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

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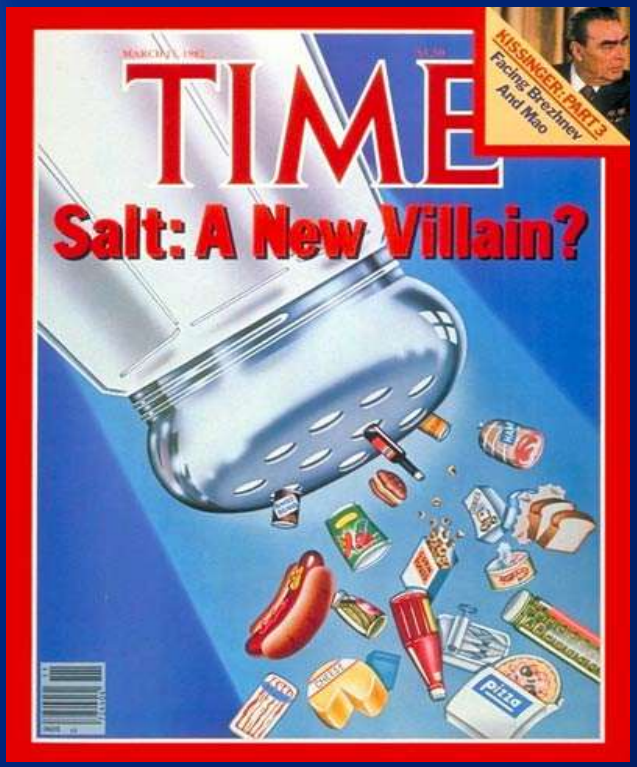
# Disclosures

I have no disclosures

# Salt – Central Hypothesis

Salt intake → Raised blood pressure → Heart attack Stroke



# Recommendations (For All)

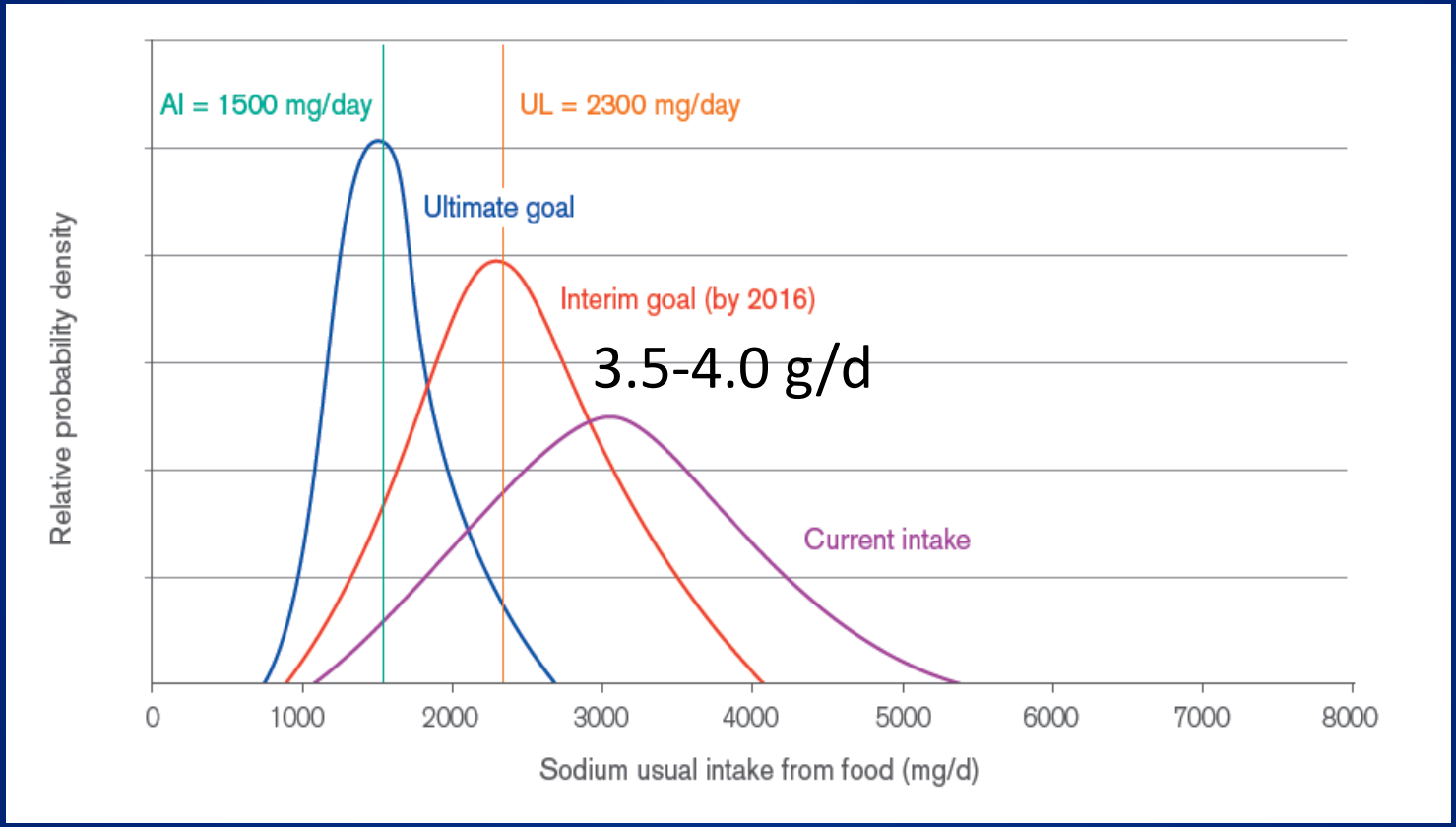
- **WHO/National Guidelines (e.g. AHA)**
  - Consume less than 2-2.4g/day (5-6g salt/day, or ~1 tsp)
  - FSAI: < 2.4g/day (achievable); < 1.6g/day (target)

- **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*

# Population-Wide vs Population-Specific

## National Guidelines



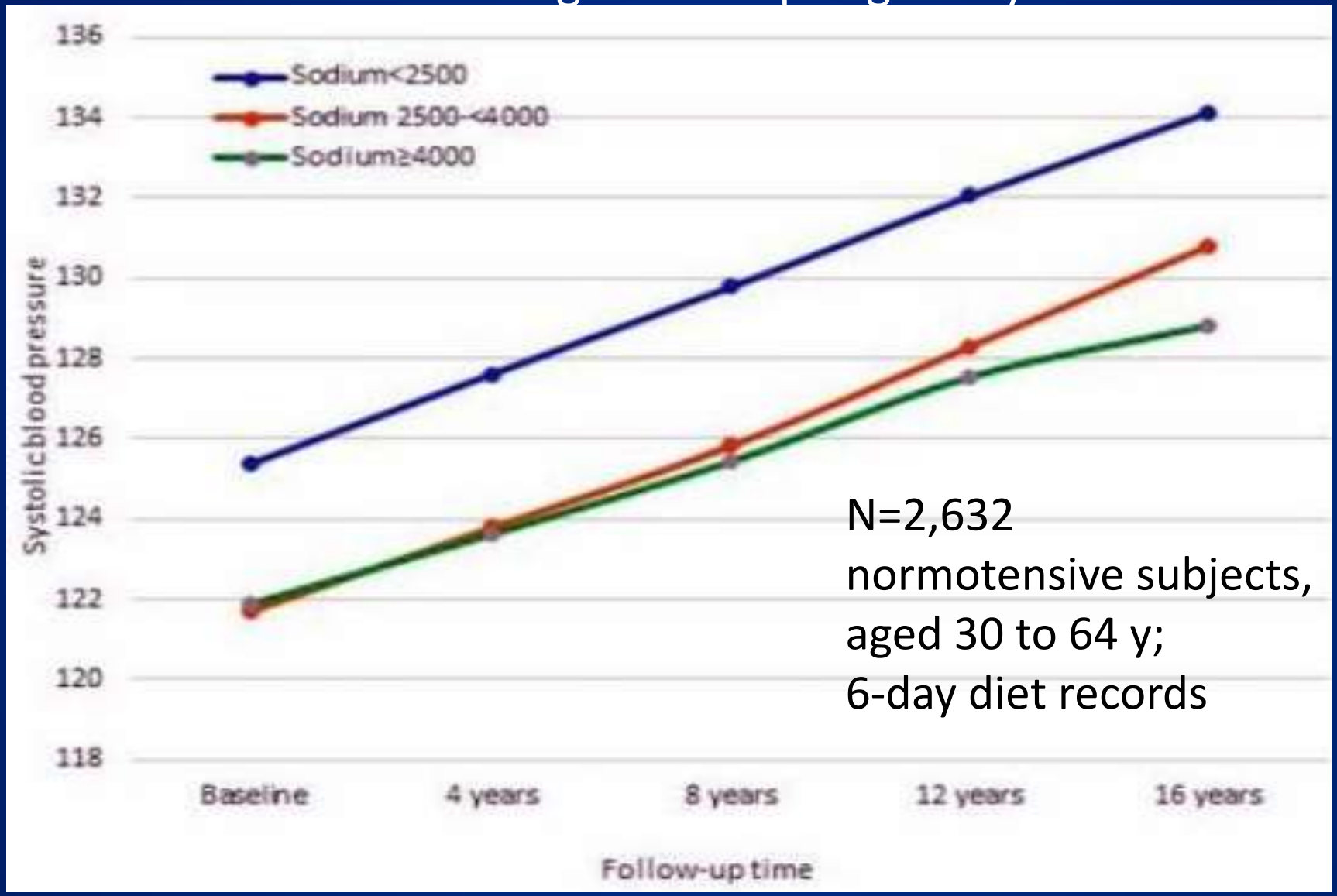

Is this 35%–65% reduction in Na consumption in millions of people necessary, safe, and feasible?

- The crux of the argument is that the blood pressure (BP) lowering effect of a reduction in Na intake (to low intake levels) will reduce CV disease
- Is this supported by evidence?

# Observational studies: Na vs BP

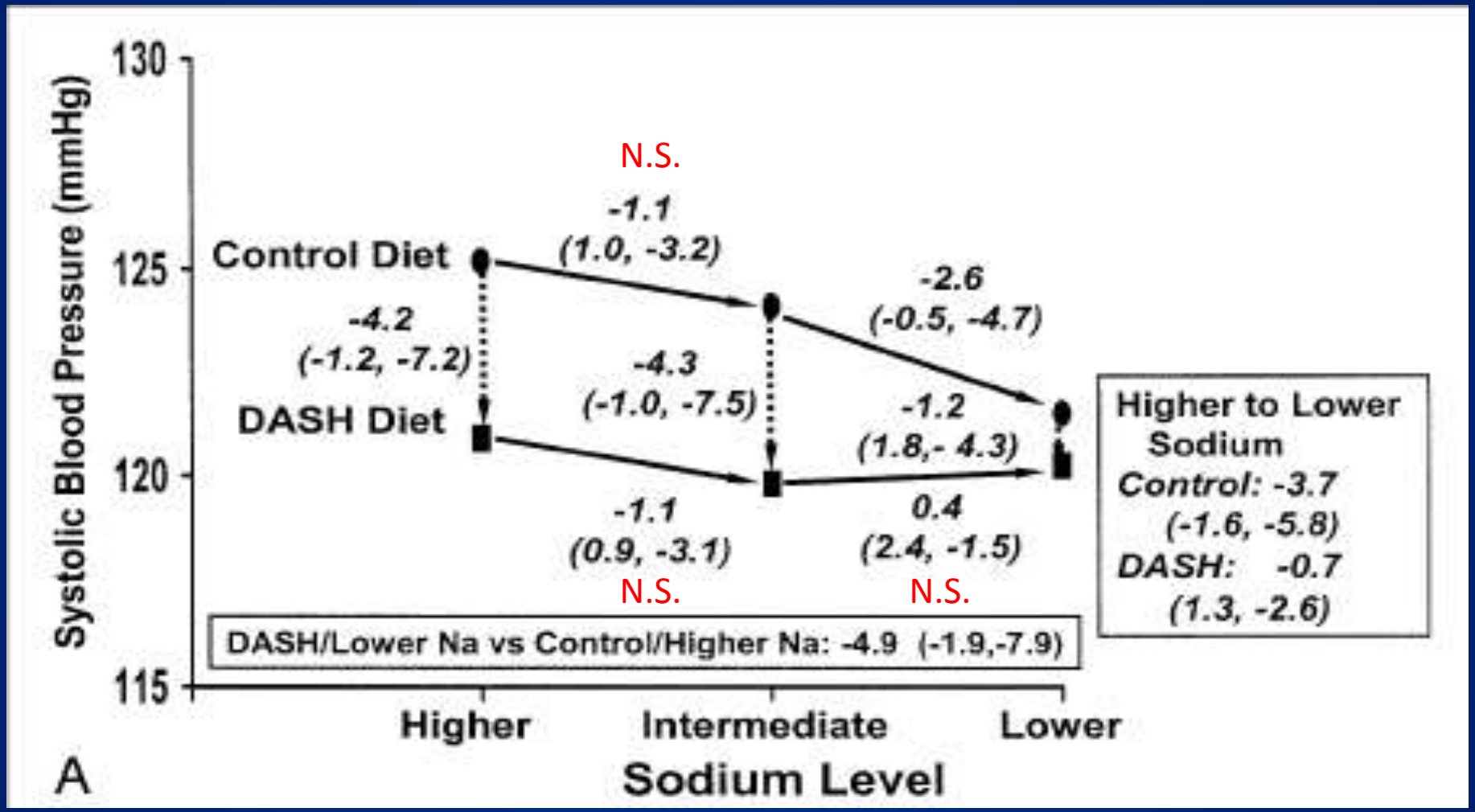
- INTERSALT study (BMJ 1988)
  - cross-sectional study (n=10,079), 52 centers worldwide
  - found a weak relationship between Na and BP (0.94/0.03 mm Hg per gram of Na)
- Scottish Heart Study (BMJ 1988)
  - 7354 people aged 40-59
  - age, pulse rate, BMI, alcohol & potassium intake related to BP
  - no relationship between Na and BP

# 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)
# <45 YEARS of AGE – NON-HYPERTENSIVES




Bray et al, *Am J Cardiol,* 7/2004

# 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

# 2011 Cochrane Review – SBP effect
# 71 RCTs – Low vs High Sodium in normotensives

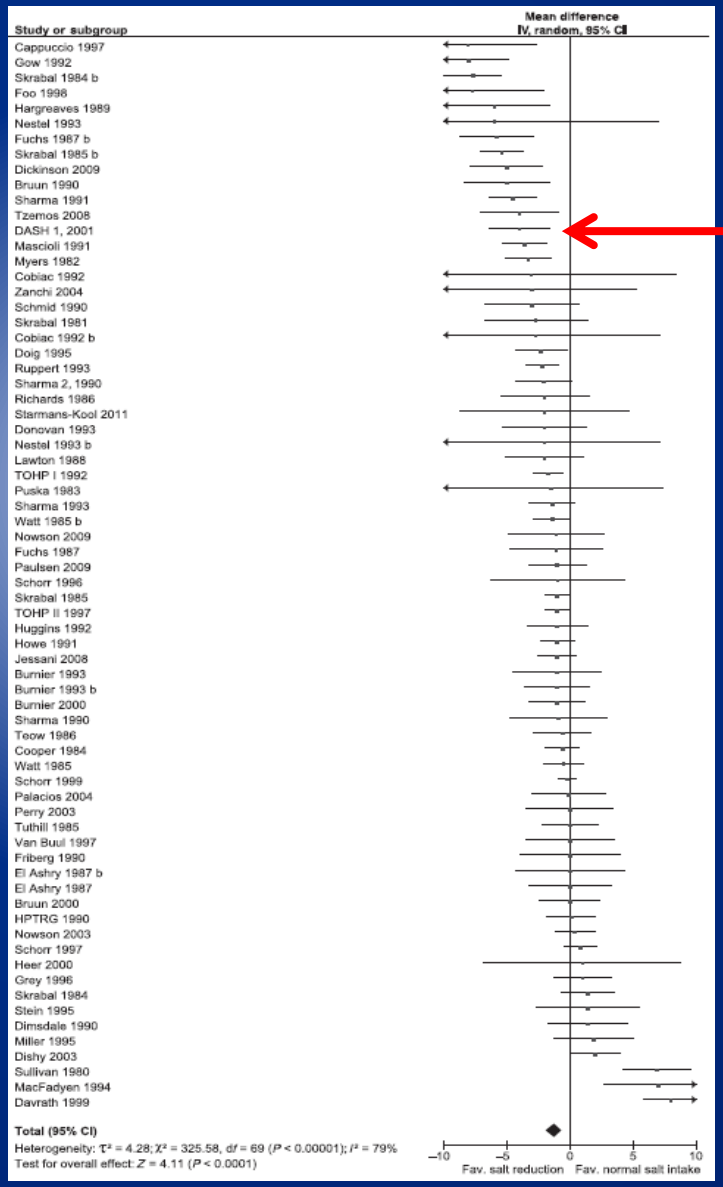
- 167 trials
- 10,0000 subjects
- normotensives & hypertensives

- Heterogeneous effect

- 150 mmol/d (3.45 g/d) decrease in Na

- 1.27 mmHg decrease in SBP **(0.37 mmHg per gram Na)**

**Modest change in SBP**




DASH Na

**Only 3 RCTs with >6 months duration**

Graudal et al. Cochrane. 2011

# 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)

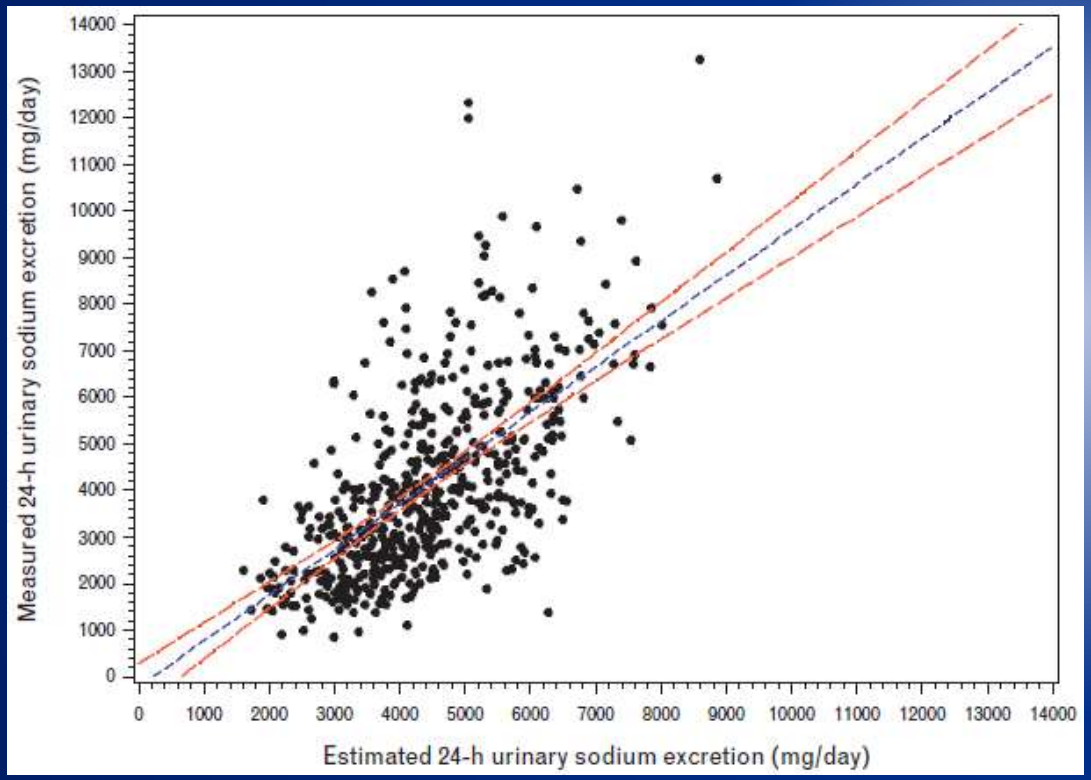
# Methods

**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)

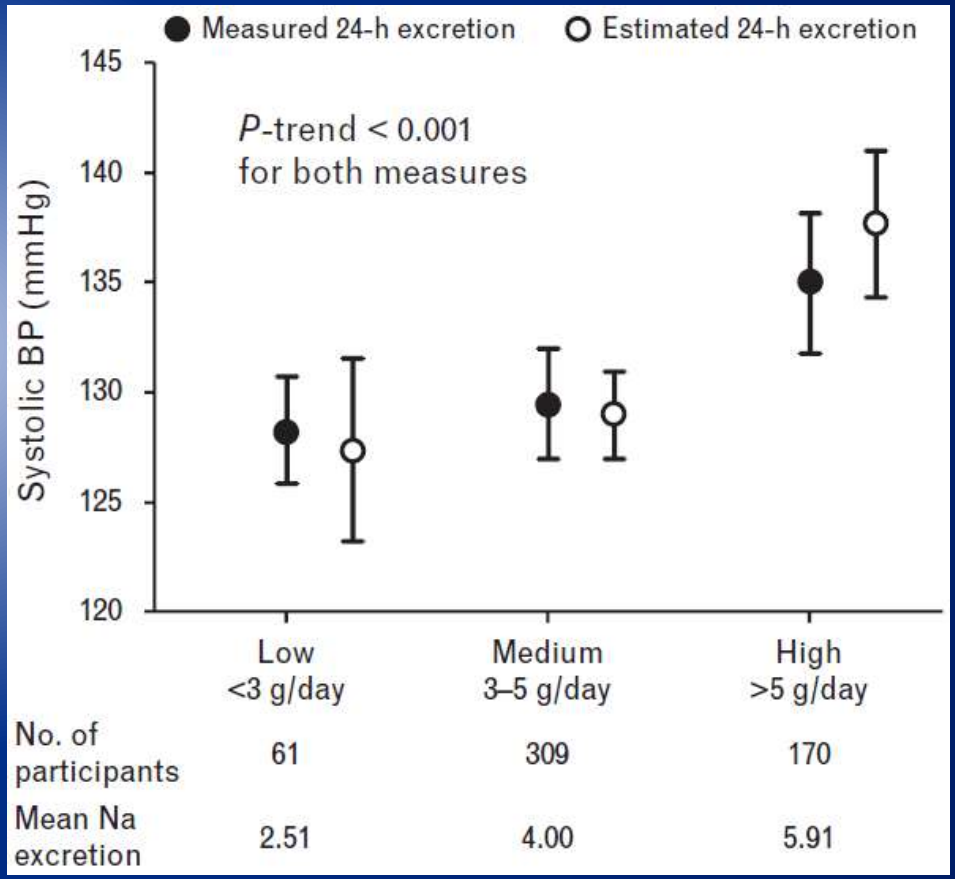
Measured vs. estimated Na excr.
ICC = 0.71, P<0.001




Test-retest: ICC=0.68

Similar results for K

## Na excr. vs Systolic BP

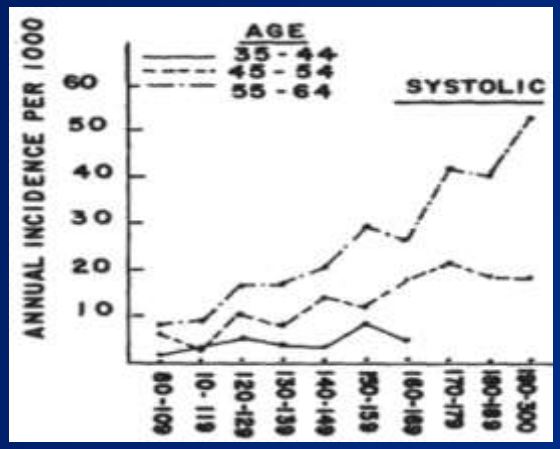



Similar results for diastolic BP

Mente A, et al, 2014, J Hypertens

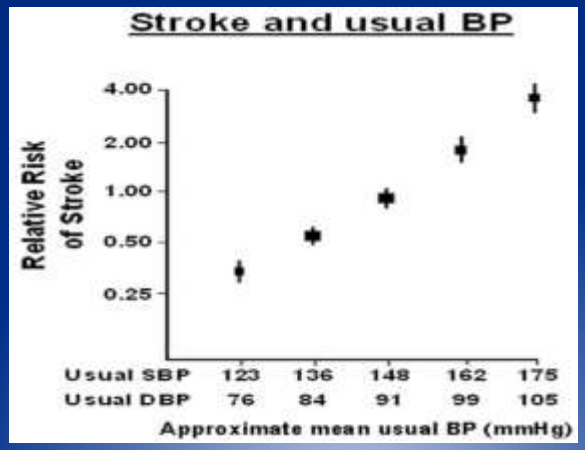
# Single clinic measures have been the foundation of epidemiology

## SBP vs CHD (N=5,127)



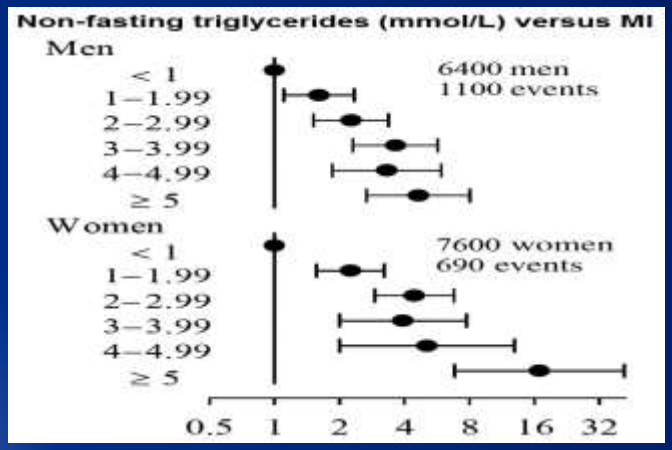

Framingham: Kannel WB. *Am J Cardiol* 1971;27:335

## SBP vs Stroke (N=420,000)



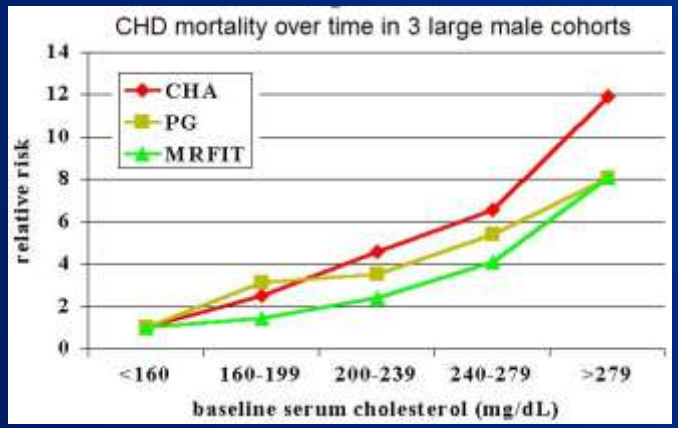

9 pooled studies: MacMahon S. Lancet 1990;335:765-74

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



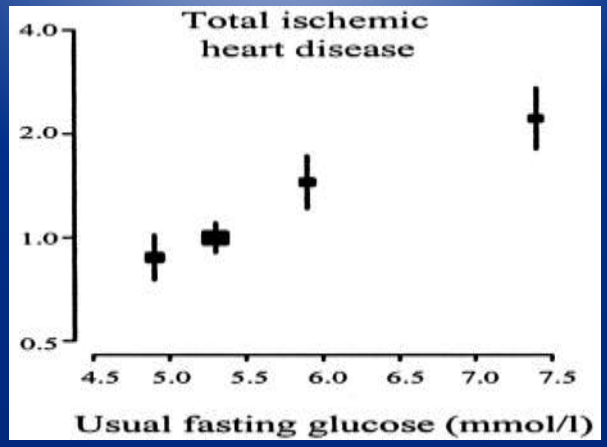

Copenhagen Heart: Nordestgaard B. *JAMA* 2007;298:299

## Cholest. vs CHD (N=81,488)



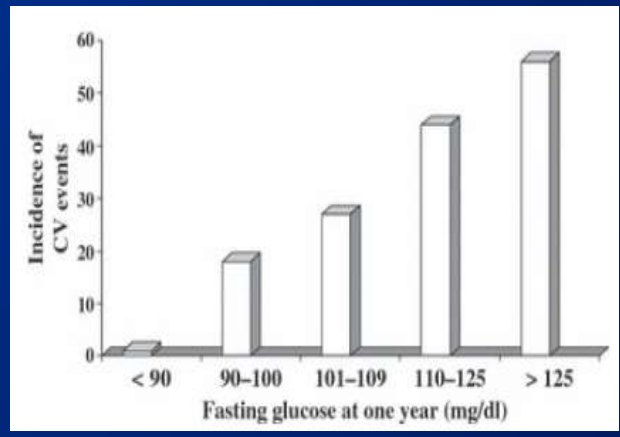

3 pooled studies: Stamler J. JAMA 2000;284:311

## 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)

The NEW ENGLAND JOURNAL of MEDICINE

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# Association of Urinary Sodium and Potassium Excretion with Blood Pressure

Andrew Mente, Ph.D., Martin J. O'Donnell, M.B., Ph.D., Sumathy Rangarajan, M.Sc., Matthew J. McQueen, M.B., B.Ch., Paul Poirier, M.D., Ph.D., Andreas Wielgosz, M.D., Ph.D., Howard Morrison, Ph.D., Wei Li, Ph.D., Xingyu Wang, Ph.D., Chen Di, B.Sc., Prem Mony, M.D., Anitha Devanath, M.D., Annika Rosengren, M.D., Aytekin Oguz, M.D., Katarzyna Zatonska, M.D., Ph.D., Afzal Hussein Yusufali, M.D., Patricio Lopez-Jaramillo, M.D., Ph.D., Alvaro Avezum, M.D., Ph.D., Noorhassim Ismail, M.D., Ph.D., Fernando Lanas, M.D., Thandi Puoane, M.P.H., Ph.D., Rafael Diaz, M.D., Roya Kelishadi, M.D., Romaina Iqbal, Ph.D., Rita Yusuf, Ph.D., Jephat Chifamba, M.Phil., Rasha Khatib, M.H.S., Koon Teo, M.B., Ph.D., and Salim Yusuf, D.Phil., for the PURE Investigators*

# Study Methods

**Design:** Cross-sectional study

**Population:** Unbiased selection from general population in 667 urban/rural communities in 18 countries

N=102,216; aged 35-70 years

**Sodium & potassium:** Estimated by morning fasting urine method, extensively validated previously in 11 countries

**Outcome:** Standardized BP measurements using automated device

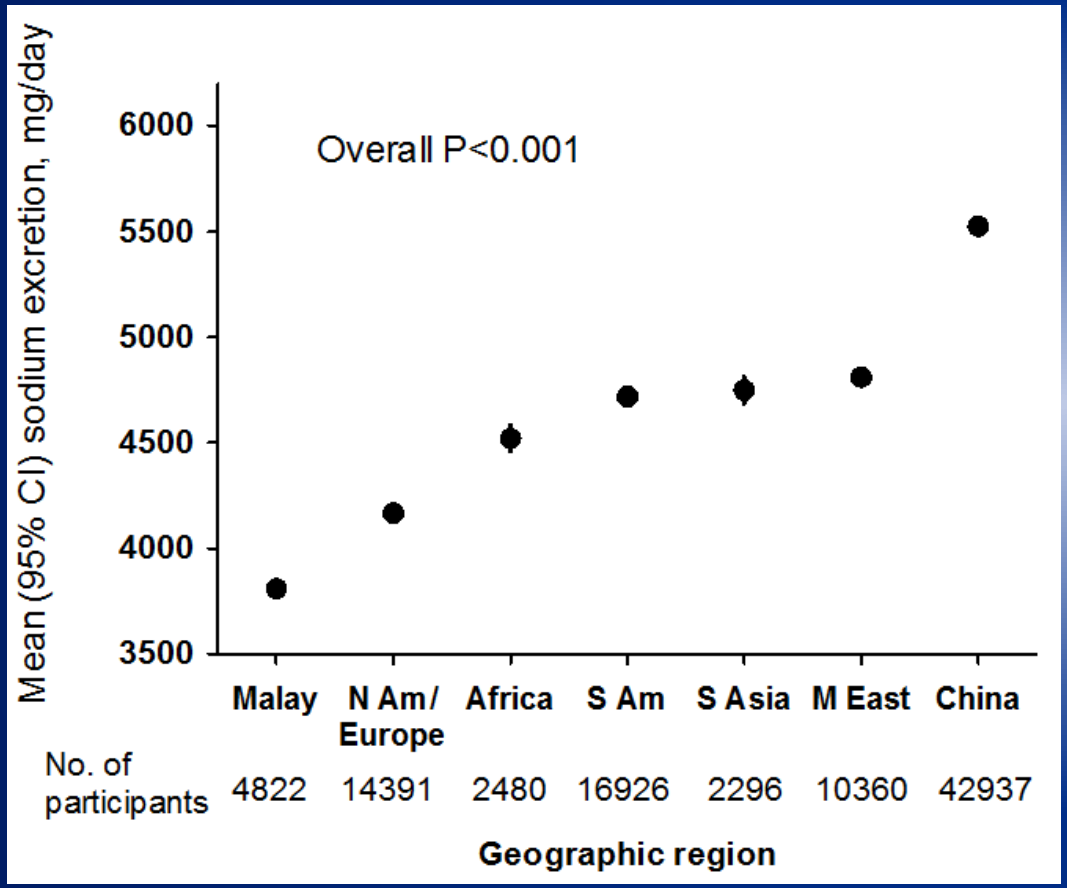
**Regression analyses:**

- association of sodium with BP levels; overall & key subgroups
- adjusted for age, sex, geography, education, BMI, alcohol

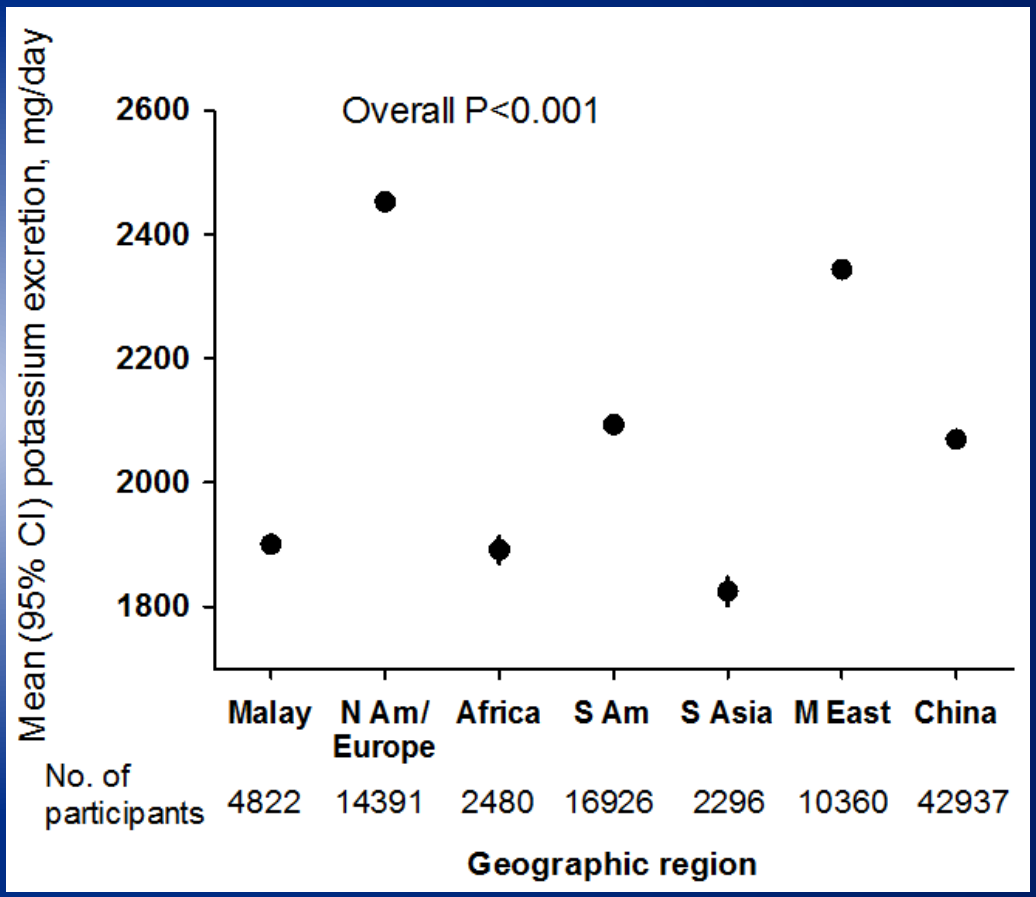
Mente A, et al. 2014, New Engl J Med

# Sodium and potassium intake by geographic region *

## Sodium excretion



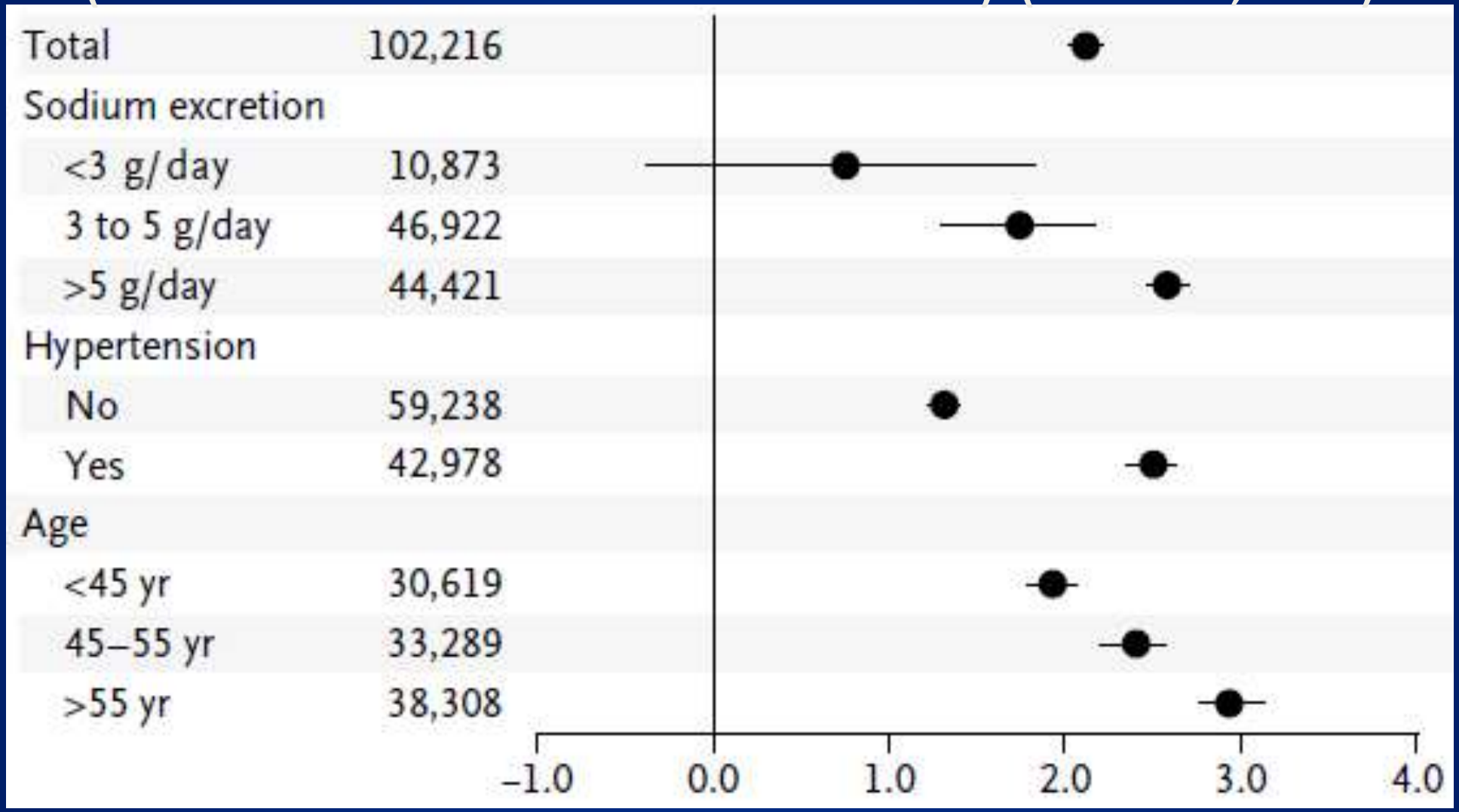

## Potassium excretion




* Adjusted for age and sex; Bars are 95% CI

Mente A, et al. 2014, New Engl J Med

# Systolic BP change per 1 g increase in Na (after random error correction) (N=102,216)

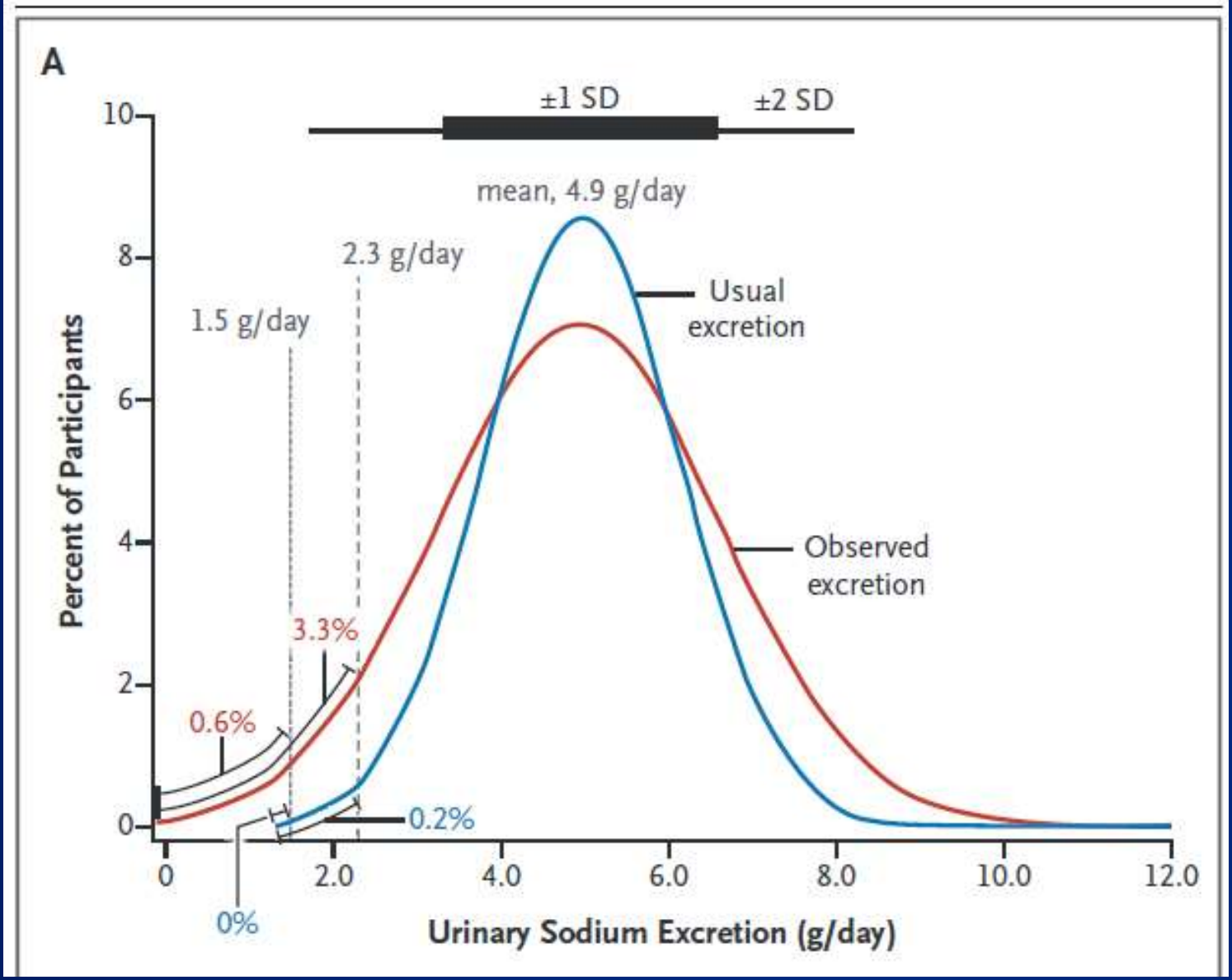



Adjusted for covariates

**Δ systolic BP, mm Hg**

Mente A, et al. NEJM 2014

# % with Na intake at current guidelines (PURE)




N=102,216

**Observed Na intake:**

3.3% with Na <2.3 g/d;

0.6% with Na <1.5 g/d

**Usual Na intake:**

0.2% with Na <2.3 g/d;

0% with Na <1.5 g/d

Mente A, et al. NEJM 2014

# 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

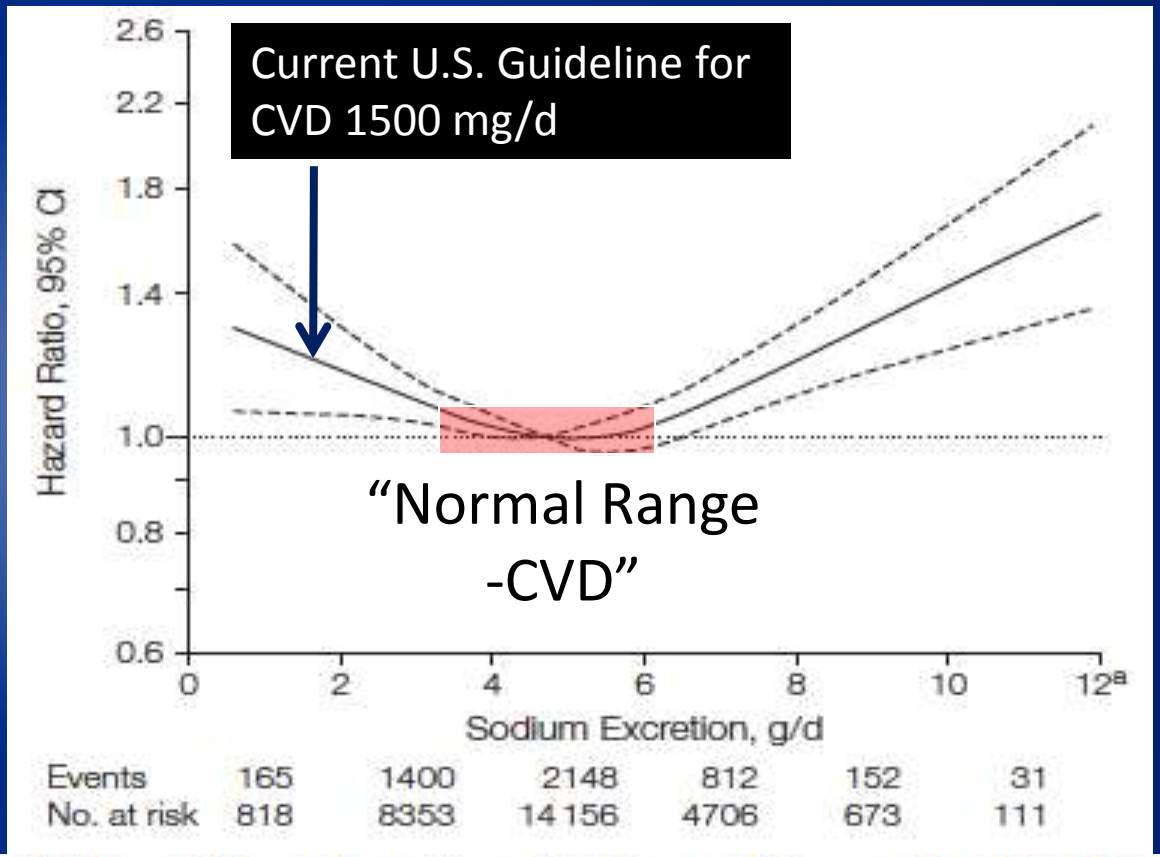



**Figure 1.** Estimated 24-Hour Urinary Excretion of Sodium and Composite of Cardiovascular Death, Stroke, Myocardial Infarction, and Hospitalization for Congestive Heart Failure

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

# LIMITATIONS

- High-risk population
- Reverse causation
  - Patients may consume lower sodium intake because of severe CHF, metastatic cancer etc.
- Majority of participants on RAAS blockers

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)

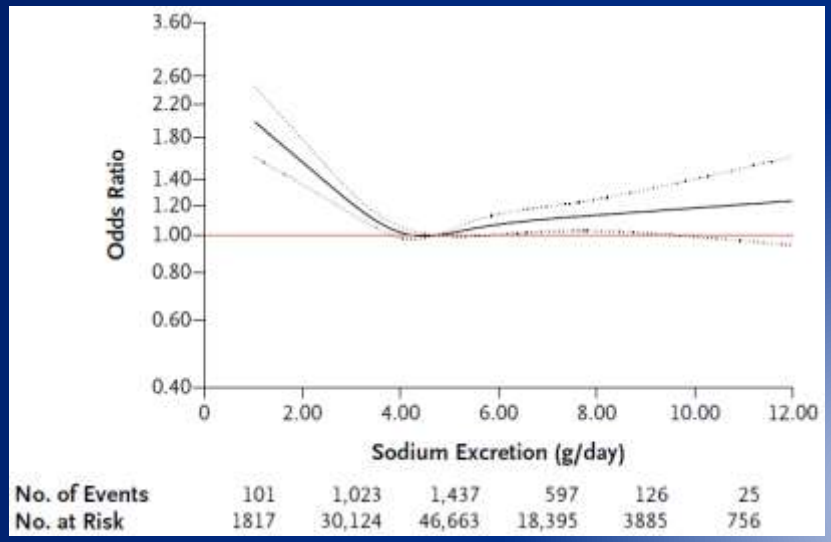
# PURE Study (Sodium Intake and CVD)

- **Population**
  - General population (n=101,945 with urine samples)
  - Prior history of CVD: n=8485 (8.3%)
- **Exposure**: Mean sodium excretion 4.93g/day (SD 1.7)
  - Fasting morning urine
  - Formula-derived 24 h urinary estimate (Kawasaki formula, CEPP, 1993)
- **Outcomes**: CV death, non-CV death, stroke, MI & CHF (n=3317)
  - All outcomes were independently adjudicated
  - Follow-up: 3.7 years (95% completed follow-up)
- **Statistical Analyses**
  - Multivariable logistic regression with GEE models
  - Analytic approaches to address confounding and reverse causality

Yusuf et al Lancet 2011

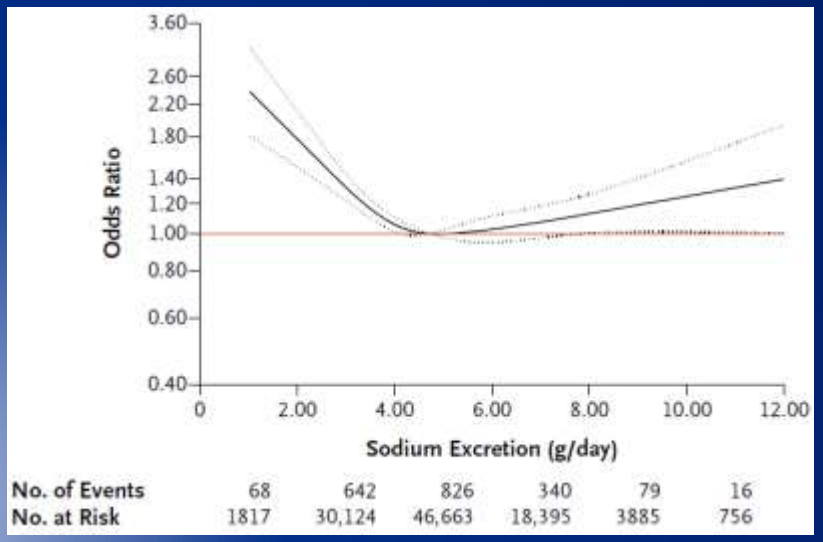
# Sodium Excretion (PURE)

## Primary Composite Outcome



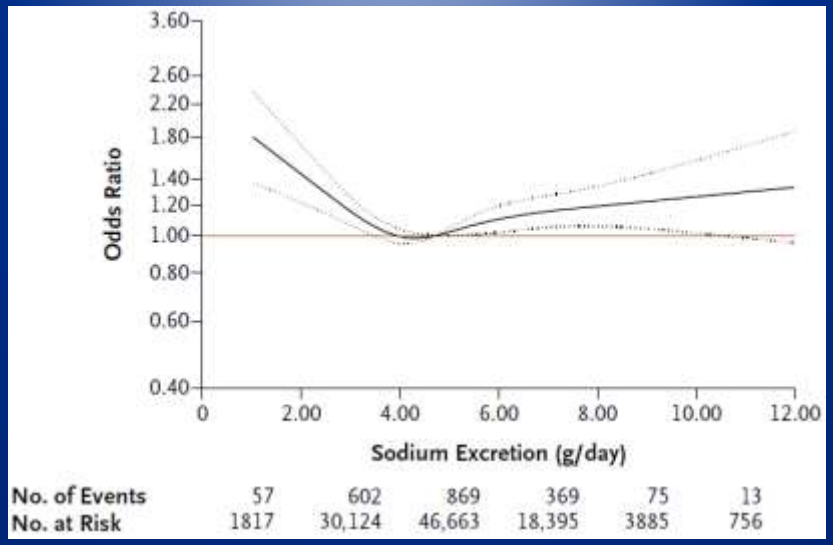

(N=101,945;
3,317 events)

## Death from any cause




(N=101,945;
1976 events)

## Major CVD events




(N=101,945;
1991 events)

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

# Models (Diet and Blood Pressure)

| | 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) |
| + LDL:HDL ratio | 1.30 (1.15-1.48) | 1.00 (0.92-1.09) | 1.00 | 1.06 (0.94-1.19) | 1.18 (1.04-1.33) |
| + 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) |

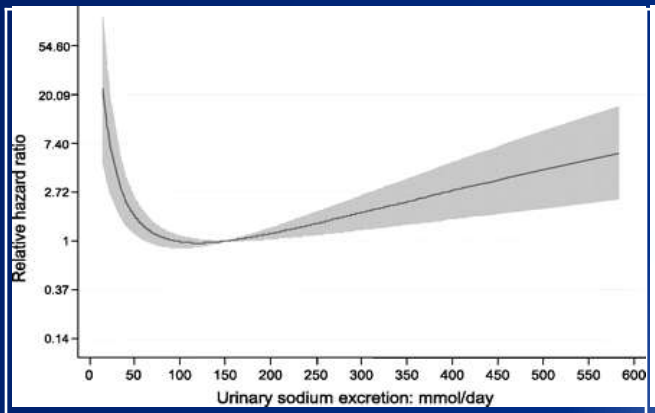
Adjusted for age, cluster, sex, education, prior CVD index, alcohol, diabetes, BMI, smoking

# 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”.

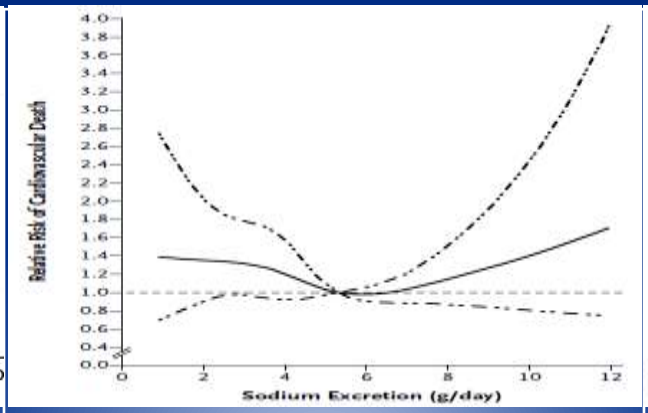
  (Oparil S. NEJM 2014;371:677-679)

# Sodium Intake and Mortality + CVD:
## Similar pattern of results with different methods of Na estimation



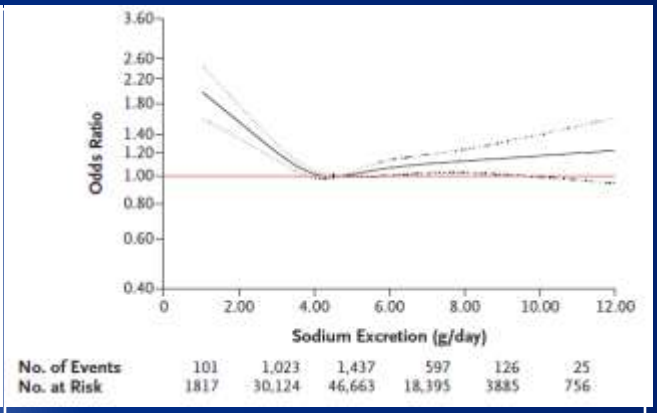

Australian DM Study (n=638; 24-h)

Thomas et al *Diabetes Care* 2011

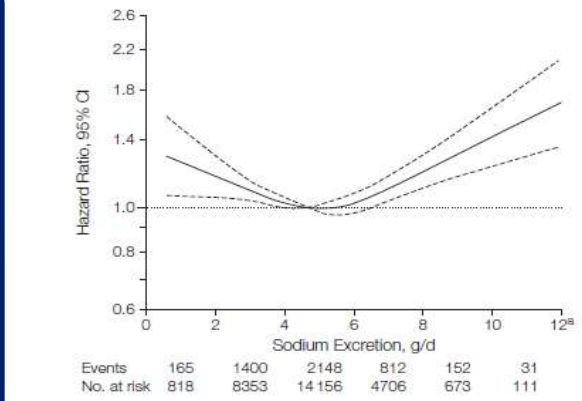



SURDIAGENE (n=1437; DM, EMU)

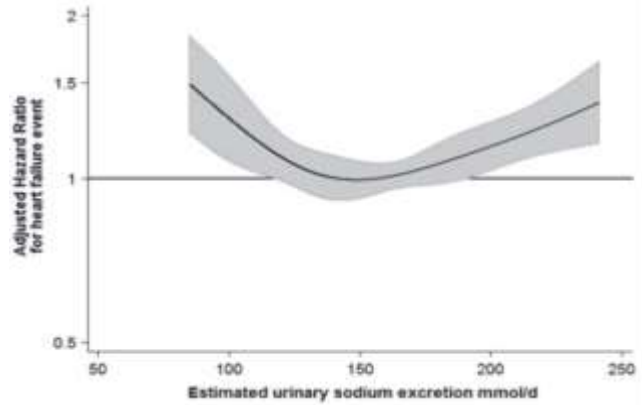
Saulnier et al *NEJM* 2014




PURE Study NEJM 2014 (n=101,945; EMU)

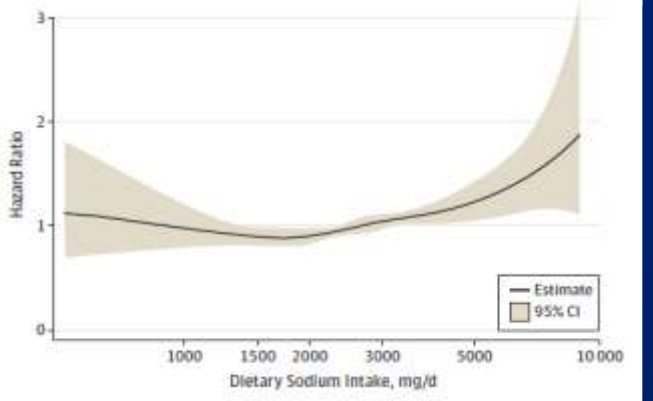



ONTARGET/TRANSCEND JAMA 2011 (n=28,880; EMU)




EPIC-Norfolk (n=19857; USE, 12.9 y)

Pfister al *EHJ* 2014

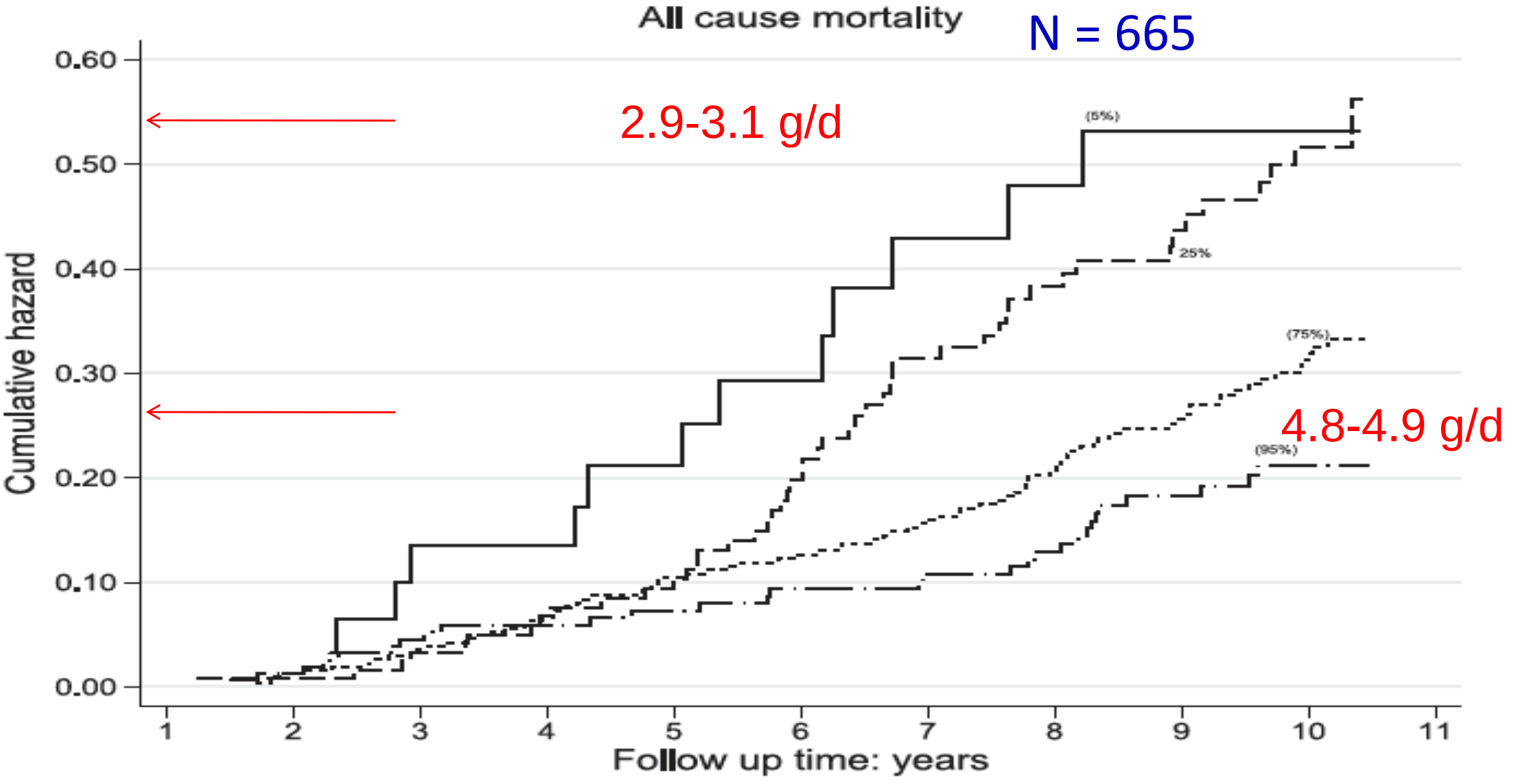



Health ABC (n=2642; FFQ, 10 y)

Kalogeropoulos et al *JAMA-Int Med* 2015

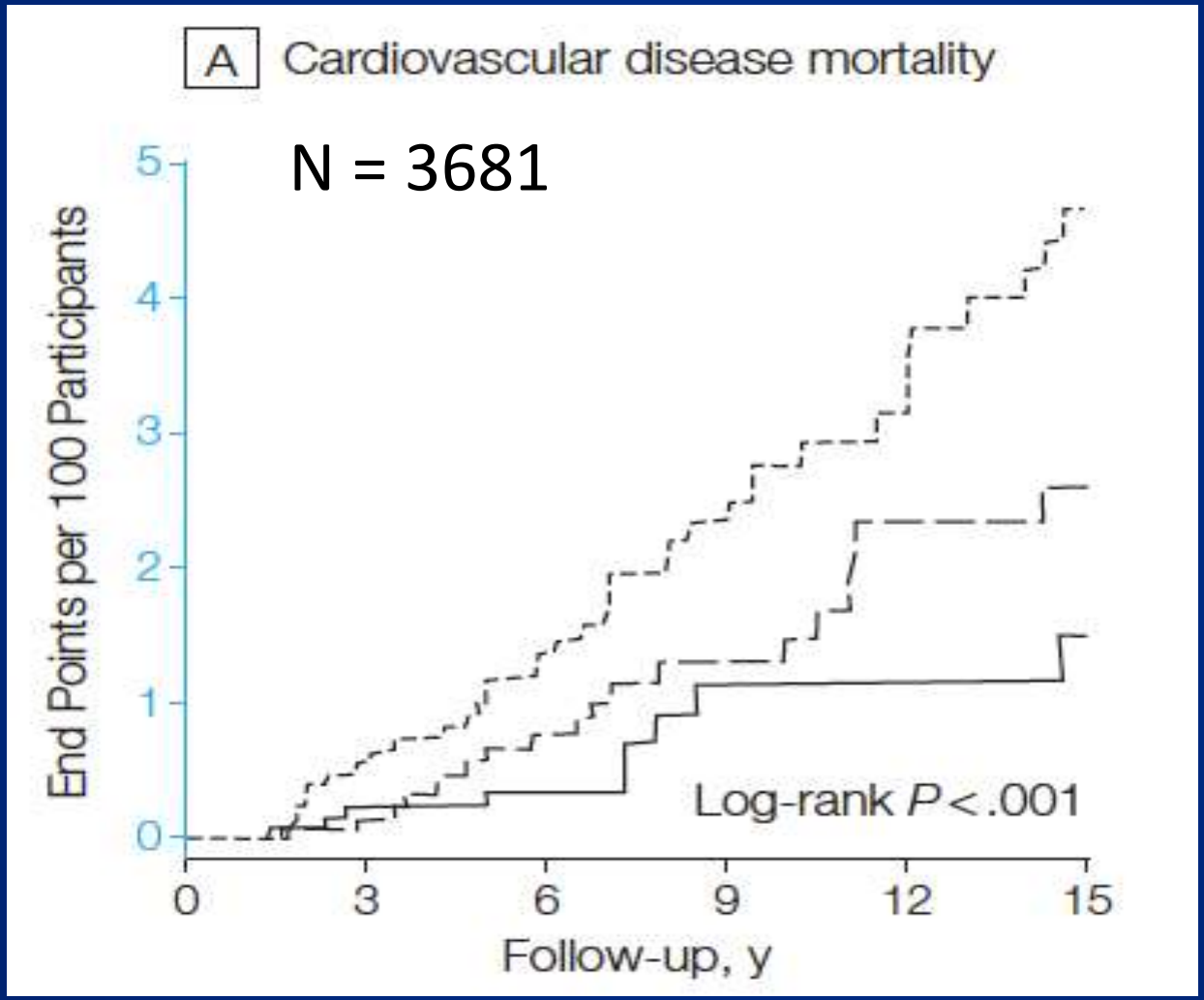
Smyth A, et al. 2015 Curr Hypertens Rep

# Higher all-cause mortality with lower 24-hr urinary Na in type 2 diabetes




Ekinci et al: *Diabetes Care;* 2011

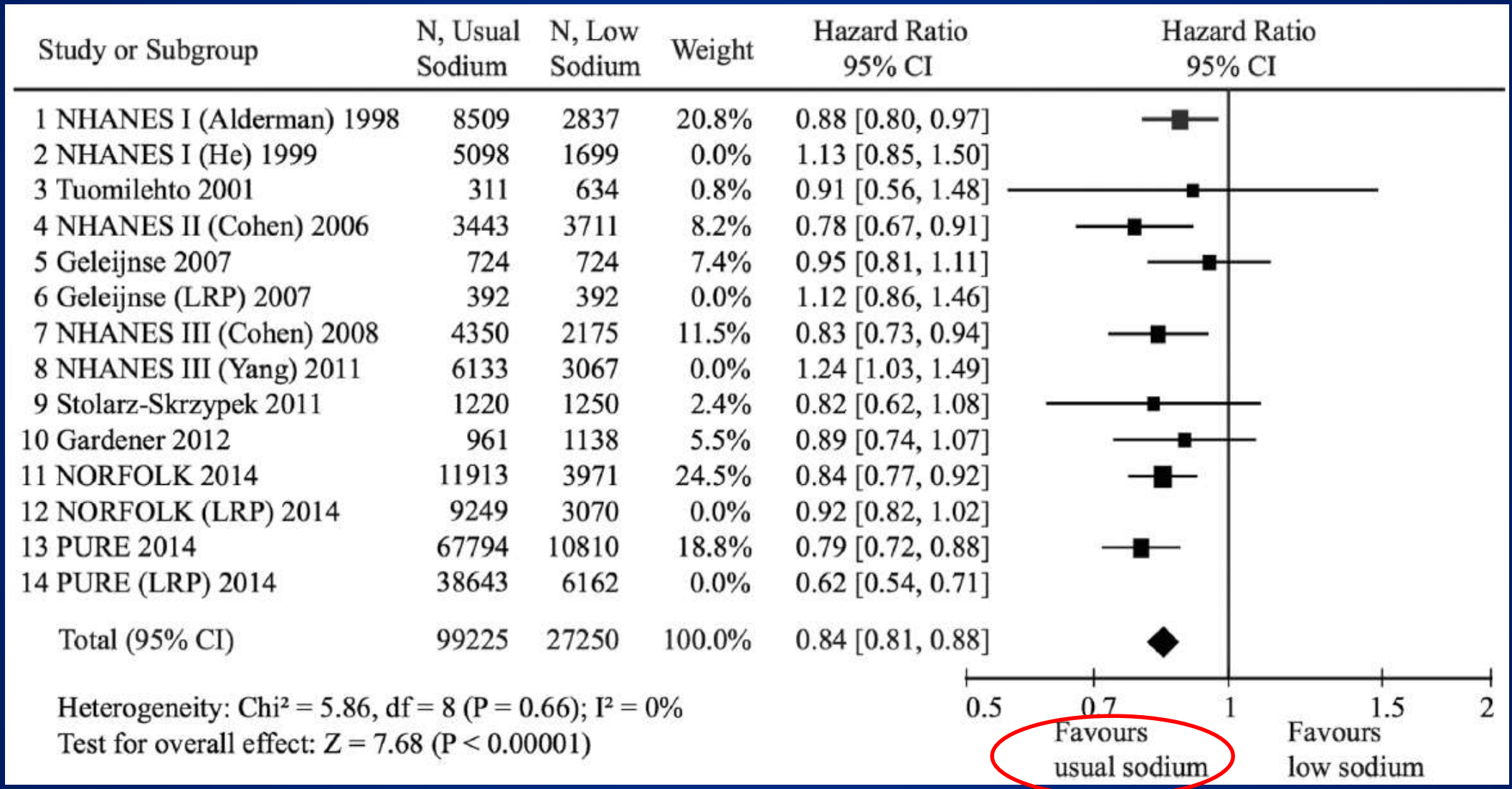
# Increased CVD deaths with lower 24-hr urinary Na in healthy adults




Stolarz-Skrzypek et al: *JAMA*; 2011

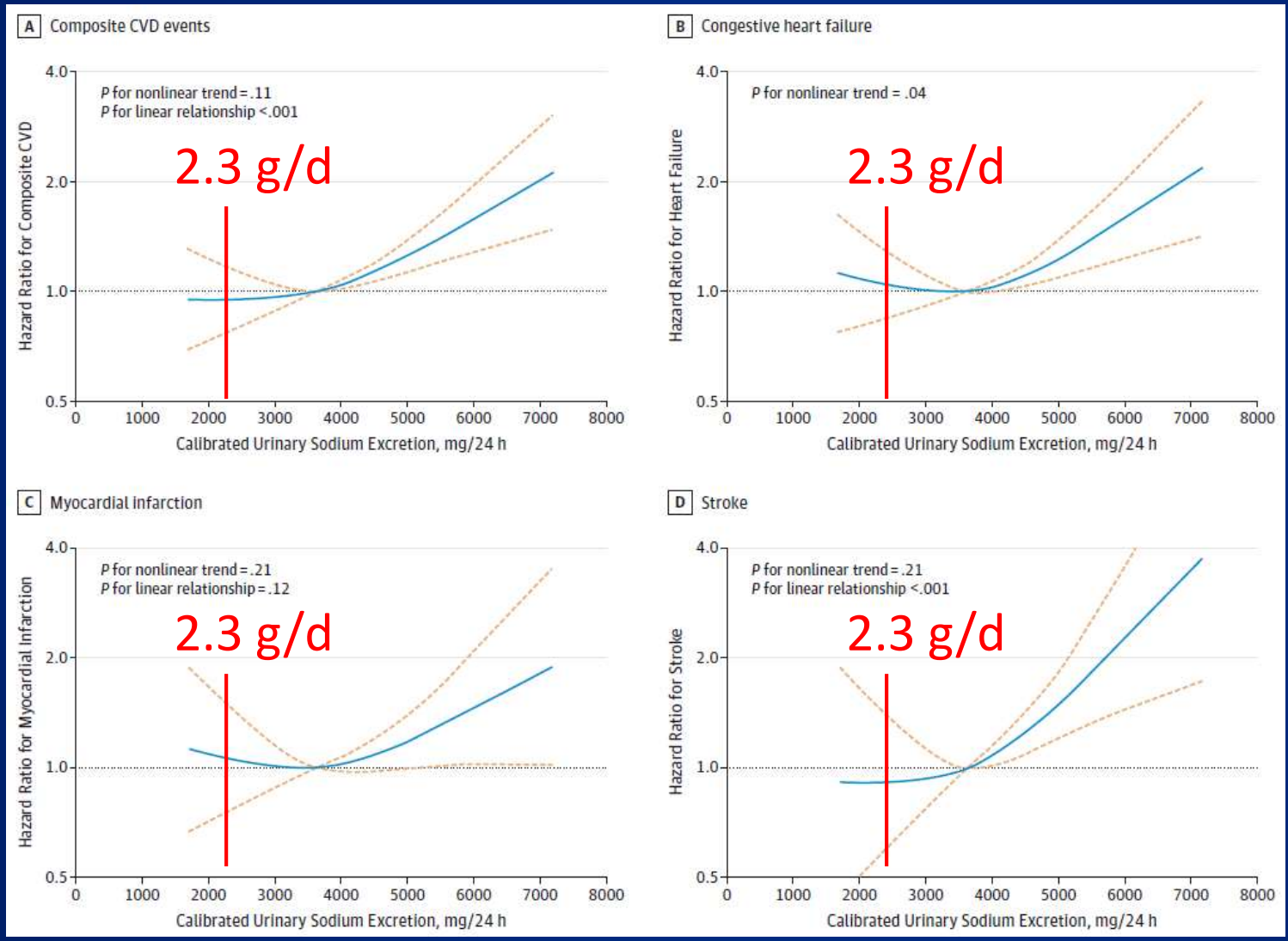
# Prospective Cohort Studies (*after* PURE)

## Moderate Vs Low Sodium Intake and All Cause Mortality




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

# Sodium Excretion and the Risk of Cardiovascular Disease in Patients With Chronic Kidney Disease




Coherence at high Na (ie, >5 g/d)

Low power at Na range of <3 g/d

Curves do not support the claim that Na of <2.3 g/d is necessary

Mills KT, 2016, JAMA

# Sodium Excretion and the Risk of Composite CVD in Patients With Chronic Kidney Disease

| | Sodium excretion, mg/day | | | |
|---|---|---|---|---|
| | **<2894** | **2894-3649** | **3650-4547** | **>4547** |
| | **HR(95%CI)** | **HR(95%CI)** | **HR(95%CI)** | **HR(95%CI)** |
| **No. of individuals** | 939 | 940 | 939 | 939 |
| **Composite CVD** | 174 | 159 | 198 | 273 |
| Model 1 | 1.00 | 0.88(0.71-1.10) | 1.14 (0.93-1.41) | **1.79 (1.46-2.19)** |
| Model 2 | 1.00 | 0.85 (0.68-1.07) | 0.99 (0.80-1.24) | **1.31 (1.05-1.63)** |
| Model 3 | 1.00 | 0.87(0.69-1.10) | 1.01 (0.81-1.26) | **1.36 (1.09-1.70)** |

**Still does not show that low is better than moderate**

Mills KT, 2016, JAMA

# Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies

*Andrew Mente, Martin O'Donnell, Sumathy Rangarajan, Gilles Dagenais, Scott Lear, Matthew McQueen, Rafael Diaz, Alvaro Avezum, Patricio Lopez-Jaramillo, Fernando Lanas, Wei Li, Yin Lu, Sun Yi, Lei Rensheng, Romaina Iqbal, Prem Mony, Rita Yusuf, Khalid Yusoff, Andrzej Szuba, Aytekin Oguz, Annika Rosengren, Ahmad Bahonar, Afzalhussein Yusufali, Aletta Elisabeth Schutte, Jephat Chifamba, Johannes F E Mann, Sonia S Anand, Koon Teo, S Yusuf, for the PURE, EPIDREAM, and ONTARGET/TRANSCEND Investigators*

## Summary

**Background** Several studies reported a U-shaped association between urinary sodium excretion and cardiovascular disease events and mortality. Whether these associations vary between those individuals with and without hypertension is uncertain. We aimed to explore whether the association between sodium intake and cardiovascular disease events and all-cause mortality is modified by hypertension status.

**Methods** In this pooled analysis, we studied 133 118 individuals (63 559 with hypertension and 69 559 without hypertension), median age of 55 years (IQR 45–63), from 49 countries in four large prospective studies and estimated

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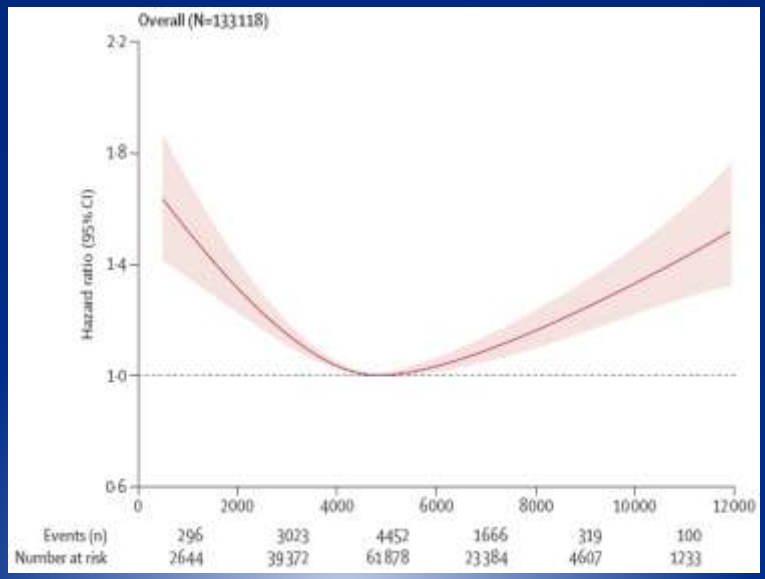
Population Health Research

Mente A, et al. 2016. *The Lancet*, May 20.

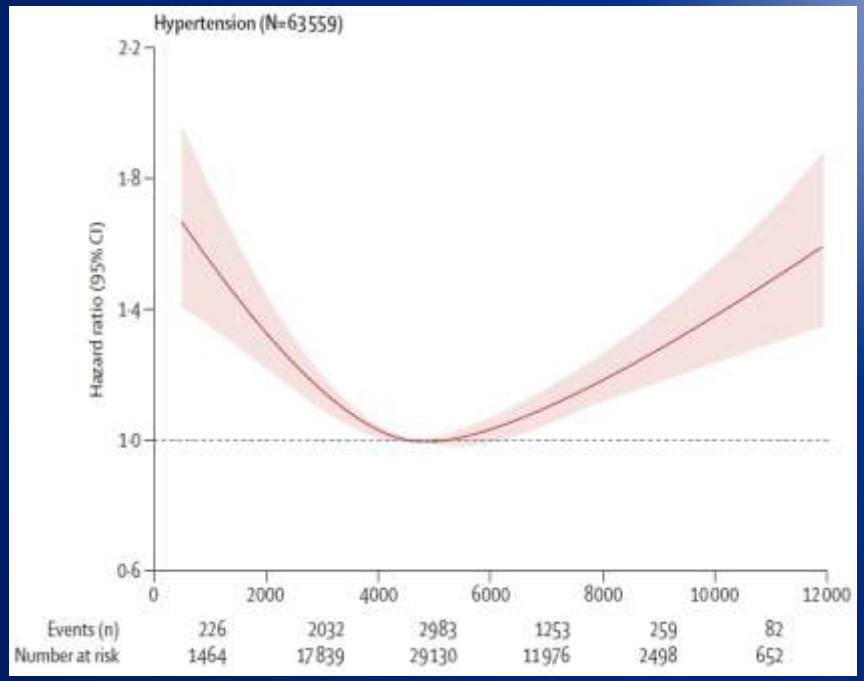
# Sodium vs CVD by hypertension status

## Overall (N=133,118)

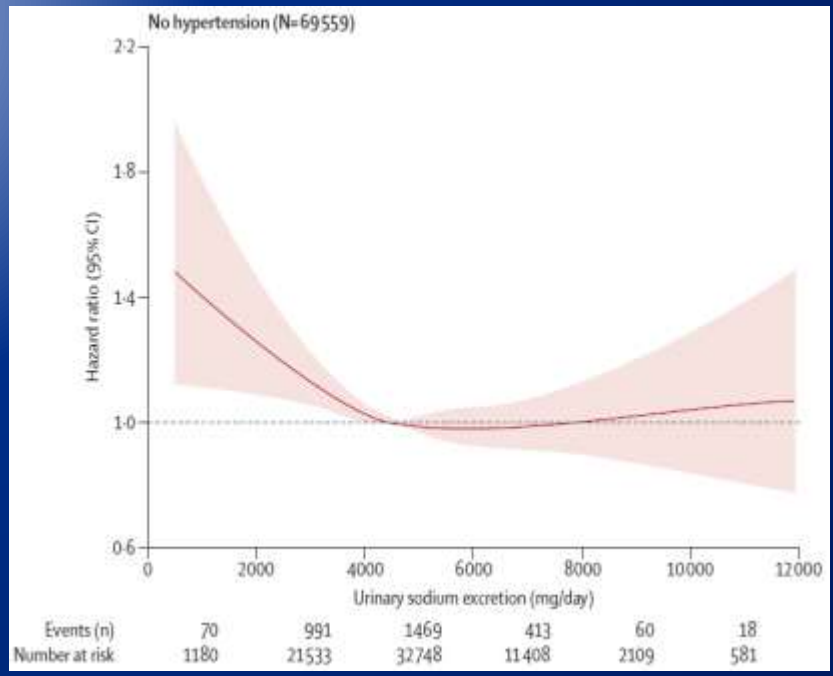



Data from PURE, EPIDREAM & ONTARGET/ TRANSCEND

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

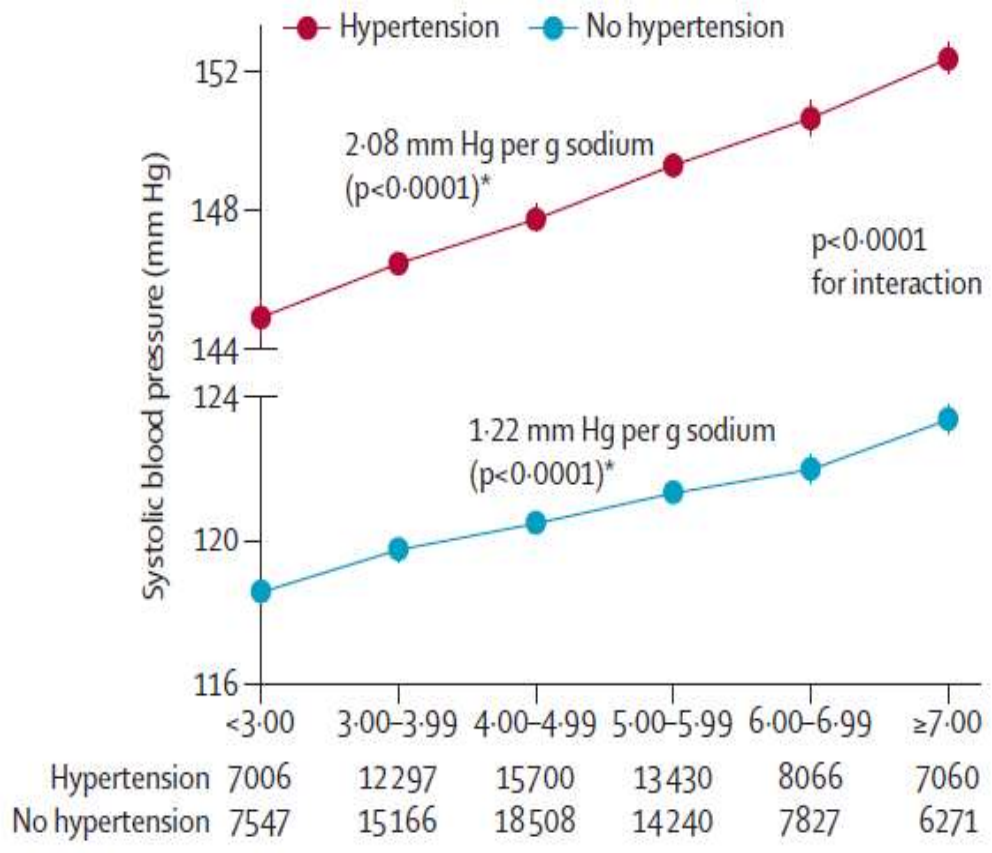



## No Hypertension (N=69,559; **3021** events)

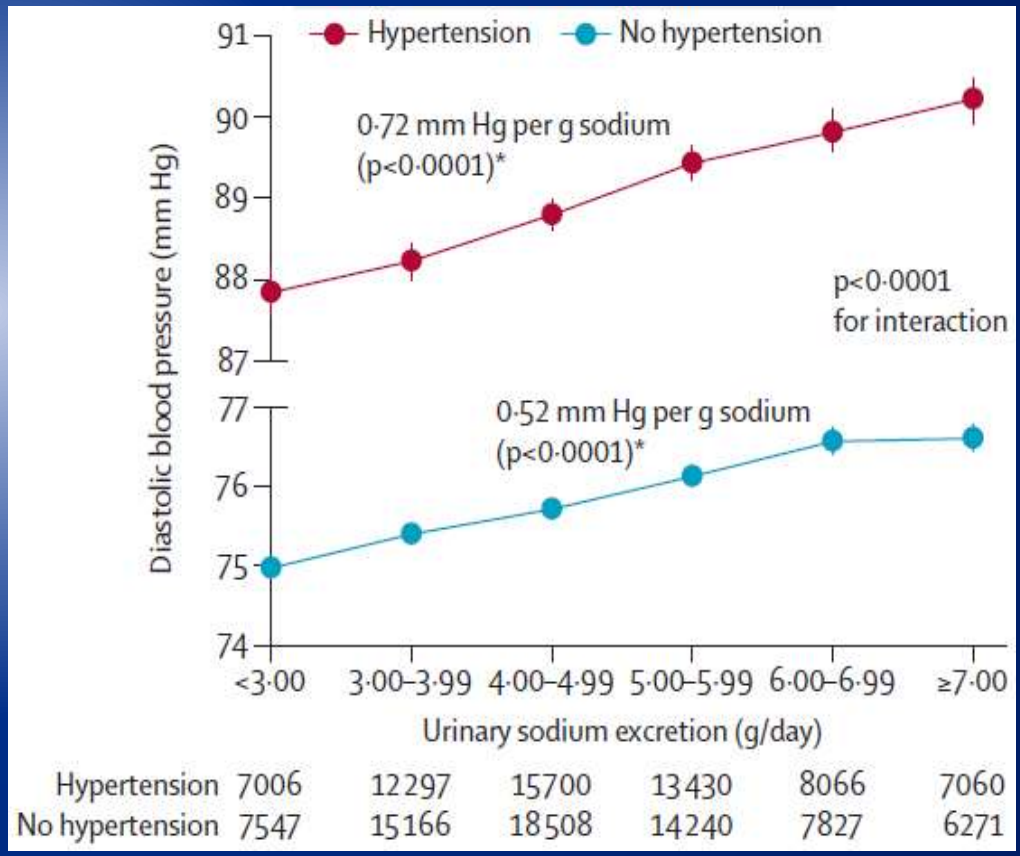


# Mean BP by Na excretion and hypertension status (N=133,118) *

## Systolic BP




## Diastolic BP




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

# Sodium Excretion vs. Plasma Renin and Aldosterone Excretion

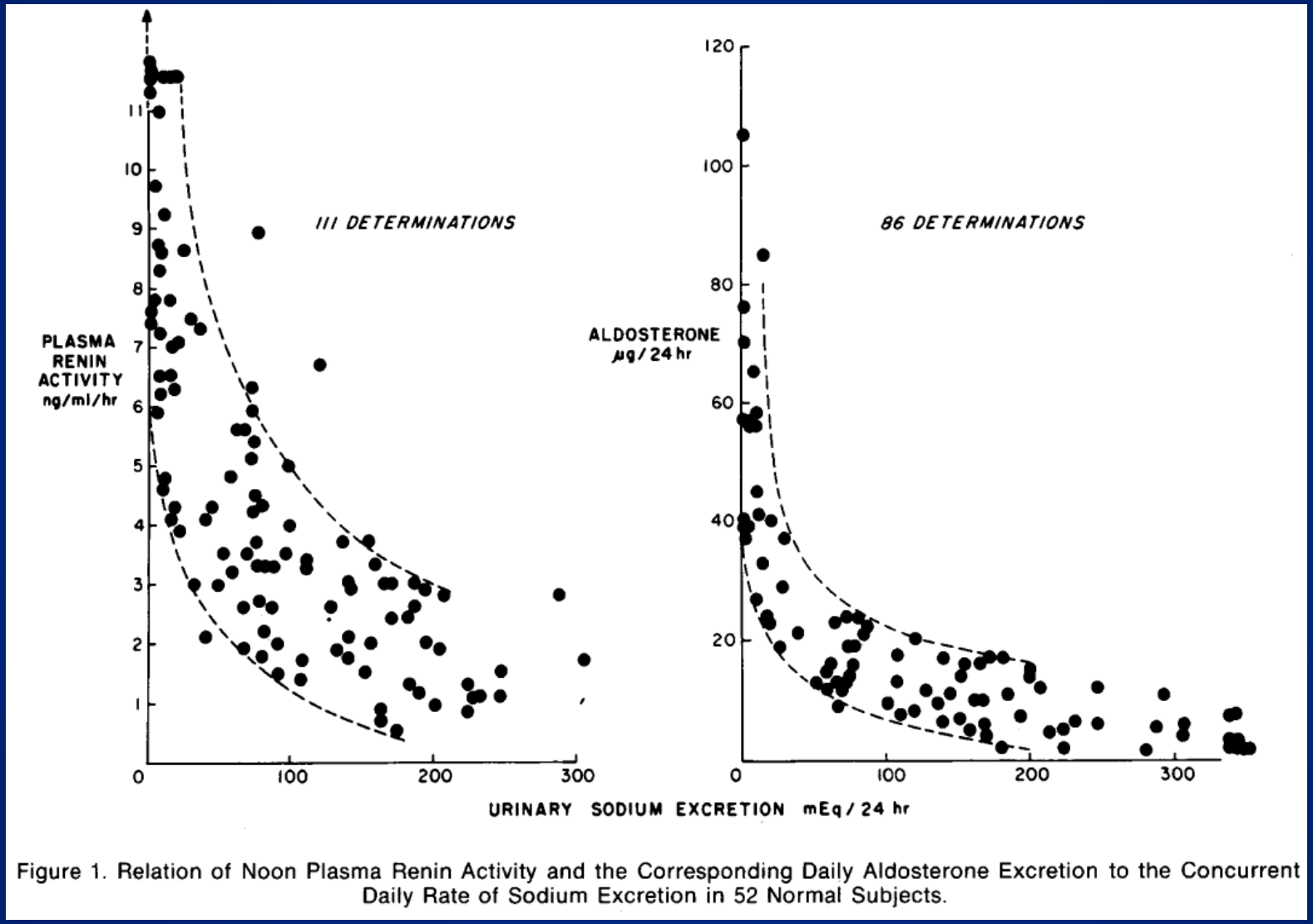



Figure 1. Relation of Noon Plasma Renin Activity and the Corresponding Daily Aldosterone Excretion to the Concurrent Daily Rate of Sodium Excretion in 52 Normal Subjects.

Brunner 1972, New Engl J Med

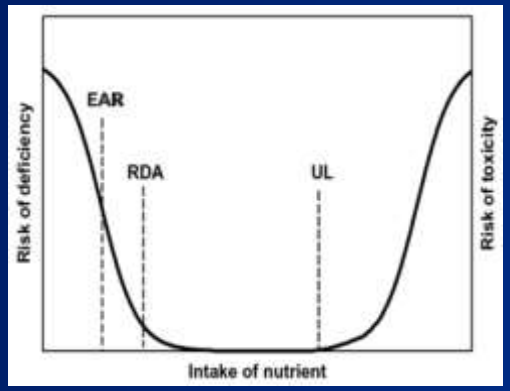
# Cochrane review: Low vs high sodium and CV biomarkers

| **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

# Essential nutrients are shown to have an optimal range with health outcomes (ie, U-shaped relationhip)

Deficiency/Toxicity Model




Heaney RP, 2013. AJH

Serum 25-vit D & mortality

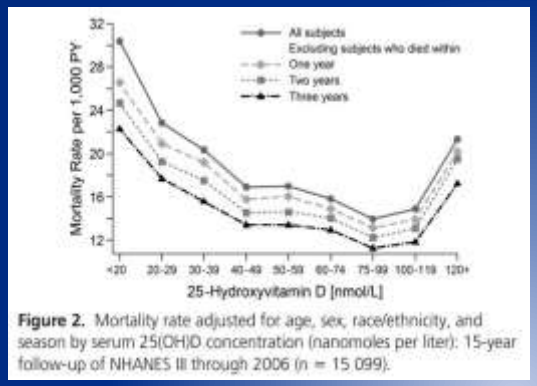
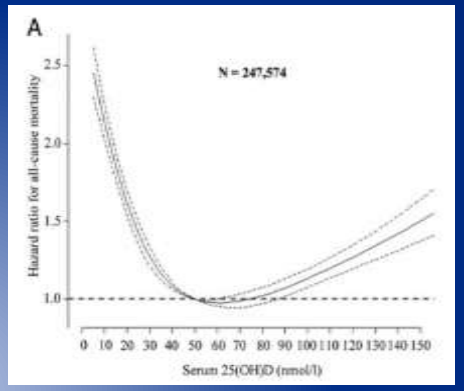



Figure 2. Mortality rate adjusted for age, sex, race/ethnicity, and season by serum 25(OH)D concentration (nanomoles per liter): 15-year follow-up of NHANES III through 2006 (n = 15 099).

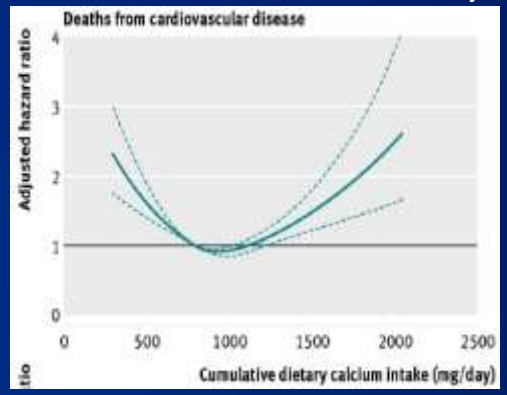
Langsetmo L, 2013 (NHANES-3)

Serum 25-vit D & mortality



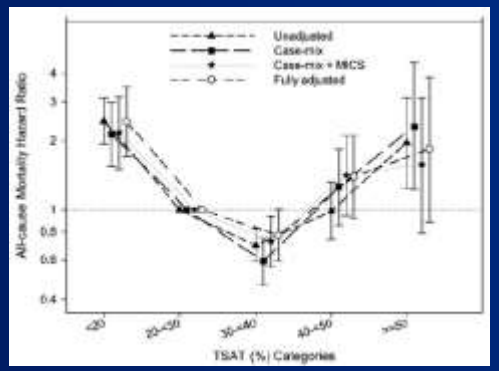

Durup D, 2012. J Clin Endocr Metab

Calcium & CV mortality



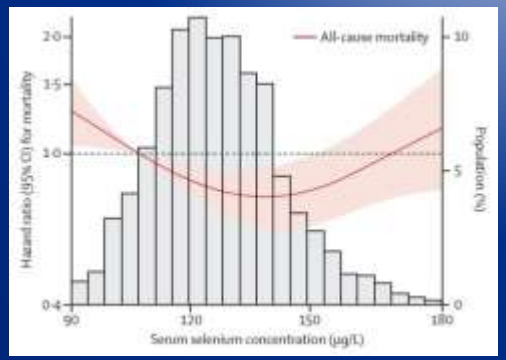

Michaelsson K, 2013. BMJ

Iron & mortality



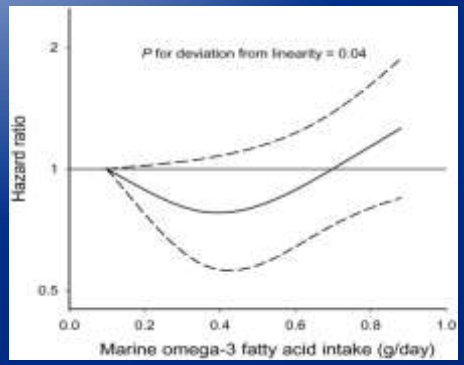

Hatamizadeh P, 2013 Nephrol Dial Trans

Serum selenium & mortality



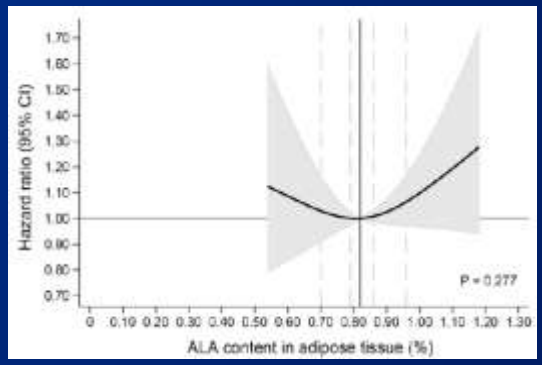

Rayman MP, 2012. Lancet

Marine n-3 & heart failure




Levitan EB, 2009. Eur Heart J

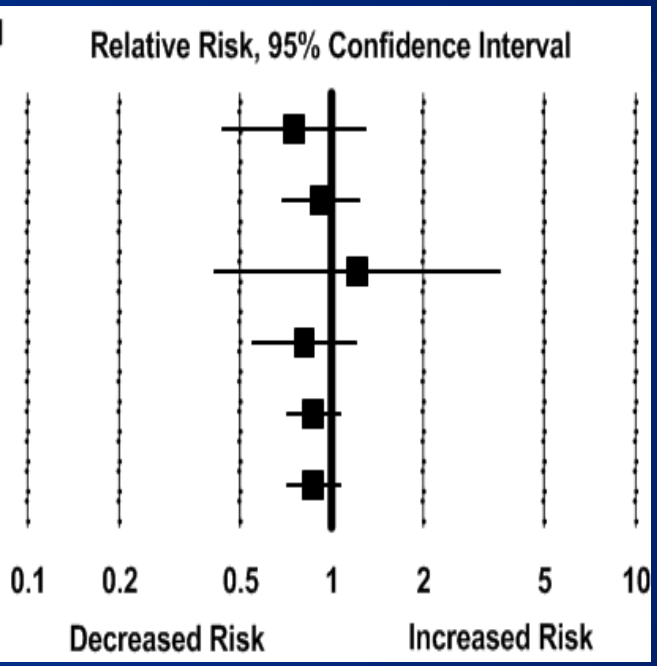
Alpha-linolenic acid & MI




Bork CS, 2016. AJCN

# 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

# Conclusions

- Na intake is related to BP, but modest in those w/o hyp, CVD or renal disease
- Association b/w Na and CVD is not linear (ie, J-shaped)
  - Increased risk of mortality and CVD (>6 g/d) (only in hypertensives, 10% of pop.)
  - Modestly lower Na intake (<3 g/d) ***increases*** CVD (hypertensives & non-hypertensives)
  - 3/4 of people consume **moderate Na intake** range (3-6g/day) which was assoc. w/ **lowest risk** of death and CVD
  - Identified the pathologic mechanisms activated by low Na
  - No net health benefit in healthy or "at risk" individuals
- Concerns about safety of too little Na intake
- Targeted strategy rather than population strategy more appropriate at present (eg, hypertensives who also consume high Na diets)

- As IOM committee chair Brian Strom stated:

  *"It's not a question of studies showing benefit being better than those showing harm; there are no studies showing benefit."*

  (Mitka M. JAMA 2013;309:2535-2536)

# Call for randomized controlled trials

- Need definitive large RCTs with ***clinical outcomes*** as the endpoint (IOM 2013) – these are underway
- The health of the public is at stake and we cannot afford to get public health messages wrong

  e.g., trans fat, low fat diets, hormone therapy

  While they do great job when correct and evidence based, they can do great harm (wasting efforts or directly damaging health)
- We should not rush to change the diet of entire nations without better evidence

# PURE Investigators Meeting, New Delhi, India
# November 2017

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

McMaster University

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