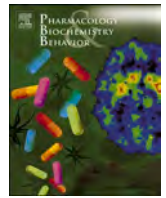


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The importance of child abuse and neglect in adult medicine

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ABSTRACT

The risk for adverse consequences and disease due to the trauma of child abuse or neglect is easily assessed using the self-administered modified ACEs questionnaire. Exposure to child maltreatment is endemic and common. At least one out of every ten USA adults has a significant history of childhood maltreatment. This is a review of the literature documenting that a past history of childhood abuse and neglect (CAN) makes substantial contributions to physical disease in adults, including asthma, chronic obstructive pulmonary disease, lung cancer, hypertension, stroke, kidney disease, hepatitis, obesity, diabetes, coronary artery disease, pelvic pain, endometriosis, chronic fatigue syndrome, irritable bowel syndrome, fibromyalgia, and auto immune diseases. Adults who have experienced child maltreatment have a shortened life expectancy. The contribution of CAN trauma to these many pathologies remains largely underappreciated and neglected compared to the attention given to the array of mental illnesses associated with child maltreatment. Specific pathophysiologic pathways have yet to be defined. Clinical recognition of the impact of past CAN trauma will contribute to the healing process in any disease but identifying specific effective therapies based on this insight remains to be accomplished. Recommendations are made for managing these patients in the clinic. It is important to incorporate screening for CAN throughout adult medical practice now.

1. Introduction

Kempe et al. (1962) first introduced clinical medicine to the “Battered Child Syndrome” only 60 years ago in 1962. A generation ago Felitti et al. (1998) first explored the prevalence and impact of child abuse and neglect (CAN) in adults with the development of the Adverse Childhood Experience (ACEs) questionnaire (Felitti et al., 1998, see Appendix A). They documented both a substantial prevalence of past CAN among adults and that CAN trauma contributes significantly to risk for adult disease. At a minimum 1 out of every 10 adults seeking medical care has a history of significant maltreatment as a child. Reflecting the broader cultural shame and gaze aversion (Krugman, 2019), clinical medicine has been slow to appreciate the pathogenic contribution of CAN trauma on adult physical health. Attention to the needs of children experiencing acute CAN will not be discussed in this paper. While the relation between past trauma and psychological turmoil and mental illness is substantial (Heim et al., 2010), this paper will focus only on the relevance of CAN history to adult physical disease. There is a growing body of research documenting permanent changes in genetic, epigenetic, neuroanatomic, neuroendocrine, immunologic, and inflammatory systems due to the toxic stress and traumatic assault on the child at this most vulnerable age of development. These physiologic changes can

contribute to the development of adult diseases beyond the effects of any CAN trauma associated dysfunctional behaviors, such as smoking and substance use. The details are best left to other discussions. Excellent reviews and summaries can be found at Kundakovic (Kundakovic and Champagne, 2015) on genetics and epigenetics, Teicher (Teicher et al., 2016) on brain structure, Nemeroff (Nemeroff, 2016) on neuroendocrinology, De Bellis (De Bellis and Zisk, 2014) on physiology, and Schreier (Schreier et al., 2020) on inflammation. Lack of attention to CAN trauma's contribution to common adult diseases has impaired basic clinical research, resulting in a paucity of evidence based, effective treatment interventions. It will be imperative in the future to expand epidemiology and clinical research; hone best practices, treatments, and social interventions in both physical and mental diseases as well as shape public policies with attention to CAN trauma. The multiplicity of chronic diseases associated with a history of CAN indicates it important to incorporate screening for CAN throughout adult medical practice.

2. Screening for history of child maltreatment

The original ACEs questionnaire (Felitti et al., 1998, Appendix A) is simple, practical, self-administered and takes only a few minutes. It consists of 10 questions covering psychological abuse or neglect,

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physical abuse, contact sexual abuse and exposure to household dysfunction during childhood. The ACEs score is a simple summation of positive answers. Responses generally show a linear dose-response relation between the number of positive categories and various pathologies, with subjects scoring 4 or more having a substantially higher risk. This is a simple and practical schema rather than a subtle one with nuances. For example, 1 rape episode or 1 traumatic brain injury would generate a score of 1 which might be of greater clinical significance than having a score of 4 (father mentally ill and used drugs and was jailed and died). The duration of, and age when exposed, are not assessed. Also multiple adverse experiences in a clustered fashion may have a more severe impact. All of these additional factors, as well as exposure to positive life influences, may differentially affect future disease development. While the original ACEs questionnaire remains simple to use, an expanded, modified screen may be more valuable. The "PEARLS - Pediatric ACEs and Related Life Events Screener" developed by the Center for Youth Wellness in partnership with the Benioff Children's Hospital and the UCSF School of Medicine (Thakur et al., 2020; Bhushan et al., 2020) can be used with adults and adds important questions about bullying, discrimination and food insecurity and is brief and functional (see Appendix A). It is easily downloadable in 12 reproducible versions from <https://nppcaces.org/document-pearls/>. Alternatively, a presumptive, universal screening approach may be taken by asking one simple generic question: "As a child did you experience any threatening or upsetting circumstances that continue to bother you now?"

The ACEs questionnaire and instruments like it are risk assessment tools not diagnostic instruments. They enumerate the circumstances that collectively are associated with the CAN trauma/stress syndrome. Individual ACEs scores are a proxy for risk. Neither the events nor the score define a disease state. Child maltreatment per se is not an illness and not all children who have adverse experiences develop sequelae or have high risk. The ACEs questionnaire is prone to false negative responses due to shame or repression, but may nonetheless facilitate a future conversation. There is a recurrent professional concern that asking such intimate and possibly upsetting questions would pose a "risk ... whether the respondents will be offended or upset by answering personal questions about ACEs or whether the ACE questionnaire will erode the trust between clinician and patient or parent." (Campbell, 2020) In fact, the ACEs screen was used as part of a comprehensive health assessment at Kaiser in over 400,000 patients without ever evoking complaints (Felitti and Anda, 2014). The use of ACEs frequently elicits gratitude from patients for having the opportunity to open up, often for the first time, about their experience, creating new intimacy in the doctor patient relationship.

3. Prevalence of child abuse and neglect

The documented prevalence of child maltreatment is consistently high. A study (Wildeman et al., 2014) of the National Child Abuse and Neglect Data System (NCANDS) which compiles all reports confirmed by Child Protective Services of significant maltreatment of U.S. children up to age 18, found that at 2011 rates, 12.5% (1 of every 8) of U.S. children will have accumulated a confirmed case of maltreatment by age 18. Girls have a higher cumulative prevalence than boys at 13.0% vs. 12.0%. By ethnicity the rates were: Black 20.9%, Native American 14.5%, Hispanic 13.0%, Asian/Pacific Islander 3.8%, and White 10.7%. The National Survey of Children's Exposure to Violence (NatSCEV) (Finkelhor et al., 2015) conducted a representative telephone sample of 4000 children 0 to 17 years old in 2014 finding in total, 37.3% of youth (2 of every 5) experienced a physical assault and 9.3% of youth experienced an assault-related injury in that study year alone. Taking another perspective, the State of Wisconsin (Wisconsin Child Abuse and Neglect Prevention Board, 2018) surveyed over 25,000 of its adults with an average age of 48.2 years between 2011 and 2015 and found 57% reported at least 1 ACEs and 14% (1 of every 7) had experienced 4 or more ACEs. A similar random-digit-dial telephone survey collecting data from

non-institutionalized adults age 18 and over in California (California Department of Public Health et al., 2020) reported ACEs data from the 2011, 2013, 2015, and 2017 in the California Behavioral Risk Factor Surveillance System (BRFSS). It found that 62.3% of adults reported at least 1 ACEs and 16.3% (1 of every 6) reported 4 or more ACEs. Four or more ACEs were reported by 12.9% of respondents with more than a high school education and by 13.1% of those earning over \$75,000 a year. In confirmation a recent CDC study using BRFSS data from 25 states not including California (Merrick et al., 2019) of nearly 150,000 non-institutionalized adults found: "Nearly one in six adults in the study population (15.6%) reported four or more types of adverse childhood experiences." It should be noted that all research using the BRFSS studied only the non-institutionalized population. It is well documented that institutionalized persons, as well as the homeless, have a substantially higher prevalence of CAN (Wolff et al., 2009; Bymaster et al., 2017; Mersky et al., 2012). Thus it is a reasonable, conservative assumption that at least 1 out of every 10 adult patients presenting for medical care has a history of significant abuse or neglect as a child.

4. Child maltreatment history and adult disease: pulmonary and coronary artery disease

Felitti et al. (1998) "found a graded relationship between the number of categories of childhood exposure and each of the adult health risk behaviors and diseases that were studied ($p < .001$). Persons who had experienced four or more categories of childhood exposure, compared to those who had experienced none, had 4 - to 12-fold increased health risks for alcoholism, drug abuse, depression, and suicide attempt; a 2- to 4-fold increase in smoking, poor self-rated health, >50 sexual intercourse partners, and sexually transmitted disease....The number of categories of adverse childhood exposures showed a graded relationship to the presence of adult diseases including ischemic heart disease, cancer, chronic lung disease, skeletal fractures, and liver disease." These findings have been repeatedly replicated in large state, national and international epidemiological surveys (Bhushan et al., 2020; Merrick et al., 2019; Hughes et al., 2017; Miller et al., 2020; Cuijpers et al., 2011). Although CAN trauma clearly can disrupt self-esteem and coping mechanisms producing a substantial burden of psychological symptoms, psychopathology, and social incapacities the following discussion will only focus on its relation to specific physical diseases in adults (Table 1).

People who have experienced CAN, perhaps self-medicating their anxiety, have a higher prevalence of cigarette exposure providing a clear pathophysiologic path between CAN and some common adult diseases. The Felitti group (Anda et al., 1999) studied over 9000 adults and "after adjusting for age, sex, race, and education...compared with those reporting no adverse childhood experiences, persons reporting 5 or more categories had substantially higher risks of early smoking initiation (odds ratio [OR], 5.4; 95% confidence interval [CI], 4.1-7.1), ever smoking (OR, 3.1; 95% CI, 2.6-3.8), current smoking (OR, 2.1; 95% CI, 1.6-2.7), and heavy smoking (OR, 2.8; 95% CI, 1.9-4.2). Each relationship between smoking behavior and the number of adverse childhood experiences was strong and graded ($p < .001$)." Excessive smoking led the linear rise Felitti et al. (Felitti et al., 1998) observed in chronic bronchitis or emphysema in adults with an increasing ACEs score (2.8% with a score of 0, 4.4% with 1 or 2, 5.7% with 3, and 8.7% with a score of 4 or more.) A large Canadian health survey (Shields et al., 2016a) also found a relation between CAN, smoking and lung disease which varied by sex, age and type of abuse. In a meta-analysis of 19 studies (Lopes et al., 2020), 11 studying asthma showed a positive relationship with CAN and 5 studying COPD showing a significant correlation with CAN. Significantly, when smoking is controlled for, CAN itself had a weak but persistent independent correlation with chronic lung disease (perhaps due to a disordered immune or inflammatory response). Using hospitalization records and the US national death records, Felitti's group was able (Brown et al., 2010) to do a 10 year follow up on a cohort of patients with positive ACEs to ascertain the incidence of lung cancer. Compared

Table 1

Association between adverse childhood experience score^{a, b} and health conditions, health risk behaviors, and socioeconomic challenges. From the Behavioral Risk Factor Surveillance System^c in 25 States, 2015–2017.

Outcome	Adverse childhood experience score		
	1	2–3	≥4
	Adjusted odds ratio (95% CI)		
Chronic condition			
Coronary heart disease	1.1 (1.0–1.3)	1.2 (1.1–1.4)	1.8 (1.6–2.1)
Stroke	1.1 (1.0–1.3)	1.3 (1.2–1.5)	2.1 (1.7–2.5)
Asthma	1.3 (1.2–1.4)	1.6 (1.4–1.7)	2.2 (2.0–2.4)
Chronic obstructive pulmonary disease	1.3 (1.1–1.4)	1.7 (1.5–1.9)	2.8 (2.5–3.1)
Cancer (excluding skin)	1.1 (1.0–1.1)	1.2 (1.1–1.3)	1.4 (1.2–1.6)
Kidney disease	1.2 (1.0–1.4)	1.3 (1.2–1.6)	1.7 (1.4–2.0)
Diabetes	1.0 (0.9–1.1)	1.1 (1.1–1.2)	1.4 (1.2–1.5)
Overweight or obesity ^d	1.0 (0.9–1.1)	1.1 (1.0–1.2)	1.2 (1.1–1.3)
Mental health			
Depression	1.6 (1.5–1.7)	2.6 (2.4–2.8)	5.3 (4.9–5.7)
Health risk behavior			
Current smoker	1.4 (1.3–1.6)	1.9 (1.8–2.1)	3.1 (2.8–3.3)
Heavy drinker	1.3 (1.2–1.5)	1.6 (1.4–1.8)	1.8 (1.6–2.0)
Socioeconomic challenge			
Less than high school education	1.0 (0.9–1.1)	1.1 (1.0–1.2)	1.4 (1.3–1.6)
Unemployment	1.1 (0.9–1.3)	1.3 (1.2–1.5)	1.7 (1.5–2.0)
No health insurance	1.0 (0.9–1.1)	1.1 (1.0–1.2)	1.3 (1.2–1.5)

Table is taken from (Merrick et al., 2019), Table 2; Note only non-institutionalized adults were studied for this data. Institutionalized adults have a significantly higher prevalence of ACE experiences and CAN trauma than the general population, see: (Wolff et al., 2009).

Abbreviation: CI = confidence interval.

^a Based on the number of adverse childhood experience types reported.

^b Referent group had zero adverse childhood experiences; all models were adjusted for sex, age group, and race/ethnicity.

^c States with state-added adverse childhood experience questions: Alaska, Kansas, Kentucky, Maryland, Ohio, South Carolina, and Texas (2015), Arizona, Arkansas, Georgia, Louisiana, Michigan, New York, Oklahoma, Pennsylvania, and Utah (2016); Connecticut, Illinois, Iowa, Nevada, Oregon, South Dakota, Tennessee, Virginia, and Wisconsin (2017).

^d Overweight: body mass index ≥ 25 kg/m²; obesity: body mass index ≥ 30 kg/m².

to persons with an ACE score of 0, those with a score of 4 or more had at least a 2.5 increase in risk for lung cancer and those with a score of 6 or more had a 3-fold increase. Persons with 6 or more ACEs were hospitalized for lung cancer and died on the average 13 years earlier than those without ACEs. When the data were controlled for smoking by the patients or their parents, those with 4 or more ACEs still had a slightly elevated risk of lung cancer compared with those with none (although the total number of cases were too few for statistical analysis) indicating the possible influence of factors other than smoking. There have been no prevalence studies of the history of CAN among a population of lung cancer patients and treatment strategies dealing directly with the impacts of child abuse (for example, trauma informed care (Millstein, 2020; Gerber, 2019) for anxiety) have thus far not been integrated in smoking cessation or pulmonary rehabilitation programs.

It is well known that smoking contributes to the risk for coronary artery disease. A CDC study (Merrick et al., 2019) found that respondents with 4 or more ACEs had an adjusted odds ratio for coronary artery disease of 1.8 (compared to 1.0 for no ACEs.) Another study (Su et al., 2015) confirmed that “Adults with 4 or more ACEs compared with those with none have a more than 2-fold higher risk of developing CVD and an almost 2-fold higher risk of premature mortality.” Drawing on data from the National Survey of Midlife Development in the United States (MIDUS) researchers (Morton et al., 2014) found “that accumulated childhood misfortune and child maltreatment increased AMI risk, net of several adult covariates, including family history of AMI. Smoking fully mediated the effects of both accumulated childhood misfortune and child maltreatment.” More ominously, a cohort study (Almuwaqqat et al., 2020) following 300 patients aged 18 to 60 showed those with a high childhood adversity score and a documented prior MI were twice as likely to have worse outcomes with more recurrent MIs, strokes, heart failure, hospitalizations, and cardiovascular deaths over a median 3-year follow-up than those without childhood adversity. This study found patients with more childhood adversity had higher interleukin-6

and CRP levels at baseline. When controlled for CRP levels, the excess subsequent morbidity for abused patients with an initial MI was not significant.

5. Child maltreatment history and adult disease: hypertension and stroke

Hypertension was found to be associated with experiencing CAN as a child among female nurses (Riley et al., 2009): “All forms of abuse had a dose-response relationship with hypertension. Adjustments for smoking, alcohol, family history of hypertension, exercise, and oral contraceptives did not alter risk estimates. Adjustment for body mass index (BMI) significantly attenuated the associations between abuse and risk of hypertension and accounted for approximately 50% of the observed association between abuse exposure and hypertension.” In a large study from the United Kingdom (Chandan et al., 2020), patients who experienced CAN had a statistically significant (<0.001) adjusted incidence rate ratio for hypertension of 1.42. The same study showed an adjusted incidence rate ratio of 2.15 ($p < 0.001$) for strokes or TIA. In their original study Felitti, et al. (Felitti et al., 1998) showed that subjects with 4 or more ACEs had an adjusted odds ratio of 2.4 for stroke compared to those with no ACEs. CAN associated hypertension is also associated with increased kidney disease and overall mortality (Ozieh et al., 2020). One of the major problems in chronic disease management is compliance with behavioral advice and prescription management. Childhood CAN experience may induce maladaptive passive aggressive responses to authority figures resulting in treatment plan non-compliance. Since stroke prevention primarily depends on long term hypertension management, attention to a history of CAN in these patients may increase compliance and successful management and both primary and secondary prevention.

6. Child maltreatment history and adult disease: obesity and diabetes

Obesity resistant to treatment was the clue that first led Dr. Felitti to explore the impact of CAN on adult health (Felitti et al., 2010). He discovered a history of childhood sexual abuse in a patient who repeatedly gained weight back after successful weight loss after she confessed to her self-protective need to appear sexually unattractive. His group's original study (Felitti et al., 1998) showed that people with 4 or more ACEs had an adjusted odds ratio of 1.6 for obesity (BMI > 35) compared to those with no ACEs. A meta-analysis (Danese and Tan, 2014) of 41 studies with over 190,000 subjects showed an overall odds ratio for obesity among those who had experienced CAN trauma of 1.36 compared to those without CAN. In this meta-analysis childhood maltreatment was associated with obesity, regardless of whether the study estimates were or were not adjusted for childhood socioeconomic status, adult socioeconomic status, current smoking, current alcohol intake, or current physical activity, but the correlation was not significant when adjusted for current depression. They estimated that on the basis of recent US prevalence estimates of obesity, NNT was 7 for adult obesity. Attention to a past history of CAN, currently largely neglected, may improve motivation resulting in better outcomes in the treatment of obesity.

Shields et al. (Shields et al., 2016b) studying over 20,000 Canadian adults found that diabetes was significantly associated with reports of severe and frequent childhood physical abuse (CPA) (OR = 1.8) and severe and frequent childhood sexual abuse (CSA) (OR = 2.2). They went on to tease out the contribution of significant known factors contributing to diabetes – all of which are independently increased in CAN. In subjects with severe or frequent CPA, “the inclusion of obesity, smoking status, and high blood pressure resulted in reductions in the standardized regression coefficients of 13, 11, and 17 % respectively. The inclusion of all 5 mediators (adding levels of depression and physical activity) simultaneously resulted in a 41 % reduction, with the association between severe and frequent CPA and diabetes approaching statistical significance ($p=0.06$). For CSA, the effects of the mediating variables were not as pronounced. The inclusion of obesity resulted in a reduction in the standardized regression coefficient for severe and frequent CSA and diabetes of 10 %. In the full model including all 5 mediators, the reduction was 17 %. For severe CSA occurring 2 times or less, the standardized regression coefficient was attenuated by 16 % with the inclusion of obesity and by 13 % with the inclusion of smoking status. In the full model, the reduction was 16 %, and the association with diabetes was no longer statistically significant.” While it is important to document the impact of these mediating variables in clinical research, it should be noted that all of them cluster around patients who have experienced CAN. Huang et al. (Huang et al., 2015) in a meta-analysis of 7 articles with nearly 90,000 subjects found a combined odds ratio of 1.36 for diabetes associated with ACEs compared to those without ACEs. Diabetes was more common among those who had experienced neglect than other adults who had experienced childhood trauma, perhaps reflecting a conscious or unconscious psychological dynamic. Patient motivation and compliance are crucial to obesity and diabetic management. Patients whose capacity is limited by CAN trauma will have the most trouble responding to treatment.

7. Child maltreatment history and adult disease: urology and gynecology

A past history of CAN has a great impact on the diseases seen in urology and gynecologic practice. Felitti et al. (Felitti et al., 1998) originally observed that adults maltreated as children reported an exceptional amount of sexual behavior, with those having 4 or more ACEs having an adjusted odds ratio of 3.2 times more likely to have had more than 50 sexual partners and 2.5 times more likely to have had an STD than those with no ACEs. CAN trauma, involving physical and

sexual abuse as well as neglect, has a well proven relation to chronic pelvic pain in women, although this relation may be mediated by depression (Sachs-Ericsson et al., 2007; As-Sanie et al., 2014). A tertiary care clinic (Schrepf et al., 2018), using the Childhood Traumatic Events Scale (CTES) and following patients over 2 years, found “ACE severity was elevated in urologic pelvic pain syndrome (UCPPS) ($n = 421$) participants compared with healthy controls ($n = 414$; $p < .001$), and was most strongly associated with factors associated with complex chronic pain, including more diffuse pain, comorbid functional symptoms/syndromes, and worse perceived physical well-being (all $p < .001$). Finally, worse physical well-being mediated the relationship between ACE severity and less likelihood of painful symptom improvement (OR = .871, $p = .007$) and a greater likelihood of painful symptom worsening (OR = 1.249, $p = .003$) at 1 year.... By our estimates, a patient one standard deviation above the mean on ACE severity would be approximately 52% more likely to have pain worsen at 1 year after adjustment for age and baseline severity, and approximately 27% less likely to have pain improve, compared with a patient with no history of ACEs—an effect mediated through worse perceived physical well-being.” Pelvic complaints after CAN trauma are not all subjective or enhanced by emotionality. Harris (Harris et al., 2018) found among the 60,595 premenopausal women in the Nurses' Health Study II cohort after 24 years of follow up there were 3394 cases of laparoscopically confirmed endometriosis. “Compared to those reporting no physical or sexual abuse, the risk of endometriosis was greater among those who experienced severe physical abuse (RR = 1.20; 95% CI = 1.06, 1.37) or severe sexual abuse (RR = 1.49; 95% CI = 1.24, 1.79). There was a 79% increased risk of laparoscopically-confirmed endometriosis for women reporting severe-chronic abuse of multiple types (95% CI = 1.44, 2.22).” There are no studies documenting the prevalence of CAN history in a population of women with endometriosis.

In regards to gynecologic cancers, a meta-analysis of 12 international studies by a group from the CDC (Holman et al., 2016) found the studies collectively recorded 20 different types of ACEs or a summary score for a total of 119,100 subjects. “Across studies, ACE summary scores were associated with an increased risk of cancer in adulthood. Of the different types of ACEs examined, physical and psychological abuse victimization was more frequently associated with adult cancer risk. Two studies also reported significant associations with regard to sexual abuse victimization.” In so far as more and abusive sexual partners increase the risk of HPV infection, one would expect more cases of cervical cancer. Nonetheless, one study showed a relation between CAN/sexual abuse and cervical cancer and one did not. No studies found a relation with CAN and breast cancer. Additionally an evaluation of data from the Nurses' Health Study II (Roberts et al., 2019) found women with high PTSD symptoms had 2-fold greater risk of ovarian cancer versus women with no trauma exposure (age-adjusted HR: 2.10). Adjustment for health and ovarian cancer risk factors only moderately attenuated this association (HR: 1.86).

8. Child maltreatment history and adult disease: autoimmune disease

Using their own hospital's records, Felitti's group was able (Dube et al., 2009) to do a prospective 10 year follow up on a cohort of patients with positive ACEs to ascertain the incidence of autoimmune diseases. They found first hospitalizations for any autoimmune disease increased with increasing number of ACEs ($p < .05$). Compared with persons with no ACEs, persons with ≥ 2 ACEs were at a 70% increased risk for hospitalizations with Th1 diseases (a cell-mediated immunopathology, which is more prevalent in men, including the following: idiopathic myocarditis, idiopathic pulmonary fibrosis, insulin-dependent diabetes mellitus, irritable bowel disease, and Wegener's granulomatosis, 80% increased risk for Th2 diseases (T helper type-2 disease that is more prevalent in women including the following: autoimmune thrombocytopenia purpura, dermatomyositis, Graves' disease, Hashimoto's thyroiditis, myasthenia gravis, rheumatoid arthritis, scleroderma,

Sjogren disease, and systemic lupus erythematosus and 100% increased risk for a subgroup of the Th2 group included specifically rheumatic diseases (dermatomyositis, rheumatoid arthritis, scleroderma, Sjogren disease, and systemic lupus erythematosus) ($p < .05$). For every increase in the ACE Score, the likelihood of a first hospitalization with any autoimmune disease increased 20% ($p < .001$) for women and 10% for men ($p < .05$). Further exploration of the physiologic impact of CAN trauma on immune function may provide new insights into the origin and treatment of these dysregulatory autoimmune diseases. Armed with insight into the long term impact of CAN clinicians can also provide better supportive care for patients with these disabling conditions.

9. Child maltreatment history and adult disease: chronic pain

Although still undergoing intense active evaluation (Young-Southward et al., 2020), it appears that CAN trauma can produce central nervous system (CNS) autonomic dysregulation producing both sensitization and blunted responsiveness. In “CNS sensitization syndromes” chronic up regulation of the peripheral nociceptive receptors or CNS hypersensitivity occurs resulting in hyperexcitation experienced by the somatosensory cortex and spinal pain processing pathways, commonly producing local allo-dynia and hyperalgesia. A recent retrospective population based open cohort study (Chandana et al., 2020) using the UK primary care data base studied 80,657 adult patients (average age at entry 23.4 years, 41.7% male) who had experienced CAN who were matched to 161,314 unexposed patients by age and sex. Outcomes of interest were the development of Central Sensitivity Pain Syndromes. Effect sizes are presented as adjusted incidence rate ratios (aIRR), adjusted for: age, sex, deprivation, anxiety, depression, material deprivation and serious mental illness. Among subjects who had experienced CAN there was an increased risk of developing fibromyalgia (aIRR 2.06), chronic fatigue syndrome (1.47), chronic lower back pain (1.99), restless leg syndrome (1.82), and irritable bowel syndrome (1.15) when compared to the unexposed group, whereas no statistical association was seen with the development of temporomandibular joint disorder (1.00), chronic headache (1.04), interstitial cystitis (1.19), vulvodynia (0.65), chronic prostatitis (0.34) and myofascial pain syndrome (0.88). Linking the origin of these diverse syndromes, often thought to be “subjective” or “functional,” to the physiologic sequelae of CAN may lead the way to uncovering causal pathways allowing development of effective treatments.

10. Child maltreatment history and adult disease: liver disease

Felitti, Anda et al. (Felitti et al., 1998) documented that people who have experienced significant CAN trauma have an increased prevalence of alcoholism, and substance use disorder, including intravenous drug use. Compared to respondents who had no ACEs, people who had 4 or more were 7.4 times as likely to self-report alcoholism, 4.7 times as likely to report use of illicit drugs, and 10.3 times as likely to self-report having injected illicit drugs. Felitti’s group later reported (Dong et al., 2003) on the relation between self-reported liver disease and ACEs. People with 4 or more ACEs had a demographically adjusted odds ratio of 1.8 times as likely to report liver disease. This relationship was decreased by 38% when adjusted for drug, alcohol use and sexual promiscuity. Although the pathophysiology linking liver disease to IV drug use and alcoholism are well known, as yet there are no citations documenting the prevalence of child maltreatment among populations of alcoholics, IV drug users or patients with cirrhosis or the various types of viral hepatitis. Thus, due to this oversight, etiologic connections have not been explored and possible preventive and therapeutic interventions are being overlooked. Alcoholism, substance misuse, and liver disease are common chronic problems in adult medicine. While supportive care and treatment of complications are well established therapies, intervention aimed at secondary prevention has defaulted to “medicine-assisted-therapy,” and self-help groups such as NA and AA with dependence on traditional psychotherapies having little lasting impact.

Adding trauma informed care (Millstein, 2020; Gerber, 2019) and psychotherapy for past CAN trauma has the potential to change this dynamic and improve outcomes.

11. Epidemiology: can and population attributable fraction

One way to appreciate the magnitude of the impact of CAN on adult illness is to calculate the “population attributable fraction or risk” (PAF) of CAN for each disease. As the CDC put it (Merrick et al., 2019) “To understand the potential impact of preventing adverse childhood experiences in reducing negative health and well-being outcomes, state survey data were used to estimate population attributable fractions representing potential percentage reductions in the number of observed cases of health conditions, health risk behaviors, and socioeconomic impacts...if adverse childhood experience exposure were incrementally reduced or eliminated in the study population.” To be clear PAFs help assess the potential impact of interventions on population health. The PAF does not describe the proportion of patients exposed to the cited risk factor(s), the proportion of cases having any risk factor(s), the probability of causation for a specific disease, nor does its estimation enable epidemiologists to discriminate between those cases caused by, and those not caused by, the risk factor(s) under consideration (Rockhill et al., 1998). Nonetheless, the PAF statistic highlights the impact of a condition on a population and helps to concretize its importance. The CDC study (Merrick et al., 2019, see Table 2) using PAFs, adjusted for

Table 2

Population attributable fractions (PAFs) for health conditions, health risk behaviors, and socioeconomic challenges, by adverse childhood experience score^a.
^b From the Behavioral Risk Factor Surveillance System^c in 25 states, 2015–2017.

	Adverse childhood experience score			Overall PAF %
	1	2-3	≥4	
	PAF %			
Chronic condition				
Coronary heart disease	2.6	3.4	6.6	12.6
Stroke	— ^a	5.0	9.6	14.6
Asthma	4.2	8.1	11.7	24.0
Chronic obstructive pulmonary disease	4.1	9.1	13.8	27.0
Cancer (excluding skin)	—	2.4	3.5	5.9
Kidney disease	3.7	5.5	6.5	15.7
Diabetes	—	2.2	3.5	5.7
Overweight or obesity ^d	—	0.7	1.0	1.7
Mental health				
Depression	6.4	14.7	23.0	44.1
Health risk behavior				
Current smoker	5.9	11.1	15.9	32.9
Heavy drinker	5.6	9.0	9.3	23.9
Socioeconomic challenge				
Less than high school education	—	—	4.6	4.6
Unemployment	—	5.7	9.2	14.9
No health insurance	—	—	3.8	3.8

Table is taken from (Merrick et al., 2019), Table 3. Note only non-institutionalized adults were studied for this data. Institutionalized adults have a significantly higher prevalence of ACE experiences and CAN trauma than the general population, see: (Wolff et al., 2009).

^a Adverse childhood experience categories that were not statistically different from the unexposed (zero adverse childhood experiences) group were not included in the PAF calculation and are indicated by a dash. All models were adjusted for sex, age group, and race/ethnicity.

^b Based on the number of adverse childhood experience types reported.

^c States with state-added adverse childhood experience questions: Alaska, Kansas, Kentucky, Maryland, Ohio, South Carolina, and Texas (2015), Arizona, Arkansas, Georgia, Louisiana, Michigan, New York, Oklahoma, Pennsylvania, and Utah (2016); Connecticut, Illinois, Iowa, Nevada, Oregon, South Dakota, Tennessee, Virginia, and Wisconsin (2017).

^d Overweight: body mass index ≥ 25 kg/m²; obesity: body mass index ≥ 30 kg/m².

age, race/ethnicity, found the estimated overall percentage reduction associated with preventing all adverse childhood experiences would be 27.0% for COPD, 24.0% for asthma, 14.6% for stroke, 15.7% for kidney disease, 5.9% for all cancers except skin, and 5.7% for diabetes. PAF analysis revealed that CAN contributes to as much as 12.6% (or two million cases annually in the US) of all coronary artery disease. A meta-analysis reviewed the lifelong effects of CAN (Bellis et al., 2019) using data from 23 high quality international studies including 1,514,254 individuals and 12 from North America, including 121,341 individuals, published since January 1990. They calculated the following PAFs associated with ACEs/CAN experience for Europe and North America: harmful alcohol use: 24.7%, 27.9%; smoking 18.2%, 23.2%; illicit drug use 34.1%, 44.1%; obesity 5.6%, 9.0%; diabetes 7.9%, 7.5%; cardiovascular disease 11.7%, 19.7%; respiratory disease 18.5%, 27.6%; and any cancer 11.3%, 10.1%. In so far as the PAF is an epidemiologic abstraction and does not aid in diagnosis or treatment, its significance is clarified by looking at the PAFs for coronary artery disease due to the contributions of several known treatable conditions (Pencina et al., 2019): for treatment adjusted blood pressure equal or greater than 130 mmHg, 28%, for treatment adjusted non-HDL cholesterol equal or greater than 130 mg/dl, 17%, for smoking, 9.8%, and for diabetes 9.6%. Clinical medicine has long emphasized, studied, and treated these four conditions to optimize primary and secondary prevention of heart disease. The here-to-for overlooked factor of CAN trauma makes equivalent sized PAF contributions to heart disease, as well as to COPD, asthma, liver and kidney disease and diabetes.

12. Child maltreatment history and adult disease: treatment considerations

Treating the persistent effects of child abuse trauma requires many levels of intervention. The first step is to assess every patient for a history of child maltreatment. The EHR should have a specified location to record the ACEs score with the same prominence as a living will. Second, it is important to acknowledge a significant positive history when you see the patient. Patients will be offended if they offer intimate information and it is overlooked or dismissed (Austin, 2021). There is no need to prod. In many circumstances this will be the first time anyone has ever explicitly raised this subject for discussion in the patient's lifetime. It is not uncommon for the patient to take the opportunity to express gratitude and be eager to tell their story. Within the constraints of the clinic schedule, even if talk therapy is not one of your competencies, it is always best to acknowledge the importance of the subject, express empathy and immediately, explicitly take personal responsibility for helping with it, then to make a specific agreement to discuss details at a future appointment and return to the presenting clinical problem. Usually just having the issue on the table is a relief for the patient, is a catalyst for an improved and more intimate clinical relationship, and is therapeutic in starting to relieve the inherent chronic tension involved. The opportunity for catharsis can be a life altering experience for the patient. Many patients who have experienced significant CAN trauma will have symptomatic psychiatric illnesses. An effective intervention plan requires a bit of prior planning. No matter what medical specialty is involved, it is recommended that a return appointment be affirmatively scheduled dedicated only to listening to the memories and making a treatment plan. It helps to have familiarity with the "trauma informed care" approach (Millstein, 2020; Gerber, 2019). Comprehensive free, self-education videos are available with CME credit from the Academy on Violence and Abuse, click on California Aces Academy at <https://www.avahealth.org/resources/california-aces-academy/caa-webinars-series.html/>. Before the first patient who needs this help arrives, assess your group, your clinic, your building, your community (Substance Abuse and Mental Health Services Administration, 2014) for capable mental health resources and be prepared to make a "warm handoff," a personal referral, to a mental health person experienced in treating CAN trauma that you can both trust. The generalist physician should be aware that patients with psychiatric illness after experiencing

CAN trauma are generally more severely ill and less responsive to psychopharmacology than other patients with similar symptoms and likely to have had disappointing encounters with therapists in the past. If the physician is comfortable, the patient may be eager to continue follow up in the most familiar setting. Psychiatric care for traumatized patients who have experienced abuse or neglect may be difficult and complex. It is beyond the purview of this review to discuss specific therapeutic approaches for CAN trauma. While optimal modalities have yet to be clearly established, important considerations are described in the references (Nemeroff et al., 2003; Cohen and Mannarino, 2015; Courtois and Ford, 2013; Ford, 2015; Shapiro, 1989). You can assume that supportive personal empathy, managing psychiatric distress, appropriate referrals, and unhinging the inherent tensions will be of significant assistance in managing both primary and secondary prevention in the presenting physical disease. The scars of distant trauma cannot be erased but this contemporary intervention will improve compliance and outcomes.

Some patients may refuse to complete the screening form; some may casually pass on talking about it; rarely some may take offense. It helps to make note of these responses, but there is no need to pursue them. The issue may not exist, be too threatening, too repressed or too upsetting for the patient to take it on. It is not uncommon in these circumstances after a period of incubation for the patient to return and raise the subject spontaneously. Some healthy adults who have experienced CAN exhibit remarkable resilience. Increasingly research and clinical attention to these individuals is providing guidance toward evidence based, effective prevention and therapies as well as a means to moderate the stigma associated with experiencing CAN. For examples of beneficial studies of this topic see the Kauai Study (Werner and Smith, 1977), Topitzes (Topitzes et al., 2013), Holmes (Holmes et al., 2015), Dubowitz (Dubowitz et al., 2012), and Bethell and Sege (Christina Bethell et al., 2019). These studies often direct attention beyond the medical model to family, school, cultural, spiritual and community interventions which can be beneficial to these patients.

13. Discussion

While there is significant attention to acute CAN and associated trauma among children, its enduring impact is not fully appreciated in adult medicine. The numerous studies reviewed here demonstrate the association between CAN and many common adult physical diseases. The population associated risk from CAN for many common adult physical diseases is significant. The dose-response nature of the epidemiology and the residual correlations after known contributing factors are removed strongly support significant pathophysiologic links to adult physical morbidity. Nonetheless, except for behavioral contributions, causal relations remain unclear. Known permanent changes in genetic, epigenetic, neuroanatomic, neuroendocrine, immunologic, and inflammatory systems due to CAN provide many possible mechanisms. Yet, currently there is no proof that these physiologic changes directly cause or mediate specific adult diseases. Every physician should be aware of the relations documented here. All adult patients should be screened for a history of CAN. We know the prevalence of alcoholism or strokes in CAN survivors, but we do not know how many people who have alcoholism or strokes have a history of CAN. Evidence based treatments based on CAN informed, disease specific, interventions await further research which should be accelerated and supported by substantial policy recognition and funding. Empathetic attention to CAN associated trauma can be therapeutic in the context of any disease, helping to overcome dysfunctional attitudes and behavior, thus improving compliance with medical therapies. Since mental illness is common in CAN survivors and therapy may be complex and difficult, trauma informed consulting therapists should be identified. All physicians should support social policies that alleviate the family stresses of poverty, homelessness and unemployment as well as the preventive work of child welfare agencies.

Appendix A. Adverse childhood experiences screening instruments

NAME _____
Date of Birth _____ DATE _____

Finding your ACE Score.

While you were growing up, during your first 18 years of life:

- Did a parent or other adult in the household often ...
Swear at you, insult you, put you down, or humiliate you? or.
Act in a way that made you afraid that you might be physically hurt?
Yes or No If Yes enter 1 _____
- Did a parent or other adult in the household often ...
Push, grab, slap, or throw something at you? or.
Ever hit you so hard that you had marks or were injured?
Yes or No If Yes enter 1 _____
- Did an adult or person at least 5 years older than you ever...
Touch or fondle you or have you touch their body in a sexual way?
or.
Try to or actually have oral, anal, or vaginal sex with you?
Yes or No If Yes enter 1 _____
- Did you often feel that ...
No one in your family loved you or thought you were important or special? or.
Your family didn't look out for each other, feel close to each other, or support each other?
Yes or No If Yes enter 1 _____
- Did you often feel that ...
You didn't have enough to eat, had to wear dirty clothes, and had no one to protect you?
Or Your parents were too drunk or high to take care of you or take you to the doctor if you needed it?
Yes or No If Yes enter 1 _____
- Were your parents ever separated or divorced?
Yes or No If Yes enter 1 _____
- Were any of your parents or other adult caregivers:
Often pushed, grabbed, slapped, or had something thrown at them?
or.
Sometimes or often kicked, bitten, hit with a fist, or hit with something hard? or.
Ever repeatedly hit over at least a few minutes or threatened with a gun or knife?
Yes or No If Yes enter 1 _____
- Did you live with anyone who was a problem drinker or alcoholic or who used street drugs?
Yes or No If Yes enter 1 _____

9. Was a household member depressed or mentally ill or did a household member attempt suicide?
Yes or No If Yes enter 1 _____.

10. Did a household member go to prison?
Yes or No If Yes enter 1 _____.

Now add up your "Yes" answers: ____ This is your ACE Score.

Supplemental questions: While you were growing up, during your first 18 years of life:

- Had you ever seen, heard, or been a victim of violence in your neighborhood, community or school? (*for example, targeted bullying, assault or other violent actions, war or terrorism*)
Yes or No If Yes enter 1 _____
 - Had you experienced discrimination? (*for example, being hassled or made to feel inferior or excluded because of their race, ethnicity, gender identity, sexual orientation, religion, learning differences, or disabilities*)
Yes or No If Yes enter 1 _____
 - Had you ever had problems with housing? (*for example, being homeless, not having a stable place to live, moved more than two times in a six-month period, faced eviction or foreclosure, or had to live with multiple families or family members*)
Yes or No If Yes enter 1 _____
 - Had you ever worried that you did not have enough food to eat or that food would run out before you or your parent/caregiver could buy more?
Yes or No If Yes enter 1 _____
 - Had you ever been separated from your parent or caregiver due to foster care, or immigration?
Yes or No If Yes enter 1 _____
 - Had you ever lived with a parent/caregiver who had a serious physical illness or disability?
Yes or No If Yes enter 1 _____
 - Had you ever lived with a parent or caregiver who died?
Yes or No If Yes enter 1 _____
 - Had you ever been detained, arrested or incarcerated?
Yes or No If Yes enter 1 _____
 - Had you ever experienced verbal or physical abuse or threats from a romantic partners? (*for example, a boyfriend or girlfriend*)
Yes or No If Yes enter 1 _____
- Now add up your "Yes" answers: ____ This is your supplemental score.

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