Prenatal and Early Life Risk Factors For Chronic Disease

A Web-based Training

Presented by IHS Division of Diabetes Treatment and Prevention
Indian Health Service

When Does Diabetes Start?

-or-

"How Adversity Gets Under the Skin"

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Our model of Diabetes has been too small…

- We've thought it was only about:
  - Genes we inherit
  - Our lifestyle choices (diet & exercise)
- But it's now clear that these alone do *not* explain all of diabetes risk
- It's also becoming clear that the roots of diabetes overlap with the roots of other chronic problems: heart disease, depression, substance abuse, domestic violence, learning problems, etc.

Childhood Trauma Predicts Adult Health

- **Children born in Helsinki, Finland between 1934-44**
- **320 were evacuated abroad during WW II—separated from their parents**
  - Average age at evacuation: 4.8 years old
  - Average duration of evacuation: 1.7 years
- **60 years later, compared with children not evacuated, evacuees were much more likely to have:**
  - Heart disease (OR 2.0) and hypertension
  - Type 2 Diabetes (OR 1.4)
  - Depressive symptoms (OR 1.7)
- **"This study is among the first to show that early life trauma predicts higher prevalence of cardiovascular disease and type 2 diabetes in late adulthood..."**

Ann Med. 2009;41(1):66-72, *Am J Epidemiol*. 2007;166(10):1126-33, *Am J Hum Biol* 2008;20(3):345-51

For diabetes risk, it matters what happened…

- To us as adults
  - Diet and exercise choices
    - But many people have access only to food of poor nutritional quality, even if plenty of calories—another stimulus to overeat
  - Stress and trauma
- To us as children
  - Stress and trauma
  - Nutrition
- To us in the womb
  - Nutrition and stress
- To our parents
  - Nutrition and stress
- To our grandparents
  - Nutrition and stress at time eggs and sperm are forming

"Adverse pre- and postnatal experiences can have a profound effect on the course of health and development over a lifetime. … biological events that occur during fetal and postnatal life predispose the child to an elevated risk of subsequent problems in physical and mental health."

"A Science-Based Framework for Early Childhood Policy: Using Evidence to Improve Outcomes in Learning, Behavior, and Health for Vulnerable Children", Center on the Developing Child at Harvard University, August 2007, p.6
http://www.developingchild.harvard.edu

"…confronting the origins of disparities in physical and mental health early in life may produce greater effects than attempting to modify health-related behaviors or improve access to health care in adulthood."

Shonkoff, Boyce, McEwen *JAMA 2009;*301(21):2252-2259

Framework for Chronic Disease

- **CD is the product of multiple stressors which accumulate over lifetime**
  - **genetic, biological, behavioral, social/experiential, economic**
- **Stressors affect both the body's physiologic systems as well as our health behaviors**
- **Different health "trajectories" are the product of risk and protective factors**
- **While stressors have effects throughout life, the body is especially vulnerable to them during critical developmental periods**

Halfon and Hochstein, *Milbank Quarterly 80(3): 433-479, 2002*

“What you walk around with are the first two to five years of your life.”

Frank Langella, actor

USA Today, p 2D

12/3/08

Early Life Experience and the Brain

- **Developing brain is remarkably shapeable and adaptable**
- **“The brain’s exquisite sensitivity to experience in early childhood allows traumatic experiences during infancy and childhood to impact all future emotional, behavioral, cognitive, social, and physiologic functioning.”**

Child Adolesc Psychiatr Clin N Am 1998;7(1):33-51

Early life risk factors combine and take their toll on the brain

- **Family Structure**
  - **Parental employment**
  - **Father's absence**
  - **Teen parenthood**
- **Human Capital**
  - **Maternal education**
  - **Maternal verbal ability**
- **Mental Health**
  - **Maternal depression**
  - **Stressful life events**
- **"…associated with lower IQ scores as early as age 2-4 years and more behavior problems by age 3."**

Fuligni and Brooks-Gunn from *Promoting Health: Intervention Strategies from Social and Behavioral Research*, 2000

Brain Development

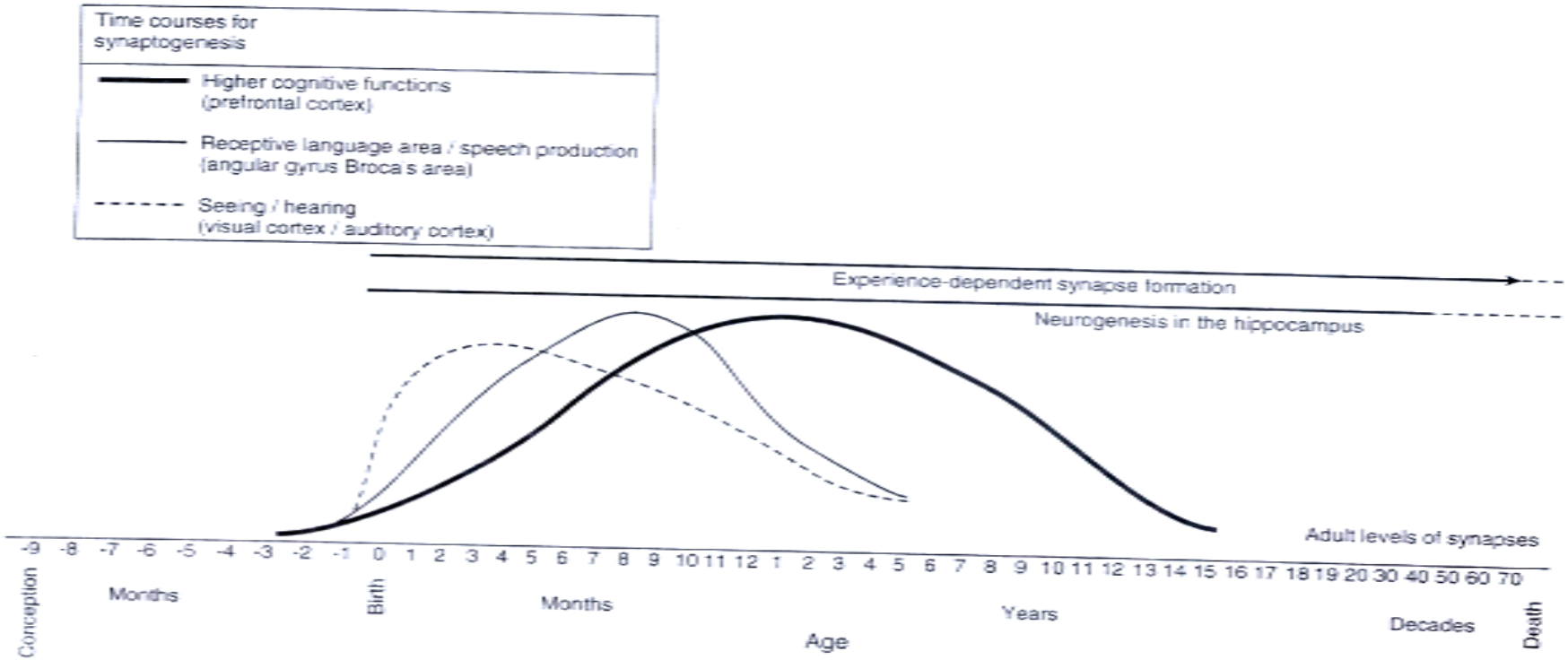


FIGURE 8-1 Human brain development. SOURCE: Charles A. Nelson, University of Minnesota. Reprinted with permission.

From Neurons to Neighborhoods: the Science of Early Child Development. National Academy of Sciences, 2000, p. 188

TABLE 8-1 Conditions and Substances that Affect the Developing Brain

Needed for Normal Brain Development	Detrimental or Toxic
Oxygen	Alcohol
Adequate protein and energy	Lead
Micronutrients, such as iron and zinc	Tobacco
Adequate gestation	Prenatal infections
Iodine	Polychlorinated biphenyls (PCBs)
Thyroid hormone	Ionizing radiation
Folic acid	Cocaine
Essential fatty acids	Metabolic abnormalities (excess phenylalanine, ammonia)
Sensory stimulation	Aluminum
Activity	Methylmercury
Social interaction	Chronic stress

Note: The listed factors are not intended to be exhaustive.

National Academy of Sciences, 2000, p. 199

Early Life Risk Factors for Obesity at Age 7 years

1. Parental obesity
2. **Birth weight**
3. **Weight gain in 1st year of life ("catch-up growth", "adiposity rebound")**
4. >8 hrs/week TV watching at age 3 yrs
5. Short sleep duration at age 3 yrs
6. ***Not*** : calories eaten, junk food, breastfeeding

Reilly, *et al*. 2005. *BMJ*, doi:10.1136/bmj.38470.670903.E0

Other studies: youth obesity predicted by depression, behavior problems, low cognitive stimulation

International Diabetes Federation

Conference on Type 2 Diabetes Etiologies

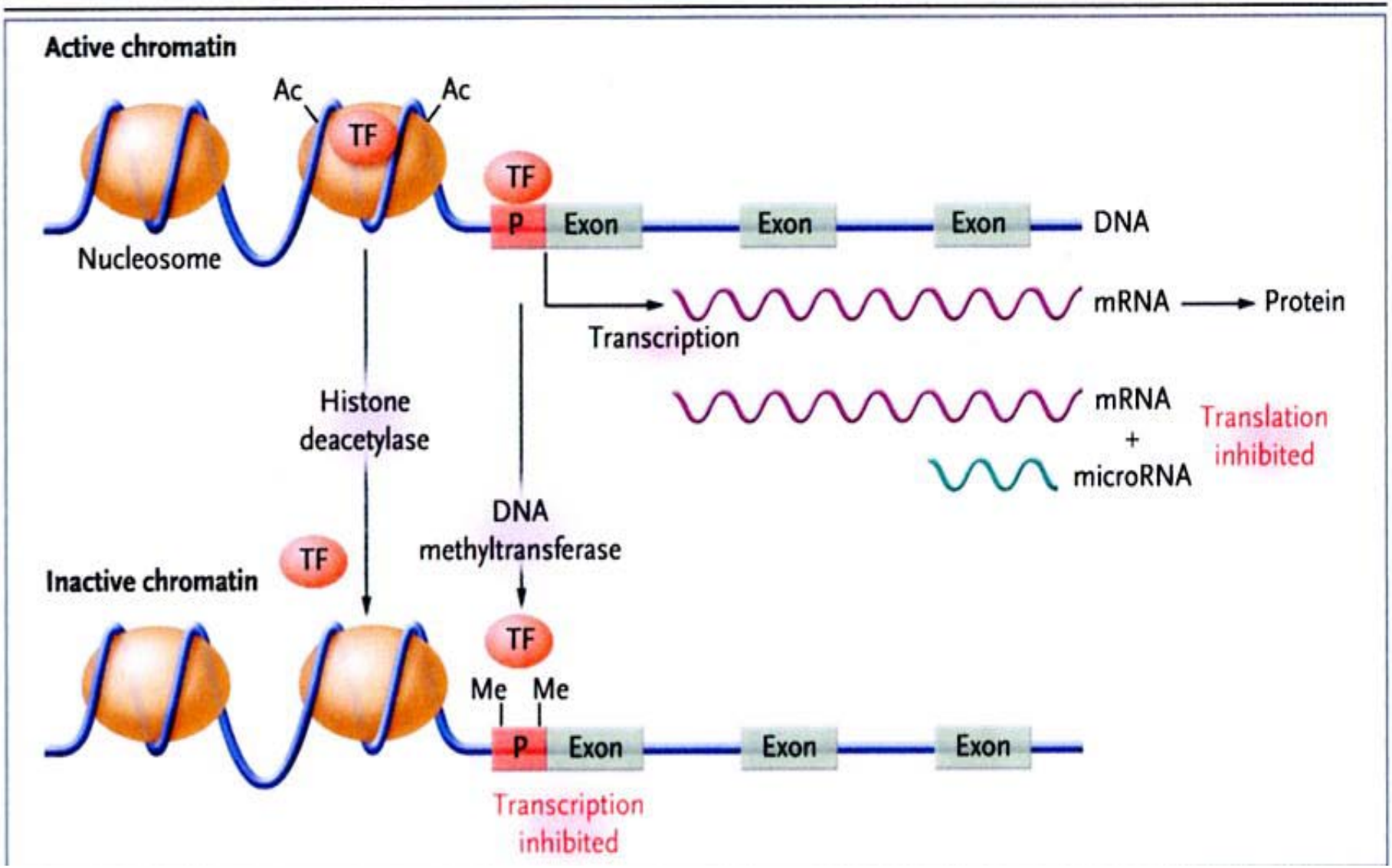
2002

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

1. Genetics

- **Genes *Inherited***
  - **It does matter what genes we inherit**
  - ***But* only 15% of genes in cells "turned on" at any given time**
- **Genes *Expressed***
  - **"Epigenetics": the "on/off switches" for genes**
    - **reaction to the environment**
    - **not always reversible if at key developmental stage of life**
    - **we know the body's "on/off switches": DNA methylation, histone acetylation, microRNA**

***JAMA* 294(17):2221-4, 2005 and *NEJM* 359:61-73, 2008**



NEJM 359:61-73, 2008

Epigenetics

- No longer “nature vs. nurture”—nurture *affects* nature
- Rat pups raised by nurturing mothers
  - Gene which affects stress hormone receptors “turned on”
  - Grow up to be stress resilient
- Rat pups raised by neglectful mothers
  - Gene which affects stress hormone receptors “turned off”
  - Grow up to be very stress reactive
- “…there is no change in gene sequence; the changes are only in…gene expression. Hence, these kinds of effects are called *epigenetic*. Epigenetic mechanisms can provide a potential pathway by which early experience can have lasting effects on behavior.” ***JAMA* 294(17):2221-4, 2005, p. 2222**

“It is biologically impossible for a gene to operate independently of its environment: genes are *designed* to be regulated by signals from their immediate surround... Just as our diet regulates certain genes, our social experiences also determine a distinct batch of such genomic on-off switches.”

Goleman D. 2006. *Social Intelligence*, p. 151

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**

Definitions

- "Preterm" baby
  - Baby born before 37 weeks of pregnancy ("gestation")
- Low Birth Weight ("SGA") baby
  - "Small for Gestational Age"
  - Baby born small for *whatever* gestational age baby born at
- Babies can be either/both "SGA" and "Preterm"—they both increase that baby's later risk for chronic disease

Prenatal Depression Effects on the Fetus and Newborn

- Mothers with depressive symptoms
  - ↑stress hormone (cortisol), ↓serotonin/dopamine levels
  - More likely to deliver prematurely and have low birth weight babies
- Newborns of mothers with depressive symptoms:
  - ↑ cortisol and ↓serotonin/dopamine levels (like mom)
  - ↓ "neurobehavioral profiles"

Infant Behavior & Development 27:216-229, 2004

- Preterm delivery risk increases with depression severity
  - 44% of 791 pregnant patients had depressive symptoms, half of them severe

Human Reproduction 2009 24(1):146-153

Prenatal Effects on Stress Hormones Persist

- Girls born to mothers who had significant anxiety during pregnancy had increased stress hormones—as ***adolescents***
- And this was associated with depressive symptoms in these adolescents

Neuropsychopharmacology 33:536-545, 2008

Risk of Type 2 Diabetes

- Review of 30 studies worldwide: Inverse relationship between birth weight and risk of diabetes
  - "U-shaped" association in Native American groups

JAMA 300:2886-2897, 2008

- Study of 6,425 people born in Sweden between 1925-1949
  - Both fetal growth (SGA) and preterm birth strongly associated with diabetes risk

Diabetes 58:523-526, 2009

Risk of Type 2 Diabetes

- Babies of obese mothers develop insulin resistance *in the womb*
  - "…maternal obesity creates a significant risk for the next generations with metabolic compromise already apparent at birth." *Diabetes Care* 2009;32:1076-1080

- Rapid weight gain in the first 3 months of life is associated with risk factors for heart disease and type 2 diabetes by early adulthood

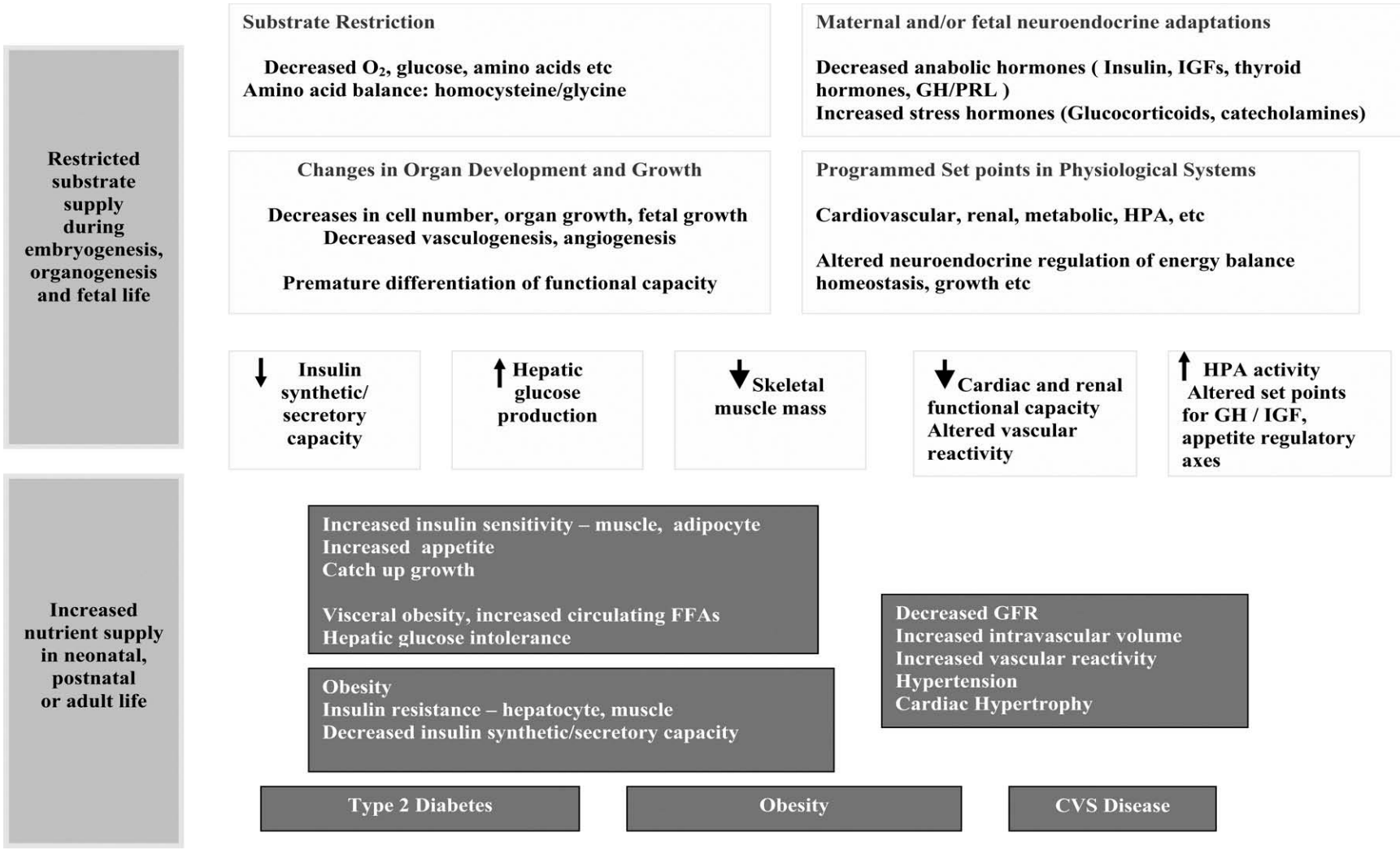
JAMA 2009;301(21)2234-2242

"Fetal Programming of Type 2 Diabetes"

"…intrauterine environment may modify gene expression permanently. …They might also be inherited transgenerationally, affecting the health of future generations. …During intrauterine life, there are waves of epigenomic modification, intimately associated with growth and development, and opportunities galore for environmental factors to influence these processes. A fetus thus programmed travels a path of limited options."

Diabetes Care 30(10): 2754-5, 2007

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;
doi:10.1152/physrev.00053.2003

PhysiologicalReviews

How mother's undernutrition and/or stress before/during pregnancy increase baby's future risk of diabetes

- Under-nutrition
  - ↓ cell number
  - ↓ organ growth
  - ↓ overall fetal growth

  ↓ Insulin ↑ sugar from liver

  Birth----------
- High calorie foods (quality?)

  ↑ Appetite, catch-up growth
  Abdominal fat, insulin resistance
  Obesity

---Type 2 Diabetes----

- ↑ Stress hormones (cortisol, adrenaline)
  - ↓ insulin, growth hormones
  - set points for heart, kidneys
  - changes programmed for life

  ↓ heart, kidney function ↑stress hormones

  Hypertension, ↑fluid
  Further ↓ in heart, kidney function

---Heart Disease---

How Parental Adversity Gets Transmitted to the Next Generation

- **Grandparents'** nutrition and stress affects risk for diabetes mortality *Eur J Human Genetics* 2007;15:784-790 and 2002;10:682-688
- Epigenetic changes in egg, sperm passed on
- Prenatal undernutrition and/or psychosocial stress:
  - Maternal cortisol reduced by placenta, but can be overwhelmed
  - Reduce cell development, even including overall fetal growth
  - Stress hormones can lead to preterm birth
  - Change stress hormone "set points" in baby
    - adaptive prediction?
- Early life exposure to parental behaviors (e.g. nuturing vs abuse) creates epigenetic changes in stress reactivity

Nature Neuroscience 12:342-348, 2009

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.

Am J Public Health. 94:2132–2138, 2004

Prenatal Stress

- "Thus, prenatal stress—whether nutritional or psychosocial in origin—shapes a wide range of traits that influence future risk of developing CVD, including how the body manages and distributes glucose and lipids, regulates blood pressure, and responds physiologically to stress."
- "…stressors experienced by one generation, such as imbalanced nutrition or psychosocial stress, can perpetuate changed biological settings to offspring…"

Am J Hum Biol 21:2-15, 2009

3. Lifestyle

Overeating as an *Adaptive* Response

- Prevalence of overweight in women increases as food insecurity increases

  Journal of Nutrition. 131:1738-1745, 2001

  – Food Insecurity associated with depression and anxiety in mothers and behavior problems in children

  Pediatrics 118(3):e859-e868, 2006

- Carbohydrates affect brain serotonin levels

  Obes Res 1995 Suppl 4:477S-480S

- "Comfort Foods" reduce stress hormone response and anxiety

  Proc Natl Acad Sci 100(20):11696-11701, 2003

  Endocrinology 145:3754-3762, 2004

Overeating and Psychological Distress

"Youths who overeat may have or be at risk for serious psychological distress, including deficits to self-esteem, compromised mood, and suicide risk. Overeating may be a tangible behavior that signals the need for intervention."

Ackard *et al*, *Pediatrics* 2003;111:67-74

4. Stress

"Toxic stress in early childhood is associated with disruptive effects on the nervous system and stress hormone regulatory systems that can damage developing brain architecture and chemistry and lead to lifelong problems in learning, behavior, and both physical and mental health."

"A Science-Based Framework for Early Childhood Policy: Using Evidence to Improve Outcomes in Learning, Behavior, and Health for Vulnerable Children", Center on the Developing Child at Harvard University, August 2007, p.10 http://www.developingchild.harvard.edu

Adverse Childhood Experiences and Adult Risk Factors for Age-Related Disease

- Dunedin Study: 32 year longitudinal study of a representative birth cohort—New Zealand
- Adverse childhood experiences in first decade of life:
  - Low SES
  - Maltreatment
  - Social Isolation
- Controlled for established risk factors including birth weight, family history, childhood BMI, adult health behaviors
- Attributable to adverse childhood experiences:
  - 31.6% of depression
  - 13% of elevated inflammation
  - 32.2% of cases with clustering of metabolic risk markers
- As severity of each ACE worsened, greater number of age-related health risks in a dose-response fashion

Arch Pediatr Adolesc Med 2009;163(12):1135-1143

"Childhood Trauma…

- "…is probably our nation's single most important public health challenge… …chronic maltreatment has pervasive effects on the development of mind and brain. Developmental trauma sets the stage for unfocused responses to subsequent stress, leading to dramatic increases in the use of medical, correctional, social, and mental health services."
- "Complex trauma": e.g. abuse; neglect; exposure to DV, community violence; poverty; caregiver psychopathology—compounded when caregiver the source of trauma or even if they are unable to support and help child process trauma experiences

van der Kolk, 2005. *Psychiatric Annals* 35(5):374-378

SIDEBAR 1.

Domains of Impairment in Children Exposed to Complex Trauma

I. Attachment

- Problems with boundaries
- Distrust and suspiciousness
- Social isolation
- Interpersonal difficulties
- Difficulty attuning to other people's emotional states
- Difficulty with perspective taking

II. Biology

- Sensorimotor developmental problems
- Analgesia
- Problems with coordination, balance, body tone
- Somatization
- Increased medical problems across a wide span (eg, pelvic pain, asthma, skin problems, autoimmune disorders, pseudoseizures)

III. Affect regulation

- Difficulty with emotional self-regulation
- Difficulty labeling and expressing feelings
- Problems knowing and describing internal states
- Difficulty communicating wishes and needs

IV. Dissociation

- Distinct alterations in states of consciousness
- Amnesia
- Depersonalization and derealization
- Two or more distinct states of consciousness
- Impaired memory for state-based events

V. Behavioral control

- Poor modulation of impulses
- Self-destructive behavior
- Aggression toward others
- Pathological self-soothing behaviors
- Sleep disturbances
- Eating disorders
- Substance abuse
- Excessive compliance
- Oppositional behavior
- Difficulty understanding and complying with rules
- Reenactment of trauma in behavior or play (eg, sexual, aggressive)

VI. Cognition

- Difficulties in attention regulation and executive functioning
- Lack of sustained curiosity
- Problems with processing novel information
- Problems focusing on and completing tasks
- Problems with object constancy
- Difficulty planning and anticipating
- Problems understanding responsibility
- Learning difficulties
- Problems with language development
- Problems with orientation in time and space

VII. Self-concept

- Lack of a continuous, predictable sense of self
- Poor sense of separateness
- Disturbances of body image
- Low self-esteem
- Shame and guilt

Cook, *et al*. 2005. *Psychiatric Annals* 35(5) p. 392

Reducing Prenatal and Early Life Risk Factors for Chronic Disease

Cultural/Group Support

- Pima Pride/Action

  -DPP pilot study

  People randomized to “Action” group

  -Structured diet/exercise meetings

  People randomized to “Pride” control group

  -Unstructured activities emphasizing

  Pima culture and history

- ***“Pima Pride” group showed more positive outcomes on every biological parameter measured***

Narayan *et al, Diabet Med 1998;15:66-72*

Breastfeeding

Exclusive breastfeeding for the first 2 months of life was associated with an odds ratio for Type 2 diabetes of 0.41 (adjusted for age, sex, parental diabetes, and birthweight) in a study in Pima Indians

Pettit et al, *Lancet* 1997;350:166-168

Disconnect between hunger and satiety happens early in life

- Study in 2 daycare centers found:

  1. Children's "disregulated energy intake" is related to mothers' weight and perceived control over eating.

  2. Instituting an age-appropriate intervention which helped children focus on their own internal cues resulted in improved ability to self-regulate eating.

Johnson, *Pediatrics* 2000;106(6):1429-1435

Harlem Children's Zone

- Led by Geoffrey Canada, focus on education
- Goal: to break the cycle of poverty in Harlem— "…to transform every aspect of the environment that poor children were growing up in; to change the way their families raised them and the way their schools taught them as well as the character of the neighborhood that surrounded them."
- "Conveyor belt" of intensive services: Baby College—day care--pre-school—kindergarten—elementary school—middle school—high school

Whatever It Takes, 2008, Paul Tough

Break the Depression Cycle

- **2-3x increased risk for anxiety and disruptive behavior disorders and major depression in children of depressed parents**
- **"These offspring problems often begin before puberty, continue into adolescence and adulthood and can be transmitted to the next generation."**
- **Treating children is difficult and controversial**
- ***But treating the mothers' depression reduces symptoms in both mothers and children***

JAMA. 2006;295:1389-1398

Stimulation in Early Childhood: Has Effects Years Later

- Weekly play sessions with mother and child over 2 years
  - Given to growth retarded children age 9-24 months
  - Intervention aimed to improve the mother-child relationship:
    - listening and talking to children, allowing them to experience success/praise, reducing punishment
  - Resulted in less anxiety, depression, attention problems and higher self-esteem ***16 years after the intervention.***

Walker, *et al*.. 2006. *BMJ*, doi:10.1136/bmj.38897.55208.2F

Parenting Groups Improve Antisocial Behavior in Children

- "Harsh, inconsistent parenting is strongly associated with antisocial behavior in children…"
- Intervention was a series of group classes which focused on parenting skills and support
- Resulted in "a large reduction in antisocial behavior" in the children

***BMJ* 2001;323:194**

The economics of early life intervention

- "…for many skills and human capabilities, later intervention for disadvantage may be possible, but it is much more costly than early remediation to achieve a given level of adult performance."
- "Simple economic models show the importance of accounting for early and late investments and for examining…economic costs of late remediation for early environmental influence."

Heckman, *PNAS* 2007;104(33):13250-13255

Nurse-Family Partnership

Program Overview

FAMILIES SERVED

- **Low income pregnant women**
  - **Usually teens**
  - **Usually unmarried**
- **First-time parents**

THREE GOALS

1. **Improve pregnancy outcomes**
2. **Improve child health and development**
3. **Improve parents' economic self-sufficiency**

Elements of the Nurse-Family Partnership

- **Mothers enroll voluntarily early in pregnancy**
- **Home visits by nurses over 2½ years**
- **Powerful relationships with families build on native strengths**
- **Construct program around each family's goals and values**
- **Nursing guidelines are rich with resources to nurture multiple, inter-related aspects of health**

Nurses and Families Attend To:

- Personal health
- Environmental health
- Life course development
- Maternal (Parental) role
- Building support systems through family, friends, community
- Connections to other health and human services as needed

TRIALS OF PROGRAM

Elmira, NY – ‘77

N = 400

- Low-income whites
- Semi-rural

Memphis, TN -‘87

N = 1,138

- Low-income blacks
- Urban

Denver, CO – ‘96

N = 735

- Large portion of Hispanics
- Nurse versus paraprofessional visitors

Consistent Program Effects*

- Improved prenatal health
- Fewer childhood injuries
- Fewer subsequent pregnancies
- Increased intervals between births
- Increased maternal employment
- Improved school readiness

*Effects observed in at least two of the three trials (Elmira, Memphis, Denver)

ELMIRA LONG-TERM RESULTS: Benefits to Mothers

Fewer convictions	**72%**
Fewer days in jail*	**98%**
Fewer arrests	**61%**

* Impact on days in jail is highly significant, but the number of cases that involved jail-time is small, so the magnitude of program effect is difficult to estimate with precision

ELMIRA LONG-TERM RESULTS: Benefits to Children

Abuse & Neglect	**48%**
Arrests	**59%**
Adjudications as PINS* **(person in need of supervision) for incorrigible behavior**	**90%**

* Based upon family-court records of 116 children who remained in study-community for 13-year period following end of program.

Effects on Child Development Memphis 6-Year

- Higher IQ’s
- Better language development
- Fewer mental health problems

Nurse-Family Partnership

- "The most rigorously evaluated example of a program that promotes safe, stable, and nurturing relationships and environments…" *JAMA* 2009;301(21):2262-4
- "in a series of rigorous experimental evaluations, the Nurse Family Partnership has produced multiple, positive impacts on families and children, including fewer subsequent pregnancies, increased maternal employment, higher cognitive performance, and better social behavior by children in the preschool years, as well as (in the study with the longest-term follow-up) fewer arrests in adolescence" (p. 13).

"A Science-Based Framework for Early Childhood Policy: Using Evidence to Improve Outcomes in Learning, Behavior, and Health for Vulnerable Children", Center on the Developing Child at Harvard University, August 2007, p.6 http://www.developingchild.harvard.edu

"…we are placing bets on the value of early intervention, beginning prenatally with a mother's first pregnancy, and extending throughout the first years of life and beyond, as one of the surest ways to begin to address past centuries of neglect and improve the prospects of American Indian and Alaska Native children in this century."

Sarche and Spicer, *Ann NY Acad Sci* (2008) 1136:126-136

<Preconception Conception--- Birth Early Childhood Adolescence >

Nutrition **Fruit/Veg Supplementation** **WIC+ Breastfeed** **WIC+** **School Food Programs "Backpack Foods"**

Depression &Substance Abuse **Screen: high schools, family planning/prenatal/well child/WIC clinics**
Treatment: CBT, EMDR, DBT, groups, dual diagnosis
Coping Skills classes: emotions (e.g. LifeSkills), racism, finances, relaxation
Find ways to help pregnant women abstain from drugs/alcohol/smoking

"Parenting" **Nurse-Family Partnership----------**
Case manage all pregnancies
Family Planning
Parenting classes—pay parents to attend----------
Play groups/psychosocial stimulation
Parent-Child Interaction Therapy Mentoring
DSS/Court referrals Pregnant teens group
Harlem Children's Zone: Strong Day Care—Head Start—Schools
Coping skills for kids, bullying interventions
Renew tribal traditional pregnancy/child-rearing practices