Global Health

Cardiovascular Disease Epidemiology and biomarkers for CVD

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Cardiovascular Disease (CVD) Epidemiology

Outline:

- CVD and their intermediate endophenotypes – some definitions and diagnostic points, overall death estimates (by cause)
- Main causes of death from CVD perspective – globally and in selected regions
- Trends in CVD deaths and disease
- Global burden of CVD
- Determinants, causes and intermediate endophenotypes of CVD
- Life-course perspective in CVD mortality and morbidity

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Types of CVD

General burden and importance relative to other diseases

Gender differences

Main types of cardiovascular disease (CVD)

- **Coronary Heart Disease (CHD) (Coronary Artery Disease)**
- **Cerebrovascular Accident (Stroke) (blockage of flow or leakage)**
- **Myocardial Infarction (Heart Attack)**
- **Angina, Atherosclerosis**
- **Aneurysm**
- **Arrhythmia**
- **High Blood Pressure (Hypertension) (Hypotension)**
- **Venous Thromboembolism**
- **Congestive Heart Failure**
- **Hypertrophic Cardiomyopathy**
- **Congenital Heart Disease**

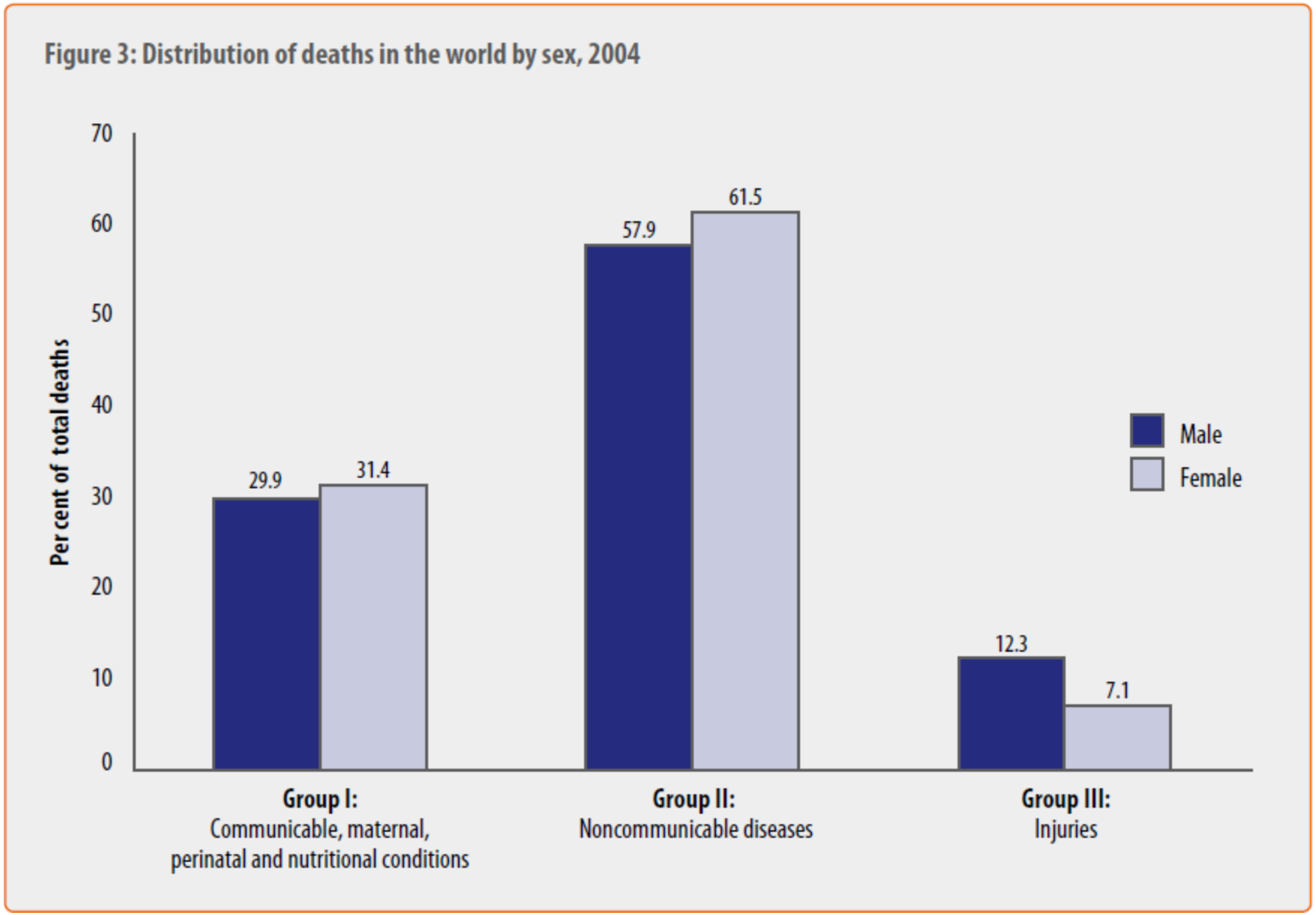
Chronic diseases (CNCDs) - BURDEN: CVD (heart disease/stroke), some Cancers, Respiratory, and T2D

- Reaching epidemic proportions worldwide (all ages, nationalities and classes), globally >17 million CVD deaths/y
- CNCDs account for ~60% of all deaths worldwide
- 80% of deaths occur in low- and middle-income countries (CNCDs account 44% of premature deaths worldwide)
- The burden is projected to rise particularly fast in the developing world
- **With "concerted action", at least 36 million premature deaths can be averted by 2015**
  - **~17 million of these prevented deaths would be among people under the age of 70**

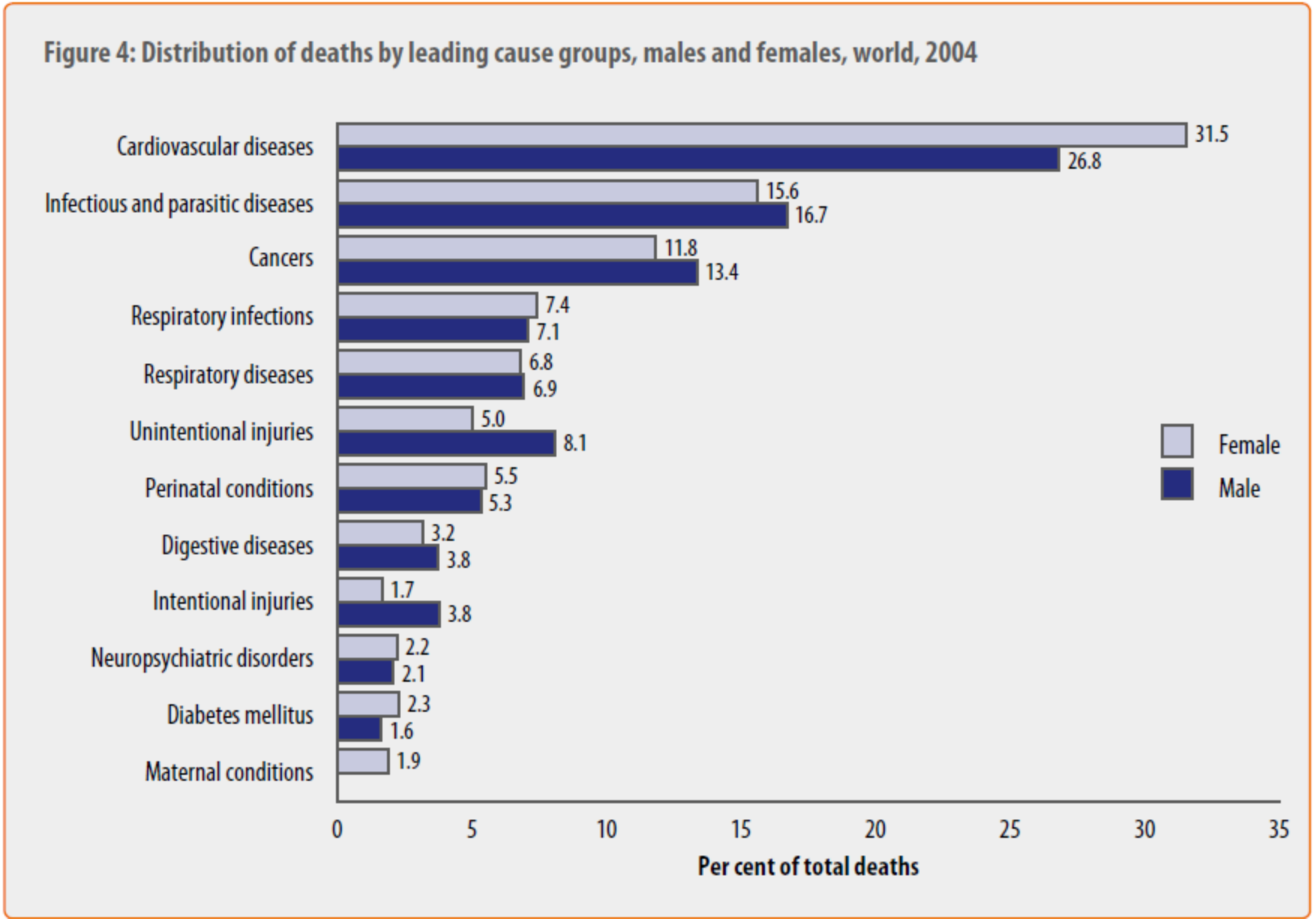
Daar et al, Nature 2007

Worldwide leading mortality rates for the year 2002

Rank	Causes/per 100,000	Rates	%
1	**Cardiovascular diseases**	**268.8**	**29.34**
1.1	Ischemic heart disease	115.8	12.64
1.2	Stroke	88.5	9.66
2	**Infectious and Parasitic diseases**	**211.3**	**23.04**
2.1	Respiratory infections	63.7	6.95
2.2	Lower respiratory tract infections	62.4	6.81
2.3	Diarrheal diseases	28.9	3.15
2.4	HIV/AIDS	44.6	4.87
2.5	Tuberculosis	25.2	2.75
2.6	Malaria	20.4	2.23
3	**Malignant neoplasms (cancers)**	**114.4**	**12.49**
3.1	Lung cancers	20	2.18
4	**Respiratory diseases**	**59.5**	**6.49**
4.1	Chronic obstructive pulmonary disease	44.1	4.82
5	**Unintentional injuries**	**57**	**6.23**
5.1	Road traffic accidents	19.1	2.09
6	**Perinatal conditions**	**39.6**	**4.32**
7	**Digestive diseases**	**31.6**	**3.45**
8	**Intentional injuries (Suicide, Violence, War, etc.)**	**26**	**2.84**
9	**Neuropsychiatric disorders**	**17.9**	**1.95**
10	**Diabetes mellitus**	**15.9**	**1.73**



WHO report, Causes of death 2004



WHO report, Causes of death 2004

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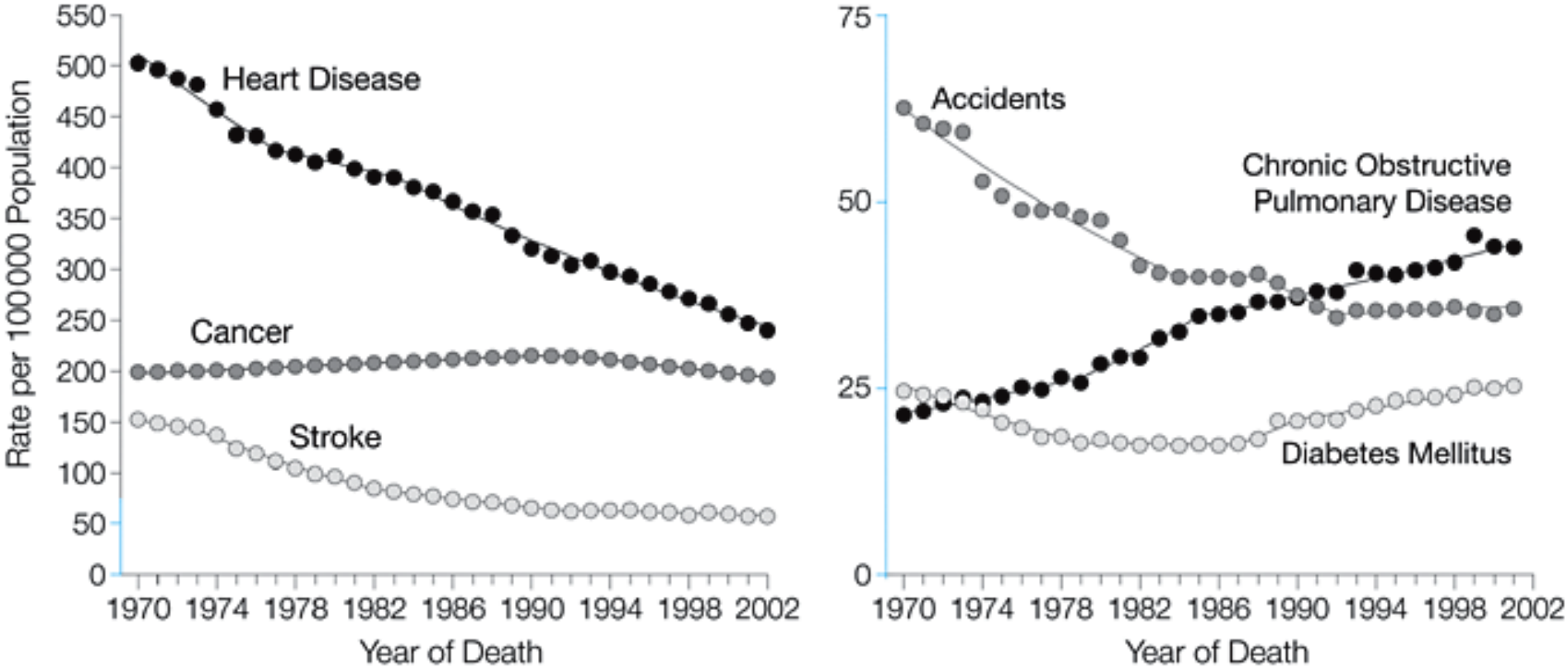
Time trends

Trends in Age-Standardized Death Rates for the 6 Leading Causes of Death in the United States, 1970-2002



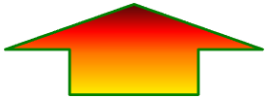
Jemal, A. et al. JAMA 2005;294:1255-1259 JAMA

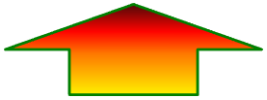
Trends of Age-Standardized Death Rates in the United States between 1970-2002

Stroke deaths: 63% 

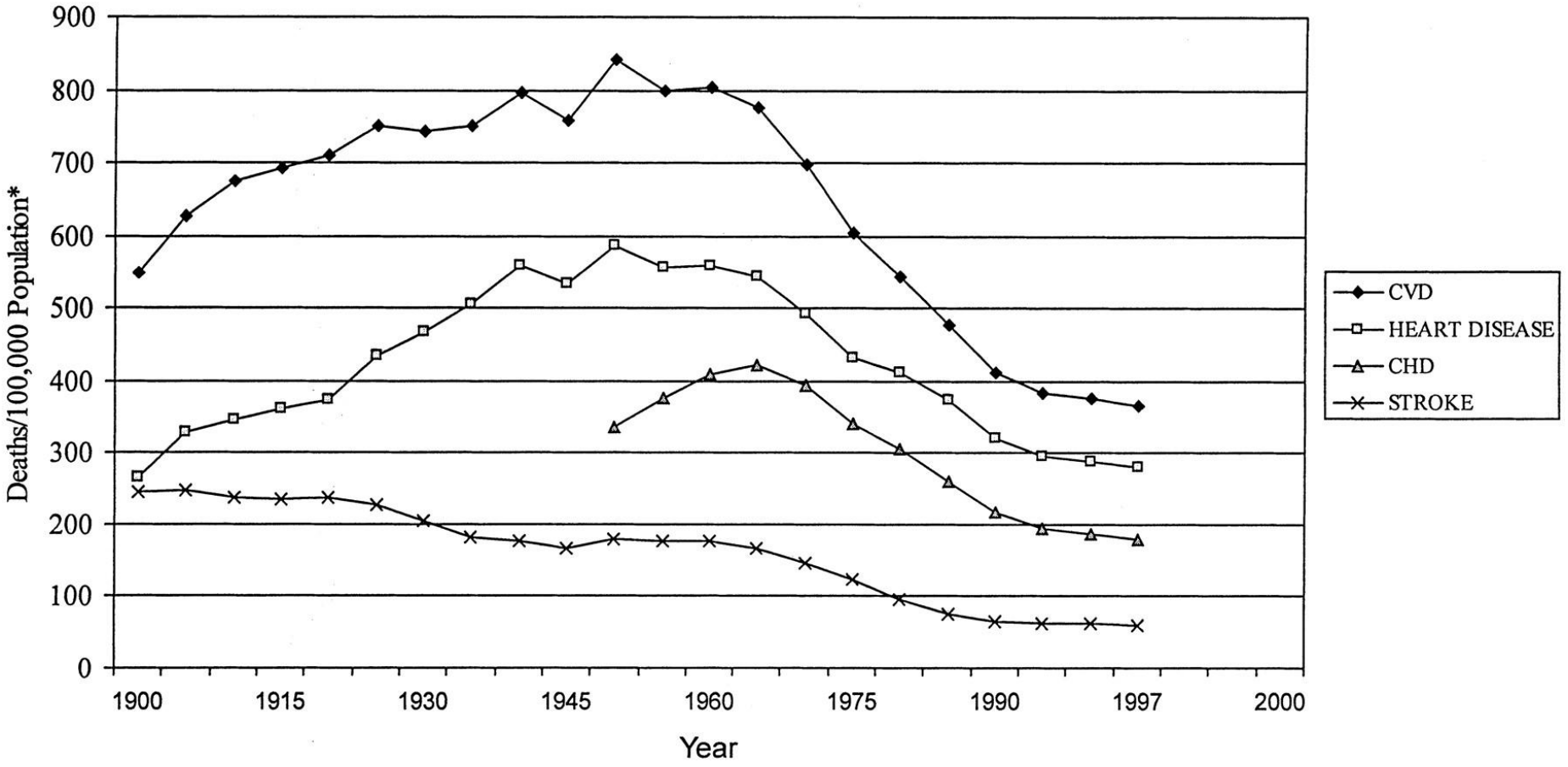
Heart disease deaths: 52% 

Cancer deaths: 2.7% 

Diabetes deaths: 45% 

COPD deaths: 102% 

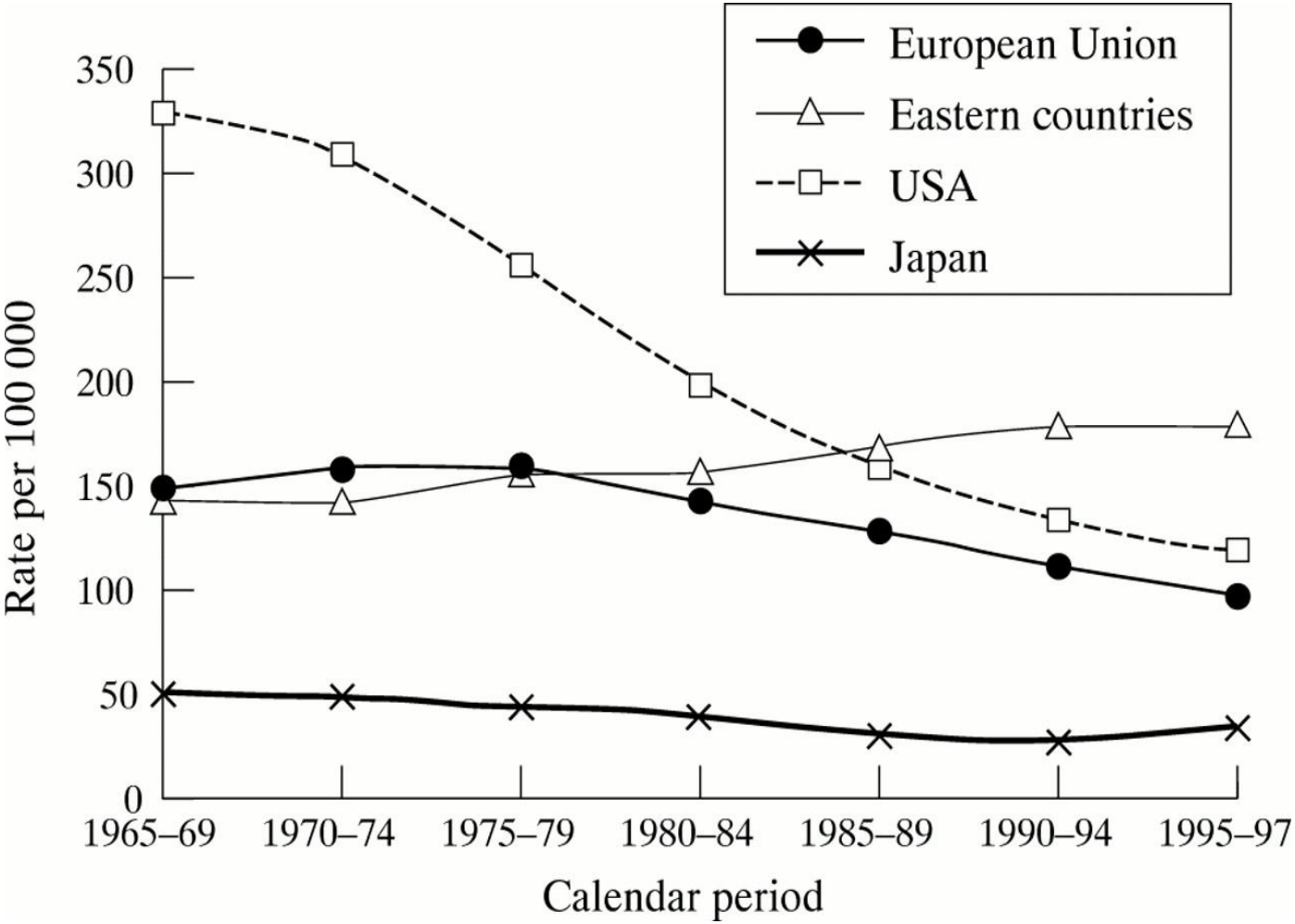
Death rates for major cardiovascular diseases in the United States from 1900 to 1997



Cooper, R. et al. Circulation 2000;102:3137-3147

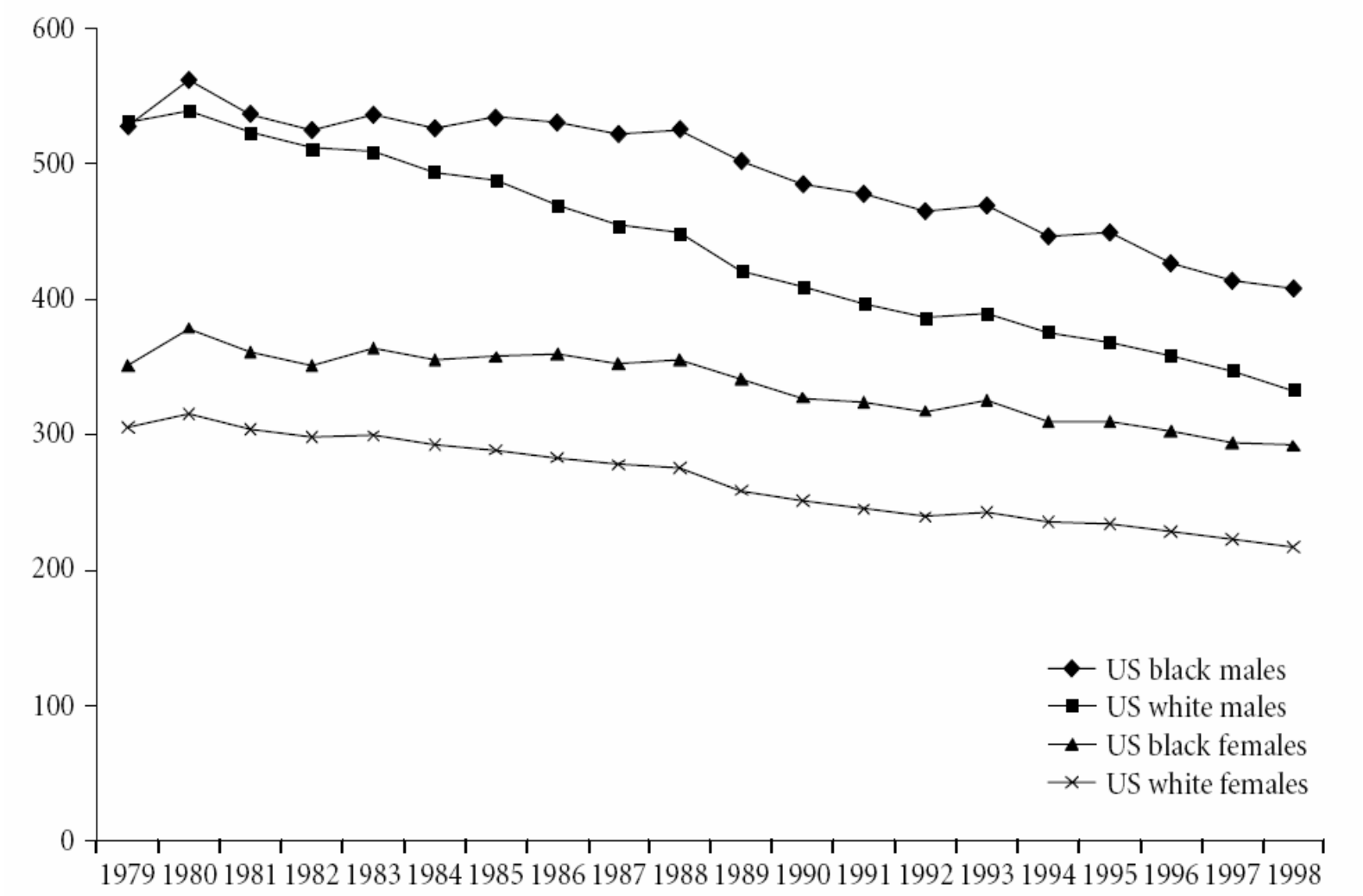
Circulation

Age standardised death rates from coronary heart diseases (CHD) in men, all ages from the European Union, eastern European countries (Bulgaria, Czech Republic, Hungary, Poland, Romania, and Slovakia), USA, and Japan, 1965-1997



Levi, F et al. Heart 2002;88:119-124

Heart disease mortality by race and gender, US, 1979-98 (per 100 000)



Data from CDC Wonder 2003

Cooper RS. Coronary heart disease among persons of African origin. In: M Marmot & P Elliott (eds). Coronary Heart Disease Epidemiology. From Aetiology to Public Health, 2005, Oxford University Press, Oxford, UK, pp73-82.

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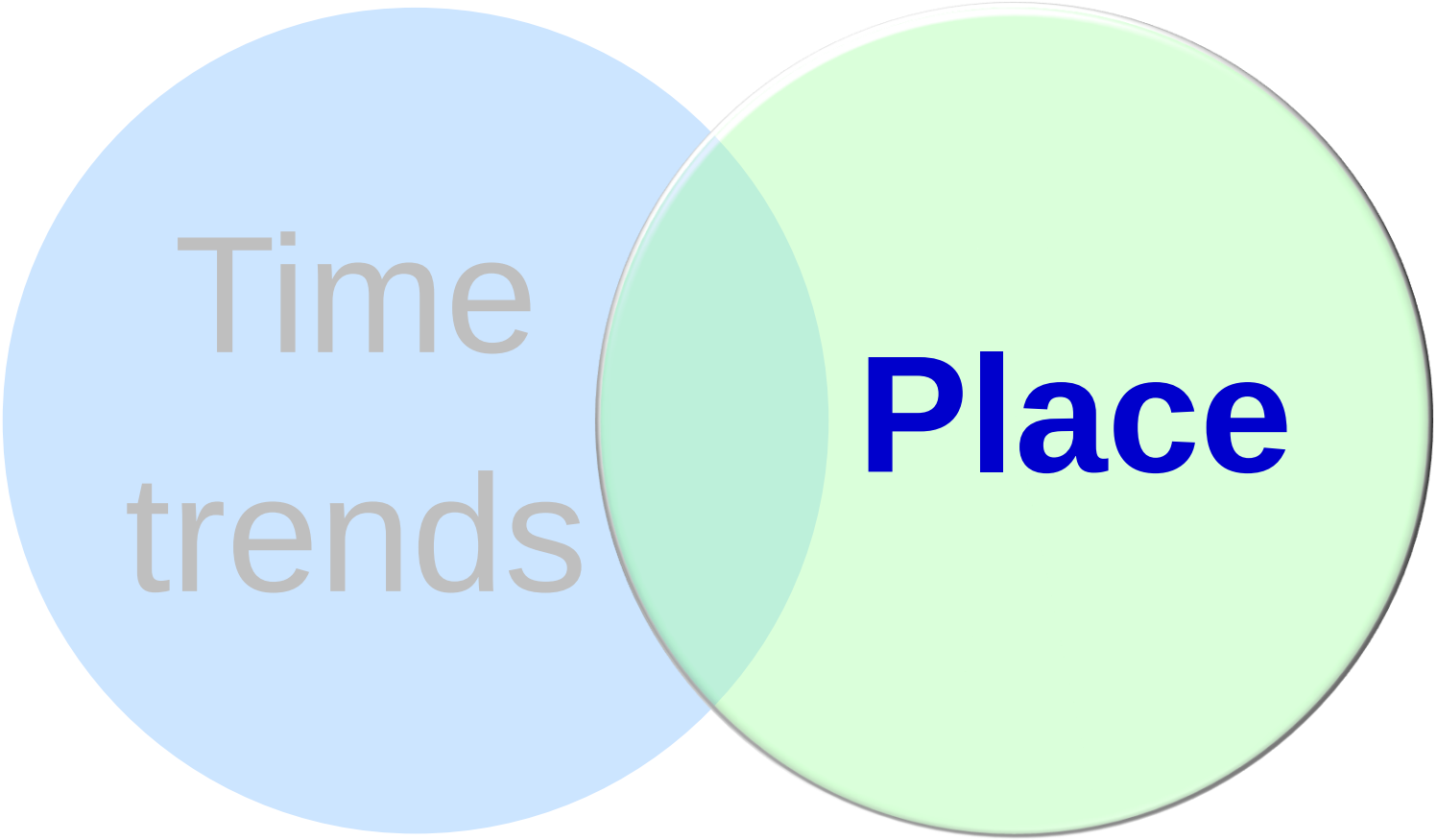
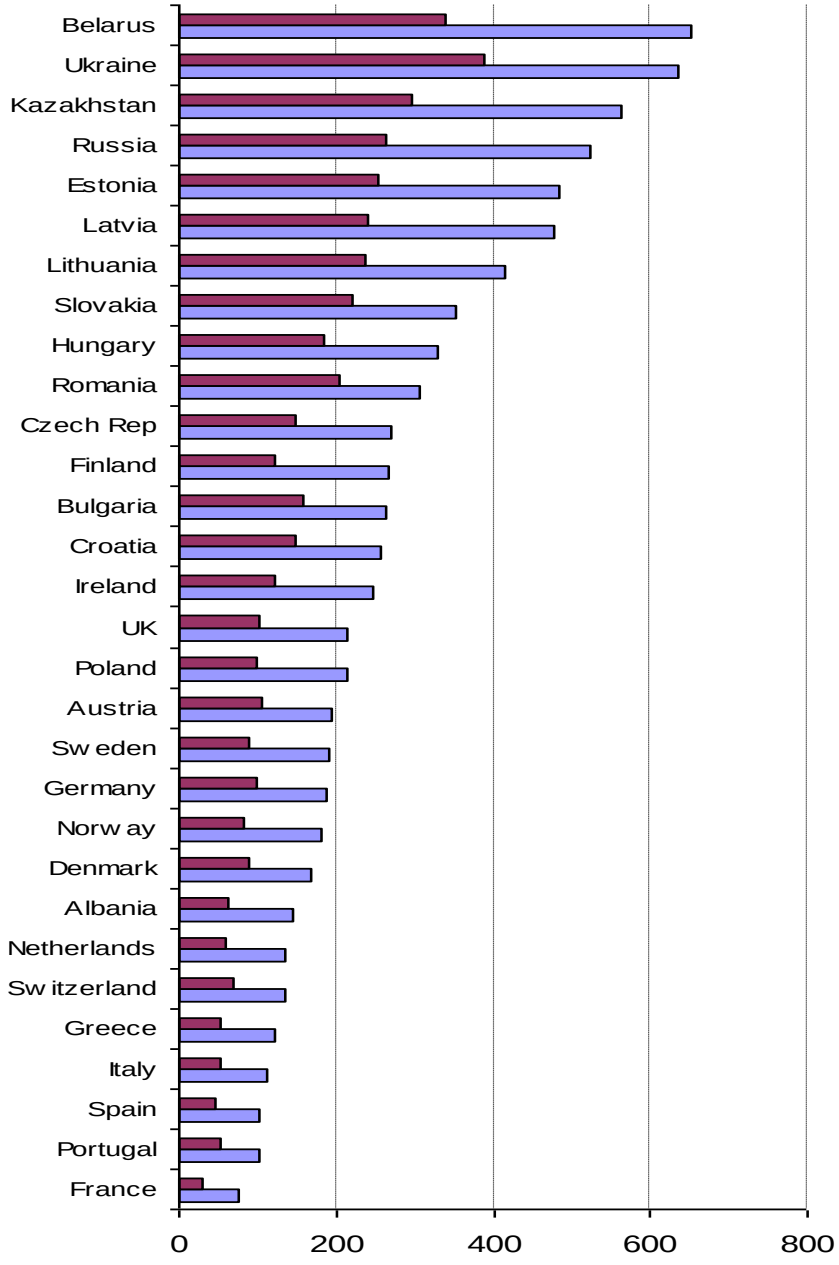
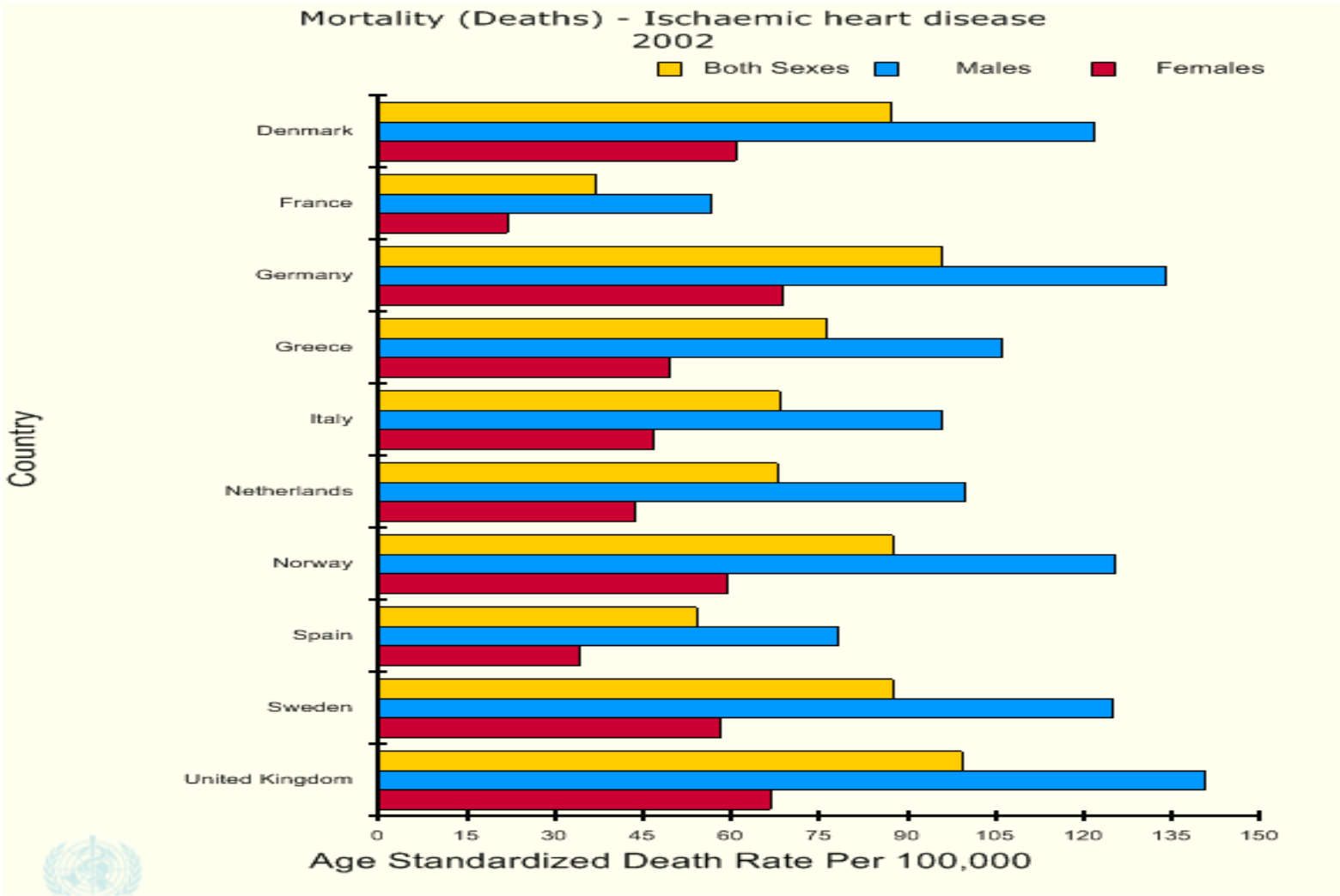




Age-standardized mortality from CHD per 100 000 in European countries in 2000 or the latest available year

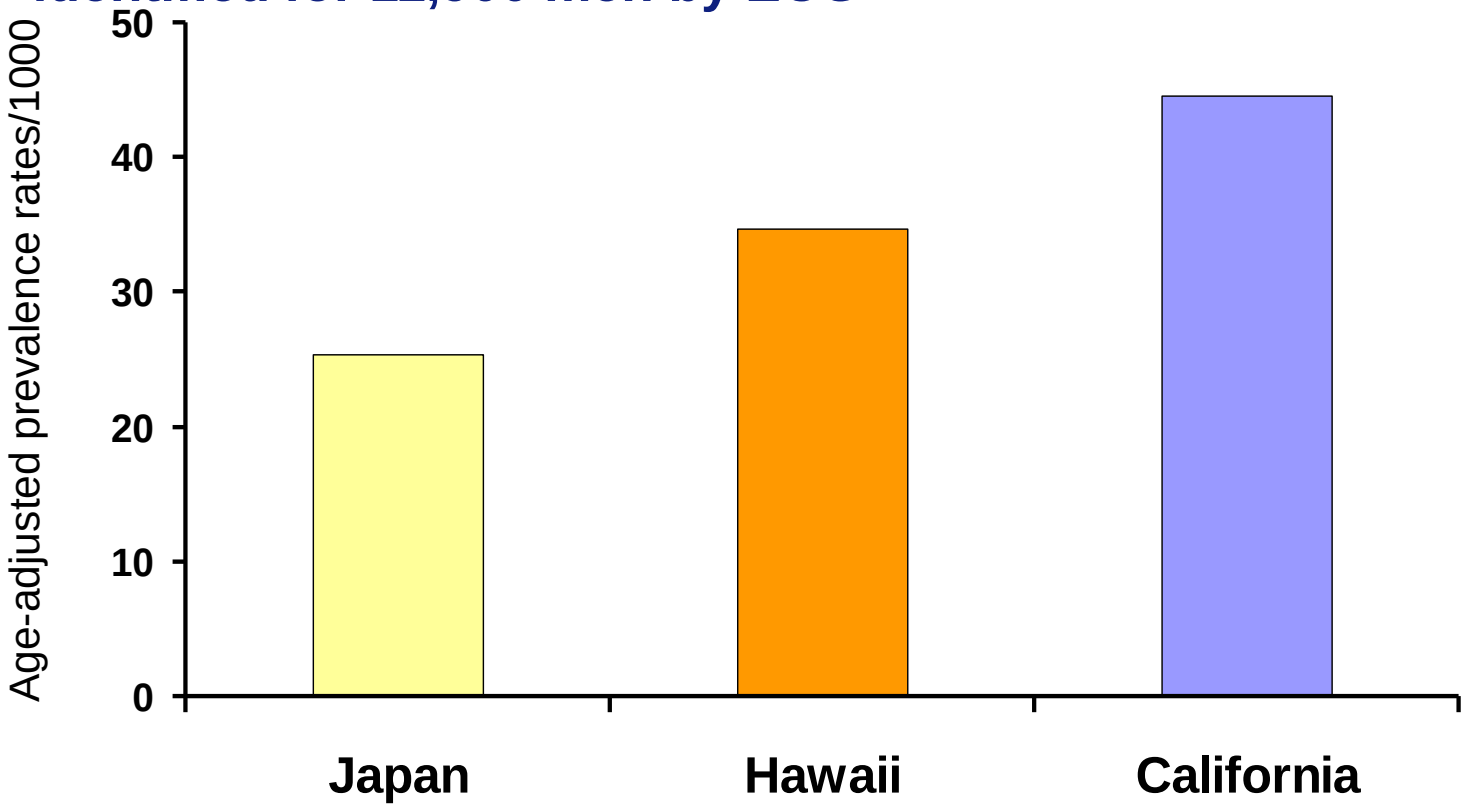
Data from the WHO Health for All database

Bobak M, Marmot M. Central and Eastern Europe and the Former Soviet Union. In: M Marmot & P Elliott (eds). Coronary Heart Disease Epidemiology. From Aetiology to Public Health, 2005, Oxford University Press, Oxford, UK, pp 83-101.



Source: Mathers, C. D. C. Bernard, K. M. Iburg, M. Inoue, D. Ma Fat, K Shibuya, C. Stein, N. Tomijima, and H. Xu. Global Burden of Disease in 2002: data sources, methods and results. 2003 (http://www.who.int/infobase IBRef: 199998)

Age-adjusted prevalence rates of definite + possible CHD identified for 11,900 men by ECG



Country of residence of men of **Japanese ancestry** aged 45-69 yrs

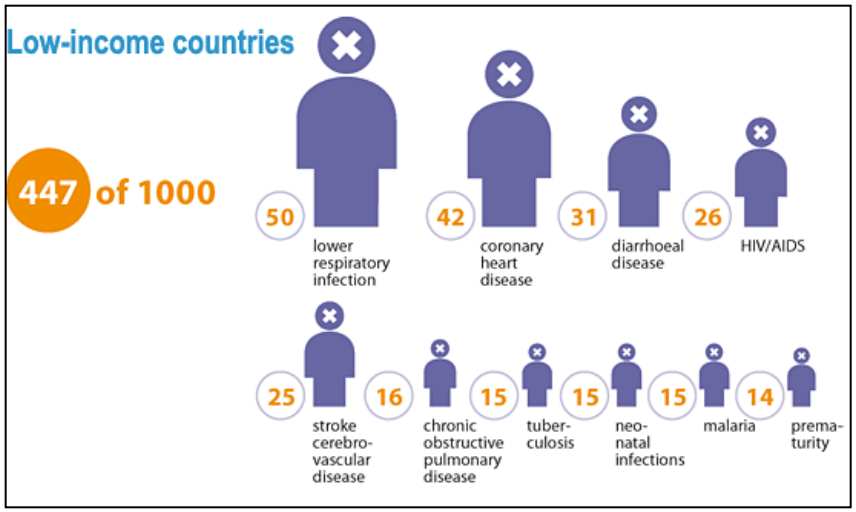
Marmot MG et al. Am J Epidemiol 1975; 102: 514-25

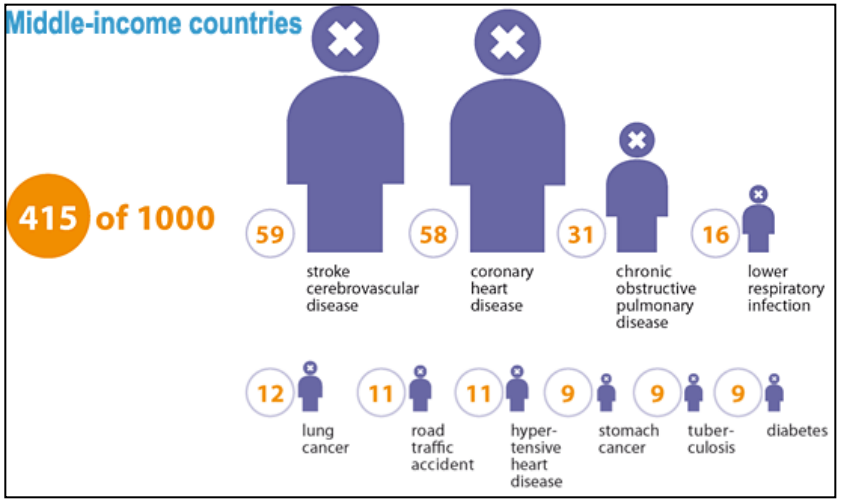
Deaths across the globe: an overview

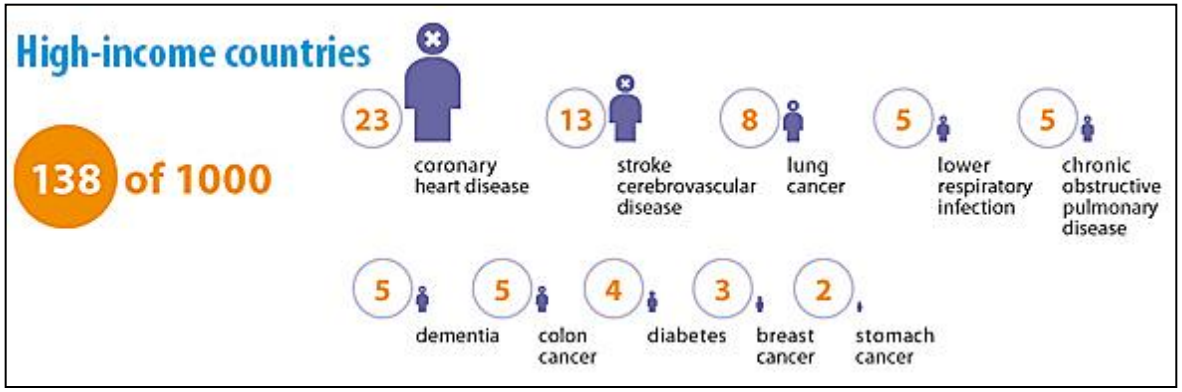
Imagine a diverse international group of 1000 individuals representative of the women, men and children from all over the globe who died in 2004. Of those 1000 people, 138 would have come from high-income countries, 415 from middle-income countries and 447 from low-income countries.

What would be the top 10 causes of their deaths?

Source: WHO, http://www.who.int/mediacentre/factsheets/fs310/en/index.html



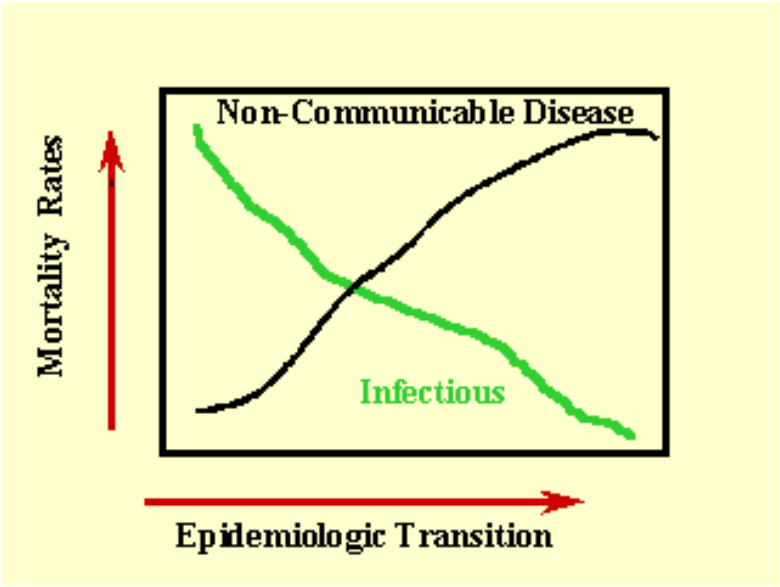




Note: In this fact sheet, we use low-, middle- and high-income categories as defined by the World Bank. Countries are grouped based on their 2004 gross national income. See *The global burden of disease 2004 update* for more information.

Epidemiologic transition and the Global Burden of Disease

During the epidemiologic transition, a long-term shift occurs in mortality and disease patterns whereby pandemics of infection are replaced by degenerative and man-made diseases….



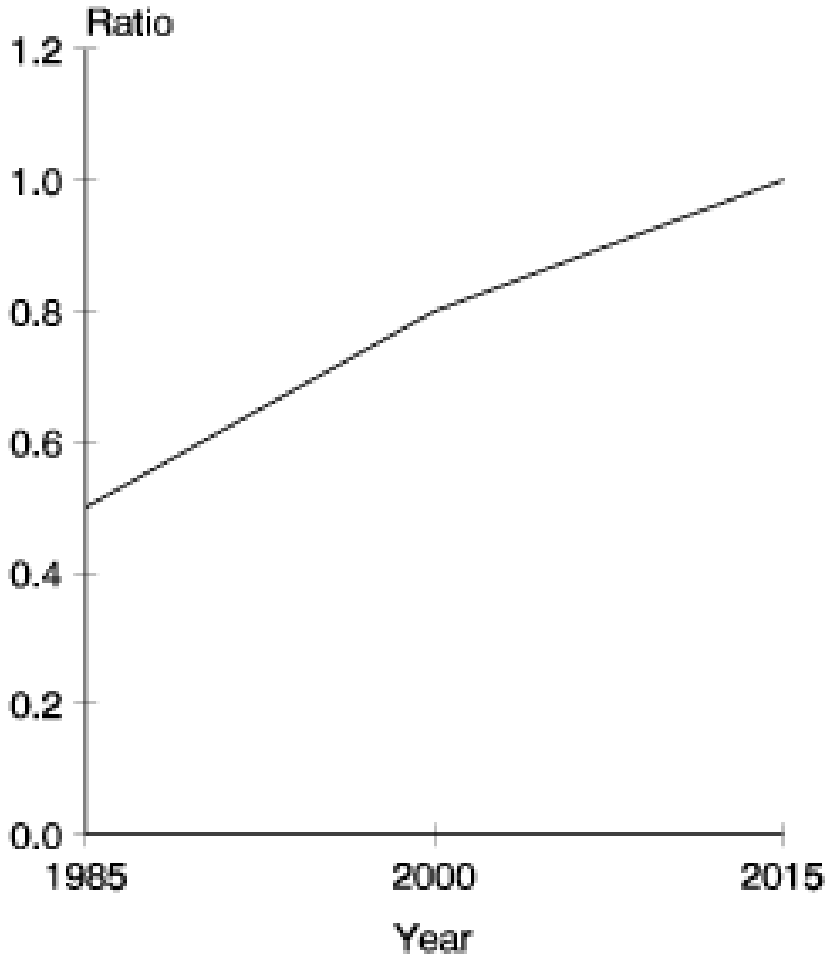
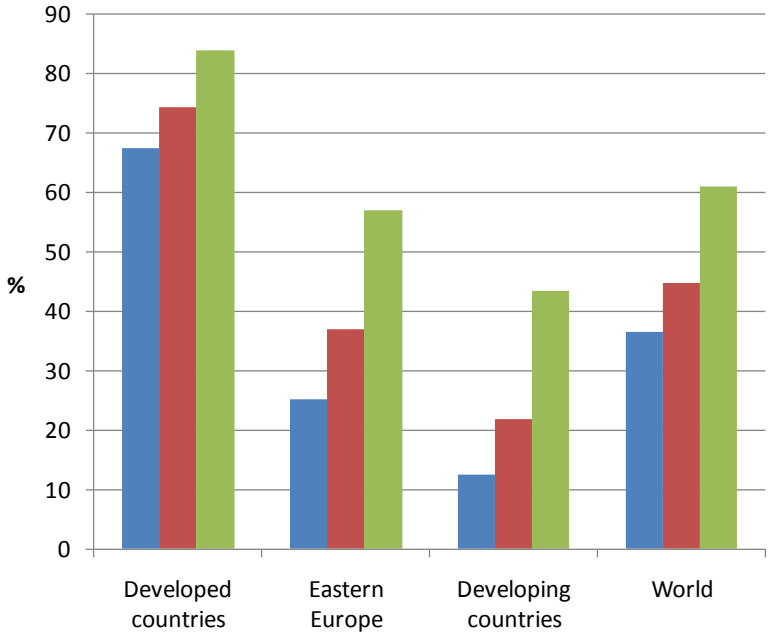


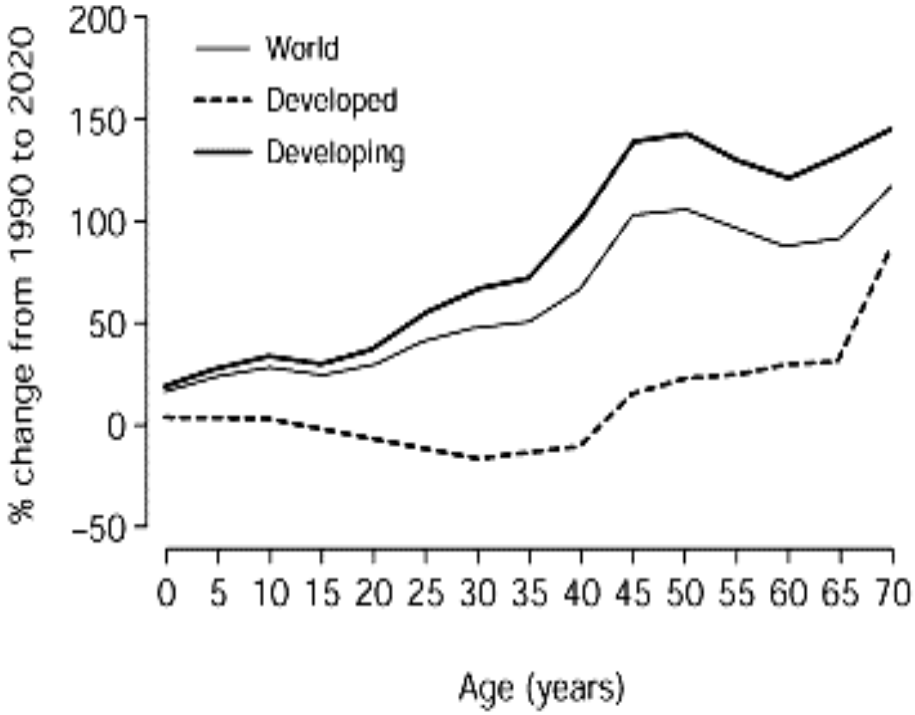
Figure 3 **Changing cause-of-death structure in the Eastern Mediterranean Region (ratio of deaths from cardiovascular diseases to deaths from infectious and parasitic diseases)**
Source: World Bank (1993)

% Living in urban settings: 1970, 1994, & 2025 (projected)

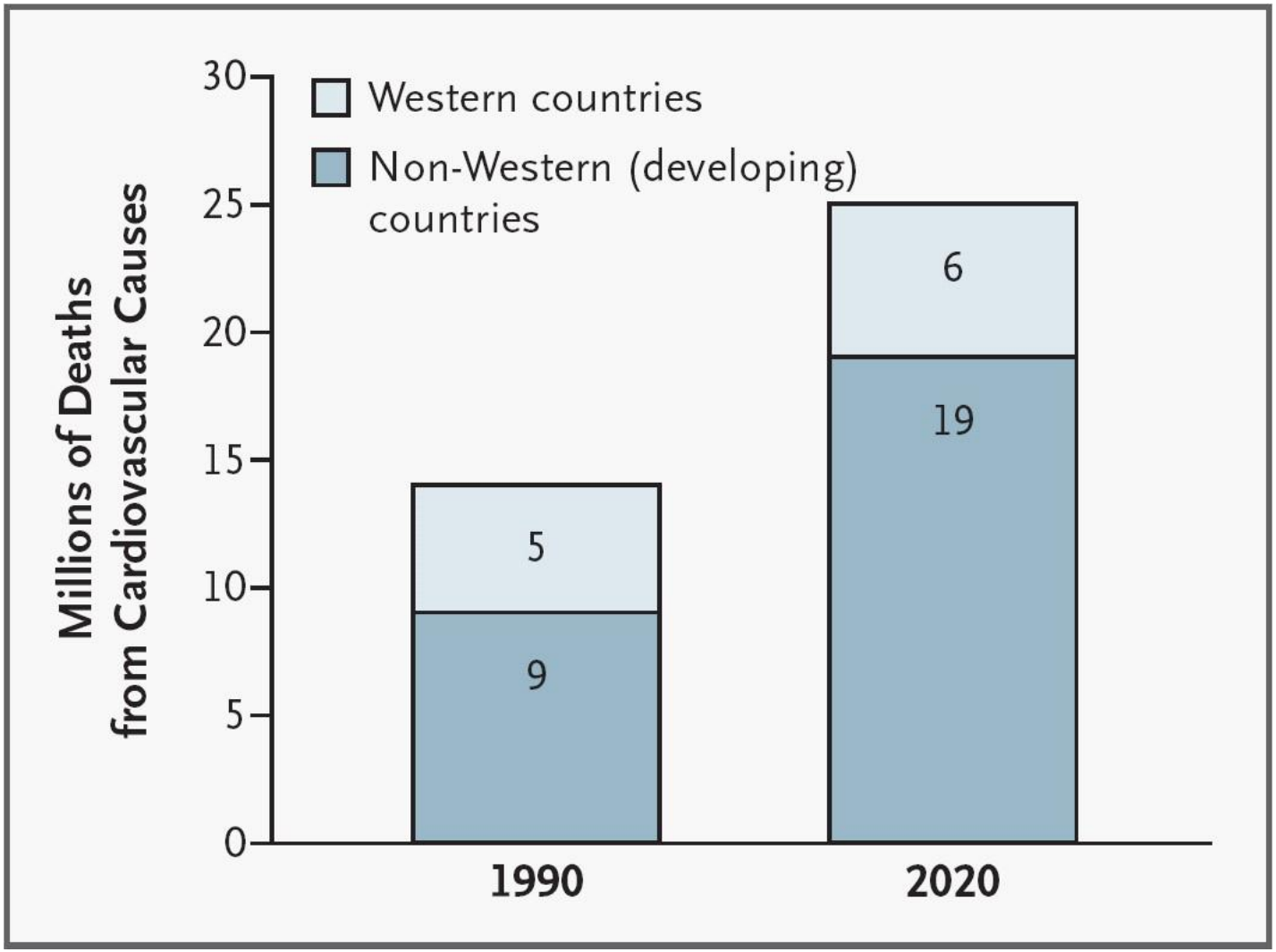


Source: Yusuf S, *Circulation* 2001;104:2746-2753

Projected change in global population 1990 to 2020



Murray CJL, Lopez AD Lancet 1997;349:1498-1504



Deaths from cardiovascular causes, worldwide, in 1990 and estimated for 2020. Data from Global Burden of Disease study

Source: Reddy KS, *NEJM* 2004;350:2438-2440

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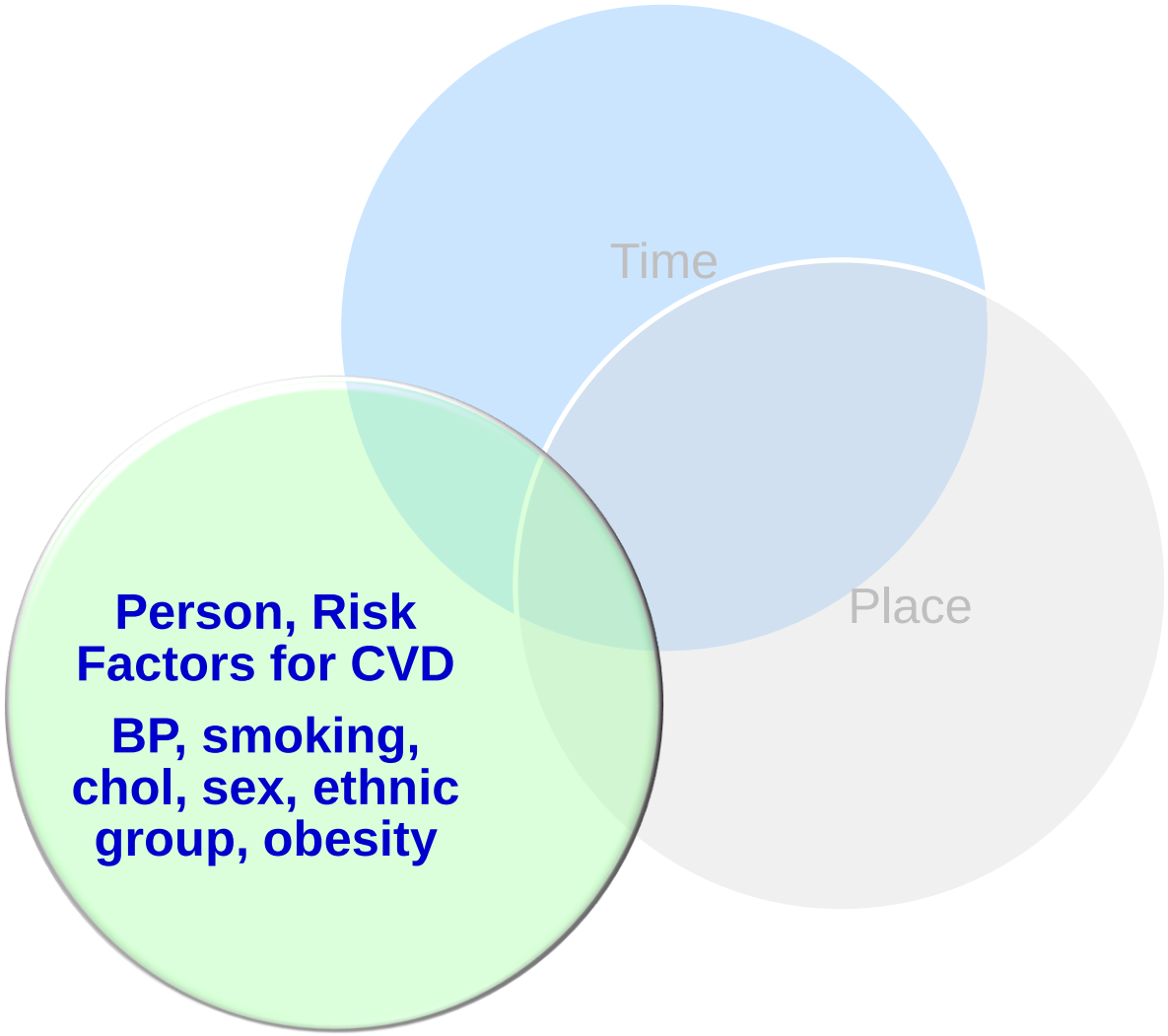
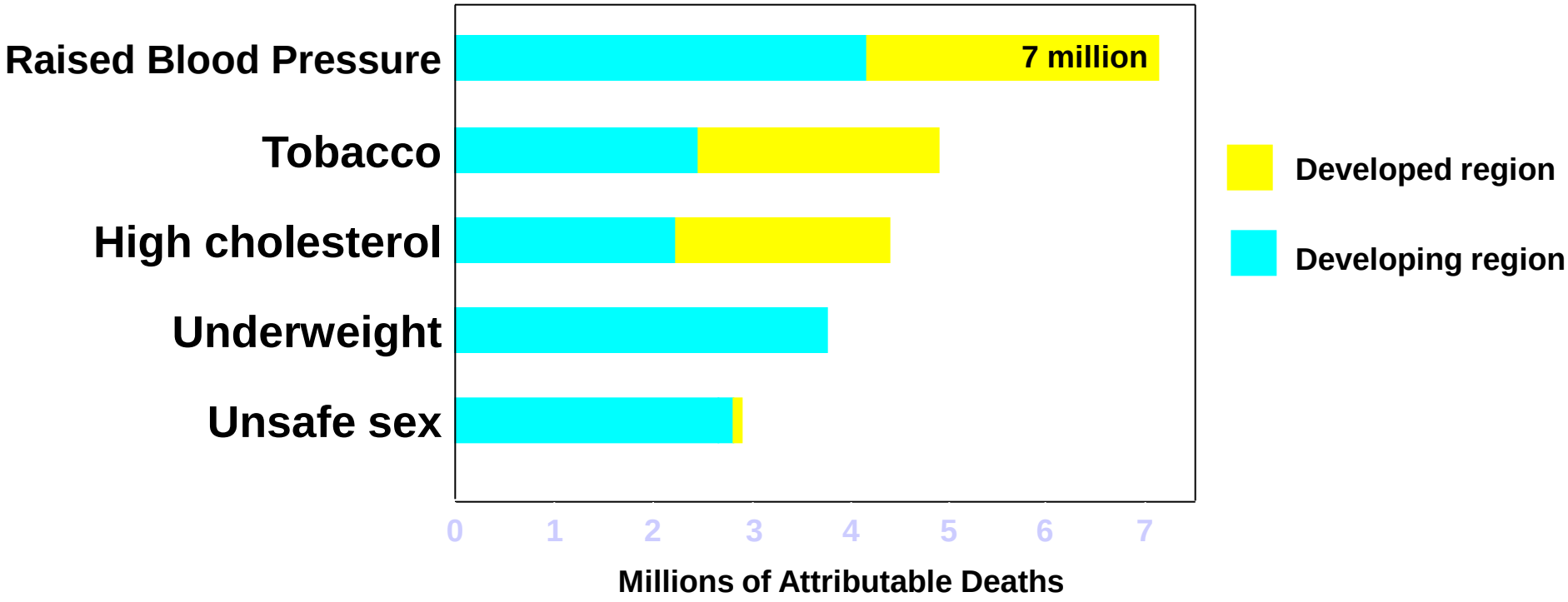


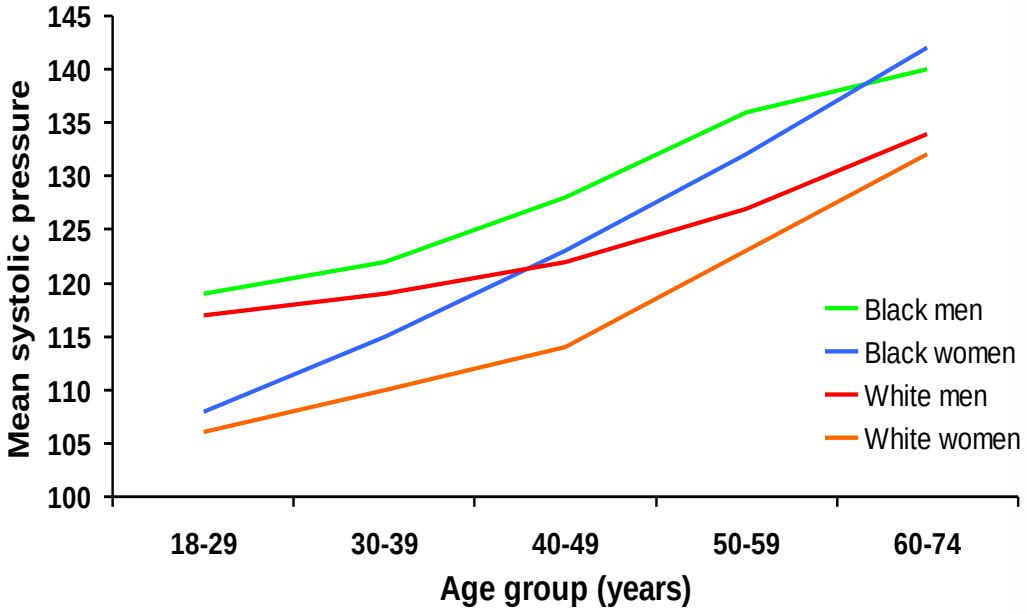
Major Risk Factors for Death Worldwide



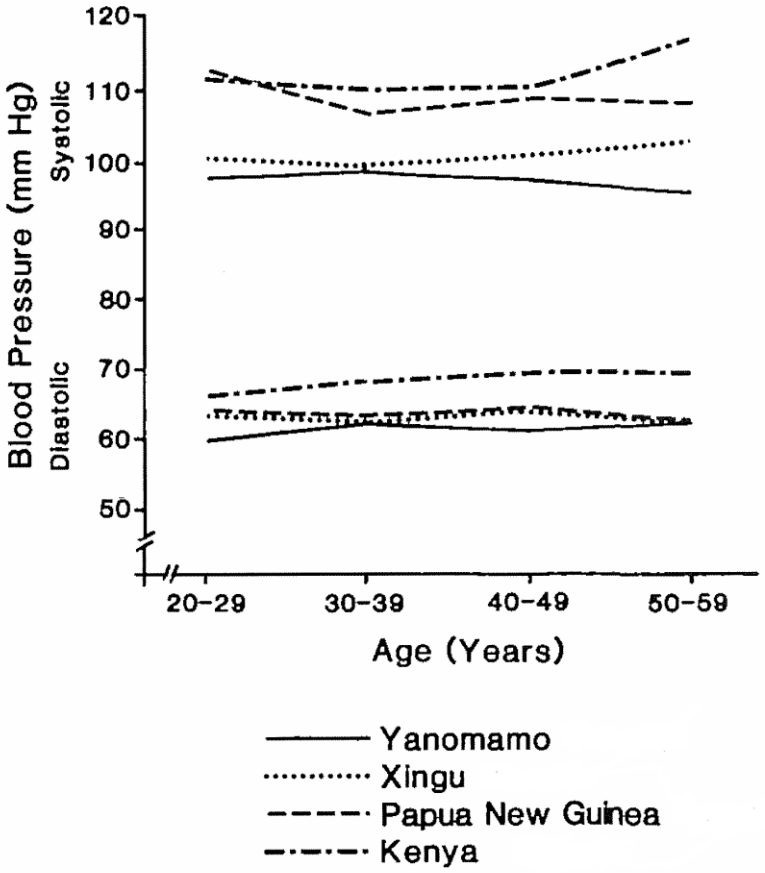
62% of all Strokes and 49% of all Heart Disease attributable to raised BP (ignored often!!)

Lancet 2002; 360: 1347-60

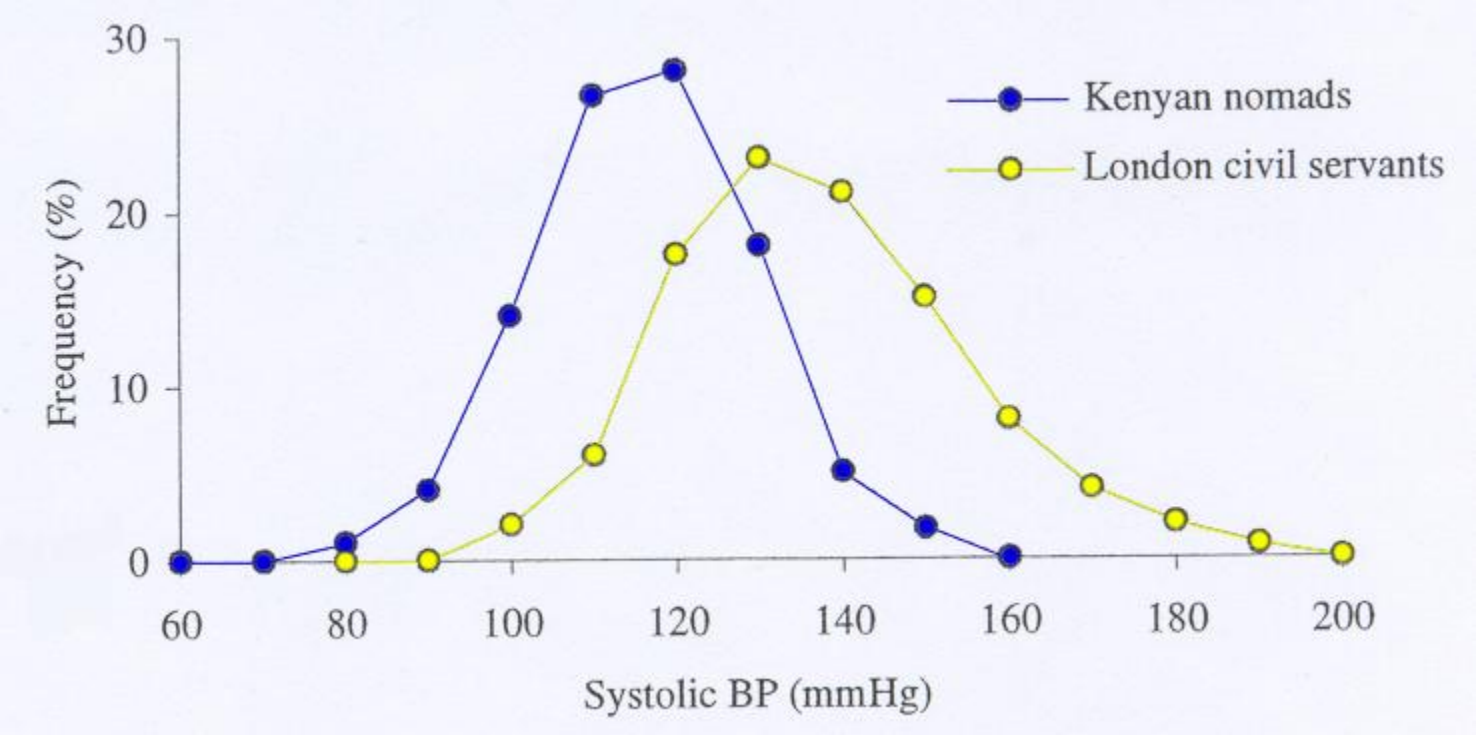
Mean systolic blood pressure (mmHg), US population, NHANES III Phase I (1988-1991) by age, ethnic group and gender



INTERSALT: Four low BP populations



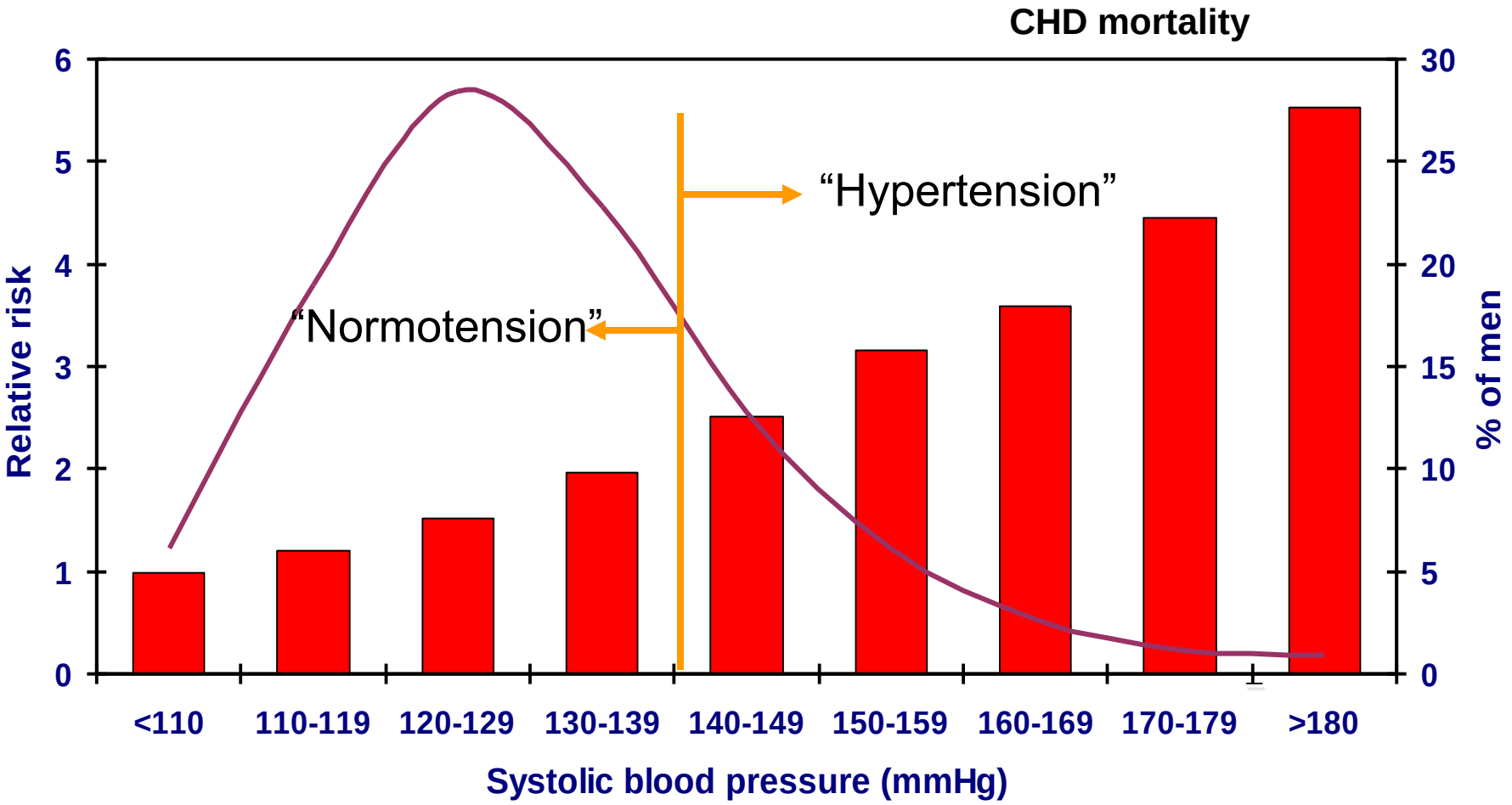
BP Distributions in Different Populations



Lifestyle factors – especially diet – are key in explaining differences between populations in the rise in BP with age and the consequent prevalence of high BP at older ages

Adapted from Rose *Int J Epidemiol* 1985; 14: 32-38

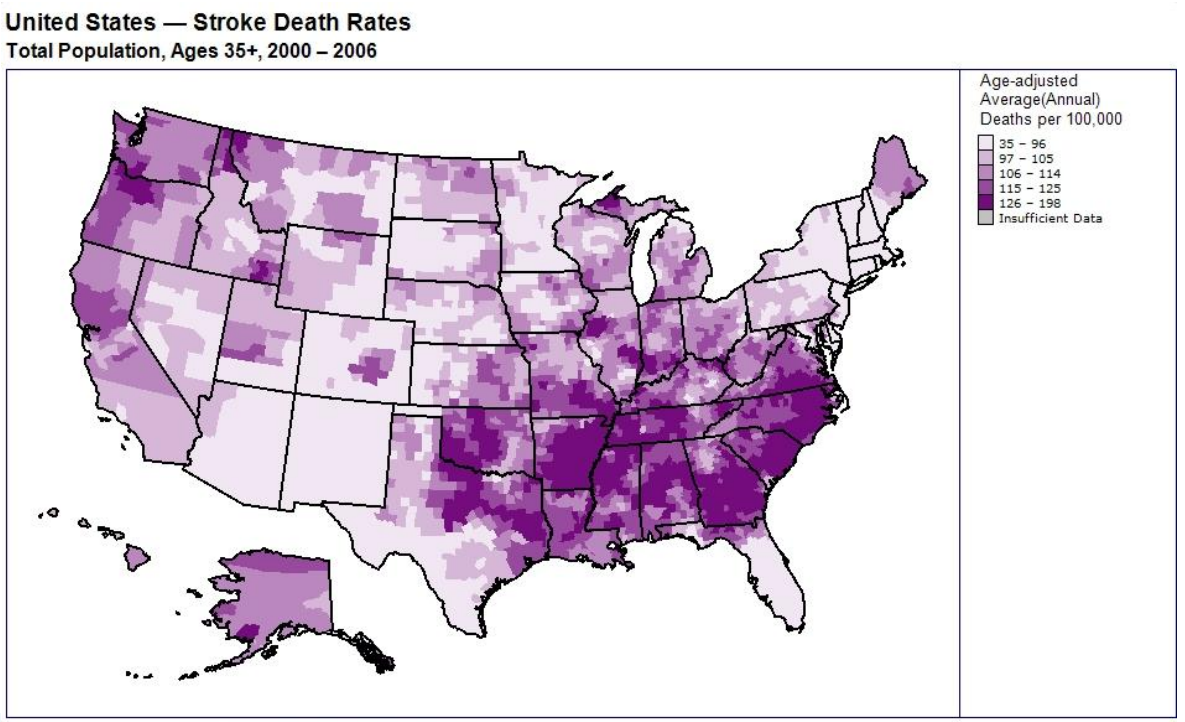
MRFIT blood pressure distribution and risk of death at 25 years follow-up

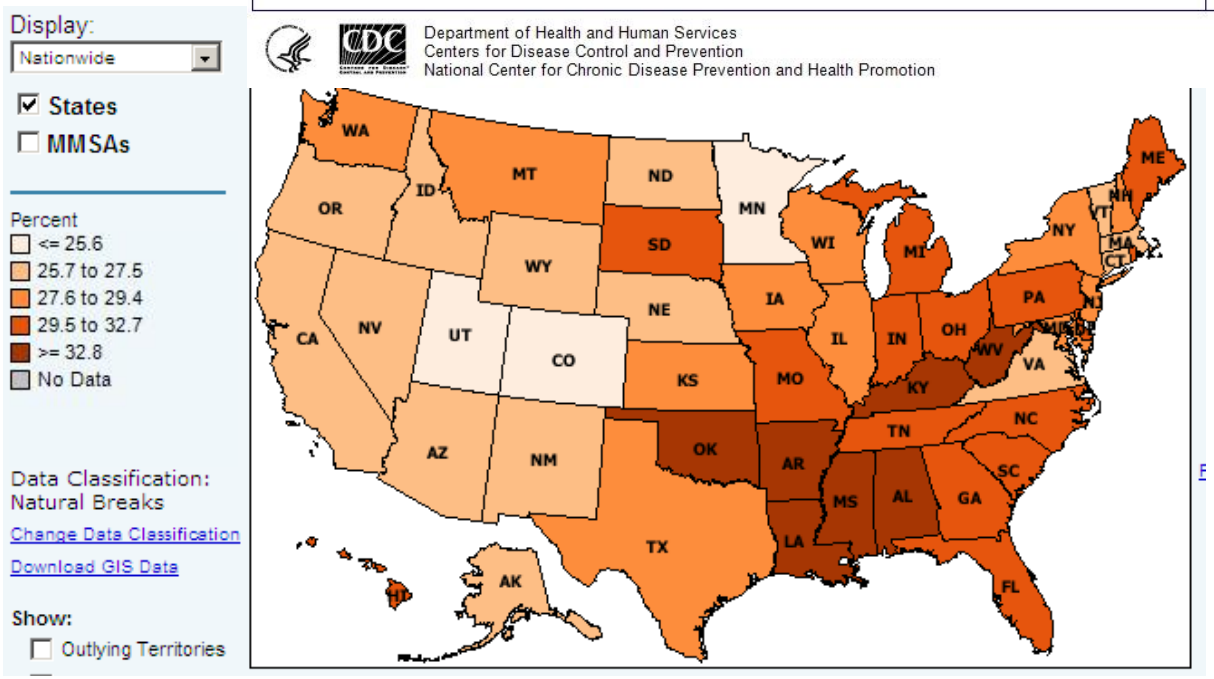


347,978 men ages 35-57 at baseline

Adapted from Elliott & Stamler 2005

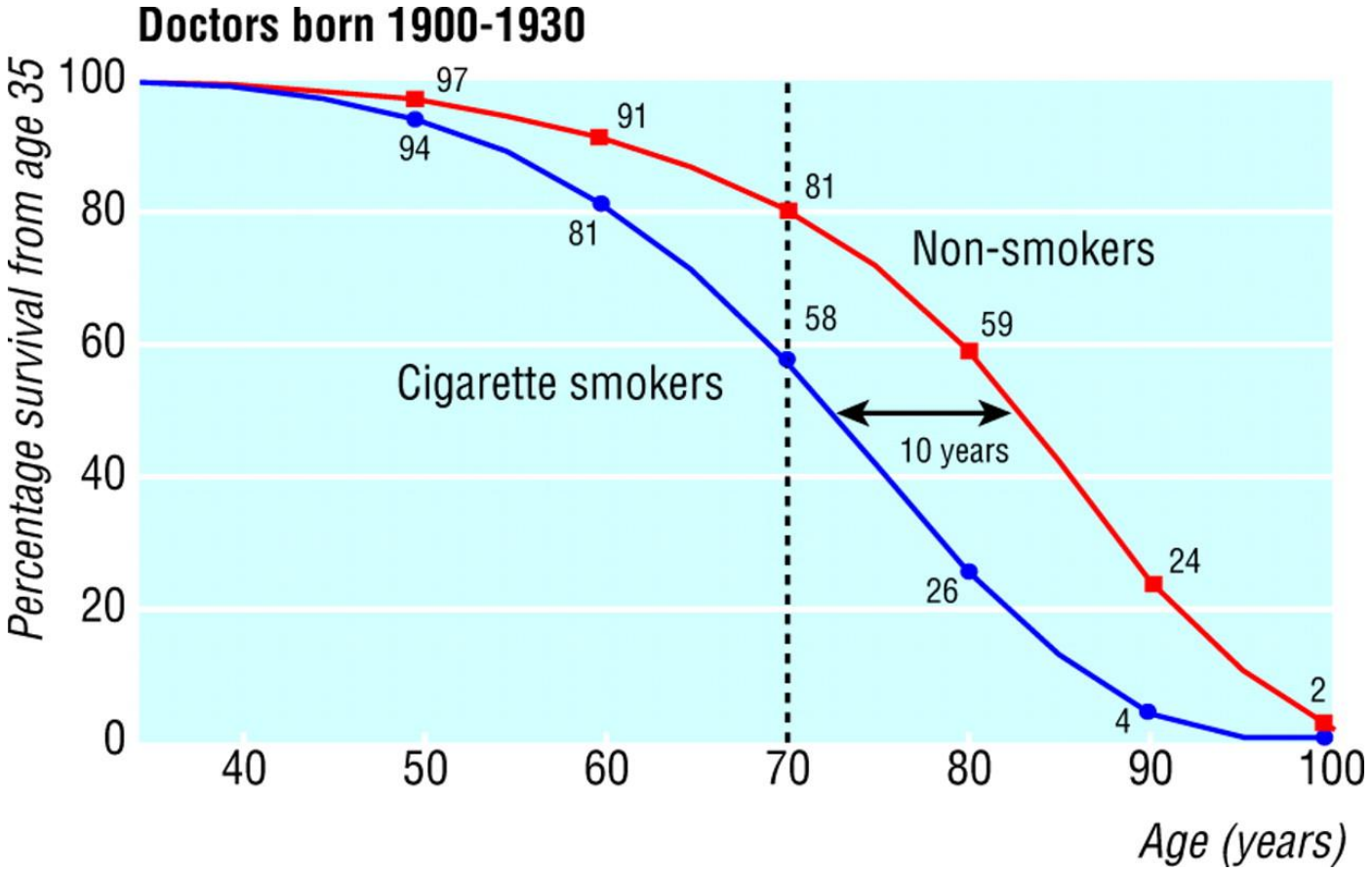
Multiple Risk Factor Intervention Trial





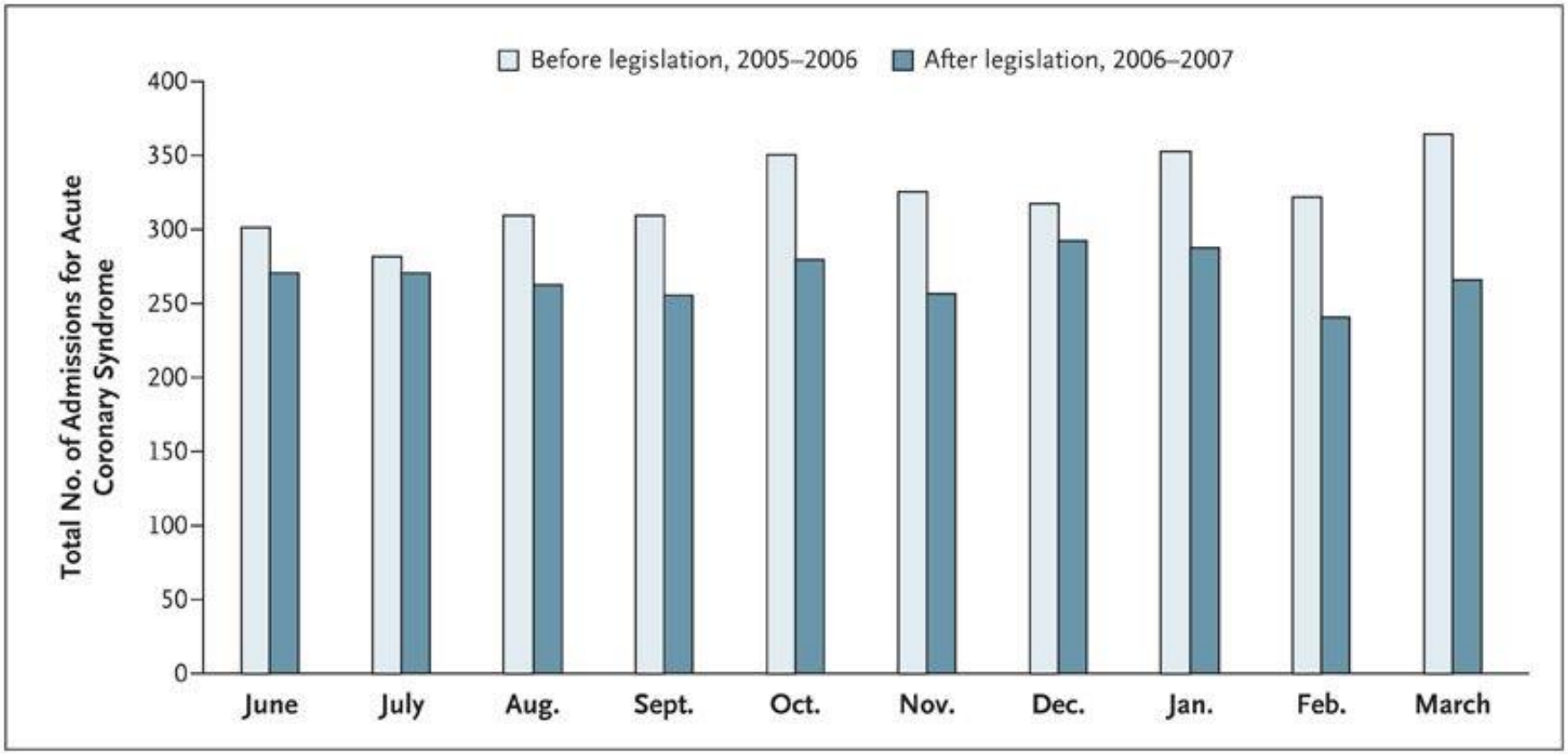
Percent reporting hypertension

Survival from age 35 for continuing cigarette smokers and lifelong non-smokers among UK male doctors born 1900-1930



Doll, R. et al. BMJ 2004;328:1519

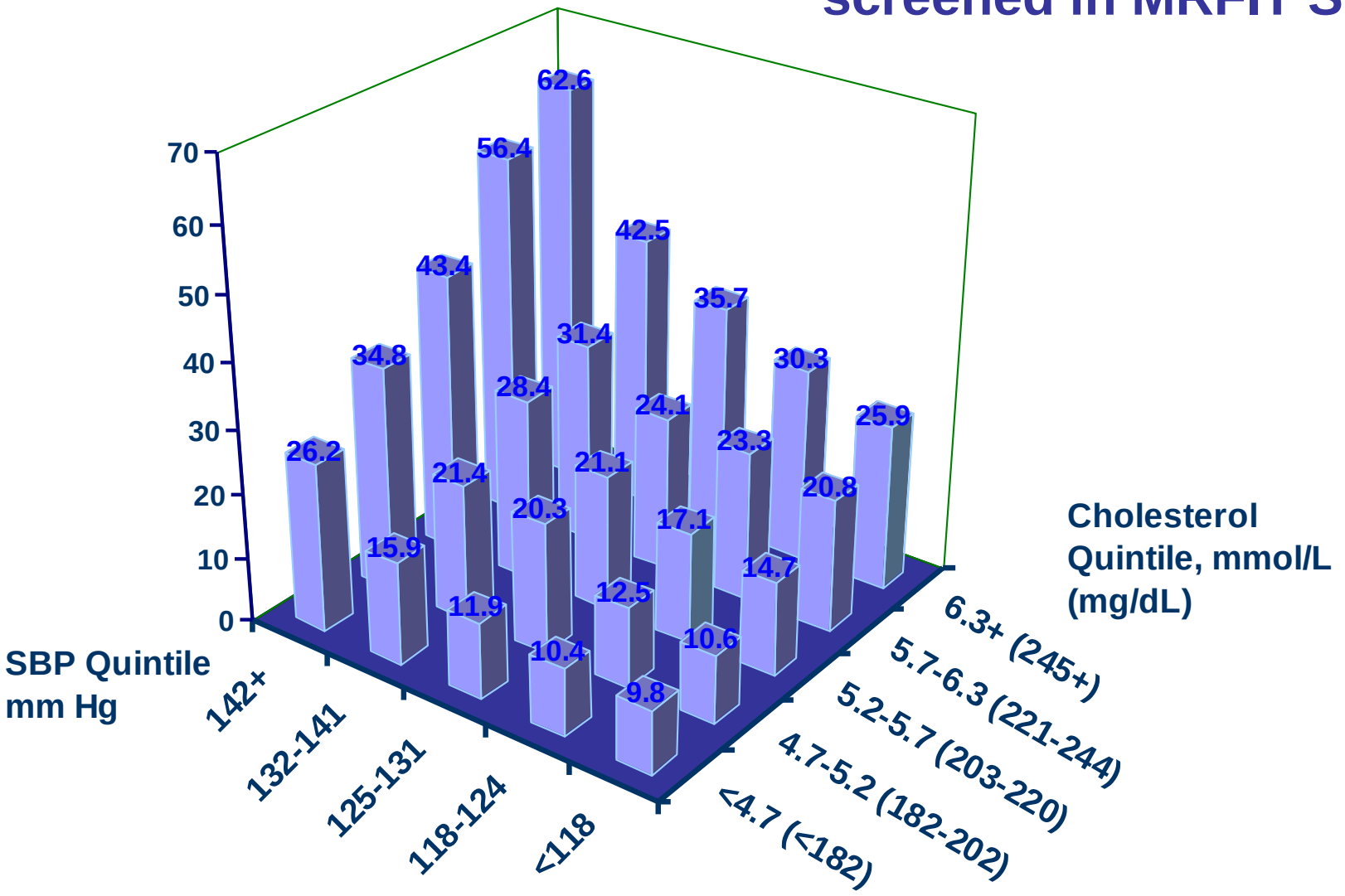
Smoking ban in Scotland



Admissions for Acute Coronary Syndrome According to Month before and after Smoke-free Legislation

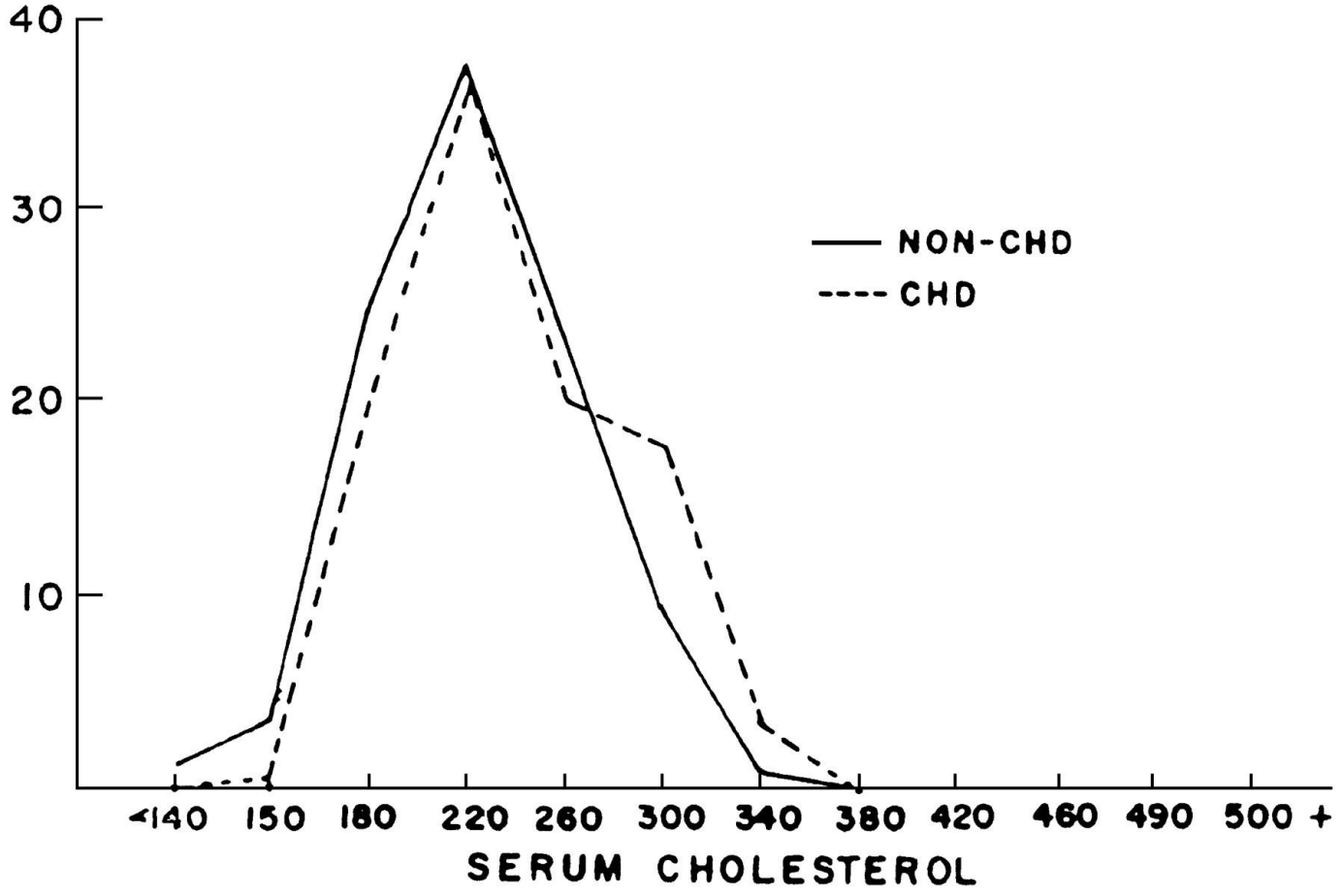
Pell J *et al. NEJM* 2008; 359:482-491

Age-adjusted CHD death rates per 10 000 person-years by level of serum cholesterol and SBP for cigarette smokers screened in MRFIT Study



Neaton JD et al. Arch Intern Med 1992; 152: 56-64

Percentage distribution of serum cholesterol levels (mg/dl) in men aged 50-62 who did or did not subsequently develop coronary heart disease (Framingham Study)



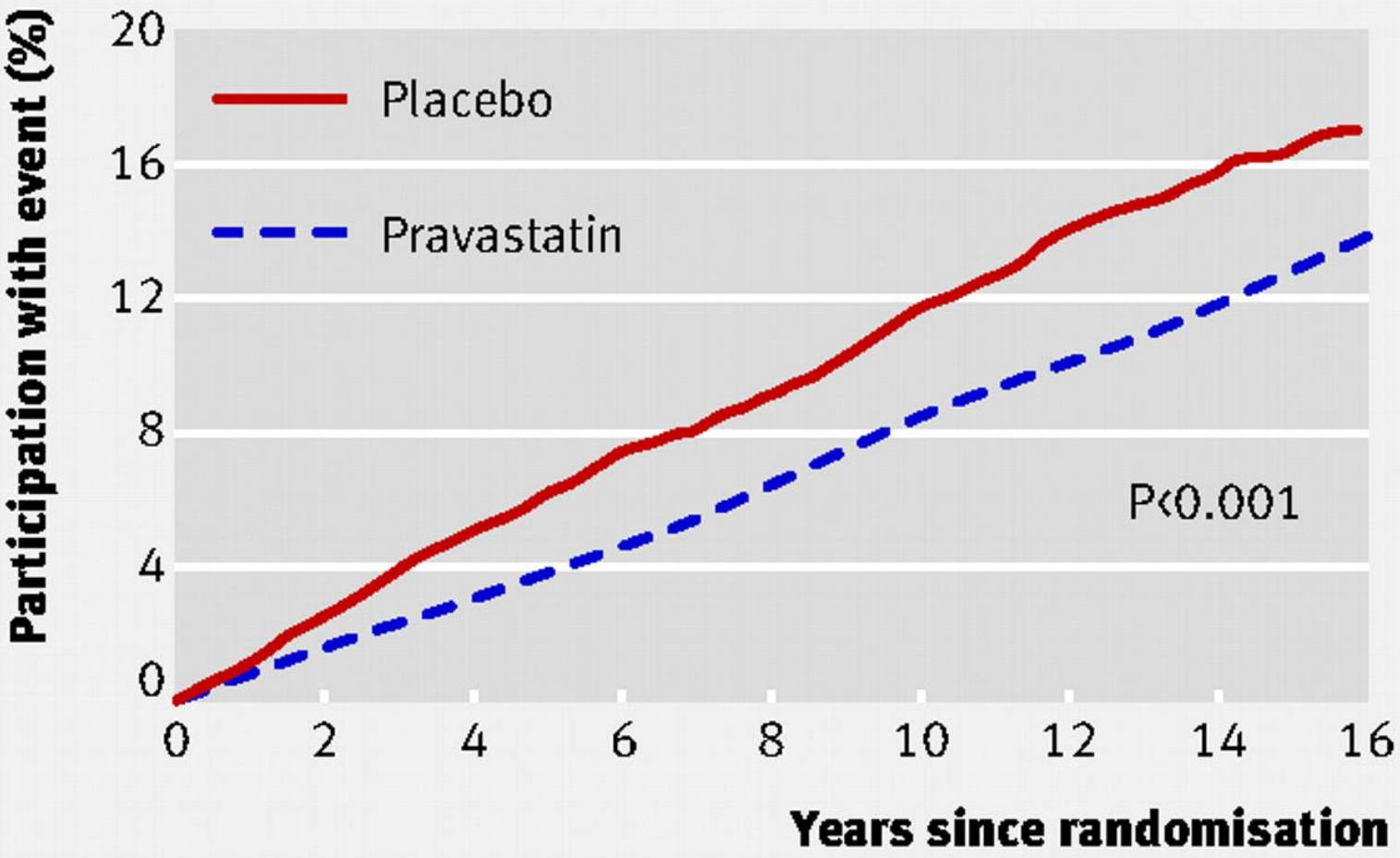
Rose, G. Int. J. Epidemiol. 1985 *Sick individuals and sick populations*

International Journal of Epidemiology

Serum Cholesterol

- Cholesterol is a good predictive marker
- Well–measured, so that a single measure characterises the population reasonably well
- Longitudinal studies show prognostic validity
- However poor ability to discriminate between cases and non-cases of heart disease

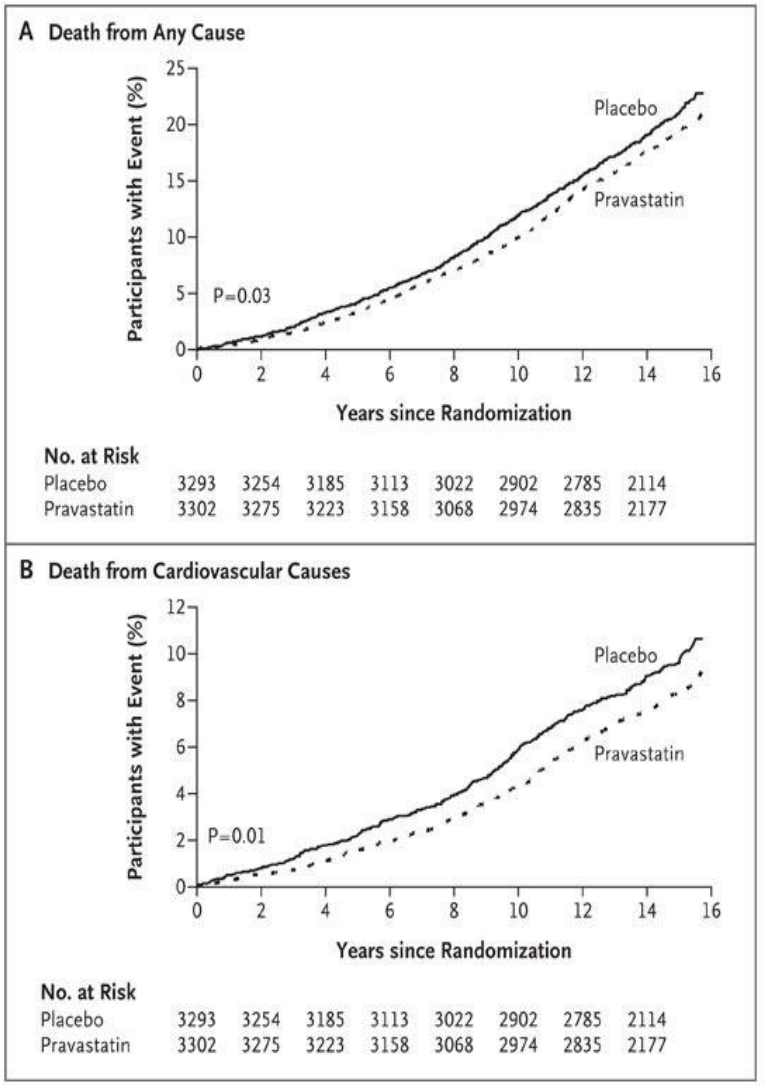
EFFECT OF PRAVASTATIN ON DEATH FROM CHD OR NON-FATAL HEART ATTACK



Adapted from *N Engl J Med* 2007;357:1477-86

Cholesterol

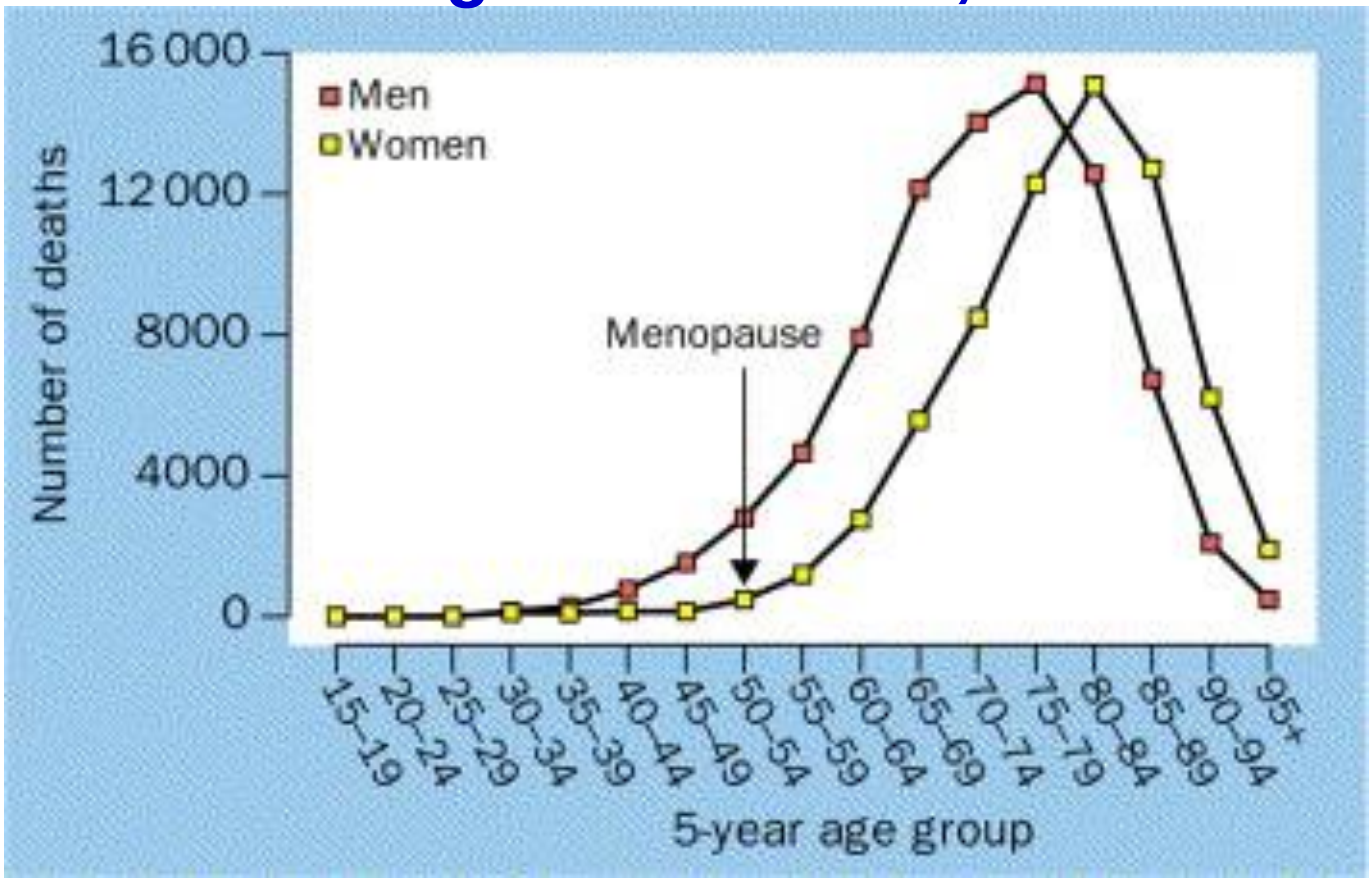
- Kaplan-Meier estimate for Deaths
- Hypercholesterolemic men (LDL > 4 mmol) with no history of myocardial infarction
- Statin treatment for an average of 5 years provided an ongoing reduction in the risk of coronary events for an additional period of up to 10 years



Ford I et al. N Engl J Med 2007;357:1477-1486

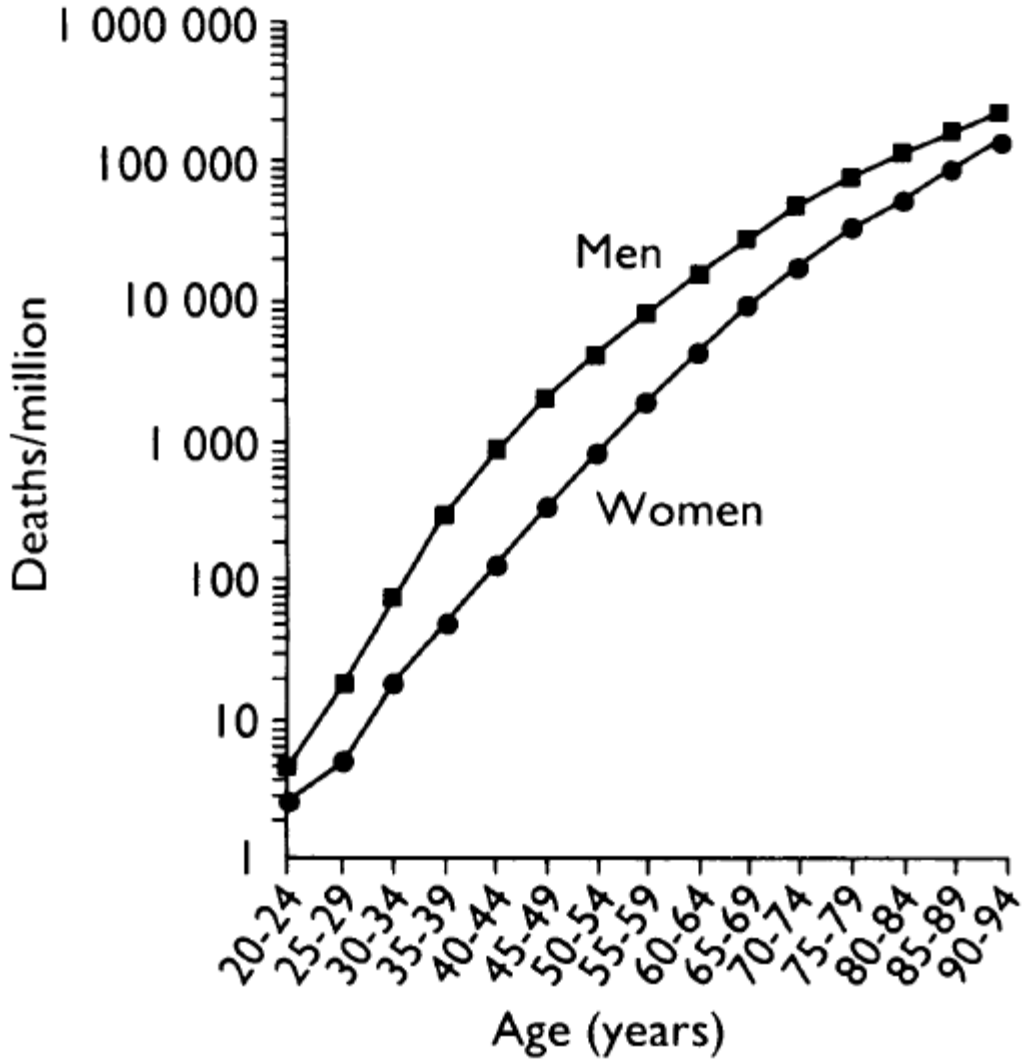
The NEW ENGLAND JOURNAL of MEDICINE

Number of deaths from CHD by age and sex in England & Wales, 1989-93



Tunstall Pedoe H. Lancet 1998

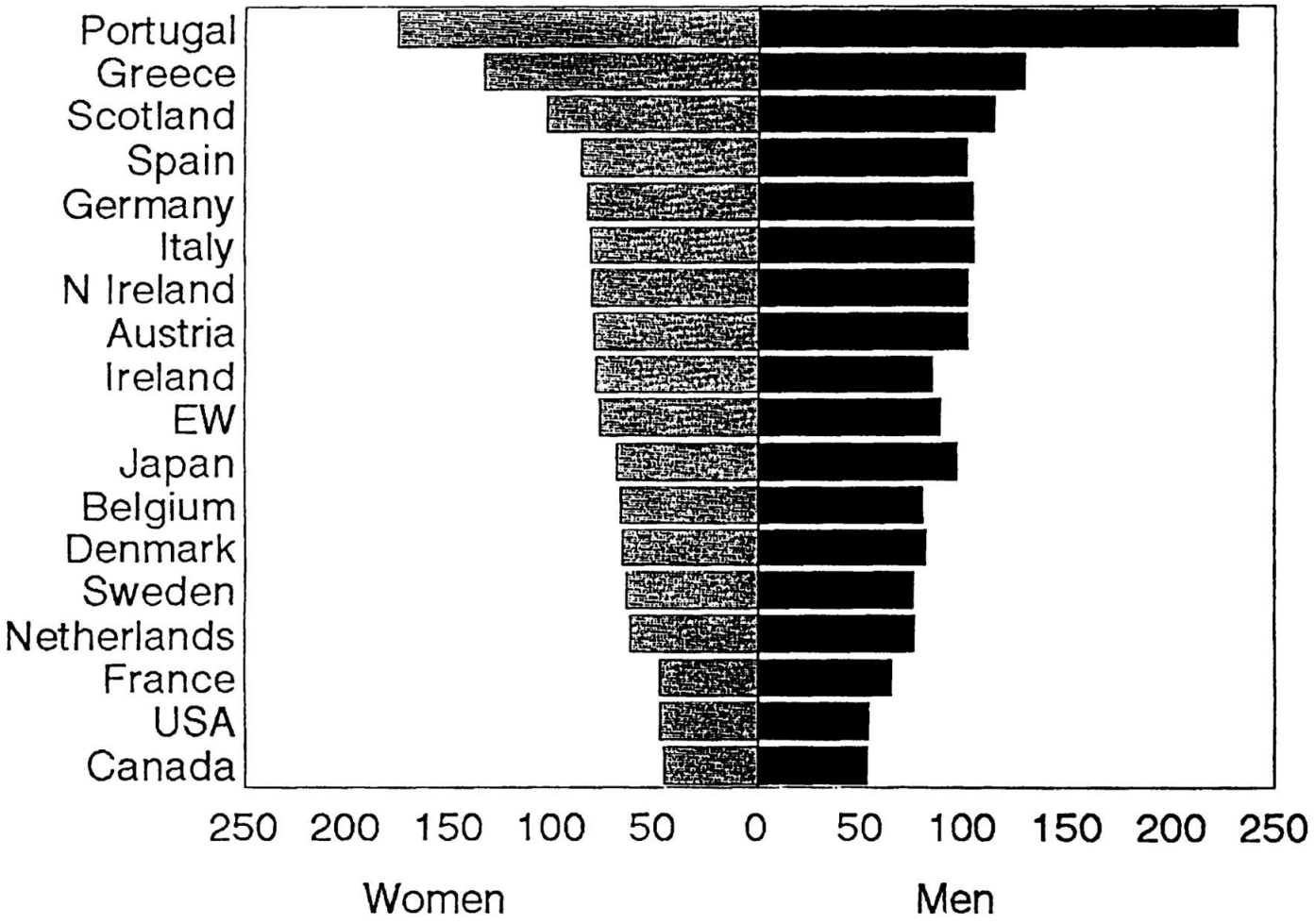
THE LANCET



Mortality from coronary heart disease by sex in England and Wales 1990

Tunstall-Pedoe h, Br Med J. 1992

International age-standardized stroke rates by sex [note:males at higher risk, review by Appelros et al 2009]

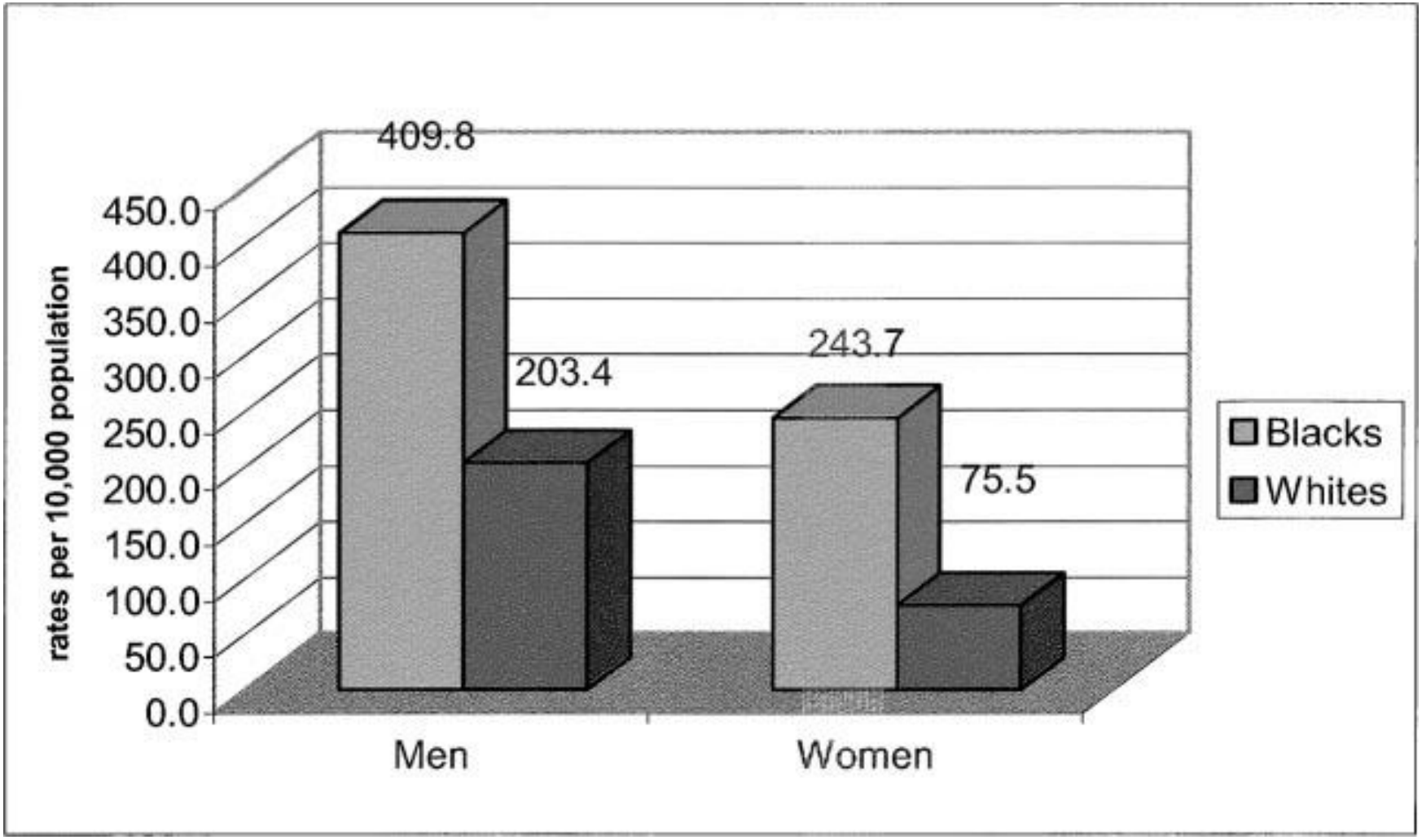


Barrett-Connor, E. Circulation 1997;95:252-264

Circulation

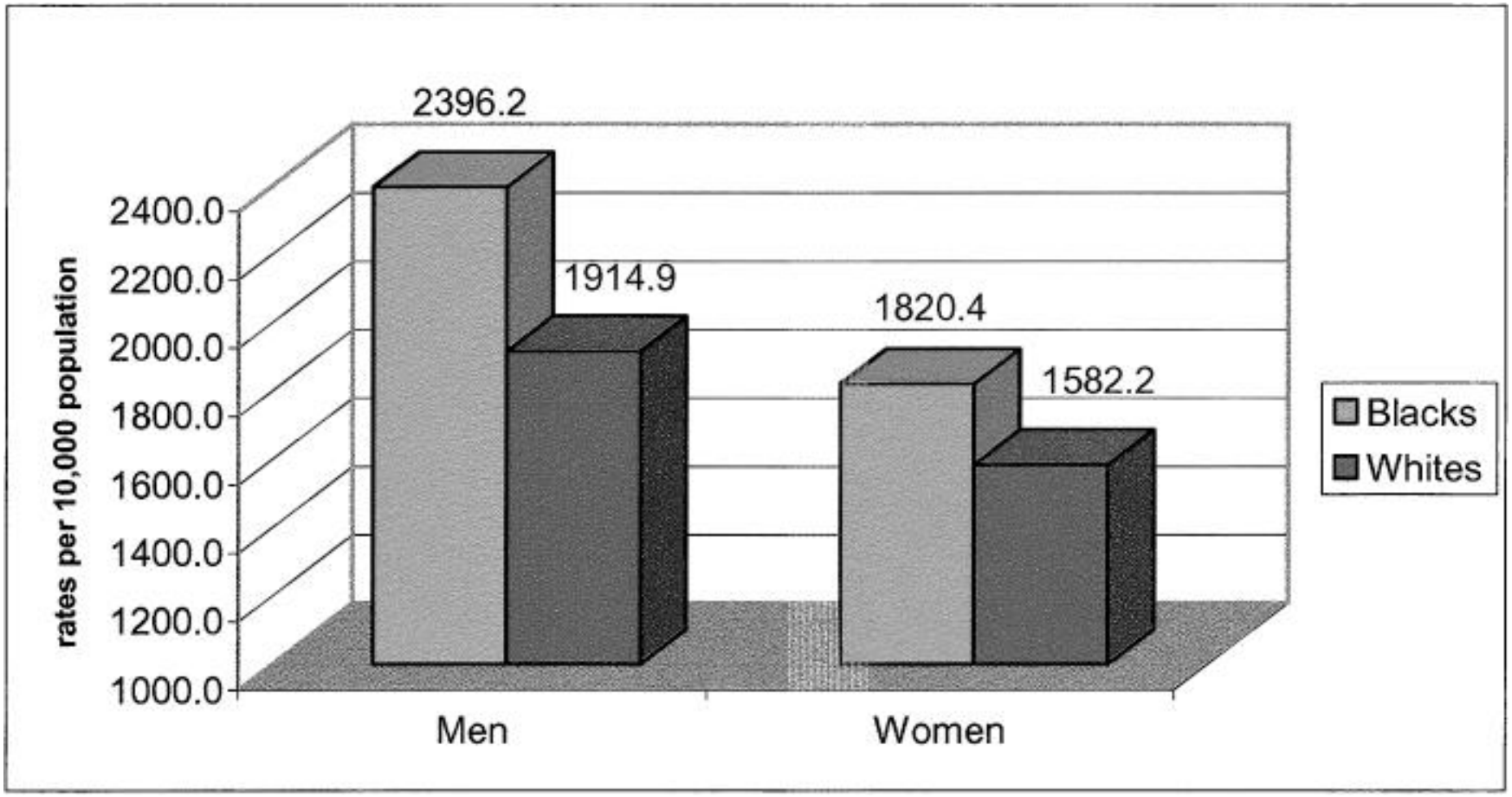
Sex difference

- Unhealthy Behaviors (cigarette smoking, heavy alcohol use, eating more red meat and fewer fruits and vegetables, and exposure to physical hazards, etc.)
- Recent studies adjusting for unhealthy behaviors show that they contribute to but do not fully explain the increased risk of CHD in men
- HDL/other lipid levels
- Role of hormones, estrogen



Race: CVD mortality rates for men and women, 45-64 years of age

Jones-Webb et al, J. Ethnicity & Disease 2004

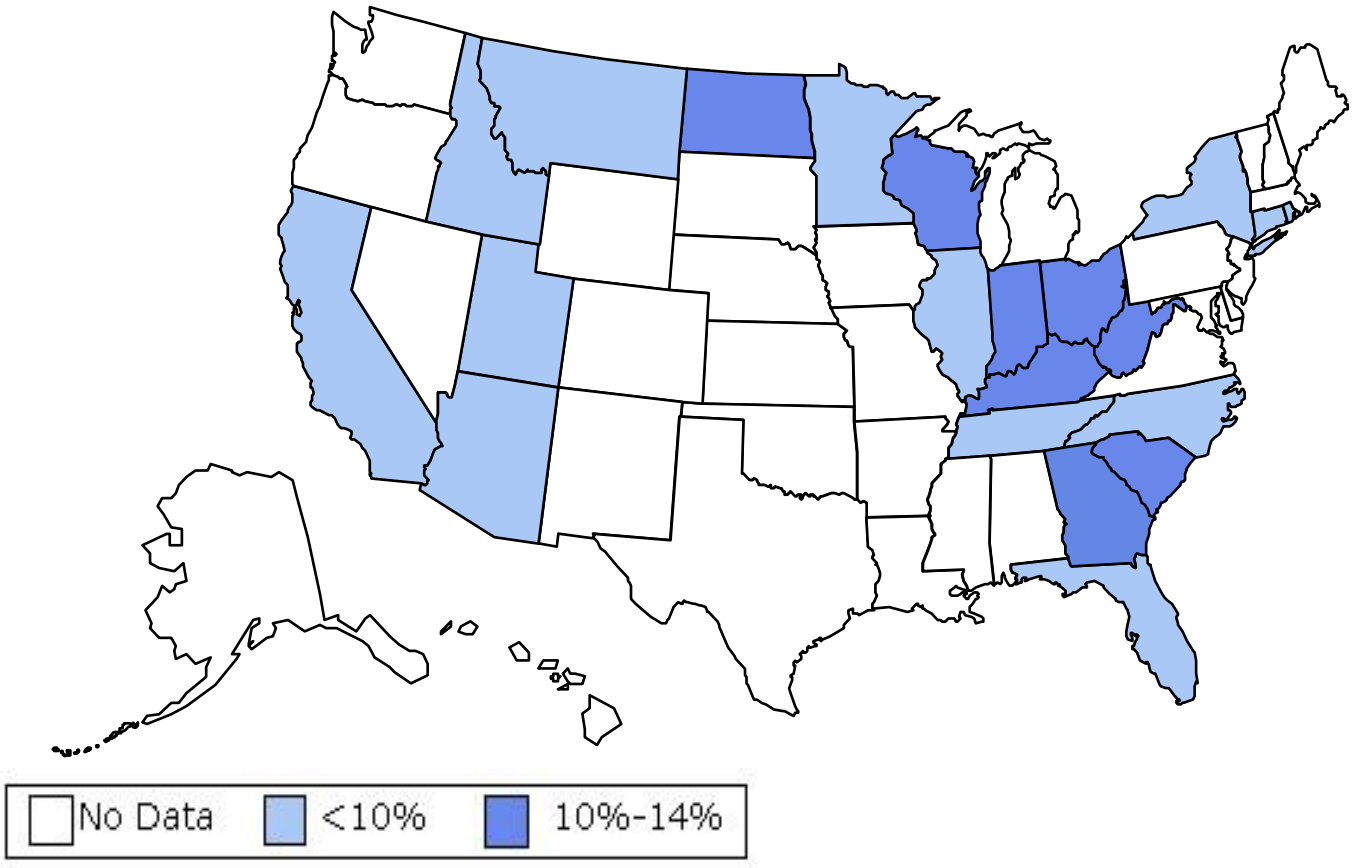


Race: CVD mortality rates for men and women, 65+ years of age

Jones-Webb et al, J. Ethnicity & Disease 2004

Obesity Trends* Among U.S. Adults
BRFSS (Behavioral Risk Factor Surveillance System), , 1985

(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)

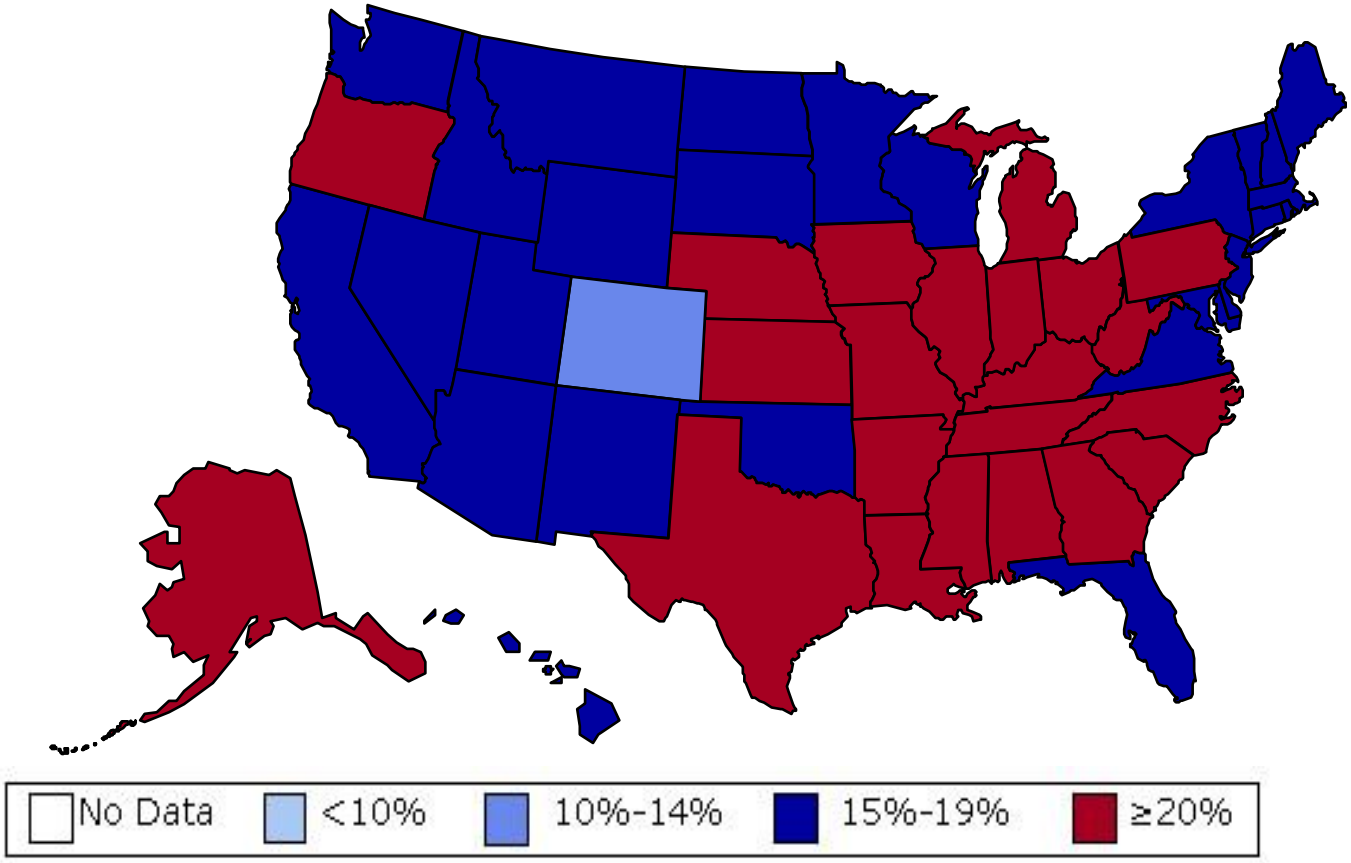


Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

Obesity Trends* Among U.S. Adults

BRFSS, 2000

(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)

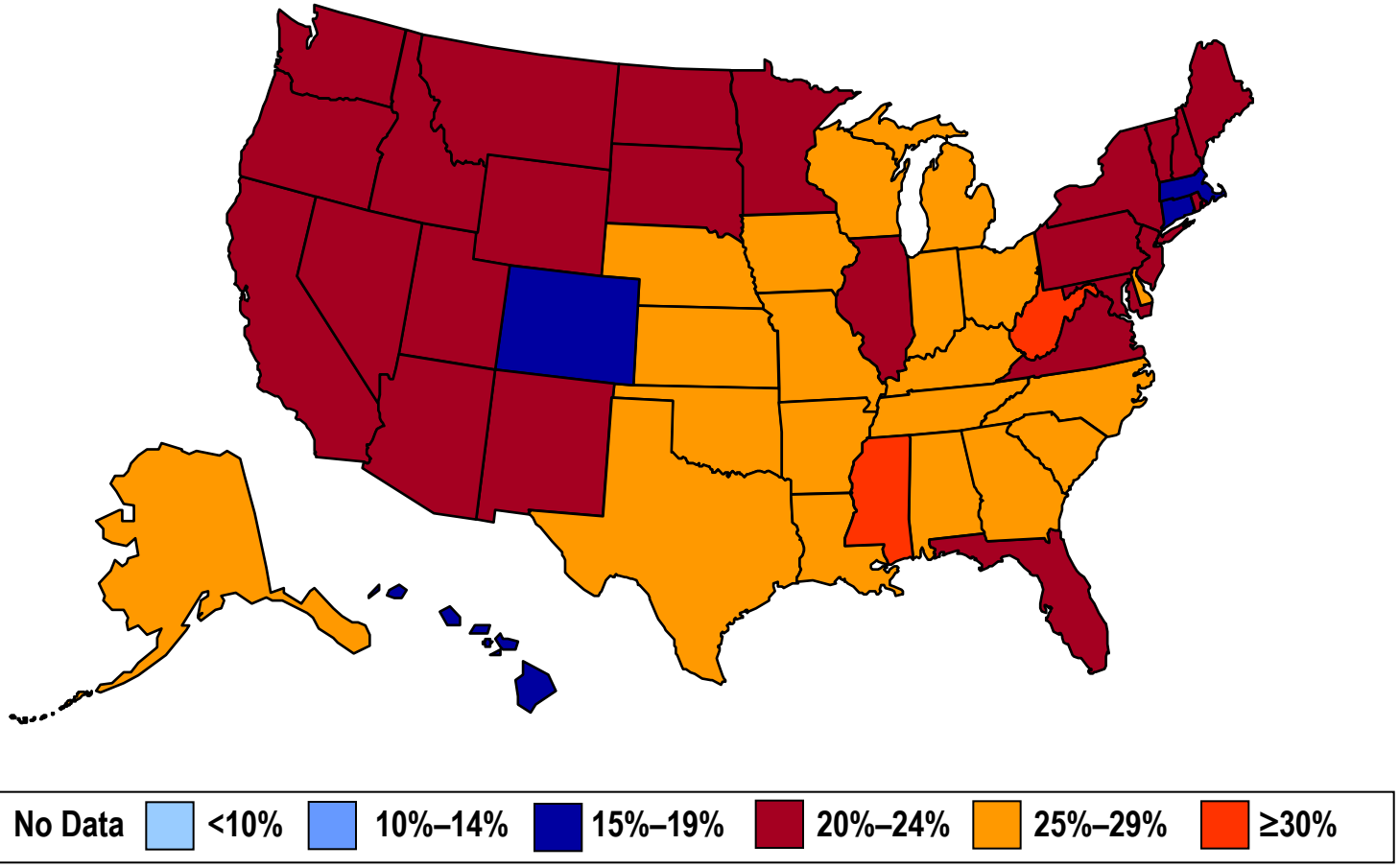


Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

Obesity Trends* Among U.S. Adults

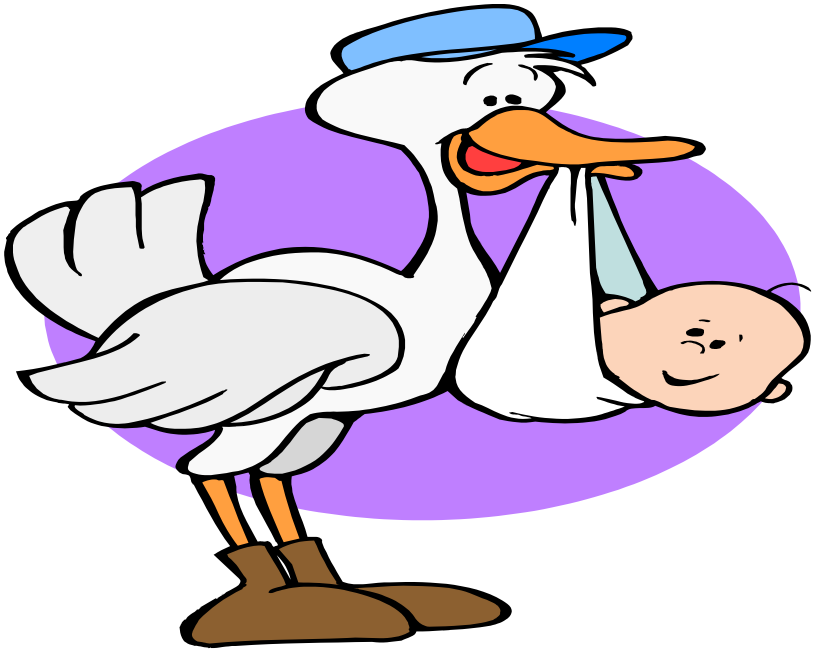
BRFSS, 2006

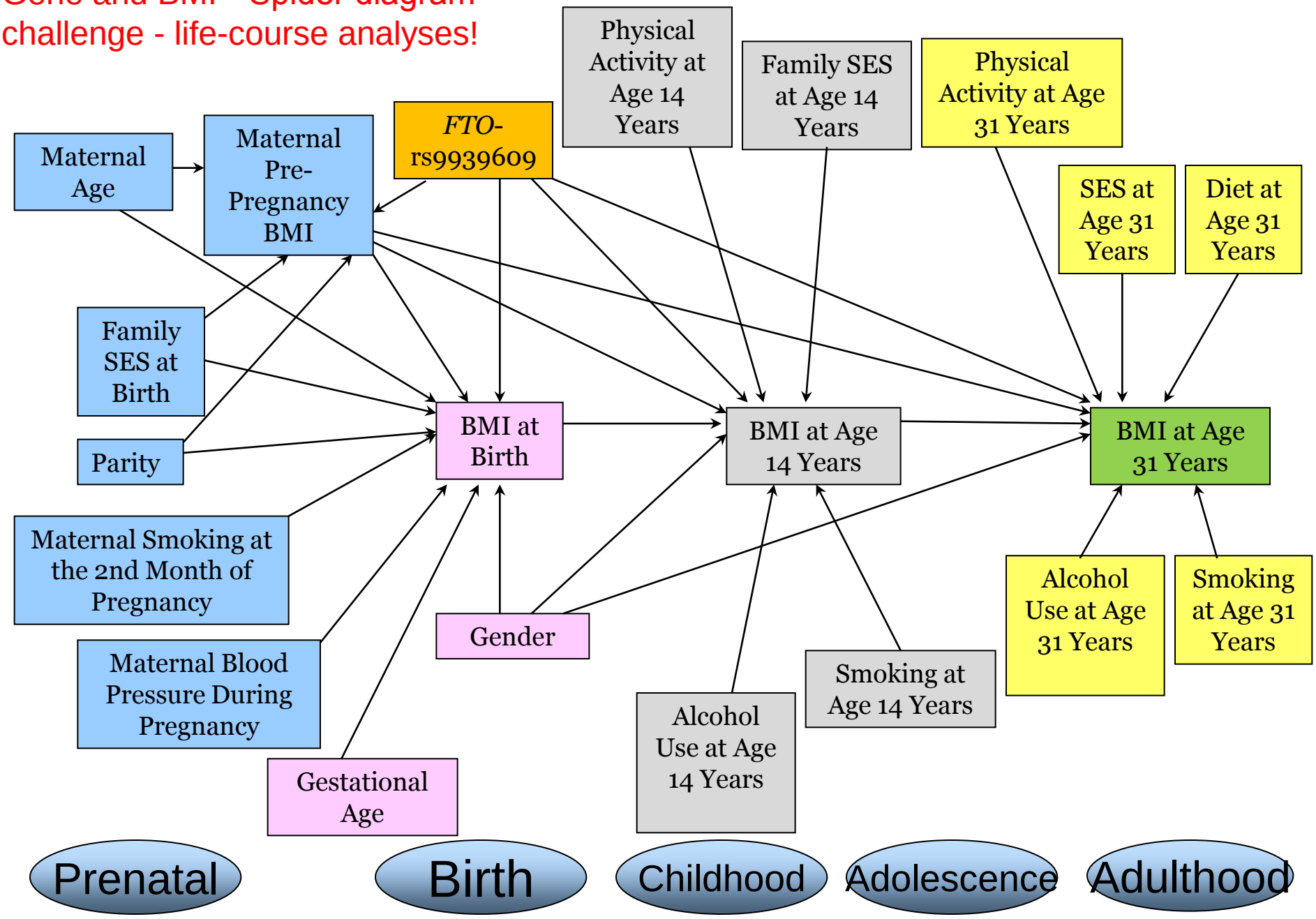
(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)



Source: CDC Behavioral Risk Factor Surveillance System

Lifecourse analyses of *FTO* – effect on body mass
Early life and CVD



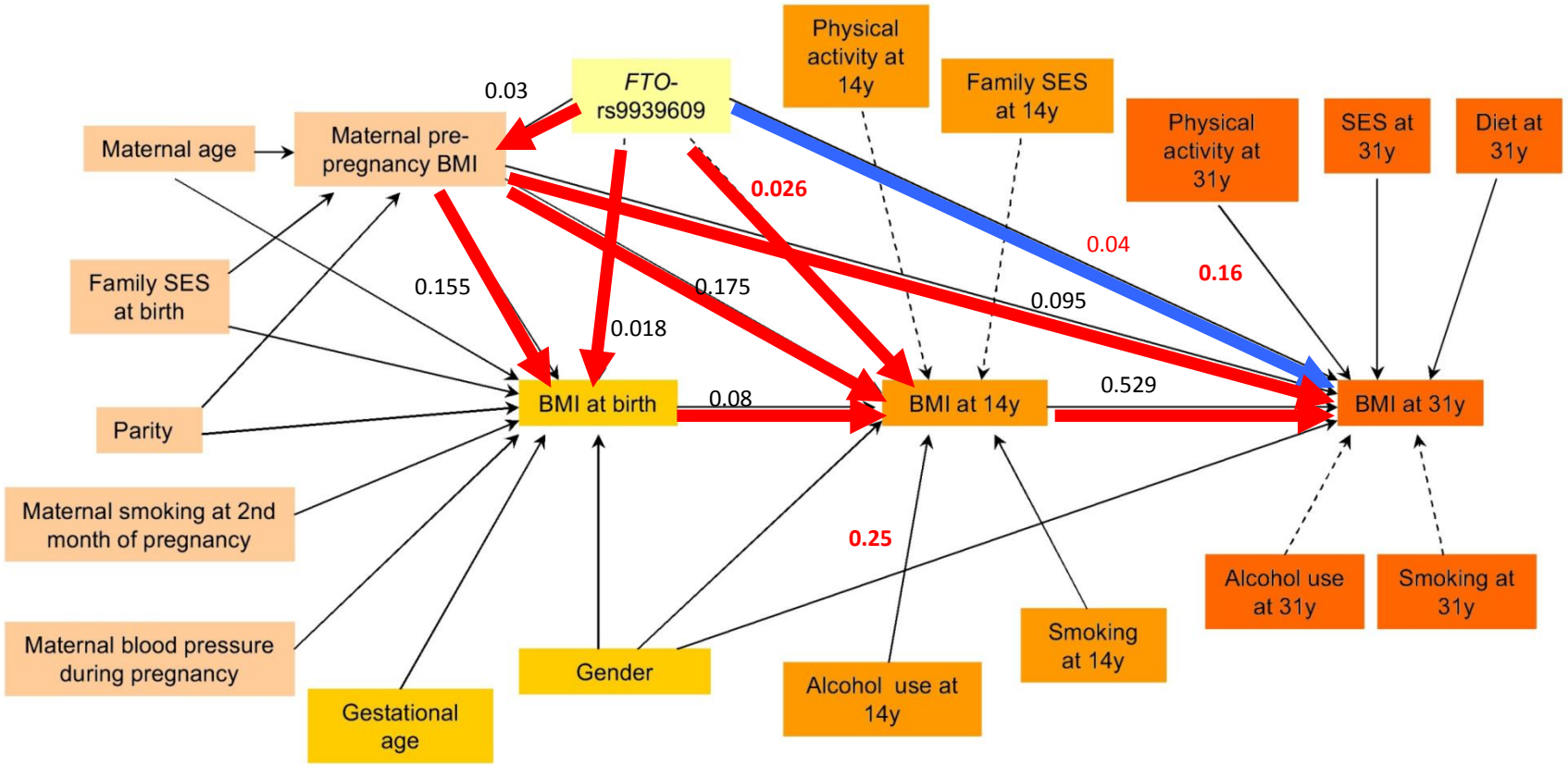

Gene and BMI- ”Spider diagram” challenge - life-course analyses!
Physical Activity at Age 14 Years
Family SES at Age 14 Years
Physical Activity at Age 31 Years
Maternal Age
Maternal Pre-Pregnancy BMI
FTO- rs9939609
SES at Age 31 Years
Diet at Age 31 Years
Family SES at Birth
Parity
BMI at Birth
BMI at Age 14 Years
BMI at Age 31 Years
Maternal Smoking at the 2nd Month of Pregnancy
Alcohol Use at Age 31 Years
Smoking at Age 31 Years
Gender
Maternal Blood Pressure During Pregnancy
Smoking at Age 14 Years
Alcohol Use at Age 14 Years
Gestational Age
Prenatal
Birth
Childhood
Adolescence
Adulthood

Structural Equation Modeling of Life Course Data in the Northern Finland Birth Cohort 1966 (submodels-> one pathway model); direct effects

Maternal pre-pregn. BMI *(first submodel, all other variables in the model)*	Standardized beta (relative importance, change in SD)	*P* value	Corresponding change in the mean level of BMI (g/m^2)	95% CI
FTO-rs9939609 (additive model, A allele =risk)	0.031	0.03	143	14.9, 279
Maternal age (years)	0.325	<0.001	157	138, 176
Parity				
nulliparous	Ref.			
1-3	0.150	<0.001	516	285, 768
>= 4	0.376	<0.001	1512	965, 2150
Socioeconomic status				
I+II professionals	Ref.			
III skilled workers	0.034	0.35	106	-111, 344
IV unskilled workers	0.088	0.04	290	11.9, 602
V farmers	0.192	<0.001	682	360, 1042

Direct, indirect and total effects of FTO on adult BMI (standardized beta values)

- **Direct effect: 0.04**
- **Indirect effects of the *FTO* variant to adult BMI:**
  - ***FTO*-mat.BMI-BMI31: 0.03*0.095=0.003**
  - ***FTO*-mat.BMI-BBMI-BMI14-BMI31: 0.03*0.155*0.08*0.529=0.002**
  - ***FTO*-BBMI-BMI14-BMI31: 0.018*0.08*0.529=0.001**
  - ***FTO*-BMI14-BMI31: 0.026*0.529=0.014**
  - **Total indirect: 0.003+0.002+0.001+0.014=0.020**
- **Total effect: 0.02+0.04=0.06**



Direct, Indirect and Total Effects of *FTO*-rs9939609 on Body Mass Index (BMI) During the Life Course in the Northern Finland Birth Cohort 1966

	Standardized b	*P* value	Corresponding change in the mean level of BMI (g/m^2)	95% CI
BMI at 31 years				
Total	**0.060**	**$5.0x10^{-5}$**	**371**	**185, 570**
Total indirect	**0.021**	**0.02**	**121**	**19.6, 227**
1) *FTO*-Mat.BMI-BMI31	0.003	0.04	17.0	1.02, 33.1
2) *FTO*-BMI14-BMI31	0.014	0.09	80.2	-13.0, 177
3) *FTO*-Mat.BMI-BMI14-BMI31	0.003	0.03	16.7	1.20, 32.2
4) *FTO*-BirthBMI-BMI14-BMI31	0.001	0.19	4.45	-2.28, 11.2
5) *FTO*-Mat.BMI-BirthBMI-BMI14-BMI31	0.000	0.05	1.19	0.02, 2.35
Direct	**0.040**	**0.001**	**239**	**89.6, 396**

Abbreviations: BMI, body mass index; CI, confidence interval., BMI log transformed

Direct, Indirect and Total Effects of *FTO*-rs9939609 on Body Mass Index (BMI) During the Life Course in the Northern Finland Birth Cohort 1966 (adjusting for all other factors). Note – SES, *physical activity*, maternal parity had large effects

Effect of *FTO*-rs99309609	*P* value	Change in the mean level of	95% CI
		BMI (g/m^2), per A-allele change	
Total	**$5.0x10^{-5}$**	**371**	**185, 570**
Total indirect (via …)	**0.02**	**121**	**19.6, 227**
Direct	**0.001**	**239**	**89.6, 396**

Abbreviations: BMI, body mass index; CI, confidence interval., BMI log transformed

Key findings:

- **No mediating effects of the *FTO* variant through behavioural factors**

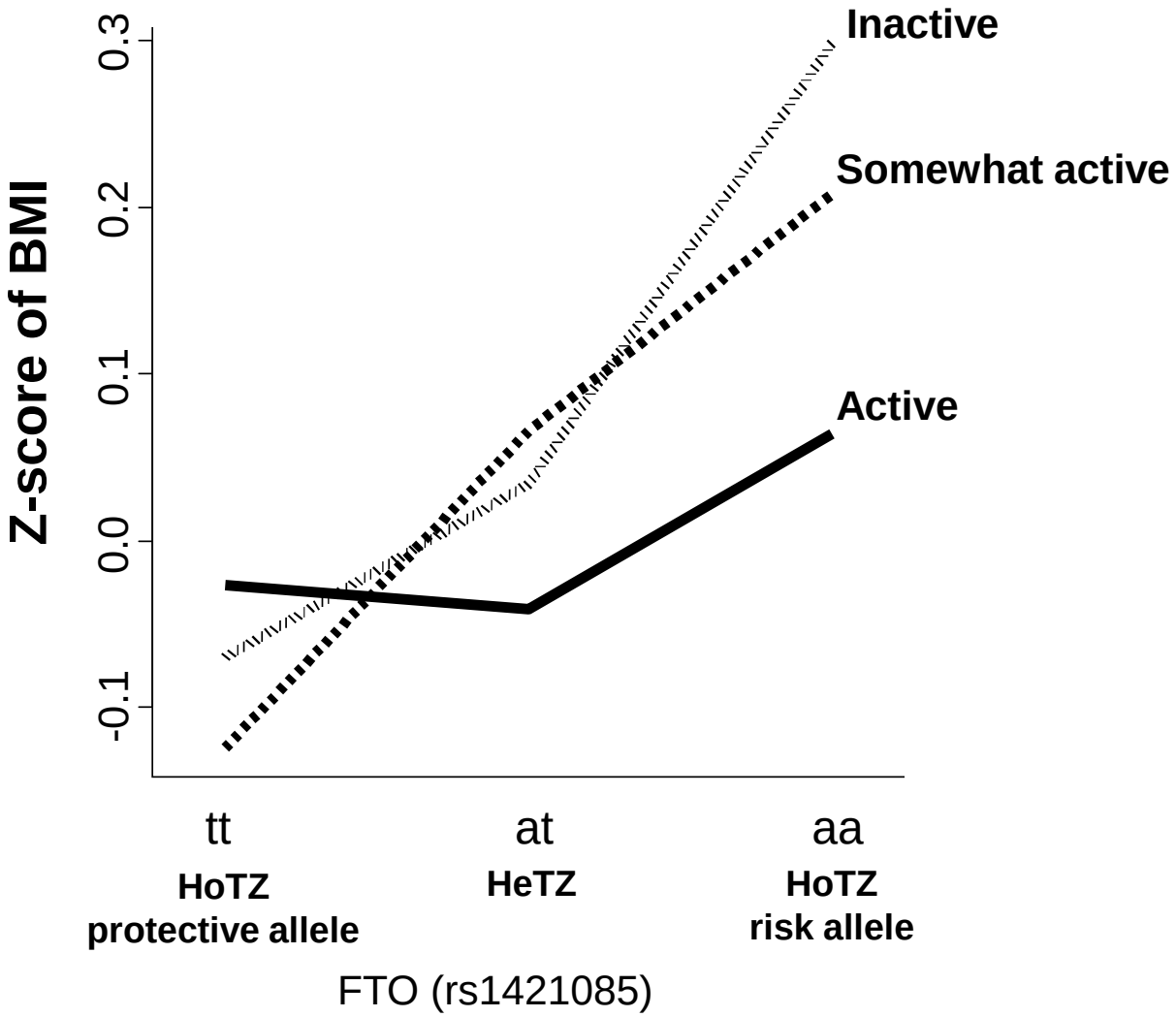
  - reflects the difficulties in measurement of behavioural factors (importance of high quality phenotype data)

  BUT STILL..

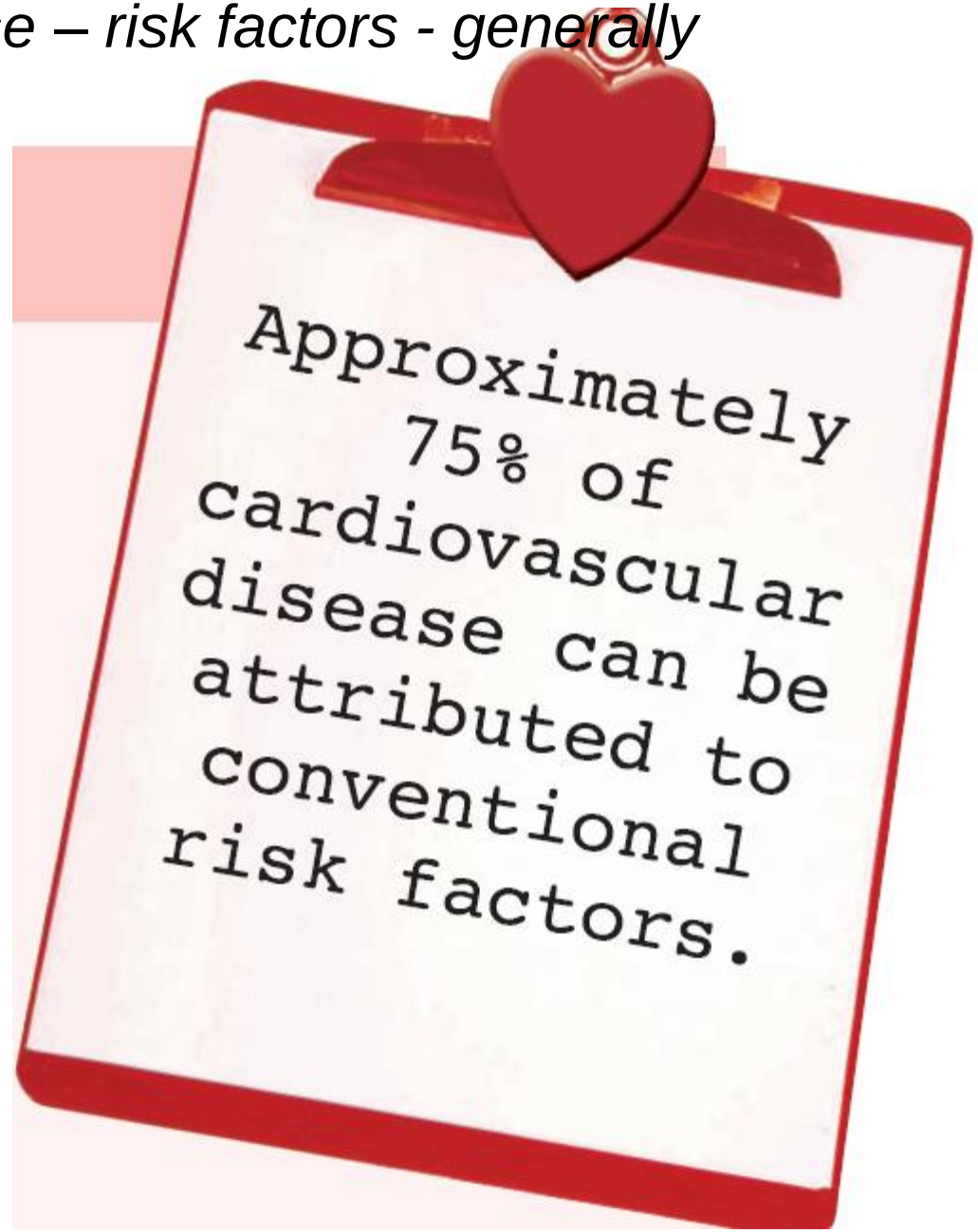
- **Many life-course factors such as physical activity (!), diet, SES in spite of not showing mediation, had a strong independent effect on BMI**
- **Mediation through earlier BMI development (1/3 of the total effect) was observed which highlights the importance of EARLY PREVENTION**
- **HOWEVER effect was not fully mediated via earlier BMI development (a direct effect persisted), indicating that the variant continues to function actively over the LATER LIFE course as well**
- Kaakinen et al, AJE, 2010

Interaction of *FTO* with physical activity on the *Z*-score of BMI at 16 years of age (*P* = 0.008) (Cauchi et al 2008).

Physical activity: 1: inactive (less than 1 hour a week); 2: somewhat active (1-3 hours a week); 3: active (4 or more hours per week).



To summarise – risk factors - generally



Major modifiable risk factors

- **High blood pressure**
  Major risk for heart attack and the most important risk factor for stroke.
- **Abnormal blood lipids**
  High total cholesterol, LDL-cholesterol and triglyceride levels, and low levels of HDL-cholesterol increase risk of coronary heart disease and ischaemic stroke.
- **Tobacco use**
  Increases risks of cardiovascular disease, especially in people who started young, and heavy smokers. Passive smoking an additional risk.
- **Physical inactivity**
  Increases risk of heart disease and stroke by 50%.

Major modifiable risk factors

- **Obesity**

  Major risk for coronary heart disease and diabetes.

- **Unhealthy diets**

  Low fruit and vegetable intake is estimated to cause about 31% of coronary heart disease and 11% of stroke worldwide; high saturated fat intake increases the risk of heart disease and stroke through its effect on blood lipids and thrombosis.

- **Diabetes mellitus**

  Major risk for coronary heart disease and stroke.

Other modifiable risk factors

- **Low socioeconomic status (SES)**
  Consistent inverse relationship with risk of heart disease and stroke.
- **Mental ill-health**
  Depression is associated with an increased risk of coronary heart disease.
- **Psychosocial stress**
  Chronic life stress, social isolation and anxiety increase the risk of heart disease and stroke.
- **Alcohol use**
  One to two drinks per day may lead to a 30% reduction in heart disease, but heavy drinking damages the heart muscle.

Other modifiable risk factors

- **Use of certain medication**

  Some oral contraceptives and hormone replacement therapy increase risk of heart disease.
- **Lipoprotein(a)**

  Increases risk of heart attacks especially in presence of high LDL-cholesterol.
- **Left ventricular hypertrophy (LVH)**

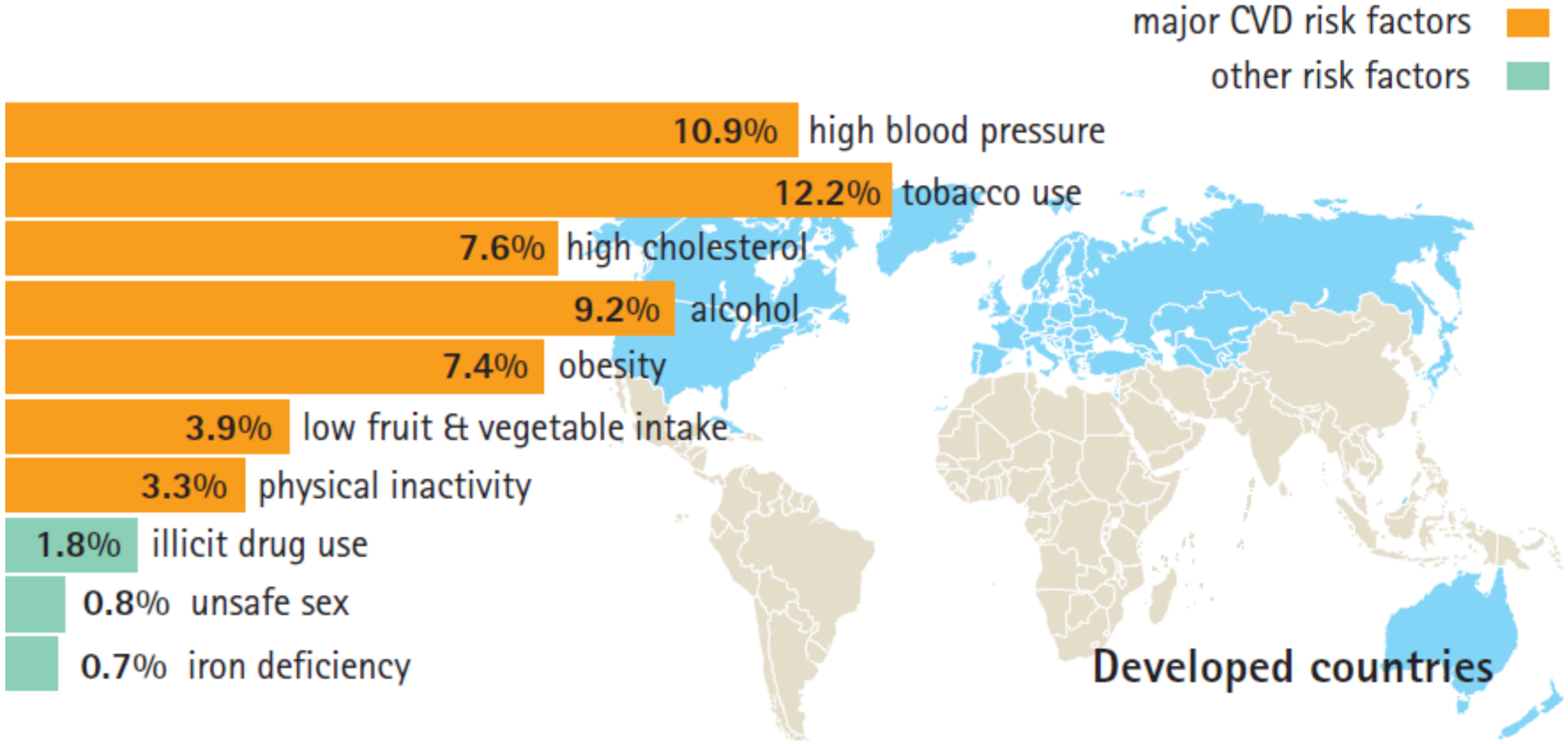
  A powerful marker of cardiovascular death.

Non-modifiable risk factors

- **Advancing age**
  Most powerful independent risk factor for cardiovascular disease; risk of stroke doubles every decade after age 55.
- **Heredity or family history**
  Increased risk if a first-degree blood relative has had coronary heart disease or stroke before the age of 55 years (for a male relative) or 65 years (for a female relative).
- **Gender**
  Higher rates of coronary heart disease among men compared with women (premenopausal age); risk of stroke is similar for men and women.
- **Ethnicity or race**
  Increased stroke noted for Blacks, some Hispanic Americans, Chinese, and Japanese populations. Increased cardiovascular disease deaths noted for South Asians and American Blacks in comparison with Whites.

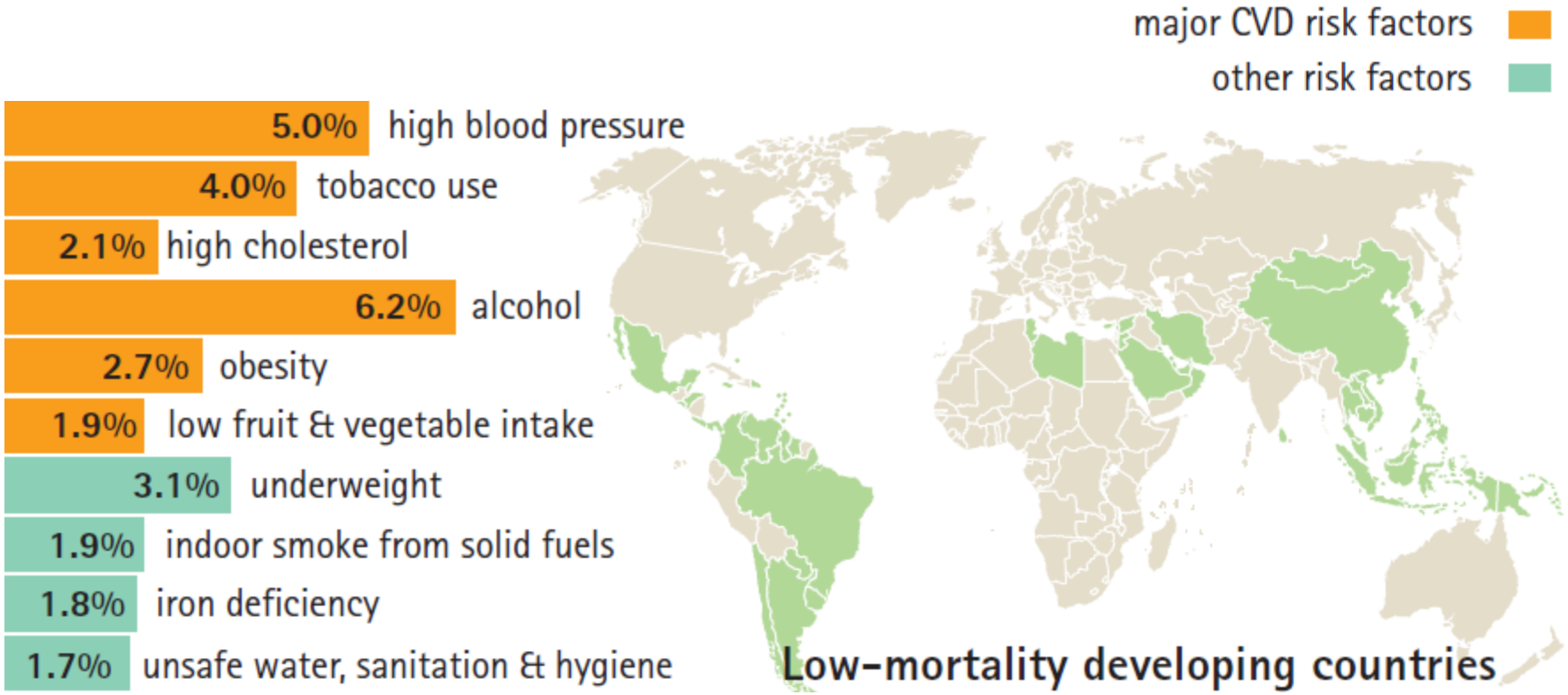
"Novel" risk factors

- **Excess homocysteine in blood**
  High levels may be associated with an increase in cardiovascular risk.
- **Inflammation**
  Several inflammatory markers are associated with increased cardiovascular risk, e.g. elevated C-reactive protein (CRP).
- **Abnormal blood coagulation**
  Elevated blood levels of fibrinogen and other markers of blood clotting increase the risk of cardiovascular complications.



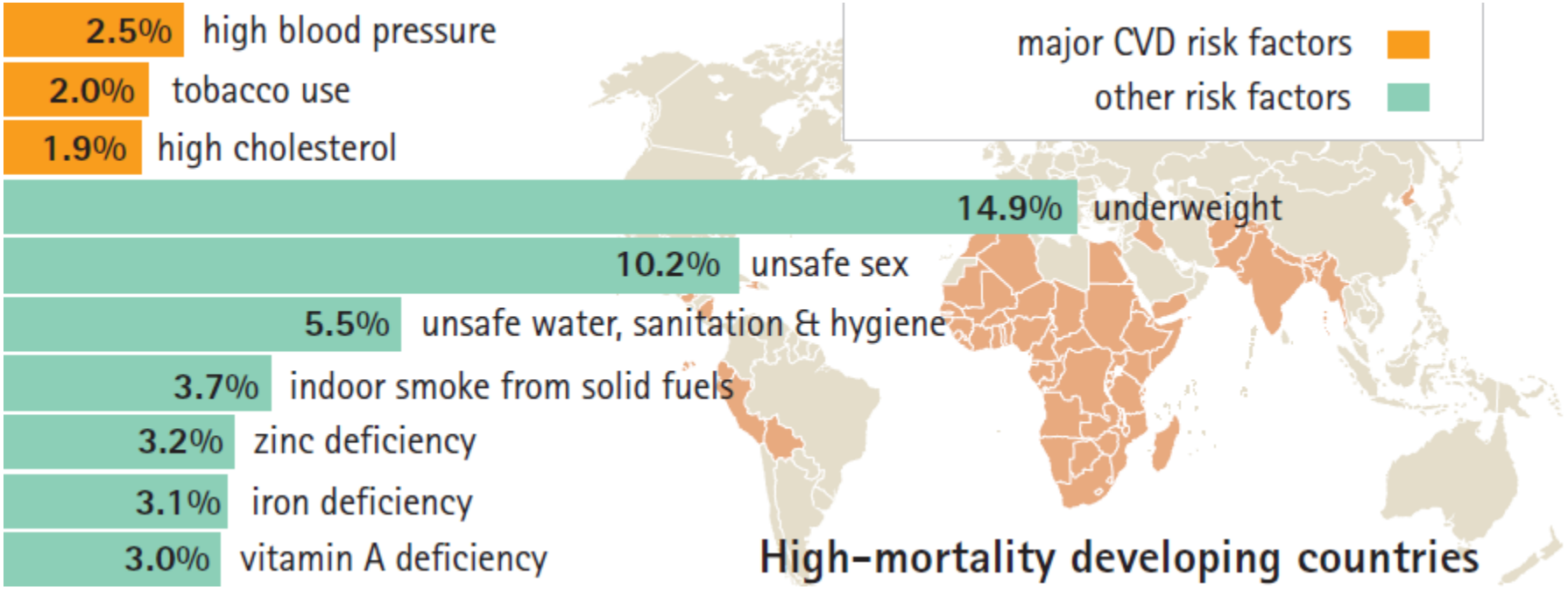
Leading risk factors As percentage burden of all diseases

WHO report, 2002



Leading risk factors As percentage burden of all diseases

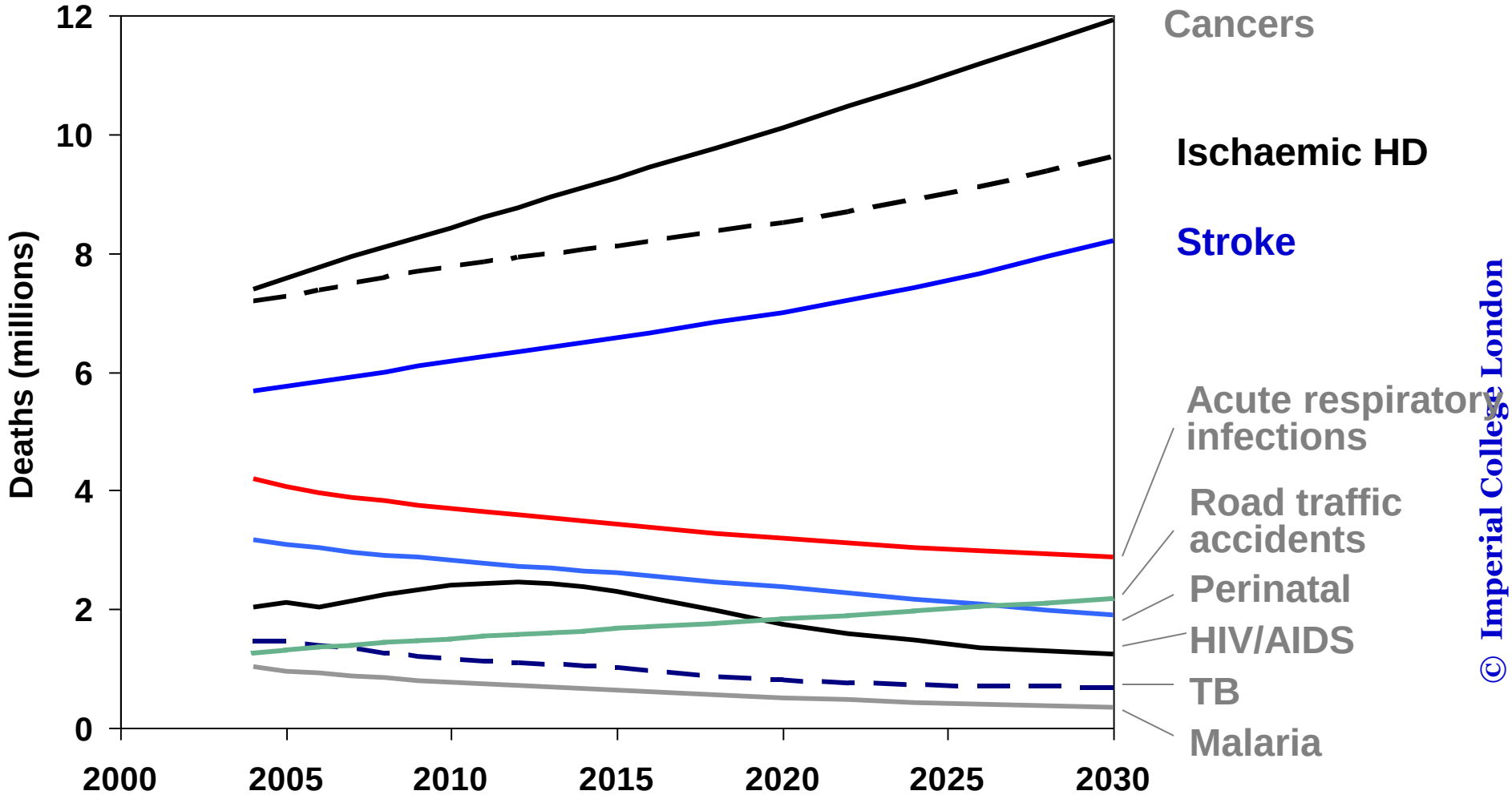
WHO report, 2002



Leading risk factors As percentage burden of all diseases

WHO report, 2002

Global projections for selected causes, 2004 to 2030



Updated from Mathers and Loncar, PLoS Medicine, 2006

WHO report, Causes of death 2004

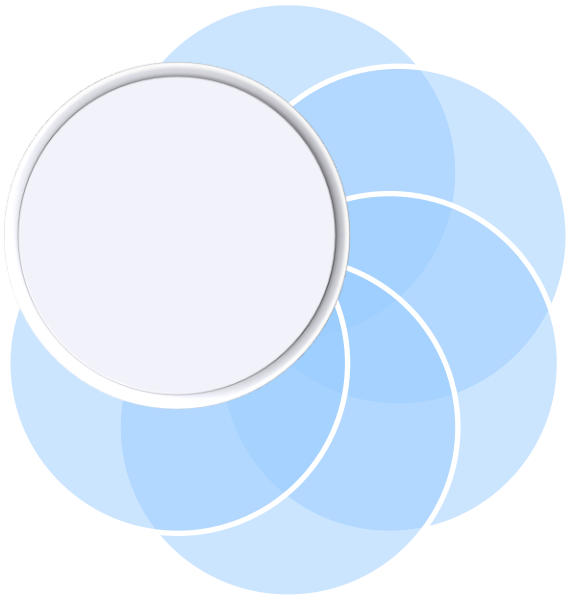
Global Health & CVD

Why Prevention Strategies

-Major course of premature death

-Atherosclerosis develops slowly

- Many preventable risk factors/risk factor modification -> mortality decreases

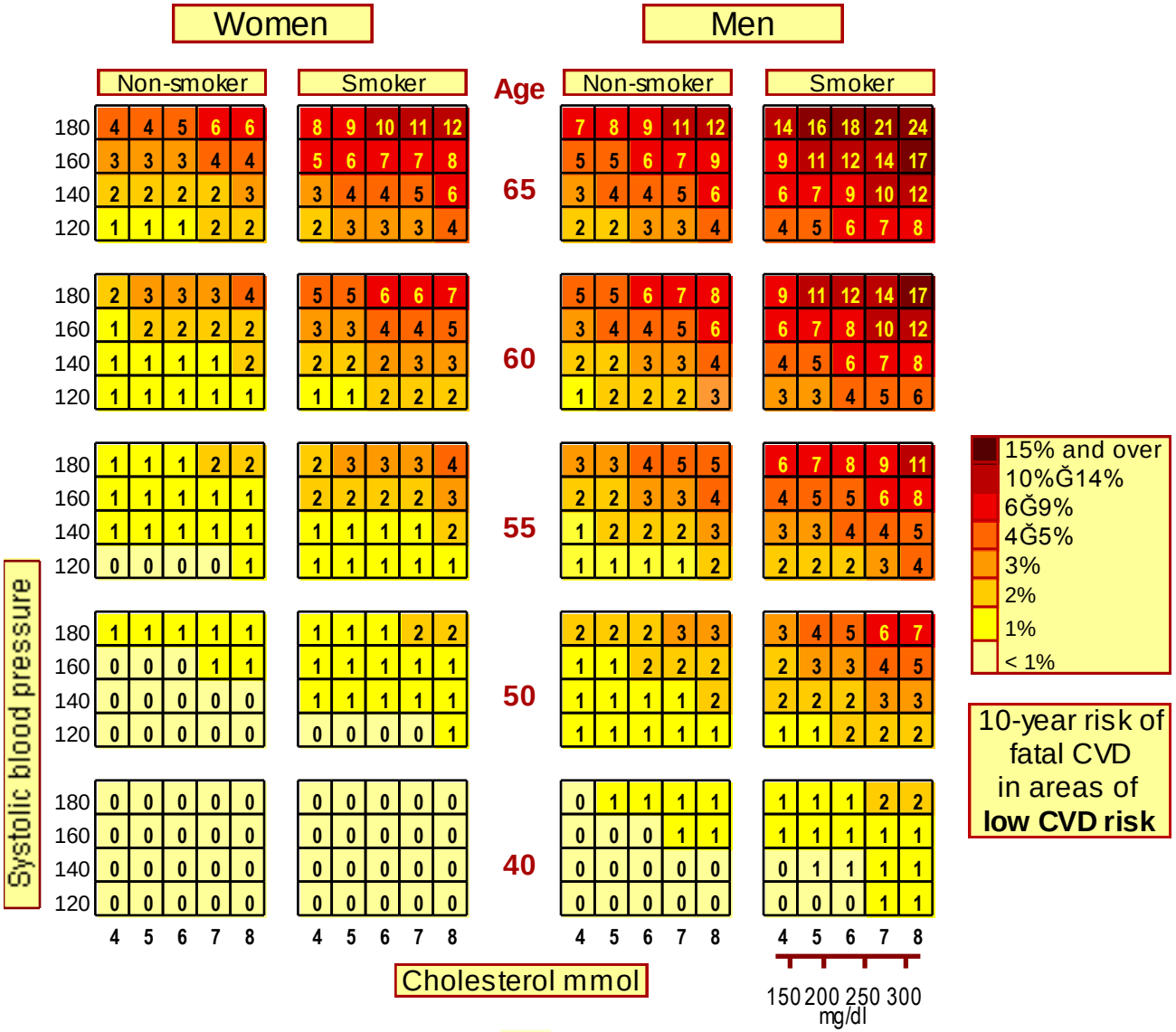


Epidemiologic Transition

Systematic COronary Risk Evaluation (**SCORE**)

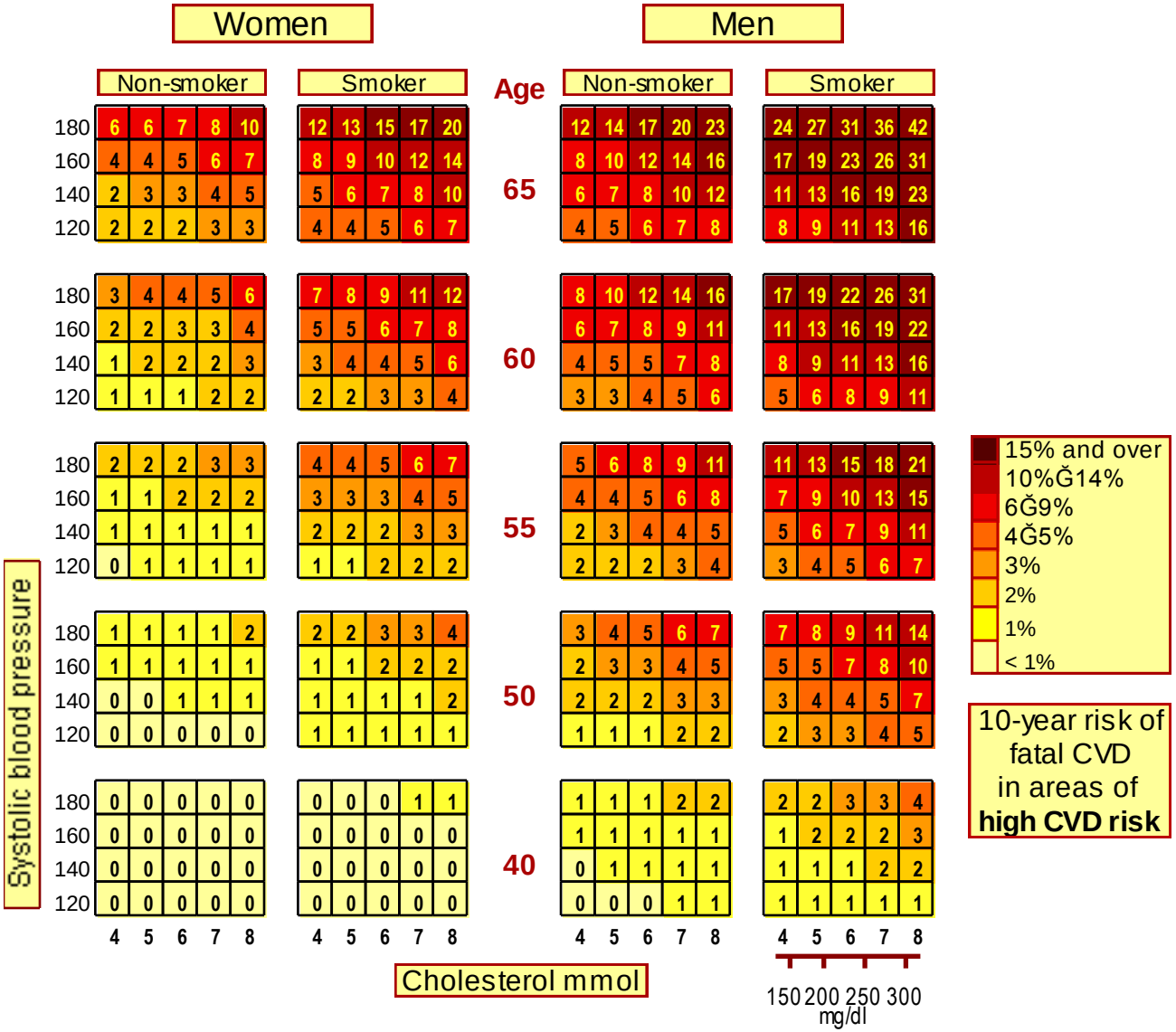
- Helps CVD risk management based on individual's total burden of risk
- Estimates the total risk of fatal atherosclerotic event (i.e. heart attack, stroke, aneurysm of the aorta, etc.) over period of 10 years for individuals aged between 45-64
- Data from 12 EU cohorts

Low CVD risk regions, risk based on total cholesterol



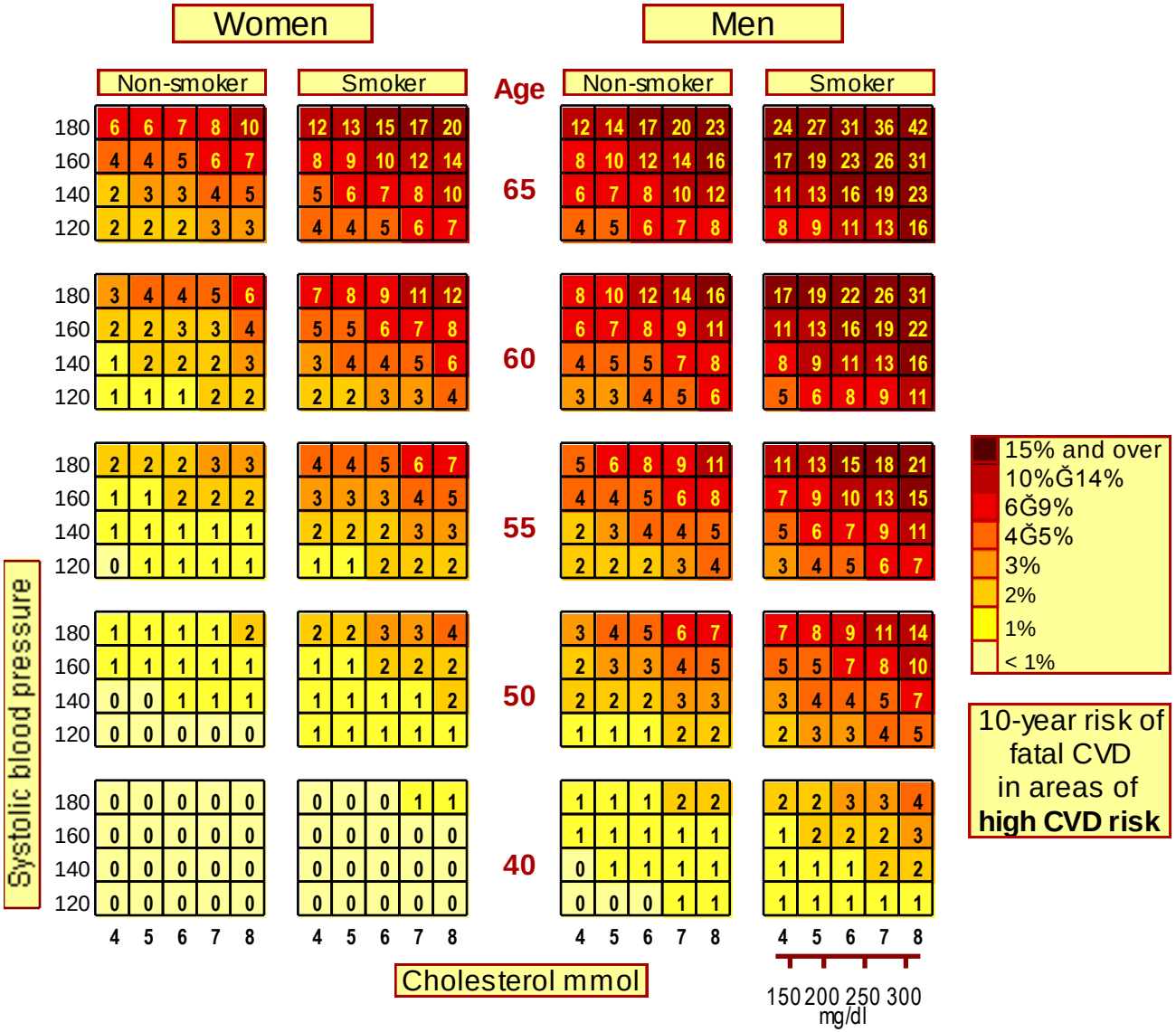
Baseline risk calculated based on **Belgian, Italian and Spanish** cohorts

High CVD risk regions, risk based on total cholesterol



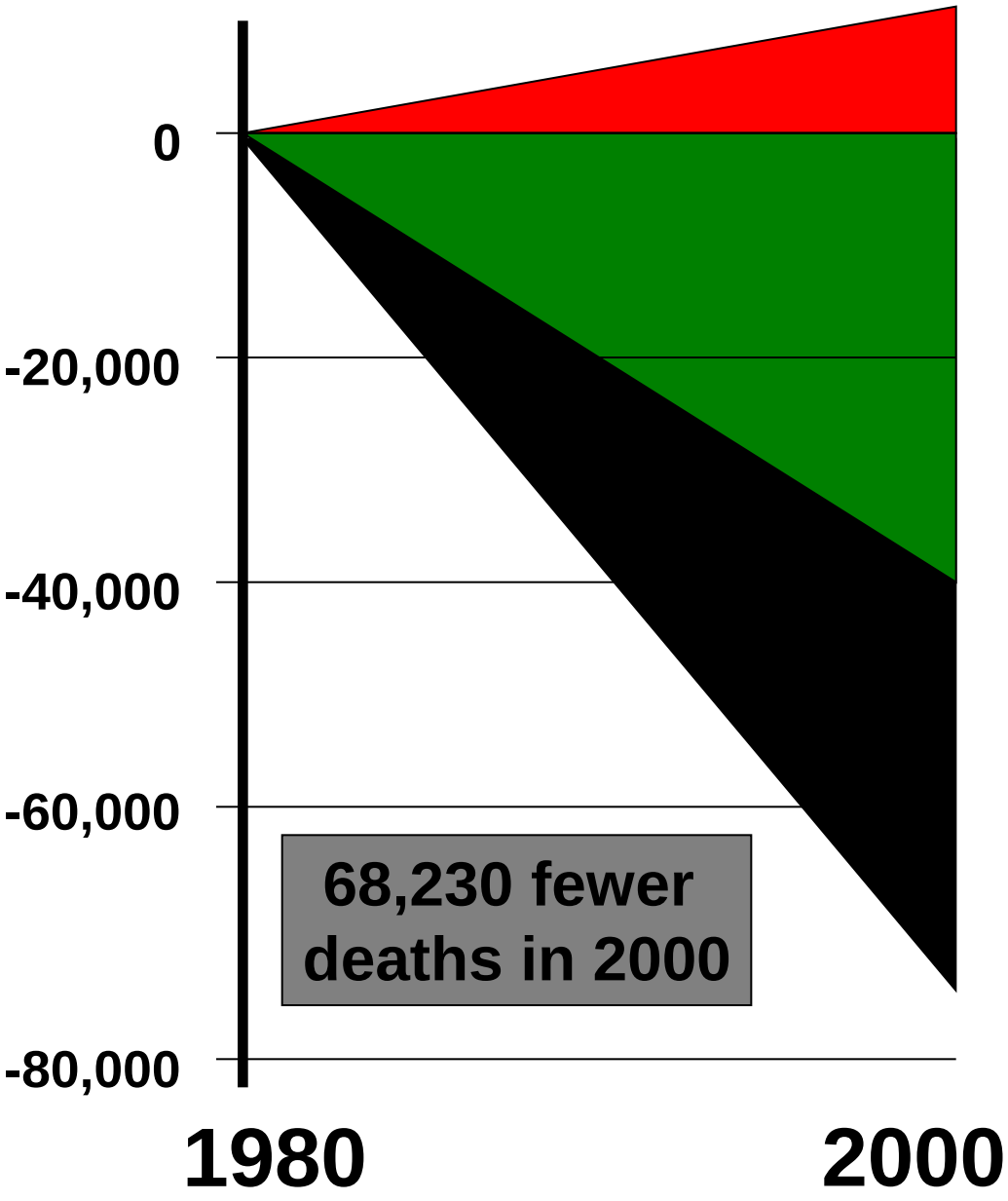
Baseline risk calculated based on **Danish**, **Finnish**, and **Norwegian** cohorts

SCORE is based on overall effects of risk factors



© Imperial College London

Deaths averted – contribution of different factors



Risk factors worse	**+13%**
Obesity	+3.5%
Diabetes	+4.8%
Less physical activity	+4.4%

Risk factors better	**-71%**
Smoking	-41%
Cholesterol	-9%
Popul'n BP fall	-9%
Deprivation	-3%
Other factors	-8%

Treatments	**-42%**
AMI treatments	-8%
Secondary prevention	-11%
Heart failure	-12%
Angina: CABG/PCI	-4%
Angina: drugs	-5%
BP treatment	-3%

Redrawn from Capewell and colleagues