Infertilitets epidemiologi

Øjvind Lidegaard

U-kursus

29. januar 2014

Infertilitet epidemiologi

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

Nogle definitioner

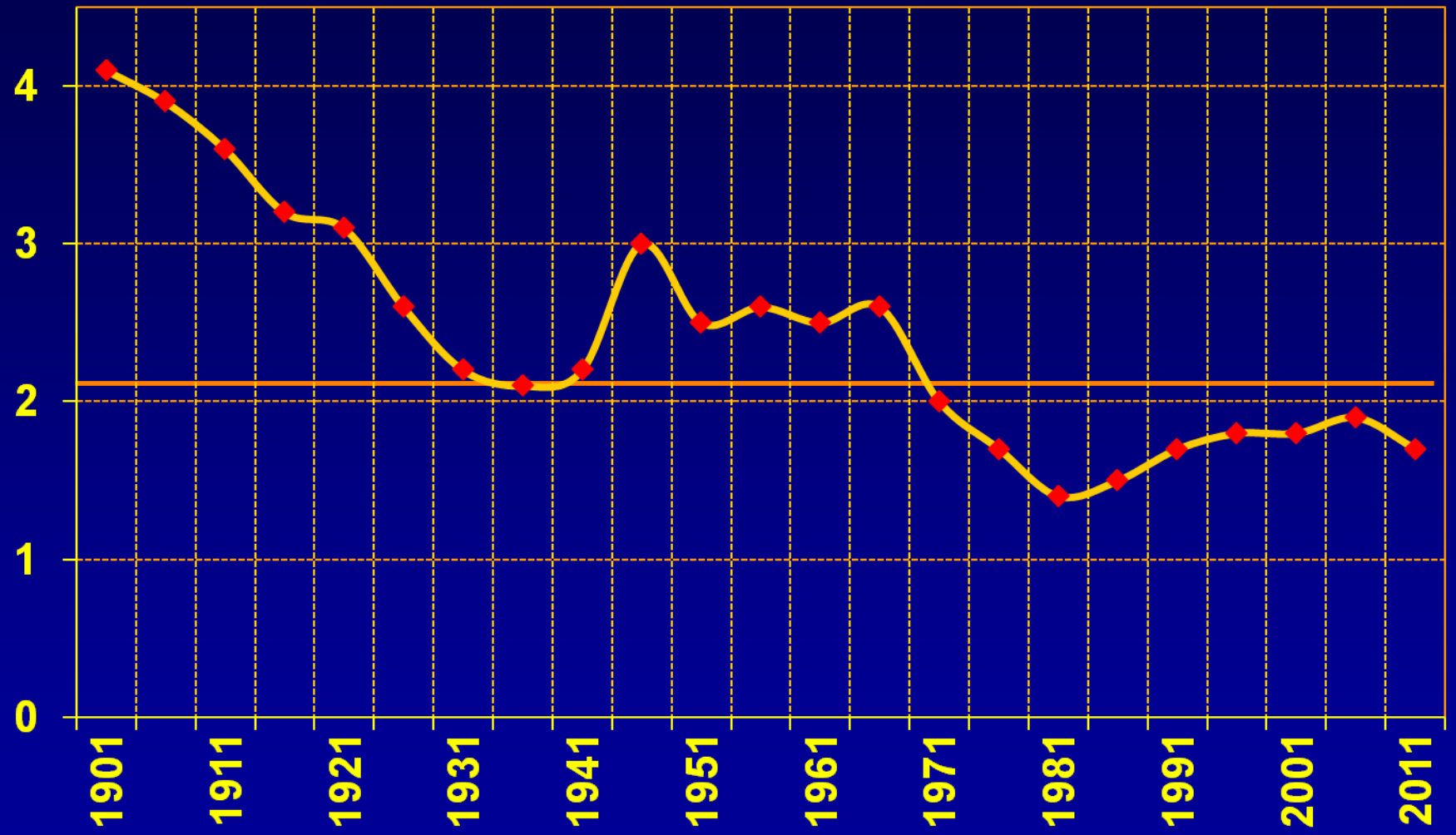
- **Infertilitet:**
  - Ikke gravid efter 1 år (i DK 15%)
- **Fecunditet:**
  - Evnen til at blive gravid og føde
- **Fecundabilitet:**
  - Graviditeter pr. cyklus (afhænger af alder)
- **Fecundabilitetsratio:**

  - Graviditetschance hos eksponerede i forhold til graviditetschance blandt ikke eksponerede

Infertilitet epidemiologi

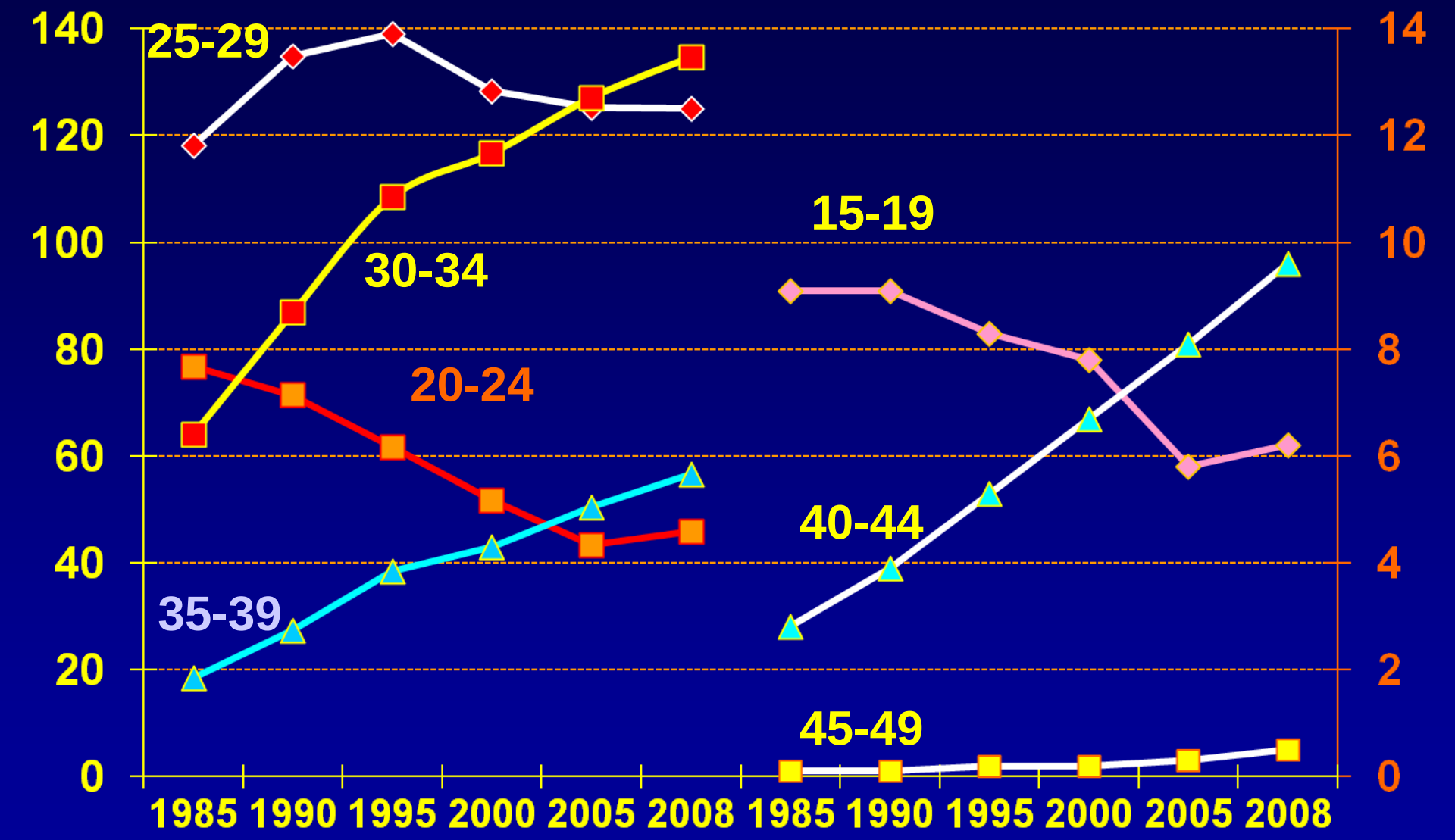
- Definitioner
- Problemets størrelse
- Alder og fertilitet
- Mandlig fertilitet
- Rygning
- Alkohol
- Kaffe
- Overvægt

Total fecundity rate in DK 1901-2011



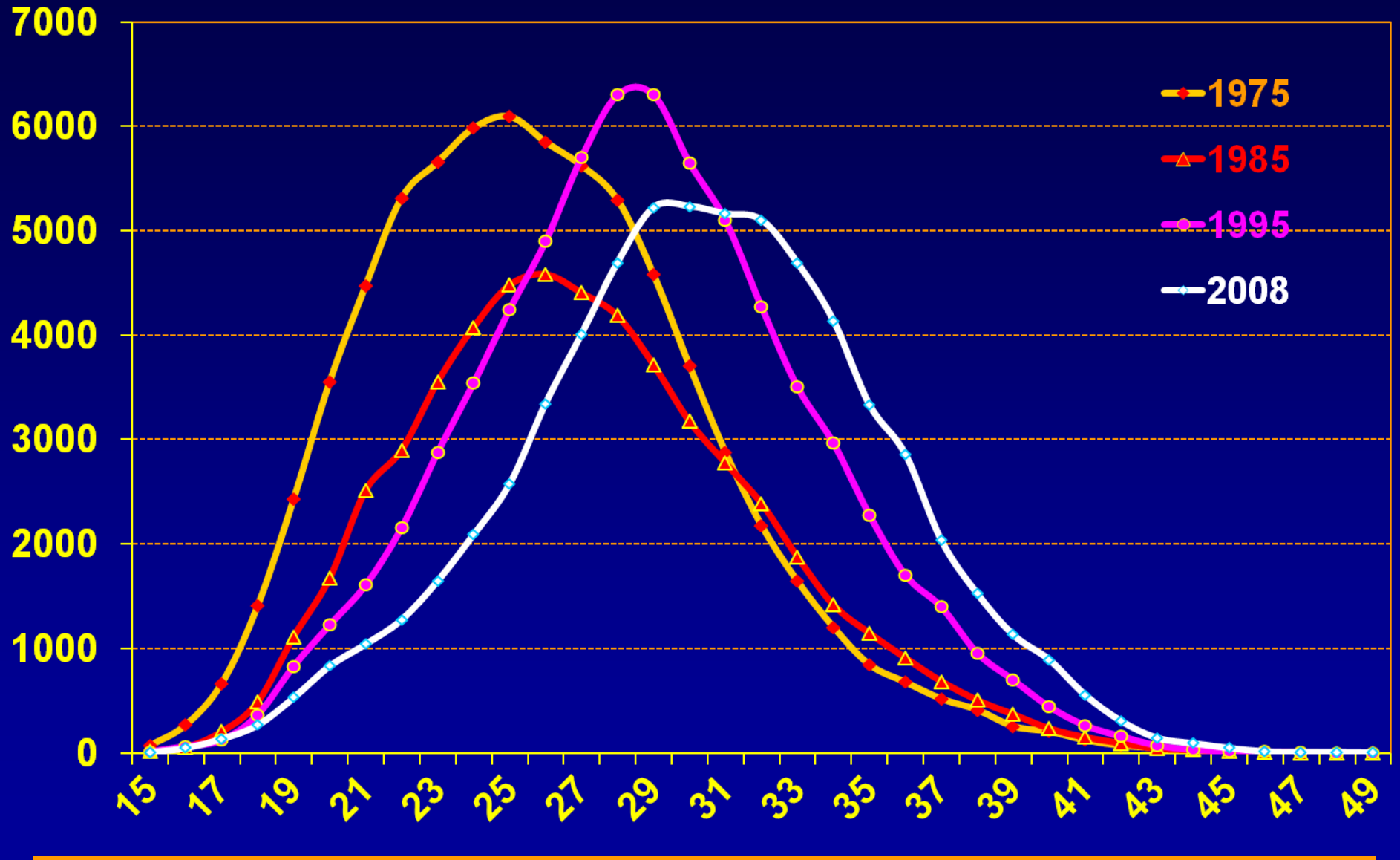
Lisbeth B Knudsen, Fertility trends in DK in the 1980s
Danmarks Statistik online: www.dst.dk

Fertility rates per 1,000 in DK 1985-2008



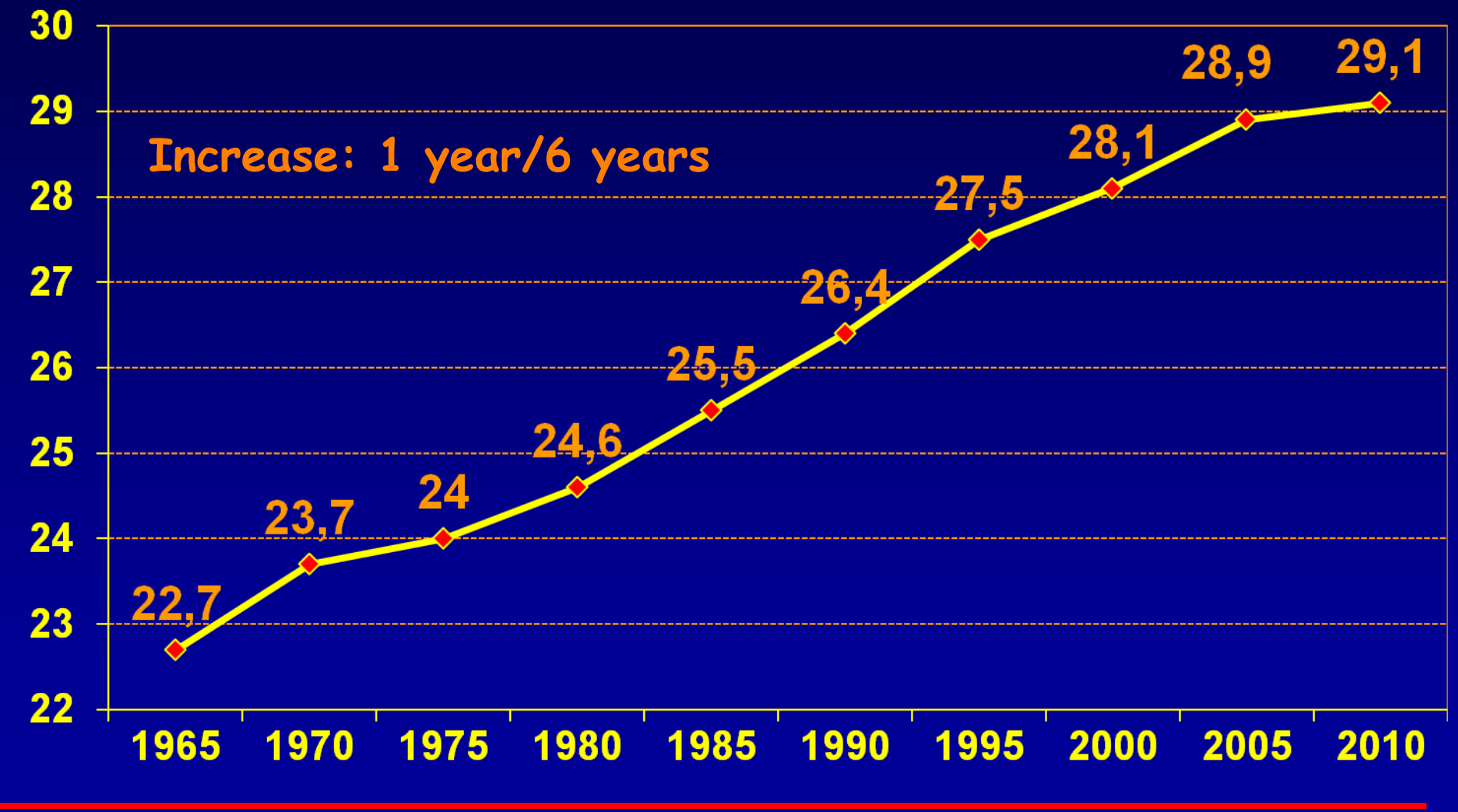
Danmarks Statistik online.

Levendefødte i DK i 1975, 85, 95 og 08



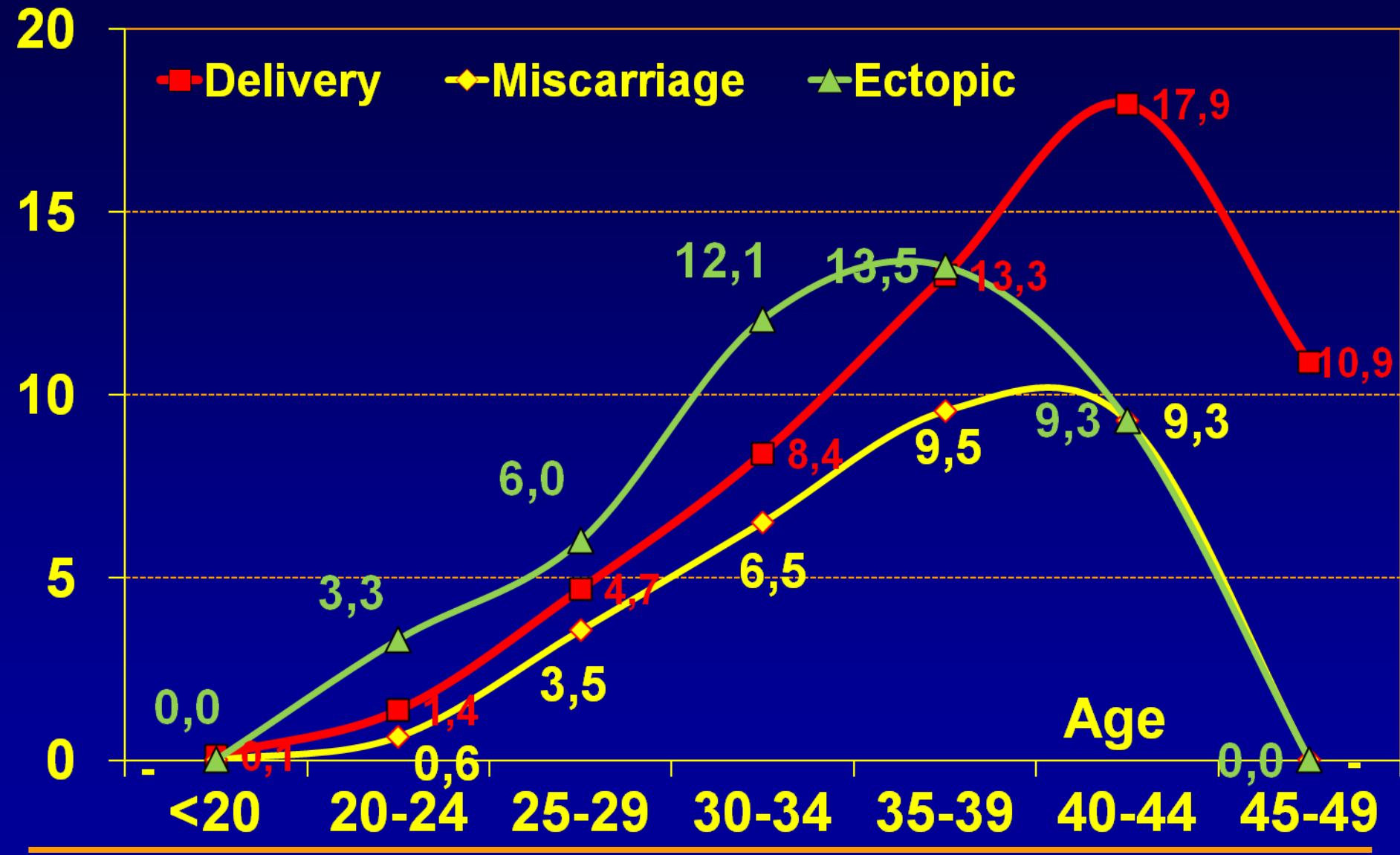
Danmarks Statistik online

Age at first birth
Denmark 1965-2010



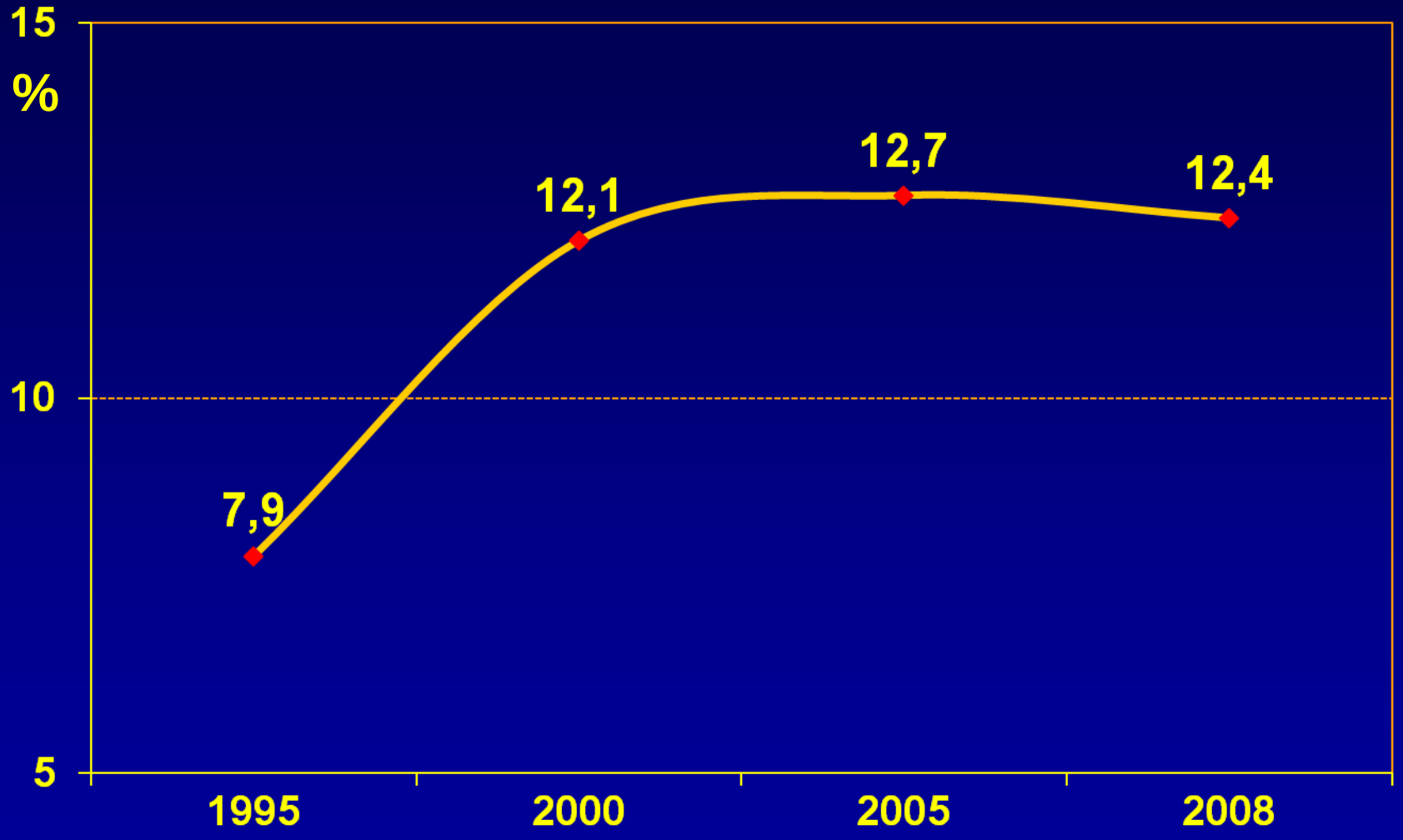
Danmarks Statistik Online: www.dst.dk

Per cent of ART pregnancies 2011



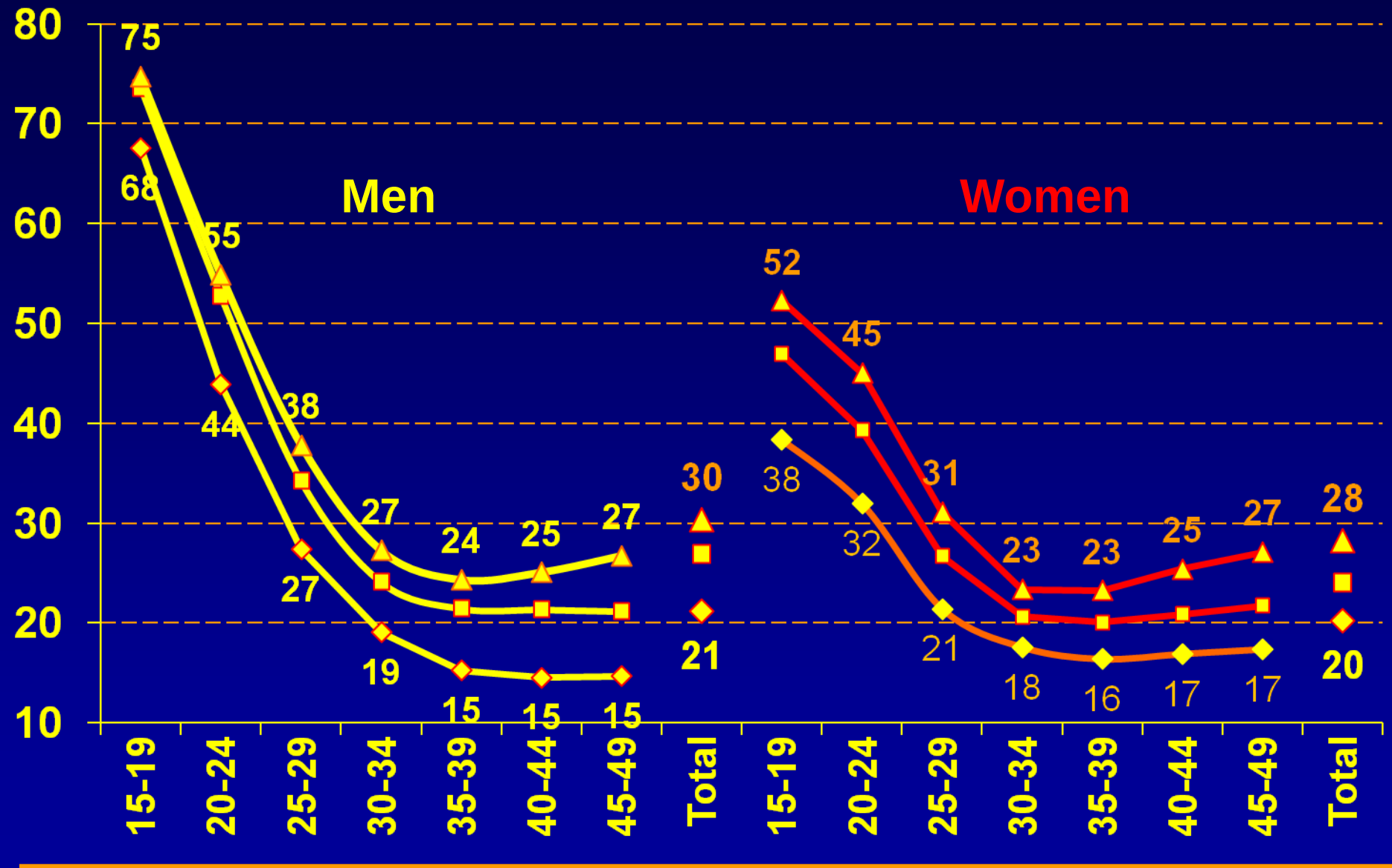
IVF registry, Danish Health Board

Childless women (%) at age 49



Danmarks statistik, online

Singles (%) in DK in 1986, 2000 and 2013



Statistics of Denmark, online: www.dst.dk

Li/13

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

Schmidt L. Hum reprod 1995; 10: 1407-18. DK statistik.

Infertilitet epidemiologi

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

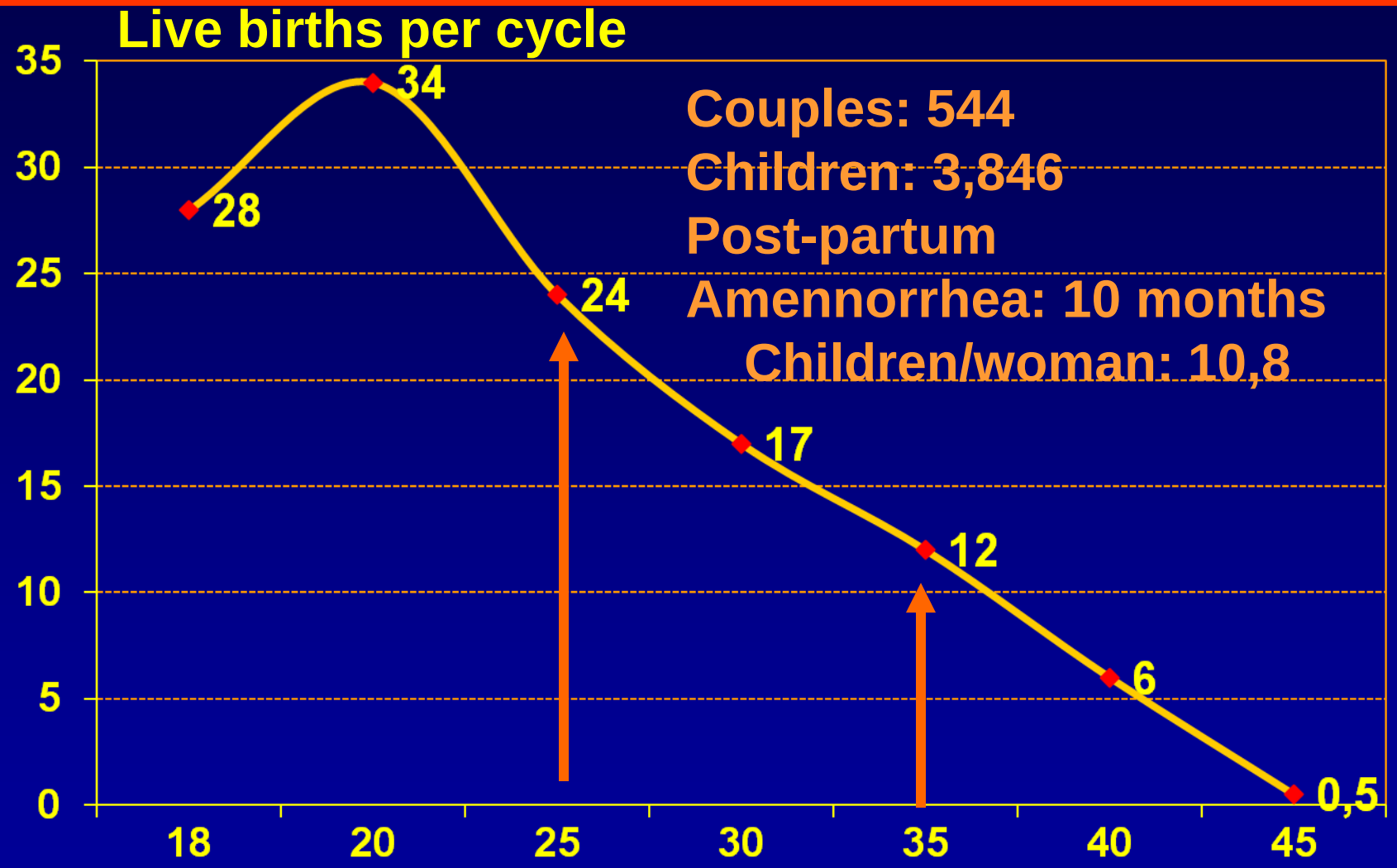
Hvad er en kvinde, og hvad kan hun

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

Larsen U et al. Social Biology 2000; 47: 34-50

Fecundity rate among Hutterite women



Larsen U et al. Social Biology 2000; 47: 34-50

Hvorfor falder fecundititen 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 fecundititen med alderen?

Mulige mekanismer:

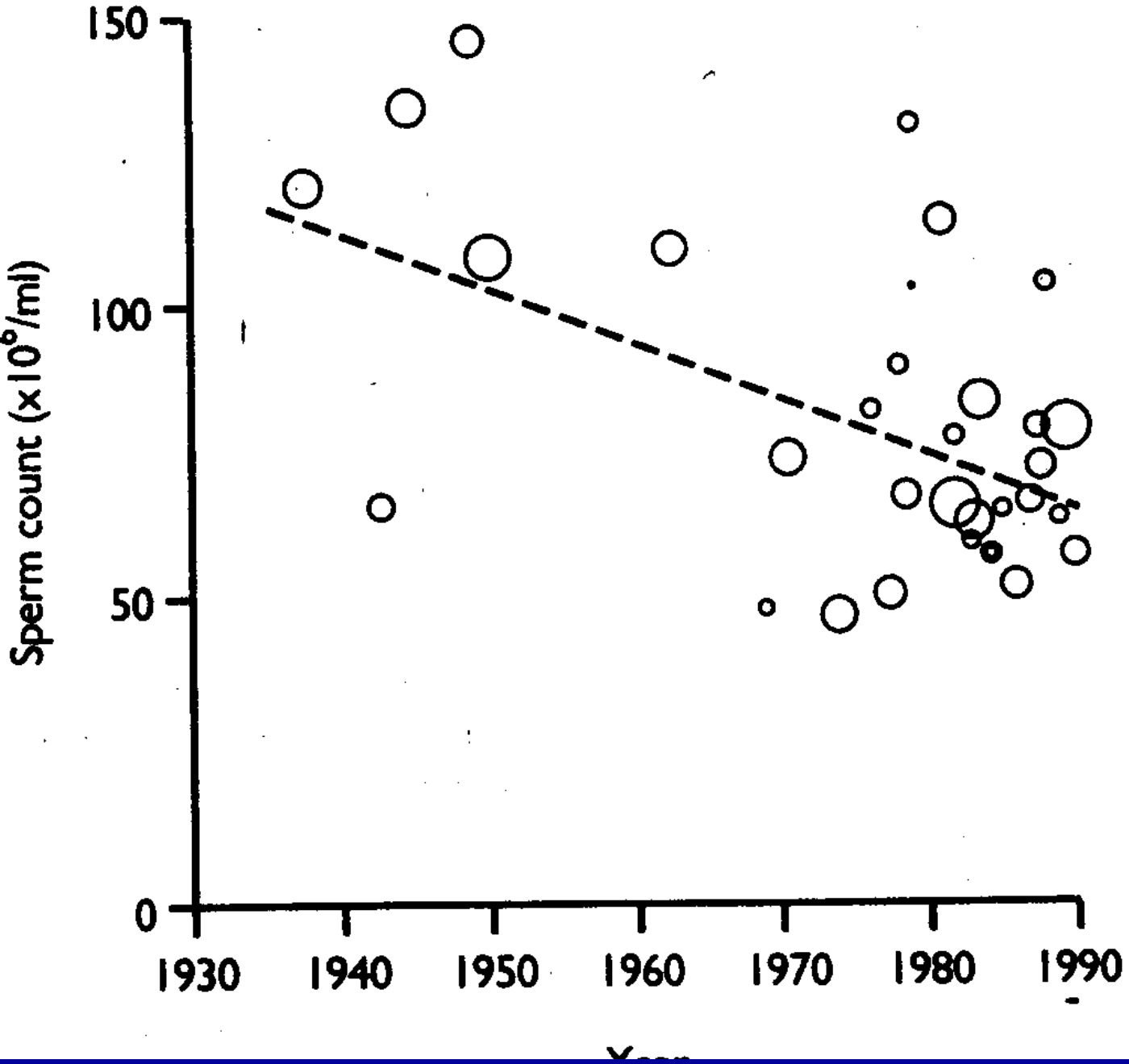
1. **Ovarie funktion**
   - Tuba funktion
   - Ændringer i endometriet
   - Ændringer i hormoner
   - Ændringer i sperm kvalitet
   - Ændringer i sexual vaner
2. **Øget abort rate**

Infertilitet epidemiologi

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

Sperm count by time

61 papers
14,947 men



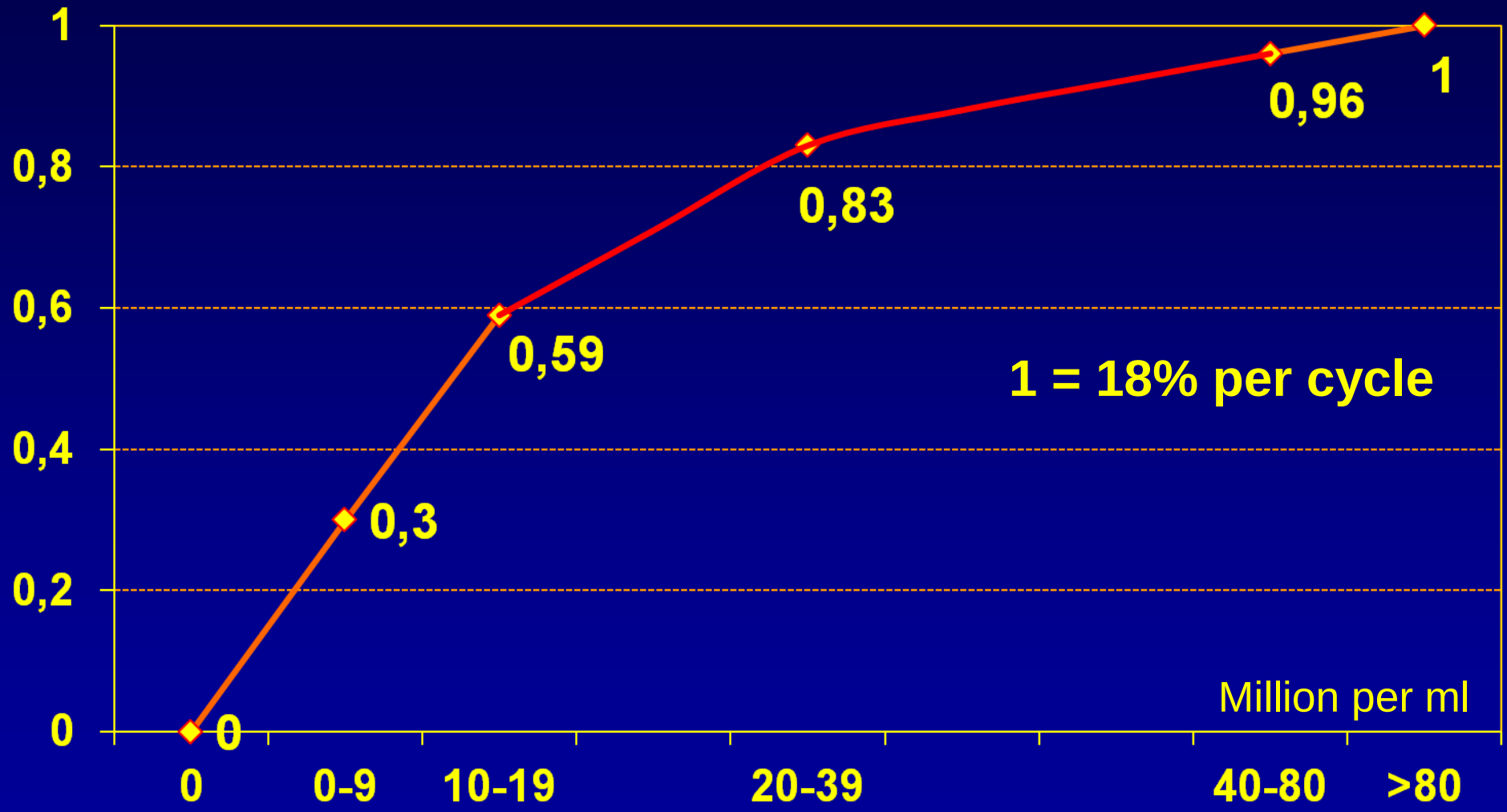
Carlsen et al. BMJ 1992; 305: 609-13

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%)**

Jørgensen et al. Månedsskr Prakt Lægegern 2003; 81: 169-75

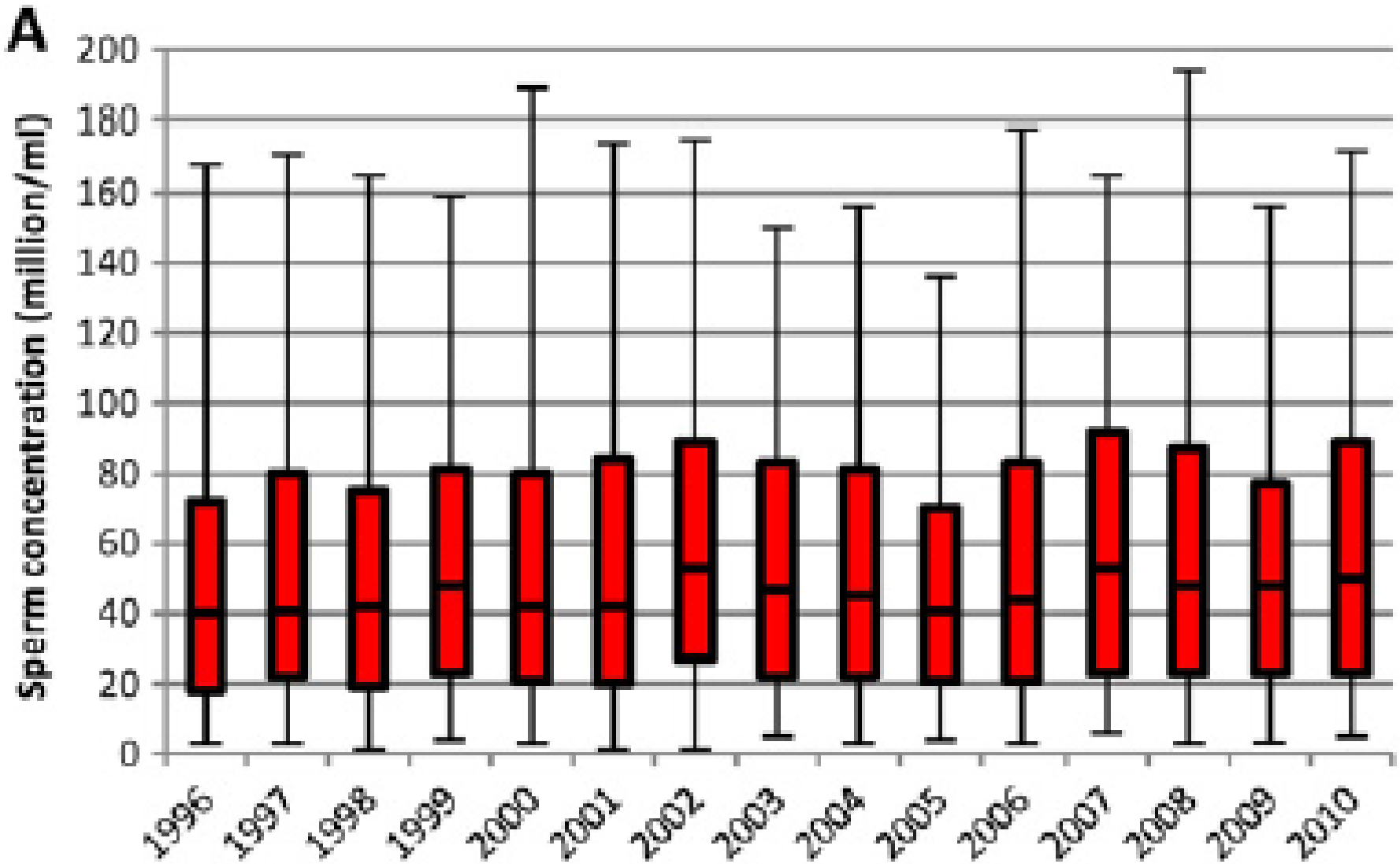
Sperm count in Nordic-Baltic area

	Denmark	Norway	Finland	Estonia
Particip.	300	240	324	104
Period	97-99	1998	98-00	97-99
Sperm count in mio/ml (median)				
All	41	41	54	57
Clean	45	42	53	63

West-east gradient

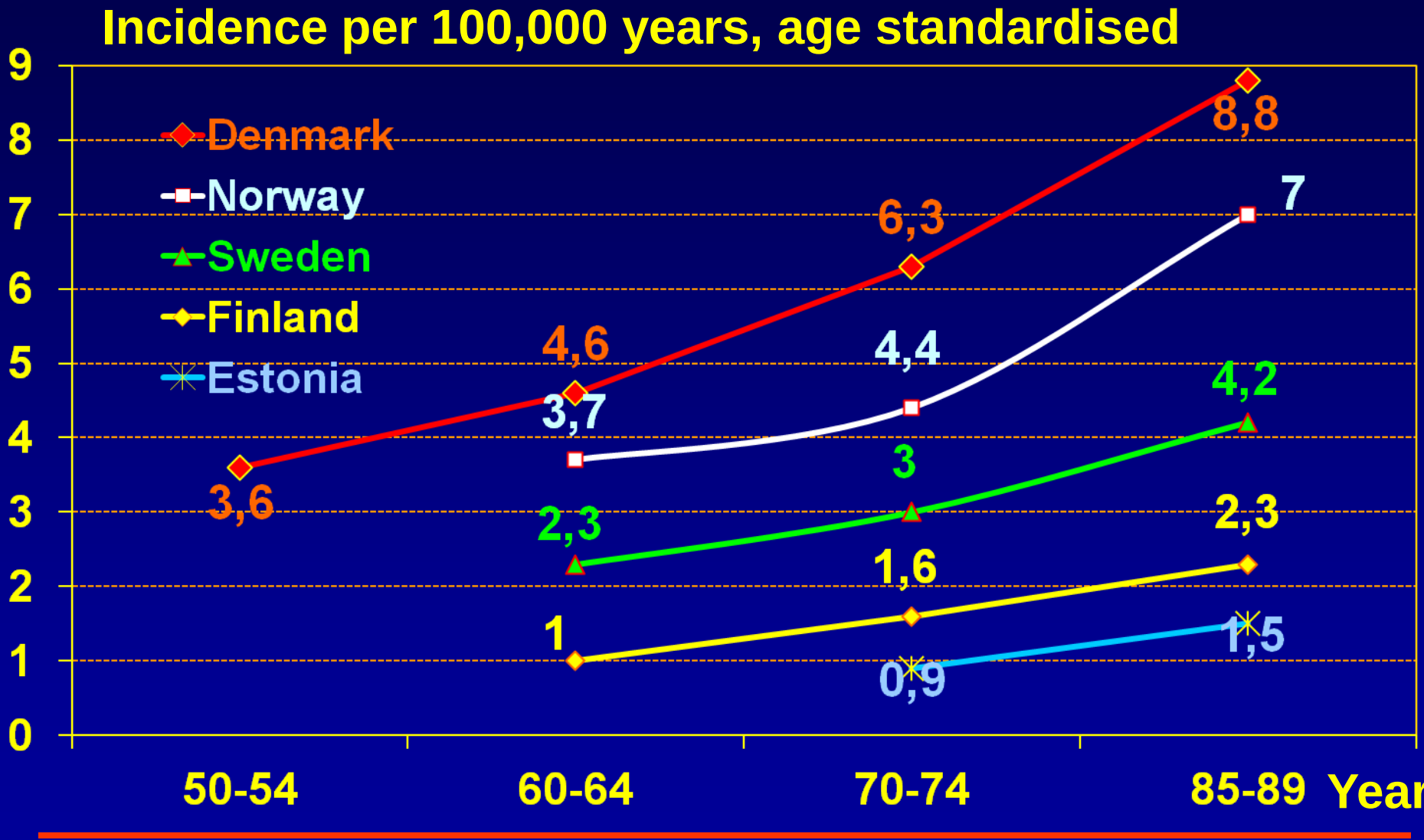
Jørgensen et al: Hum Reprod 2002; 8: 2199-2208

Sperm count in Denmark 1996-10



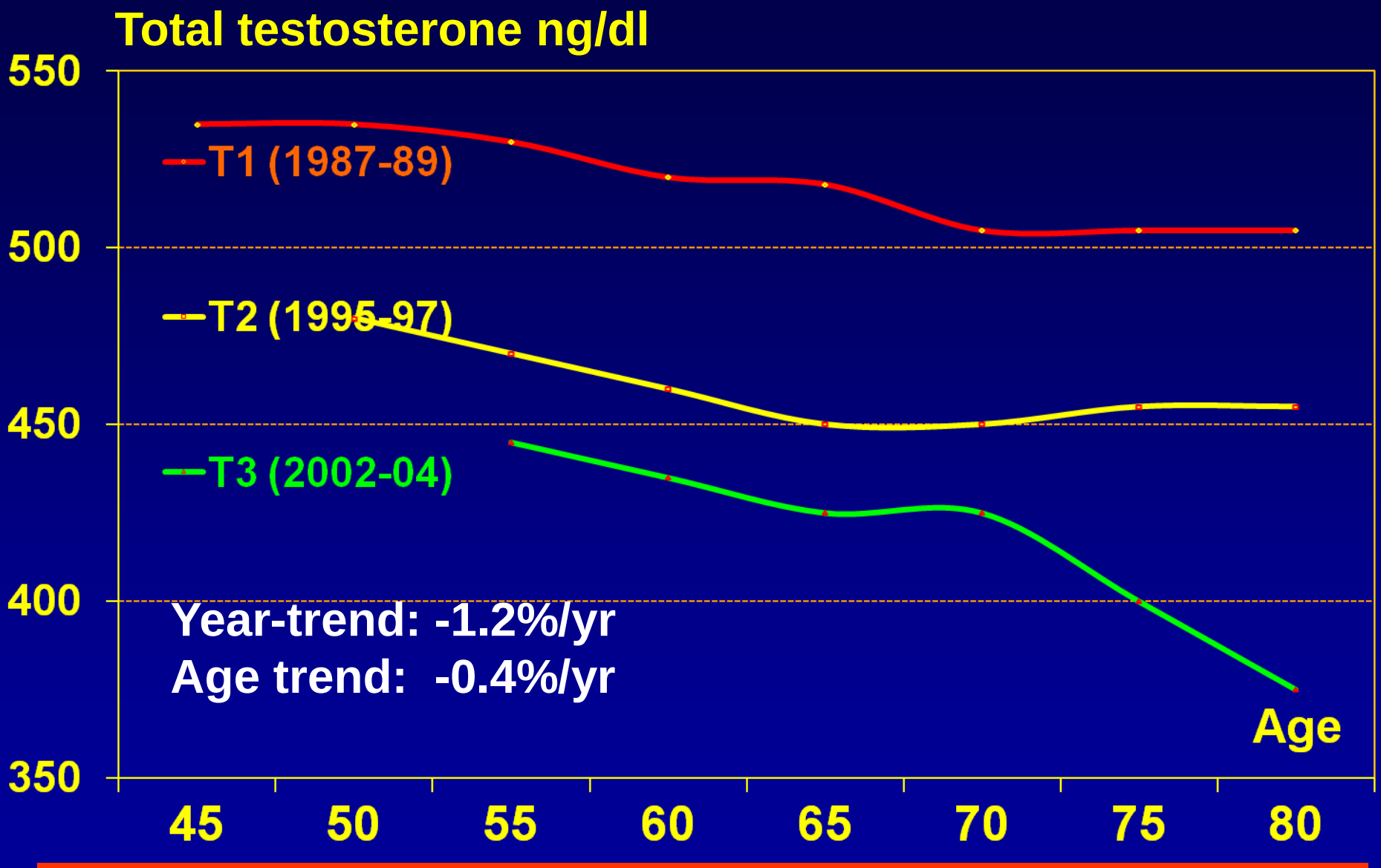
Jørgensen et al. BMJopen 2012; 2: doi 10.1136

Testicular cancer: west-east gradient



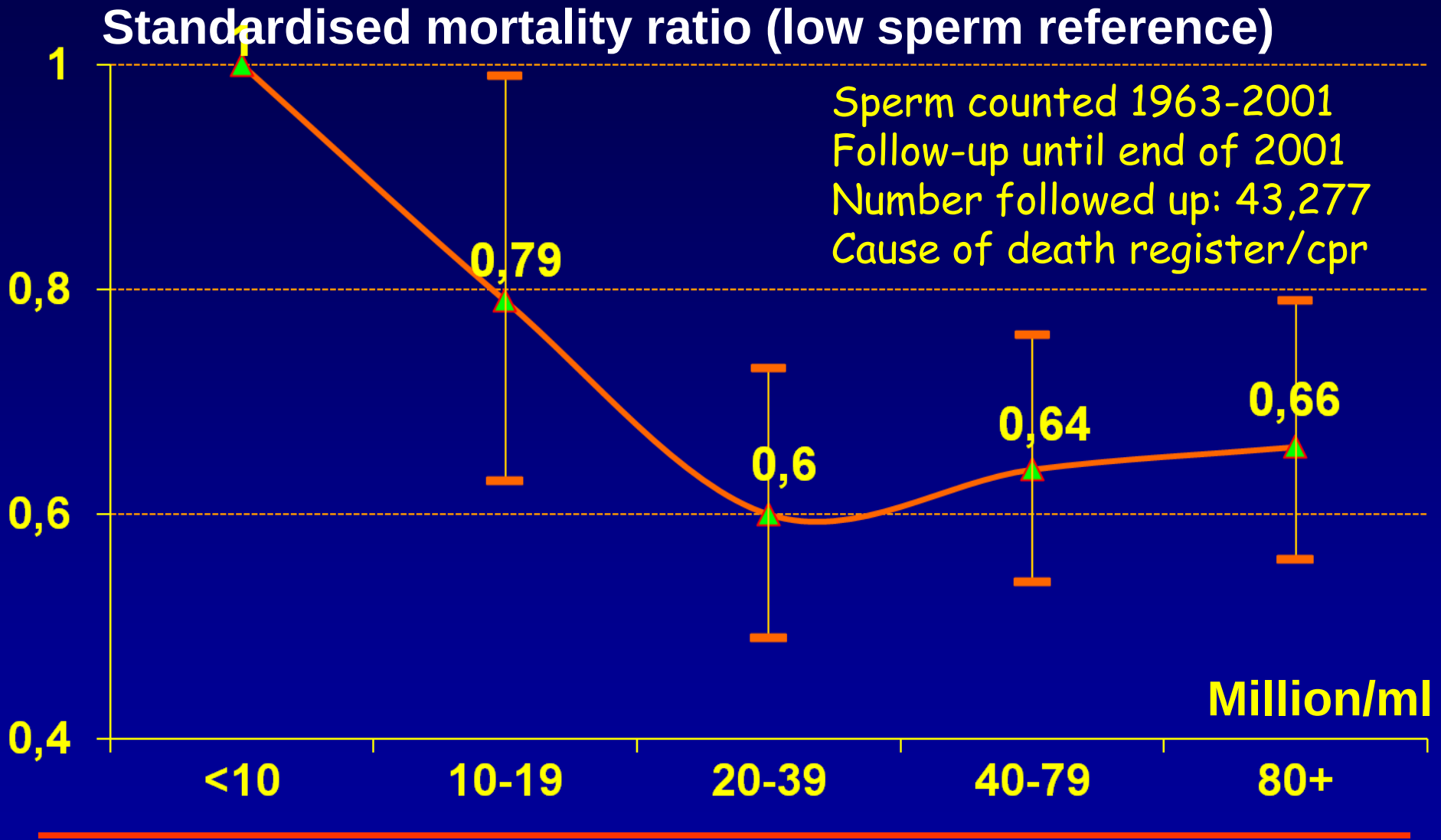
Adami et al. Int J Cancer 1994; 59: 33-38.

Testosterone: Does it change?



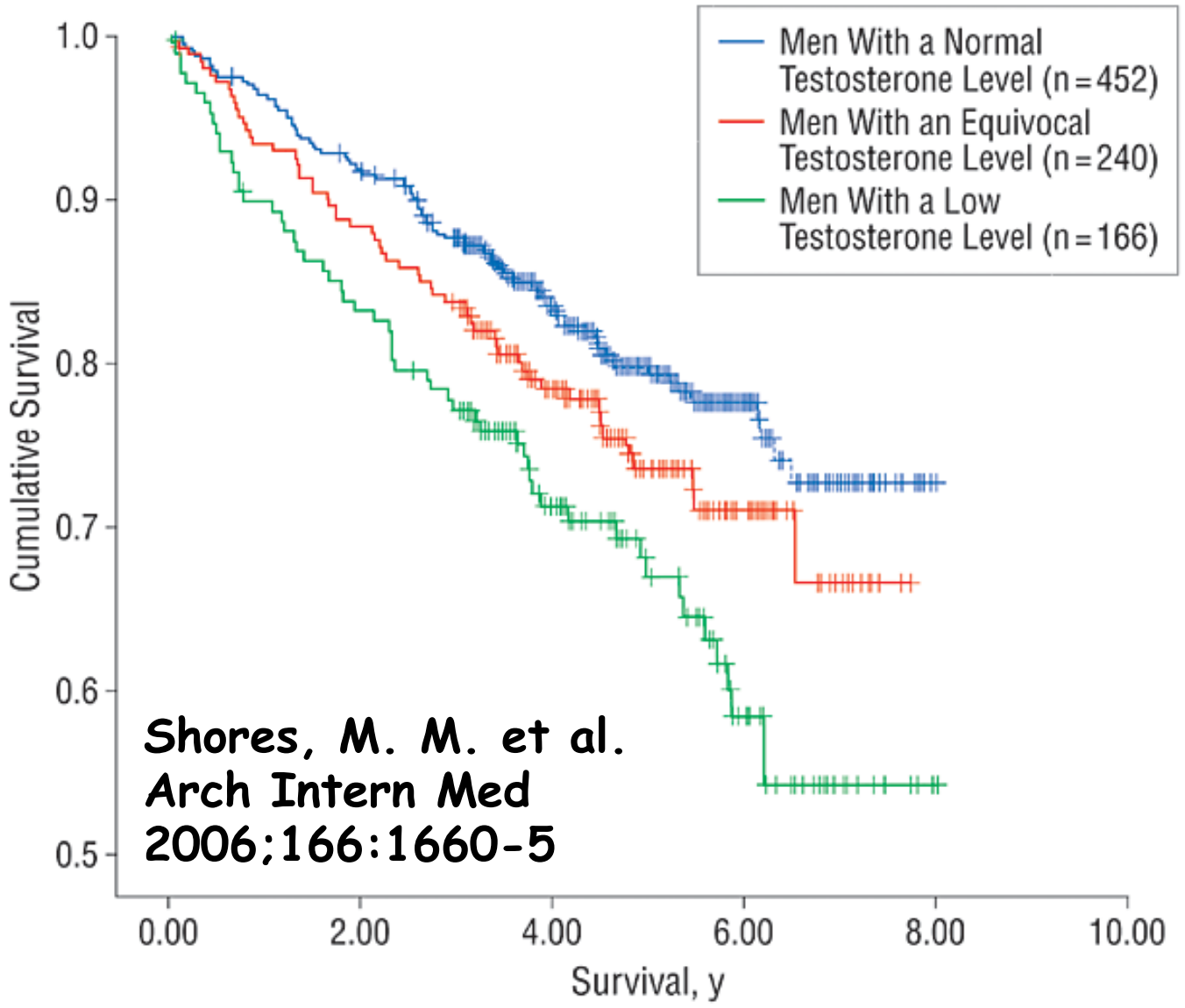
Travison et al. J Clin Endocrinol Metab 2007; 92: 196-202

Sperm count and mortality



Jensen TK. Am J Epidemiol 2009; 170: 559-65

Influence of s-testosterone on survival



858 men
>40 years
sampled 94-99

Follow-up:
Mean 4.3 years
Up to 8 years

Adjusted for:
Age, DM, BMI

Mortality: RR

Normal	1
Reduced	1.4
Low	1.9

Normal:
≥ 8.7 nmol/l
total testost.

Testosterone and mortality

1954 German men 20-79 years old, followed 7.2 years. S-testosterone <8.7 nmol/l defined low.
Total number of deaths: 195

Control for age, waist circum, smoking, alcohol, and physical activity	HR (95% CI)
All cause mortality	2.3 (1.4-3.9)
Deaths from CaVD	2.8 (1.1-7.2)
Deaths from cancer	3.6 (1.8-7.5)
Deaths from respiratory diseases	1.6 (0.2-14)
Other causes	1.6 (0.5-5.6)

Haring et al. Eur Heart J 2010; 31: 1494-1501.

Testosterone and metabolic syndrome

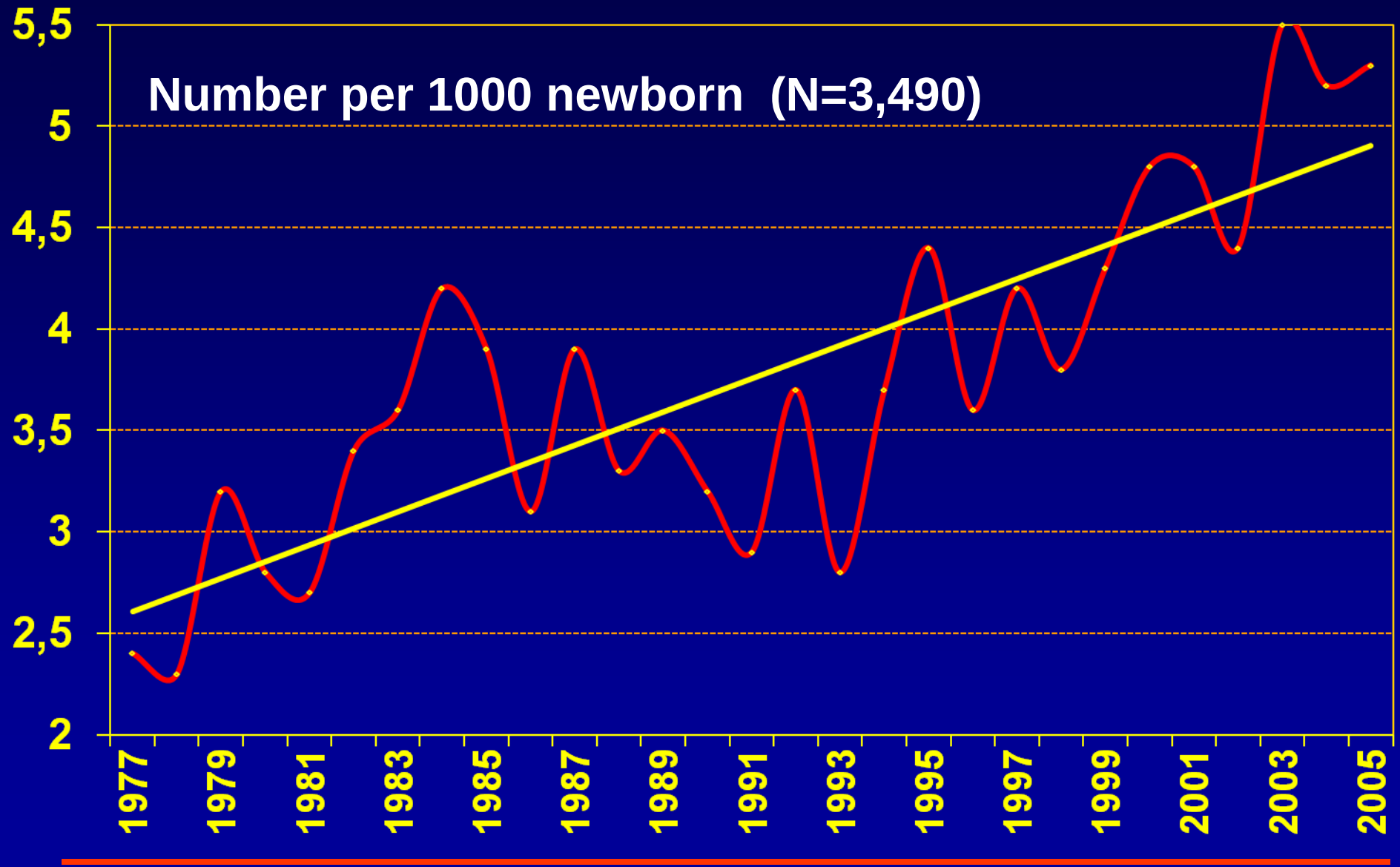
Cross sectional study in US, Health survey 1988-91, 1,226 men ≥20 years.

Control for age, smoking, alcohol, physical activity, s-cholesterol, CRP (Model 2) and in addition insulin resistance (Model 3)

	Prevalence ratio	
Total testosterone	Model 2	Model 3
1st quartile (low)	4.0 (2.6-6.1)	2.2 (1.5-3.1)
2nd quartile	4.1 (2.7-6.3)	2.5 (1.9-3.4)
3rd quartile	1.4 (0.8-2.3)	1.2 (0.8-2.0)
4th quartile (high)	1	1

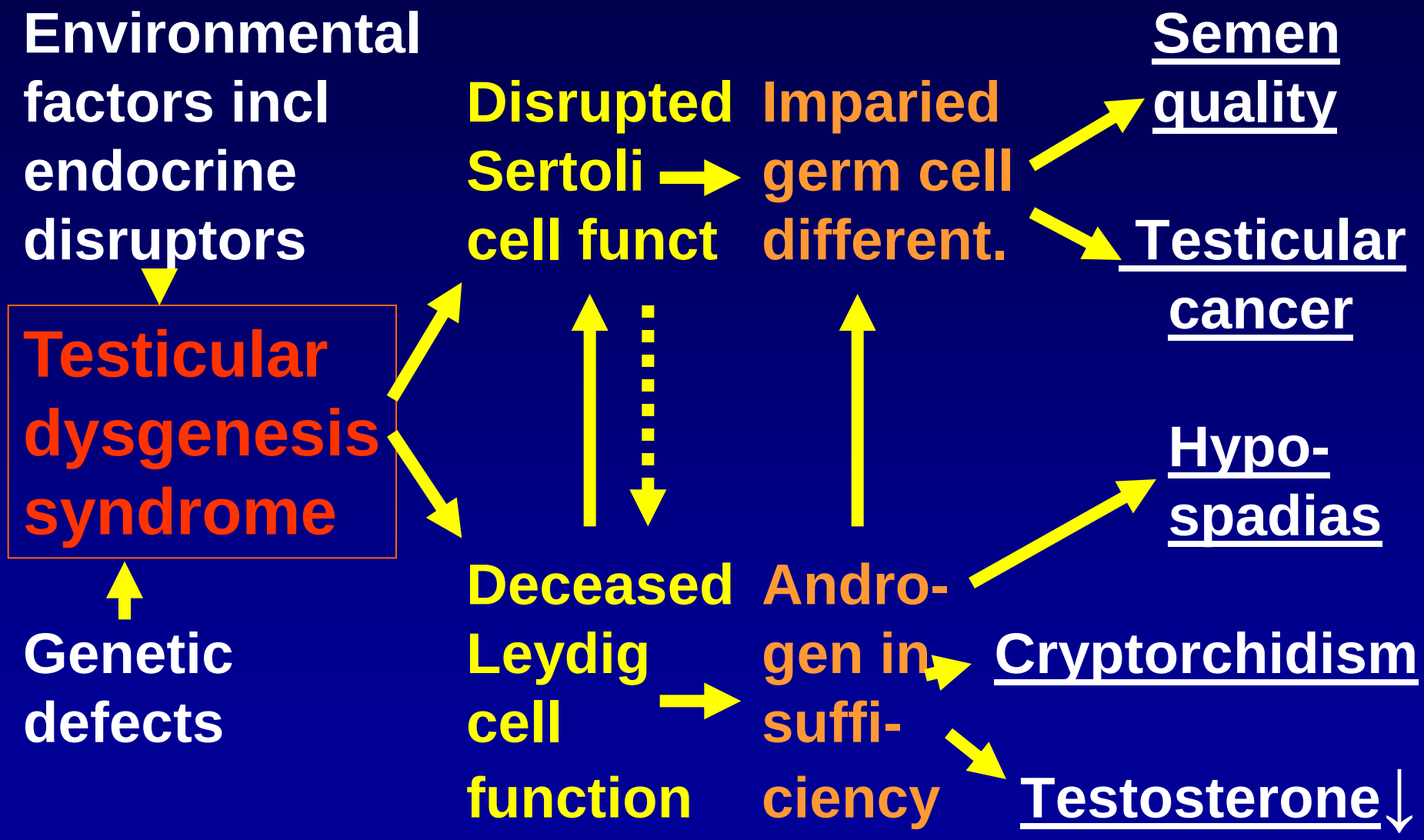
Li et al. Diabetes Care 2010; 33: 1618-24

Hypospadias in DK 1977-2005



Lund et al. Eur Urol 2009; 55: 1022-6

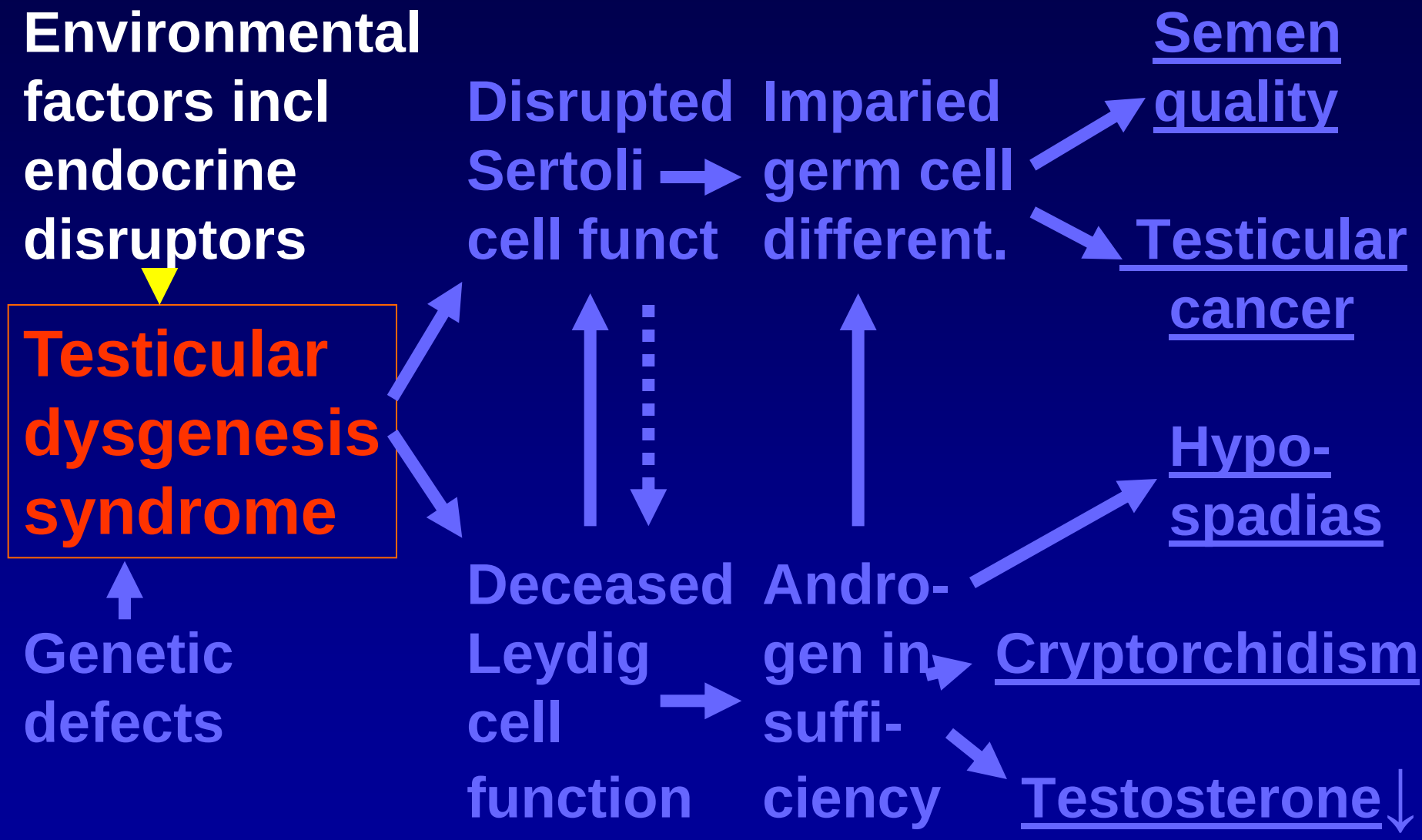
Testicular Dysgenesis Syndrome



Skakkebæk et al. Hum Reprod 2001; 16: 972-8.

Li/09

Testicular Dysgenesis Syndrome



Skakkebæk et al. Hum Reprod 2001; 16: 972-8.

Li/09

Phthalate exposure and anogenital distance (AGD) in male infants

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

Swan et al. Environmental Health Perspect 2005; 113: 1056-61.

Li/06

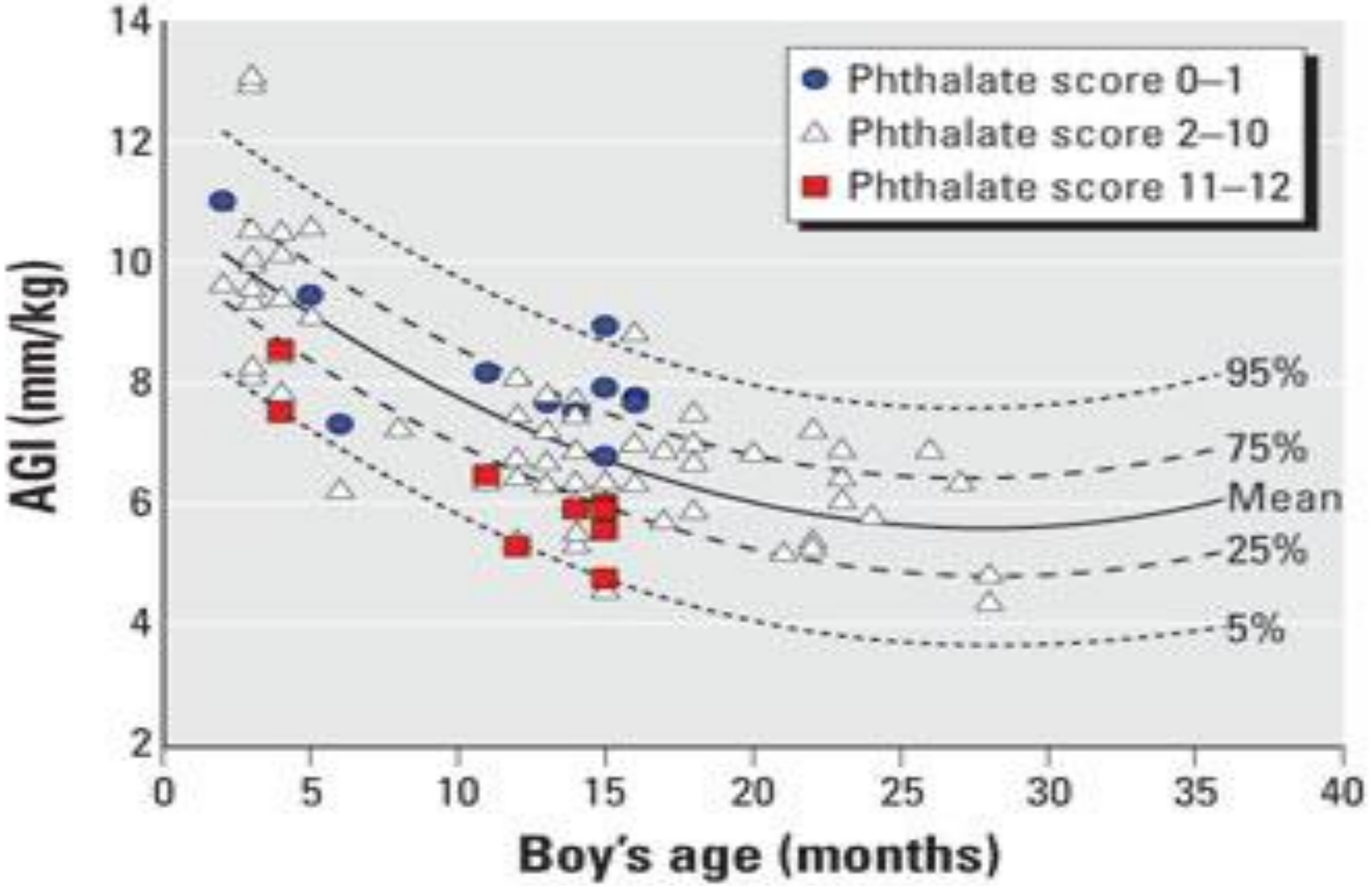
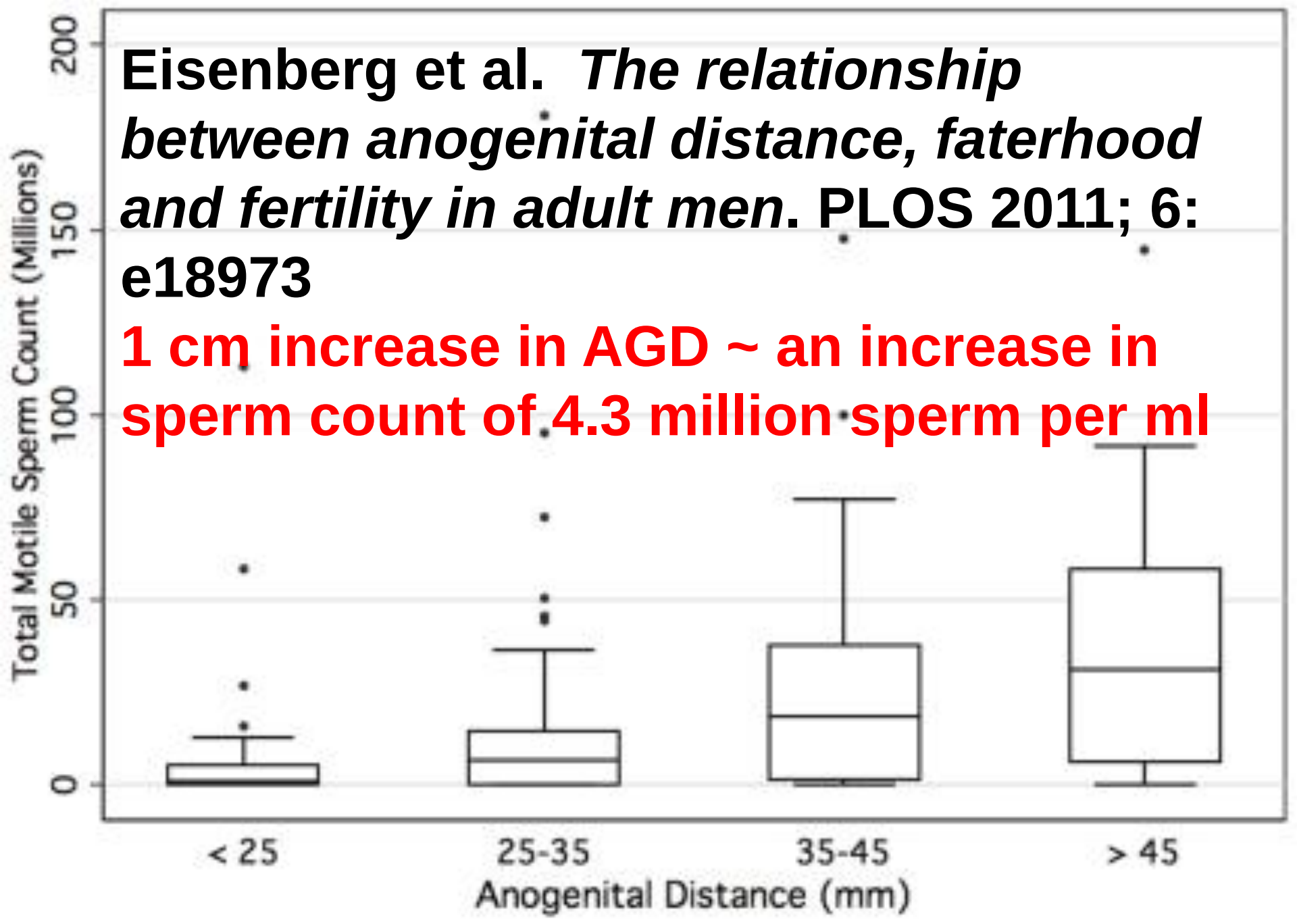


Figure 1. Mean AGI (mm/kg) in relation to boys' age at examination (months).

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.

Mahood et al. Endocrinology 2005; 146: 613-23


Eisenberg et al. *The relationship between anogenital distance, faterhood and fertility in adult men*. PLOS 2011; 6: e18973
1 cm increase in AGD ~ an increase in sperm count of 4.3 million sperm per ml
Total Motile Sperm Count (Millions)
0
50
100
150
200
< 25
25-35
35-45
> 45
Anogenital Distance (mm)

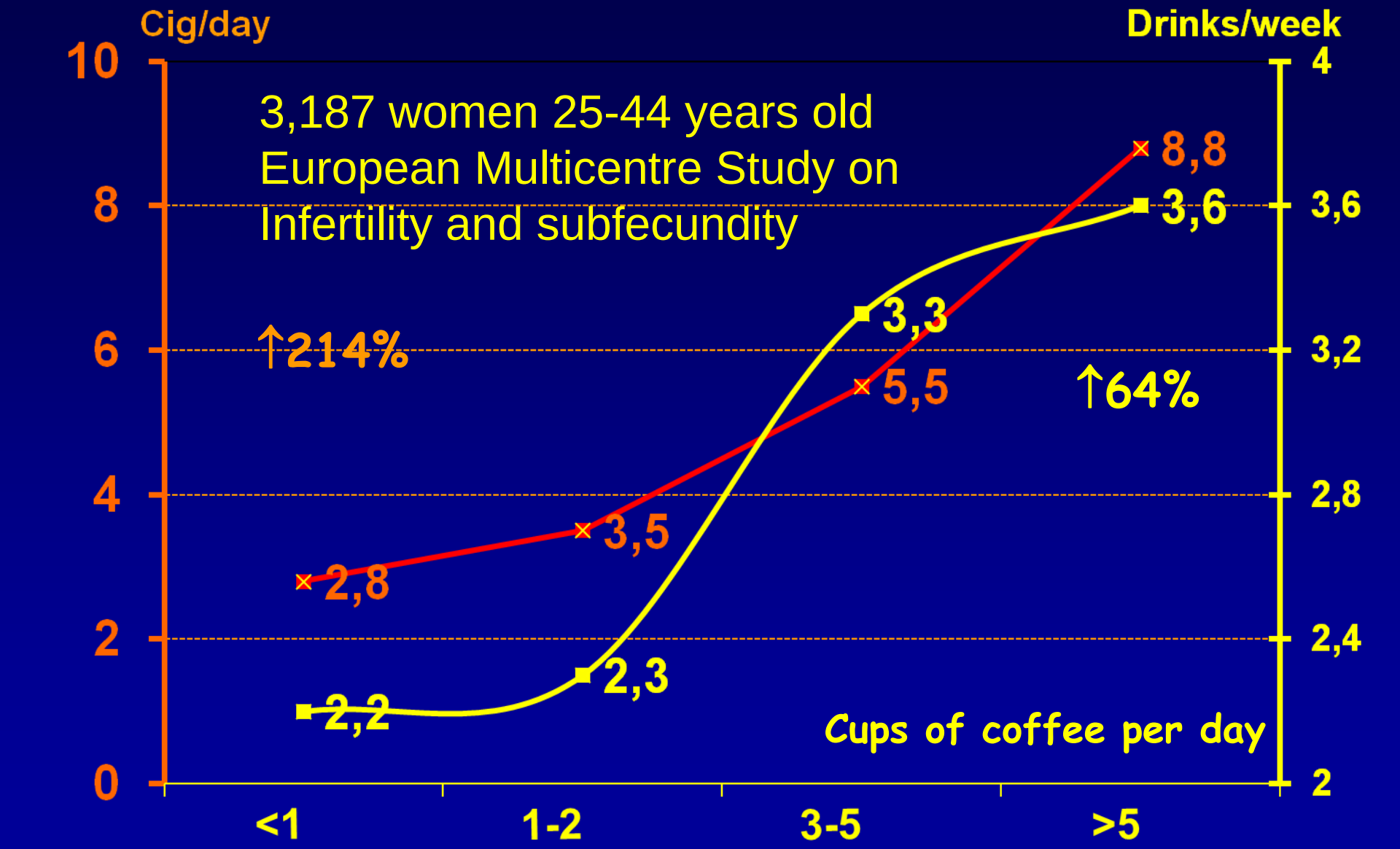
Konklusion

- Gravide kvinder er eksponeret for hormonforstyrrende stoffer, som kan påvirke mandlige fostres reproduktion livslangt.
- Ud over pthalater drejer det sig om konserveringsstoffer (parabener) tilsætningsstoffer (bromerede flamme-hæmmere), UV-blokkere (solcreme) og om hovedpine piller (paracetamol og NSAID)
- Det er især fra 6.-12. graviditetsuge, at ekspositionen er kritisk.

Infertilitet epidemiologi

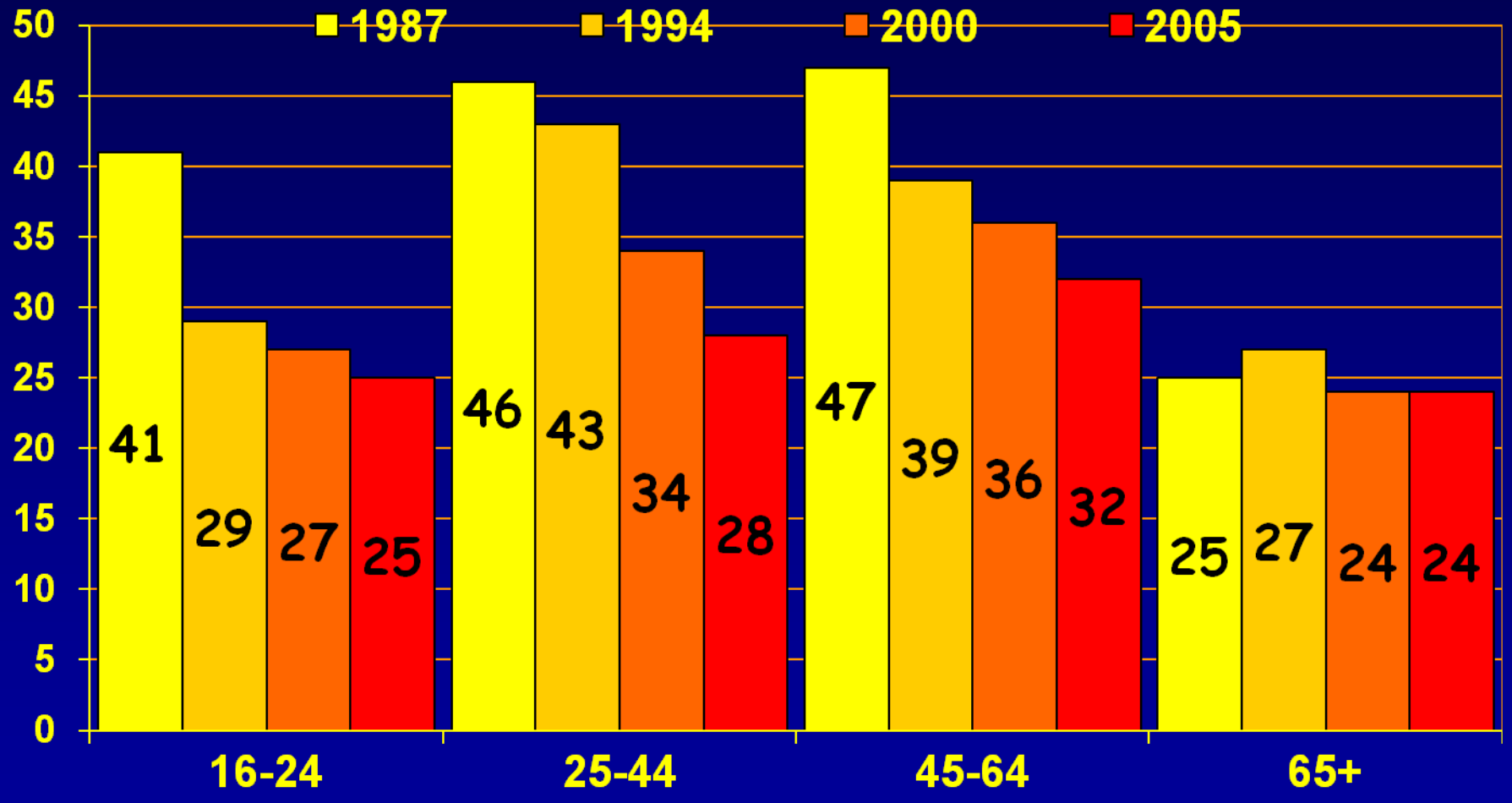
- Definitioner
- Problemets størrelse
- Alder og fertilitet
- Mandlig fertilitet
- Rygning
- Alkohol
- Kaffe
- Overvægt

Naughty girls



Bolumar et al. Am J Epidemiology 1997; 145: 324-34.

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

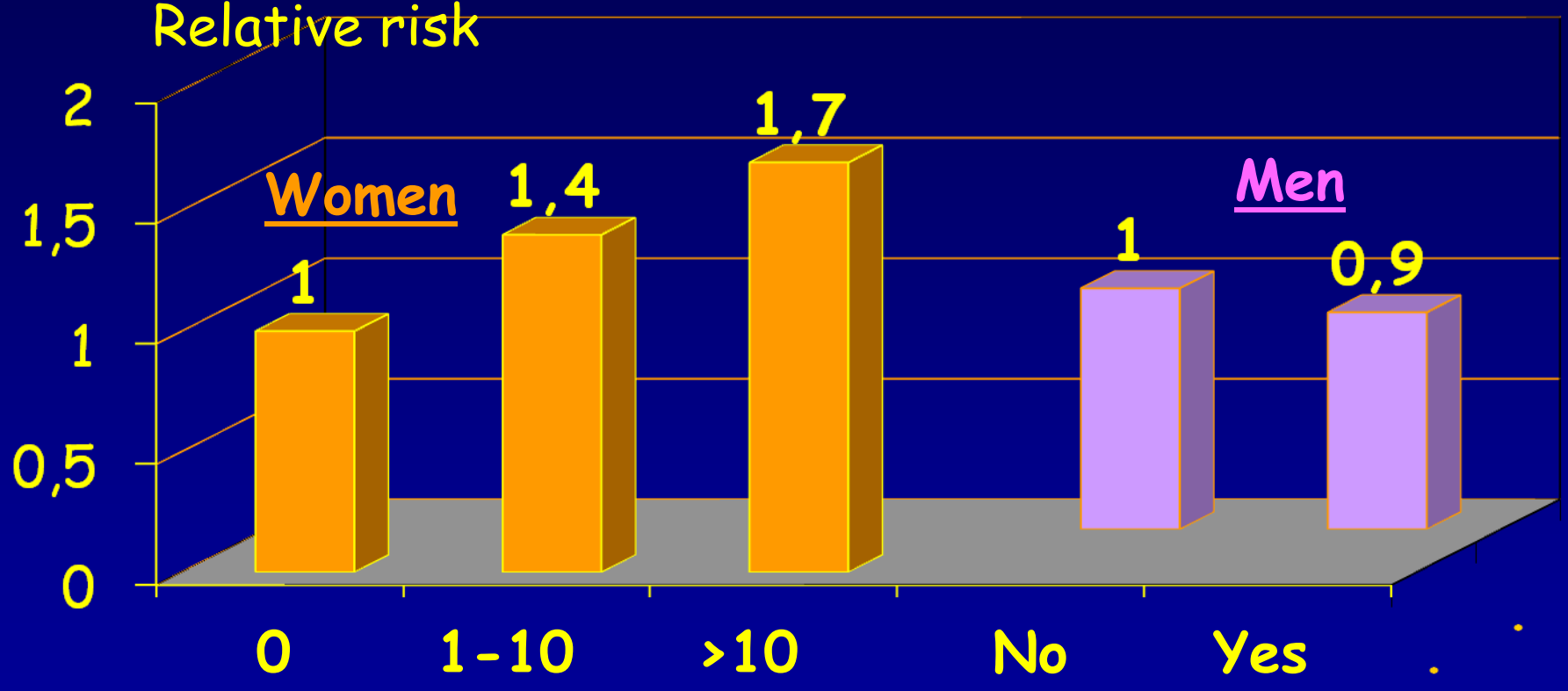


Sundhed og Sygelighed i DK 2006. SIF 2006

Li/08

Fertility and smoking

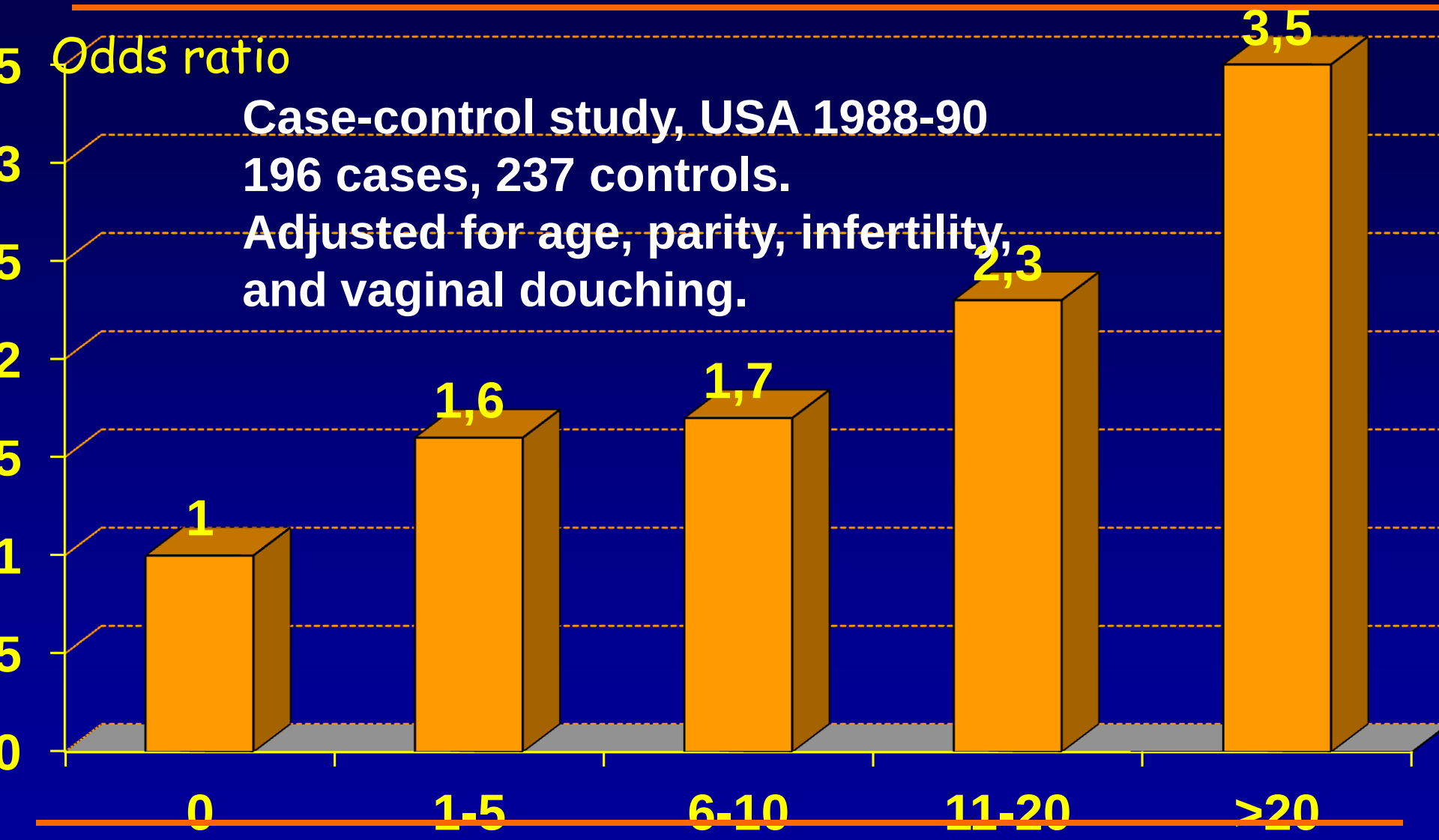
Risk of waiting time >9,4 months



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

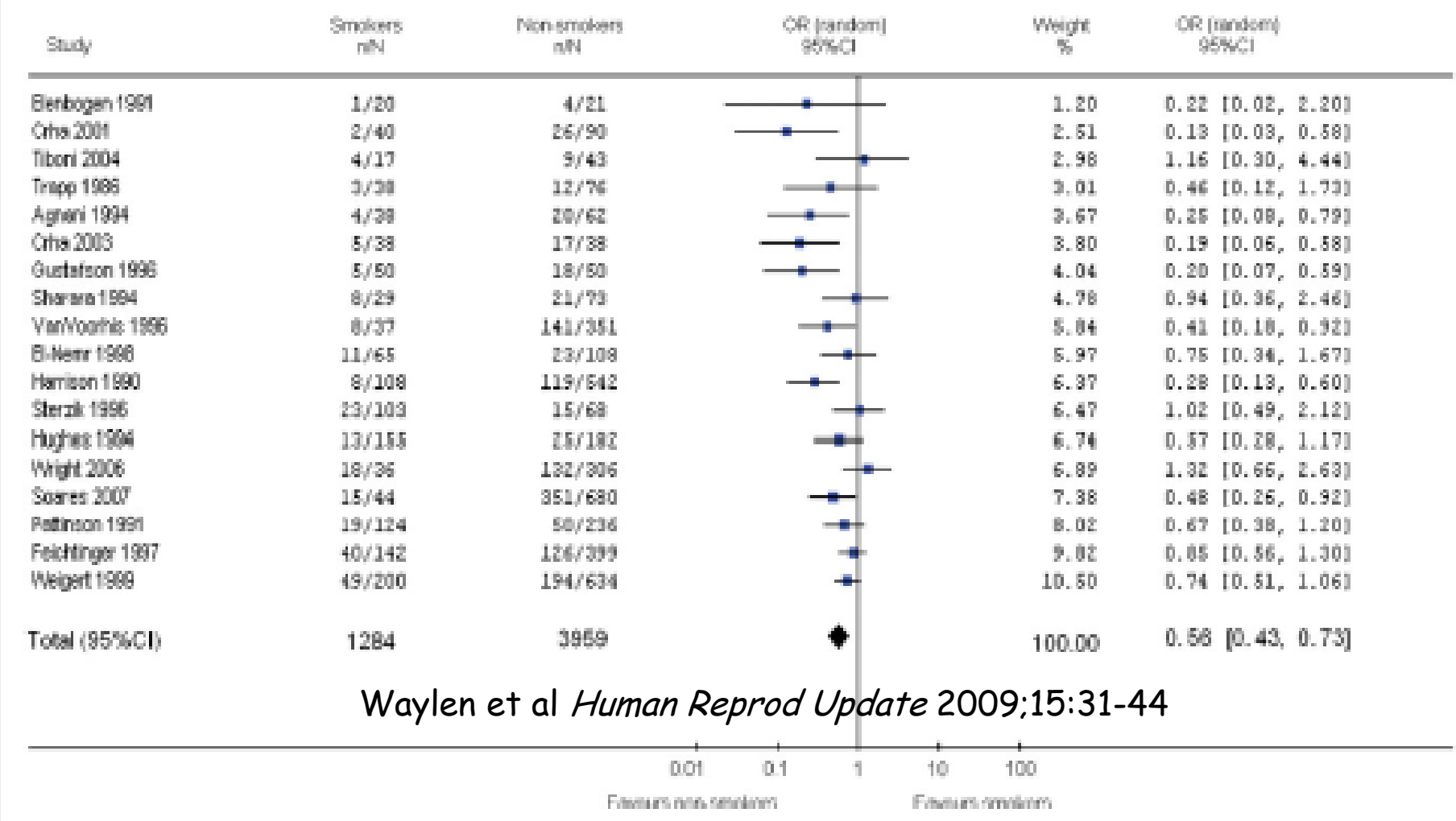
Li/01

Smoking and ectopic pregnancy



Am J Obstet Gynecol 1998; 178: 393-8

Smoking and clinical IVF pregnancy



Waylen et al *Human Reprod Update* 2009;15:31-44

Figure 2 Odds ratio of clinical pregnancy rate per cycle.

Total events: 236 (smokers), 1308 (non-smokers). Test for heterogeneity: $\chi^2 = 33.27$, df = 17 ($P = 0.01$), $I^2 = 48.9\%$. Test for overall effect: $z = 4.26$ ($P < 0.0001$).

Smoking & miscarriage

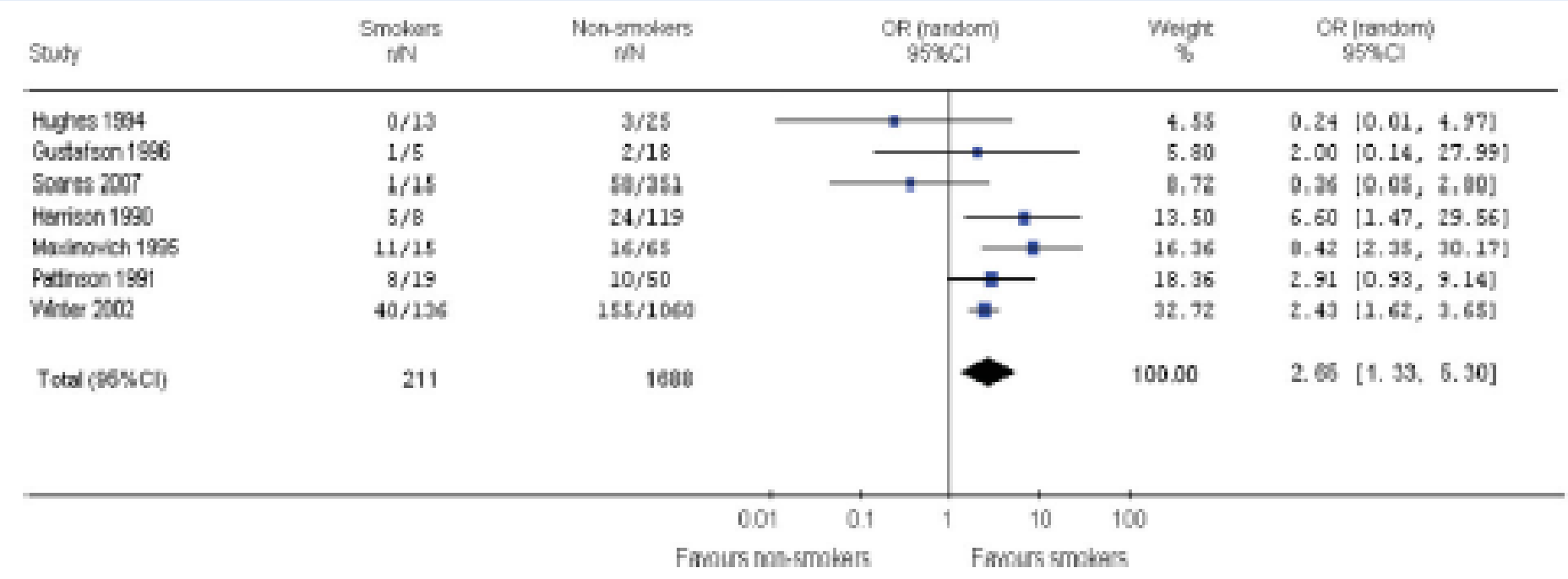


Figure 3 Odds ratio of miscarriage per pregnancy.

Total events: 66 (smokers), 268 (non-smokers). Test for heterogeneity: $\chi^2 = 10.98$, $df = 6$ ($P = 0.09$), $I^2 = 45.4\%$. Test for overall effect: $z = 2.77$ ($P = 0.006$).

Conclusion:

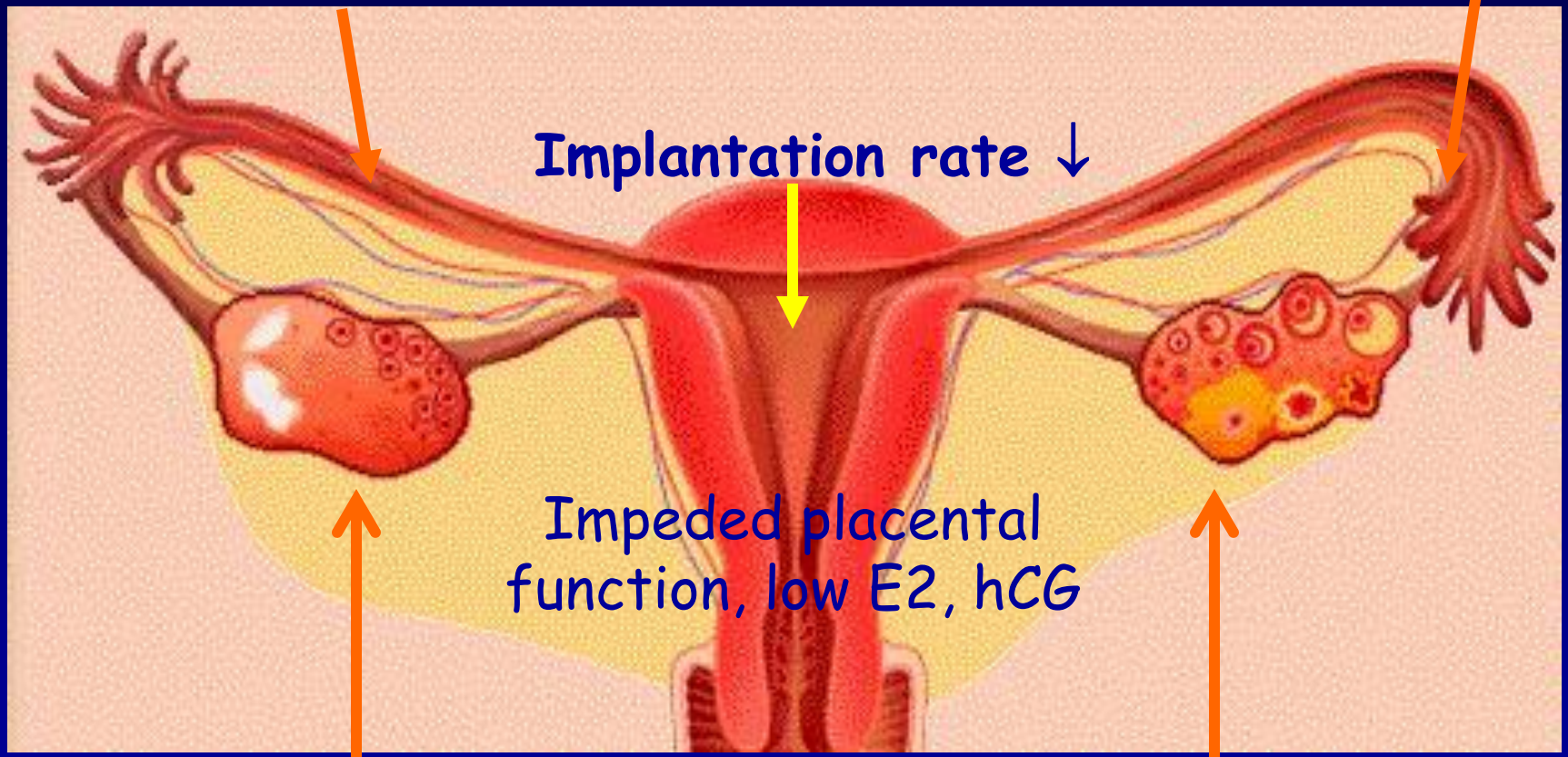
Smoking reduces the chance of pregnancy with 44% and more than double the risk of miscarriage

Waylen et al *Human Reprod Update* 2009;15:31-44

Smoking and fertility

Impeded ciliary function:

Pick-up function ↓



E2-production ↓

Abortion rate ↑

↓ progesterone in granulosa cells

Shiverick et al: Placenta, 1999; 20: 265-72

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

Int J Andrology 1996; 19: 323-37

Infertilitet epidemiologi

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

Alkohol og fertilitet

Nedsætter beskedne mængder alkohol fertiliteten?

- Kun få undersøgelser
- Modstridende resultater
- Store velgennemførte studier

Alkohol og fertilitet

Foreløbig konklusion:

≥ 1-2 genstande/dag

1. Nedsætter den spontane graviditetschance
2. Øger risikoen for spontan abort

< 1-2 genstande/dag

3. Synes ikke at påvirke IVF-resultater

Nybo Andersen et al. ***Int J Epidemiol*** 2012; Ahead of print

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
- Mandlig fertilitet
- Rygning
- Alkohol
- Kaffe
- Overvægt

Koffein

Koffein findes i

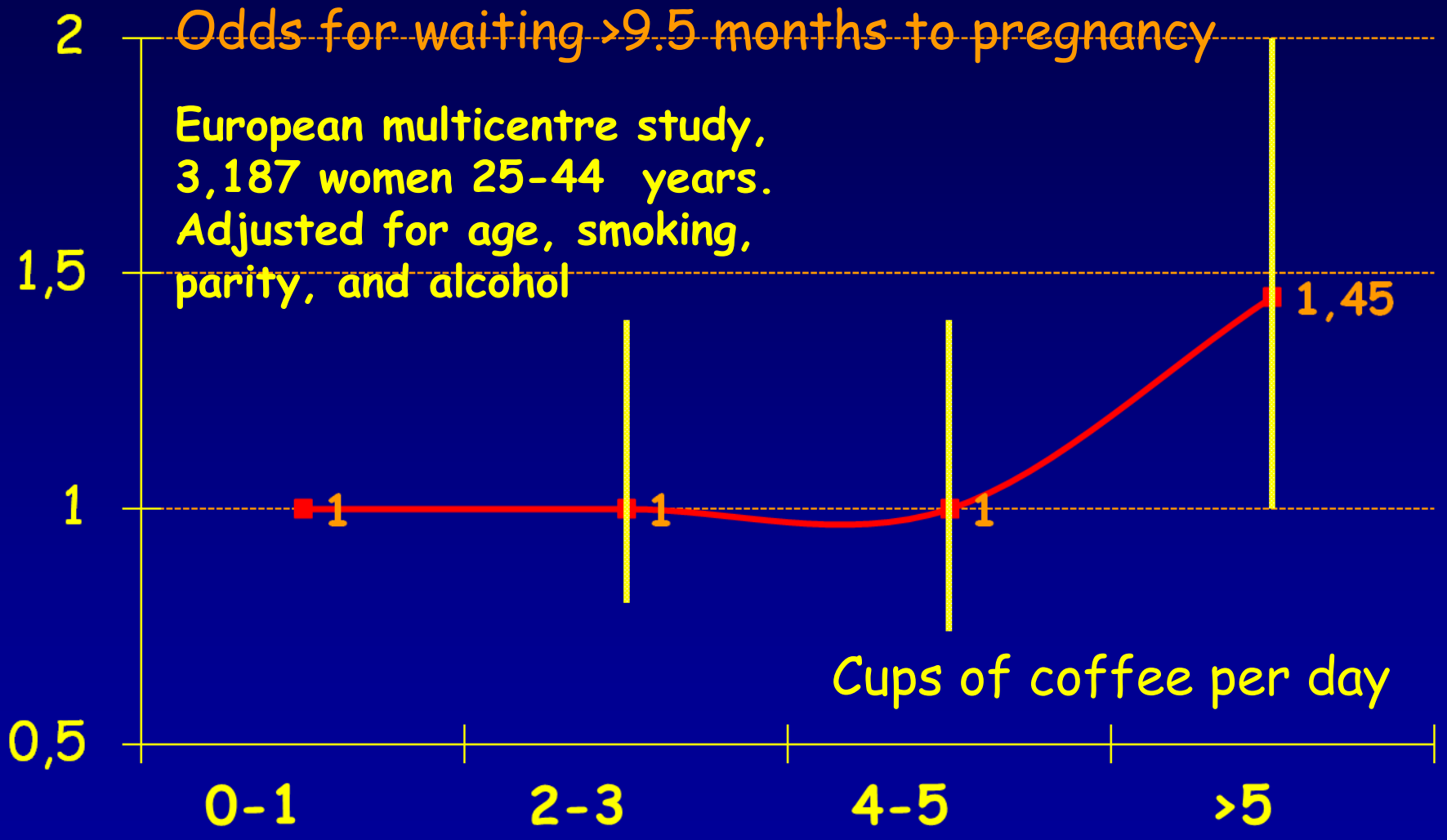
- 1 kop kaffe = 100 mg
- 1 kop te = 50 mg
- ½ liter cola = 50 mg
- 30 g chokolade = 10 mg
- 1 kop kakao = 5 mg
- medicin.
- Koffein passerer alle biologiske membraner inkl.. placenta-barrieren
- Koffein findes i alle kropsvæsker kort efter indtag

Jensen et al. BMJ; 1998: 505-10

Li/01

Fertility and coffee

Fecundability odds, 95% CI



Bolúmar et al. Am J Epidemiol 1997; 145: 324-34

Li/01

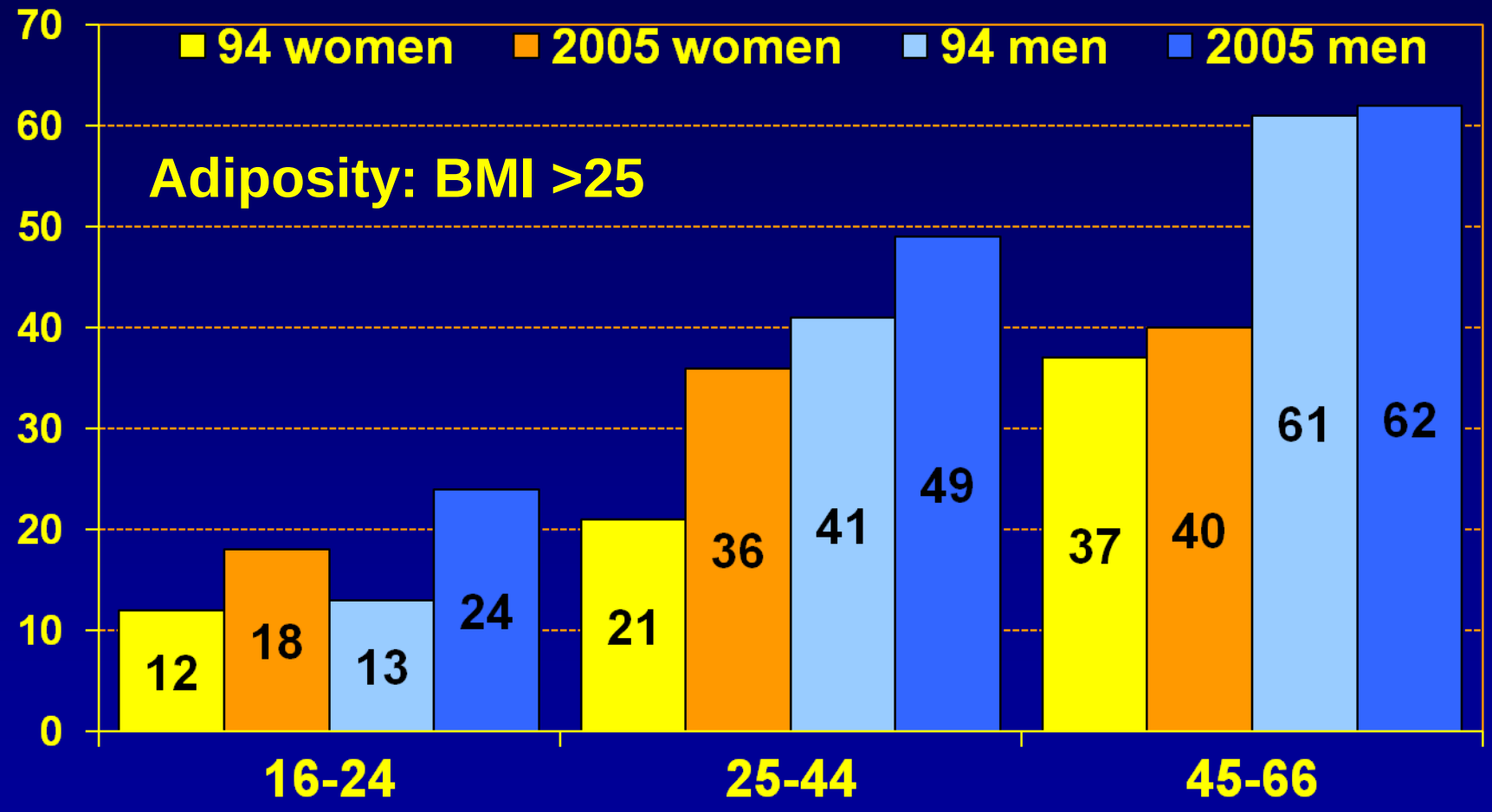
Kaffe og fertilitet: Konklusion

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

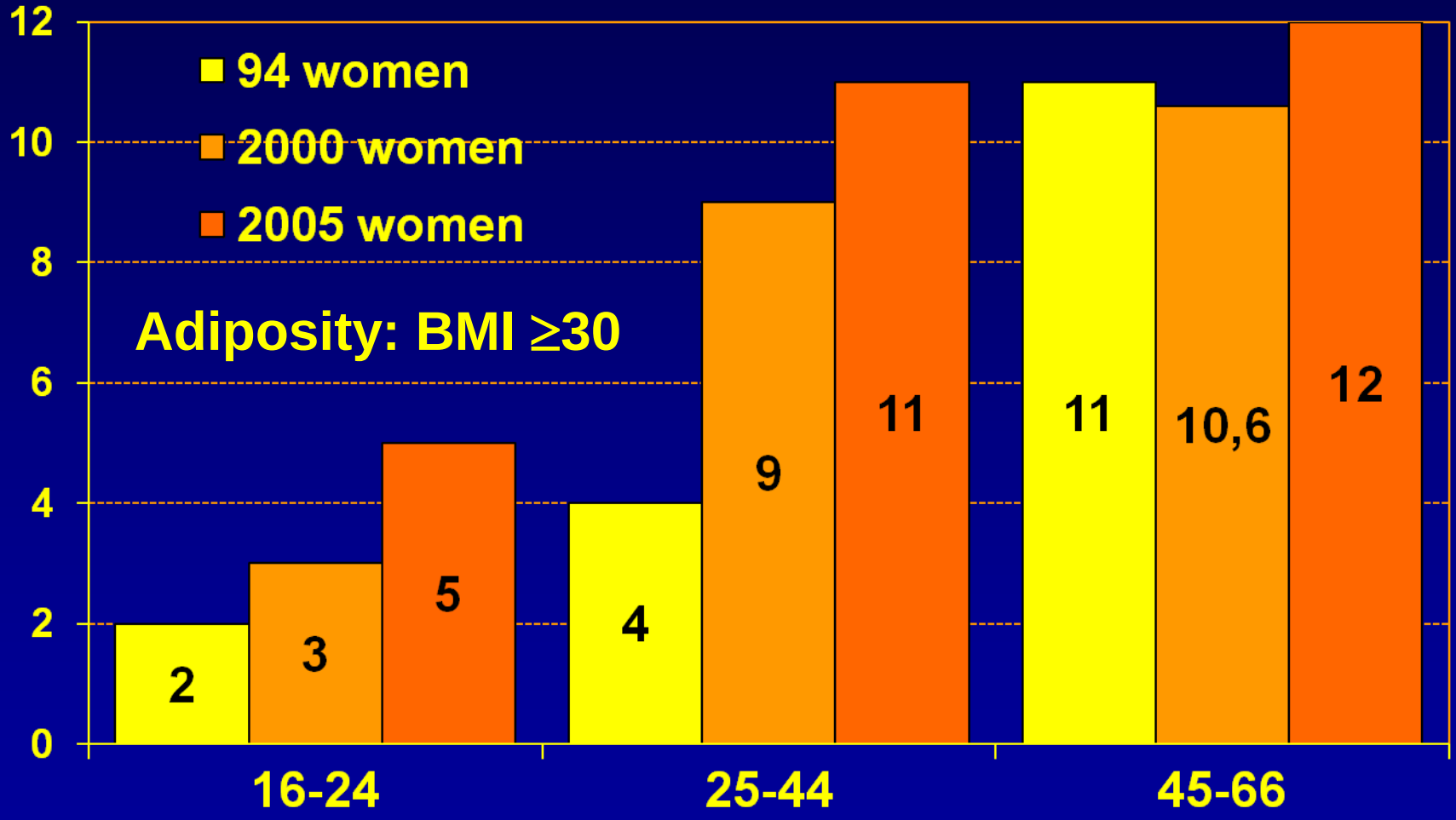
Adiposity in Danish women and men in 1994 and 2005. N=16,000



Statens Institut for Folkesundhed. SUSY 2006

Li/08

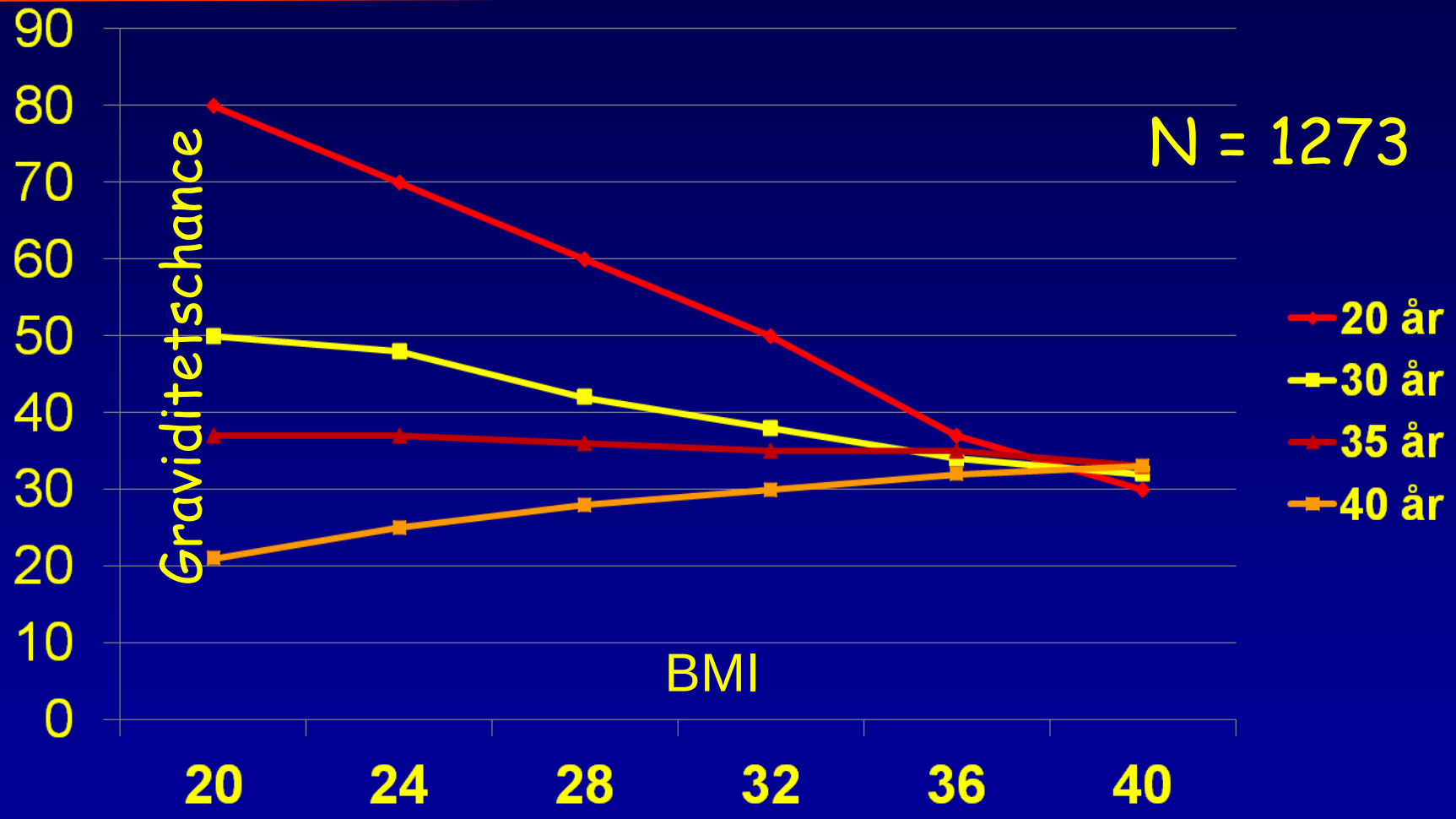
Severe adiposity in Danish women in 1994, 2000 and 2005



Statens Institut for Folkesundhed, SUSY 2006

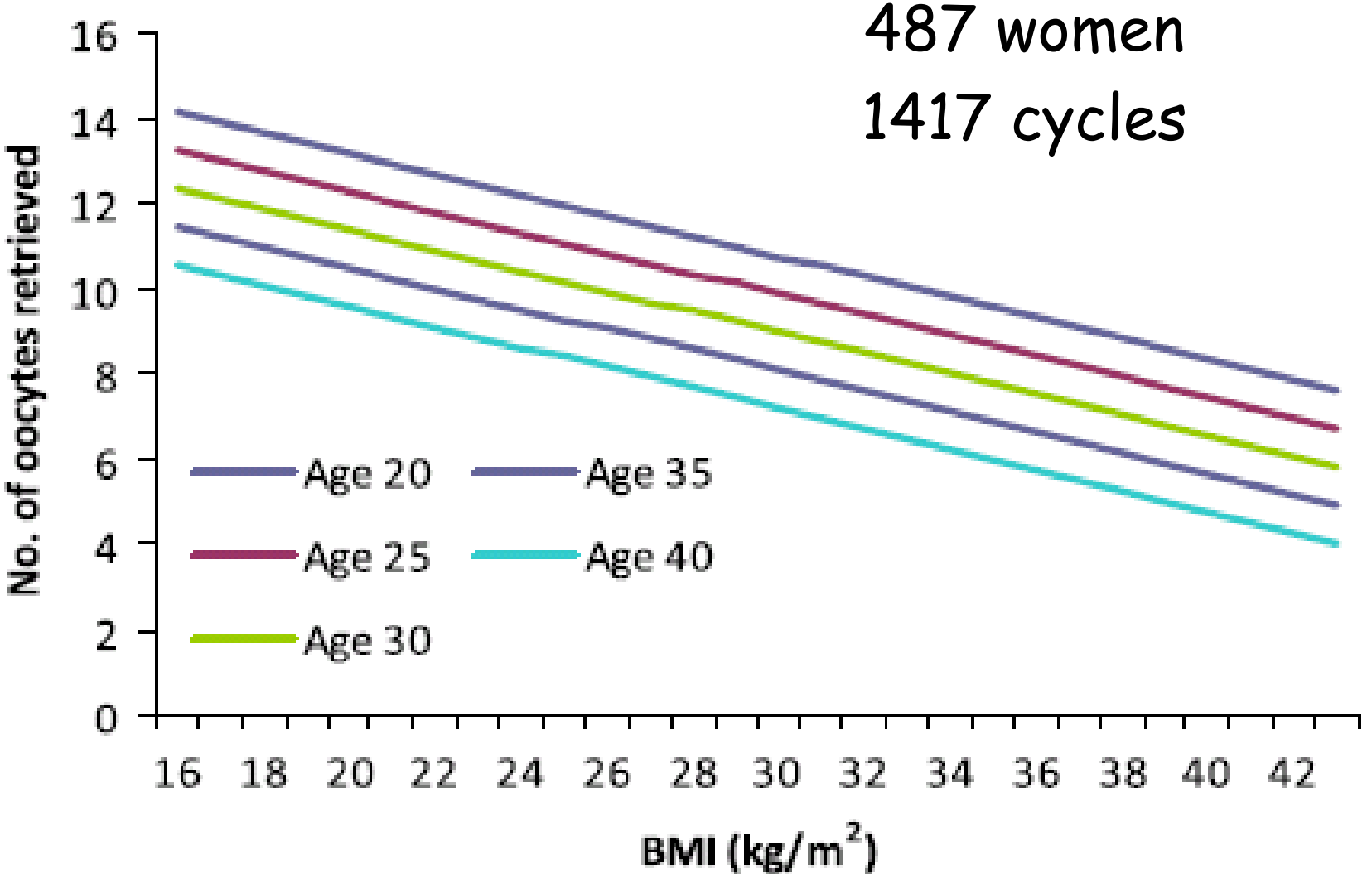
Li/08

Effekten af BMI er aldersafhængig



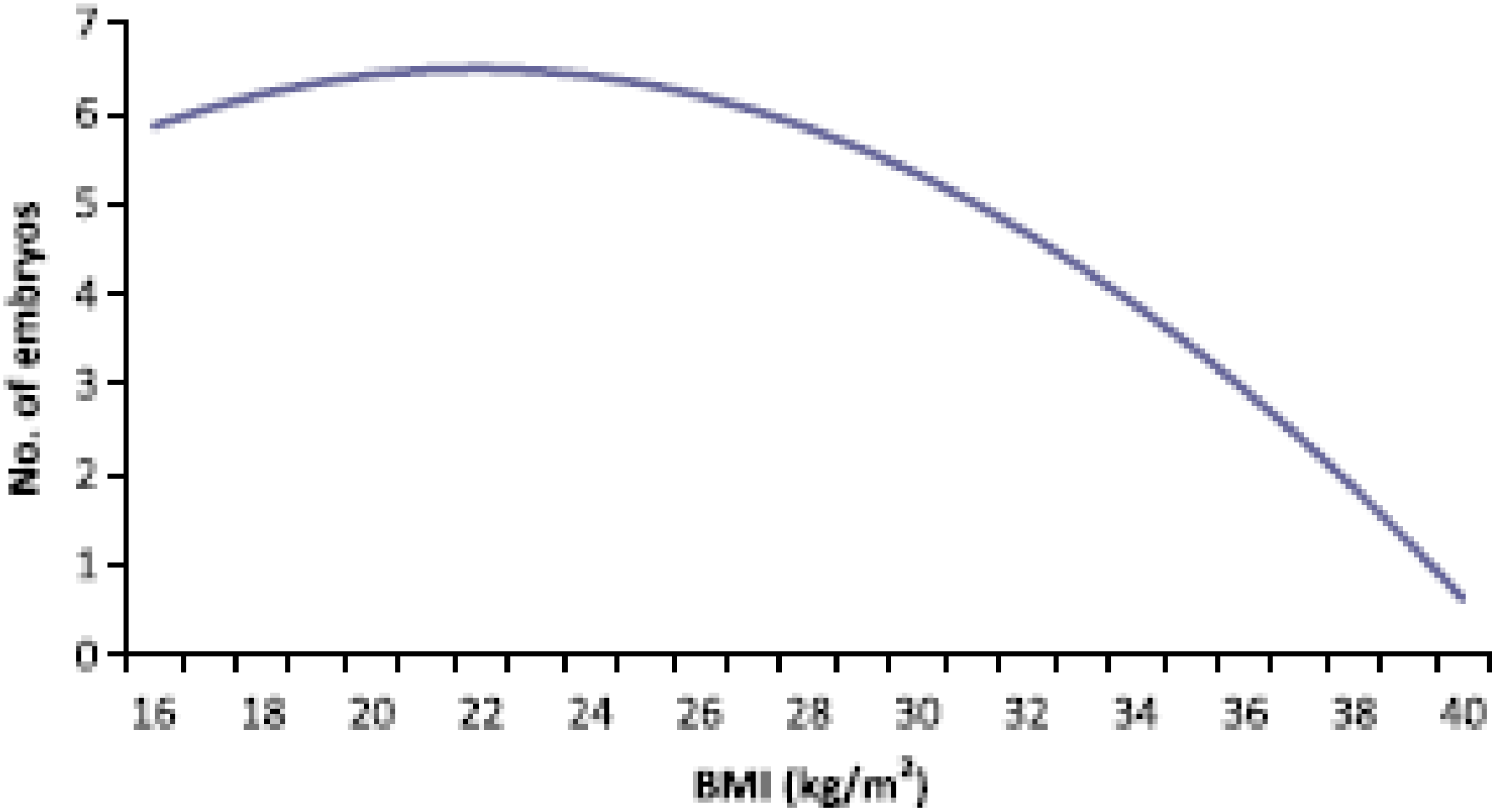
Sneed et al *Human Reprod* 2008; 23: 1835-1839

Expected oocytes retrieved by IVF



Pinborg et al. *RBM Online* 2011; 23: 490-9

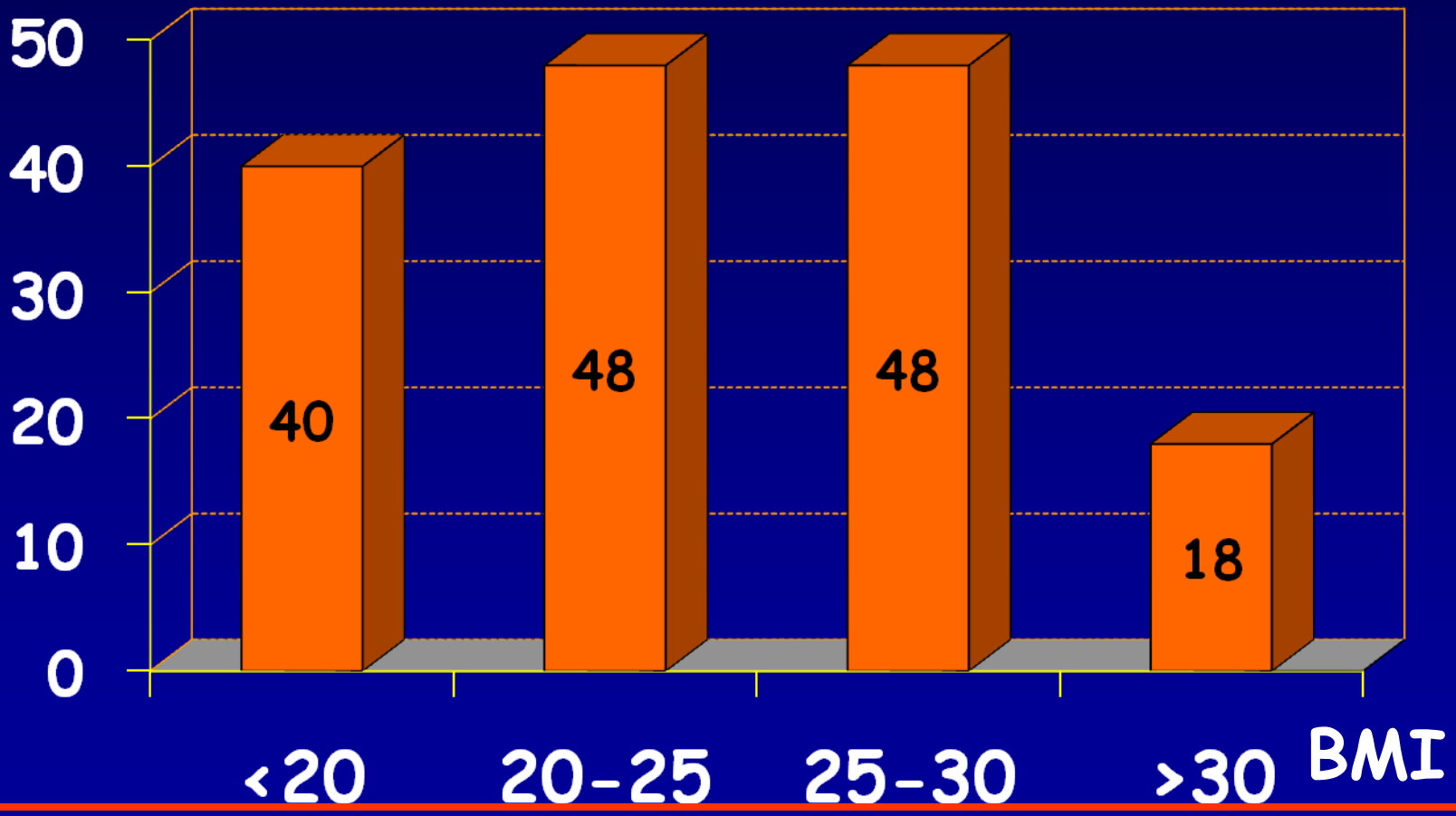
Expected embryos according to BMI



Pinborg et al. *RBM Online* 2011; 23: 490-9

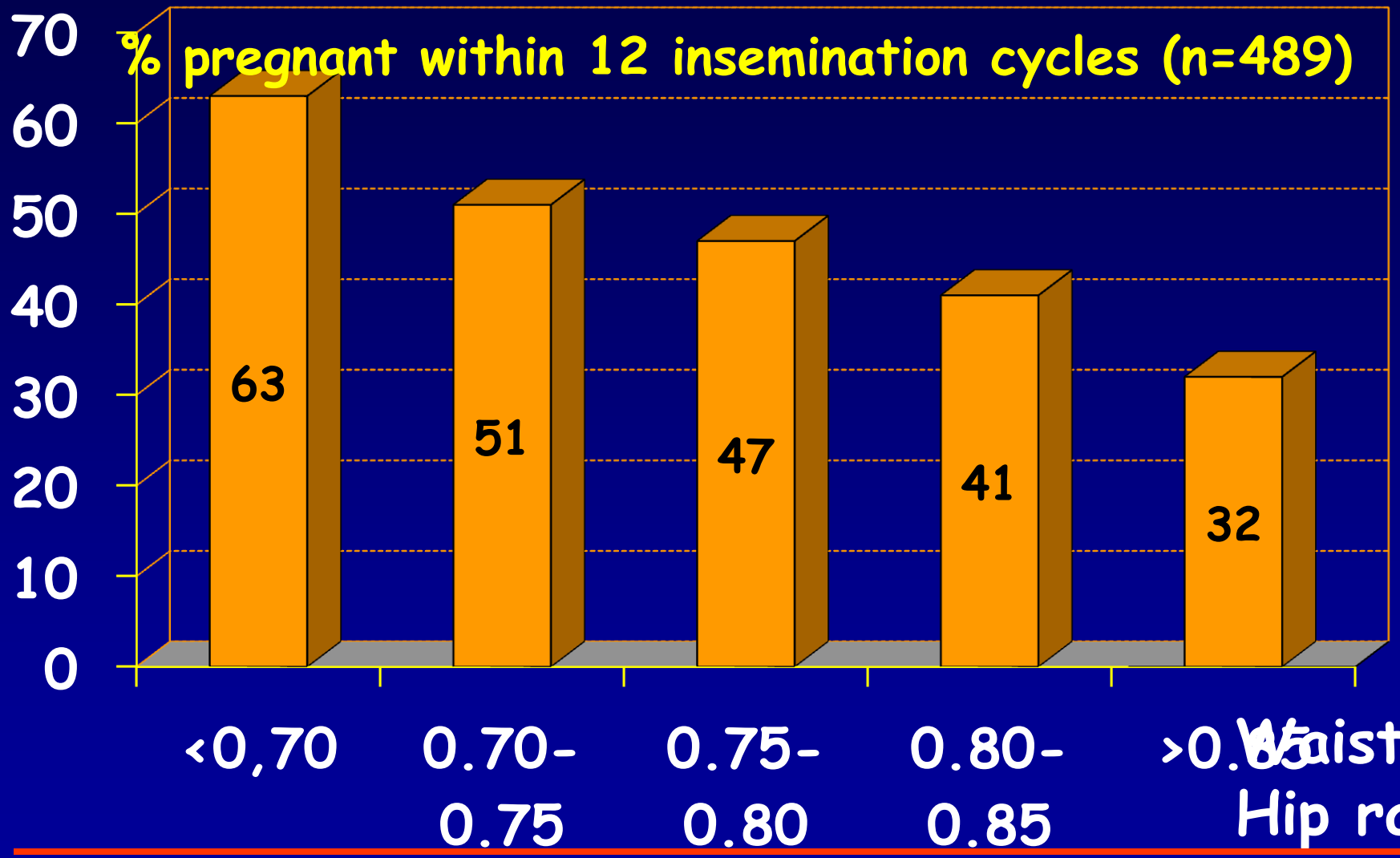
Fat and fecundity

% pregnant within 12 insemination cycles (n=489)



Zaadstra et al. BMJ 1993; 306: 484-7.

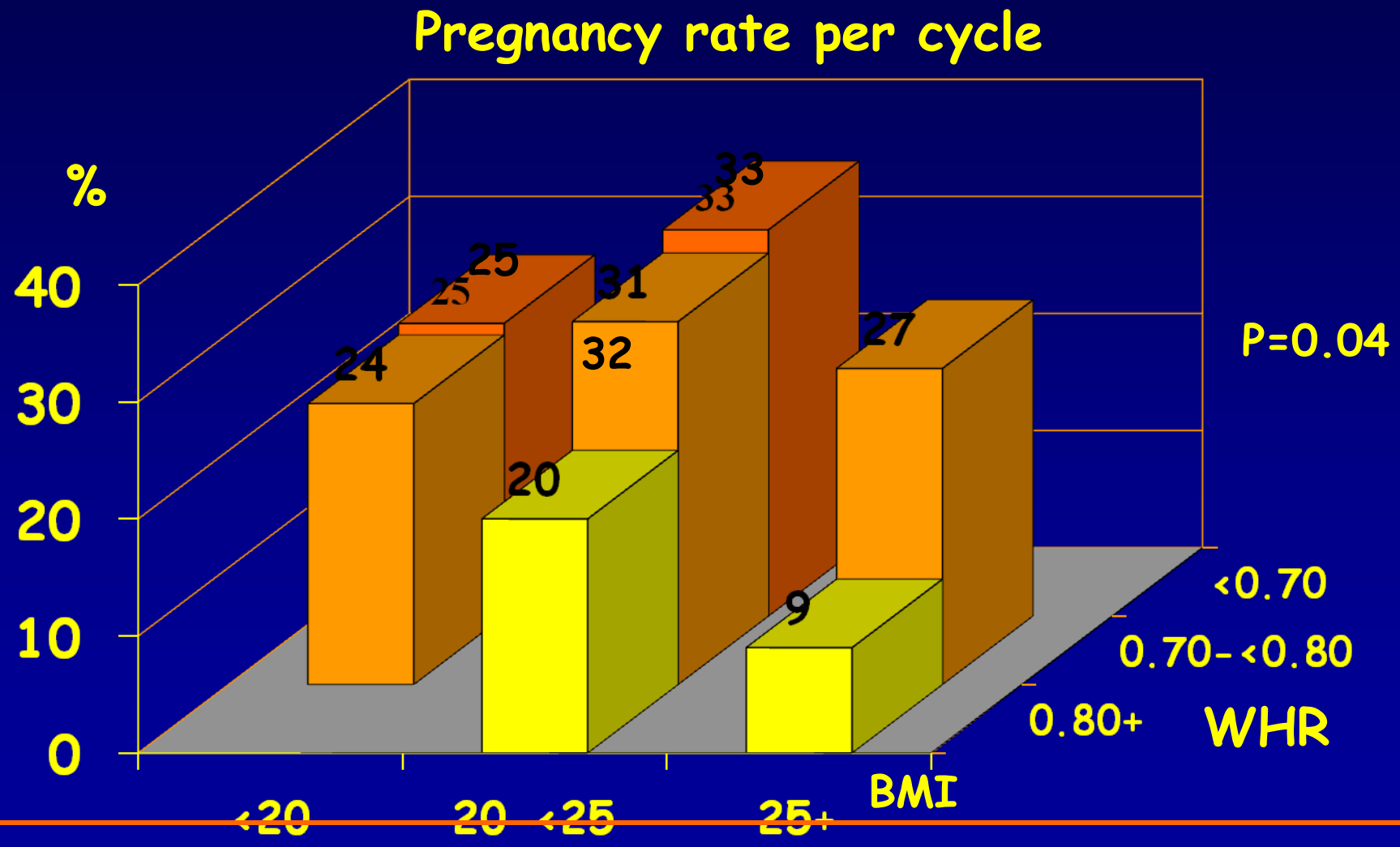
Fat and fecundity



Zaadstra et al. BMJ 1993; 306: 484-7.

Fat and fecundity

Pregnancy rates in 220 IVF cycles



Wass et al. Hum Reprod 1997; 12: 2057-60

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

Dansk Fertilitetsselskab

www.fertilitetsselskab.dk

www.sst.dk

www.dst.dk

www.lidegaard.dk