Dietary Sodium Consumption and Cardiovascular Disease and Mortality: What is the Current Evidence?

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Disclosures

I have no disclosures

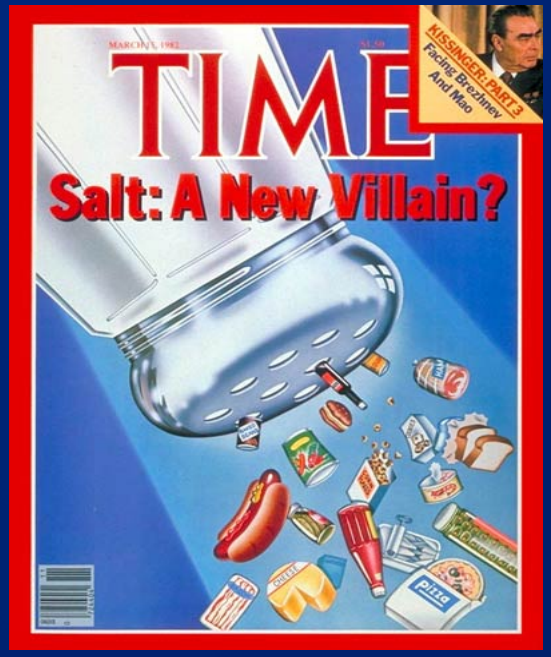
I have received no honorarium for my participation

PHRI is covering the full costs of my participation

Salt – Central "*Hypothesis*"

Salt (sodium) intake → Raised blood pressure → Heart attack, Stroke, Death

- assumes that sodium has no other effects on biological systems



Recommendations (For All)

- **WHO/National Guidelines (e.g. AHA)**
  - Consume less than 2-2.4g/day (5-6g salt/day, or ~1 tsp)
  - FSAI: < 2.4g/day (achievable); < 1.6g/day (target)

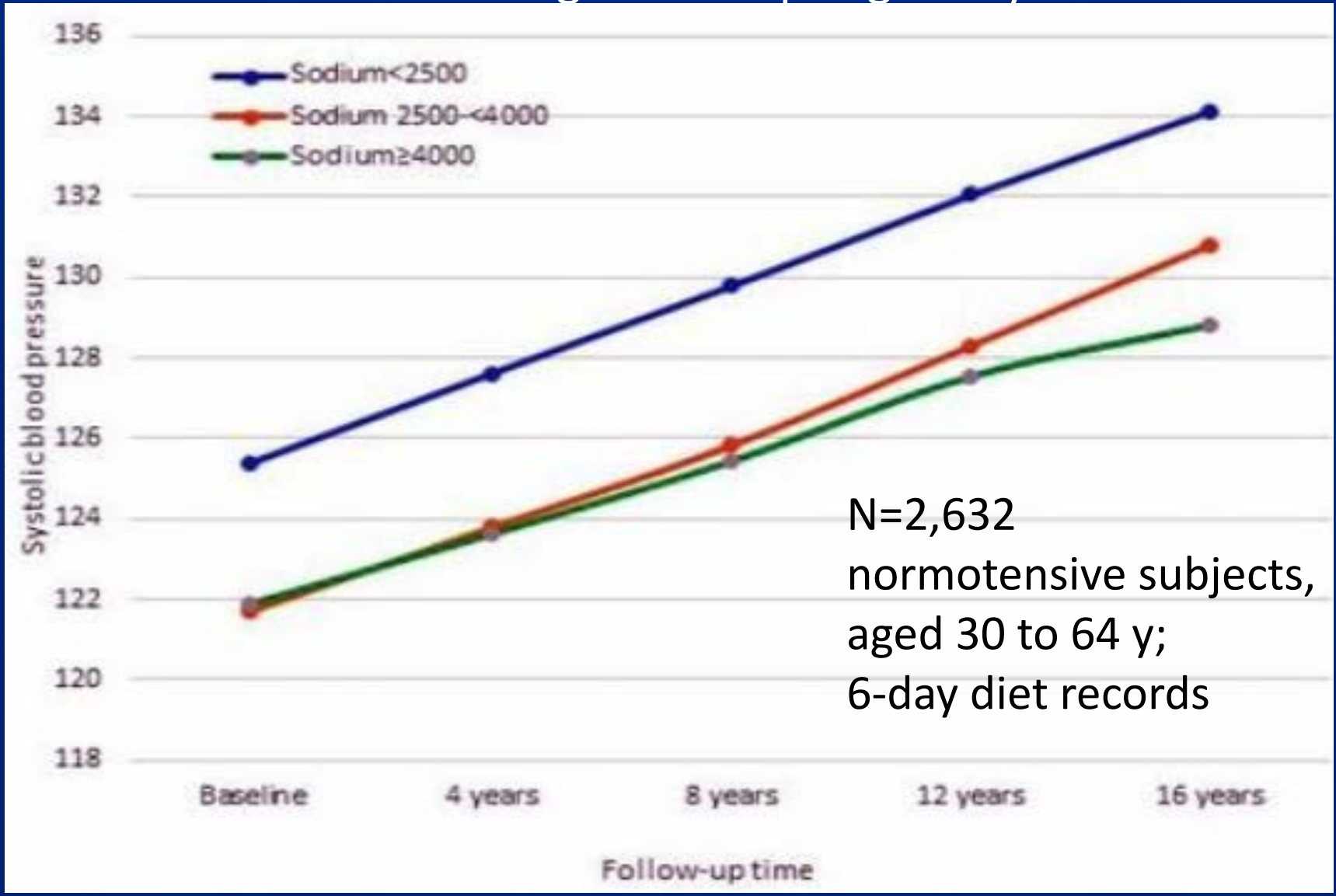
- **Guideline Variations**
  - High-risk candidates < 1.5g/day (3.8g salt/day, or ~0.7 tsp)
    - Some guidelines only

Achieving these targets will require substantial change in diet for most people

Na vs BP: Observational studies

- INTERSALT study (BMJ 1988)
  - cross-sectional study (n=10,079), comparing mean Na intake bs mean BP, from 52 centers
  - weak relationship between Na and BP (0.94/0.03 mm Hg per gram of Na)
- Scottish Heart Study (BMJ 1988)
  - 7354 people aged 40-59
  - age, pulse rate, BMI, alcohol & potassium intake related to BP
  - no relationship between Na and BP
- INTERMAP (Hypertension 2018)
  - 4680 people aged 40-59, 17 centres in 4 countries
  - No relationship between Na and BP (0.22 mmHg per gram)

Low Na intake is associated with higher BP over 16 y of follow-up: Framingham Offspring Study



Moore L, et al, presented at "Experimental Biology 2017" meeting in Chicago, IL, April 25, 2017

DASH Trial (NEJM 2001)

- Primary basis for the current AHA guidelines and the 2010 U.S. National Dietary Guidelines
- A “proof of concept” study as to whether changes in multiple aspects of diet (including Na reduction) would lower BP under controlled situations (all meals were provided to the participants and their spouses) over 5 weeks
- Not designed to assess if Na reduction also reduces CVD & mortality in free living populations

Measuring of Na intake

- 24-hr urine is the reference method for measuring Na intake, but not feasible in large studies; under-collection a problem
- Fasting morning urine (FMU) has been used to estimate 24-hr urine excretion using a mathematical formula (Kawasaki 1993)

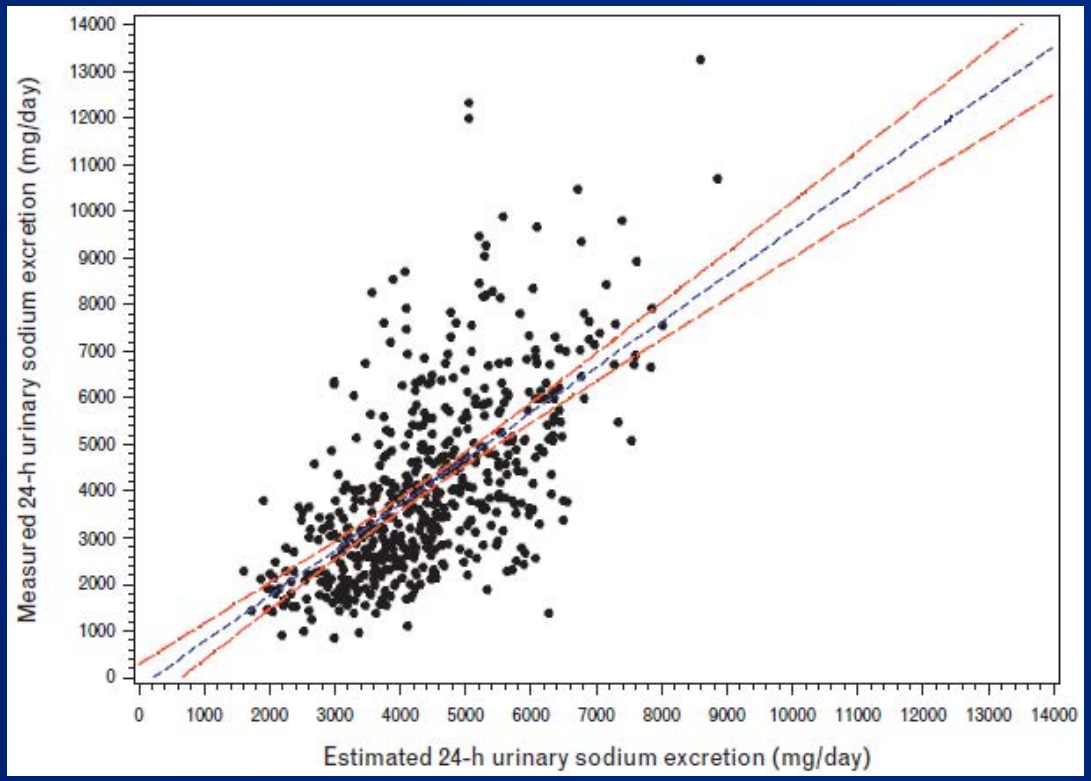
Methods

Development and validation of a widely practical method to estimate 24-hr Na and K intake in multiple countries:

- FMU obtained from 1083 PURE participants in 11 countries
- Na and K excr. estimated using Kawasaki formula
- Estimated excr. was validated with 24-hr urine obtained on the same day

Estimated vs. measured 24-hr excr. (n=1083; 11 countries)

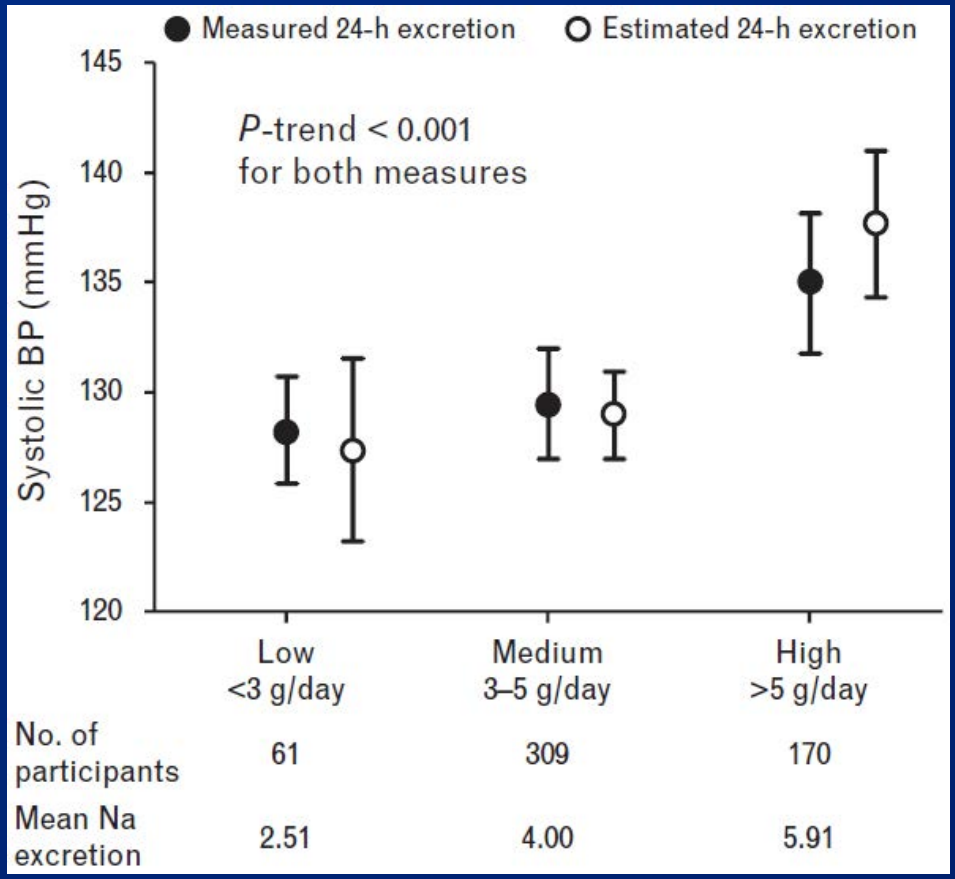
Measured vs. estimated Na excr.
ICC = 0.71, P<0.001



Test-retest: ICC=0.68

Similar results for K

Na excr. vs Systolic BP

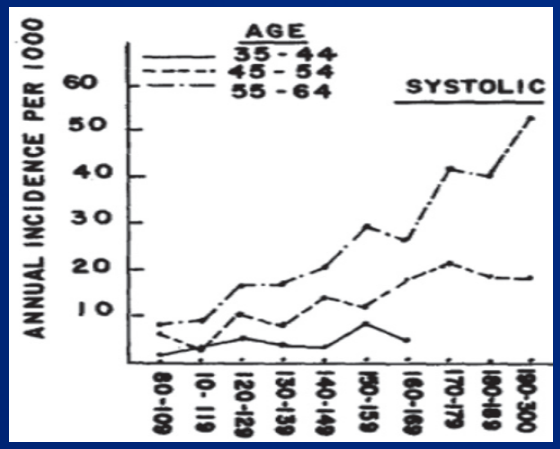


Similar results for diastolic BP

Mente A, et al, 2014, J Hypertens

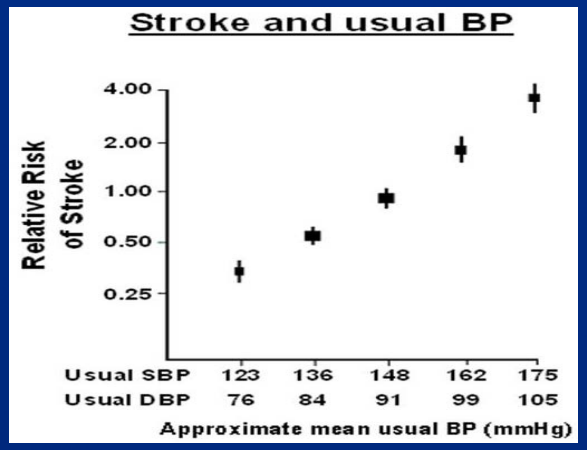
Single clinic measures have been the foundation of epidemiology

SBP vs CHD (N=5,127)



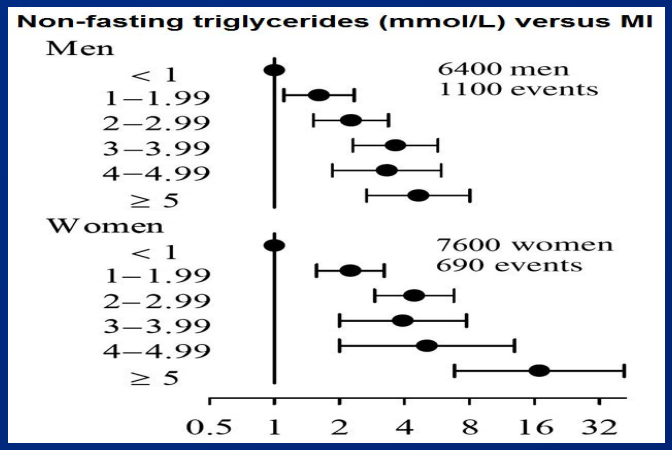
Framingham: Kannel WB. *Am J Cardiol* 1971;27:335

SBP vs Stroke (N=420,000)



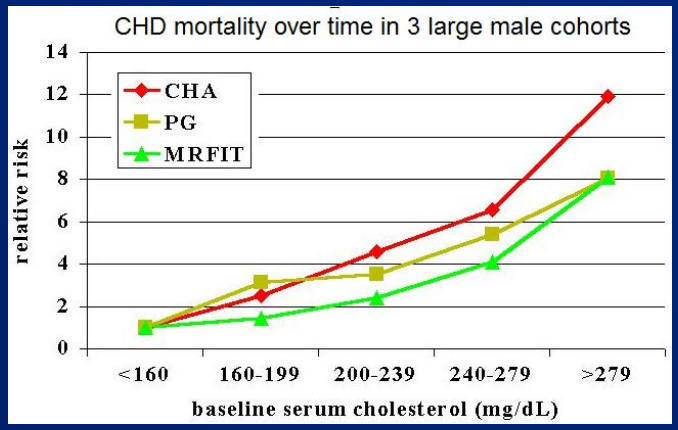
9 pooled studies: MacMahon S. Lancet 1990;335:765-74

Nonfast. TG vs MI (N=13,981)



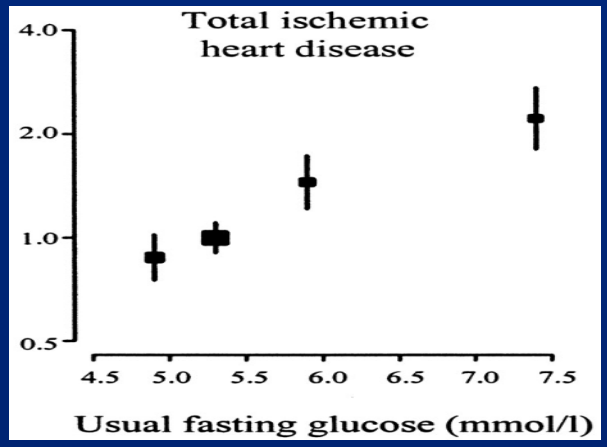
Copenhagen Heart: Nordestgaard B. *JAMA* 2007;298:299

Cholest. vs CHD (N=81,488)



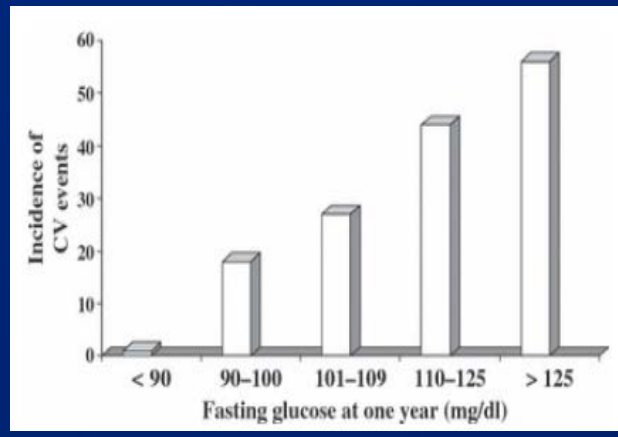
3 pooled studies: Stamler J. JAMA 2000;284:311

Glucose vs IHD (N=27,996)



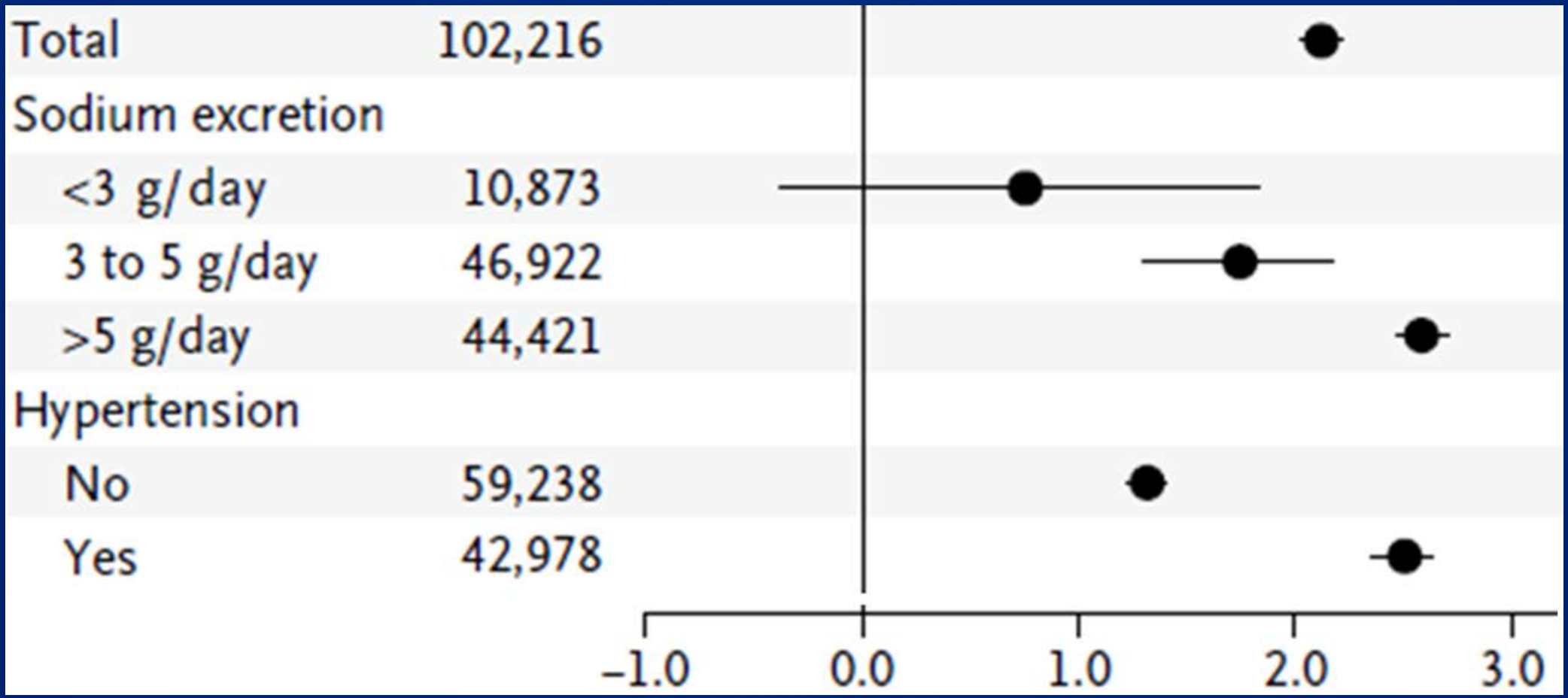
Asia Pacific Cohort Studies Collab. Diab Care 2004;27:2836

Glucose vs CVD



Report of Expert Committee on Diabetes 2003 (Bodziak K. Transplant Intern 2008)

SBP change per 1 g increase in Na is non linear (PURE: N=102,216)



Adjusted for covariates

Δ systolic BP, mm Hg

Mente A, et al. NEJM 2014

Effect of Na lowering on systolic BP in RCTs, overall and by Htn status: Meta-analyses

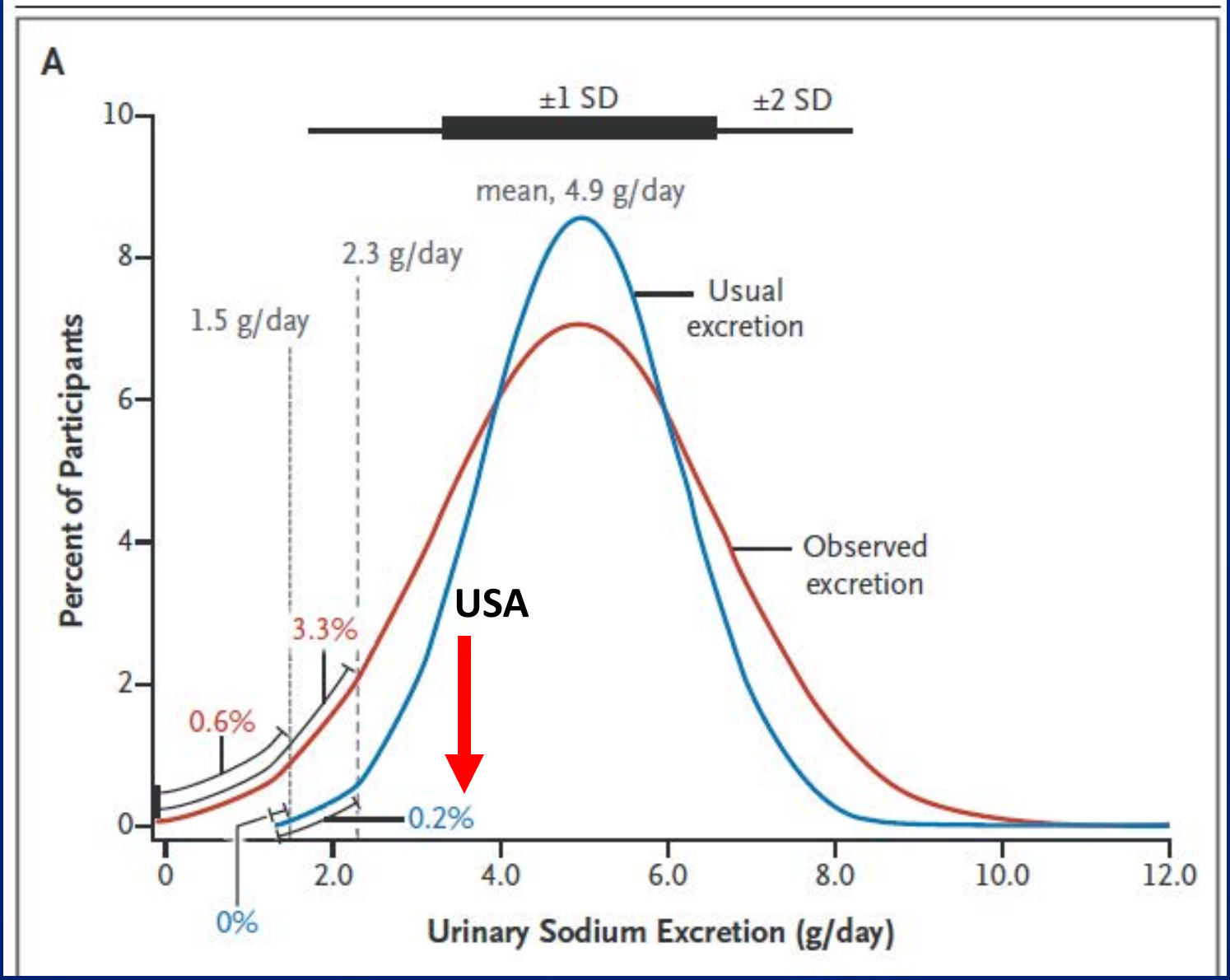
	Studies	N	Change in SBP per 1 g (95% CI)
Overall	34	3230	**2.46 (1.87 to 3.05)**
BP status at BL			
no hypertens.	12	2242	**1.42 (0.76 to 2.09)**
hypertension	22	990	**3.17 (2.62 to 3.89)**

However, most RCTs were < 6 months duration

A 1 mmHg diff in SBP = 2.5% change in CVD

Aburto et al 2013 BMJ & He et al 2013 BMJ

% with Na intake in the recommended range is *rare* (PURE)



N=102,216

Usual Na intake:

0.2% with Na <2.3 g/d;

0% with Na <1.5 g/d

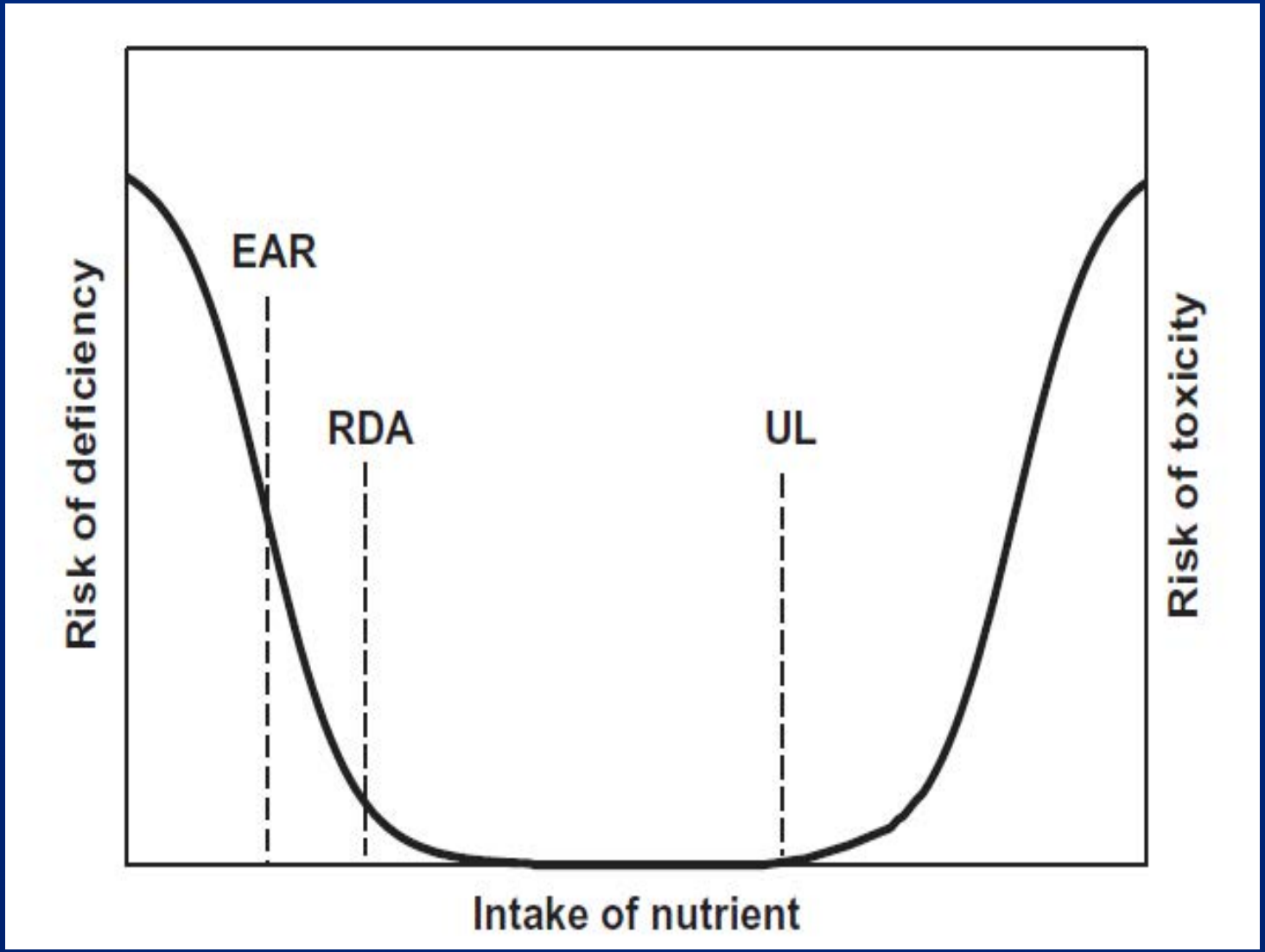
Mente A, et al. NEJM 2014

Mean (SD) sodium and potassium excretion, by region

	Sodium excretion, mg/day	Potassium excretion, mg/day
Rest of world (n=55116)	4452 (1465)	2149 (649)
China (n=39628)	5606 (1840)	2069 (535)

Mente A, et al. NEJM 2014

Recommendation on Essential Nutrient (IOM)



Heaney R *AJH* 2013

Sodium Intake and CVD in CVD Patients (J-shaped Association)

- N=28,880
- High CV Risk
- ONTARGET/TRANSCEND
- 56 months FU
- Morning fasting Urine to estimate 24-hour intake

Outcomes (N=4729)

- Mortality
- Stroke
- MI
- CHF

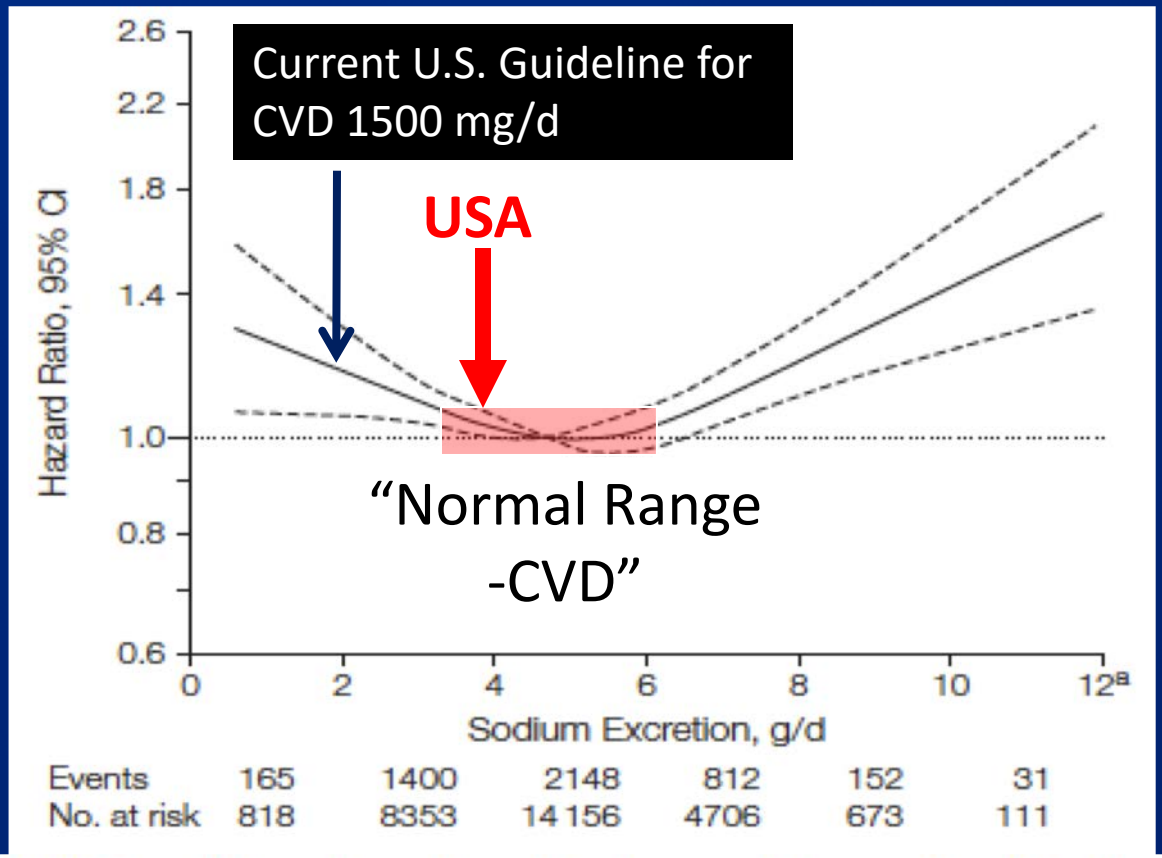


Figure 1. Estimated 24-Hour Urinary Excretion of Sodium and Composite of Cardiovascular Death, Stroke, Myocardial Infarction, and Hospitalization for Congestive Heart Failure

O'Donnell, Yusuf, Mente, et al: *JAMA;* 2011

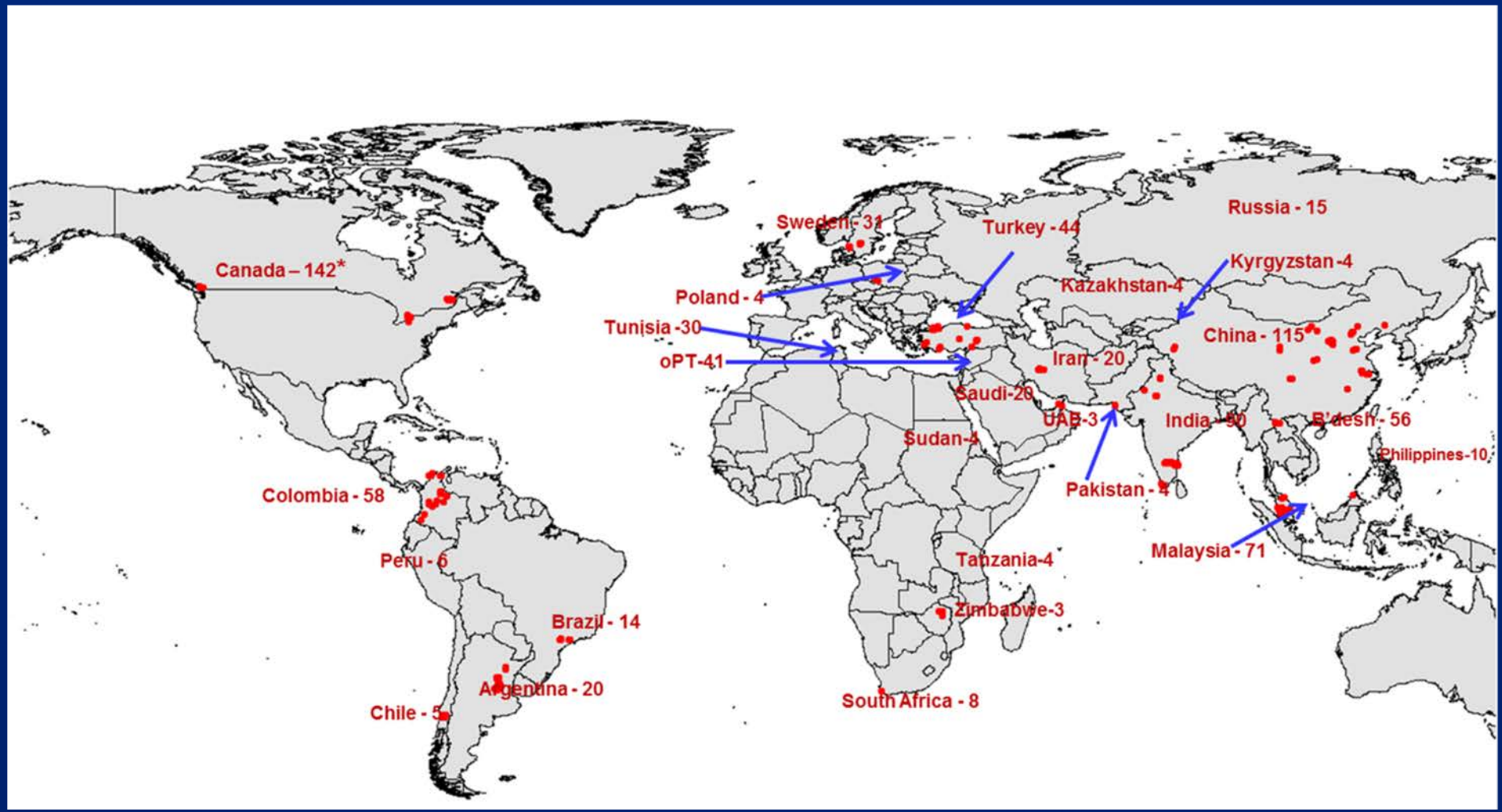
ORIGINAL ARTICLE

Urinary Sodium and Potassium Excretion, Mortality, and Cardiovascular Events

Martin O'Donnell, M.B., Ph.D., Andrew Mente, Ph.D., Sumathy Rangarajan, M.Sc., Matthew J. McQueen, M.B., Ph.D., Xingyu Wang, Ph.D., Lisheng Liu, M.D., Hou Yan, Ph.D., Shun Fu Lee, Ph.D., Prem Mony, M.D., Anitha Devanath, M.D., Annika Rosengren, M.D., Patricio Lopez-Jaramillo, M.D., Ph.D., Rafael Diaz, M.D., Alvaro Avezum, M.D., Ph.D., Fernando Lanas, M.D., Khalid Yusoff, M.B., B.S., Romaina Iqbal, Ph.D., Rafal Ilow, Ph.D., Noushin Mohammadifard, M.Sc., Sadi Gulec, M.D., Afzal Hussein Yusufali, M.D., Lanthe Kruger, Ph.D., Rita Yusuf, Ph.D., Jephat Chifamba, M.Phil., Conrad Kabali, Ph.D., Gilles Dagenais, M.D., Scott A. Lear, Ph.D., Koon Teo, M.B., Ph.D., and Salim Yusuf, D.Phil., for the PURE Investigators*

- N=101,945 from general population (PURE Study)
- Outcomes: CV death, non-CV death, stroke, MI & CHF (3317 events)
- Follow-up: 3.7 years (95% completed follow-up)

PURE: 101,945 from 667 communities in 18 (Phase 1) countries from 5 continents



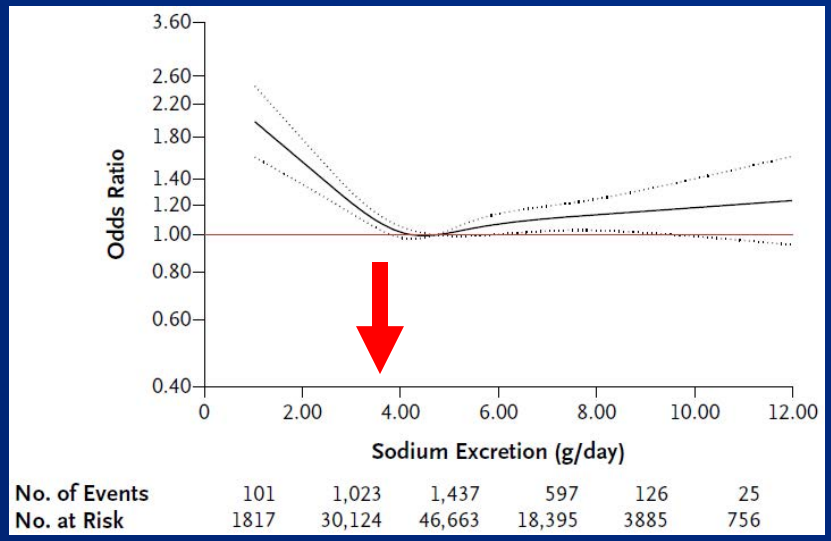
PURE Study (Sodium Intake and CVD)

- **Population**
  - General population (n=101,945)
  - Prior history of CVD: n=8485 (8.3%)
- **Exposure**: Mean sodium excretion 4.93g/day (SD 1.7)
  - Fasting morning urine
  - Validated formula-derived 24 h urinary estimate (Kawasaki formula)
- **Outcomes**: CV death, non-CV death, stroke, MI & CHF (n=3317)
  - Follow-up: 3.7 years (95% completed follow-up)
- **Statistical Analyses**
  - Analytic approaches to address confounding and reverse causality

O'Donnell M, et al. *New Engl J Med* 2014

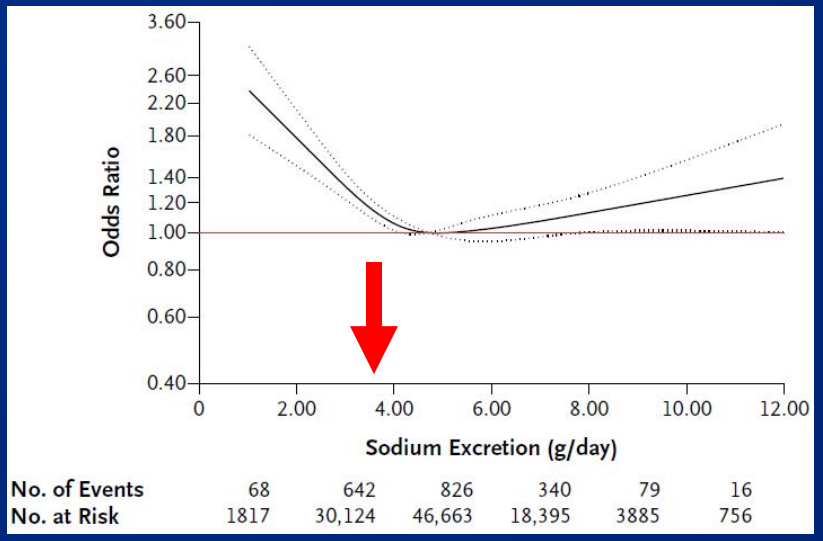
Sodium Intake and Events (PURE)

Primary Composite Outcome



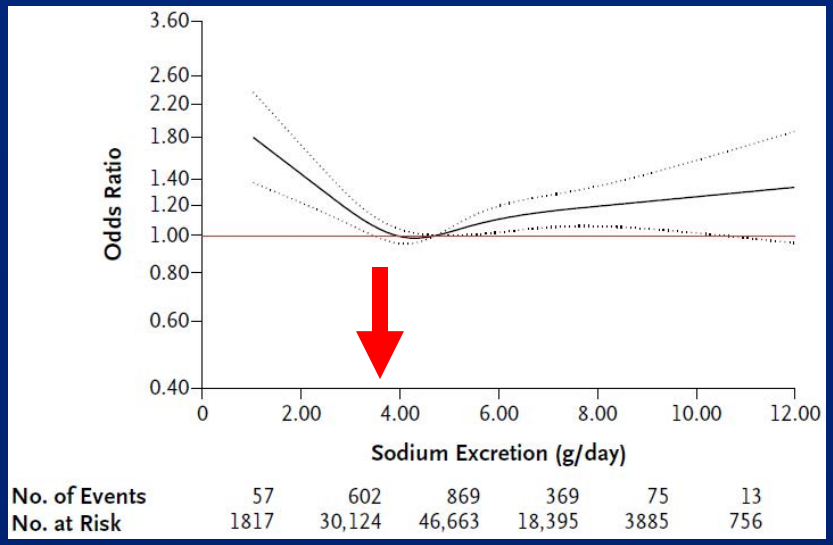
(3,317 events)

Death



(1976 events)

Major CVD



(1991 events)

O'Donnell MJ, et al. 2014, New Engl J Med

PURE Study (Addressing Confounding & Reverse Causality)

	Sodium excretion g/day				
	<3 g/d	3-3.99 g/d	4-5.99 g/d	6-6.99 g/d	≥ 7 g/d
	OR(95%CI)	OR(95%CI)	OR(95%CI)	OR(95%CI)	OR(95%CI)
No. of individuals	10,810	21,131	46,663	12,324	11,017
Composite Death or CV event	462 (4.3%)	662 (3.1%)	1437 (3.1%)	391 (3.2%)	365 (3.3%)
Univariate (GEE)	**1.24 (1.09- 1.41)**	0.96 (0.89- 1.05)	1.00	1.07 (0.96- 1.19)	1.18 (1.05- 1.32)
Multivariable	**1.27 (1.12- 1.44)**	1.01 (0.93- 1.09)	1.00	1.05 (0.94- 1.17)	1.15 (1.02- 1.30)
+ Dietary Factors	**1.19 (1.04- 1.35)**	1.00 (0.92- 1.09)	1.00	1.06 (0.95- 1.18)	1.15 (1.02- 1.30)
Excluding CVD	**1.24 (1.07- 1.42)**	1.00 (0.91- 1.10)	1.00	1.06 (0.95- 1.19)	1.14 (1.01- 1.29)
Excluding Cancer	**1.26 (1.11- 1.43)**	1.02 (0.93- 1.11)	1.00	1.06 (0.95-1.18)	1.15 (1.02- 1.29)
Very low risk cohort	**1.62 (1.29-2.05)**	1.07 (0.90-1.26)	1.00	1.15 (0.98-1.35)	1.14 (0.95-1.36)
Excl. event yr 1 & 2	**1.34 (1.14-1.57)**	1.04 (0.93-1.16)	1.00	1.15 (1.00-1.32)	1.11 (0.96-1.28)

Adjusted for age, cluster, sex, education, prior CVD index, alcohol, diabetes, BMI, smoking

New Engl J Med Commentary on the PURE study results

- "These provocative findings beg for a randomized, controlled outcome trial to compare reduced Na intake with usual diet. In the absence of such a trial, the results argue ***against*** reduction of dietary Na as an isolated public health recommendation".

  (Oparil S. NEJM 2014;371:677-679)

Cohort studies using 24-hour urines

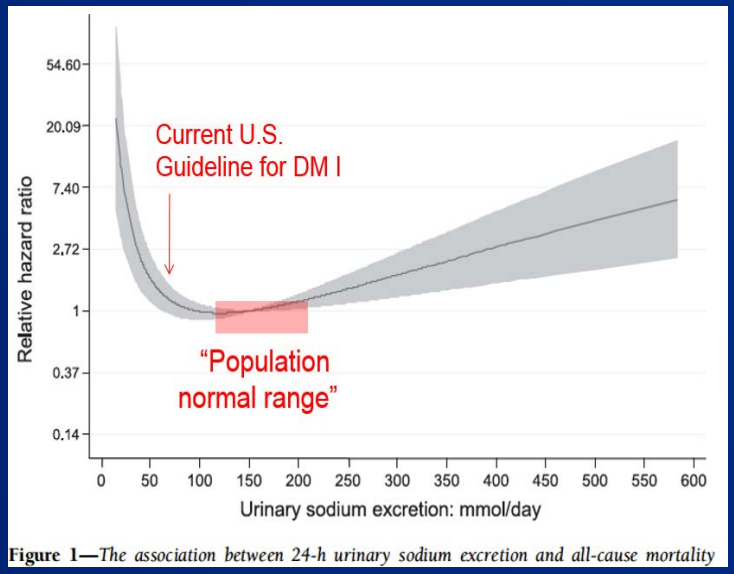


Figure 1—*The association between 24-h urinary sodium excretion and all-cause mortality*

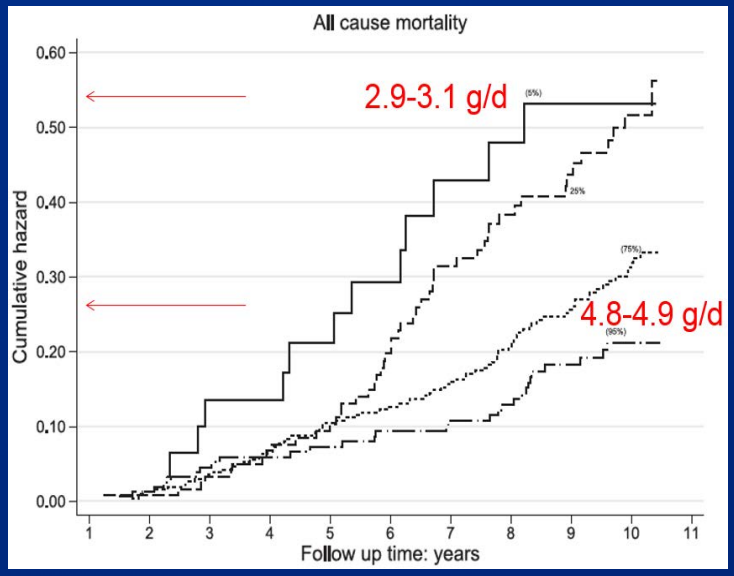
Population:
Type 1 DM

N=2807

Follow-up:
10 yrs

No. events:
217 deaths

Thomas: *Diabetes Care;* 2011



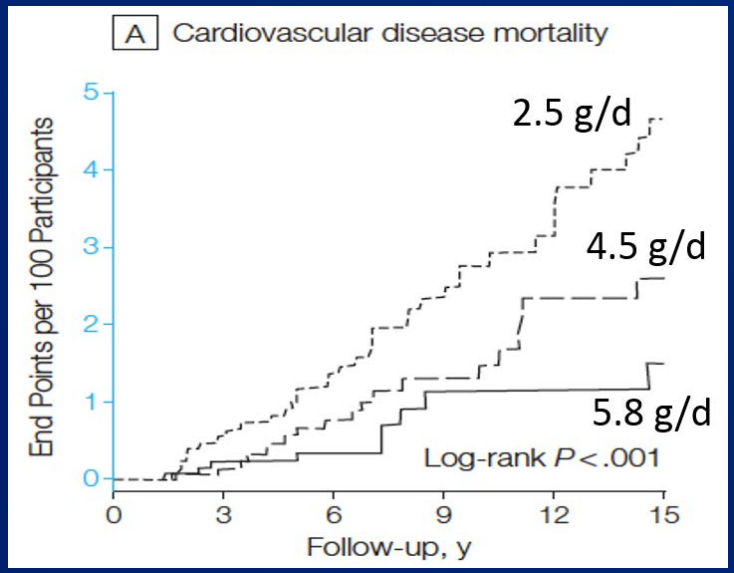
Population:
Type 2 DM

N=665

Follow-up:
9.9 yrs

No. events:
175 deaths

Ekinci: *Diabetes Care;* 2011



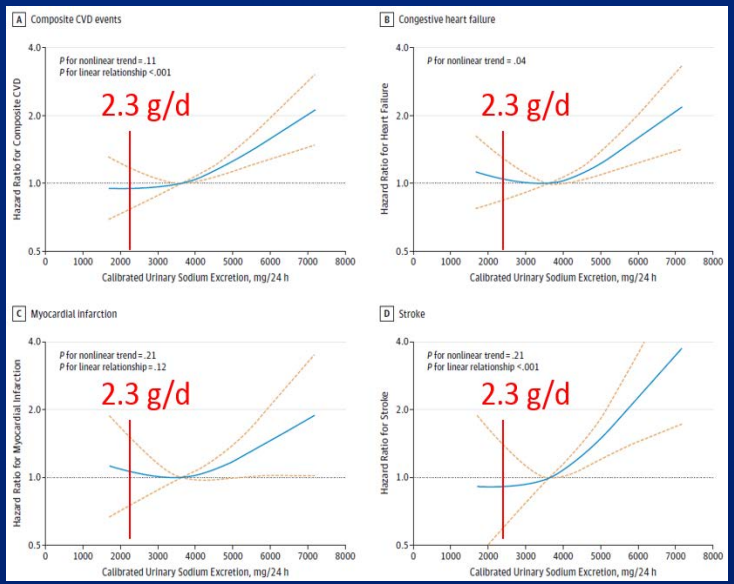
Population:
Healthy adults

N=3681

Follow-up:
7.9 yrs

No. events:
84 CV deaths

Stolarz-Skrzypek: *JAMA*; 2011



Population:
CKD pts.

N=3757

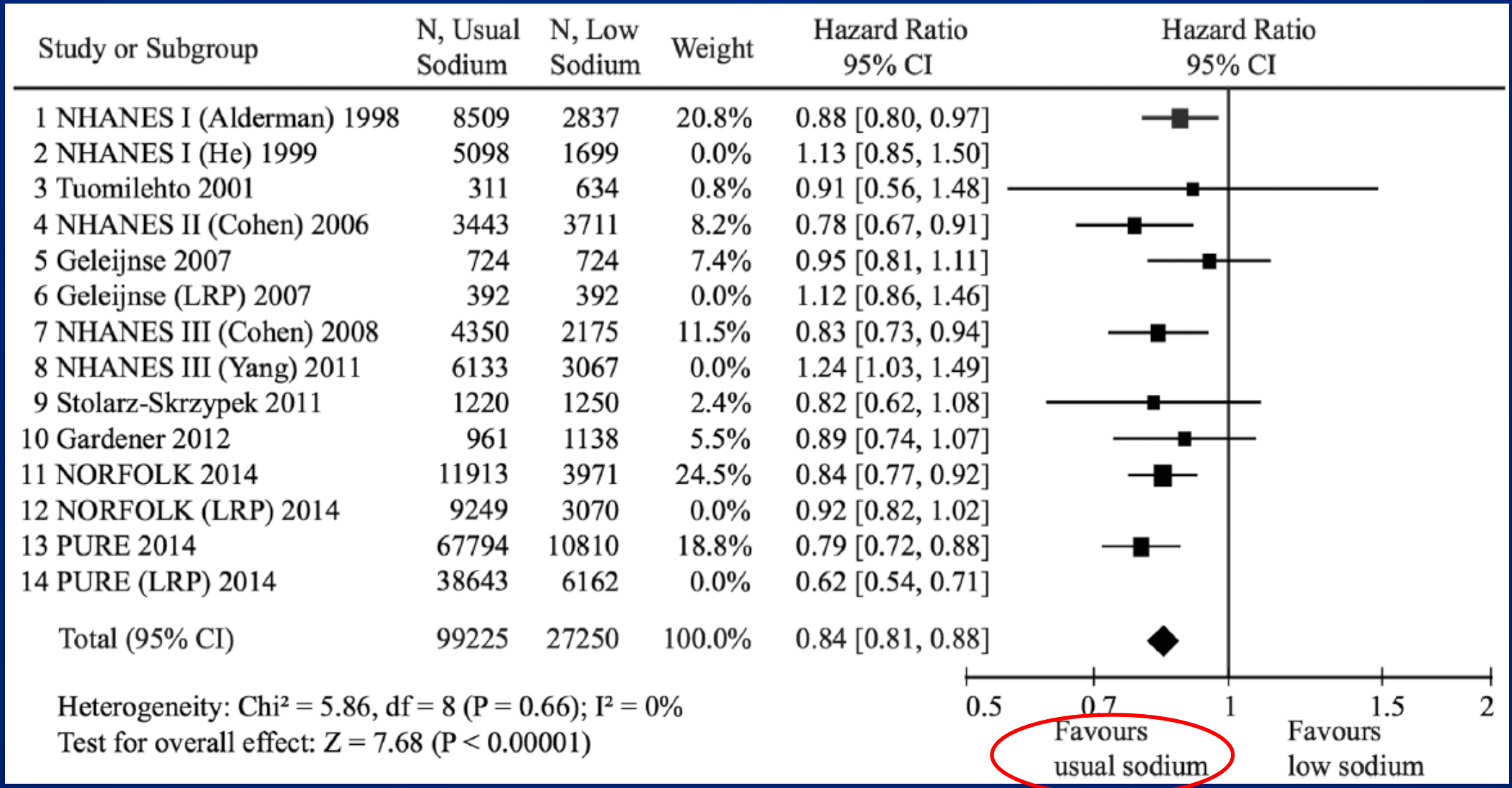
Follow-up:
6.8 yrs

No. events:
804 CVD

Mills, 2016, *JAMA* (CRIC)

Prospective Cohort Studies (*after* PURE)

Moderate Vs Low Sodium Intake and All Cause Mortality

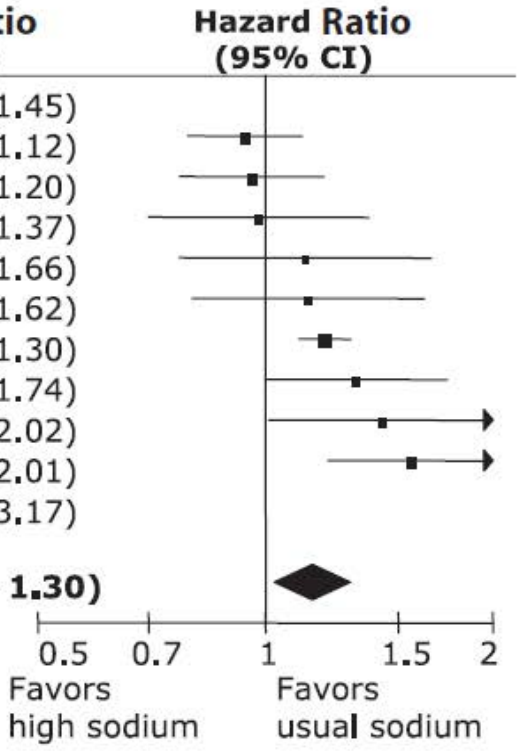


Graudal N, et al, 2016. Am J Hypertens 29;543-548

Prospective Cohort Studies
High Vs Moderate Sodium Intake

Study	Total	Weight	Hazard Ratio (95% CI)
Yang,[30] NW	2,667	0.0%	0.86 (0.51 – 1.45)
Cohen[29] (NH III)	6,525	15.5%	0.94 (0.79 – 1.12)
Tunstall-Pedoe,[20] M	4,604	12.7%	0.96 (0.77 – 1.20)
Tuomiletho,[24] M, NW	659	7.9%	0.98 (0.70 – 1.37)
Stolarz-Skrzypek[37]	2,454	6.5%	1.13 (0.77 – 1.66)
Tunstall-Pedoe,[20] F	3,525	7.3%	1.14 (0.80 – 1.62)
O'Donnel[38]	25,408	21.5%	1.20 (1.11 – 1.30)
Gardener[16]	2,337	10.0%	1.32 (1.00 – 1.74)
Thomas[15]	2,105	7.5%	1.43 (1.01 – 2.02)
Tuomilehto,[24] M, OW	514	11.0%	1.56 (1.21 – 2.01)
Yang,[30] OW	3,467	0.0%	2.07 (1.35 – 3.17)
Total (95% CI)	**48131**	**100.0%**	**1.16 (1.03 – 1.30)**

Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 17.61$, df = 8 ($P = 0.02$); $I^2 = 55\%$
Test for overall effect: $Z = 2.46$ ($P = 0.01$)



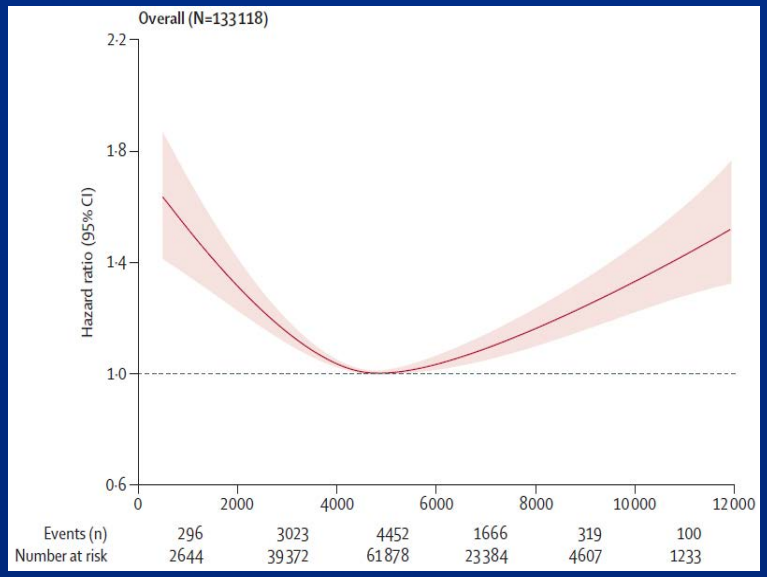
CV Events + Mortality: HR 1.16 (95%CI 1.03-1.30)

Range of Lowest Risk: 2.7-5.0g/day

Graudal et *AJH* 2014

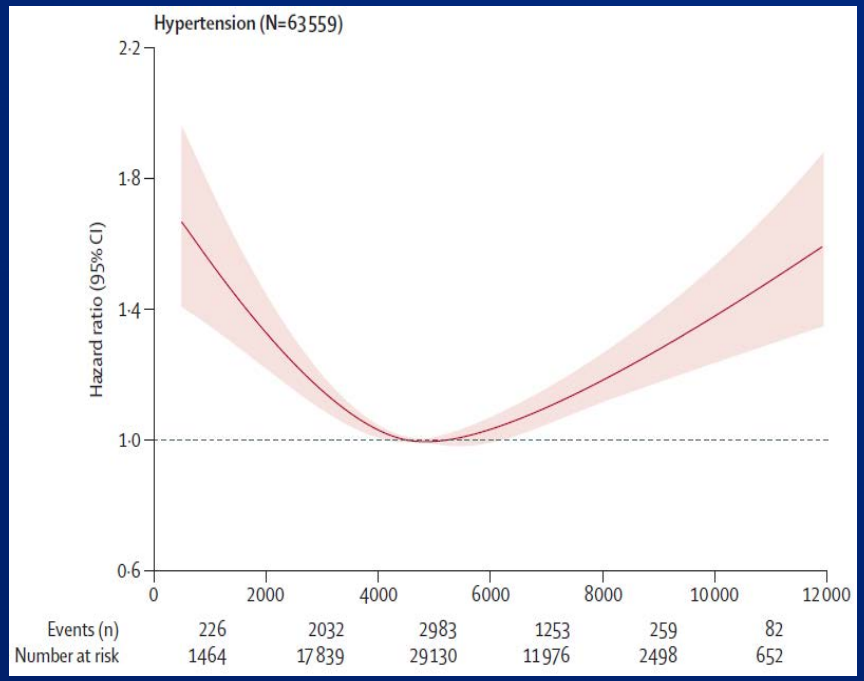
Sodium vs CVD by hypertension status

Overall (N=133,118)

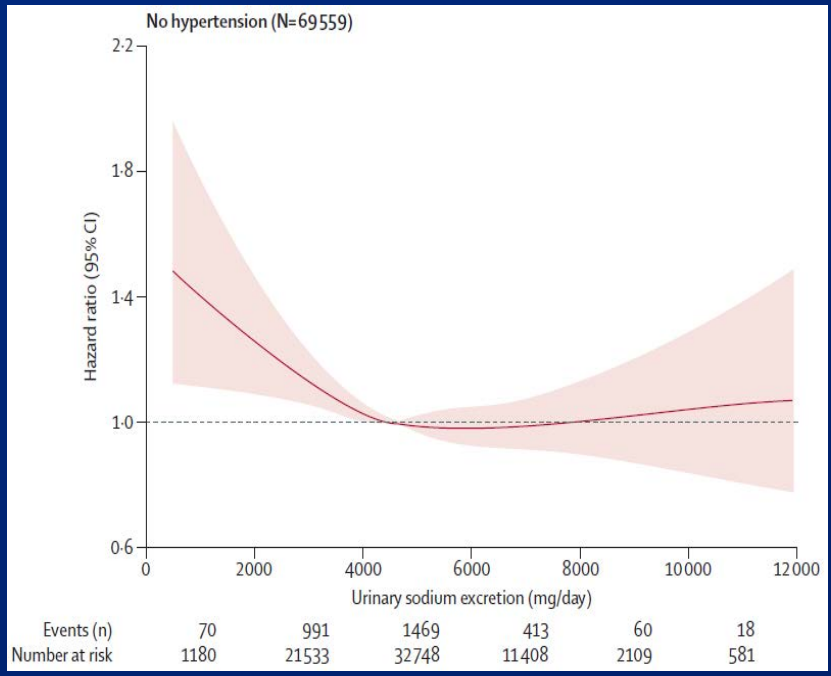


Data from PURE, EPIDREAM & ONTARGET/ TRANSCEND

Hypertension (N=63,559; **6835** events)

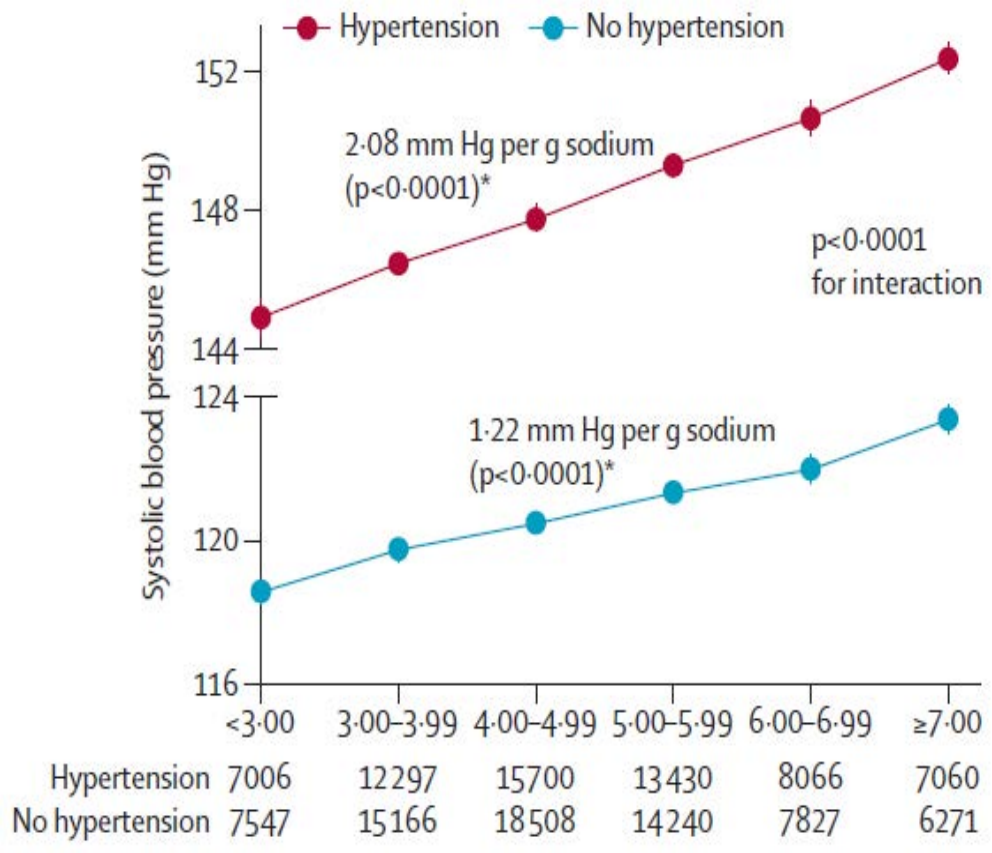


No Hypertension (N=69,559; **3021** events)

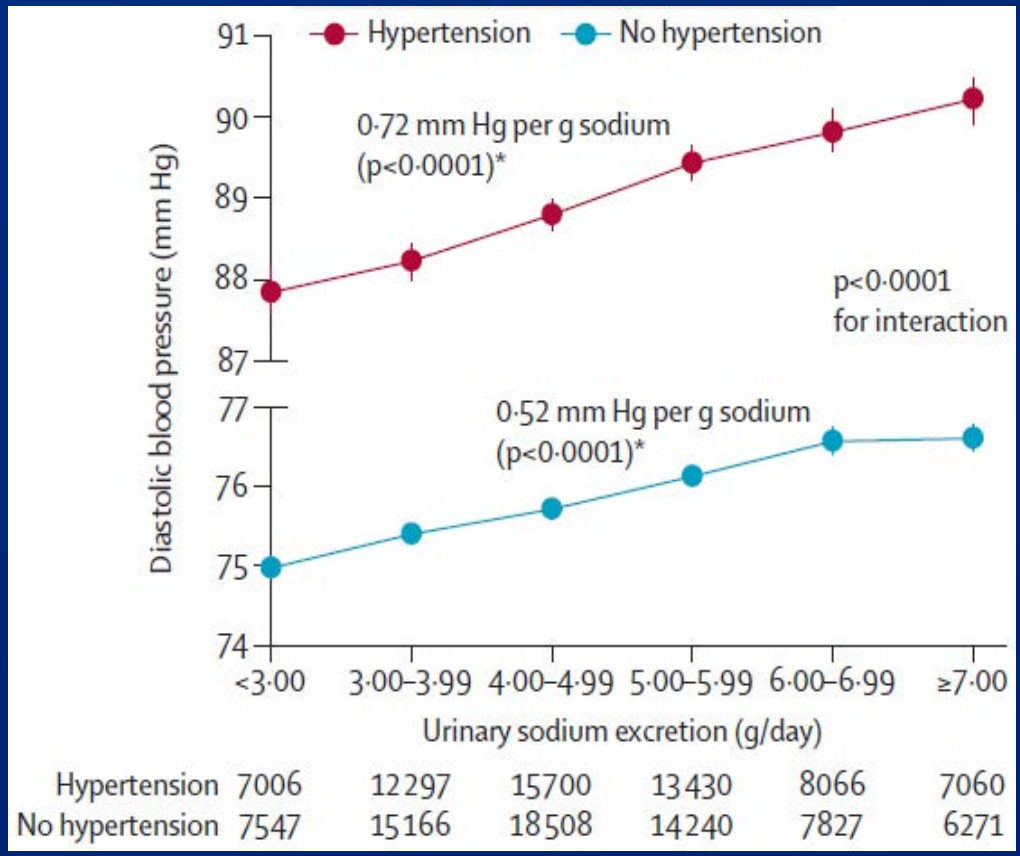


Mean BP by Na excretion and hypertension status (N=133,118) *

Systolic BP



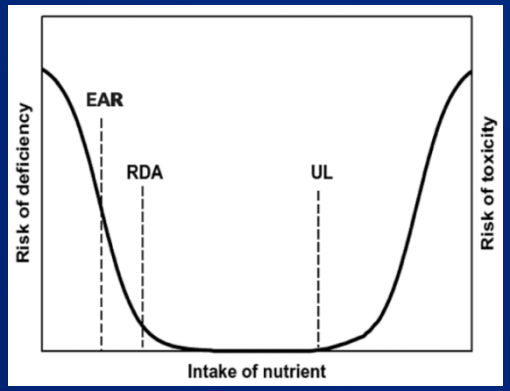
Diastolic BP



* Adjusted for age, sex, education, BMI, alcohol, smoking, and geographic region

Essential nutrients have an optimal range vs health outcomes (ie, U-shaped relationhip)

Deficiency/Toxicity Model



Heaney RP, 2013. AJH

Serum 25-vit D & mortality

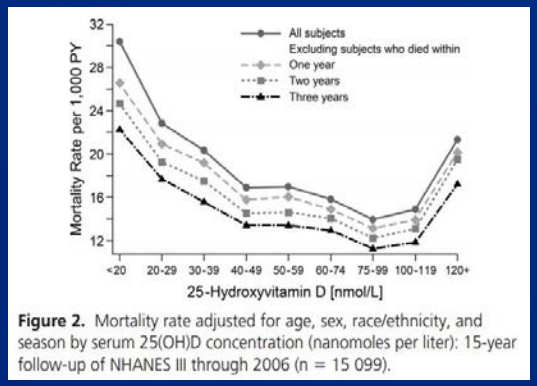
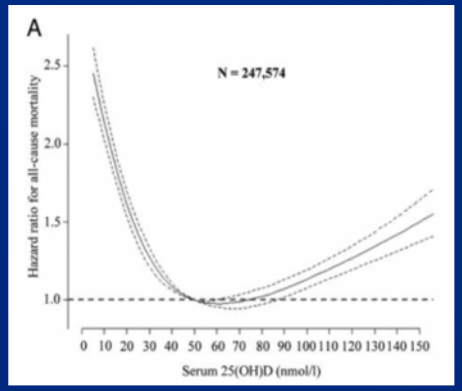


Figure 2. Mortality rate adjusted for age, sex, race/ethnicity, and season by serum 25(OH)D concentration (nanomoles per liter): 15-year follow-up of NHANES III through 2006 (n = 15 099).

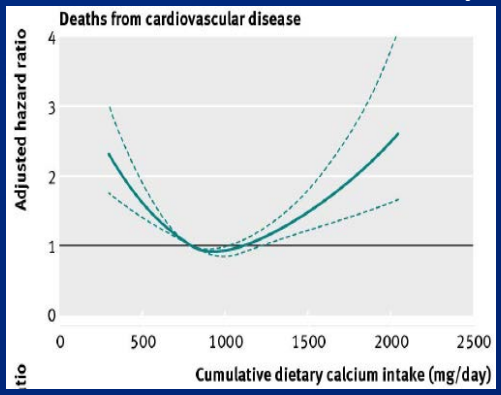
Langsetmo L, 2013 (NHANES-3)

Serum 25-vit D & mortality



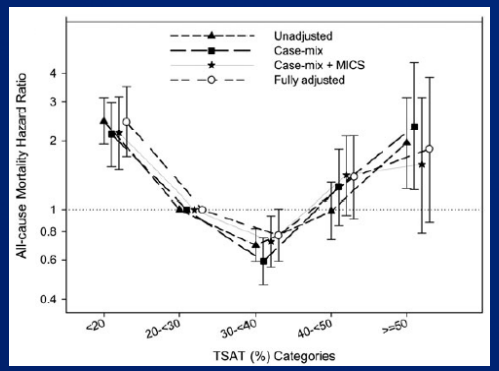
Durup D, 2012. J Clin Endocr Metab

Calcium & CV mortality



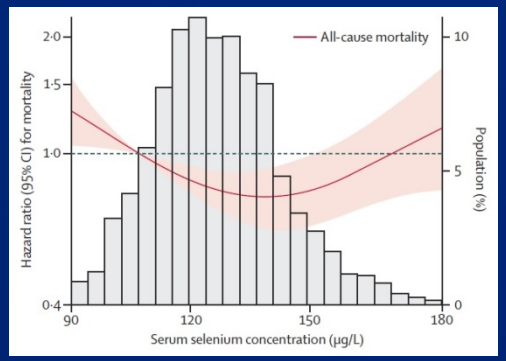
Michaelsson K, 2013. BMJ

Iron & mortality



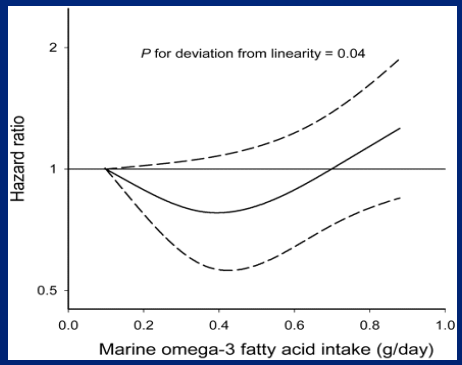
Hatamizadeh P, 2013 Nephrol Dial Trans

Serum selenium & mortality



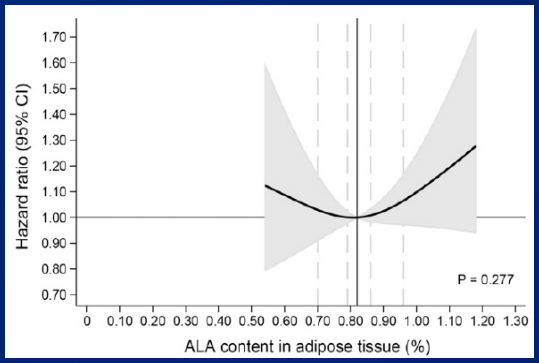
Rayman MP, 2012. Lancet

Marine n-3 & heart failure



Levitan EB, 2009. Eur Heart J

Alpha-linolenic acid & MI



Bork CS, 2016. AJCN

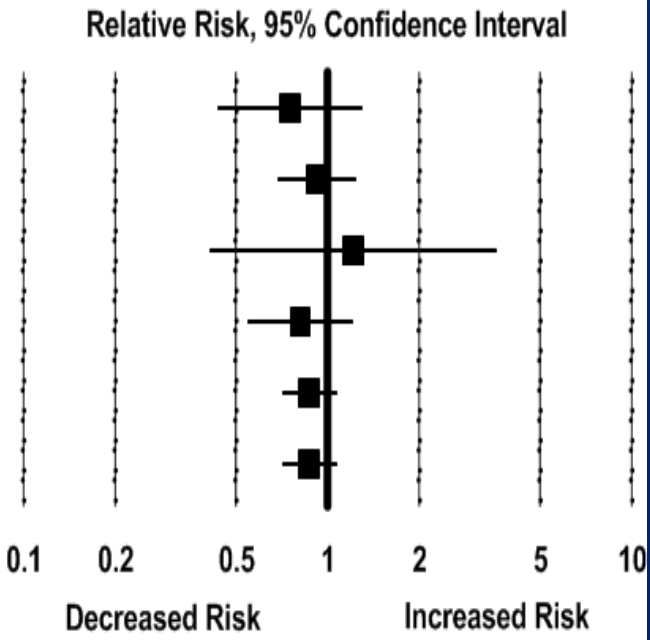
Cochrane review: Low vs high sodium and CV biomarkers

Biomarker	Studies	N	Standard mean difference (95% CI)	P
Renin	29	825	+0.67 (0.53 to 0.82)	<0.0001
Aldosterone	20	585	+0.99 (0.70 to 1.28)	<0.0001
Epinephrine	8	169	+0.21 (-0.00 to 0.43)	0.05
Norepinephrine	12	288	+0.17 (0.00 to 0.33)	0.04
Triglycerides	11	366	+7.78 (2.23 to 13.34)	0.006
LDL	8	273	+2.45 (-3.15 to 8.06)	0.39
HDL	11	342	-0.61 (-2.70 to 1.47)	n.s.
Cholesterol	13	424	+2.48 (-2.18 to 7.14)	0.30

Graudal N, et al. Am J Hypertens 2012;25:1-15

Meta-analysis (RCTs)

	Reduced Sodium		Controls		Relative	95% Confidence Interval	
	Events	Total	Events	Total	Risk	Lower	Upper
TOHP I 2007	17	231	32	311	0.72	0.41	1.26
TOHP II 2007	71	938	80	935	0.88	0.65	1.20
Morgan 1978	6	34	5	33	1.16	0.39	3.45
TONE 1998	36	332	46	331	0.78	0.52	1.17
Summary Estimate (Fixed)	13	1535	163	1610	0.83	0.67	1.04
Summary Estimate (Random)	13	1535	163	1610	0.83	0.67	1.04
Heterogeneity: p=0.840, I^2=0.00							



Cook et al *BMJ* 2007

CV Events: RR 0.83 (0.67-1.04)

O'Donnell, Mente, Smyth, Yusuf (*Eur Heart J* 2013)

Loss to Follow-up:
CV Events = 23%;
Records on CVD unavailable in 1/3

Observational follow-up

Summary

- Sodium intake > 5 g/d is associated with higher CVD & deaths
- Such high levels of sodium intake is seen mainly in China; less common in other countries
- ***Low*** sodium intake associated with ***higher*** mortality and CVD in *individuals* and persists after adjustment for confounders and control of reverse causality.
-
- Potassium is associated with lower risk of CVD & deaths

Implications

- A ***population strategy*** for sodium reduction appropriate only in populations with high intakes (eg, >5 g/day; China)
- ***A targeted approach*** more appropriate in other countries such as US and Canada (eg those with hypertension and intakes >5 g/d)
- In N America (intake of ~3.5 g/d), policy of reducing Na in all to below 2.3 g/d may ***increase*** mortality
- Large RCTs of low (<3 g/d) vs moderate intake (3 to 5 g/d) are ***essential***

European Heart Journal (2017) **0**, 1–9
doi:10.1093/eurheartj/ehw549

REVIEW

Controversies in Cardiovascular Medicine

The technical report on sodium intake and cardiovascular disease in low- and middle-income countries by the joint working group of the World Heart Federation, the European Society of Hypertension and the European Public Health Association

Giuseppe Mancia[1]*, Suzanne Oparil[2], Paul K. Whelton[3], Martin McKee[4], Anna Dominiczak[5], Friedrich C. Luft[6], Khalid AlHabib[7], Fernando Lanas[8], Albertino Damasceno[9], Dorairaj Prabhakaran[10], Giuseppe La Torre[11], Michael Weber[12], Martin O'Donnell[13], Sidney C. Smith[14], and Jagat Narula[15]

"***We support the conduct of definitive RCTs, comparing low sodium intake (< 2.4 g/day) to moderate intake (2.4–5 g/day) on cardiovascular events and mortality***……. insufficient information to reliably answer this question… competing evidence from BP trials (which report reductions in BP) and epidemiologic studies (reporting higher risk with low sodium intake)".

European Heart J 2017

Salt—too much or too little?

When apparent dogma is challenged, we should speak not of controversy but rather accede to the all-encompassing expression of so-called scientific uncertainty, so as to avoid unbecoming rhetoric. The issue of population strategies for salt consumption is a good case in point. There is no argument other than "excessive salt in the diet raises blood pressure", and that strategies to reduce salt in individuals with hypertension prevent the cardiovascular consequences of the disease. However, the corollary that reducing sodium intake across populations will be beneficial to all, has been challenged with the assertion that doing so might

annually, it behoves the scientific community to evaluate any population-based strategy, such as salt reduction, that might halt this epidemic. The editorial argued that the issue could only be decided by doing a randomised, controlled outcome trial, and that "in the absence of such a trial, the results argue against reduction of dietary sodium as an isolated public health recommendation".[6]

Support for this viewpoint has been added to by a large meta-analysis[7] and a cohort study,[8] but the most persuasive evidence is reported in this issue of *The Lancet* by Andrew Mente and colleagues.[9] Sodium excretion in 133 118 individuals from more than 49 countries of

Rita Maas/Getty Images

Published Online
May 20, 2016

"The corollary that reducing sodium intake across populations will be beneficial to all, has been challenged with the assertion that doing so might indeed be harmful."
--O'Brien E, 2016. *The Lancet*, 2016; 388:439

Editorial

Evidence-based policy for salt reduction is needed

AP Peter Dazeley/Getty

See Comment page 439
See Articles page 465

Evidence-based medicine has become the bedrock of treatment guidelines, but why does evidence-based medicine not translate into evidence-based policy? Governments and health organisations around the world are advocating salt intake be reduced, but little robust evidence exists to support a reduction in salt for the general population. Indeed, the few randomised controlled trials (RCTs) available have not strongly supported the benefit of salt reduction in normotensive populations. There is no real disagreement that high salt intake is associated with high blood pressure, and most studies indicate that high blood pressure is associated with more

The paper by Andrew Mente and colleagues in today's *Lancet* provides reasonable evidence that current dietary levels of salt in most populations are associated with the lowest incidence of cardiovascular events. More importantly, they show the proposed reductions to below 3 g of sodium intake daily are likely to result in harm in both hypertensive and normotensive people. Although not from an RCT, these data are as robust as the data used to advocate reductions to low levels. At the very least, these data should demand re-evaluation of the wisdom of reducing levels of dietary salt without high grade evidence to support such reductions

"Before non-legislated salt reduction programmes are imposed, the public should demand that the harms, as well as the benefits, are based solely on robust scientific evidence. Enacting potentially harmful changes without strong supportive evidence should be avoided."
--*Editorial in The Lancet*, 2016; 388:438

Call for Dietary Sodium Outcomes Clinical Trial

Can We End the Salt Wars With a Randomized Clinical Trial in a Controlled Environment?

Daniel W. Jones, Friedrich C. Luft, Paul K. Whelton, Michael H. Alderman, John E. Hall, Eric D. Peterson, Robert M. Califf, David A. McCarron

The 2013 Institute of Medicine (IOM; now the National Academy of Medicine) Report: Sodium intake in populations recommended that "clinical trials might focus on examining the effects of a range of sodium levels on risk of cardiovascular events, stroke, and mortality among patients in controlled environments."[1] This recommendation was specific in 2 regards. It recommends a cardiovascular outcomes trial of dietary sodium reduction, and it recommends this be done in people in controlled environments. There are important reasons behind these specific recommendations.

that the trial be performed in "patients in controlled environments." This statement recognizes the challenges of implementing a sodium reduction clinical outcomes trial. Such a trial would require a large number of participants in the intervention arm to maintain a reduced level of sodium intake for several years. Experience from behavioral intervention trials focused on blood pressure reduction demonstrates that in free-living people in the United States, maintaining even a modest reduction in sodium intake for >6 months is difficult for many adults.[8–10] Adherence to 1800 to 2300 mg/d level of sodium

Jones DW, et al. 2018 *Hypertension*

First and foremost, do no harm (Hippocrates)

Public health has potential to do great good when right, but can do great harm when incorrect

PURE Investigators Meeting, New Delhi, India
November 2017