Supplemental Information

SUPPLEMENTAL TABLE 3 Potential Domains for Measuring Stress Activation

Domain of measurement	Description	Examples of potential markers
Neuroendocrine function	The hypothalamic-pituitary-adrenal axis is the main neuroendocrine system involved in the stress response. This axis has cortisol (a glucocorticoid hormone) secreted by the adrenal glands as the key effector acting on many organs and tissues, including circuits in the brain. Glucocorticoids are strategic molecules for survival because they regulate many of the other components involved in the stress response (eg, inflammation, metabolic regulation, prefrontal function). However, because of its circadian rhythm secretion, isolated cortisol values are complex to interpret in the context of chronic stress exposure. Cumulative measures such as hair cortisol, reflecting levels in the past several months, were significantly associated with childhood adversity exposure in a recent metanalysis.[57] Other steroids like dehydroepiandrosterone, an adrenal androgen, are related to childhood adversity exposure in adolescents,[58] adults and their offspring,[59] with sex specific associations.[58] Hair cortisone concentrations, likely converted from cortisol, are elevated in children experiencing psychosocial stress.[60] Other elements of the neuroendocrine axis also participate in the response to stress and specifically to childhood adversity, such as the hypothalamic-pituitary-thyroid[61] and hypothalamic-pituitary-gonadal axis,[62] with some markers that can be also measured in hair.	Cortisol, cortisone, DHEA, progesterone, testosterone, triiodothyronine (T3)
Inflammation	Although the acute inflammatory response is a vital part of the process to fight against diseases or injury, chronic inflammation has a negative impact on different bodily systems. The continued state of alert associated with chronic inflammation damages cells, tissues, and organs. It has been shown that a history of exposure to childhood adversity is linked to higher levels of low-grade systemic inflammation in adults.[63–66] Many adult chronic diseases are related to increased systemic inflammation (eg, cardiovascular disease, diabetes, psychopathology, cancer). Therefore, altered inflammatory functioning may be the link by which early experiences connect to poorer adult health. A new metanalysis suggests that the evidence linking adversity to inflammatory changes in pediatric samples is still limited.[67] We have shown recently that variation in the patterns of salivary cytokine levels reflect differences in children's response to environmental adversity.[68]	C-reactive protein, proinflammatory cytokines, IgA, IgE, S100B, α 1 antichymotrypsin, soluble urokinase plasminogen activator receptor (suPAR)
Metabolic regulation	In response to stress exposure, many metabolic processes are activated to redirect energy resources to face the challenge. When excessive metabolic activation is established in response to chronic adversity exposure, damage and dysregulation may occur. Exposure to prenatal or postnatal adversity has been shown to be 1 of the major risk factors for the development of metabolic disorders, such as insulin resistance, type II diabetes mellitus, and hyperlipidemia.[69–73] One study has shown an association between reported childhood adversity exposure and altered levels of metabolic markers like serum leptin, adiponectin and irisin.[74]	Fasting insulin, glucose, leptin, irisin, HbA1c, cholesterol (HDL, LDL), fructosamine, triglycerides, free fatty acids.
Cardiovascular reactivity	Markers of variability in vital signs like heart rate or blood pressure reflect differential activation of the autonomic system (sympathetic and parasympathetic activity), which characterizes the most immediate response of the body when facing stress. Heart rate variability associated with breathing is a reflection of activity of the parasympathetic nervous system. Pre-ejection period, or the time between the electrical depolarization of the left ventricle and the beginning of ventricular ejection, reflects activity of the sympathetic nervous system. The balance between sympathetic and parasympathetic activation of the heart changes with development over the first years of life, with an increase in parasympathetic tone relative to sympathetic tone. Early childhood adversity may affect the trajectories of this	Heart rate variability, systolic and diastolic blood pressure, pulse pressure, pre-ejection period.

SUPPLEMENTAL TABLE 3 Continued

Domain of measurement	Description	Examples of potential markers
	balance, with high adversity in the absence of caregiver buffering resulting in higher sympathetic to parasympathetic tone from infancy through age 5, whereas responsive caregiving mitigates the impact of adversity, resulting in increasing parasympathetic and decreasing sympathetic tone at rest over this period.[75] Mild exercise induces decreases in systolic and diastolic blood pressure, pulse pressure and perceived stress in response to a cognitive stressor in children.[76]	
Oxidative stress	Reactive oxygen species (ROS) are highly reactive molecules derived from molecular oxygen, and their production is a consequence of the aerobic feature of the human condition. An imbalance between the production and elimination of ROS and reactive nitrogen species alters cell physiology. This process is called oxidative stress, as these molecules oxidize and modify the structure of biological molecules like proteins, lipids and nucleic acids causing functional changes, cellular malfunction, and tissue damage.[77] Although still challenging to measure, some markers of oxidative stress seem promising. Mitocondrial DNA (mtDNA) is easily measured in saliva and increased in adults who experienced significant adversity in childhood.[78,79] The mtDNA is highly susceptible to oxidative damage, and to overcome possible energy deficiencies because of mtDNA malfunction, mitochondria can increase their mass and genomic content. Increases in mtDNA therefore signify mitochondrial dysfunction, which can induce apoptosis or senescence and accelerate biological aging.[80] As mentioned above, environmental stressors induce rapid changes in intracellular enzymatic cascades and release intracellular ROS, that modify lipid composition (lipid peroxidation), which in excess can reflect high oxidative stress. F2-isoprostane (IsoP) is a bioactive compound formed in this process, and it has been proposed as a marker of endogenous oxidative stress that can be measured in urine.[77] Adolescents who report exposure to several adverse childhood experiences have elevated IsoP levels.[81] Finally, ROS resulting from chronic stress exposure also can modify lipid composition, reactivity, and distribution on the skin, which makes large scale analysis of skin lipids an interesting potential maker of chronic stress exposure in children.[82]	Skin lipidomics, F2-isoprostane, fe-ROM, d-ROM, Malondialdehyde (MDA), mtDNA content
DNA sequence variation (polygenic risk scores) and GxE interactions	Large inter-individual variability (ie, heterogeneity) in responses to childhood adversity are an important aspect to consider, especially because of the multitude of interactive processes that occur during development. Genetic background operates in concert with clinically relevant adversities to determine specific health outcomes. An assay that captures relevant genetic background could improve the identification of children at high risk for such outcomes. Genome-wide association studies have permitted large scale analyses of common markers,[83] and it is now widely accepted that the genetic contribution to most conditions is derived from a combination of small effects from multiple genetic variants. To take into account the effects of many single nucleotide polymorphisms, the concept of polygenic risk score (PRS) was introduced. PRS summarizes an individual's genetic risk for a specific condition,[84] and can be calculated for each subject in a target sample as a sum of the risk alleles count, weighted by the effect size described in discovery genome-wide association studies.[85,86] PRSs are a measure of genetic heritability, being better suited for detecting genetic main effects[87] (though there are exceptions).[88] Nonetheless, new functional genomics methods making use of the PRS technology in a biologically informed manner have been successful in identifying gene-environment interactions[89,90] and characterizing children that are at an increased risk to develop poor outcomes in response to childhood adversity.	Polygenic risk scores, expression-based polygenic scores, PrediXcan
Epigenetic processes	Developmental and health outcomes are determined by interactions among genetic and environmental variations, which together regulate	Cellular aging (epigenetic clocks), polyepigenetic risk scores

SUPPLEMENTAL TABLE 3 Continued

Domain of measurement	Description	Examples of potential markers
	gene expression through epigenetic processes. These processes include a wide range of mechanisms that affect gene expression in response to either the environmental stimulus or to the genetic sequence itself (DNA methylation, DNA h/ydroxymethylation, DNA formylation, DNA carboxylation, chromatin modifications and changes in chromatin accessibility, histone modifications and variants, noncoding RNAs, micro-RNAs, RNA modifications).[91] DNA methylation is one of the most well studied epigenetic mechanisms in the context of the embedding of childhood experiences.[92–94] Though initial studies focused on candidate-genes exploration, epigenome-wide association studies of markers are more recently employed. Leveraging on EWAS of DNA methylation, composite polyepigenetic scores can be calculated including multiple differently methylated CpG sites spread across multiple genes. A recent study shows for example that polyepigenetic scores for inflammation and for tobacco smoking (but not for obesity) are markers of exposure to socioeconomic disadvantage in children.[95] Epigenetic "clocks" are composite DNA methylation markers of chronological age, so that deviations (age acceleration or deceleration) reflect cellular aging.[96] In adults, these deviations are correlated with several age-related phenotypes like mortality and cognitive decline.[96] Recently, a highly accurate and noninvasive biological measure of cellular age specific to pediatric samples using buccal epithelial cell DNA methylation markers was developed.[97]	
Endocannabinoids	The endocannabinoid system is a neuromodulatory lipid system, consisting of the cannabinoid receptors type 1 and type 2[98–100] and 2 major endogenous ligands, anandamide and 2-arachidonoyl glycerol. The activation of this system at the synapse leads to a suppression of neurotransmitter release from the presynaptic compartment.[101] The endocannabinoid system is an important regulator of different aspects of the stress response, from stress perception to hypothalamic-pituitary-adrenal axis activation, and also memory formation, pain sensitivity, reward regulation, and synaptic plasticity.[101] These neuromodulators are accumulated over time in hair, and their measurement in this compartment provides a stable and reliable assessment. Hair endocannabinoids levels have been associated with post-traumatic stress disorder symptom severity in adults[102] and to childhood maltreatment exposure in adults and their offspring.[103]	anandamide, ratio 1:2-Arachidonoyl glycerol, Oleoylethanolamine, Stearoylethanolamide, N-acyl-ethanolamides, palmitoylethanolamide
Telomere structure	Telomeres are caps at the ends of chromosomes that are involved in facilitating chromosome replication. They normally ensure that the entire DNA strand is copied, up until the very end of the gene coding sequence. The length of the telomere is important for determining a cell's ability to proliferate, but with each round of cell division, a small portion of the telomere is lost. Telomere attrition is among the well-known cell-intrinsic events associated with normal cellular aging[104] being a marker of exposure to chronic stress.[105] A meta-analysis has shown that the association between childhood adversity and telomere shortening in children is quite consistent, encompassing a broad range of different negative experiences such as family and community poverty, household violence, family disruption, social deprivation, institutionalization and maternal depression.[106]	Telomere length measured from buccal cell DNA samples.
Gut, airway, and skin microbiome	The human microbiome consists of trillions of microorganisms,[107] whose diversity, composition and function vary across body sites, including the gut, skin, and airway.[107] The relationship between the human host and these commensal microorganisms is mutual. For example, the gut microbiome modulates immune responses,[108] gut permeability, digestion, and function of enteric and central nervous system activity.[109] Disruptions of this relationship are associated with multiple chronic diseases such as obesity, cardiometabolic diseases, cancer, autoimmune conditions, and psychological disorders.[110] In the skin, disruptions of host-microbe mutualism are associated with atopic	Gut, airway, and skin microbiome genomic analysis

SUPPLEMENTAL TABLE 3 Continued

Domain of measurement	Description	Examples of potential markers
	dermatitis[111] and psoriasis.[112] Alterations of the lung microbiota are associated with chronic obstructive pulmonary disease, asthma, and cystic fibrosis.[113] Stress modulates microbiome structure and activity, and may be one causal factor in host-microbiome disruptions that lead to chronic disease.[114,115]	
Organ remodeling	Growth and remodelling are key phenomena of the developmental trajectory, playing important roles during morphogenesis in early life as well as in homeostasis and pathogenesis in adult tissues; these soft tissues and organs adapt to changes in their environment as a result of ageing, diseases or injury.[116] One of the most well-known examples of organ remodelling in the context of early development is related to exposure to prenatal adversity (eg, placental insufficiency, cigarette smoking, maternal malnutrition, chronic stress). These conditions are associated with impaired achievement of full growth capacity in utero,[117] with poorer pancreas development (diminished β cell mass)[118] and decreased number of nephrons.[119] These organ remodelling effects are adaptive for fetal survival in the short term but are associated with increased risk for adult chronic diseases like type II diabetes,[70] and hypertension.[120]	Growth trajectories
Prefrontal function	The prefrontal cortex has a protracted development and only reaches full maturation in adulthood.[121,122] Behavioral measures of prefrontal function are associated with educational achievement across multiple domains.[123] Family socioeconomic environment is associated with child prefrontal functioning[124–126] and prefrontal activation in the context of learning.[127]	Behavioral measures of executive function
Brain electrical activity	The brain exhibits spontaneous electrical activity, resulting in voltage fluctuations derived from the neuronal membrane and action potentials. An EEG records this activity on the scalp and can reflect brain developmental trajectories.[128] Exposure to maternal stress in infancy is associated with reduced brain activity.[129] Severe forms of social deprivation in children are also linked to alterations in brain electrical activity.[128–130]	EEG
Wearable transdermal sensors	Several devices aimed at monitoring real-time stress have been developed using photoplethysmography data,[131] although sensing of biomarkers themselves (rather than their consequent bodily response) is more accurate. Recent developments include portable salivary cortisol detection devices, portable differential pulse voltammetry systems and wearable sweat cortisol sensors.[132] Skin-interfaced sensing platforms are in development, indicating a trend toward flexible sensing as opposed to rigid circuitry.[133,134] A new, promising, printed, 3-graphene electrode system with an integrated Bluetooth module and microfluidic sample collection provides cortisol measurement in minutes.[135]	Cortisol, cardiovascular reactivity

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