Perinatal Nutrition and Environmental Exposures: Effects on Metabolic Homeostasis and the Epigenome

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PEPH Webinar
Diet, Nutrition, and Environmental Public Health
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Overview

- **Brief Introduction:** Environmental & Nutritional Epigenetics & the Developmental Origins of Health and Disease

- **Conceptual Framework of U-M Children's Environmental Health Center:** Focus on Nutrient-Toxicant Interactions & Combines Animal Model and Human Population Approaches

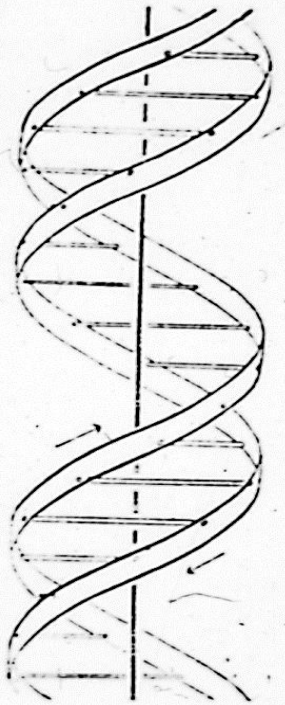
- **Perinatal Exposures and Epigenetic Effects:**
  - **(A) Diet matters** (mitigate and exacerbate toxicant effects)
  - **(B) Lifecourse matters** (epigenetic drift with age)
  - **(C) Future generations matter** (Somatic vs germline vs transgenerational)

A Tail of Two Mice
- or -
Why DNA is Not (Necessarily) Your Destiny

No. 4356 April 25, 1953 NATURE

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

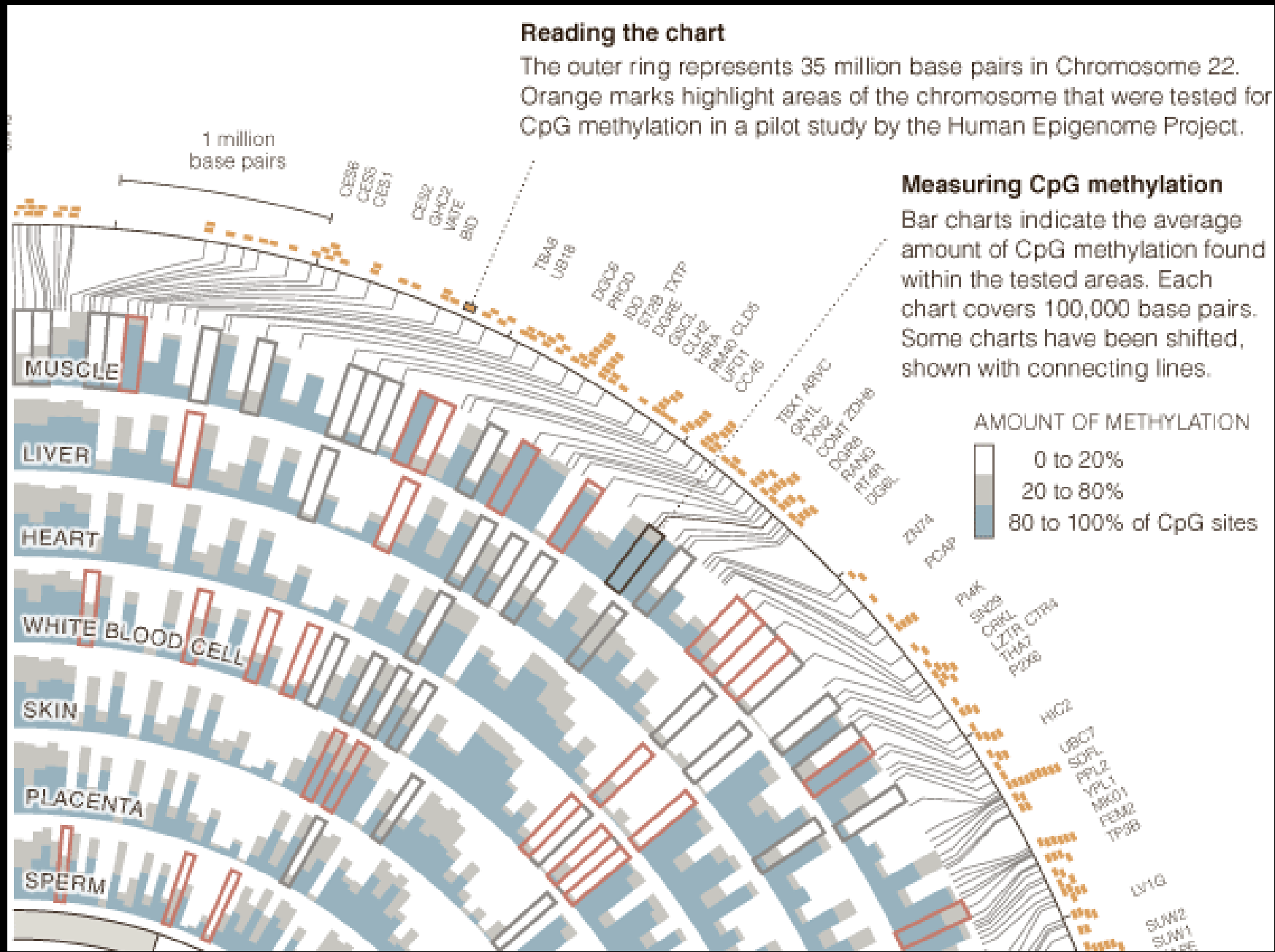


J. D. WATSON
F. H. C. CRICK

Medical Research Council Unit for the
Study of the Molecular Structure of
Biological Systems,
Cavendish Laboratory, Cambridge.

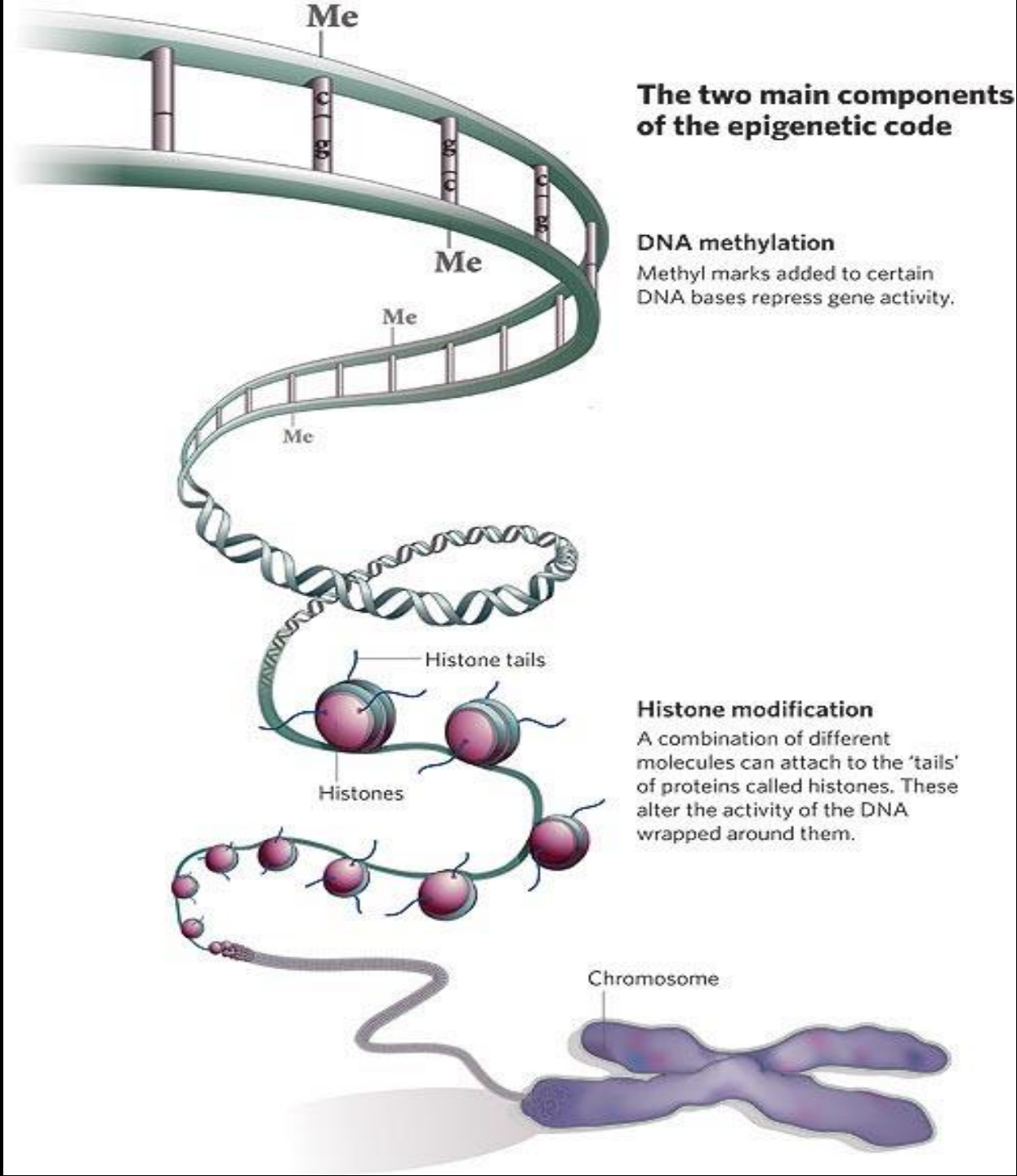
April 2.

The Epigenome



The Agouti Sisters

Epigenetic Switches

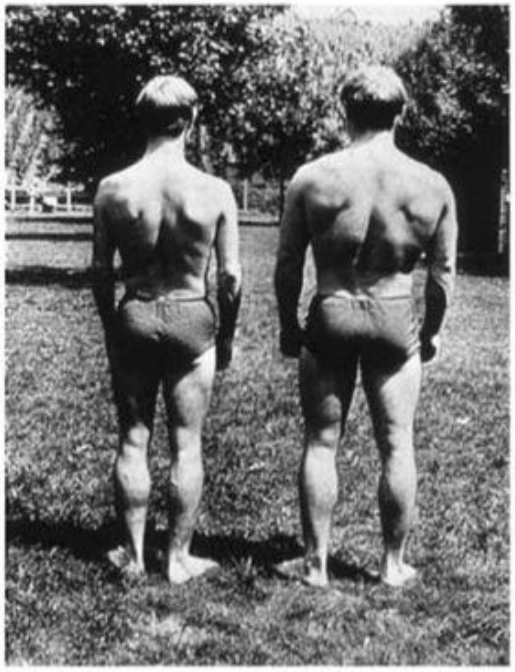


The Agouti Sisters

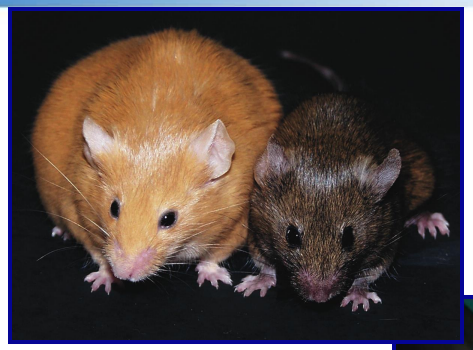
Bisphenol A (BPA)

From Mice to People

Otto Ewald



Conceptual Framework for Environmental Epigenetics Research



A^{vy} Mouse Model

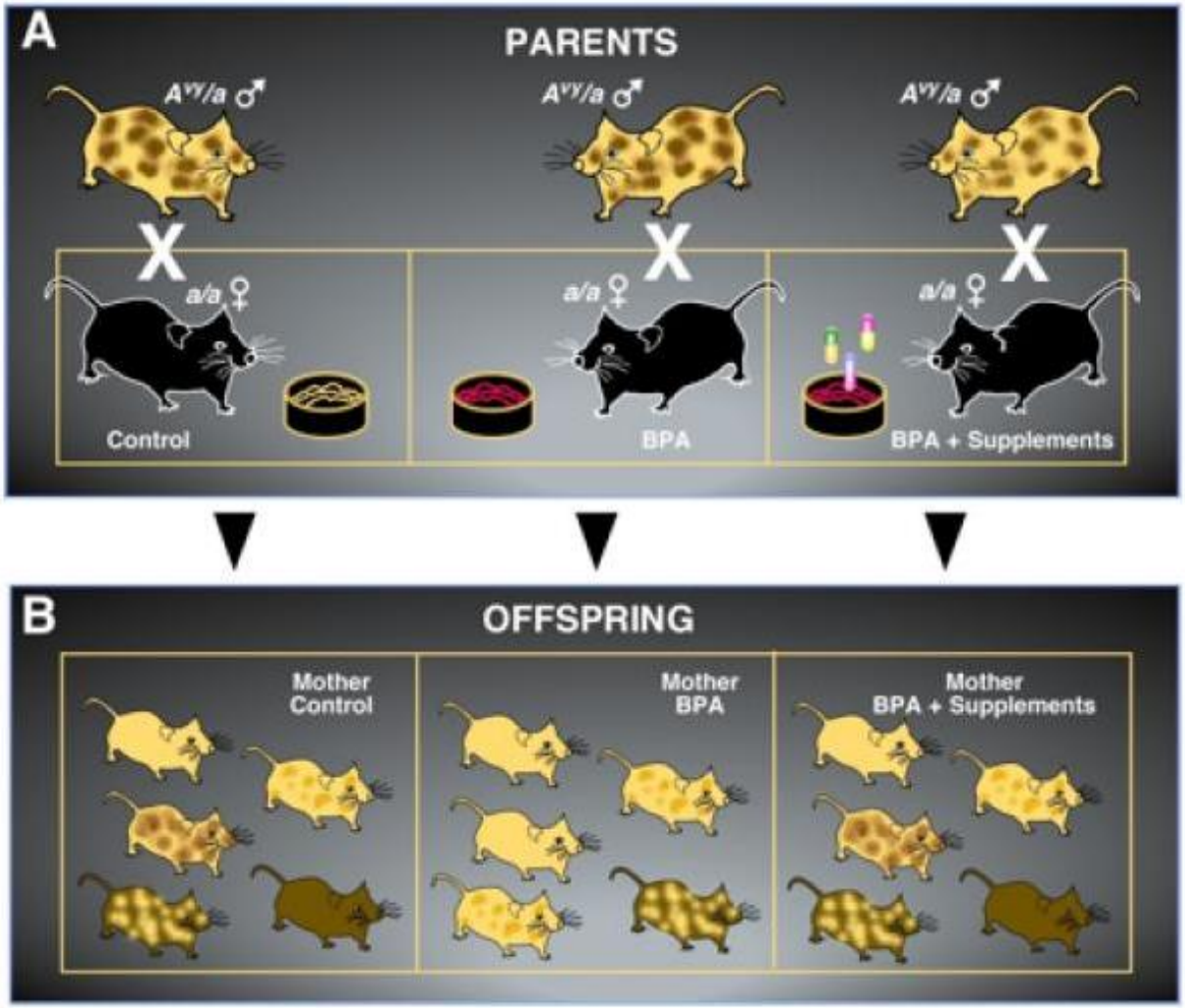
Population-based Birth Cohorts and prospectively collected samples

Perinatal Bisphenol A (BPA) Exposure, Epigenetics, and Metabolic Homeostasis

Perinatal Lead (Pb) Exposure, Epigenetics, Metabolic Homeostasis, and Adult Neuropathology

Perinatal Exposures & Life Course Follow-up
Dietary Assessment
Epigenetic Drift with Age
Tissue and Cell Specific Epigenetic Alterations

(A) Diet Matters: Maternal Supplementation Counteracts BPA



Dolinoy et al PNAS 2007
Bernal and Jirlte Birth Def Res 2010

(A) Diet Matters:
BPA + High Fat Diets: Humanized Diets

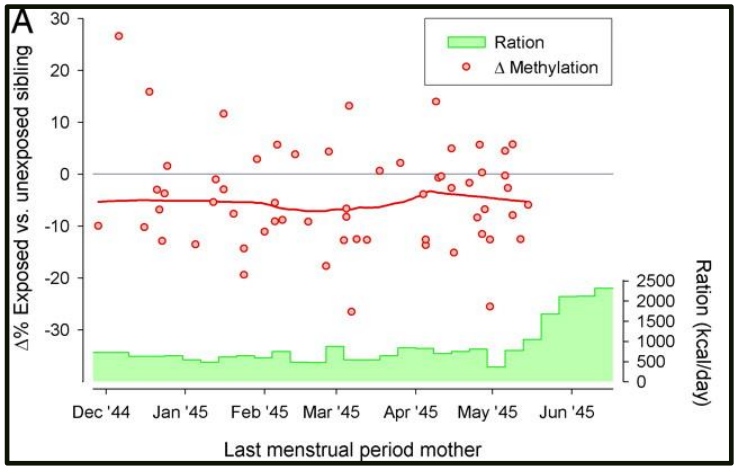
Chow Ingredients	Control	Mediterranean	Western
Kcal/g Diet	3.98	4.53	4.72
% Calories from Fat	16%	42%	40%
PUFA:SFA:MUFA	1 : 0.2 : 0.5	1 : 1.3 : 5.6	1 : 1.9 : 1.6
Protein (casein)	20	19	19
Carbohydrate Content (g/100g chow)			
Cornstarch	40	23	14
Sucrose	10	9.2	25.5
Cellulose	5	8	2

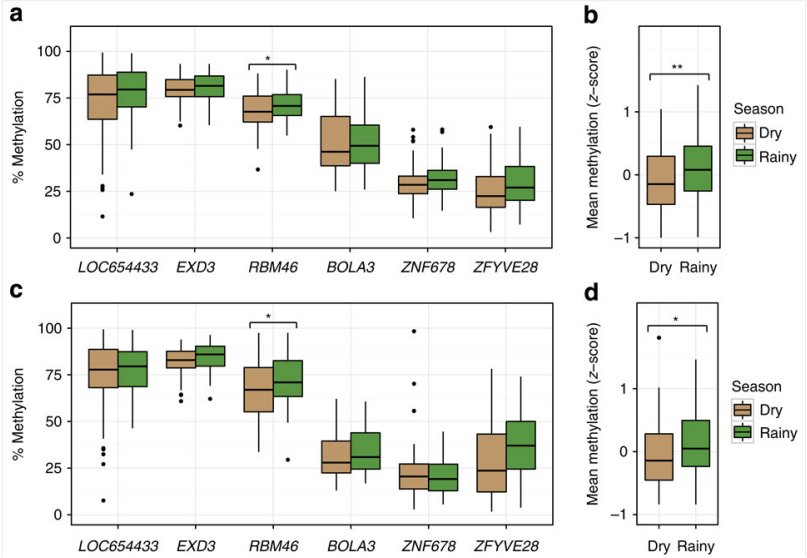
Lipid composition and type of carbohydrate were altered and protein kept constant.

Vitamins and minerals were altered to mimic human HFDs

Med diet based on human Cretan diet (Kafatos et all 2000 *JADA*) and Western chow was based on US. Junk food diet (USDA 2012)

(A) Diet Matters: Maternal Diet and Epigenetics in Humans





Heijmans B T et al. *PNAS* 2008;105:17046-17049

Waterland RA. et al PLoS Genetics 2010
Dominguez-Salas P. et al Nature Communications 2014

(B) Lifecourse Matters: Epigenetic Reprogramming

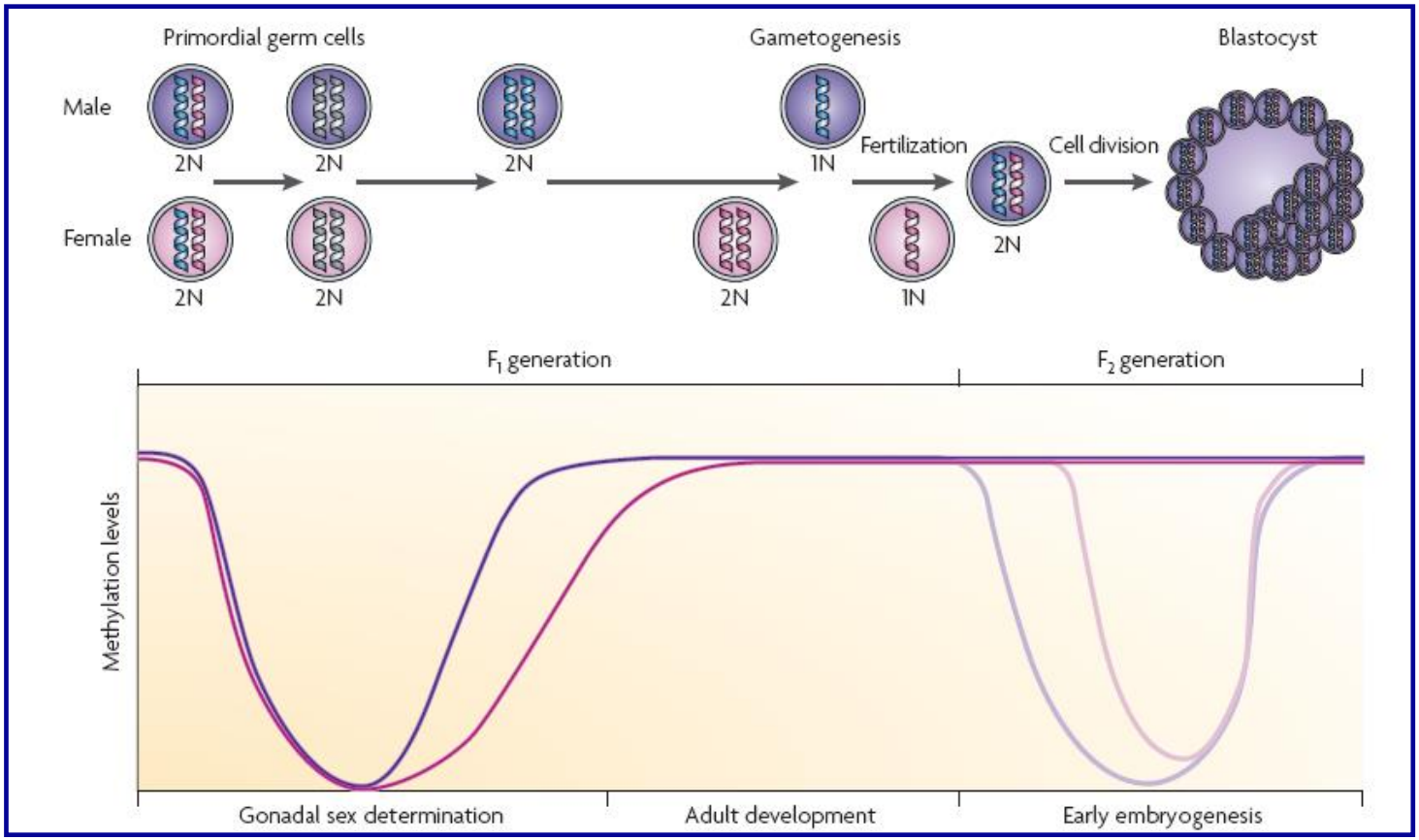
Gametogenesis

Pre-implantation stage of embryogenesis

Fetal/neonatal development

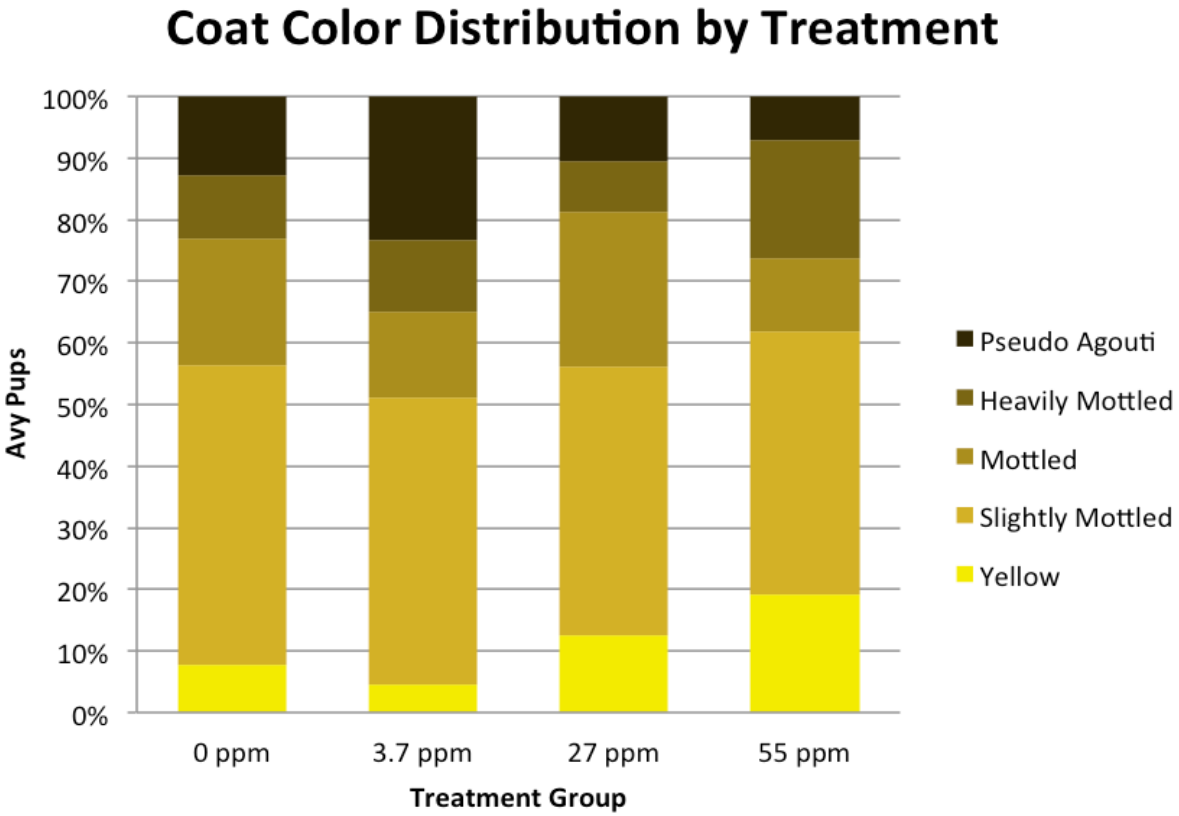
Puberty

Old age



Jirtle and Skinner *Nature Reviews Genetics* 2007

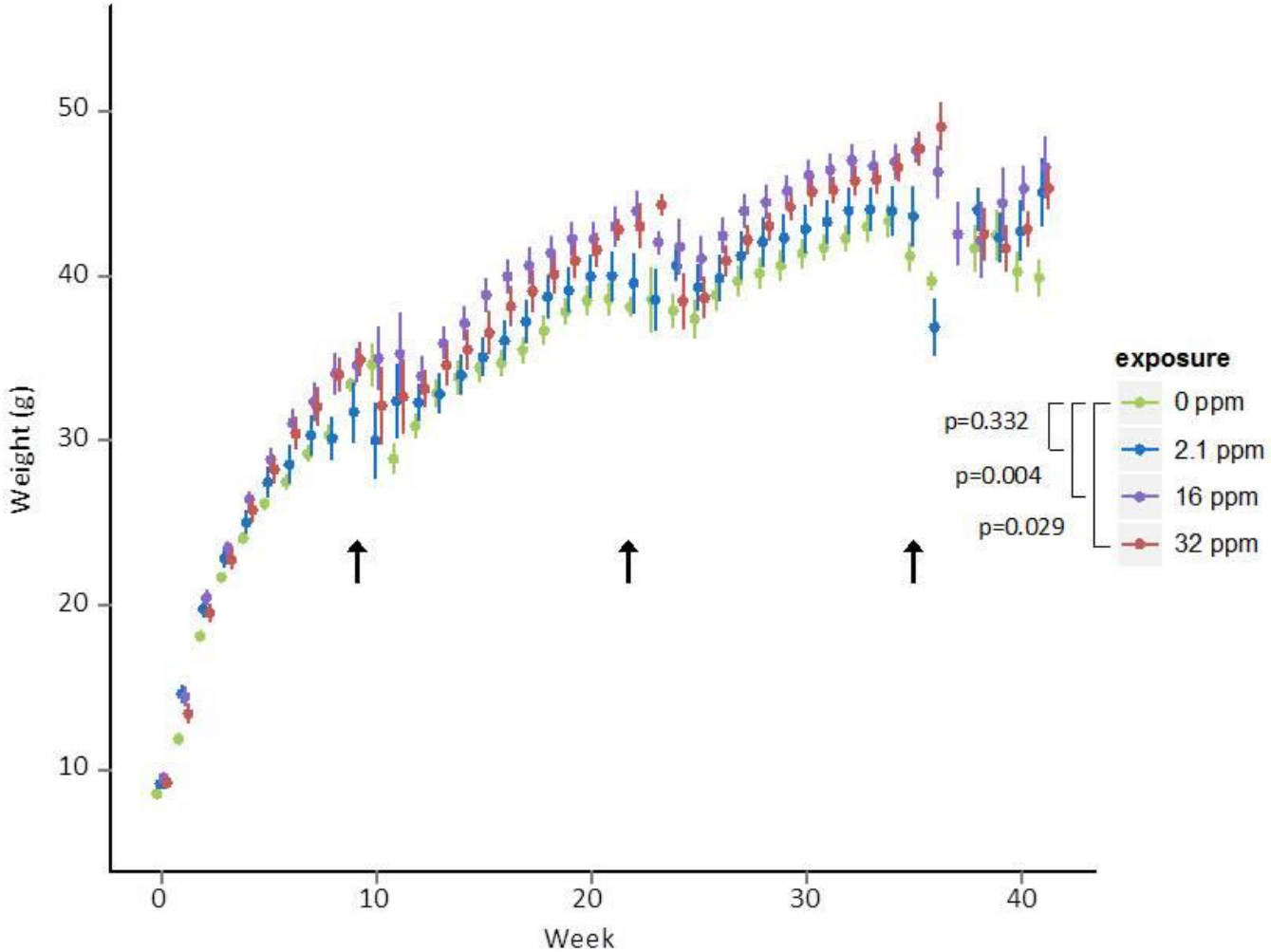
(B) Lifecourse Matters: Perinatal Lead (Pb) Exposure and Coat Color



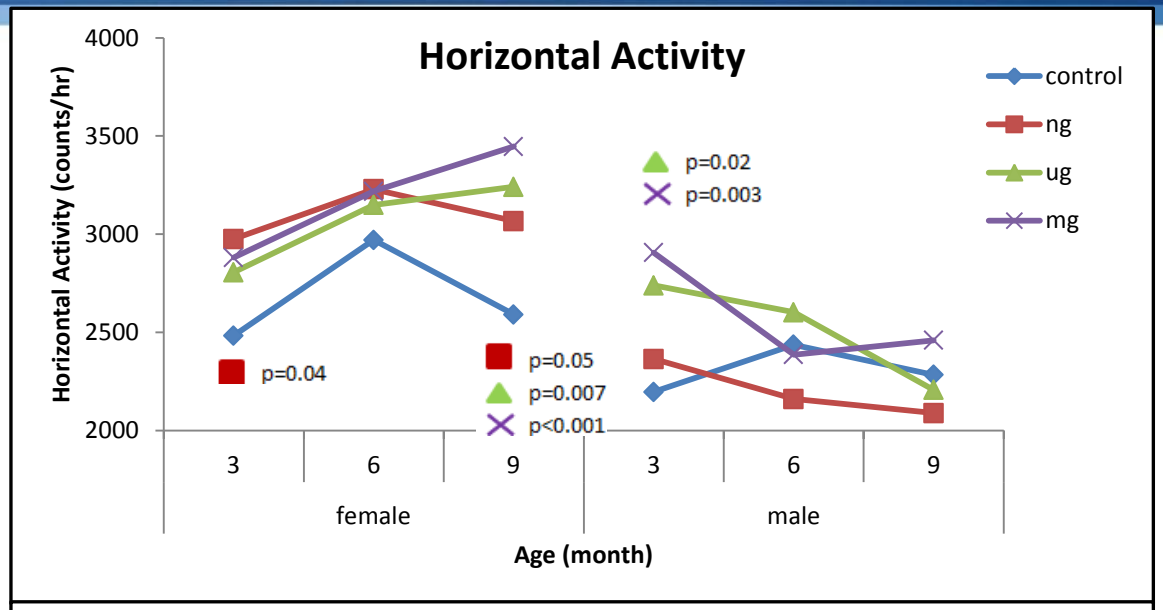
n=	39	43	48	42

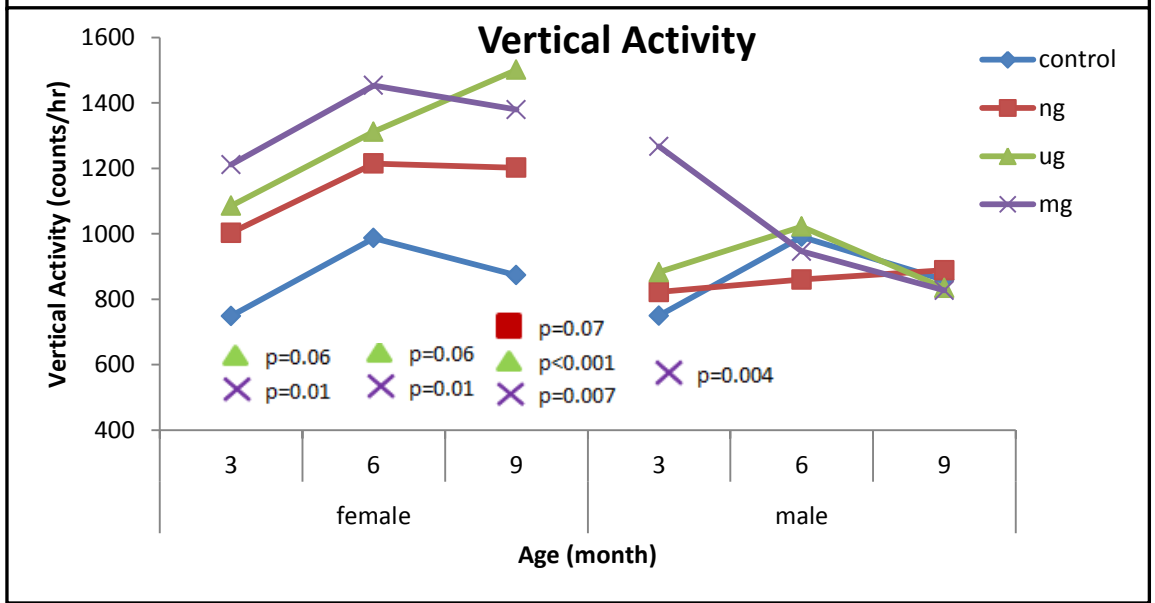
(B) Lifecourse Matters: Pb & Persistent Effects on Male Body Weight

Body weight was higher at weaning and persisted across lifespan in the males exposed to Pb perinatally.



(B) Lifecourse Matters: Perinatal BPA and Physical Activity



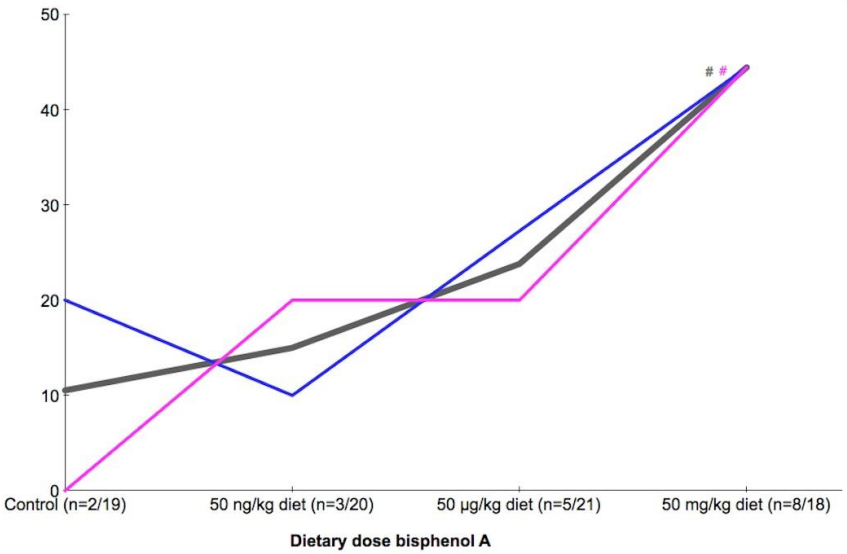


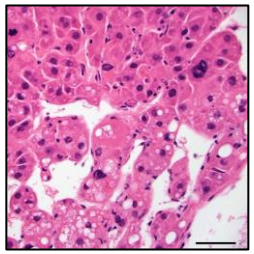
Anderson *et al.*
FASEB 2013

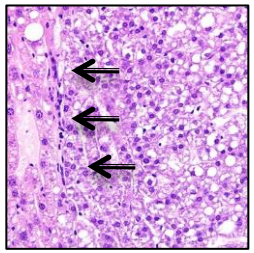
(B) Lifecourse Matters: Perinatal BPA and Liver Tumors

Percentage of animals with neoplastic and pre-neoplastic lesions

* p<0.05 on exact test and test of trend

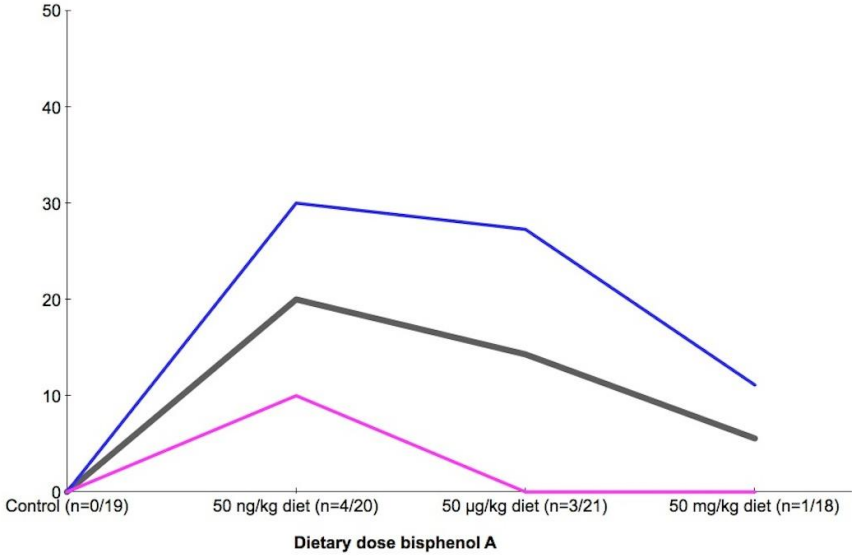


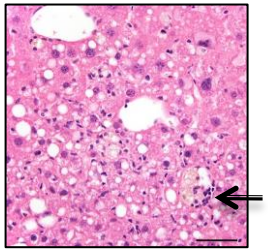




Low dose incidence of multinucleated hepatocytes

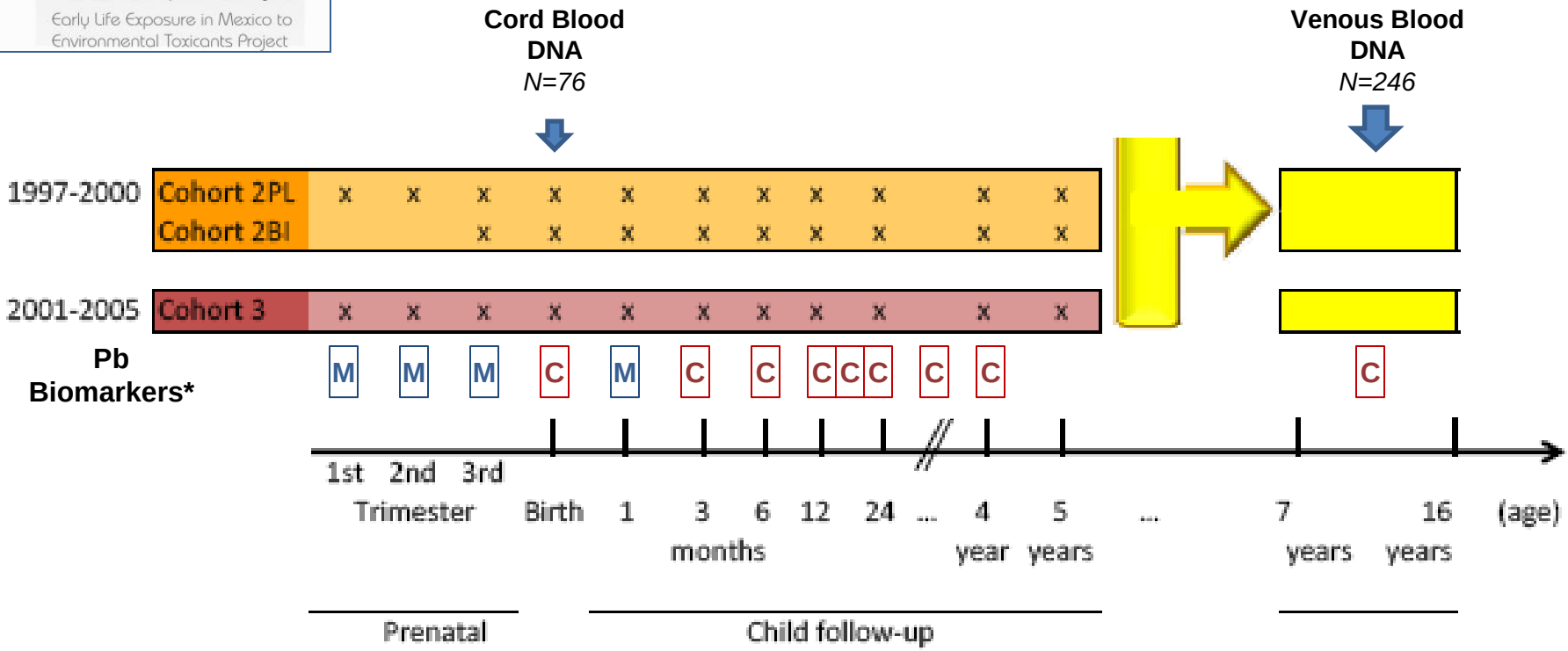
(non-significant)





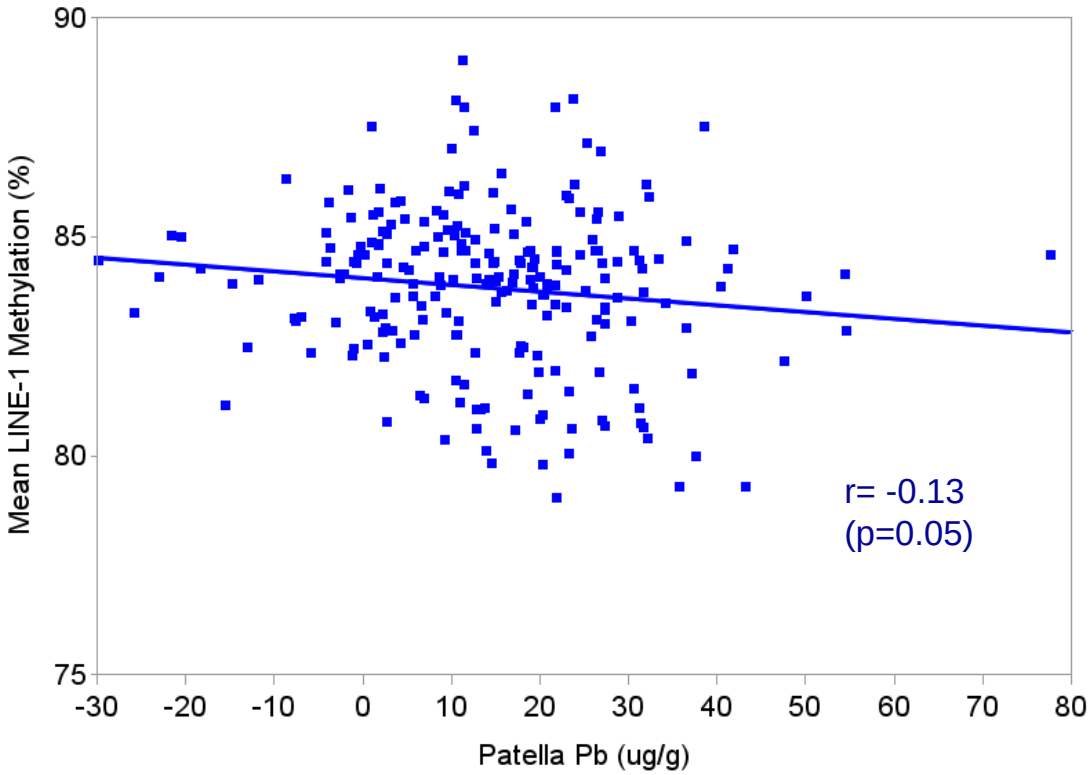
Weinhouse *et al.* EHP 2014

(B) Life Course Matters
Early Life Pb Exposure and Epigenetic Drift in the ELEMENT Cohort



*M=maternal (blood during pregnancy, tibia and patella Pb at 1 month PP)
C=children (cord blood at birth, venous blood for the rest)

Perinatal Lead (Pb) Exposure and LINE-1 Methylation

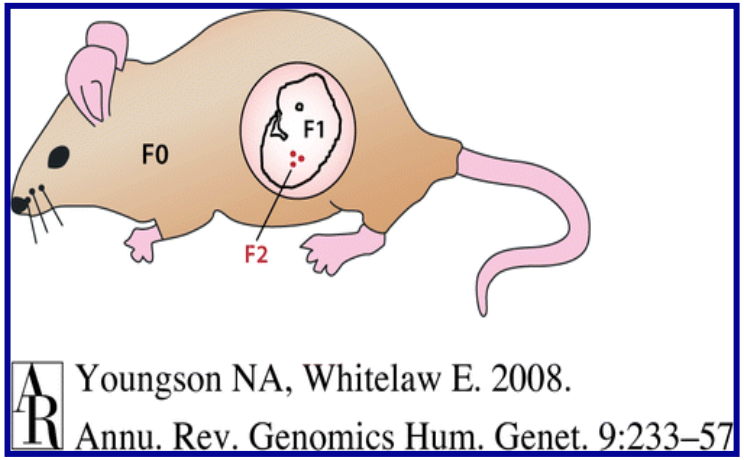


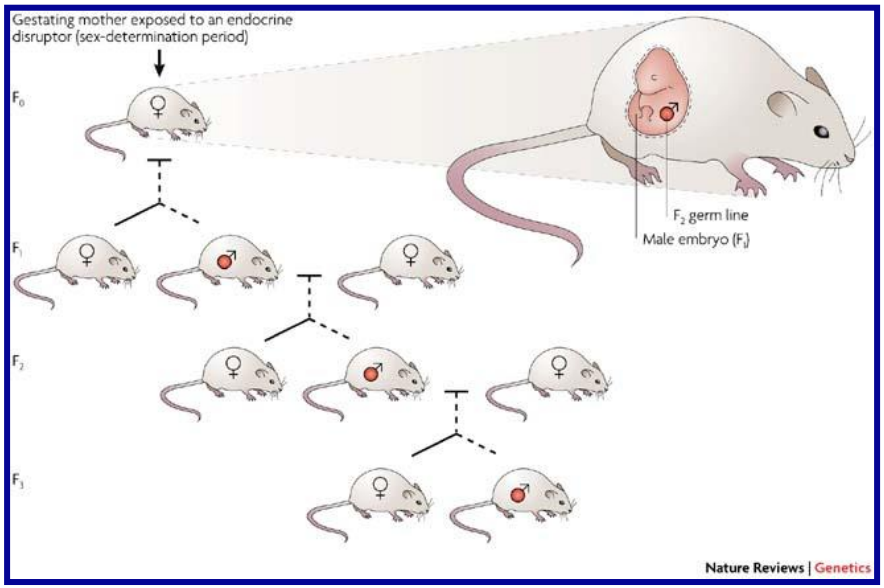
Adjusted for gestational age, gender, maternal folate intake in linear regression model:

Beta= -0.02 (p= 0.04)

LINE-1 methylation decreases by 0.02% per each µg/g maternal patella Pb

(C) Future Generations Matter:



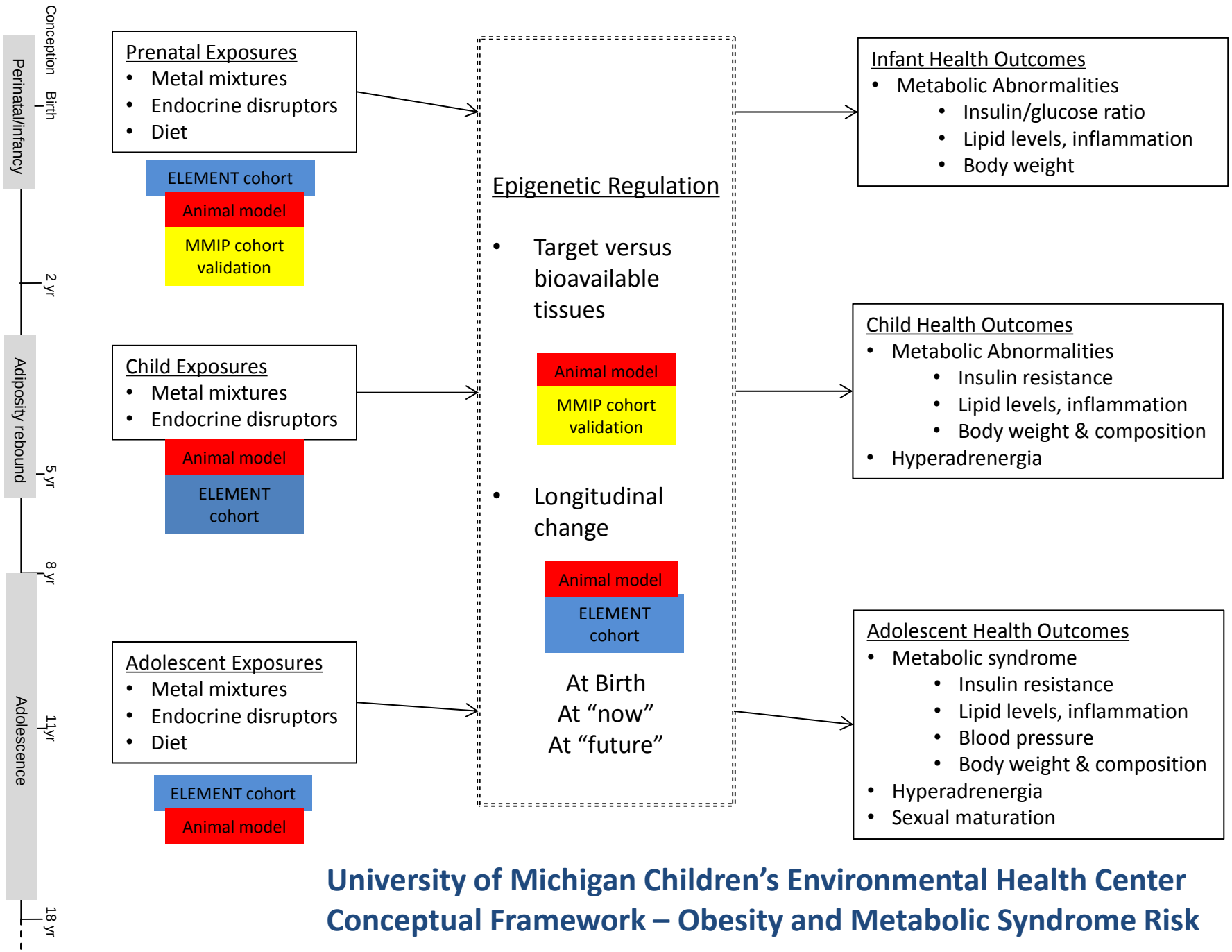


Inter- or Multi-generational (F1, F2)

http://www.germlineexposures.org

Transgenerational (F3 or beyond)

PLoS ONE 2010; Anway et al 2005
Science; Anway et al 2006
Endocrinology



University of Michigan Children's Environmental Health Center
Conceptual Framework – Obesity and Metabolic Syndrome Risk

Acknowledgements & Questions

P01 Children's Environmental Health & Disease Prevention Center

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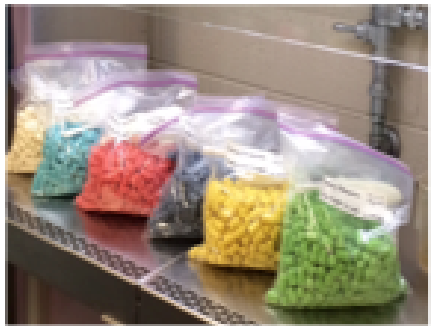
(A) Diet Matters: BPA + High Fat Diets: Humanized Diets

Macro & Micronutrient Content of 3 Mouse Diets			
Diet Ingredients	Control	Mediterranean	Western
MACRONUTRIENTS			
Kcal/g Diet	3.98	4.53	4.72
% Calories from Fat	16%	42%	40%
PUFA:SFA:MUFA	1 : 0.2 : 0.5	1 : 1.3 : 5.6	1 : 1.9 : 1.6
Protein (casein)	20	19	19
Carbohydrate Content (g/100g chow)			
Cornstarch	40	23	14
Sucrose	10	9.2	25.5
Cellulose	5	8	2
VITAMINS & MINERALS			
Vitamin A (IU)	4000	8000	4000
Vitamin C (mg)	0	500	0
Vitamin D (IU)	1000	1000	400
Vitamin E (IU)	75	75	25
Folic Acid (mg)	2	4	1
Sodium (mg)	1039	1039	7000
Potassium (mg)	3600	8000	3600
Magnesium (mg)	513	850	513



- Lipid composition and type of carbohydrate were altered; protein was kept constant. Vitamins & minerals were altered to mimic the human HFDs.
- Mediterranean HFD chow was based on the human Cretan diet [Kafatos et al. 2000. *JADA. 100:1487-1493*].
- Western HFD chow was based on the US junk food diet [USDA 2012].