The Polypill: a new approach to the prevention and treatment of cardiovascular disease

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Declaration of interest

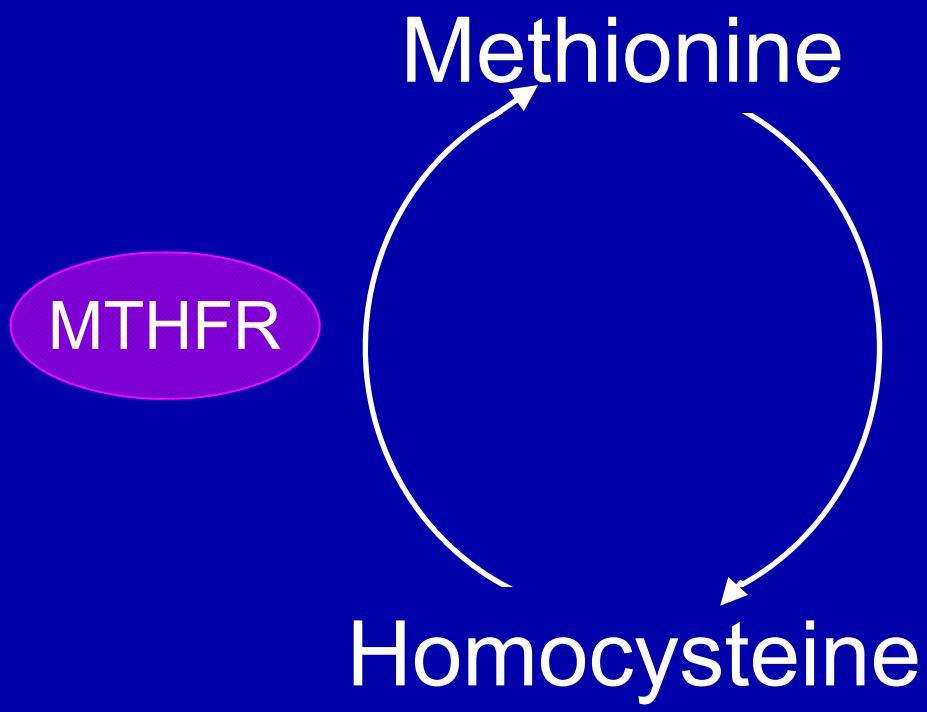
Nicholas Wald and Malcolm Law have applied for patents for the Polypill (granted in UK) and for trademark protection

Ischaemic Heart Disease (IHD) and stroke are responsible for about one third of all deaths in Western countries.

Risk of IHD and stroke can be reduced by decreasing:

LDL cholesterol	proven
Blood pressure	proven
Platelet aggregation	proven
Serum homocysteine	probable

Homocysteine and MTHFR (Methylenetetrahydrofolate reductase)



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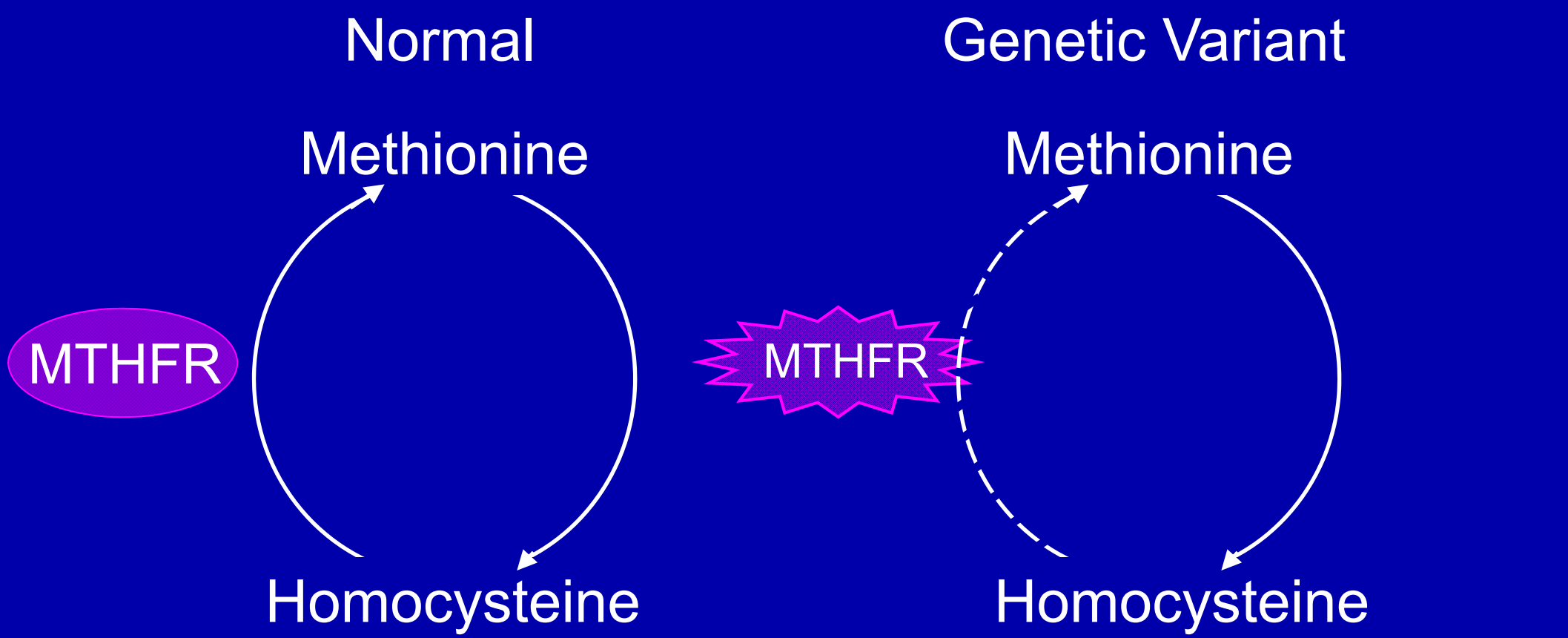
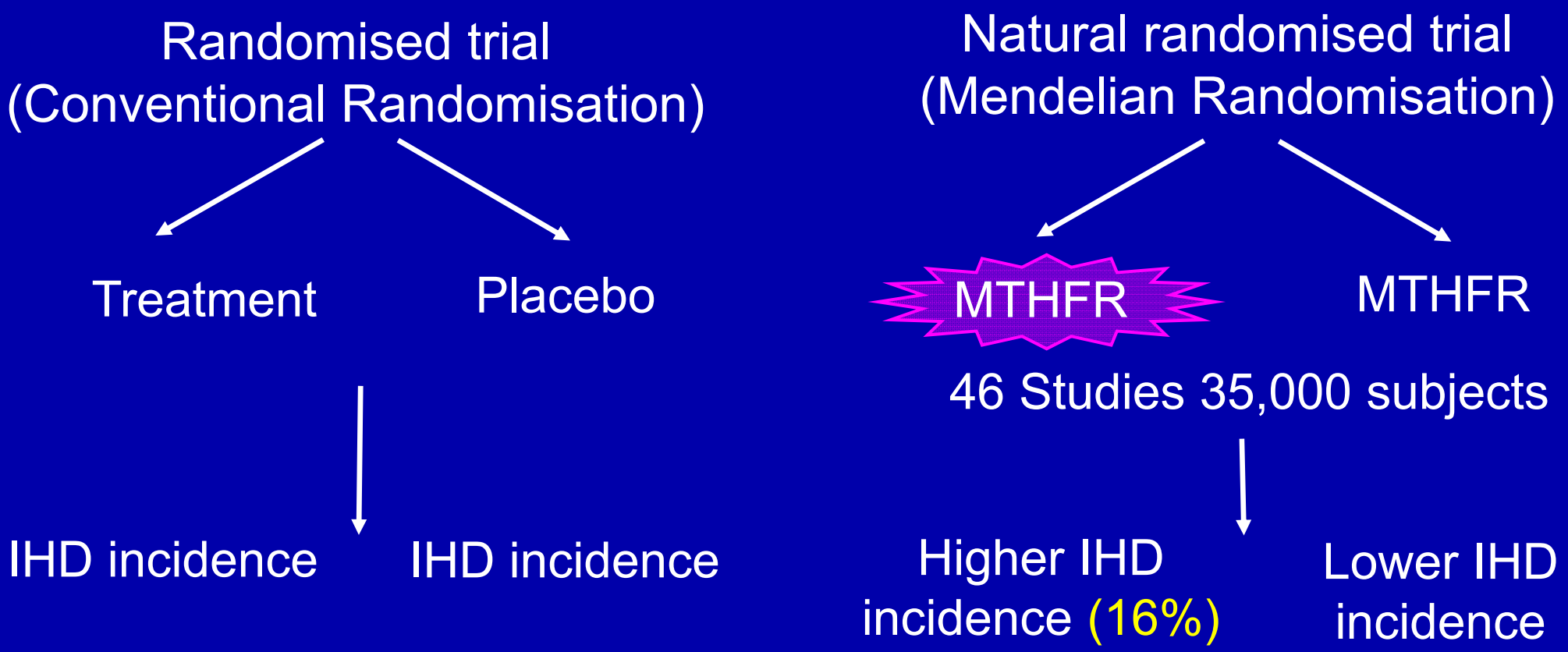


Homocysteine level is 2.7μmol/L higher

Common: about 10% are homozygous for the genetic variant

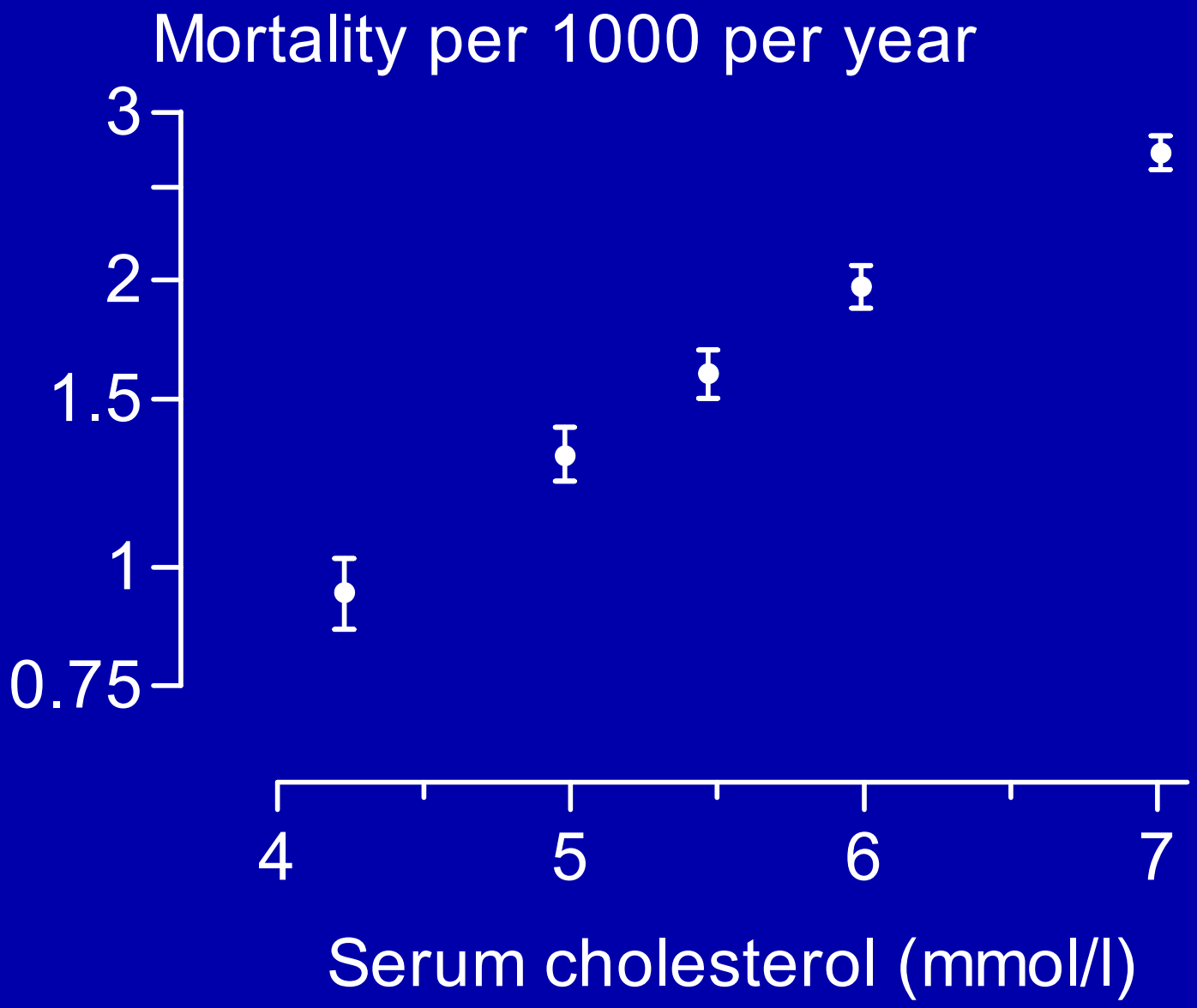
Mendelian Randomisation:Evidence that homocysteine (Hcy) is a cause of IHD



Similar **(14%)** lower incidence observed in cohort studies for the same homocysteine difference

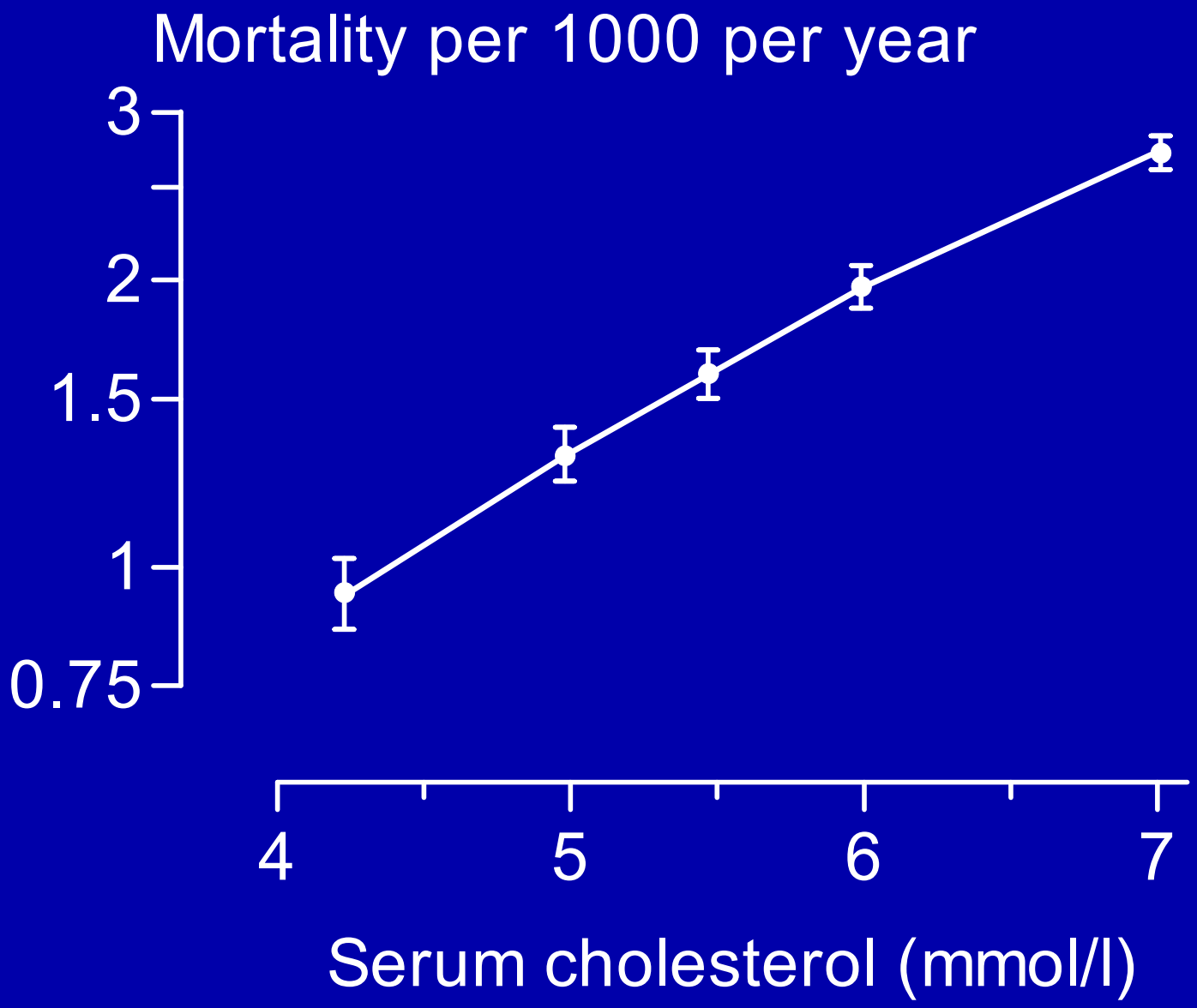
Examination of the dose-response relationship

IHD & cholesterol in a large cohort study



Neaton et al *Arch Intern Med* 1992

IHD & cholesterol in a large cohort study



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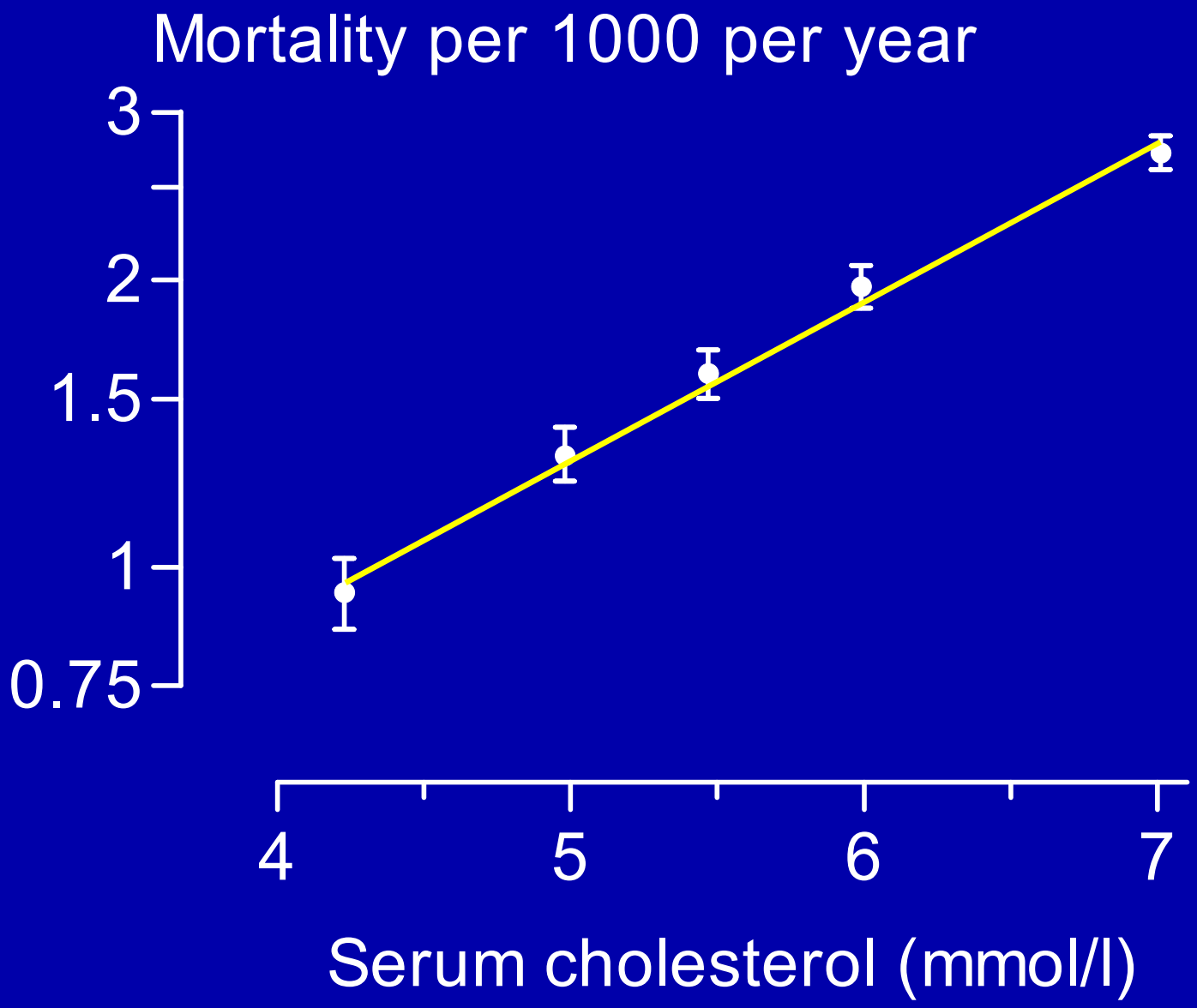
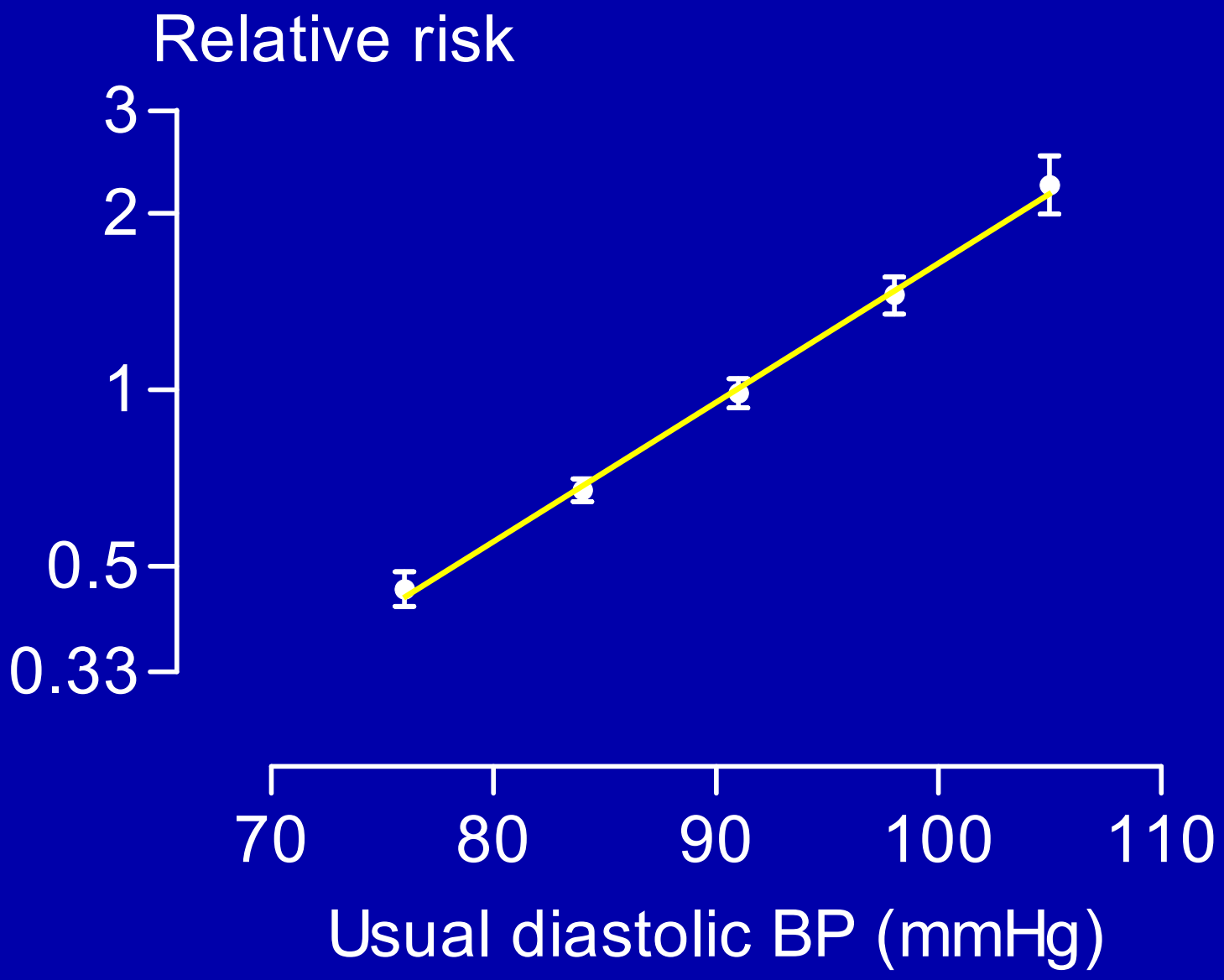


Neaton et al *Arch Intern Med* 1992

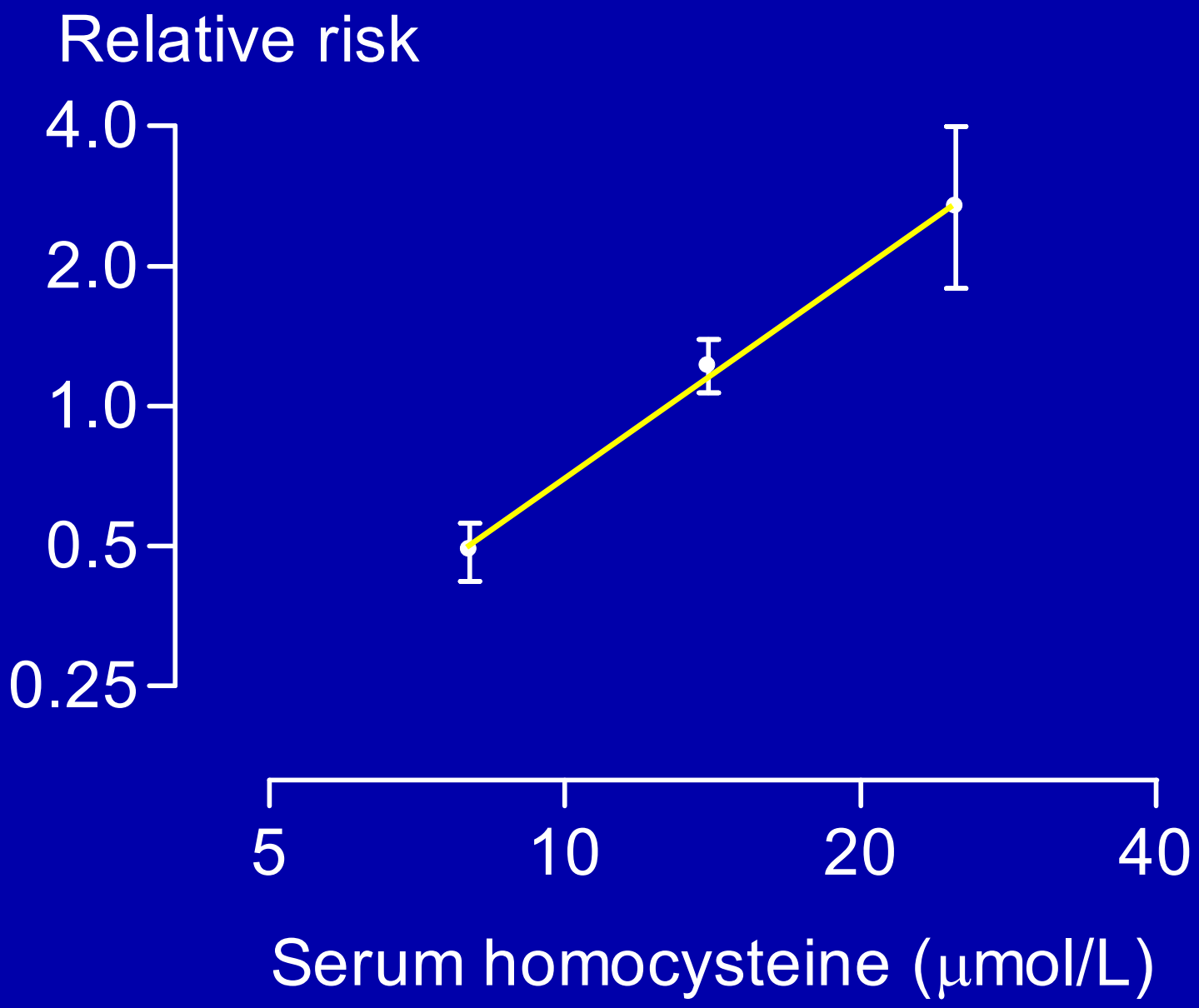
IHD and blood pressure meta-analysis



(age 60)

McMahon et al, *Lancet* 1990

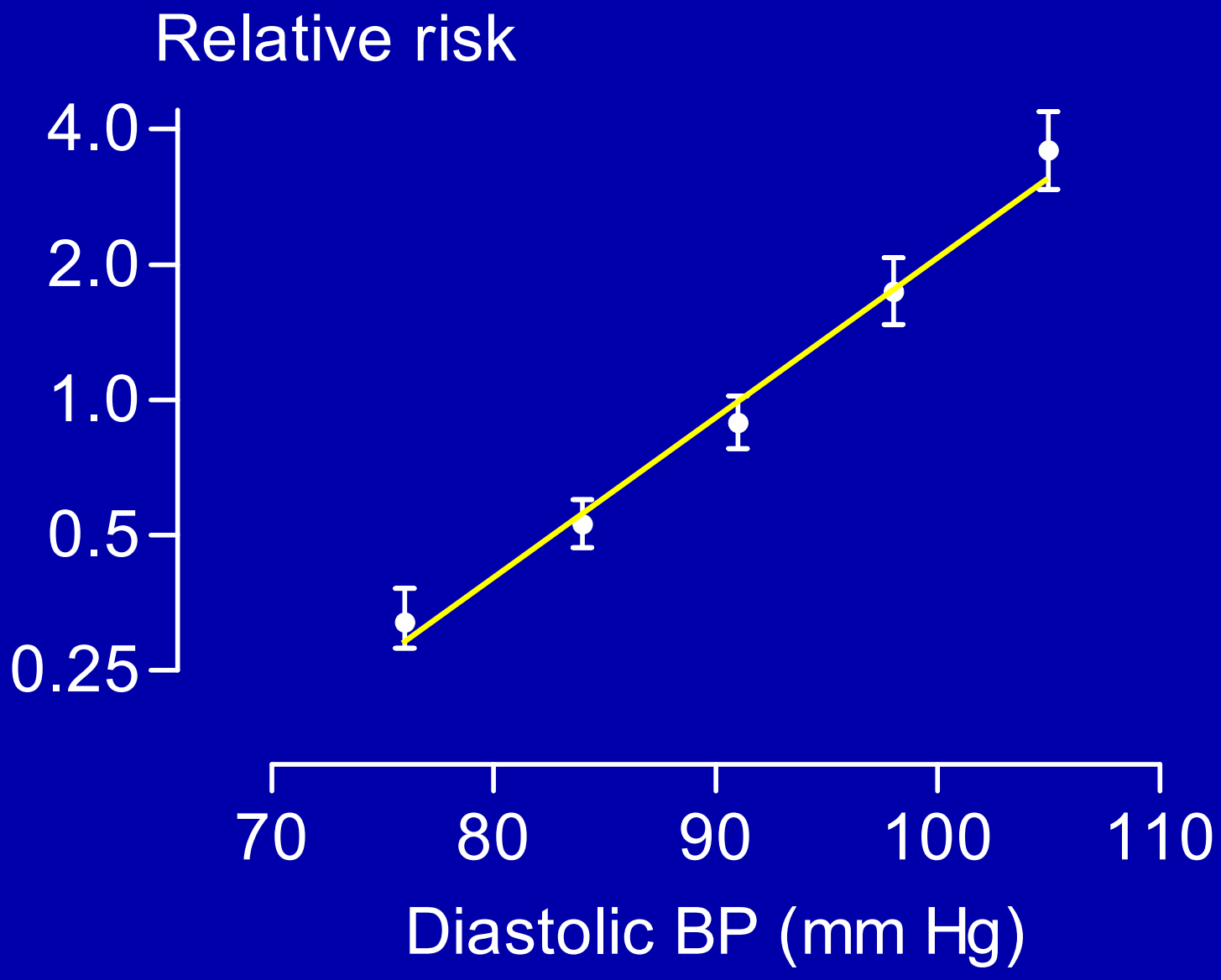
IHD & serum homocysteine in the BUPA study



Wald et al, Arch Internal Med 1998; 158: 862 – 7

Stroke & blood pressure meta-analysis

No threshold – the lower the blood pressure the lower the risk

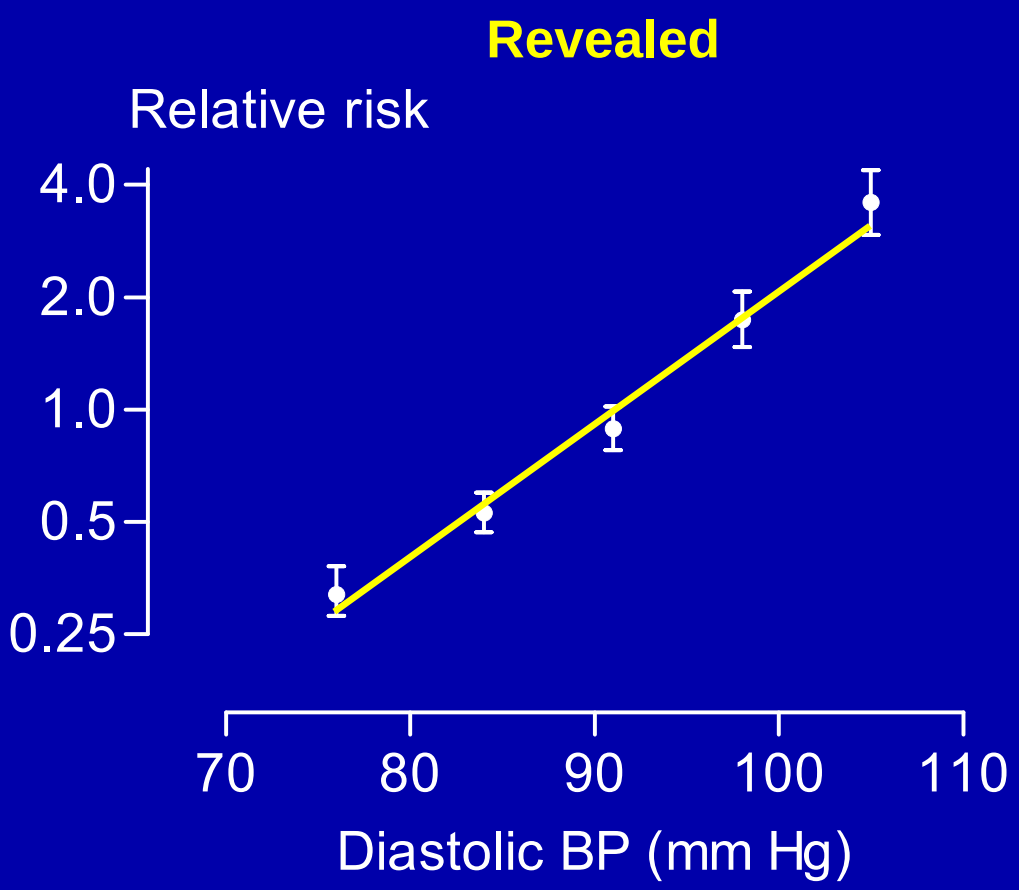


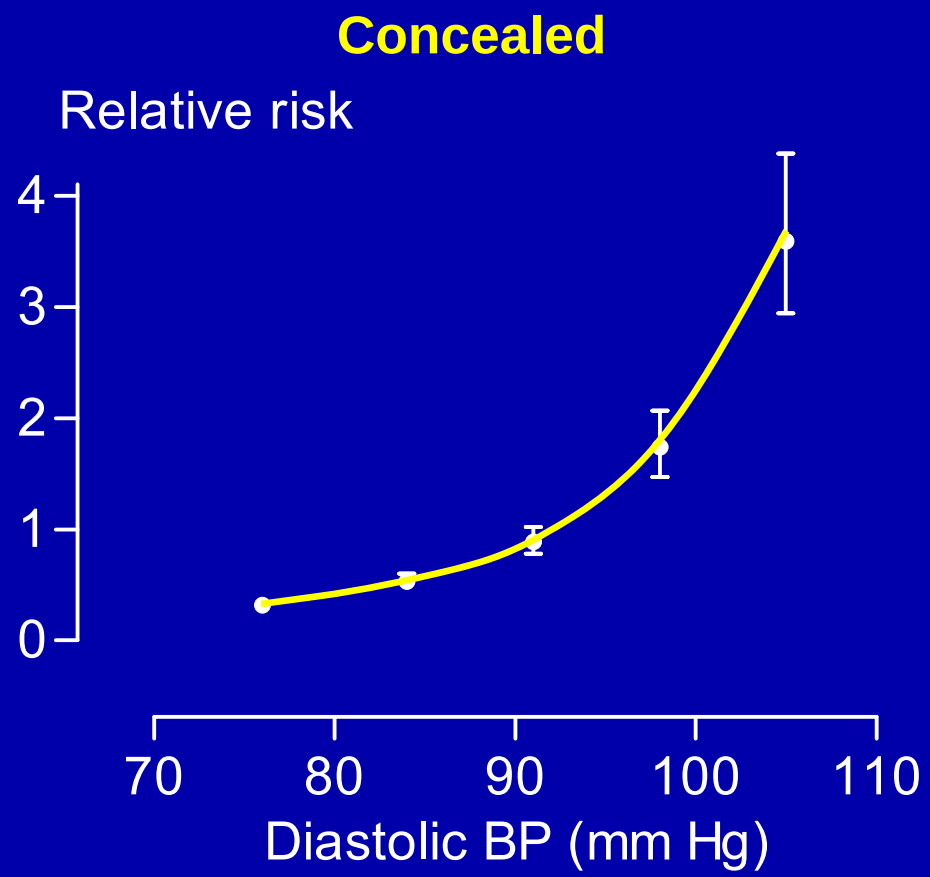
McMahon et al, *Lancet* 1990

Stroke & blood pressure meta-analysis

No threshold – the lower the blood pressure the lower the risk

Constant proportional change in risk for a given change in risk factor





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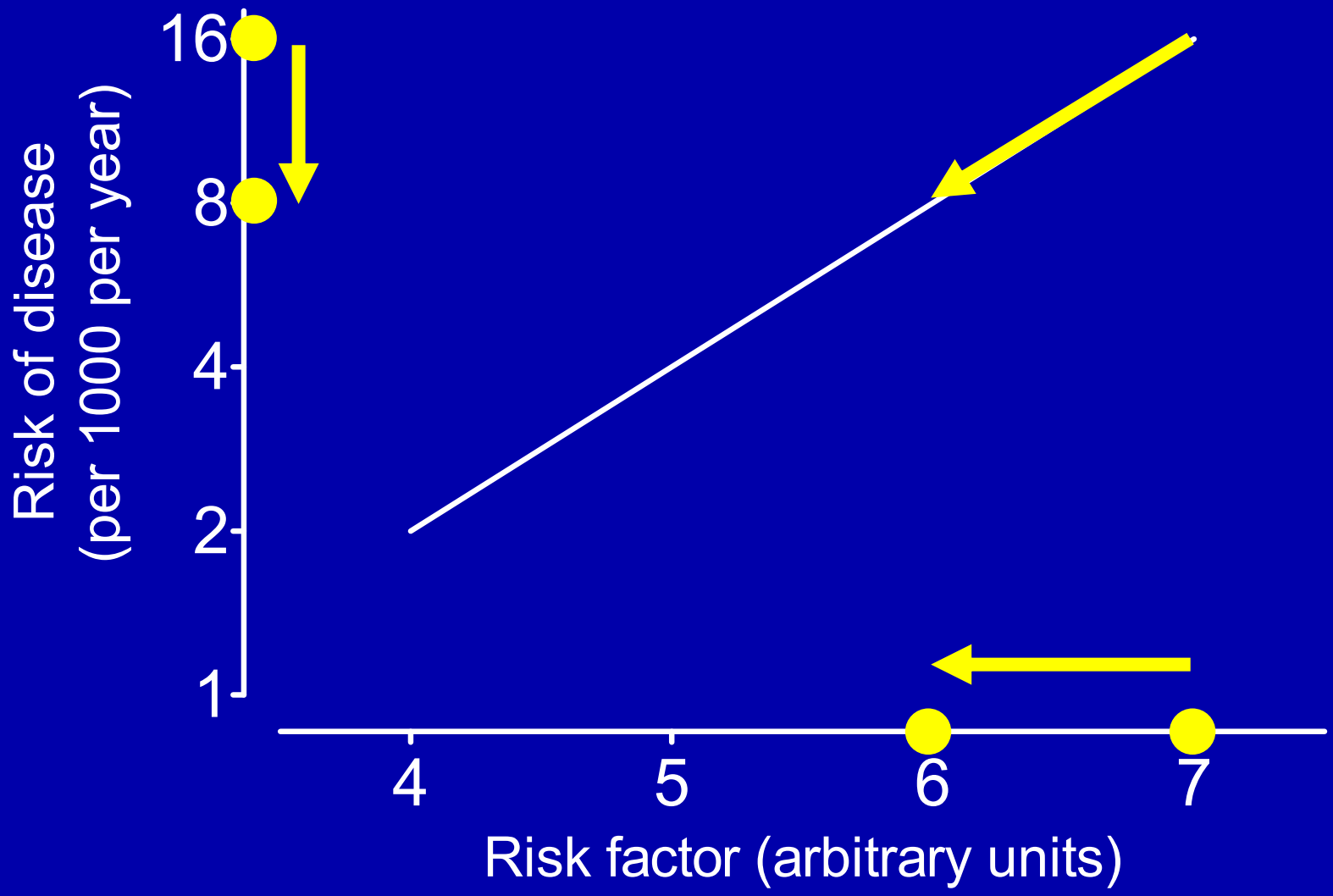
Implications of the constant proportional risk reduction from risk factor modification



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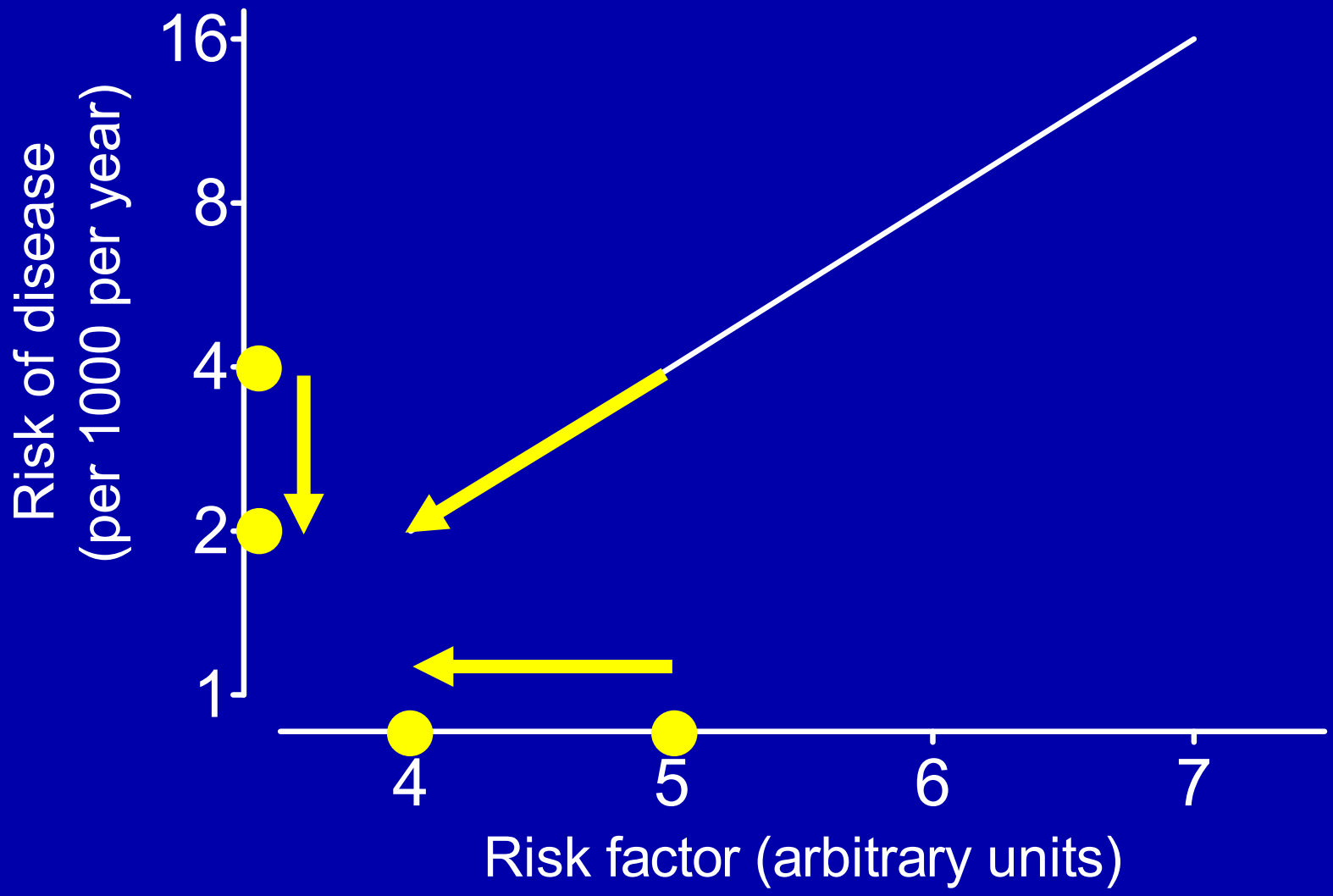

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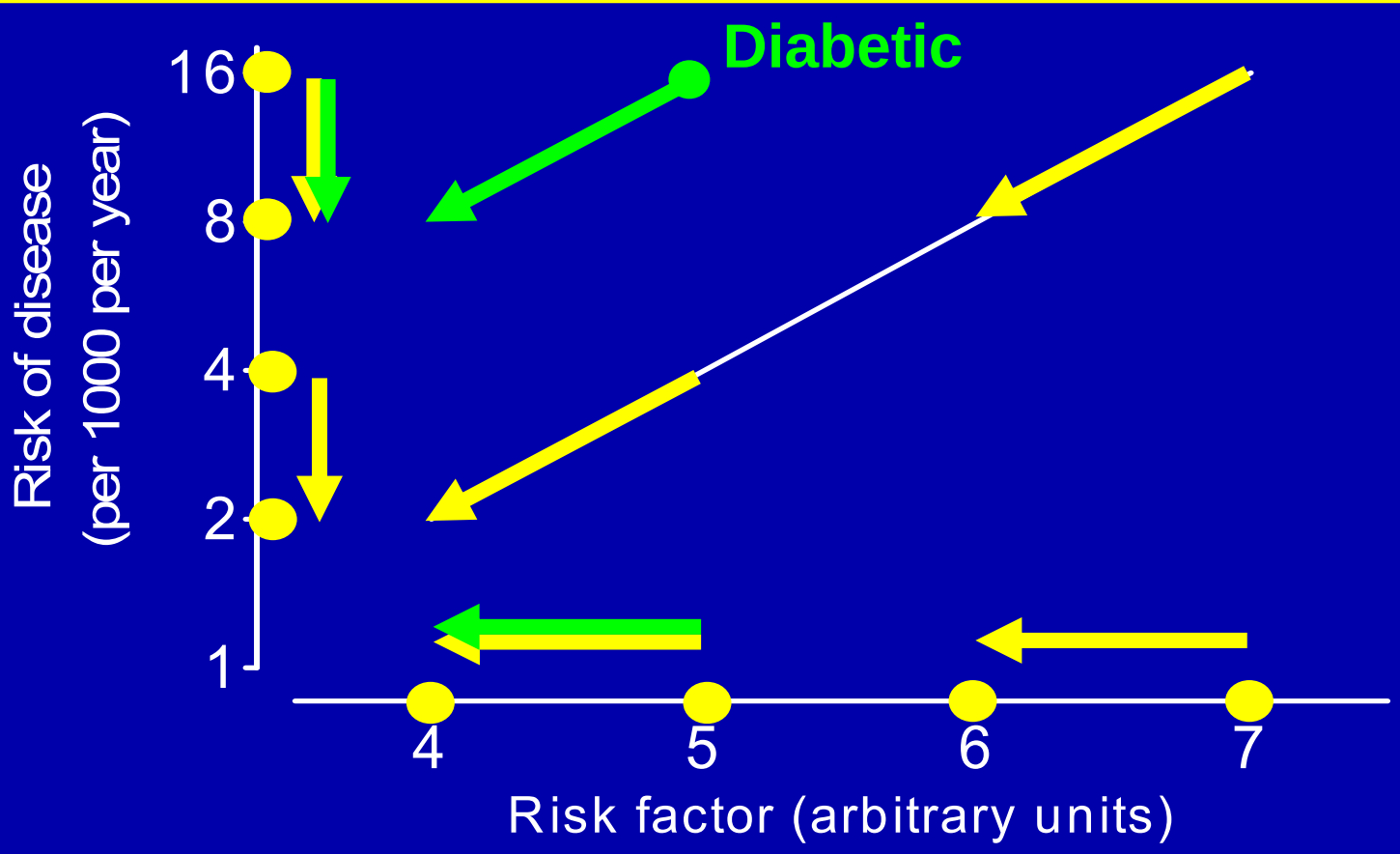

	Reduction in risk	
Reduction in risk factor	Relative	Absolute
1 unit (7 to 6)	50%	8 per 1000 per year
1 unit (5 to 4)	50%	8 X per 1000 per year

Practical implications of the straight line proportional dose-response relationship

A given reduction in a risk factor reduces the risk of disease by a constant proportion of the existing risk irrespective of the starting level of the risk factor or of the existing risk.

What is the effect of lifestyle changes on these risk factors?

Effect of lifestyle changes

	Approximate risk factor reduction
LDL cholesterol	0.3 mmol/L
Blood pressure	2.5 mm Hg diastolic
Serum homocysteine	3%
Platelet aggregation	–

Effect of lifestyle changes

	Approximate risk factor reduction	Reduction in risk	
		IHD	Stroke
LDL cholesterol	0.3 mmol/L	14%	3%
Blood pressure	2.5 mm Hg diastolic	11%	19%
Serum homocysteine	3%	3%	2%
Platelet aggregation	–	–	–

Effect of lifestyle changes

	Approximate risk factor reduction	Reduction in risk	
		IHD	Stroke
LDL cholesterol	0.3 mmol/L	14%	3%
Blood pressure	2.5 mm Hg diastolic	11%	19%
Serum homocysteine	3%	3%	2%
Platelet aggregation	–	–	–
Combined effect		**26%**	**23%**

Is medical intervention more effective?

Absolute reductions in serum LDL cholesterol concentration according to statin and daily dose (summary estimates from 164 randomised placebo controlled trials)

	Daily dose (mg)				
	5	10	20	40	80
Statin	Reduction (mmol/L)				
Atorvastatin	1.5	1.8	2.1	2.4	2.6
Rosuvastatin	1.8	2.1	2.3	2.6	2.8
Simvastatin	1.1	1.3	1.5	1.8	2.0

Absolute reductions are standardised to usual serum LDL cholesterol concentration of 4.8mmol/L before treatment (mean concentration in trials).

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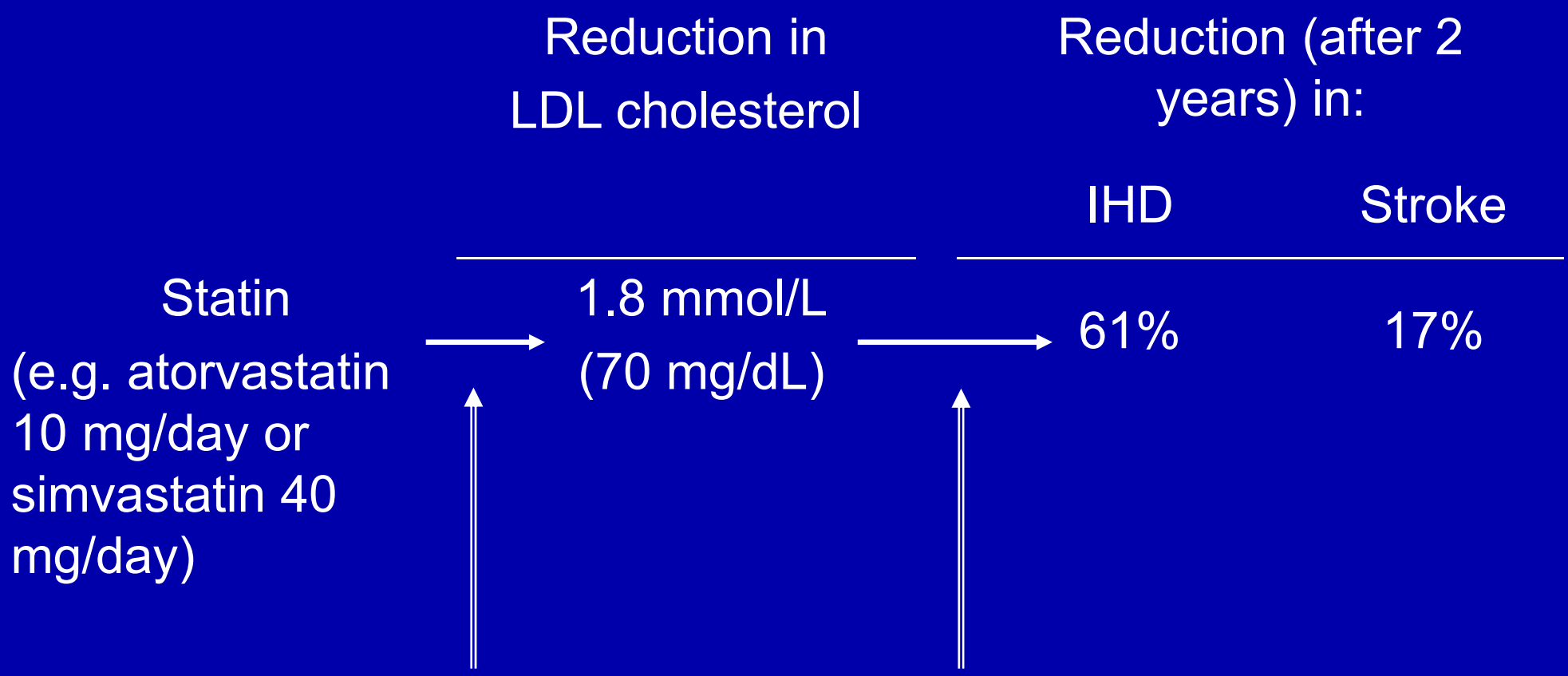
Absolute reductions are standardised to usual serum LDL cholesterol concentration of 4.8mmol/L before treatment (mean concentration in trials).

Percentage reductions in serum LDL cholesterol concentration according to statin and daily dose (summary estimates from 164 randomised placebo controlled trials)

	Daily dose (mg)				
	5	10	20	40	80
Statin	Reduction (%)				
Atorvastatin	31	37	43	49	55
Rosuvastatin	38	43	48	53	58
Simvastatin	23	27	32	37	42

Percentage reductions are independent of pre-treatment LDL cholesterol concentrations.

LDL cholesterol



Reduction in risk of IHD events in 58 randomised trials (excluding first two years of treatment) compared with expected reductions from cohort study data

LDL cholesterol reduction (mmol/L)	Mean reduction (mmol/L)	IHD events	% reduction in IHD events (95% CI)	
			Observed in trial data	Expected from cohort study data*
0.2	0.5	2311	20 (7 to 31)	23 (20 to 26)
0.8	1.0	3556	32 (27 to 36)	41 (37 to 45)
≥1.5	1.6	705	51 (42 to 58)	57 (52 to 61)

At age 60 years (average age at which IHD events occurred)

BP lowering drugs

Meta-analysis of 354 randomised trials

Dose	Diastolic BP reduction	95% confidence interval
Half standard	4.4	4.2 – 4.6
Standard	5.5	5.4 – 5.7
Twice standard	6.5	6.3 – 6.7

Half v. standard dose – 20% less

Mean starting blood pressure 154/97

Blood pressure

Half standard dose	Reduction in diastolic blood pressure
1 drug	3.7 mmHg
2 drugs	7.3 mmHg
3 drugs	10.7 mmHg

from meta-analysis of 354 placebo-controlled trials

Starting blood pressure 150/90

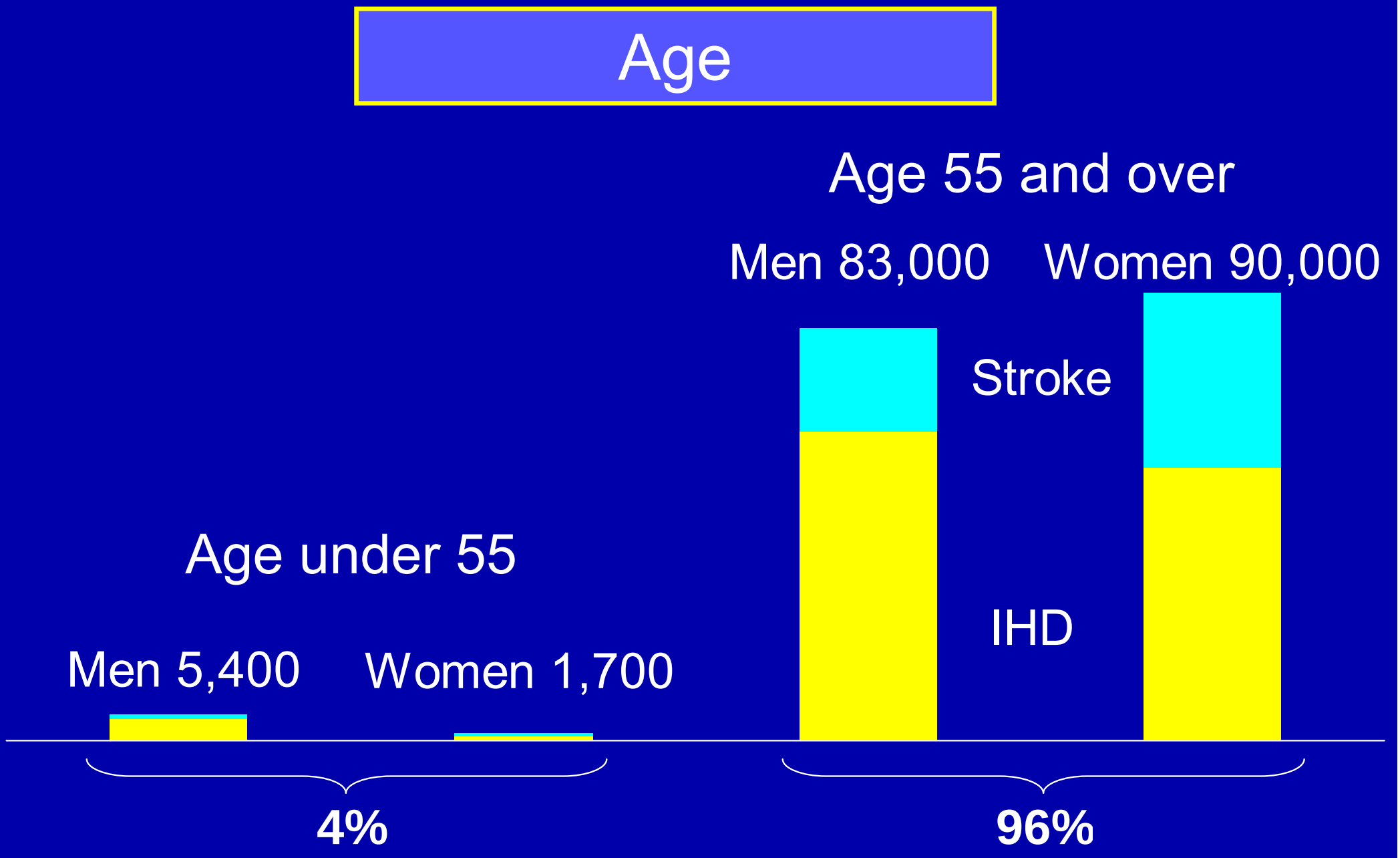
Blood pressure

Half standard dose	Reduction in diastolic blood pressure	Reduction in: IHD	Reduction in: Stroke
1 drug	3.7 mmHg	19%	29%
2 drugs	7.3 mmHg	34%	49%
3 drugs	10.7 mmHg	46%	63%

from meta-analysis of 354 placebo-controlled trials

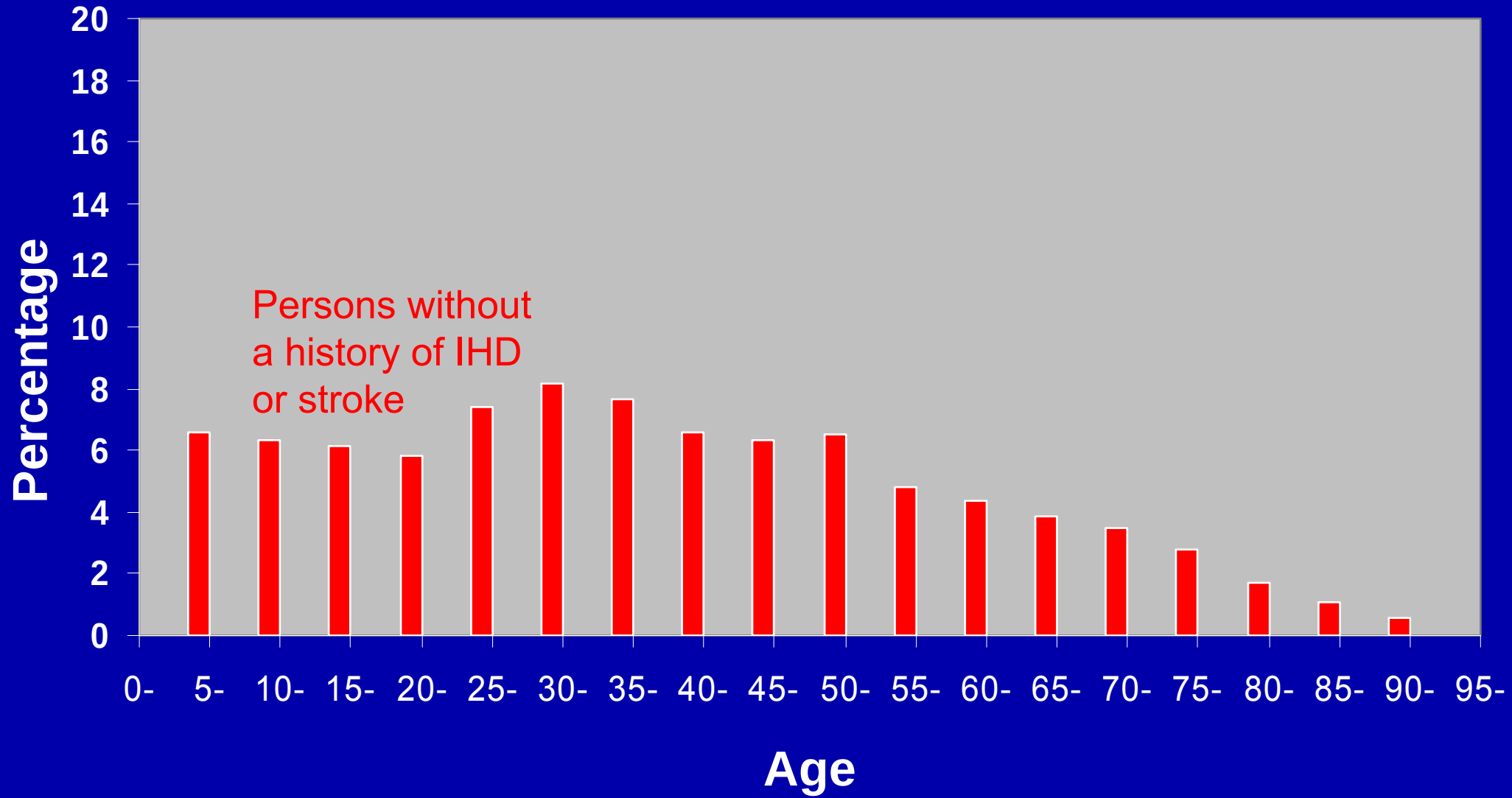
from meta-analysis of 61 cohort studies supported by 69 trials

Starting blood pressure 150/90



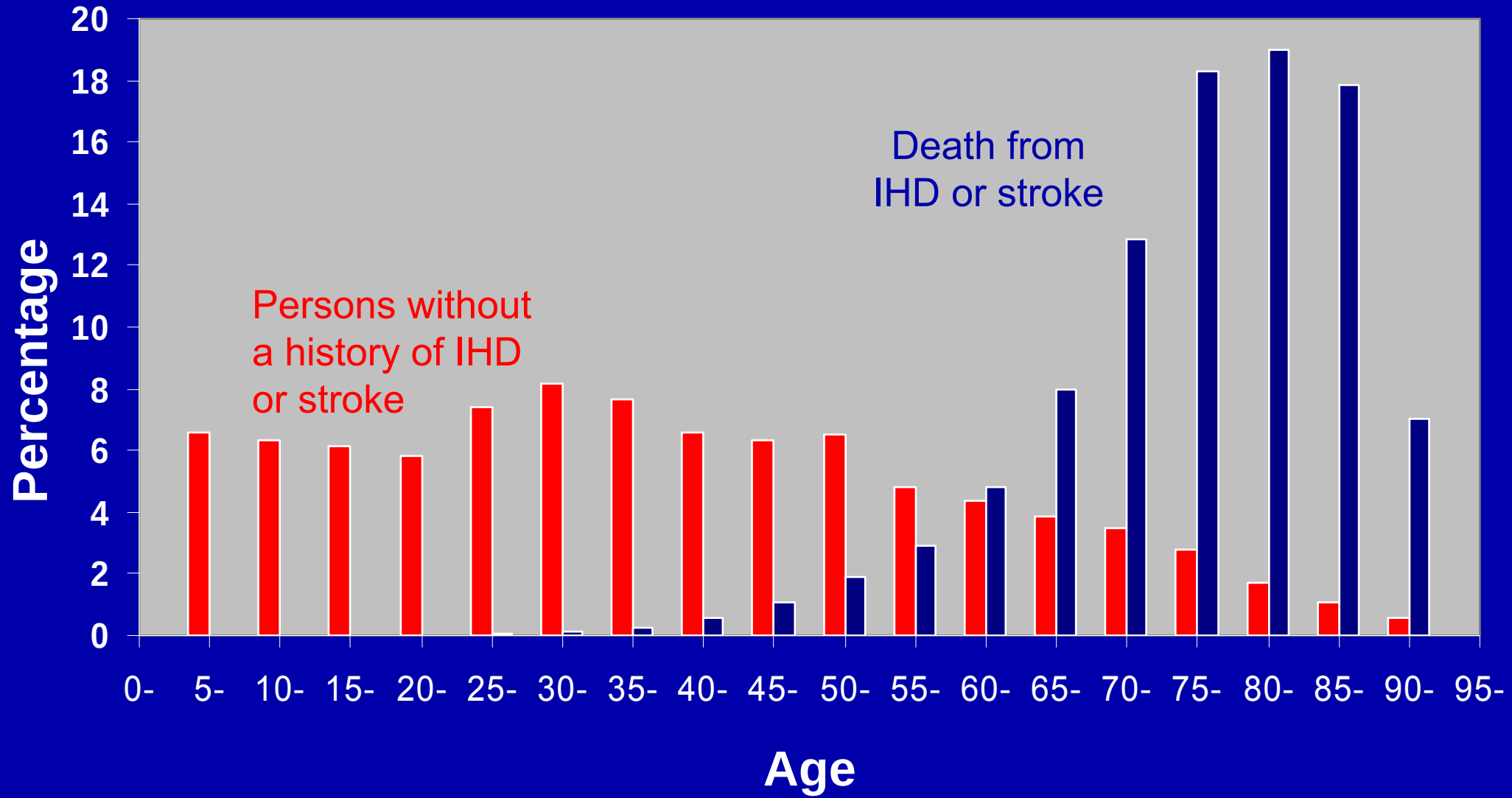
IHD and stroke deaths (England and Wales 1997)

England and Wales 1998



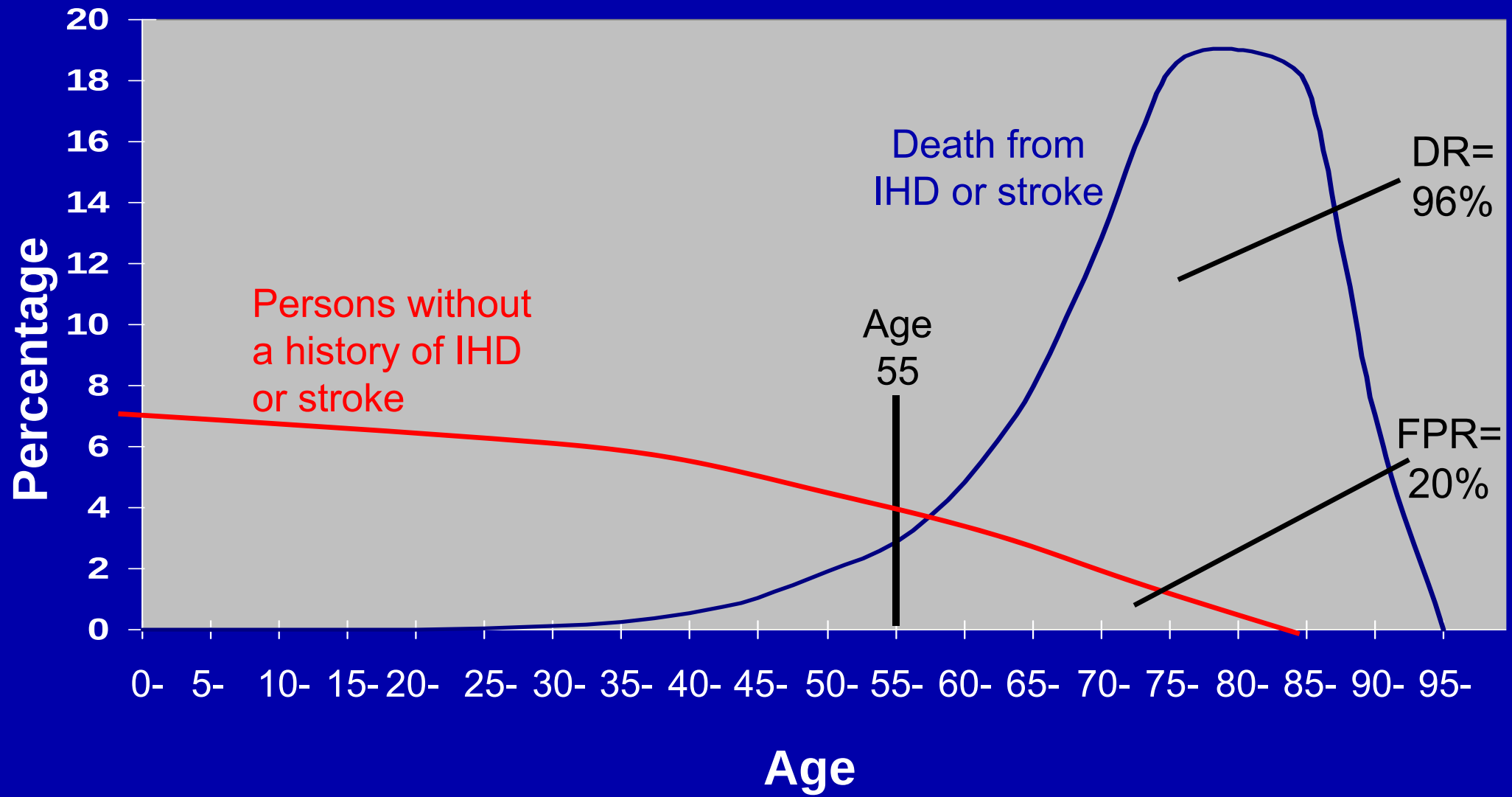
images/009/red.xls

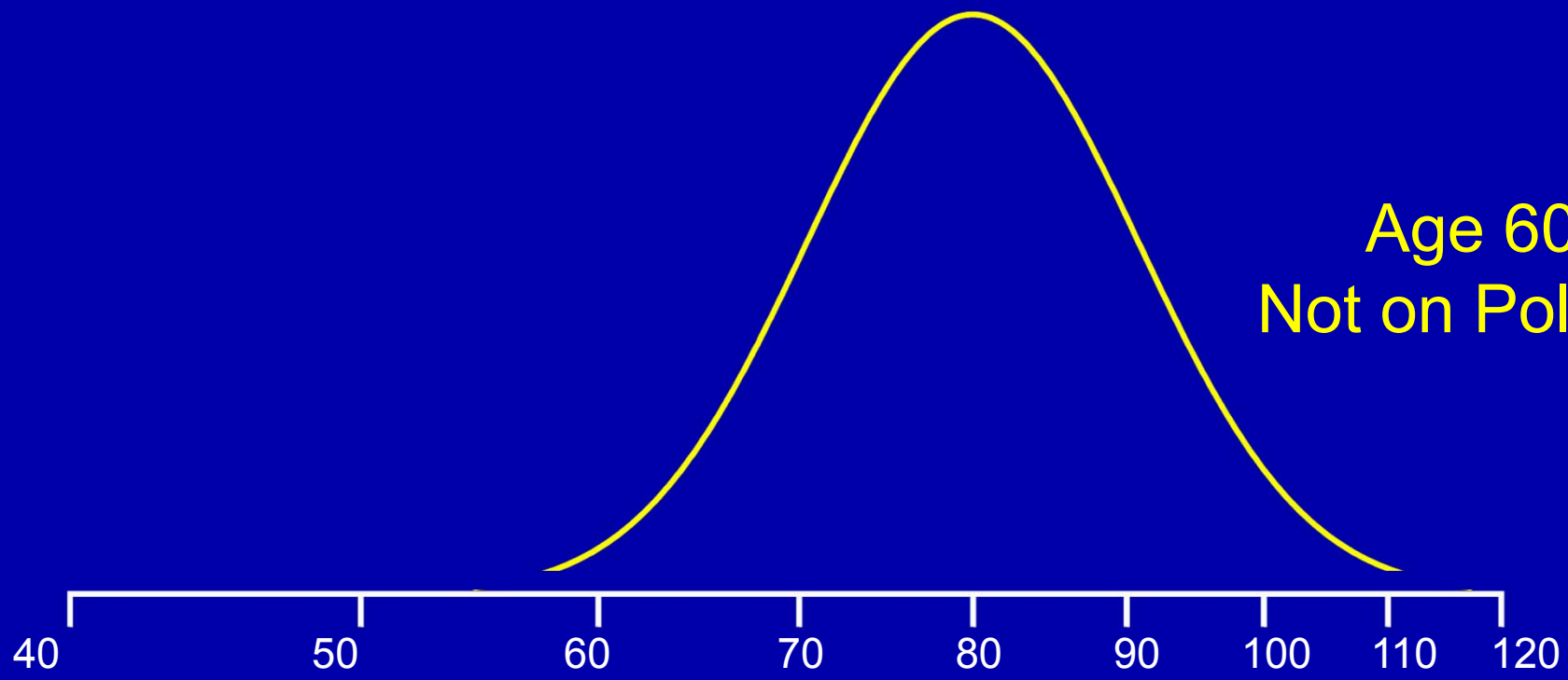
England and Wales 1998



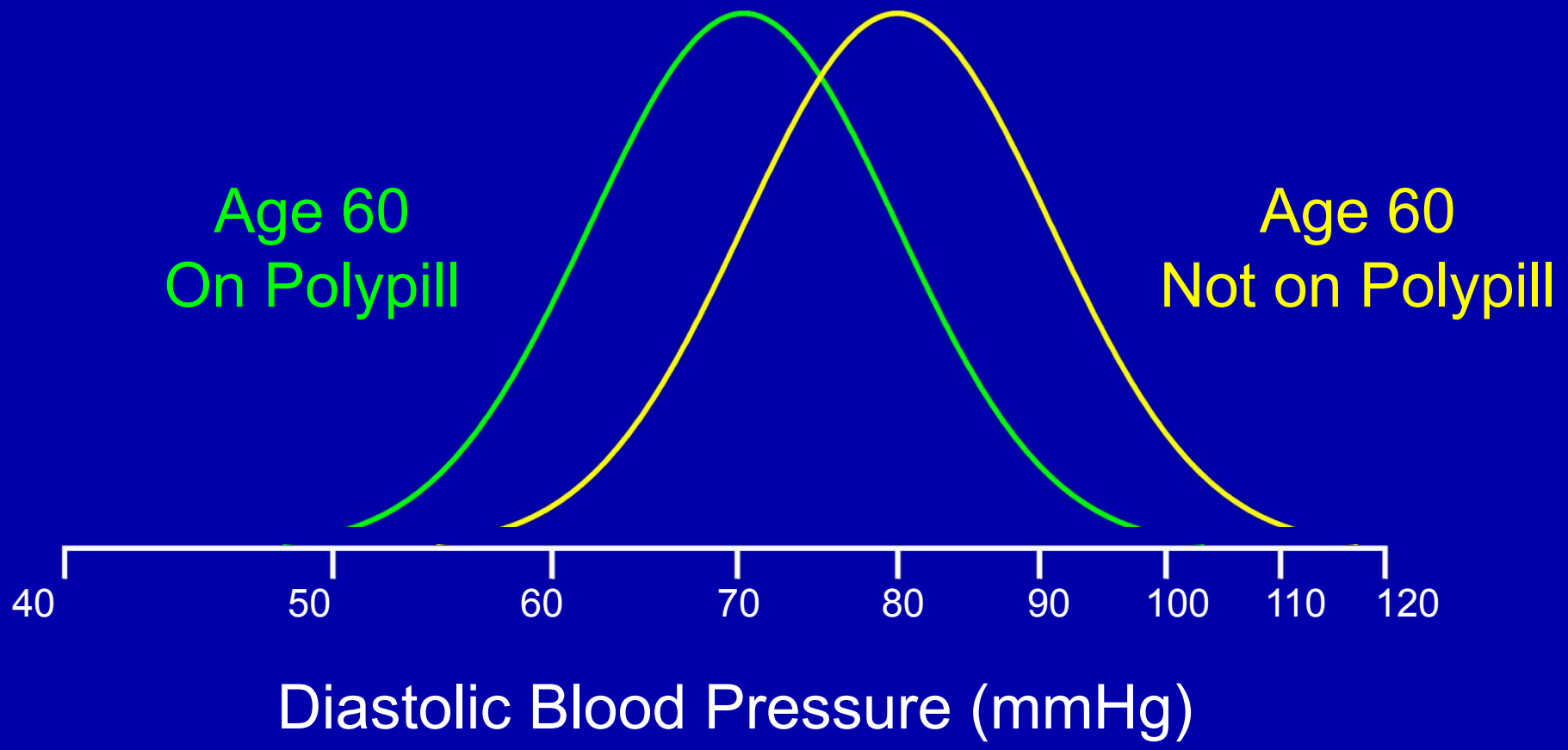
ONS 1998

Age as a screening test for ischaemic heart disease and stroke





The Dietary and Nutritional Survey of British Adults, 1987



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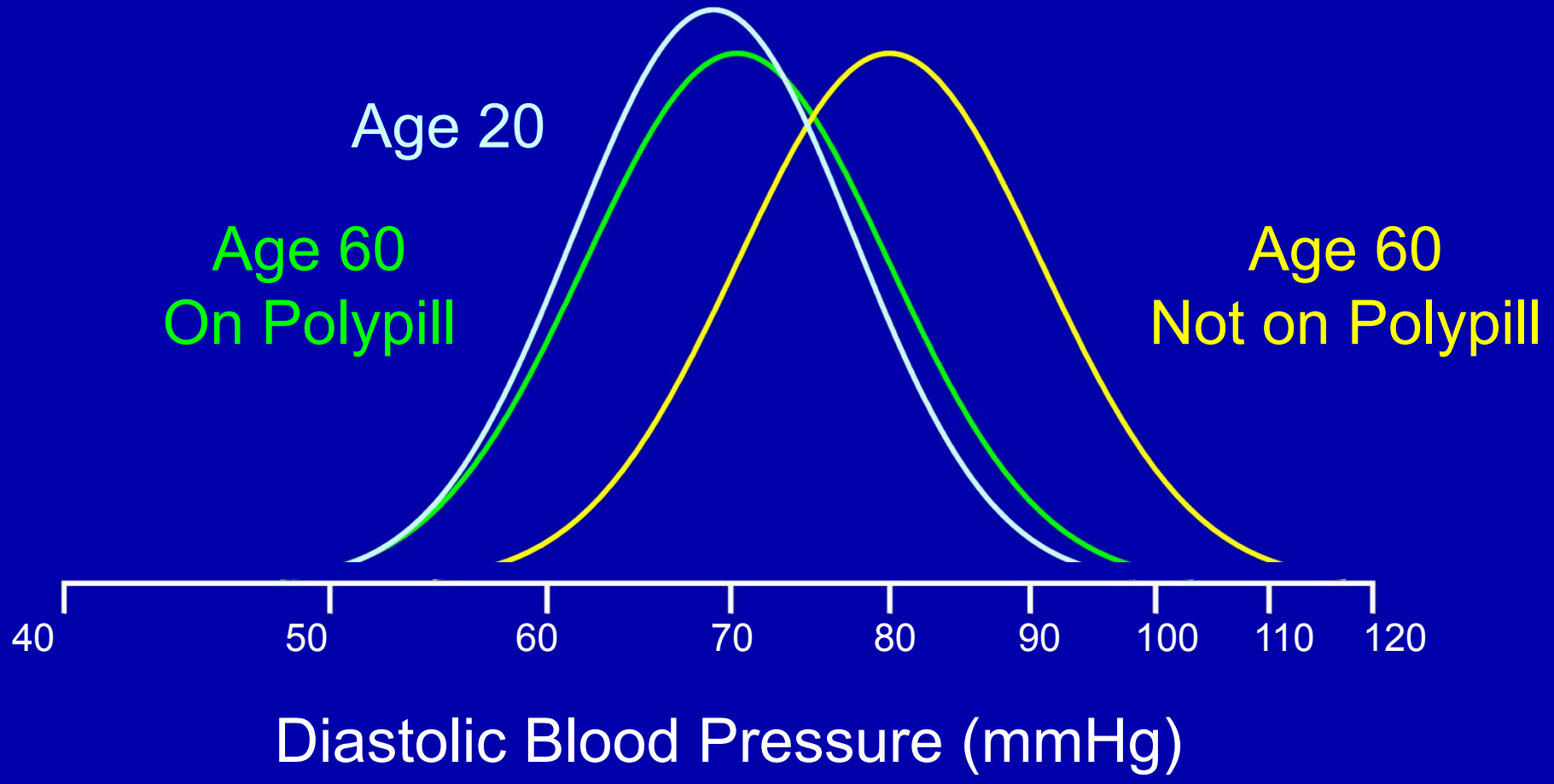

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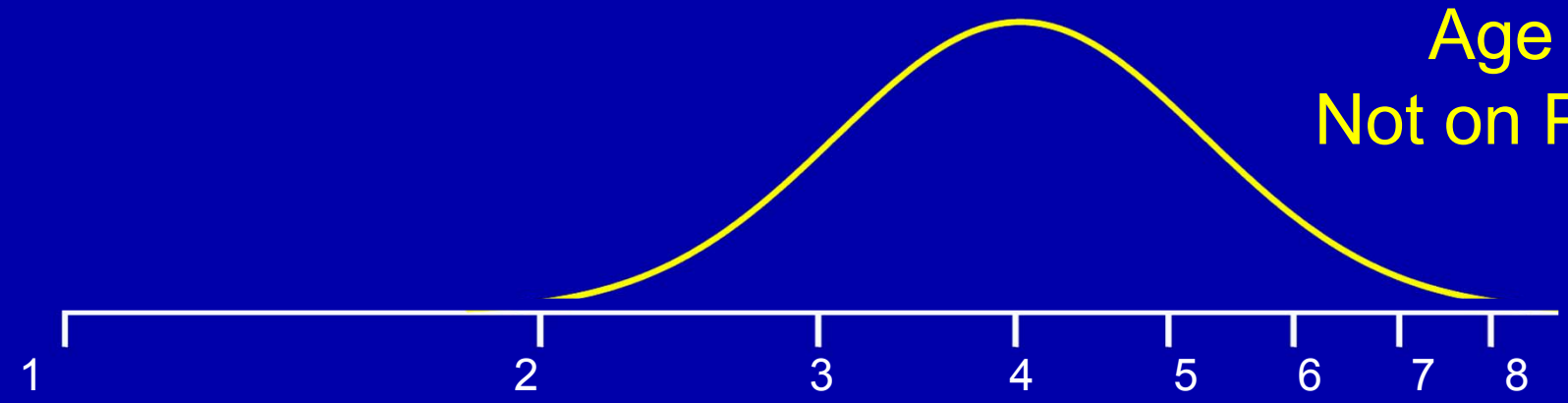
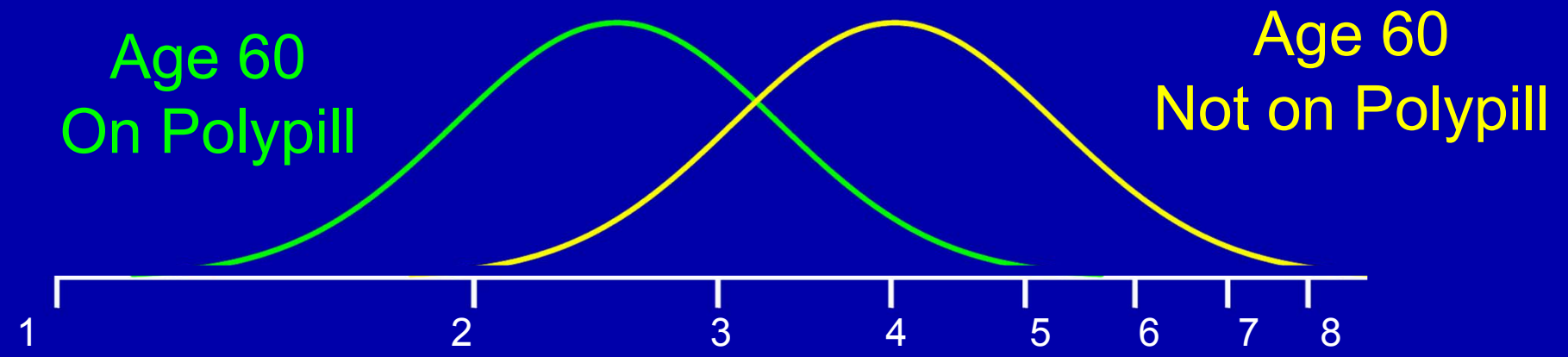


Health Survey of England, 1994



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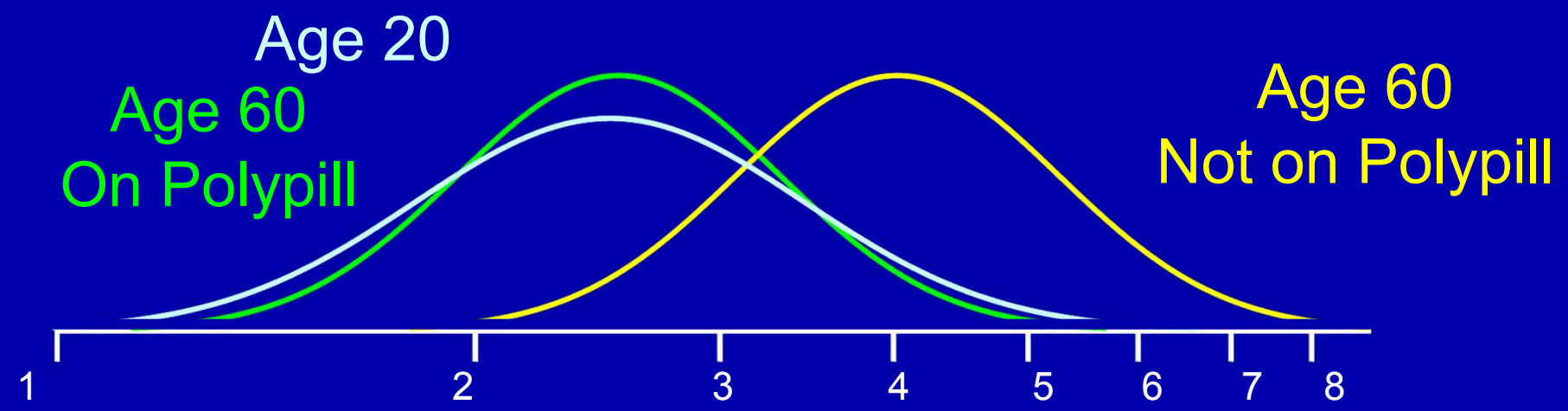
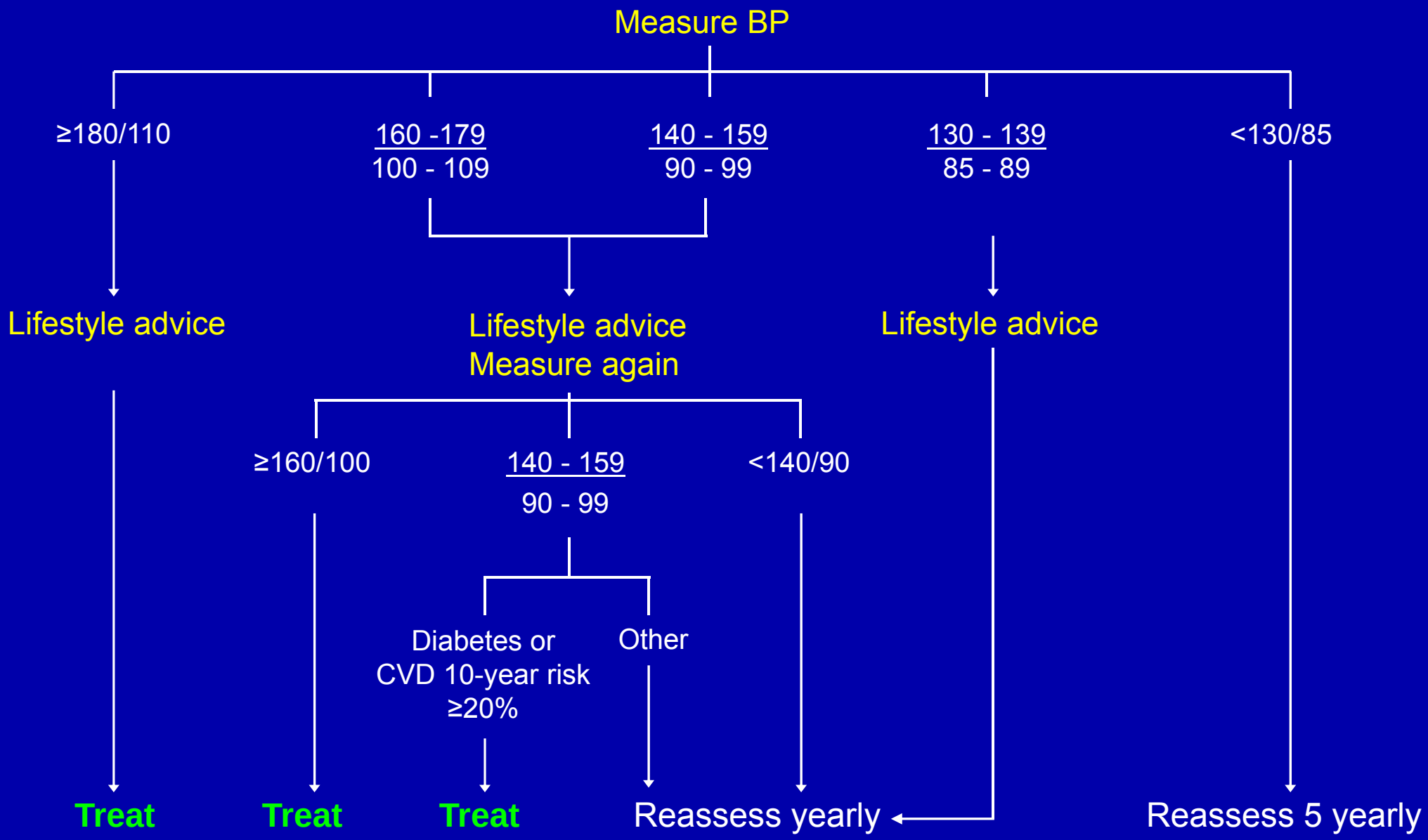


Health Survey of England, 1994

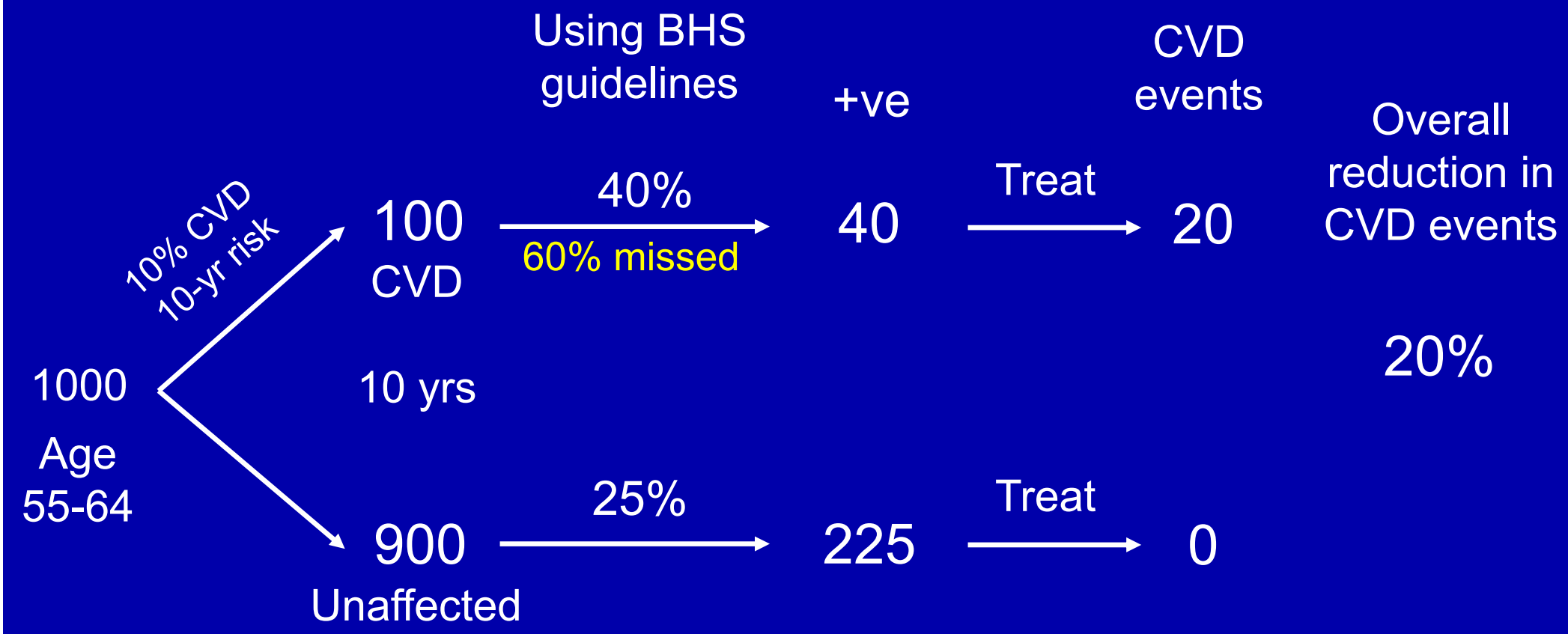
Guidelines

British Hypertension Society Guidelines 2004 (Simplified)



BMJ Vol 328: 634-640, 13 March 2004

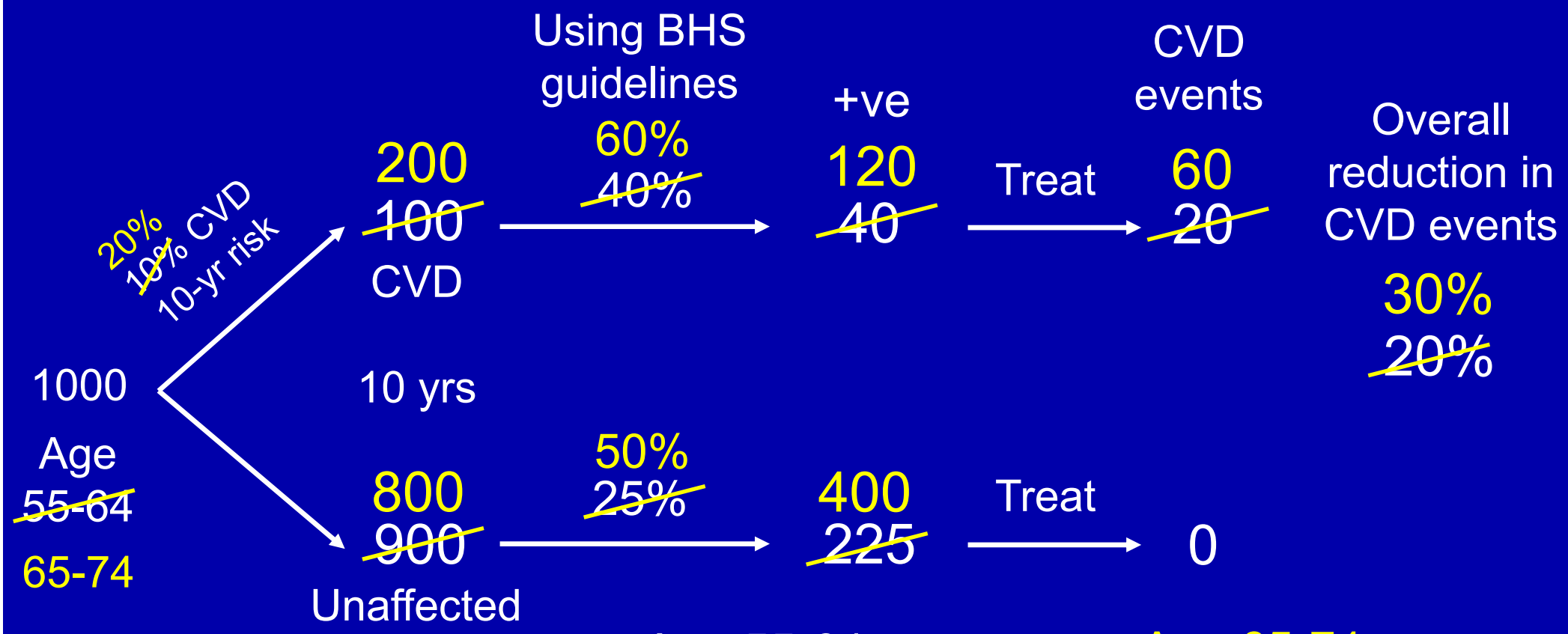
Application of BHS Guidelines in people aged 55-64



Risk in positives: $\frac{40}{225+40} = 15\%$

Risk in remainder: $\frac{60}{675+60} = 8\%$

Application of BHS Guidelines in people aged 65-74



	Age 55-64	Age 65-74
Risk in positives:	$\frac{40}{225+40} = 15\%$	$\frac{120}{400+120} = 23\%$
Risk in remainder:	$\frac{60}{675+60} = 8\%$	$\frac{80}{400+80} = 17\%$

Using risk factors

There is little point in estimating a person's risk using blood pressure, serum cholesterol and smoking habits because those who are thereby "positive", but "negative" on the basis of their age alone, would anyway become "positive" when they are a few years older.

It is not worth the considerable cost and effort simply to delay the start of treatment.

Guidance on Guidelines

We need simpler,
more effective guidelines.

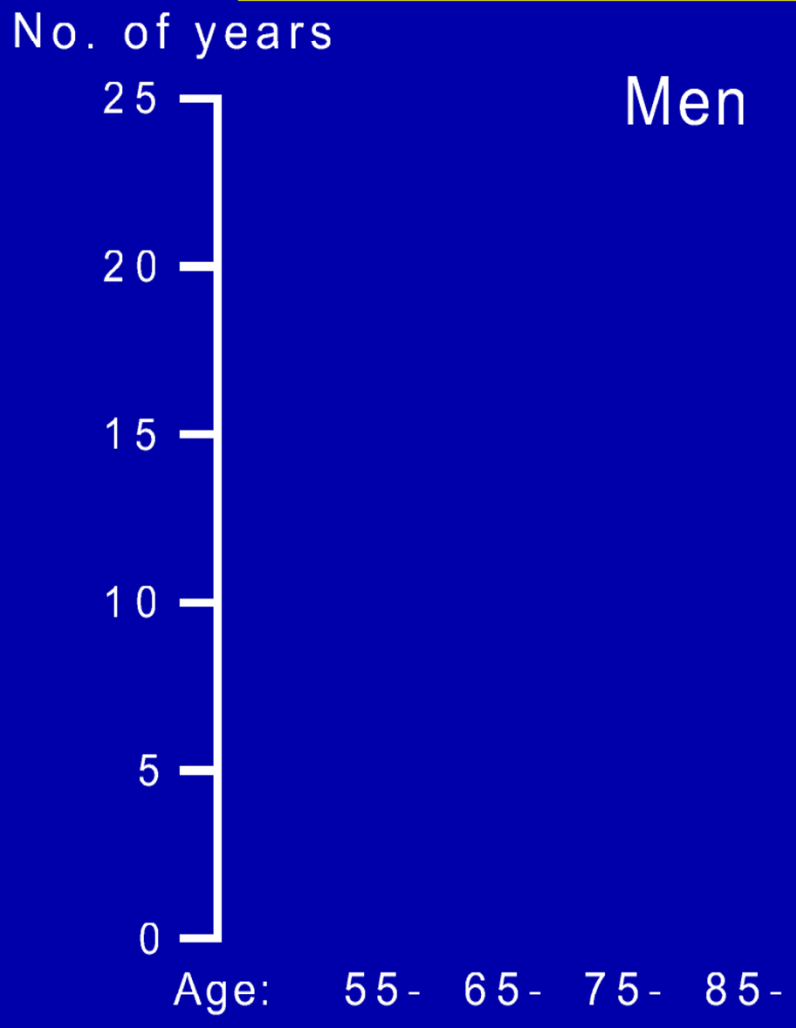
Proposed Guidelines on Cardiovascular Disease Prevention

1. Lifestyle changes for all
2. Combination drug treatment for all with cardiovascular disease or diabetes
3. Combination drug treatment for all above a given age (55)
4. Less testing and monitoring

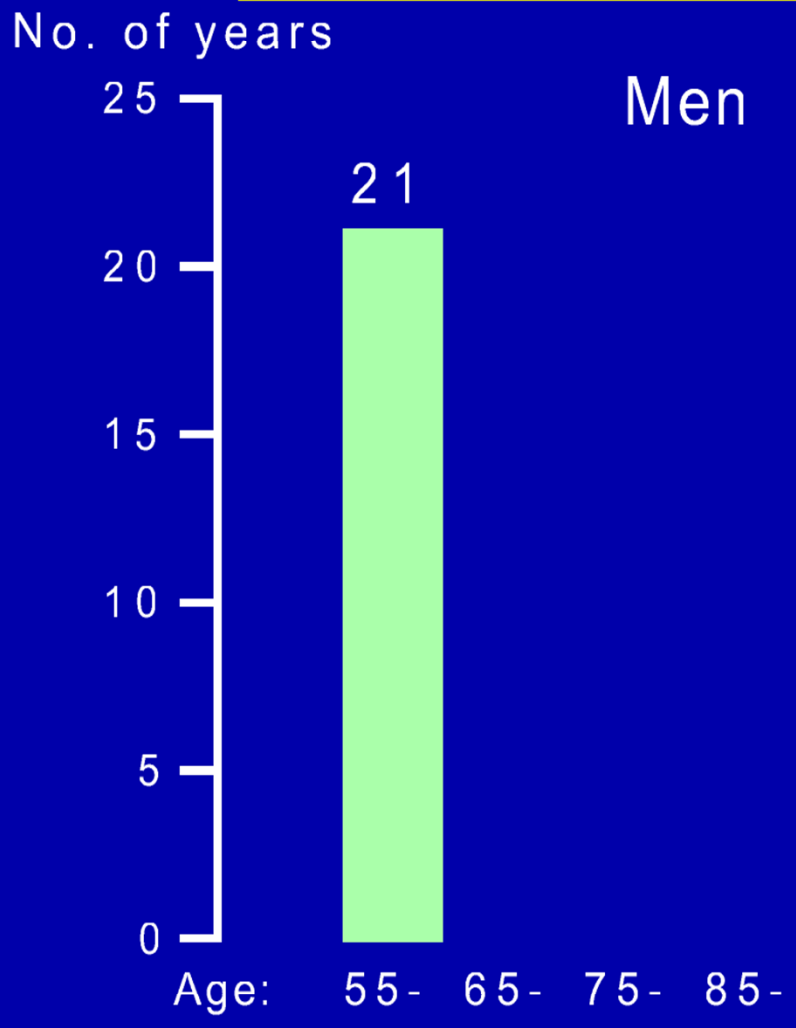
No. of men with IHD event or stroke delayed or avoided in 100 without a previous IHD event or stroke who start taking the Polypill from age 55

Age	55 -	65 -	75 -	85 -
No. of persons with IHD event or stroke delayed or avoided	7	11	13	6

Average event-free years of life gained in
100 men without a previous IHD event or stroke
who start taking the Polypill from age 55



Average event-free years of life gained in 100 men without a previous IHD event or stroke who start taking the Polypill from age 55



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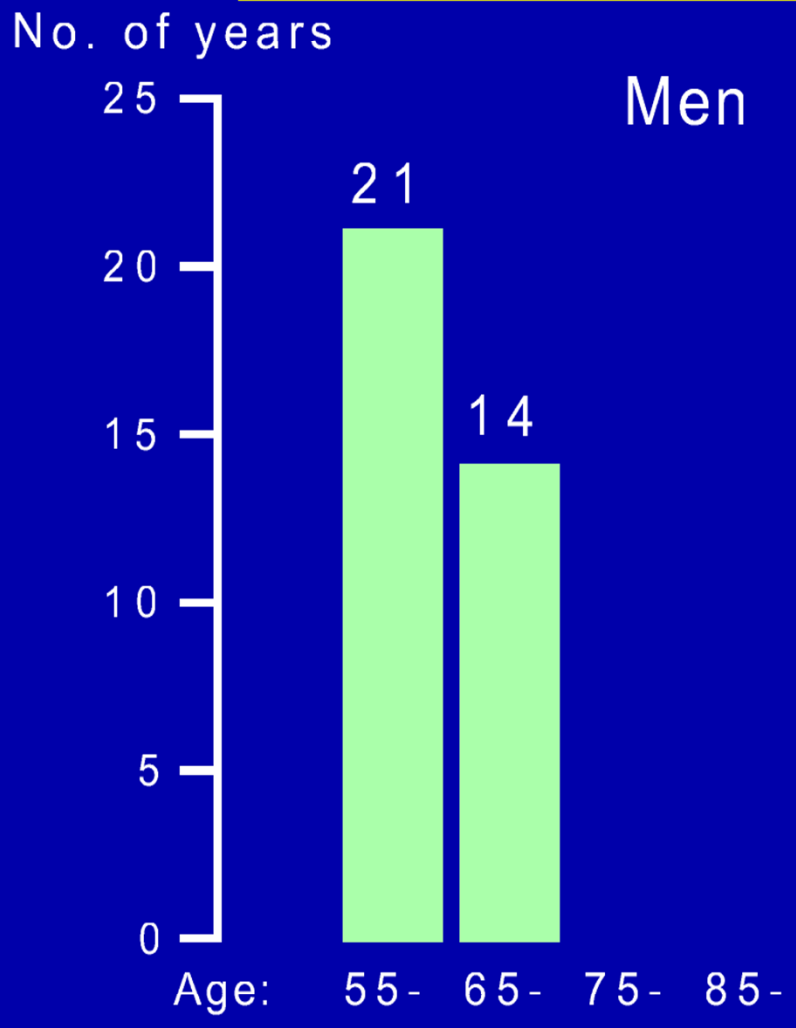

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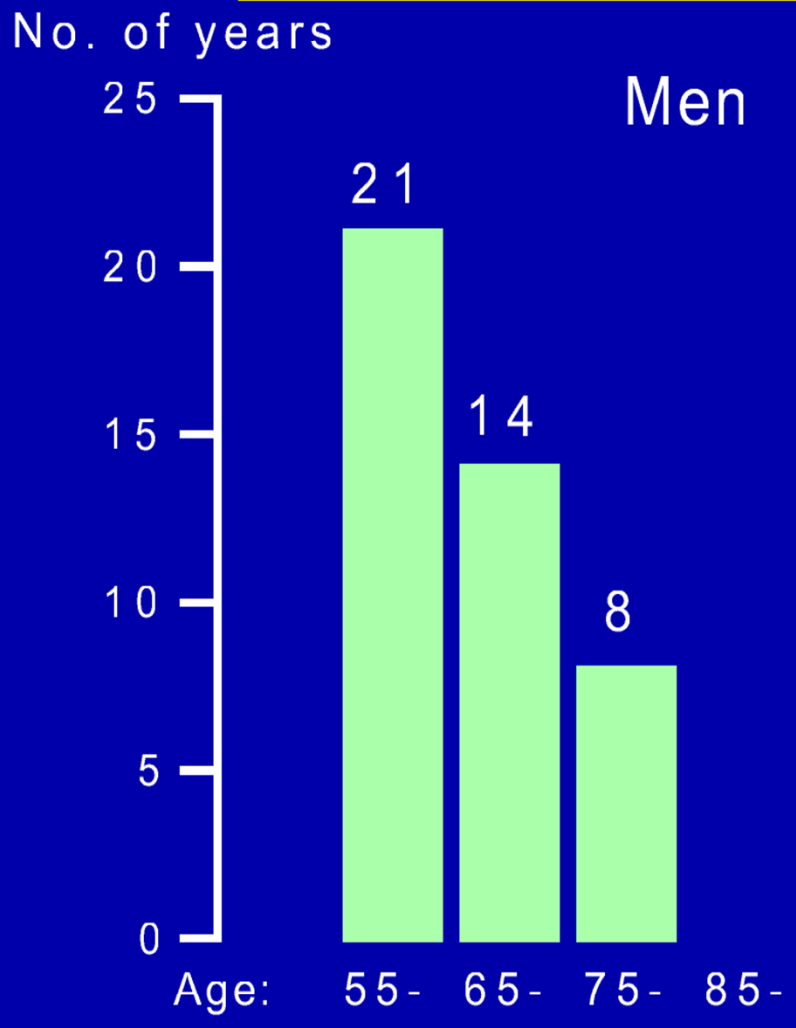

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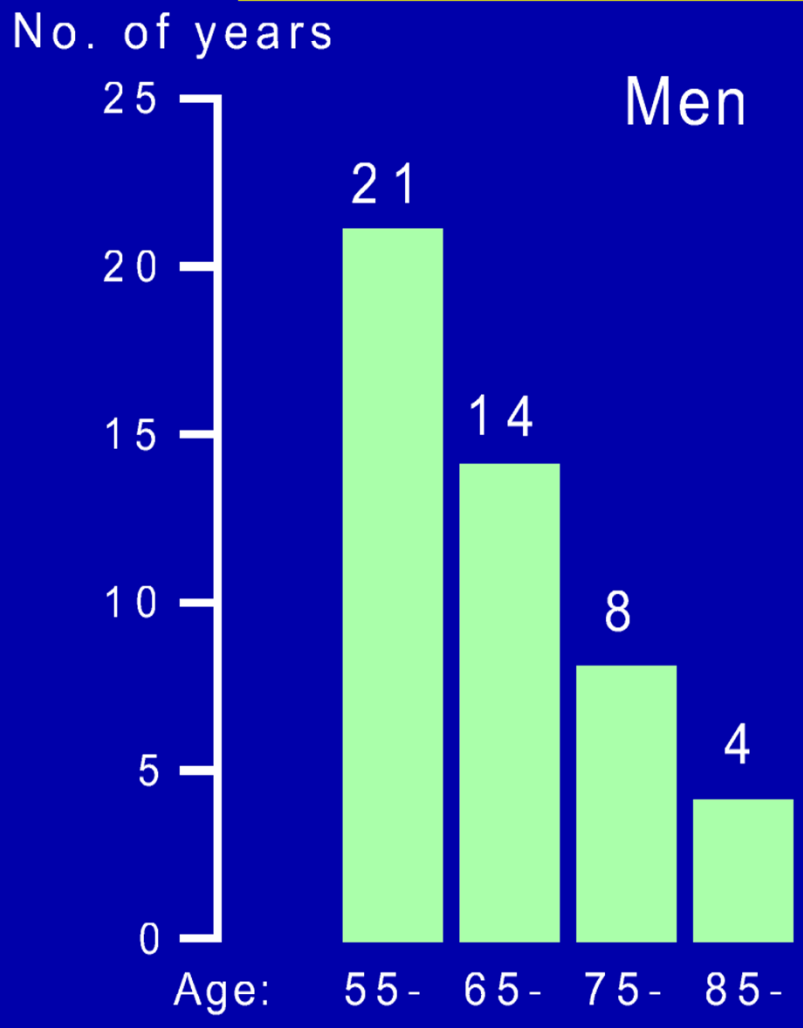
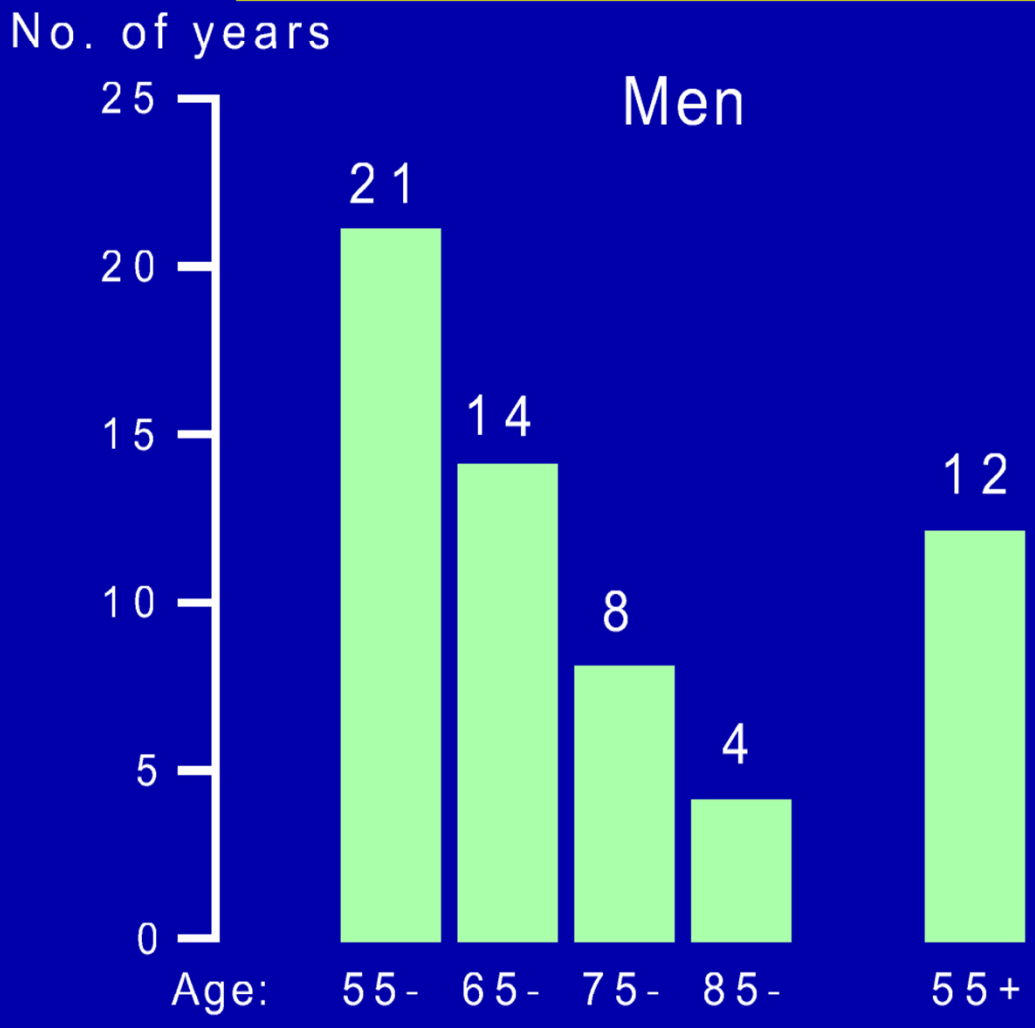
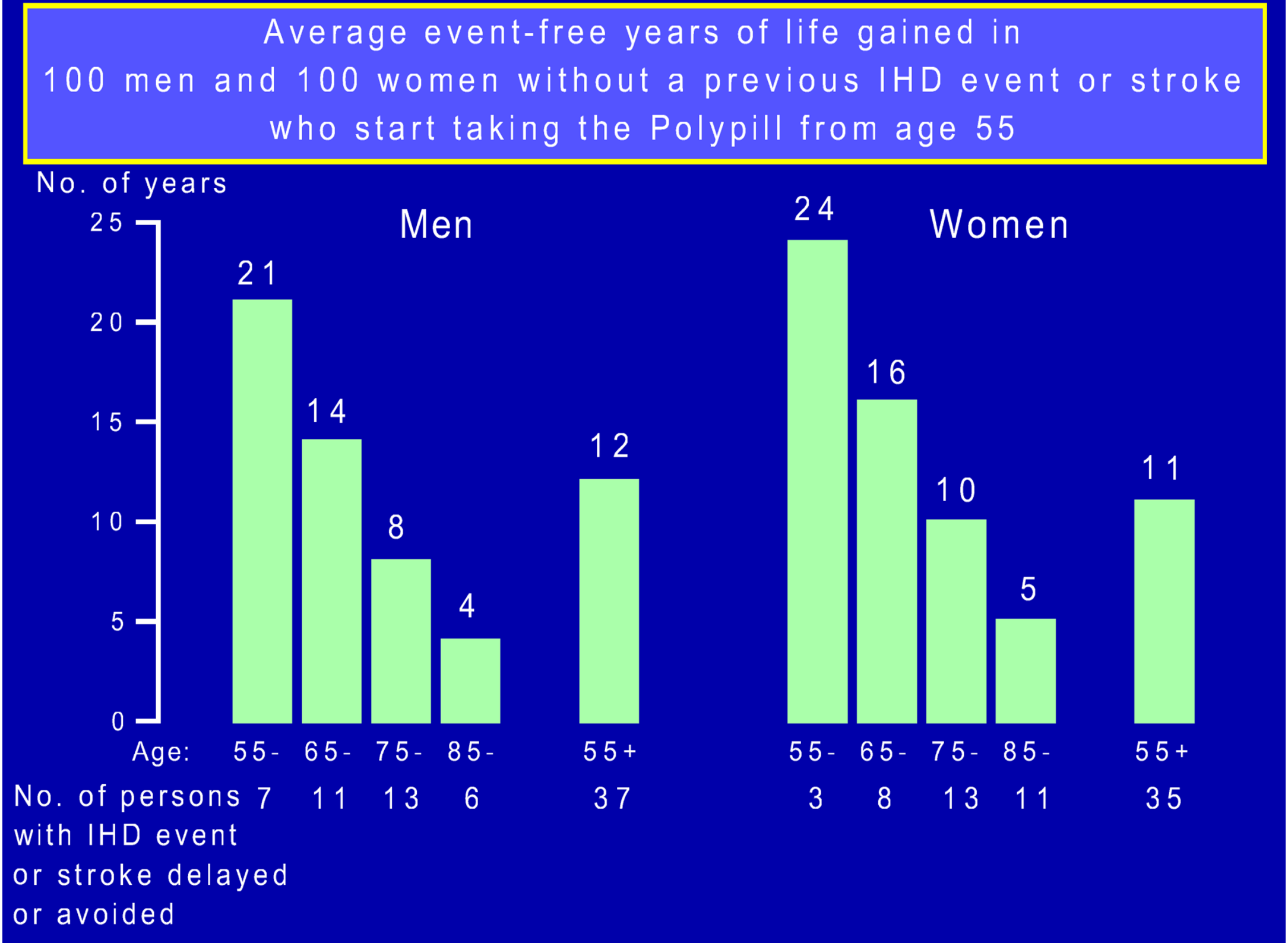


Average event-free years of life gained in 100 men without a previous IHD event or stroke who start taking the Polypill from age 55




Average event-free years of life gained in
100 men and 100 women without a previous IHD event or stroke
who start taking the Polypill from age 55
No. of years
25
20
15
10
5
0
Men
21
14
8
4
12
Women
24
16
10
5
11
Age:
55-
65-
75-
85-
55+
55-
65-
75-
85-
55+
No. of persons with IHD event or stroke delayed or avoided
7
11
13
6
37
3
8
13
11
35

Prevention strategy

A single Polypill per day composed of six active ingredients, to be taken, without medical examination, by:

- all aged 55 or more
- anyone under 55 with a history of cardiovascular disease or diabetes

Conclusion

- The Polypill approach represents a departure from current practice in the prevention of cardiovascular disease.
- It is much simpler and much more effective than conventional cardiovascular screening strategies.
- It ensures that those who stand to benefit from treatment receive it.