

# Infertilitets epidemiologi

---

Øjvind Lidegaard

U-kursus

23. januar 2008

---

# Infertilitet epidemiologi

---

- **Definitioner**
- **Problemetets størrelse**
- **Alder og fertilitet**
- **Rygning**
- **Alkohol**
- **Kaffe**
- **Overvægt**
- **Mandlig fertilitet**

# Nogle definitioner

---

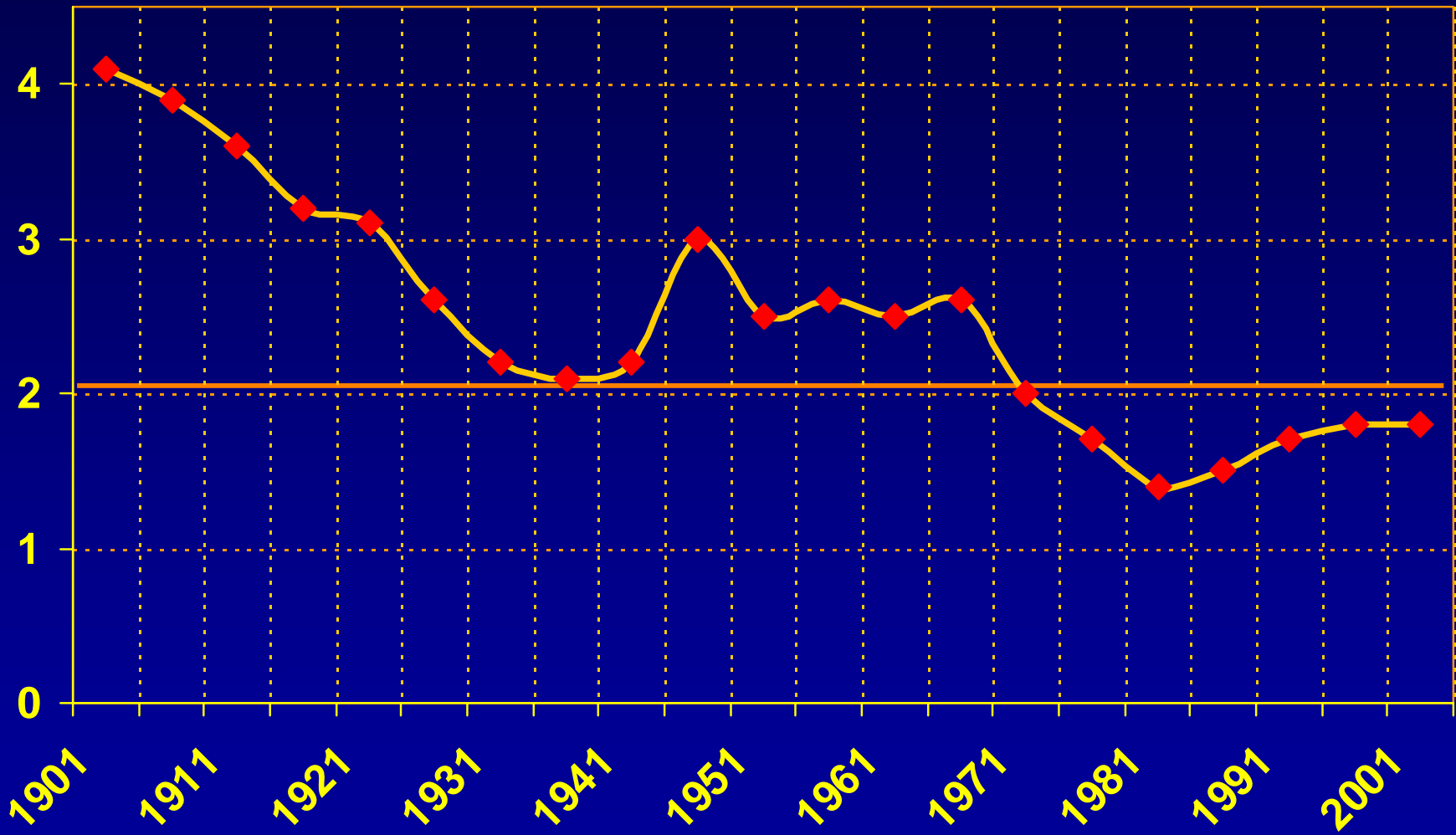
- **Infertilitet:**
    - Ikke gravid efter 1 år (i DK 15%)
  - **Fecunditet:**
    - Evnen til at blive gravid og føde
  - **Fecundabilitet:**
    - Graviditeter pr. cyklus (raske 20%)
  - **Fecundabilitetsratio:**
    - Graviditetschance hos eksponerede i forhold til graviditetschance blandt ikke eksponerede
-

# Infertilitet epidemiologi

---

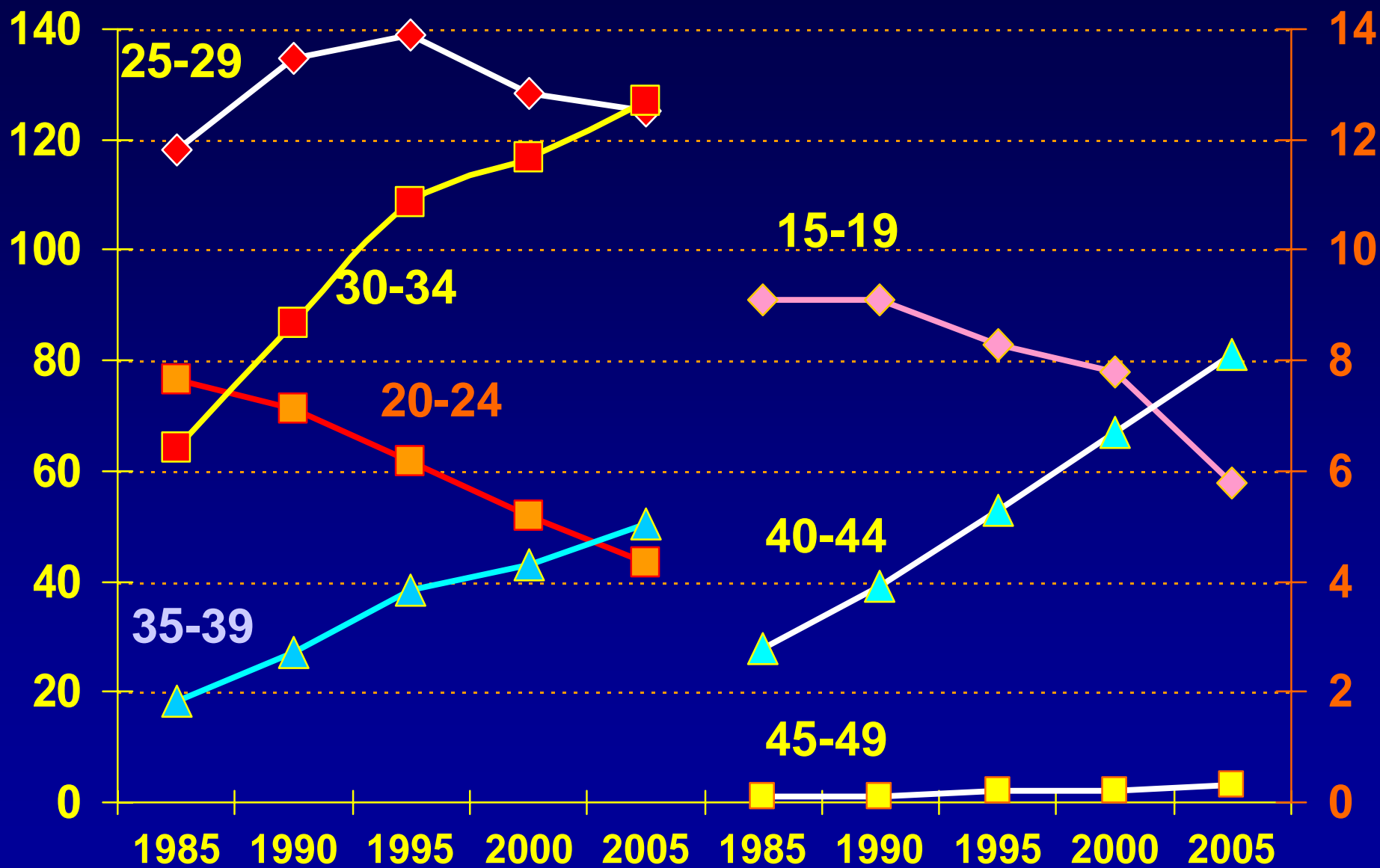
- Definitioner
- **Problemetets størrelse**
- Alder og fertilitet
- Rygning
- Alkohol
- Kaffe
- Overvægt
- Mandlig fertilitet

# Total fecundity rate in DK 1901-2007

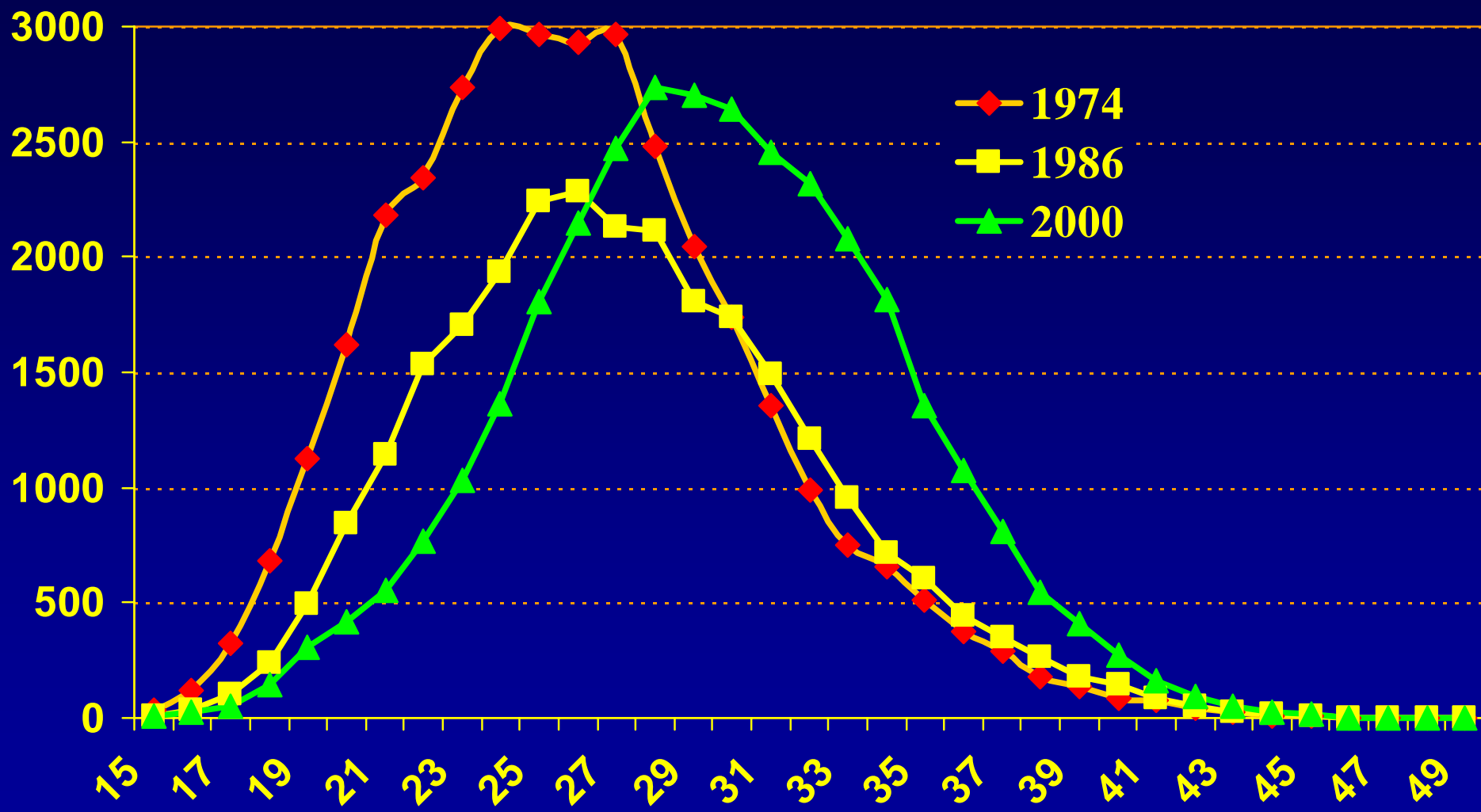


Lisbeth B Knudsen, Fertility trends in DK in the 1980s  
Danmarks Statistik online: [www.dst.dk](http://www.dst.dk)

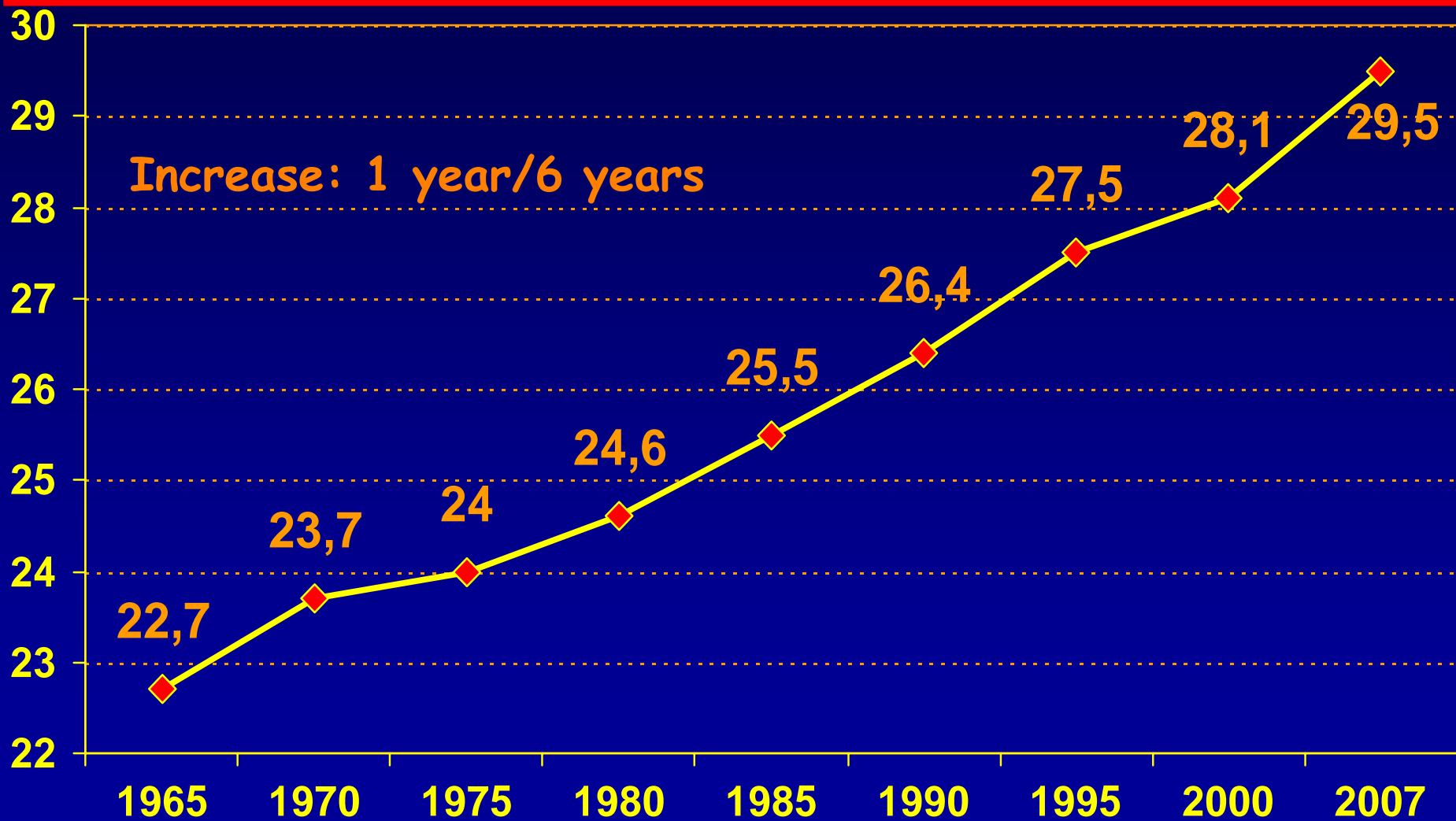
# Fertility rates per 1,000 in DK 1985-2005



# Levendefødte i DK i 1974, 1986 og 2000

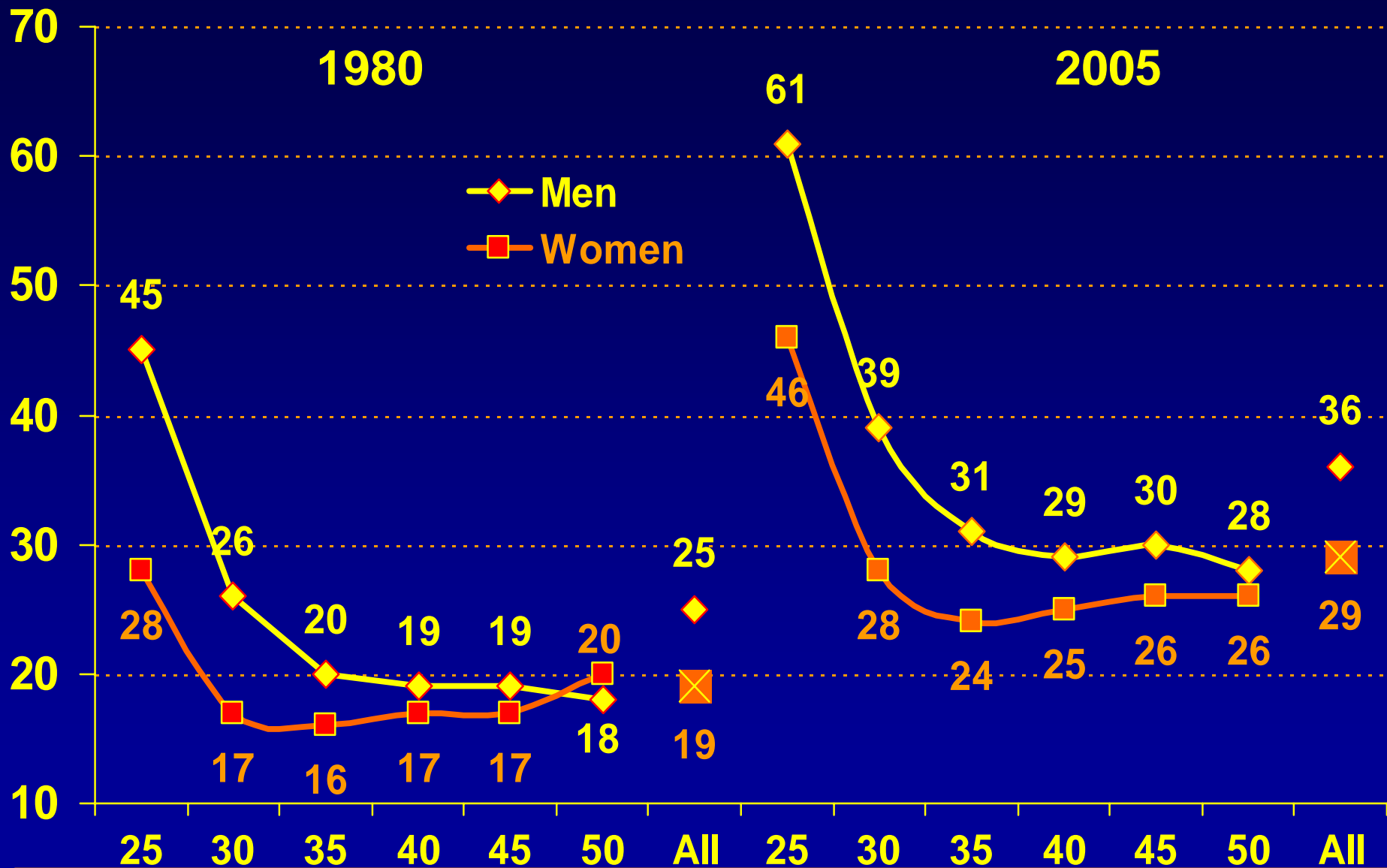


# Age at first birth Denmark 1965-2007





# Singles (%) in Denmark in 1980 and 2005



# Infertilitet epidemiologi

---

## Hvor stort er problemet i Danmark?

**Infertilitets prævalens (nu):** Kvinder i fertil alder: 6%

**Intertilitets prævalens (ever):** Kv i fertil alder: 15%

**Infertilitets life time risk:** Par: 25%

**Anmodn. om lægehjælp for infertilitet:** 10%

**Ufrivillig barnløshed:** 7%

**Barnløse ved menopause:** 12%

Er problemet stigende? Ja. Mulige årsager er

- Flere infertile i given alder
  - Større søgning om hjælp blandt infertile
  - Ændret fertilitet som følge af aldersforskydning
-

# Infertilitet epidemiologi

---

- Definitioner
- Problemets størrelse
- **Alder og fertilitet**
- Rygning
- Alkohol
- Kaffe
- Overvægt
- Mandlig fertilitet

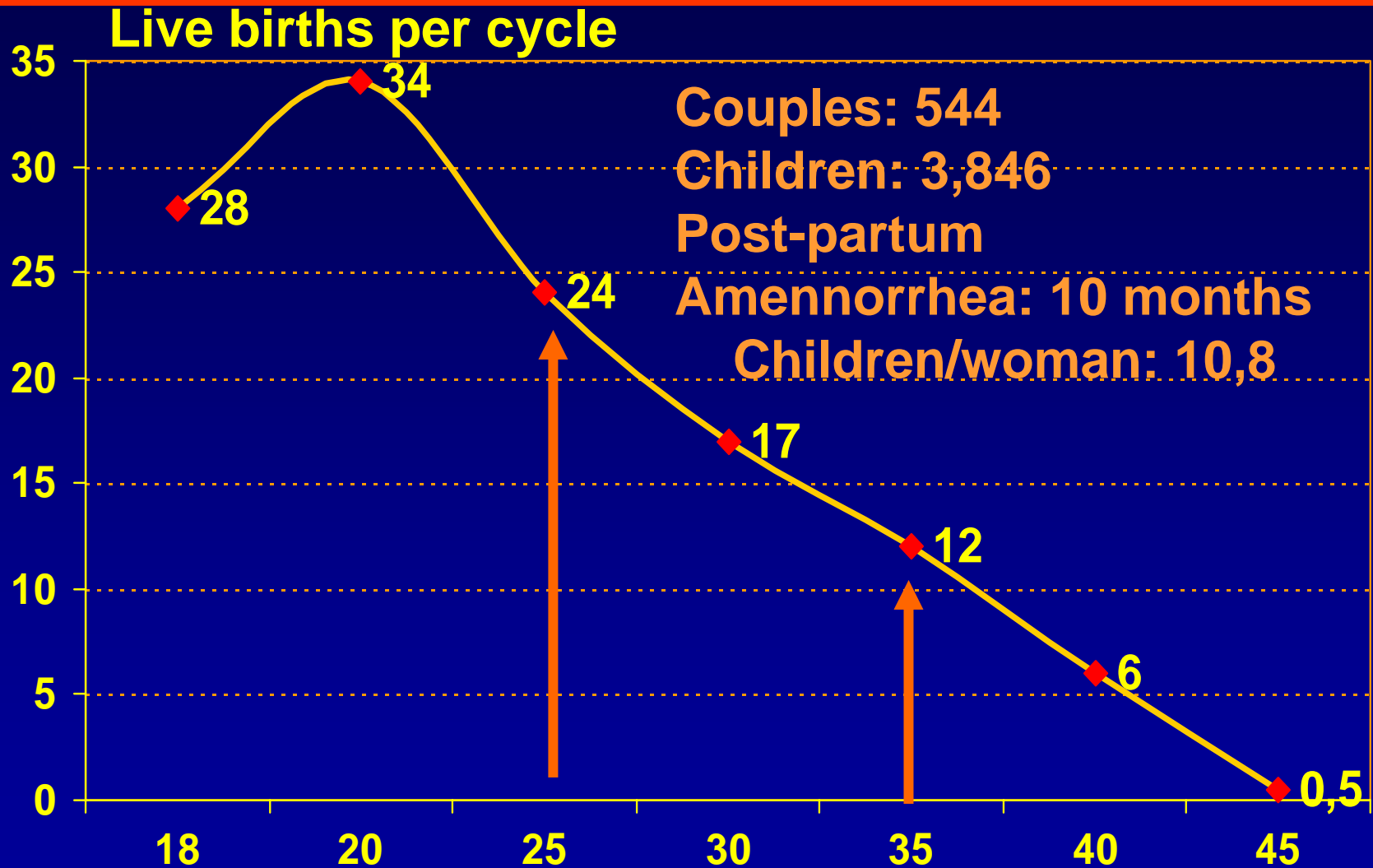
# Hvad er en kvinde, og hvad kan hun

---

Vi skal til North & South Dakota hvortil *Hutteritter* immigrerede i slutningen af det 19. århundrede. Der immigrerede 215 personer omkring 1870, i 1960 var de 5.450

- De må ikke anvende kontraception
  - Børn prioriteres højt, jo flere jo bedre
  - Socialt ligestillede med resten af befolkning.
  - Vi skal følge 544 par, alle gift, og alle med mindst et barn for at se hvad kvinderne kan
-

# Fecundity rate among Hutterite women



# Hvorfor falder fecunditeten med alderen?

---

## Mulige mekanismer:

- Ovarie funktion
  - Tuba funktion
  - Ændringer i endometriet
  - Ændringer i hormoner
  - Ændringer i sædkvalitet
  - Ændringer i sexual vaner
  - Øget abort rate
-

# Hvorfor falder fecunditeten med alderen?

---

## Mulige mekanismer:

### 1. Ovarie funktion

Tuba funktion

Ændringer i endometriet

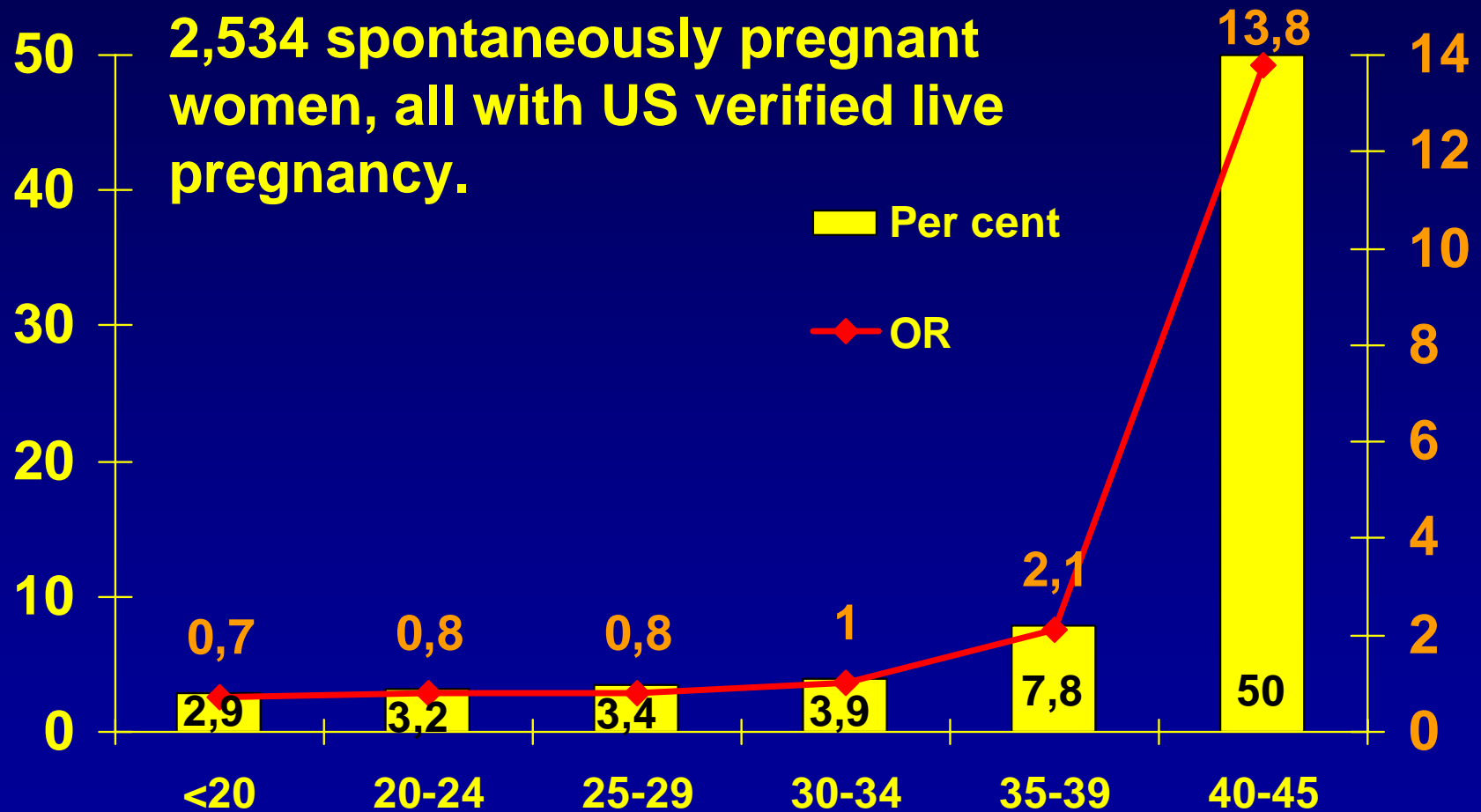
Ændringer i hormoner

Ændringer i sperm kvalitet

Ændringer i sexual vaner

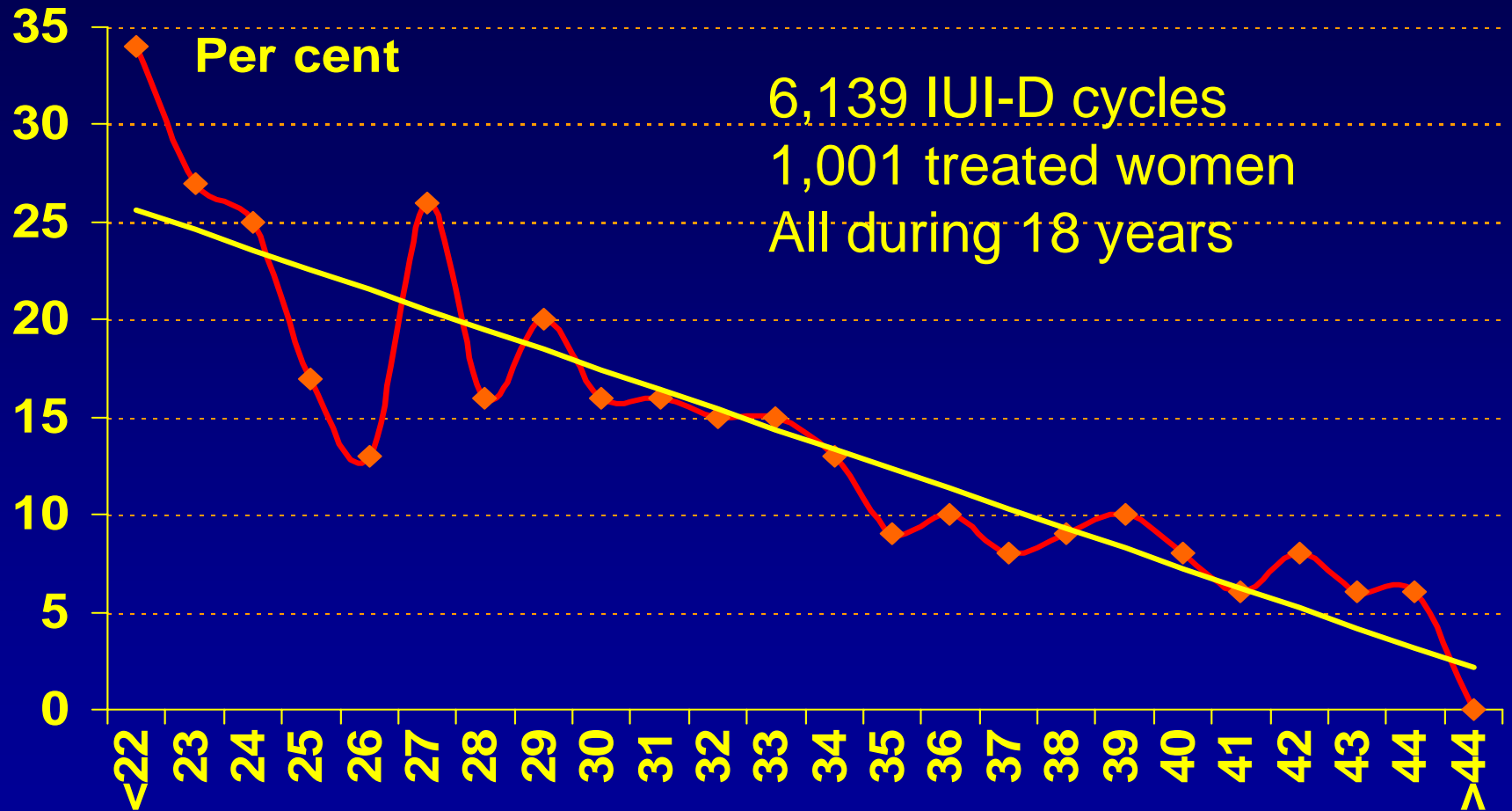
### 2. Øget abort rate

# Spontaneous fetal loss week 12-24 after early living pregnancy.





# Donor IUI. Pregnancies/100 cycles

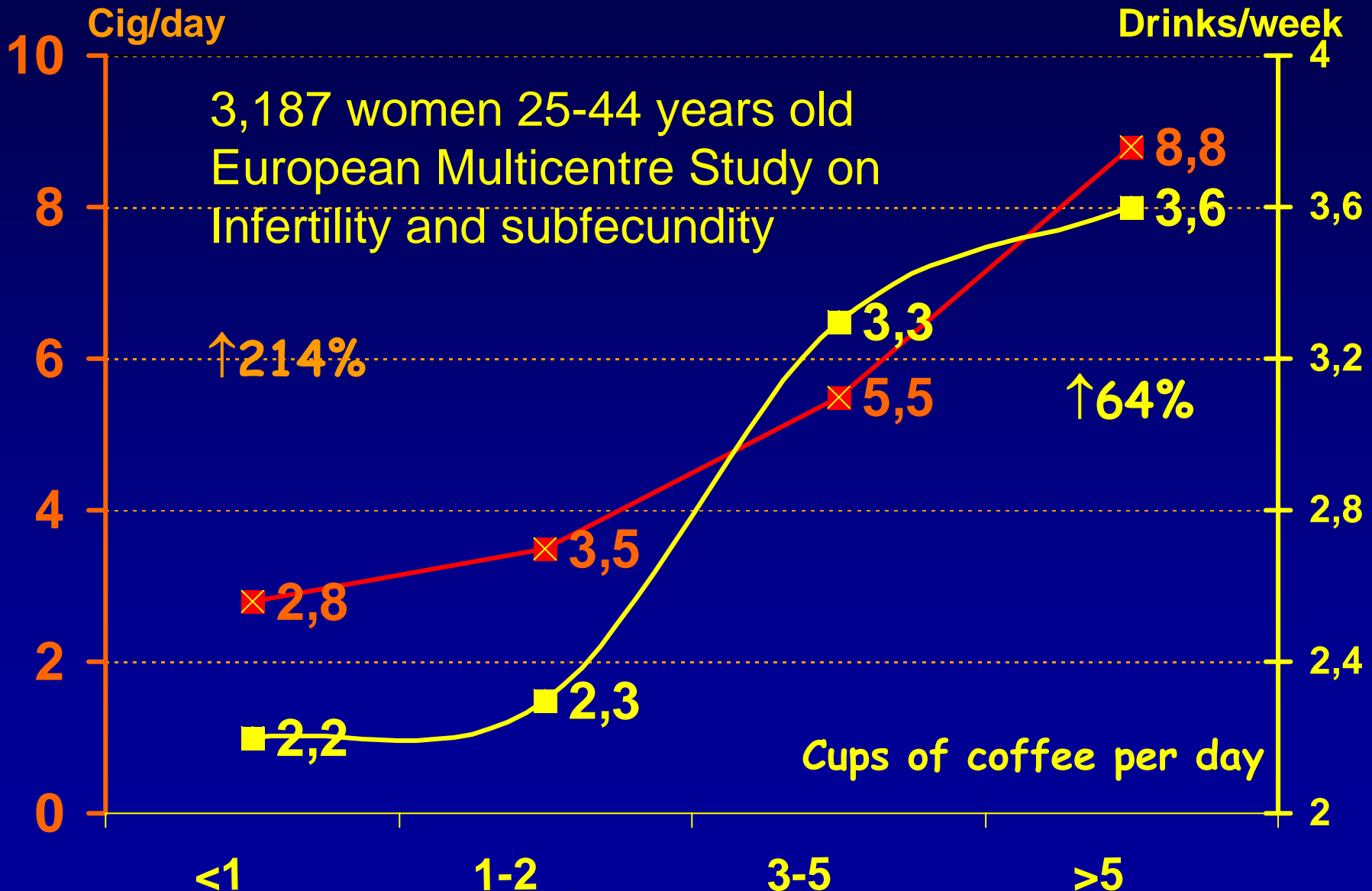


# Infertilitet epidemiologi

---

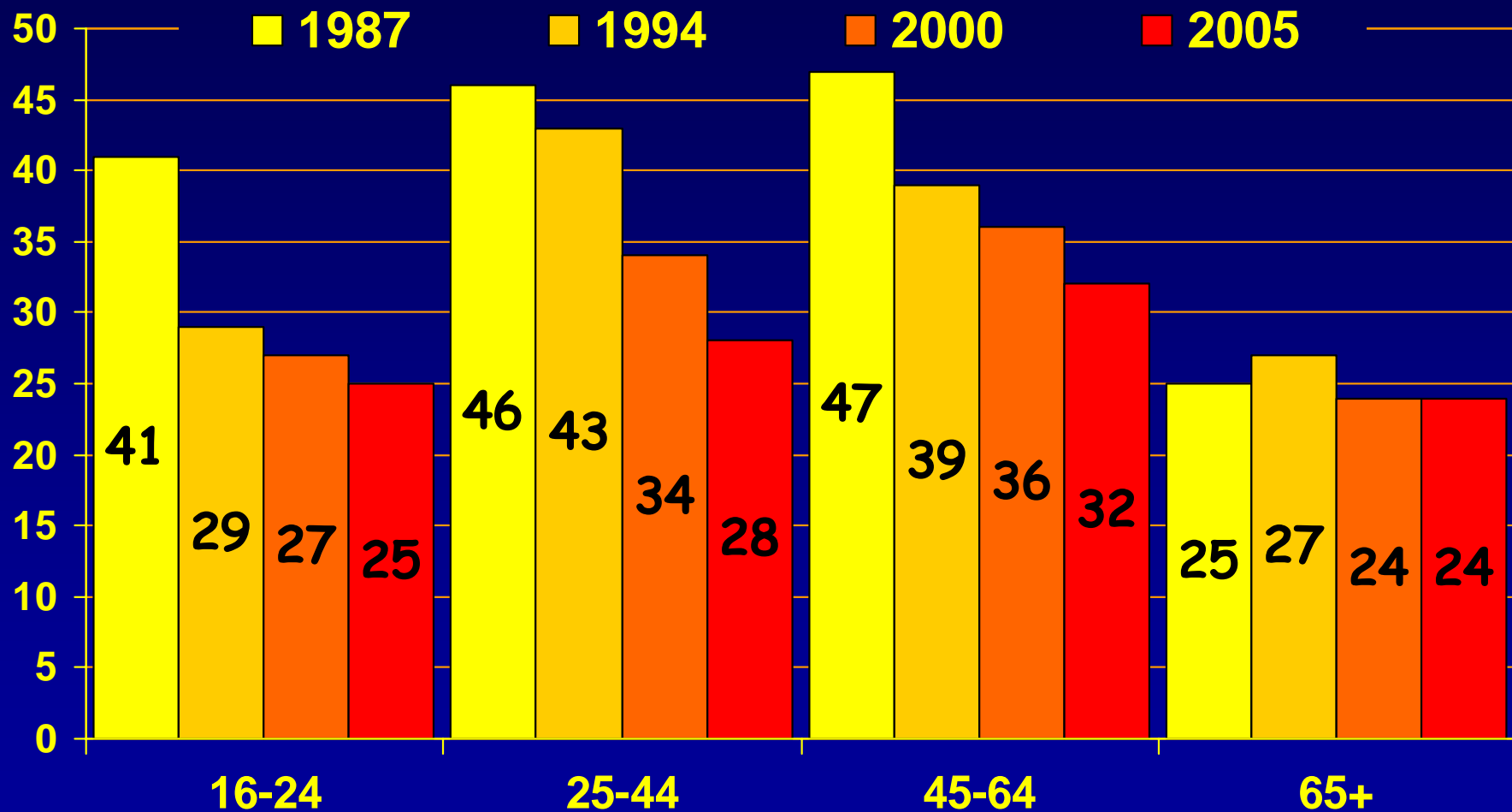
- Definitioner
- Problemets størrelse
- Alder og fertilitet
- **Rygning**
- Alkohol
- Kaffe
- Overvægt
- Mandlig fertilitet

# Naughty girls



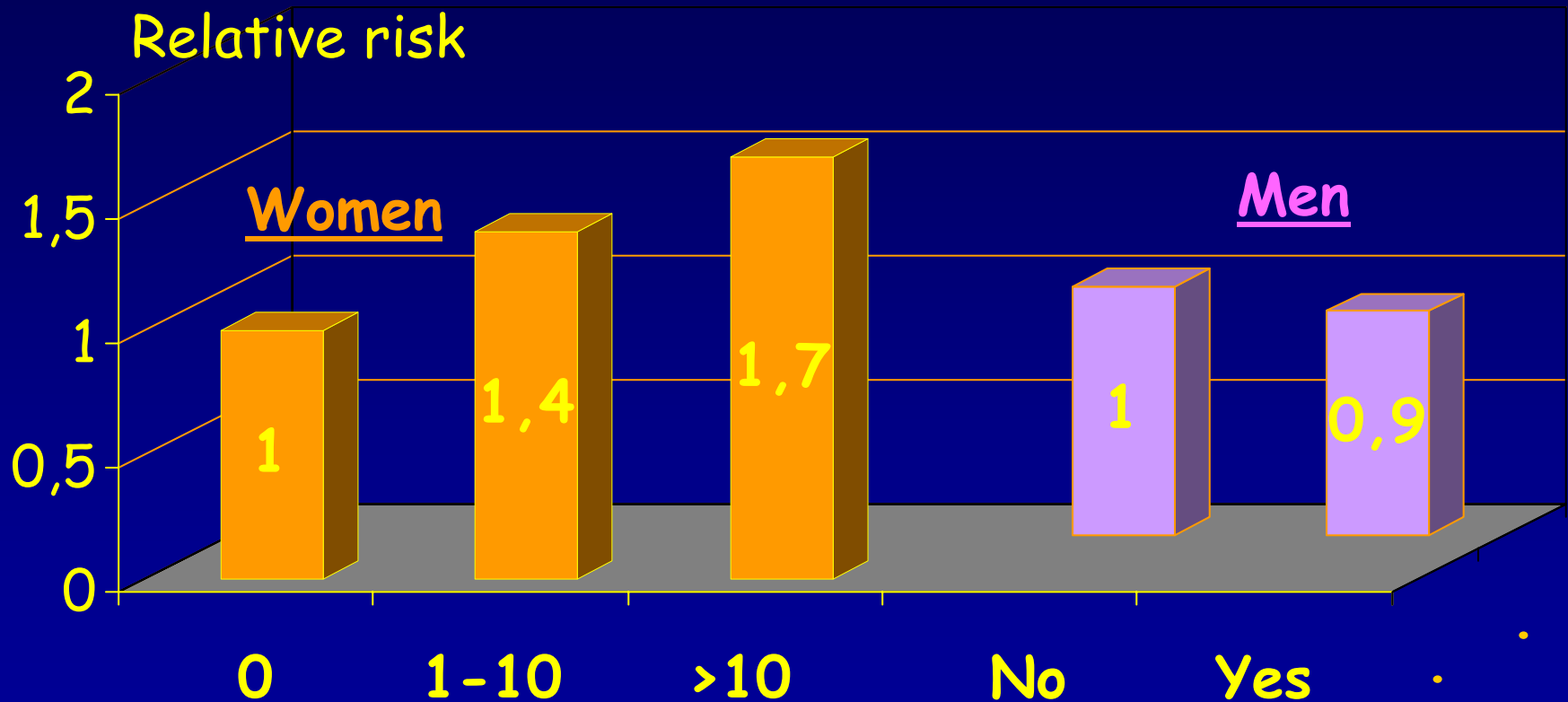
3,187 women 25-44 years old  
European Multicentre Study on  
Infertility and subfecundity

# Smoking in women in DK in 1987, 1994, 2000 and 2005



# Fertility and smoking

Risk of waiting time >9,4 months

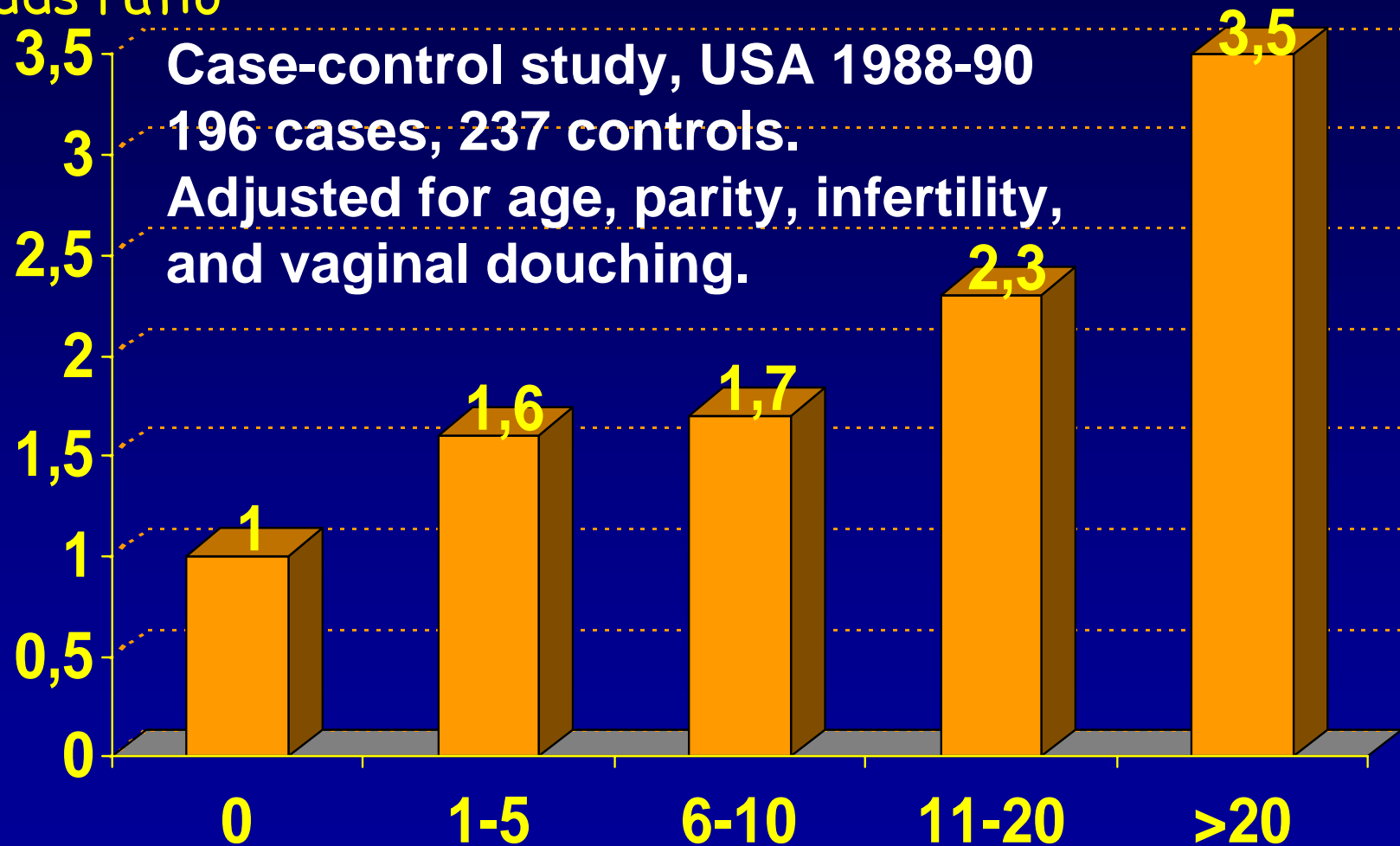


Bolumar et al. Am J Epidemiology 1996; 143: 578-87.  
European multicenter study on infertility and subfecundity

Li/01

# Smoking and ectopic pregnancy

Odds ratio



# Smoking - IVF

---

	-smo	ex-smo	+smo
No	499	351	111
Ø2/FSU U	82	71	60
Oocytes	13.5	13.6	12.6
Fertilis. rate	54%	54%	50%
Embryos	8.0	8.2	6.6
Embr. transf	3.6	3.5	3.6
Implant. rate	16%	16%	6.7%

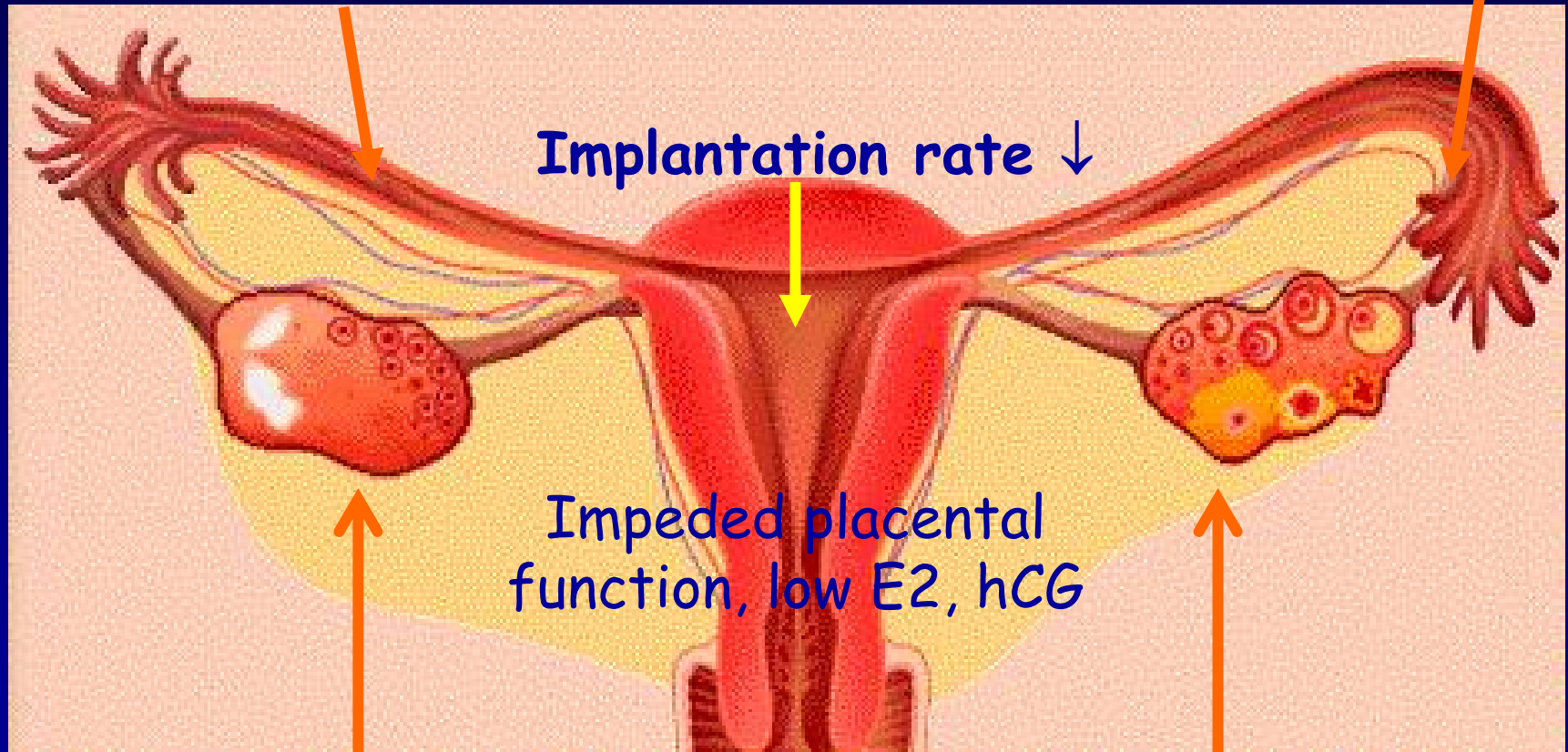
---

Voorhis et al. Obstet Gynecol 1996; 8: 785-91

# Smoking and fertility

Impeded ciliary function:

Pick-up function ↓



Implantation rate ↓

Impeded placental  
function, low E2, hCG

E2-production ↓

Abortion rate ↑

↓ progesterone  
in granulosa cells



# Rygning hos mænd

---

- Mindsker sædkvaliteten lidt  
Kun betydning ved excessiv rygning eller dårlig sædkvalitet
- Udsætter kvinden for passiv rygning  
(Betydning aldrig dokumenteret)
- Mindsker chancen for at kvinden kan ophøre med at ryge
- Skaber et dårligt indeklima for et kommende barn

# Infertilitet epidemiologi

---

- Definitioner
- Problemets størrelse
- Alder og fertilitet
- Rygning
- **Alkohol**
- **Kaffe**
- **Overvægt**
- **Mandlig fertilitet**

# Alkohol og fertilitet

---

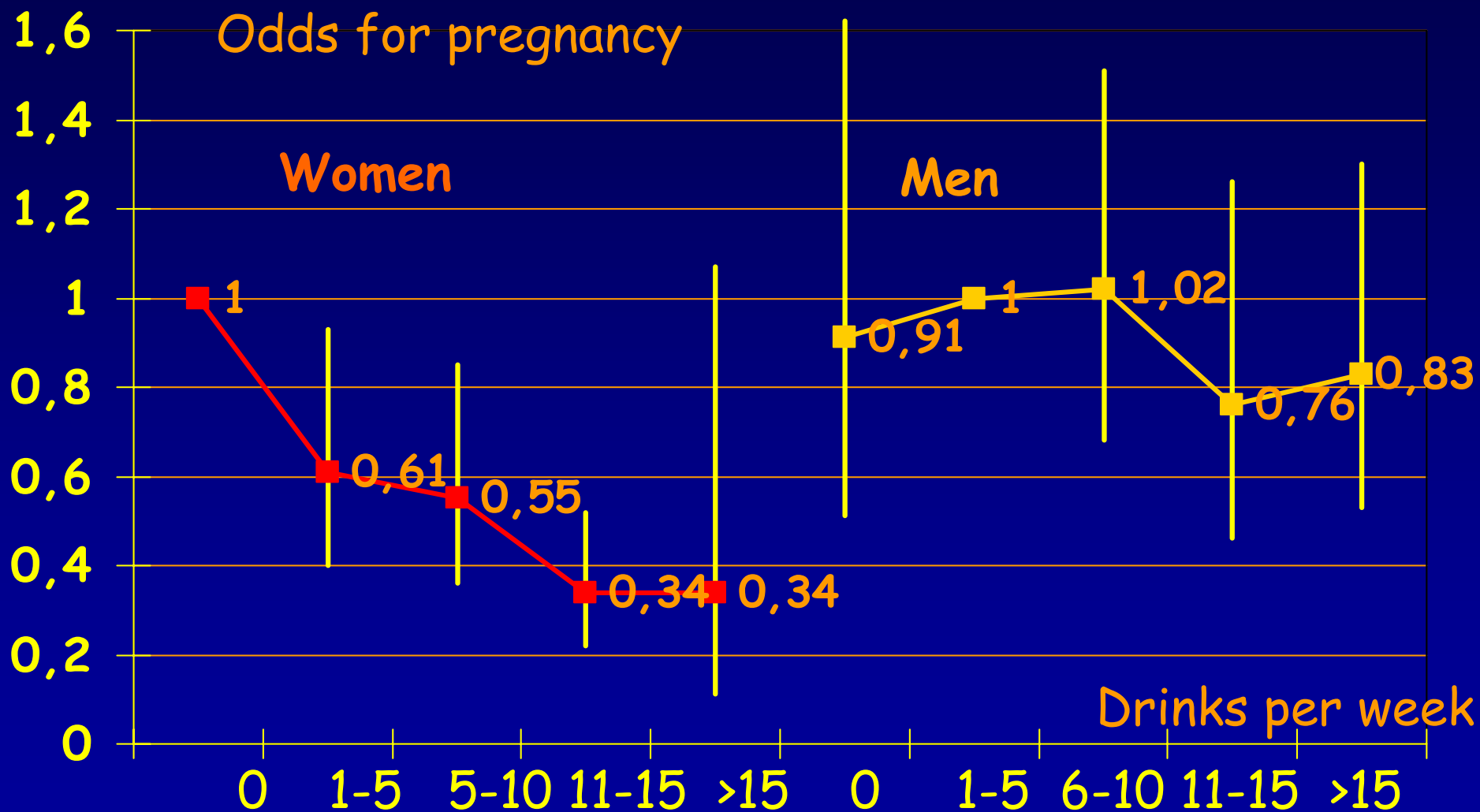
Nedsætter beskedne mængder alkohol fertiliteten?

- Kun få undersøgelser
  - Dansk prospektivt studie 1992-94 med 430 par, 20-35 år, som prøvede at opnå graviditet for første gang.
  - Alkohol indtag blev registreret tæt gennem 6 cykli
  - Kontrol for rygning, BMI, sædkvalitet, kaffe
- 

Jensen et al. *BMJ* 1998; 317: 505-10

# Fertility and alcohol

Fecundability odds, 95% CI



Jensen TK et al. BMJ 1998; 317: 505-10.

# Alcohol and time to pregnancy

---

**Cross sectional study** DK 1997-2000 including 39,612 pregnant women (Danish birth cohort). 29,933 planned pregnancies included.

**Included:** 60% of invited = 1/3 of all pregnant.

**Asked about** alcohol habits before pregnancy, which was correlated to time to pregnancy.

**Included confounders:** Smoking (in pregnancy), BMI, parity and age.

**Outcome measure:** Subfecundity odds ratio

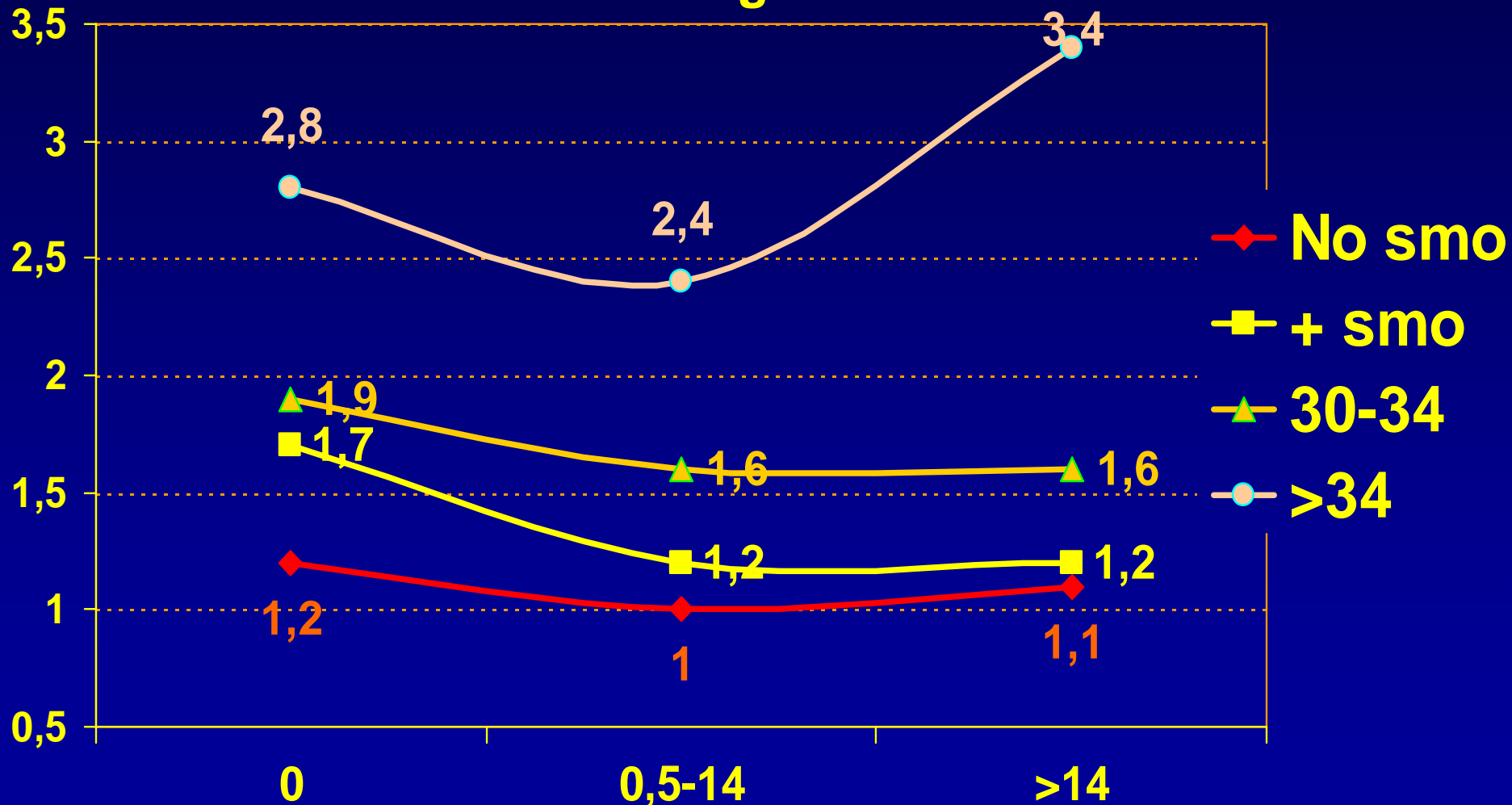
---

# Subfecundity OR and drinks per week



# Time to pregnancy and alcohol, stratified according to age and smoking

Risk of increase in waiting time



# Alkohol og graviditet

---

- Studie over "den århusianske fødselskohorte" 1989-96 med 25.000 gravide og disses fødsler dokumenterer at 5 genstande/uge =>
- 2,5 x risiko for dødfødsel
- 3 x øget risiko for abort i 7.-12. uge
- øget risiko for tidlig fødsel
- øget risiko for lav fødselsvægt

---

Kesmodel U. Am J Epidemiol 2002; 155: 305-12  
Kesmodel U. Alcohol 2002; 37: 87-92



# Alkohol hos mænd

---

- Mindre end 10 genstande om ugen betyder ingenting for
  - sædkvalitet
  - fertilitet
  - abortrisiko
  - misdannelser
- Mere end 10 genstande om ugen mindsker sædkvalitet lidt

# Infertilitet epidemiologi

---

- Definitioner
- Problemets størrelse
- Alder og fertilitet
- Rygning
- Alkohol
- **Kaffe**
- Overvægt
- Mandlig fertilitet

# Koffein

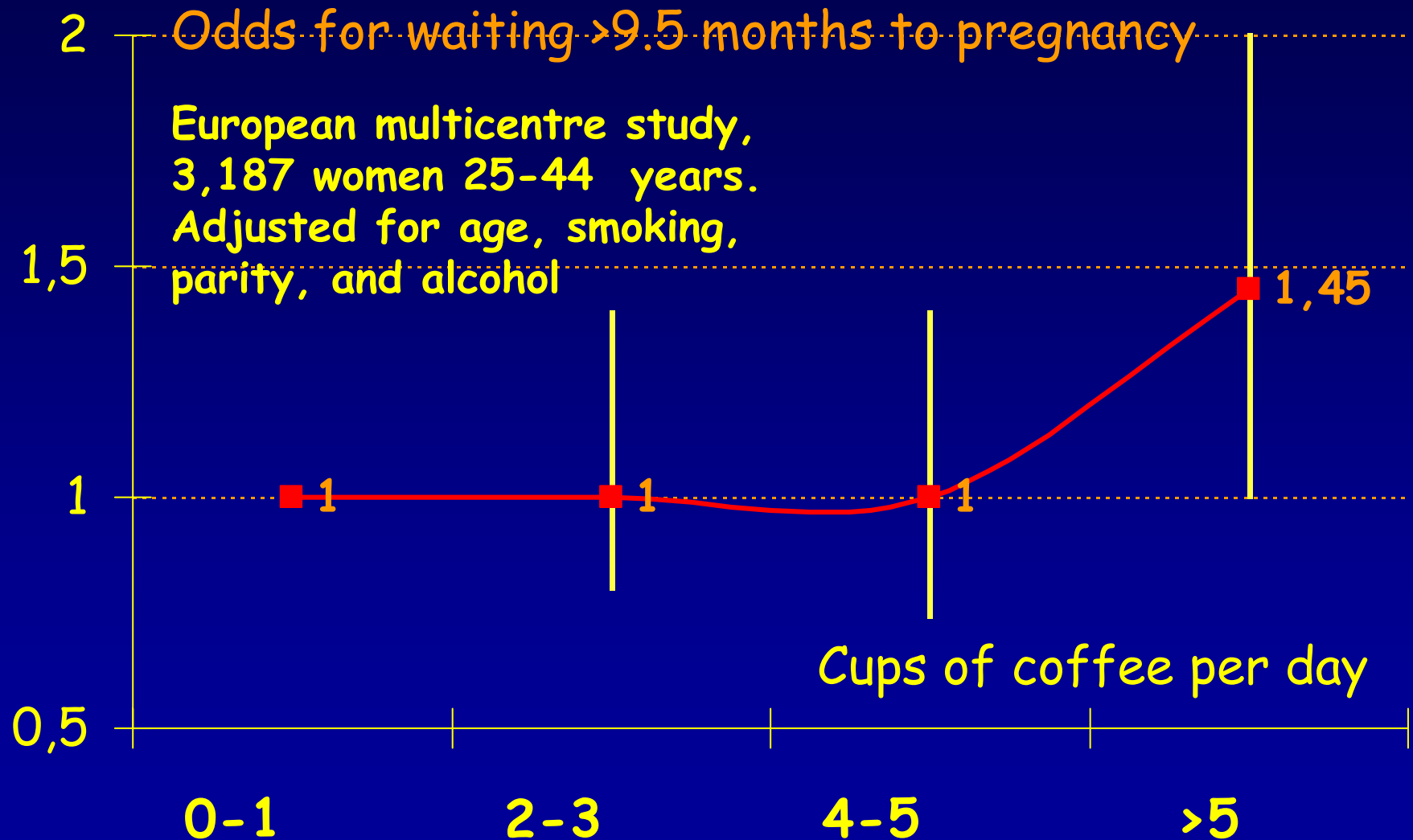
---

## Koffein findes i

- 1 kop kaffe = 100 mg
- 1 kop te = 50 mg
- ½ liter cola = 50 mg
- 30 g chokolade = 10 mg
- 1 kop kakao = 5 mg
- medicin.
- Koffein passerer alle biologiske membraner inkl.. placenta-barrieren
- Koffein findes i alle kropsvæsker kort efter indtag

# Fertility and coffee

Fecundability odds, 95% CI



# Kaffe og fertilitet: Konklusion

---

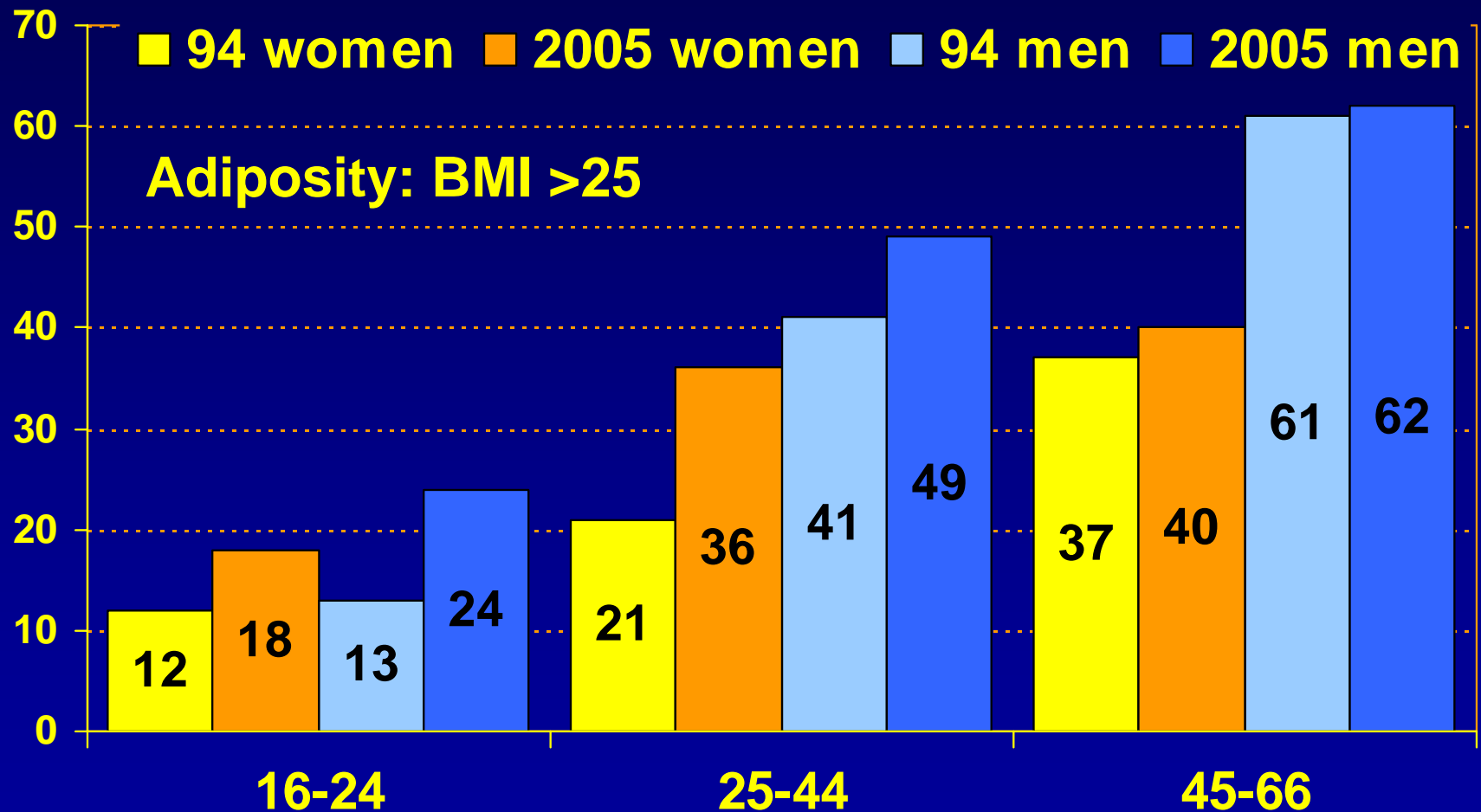
- Mindre end fem kopper kaffe om dagen påvirker ikke fertiliteten
- Mindre end fem kopper kaffe om dagen påvirker ikke risikoen for spontan abort
- Mere end fem kopper kaffe om dagen mindsker fertiliteten
- Mere end fem kopper kaffe om dagen øger risikoen for første trimester spontan abort (blandt ikke rygere)

# Infertilitet epidemiologi

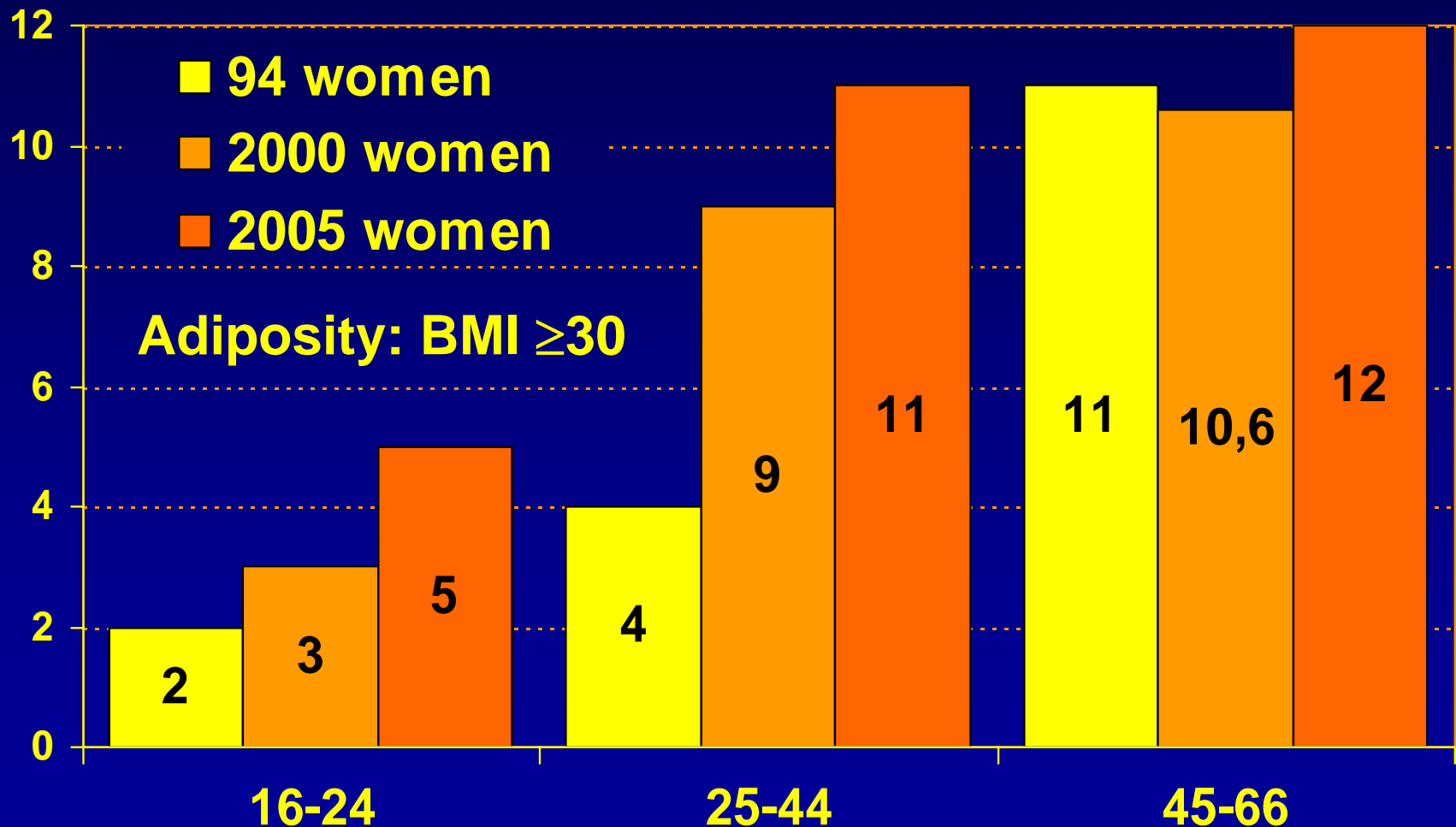
---

- Definitioner
- Problemetets størrelse
- Alder og fertilitet
- Rygning
- Alkohol
- Kaffe
- **Overvægt**
- **Mandlig fertilitet**

# Adiposity in Danish women and men in 1994 and 2005. N=16,000



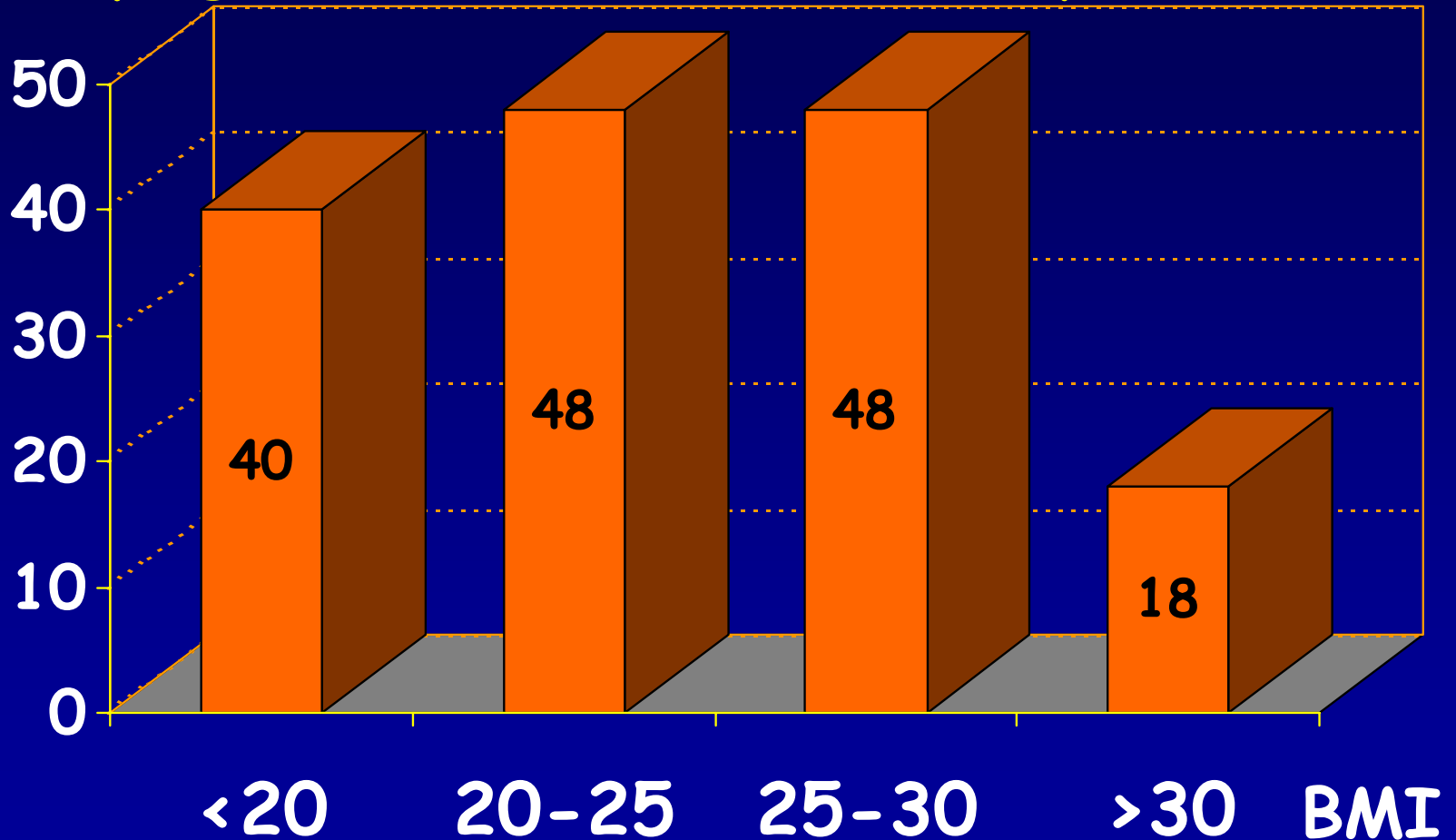
# Severe adiposity in Danish women in 1994, 2000 and 2005





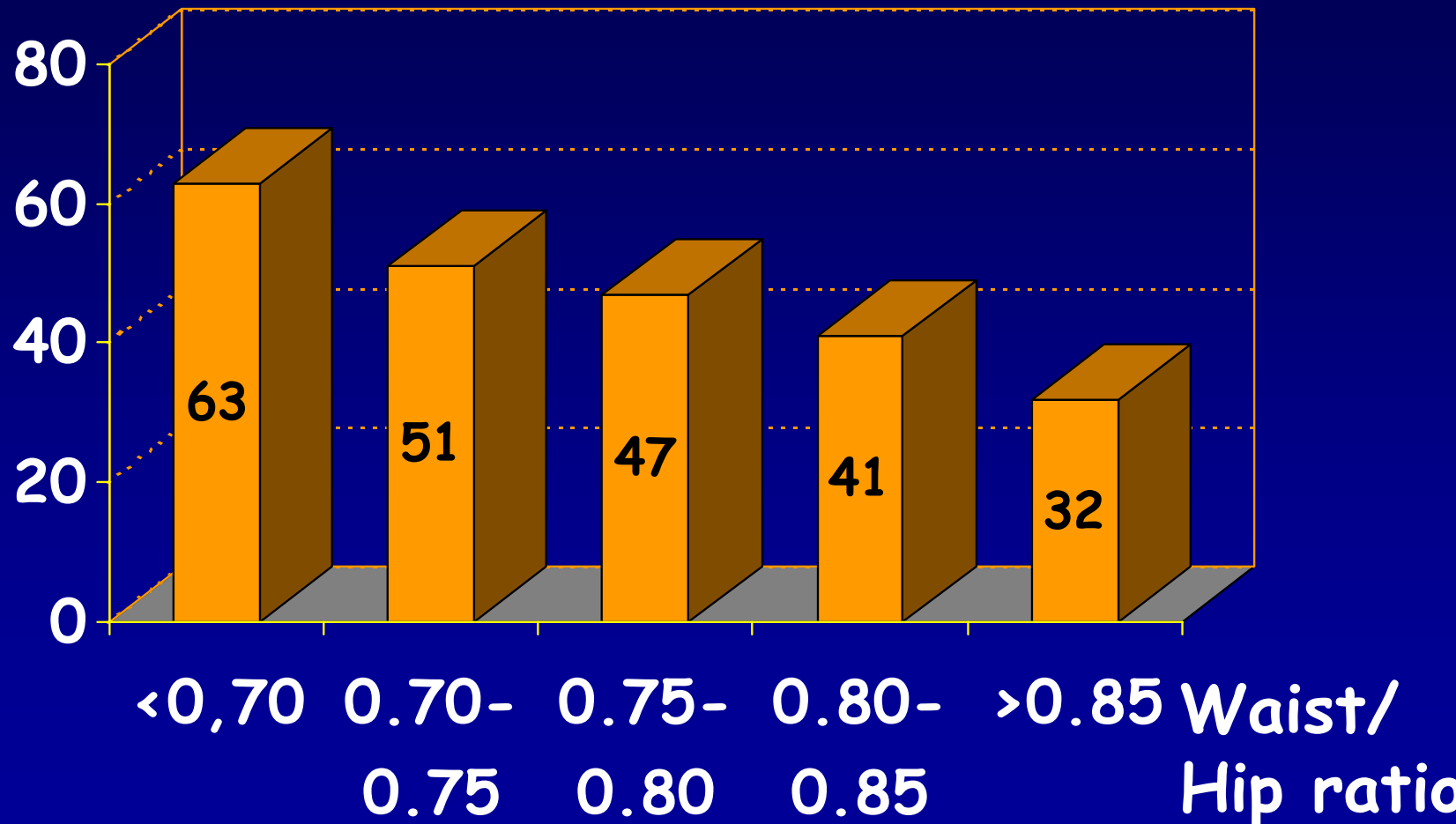
# Fat and fecundity

% pregnant within 12 insemination cycles (n=489)

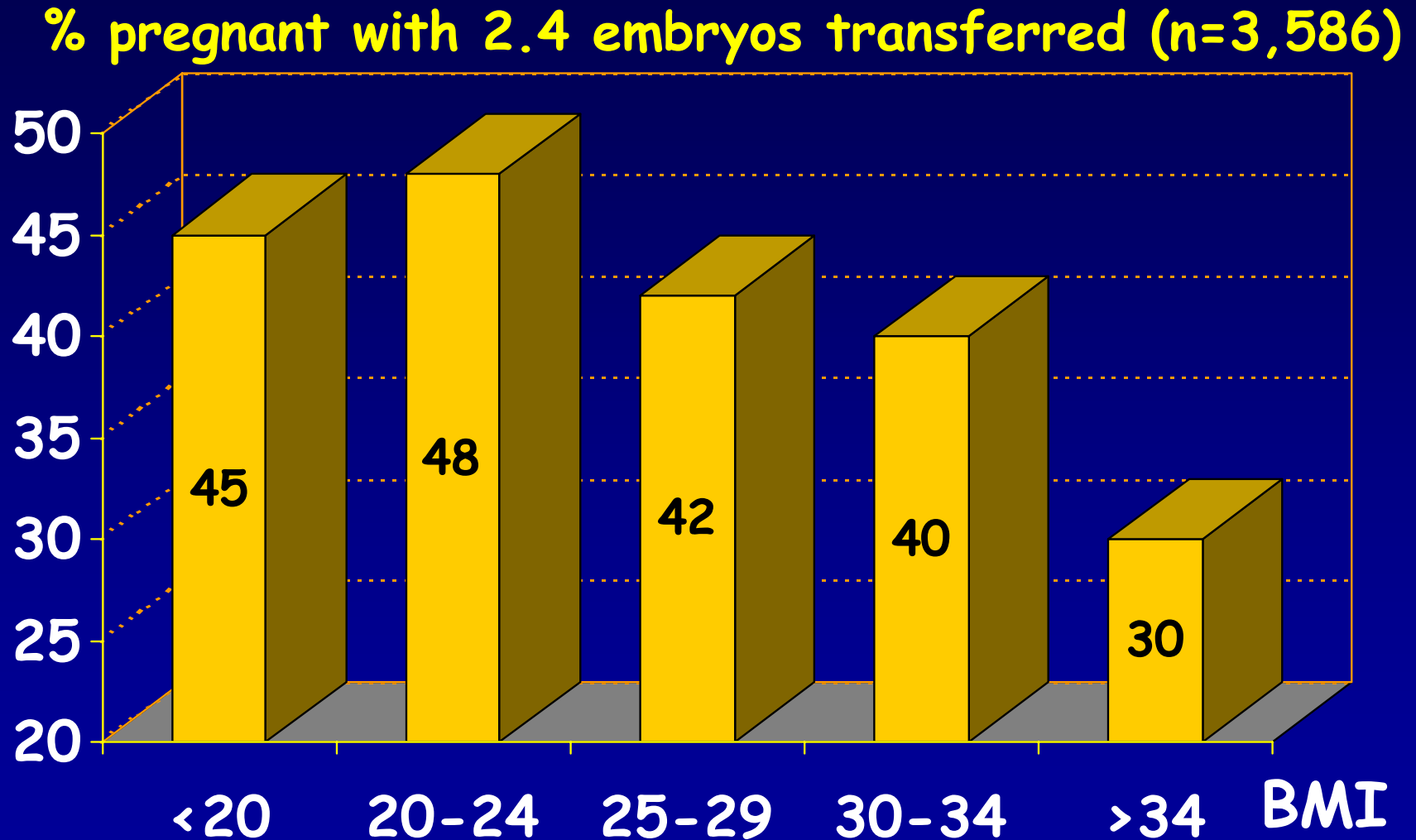


# Fat and fecundity

% pregnant within 12 insemination cycles (n=489)

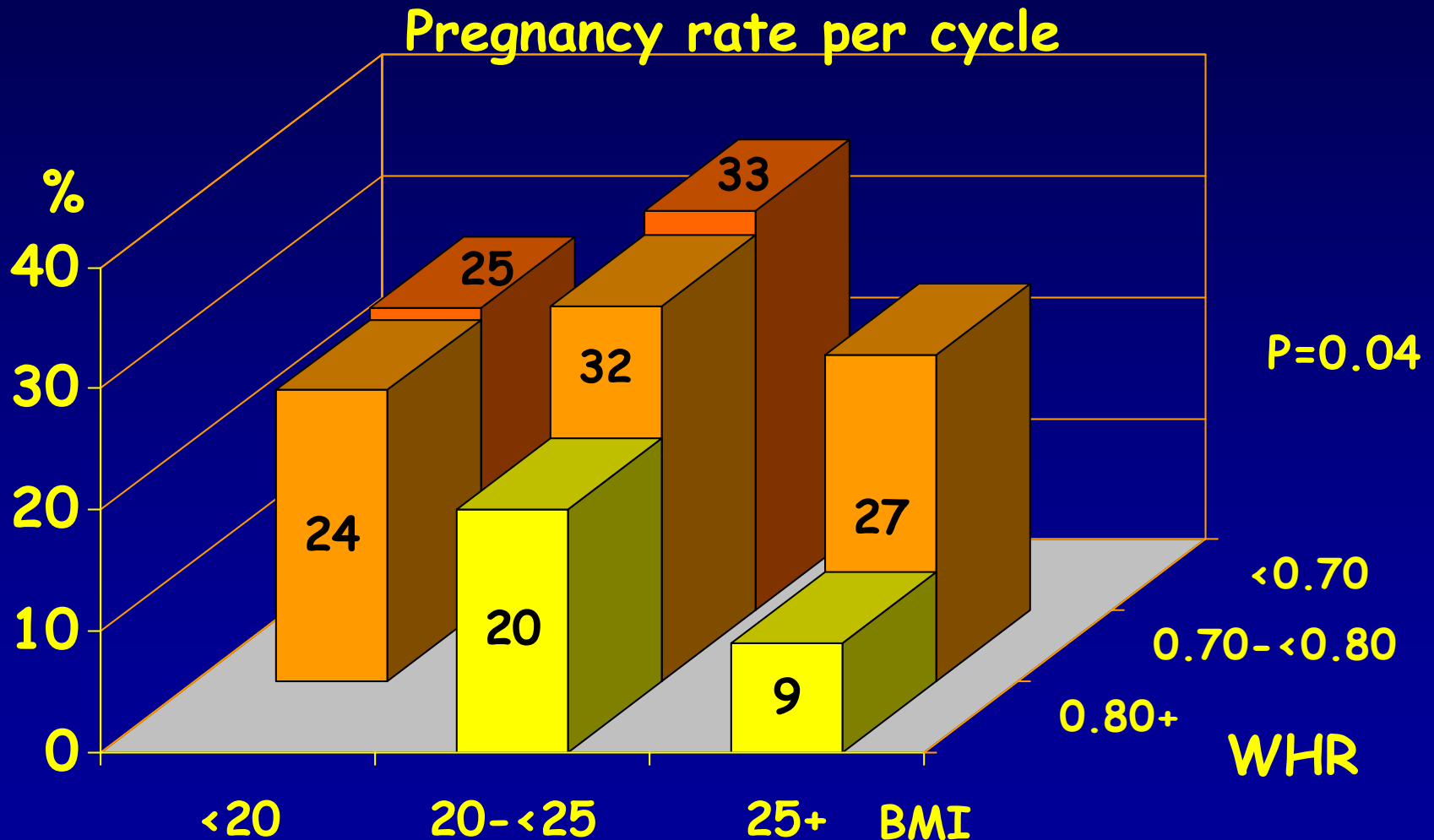


# BMI & IVF: Clinical pregnancy rate



# Fat and fecundity

Pregnancy rates in 220 IVF cycles



# Pregnancy loss after IVF/ICSI

BMI	<25	≥25	p
Number	304	79	
Oocytes recovered	10	8	0.03
Fertilisation rate	79%	82%	ns
Live birth	75%	63%	0.04
Abortion <week 6	<b>12%</b>	<b>22%</b>	0.03
Abortion week 6-12	9%	13%	ns
Abortion >week 12	1.3%	1.3%	ns

Fedorcsák et al. Acta Obstet Gynecol  
Scand 2000; 79: 43-48.

Li/00

# Fedme og fertilitet: Konklusion

---

- Overvægt reducerer chancen for spontan graviditet ved især at påvirke ovariefunktionen
- Overvægt mindsker chancen for graviditet ved IUI og IVF behandling
- Overvægt øger risikoen for tidlig spontan abort
- Vægttab bedrer muligheden for spontan graviditet

# Infertilitet epidemiologi

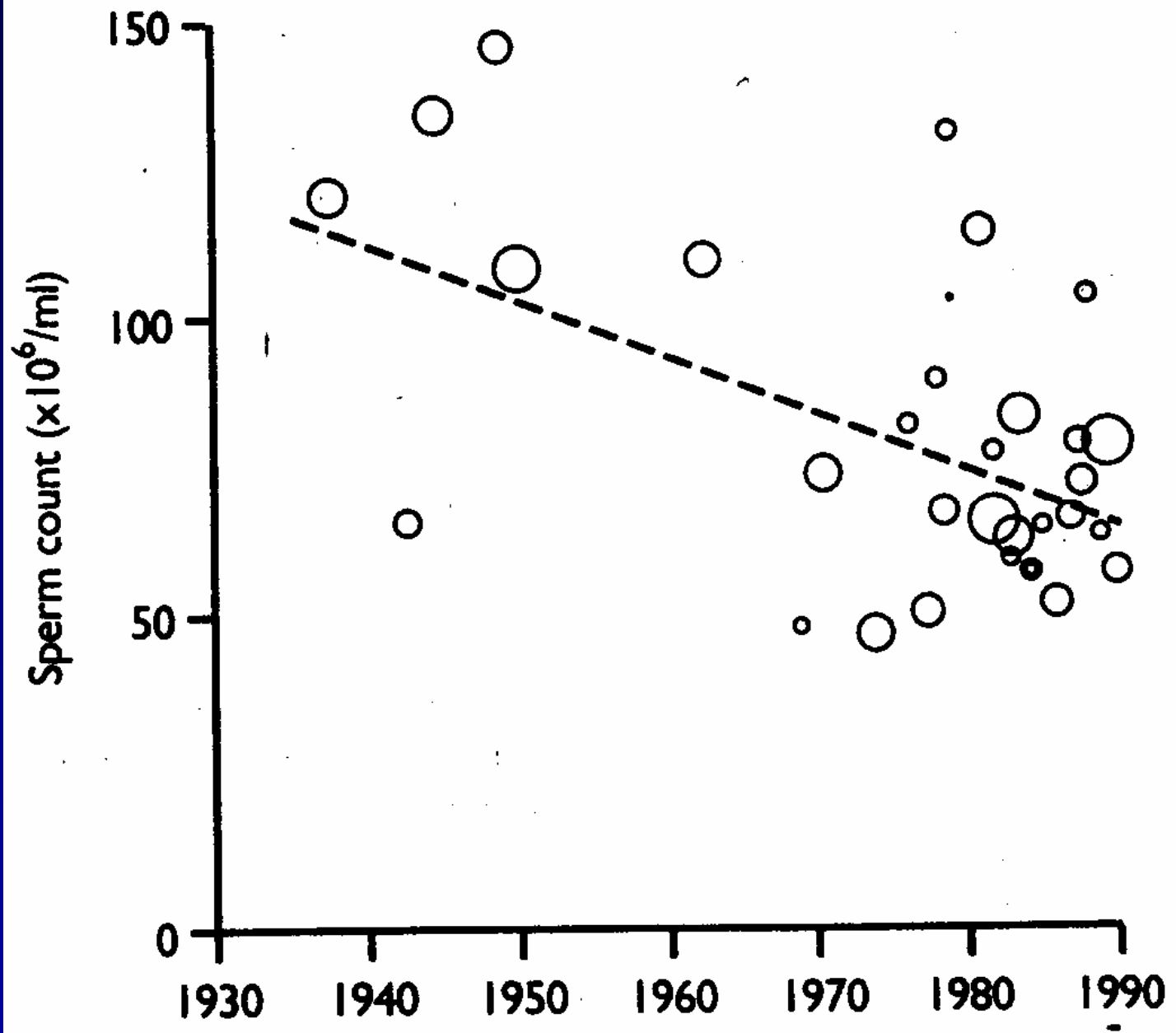
---

- Definitioner
- Problemetets størrelse
- Alder og fertilitet
- Rygning
- Alkohol
- Kaffe
- Overvægt
- **Mandlig fertilitet**

# Sperm count by time

61 papers  
14,947 men

Carlsen et al. BMJ 1992; 305: 609-13





# **Sperm count and fecundity**

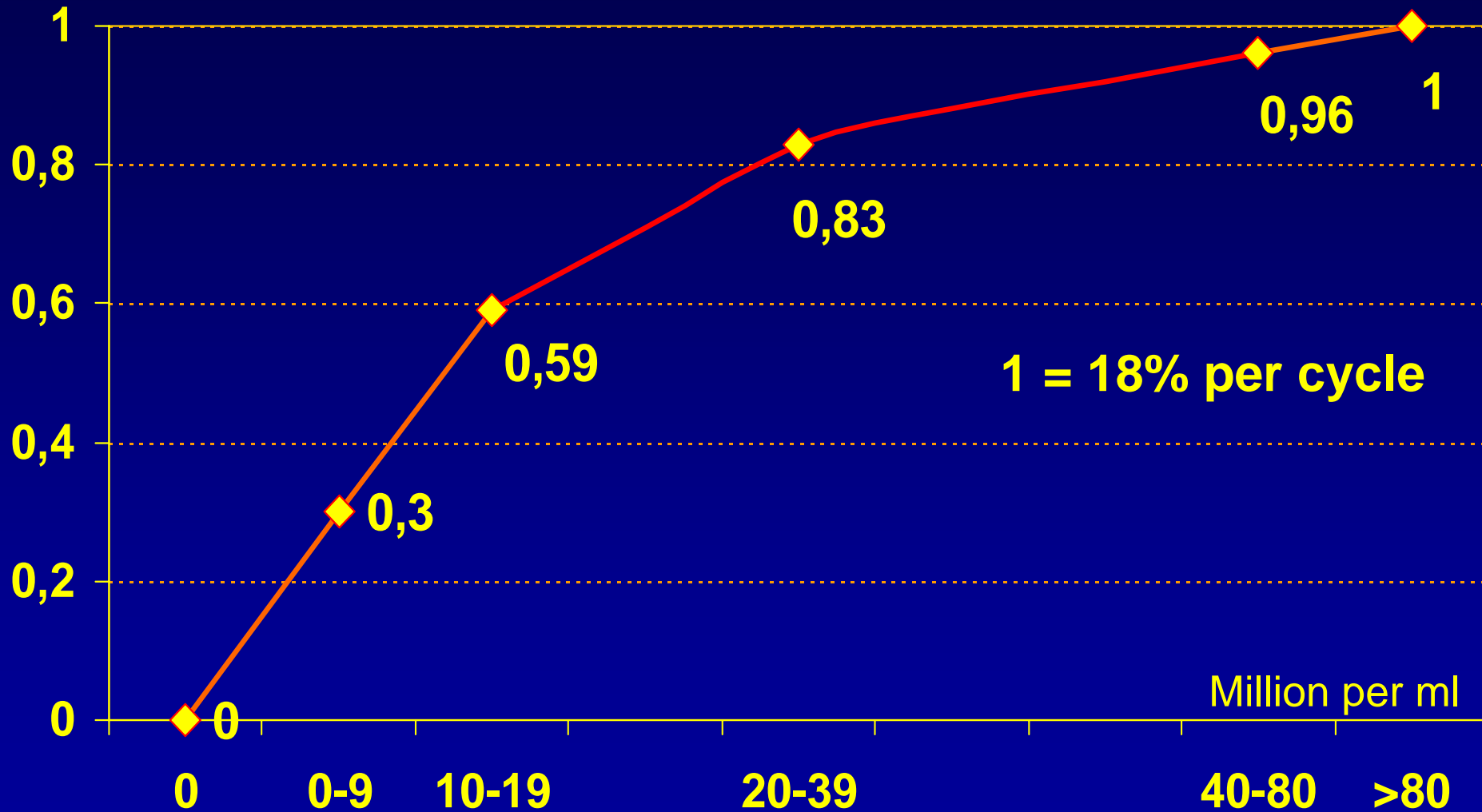
---

- 430 couples with first pregnancy wish
- Followed through 6 menstrual cycles
- Delivering a sperm sample at enrolment
- Information about smoking habits, age of woman, occupation of women, urogenital disorders, BMI, and woman's smoking habits
- Outcome: pregnancy chance per cycle

---

**Bonde JPE et al. Lancet 1998; 352: 1172-7.**

# Sperm count and fecundity



Bonde et al. Lancet 1998; 352: 1172-7.

# Sperm count in Danish men

---

- 1.868 men, 18-22 years old, median 19 years
- Military session, 1996-2001
- Delivering a sperm sample
- Abstinence for 48 hours
- Median sperm count: 46 mio/ml (41-51)
- Sperm count **<40 mio/ml: 44% (-17%)**
- Sperm count **<20 mio/ml: 22% (-41%)**

# Sperm count in Nordic-Baltic area

**Denmark** **Norway** **Finland** **Estonia**

---

<b>Particip.</b>	<b>300</b>	<b>240</b>	<b>324</b>	<b>104</b>
<b>Period</b>	<b>97-99</b>	<b>1998</b>	<b>98-00</b>	<b>97-99</b>

## Sperm count in mio/ml (median)

<b>All</b>	<b>41</b>	<b>41</b>	<b>54</b>	<b>57</b>
<b>Clean</b>	<b>45</b>	<b>42</b>	<b>53</b>	<b>63</b>

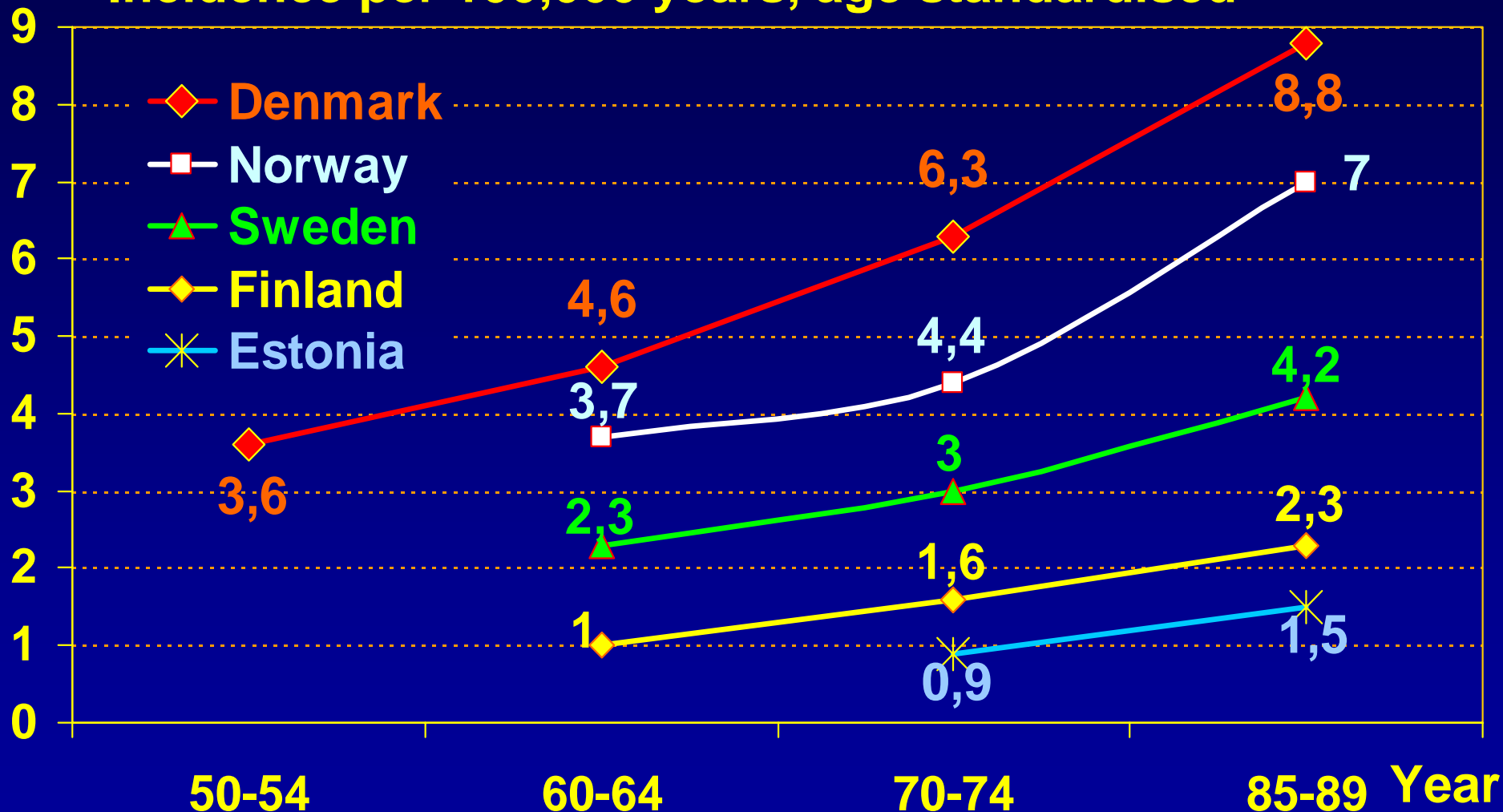
## West-east gradient

Jørgensen et al: Hum Reprod 2002; 8: 2199-2208



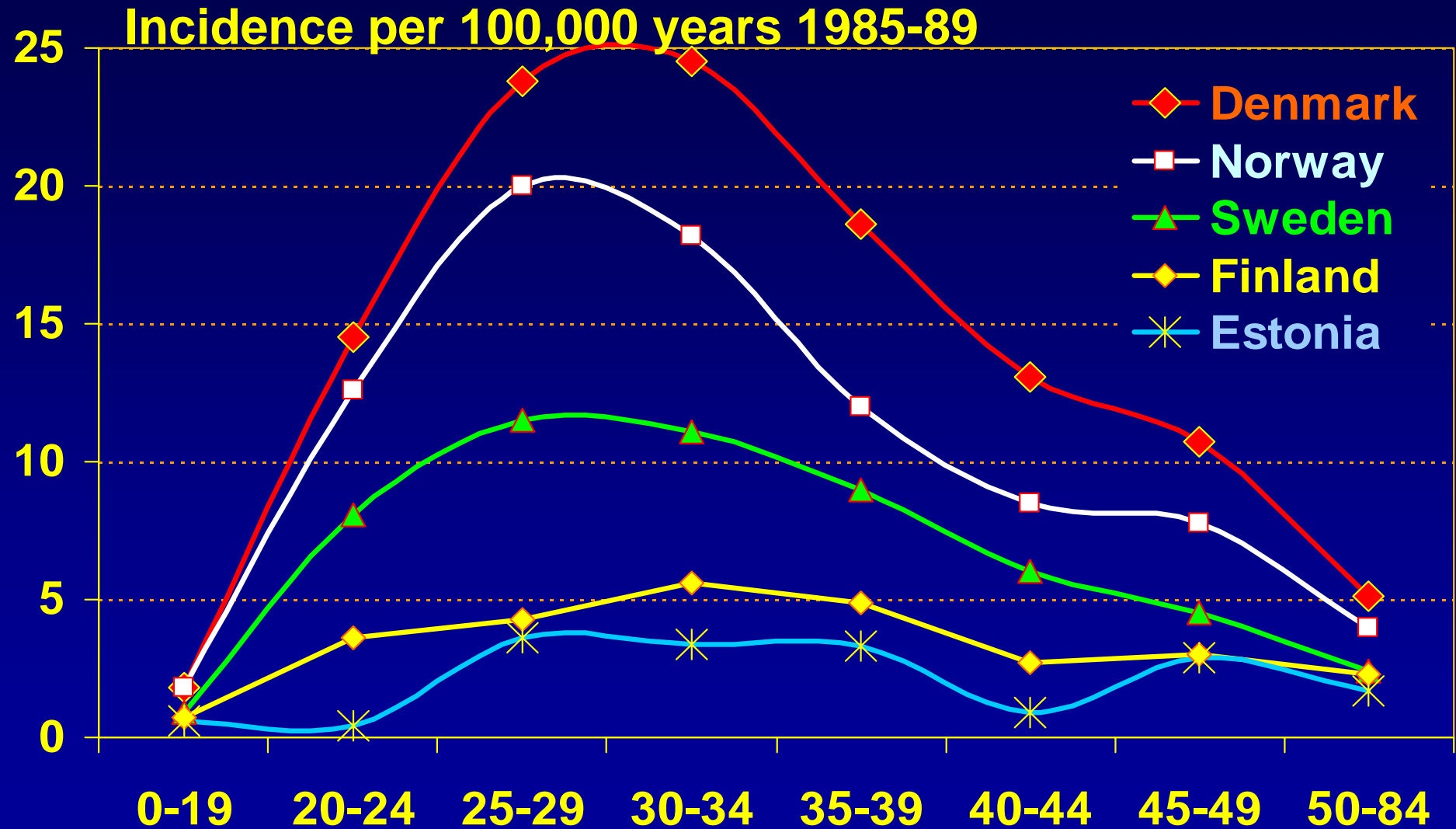
# Testicular cancer: west-east gradient

Incidence per 100,000 years, age standardised

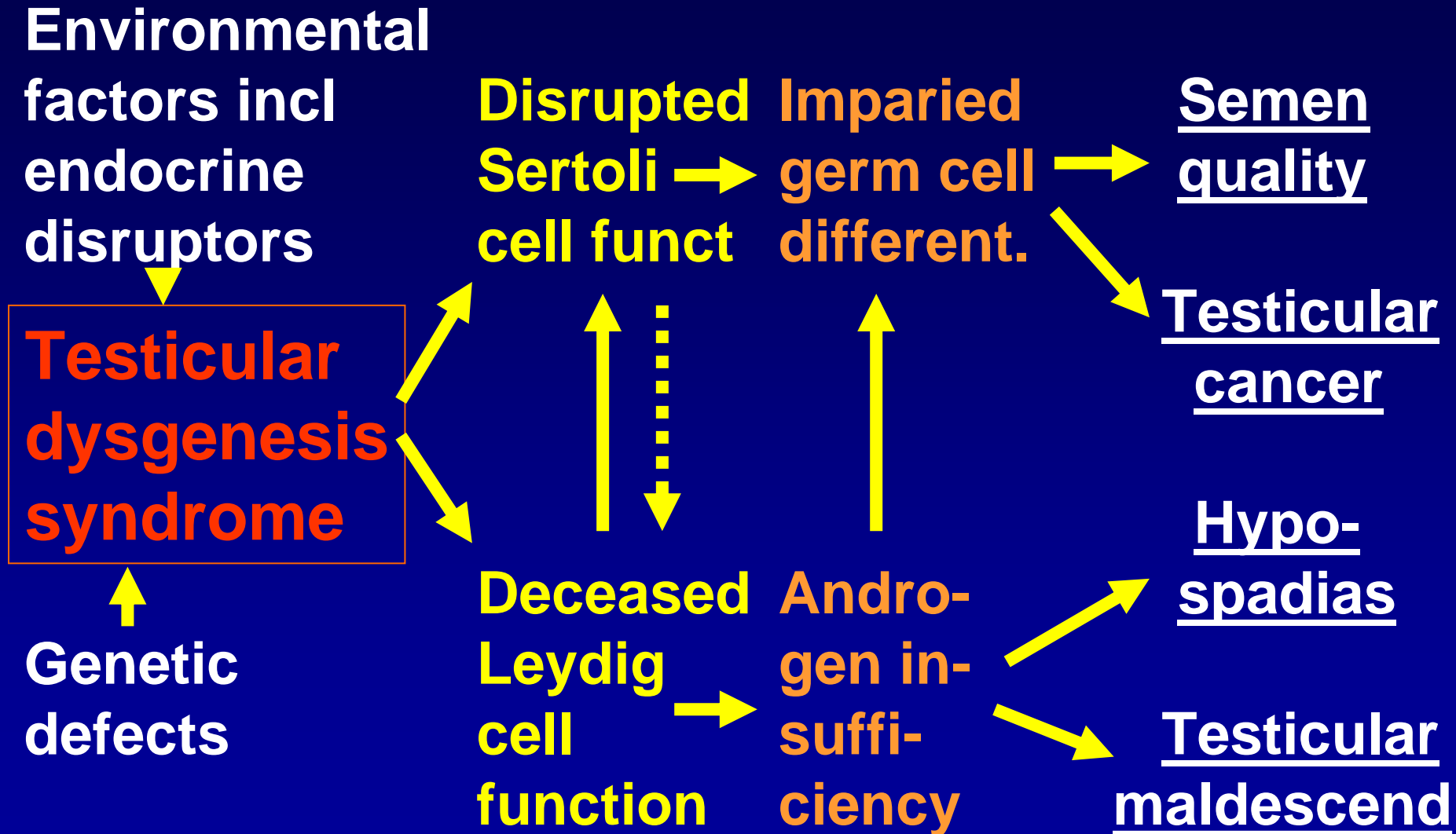


Adami et al. Int J Cancer 1994; 59: 33-38.

# Testicular cancer according to age



# Testicular Dysgenesis Syndrome



# Testicular dysgenesis syndrome

Environmental factors incl endocrine disruptors

Testicular dysgenesis syndrome

Genetic defects

Disrupted Sertoli cell funct

Impaired germ cell different.

Semen quality

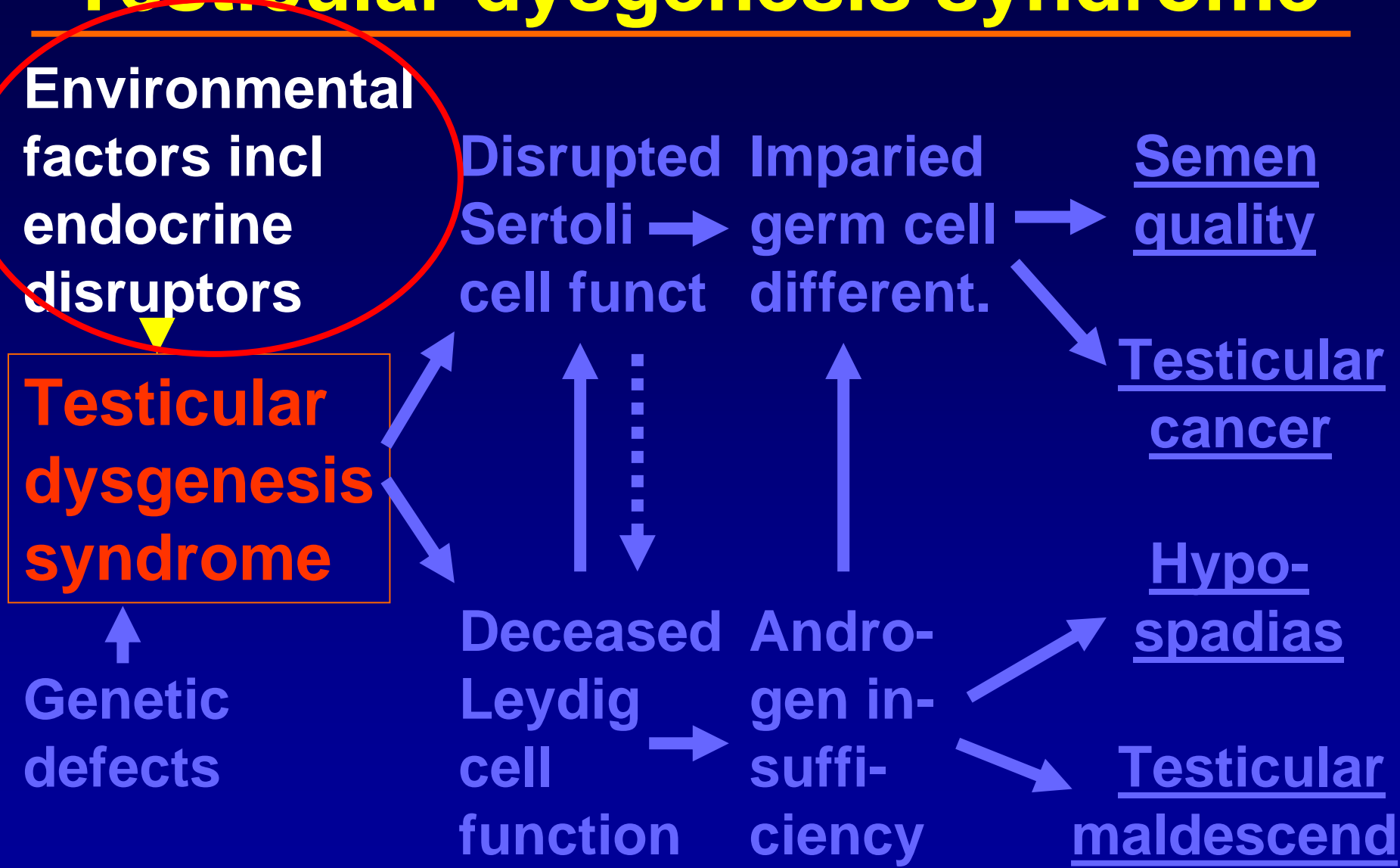
Testicular cancer

Hypospadias

Testicular maldescend

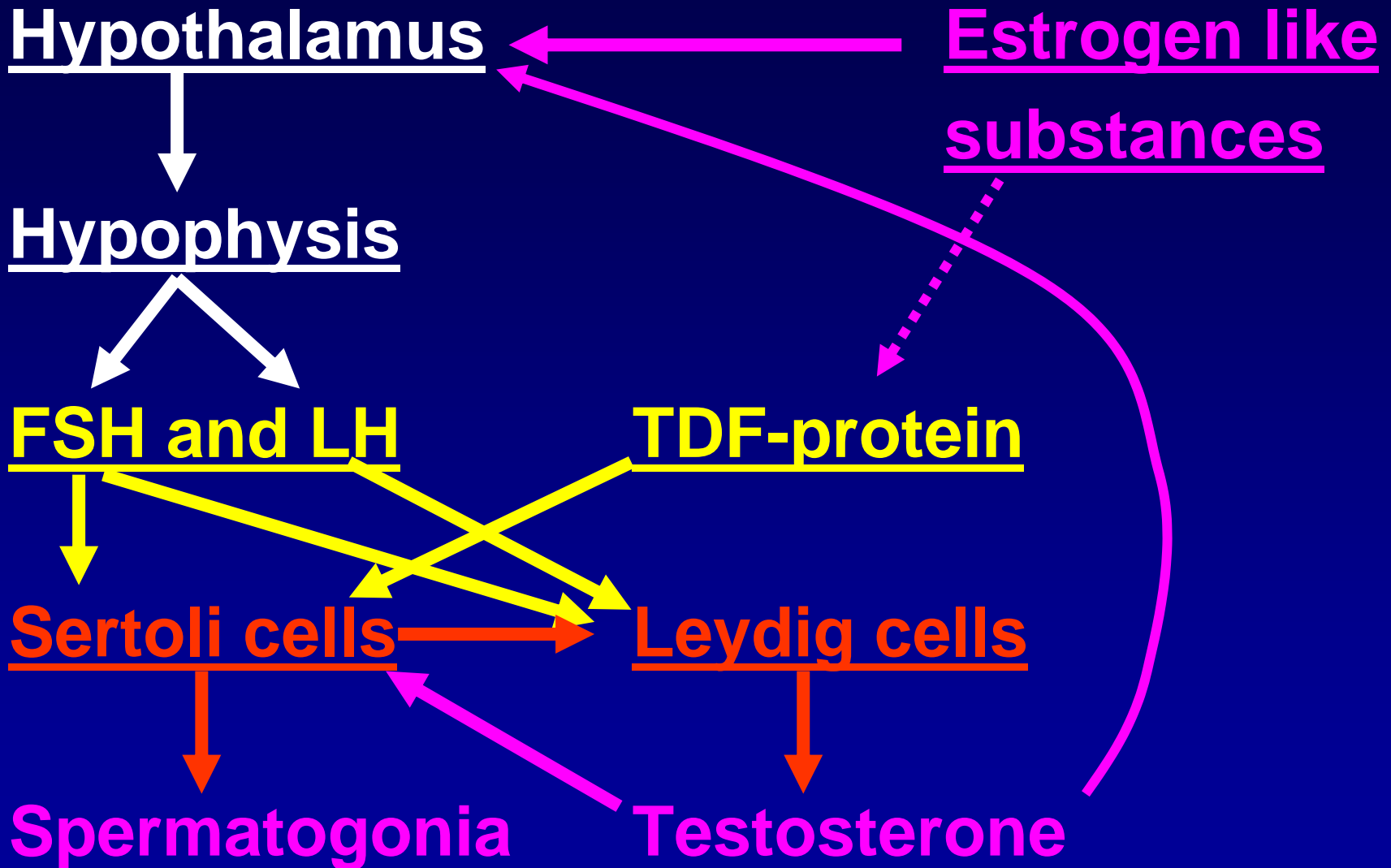
Decreased Leydig cell function

Androgen insufficiency





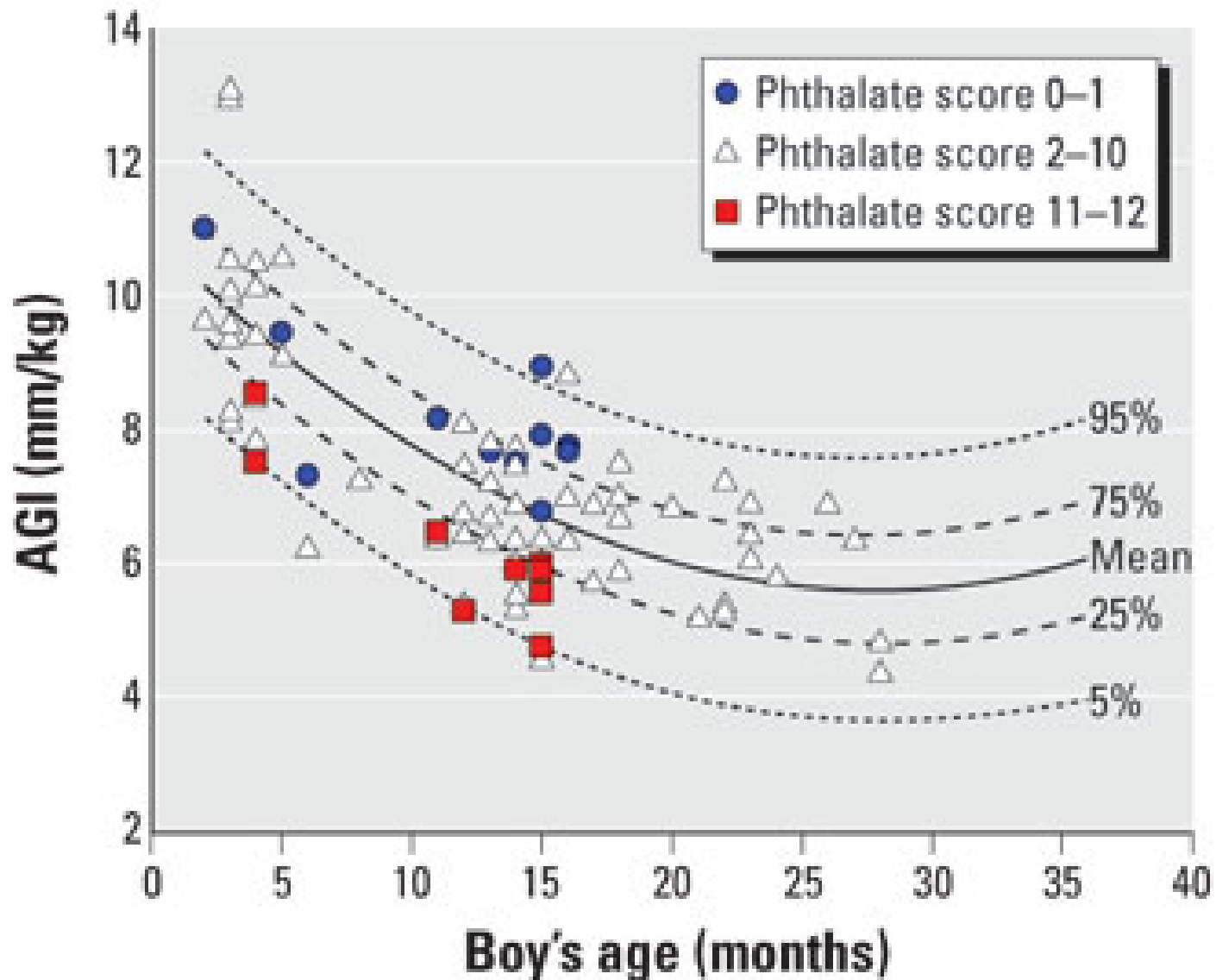
# Male gonadogenesis



# Phthalate exposure and anogenital distance (AGD) in male infants

---

- 134 boys 2-36 months
- Measure of AGD, weight and age.
- Anogenital index =  $AGD / \text{weight}$  mm/kg
- Measurement of urine phthalates during pregnancy.
- Correlation between ADI and phthalates
- Correlation AGD with penile volume and incomplete testicular descent



**Figure 1.** Mean AGI (mm/kg) in relation to boys' age at examination (months).

# Phthalate exposure in rats

---

- Exposure of phthalates day 13-20 in 32 pregnant rats. Control group of 32 pregnant rats exposed to corn oil.
- Rats killed on day 15, 17, 19 and 21 of fetal life, and post partum at day 4, 25 and 90.
- Testes analysed immunohistochemistry
- Abnormal Leydig cell aggregation from fetal day 17. In addition dysgenetic tubules later Sertoli Cell only syndrome.

# Male fertility

---

- Pregnant women are exposed to endocrine disruptors affecting the fertility of their male offspring lifelong.
- Phthalate exposure in rats causes TDS like changes in male rats.
- Phthalates are the most likely but probably not the only candidate for the responsibility of TDS in humans

# Dansk Fertilitetselskab

---

[www.fertilitetselskab.dk](http://www.fertilitetselskab.dk)

[www.sst.dk](http://www.sst.dk)

[www.dst.dk](http://www.dst.dk)

[www.lidegaard.dk](http://www.lidegaard.dk)

---