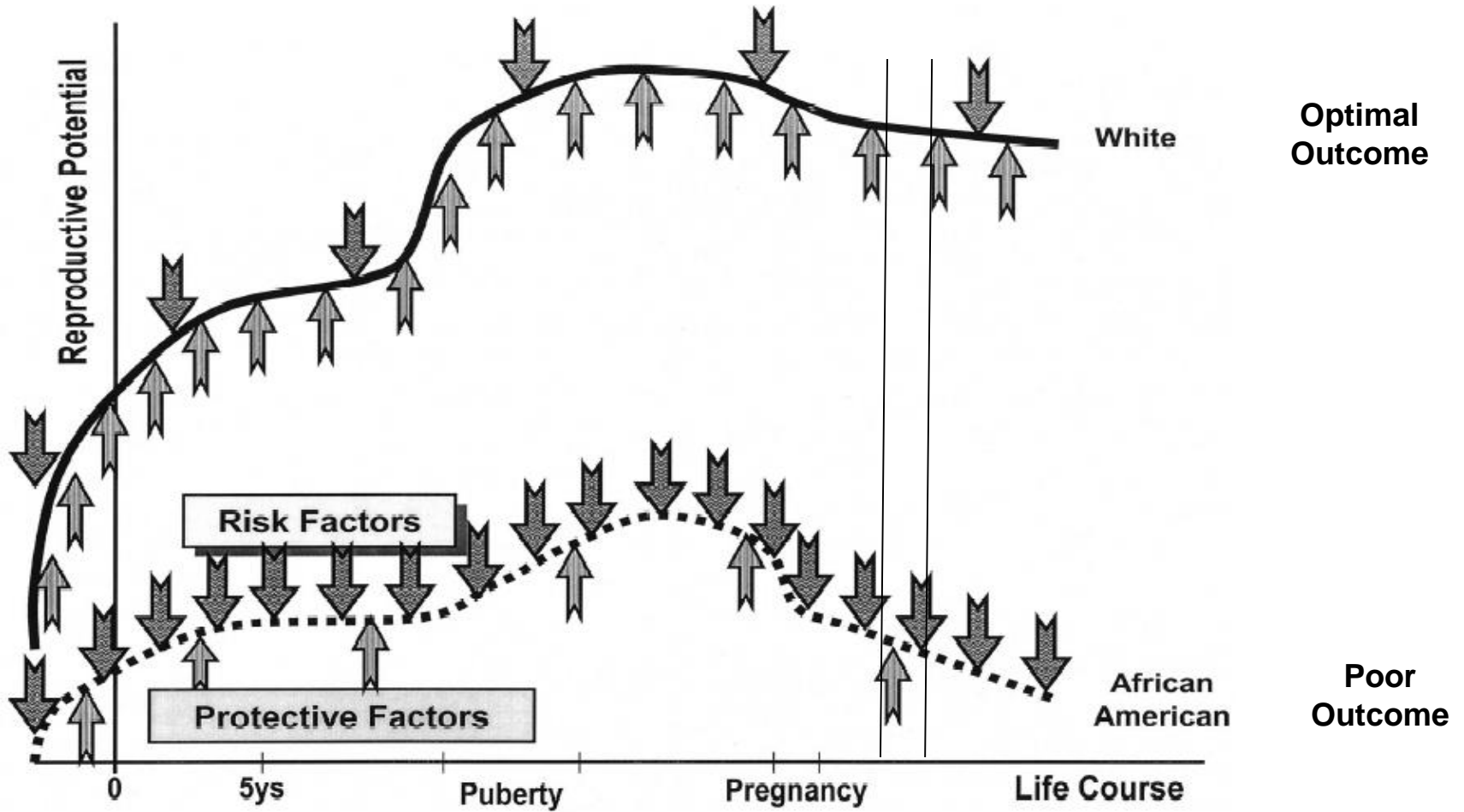


Adverse Childhood Events Neonatal Abstinence Syndrome Connecting the Dots

Kentucky Drug and Alcohol Summit

Lori Devlin DO, MHA

Associate Professor University of Louisville School of Medicine
Department of Pediatrics/Division of Neonatology



¹ Lu and Halfon, 2003

Epigenetics

Changes in DNA
(methylation, histone modification,
SNP) affecting function without a
change in sequence

- Volume Control for Genes
- Environmental triggers can lead to gene silencing
- Can be passed on through generations



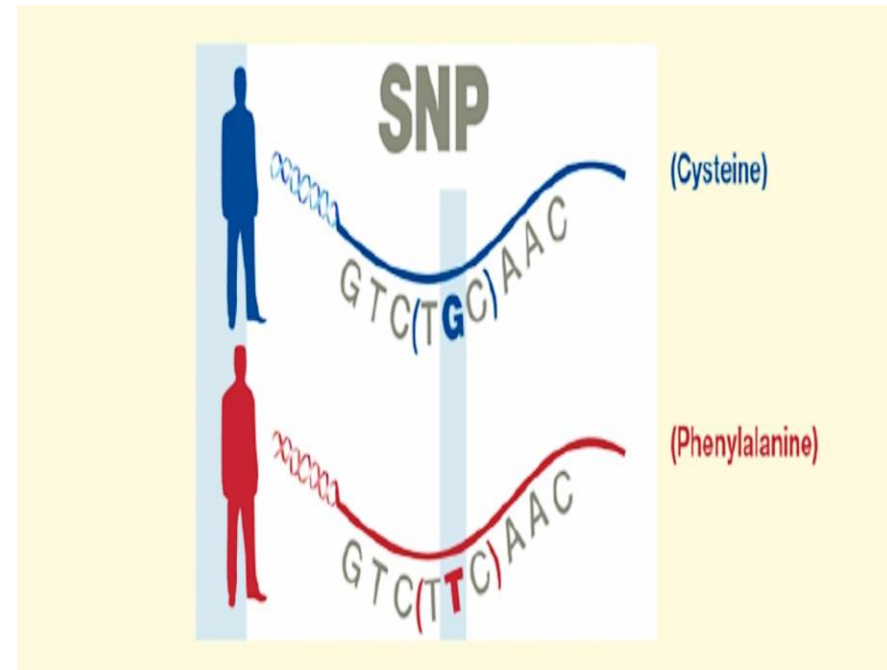
www.pbs.org/wgbh/nova/body/epigenetic-mice.html

Agouti mice from same genetic strain. 2 groups:

- (1) Mothers fed normal diet while pregnant
- (2) Mothers fed extra folic acid during pregnancy (methyl groups)

Single polymorphisms (SNPs)

- Increase the risk for substance abuse in adults
- Can be passed to the next generation
- Infants with OPRM1 rs1799971AG or GG had improved outcomes compared to those the AA genotype



Hypermethylation and NAS



Chronic opioid exposure - methylation at CpG sites within the *OPRM1* gene

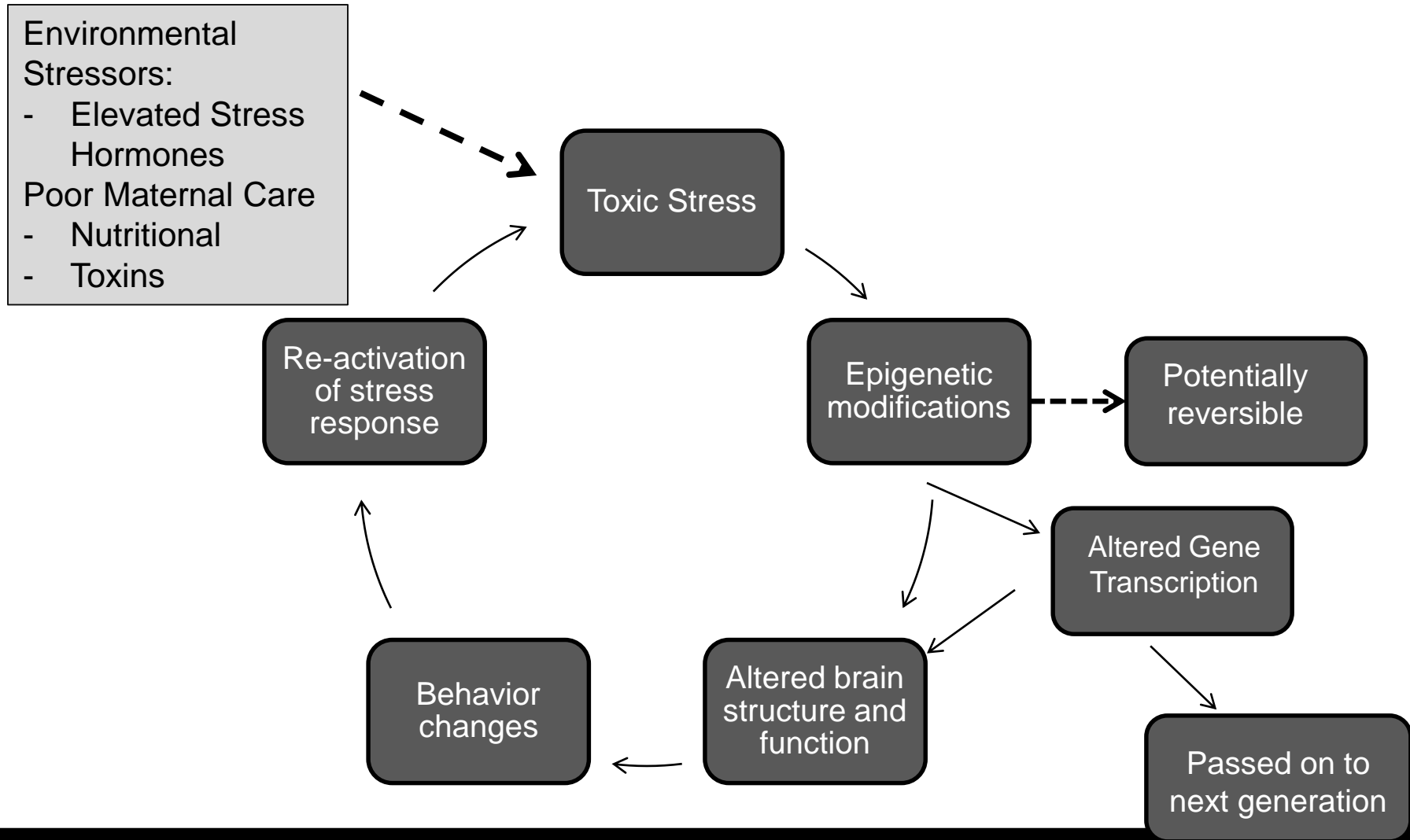
NAS babies with hypermethylation on the *OPRM1* gene at 10CpG had worse withdrawal

- Babies treated with ≤ 1 medication
2.5% (95% CI 1.6, 3.5)
- Babies treated with ≥ 2 meds
6.5% (95% CI 3.4, 9.7)

Pregnancy and Childhood Epigenetics (PACE) Consortium

Daily tobacco exposure during pregnancy correlated with 6,073 places where their babies' DNA was methylated differently than the DNA of non-smokers.

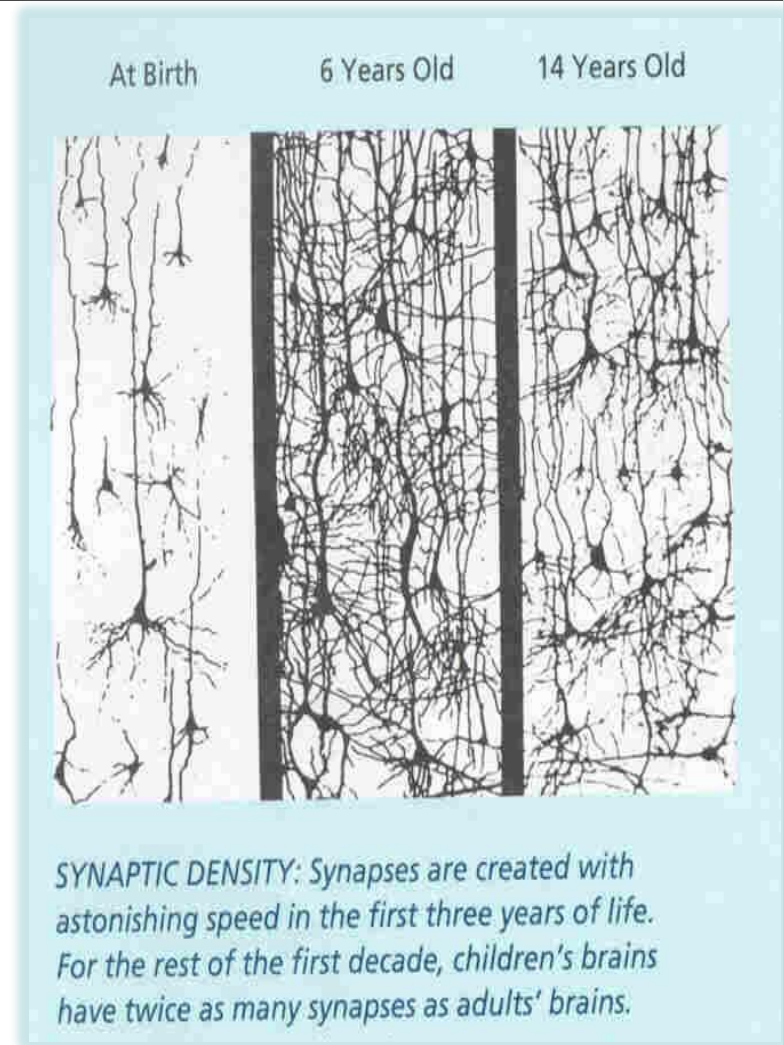
- Many differences were found on or near a collection of genes related to lung and nervous system development, smoking-related cancers, and birth defects such as cleft lip and palate.
- More methylation in sustained smoking than any smoking
- Some changes persisted in older children



Adverse Experiences during critical periods can cause irreversible change

The brain is not structurally complete at birth

- Synaptic connections, myelination glial and circulatory support systems all develop after birth
- “Use it or Lose it”
- Brain 90% complete by age 4





Birth – 2 years

- Critical window for hardwiring the brain for social-emotional development

Attachment

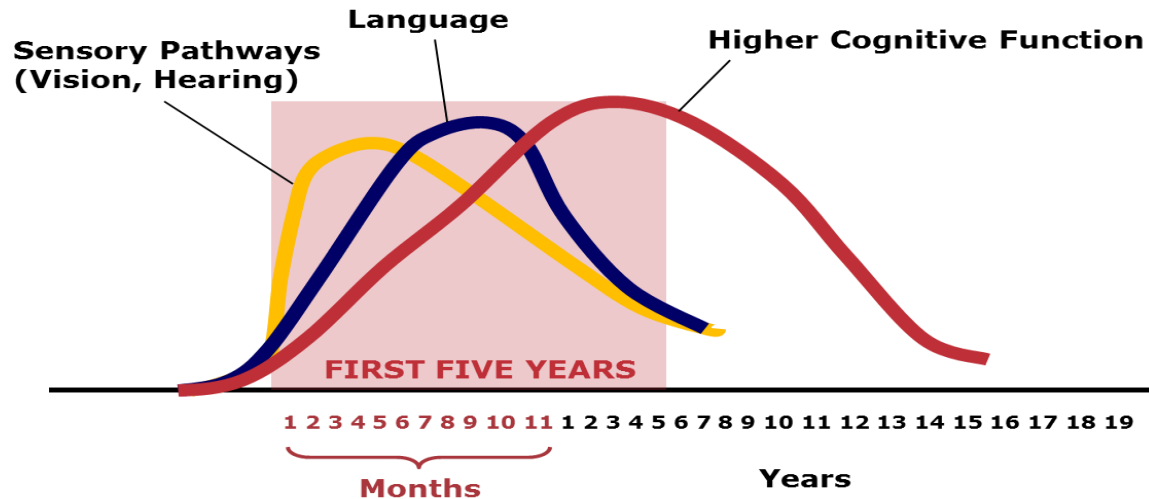
- Comes from a **nurturing relationship** with a caregiver that is consistent and caring

Social-Emotional Development

- Is based on **secure attachment** and becomes the foundation for self identity, self regulation, empathy, and cognitive development



Neural Circuits are Wired in a Bottom-Up Sequence (700 synapses formed per second in the early years)



Source: C.A. Nelson (2000)

Weak social-emotional pathways provide a weak foundation for other skills, including cognitive and executive function.

We are not born with the skills that enable us to make plans, control impulses, and stay focused. We are born with the **potential** to develop these capacities...



Nurturing and stable **RELATIONSHIPS** with caring adults are essential to healthy human development. **Early, secure attachments** contribute to the growth of a broad range of competencies, including love of learning, sense of one's self, positive social skills, successful relationships at later ages, and an understanding of emotions, commitment, morality, and other aspects of human relationships.”

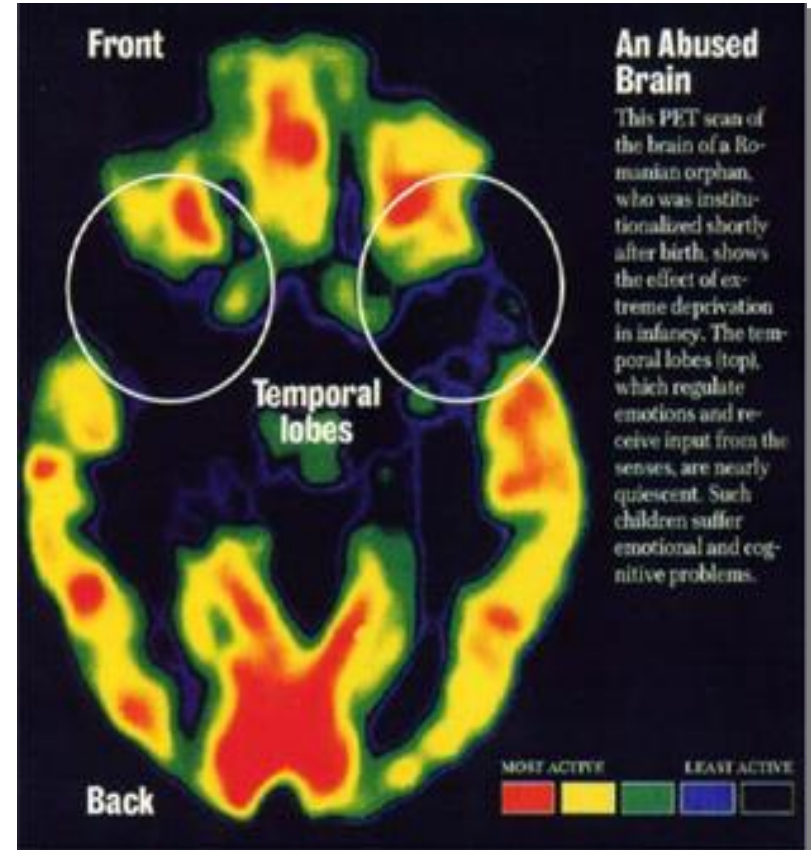
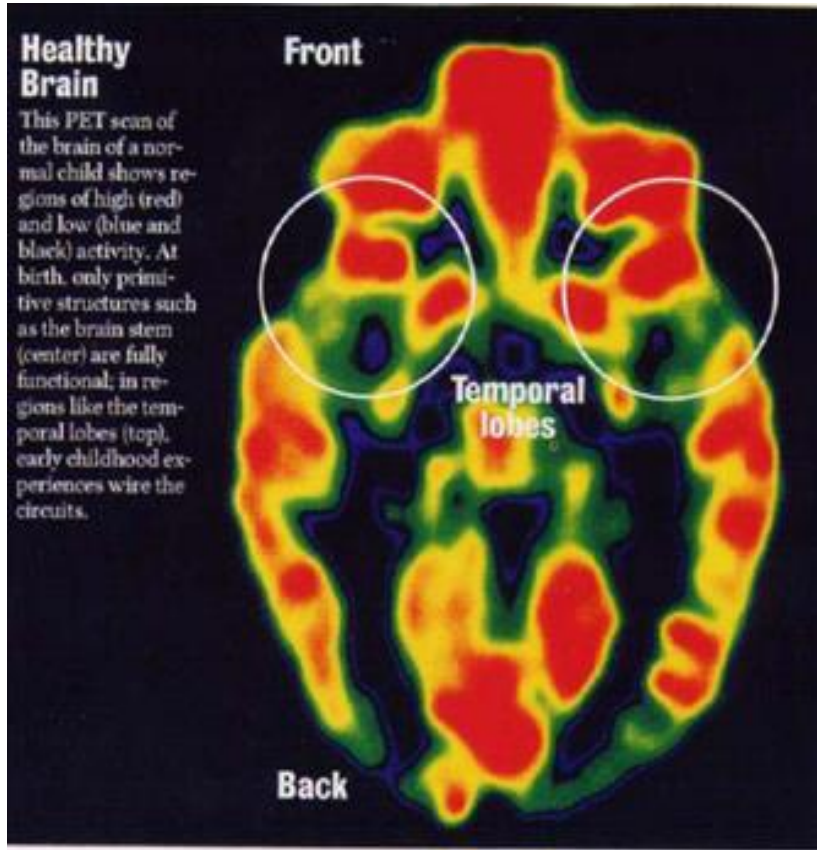
Emotional **well-being and social competence provide a strong foundation** for emerging cognitive abilities, and together they are the bricks and mortar that comprise the foundation of human development.

The emotional and physical health, social skills, and cognitive-linguistic abilities that emerge in the early years are **all important pre-requisites for success** in school and later in the workplace and community.”

Adversity impacts brain development

- Permanently alters brain structure and function
- Lack of stimulation results in pruning away of circuits
- Lack of social-emotional hardwiring provides weak foundation for later cognitive abilities
- In a repetitive setting of a stress-survival response the amygdala enlarges, the hippocampus is smaller, and the brain is smaller

Two Year window – results of extreme deprivation of stimulation



The Plasticity of Brain Architecture *Decreases Over Time*

Plasticity = the brain's ability to change in response to repeated stimulation

- **Early plasticity makes the young brain *both* more vulnerable to harm and more capable of recovery**
- Brain circuits consolidate with increasing age, making them more difficult to rewire
- **However, even later brain plasticity allows us to keep learning into adulthood and throughout our lives.**
- At all ages it is more efficient – biologically and economically – to intervene at young ages to prevent later difficulty than to try to remedy problems that emerge



Adverse Childhood Experiences (ACE Study)

- **Public/Private Partnership**
- **Started in 1985 – Ongoing**
- **1995 CDC Partnership - Ongoing**
- **Largest of kind – 17,000**

Changed Nation's Views on Children's Behavioral Health



Dr. Vincent J. Felitti, MD
Internist, Kaiser Permanente



Dr. Robert F. Anda MD (plus MS in Epidemiology)
Centers for Disease Control (CDC) & Prevention

Adverse Childhood Experiences

When you were growing up, during your first 18 years of life, did you experience:

- Physical abuse
- Emotional abuse
- Sexual abuse
- Domestic violence (mother treated violently)
- Substance abuse in home
- Mental illness in parent
- Lost parent due to separation or divorce
- Household member in jail

Adverse Childhood Experiences (ACE) Score

Number of individual adverse childhood experiences were summed...

<i>ACE score</i>	<i>Prevalence</i>	
0	36.4%	
1	26.2%	64% reported experiencing one or more
2	15.8%	
3	9.5%	
4	6.0%	37% reported experiencing two or more
5	3.5%	
6	1.6%	
7 or more	0.9%	

Avg Age 56, Middle Class, working, well educated (75% some college)

Children's Exposure to Violence

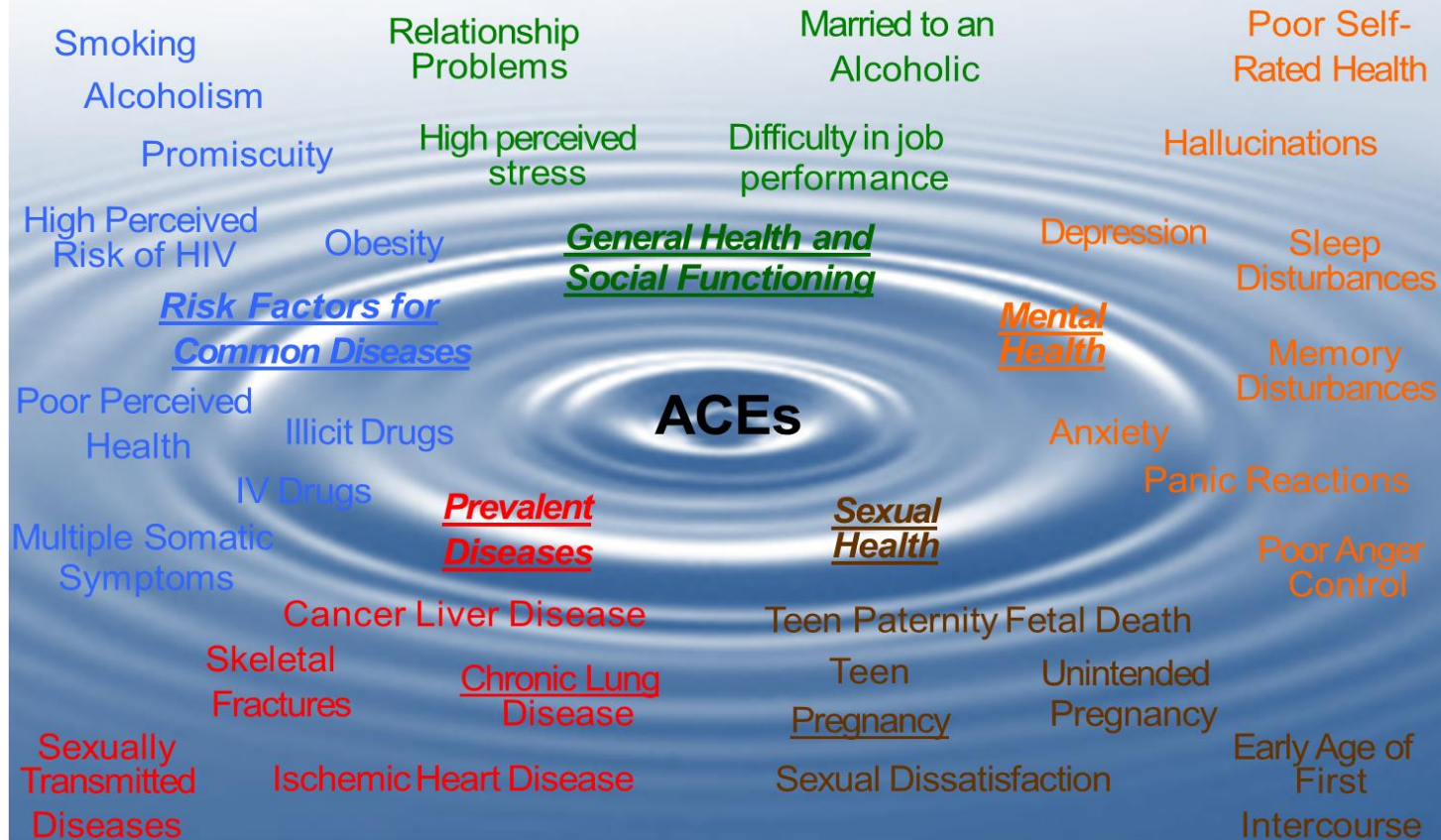
60% of American children were exposed to violence, crime, or abuse in their homes, schools, and communities.

Almost 40% of American children were direct victims of TWO or more violent acts, and one in 10 were victims of violence five or more times.

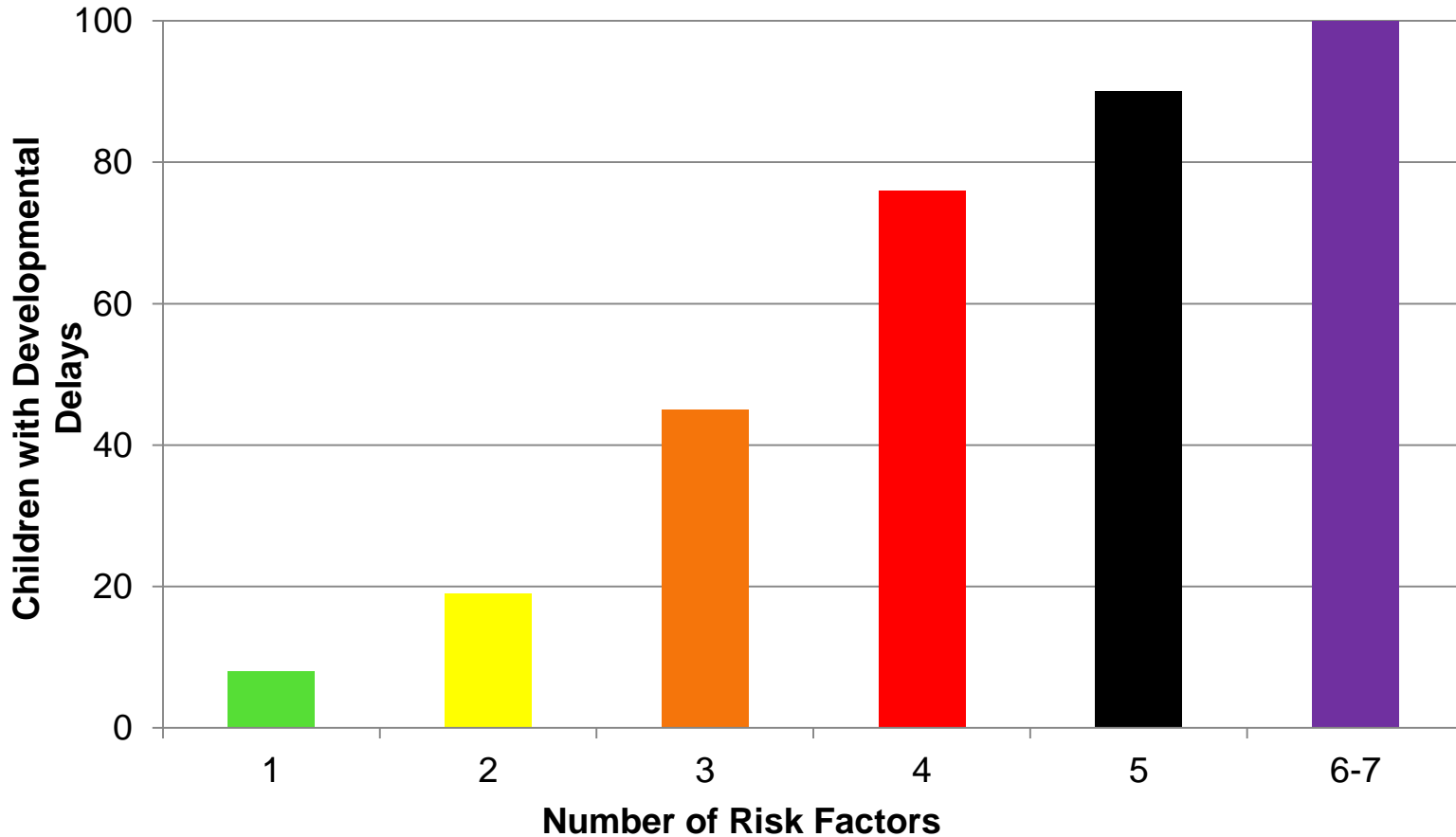
Almost **1 in 10** American children saw one family member assault another family member, and more than 25% had been exposed to family violence during their lifetime.

Exposure to one type of violence increased the likelihood that a child would be exposed to other types of violence and exposed multiple times.

ACEs Impact Multiple Outcomes

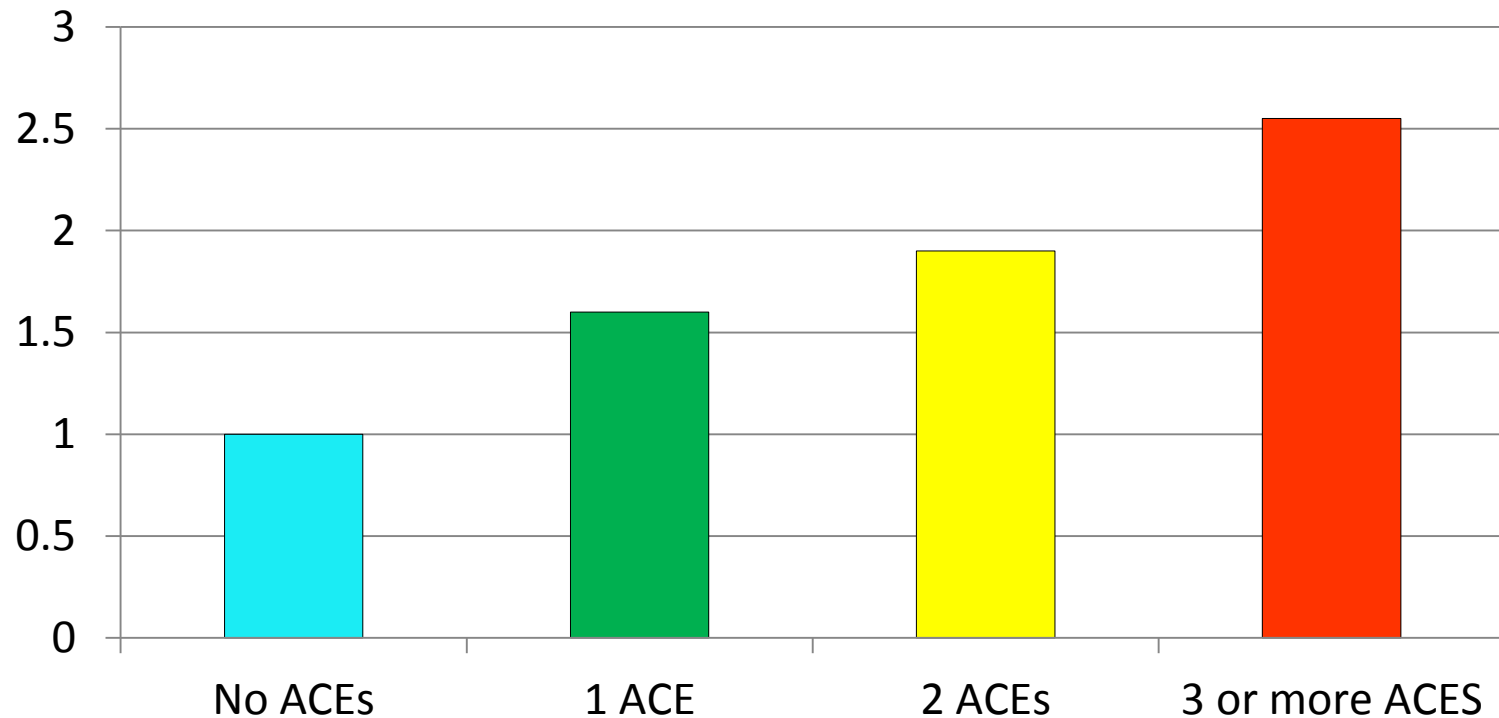


Significant Adversity Impairs Development

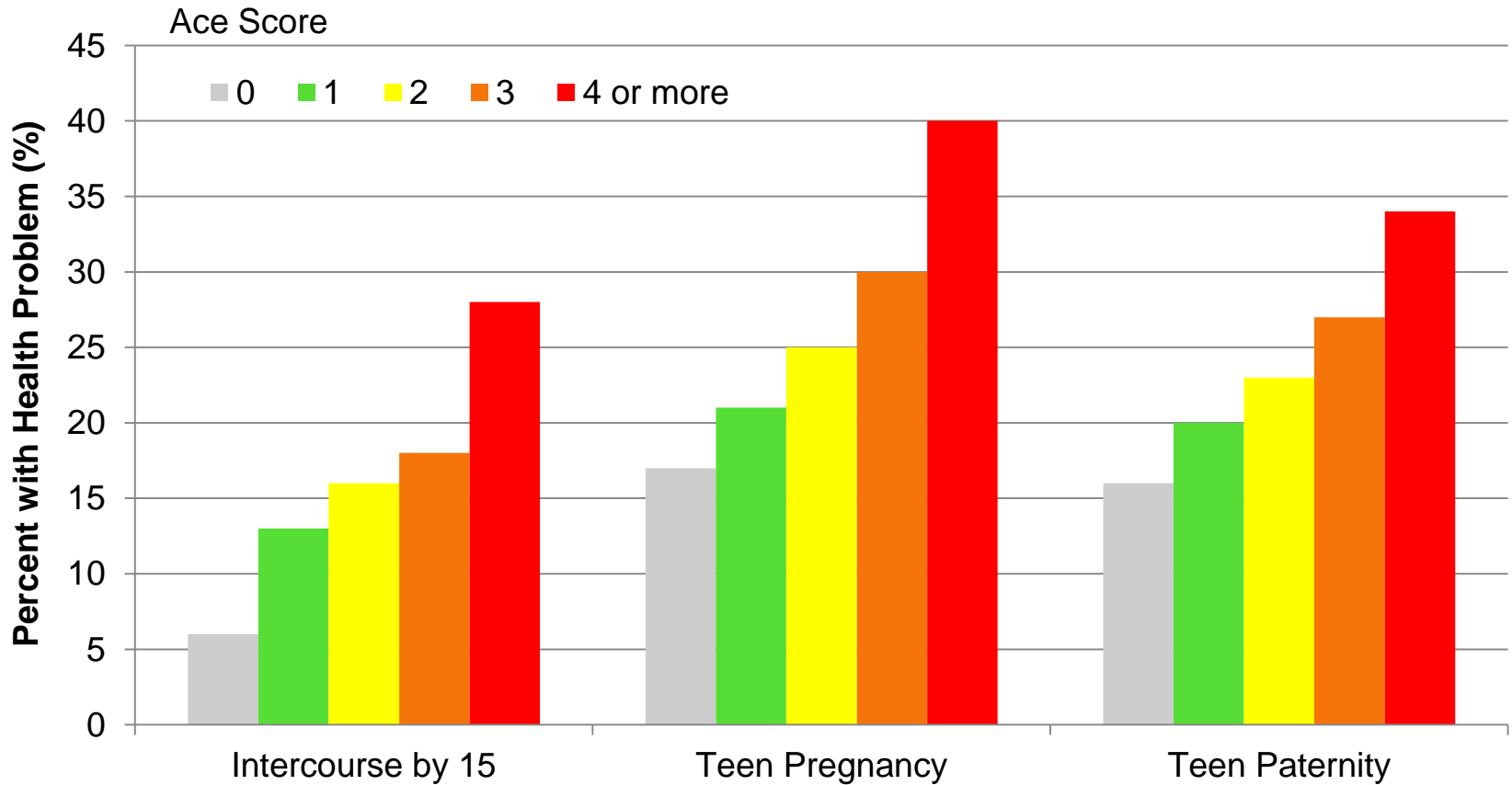


ACEs and Oral Health

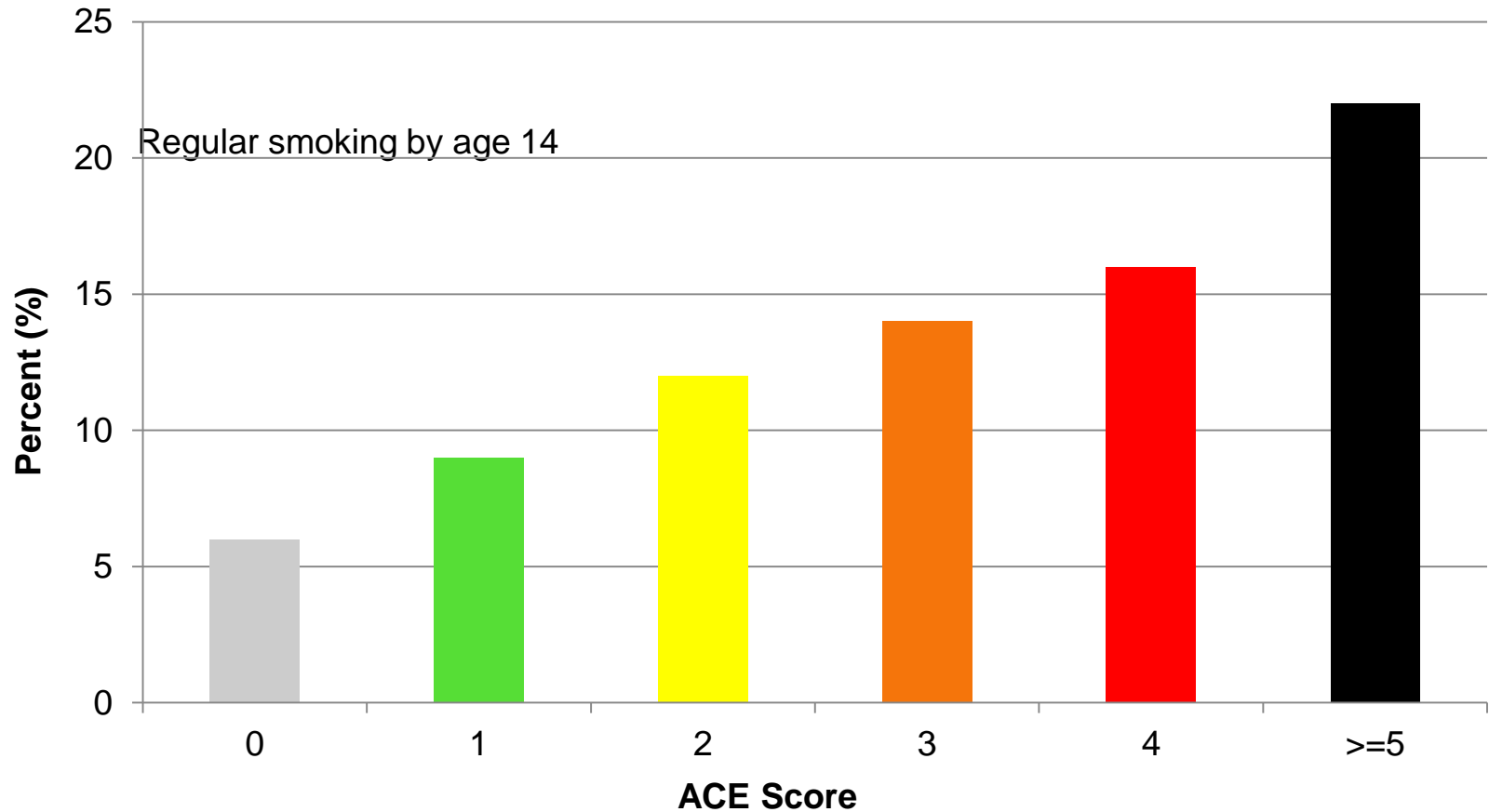
Decay or untreated cavities



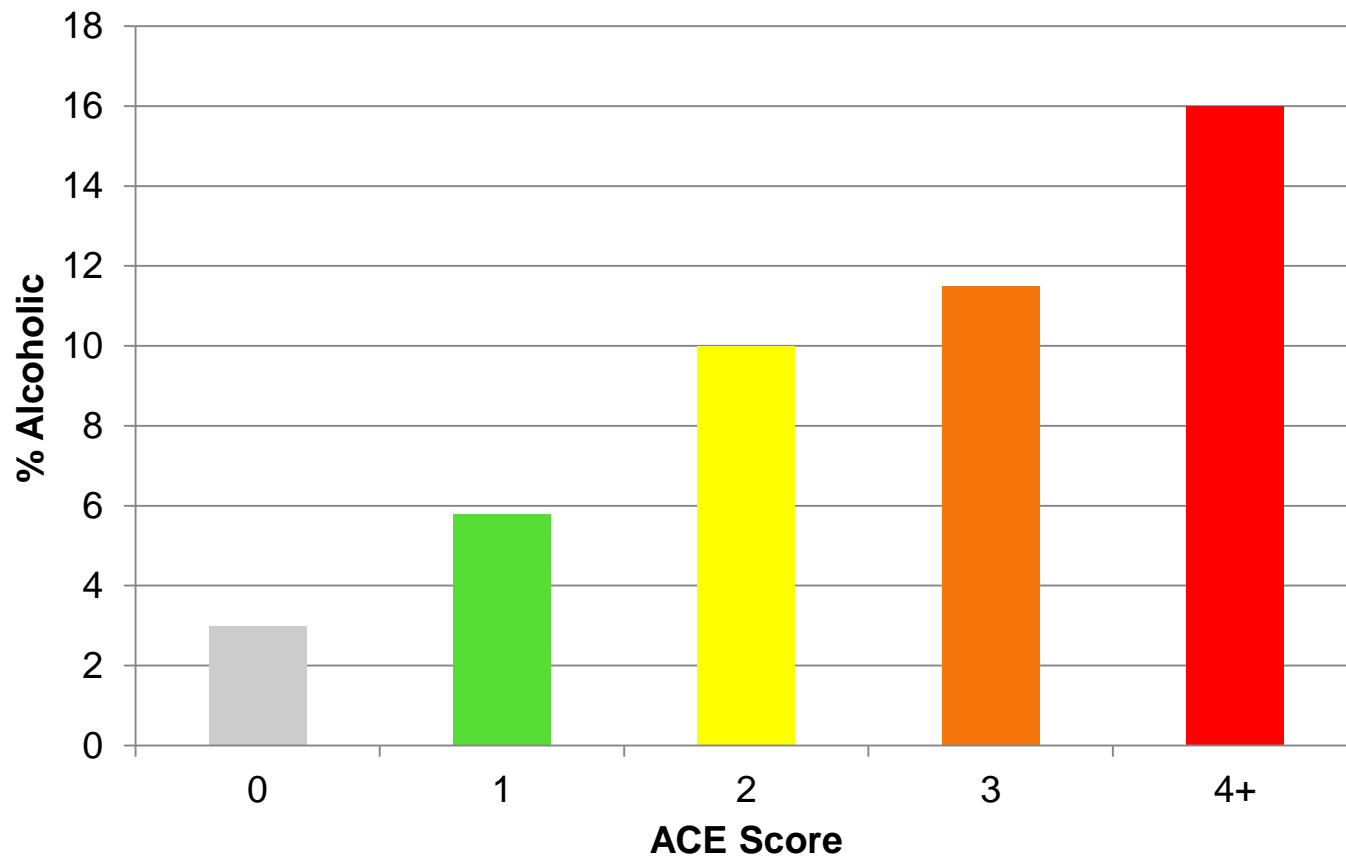
Ace Score and Teen Sexual Behaviors



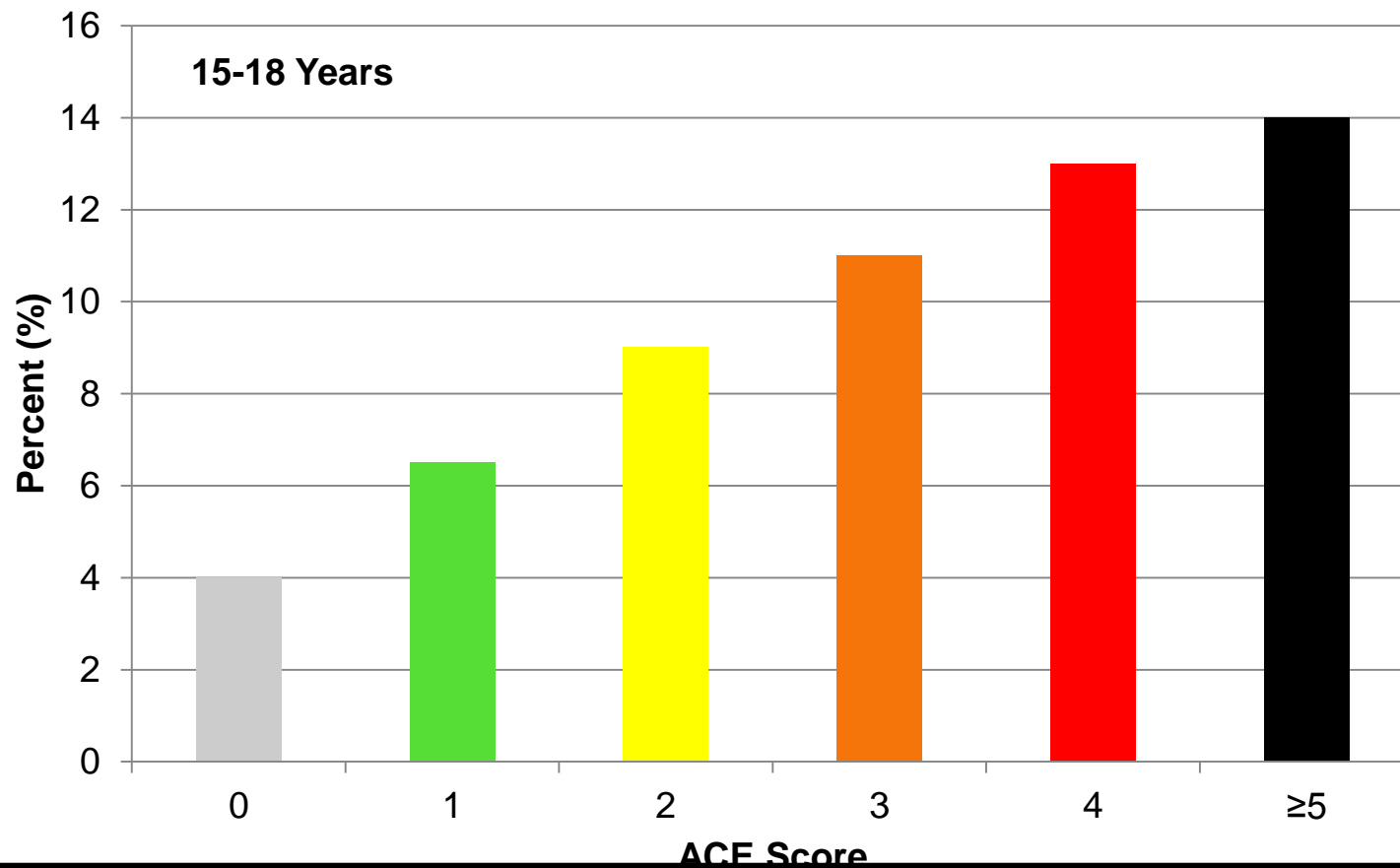
ACE Score and Early Cigarette Smoking



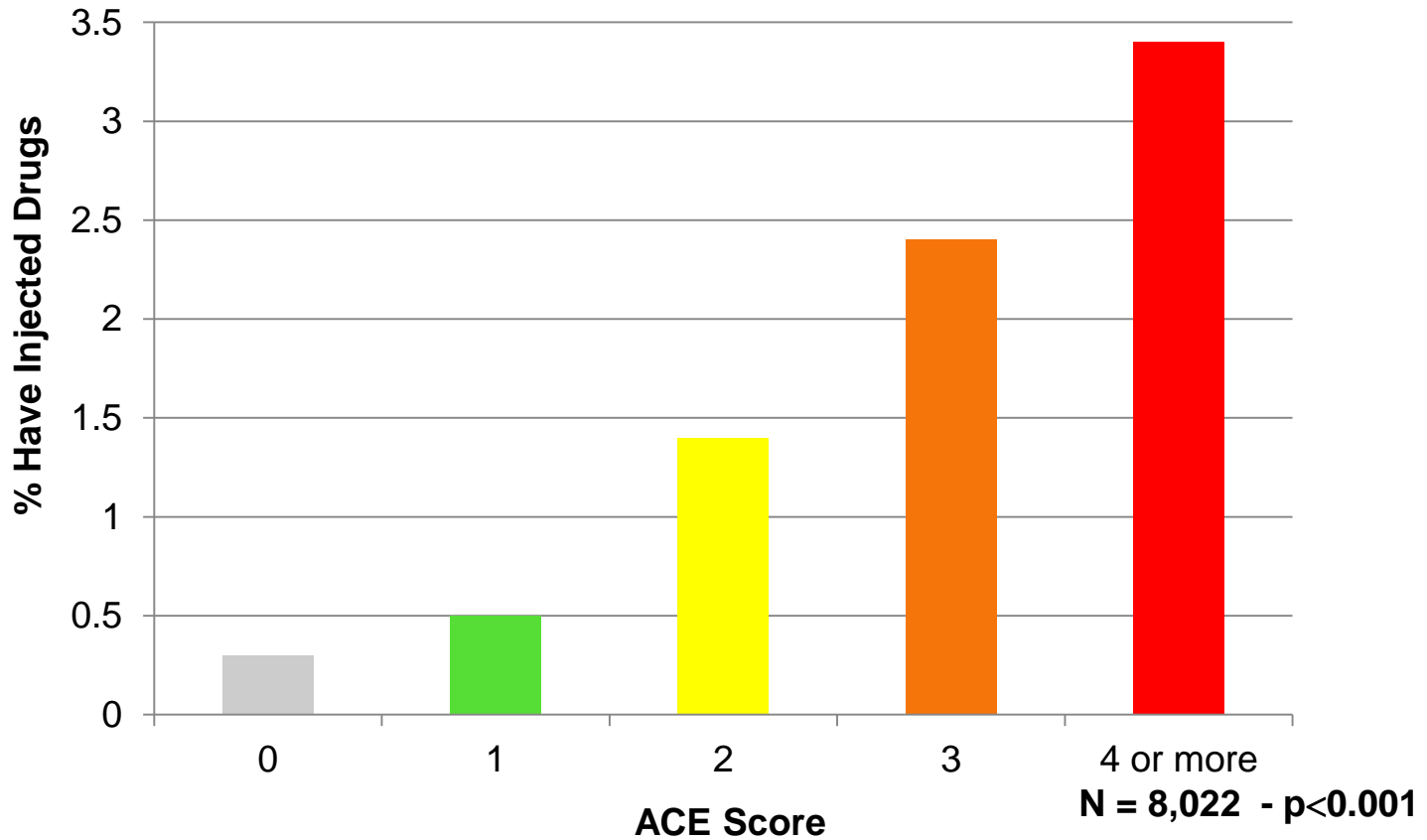
ACE Score and Risk of Self-Reported Alcoholism



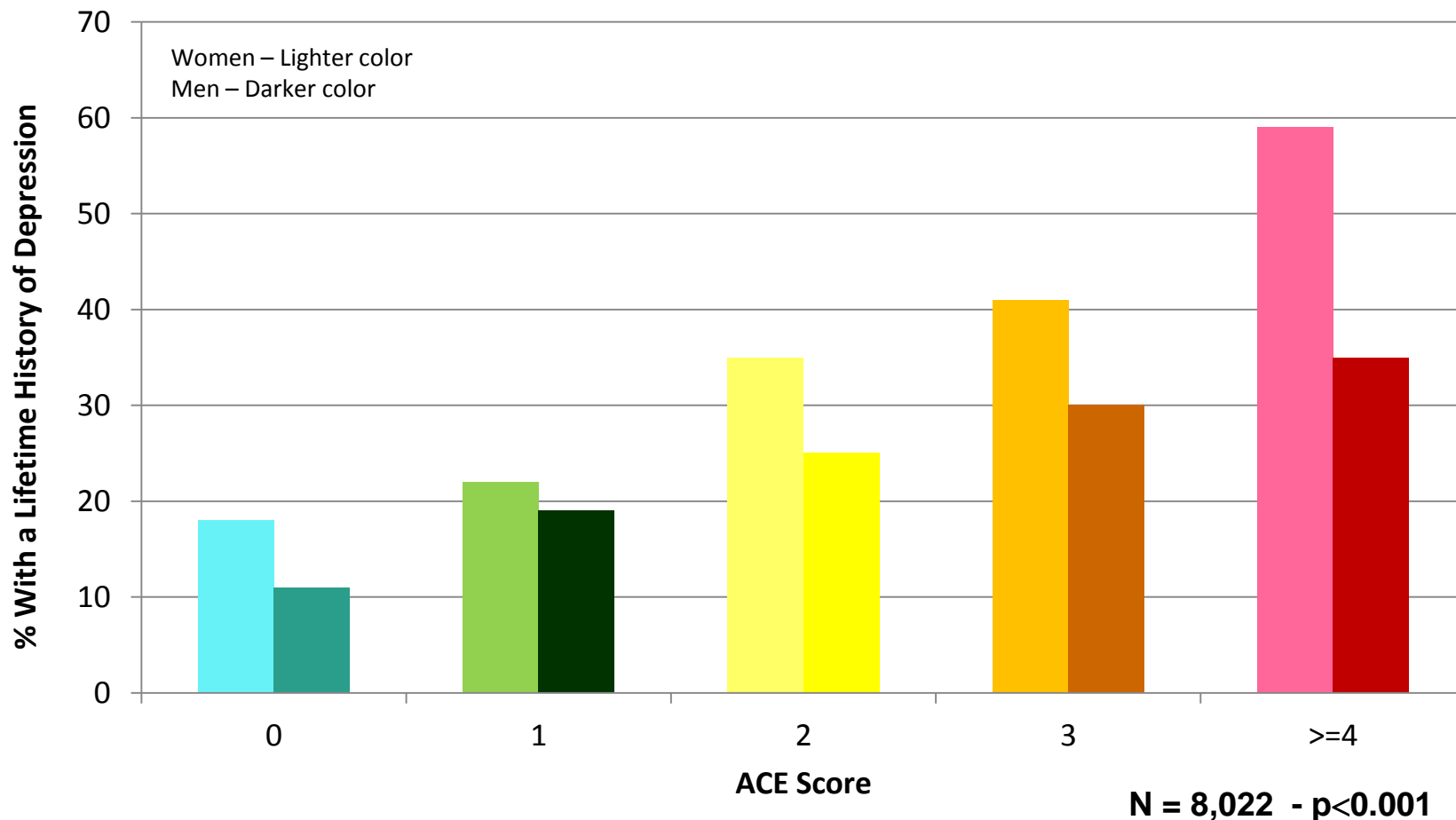
Number of ACEs and Age of Illicit Drug Use



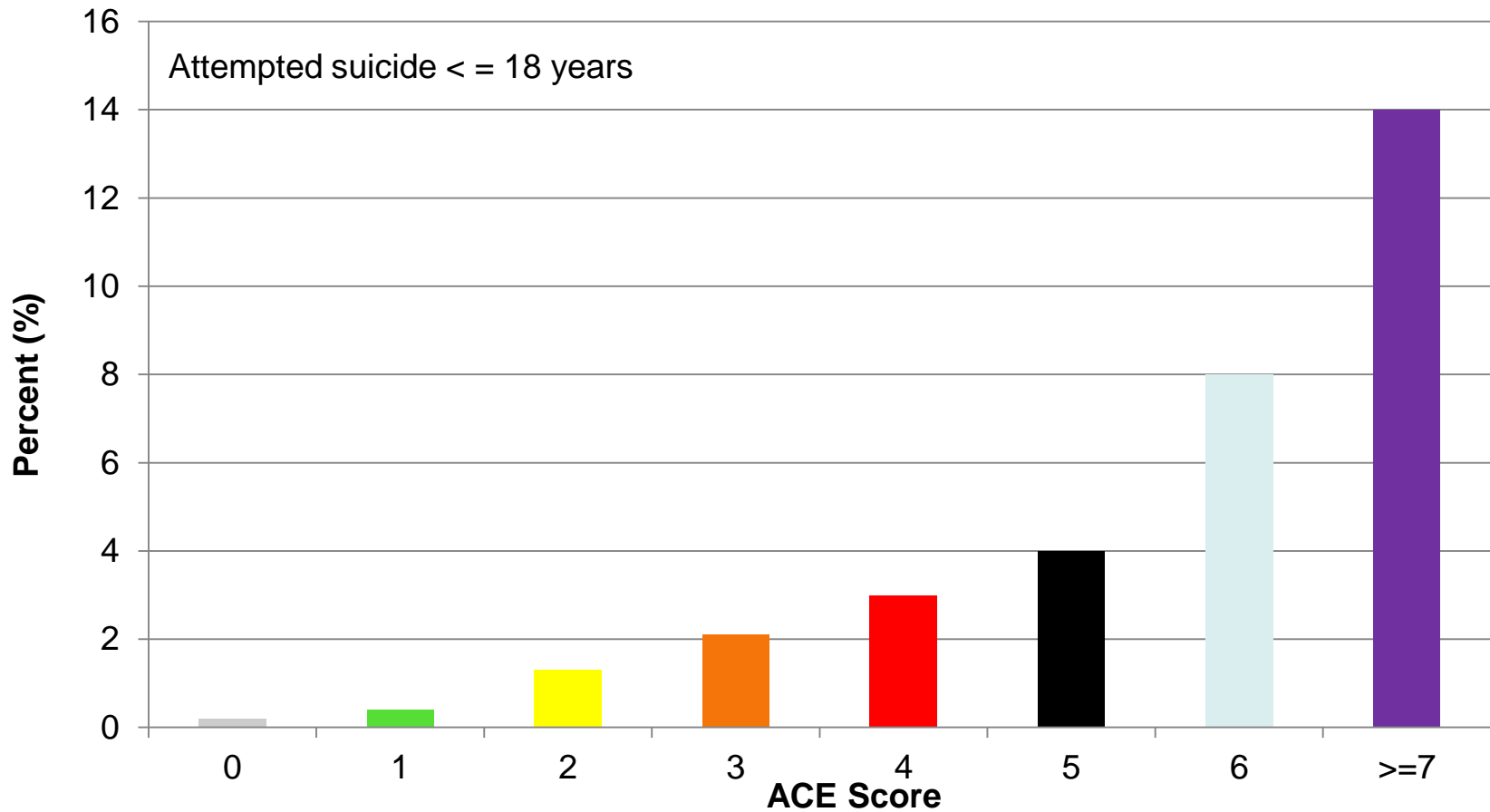
ACE Score and Intravenous Drug Use



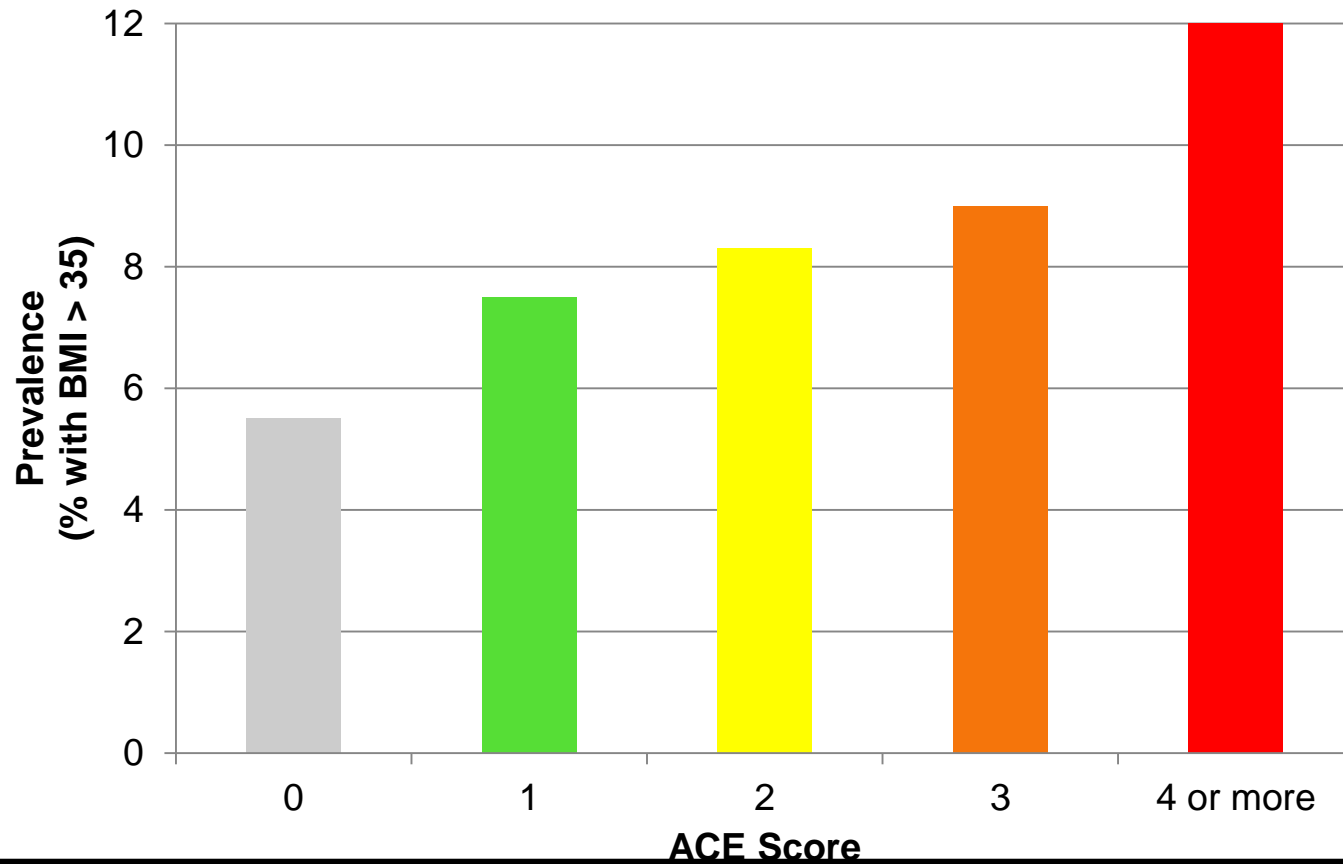
ACE Score and Chronic Depression as Adult



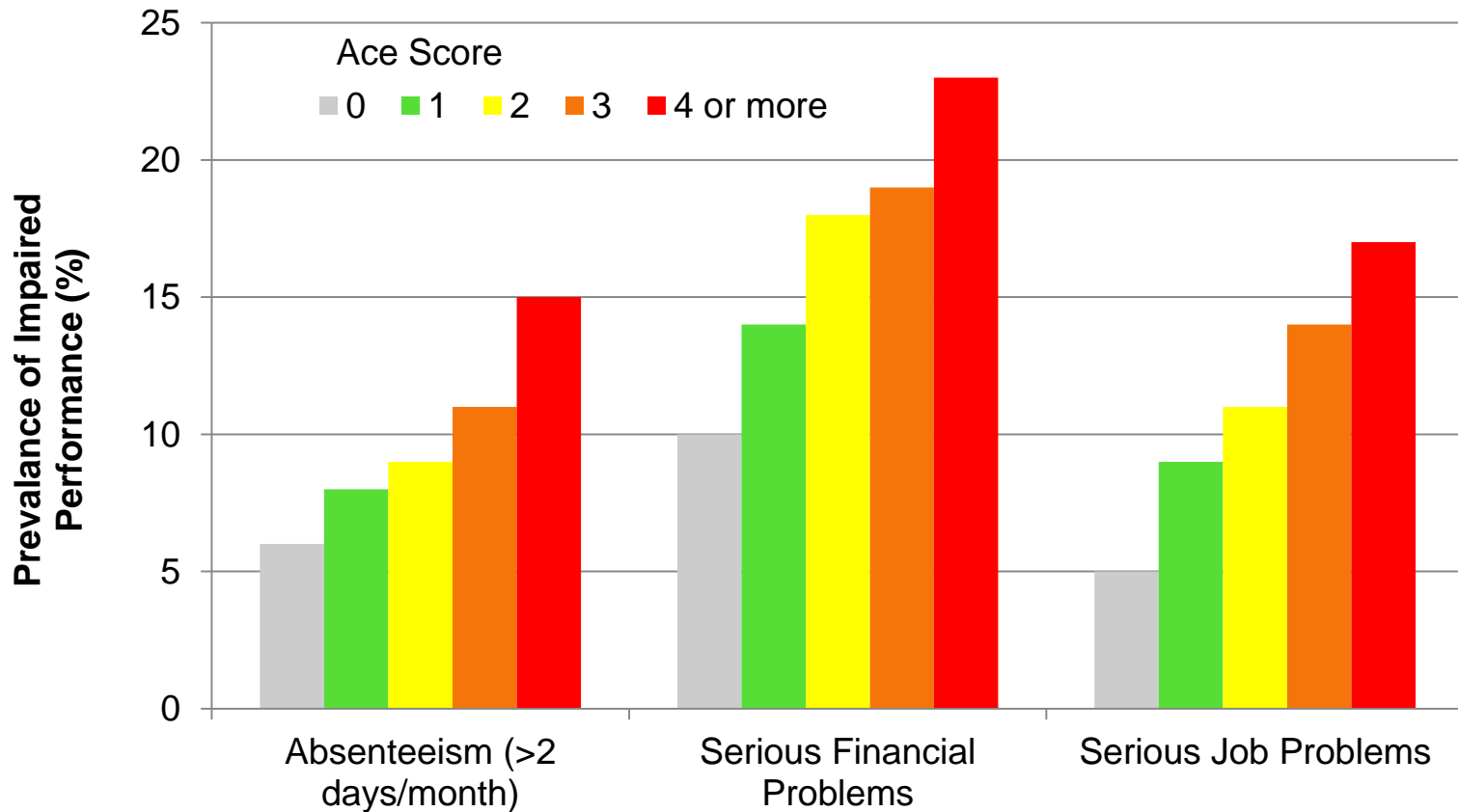
ACE Score and Attempted Suicide



ACEs and Obesity



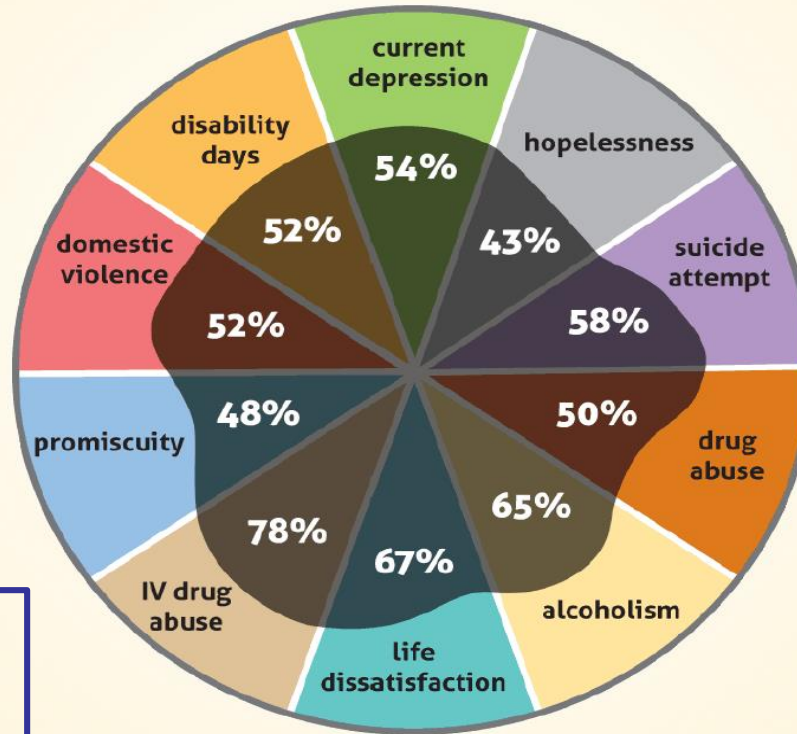
ACE Score and Indicators of Impaired Worker Performance



Seeking to Cope

- The risk factors/behaviors underlying these adult diseases are actually effective coping devices.
 - **What is viewed as a problem by the health care provider is actually a solution to bad experiences for the patient.**
 - Dismissing these coping devices as “bad habits” or “self destructive behavior” misses their source of origin [trauma]
-

ACEs and Population Attributable Risks

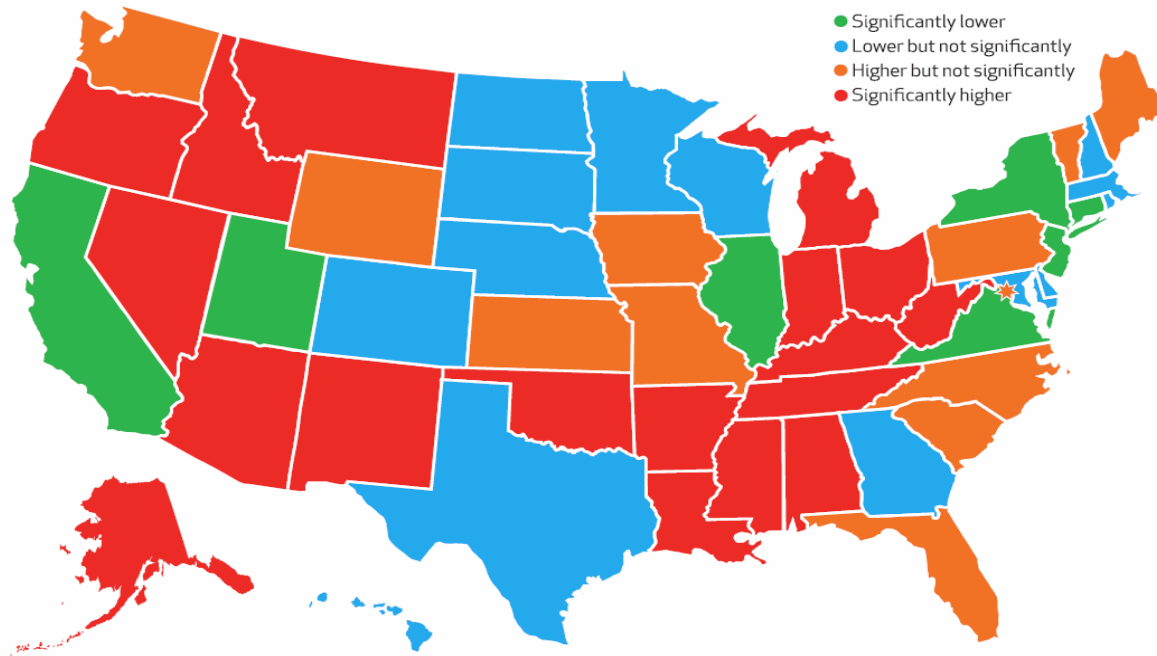


People with 6 or more ACEs died 20 years earlier than those without ACEs

ADVERSE CHILDHOOD EXPERIENCES are
the most basic and long lasting cause of:
health risk behaviors,
mental illness,
social malfunction,
disease
disability
death
healthcare costs

ACE Prevalence Among US Children (2011-12 National Survey of Children's Health)

Prevalence Of Children Ages 0-17, By State, Who Experienced Two Or More Of The Nine Adverse Childhood Experiences Evaluated In The 2011-12 National Survey Of Children's Health



47% of children in the US have had at least one ACE

Adverse Child or Family Experiences	National Prevalence	State Range
Child had ≥ 1 Adverse Child/Family Experience	47.9%	40.6% (CT) – 57.5% (AZ)
Child had ≥ 2 Adverse Child/Family Experiences	22.6%	16.3% (NJ) – 32.9% (OK)
Extreme economic hardship	25.7%	20.1% (MD) – 34.3% (AZ)
Family discord leading to divorce or separation	20.1%	15.2% (DC) – 29.5% (OK)
Having lived with someone who had an alcohol or drug problem	10.7%	6.4% (NY) – 18.5% (MT)
Having been a victim or witness of neighborhood violence	8.6%	5.2% (NJ) – 16.6% (DC)
Having lived with someone who was mentally ill or suicidal	8.6%	5.4% (CA) – 14.1% (MT)
Witnessing domestic violence in the home	7.3%	5.0% (CT) – 11.1% (OK)
Parent served time in jail	6.9%	3.2% (NJ) – 13.2% (KY)
Treated or judged unfairly due to race/ethnicity	4.1%	1.8% (VT) – 6.5% (AZ)
Death of parent	3.1%	1.4% (CT) – 7.1% (DC)

EXHIBIT 3

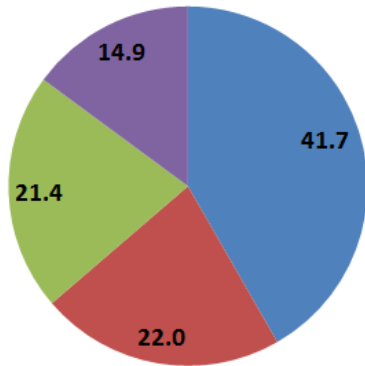
Prevalence Of Adverse Childhood Experiences (ACEs) Among Children Age 0–17, By Eleven Child And Risk Factors, By Number Of ACEs, 2011–12

Category of children	Study population (%)	Prevalence of ACEs (%)	
		1 ACE	2 or more ACEs
All	100.0	25.3	22.6
In fair or poor overall health	3.2	31.8	39.3
With special health care needs	19.8	25.9	36.0
With special health care needs and EBD	7.2	23.7	51.9
At high or moderate risk for developmental, behavioral, or social delays	26.2	26.9	18.8
With asthma	8.8	27.3	33.4
With ADHD	7.9	24.8	45.2
With autism spectrum disorder	1.8	27.1	34.4
Who are overweight or obese	31.3	25.5	37.1
With a behavior problem	3.2	23.6	61.4
Who bully ^d	2.2	23.0	55.4

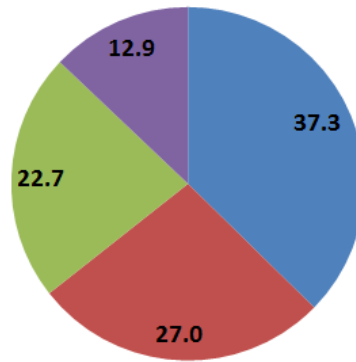
SOURCE Authors' analysis of data from the 2011–12 National Survey of Children's Health. **NOTES** AOR is adjusted odds ratio (by race/ethnicity). EBD is emotional, behavioral, or developmental problems. ADHD is attention deficit hyperactivity disorder. ^d Variation remains ($p < 0.05$), after adjustment for child-level characteristics across states using multivariate analysis.

Number of ACEs by Race/Ethnicity

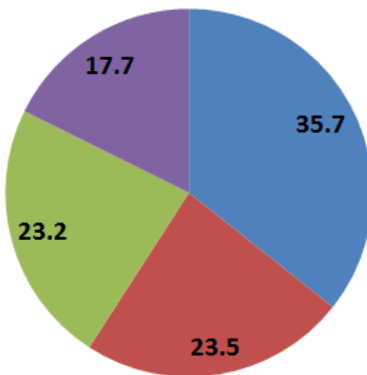
White



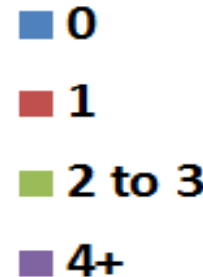
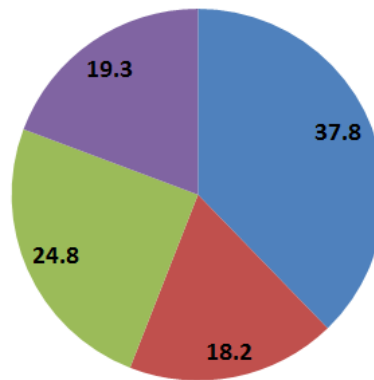
Black



Hispanic



Other



Percentage of adults aged ≥ 18 years reporting ACEs by race— Behavioral Risk Factor Surveillance System five states, 2009. MMWR Dec 17, 2010 AK, LA, TN NM, WA

*“For us, one of the most compelling results of the research is that **trauma doesn’t discriminate.**”*

Suzanne Mineck, Mid Iowa Health Foundation, source: the Community Resilience Cookbook



Science Tells Us that Early Life Experiences Are Built Into Our Bodies

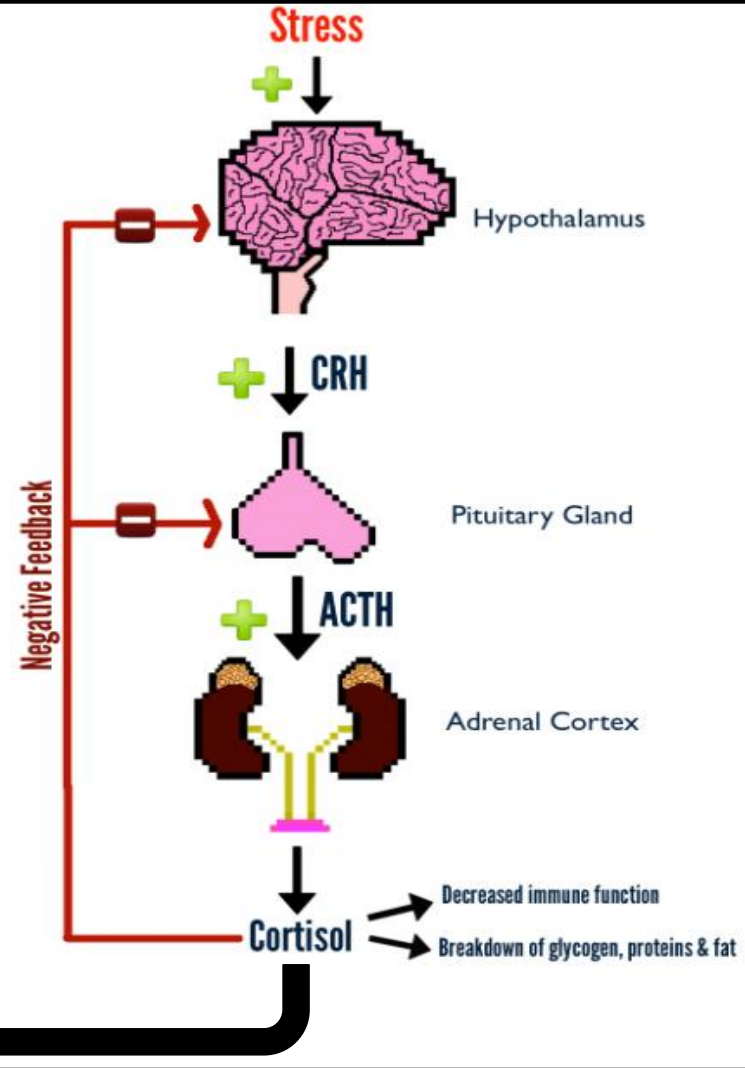
Research on the biology of stress illustrates how threat

- raises heart rate, blood pressure, and stress hormone levels, which can
- impairs brain architecture, immune status, metabolic systems, and cardiovascular function.

Body's Response to Stress

(Hypothalamic-Pituitary Axis)

- Increased Heart Rate
- Rapid Breathing
- Increased Blood flow to muscles
- Anxious, on edge



Three Levels of Stress

Positive

Brief increases in heart rate,
mild elevations in stress hormone levels.

Tolerable

Serious, temporary stress responses,
buffered by supportive relationships.

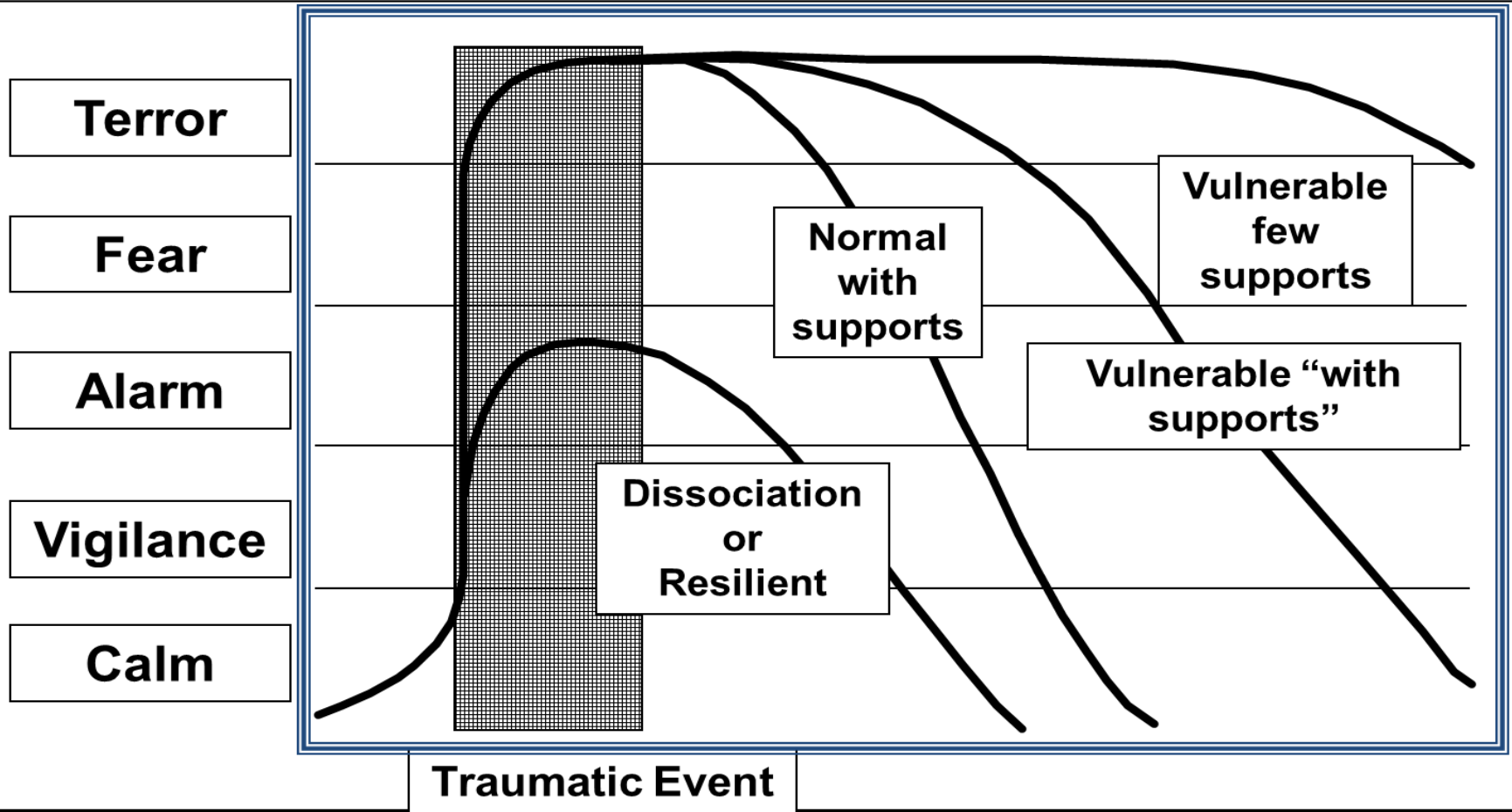
Toxic

Prolonged activation of stress response systems
in the absence of protective relationships.

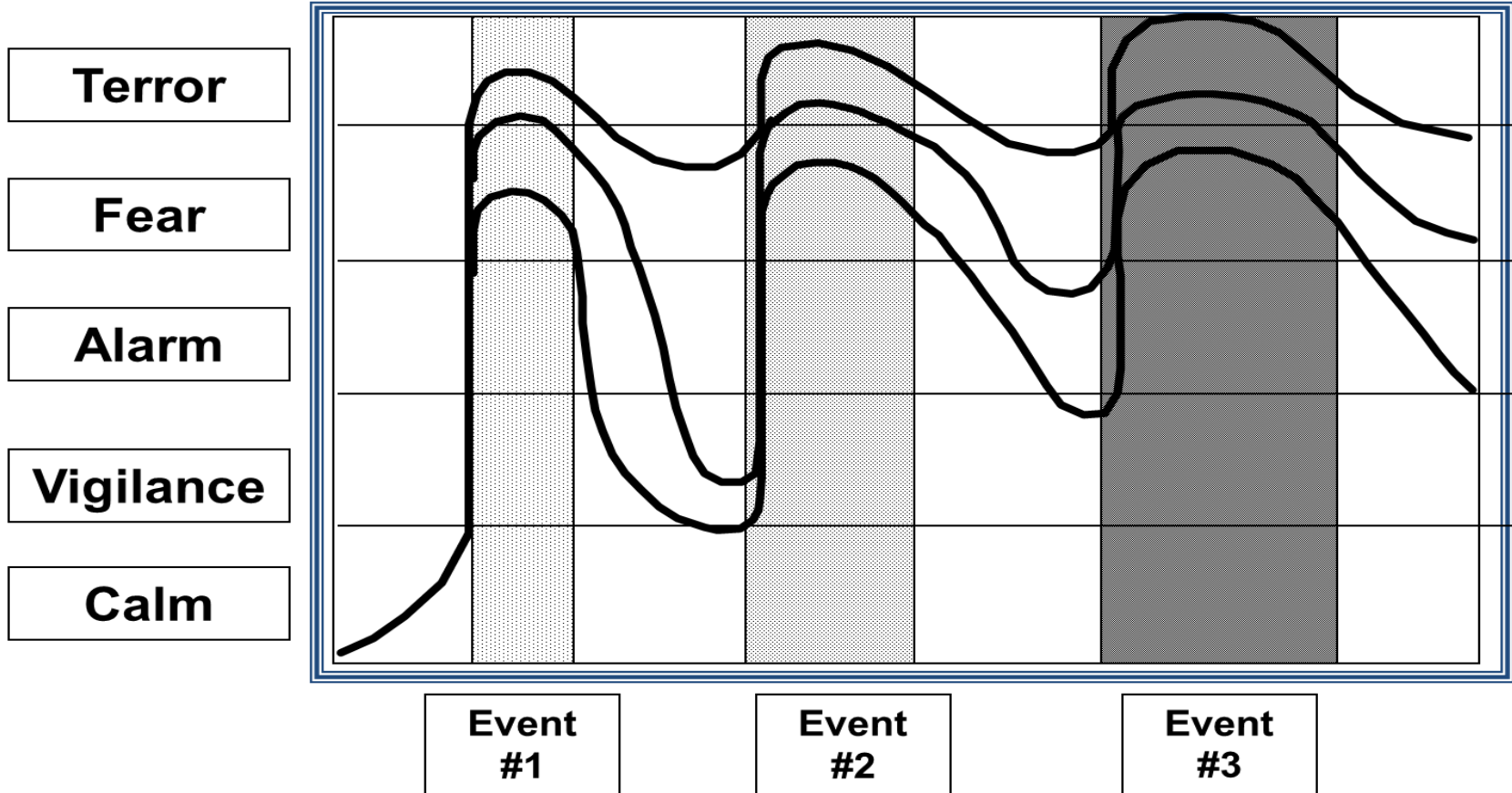
Traumatic Stress

- Physical and emotional responses of a child to events that are *perceived* to threaten the life or physical integrity of the child, or someone critically important to the child (such as a parent or sibling).
- This out-of-control physiologic response that *overwhelms the capacity to cope* is the hallmark of stress that becomes traumatic and damaging.
- Effects multiply when the trauma continues.
- Varies with child's age, developmental status, prior experiences, support systems, relationship to victim, witness or experiencing the violence

Acute Response To Trauma



Multiple Traumatic Events



Trauma/Toxic Stress in Children

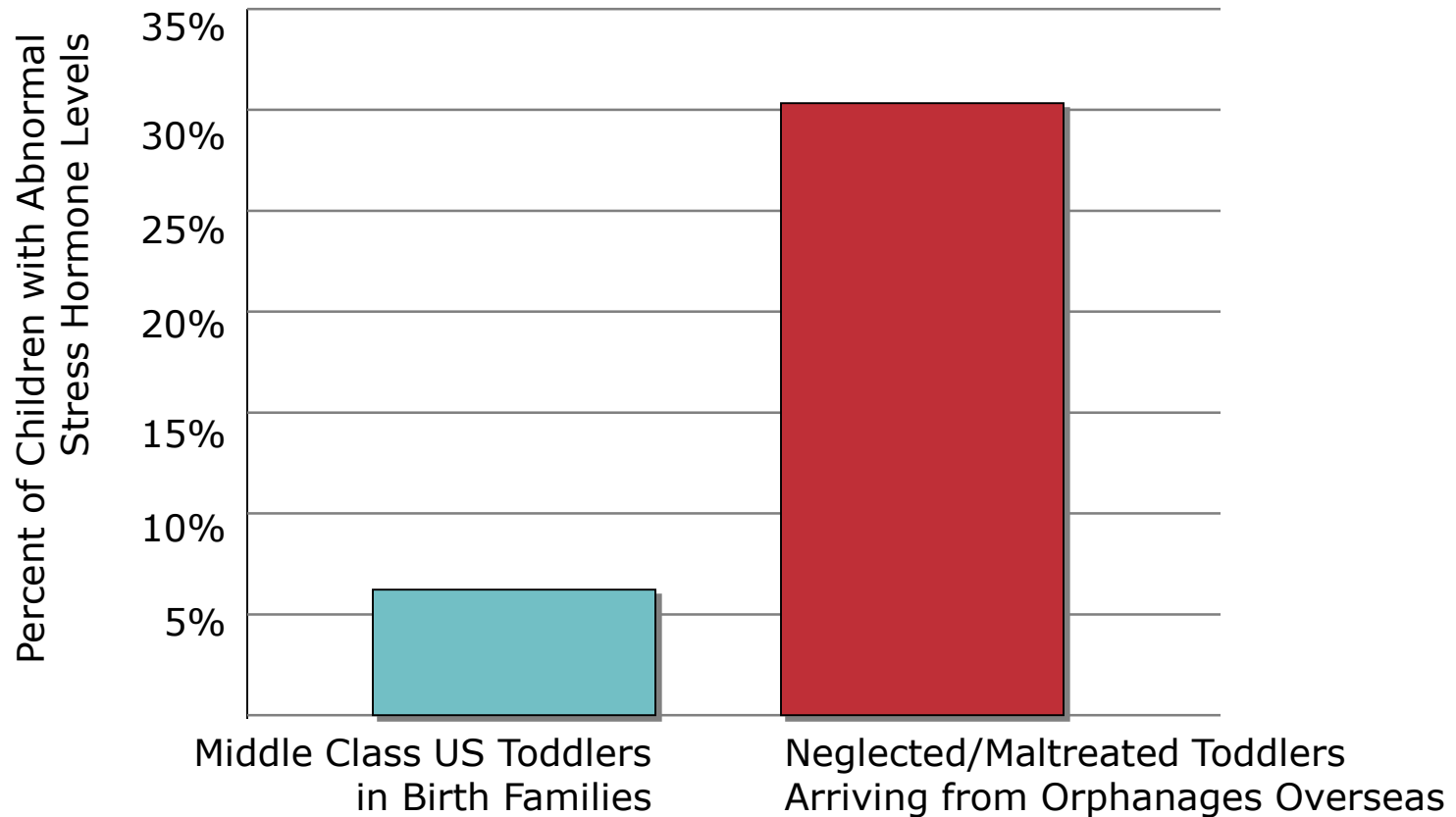
Effects on Relationships

- Difficulty forming positive relationships
- Poor sense of self
- Lowered self esteem
- Expectation of being treated poorly
- Loss of secure base
- Loss of sense of trust

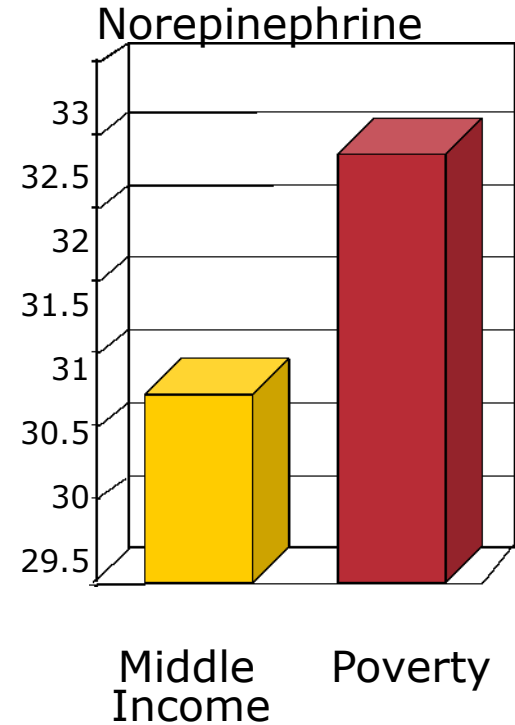
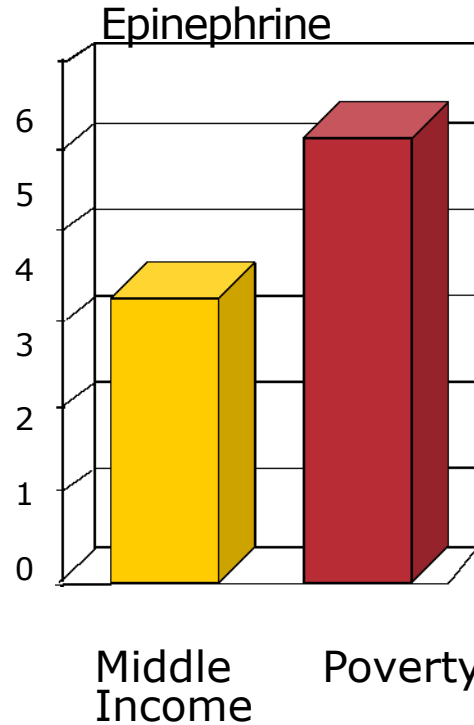
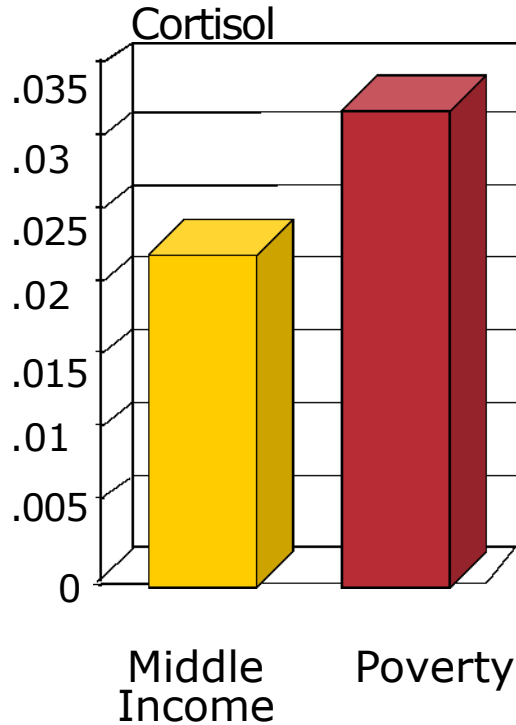
Altered Neurodevelopment

- Altered cardiovascular regulation
- Behavioral impulsivity
- Increased anxiety
- Increased startle response
- Sleep abnormalities



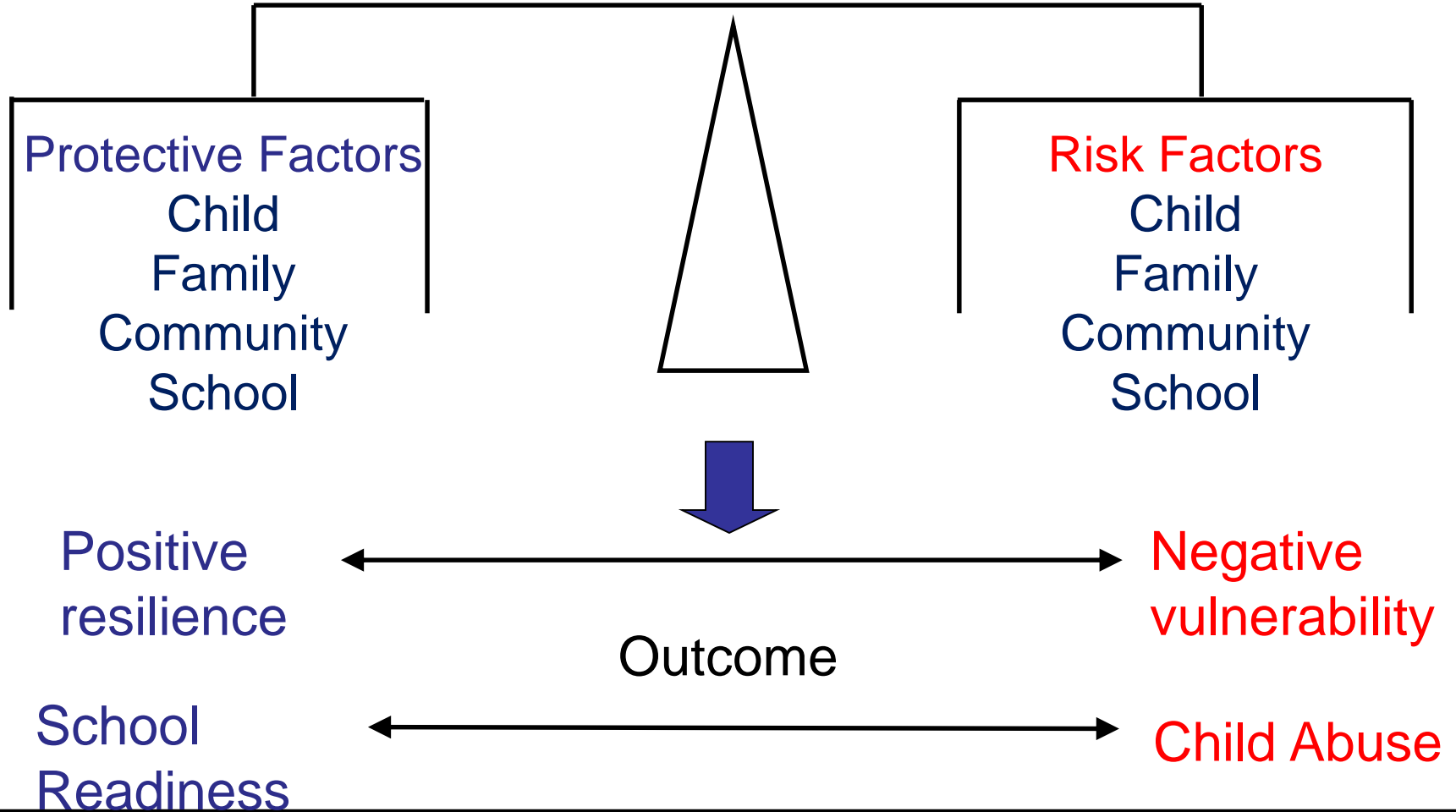


Poor Children Experience Elevated Stress

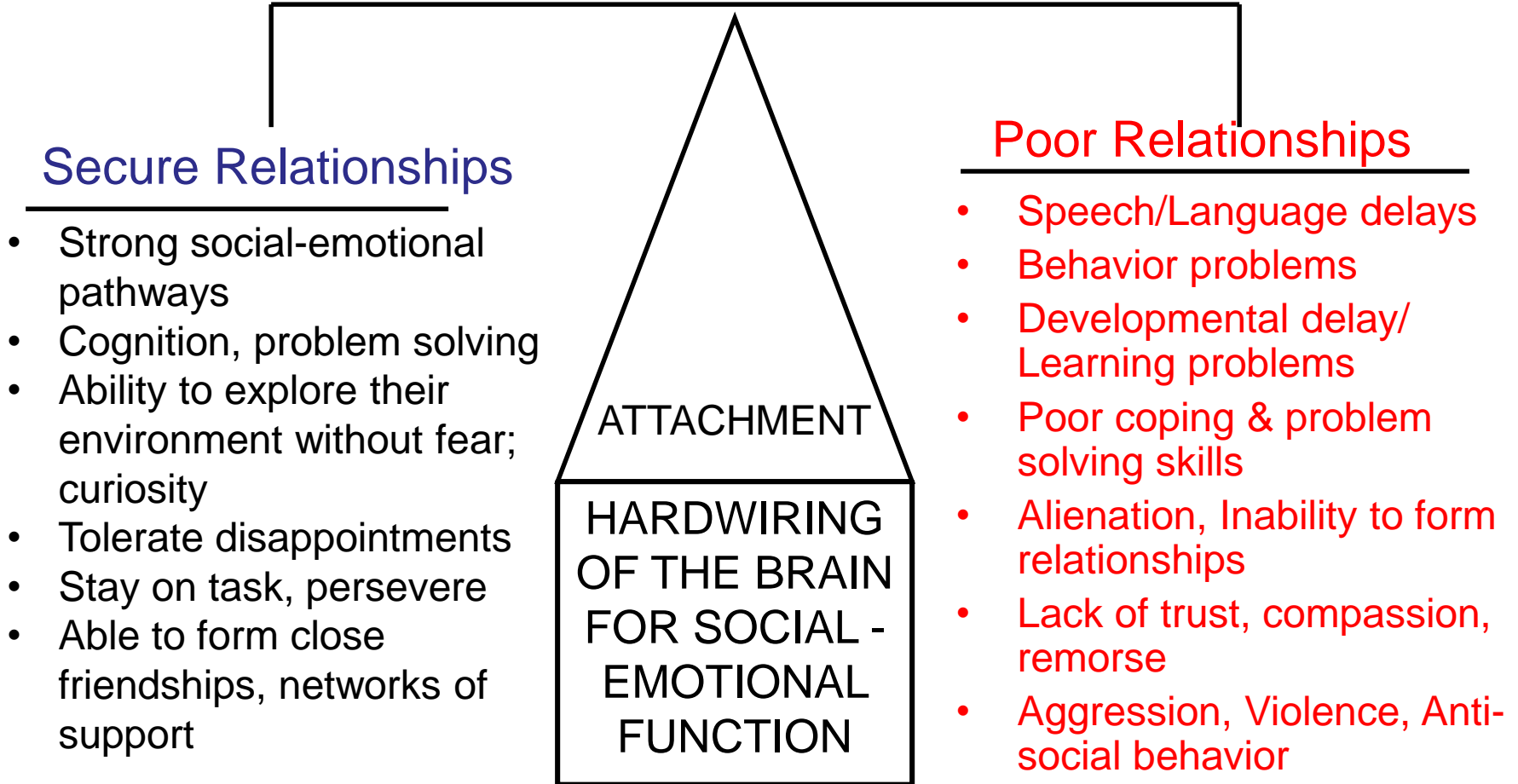


Overnight levels in rural 9-year-old white children

A Balance of Risk and Protective Factors



A Balance of Risk and Protective Factors



A Balance of Risk and Protective Factors

Executive Function

- Able to plan
- Self-control
- Self confidence
- Able to calm self
- Ability to problem solve
- Follows directions
- Persists on task
- Able to delay gratification
- Able to manage their tempers when provoked

Responses
to chronic/
toxic stress

“Amygdala Hijack”

- Impaired memory, esp. “working” and contextual memory
- Inability to concentrate
- Harder to follow directions
- Hard to sit still
- Constantly on edge
- Easily provoked
- Impulsive

PRESENT <- SUPPORTIVE RELATIONSHIP -> ABSENT



THE OFFICIAL NEWSMAGAZINE OF THE AMERICAN ACADEMY OF PEDIATRICS

AAP News

PAS Meeting Update

May 6, 2014

www.aapnews.org

Study finds ADHD and trauma often go hand in hand

Children with attention-deficit/hyperactivity disorder experienced more adversities than those without ADHD

by **Carla Kemp** • Senior Editor

VANCOUVER, BRITISH COLUMBIA – When children struggle with focusing on tasks, staying organized, controlling their behavior and sitting still, they may be evaluated for attention-deficit/hyperactivity disorder (ADHD). Clinicians, however, shouldn't stop there, according to a study to be presented Tuesday, May 6, at the Pediatric Academic Societies (PAS) annual meeting in Vancouver, British Columbia, Canada.

Researchers found that many children with ADHD also face challenges such as poverty, divorce, neighborhood violence and substance abuse among family members.

“Our findings suggest that children with ADHD experience significantly higher rates of trauma than those without ADHD,” said lead author Nicole M. Brown, M.D., M.P.H., M.H.S., FAAP. “Providers may focus on ADHD as the primary diagnosis and overlook the possible presence of a trauma history, which may impact treatment.”

Dr. Brown and her colleagues analyzed data from the 2011 National Survey of Children's Health. They identified 65,680 children ages 6-17 years whose parents answered questions regarding ADHD diagnosis, severity and medication use as well as nine adverse childhood experiences (ACEs): poverty, divorce, death of a parent/guardian, domestic violence, neighborhood violence, substance abuse, incarceration, familial mental illness and discrimination.

About 12% of the children were diagnosed with ADHD. Their parents reported a higher prevalence of all of the adverse events than parents of children without ADHD.

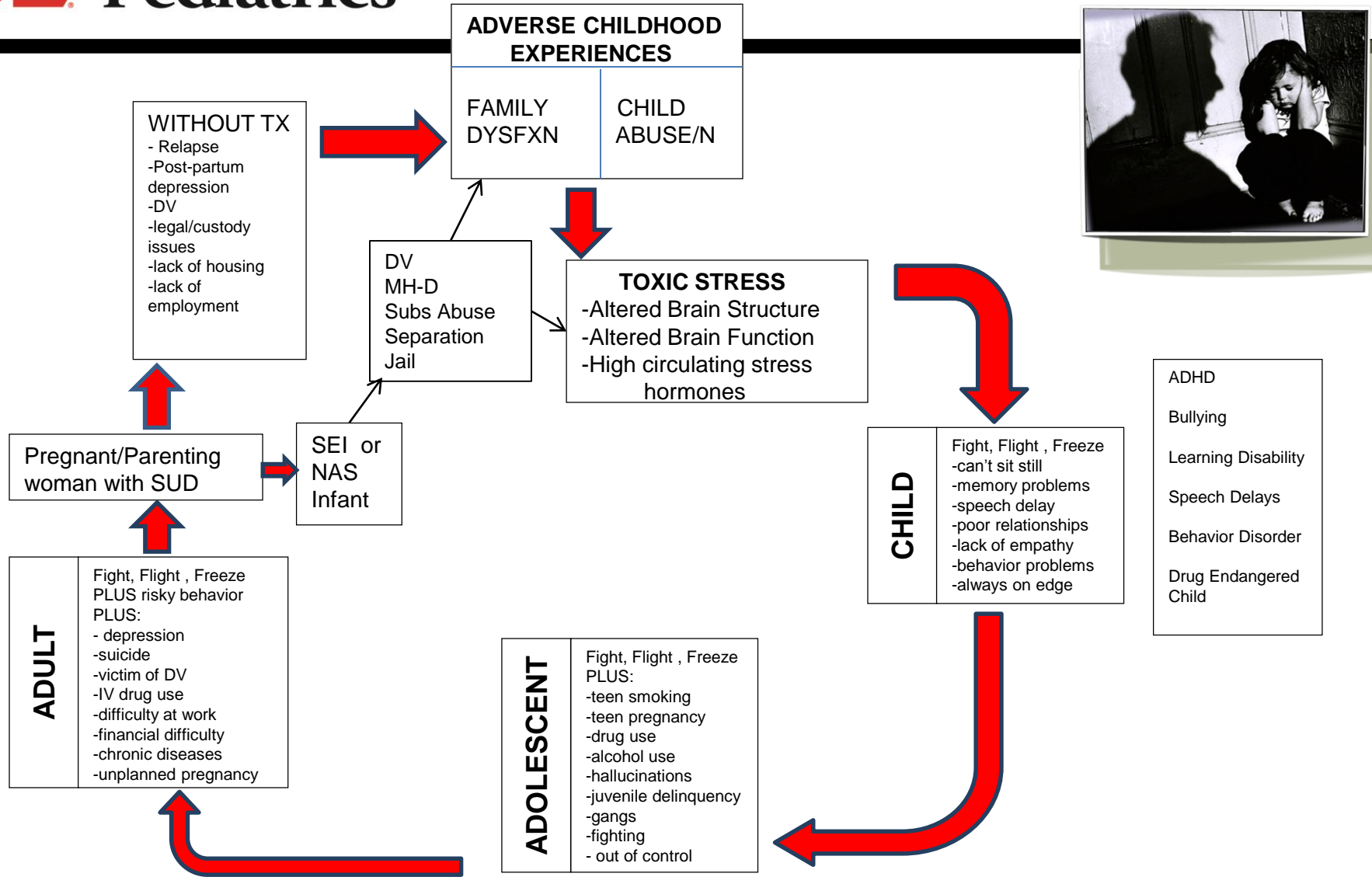
Parents of children with ADHD also reported a higher number of adverse childhood experiences compared to children without ADHD; 17% of children with ADHD had four or more ACEs compared to 6% of children without ADHD.

Children dealing with four or more adverse experiences were almost three times more likely to use ADHD medications compared to children with three or fewer adverse experiences. Children with four or more adverse experiences also were more likely to have a parent rate their ADHD as moderate to severe compared to children with three or fewer ACEs.

“Knowledge about the prevalence and types of adverse experiences among children diagnosed with ADHD may guide efforts to address trauma in this population and improve ADHD screening, diagnostic accuracy and management,” said Dr. Brown, assistant professor of pediatrics, Division of General Pediatrics, The Children's Hospital at Montefiore, Albert Einstein College of Medicine, New York.

“Pediatric providers should consider screening for adverse childhood experiences in children who they suspect may have ADHD and/or those who carry the diagnosis, and initiate evidence-based treatment/intervention plans for children who screen positive for ACEs,” she concluded.

To view the study abstract, go to http://www.abstracts2view.com/pas/view.php?nu=PAS14L1_4670.7.



Substance Exposed Infants/Neonatal Abstinence “Drug Endangered Children”

Emotional Problems

- Attachment Disorders
- Anxiety
- Depression
- Complex emotions

Behavioral Problems

- Interpersonal Problems
- Inappropriate sexual behaviors
- Impulsive, low threshold for stimulation
- Eating disorders

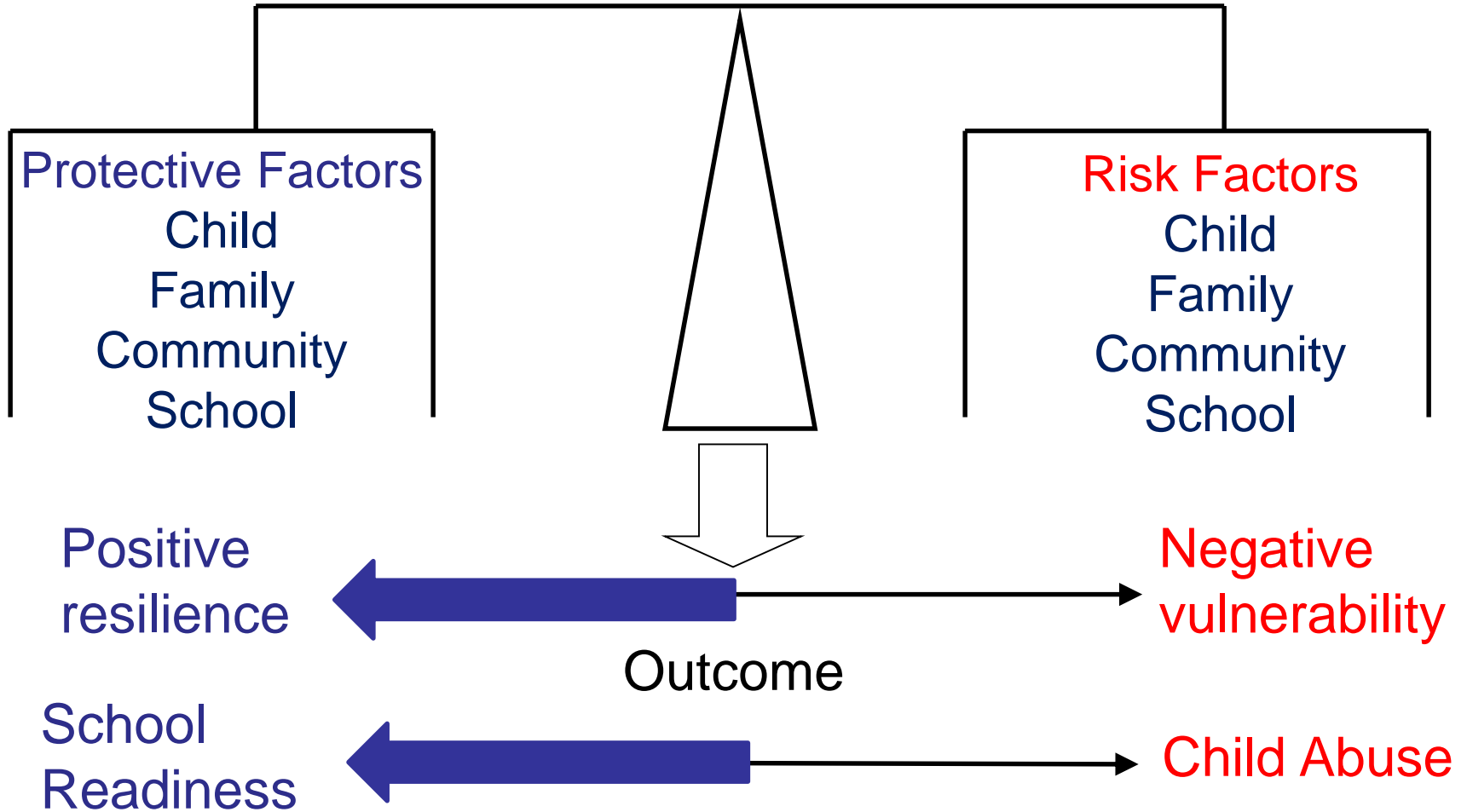
Cognitive Problems

- Difficulty talking and listening
- Difficulty Paying Attention
- Difficulty Remembering
- Trouble reading
- Do not learn from mistakes or experiences
- Do not pick up on social cues

Growing scientific understanding into causal mechanisms that link early adversity into later impairments in learning, behavior, and both physical and mental well-being are potentially **TRANSFORMATIONAL.**

- Toxic stress in young children can lead to less outwardly visible yet permanent changes in brain structure and function.
- Altered brain architecture in response to toxic stress in early childhood could explain, at least in part, **the strong association between early adverse experiences and subsequent problems in the development of linguistic, cognitive, and social-emotional skills**, all of which are inextricably intertwined in the wiring of the developing brain.

A Balance of Risk and Protective Factors



+ Family Skills and Support -

Resilience

The ability to recover quickly from difficulties; toughness

1. The ability to cope with or easily adjust to misfortune or change
 2. The capacity of a strained body to recover its size and shape after being bent, compressed, or stretched
-

Building Resilience

- The foundation of resilience is the combination of
 - (1) Supportive relationships- every child needs a nurturing adult to care about them, accept them unconditionally, and encourage them to be their best.
 - (2) Adaptive skill building- the ability to learn to face challenges and build a sense of accomplishment and confidence
 - (3) Experience a feeling of belonging and making a contribution
- The capabilities that underlie resilience can be strengthened at any age

Building Resilience

AAP 5R's of building healthy brains

Relationship

Routines

Reward

Rhymes

Reading

Unpredictable environment – random, episodic story structure (Payne, 1996)

Never learn to plan/see things in sequence/persist on task

Cannot predict/delay gratification

Cannot identify cause → effect → consequence

No impulse control, self regulation

Tendency to risky behaviors

Building Resilience

Home visiting

- **Builds Relationships**
- Strengths-based, building parent skills
- Nurturing and Attachment
- Positive parenting, early brain development
- **Builds self sufficiency in parents** – education, goal setting, anger management, planning, resourcing
- TWO GENERATION APPROACH

IMPROVED OUTCOMES

- ❖ *31% less Prematurity*
- ❖ *33% less LBW*
- ❖ *55% less VLBW*
- ❖ *50% less Pregnancy Induced Hypertension*
- ❖ *50% less ER Usage*
- ❖ *40% less Child Abuse and Neglect*
- ❖ *26% improved/increased Education*



Cabinet for Health and Family
Services
Department for Public Health

“We don’t lift these families out of poverty, we help them build the skills they need to face their adversity.”

Confidence

A sense of self-worth and mastery; having a sense of self-efficacy (belief in one's capacity to succeed).

Character

Taking responsibility; a sense of independence and individuality; connection to principles and values.

Connection

A sense of safety, structure, and belonging; positive bonds with people and social institutions.

Competence

The ability to act effectively in school, in social situations, and at work.

Contribution

Active participation and leadership in a variety of settings; making a difference in the community.

Caring

A sense of sympathy and empathy for others; commitment to social justice.

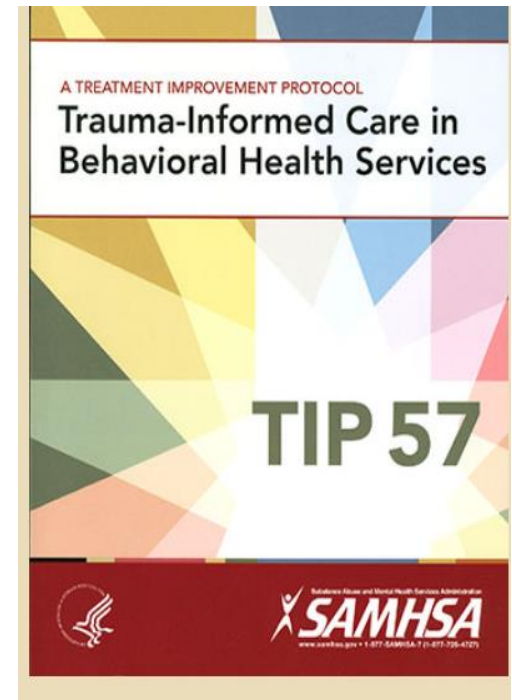
Public Health Approach to ACEs and Trauma

- Primary Prevention (Universal)
 - Raise awareness; reduce stigma; **trauma-aware**
 - Build protective factors for all – every family faces adversity
- Secondary Prevention (Targeting at risk)
 - Routine screening for early detection, anticipatory guidance, early intervention: **Trauma-Informed systems**
 - Reducing the dose of adversity; avoid re-traumatizing
 - Build Adaptive skills: Parenting programs, home visiting programs
- Tertiary Prevention (Treating those affected)
 - **Trauma-Specific Treatment**
 - Mental health, social work, two generation interventions
 - Evidence-based treatments (TF-CBT, CPP, PCIT, etc.)

Trauma Informed Approach

SAMHSA: A program, organization, or system that is trauma-informed:

- 1. Realizes the widespread impact of trauma and understands potential paths for recovery.
- 2. Recognizes the signs and symptoms of trauma in clients, families, staff, and others involved with the system
- 3. Responds by fully integrating knowledge about trauma into policies, procedures, and practices; and
- 4. Seeks to actively resist re-traumatization.



Instead of saying “**what is wrong with you?**”

Ask “**what happened to you?** ”

(Bloom, 2002)

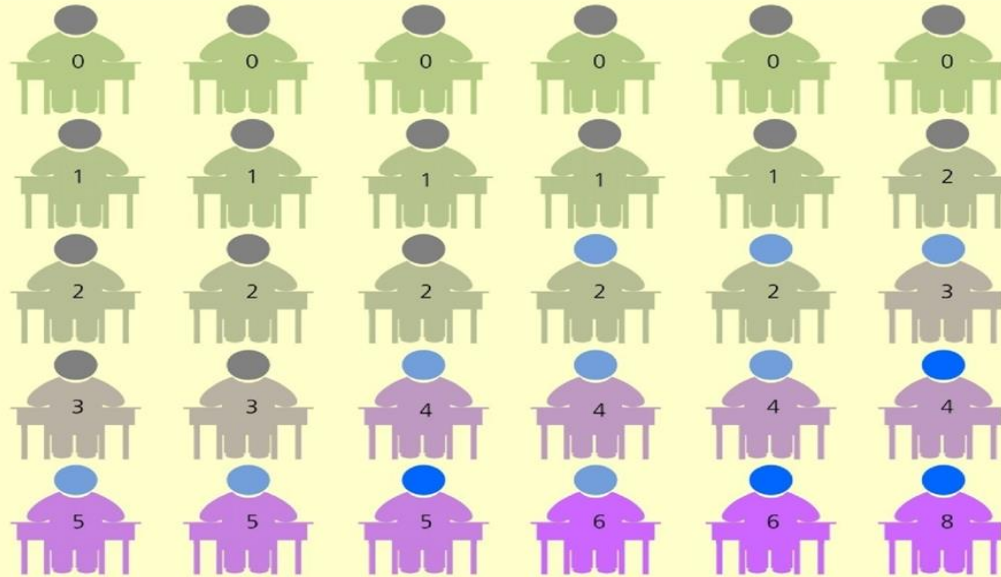
ACEs and High School Sophomores and Seniors

Washington School Classroom (30 Students)
Adverse Childhood Experiences (ACEs)

- 6 students with no ACE
- 5 students with 1 ACE
- 6 students with 2 ACEs
- 3 students with 3 ACEs
- 7 students with 4 or 5 ACEs
- 3 students with 6 or more ACEs

Washington State determined that 13 out of every 30 students will have toxic stress from 3 or more traumatic experiences

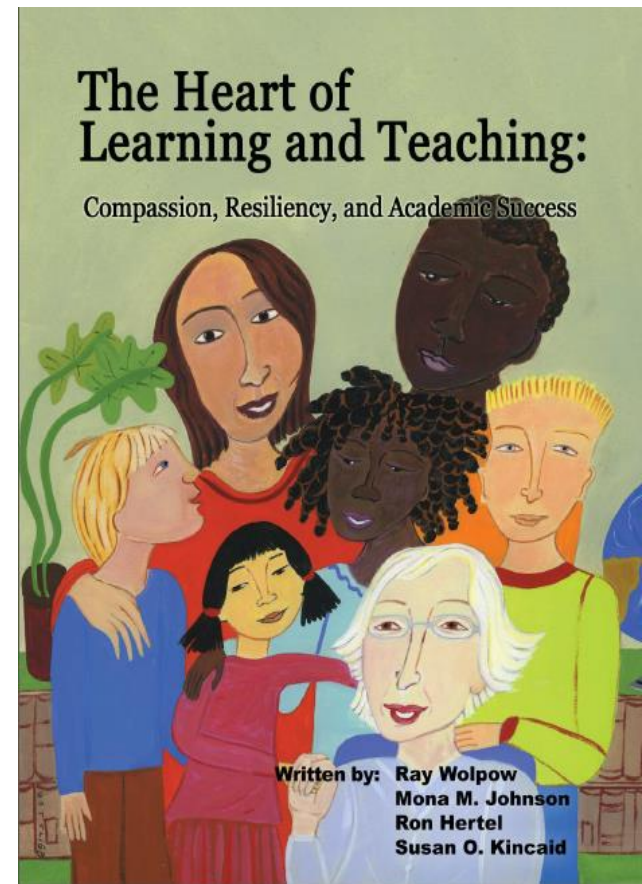
Population Average



Trauma-Sensitive Schools

Kids who are experiencing the toxic stress of severe and chronic trauma just can't learn...

- In trauma-sensitive schools, **teachers don't punish a kid for "bad" behavior**— they don't want to traumatize an already traumatized child.
- They dig deeper to help a child feel safe. Once a child feels safe, she or he can move out of stress mode, and learn again.





WEST VIRGINIA CENTER FOR CHILDREN'S JUSTICE

PROTECT • HEAL • THRIVE



www.handlewithcarewv.com

The "Handle With Care" Model:

If a law enforcement officer encounters a child during a call, that child's information is forwarded to the school before the school bell rings the next day. The school implements individual, class and whole school trauma-sensitive curricula so that traumatized children are "Handled With Care". If a child needs more intervention, on-site trauma-focused mental healthcare is available at the school.



Accessible • Fair • Effective • Responsive • Accountable

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TEXT SIZE PRINT SHARE

Trauma and Child
Development

The Problem

The Solution

The Goal 

Court Implications

Resources

The Goal

The goal of a trauma-responsive, developmentally-informed court is to change the trajectory for children and families who have experienced trauma - "...improving the long-term health and well-being of children and families and disrupting intergenerational cycles of adversity."

(Shawn C. Marsh, Ph.D. and Carly B. Dierkhising, MA, Juvenile and Family Justice Today, Summer 2013)

CHANGING THE TRAJECTORY

“Future efforts to minimize the effects of childhood adversity should focus on expanding the capacity of caregivers and communities to promote

- (1) the safe, stable, and nurturing relationships that buffer toxic stress, and
- (2) the rudimentary but foundational social-emotional, language, and cognitive skills needed to develop healthy, adaptive coping skills.”

The FUTURE is NOW

Take Home Messages

- Exposure to violence/trauma is the single most prevalent risk factor for children today.
- Adversity is necessary for life and learning; toxic stress disrupts life and learning
- Relationships are necessary for Resilience.
- The lifelong toll of unaddressed Adverse Childhood Experiences is a [*perhaps THE*] major cause of death and disability in adults
- Knowing what we know, we can do better in preventing, mitigating, and treating toxic stress.

C O N N E C T

T H E D O T S

Neonatal Abstinence Syndrome (NAS):

- A withdrawal syndrome that occurs in newborns after birth.
- The classic presentation is associated with opioid use during pregnancy.
- Not addiction
 - APA defines addiction as a chronic brain disease that causes compulsive substance use despite harmful consequences

Clinical Presentation is variable and dependent upon:

- Drug(s) misused
- The timing and the dose of the last drug used
 - The longer the $1/2$ life of the drug the later withdrawal symptoms will be seen
- Maternal and infant metabolism and excretion

Classic Symptoms of NAS

Central Nervous System Irritability

Autonomic System Dysfunction

Gastrointestinal Dysfunction

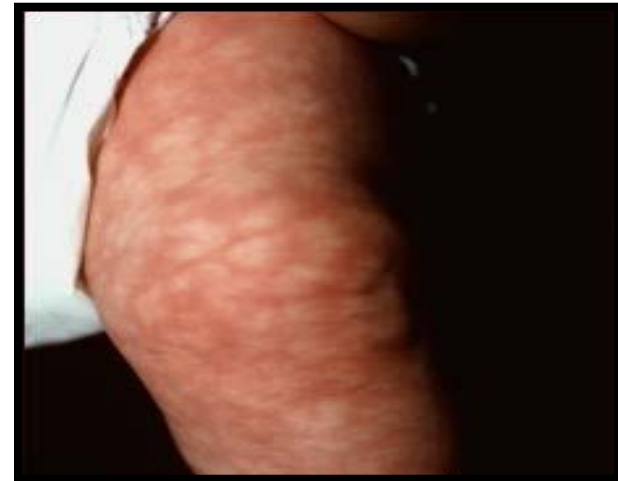
CNS Irritability

- Hypertonia
- Tremors
- Hyperreflexia
- Agitation and Restlessness
- High-pitched cry
- Sleep Disturbances
- Seizures – 2-11% of withdrawing infants



Autonomic System Dysfunction

- Yawning
- Nasal Stuffiness
- Sweating
- Sneezing
- Low-grade Fever
- Skin Mottling



Gastrointestinal Abnormalities

- Diarrhea
- Vomiting
- Poor Feeding
- Regurgitation
- Uncoordinated Swallow
- Failure to Thrive



Additional Symptoms

- Tachypnea
- Apnea
- Skin Excoriation



Symptoms may be present at birth, but often do not reach a peak until 2-3 days after delivery and may be delayed until 5-7 days of life.

AAP Recommendations:

Reasonable for neonates with known antenatal exposure to opiates and benzodiazepines to be “prudently observed” in the hospital for 4-7 days for signs of withdrawal.

Clinical Case - Nicholas

(Thanks to Gateway Health Plan, Mike Madden, M.D. and Robert Chico, M.D.)



Heroin



Methadone



Subutex

Demerol



Oxycontin

ZoHydro - ER



In the United States - 10.3 million people reported the non-medical use of prescription opiates in 2014

- Approximately 4% of those who use opiates non-medically initiate heroin use
- $\frac{3}{4}$ of current heroin users report a previous history of non-medical use of opiates

National Survey on Drug Use and Health found significant increase in heroin initiation, use and dependence in women

- Proportion of pregnant women who entered treatment who reported opioids as their primary substance increased from 1% in 1992 to 19% in 2012
 - 124 to 4,268 Women

Four-fold increase in Neonatal Abstinence Syndrome (NAS) NICU admissions nationally

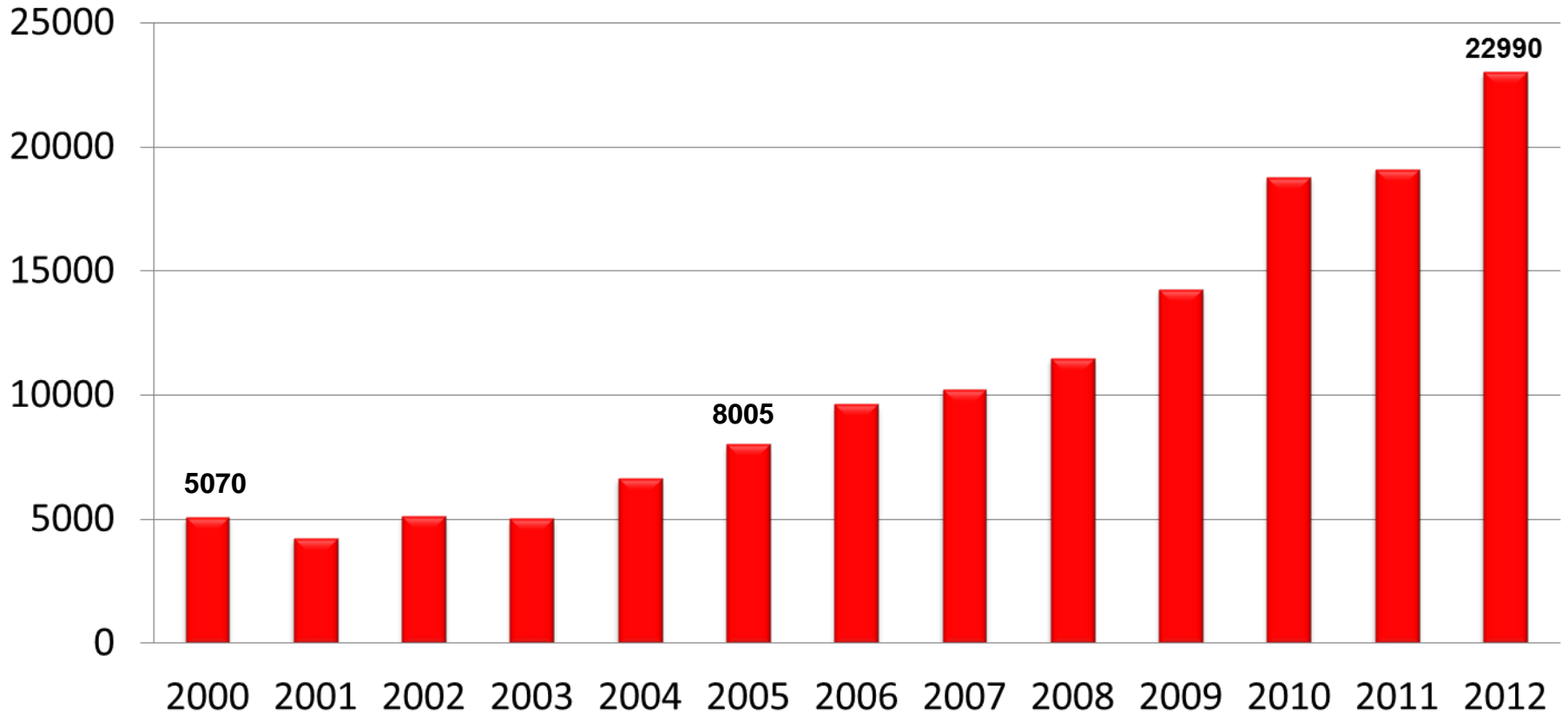
- 7 cases/1000 admissions 2004
- 27 cases/1000 admissions 2013

Pharmacotherapy for NAS has increased

- 74% 2004–2005
- 87% 2012–2013

35% increase in hospital costs

National Incidence of NAS



Census Regions and Divisions of the United States



NORTHEAST

New England - 13.7%

Middle Atlantic - 6.8%

MIDWEST

East North Central – 6.9%

West North Central - 3.4%

SOUTH

South Atlantic - 6.9%

East South Central - 16.2%

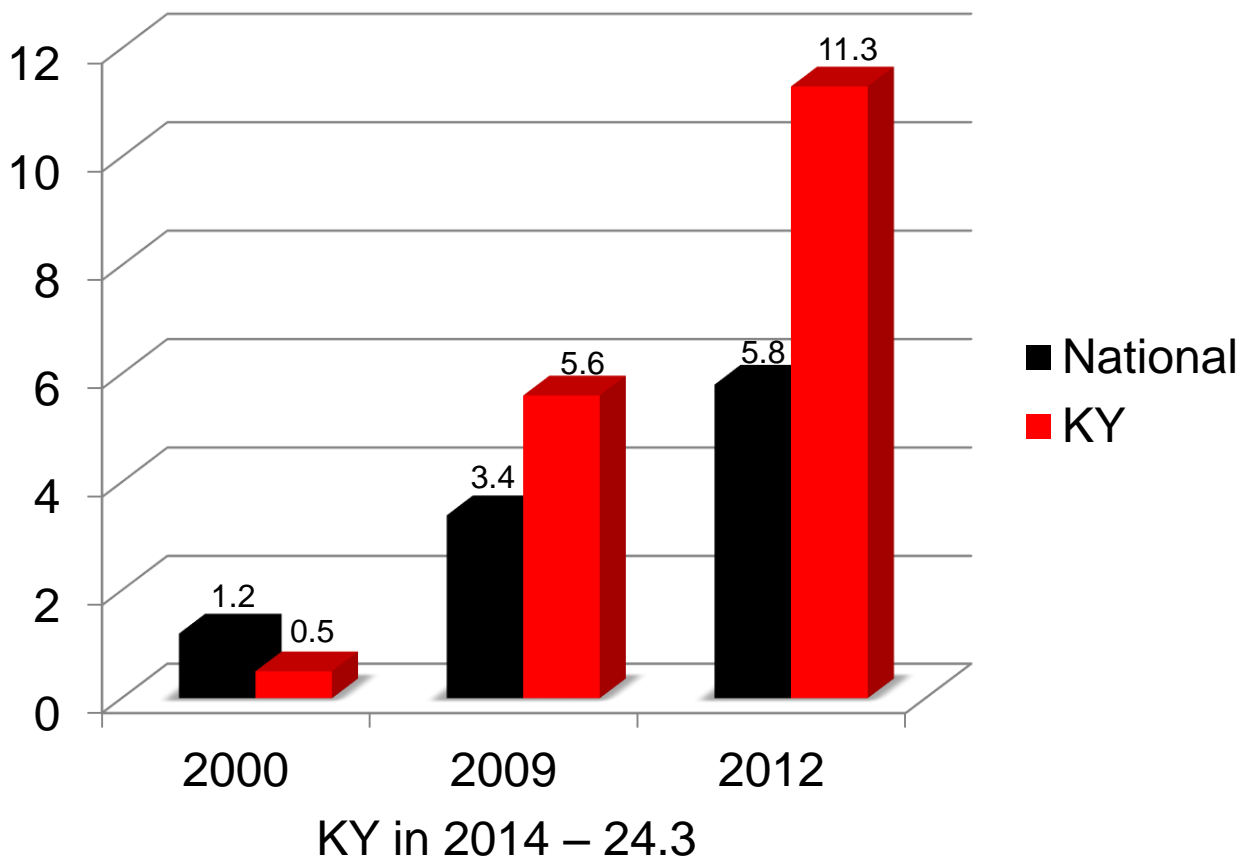
West South Central - 2.6%

WEST

Mountain - 5.1%

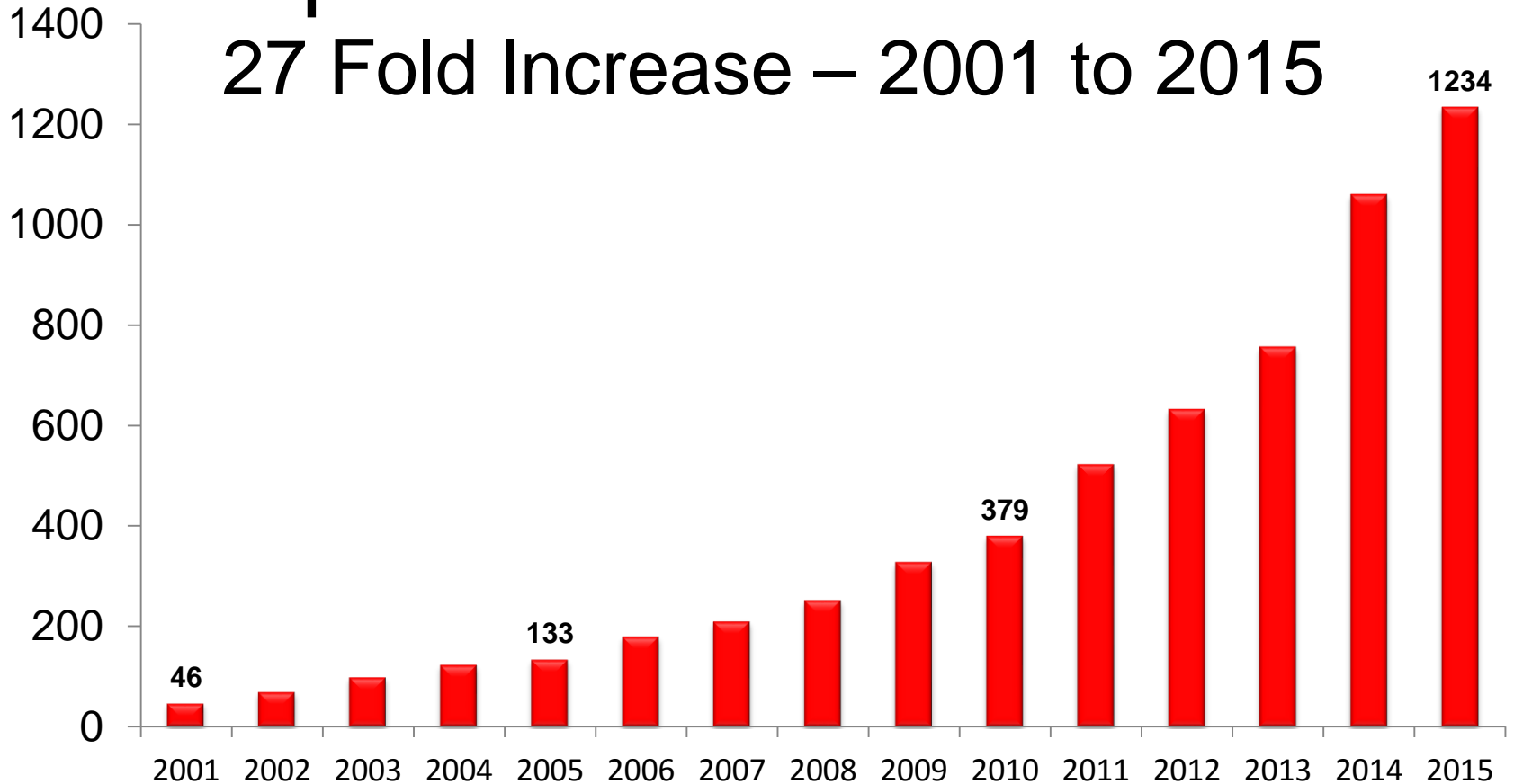
Pacific - 3%

Incidence per 1000 Hospital Births

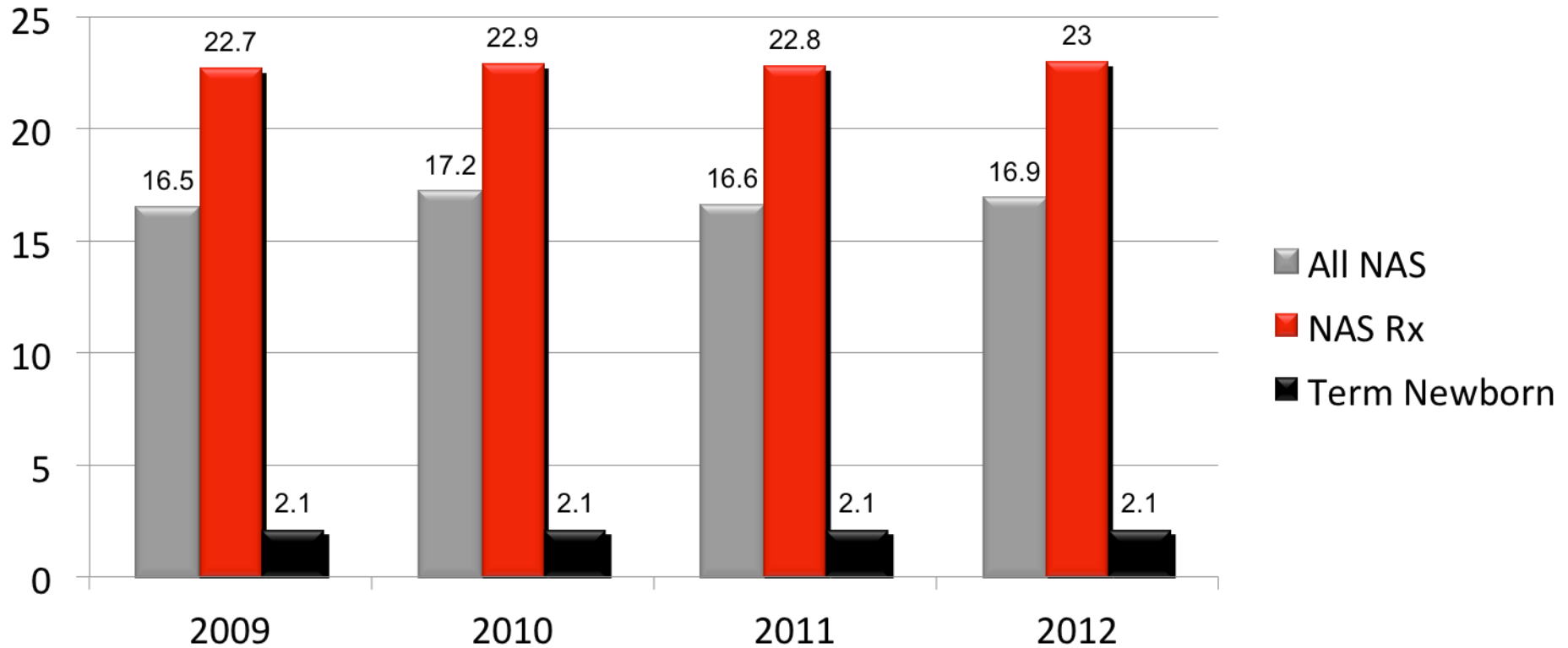


Hospitalizations for NAS in KY

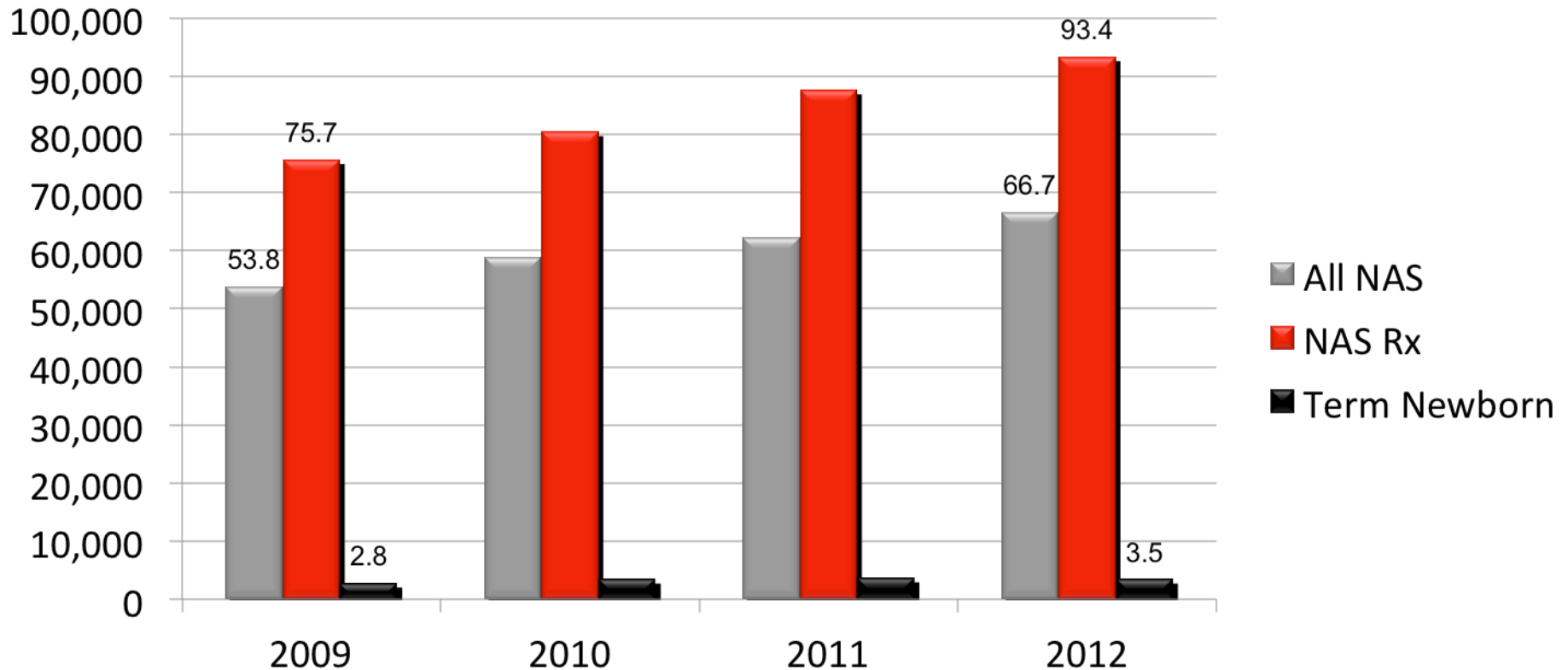
27 Fold Increase – 2001 to 2015



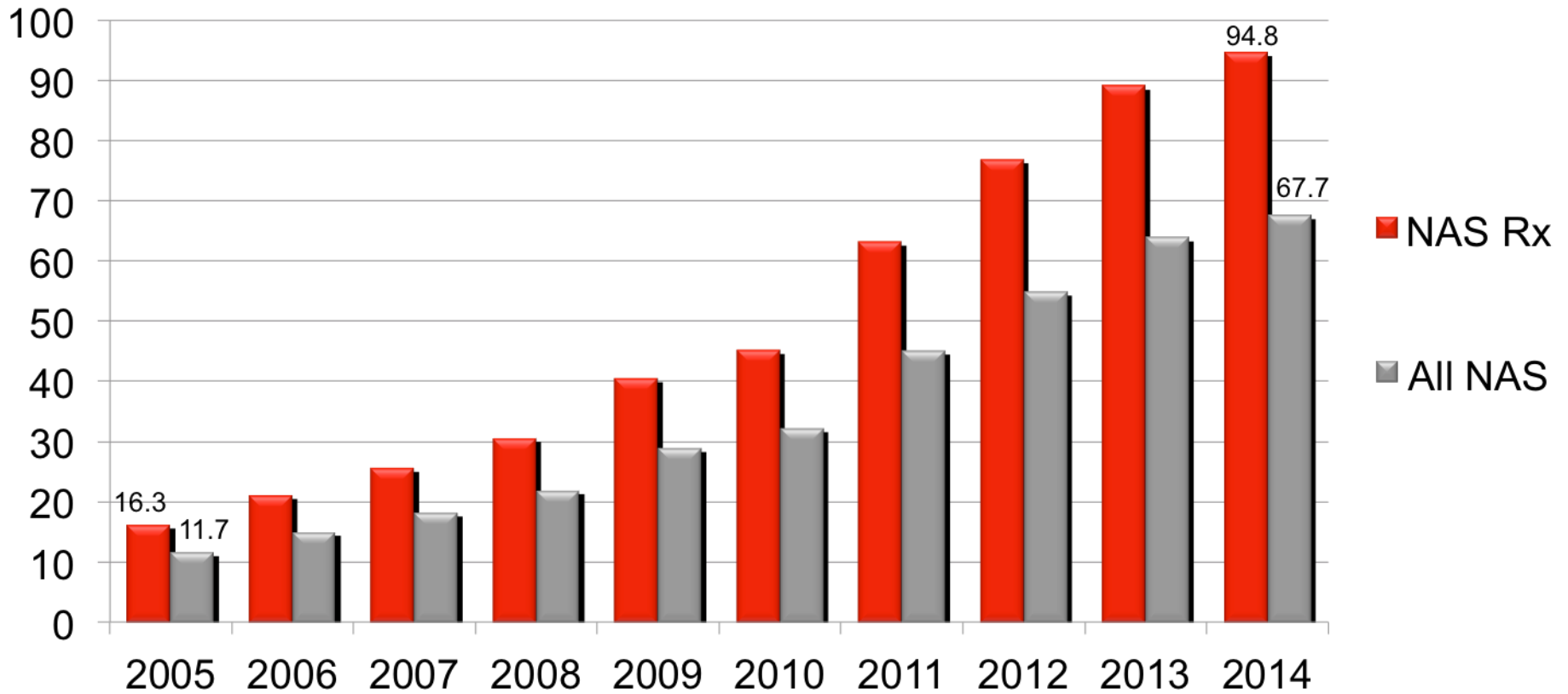
Mean Length of Hospital Stay



Inflation Adjusted Hospital Charges in Thousands 2012 US \$



KY Cumulative Hospital Charges in Millions 2012 US \$



Opiate Misuse and Abuse During Pregnancy

Screening

Current Maternal Indications for Screening

- No Prenatal Care
- Previous Unexplained Fetal Demise
- Precipitous Delivery
- Placental Abruption
- Repeated Spontaneous Abortions
- Cerebrovascular Accidents and Myocardial Infarctions

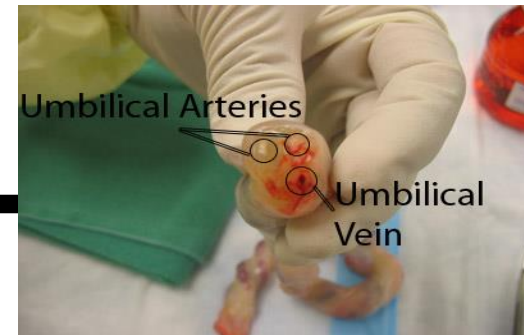


Screening in the Mother

Detailed Maternal Drug History

- Should be obtained if concern for drug use during pregnancy
 - Prescription and nonprescription drug intake
 - Herbal preparations used during pregnancy
 - The social habits of the parents
- Inexpensive and practical method for identifying substances of abuse
- Accurately determine timing of exposure
- Maternal self-reporting underestimates drug exposure

Identification of perinatal exposure is more likely if a biological specimen is collected in conjunction with a thorough history



No random biologic specimen identifies prenatal drug use with 100% accuracy

- A negative drug screening result does not ensure that the pregnancy was drug free
- Confirmation of the presence of a drug is not always associated with drug abuse

Maternal Urine

- Most drugs and their metabolites are found in higher concentrations in the urine of the mother than in her blood
 - Urine drug levels 100x that found in the plasma
 - It takes 6–8 hours or more post-consumption for drug to be metabolized and excreted in urine
- Opiates and benzodiazepines administered during labor and delivery may lead to positive urine toxicology screen

Urine screening may fail to identify drugs of abuse due to a limited time span for detection

- Alcohol 7-12 hours
- Marijuana
 - Single use 3 days
 - Moderate use 5-7 days
 - Daily use 10-15 days
 - Long term use >30 days
- Cocaine 2-4 days
- PCP 2-4 days
- Opioids
 - Heroin 2 days
 - Morphine 2-3 days
 - Oxycodone 2-4 days
 - Methadone 3 days
- Methamphetamines 2 days
- Benzodiazepines
 - Short acting 3 days
 - Long acting 30 days



Screening in the Neonate

Neonatal Urine

- Advantages
 - Noninvasive matrix
- Disadvantages
 - Limited urinary output in the immediate postnatal period
 - Only identifies recent drug use
 - Difficult to obtain first voided specimen
 - The neonatal kidneys have a delayed ability to concentrate urine
 - The concentration of substances of abuse in the urine often falls below the federally established thresholds for detection

Meconium

- Advantages
 - Noninvasive matrix unique to the neonate
 - Identifies substances abused by the mother from the beginning of the second trimester until birth.
 - 93% sensitivity
- Disadvantages
 - To maximize window of fetal exposure, the entire quantity of meconium is essential.
 - Meconium is a HETEROGENEOUS material that is not subjected to mixing in the fetal intestine
 - If cannot obtain the entire meconium then minimum of 2g required – up to 22% of specimens are rejected due to insufficient quantity
 - Contamination with urine or transitional stool



Maternal Hair

Provides a detailed record of gestational drug use.

9 cm should provide a detailed account of drug use throughout pregnancy

False positive results associated with passive drug exposure

Need approximately 200 stands

Requires technical expertise - limited centers to analyze

Neonatal Hair

Indicates exposure during the third trimester

0.5 inch corresponds to about 30 days of gestation.

Comparable sensitivities to meconium

Neonates have little hair

Difficult to obtain a sample

Umbilical Cord

- D. Montgomery, *et al.* (2006) were the first to compare the efficacy of umbilical cord tissue to meconium in detecting drug abuse during pregnancy.
 - 118 paired samples of umbilical cord specimens and meconium were analyzed
 - Agreement between umbilical cord and meconium samples was greater than 90% for amphetamines, cocaine, opiates and cannabinoids

Multicenter trial – 2008 D Montgomery, et al.

Confirmed the feasibility of using umbilical cord tissue to determine drug abuse during pregnancy.

- Negative Predictive Value >98%
 - If no drug is detected in the sample, assurance is high that none of the drugs tested for were in the sample.
- Positive Predictive Value 70-95%
 - If drug is detected in the sample, assurance is high that the drug was in the sample
 - Positive predictive values increased to nearly 100% if positive samples were retested using mass spectrometric methods

Umbilical Cord

- Commercial drug screening on umbilical cord tissue has been available in the United States since October 2007.
- 4 drug screening panels are available
 - 5 drug panel
 - 7 drug panel
 - 9 drug panel
 - 12 drug panel
 - EtOH testing is also available

5 Drugs	7 Drugs	9 Drugs	12 Drugs
Amphetamines	Amphetamines	Amphetamines	Amphetamines
Cannabinoids	Cannabinoids	Cannabinoids	Cannabinoids
Cocaine	Cocaine	Cocaine	Cocaine
Opiates	Opiates	Opiates	Opiates
PCP	PCP	PCP	PCP
	Methadone	Methadone	Methadone
	Barbituates	Barbituates	Barbituates
		Benzodiazepines	Benzodiazepines
		Propoxyphene	Propoxyphene
			Meperidine
			Oxycodone
			Tramadol

Umbilical Cord

- 5 Drug Screen - \$149
 - 5 Drug Screen + ETOH - \$209
- 7 Drug Screen - \$169
 - 7 Drug Screen + ETOH - \$229
- 9 Drug Screen - \$189
 - 9 Drug Screen + ETOH - \$249
- 12 Drug Screen - \$209
 - 12 Drug Screen + ETOH - \$269

Urine

- 5 Drug Screen - \$32

Hair

- 5 Drug Screen - \$95

Meconium

- 5 Drug Screen - \$50

Exposure During Pregnancy



The Placenta and Drugs of Abuse

- Illicit substances, prescription opiates and benzodiazepines are highly lipophilic and of a relatively low molecular weight
- Not filtered by the placenta and pass readily from the maternal circulation to the fetal circulation

Implications for the Fetus

- Once a drug crosses the placenta it accumulates in the fetus
 - Developmental deficiencies of the enzymes required for glucuronidation and oxidation delay metabolism of the drug.
 - Renal immaturity delays the excretion of the drug once it is metabolized

Classic Neonatal Drug Withdrawal

- 60-80% of neonates exposed in utero to opiates will develop signs and symptoms of withdrawal
- Opioid exposed infants demonstrate a high rate of perinatal morbidity and mortality

Heroin

Synthesized from morphine

- Usually appears as a white or brown powder or as a black sticky substance, known as “black tar heroin.”
- Can be injected, inhaled by snorting or sniffing, or smoked
 - All three routes of administration deliver the drug to the brain very rapidly
- Nearly half of young people who inject heroin surveyed in three recent studies reported abusing prescription opioids before starting to use heroin.



Heroin



Heroin use during pregnancy is associated with increased fetal morbidity and mortality including:

- Growth Restriction
- Placental Insufficiency
- Preeclampsia
- Premature rupture of membranes

Zohydro ER

1st

Oral, Extended Release
Hydrocodone without
Acetaminophen for Treating
Chronic Pain

PDUFA Date March 1, 2013

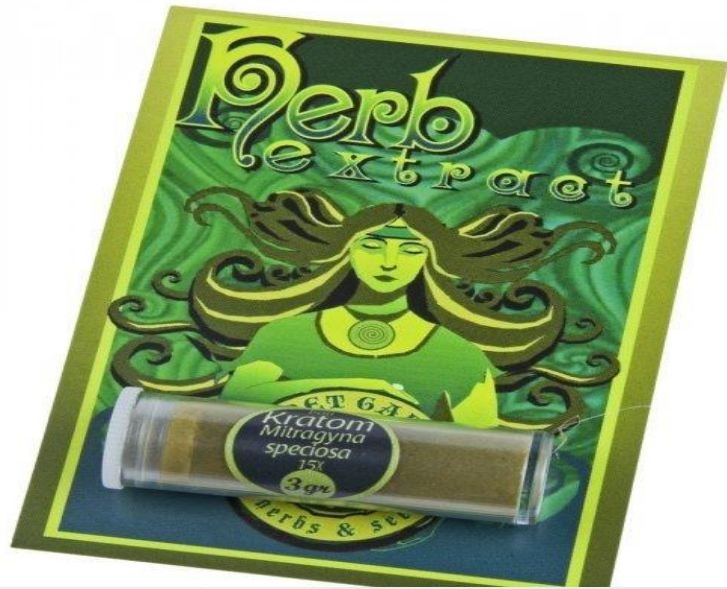


Extended release hydrocodone

- Indicated for the management of pain severe enough to require daily around the clock long-term opioid treatment for which alternative treatment options are inadequate
- Only for patients who are opioid tolerant
- Crushing chewing or dissolving the capsules can lead to uncontrolled delivery
- Approximately 5x more potent than oxycontin



- *Mitragyna speciosa*
- A 4 to 16 meter high tropical tree indigenous to South East Asia, the Philippines and New Guinea but now cultivated elsewhere.
- Kratom is in the same family as the coffee tree



Kratom

- Traditionally, fresh or dried leaves are chewed or made into tea; they are seldom smoked
- Stimulant effects at low doses
- Sedative, narcotic and euphoric effects at high dosages
 - Effects occur within 5 to 10 minutes after ingestion and last for 2 to 5 hours
 - Used in traditional medicine and as an opium substitute

Kratom

- Large, sedating doses (10–25 g) of dried leaves
- Initially may produce sweating, dizziness, nausea and dysphoria
- These effects are shortly superseded with calmness, euphoria and a dreamlike state that last for up to six hours.

Kratom

- Regular use may produce dependence.
 - The withdrawal symptoms in humans are relatively mild and typically diminish within a week.
 - Craving, weakness and lethargy, anxiety, restlessness, rhinorrhea, myalgia, nausea, sweating, muscle pain, jerky movements of the limbs, tremor, sleep disturbances and hallucination
 - Can precipitate withdrawal symptoms in Neonates
-

Kratom

- Mitragynine and 7-hydroxymitragynine, are selective and full agonists of the μ -subtype opioid receptor.
 - 5-HT_{2a} and postsynaptic α_2 adrenergic receptors, as well as neuronal Ca²⁺ channels are also involved in the unique pharmacological activity of mitragynine.
-

Kratom and Animal Studies

- Cough-suppressant effects of mitragynine were comparable to those of codeine
- The analgesic effect of 7-hydroxymitragynine was several times more potent than morphine
- Mice chronically treated with 7-hydroxymitragynine developed tolerance and cross-tolerance to morphine
- Withdrawal precipitated by naloxone administration

Kratom Tea



- Traditionally, the fresh or dried leaves of kratom are chewed or brewed into tea.
- Lemon juice is often added to facilitate the extraction of plant alkaloids
- Sugar or honey may be added to mask the bitter taste

Ketum Drinks



- Prepared by extended boiling of fresh leaves in water
- One 250 ml glass of 'ketum' contained 22.5–25 mg mitragynine
- About three such drinks a day are said to be sufficient to diminish opiate withdrawal symptoms

4x100

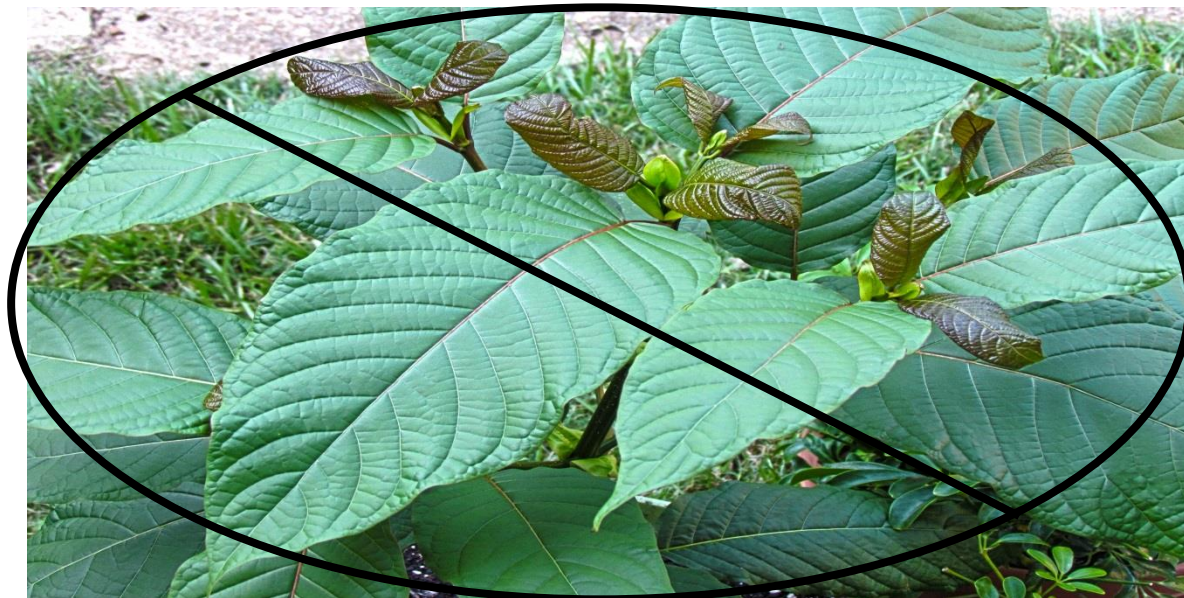
- Ice-cold cocktails made from:
 - Kratom leaves
 - Caffeine-containing soft drink
 - Codeine- or diphenhydramine-containing cough syrup
 - May also add anxiolytic, antidepressant or an analgesic drug



Kratom

- Is listed by DEA as a drug of concern
- Not scheduled under the Controlled Substances Act in the US.
- No legitimate medical use in the U.S.
- Widely available on the Internet.
- There are numerous vendors within and outside of the U.S.

Several countries in Europe, Australia, New Zealand, Malaysia, Myanmar and Thailand control Kratom under their narcotic laws





Acetyl Fentanyl

- Potent synthetic opiate
- Not a part of most illicit drug screens
 - ELISA does not differentiate fentanyl and acetyl fentanyl
 - Confirmatory analysis such as gas chromatography/mass spectrometry (GC/MS) is required to confirm the presence of acetyl fentanyl
- Not approved for medical use in the United States
- No published studies on safety for human use.

Acetyl Fentanyl

- May serve as a direct substitute for heroin or other μ -opioid receptor agonist substances in opioid dependent individuals
- Has been detected in tablets that mimic pharmaceutical opiate products, in powder form and spiked on blotter papers
- At least 52 confirmed fatalities involving acetyl fentanyl in the United States in 2013-2015
- Schedule I Substance as of May 2015

Methadone and Buprenorphine

- Used in an attempt to minimize the poor outcomes associated with illicit opiate use
 - Improved birth weight and decreased other risks of IV drug abuse
 - 2.5 fold increase in the rate of preterm birth in methadone exposed fetuses



Maternal Dose of Methadone

- Longer gestation contributes to NAS severity due to the high permeability of the placental barrier during the third trimester that results in increased levels of fetal methadone exposure nearing delivery.
- There are also genetic contributions to need for postnatal pharmacological treatment.
 - Single nucleotide polymorphisms of the m-opioid receptor (OPRM1, variant A11AG) and catecholomethyltransferase (COMT) genes.

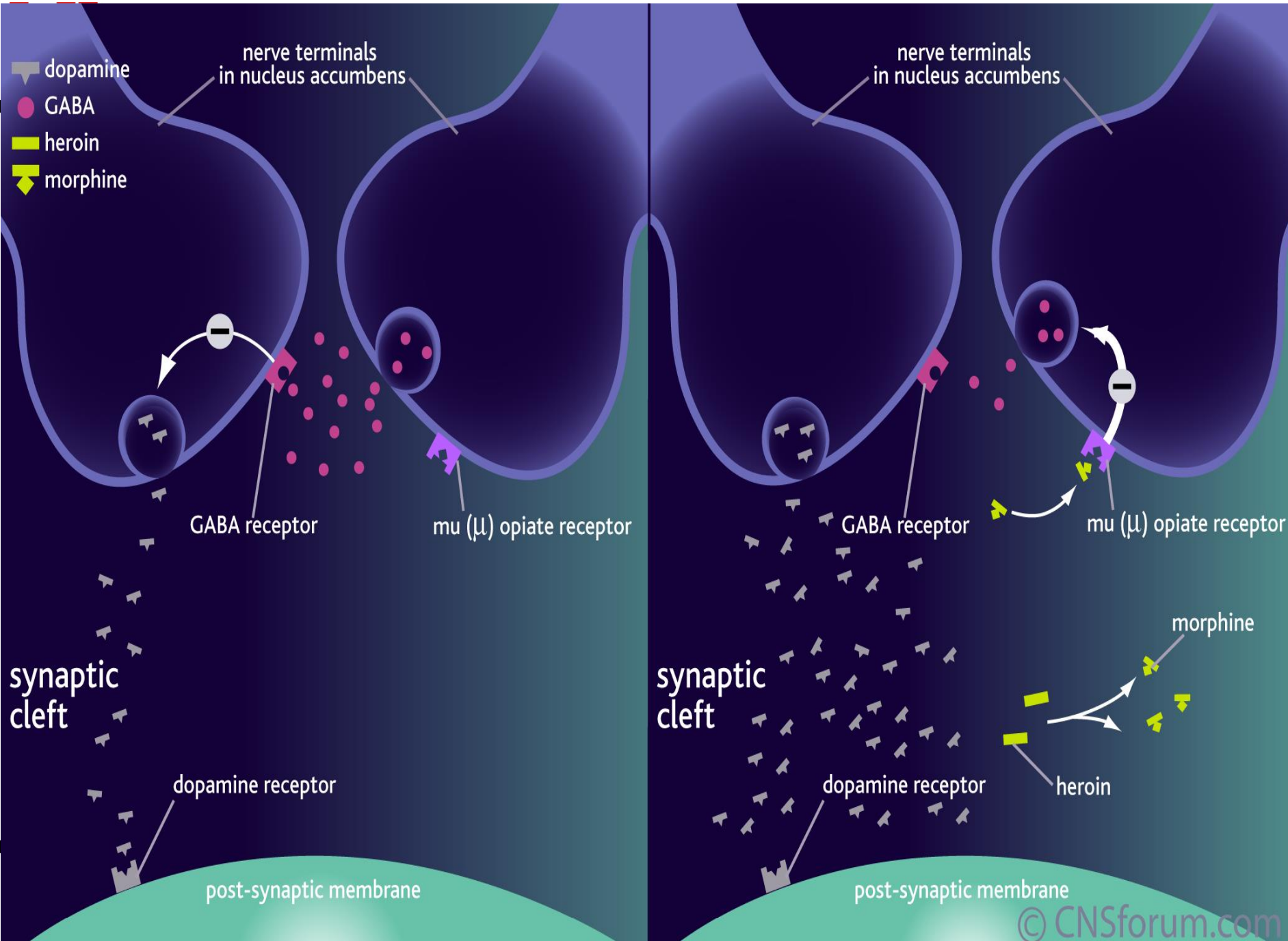
Methadone and Buprenorphine

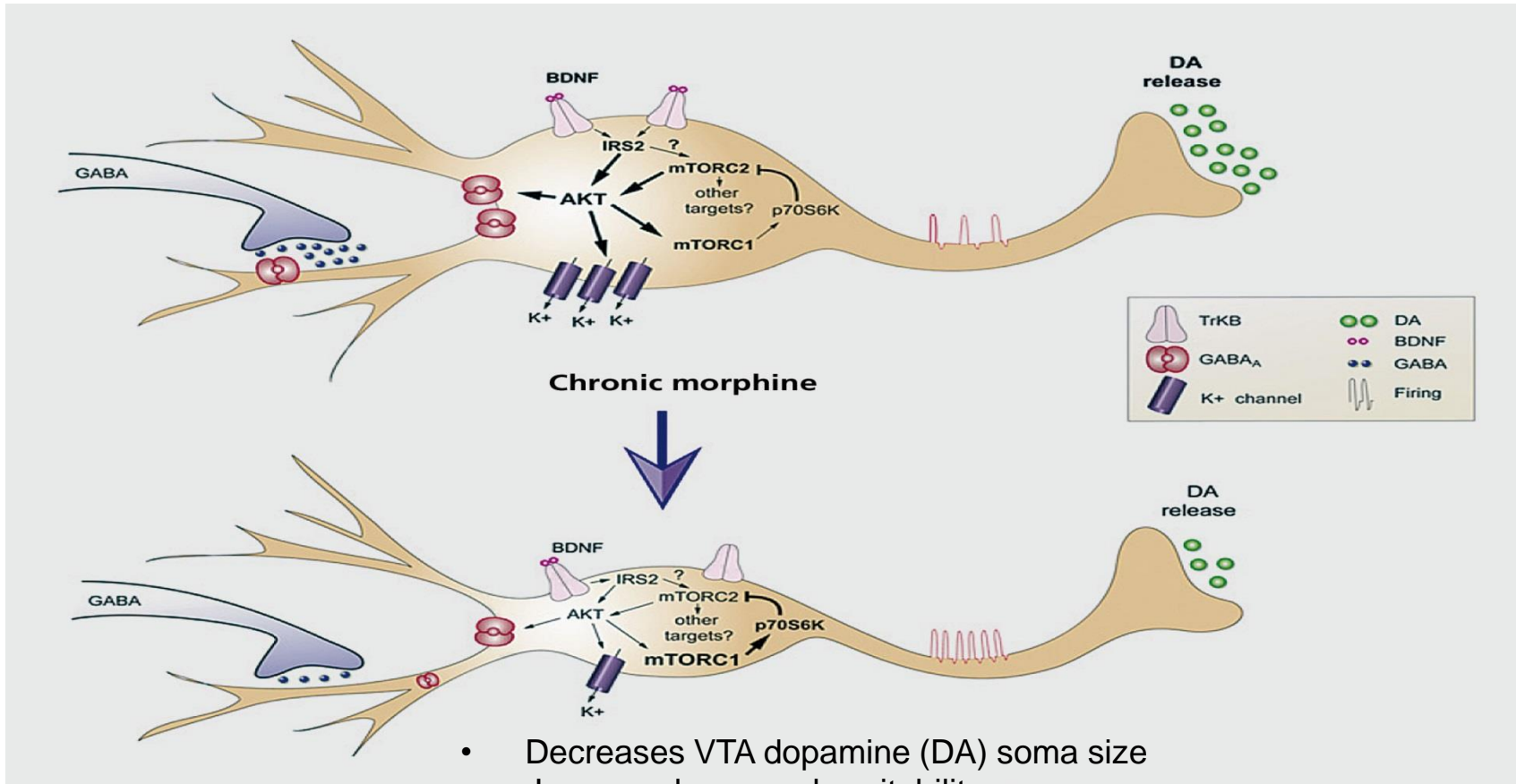
Significant duration of drug withdrawal

- **MOTHERS Study**
 - Buprenorphine maintenance during pregnancy was associated with a decreased need for morphine treatment in the neonate and decreased neonatal length of stay when compared with the use maternal methadone

Mechanism of NAS

- Multifactorial and poorly understood
- Impact of opioid exposure on the development of the fetus is unclear
- Effect on the developing brain is typically functional and therefore may not be detected at birth but are seen later in childhood, adolescence or adulthood





- Decreases VTA dopamine (DA) soma size
- Increased neuronal excitability
- Dopamine transmission decreased
- The net effect of morphine is a less responsive reward pathway, ie, reward tolerance.

Withdrawal from Opiates

- Down Regulation of the μ Opioid receptors
 - Inadequate production of dopamine and endogenous endorphins
- Increased GABA Release
 - Rapid and marked decrease in dopamine release in the neuronal synapses
- Sympathetic Hyperactivity
 - Up-regulation of the Locus Ceruleus due to elevated cAMP
- Clinical Signs of Withdrawal

Assessing the Severity of Withdrawal

- The tools available for evaluating the severity of withdrawal and need for pharmacological treatment are observer rated scales
- The Finnegan Scale and Lipsitz Tool are the most commonly used scales.

Finnegan Scale/Modified Finnegan Scale

- Most commonly used scoring systems
- Created to assess the severity of disease in infants with known opiate exposure
- On day of life 2 a score of 7 corresponds with the 95th percentile for non-exposed infants
 - Score of 8 or greater is highly suggestive of in utero opioid exposure

Finnegan Scoring System

- Weighted scoring of 21 signs and symptoms of withdrawal
- Developed for term infants

SYSTEMS	SIGNS AND SYMPTOMS	SCORE
CENTRAL NERVOUS SYSTEM DISTURBANCES	High Pitched Cry	2
	Continuous High Pitched Cry	3
	Sleeps < 1 Hour After Feeding	3
	Sleeps < 2 Hours After Feeding	2
	Hyperactive Moro Reflex	2
	Markedly Hyperactive Moro Reflex	3
	Mild Tremors Disturbed	2
	Moderate Severe Tremors Disturbed	3
	Mild Tremors Undisturbed	1
	Moderate Severe Tremors Undisturbed	2
	Increased Muscle Tone	2
	Excoriation (specify area): _____	1
	Myoclonic Jerks	3
Generalized Convulsions	3	
METABOLIC VASOMOTOR/ RESPIRATORY DISTURBANCES	Sweating	1
	Fever < 101 ^o F (39.3 ^o C)	1
	Fever > 101 ^o F (39.3 ^o C)	2
	Frequent Yawning (> 3-4 times/interval)	1
	Mottling	1
	Nasal Stuffiness	1
	Sneezing (> 3-4 times/interval)	1
	Nasal Flaring	2
	Respiratory Rate > 60/min	1
	Respiration Rate > 60/min with Retractions	2
GASTROINTESTINAL DISTURBANCES	Excessive Sucking	1
	Poor Feeding	2
	Regurgitation	2
	Projectile Vomiting	3
	Loose Stools Watery Stools	2 3
SUMMARY	TOTAL SCORE	
	SCORER'S INITIALS	

Assessing the Severity of Withdrawal

Observer-rated scales are an essential component in the assessment and treatment of neonatal drug withdrawal but they do have some shortcomings

- Lengthy training and administration times
- Subjective

We need less complicated and more objective diagnostic tools to assess the severity of drug withdrawal.

Ideal Treatment Regimen

A protocol driven approach which incorporates symptomatic care and a drug titration schedule to control symptoms

Goal of Treatment

- Ensure proper feeding and growth
- Facilitate appropriate development
- Foster the maternal-infant bond
- Prevent neurologic sequelae

- Not to prevent withdrawal

Symptomatic Care

- Forty percent of infants withdrawing from opiates will only need symptomatic care
 - Tightly swaddling
 - Holding
 - Rocking
 - Environmental Control
- Withdrawal scores less than eight

Initiation Pharmacologic Therapy

- Based on Finnegan scores:
 - 3 consecutive scores of 8 or greater
 - 2 consecutive scores of 12 or greater
- No definitive evidence to determine most effective starting score

Pharmacologic Therapy

The American Academy of Pediatrics and experts in the field have identified opioid replacement as the first line therapy for withdrawal symptoms after in utero exposure to opiates

Opioid Replacement

- Improves weight gain but lengthens hospitalization when compared to symptomatic care
- High quality data on the safety and efficacy of specific opioids and the optimal dosing regimens are lacking

Morphine

- Most commonly used opioid for replacement therapy
 - Physiologic Replacement
 - Controls all of the symptoms of withdrawal
 - Preservative Free Solution
 - Potent analgesic properties and has high addictive potential

Morphine

- Pharmacodynamics in the neonate are affected by:
 - Immature metabolic enzymes, and renal function
 - Changes in fat and extracellular fluid balance during the neonatal period
- Pharmacokinetics of orally administered morphine in the neonate are not fully understood

Methadone

- Long acting synthetic opioid
 - Less flux between peak and trough levels
 - Ease of administration
 - Difficult to wean
- Oral formulation contains 8% ethanol

Methadone

- Pharmacokinetic modeling in the neonate suggests significant inter-patient and developmental variability
- Absorption, distribution, metabolism and excretion of methadone are impacted by:
 - Gestational age of the infant
 - Body adiposity
 - Pharmacogenetics
 - Disease states

Methadone

- Individualized dosing and tapering schedules should be used to control symptoms
 - Titrate dose to effect
 - Max 10mg/day
- Tapering dose by 10-20% per wk. over 1 to 1.5 months

Methadone

- The elimination half life is significantly longer than its duration of analgesic action
 - Respiratory depressant effects of methadone occur later and persist longer than its peak analgesic effects
- Prolonged QT syndrome and torsades de pointes
 - Baseline EKG to assess QT interval prior to the initiation of therapy and then intermittent monitoring

Phenobarbital

- Adjunctive therapy
- Allows for a lower doses of opiates.
- Side effects – especially at higher doses
 - Sedation
 - Poor Sucking
- It does not control diarrhea that occurs with withdrawal.
- The elixir contains 20% alcohol.
- IV solution 5% alcohol 60% polyethylene glycol

Clonidine

- Adjunctive therapy
 - Alpha II Receptor Agonist
 - Decreases sympathetic outflow through the activation of inhibitory neurons
-

Clonidine

- A multicenter randomized, double blinded clinical trial conducted in 2009 found that clonidine in combination with DTO stabilized and detoxified infants with moderate to severe drug withdrawal more rapidly than DTO alone.
- No adverse cardiovascular effects
- Further studies are needed to determine long-term safety

Clonidine vs. Phenobarbital

- A prospective non-blinded block randomized controlled trial that compared the efficacy of clonidine vs. Phenobarbital in reducing neonatal morphine sulfate therapy days for NAS.
 - 68 infant were randomize to 1 of 2 study arms; adjunctive therapy with either clonidine or Phenobarbital.

Clonidine vs. Phenobarbital

- Phenobarbital or clonidine was started at the same time morphine was initiated.
- They found that for both groups the length of treatment was improved verses the length of stay prior to study implementation.

Clonidine vs. Phenobarbital

- The infants on Phenobarbital had a 4.5 day decrease in the length of morphine therapy but were discharged home on Phenobarbital.
 - Stayed on this medication for 1-8 months with a mean of 3.8 months.
 - Six of the infants in Phenobarbital group were lost to follow-up after discharge.

Clonidine vs. Phenobarbital

- The overall length of NAS treatment was shorter with the clonidine group and no outpatient therapy was required
- Infants were on morphine sulfate for a longer period of time.

Clonidine

- Short and long term side effects have not been well studied in neonates
- Been used in adults and children for years
- CV side effects do not seem to be an issue at NAS dosing

Phenobarbital

- Animal studies suggest inhibited neurogenesis and survival with long term Phenobarbital use.
- Human Studies show neurodevelopmental and behavioral compromises with long term therapy.

Breastfeeding and NAS



WHO and AAP

Recommend that infants should be exclusively breastfed for the first 6 months of life to achieve optimal health and development



AAP - Breastfeeding and Illicit Drug Use

- The use of marijuana, illicit opiates, cocaine, methamphetamine and other street drugs is a contraindication to breastfeeding.
- For most street drugs the risks to the infant of ongoing active use by the mother outweigh the benefits of breastfeeding.
 - The doses of the drug and the contaminants within the drug are unknown.

AAP - Breastfeeding and Illicit Drug Use

- Marijuana, cocaine, opiates and methamphetamines have an affinity for lipids and accumulate in human milk
 - Marijuana has been shown to alter brain neurotransmitters as well as brain biochemistry, resulting in decreased protein, nucleic acid, and lipid synthesis.
 - What does this do to a developing brain??

Breastfeeding & Medication Assisted Treatment

- Supervised methadone and buprenorphine use is compatible with breast feeding
 - No other drugs of abuse on routine toxicology screens
 - Ingestion of maternal breast milk can decrease the severity of withdrawal
 - The magnitude of response is correlated with volume of MBM ingested
 - The transmission of methadone in the breast milk could be as high as 0.05mg/kg/day

Clinical Studies to Date

- No randomized controlled studies
- Most are observational studies
 - Introduce bias
- The differences in how outcomes were measured makes direct comparisons impossible

Study Findings

- Infant who received MBM appeared to require less pharmacologic therapy and spent a shorter time in the hospital
- These findings may be due to confounders
 - Less psychological comorbidity
 - Better adherence to supervised treatment program
 - More supportive staff attitudes towards mother and infant dyad who breastfeed vs. those who bottle feed

Study Findings

- All studies suggest that breastfeeding (in mothers on methadone or buprenorphine) is associated with:
 - Reduction in severity
 - Decreased need for pharmacologic therapy
 - Decreased length of hospitalization

Breast feeding and/or provision of expressed breast milk should be encouraged unless there is a clear contraindication

HIV and/or illicit drugs of abuse



Additional Thoughts on Breastfeeding

- The infant must be able to gain appropriate weight.
- Breast milk does not induce clinically important sedation
- Abrupt cessation and/or rapid weaning of maternal breast milk can precipitate rebound withdrawal.
- Close postpartum follow-up of the mother and infant are essential



Kentucky Statistics for Child Maltreatment

- 69.7% of childhood fatalities and near fatalities as a result of child maltreatment between 2010 and 2014 were associated with caregiver substance abuse
 - Children less than 1 year of age account for the largest group
 - Domestic Violence was noted in 68.7% of cases
 - Opiate and other prescription drugs were commonly found in the affected homes

Kentucky Statistics for Child Maltreatment - 2015

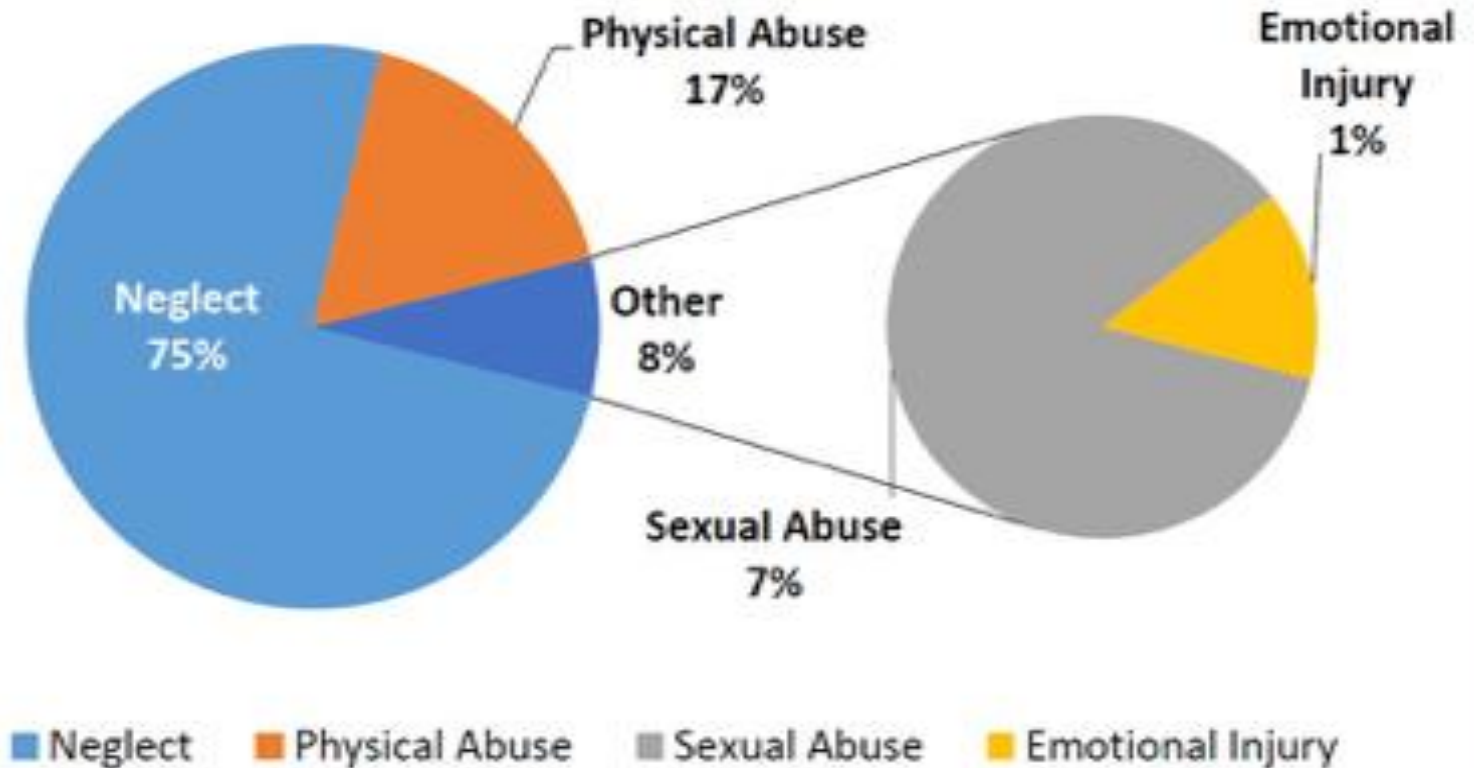
CPS reports found to be substantiated

- 26,962 children

Neglect - most common form of maltreatment

- 20,165 children

Maltreatment Type CY 2015



Kentucky Statistics for Child Maltreatment - 2015

5 years or younger

– 12,402 (46%)

Substance Abuse as a Risk Factor

– 15,368 children (57%)

Family Violence as a Risk Factor

– 10,515 children (39%)

Follow-Up

A safe, stable and nurturing home environment is essential during the early years of brain development to address the stress of early adverse experiences

Follow-Up

- Infants who have been identified as having been drug exposed in utero need a pediatric medical home in which they can easily receive
 - Regular growth and nutritional assessments
 - Evaluation for developmental and social/emotional delays
 - Close follow-up for subtle signs of neglect and abuse

What we have learned to date:

- NAS is 3 letter acronym that will be a permanent part of the practice of pediatrics.
- Robust objective assessment tools and treatment regimens are needed improve the quality of care
- Support for drug exposed infants should not stop at hospital discharge

