Nuclear Receptor（AhR, ERa, ERb, PXR, CAR, RXR) Network and Cytochrome P450

Produced by KeyMolnet Draw (IMMD Inc.)
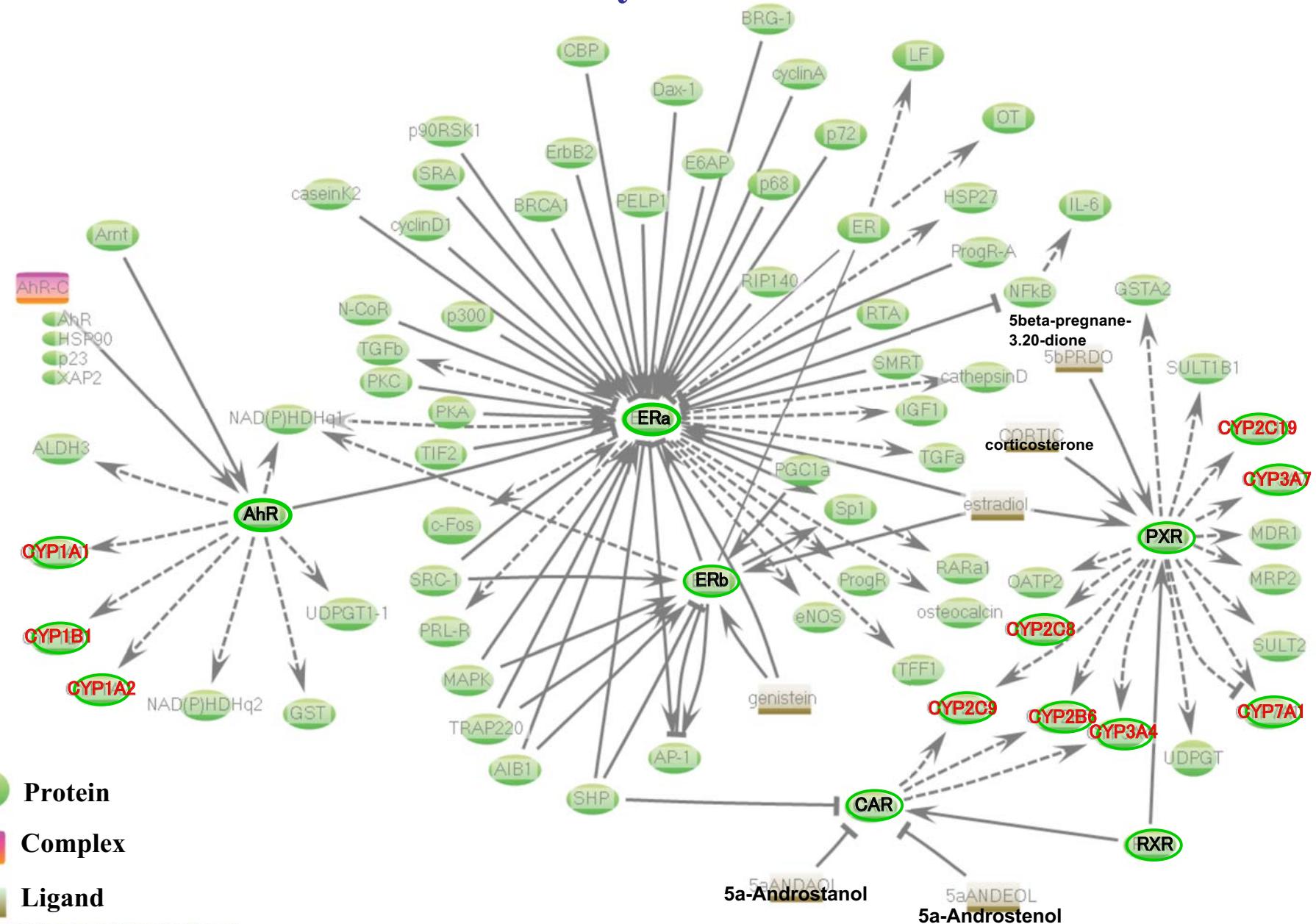
Analysis of Association of Disease-susceptibility Genes with Polymorphism of Genes Responsive to Environmental Chemicals

- Obtain genotype data by informatics
- tag SNP selection based on statistical analysis

Int. Hap Map project（www.hapmap.org) & NCBI (SNP database)

Ex.drug responsive genes

SNP

tag SNP
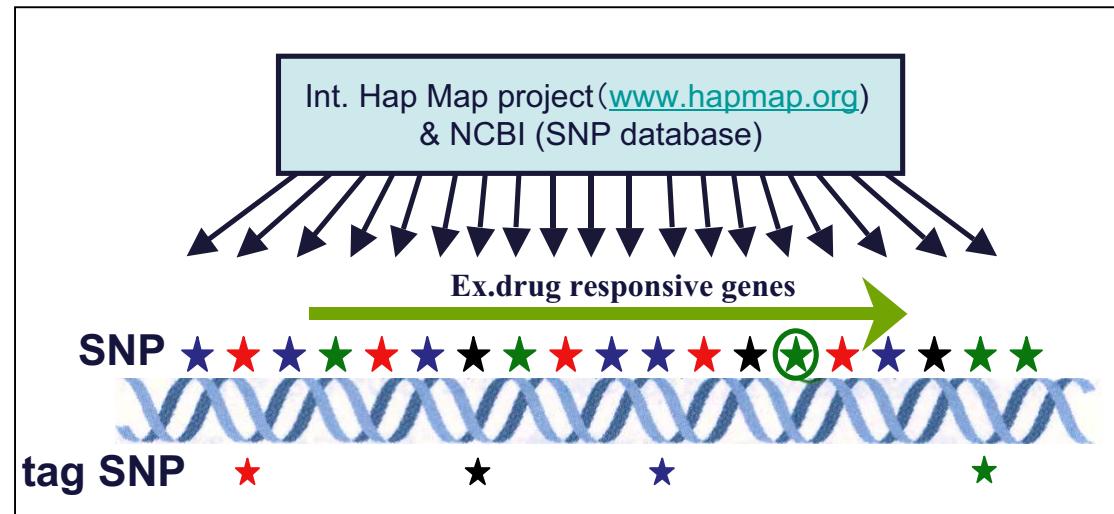
- 15 genes, 384 SNPs
- Analyze SNPs by a haplotype

A/A A/G G/G

33 45 16

**210 samples
378 SNP**

- Biological significance of 384 SNPs
- Association with disease-related genes
- Estimate the effects of environmental factors, association of disease

Disease-related genotype Ⅰ

Disease-related genotype Ⅱ

f

tagSNP

f

tagSNP
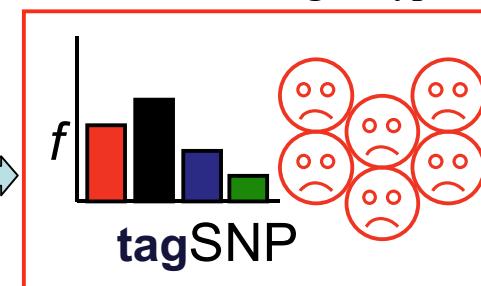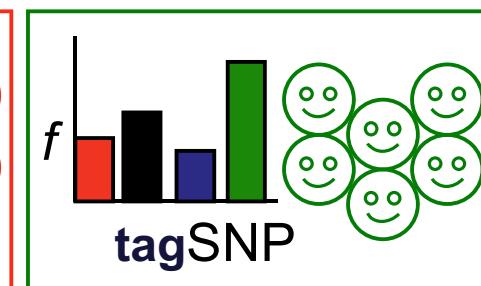
# Topics on Endocrine Disruptor Research

- Status of Japanese men's reproduction
- Phthalate esters
- New chemicals, PBDE, PFOS, PFOA

Relative Difference in Sperm Concentration in Fertile Men
International Comparison
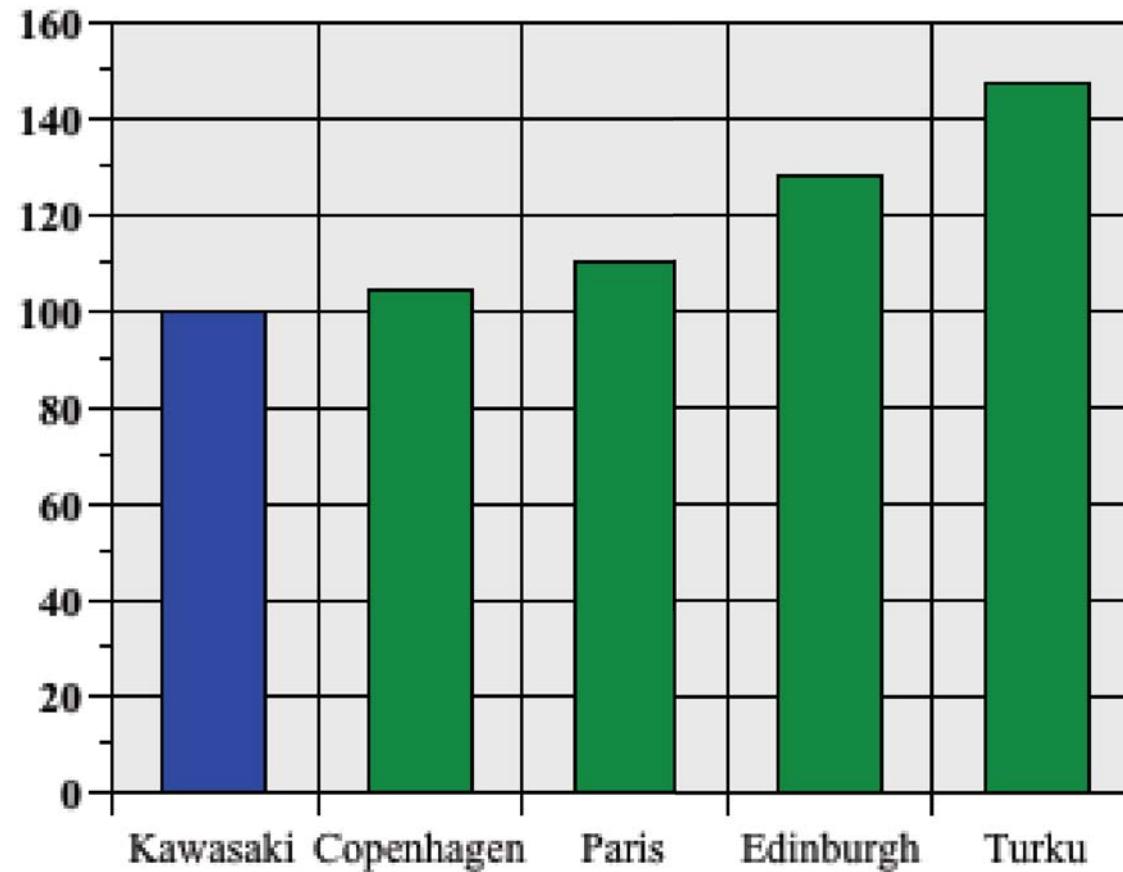
Iwamoto et al. (2006)

Temporal Changes in Testis Weight by Birth Year

Testis-Weight (g) vs Age

Birth Year:
— 1920 — 1930 — 1940 — 1950
— 1960 — 1970 — 1980
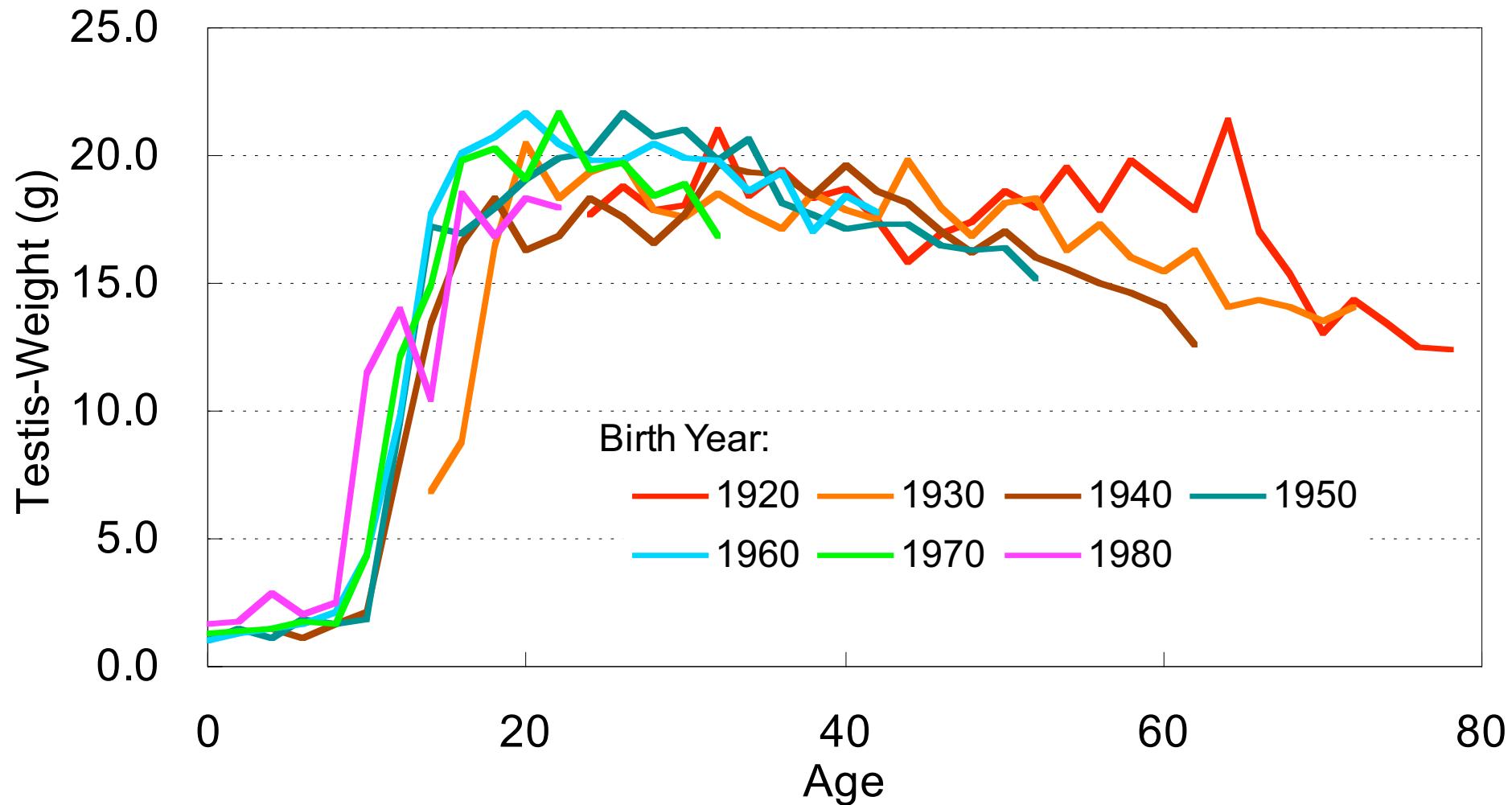
(Mori et al. 2002)

Schematic Description of Temporal Testis Weight Change

(Mori et al. 2002)
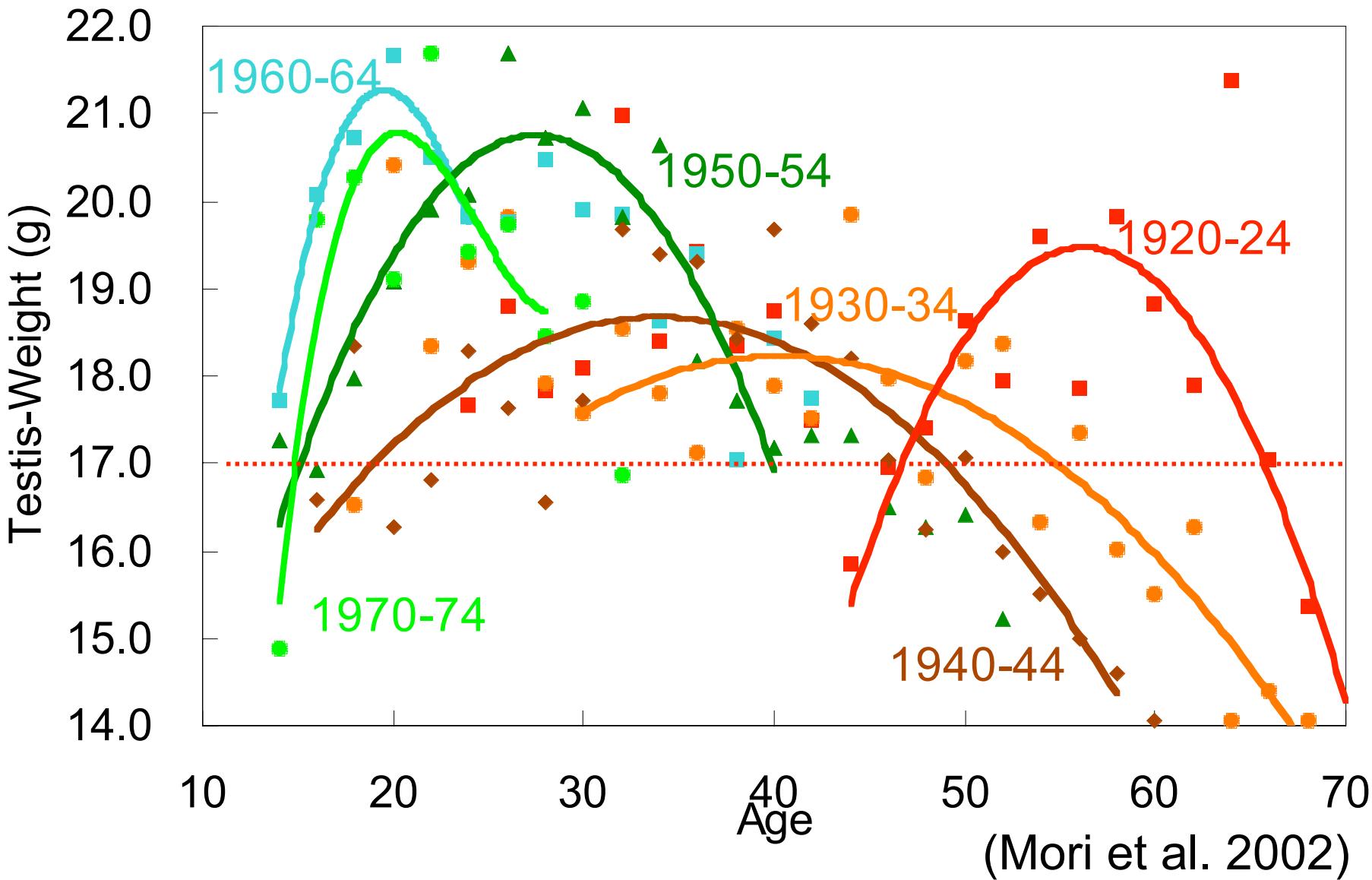
Sex ratio
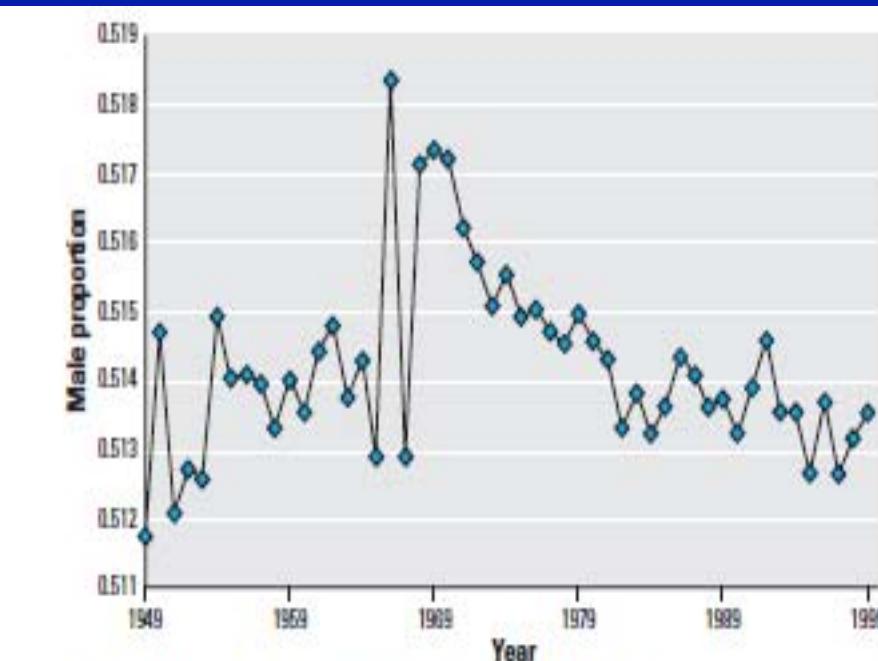
Figure 1. Proportion of male live births, Japan, 1949–1999.
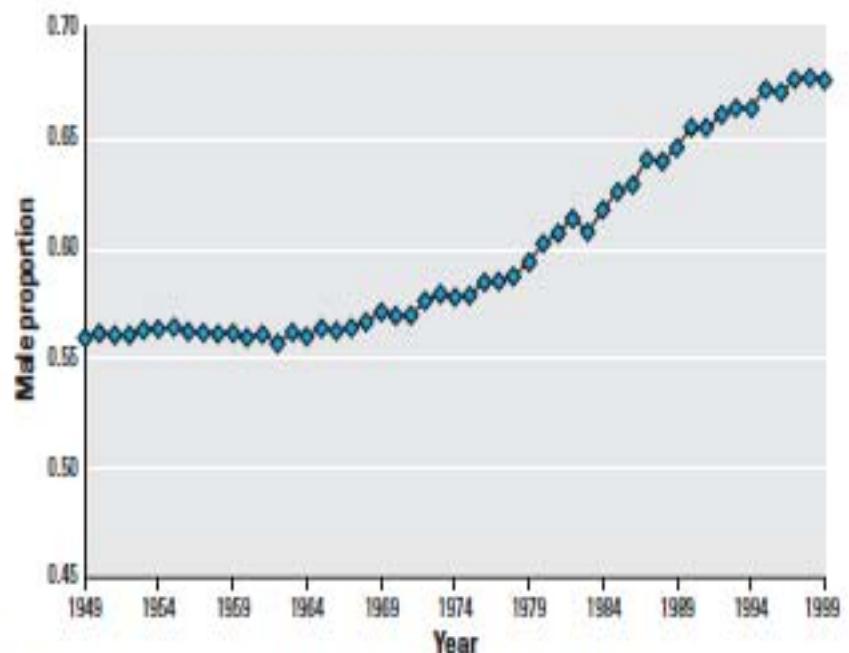
Figure 2. Proportion of male fetal deaths, Japan, 1949–1999.

Davis et al., 2007

Phthalate Esters

- AGD

  Monoester level in urine in pregnancy and AGD (Swan et al., 2005)

- T4

  MEHP in urine and free T4 (Meeker et al., 2007)

- Obesity, Insulin resistance

  Four metabolite and obesity (Stahlhut et al., 2007)

- Semen parameter

  Monobutyl, monobenzyl phthalate and semen parameter (Duty et al., 2003)

Anogenital index
Monobuthyl phthalate
(n=85, boy)

Exposure quartile	Low anogenital index		Odds ratio (95% CI)
	yes	no	
1	5	15	1
2 – 3	24	19	3.8 (1.2-12.3)
4	17	5	10.2 (2.5-42.2)

Swan et al. 2005

New Chemicals

- PFOS, PFOA- birth weight
- PBDE-cryptorchidism

PFOS, PFOA and Birth Weight
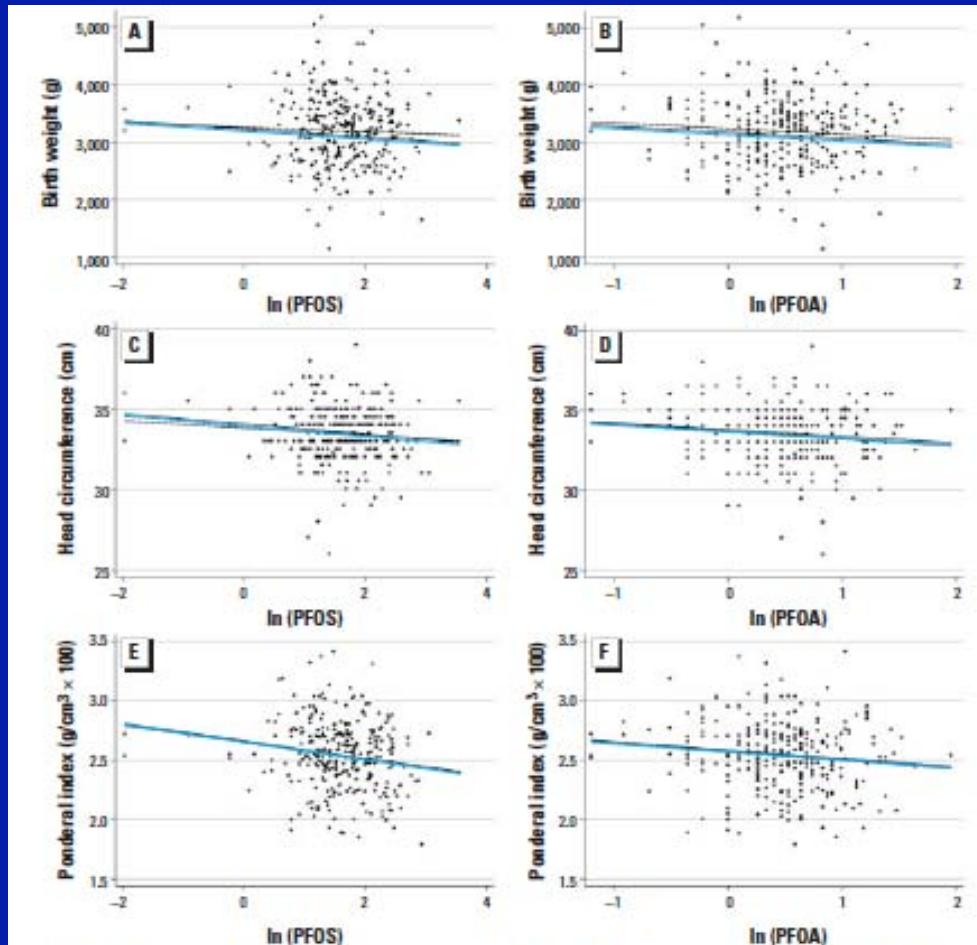
Figure 1. Birth weight (A, B), head circumference (C, D), and ponderal index (E, F) versus ln(PFOS) and ln(PFOA) concentrations, before and after adjustment for potential confounders. The black dotted lines denote the predicted fit from a simple linear regression model. The blue solid lines denote the predicted fit from the fully adjusted multivariate regression model. Corresponding regression coefficients are presented in Table 3.

Apelberg et al., 2007

PBDEs in Breast Milk and Cryptorchidism

Denmark   Finland
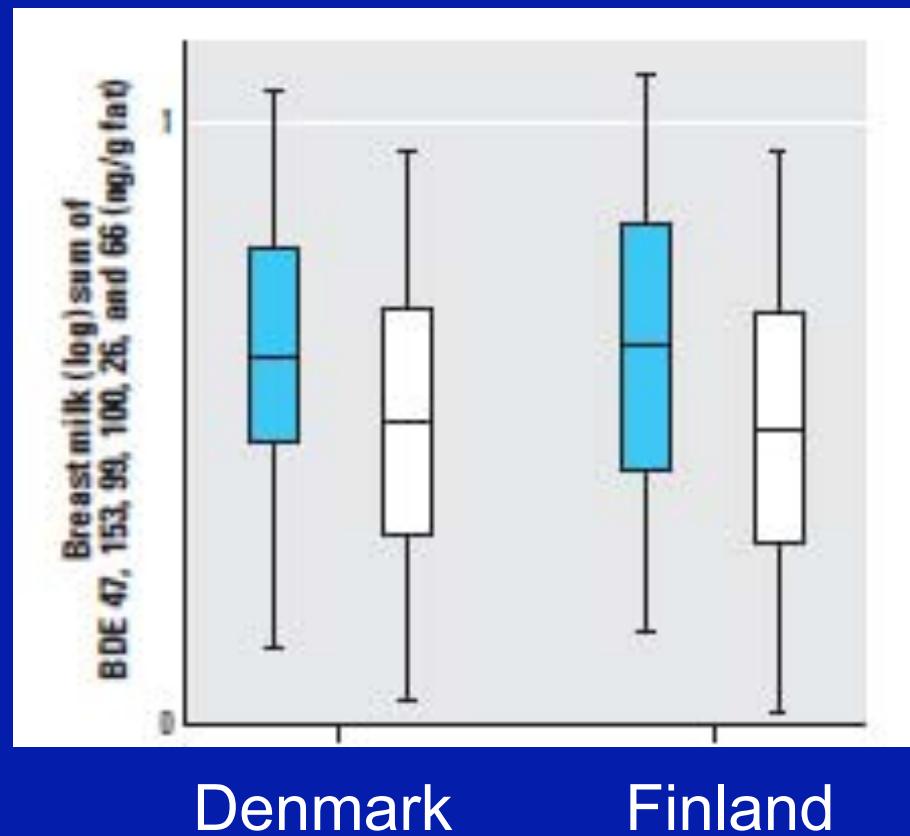
Main et al., 2007

Summary

More concern about the susceptibility factors

- Critical windows

  Importance of prospective cohort design for early life studies.

  Specimen banking

- Genetic susceptibility

  Genome (molecular) epidemiology

Acknowledgments

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