What a difference a day makes: Critical exposure periods for adverse birth outcomes

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EPA Temporal Exposure Workshop
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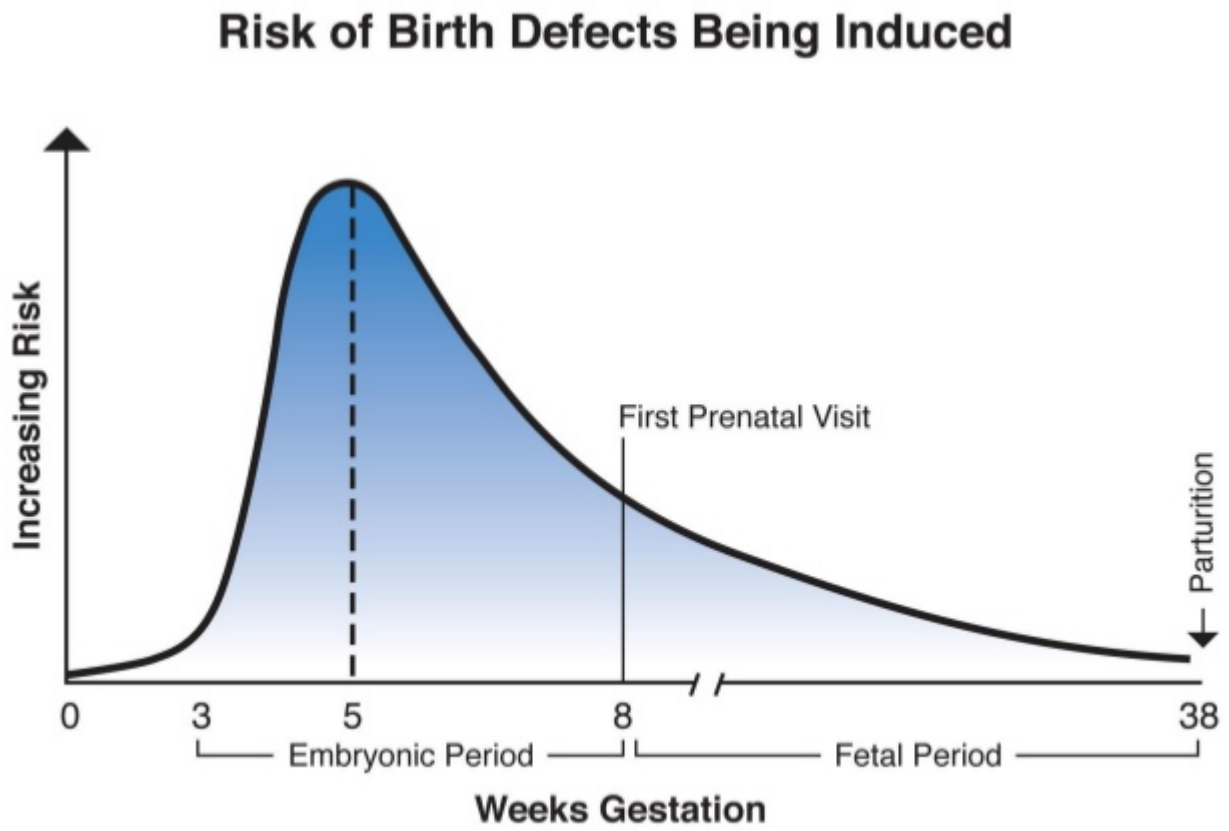
Overview

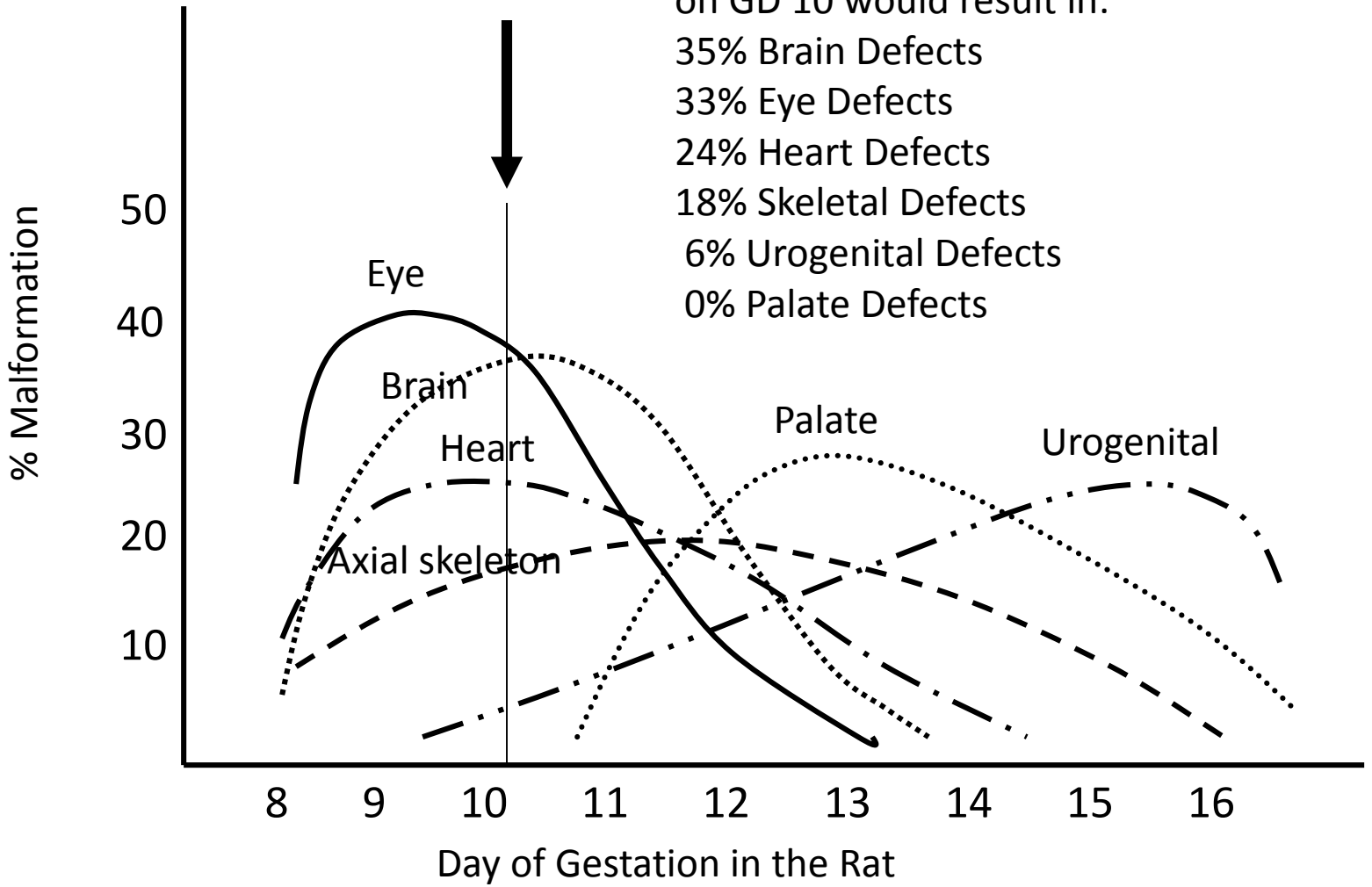
- Examples of critical periods of sensitivity to exposure
  - Lab animal and human
- Epigenetics and transgenerational effects
- DOHaD and epigenetics
  - The example of parental smoking
- Cumulative risk – when does it start, what does it include?
  - And when is an outcome adverse?

Critical periods of sensitivity to teratogenesis



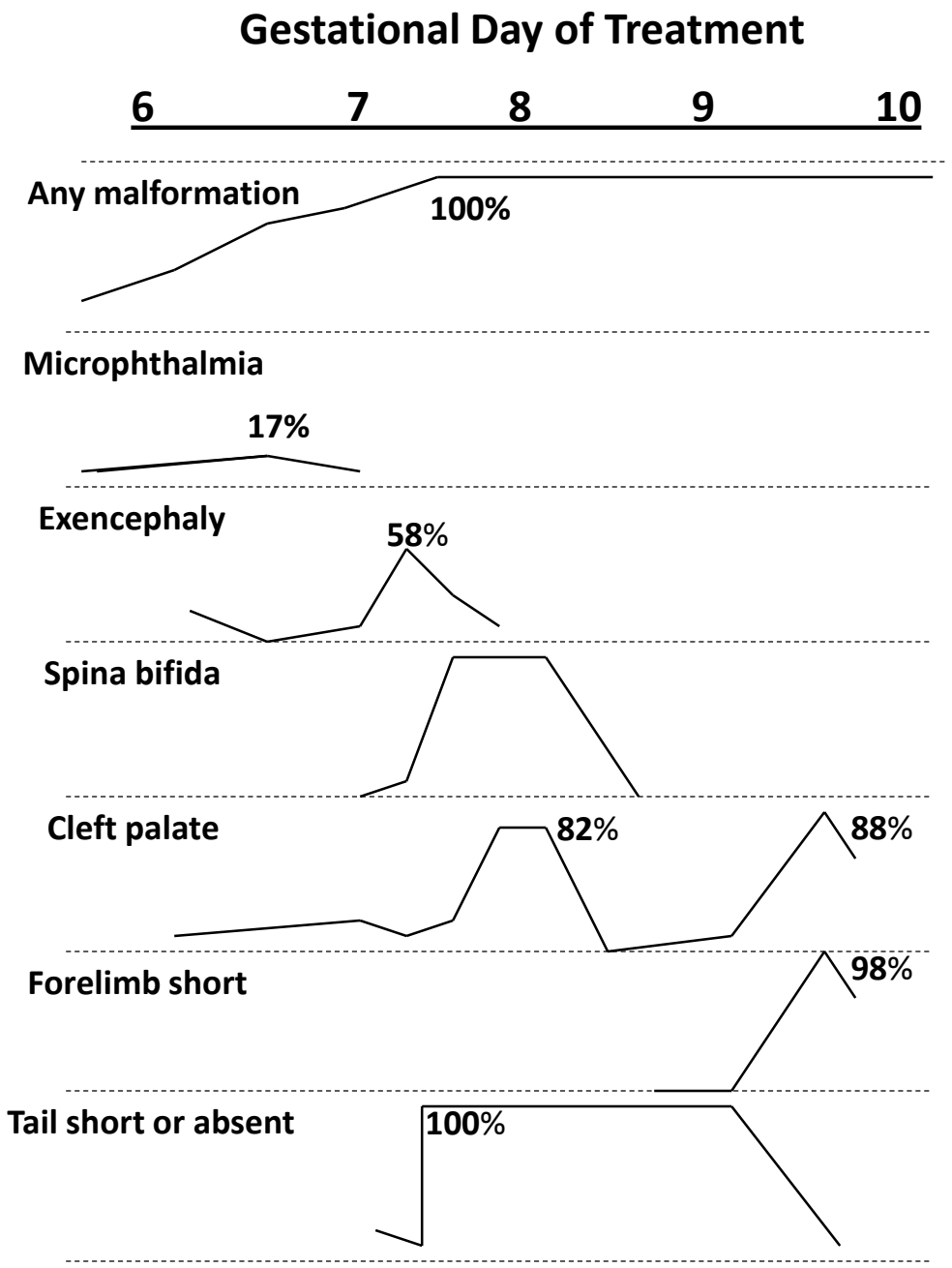
Critical Periods of Susceptibility (Wilson)

A brief pulse of teratogenic treatment on GD 10 would result in:
35% Brain Defects
33% Eye Defects
24% Heart Defects
18% Skeletal Defects
6% Urogenital Defects
0% Palate Defects

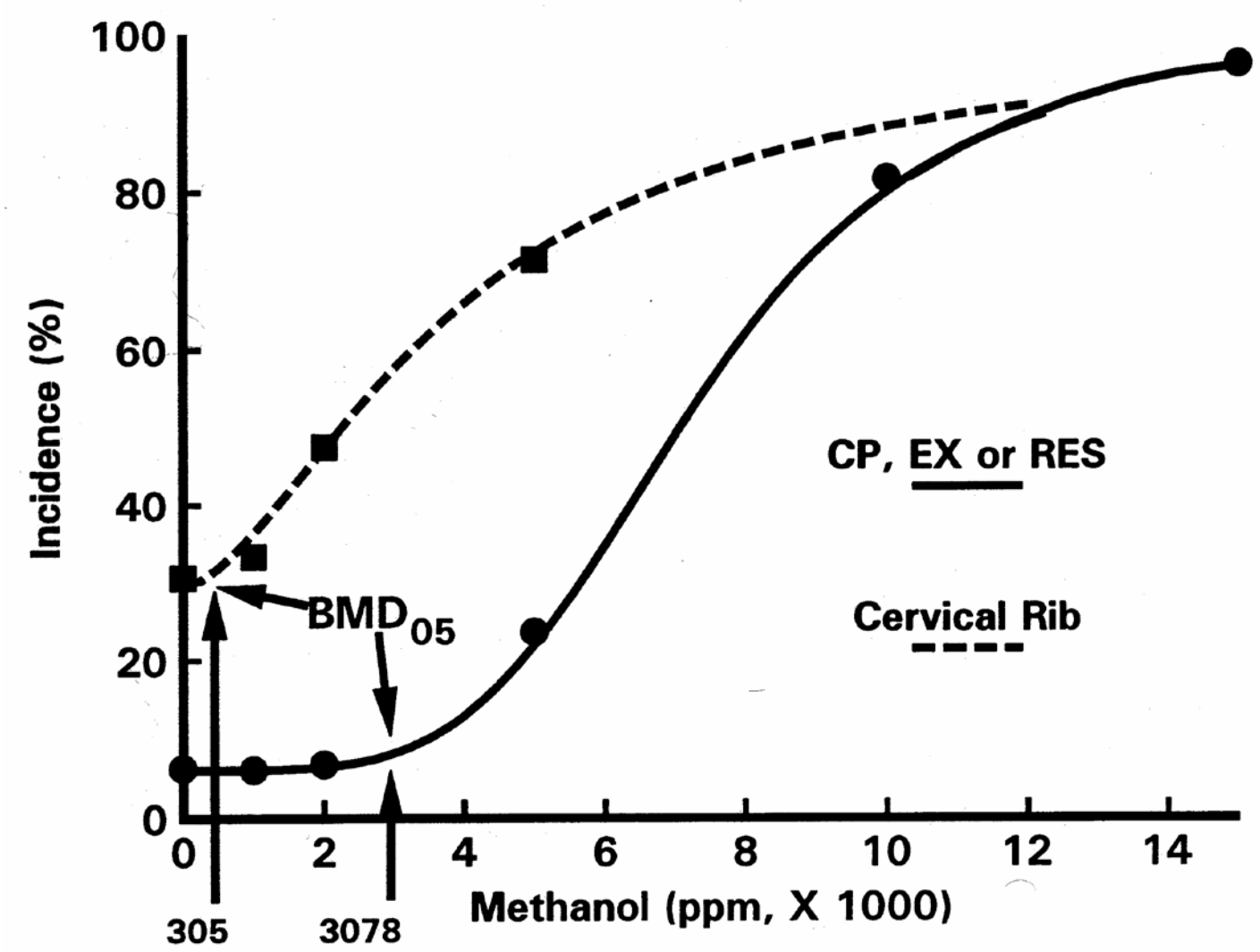


After J.G. Wilson, 1973

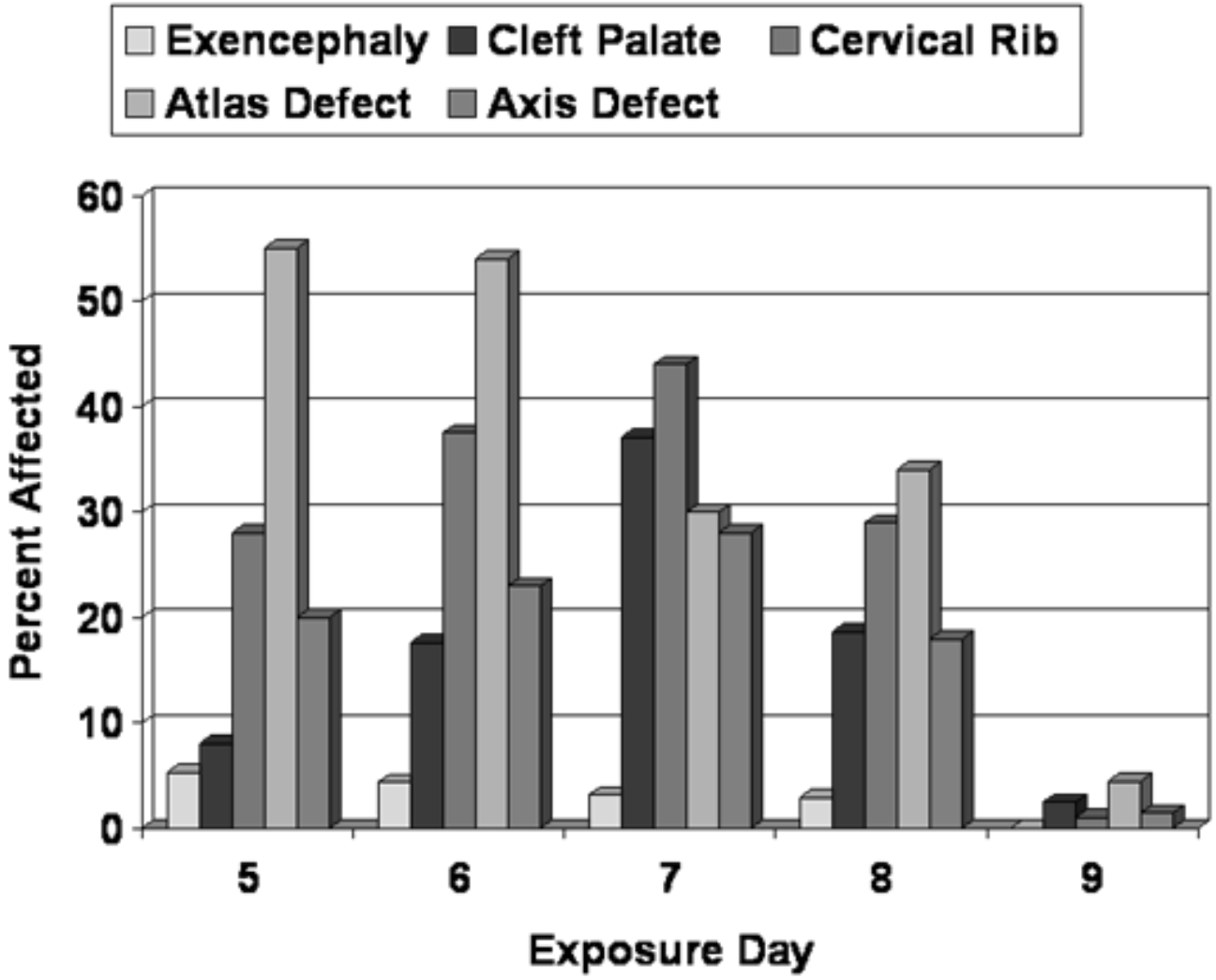
Timed exposure to retinoic acid in the hamster (Shenefelt)



Methanol dose response



Effects of single day exposure: CD-1 mouse

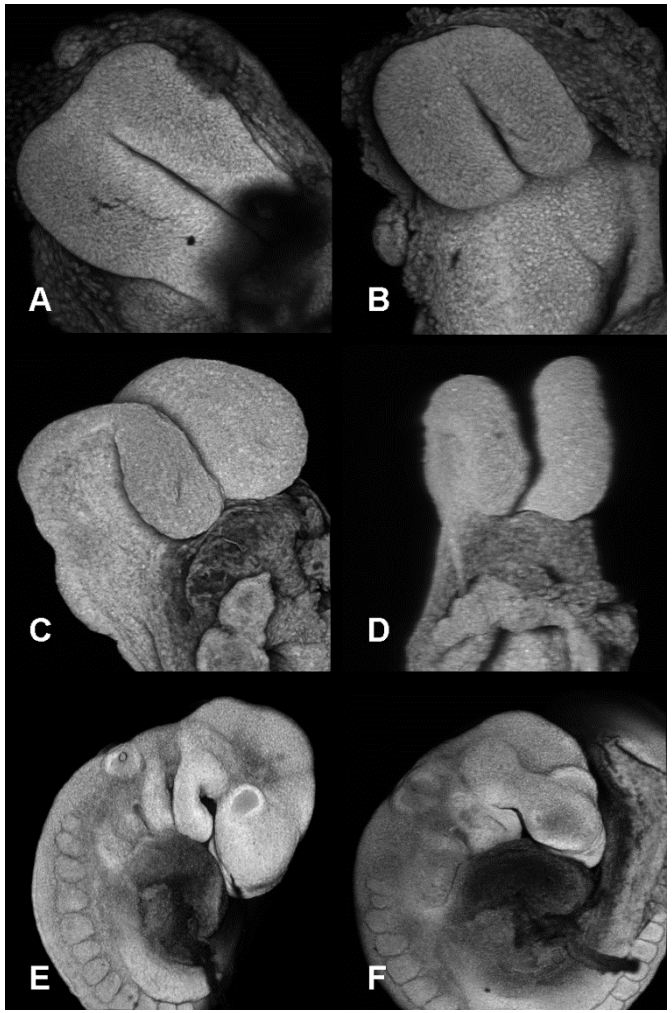


Effects of methanol on the C57/BL6 mouse embryo

GD 7

GD 8

GD 9



Control Methanol

GD 9

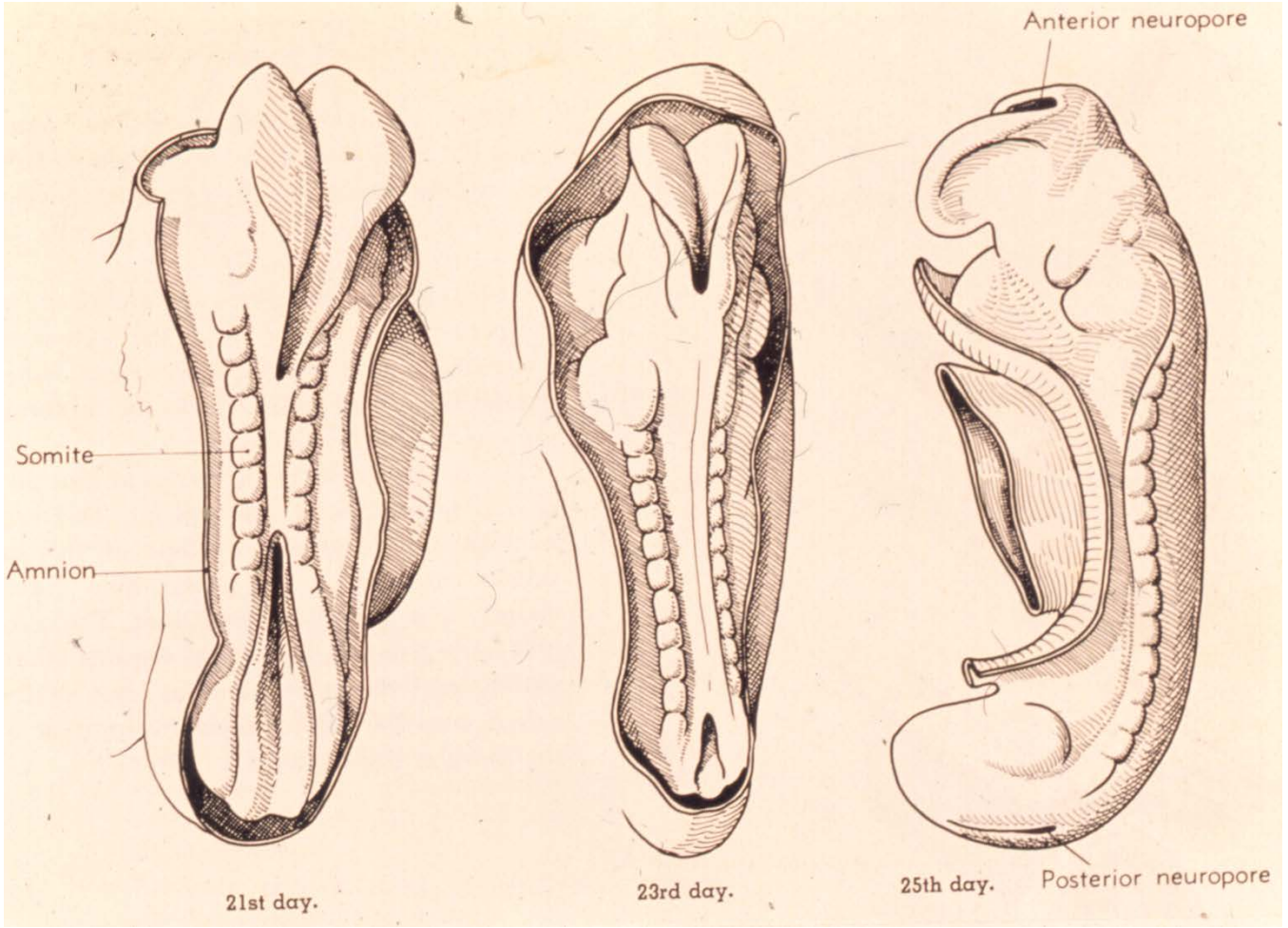
Holoprosencephaly

Gastrulation stage human embryo

Primitive streak

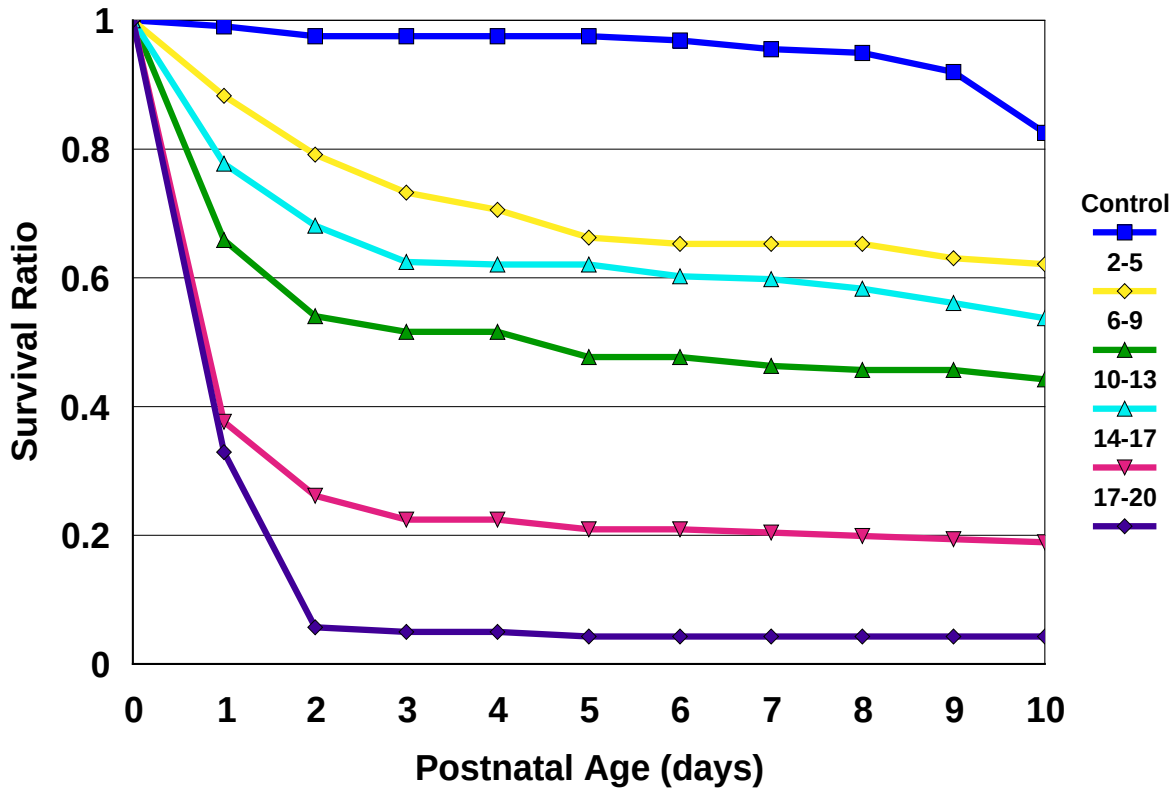
Day 18

Neural tube closure in the human embryo



Day 21 Day 23 Day 25

PFOS: Critical periods for postnatal mortality

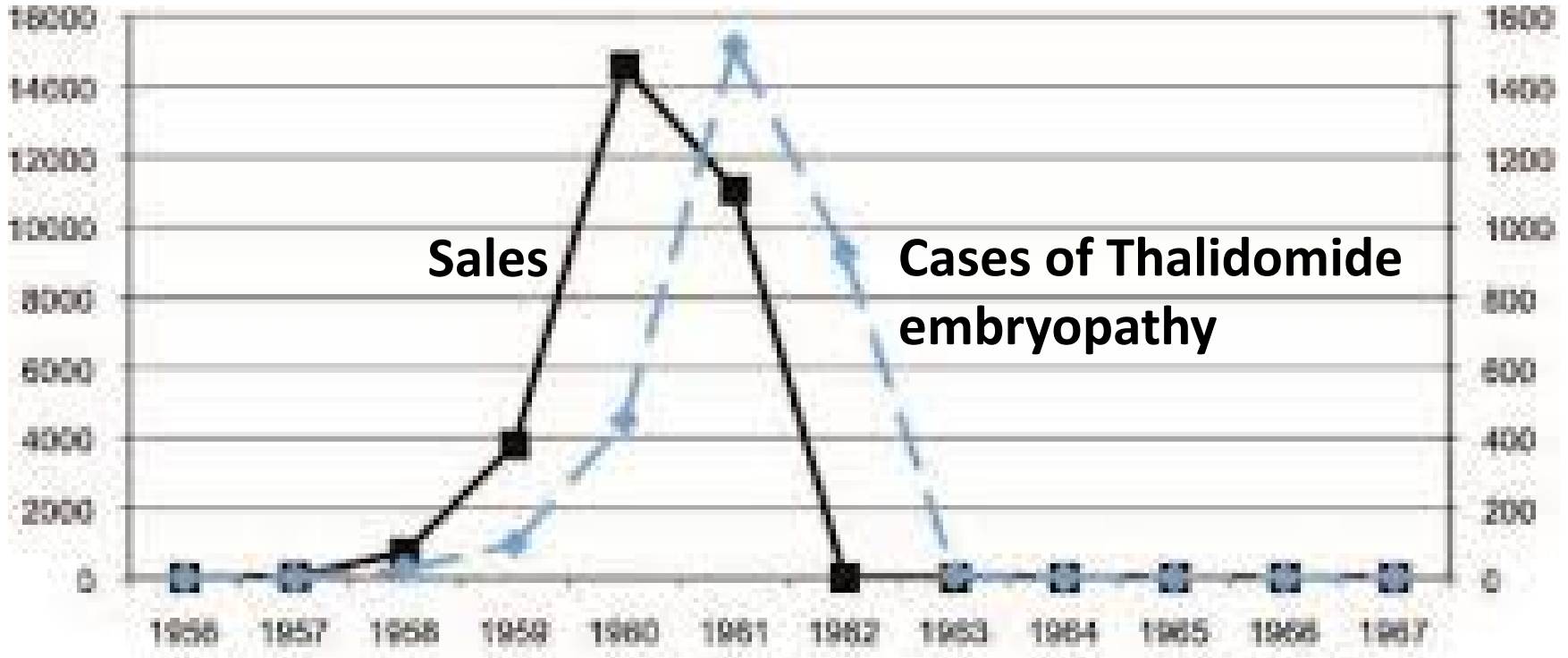


Thalidomide

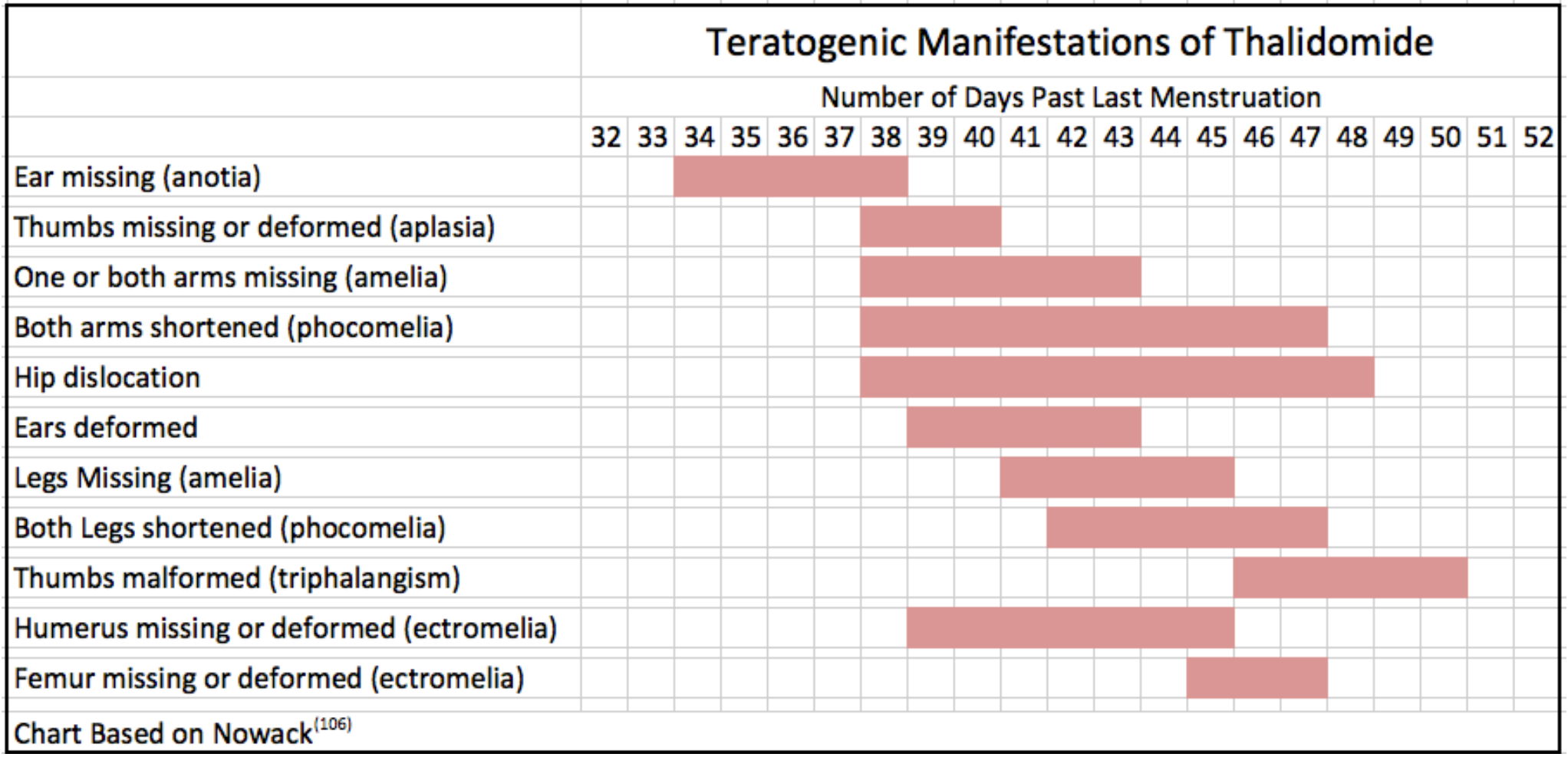
1962: Frances Kelsey awarded the President's Award for Distinguished Federal Civilian Service by President John F. Kennedy

2014: Thalidomide teratogenesis in Brazil
Used as treatment for leprosy

Thalidomide 1958-1963



Critical periods for thalidomide malformations



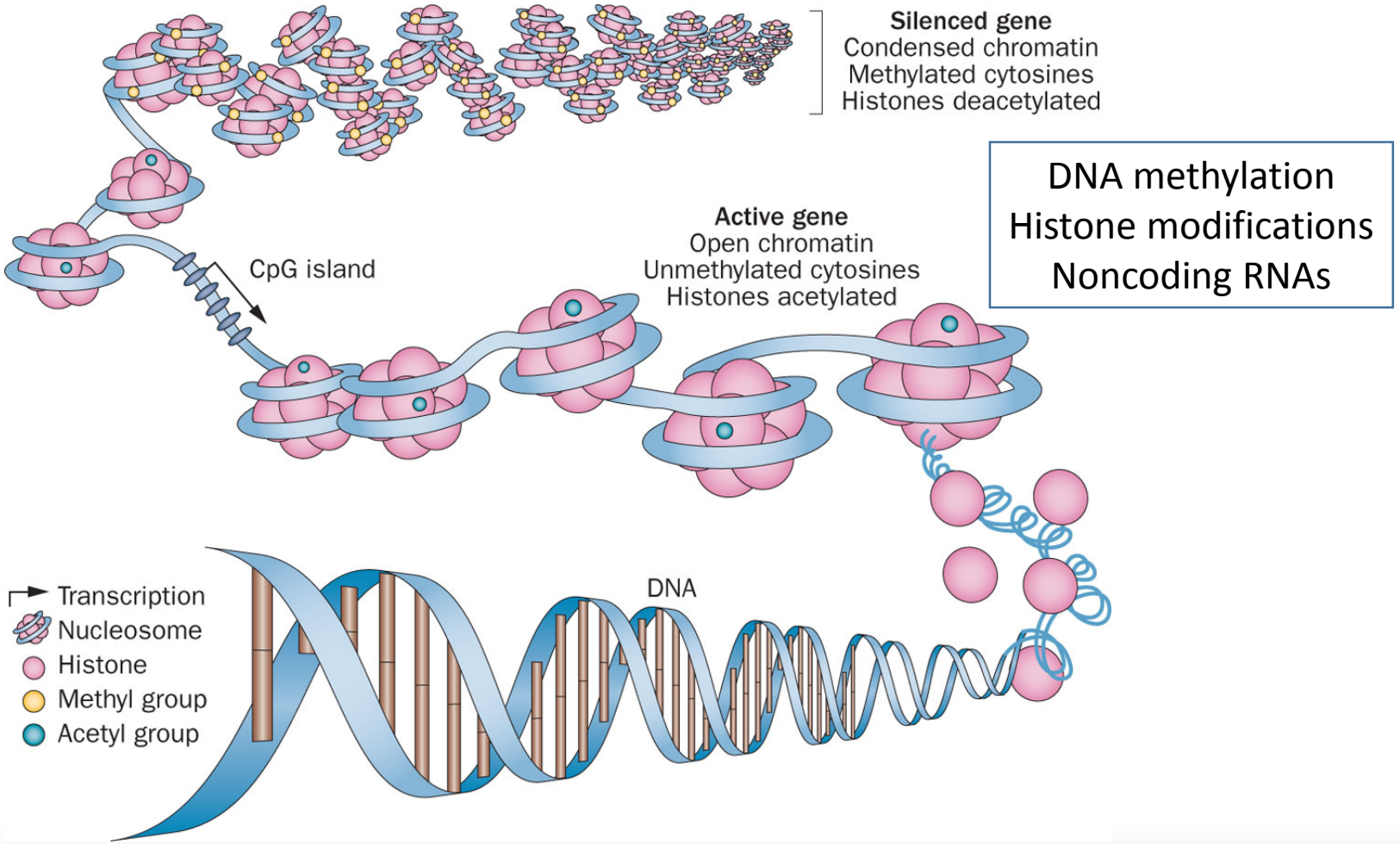
Critical periods of susceptibility in studies of autism spectrum disorders

Trimester	First									Second			Third	
Gestational Weeks	1	2	3	4	5	6	7	8	9	16	20	22	28	38
Brain pathology														
Neurogenesis[145,151,152]	Weeks 1-20													
Neuronal migration[145, 153]	Weeks 1-16													
Neuronal maturation[145,154]	Weeks 1-24													
Exposure														
Freeway proximity[92]													3rd trimester	
Traffic-related Air Pollution[93]	1st, 2nd, and 3rd trimesters													
Pesticides[109,110]				Days 26-81										
Prenatal vitamins[155]	1st month and 3 months before													
Folic acid[27,29]	1st Month[a]													
Rubella infection[144, 156]	Weeks 1-8													
Fever[142,157]	1st and 2nd trimesters													
Thalidomide[158]				Days 20-24										
Valproic Acid[8,159]				Day 22-28										
SSRI[84,160]	1st trimester[b]													
Prenatal stressors[161]												Weeks 25-28		

Kristen Lyall et al. Int. J. Epidemiol. 2014;43:443-464

International Journal of Epidemiology

Epigenetic regulation of gene expression



DNA methylation
Histone modifications
Noncoding RNAs

Adapted from Figueiredo, L. M. et al. (2009) Nat. Rev. Microbiol. **7**: 504–13

Transgenerational Effects of Vinclozolin

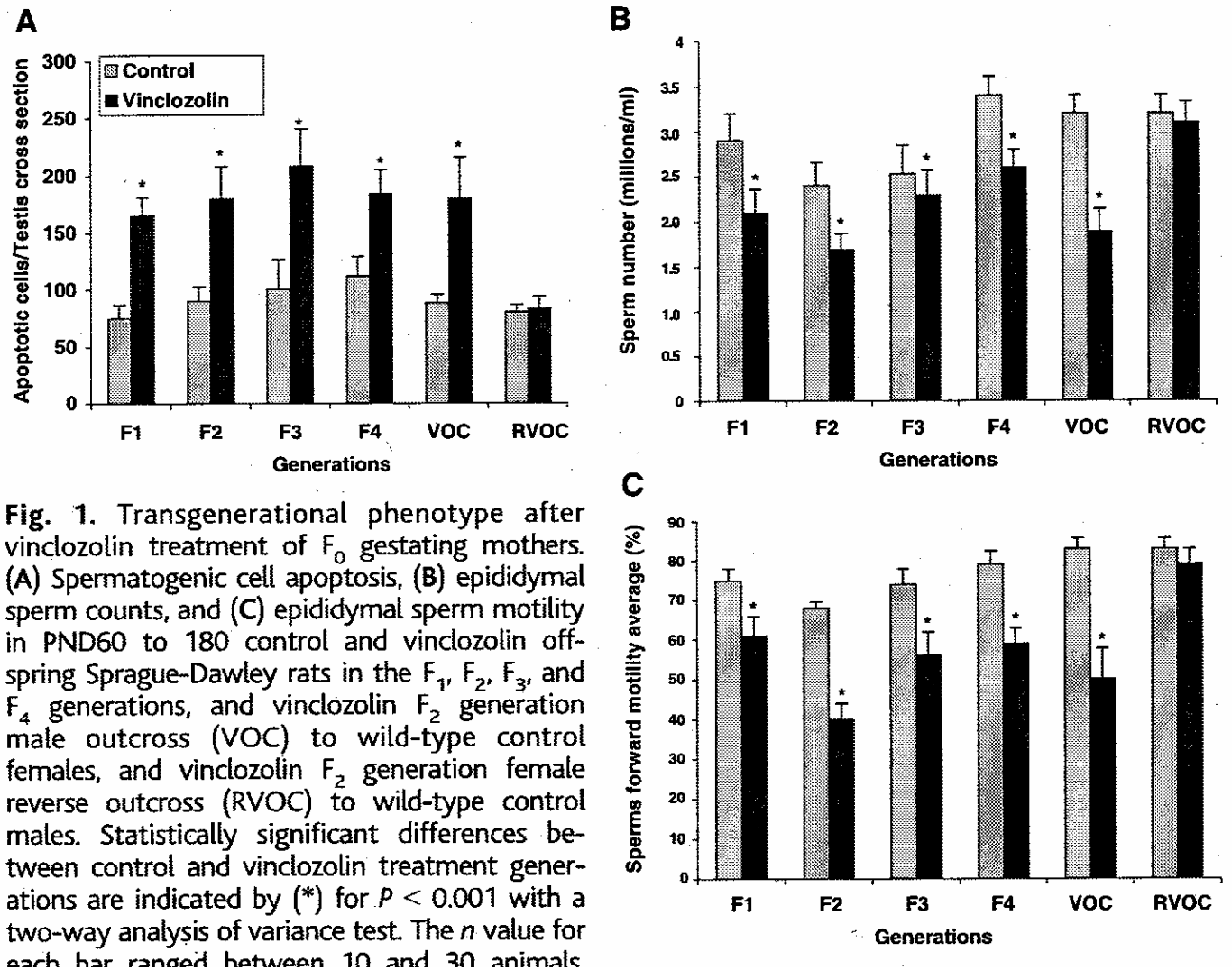
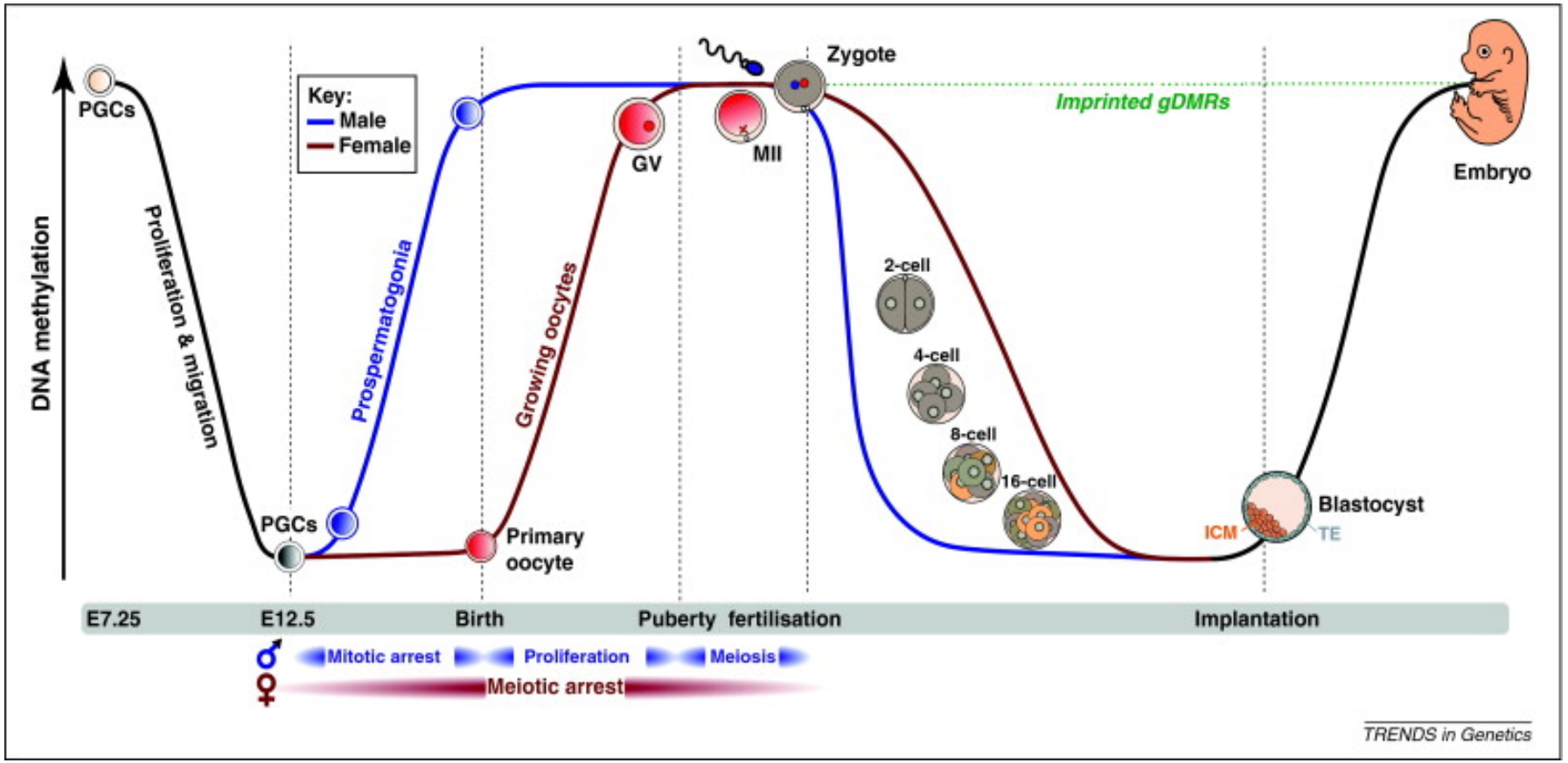


Fig. 1. Transgenerational phenotype after vinclozolin treatment of F_0 gestating mothers. (A) Spermatogenic cell apoptosis, (B) epididymal sperm counts, and (C) epididymal sperm motility in PND60 to 180 control and vinclozolin offspring Sprague-Dawley rats in the F_1, F_2, F_3, and F_4 generations, and vinclozolin F_2 generation male outcross (VOC) to wild-type control females, and vinclozolin F_2 generation female reverse outcross (RVOC) to wild-type control males. Statistically significant differences between control and vinclozolin treatment generations are indicated by (*) for $P < 0.001$ with a two-way analysis of variance test. The *n* value for each bar ranged between 10 and 30 animals

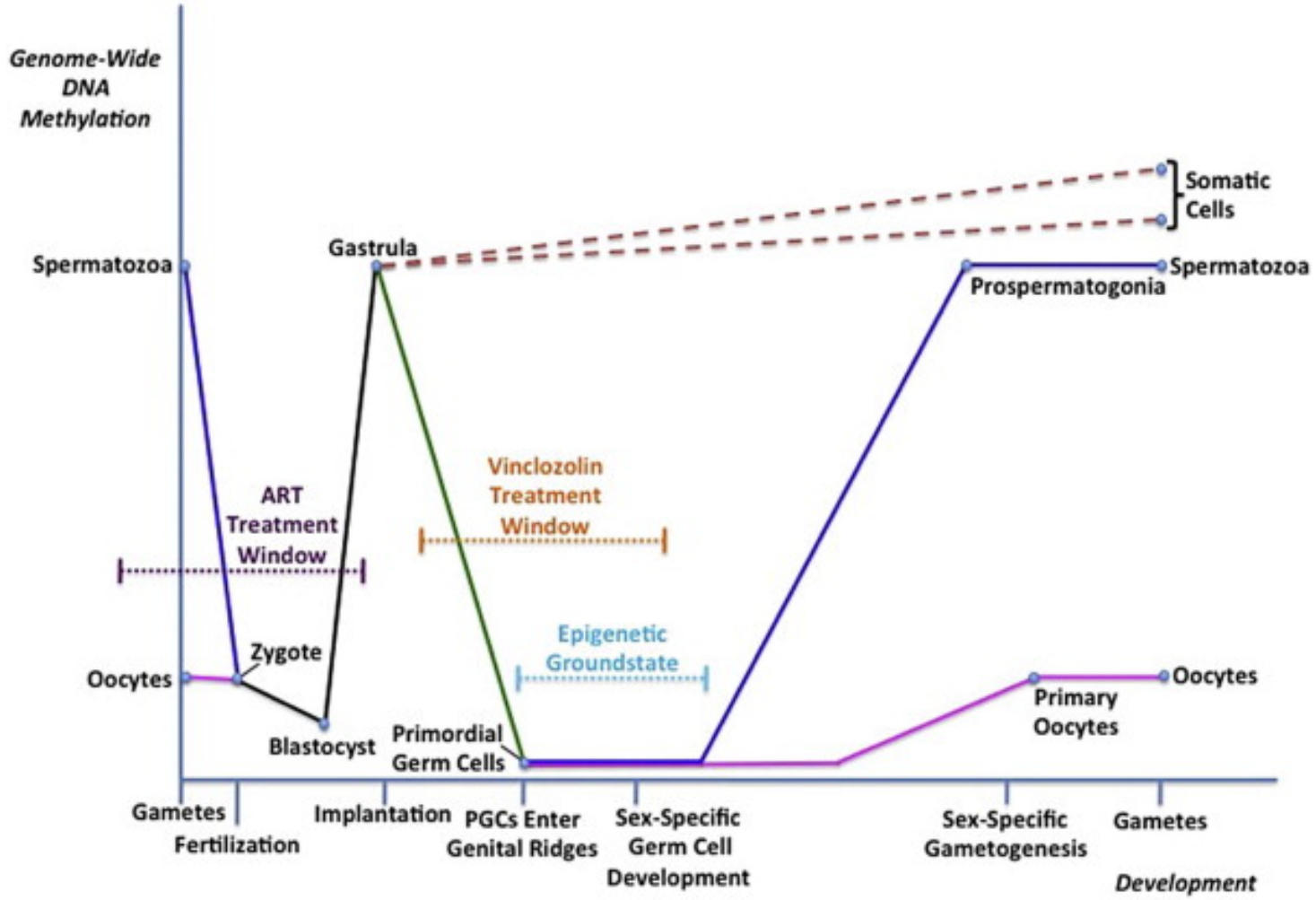
(Anway et al., Science, 2005)

DNA methylation changes during developmental epigenetic reprogramming



Smallwood SA, Kelsey G (2012) Trends Genet 28:33-42

Epigenetic reprogramming in the germ line of the mouse



McCarrey JR (2014) Mol Cell Endocrinol 398:13-23

Human transgenerational epigenetic phenomena?

Don't Count Dad Out

So if a pregnant mother's diet can affect the child's epigenetic outcome, can dad's diet do the same? Quite possibly, according to scientists who delved into the well-kept, historical records of annual harvests from a small Swedish community.

These records showed that food availability between the ages of nine and twelve for the paternal grandfather affected the lifespan of his grandchildren. But not in the way you might think.

Shortage of food for the grandfather was associated with extended lifespan of his grandchildren. Food abundance, on the other hand, was associated with a greatly shortened lifespan of the grandchildren. Early death was the result of either diabetes or heart disease. Could it be that during this critical period of development for the grandfather, epigenetic mechanisms are "capturing" nutritional information about the environment to pass on to the next generation?

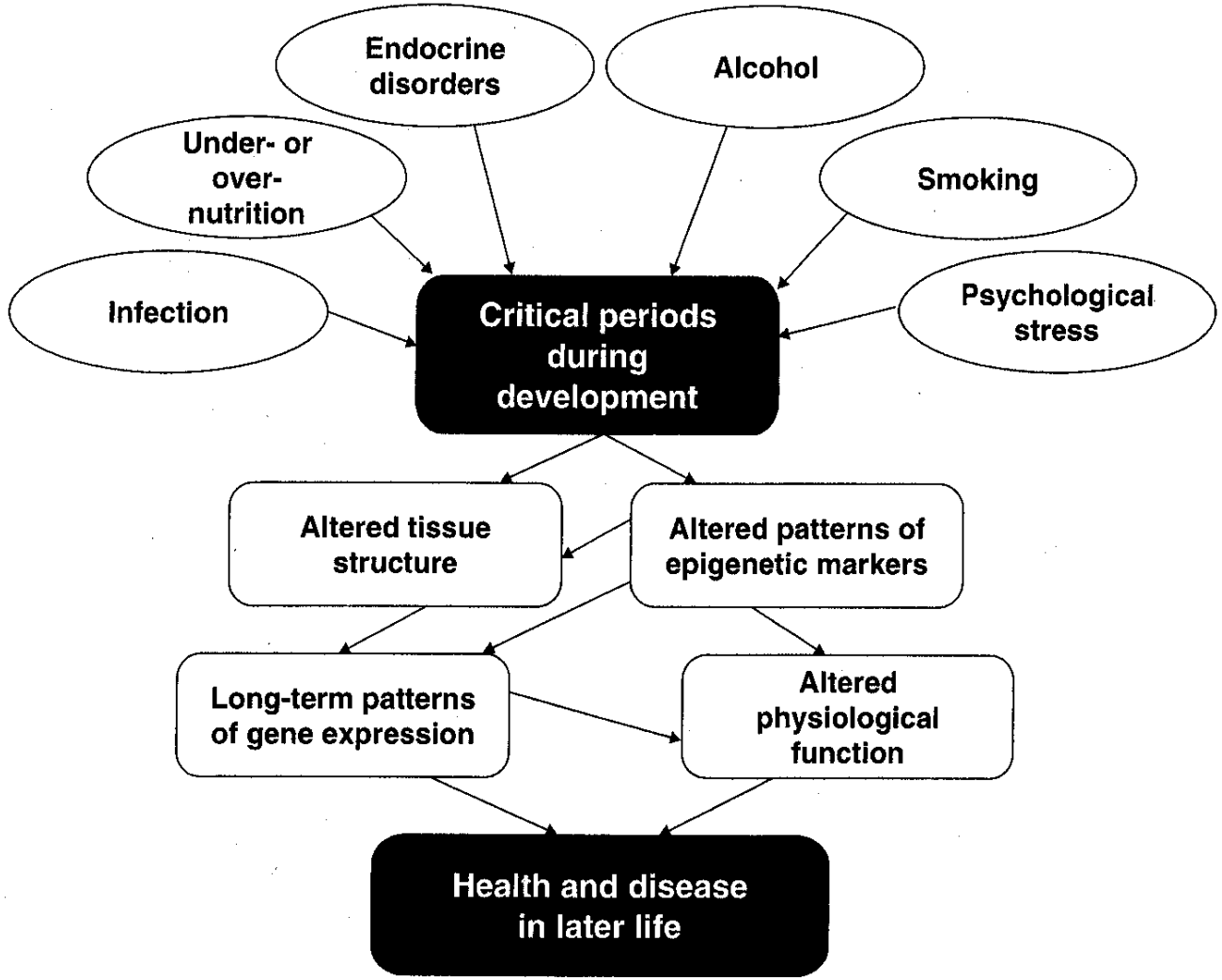
Food abundance for the grandfather was associated with a reduced lifespan for his grandchildren.

ENLARGE PHOTO+

Three generations: Dr. Lars Olov Bygren, with son Magnus and grandson Ludvig in Stockholm

Lars Tunbjork / VU

DOHaD: Agents, Timing and Mechanisms



The Dutch Hunger Winter

A period of severe food shortage in the Netherlands in 1944.

Energy intakes dropped from 1800 to between 400 and 800 kcal per day (equivalent 100 - 200g pasta).

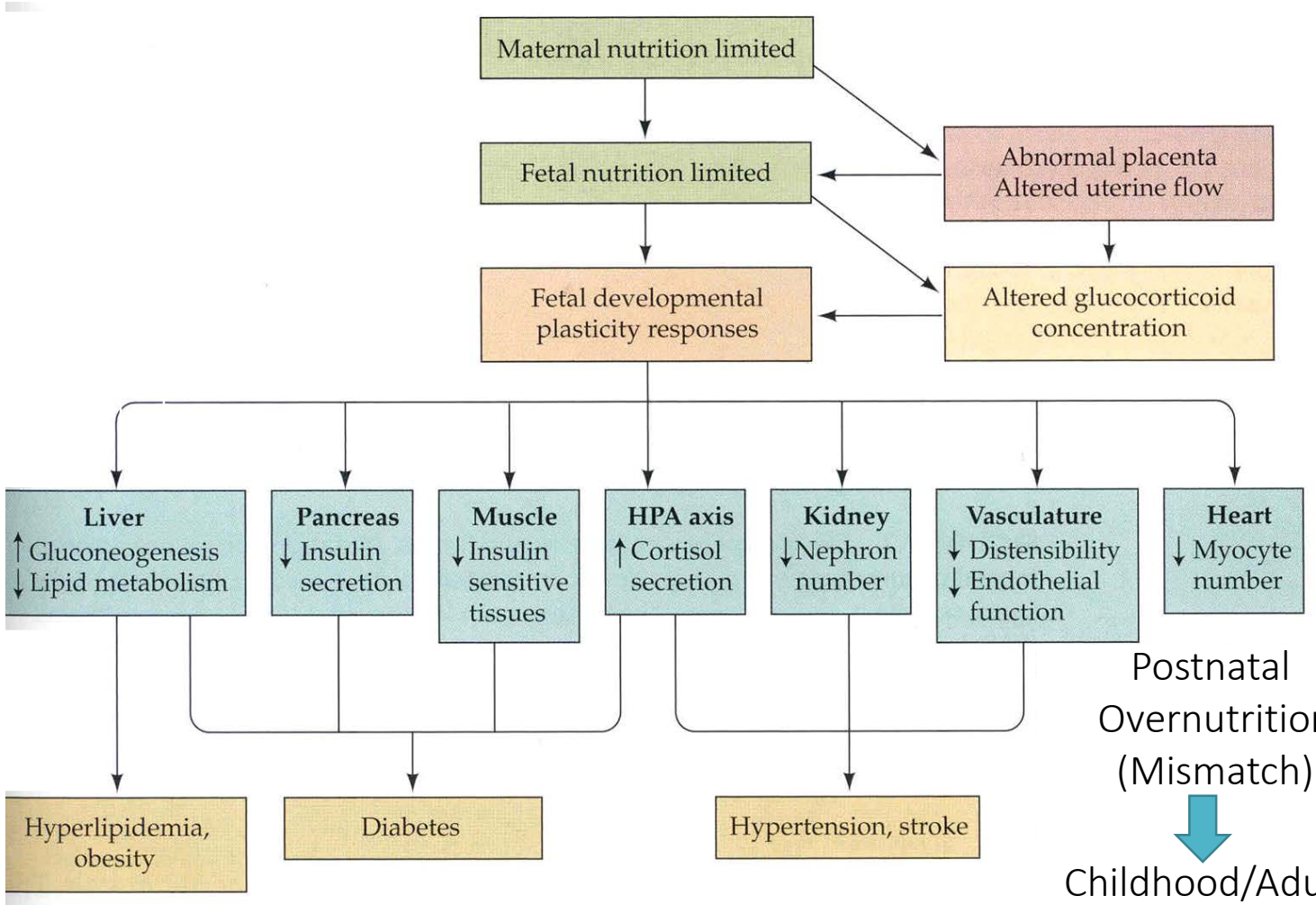
Despite the famine, recording of detail birth records was maintained.

Early gestation → ↑ Obesity, CVD

Late gestation → ↑ Insulin resistance, hypertension

Universiteit Leiden

The Thrifty phenotype hypothesis



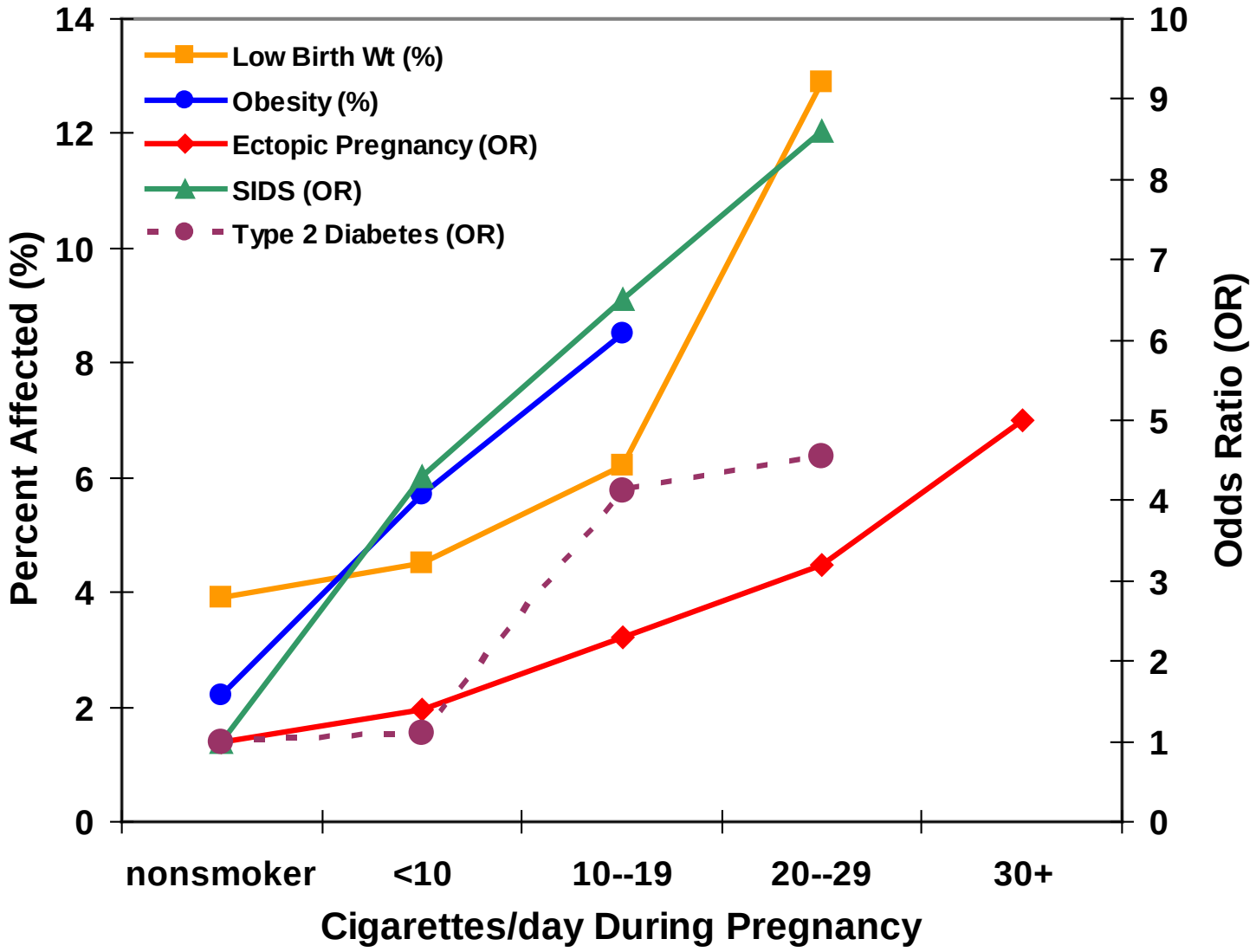
Predictive Adaptive Responses (Match)

Postnatal Overnutrition (Mismatch)

Childhood/Adult Disease

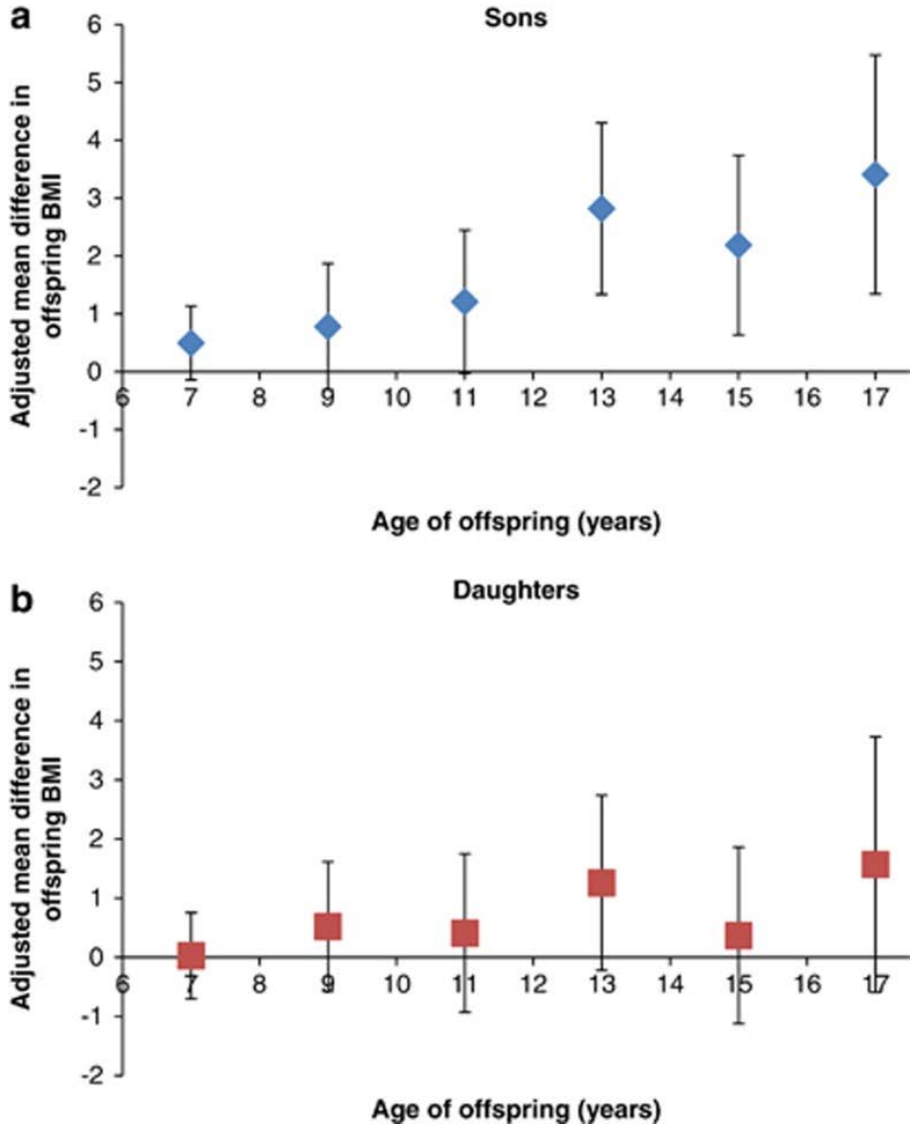
Adapted from Gilbert, S: Ecological Developmental Biology

Effects of maternal smoking on offspring



Paternal smoking and offspring BMI

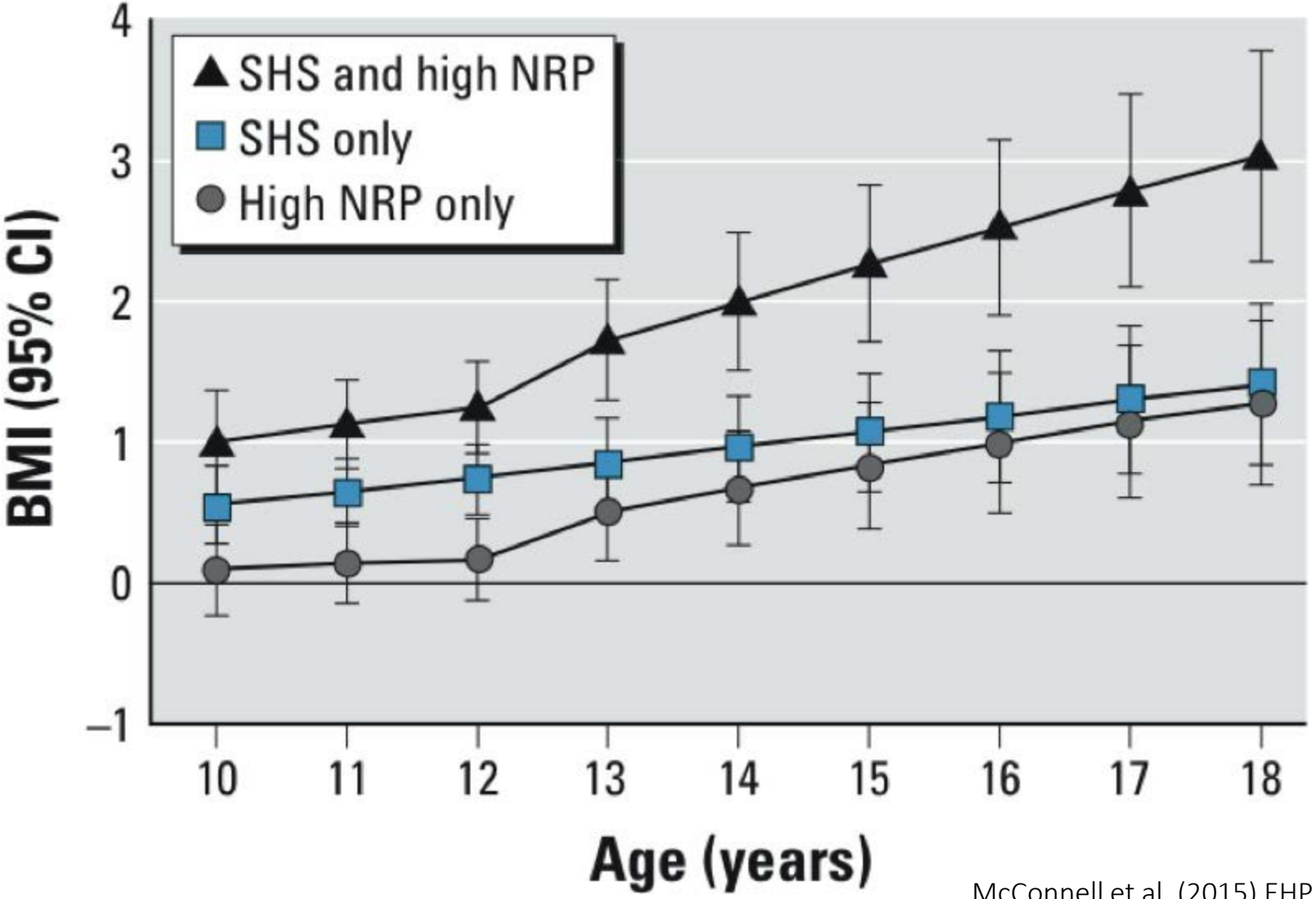
Father started smoking <11 years old vs later or never



Gender-specific effect on BMI

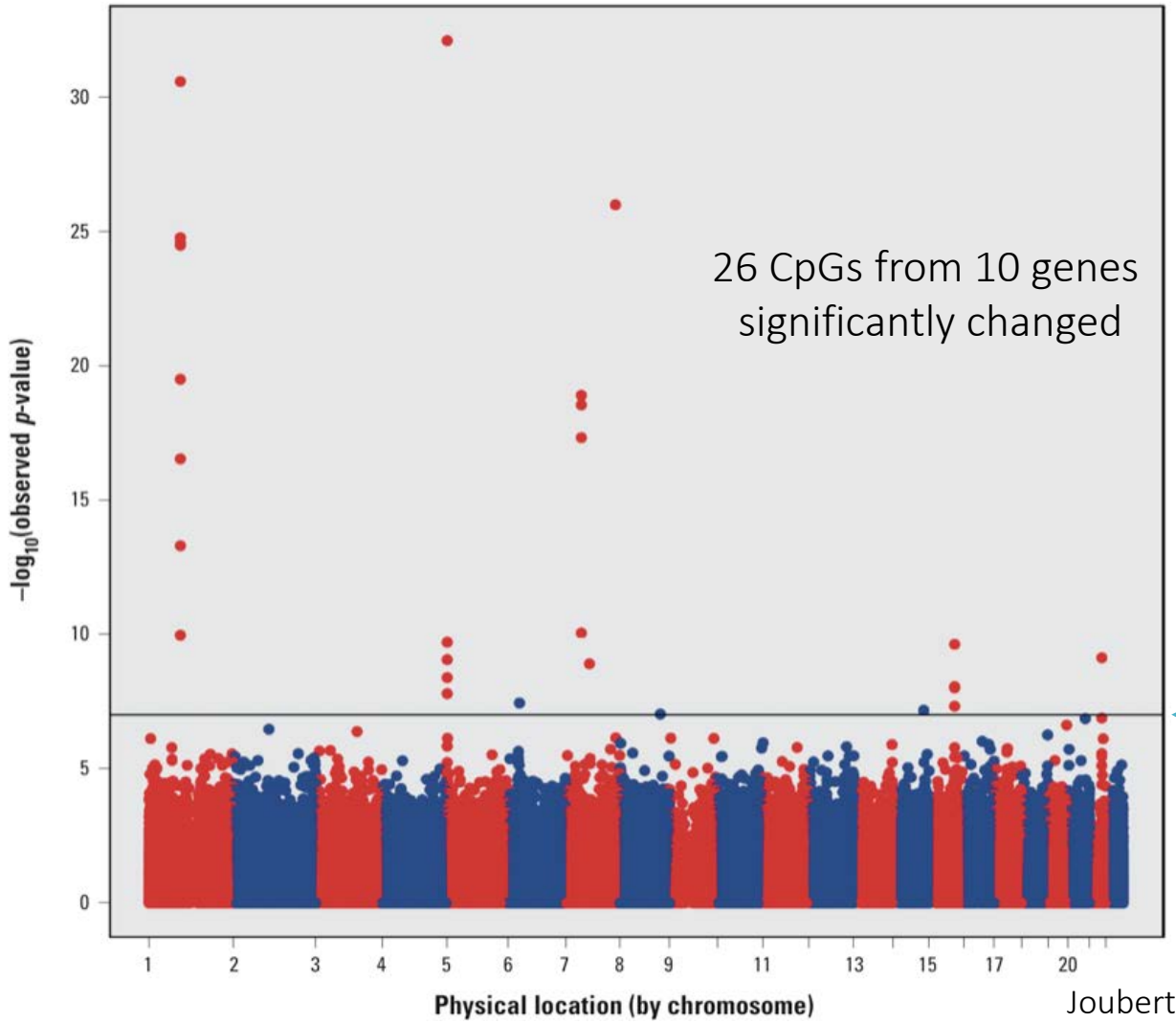
Northstone K et al (2014) Eur J Hum Genet 22:1382-86

2nd-hand smoke and near road pollution: Effects on BMI at age 10-18



McConnell et al. (2015) EHP 123:360-66

Maternal cotinine and CpG methylation
MoBa cord blood

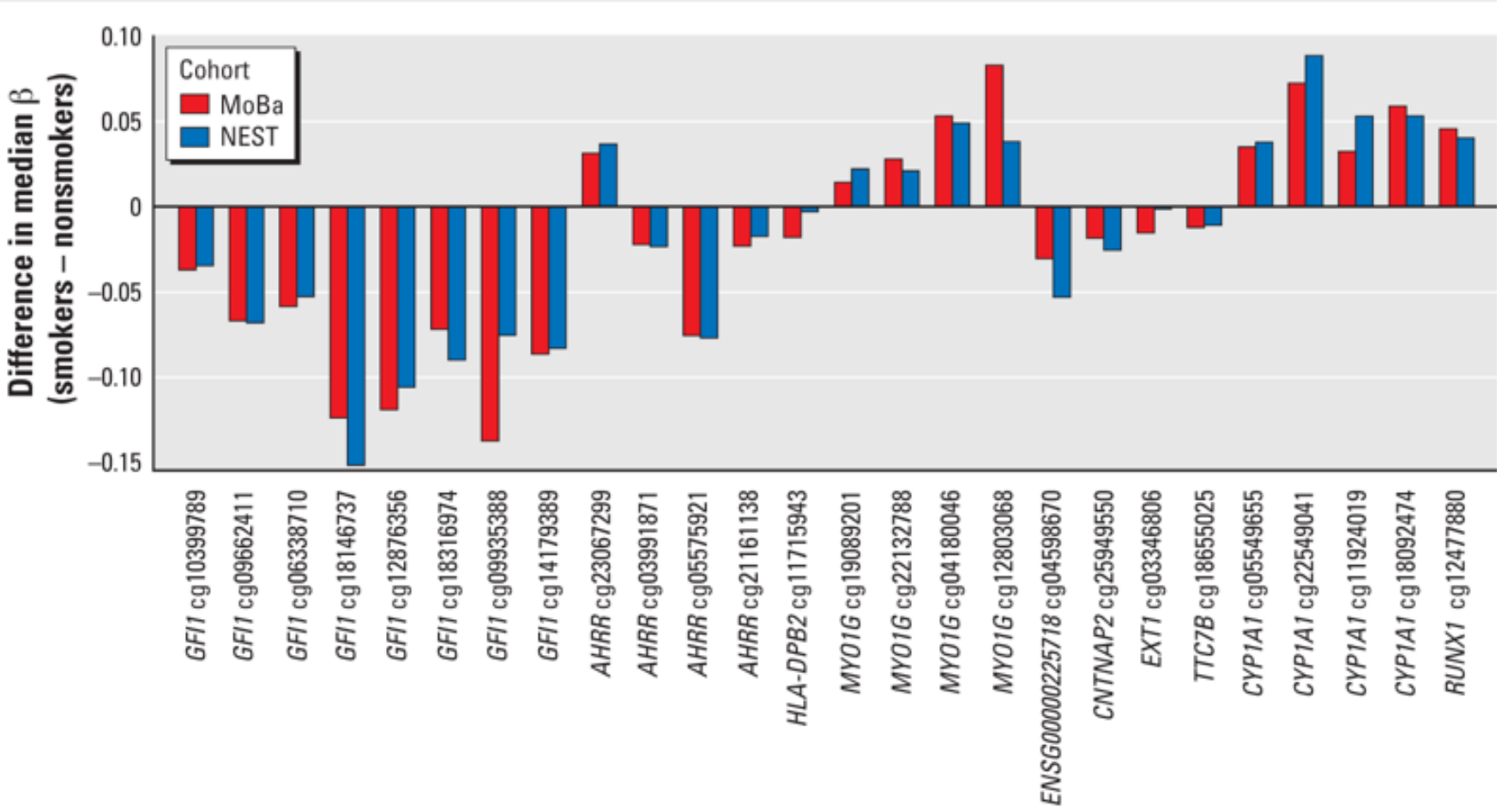


Bonferroni-corrected
significance $p<1.06 \times 10^{-7}$

Joubert BR et al (2012) EHP 120:1425-31

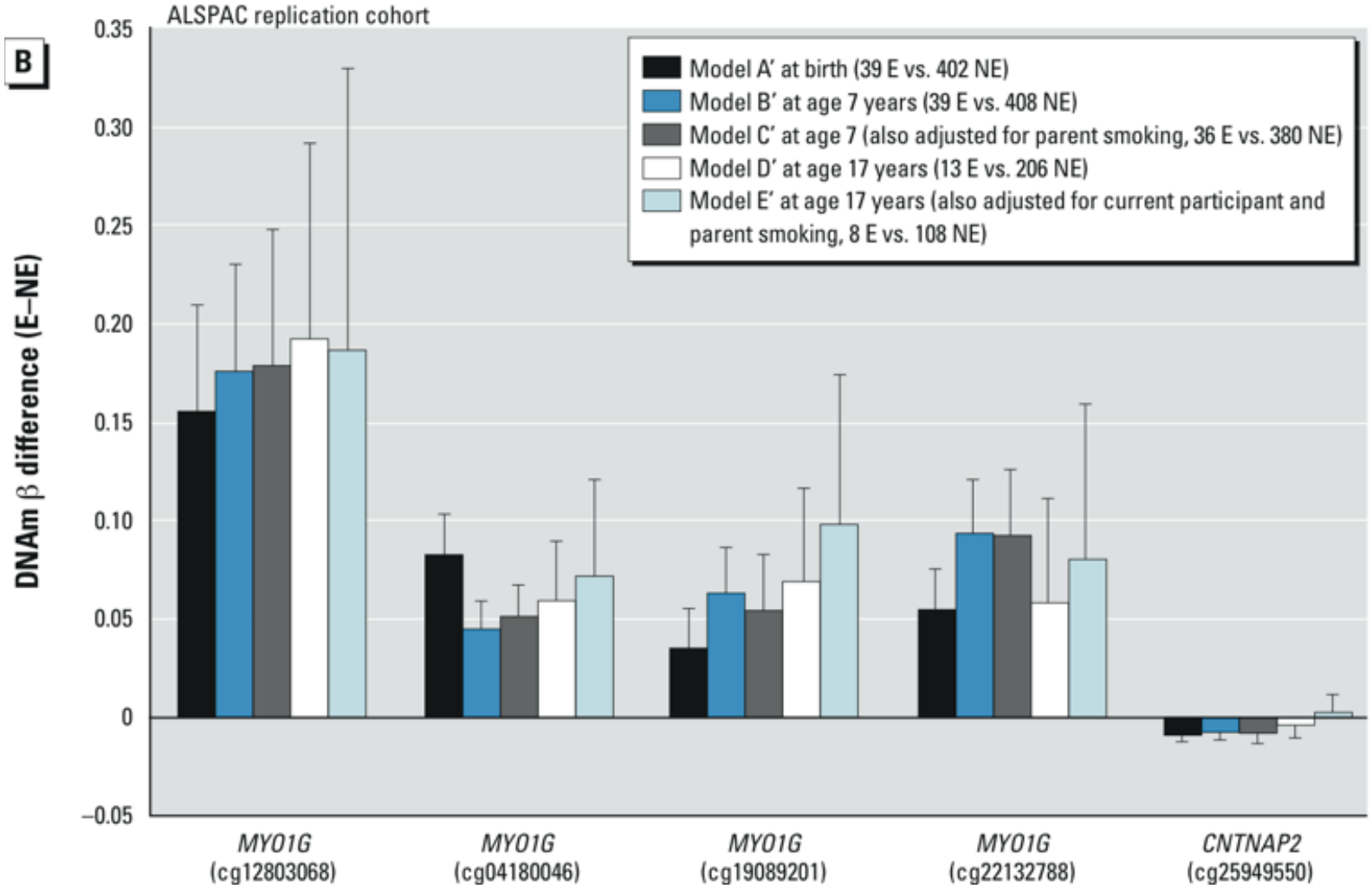
Methylation changes by smoking in top 26 CpGs

MoBa vs NEST



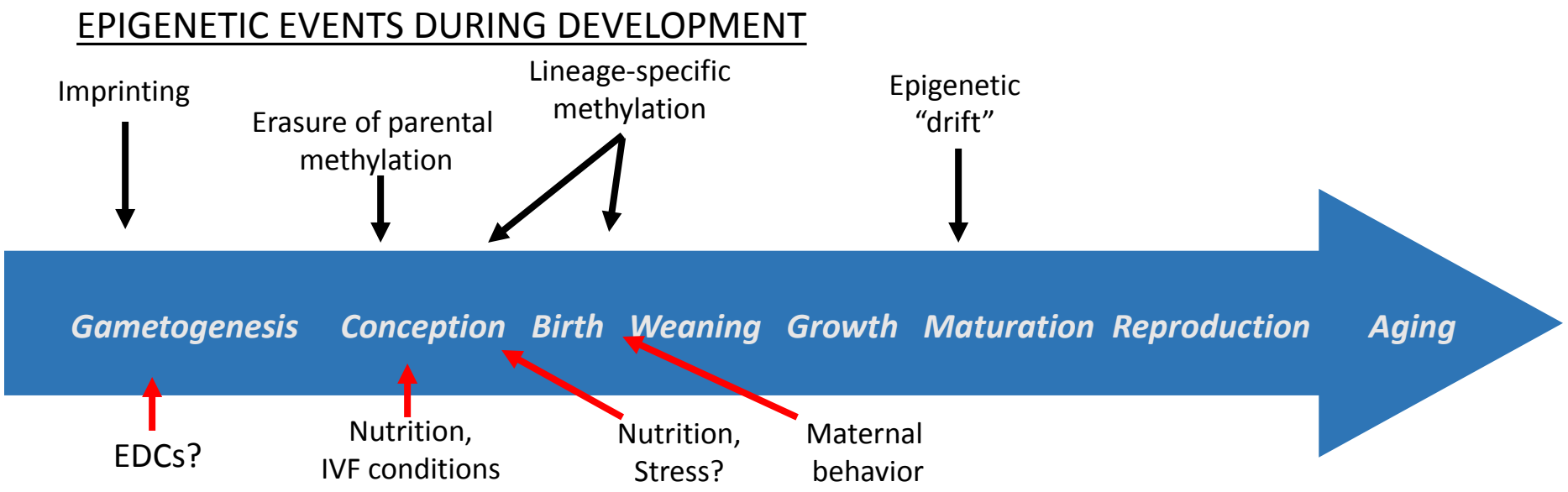
Joubert et al (2012) EHP 120:1425-31

Maternal smoking and altered DNA methylation
Postnatal persistence

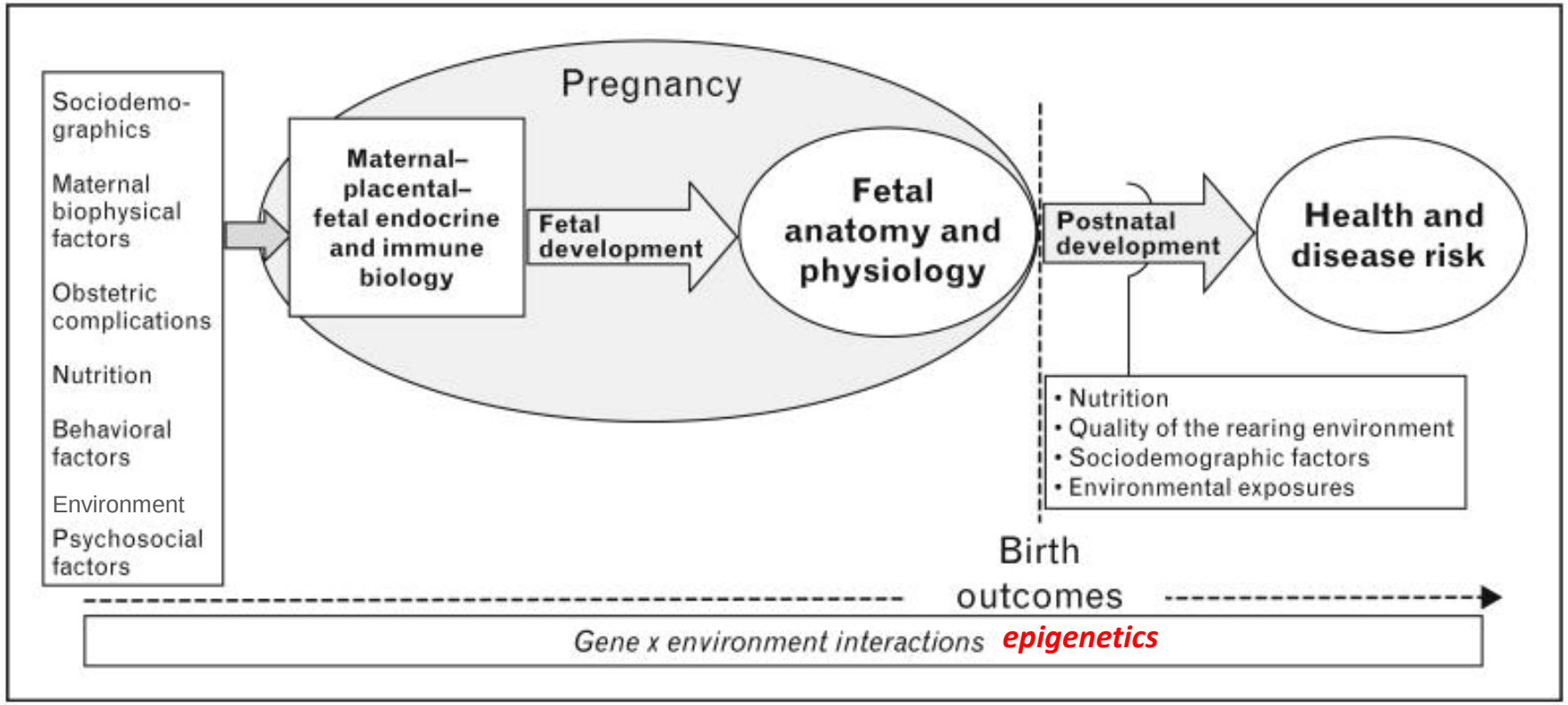


Lee KW et al (2015) EHP 123: 193-9

Epigenetic events and susceptibilities



The environment and pregnancy



Entringer, Buss, Wadhwa (2010) Curr Opin Endocrinol Diabetes Obes 17: 507–16

A New paradigm: Activation of toxicity pathways