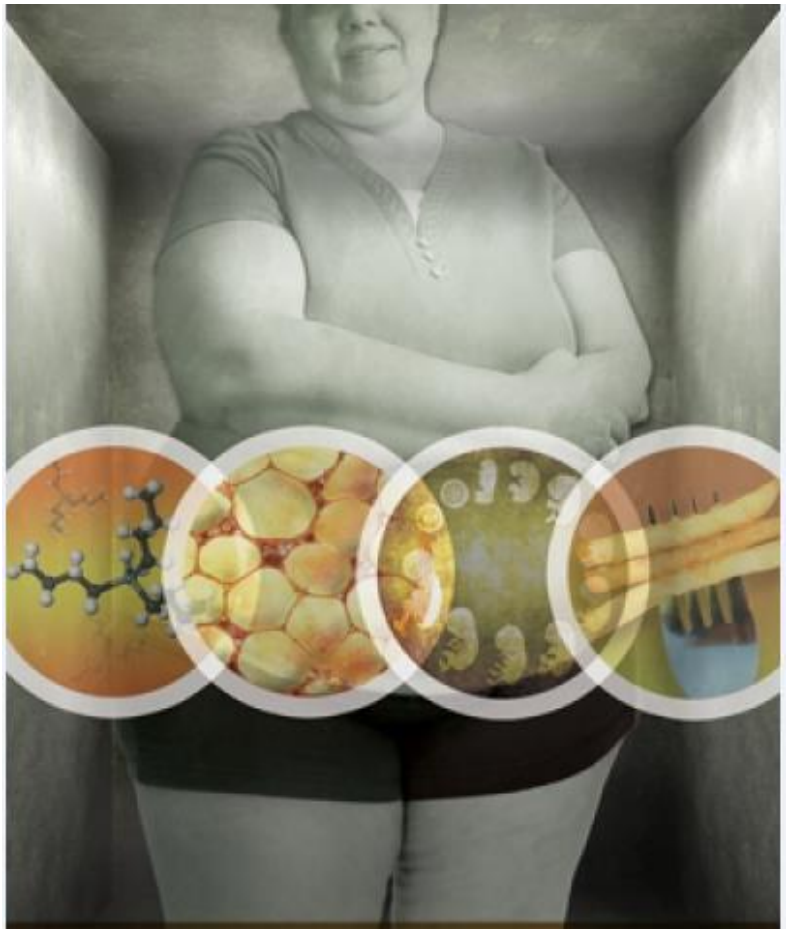
Prenatal and postnatal environmental causes of obesity

Ladan Giahi (PhD)
Dietitian & Immunonutritionist
Avicenna Research Institute

The 6th Congress of Obesity Prevention and Treatment
&
The 3rd International Congress on Obesity Surgery

Why Focusing on traditional root causes of obesity has not prevented obesity Epidemic



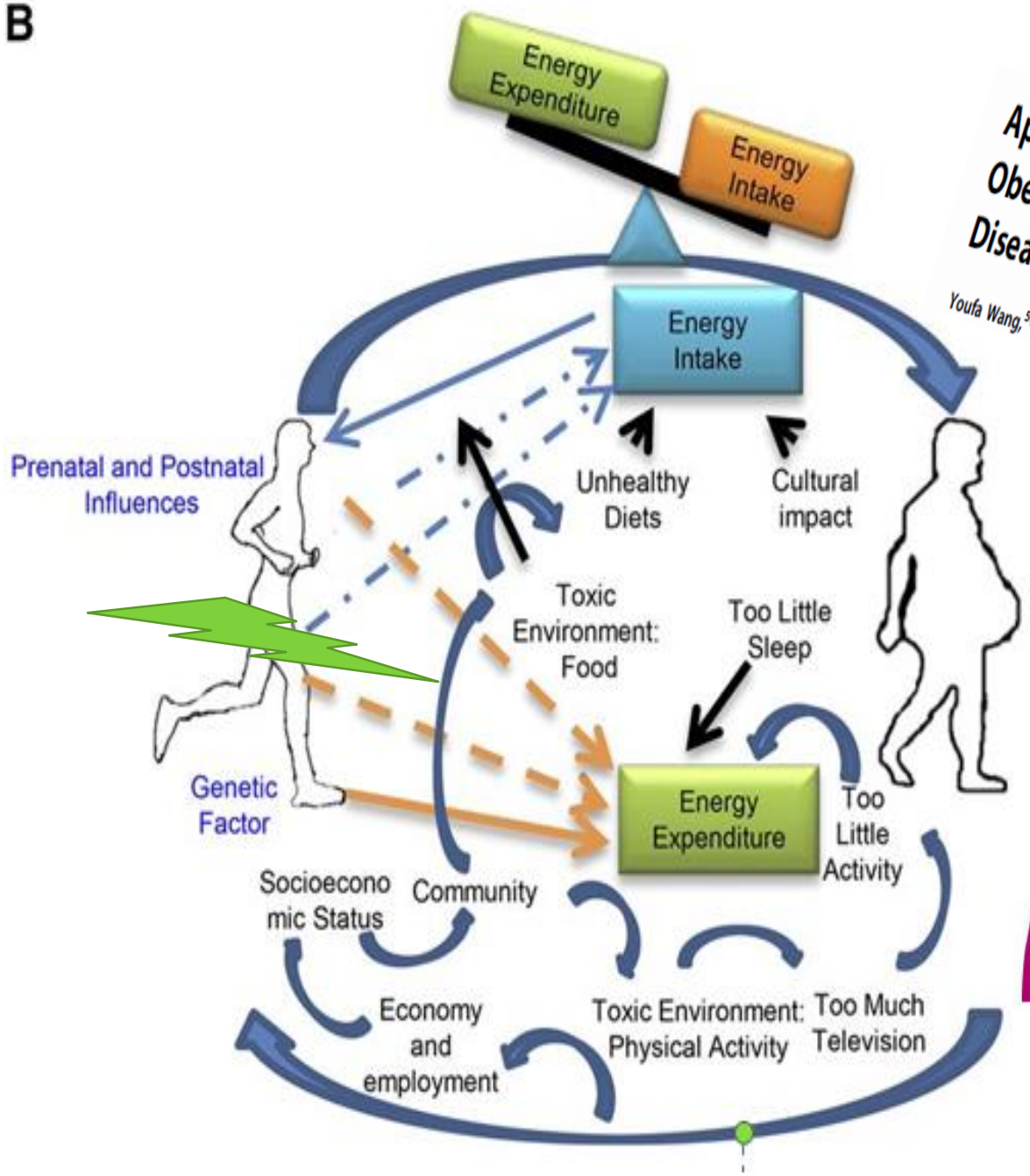
Upstream causes:

(Intake > Expenditure)

Down stream factors:

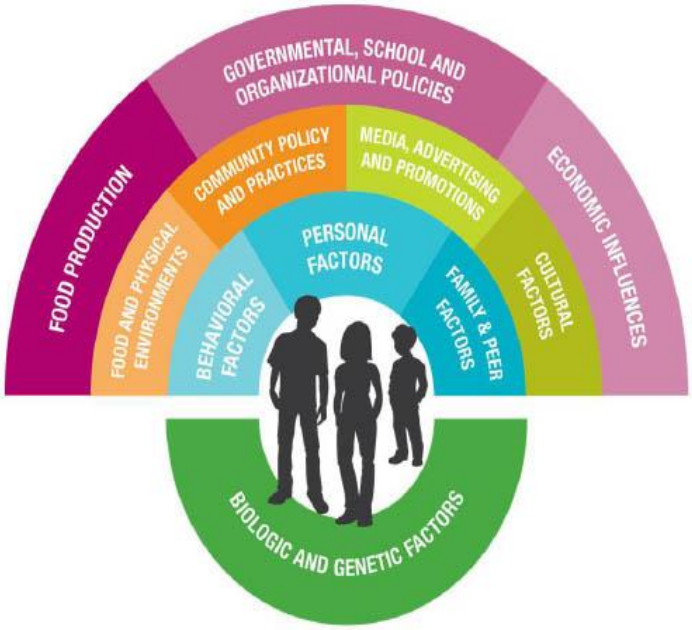
- Fetal environment
- Environmental risk factors
- Stress
- Nutrient quality
- Pharmaceutical or chemical exposure

B



Applications of Complex Systems Science in Obesity and Noncommunicable Chronic Disease Research [1–4]

Youfa Wang,[5]* Hong Xue,[5] Layla Esposito,[6] Michael J. Joyner,[7] Yaneer Bar-Yam,[8] and Terry T.-K. Huang[9]



Food choice complexity

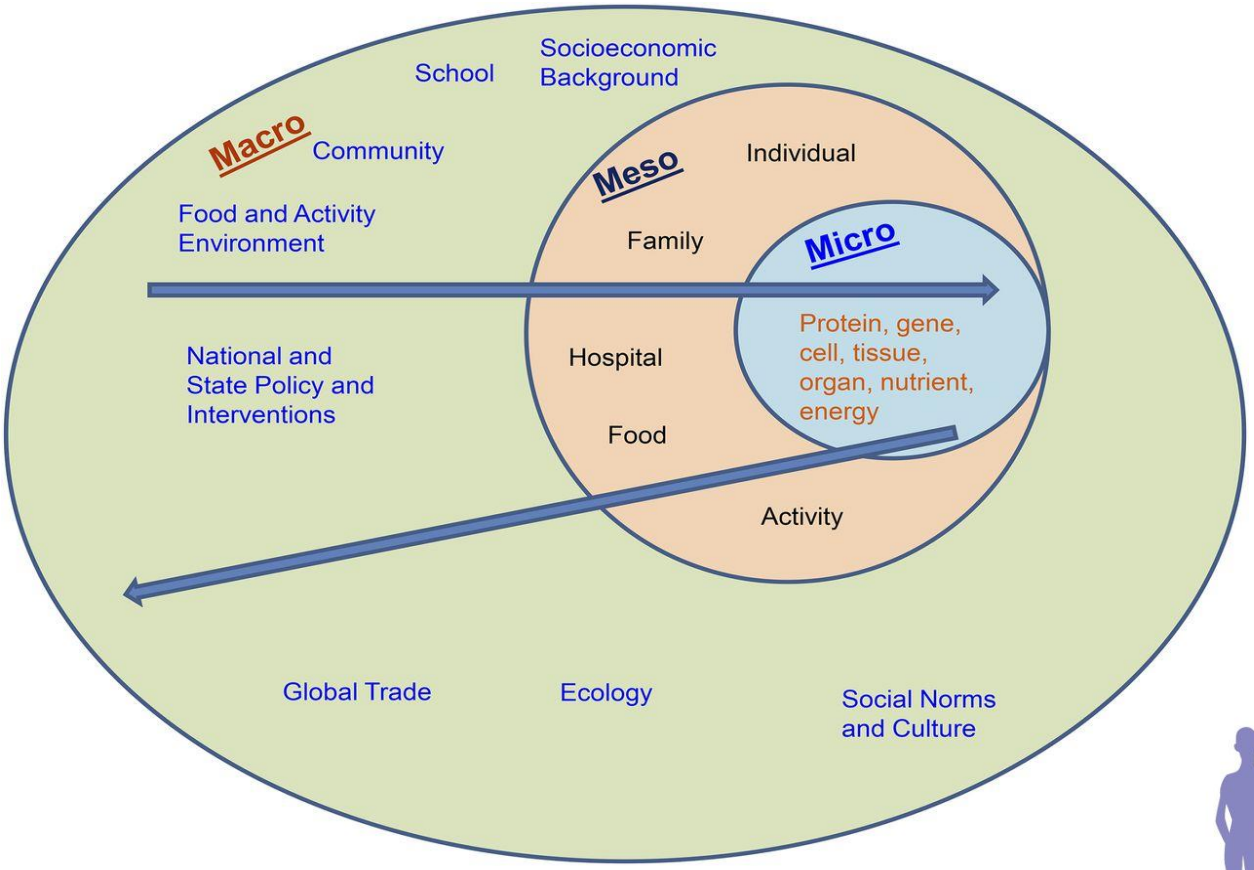
- individual
- family : strong correlation between the eating patterns of mothers and children
- Physical environment
- Social environment
- Social policy: ways that governments support farmers

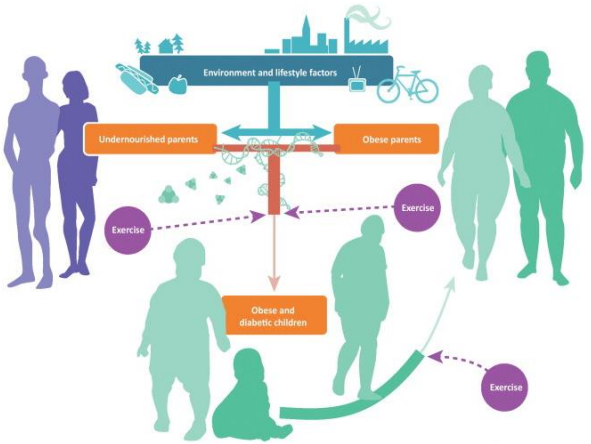
Our food systems are making people sick

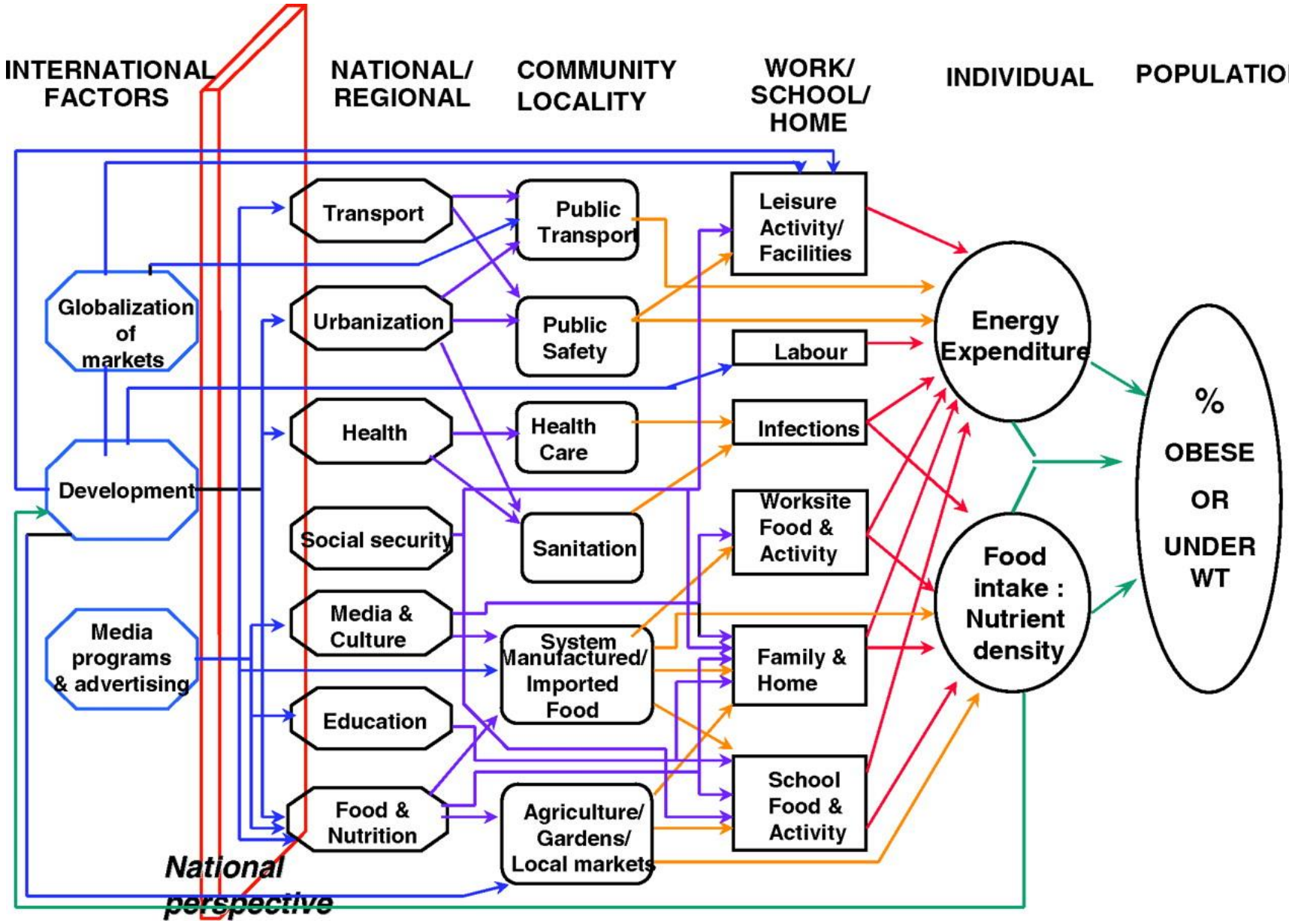
- taxing unhealthful foods and drinks
- curbing junk food marketing to all groups (not just children),
- realigning agricultural subsidies with health

Systems science research at different scales.

Youfa Wang et al. Adv Nutr 2015;6:88-95

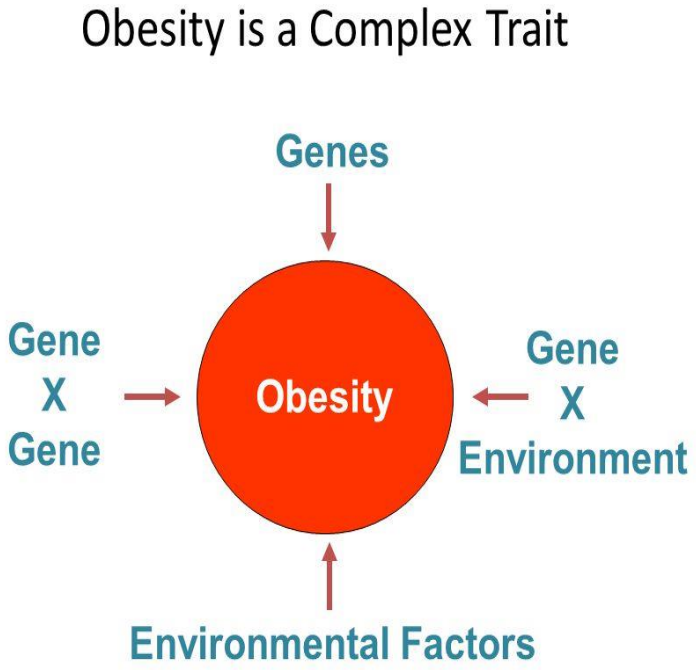


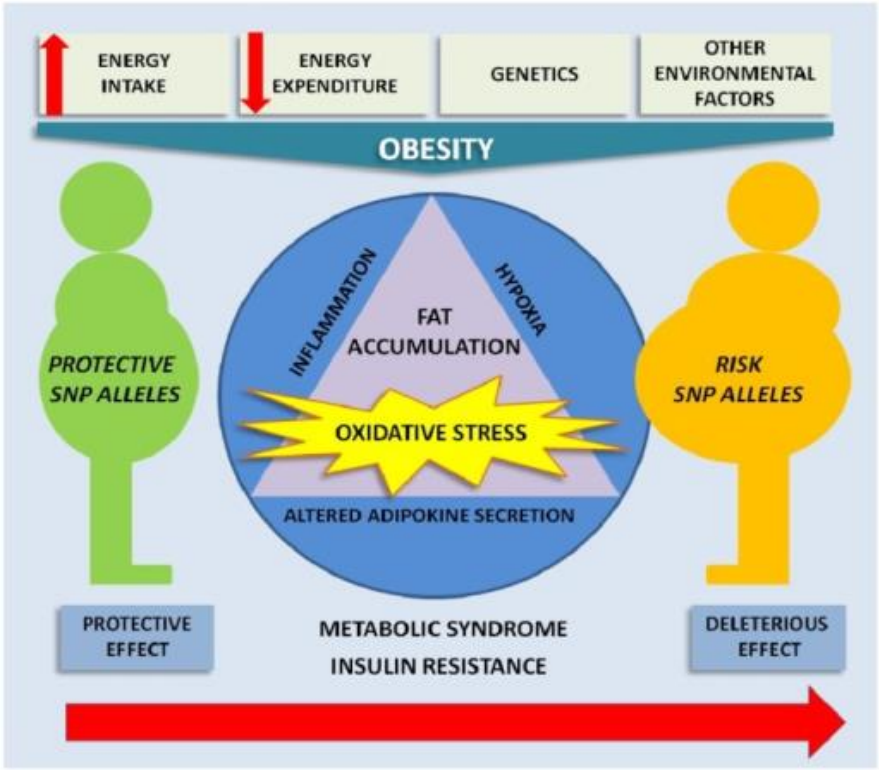



INTERNATIONAL FACTORS
NATIONAL/ REGIONAL
COMMUNITY LOCALITY
WORK/ SCHOOL/ HOME
INDIVIDUAL
POPULATION
Globalization of markets
Development
Media programs & advertising
Transport
Urbanization
Health
Social security
Media & Culture
Education
Food & Nutrition
Public Transport
Public Safety
Health Care
Sanitation
System Manufactured/ Imported Food
Agriculture/ Gardens/ Local markets
Leisure Activity/ Facilities
Labour
Infections
Worksite Food & Activity
Family & Home
School Food & Activity
Energy Expenditure
Food intake : Nutrient density
% OBESE OR UNDER WT
National perspective

Energy balance required to maintain fat mass varies among individuals due to differences: metabolism and lipostatic set point

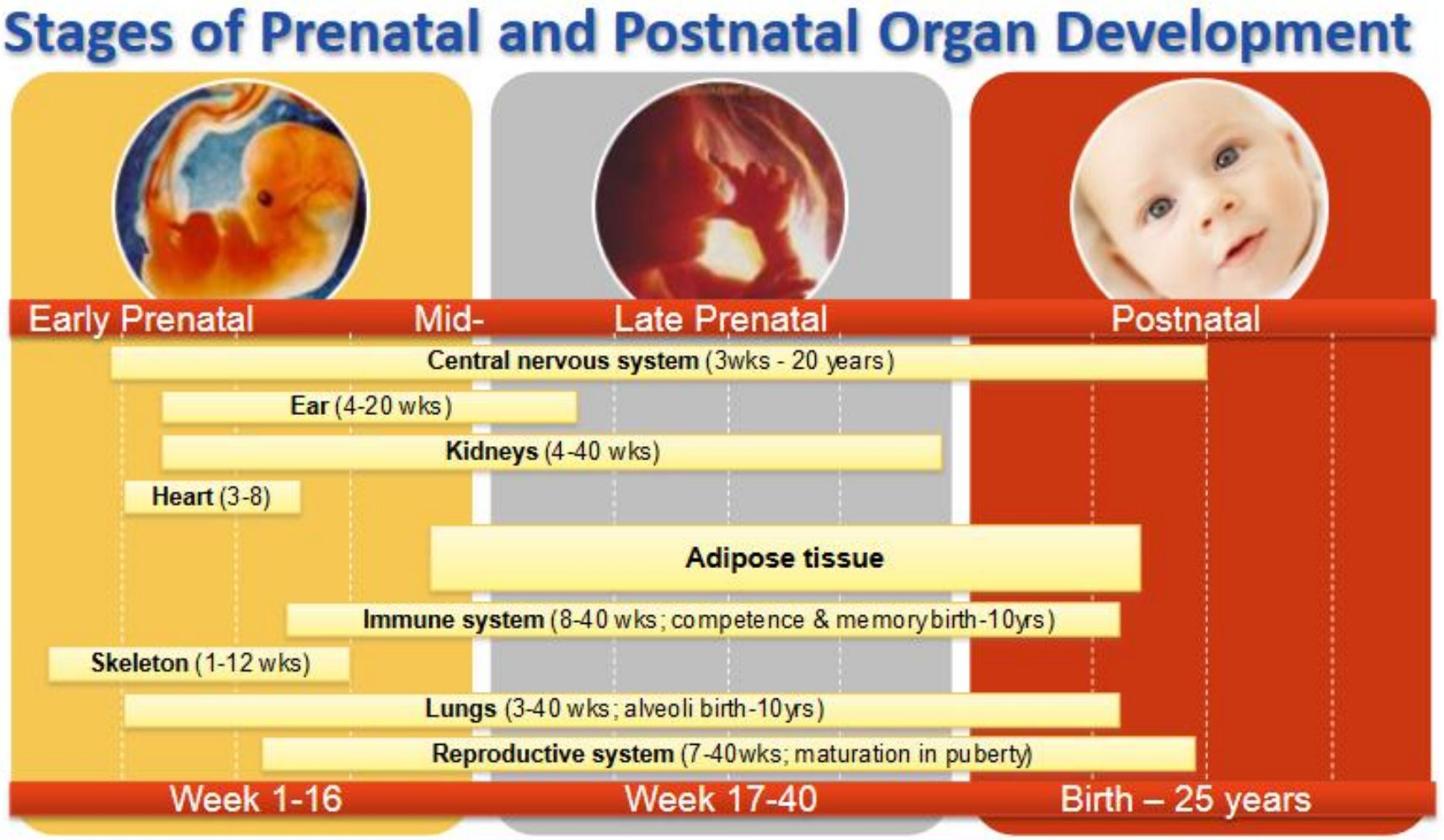
Genetic : 30-40% Environment: 60- 70 %



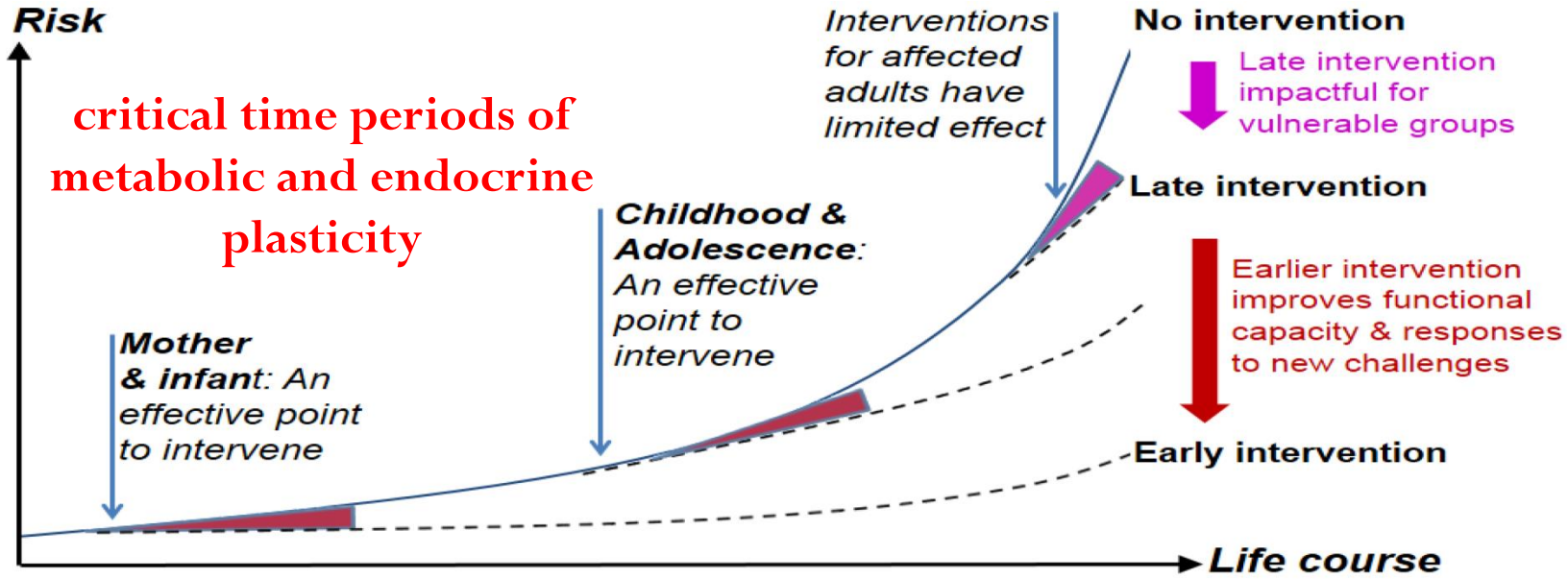


longitudinal interaction may be important for intervention strategies

Abad start lasts a life time



Source: Altshuler, K; Berg, M et al *Critical Periods in Development* NCHP Paper Series on Children's Health and the Environment, February 2003.


Risk
critical time periods of metabolic and endocrine plasticity
Interventions for affected adults have limited effect
No intervention
Late intervention impactful for vulnerable groups
Late intervention
Childhood & Adolescence: An effective point to intervene
Earlier intervention improves functional capacity & responses to new challenges
Mother & infant: An effective point to intervene
Early intervention
Life course


Plasticity
Inadequate response to new challenges


Malnutrition
Stress
Chemicals
Steroids
Epigenetic changes
DNA methylation etc.
Adult-onset
Obesity
Diabetes
Dyslipidemia
Metabolic syndrome

Most discussed topics:

Prenatal Influences on Obesity

- Mother's smoking habits during pregnancy
- Mother's weight gain during pregnancy
- Mother's blood sugar levels during pregnancy, specifically (gestational) diabetes

Postnatal Influences on Obesity

- How rapidly an infant gains weight
- Breastfeeding Vs bottle feeding:
- Duration of breastfeeding(Each additional month breastfeeding associates with 4 % lower risk of obesity later in life)
- Late introduction of solid foods at weaning
- How much an infant sleeps

Preadolescent obesity is associated with mother's pre-pregnancy weight, age and heavy smoking at conception and mother's BMI change after gestation

Conflicts cont'd

Maternal Effect Persists into F2?

Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life

RC Painter,[a] C Osmond,[b] P Gluckman,[c] M Hanson,[d] DIW Phillips,[b] TJ Roseboom[a]

[a]Department of Clinical Epidemiology and Biostatistics, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands [b]MRC Epidemiology Resource Centre, University of Southampton, Southampton, UK [c]Liggins Institute, University of Auckland, Auckland

- F1 women exposed to famine as fetuses had F2 babies with ↑ neonatal adiposity & poor adult health

No Maternal, but Paternal effect?

Transgenerational effects of prenatal exposure to the 1944–45 Dutch famine

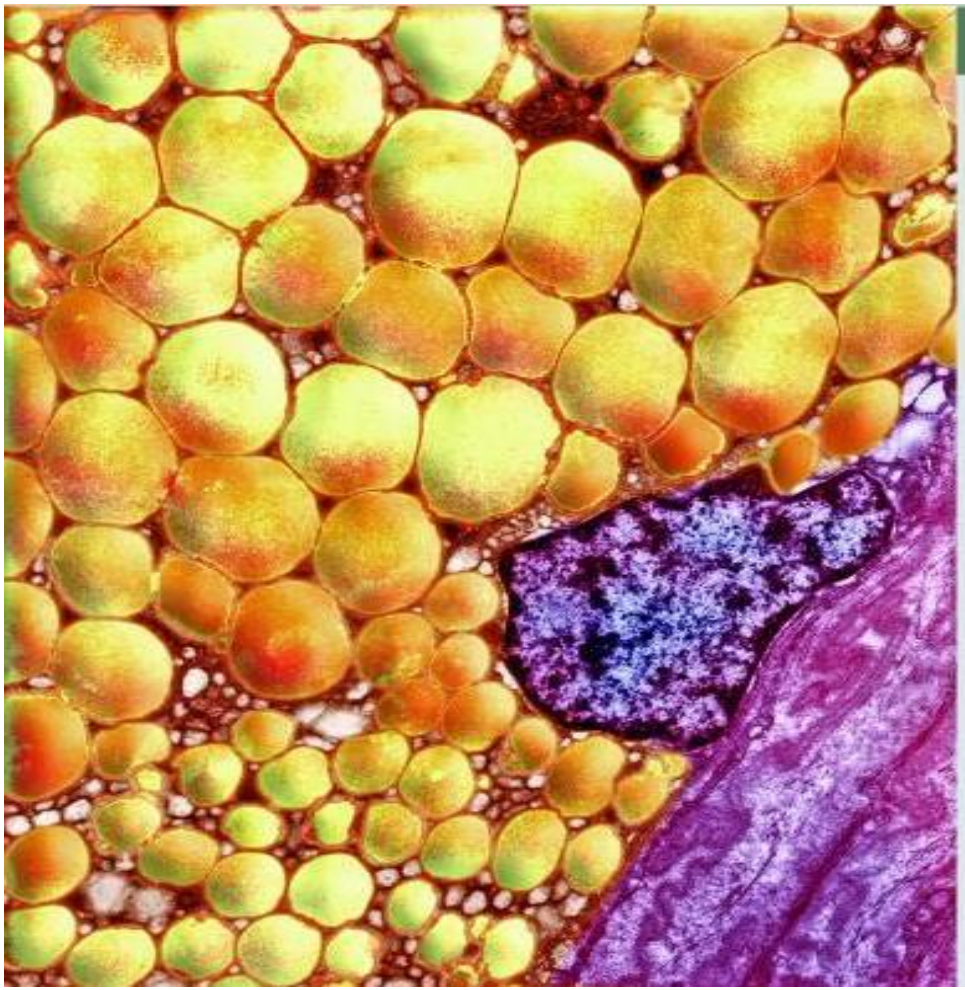
MVE Veenendaal,[a] RC Painter,[b] SR de Rooij,[a] PMM Bossuyt,[a] JAM van der Post,[b] PD Gluckman,[c] MA Hanson,[d] TJ Roseboom[a]

[a]Department of Clinical Epidemiology, Biostatistics and Bioinformatics, [b]Department of Obstetrics and Gynaecology, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands [c]Liggins Institute, University of Auckland, Auckland, New Zealand

- No transgenerational effects if the grandmother had been UN
- ↑ adiposity in offspring of prenatally UN *fathers*

Our Environment is Obesogen

- Fetal and early-life exposures to certain obesogens may alter some individuals' metabolism and fat-cell makeup for life.



Known and Suspected Obesogens

Diet
- Fructose
- Genistein
- Monosodium Glutamate

Smoking*
- Nicotine

Pharmaceuticals
- Diethylstilbestrol
- Estradiol

Industrial Chemicals
- Bisphenol A (BPA)
- Organotins
- Perfluorooctanoic Acid (PFOA)
- Phthalates
- Polybrominated Diphenyl Ethers (PBDEs)
- Polychlorinated Biphenyl Ethers (PCBs)

Organophosphate Pesticides
- Chlorpyrifos
- Diazinon
- Parathion

Other Environmental Pollutants
- Benzo[*a*]pyrene
- Fine Particulate Matter ($PM_{2.5}$)
- Lead

* Cigarette smoke is also a source of exposure to benzo[*a*]pyrene and $PM_{2.5}$.

Environmental estrogens and obesity

- Estrogen in the form of chemicals (xenoestrogens)
- Foods and plants (phytoestrogens)

- Developmental exposure to environmental estrogens during critical stages of differentiation:
- Abnormal programming of various differentiating estrogen-target tissues.
- Adipocyte differentiation
- molecular mechanisms involved in weight homeostasis
- Disrupt the programming of endocrine signaling pathways

How obesogenic compounds act:

- Number of fat cells
- Size of fat cells
- Hormones that affect appetite, satiety
- Food preferences
- Energy metabolism

Transgenerational effect through epigenetic changes

Endocrine Disrupting Chemicals

HERBICIDES
2,4,-D
2,4,5,-T
Alachlor
Amitro
Atrazine
Linuron
Metribuzin
Nitrofen
Trifluralin

FUNGICIDES
Benomyl
Ethylene thiourea
Fenarimol
Hexachlorobenzene
Mancozeb
Maneb
Metiram - complex
Tri-butyl-tin
Vinclozolin
Zineb

METALS

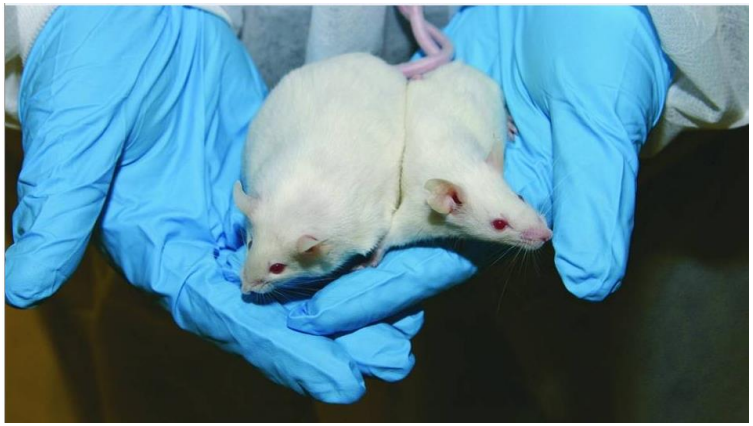
INSECTICIDES
Aldicarb
beta-HCH
Carbaryl
Chlordane
Chlordecone
DBCP
Dicofol
Dieldrin
DDT and metabolites
Endosulfan
Heptachlor / H-epoxide
Lindane (gamma-HCH)
Malathion
Methomyl
Methoxychlor
Oxychlordane
Parathion
Synthetic pyrethroids
Transnonachlor
Toxaphene

INDUSTRIAL CHEMICALS
Bisphenol - A
Polycarbonates
Butylhydroxyanisole
Cadmium
Chloro- & Bromo-diphenyl
Dioxins
Furans
Lead
Manganese
Methyl mercury
Nonylphenol
Octylphenol
PBDEs
PCBs
Pentachlorophenol
Penta- to Nonylphenols
Perchlorate
PFOA
p-tert-Pentylphenol
Phthalates
Styrene

Testosterone synthesis inhibitor
Thyroid hormone disruptor
Estrogen receptor agonist
Androgen receptor antagonist

Role of environmental chemical exposures in obesity:

- Since 2011
  - Presidential Task Force on Childhood Obesity
  - National Institutes of Health (NIH) Strategic Plan for Obesity Research.



the 1970s in which low-dose chemical exposures were associated with weight gain in experimental animals.

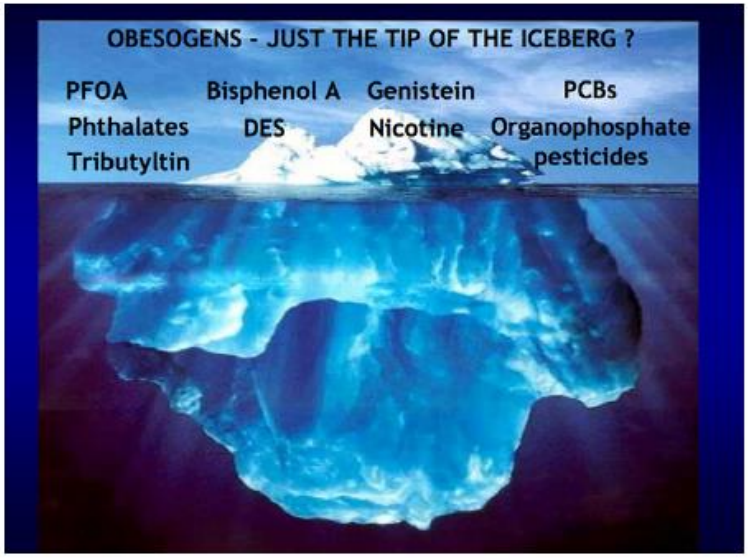


Fig. 2. The "tip of the iceberg" indicates that while there is evidence that exposure during development to a few endocrine disrupting chemicals results in obesity in laboratory animals studies, only a few chemicals have been studied. It is thus possible that many more chemicals will be found to impact obesity.

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Molecular and Cellular Endocrinology

Volume 304, Issues 1–2, 25 May 2009, Pages 90-96

Review

Role of nutrition and environmental endocrine disrupting chemicals during the perinatal period on the aetiology of obesity ☆

Jerrold J. Heindel [a], Frederick S. vom Saal [b]

Developmental exposure to environmental chemicals

Interaction of nutrition and environmental chemical exposures

Endocrine disrupting chemicals can create abnormalities in **homeostatic control** systems required to maintain a normal body weight throughout life

Molecular and Cellular Endocrinology
Volume 304, Issues 1–2, 25 May 2009, Pages 90-96

Review

Role of nutrition and environmental endocrine disrupting chemicals during the perinatal period on the aetiology of obesity ☆

Jerrold J. Heindel [a], Frederick S. vom Saal [b]

The developmental basis of obesity.

An emerging hypothesis is that the obesity epidemic could be due to the interaction of nutrition and chemical exposures during vulnerable windows in development

We hypothesize that environmental agents and/or nutrition act during development to:
Alter the pathways responsible for control of adipose tissue development
Increase the number of fat cells
Alter food intake and metabolism
Alter insulin sensitivity and lipid metabolism via effects on pancreas, adipose tissue, liver, GI tract, brain and muscle

The consequence is alteration of the "setpoint" or sensitivity for developing obesity later in life.

Gene–environment interaction: the focus is on development

The environment alters gene expression during vulnerable windows in development, resulting in altered epigenetic signals and increased susceptibility to obesity later in life.

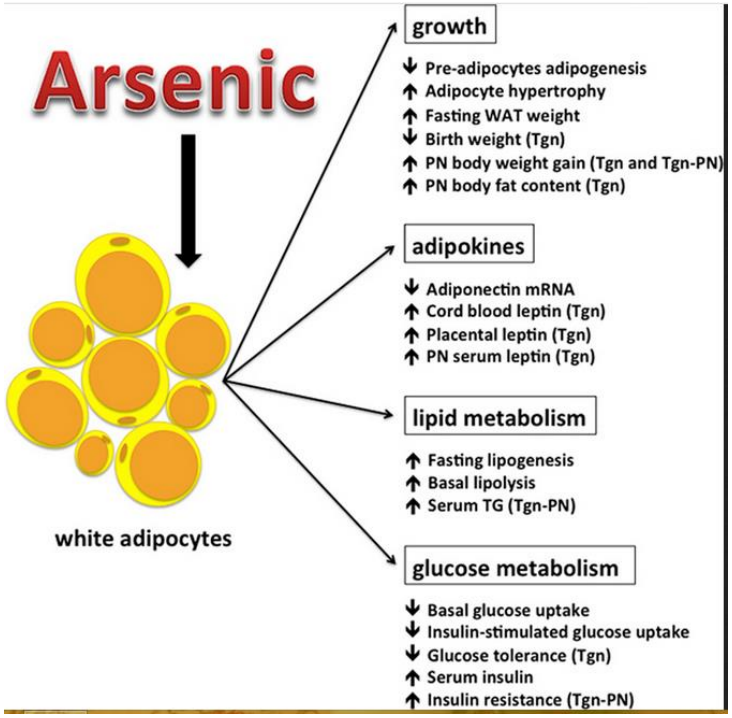
Molecular and Cellular Endocrinology
Volume 452, 5 September 2017, Pages 25-32

Effects of arsenic on adipocyte metabolism: Is arsenic an obesogen?

Zeltzin A. Ceja-Galicia [a, b, 1], Alberto Daniel [a, c, 1], Ana María Salazar [a], Pablo Pánico [a, d], Patricia Ostrosky-Wegman [a], Andrea Díaz-Villaseñor [a]

Highlights

- Arsenic diminishes pre-adipocytes adipogenesis and increases size of mature adipocytes.
- Arsenic increases basal lipolysis *and* down-regulates adiponectin mRNA expression.
- Arsenic reduces basal and insulin-stimulated glucose uptake.
- Arsenic induces transgenerational effects related to the metabolism of adipose tissue.
- Arsenic is a potential obesogeno that impairs basic metabolic functions of adipocytes.

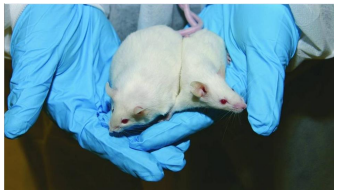


Perinatal exposure to bisphenol A alters early adipogenesis in the rat.

Environ Health Perspect. 2009;117(10):1549–1555.

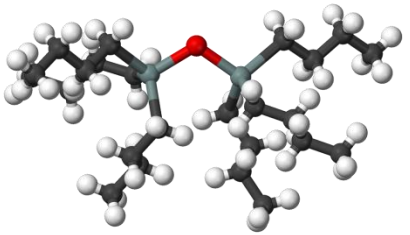
bisphenol A (BPA) : in medical devices, in the lining of some canned foods, and in cash register receipts.

- Direct effects on adipogenesis
- Reduces the number of fat cells but programs them to incorporate more fat, so there are fewer but very large fat cells
- pancreas development and function
- insulin-resistant phenotype
  - In animals, BPA exposure is producing in animals the kind of outcomes that we see in humans born light at birth: an increase in abdominal fat and glucose intolerance."



Obesity (Silver Spring). 2015 September ; 23(9): 1864–1871. doi:10.1002/oby.21174.

Tributyltin Differentially Promotes Development of a Phenotypically Distinct Adipocyte



- TBT to pregnant mice:
- Heavier offspring
- even if they eat normal food, they get slightly fatter."
- Activation of proliferator–activated receptor gamma PPARγ:
  - Preadipocyte…… adipocyte
  - PPARγ selectively causes multipotent stromal cells to differentiate into bone or fat
  - TBT exposure caused these stem cells to show an increased commitment to becoming adipocytes at the expense of the bone lineage
  - In fact cell….., puts more fat in the cell… more and bigger fat cells

ELSEVIER

Science of The Total Environment

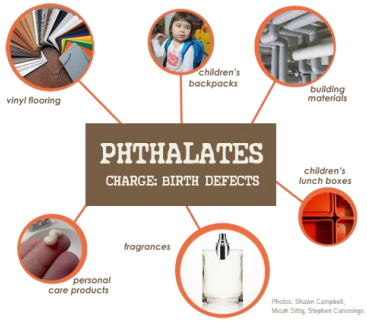
Volume 612, 15 January 2018, Pages 1072-1078

Relationship between maternal phthalate exposure and offspring size at birth

Phthalates increase risk of obesity

plasticizers and vehicles for cosmetic ingredients

- Direct effects on liver function… (hepatic fat accumulation)
- Disrupt thyroid function …..(dysregulation of energy balance and metabolism)



J Steroid Biochem Mol Biol. 2011 Oct; 127(1-2): 16–26.
Published online 2011 Mar 21. doi: 10.1016/j.jsbmb.2011.03.011

Endocrine disrupting properties of perfluorooctanoic acid

- PFOA is a known developmental toxicant
  - Exposure during pregnancy has induced both early and later life adverse effect
- perfluorooctanoic acid (PFOA), a potential endocrine disruptor and known PPARγ agonist
- Elevated levels of leptin….affects appetite and metabolism.

Molecular and Cellular Endocrinology 304 (2009) 84–89

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journal homepage: www.elsevier.com/locate/mce

Review

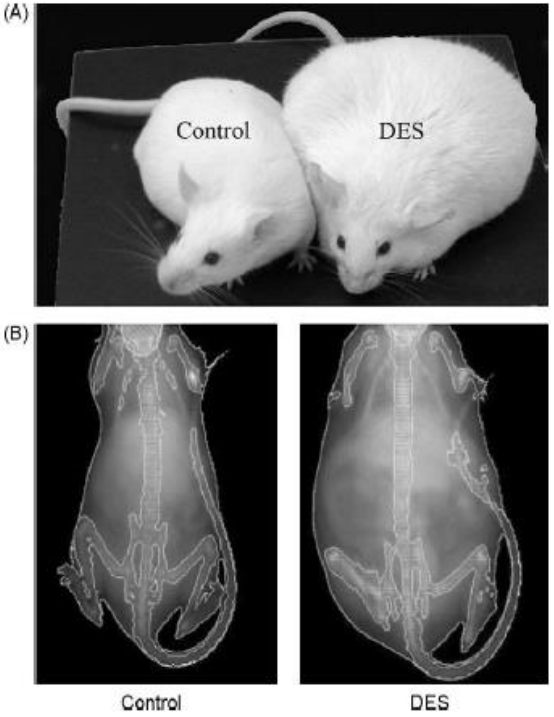
Environmental estrogens and obesity

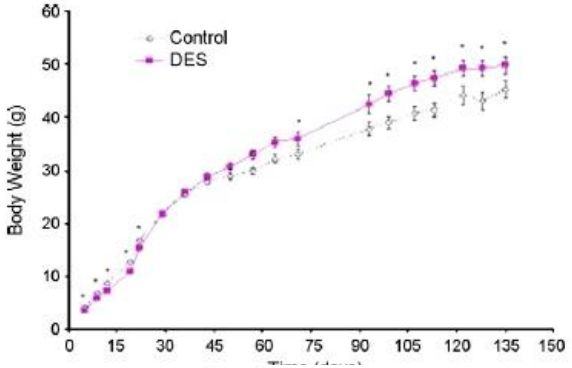
Retha R. Newbold *, Elizabeth Padilla-Banks, Wendy N. Jefferson

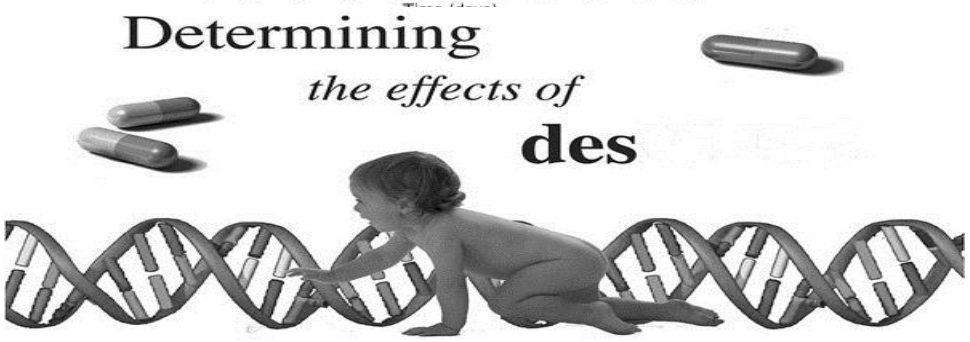
Developmental Endocrinology and Endocrine Disruptor Section, Laboratory of Molecular Toxicology, National Institute of Environmental Health Sciences, NIH, DHHS, Research Triangle Park, NC 27709, United States

diethylstilbestrol (DES)

estimated 3 million pregnant women in the USA were prescribed DES from 1941 through 1971





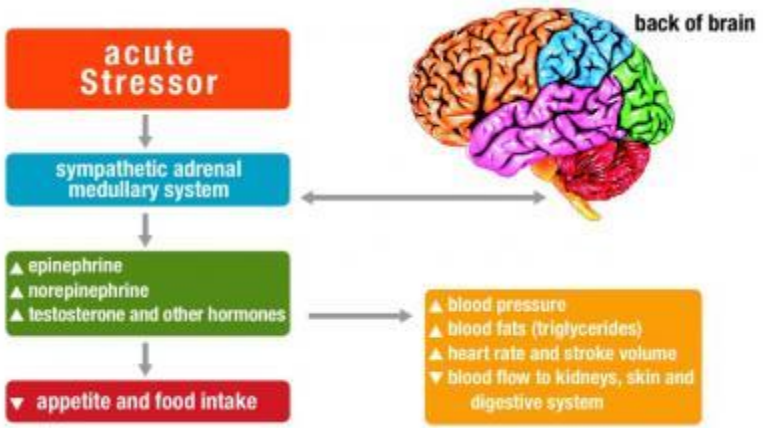


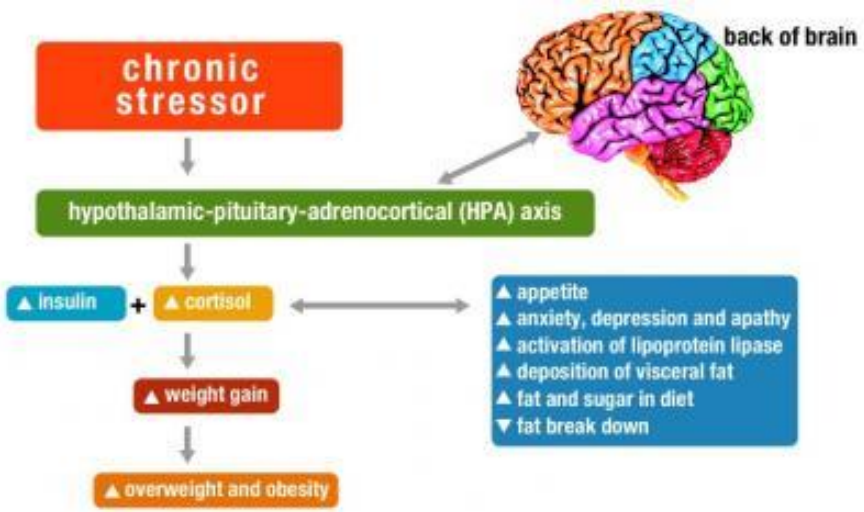
Endocrine disruptors exhibit an inverted U-shaped dose–response curve

- some endocrine disruptors have greater effects at low than at high doses
- most toxic response occurs at intermediate doses
  - BPA affected rodent fat cells at very low doses, 1,000 times below the dose that regulatory agencies presume causes no effect in humans, whereas at higher doses he saw no effect.
- High doses cause "receptor down regulation
  - Receptors typically respond to very low levels of hormone, whereas high levels of a chemical may actually cause receptors to shut down altogether, preventing any further; different mechanisms may be operating

A pathway from stress to obesity

- inflammatory mechanisms
- Arousal of the hypothalamic–pituitary–adrenal axis:
- cortisol levels
- Metabolic disruption
- Increased hunger

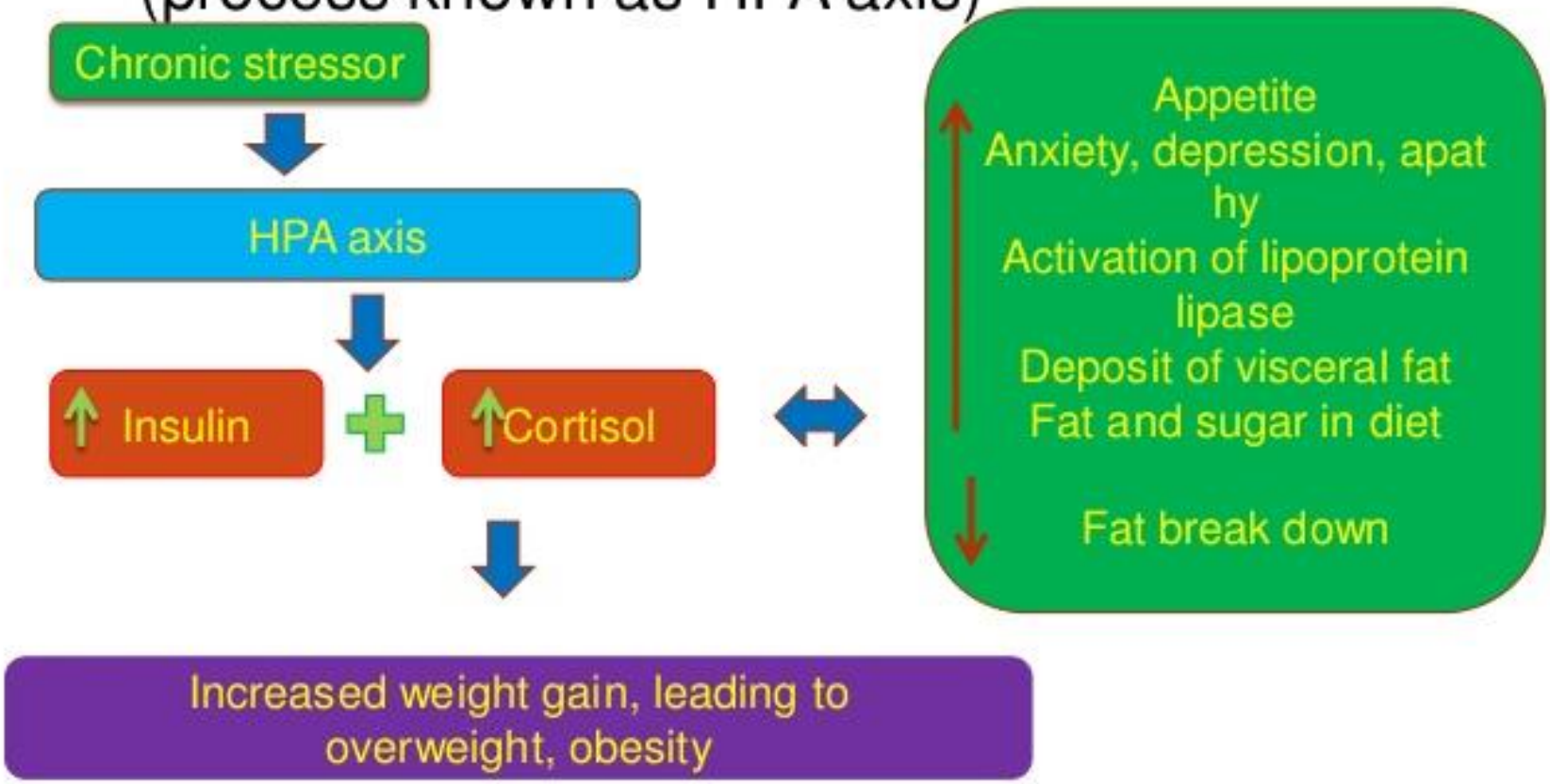




Bidirectional causation of Depression and obesity in both children and adults

The body responds to **chronic stress**

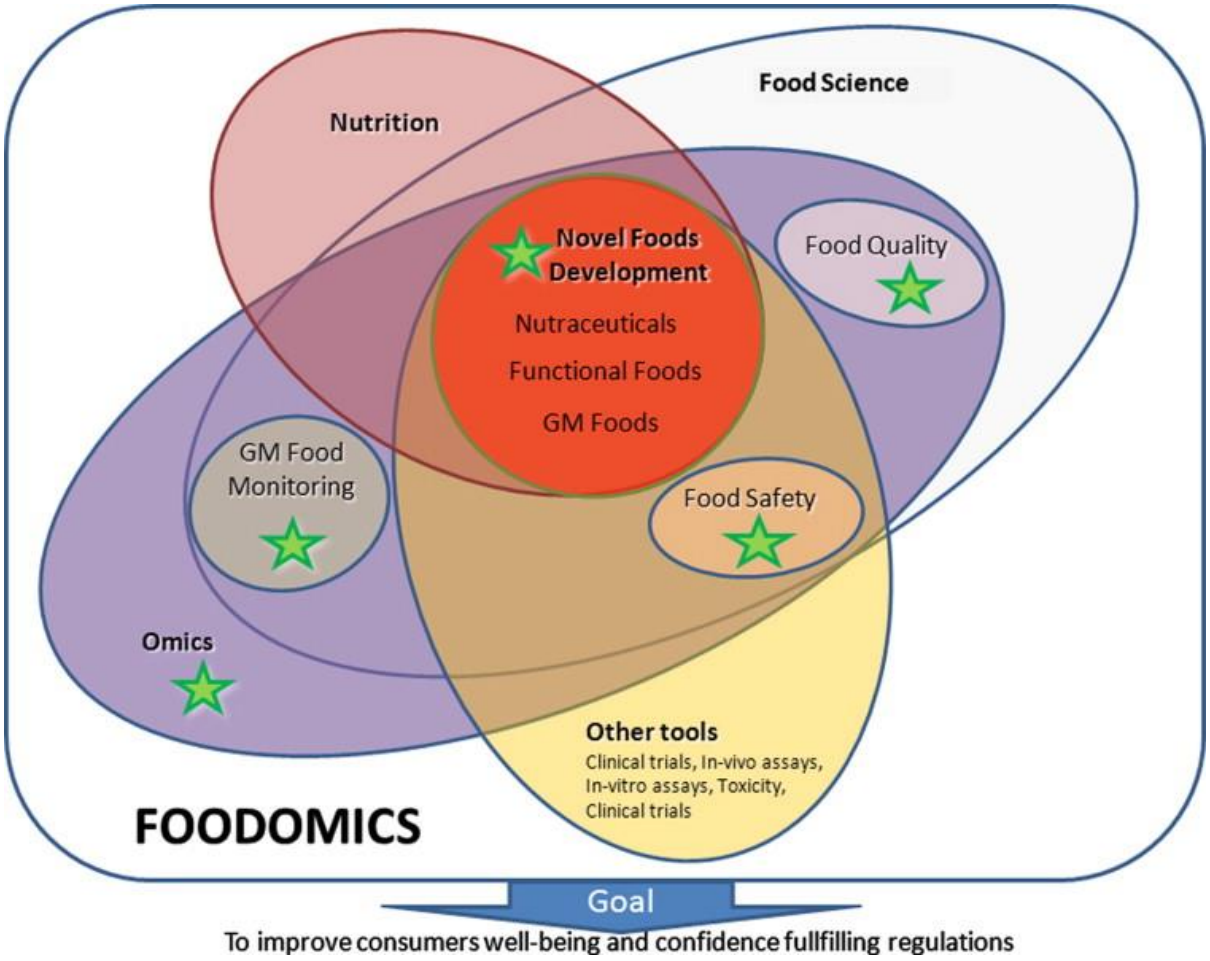
- Release of cortisol via message hormone ACTH (process known as HPA axis)



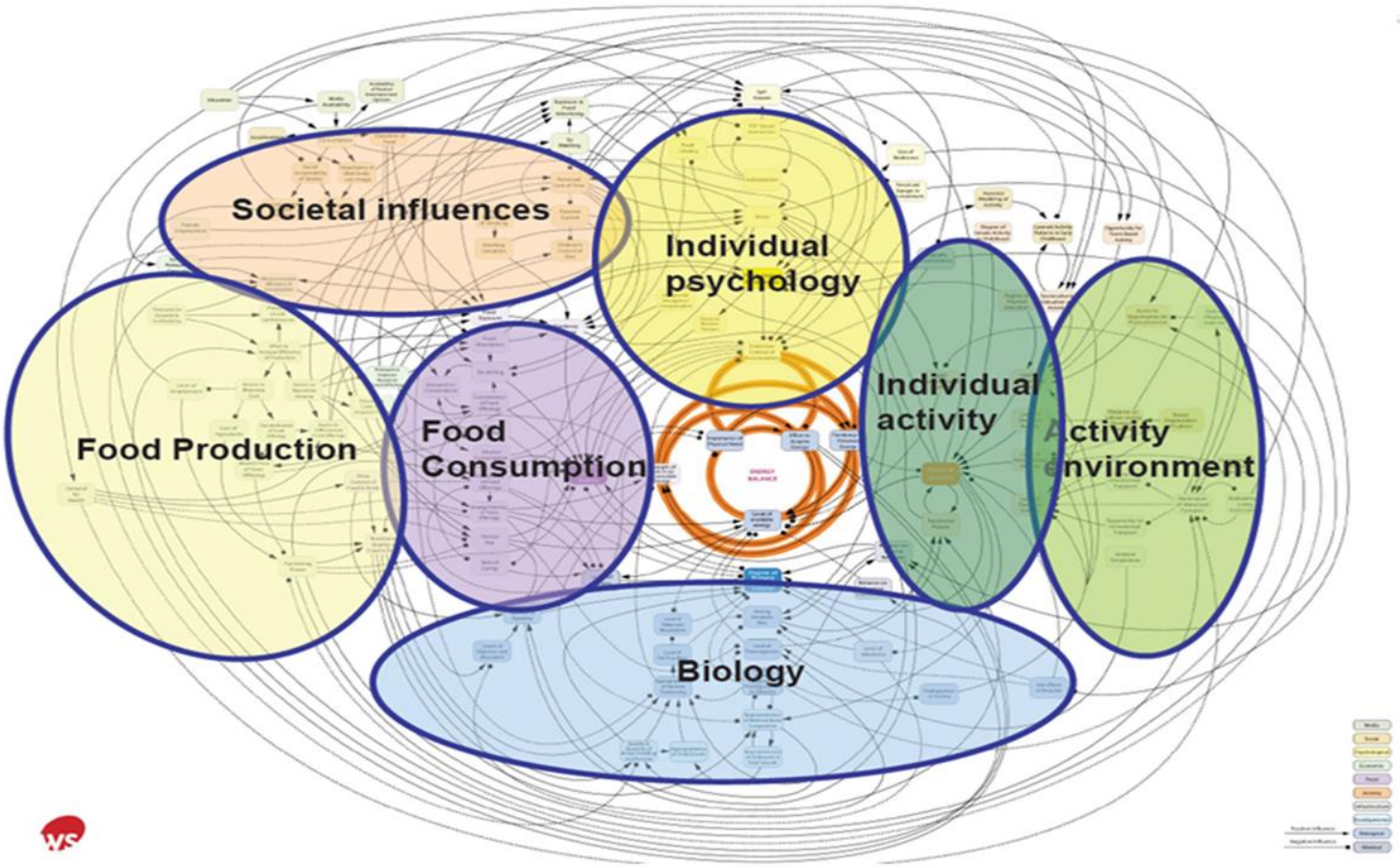
key messages for clinicians to give to women of childbearing age limit the current epidemic of obesity:

- Strive for a healthy weight before pregnancy.
- Don't smoke during pregnancy.
- Aim for a reasonable weight gain during pregnancy.
- Breastfeeding
- Ensure infants get adequate sleep during the first few years of life.
- Remove toxins … loose weight
- Avoidance of chemical modifiers especially during critical windows of development
- Stress reduction

- Improving the food environment will require concerted work across a wide range of sectors and settings, from government and industry to local institutions and families
- Emergence of new science of foodomics approach



whole system really does influence obesity



Thanks for your Attention

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