Christ's College Medical Alumni Association
Open Public Lecture

Epidemiological Perspectives on the Cardiovascular Disease Epidemic

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MRC-PHE Centre for Environment & Health

Public Health England | MRC Medical Research Council | Imperial College London | King's College London

Outline

- Trends in cardiovascular disease
  - Temporal
  - Spatial
- Global burden of CVD
- Risk factors
  - Smoking
  - Raised cholesterol
  - Raised BP (salt, diet)
  - Obesity
- Metabolic profiling
  - Metabolome-Wide Association Study

FEATURE

Grand challenges in chronic non-communicable diseases

The top 20 policy and research priorities for conditions such as diabetes, stroke and heart disease.

Abdallah S. Daar[1], Peter A. Singer[1], Deepa Leah Persad[1], Stig K. Pramming[2], David R. Matthews[3], Robert Beaglehole[4], Alan Bernstein[5], Leszek K. Borysiewicz[6], Stephen Colagiuri[7], Nirmal Ganguly[8], Roger I. Glass[9], Diane T. Finegood[10], Jeffrey Koplan[11], Elizabeth G. Nabel[12], George Sarna[6], Nizal Sarrafzadegan[13], Richard Smith[14], Derek Yach[15] and John Bell[16]

Chronic non-communicable diseases (CNCDs) are reaching epidemic proportions worldwide[1–3]. These diseases — which include cardiovascular conditions (mainly heart disease and stroke), some cancers, chronic respiratory conditions and type 2 diabetes — affect people of all ages, nationalities and classes.

The conditions cause the greatest global share of death and disability, accounting for around 60% of all deaths worldwide. Some 80% of chronic-disease deaths occur in low- and middle-income countries. They account for 44% of premature deaths worldwide. The number of deaths from these diseases is double the number of deaths that result from

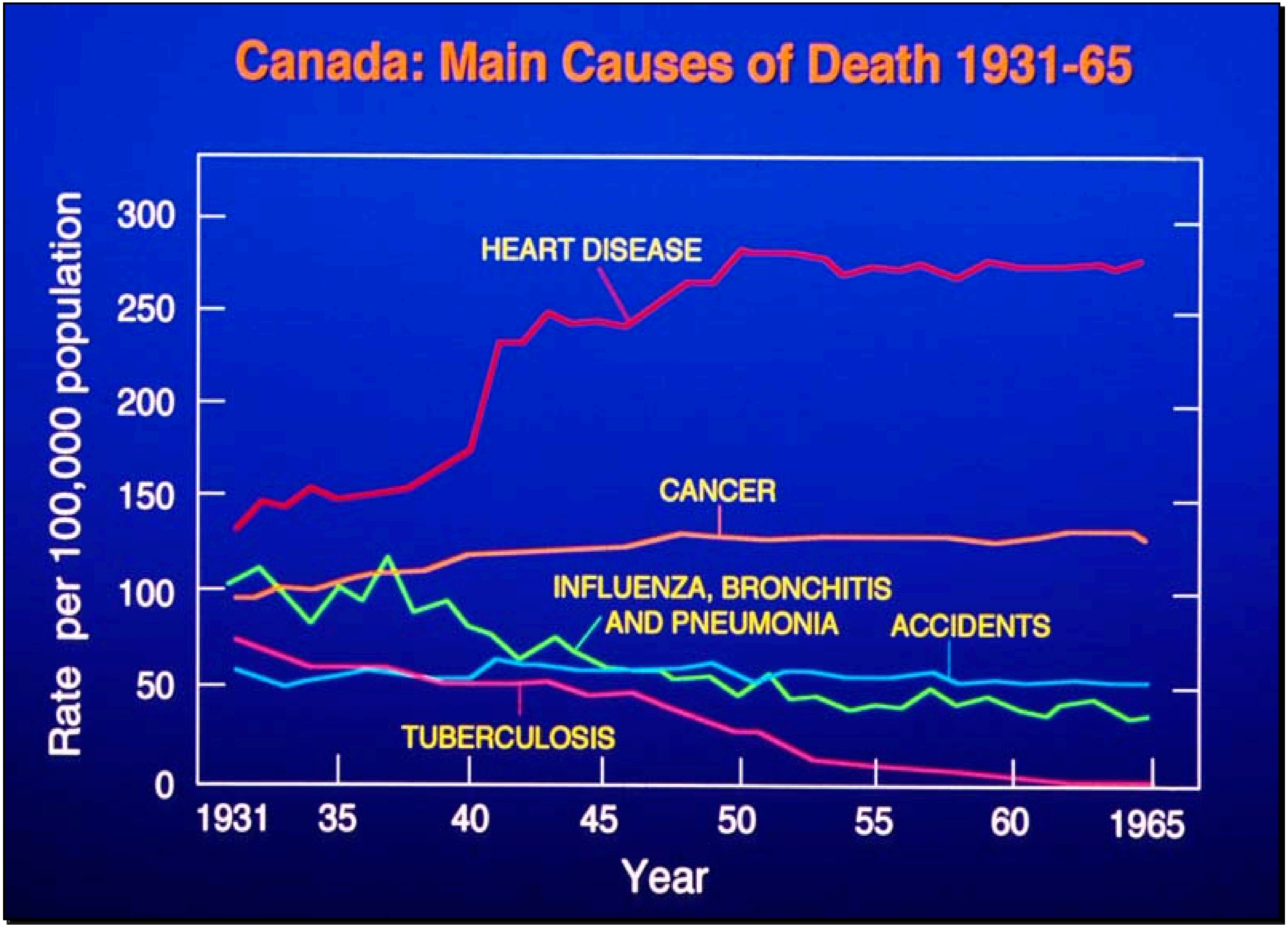
Poor diet and smoking are two factors that contribute to the millions of preventable deaths that occur each year.

R. CANDIA/AP

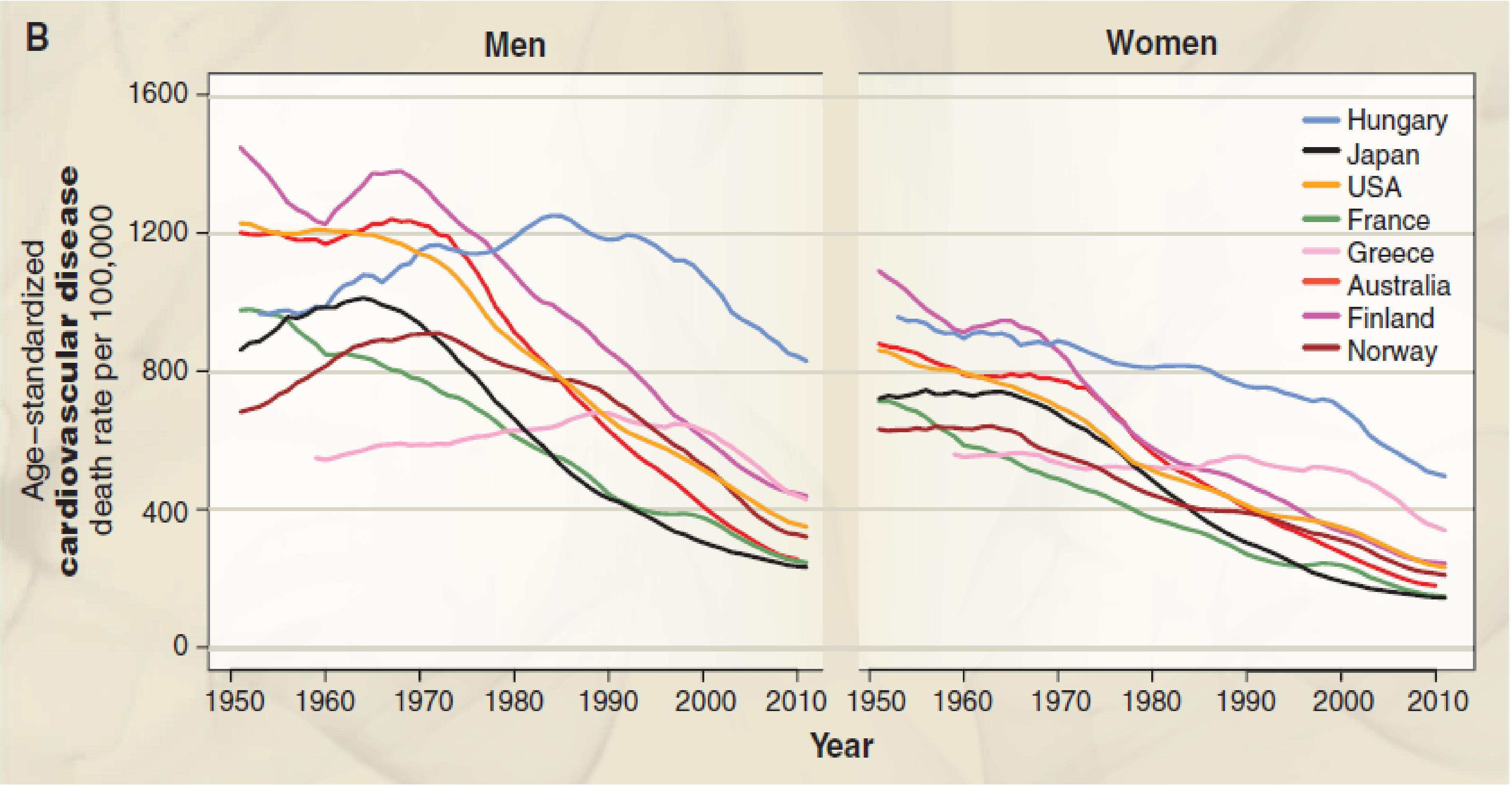
P. PARKS/AFP/GETTY

with known behavioural and pharmaceutical

meet the challenges, and brings new talent

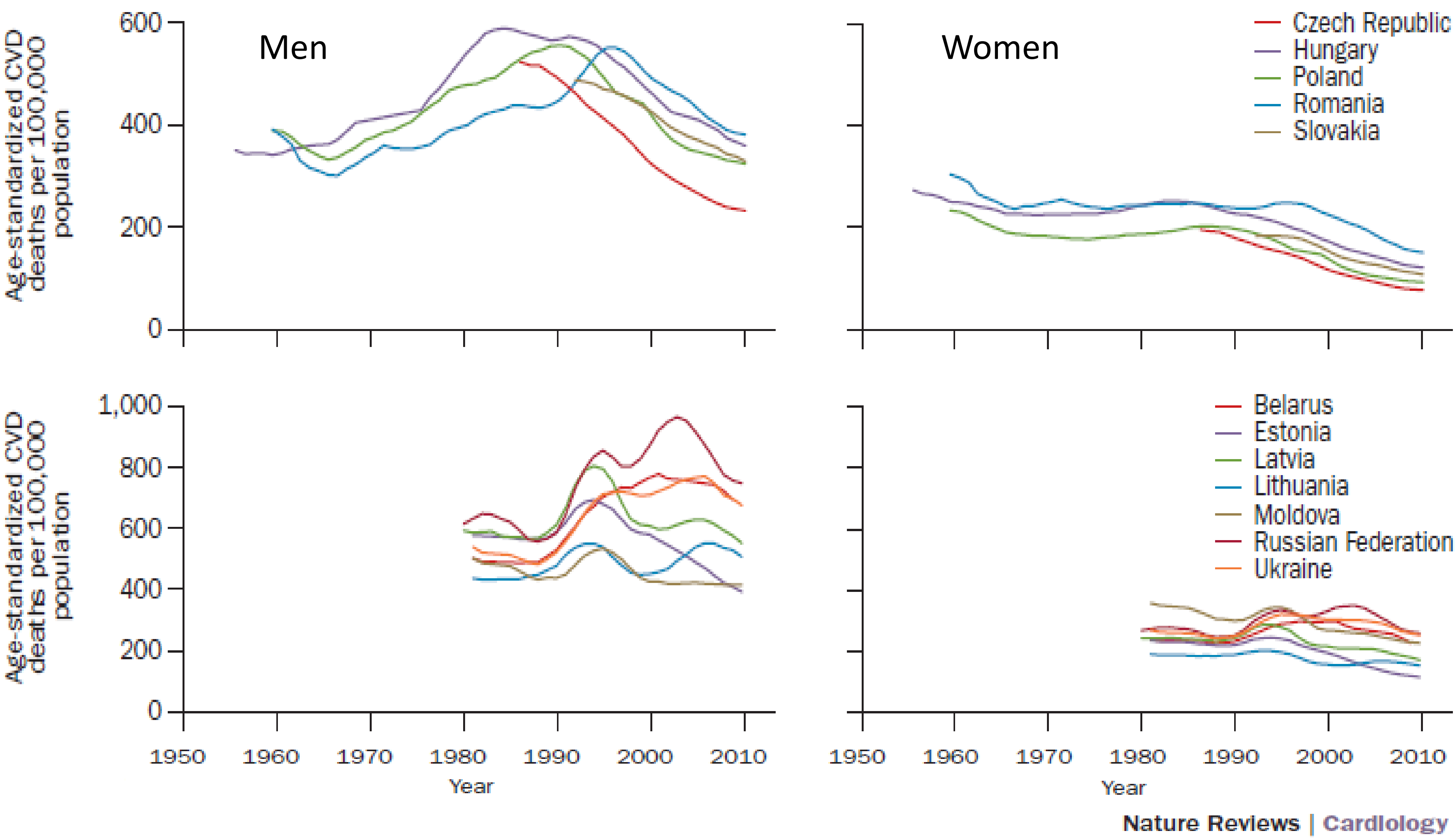

Canada: Main Causes of Death 1931-65
Rate per 100,000 population
300
250
200
150
100
50
0
HEART DISEASE
CANCER
INFLUENZA, BRONCHITIS AND PNEUMONIA
ACCIDENTS
TUBERCULOSIS
1931
35
40
45
50
55
60
1965
Year

Cardiovascular Disease Death Rate per 100,000/year 1950-2010



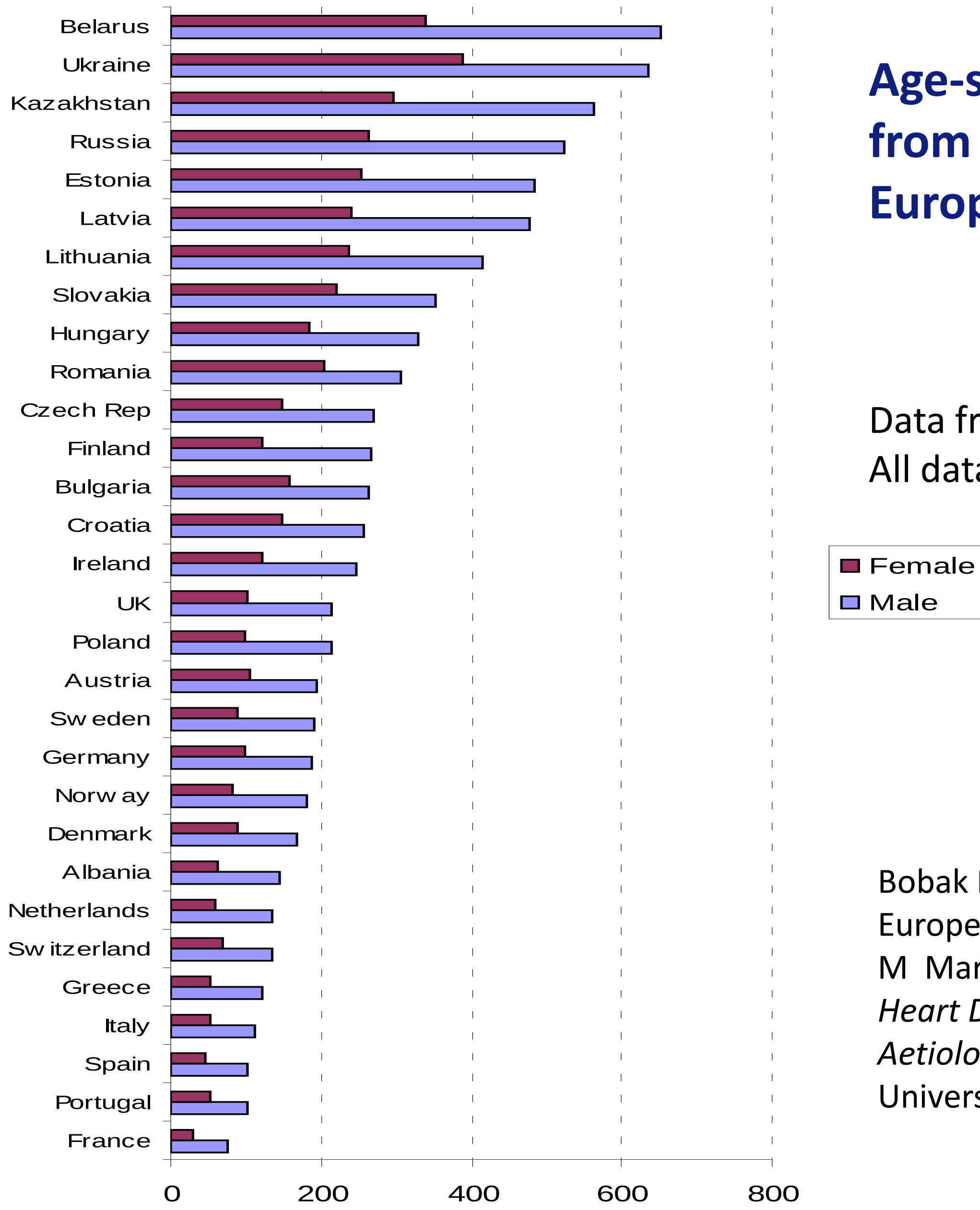
DISEASE PREVENTION
www.sciencemag.org/special/prevention

Ezzati M and Riboli E 1485-1487
SCIENCE VOL 337 21 SEPTEMBER 2012



Age-standardized trends in CVD death rates, ages 30-69 years

Ezzati M, Obermeyer Z, Tzoulaki I, Mayosi BM, Elliott P, Leon DA Nat. Rev. Cardiol. 12, 508-530 (2015)



Age-standardized mortality from CHD per 100 000 in European countries in 2000

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.

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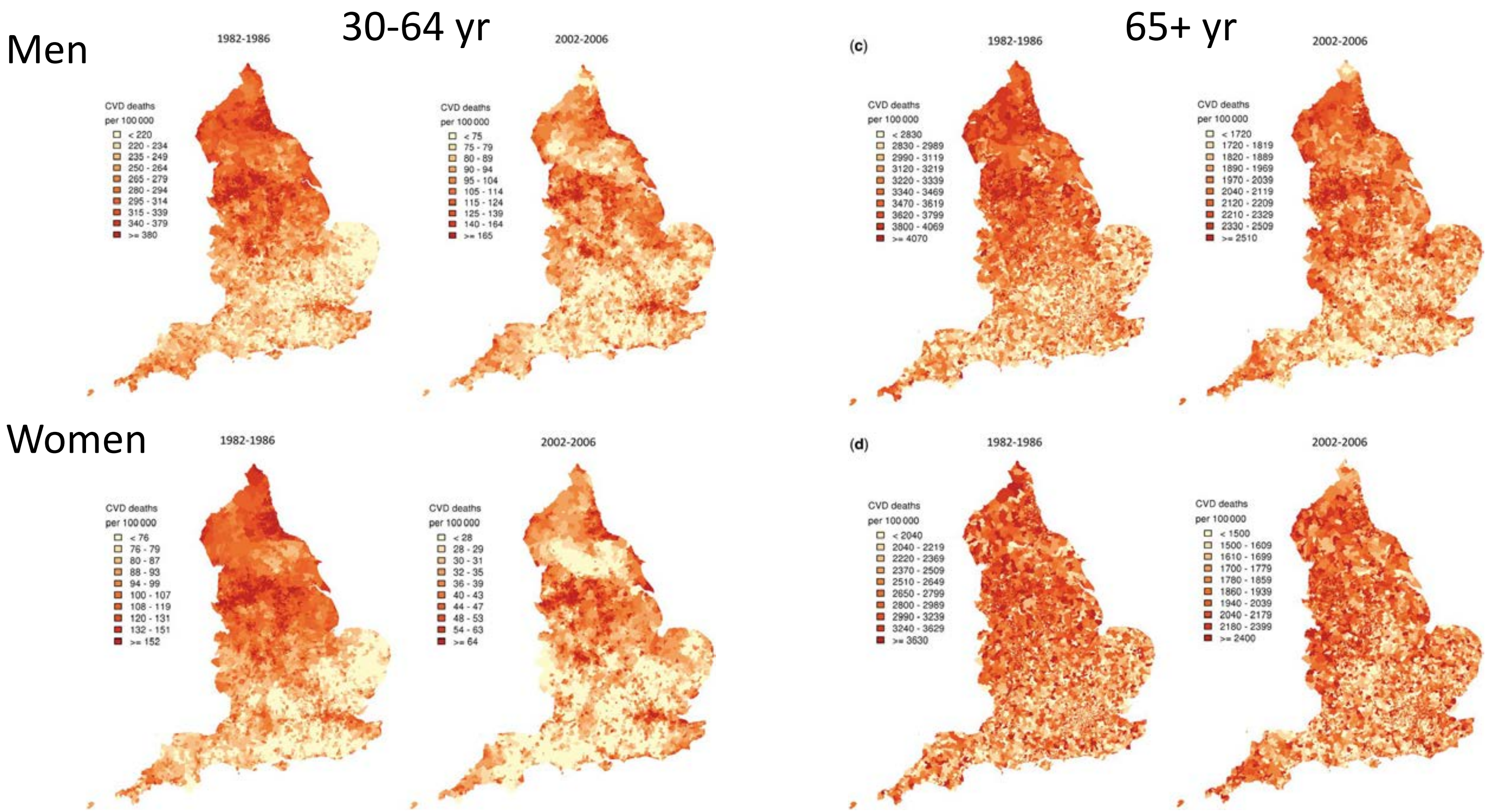
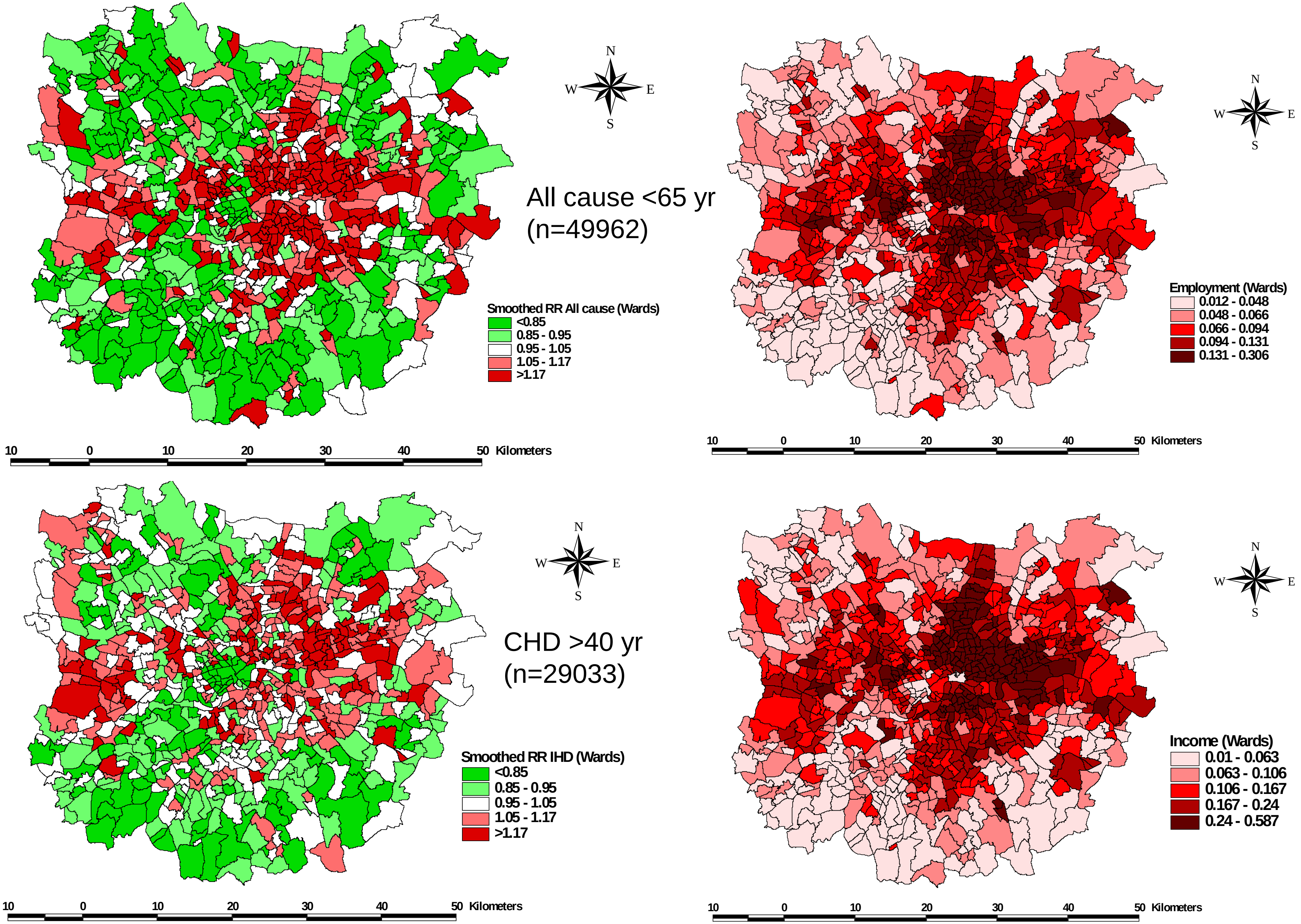
Trends and inequalities in cardiovascular disease mortality across 7932 English electoral wards, 1982–2006: Bayesian spatial analysis



Asaria P, Fortunato L, Fecht D, Tzoulaki I, Abellan JJ, Hambly P, de Hoogh K, Ezzati M, Elliott P. Int. J. Epidemiol. 2012; 41(6):1737-49



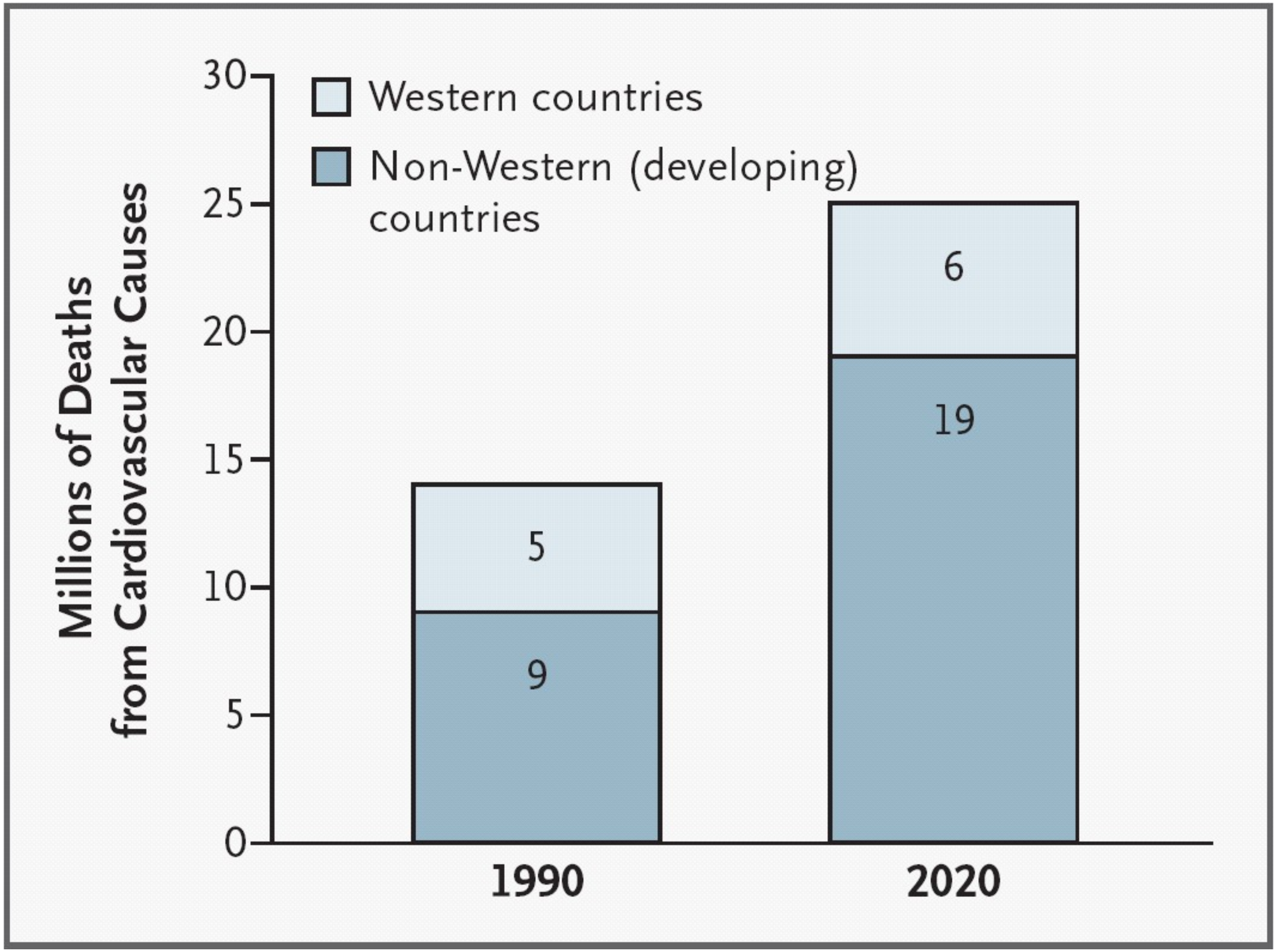
Smoothed SMRs by ward (n=791), London 1998-2001, Employment & Income

“Genetics loads the gun, but Environment pulls the trigger”

After Elliott Proctor Joslin MD,

A pioneering American diabetologist and founder of the Joslin Diabetes Center, 1869-1962

Br Med J 1991; 302: 1231



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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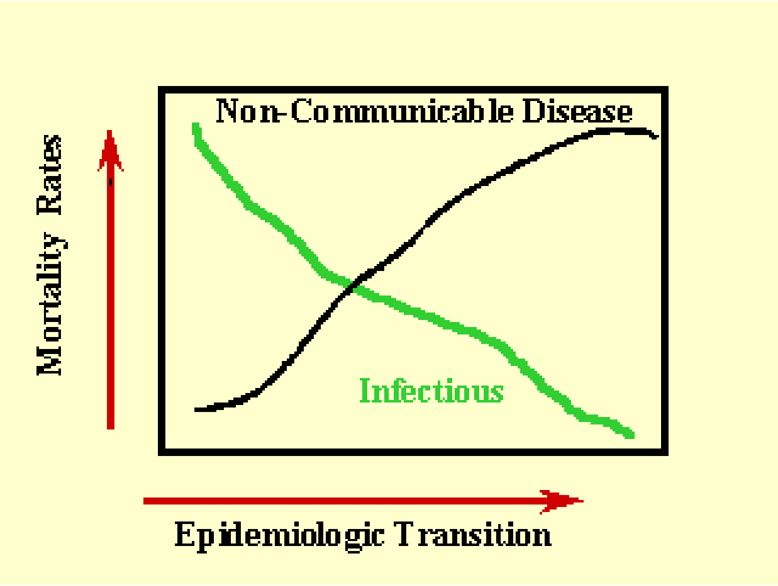
Epidemiologic transition and the Global Burden of Disease

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….



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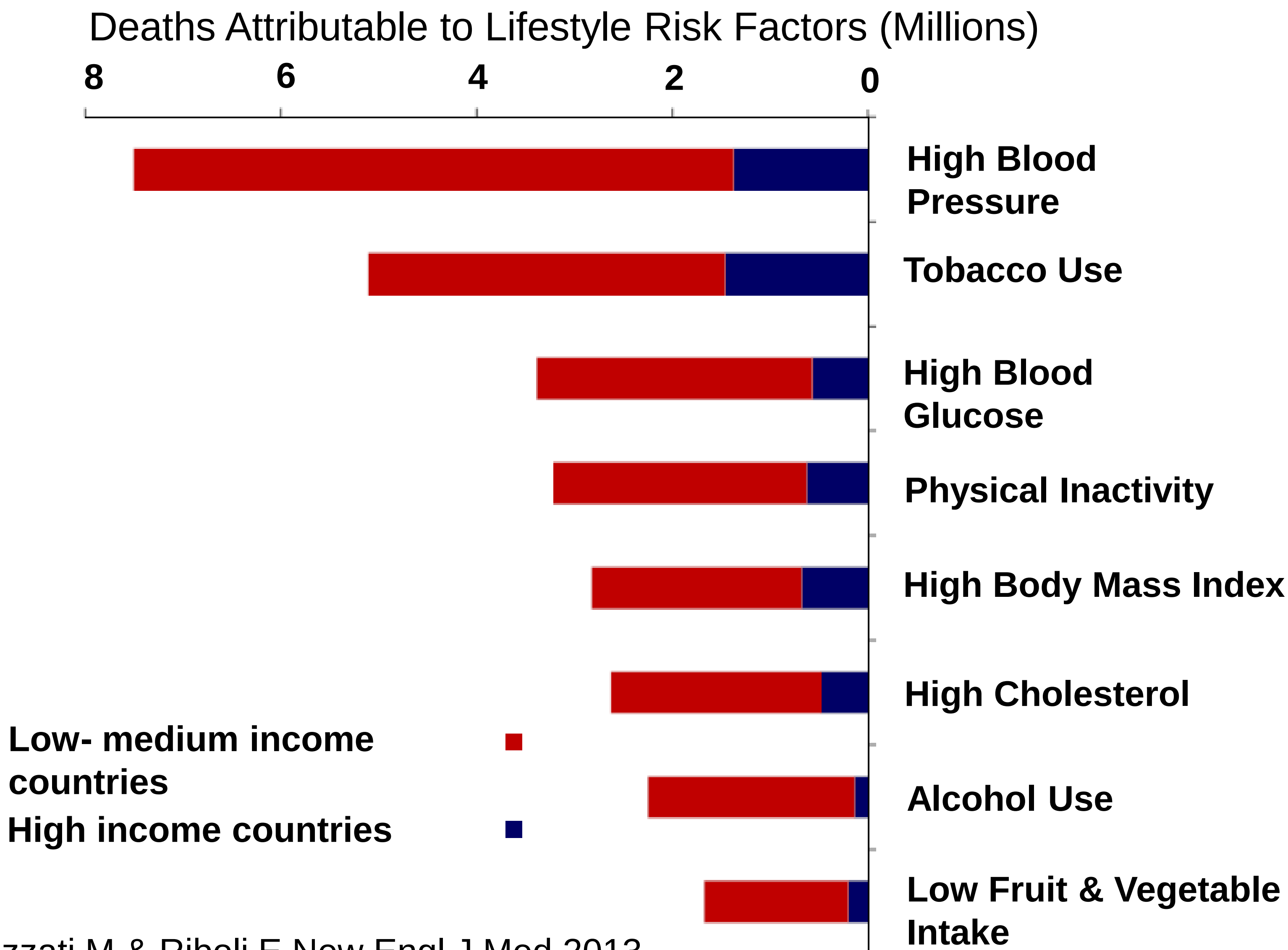
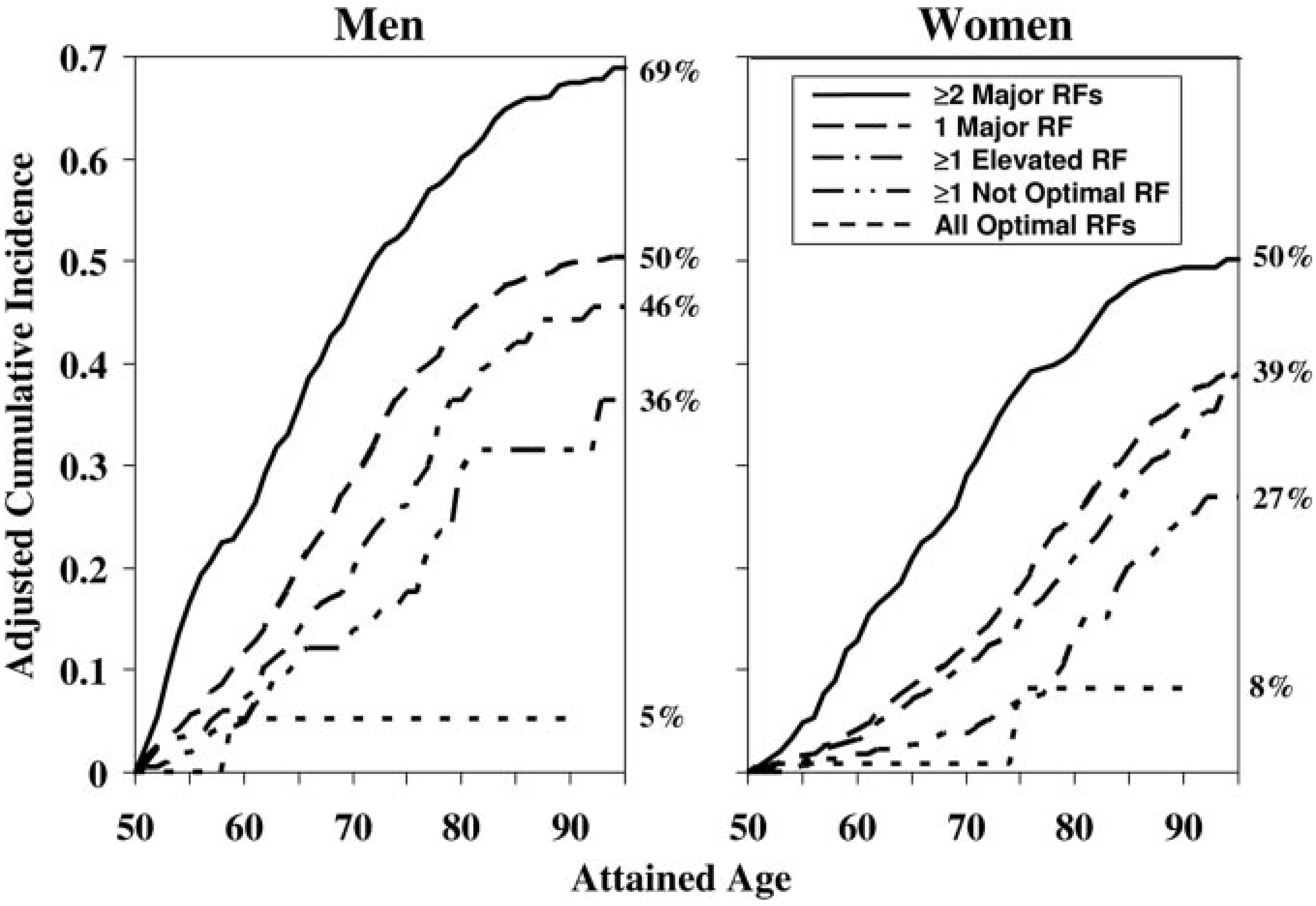
Modifiable Risk Factors for Mortality Worldwide



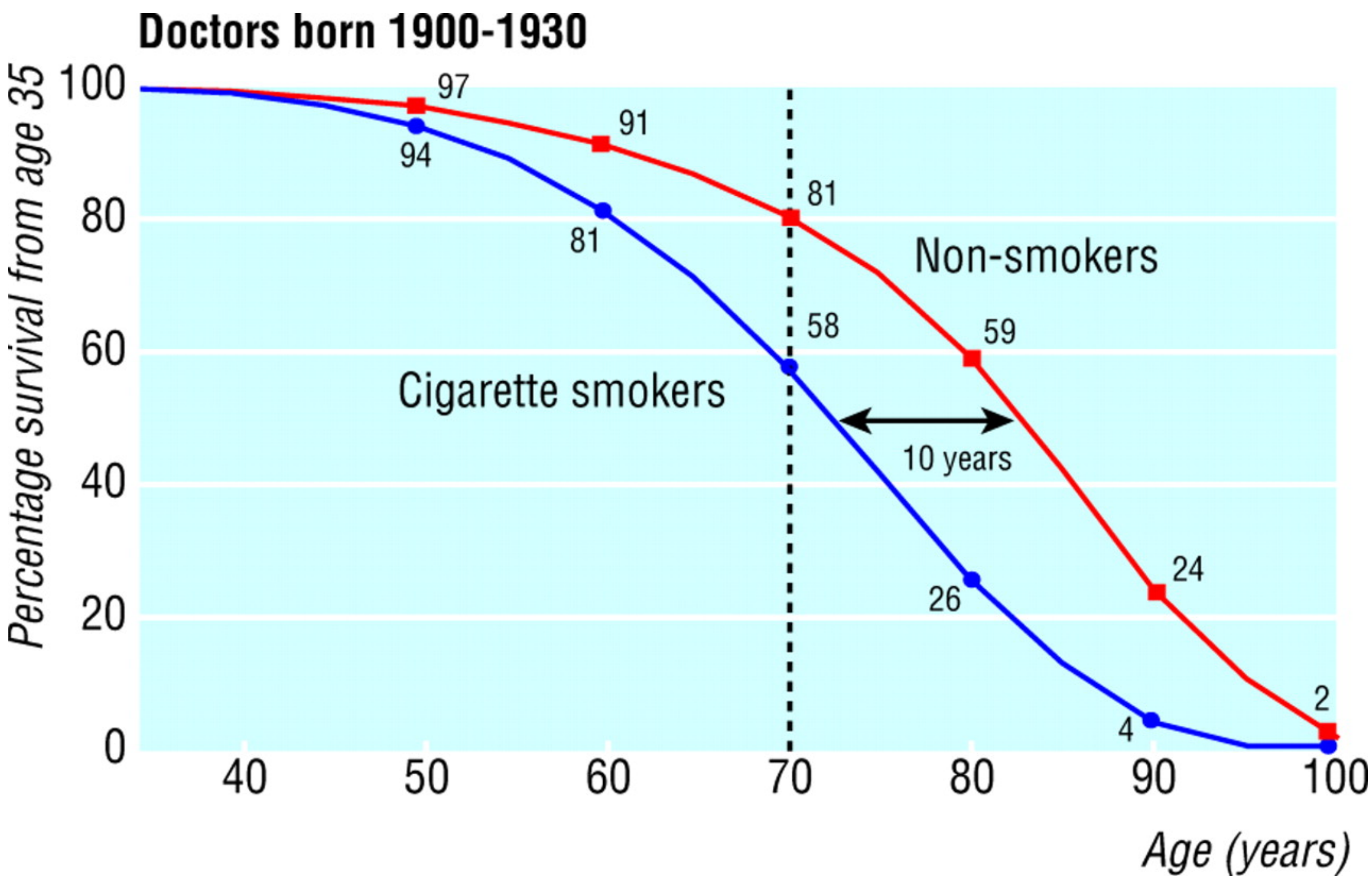
Ezzati M & Riboli E New Engl J Med 2013

Lifetime risk of CVD according to number of risk factors



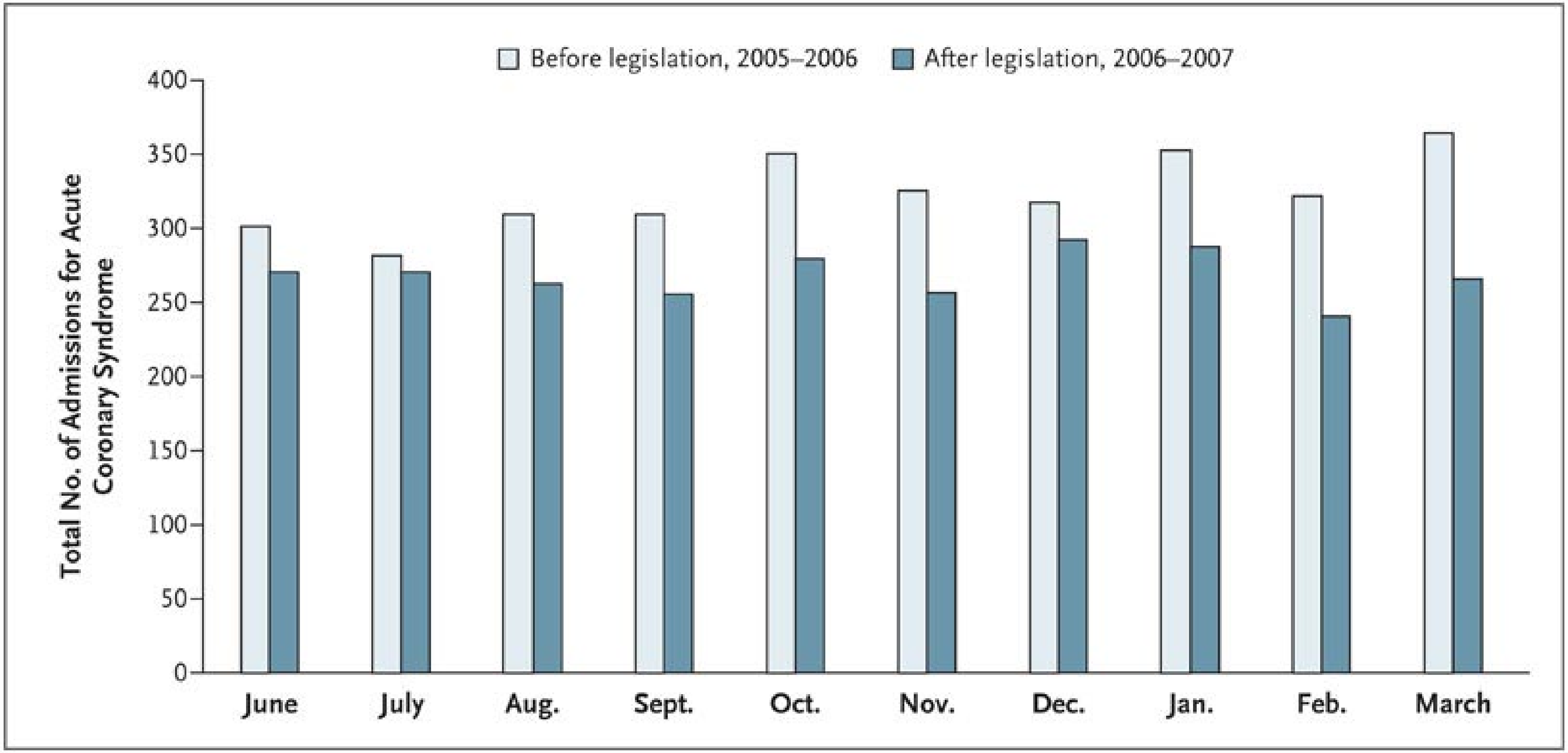
Lloyd-Jones et al. *Circulation* 2006;**113**;791-798

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

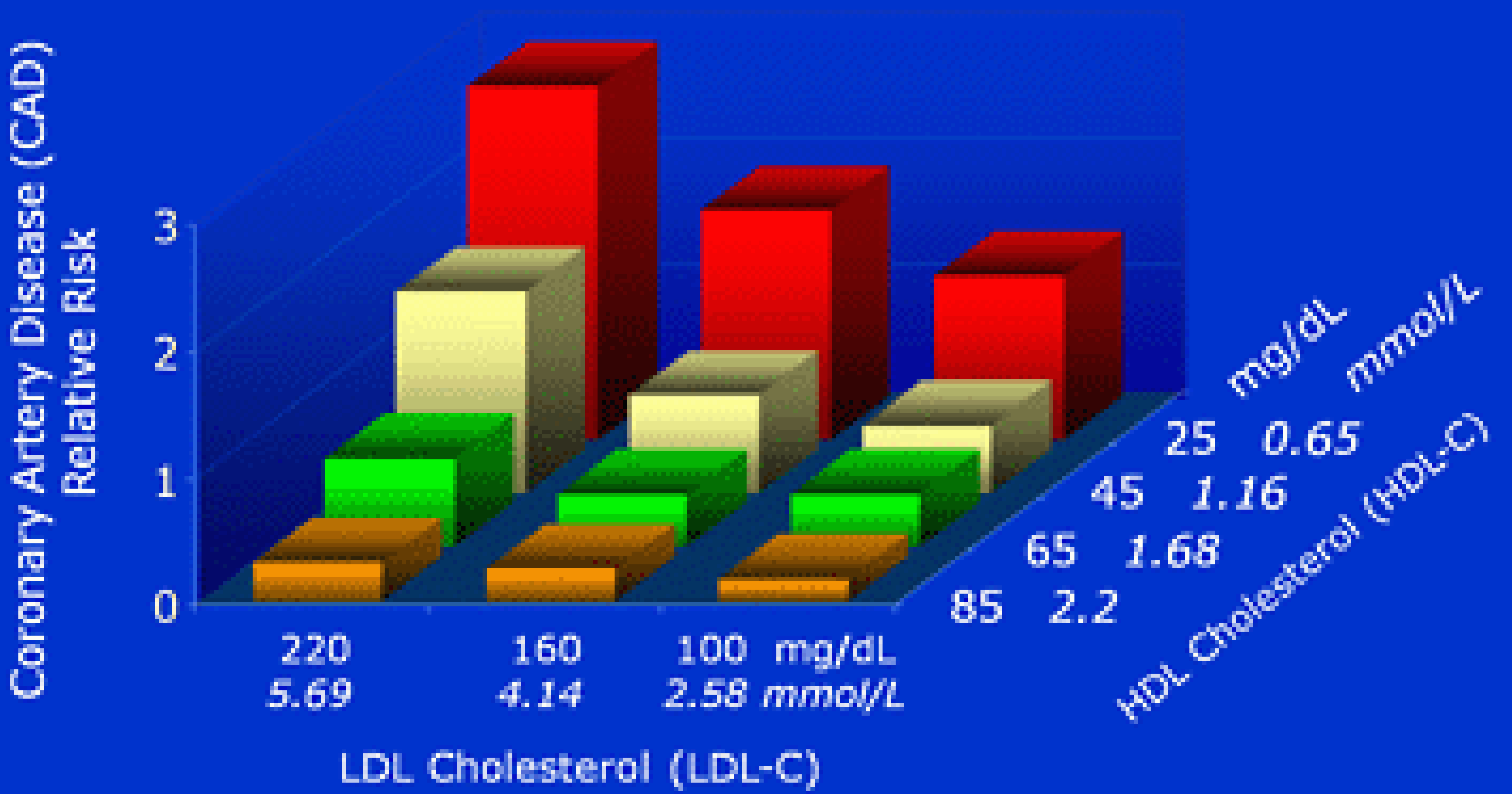
Smoking ban in Scotland



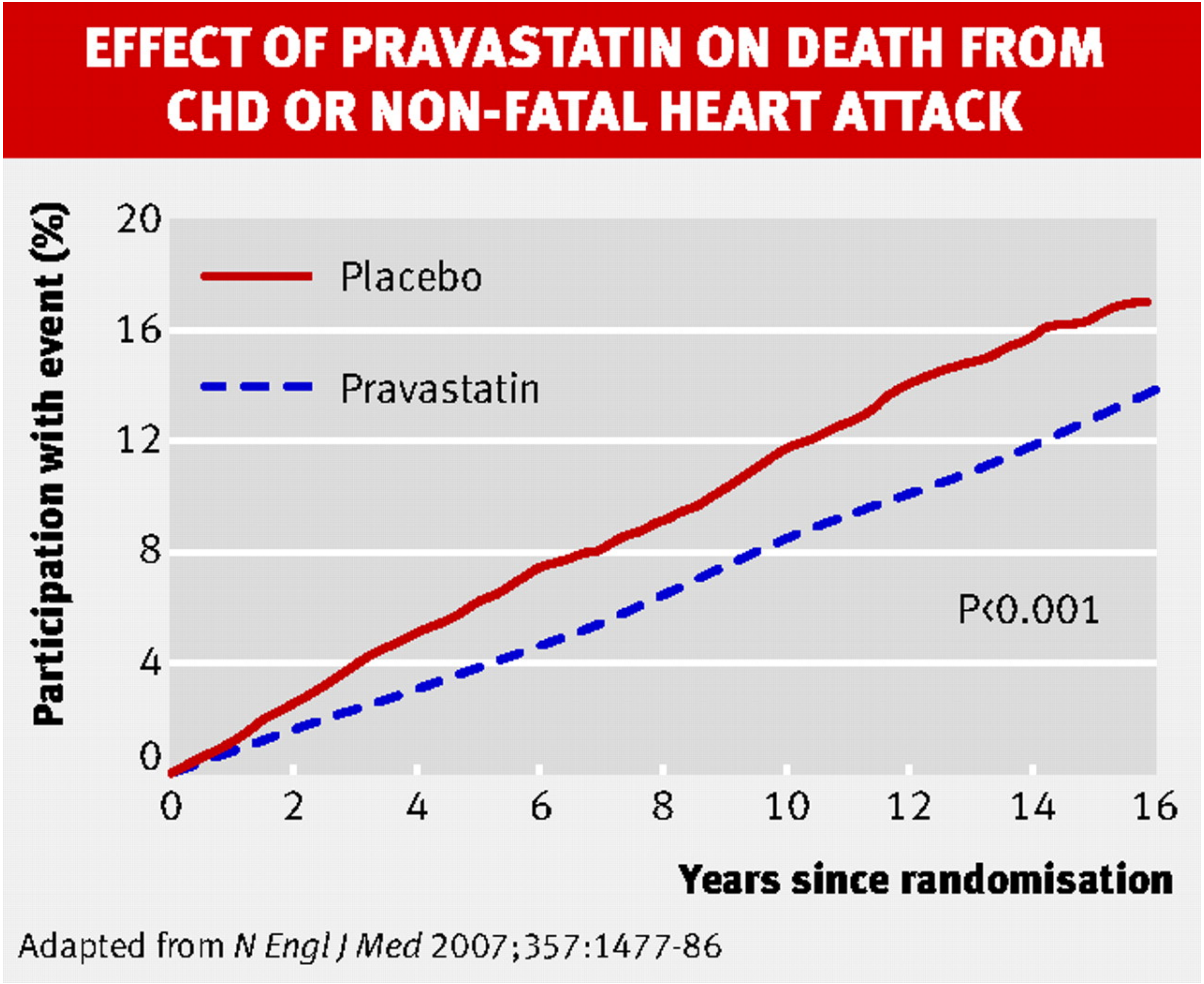
Admissions for Acute Coronary Syndrome by Month, before and after Smoke-free Legislation

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

CAD Risk as a Function of LDL-C and HDL-C in Men (Ages 50 to 70 Years Old): *Framingham Heart Study*



Reprinted from Castelli WP. *Can J Cardiol.* 1988;4: 5A–10A, with permission from Pulsus Group Inc.


EFFECT OF PRAVASTATIN ON DEATH FROM CHD OR NON-FATAL HEART ATTACK
Participation with event (%)
20
16
12
8
4
0
Placebo
Pravastatin
P<0.001
0
2
4
6
8
10
12
14
16
Years since randomisation
Adapted from N Engl J Med 2007;357:1477-86

Blood Pressure
347,978 men screened for MRFIT

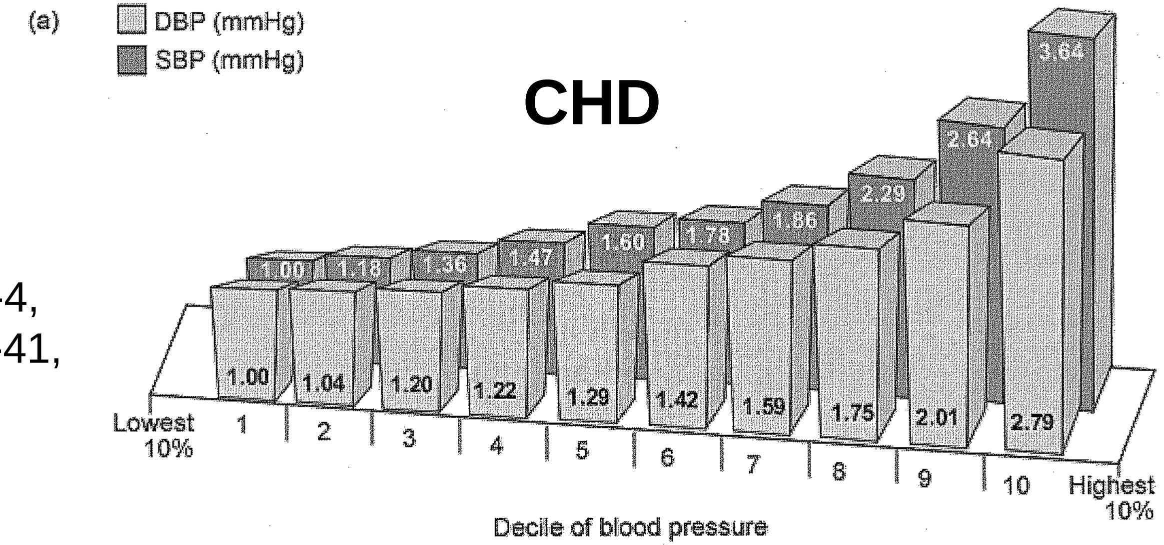
SBP deciles:

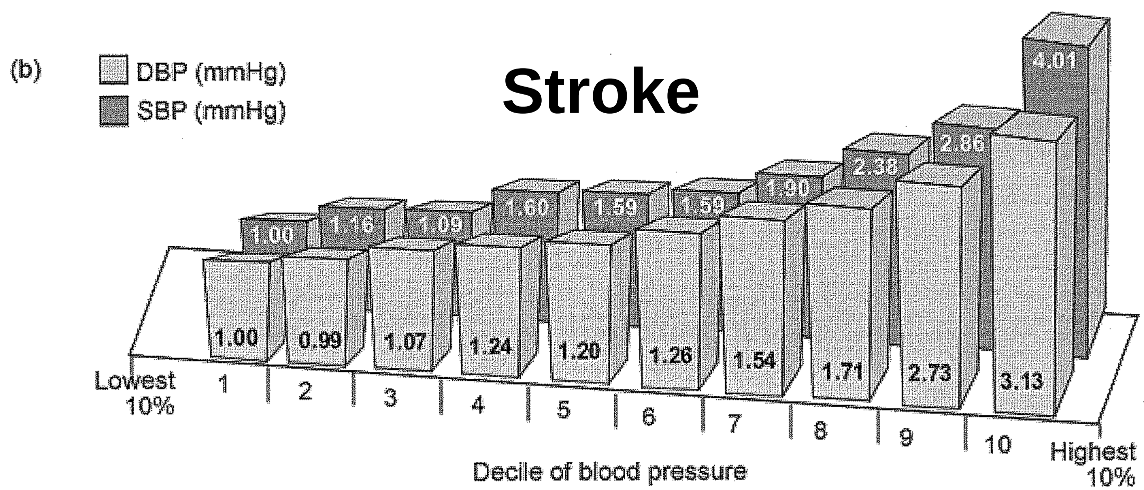
<112, 112-17, 118-20, 121-4, 125-8, 129-31, 132-6, 137-41, 142-50, >151 mmHg

DBP deciles:

<71, 71-5, 76-8, 79-80, 81-3, 84-5, 86-8, 89-91, 92-7, >98 mmHg

Ages 35-57 at baseline, without history of hospitalization for heart attack



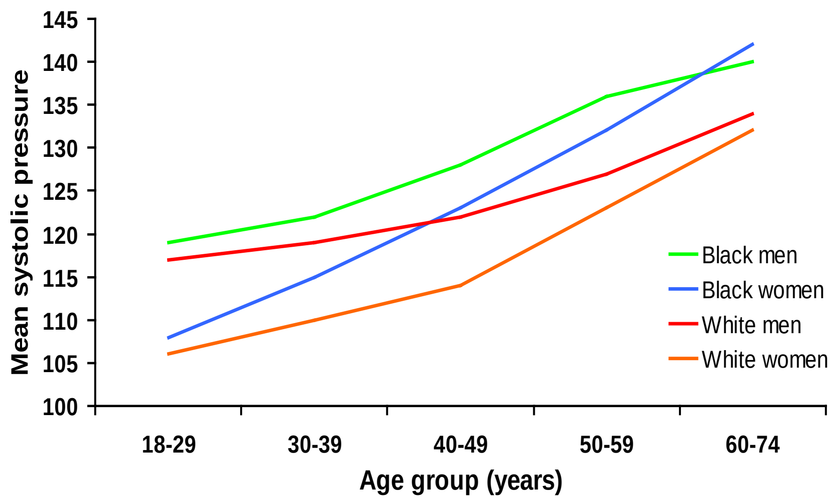


After Stamler

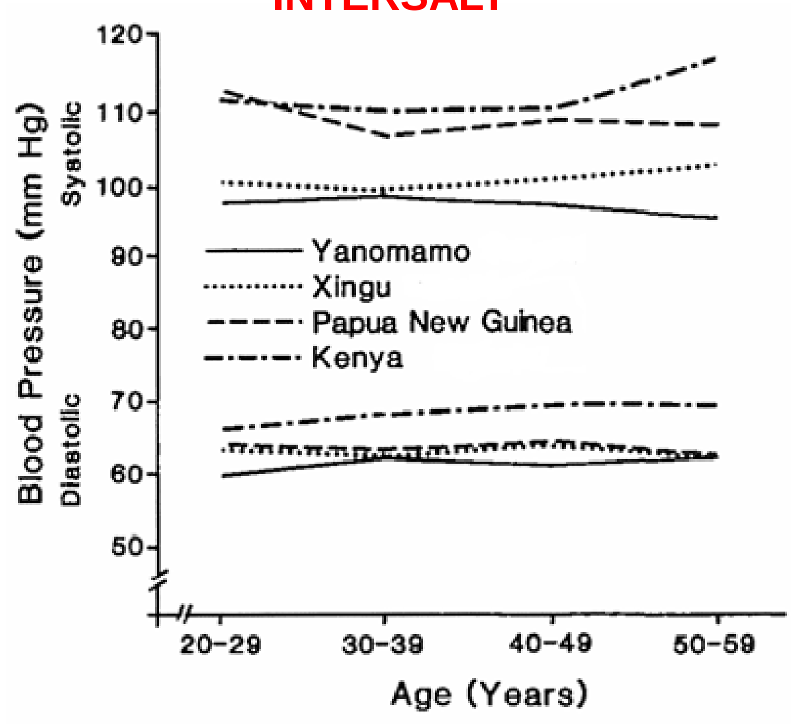
25-year risk of death

Blood Pressure Rise with Age

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



INTERSALT



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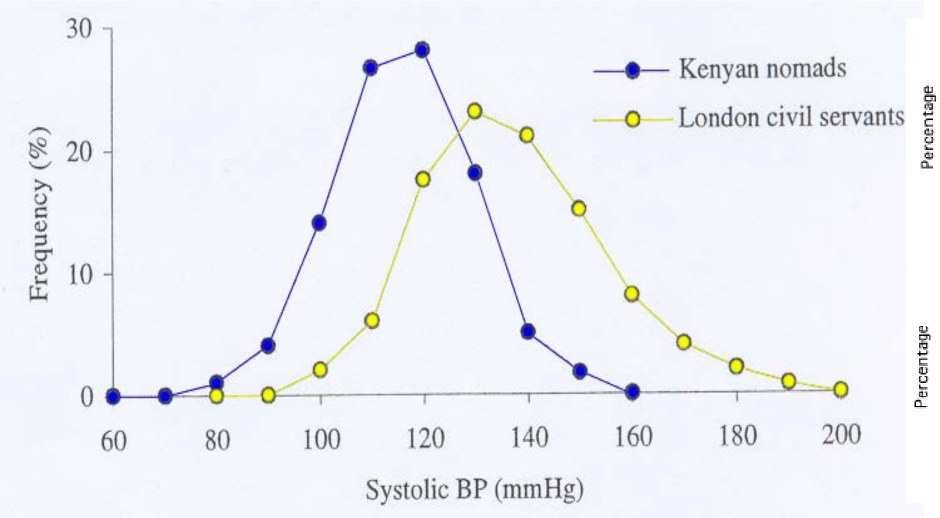
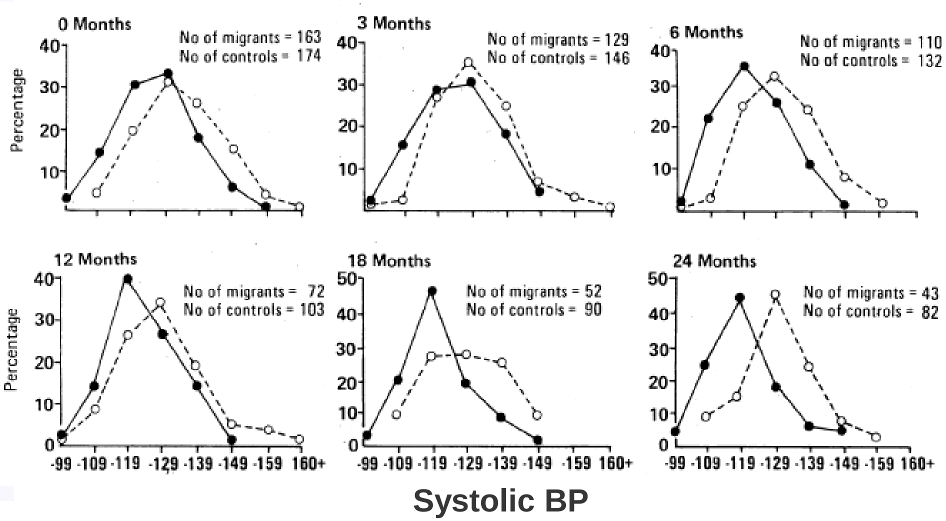
Shift in the BP Distribution



Adapted from Rose G “Sick individuals and sick populations”
Int J Epidemiol 1985; 14: 32-38

Kenyan Luo: Male migrants to Nairobi



Poulter et al. *BMJ* 1990; 300: 967-72

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

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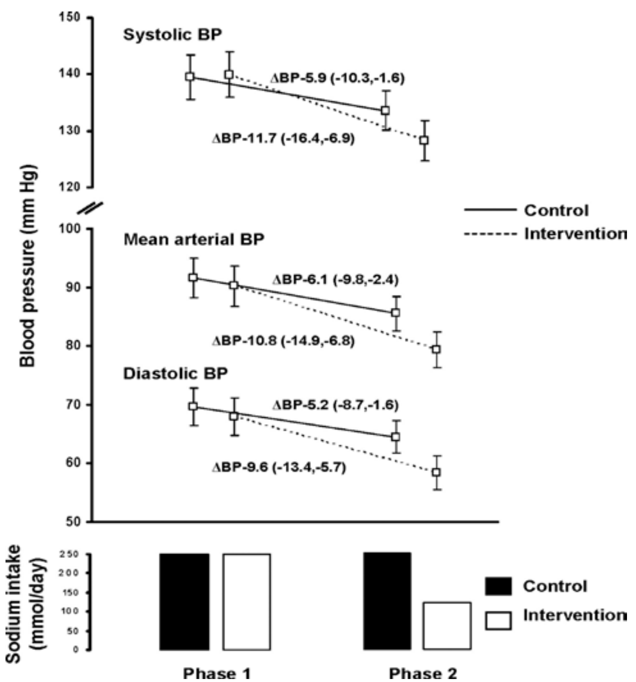
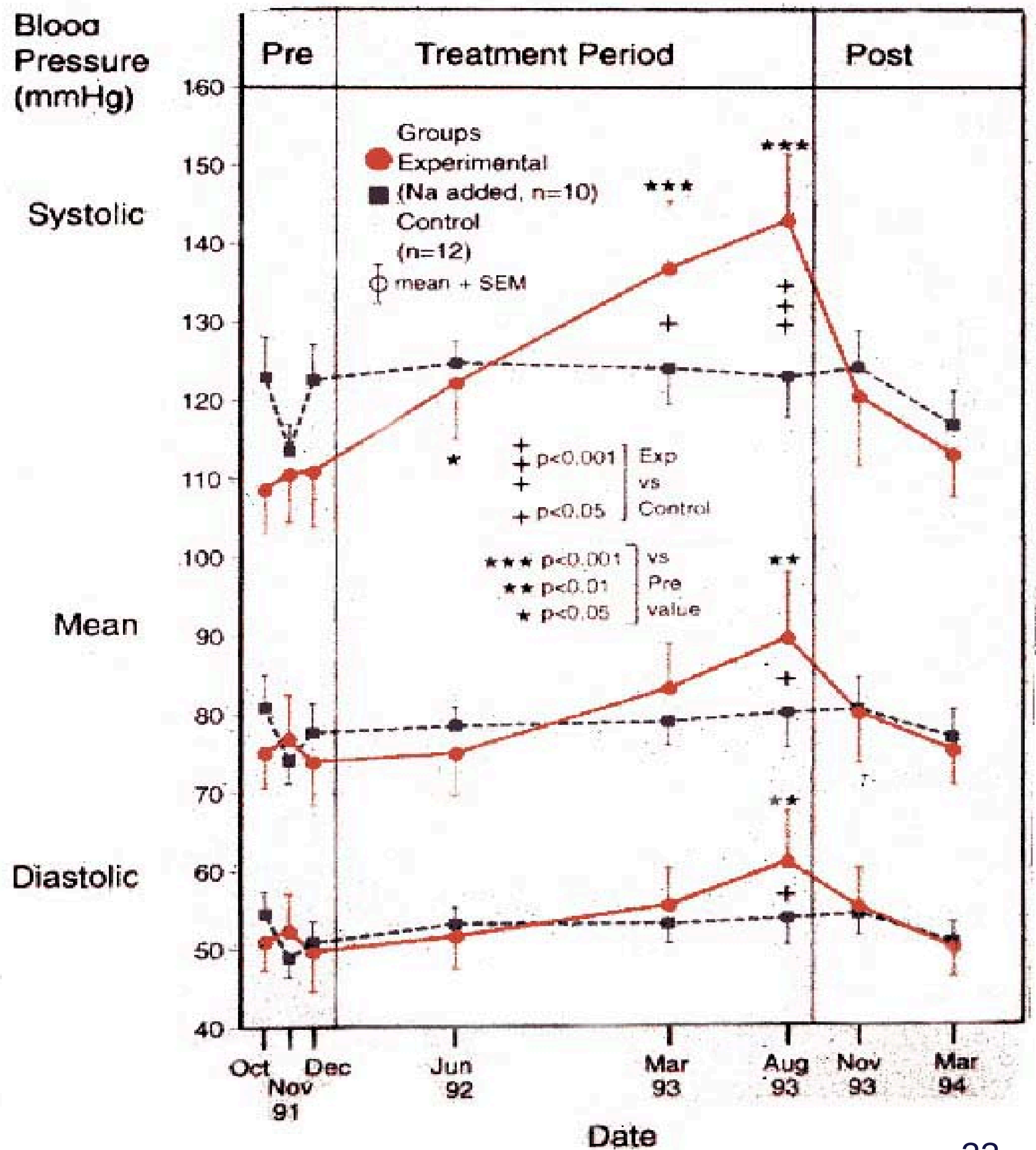
Salt and Blood Pressure

- Animal studies
- Epidemiological studies
  - INTERSALT Study
- Clinical trials

Salt & BP in chimpanzees

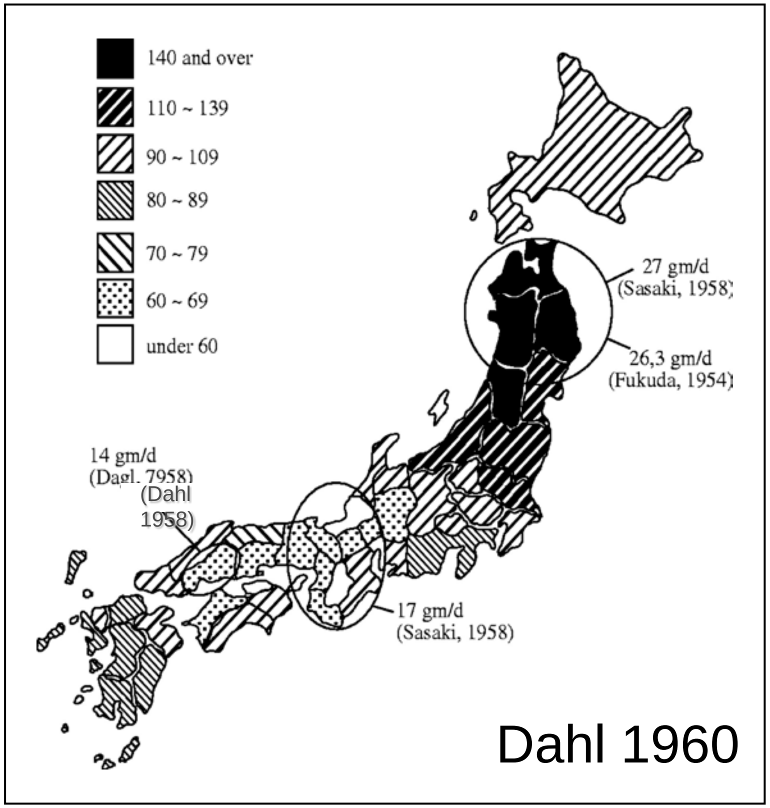


Elliott P et al. *Circulation* 2007



Denton et al. *Nat Med* 1995

Salt and BP



Sodium chloride: 1 g = 393.4 mg Na = 17 mmol Na

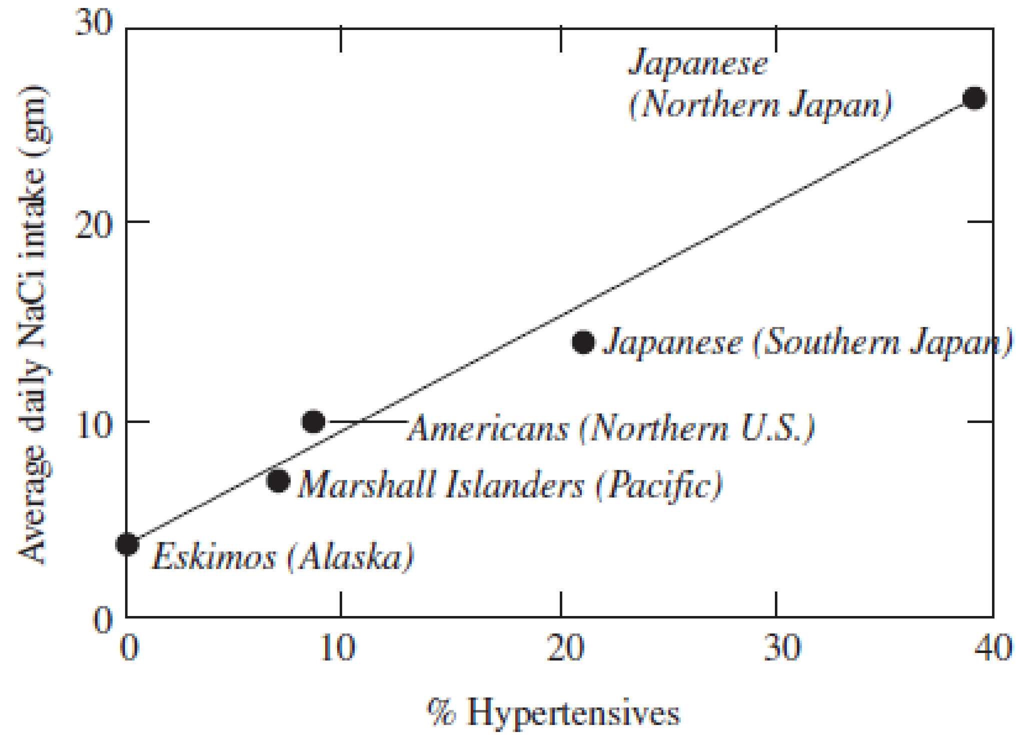


Figure 1 Correlation of average daily salt (NaCl) intakes with prevalence of hypertension in different geographic areas and among different races

Strong ecologic association but within-population studies (1970s-early 80s) inconsistent

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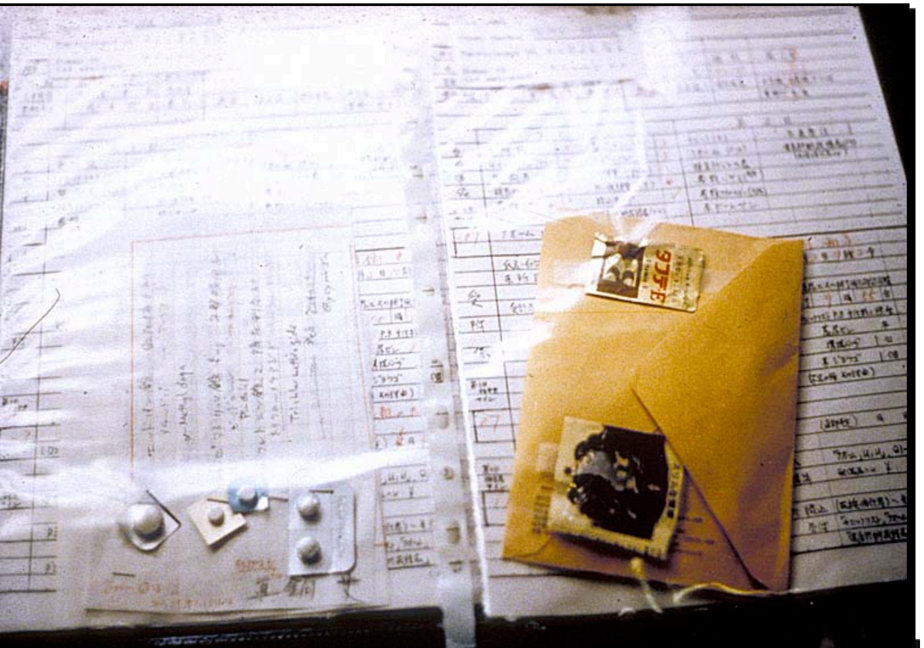


INTERSALT

- 52 population samples in 32 countries
- 10,079 men & women,
  20-59 years
- 8% repeat 24-hr urine collections
- Standardized international training and quality control

Results

Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion

Intersalt Cooperative Research Group

BMJ VOLUME 297 30 JULY 1988

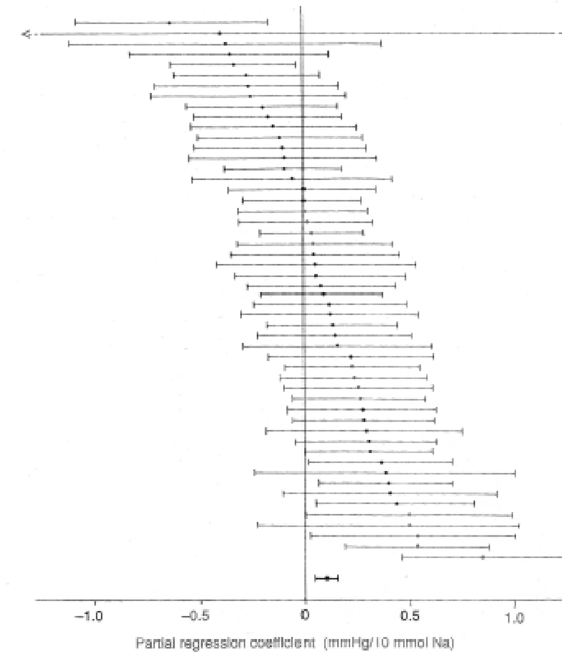
Abstract

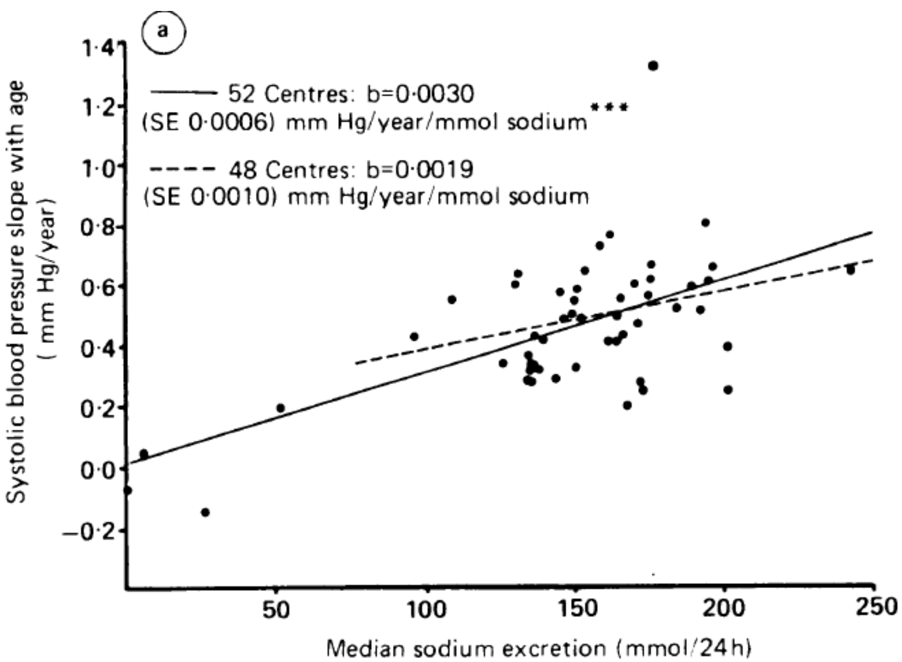
The relations between 24 hour urinary electrolyte excretion and blood pressure were studied in 10 079 men and women aged 20-59 sampled from 52 centres around the world based on a highly standardised protocol with central training of observers, a central laboratory, and extensive quality control. Relations between electrolyte excretion and blood pressure were studied in individual subjects within each centre and the results of these regression analyses pooled for all 52 centres. Relations between population median electrolyte values and population blood pressure values were also analysed across the 52 centres.

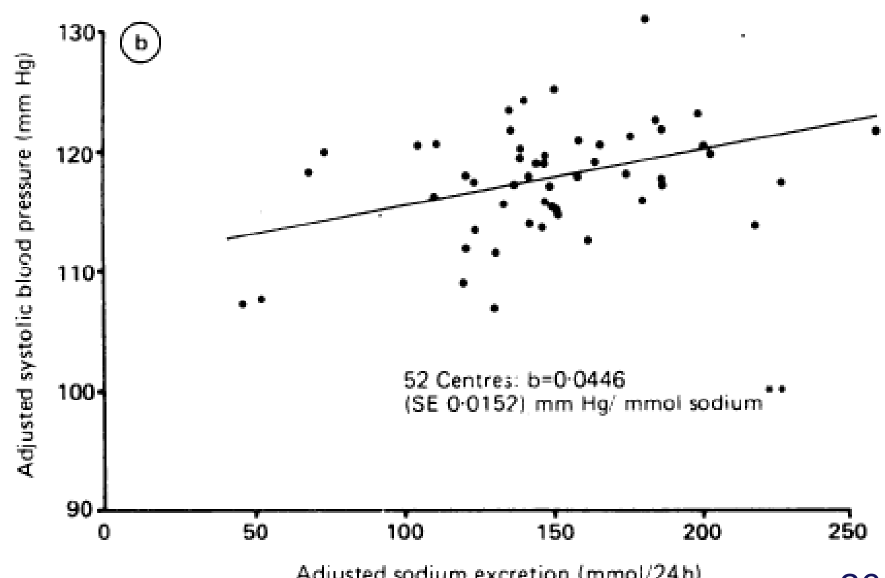
based on data from separate, individual studies, with unstandardised measurement of both sodium intake and blood pressure; confounding factors other than age and sex were largely ignored.

The purpose of Intersalt is for the first time to investigate in a systematic and standardised way the relations between electrolyte excretion and blood pressure based on samples from many countries and with assessment of relevant confounding variables. It is also unlike previous international studies in providing data on individual subjects as well as on populations.

This report analyses sodium excretion, potassium excretion, and sodium to potassium ratio in 24 hour urine samples in relation to blood pressure among over







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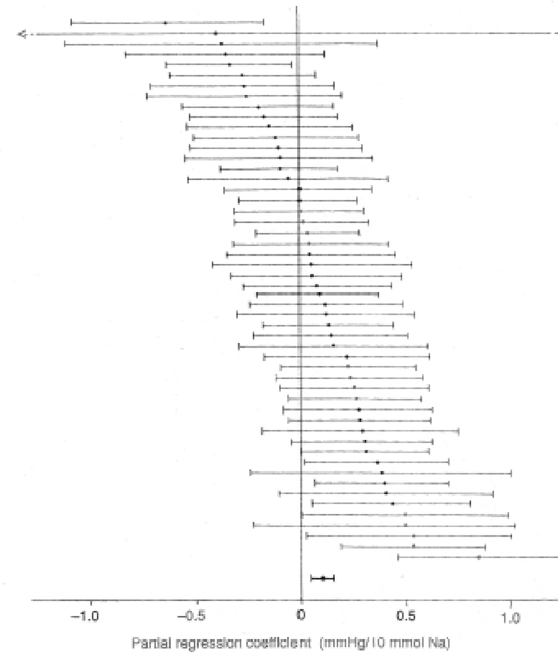
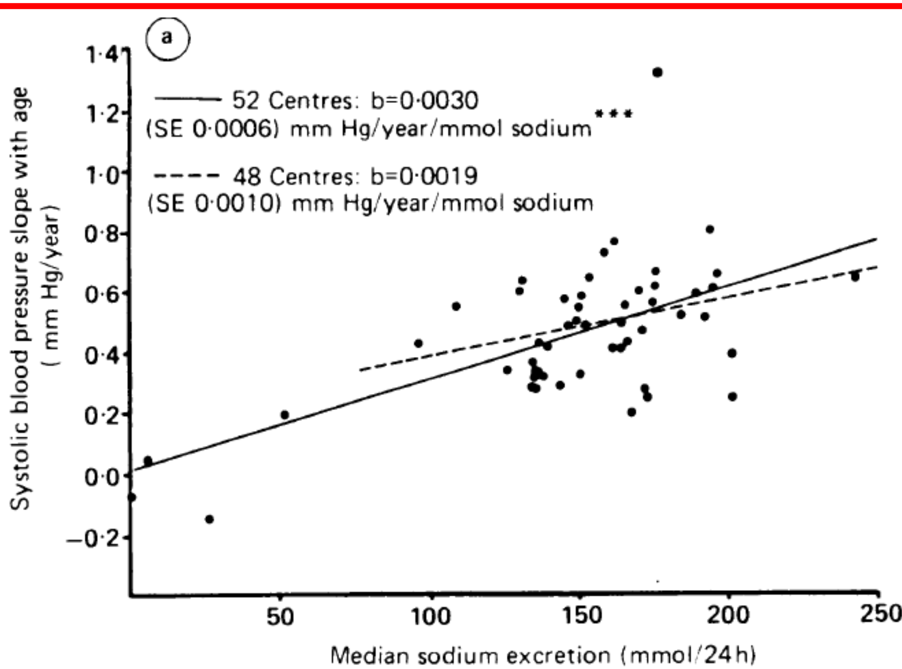
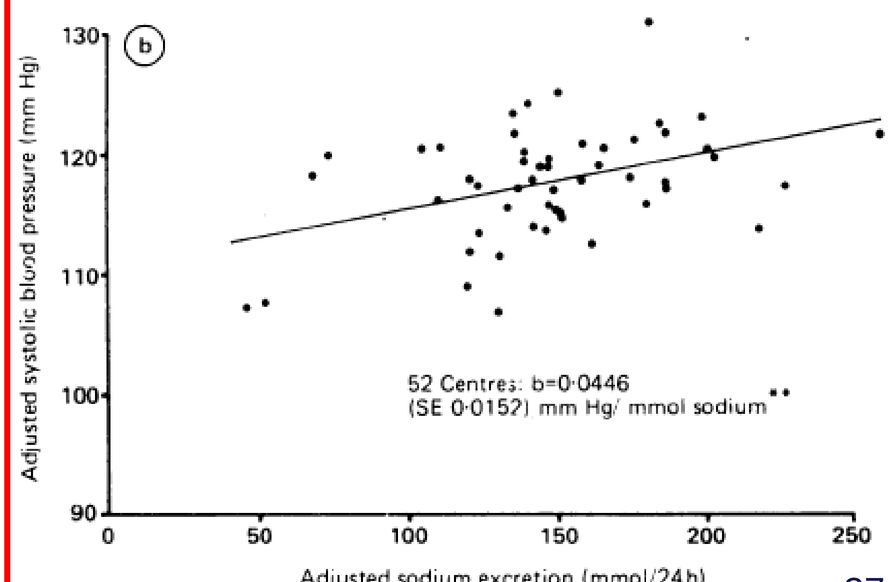






Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations

BMJ VOLUME 312 18 MAY 1996

Paul Elliott, Jeremiah Stamler, Rob Nichols, Alan R Dyer, Rose Stamler, Hugo Kesteloot, Michael Marmot for the Intersalt Cooperative Research Group

Greater difference in average BP over 30 years (age 25-55) per 100 mmol/day Na

Model	SBP difference [mm Hg]† greater by (t-value)	DBP difference [mm Hg]† greater by (t-value)
Linear	10.2 (5.7)***	6.3 (6.6)***
Linear adj.†	8.7 (5.2)***	5.3 (5.7)***
Difference	10.7 (5.1)***	5.7 (5.0)***
"Best fit"	11.3 (6.1)***	6.4 (6.7)***

† Age and sex standardised & adjusted across 52 samples for median BMI, median alcohol intake in drinkers, and prevalence of alcohol drinking *** p<0.001

Commentary: Sodium and blood pressure in the Intersalt study and other studies—in reply to the Salt Institute

Jeremiah Stamler, Paul Elliott, Alan R Dyer, Rose Stamler, Hugo Kesteloot, Michael Marmot, for the Intersalt Steering and Editorial Committee

The Salt Institute continues to misrepresent the findings of Intersalt (and other studies)....

INTERSALT Study

Difference in SBP per 100 mmol Na
Men & women ages 20-59

	mm Hg
Within populations (n=10,074)	3 - 6
Across populations (n=52)	4.5
30-year greater difference in BP (n=52)	9 - 11

Adjusted for age, sex, K, alcohol, with/without BMI & reliability within populations); and age, sex, alcohol, BMI (across populations)

Elliott et al. *BMJ 1996; 312:1249-1253*

Hazard ratios (95% CI) for mortality associated with 100 mmol/d higher Na intake, men and women, Finnish cohort (N = 2,436)

	Adjustment	
	Age & Year	Multiple†
CHD (N=61)	1.51 (1.14-2.00)	1.56 (1.15-2.12)
CVD (N=87)	1.45 (1.14-1.84)	1.36 (1.05-1.76)
All causes (N=180)	1.26 (1.06-1.50)	1.22 (1.02-1.47)

† Adjusted age, sex, year, smoking, serum total & HDL cholesterol, SBP, BMI

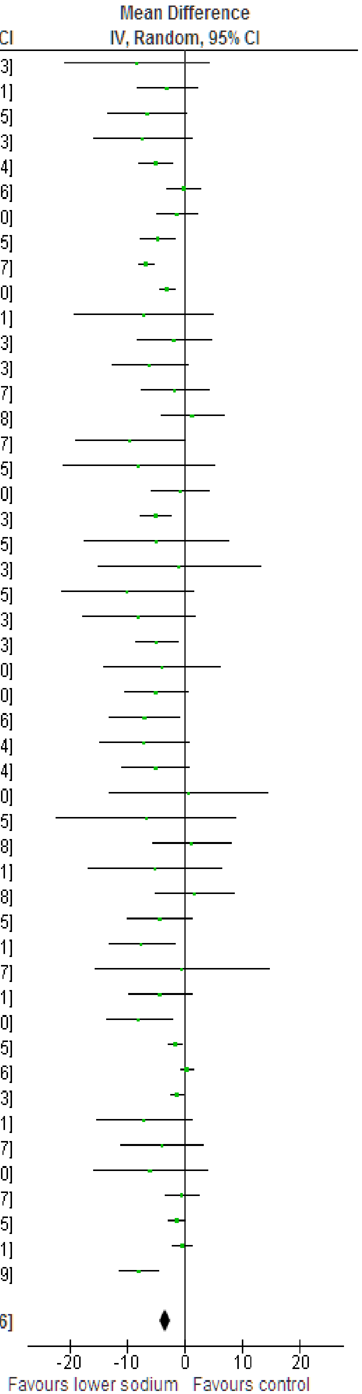
Tuomilehto J *et al.* Lancet 2001; 357: 848-51

RCTs:

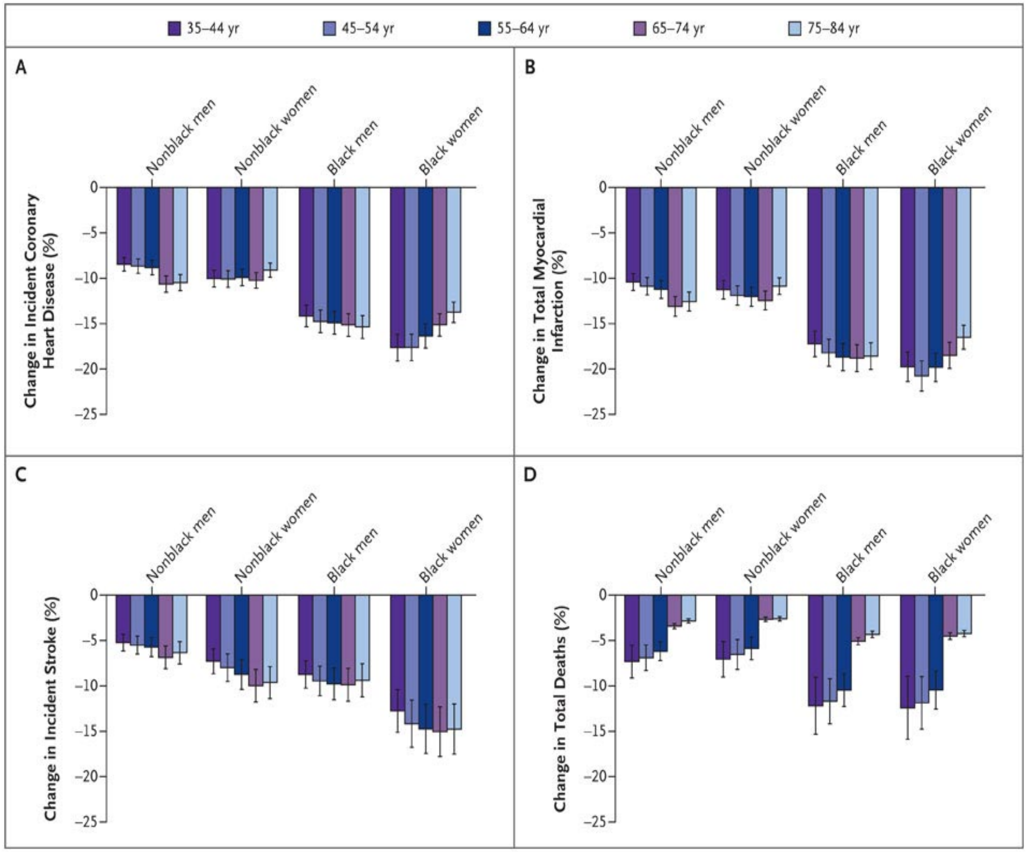
Effect of reduced sodium intake on resting systolic blood pressure in adults
(Aburto et al., BMJ, 2013)

Study or Subgroup	Lower sodium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
ANDERSSON 1984	138	15.5	10	146.4	14.8	13	0.5%	-8.40 [-20.93, 4.13]
ANHMRC 1989	149.1	13	50	152.2	14	53	2.0%	-3.10 [-8.31, 2.11]
BENETOS 1992	142.6	12	20	149.1	10	20	1.4%	-6.50 [-13.35, 0.35]
CAPPUCCIO 1997	155.9	21.6	47	163.2	20.6	47	1.0%	-7.30 [-15.83, 1.23]
CHALMERS 1986	-8.9	7.2	48	-3.8	7.4	52	3.5%	-5.10 [-7.96, -2.24]
CHALMERS 1986	-7.9	6.6	51	-7.7	7.9	49	3.5%	-0.20 [-3.06, 2.66]
COBIAC 1992	126.3	7.42	25	127.7	5.14	27	3.0%	-1.40 [-4.90, 2.10]
COBIAC 1992	127.8	5.05	26	132.5	5.99	28	3.5%	-4.70 [-7.65, -1.75]
DASH 2001	126	6.75	192	132.7	6.5	192	4.8%	-6.70 [-8.03, -5.37]
DASH 2001	123.8	6.6	198	126.8	6.6	198	4.8%	-3.00 [-4.30, -1.70]
DODSON 1989	160.5	22.5	17	167.6	11.5	17	0.5%	-7.10 [-19.11, 4.91]
ERWTEMAN 1984	141	15.4	44	142.9	16.4	50	1.5%	-1.90 [-8.33, 4.53]
ERWTEMAN 1984	128.5	16.3	44	134.6	15.9	50	1.5%	-6.10 [-12.63, 0.43]
ERWTEMAN 1984	135.3	14.8	44	137	13.6	50	1.7%	-1.70 [-7.47, 4.07]
ERWTEMAN 1984	128.1	15	44	126.8	11.6	50	1.9%	1.30 [-4.18, 6.78]
FAGERBERG 1984	138.8	13.17	15	148.3	13.17	15	0.8%	-9.50 [-18.93, -0.07]
FOTHERBY 1993	171	21	17	179	18	17	0.5%	-8.00 [-21.15, 5.15]
GROBBEE 1987	135.7	9	40	136.5	13	40	2.1%	-0.80 [-5.70, 4.10]
HE 2009	141	12	169	146	13	169	3.7%	-5.00 [-7.67, -2.33]
HOWE 1994	135	18.71	14	140	14.97	14	0.5%	-5.00 [-17.55, 7.55]
HOWE 1994	138	14.97	14	139	22.45	14	0.4%	-1.00 [-15.13, 13.13]
MACGREGOR 1982	144	18	19	154	18	19	0.6%	-10.00 [-21.45, 1.45]
MACGREGOR 1989	155	13	20	163	18	20	0.8%	-8.00 [-17.73, 1.73]
MCCARRON 1997	133.6	12.6	97	138.5	12.8	97	3.0%	-4.90 [-8.47, -1.33]
MELAND 1997	141	12.24	16	145	16.33	16	0.7%	-4.00 [-14.00, 6.00]
MELAND 2009	-5.001	9.52	23	-0.001	9.52	23	1.8%	-5.00 [-10.50, 0.50]
MELANDER 2007	125	12.4	39	132	14.7	39	1.6%	-7.00 [-13.04, -0.96]
MUHLHAUSER 1996	128	8	8	135	8	8	1.1%	-7.00 [-14.84, 0.84]
NESTEL 1993	123	10	32	128	14	34	1.7%	-5.00 [-10.84, 0.84]
PARIJS 1973	154.6	21.8	16	154	17.7	17	0.4%	0.60 [-13.00, 14.20]
PARIJS 1973	167.8	24.3	15	174.5	20.02	17	0.3%	-6.70 [-22.25, 8.85]
PUSKA 1983	137.2	16	34	136	13	38	1.4%	1.20 [-5.58, 7.98]
RICHARDS 1984	144.7	14	12	149.9	15	12	0.6%	-5.20 [-16.81, 6.41]
RUPPERT 1993	112	11	25	110.3	13	25	1.4%	1.70 [-4.98, 8.38]
SCIARRONE 1992	-7.6	10.9	19	-3.3	6.5	24	1.8%	-4.30 [-9.85, 1.25]
SCIARRONE 1992	-9.3	9.8	27	-1.8	10.1	21	1.8%	-7.50 [-13.19, -1.81]
SILMAN 1983	138.6	19.62	10	139.1	17.25	15	0.4%	-0.50 [-15.47, 14.47]
SUCKLING 2010	131.2	12.89	46	135.5	13.56	46	1.9%	-4.30 [-9.71, 1.11]
SWIFT 2005	151	13	40	159	13	40	1.8%	-8.00 [-13.70, -2.30]
TOHP 1992	-4.86	7.81	327	-3.16	8.11	417	4.9%	-1.70 [-2.85, -0.55]
TOHP 1997	-0.5	9	537	-0.8	8.7	527	5.0%	0.30 [-0.76, 1.36]
TOHP 1997	-0.7	9	515	0.6	8.5	514	5.0%	-1.30 [-2.37, -0.23]
VOGT 2008	128	17.23	33	135	17.23	33	1.0%	-7.00 [-15.31, 1.31]
VOGT 2008	121	11.49	33	125	17.23	33	1.3%	-4.00 [-11.07, 3.07]
VOGT 2008	137	17.23	33	143	22.98	33	0.8%	-6.00 [-15.80, 3.80]
WATT 1983	136	4.6	18	136.5	4.5	18	3.4%	-0.50 [-3.47, 2.47]
WATT 1985	112.2	3.1	35	113.6	3.1	35	4.7%	-1.40 [-2.85, 0.05]
WATT 1985	110.2	3.23	31	110.7	3.23	31	4.6%	-0.50 [-2.11, 1.11]
WEIR 2010	131.9	12.9	115	139.9	14.2	115	3.0%	-8.00 [-11.51, -4.49]
Total (95% CI)			3304			3432	100.0%	-3.39 [-4.31, -2.46]

Heterogeneity: $Tau^2 = 4.17$; $Chi^2 = 135.80$, df = 48 ($P < 0.00001$); $I^2 = 65\%$
Test for overall effect: $Z = 7.18$ ($P < 0.00001$)

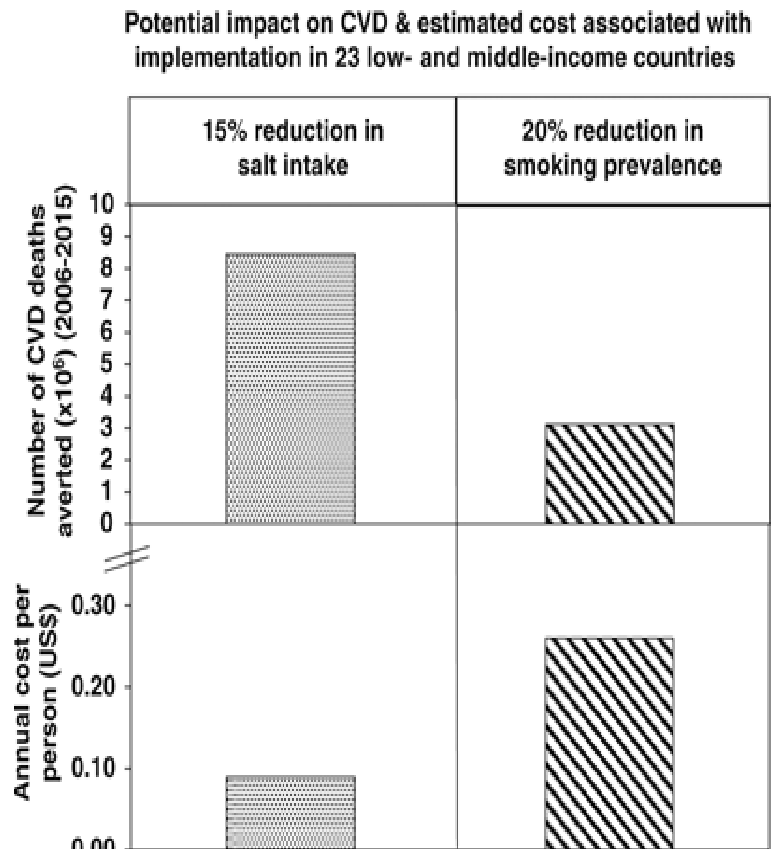


Projected Annual Reductions in CVD Events For a Dietary Salt Reduction of 3 g/d



Bibbins-Domingo *et al.* NEJM 2010; 362:590-599

Salt Reduction vs. Tobacco Control



Asaria P et al. *Lancet* 2007;370: 2044-53

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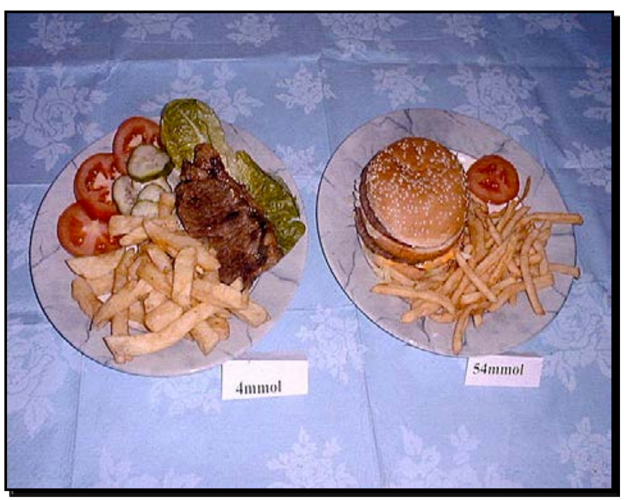
Sources of Salt in the Diet

- **Natural salt content of foods 10%**
- **Food manufacture and processing 75 %**
- **Added in cooking and at table 15 %**

Sanchez-Castillo et al. *Clin Sci 1987; 72:95-102*



BMJ

LONDON, SATURDAY 18 MAY 1996

Godlee F *BMJ* 1996;312(7041):1239-40.

The food industry fights for salt

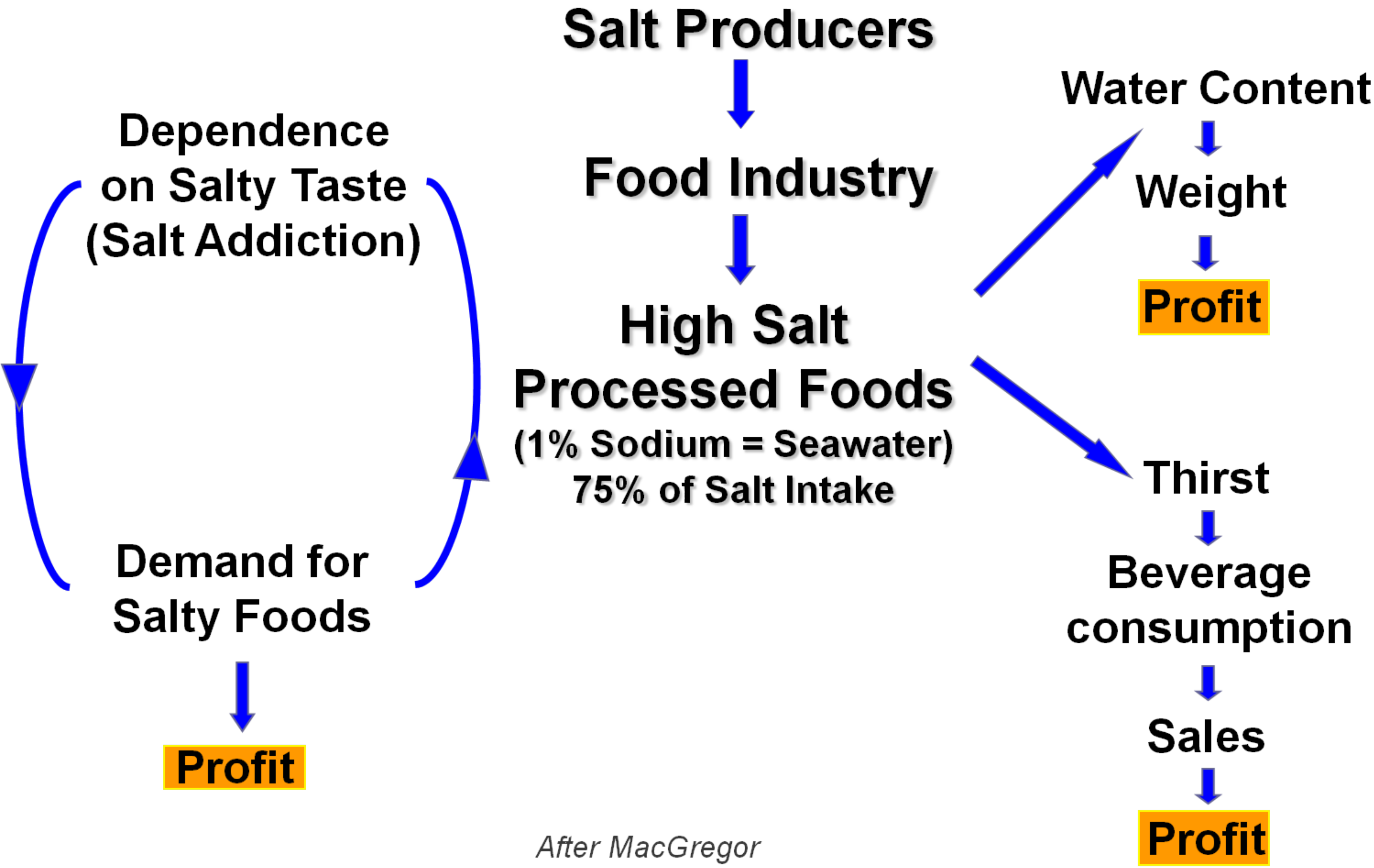
See pp 1249, 1283, 1284, 1285

But delaying salt reductions has public health and commercial costs

Like any group with vested interests, the food industry resists regulation. Faced with a growing scientific consensus that salt increases blood pressure[1 2] and the fact that most dietary salt (65-85%) comes from processed foods,[3] some of the world's major food manufacturers have adopted desperate measures to try to stop governments from recommending salt reduction. Rather than reformulate their products, manufacturers have lobbied governments, refused to cooperate with expert working parties, encouraged misinformation campaigns, and tried to discredit the evidence. This week's *BMJ* finds them defending their interests as vigorously as ever.

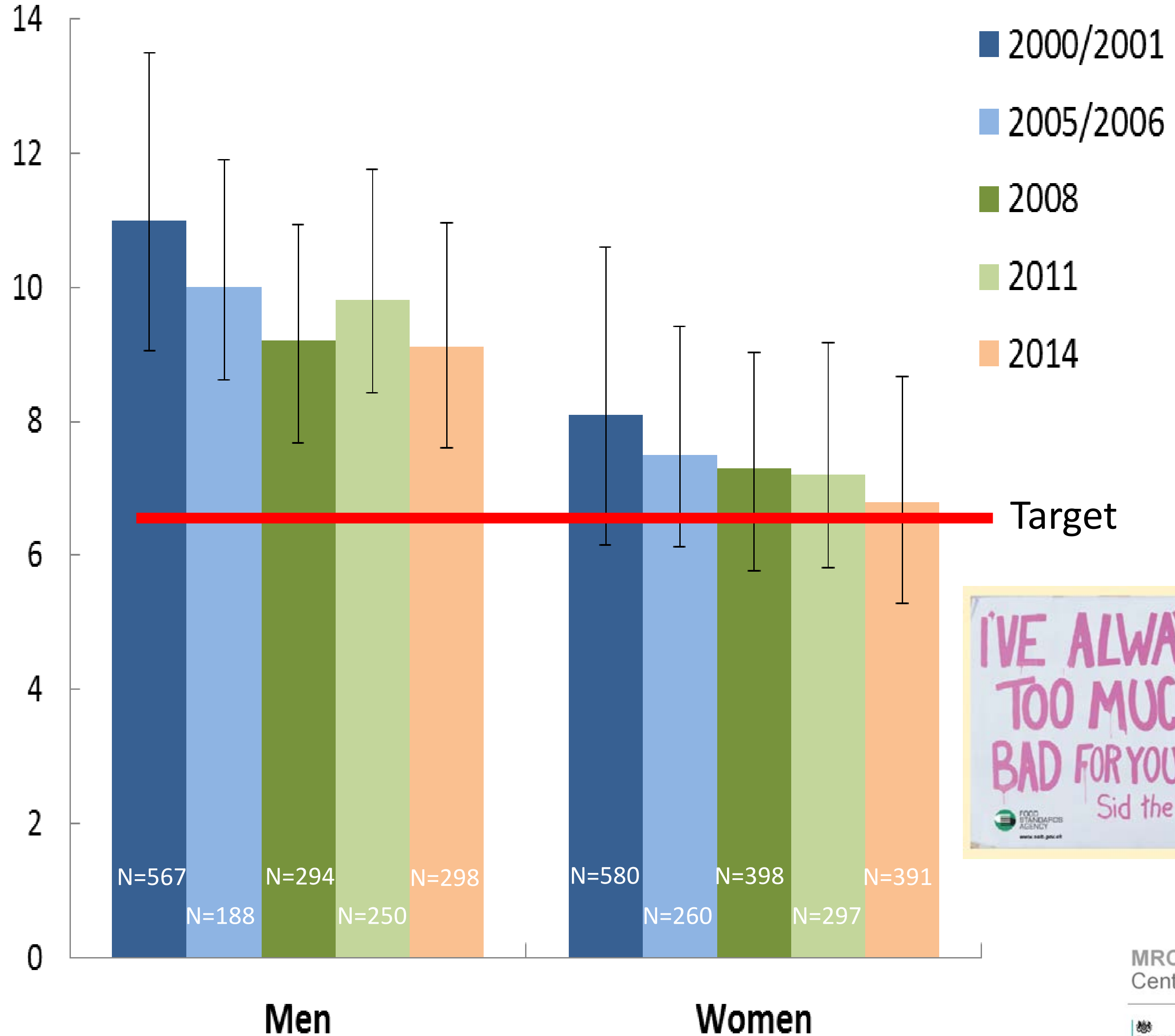
The food industry has everything to gain from keeping controversy alive.[11] Common salt is the main source of flavour in processed foods. Tasting panels show that low salt foods are often unappetising, and there is currently no good alternative to sodium chloride. Improving flavour by adding more natural ingredients (such as fruit and vegetables) would be expensive.

The food industry has lobbied fiercely against the threat to its profits. In June 1994, after confidential drafts of the cardiovascular review group's report were circulated to the government's nutrition task force (which included at least one consultant to the food industry), representatives of Britain's



After MacGregor

Monitoring salt intake in UK population by gender
24-hour urine collections



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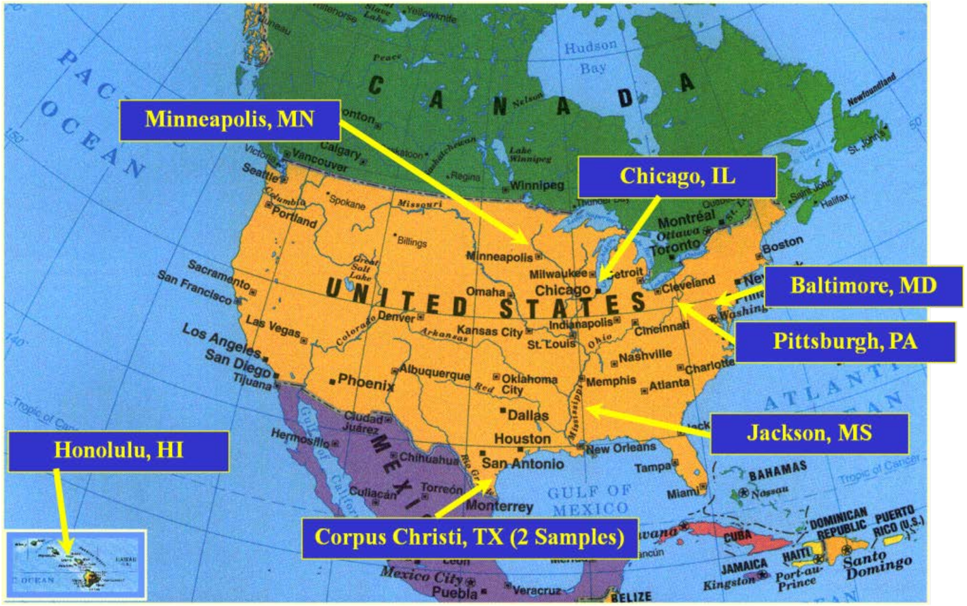
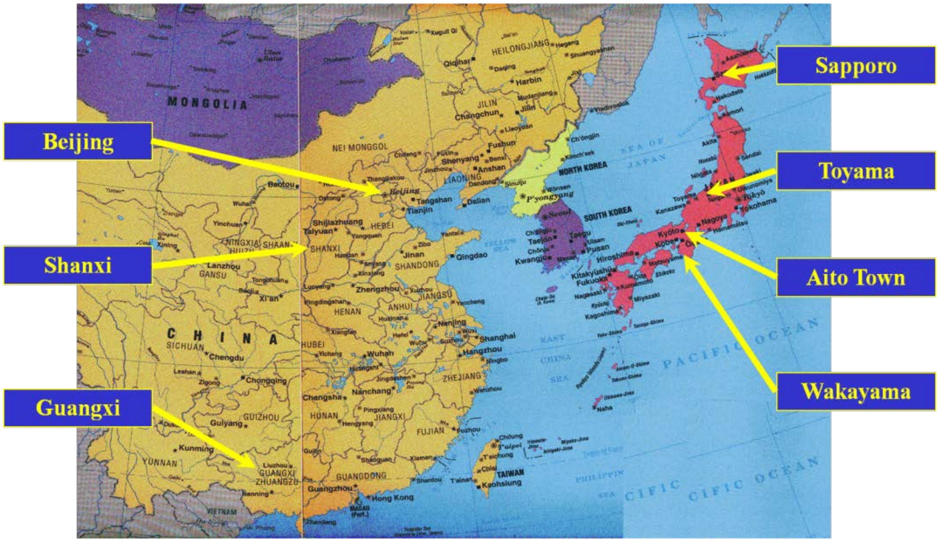
INTERMAP Study





- Multi-centre cross-sectional study of 4,680 men & women ages 40-59 in China, Japan, UK, USA

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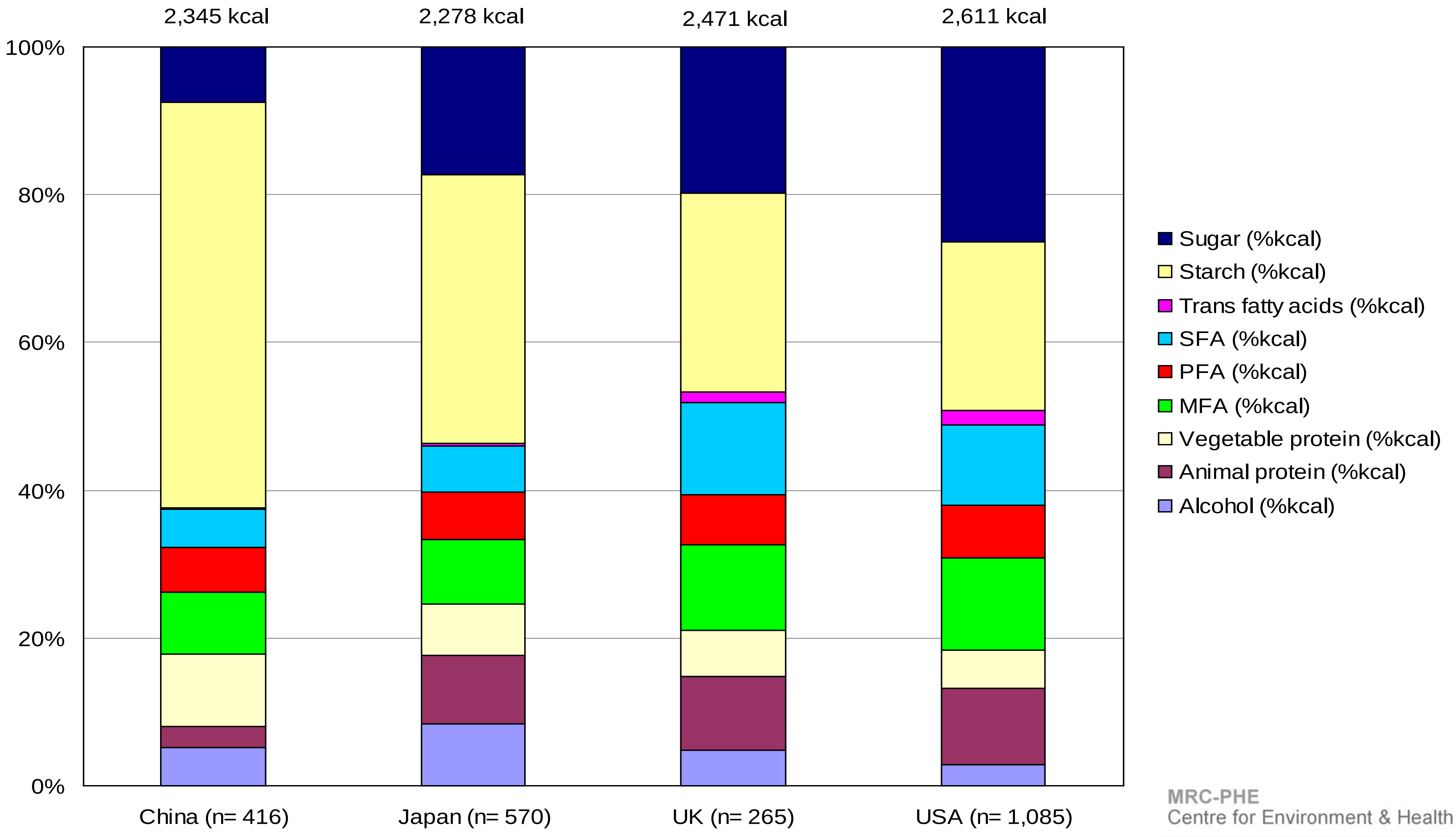
INTERMAP

4 visits per participant:

- 8 BP measurements
- 4 x height, weight
- 4 x 24 h dietary recalls: foods, 83 nutrients – updated to 163 nutrients/ratios
- 2 x 7d alcohol
- Dietary supplements
- Questionnaire
- 2 x 24h urine collections
- ^{1}H NMR urinary spectroscopy/MS

INTERMAP Study



Holmes et al, ***Nature***, *2008*

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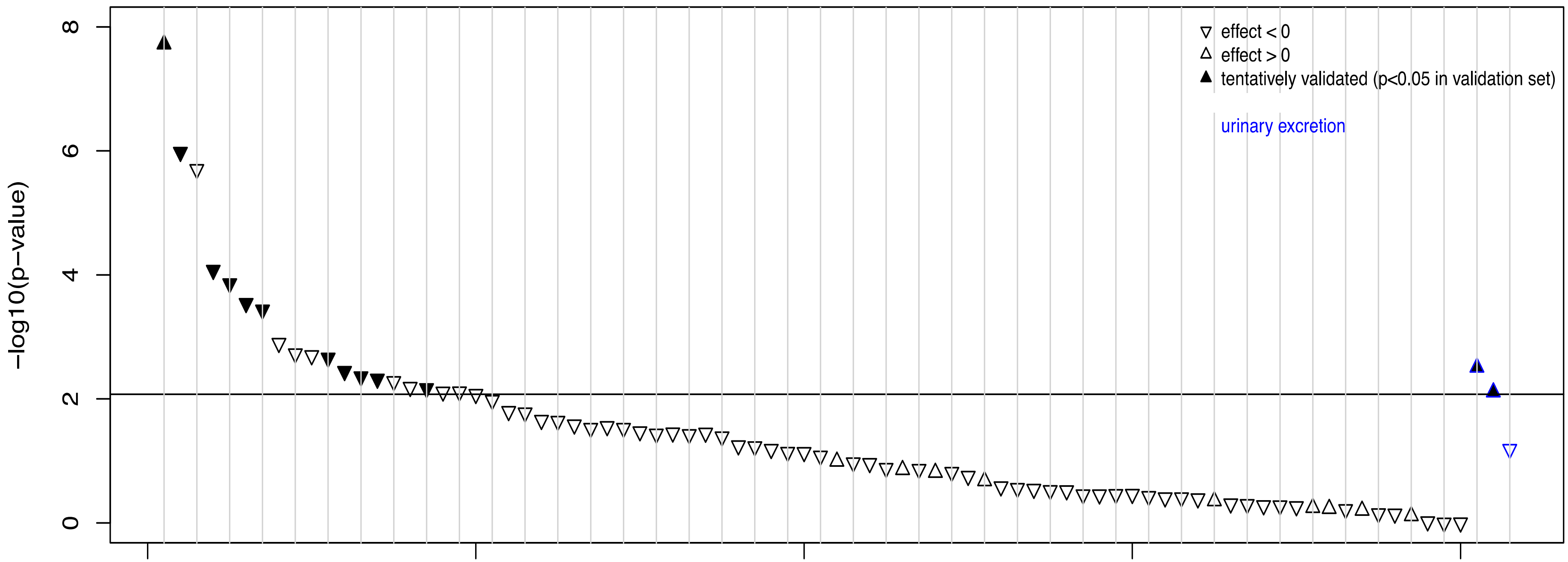
Estimated Effect on Average SBP of More Favourable Diet: INTERMAP

Variable	Improvement in level	Estimated lower average SBP (mm Hg) *Multivariate models with BMI*			
		Model 1	Model 2	Model 3	Model 4
Sodium (mmol/24h)	-110	-0.7‡	-0.7‡	-0.7	-0.7‡
Potassium (mmol/24h)	+60	-2.8***	-2.7***	-2.8***	-2.8***
Calcium (mg/1000kcal)	+240	-1.4*	-1.2**	-1.2‡	-1.1
Phosphorus (mg/1000kcal)	+232	-0.5	--	-0.2	--
Magnesium (mg/1000kcal)	+76	--	--	-0.8	-0.2
Non-heme Fe (mg/1000kcal)	+4.1	--	-0.9‡	--	-1.3**
PFA (%kcal)	+4.1	-0.6	-0.6	-0.6	-0.7
Vegetable protein (%kcal)	+2.8	-1.2**	-0.8‡	--	--
Heavy alcohol intake	None	(-3.3***) -0.6†	(-3.3***) -0.6†	(-3.5***) -0.6†	(-3.4***) -0.6†
BMI (kg/m^2)	-4	-3.4***	-3.4***	-3.5***	-3.5***
Sum – All Variables	**--**	**-11.2**	**-10.9**	**-10.4**	**-11.0**
Sum – Na, K, Alcohol, BMI	**--**	**-7.5**	**-7.4**	**-7.6**	**-7.7**

*** p<0.001 ** p<0.01 * p<0.05 ‡p<0.1 †Effect of alcohol calculated as regression coefficient x prevalence of heavy drinking

Stamler J et al . In: *Nutritional and Metabolic Bases of Cardiovascular Disease:* Mancini M, *et al*. eds. Blackwell Publishing, 2011

Nutrient wide Association Study (NWAS) (SBP)



B-vitamins

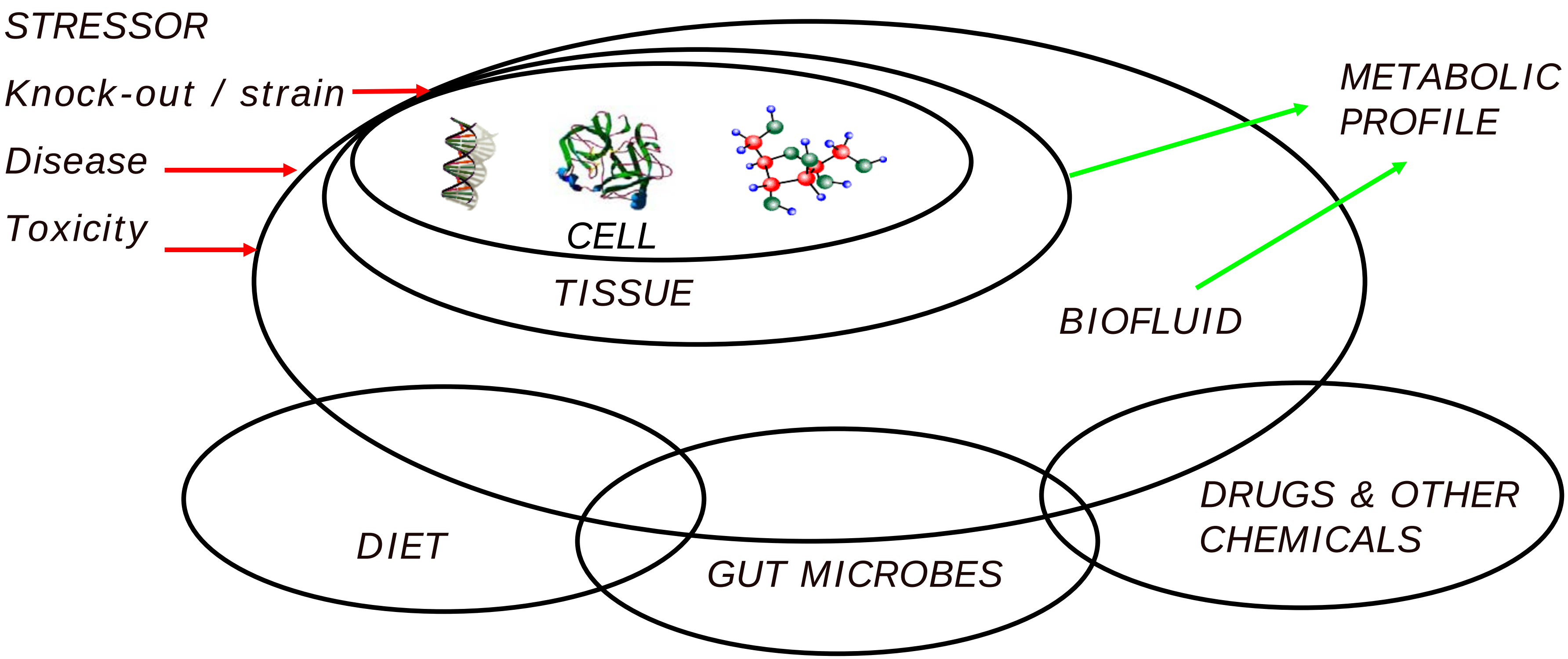
Tzoulaki et al *Circulation* 2012

Metabolic Profiling

Study of the complement of small molecules within biological systems

Also known as metabolomics or metabonomics

Untargeted: No prior hypothesis of specific metabolites involved



System ⇔ Environment

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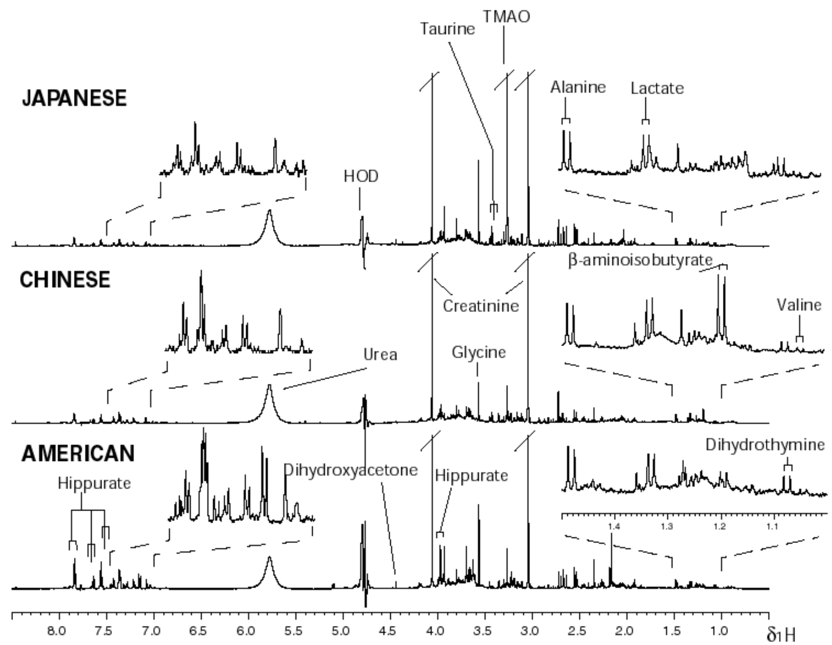
nature Vol 453|15 May 2008|doi:10.1038/nature06882

LETTERS

Metabolome-Wide Association Study (MWAS)

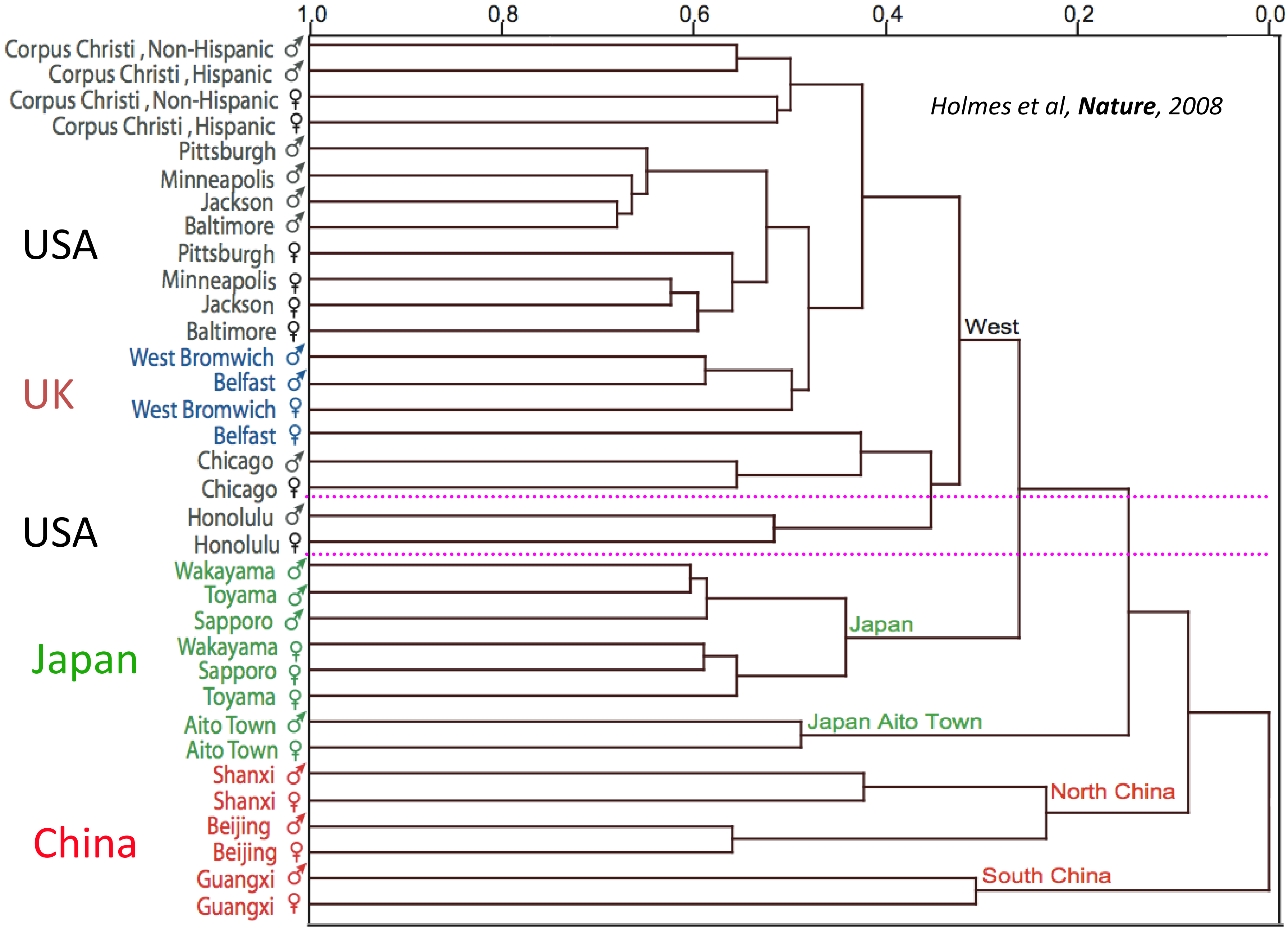
Human metabolic phenotype diversity and its association with diet and blood pressure

Elaine Holmes[1]*, Ruey Leng Loo[1,2]*, Jeremiah Stamler[3], Magda Bictash[1,2], Ivan K. S. Yap[1,2], Queenie Chan[2], Tim Ebbels[1], Maria De Iorio[2], Ian J. Brown[2], Kirill A. Veselkov[1], Martha L. Daviglus[3], Hugo Kesteloot[4], Hirotsugu Ueshima[5], Liancheng Zhao[6], Jeremy K. Nicholson[1] & Paul Elliott[2]

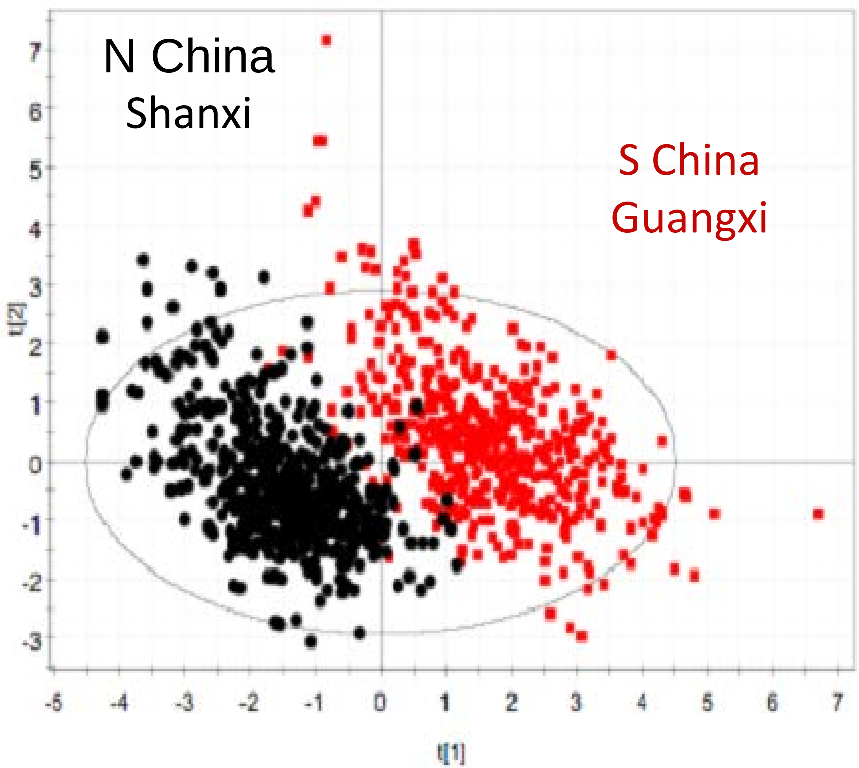


Population Metabolic Phenotype Mapping (INTERMAP)

China, Japan, UK, USA - 17 sub-populations, male/female, N = 4630 (24-h urine)



INTERMAP Study – Chinese samples



	Mean (SD)	
Trait	**N China (N=523)**	**S China (N=244)**
SBP mm Hg	123.8 (18.6)	115.4 (13.0)
Ur Na mmol/24h	271.4 (88.3)	139.2 (55.5)
Ur Na/K ratio	7.8 (2.4)	3.7 (1.5)
Ca mg/1000 kcal	136.5 (48.4)	175.0 (62.5)
Mg mg/1000 kcal	133.2 (38.7)	198.2 (27.2)

Yap et al. *J Proteome Res* 2010;9(12):6647-54

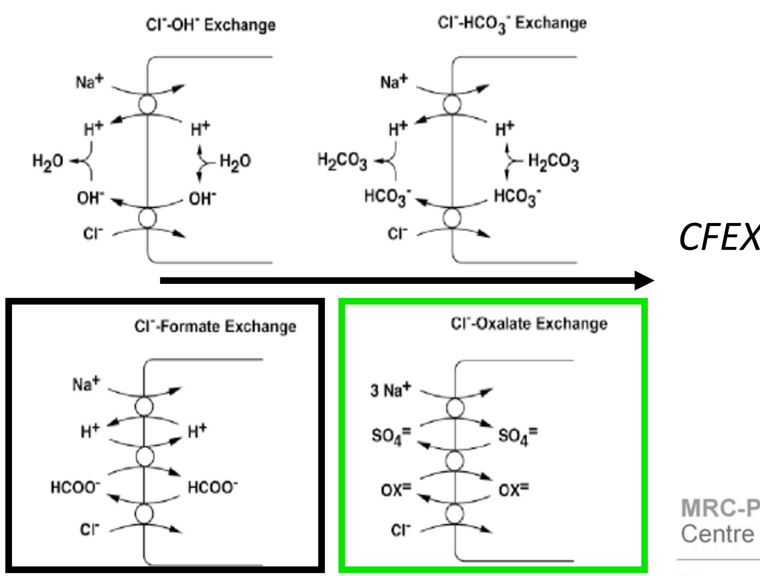
METABOLOME WIDE ASSOCIATION STUDIES: METABOLIC PHENOTYPE LINKAGE TO HUMAN BLOOD PRESURE

Table 1: Estimated mean differences* in systolic and diastolic BP (Z-scores‡)

Urinary metabolite	A				B			
			Adjusted for BMI†				Adjusted for BMI†	
	Systolic blood pressure							
Alanine	**2.69**	**(6.06)**	0.40	(0.92)	2.66	(5.54)	1.13	(2.43)
Formate	**-1.19**	**(-2.62)**	-1.42	(-3.29)	-1.94	(-3.92)	-1.04	(-2.20)
Hippurate	**-2.10**	**(-4.85)**	-1.63	(-3.95)	-1.72	(-3.70)	-0.82	(-1.83)
NMNA**	**-0.09**	**(-0.21)**	0.20	(0.49)	0.00	(0.00)	0.65	(1.53)

***N* methyl-nicotinate

"Metabolome-Wide Association Studies" for novel hypothesis generation… e.g.….A possible new role for formate in human BP regulation?



*Holmes et al, **Nature**, 2008*

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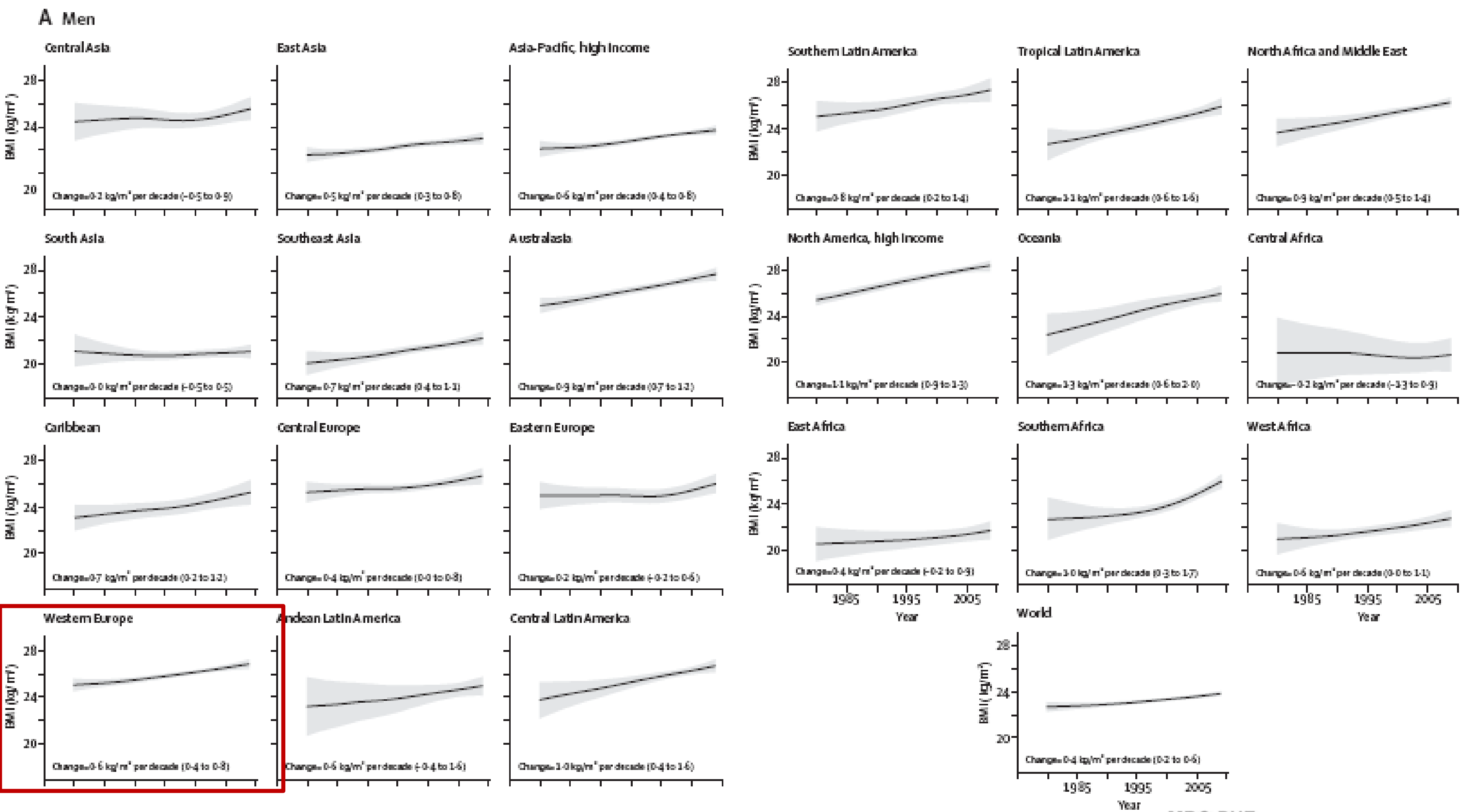
Obesity trends worldwide



Finucane et al. *Lancet* 2011; 377:557-67

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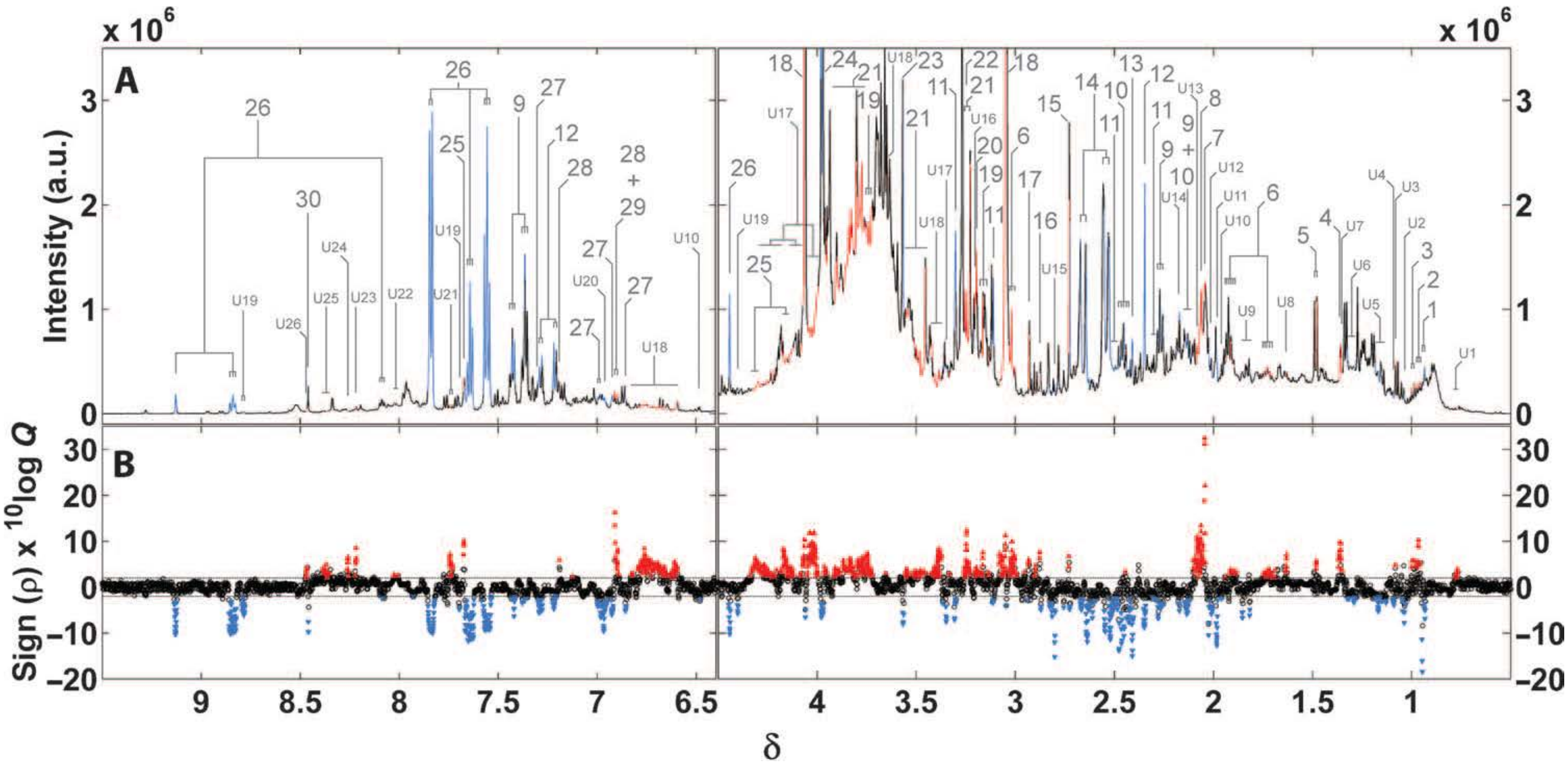
RESEARCH ARTICLE www.ScienceTranslationalMedicine.org 29 April 2015 Vol 7 Issue 285 285ra62

METABOLOMICS

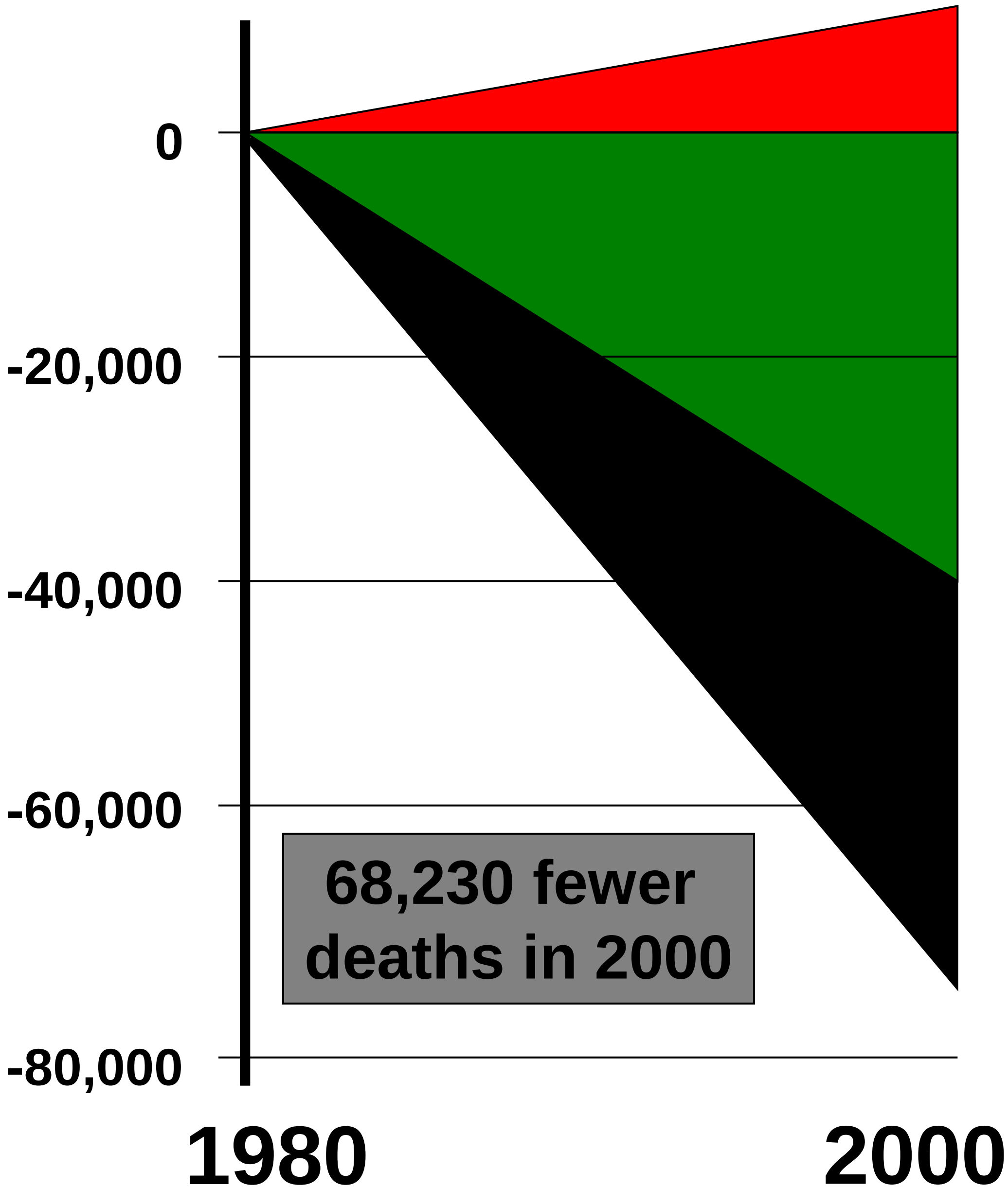
Urinary metabolic signatures of human adiposity

Paul Elliott,[1*†] Joram M. Posma,[1,2†] Queenie Chan,[1] Isabel Garcia-Perez,[2] Anisha Wijeyesekera,[2] Magda Bictash,[2] Timothy M. D. Ebbels,[2] Hirotsugu Ueshima,[3] Liancheng Zhao,[4] Linda van Horn,[5] Martha Daviglus,[5,6] Jeremiah Stamler,[5] Elaine Holmes,[2] Jeremy K. Nicholson[2]*



1: ketoleucine, 2: leucine, 3: valine, 4: 2-hydroxyisobutyrate, 5: alanine, 6: lysine, 7: N-acetyl signals from urinary glycoproteins, 8: N-acetyl neuraminate, 9: phenylacetylglutamine, 10: glutamine, 11: proline betaine, 12: 4-cresyl sulfate,13: succinate, 14: citrate, 15: dimethylamine, 16: TMA, 17: dimethylglycine, 18: creatinine, 19: ethanolamine, 20: O-acetyl carnitine, 21: glucose, 22: 3-methylhistidine, 23: glycine, 24: hippurate, 25: pseudouridine, 26: NMNA, 27: 3-hydroxymandelate, 28: tyrosine, 29: 4-hydroxymandelate, 30: formate, U1 to U26 unidentified

Deaths averted



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


THE BEST THING YOU CAN DO IS GIVE UP SMOKING, DRINKING AND FRIED FOOD
WHAT'S THE SECOND BEST ?