.S. The Costs of Chronic Disease in the U.S. Milken Institute. 2018. Available from: milkeninstitute.org/reports/costs-chronic-disease-us

[4] Crawford C. CDC: Preventing ACEs May Mitigate Chronic Health Issues [Internet]. AAFP Home. American Academy of Family Physicians (AAFP). 2019. Available from: http://www.aafp.org/news/health-of-the-public/20191113mmwraces.html

[5] Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. American Journal of Preventive Medicine. 1998;**14**(4):245-258. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9635069

[6] Hughes K, Bellis MA, Hardcastle KA, Sethi D, Butchart A, Mikton C, et al. The effect of multiple adverse childhood experiences on health: A systematic review and meta-analysis. The Lancet. 2017;**2**(8):e356-e366. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29253477

[7] Chang X, Jiang X, Mkandarwire T, Shen M. Associations between adverse childhood experiences and health outcomes in adults aged 18-59 years. PLoS One. 2019;**14**(2):e0211850. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6366931/

[8] Food Security and Nutrition Assistance. USDA ERS - Food Security and Nutrition Assistance. 2019. Available from: https://www.ers.usda.gov/data-products/ag-and-food-statistics-charting-the-essentials/food-security-and-nutrition-assistance/

[9] Reed RV, Fazel M, Jones L, Panter-Brick C, Stein A. Mental health of displaced and refugee children resettled in low-income and middle-income countries: Risk and protective factors. The Lancet. 2011;**379**(9812):250-265. Available from: https://www.sciencedirect.com/science/article/pii/S0140673611600500

[10] McEniry M, Samper-Ternent R, Flórez CE, Cano-Gutierrez C. Early life displacement due to armed conflict and violence, early nutrition, and older adult hypertension, diabetes, and obesity in the middle-income country of Colombia. Journal of Aging and Health. 2019;**31**(8):1479-1502. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29916766

[11] Calam R. Public health implications and risks for children and families resettled after exposure to armed conflict and displacement – Rachel Calam. SAGE Journals. 2017, 2016;**45**(3):209-211. Available from: https://journals.sagepub.com/doi/10.1177/1403494816675776

[12] Berens AE, Jensen SKG, Nelson CA. Biological embedding of childhood adversity: from physiological mechanisms to clinical implications. BMC Medicine. 2017;**15**(1):135.

Available from: http://www.ncbi.nlm.nih.gov/pubmed/28724431

[13] Danese A. Adverse childhood experiences, allostasis, allostatic load, and age-related disease: Request PDF. ResearchGate. 2011;**106**(1):29-39. Available from: https://www.researchgate.net/publication/51616220_Adverse_childhood_experiences_allostasis_allostatic_load_and_Age-related_disease

[14] Su S, Jimenez MP, Roberts CTF, Loucks EB. The role of adverse childhood experiences in cardiovascular disease risk: A review with emphasis on plausible mechanisms. Current Cardiology Reports. 2015;**17**(10):88. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4941633/

[15] Tsalamandris S, Antonopoulos AS, Oikonomou E, Papamikroulis G-A, Vogiatzi G, Papaioannou S, et al. The role of inflammation in diabetes: Current concepts and future perspectives. European Cardiology. 2019;**14**(1):50-59. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6523054/

[16] Alonzo A. The experience of chronic illness and post-traumatic stress disorder: The consequences of cumulative adversity. Social Science & Medicine. 1982;**50**(10):1475-1484. Available from: https://pubmed.ncbi.nlm.nih.gov/10741582/

[17] Wyckoff AS. Preventing ACEs has potential to reduce leading causes of death in adults: Study. American Academy of Pediatrics. 2020. Available from: http://www.aappublications.org/news/2019/11/05/aces11519

[18] Dube SR, Anda RF, Felitti VJ, Chapman DP, Williamson DF, Giles WH. Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: Findings from the adverse childhood experiences study. JAMA. 2001;**286**(24):3089-3096. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11754674

[19] Jones CM, Merrick MT, Houry DE. Identifying and preventing adverse childhood experiences: Implications for clinical practice. JAMA. 2019. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31689343

[20] Shenoda S, Kadir A, Pitterman S, Goldhagen J, Health SOIC. The effects of armed conflict on children. American Academy of Pediatrics. 2018;**142**(6):e20182585. Available from: https://pediatrics.aappublications.org/content/142/6/e20182585

[21] Chanlongbutra A, Singh GK, Mueller CD. Adverse childhood experiences, health-related quality of life, and chronic disease risks in rural areas of the United States. Journal of Environmental and Public Health. 2018. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6077617/

[22] Lopez-Candales A, Hernández Burgos PM, Hernandez-Suarez DF, Harris D. Linking chronic inflammation with cardiovascular disease: From normal aging to the metabolic syndrome. Journal of Nature and Science. 2017;**3**(4):e341. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5488800/