Infertilitets epidemiologi

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U-kursus

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Infertilitet epidemiologi

- **Definitioner**
- **Problemets 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

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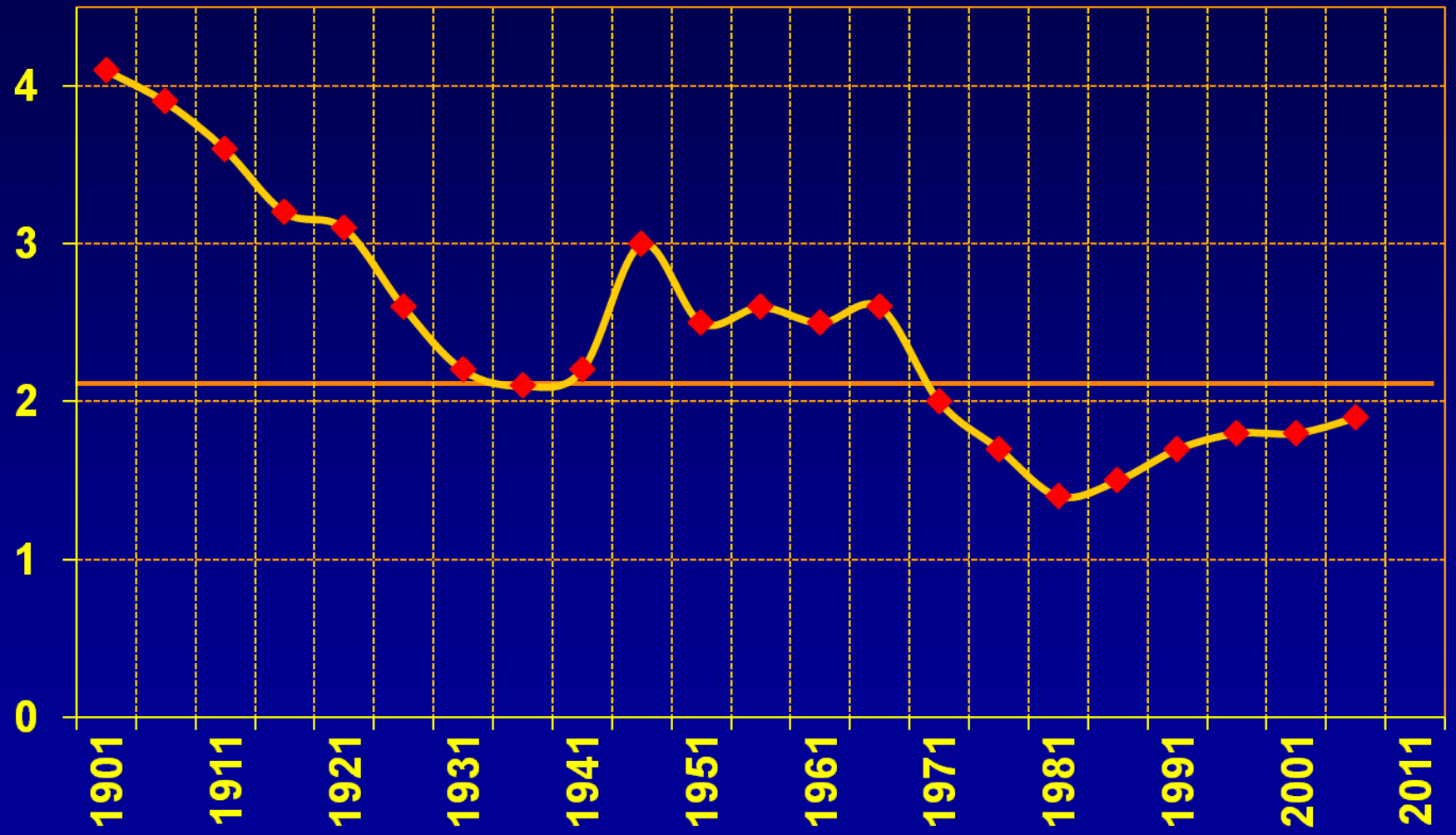
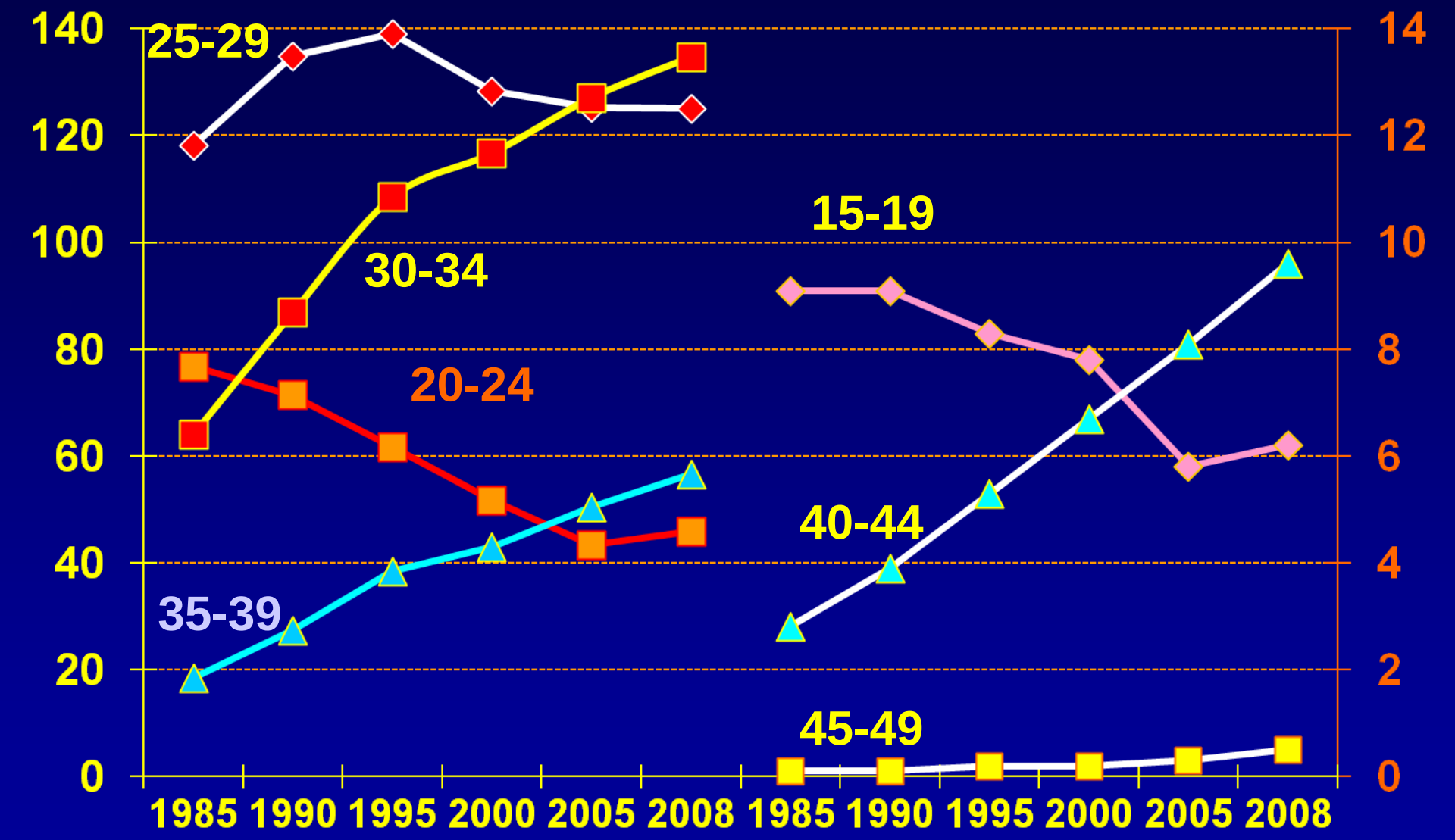
Total fecundity rate in DK 1901-2008



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

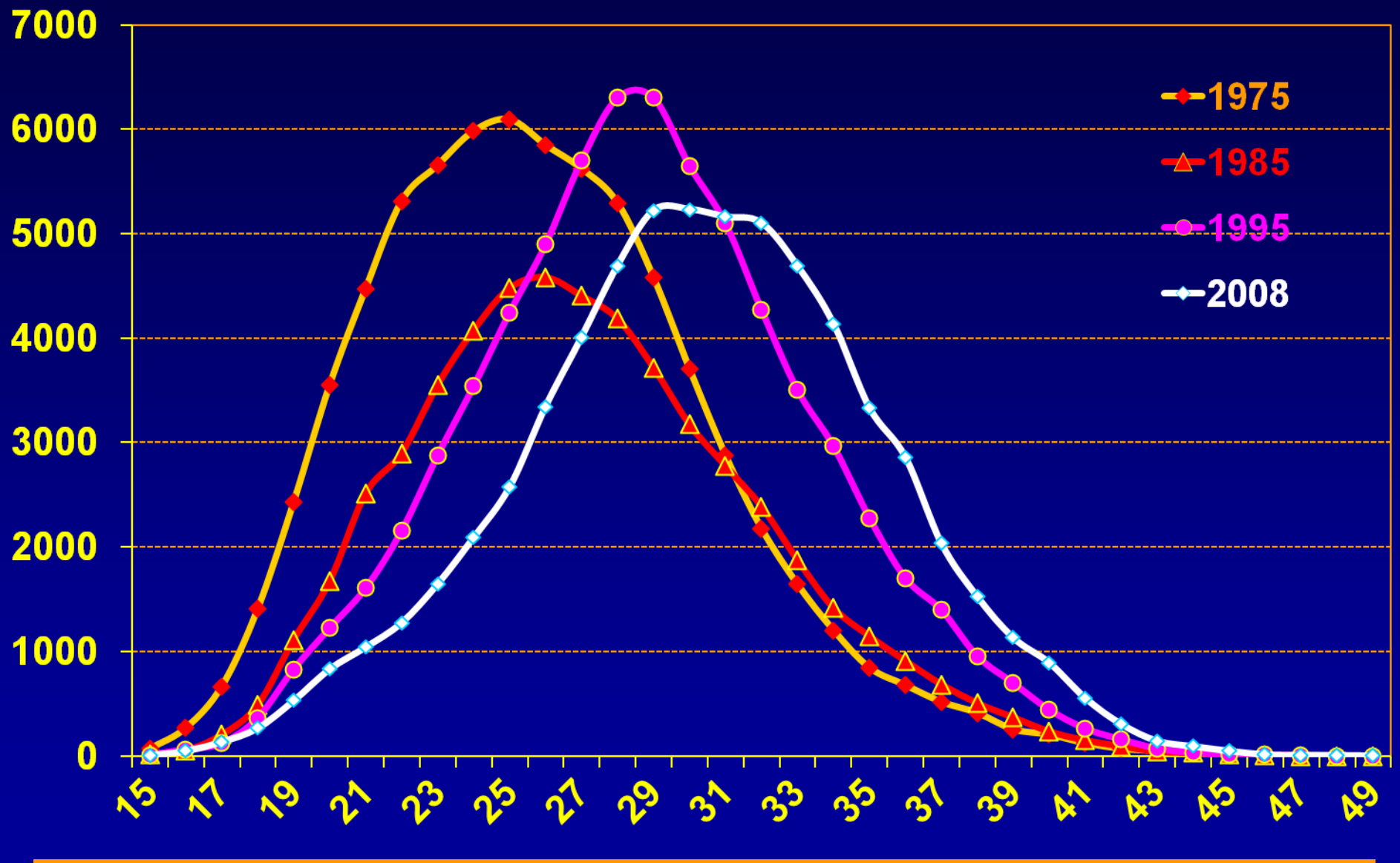
Li/08

Fertility rates per 1,000 in DK 1985-2008



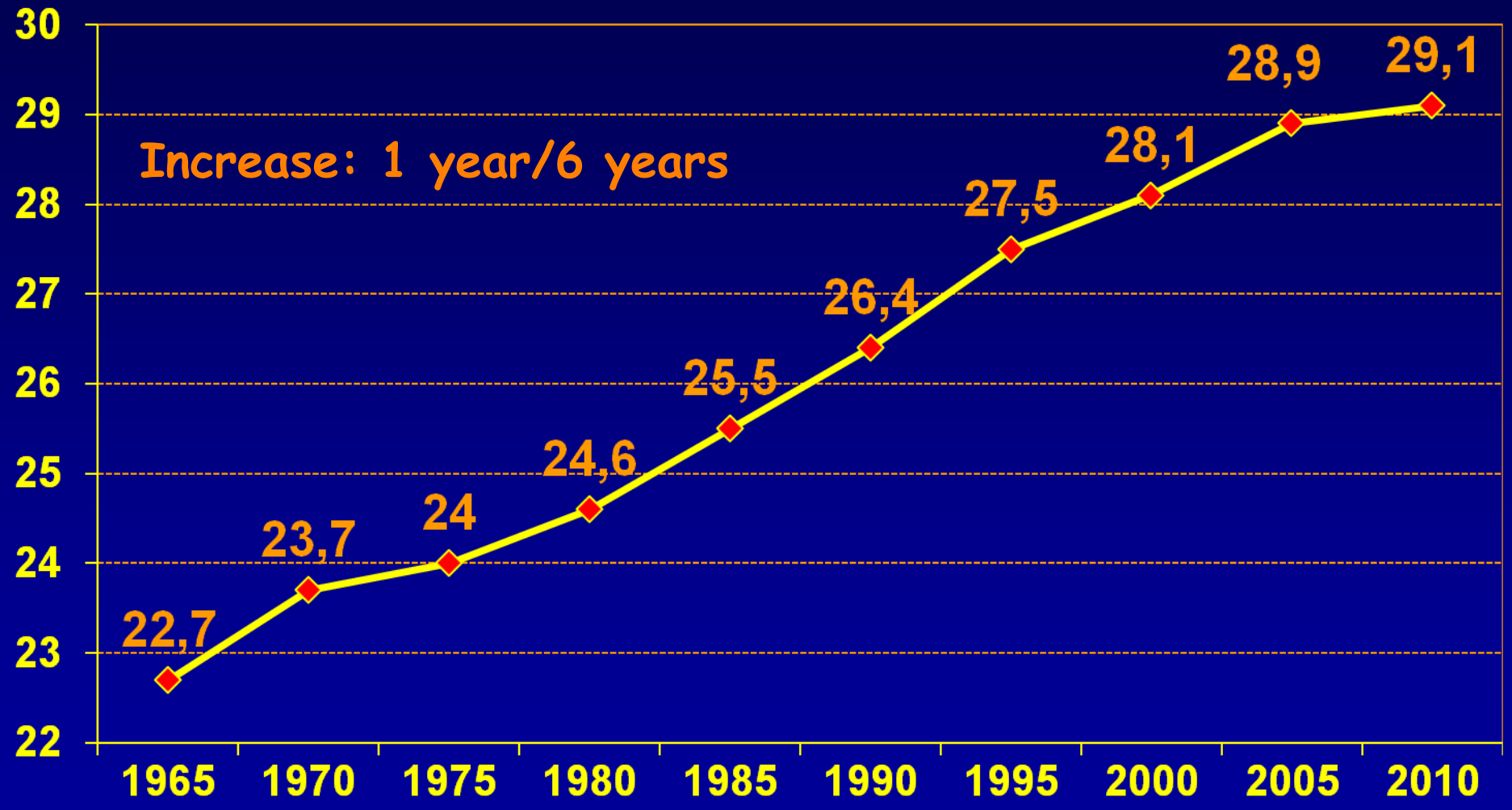
Danmarks Statistik online.

Levendefødte i DK i 1975, 85, 95 og 08

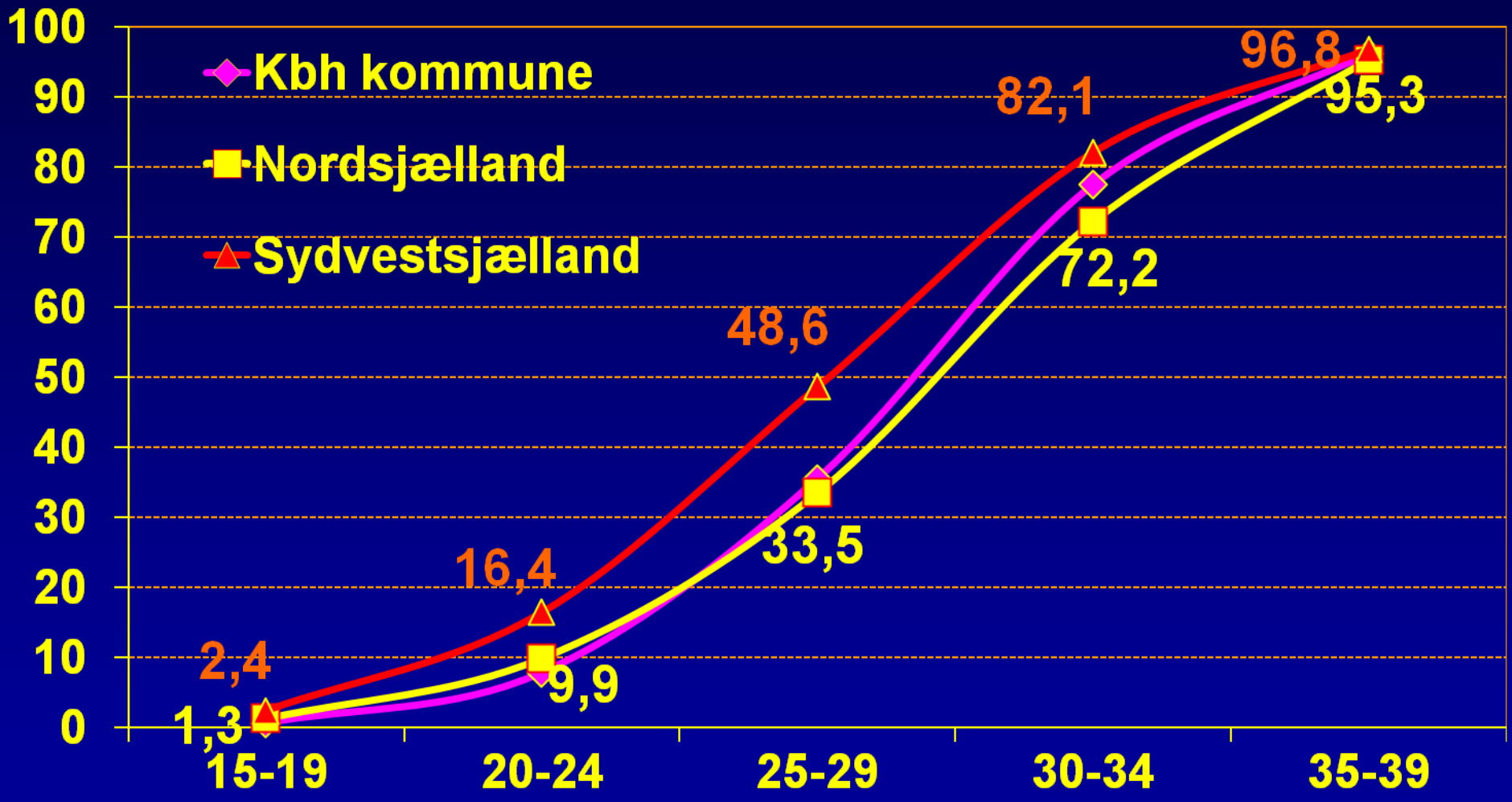


Danmarks Statistik online

Age at first birth
Denmark 1965-2010

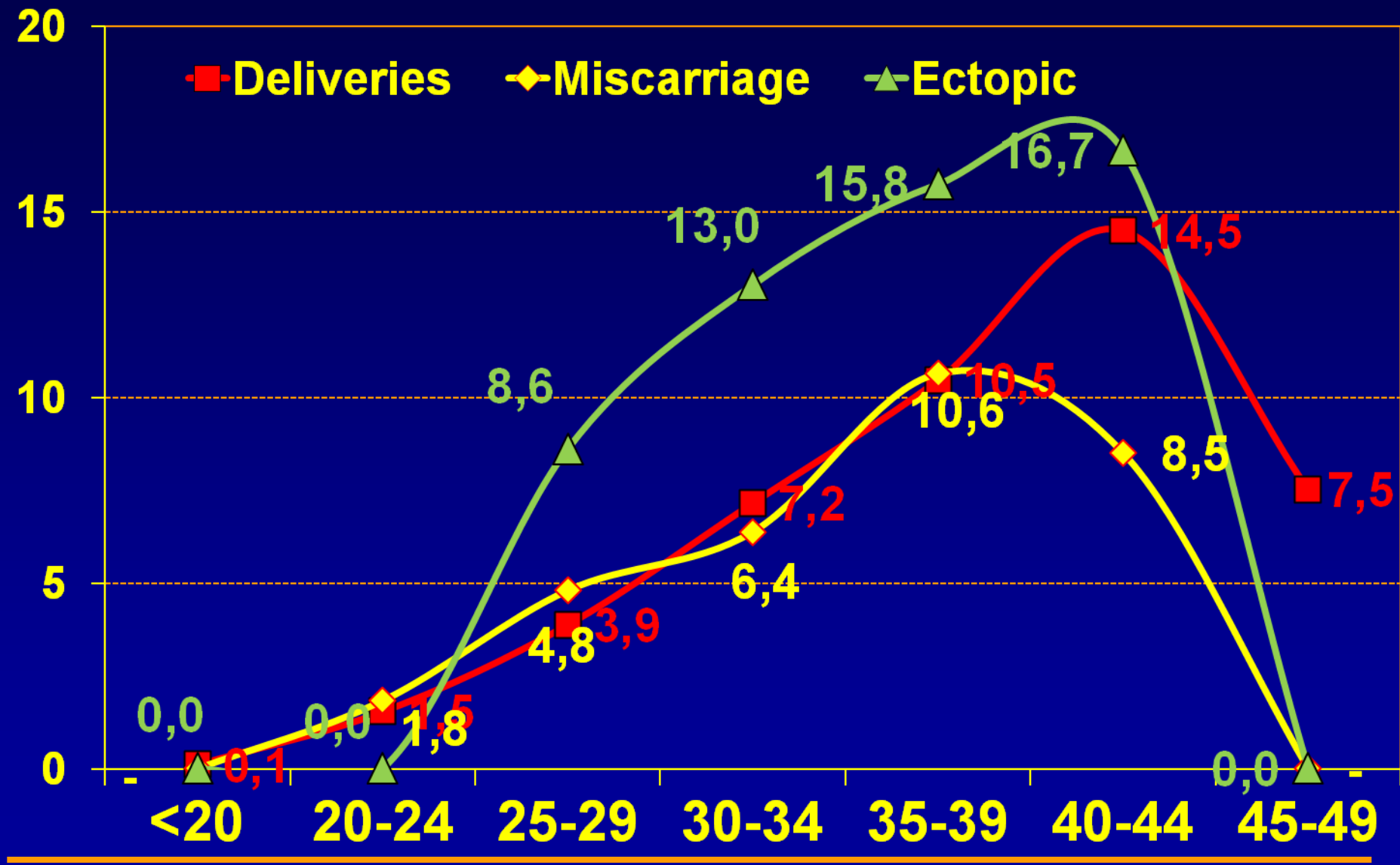


Liveborn in three regions in 2008 according to maternal age



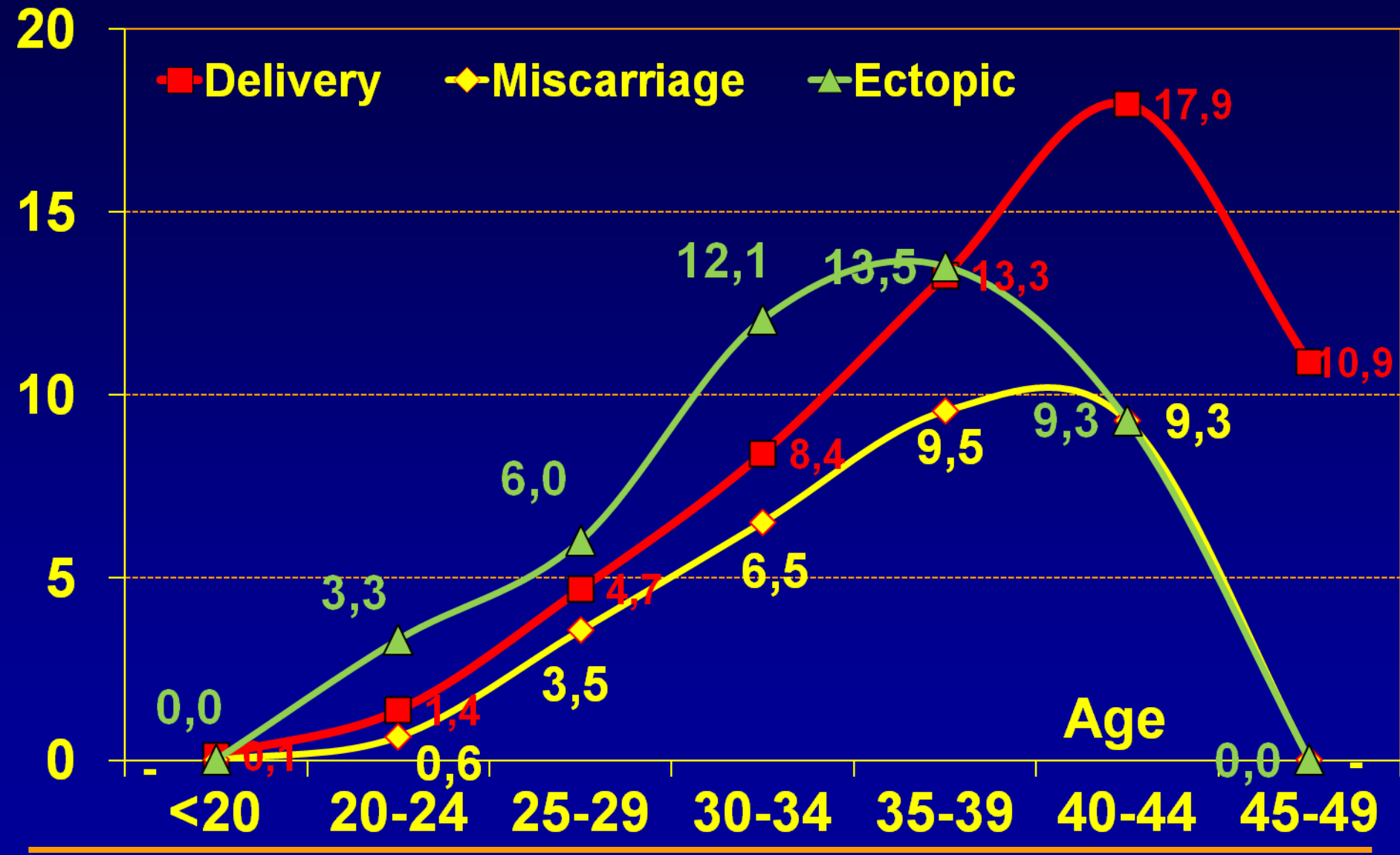
Danmarks Statistik online

Per cent of ART pregnancies 2010



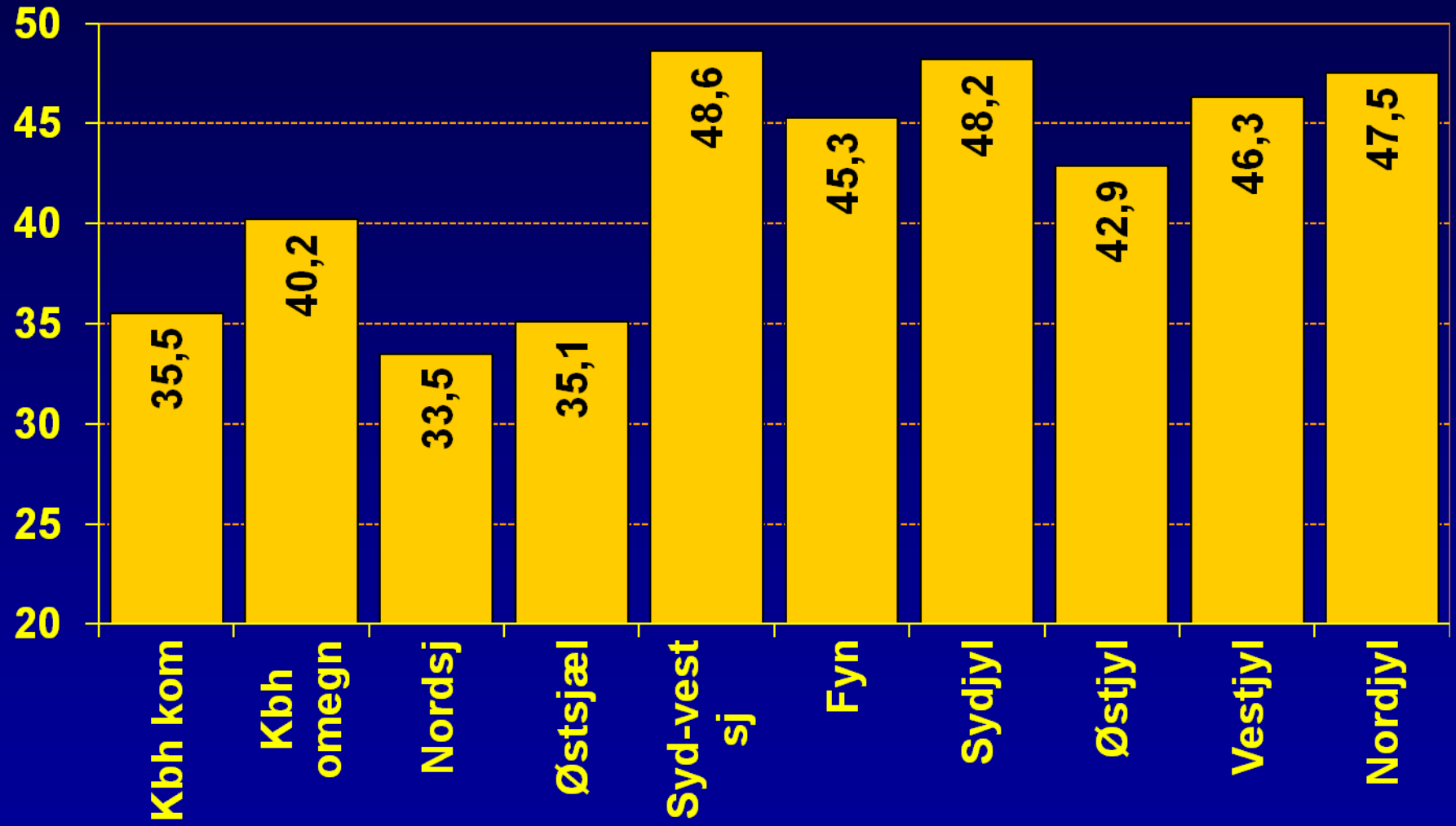
IVF registry, Danish Health Board

Per cent of ART pregnancies 2011



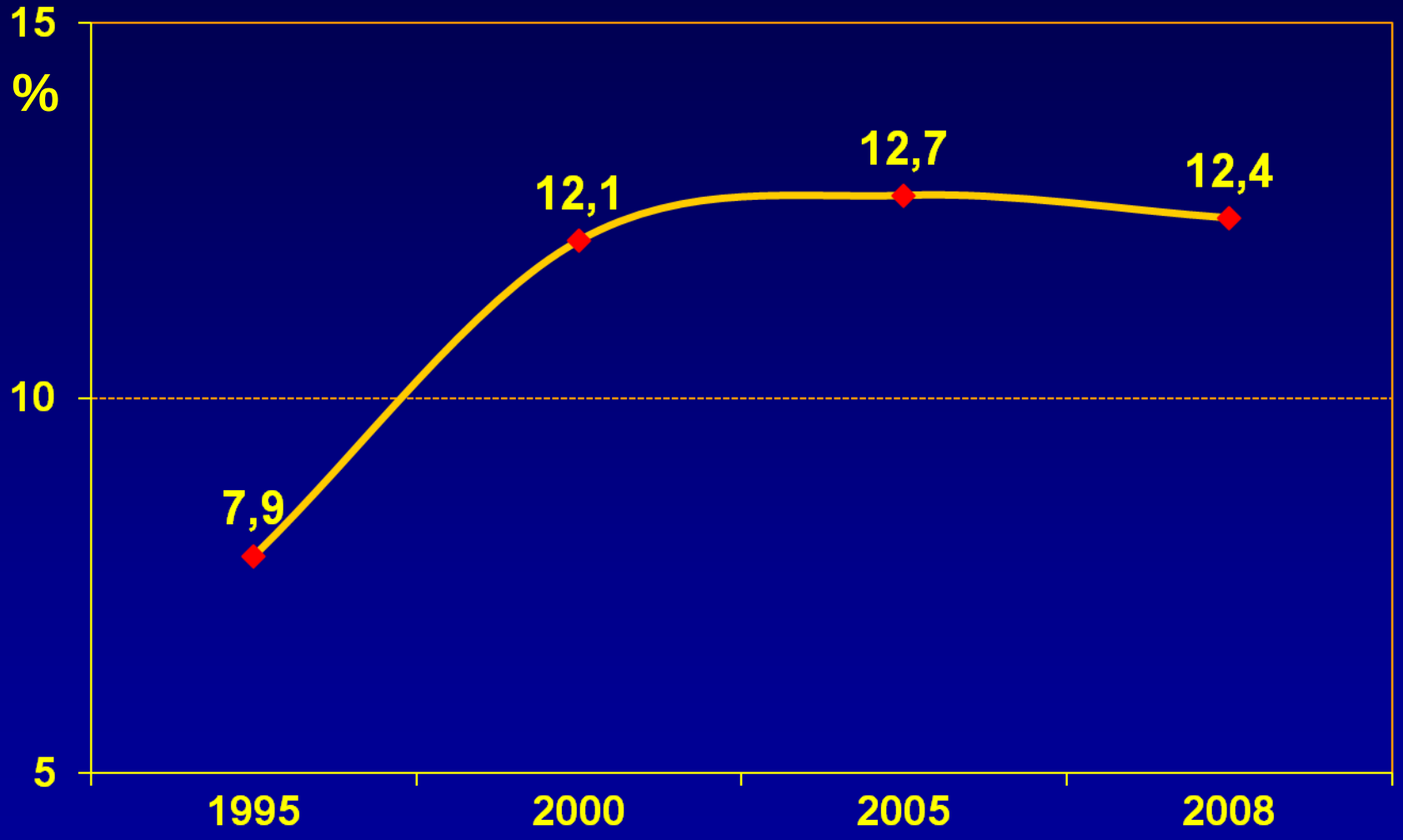
IVF registry, Danish Health Board

Proportion of children born at age 30 years in 10 regions in DK 2008



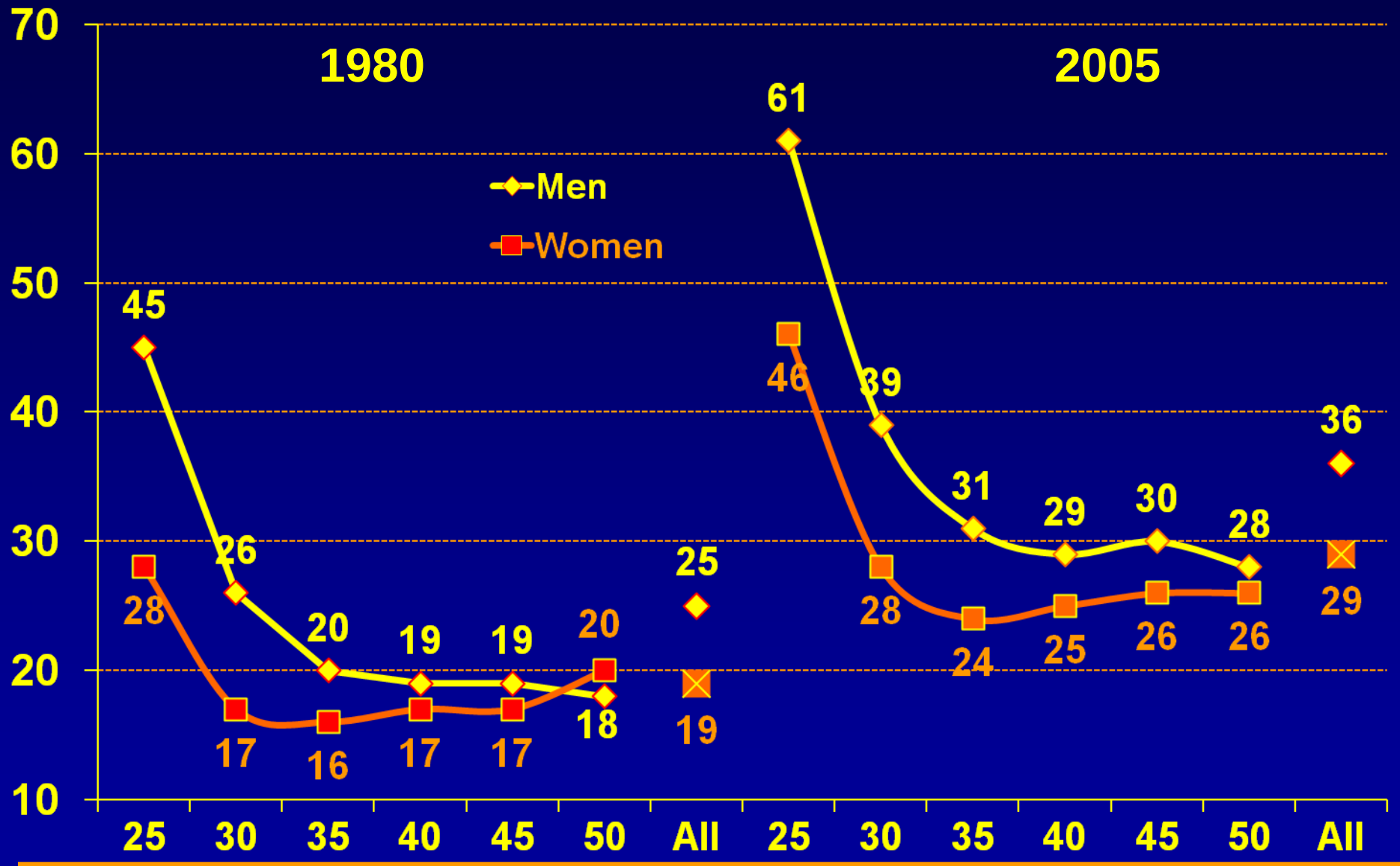
Danmarks statistik, online

Childless women (%) at age 49



Danmarks statistik, online

Singles (%) in Denmark in 1980 and 2005



Statistics of Denmark, online: www.dst.dk

Li/07

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.

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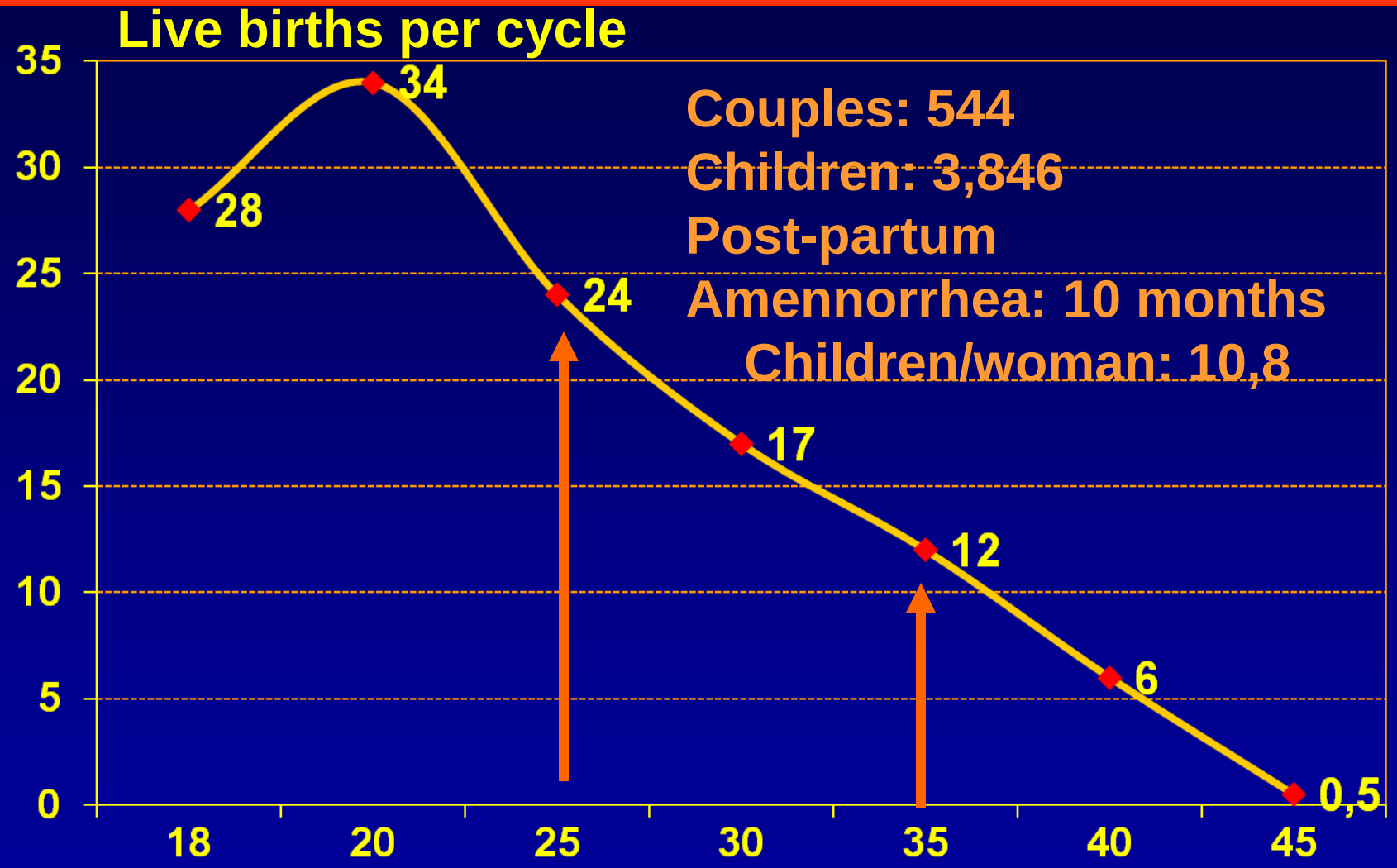
Hvad er en kvinde, og hvad kan hun

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

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:

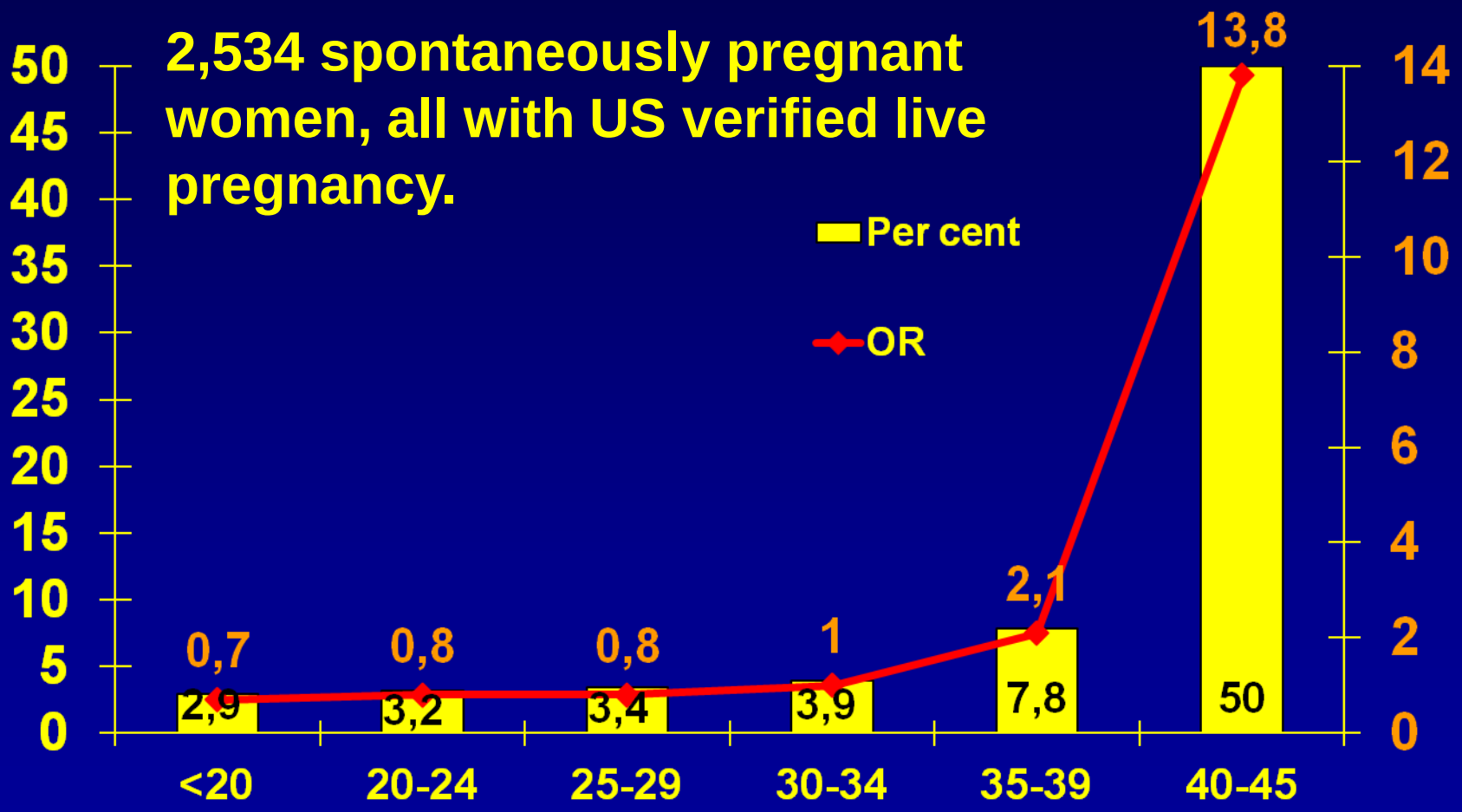
- Ovarie funktion
- Tuba funktion
- Ændringer i endometriet
- Ændringer i hormoner
- Ændringer i sædkvalitet
- Ændringer i sexual vaner
- Øget abort rate

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**

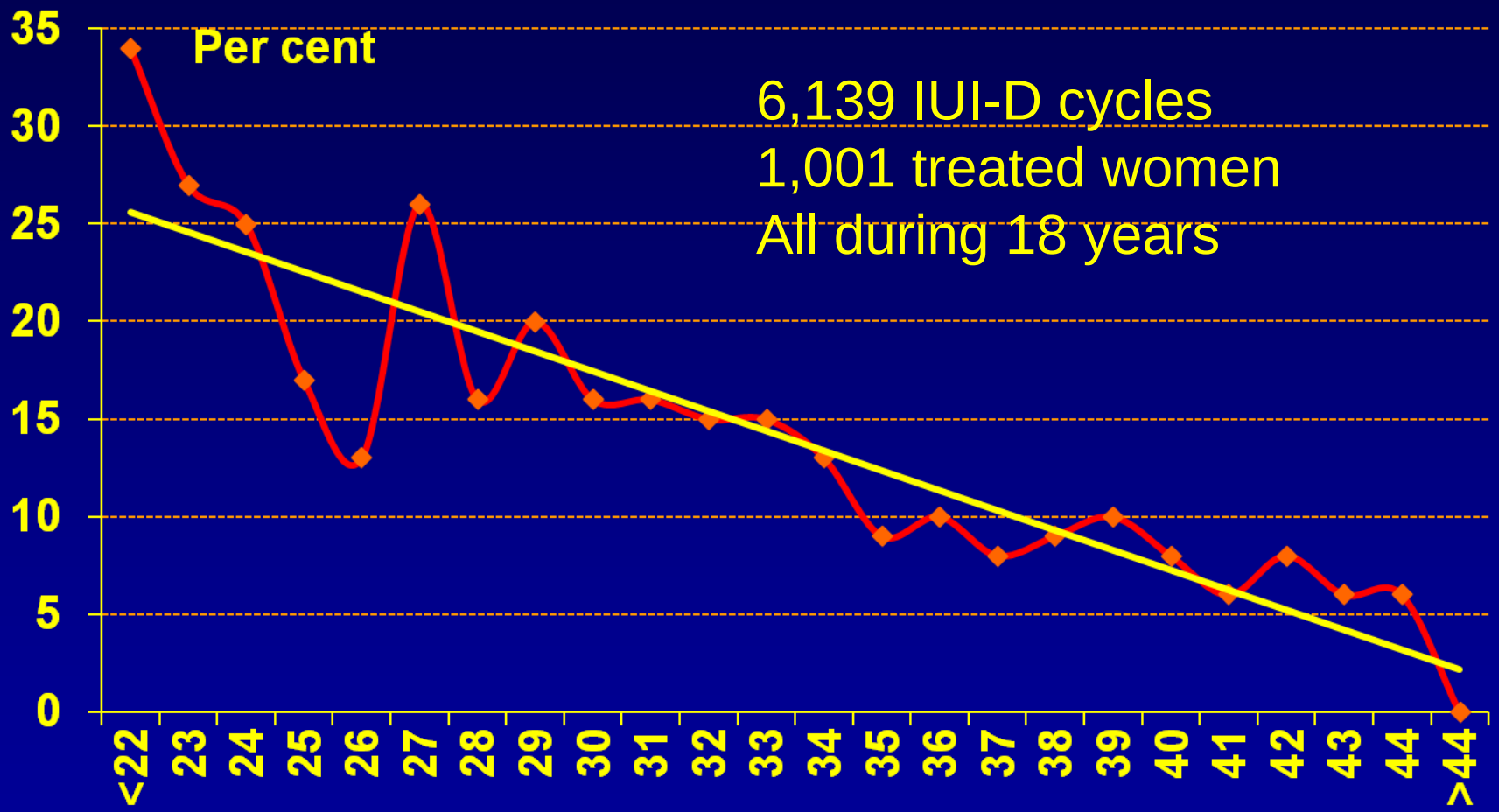
Spontaneous fetal loss week 12-24 after early living pregnancy.



Hoesli et al. Am J Med Genet 2001; 100: 106-9

Li/08

Donor IUI. Pregnancies/100 cycles



Botchan A et al. Hum Reprod 2001; 16: 2298-2304

Li/02

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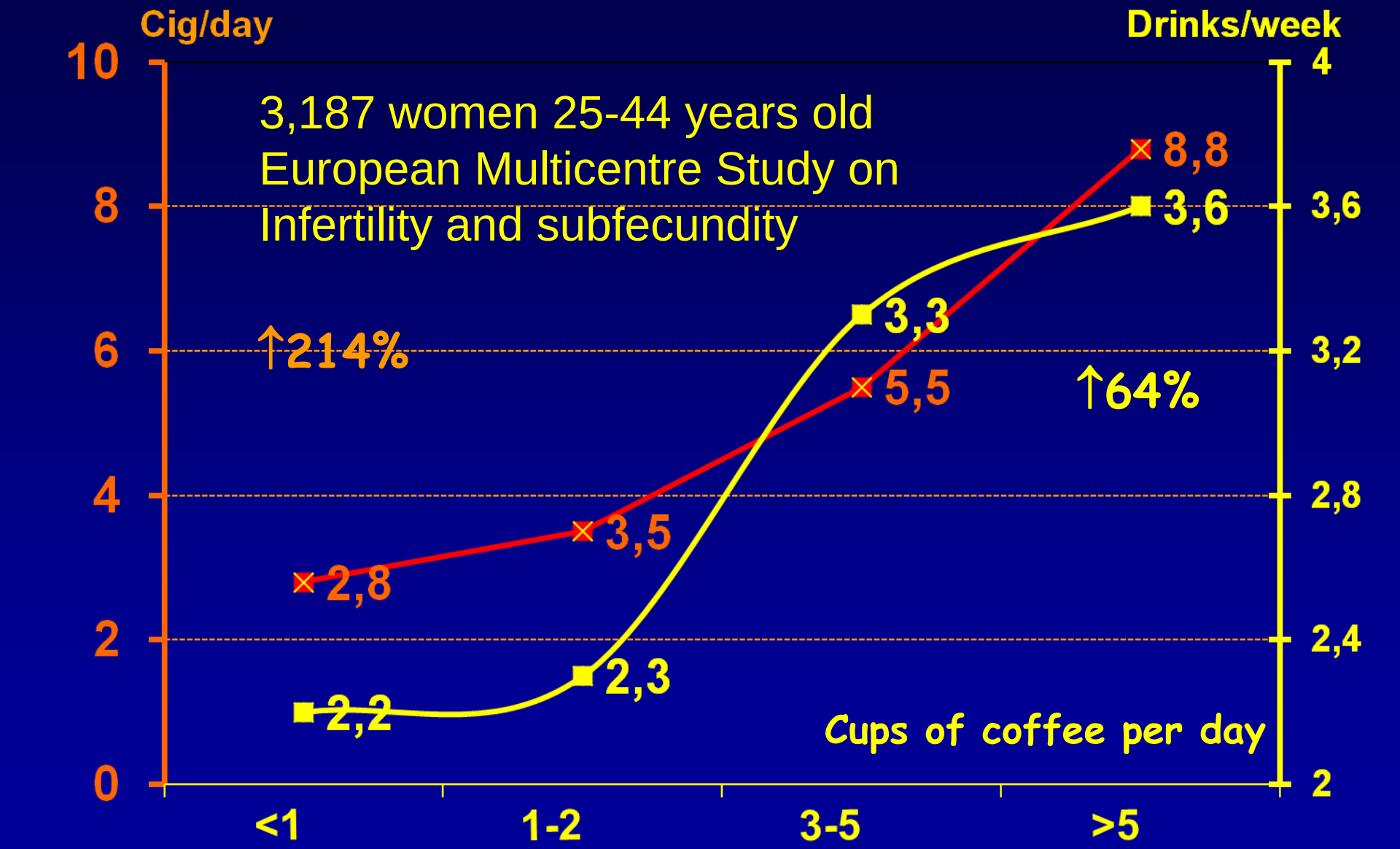
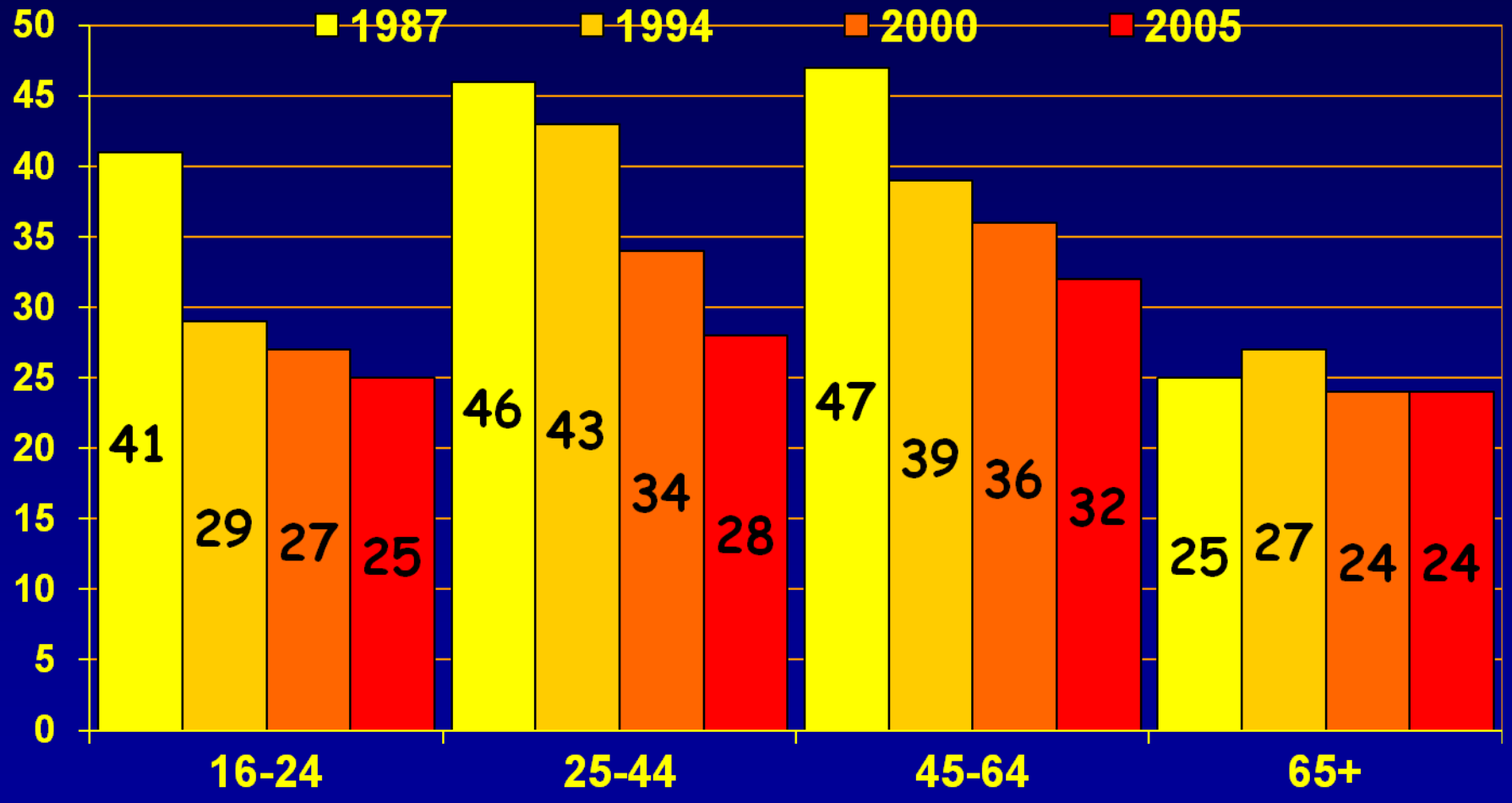
Naughty girls



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

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

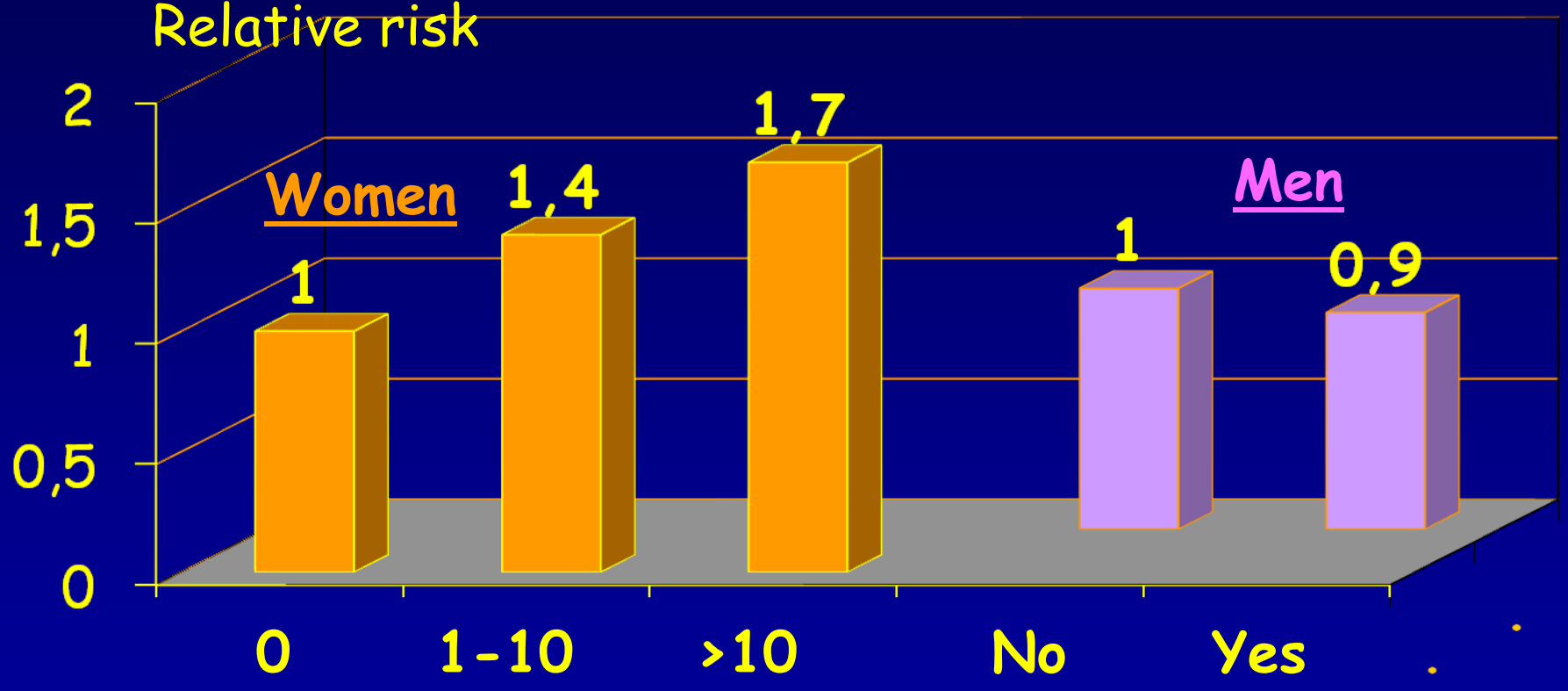


Sundhed og Sygelighed i DK 2006. SIF 2006

Li/08

Fertility and smoking

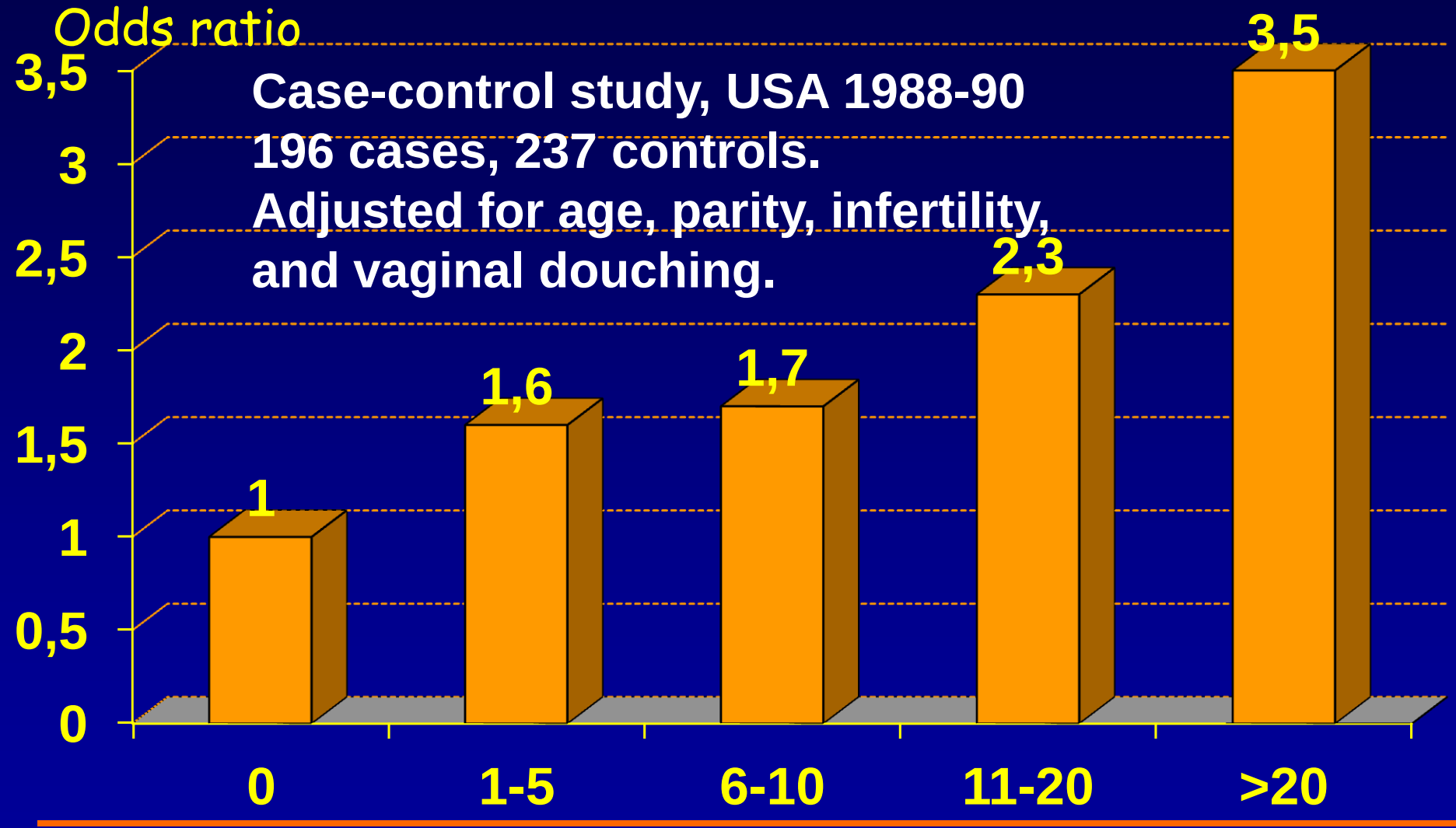
Risk of waiting time >9,4 months



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 - IVF

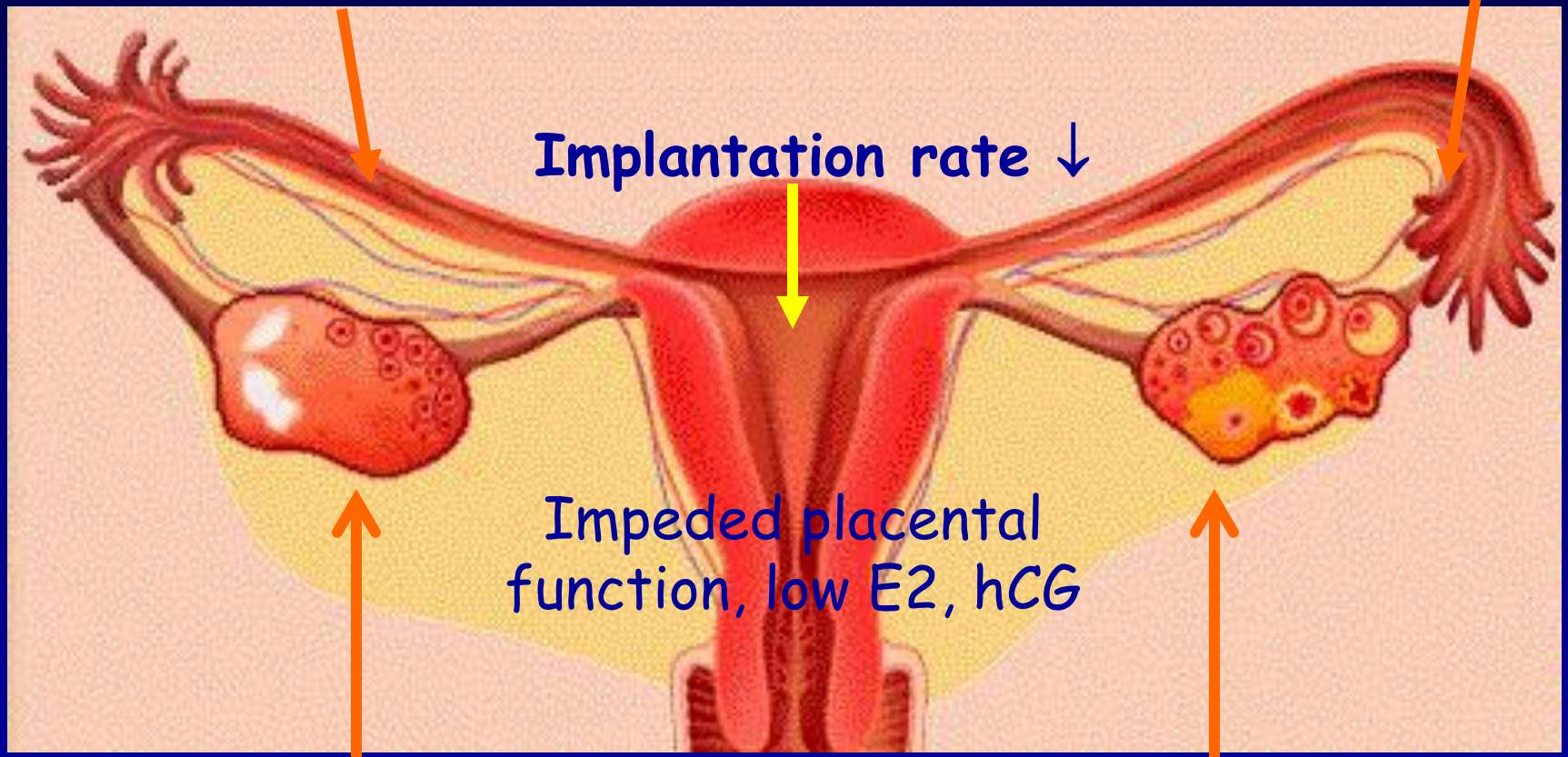
	-smo	ex-smo	+smo
No 499	351	111	37
Ø2/FSU U	82	71	60
Oocytes	13.5	13.6	12.6
Fertilis. rate	54%	54%	50%
Embryos	8.0	8.2	6.6
Embr. transf	3.6	3.5	3.6
Implant. rate	16%	16%	6.7%

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

Smoking and fertility

Impeded ciliary function:

Pick-up function ↓



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

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Alkohol og fertilitet

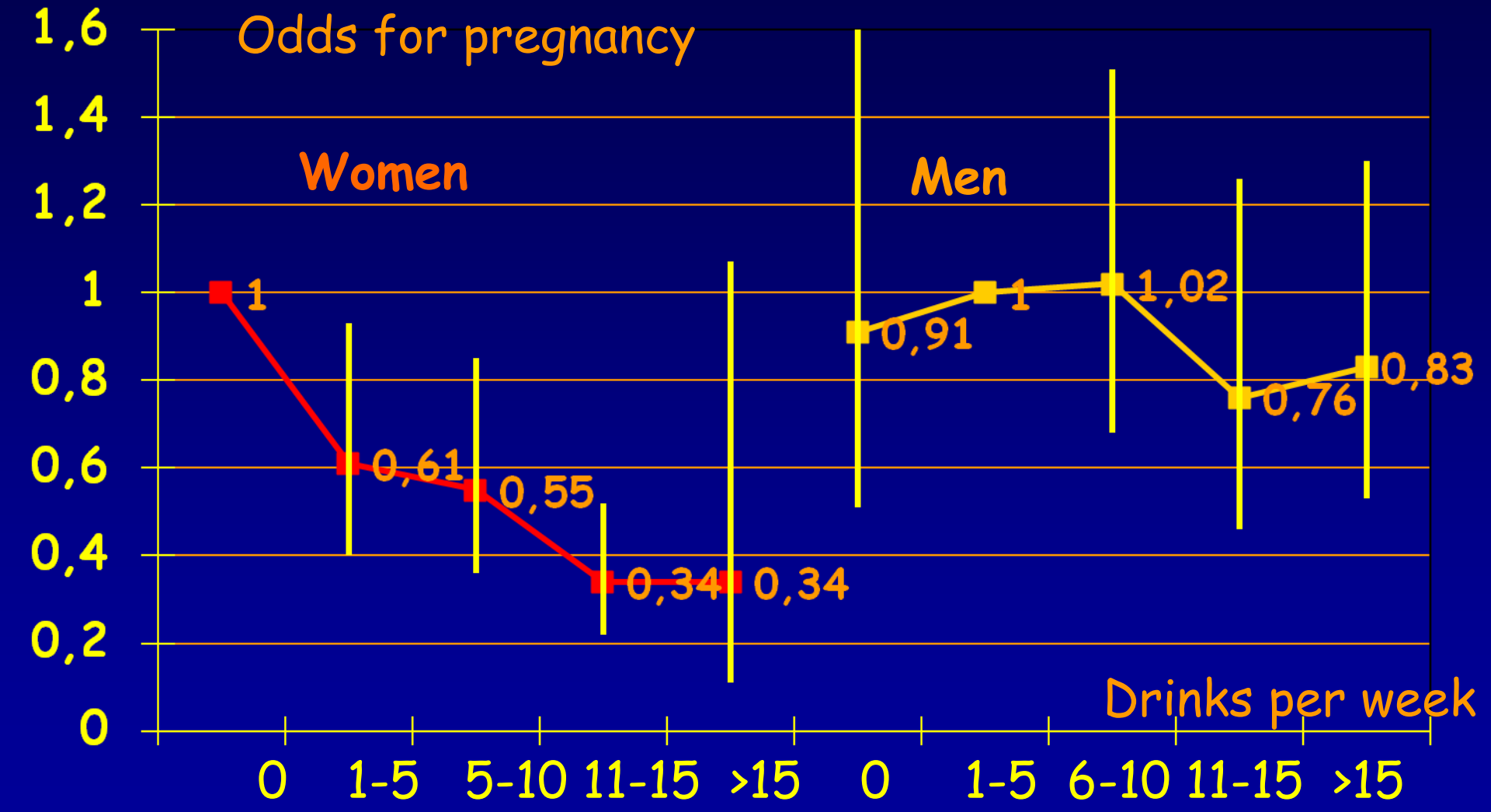
Nedsætter beskedne mængder alkohol fertiliteten?

- 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.

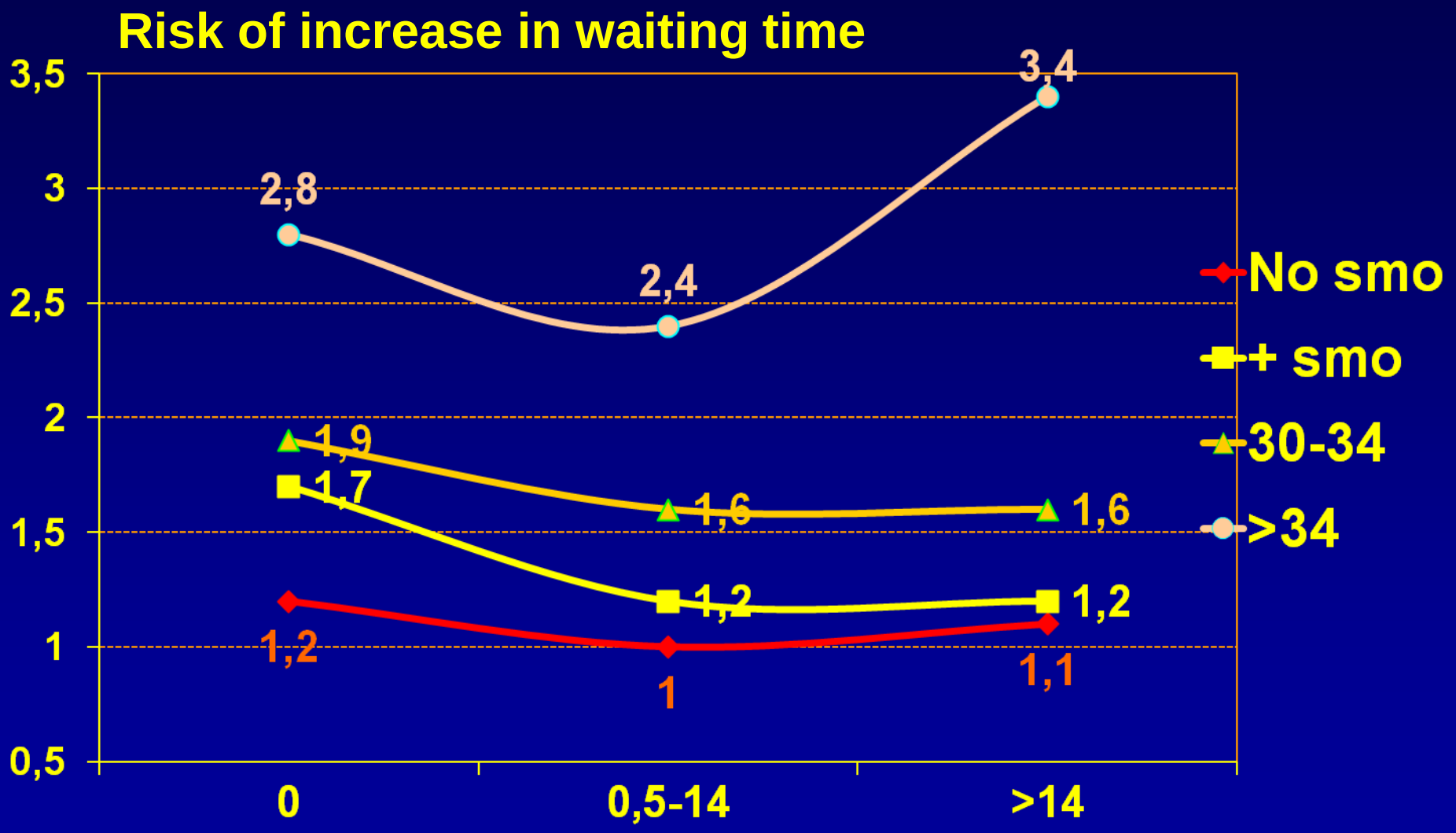
Outcome measure: Subfecundity odds ratio

Juhl M et al. Human reprod 2002; 16: 2705-9.

Subfecundity OR and drinks per week

Juhl M, et al. Human Reprod 2002; 16: 2705-9

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



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

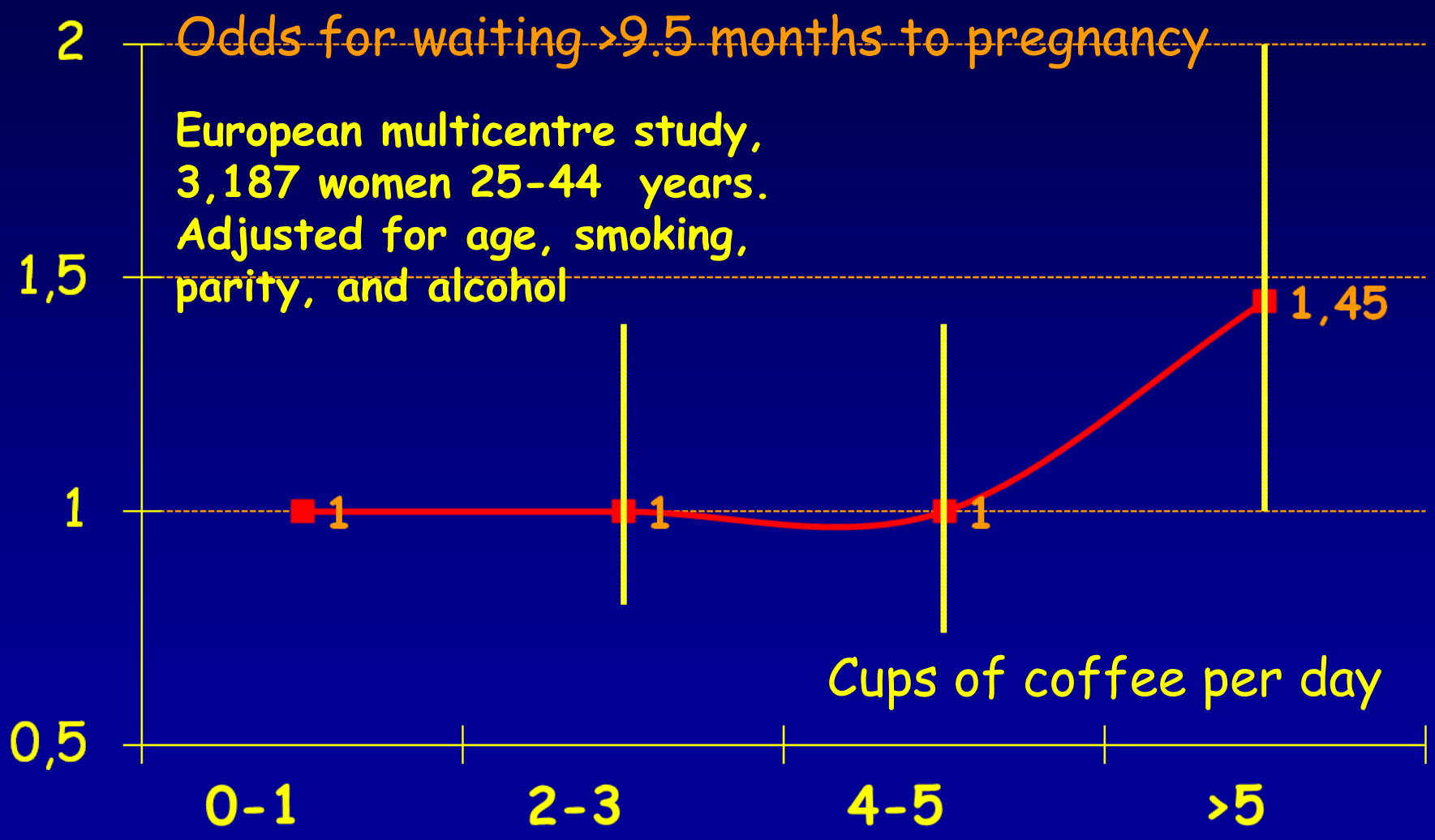
- 1 kop kaffe = 100 mg
- 1 kop te = 50 mg
- ½ liter cola = 50 mg
- 30 g chokolade = 10 mg
- 1 kop kakao = 5 mg
- medicin.
- Koffein passerer alle biologiske membraner inkl.. placenta-barrieren
- Koffein findes i alle kropsvæsker kort efter indtag

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)

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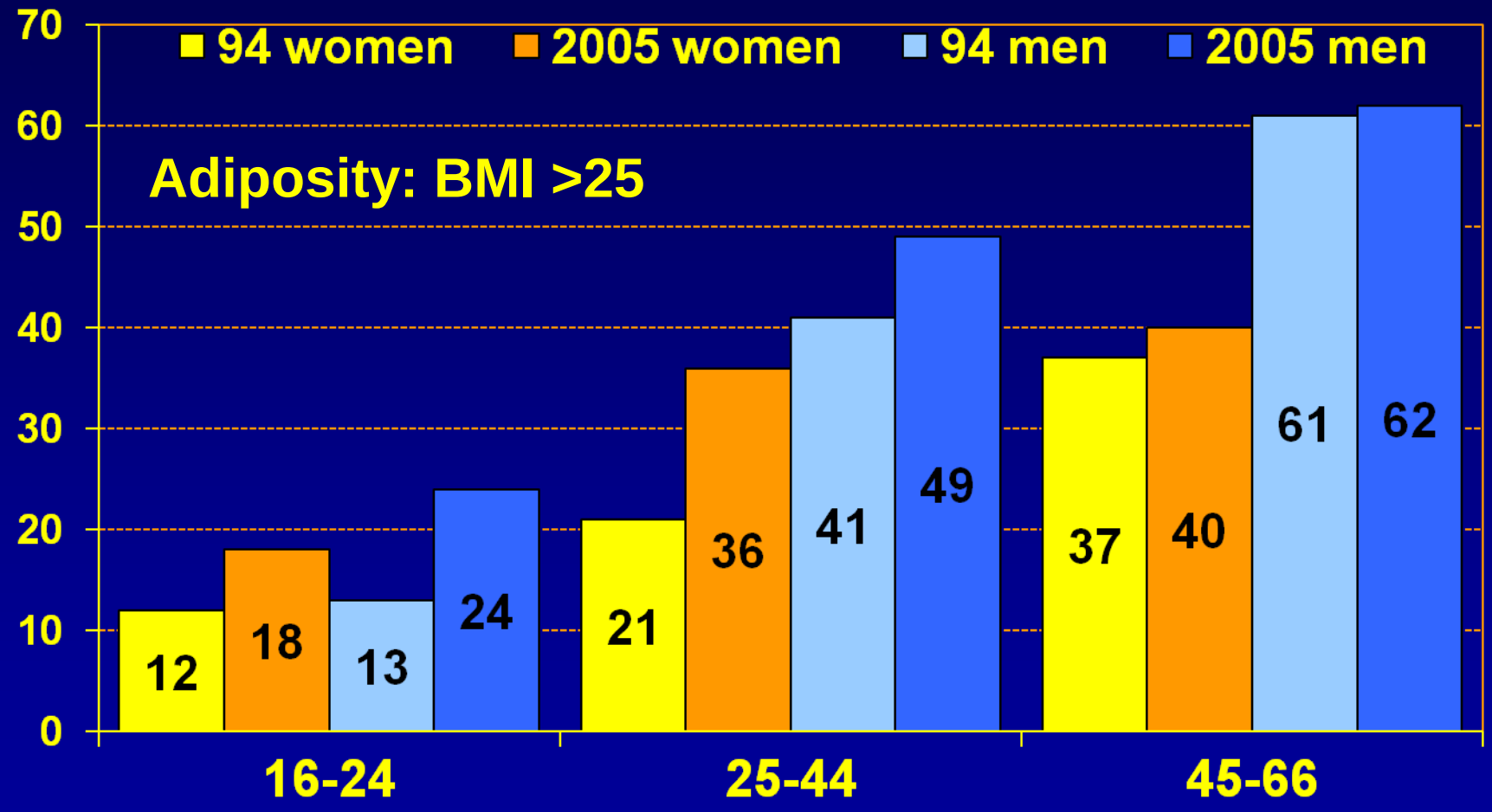
Adiposity in Danish women and men in 1994 and 2005. N=16,000



Statens Institut for Folkesundhed. SUSY 2006

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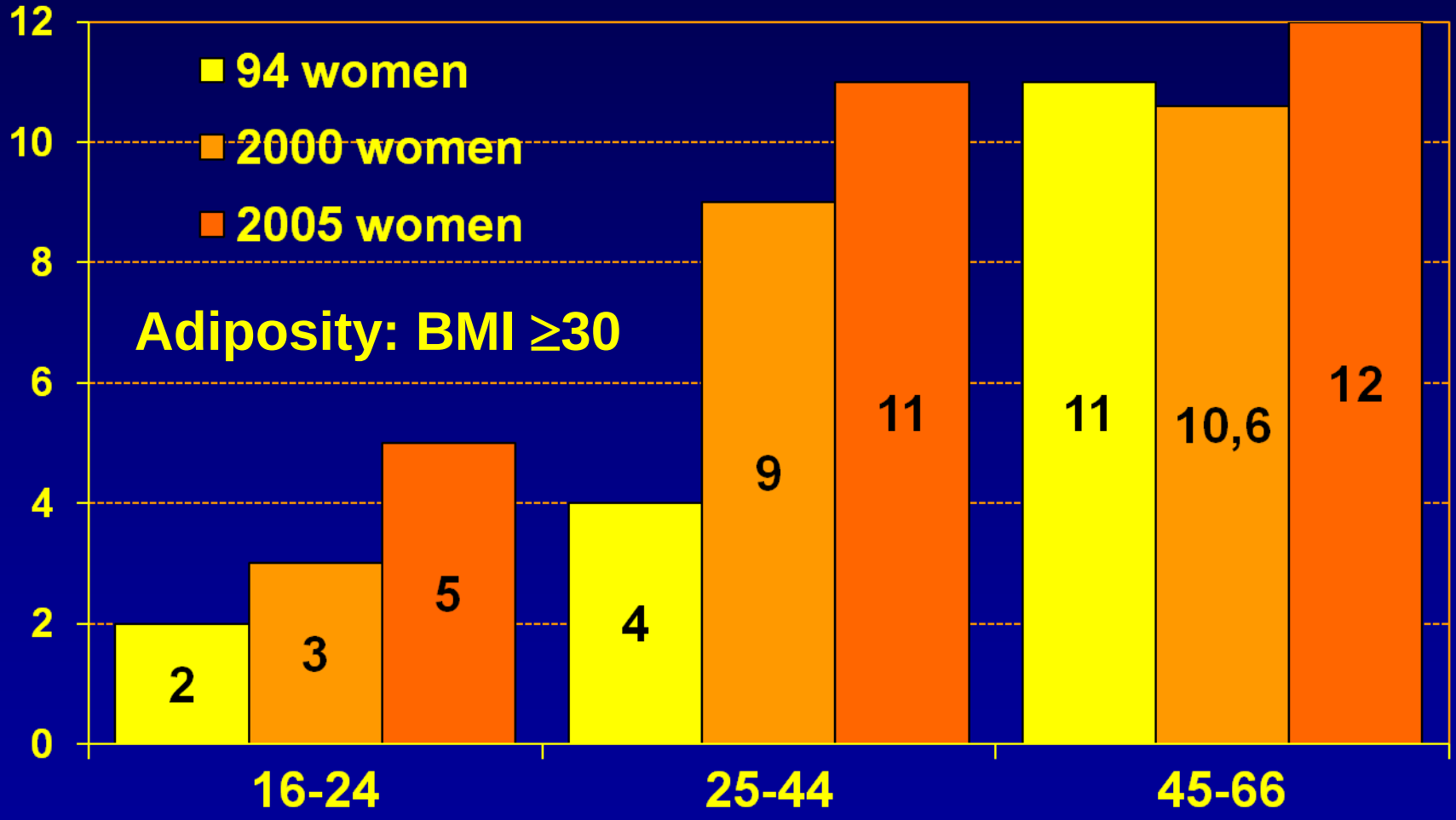
Severe adiposity in Danish women in 1994, 2000 and 2005



Statens Institut for Folkesundhed, SUSY 2006

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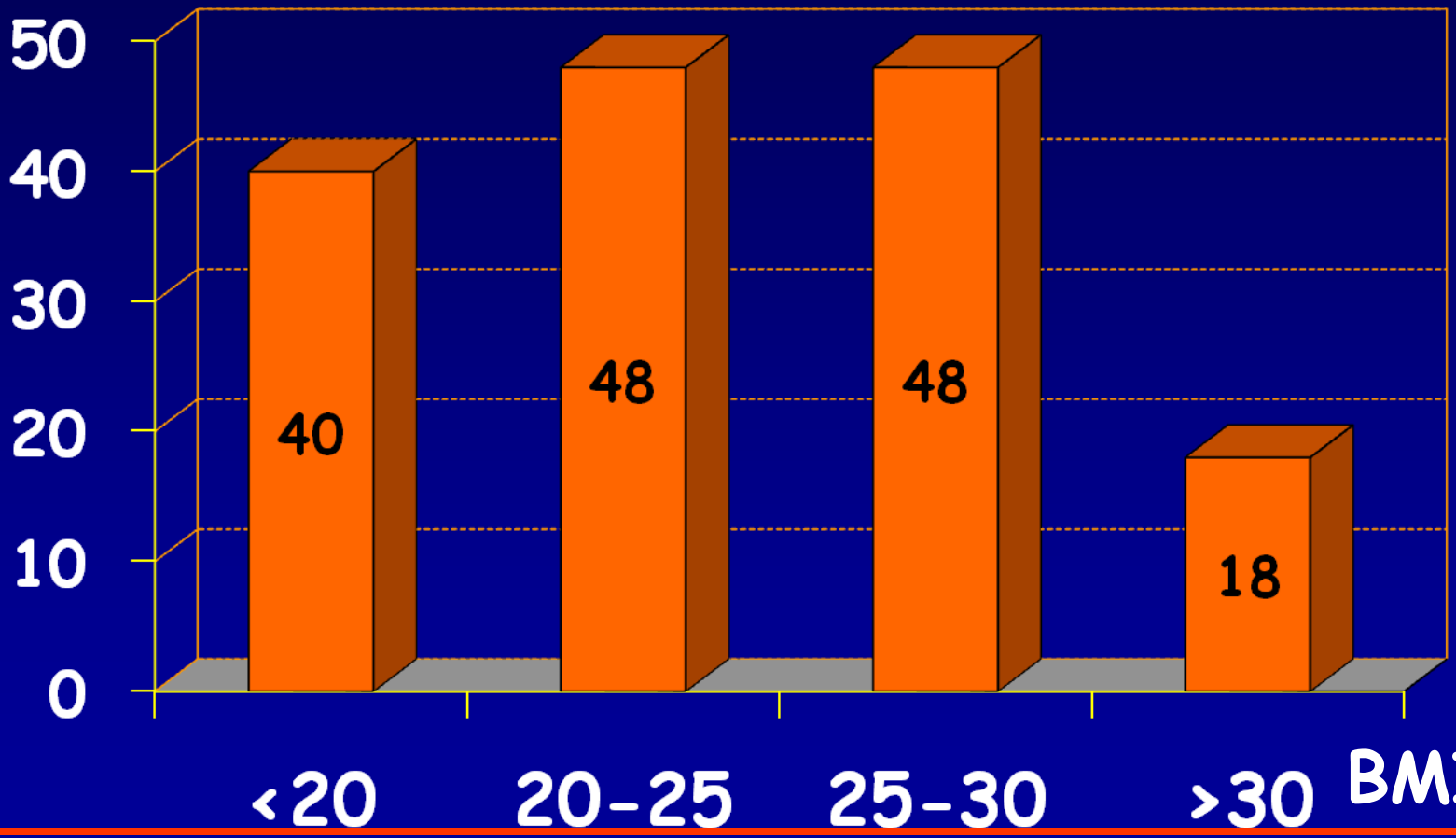
Fat and fecundity

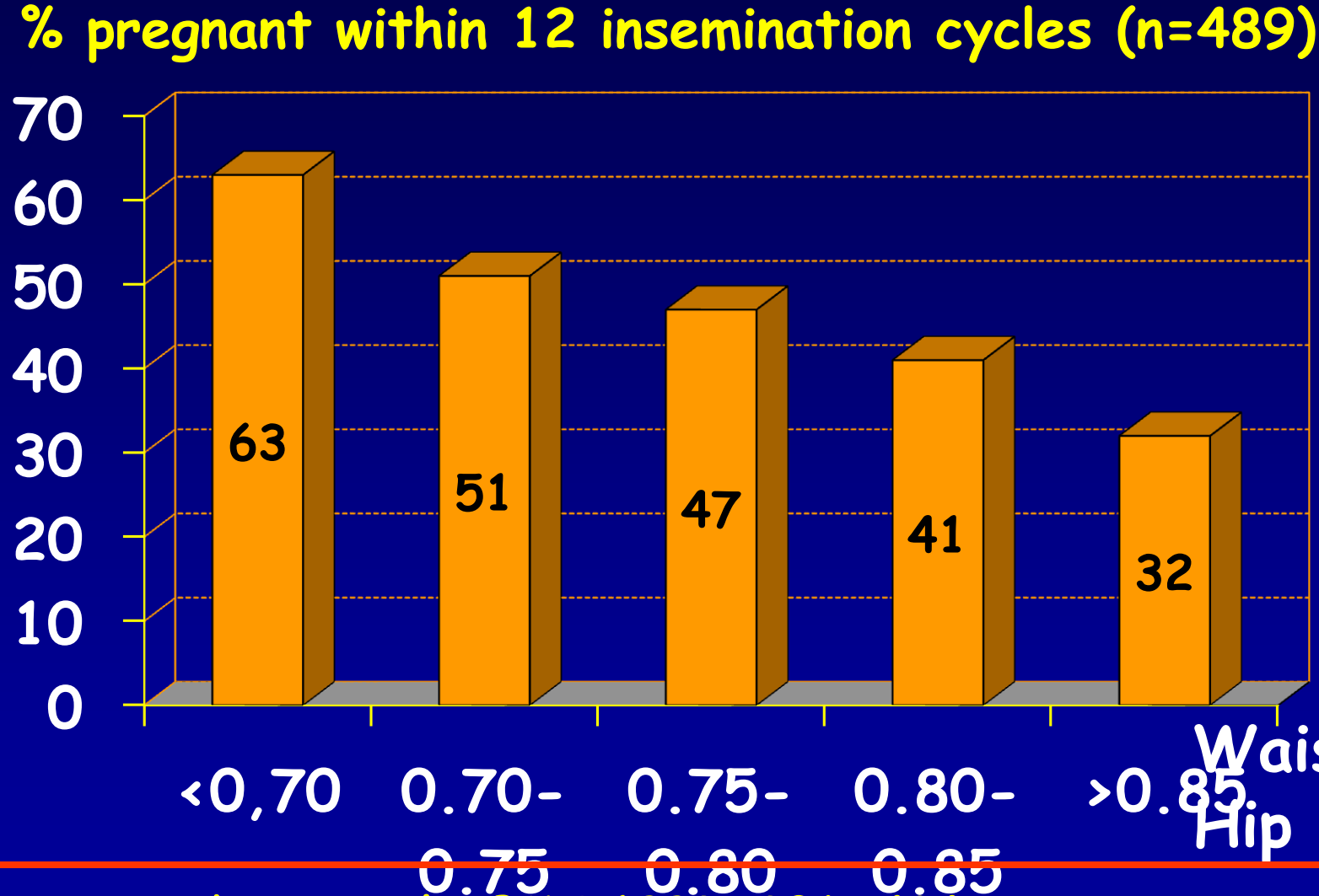
% pregnant within 12 insemination cycles (n=489)



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

Li/00

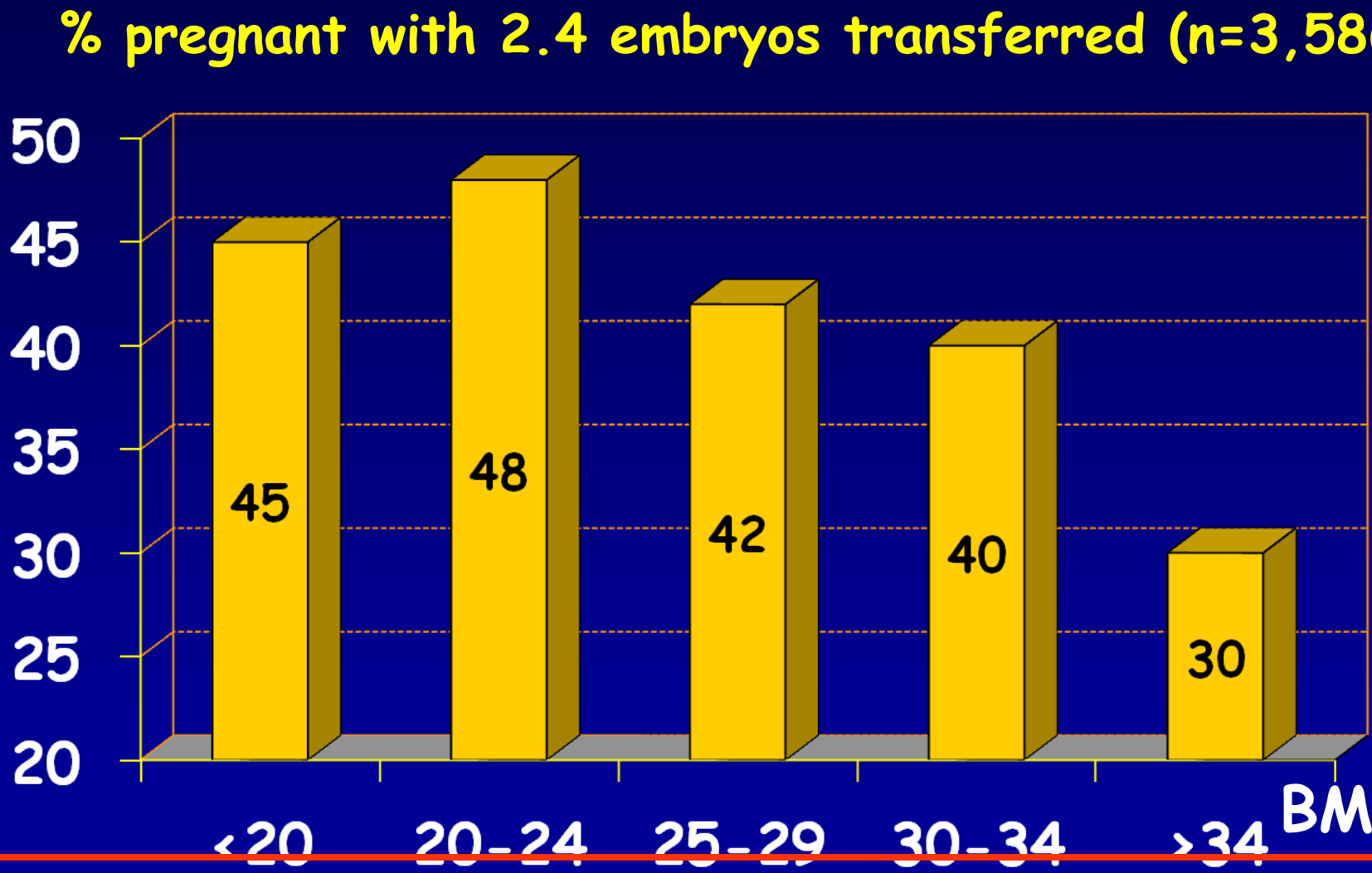
Fat and fecundity



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

Li/00

BMI & IVF: Clinical pregnancy rate

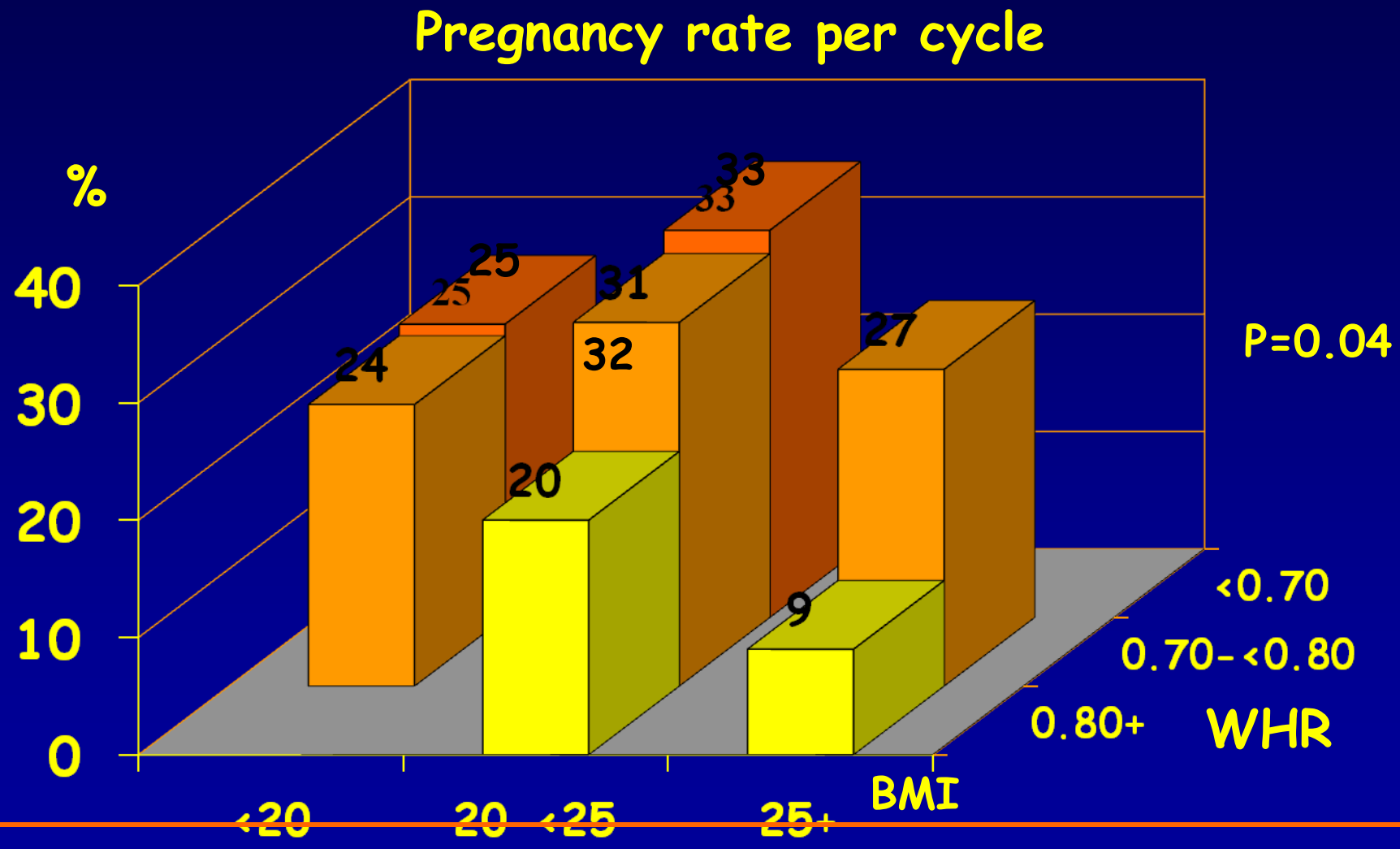


Wang et al. BMJ 2000: 321: 1320-1.

Li/01

Fat and fecundity

Pregnancy rates in 220 IVF cycles



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

Li/00

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	**12%**	**22%**	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

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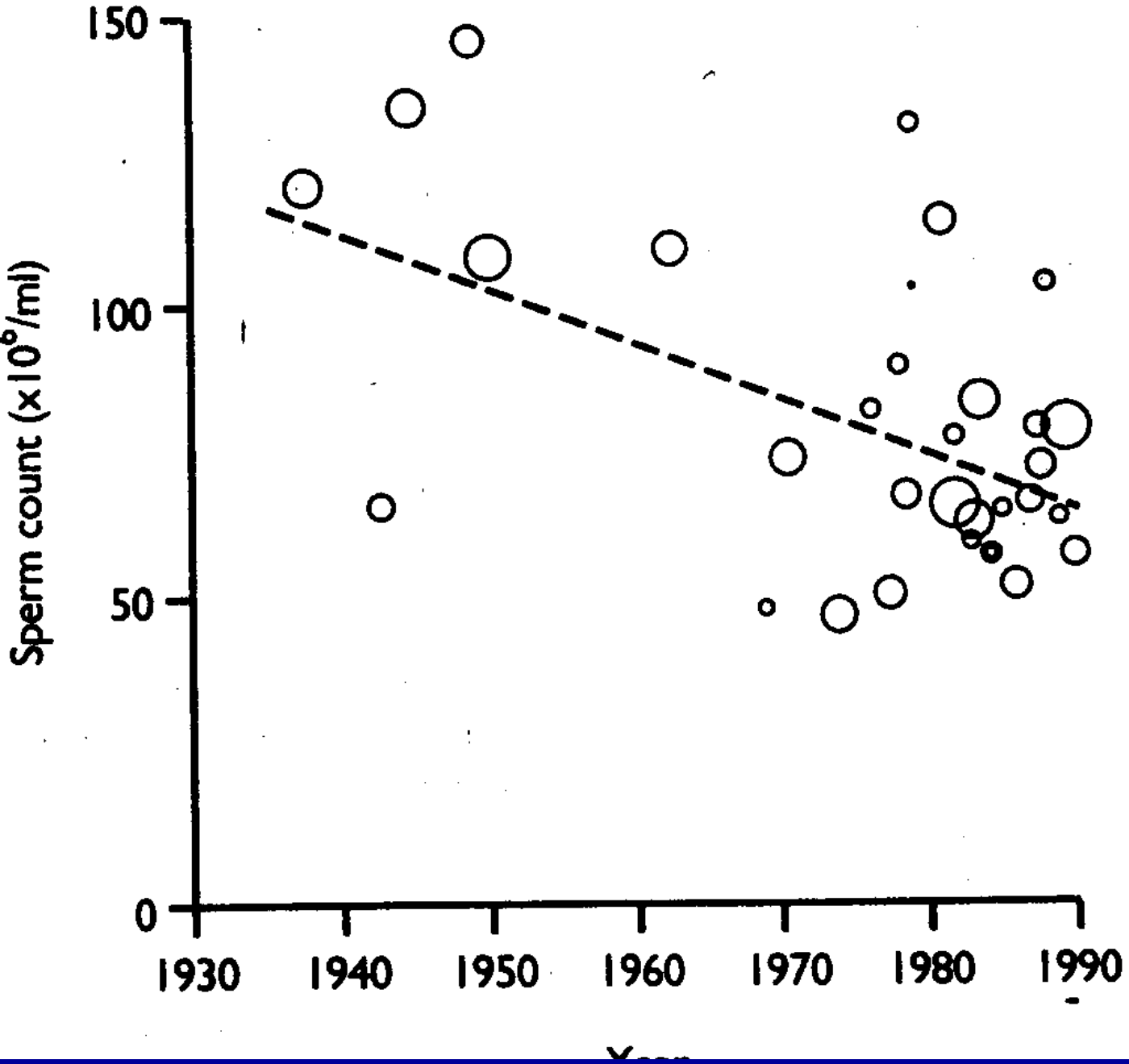
- **Mandlig fertilitet**

Sperm count by time

61 papers
14,947 men



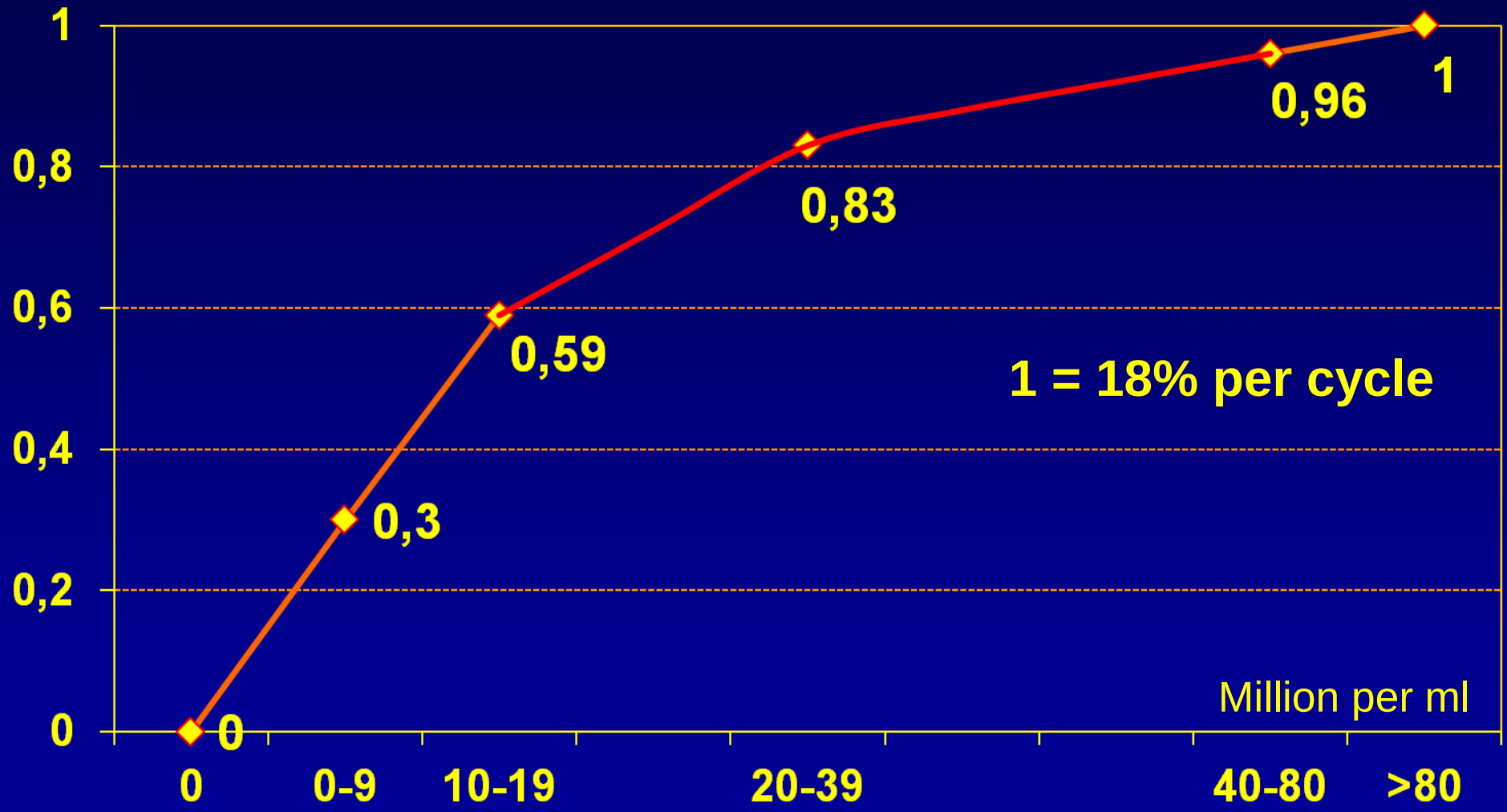
Carlsen et al. BMJ 1992; 305: 609-13

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%)**

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

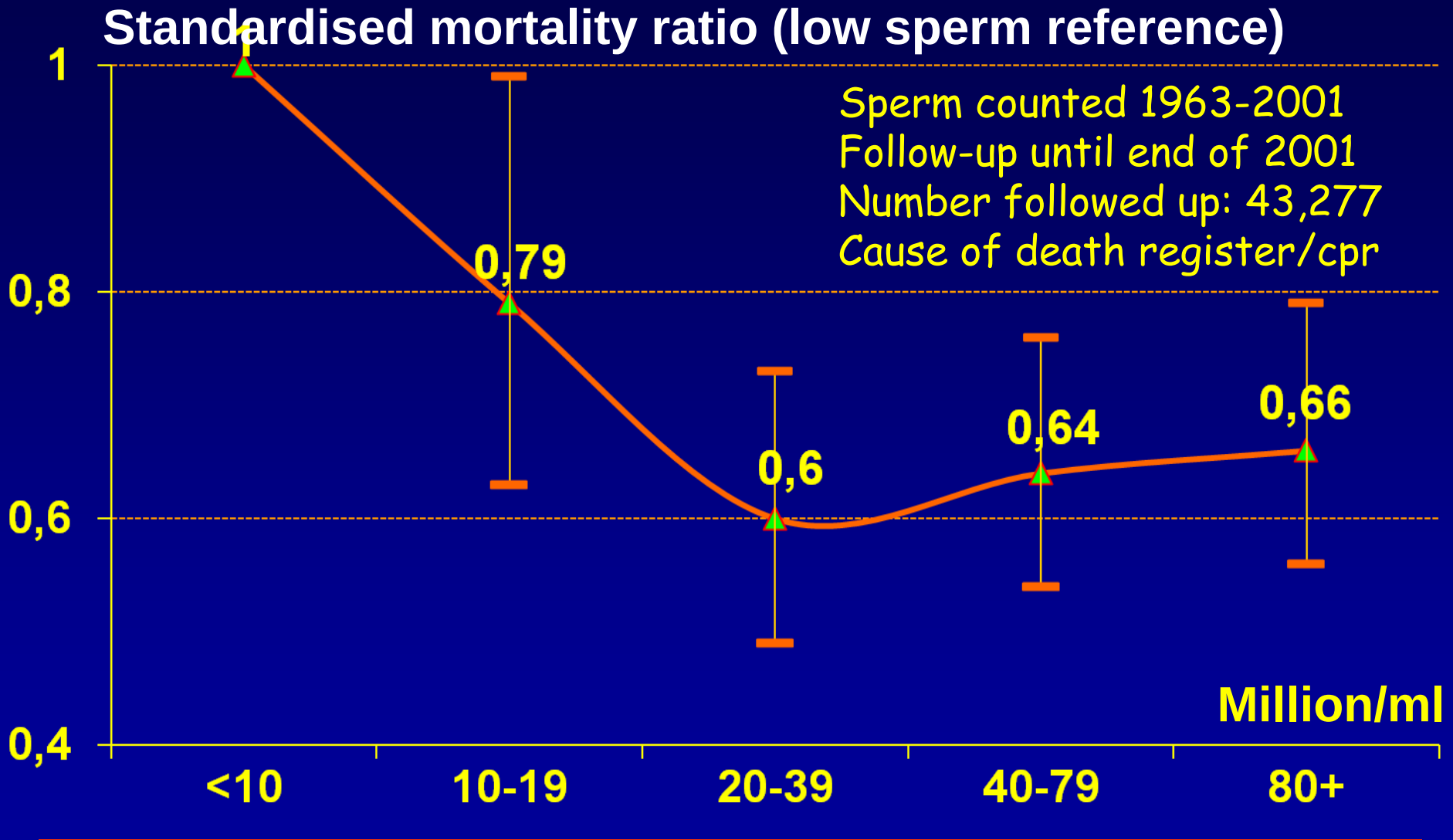
Sperm count in Nordic-Baltic area

	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

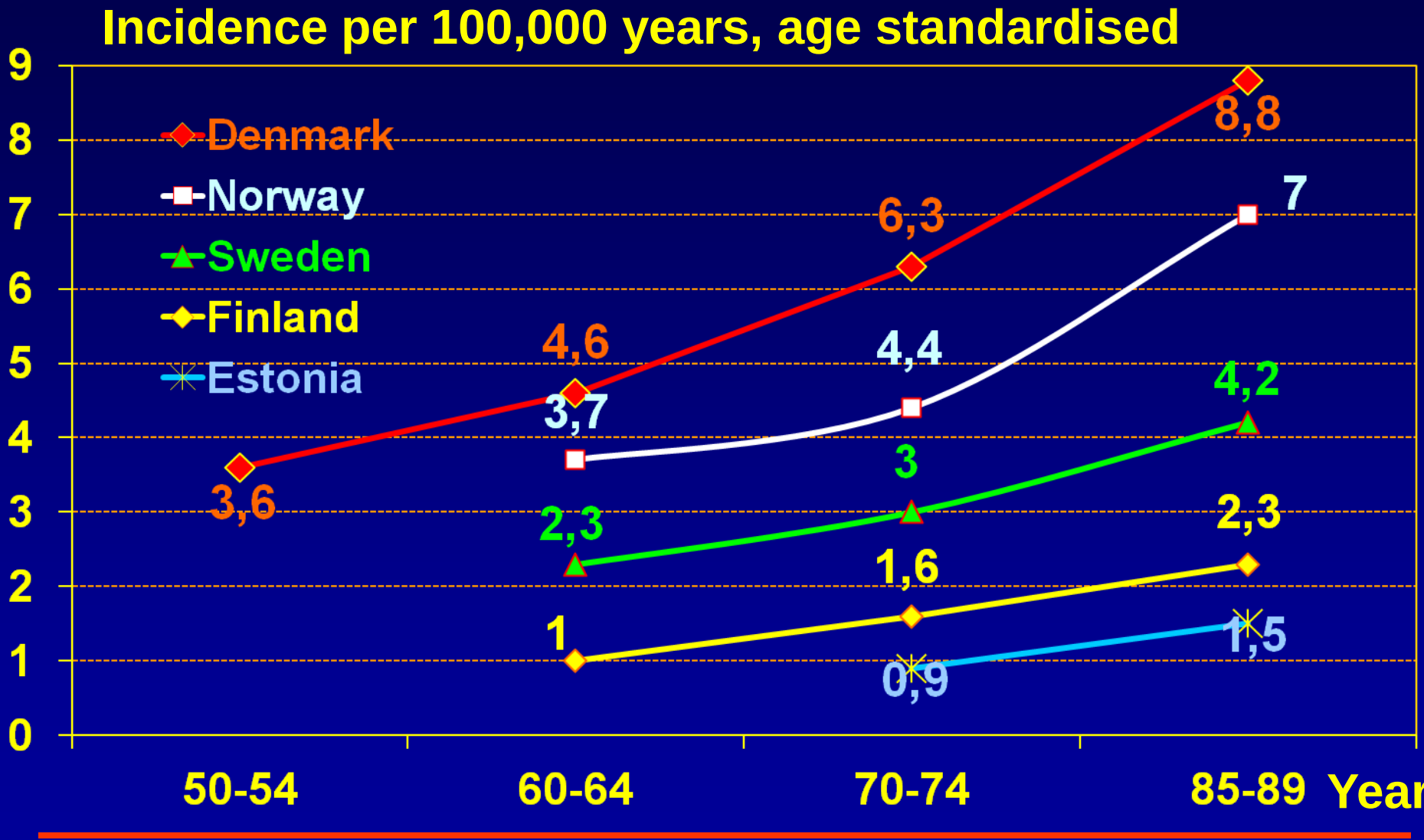
Jørgensen et al: Hum Reprod 2002; 8: 2199-2208

Sperm count and mortality



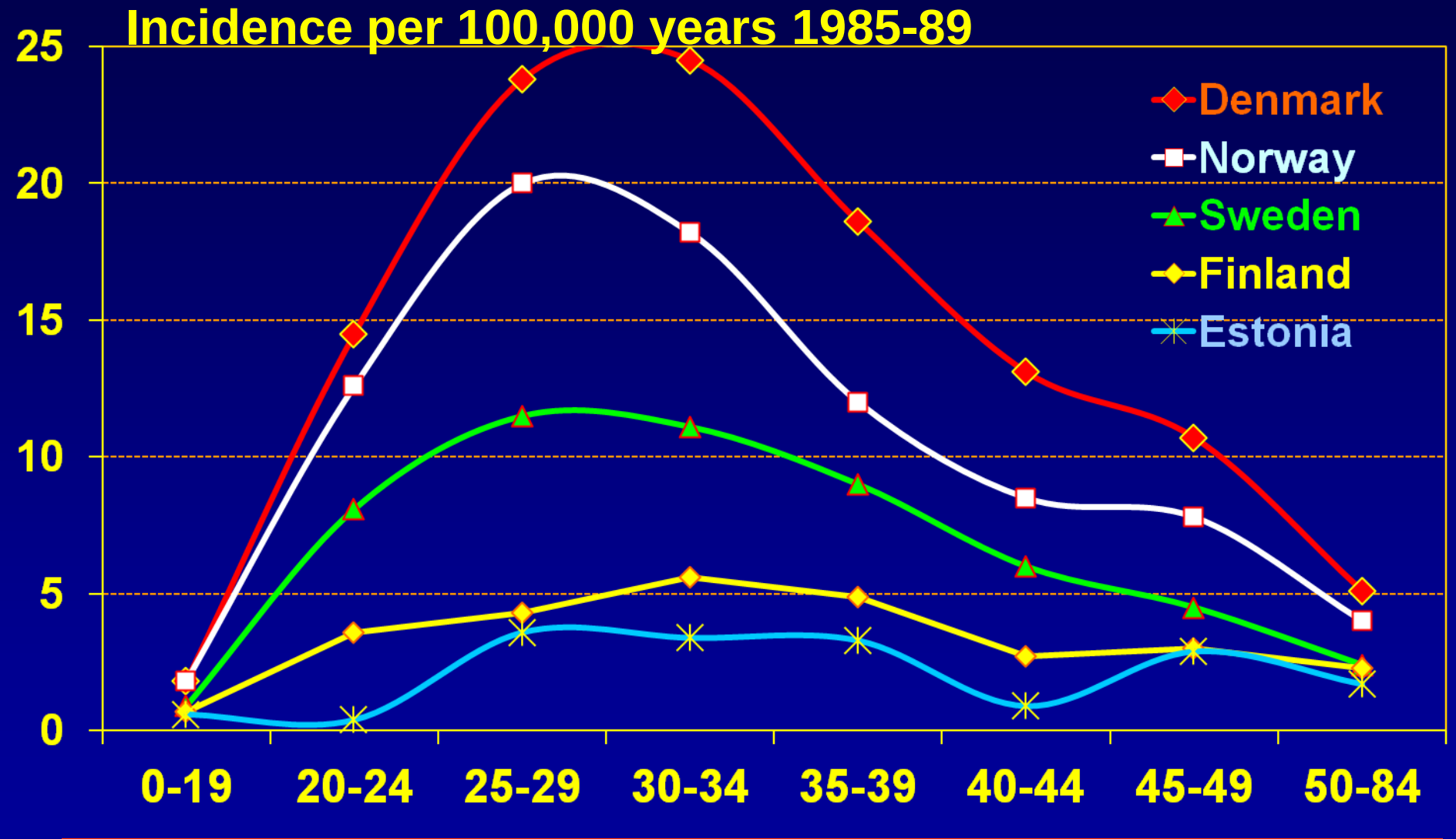
Jensen TK. Am J Epidemiol 2009; 170: 559-65

Testicular cancer: west-east gradient



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

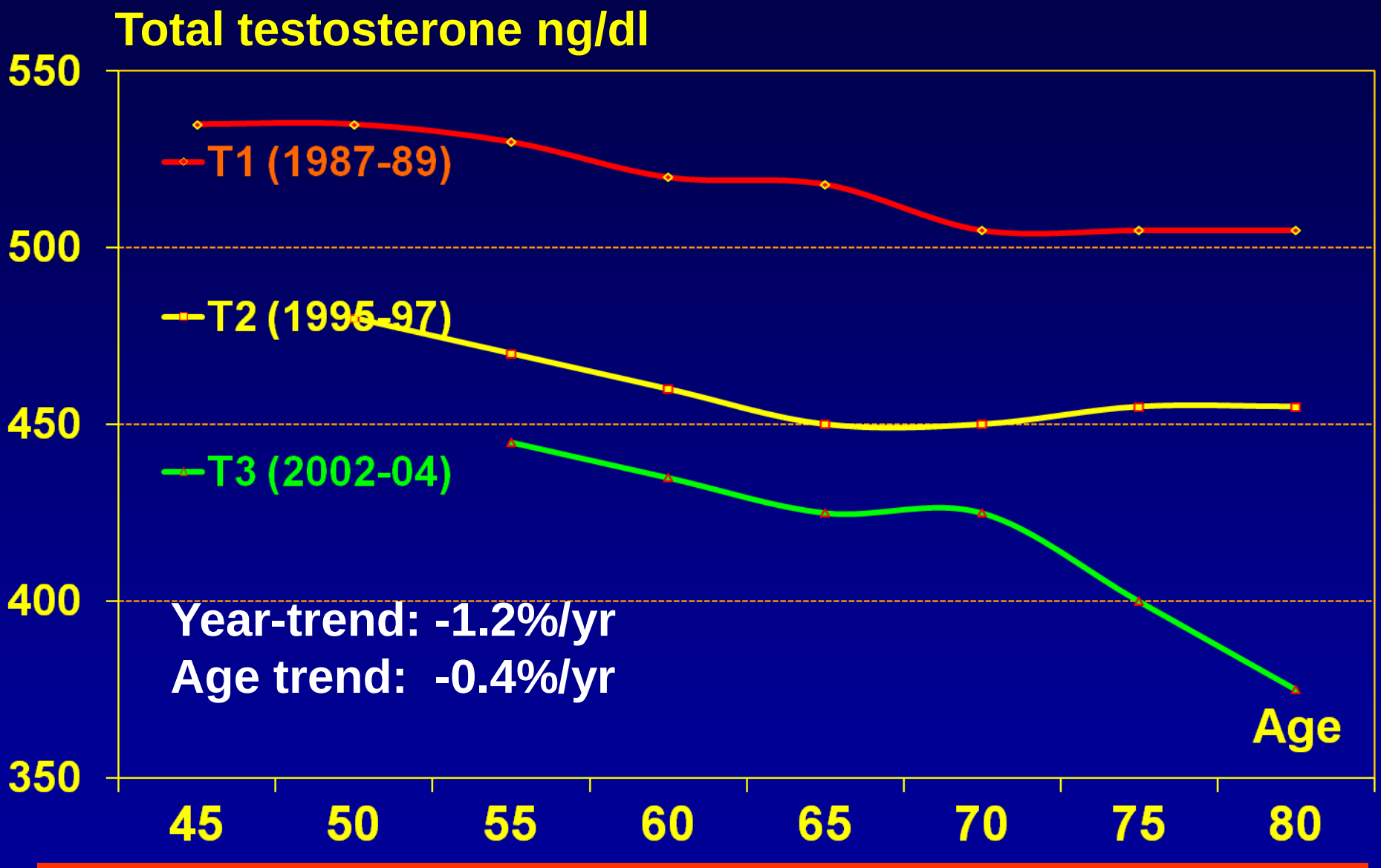
Testicular cancer according to age



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

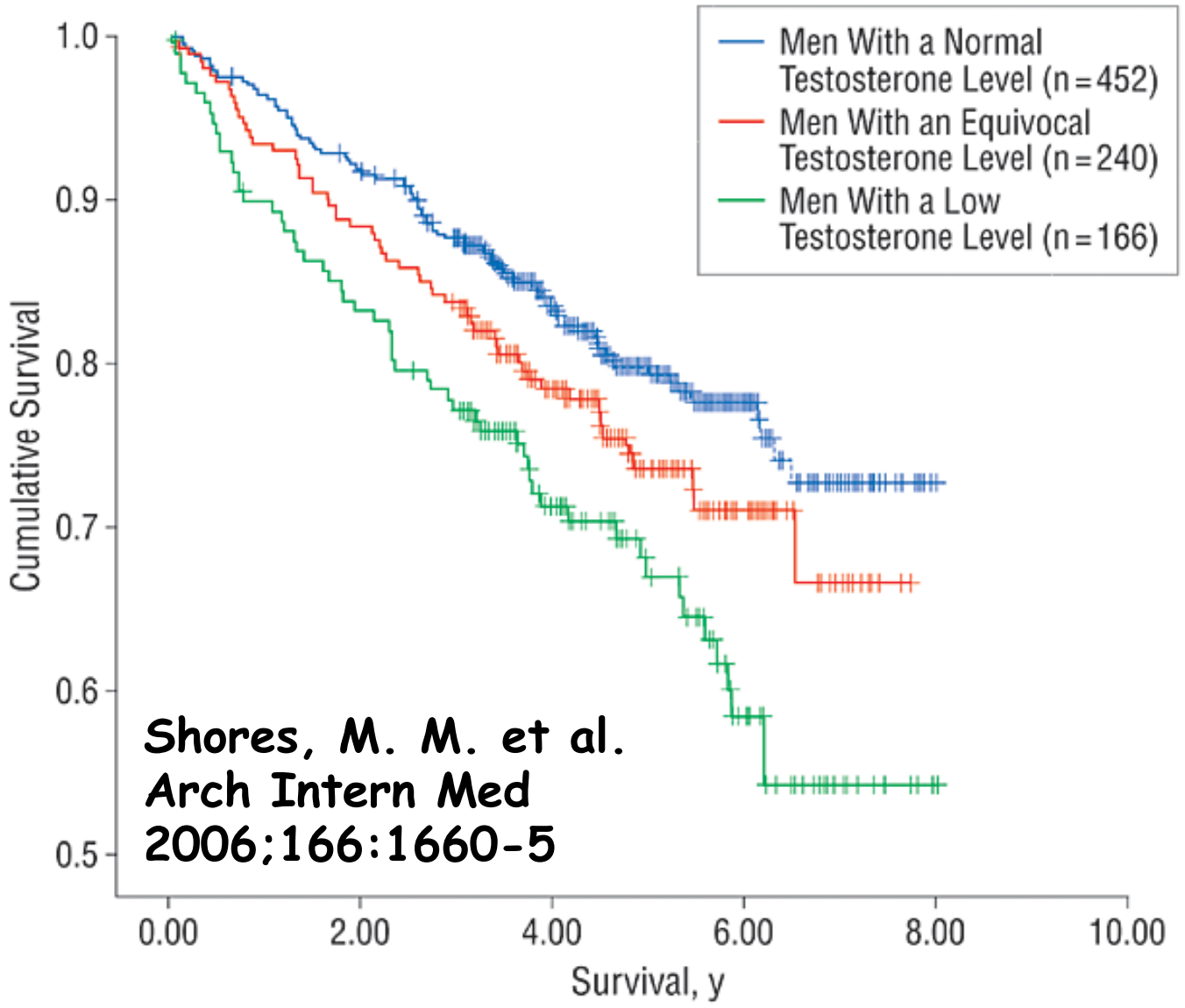
Li/05

Testosterone: Does it change?



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

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

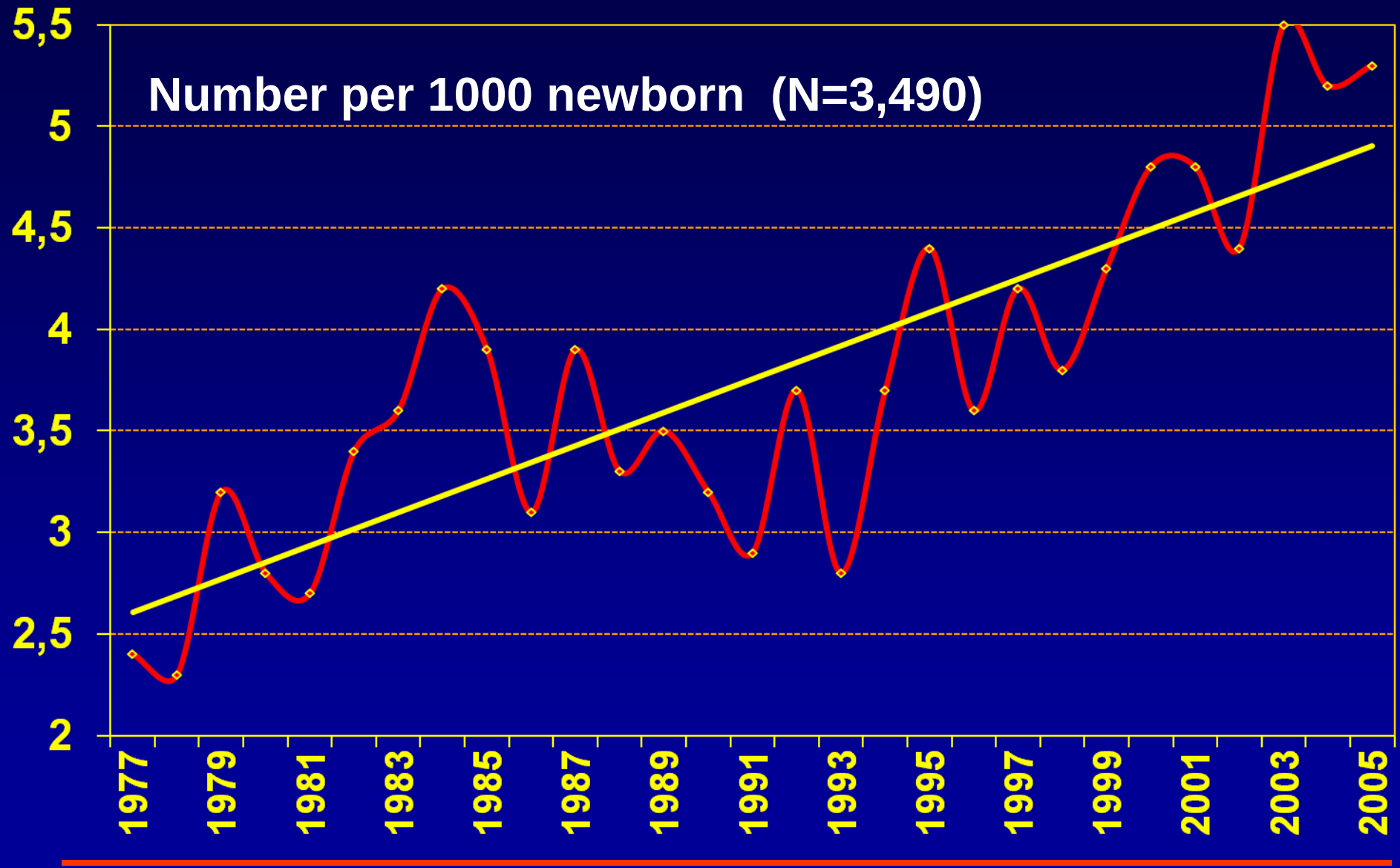
Cross sectional study in US, Health survey 1988-91, 1,226 men ≥20 years.

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

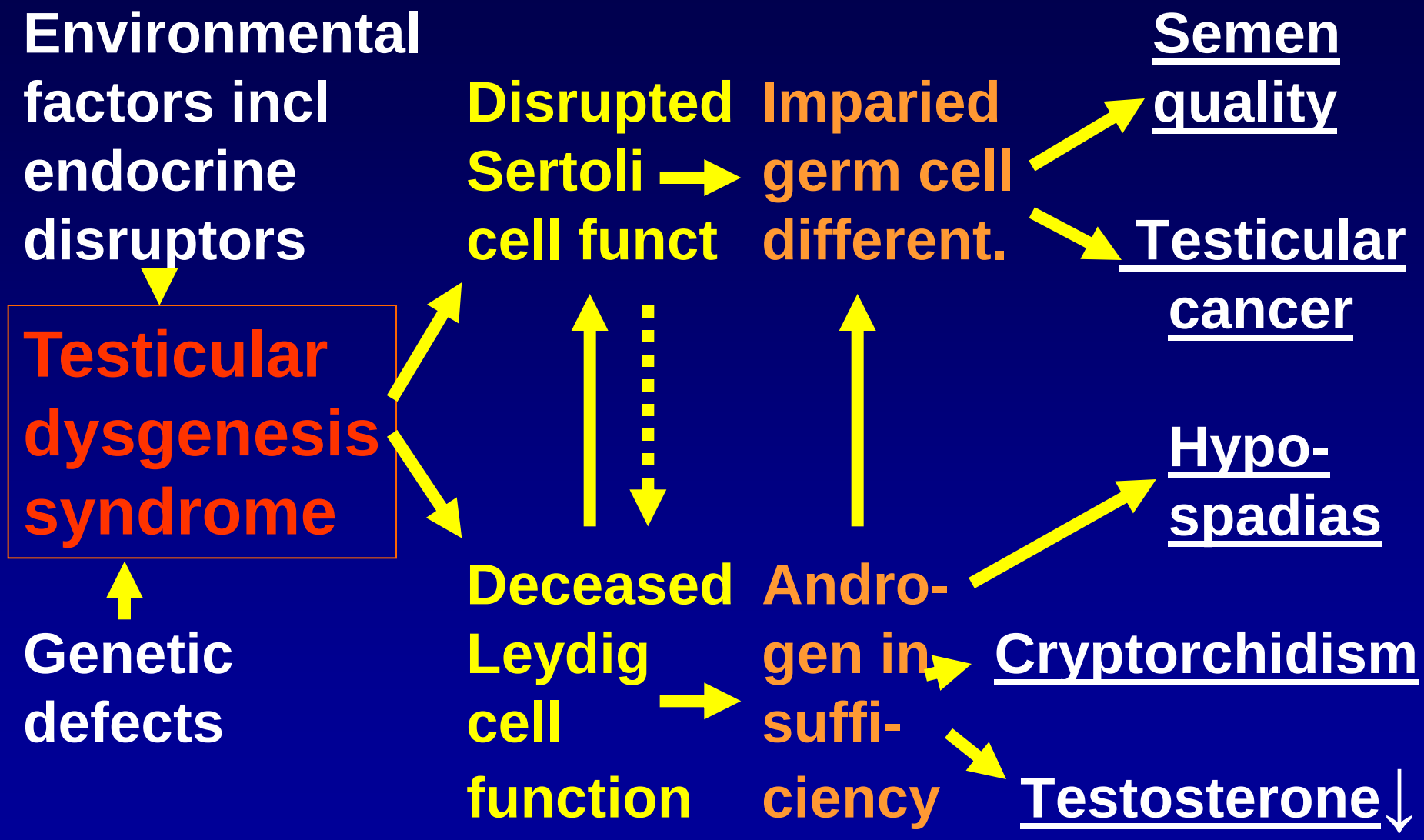
Li et al. Diabetes Care 2010; 33: 1618-24

Hypospadias in DK 1977-2005



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

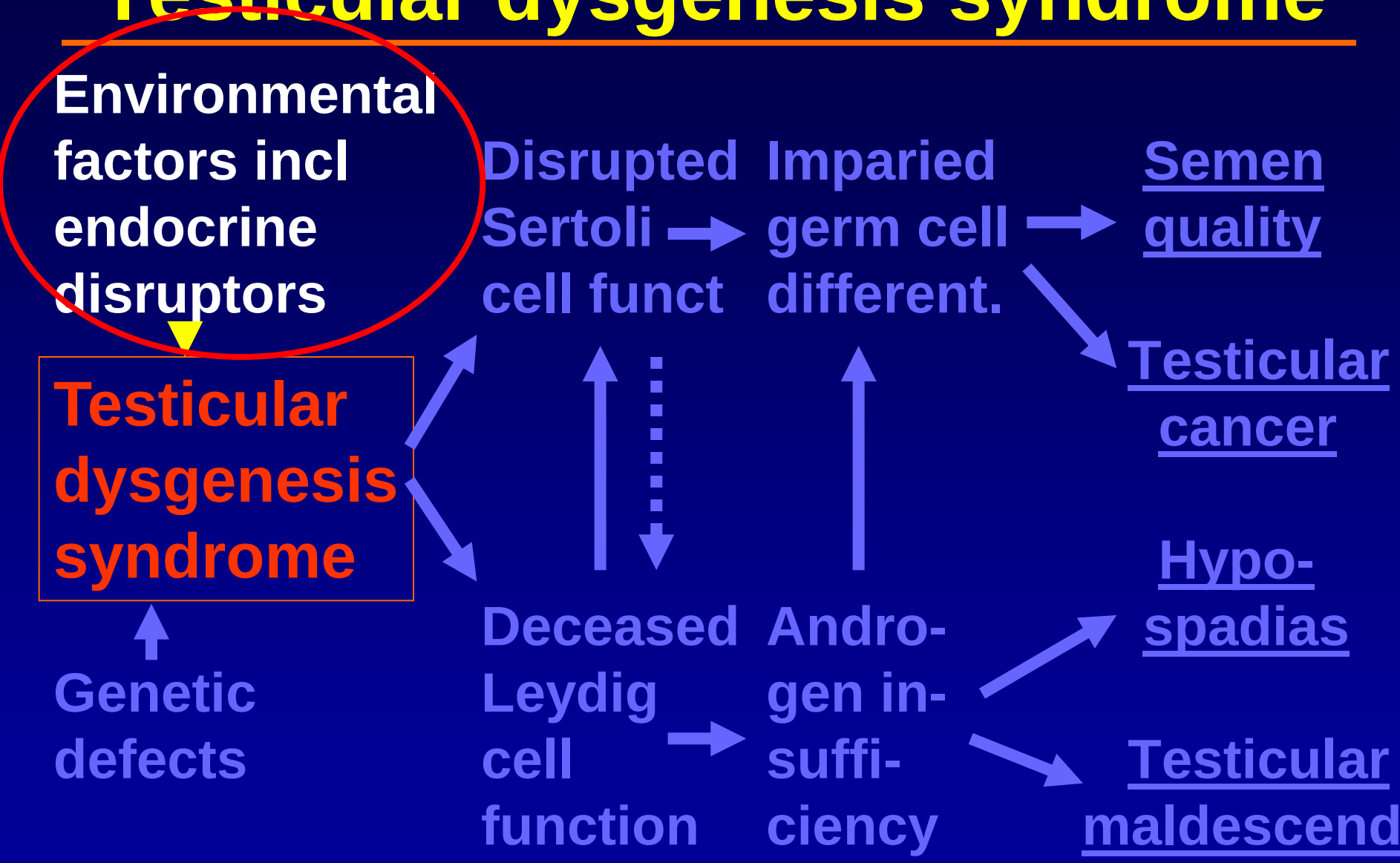
Testicular Dysgenesis Syndrome



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

Li/09

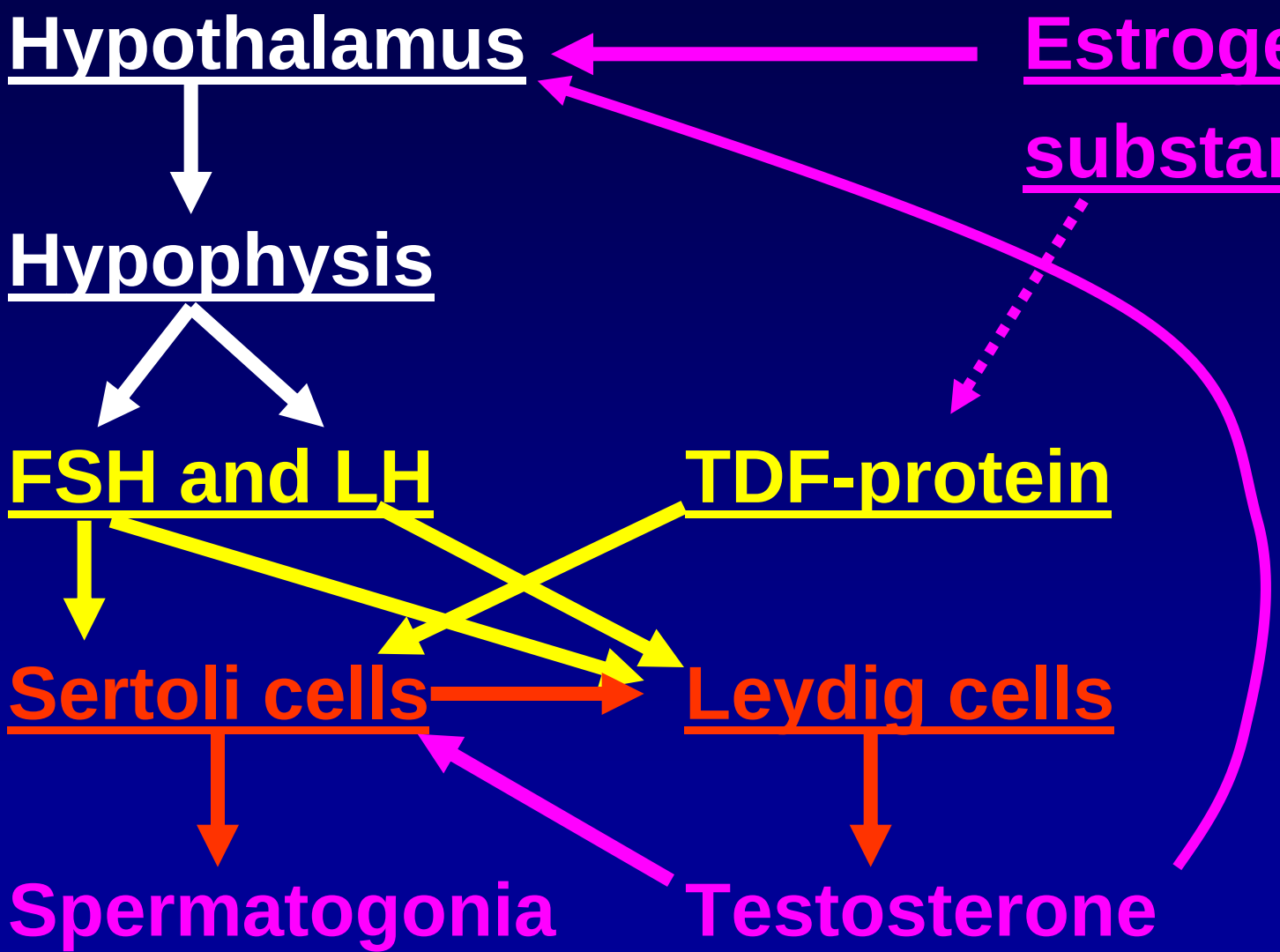
Testicular dysgenesis syndrome



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

Li/05

Male gonadogenesis



Jensen CB & Paludan-Müller P. Økotoksikologi. Nucleus 1997

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

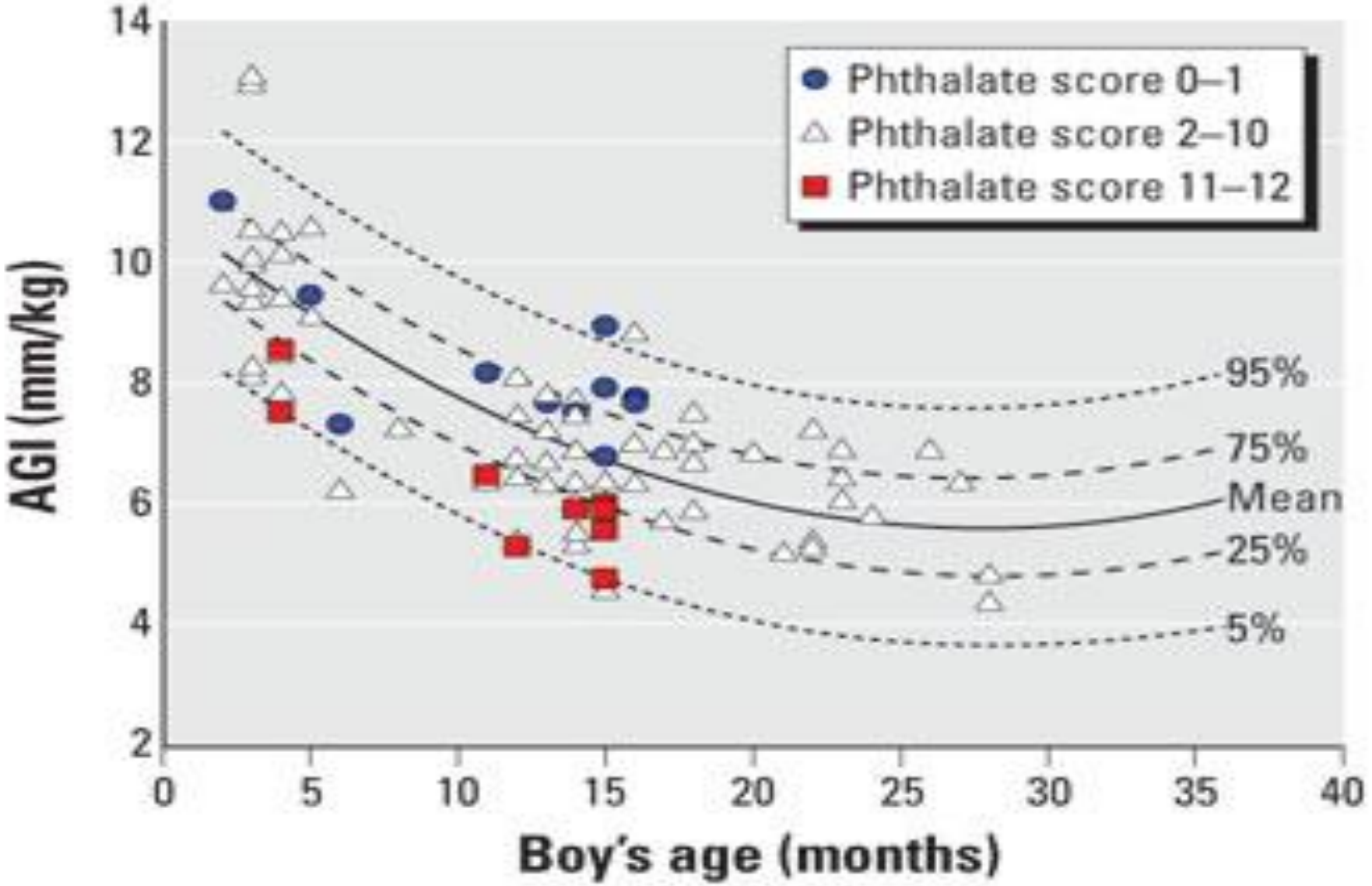


Figure 1. Mean AGI (mm/kg) in relation to boys' age at examination (months).

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

Male fertility

- Pregnant women are exposed to endo-crine disrupters 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

Intergenerational crimes

Definition

- Actions or lack of actions from our generation due to scientific ignorance or denial which have devastating consequences for the next generation, consequences which could have been prevented by appropriate actions by our generation, for costs for us which amounts few per cent of the costs for the next generation to adapt to our hand over.

Intergenerational crimes

- Human made global warming
- Overuse of non-renewable resources
- Emission of toxic industrial products into the environment damaging male reproductive capacity in next generation
- Paid media crusade to deny or cloud scientific evidence of our footprint delaying appropriate actions in due time
- Nuclear waste deposits

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