

# Getting to the Roots: The Benefits of Early Life Intervention



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**Division of Diabetes Treatment and Prevention  
Indian Health Service**

“As human beings we belong to an extremely resilient species. Since time immemorial we have rebounded from our relentless wars, countless disasters (both natural and man-made), and the violence and betrayal in our own lives. But traumatic experiences do leave traces, whether on a large scale (on our histories and cultures) or close to home, on our families, with dark secrets being imperceptibly passed down through generations. They also leave traces on our minds and emotions, on our capacity for joy and intimacy, and even on our biology and immune systems.”

*The Body Keeps the Score: Brain, Mind, and Body in the Healing of Trauma, p. 1*

Bessel van der Kolk, 2014

# An all-too-common story: “Mary”

## ■ Pre-conception

- Mother’s grandparents went to boarding school, parents have had trouble with alcohol; most of them developed diabetes
- Family income below poverty line, buy food at reservation store

## ■ Pregnancy and Birth

- Single 15 year old, won’t say who FOB is
- Intermittent prenatal care
- WIC foods have to be shared with family
- Stopped using drugs when found out she was pregnant, cut down but continued smoking and got drunk “just a few times”
- Mostly kept going to high school thru pregnancy
- Mary born slightly SGA at 35 weeks gestation, spent 2 wks in hosp.

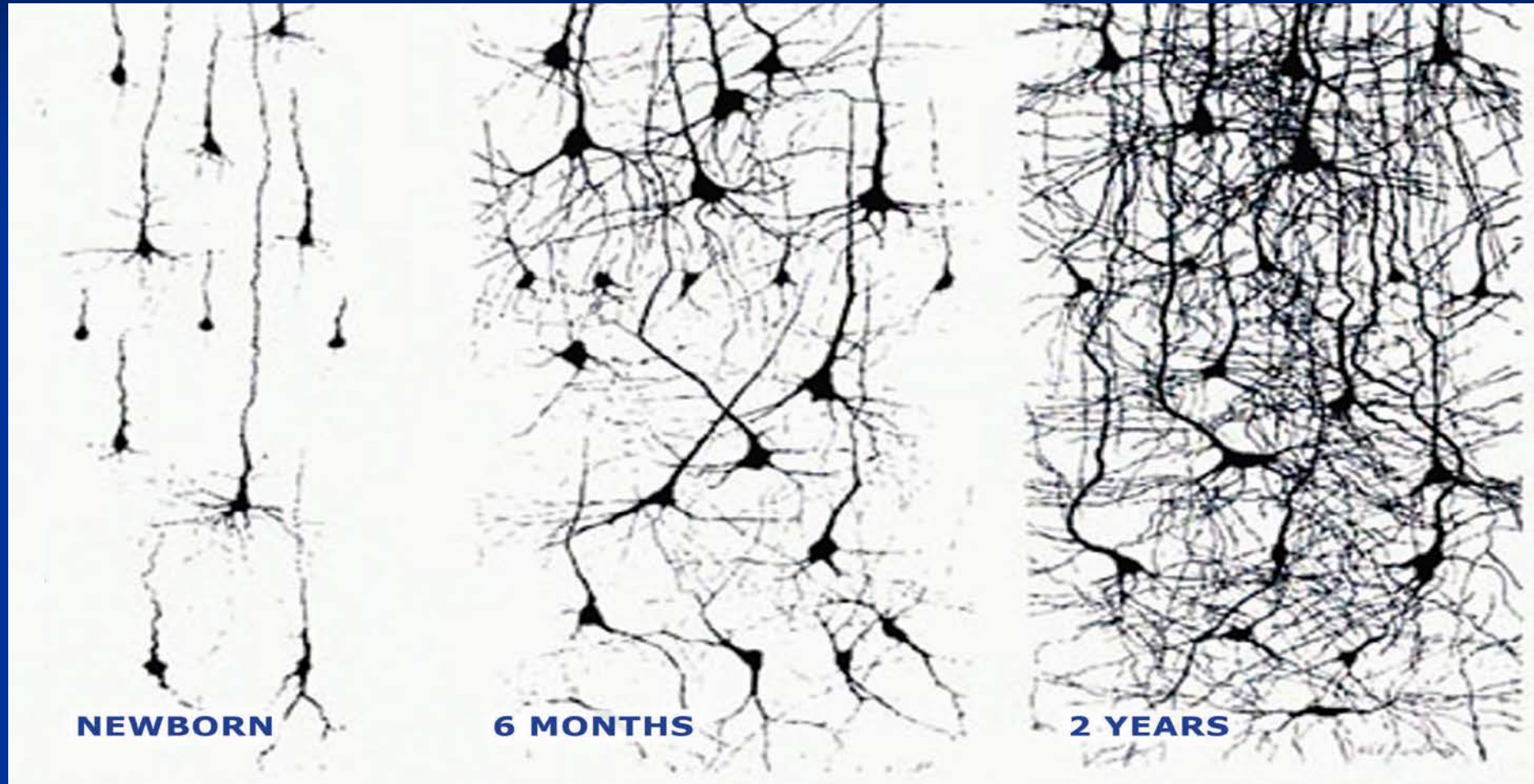
# “Mary”

## ■ Early Life

- Grandmother already overwhelmed caring for other grandchildren, but agreed to watch Mary while mother tried to stay in school
  - Mary often sitting in front of TV most of day
- Then put into tribal child care
  - High staff turnover, minimal teacher-student ratio
- Family got by on commodities and WIC foods
- Mary gained weight rapidly in 1<sup>st</sup> yr, then stayed >95<sup>th</sup> % ile
- Mother’s boyfriend moved in
  - Intermittently employed, binged on alcohol and drugs, sometimes hit mother in front of Mary
- Mary held back to repeat 2<sup>nd</sup> grade as reading difficulties
- Mary left school after 10<sup>th</sup> grade

## ■ Now Mary becomes pregnant...

# 700 New Neural Connections per Second

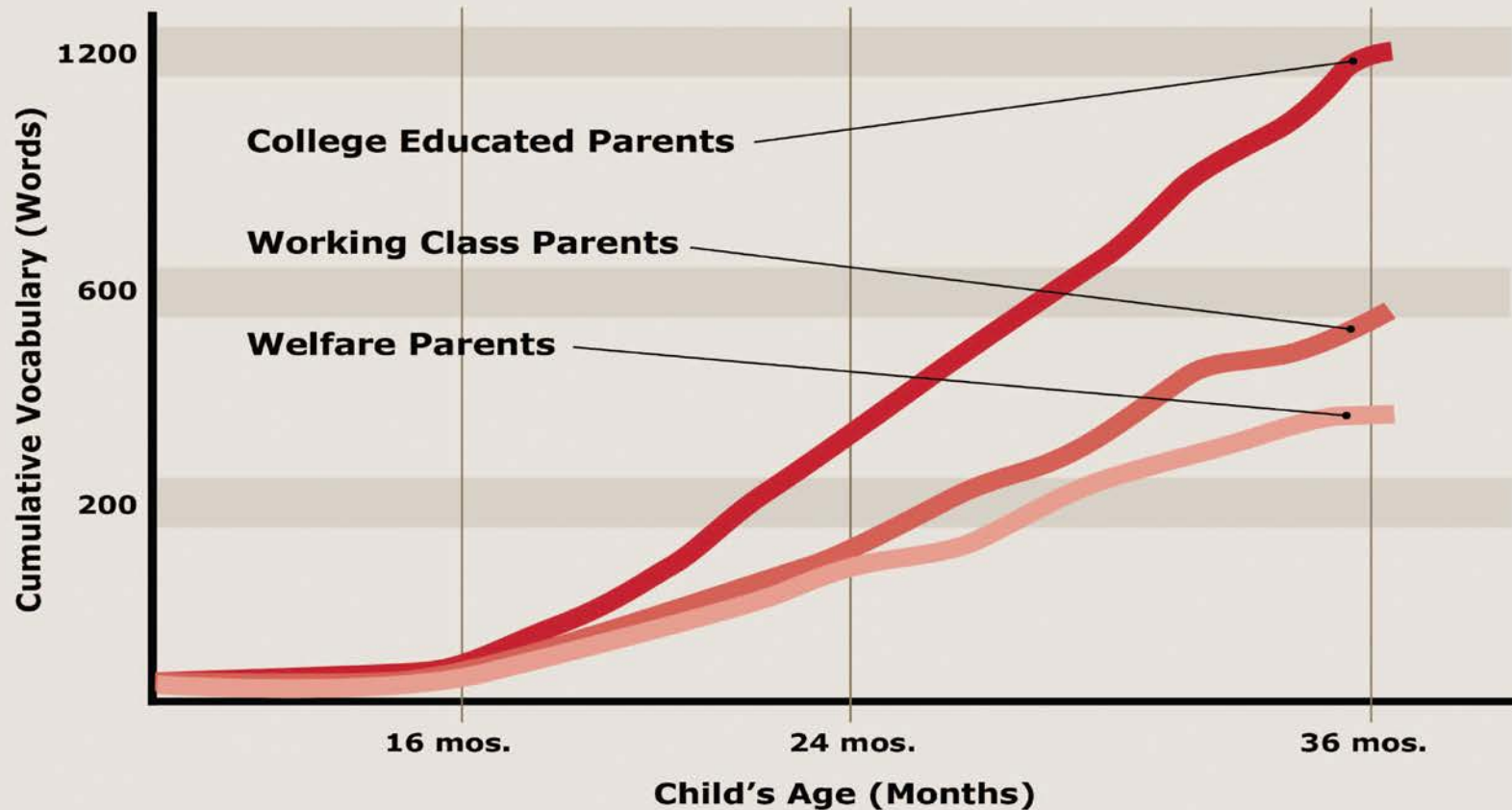


*Center on the Developing Child at Harvard website*

*Image source: Conel, J.L. The postnatal development of the human cerebral cortex.*

*Cambridge, Mass: Harvard University Press, 1959*

# 18 Months: Age at which disparities in vocabulary begin to appear

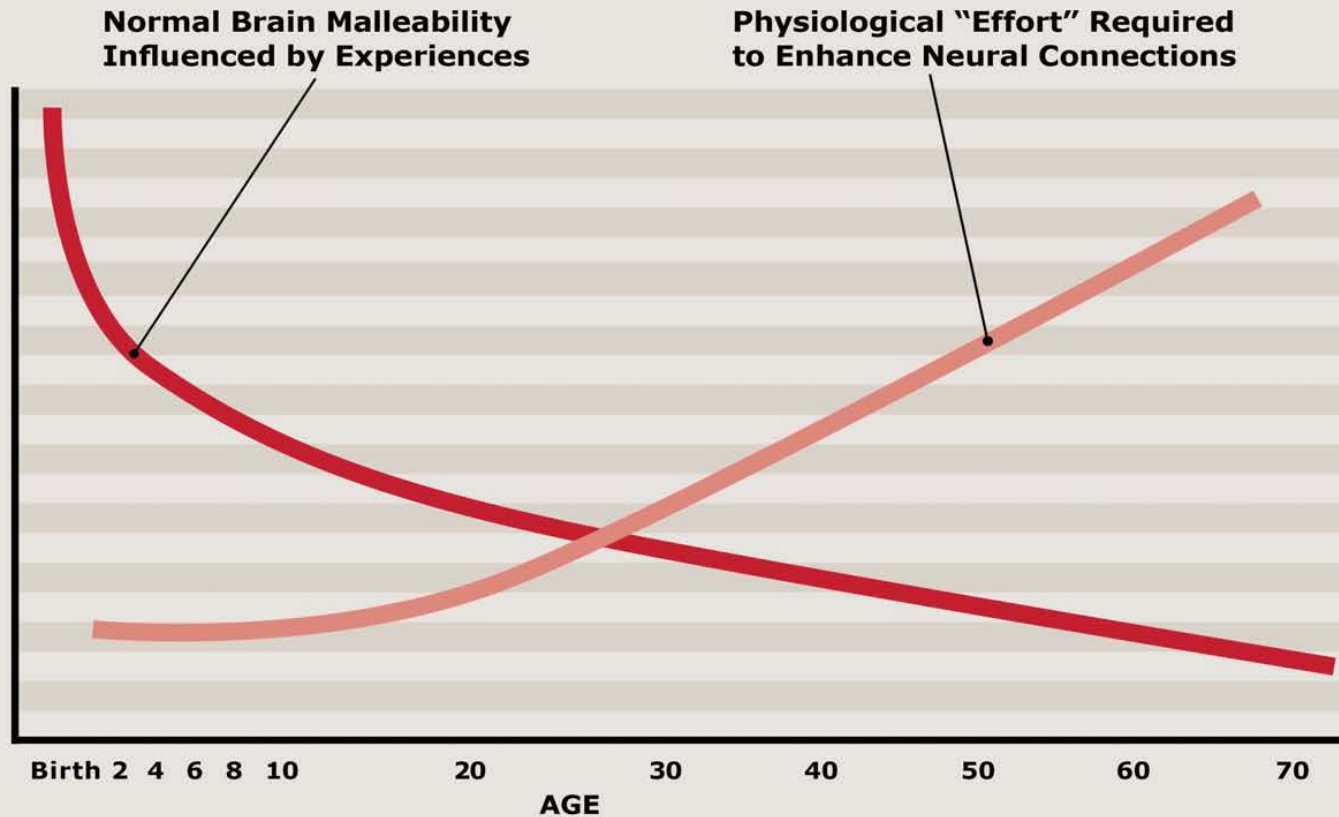


Center on the Developing Child at Harvard website

Source: Hart, B., & Risley, T. (1995). *Meaningful differences in the everyday experiences of young American children*. Baltimore, MD: Brookes.

# CORE CONCEPTS IN THE SCIENCE OF EARLY CHILDHOOD DEVELOPMENT

The Ability to Change Brains and Behavior Decreases Over Time



Center on the Developing Child website [www.developingchild.harvard.edu](http://www.developingchild.harvard.edu)

Graph Source: P. Levitt (2009)

# International Diabetes Federation

## Conference on Type 2 Diabetes Etiologies

2002

1. Genetics
2. Fetal Origins
3. Lifestyle
4. Stress



# 1. Genetics

## ■ Genes *Inherited*

### ■ It does matter what genes we inherit

- But proportion of predisposition explained for type 2 DM (5-10%) is fairly small  
*NEJM 2010;363:2339-50*
- And genes which are associated with ↑ diabetes risk are as common in non-minority as in minority people  
*Diabetes Care 2012;35:193 -195*

### ■ Only 15% of genes in cells “turned on” at any one time

## ■ Genes *Expressed*

### ■ “Epigenetics”: the “on/off switches” for genes

- Reaction to the environment
- Not always reversible if at key developmental stage of life
- Heritable—some are passed to next generation
  - How the experiences of one generation help prepare the next
- We know the body’s “on/off switches”: DNA methylation, histone acetylation, microRNA

*JAMA 2005;294:2221-4 and NEJM 2008;359:61-73*

# Epigenetics: Experiences “Programmed In”

- Rat pups raised by nurturing mothers
  - Gene which codes for stress hormone receptors “turned on”
    - Grow up to be stress resilient
  - Opposite is true in rat pups raised by neglectful mothers
  - Same process occurs in humans *Nat Neurosci 2009;12:342-348*
- Experiences of one generation transmitted epigenetically to subsequent generations
  - Mice trained to fear an odor→methylation change in Olfr 151→F1 & F2 generations exhibit startle response to same odor *Nat Neurosci 2014;17: 89-96 and 2-4*
  - First demonstration of transmission of pre-conception stress effects resulting in epigenetic changes in both the exposed parents (Holocaust) and their offspring in humans--associated with stress response *Biological Psychiatry* <http://dx.doi.org/10.1016/j.biopsych.2015.08.005>

# Epigenetics and Diabetes Predisposition

- Methylation of gene involved with fat storage at age 5yrs predicted greater likelihood of obesity at age 14  
*Diabetes* 2014;doi:10.2337/db13-0671
- “...epigenetic changes occurring during gestation, possibly maternal nutrition-mediated, appear to influence adiposity and related metabolic phenotypes.”  
*Diabetes* 2011;60:1859-60
- Genome-wide survey: clear-cut diabetes-predisposing DNA methylation signature in patients with vs. without diabetes
  - Prospective study: different methylation patterns in young people who later developed diabetes vs. those who did not  
*Hum Mol Genet* 2012;21:371-383

# 2. Fetal Origins



- Alcohol/Drugs
- Nutrition
- Smoking
- Maternal Diabetes
- Toxic/Infectious Exposures
- Maternal Low Birth Weight
- Maternal Stress/Mental Health
  - Mother's own Childhood
  - Current/Prenatal

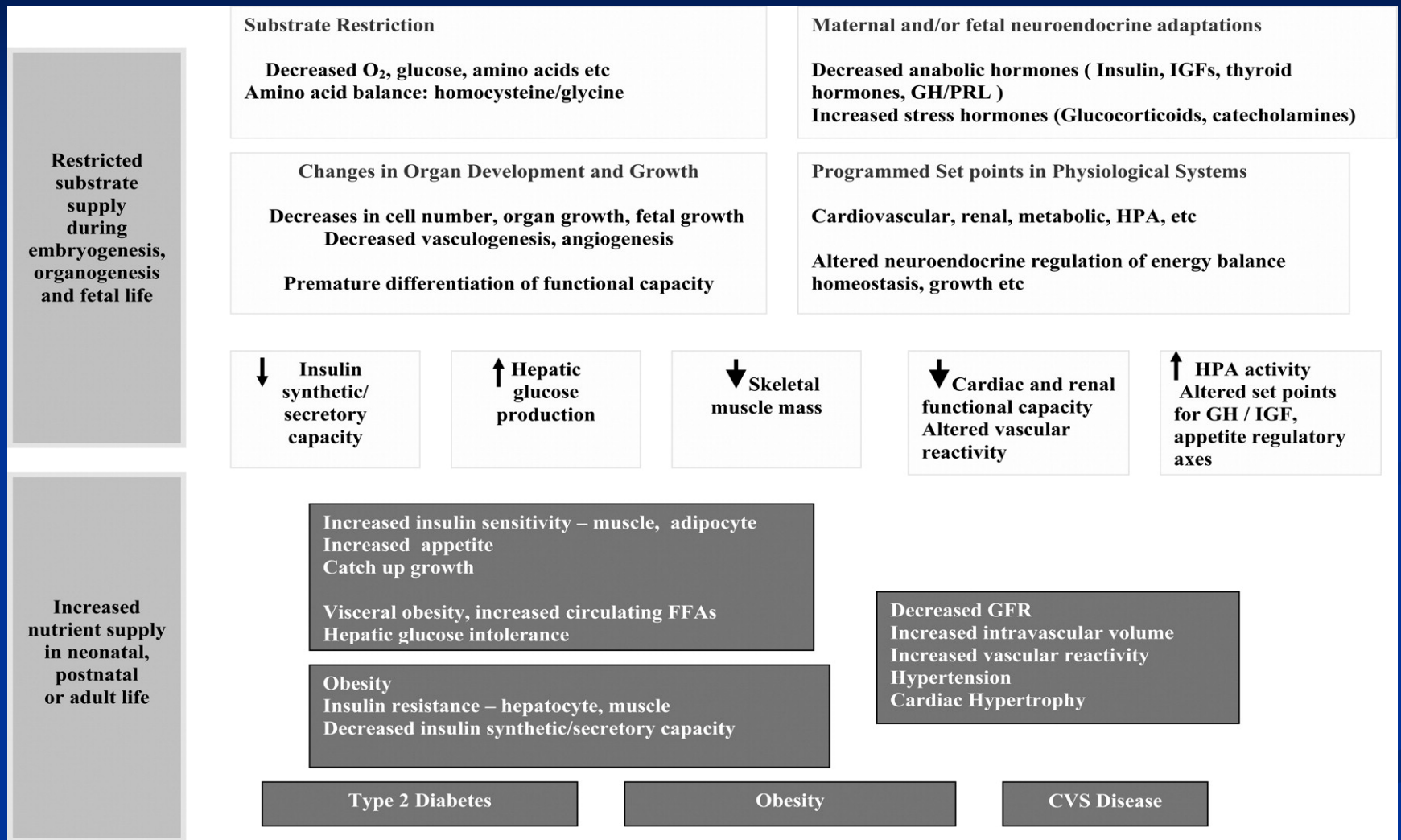
# Low Birth Weight (SGA) and Preterm

- Babies can be either/both SGA and Preterm
  - they both are strongly associated with that baby's later risk for chronic disease *Diabetes 2009;58:523-526*
  - Inverse assoc between gest age and insulin levels at birth and early childhood *JAMA 2014;311:587-596*
- Maternal stressful life events during 1<sup>st</sup> trimester ↑ risk of preterm birth (OR 2.4) and SGA

*Am J Obstet Gynecol 2010;203:34.e1-8*



**FIG. 7. The physiological mechanisms underlying the programming of the separate and combined elements of the metabolic syndrome**



McMillen IC, et al. *Physiol. Rev.* 85: 571-633 2005;

# *In utero* Risks for Later Type 2 Diabetes

- Fetuses of obese mothers develop insulin resistance *in utero*  
*Diabetes Care* 2009;32:1076-1080
- Maternal diet during pregnancy:
  - Epigenetically affects child's adiposity at age 9 yrs *Diabetes* 2011;60:1528-1534  
“Our findings suggest a substantial component of metabolic disease risk has a prenatal developmental basis.”
  - Affects adipose tissue development leading to insulin resistance  
*Cell Death Diff* 2012;doi:10.1038/cdd.2011.183
- Inverse relationship between birth weight and risk of diabetes  
*JAMA* 2008;300:2886-2897
- Rapid weight gain in first 3 months of life associated with ↑CVD and diabetes risk factors by early adulthood  
*JAMA* 2009;301:2234-2242
- Low birth weight is related to nephron number and future risk of kidney disease  
*Kidney Int* 2005;68:S68-S77

# “Fetal Programming of Type 2 Diabetes”

- “It is important to understand that the story is not about birth weight but about fetal programming, and that intergenerational prevention of type 2 diabetes (primordial prevention) will need to target maternal nutrition and metabolism. ...Prevention of fetal programming of diabetes will need to concentrate on the health of young girls.”

*Diabetes Care* 2010;33:1146-8



# 3. Lifestyle

## Overeating as an *Adaptive* Response

### ■ Food Insecurity:

- Prevalence of overweight in women ↑'s as food insecurity ↑  
*Journal of Nutrition*. 2001;131:1738-1745
- Pregnancy: food insecurity assoc with pregravid obesity, ↑ gest wt gain, and gest diabetes  
*J Am Diet Assoc* 2010;110:692-701
- 42% of households below poverty level are food insecure, 21% of all households with children  
*NEJM* 2010;363:6-9
- Independent risk factor for poor glycemic control  
*Diabetes Care* 2012;35:233-238

### ■ Carbohydrates affect brain serotonin levels

*Obes Res* 1995 Suppl 4:477S-480S

### ■ “Comfort Foods” ↓ HPA axis stress response

*Proc Natl Acad Sci* 2003;100:11696-11701

## 4. Stress

- Chronic exposure to Intimate Partner Violence almost doubles (OR 1.8) risk of obesity at age 5 years

*Arch Pediatr Adolesc Med* 2010;164:540-546

- Early life adversity associated with ↑ leptin/irisin and ↓ adiponectin in midlife adults

*J Clin Endocrinol Metab* 2014;doi:10.1210/jc.2013-3669

- “...reducing toxic stress can target the common physiologic pathway implicated in an enormous array of health outcomes from asthma to cardiovascular disease.”

*Pediatrics* 2013;131:319-327

# Adverse Childhood Experiences (ACE)

- Physical, emotional, sexual abuse; mentally ill, substance abusing, incarcerated family member; seeing mother beaten; parents divorced/separated

--Overall Exposure: 86% (among 7 tribes)

	<u>Non-Native</u>	<u>Native</u>
Physical Abuse-M	30%	40%
Physical Abuse-F	27	42
Sexual Abuse-M	16	24
Sexual Abuse-F	25	31
Emotional Abuse	11	30
Household alcohol	27	65
Four or More ACEs	6	33

# ACEs and Adult Health

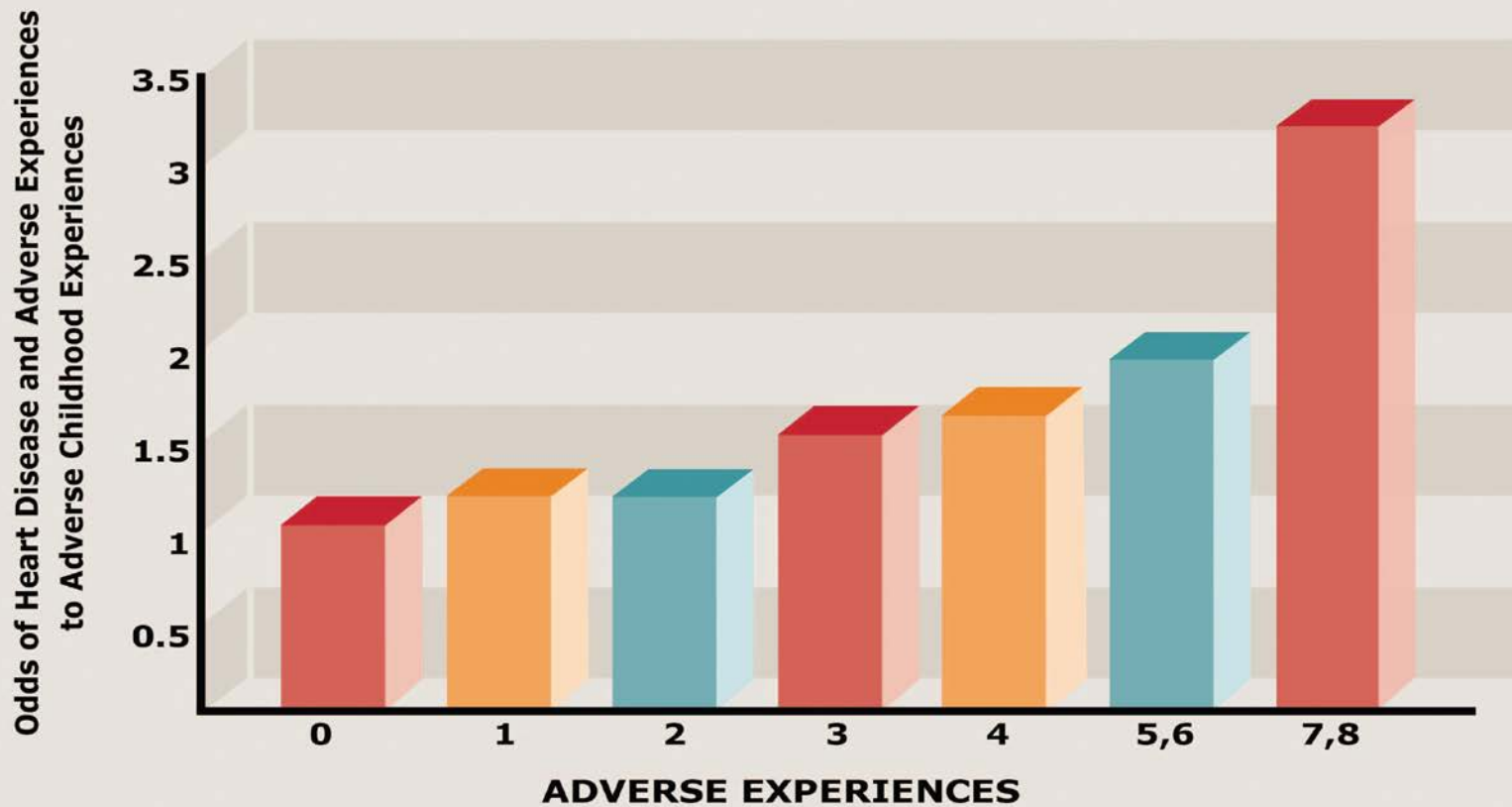
- ACE Score  $\geq 4$ 
  - 4-12 x risk for alcoholism, drug abuse, depression and suicide attempt
  - 2-4 x risk for smoking, teen pregnancy, STDs, multiple sexual partners
  - 1.4-1.6 x risk for severe obesity
  - Strong graded relationship at all levels of ACEs for almost all outcomes, including heart disease

*Am J Prev Med* 1998;14:245-258 and *Circulation* 2004;110:1761-6

- Across 10 countries, adults who experienced  $\geq 3$  childhood adversities
  - Hazard ratios 1.59 for diabetes, 2.19 for heart disease
  - Risk similar to the association between cholesterol and heart disease
    - Both in magnitude as well as population prevalence

*Arch Gen Psychiatry* 2011;68:838-844

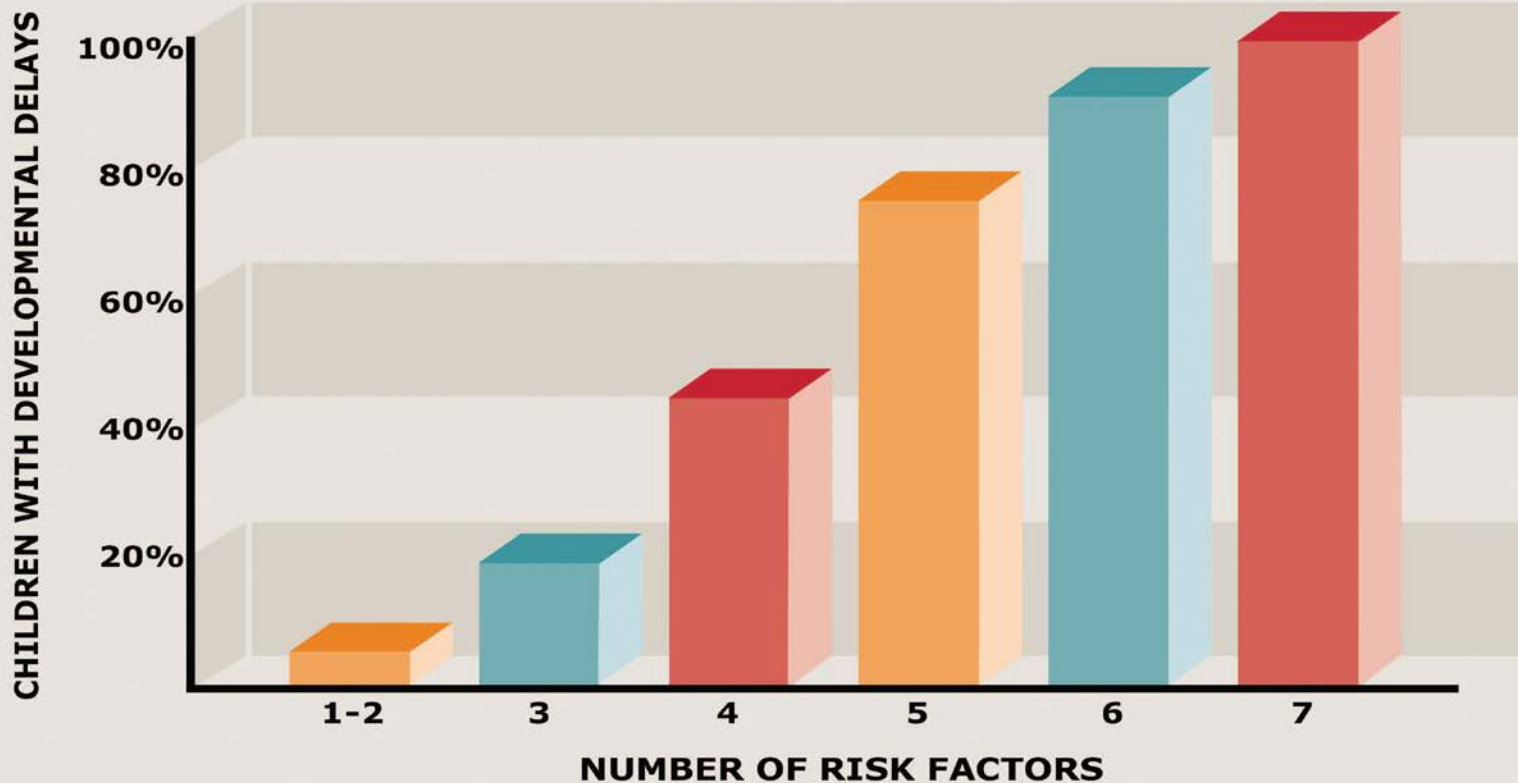
# 3:1 odds of adult heart disease after 7-8 adverse childhood experiences



Center on the Developing Child at Harvard website

Source: Dong et al. (2004)

# 90-100% chance of developmental delays when children experience 6-7 risk factors



Center on the Developing Child at Harvard website

Source: Barth, et al. (2008)

# Stress in Children

## ■ Positive

- Normal/necessary part of healthy development
  - First day with new caregiver; immunization
- Brief increases in heart rate and stress hormones

## ■ Tolerable

- More severe, longer lasting stressor
  - Loss of a loved one, natural disaster, injury
- If buffered by relationship with supportive adult(s), brain and body can recover

## ■ Toxic

- Strong, frequent, prolonged adversity
  - Abuse, neglect, caregiver mental illness, poverty
- If no adult support, can disrupt brain and organ development long-term

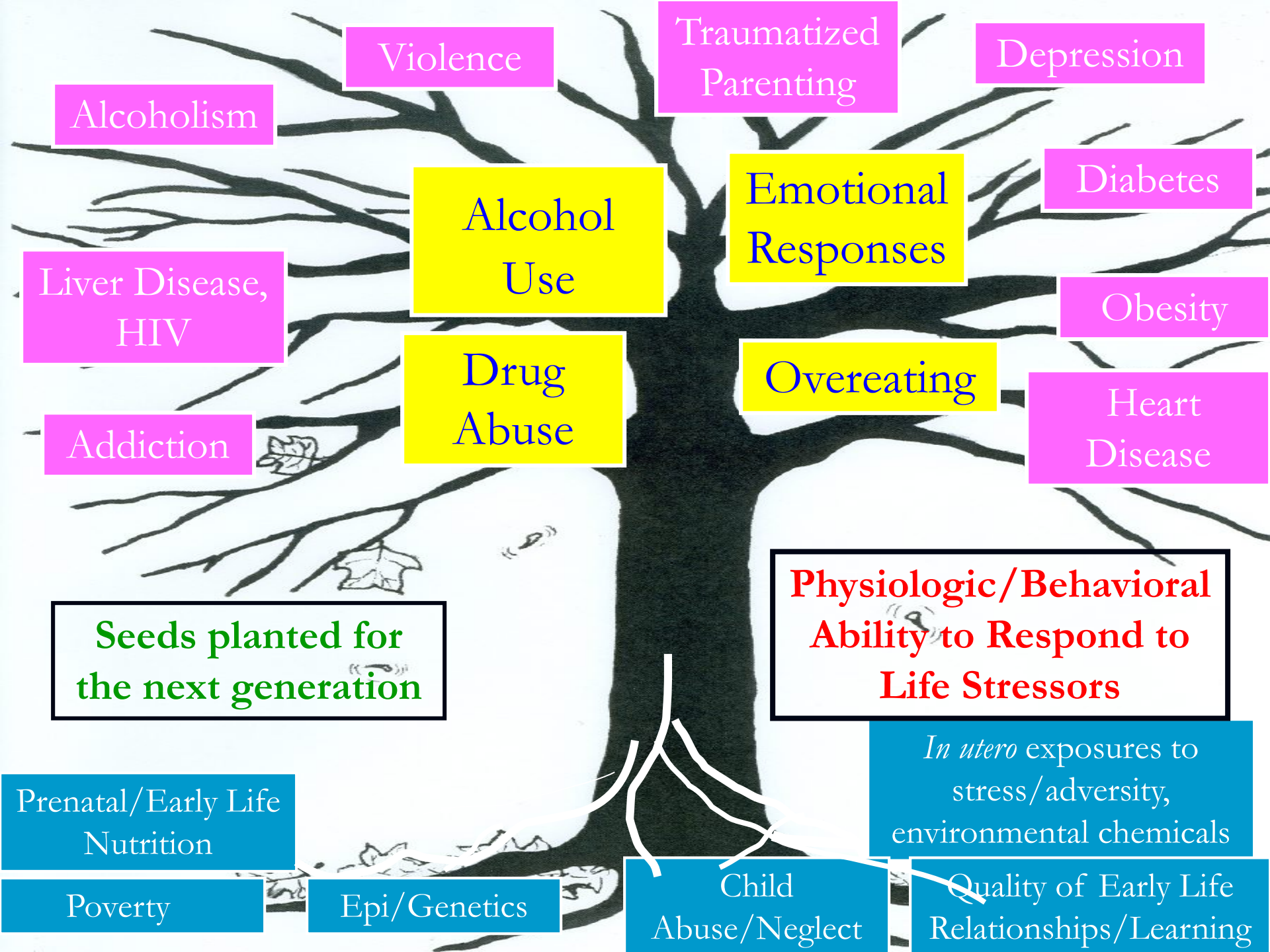
## Domains of Impairment in Children Exposed to Complex Trauma

I. Attachment	IV. Dissociation	VI. Cognition
<ul style="list-style-type: none"> <li>Problems with boundaries</li> <li>Distrust and suspiciousness</li> <li>Social isolation</li> <li>Interpersonal difficulties</li> <li>Difficulty attuning to other people's emotional states</li> <li>Difficulty with perspective taking</li> </ul>	<ul style="list-style-type: none"> <li>Distinct alterations in states of consciousness</li> <li>Amnesia</li> <li>Depersonalization and derealization</li> <li>Two or more distinct states of consciousness</li> <li>Impaired memory for state-based events</li> </ul>	<ul style="list-style-type: none"> <li>Difficulties in attention regulation and executive functioning</li> <li>Lack of sustained curiosity</li> <li>Problems with processing novel information</li> <li>Problems focusing on and completing tasks</li> <li>Problems with object constancy</li> <li>Difficulty planning and anticipating</li> <li>Problems understanding responsibility</li> <li>Learning difficulties</li> <li>Problems with language development</li> <li>Problems with orientation in time and space</li> </ul>
II. Biology	V. Behavioral control	VII. Self-concept
<ul style="list-style-type: none"> <li>Sensorimotor developmental problems</li> <li>Analgesia</li> <li>Problems with coordination, balance, body tone</li> <li>Somatization</li> <li>Increased medical problems across a wide span (eg, pelvic pain, asthma, skin problems, autoimmune disorders, pseudoseizures)</li> </ul>	<ul style="list-style-type: none"> <li>Poor modulation of impulses</li> <li>Self-destructive behavior</li> <li>Aggression toward others</li> <li>Pathological self-soothing behaviors</li> <li>Sleep disturbances</li> <li>Eating disorders</li> <li>Substance abuse</li> <li>Excessive compliance</li> <li>Oppositional behavior</li> <li>Difficulty understanding and complying with rules</li> <li>Reenactment of trauma in behavior or play (eg, sexual, aggressive)</li> </ul>	<ul style="list-style-type: none"> <li>Lack of a continuous, predictable sense of self</li> <li>Poor sense of separateness</li> <li>Disturbances of body image</li> <li>Low self-esteem</li> <li>Shame and guilt</li> </ul>
III. Affect regulation		
<ul style="list-style-type: none"> <li>Difficulty with emotional self-regulation</li> <li>Difficulty labeling and expressing feelings</li> <li>Problems knowing and describing internal states</li> <li>Difficulty communicating wishes and needs</li> </ul>		



# Stress of Racism

- “The lifelong accumulated experiences of racial discrimination by African American women constitute an independent risk factor for preterm delivery.”
  - Odds ratio of 2.6
  - Independent of maternal sociodemographic, biomedical, and behavioral characteristics.





**“We ...know that sound maternal and fetal nutrition, combined with positive social-emotional support of children through their family and community environments, will reduce the likelihood of negative epigenetic modifications that increase the risk of later physical and mental health impairments.”**

Center on the Developing Child at Harvard University

Working Paper 10, 2010

# Association Between Casino Opening and Obesity

- 117 school districts that encompassed tribal lands in California between 2001 and 2012
  - 57 gained/expanded a casino
  - 24 had a preexisting casino but did not expand
  - 36 never had a casino
- Every slot machine per capita gained was assoc with a \$541 ↑ in per capita annual income and a decrease in percentage in poverty of 0.6% among AI living on tribal lands
  - **And ↓ probability of overweight/obesity of 0.19% in AI children**

# Stronger Parents Raise Stronger Children

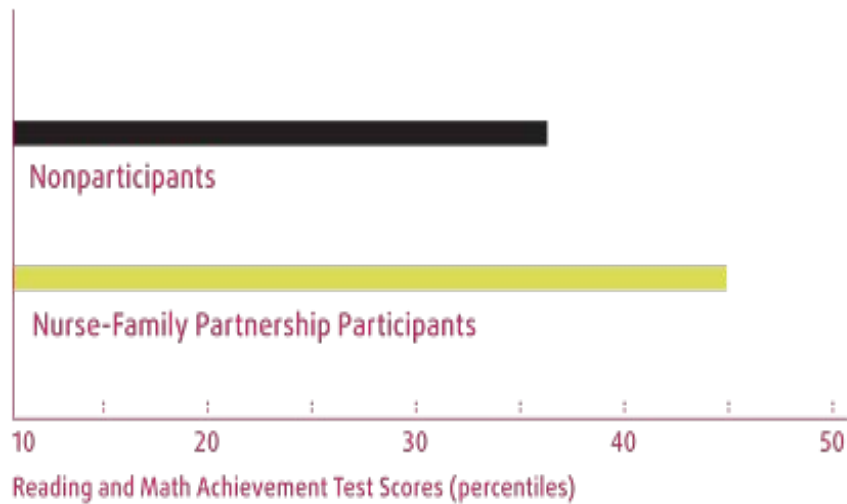
- Prenatal/Early Life Home Visiting
  - Evidence-based interventions proven to improve the life trajectories of low income women and children
  - Positive effects now shown up to *age 19 yrs*

*Arch Pediatr Adolesc Med* 2010;164:9-15, 412-418, 419-424



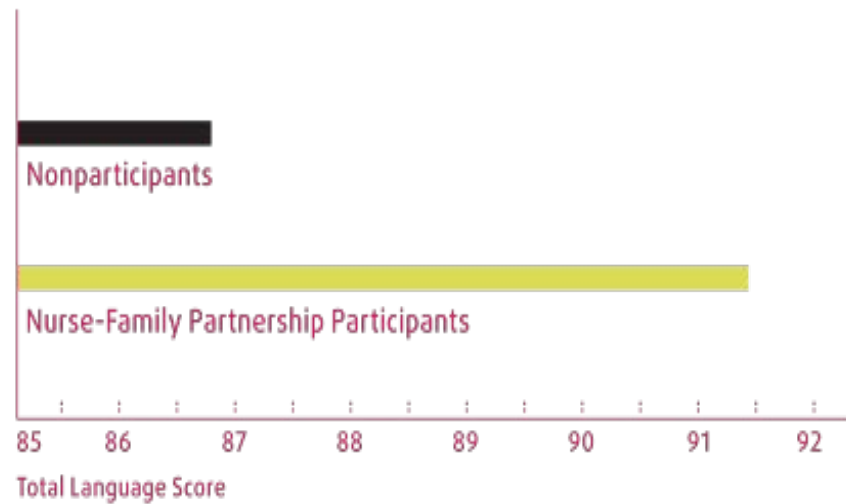
## Academic Achievement

Grades 1-3, Age 9—Memphis  
(Born to low-resource mothers)



## Preschool Language Scale

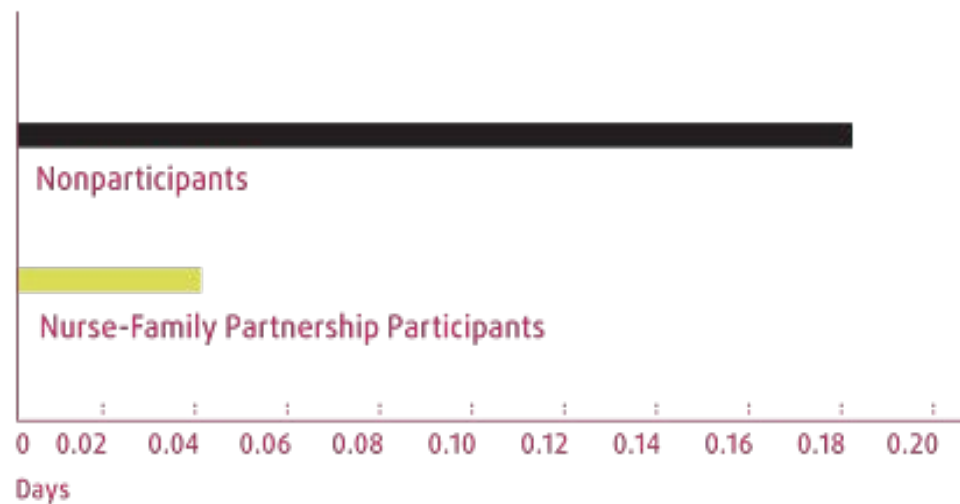
Age 4—Denver  
(Born to low-resource mothers)





## Days Hospitalized for Injuries

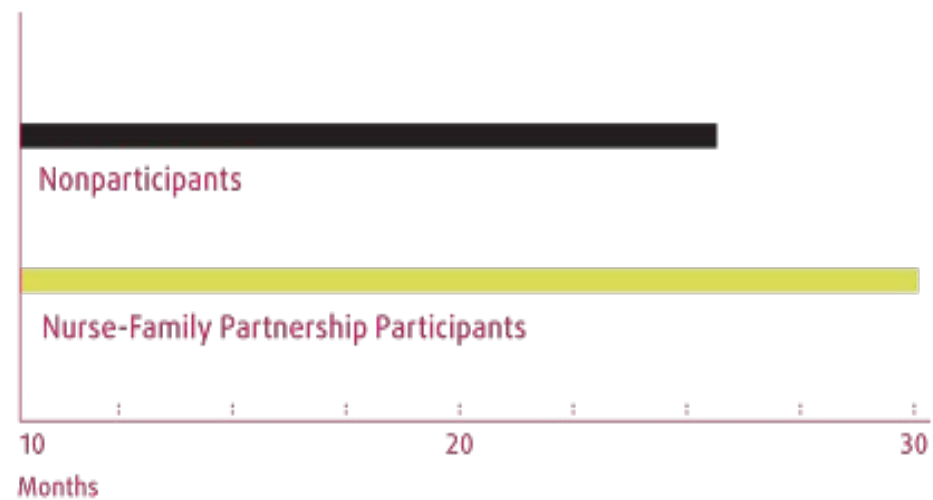
Birth to age 2—Memphis



Source: *JAMA*, 1997, Vol. 278, 650, Copyright © 1997, American Medical Association. All rights reserved.

## Months Between Births

Between first and second child  
(by first child's fifth birthday)—Memphis



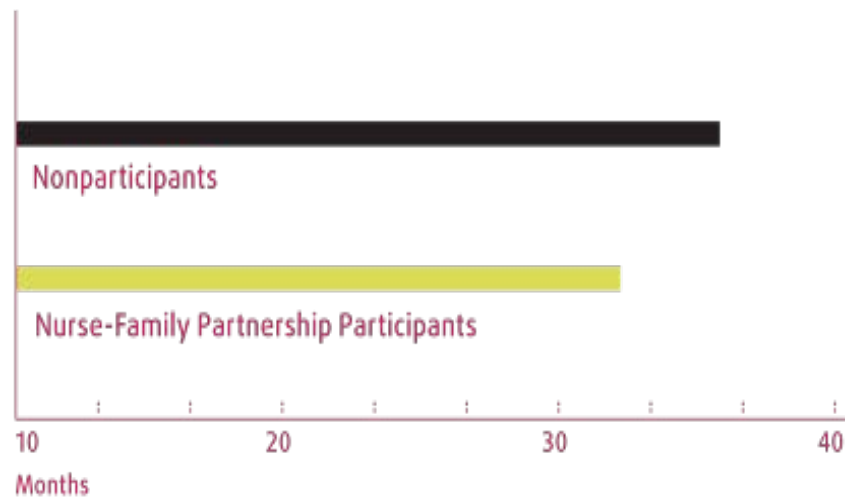
Source: *JAMA*, 2000, Vol. 283, 1987, Copyright © 2000, American Medical Association. All rights reserved.





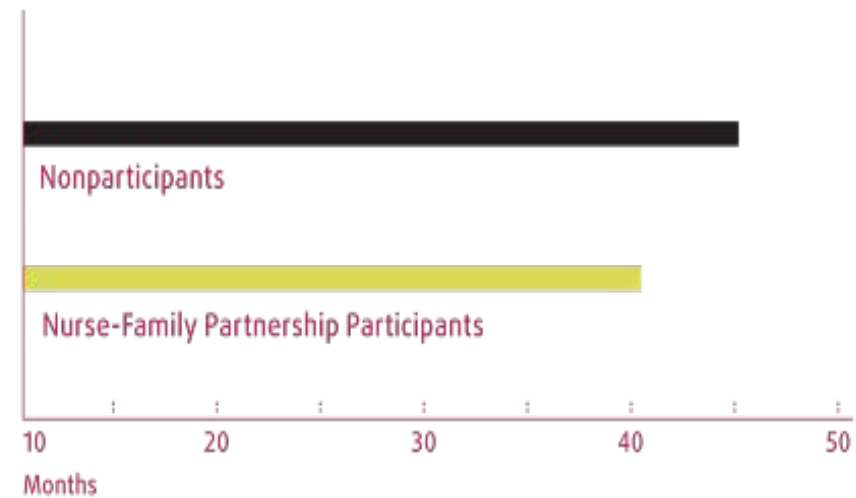
## Months Receiving Welfare Assistance (AFDC)

Birth through age 5—Memphis

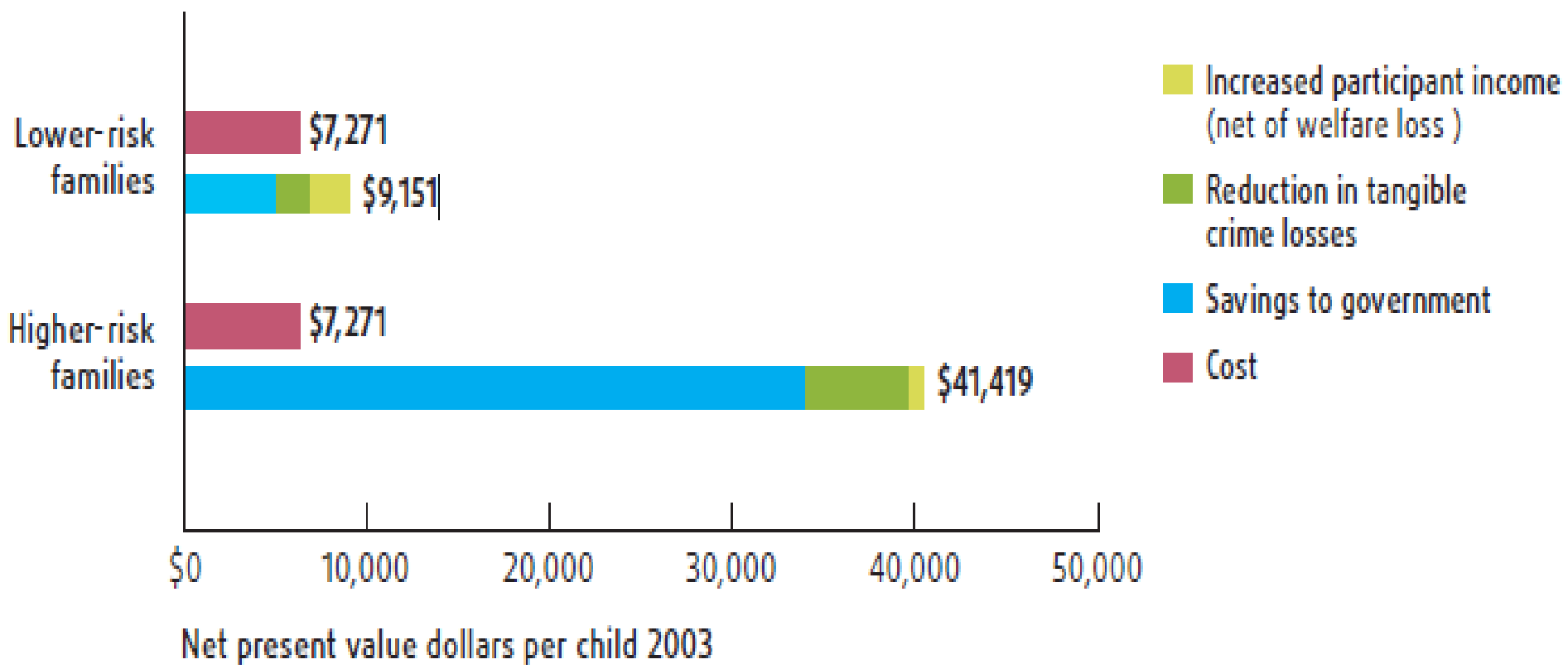


## Months Receiving Food Stamps

Birth through age 5—Memphis



# Monetary Benefits



Source: 2005 RAND Corporation Study

“Home visits are an important mechanism for improving the capacity of caregivers to (1) promote the safe, stable, and nurturing relationships that buffer toxic stress, and (2) encourage the rudimentary but foundational social-emotional, language, and cognitive skills that promote resiliency and the adoption of healthy, adaptive coping skills.”

“Home Visiting and the Biology of Toxic Stress: Opportunities to Address Early Childhood Adversity”

*Pediatrics* 2013;132:S65-S73

# Family Spirit Impact: Pregnancy to Age 3

## Parenting

- Increased maternal knowledge<sup>1,2,3,4</sup>
- Increased parent self-efficacy<sup>3,4</sup>
- Reduced parent stress<sup>2,4</sup>
- Improved home safety attitudes<sup>3</sup>

## Mothers' Outcomes

- Decreased depression.<sup>1,2,4</sup>
- Decreased substance use<sup>4</sup>
- Fewer risky behaviors<sup>3,4</sup>

## Child Outcomes

- Fewer social, emotional and behavior problems through age 3.<sup>2, 3, 4</sup>
- Lower clinical risk of behavior problems over life course<sup>4</sup>



Decreased Externalizing,  
Internalizing and Dysregulation

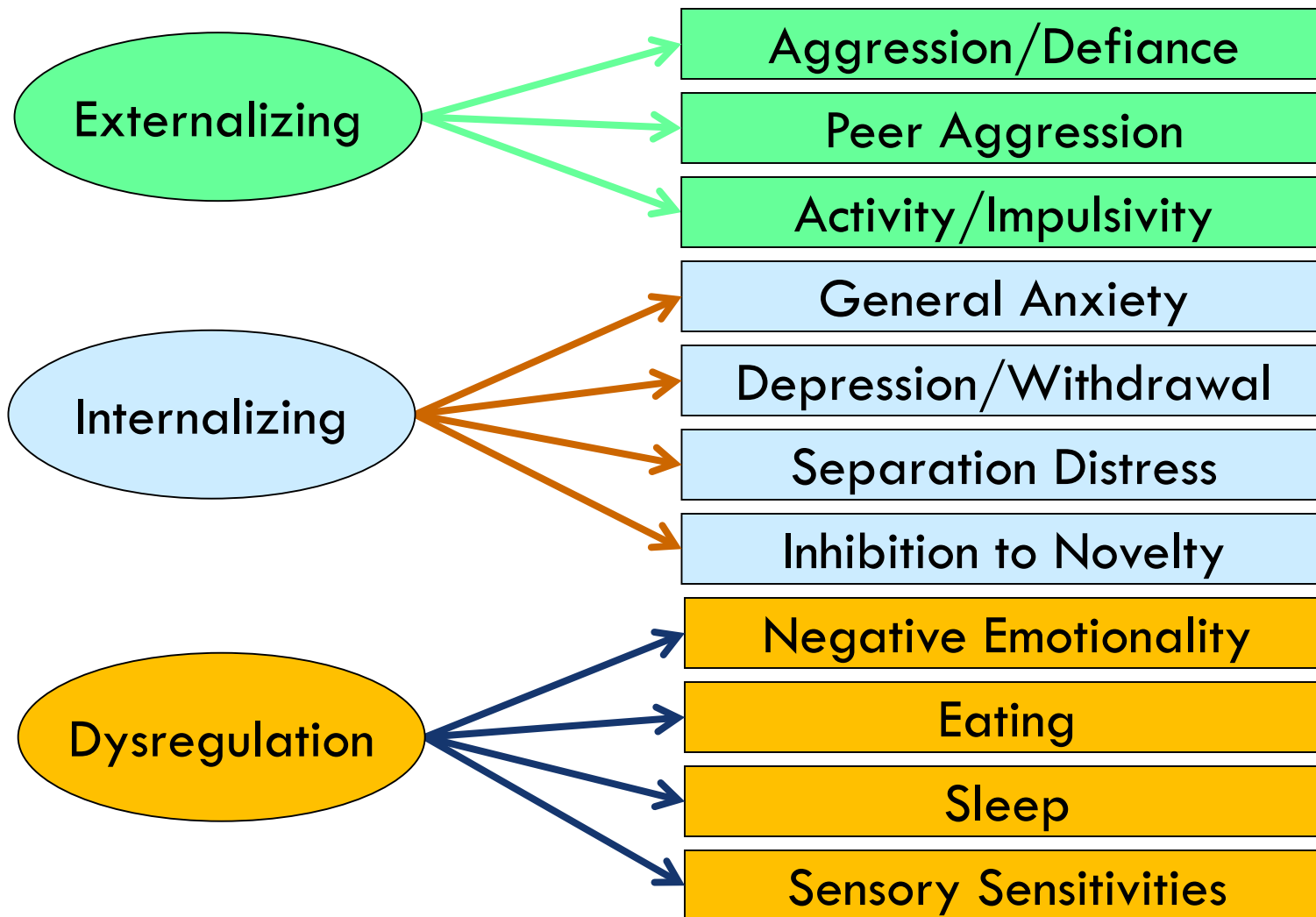
1 Barlow A, Varipatis-Baker E, Speakman K, et al *Arch Pediatr Adolesc Med.* 2006; 160:1101-1107

2 Walkup J, Barlow A, Mullany B, et al. *Journal of the American Academy of Child and Adolescent Psychiatry.* June 2009.

3 Barlow A, Mullany B, Neault N, et al. *American Journal of Psychiatry.* January 2013.

4 Barlow A, Mullany B, Neault N, et al. *American Journal of Psychiatry.*, February 2015.

# ITSEA Problem Domains and Subscales within Domains



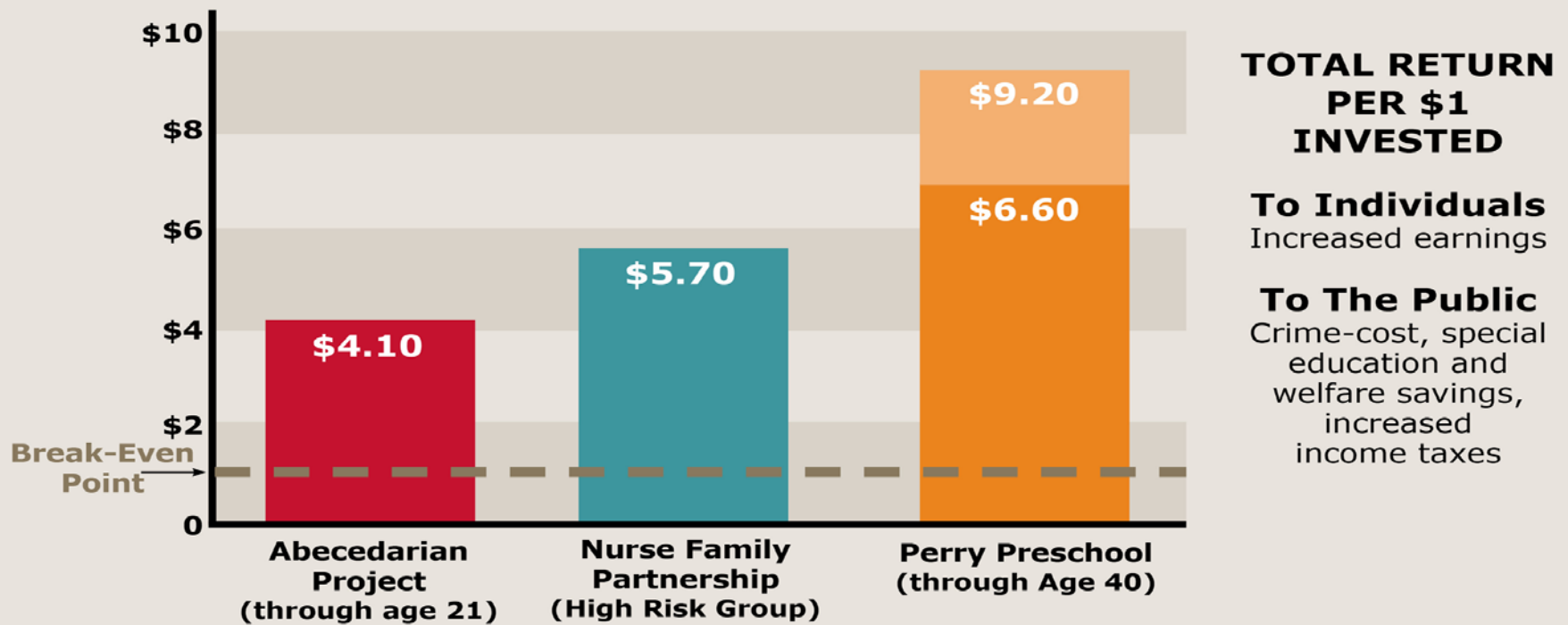
# Parenting and Early Childhood Behavior Problems Associated with Obesity



- Negative parenting (inconsistent discipline; restrictive, coercive parenting) associated with increased obesity risk in children.
  - [Int J Obes \(Lond\)](#). 2006 Dec;30(12):1766-74.
  - [Trends Endocrinol Metab](#). 2013 Apr 19 E-pub
  
- Externalizing behaviors at 24 mos associated with higher BMI at 24 months and thru age 12
  - [BMC Pediatr](#). 2010 Jul 14;10:49
  
- Obese children have higher rates of externalizing and internalizing disorders.
  - [Acad Pediatr](#). 2013 Jan-Feb;13(1):6-13



# \$4-\$9 in returns for every dollar invested in early childhood programs



[Center on the Developing Child at Harvard website](#)

Sources: Masse, L. and Barnett, W.S., A Benefit Cost Analysis of the Abecedarian Early Childhood Intervention (2002); Karoly et al., Early Childhood Interventions: Proven Results, Future Promise (2005); Heckman et al., The Effect of the Perry Preschool Program on the Cognitive and Non-Cognitive Skills of its Participants (2009)

# “Early Life Investments Substantially Boost Adult Health”

- Carolina Abecedarian Project
  - 4 cohorts of disadvantaged children born 1972-77
    - Intervention provided from birth to age 5 years
  - Intervention:
    - Level of language, emotional regulation, cognitive skills
    - Caregiving/supervised play
    - Nutrition: 2 meals and a snack at childcare center
    - Primary pediatric care
- In their mid-30s: lower prevalence of CVD and metabolic disease risk factors including BP, A1C, obesity, HDL





# The Path We *Could* Take

## Rewind: “Mary’s” life

- As soon as mother’s pregnancy diagnosed:
  - Matched with a home visitor/case manager
    - Weekly/biweekly visits focusing on developing a mentoring-type relationship, building on mother’s strengths, helping her to set goals, teaching her new skills
    - All services needed were offered and tailored to her needs
    - WIC foods supplemented so mother had enough good food even though shared with family
    - Mother rewarded for participation in each component
  - Mother went to 90% of her prenatal appointments
    - All but first urine drug screen negative and most cotinine screens
  - Mary born at 39 wks gest, normal weight for gestation

# Rewind: “Mary”

- Visits from home visitor continued until Mary was 3 yrs old
- Mother set/achieved goals: became a CNA through health occupations class and graduated from high school
  - Mary cared for during day by excellent tribal child care program: bonding, learning, good food, social skills, active play, tribal language all emphasized
- Mother attended parenting classes
  - Praised and hugged Mary, appropriately disciplined her
  - Ate dinner together and read to Mary most evenings
  - Left her boyfriend when he wouldn't stop drinking
- Mary's weight stayed around the 90<sup>th</sup> percentile
- Mary graduated from high school, went to tribal college, got a good job, married a guy she met at college
- Now Mary becomes pregnant...



Isn't this among the most important work we can do?

“The medicine is already within the pain and suffering. You just have to look deeply and quietly. Then you realize it has been there the whole time.” Duran, 2006