Cells To Solutions

Exploring multidisciplinary, physiology-based healing strategies for toxic stress as part of routine clinical care

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Disclosures

Rachel Gilgoff MD, FAAP

Has documented no financial relationships to disclose or Conflicts of Interest (COIs) to resolve.

She has documented this presentation ***will not*** involve discussion of unapproved or off-label, experimental or investigational use.

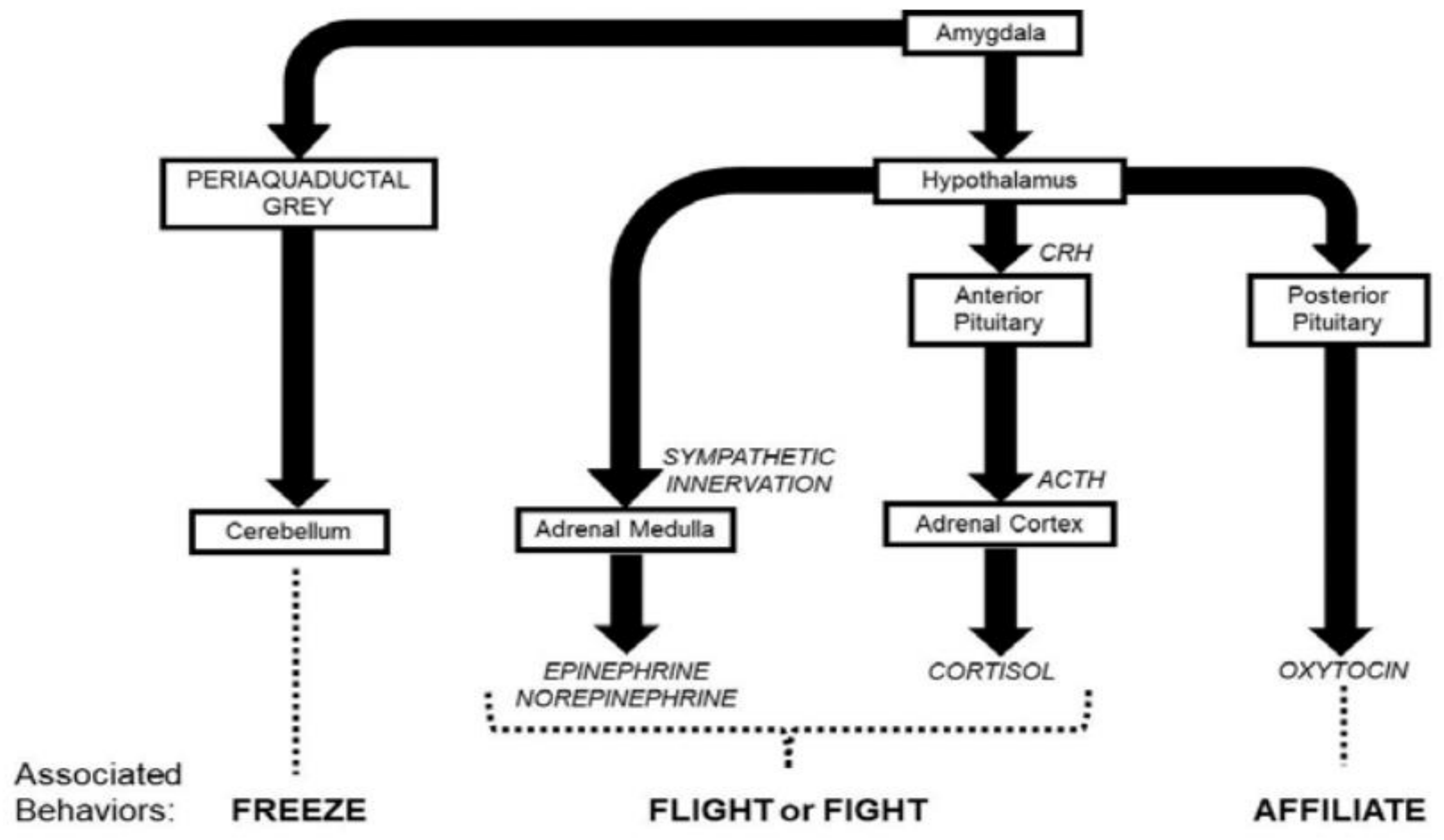
Learning Objectives

- Describe how the science of stress biology can be applied to our clinical response for children and adults who have experienced early life adversity.
- Identify examples of clinical interventions for stress-mitigation strategies.
- Identify examples of community-based support services for stress-mitigation strategies.

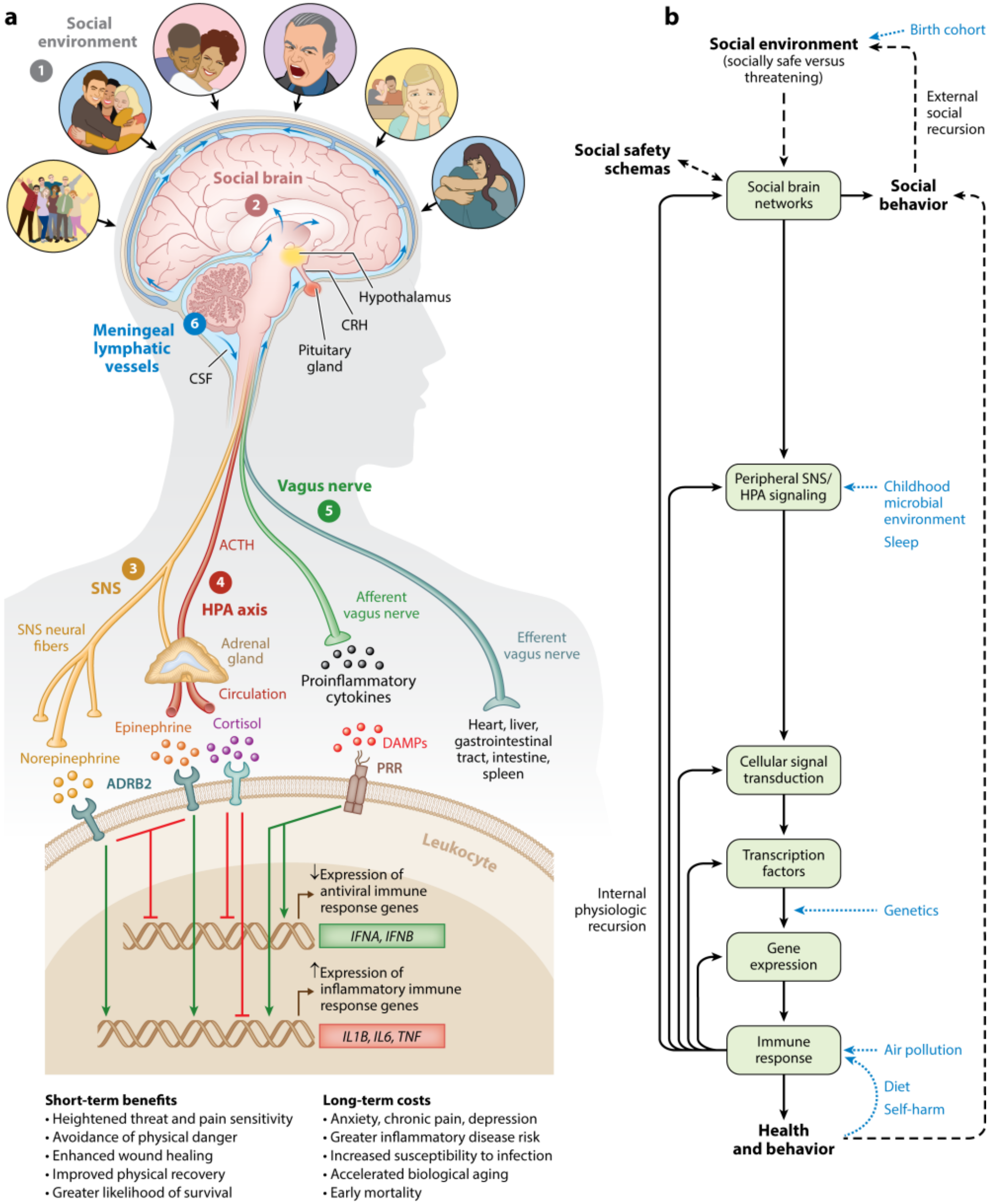
Stress Biology and Toxic Stress

Experiences Change Our Biology

- Expectancy Theory
- Placebo/Nocebo
- Positive Psychology
- Interpersonal Biology
- Social Safety Theory
- Stress Biology



Garner, A and Saul B. Thinking Developmentally, AAP Press, 2018.

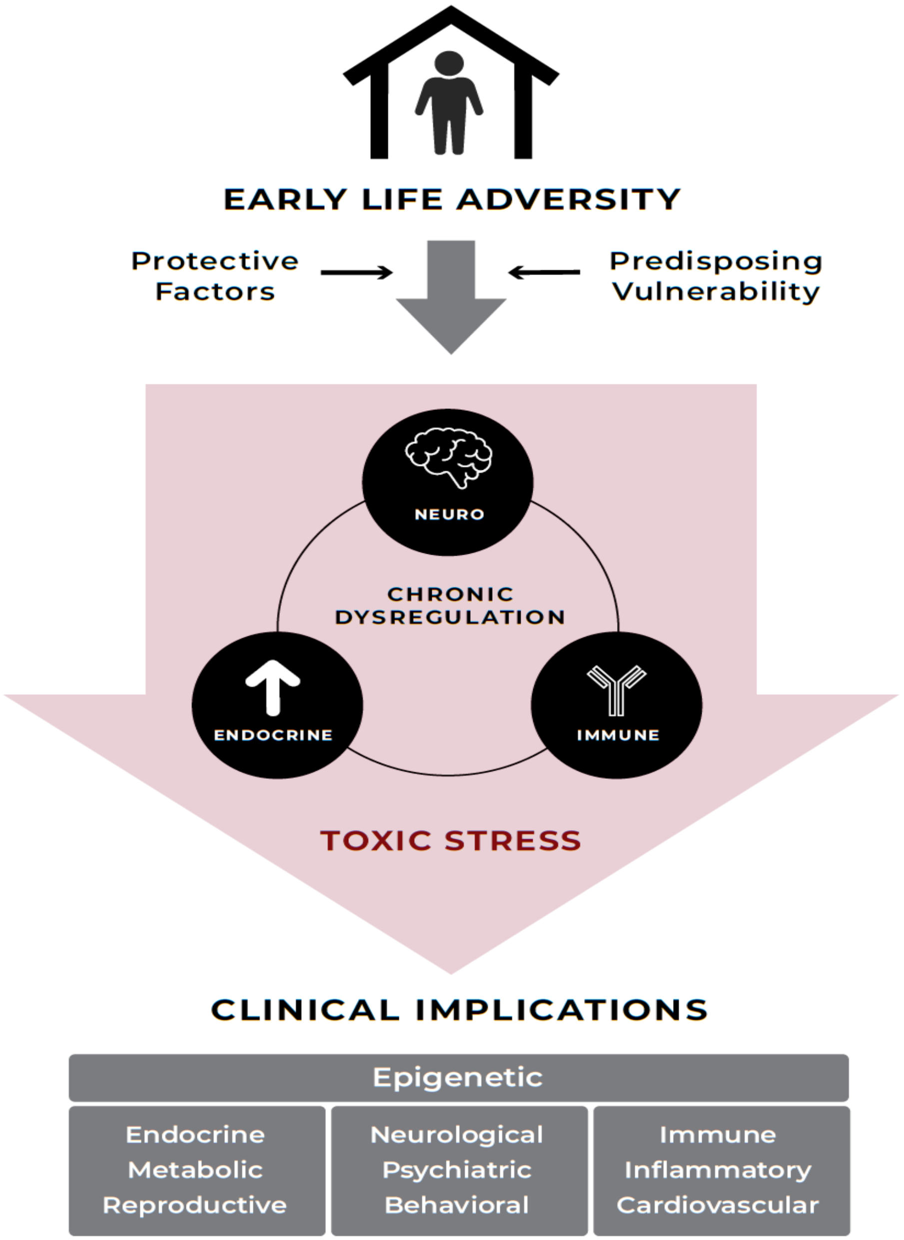


Social Threat Theory

Slavich, G. *Annual Reviews* 2020

Adverse Childhood Experiences (stressors) can generate chronic activation of the stress response system

Toxic stress is a physiological stress response



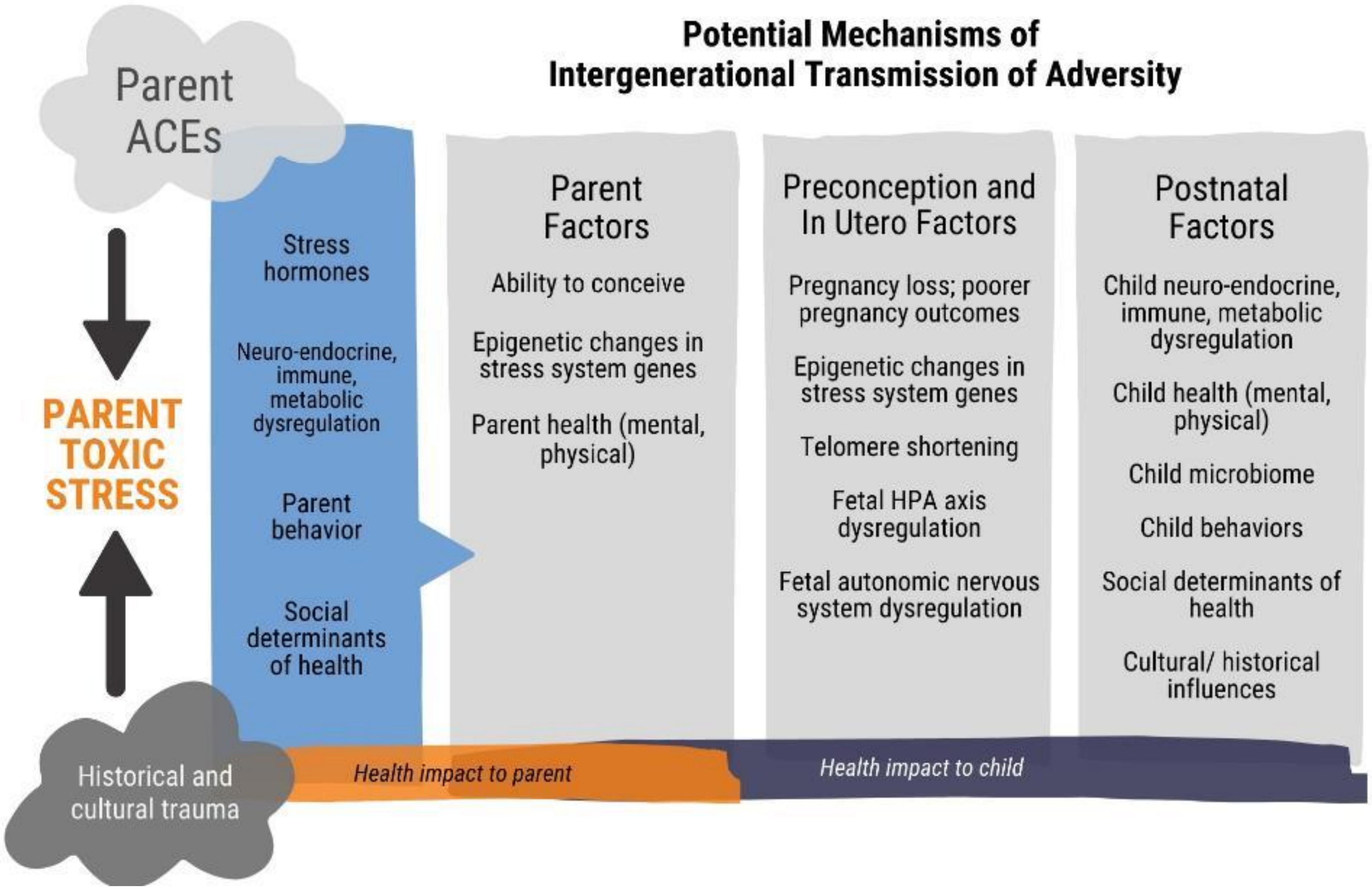
Source: Adapted from Bucci, M., Marques, S. S., Oh, D., & Harris, N. B. (2016). Toxic stress in children and adolescents. Advances in Pediatrics, 63(1), 403-428.

Biological Systems Disrupted by Early Life Adversity and Toxic Stress

aces aware
SCREEN. TREAT. HEAL.

System	Mechanism(s)	Health Impact
Neurologic; Neuroendocrine	Dysregulation of sympathetic and hypothalamic-pituitary-adrenal axes; autonomic imbalance	Difficulty modulating, sustaining, or dampening the stress response; heightened or blunted stress sensitivity
	Altered reactivity and size of the amygdala	Increased fear responsiveness, impulsivity, and aggression
	Altered pain processing through endogenous opioid and cannabinoid system	Increased risk for chronic pain syndromes
	Inhibition of the prefrontal cortex	Impaired executive function, with poorer planning, decision-making, impulse control, and emotion regulation
	Hippocampal neurotoxicity	Difficulty with learning and memory
	Ventral Tegmental Area and reward processing dysregulation	Increased risky behaviors and risk of addiction
Immunologic; Inflammatory	Increased inflammatory markers, especially Th2 response; inhibition of anti-inflammatory pathways; gut microbiome dysbiosis	Increased risk of infection, auto-immune disorders, cancers, chronic inflammation; cardiometabolic disorders
Endocrine; Metabolic	Changes in growth hormone, thyroid hormone, and pubertal hormonal axes	Changes in growth, development, basal metabolism, and pubertal events
	Changes to leptin, ghrelin, lipid and glucose metabolism, and other metabolic pathways	Increased risk of overweight, obesity, cardiometabolic disorders, and insulin resistance
Epigenetic; Genetic	Sustained changes to the way DNA is read and transcribed	Mediates all aspects of the toxic stress response
	Telomere erosion, altered cell replication, and premature cell death	Increased risk for disease, cancer, and early mortality

Source: Bhushan D et al. Office of the California Surgeon General. Roadmap for Resilience: The California Surgeon General's Report on Adverse Childhood Experiences, Toxic Stress, and Health. Office of the California Surgeon General, 2020



Source: Bhushan D, Kotz K, McCall J, Wirtz S, Gilgoff R, Dube SR, Powers C, Olson-Morgan J, Galeste M, Patterson K, Harris L, Mills A, Bethell C, Burke Harris N, Office of the California Surgeon General. Roadmap for Resilience: The California Surgeon General's Report on Adverse Childhood Experiences, Toxic Stress, and Health. Office of the California Surgeon General, 2020.

Using Stress Biology to Inform Our Clinical Approach

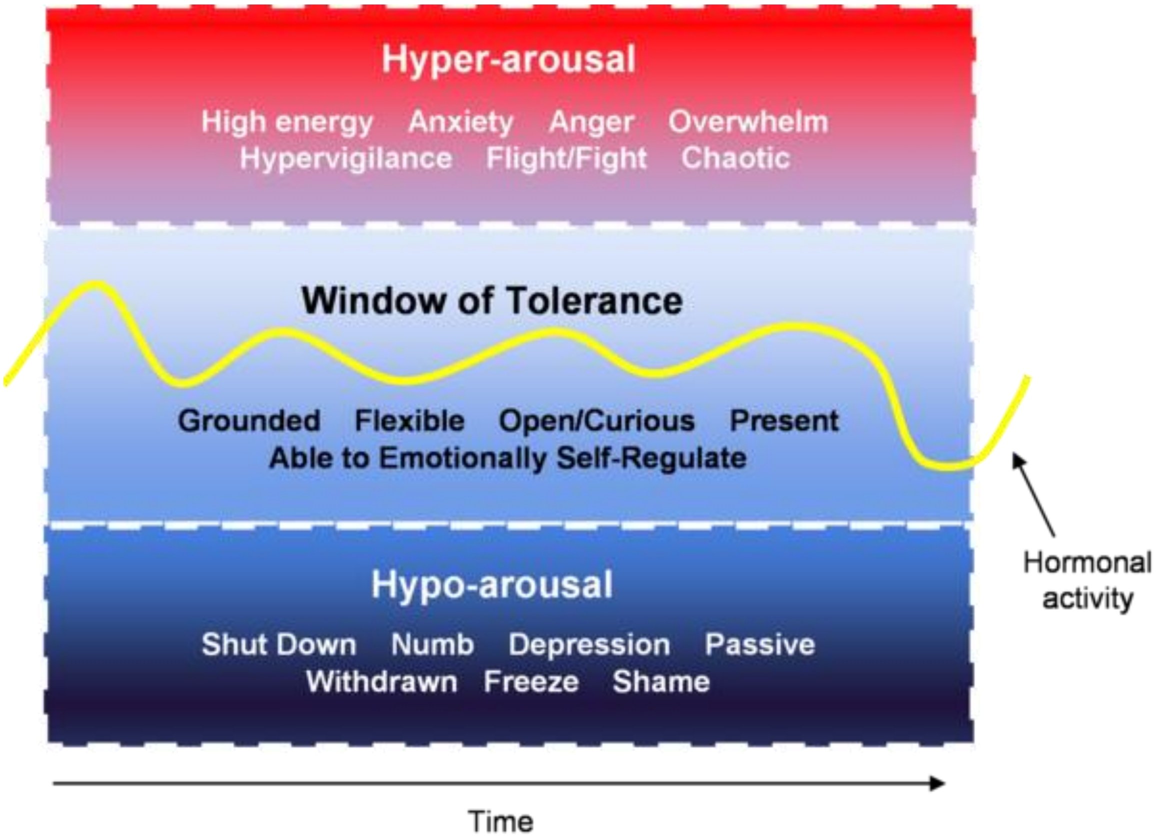
3 Focus Areas for Responding to ACEs and Toxic Stress

1. Address current **stressors**
2. Support the **"in the moment" stress response**
3. Support **long-term healing from toxic stress**

1. Stressors:
Help decrease your patient's current stressor load.

- Assess current safety and provide any needed resources
- Find tools and resources on www.acesaware.org/managestress
- Connect them with resources from www.findhelp.org your local 2-1-1 which can also provide resources such as housing, food, childcare, and legal services.
- Leverage your networks of care resource list for the resources most often needed in your community.

2. Immediate Stress Response:
Build skills and coping strategies

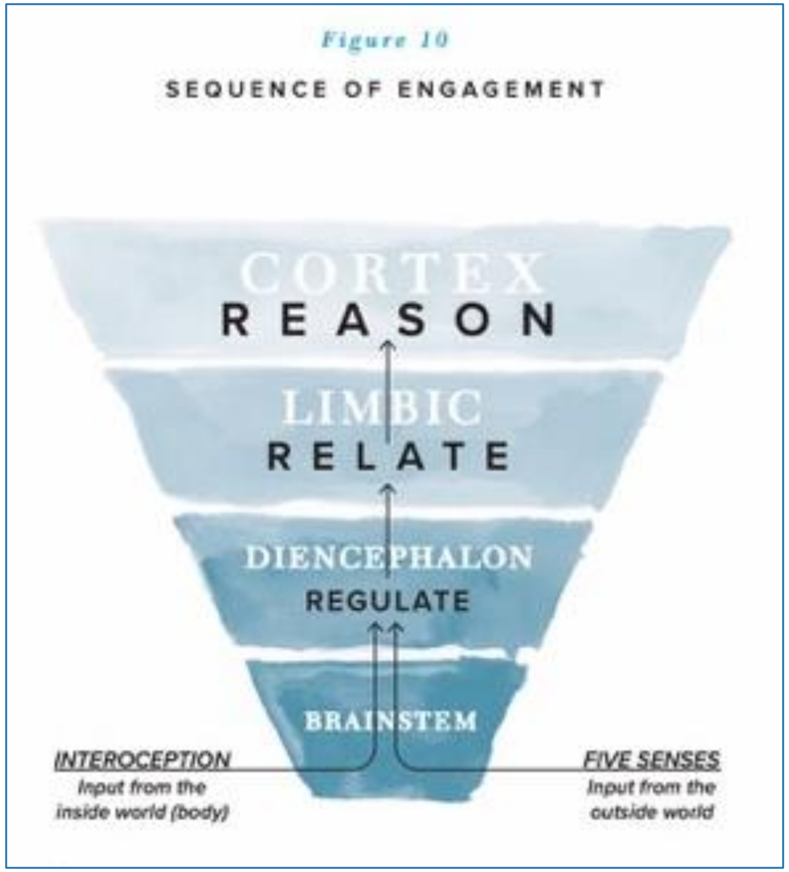


- Grounding techniques.
- Breathing techniques.
- Sensory support.
- Progressive muscle relaxation.
- Move your body
- **Reach out to your support person**

Source: Cole, E. Expanding the "Window of Tolerance" Psychology Today. April 10, 2020

Dr. Bruce Perry's Regulate Relate Reason A Neurosequential Approach

1. Brainstem: First, regulate ourselves and co-regulate the other person. Help them feel safe and calm, reducing their stress responses.
2. Limbic: Then relate to their emotions. Help them feel understood and connected.
3. Cortex: Once the other person feels safe, connected, and understood, engage them to process what happened through reason.



Source: Dr. Bruce Perry. The Neurosequential Model.

Skill Building and Collaborative Problem Solving

- **Behavior as communication:** When children are acting out, they are trying to communicate something.

- **Teach skills:** Often kids who are not doing well, cannot do well because they are missing a skill (usually affect regulation). It is not because they need more "motivation" but rather they were not taught or modeled these skills.

"Kids with challenging behavior don't lack the *will* to behave well.

They lack the *skills* to behave well."

Collaborative Problem Solving

www.thinkkids.org
www.livesinthebalance.org

3. Stress Busters as a Framework for Long-Term Healing

Long-term healing:
Address long-term effects from toxic stress

Consider strategies and interventions that can improve neurologic, endocrine, immune, and metabolic function.

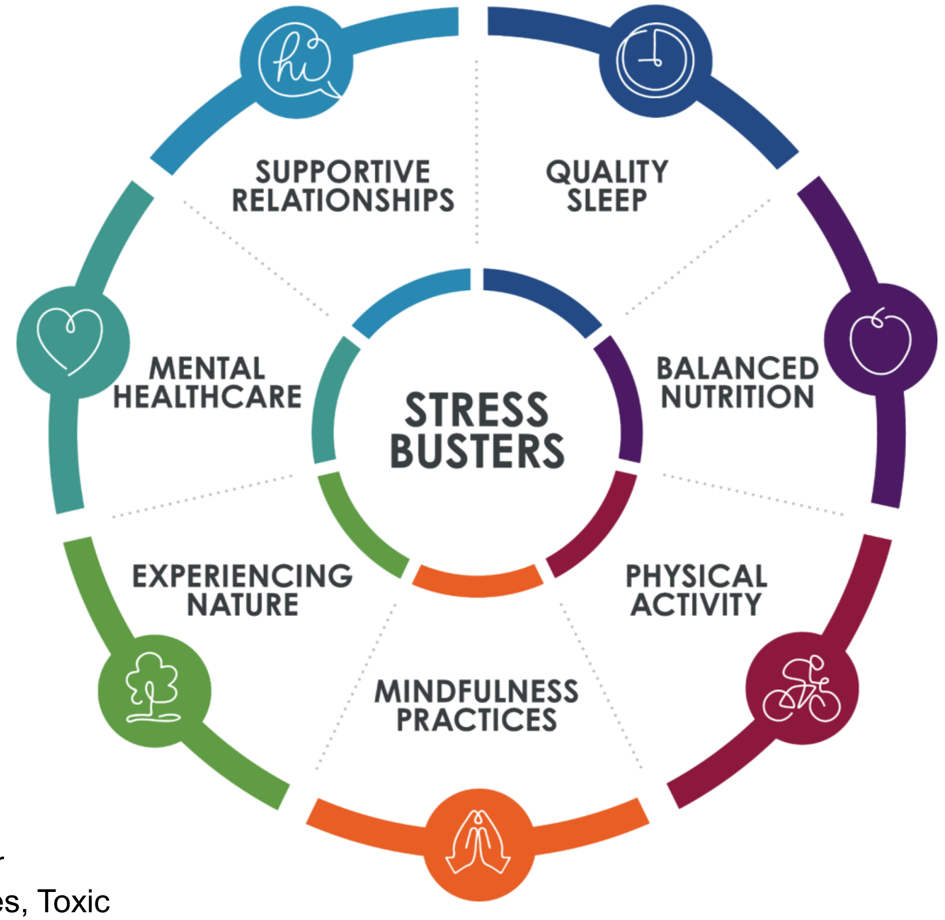
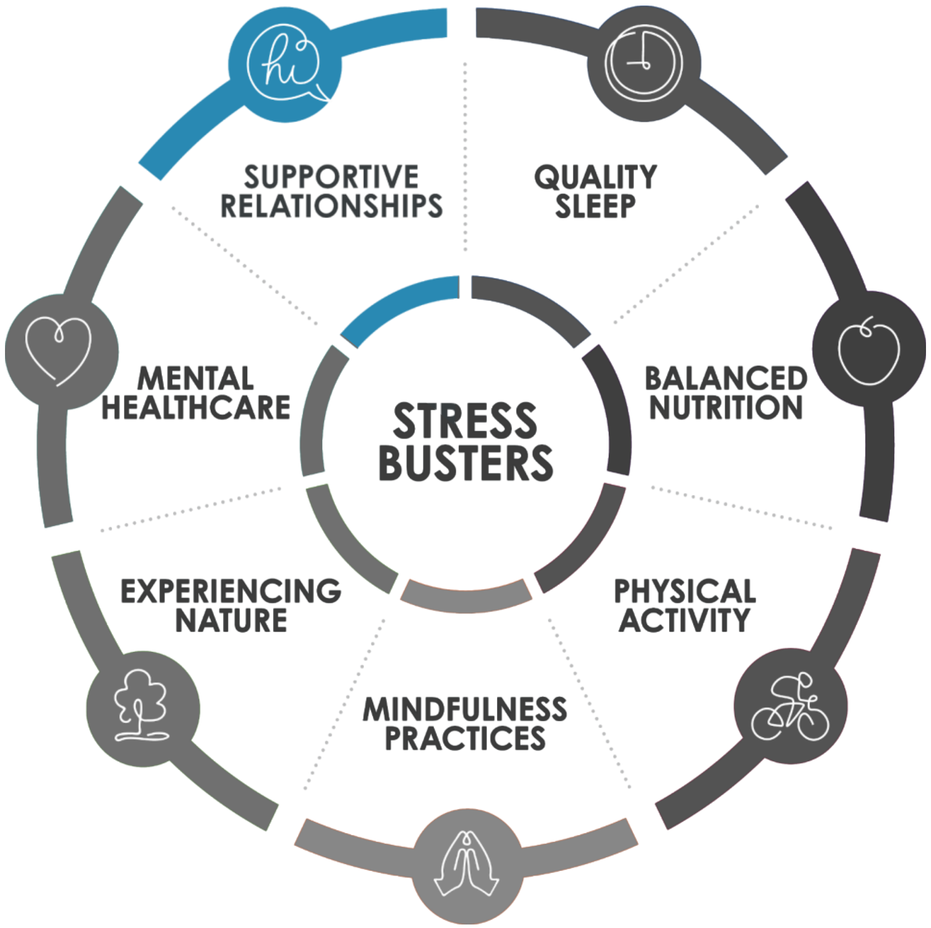


Image Source: Bhushan D et al. Office of the California Surgeon General. Roadmap for Resilience: The California Surgeon General's Report on Adverse Childhood Experiences, Toxic Stress, and Health. Office of the California Surgeon General, 2020



Supportive Relationships

Impacts of Supportive Relationships and Social Engagement

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SCREEN. TREAT. HEAL.

Neurologic and HPA Axis

- Larger hippocampus
- Improves cortisol reactivity

ANS and Cardiovascular Reactivity

- Lower blood pressure
- Lower catecholamines

Oxytocin

- Oxytocin receptors on the amygdala allowing oxytocin to inhibit ANS and HPA response
- Protects against stress-induced cell death,
- Anti-inflammatory effects,
- Enhances metabolic homeostasis

Immune Function

- Decreased inflammation
- Protects against the common cold
- Decreased asthma symptoms

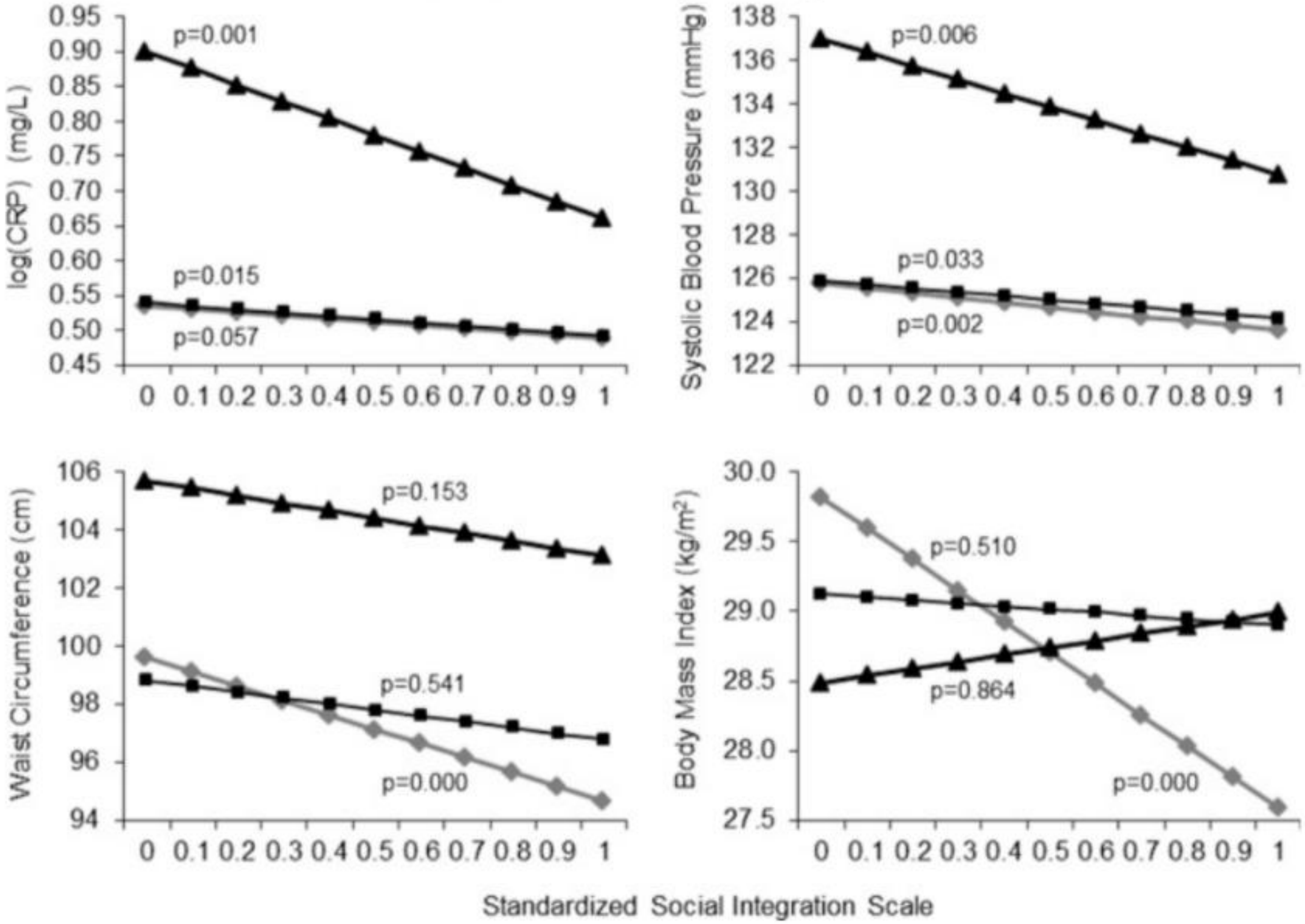
(Uchino 2006; Blaisdell, Imhof et al. 2019; Slopen, McLaughlin et al. 2014; Meyer 2020; Ditzen 2007; Heinrichs 2009; Suglia J of Epi and Comm Health 2010; Lim J of Fam Psych 2008; Manczak Health Psch 2017; Wang J of Neuroimm 2015; Li Frontiers in Imm 2017; Cohen 2004, 2015)

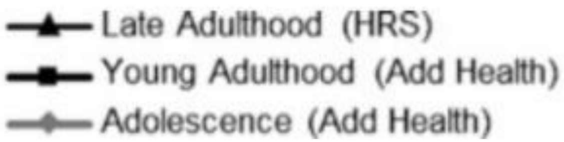
Interventions that Improve Social Relationships Can Improve Stress Hormones and Health

Slopen, 2014	Marie-Mitchell, 2018	Purewal Boparai, 2018
• Interventions designed to improve social relationships, environments or psychosocial functioning in children associated with improved cortisol activity.	• Multicomponent interventions including parenting education, mental health support, and social service referrals were associated with improvements in parent–child relationship and behavioral and mental health problems.	• Three key intervention elements – a focus on strong parenting skills, earlier intervention placement, and greater intervention engagement – improved or even normalized stress hormone profiles and decreased the impact of toxic stress on brain development and epigenetic regulation.

Social Integration

- Lower C-reactive protein (CRP)
- Lower systolic blood pressure (SBP)
- Lower Waist Circumference
- Lower body-mass index (BMI) in adolescence
- Higher BMI in late adulthood





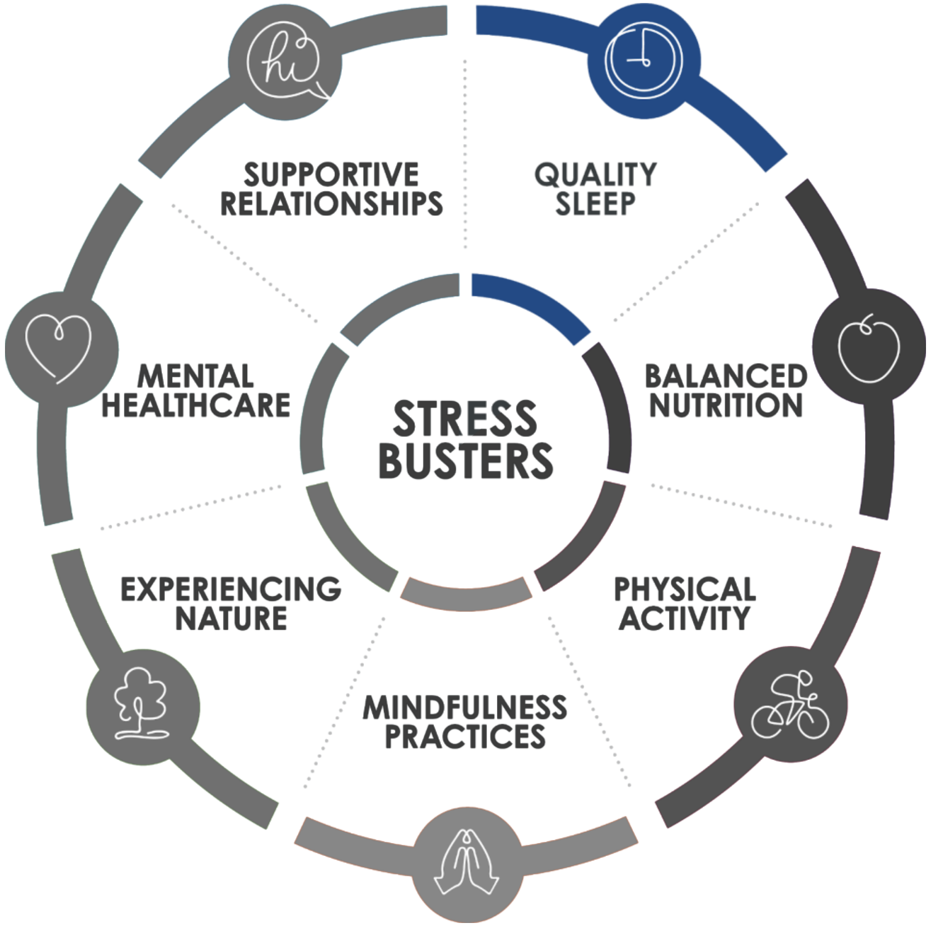
Yang Claire, et al. "Social relationships and physiological determinants of longevity across the human life span." Proceedings of the National Academy of Sciences 113.3 (2016): 578-583.

Supportive Relationships - Clinical Practice

- Anticipatory guidance:
  - We live longer!
  - Hugs are protective!
- Talk Read Sing and Reach Out and Read
- Encourage “time in” – with your children, friends and relatives!
- Universal home visiting
- Multidisciplinary group clinic visit model

- Connect with community programs, faith programs
- Support groups
- Parenting programs: Triple P, Video Interaction Project, Incredible Years

- Mental health, Family Therapy, and targeted dyadic interventions:
  - Couples Counseling, EFT and Gottman, Attachment and Biobehavioral Catch-up (ABC), Child-Parent Psychotherapy (CPP), and Parent-Child Interaction Therapy (PCIT)



Quality Sleep

Impacts of Quality Sleep

Neurologic

- Memory consolidation
- Allows for normal circadian rhythms of cortisol

ANS and Cardiovascular Reactivity

- Decreases SNS output

Endocrine/Metabolic

- Increases growth hormone, prolactin, melatonin
- (Poor sleep increases insulin, blood glucose, appetite and caloric intake)

Immune Function

- Decreased inflammation
- Improved response to vaccination
- Decreased risk of infection

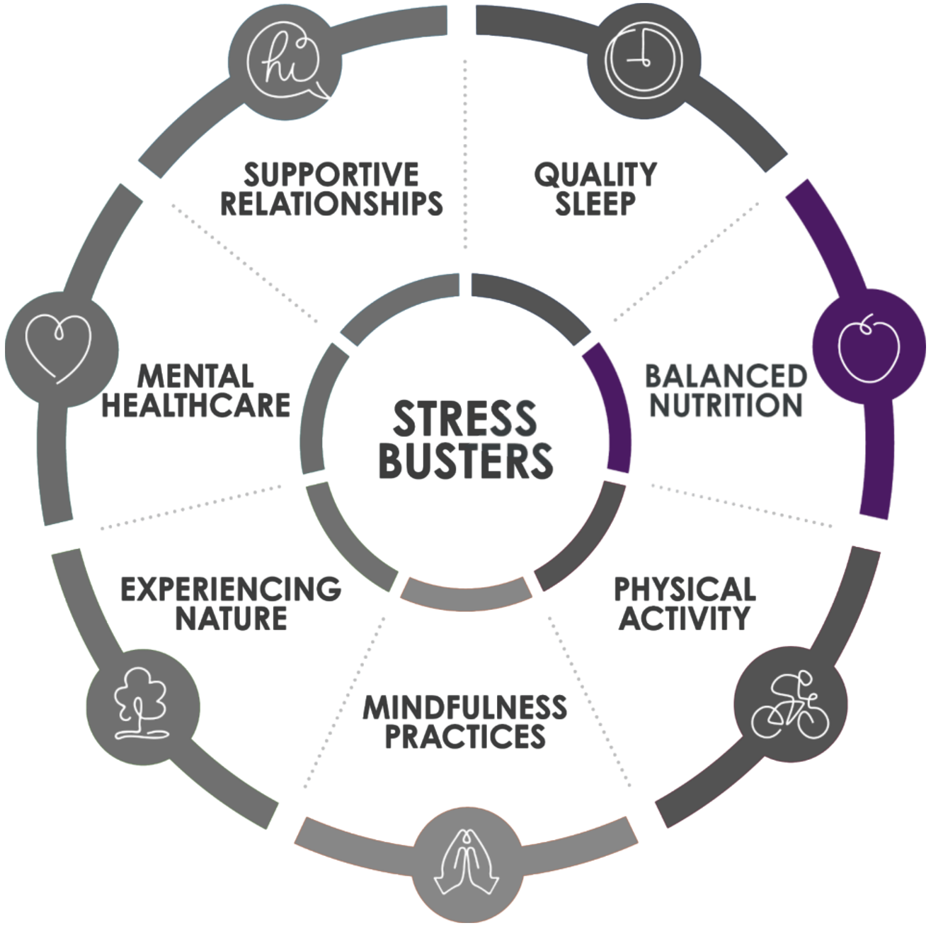
Sadeh 1996; Kajeepeta 2015; Brock 2019; Nurius 2015; Chatburn 2014; Greenfield 2011; Luyster 2012; Besedovsky 2019; Itani 2017; McEwen 2015; Mindell 2018; Irwin 2015; Besedovsky 2012

Quality Sleep - Clinical Practice

- Anticipatory guidance:
  - Sleep disturbances are common.
  - Healthy sleep can improve neurological, endocrine, metabolic and immune regulation
  - Sleep hygiene

- Additional support: night light, weighted blanket, relaxation techniques, journaling, or conversations with a trusted adult/friend to address specific worries.
- Meditation, yoga, exercise during the day

- Medications
- Sleep Study and referral to sleep specialist
- Referral to mental health for cognitive-behavioral therapies.



Balanced Nutrition

Science of Nutrition and ACEs

Stress can affect food behavior, digestive processes, and metabolism

SNS
Norepinephrine/Epinephrine

- Increase glucose mobilization, insulin resistance, and glucagon secretion
  - Glucagon, in turn, decreases appetite
- Decrease gut motility and gastric emptying

HPA
Cortisol

- Increases appetite and motivates consumption of energy-dense, high-fat, high-sugar foods
  - Increased fat storage, called abdominal or central obesity

Reward Circuitry

- Changes in brain circuitry that reinforce stress-eating strategy as a coping mechanism when stressed, or even in anticipation of stress.

Descheness 2018; Isohookana 2016; Guillaume 2016; Campbell 2018; Kimber 2017; Molendijk 2017; Pginatelli 2017; Coffino 2020; Lindsay 2019; Romeo 2008; Lindsay 2017; Kiecolt-Glaser 2010; Lyte 2018; Sapolsky 2004

Impacts of Nutrition

Neurologic

- Nutrients such as magnesium, zinc, and Omega-3 fatty acids support brain function, cell membrane transport and neurotransmitter production

Cardiovascular Reactivity/ Endocrine/Metabolic

- Excessive sugar consumption increases risk for heart disease, HTN, dyslipidemia, insulin resistance and hepatic dysfunction
- Omega-3 fatty acids lower NE, ACTH and plasma cortisol in response to endotoxin challenge

Immune Function

- Pesticides, fast food, overly processed foods are pro-inflammatory
- Vegetables, whole grains, omega-3 decrease inflammation

Descheness 2018; Isohookana 2016; Guillaume 2016; Campbell 2018; Kimber 2017; Molendijk 2017; Pginatelli 2017; Coffino 2020; Lindsay 2019; Romeo 2008; Lindsay 2017; Kiecolt-Glaser 2010; Lyte 2018; Sapolsky 2004; Lustig 2012 Nature

Balanced Nutrition - Clinical Practice

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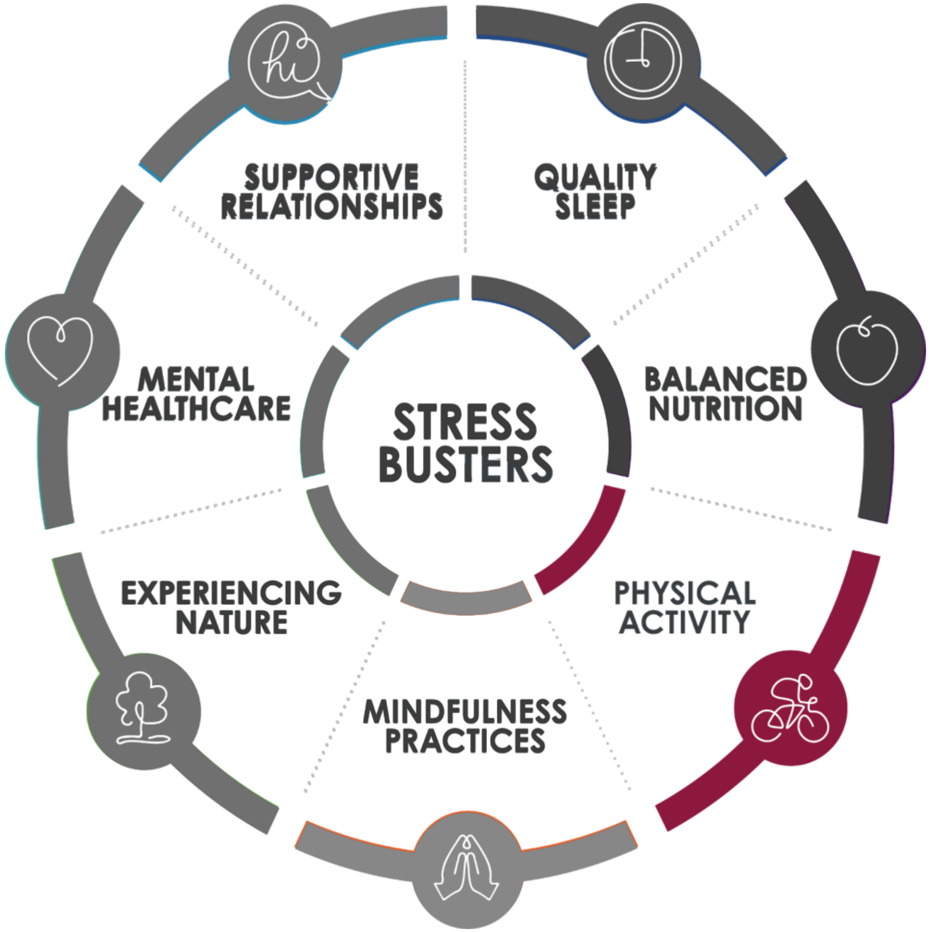
- Anticipatory guidance:
  - Stress can INCREASE or DECREASE appetite
  - Stress can increase cravings for high-fat and high-sugar foods
  - Western diet associated with increased inflammation
  - Anti-inflammatory diet: fruit, vegetables, fish, whole grains

- Consider Omega-3 Fatty Acid supplementation
- Trauma-informed weight loss programs
- Tie into other domains - eat with family and friends, physical activity, mindful eating
- Nutritionist or Dietician support

- Referral to needed specialist (anorexia clinics, obesity clinics, Cardiology, Endocrinology, GI, etc.)



Physical Activity

Impacts of Physical Activity

Neuro, Endocrine, Metabolic

- Increased hippocampal neurogenesis, blood flow and volume
- Improved memory, attention, cognition, psychosocial functioning
- Increased BDNF< dopamine, endogenous opioids, cortisol and catecholamines
- Decreases insulin

Immune Function

- Improved immune function and competency
- General anti-inflammatory effect over time

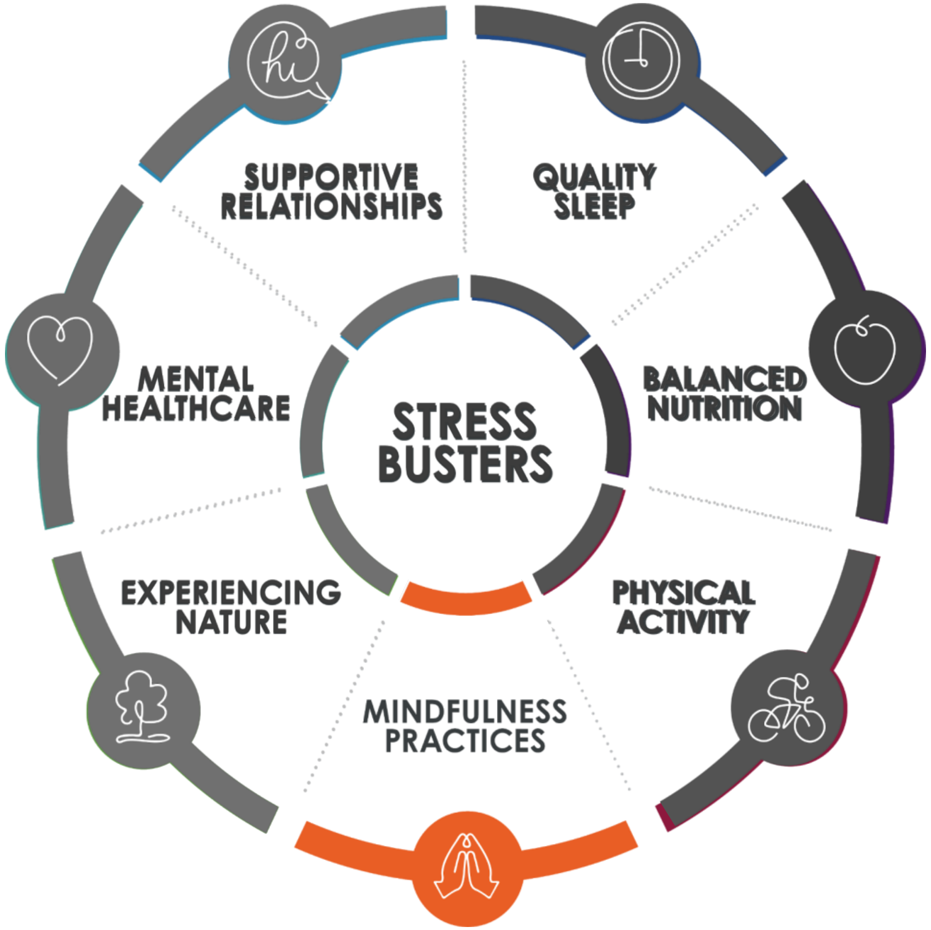
Di Liegro 2019; Coelho 2013; De Assis 2018; Bathina 2105; Verbickas 2018; Firth 2018; Li 2017; Erickson 2011; Woon 2008; Northey 2018; Hansen 2012; Van Bruggen 2011; Kandola 2016; Rimmele 2009; Dhabar 2018; Flesner 2005; Pedersen 2000; Gleeson 2011; Campbell 2018;

Physical Activity - Clinical Practice

- Anticipatory guidance:
  - Physical activity - improved memory, attention, cognition, mental health, immune function
  - May help promote the positive stress response, metabolize increased energy associated with anxiety or stress, and increase resilience factors

- Brief physical activity breaks to release excess energy
- Moderate-intensity aerobic activity, for longer durations, three times or more a week
- Activities that combine physical activity with self-regulation skills and breathing techniques, such as martial arts and yoga, may also be beneficial

- Low mood and stress have been identified as barriers to exercising; professional support may help patients overcome these barriers.



Mindfulness Practices

Impacts of Mindfulness

Neurologic

- Involves PFC, anterior cingulate cortex, insula, amygdala and hippocampus
- Improves default mode network processing and self-referential thinking

ANS and Cardiovascular Reactivity

- Decreased sympathetic activation
- Improved parasympathetic activity
- Decreased cardiovascular disease

Immune Function

- Improved immune function

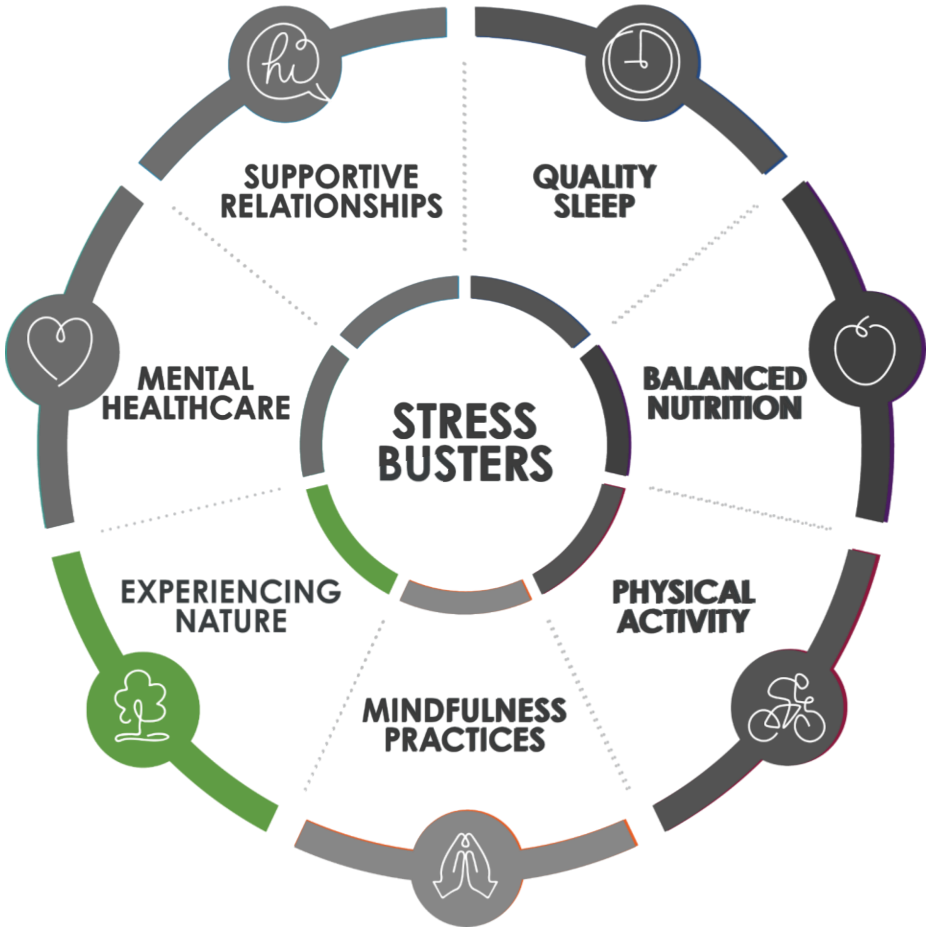
King 2016; Marchand 2012; Marchand 2014; Cahn 2017; Burg 2012; Ortiz 2017; Bethel 2016; Chiesa 2009; Roemer 2015; Castillo-Richmond 2000; Zamarra 1996; Levine 2017; Black 2016

Mindfulness Interventions - Clinical Practice

- Anticipatory guidance:
  - Nonjudgmental, moment-to-moment awareness that involves attention, intention, and a kind attitude
  - Can support trauma healing and regulation of stress
  - Improved cardiovascular and immune health

- Online resources and downloadable apps
  - UCLA Mindful, Mindfulness Coach, Sesame Street in Communities
- Other mind-body practices: including tai chi, yoga, acupuncture, breathing techniques, and massage therapy

- Mindfulness-based stress reduction (MBSR) and Mindfulness Based Cognitive Behavioral Therapy (MB-CBT)



Experiencing Nature

Impacts of Experiencing Nature

Neurologic

- Improved cognitive function, attention, psychological well-being, meaningfulness and energy

ANS and Cardiovascular Reactivity

- Decreased SNS activity, increased PNS activity
- Decreased blood pressure

Endocrine

- Decreased perceived stress and cortisol levels
- Decreased blood glucose

Immune Function

- Reduced inflammatory cytokines

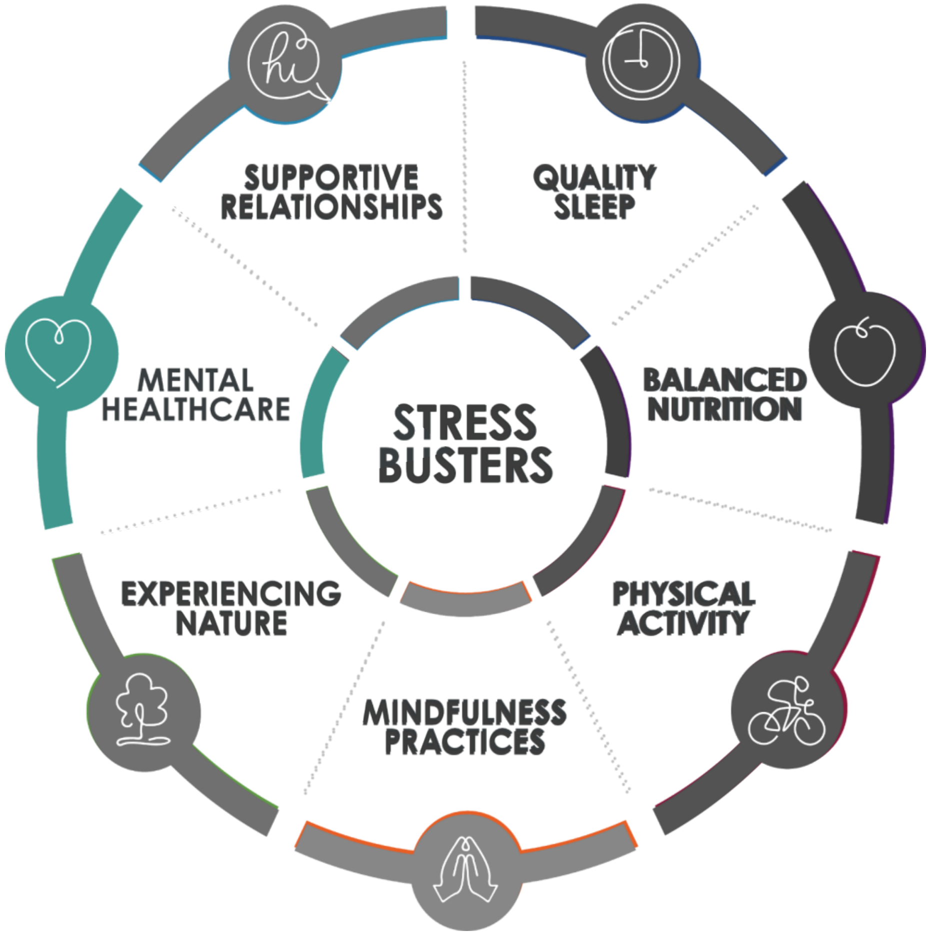
Razani 2018; Kuo 2015; Kim 2010; Summer 2018; Berman 2012; Cervinka 2012; Aspinal 2015; Razani 2020; Hu 2008; Mock 2016; Gross 2017

Experiencing Nature - Clinical Practice

- Anticipatory guidance:
  - Parks, local green spaces, playgrounds, and even indoor plants.
  - Decreases diabetes, depression, heart rate, blood pressure, and mortality
  - Calms the stress response system and increases healthy behaviors such as physical activity, mindfulness, and relational health

- Park Prescriptions! Visit Parkrx.org, and the Children and Nature Network
- Encourage green space.
- Providers can recognize that there may be cultural, community, and policy barriers to equal access to nature. Access to nature is a social justice health issue.

- Referral to ecotherapy or adventure-based treatment programs.



Mental Health

Science of Mental Health and ACEs

- Mental and behavioral healthcare can help patients build skills and capacities for resilience, directly address trauma-related symptoms, and scaffold with medications as necessary, all in the context of safe, supportive, and trusting relationships.

- Multidisciplinary care should include bidirectional flow of information.

- Psychological interventions may improve both the mental and the physical health consequences of toxic stress.

Fallot 2009 Creating Cultures of Trauma Informed Care; NASEM 2019 Fostering Health Mental, Emotional and Behavioral Development in Children and Youth; The National Child Traumatic Stress Network (NCTSN); The Substance Abuse and Mental Health Services Administration (SMHSA) and The California Clearninghouse for Child Welfare (CEBC)

Impacts of Mental Health Interventions

- CBT improves patient awareness of negative thoughts, behaviors, and feelings about their disease, increase compliance with medical recommendations, and support healthy self-care behaviors.
- Cognitive therapy may enhance prefrontal cortex function and inhibit amygdala activation.
- CBT may decrease children's medical symptoms including asthma and anxiety
- Patients with heart disease who received traditional care plus CBT had a 41% lower rate of recurrent cardiovascular disease event and 45% fewer heart attacks than patients who received traditional care alone.

Pan 2020; Davidson 2012; Santarnecci 2019; Ghosh 2011; Slopen 2014; Boparai 2018; Lieberman 2011; Lieberman 2006; Lieberman 2005; Ghosh Ippen 2011; Bush in review

Mental and Behavioral Health – Clinical Practice

- Everyday Education:
  - Decrease stigma
  - Talk about everyday practices that can support mental health and well-being: gratitude, fun-time, activities that provide meaning and purpose, stress busters

- Address barriers to mental health services (access, engagement, stigma)
- Teach coping skills to widen the window of tolerance
- Teach Dr. Bruce Perry's 3 R's

- Consider the underlying stress biology to inform trauma-responsive treatment plan
- Medications

Trauma Therapies

- Child-Parent Psychotherapy (ages birth to 6 years): Dyadic intervention for young children and their caregivers that supports family strengths and relationships.
- Parent-Child Interaction Therapy (2 to 12 years): Dyadic parent training treatment that emphasizes improving the quality of the parent-child relationship and pattern of parent-child interactions.
- Attachment & Biobehavioral Catch-up (ABC) (Birth to middle school): A strengths-based, focused, brief (10, 1-hour weekly sessions) dyadic, home-visiting program.
- Trauma-Focused Cognitive Behavioral Therapy (TF-CBT) (verbal children and adults): A structured, short-term treatment model for children and adults who have experienced trauma.
- Eye Movement Desensitization Reprocessing (EMDR) (adolescents and adults): EMDR is focused on helping clients resolve unprocessed traumatic memories.
- Family Systems Therapy (verbal children and adults): Supports resolving family conflict or issues.
- Cognitive Processing Therapy (adolescents and adults): A type of cognitive behavioral therapy, generally 12 sessions, that helps modify maladaptive thinking related to their trauma.
- Prolonged Exposure Therapy (adolescents and adults): A cognitive behavioral therapy approach that helps clients gradually approach their memories, feelings and situations of trauma.
- Somatic Therapy (all ages): An approach that focuses on how emotions and stress appear in the body and that focuses on tools to regulate the autonomic nervous system.
- Biofeedback and Neurofeedback (young children to adults): A type of therapy that allows the client to see their physiology in real-time (e.g. heart rate, coherence, brain wave patterns) to learn strategies to control their physiology.

Internal Stress Response:
Getting to a Precision Medicine Approach

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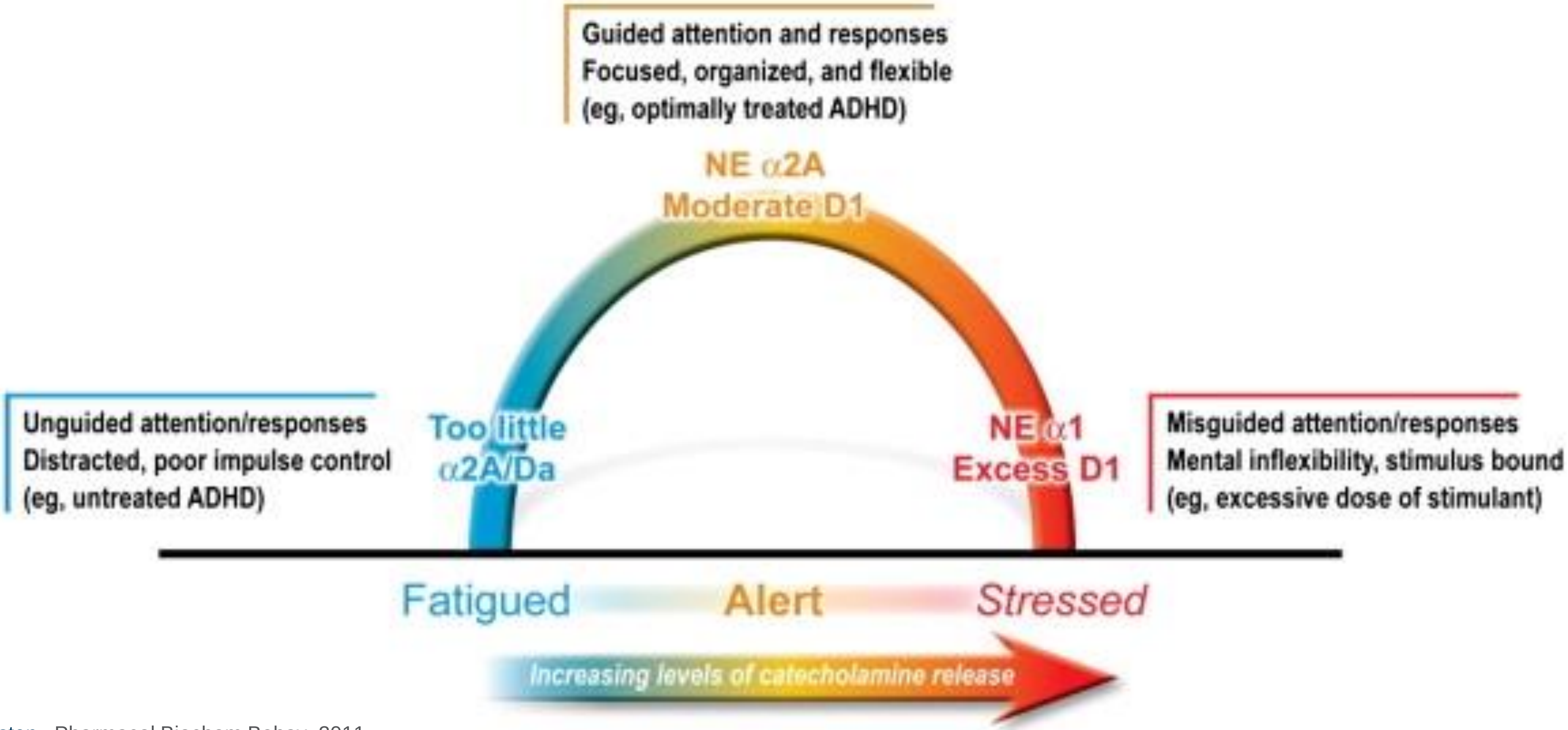
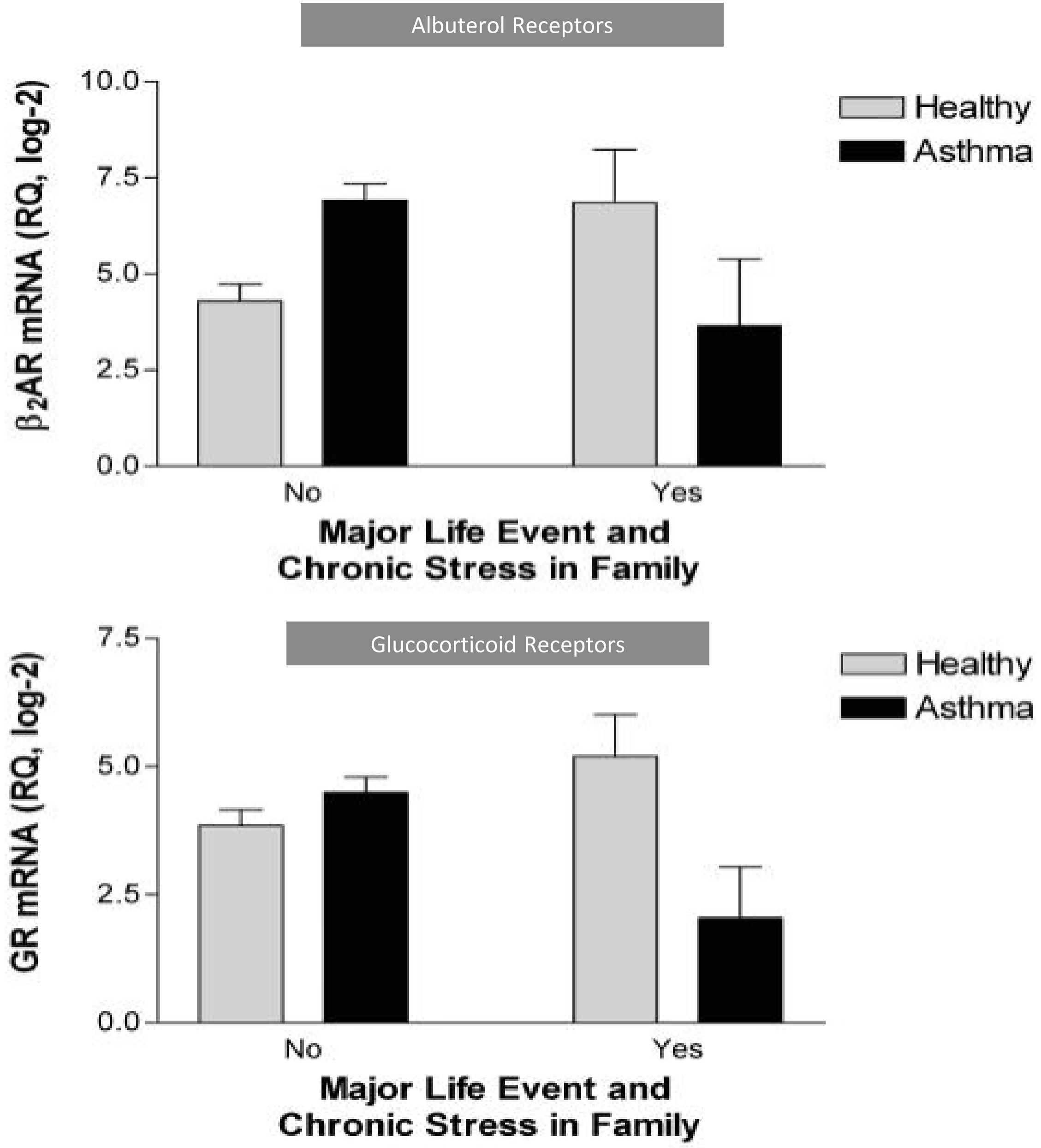
Cognition (TF-CBT, DBT)	Relational Health (Dyadic and Family Therapy)	Hypothalamic-Pituitary-Adrenal (Stress busters)	Autonomic Nervous System (Stress busters, EMDR, biofeedback)
Reward Processing (Dual Dx, TMS, Brain training, Ketamine)	Pain Processing (PT, OT, EMDR, Guided Imagery, Acupuncture)	Sensory Processing (somatic tx, massage, music)	Energy, Sleep (Neurofeedback, mindfulness, CBT-I)
Immune System (Anti-inflammatory diet, Curcumin)	Endocrine, Metabolic (Stress busters)	Gut-Brain Axis (Nutrition, Stress Busters)	Genetics and Epigenetics

Considerations for Medication Management Based on Toxic Stress Physiology

Disease Management:
PFC Activity Relative to Catecholamine



Arnsten. Pharmacol Biochem Behav. 2011



Childhood adversity is associated with glucocorticoid insensitivity and reduced sensitivity to adrenergic agonists

Miller, Gregory E., and Edith Chen. "Life stress and diminished expression of genes encoding glucocorticoid receptor and β2-adrenergic receptor in children with asthma." *Proceedings of the National Academy of Sciences* 103.14 (2006): 5496-5501.

Resources

ACEs Aware Resources

- Becoming ACEs Aware in California Training: https://training.acesaware.org
- ACEs Aware Stress Busters Resource Page: www.acesaware.org/managestress
- Stress Busters online curriculum coming soon
- Wellness Corner by the VTA and PACEs Connection

Office of the CA Surgeon General Resources

- OSG Video: ”What Are ACEs”
- SAFE Spaces: Free, on-line training for educators

Gilgoff R, Schwartz T, Owen M, Bhushan D, Burke Harris N. Opportunities to Treat Toxic Stress. Pediatrics. 2023 Jan 1;151(1):e2021055591.

A Call to Action

- Help patients understand the potential links between childhood adversity, stress, and their health condition(s) or risks.
- Assess patients for clinical risk of toxic stress.
- Supplement standard care with evidence-based and evidence-informed toxic stress mitigation interventions that could specifically regulate the underlying neuro-endocrine-immune-metabolic disruptions.
- Partner with cross-sector community networks of care.
- Develop resources and referral networks for trauma-specific mental health interventions.
- Create policies and systems that provide clinicians with the time, resources, and support to implement assessment and intervention strategies for adversity and toxic stress into routine workflows.
- Create trainings, continuing education opportunities, models of care, and quality improvement tools.
- Advocate to expand funding and incentives for toxic stress research.

Gilgoff R, Schwartz T, Owen M, Bhushan D, Burke Harris N. Opportunities to Treat Toxic Stress. Pediatrics. 2023

Thank You!

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Q & A