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Born this Way?
The Role of Early Life Stress in Adult Mental Illness

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This program is paid for by
Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) and Lundbeck, LLC.

Objectives

1. Recognize early life adversity as a risk factor for the development of psychiatric illness across diagnostic boundaries
2. Characterize biological and neurobiological mechanisms that implicate childhood trauma and stress in adult mental illness
3. Understand the importance of assessing early life events in the clinical setting

What are Adverse Childhood Experiences (ACEs)?

Traumatic events that occur 0-17 years of age

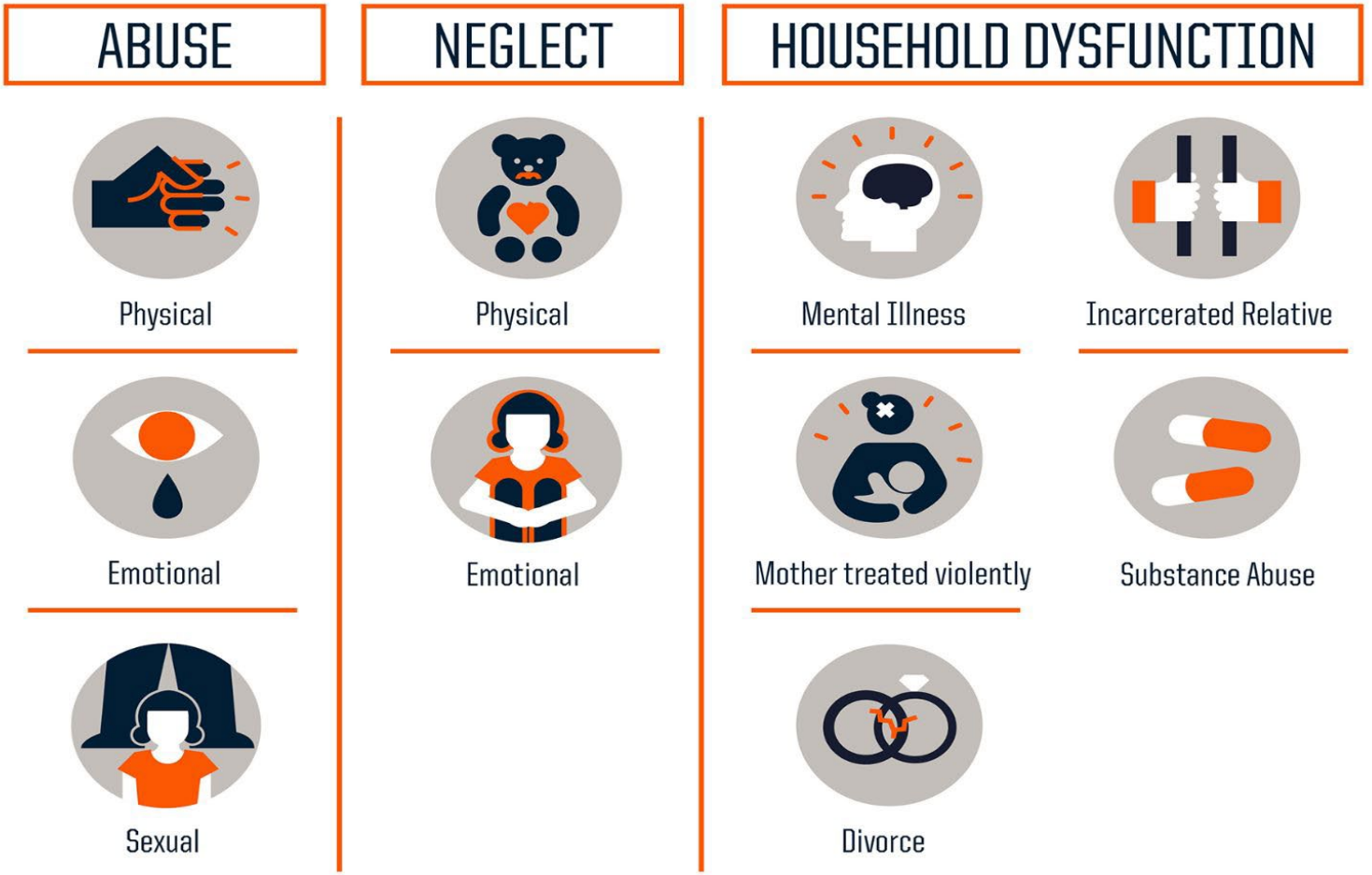
- Experiencing violence, abuse, or neglect
- Witnessing violence in the home or community
- Having a family member attempt or die by suicide

An environment that can undermine safety, stability, and bonding. Growing up in a household with…

- Substance misuse
- Mental health problems
- Instability due to parental separation
- Household members being in jail or prison

https://www.cdc.gov/violenceprevention/childabuseandneglect/aces/fastfact.html Accessed 7/2/2020

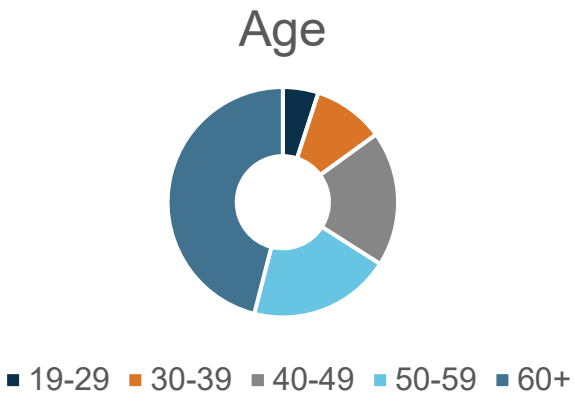
What are Adverse Childhood Experiences (ACEs)?

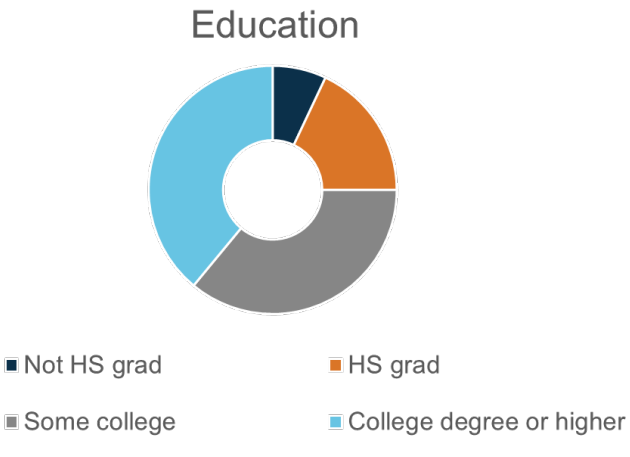


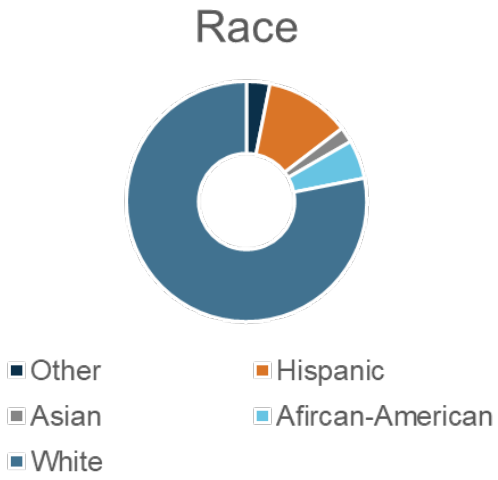
The ACE Study

Who participated in the ACE Study?

Between 1995 and 1997, over 17,000 people receiving physical examinations completed confidential surveys containing information about their childhood experiences and current health status and behaviors. The information of these surveys were combined with results from the physical examinations to form the study's findings. Participants in this study represented a cross-section of middle-class American adults.



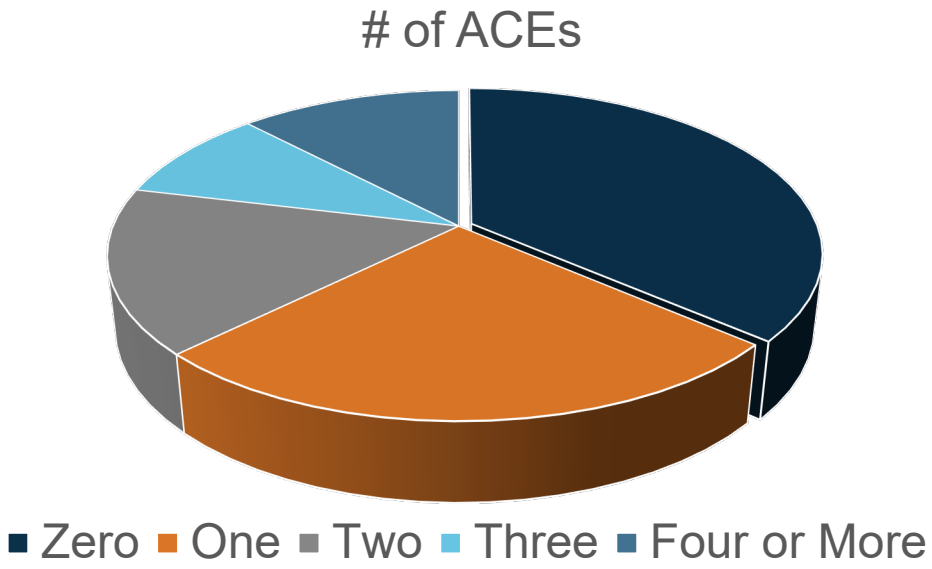




https://vetoviolence.cdc.gov/apps/phl/images/ACE_Accessible.pdf Accessed 7/2/2020

Rates of Childhood Trauma Experienced by Adults

Almost two-thirds of adults surveyed reported at least one Adverse Childhood Experience and the majority of respondents who reported at least one reported more than one.[1]



25% of adults report physical abuse as a child[2]

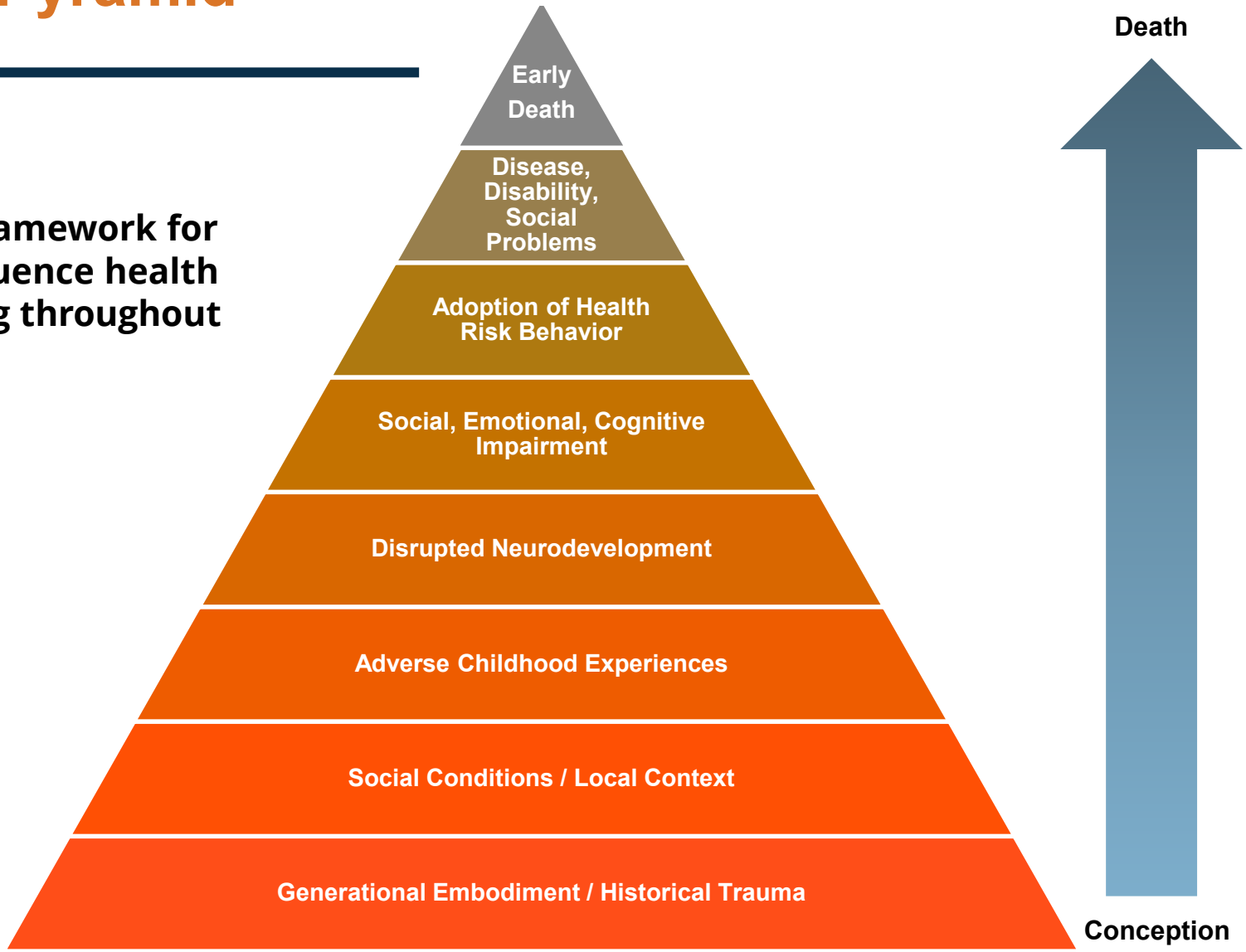
1 in 7 children experienced child abuse in 2018[3]

1 in 5 women and 1 in 13 men report childhood sexual abuse[2]

1. https://www.cdc.gov/violenceprevention/childabuseandneglect/acestudy/about.html Accessed 7/2/2020
2. Aas et al. *Int J Bipolar Disord* (2016) 4:2
3. https://www.cdc.gov/violenceprevention/childabuseandneglect/fastfact.html

The ACE Pyramid

Conceptual framework for how ACEs influence health and well-being throughout the lifespan



ACE = adverse childhood experience

https://www.cdc.gov/violenceprevention/childabuseandneglect/acestudy/resources.html Accessed 7/2/2020

Image taken from Centers for Disease Control and Prevention

Early Life Adversity has Lasting Individual and Population Impacts

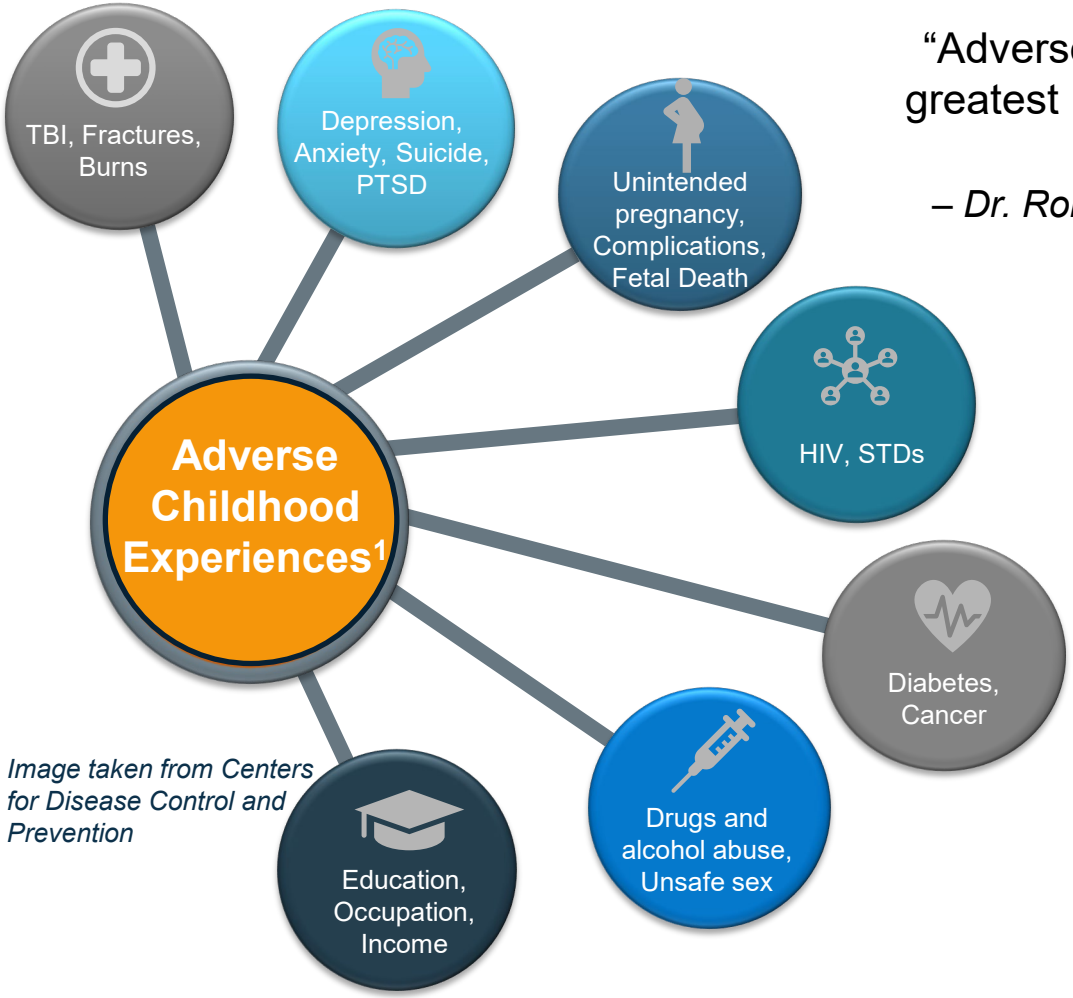


Image taken from Centers for Disease Control and Prevention

"Adverse childhood experiences are the single greatest unaddressed public health threat facing our nation today."

– Dr. Robert Block, former President of the American Academy of Pediatrics[2]

4 or more ACEs[2]

- **3x** the levels of lung disease and adult smoking
- **11x** the level of IV drug abuse
- **14x** the number of suicide attempts
- **4.5x** more likely to develop depression
- **4x** as likely to have begun intercourse by age 15
- **2x** the level of liver disease

ACE = adverse childhood experience, IV=intravenous, TBI = traumatic brain injury, PTSD = post-traumatic stress disorder, HIV = human immunodeficiency virus, STDs = sexually transmitted diseases, IV = intravenous

1. https://www.cdc.gov/violenceprevention/childabuseandneglect/acestudy/about.html Accessed 7/2/20 2. https://annemarieproject.org/adverse-child-experience/ Accessed 7/2/20

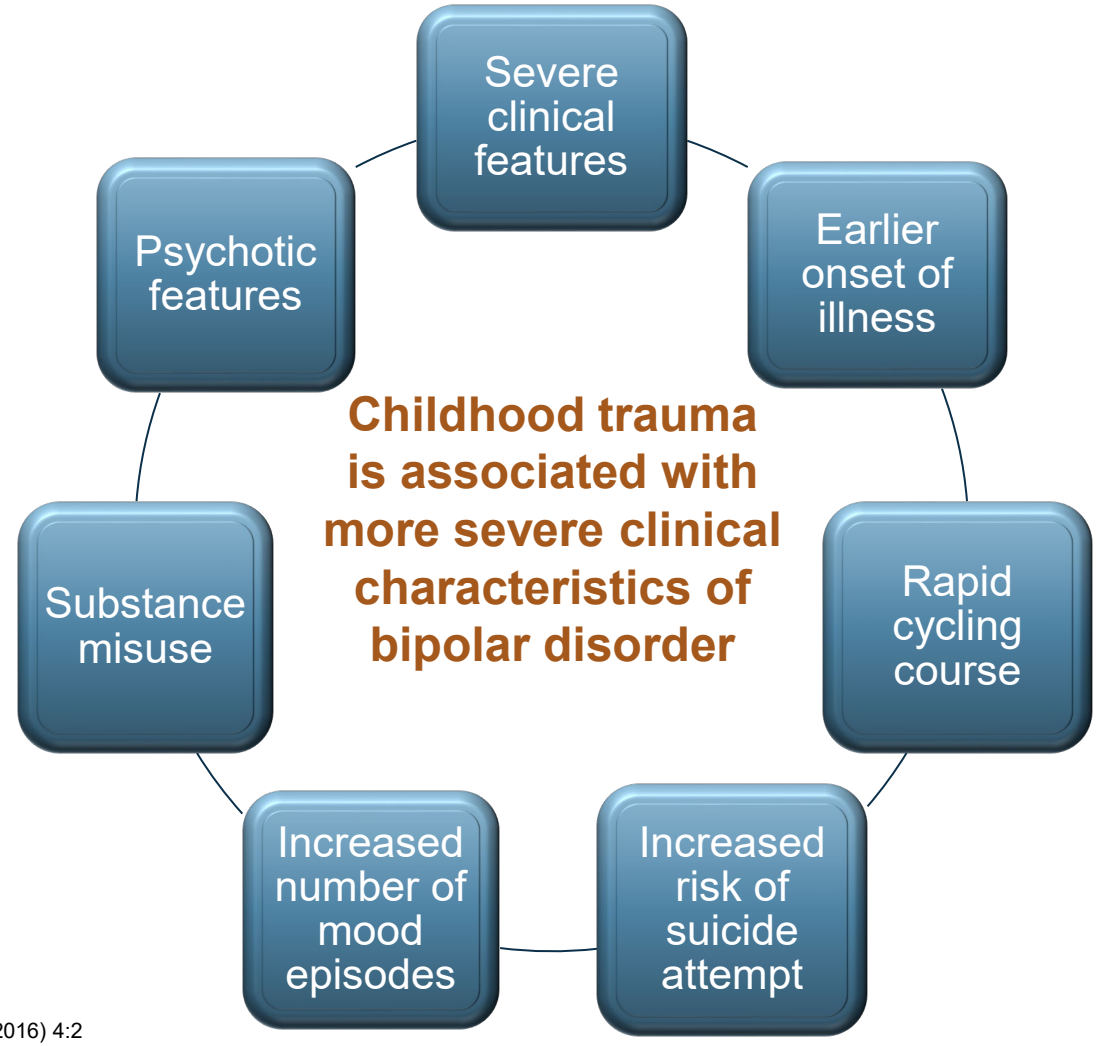
Childhood Physical Abuse and Risk of Psychiatric Disorder

This US study (N = 43,093) of adults who report being physically abused during childhood, examines associations of type and frequency of abuse with adult mental health. Data were derived from the 2000–2001 and 2004–2005 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

Psychiatric Disorder	Risk (odds ratio)
Substance use Disorders	1.24
Psychotic Disorder	1.27
Any Mood Disorders	1.41
Any Anxiety Disorders	1.56
Any Suicide Attempts	1.57

Aas et al. *Int J Bipolar Disord* (2016) 4:2

Childhood Trauma and Bipolar Disorder Severity



Aas et al. *Int J Bipolar Disord* (2016) 4:2

Childhood Abuse and Bipolar Disorder

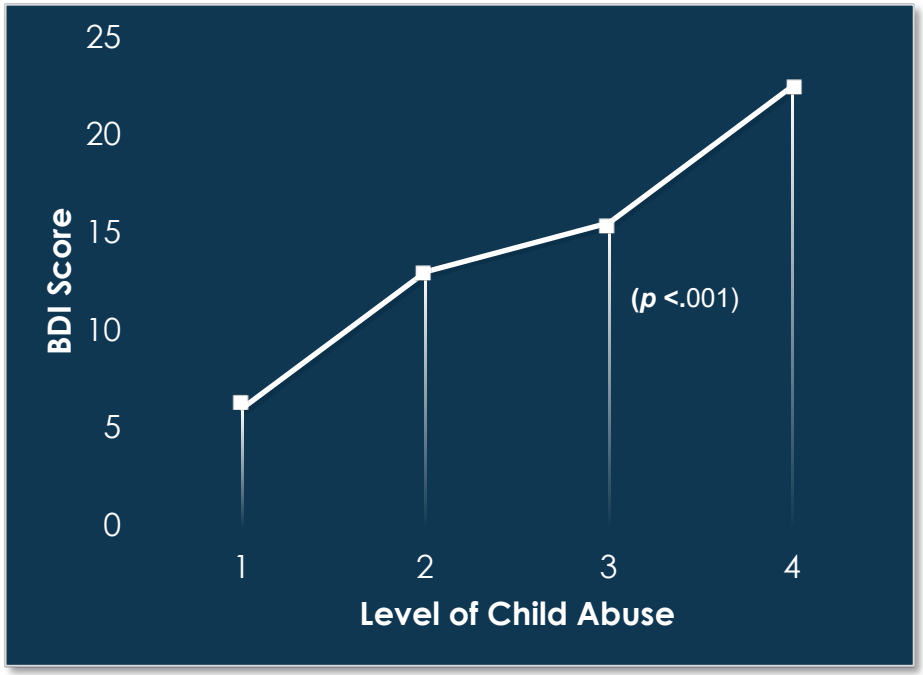
Compared to healthy individuals:

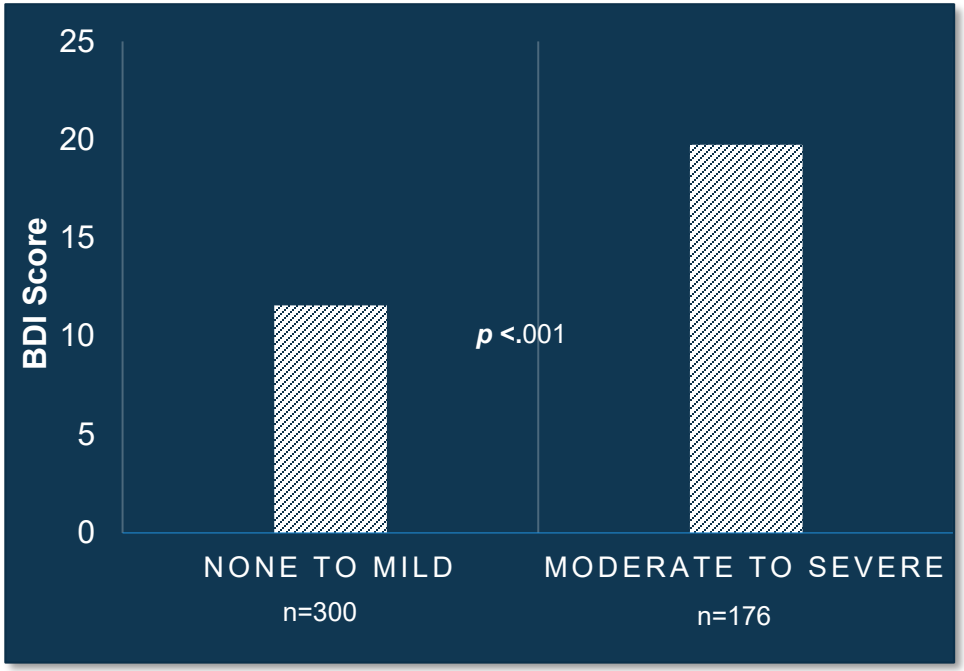
- BD type I patients report higher rates of child sexual abuse
- BD type II patients differ for emotional neglect

Childhood trauma appears highly associated with bipolar disorder. The specific role of each trauma subtype (emotional, physical or sexual abuse) remains a subject of debate.

Aas et al. *Int J Bipolar Disord* (2016) 4:2

Early Life Stress Increases Risk for Depression in Adults





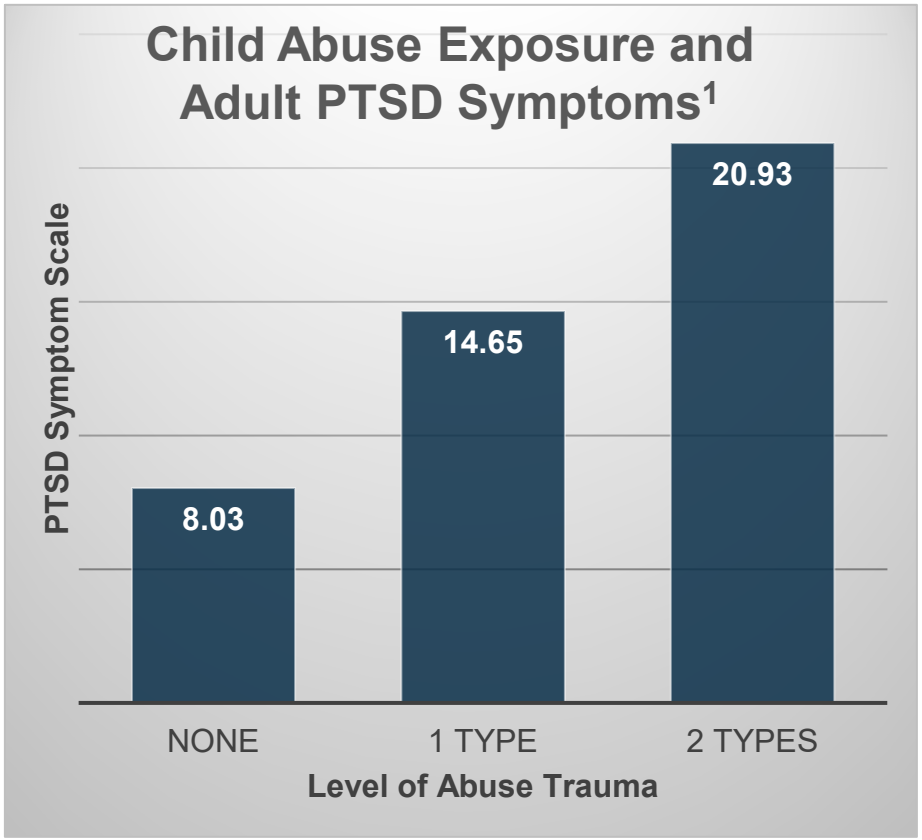
Higher CTQ abuse scores predicted higher adult BDI scores. Mean BDI scores (n=476) were predicted by continuous scores on the CTQ.

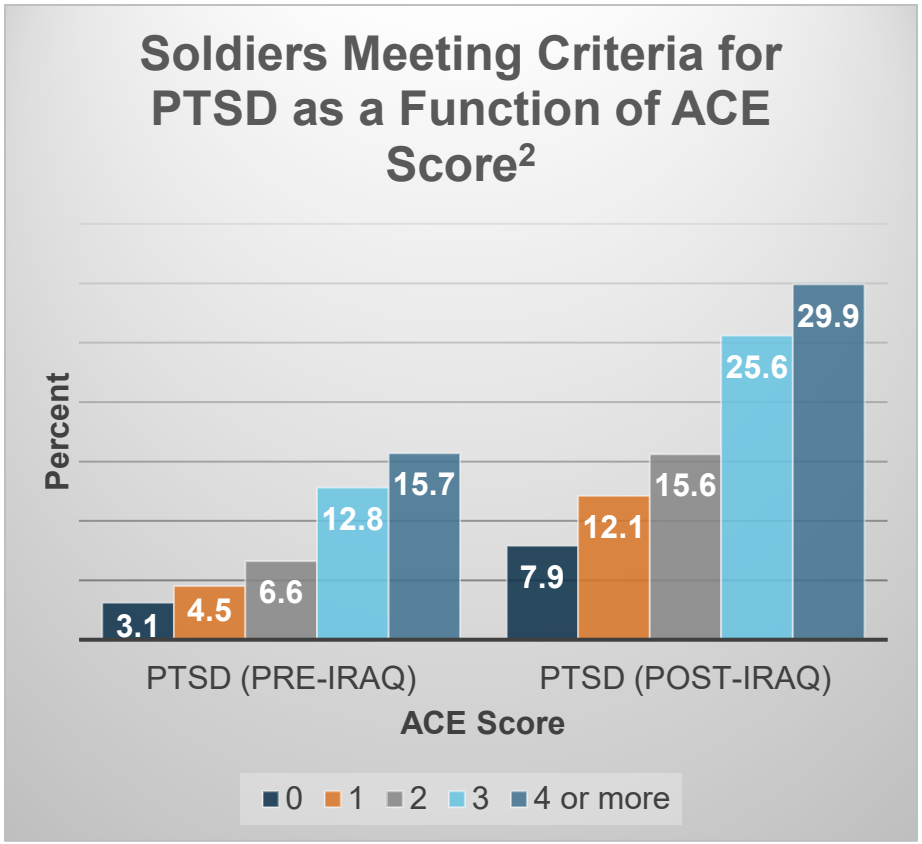
When child abuse was divided into none to mild and moderate to severe groups, there was a significant difference in BDI scores.

CTQ = Childhood Trauma Questionnaire; BDI = Beck Depression Inventory

Bradley et al. *Arch Gen Psyc* 2008. 65:190-200

Level of Child Abuse May Predict Adult PTSD

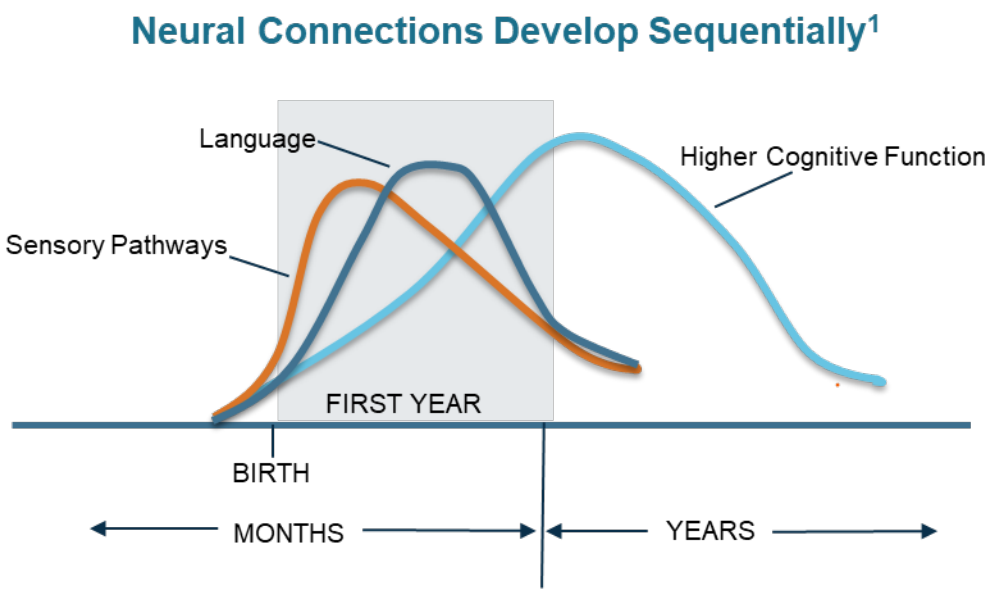




ACE = Adverse Childhood Experiences scale; PTSD = Post-Traumatic Stress Disorder

1. Binder et al. *JAMA* 2008. 299:1291-1305 2. Cabrera et al. *Am Jn Prev Me*d 2007. 33(2)

Early Life Stress in Childhood & Adolescence Has Adverse Impact on the Brain



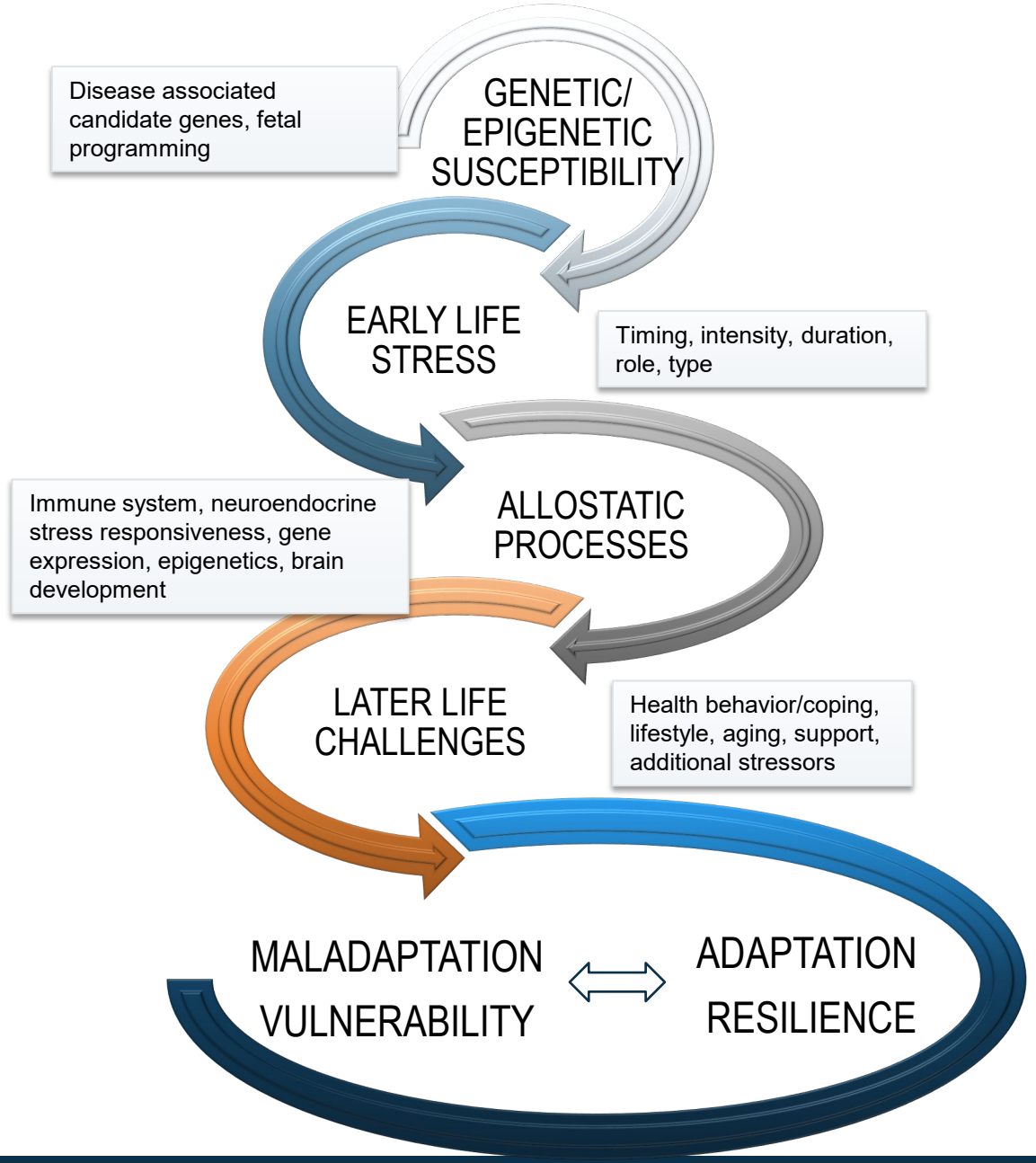
During proliferation and pruning, simpler connections form first, followed by more complex circuits.

- Neural consequences of early life trauma depend on which developmental stage the stress occurs.[2]
- For example, girls who were sexually abused between the ages of 3-5 were related to smaller hippocampal volume. But sexual abuse occurring between the ages of 9-10 and 11-14 were linked to dysfunctions in the corpus collosum and prefrontal cortex respectively.[2]
- Brain regions with extended postnatal development are more vulnerable to long-term effect of stress.[2]

1. Figure adapted from https://developingchild.harvard.edu/resources/inbrief-science-of-ecd/ Accessed 7/2/20
2. Pechtel P Psychopharmacology (Berl) 2011;214(1):55-70

Mood Disorders and Anxiety Are Ultimately about How the Brain Responds to the Environment

Early life stress can lead to disruption of brain development and an evolving programmed phenotype with altered allostatic processes and reduced adaptability to stress.



Agorastos A et al. *Frontiers in Psychiatry* 2019; 10:118

Regulation of Stress Response by CRH and HPA Axis

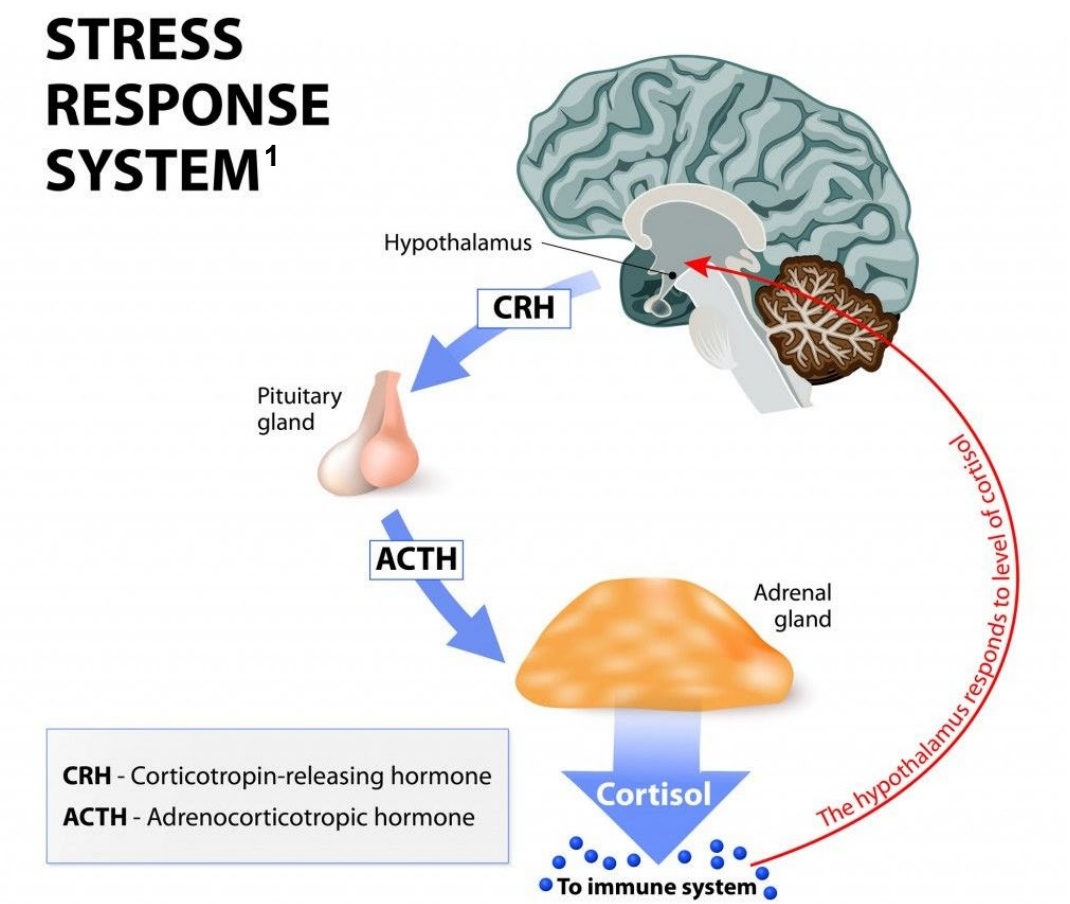


Image taken from Integrative Pain Science Institute

- This cascade releases glucocorticoids throughout the brain and body and binding to glucocorticoid receptors, impairing neuroplasticity[1]
- Explains why areas with higher density of glucocorticoid receptors and with longer postnatal developmental timeline are more susceptible to disturbances (ex. prefrontal cortex, hippocampus)[2]

HPA Axis = hypothalamic pituitary adrenal axis

1. https://www.integrativepainscienceinstitute.com/how-your-brain-changes-with-pain/ Accessed on 7/2/20 2. Pechtel P Psychopharmacology (Berl) 2011;214(1):55-70

Timing of ELS Dictates Responsiveness of HPA Axis

- ELS has been associated with both *higher and lower* circulating cortisol levels in adulthood
  - Depends on the type of trauma, the number of exposures, and in particular ***the age at the time of occurrence*** **- TIMING**

- ELS at different developmental stages of the brain correlated with impact on cortisol activity
  - ELS exposure in first 2 years of life: prolonged cortisol reactivity and hyper-active HPA axis
  - ELS exposure in adolescence/puberty: hypo-active and hypo-responsive HPA axis

ELS = early life stress; HPA Axis = hypothalamic pituitary adrenal axis

Agorastos A et al. *Frontiers in Psychiatry* 2019; 10:118.

ELS and Inflammation

*"There is a growing evidence suggesting that positive ELS/CT history is an **independent risk factor for peripheral immune dysregulation and long term, low grade, inflammatory excess** (i.e. pro-inflammatory phenotype) in adulthood."*

ELS = early life stress; CT = childhood trauma

Agorastos A et al. *Frontiers in Psychiatry* 2019; 10:118

Glial-Neuron Interactions

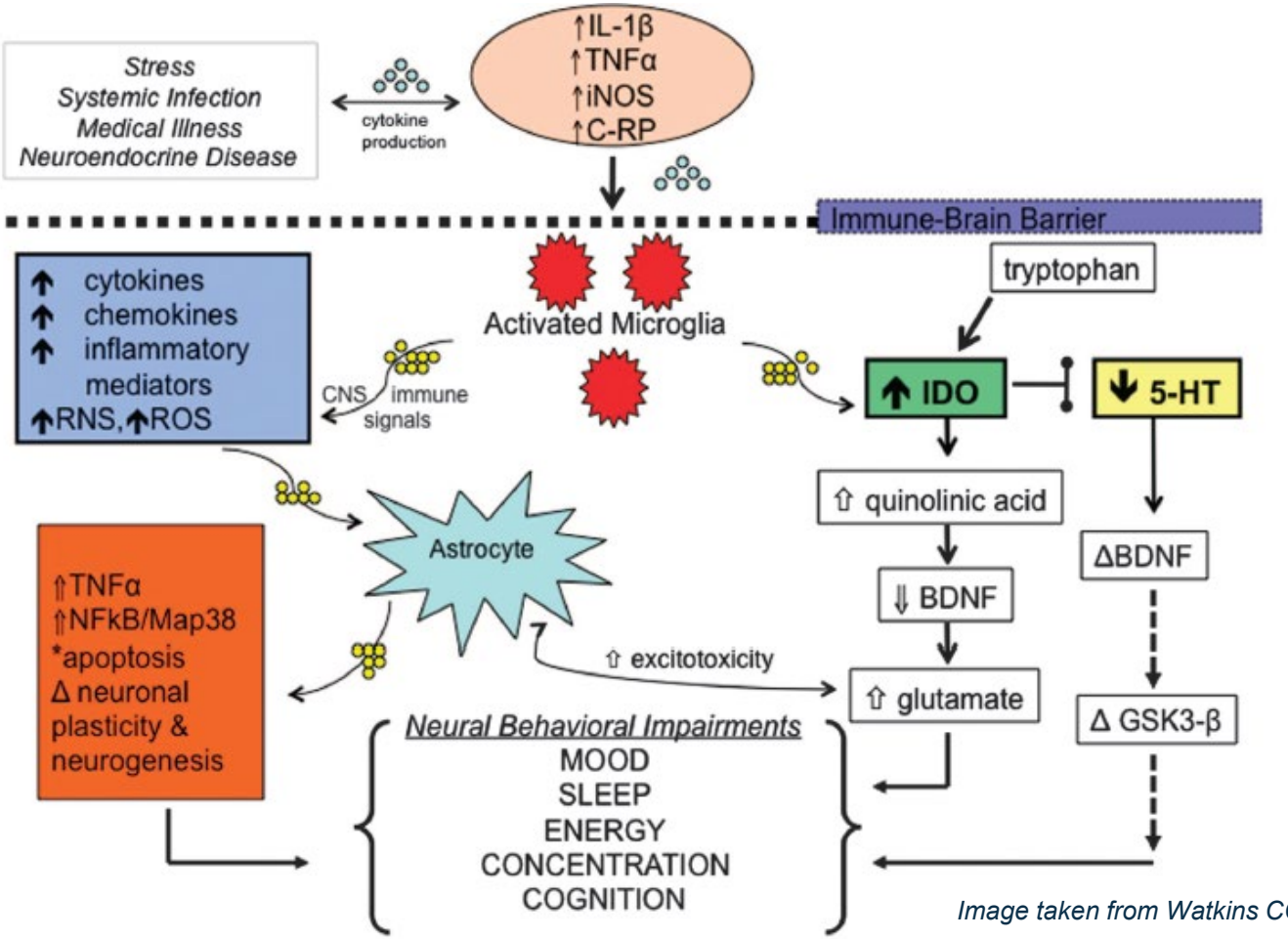


Image taken from Watkins CC. 2014

5-HT, serotonin; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; C-RP, C-reactive protein; GSK3-β, glycogen synthase kinase 3 beta; IDO, indoindoleamine 2,3-dioxygenase; IL-1β, interleukin-1 beta; iNOS, inducible nitric oxide synthase; Map38, p38 mitogen-activated protein kinase; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells; RNS, reactive nitrogen species; ROS, reactive oxygen species; TNFα, tumor necrosis factor alpha.

Watkins CC, et al. *Transl Psychiatry*. 2014;4:e350.

Immune System Hypothesis

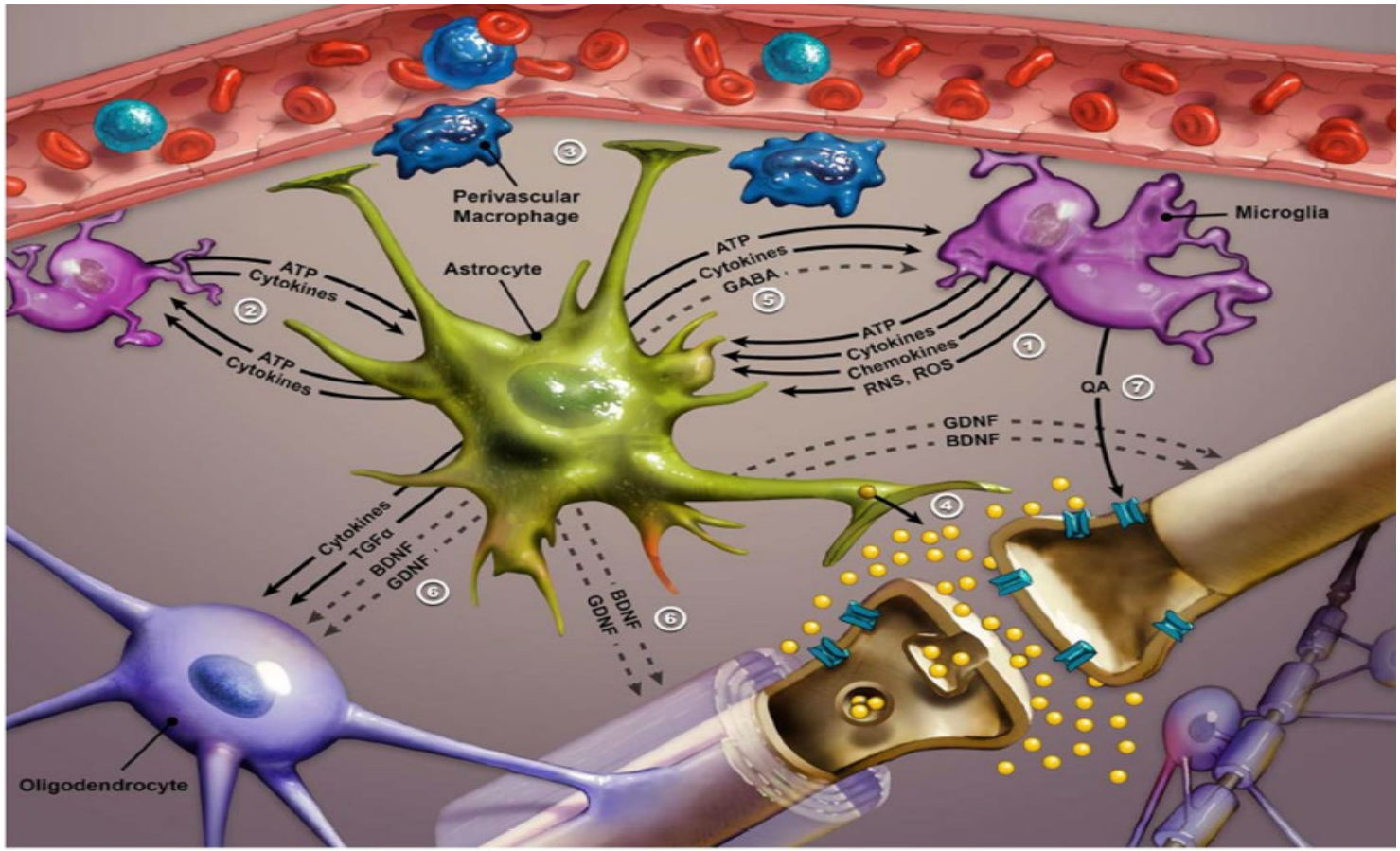


Image taken from Maletic V, Raison C. 2014

ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; GABA, gamma-aminobutyric acid; GDNF, glial cell-derived neurotrophic factor; QA, quinolinic acid; RNS, reactive nitrogen species; ROS, reactive oxygen species; TGFα, transforming growth factor alpha.

Maletic V, Raison C. *Front Psychiatry*. 2014;5:98.

Early Life Trauma and the Connection to Inflammation

- IL-6 stimulates HPA axis at hypothalamic, pituitary, and adrenal level[1]
  - Basal IL-6 is required for sustained cortisol response to chronic stress
- Increased inflammatory response to acute stress in adulthood with children exposed to ELS[2]
  - Shown by increased IL-6 production and increased binding to DNA of key pro-inflammatory transcription factors
- Recent meta-analysis with 20,000 samples confirmed individuals exposed to ELS show significantly elevated baseline peripheral levels of CRP, IL-6 and TNF-α[1]
- Stress in vulnerable phase when the immune system is more plastic hypersensitizes the immune system towards a chronic pro-inflammatory state[2]

IL-1β, interleukin-1 beta; HPA Axis = hypothalamic pituitary adrenal axis; ELS = early life stress; C-RP, C-reactive protein; TNFα, tumor necrosis factor alpha.

1. Agorastos A et al. Frontiers in Psychiatry 2019; 10:118
2. Cattaneo A et al. Frontiers in Celluar Neuroscience 2015 March; 9 (40): 1-12

Epigenetics – The Linking Mechanism?

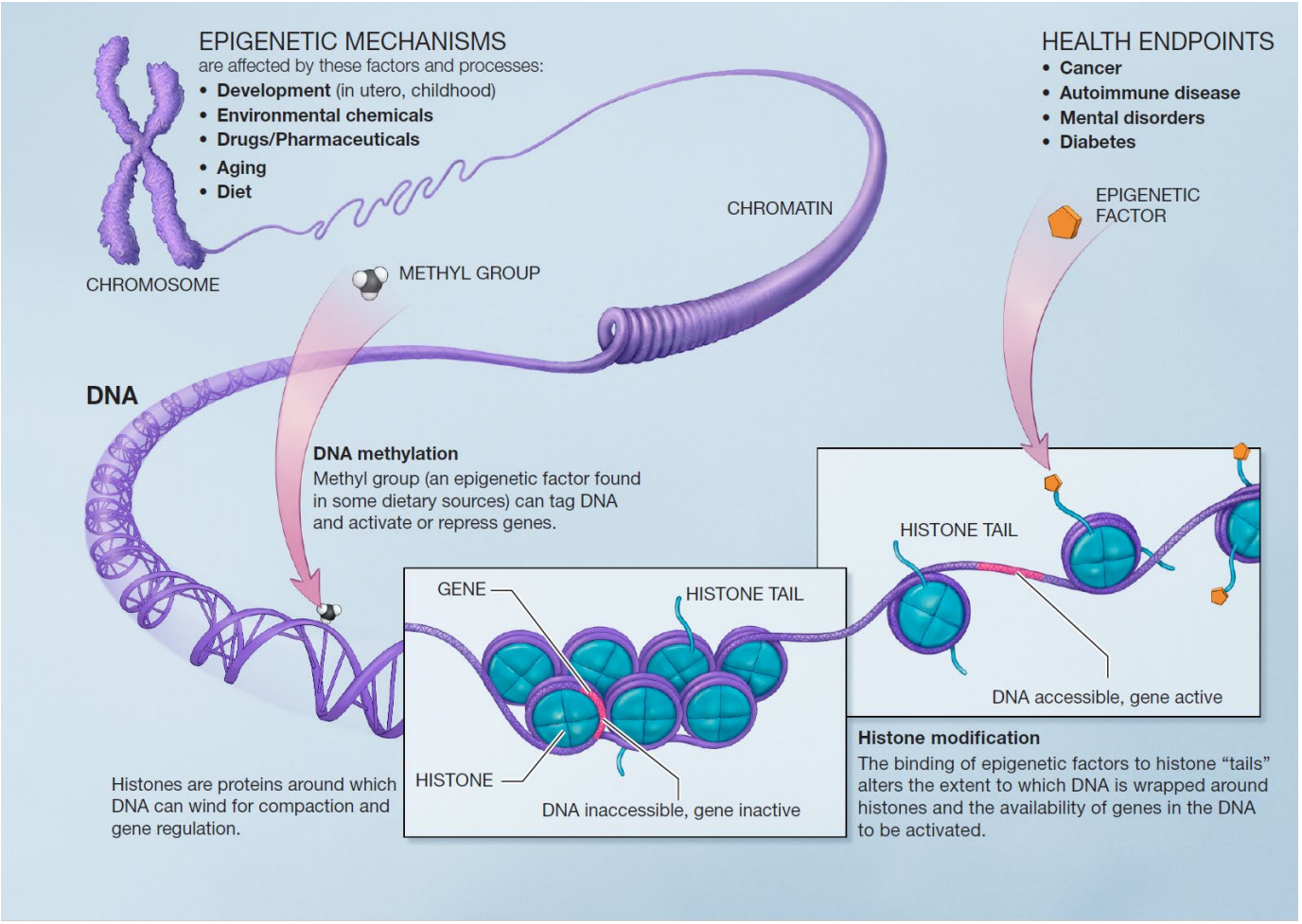


Image taken from National Institutes of Health

Epigenetics refers to modifications of DNA or associated factors that do not involve changes in the DNA sequence.[1]

Stress can indirectly activate epigenetic mechanisms that target the same stress genes.[1]

During early brain development, these processes can function as 'developmental switches' that contribute to stability of long-term effects of early environmental influences by programming feedback mechanisms of the HPA axis and other neural networks.[2]

1. Nemeroff et al. *Nueron* 2016 2. Lux et al. *Current Genomics* 29018 3. image: https://commonfund.nih.gov/sites/default/files/epigeneticmechanisms.pdf Accessed 7/2/20

Child Maltreatment Associated with DNA Methylation within Stress Genes

CRH= Corticotrophin Releasing Hormone
CRH-R1= Receptor 1 of Corticotrophin Releasing Hormone
GR= Glucocorticoid Receptor
ACTH= Adrenocorticotropic Hormone
GRE= Glucocorticoid Response Element

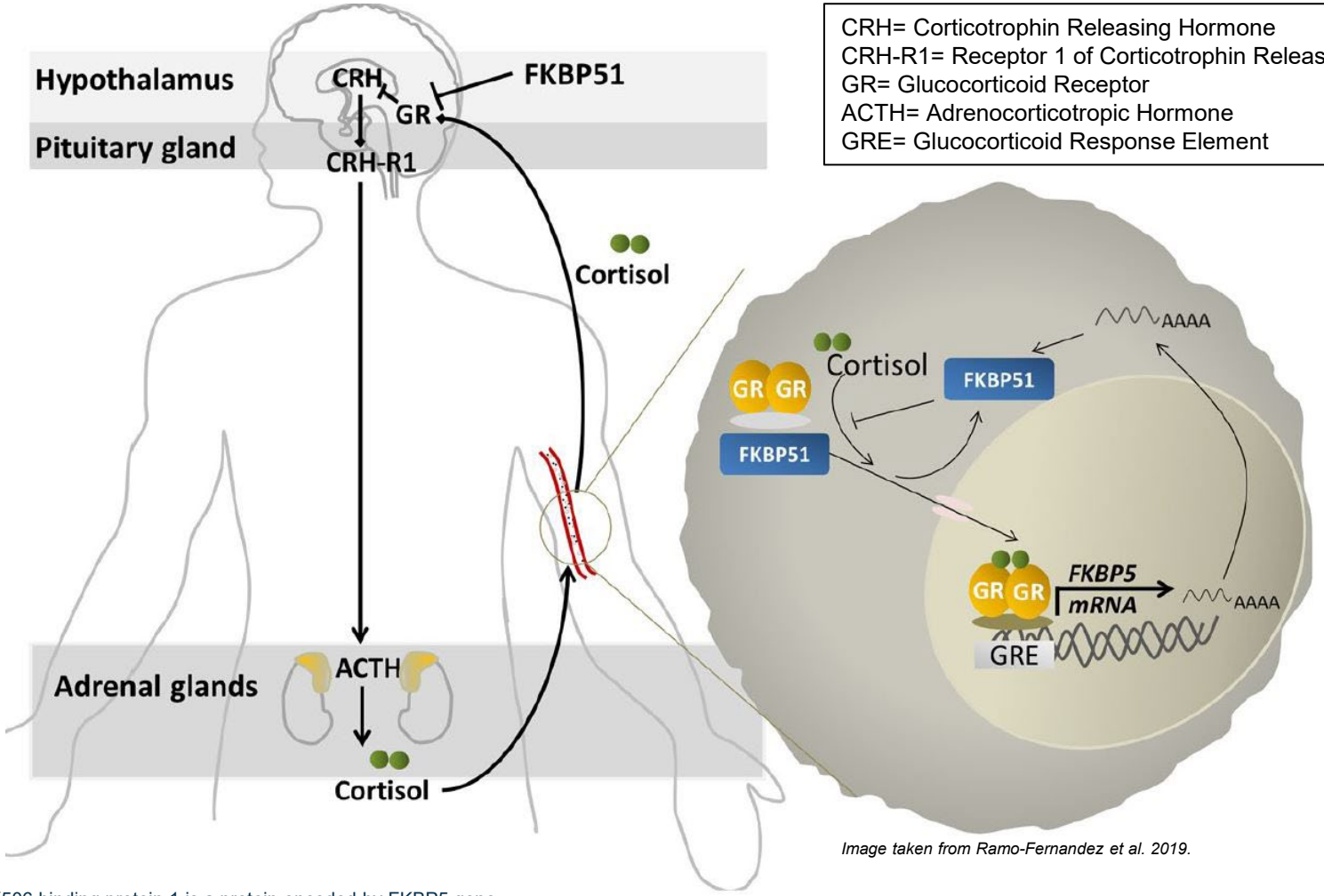


Image taken from Ramo-Fernandez et al. 2019.

RFKBP51= FK506 binding protein 1 is a protein encoded by FKBP5 gene

Ramo-Fernandez L et al. Nature.com scientific reports 2019; 9 (983):1-12

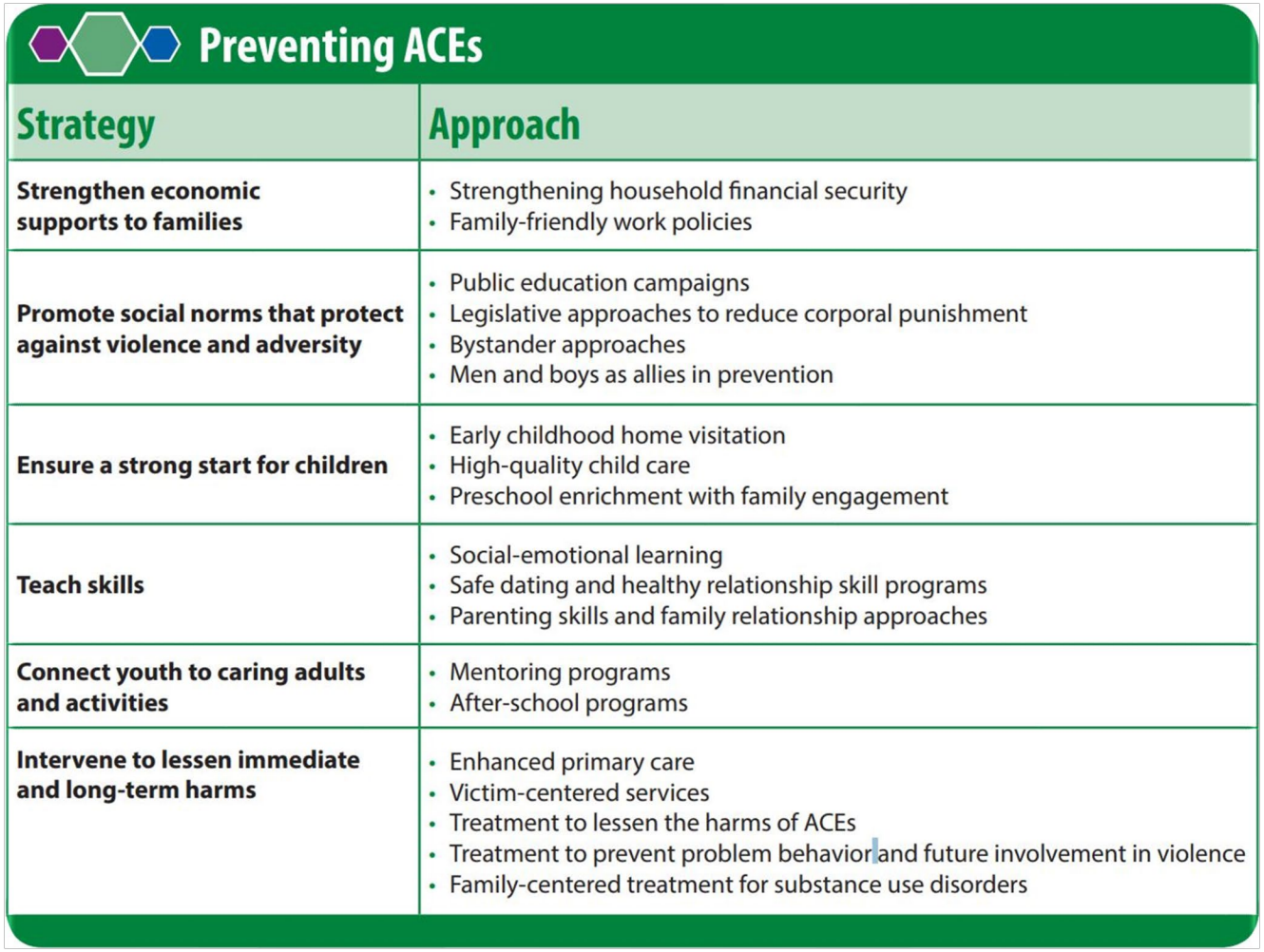
PTSD: Relationship Between Genes and Environment

- Four Single Nucleotide Polymorphisms (SNPs) in the FKBP5 gene robustly interacted with the level of child abuse to predict the level of adult PTSD symptoms (minimum p = .0004)
- Healthy carriers showed less dexamethasone suppression and thus more GR resistance
- The SNP genotypes associated with highest FKBP5 mRNA induction in peripheral blood mononuclear cells by cortisol, associated with highest vulnerability to PTSD
- Abnormal FKBP5 expression leads to maladaptive changes in GR sensitivity, associated with higher dexamethasone suppression ratio, thus increased GR sensitivity which is associated with PTSD

SNPs = single-nucleotide polymorphisms, mRNA = messenger RNA, GR = glucocorticoid receptor, HPA = hypothalamic-pituitary-adrenal axis, PTSD = post-traumatic stress disorder, FKBP5= FK506 binding protein 1 is a protein encoded by FKBP5 gene

Binder et al. *JAMA* 2008.

Preventing Adverse Childhood Experiences



Preventing ACEs

Strategy	Approach
Strengthen economic supports to families	• Strengthening household financial security • Family-friendly work policies
Promote social norms that protect against violence and adversity	• Public education campaigns • Legislative approaches to reduce corporal punishment • Bystander approaches • Men and boys as allies in prevention
Ensure a strong start for children	• Early childhood home visitation • High-quality child care • Preschool enrichment with family engagement
Teach skills	• Social-emotional learning • Safe dating and healthy relationship skill programs • Parenting skills and family relationship approaches
Connect youth to caring adults and activities	• Mentoring programs • After-school programs
Intervene to lessen immediate and long-term harms	• Enhanced primary care • Victim-centered services • Treatment to lessen the harms of ACEs • Treatment to prevent problem behavior and future involvement in violence • Family-centered treatment for substance use disorders

Image taken from Centers for Disease Control and Prevention

Centers for Disease Control and Prevention (2019). Preventing Adverse Childhood Experiences: Leveraging the Best Available Evidence. Atlanta, GA: National Center for Injury Prevention and Control, Centers for Disease Control and Prevention. Accessed June 17, 2020

Evaluating Adverse Childhood Experiences in Clinical Settings

ACE Screening Tool[1]

Adverse Childhood Experience Questionnaire for Adults

California Surgeon General's Clinical Advisory Committee

aces aware
SCREEN. TREAT. HEAL.

Our relationships and experiences—even those in childhood—can affect our health and well-being. Difficult childhood experiences are very common. Please tell us whether you have had any of the experiences listed below, as they may be affecting your health today or may affect your health in the future. This information will help you and your provider better understand how to work together to support your health and well-being.

Instructions: Below is a list of 10 categories of Adverse Childhood Experiences (ACEs). From the list below, please place a checkmark next to each ACE category that you experienced prior to your 18th birthday. Then, please add up the number of categories of ACEs you experienced and put the *total number* at the bottom.

Did you feel that you didn't have enough to eat, had to wear dirty clothes, or had no one to protect or take care of you?	☐
Did you lose a parent through divorce, abandonment, death, or other reason?	☐
Did you live with anyone who was depressed, mentally ill, or attempted suicide?	☐
Did you live with anyone who had a problem with drinking or using drugs, including prescription drugs?	☐
Did your parents or adults in your home ever hit, punch, beat, or threaten to harm each other?	☐
Did you live with anyone who went to jail or prison?	☐
Did a parent or adult in your home ever swear at you, insult you, or put you down?	☐
Did a parent or adult in your home ever hit, beat, kick, or physically hurt you in any way?	☐
Did you feel that no one in your family loved you or thought you were special?	☐
Did you experience unwanted sexual contact (such as fondling or oral/anal/vaginal intercourse/penetration)?	☐
Your ACE score is the total number of checked responses	

Do you believe that these experiences have affected your health? ◯ Not Much ◯ Some ◯ A Lot

Experiences in childhood are just one part of a person's life story.
There are many ways to heal throughout one's life.

Please let us know if you have questions about privacy or confidentiality.

5/5/20

Treatment plans after screening[2]

Adverse Childhood Experiences (ACEs) and Toxic Stress Risk Assessment Algorithm | Adults

aces aware
SCREEN. TREAT. HEAL.

	Low Risk	Intermediate Risk	High Risk	Unknown Risk
ACE screen (top box)	Score of 0-3	Score of 1-3	Score of 4+	Score unknown (incomplete)
Assess for associated health conditions	**Without** associated health conditions	**With** associated health conditions	**With or without** associated health conditions	
Determine response and follow-up	Provide education about ACEs, toxic stress, and resilience. Assess for protective factors.	Provide education about toxic stress, its likely role in patient's health condition(s), and resilience. Assess for protective factors and jointly formulate treatment plan. Link to support services and treatment, as appropriate.	Provide education about toxic stress, its likely role in patient's health condition(s), and resilience. Assess for protective factors and jointly formulate treatment plan. Link to support services and treatment, as appropriate.	Provide education on ACEs/ toxic stress and buffering/ resilience. Re-offer at next physical.

Images taken from aces aware

Disclaimer: Questionnaires and scales provided for PsychU members' screening and educational purposes only and are not to be used as a diagnostic tool.

1. https://www.acesaware.org/screen/screening-tools/ Accessed 7/7/20 2. https://www.acesaware.org/treat/clinical-assessment-treatment-planning/ Accessed 7/7/20

Principles of Trauma Informed Care (TIC)

Key Ingredients for Trauma-Informed Care

ORGANIZATIONAL

- Lead and communicate about the transformation process
- Engage patients in organizational planning
- Train clinical as well as non-clinical staff members
- Create a safe physical and emotional environment
- Prevent secondary traumatic stress in staff
- Hire a trauma-informed workforce

CLINICAL

- Involve patients in the treatment process
- Screen for trauma
- Train staff in trauma-specific treatment approaches
- Engage referral sources and partner organizations

Images taken from Center for Health Care Strategies, Inc.

https://www.chcs.org/resource/key-ingredients-trauma-informed-care/ Accessed June 18, 2020

Summary

- The impact of adverse childhood experiences can be long lasting with consequences spanning from mental disorders, substance abuse, risky behaviors, metabolic disturbances, to early mortality.
- The level and severity of trauma appear to impact severity of adult psychiatric illnesses in an exposure manner.
- Evidence shows dysregulation of immune system with prolonged inflammation caused by ELS, which may give rise to multiple diseases.
- There is mounting evidence that a vulnerable variant of certain genes in the glucocorticoid receptor and HPA axis system interact with the environment most commonly via methylation to modify genetic information. This has been demonstrated in multiple PTSD studies.
- Screening for ACEs in adults combined with trauma informed care can help patients understand the role of toxic stress in their overall health.

ELS = early life stress; HPA = hypothalamic-pituitary-adrenal axis, PTSD = post-traumatic stress disorder, ACE = adverse childhood experience

Closing

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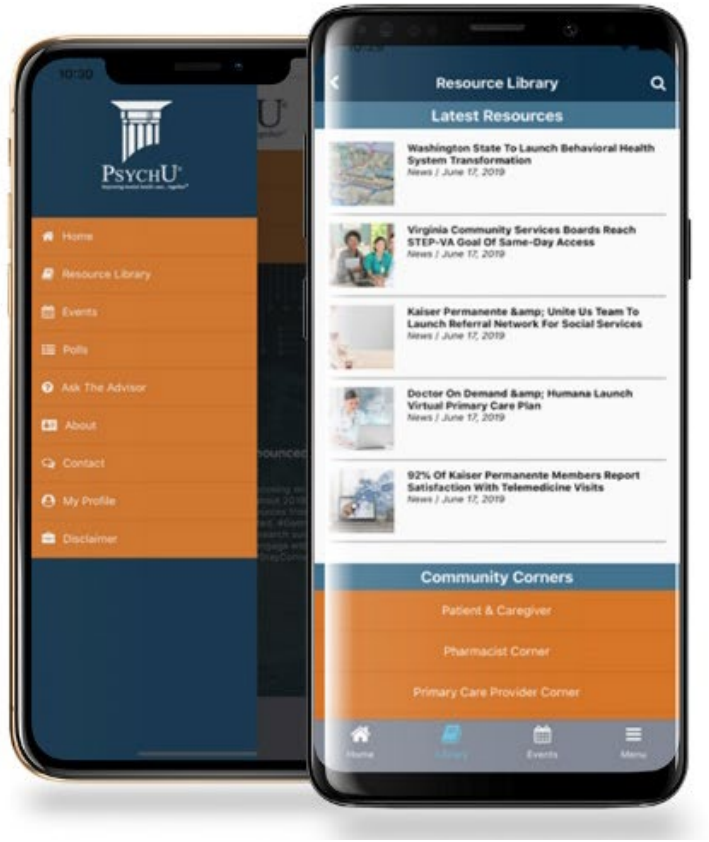

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