Connections Among Biologic Embedding of Childhood Adversity, Adult Chronic Illness, and Wound Care: A Review of the Literature

Rebecca Bryan, DNP, AGPCNP-BC; and Janice M. Beitz, PhD, RN, CS, CNOR, CWOCN-AP, MAPWCA, ANEF, FNAP, FAAN

ABSTRACT

Adverse childhood experiences (ACEs) biologically embed by altering brain development and influencing epigenetic mechanisms. These experiences may generate health risk factors. PURPOSE: A literature review was conducted to compare ACE-generated health risk factors with risk factors for wound development and aberrant healing, as well as to identify a gap in literature regarding critical connections between ACEs, chronic illness, and wound development/healing, with associated practice implications. METHODOLOGY: A literature search of English-language articles was conducted using the Cumulative Index of Nursing and Allied Health Literature, MEDLINE, and PubMed using the search terms adverse childhood experiences, adults, wounds, chronic disease or illness, and epigenetics. The searches yielded 561 publications regarding ACEs, chronic illness or disease, and adult; 182 for ACEs; and 547 for epigenetics and wounds. Abstracts were reviewed to remove duplicates and studies with participants who were <18 years old. Publications were reviewed for salience; those discussing the biologic plausibility of ACEs contributing to adult illnesses and associated wound development and healing were reviewed for inclusion. RESULTS: Sixty-eight (68) publications were found appropriate for review and included population-based studies; literature reviews; epidemiologic data; meta-analyses; and systematic, cross-sectional, observational, and prospective studies as singular or mixed methods designs. A substantial overlap was found in terms of risk factors generated by ACE exposure and risk factors for wound development/healing, as was a gap in the literature regarding this relationship. Epigenetic mechanisms and altered brain development are implicated in processes through which childhood adversity erodes human health. CONCLUSION: Adult health risks as a result of exposure to ACEs and critical connections with risks for wound development and disrupted wound healing via epigenetic influences are recognized in the literature. Practice implications include considering screening for the risk factor of ACEs exposure in adult patients to identify this additional risk factor and practicing patient-centered, trauma-informed care. Further research into the integrative roles of these factors is warranted.

KEYWORDS: adverse childhood experiences, wounds and injuries, epigenomics, health behavior, chronic disease

INDEX: Wound Management & Prevention 2019;65(10):18–28 doi: 10.25270/wmp.2019.10.1828

POTENTIAL CONFLICTS OF INTEREST: none disclosed

Adverse childhood experiences (ACEs) are defined as "childhood events, varying in severity and often chronic, occurring within a child's family or social environment that cause harm or distress, thereby disrupting the child's physical or psychological health and development."[1] ACEs differ from single types of traumatic experiences in that they capture the cumulative impact of growing up with toxic stress; they are "a better assessment of the breadth of childhood adversity"[2] than focusing on any single type of adversity. A systematic review/meta-analysis[2] has shown health care providers (HCPs) are gaining awareness that exposure to ACEs causes biological changes that persist through adulthood and that ACEs contribute to many of the leading causes of death in the United States along with unhealthy risk behaviors.[3,4] Significant ACEs have been shown in multiple population-based studies[5] to put exposed persons at risk of premature mortality; according to a national survey in the United Kingdom, an ACEs score as determined by the 10-item/point questionnaire (see Figure 1) >6 puts a person at risk of dying 20 years younger than a person with an ACEs score of zero.[5] Globally, the association of childhood trauma with adverse health consequences has been recognized since the early

Dr. Bryan is a trauma-informed training consultant, Rebecca Bryan Consulting LLC, Haddonfield, NJ. Dr. Beitz is a Professor of Nursing, WOCNEP Director, School of Nursing-Camden, Rutgers University, Camden, NJ. Please address correspondence to: Rebecca Bryan, DNP, AGPCNP-BC, 124 W. Summit Avenue, Haddonfield, NJ 08033; email: rhbryan64@gmail.com.

PRIOR TO YOUR 18TH BIRTHDAY:

1. Did a parent or other adult in the household often or very 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?
   No___If Yes, enter 1 __
2. Did a parent or other adult in the household often or very often… Push, grab, slap, or throw something at you? or Ever hit you so hard that you had marks or were injured?
   No___If Yes, enter 1 __
3. 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 Attempt or actually have oral, anal, or vaginal intercourse with you?
   No___If Yes, enter 1 __
4. Did you often or very 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?
   No___If Yes, enter 1 __
5. Did you often or very 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?
   No___If Yes, enter 1 __
6. Were your parents ever separated or divorced?
   No___If Yes, enter 1 __
7. Was your mother or stepmother: Often or very often pushed, grabbed, slapped, or had something thrown at her? or Sometimes, often, or very 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?
   No___If Yes, enter 1 __
8. Did you live with anyone who was a problem drinker or alcoholic, or who used street drugs?
   No___If Yes, enter 1 __
9. Was a household member depressed or mentally ill, or did a household member attempt suicide? No___If Yes, enter 1 __
10. Did a household member go to prison?
    No___If Yes, enter 1 __

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

FIGURE 1. The Adverse Childhood Experiences Survey (from https://acestoohigh.com/got-your-ace-score/).

KEYPOINTS

- Associations between adverse childhood experiences (ACEs) and long-term adverse physical and psychological health consequences have been recognized for many years, and epigenetic processes influence wound and skin repair.
- The authors conducted a literature review to explore potential connections between the health risks associated with ACEs and risk factors for wound development and healing.
- A review of the 68 publications identified showed that higher numbers of ACEs substantially increased the risk for conditions known to affect the risk of wound development and delayed healing, including diabetes, malnutrition, vascular disease, obesity, and substance abuse disorders.
- Although studies to examine the impact of ACEs on wound development and altered healing have not been conducted, existing evidence suggests that trauma-informed care, including ACEs screening, may help elucidate wound care challenges and improve patient care.

1900s, having been examined in both developed and developing countries.[1]

The seminal ACEs study[6] was conducted in the mid-1990s by Kaiser Permanente together with the Centers for Disease Control and Prevention (CDC) in response to a failed weight loss study.[3] Morbidly obese individuals who initially participated successfully in a weight loss program experienced high rates of recidivism, prompting a thorough exploration of the life histories of 286 participants (out of 5000). Sexual abuse was common in this group, as was a childhood with marked household dysfunction. Disordered eating with excessive weight gain was identified as a way to manage the emotions from these experiences.[3] Eventually these discoveries led to a retrospective cohort ACEs study[6] in which more than 17 000 adults (70% Caucasian and college educated) were screened for 10 categories of childhood adversity: physical, emotional, and sexual abuse; physical and emotional neglect; and household dysfunction, including living with someone with mental illness, substance abuse, incarceration, witnessing domestic violence, and losing a parent to separation or divorce (see Figure 2). Each category with a yes response was given 1 point, with a maximum score

TABLE 1. GENETIC TERMINOLOGY[15,72,77]

TERM	DEFINITION/EXPLANATION
CHROMOSOME	Structure consisting of a long strand of DNA containing many genes
DNA METHYLATION	A methyl group (an epigenetic factor found in some dietary resources) can "tag" DNA and activate or repress genes
EPIGENETICS	The study of heritable phenotype (displayed characteristics) (gene expression) changes that do not involve changes in the DNA sequence (genetic code) itself; a biologic mechanism switching genes on and off
GENE	Basic unit of heredity which is transferred from parents to offspring and held to determine some characteristic of the offspring
GENOME	The complete set of genes or genetic material present in a cell or organism. Each genome contains all information needed to build and maintain the organism
HISTONES	Highly alkaline proteins that package and order the DNA into structural units called nucleosomes. They act as spools around which DNA winds and play a role in gene regulation
NUCLEOSOME	A structural unit of a eukaryotic (an organism whose cells contain a nucleus within a membrane) chromosome consisting of a length of DNA coiled around a core of histones (like thread around a spool)
TELOMERE	A compound structure at the ends of chromosomes that functions to keep them from sticking to each other and to project genetic information during cell division

of 10. Responses were correlated with health outcomes and the findings were profound: ACEs were common, with 64% of participants having 1 or more, and also cumulative, in that exposure to 1 ACE increased risk of having more ACEs by 87%.

Dose-response relationships (ie, the magnitude of the response is a function of the dose) between ACEs score and the leading causes of death in the US also have been demonstrated, including ischemic heart disease, cancer, stroke, chronic obstructive lung disease, diabetes, and suicide, as well as dose-response relationships between ACEs score and health risk behaviors such as substance abuse, disordered eating, and physical inactivity. An ACEs score of 4 was identified as the significant threshold for increased risk of both chronic diseases and health risk behaviors.[2,6] In 2009, the CDC began offering an optional ACEs module for the Behavioral Risk Factor Surveillance System (BRFSS), and together with Kaiser Permanente's continued screening, more than 500 000 adults have been screened for ACEs, with results remaining remarkably consistent across the US.[7]

Ongoing population-based research and narrative reviews are recognizing expanded categories of ACEs, such as bullying, witnessing community violence, racism, living in an unsafe neighborhood, and living in foster care.[8,9] According to Levine and Kline,[10] "trauma happens when any experience stuns us like a bolt out of the blue; it overwhelms us, leaving us altered and disconnected from our bodies"[10]; thus, the reality is that almost everyone has had a traumatic experience at some point in their lives. ACEs are being called the noninfectious disease equivalent to the germ theory by leading experts in the field.[9,11]

Improvements in the fields of neuroscience, immunology, and genetics are increasingly demonstrating the biologic plausibility of the relationship between ACEs and adult health outcomes.[2,4,5] A longitudinal, population-focused study[12] of Holocaust survivors and their offspring showed ACEs exposure can impact brain development and genetic expression, imposing changes that persist across the lifespan and can be passed down intergenerationally.

BRAIN DEVELOPMENT: NEUROSCIENCE CONNECTIONS

The brain is composed of neurons that communicate with one another, forming connections based on lived experience. Infants are born with brains wired for survival but with little cortex to interpret or contextualize life experiences; they rely on their parents for nurturing and protection.[9] Exposure to early childhood adversity has been demonstrated in literature reviews[13,14] of available clinical evidence to alter brain development in profound ways by impacting the prefrontal cortex, which is responsible for executive function, attention, and self-regulation; the limbic system, which is responsible for emotions and fight/flight/freeze responses; and global brain volume via reduced size. Early childhood adversity results in fewer receptors to absorb the stress hormone, cortisol, in the brain; when stressed, this inflammatory hormone circulates in the bloodstreams of trauma-impacted individuals for longer periods of time than their nontrauma-impacted counterparts. These changes persist through adulthood, although the brain remains plastic across the lifespan, thus enabling response to continued life experiences.[13,14] Consequently, history is not destiny; positive, healing experiences have the potential to reduce risk from earlier adversity.[9,10]

EPIGENETICS: GENOMIC CONNECTIONS

The human genetic template is comprised of 23 000 genes and has been likened to a computer's hardware.[15] However, the genetic template is responsible for only about 2% of genetic expression.[16] The primary drivers of genetic expression are epigenomes, proteins that interact with the human genome and seem to be the link between genetic expression and the environment.[15,16] Epigenomes have been compared to a computer's software.[15]

Epigenetics is the process by which gene activity is altered without changes

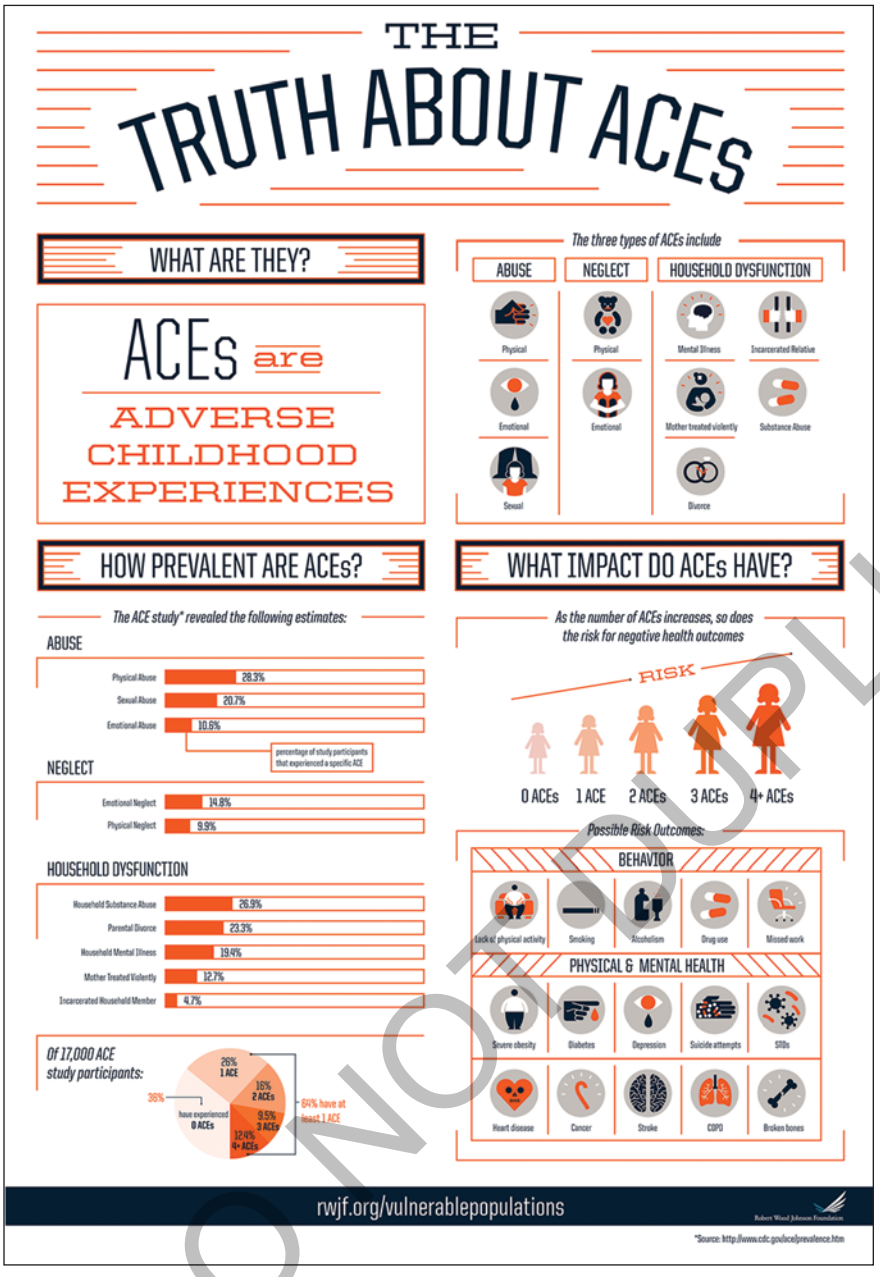

FIGURE 2. Poster for adverse childhood experience awareness. Availableat:https://www.rwjf.org/en/library/infographics/the-truth-about-aces.html. Accessed August 12, 2019.

in the genetic code. Epigenetics plays a role in every aspect of life, from the differentiation of stem cells to the regulation of and metabolism and growth of healthy (or aberrant) cells.[15] In a matched, retrospective cohort study (N = 192), maltreated and control children were shown to have significantly different DNA methylation values at 2868 CpG sites on genes that code for numerous markers of chronic disease that are associated with ACEs, altering genetic expression involved with immune system function, psychiatric and substance abuse disorders, and many cancers.[16] Parental nurturing throughout childhood is a determinant of epigenome activity—that is, the epigenome develops over time based on positive and negative life experiences.[16]

Exposure to childhood adversity also prematurely shortens telomeres, the end caps (like shoelace tips) on chromosomes responsible for protecting genetic material during cell replication. Telomeres naturally shorten as a part of the aging process, contributing to gradual loss of function and eventual cell death. A meta-analysis[17] of 24 studies demonstrated how chronic stress speeds up this process, contributing to premature aging as well as increased risk of cancer.

Perhaps the most stunning of recent discoveries is that epigenetic changes caused by traumatic experiences are passed down intergenerationally. In a matched cohort study[12] of Holocaust survivors and their offspring, an association was demonstrated of preconception trauma with epigenetic alterations, with a greater risk in offspring of traumatized parents for posttraumatic stress disorder and mood and anxiety disorders.

ALLOSTATIC LOAD: WHAT'S IN THE "INVISIBLE BACKPACK"?

The belief that events in childhood affect physical and mental health 30 years later involves the concept of allostatic load, the cumulative biologic burden of elevated inflammatory and metabolic biomarkers in adulthood that has been described as akin to carrying an invisible backpack. Brains wire first and foremost for survival.[14] With exposure to early childhood adversity, the stress response has a lower threshold, leading to a chronically activated hypothalamus-pituitary-adrenal axis. This causes chronically elevated inflammatory markers, changes that persist even when trauma-impacted adults live in safe, stable environments.[18-21] A review[18] of evidence suggesting that early experiences influence interactions between brain and immune system development introduced a model to explain risk of chronic inflammation in adulthood. A multivariate regression study[19] looking at 327 African American women demonstrated that childhood stressors predicted allostatic load.[19] A recent prospective study[21] (N = 837) of a population-representative cohort in New Zealand with nearly 40 years of data demonstrated an

association between ACEs and elevation of a new inflammation marker, soluble urokinase plasminogen activator receptor, a marker more stable and sensitive than the routinely used C-reactive protein. Inflammation underscores multiple chronic conditions including diabetes, cancer, and vascular disease.

Within a patient's invisible backpack are emotions relating to ACEs that have been perceived as too threatening to feel; patients exhibit high-risk health behaviors, including substance abuse, disordered eating, and physical inactivity, as solutions to managing such emotions, even though these behaviors contribute to disease.[3] The quality of relationships, known to lessen stress and improve health, is at risk in ACE-impacted patients because early childhood adversity can cause adults to view the world as threatening.[14] Chronic inflammation, suppressed emotions, and troubled relationships are often the contents inside trauma-impacted adults' invisible backpacks, comprising their allostatic loads.

Disruption of wound healing and chronic wound development, including adverse surgical outcomes, is a multifaceted phenomenon. A recent literature review[22] showed infection, smoking, aging, malnutrition, immobilization, diabetes, vascular disease, immunosuppressive therapy, and obesity are risk factors for wound development; conversely, once these factors (eg, malnutrition, morbid obesity) are in evidence, chronic illnesses in adults exert a profound negative effect on wound healing capacities via epigenetic influences of the disease(s).

The purpose of this literature review was to explore the connections between health risks associated with higher numbers of ACEs and risk factors for wound development and wound healing (see Figure 3). Chronic wound development is viewed through a trauma-informed perspective to help identify the potential root causes of wound risk factors as well as the challenges of comorbidities to wound healing. The role of epigenetics influenced by ACEs as a cause-and-effect consequence of wound development and poorer healing is analyzed.

METHODS AND PROCEDURES

The authors conducted a literature review of 3 databases: the Cumulative Index to Nursing and Allied Health Literature (CINAHL; C), MEDLINE (M), and PubMed (P) for the years 2009 to 2019 of English language articles using the terms adverse childhood experiences, adults, wounds, chronic disease or illness, and epigenetics. Although not specified as a search term, wound healing was a topical output when wounds and epigenetics were combined. Additionally, articles included for review were limited to studies comprising participants of at least 18 years of age (by their definition, ACEs occur before the age of 18). Abstracts were reviewed, and duplicates and articles not pertinent to the topics or with the wrong participant age were removed. Seminal articles outside of year delimitations were used selectively. Articles matching the literature search topical foci were reviewed; narrative reviews were used to inform theoretical constructs of current knowledge. Research studies were reviewed for topical focus, populations studied, critical outcomes and strength of relationships.

Data collection. The literature was reviewed systematically by culling and examining the publications for information and data that support the premise that ACEs exert a negative effect on a number of critical factors that may put a person at risk for compromised health and consequently the development and extended treatment of chronic wounds.

RESULTS

The searches yielded the following number of articles for search term combinations, respectively: ACEs, chronic illness or disease, and adult — C = 67, M = 233, P = 261; ACEs and wounds — C = 28, M = 97, P = 57; epigenetics and wounds — C = 41, M = 337, P = 170. Sixty-eight (68) articles were selected for use and included population-based studies; literature reviews; epidemiologic data; meta-analyses; and systematic, cross-sectional, observational, and prospective studies as singular or mixed methods designs.

ACEs, epigenetics, and wound care: critical connections. A substantive overlap was noted between the risk factors generated by ACEs exposure, both for chronic diseases and health-risk behaviors, and the risk factors for wound development and disrupted healing. Because a higher number of ACEs via epigenetic influences affect gene expression, the development of adult chronic illnesses and factors such as chronic inflammation associated with wound development were shown to be accelerated.[16,20,21] However, epigenetics and life experiences also affect wound healing via influences of comorbidities on cell activities and physiologic regulators.[23]

Wound development. Childhood adversity has a clear association with wound development given the research surrounding epigenetic science and subsequent adult chronic diseases and risky health behaviors that are associated with chronic wounds. Multiple population-based research studies and literature reviews support that persons with higher ACE scores are at greater risk for eating disorders (anorexia nervosa [AN], bulimia),[24,25] cardiovascular disease,[26,27] diabetes mellitus (DM),[28-30] immune disorders,[18,31] obesity,[32] poor cardiometabolic outcomes,[33] high-risk behaviors (heavy drinking, risky sexual behaviors, substance abuse), myocardial infarction, and depression and mood disorders.[34-36] These risk behaviors and chronic diseases associated with higher ACEs scores are the risk factors consistently identified as predecessors to the morbidities associated with chronic wound healing [22,35] (see Figure 2).

Afifi et al[24] used epidemiological data that were nationally representative of adults in the US (N = 36 309) to examine lifetime eating disorders. AN, bulimia, and binge-eating disorders were positively associated with childhood adversity and maltreatment.

The Huffhines et al[29] review (N = 38) on diabetes and ACE was particularly compelling; the studies reviewed demonstrated a dose-response relationship wherein a threshold response (4 or more ACEs) was linked to diabetes development. The authors suggested that diabetologists and other care providers routinely screen for ACEs.

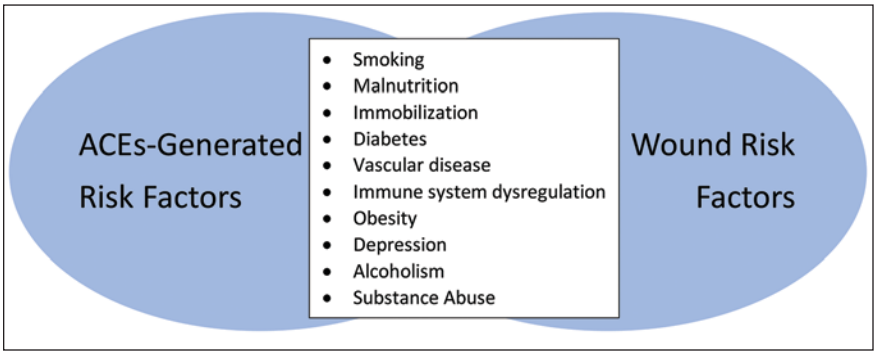

FIGURE 3. Conditions that may result from adverse childhood experiences that, in turn, are risk factors for wounds.[1, 2, 22]

In a population-based, cross-sectional study of nationally representative US adults (N = 34 653), Raposo et al[36] examined ACE association with mood and personality disorders. A higher number of ACEs was significantly correlated (P <.05) with higher rates of these mental health conditions, even after adjusting for covariates.

Notably, relationships between ACE scores above 4 and adult chronic illness and risky behaviors persist whether studies were performed retrospectively or prospectively.[37] Population-based studies[6,38] have shown higher ACEs scores also were associated with obesity and morbid obesity, especially in the presence of childhood sexual and physical abuse.

Higher ACEs scores are evident in more subtle ways as well. In reviewing adult disability in a cross-sectional, state-based, population-based survey (14 states and the District of Columbia), Schüsser-Fiorenza Rose et al[39] used population data from the CDC BRFSS ACEs module for self-reported disability (N = 81 184); adult disability was positively associated with higher ACEs scores. Because >4 ACEs were reported, the odds ratios for adult disability was as high as 5.8 compared to persons with low ACEs scores. In a prospective, longitudinal study conducted among 233 adult patients, Lodhia et al[40] examined surgical weight loss after bariatric surgery. Higher ACEs scores were associated with less weight loss postsurgery and also with higher total and LDL cholesterol levels postsurgery (P <.05).

In a state population health surveillance system (BRFSS) survey conducted annually by the CDC, Chanlongbutra et al[41] examined the relationship between ACEs exposure and chronic disease risks and perceived health-related quality of life in residents of 9 states for the years 2011–2012. The researchers compared the responses of rural and urban dwellers >18 years of age to the CDC's BRFSS (N = 79 810). Approximately 55% of rural respondents reported at least 1 ACE and nearly 15% reported 4 or more ACEs. Controlling for sociodemographic factors, rural respondents with higher ACEs scores reported poorer health, activity limitations, and heart disease. The odds of experiencing a heart attack, DM, asthma, and poorer mental health were significantly higher for persons with 3 or more ACEs (P <.05).

In their retrospective observational study, Crouch et al[42] examined the association between ACEs and smoking-exacerbated illnesses (asthma, diabetes, chronic obstructive pulmonary disease) using 2014–2015 BRFSS data from South Carolina for persons who reported a smoking-exacerbated illness (N = 6321). More than 20% of the respondents had 4 or more ACEs, and persons with this higher score were significantly more likely to smoke even in the presence of smoking-exacerbated illnesses. Researchers suggest that ACEs exposure increases risky behavior, with smoking serving as a coping mechanism and pursued despite awareness of negative health consequences.

TABLE 2. WOUND RISK FACTORS[22,78]
Aging
Alcoholism
Chemotherapy
Diabetes
Depression
Immobility
Immune suppression
Infection
Malnutrition
Medications (steroids, etc.)
Obesity/morbid obesity
Radiation therapy
Sickle cell disease
Smoking
Substance abuse
Vascular disease

Epigenetics science consistently and persistently supports that higher ACEs scores are associated with chronic illness development and increased risk factors for wounds. Epigenetic influences manifest in interesting ways. Using a large, genealogical population database of >2 million of Utah's founders and their descendants, Lee et al[43] conducted a study where family genealogical information was readily available and analyzed susceptibility to surgical site infections (SSIs). When SSIs among 651 persons and their relatives were examined, an excessive relative risk (RR) for third-degree relatives was noted (RR = 1.62; P = .029). The researchers also noted a possible epigenetic influence (in addition to genetic connections) via environmental factors.

Wound healing. Multiple literature sources support that epigenetic processes influence wound/skin repair. In a literature review, Lewis et al[44] described how epigenetic regulators dynamically influence keratinocyte proliferation, differentiation, and migration, thereby affecting dermal regeneration. These regulators also alter neoangiogenesis and the development of healing catalytic blood supply. In describing the development of liver fibrosis as a pathological disease

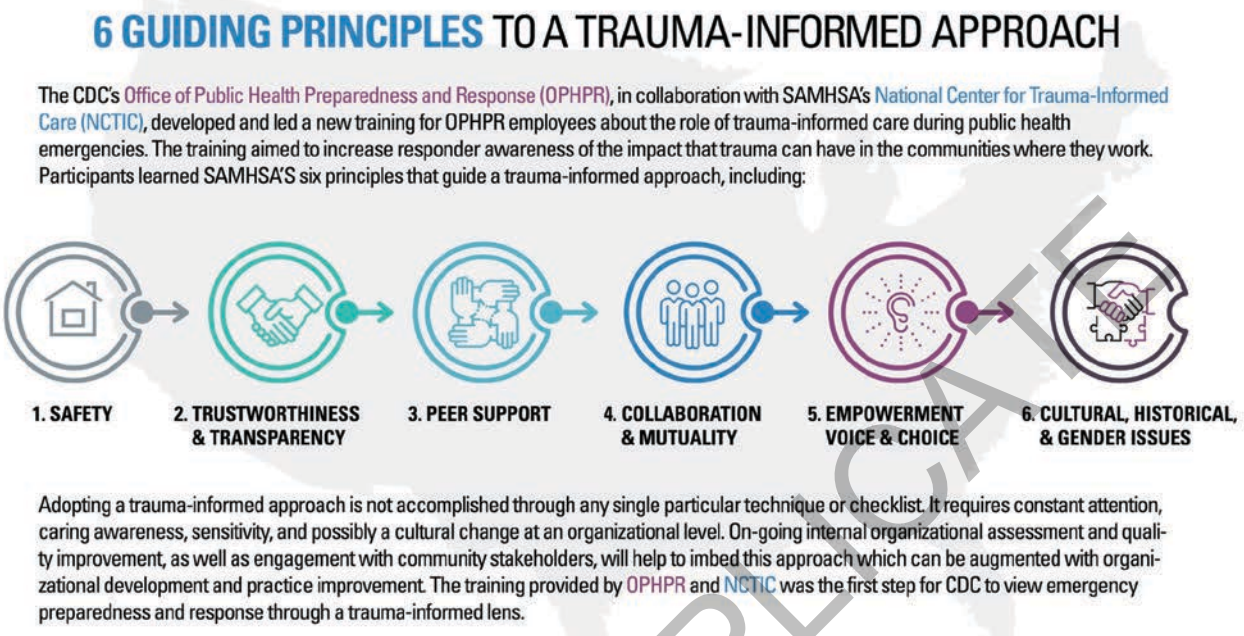

FIGURE 4. Principles for trauma-informed care. Available at: https://www.cdc.gov/cpr/infographics/00_docs/TRAINING_EMERGENCY_RESPONDERS_FINAL.pdf. Accessed August 11, 2019.

process, Mann and Mann[45] used data in the literature to note the impact of 3 epigenetic processes (DNA methylation, histone protein modification, and regulatory noncoding RNAs [micro RNAs]), on fibroblasts and myofibroblasts, subsequently affecting wound contraction, wound healing, and fibrotic disorders (eg, cirrhosis). A fascinating footnote to their discussion was their description of the influence of epigenetic traits on downstream fibrosis processes; these traits may be inherited from generation to generation to support adaptive responses in offspring in danger of similar insults.[45] The literature supports the role of epigenetics in "overhealing" fibrotic wounds.[46] Multiple literature reviews[47,48] support the transgenerational influence of environment on wound healing; this linkage of exposure to childhood trauma[49,50] to subsequent adult pathology in following generations is mediated through altered inflammatory processes.[21,51]

Using theoretical and clinical evidence reviews, the literature consistently supports that epigenetic processes via comorbidities influence "torpid" wound healing in the presence of chronic disease such as DM type 2 (DM2).[52-54] Epigenetic changes in bone marrow progenitor cells influence subsequent inflammatory phenotypes and affect wound healing. A classic example is the influence of DM2 on macrophages, where DM2 affects macrophage activity with altered inflammatory "clean-up" of wounds[55] and a persistent proinflammatory phenotype, creating a pattern of unrestrained inflammation characteristic of nonhealing wounds.

DISCUSSION

Although more scientific study, particularly more prospective studies, is required for richer understanding, research to date on hundreds of thousands of Americans supports that ACEs are associated with the development of adult risk behaviors and subsequent chronic illnesses via epigenetic processes. Once acquired, chronic diseases and ongoing unhealthy lifestyle behaviors affect wound healing processes via epigenetic influences on physiology. An argument for causality is emerging.[3]

Facing a tsunami of chronic illness and associated chronic wounds, wound care practitioners would benefit by thinking like epidemiologists — that is, upstream risk factor identification. An estimated 3.5 million children in the US were noted as being abused or neglected, with 676 000 reported victims in 2016.[7] One in 4 children will experience some form of childhood maltreatment in their lifetime.[35] Some authors suggest it should be considered a public health crisis.[9,56] Translating this situation to current chronic wound patients and chronic illness incidence and prevalence suggests a potential link between ACEs and the substantive increase in chronic illness in adults (including younger adults) while national health statistics show US life expectancy is decreasing.[57]

Whether to perform ACEs screening is subject to debate. Echoing classic epidemiological perspectives, a narrative review by Finkelhor[58] suggests ACEs screening should not be done because evidence-based interventions and responses have not been clearly established. In a public health report, Dube[59] conversely supports that ACE screening helps clinicians become empowered by knowing patients' experiences from their perspective as a means of optimizing patient-centered care. When practitioners shift from an etic (perspective of the observer) to an emic (perspective from the patient's point of view) approach to patient care, knowledge becomes powerful because it informs medical practice.[59] Screening feasibility in the outpatient setting has been repeatedly demonstrated in controlled mixed methods clinical studies.[60,61] The narrative review by Mitchell et al[49] supports intervention in early life experiences-related outcomes by noting the well-accepted use of folic acid to prevent neural tube disorders by altering maternal DNA methylation.

Two literature reviews have shown that wound care clinicians can help their patients by acknowledging and learning more about the science of epigenetics and the biologic embedding of social adversity[62] and by understanding that patients' bodies "keep score" related to trauma.[63] Practitioners can become informed about measurement of epigenetic influences through available ACEs instruments[1,7,64] and potentially include them in clinical assessments. A literature review[65] demonstrated the nascent science of epigenetics and the influences on body physiology can be understood as the consequence of epigenetic activity resulting from childhood adversity as a form of "molecular scarring," with DNA methylation acting as a "light dimmer switch," up- or down-regulating gene activity. Wound practitioners can benefit by understanding this new frontier of psychoneuroimmunology[18] undergirding the link between ACEs and adult chronic illnesses. To wit: the federal government has recognized the link; the BRFSS has a module on ACEs.[7,39]

Practical application of epigenetics and ACEs. More pragmatically, quality wound care can benefit from incorporating epigenetics science. Clinicians need to solicit a comprehensive patient history. This includes asking adults about childhood adversity, especially sexual and physical abuse. Editorial descriptions, and retrospective and prospective population studies[6,16,66,67] suggest that asking about ACEs is not traumatic but actually beneficial for patients. Clinicians need to consider wound risk factors inherent in wound care patients and seek the science behind ACEs and risk factors (see Table 2). Epigenetics-related publications suggest adult chronic diseases such as depression, DM, coronary artery disease, cancer, and stroke and even suicide may be derived from earlier life events. ACEs contribute to 7 out of 10 leading causes of death in the US,[1,2,7] the same disorders commonly associated with wounds. Most importantly, clinicians need to be alert to the impact of patient history on physical findings.

Wound care providers can implement improved care not only by asking "What's wrong with you?" (ie, what is the patient's chief complaint) but by also asking "What happened to you?"[68] thus shifting to the emic paradigm of trauma-informed care. If patients screen positive for ACEs exposure, they need to be acknowledged by saying "I see you said yes to this (ACEs) question. How has it affected you in later life?"[67] The ACE literature repeatedly supports active listening as an intervention.[3,6,62,66,67] The Substance Abuse and Mental Health Services Administration (SAMHSA) published SAMHSA's Concept of Trauma and Guidance for a Trauma-Informed Approach in 2014, putting forth a framework suitable across health and social sectors, with 6 guiding principles of trauma-informed care: safety; trustworthiness and transparency; peer support; collaboration and mutuality; empowerment; voice and choice; and cultural, historical, and gender issues[69] (see Figure 4).

Strengths-based resilience building may be a goal in managing chronic wound patients with a history of ACEs; after asking "What happened to you?"

assessing resilience through asking "What got you through it?" can be helpful, as experienced in the authors' clinical patient interactions.[70] Modalities including mindfulness, bodywork therapies including yoga and massage, and expressive therapies (ie, art, theater, and music) facilitate healing.[63] Referrals can include referral to a clinical psychologist and support groups and bibliotherapy (reading helpful informative literature). An extensive body of science is available on ACEs, and research on epigenetics, stress, and downstream effects is emerging. In their review of current clinical evidence, D'Addario et al[71] discussed the possibility of epigenetic therapy as the science improves. One literature review ponders the possibilities of new genetic targets in wound healing promotion.[72]

Wound care clinicians have a golden opportunity to learn about the emerging science of epigenetics in journals such as Epigenomics, Epigenetics, Physiology and Behavior, and Neuropsychopharmacology. More literature is addressing critical connections among life experiences, genetic impact, and epigenetic repercussions. The science of genetics, genomics, and epigenetics can appear intimidating to learn (and it is hard), but metaphors can assist with understanding. The research covered in this literature review spoke of DNA methylation likened to a "dimmer switch" up- or downregulating genes[73]; DNA methylation also acts as a chemical "tag" on the DNA affecting its expression[5]; child abuse leaves "molecular scars" via epigenetic processes[65,74]; telomeres act like the plastic tips of shoelaces preventing unraveling of genes[17]; and methyl groups added to the "elevator doors" of histones act like umbrellas sticking out of them, altering cell function.[74]

LIMITATIONS

The limitations of an epidemiological, population-based study design have been noted for decades.[75,76] Observational, nonintervention studies cannot prove causality. However, tens of thousands of ACEs-affected persons are demonstrating a visible trend of causal relationship to subsequent morbidity and mortality to the extent that ACEs are formally recognized by the CDC, the World Health Organization, and the American Heart Association as being worthy of study. The examples of past observational studies on diet and cancer risk and the effect of horrific radiation exposure in Hiroshima and Nagasaki blast survivors on subsequent cancer development show that eventual causal relationships emerge.[75]

The science of epigenetics requires major development both in disease causation and illness prevention. Epigenetic processes in wound development via the relationship of risk factors to wounding also need further scrutiny. The science of how epigenetic processes may be harnessed to promote wound healing is in its infancy and provides an exciting future opportunity.

Contemporary health care providers' understanding of genetics/genomics and epigenetics processes is expanding as the science continues to emerge. The clinical applications of this science provide an interesting focus for future research. The effect of environment and life experiences on patient physiology and psychology is an area where knowledge about the full dimensions of impact are limited.

Future research needs to investigate how best to utilize ACEs screening into modern wound and health care to enable HCPs to identify another risk factor for wound development and potential for disrupted healing. Research also is needed on how best to integrate principles of trauma-informed care into practice, which benefits patients regardless of ACEs score and can guide more effective treatment.[70] Science about efficient, effective use of ACEs is still emerging. Acknowledging that patients' lived experiences influence their care today provides a way of "getting to the why"[70] the comorbidities and wound occurred.

CONCLUSION

This review of the relevant literature described the adult health risks incurred from exposure to ACEs and critical connections with risks for wound development and disrupted wound healing via epigenetic influences. Overlap was noted between ACEs-generated health risks for chronic disease and risky behaviors with risks for wound development and altered healing, recognizing the limitations of epidemiologic research. Trauma-informed care, including screening for ACEs by wound care providers, seems an important consideration for patient-centered, evidence-based practice. ■

REFERENCES

1. Kalmakis KA, Chandler GE. Adverse childhood experiences: toward a clear conceptual meaning. J Adv Nurs. 2014;70(7):1489–1501.
2. Hughes K, Bellis MA, Hardcastle KA, et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. Lancet Public Health. 2017;2(8):e356–366.
3. Felitti VJ, Jakstis K, Pepper V, Ray A. Obesity: problem, solution, or both? Perm J. 2010;14(1):24–30. doi: 10.7812/TPP/09-107.
4. Anda RF, Felitti VJ, Bremner JD, et al. The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. Eur Arch Psychiatry Clin Neurosci. 2006;2561(3):174–186.
5. 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. J Public Health. 2015;37(3):445–454.
6. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of child abuse and household dysfunction to many of the leading causes of death in adults. Am J Prev Med. 1998;14(4):245–258.
7. Centers for Disease Control and Prevention. Adverse childhood experiences. Available at: www.cdc.gov/violenceprevention/childabuseandneglect/acestudy/. Accessed July 24, 2019.
8. Cronholm PF, Forke CM, Wade R, et al. Adverse childhood experiences: expanding the concept of diversity. Am J Prev Med. 2015;49(3):354–361.
9. Harris NB. The Deepest Well: Healing the Long-Term Effects of Childhood Adversity. New York, NY: Houghton Mifflin Harcourt;2018.
10. Levine PA, Kline M. Trauma Through a Child's Eyes. Awakening the Ordinary Miracle of Healing. Berkeley, CA: North Atlantic Books;2007.
11. Blanch AK, Shern DL. Implementing The New "Germ" Theory For The Public Health's Action: A Call to Action. Alexandria, VA: Mental Health America; 2011. Available at: www.theannainstitute.org/Andrea%20Blanch%20TIWA/ImplementingGermTheoryforPublicHealth.pdf. Accessed July 24, 2019.
12. Yehuda R, Daskalakis NP, Bierer LM, et al. Holocaust exposure induced intergenera-

tional effects on FKBP5 methylation. Biol Psychiatr. 2016;80(5):372–380.
13. Bick J, Nelson CA. Early adverse experiences and the developing brain. Neuropsychopharmacology. 2016;41(1):177–196.
14. Cozolino L. The Neuroscience of Human Relationships: Attachment and the Developing Social Brain. 2nd ed. New York, NY: W. W. Norton & Company;2014.
15. National Scientific Council on the Developing Child. Early Experiences Can Alter Gene Expression and Affect Long-Term Development. Cambridge, MA: Center on the Developing Child at Harvard University; 2010. Working Paper No. 10. Available at: www.developingchild.net. Accessed July 25, 2019.
16. Yang B, Zhang H, Ge W, et al. Child abuse and epigenetic mechanisms of disease risk. Am J Prev Med. 2013;44(2):101–107.
17. Li Z, He Y, Wang D, Tang J, Chen X. Association between childhood trauma and accelerated telomere erosion in adulthood: a meta-analytic study. J Psychiatr Res. 2017;93:64–71.
18. Danese A, Lewis SJ. Psychoneuroimmunology of early-life stress: the hidden wounds of childhood trauma. Neuropsychopharmacology. 2017;42(1):99–114.
19. Berg MT, Simons RL, Barr A, Beach, SR, Philibert RA. Childhood/adolescent stressors and allostatic load in adulthood: support for a calibration model. Soc Sci Med. 2017;193(11):130–139.
20. Danese A, McEwen BS. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. Physiol Behavior. 2012;106(1):29–39.
21. Rasmussen LJH, Moffit TE, Eugen-Olsen J, et al. Cumulative childhood risk is associated with a new measure of chronic inflammation in adulthood. J Child Psychol Psychiatr. 2019;60(2):199–208.
22. Armstrong DG, Meyr AJ. Risk factors for impaired wound healing and wound complications. UpToDate. 2019. Available at: www.uptodate.com. Accessed July 25, 2019.
23. Ti D, Li M, Fu X, Han W. Causes and consequences of epigenetic regulation in wound healing. Wound Repair Regen. 2014;22(3):305–312.
24. Afifi TO, Sareen J, Fortier J, et al. Childhood maltreatment and eating disorders in men and women in adulthood: results from a nationally representative United States sample. Int J Eat Disord. 2017;50(11):1281–1296.
25. Bakalar JL, Barmine M, Druskin L, et al. Childhood adverse life events, disordered eating, and body mass index in US Military service members. Int J Eat Disord. 2018;51(5):465-469.
26. Logan JG, Barksdale DJ. Allostasis and allostatic load: expanding the discourse on stress and cardiovascular disease. J Clin Nurs. 2018;17(7B):201–208.
27. Su S, Jimenez MP, Roberts CT, Loucks E. The role of adverse childhood experiences in cardiovascular disease risk: a review with emphasis on plausible mechanisms. Current Cardiol Reports. 2015;88(17):10.
28. Huang H, Yan P, Shan Z, et al. Adverse childhood experiences and risk of type 2 diabetes: a systematic review and meta-analysis. Metabolism. 2015;64(11):1408–1418.
29. Huffhines L, Noser A, Patton SR. The link between adverse childhood experiences and diabetes. Curr Diabetes Reports. 2016;16(56):54–62.
30. Lynch L, Waite R, Davey MP. Adverse childhood experiences and diabetes in adulthood: support for a collaborative approach to primary care. Contemp Fam Ther. 2013;35(4):639–655.
31. Dube SR, Fairweather D, Pearson WS, Felitti VJ, Anda RF, Croft JB. Cumulative childhood stress and autoimmune diseases in adults. Psychosomat Med. 2009;71(2):243–250.
32. Danese A, Tan M. Childhood maltreatment and obesity: systematic review and meta-analysis. Molecular Psychiatr. 2014;19(5):544–554.
33. Suglia SF, Koenen KC, Boynton-Jarrett R, et al; American Heart Association Council on Epidemiology and Prevention; Council on Functional Genomics and Translational Biology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research. Childhood and adolescent adversity and cardiometabolic outcomes: a scientific statement from the American Heart Association. Circulation. 2018;137(5):e15–e28.
34. Allem JP, Soto DW, Baezconde-Garbanati L, Unger JB. Adverse childhood experiences and substance abuse among Hispanic emerging adults in southern California. Addict Behav. 2015;11(50):199–204.
35. Campbell JA, Walker RJ, Egede LE. Associations between adverse childhood experiences, high-risk behaviors, and morbidity in adulthood. Am J Prevent Med. 2016;50(3):344–352.
36. Raposo SM, Mackenzie CS, Henriksen CA, Afifi TO. Time does not heal all wounds: Older adults who experienced childhood adversities have higher odds of mood, anxiety, and personality disorders. Am J Geriatr Psychiatry. 2014;22(11):1241–1250.
37. Reuben A, Moffitt TE, Caspi A, et al. Lest we forget: comparing retrospective and prospective assessments of adverse childhood experiences in the prediction of adult health. J Child Psychol Psychiatry. 2016;57(10):1103–1112.
38. Sexual abuse as a child changes the body's biochemical response to stress. Medicalxpress. 2018. Available at: https://medicalxpress.com/news/2018-10-sexual-abuse-child body-biochemical.html. Accessed October

10, 2018.
39. Schüssler-Fiorenza Rose SM, Xie D, Stineman M. Adverse childhood experiences and disability in U.S. adults. Phys Med Rehabil. 2014;6(8):670–680.
40. Lodhia NA, Rosas US, Moore M, et al. Do adverse childhood experiences affect surgical weight loss outcomes? J Gastrointestinal Surg. 2015;19(6):993–998.
41. 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. J Environ Public Health. 2018;2018:7151297.doi: 10.1155/2018/7151297.
42. Crouch E, Radcliff E, Strompolis M, Wilson A. Examining the association between adverse childhood experiences and smoking-exacerbated illnesses. Public Health. 2018;157:62–68.
43. Lee JP, Hopf HW, Cannon-Albright LA. Empiric evidence for a genetic contribution to predisposition to surgical site infection. Wound Repair Regen. 2013;21(2): 211–215.
44. Lewis CJ, Mardaryeu AN, Sharov AA, Fessing MY, Botchkarev VA. The epigenetic regulation of wound healing. Adv Wound Care. 2014;3(7):468–475.
45. Mann J, Mann DA. Epigenetic regulation of wound healing and fibrosis. Curr Opin Rheumatol. 2013;25(1):101–107.
46. Neary R, Watson CJ, Baugh JA. Epigenetics and the overhealing wound: the role of DNA methylation in fibrosis. Fibrogenesis Tissue Repair. 2015;818.
47. Chernomas R, Hudson I, Chernomas G. Can neoliberal capitalism affect human evolution? Int J Health Serv. 2018;48(1):166–188.
48. Miller GE, Chen E, Parker K J. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychol Bull. 2011;137(6):959–997.
49. Mitchell C, Schneper LM, Notterman DA. DNA methylation, early life environment, and health outcomes. Pediatr Res. 2016;79(1):212–219.
50. Monnat SM, Chandler RF. Long term physical health consequences of adverse childhood experiences. Sociol Q. 2015;56(4):723–752.
51. Danese A, Baldwin JR. Hidden wounds? Inflammatory links between childhood trauma and psychophathology. Ann Rev Psychol. 2017;68(1):517–544.
52. Berlanga-Acosta J, Mendoza-Mari Y, Fernández-Mayola M, et al. Torpid diabetic wound healing: evidence on role of epigenetic forces. Int J Diabetes Clin Res. 2015;2(1)1–4.
53. Jhamb S, Vangaveti VN, Malabu UH. Genetic and molecular basis of diabetic foot ulcers: clinical review. J Tissue Viability. 2016;25(4):229–236.
54. Rahefi H, El-Osta A, Karagiannis TC. Genetic and epigenetic events in diabetic wound healing. Int Wound J. 2011;8(1):12–21.
55. Gallagher KA, Joshi A, Carson W, et al. Epigenetic changes in bone marrow progenitor cells influence the inflammatory phenotype and alter wound healing in type 2 diabetes. Diabetes.2015;64(4):1420–1430.doi:10.2337/DB14-0872.
56. Blakemore E. Should childhood trauma be treated as a public health crisis? NPR. 2018. Available at: www.npr.org/sections/health-shots/2018/11/09/66143092/should-childhood-trauma-be-treated-as-a-public-health-crisis?utm_source=facebook.com&utm-medium=social&utm_campaign=npr&utm_terms=nprnens&utm_content=202909. Accessed November 9, 2018.
57. Kochanek K, Murphy SL, Xu J, Arias E. Mortality in the United States. Hyattsville, MD: National Center for Health Statistics; 2017. NCHS Data Brief No. 293.
58. Finkelhor D. Screening for adverse childhood experiences (ACEs): cautions and suggestions. Child Abuse Negl. 2018;85:174–179.
59. Dube SR. Continuing conversations about adverse childhood experiences (ACEs) screening: a public health perspective. Child Abuse Negl. 2018;85:180–184.
60. Goldstein E, Athale N, Sciolia AF, Catz SL. Patient preferences for discussing childhood trauma in primary care. Perm J. 2017;21:16-055. doi: 10.7812.TPP/16-055.
61. Kalmakis KA, Chandler GE, Roberts SJ, Leung K. Nurse practitioner screening for childhood adversity among adult primary care patients: a mixed method study. J Am Assoc Nurse Pract. 2017;29(1):35–45.
62. Cunliffe V. The epigenetic impacts of social stress: how does social adversity become biologically embedded? Epigenomics. 2016;8(12):1653–1669.
63. Van Der Kolk B. The Body Keeps the Score: Brain, Mind, and Body in the Healing of Trauma. New York, NY: Penguin Publishing Co;2015.
64. World Health Organization. Adverse Childhood Experiences International Questionnaire. Available at: www.who.int. Accessed January 5, 2018.
65. Child Abuse Could Leave "Molecular Scars" on its Victims. MedicalXpress. 2018. Available at: https://m.medicalxpress.com/news/2018-10-child-abuse-molecular-scars-victims.html. Accessed October 2, 2018.
66. Edwards VJ, Dube SR, Felitti, VJ, Anda RF. It's ok to askaboutpastabuse.AmPsychol.2007;62(4):327–328. doi: 10.1037/0003.066X62.4.327.
67. Felitti VJ. How we integrated ACE screening into the health appraisal center at Kaiser Permanente in San Diego. October 28, 2012. Available at:www.acesconnection.com/blog/how-we-integrated-ace-screening-into-the-health-appraisal-center-at-kaiser-permanente-in-san-diego. Accessed July 20, 2019.
68. Bloom S L. The sanctuary model: developing generic inpatient programs for the treatment of psychological trauma. In: Williams MB, Sommer JF (eds). Handbook of Post-Traumatic Therapy: A Practical Guide to Intervention, Treatment and Research. Portsmouth, NH: Greenwood Publishing;1994:474–491.
69. Substance Abuse and Mental Health Services Administration. SAMHSA's Concept of Trauma and Guidance for a Trauma-Informed Approach. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2014. HHS Publication No. (SMA) 14-4884.
70. Bryan R. Getting to why: adverse childhood experiences' impact on adult health. J Nurs Pract. 2019;15(2):153–157.
71. D'Addario C, DiFrencesco A, Pucci M, Finazzi Agró A, Maccarrone M. Epigenetic mechanisms and endocannabinoid signaling. FEBS J. 2013;280(9): 1905–1917. doi: 10.1111/febs.12125.
72. Palmieri B, Vadalà M, Laurino C. Review of molecular mechanisms in wound healing: new therapeutic targets? J Wound Care. 2017;26(12):765–775.
73. Lazar M. Dimmer switch for regulating cells read of DNA code. 2013. Available at: www.sciencedaily.com/releases/2013/01/13010915118.htm. Accessed January 14, 2019.
74. Hurley D. Grandma's experiences leave a mark on your genes. 2013. Available at: http://discovermagazine.com/2013/may/13-grandmas-experiences-leave-epigenetic-mark-on-your-genes. Accessed January 19, 2019.
75. Colditz G. Overview of the epidemiology methods and applications: strengths and limitations of observational study designs. Crit Rev Food Sci Nutri. 2010;(suppl 1):10–12.
76. Lilienfeld AM. Practical limitations of epidemiologic methods. Environment Health Perspect. 1983;52:3–8.
77. National Institutes of Health. National Human Genome Research Institute. Talking glossary of genetic terms. 2019. Available at: www.genome.gov/glossary. Accessed January 16, 2019.
78. Beitz J. Pharmacologic impact (AKA "Breaking Bad") of medications on wound healing and wound development: a literature-based overview. Ostomy Wound Manage. 2017:63(3):18–35.