SALT 2018

Reducing salt intake for cardiovascular prevention

Times are changing

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A scientific issue or a matter of faith?*

Complex statistical modelling suggests that a population-wide decrease of salt intake might substantially reduce CV complications and health care costs.

- The association between BP and salt intake in populations is inconsistent;
- Short-term and extreme interventions in selected NT subjects or HT patients cannot be extrapolated to the general population;
- A generalised reduction of salt consumption is not feasible and not necessary.
- Prospective outcome studies did not conclusively prove benefit associated with low salt intake and suggest that a too low salt intake might even cause harm.

* Robertson JIS, *J Eval Clin Pract 2003*; 9: 1-22

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Summary of the evidence

How it all started

Intersalt

BP *vs* sodium in within-centre analyses (n° of centres)

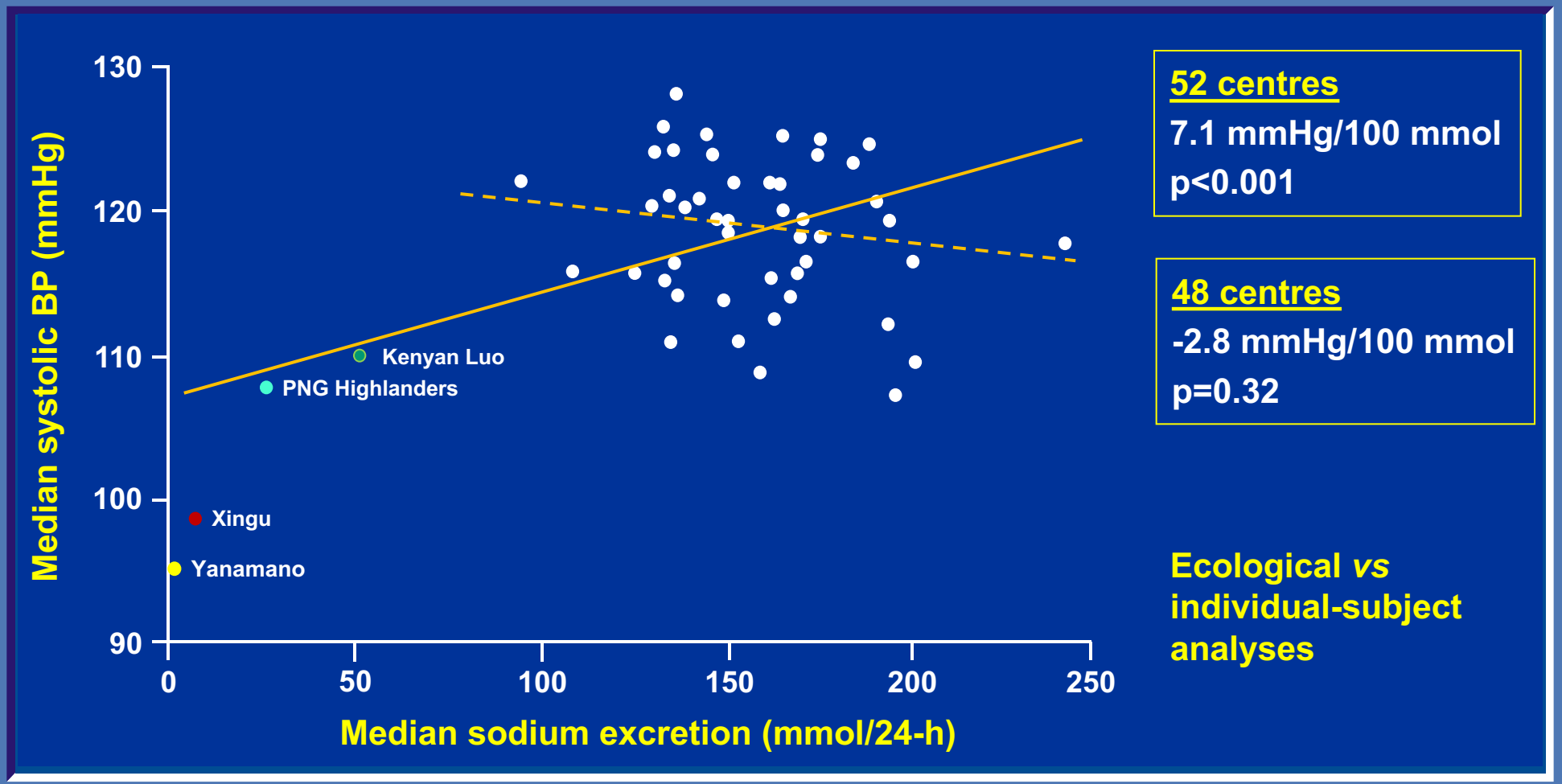
	SBP		DBP	
	Partial	Full	Partial	Full
Positive	39	33	33	25
Positive, p<0.05	15	8	4	3
Negative	13	19	19	27
Negative, p<0.05	2	2	1	3

Partial: sex and age; **full:** plus BMI, alcohol and UK

BMJ 1988; 297: 319-28

Intersalt

SBP *vs* sodium excretion in between-centre analyses

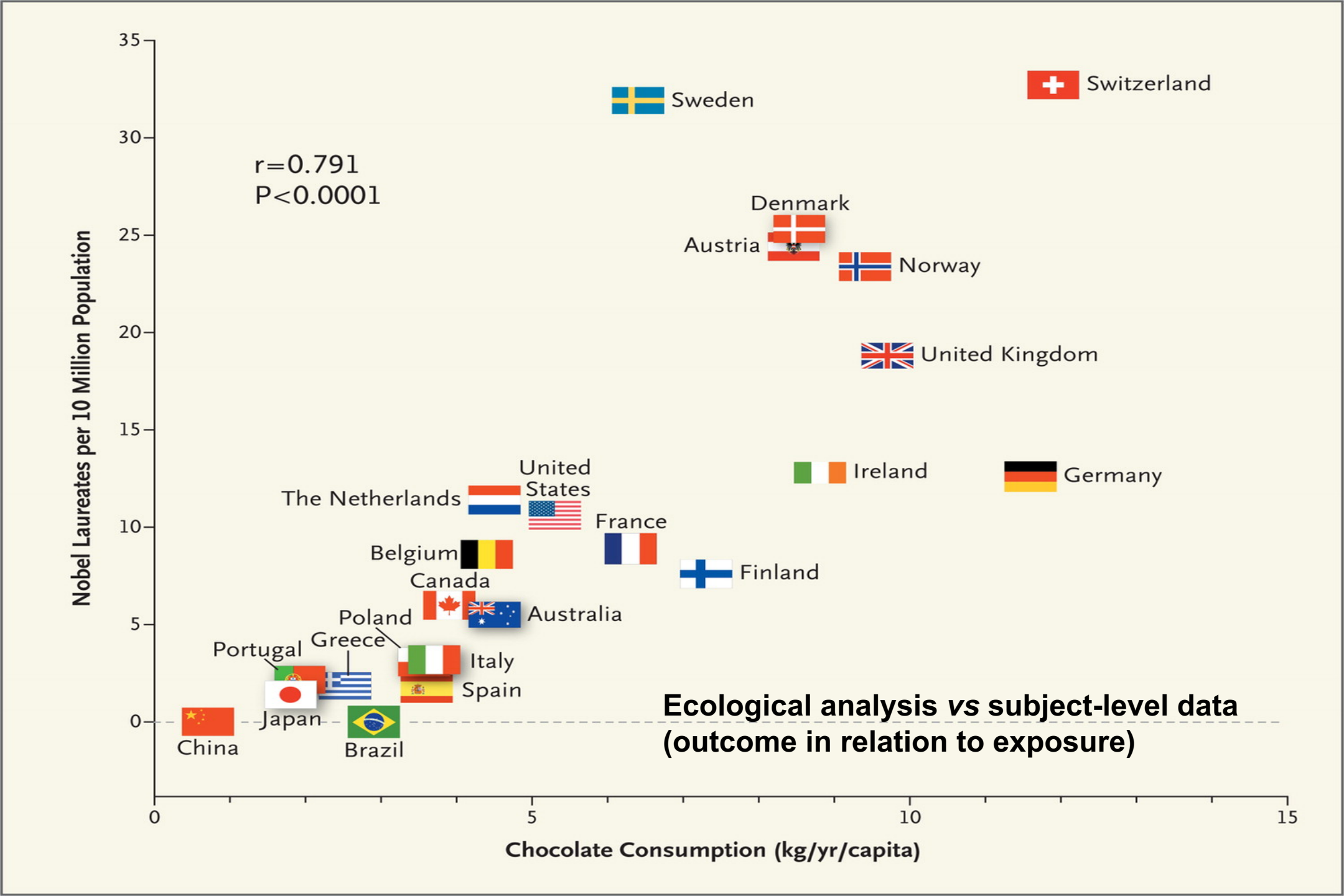


52 centres
7.1 mmHg/100 mmol
p<0.001

48 centres
-2.8 mmHg/100 mmol
p=0.32

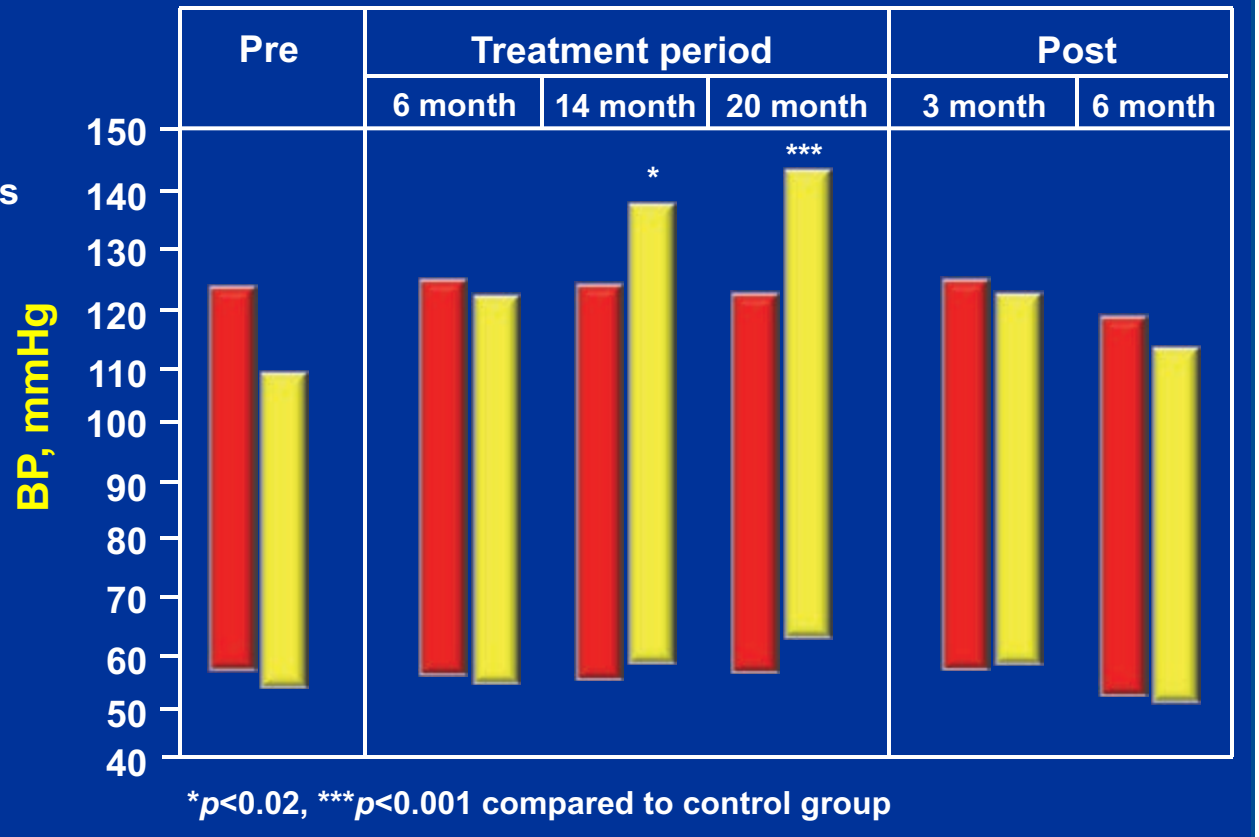
Ecological *vs* individual-subject analyses

BMJ 1988; 297: 319-28


r=0.791
P<0.0001
Sweden
Switzerland
Denmark
Austria
Norway
United Kingdom
Ireland
Germany
United States
The Netherlands
France
Belgium
Finland
Canada
Australia
Poland
Greece
Portugal
Italy
Spain
Japan
China
Brazil
Ecological analysis *vs* subject-level data
(outcome in relation to exposure)
Nobel Laureates per 10 Million Population
Chocolate Consumption (kg/yr/capita)
0
5
10
15
20
25
30
35

SALT Trial in chimpanzees

- Control group: 0.5 g salt per day
- Experimental group: increased salt intake to 15 g/d for 20 months
- Rise in systolic BP: 26 mmHg



Denton et al, *Nat Med 1995;* 1: 1009-16

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Meta-analyses of intervention trials

	Normotensive	Hypertensive
Grobbee & Hofman, 1988	3.6/2.0	
Midgley, 1996	1.0/0.1	3.7/0.9
Cutler, 1997	1.9/1.1	4.8/2.5
Graudal , 1998	1.2/0.3	3.9/1.9
He & MacGregor, 2000	1.6/0.6	4.2/2.4

Robertson JIS, *J Eval Clin Pract 2003;* 9: 1-22

Finland

HRs for 100 mmol/day increase in UNa^+

	Women (*n*=1263)	Men (1173)	Lean men (659)	Obese men (514)
CHD death	2.07 (0.80–2.36)	1.45 (1.07–1.97)	1.23 (0.76–1.98)	1.44 (1.02–2.00)
CV mortality	1.43 (0.73–2.78)	1.43 (1.10–1.86)	…	…
CHD	1.30 (0.79-2.14)	1.34 (1.07–1.68)	…	…
Stroke	1.39 (0.93–2.07)	1.14 (0.78–1.66)	…	…

Interpretation High sodium intake predicted mortality and risk of coronary heart disease, independent of other cardiovascular risk factors, including blood pressure. These results provide direct evidence of the harmful effects of high salt intake in the adult population.

Adjusted for study year and age.

Tuomilehto J et al, *Lancet* 2001; 357: 848-851

NHANES III

HRs for CHD (825) and CV (433) mortality across quartiles and in continuous analyses

		II	III	IV	p	+1 g/d (+1 unit)
Na^+ (0.8–5.1)	CHD	1.17	1.36	1.70	0.36	1.20 (0.81–1.77)
	CV	0.95	0.90	0.83	0.72	0.94 (0.73–1.44)
K^+ (0.6–8.8)	CHD	0.67	0.46	0.26	0.005	0.51 (0.32–0.81)
	CV	0.75	0.58	0.39	0.005	0.63 (0.46–0.87)
Na^+/K^+ (0.98–1.57)	CHD	1.28	1.57	2.15	<0.001	3.66 (1.94–6.90)
	CV	1.13	1.25	1.46	0.01	1.90 (1.20–3.03)

Yang Q et al, *Arch Intern Med* 2011; 171: 1183-91

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Summary of the evidence

How the story recently unfolded

Anneke

ORIGINAL CONTRIBUTION

Fatal and Nonfatal Outcomes, Incidence of Hypertension, and Blood Pressure Changes in Relation to Urinary Sodium Excretion

Katarzyna Stolarz-Skrzypek, MD, PhD
Tatiana Kuznetsova, MD, PhD
Lutgarde Thijs, MSc
Valérie Tikhonoff, MD, PhD
Jitka Seidlerová, MD, PhD
Tom Richart, MD
Yu Jin, MD
Agnieszka Olszanecka, MD, PhD
Sofia Malyutina, MD, PhD
Edoardo Casiglia, MD, PhD
Jan Filipovský, MD, PhD
Kalina Kawecka-Jaszcz, MD, PhD
Yuri Nikitin, MD, PhD
Jan A. Staessen, MD, PhD
for the European Project on Genes in Hypertension (EPOGH) Investigators

Context Extrapolations from observational studies and short-term intervention trials suggest that population-wide moderation of salt intake might reduce cardiovascular events.

Objective To assess whether 24-hour urinary sodium excretion predicts blood pressure (BP) and health outcomes.

Design, Setting, and Participants Prospective population study, involving 3681 participants without cardiovascular disease (CVD) who are members of families that were randomly enrolled in the Flemish Study on Genes, Environment, and Health Outcomes (1985-2004) or in the European Project on Genes in Hypertension (1999-2001). Of 3681 participants without CVD, 2096 were normotensive at baseline and 1499 had BP and sodium excretion measured at baseline and last follow-up (2005-2008).

Main Outcome Measures Incidence of mortality and morbidity and association between changes in BP and sodium excretion. Multivariable-adjusted hazard ratios (HRs) express the risk in tertiles of sodium excretion relative to average risk in the whole study population.

Results Among 3681 participants followed up for a median 7.9 years, CVD deaths decreased across increasing tertiles of 24-hour sodium excretion, from 50 deaths in the low (mean, 107 mmol), 24 in the medium (mean, 168 mmol), and 10 in the high excretion group (mean, 260 mmol; $P < .001$), resulting in respective death rates of 4.1% (95% confidence interval [CI], 3.5%-4.7%), 1.9% (95% CI, 1.5%-2.3%), and 0.8% (95% CI, 0.5%-1.1%). In multivariable-adjusted analyses, this inverse association retained significance ($P = .02$): the HR in the low tertile was 1.56 (95% CI, 1.02-2.36; $P = .04$). Baseline sodium excretion predicted neither total mortality ($P = .10$) nor fatal combined with nonfatal CVD events ($P = .55$). Among 2096 participants followed up for 6.5 years, the risk of hypertension did not increase across increasing tertiles ($P = .93$). Incident hypertension was 187 (27.0%; HR, 1.00; 95% CI, 0.87-1.16) in the low, 190 (26.6%; HR, 1.02; 95% CI, 0.89-1.16) in the medium, and 175 (25.4%; HR , 0.98; 95% CI, 0.86-1.12) in the high sodium excretion group. In 1499 participants followed up for 6.1 years, systolic blood pressure increased by 0.37 mm Hg per year ($P < .001$), whereas sodium excretion did not change (−0.45 mmol per year, $P = .15$). However, in multivariable-adjusted analyses, a 100-mmol increase in sodium excretion was associated with 1.71 mm Hg increase in systolic blood pressure ($P < .001$) but no change in diastolic BP.

Conclusions In this population-based cohort, systolic blood pressure, but not diastolic pressure, changes over time aligned with change in sodium excretion, but this association did not translate into a higher risk of hypertension or CVD complications. Lower sodium excretion was associated with higher CVD mortality.

JAMA. 2011;305(17):1777-1785

www.jama.com

THE EVIDENCE RELATING BLOOD pressure to salt intake in humans originates from population-based studies[1] and ran-

report.[2] In a meta-analysis of 31 trials with a minimum duration of 4 weeks,

Author Affiliations are listed at the end of this article.
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APPENDIX 1

Journal of Epidemiology and Community Health, 35 : 256-261, 1981

55

Salt and blood pressure in Belgium

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From the Hypertension and Cardiovascular Rehabilitation Unit, Department of Pathophysiology, University of Leuven, Belgium

C. BULPITT
From the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine

J. V. JOOSSENS
From the Division of Epidemiology, School of Public Health, Leuven, Belgium

SUMMARY Blood pressure, pulse rate, body weight, and height were measured on two occasions in the inhabitants of a random 10% sample of households in a Belgian village. Twenty-four-hour urinary excretion of creatinine, sodium, and potassium was also determined. In men aged 19 there was a significant correlation between systolic blood pressure and body weight and, in women, also [illegible] and the [illegible] systolic blood pressure [illegible]

EPOGH

Change over 6.1 y in BP cohort

	Nº	24-h urinary sodium			Systolic/diastolic BP		
		BL	FU	Δ/y	BL	FU	Δ/y
BE	1109	165	166	+0.1	122/74	124/78	+0.2/+0.4
CZ	69	181	188	+1.3	117/74	117/78	-0.0/+0.6
IT	148	173	169	-0.4	120/77	126/84	+0.9/+0.9
PL	107	230	188	-6.3*	120/75	130/78	+1.5/+0.6
RU	66	198	187	-1.4	116/73	119/77	+0.4/+0.5

* $p<0.05$

Stolarz-Skrzypek et al, JAMA 2011; 305: 1777-85

Mortality

Average annual percentage change in death rates in European (1998-2007)

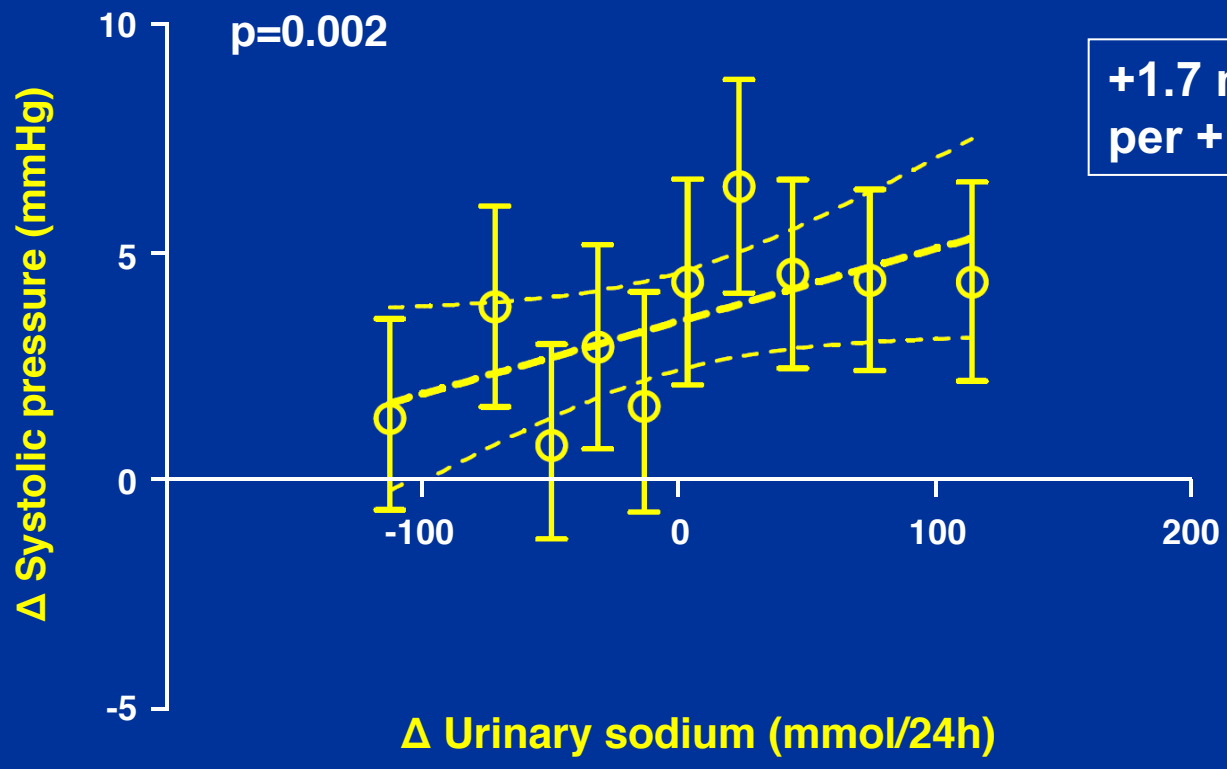
	Women		Men	
	East	West	East	West
All cardiovascular	-2.8	-2.8	-2.5	-3.2
Ischaemic heart disease	-2.0	-2.9	-2.2	-2.5
Stroke	-3.2	-3.9	-3.2	-4.8

East: Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia and Slovenia
West: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxemburg, Netherlands, Portugal, Spain, Sweden, United Kingdom

Helis E et al, *Cardiovasc Prev Rehab 2011;* 18: 347-59

EPOGH

Δ systolic BP *vs* Δ 24-h sodium



Stolarz-Skrzypek et al, JAMA 2011; 305: 1777-85

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Meta-analyses of intervention trials

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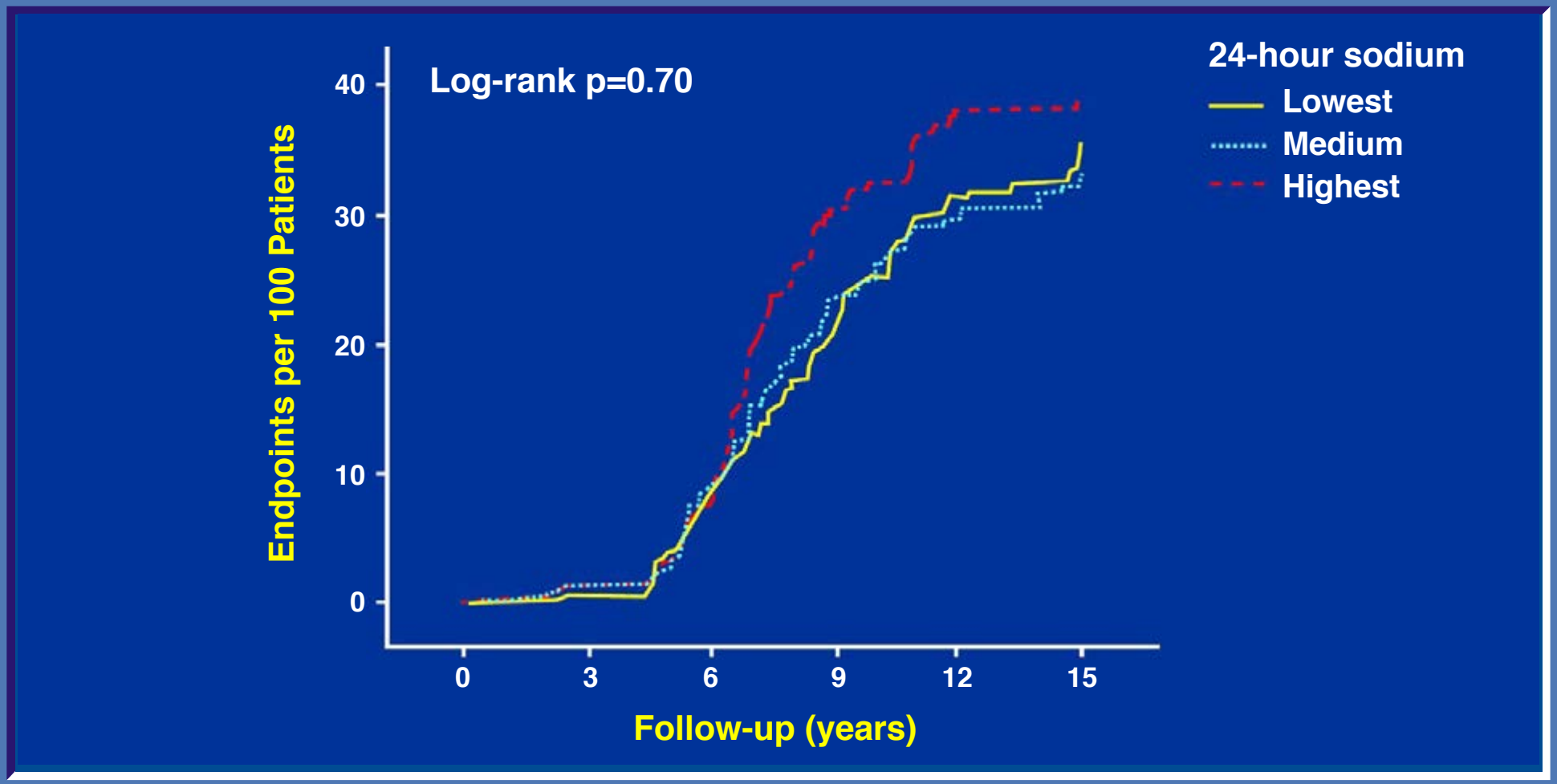
Robertson JIS, *J Eval Clin Pract 2003;* 9: 1-22

EPOGH

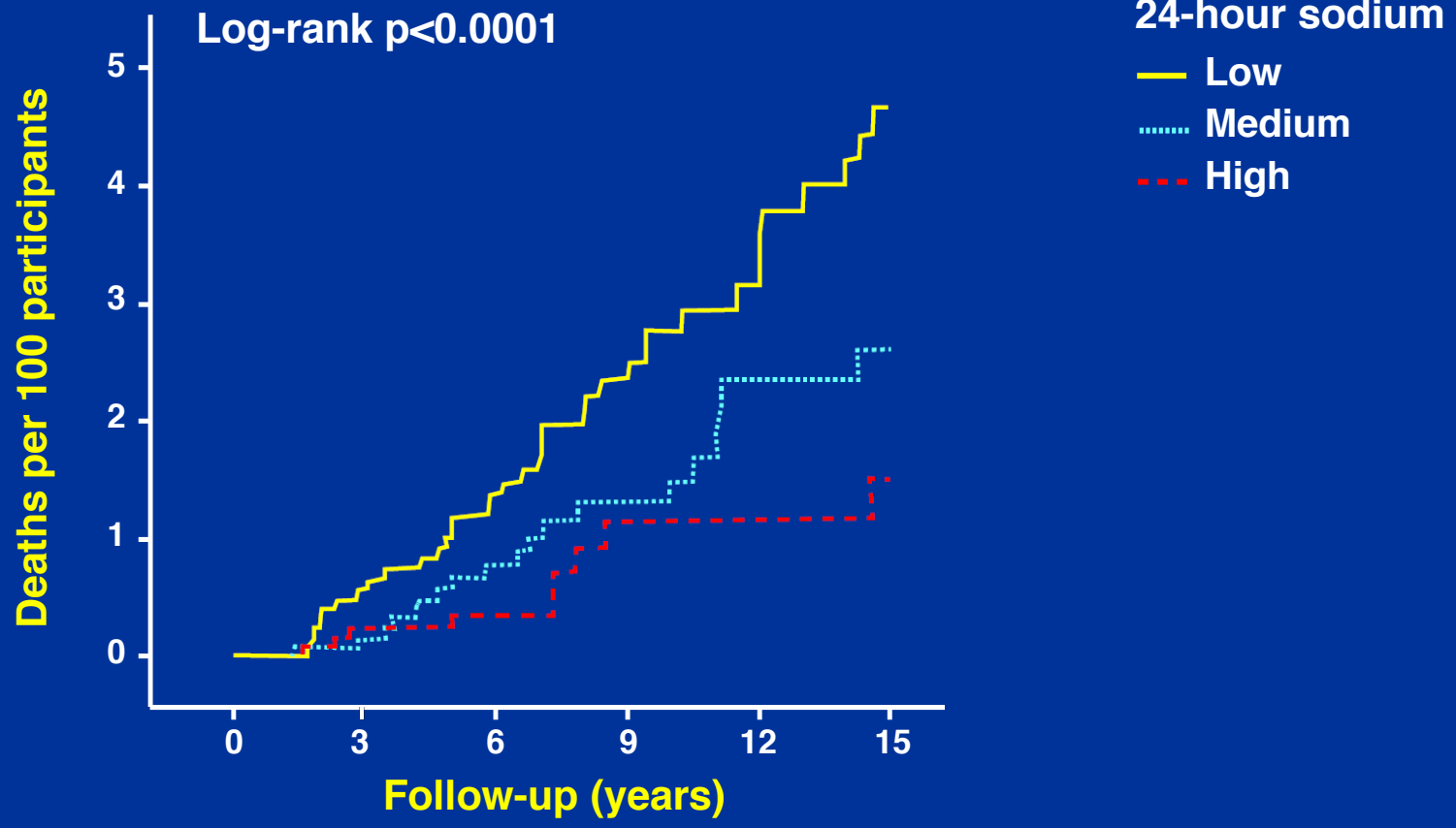
Incidence of hypertension



Stolarz-Skrzypek et al, JAMA 2011; 305: 1777-85

EPOGH

Cardiovascular mortality



Stolarz-Skrzypek et al, JAMA 2011; 305: 1777-85

EPOGH

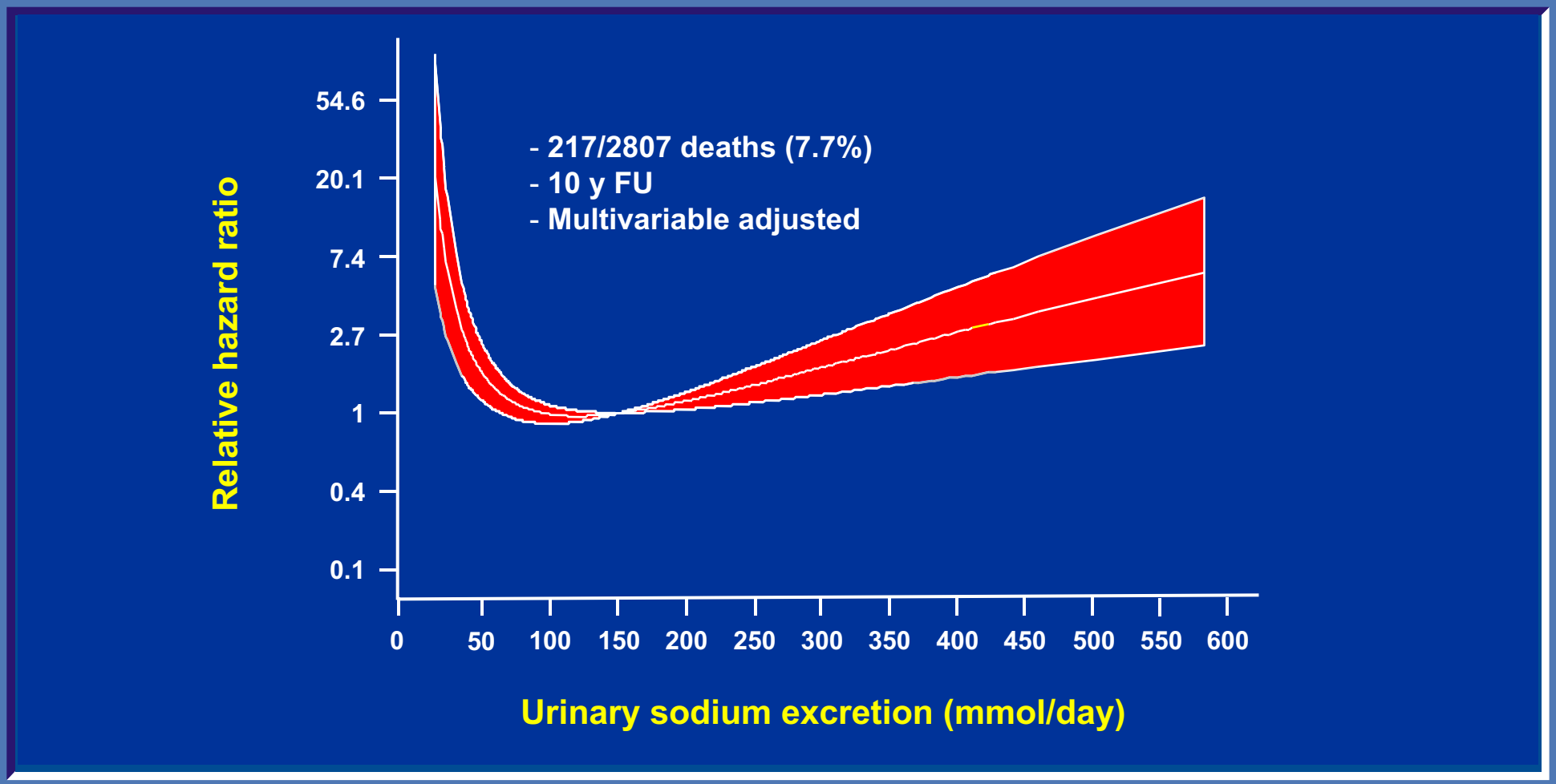
CV mortality – sensitivity analyses

	Low	Medium	High	p
Sodium-to-creatinine ratio	1.54	1.04	0.63	0.01
Hypertensive patients	1.37	0.81	0.90	0.17
Overweight and obese	1.82	0.76	0.72	0.02
≥60 years	1.52	1.06	0.94	0.056
FLEMENGHO	1.40	0.79	1.27	0.14
Unadjusted BP and treatment	1.42	0.98	1.02	0.03

Staessen J, *JAMA 2011;* 307: 1083-87

FinnDiane

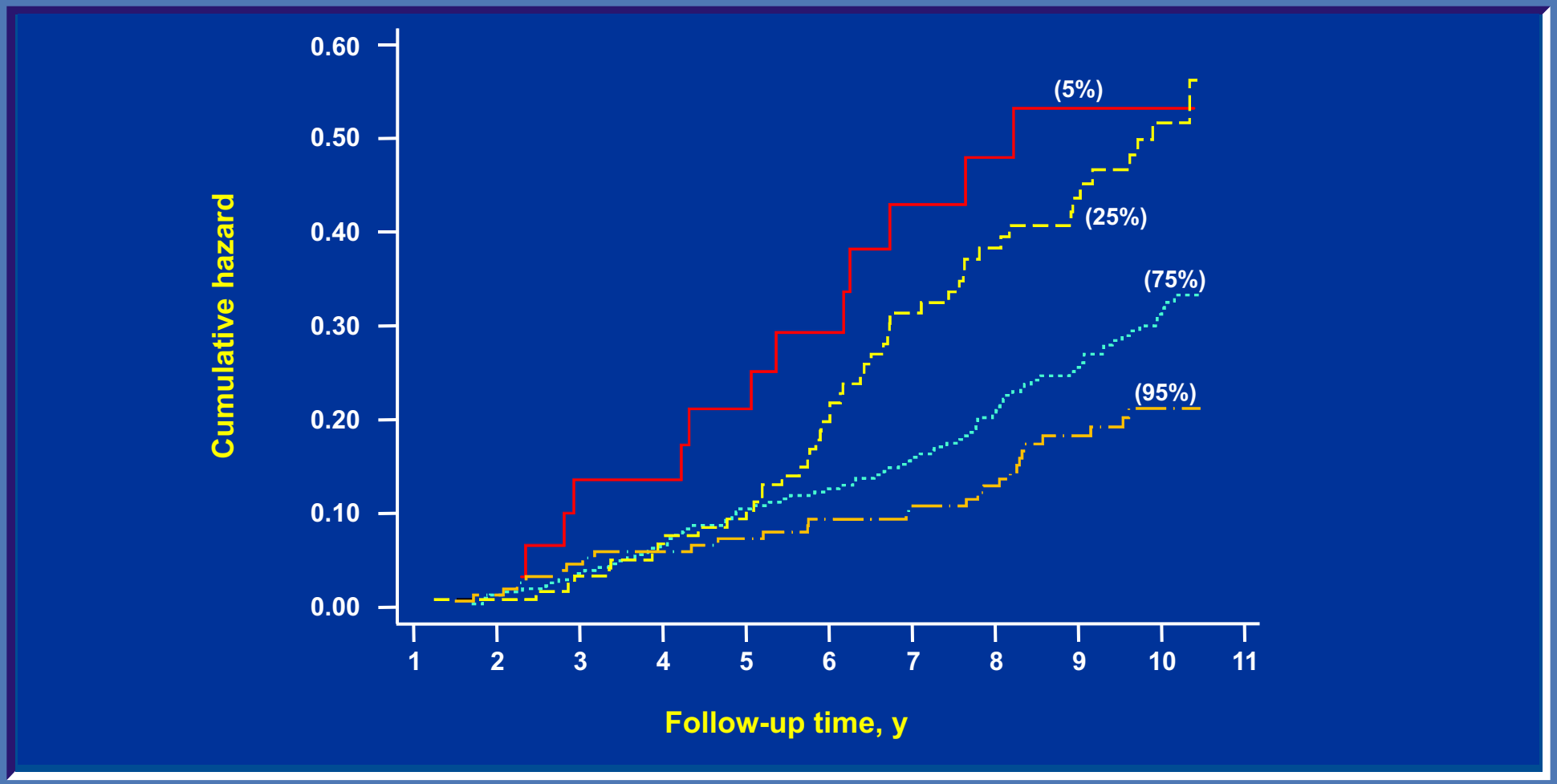
All-cause mortality



Thomas et al, *Diabetes Care 2011*; 34: 861-66

DM2

All-cause mortality



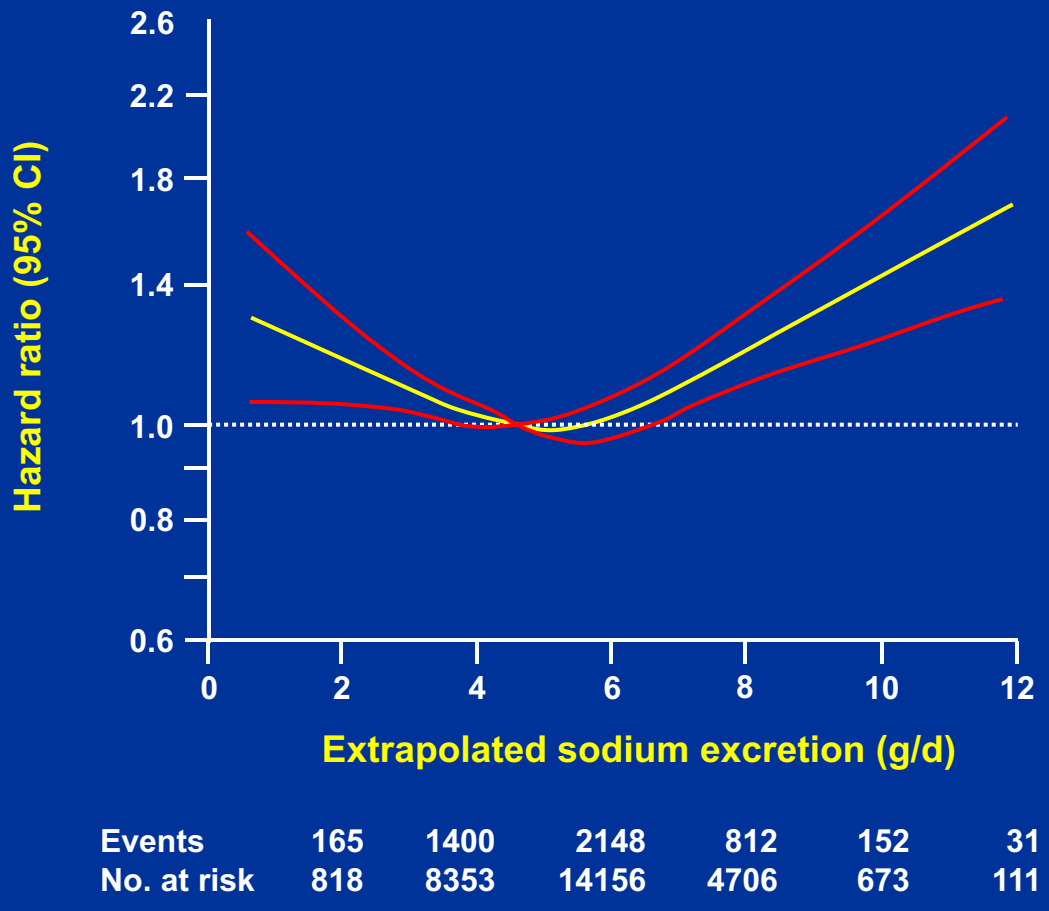
Ekinci EI et al, *Diabetes Care 2011*; 34: 703-9

OnTarget
Transcend

Primary endpoint*
Spline plot for adjusted Cox model

Characteristics

N°	28,880
Endpoint, n (%)	4729 (16.4)
Women,%	29.4
White,%	71.4
Age, y	66.5
BP, mm Hg	142/68
Na^+, g (mmol)	4.8 (207)
K^+, g (mmol)	2.2 (56)



* CV death, MI, CVA and CHF

O'Donnell MJ et al, *JAMA 2011*; 306: 2229-38

PURE Methods

- **Participants:**
  - 102,216 adults from 18 countries and 5 continents (42.0% Chinese);
  - Mean age 51.0±9.7 years; 57.2% women.
- **Assessment of 24-h sodium and potassium intake:**
  - Estimated from a fasting morning urine specimen;
  - Using validated Kawasaki formula.

N Engl J Med 2014; 371: 601-611

PURE Characteristics of participants

Characteristic	Estimate	Characteristic	Estimate
Women,	57.2	CHD, %	4.7
Age, y	51.0	Stroke, %	1.9
BMI, kg/m^2	26.1	CHF, %	0.9
SBP/DBP, mmHg	131.7/81.9	CV disease, %	8.5
Diabetes, %	7.1	HT, %	42.0

N Engl J Med 2014; 371: 601-611

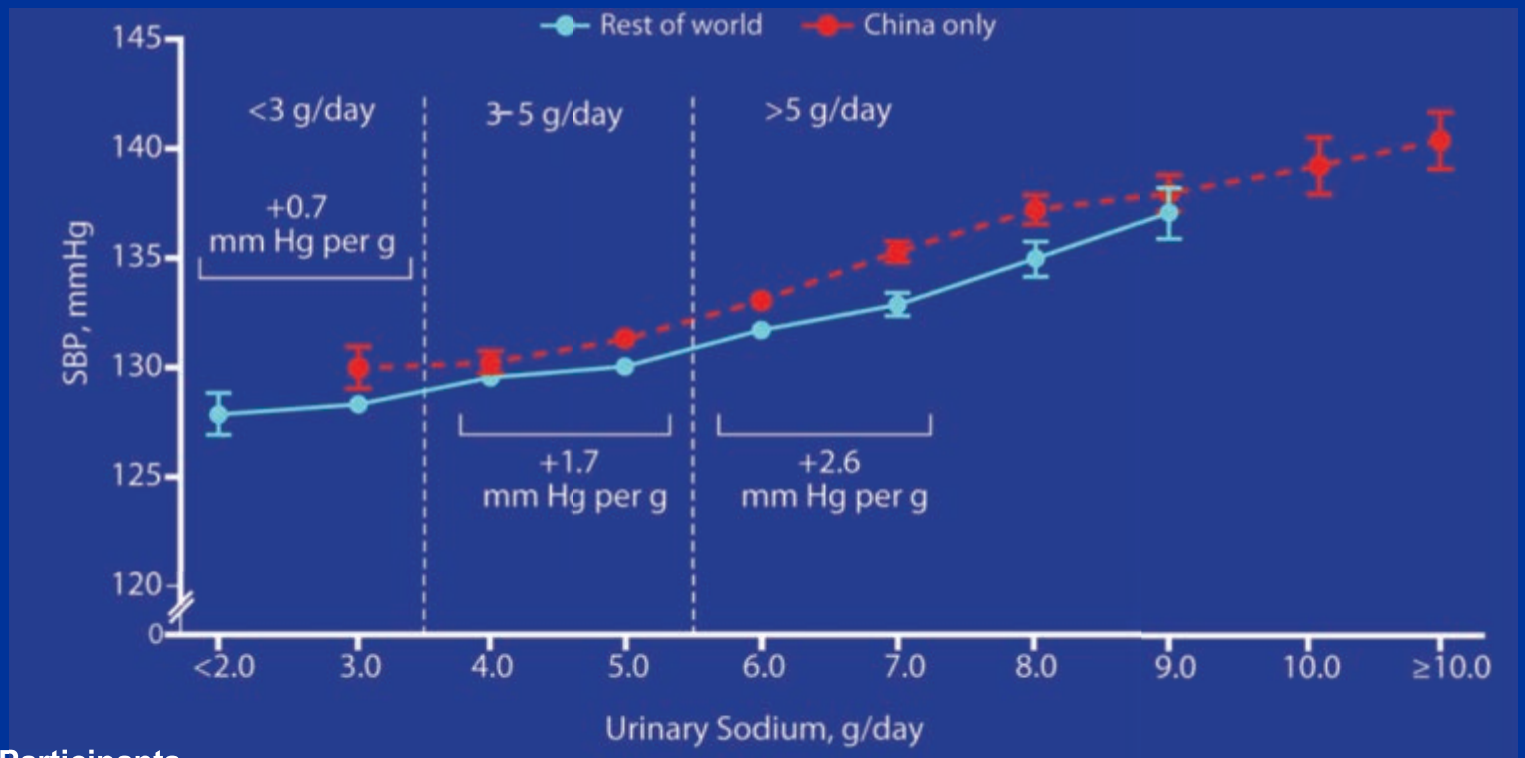
PURE Results

- Sodium excretion: 4.9±1.7 mg/d (213±74 mmol/d);
- Potassium excretion is 2.1±0.6 mg/d (54±15 mmol/d);
- Mean follow-up: 3.7 years;
- Primary outcome occurred in 3317 (3.3%) participants:
  - 1976 deaths (650 CV causes)
  - 857 MI
  - 872 stroke
  - 261 heart failure

N Engl J Med 2014; 371: 612-623

PURE

SBP according to sodium excretion



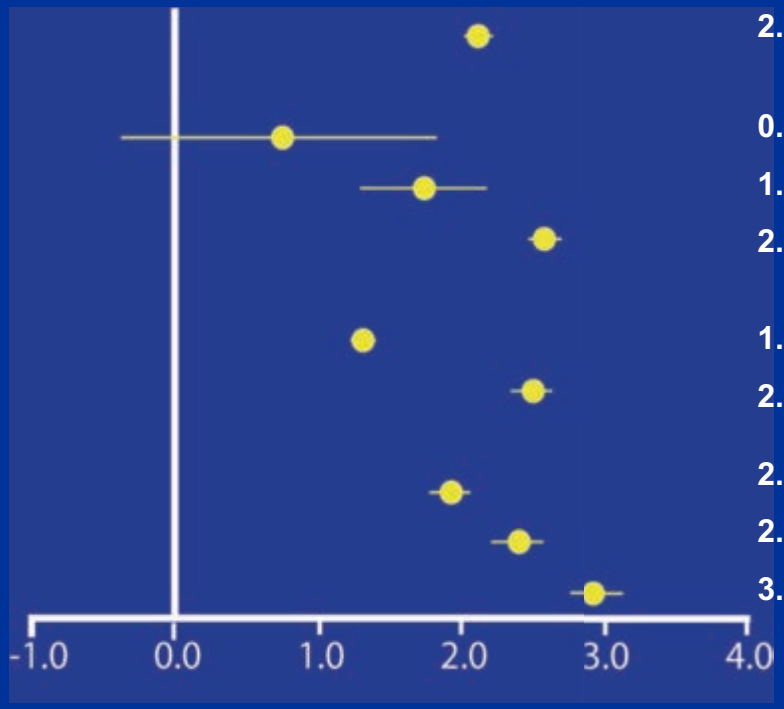
Nº of Participants										
China		1876	6012	9,794	10,101	7177	4093	2035	1002	952
Other countries	1613	7384	15,101	16,015	10,810	5211	2048	992		

N Engl J Med 2014; 371: 601-611

PURE

ΔSBP for every 1-g increase in sodium excretion

	Nº		p for interaction
Total	102,216	2.1 (2.2 to 2.2)	
Na^+, g/day			<0.001
<3	10,873	0.7 (–0.4 to 1.8)	
3–5	46,922	1.7 (1.3 to 2.2)	
>5	44,421	2.6 (2.4 to 2.8)	
HT			<0.001
No	59,238	1.3 (1.2 to 1.4)	
Yes	42,978	2.5 (2.3 to 2.6)	
Age, yr			<0.001
<45	30,619	2.0 (1.8 to 2.1)	
45–55	33,289	2.4 (2.3 to 2.6)	
>55	38,308	3.0 (2.8 to 3.2)	



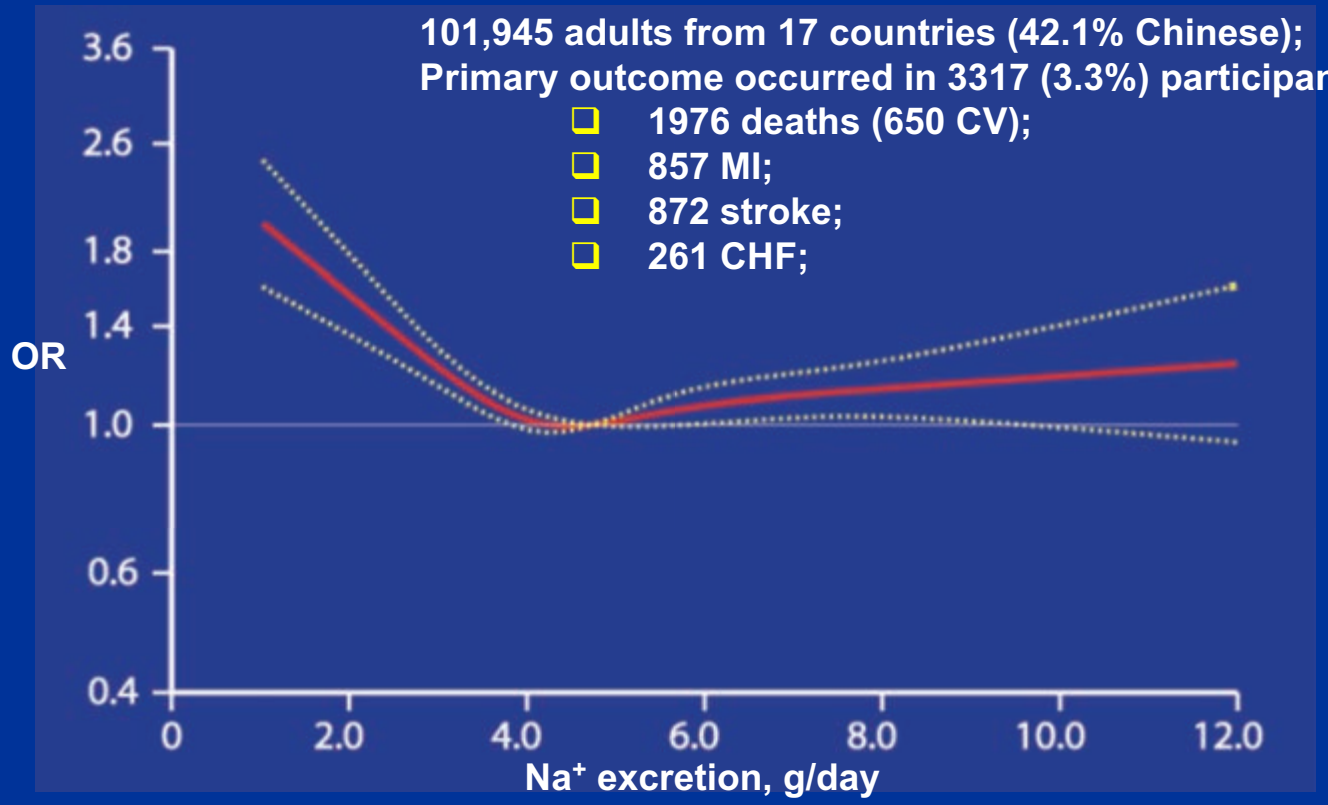
N Engl J Med 2014; 371: 601-611

PURE

Risk of death or CV event in relation to sodium excretion

101,945 adults from 17 countries (42.1% Chinese);
Primary outcome occurred in 3317 (3.3%) participants:

- 1976 deaths (650 CV);
- 857 MI;
- 872 stroke;
- 261 CHF;



Nº of events	101	1,023	1,437	597	126	25
Nº at risk	1817	30,124	46,663	18,395	3885	756

Restricted cubic spline plot

N Engl J Med 2014; 371: 612-623

PURE Conclusions

- Sodium and potassium excretion estimated in 102,216 adults from 18 countries showed a nonlinear association with BP, which was most pronounced among persons consuming high-sodium diets, patients with HT, and older persons.
- The lowest risk of death and CV events was observed among participants, who had a sodium excretion between 3 g and 6 g per day; both higher and lower levels of estimated sodium excretion were associated with increased risk.

N Engl J Med 2014; 371: 612-623

RCTs

Cochrane review – total mortality

	Low	High	Δ (95% CI)	p
Normotension (3)	36/1714	43/1804	0.90 (0.58-1.40	0.64
Hypertension (2+1)	220/947	345/1402	0.96 (0.83-1.11)	0.61
Heart failure (1)	15/114	6/118	2.59 (1.04-6.44)	0.04

The 2014 update included 8 studies (NT, n=3; HT or mixed, n=5), but showed equally inconclusive results for CV mortality.
(Adler Aj et al, Cochrane Review 2014;26:CD009217)

Δ: 27-39 mmol/24-h; 1-4 mmHg; follow-up <36 months.

Taylor RS et al, *AJH 2011;* 24: 843-53.

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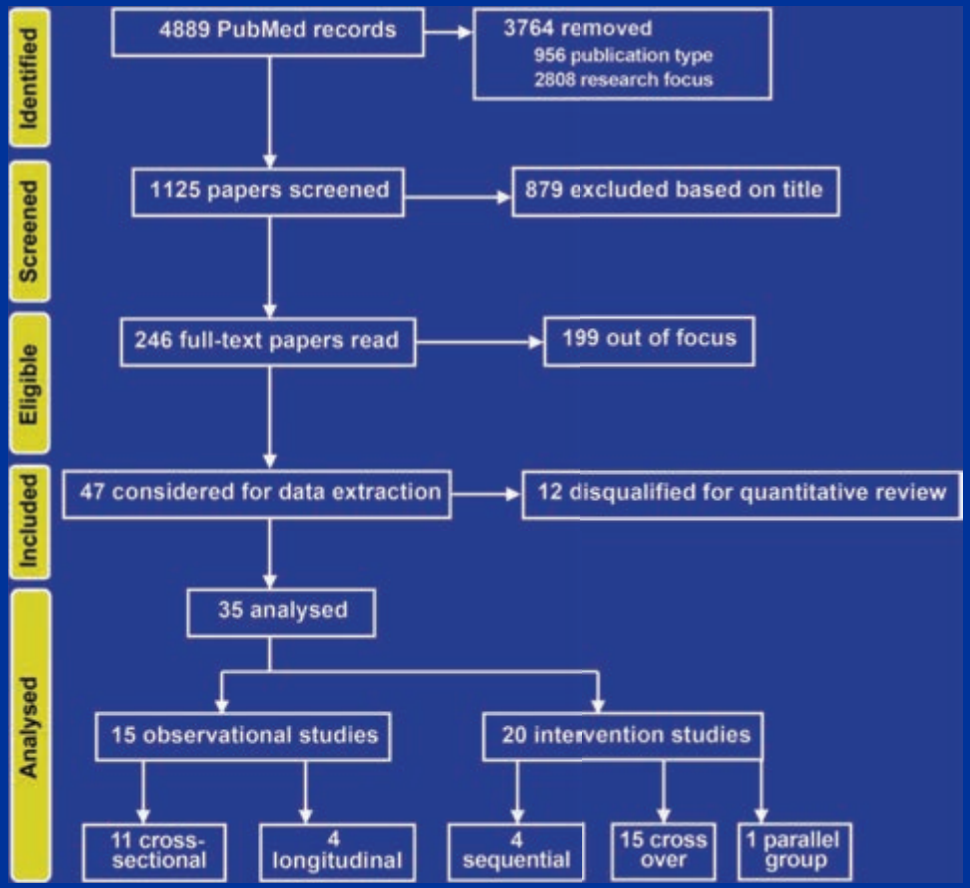
Salt restriction for CKD prevention

Kidney International 2017; 92: 67-78

CKD Flow chart



Kidney Int 2017; 92: 67-78

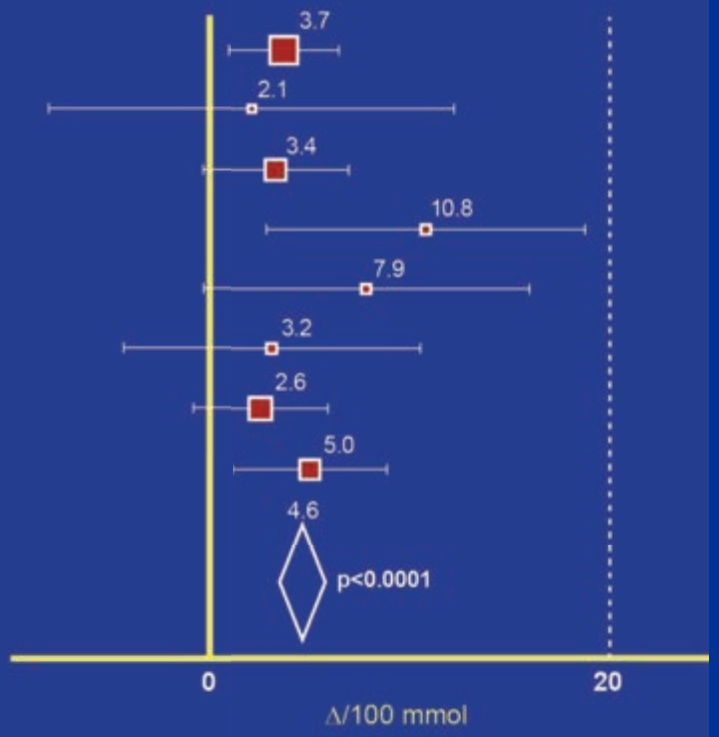
CKD

eGFR / creatinine clearance

	Lowest		Highest	
	N°	Na (mmol)	N°	Na (mmol)
Bruun (1990)	22	50	22	330
Campese (1991)	26	20	26	200
Cianciaruso (1996)	21	35	21	235
Mallamaci (1996)	21	41	21	213
Yoshioka (1998)	19	85	19	255
Campese (1998)	19	20	19	250
Bruun (2000)	42	50	42	300
Chiolero (2000)	65	57	65	237
All	782		784	

9 other RCTs:

(I^2=0%; Q=10.2; p=0.86)



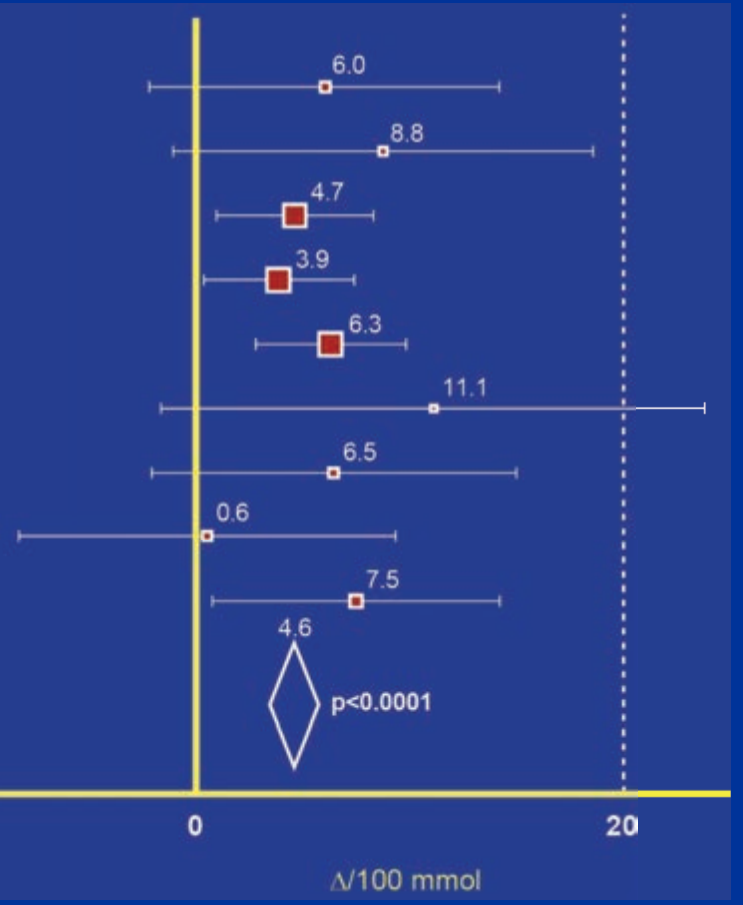
Kidney Int 2017; 92: 67-78

CKD

eGFR / creatinine clearance

9 other RCTs:				
Konishi (2001)	38	86	38	207
Imanishi (2001)	16	80	16	200
Luik (2002)	48	50	48	200
van Berge-Landry (2004)	48	24	48	309
Visser (2009)	78	50	78	200
Pimenta (2009)	12	50	12	250
Mallamaci (2013)	32	15	32	200
de Brito-Ashurst (2013)	23	141	25	246
Campbell (2014)	20	70	20	190
All	782		784	

(I^2=0%; Q=10.2; p=0.86)



Kidney Int 2017; 92: 67-78

CKD Conclusions

- There is no robust evidence suggesting that long-term reduction of salt intake would prevent CKD or delay its progression.
- Our current findings were mainly obtained in people with slight renal impairment and cannot be extrapolated to patients with moderate to severe CKD.

Kidney Int 2017; 92: 67-78

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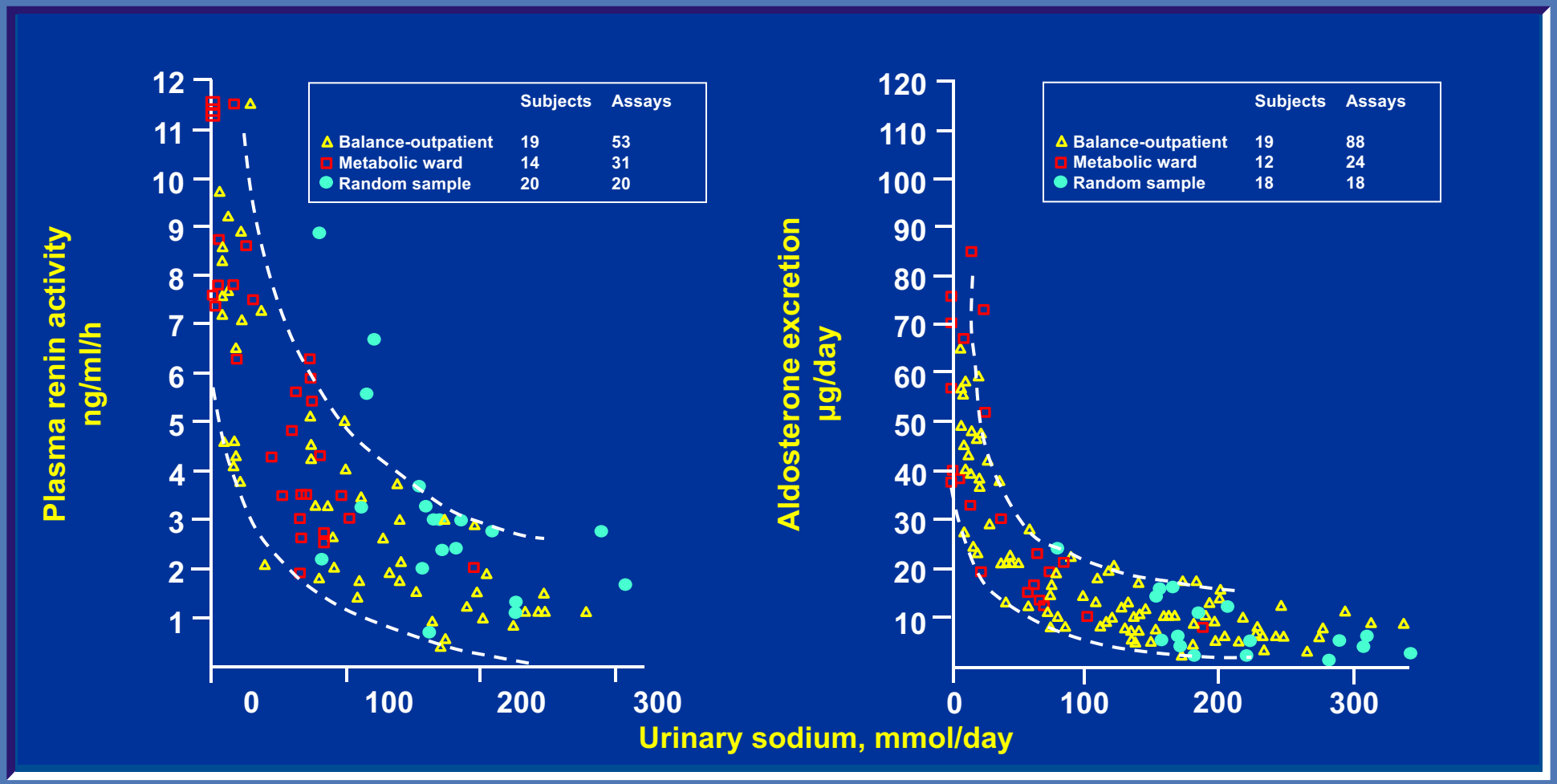
Is there an explanation?

The renin system

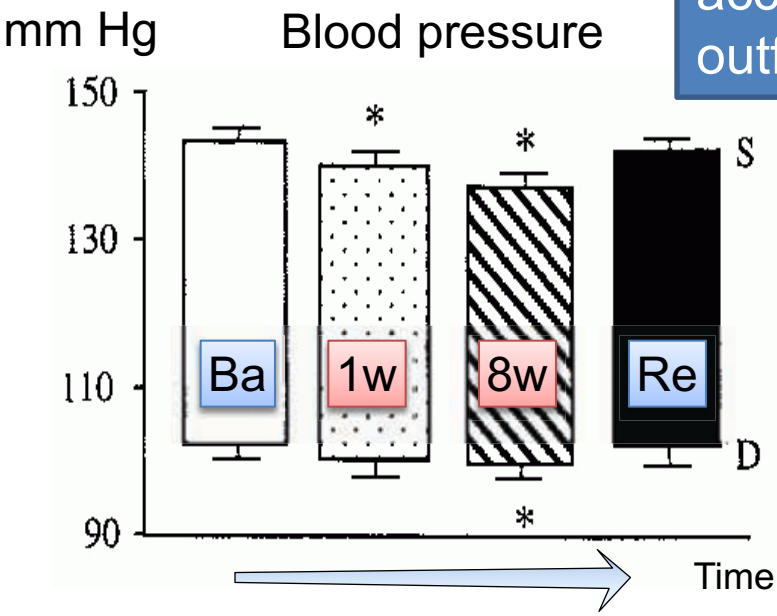
Salt

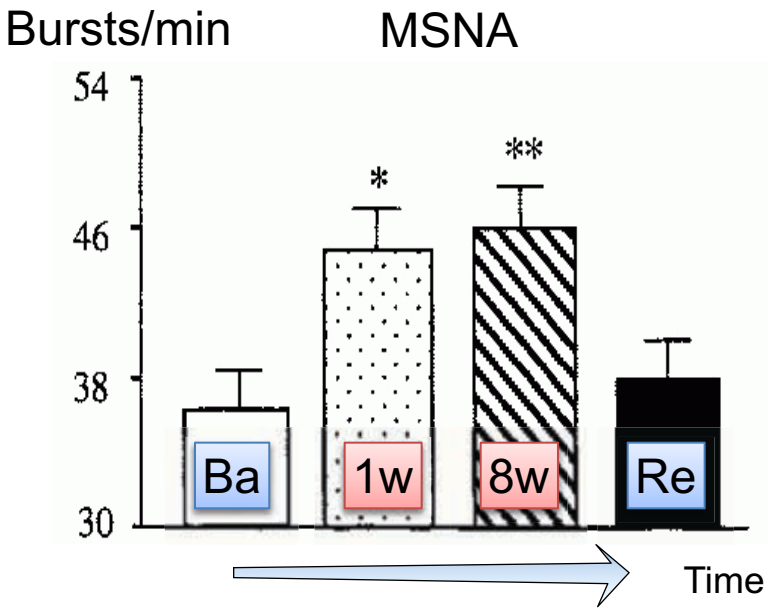
Activation of the renin system in normal ambulatory subjects

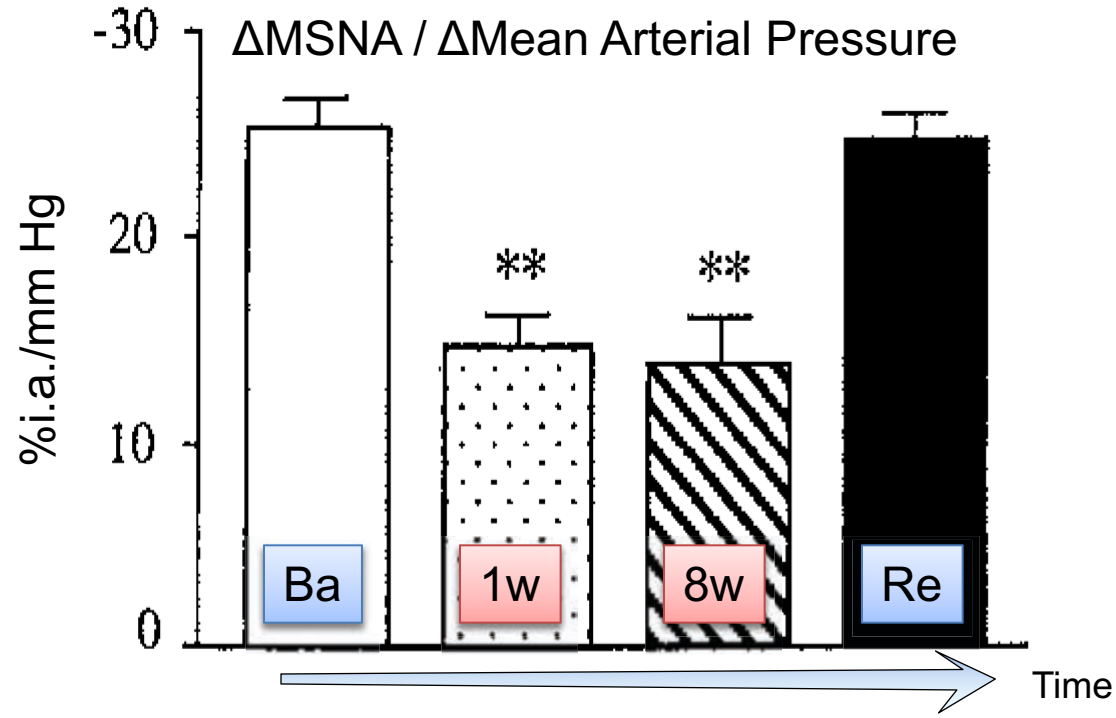


Laragh J and Sealey J, *Am J Hypertens 2011;* 11: 1164-80

A moderate reduction in sodium intake (80 mmol/d) is accompanied by a clear-cut increase in sympathetic outflow to the skeletal muscles.







MSNA: Muscle sympathetic nerve traffic
Ba: Baseline, 220 mmol/d NaCl diet
1w: 1 week after 80 mmol/d NaCl diet
8w: 8 weeks after 80 mmol/d NaCl diet
Re: Again 1 week after 220 mmol/d NaCl diet

Grassi G, et al. *Circulation* 2002

SALT 2018

Recommendations for populations

“In medio stat virtus”!

Sodium

"In medio stat virtus"

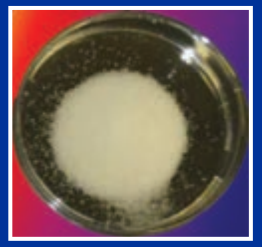
4%

106 mmol
2.5 g
6.0 g

2%

170 mmol
4.0 g
10.0 g

1%



260 mmol
6.0 g
15.0 g

65 mmol
1.5 g
4.0 g

Appel LJ et al, *Circulation* 2011; 123: 1138-43

IOM Conclusions

- IOM failed to find robust evidence to support current guidelines promoted by CDC or AHA to reduce NA intake population-wide from the current 3,400 mg/d (148 mmol/d) to <2,300 mg/d (100 mmol/d) or to <1,500 mg/d (65 mmol/d) for 50% of the US population at high CV risk.
- IOM recognised the heterogeneity of the results among observational and experimental studies, baseline BP level and NA intake being the major determinants of BP responses to NA restriction.

Sodium Intake in Populations: Assessment of the Evidence (National Academic Press, Washington DC, 2013)

SALT Conclusions

- IOM cautioned against sodium intakes <1,500 mg/d. Of US adults only 9% consume <2,300 mg/d and 0.6% <1,500 mg/d, making the ban on salt – if at all feasible – the most aggressive lifestyle change ever planned in the history of mankind.
- The guidelines completely disregards potential harm caused by the stimulation of the RAAS and the sympathetic nervous system and by adverse changes in serum lipids and insulin resistance.
- The answer to the question "*Should all Americans reduce their consumption of Na substantially from current average intake levels?*" is "*We don't know, and definitely not yet.*" *(Yusuf S et al, AJH 2013;26:1187-90)*