A Developmental Programming Perspective on Health and Disease Risk

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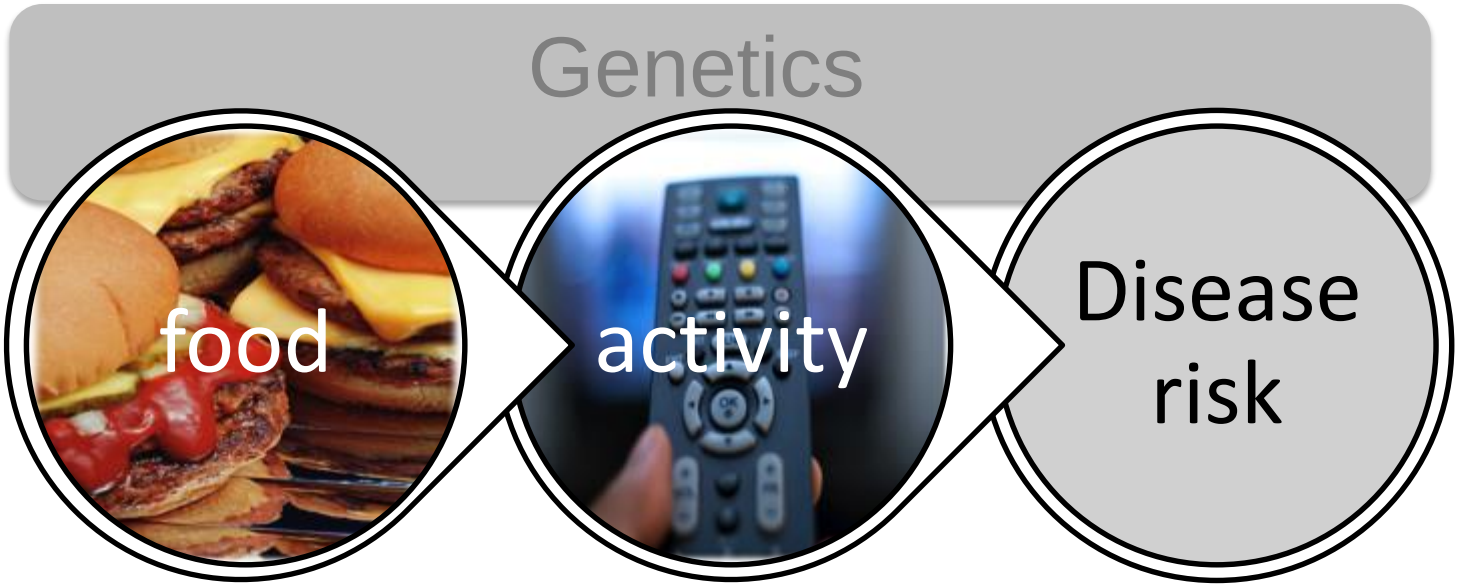
7th National Biennial Conference on Adolescents and Adults with Fetal Alcohol Spectrum Disorder (FASD) April 7 2016

What determines our health & disease risk?

Worldwide availability and consumption of highly processed, energy dense, low nutritional value foods

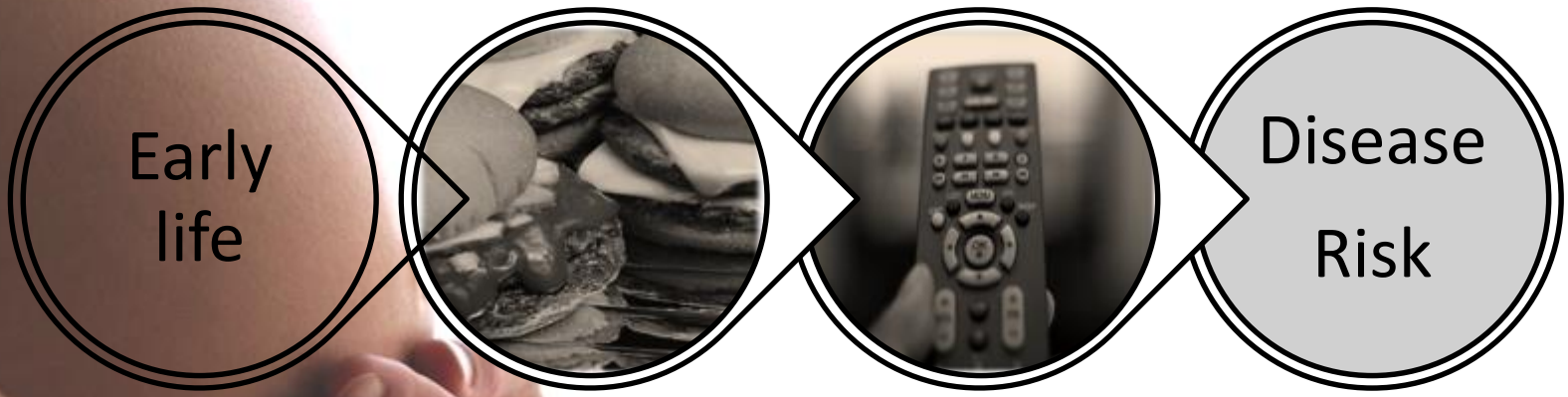
Decreased energy expenditure and increased mechanization

What determines our health potential?



What determines our health & disease risk?

Interactions between early life and postnatal environments



Historical data

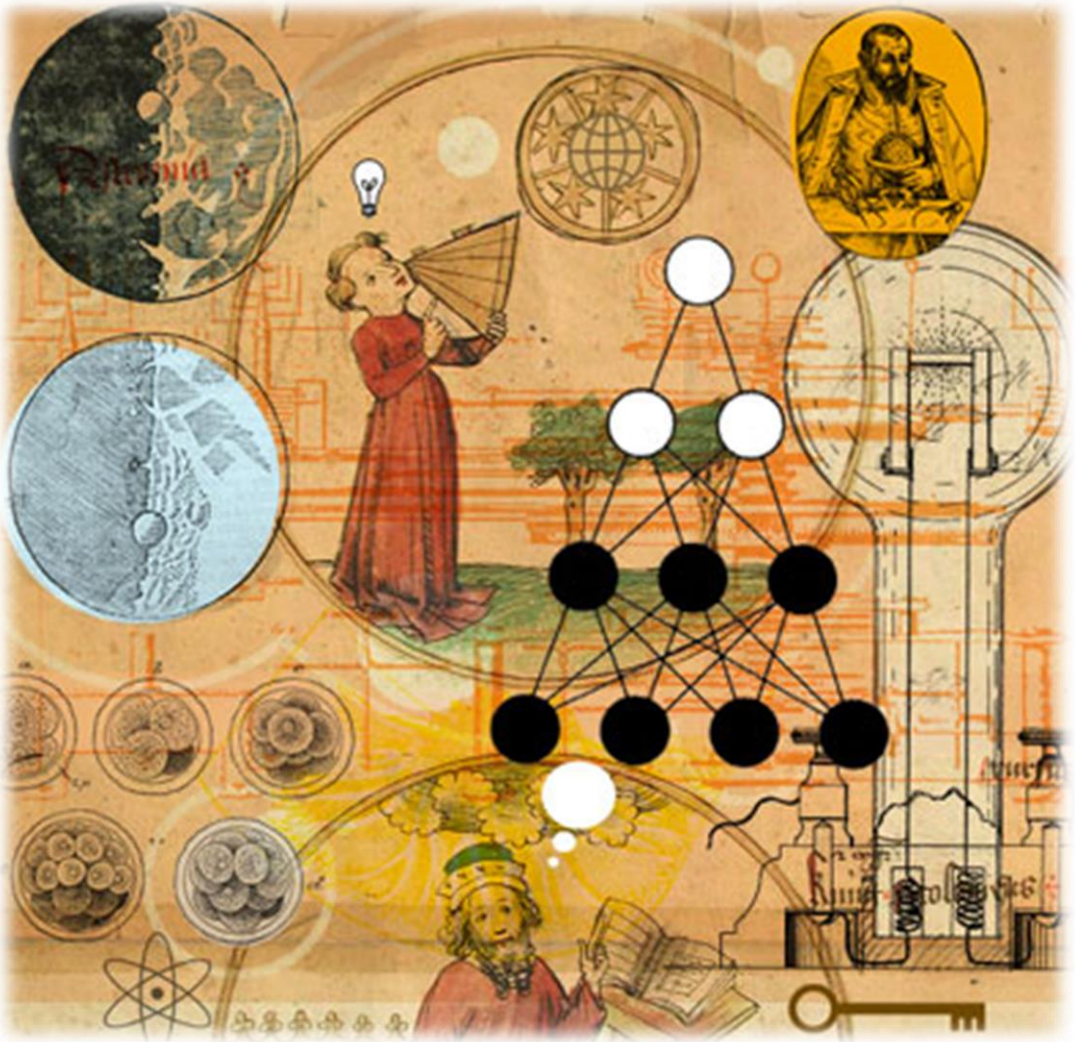


FIG 3.1—*Mothers in Hitchin, Hertfordshire at the turn of the century.*

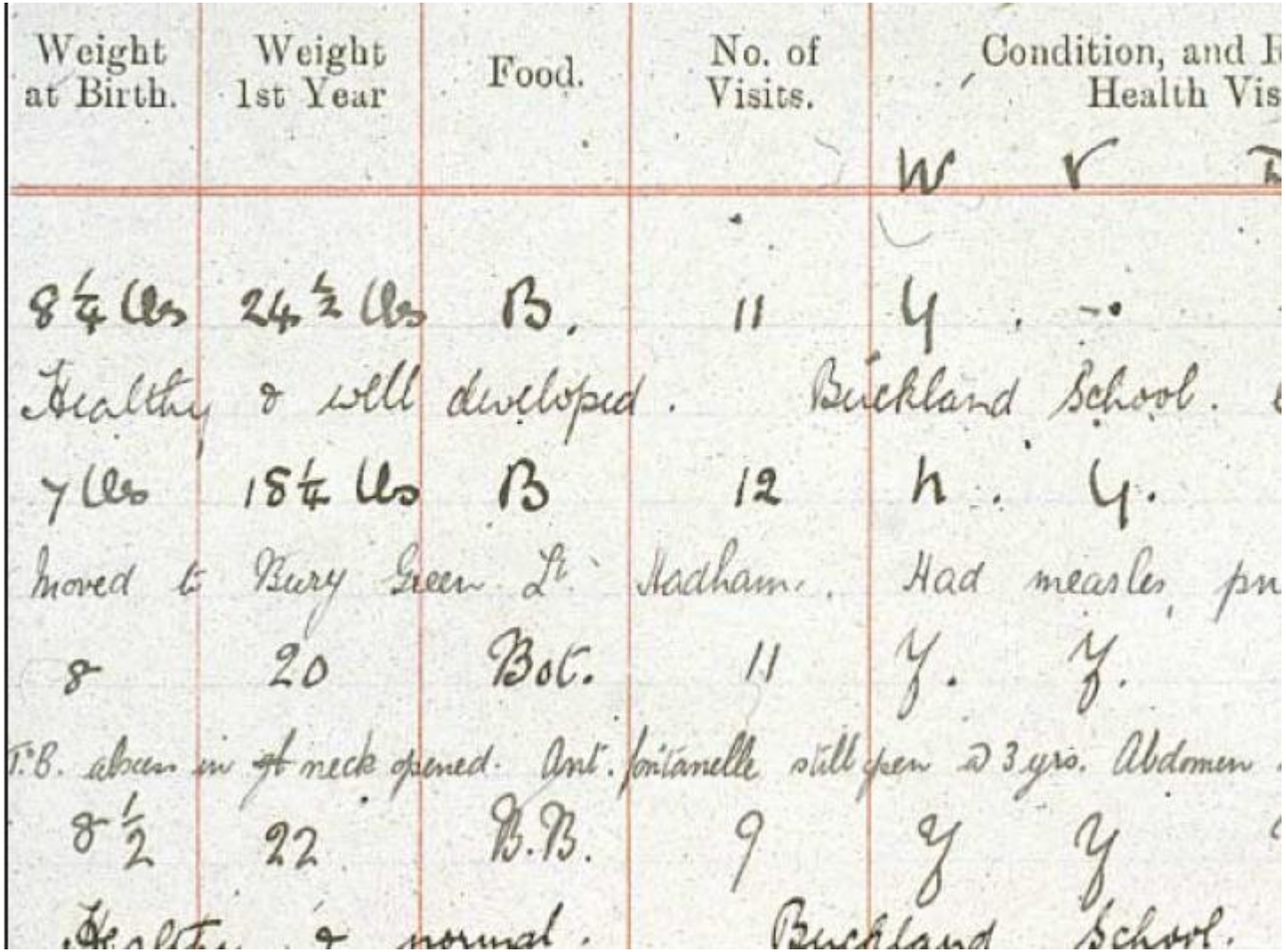
Hertfordshire, UK, early 1900s

FIG 3.3—*Ethel Margaret Burnside aged 17 years.*

Ethel Margaret Burnside

- Chief health inspector and Lady Inspector of Midwives
- Records enabled tracing of 16000 men and women born in Hertfordshire between 1911-1930

Information from one of Miss Burnside's birth and infant growth records, *c*1917



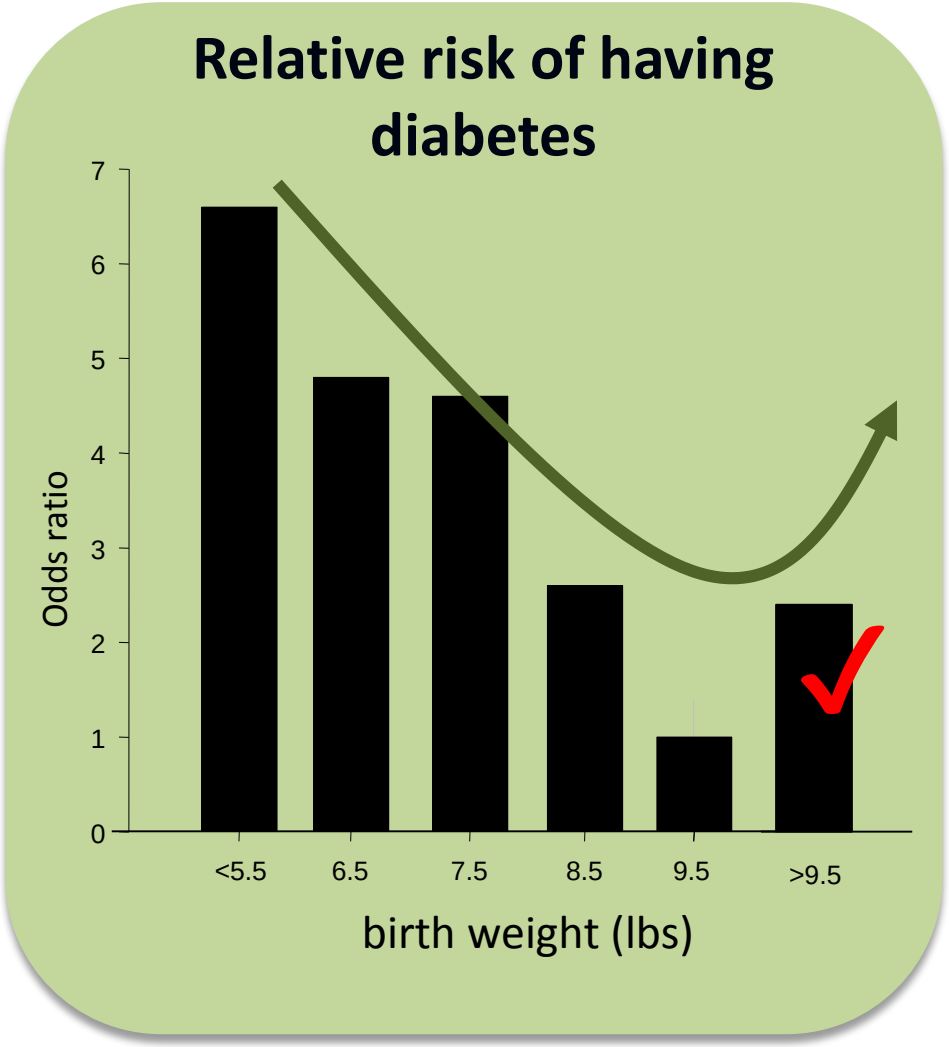
Weight at Birth.	Weight 1st Year	Food.	No. of Visits.	Condition, and H Health Vis
				W V
8¼ lbs	24½ lbs	B.	11	Y . -
Healthy & well developed.				Buckland School.
7 lbs	18¼ lbs	B	12	h . Y.
Moved to Bury Green Lt.			Stadham.	Had measles, pn
8	20	Bot.	11	Y. Y.
T.B. absent in ft neck opened. Ant. fontanelle still open @ 3 yrs. Abdomen				
8½	22	B.B.	9	Y Y
Healthy & normal.				Buckland School.

Early studies in early life origins of health and disease risk

Prof David Barker

What is the relationship between chronic disease and birth weight?

Birth weight is associated with chronic disease risk



What did Dr Barker find?

- relationship between birth weight and type 2 diabetes in adult men

Barker & Osmond The Lancet 1(8489): 1077 1986

"Developmental Programming"

The fetal and infant origins of adult disease

The womb may be more important than the home

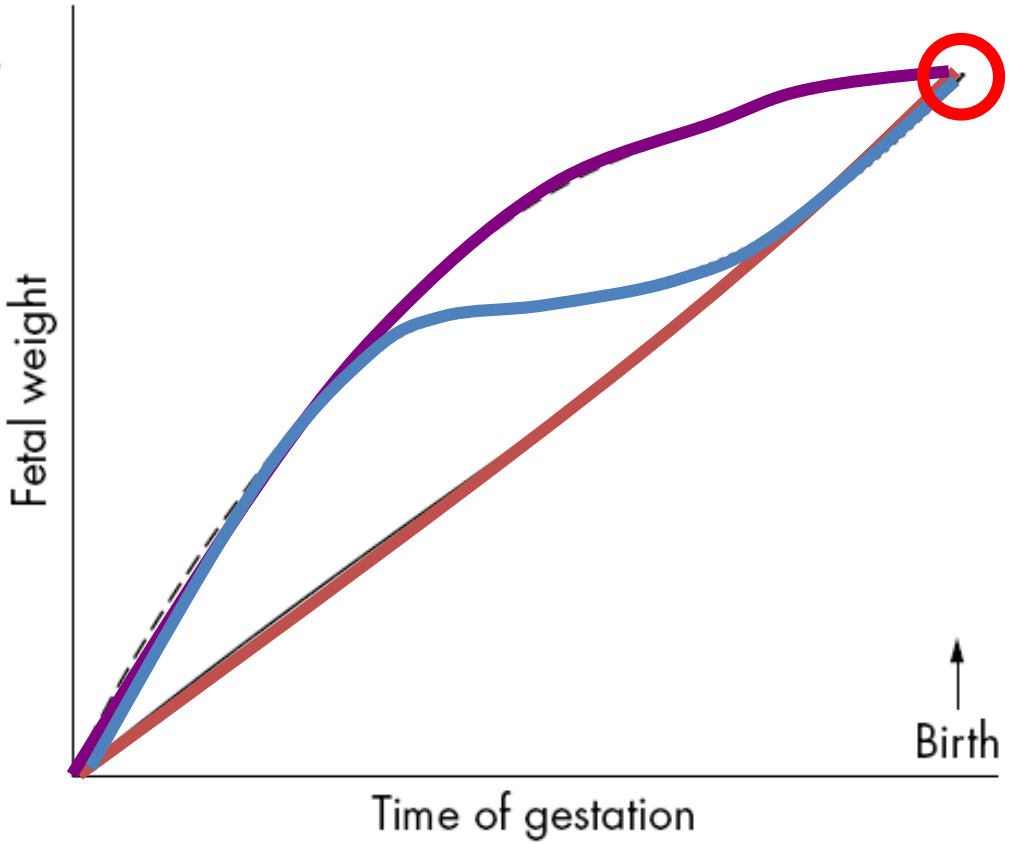
BMJ VOLUME 301 17 NOVEMBER 1990

Developmental Programming

Birth weight is a “marker” of the prenatal environment

Low birth weight indicates some adversity (or insult) during the early life environment

Birth weight poor indicator of growth ***pattern***



Bloomfield et al. Arch Dis Child Fetal Neonatal Ed 91:F299 2006

How is this happening?

The fetal and infant origins of adult disease

The womb may be more important than the home

BMJ VOLUME 301 17 NOVEMBER 1990

What could be causing this?

Dutch Hunger Winter

What about nutrition?

1944 - 1945

Only 400 - 800 Calories a day


22,000 people affected by famine and cold.
Among them were pregnant women

Maternal famine→
Children born to these mothers had as adults*:

- *Obesity*
- *Type 2 diabetes*
- *High blood pressure*
- *Heart disease*

***after controlling for lifestyle and behaviour**

Schizophrenia After Prenatal Exposure to the Dutch Hunger Winter of 1944-1945

Ezra S. Susser, MD, Dr PH; Shang P. Lin, PhD

[+] Author Affiliations

Arch Gen Psychiatry. 1992;49(12):983-988.
doi:10.1001/archpsyc.1992.01820120071010

…not just “classic” chronic diseases…

Brief Report

Prenatal Exposure to Famine and Brain Morphology in Schizophrenia

Hilleke E. Hulshoff Pol, Ph.D.
Hans W. Hoek, M.D., Ph.D.
Ezra Susser, M.D., Dr.P.H.
Alan S. Brown, M.D.
Alexandra Dingemans, M.S.
Hugo G. Schnack, Ph.D.
Neeltje E.M. van Haren, M.S.
Lino Moreira Pereira Ramos, M.D.
Christine C. Gispen-de Wied, M.D., Ph.D.
René S. Kahn, M.D., Ph.D.

Objective: The authors assessed the effects of nutritional deficiency during the first trimester of pregnancy on brain morphology in patients with schizophrenia.

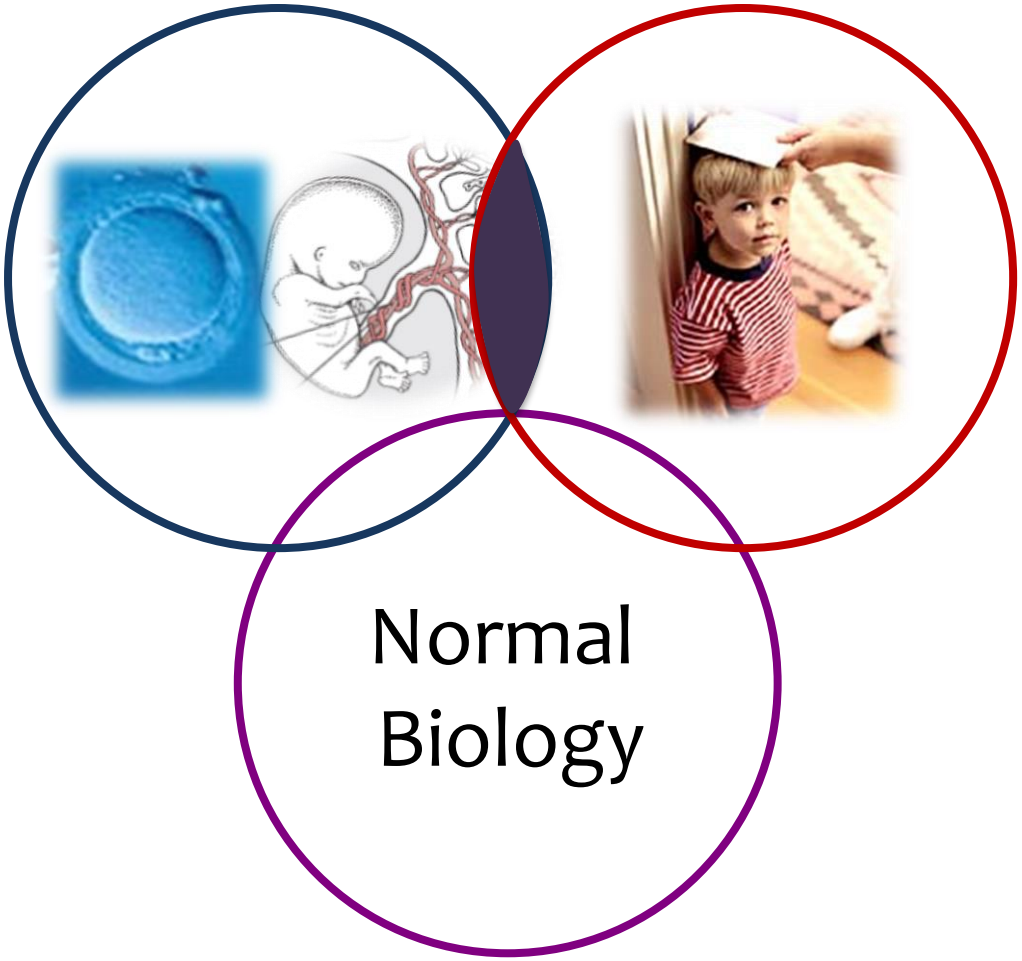
Method: Nine schizophrenic patients and nine healthy comparison subjects exposed during the first trimester of gestation to the Dutch Hunger Winter were evaluated with magnetic resonance brain imaging, as were nine schizophrenic patients and nine healthy subjects who were not prenatally exposed to the famine.

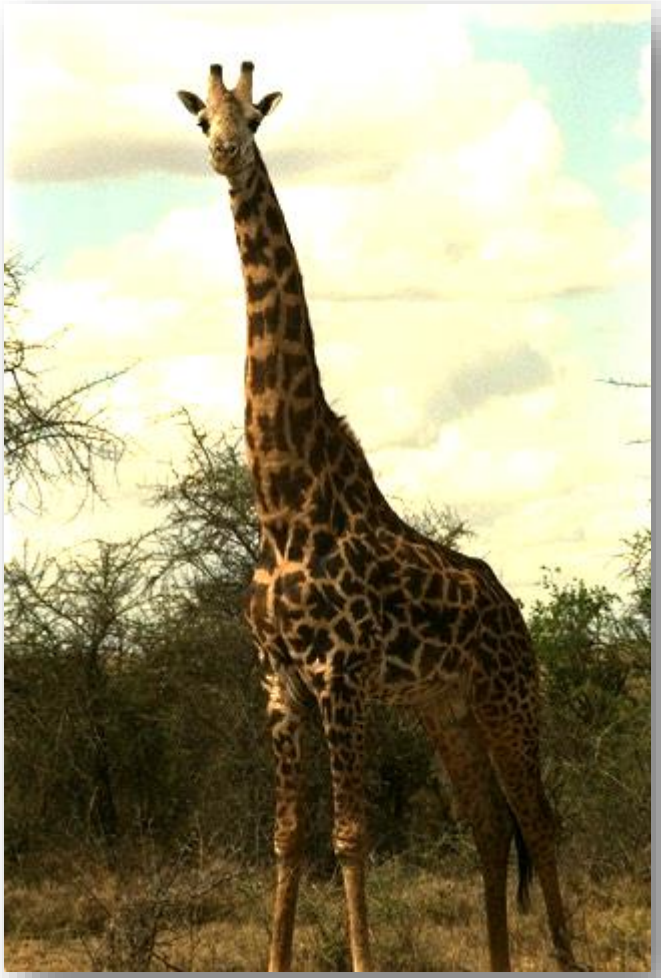
Results: Prenatal famine exposure in patients with schizophrenia was associated with decreased intracranial volume. Prenatal Hunger Winter exposure alone was related to an increase in brain abnormalities, predominantly white matter hyperintensities.

Conclusions: Nutritional deficiency during the first trimester of gestation resulted in an increase in clinical brain abnormalities and was associated with aberrant early brain development in patients with schizophrenia. Stunted brain development secondary to factors that affect brain growth during the first trimester of gestation may thus be a potential risk factor for developing schizophrenia.

(Am J Psychiatry 2000; 157:1170–1172)

What are the causes?





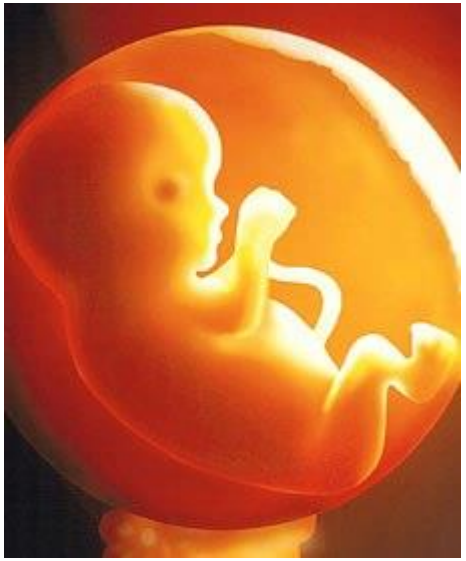
Early life adversity

Changes in biology = Disease

Changes in health expectancy and biological function

Relationships between the developmental and postnatal environment impact on health and disease risk

Developmental Environment

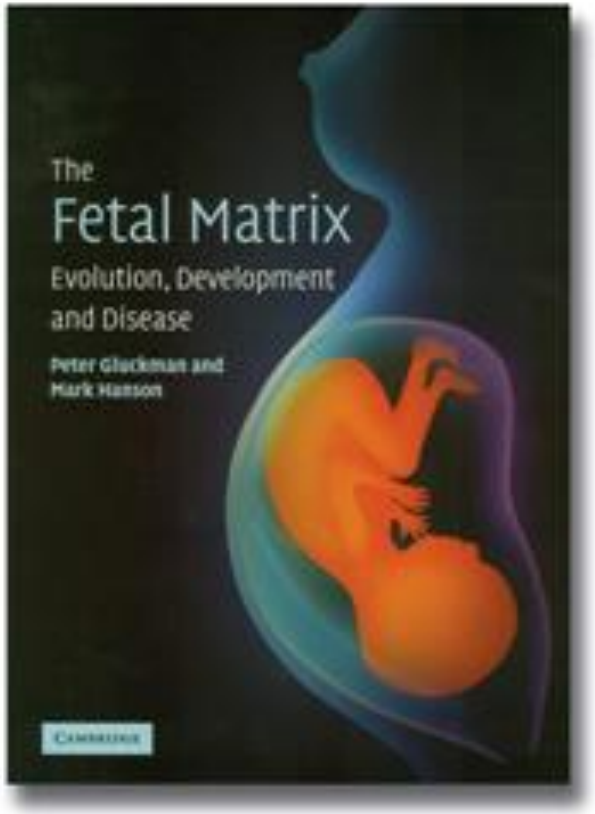


Postnatal Environment

Risk of disease

- diabetes
- heart disease
- Obesity

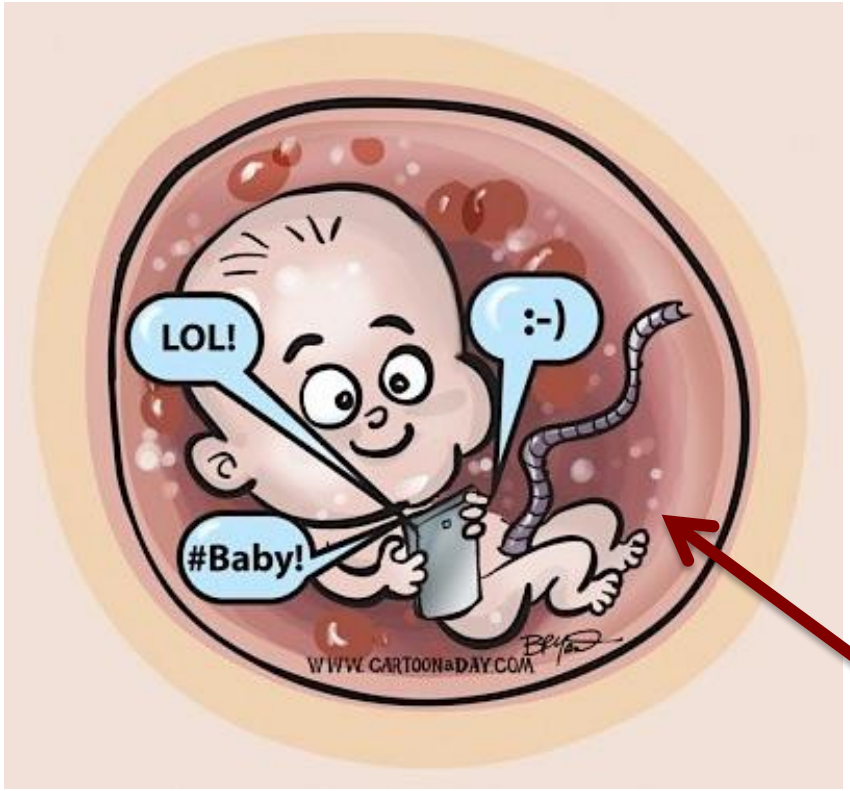
Developmental Programming:



"Fetal Fortune Telling"

The developing organism uses information (from the mother) to predict its future environment so that it can adapt its development and better its chances of survival.

Predictive Adaptive Responses



The Prediction:

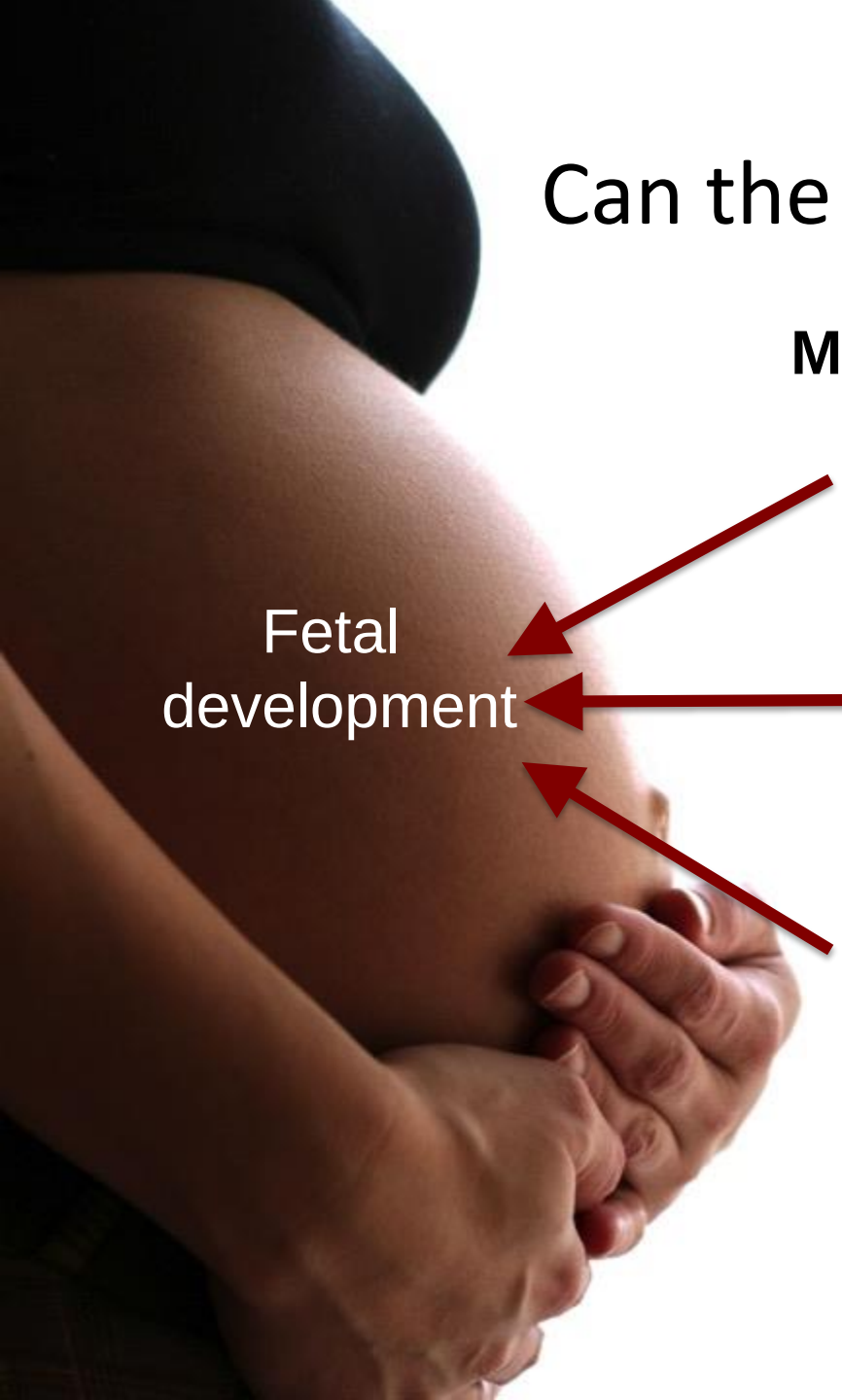
The developing fetus receives information from the mother in the form of hormones, nutrients or oxygen and uses these to predict the environment

These predictions may not be accurate & adaptations not necessary and thus may result in disease

The Adaptation:

The developing fetus will then use this information to adapt it's development to better it's chances of survival after birth

Can the fetus be “misinformed”?



Maternal disease

- *Inflammatory diseases*
  - Asthma
  - Periodontal disease

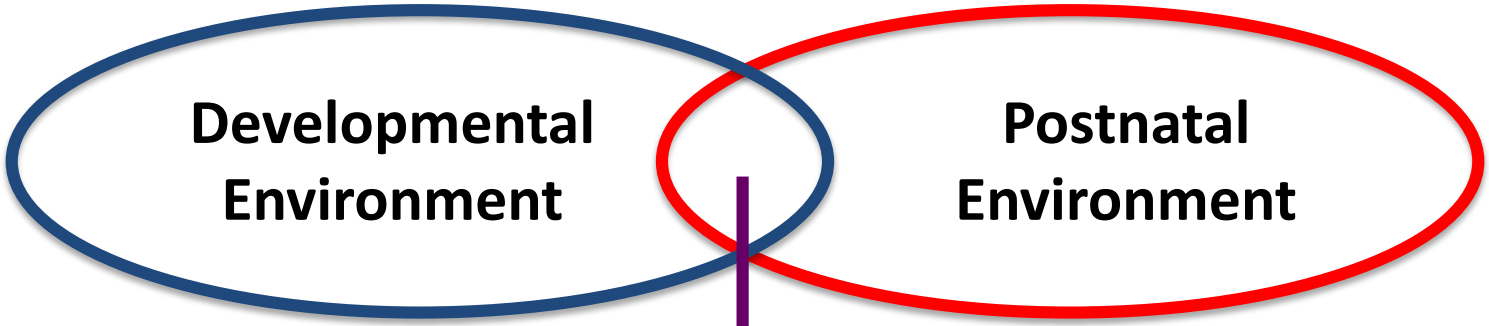
Pharmaceutical exposures

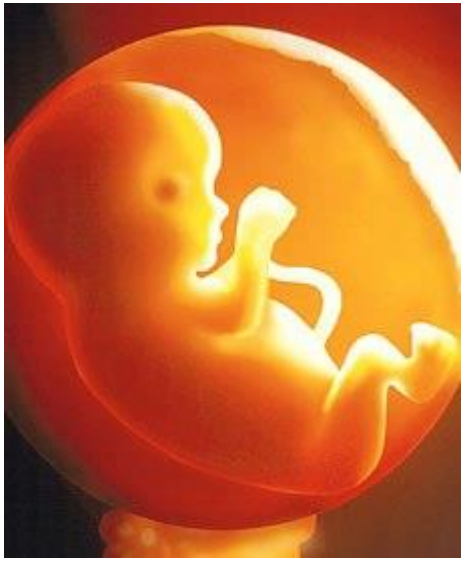
- *Antidepressants*
  - SSRIs

Drugs

- *Smoking*
  - Nicotine
  - THC
- Alcohol intake

The Developmental Origins of Health and Disease





Risk of disease

- diabetes
- heart disease
- obesity
- stress/anxiety

welcome to the

sloboda laboratory

DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE AT MCMASTER UNIVERSITY

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Understanding the mechanisms: animal models

Balanced Diet (Control)

Undernourished

High Fat

Mothers' Diet during pregnancy

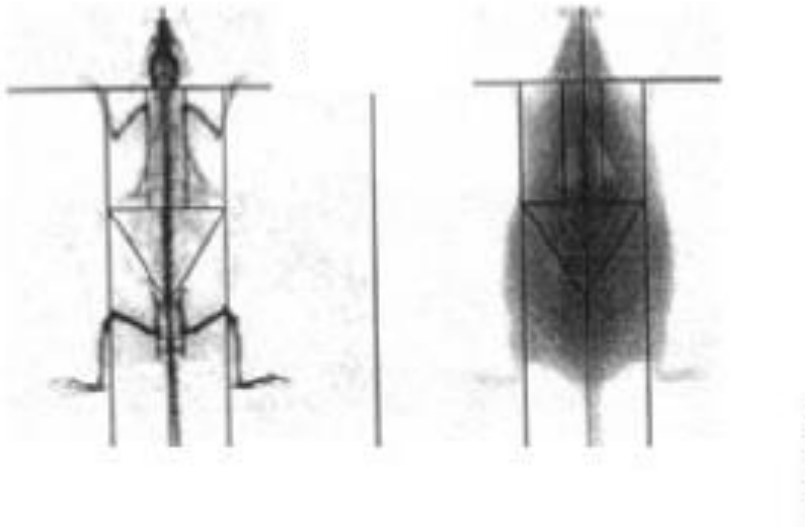
Maternal Undernutrition

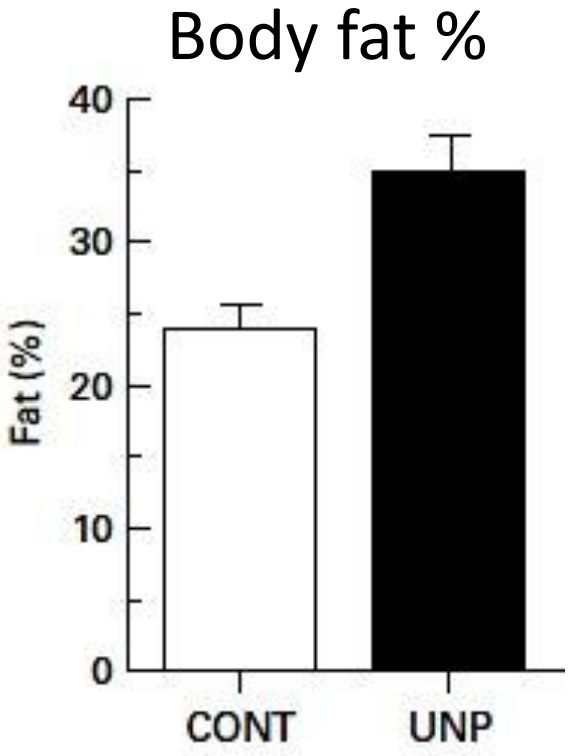
- Pregnant rats fed 30-50 % of control diet
  - decreases birth weight
  - followed by accelerated postnatal growth

Vickers et al, 2000, Am J Physiol Endo Metab

Maternal Undernutrition:

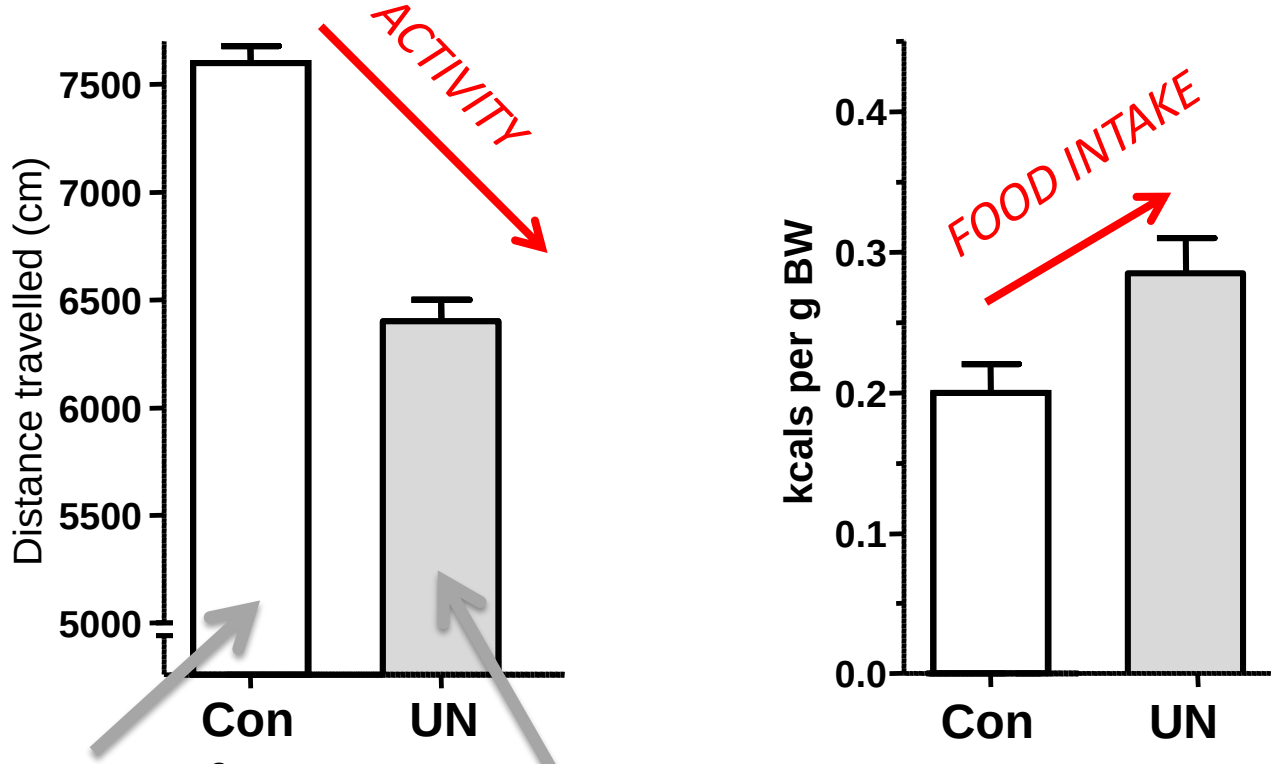
- Offspring are obese despite eating control diet!





How is this happening?

The "Couch Potato" Syndrome

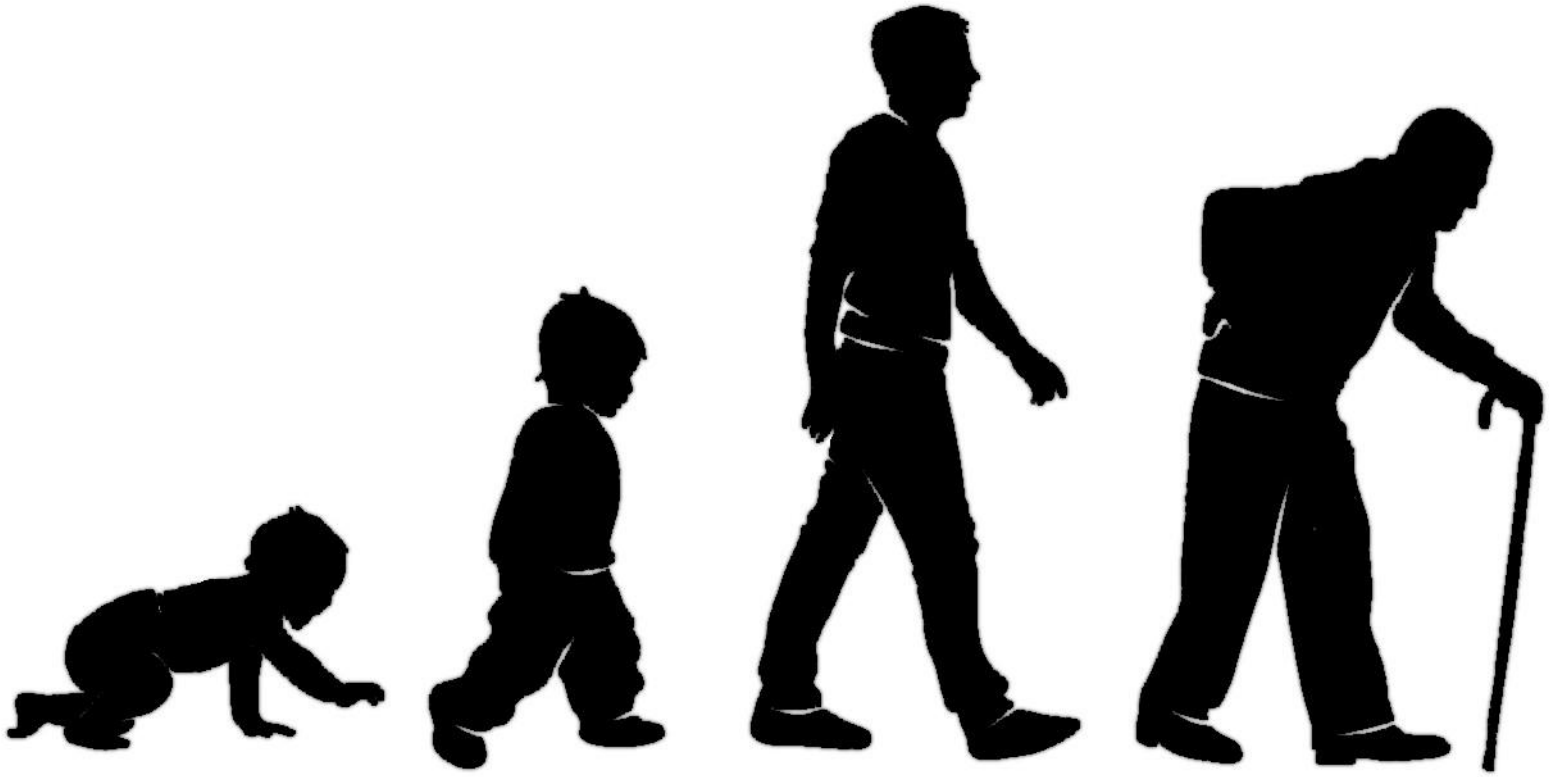


Offspring of control mothers

Offspring of undernourished mothers

Vickers et al, Am J Physiol, 2003

Accelerated Aging?



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PLoS one

Pre- and Postnatal Nutritional Histories Influence Reproductive Maturation and Ovarian Function in the Rat

Deborah M. Sloboda[1]*, Graham J. Howie[1], Anthony Pleasants[2], Peter D. Gluckman[1], Mark H. Vickers[1]

1 The Liggins Institute and the National Research Centre for Growth and Development, The University of Auckland, Auckland, New Zealand, 2 AgResearch, Hamilton, New Zealand

EARLY PUBERTY!

OPEN ACCESS Freely available online

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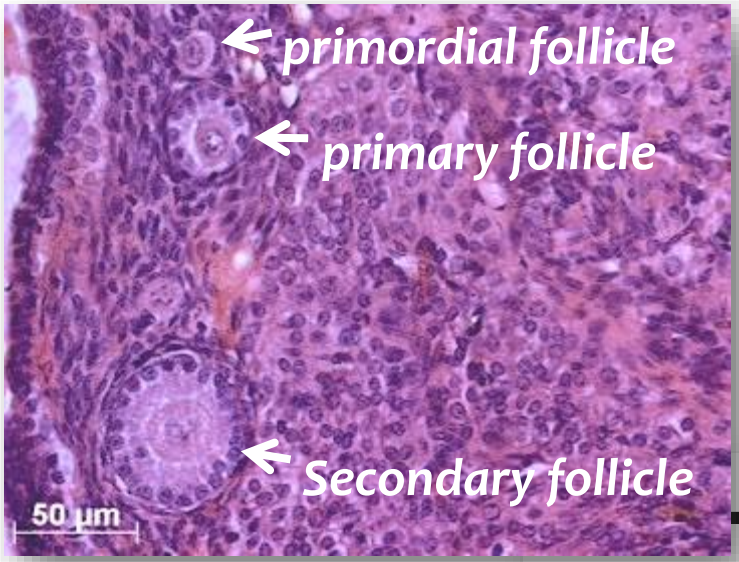
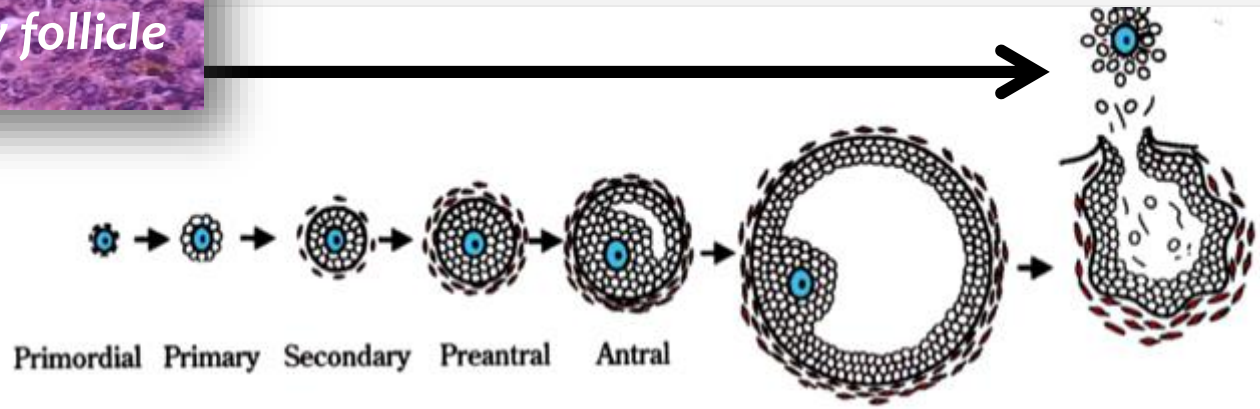


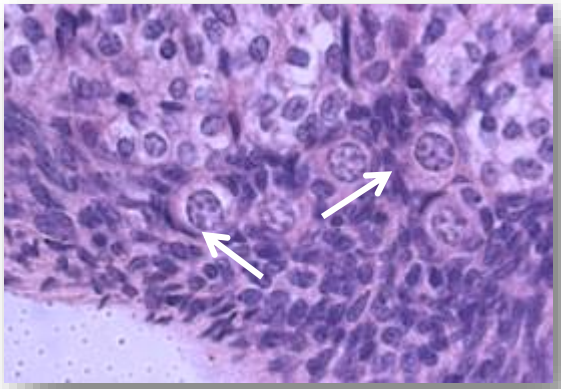
What happens to the eggs?

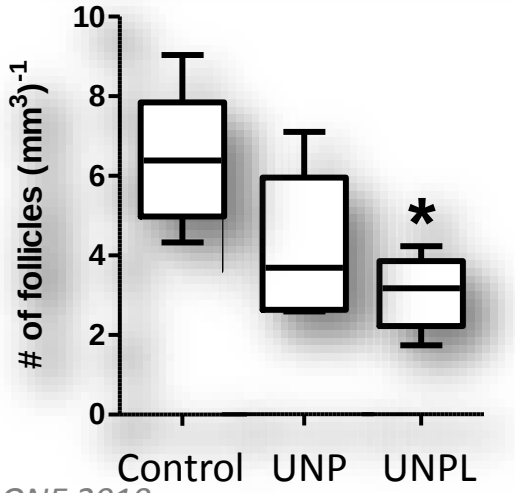


Bernal et al. PLoS ONE 2010

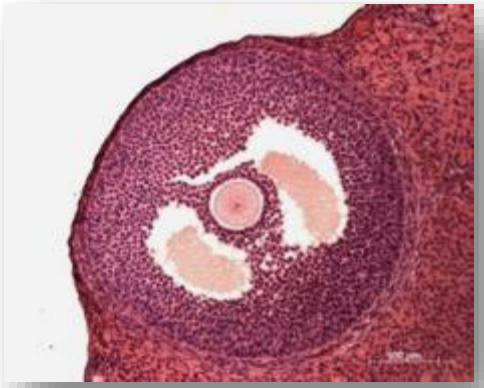
Maternal undernutrition decreased follicle (egg) #'s in offspring ovaries

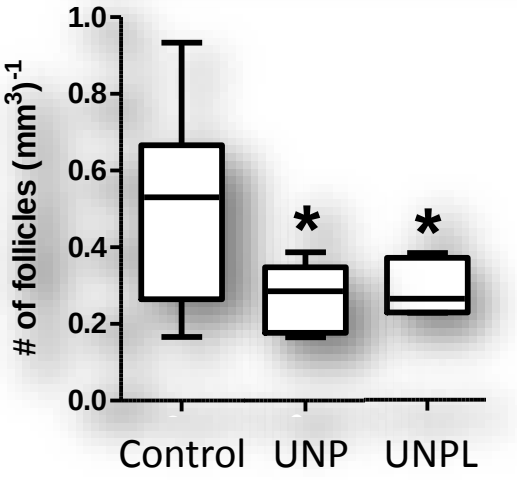
Primordial follicles decreased





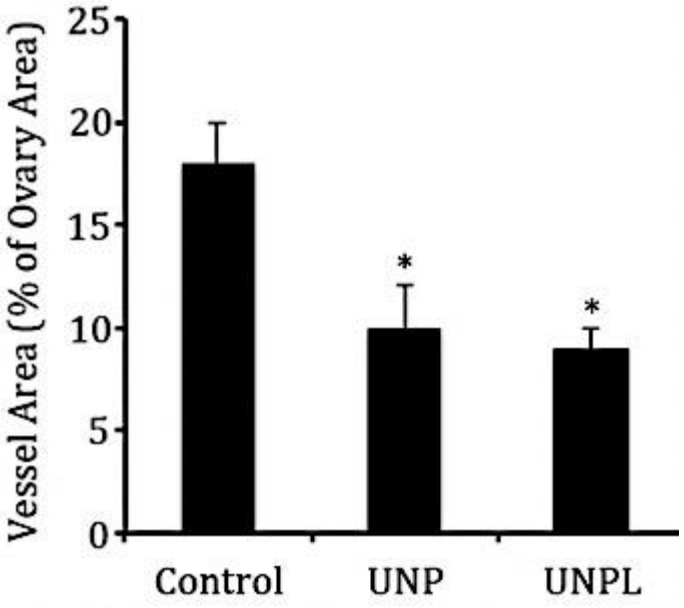
Antral follicles decreased

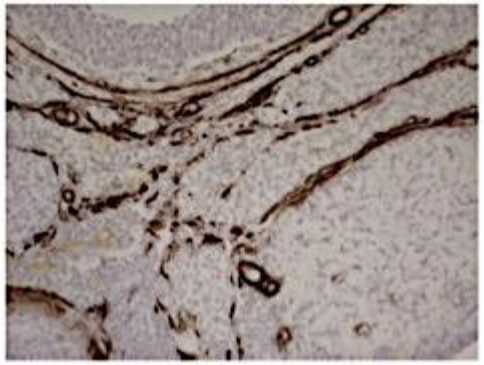




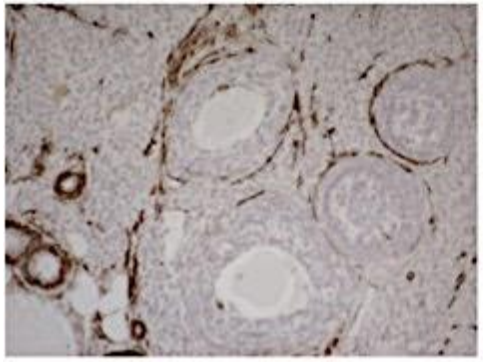
Bernal et al. PLoS ONE 2010

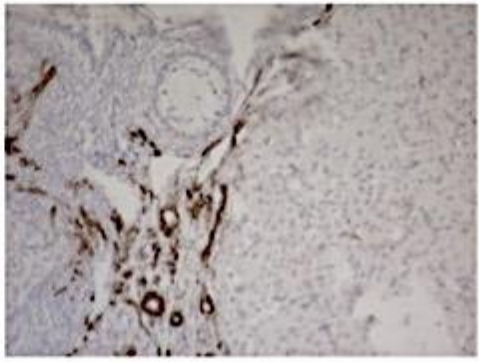
Maternal undernutrition decreased blood vesssel density in offspring ovaries





Control





UNP

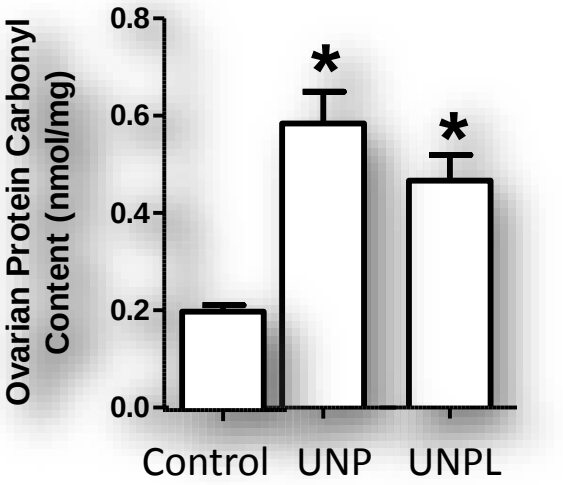
UNPL

Chan et al. 2015, Biology of Reproduction

Maternal undernutrition increases oxidative stress levels in offspring ovaries

Andy Oxidant meets Free Radical.

↑ ovarian oxidative stress



Bernal et al. PLoS ONE 2010

The impacts of prenatal undernutrition

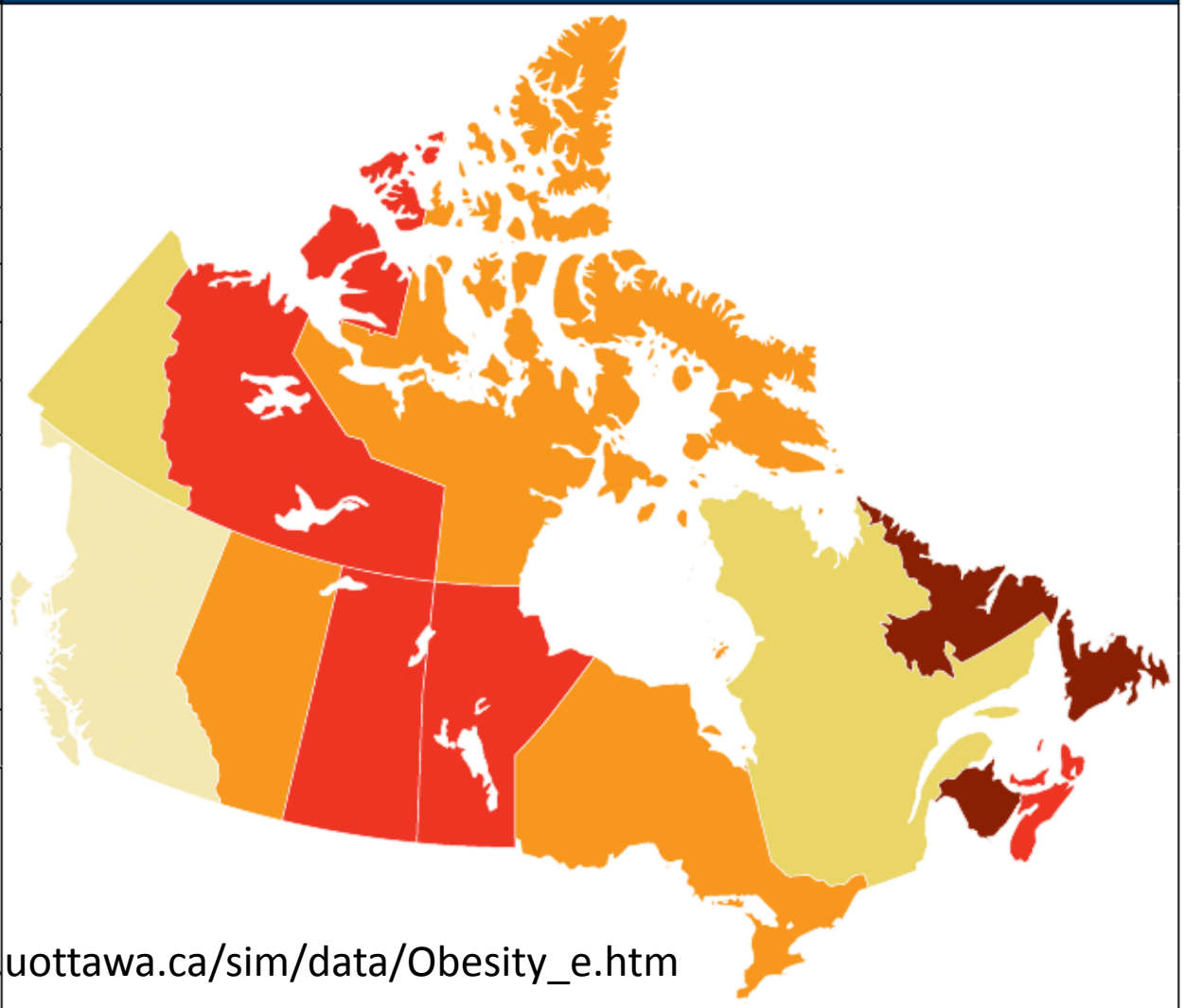
- Fetal Growth Restriction
- Early puberty
- Obesity
- Sarcopenia
- Fatty liver
- Hypertension
- Endothelial dysfunction
- Insulin resistance
- Leptin resistance
- Increased anxiety
- Altered appetite
- Hyperphagia
- Fat preference in diet
- Altered stress hormones
- Increased oxidative stress

Vickers, et al. 2001, 2002, 2003, 2007, Sloboda et al. 2009, Howie et al. 2011, Bernal et al. 2010

Maternal nutrient excess and Maternal obesity

Percent of people that are classified as overweight and obese in Canada in 2009-10

	Age-standardized prevalence (%)
Newfoundland and Labrador	62.3
Prince Edward Island	55.7
Nova Scotia	57.9
New Brunswick	61.5
Quebec	48.0
Ontario	50.6
Manitoba	58.3
Saskatchewan	58.1
Alberta	52.9
British Columbia	42.9
Yukon	49.0
Northwest Territories	56.7
Nunavut	54.7

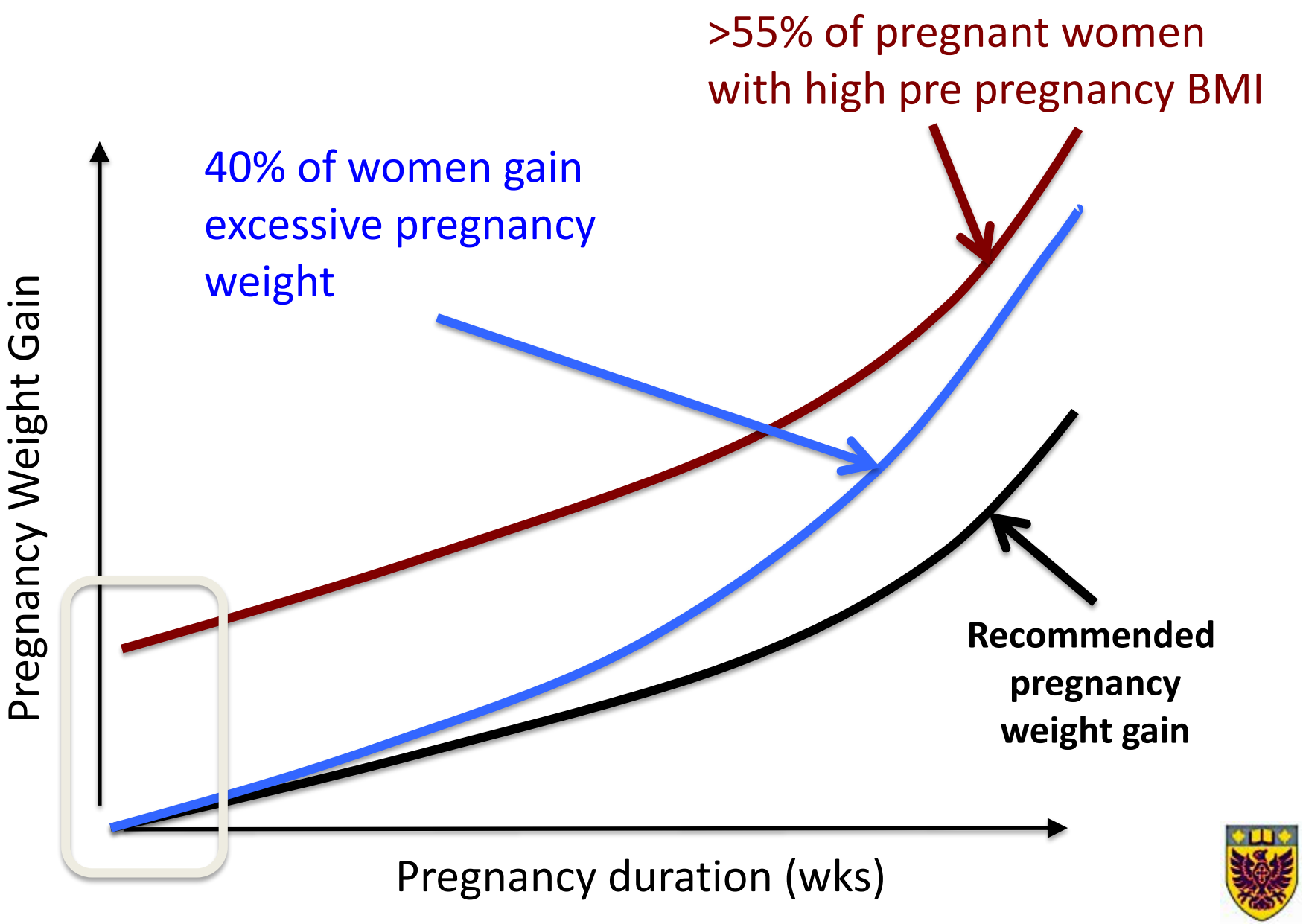


http://www.med.uottawa.ca/sim/data/Obesity_e.htm

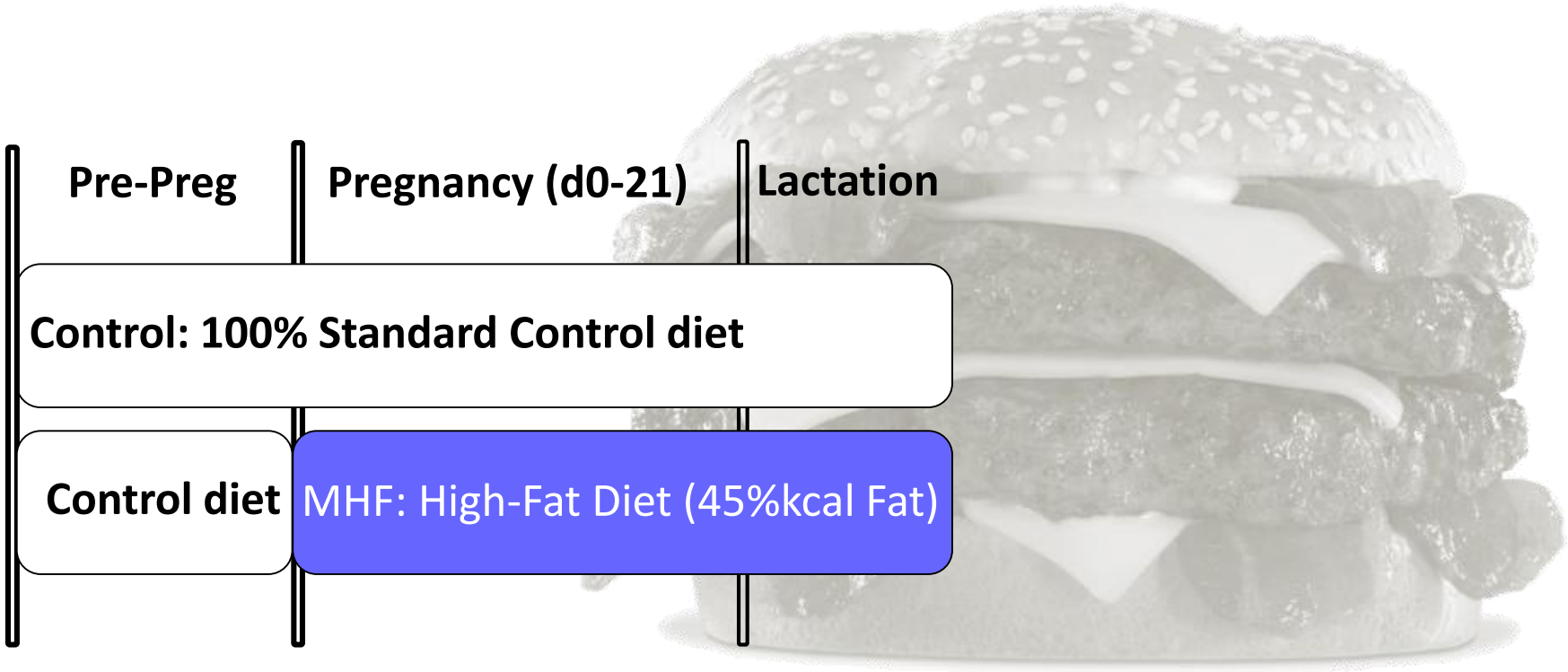
Maternal obesity and pregnancy….

- Overweight (BMI 25.0–29.9) and obese women (BMI >30) had significantly increased risk for:
  - gestational diabetes
  - preeclampsia
  - cesarean delivery
  - large-for gestational-age infants

Maternal obesity vs *excessive pregnancy weight gain*



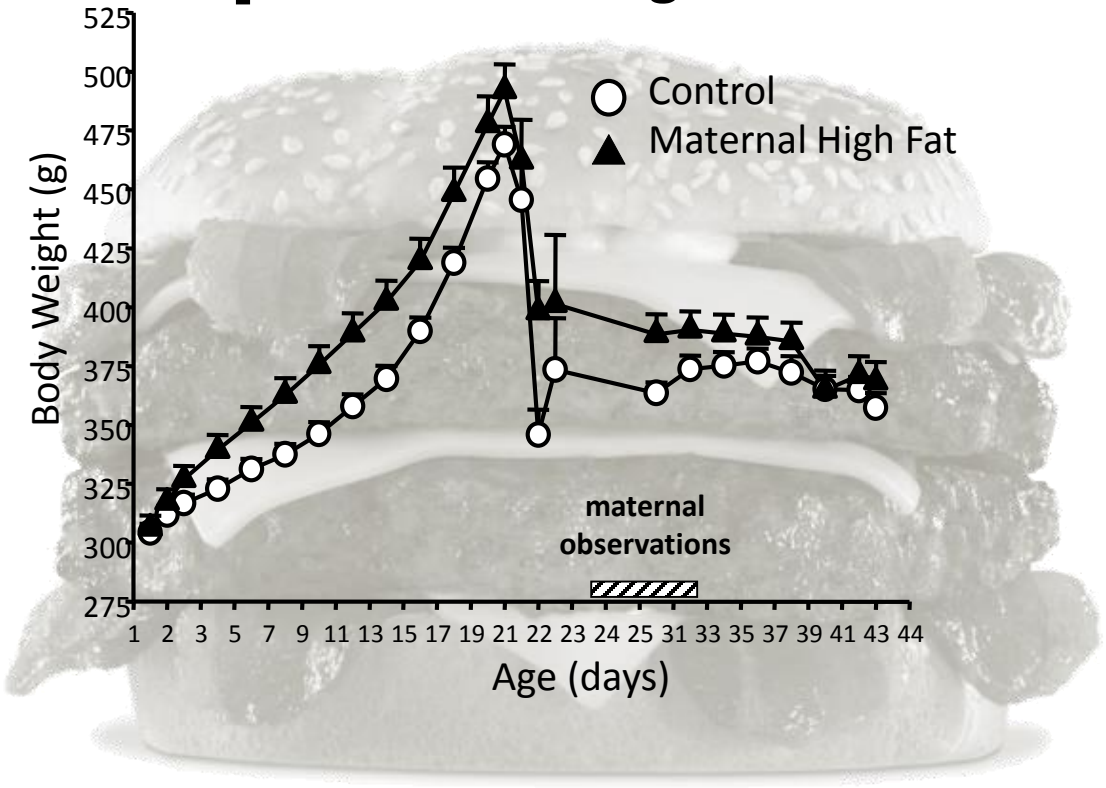
Excessive pregnancy weight gain & maternal high fat diet



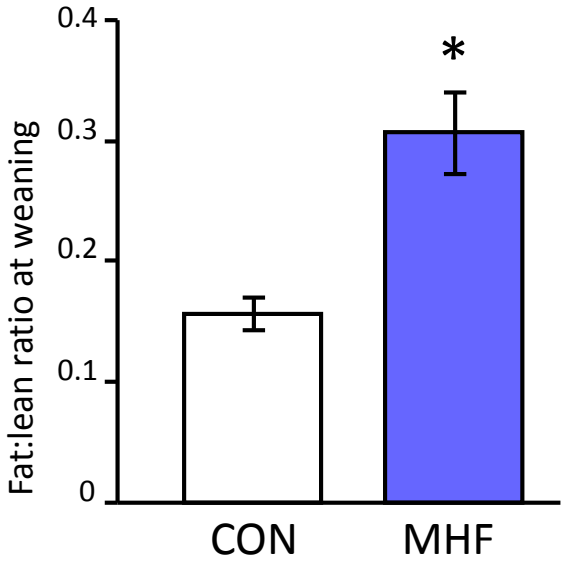
Connor et al. 2012; J Physiol, Tsoulis et al. 2016, Biology of Reproduction

Excessive pregnancy weight gain & maternal high fat diet

↑ Maternal Weight Gain



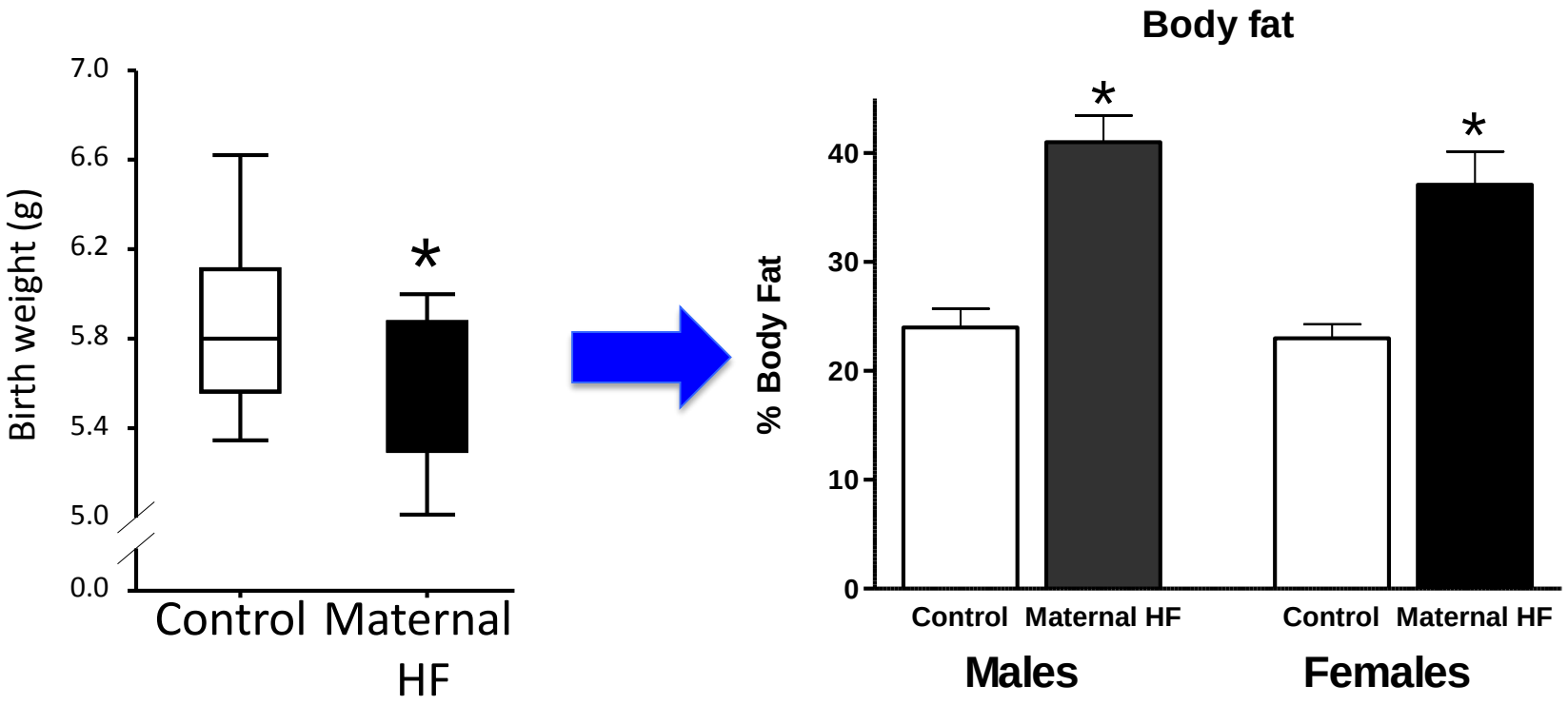
↑ Maternal Fat: lean ratio



Connor et al. 2012; J Physiol

Excessive pregnancy weight gain & high fat diet

- offspring of mothers fed a HF diet are born small and end up obese and insulin resistant
  - **DESPITE** eating a control diet



Howie et al, J Physiol, 2009

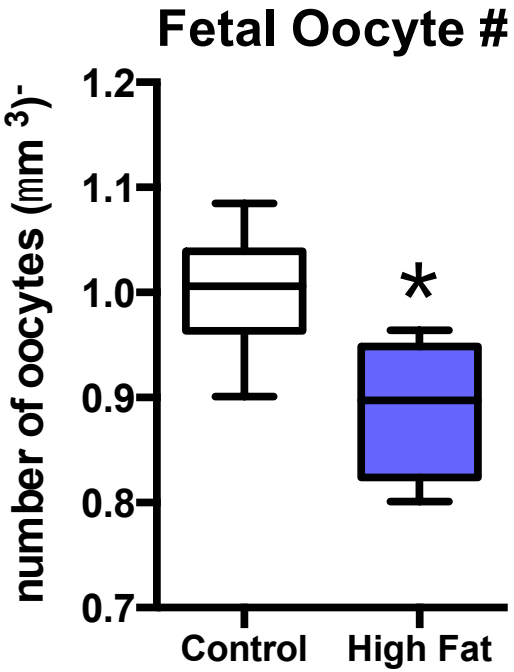
Maternal HF diet accelerates pubertal onset, disrupts reproductive cycles in offspring

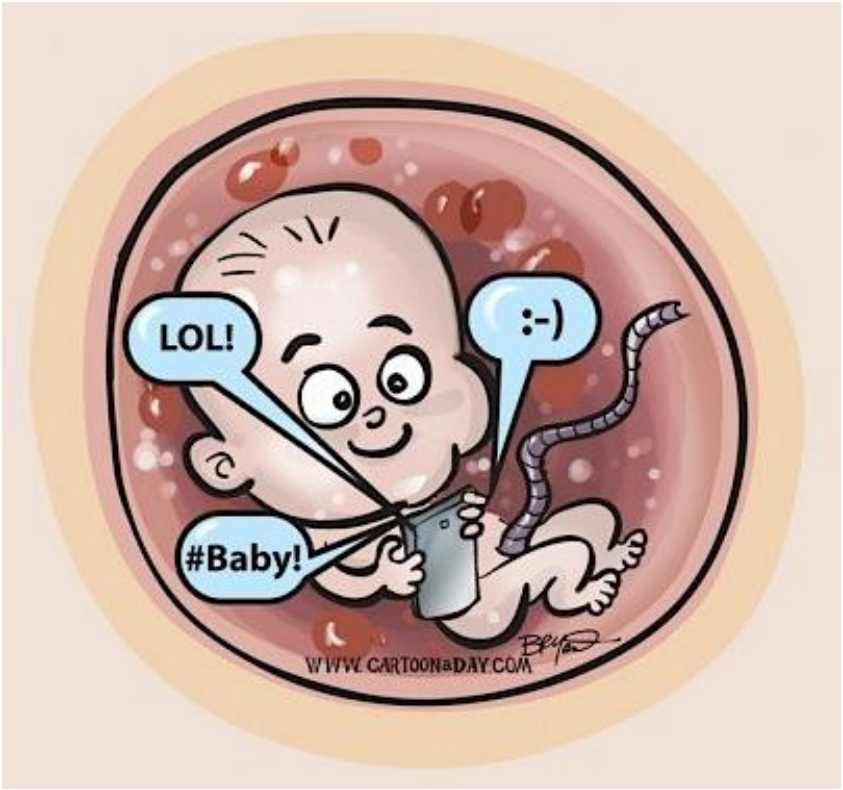
Indicator of ovarian aging

Connor et al. 2012; J Physiol.

Sloboda et al. 2009 PLoS ONE

Maternal high fat diet results in fetal oocyte loss





Tsoulis et al. 2016, Biology of Reproduction


FEED ME
I'm eating for TWO

Disparate nutritional diets = similar offspring outcomes

Balanced Diet (Control)

Undernourished

High Fat

Offspring have:

- ✓ **Obesity**
- ✓ **Diabetes**
- ✓ **Fatty liver**
- ✓ **Early puberty**
- ✓ **Early reprod aging**

DOI: 10.1111/j.1471-0528.2008.01822.x
www.blackwellpublishing.com/bjog

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

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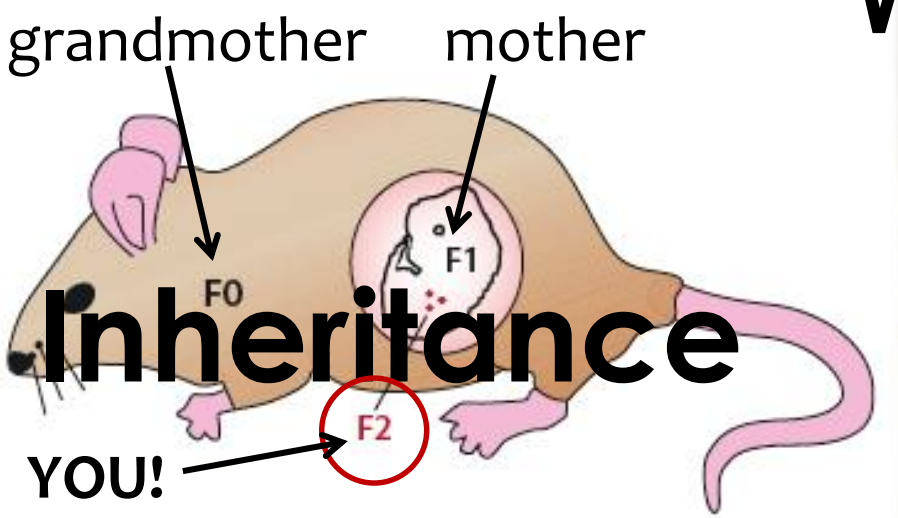
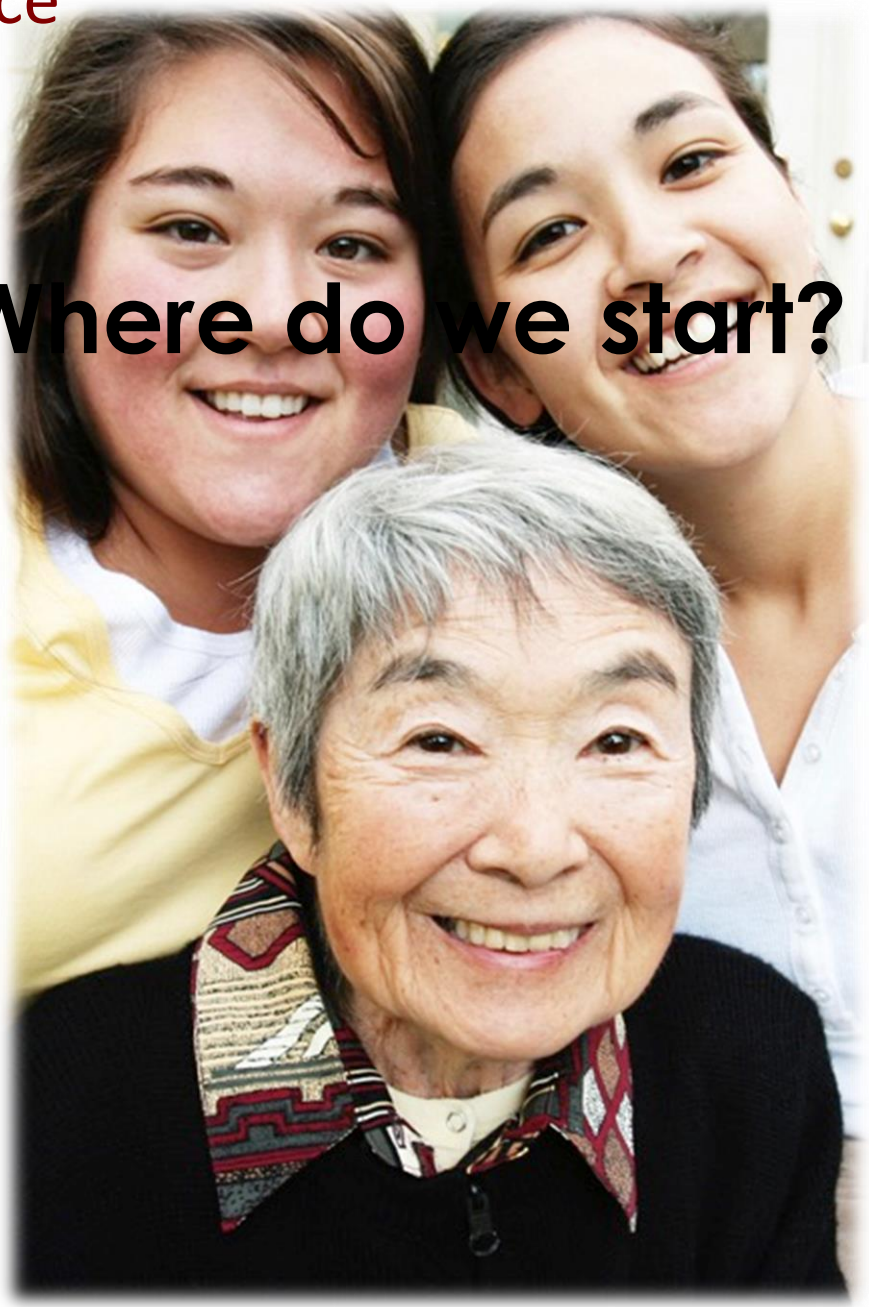
Transgenerational transmittance of disease risk

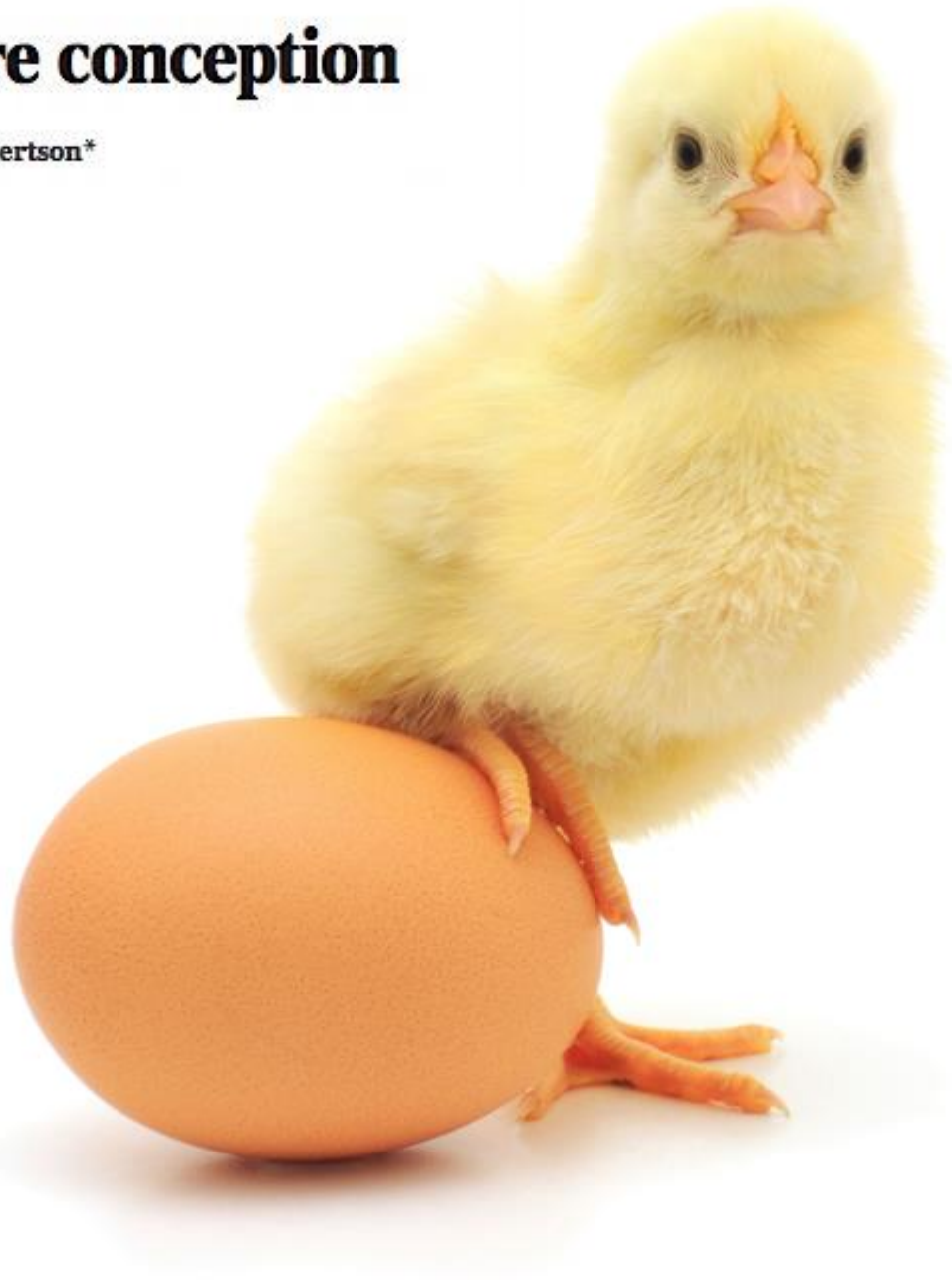




REVIEW

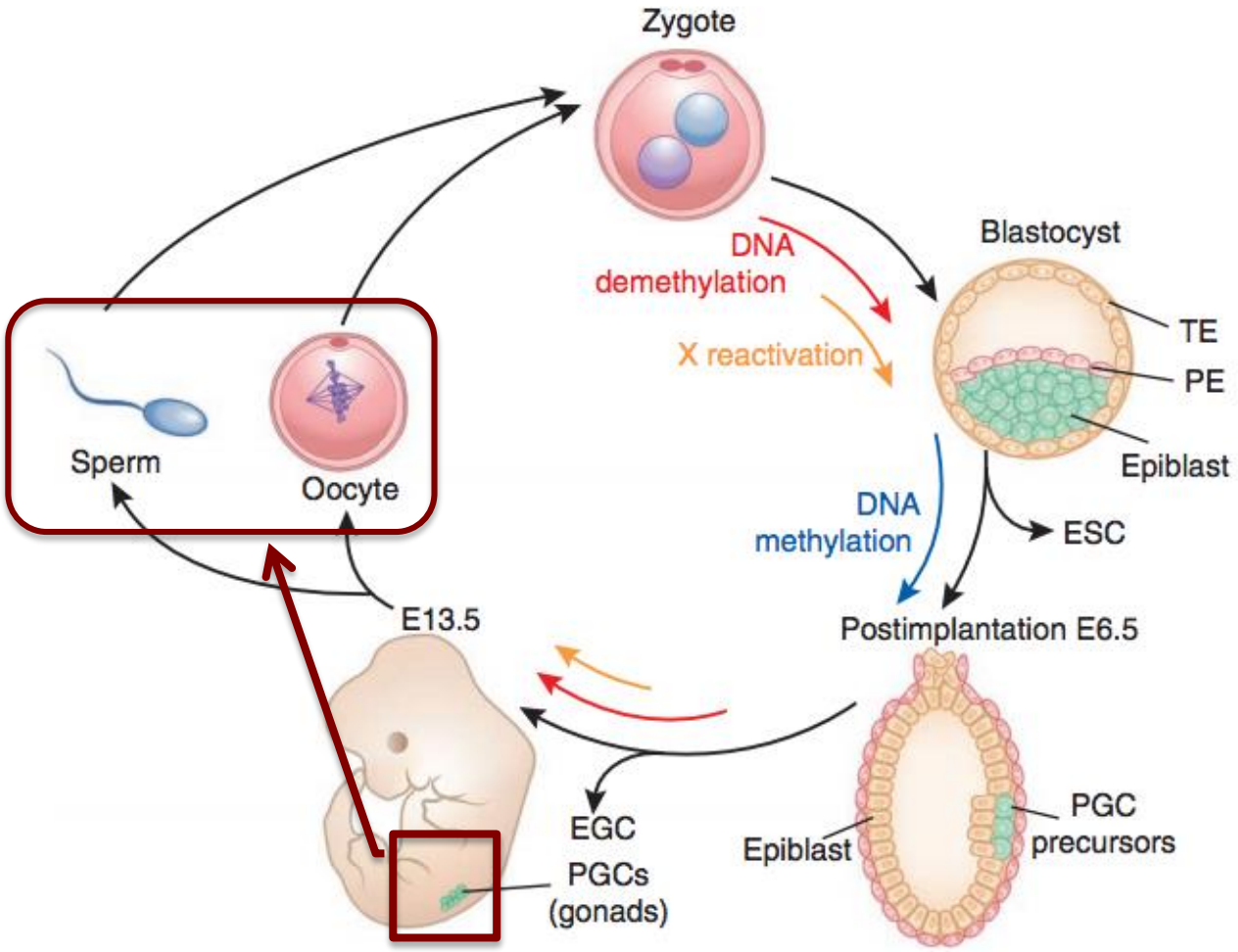
Parenting from before conception

Michelle Lane, Rebecca L. Robker, Sarah A. Robertson*

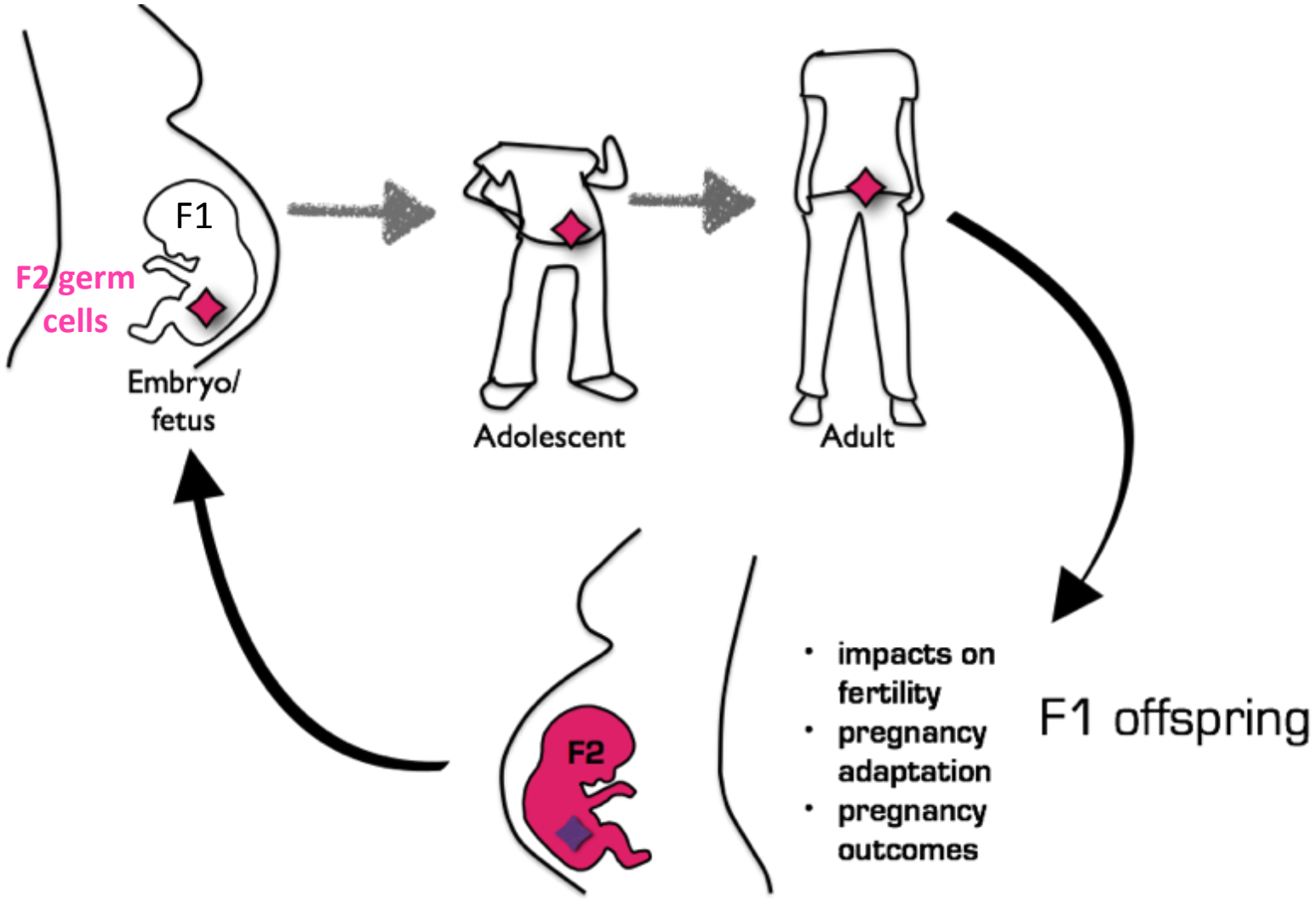


Science 2014 (345) 6198 p756

Germ cells determine the next generation



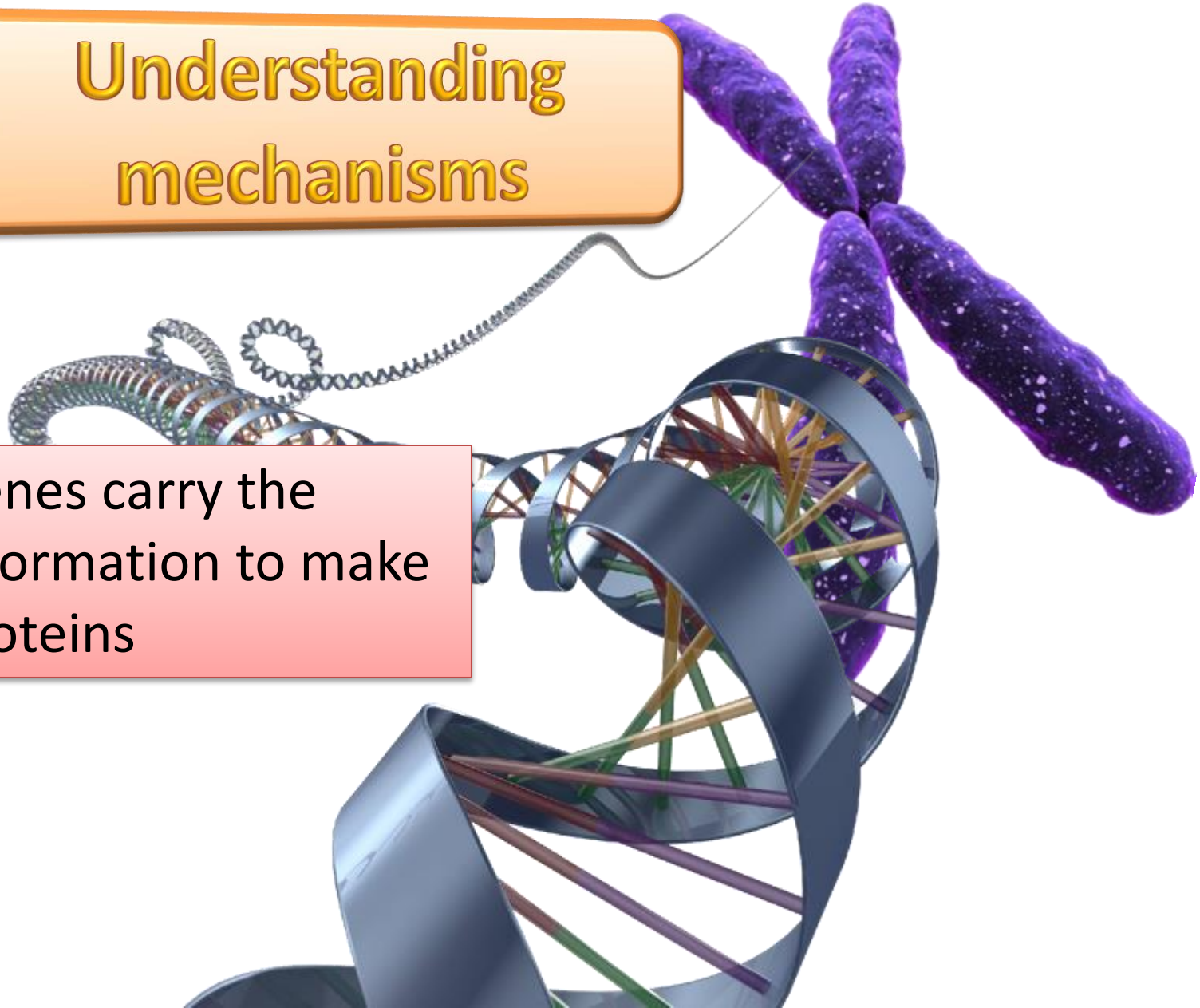
Early life impacts on reproductive development= Transgenerational impacts?



Chan et al. Journal of Endocrinology 2014

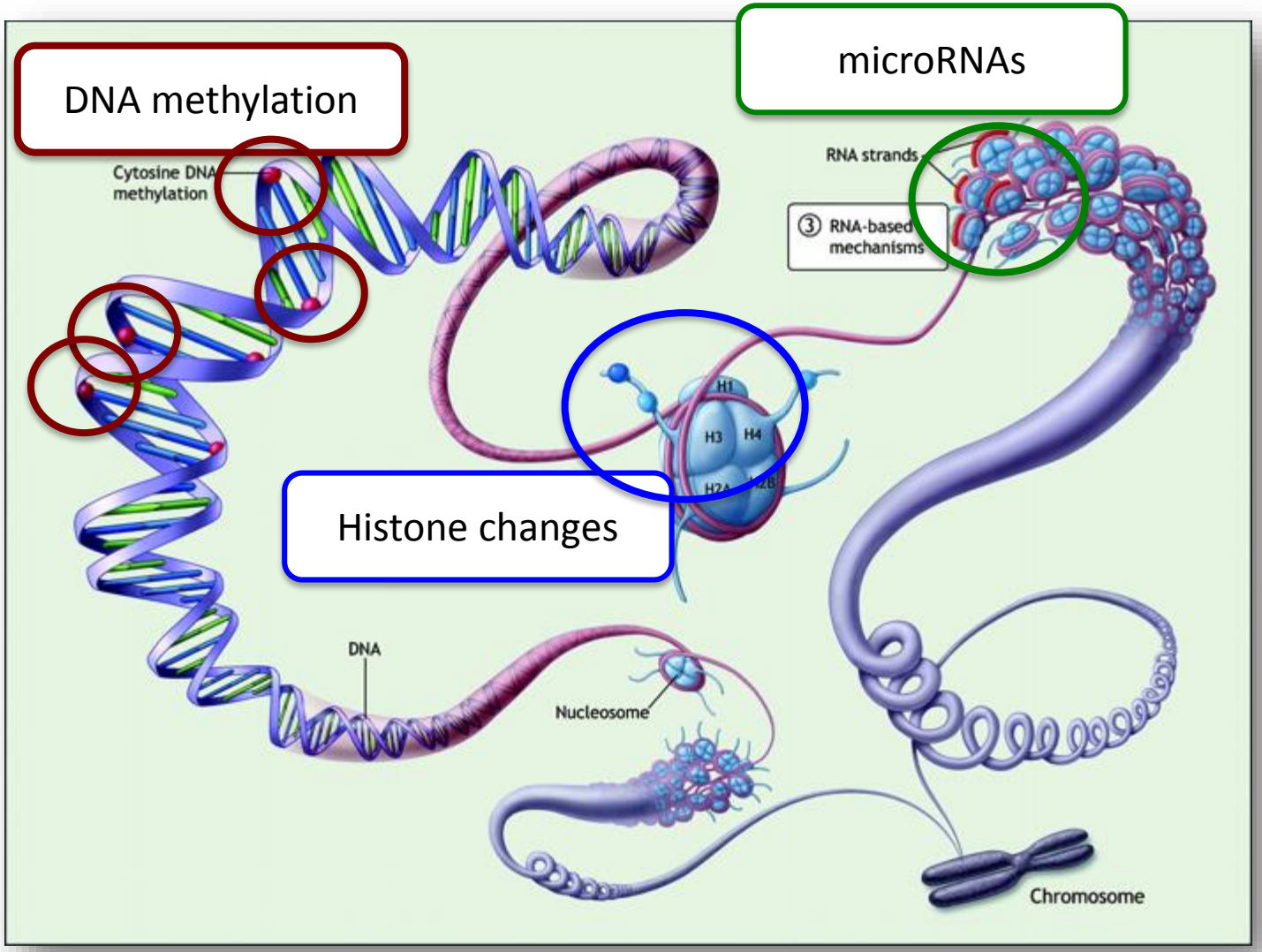
EPIGENETICS

Understanding mechanisms



Genes carry the information to make proteins

- epigenetics = “on top of” genetics
- genes are turned on and off because of environmental induced changes that occur “on top of” the DNA sequence
  - But NOT in the DNA sequence itself

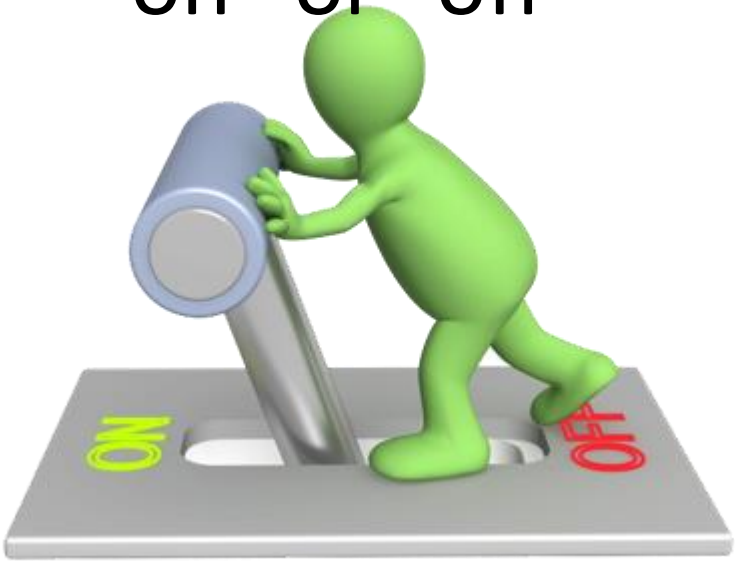


Epigenetic marks on the DNA control whether genes are “on” or “off”

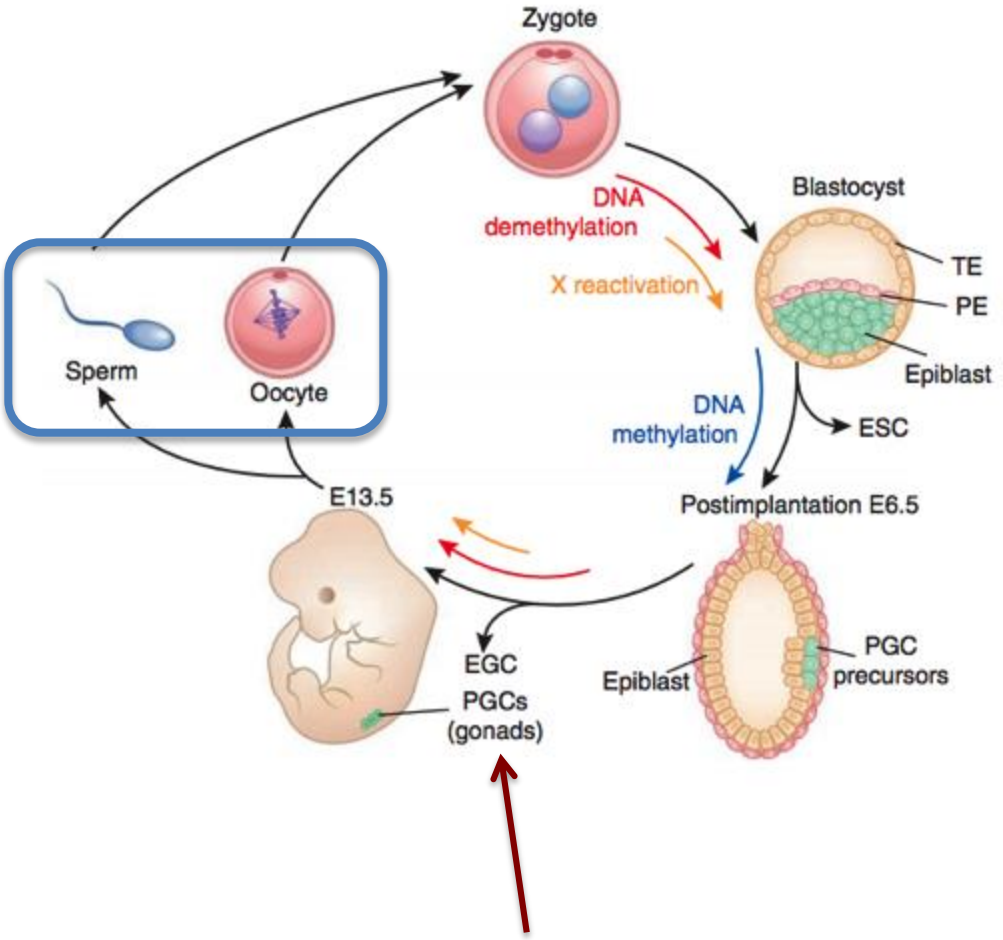
DNA methylation

microRNAs

Histone changes



Epigenetics during development: a window of vulnerability?



- Epigenetic modifications regulate cell destiny
- Important in primordial germ cells (sperm and oocyte)

This gene regulates growth

Table 1. *IGF2* DMR methylation among individuals periconceptionally exposed to famine and their unexposed, same-sex siblings

IGF2 DMR methylation	Mean methylation fraction (SD)				Relative change exposed	Difference in SDs	*P*
	Exposed ($n = 60$)		Controls ($n = 60$)				
Average	0.488	(0.047)	0.515	(0.055)	−5.2%	−0.48	5.9×10^{-5}
CpG 1	0.436	(0.037)	0.470	(0.041)	−6.9%	−0.78	1.5×10^{-4}
CpG 2 and 3	0.451	(0.033)	0.473	(0.055)	−4.7%	−0.41	8.1×10^{-3}
CpG 4	0.577	(0.114)	0.591	(0.112)	−2.3%	−0.12	.41
CpG 5	0.491	(0.061)	0.529	(0.068)	−7.2%	−0.56	1.4×10^{-3}

P values were obtained using a linear mixed model and adjusted for age.

Persistent epigenetic differences associated with prenatal exposure to famine in humans

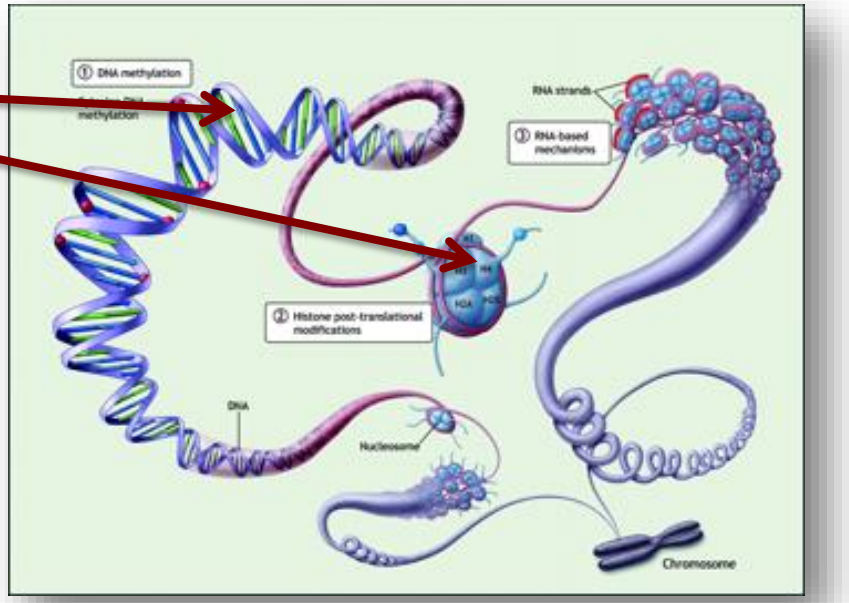
Bastiaan T. Heijmans[a,1,2], Elmar W. Tobi[a,2], Aryeh D. Stein[b], Hein Putter[c], Gerard J. Blauw[d], Ezra S. Susser[e,f], P. Eline Slagboom[a], and L. H. Lumey[e,1]

Are these changes to developmental pathways permanent?

Nutritional Interventions: can we rescue this?

Methyl Donors

- Choline
- Folate
  (your mom told you to eat spinach right?)



Essential Amino Acids

- Taurine

Antioxidants

- Vitamin C
- Melatonin

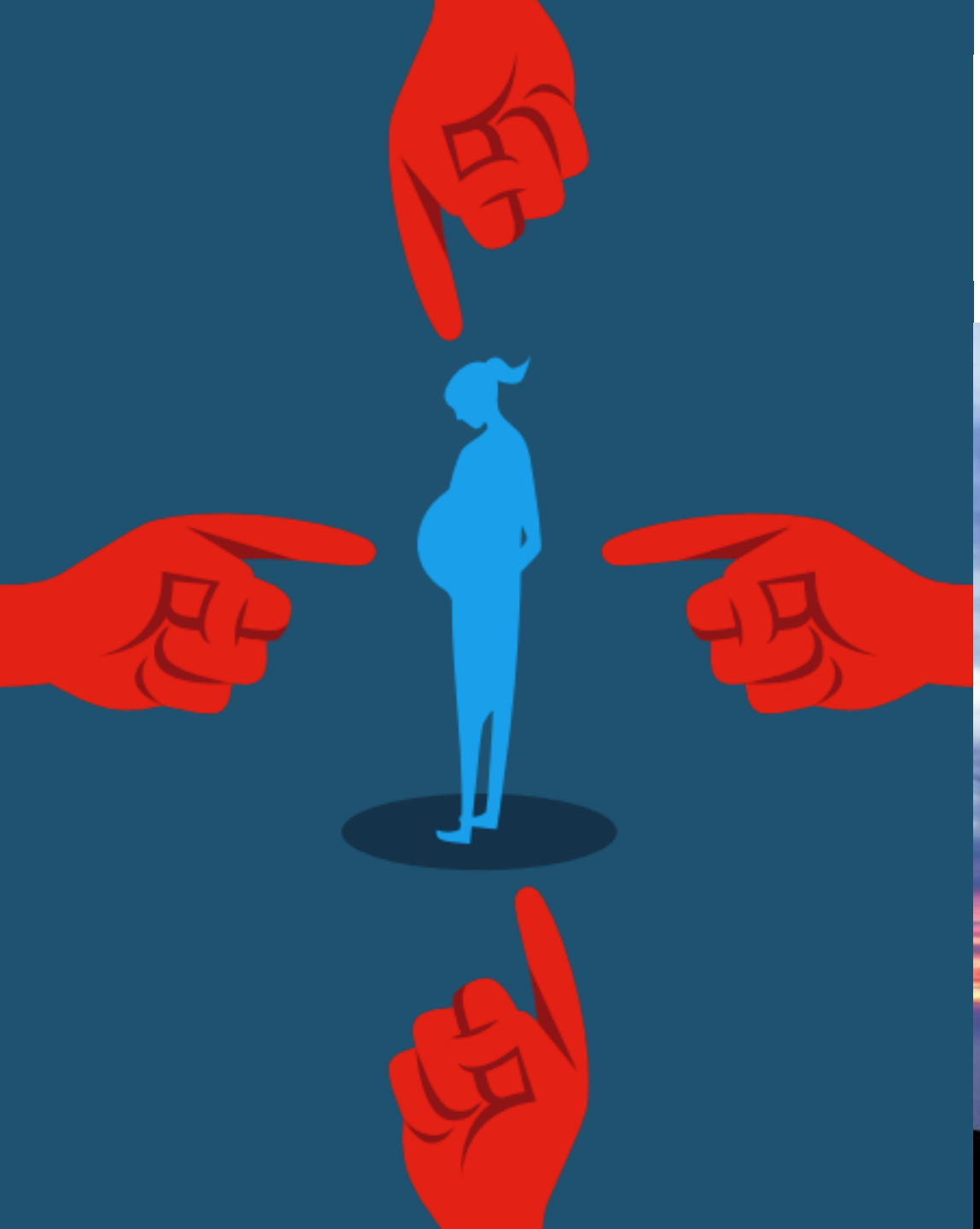
ARTICLE

Received 27 Nov 2013 | Accepted 26 Mar 2014 | Published 29 Apr 2014

DOI: 10.1038/ncomms4746 OPEN

Maternal nutrition at conception modulates DNA methylation of human metastable epialleles

Paula Dominguez-Salas[1], Sophie E. Moore[1], Maria S. Baker[2], Andrew W. Bergen[3], Sharon E. Cox[1], Roger A. Dyer[4], Anthony J. Fulford[1], Yongtao Guan[2,5], Eleonora Laritsky[2], Matt J. Silver[1], Gary E. Swan[6], Steven H. Zeisel[7], Sheila M. Innis[4], Robert A. Waterland[2,5], Andrew M. Prentice[1] & Branwen J. Hennig[1]



Don't blame the mothers

14 AUGUST 2014 | VOL 512 | NATURE | 131

Paternal Lineage

Stuppia *et al. Clinical Epigenetics* (2015) 7:120
DOI 10.1186/s13148-015-0155-4

CLINICAL EPIGENETICS

REVIEW Open Access

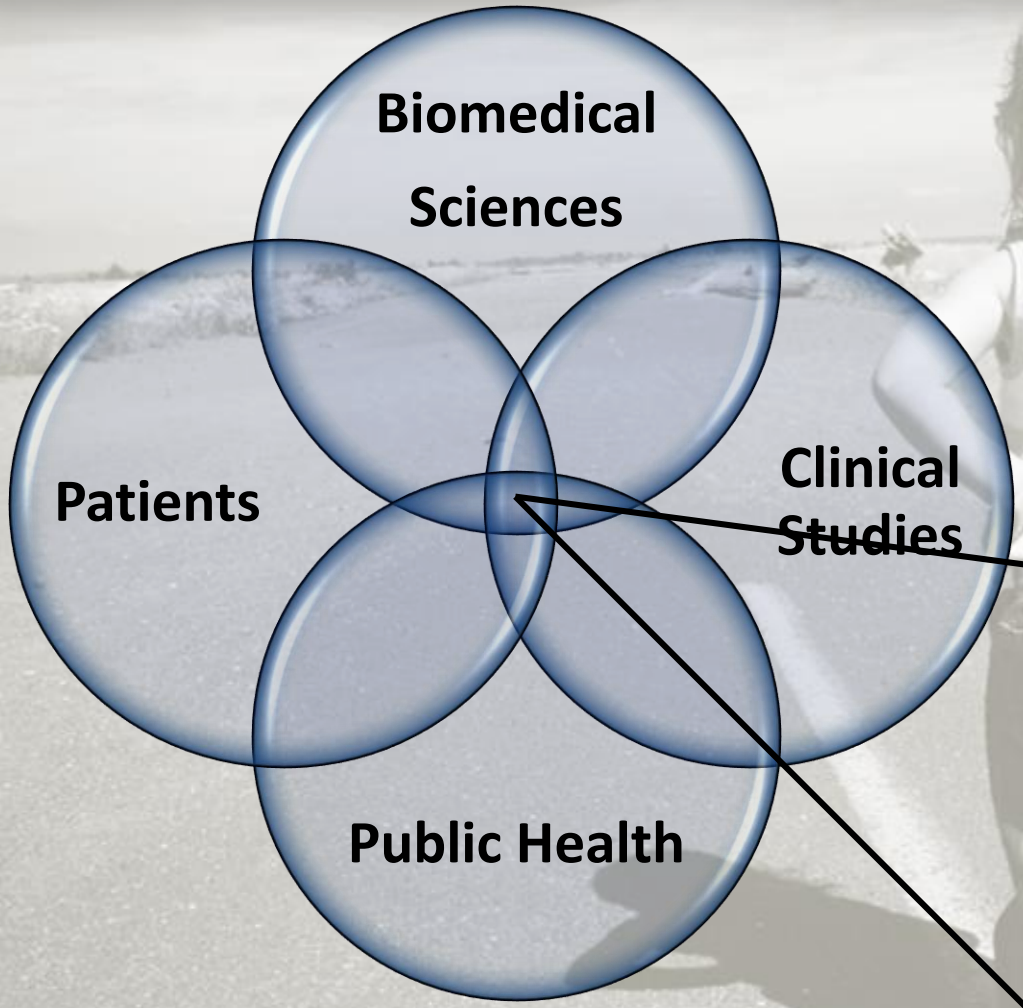
Epigenetics and male reproduction: the consequences of paternal lifestyle on fertility, embryo development, and children lifetime health

Liborio Stuppia[1,3*], Marica Franzago[1], Patrizia Ballerini[2], Valentina Gatta[1,3] and Ivana Antonucci[1,3]

Looking ahead …

…Unravelling mechanisms

Long term approach to the early life origins of health and disease risk



Integrated, Capacity-building approach

AKNOWLEDGEMENTS

McMaster University

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