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REVIEW ARTICLE

The social ecology of childhood and early life adversity

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An increasing prevalence of early childhood adversity has reached epidemic proportions, creating a public health crisis. Rather than focusing only on adverse childhood experiences (ACEs) as the main lens for understanding early childhood experiences, detailed assessments of a child's social ecology are required to assess "early life adversity." These should also include the role of positive experiences, social relationships, and resilience-promoting factors. Comprehensive assessments of a child's physical and social ecology not only require parent/caregiver surveys and clinical observations, but also include measurements of the child's physiology using biomarkers. We identify cortisol as a stress biomarker and posit that hair cortisol concentrations represent a summative and chronological record of children's exposure to adverse experiences and other contextual stressors. Future research should use a social–ecological approach to investigate the robust interactions among adverse conditions, protective factors, genetic and epigenetic influences, environmental exposures, and social policy, within the context of a child's developmental stages. These contribute to their physical health, psychiatric conditions, cognitive/executive, social, and psychological functions, lifestyle choices, and socioeconomic outcomes. Such studies must inform preventive measures, therapeutic interventions, advocacy efforts, social policy changes, and public awareness campaigns to address early life adversities and their enduring effects on human potential.

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IMPACT:

- Current research does not support the practice of using ACEs as the main lens for understanding early childhood experiences.
- The social ecology of early childhood provides a contextual framework for evaluating the long-term health consequences of early life adversity.
- Comprehensive assessments reinforced with physiological measures and/or selected biomarkers, such as hair cortisol concentrations to assess early life stress, may provide critical insights into the relationships between early adversity, stress axis regulation, and subsequent health outcomes.

The social ecology of childhood includes positive and negative experiences, providing children with a socio-biological framework to meet age-specific developmental goals. Disruptions in this ecology, including frequent low-grade stressors (insecurity, inattention), marked variability (life changes), and trauma (abuse/neglect), can have deleterious effects on children's health and wellbeing *that may continue into adulthood*.[1,2] Researchers studying the lifelong effects of a child's social ecology have focused primarily on major adverse events. Metrics like the adverse childhood experiences (ACEs) questionnaire are administered in public health efforts to evaluate, understand, and prevent the health outcomes associated with childhood trauma.[3,4] Beyond the ACEs, however, preventable sources of early life stress (ELS) may include food and housing insecurity, bullying, discrimination, inattentive parenting, or family separations. Clinicians do not routinely screen for trauma or the child's social ecology, partly due to the lack of validated, objective metrics that can be assessed longitudinally.

We review the current discourse on the social ecology of early childhood in relation to the child, adolescent, and adult health outcomes, summarize previous social ecology theories, and compare quantitative metrics. We argue that the practice of using ACEs as a method for understanding early life experiences paints a two-dimensional picture of the many interacting factors that comprise a growing child's multi-dimensional environment. We review the underlying physiology of neuroendocrine stress responses and further contend that biomarkers, such as hair cortisol concentrations (HCCs), may provide critical insights into the relations among early adversity, stress, hypothalamic-pituitary-adrenal (HPA)-axis regulation, and subsequent health outcomes.

SOCIAL ECOLOGY OF CHILDHOOD: A HISTORICAL PERSPECTIVE

French philosopher Jean-Jacques Rousseau (1712–1778) first proposed that early childhood experiences establish adult behaviors. Lev Vygotsky (1896–1934) from Moscow proposed the role of social and cultural factors in his theory of speech development, described in his book *Thought and Language* (1934).

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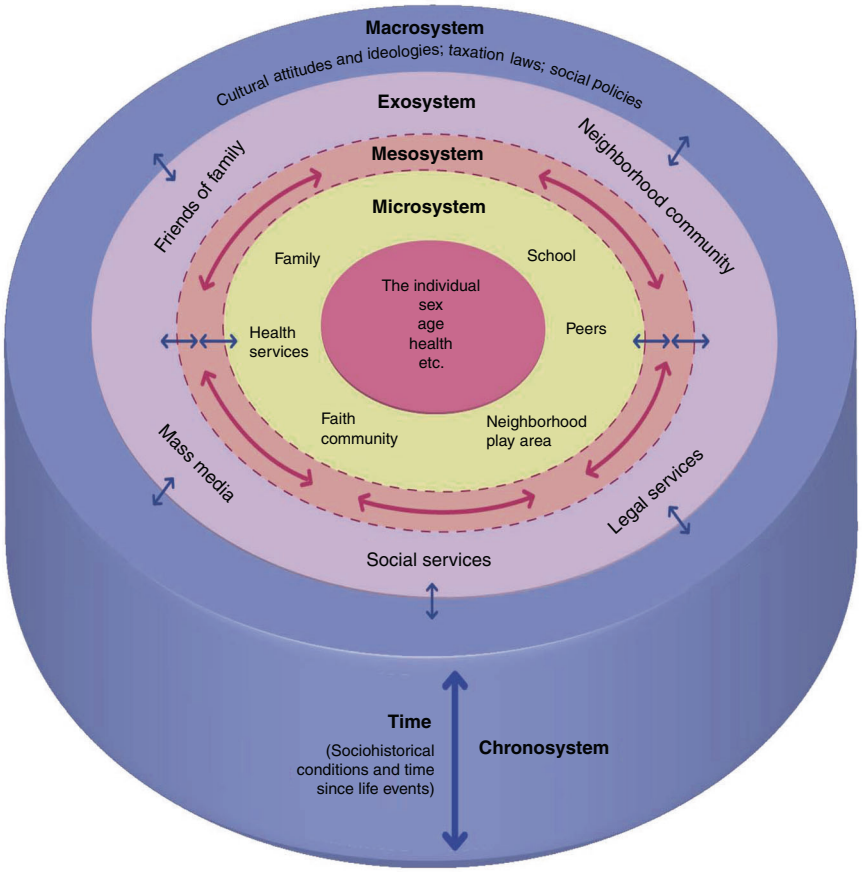

Fig. 1 Bronfenbrenner's Ecological Systems Theory of Human Development. Bronfenbrenner's Ecological Systems Theory presented a breakthrough model for theorizing how the complex, hierarchically organized systems in societies can interact with a child's life, with a rich interplay between systems leading to the variable or opposing effects on early life adversity (ELA).

This work influenced many, including Jean Piaget (1896–1980), to propose theories of cognitive development in early childhood. Thomas and Znaniecki established a life-course perspective through their longitudinal studies (1918–1920) of Polish peasants in Europe and America.[5] Across the twentieth century,[6–10] early childhood experiences were associated with cognitive, behavioral, social, and psychological outcomes, including the influences of family size and socioeconomic status,[9] kindergarten enrollment,[10,11] and social class.[8]

These factors were integrated into the Ecological Systems Theory by Urie Bronfenbrenner (1979), a Russian-American psychologist. Bronfenbrenner conceptualized that human development is shaped by complex relationships between individuals and their environments.[12] He argued that contemporary understanding of human development had failed to consider interactive, layered systems within a child's environment.[13] These limitations led him to develop the Ecological Systems model.

Bronfenbrenner's model depicts four systems—the microsystem, mesosystem, exosystem, and macrosystem—embedded in a chronosystem representing the era in which an individual grows up (Fig. 1). The *microsystem* comprises interactions, roles, and relationships within the home, child-care centers, or playgrounds.[12] The interplay among different microsystems is the *mesosystem*.[12] The *exosystem* consists of extrinsic environments that affect the child indirectly (where the child is not an active participant), like the parents' work environments, sibling's school, or local government.[12] Lastly, the *macrosystem* encompasses greater societal characteristics, such as norms, customs, beliefs, and political structures. Bronfenbrenner's model serves as a useful tool for exploring, categorizing, and interpreting different facets of children's environments and experiences. It identifies a plethora of micro- and macro-level characteristics and encourages us to consider factors that impact a child's life outside their insular family unit. This model presented a major breakthrough in theorizing the complicated structures of societies, and allowed us to organize complex, hierarchical systems within a Person, Process, Context, and Time framework[14] to address issues at the core of programs and policies targeting children at the family and community level.

Other conceptual models have since been developed to assess the relationship between children's broader social contexts and their health. In his 1992 book, *The Strategies of Preventive Medicine*, Geoffrey Rose stated that "the primary determinants of disease are mainly economic and social, and therefore its remedies must also be economic and social."[15] His colleagues, Michael Marmot and Richard Wilkinson, as part of a World Health Organization initiative, expanded on his work to identify the social and economic characteristics that significantly influenced individuals' wellbeing and life expectancy, and referred to these as the Social Determinants of Health.[16] They focused on poverty, drug addiction, working conditions, unemployment status, access to food, social support, and transportation infrastructure. Other determinants identified since then include social organization, race/ethnicity, gender, immigrant status, neighborhood, and housing characteristics.[16]

The Life Course Theory emphasizes the timing and temporal context of lived experiences and how they can impact an individuals' development and wellbeing.[5] In response to the notion that "changing lives alter developmental trajectories,"[5] Glen H. Elder proposed the four principles of Life Course Theory in

1998 as: (1) "the life course of individuals is embedded in and shaped by historical times and places they experience over their lifetime"; (2) "the developmental impact of a succession of life transitions or events"; (3) "lives are lived independently, and social and historical influences are expressed through this network of shared relationships"; and (4) "individuals construct their own life course through the choices and actions they take within the opportunities and constraints of history and social circumstances."[5]

Epidemiologist Nancy Krieger proposed the concept of "embodiment" in 2005, which she defined as "referring to how we literally incorporate biologically, the material and social world in which we live, from conception to death," arguing that human biology could not be understood without "knowledge of history and individual and societal ways of living."[17] Through this lens, human interactions "become" human biology. Anthropologist Clarence Gravlee applied this concept to explain how and why racialized experiences and social constructs can negatively impact the health of racial and ethnic minorities in the United States.[18]

Despite widespread acceptance of these theoretical constructs, most studies focus solely on adversities within the home, testing their associations with physical,[19–22] and mental health outcomes.[23] Many authors use the term ELS to link adverse experiences in a child's life with negative health outcomes;[1,2,24–26] other scholars refer to this phenomenon as "toxic stress",[27,28] with no consensus on the nomenclature used to describe relationships between childhood adversity and potential health outcomes. While the 'stress' caused by adversity may explain many long-term consequences, 'stress' is not the operative factor for all observed outcomes.[1,24] Instead, we prefer early life adversity (ELA) as a more holistic term, including family functions, socioeconomic factors, social supports, neighborhood characteristics, and other factors, more suited for linking early adversities with long-term outcomes. Several measures have been developed to study ELA, with most relying on adult retrospective recall.

MEASURES OF ELA

Several inventories, systematically reviewed by Vanaelst et al.,[29] assess the frequency of adverse childhood events (Table 1). These were adapted from existing stress questionnaires and modified to inquire about major life events, chronic environmental strains (family, school, relationships, health), and other childhood-related stressors.[29–31] A cumulative risk approach was first proposed by Holmes and Rahe[32] in their *Social Readjustment Rating Scale*, then applied to child adversities by Rutter,[33] and subsequently followed in other studies.[34,35] This approach rests on the scientific premise that challenges in one domain are easier to negotiate than challenges in multiple domains. It was simple to use, easy to understand, generated strong statistical associations to engage non-academic stakeholders,[36] accounted for the co-occurrence of childhood adversities,[37] and helped to identify people at highest risk for poor outcomes.[22]

Against this backdrop, Vincent Felitti decided to focus on a specific set of ACEs. Felitti[38] observed that dropouts from an adult obesity program had experienced adverse events as children or youth. Detailed patient interviews revealed that childhood abuse was common and predated their obesity; thus, obesity was a self-protective *solution* to prior adverse experiences and not their primary problem. With Robert Anda and others, Felitti designed the ACE study, which surveyed 9508 adults with about ten adverse experiences.[30,39–41] Compared to individuals with no ACEs, persons exposed to four or more ACEs had 4- to 12-fold higher risks for drug abuse, alcoholism, depression, and suicide, 2- to 4-fold increased risks for smoking, poor health, multiple sexual partners, and sexually transmitted diseases, and 1.4- to 1.6-fold increased risks for physical inactivity and obesity.[36,38] ACEs also showed linear relations with heart disease, cancer, lung disease, fractures, liver disease, and multiple health outcomes.

By summing a fixed number of ACEs, Felitti and others created a quantitative method for estimating childhood adversities.[36,38] Their work stimulated research, social policy, and public health measures to combat the increasing prevalence of ACEs, and extended the movement for trauma-informed care into the pediatric age groups.[31]

PREVALENCE OF ACEs

The increasing prevalence of ACEs is a major public health concern.[29,30,42,43] In the ACEs study, 63.5% of adults recalled at least one ACE and 12% recalled four or more ACEs.[44] Subsequent studies, not limited to adult respondents, reported higher prevalence rates of 67–98%.[45–47] Preschool children are at greatest risk for child abuse and neglect,[48] or domestic violence,[38,49] but cannot report these experiences due to limited behavioral or verbal expressions.[38] ACEs in early childhood remain underreported and underestimated.[28,37,48,50]

The US Children's Bureau reported that 678,000 children suffered abuse and neglect in 2018, with a crude prevalence rate of 9.2 per 1000 children. Of these, 60.8% were neglected, 10.7% physically abused, 7.0% sexually abused, and 15.5% suffered two or more types of abuse.[51] Although caregivers often minimize or fail to report the maltreatment of preverbal children,[52] children <1 year of age had the highest rates of abuse (26.7 per 1000 children). In 2018, 1770 children died of abuse/neglect (case fatality rate 2.39 per 100,000 children), with the highest case fatality rates in infants below 1-year (case fatality rate 22.8/100,000 children).[51] Cumulative exposures have multi-layered effects on child development, with a "mediated net of adversity" that simultaneously augments their risk across cognitive, quality of life, social, economic, psychiatric, and physical health outcomes.[53]

HEALTH IMPLICATIONS OF ACEs

A systematic review of pediatric health outcomes associated with ACEs found prospective evidence for impaired physical growth and cognitive development, higher risks for childhood obesity, asthma, infections, non-febrile illnesses, disordered sleep, delayed menarche, and non-specific somatic complaints.[54] These outcomes depended on the ACE characteristics, age of occurrence, and specific types of exposures. For example, prospective studies showed that parental discord or violence was associated with obesity in childhood,[55,56] and other prospective studies showed that physical or sexual abuse was associated with youth obesity.[57–59] From prospective data, Brown et al.[39] clustered the specific ACEs that led to specific risks, to form an ACE-directed tree for identifying health outcomes. For each additional ACE, children were 29-44% more likely to have complex health problems, with multiple needs across developmental, physical, and mental health.

Children aged 2–5 years exposed to caregiver mental illness were most likely (56–57%) to have complex health concerns, with the additive effects of other risk factors.[39] A significantly higher prevalence of four or more ACEs was found in children with multiple unexplained chronic symptoms in six functional domains (executive dysfunction, sleep disturbances, autonomic dysregulation, somatic complaints, digestive symptoms, emotional dysregulation) compared to matched controls (88% vs. 33%);[60] suggesting a syndrome of nervous system dysregulation in these children, much like that seen in Gulf War veterans.[61]

Retrospective studies based on adult recall linked ACEs with an increased vulnerability to chronic non-communicable diseases, substance abuse, sexual risk-taking behaviors,[45,46,50,62–65] suicide, domestic violence,[63,66–69] and worse physical and mental health.[42,57,70–72] From 24,000 adults in the World Mental Health Surveys, retrospective data on childhood adversities doubled the

Table 1. Early life adversity screening tools.

	ACEQ: Child, Teen	CTQ	CTES/CTES-A	CTAC-TSC	PAPA	THC	TESI-CFR/PPR	WHO-WMH-CIDI
Age	0–12 years, 13–19 years	>12 years	0–19 years	0–18 years	2–5 years	>13 years	0–18 years	>16 years
Length	17 items, 19 items: (caregiver and self-report versions)	28 items, self-report	26–30 items, self-report, parent report	40 items, clinician report	15–20 min, structured parental interview	20 items, structured interview	24 items, structured interview and parental report	10-min, structured interview
Method	Assess all four categories that define adversity							
	Category		Definition					
	Abuse: physical emotional sexual		• Someone pushed, grabbed, slapped, or threw something at child or child was hit so hard that she/he was injured or had marks • Household member swore at, insulted, humiliated, or put down child in a way or household member acted in ways to make child afraid of being physically hurt • Someone touched child's private parts or asked child to touch that person's private parts in a sexual way that was unwanted, against child's will, or made child feel uncomfortable					
	Neglect: physical emotional		• More than once, child went without food, clothing, or a place to live, or had no one to protect her/him • Child often felt unsupported, unloved, and/or unprotected					
	Household dysfunction		• Child's parents or guardians were separated or divorced • Child saw or heard household members hurt or threaten to hurt each other • Household member was depressed, mentally ill, or attempted suicide • Household member had a problem with drinking or using drugs • Household member served time in jail or in prison					
	Other adversities		• Child lived with a parent or guardian who died • Child was placed in foster care • Child was separated from primary caregiver through deportation or immigration • Child had a serious medical procedure or life-threatening illness • Child experienced harassment or bullying at school • Child experienced verbal or physical abuse or threats from a romantic partner • Child often saw or hear violence in the neighborhood or school • Child was detained, arrested, or incarcerated • Child was treated badly because of race, sexual orientation, place of birth, disability, or religion					

Table 2. Outcomes following exposure to ≧4 adverse childhood experiences.

	Odds ratio (95% confidence intervals)	Heterogeneity (I^2)
Physical inactivity	1.25 (1.03–1.52)	65.2% (23.6–79.7)
Overweight or obesity	1.39 (1.13–1.71)	75.1% (39.6–86.0)
Diabetes	1.52 (1.23–1.89)	48.3% (0–75.2)
Cardiovascular disease	2.07 (1.66–2.59)	23.7% (0–65.9)
Heavy alcohol use	2.20 (1.74–2.78)	75.0% (43·5–85.6)
Poor self-rated health	2.24 (1.97–2.54)	0% (0–64.1)
Cancer	2.31 (1.82–2.95)	0% (0–67.9)
Liver or digestive disease	2.76 (2.25–3.38)	0% (0–61.0)
Smoking	2.82 (2.38–3.34)	87.1% (82.1–90.2)
Respiratory disease	3.05 (2.47–3.77)	0% (0–56.3)
Multiple sexual partners	3.64 (3.02–4.40)	16.5% (0–61.5)
Anxiety	3.70 (2.62–5.22)	82.2% (59.7–89.7)
Early sexual initiation	3.72 (2.88–4.80)	75.5% (54.0–84.5)
Teenage pregnancy	4.20 (2.98–5.92)	77.1% (33.6–88.0)
Low life satisfaction	4.36 (3.72–5.10)	0% (0–64.1)
Depression	4.40 (3.54–5.46)	80.0% (64.8–86.9)
Illicit drug use	5.62 (4.46–7.07)	76.4% (59.6–84.3)
Problematic alcohol use	5.84 (3.99–8.56)	79.7% (60.0–87.5)
Sexually transmitted infections	5.92 (3.21–10.92)	78.4% (39.7–88.5)
Violence victimization	7.51 (5.60–10.08)	59.0% (0–81.3)
Violence perpetration	8.10 (5.87–11.18)	68.2% (12.8–83.1)
Problematic drug use	10.22 (7.62–13.71)	12.0% (0–68.2)
Suicide attempt	30.14 (14.73–61.67)	77.4% (42.5–87.5)

Pooled odds ratios (ORs) from random-effects meta-analyses.
Modified with permission from Hughes et al.[41]

risk of adult psychotic episodes, accounting for 31% of psychotic episodes globally.[73] Sexual abuse, physical abuse, and parent criminality had the strongest associations with later psychotic episodes.[73]

A meta-analysis of adult health outcomes following four or more ACEs found increased risks for all 23 health and social outcomes, with *weak* associations for physical inactivity, weight gain, and diabetes; *moderate* associations for smoking, heavy alcohol use, poor self-rated health, cancer, heart, lung, and digestive diseases; *stronger* associations for sexual risk taking, mental ill health, problematic alcohol use, and decreased life satisfaction; and *the strongest* associations for drug abuse, interpersonal violence, and suicide[41] (Table 2). Thus, ACEs not only contribute to global burdens of adult disease, but their strongest associations with drug abuse, domestic violence, and suicide may directly inflict ACEs onto the next generation.[74–76]

GENETIC AND EPIGENETIC CHANGES

These intergenerational effects are accentuated via altered gene expression through conserved transcriptional responses to adversity (CTRA),[77] coupled with epigenetic changes, such as telomere shortening, reduced stem cell populations, elevated methylation, and nitration states, among genes in the stress-responsive, inflammatory, or other pathways.[78–81] Stress-associated epigenetic changes contribute to aberrant neuronal plasticity,[82] affect disorders,[82] post-traumatic stress disorder, alcohol use disorder,[83] and depression,[84–87] transmitting their physical and mental health risks to future generations.[41,88,89] Mechanisms of stress-associated epigenetic changes may involve DNA methylation or histone acetylation[80,84,86,90], changes in mitochondrial DNA copy number and mitochondrial dynamics,[80] and microRNAs that are transported via exosomes or binding proteins[91] to regulate the signaling pathways for gene silencing, cellular differentiation, autophagy, and apoptosis.[92]

From a systematic review of epigenetic changes in HPA-axis genes, Argentieri et al.[78] found prospective evidence for methylation of *HSD11beta2* with hypertension, *NR3C1* with small cell lung cancer and breast cancer, and *FKBP5* and *NR3C1* with post-traumatic stress disorder (PTSD), as well as plausible associations of *FKBP5* methylation with Alzheimer's disease. In particular, the glucocorticoid nuclear receptor gene *NR3C1* undergoes methylation in varying gene regions from different social and environmental exposures, associated with different mental health outcomes.

Focusing solely on PTSD-associated genetic changes, Blacker et al.[79] found 3989 genes upregulated and 3 genes downregulated from 4 GWAS studies in PTSD patients. Among the differentially methylated genes, *DOCK2* (dedicator of cytokinesis 2) and *MAN2C1* (α-mannosidase), were associated with immune system dysregulation in PTSD subjects. Urban African-American males with PTSD showed increased global DNA methylation and differential DNA methylation in several genes: decreased in *TPR* (nuclear membrane trafficking) and *ANXA2* genes (calcium-regulated membrane-binding protein), increased in *CLEC9A* (activation receptor on myeloid cells), *ACP5* (leukemia-associated glycoprotein), and *TLR8* genes (innate immunity activation).[93] In African-American women with PTSD, this study found a higher methylation of the *HDAC4* (histone deacetylase 4) gene.[93] A systematic review of stress-associated epigenetic changes and depression found differential methylation of *NRC31*, *SLCA4*, *BDNF*, *FKBP5*, *SKA2*, *OXTR*, *LINGO3*, *POU3F1*, and *ITGB1*, associated with altered glucocorticoid signaling (*NR3C1*, *FKBP5*), serotonergic signaling (*SLC6A4*), and neurotrophin genes (*BDNF*).[81] Another systematic review confirmed that ELS-triggered epigenomic modulation of *NR3C1* was correlated with major depressive disorder.[94]

Childhood socioeconomic deprivation and ACEs can lead to adult diseases by increasing their inflammatory burden via multiple genetic factors, including single-nucleotide polymorphisms, and epigenetic factors, including nuclear factor-κB-mediated gene methylation and histone acetylation. These changes increase expression of pro-inflammatory cytokines, reactive oxygen species, reactive nitrogen species, and induce several microRNAs (*miR-155, miR-181b-1*, and *miR-146a*), with widespread effects on the immune system.[80] ELA also alters HPA-axis reactivity in adulthood by (i) genetic factors, such as glucocorticoid receptor polymorphisms; (ii) epigenetic factors altering glucocorticoid receptor function, including methylation of *NR3C1*, *FKBP5*, and *HSD11beta2*; (iii) chronic inflammation due to chronic nitrosative and oxidative stress; and (iv) brain mitochondrial DNA copy number and transcription, with altered mitochondrial dynamics, structure, and function in adulthood.[80]

LIMITATIONS OF THE ACE SCORE

Despite the known effects of ACEs on genetic/epigenetic changes and long-term health outcomes, it is short-sighted to focus only on ACEs for clinical decisions related to ELA. Newer frameworks must include factors ignored by ACE scores, including (a) the age of onset and offset; (b) severity of trauma; (c) frequency of

traumatic events; (d) periodicity of trauma within specific developmental periods; (e) concurrence of traumatic events; and (f) multiplicity of events across childhood.[44] Thus, popular use of the ACE score as a proxy for toxic stress appears grossly inadequate.

The American Academy of Pediatrics defines toxic stress "as the excessive or prolonged activation of physiologic stress response systems in the absence of the buffering protection afforded by stable, responsive relationships".[27,28] However, toxic stress depends on the child's complete social ecology, including multiple variabilities in their adverse experiences, environmental conditions, and protective factors.[1,31,95,96] Lacey and Minnis[44] argued that because all ACEs do not carry the same emotional weight or elicit similar distress levels, binary "yes/no" responses cannot represent their impact on the child. Lack of consistency in defining ACEs also makes it difficult to compare childhood adversities across different studies;[44] further limited by the lack of self-report, absence of protective factors, and dependence on caregiver report.[29,44] Caregivers may be more inclined to report their child's behaviors as "problematic" than to divulge personal difficulties, family dynamics, or household dysfunctions.[29]

The ACE score originated as an epidemiological research tool based on adult interpretations of their childhood experiences, but has since been extrapolated to clinical settings.[97,98] California launched a public health initiative in 2020 to screen children for ACEs in all outpatient visits.[43] However, there is a limited practical experience of ACE screening in the clinic, limited resources to address the identified ACEs, and nominal evidence-based algorithms for managing children with multiple ACEs.[29,44] If clinically screened ACEs do not relate to recent trauma and the patient appears asymptomatic, the next steps remain unclear.[40,43] Potential outcomes of this policy may include unnecessary referrals to child-protective services or pediatric subspecialists.[30,43] The inconsistent description of ACEs in different inventories highlights the broader point that there is no consensus on how to define childhood adversity or grade its intensity.[44] This has serious implications for how the ACEs questionnaire is used outside of epidemiology, especially to inform clinical, social, or policy interventions.

OTHER FACTORS IN THE SOCIAL ECOLOGY OF CHILDHOOD

ELA incorporates broader features beyond the individual experiences identified as ACEs.[99] For instance, the association between ACEs and child health was strengthened when researchers also accounted for interpersonal victimization (community violence, property crime, bullying), highlighting the cumulative harm from different forms of trauma.[66] ELA can be attributed to factors within all ecological systems affecting individuals, families, communities, or broader societies.[50,100] The rich interplay between these systems must be emphasized, since significant ecological factors are not "stand-alone" but can alter multiple systems at once.

Individual factors

Effects of childhood adversity typically emphasize the unidirectional effect of negative experiences on child development, disregarding individual demographics, or personality factors. Substantial theoretical work on child development highlights the transactional and dynamic interplay between individuals and their environment.[101] Sameroff and Chandler[102] consider developmental outcomes to be a function of such transactions, which exert continual effects on one another. Similarly, individuals function as active and self-regulating entities, changing dynamically with the environment and also changing their environment.[103] Thus, explanations for emerging health outcomes must account for mutual interactions between individual children and their environmental inputs.[101]

Household factors

Family environments, characterized by overt conflict, neglect, passive aggression, or unaffectionate interaction styles[104] are associated with a broad range of mental and physical health disorders.[38,88] Parental traumatic experiences and environments can affect the quality of parenting and child development.[88] Maternal depression and trauma are associated with increased rates of insecure attachment in children,[105–108] related to decreased maternal responsiveness and affective availability.[105,109,110]

Sustained economic problems affect children directly by limiting material resources and indirectly through parental distress, which undermines the parents' capacity for supportive and consistent parenting.[111,112] For example, fathers facing financial losses became more irritable, tense, and explosive, with punitive, rejecting, and inconsistent disciplining behaviors, associated with emotional difficulties in their children.[112–114]

Community factors

Neighborhood deprivation negatively impacts mental and physical health lasting into adulthood,[115] likely related to telomere shortening,[116,117] altered cortisol regulation,[117] increased inflammation,[118] and differential DNA methylation.[119] Children who grow up in communities with higher rates of violence, crime, and noise may suffer from increased stress and lasting trauma.[120–122] Poor local infrastructure can also affect access to resources, such as food and healthcare, which can exacerbate health issues.[122]

Broader societal factors

Negative societal attitudes and biases, like racial discrimination or segregation, pervade all aspects of a child's ecology and persist over time; therefore, evaluating these factors is particularly important for long-term health outcomes in children of color.[123–125] Perceived racial discrimination and stereotype threat can trigger stress responses and can affect cognitive processes and academic performance.[126] For example, greater perceived discrimination was associated with greater cortisol output in Mexican–American youth.[127] Childhood exposures to interpersonal racial discrimination and structural racism stemming from media, schools, law enforcement, government policies, and other cultural stressors also lead to psychological distress and changes in allostatic load for racial minorities in the United States[124,125] While negative inputs clearly affect the developing brain, positive inputs and protective factors, such as social buffering or individual resilience, play equally important roles[44,101] (Fig. 2).

PROTECTIVE FACTORS IN THE CHILD'S SOCIAL ECOLOGY

ELA research must account for the factors that temper adversity, including support, temperament, resilience, and adaptation. For example, the Risky Families questionnaire includes supportive factors (e.g., parental love and support, household dynamics) and ACEs.[128] Although stress biology is highly susceptible to early experiences, it is just as malleable to supportive and protective factors.[129,130] We discuss the role of positive experiences, social relationships, and resilience factors that help children cope with adversity.

Positive experiences

Greater emphasis on positive and supportive experiences, fundamental to developing healthy brain architectures and buffering children against the effects of contextual stressors,[131,132] would complement existing data on the health consequences of ELA. A validated method to assess positive/protective experiences in ELA is the Benevolent Childhood Experiences scale.[133]

The Healthy Outcomes from Positive Experiences (HOPE) framework led by Sege et al.[134] focuses on promoting positive childhood experiences to prevent or mitigate the effects of ELA. HOPE creates a strong foundation for learning, productive behavior, physical, and

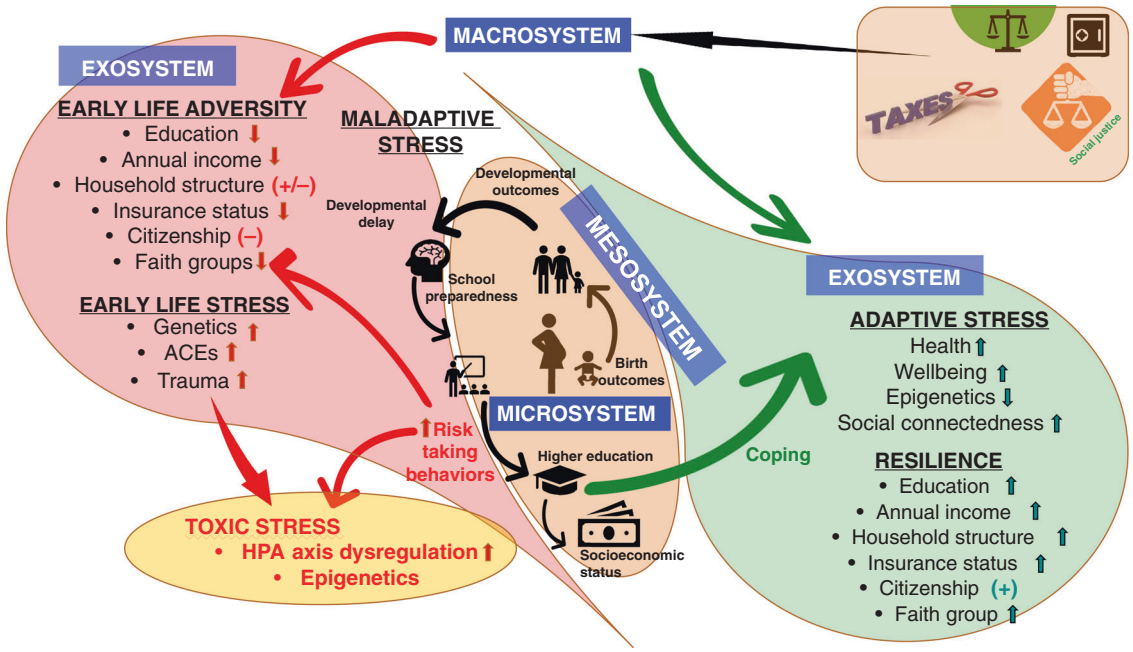

Fig. 2 Adverse and protective factors in a child's life are organized by Bronfenbrenner's ecological systems model. Governmental, socioeconomic, and cultural factors in the macrosystem may steer the child's exosystem either towards adversity or adaptation. ELA (red box/arrows) and adaptation (green box/arrows) may work in tandem to build a child's resilience, support education, income adequacy, health equity, and access to basic social services. The mesosystem forms an interface between the exosytem and the family unit with variable effects on the child's milieu. In the microsystem, children are exposed to ELA or pro-social affiliations that affect their developmental, cognitive, behavioral, and health outcomes.

mental health. Given that young children experience their world through their relationships with parents and other caregivers, positive childhood experiences that engage the child, the parent, and the parent–child relationship are essential.[131,132] In Wisconsin, positive childhood experiences were associated with dose-dependent reductions in the adult mental health and relational health impairments resulting from ACE exposures.[135]

HOPE identifies four broad categories of positive experiences and their effects on child development: (1) *Sustained supportive relationships* are associated with better physical and mental health, fewer behavior problems, higher educational achievement, more productive employment, and less involvement with social services and criminal justice systems.[131] (2) Growing and learning in *safe, stable environments* are important for children's physical, emotional, social, cognitive development, and behavioral health, conferring lifelong benefits.[100,131] (3) Opportunities for constructive *social engagement and connectedness* can promote secure attachment, belonging, personal value, and positive regard.[131,136,137] (4) *Social and emotional competencies* cultivate self-awareness and confidence, laying the foundation for learning and problem-solving, identity development, communication skills, and secure personal relationships.[131]

Social relationships

Bowlby[138] observed that children separated from their mothers showed intense distress and later maladjustments. In the *Attachment Theory*, he posited that uninterrupted, secure maternal–infant bonding was evolutionarily adaptive. Beginning with maternal–infant bonding, the layering of nurturing, supportive relationships throughout child development enriches self-perception, self-image, and coping skills. Positive social relationships also reduce pain ratings, HPA-axis reactivity, and aberrant brain activation.[129,139–142] Perceived social support from friends (not family members) was associated with fewer trauma symptoms in adult survivors of childhood maltreatment.[143] Culture-related protective factors can also be leveraged to overcome ELA and promote normal development.[144] Thus, social connections with family and non-family members may protect against stress responses to adversity across the lifespan.

Resilience

Resilience science grew out of concerted efforts to understand, prevent, and treat mental health problems.[145] Scientists observed that some children adapted remarkably well despite high levels of adversity. Resilience generally refers to the capacity of any system to recover from exposure to stressors or adversity; it is a mirror image of vulnerability, with processes and capacities common to both.[145–147] Feldman argues that the construct of resilience involves systems and processes that tune the brain to its social ecology and adapt to its hardships.[148] In traumatized children, Happer et al.[149] found stronger evidence for resilience as a process, partial support for resilience as an outcome, but none for resilience as a trait.

While resilience research is summarized elsewhere,[147,148,150,151] an emerging list of resilience factors in children is featured in Table 3.[147] Resilience science distinguishes between protective and promotive factors; protective factors have greater effects in the context of adversity, but promotive factors improve outcomes more broadly.[147,152,153]

Early life adversities, particularly in the absence of protective factors, can trigger a set of emotional responses, metabolic adjustments, physical/behavioral responses, and immune changes contributing to allostasis through the "fight or flight or freeze response." Many stress responses are regulated through the neuroendocrine system, studied most extensively for the HPA axis.

NEUROENDOCRINE REGULATION OF STRESS RESPONSES

Stress activates the neuroendocrine system, resulting in cortisol and catecholamine release.[29,42] The stress response evolves through two phases: the first is dominated by catecholamine release, and the second by cortisol. Simultaneous activation of

the *salience neuronal network* and deactivation of the *executive control network* mediates the first phase.[42] The salience network includes the anterior insula, amygdala, hippocampus, striatum, medial prefrontal, and anterior cingulate cortices; it integrates cognitive processes for responding to threats, with swift actions to promote survival.[42,154] The executive control network includes prefrontal and parietal cortices to mediate working memory, impulse control, and emotional regulation.[42,154] The second phase mediates recovery from stress responses by deactivating the salience network and re-engaging executive control. Such restoration of homeostasis after stress is termed the "adaptive stress response".[42]

Table 3. Resilience-associated factors in the child's social ecology.

Domains	Common resilience factors
Individual factors	Active coping mastery Hope, faith, optimism
Household factors	Nurturing family members, strong friendships, supportive non-relative mentors Family cohesion, belonging, skilled family management Collaborative problem-solving, flexibility, family role organization Balancing family/work needs Positive family outlook Family routines and rituals (reading aloud, sleep hygiene, family prayer) High-quality child-care facilities and schools
Community factors	Parent engagement in a well-functioning school Safe, clean, and stable neighborhoods Interaction with next-door peers, classmates, teachers, faith-based groups Connections with well-functioning communities Stable income sources Positive workplace relationships
Broader societal factors	Family-focused social policies, taxation laws, welfare programs Healthcare access, health insurance Social and economic equity, diverse communities Inter-faith dialogue, social justice

Adapted from Table 2 in Masten and Barnes.[147]

Emotional stimuli can activate salience network activity at lower thresholds in the "maladaptive stress response," resulting in conditioned hyperarousal.[42] Allostasis, the HPA-axis adaptation to stress, is maintained in maladaptive stress responses, although resulting in somewhat delayed homeostasis.[29,42,154] Allostatic load results from the repetitive activation of HPA mechanisms attempting to restore homeostasis without returning to baseline.[42] Excessive HPA activation causes allostatic components to be unbalanced, leading to architectural and functional changes in the salience and executive control networks.[29,31,41,154] Indeed, higher bedtime cortisol levels predicted the reduced prefrontal cortex volumes in traumatized adolescents.[155] Chronic adversities overload the neuroendocrine system's capacity to maintain homeostasis and, especially during periods of heightened neuroplasticity (from pregnancy to early childhood), affect crucial aspects of brain development implicated in cognition, self-regulation, and physical and mental health.[39,41,42,154]

The HPA axis and executive functions mature by age 4–6 years,[156–158] and a normally functioning HPA axis limits cortisol exposures through negative feedback loops to the anterior pituitary and hypothalamus. These negative feedback loops become ineffective in children with HPA-axis dysregulation.[159] Thus, toxic stress may lead to hyper- or hypo-responsivity of the HPA axis, with failed adaptation and eventual exhaustion[160] (Fig. 3). HPA-axis dysregulation manifests as emotional problems in preschool children, such as internalizing and externalizing behaviors.[161–165] Considering the harmful manifestations of HPA-axis dysregulation in children and the vulnerability of their immature HPA axis, it is critical that we establish biomarkers for screening preschool children.

CORTISOL AS A BIOMARKER OF ELA

Long-term consequences of ELA are mediated through the neuroendocrine system, with downstream effects on neuroimmune, neuroenteric, and cardiometabolic regulation.[41,48] Measuring stress biomarkers could overcome the inherent limitations of subjective questionnaires and difficulties of implementing the ACE checklist in children.[42] Cortisol, the end-product of HPA-axis activation, regulates the HPA axis through negative feedback loops, activates the autonomic nervous system, alters intermediary metabolism, modulates physiological and immune responses, and contributes to the memory and learning from traumatic

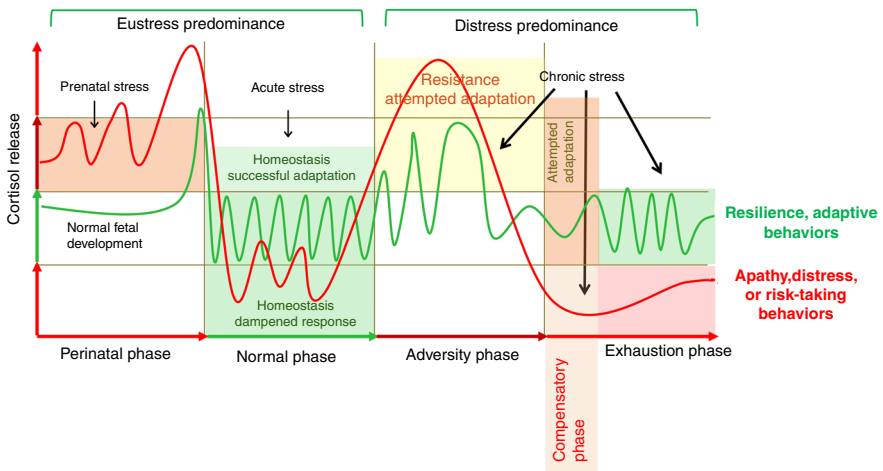

Fig. 3 Representative patterns of adaptive (green) and dysregulated (red) HPA-axis responses. In the perinatal phase, the fetal brain may be exposed to maternal cortisol levels resulting from prenatal stress, usually associated with dampening of the infant's HPA axis postnatally, often lasting into infancy and early childhood. Exposures to ELA/stress then manifest as hyperactive responses to acute stress, which, if prolonged or repetitive, can lead to chronically dysregulated diurnal rhythms and HPA-axis exhaustion.

experiences.[166,167] Therefore, cortisol is an important biomarker for ELA.[168]

Plasma, salivary, or urinary cortisol levels reflect *acute stress reactivity*, but cannot assess chronic stress because of its diurnal cycles, high state reactivity, pulsatile secretion patterns, and robust changes across age, sex, reproductive cycles, and food intake.[169–171] A systematic review concluded that HCC represents a measure of recent stress, but it included studies from 16 species, which only collected cross-sectional data.[172] Measuring acute cortisol responses has significant limitations; repeated sampling over prolonged periods is time-consuming, expensive, and subject to non-compliance. Blood sampling is painful, difficult in children, requires trained staff, and stringent laboratory conditions. Salivary sampling is inexpensive and less invasive,[29,154] but limited by inconsistent collection methods and food-related variability.[29,154,169] Urine sampling from children is challenging, with low participant compliance, sample refrigeration, and urinary metabolites interfering with cortisol measurements.[29] In contrast, hair sampling is non-invasive, independent of diurnal cycles, stored at room temperature, and provides chronologically distinct data for cortisol activity up to 6 months.[29,173,174]

Emerging research suggests that human hair follicles are neuroendocrine organs that index physiological stress responses.[175,176] Hair grows about 1 cm per month[177] and incorporates the circulating free cortisol,[178,179] although the underlying mechanisms remain unknown.[180,181] Russell et al.[181,182] proposed that free cortisol from the follicular vasculature passively diffuses into the hair shaft, or the hair follicle, sweat, and sebaceous glands may secrete and deposit cortisol into the hair shaft. Like hemoglobin A_{1c} for blood glucose, HCCs summate the cortisol release over time.[183–185] Earlier concerns about hair washing[186,187] and HCC contamination from cortisol secreted by sebaceous or sweat glands have been refuted.[182,188] HCC show high test–retest reliability, were validated against serum, salivary, and urine cortisol, and are widely accepted as measures of chronic stress in adults[185,189] and children.[178,184,190]

Effects of sex, age, and race

Previous studies reported higher HCC in boys than in girls.[186,191] However, current data show no sex differences among preschool children,[26,178] higher HCC in pre-pubertal boys than girls, and no differences after puberty.[192] Variations of HCC with age are unclear, with most studies showing age-related decreases in preschool years.[26,193,194] Racialized experiences and structural racial discrimination may contribute to the higher HCC in African-American children compared to children from other races.[26,195]

Effects of prenatal and postnatal environments

Higher HCC in 1-year-old infants was associated with maternal parenting stress, depression, and psychological distress.[195] Prenatal traumatic events were significantly associated with their child's HCC at age 3 and 4 years, even after adjustments for known mediators like postpartum depression, parenting stress, psychological distress, and child abuse potential, as well as preterm birth or body mass index (BMI).[196]

Other studies found higher HCC in newborns following neonatal intensive care,[197] children with early trauma,[198,199] and children with high fearfulness ratings upon school entry.[190] In 6–7 year olds, low HCC values suggestive of HPA-axis dysregulation were associated with exposures to frequent neonatal pain,[200] or harsh parenting.[201] Although *perinatal* adversities may alter long-term HPA-axis regulation into the school-age period, the most prominent *postnatal* influences on HPA activity result from poverty and early deprivation.[194,202,203]

Effects of socioeconomic adversity

Children raised in poverty are often exposed to chronic stress, either *directly* (from food, housing, energy insecurity,[204] bullying,[205,206] or neighborhood violence[117]) or *indirectly* via parental stress.[207] Higher HCCs were associated with lower parental education,[208] lower family income, more household members, single-parent households,[186] and deprived neighborhoods.[203] Similar associations between ELA and chronic stress[209–212] may result from insensitive or rigid parenting,[201] parenting stress,[195,196] neighborhood effects,[117,203] and other poverty-related factors.[213–215] To understand the importance of these differences, we explore the implications of HCC as a chronic stress marker and subsequent health outcomes.

HAIR CORTISOL CONCENTRATIONS: IMPLICATIONS FOR HEALTH

Epidemiologic studies have established links between chronic stress, HPA-axis dysregulation, and subsequent physical and mental health outcomes,[25,216] but only a few of these studies have included HCC as a biomarker for chronic stress.[174,178]

Higher HCC in preschool children were associated with impaired social–emotional development and increased risks for developmental delay.[26,195] In 6–8-year-old children, increased HCCs were associated with higher BMI in girls and somatic complaints in boys.[191] In older children, increased HCCs were associated with higher BMI,[192] other measures of obesity,[186,191,217,218] and vulnerability to common childhood illnesses,[219] even after controlling for factors such as race, age, gestational age, and birth weight. HCCs were reduced in children with asthma,[220] possibly from HPA-axis suppression due to inhaled corticosteroids.[221–223] Higher HCC also occurred in children with epilepsy[224] and girls with anorexia nervosa,[225] but no differences were found in children with anxiety[226] or depression[199,226] as compared to controls.

In adults, HCC was increased in major depression and decreased in general anxiety disorder, whereas HCC changes in PTSD were dependent on the type of traumatic experience and elapsed time since the trauma.[227,228] Increased HCC was used as a biomarker for stratifying cardiovascular risk and linked to obesity, hypertension, diabetes, metabolic syndrome, and cardiovascular disease.[227,229] In the survivors of physical and sexual abuse, higher HCCs during pregnancy were associated with preterm labor.[230–232]

Since HCC has been correlated with physical and mental illnesses in children and adults, it can be used to probe the connections between ELA, HPA-axis activity, and health outcomes. HCC may also provide unique insights into the physiological ramifications of adversities located and perpetuated in a child's social ecology.

CURRENT KNOWLEDGE GAPS AND FUTURE DIRECTIONS

Significant gaps in our knowledge of ELA must be addressed to understand the relationships between ELA and health outcomes. Research using subjective and objective methods should assess community and societal factors alongside household conditions and parental factors, complemented concurrently by biomarkers.

The ACEs questionnaire was created using patients' recollection of childhood experiences and correlated with subsequent health conditions. However, the equivalence between adult recollections of ACEs and caregivers' responses on behalf of their child's current lived experiences remains undetermined. Caregivers may be unreliable historians of their young child's experiences, with significant differences between their and the child's perceptions. In addition, serial ACEs screening in children does not help us to understand how to prevent or treat ACEs, and potentially reinforces the negative emotions that children have of their experiences.

Historically, the relations among ELA, ELS, and health were studied using lab stress tests, sleep studies, neuroimaging, anthropometrics, epigenetic markers, or galvanic skin responses.[233,234] This research included small sample sizes, failed

to account for developmental differences, and inconsistently sampled age, sex, and racial/ethnic subgroups. Large, population-based studies can overcome these weaknesses using less invasive and less expensive means for recording ELA/ELS, child-centered measurements of stress responses, recording protective/supportive factors, and web-based data entry to minimize costs and increase compliance. Monitoring vital signs for ELA assessments may be less useful if these measures are temporally separated from the adverse experiences. Researchers should consider real-time measures of chronic stress through wearables to index the impact of ELA on health.

ELA alters gene expression through the CTRA[77] contributing to aberrant neuronal plasticity, affect disorders, PTSD, depression, and substance abuse.[82–87] Mechanisms of stress-associated epigenetic changes,[80,84,86,90] mitochondrial DNA copy number, telomere shortening,[235] and secreted microRNAs[91,92] must be investigated in children and adolescents, while also examining the reversibility of these epigenetic modifications and their contributions to later health outcomes.

Social interactions with attentive caregivers reduce infant stress responses and facilitate development.[236] Nurturing experiences like "kangaroo care" can reduce neurodevelopmental risks in preterm infants.[237,238] Secure attachments and friendships across the lifespan play protective roles in cognitive function, physical health, and emotional self-regulation.[239] Parent–child involvement in mindfulness-based, mind-body approaches can reduce stress and enhance recovery.[240] We encourage researchers to explore the underlying biological mechanisms for social buffering, positive experiences, and other protective/supportive factors.

Screening for ELA without concurrent efforts to abolish the social injustices that promote such adversities is futile. Individual screening cannot, and should not, replace efforts to address the root causes of health inequity, including poverty, lack of healthcare, community violence, racism, and gender-based discrimination. Researchers should work alongside clinicians, politicians, educators, social workers, and community members to develop intervention programs that promote resilience in children *and* to deconstruct the societal and legal infrastructures that perpetuate systemic inequities. We recommend the use of biomarkers such as HCC to supplement existing research efforts and public health interventions as a quantitative, biological marker, firstly, to enhance our understanding of the underlying pathophysiology that mediates the association of ELA with poor health outcomes, and secondly, to improve evaluations of the impact of preventive or therapeutic interventions on their intended beneficiaries (i.e., children) in the community.

CONCLUSIONS

Research to ensure that ELA can be assessed in the context of a child's social ecology, not just their ACEs score, is urgently needed. ELA and ELS increase the child's vulnerability to short-term effects on behaviors, emotions, lifestyle choices, and relationships, with long-term effects on their physical health, psychiatric, social, and economic outcomes. Positive experiences and protective factors must also be considered when investigating the long-term consequences of ELA. Cumulative knowledge from these studies can then guide practical interventions for improving childhood ecologies to decrease ELA and improve health outcomes.

Significant knowledge gaps need to be filled through research in this area. Objective biomarkers for ELA/ELS and protective factors should be validated and used to probe the social ecology of childhood. Intergenerational effects of ELA through epigenetic changes associated with increased vulnerability or resilience must be identified and incorporated into therapeutic trials. Novel approaches for studying the child's social ecology, possibly from wearables, other real-time measures, or biomarkers, will supplement the parent/caregiver surveys and clinic-based observations. This will inform the development of screening programs, investigations of the underlying mechanisms, and the interventions designed to address the short- and long-term outcomes of ELA across the lifespan. Well-designed trials are essential to establish a scientific framework for proposed preventive measures, therapeutic interventions, social policy changes, or public awareness campaigns. Lack of sufficient investment in investigating and/or addressing the pervasive, pernicious effects of ELA will only escalate its prevalence and long-term consequences for future generations, thereby trapping at-risk families, communities, and neighborhoods into further early life adversities and reduced human potential.

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AUTHOR CONTRIBUTIONS

M.L. drafted the manuscript outline; M.L., M.O.R., C.R.R., G.K.-Y.T., J.H., and K.J.S.A. wrote initial drafts and edited the manuscript; C.R.R. developed initial concepts and created the figures; K.J.S.A. developed initial concepts and provided grant funding; I.H.G., D.A.B., and V.G.C. reviewed and made critical revisions of the manuscript; and all authors approved the final version to be published.

ADDITIONAL INFORMATION

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