

Infertilitets epidemiologi

Øjvind Lidegaard

U-kursus

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Infertilitet epidemiologi

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

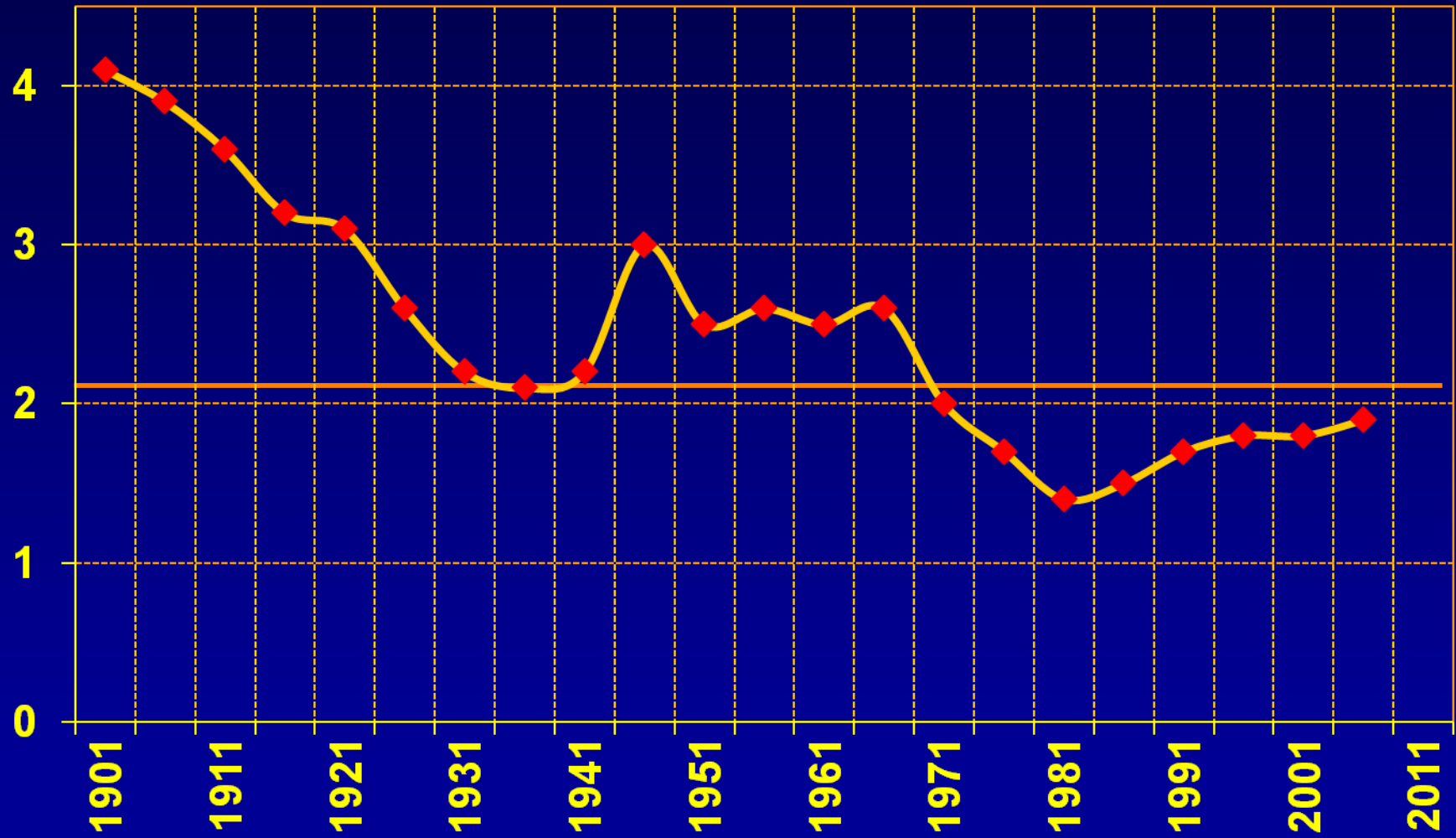
Nogle definitioner

- **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
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Infertilitet epidemiologi

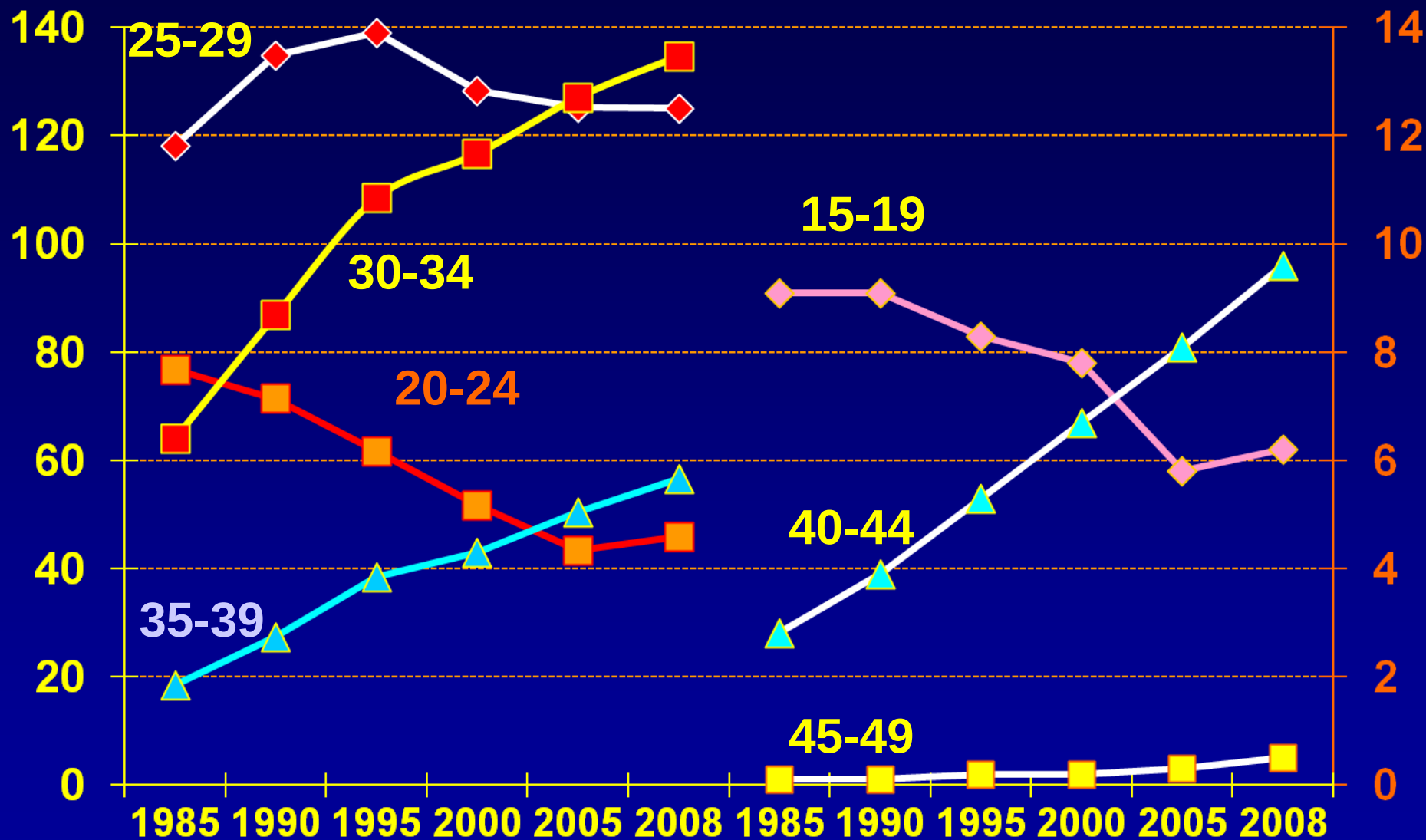
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Total fecundity rate in DK 1901-2008

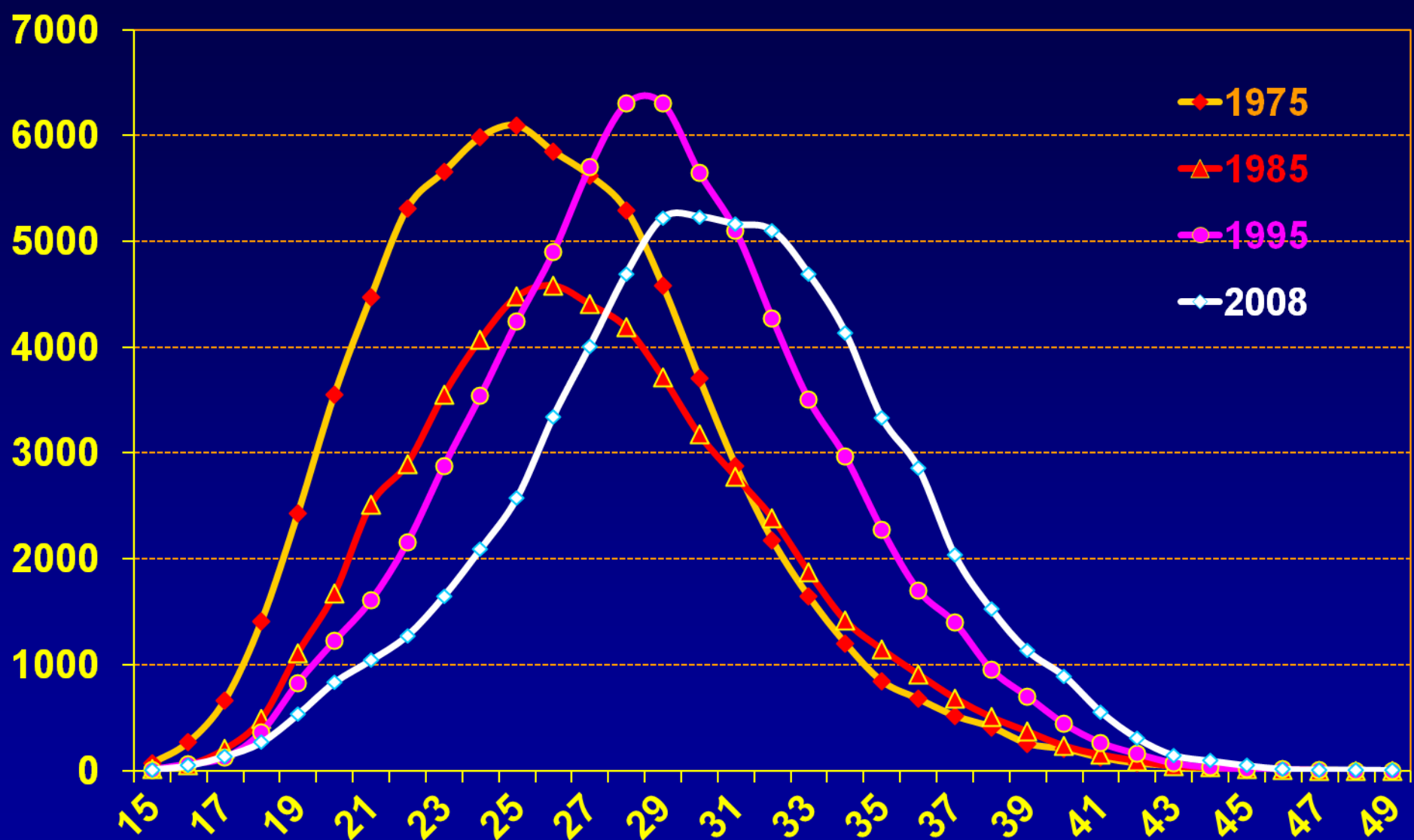


Lisbeth B Knudsen, Fertility trends in DK in the 1980s
Danmarks Statistik online: www.dst.dk

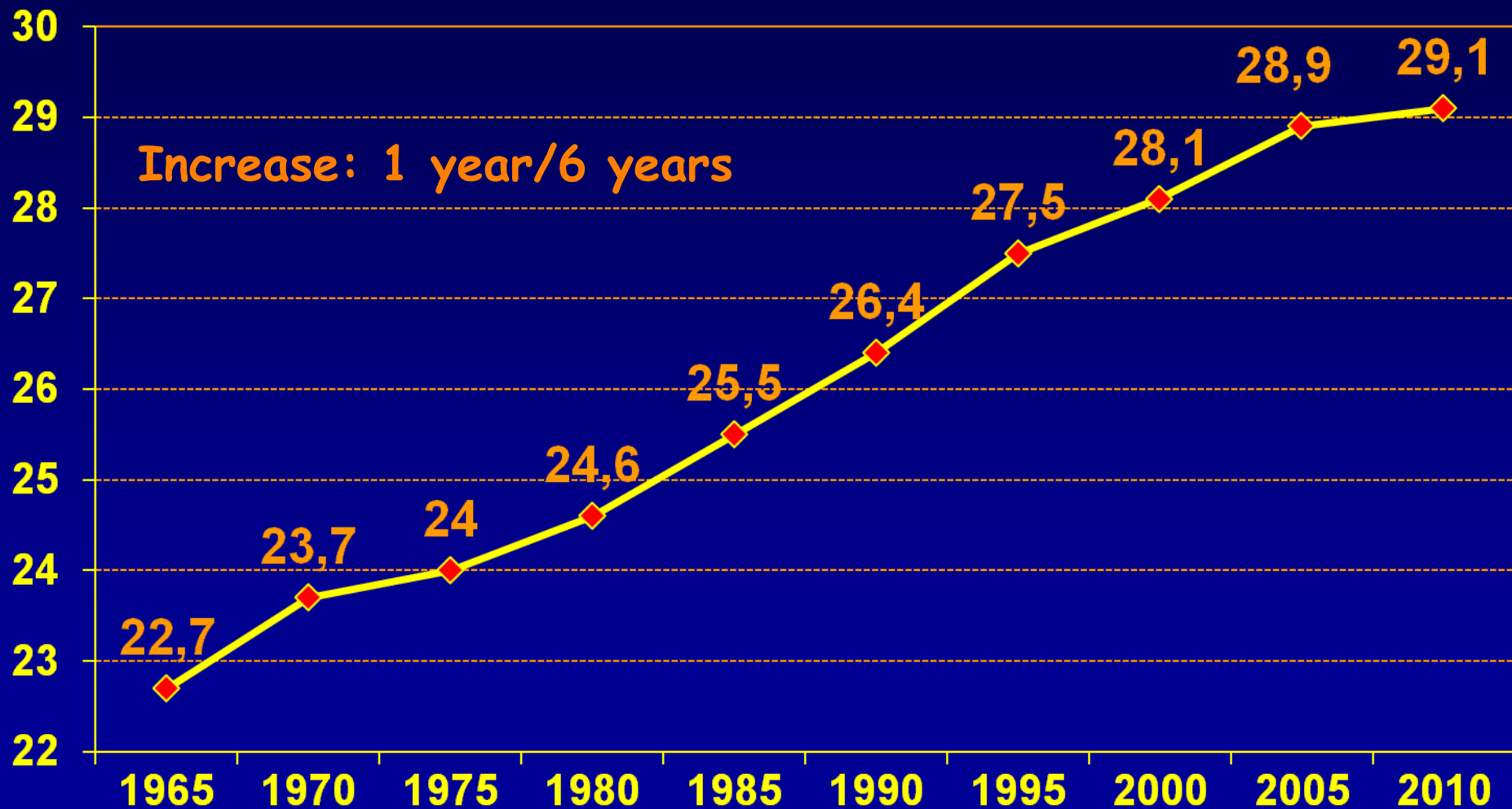
Fertility rates per 1,000 in DK 1985-2008



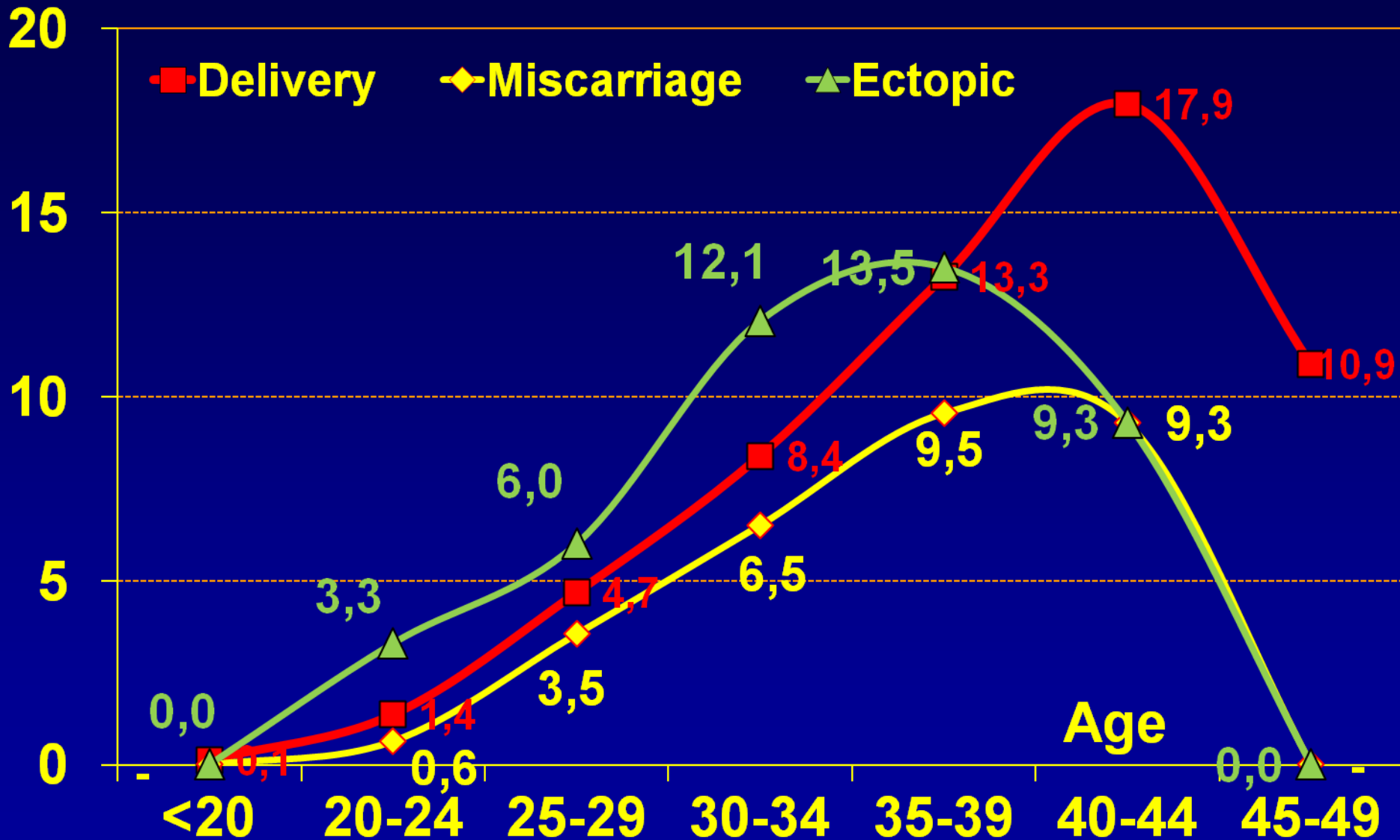
Levendefødte i DK i 1975, 85, 95 og 08



Age at first birth Denmark 1965-2010

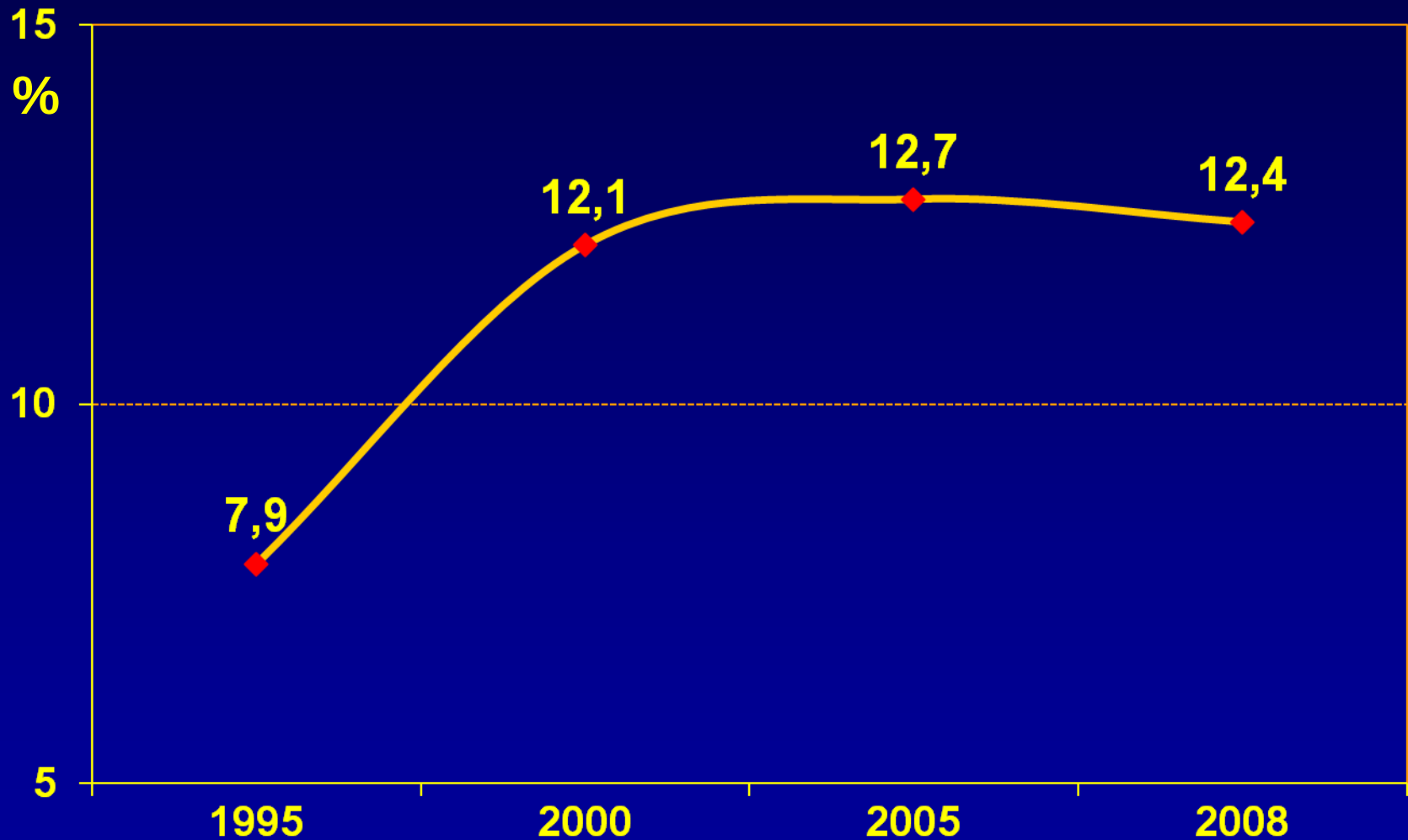


Per cent of ART pregnancies 2011

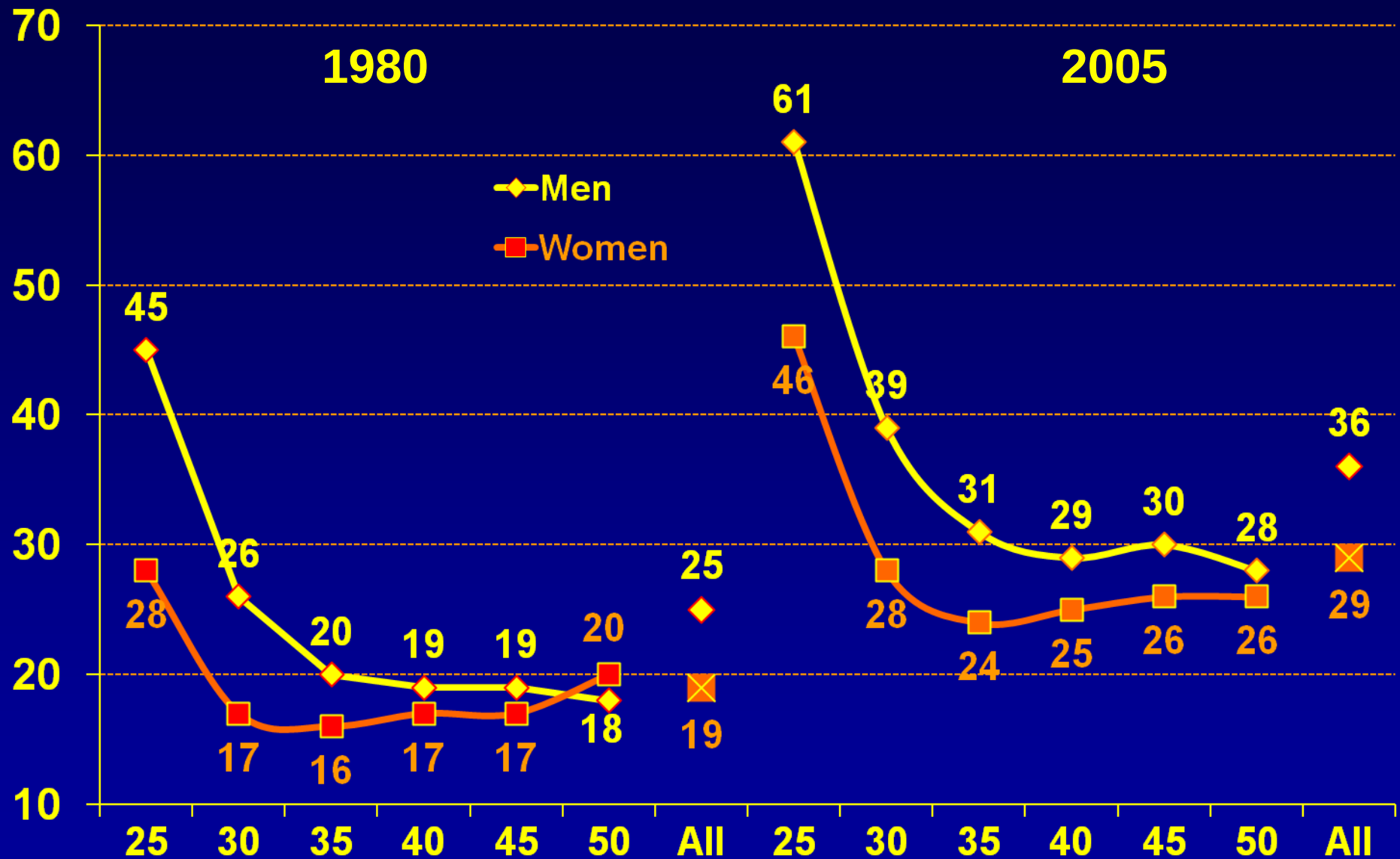


IVF registry, Danish Health Board

Childless women (%) at age 49



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

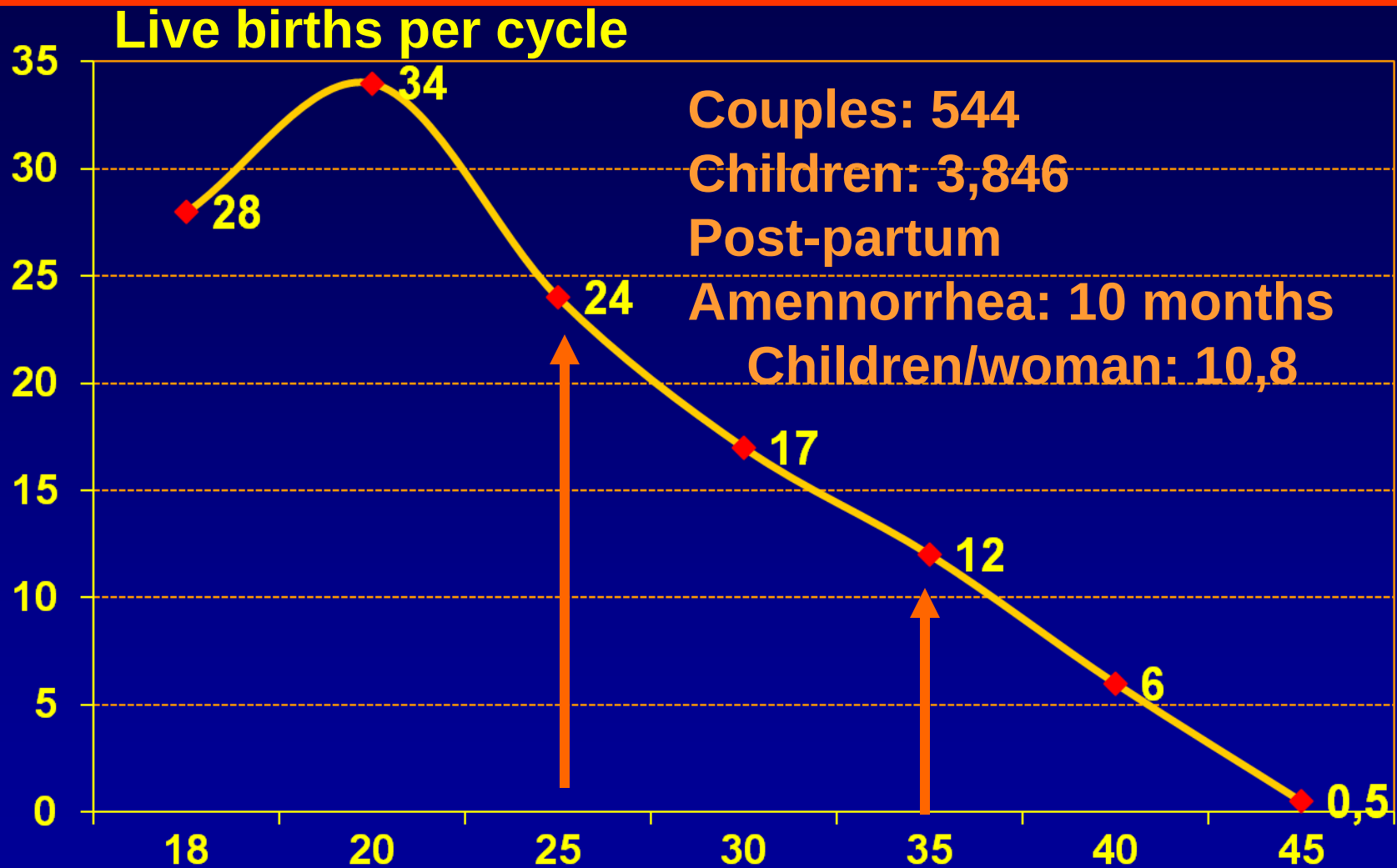
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Hvad er en kvinde, og hvad kan hun

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

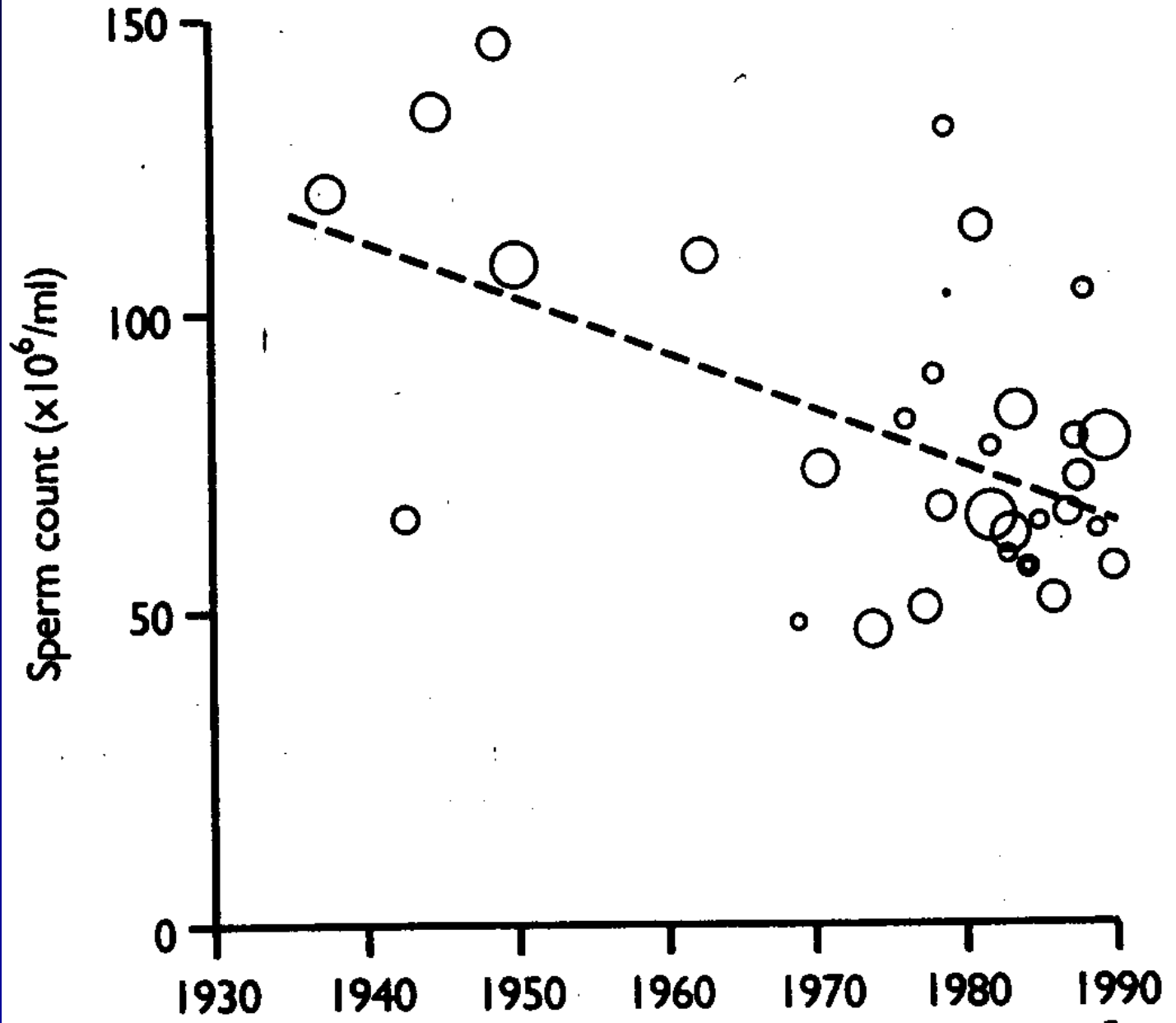
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Sperm count by time

61 papers
14,947 men

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

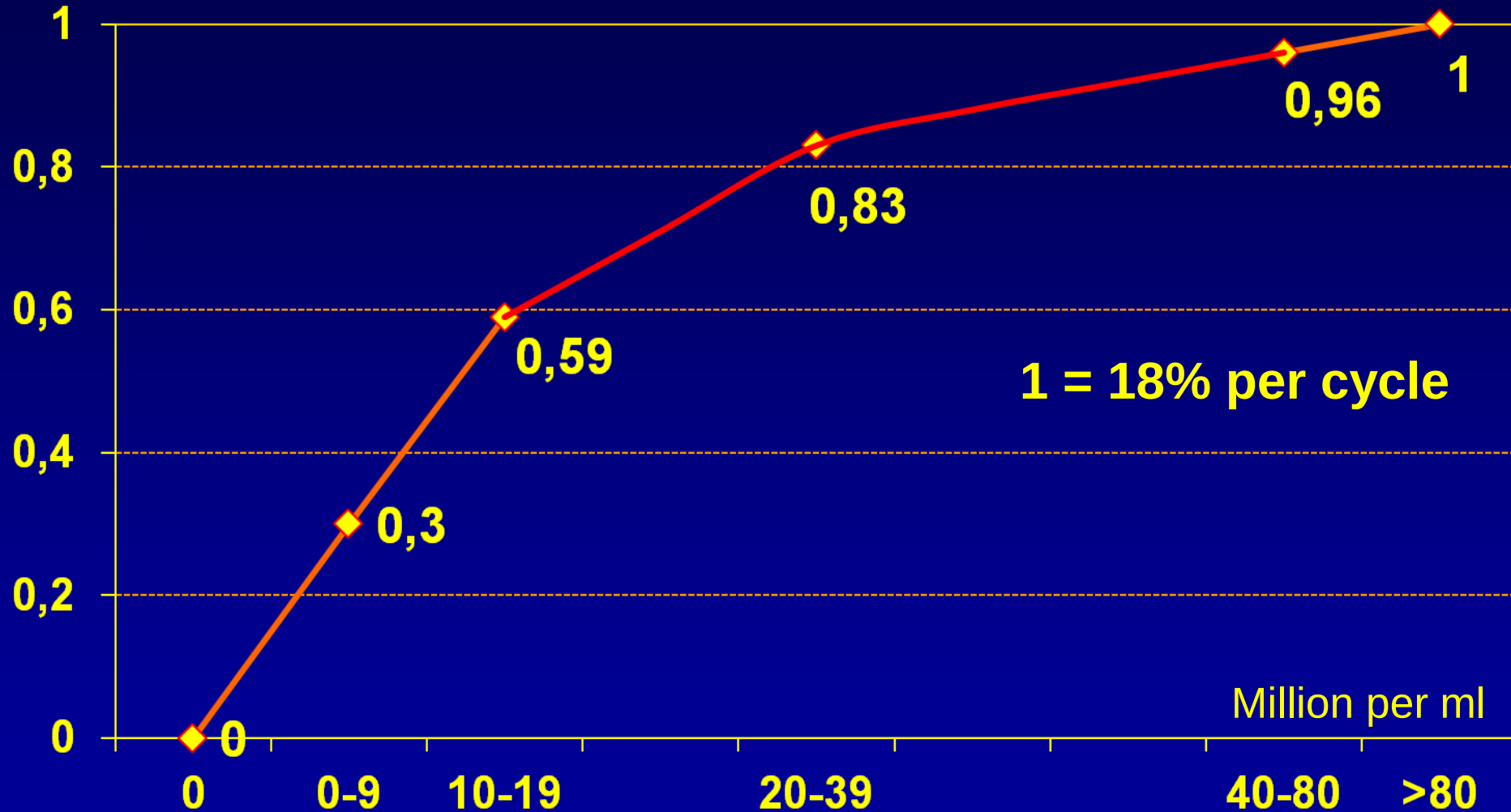


Sperm count and fecundity

- 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**

Particip. **300** **240** **324** **104**

Period **97-99** **1998** **98-00** **97-99**

Sperm count in mio/ml (median)

All **41** **41** **54** **57**

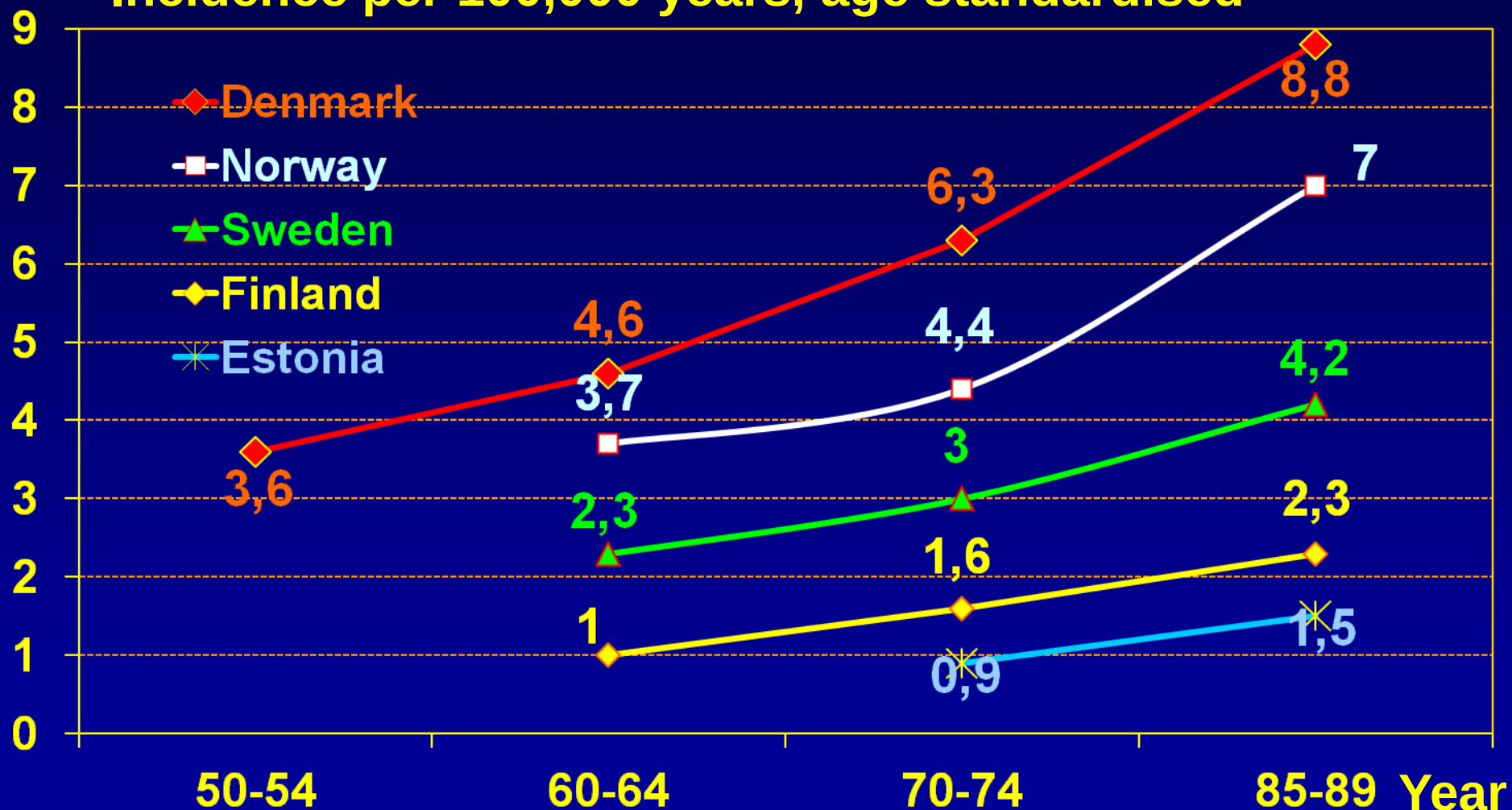
Clean **45** **42** **53** **63**

West-east gradient

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

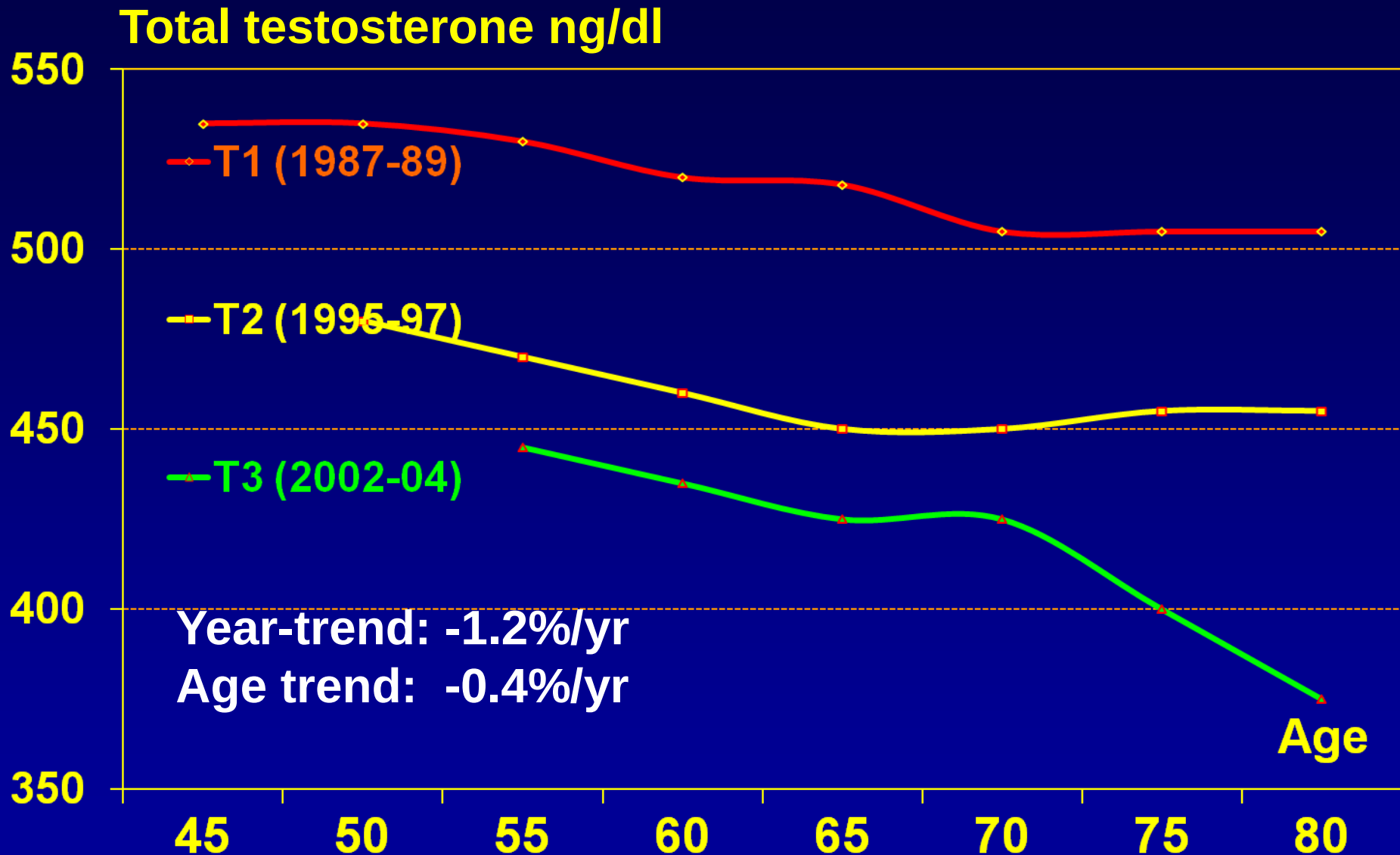
Testicular cancer: west-east gradient

Incidence per 100,000 years, age standardised



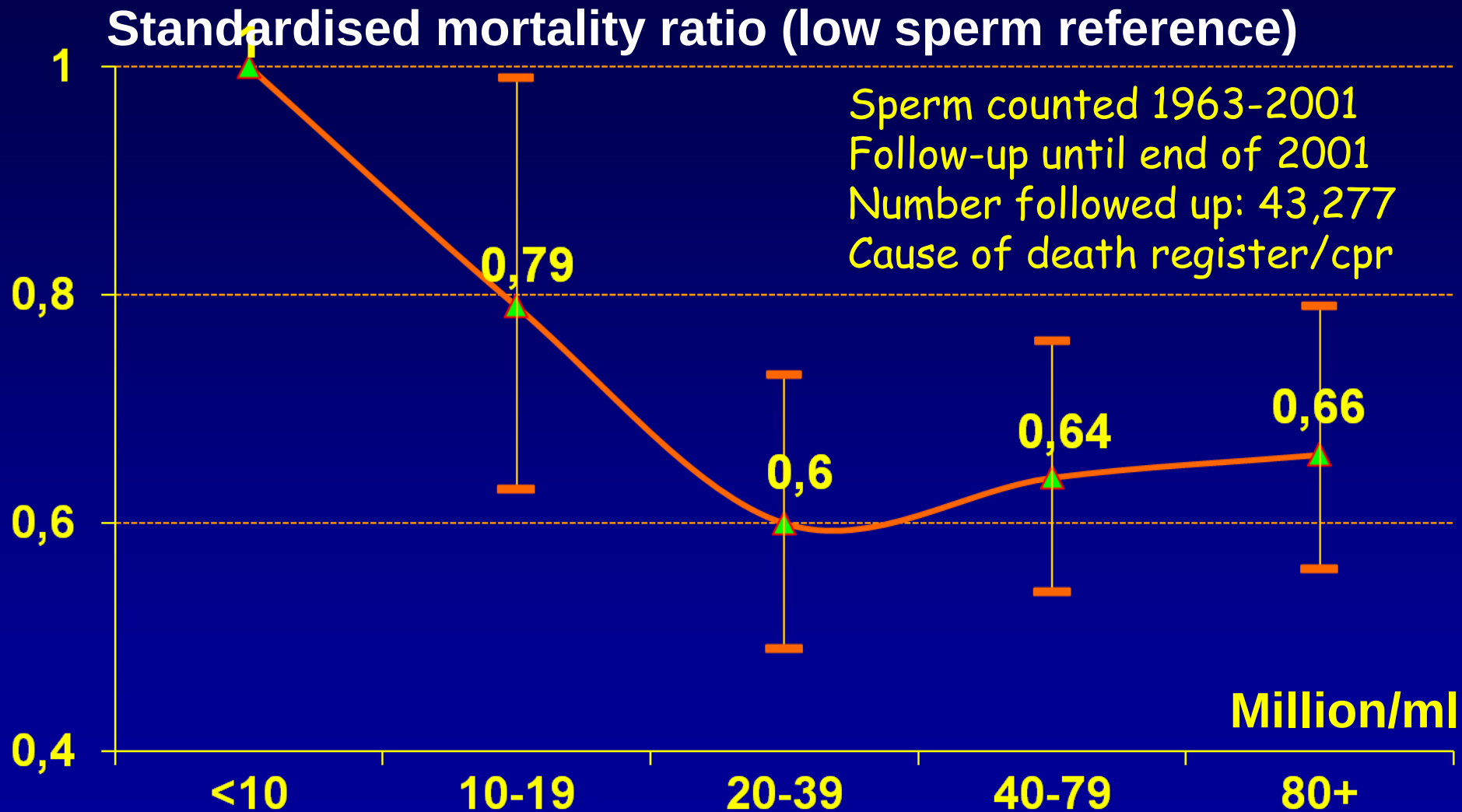
Adami et al. Int J Cancer 1994; 59: 33-38.

Testosterone: Does it change?

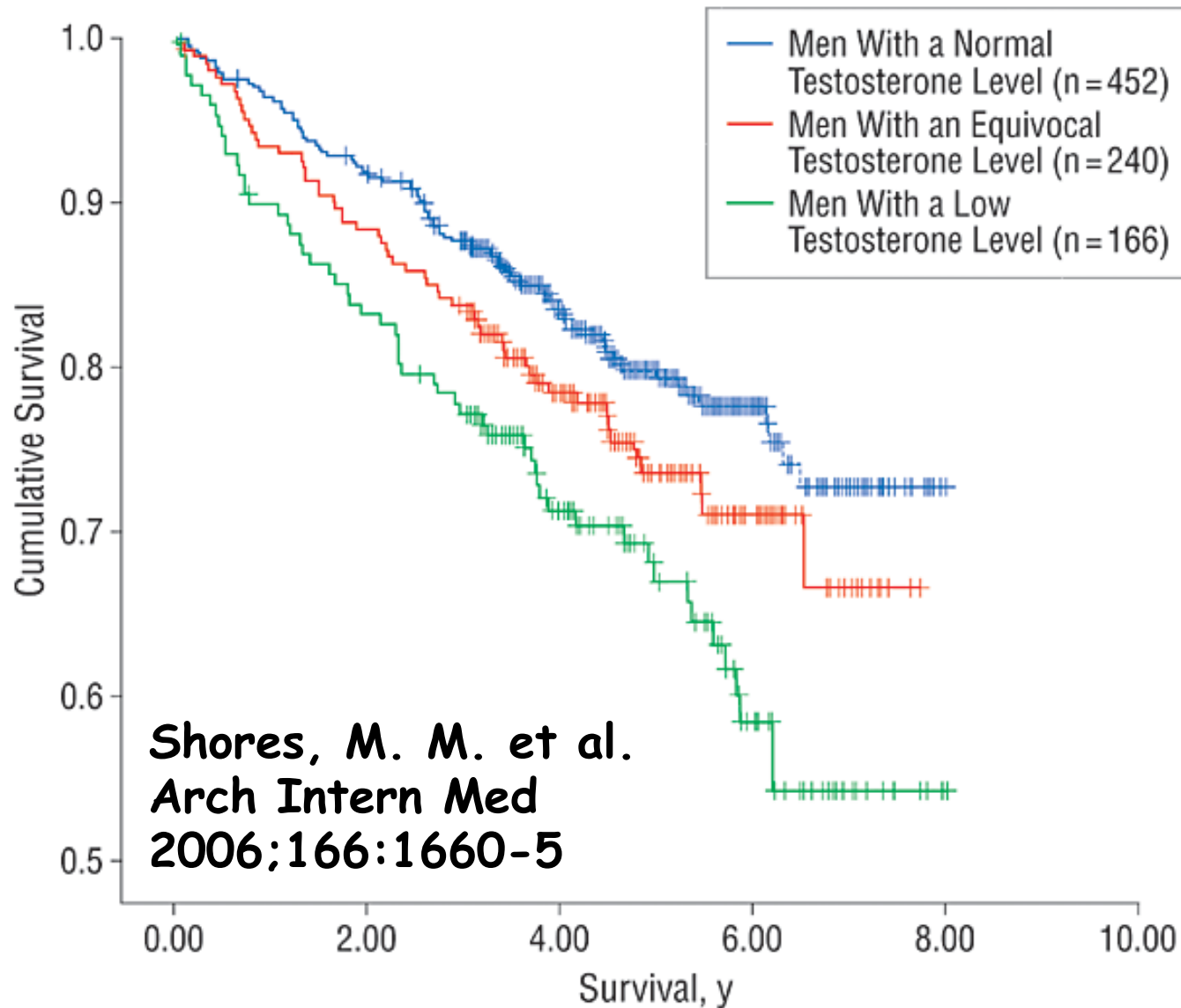


Travison et al. J Clin Endocrinol Metab 2007; 92: 196-202

Sperm count and mortality



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.

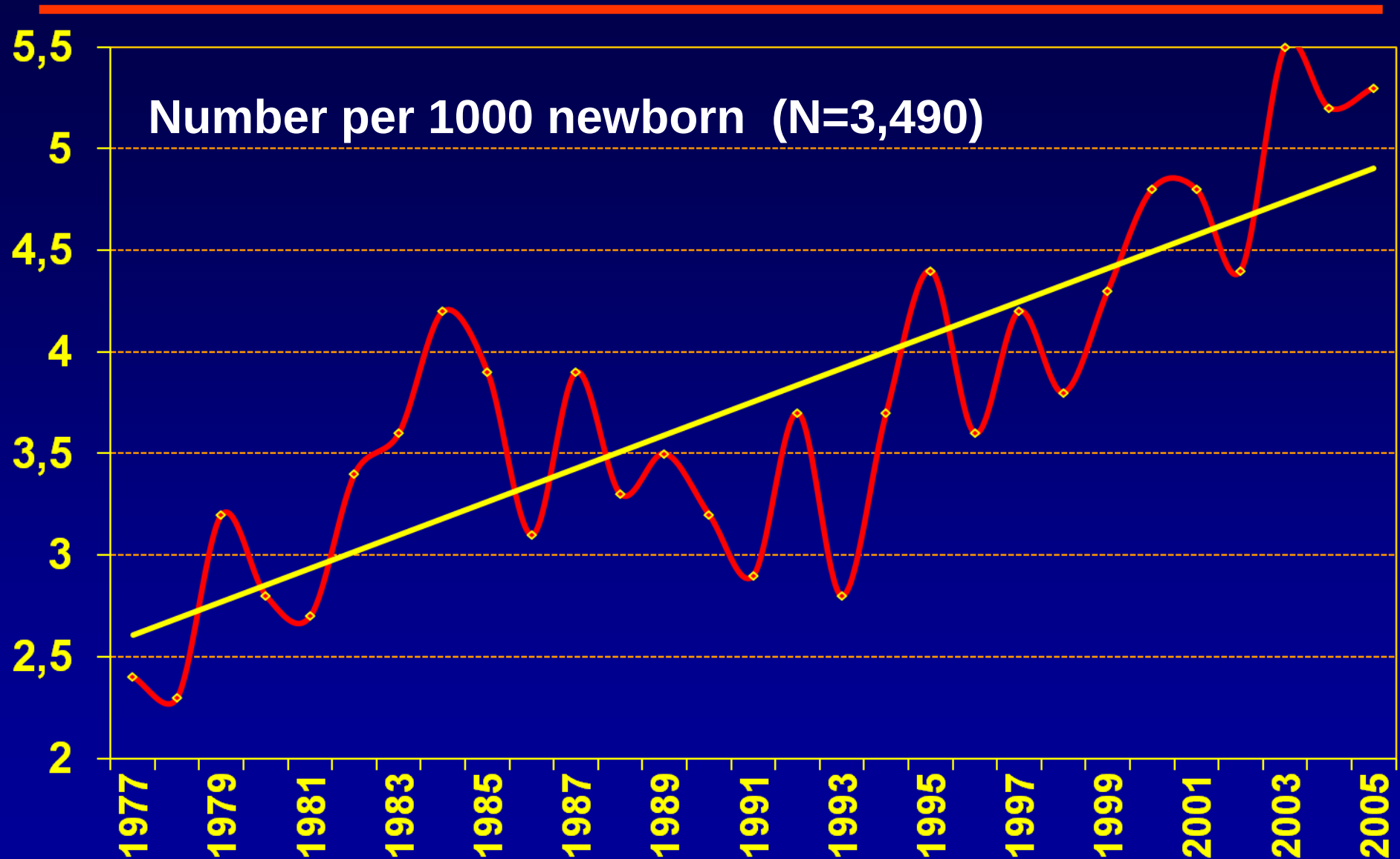
Testosterone and metabolic syndrome

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)

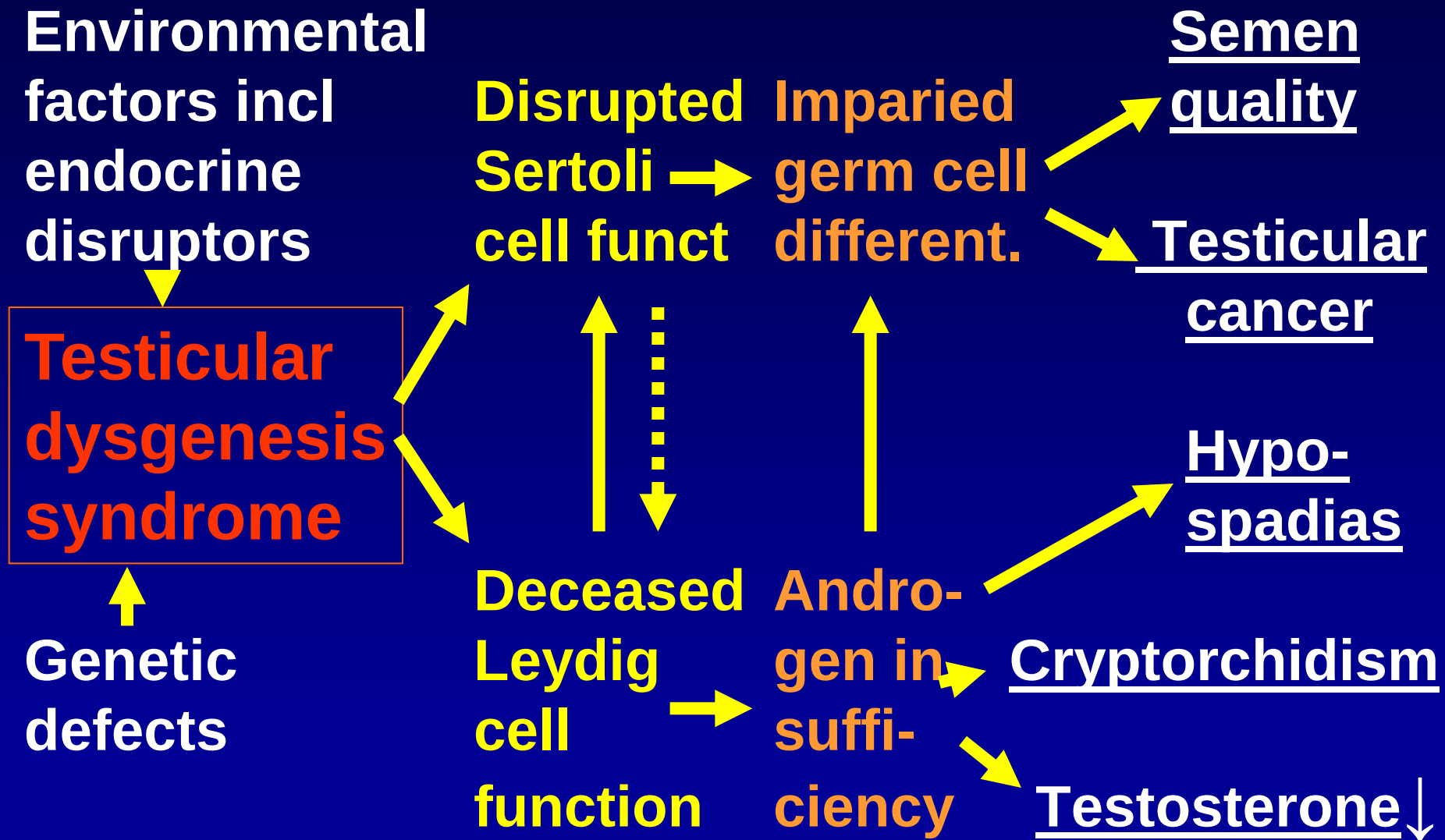
	Prevalence ratio	
Total testosterone	Model 2	Model 3
1st quartile (low)	4.0 (2.6-6.1)	2.2 (1.5-3.1)
2nd quartile	4.1 (2.7-6.3)	2.5 (1.9-3.4)
3rd quartile	1.4 (0.8-2.3)	1.2 (0.8-2.0)
4th quartile (high)	1	1

Hypospadias in DK 1977-2005



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

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

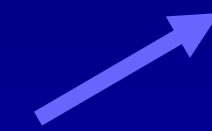
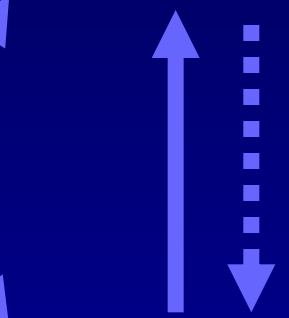
Testicular cancer

Hypo-spadias

Testicular maldescend

Decreased Leydig cell function

Androgen insufficiency



Phthalate exposure and anogenital distance (AGD) in male infants

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

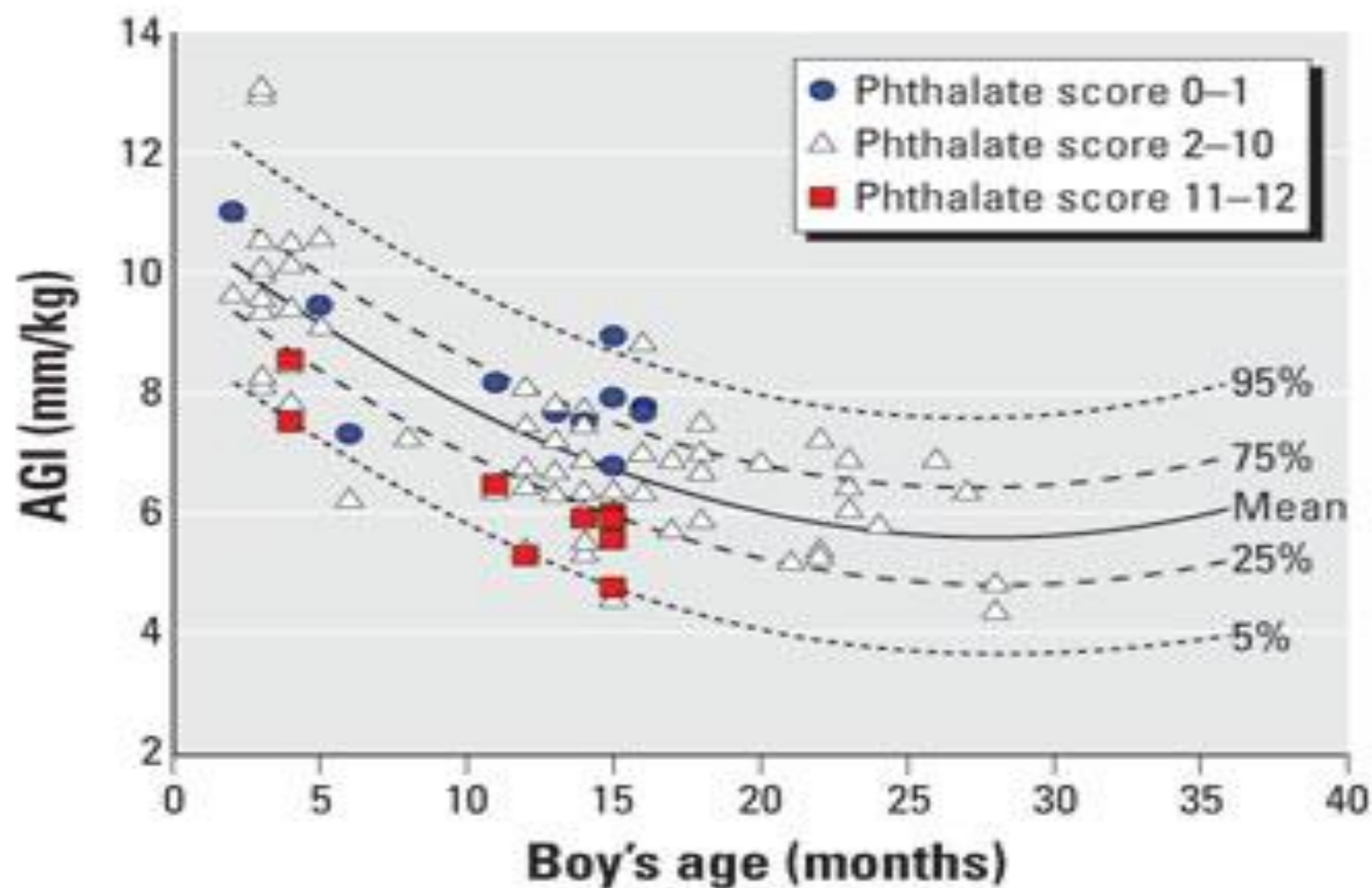


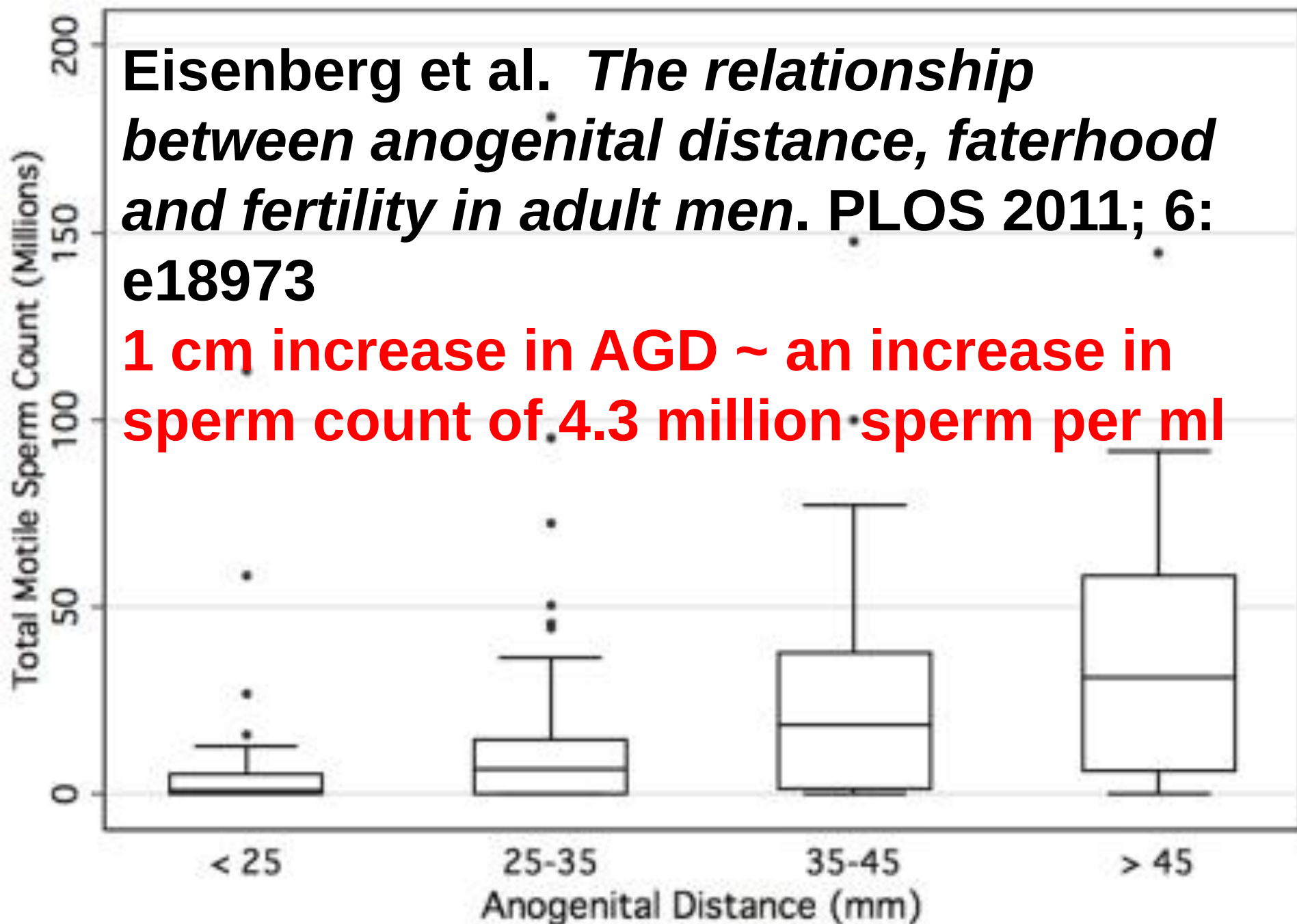
Figure 1. Mean AGI (mm/kg) in relation to boys' age at examination (months).

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.

Eisenberg et al. *The relationship between anogenital distance, fatherhood 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



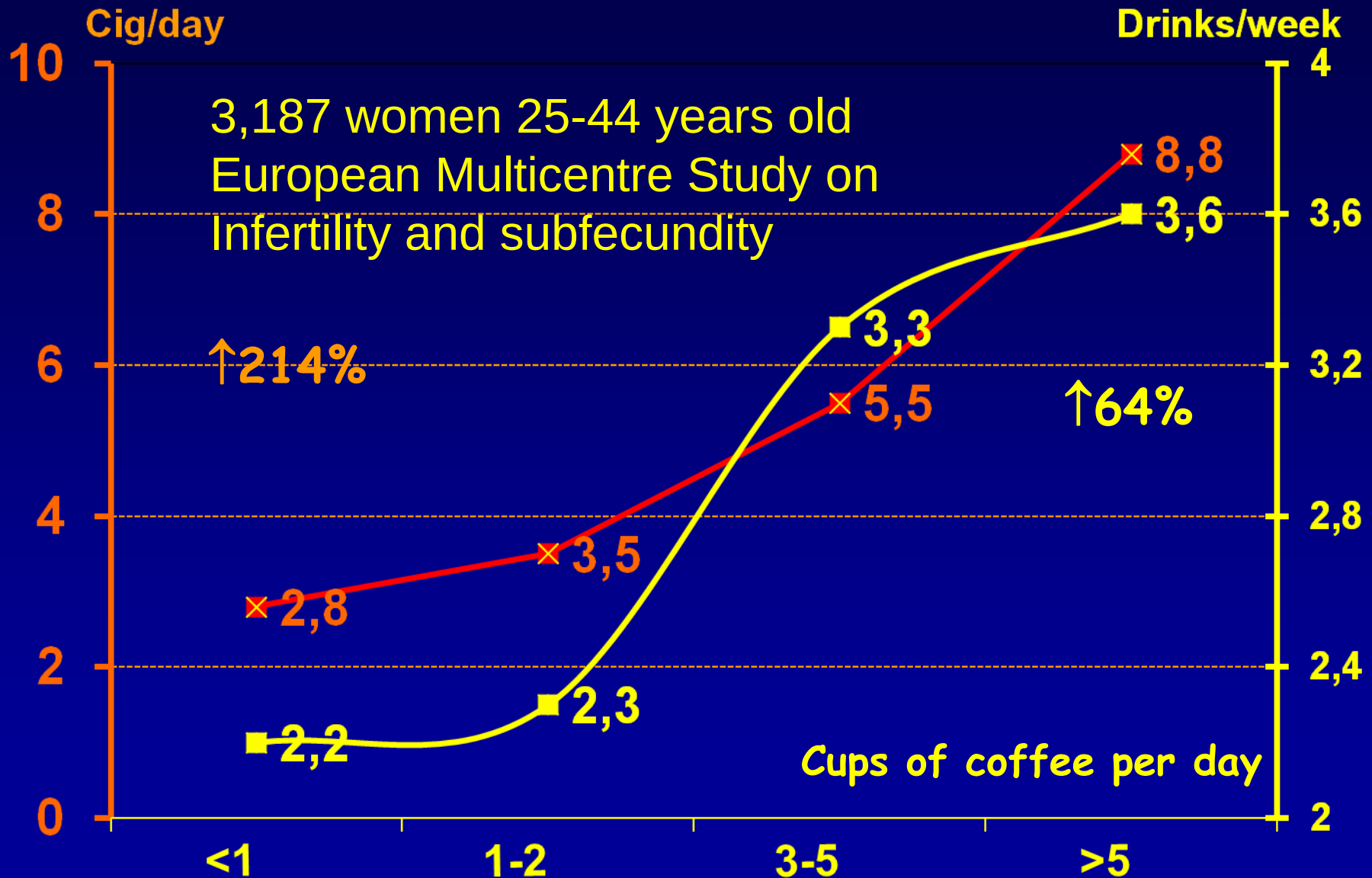
Konklusion

- 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

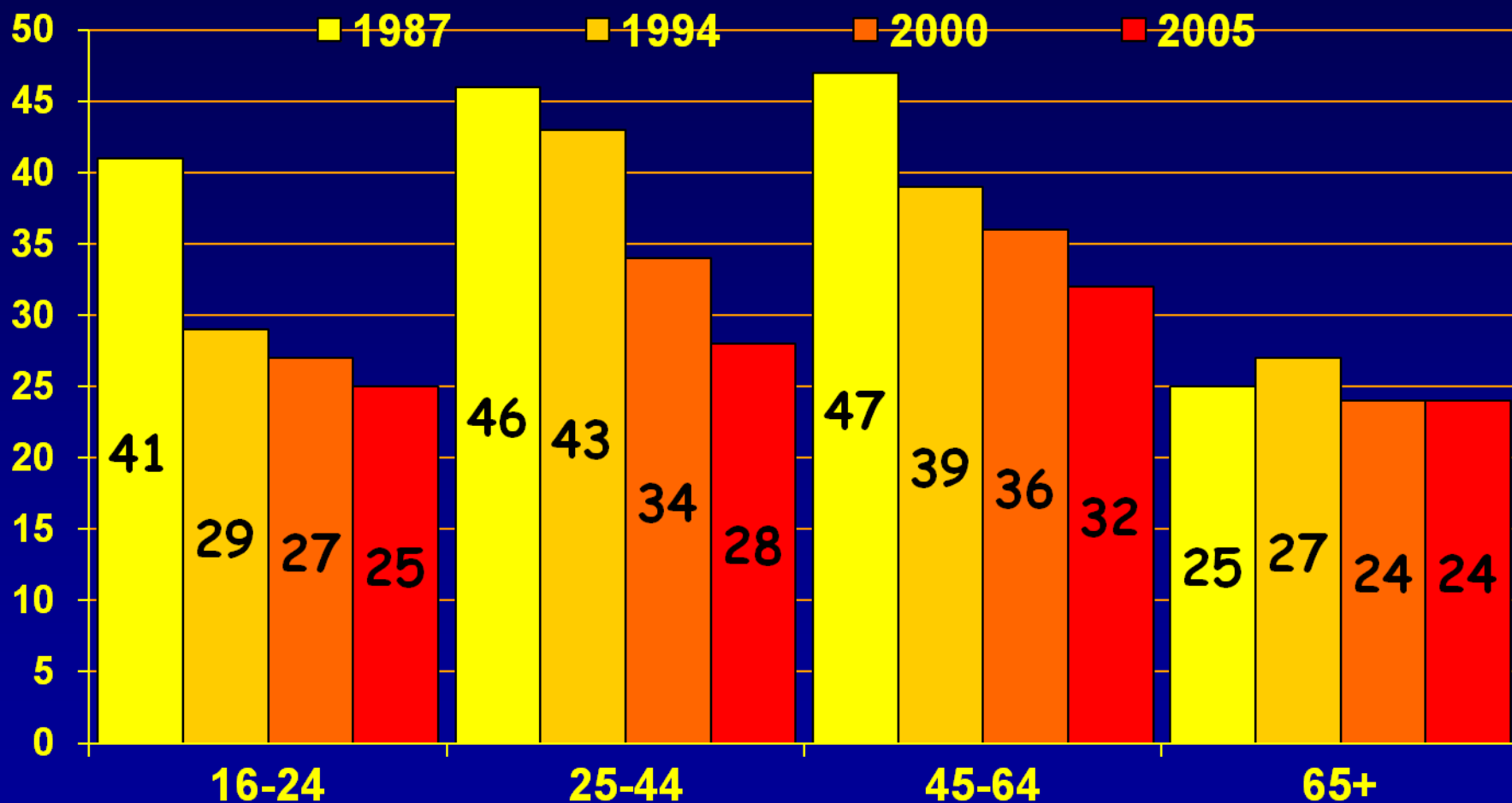
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Naughty girls



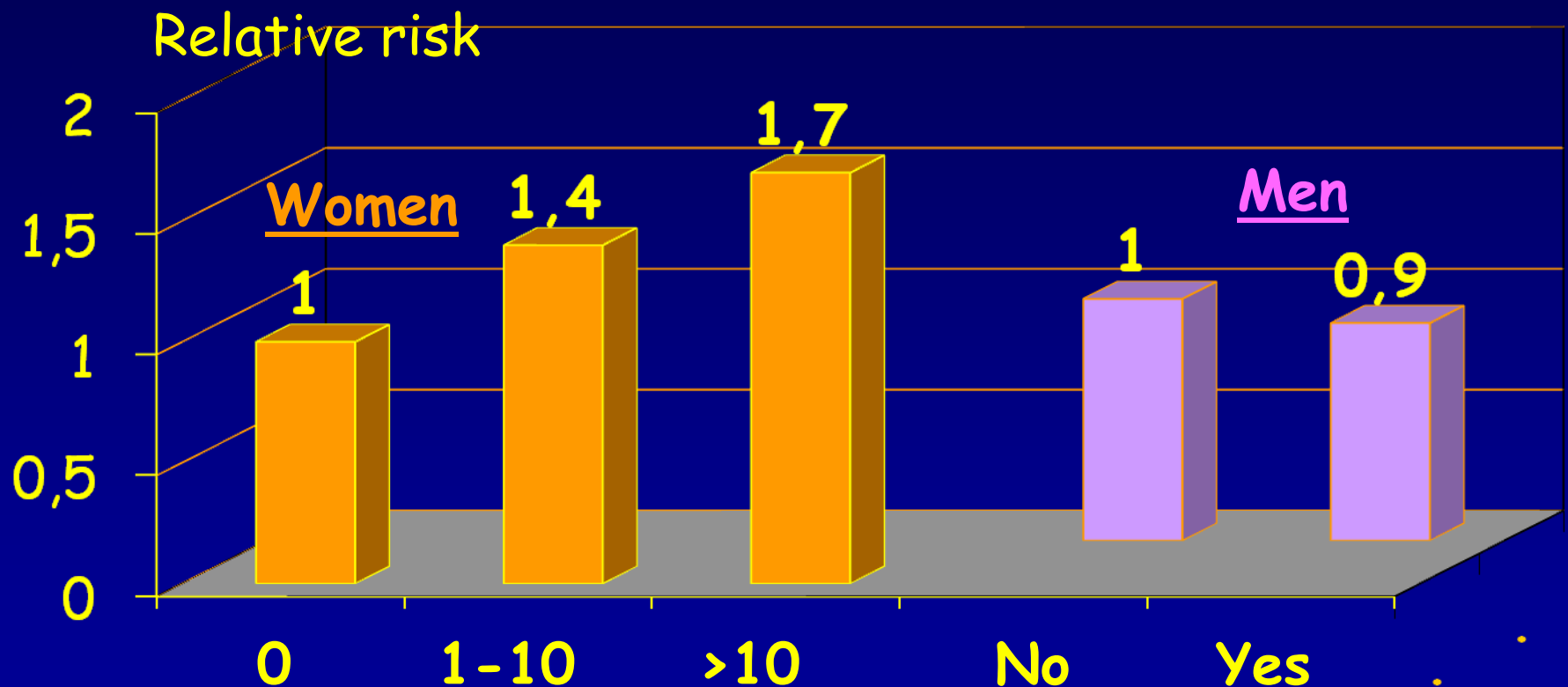
Bolumar et al. Am J Epidemiology 1997; 145: 324-34.

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



Fertility and smoking

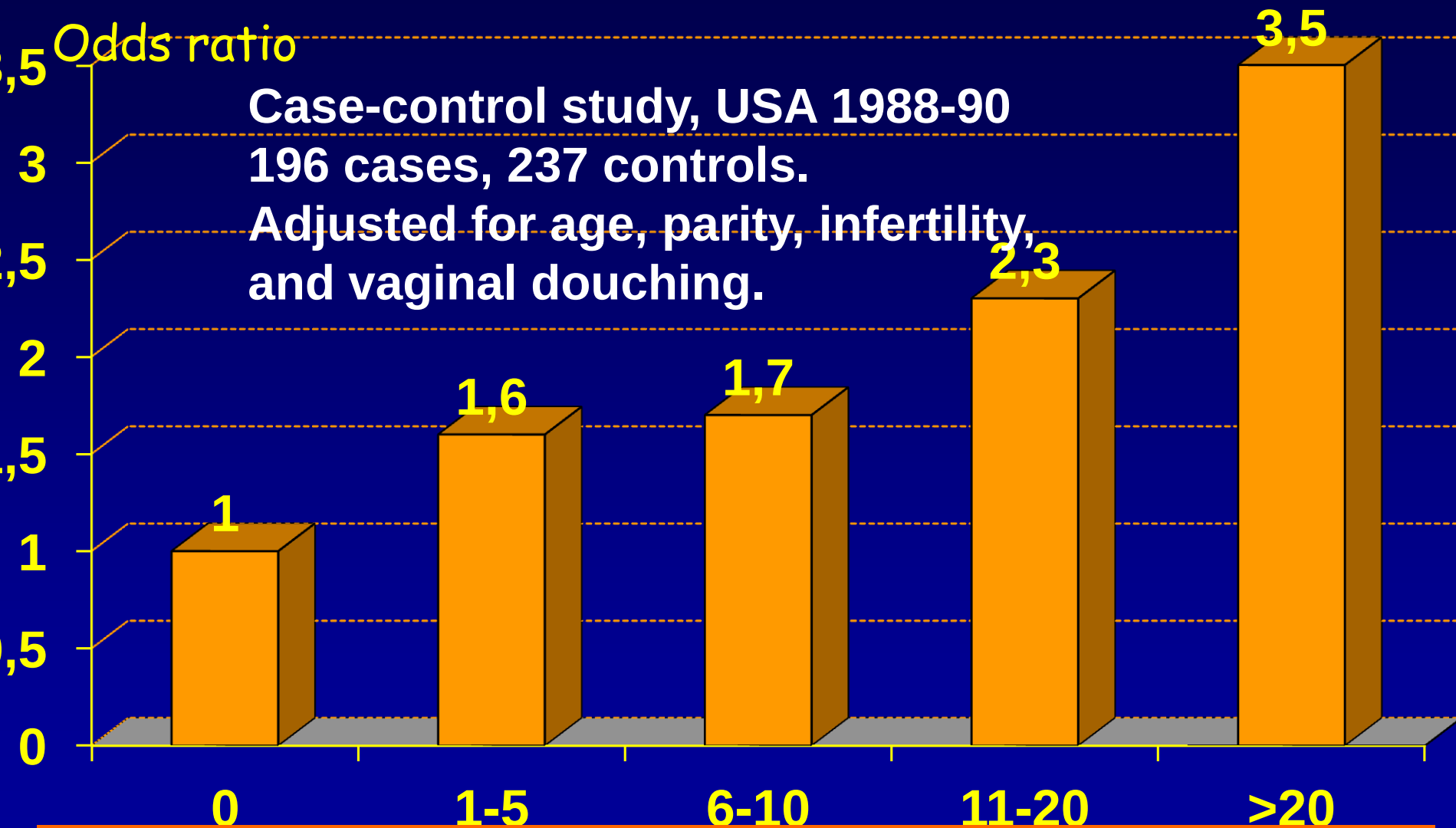
Risk of waiting time >9,4 months



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

Li/01

Smoking and ectopic pregnancy



Smoking and clinical IVF pregnancy

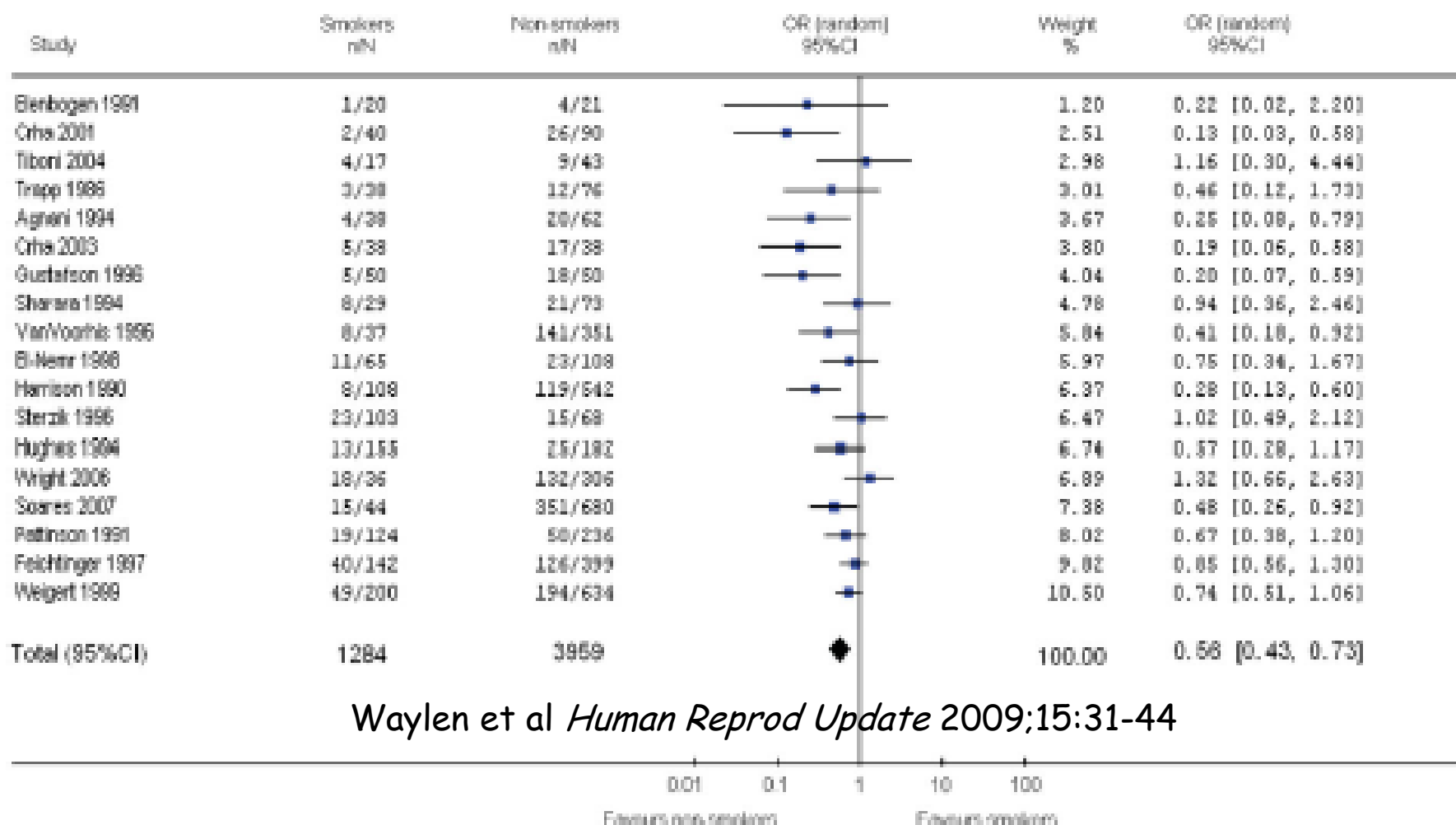


Figure 2 Odds ratio of clinical pregnancy rate per cycle.

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

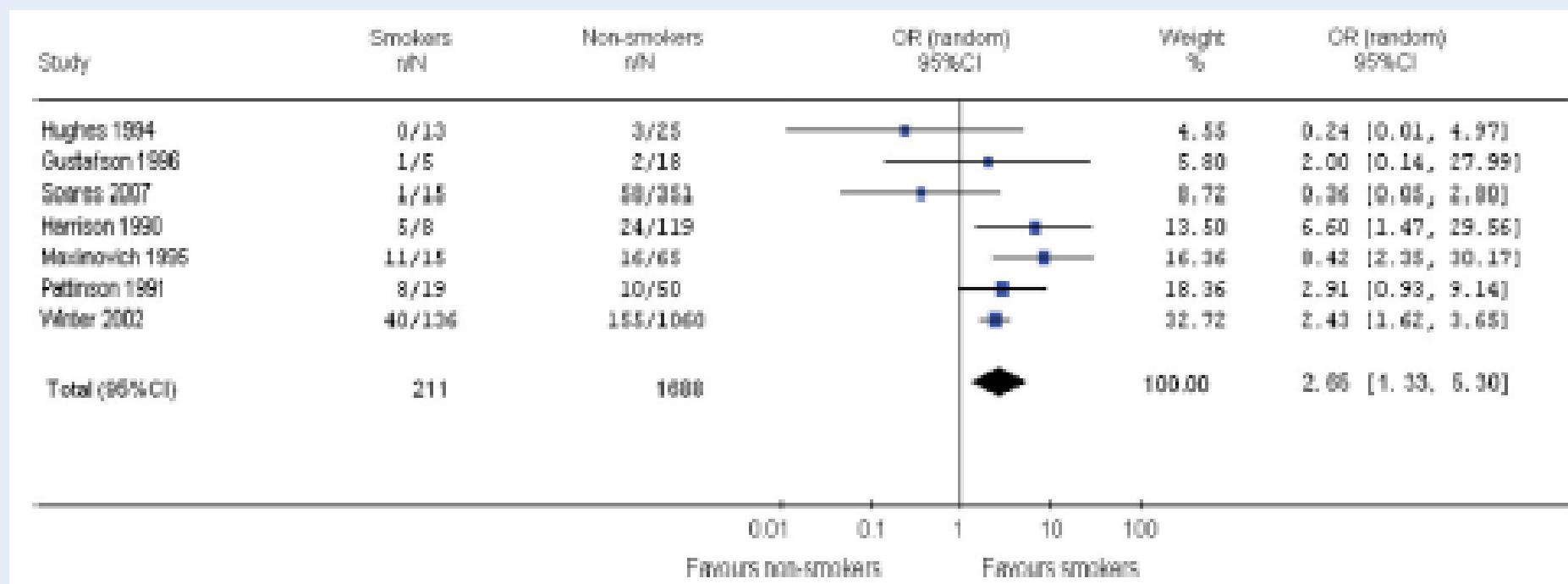


Figure 3 Odds ratio of miscarriage per pregnancy.

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: $z = 2.77$ ($P = 0.006$).

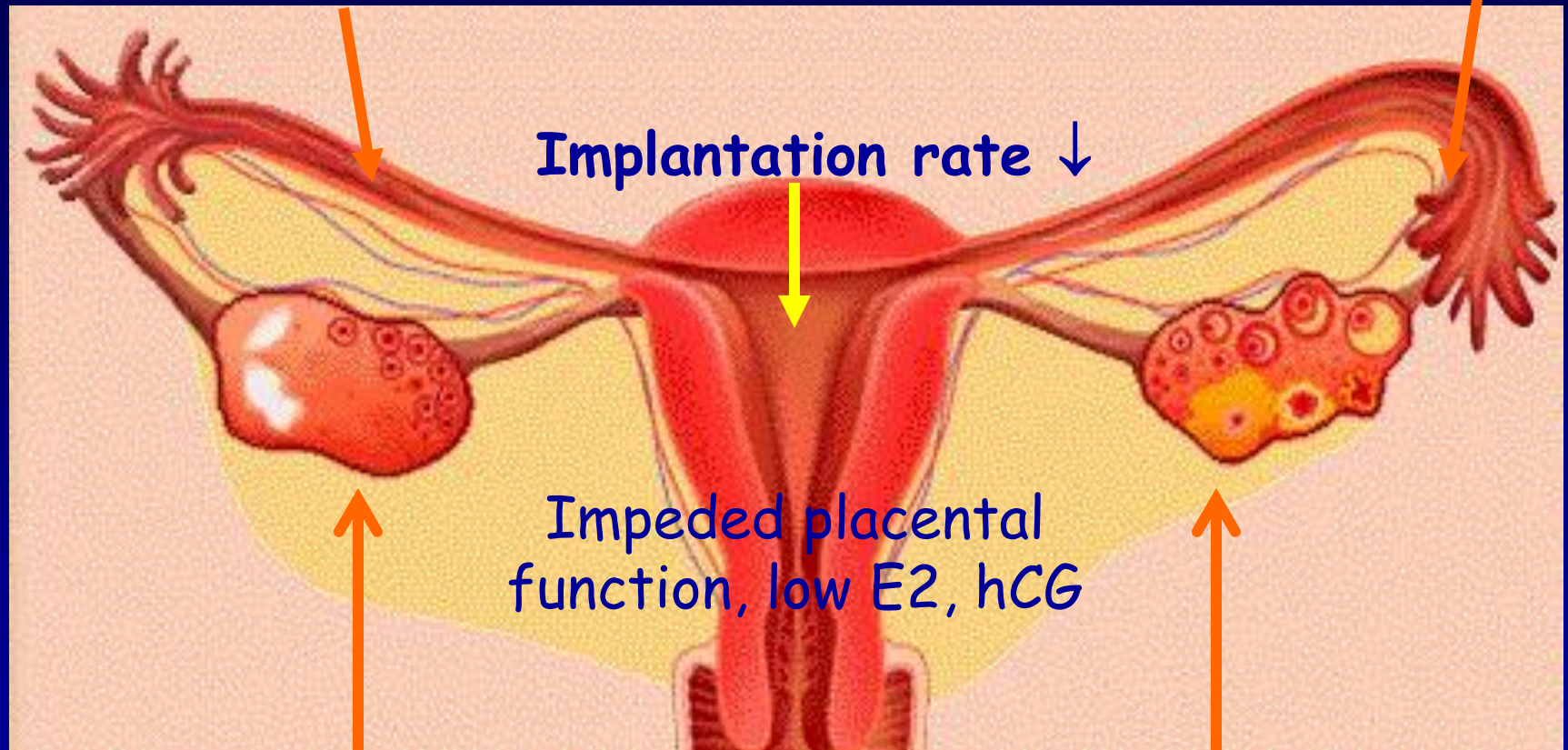
Conclusion:

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

Smoking and fertility

Impeded ciliary function:

Pick-up function ↓



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
-

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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

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

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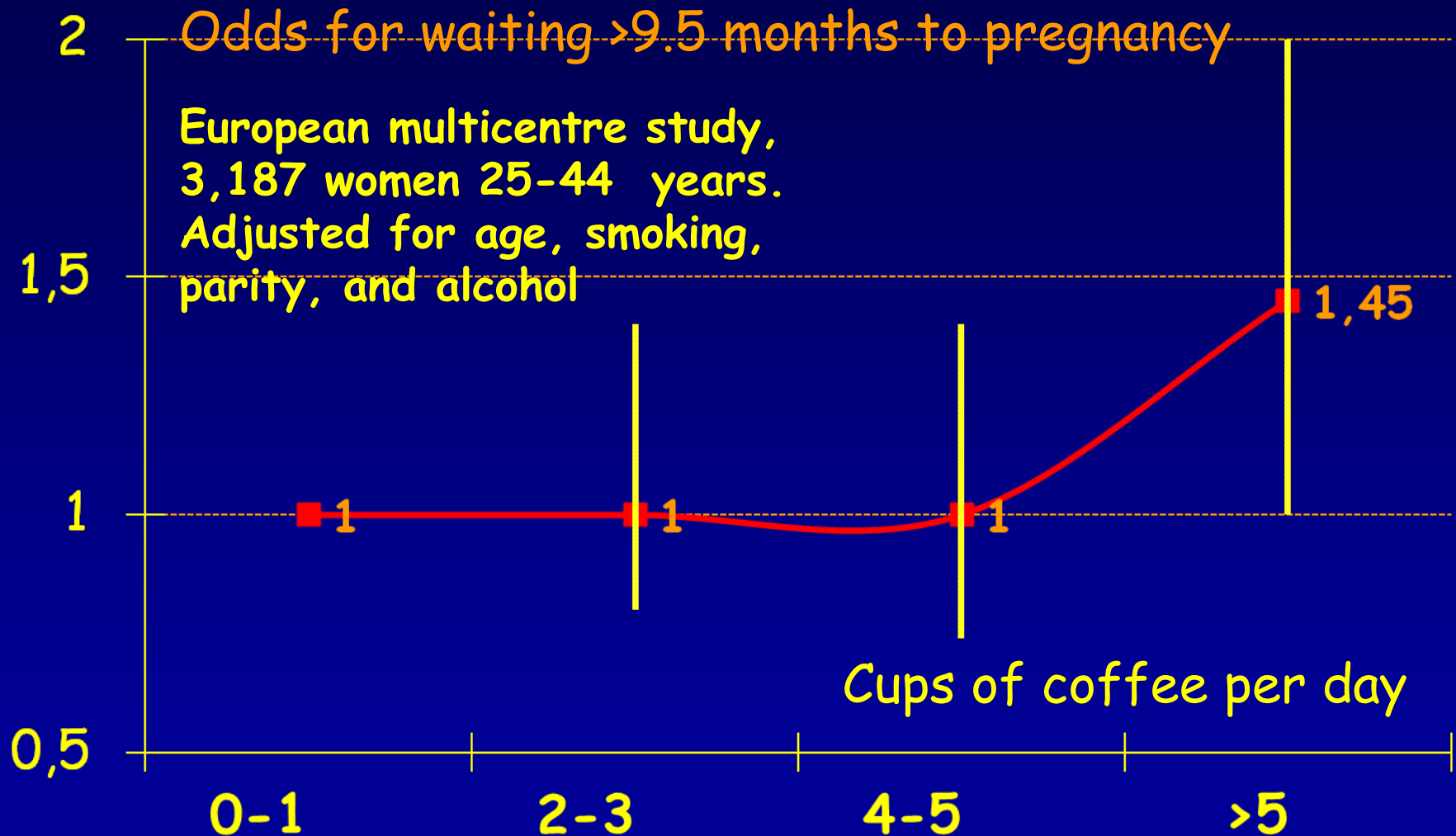
Koffein

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



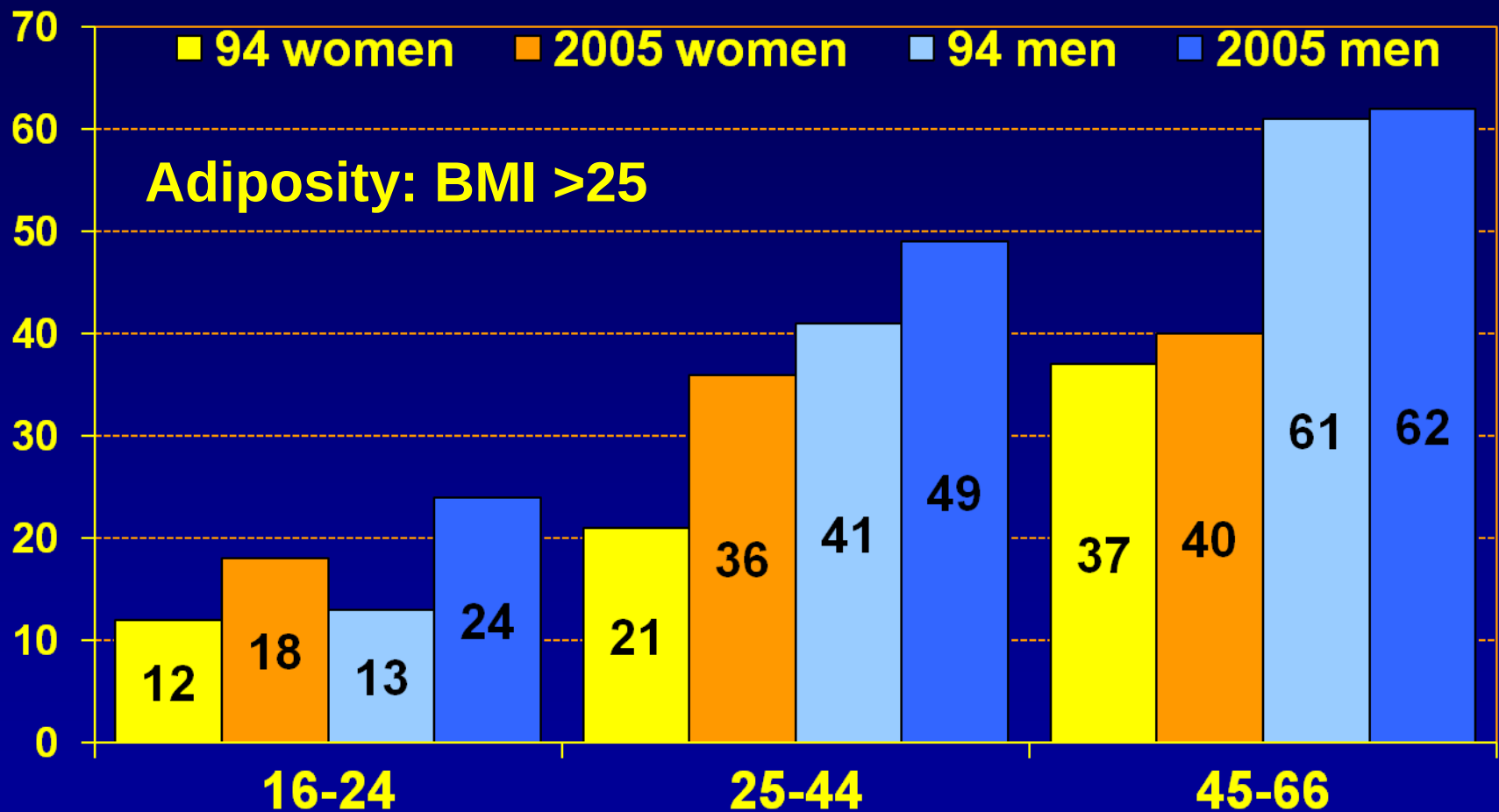
Kaffe og fertilitet: Konklusion

- 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)
-

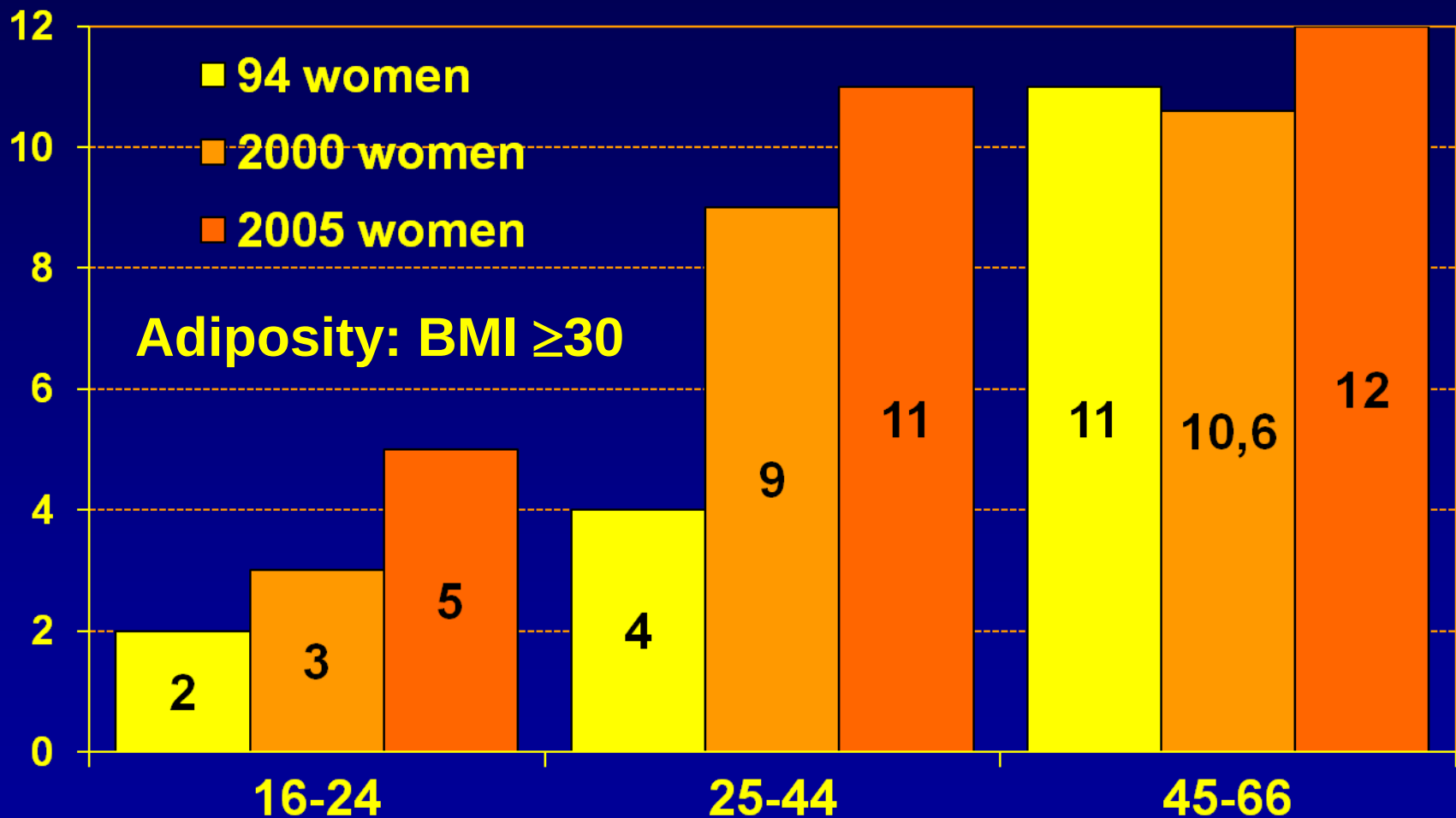
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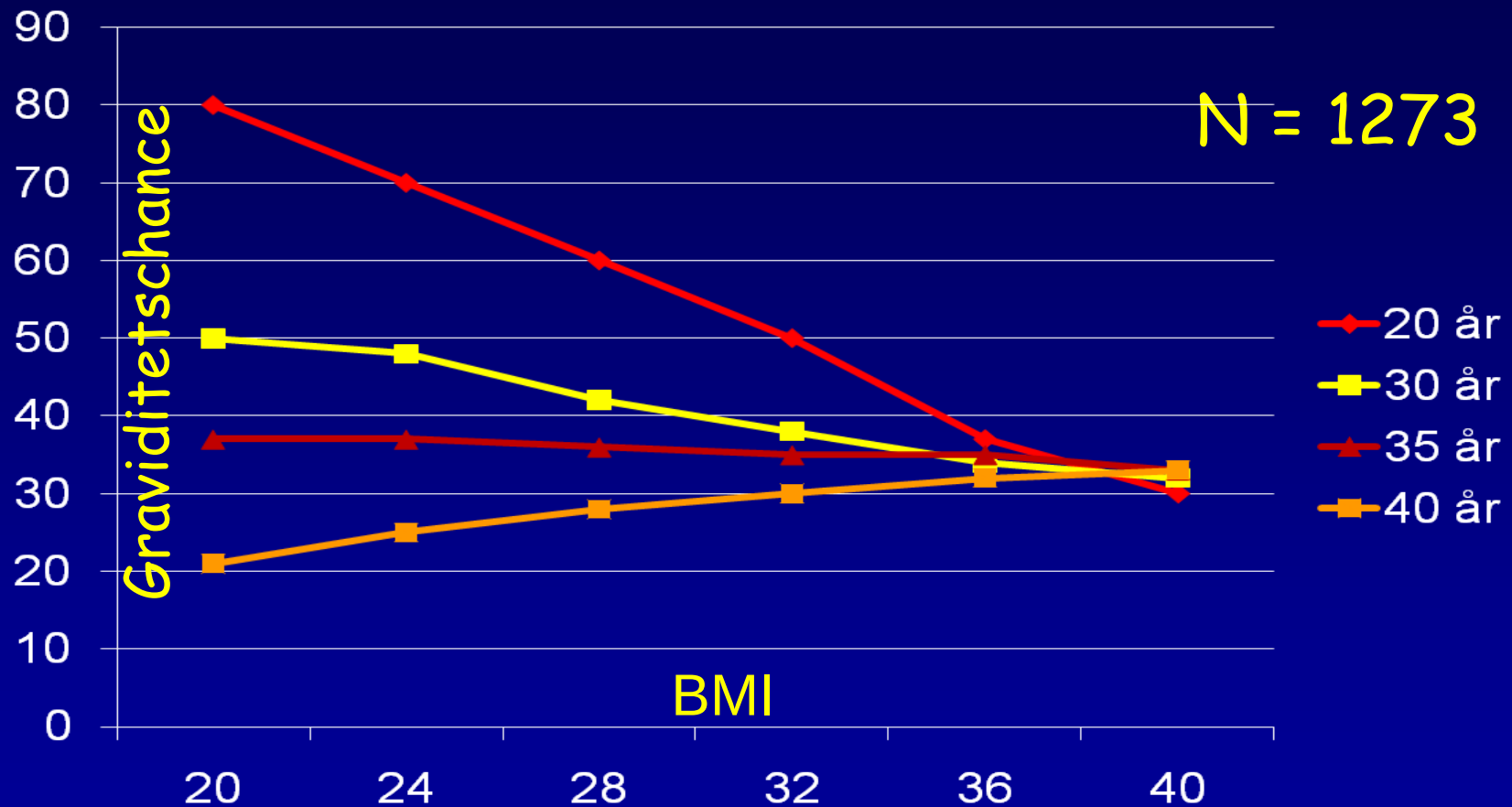
Adiposity in Danish women and men in 1994 and 2005. N=16,000



Severe adiposity in Danish women in 1994, 2000 and 2005

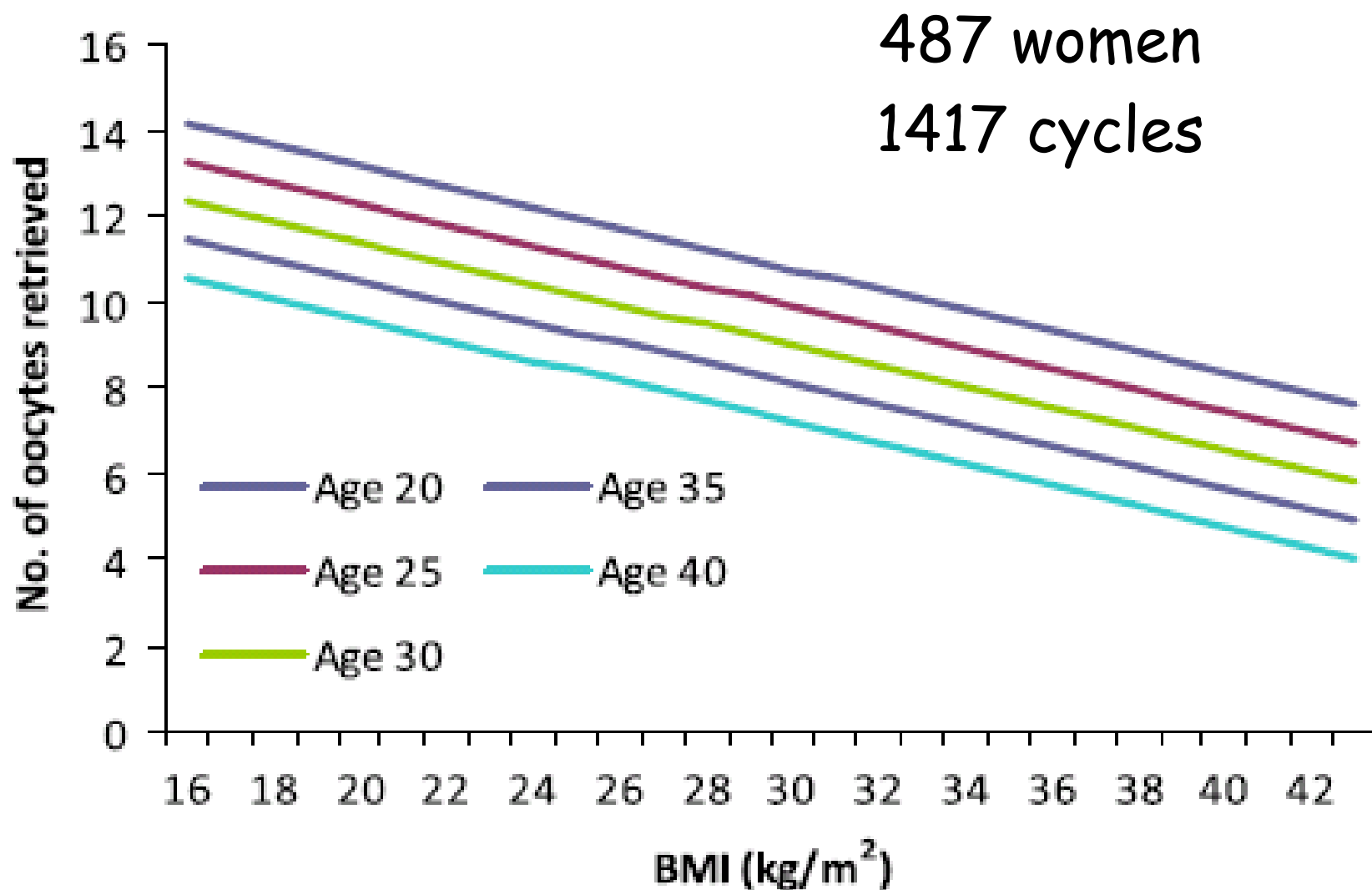


Effekten af BMI er aldersafhængig

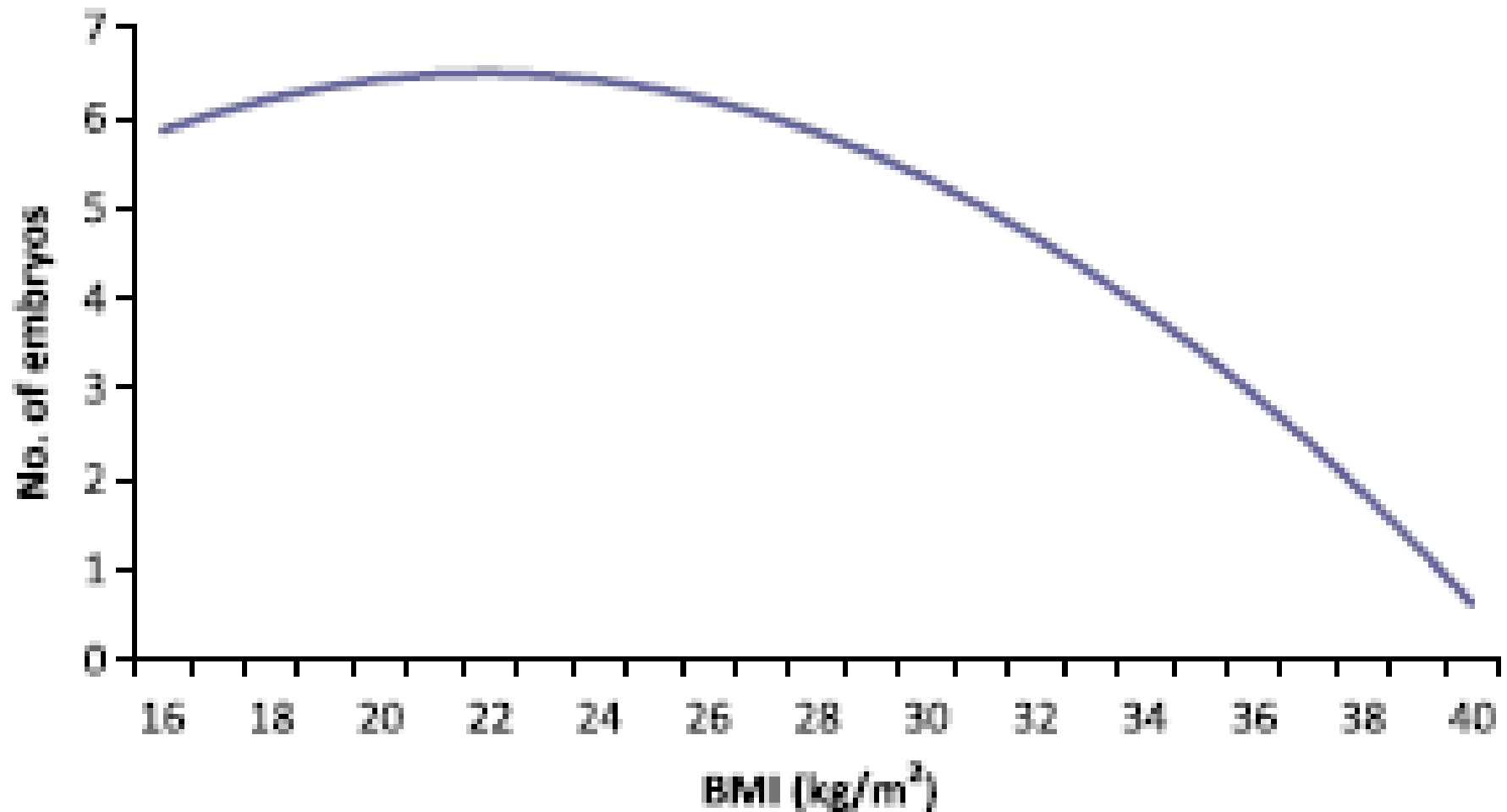


Sneed et al *Human Reprod* 2008; 23: 1835-1839

Expected oocytes retrieved by IVF

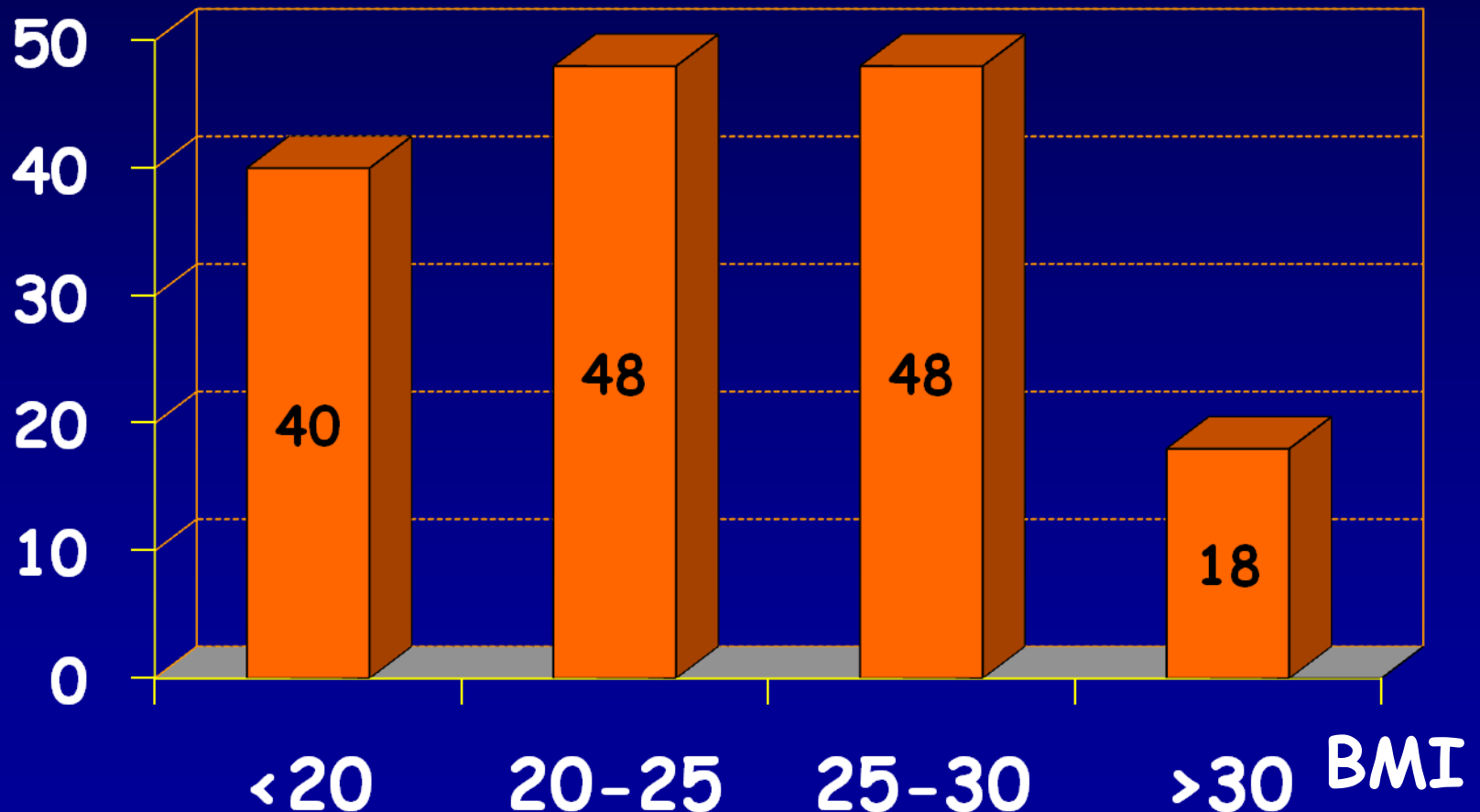


Expected embryos according to BMI



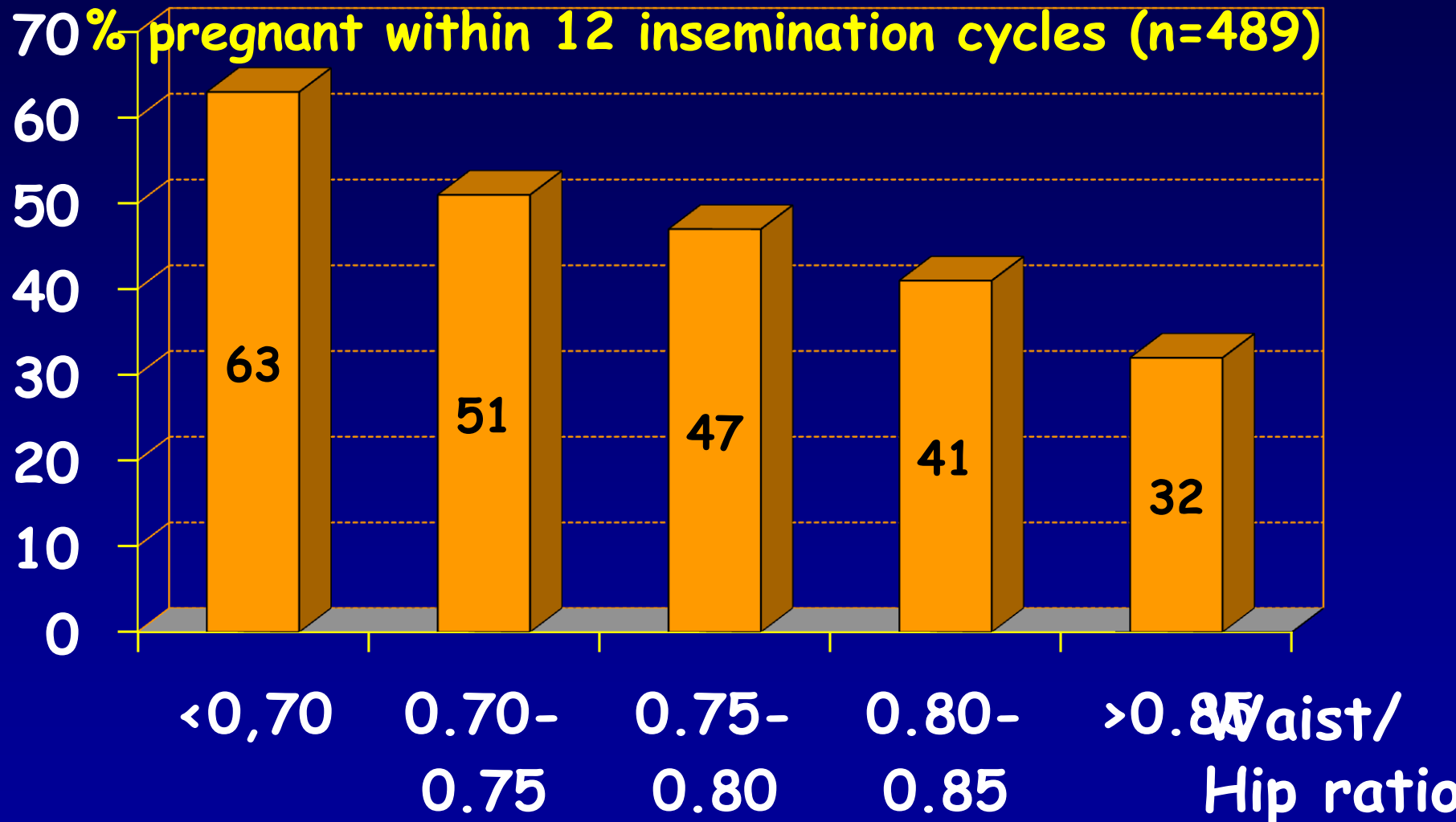
Fat and fecundity

% pregnant within 12 insemination cycles (n=489)



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

Fat and fecundity

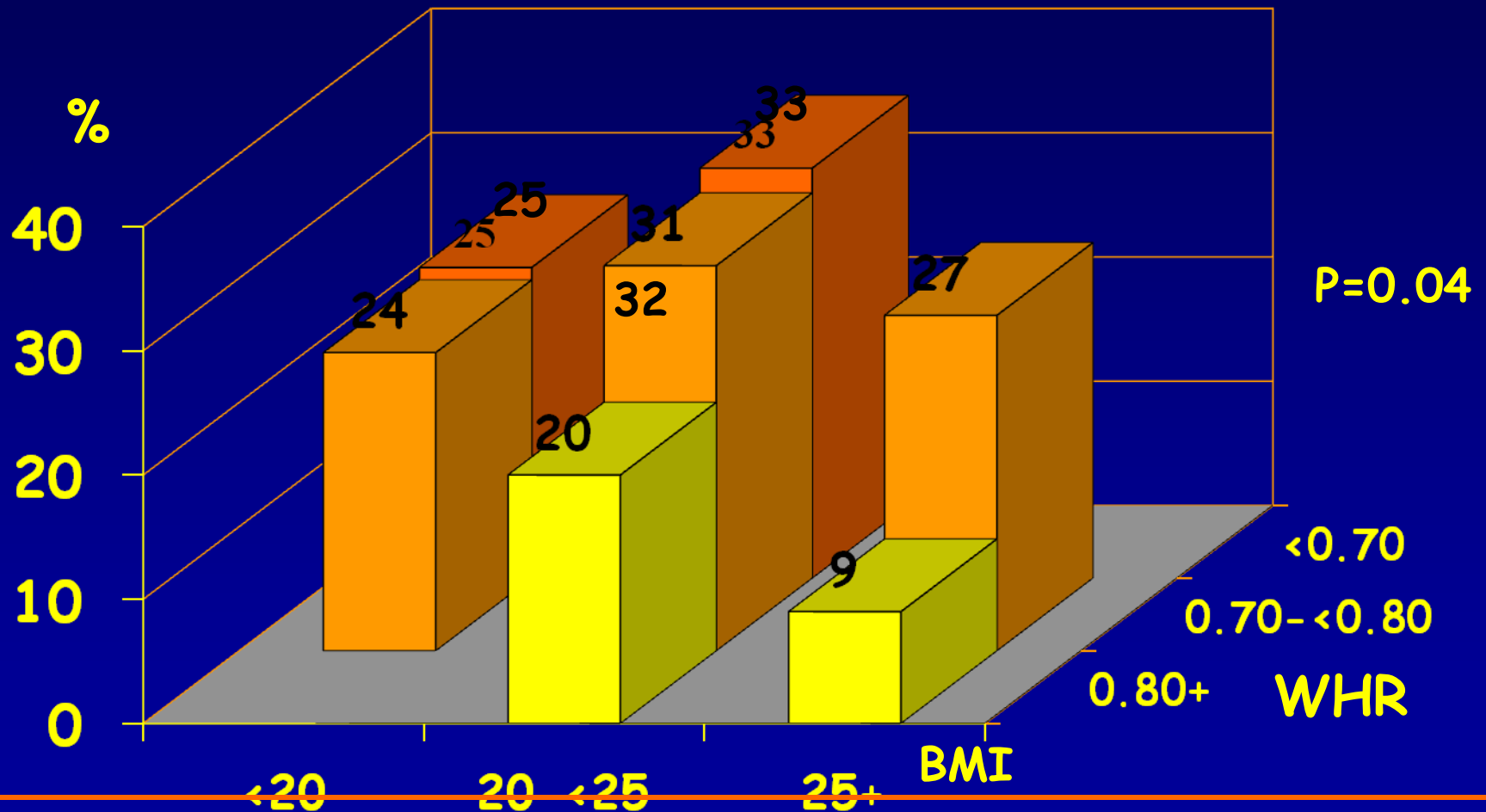


Zaadstra et al. BMJ 1993; 306: 484-7.

Fat and fecundity

Pregnancy rates in 220 IVF cycles

Pregnancy rate per cycle



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
