

Sex, gender, and the brain

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Outline

1. Sex

- Chromosomes
- Hormones
- Reproduction

2. Gender

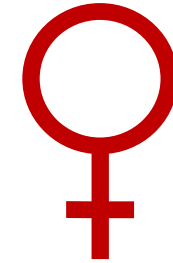
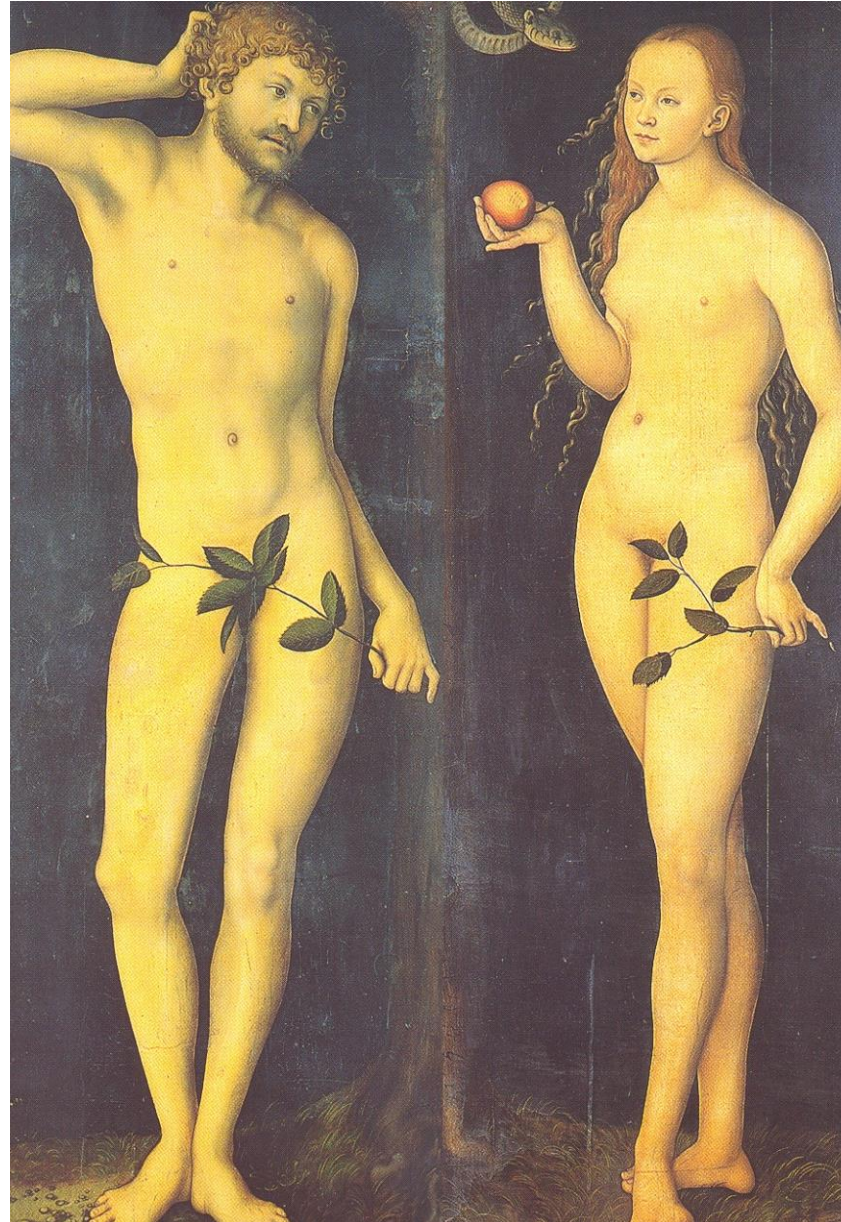
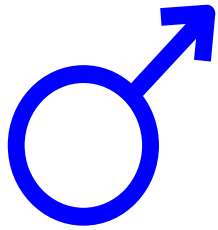
- Subjective, personal identity
- Social and cultural (political)

3. Dementia

- Incidence and time trends
- Risk factors

4. Conclusions

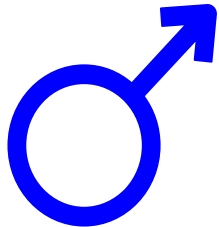
Body dimorphism



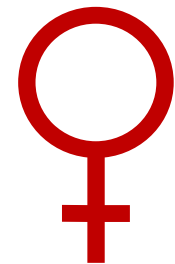
Cranach the Elder, 1528

Brain dimorphism

Men

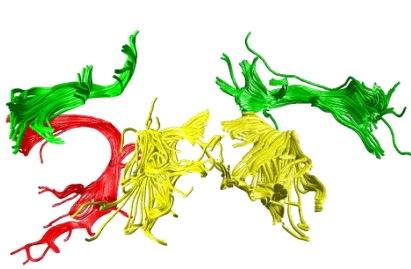


Women

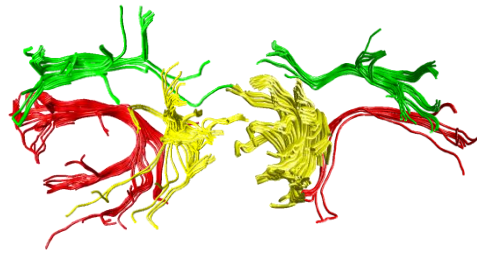


Scientific American MIND, May/June 2010

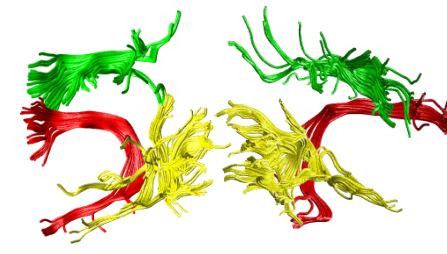
Language lateralization



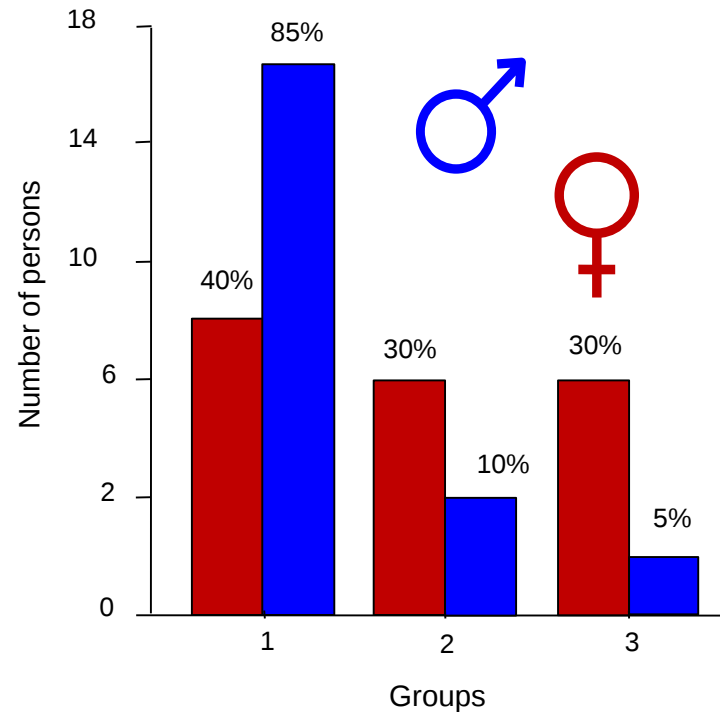
Group 1: strong left lateralization (62.5%)



Group 2: bilateral, left predominant lateralization (20.0%)



Group 3: bilateral, symmetrical (17.5%)



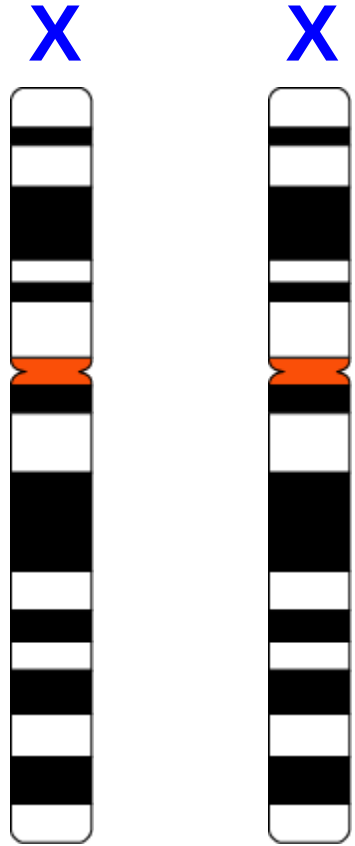
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Sex

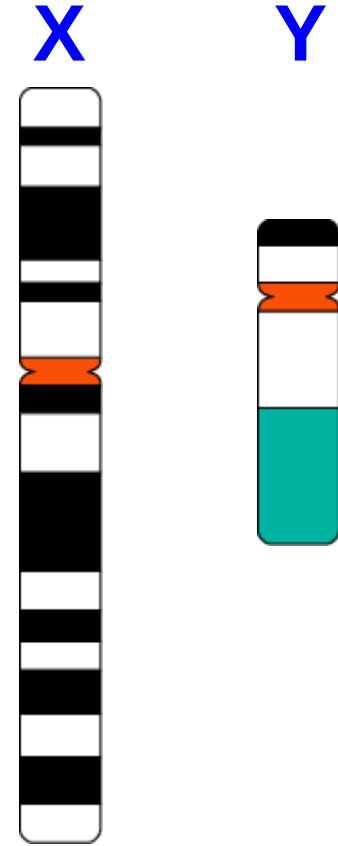
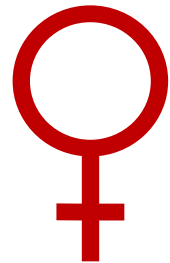
Sex = biology

- Chromosomes: XX vs. XY
- Gonads: ovaries vs. testicles
- Hormones: estrogen and progesterone vs. testosterone
- Reproduction: pregnancy, breast feeding, oral contraception

Sex chromosomes

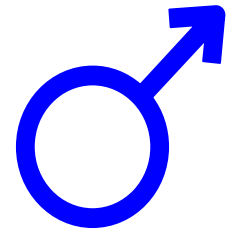


Female



SRY

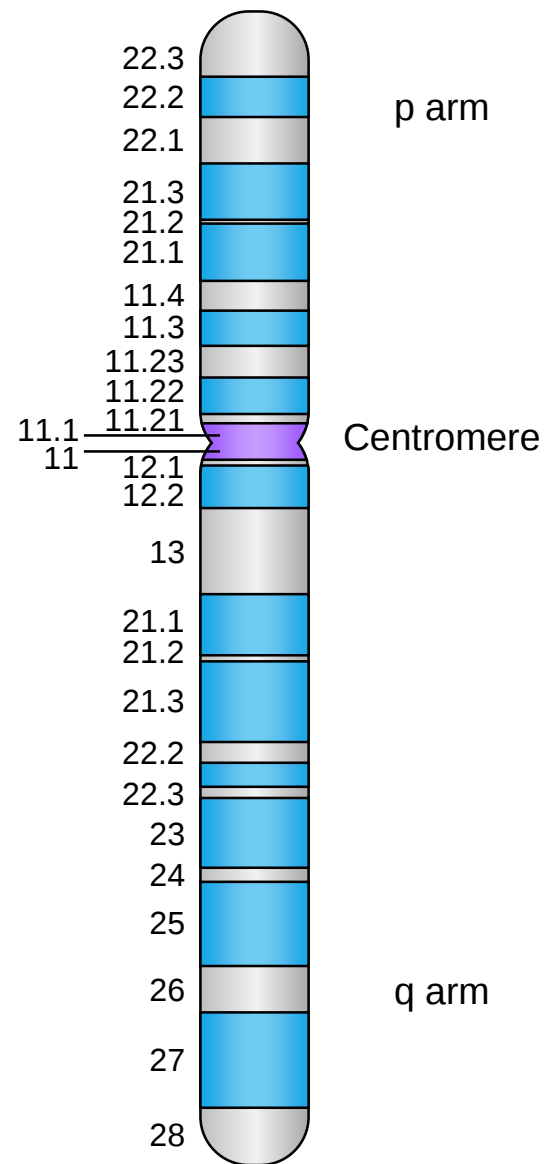
Male



Chromosome X inactivation

1,669 genes
153 million base pairs

- Pseudoautosomal – escapes inactivation
- Escapes inactivation
- Heterogeneous expression
- Subject to X-chromosome inactivation



Brain

Mental retardation
Cognitive function, social
Cerebellar ataxia
Color blindness/night blindness

Cancer

Melanoma/antigens
Testicular cancer
Prostate cancer

Cardiovascular

Cardiac valvular dysplasia
Dilated cardiomyopathy

Cell regulation and metabolism

Apoptosis inhibitor
Glycogen storage disease
Mucopolysaccharides

Endocrine

Type 1 Diabetes
Hypoparathyroidism
Adrenal Hypoplasia

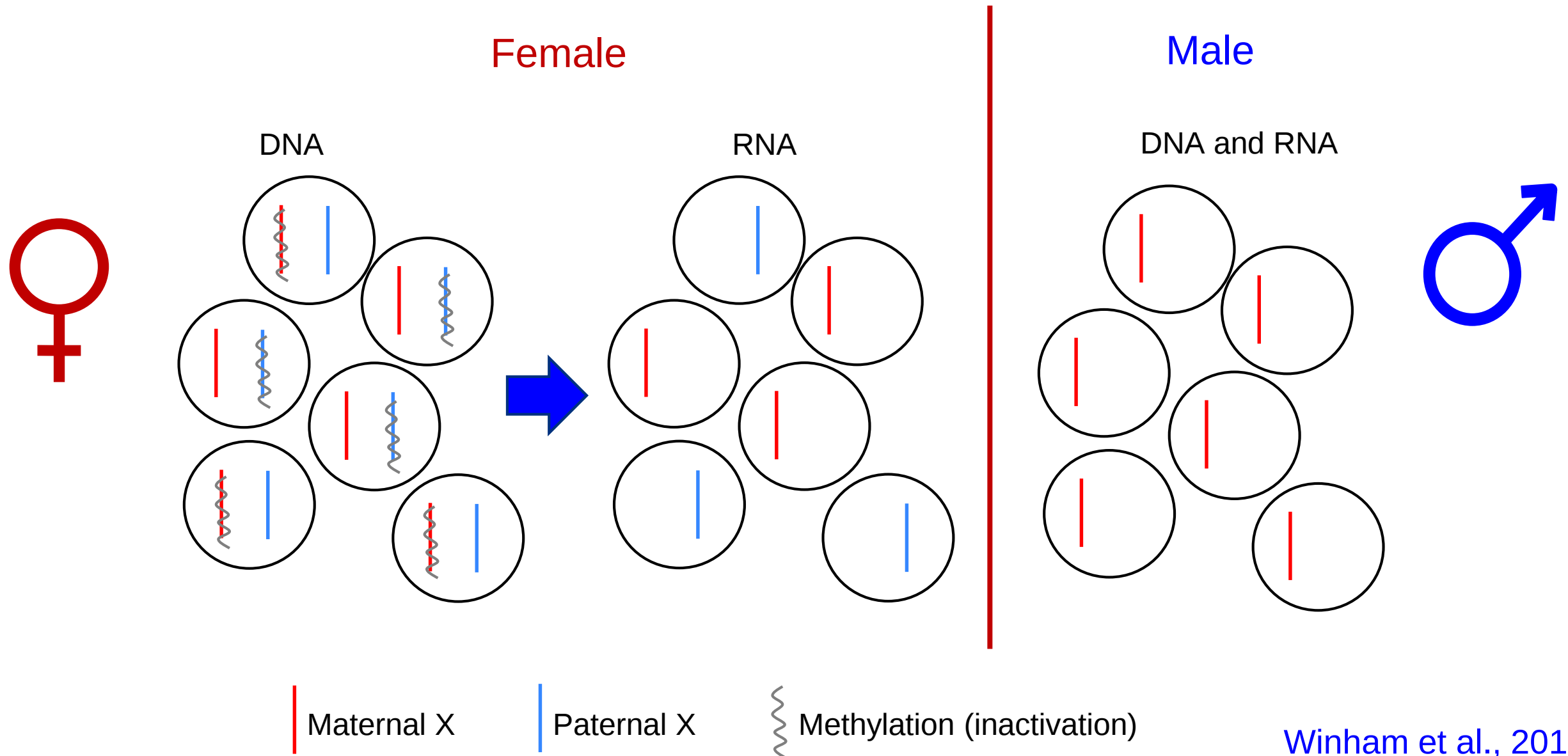
Immunology

Severe combined immunodeficiency
Agammaglobulinemia
Mature T cell proliferation

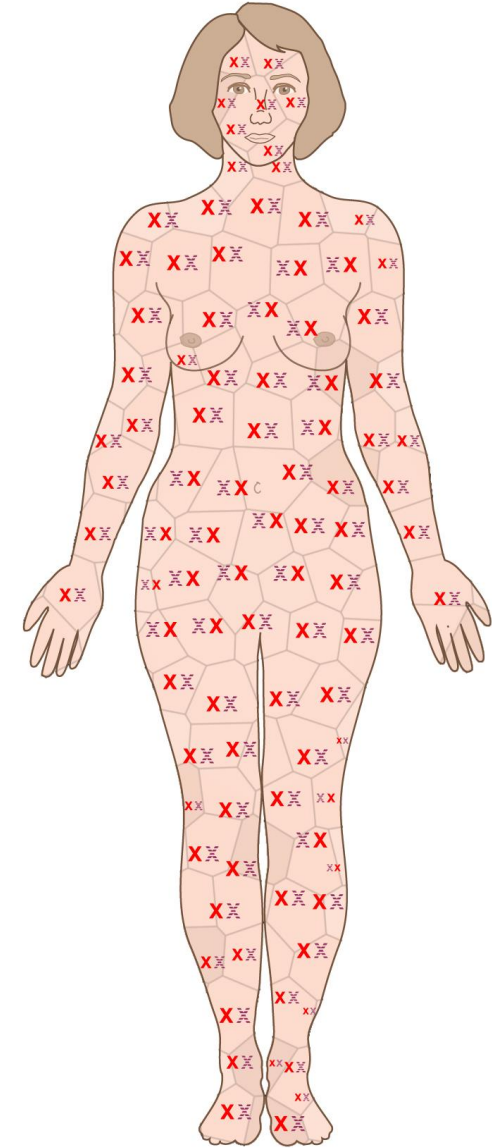
Reproduction

Androgen insensitivity
Premature ovarian insufficiency
Hypogonadotropic hypogonadism

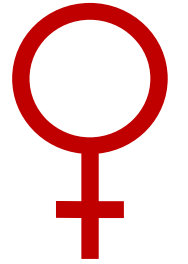
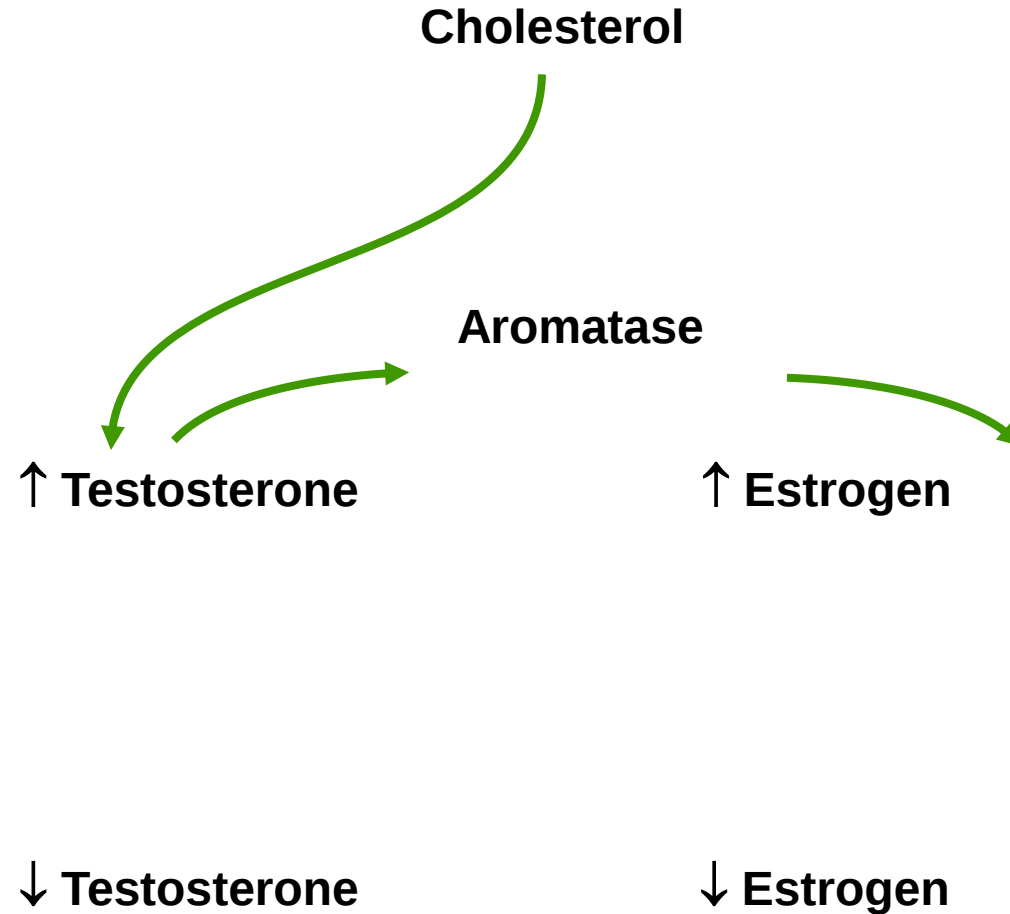
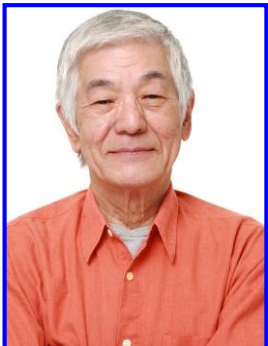
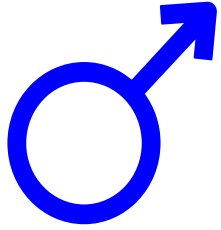
Chromosome X inactivation



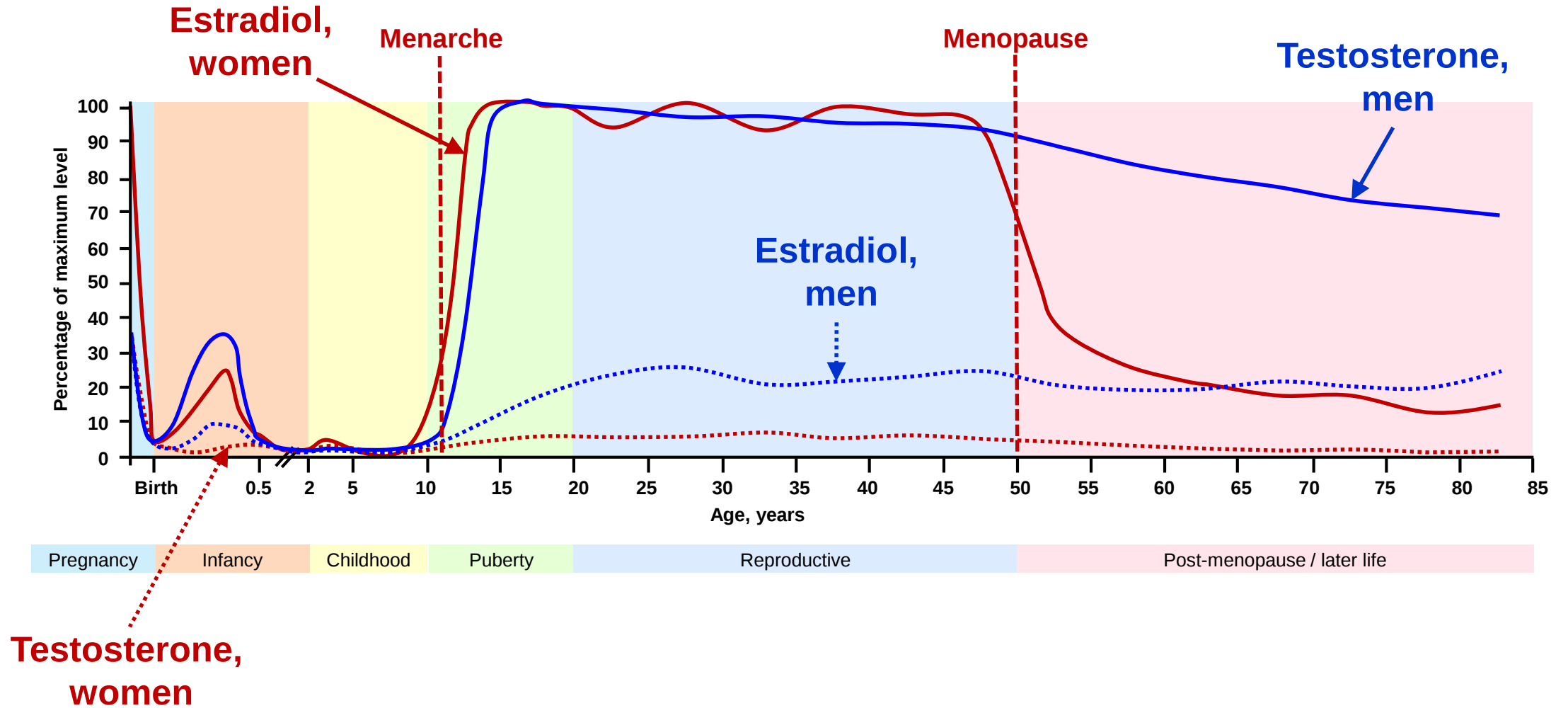
Women are mosaics of X



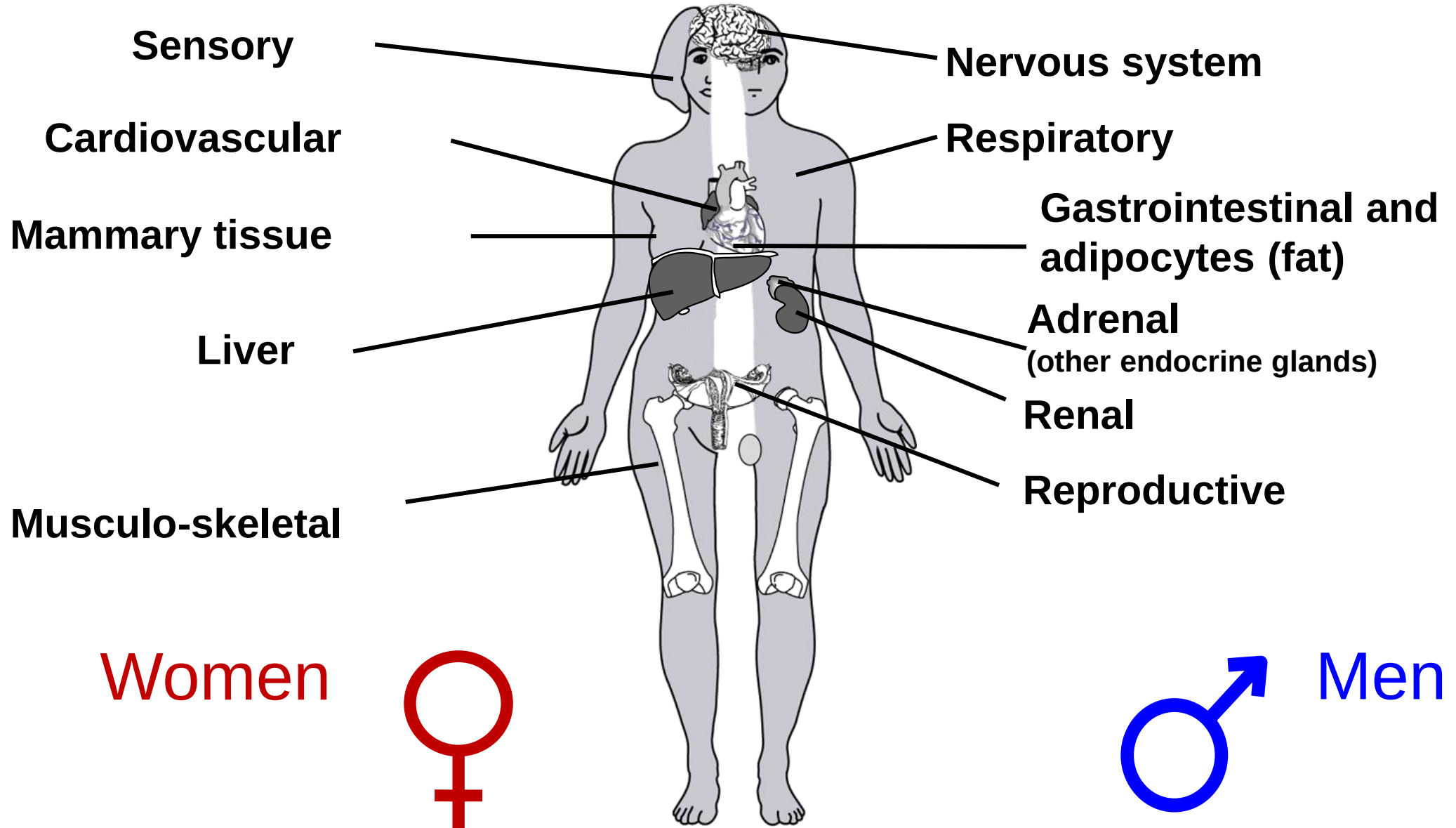
Sex hormones



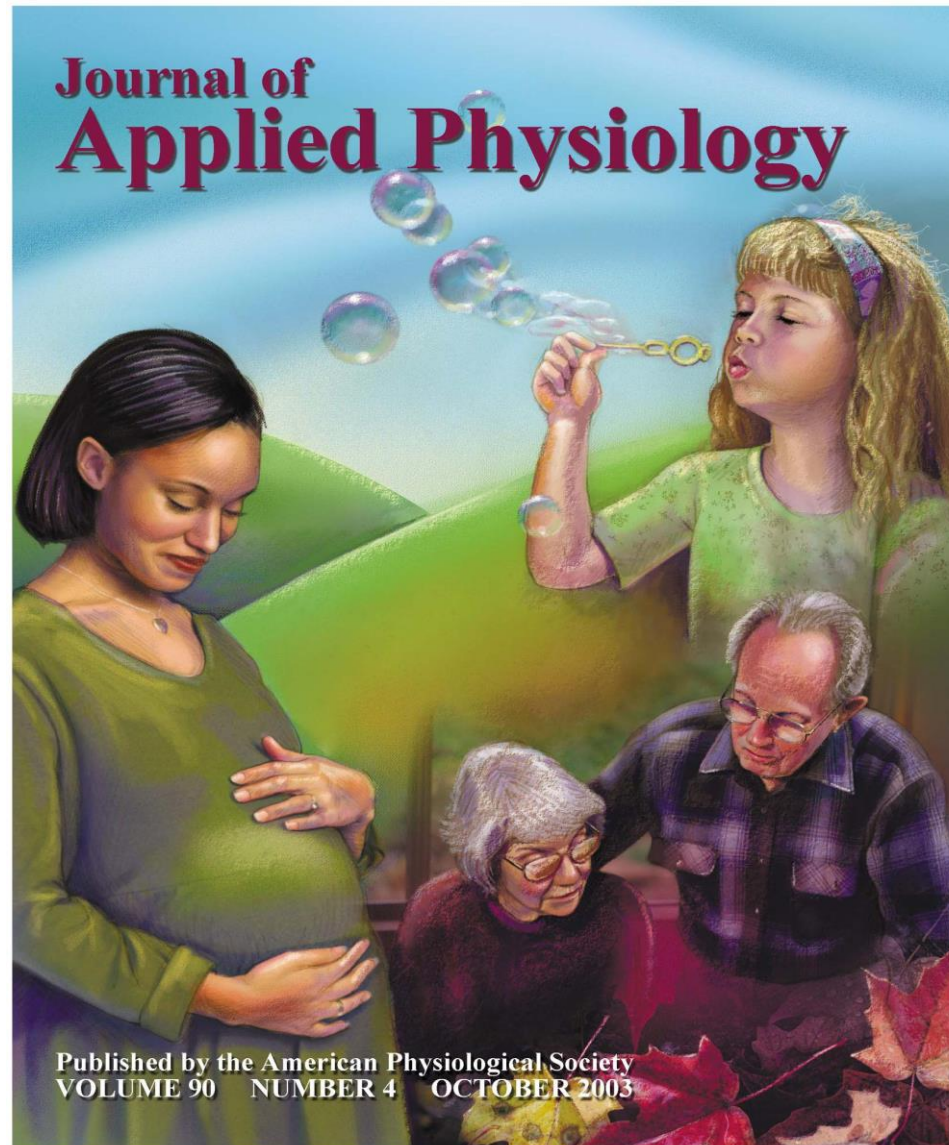
Sex hormones over life



Target tissues of sex hormones



Reproduction and life cycle



Reproduction

- Women have hormonal cycles
- Women can use hormonal contraceptives
- Women can experience pregnancy
 - Positive effects of pregnancy on body
 - Adverse effects of pregnancy on body
 - Pregnancy related diseases
 - Exchanges with the fetus
- Women can breast feed
- Women experience menopause

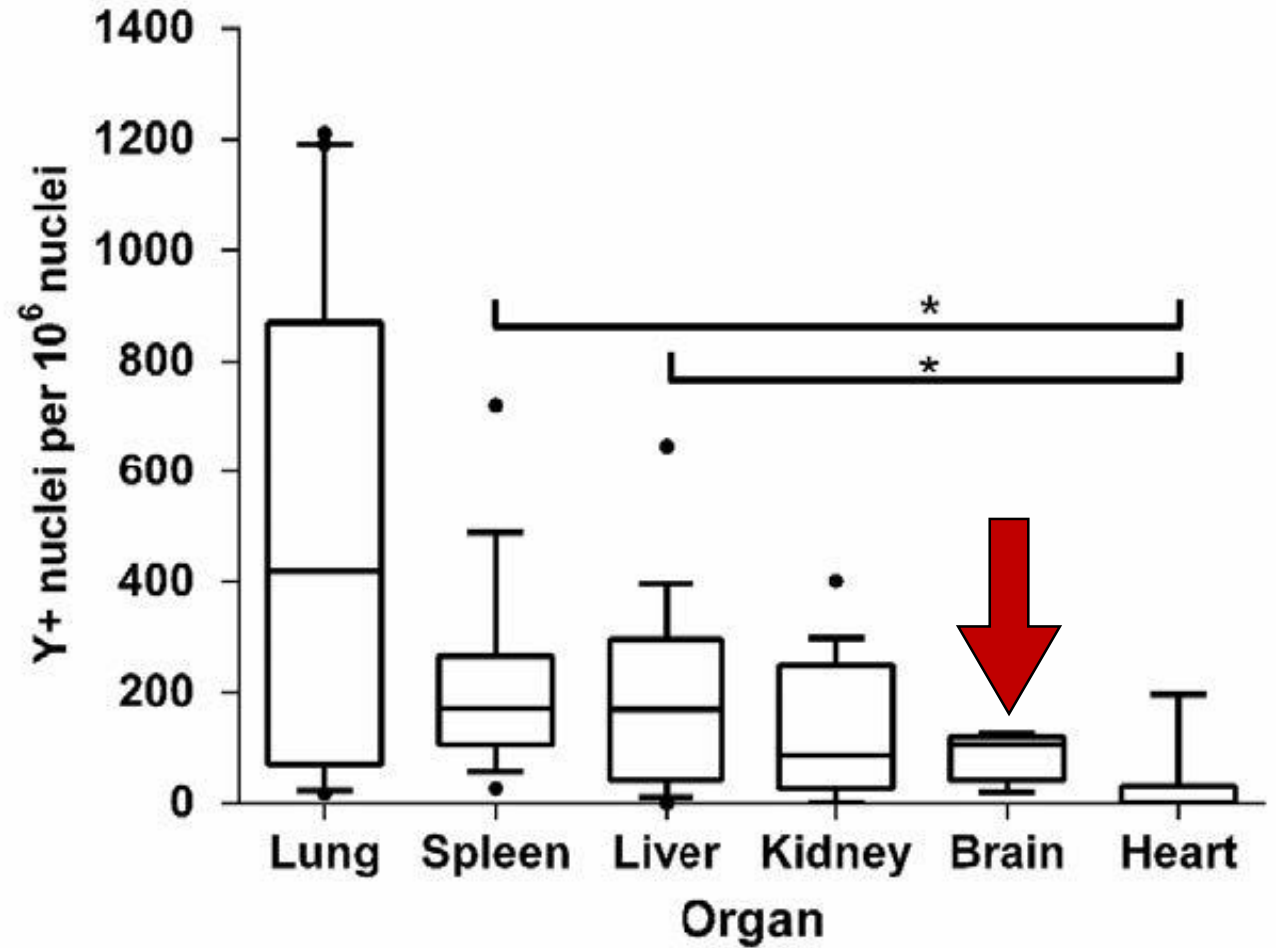
Microchimerism

- Cells from the fetus may enter the mother's body and populate organs
- Cells containing chromosome Y from male fetus
- Found in lung, spleen, liver, kidney, **brain**, and heart
- May remain life-long
- Impact on immune system

Microchimerism, organ specific



Greek mythology
Chimera: part lion, goat,
and dragon



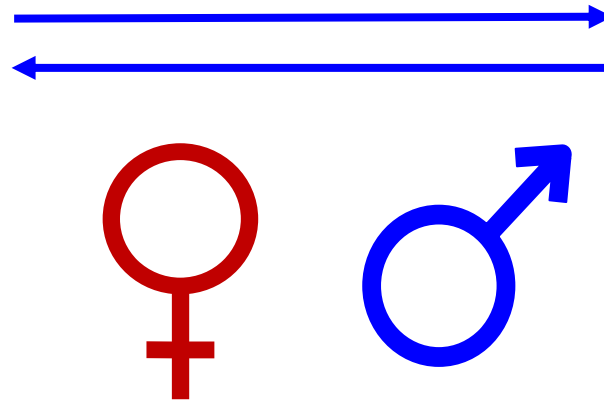
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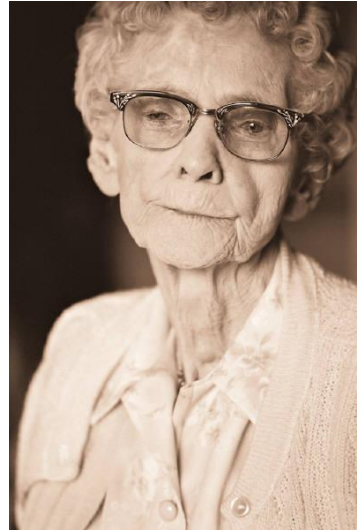
Gender

Gender = culture and society

- Subjective
 - Masculinity vs. femininity
 - Gender identity
- Societal and cultural (political)
 - Access to education
 - Access to jobs or sports
 - Access to medical care
 - Allowed to drive a car, vote for the president, or choose a partner

Sex and gender interactions





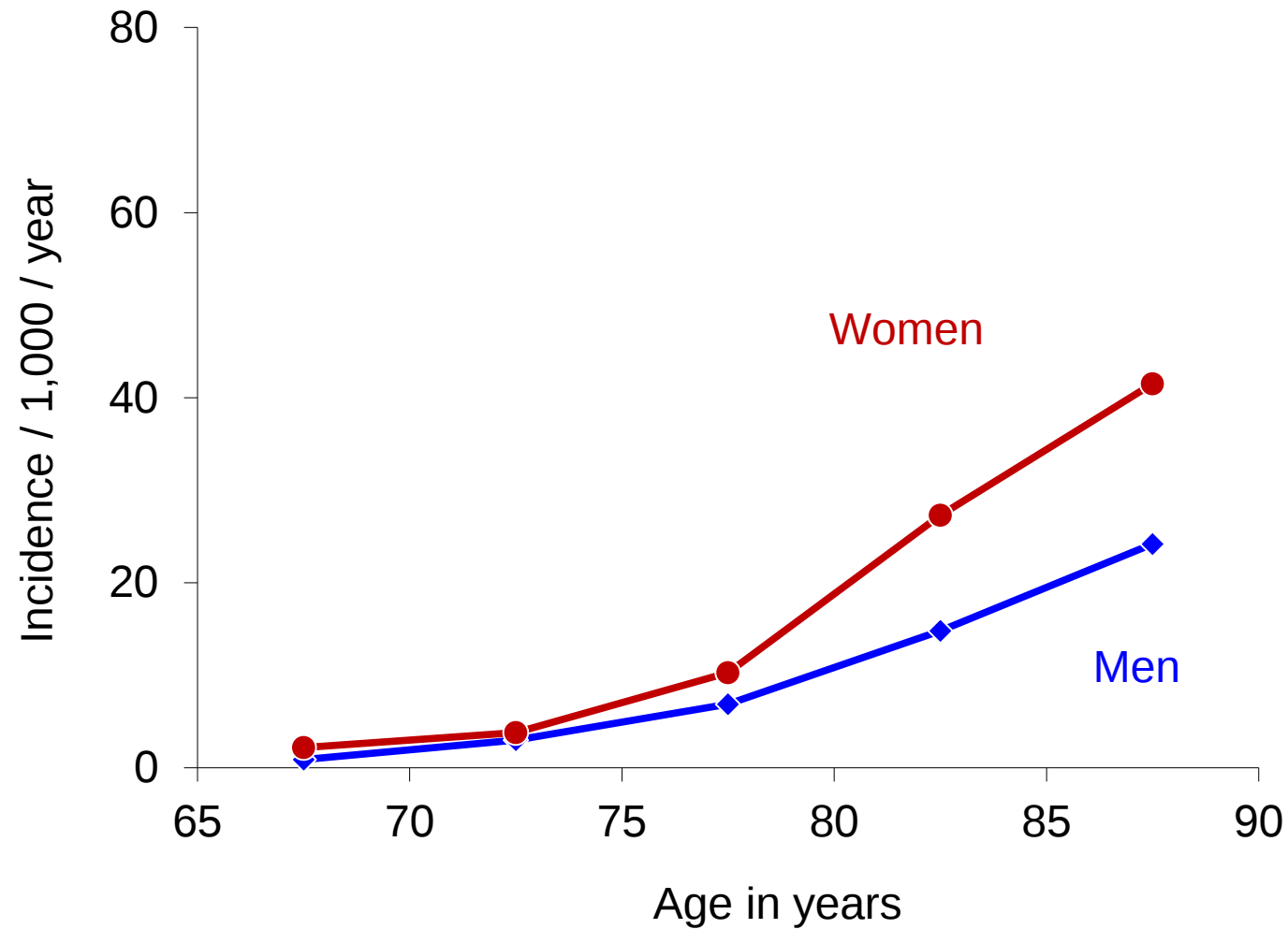
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Alzheimer's disease (AD) and dementia

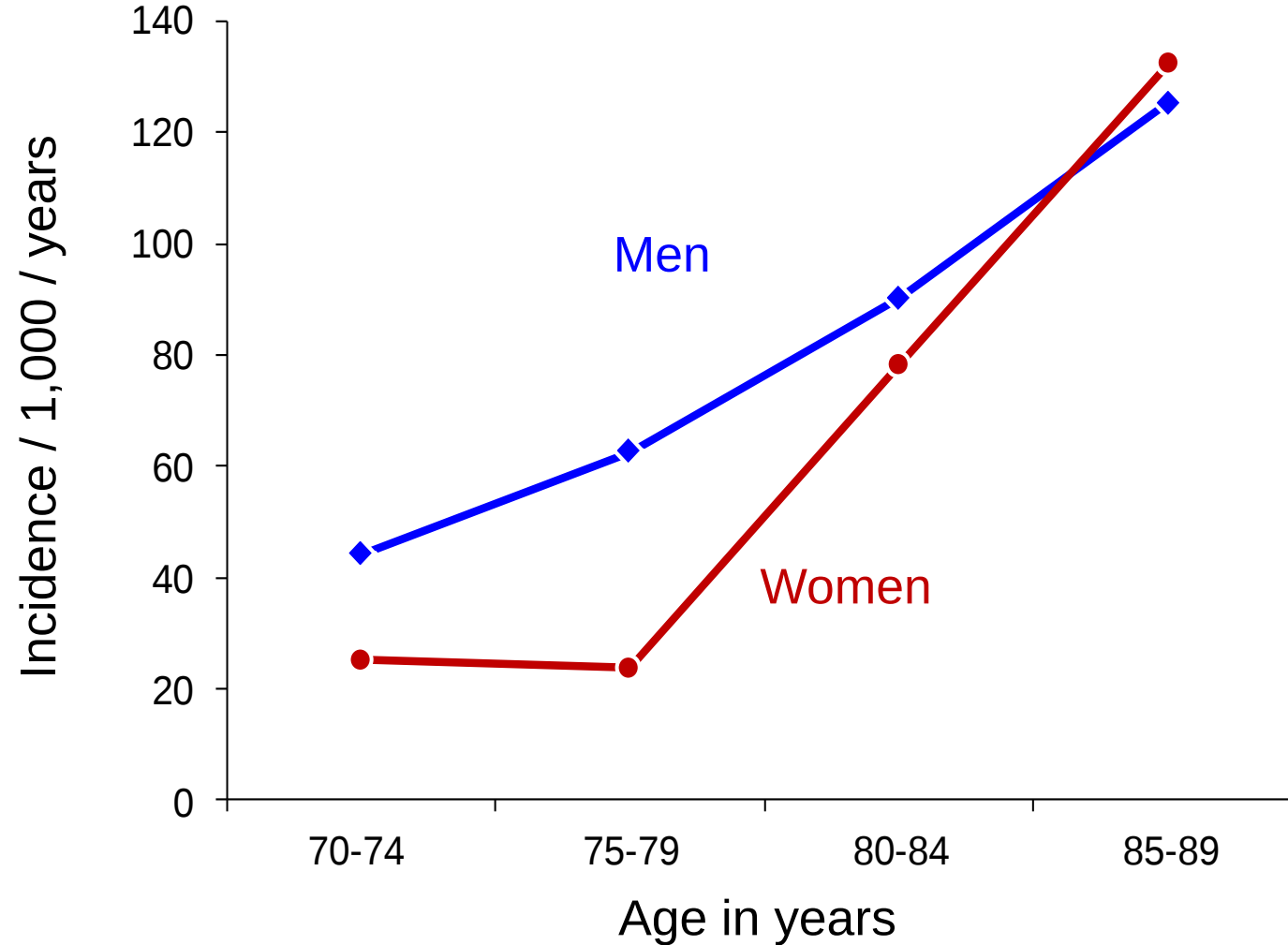
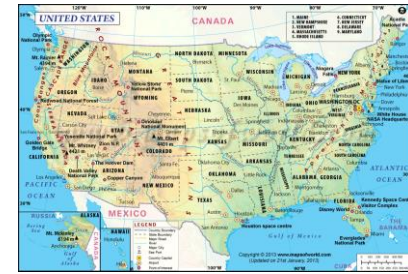
3a

Incidence and time trends

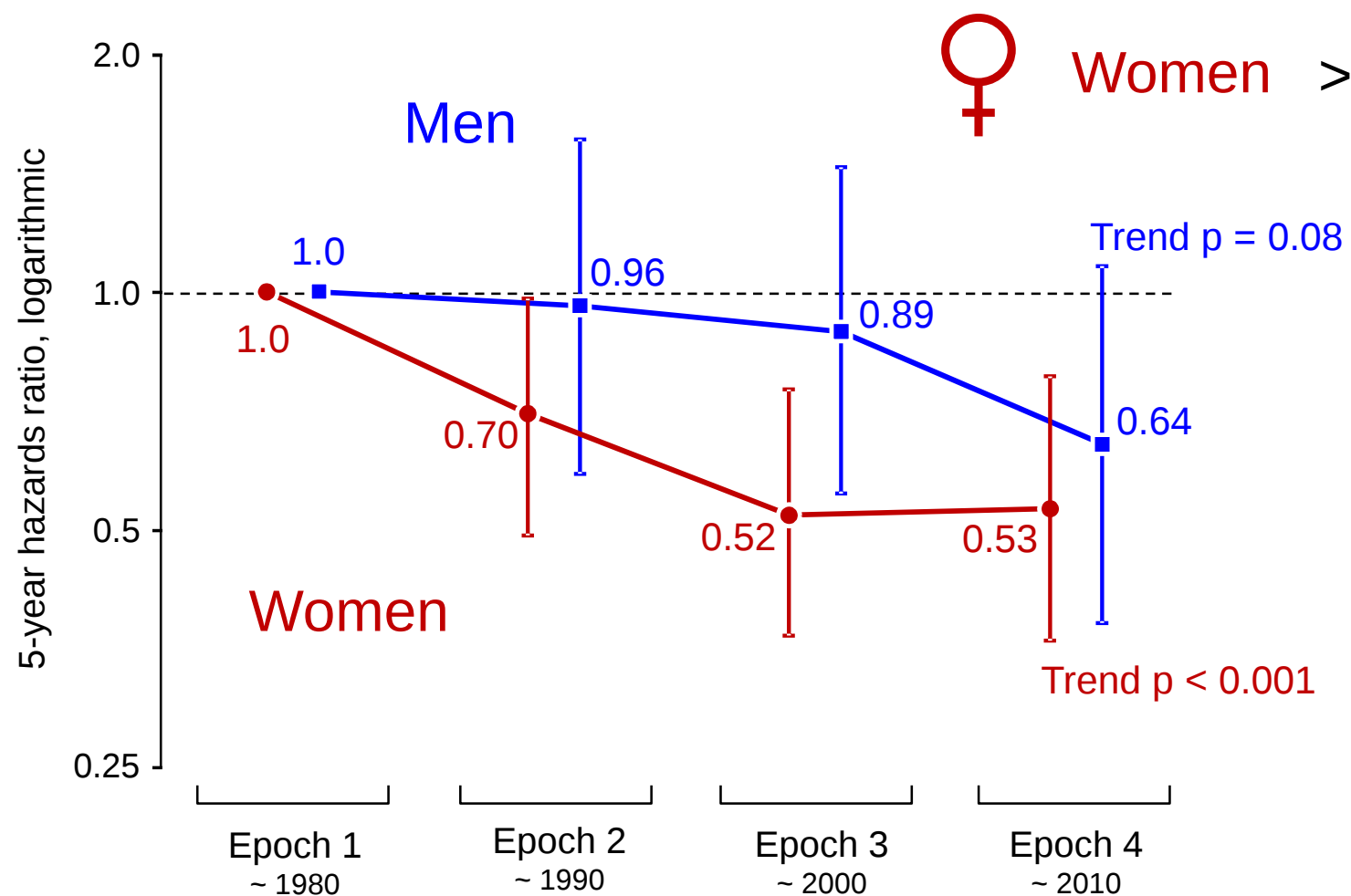
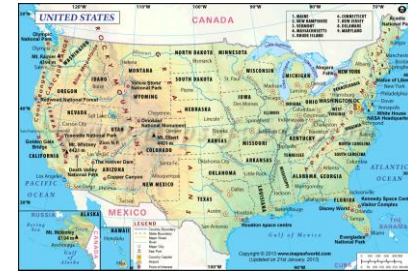
Incidence of AD: European studies



Incidence of mild cognitive impairment (MCI) - Minnesota

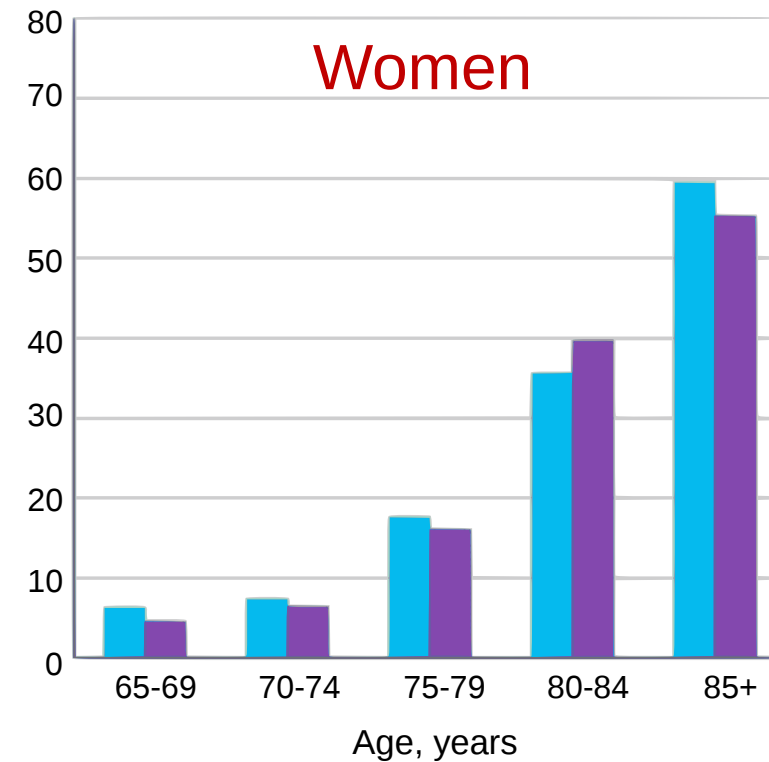
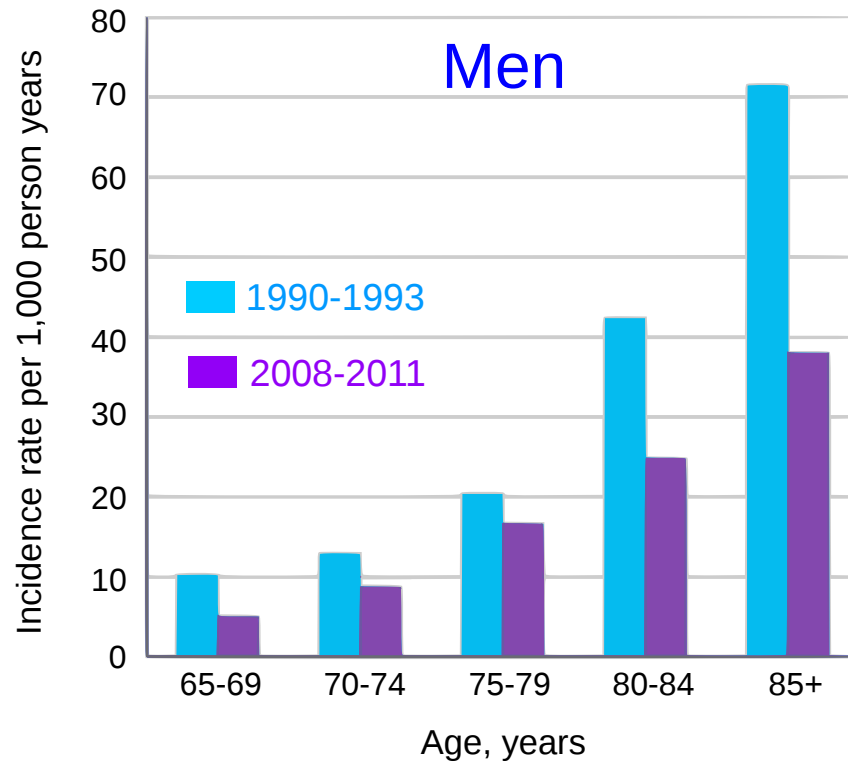


2016: Time trends for dementia Framingham, Massachusetts



2016: Time trends for dementia United Kingdom - 3 areas

Men ♂ > ♀ Women



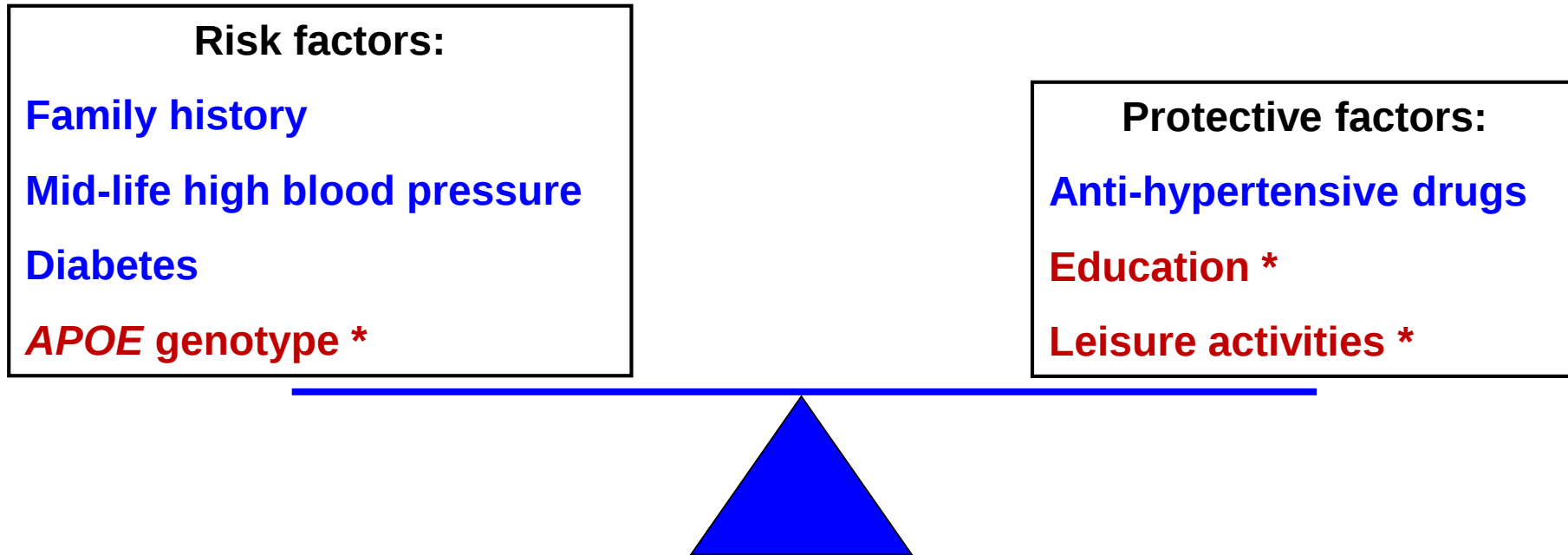
Incidence and time trends

- More women affected by dementia and AD
- Higher prevalence may relate to higher incidence or longer survival
- Higher incidence in women in Europe but not in the US
- Higher incidence of mild cognitive impairment (MCI) in men in the US and Europe
- Decline in incidence varies in women or in men

3b

Risk factors

Risk and protective factors: moderate or strong evidence



* Sex or gender related

Risk and protective factors: limited or insufficient evidence



Risk factors:

Mid-life high cholesterol

Late-life high cholesterol

Late-life high blood pressure

BMI, CVD, homocysteine

Diet, B12 deficiency

Smoking *

Depression *

SES, personality *

Occupational exposures *

Protective factors:

Statins

NSAIDs

Moderate alcohol *

Estrogen treatment *

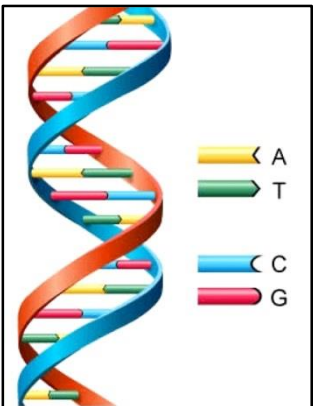
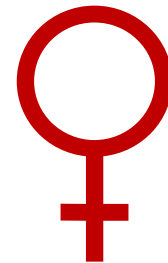
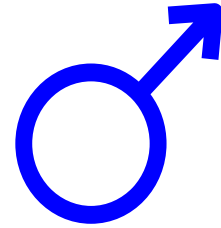
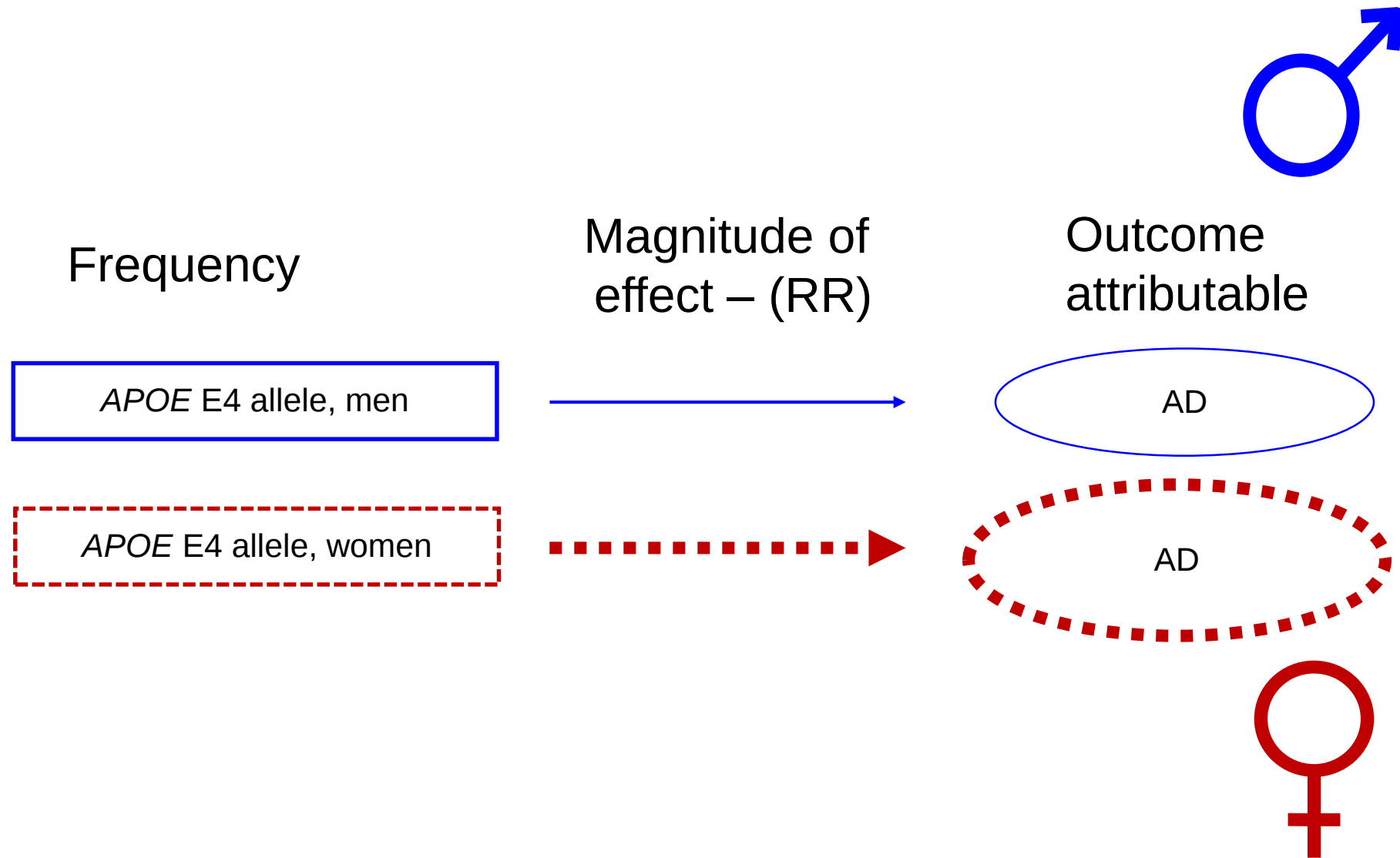
Social networking *

* Sex or gender related

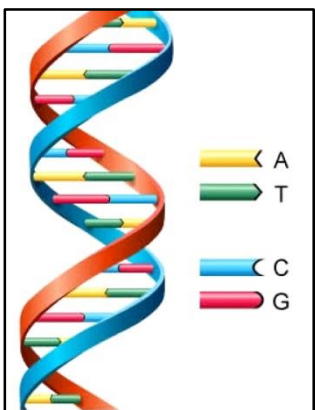
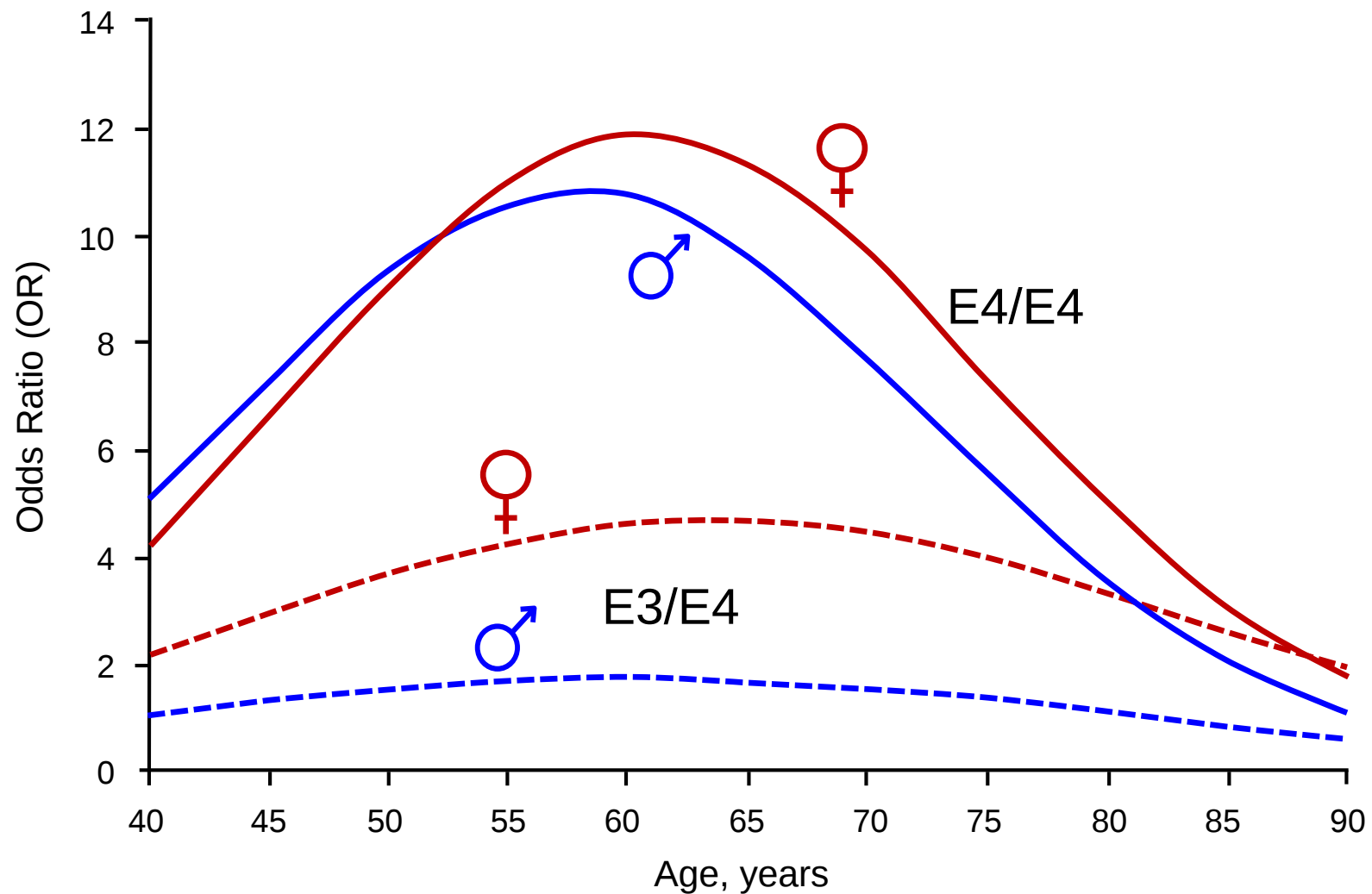
Men vs women

- Same frequency, different effect (*APOE E4* and other genetic variants)
- Same effect, different frequency (*education*, smoking, head trauma)
- Both different frequency and different effect
- Restricted to one sex (*bilateral oophorectomy*)

Same frequency, different effect

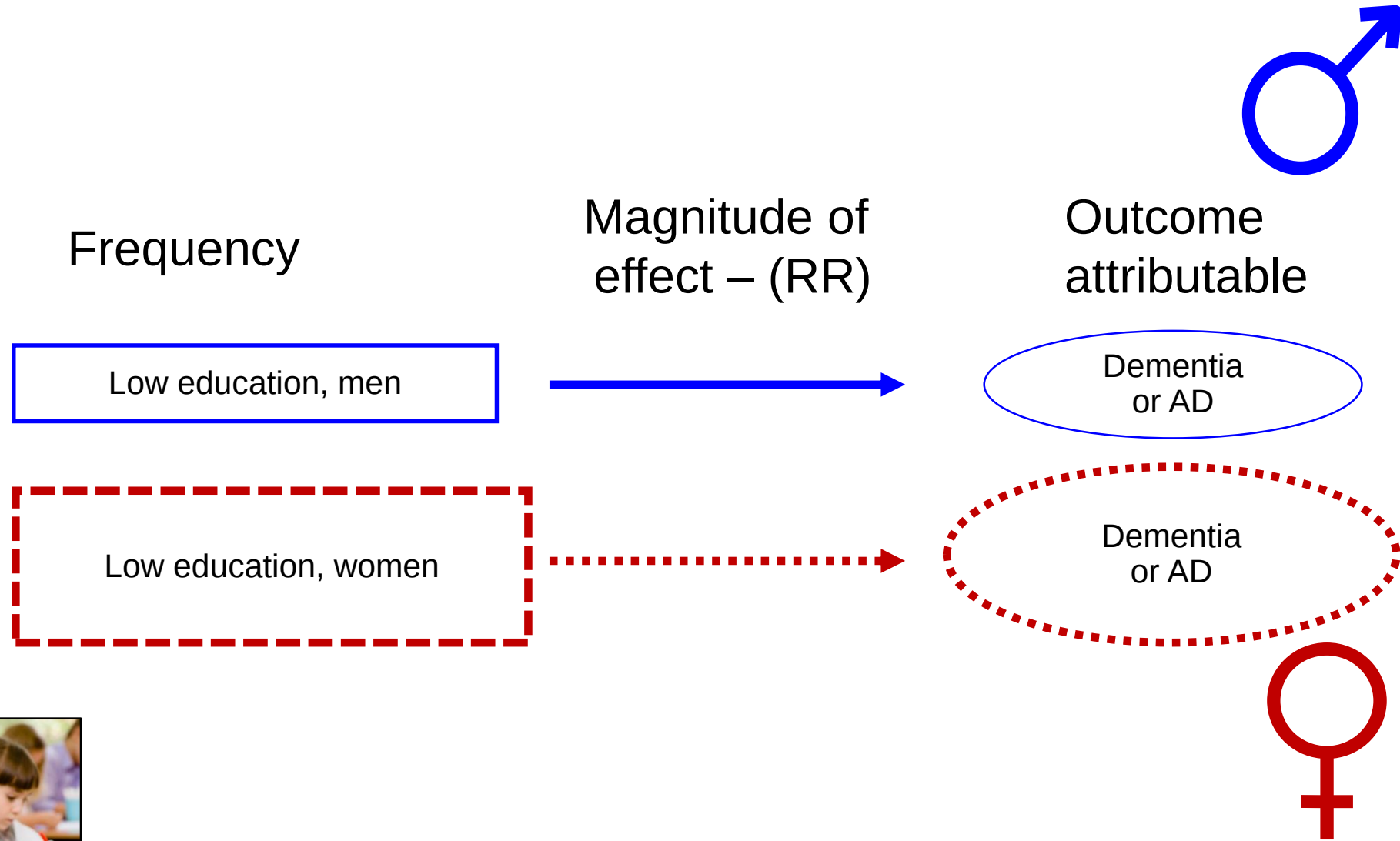


APOE and risk of AD

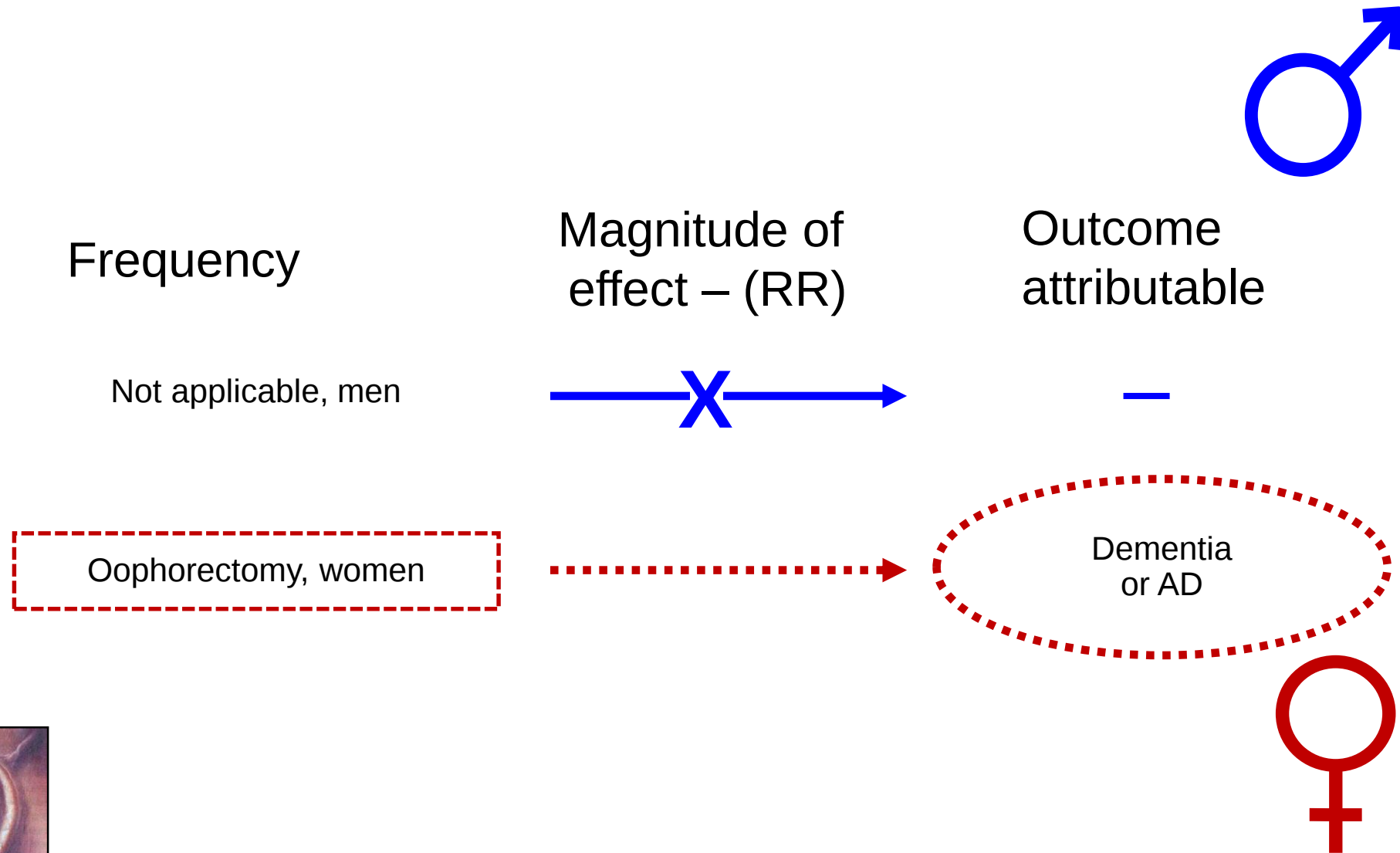


Adapted from Farrer et al., 1997

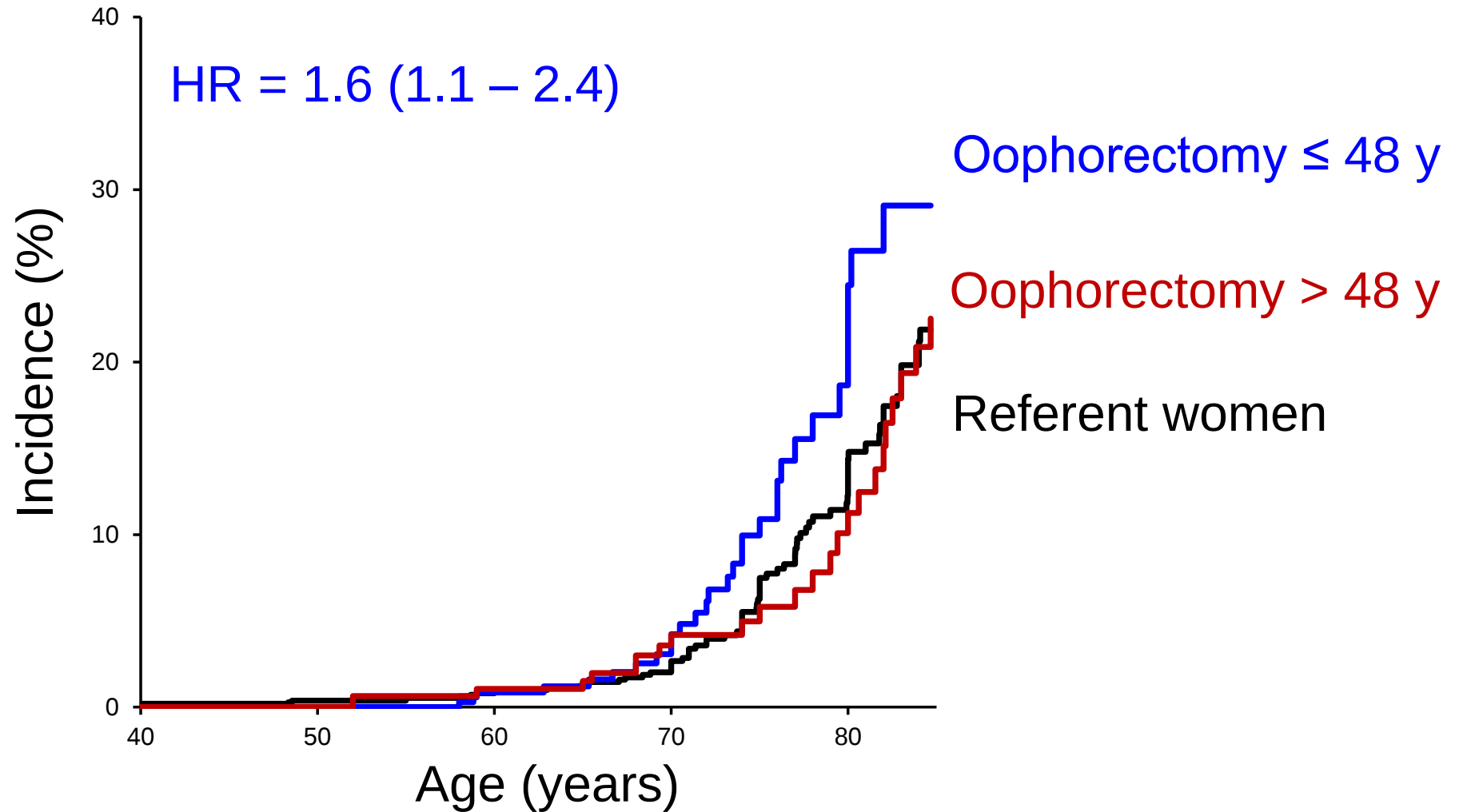
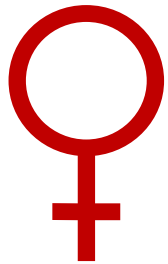
Same effect, different frequency



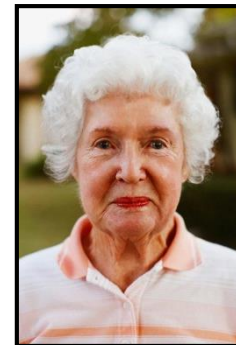
Restricted to one sex



Bilateral oophorectomy and risk of cognitive impairment or dementia



Dimorphic life course approach



Protective factors -

Risk factors +



Dementia

4

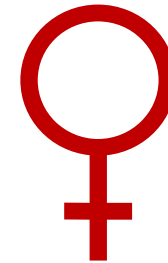
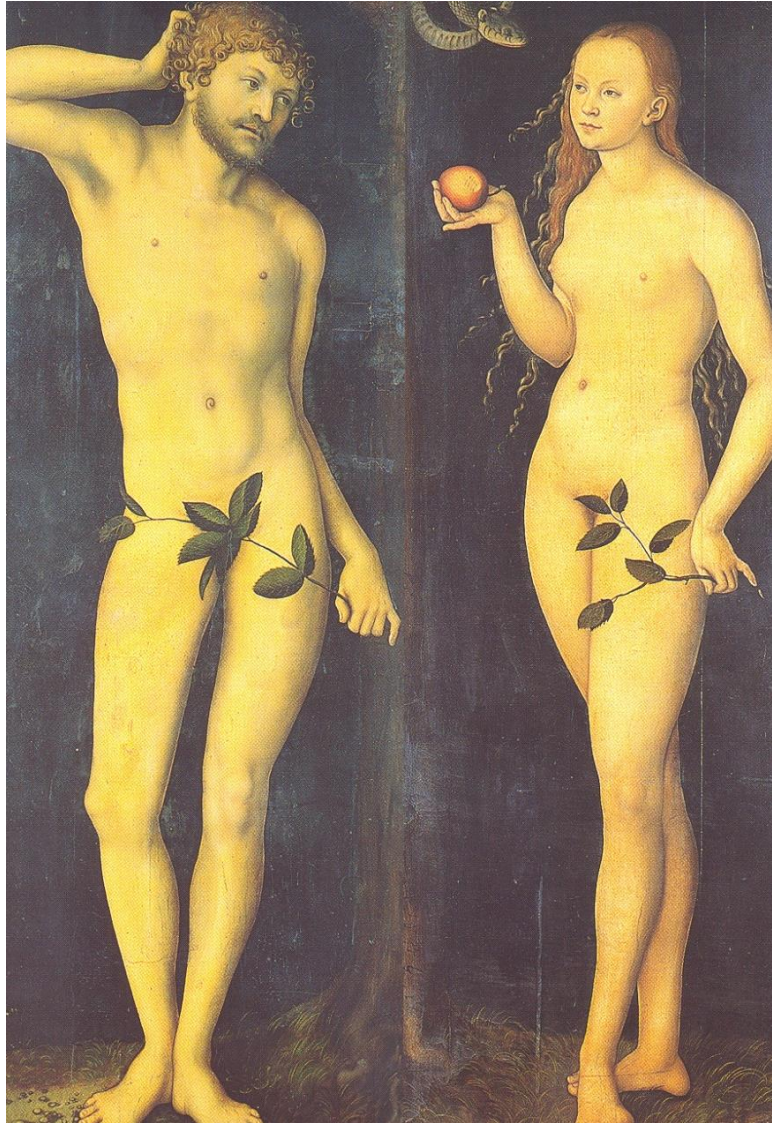
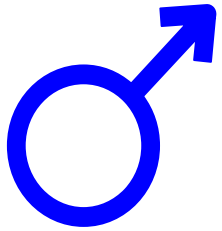
Conclusions

Conclusions

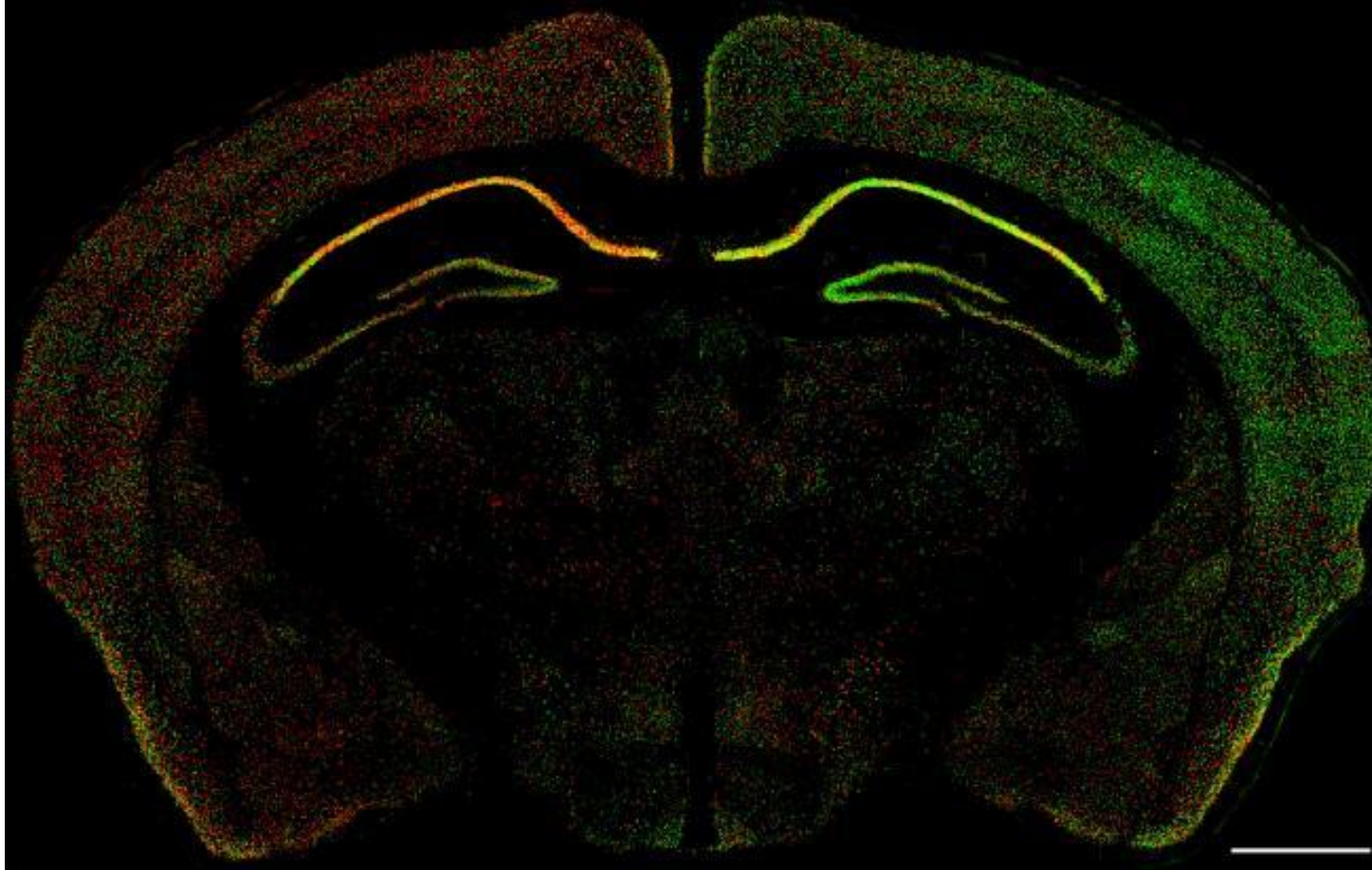


- Sex
 - Chromosomes
 - Hormones
 - Reproduction
- Gender
 - Subjective, personal identity
 - Social, cultural, political
- The incidence of dementia and MCI, and the time trends vary in men and women
- Risk factors are different in men and women (e.g., *APOE*, education)
- Some risk factor are sex specific (e.g., oophorectomy, estrogen)
- Need to move toward a dimorphic neurology

Thank you - Grazie



Laterality in X inactivation: brain cortex (mice)



Red and green dots indicate paternal or maternal inheritance of X chromosome

Sex, gender, age, time, and history

