Halving premature death

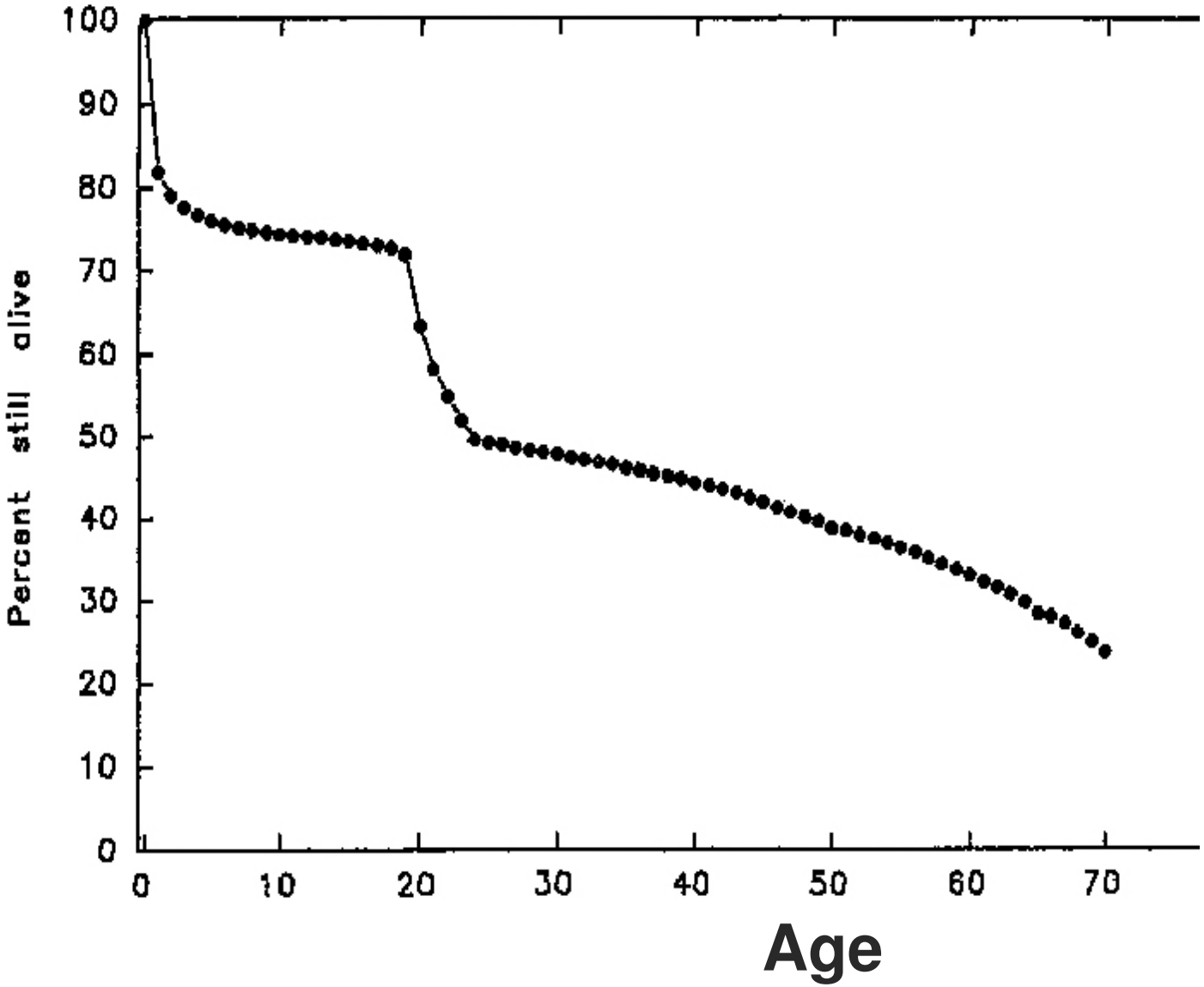
Richard Peto, CTSU

University of Oxford, UK

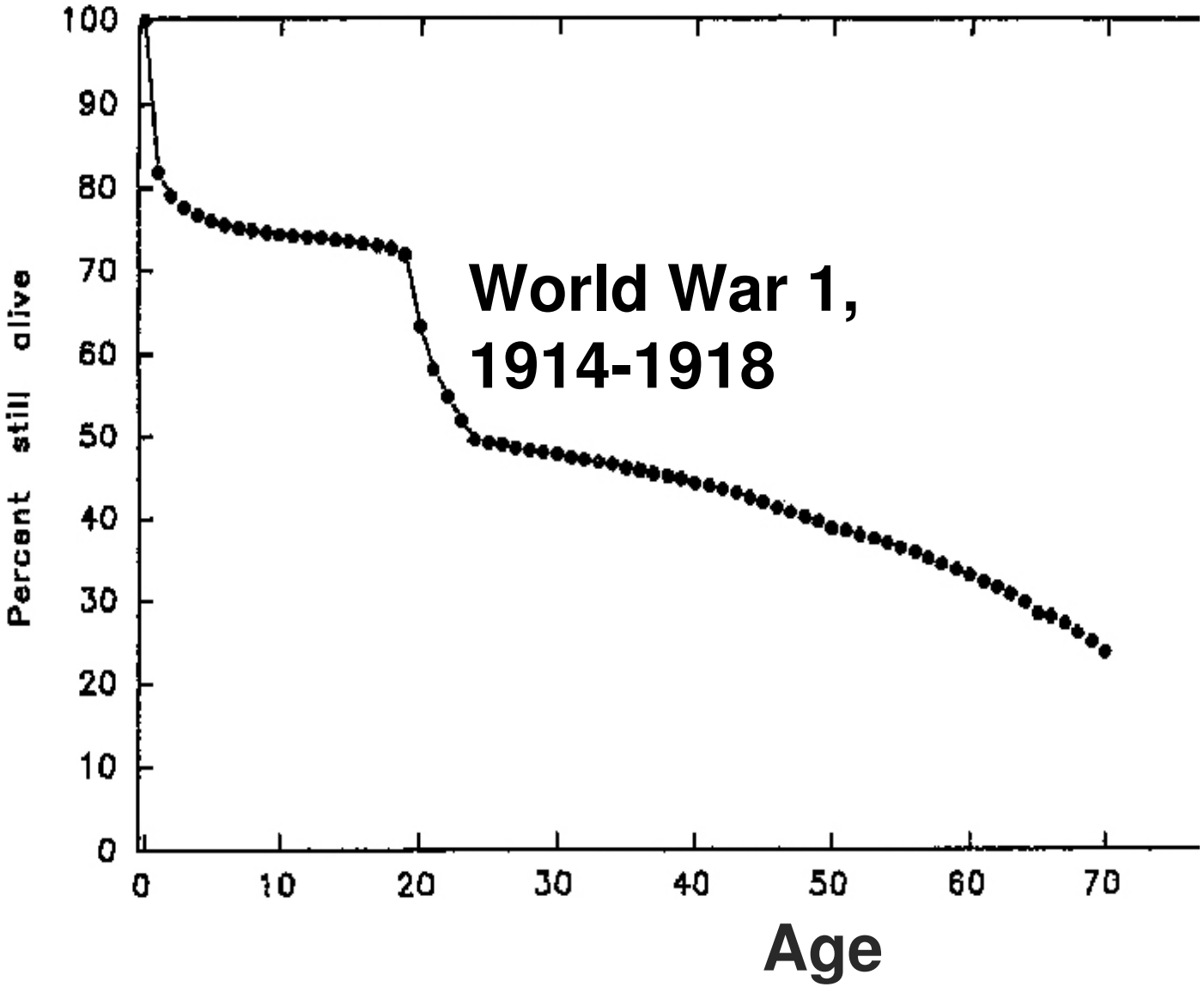
Halving premature death

considering separately ages 0-4, 5-34 & “middle age” (here defined as 35-69)

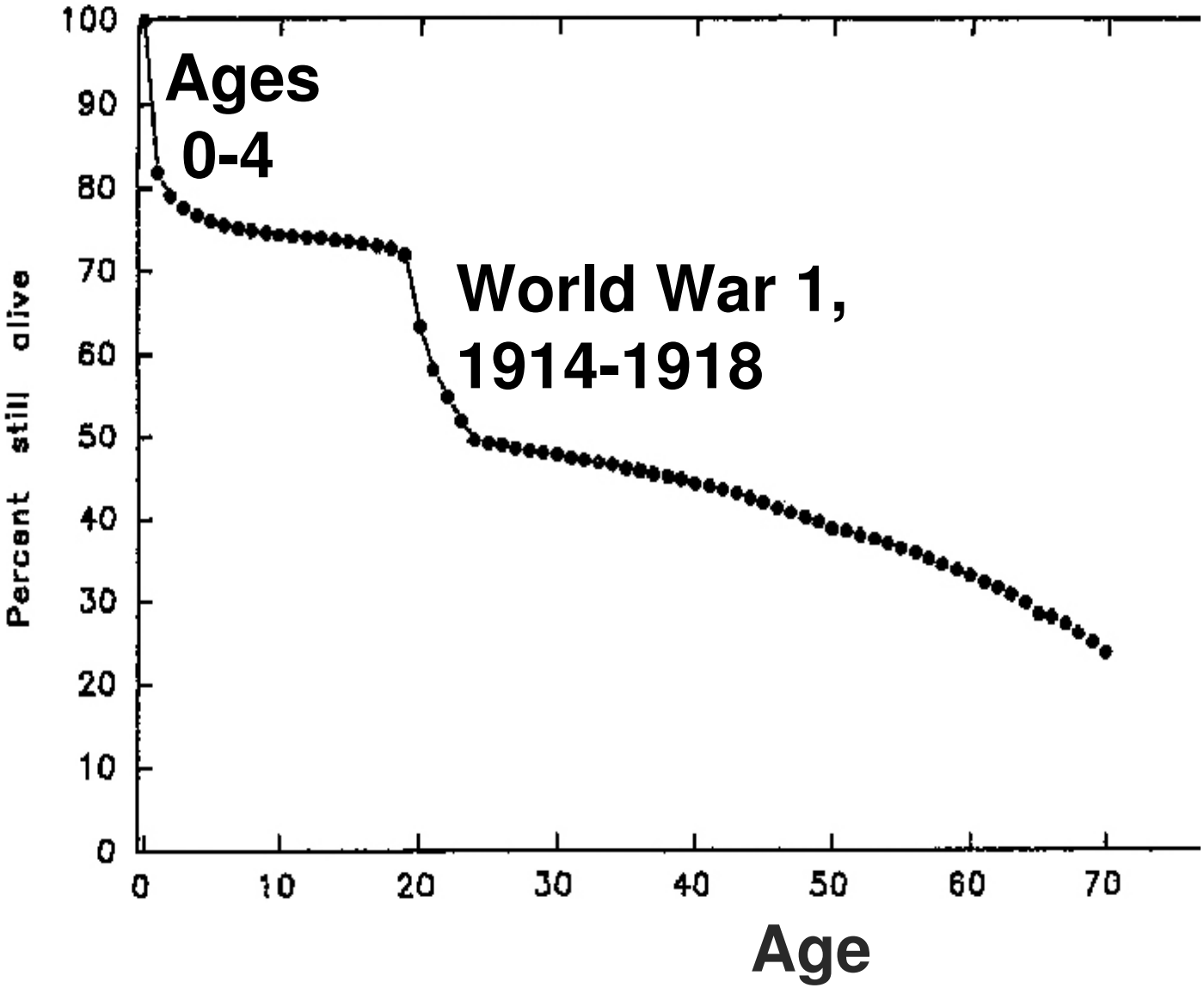
% survival to age 70: an example from the past



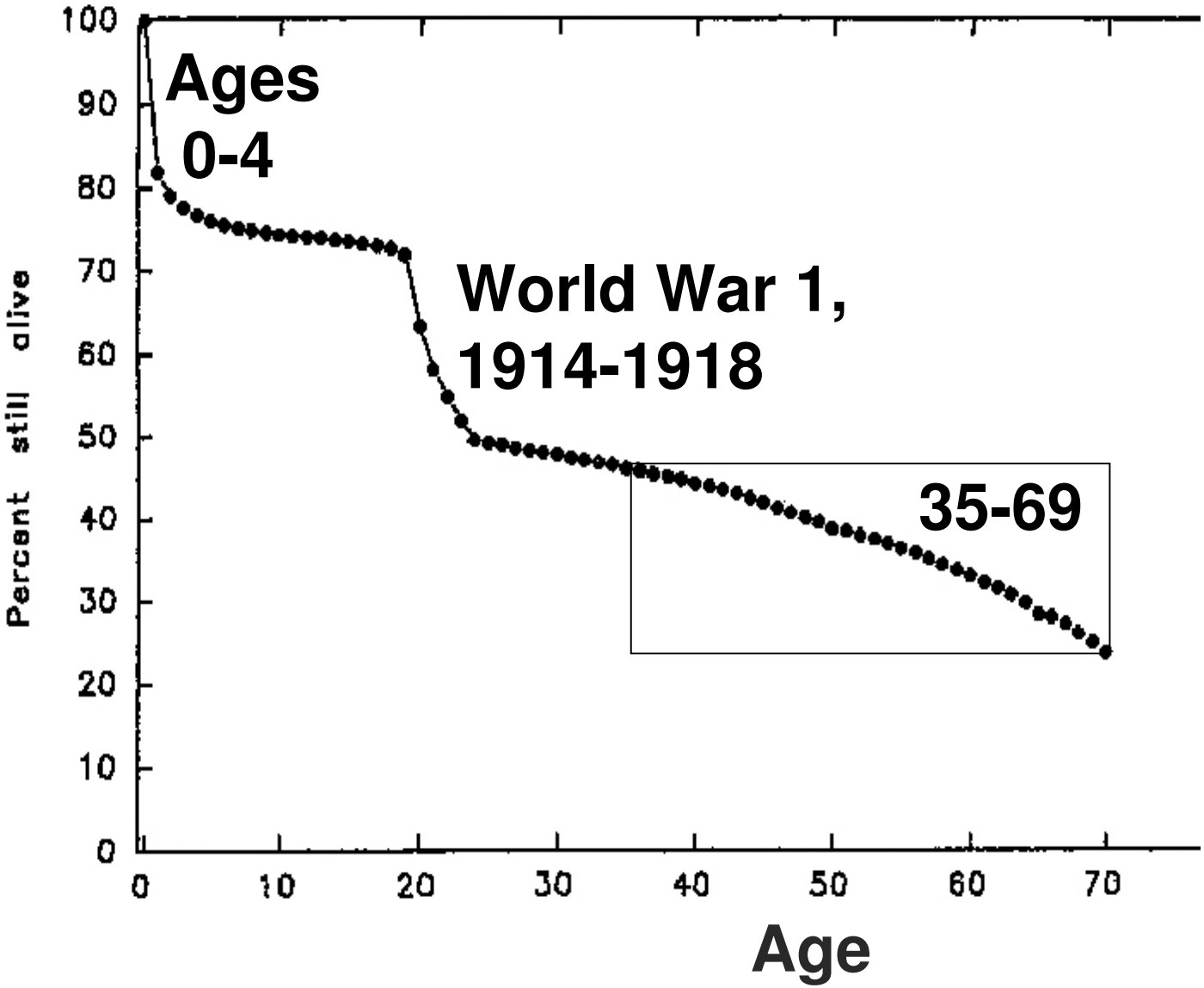
% survival to age 70: French males born in 1896



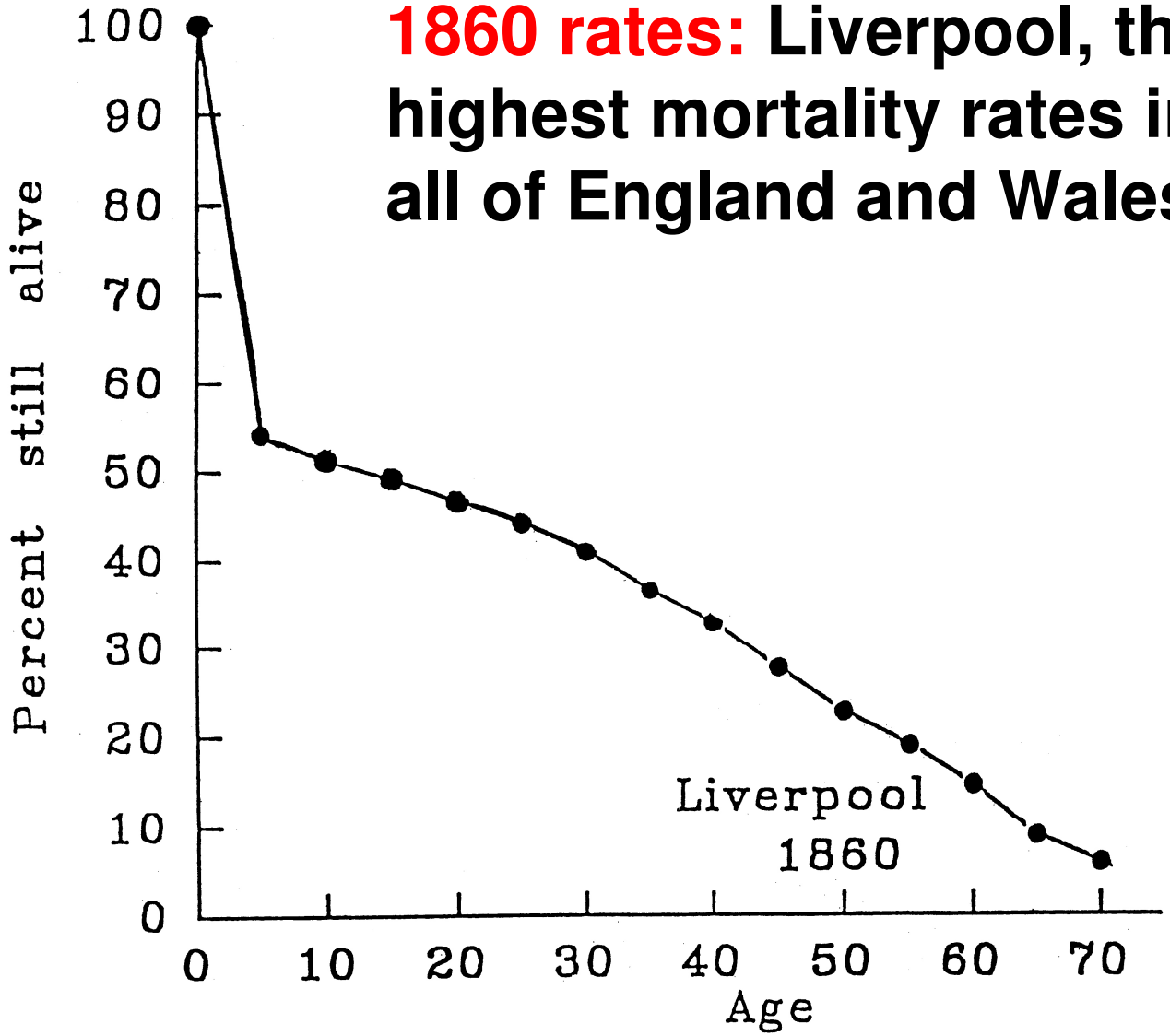
% survival to age 70: French males born in 1896

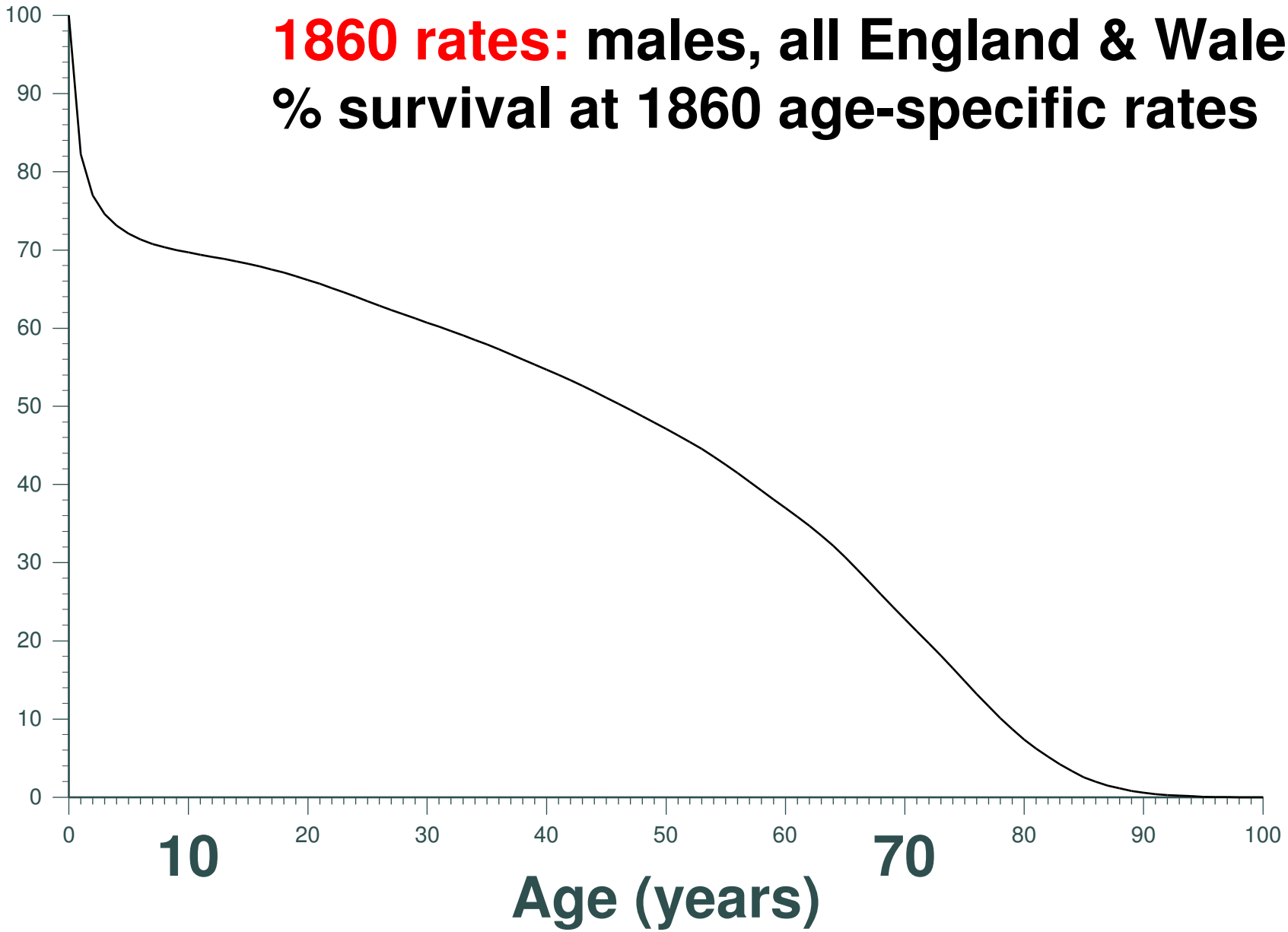


% survival to age 70: French males born in 1896



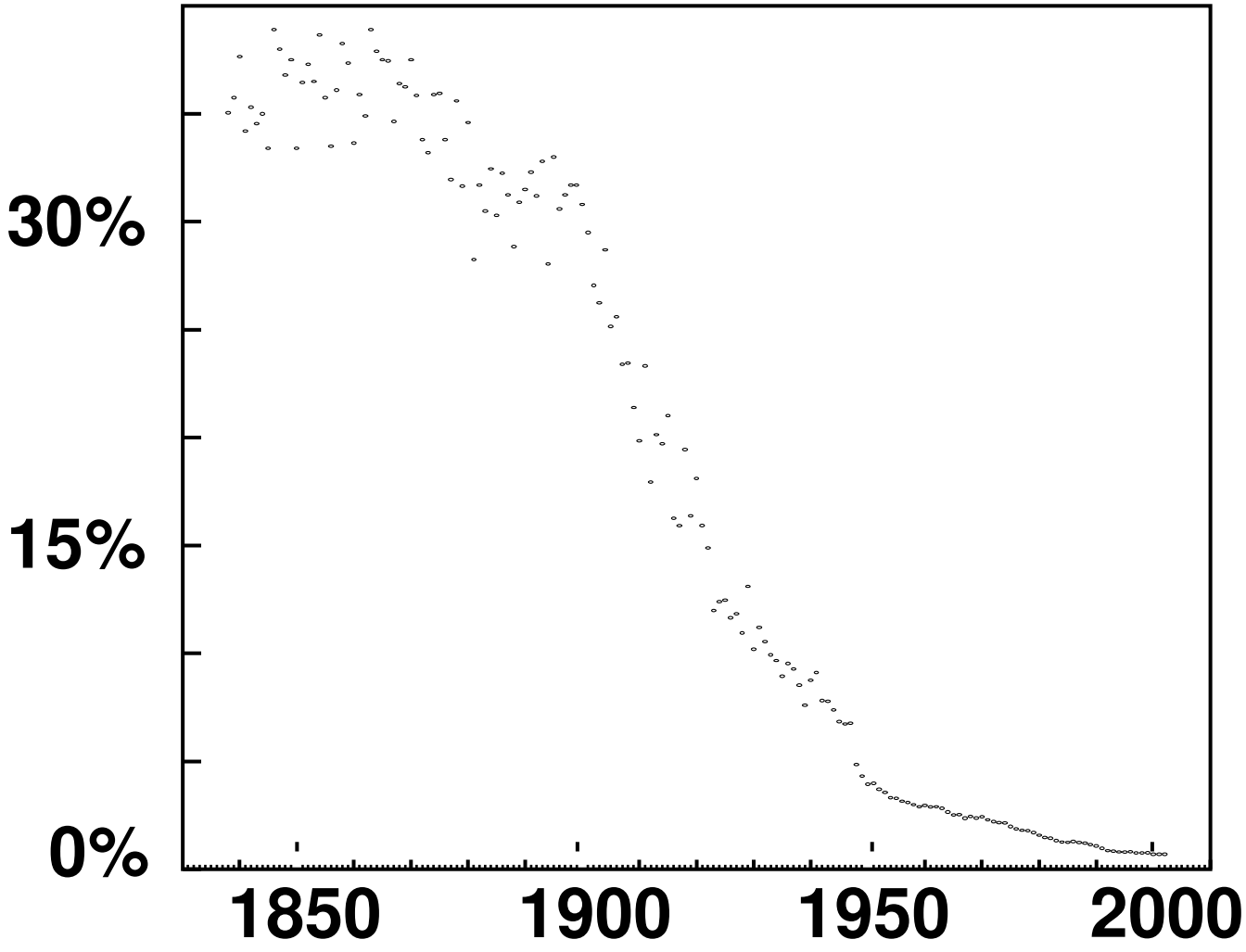
1860 rates: Liverpool, the highest mortality rates in all of England and Wales



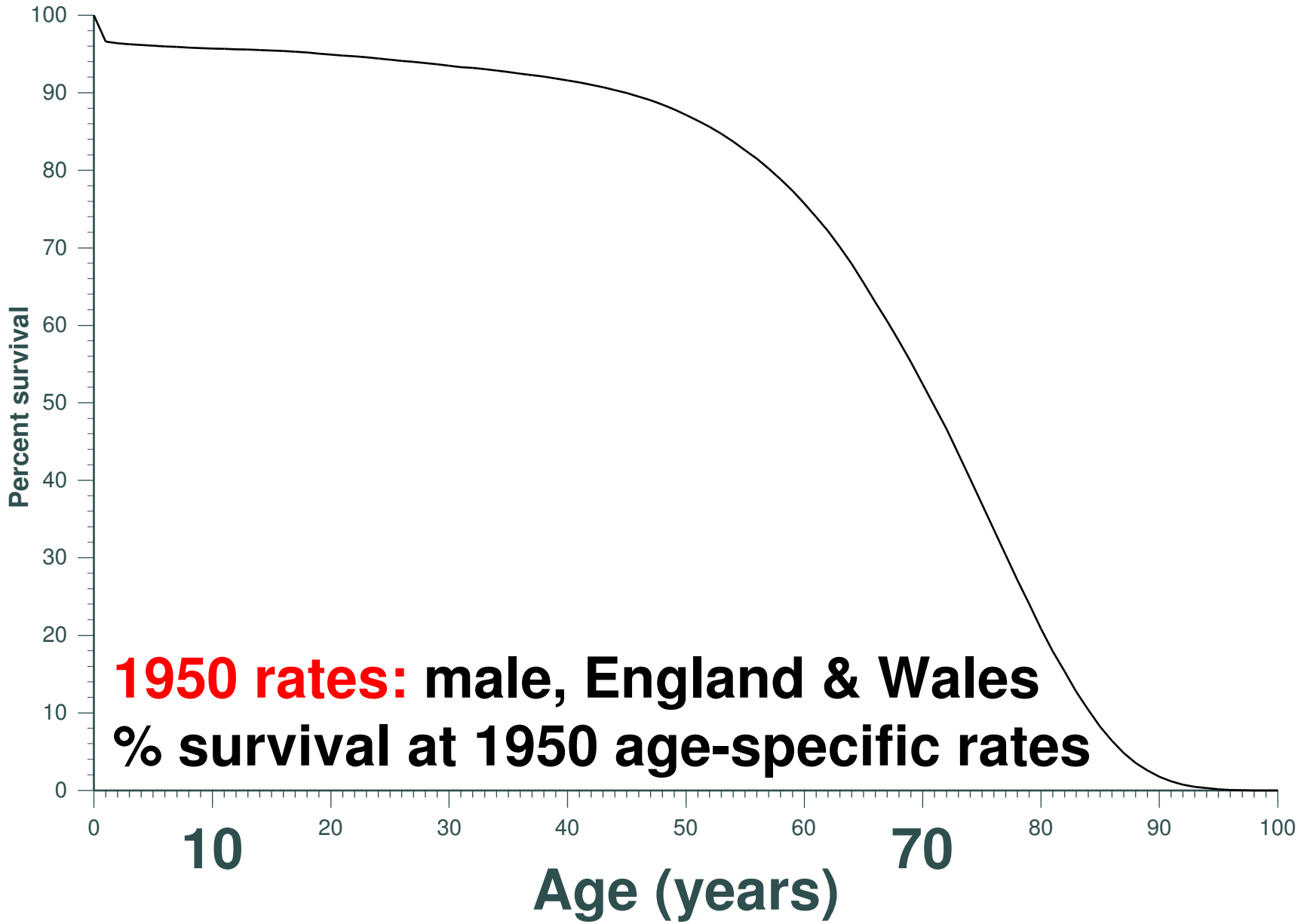

1860 rates: males, all England & Wales
% survival at 1860 age-specific rates
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
100
Age (years)

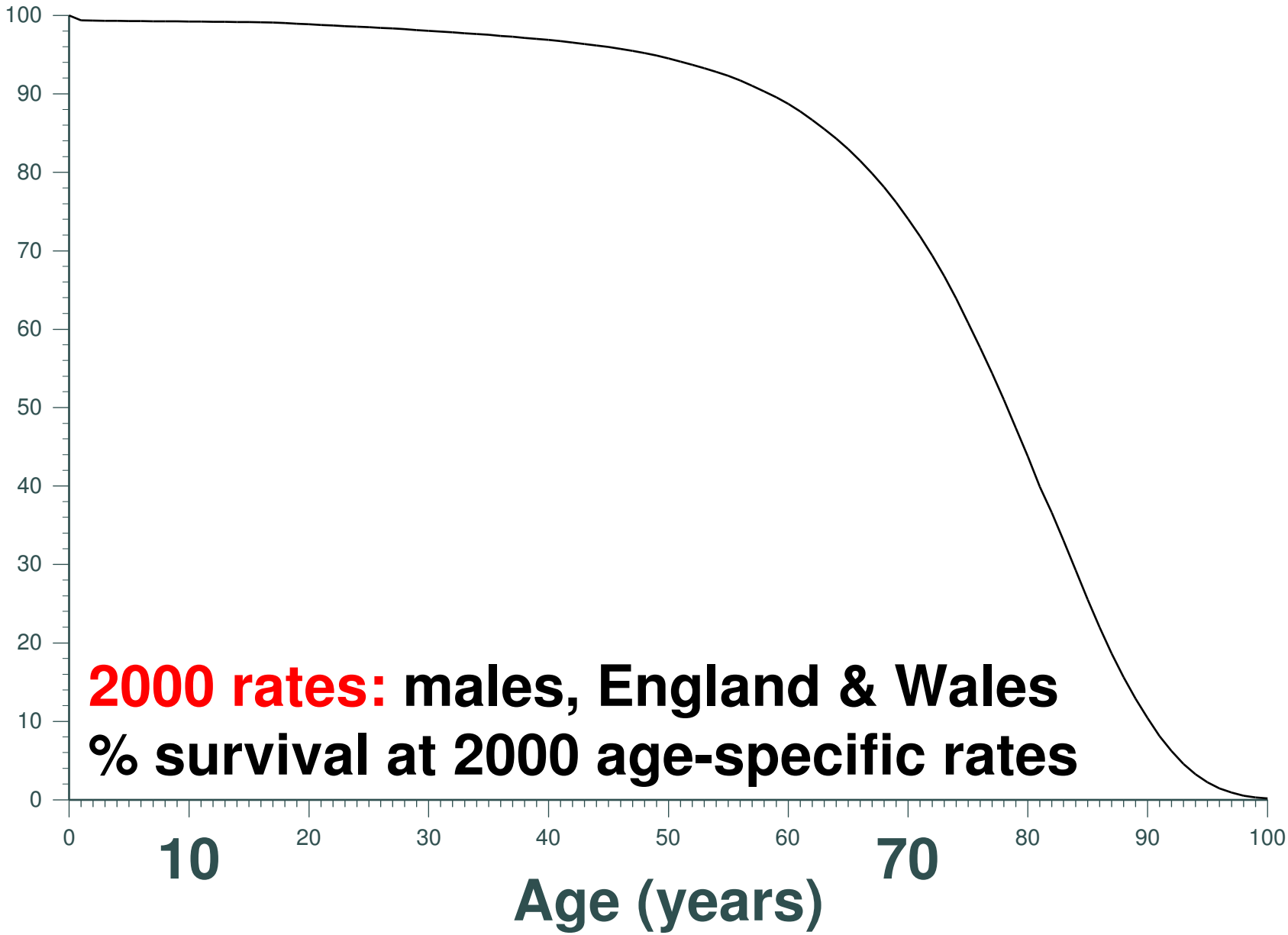

1900 rates: males, England & Wales
% survival at 1900 age-specific rates
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
100
Age (years)

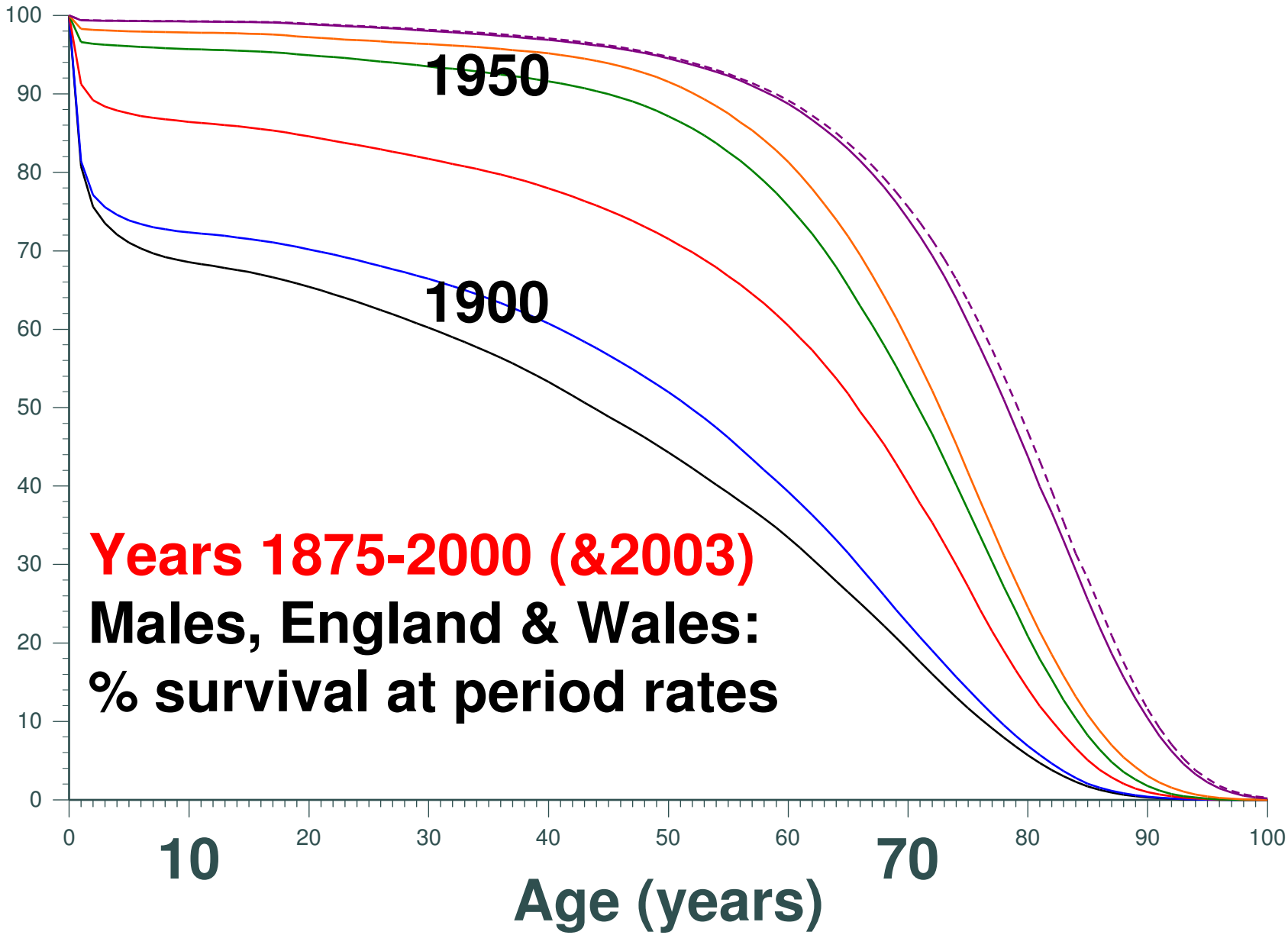
Male under- 5 mortality, England & Wales 1838-2002



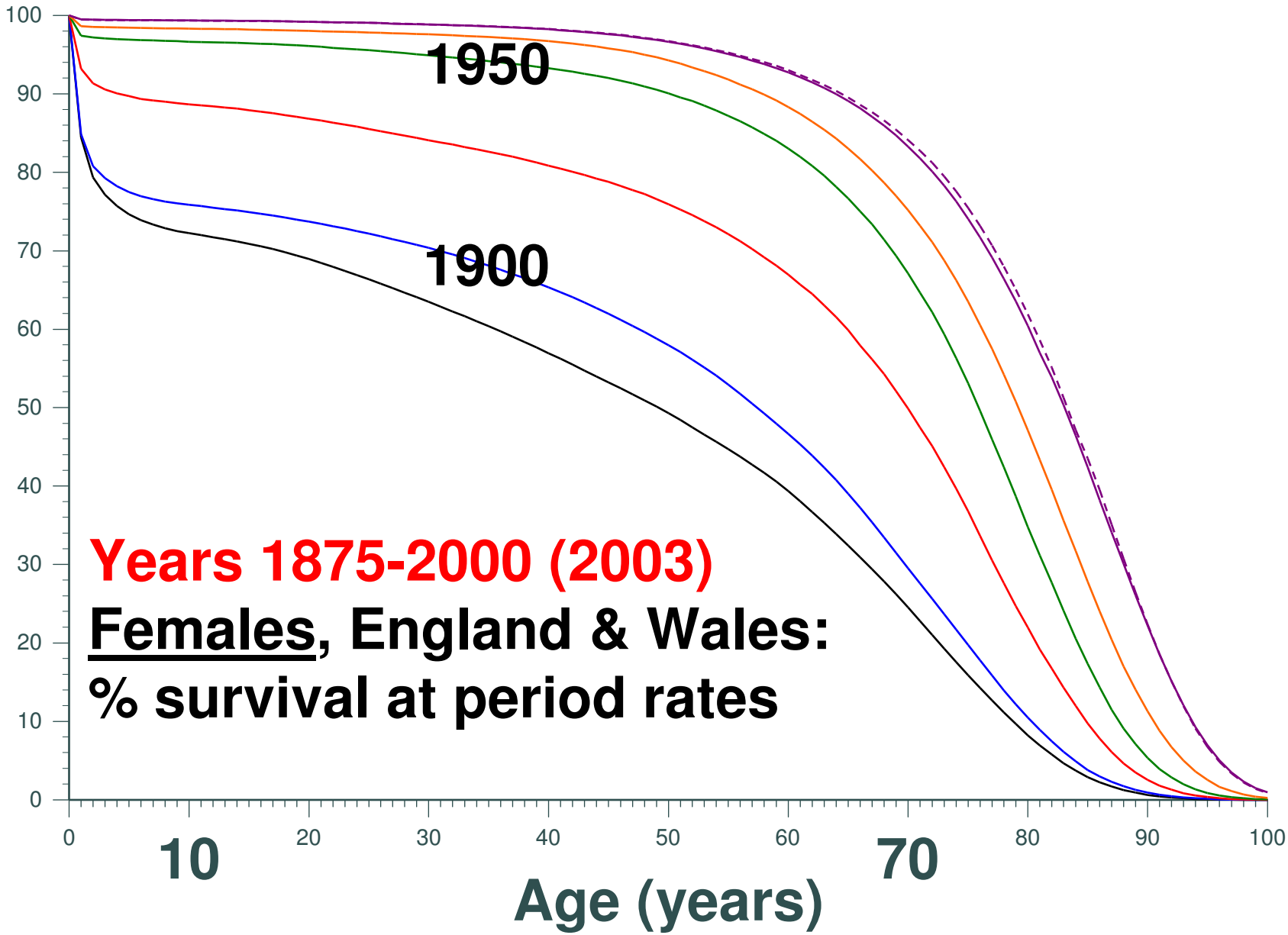
Source: Gary Whitlock, CTSU, from the reports of the Registrars-General for England & Wales


1950 rates: male, England & Wales
% survival at 1950 age-specific rates
Percent survival
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
100
Age (years)


100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
100
Age (years)
2000 rates: males, England & Wales
% survival at 2000 age-specific rates


100
90
80
70
60
50
40
30
20
10
0
1950
1900
Years 1875-2000 (&2003)
Males, England & Wales:
% survival at period rates
0
10
20
30
40
50
60
70
80
90
100
Age (years)

1 April 2008


100
90
80
70
60
50
40
30
20
10
0
1950
1900
Years 1875-2000 (2003)
Females, England & Wales:
% survival at period rates
0
10
20
30
40
50
60
70
80
90
100
Age (years)

Worldwide childhood mortality decreasing, 1950s-2000s

Year of birth	Under-5 mortality
1950-4	23%
1970-4	14%
1990-4	9%
Present decade	~7% (~10M / 130M)

Source: AD Lopez

130M/year now being born: future deaths among them

(at current age-specific death rates)

Age range	Future deaths
0-34	~20M
35-69	~40M
(70+)	(~70M)

Worldwide deaths, all causes: 60 M/year dying in the 2000s

Age range	Deaths per year
0-34	~20M
35-69	~20M
(70+)	(~20M)

M = Million

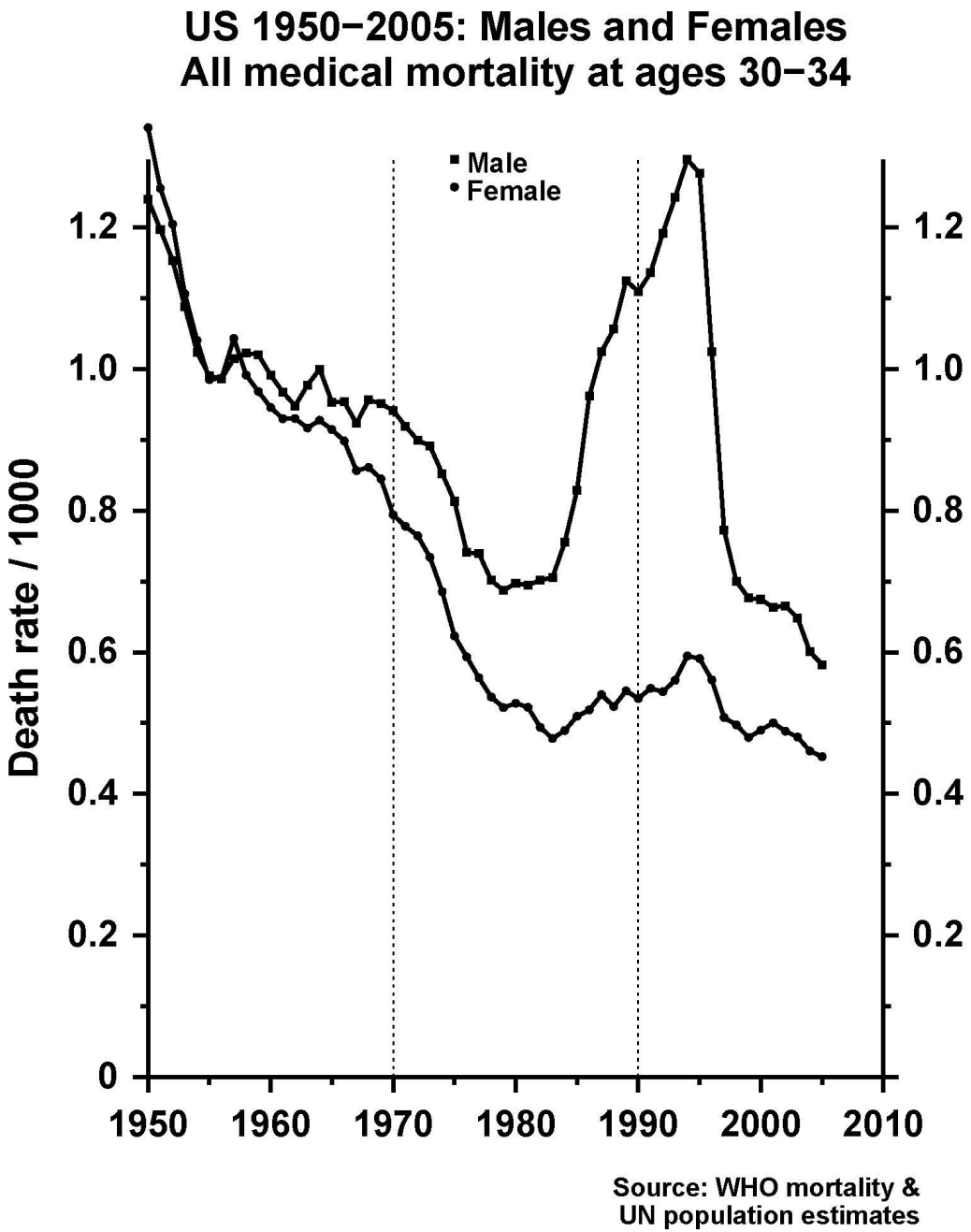
Main causes of the ~10M deaths per year at ages 0-4

2.5	Perinatal (and, ~0.5M mothers die)	8M
1.9	Acute respiratory infection (ARI)	
1.6	Diarrhoea	
1.1	Malaria	
1.1	Vaccine-preventable diseases (0.6 measles, 0.3 pertussis, 0.2 tetanus)	
0.3	HIV	
~2M	other causes	

7M annual deaths, age 5-34:

~2M HIV + ~5M other

Many from external causes (accident, violence & suicide): important, & can be influenced


US 1950−2005: Males and Females
All medical mortality at ages 30−34
Male
Female
Death rate / 1000
0
0.2
0.4
0.6
0.8
1.0
1.2
1950
1960
1970
1980
1990
2000
2010
Source: WHO mortality &
UN population estimates

Worldwide, HIV still increasing

~3M deaths / year;

~ 6M new infections / year

Treatment, male circumcision & reducing infection via concurrent partners, sex workers & needles might halve 2020s HIV mortality

Worldwide deaths, all causes: 60 M/year dying in the 2000s

Age range	Deaths per year
0-34	~20M
35-69	~20M
(70+)	(~20M)

M = Million

130M/year now being born: future deaths among them

(at current age-specific death rates)

Age range	Future deaths
0-34	~20M
35-69	~40M
(70+)	(~70M)

130M BIRTHS/YEAR:
at current death rates,

~20 M will die before middle age, &

~40M will die in middle age

(~15M vascular, 10M cancer)

Can current vascular & cancer death rates in middle age be halved?

Changing vascular mortality: prevention & treatment

Tobacco
(smoker @ 3x non-smoker risk)

Blood lipids*
Blood pressure*
Obesity

*** Secondary prevention: high annual risk ÷ 3 by long-term statin, BP lowering & aspirin**

Changing vascular mortality: secondary (2ry) prevention

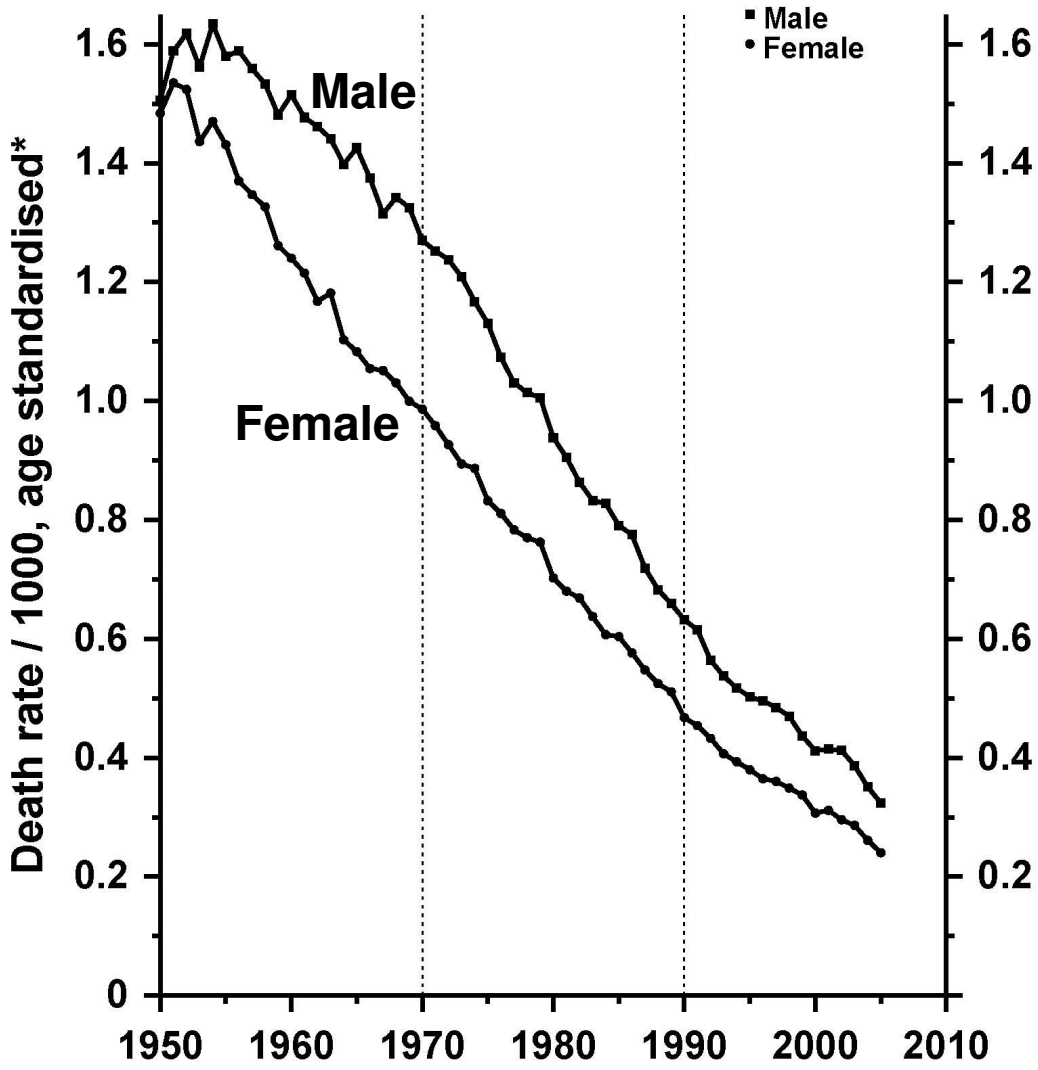
- **Long-term drug treatment of high risk: statin, BP lowering & aspirin in 1 pill**
- **Particularly relevant to <u>2ry prevention</u> in middle age with good quality of life: 10-year recurrence risk is <u>1/6, not 1/2</u>**

Primary prevention: evidence for avoidability

- Every vascular disease common in one place is much less common elsewhere.
- Differences between population vascular disease rates are <u>not</u> chiefly genetic.

- Many big causes are already known.
- Many diseases <u>vary</u>, becoming much more or less common over a few decades.

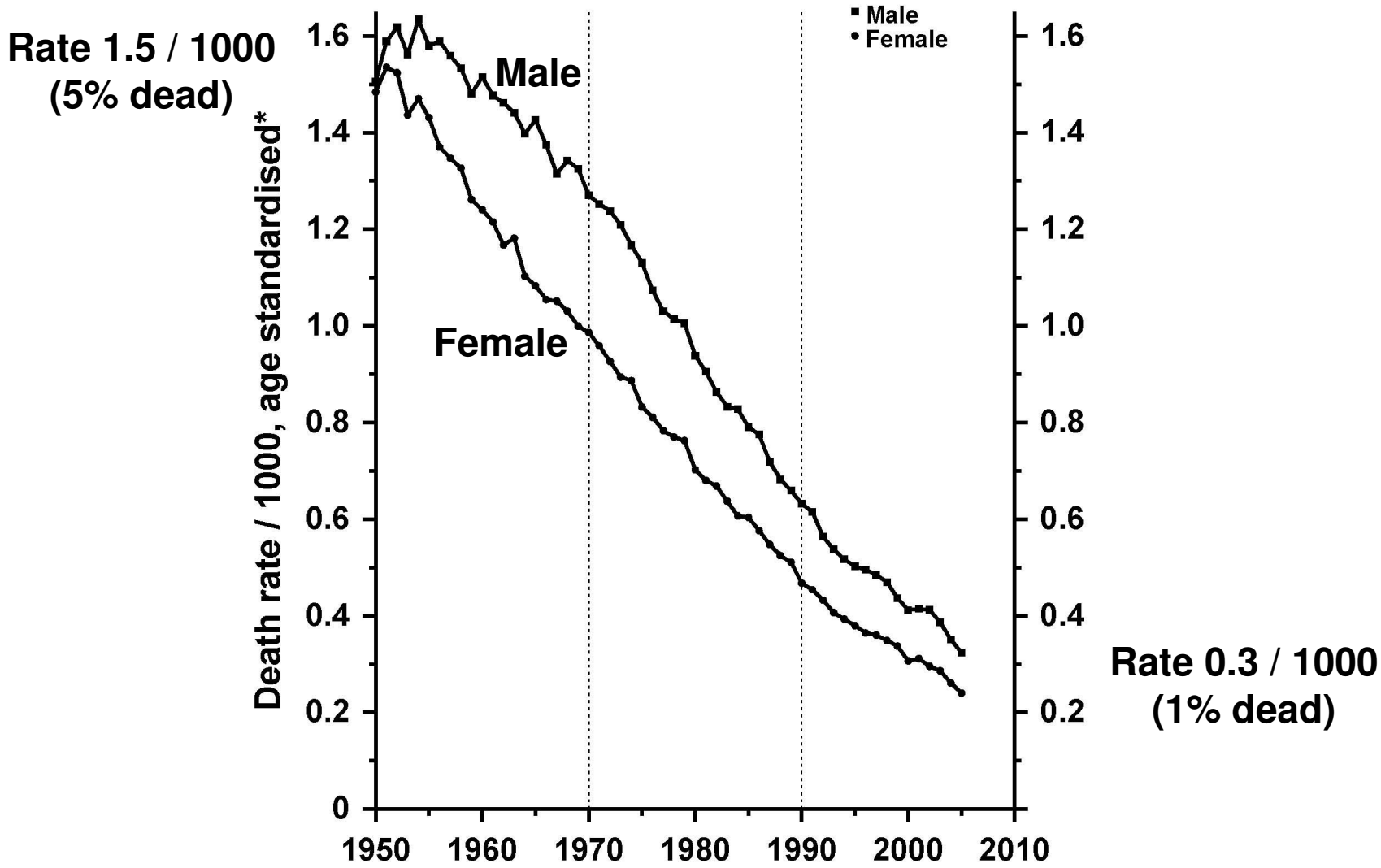
UNITED KINGDOM 1950−2005: Males & Females
Cerebrovascular disease mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

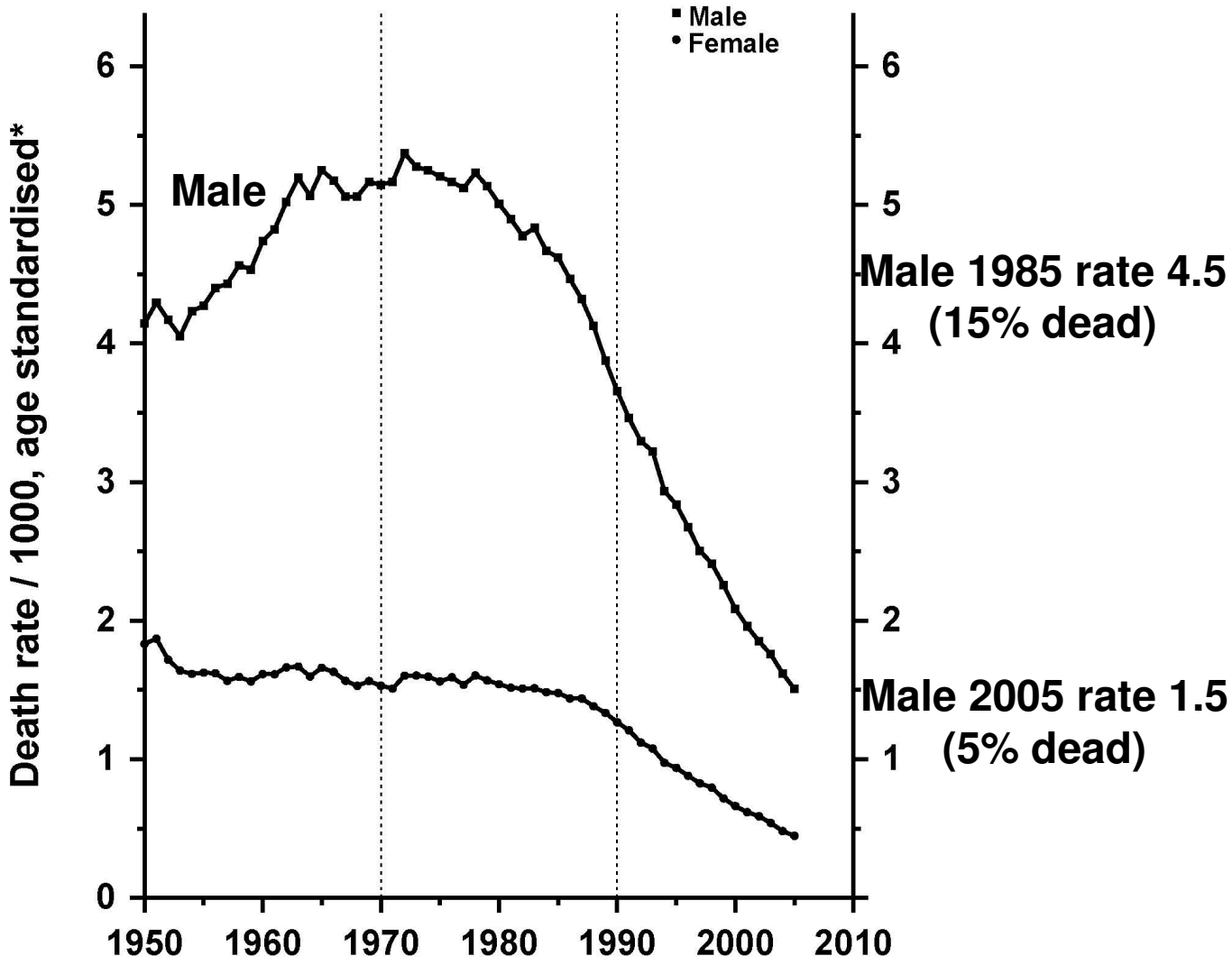
UNITED KINGDOM 1950−2005: Males & Females
Cerebrovascular disease mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

UNITED KINGDOM 1950−2005: Males & Females
Ischaemic heart disease mortality at ages 35−69

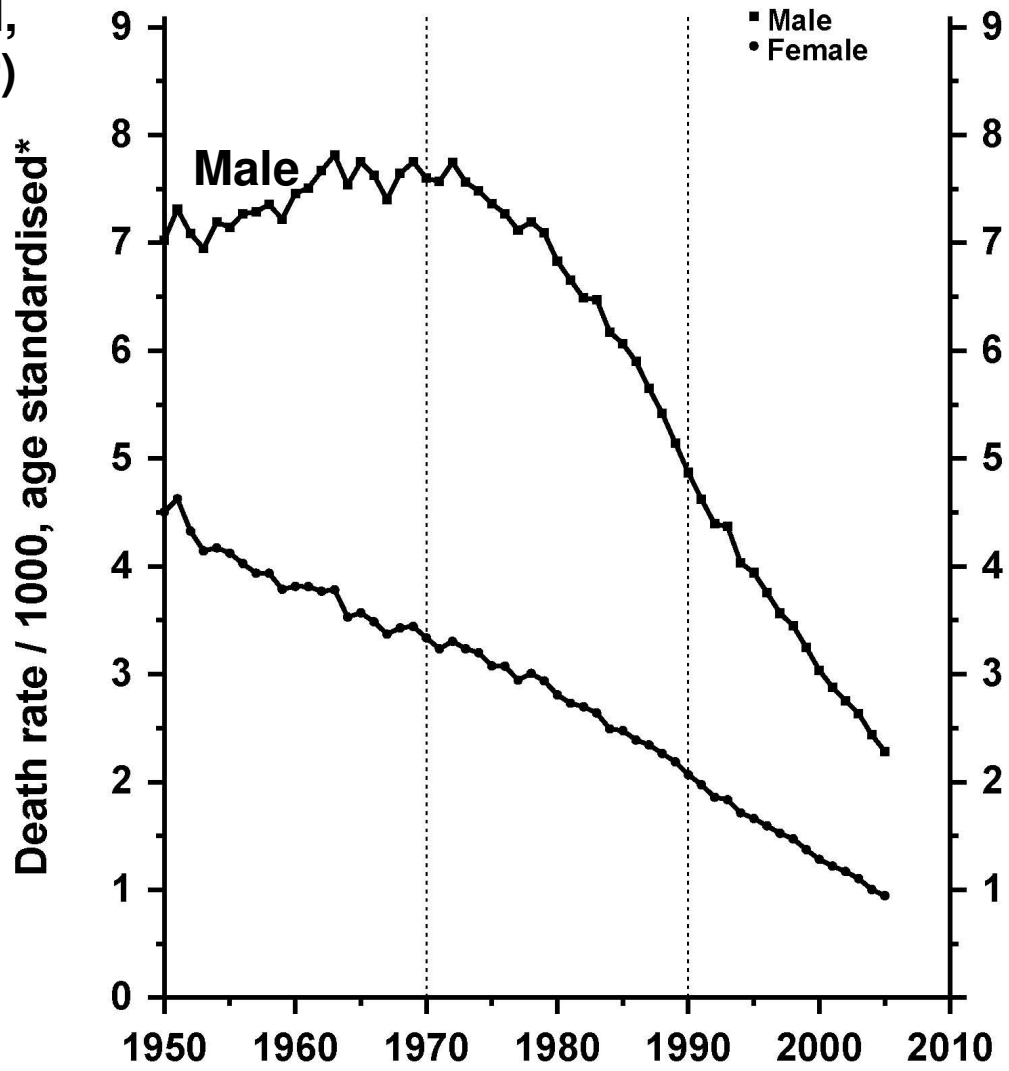


*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

UNITED KINGDOM 1950−2005: Males & Females
All vascular mortality at ages 35−69

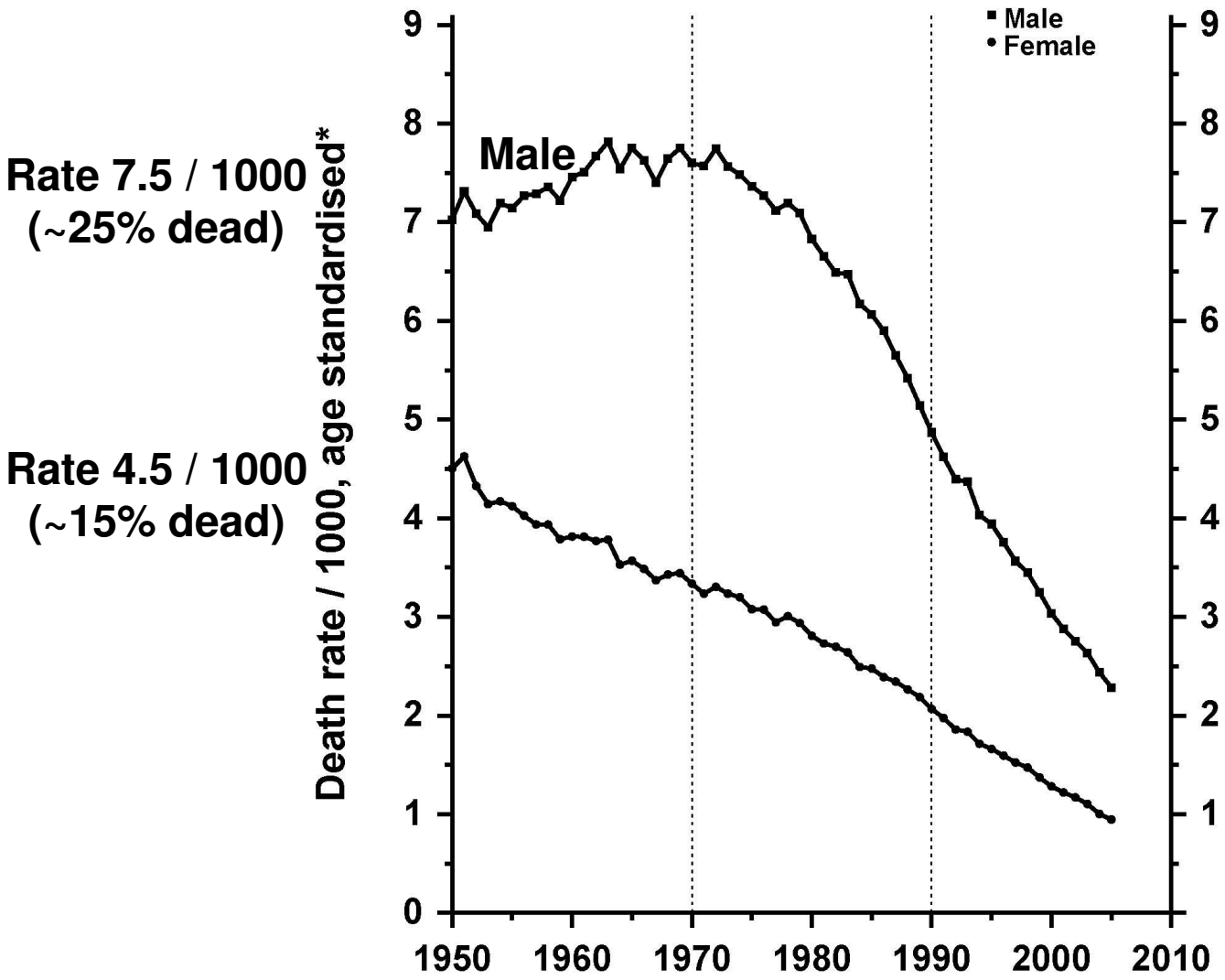
Top: 9 / 1000 (~30% dead, all vascular)



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

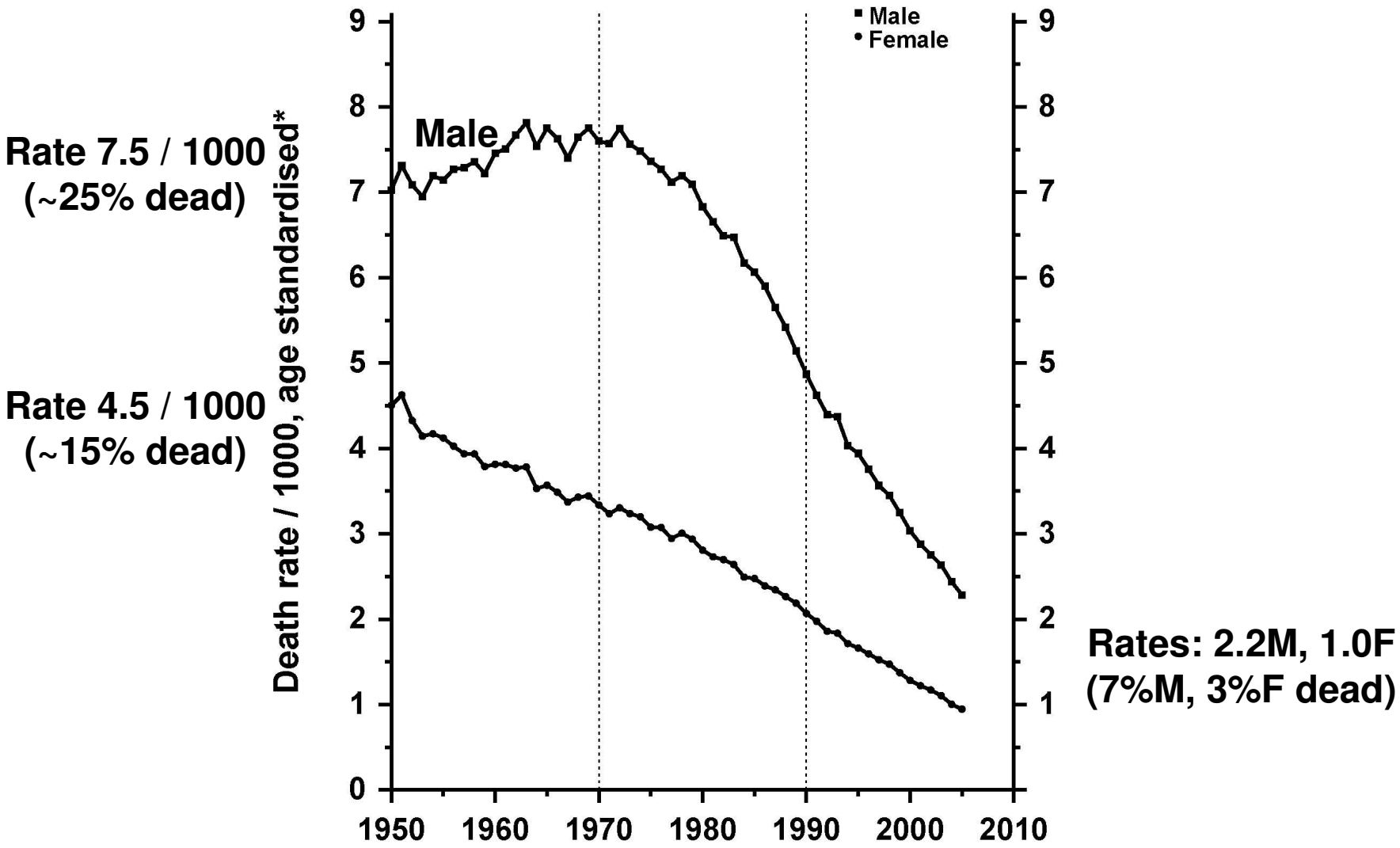
UNITED KINGDOM 1950−2005: Males & Females
All vascular mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

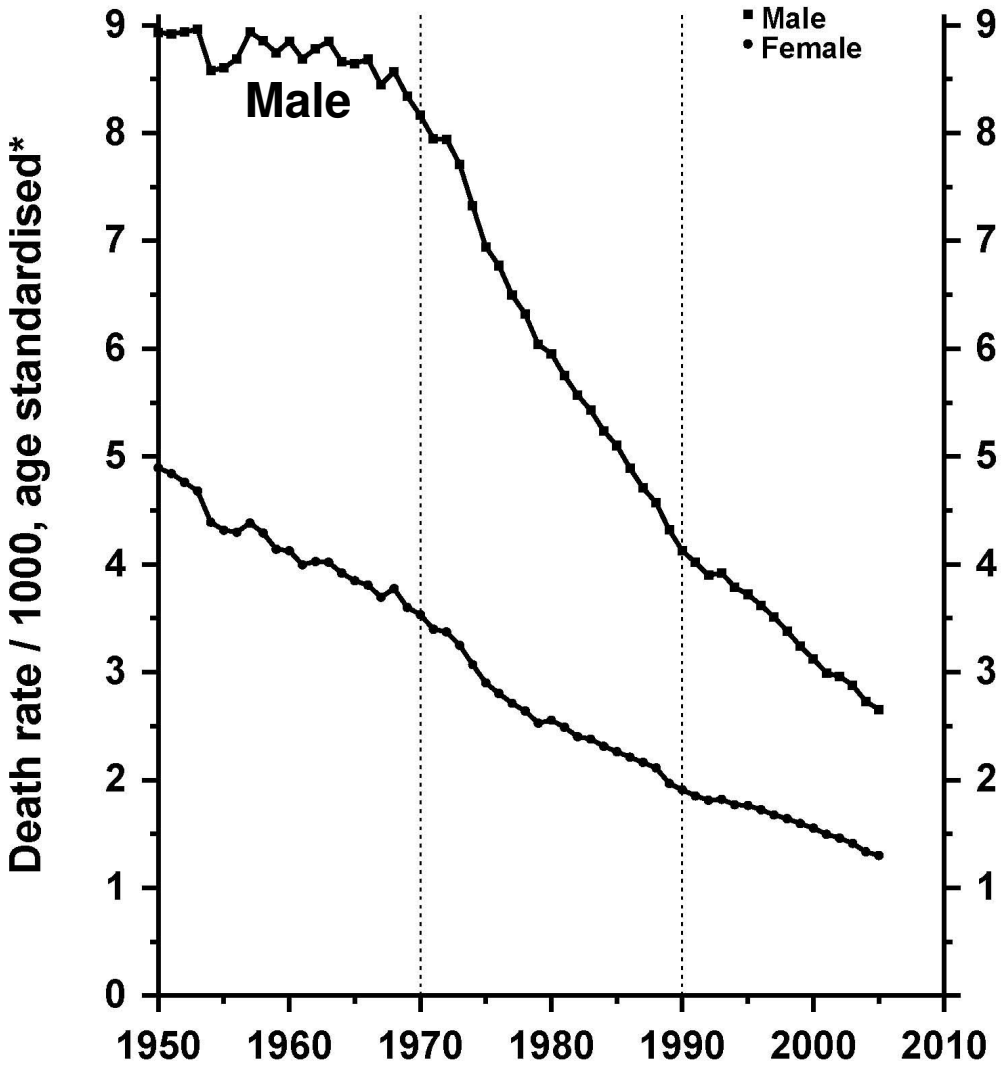
UNITED KINGDOM 1950−2005: Males & Females
All vascular mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

UNITED STATES 1950−2005: Males & Females
All vascular mortality at ages 35−69

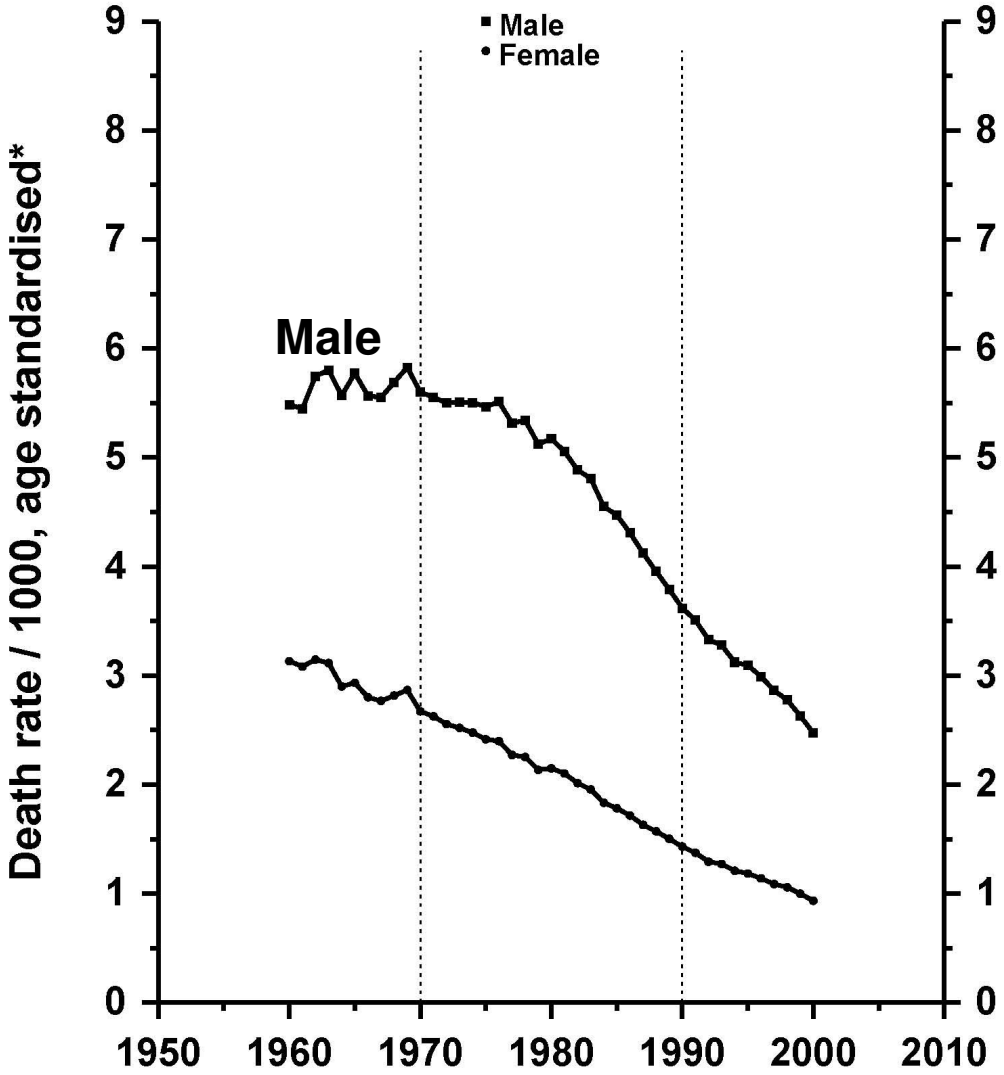


Rates: 2.6M, 1.3F
(risks: 9%M, 4%F)

*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

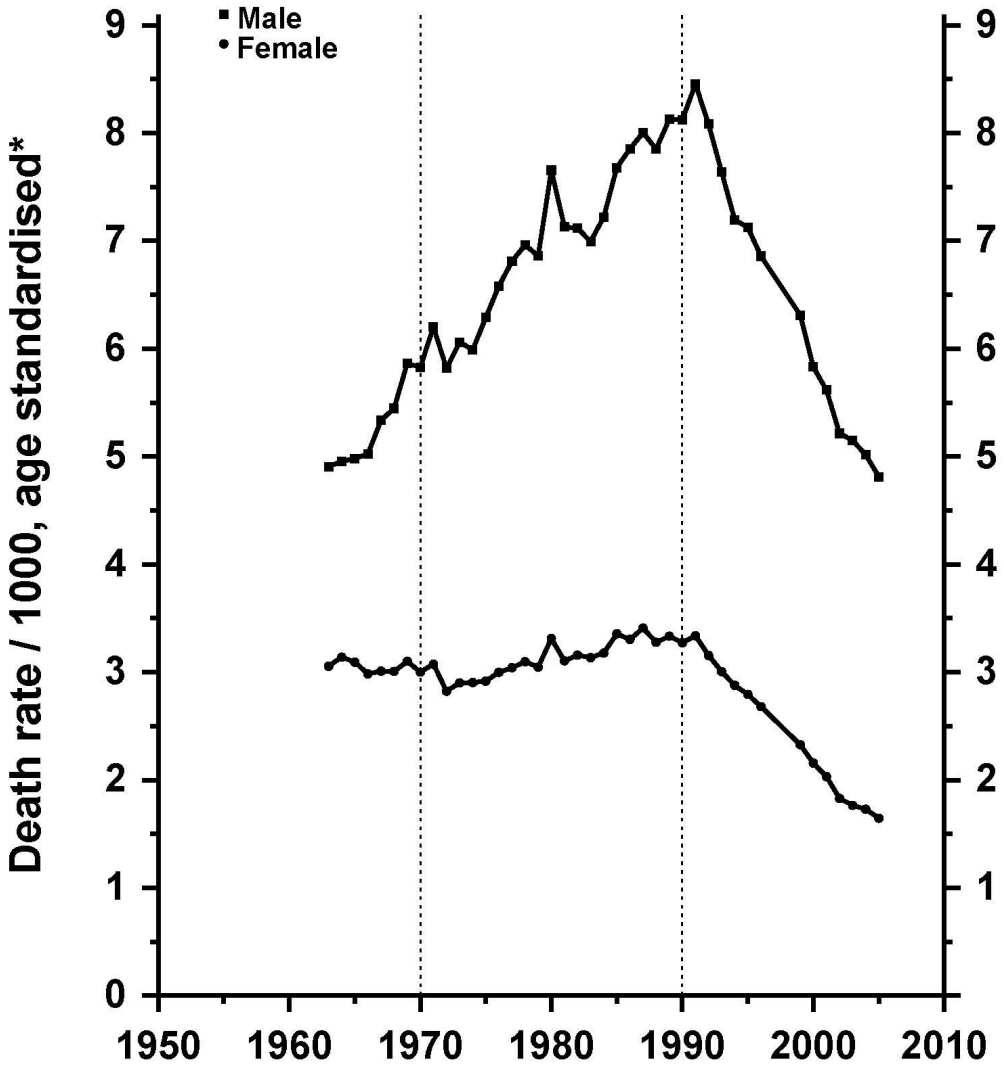
EU15 (15 countries) 1960−2000: Male & Female
All vascular mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

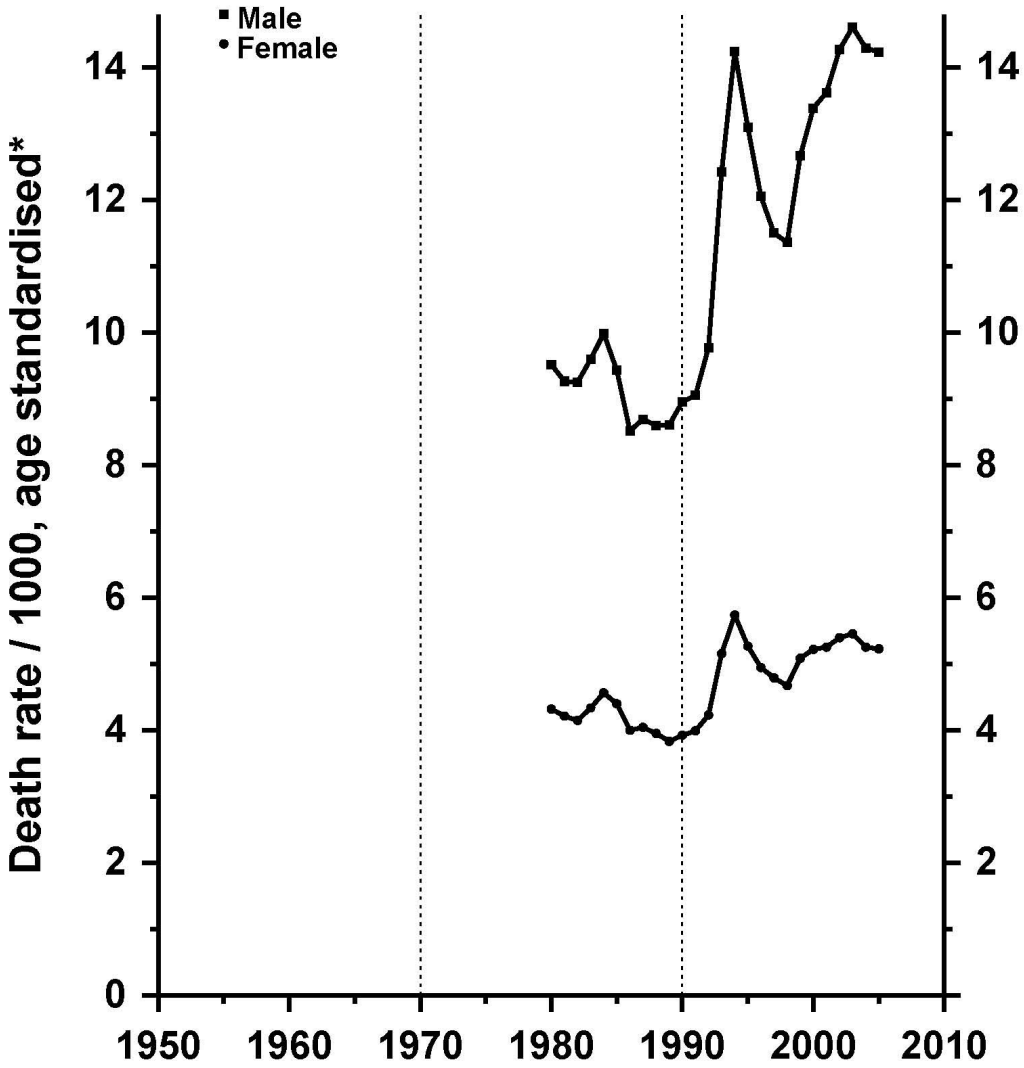
POLAND 1963−2005: Males & Females
All vascular mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

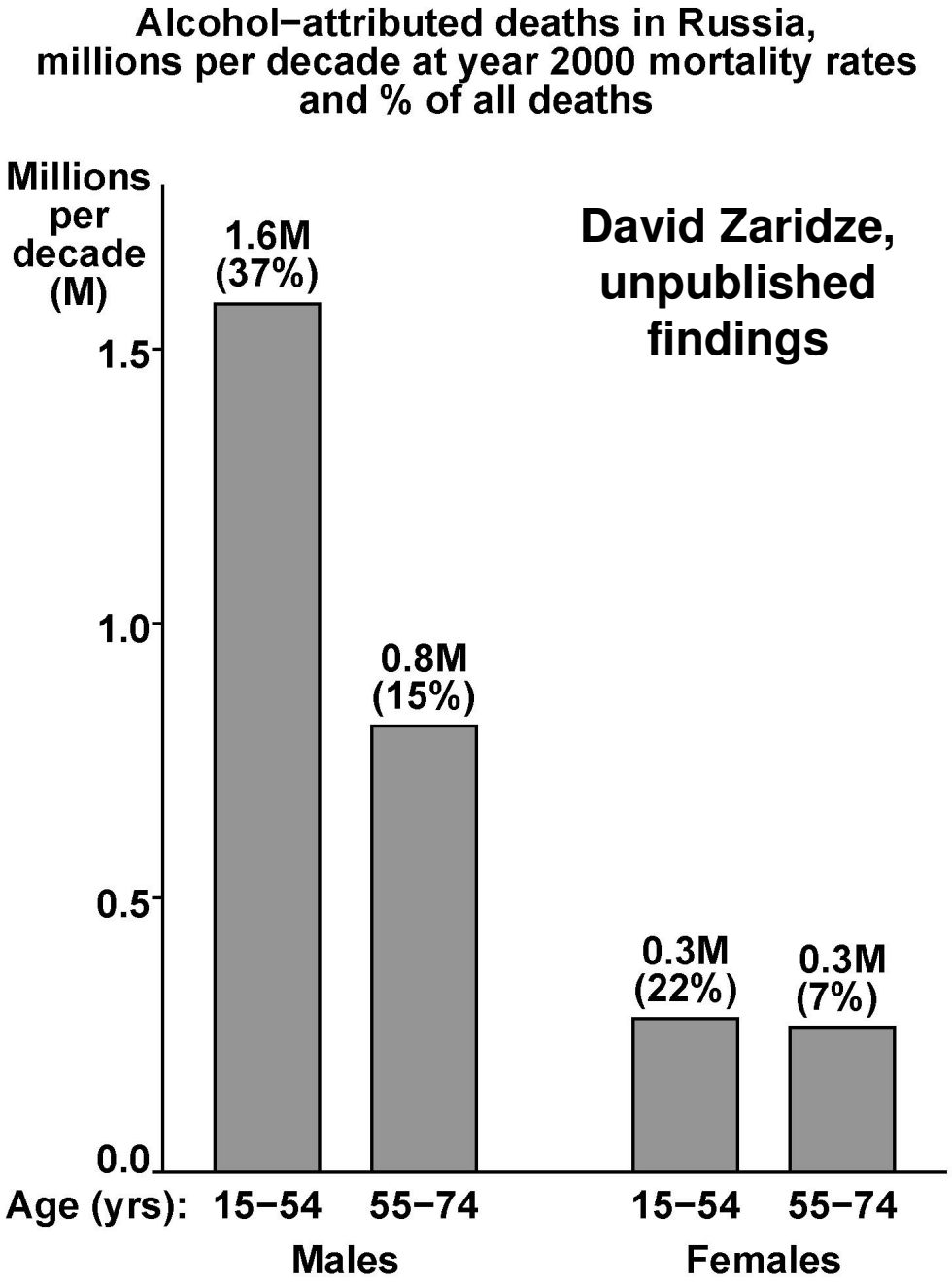
Source: WHO mortality & UN population estimates

RUSSIAN FEDN. 1980−2005: Males & Females
All vascular mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates


Alcohol−attributed deaths in Russia,
millions per decade at year 2000 mortality rates
and % of all deaths
Millions per decade (M)
1.5
1.0
0.5
0.0
1.6M (37%)
0.8M (15%)
0.3M (22%)
0.3M (7%)
David Zaridze, unpublished findings
Age (yrs): 15−54 55−74 15−54 55−74
Males
Females

Changing vascular mortality rates in middle age (35-69): <u>prevention</u>

Tobacco, physical inactivity, obesity, <u>type</u> of dietary fat, <u>extreme</u> alcoholism

(all relevant to 1ry & 2ry prevention)

Tobacco

Blood pressure

Blood lipids

Obesity

THE MILLION WOMEN STUDY

Prof. Valerie Beral, Univ. Oxford & Cancer Research UK
(1,300,000 followed for 7 years: 1st public results on smoking)

First large prospective study of women who have smoked throughout adult life

Shows the full hazards (in middle age) of cigarette smoking for women

Big risks, even though UK cigarette yields have been lowered in recent decades

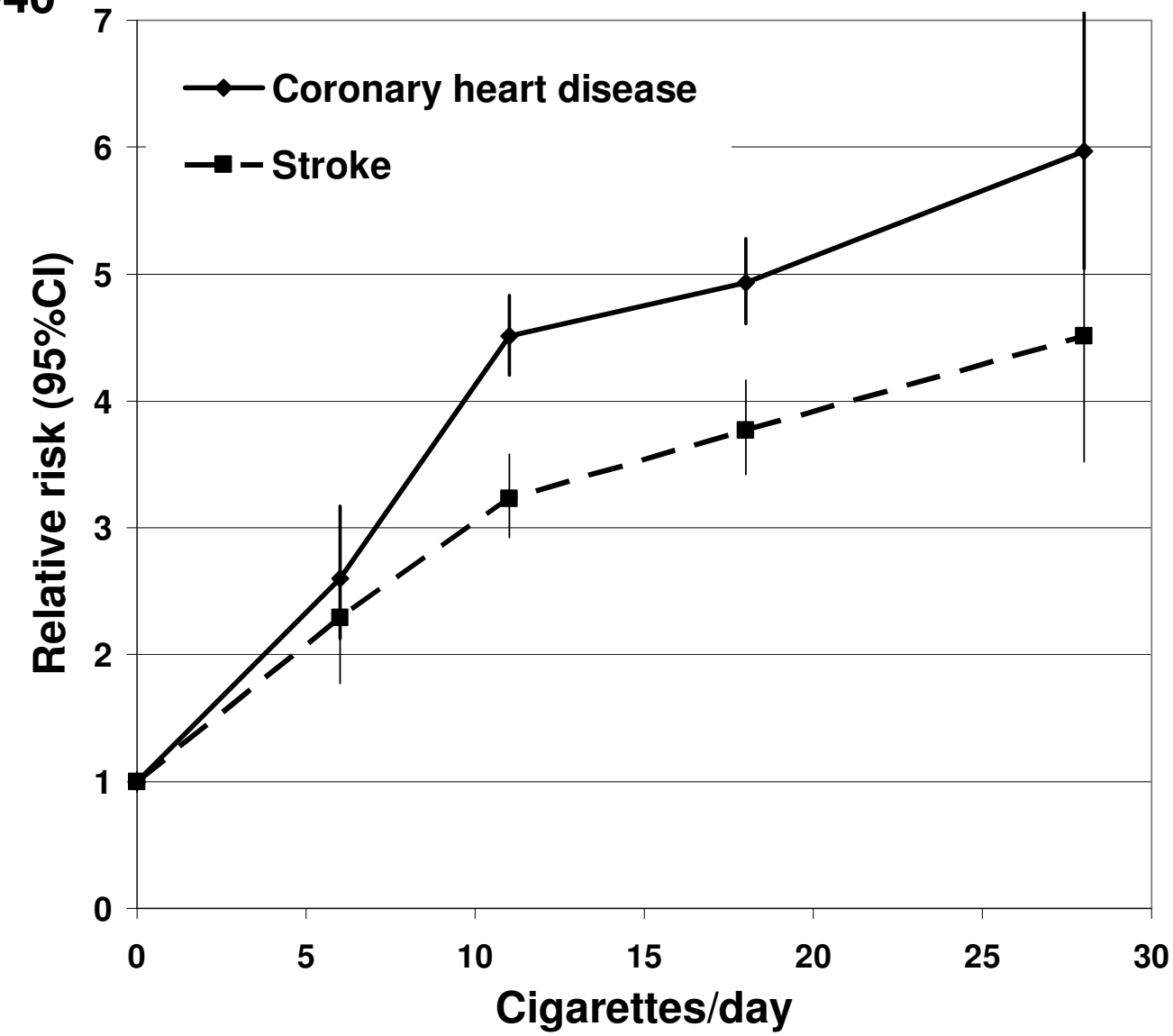
THE MILLION WOMEN STUDY

UK women born ~1940

VASCULAR mortality at age ~60+

Relative risk & CI, current versus never-smoker

Standardised for age, FU duration, BMI, 10 UK regions & 5 socioec. groups



Tobacco

<u>Blood pressure</u>

Blood lipids

Obesity

How important is blood pressure to vascular death?

20 mmHg systolic BP halves vascular mortality at 35-69

PSC: Prospective Studies Collaboration
(60 studies, 1M adults, 0.1M deaths)
Lancet 2002; 360: 1903

PSC

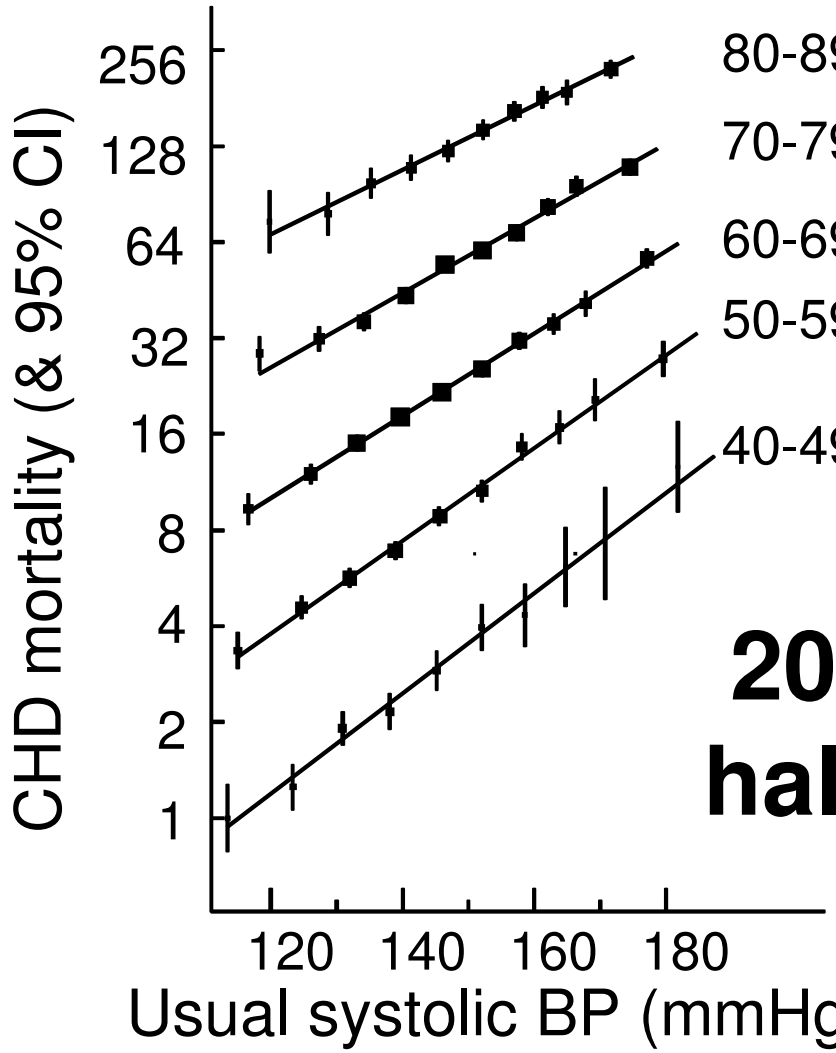
Prospective Studies Collaboration (PSC)

Atherosclerosis Risk in Communities (ARIC): L Chambless; *Belgian Inter-university Research on Nutrition and Health (BIRNH):* G De Backer, D De Bacquer, M Kornitzer; *British Regional Heart Study (BRHS):* P Whincup, SG Wannamethee, R Morris; *British United Provident Association (BUPA):* N Wald, J Morris, M Law; *Busselton:* M Knuiman, H Bartholomew; *Caerphilly and Speedwell:* G Davey Smith, P Sweetnam, P Elwood, J Yarnell; *Cardiovascular Health Study (CHS):* R Kronmal; *CB Project:* D Kromhout; *Charleston:* S Sutherland, J Keil; *Copenhagen City Heart Study:* G Jensen, P Schnohr; *Evans County:* C Hames (deceased), A Tyroler; *Finnish Mobile Clinic Survey (FMCS):* A Aromaa, P Knekt, A Reunanen; *Finrisk:* J Tuomilehto, P Jousilahti, E Vartiainen, P Puska; *Flemish Study on Environment, Genes and Health (FLEMENGHO):* T Kuznetsova, T Richart, J Staessen, L Thijs; *Research Centre for Prevention and Health (Glostrup Population Studies):* T Jorgensen,T Thomsen; *Honolulu Heart Program:* D Sharp, JD Curb; *Ikawa, Noichi and Kyowa:* H Iso, S Sato, A Kitamura, Y Naito; *Imperial College, London* and *Oxon Clinical Epidemiology Limited*: N Qizilbash; *Centre d'Investigations Preventives et Cliniques (IPC), Paris:* A Benetos, L Guize; *Israeli Ischaemic Heart Disease Study:* U Goldbourt; *Japan Railways:* M Tomita, Y Nishimoto, T Murayama; *Lipid Research Clinics Follow-up Study (LRC):* M Criqui, C Davis; *Midspan Collaborative Study:* C Hart, G Davey-Smith, D Hole, C Gillis; *Minnesota Heart Health Project (MHHP)* and *Minnesota Heart Survey (MHS):* D Jacobs, H Blackburn, R Luepker; *Multiple Risk Factor Intervention Trial (MRFIT):* J Neaton, L Eberly; *First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHEFS):* C Cox; *NHLBI Framingham Heart Study:* D Levy, R D'Agostino, H Silbershatz; *Norwegian Counties Study:* A Tverdal, R Selmer; *Northwick Park Heart Study (NPHS):* T Meade, K Garrow, J Cooper; *Nurses' Health Study:* F Speizer, M Stampfer; *Occupational Groups (OG), Rome:* A Menotti, A Spagnolo; *Ohasama:* I Tsuji, Y Imai, T Ohkubo, S Hisamichi; *Oslo:* L Haheim, I Holme, I Hjermann, P Leren; *Paris Prospective Study:* P Ducimetiere, J Empana; *Perth:* K Jamrozik, R Broadhurst; *Prospective Cardiovascular Munster Study (PROCAM):* G Assmann, H Schulte; *Prospective Study of Women in Gothenburg:* C Bengtsson, C Björkelund, L Lissner; *Puerto Rico Health Heart Program (PRHHP):* P Sorlie, M Garcia-Palmieri; *Rancho Bernado:* E Barrett-Connor, M Criqui, R Langer; *Renfrew and Paisley study:* C Hart, G Davey Smith, D Hole; *Saitama Cohort Study:* K Nakachi, K Imai; *Seven Cities China:* X Fang, S Li; *Seven Countries (SC) Croatia:* R Buzina; *SC Finland:* A Nissinen; *SC Greece (Greek Islands Study):* C Aravanis, A Dontas, A Kafatos; *SC Italy:* A Menotti; *SC Japan:* H Adachi, H Toshima, T Imaizumi; *SC Netherlands:* D Kromhout; *SC Serbia:* S Nedeljkovic, M Ostojic; *Shanghai:* Z Chen; *Scottish Heart Health Study (SHHS):* H Tunstall-Pedoe; *Shibata:* T Nakayama, N Yoshiike, T Yokoyama, C Date, H Tanaka; *Tecumseh:* J Keller; *Tromso:* K Bonaa, E Arnesen; *United Kingdom Heart Disease Prevention Project (UKHDPP):* H Tunstall-Pedoe; *US Health Professionals Follow-up Study:* E Rimm; *US Physicians' Health Study:* M Gaziano, JE Buring, C Hennekens; *Värmland:* S Törnberg, J Carstensen; *Whitehall:* M Shipley, D Leon, M Marmot; *Clinical Trial Service Unit (CTSU):* J Armitage, C Baigent, Z Chen, R Clarke, R Collins, J Emberson, J Halsey, M Landray, S Lewington, A Palmer (deceased), S Parish, R Peto, P Sherliker, G Whitlock.

Steering Committee — S Lewington (coordinator and statistician), S MacMahon (chair), R Peto (statistician), A Aromaa, C Baigent, J Carstensen, Z Chen, R Clarke, R Collins, S Duffy, D Kromhout, J Neaton, N Qizilbash, A Rodgers, S Tominaga, S Törnberg, H Tunstall-Pedoe, G Whitlock.

http://www.ctsu.ox.ac.uk/projects/psc/

34,000 IHD deaths at ages 40-89: age-specific risks vs. usual SBP

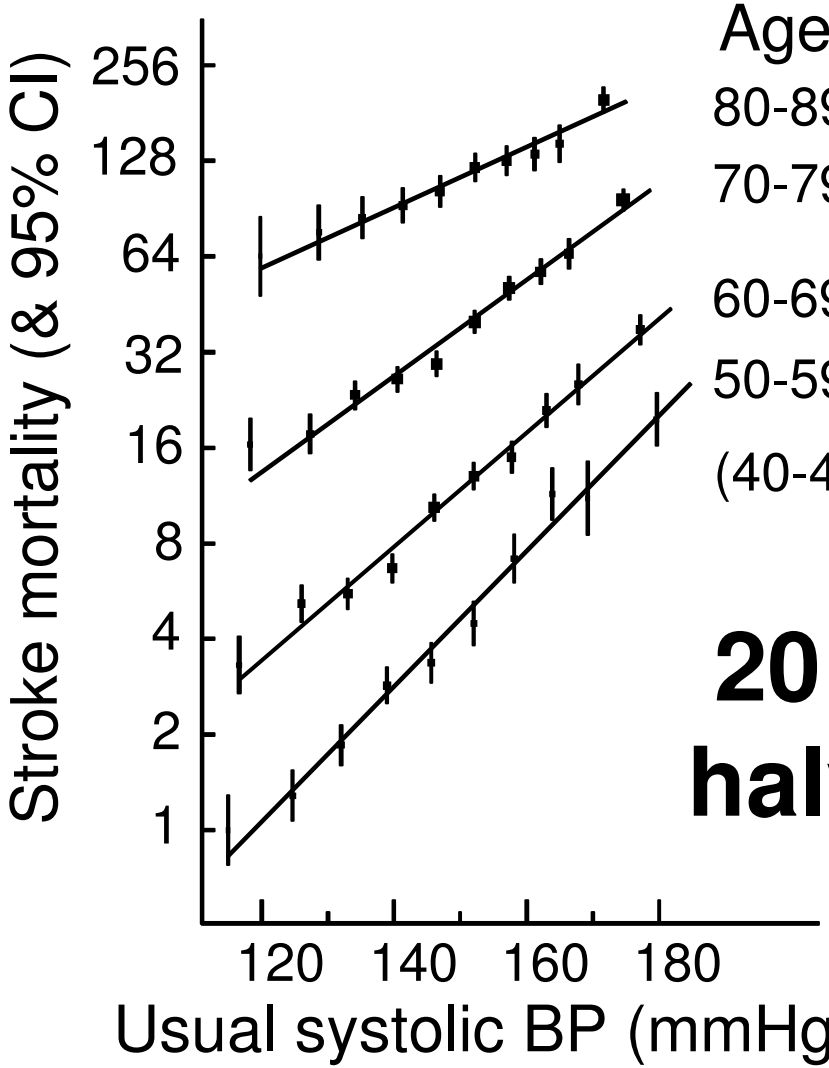


Age	20 mm↓Hg
80-89	31% ↓ risk
70-79	40% ↓ risk
60-69	46% ↓
50-59	50% ↓ risk
40-49	51% ↓ risk

20 mmHg halves risk

Lancet 2002; 360:1903-13

11,000 stroke deaths at ages 40-89: age-specific risks vs. usual SBP



Age	20 mm↓Hg
80-89	33% ↓ risk
70-79	50% ↓ risk
60-69	57% ↓ risk
50-59	62% ↓ risk
(40-49	64% ↓ risk)

20 mmHg halves risk

Lancet 2002; 360:1903-13

Tobacco

Blood pressure

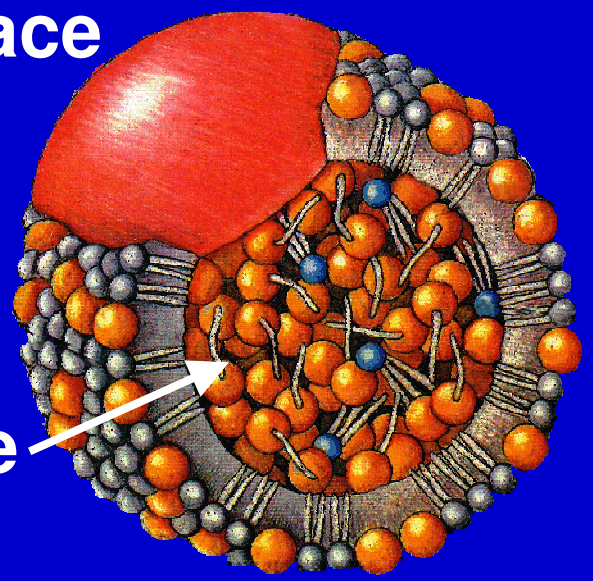
<u>Blood lipids</u>

Obesity

LDL and HDL particles carry most of the cholesterol (C) in the blood

apo B on surface

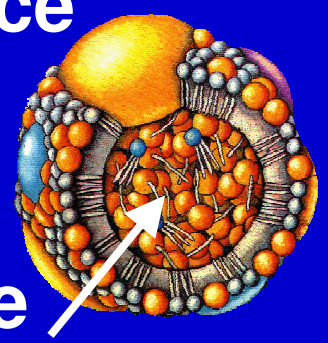
Bad (B): some or all types of LDL particle



LDL-C inside

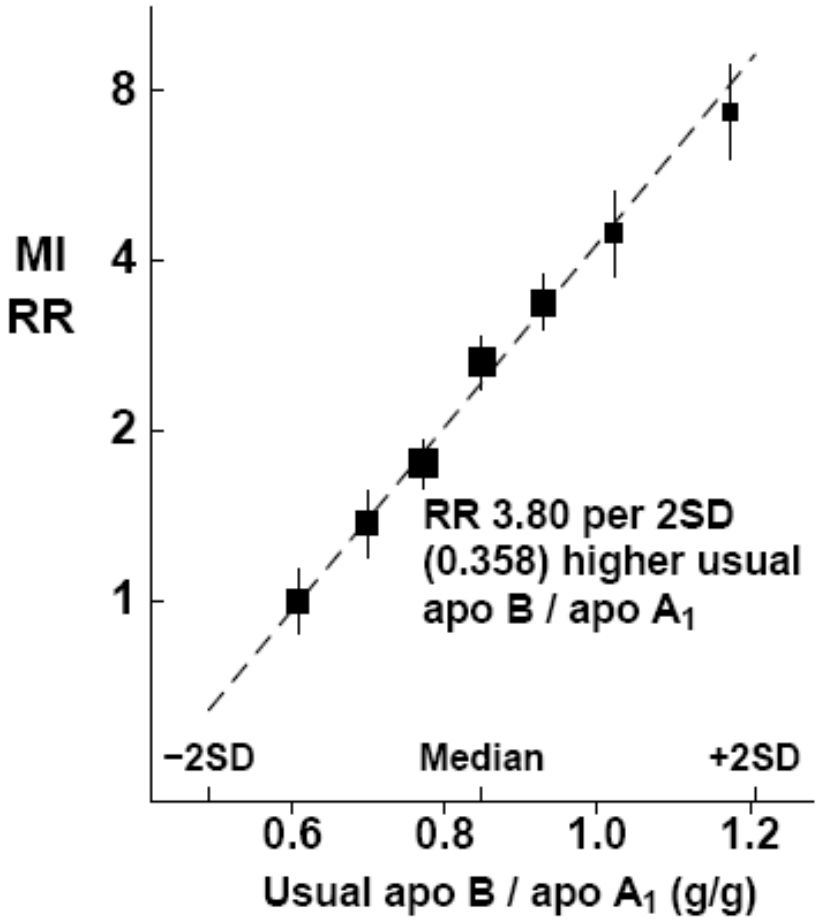
apo A_1 on surface

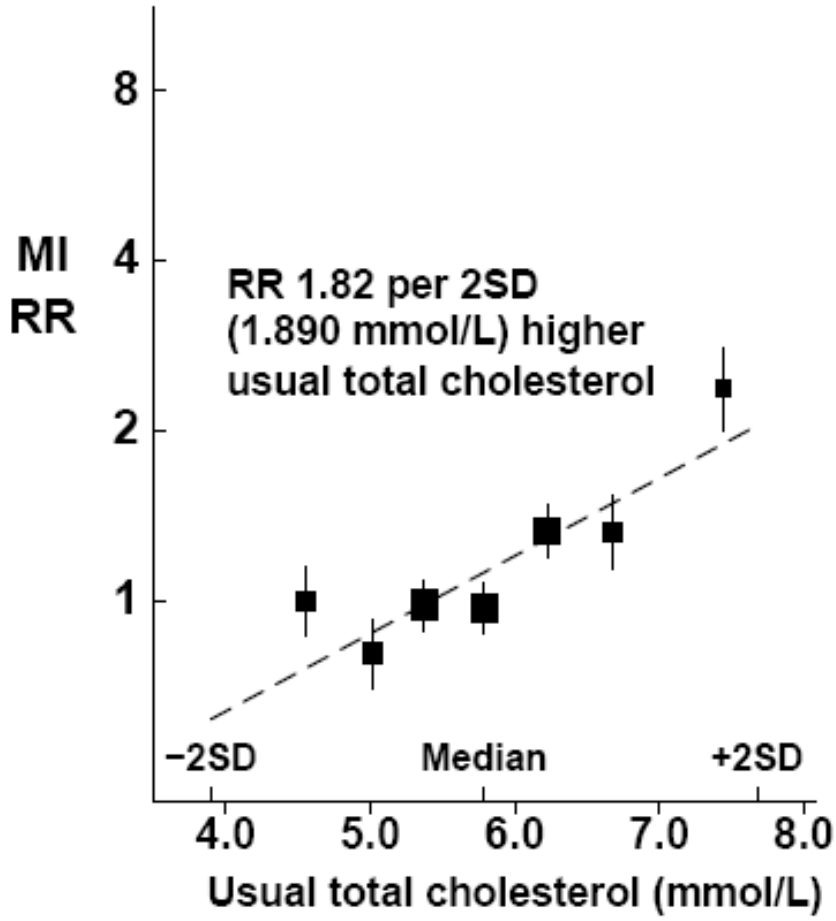
All right (A1): some types of HDL particle



HDL-C inside

ISIS case-control study of acute MI, UK, early 1990s: RR per 2SD higher 1. lipoproteins, 2. total cholesterol





Statins: efficacy & safety of big reductions in LDL chol.

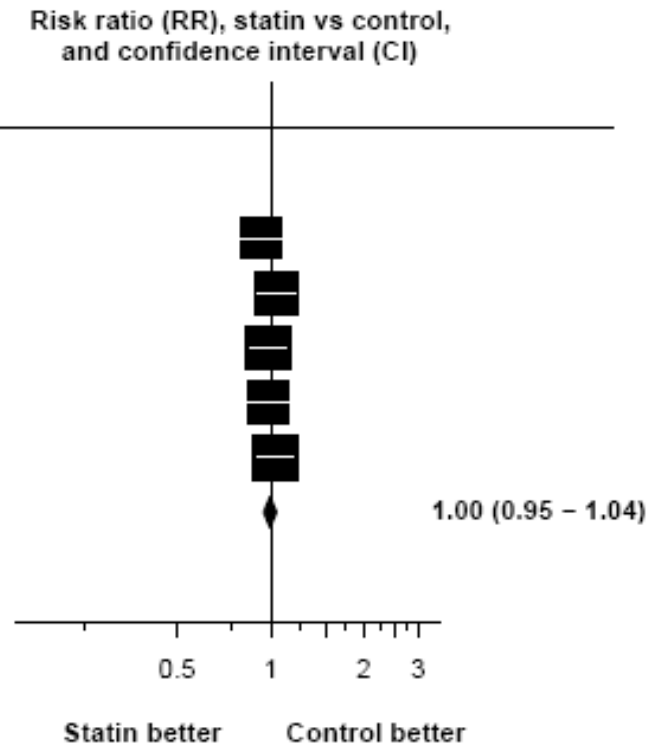
1. Large-scale randomised evidence

2. Worldwide overview, with few subgroups

CTT collaborative meta-analysis, cancer incidence: 14 statin trials, 400,000 person-years, no sigt. hazard

Years	No. with cancer onset Statin	Control
	(n=45,054)	(n=45,002)
0–1 year	488	534
1–2 years	616	589
2–3 years	582	588
3–4 years	511	503
4+ years	613	590
All years	**2810/ 199,063 py (1.4% pa)**	**2804/ 197,681 py (1.4% pa)**

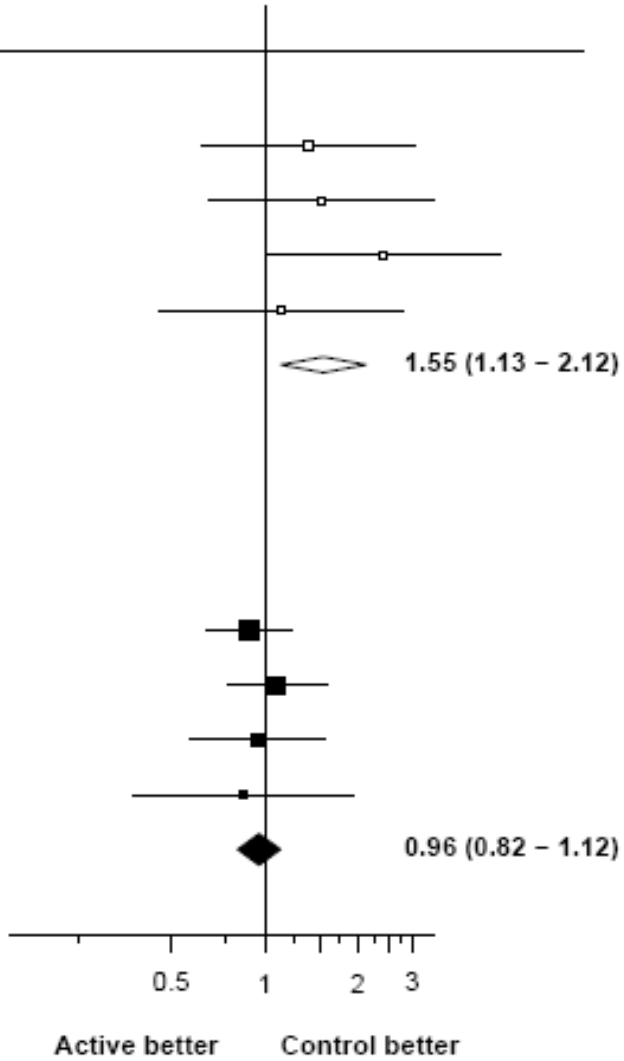
Trend test: $\chi^2_1 = 0.68$ (p = 0.41)



99% or 95% CI

Hypothesis generating: excess of cancer in 1 ezetimibe trial?
Hypothesis testing: no apparent hazard in 2 other such trials

Years	No. with cancer onset Active	Control	Risk ratio (RR), active vs control, and confidence interval (CI)
SEAS	(n=944)	(n=929)	
0–1 year	28	20	
1–2 years	26	17	
2–3 years	28	11	
3+ years	19	17	
All years	**101/ 3810 py (2.7% pa)**	**65/ 3826 py (1.7% pa)**	**1.55 (1.13 – 2.12)**
Trend test: $\chi^2_1 = 0.00$ (p = 1.00)			
SHARP/IMPROVE–IT	(n=10,319)	(n=10,298)	
0–1 year	128	144	
1–2 years	109	99	
2–3 years	56	59	
3+ years	20	24	
All years	**313/ 18,246 py (1.7% pa)**	**326/ 18,255 py (1.8% pa)**	**0.96 (0.82 – 1.12)**
Trend test: $\chi^2_1 = 0.04$ (p = 0.84)			



99% or 95% CI

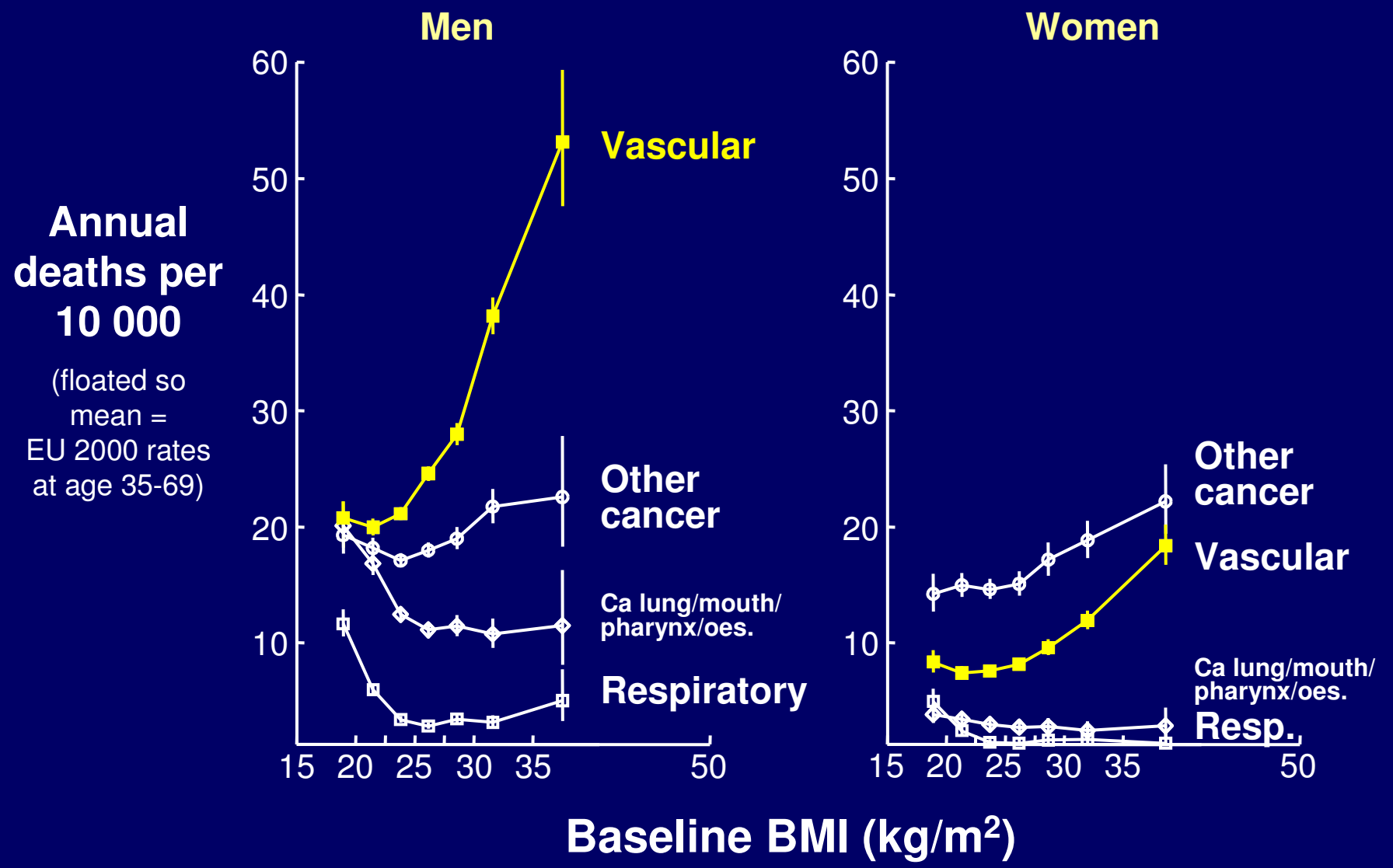
Tobacco

Blood pressure

Blood lipids

<u>Obesity</u>

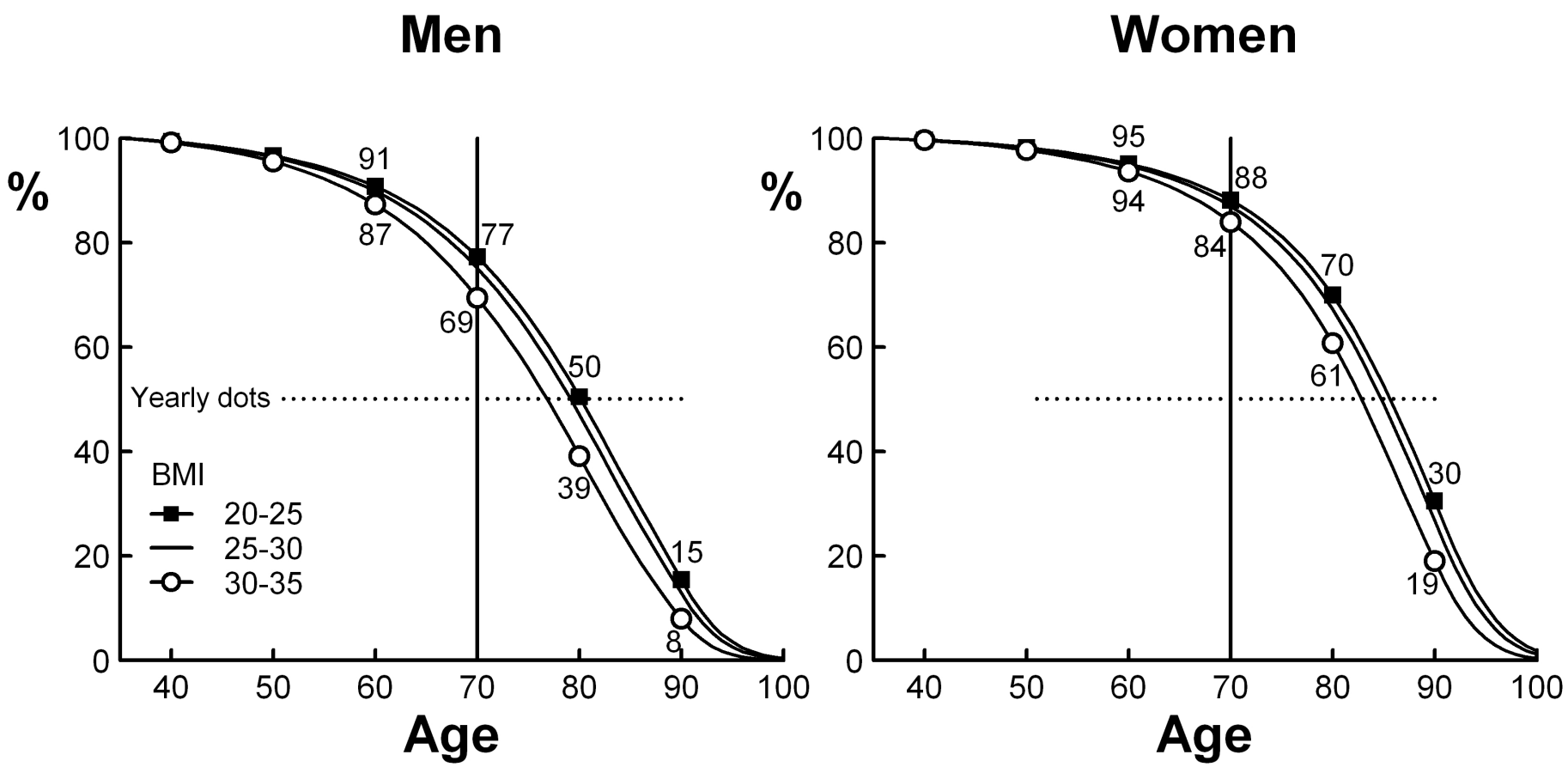
BMI & main disease categories: PSC



Adjusted for age, smoking & study; 1st 5 years of follow-up excluded

Effects of obesity on survival: PSC

% survival from age 35 yrs: normal build, overweight, obese

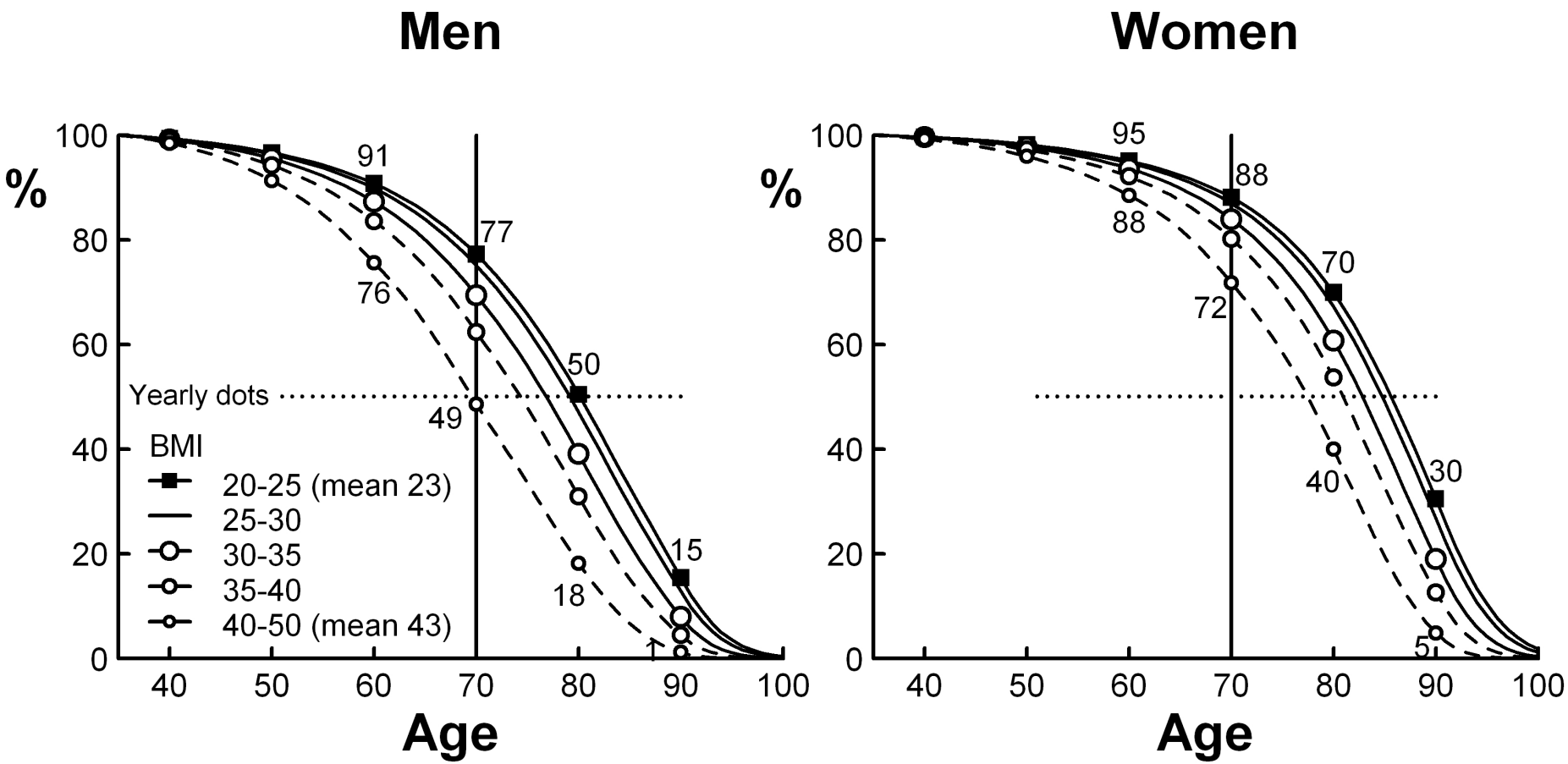


Median life expectancy at age 35: **3 yrs less if BMI 33 than if 23**

PSC (& Cancer Prevention Study II) relative risks applied to EU15 mortality rates in 2000

Effects of severe obesity: PSC

% survival from age 35 yrs: moderate & severe obesity (dotted lines)



Median life expectancy at age 35: **10 yrs less if BMI 43 than if 23**

PSC (& Cancer Prevention Study II) relative risks applied to EU15 mortality rates in 2000

Cancer mortality: screening, treatment and prevention

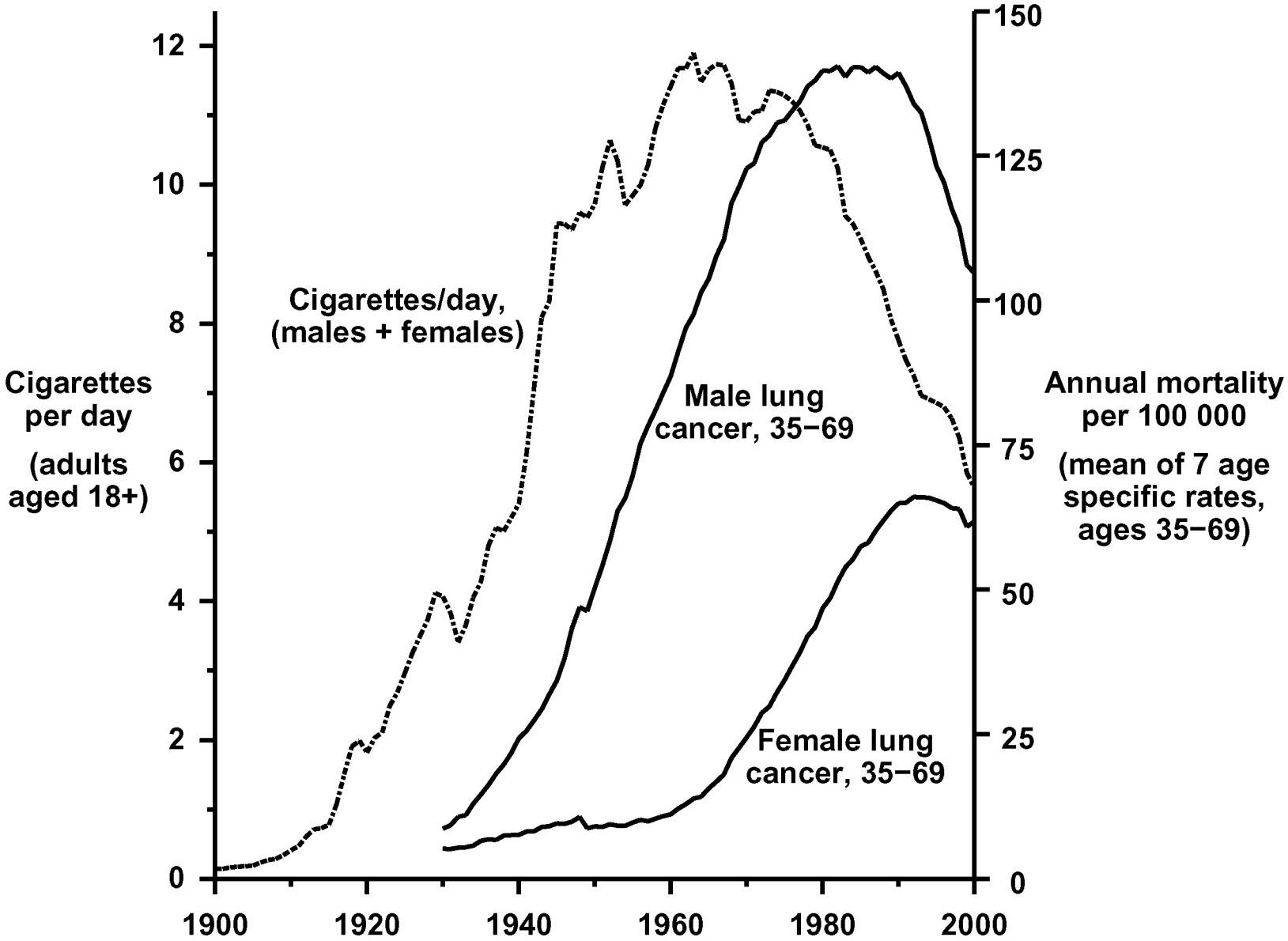
- Chronic infection, mainly in developing countries (eg, HBV, HCV, HPV, H. pylori, EBV, HIV, HHV, flukes, schistosomiasis)
- Occupational factors (eg, asbestos, radon, benzidine, coal & other smoke) worldwide
- Hormonal factors (eg, HRT, kids, obesity)
- Tobacco, first in developed and then in developing countries

Nationwide delay between increase in smoking by young adults

& main increase in tobacco deaths when those young adults reach middle & old age

eg, USA 1900-2000

US trends in cigarette consumption & lung cancer mortality



Source: US Mortality Public Use Data Tapes 1960−2000, US Mortality Volumes 1930−1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2003.

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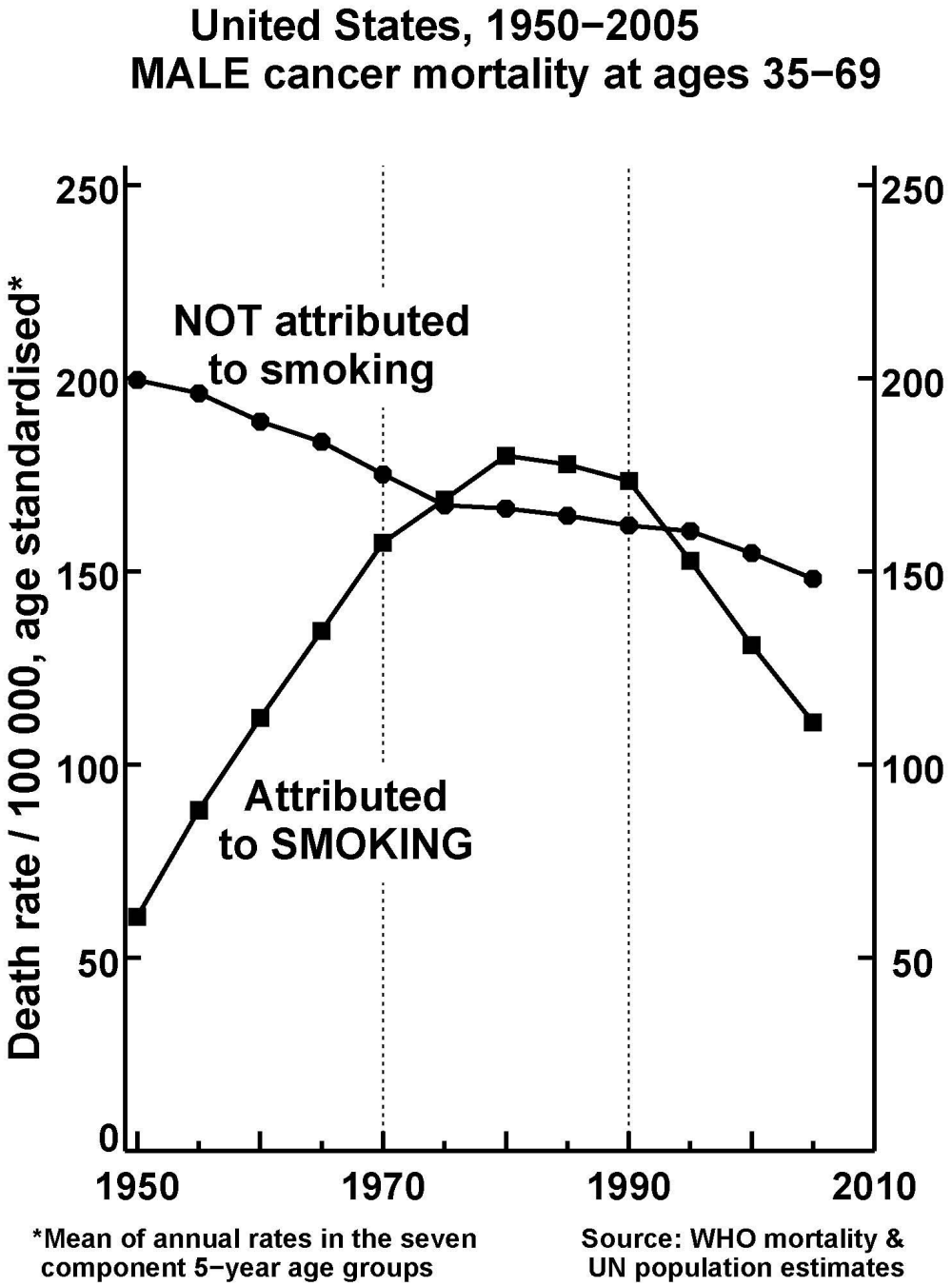
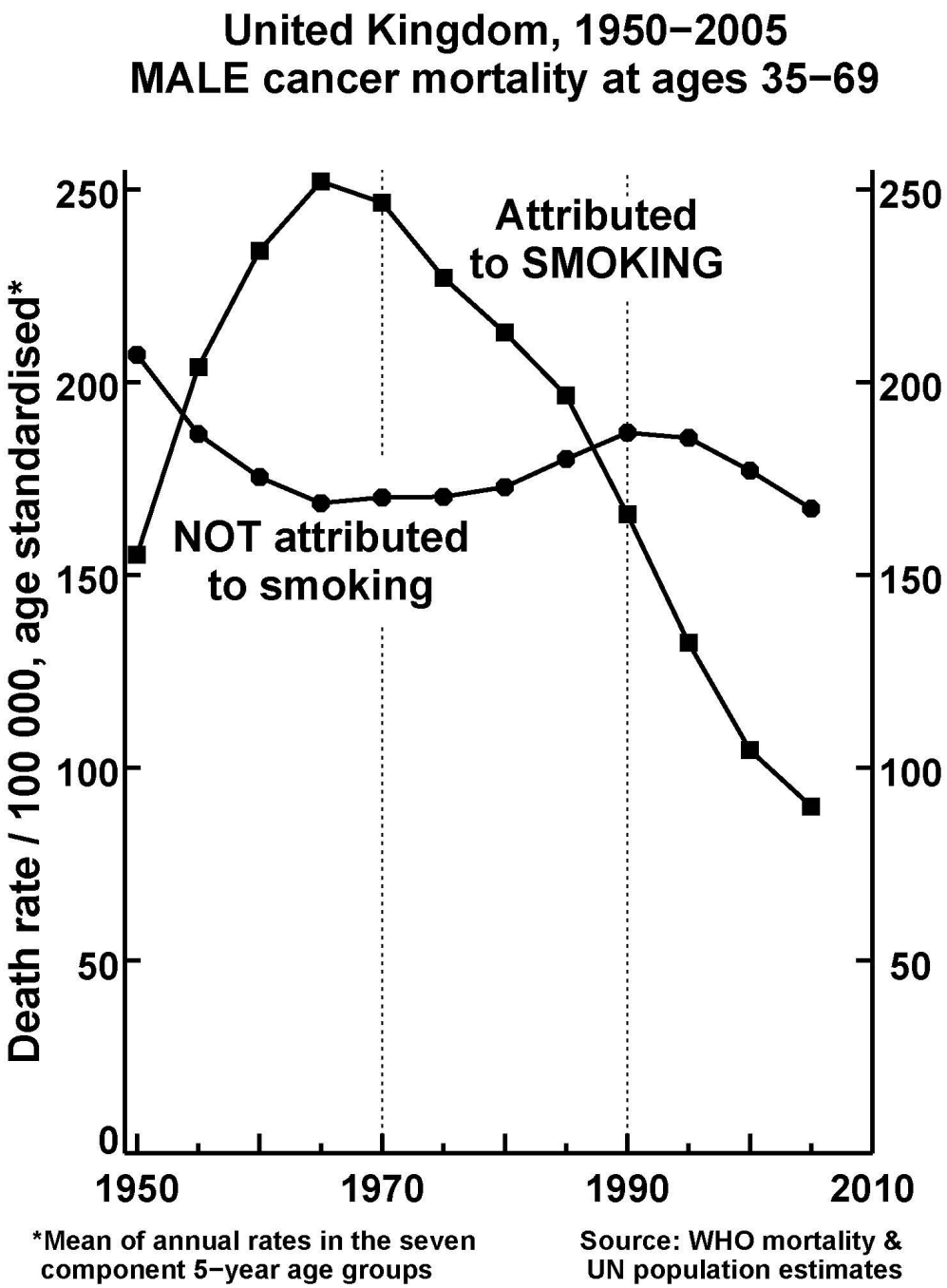

United States, 1950−2005
MALE cancer mortality at ages 35−69
Death rate / 100 000, age standardised*
NOT attributed to smoking
Attributed to SMOKING
250
200
150
100
50
0
1950
1970
1990
2010
*Mean of annual rates in the seven component 5−year age groups
Source: WHO mortality & UN population estimates

1950-2000 cancer mortality:

Effects of tobacco even more dominant in UK than in US men


United Kingdom, 1950−2005
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Attributed to SMOKING
NOT attributed to smoking
250
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50
0
1950
1970
1990
2010
*Mean of annual rates in the seven component 5−year age groups
Source: WHO mortality & UN population estimates

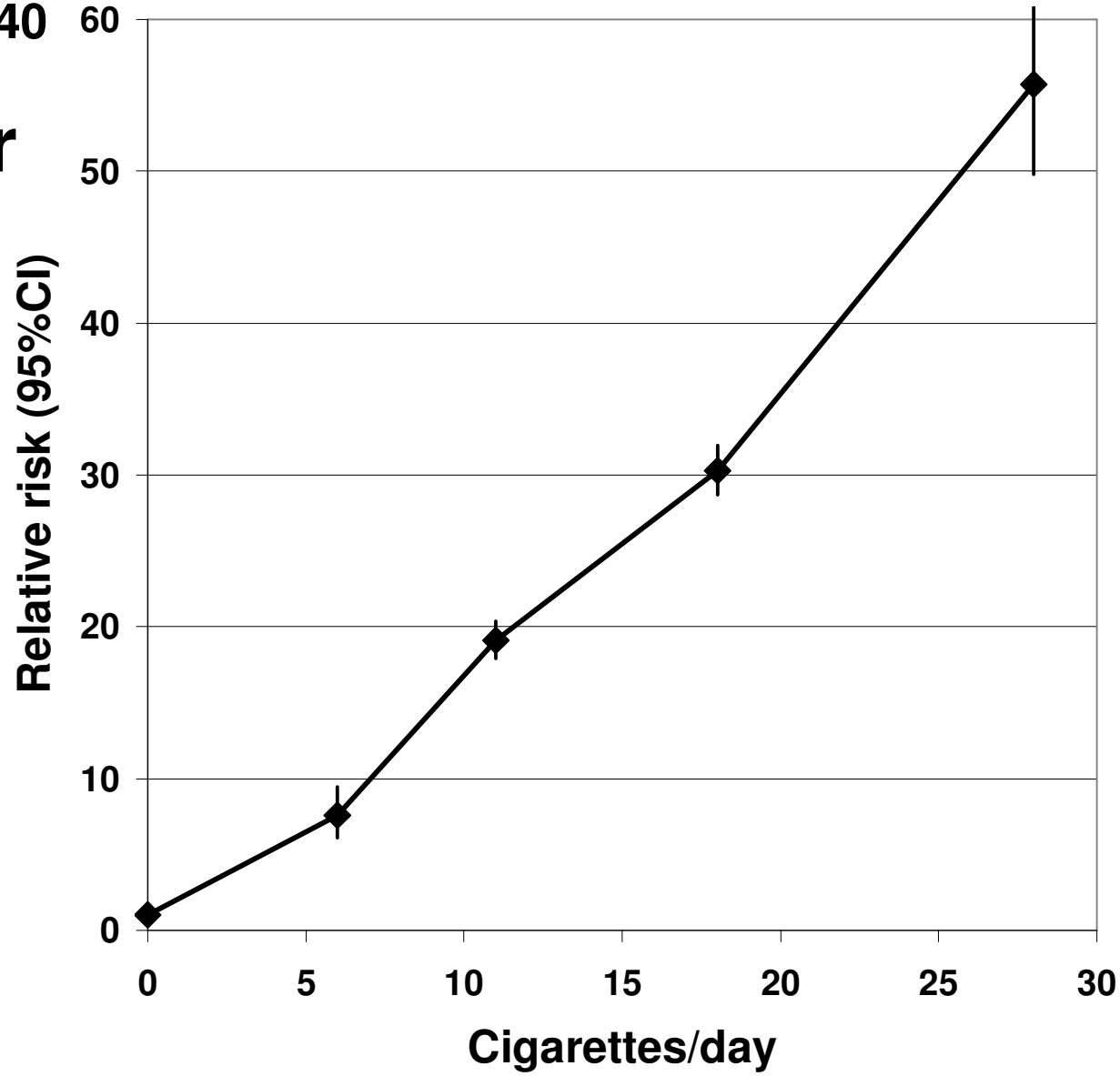
THE MILLION WOMEN STUDY

UK women born ~1940

LUNG cancer mortality at age ~60+

Relative risk & CI, current versus never-smoker

Standardised for age, FU duration, BMI, 10 UK regions & 5 socioec. groups



Tobacco & all-cause mortality

Blood pressure

Blood lipids

Obesity

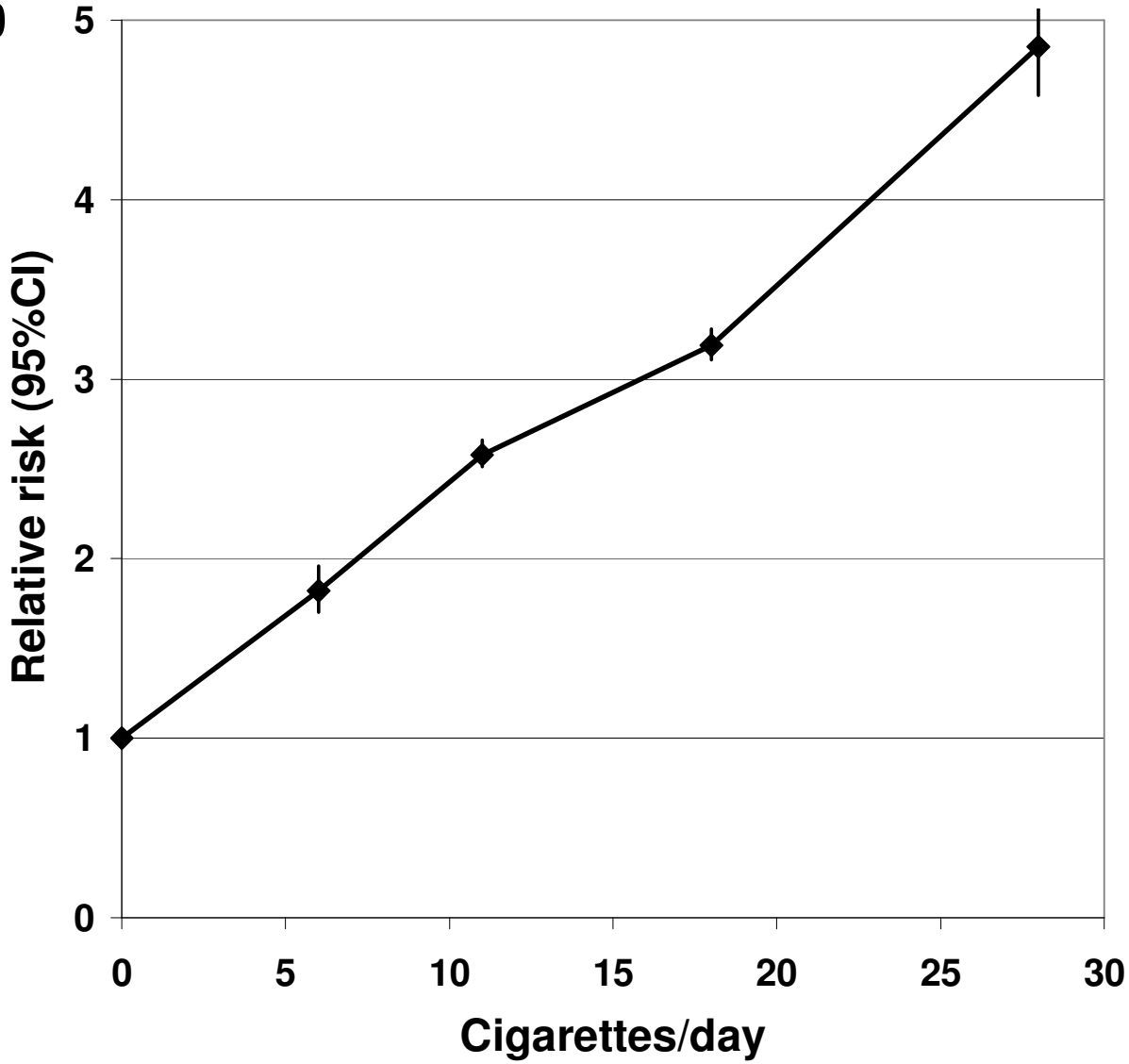
THE MILLION WOMEN STUDY

UK women born ~1940

ALL-CAUSE mortality at age ~60+

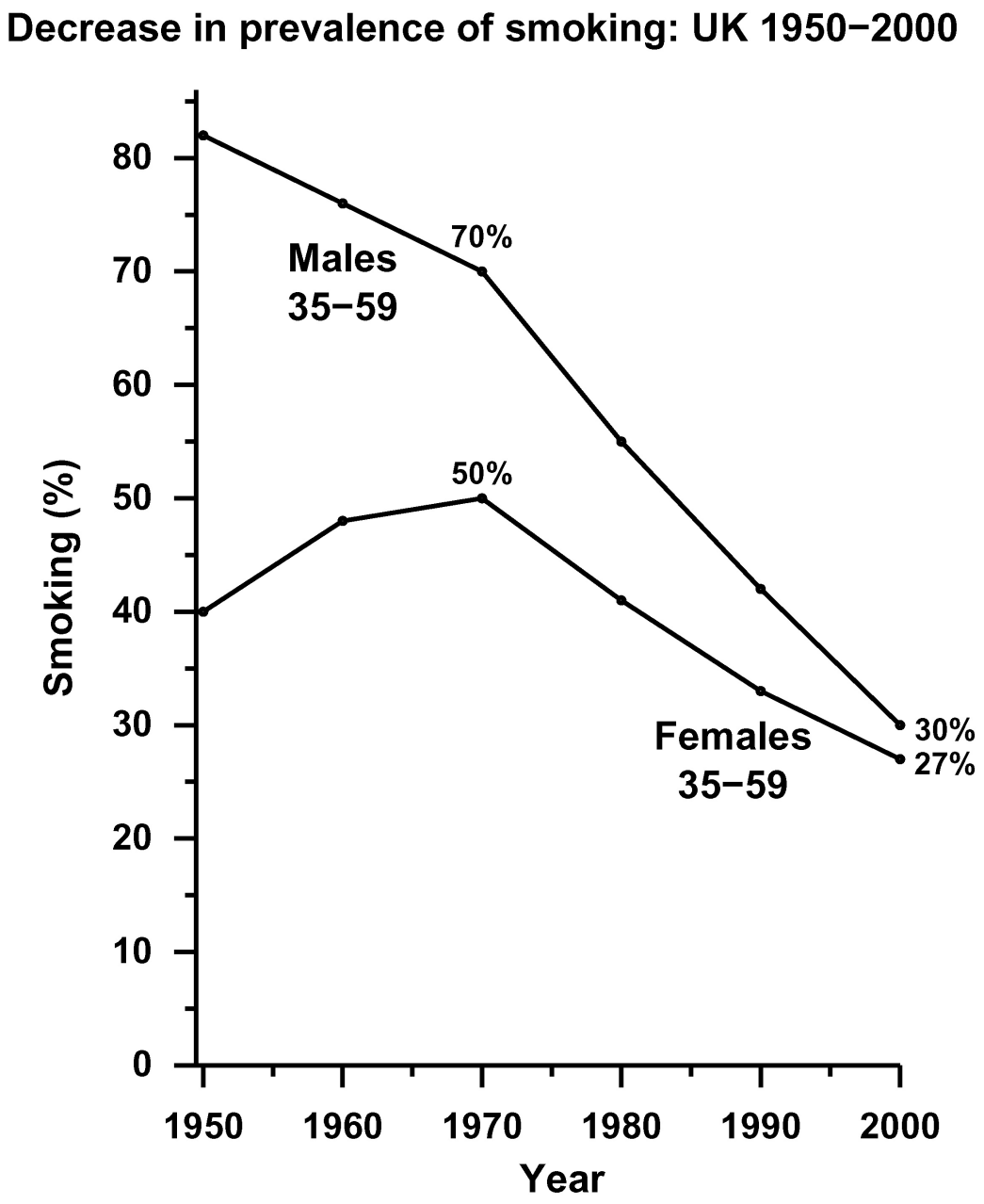
Relative risk & CI, current versus never-smoker

Standardised for age, FU duration, BMI, 10 UK regions & 5 socioec. groups



Three main messages for the individual smoker:

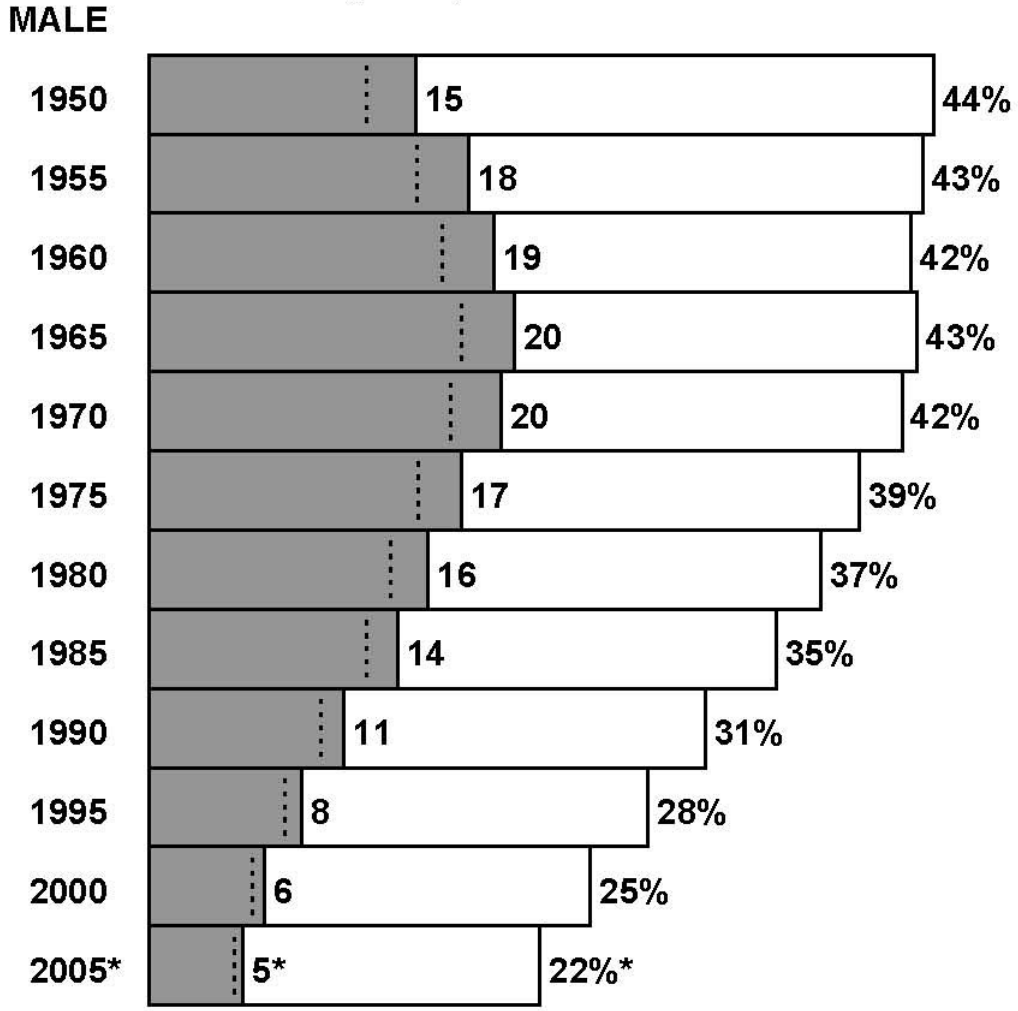
1. Risk is BIG: half are killed
2. 1/4 are killed in MIDDLE age (35-69), losing many years
3. STOPPING smoking works


Decrease in prevalence of smoking: UK 1950−2000
Smoking (%)
80
70
60
50
40
30
20
10
0
Males
35−59
70%
50%
Females
35−59
30%
27%
1950
1960
1970
1980
1990
2000
Year

1950-2005: UNITED KINGDOM

Population risk of a 35−year−old dying at ages 35−69 from smoking (shaded) or from any cause (shaded and white)

*eg, at year 2005 male death rates, out of 100 men aged 35, 22 would die before age 70 (with 5 of these deaths attributed to smoking)



INDIA: 1 million smoking deaths per year during the 2010s

- **Smoking: 10% of all Indian deaths at any age**

- **70% of smoking deaths are at ages 30-69 (600,000 men and 100,000 women/year)**

Jha et al, NEJM 2008

Chinese cigarette increase 40 years after US increase

Delayed hazard: proportion of all deaths at ages 35-69 due to tobacco

US, all adults		China (men)	
1950	12%	1990	12%
1990	33%	2030	33%

World: ~30 million new smokers per year (50% of young men, 10% of young women).

If this continues, & most don't stop, world tobacco deaths eventually >10 million/year (100 million/decade)

World tobacco deaths, if current smoking patterns continue

2000-2025	**~150M**
2025-2050	**~300M**
2050-2100	**>500M**
TOTAL for the 21st century	**~1000M (1 billion)**
Compare with 20th century total	~100M (0.1 billion)

HIV & TOBACCO
& <u>maybe</u> OBESITY

are the only big causes of death increasing substantially,

after allowing for worldwide growth of population

HALVING PREMATURE DEATH

Child survival (improving)

HIV (worsening, despite better treatment)

Unrelated infectious & parasitic (improving: vaccination, TB control, IMCI & better drugs)

Vascular and neoplastic death

Attention to statistical detail has greatly increased the known importance of “classical” risk factors such as blood lipids, blood pressure & tobacco, and of many widely practicable treatments.