

Case 2

32 årig kvinde, som fødte sit første barn for 6 måneder siden. Hun søger nu råd vedr. kontraception.. Hun har før graviditeten anvendt p-piller i 12 år uden problemer, og vil gerne starte igen. Hun ryger 5-10 cigaretter daglig. En søster har udviklet DVT under graviditet og hendes møster er i behandling for ovariecancer. BT 130/80, BMI 26.

Kan hun anvende p-piller ???

Hvorfor/hvorfor ikke ?????

Risk of vascular disease during OC

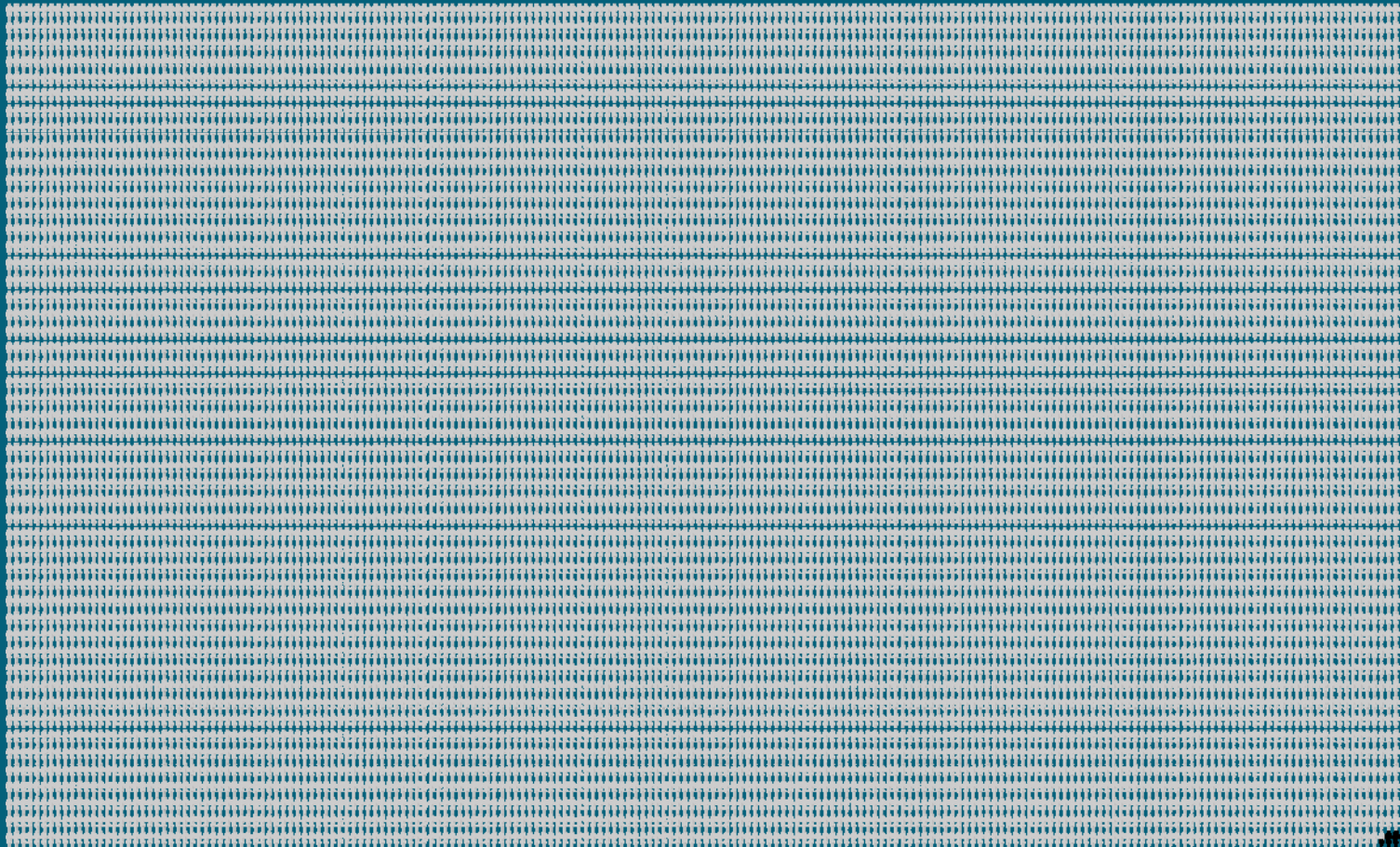
- OCs introduced in 1960
- 1961 – Deep venous thrombosis and PE
- 1962 – Apoplexia cerebri
- 1963 – Myocardial infarction

Venous thrombosis in fertile women

Absolute risk figures

- No OC and not pregnant: 1 case
of DVT pr. 10.000 women pr. Y
- Pregnancy:
6-7 cases of DVT per 10.000 women per y.
- OC use:
3-4 cases of DVT pr 10.000 women pr. Y

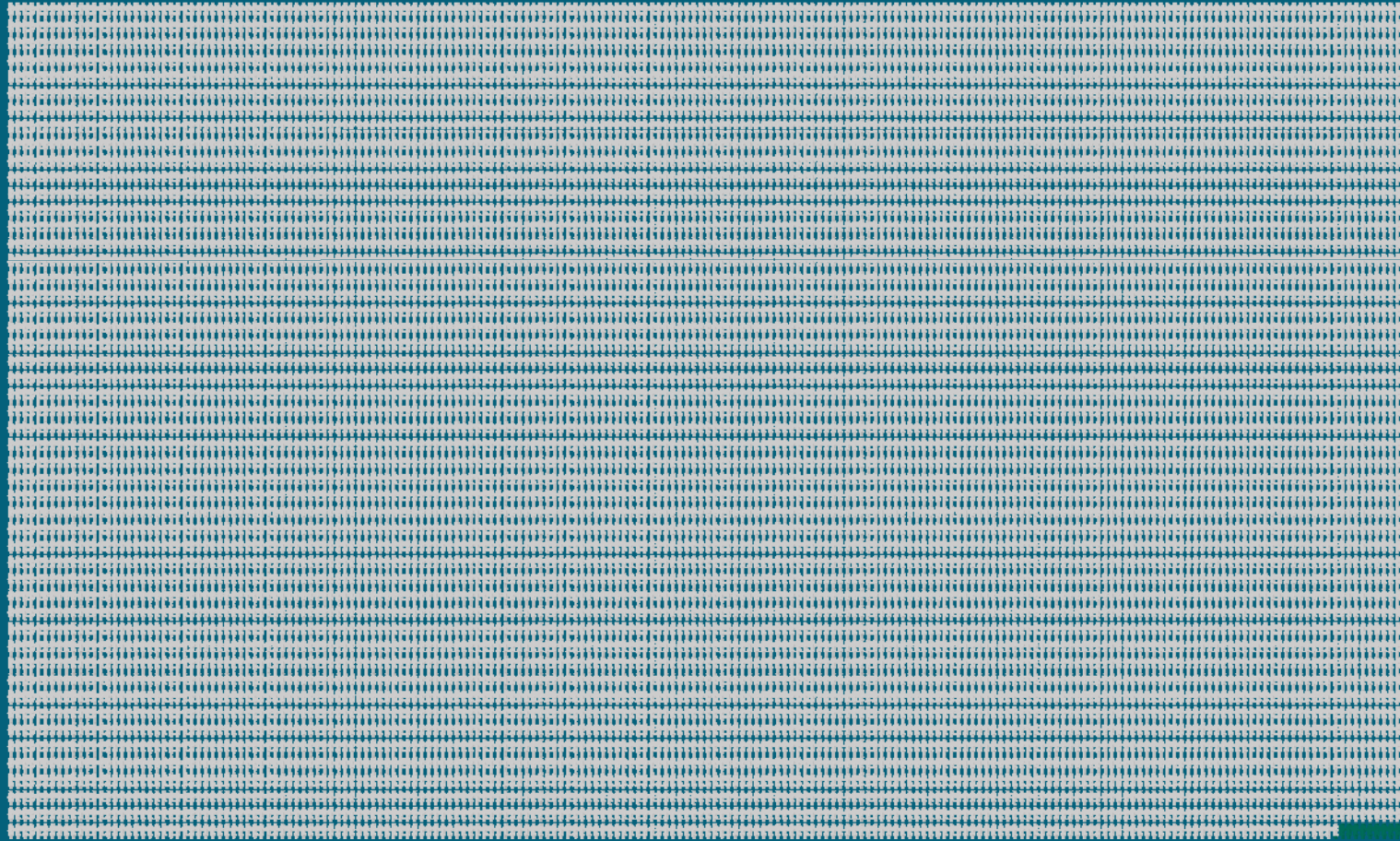
Venetromboser hos kvinder 15-45 år. Ikke gravide, ingen p-piller



Non Pregnant Non Users

Based on a representative survey of 48,525 German women using EURAS methodology (Dinger Contraception 2007)

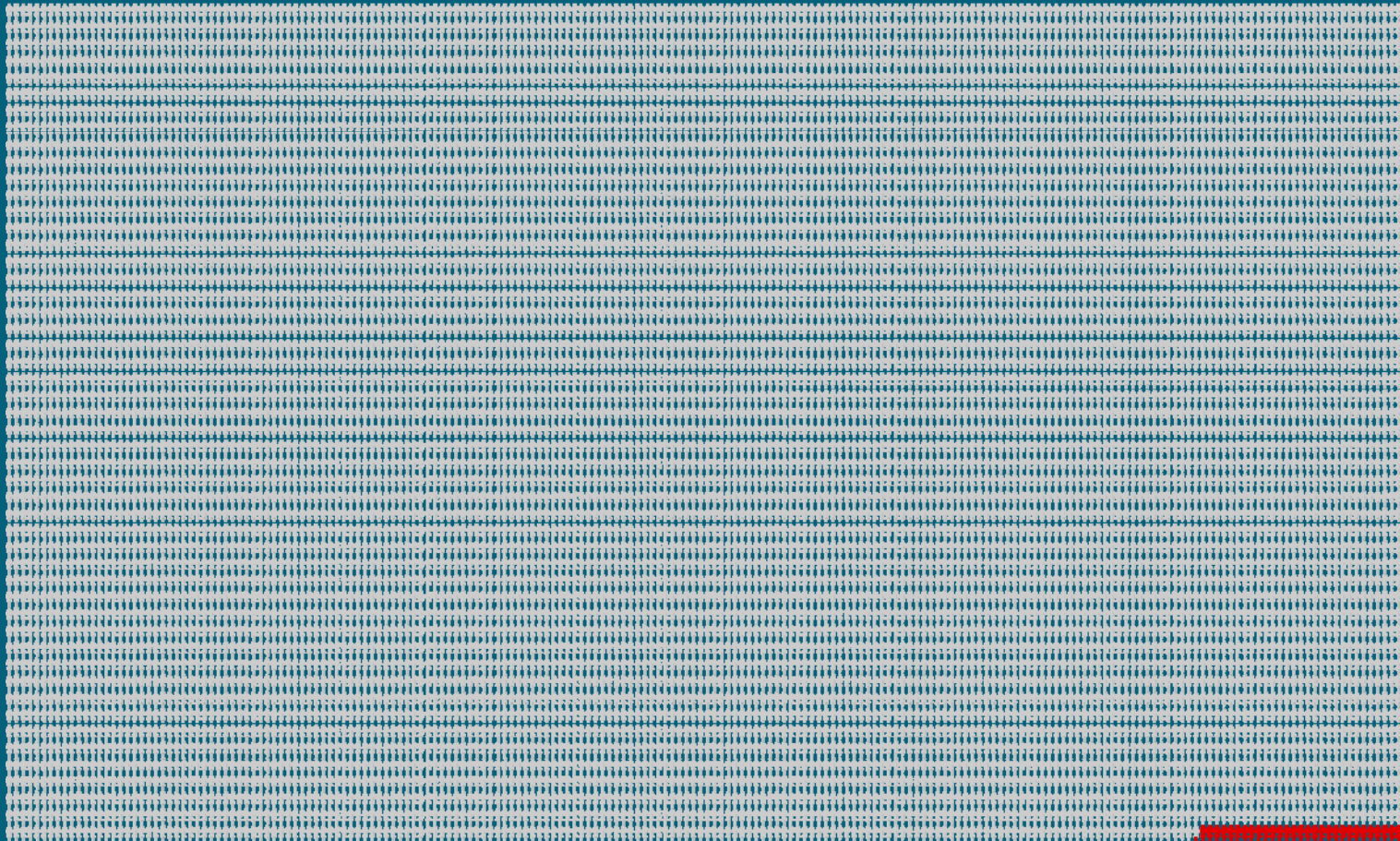
Venetromboser hos kvinder 15-45 år, der bruger p-piller



OC Users

Based on a representative survey of 48,525 German women using EURAS methodology (Dinger Contraception 2007)

Venetromboser hos gravide



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Pregnancy

Based on a representative survey of 48,525 German women using EURAS methodology (Dinger Contraception 2007)

We do have a problem with sex steroids
and haemostasis !



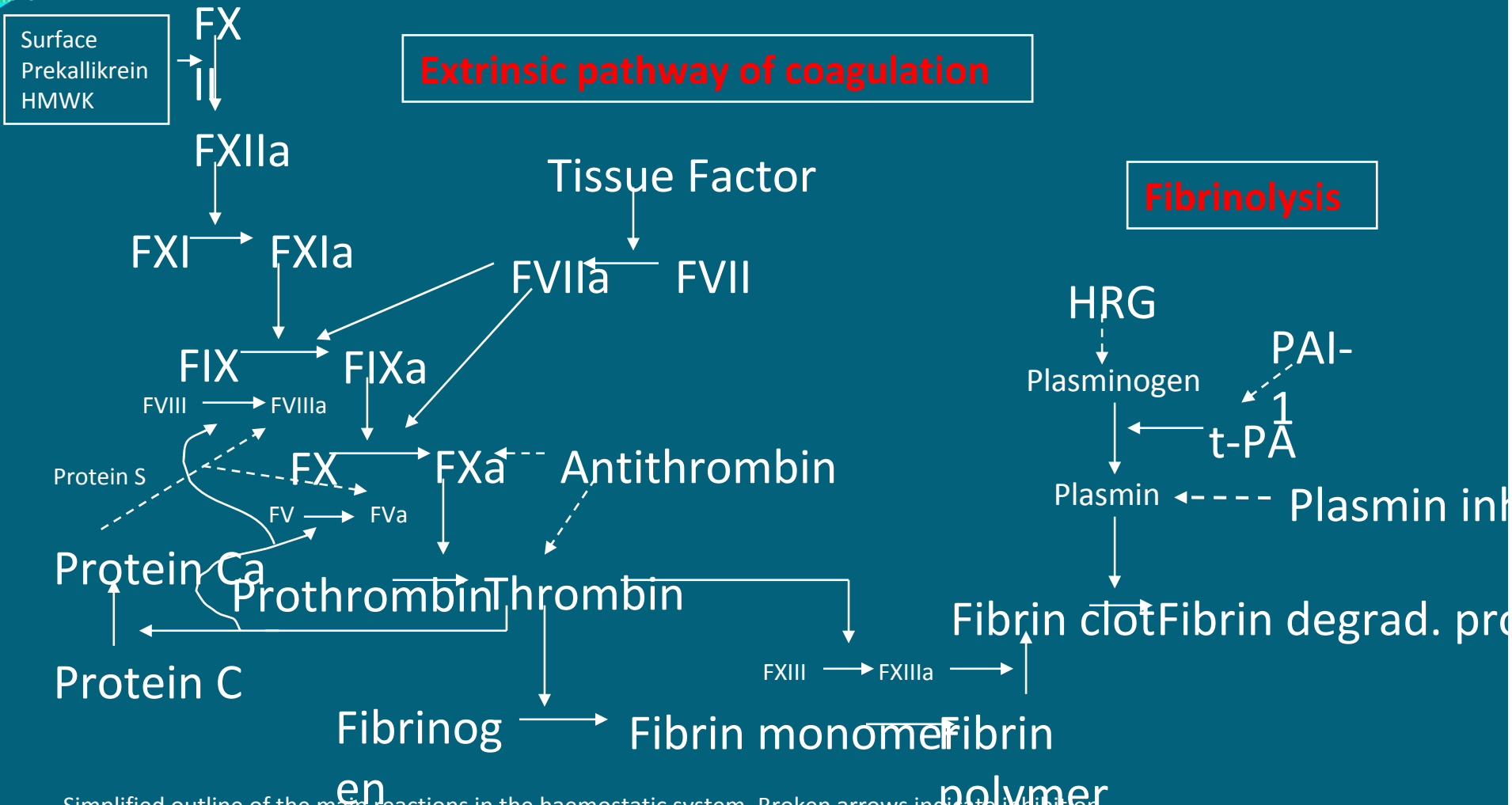
Genetic risk factors for primary VTE

Genetic change	Frequency in population (%)	Frequency in non-pregnant VTE populations (%)	Relative risk
Factor V Leiden	7	25	3-4 (13 for HZ)
Prothrombin	2	3-4	2-3 (unknown for HZ)
Antithrombin def.	Unknown	1	25-40
Protein C def.	Unknown	3	10-15
Protein S def	Unknown	2	10-15

Intrinsic pathway of coagulation

Extrinsic pathway of coagulation

Fibrinolysis



Simplified outline of the main reactions in the haemostatic system. Broken arrows indicate inhibition.
 Abbreviations: HMWK: High molecular weight kininogen. t-PA: Tissue-plasminogen activator,
 PAI: Plasminogen activator inhibitor, HRG: Histidine-rich glycoprotein.

Modified from Gram and Jespersen 1999.

Effects of Factor V Leiden mutation on VTE in OC users

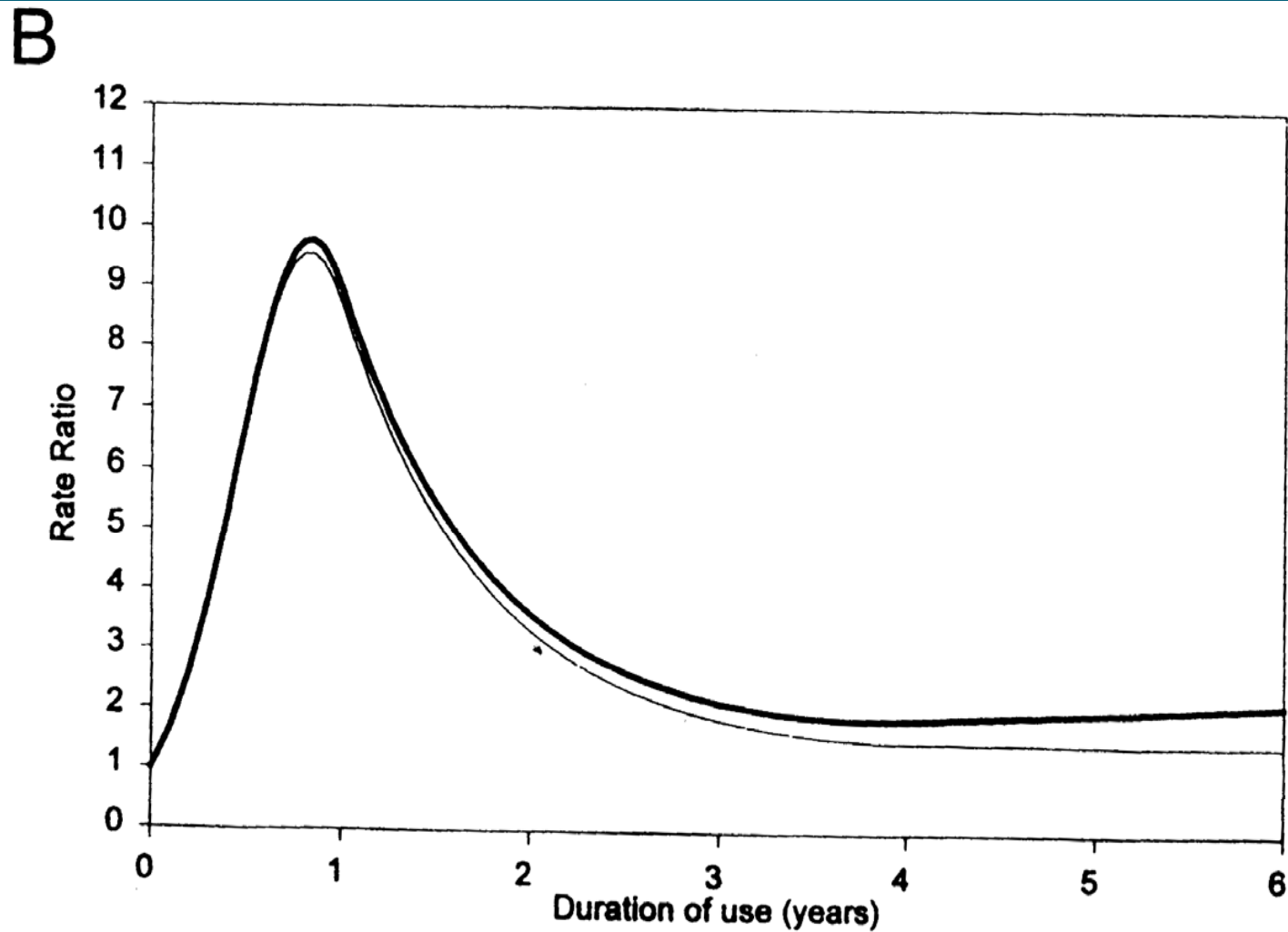
	Patients	Women y.	Inc. Of VTE per 10000
<u>Factor V neg</u>			
No OC	34	437870	0.8
OC	84	275858	3.0
<u>Factor V pos</u>			
No OC	10	17515	5.7
OC	25	8757	28.5

Effects of Prothrombin mutation on VTE in OC users

	VTE	Controls	Odds ratio
Normal GT, no OC	35	127	1 (ref.)
Normal GT, +OC	52	41	4.6 (2.6-8.0)
Protr.Mut, no OC	3	4	2.7 (0.6-12.7)
Protr.Mut, +OC	9	2	16.3 (3.4-79.1)

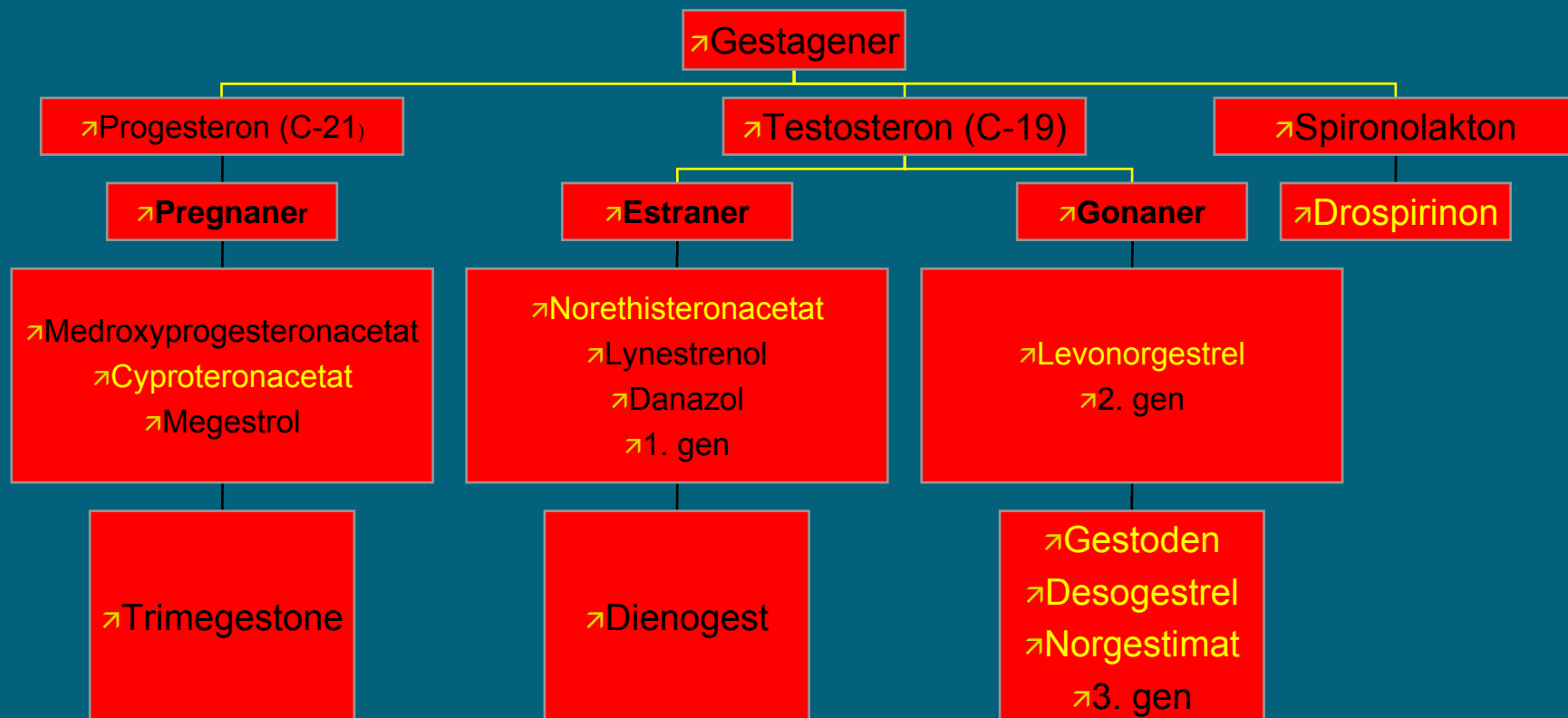
Martinelli. *Arterioscler Thromb Vasc Biol* 1999;19:700-3

Effect of duration of use on VTE risk in OC users



Division of progestagens

➤Classes of progestogens



OCs and venous thrombosis - effect of progestogens 1995-6 studies

	WHO	Leiden	GPRD	Transna- tional
2. gen. (RR)	3.6	3.8	-	3.2
3. gen (RR)	7.4	8.7	-	4.6
3. vs. 2. Gen	2.6*	2.2*	2.2*	1.5*

2. gen: EE+LNG

3. gen: EE+DSG or GST

Ocs and DVT – Danish study (987 cases, 4954 con)

Progestogen

Relative risk

Non-users

1

2. Gen

2.9 (2.2-3.8)

3.gen

4.0 (3.2-4.9)

3 vs 2.

1.3 (1.0-1.8)

Ocs and AMI – effects of progestogens (248 cases, 925 con)

Progestogen	Relative risk
Non-users	1
Any OC	2.0 (1.5-2.8)
2. Gen	2.7 (1.6-4.3)
3.gen	1.6 (0.9-2.9)
3 vs 2.	0.5 (0.2-1.1)

Tanis. N Eng J Med 2001;345:1787-93

OCs and stroke - effect of progestogens

(626 cases, 4054 con.)

	Relative risk
No use	1.0
2. gen. vs no use	2.2 (1.6-3.0)
3. gen vs. no use	1.4 (1.0-1.9)
3. gen. vs. 2. gen	0.6 (0.4-0.9)

New progestogens

Drospirinone

Derived from spironolactone

Competitive aldestorone receptor antagonist

High progestogenic effects

Antiandrogen effects similar to Cyproteroneacetat

No estrogenic effects

Is Yasmin more dangerous than other OCs ??
Dinger et al. Contraception 2007;75:344-54
(Euras-Study)

Treatment	No.	Women- Yeras
Drospirinone	16534	28621
Levonorgestrel	15428	31415
Other OC	26341	52623
NOHC	371	4049
Total	58674	142475

Is Yasmin more dangerous than other OCs ??

	Inc/10.000 WY			Rel. Risk of Drospirinone vs.	
	Dros	LNG	Other	LNG	Other
VTE	9,1	8,0	9,9	1,1 (0,7-2,0)	0,9 (0,6-1,5)
ATE	0,7	2,9	1,7	0,3 (0,1-1,4)	0,4 (0,1-1,9)
Death	1,4	2,5	1,7	0,6 (0,2-1,8)	0,8(0,3-2,6)

Is Yasmin more dangerous than other OCs ??
Seeger et al Obstet Gynecol 2007;110:587-93

Treatment	No.	Women- Yeras
Drospirinone	22429	14081
Other OC	44858	27575
Total	67287	41650

Is Yasmin more dangerous than other OCs ??

Incidence of VTE/10.000 WY		RR of Dros. Vs other OC
Dros	Other OC	
13	14	0,9 (0,5-1,6)

Each year a clinician can expect to see one case of VTE

- in 714 women on EE+DSP
- in 764 women on other OCs

Hormonal contraception and risk of VTE.

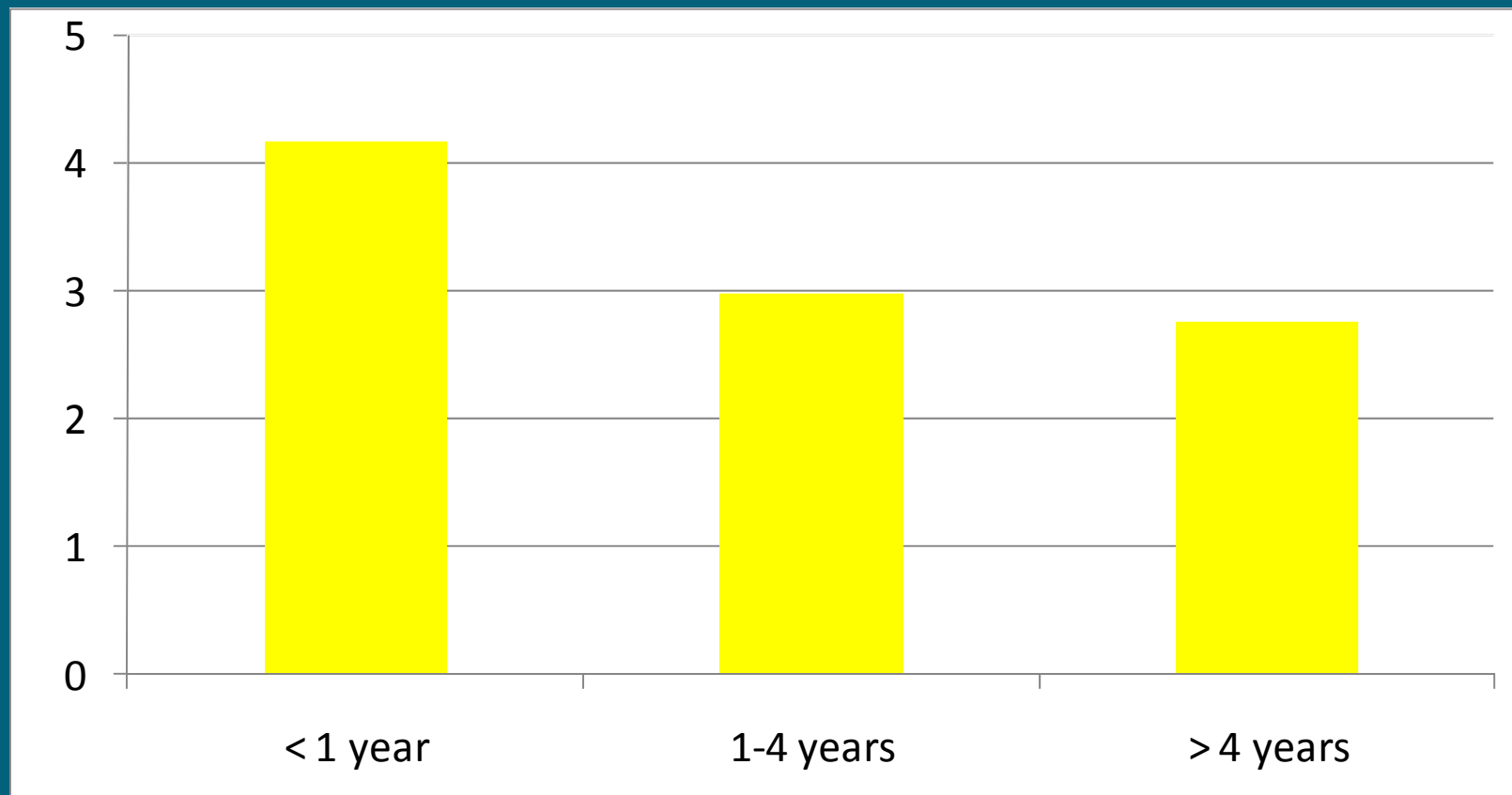
Lidegaard et al. BMJ 2009;339:b2890

10 mill women years in DK between 1995-2005
3 mill women years on OCs
7 mill women years without.

	Women y.	VTE pr. 10.000 wom y.
Non users	7,2 mill	3.01
Current users	3,3 mill	6,29

Hormonal contraception and risk of VTE. Effect of duration of use

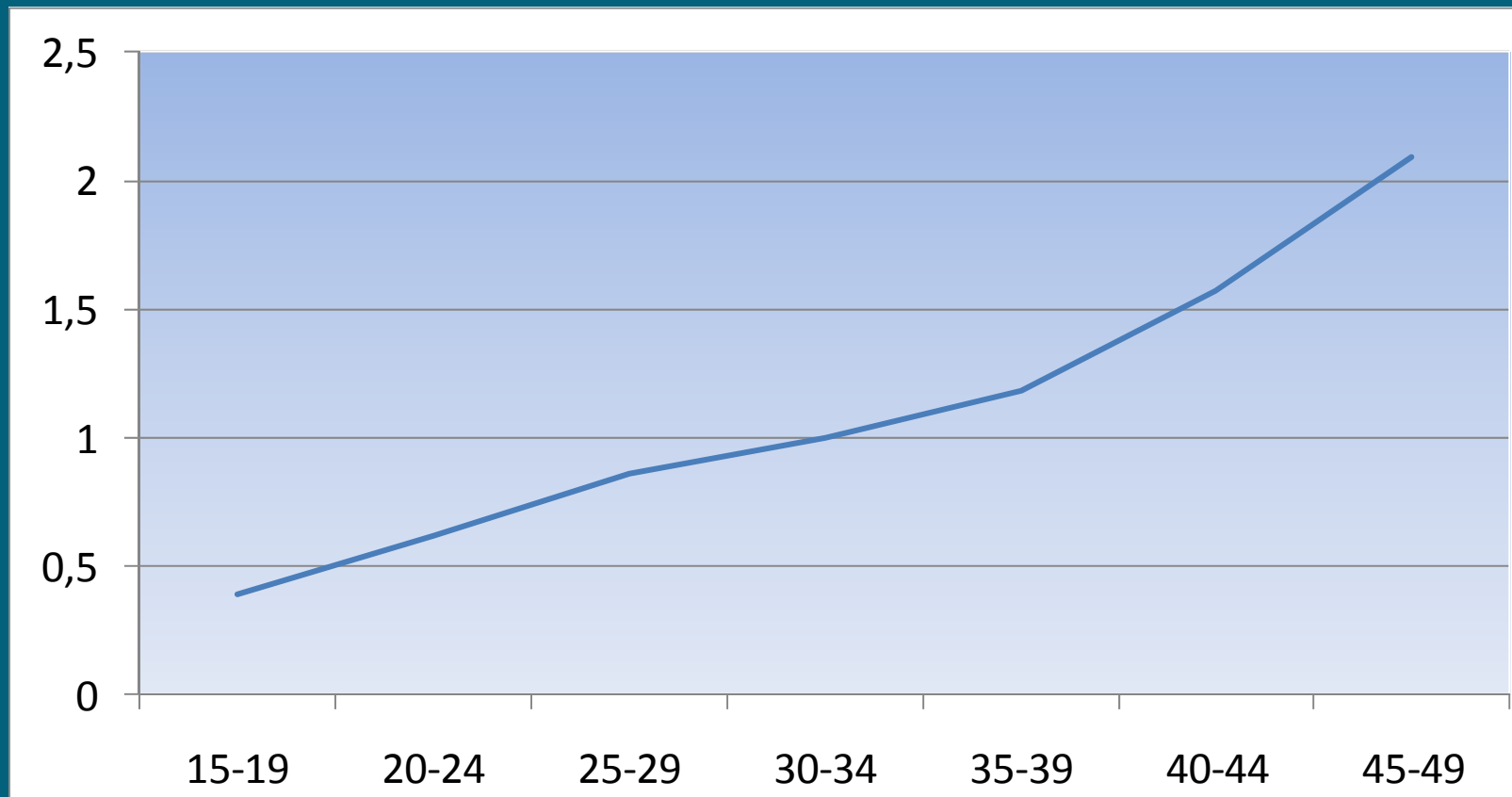
Adjusted RR



Lidegaard et al. BMJ 2009;339:b2890

Hormonal contraception and risk of VTE.

Effect of age. Adj. RR when 30-34 y = 1

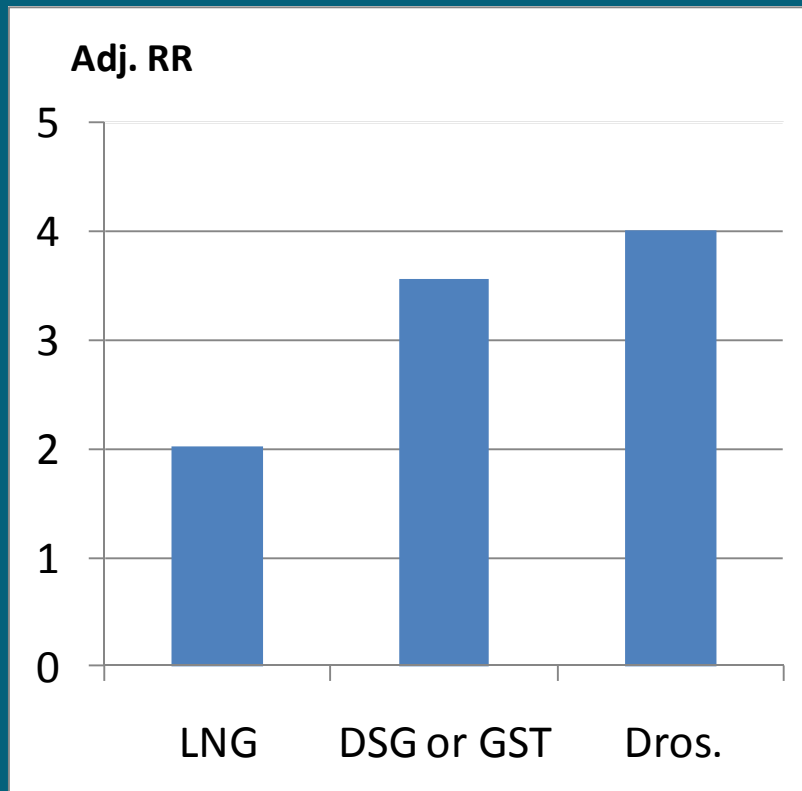


Lidegaard et al. BMJ 2009;339:b2890

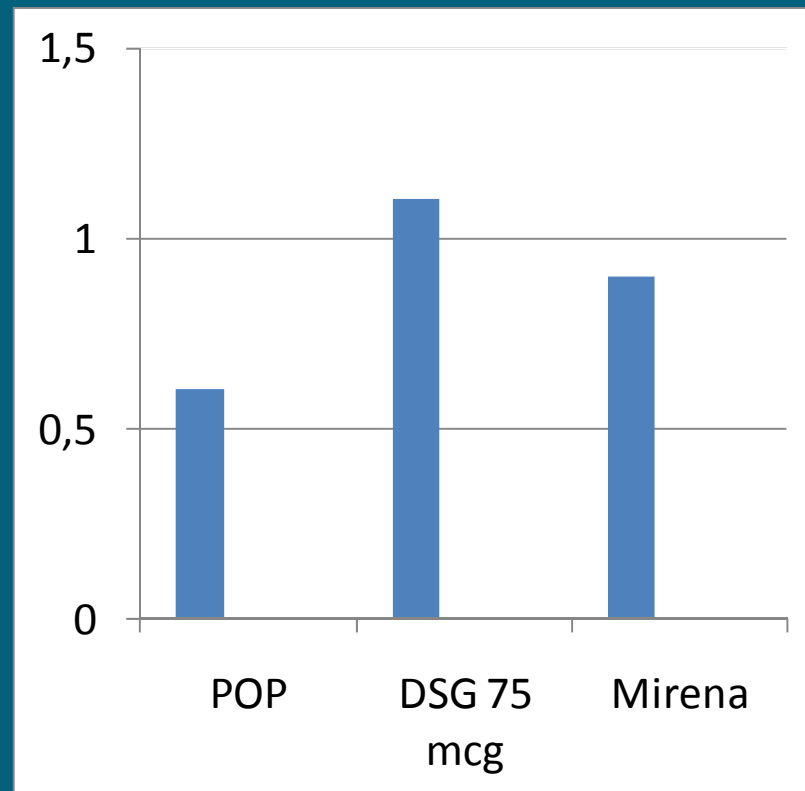
Hormonal contraception and risk of VTE.

Effects of progestogens

Low dose combined OC



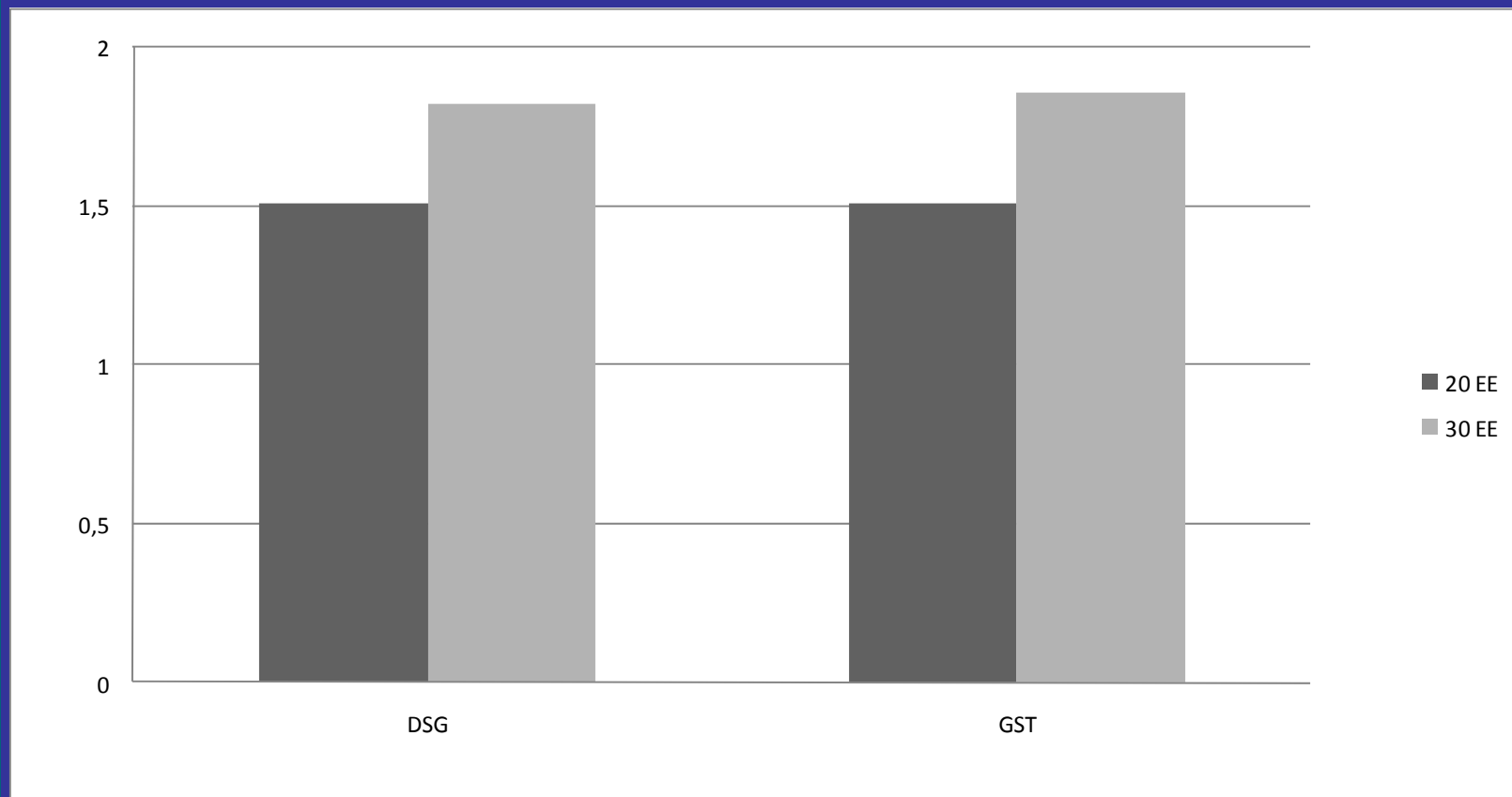
Progesterone only



Lidegaard et al. BMJ 2009;339:b2890

Hormonal contraception and risk of VTE. Effect of Estrogen dose

Adjusted RR



VTE risiko ved forskellige gestagener

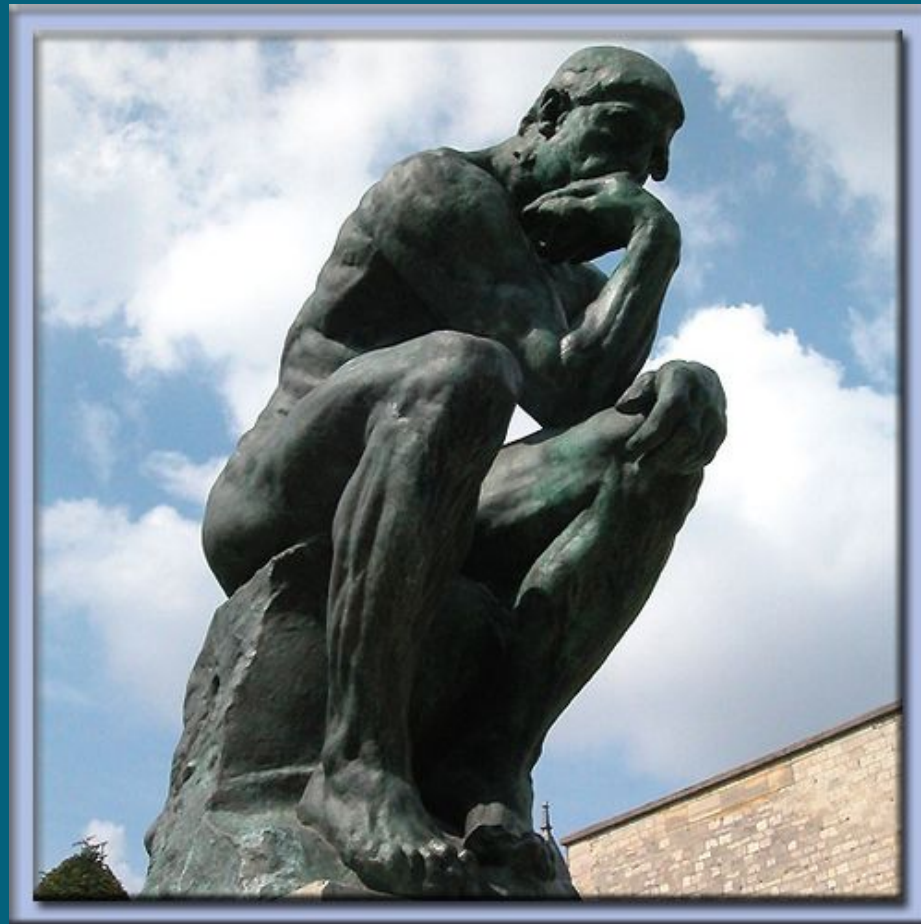
Sættes p-piller med levonorgestrel til RR 1 er den for p-piller med :

- Norestisteron = 0.98
- Norgestimat = 1.19
- Desogestrel = 1.82
- Gestoden = 1.86
- Drospirenone = 1.64
- Cyproteron = 1.88

Ingen øget risiko ved ren gestagenbehandling.

Risikoen reduceres med ca 20% ved reduktion af EE fra 30 til 20 mcg

Hvad skal man dog mene om
alt det epidemiologi ???



WHO – medical eligibility for contraceptive use 2004

The eligibility was graded in four categories:

- 1: OCs can be used in any circumstances
- 2: OCs can generally be used
- 3: OCs not usually recommended unless other more appropriate methods are not available or not acceptable
- 4: OCs should not be used

WHO – medical eligibility for oral contraceptive use – DVT or PE

- Previous 4
- Current 4

- Major surgery
- with prolonged immobilization 4
- without prol. immobil. 3-4
- minor surg without immobil 1

WHO – medical eligibility for oral contraceptive use - Smoking:

Age < 35 y 2

Age ≥ 35 y.

Light 3

Heavy (>20 cig/day) 4

Absolute risk of AMI per 100,000 fertile women per y. according to smoking and OC use

	<u>< 35 years</u>	<u>> 35 years</u>
No OC non-smokers	4	10
No OC, smokers	8	88
+OC, non-smokers	4	40
+ OC, smokers	43	485

WHO – medical eligibility for oral contraceptive use - Headache

- Mild 1
- Severe (recurrent incl. Migraine without focal neurological sympt). 2
- With focal neurological sympt 4

P-piller til kvinder med særlige risici

Kliniske rekommendationer

- **Absolutte kontraindikationer (c):**
- Aktuel eller tidligere tromboembolisk sygdom,
- diabetes eller hypertension med komplikationer
- Migræne med aura eller fokale symptomer
- aktuel parenchymatøs leversygdom
- homozygoti for Leiden faktor V .

P-piller og tromboser

Kliniske rekommandationer

- Start med lavdosis pp dvs med 20-30 μ g ethinylestradiol (b).
- Kvinder med risikofaktorer for kredsløbssygdomme bør anvende anden kontraception (d)
- Til kvinder med risikofaktorer for VTE: Minipille eller lavdosis 2. generations pp (c).
- Til kvinder med risikofaktorer for arteriel trombose: Minipille eller lavdosis 3. generations pp (d).
- Alle kvinder skal informeres om den tromboemboliske risiko ved brug af pp.
- Kvinder, som tidligere har udviklet tromboembolisk sygdom, bør ikke ordineres kombinationsp-piller (c).

Kombineret parenteral hormonal kontraception – EVRA og NuvaRing – Kredsløb

Ingen nye data vedr. NuvaRing

Evra sammenlignet med OC med samme hormon-
komponenter

**EVRA: 20mcgEE/150NGT, OC: 35 mcg EE/250
mcgNGT):**

- Cole, Obstet Gynecol 2007: RR på 2.4 for VTE (18/100000, EVRA: 41/100.000)
- Jick, Contraception 2007: Samme risiko
- Ingen af studierne finder forskel vedr. AMI og stroke.

Pharmacokinetics of EE in different contraceptive formulations:

Daily hormonal dose:

- AUC 0-21 value for EE (ng x h/ml)

Ring:

15 mcg EE/120 mcg ENG

- Ring: 10.6

OC:

30 mcg EE/150 mcg LNG

- OC: 21.9

Patch:

20 mcgEE/150 mcg NGT

- Patch: 35.8



- Oral contraceptives and gynecological cancer

- Good news !!!

OCs and reprod. cancer

Oxford FPA: 17032 w recr. from 1968-74

540.000 w. years

	Never users (35%)	Ever users (65%)
Breast	1 (314)	1.0 (530)
Cervix	1 (6)	4.2* (53)
Endometrial	1 (50)	0.3* (27)
Ovary	1 (58)	0.5* (48)
Gyn. Combined	1	0.7*

OCs and reprod. cancer

RCGP: 46.000 w recr. from 1968-69 1.083.000 w. years

	Never users (31%)	Ever users (69%)
Breast	1 (448)	0.98 (891)
Cervix	1 (36)	1.33 (118)
Endometrial	1 (75)	0.58* (81)
Ovary	1 (93)	0.54* (96)
Gyn. Combined	1	0.71*

Ovarian cancer and oral contraceptives

Collaborative Group on Epidemiological Studies of Ovarian Cancer
Lancet 2008;371:303-14

- 45 epidemiological studies from 21 countries
- 23257 women with ovarian cancer.
- 87303 controls without ovarian cancer
- Median age of cancer diagnosis: 56 y.
- Median year of diagnosis: 1993
- Average duration of use: 4.4 y (cancer) 5.0 y (controls)

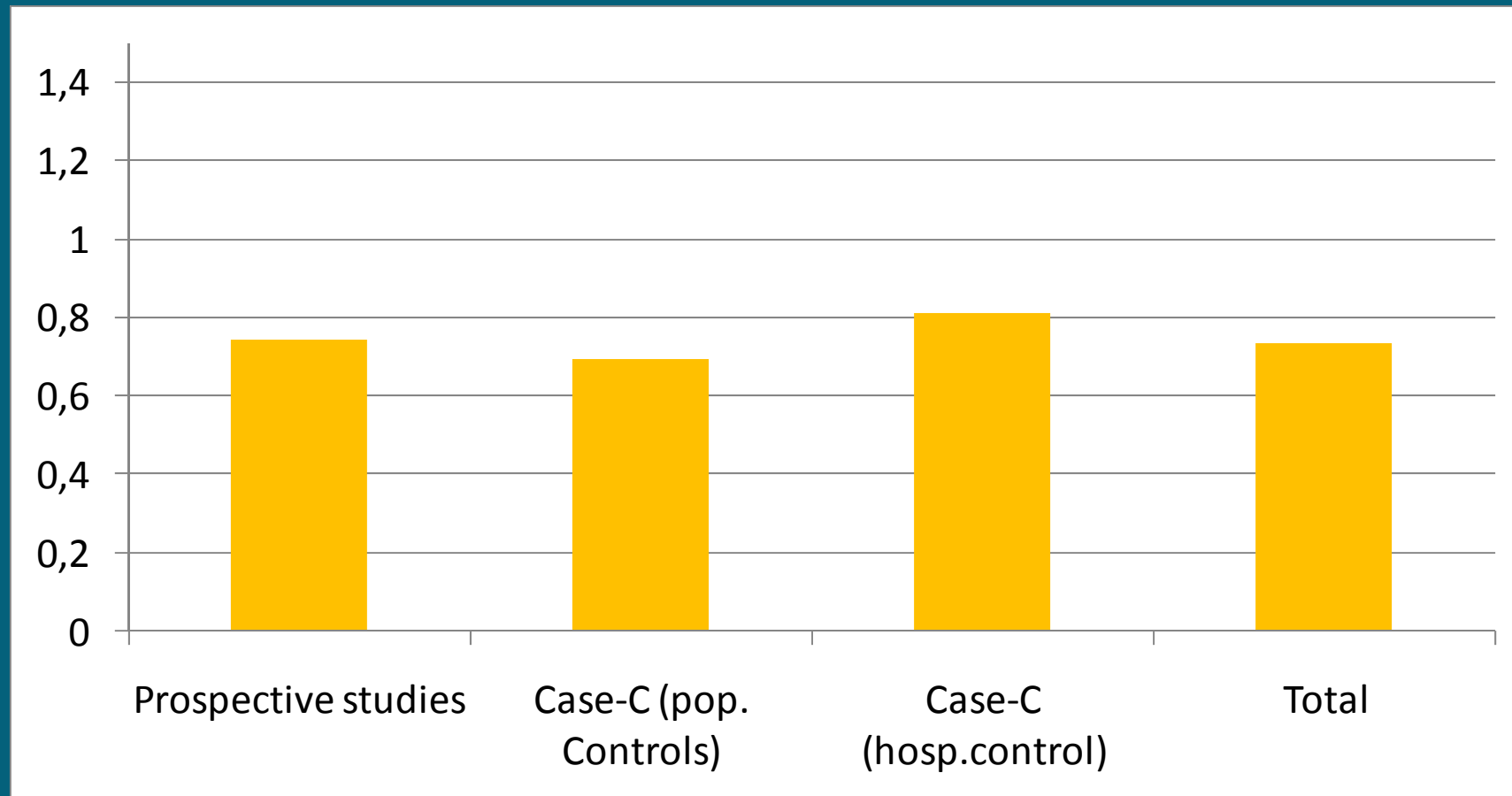
Ovarian cancer and oral contraceptives

Collaborative Group on Epidemiological Studies of Ovarian Cancer
 Lancet 2008;371:303-14

Study	Ever users of OC		Never users of OC		Total	
	Cases	Cont.	Cases	Cont.	Cases	Cont.
13 prospective	2593	12561	5133	19640	7726	32201
19 case- control (population control)	3835	10269	5872	11091	9707	21360
13 case control (hospital control)	880	9527	4944	23855	5824	33382
Total	7308	32717	15949	54586	23257	87303

Relative risk of ovarian cancer in ever users.

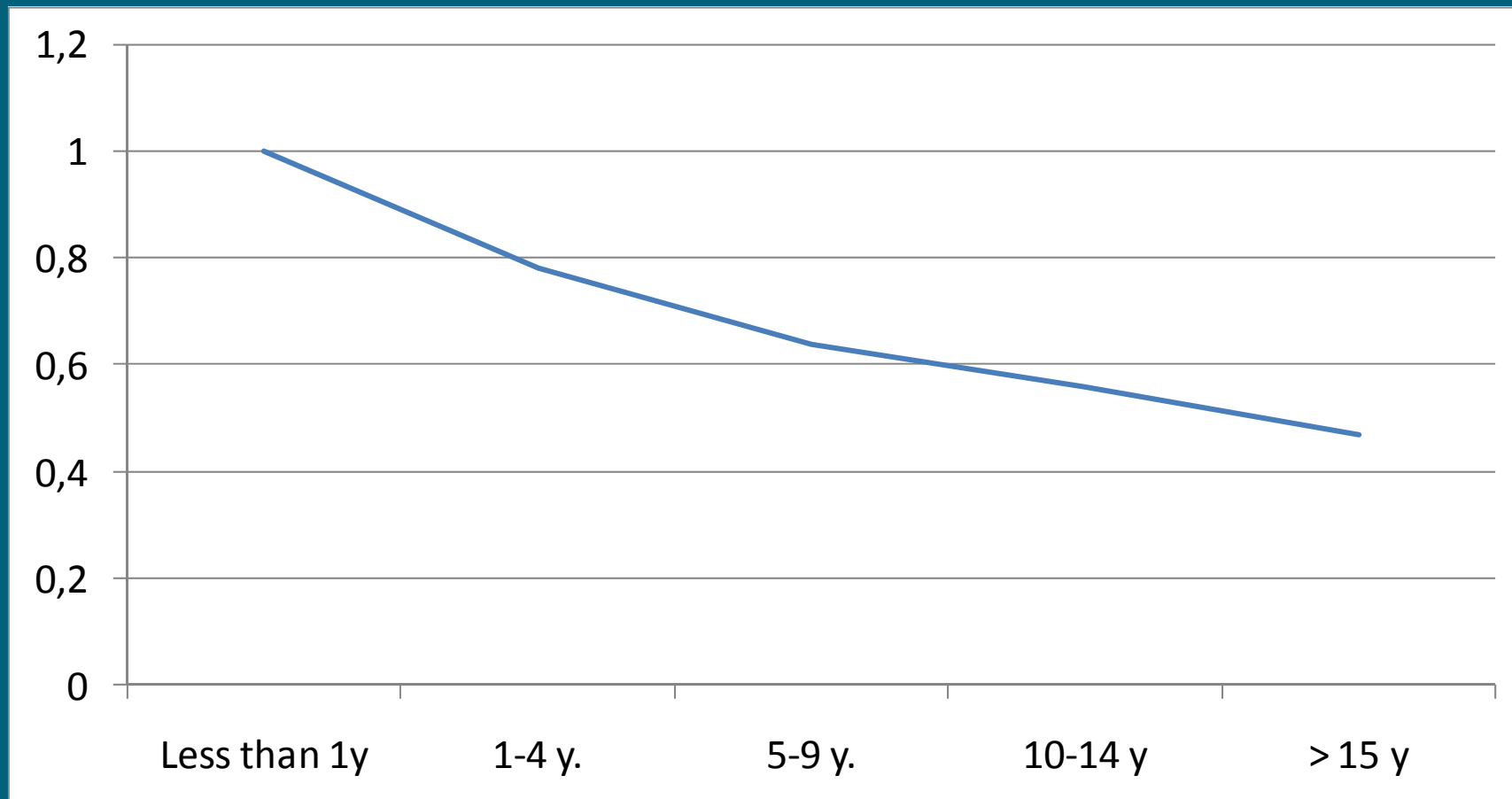
Effect of different studies designs.
Never users = 1



Relative risk of ovarian cancer in ever users.

Effect of duration of use

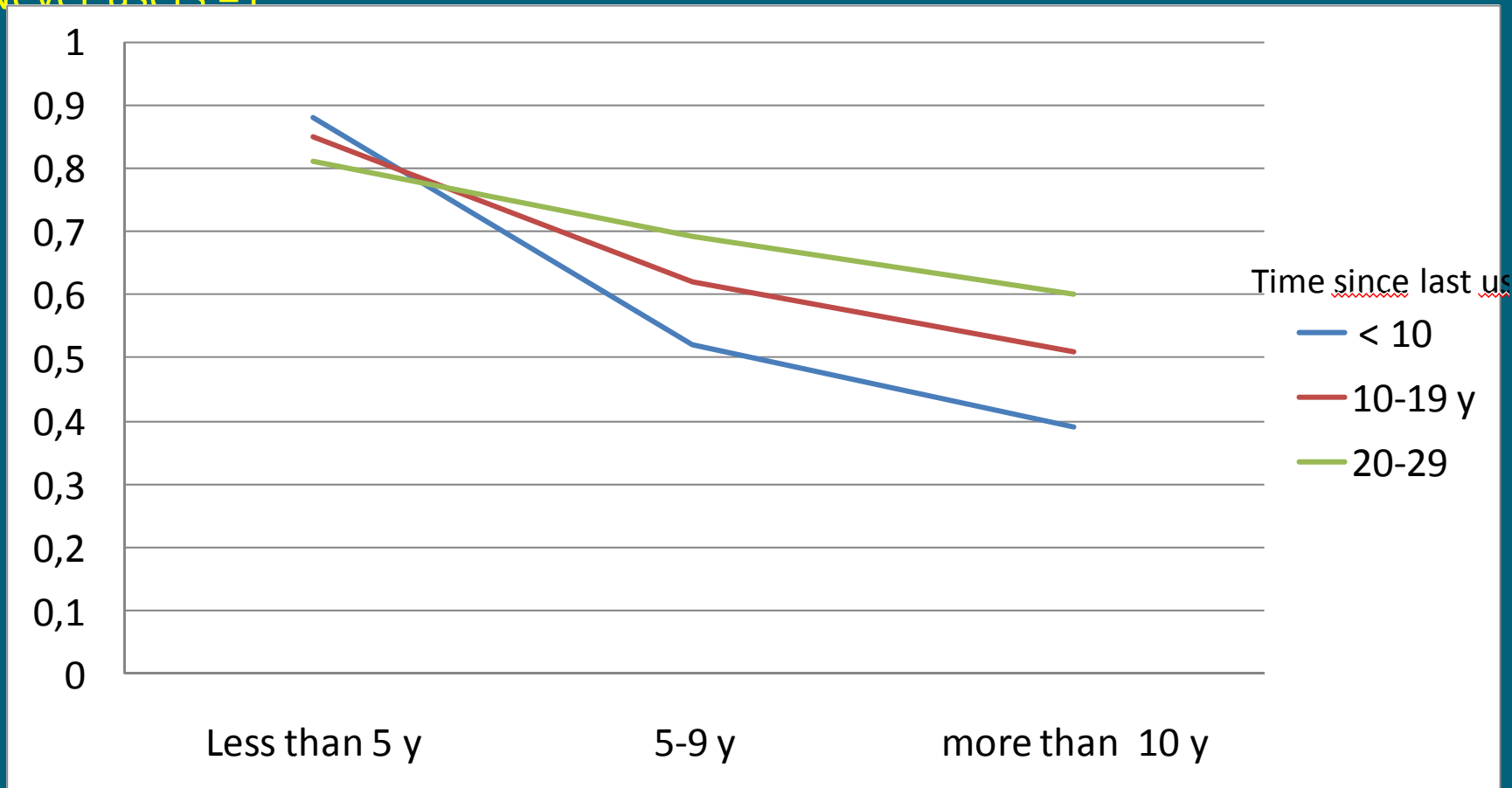
Never users = 1



Relative risk of ovarian cancer in ever users.

Effect of duration of use and time since last use

Never users = 1

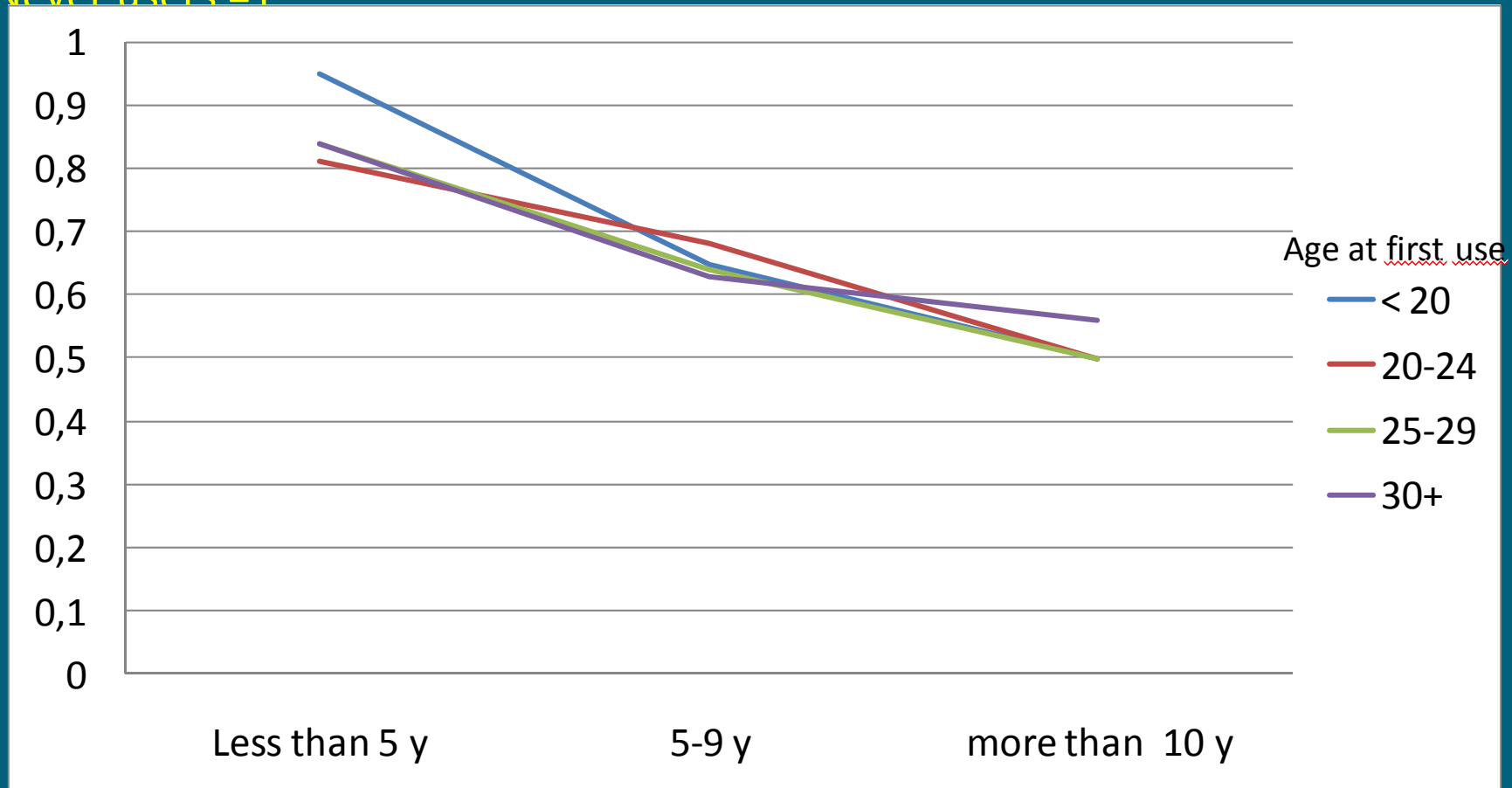


Duration of use

Relative risk of ovarian cancer in ever users.

Effect of duration of use and age at first use

Never users = 1

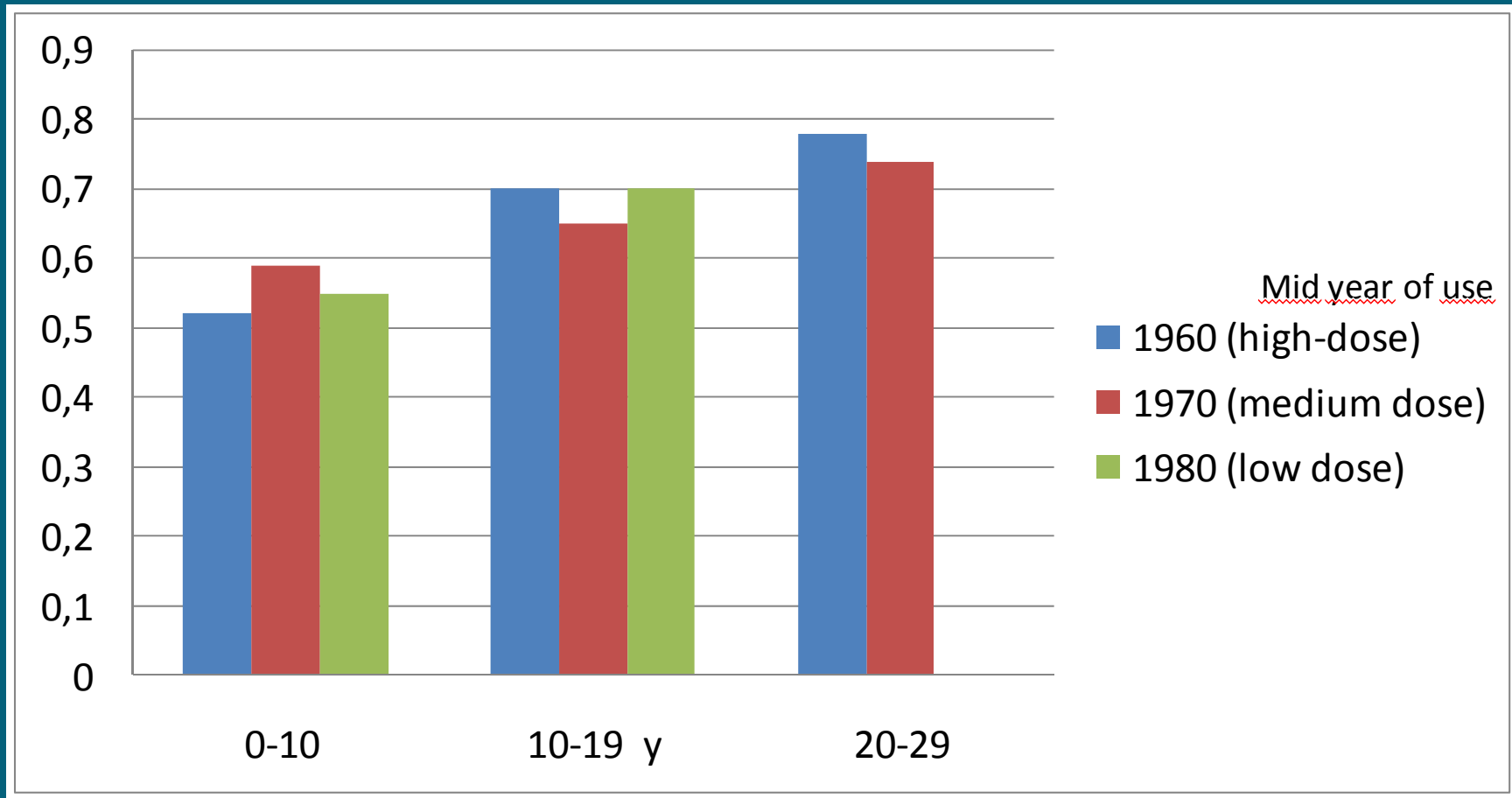


Duration of use

Relative risk of ovarian cancer in ever users.

Effect of time since stopping and mid-year of use

Never users =1



Duration of use

Ovarian cancer and oral contraceptives

Collaborative Group on Epidemiological Studies of Ovarian Cancer
Lancet 2008;371:303-14

- Conclusion:
- Oral contraceptives reduces the risk of ovarian cancer.
- The protection increases with duration of use
- The protection attenuates over time but is still present 30 y after stopping.
- 5 years of OC use reduces the risk of ovarian cancer with 20 %
- 10 y. of OC use reduces the incidence of ovarian cancer from 1.2 to 0.8 pr. 100 w.
- With the current use of OC about 30.000 cases of ovarian cancer is prevented each y.

Ovarian cancer and oral contraceptives

Editorial, Lancet 2008;371:275

- "We strongly endorse more widespread over-the-counter access to a preventive agent that can not only prevent cancers but also demonstrably save the lives of ten thousands of women"