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Faculty of Biology and Medicine

The impact of salt reduction on blood pressure

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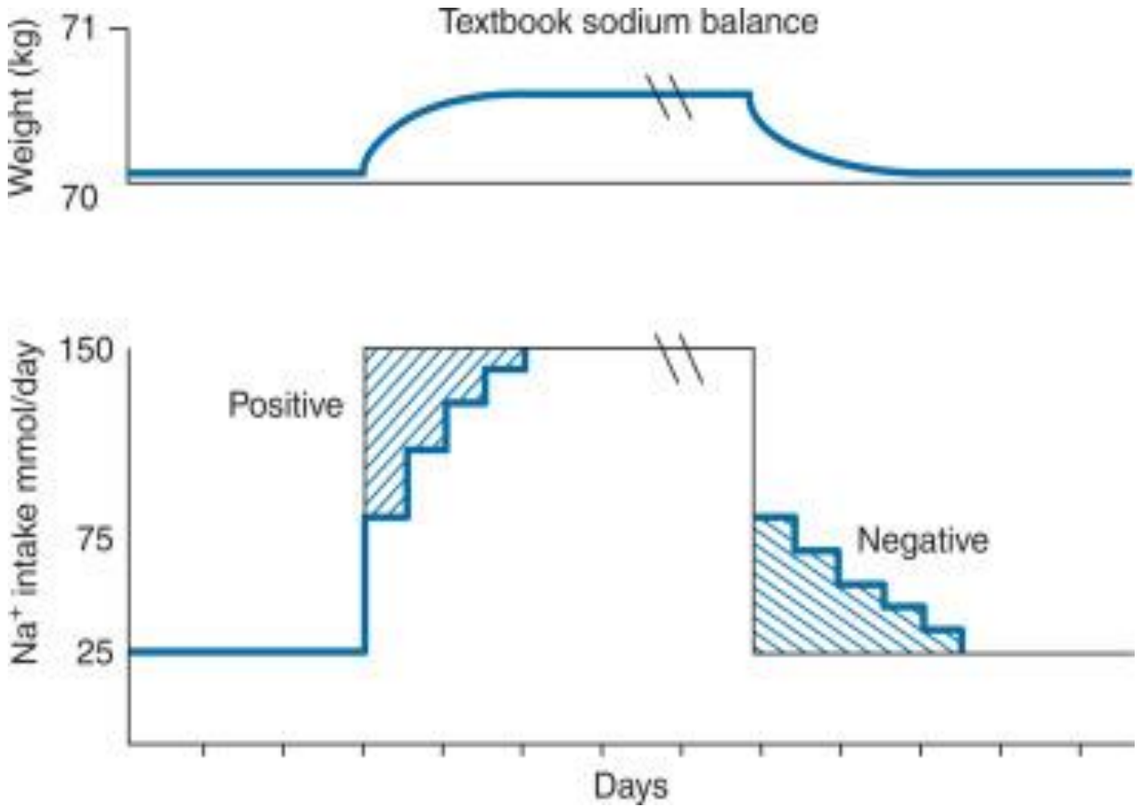
Disclosure potential conflicts of interest

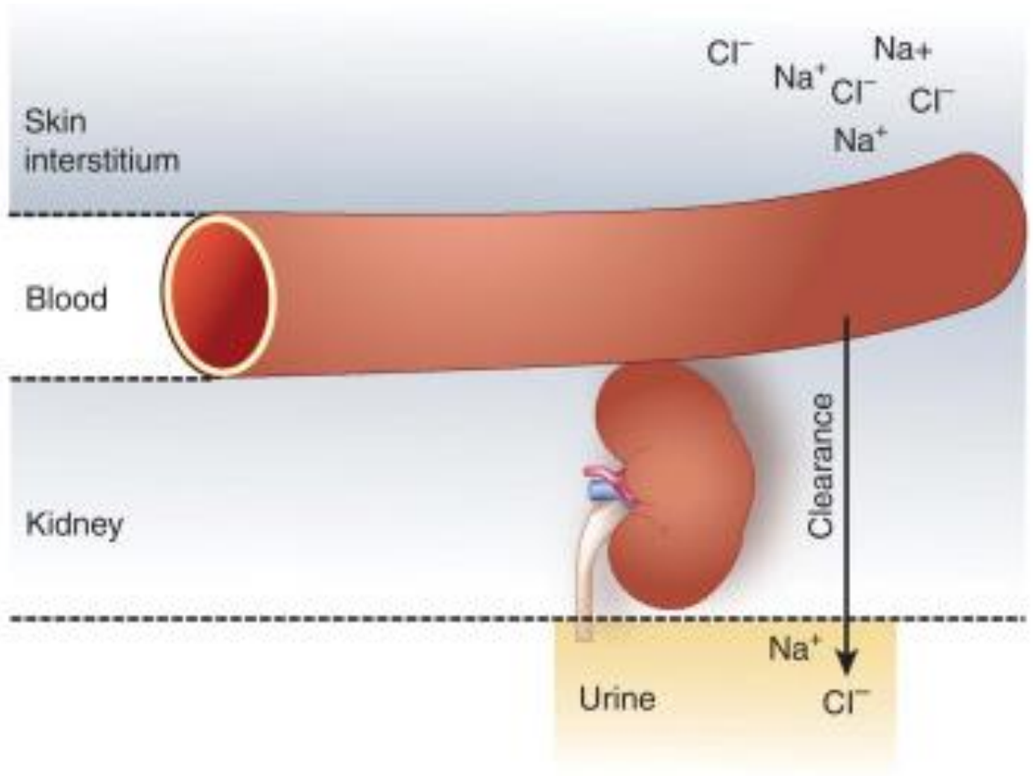
No (potential) conflict of interests for this presentation

Presentation outline

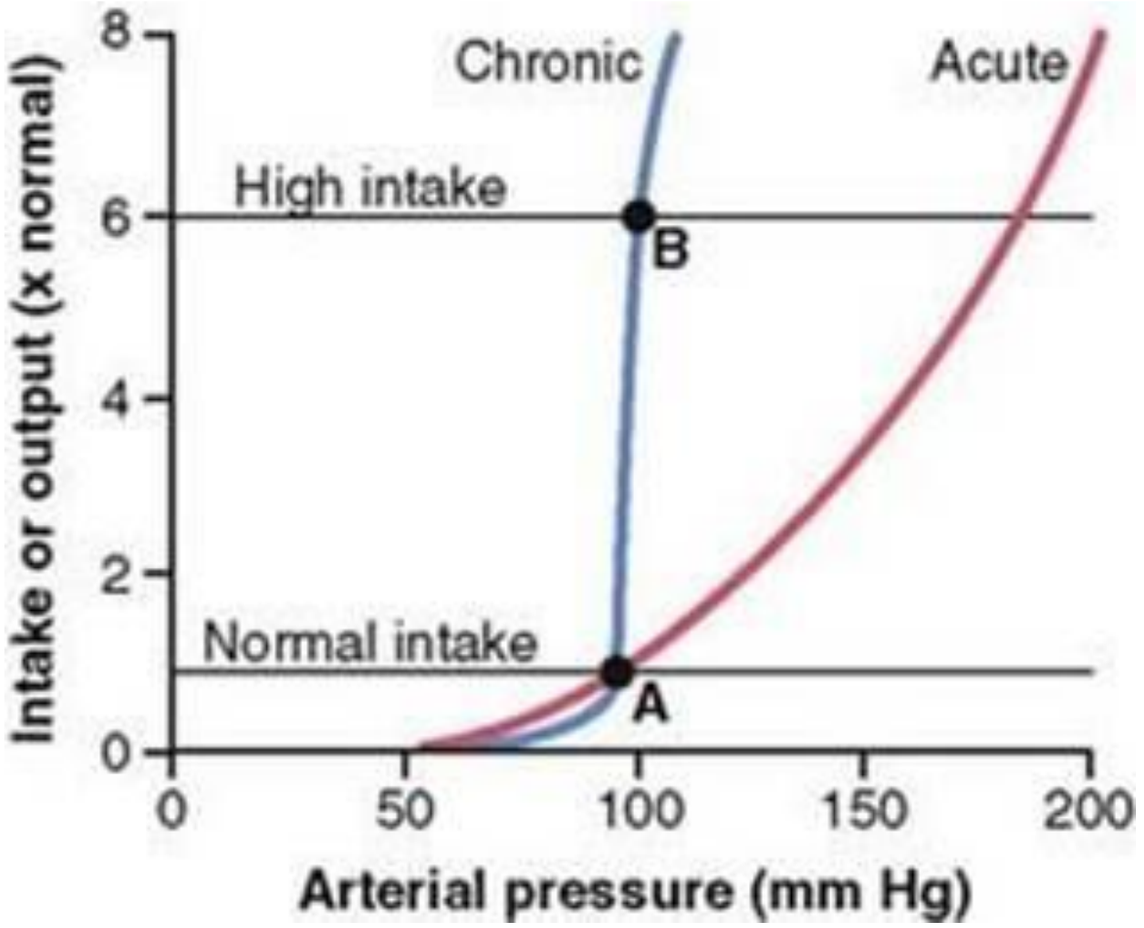
1. Salt and the regulation of blood pressure: new pathophysiological pathways
2. Salt intake, blood pressure and hypertension
3. Salt and blood pressure: the role of other ions
4. Impact of lowering salt intake on blood pressure
5. When is a high salt intake needed to maintain blood pressure?

Classical schemes of regulation of sodium balance





The pressure-natriuresis curve



Guyton and Hall Textbook of Medical Physiology, 12th Ed

Mechanisms Mediating Dietary Sodium-Induced Alterations in BP

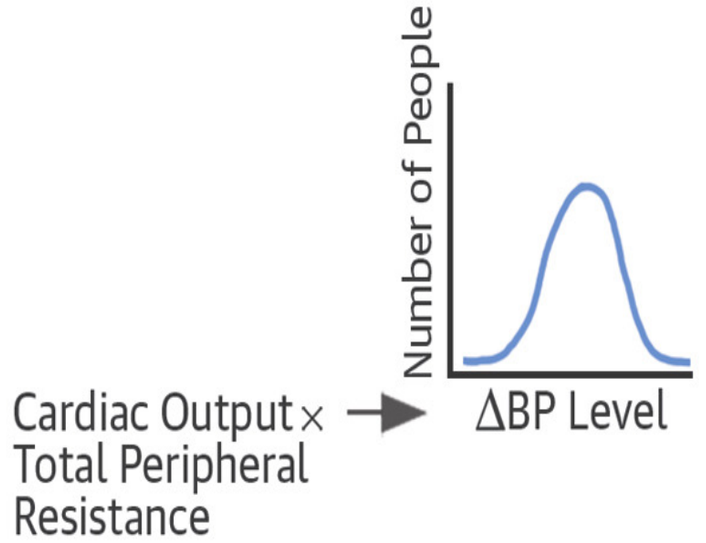
Environmental-Genetic Interactions

↑Dietary Sodium Intake

Physiological Mechanisms Mediating Changes in BP

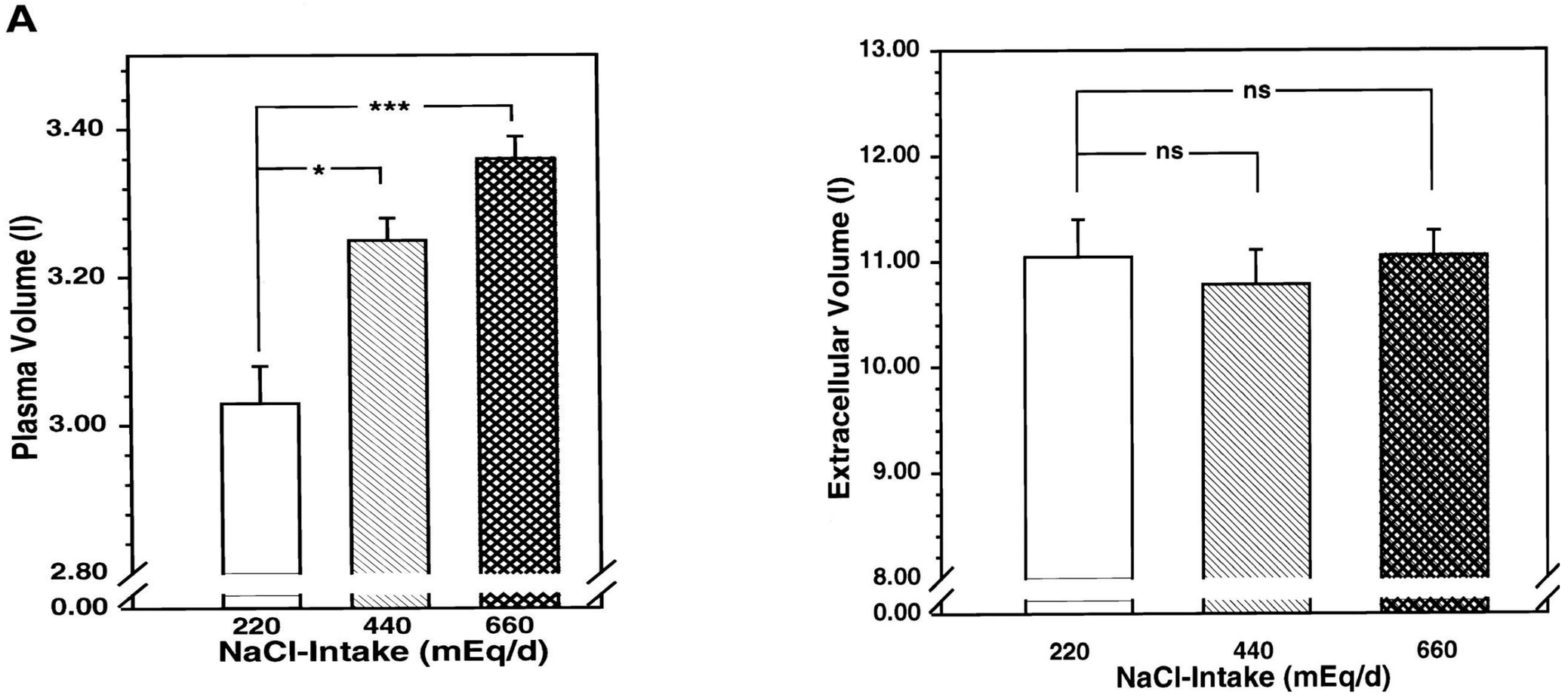
- Renal Function
- Fluid Volumes and Regulatory Hormones
- Non-Renal Vasculature
- Cardiac Function
- Autonomic Nervous System

Effect on BP



Farquhar, W.B. et al. J Am Coll Cardiol. 2015; 65(10):1042-50.

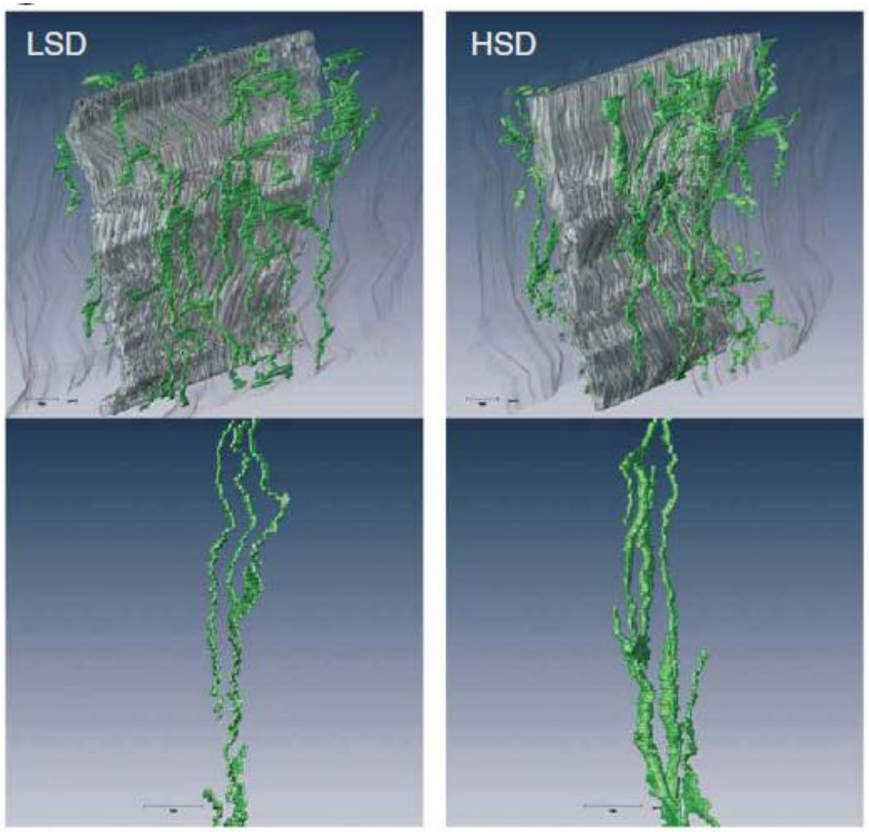
High salt diet increases plasma volume but not extracellular volume in healthy subjects



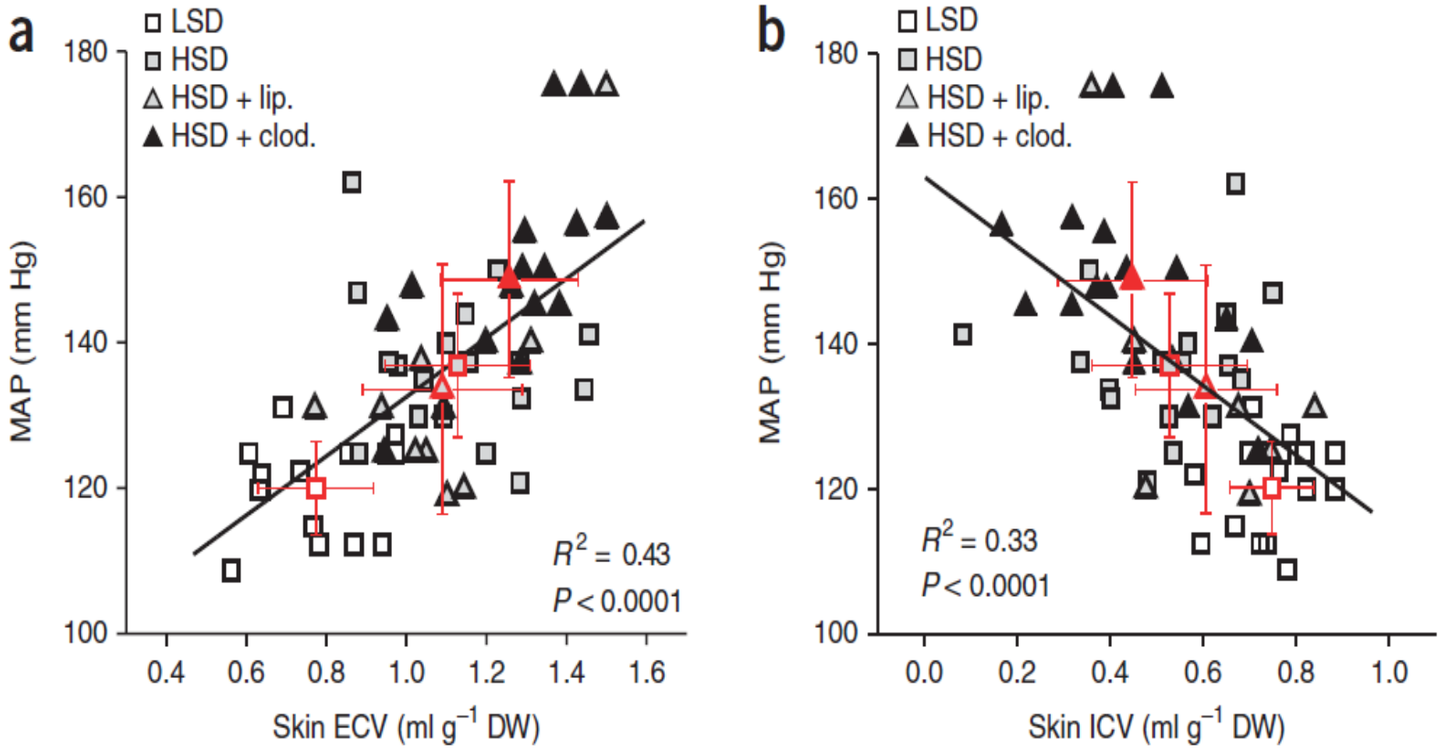
Heer M et al. Am J Physiol Renal Physiol; 2000, 278(4)

Role of lymph vessels and macrophages in the regulation of salt-dependent volume and blood pressure

Lymph vessel hyperplasia in response to dietary salt loading.

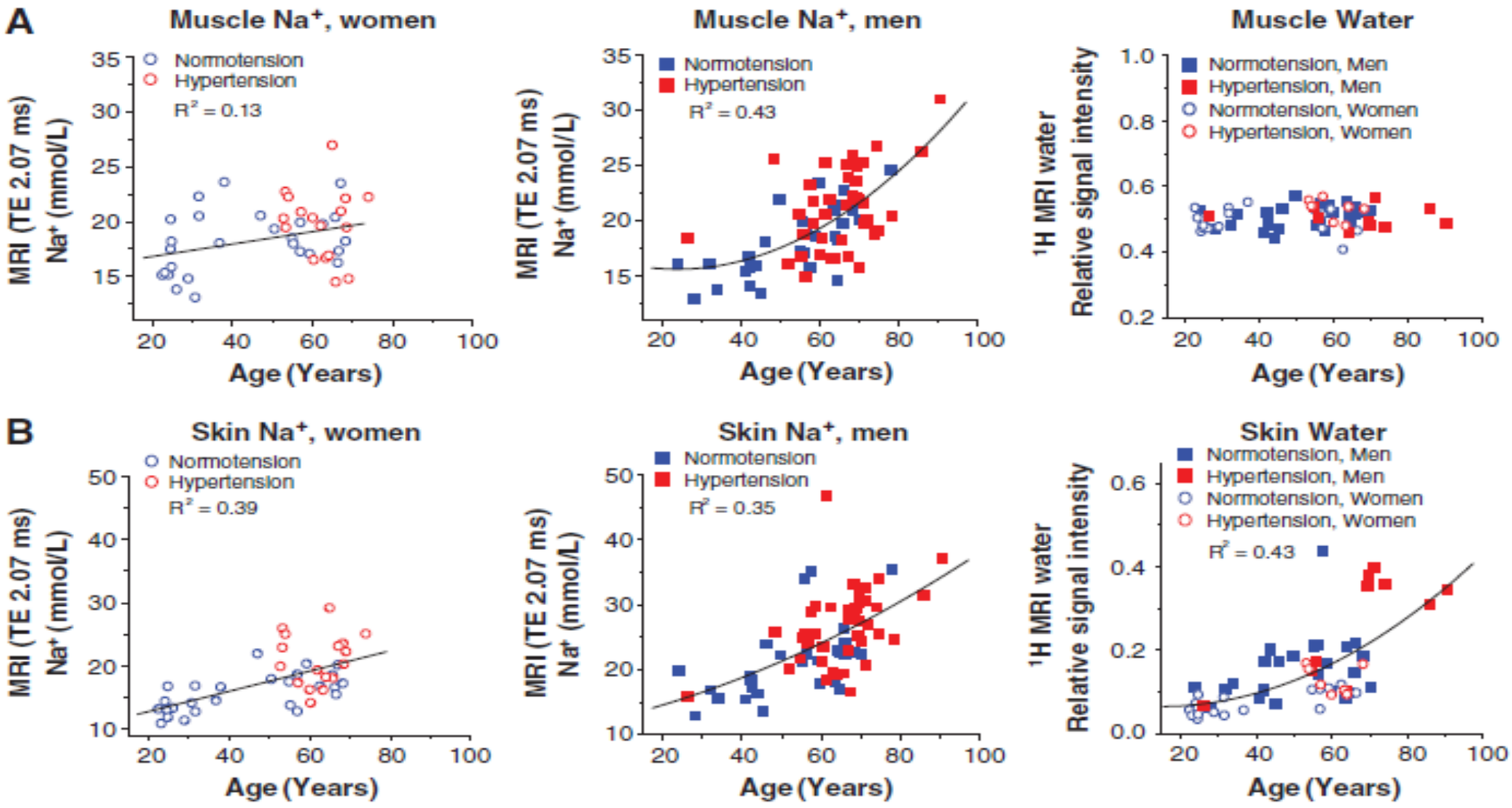


Mononuclear phagocyte system depletion leads to augmented volume retention and blood pressure increase in response to HSD



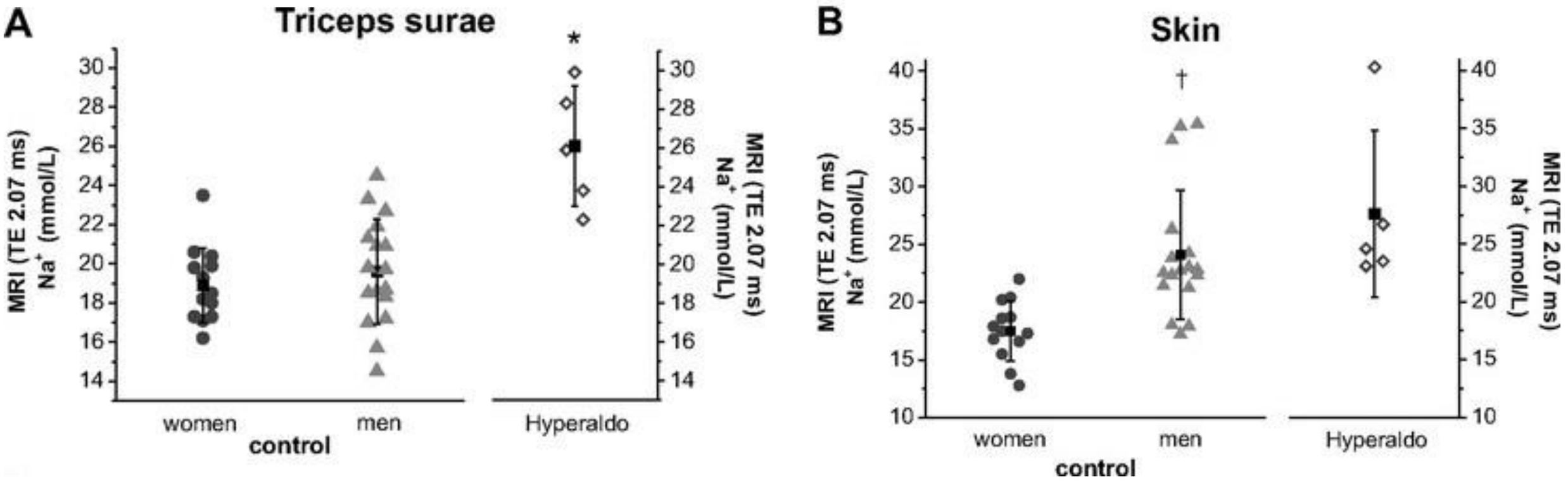
Machnik A, et al. Nature Medicine 2009; 15 (5): 545-552
Machnik A, et al. *Hypertension.* 2010;55:755-761

^{23}Na Magnetic Resonance Imaging-Determined Tissue Sodium in Healthy Subjects and Hypertensive Patients



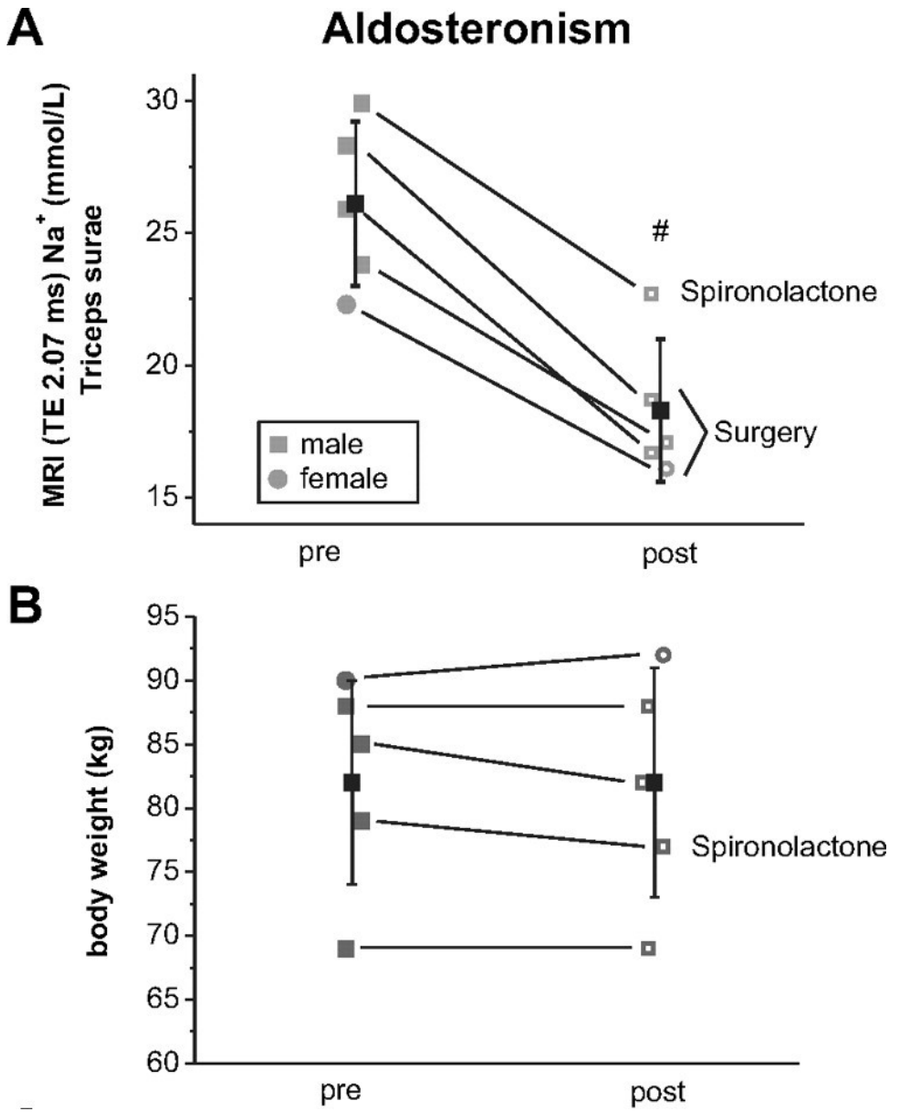
Kopp C et al. Hypertension. 2013;61:635-640

Tissue sodium concentration in patients with primary hyperaldosteronism



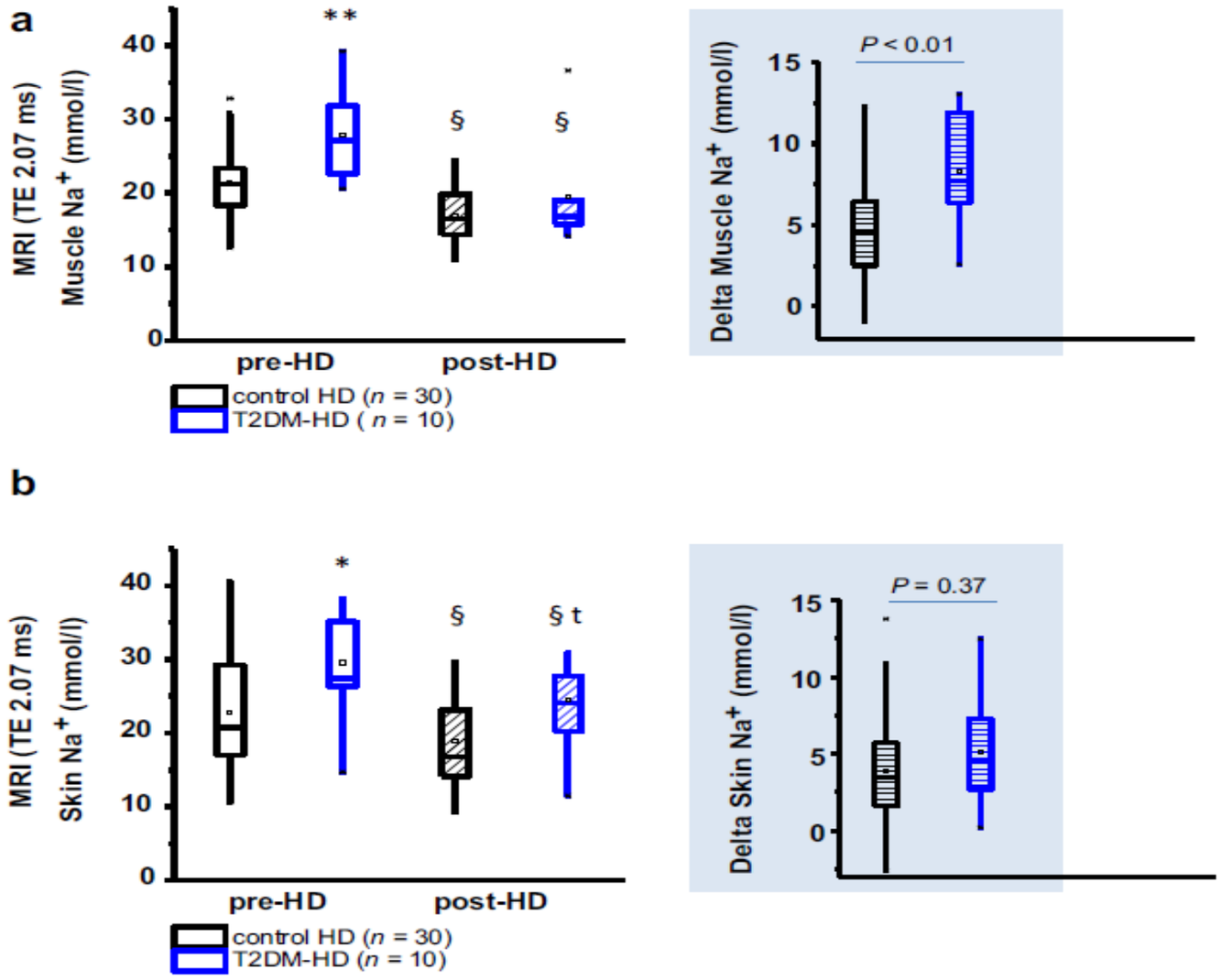
Kopp C et al; Hypertension. 2012;59:167–172

Effect of spironolactone or surgery on tissue sodium in primary hyperaldosteronism



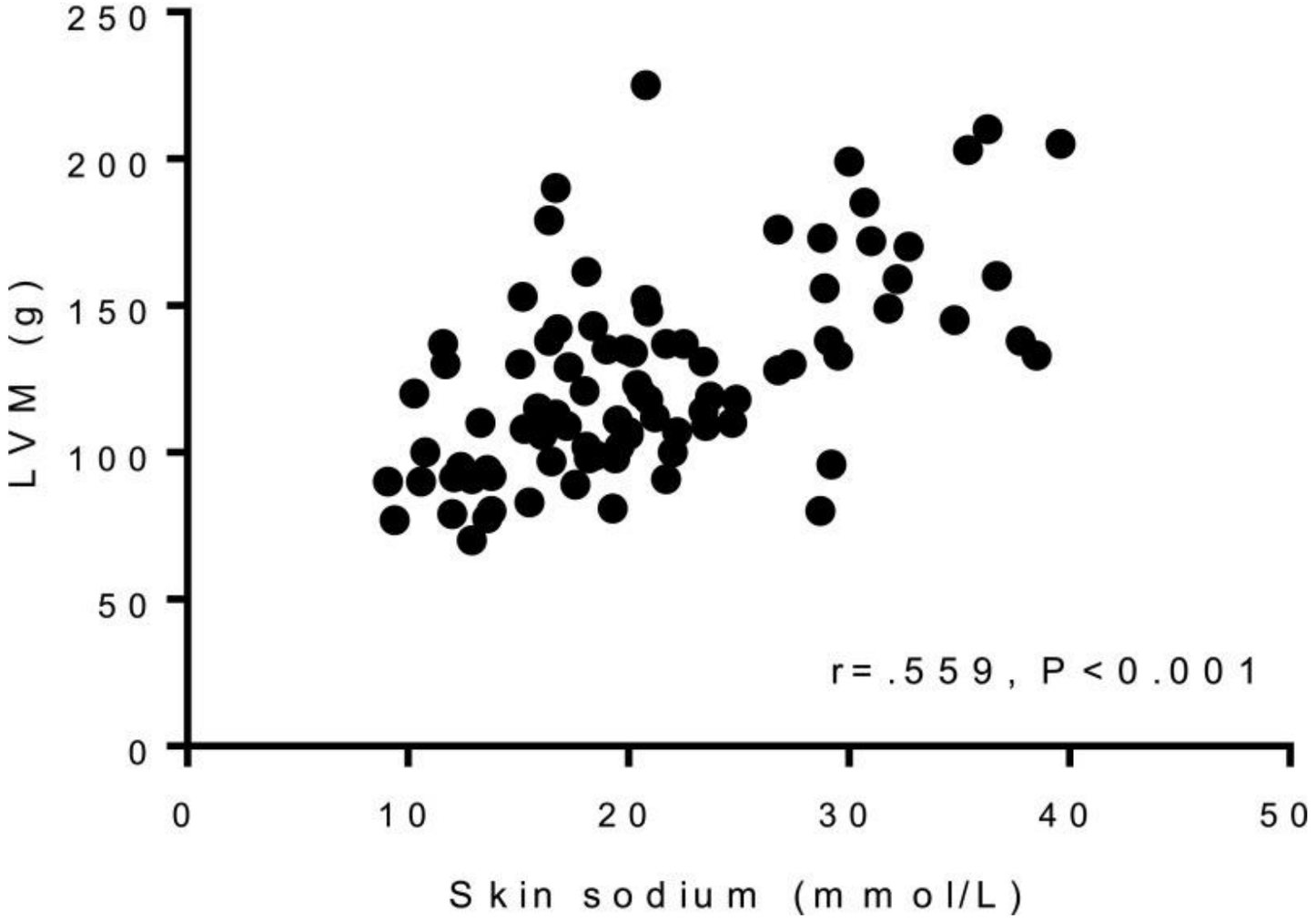
Kopp et al. Hypertension. 2012;59(1):167-72

Higher mobilization rate of muscle Na during hemodialysis treatment in patients with type 2 diabetes mellitus undergoing HD versus HD controls



Kopp, C et al. Kidney International (2018) 93, 1191–1197

Skin Sodium Concentration Correlates with Left Ventricular Hypertrophy in CKD

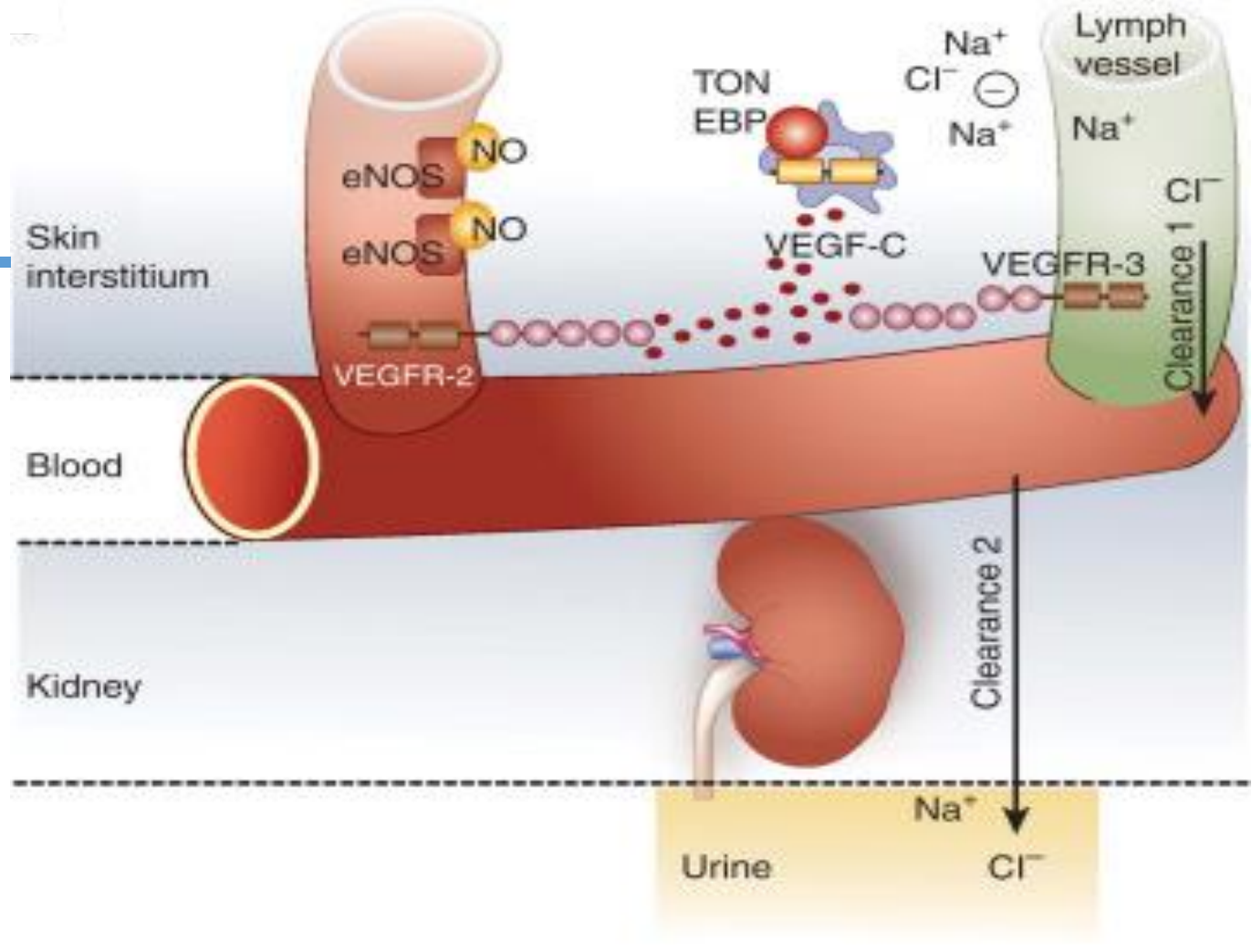


99 patients with mild to moderate CKD
42 women;
median [range] age, 65 [23-78] years

Schneider MP et al. J Am Soc Nephrol. 2017; 28(6): 1867–1876.

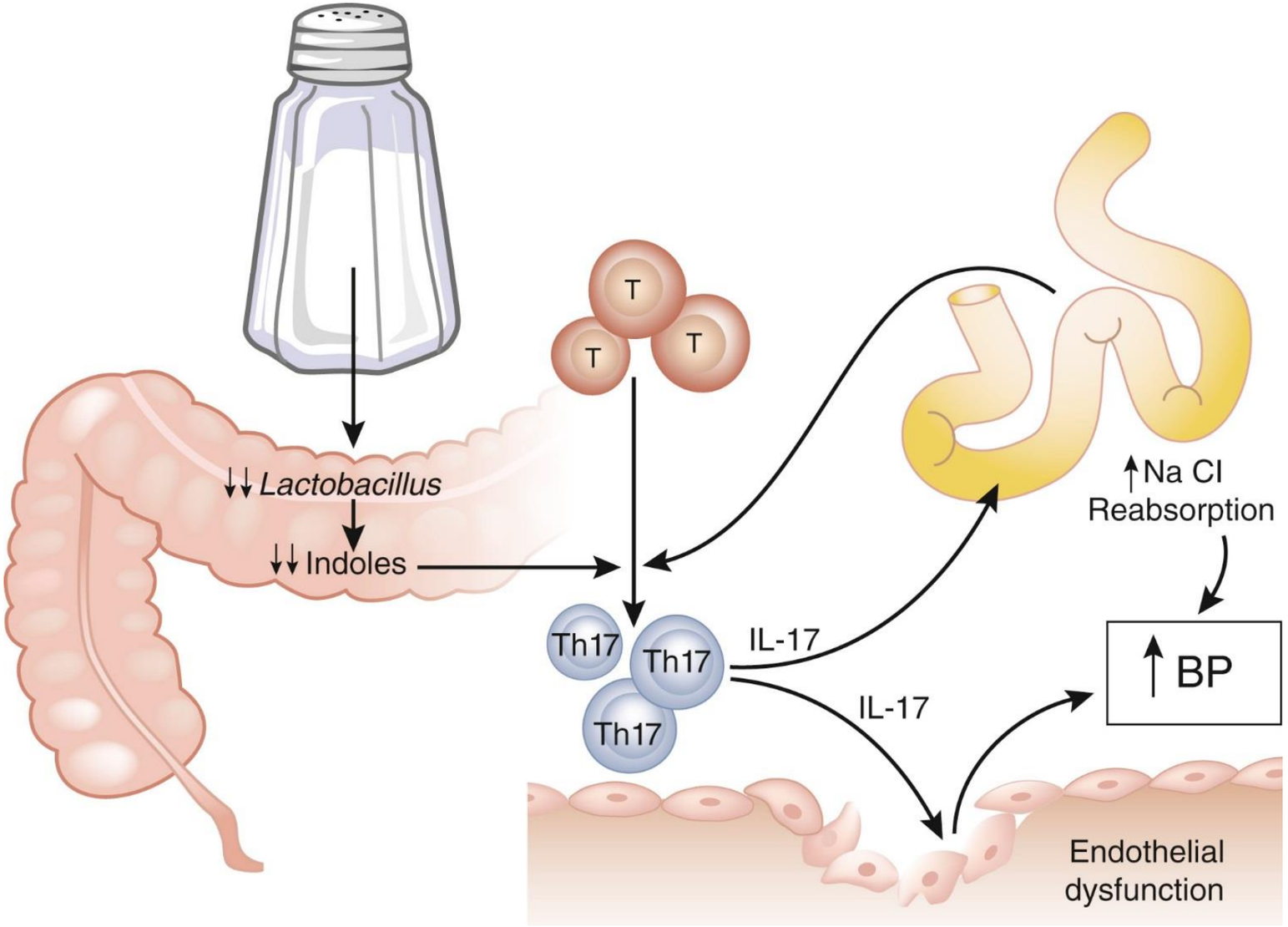
Revised representation of the accumulation of sodium in the skin

Sweat



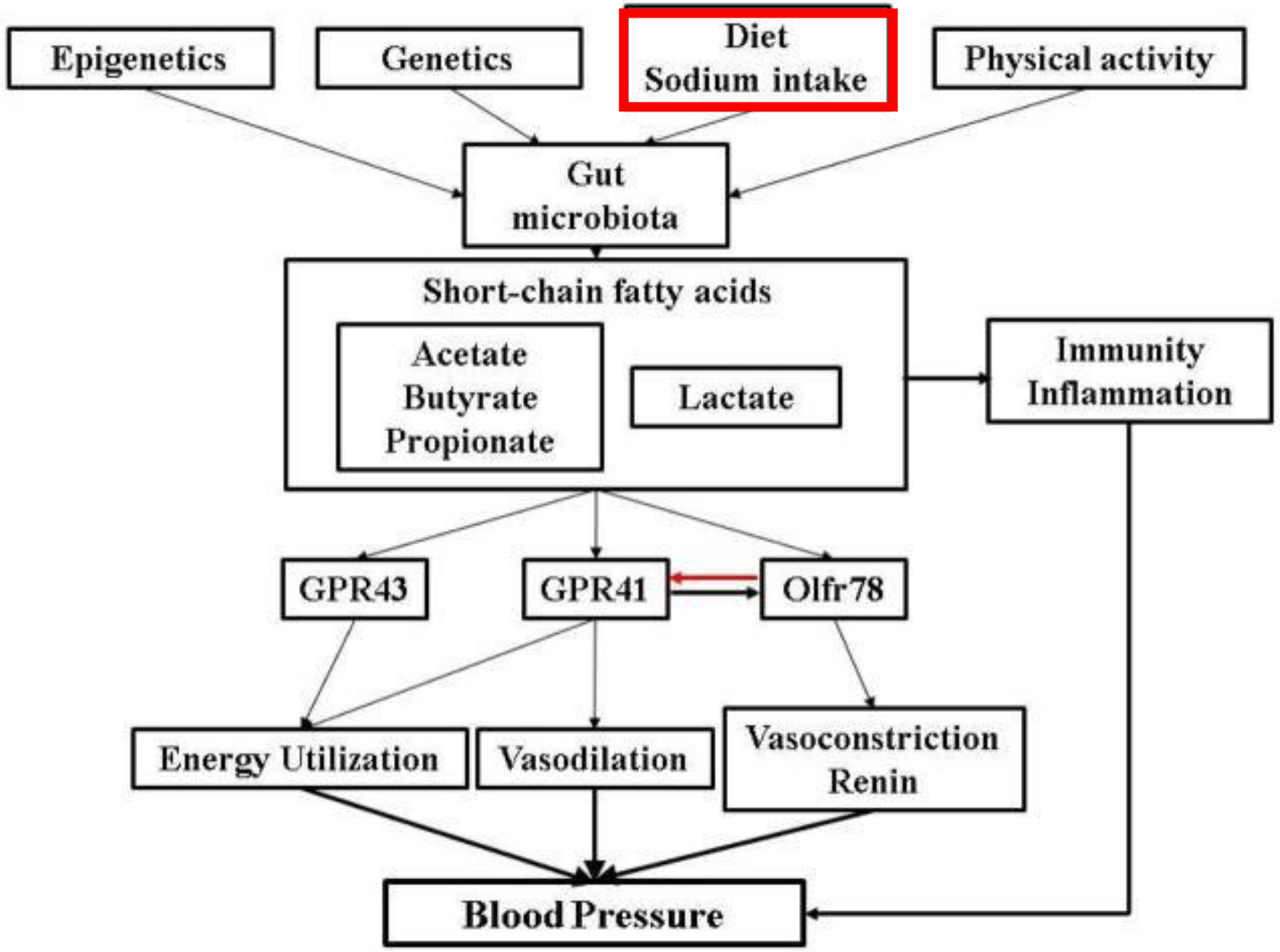
J Titze etal. Kidney International 2014; 85(4): 759-767

High-salt intake and pro-inflammatory immune cells are implicated in the pathogenesis of hypertension



Kidney International 2018 93, 532-534DOI: (10.1016/j.kint.2018.01.001)

Role of salt and the gut microbiota on the regulation of blood pressure

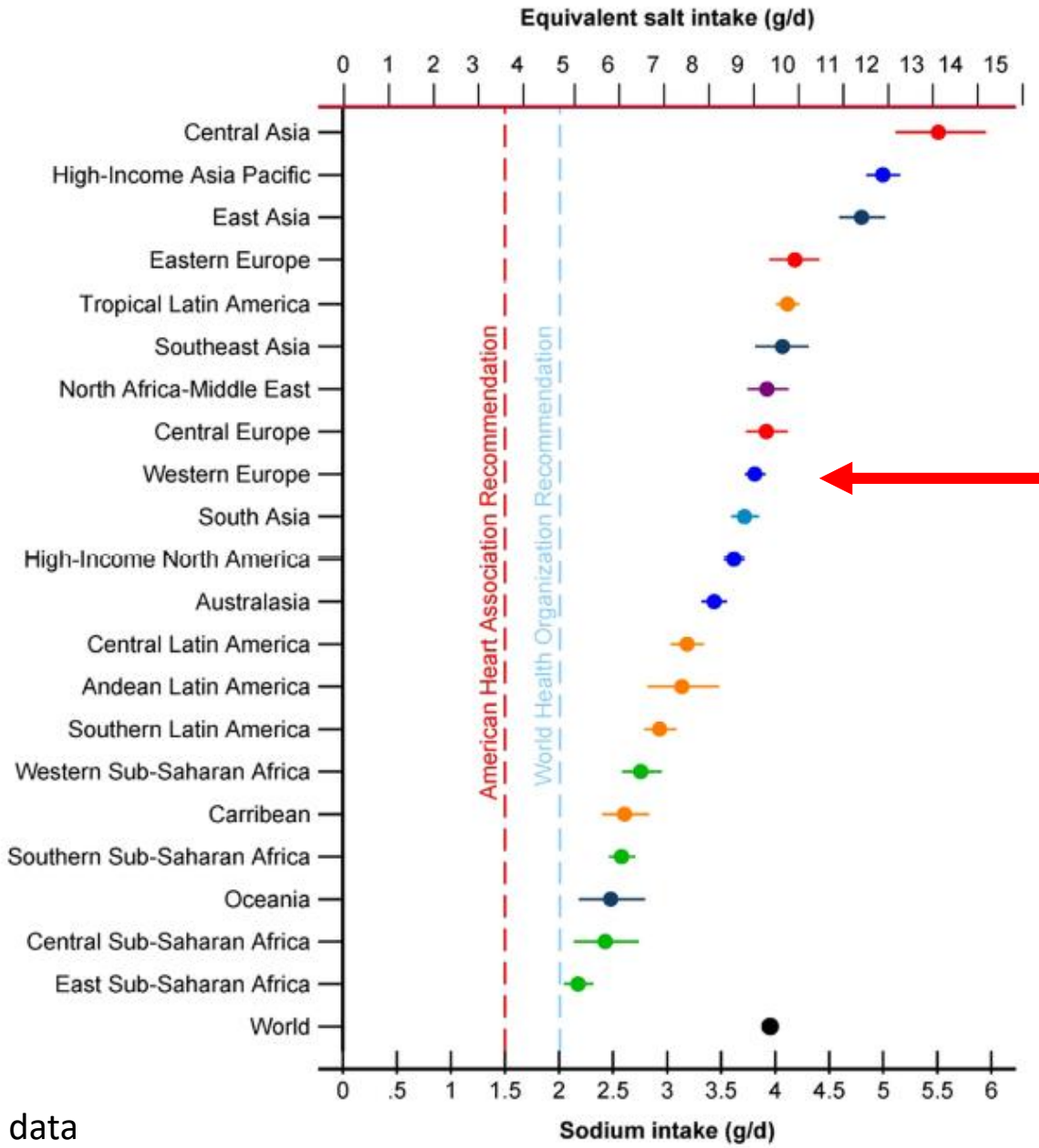


Jose and Raij, Curr Opin Nephrol Hypertens 2015;24(5):403-9

International target recommendations for sodium intake

World Health Organization	<2g Na/d (<5g NaCl/d)
American Heart Association	< 1.5g Na/d
US FDA	< 2.3g Na/d (6g NaCl/d)
ESC/ESH guidelines 2018	<2g Na/d

Sodium consumption around the world in 2010

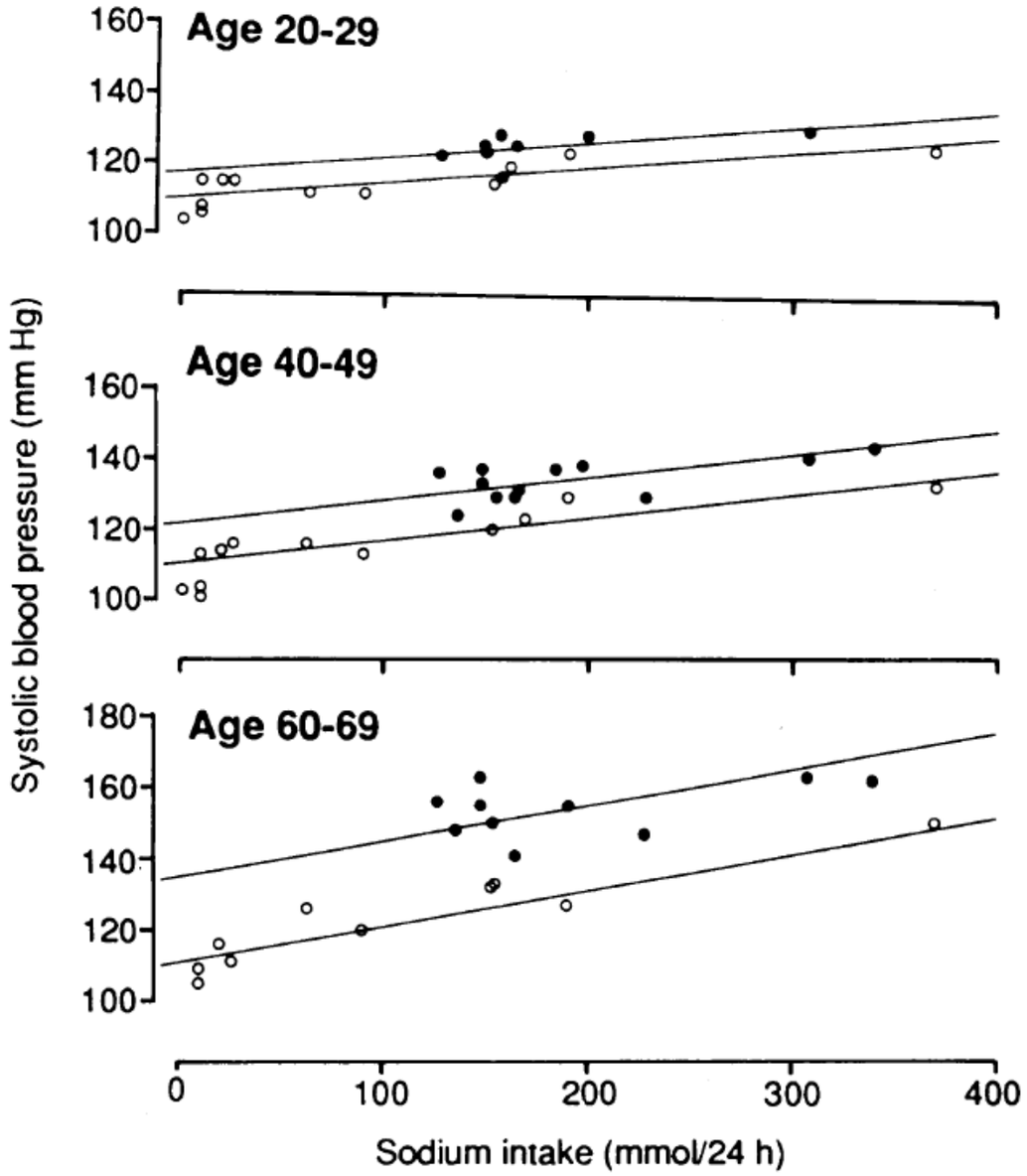


About 9 g NaCl/d

Uncorrected data

Powles et al, BMJ Open 2013;3:e003733

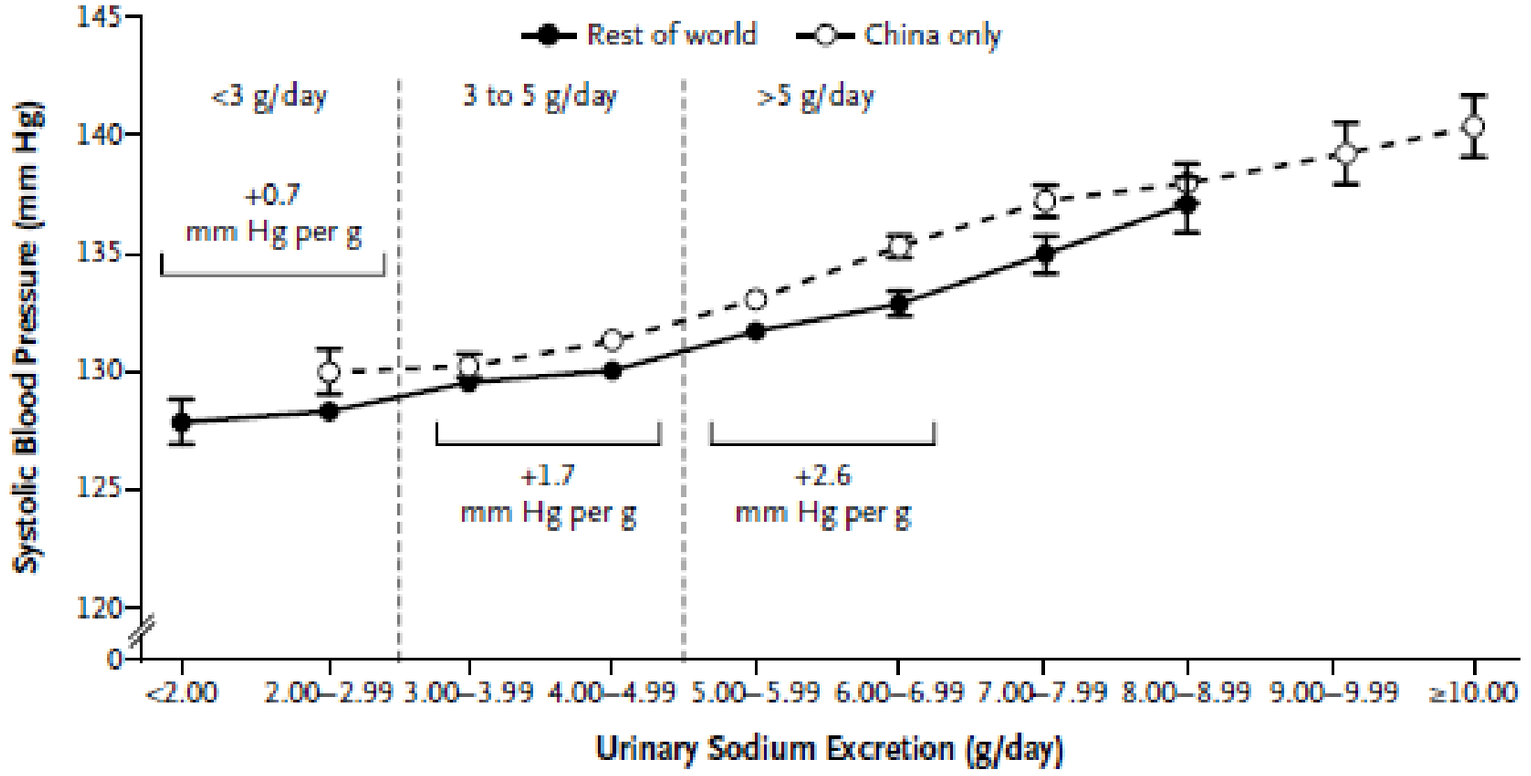
Systolic BP according to sodium intake in three age groups



Economically developed (●)
and undeveloped (○)

Law et al. BMJ 1991

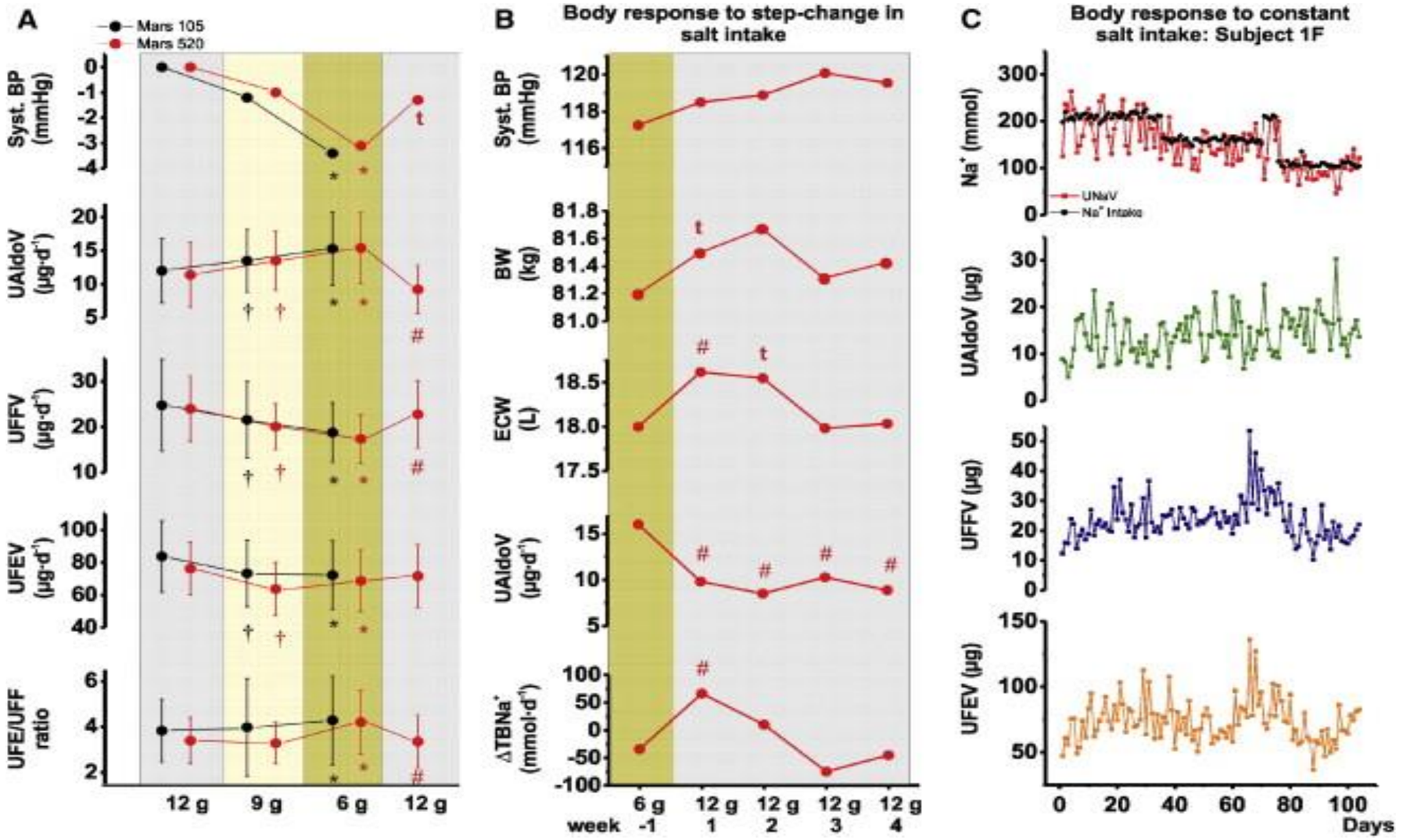
Mean Systolic Blood Pressure According to Sodium Excretion in PURE



No. of Participants										
China		1876	6,012	9,794	10,101	7177	4093	2035	1002	952
Other countries	1613	7384	15,101	16,015	10,810	5211	2048	992		

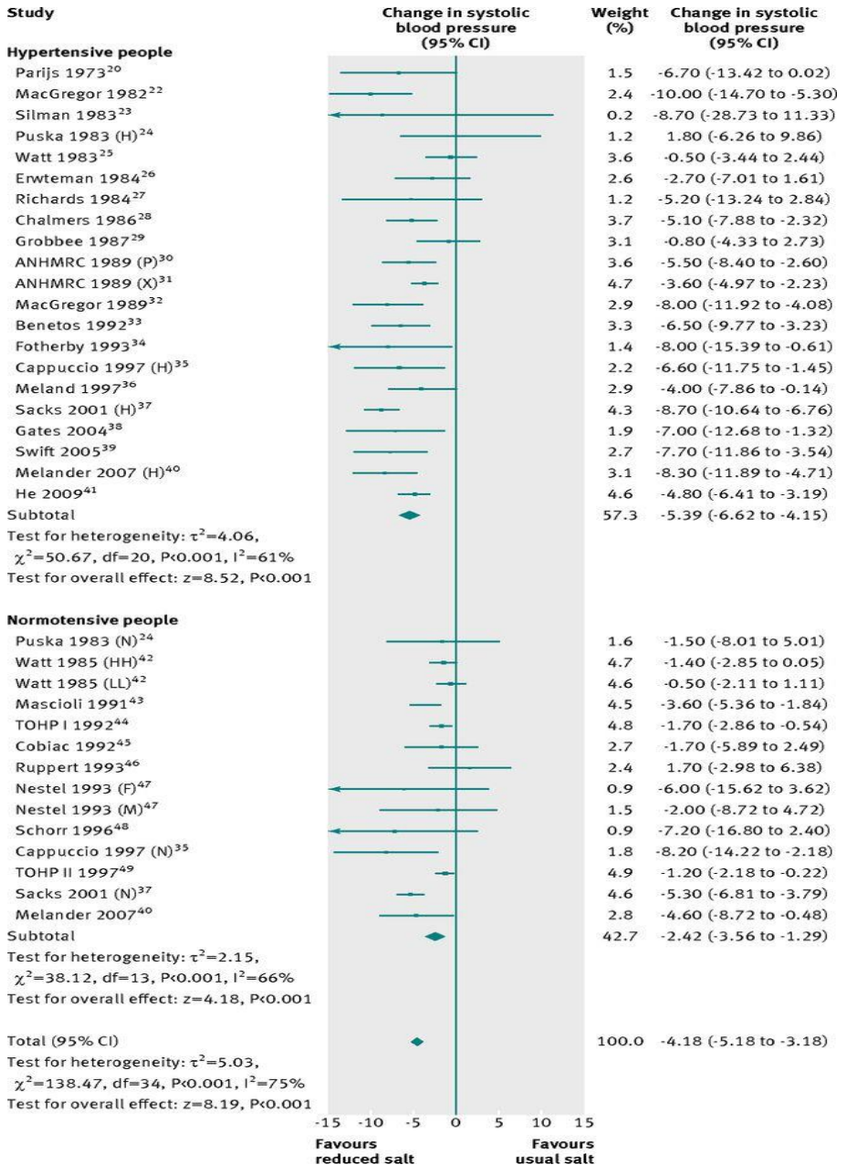
Mente et al, N Engl J Med 2014;371:601-11

Response of the Body to Step Changes in Salt Intake during the Mars105 and the Mars 520 Balance Studies



Rakova et al, Cell Metabolism. 2013, 17 (1): 125-131

Change in systolic blood pressure in individual trials included in meta-analysis and mean effect size.



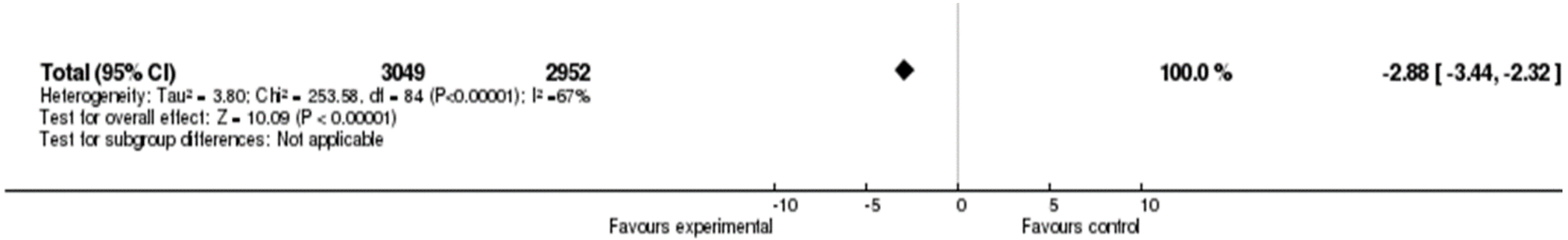
Hypertension: -5.39 mmHg (p<0.001)

Normotension: -2.42 mmHg (p<0.001)

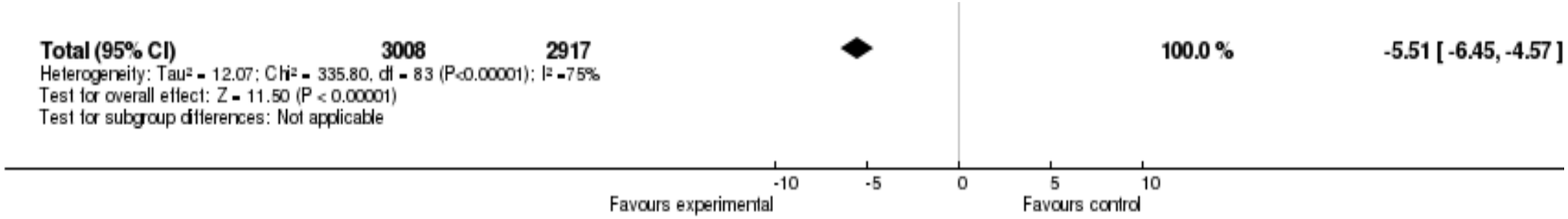
Feng J He et al. BMJ 2013;346:bmj.f1325

Effects of low sodium diet versus high sodium diet on blood pressure: a Cochrane analysis

Caucasians, elevated diastolic BP

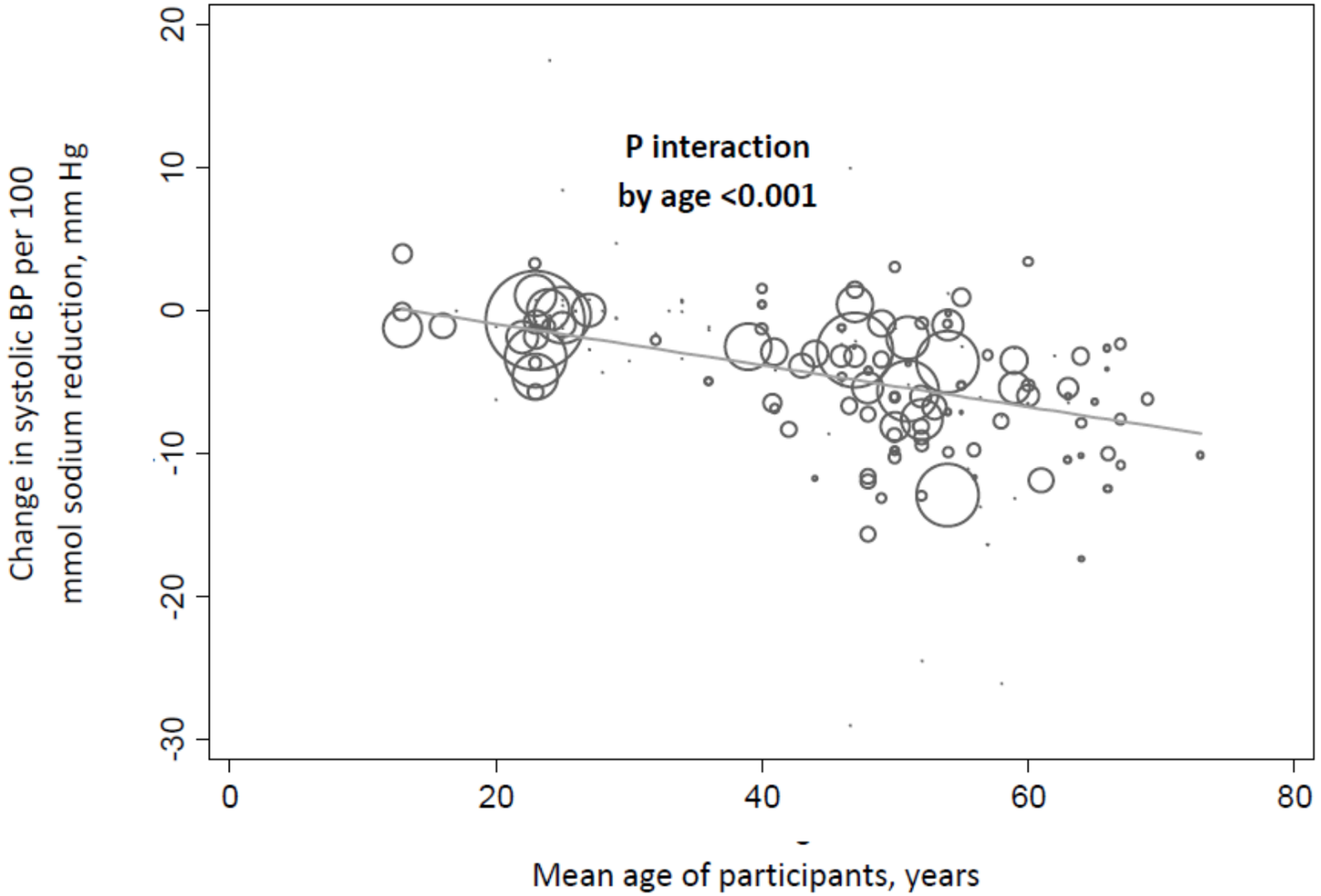


Caucasians, elevated systolic BP



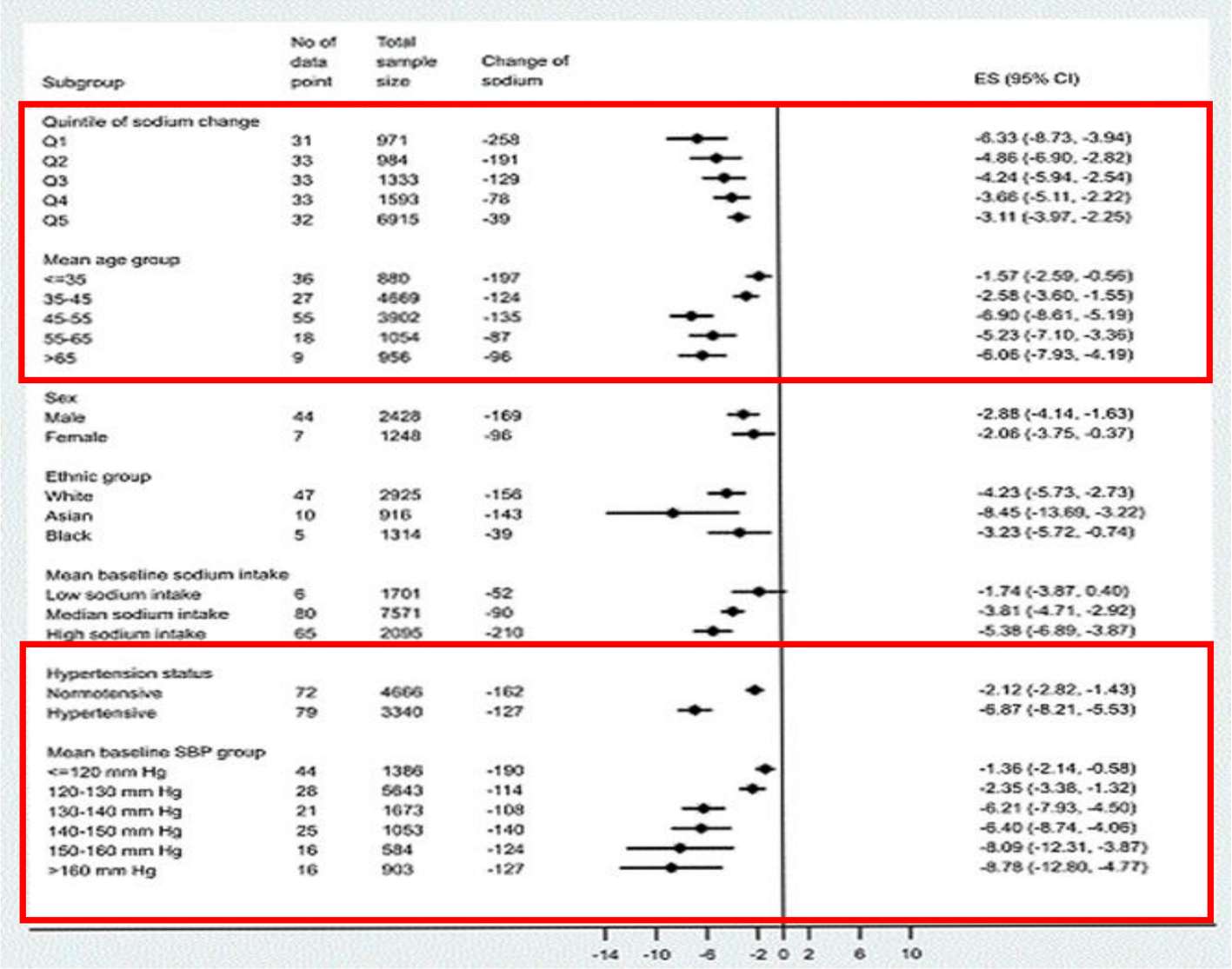
Gradual et al. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. Cochrane Database Syst Rev. 2017 Apr 9;4:CD004022

Effects of sodium reduction on systolic blood pressure in randomized controlled trials, by age (103 trials)



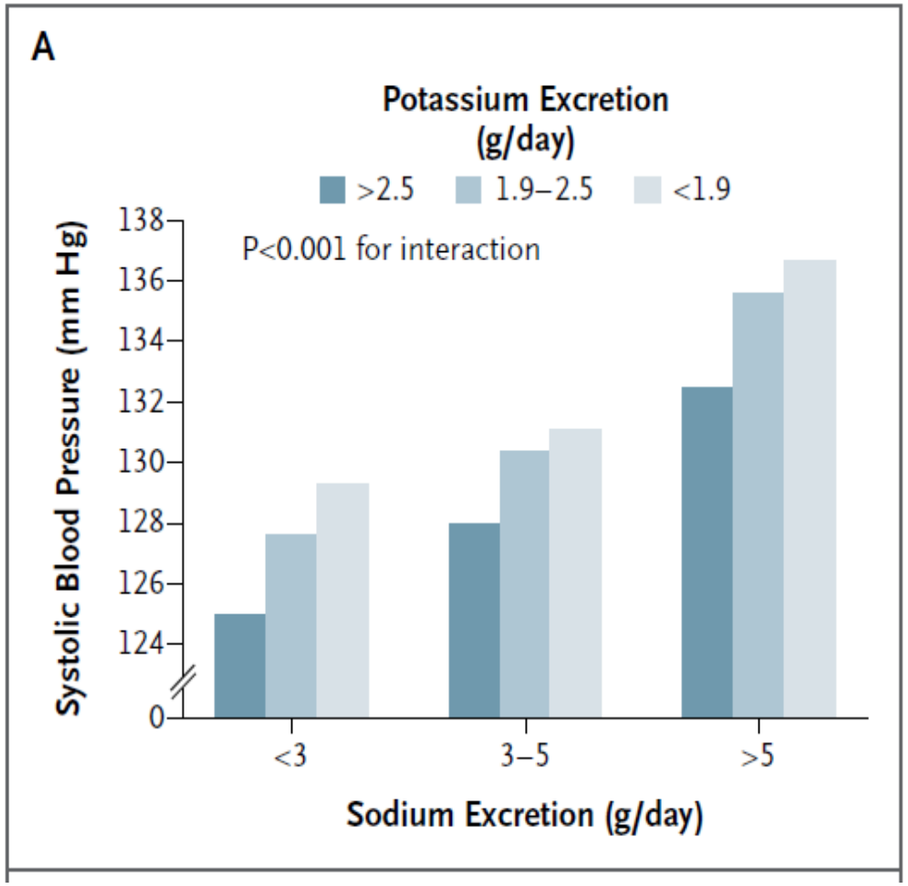
Supplement to: Mozaffarian D, Fahimi S, Singh GM, et al. Global sodium consumption and death from cardiovascular causes. N Engl J Med 2014;371:624-34.

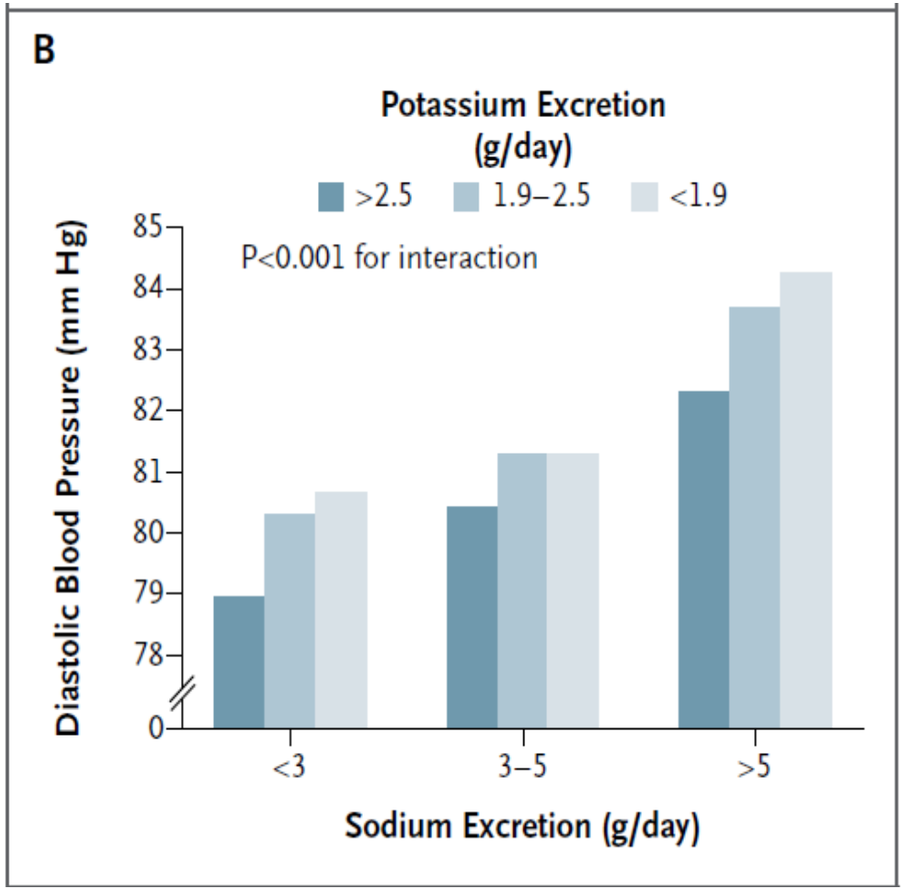
Impact of dietary salt reduction on blood pressure levels: systematic review and meta-analysis of randomized trials



Huang et al; European Heart Journal, 2019; 40 (Supplement 1) October 2019

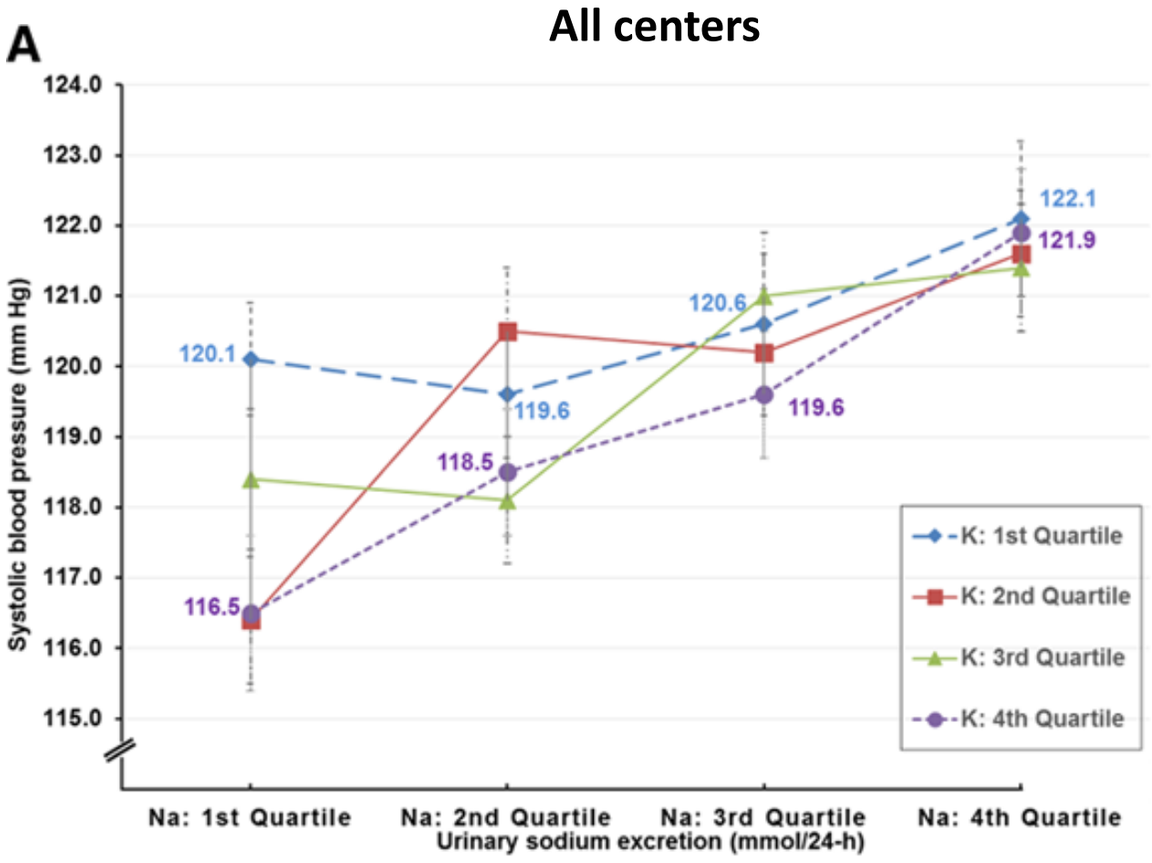
Mean Systolic and Diastolic Blood Pressure according to Sodium and Potassium Excretion in the PURE Study.

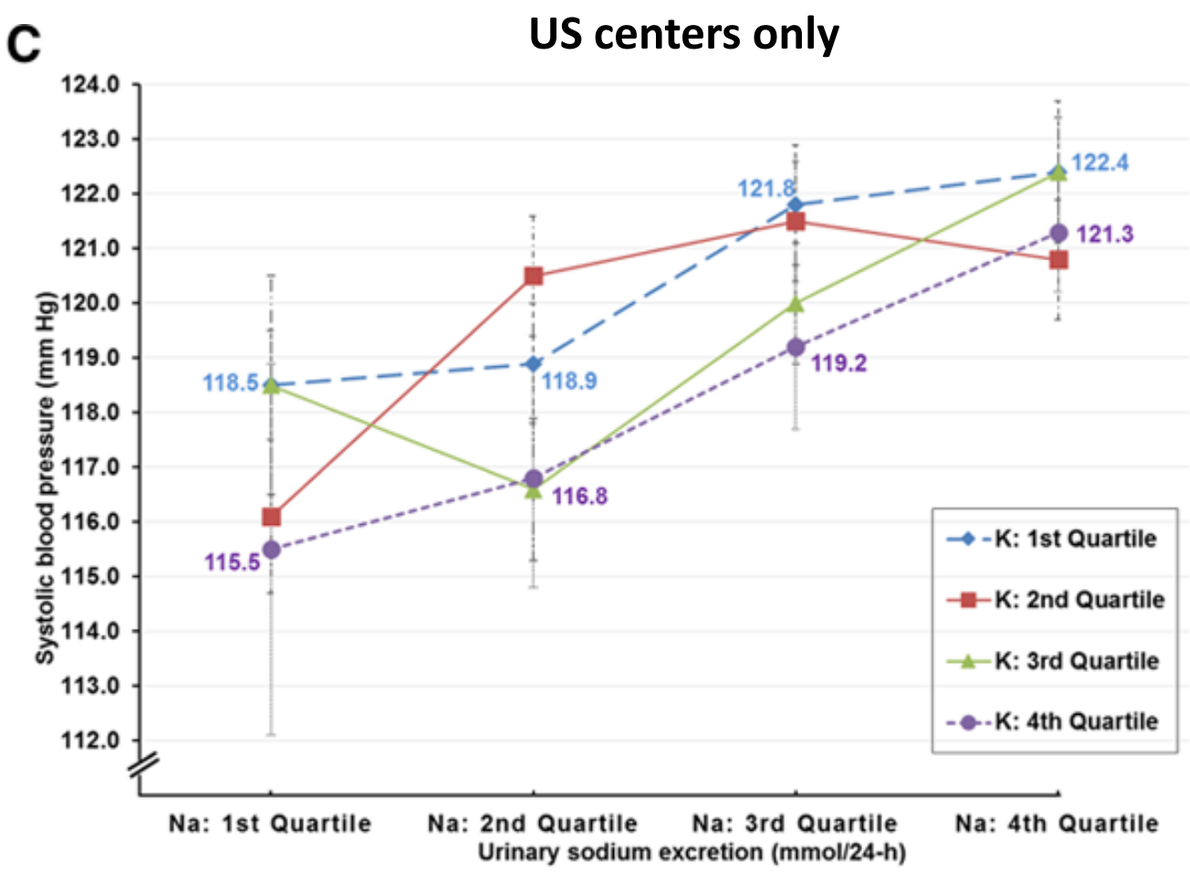




Mente et al, NEJM, 2014

Relation of Dietary Sodium (Salt) to Blood Pressure and Its Possible Modulation by Other Dietary Factors: The INTERMAP Study





Stamler J. et al. Hypertension. 2018;71:631-637

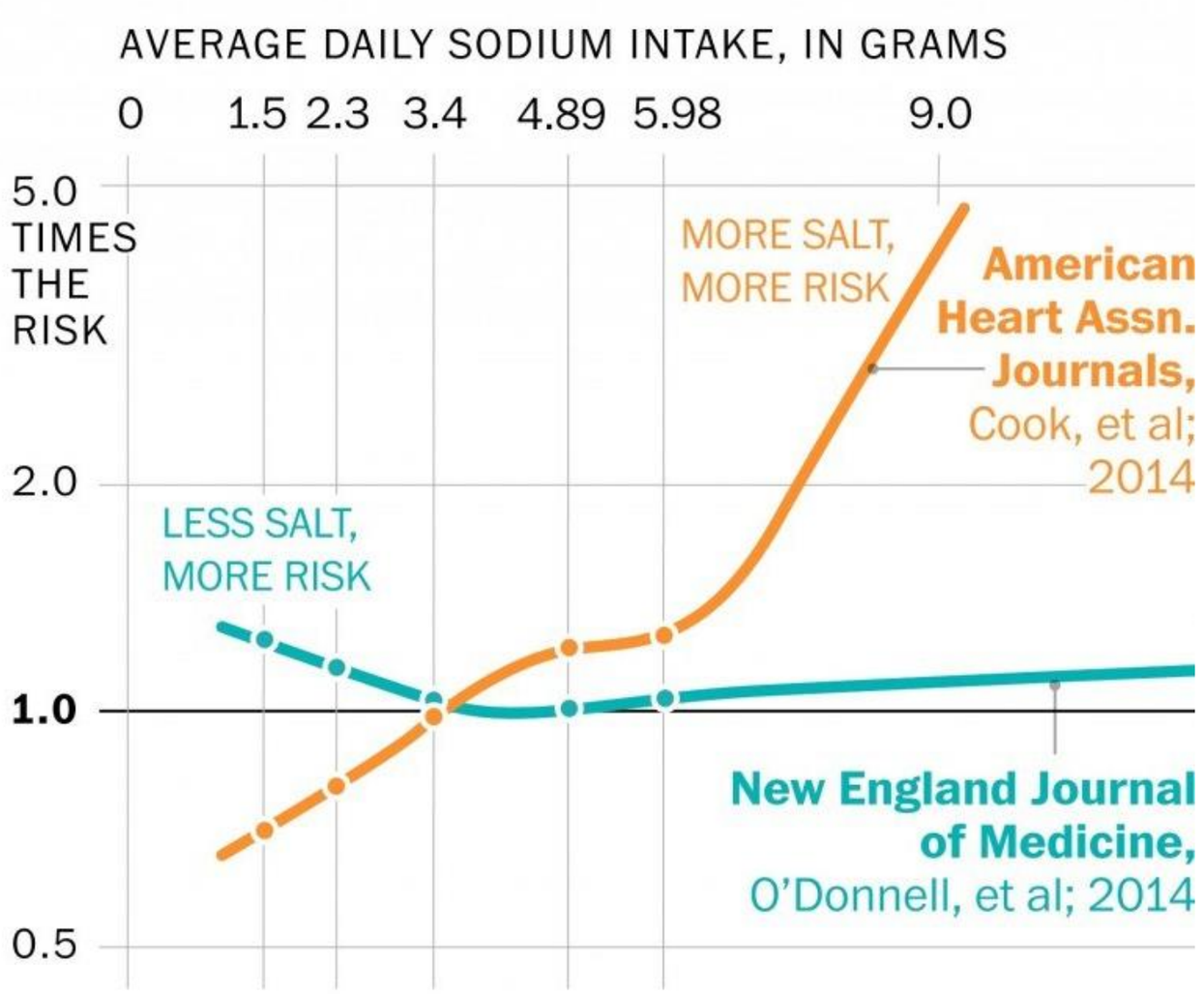
Doubts on the safety of a low sodium intake for the general population

Is a low salt intake really good for all?

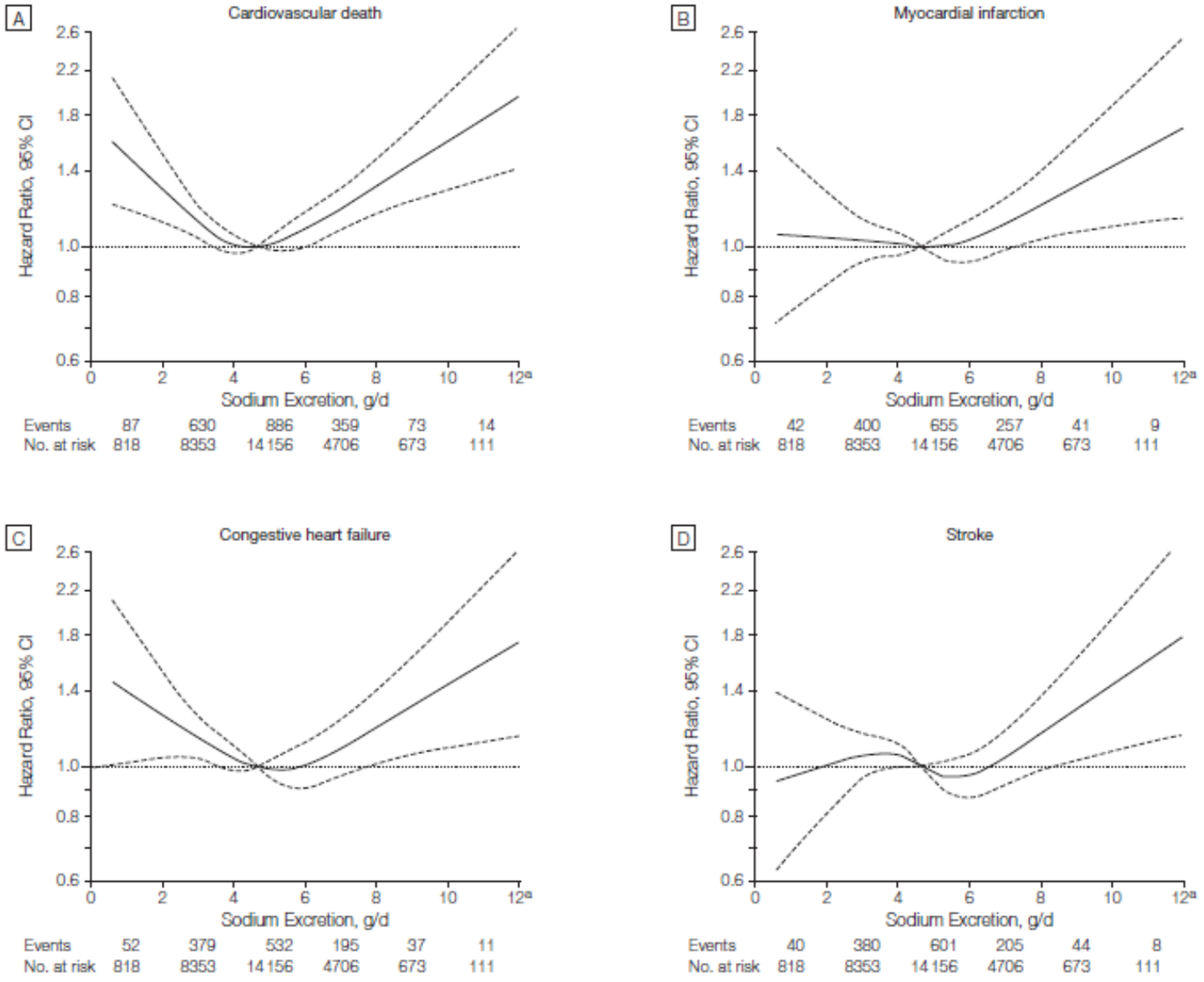
Are there dangers associated with a low salt intake, i.e. eating < 5-6 g of salt per day ?

Same recommendations for the general population and for patients with a CV risk ?

Risk of cardiovascular diseases according to sodium intake: the controversy

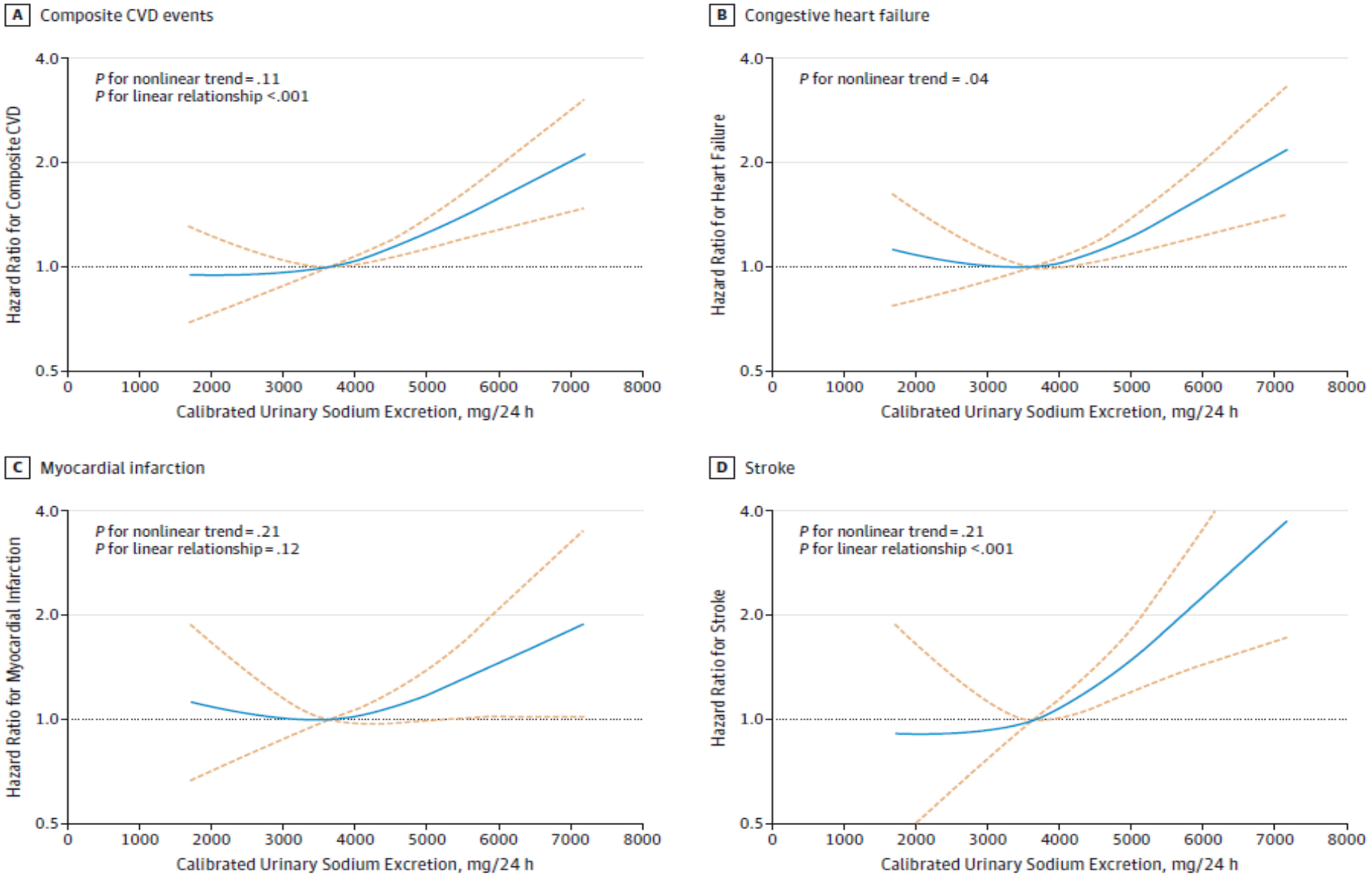


Salt intake and CV events in ONTARGET



O'Donnell, JAMA. 2011;306(20):2229-2238

Cardiovascular Diseases Associated With Calibrated 24-H Urinary Na Excretion in CKD patients: the CRIC prospective cohort (n=3757)



Mills et al, JAMA. 2016;315(20):2200-2210.

Questions regarding the PURE results

What about reverse causality ?

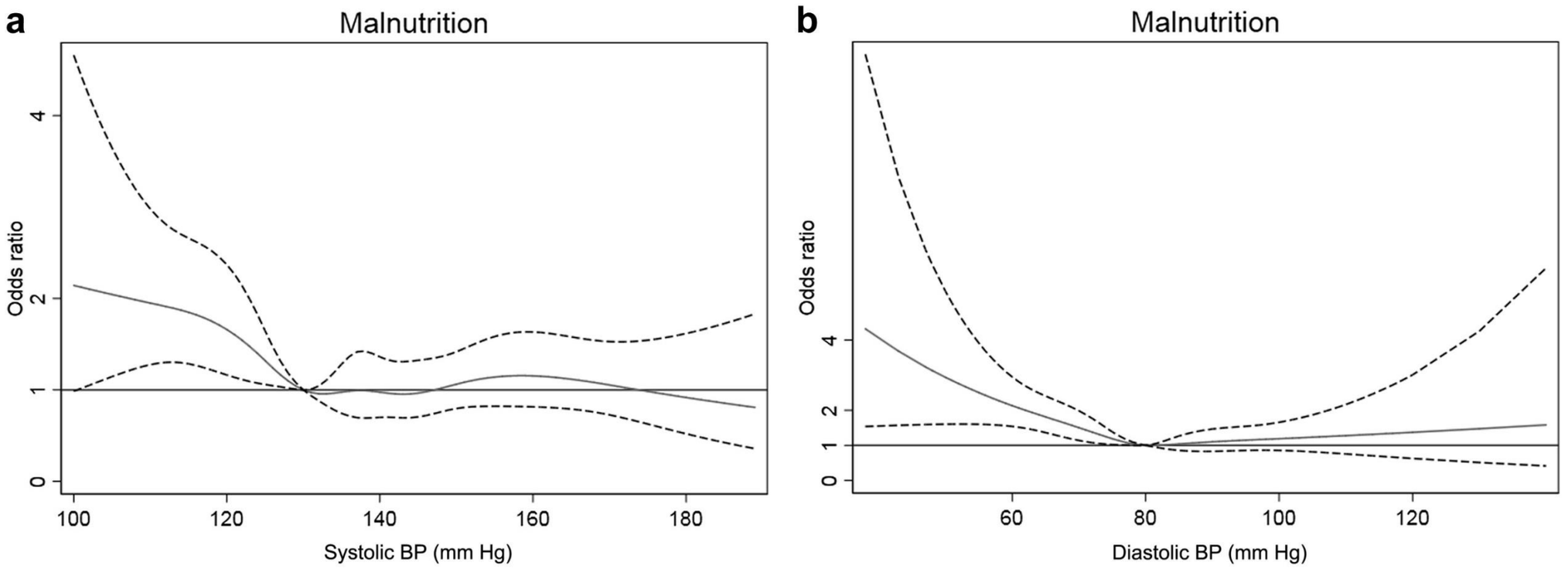
1) Low sodium intake → ↑ total and CV mortality

2) Baseline disease → low sodium intake and/or excretion

Baseline disease → ↑ total and CV mortality

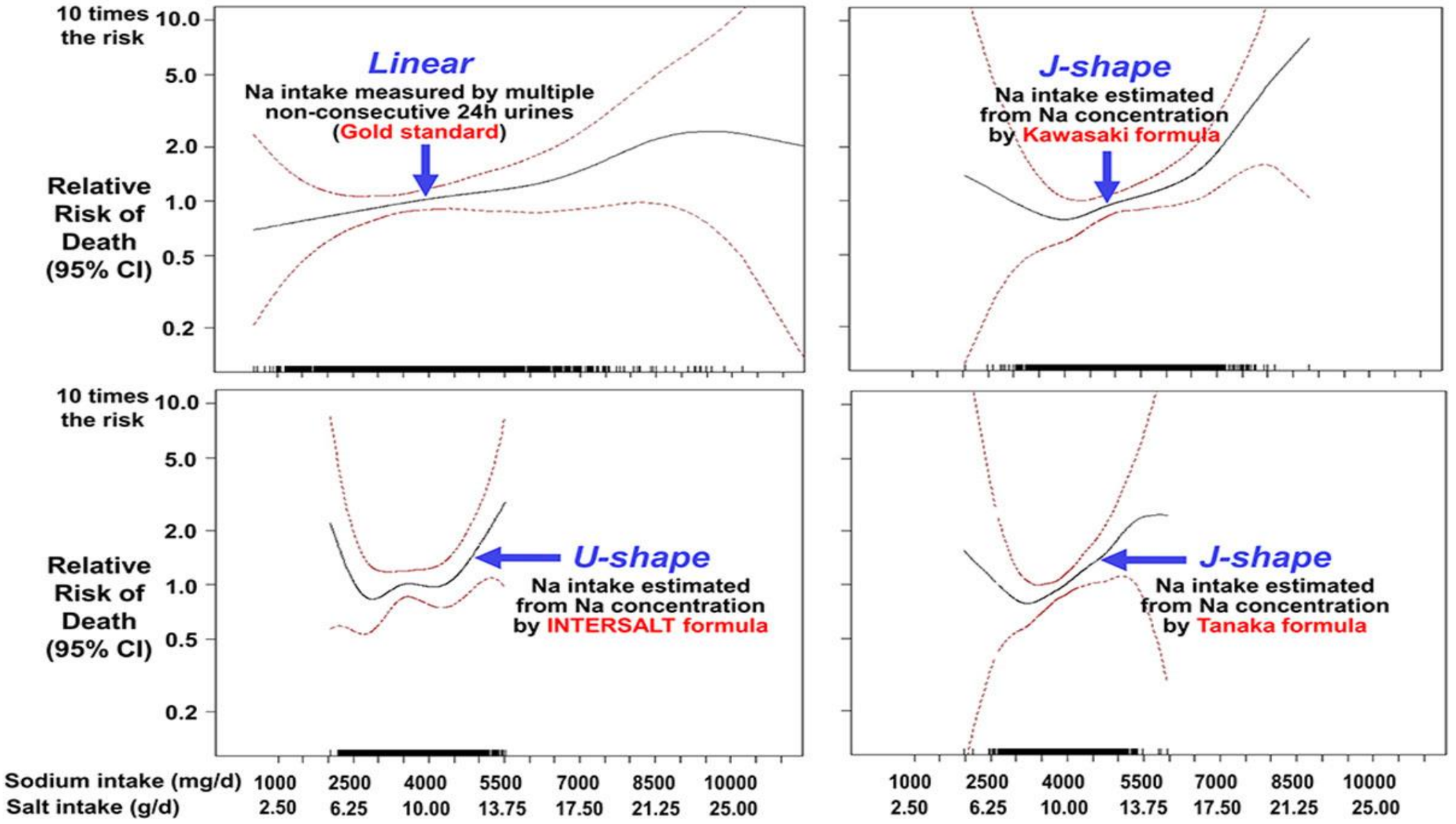
Who are these people eating less than 2 g of sodium per day and being at high risk of dying from a CV event ?

Blood pressure and odds for malnutrition-inflammation-cachexia syndrome in patients with CKD stages 3-5.



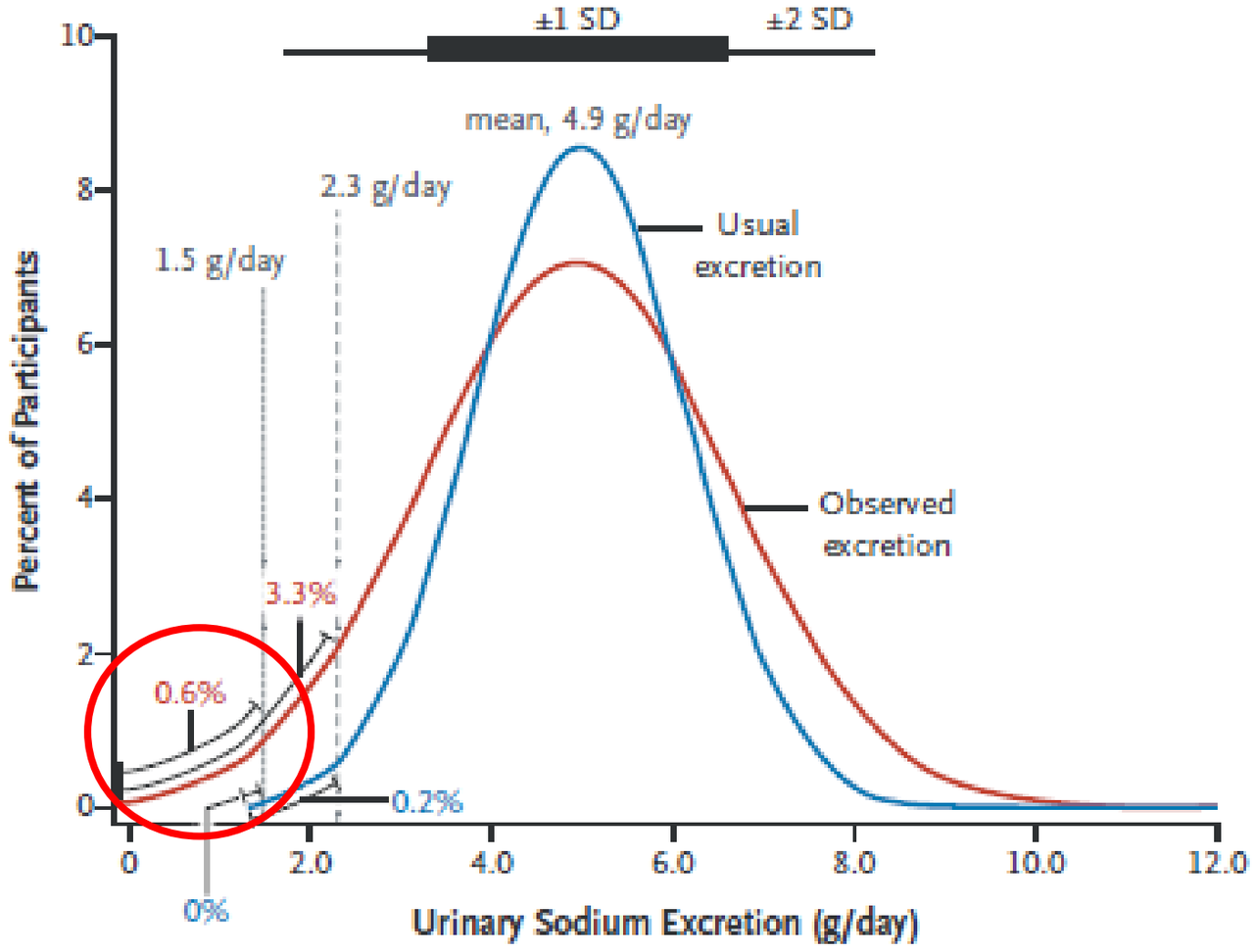
Blood pressure modifies outcomes in patients with stage 3 to 5 chronic kidney disease
Chiang, Heng-Pin et al. Kidney International. 2020; 97 (2), 402 - 413

The significant linear association between measured sodium (Na) intake and death is altered when using estimated Na intakes, Trials of Hypertension Prevention (TOHP), N=2974



Formulas to Estimate Dietary Sodium Intake From Spot Urine Alter Sodium-Mortality Relationship
Feng J. He , et al. Hypertension 2019

Distribution of Sodium and Potassium Excretion in 102,216 Study Participants of the PURE Observational Study



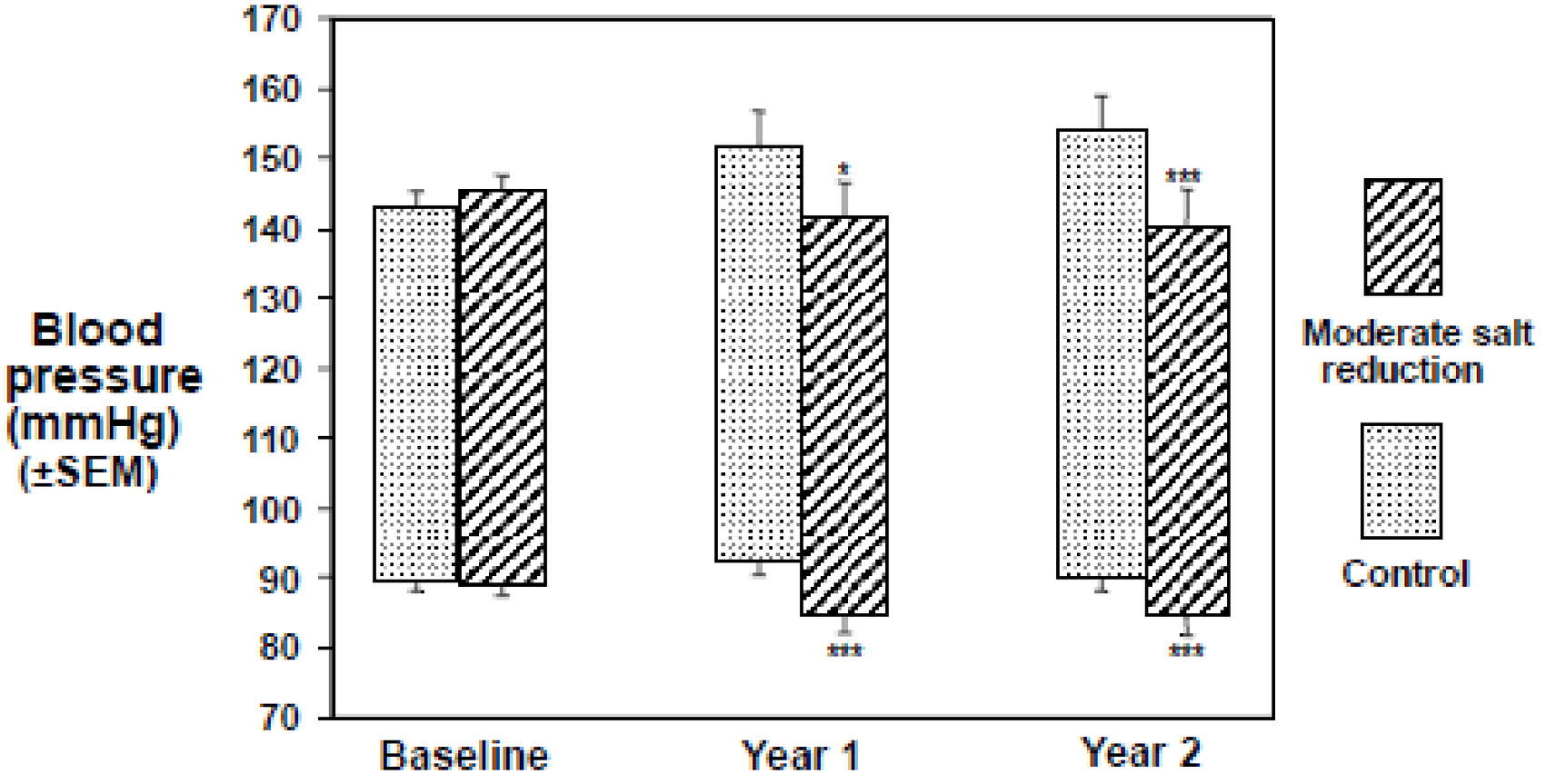
Mente et al, N Engl J Med 2014;371:601-11

Multivariable logistic regression of eating less than 5 g of salt per day in the Swiss population

N=1379	OR	95%CI	P value
Age, years	1.006	0.996;0.016	0.231
Sex (being women)	**1.73**	**1.10;2.72**	**0.018**
Current smoking (yes=1)	**0.62**	**0.36;1.04**	**0.072**
BMI < 25	1 (ref)		
Overweight	0.81	0.53;1.25	0.343
Obesity	**0.36**	**0.17;0.76**	**0.008**
French-speaking	1 (ref)		
German-speaking	0.60	0.40;0.91	0.015
Italian-speaking	0.61	0.35;1.07	0.085
Estimated protein intake (10g/day)	**0.56**	**0.47;0.65**	**<0.001**
Urinary K excretion (10 mmol/24h)	0.87	0.77; 0.98	0.026
Urinary Ca excretion (mmol/24h)	0.87	0.77;0.98	0.024
Urine volume (L/24h)	0.69	0.53;0.90	0.005

Age and sex were forced into the model.
The other variables needed to have P<0.10 to stay in the model.

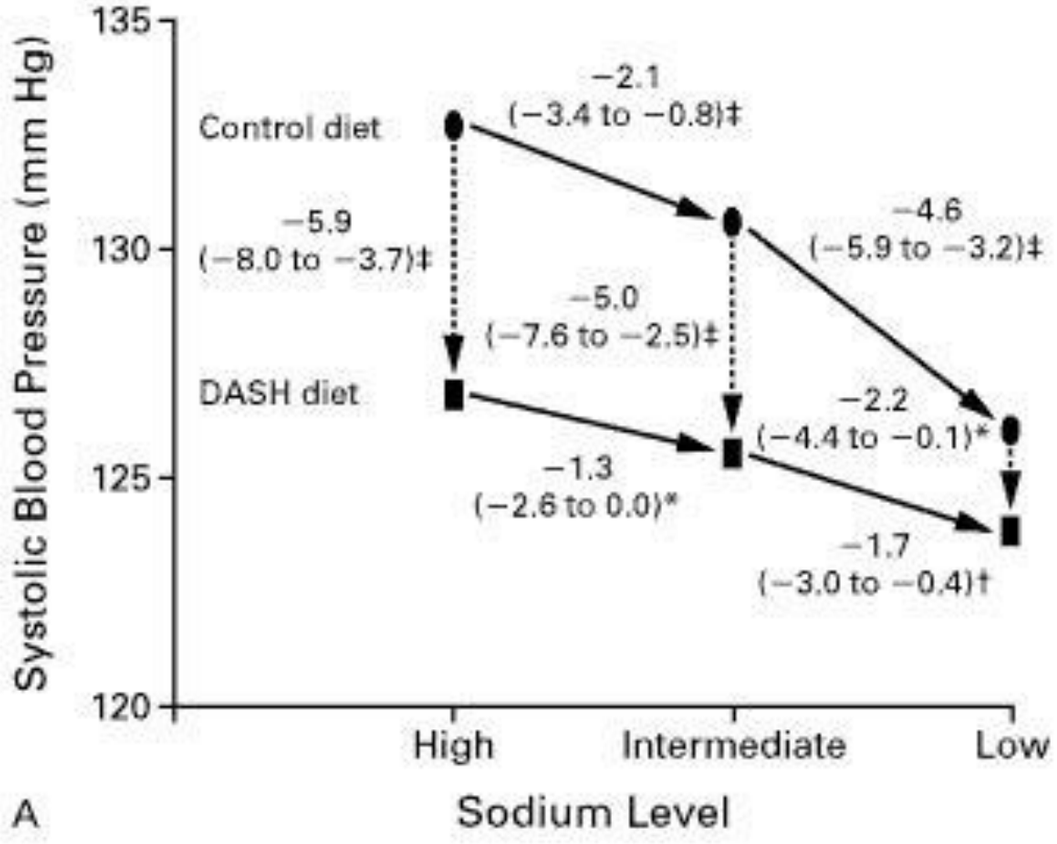
Intervention study in two Portuguese villages

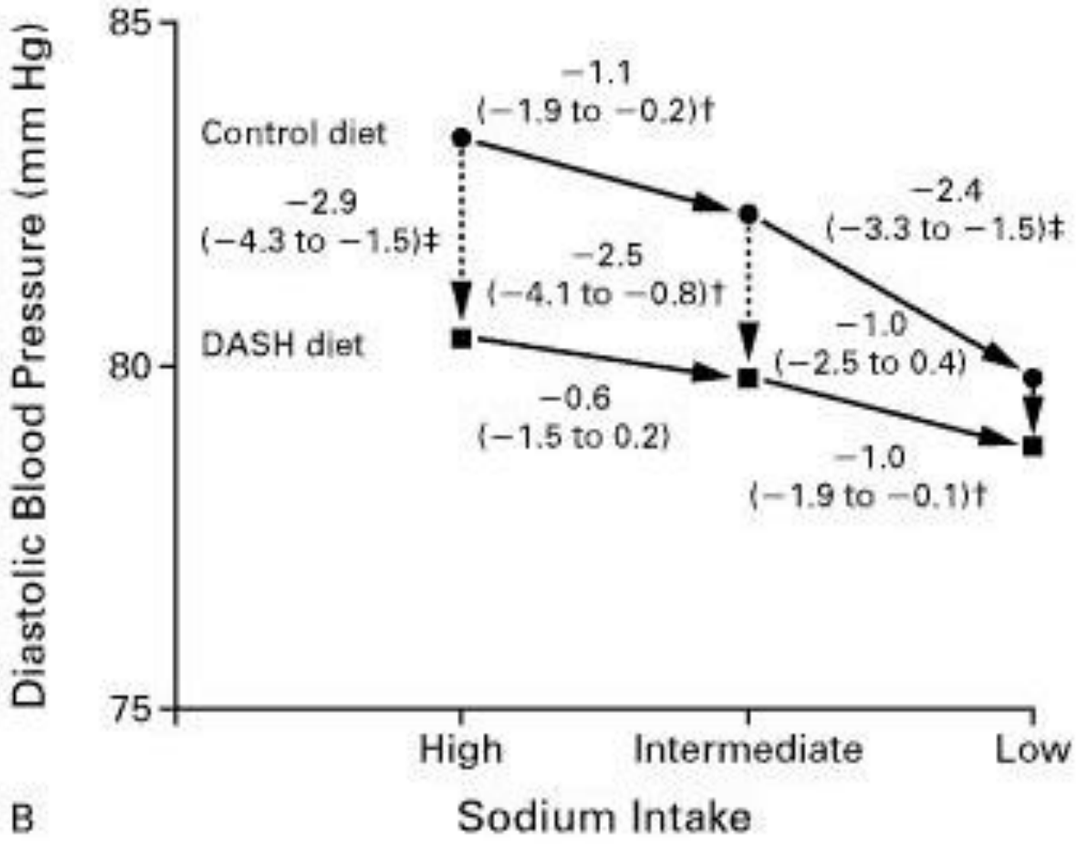


* P<0.05, *** P<0.001 compared to control group.

Forte JG et al, J Human Hypertens, 1989

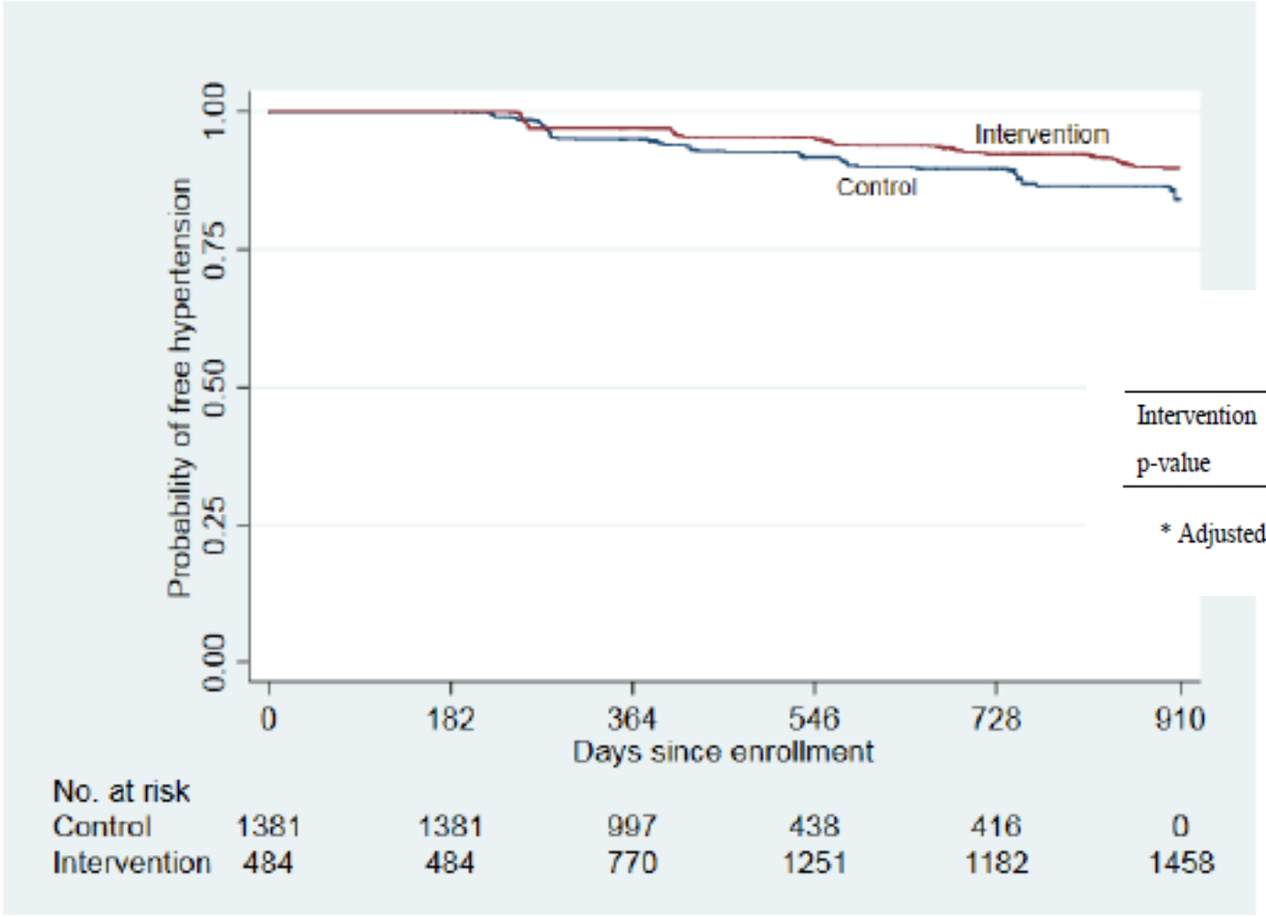
The Effect on Systolic BP and Diastolic BP of Reduced Sodium Intake and the DASH Diet.





Sacks et al, NEJM, 2001; Jan 4;344(1):3-10

Rate of progression toward hypertension after replacement of normal salt with potassium-enriched substitutes in 6 Peruvian villages



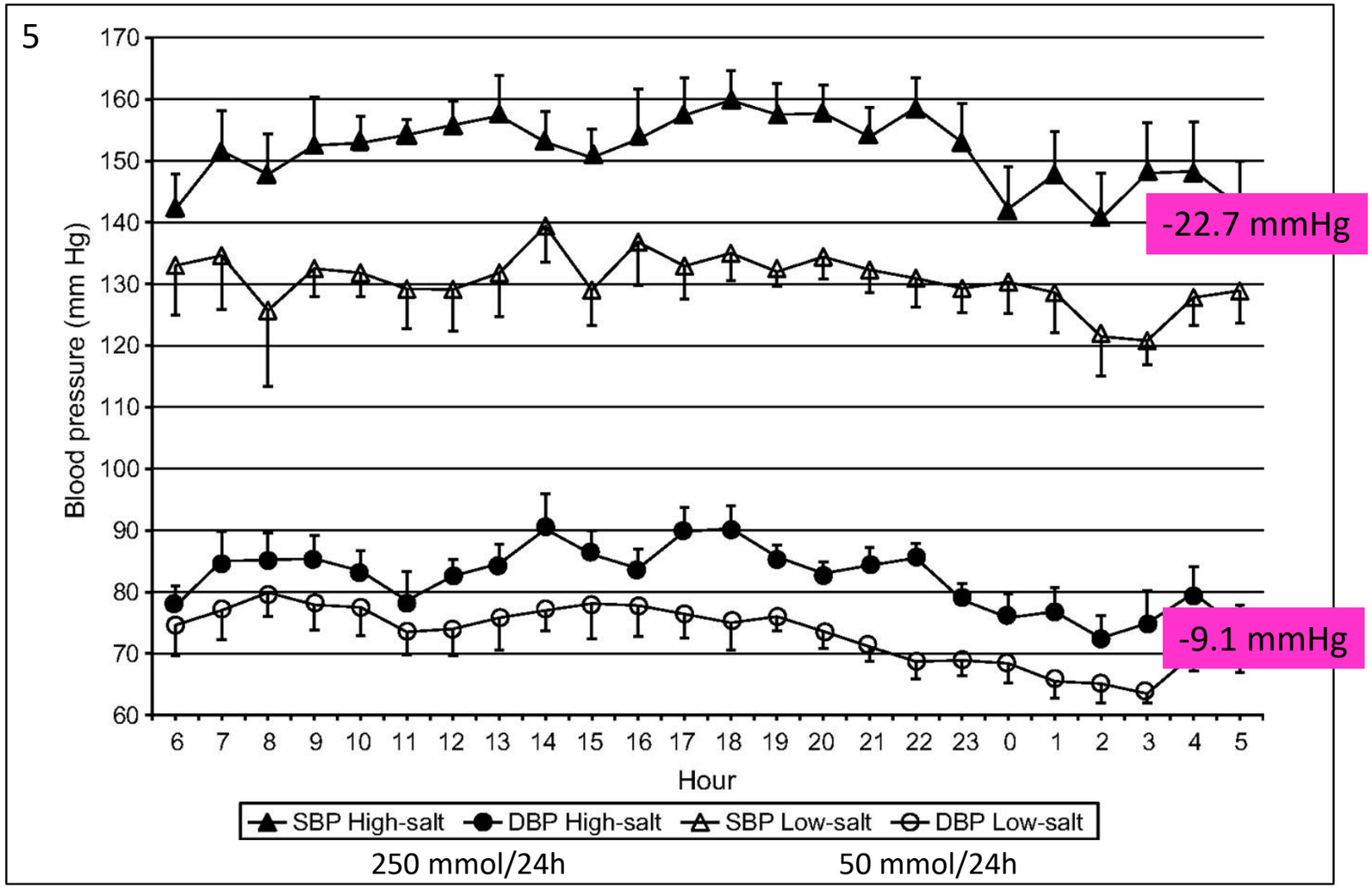
Outcome	Unadjusted model HR (95% CI)	Adjusted model HR (95% CI)
Intervention	0.49 (0.34 – 0.71)	0.45 (0.31 – 0.66)
p-value	<0.001	<0.001

* Adjusted by age, sex, education, wealth index, and body mass index

Bernabe-Ortiz A et al.Trials. 2014 Mar 25;15:93.

Bernabe-Ortiz A et al, European Heart Journal, in press

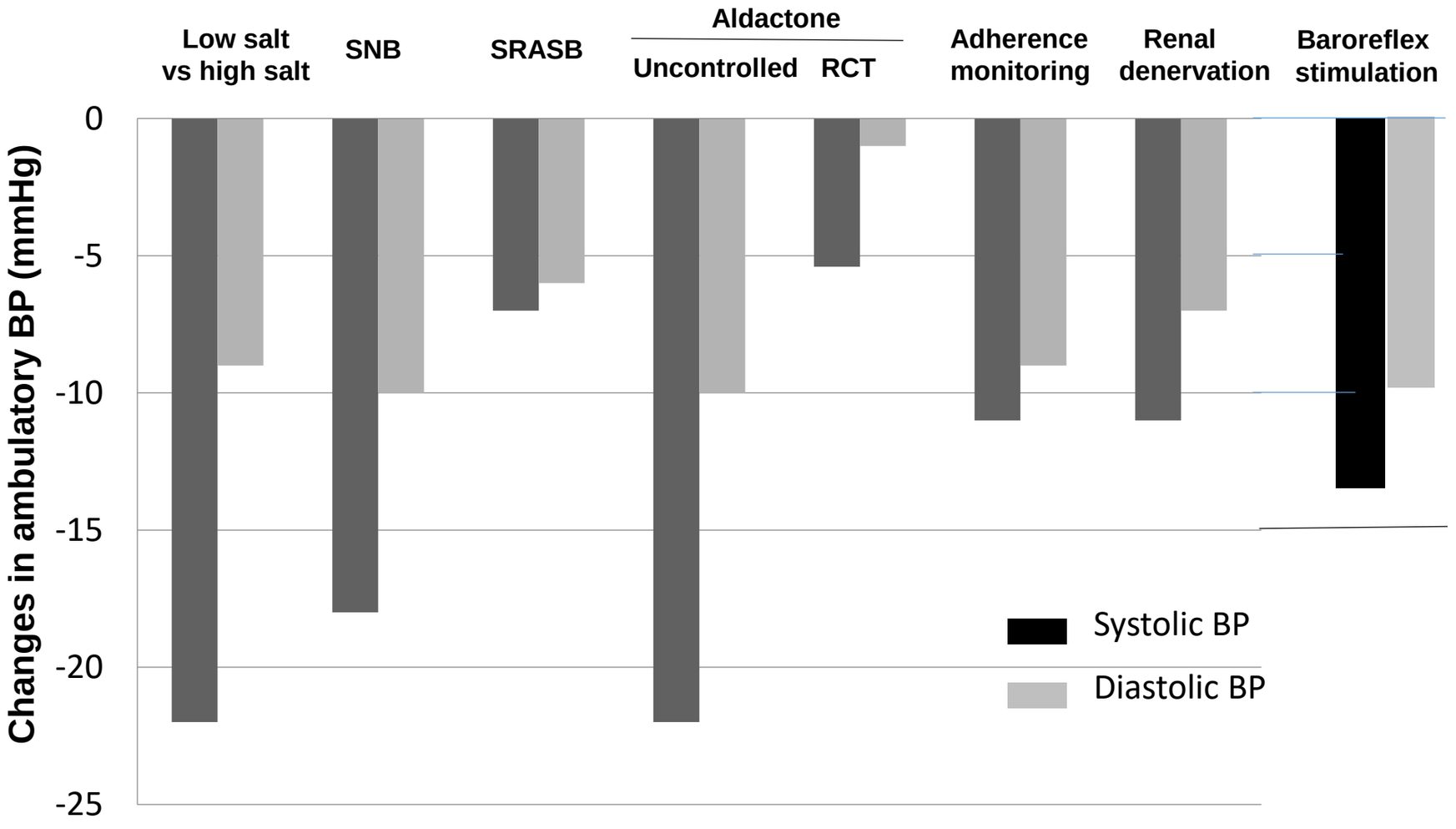
Effect of sodium restriction on ambulatory BP in patients with resistant hypertension



N=12
Mean Nr drugs: 3.4

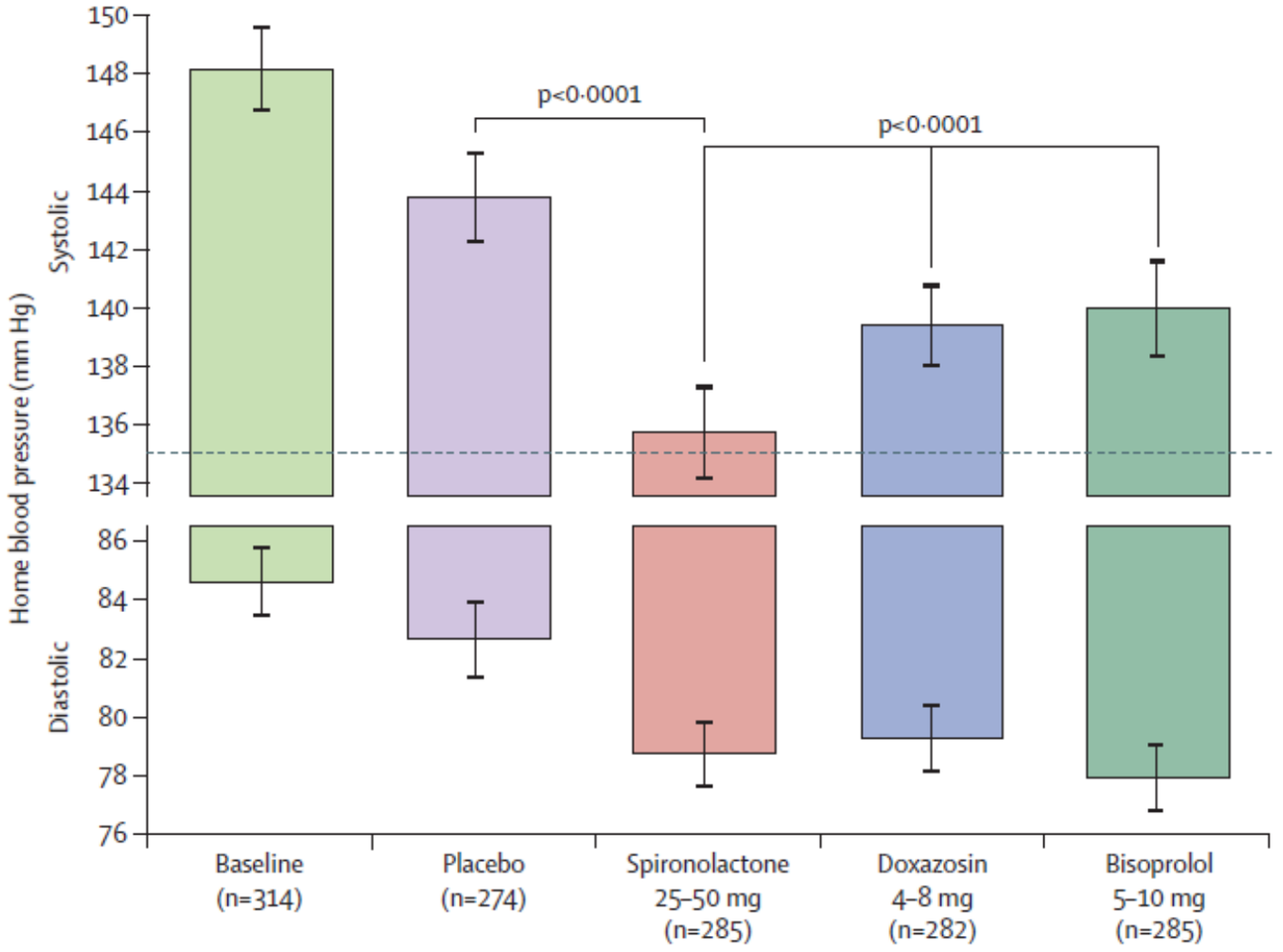
Pimenta, E. et al. Hypertension 2009;54:475-481

Therapeutic approaches in resistant hypertension



SNB: sequential nephron blockade, SRASB: sequential RAS blockade,
RCT: randomized control trial

Treatment of resistant hypertension: what drug as #4 ?



Williams B, *Lancet* 2015; 386: 2059–68

Comparative health benefits of physical activity and salt reduction

Health Benefit	Physical Activity	Reduced Sodium Intake
Reduces BP	(Whelton et al., 2002; Pescatello et al., 2004)	(Law et al., 1991; Aburto et al., 2013)
Reduces BP increase with age	(Carnethon et al., 2010)	(Elliott et al., 1996; Van Vliet & Montani, 2008; Takase et al., 2015)
Improved endothelial function	(Seals et al., 2009; Pahkala et al., 2011)	(Dupont et al., 2013; Jablonski et al., 2013b; Jablonski et al., 2009)
Reduced arterial stiffness	(Seals et al., 2009; Kawano et al., 2013)	(Adamopoulos et al., 2010; Safar et al., 2009; Avolio et al., 1986; Jablonski et al., 2013a)
Improved cognitive function; reduced risk of dementia	(Brown et al., 2012; Khan et al., 2012; DeFina et al., 2013)	(Fiocco et al., 2012; Salerno-Kennedy & Cashman, 2007; Afsar, 2013)
Reduced inflammation	(Hamer et al., 2012)	(Rodrigues Telini et al., 2013; Yilmaz et al., 2012)
Reduced risk of cardiovascular disease	(Khan et al., 2012; Cornelissen & Fagard, 2005; Kodama et al., 2009)	(Cook et al., 2007; Cook et al., 2009; Aburto et al., 2013; Cook et al., 2014; Yang et al., 2011; Rodriguez et al., 2011)
Reduced risk of stroke	(Khan et al., 2012)	(Perry & Beevers, 1992; Gardener et al., 2012; Aburto et al., 2013)
Reduced risk of coronary heart disease	(Khan et al., 2012)	(Aburto et al., 2013)
Reduced insulin resistance and risk of diabetes	(Cornelissen & Fagard, 2005; Khan et al., 2012)	(He & MacGregor, 2008)
Reduced risk of osteoporosis	(Khan et al., 2012)	(He & MacGregor, 2008; Kim et al., 2015)
Reduced risk of stomach, renal cell & bladder cancers	(Singh et al., 2014; Keimling et al., 2014; Moore et al., 2008)	(Deckers et al., 2013; Brinkman & Zeegers, 2008; Hu et al., 2011)
Reduced risk of colon & breast cancers	(Khan et al., 2012)	–
Reduced risk of depression	(Khan et al., 2012)	–
Reduced all cause mortality	(Khan et al., 2012; Kodama et al., 2009)	(Yang et al., 2011)

Turner and Avolio. International Journal of Sport Nutrition and Exercise Metabolism, 2016, 26, 377 -389

Effect of dietary sodium intake on sodium elimination in sweat

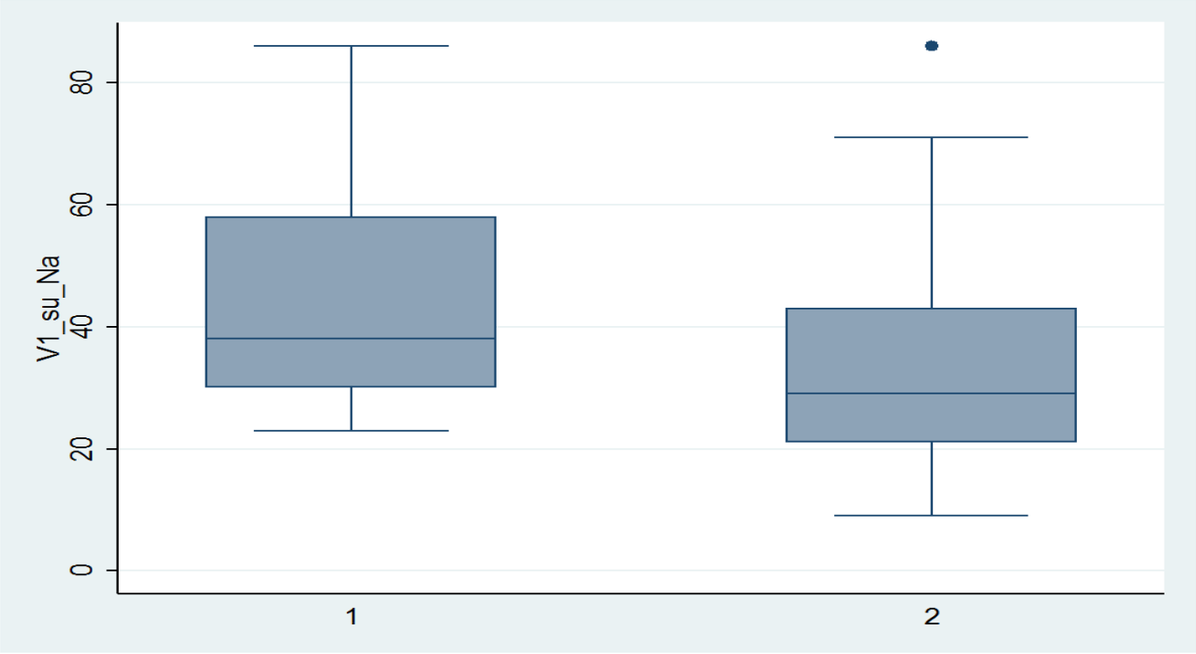
Variable	HS	LS	p
Weight (kg)	63.7	63.1	0.04
eGFR (CKD-EPI)	105.8	104.0	0.27
Blood sodium	140.2	139.4	0.05
24h urinary sodium excretion (mmoles)	235.2	37.9	<0.001
24h urinary chloride excretion	240.4	39.0	<0.001
24h urinary potassium excretion	62.2	71.3	0.2
24h urinary salt excretion	13.8	2.2	<0.001
Sweat sodium concentration (mmol/l)	44.9	34.6	0.01
Sweat chloride concentration	25.6	17.8	0.02
Sweat potassium concentration	8.1	10.4	0.01

Braconnier et al. J Hypertens. 2020 Jan;38(1):159-166.

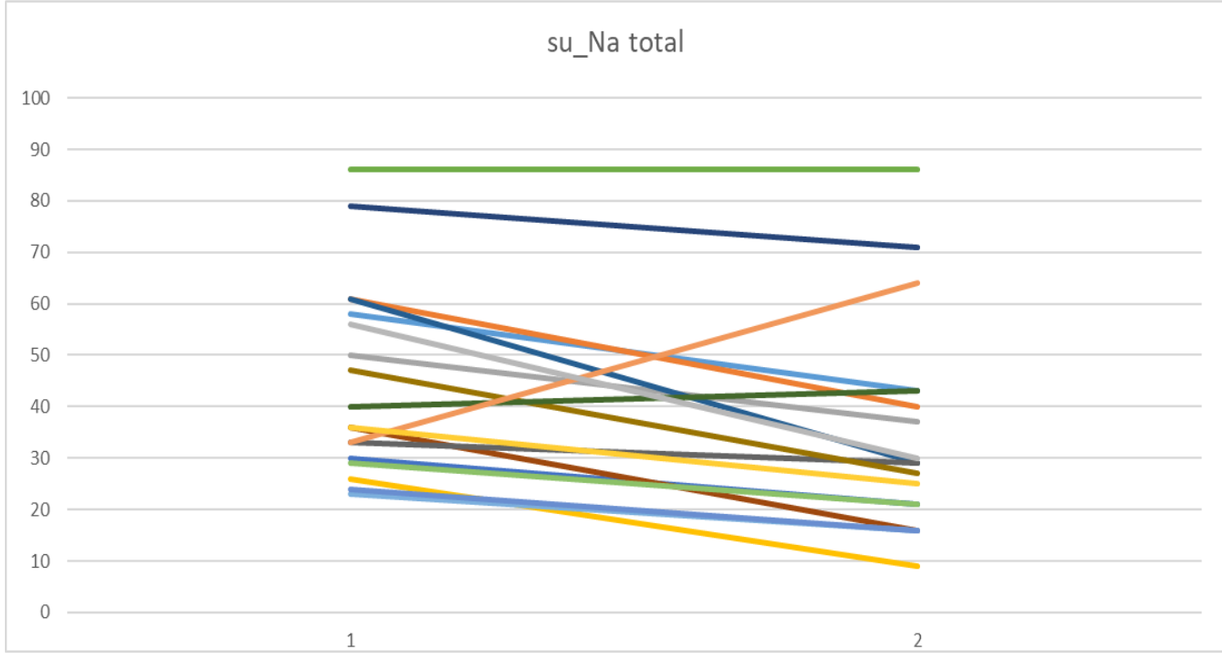
Effect of dietary sodium intake on sodium elimination in sweat: changes in sweat sodium concentration

High salt

Low salt



Individual changes

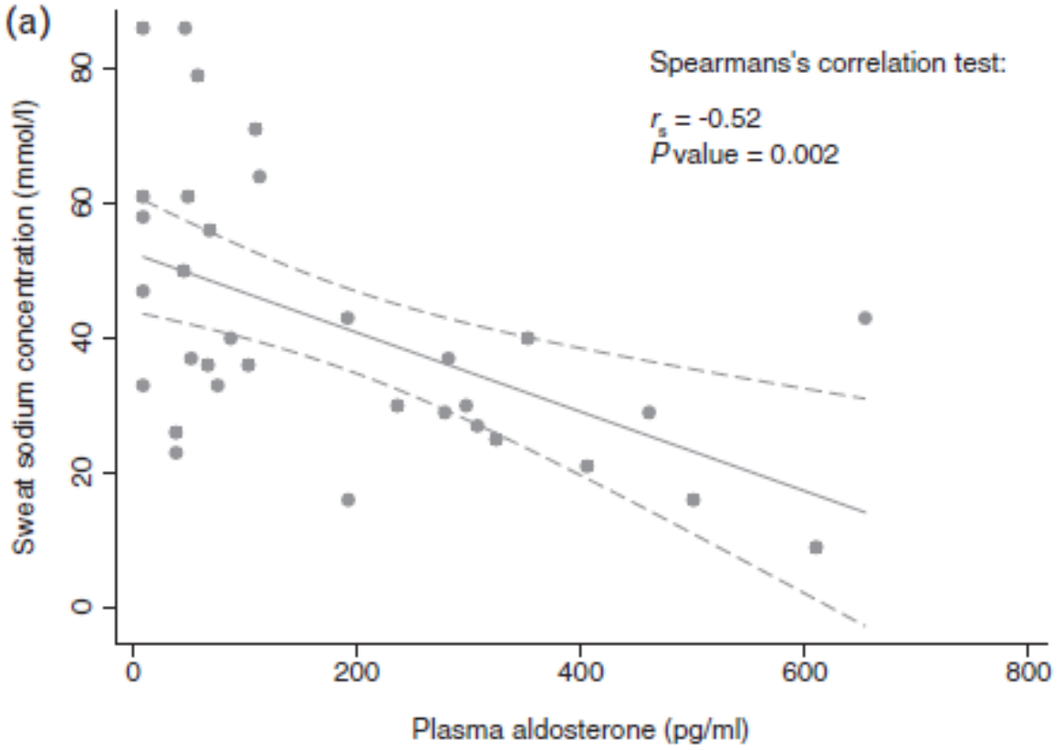


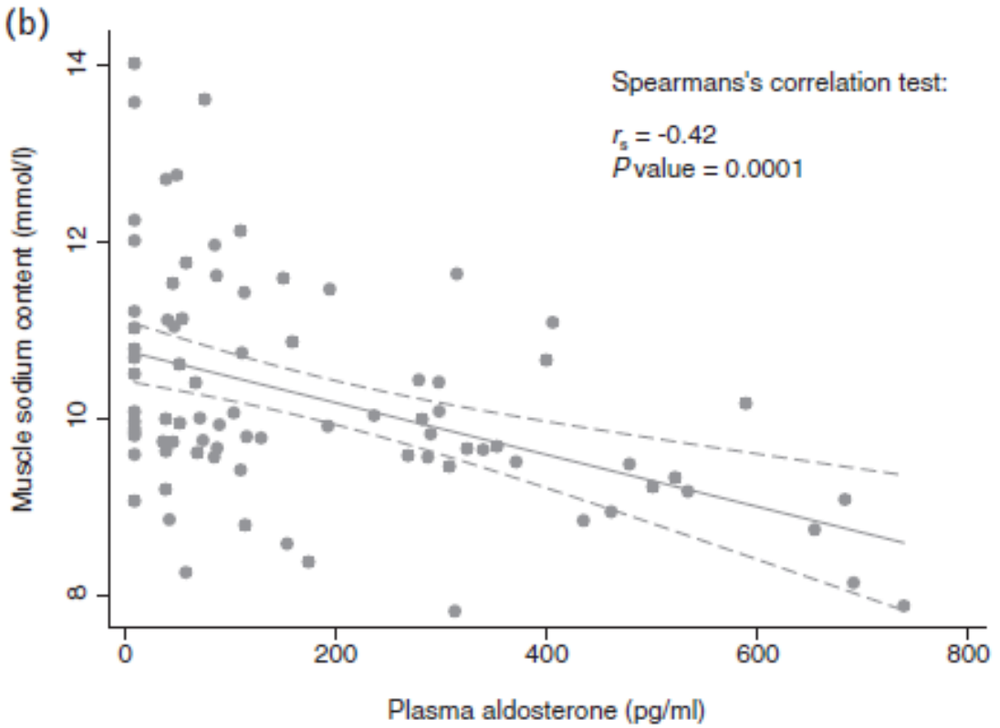
44.9±18 (mmol/l)

34.6±20.7 (mmol/l)

Braconnier et al. J Hypertens. 2020 Jan;38(1):159-166.

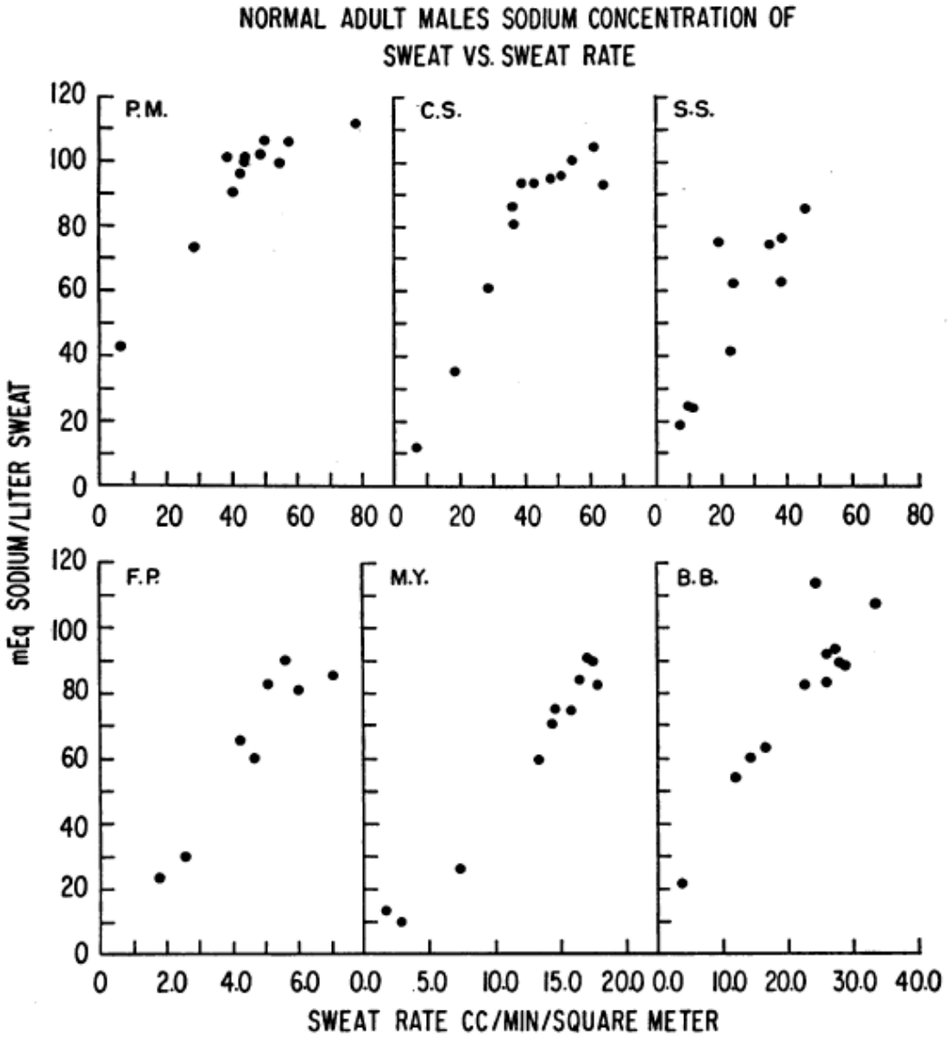
Correlation between sweat sodium and muscle sodium with plasma aldosterone in healthy subjects.





Braconnier et al. J Hypertens. 2020 Jan;38(1):159-166.

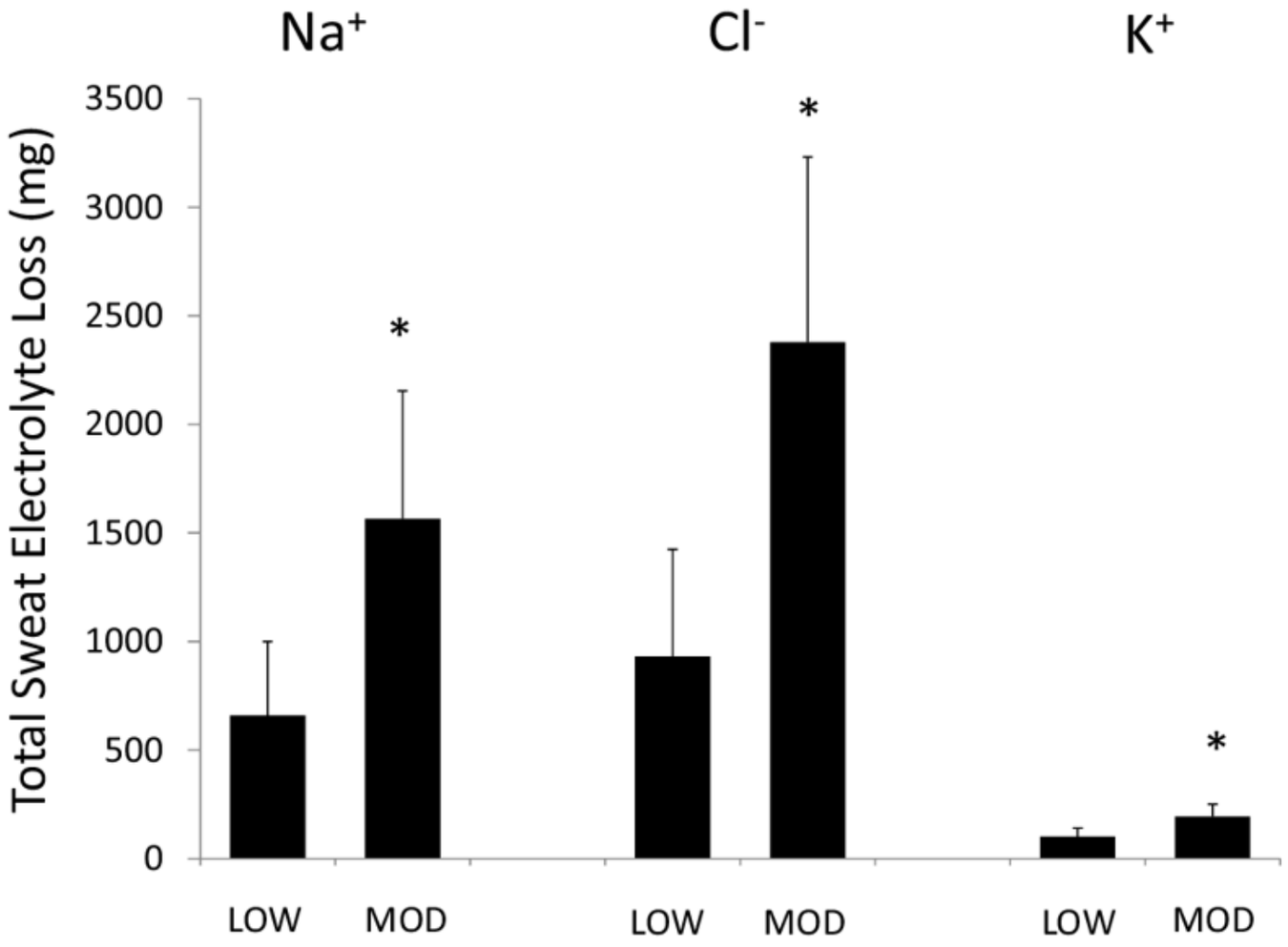
Sodium secretion and reabsorption in the human eccrine sweat gland



Subject	Range of sweat rate	Range of sodium concentration	Sweat rate at which sodium concentration is 70 mEq/L
	ml/min/m²	*mEq/L*	*ml/min/m²*
PM	6.7–65.6	43–111	28
CS	5.9–63.5	12–104	31
SS	7.2–45.1	19– 85	36
FP	1.8– 7.1	24– 90	5
MY	1.7–17.9	10– 91	15
BB	3.5–32.9	21–107	19

Cage GW, Dobson RL. J Clin Invest. 1965;44(7):1270-1276.

Loss of electrolytes during a low or moderate exercise in healthy subjects



LOW: 45% of VO2max
MOD: 65% of VO2max

Baker L et al. European Journal of Applied Physiology. 2019; 119 (2); 361–375

Does Replacing Sodium Excreted in Sweat Attenuate the Health Benefits of Physical Activity?

- One hour of exercise per day at commonly achieved sweat rates and sweat sodium concentrations results in losses of 20–80 mmol of sodium.
- Individuals with a sodium intake of ~150 mmol/day may excrete 10–50% of their dietary sodium in sweat by exercising for 30–60 min/day.

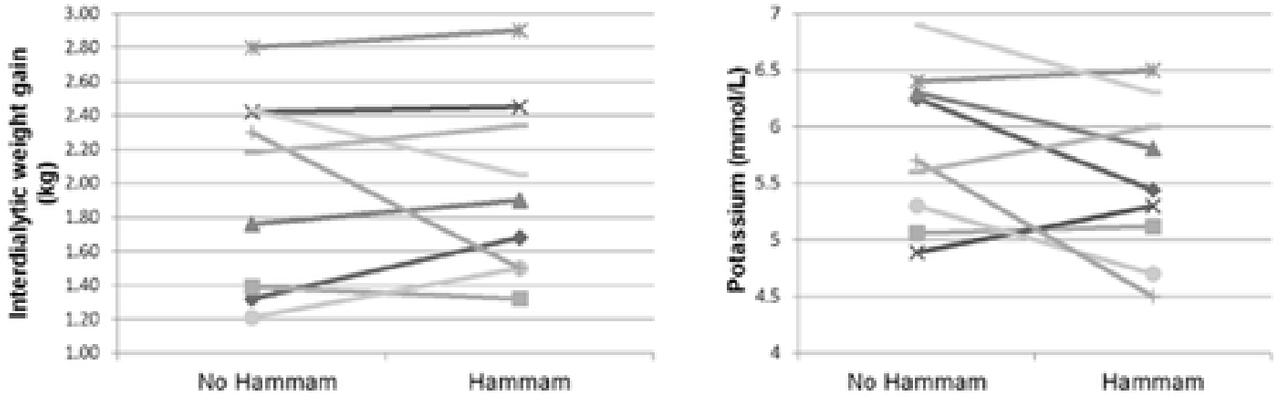
Table 2 Sodium Loss in Sweat (mmol) at Various Sweat Rates and Sweat Sodium Concentrations Per Hour of Physical Activity

	Sweat sodium concentration (mmol/L)				
Sweat rate (L/h)	10	20	40	60	90
0.2	2	4	8	12	18
0.5	5	10	20	30	45
1.0	10	20	40	60	90
1.5	15	30	60	90	135
2.0	20	40	80	120	180
3.0	30	60	120	180	270

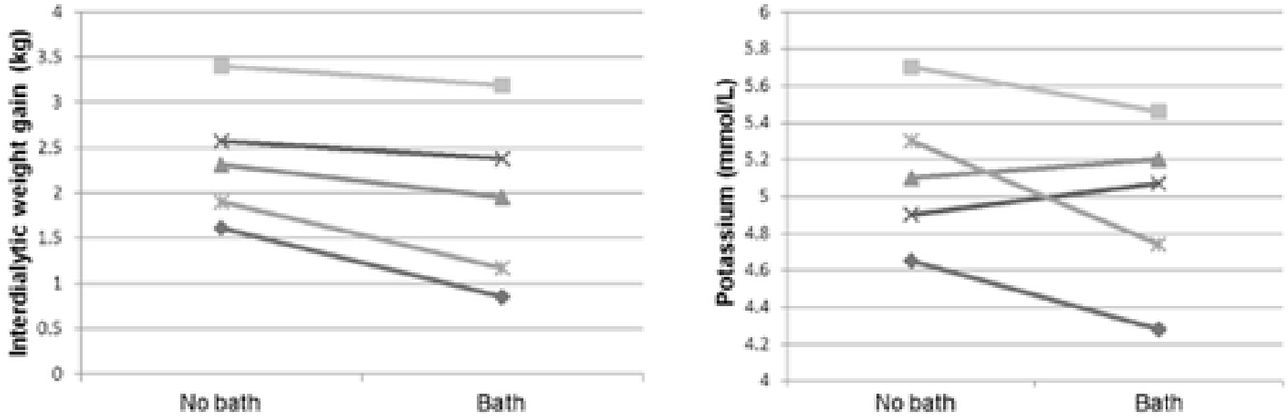
Should sodium losses during physical activity be fully compensated ?

Stimulated sweating as a therapy to reduce interdialytic weight gain and improve potassium balance in chronic hemodialysis patients: A pilot study

SFAX



LAUSANNE

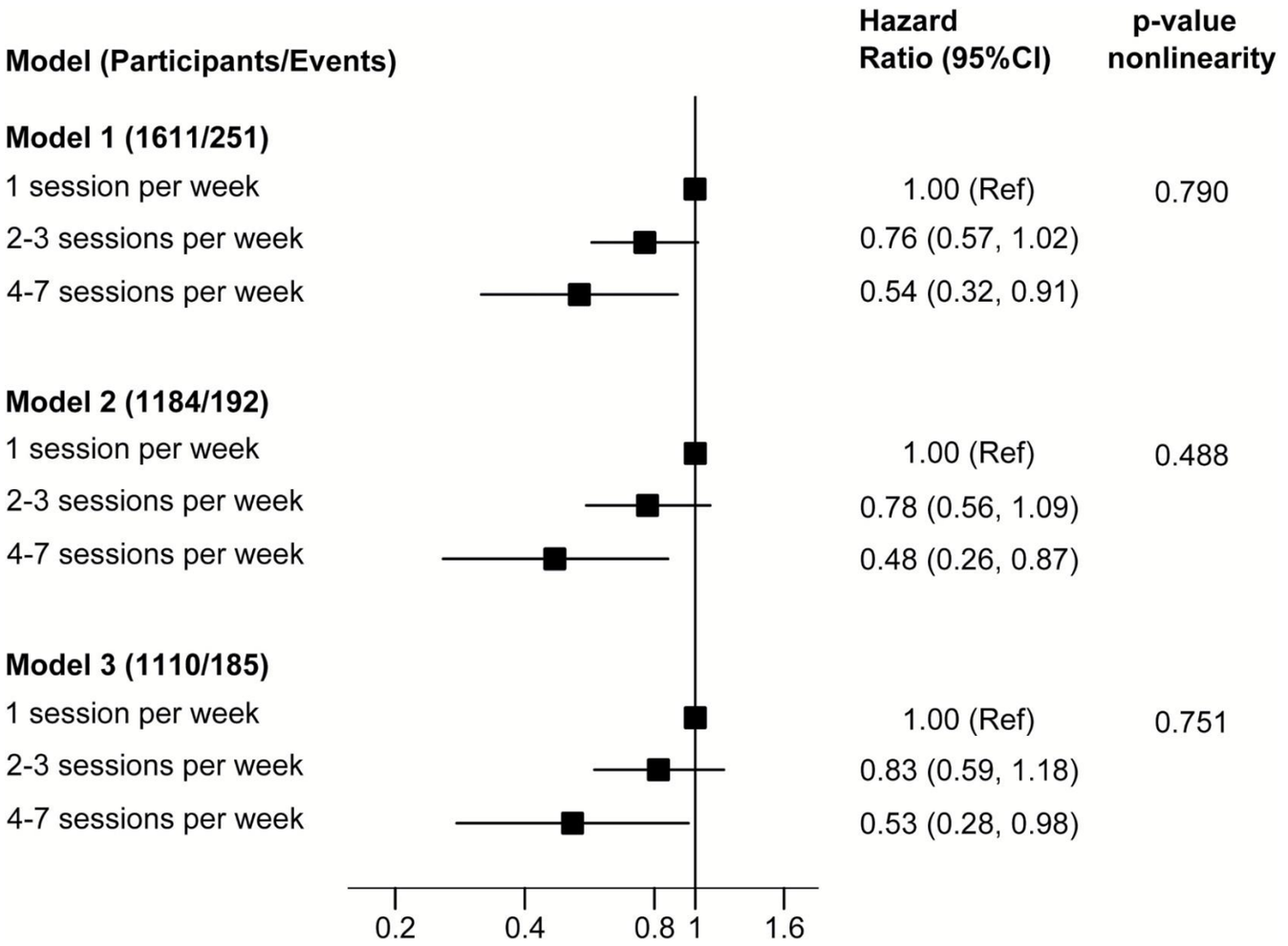


2.3 ±0.9 to 1.8 ± 1.0 (p<0.004)

5.9 ±0.8 to 5.5 ± 0.9 (p<0.04)

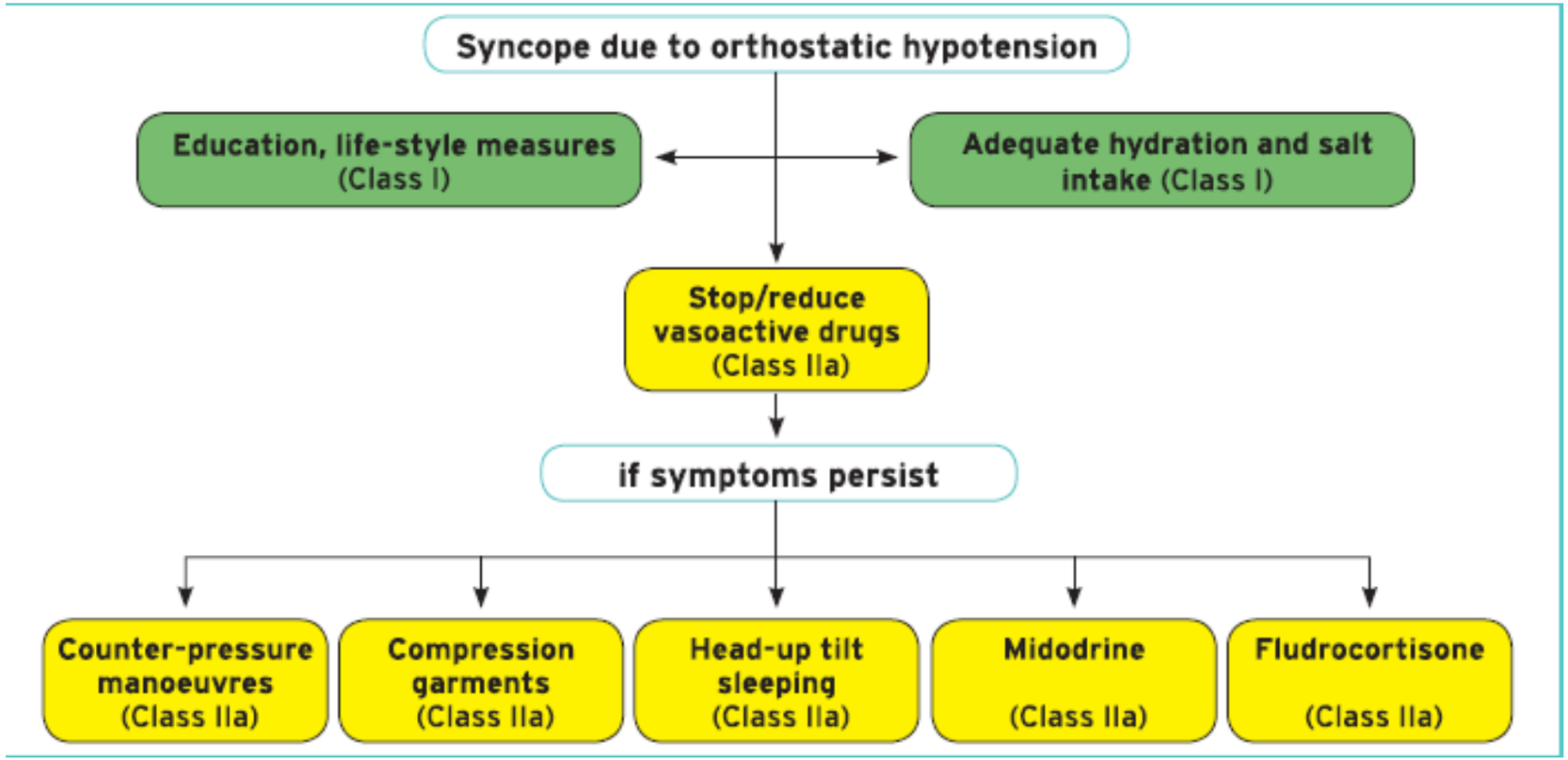
Pruijm, M et al. Hemodialysis International, 2013; 17 (2): 240-248

Risk of hypertension according the frequency of sauna: a prospective cohort of 1621 men aged 42-60 followed for 25 years



Zaccardi F et al. American Journal of Hypertension, 2017; 30 (11), 1120–1125, https://doi.org/10.1093/ajh/hpx102

Salt in patients with orthostatic hypotension



The expansion of extracellular volume is an important goal.
In the absence of hypertension, patients should be instructed to have a sufficient salt and water intake, **targeting 2–3 L of fluids per day and 10 g of sodium chloride**

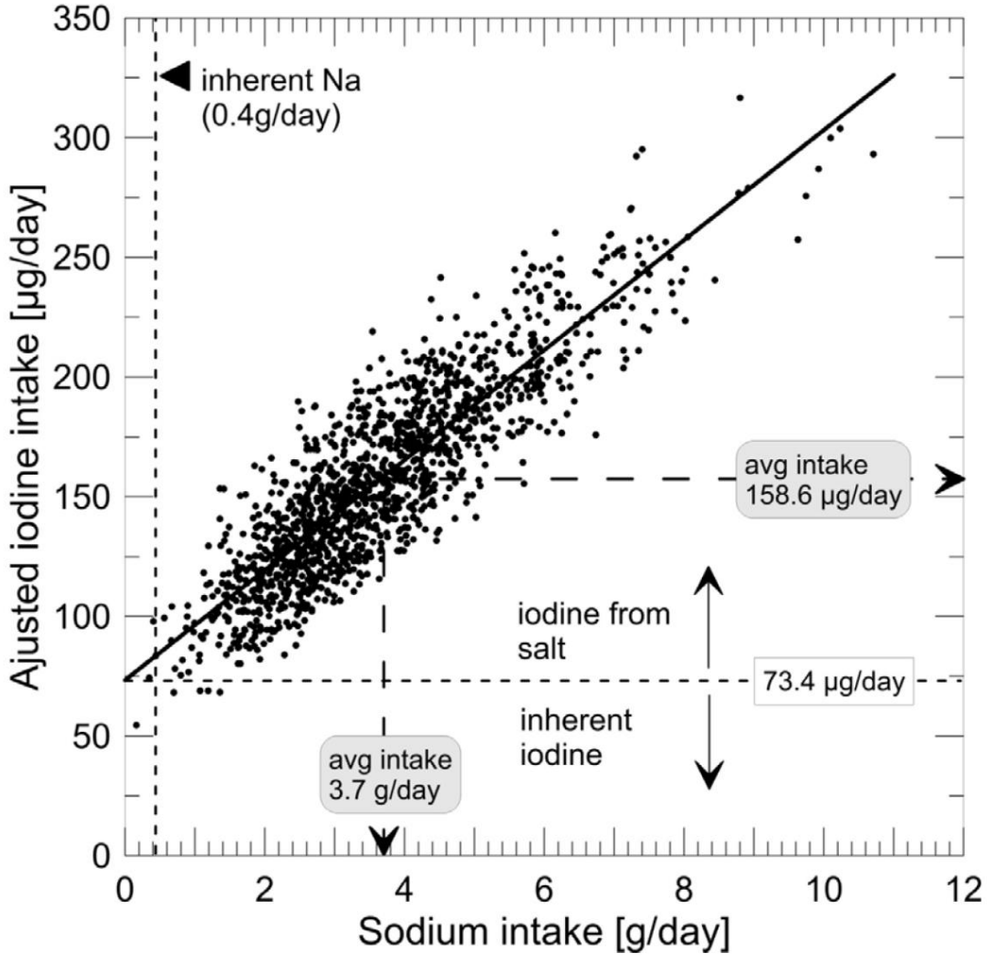
Brignole et al, European Heart Journal (2018) 39, 1883–1948

Salt iodization in Switzerland

- In Switzerland, the legal implementation of salt iodization began in1922 with gradual increases:
  - 3.75 mg/kg in 1922
  - 7.5 mg/kg in 1962
  - 15 mg/kg in 1980
  - 20 mg/kg in 1998
  - 25 mg/kg in 2014.
- The Swiss Federal Office of Public health has launched a strategy to reduce dietary salt intake in the general population (2008-2012), extended for 2013-2016.
- This strategy may affect the iodine supply of the population.

Relationship between iodine intake and sodium intake based on 24H urine collections in the Swiss population.

In Switzerland, 54% of the dietary iodine intake can be attributed to iodized salt



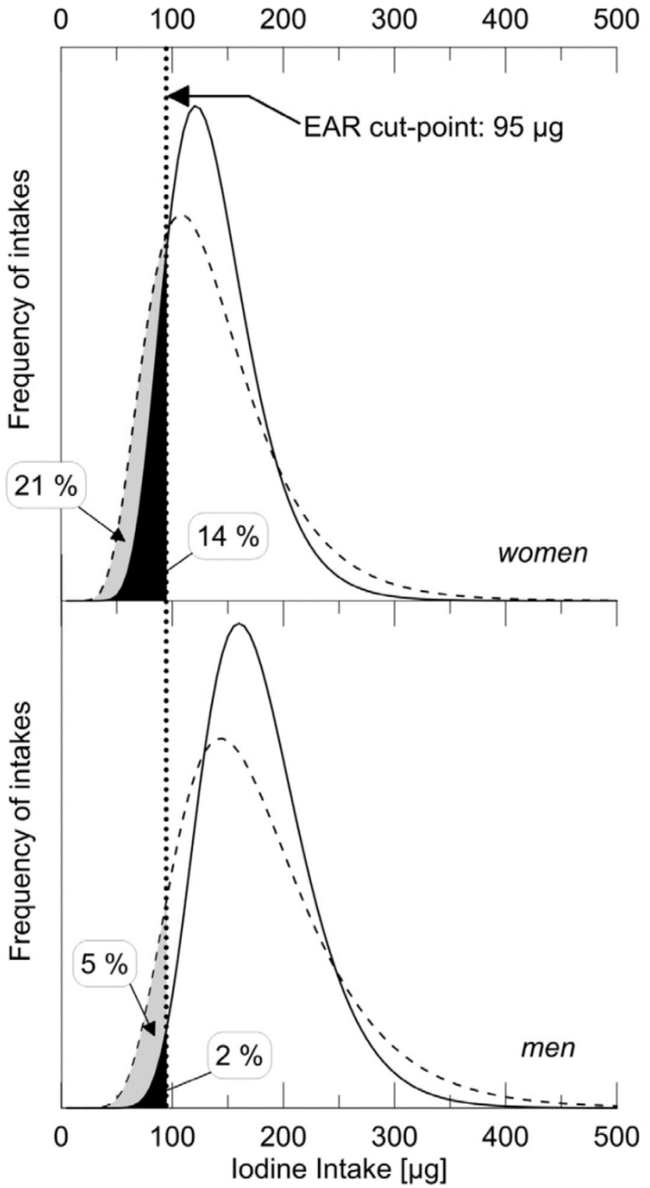
Haldimann et al, Public Health Nutrition, 2015; 18(8), 1333–1342

Estimated prevalence of inadequate iodine intake in Swiss adults

- 14% of women
- 2% of men

- The usual intake distributions (solid line) of iodine were obtained from single-day intake data (broken line) and adjusted with replicate intake data.

- The fractions below the estimated average intake (EAR) of 95 µg/d correspond to the prevalence of inadequacy.



Haldimann et al, Public Health Nutrition, 2015; 18(8), 1333–1342

Arguments in favor of salt reduction

1. We eat too much salt in Western countries

2. Salt reduction has beneficial effects in :

   Essential hypertension
   Resistant hypertension
   Patients with metabolic syndrome
   Patients with renal diseases and proteinuria
   Patients with heart failure

3. It does not harm normotensive subjects