

# Oral contraceptives

## Epidemiological aspects

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# OC: Epidemiological aspects

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- **OC use**
- OC and thrombosis
  - venous thromboembolism
  - cerebral thrombosis
  - AMI
- OC and cancer
- OC and women at risk

# OC use in Denmark 1966-2005



Calculated from total sale in DDD/fem pop 15-44 years.

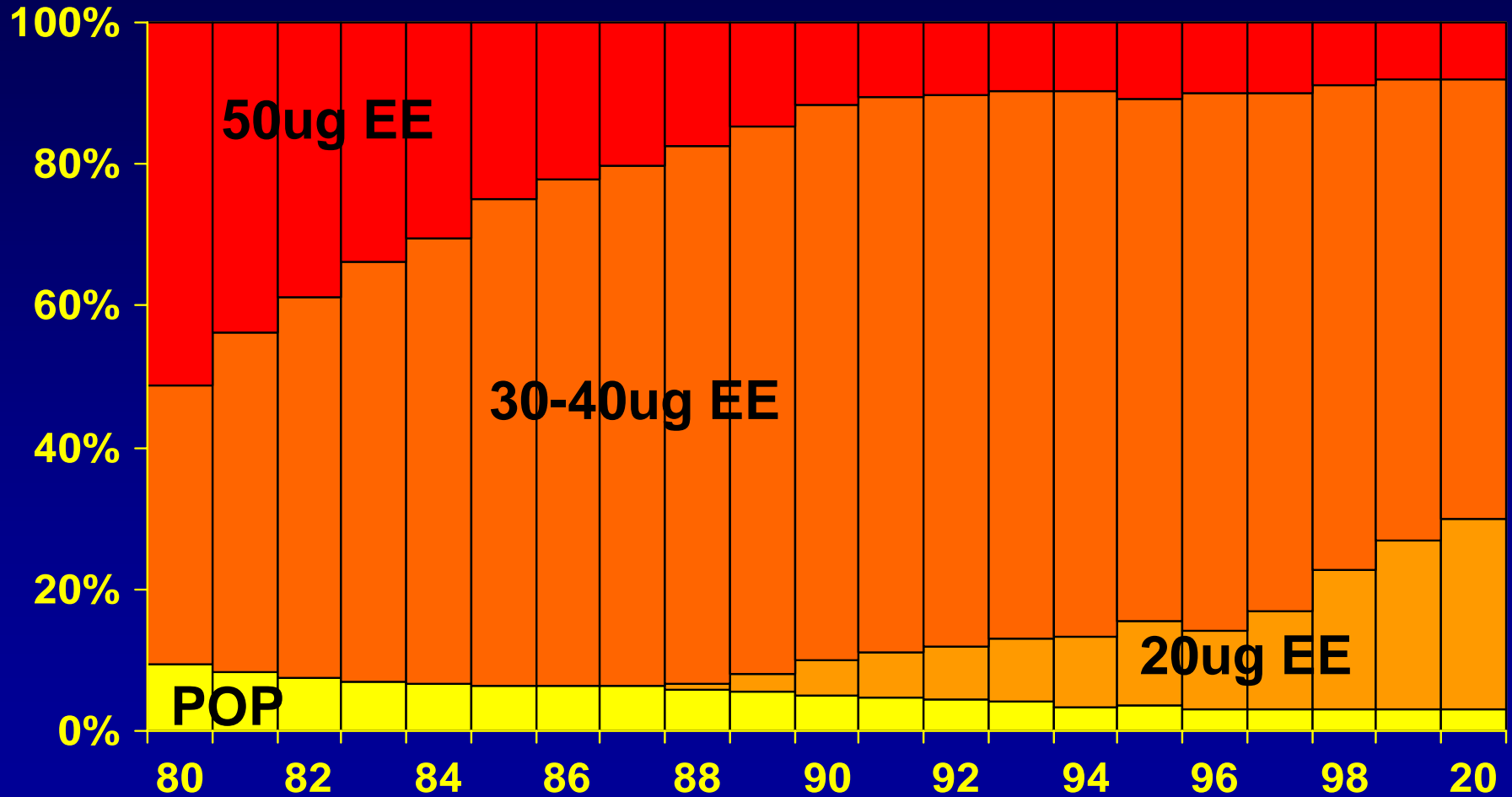
# OC generations according to estrogen dose and progestagen type

## Progestagen generation

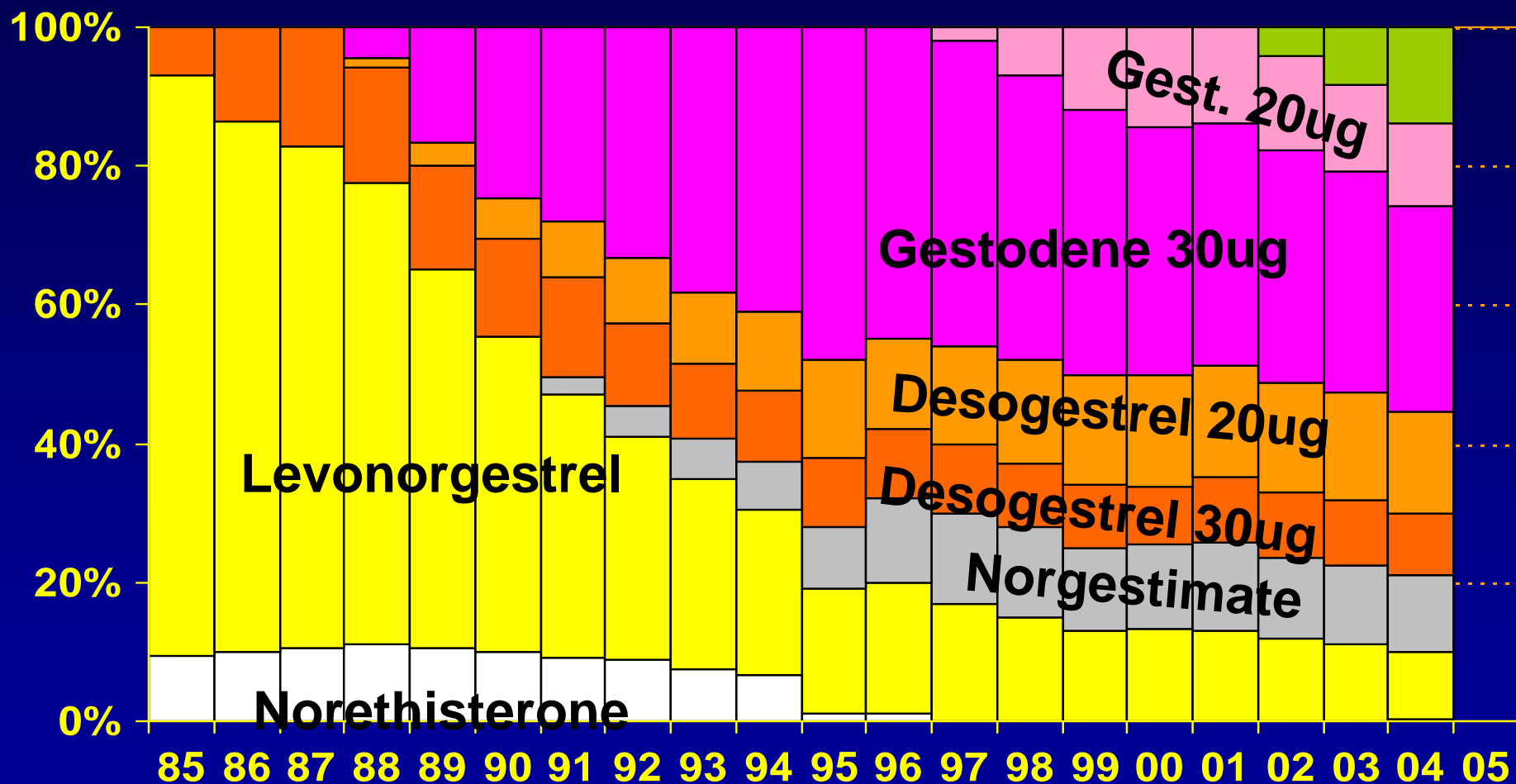
	1	2	"2"	3	3	4
	Estrans NETA	Levonor- gestrel	Norges- timate	Deso- gestrel	Gesto- dene	Dros- pirenon
50	-	<b>1st+</b>	EVRA	-	-	-
30-40	-	+ <b>2nd</b> +		+ <b>3rd</b> +		+ <b>4th</b>
20	-	-	-	Nuvaring	+	+
POP	+	+	-	+	-	-

Low dose = 20-40ug EE

# OC types in DK according to estrogen dose during the period 1980-2000

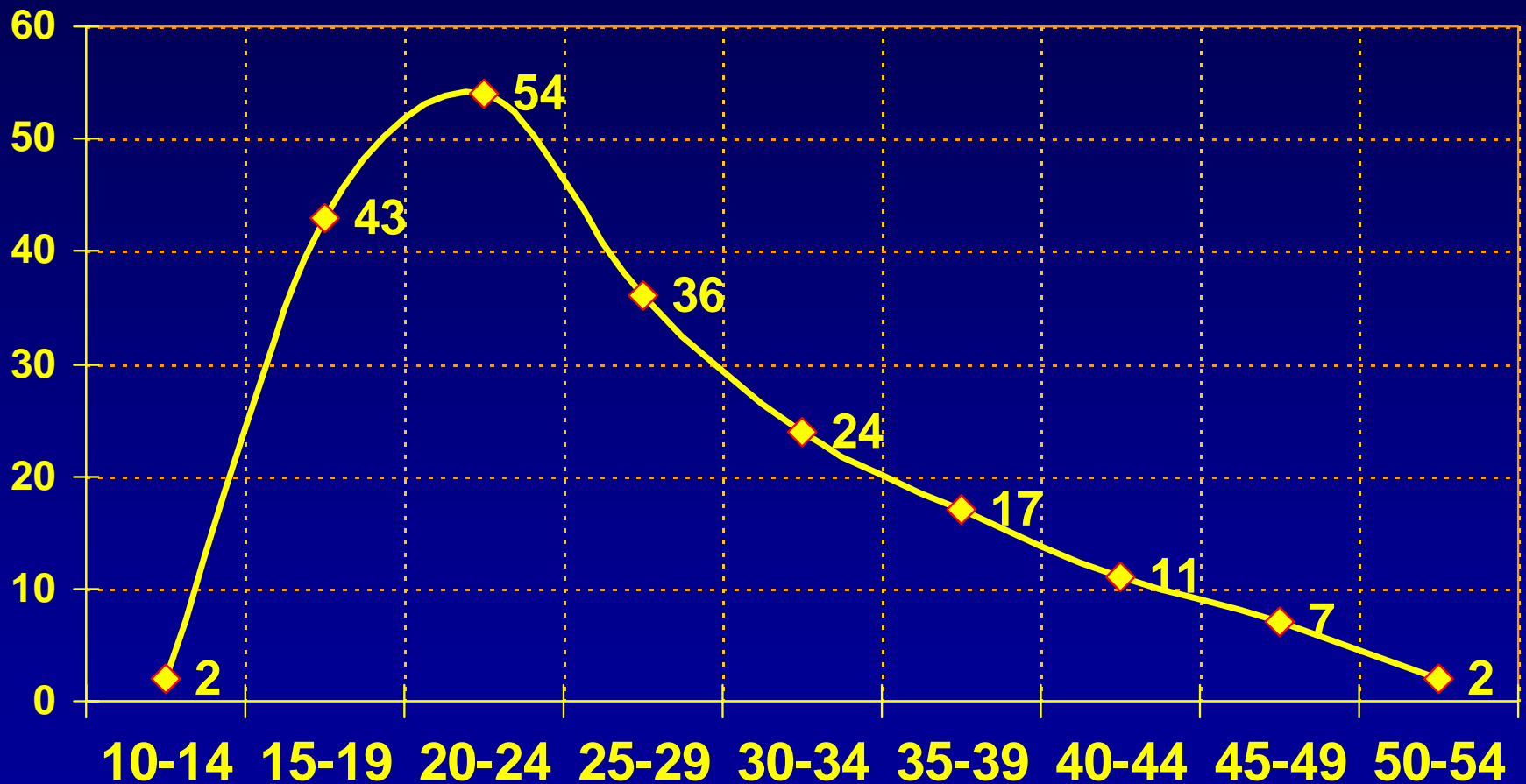


# Progestagen types in combined OC in Denmark 1985-2004 (%)



# Use of oral contraceptives in DK 2003

DDD/100 women/day at different ages



# OC: Epidemiological aspects

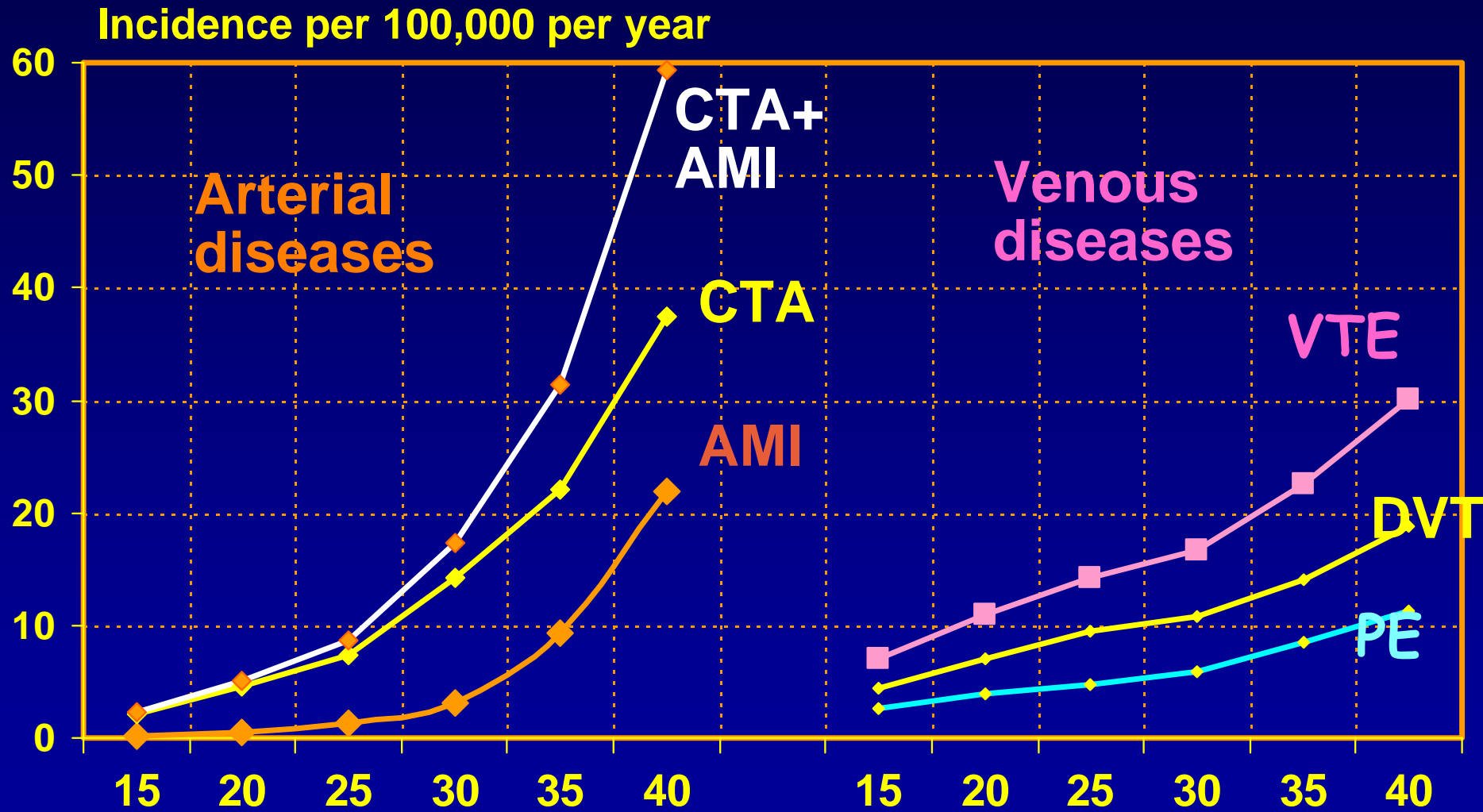
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# CTA, AMI and VTE in DK 1980-93

## Pregnant and puerperal women excluded



# Thrombotic diseases in young women

## Quantitative and qualitative impact

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- Incidence rate of disease
  - Mortality/case-fatality rate
  - Disability among survivors
  - Long-term survival
  - Age differentiation
-

# Thrombotic diseases in young women

<u>Per 1 million per year</u>	<b>CTA</b>	<b>AMI</b>	<b>VTE</b>
Incidence	170	62	230
Non pregnant	150	60	170
Mortality	3	15	2.7
Non pregnant	3	15	2.3
Case-fatality rate	2.3%	25%	1.3%
Significant disability	30%	30%	5%
Long-term survival	↓	↓↓	→

# Risk factors for cardiovascular diseases in women of reproductive age

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	CTA	AMI	VTE
High age	+	+	+
Smoking	+	+	-
Hypertension	+	+	-
Diabetes	+	+	-
Family VTE	-	-	+
Family AMI	+	+	-
Family CTA	+	+	-
BMI >30	-	+	+
Migraine	+	-	-
Varicose veins	-	-	+
Leiden fact V	-	-	+

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# VTE: Genetic risk factors

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<b>Risk factor</b>	<b>Prevalence</b>	<b>RR</b>
Leiden fact V hetero	5%	8
Leiden fact V homoz	0.2%	64
Protein C insufficiency	0.2%	15
Protein S insufficiency	<0.1%	>10
Antithrombin III insuff.	0.02%	50
Prothrombin 20210A	2%	3
Hyperhomocysteinaemia	3%	3

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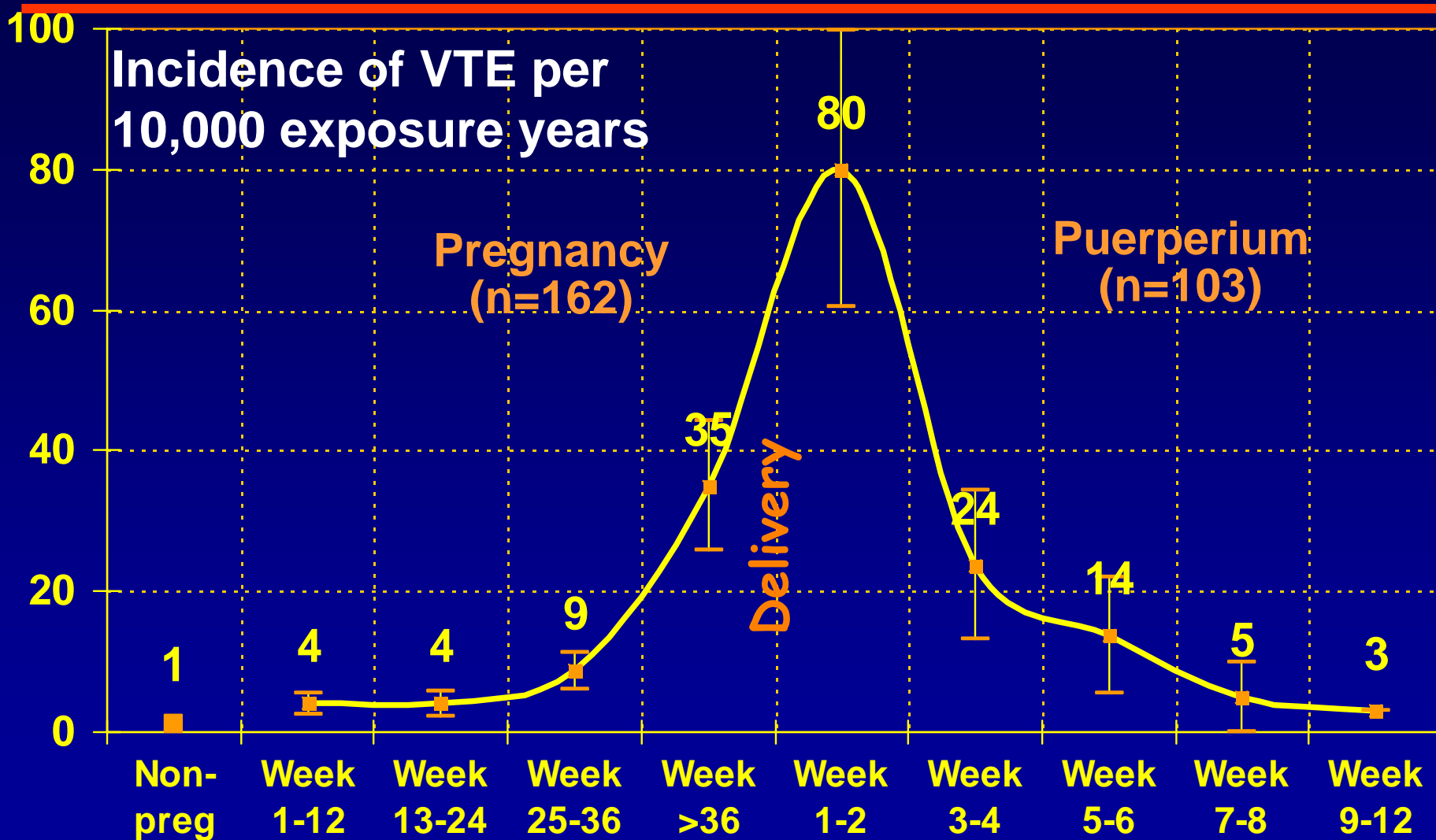
# VTE: Acquired risk factors

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	Prevalence	RR
Age $\geq 30$ vs $< 30$	50%	2.5
Pregnancy	4%	8
Adiposity (BMI $> 25$ )	36%	2
Varicose veins	8%	2
Immobilisation/trauma	?	2-10
Oral contraceptives	33%	3-4
Medical diseases	5%?	2-5

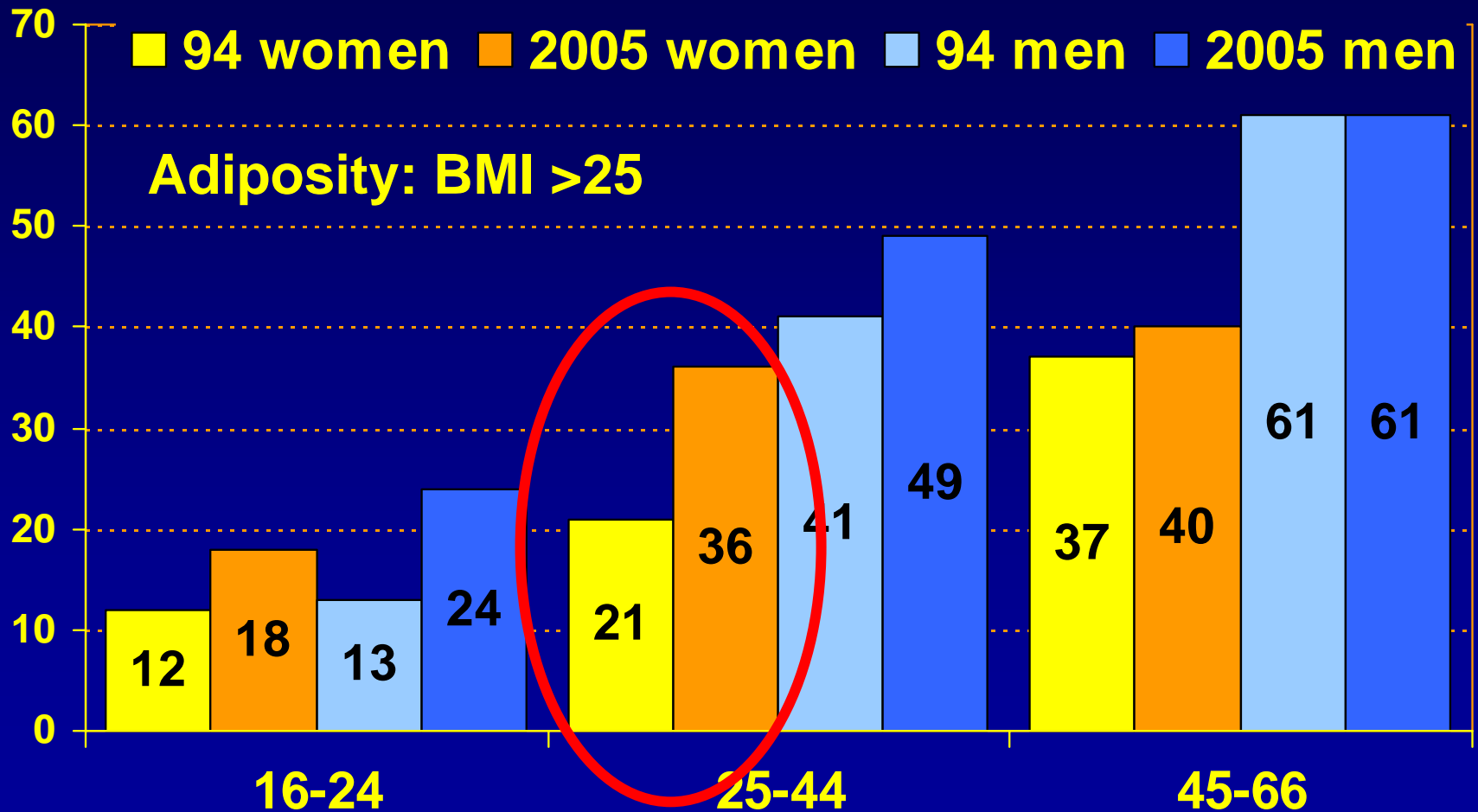
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# Incidence rate of VTE among pregnant and puerperal women, DK 1994-96. N=265

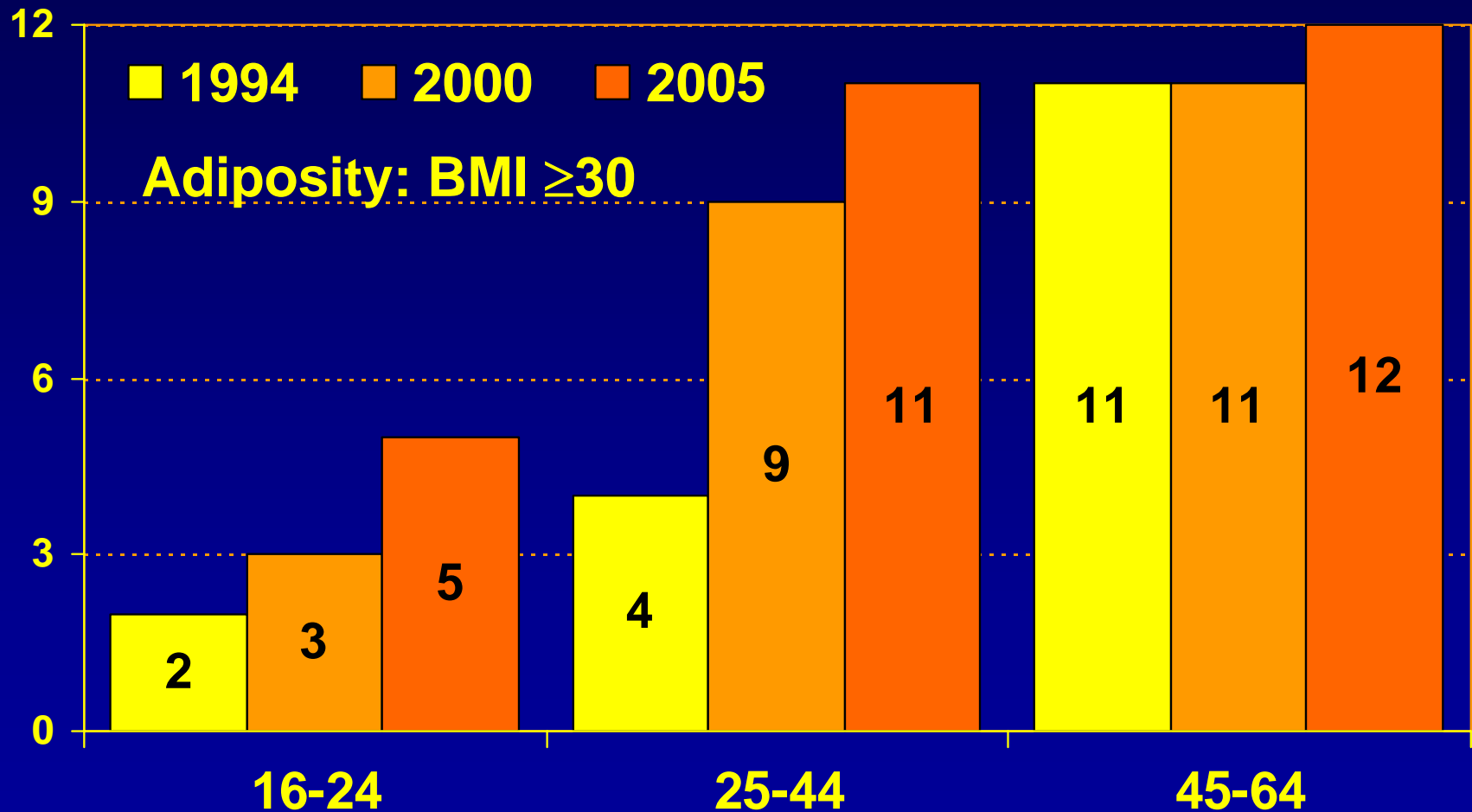




# Adiposity in Danish women and men in 1994 and 2005



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



# OCs and VTE studies

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	PDS	cas/con	2nd	3rd
Blomenkamp	88-92	126/159	3.8	8.7
WHO, Eur	89-93	433/1044	3.6	8.7
Jick, UK	91-94	80/cohort	ref	1.8
Spitzer	91-95	471/1722	3.2	4.8
Lewis	93-95	502/1864	2.9	2.3
Farmer	91-95	85/cohort	3.1	5.0
Todd	92-97	99/cohort	ref	1.4
Blomenkamp	82-95	185/591	3.7	7.0
Lidegaard	94-98	987/4054	2.9	4.0
Dinger	00-04	118/cohort	4.gen: 4	
Seeger	01-04	57/cohort	4th vs ot: 0.9	

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# OCs and AMI studies

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Study	PDS	cas/con	2nd	3rd
WHO, Eur	89-95	198/480	1.6	1.0
95% CI:			0.5-5.5	0.1-7.0
Lewis (97)	93-96	182/635	3.0	0.8
95% CI:			1.5-5.7	0.3-2.3
MICA (99)	93-95	448/1728	1.3	1.8
95% CI:			0.6-2.6	0.8-4.1
Lidegaard	94-98	264/4054	1.2	1.8
95% CI:			0.6-2.3	1.1-3.0

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# OCs and thrombotic stroke

Study	PDS	Cases/ controls	OR 2nd/3rd
WHO	89-93	489/3967	2.7/1.7
Schwartz	91-95	175/1191	1.1
Heinemann	93-96	220/439	2.7/3.4
Lidegaard	94-98	626/4054	2.2/1.4

Lidegaard et al. Contraception 2002; 65: 197-205

# OCs and thrombosis

## Current status November 2007

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	CTA	AMI	VTE
2nd gen:	2.5	1.5	3.0
3rd gen:	1.5	1.5	4.0
4th gen:	?	?	4.0

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# OCs and cancer risk

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	Relative risk
• Breast cancer:	1,0
• Endometrial cancer:	0,5
• Ovarian cancer:	0,5
• Cervical cancer:	1,2
• All cancers:	No change
• All cause mortality:	No change

**Conclusion:** No change in risk of cancer in general in ever-users of OCs

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# Clinical guidelines

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## When OCs are prescribed

- Careful clinical history including risk factors and family disposition
- Previous VTE: No OCs
- Genetic predisposition

VTE risk factor  $\geq 5$ : No OCs

VTE risk factor  $< 5$ : Careful inf, 2<sup>nd</sup> gen

No risk factors: Any low dose pill

Arterial risk factors: 3<sup>rd</sup> gen. pill

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# Migraine and OCs

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<b>Risk of cerebral thrombosis:</b>	<b>RR</b>
Migraine in general	3
Migraine with aura	6
Migraine without aura	2
2. Gen. OCs	2,5
3. Gen. OCs	1,5
Migraine + 2. Gen OCs	7,5
Migraine + 3. Gen OCs	4,5

**Conclusion:** No OCs to women with migraine with aura. Otherwise 3. gen.

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# Smoking and OCs

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<b>Risk of thrombosis:</b>	<b>Brain</b>	<b>Heart</b>
Smoking <10/day	1.0	4
Smoking 10-20/day	1.5	6
Smoking >20/day	2.0	8
2. Gen. OCs	2.5	1.5
3. Gen. OCs	1.5	1.5

**Conclusion:** No OCs to women smoking  $\geq 20$  cigarettes/day and who are  $>35$  yrs.

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# History when OCs are prescribed

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- Previous thrombosis?
  - Smoking, diabetes, hypertension
  - Migraine, with or without aura
  - Family thrombosis?
  - Previous compliance with OCs
  - Menstrual bleedings
  - Actual liver disease
  - Sexual practice
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# Clinical examination when OCs are prescribed

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- Women >25 years: BP
- Women with risk factors: BP
- BMI (=weight / height<sup>2</sup>)
- Varicose veins

**Time for a control after three months where BP is measured on all women.**

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# Routine information when OCs are prescribed

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- How to manage a forgotten pill.
- **Warning signs:** New migraine, dizziness, visual disturbances
- Adaptation take few months
- Increased risk of venous thrombosis, the absolute risk however low
- Common not serious side effects
- Common non-contraceptive benefits