ANYTHING WORTH DOING TAKES MORE THAN A LIFETIME
THE RESOLUTION OF THE SODIUM AND HEALTH DEBATE

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Research Associate, Adjunct Professor
UC Davis, Department of Nutrition

DISCLOSURES

- Consultant – Grocery Manufacturers Association
- Board of Directors – American Society Nutrition

MY LONGSTANDING CONCERNS

EXPERTS CHALLENGE LOW-SODIUM DIET
By PHILIP M. BOFFEY, Special to the New York Times
Published: **September 14, 1982**

ARLINGTON, Va., Sept. 13— The widely held view that most Americans should reduce their salt or other sodium intake to prevent the development of high blood pressure was challenged by experts at a scientific conference here today.

David A. McCarron, director of the hypertension program at Oregon Health Sciences University, warned that widespread restriction of sodium intake may actually end up harming more people than it helps……..

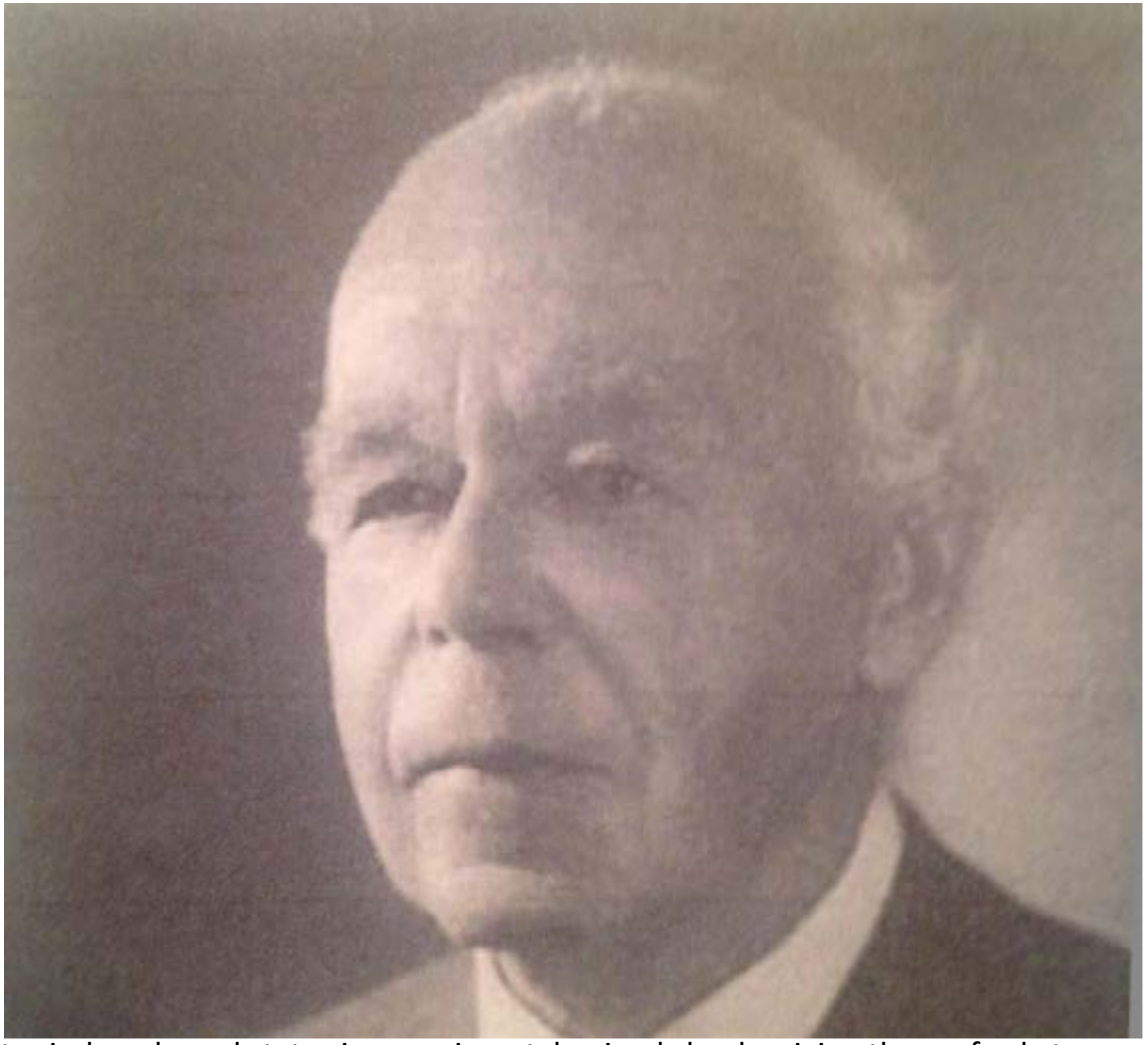
''*I don't recommend sodium restriction as a broad public health measure.*" he said. ''*We could turn around 20 years from now and see that it had caused more problems than it prevented.*''

Robert Tigerstedt – 1898 - Renin

FIGURE 1. *Robert Adolph Armand Tigerstedt, 1853–1923, in his laboratory at the University of Helsinki, circa 1910.*

Tigerstedt, who was first to ask and answer the question, "Is there something made in the kidney which can influence the circulation?"

Curt Richter – 1936
Neural Control of Sodium Appetite



Richter induced need states in experimental animals by depriving them of substances essential to survival, or manipulating the hormone levels, and showed that *these need states generate appetites*, and behaviours precisely fitting the animal's need

Science: 1979

NIH Deals Gingerly with Diet-Disease Link

Federal dietary guidelines for disease prevention have scant support from NIH, but pressure to take a stand is building

A battle over what we should eat to prevent disease has split the federal establishment down the middle. Congress, appalled by the rising cost of health care, sees prevention as a new panacea. It

This is the second of a two-part series on the politics of nutrition.

nanas, beans, hot dogs, and a salt shaker sang and danced for health, warning the audience of children about the consequence of a bad diet.

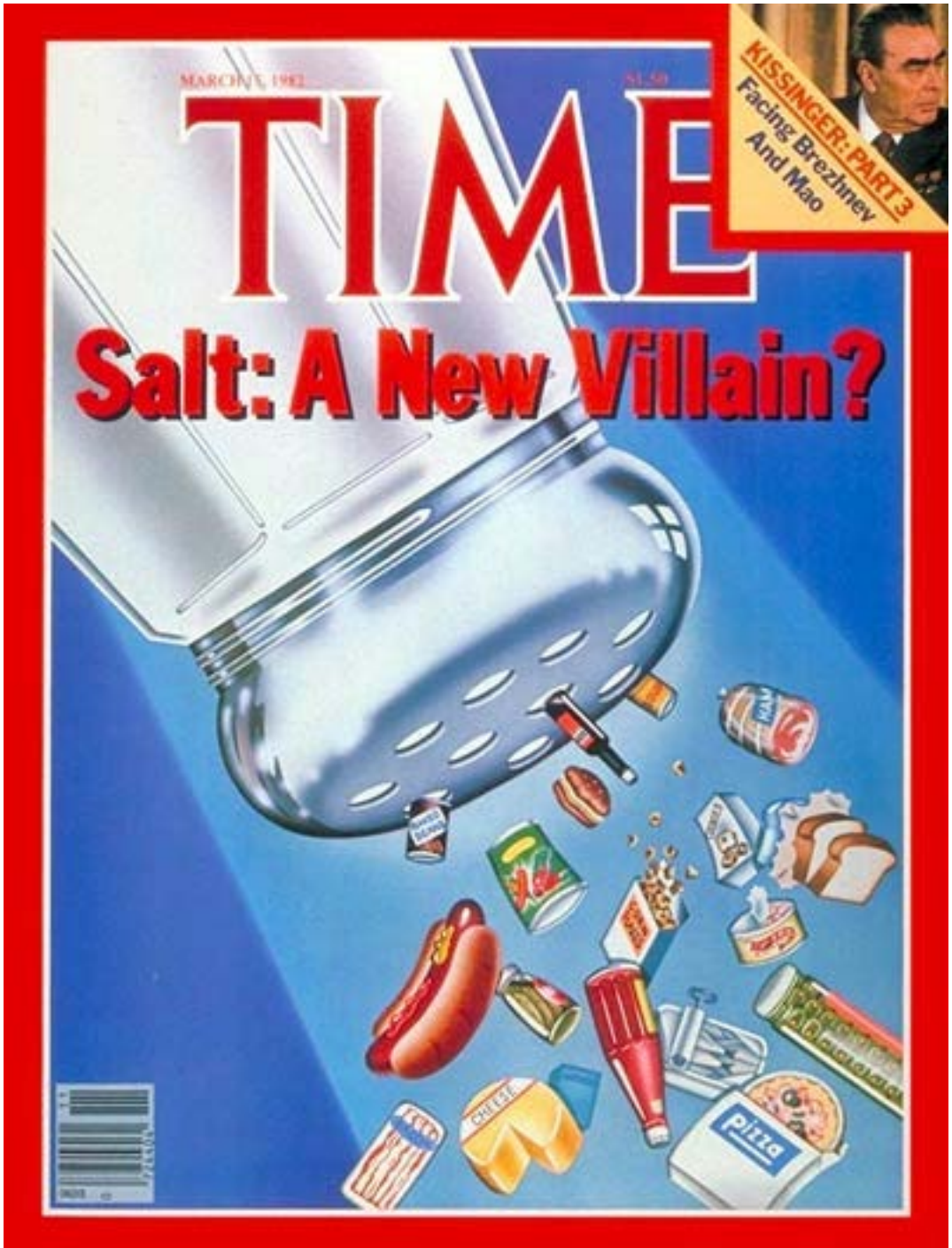
Pressure on NIH to educate the public has been building for the past 2 years. It comes from USDA. It comes from consumer-interest groups, such as the Cen-

(Mark Hegsted, the Harvard biologist who helped edit *Dietary Goals*, has since become the director of USDA's human nutrition center.) Although a contract with NAS was written, USDA never signed it. They got wind of a speech that Gilbert Leveille, then chairman of the NAS Food and Nutrition Board, made in

- NIH Director: " I feel the problem we still have is that we can't bring you *proof* that changing the diet …will lengthen his life"

- Harvard Biologist/USDA Advisor: The question to be asked is *not* why…but why *not*. What are the risk…less salt? There are *none* that can be identified and important benefits.

- Rockefeller Scientist: "an experiment on the American people …treating them like Sprague-Dawley rats."



TIME: March 15, 1982

NHANES I – THE DASH DIET

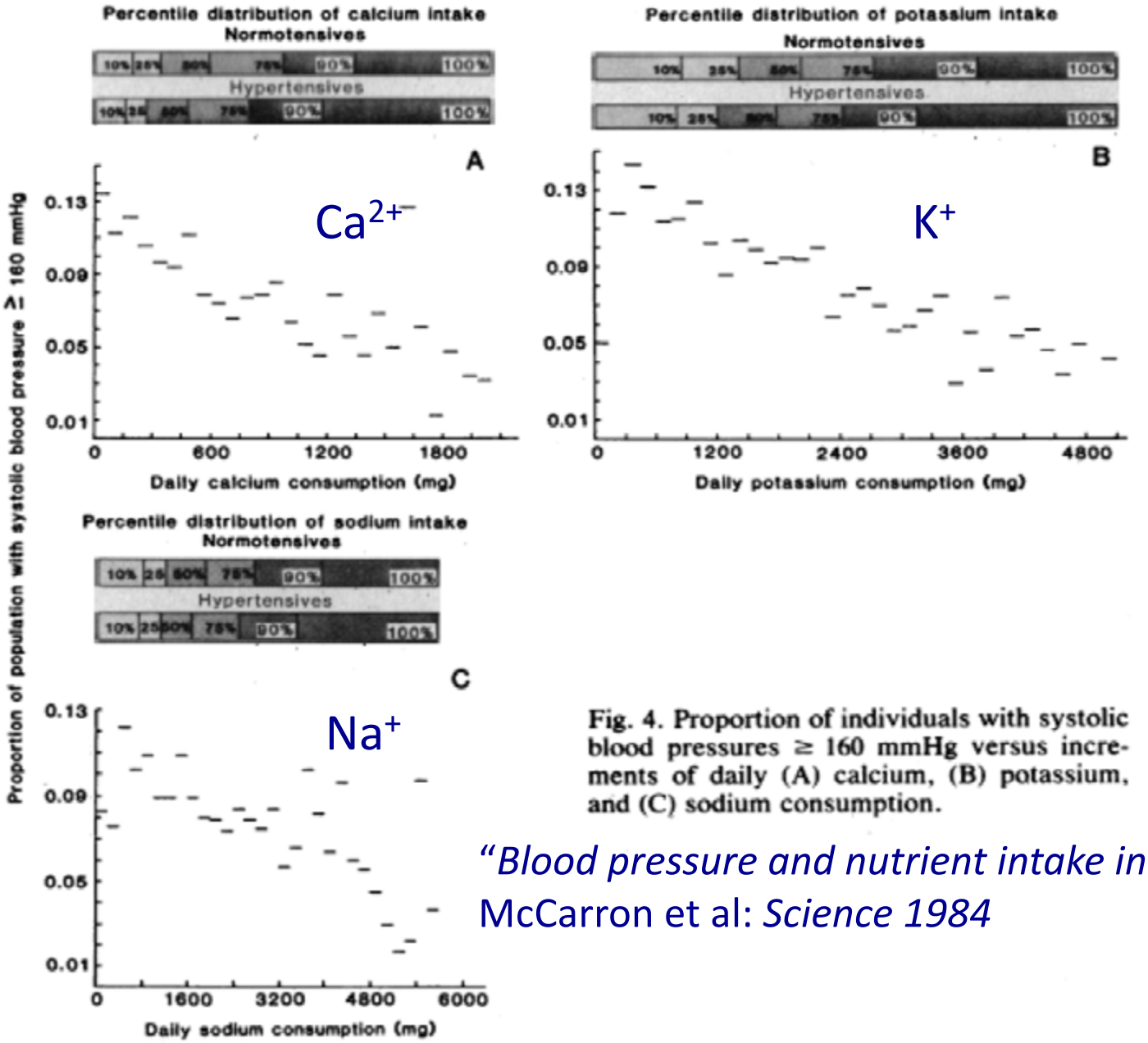


Fig. 4. Proportion of individuals with systolic blood pressures ≥ 160 mmHg versus increments of daily (A) calcium, (B) potassium, and (C) sodium consumption.

"Blood pressure and nutrient intake in the U.S.
McCarron et al: *Science 1984*

NATIONAL HEART LUNG BLOOD INSTITUTE'S RESPONSE

" …McCarron *et al* were remiss in not attempting to *square* their conclusions with the abundance of population-based and experimental data suggesting that dietary sodium indeed plays an important role in hypertension ."

Dr. Claude Lenfant

NHLBI Director

Science 1984

“ … the obstacle to discovery is the illusion of knowledge.”

Daniel J. Boorstin

The Discoverers

"Ignorance is a powerful tool if applied at the right time, even, usually surpassing knowledge."

E.J.Potter

Michigan Mad Man of Motorcycle Racing

New York Time's Obituary May 12, 2012

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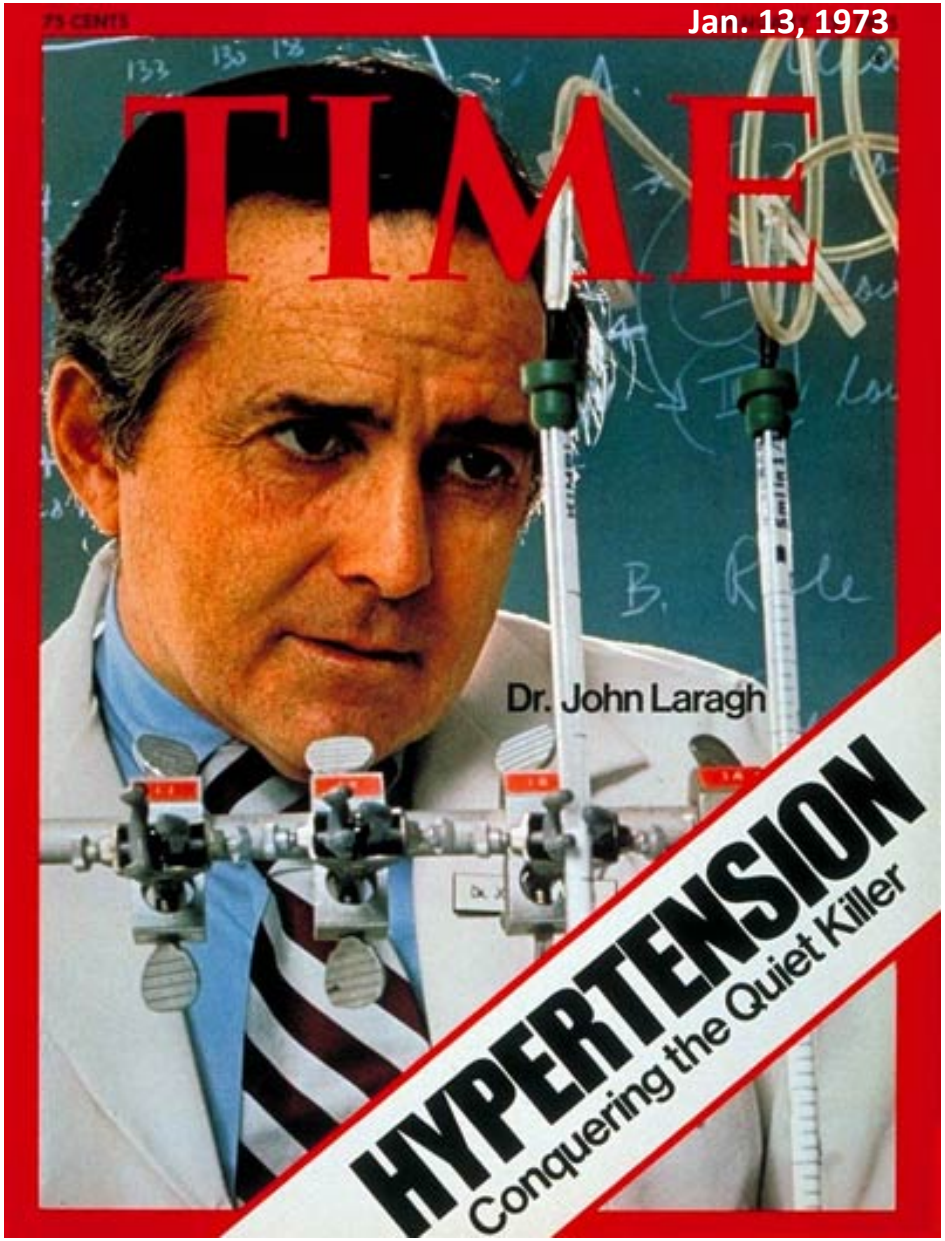
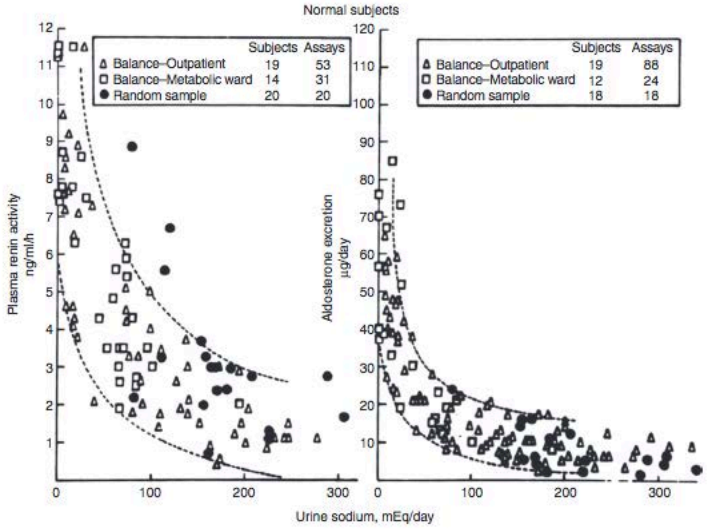
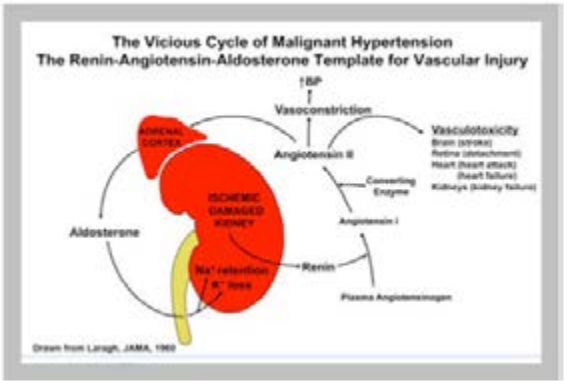


Recipient of the Stouffer Prize for Hypertension Research, American Heart Association, 1969. (Conn, Gross, Laragh)

How Ang II regulates ALD release





UNaV Relationship to PRA and Aldosterone

1972-NEJM

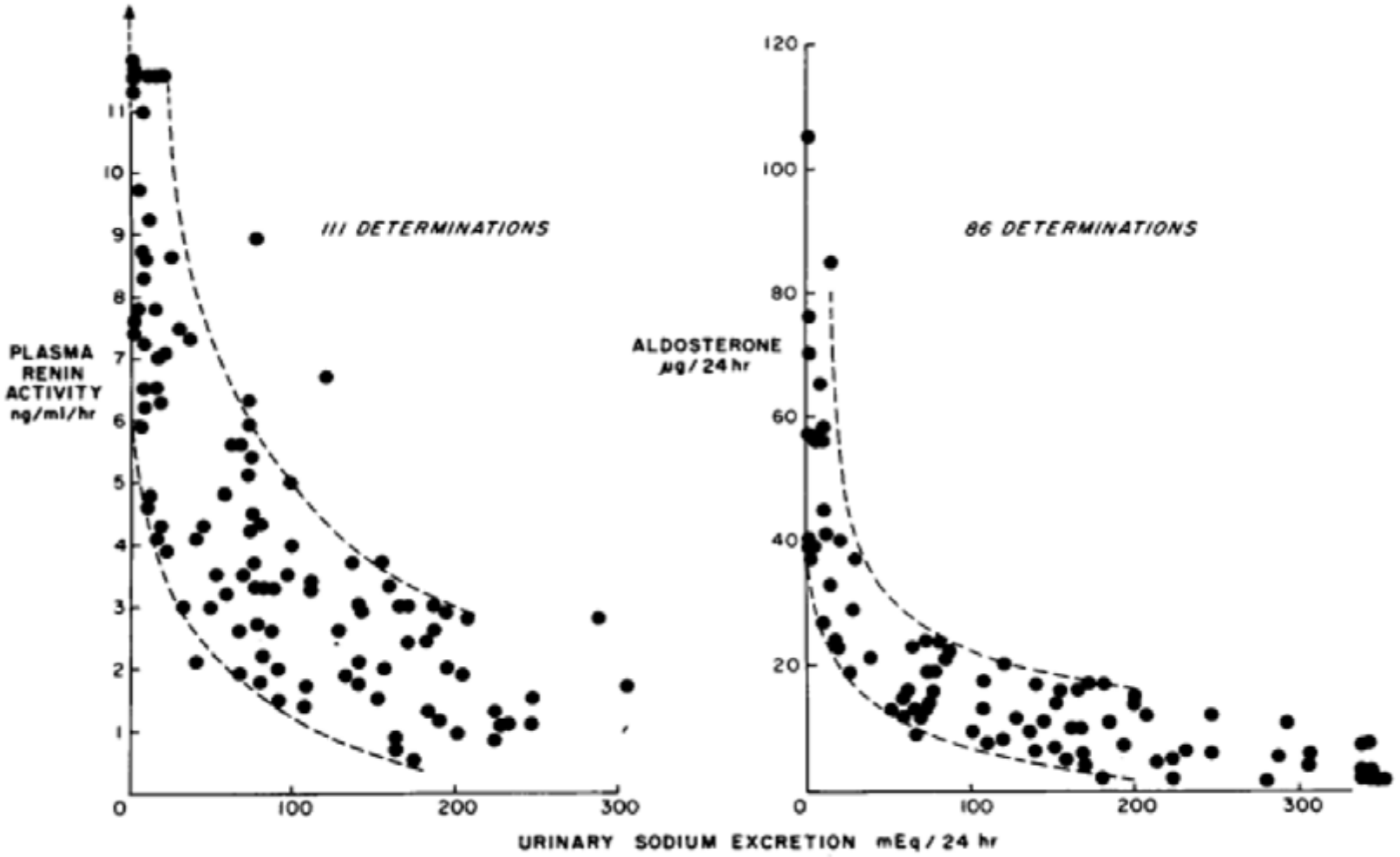


Figure 1. Relation of Noon Plasma Renin Activity and the Corresponding Daily Aldosterone Excretion to the Concurrent Daily Rate of Sodium Excretion in 52 Normal Subjects.

Brunner et al; *NEJM, 1972*

PARABOLIC RELATIONSHIP OF NUTRIENT TO HEALTH RISK

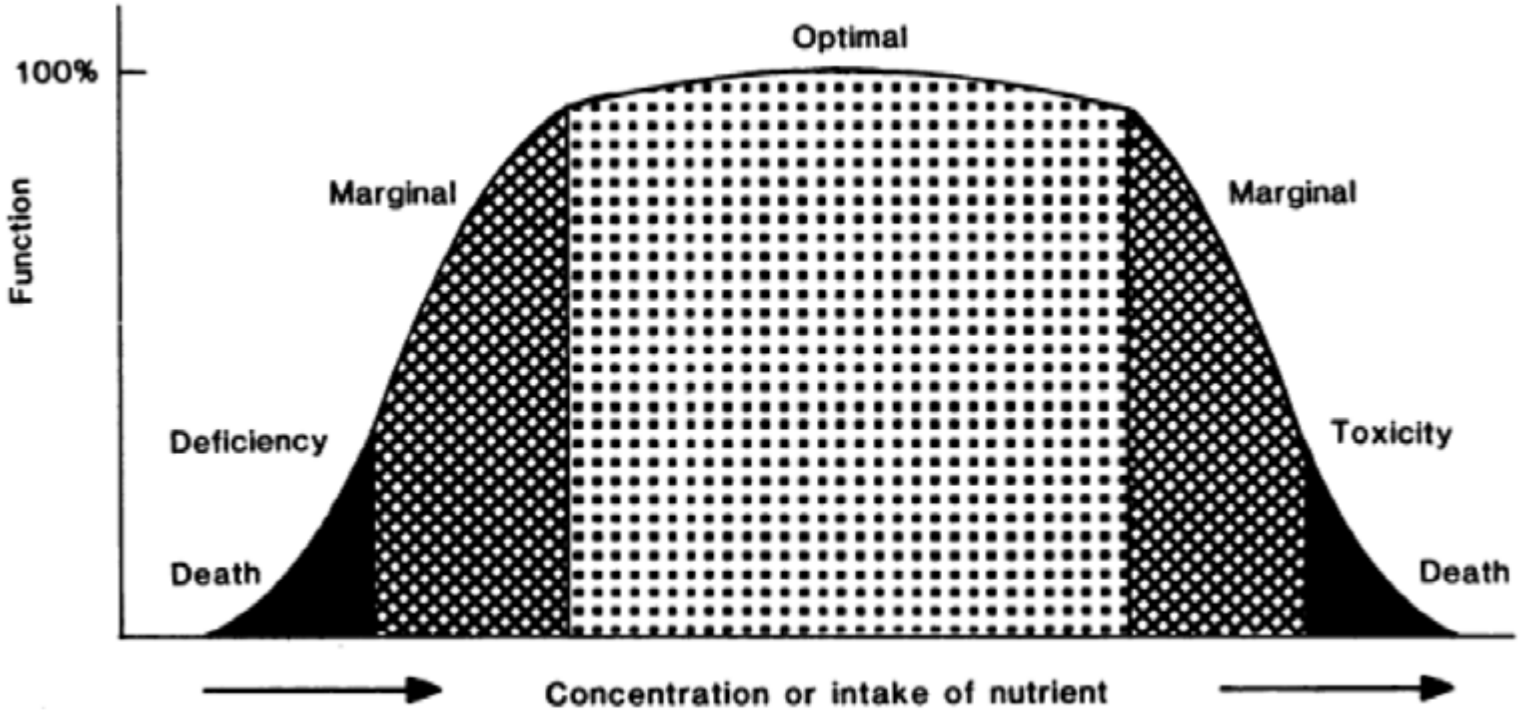


Fig. 2. Dependence of biological function on tissue concentration on intake of a nutrient.

Mertz: *Science*, 1981

INTERSALT
SODIUM INTAKE WORLDWIDE

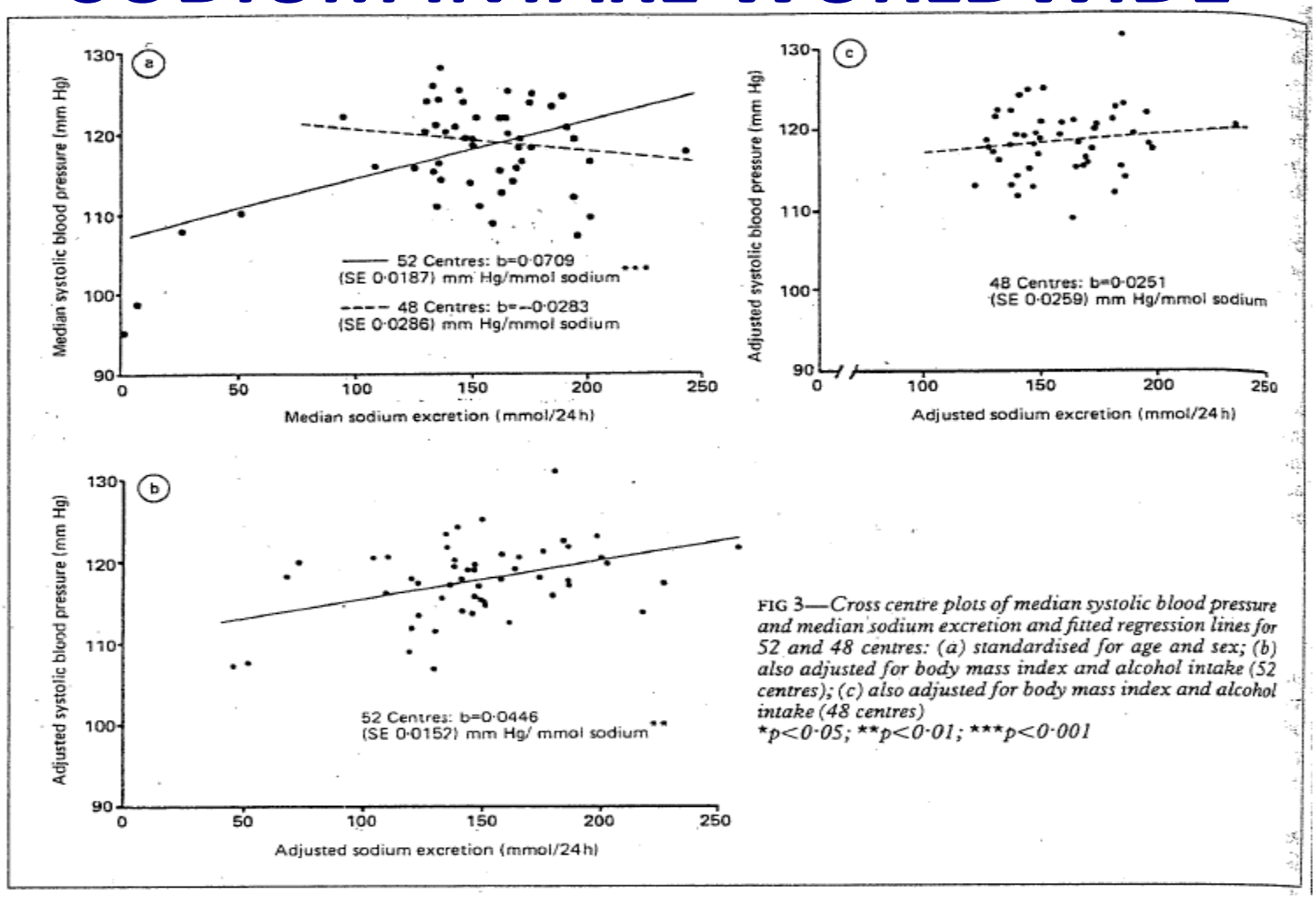


FIG 3—*Cross centre plots of median systolic blood pressure and median sodium excretion and fitted regression lines for 52 and 48 centres: (a) standardised for age and sex; (b) also adjusted for body mass index and alcohol intake (52 centres); (c) also adjusted for body mass index and alcohol intake (48 centres)*
*$p<0·05$; **$p<0·01$; ***$p<0·001$

Study hypothesis: Na predicts HTN and Population mean BP - Rejected

BMJ 1988

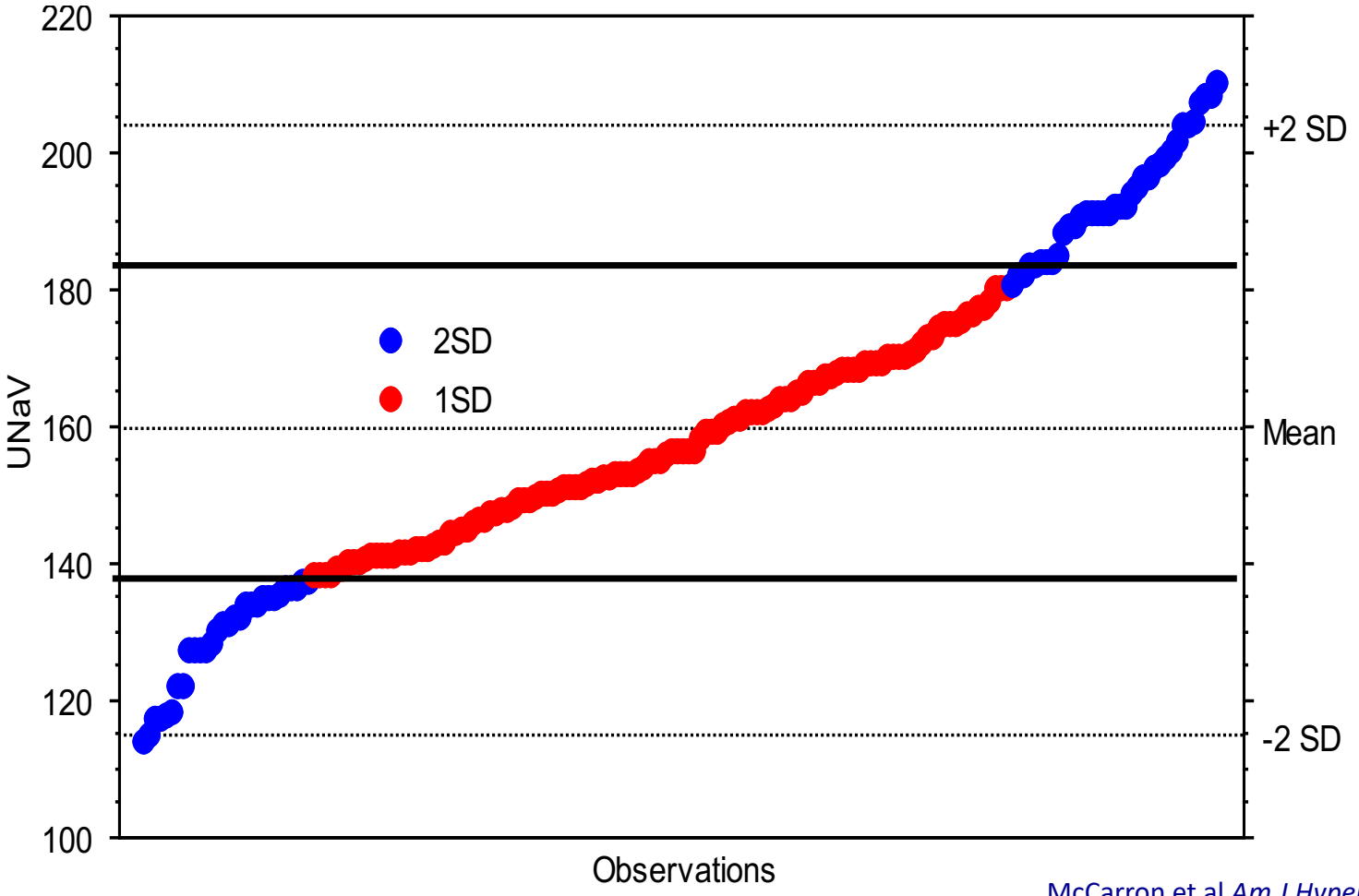
PHYSIOLOGIC RANGE OF HUMAN SODIUM INTAKE

BASED ON 24hr UNaV IN 69,011 SUBJECTS WORLDWIDE

5 DECADES – 45 COUNTRIES

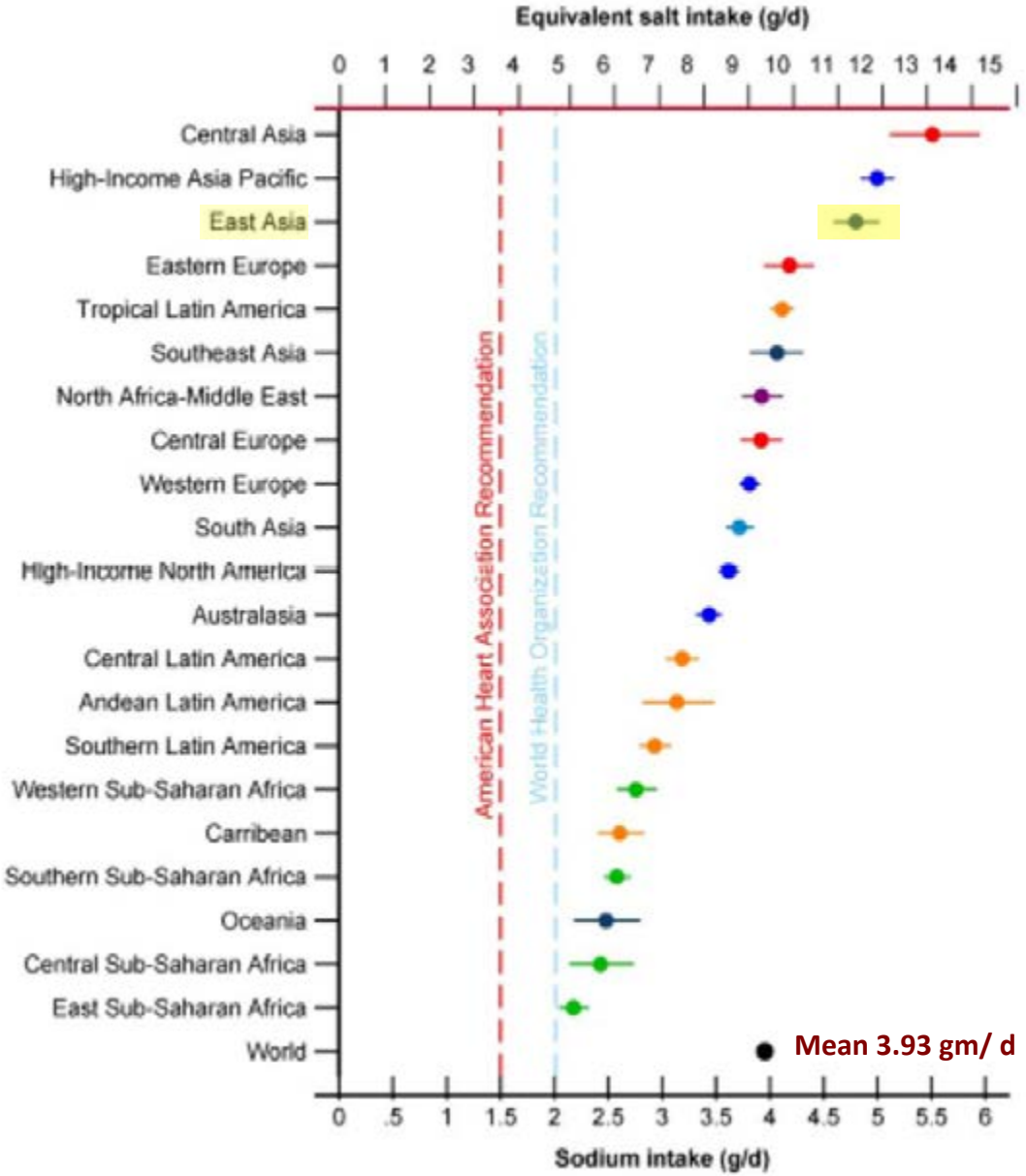
Mean: 159.4 +/- 22.3 mmols/d

Range: 114 – 210 mmols/d (2622-4830 mg/d)



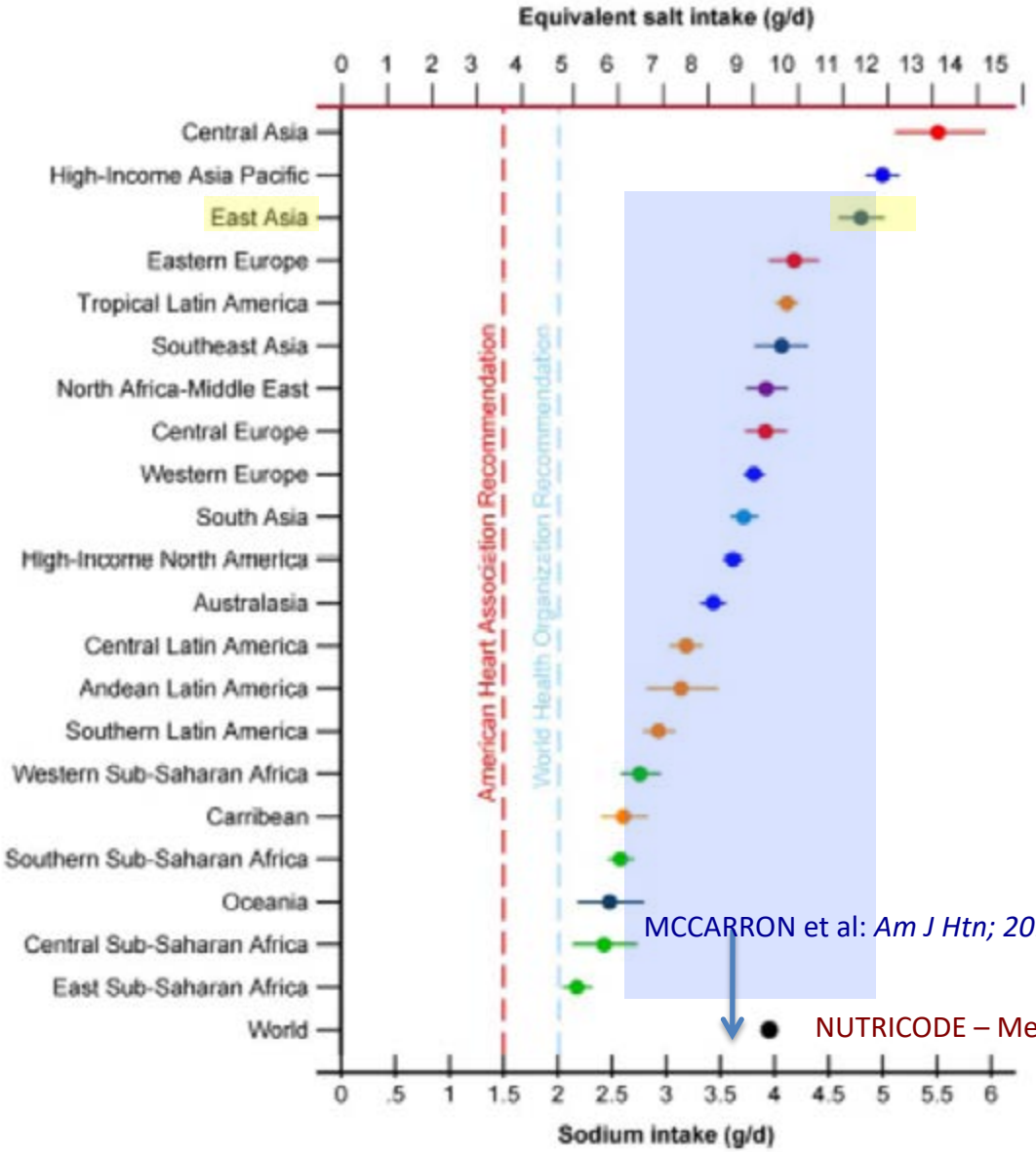
McCarron et al *Am J Hyper* 10/2013

WORLDWIDE SODIUM INTAKE g/d
NUTRICODE – MEAN 3.93 gm/d



BMJ OPEN: 2013

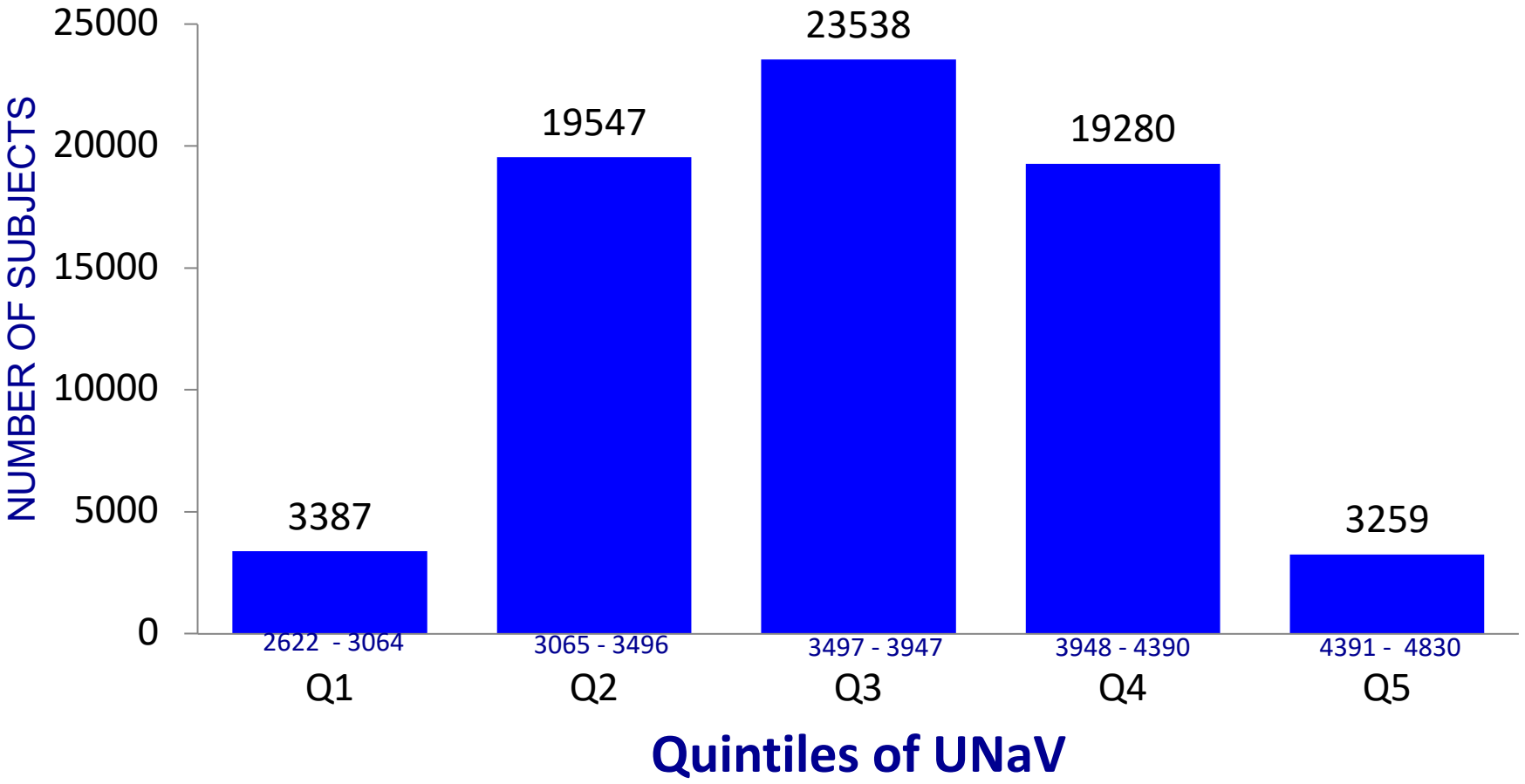
COMPARISON - WORLDWIDE SODIUM INTAKE g/d
NUTRICODE vs McCarron Am J HTN



MCCARRON et al: *Am J Htn; 2013 – Mean 3.7 gm/d*

NUTRICODE – Mean 3.93 gm/d

Number of Participants by Quintile of 24 hr UNaV – mg/d



McCarron et al: *Am J HTN, 2013*

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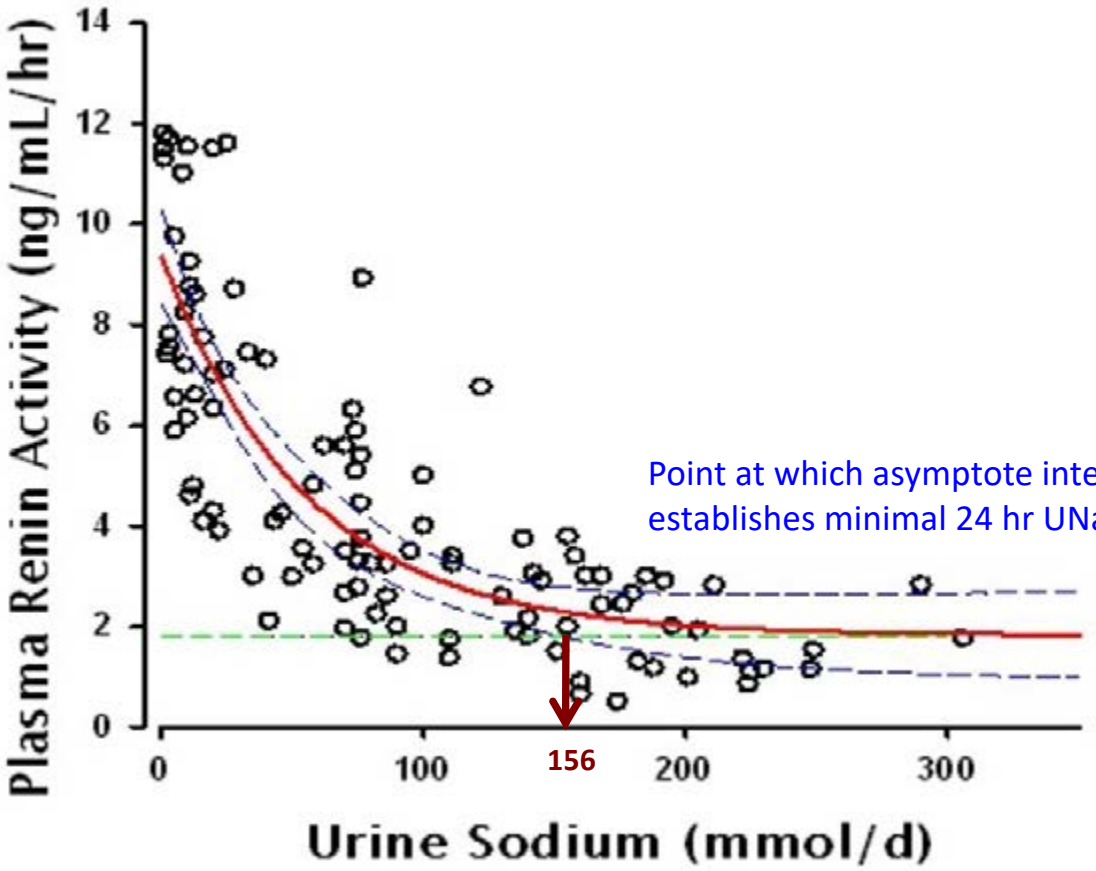
PHYSIOLOGIC RELATIONSHIP OF 24 hr UNaV to PRA PREDICTS MEAN SODIUM INTAKE



Point at which asymptote intersects confidence interval establishes minimal 24 hr UNaV for PRA suppression

Based on Brunner et al, *NEJM 1972*

Journal of Human Hypertension (2013), 1–8
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www.nature.com/jhh

REVIEW

Salt reduction in the United Kingdom: a successful experiment in public health

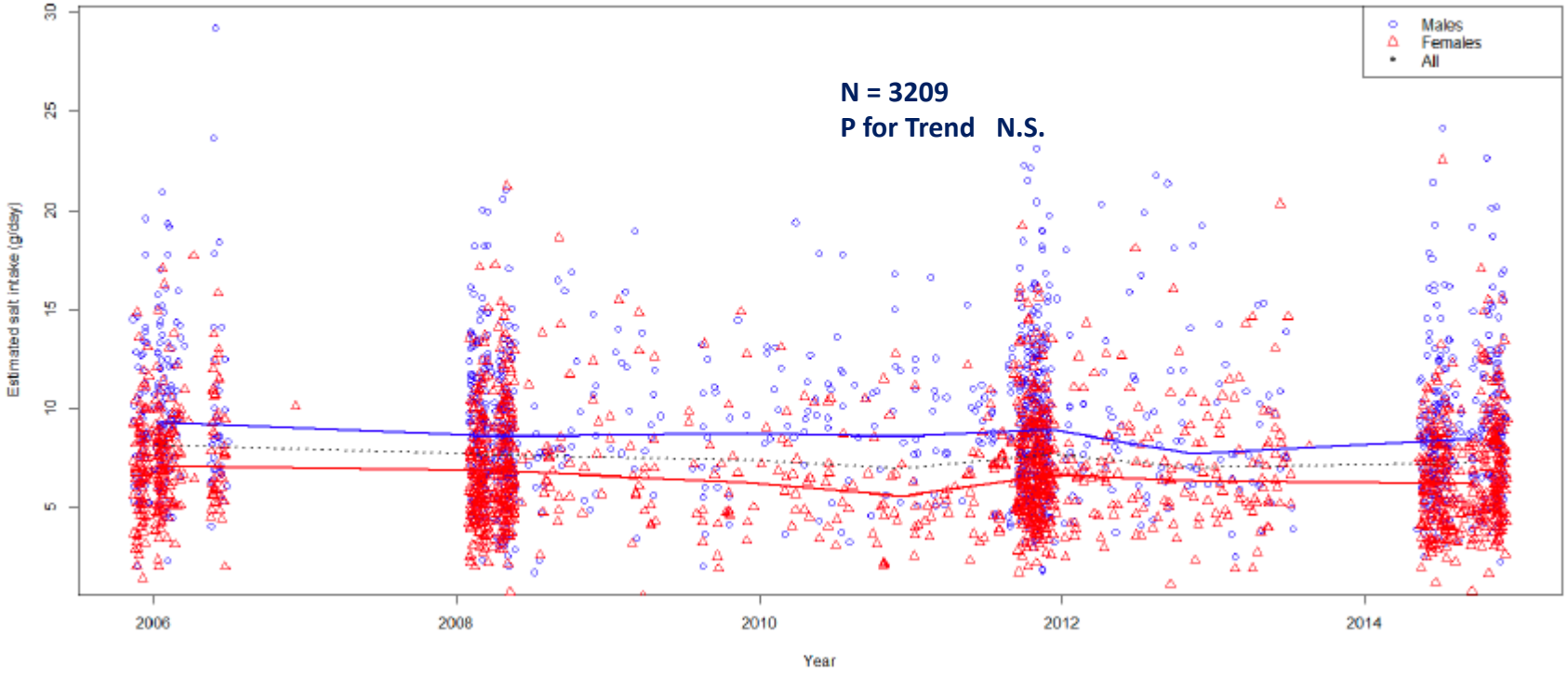
FJ He[1], HC Brinsden[2] and GA MacGregor[1]

- Campaign started 2006 – but compared 2011 to 2001 survey
  - Reported average of ***35-40%*** reduction in food sodium across all categories
  - Stated that 2011 UNaV was reduced ***15%*** compared 2001
- Appropriate comparison actually was 2006 survey to 2011
  - Actual Na+ intake decreased ***9%*** - UK government site states *non-significant*
  - This decrease is well within 1 SD of the NI range of UNaV, i.e. NS change
  - Discordance between decrease in food exposure to decrease UNaV
  - Suggests population shifted to foods higher in Na+ or ate more calories
  - With dramatic reduction in food Na+, but NS change in intake – campaign was ***not*** successful

NATIONAL DIET AND NUTRITION SURVEY

ASSESSMENT OF DIET SODIUM (24 Hr UNaV)

Adults 19-64 Years –England 2005-2014



UK- Medical Research Council National Diet and Nutrition Survey: assessment of dietary sodium. Adults (19 to 64 years) in England, 2014

UNaV Range Defined in NIH's Trial of Hypertension Prevention II

Protocol Na^+ Goal: 85 mmols/day

Actual Achieved *UNaV ….mmols/day*

	Na+ Reduction Only	Na+ Reduction + Wt Loss
Baseline	186.1	179.3
6 Months	108.1	115.0
18 Months	127.5	134.9
36 Months	135.2	145.8

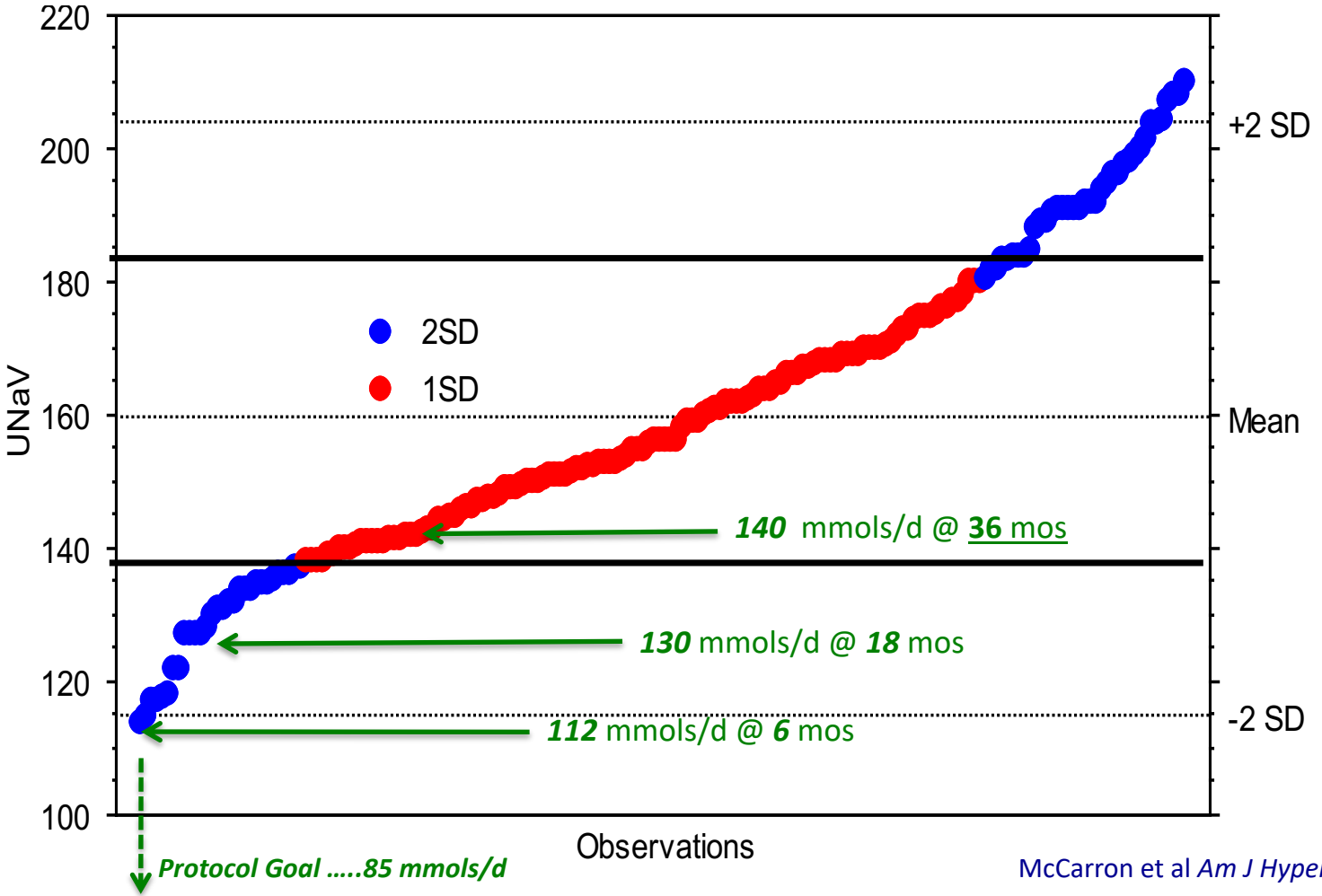
TOHPS II Failed to reduce Na^+ below the lower limit of human intake…..110 mmols/d
Over the following 30 mo. Na^+ regressed to within the mean human intake …140 mmols/d

Appel et al *Archive Int Med,* 1997

UNaV in TOHP II – REGRESSION TO THE MEAN

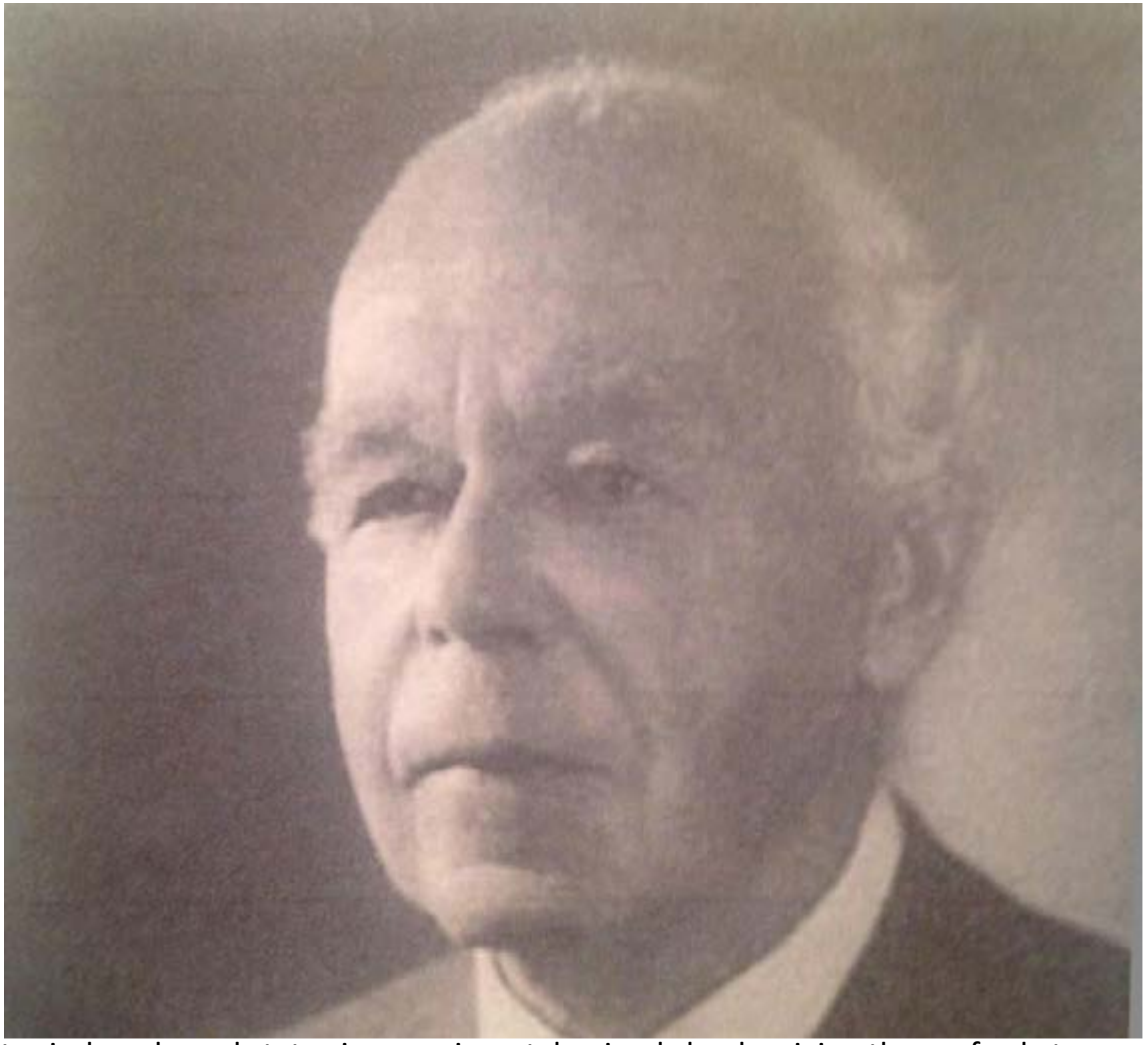
NIH's Largest Sodium Reduction Trial

PROTOCOL GOAL…..85 mmols/d (2.0 gm/d)



McCarron et al *Am J Hyper* 10/2013

Curt Richter – 1936
Neural Control of Sodium Appetite



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CAN POLICY TRUMP PHYSIOLOGY ?

Experimental **Physiology**

Central regulation of sodium appetite

Joel C. Geerling and Arthur D. Loewy

Exp Physiol 2008;93;178-209; originally published online Nov 2, 2007;

DOI: 10.1113/expphysiol.2007.039891

This information is current as of February 7, 2008

This is the final published version of this article; it is available at:
http://ep.physoc.org/cgi/content/full/93/2/178

NEURO-PHYSIOLOGY OF SODIUM APPETITE

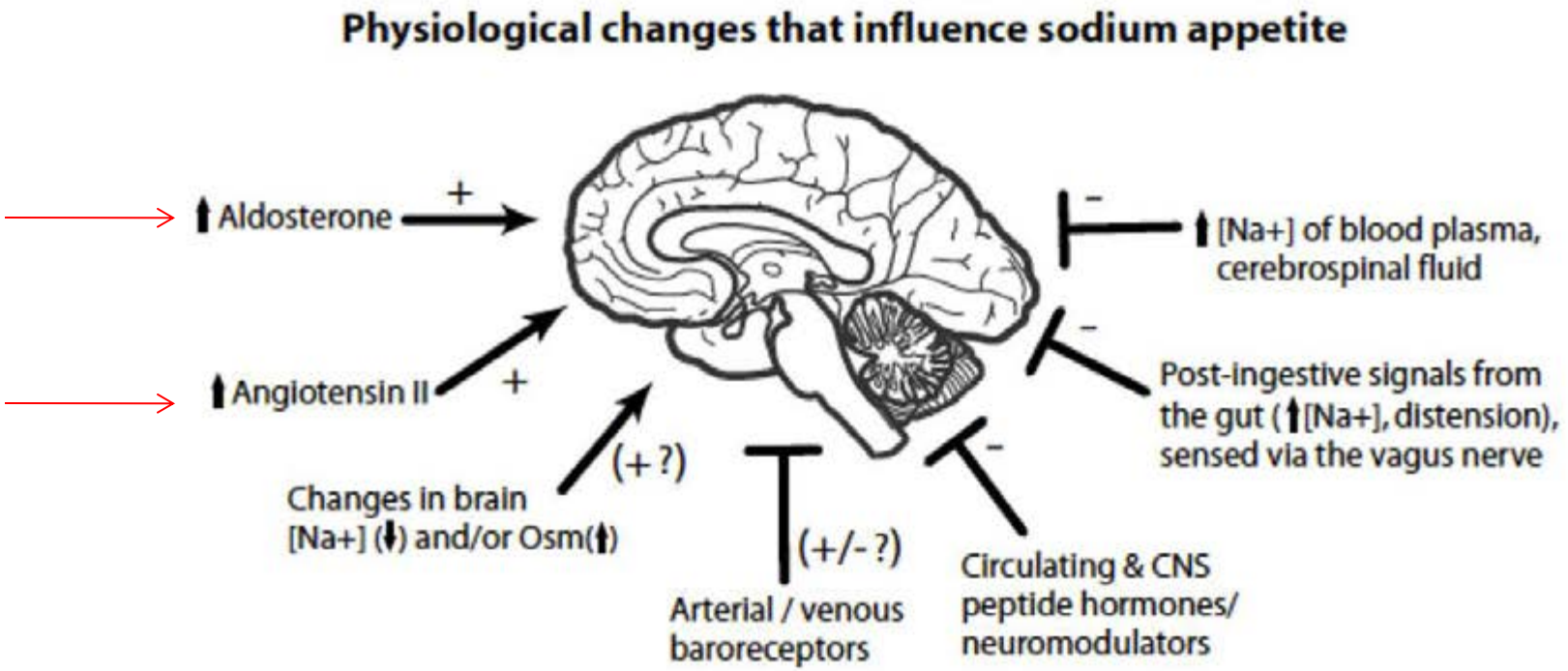
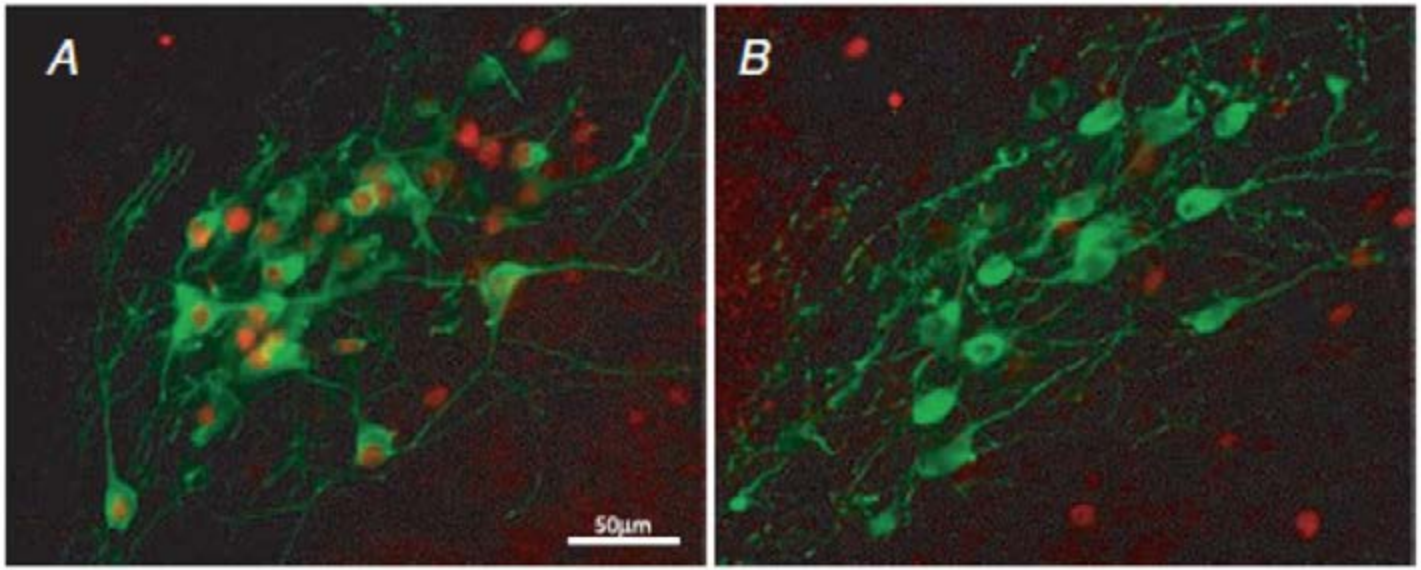


Figure 4. Various stimulatory and inhibitory signals act on the brain to regulate sodium appetite
See text for details, discussions and references regarding evidence in support of each mediator.

Geerling and Loewy *Exp Physol*: 2008

ALDOSTERONE SENSITIVE NEURONS ACTIVATION BY Na+ DEPRIVATION



SODIUM DEPRIVATION

SODIUM REPLETION

Geerling et al:
J.Neurosci: 2006

nature neuroscience
December 6, 2016

HSD2 neurons in the hindbrain drive sodium appetite

Brooke C Jarvie[1] & Richard D Palmiter[1,2]

Sodium-depleted animals develop an appetite for aversive concentrations of sodium. Here we show that chemogenetic activation of aldosterone-sensitive neurons that express 11β-hydroxysteroid dehydrogenase type 2 (HSD2) in the nucleus of the solitary tract is sufficient to drive consumption of sodium-containing solutions in mice, independently of thirst or hunger. These HSD2-positive neurons are necessary for full expression of sodium appetite and have distinct downstream targets that are activated during sodium depletion.

INDEX REPORT OF INCREASED CVD WITH INCREASED RENIN AND LOWER Na^+

Table 3. Cardiovascular Complications.

Renin Activity	Patients with Left Ventricular Enlargement	Patients with Strokes or Heart Attacks*		
		Total	Strokes	Heart Attacks
Low	12 (20%)	0	0	0
Normal	18 (15%)	14 (11%)	8 (6%)	6 (5%)
High	8 (22%)	5 (14%)	4 (11%)	2 (6%)
Totals	38 (17%)	19 (9%)	12 (5%)	8 (4%)

*One patient in group with high renin activity had both stroke & heart attack.

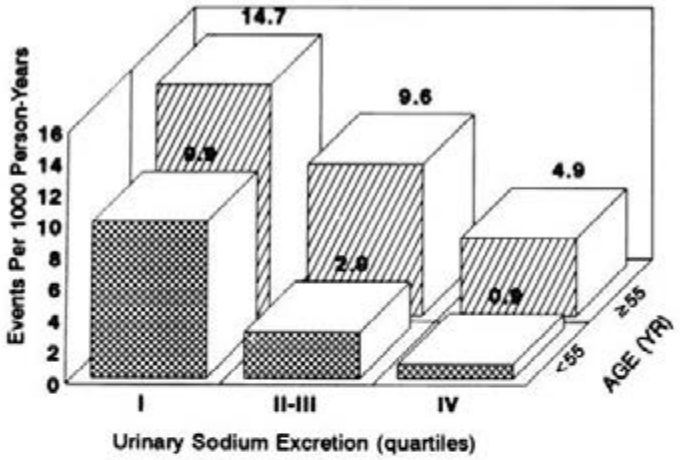
Brunner …Laragh: *NEJM 1972*

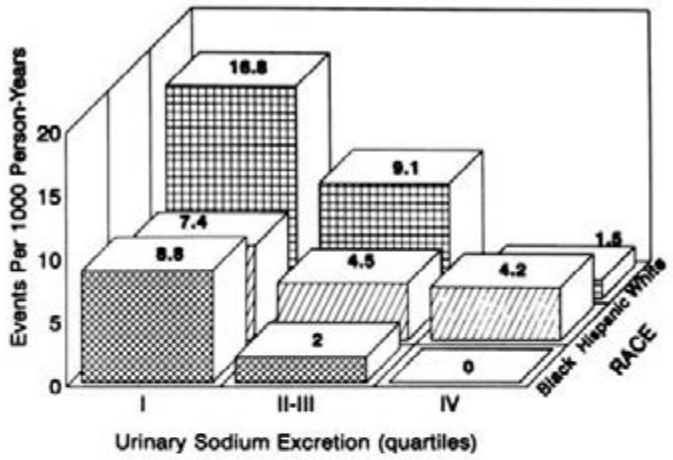
Dr. Michael Alderman's Contribution

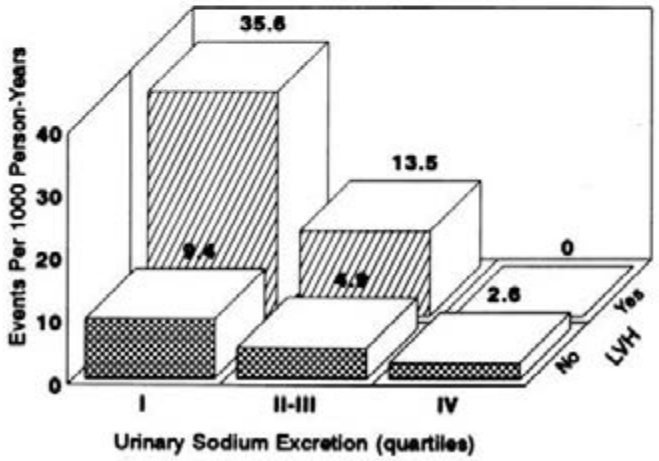
The *J* Shape Na^+ / Mortality Relationship

- *Hypertension* – 1995 NIH Worksite project
- *Lancet* – 1998 An analysis of NHANES I
- *Am J Med* – 2006 An analysis of NHANES II
- *J Gen Int Med* – 2008 An analysis of NHANES III
- *Am J Hyperten* – 2014 *Meta-analysis 23 Trials*

Bar graphs show incidence of myocardial infarction according to quartile of urinary sodium excretion and age, race, and left ventricular hypertrophy (LVH) in men.







Alderman M H et al. Hypertension. 1995;25:1144-1152

American Heart Association

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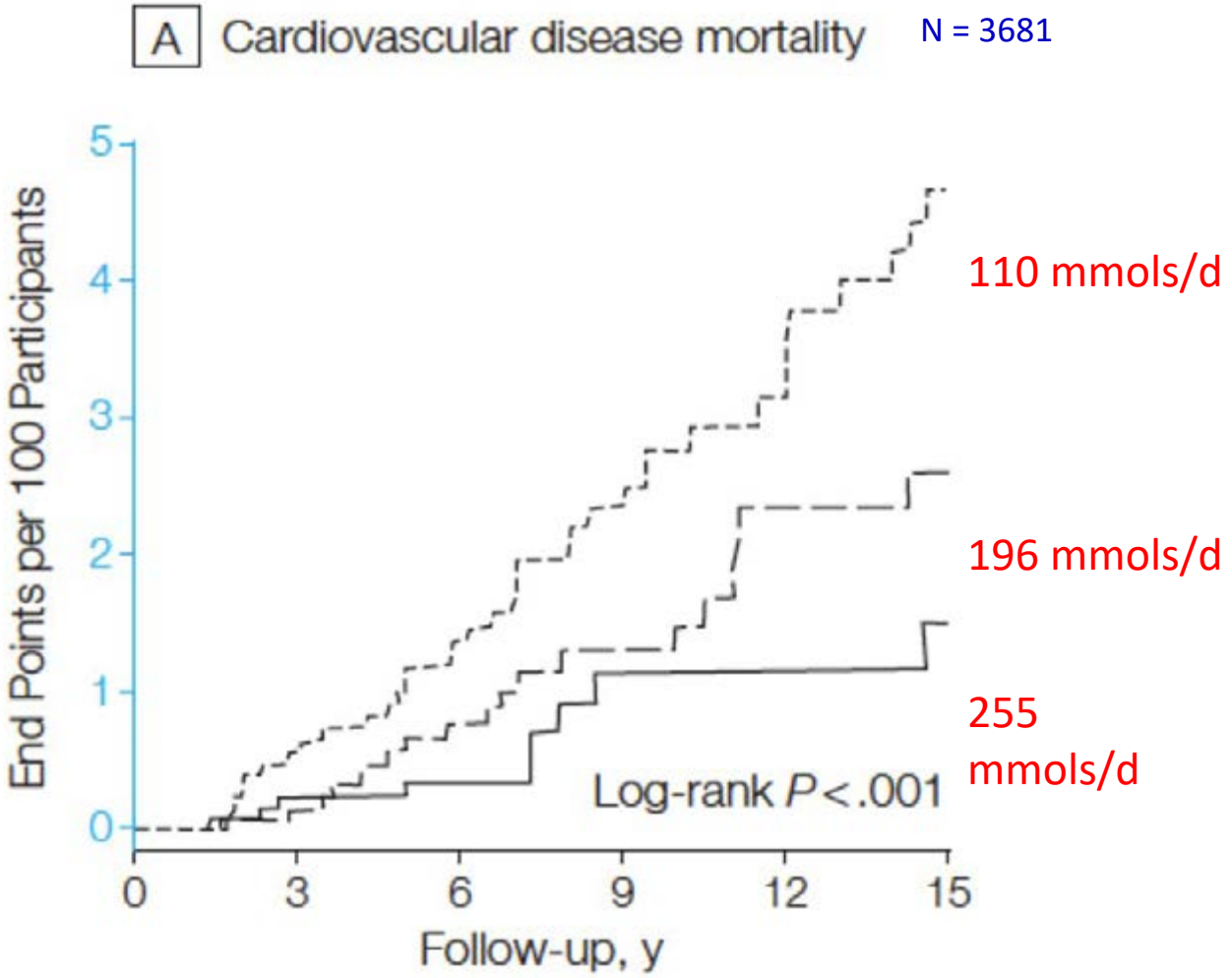
INCREASED CVD DEATHS WITH LOWER SODIUM IN HEALTHY ADULTS



Stolarz-Skrzypek et al: *JAMA*; 2011

LOWER Na+ INTAKE INCREASES CHD EVENTS

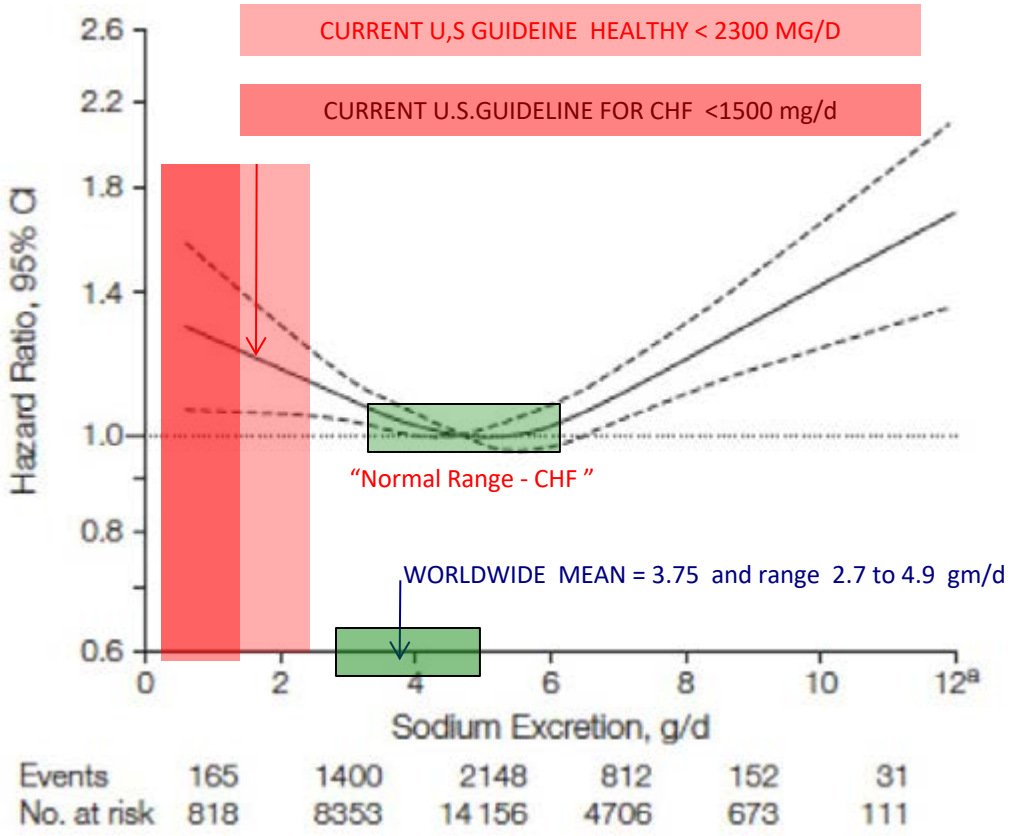
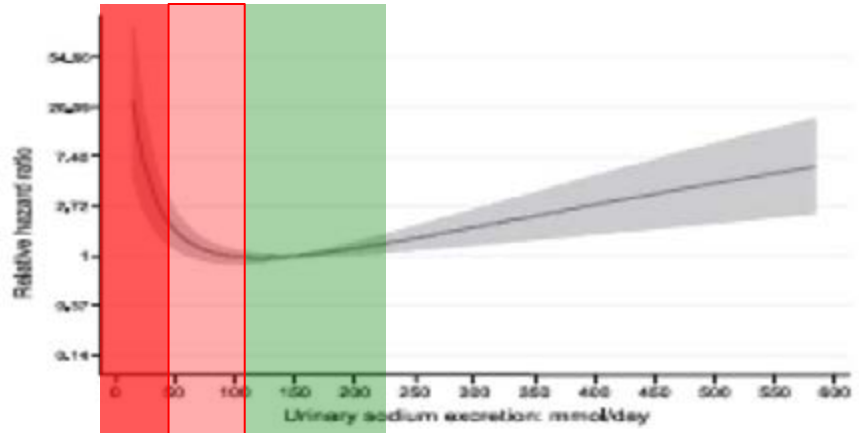


Figure 1. Estimated 24-Hour Urinary Excretion of Sodium and Composite of Cardiovascular Death, Stroke, Myocardial Infarction, and Hospitalization for Congestive Heart Failure

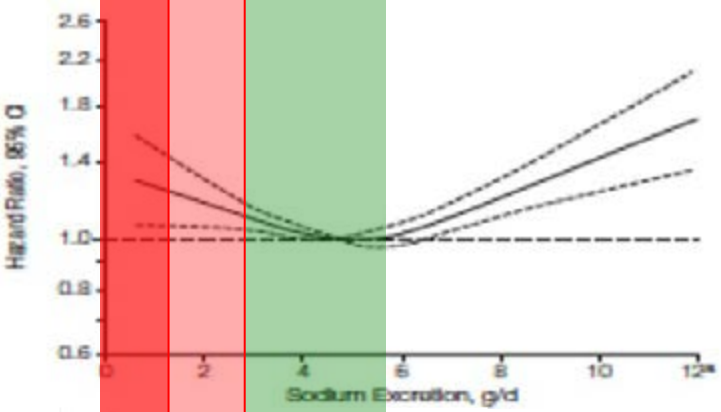
O'Donnell et al: *JAMA;* 2011

Lower UNaV and Increased CVD Risk

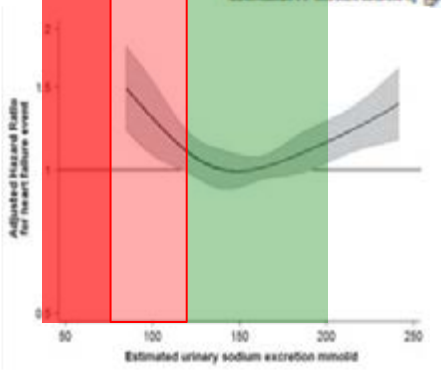
DM I – Na+ Intake
All-Cause Mortality
Diabetes Care 2011



Na+ Intake & CVD Events
Death, MI, CHF, Stroke
JAMA 2011



Na+ Intake & Risk of
CHF
Euro J Ht Fail 2014



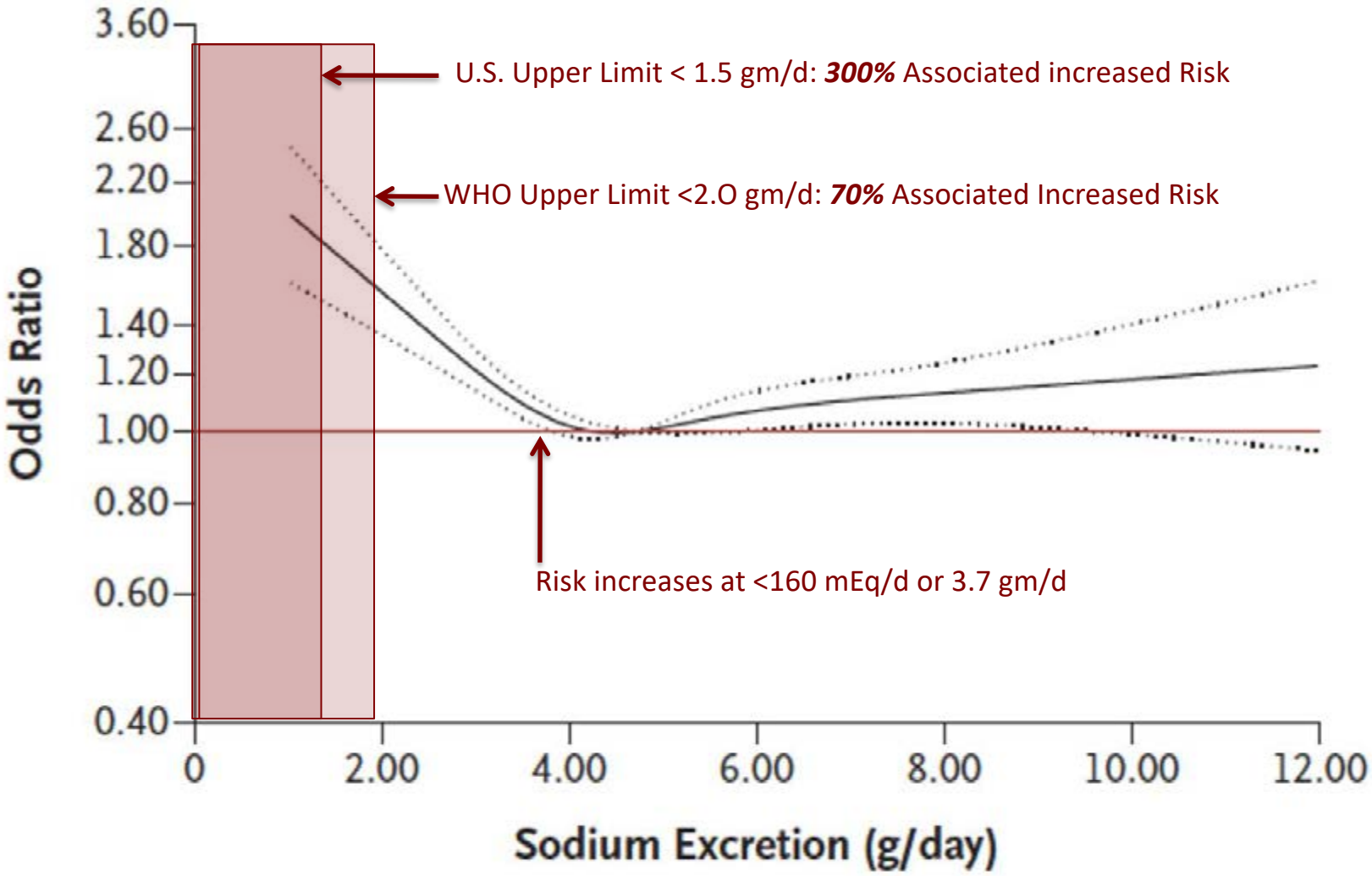
< 1500 mg/d

< 2300 mg/d

>2800-5000< mg/d

SODIUM EXCRETION - RISK OF CVD DEATH OR EVENT

ADAPTED FROM: O'DONNELL: *NEJM; 2014*



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

PURE STUDY: N=101,000
24 hr UNaV – CVD EVENTS AND DEATH

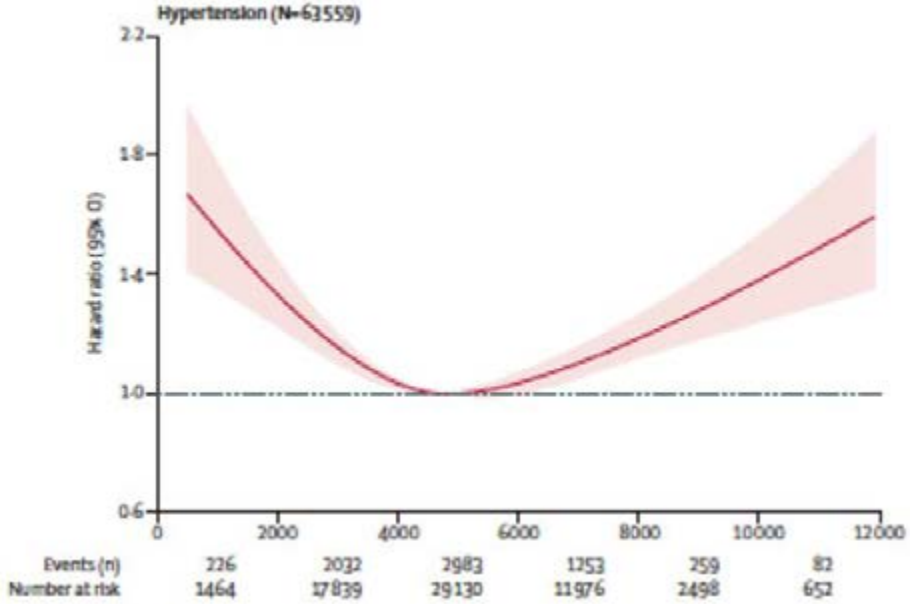
Table 2. Association of Estimated Urinary Sodium Excretion with Death and Major Cardiovascular Events.*

Variable	Estimated Sodium Excretion				
	<3.00 g/day (N=10,810)	3.00–3.99 g/day (N=21,131)	4.00–5.99 g/day (N=46,663)	6.00–6.99 g/day (N=12,324)	≥7.00 g/day (N=11,017)
Death or cardiovascular event — no. of participants (%)	462 (4.3)	662 (3.1)	1437 (3.1)	391 (3.2)	365 (3.3)
Analysis — odds ratio (95% CI)					
Univariate analysis†	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)
Multivariate analysis					
Primary analysis‡	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)
Analysis including 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)
Analysis including 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)
Analysis including dietary factors and blood pressure¶	1.19 (1.05–1.36)	1.01 (0.93–1.10)	1.00	1.03 (0.92–1.15)	1.08 (0.96–1.22)
Analysis excluding cardiovascular disease at baseline‖	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)
Analysis 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)
Analysis excluding events in yr 1‖	1.33 (1.17–1.52)	1.02 (0.93–1.13)	1.00	1.12 (0.99–1.27)	1.16 (1.01–1.33)
Analysis excluding events in yr 1 and 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)

** The very-low-risk cohort included 57,988 participants and excluded participants who had prior cardiovascular disease, who had been prescribed medications for cardiovascular disease, who had a history of cancer or a diagnosis of cancer on follow-up, who were smokers, or who had diabetes.

O"DONNELL et al: *NEJM; 2014*

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



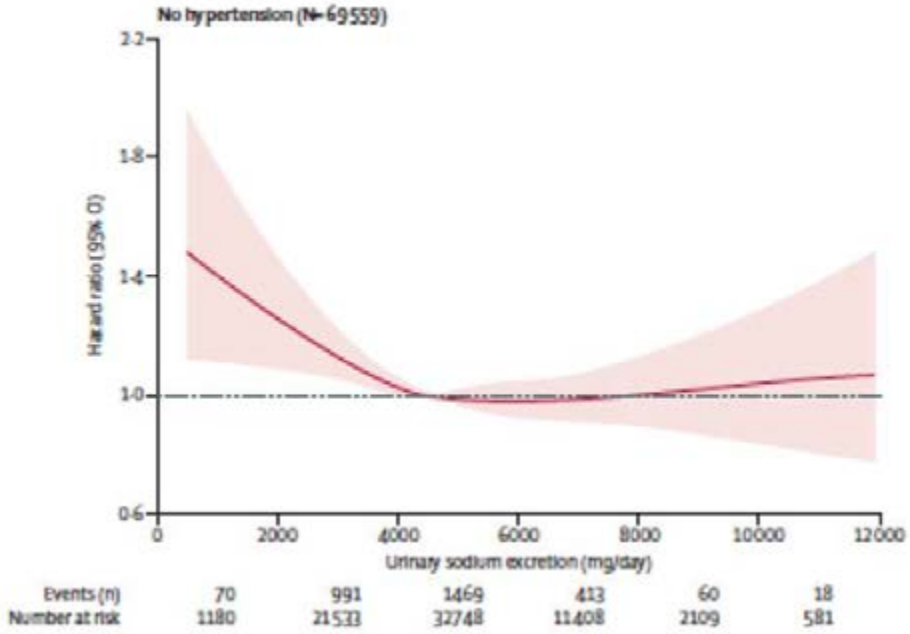


Figure 1: **Sodium excretion versus composite outcome events**
Cubic splines for the association between sodium excretion and composite outcome events (risk of death and major cardiovascular events), overall and by hypertension status in the four included studies (N=133 118). The analyses were adjusted for the variables in the primary model which included age, sex, ancestry (Asian vs non-Asian), body-mass index, educational level, alcohol intake, current smoking, physical activity, status with respect to diabetes mellitus, a history of cardiovascular events, treatment allocation (ramipril, telmisartan, or both, and treatment with statins, β blockers, diuretic therapy, calcium antagonist, and antidiabetes medication).

Mente et al: *Lancet 05/2016*

NEILS GRAUDAL AND FRIEND'S FAVORITE TOPIC

META-ANALYSIS: STUDIES OF HEALTH OUTCOMES AND UNaV

23 cohort studies and 2 follow-up studies (N=274,683)

- All-cause mortality was consistently ***reduced*** in usual sodium vs low sodium:
  - HR = 0.86, CI 0.81-0.92, *P* < 0.0001
- All-cause mortality was ***not*** increased in high sodium vs usual sodium:
  - HR = 1.04, CI 0.91-1.18, *P* = NS
- Consistent with *J shape* curve-increased mortality at sodium intakes less than 2800-3000 mg/day
- Mortality was present in CVD and *healthy subjects*

Graudal et al: *American J. Hypertension; 2014*

SALT INTAKE WORLWIDE:
WHAT WE KNOW TODAY

- Consistent 24 hr UNaV data available from:
  - 66 countries and their diverse food cultures
  - Spanning 5 decades and changes in food supply
  - Demographically represents of 75% of the world's population
- Reproducible range / mean of human intake
  - Range 2.6 to 5.5 gm/d
  - Mean 3.7 to 4.4 gm/d
- East Asian populations have higher intakes
  - Range 4.8 to 7.0 gm/d
  - China highest at mean of 5.6 gm/d
- Lower limit (2550 mg/d) confirmed in 2 NIH RCT

SCIENCE vs POLITICS

The salt controversy is the "number one perfect example of why science is a destabilizing force in public policy."

Sanford Miller, M.D.
Former Deputy FDA Commissioner, Foods
Science, 8/14/98

By Ronald Bayer, David Merritt Johns, and Sandro Galea

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The People-to-People Health
Foundation, Inc.

Salt And Public Health: Contested Science And The Challenge Of Evidence-Based Decision Making

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ABSTRACT For more than four decades, starting in the late 1960s, a sometimes furious battle has raged among scientists over the extent to which elevated salt consumption has adverse implications for population health and contributes to deaths from stroke and cardiovascular disease. Various studies and trials have produced conflicting results. Despite this scientific controversy over the quality of the evidence implicating dietary salt in disease, public health leaders at local, national, and international levels have pressed the case for salt reduction at the population level. This article explores the development of this controversy. It concludes that the concealment of scientific uncertainty in this case has been a mistake that has served neither the ends of science nor good policy. The article poses questions that arise from this debate and frames the challenges of formulating evidence-based public health practice and policy, particularly when the evidence is contested.

HEALTH AFFAIRS; DECEMBER, 2012

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

"Unfortunately there are no large randomized controlled trials comparing low sodium intake (< 3 gm/d) to moderate sodium intake (3-5gm/d) in the general population to determine the net clinical effects of low sodium intake…… This working group calls for the completion of large definitive clinical trials to clarify the range of sodium intake for optimal cardiovascular health within the moderate to low sodium range."

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.

Despite the large body of data on the relationship between cardiovascular disease and dietary sodium from observational studies and the positive impact on blood pressure in randomized controlled clinical trials and current national guidelines recommending daily sodium intakes of ≤2300 mg/d, mean daily intake for Americans remains in the 3400 to 3500 mg/d range.[2] Some scientists have questioned the justification for a reduced intake of dietary sodium.[3] This disagreement within the scientific community has been reported in the lay press, leading both clinicians and some in the public to express uncertainty on the issue.[4–6]

The Idea Subjects for a Salt Study? Maybe Prisoners

Leading scientists propose to track salt's effects on health by controlling how much is given to inmate volunteers.

NEW YORK TIMES

By **Gina Kolata**

June 4, 2018

Facts are stubborn things; and whatever may be our wishes, or inclinations, or dictates of our passion, they cannot alter the state of facts and evidence.

John Adams, ***1770***

“….only a raccoon can eat an egg without salt…”

Ronald Reagan

Parade Magazine – mid-1980’s

Gertrude Baines, 115, Oldest in World

LOS ANGELES (AP) — Gertrude Baines, who lived to be the world's oldest known living person on a steady diet of crispy bacon, fried chicken and ice cream, died here Friday. She was 115.

She died in her sleep, said Emma Camanag, the administrator at Western Convalescent Hospital. Ms. Baines's longtime physician, Dr. Charles Witt, said she had probably suffered a heart attack. An autopsy is scheduled.

Born in 1894 in Shellman, Ga., Ms. Baines took over the title of the world's oldest living person when a 115-year-old woman, Maria de Jesus, died in Portugal in January.

Ms. Baines, after casting her vote for Barack Obama in the presidential election in November, said: "I'm glad I'm here. I don't care if I live a hundred more. I enjoy nothing but eating and sleeping."

She celebrated her birthday at the nursing home April 6 with music, two cakes and a letter from President Obama.

"She told me that she owes her longevity to the Lord, that she never did drink, she never did smoke and she never did fool around," Dr. Witt said at the party.

The oldest person in the world is now Kama Chinen, 114, who lives in Japan, said Dr. L. Stephen Coles of the Gerontology Research Group, which tracks claims of extreme old age.

Ms. Baines outlived her entire family, including her only daughter, who died of typhoid. She worked as a maid in Ohio State University dormitories until her retirement, and lived at the Western Convalescent Hospital after breaking a hip at 107.

DAMIAN DOVARGANES/ASSOCIATED PRESS

Gertrude Baines on April 6.