Ingesta de Na i evolució de la funció renal en el pacient diabètic hipertens: un nou paradigma?

Àlex de la Sierra

Hospital Mútua Terrassa.
Universitat de Barcelona

China (2,500 years bc)

- “Too much salt in food, pulse becomes stronger”

Nei Ching

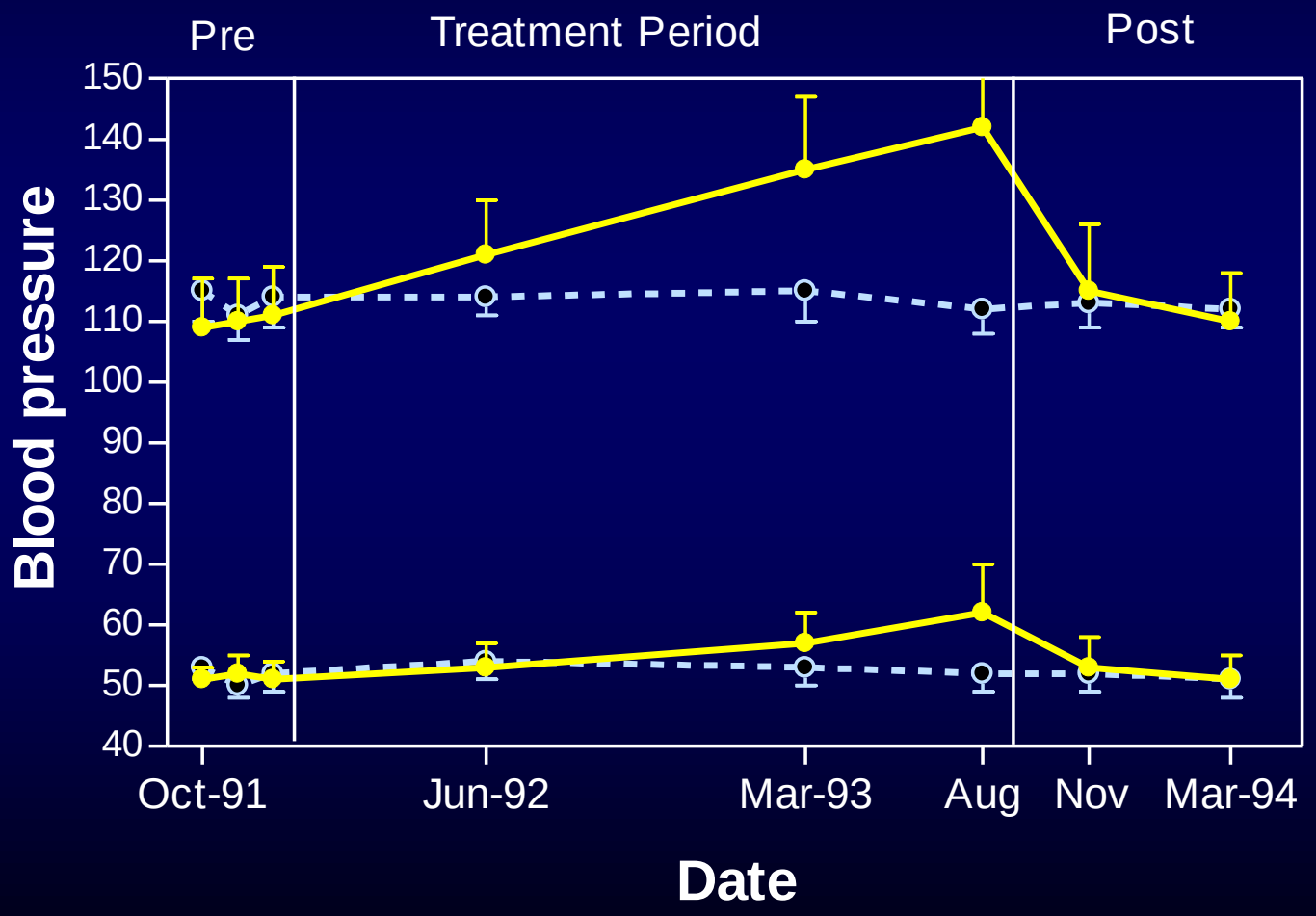
Sodium, BP and CV prevention

- Salt intake, BP and hypertension
- Salt intake and cardiovascular morbidity/mortality
- Salt sensitivity and BP

Sodium, BP and CV prevention

- Salt intake, BP and hypertension
  - Studies in diabetes
- Salt intake and cardiovascular morbidity/mortality
- Salt sensitivity and BP

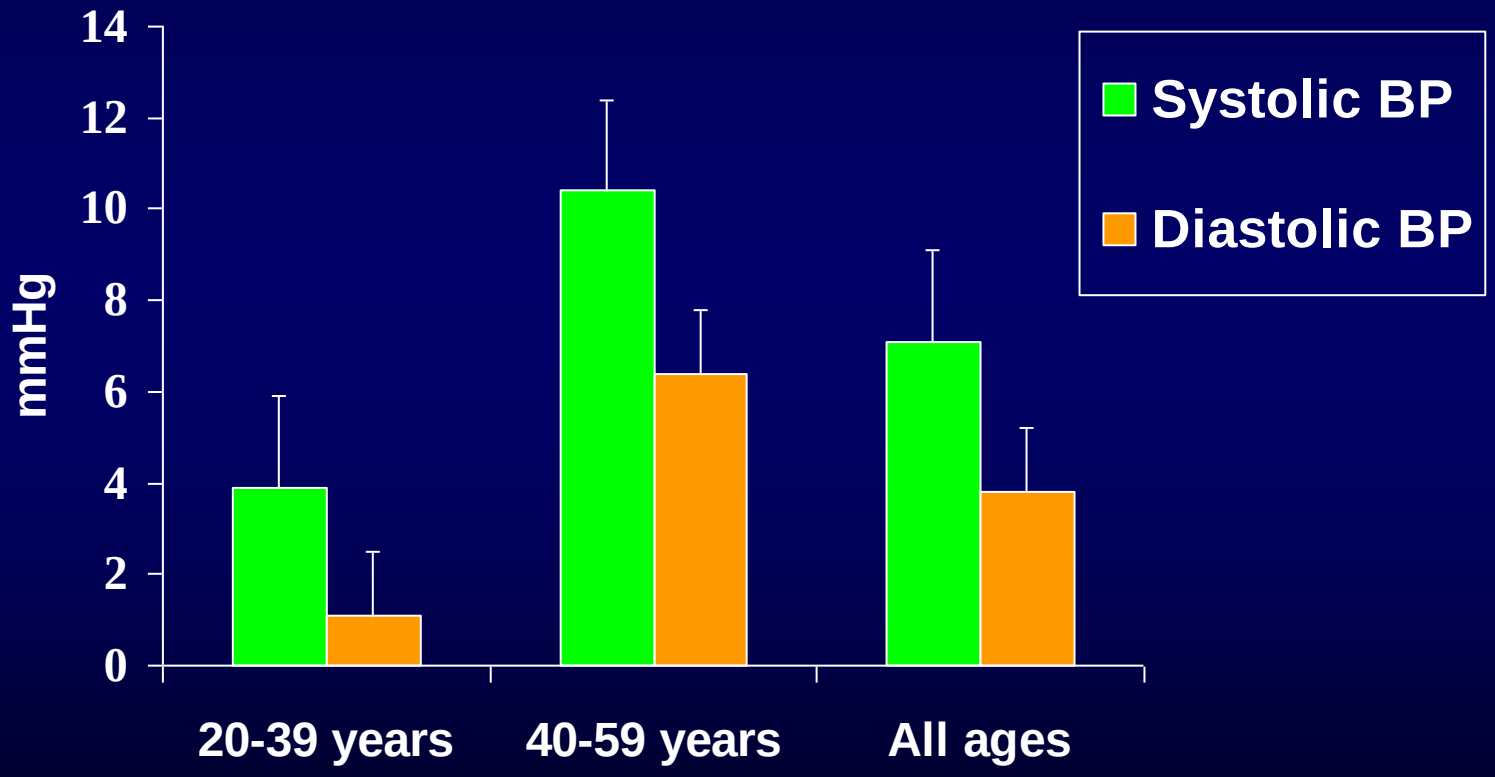
Effect of salt intake on blood pressure in chimpanzees



Denton D, et al. Nature Medicine 1995

Across population blood pressure differences for a urinary sodium excretion change of 100 mmol/day

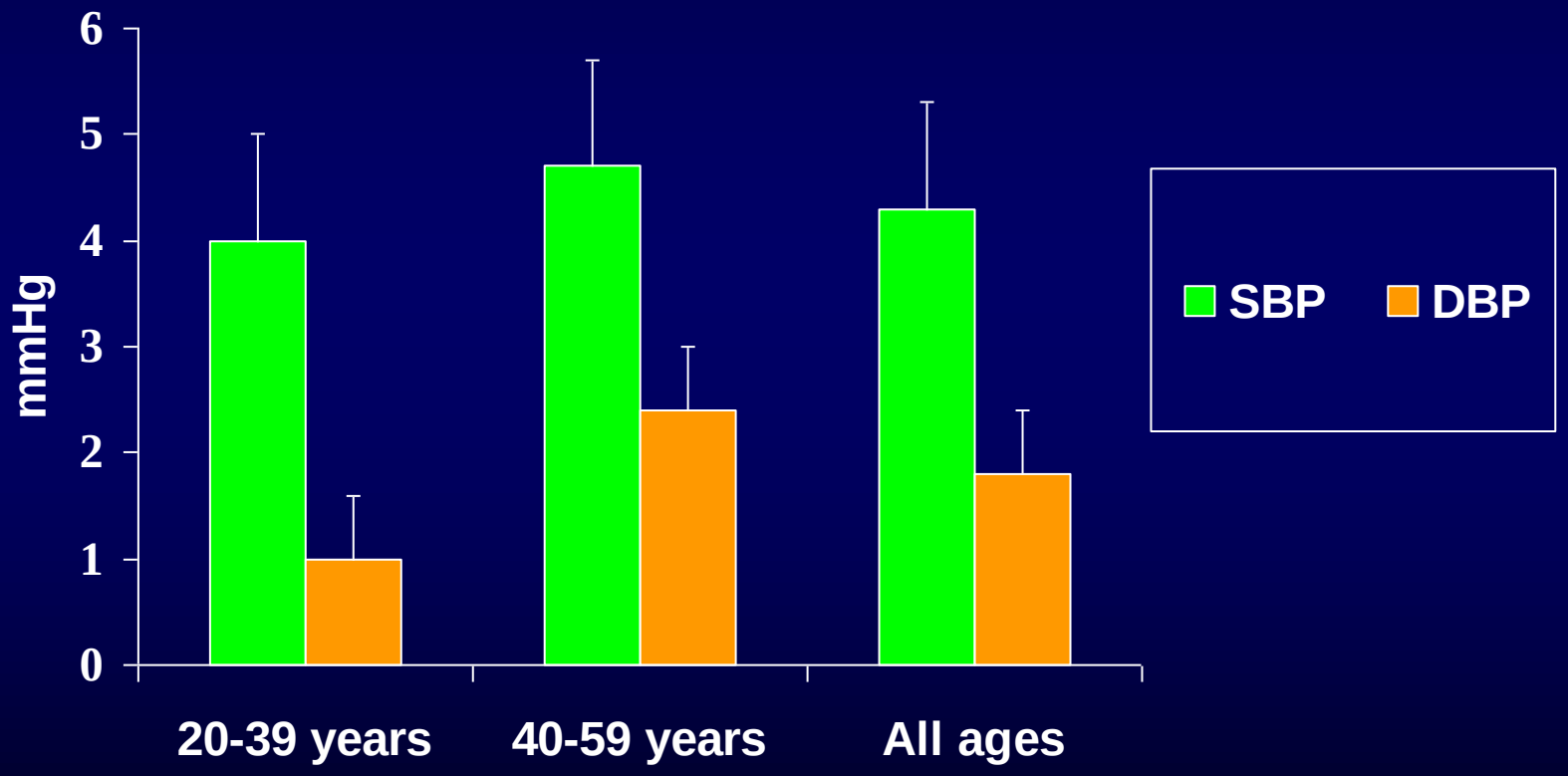
INTERSALT Study



Elliott P. BMJ 1996; 312: 1249.

Whitin population blood pressure differences for a urinary sodium excretion change of 100 mmol/day.

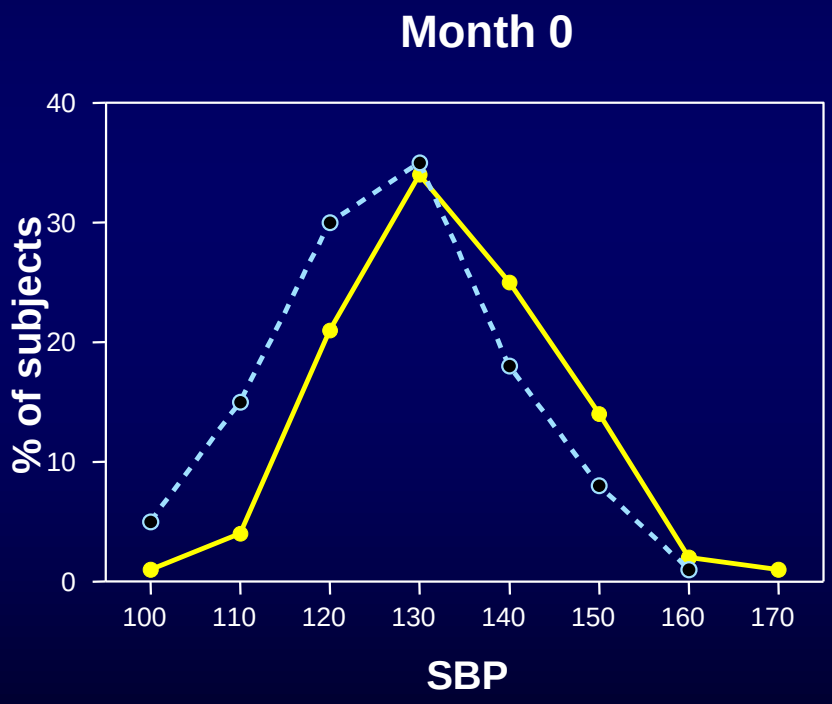
INTERSALT Study

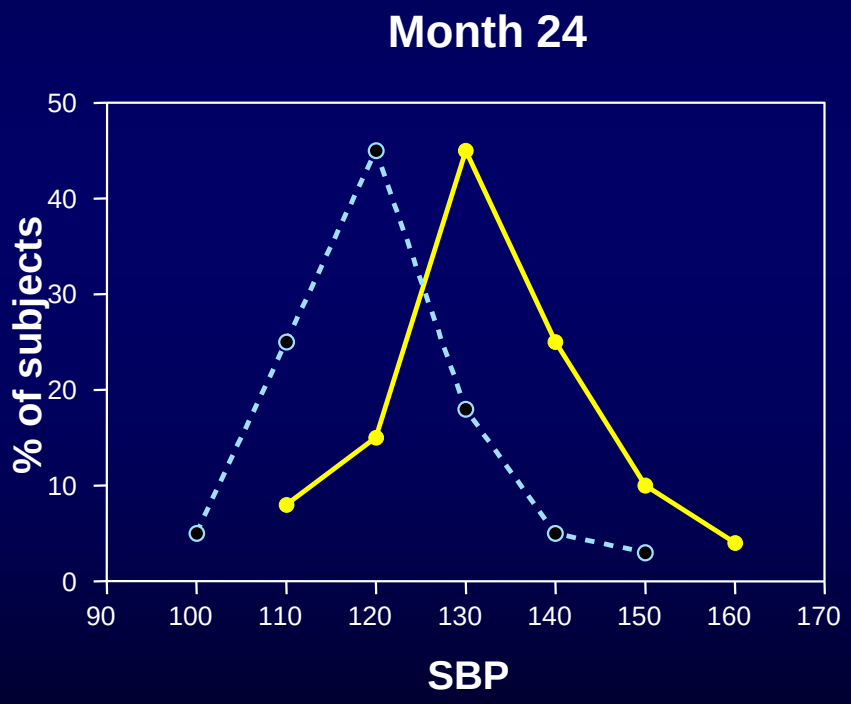


Elliott P. BMJ 1996; 312: 1249.

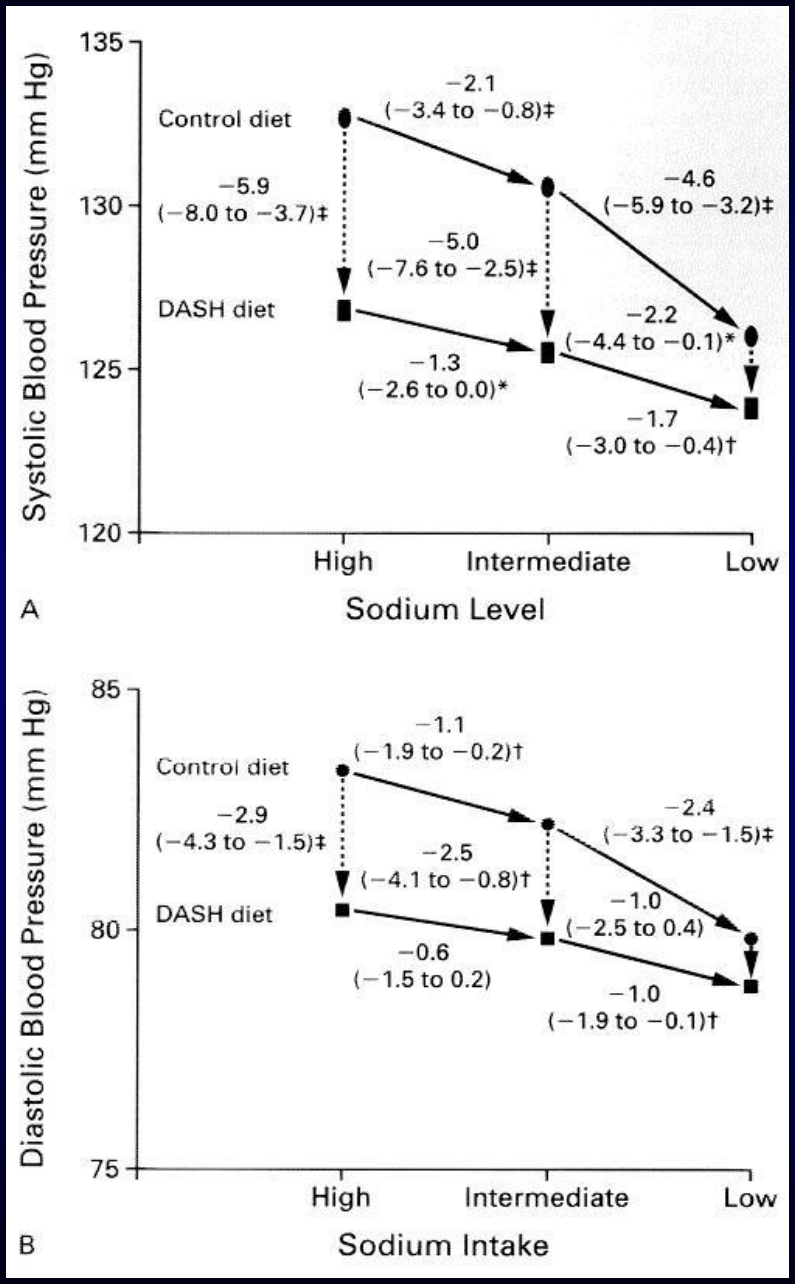
Systolic BP distribution among Luo natives in Kenia depending on migration to army

40mmol/24h differences in Na+ excretion





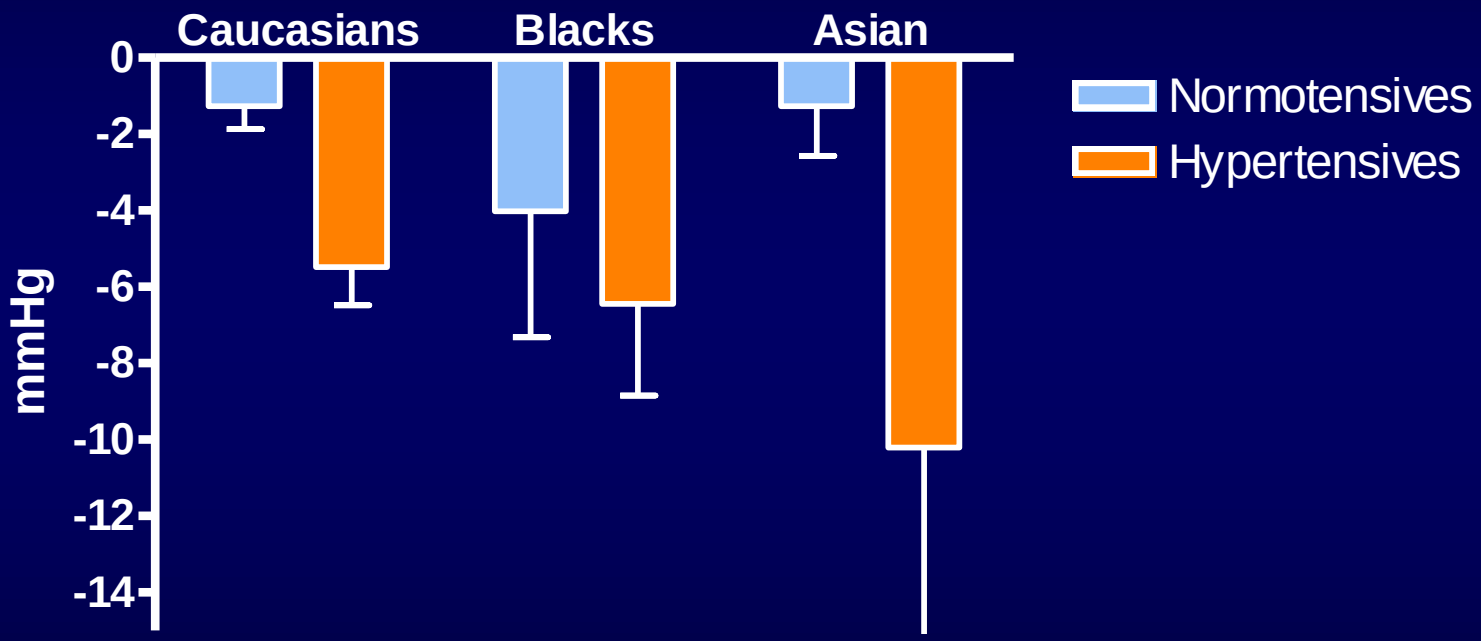
Poulter NR, et al. BMJ 1990.



Combined effects of DASH diet and sodium restriction on blood pressure

Sacks FM, et al. N Engl J Med 2001

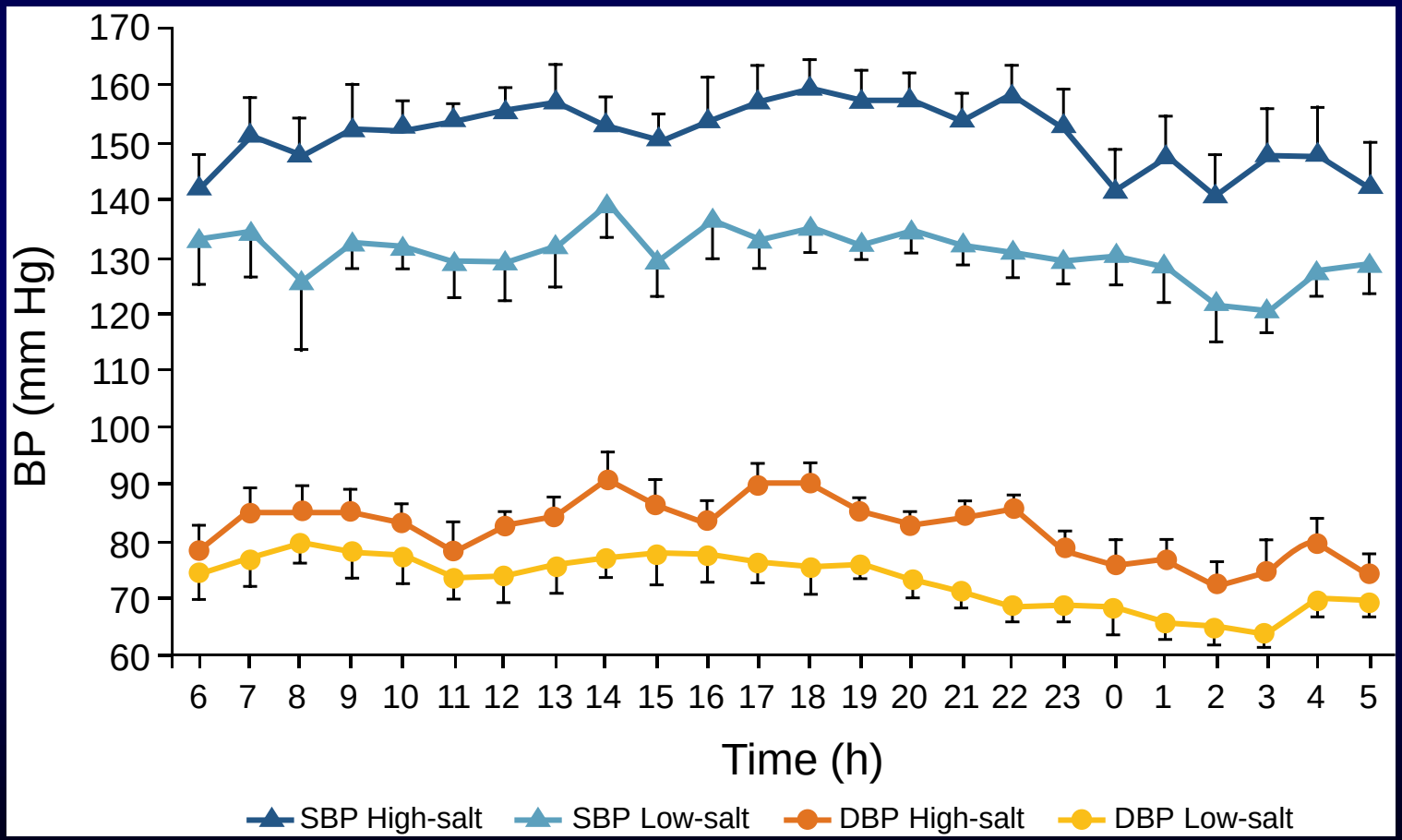
Meta-analysis of trials of salt restriction. BP-lowering effects



Graudal NA, et al. Am J Hypertens 2012

Impact of Dietary Salt Restriction in Patients With Resistant Hypertension

24-Hour Ambulatory BP Values During Low- and High-Salt Diets

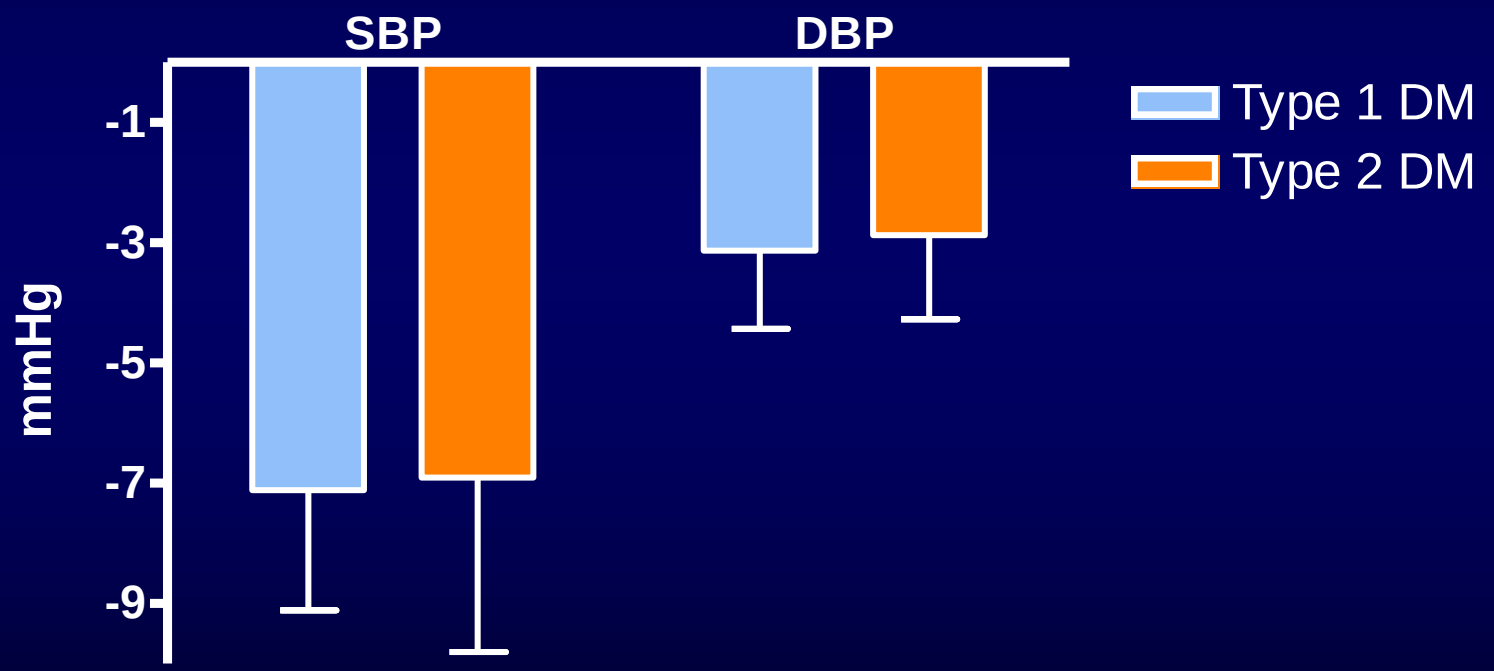


-22.7mmHg

-9.1 mmHg

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

Meta-analysis of trials of salt restriction. BP-lowering effects Studies in diabetic subjects



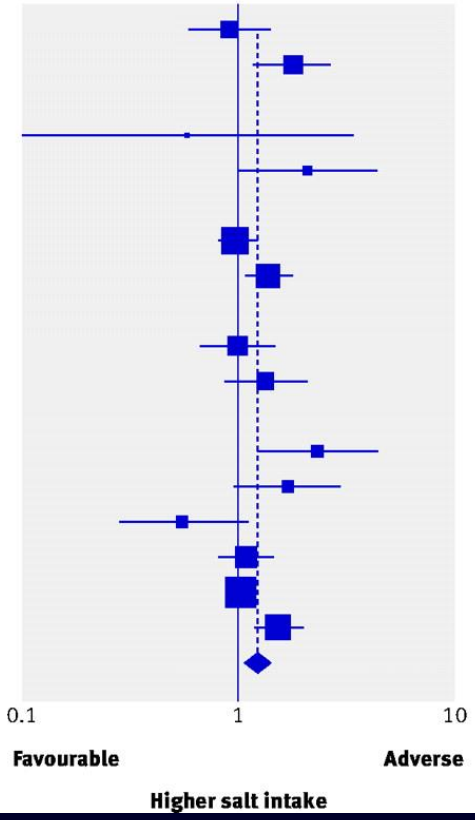
Suckling RJ, et al. Cochrane Reviews 2010

Sodium, BP and CV prevention

- Salt intake, BP and hypertension
- Salt intake and cardiovascular morbidity/mortality
  - Studies in diabetics
- Salt sensitivity and BP

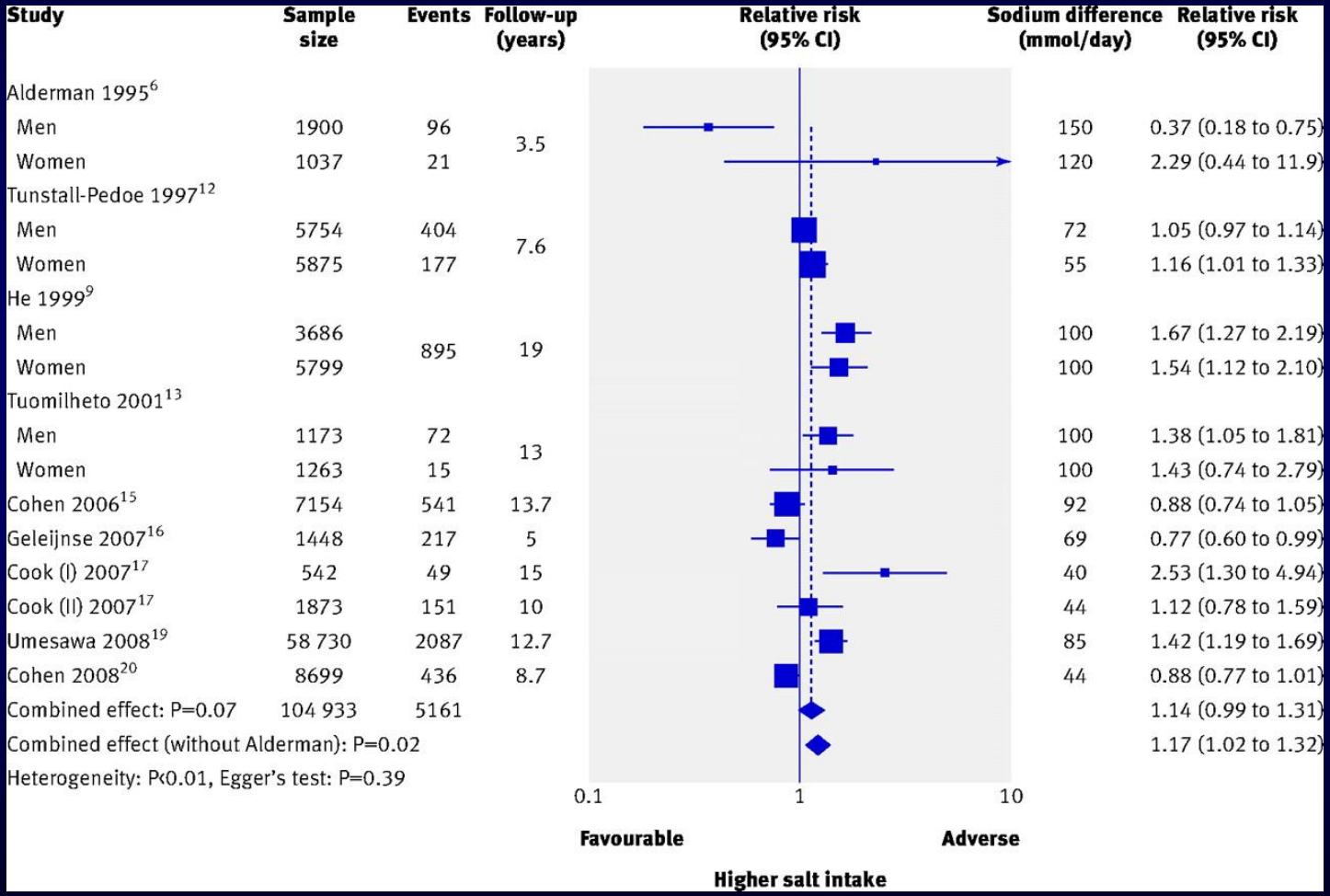
Meta-analysis of prospective studies of sodium consumption and stroke incidence

Study	Sample size	Events	Follow-up (years)	Sodium difference (mmol/day)	Relative risk (95% CI)
Kagan 1985[10]	7895	238	10	100	0.92 (0.60 to 1.42)
Hu 1992[11]	8562	104	4		1.79 (1.18 to 2.70)
Alderman 1995[6]					
Men	1900	17	3.5	150	0.59 (0.10 to 3.43)
Women	1037	6		120	2.10 (1.01 to 4.33)
He 1999[9]					
Normal weight	6797	430	19	100	0.99 (0.81 to 1.20)
Overweight	2688	250		100	1.39 (1.10 to 1.76)
Tuomilheto 2001[13]					
Men	1173	43	13	100	1.00 (0.68 to 1.48)
Women	1263	41		100	1.34 (0.87 to 2.06)
Nagata 2004[14]					
Men	13 355	137	7	110	2.34 (1.23 to 4.47)
Women	15 724	132		92	1.70 (0.96 to 3.00)
Cohen 2006[15]	7154	79	13.7	92	0.56 (0.28 to 1.11)
Geleijnse 2007[16]	1448	181	5	69	1.08 (0.81 to 1.45)
Larsson 2008[18]	26 556	2702	13.6	84	1.04 (0.93 to 1.17)
Umesawa 2008[19]	58 730	986	12.7	85	1.55 (1.20 to 2.00)
Combined effect: P=0.007	154 282	5346			1.23 (1.06 to 1.43)
Heterogeneity: P=0.04, Egger's test: P=0.26					



Strazzullo P, et al. BMJ 2009

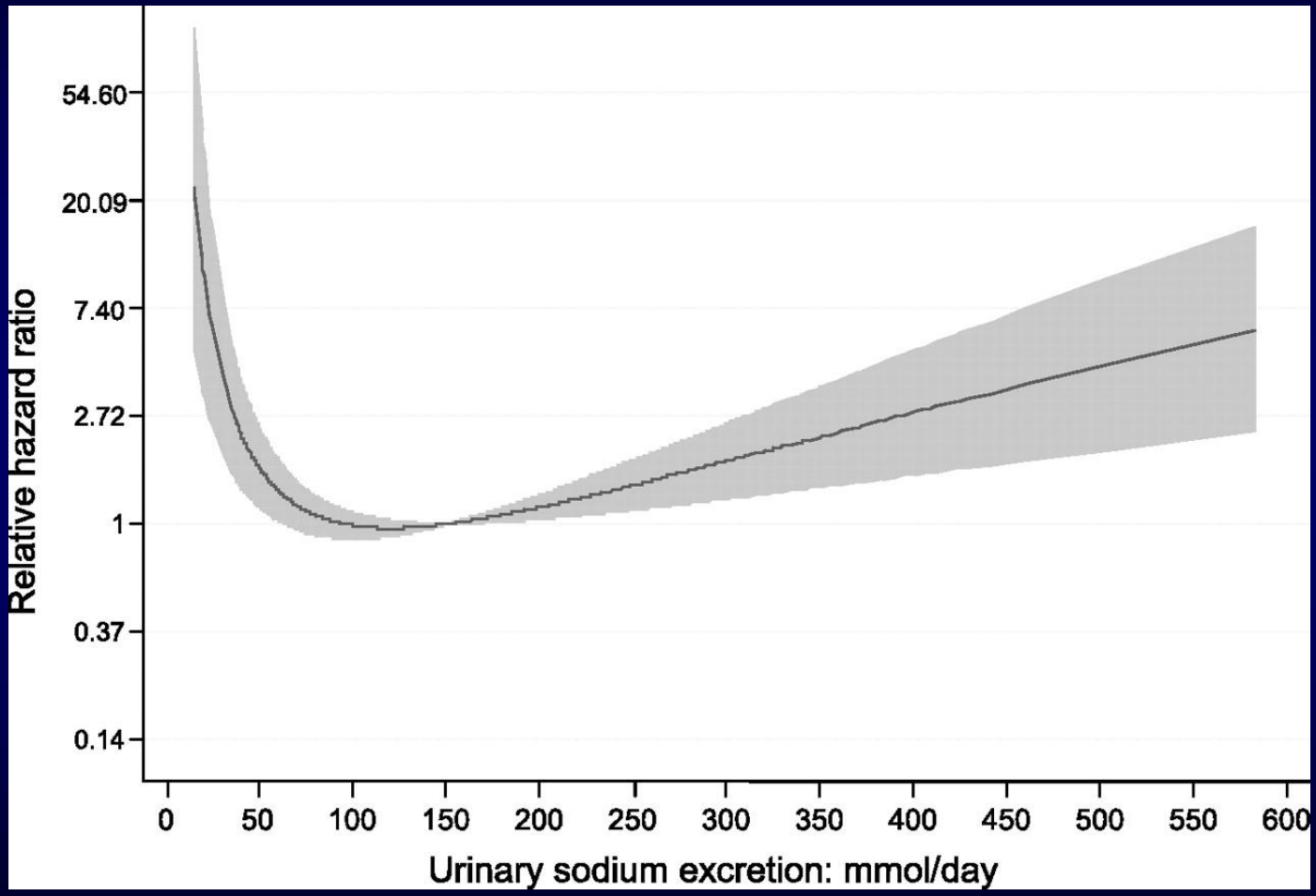
Meta-analysis of prospective studies of sodium consumption and CVD incidence



Study	Sample size	Events	Follow-up (years)	Sodium difference (mmol/day)	Relative risk (95% CI)
Alderman 1995[6]					
Men	1900	96	3.5	150	0.37 (0.18 to 0.75)
Women	1037	21		120	2.29 (0.44 to 11.9)
Tunstall-Pedoe 1997[12]					
Men	5754	404	7.6	72	1.05 (0.97 to 1.14)
Women	5875	177		55	1.16 (1.01 to 1.33)
He 1999[9]					
Men	3686	895	19	100	1.67 (1.27 to 2.19)
Women	5799			100	1.54 (1.12 to 2.10)
Tuomilheto 2001[13]					
Men	1173	72	13	100	1.38 (1.05 to 1.81)
Women	1263	15		100	1.43 (0.74 to 2.79)
Cohen 2006[15]	7154	541	13.7	92	0.88 (0.74 to 1.05)
Geleijnse 2007[16]	1448	217	5	69	0.77 (0.60 to 0.99)
Cook (I) 2007[17]	542	49	15	40	2.53 (1.30 to 4.94)
Cook (II) 2007[17]	1873	151	10	44	1.12 (0.78 to 1.59)
Umesawa 2008[19]	58 730	2087	12.7	85	1.42 (1.19 to 1.69)
Cohen 2008[20]	8699	436	8.7	44	0.88 (0.77 to 1.01)
Combined effect: P=0.07	104 933	5161			1.14 (0.99 to 1.31)
Combined effect (without Alderman): P=0.02					1.17 (1.02 to 1.32)
Heterogeneity: P<0.01, Egger's test: P=0.39					

Strazzullo P, et al. BMJ 2009

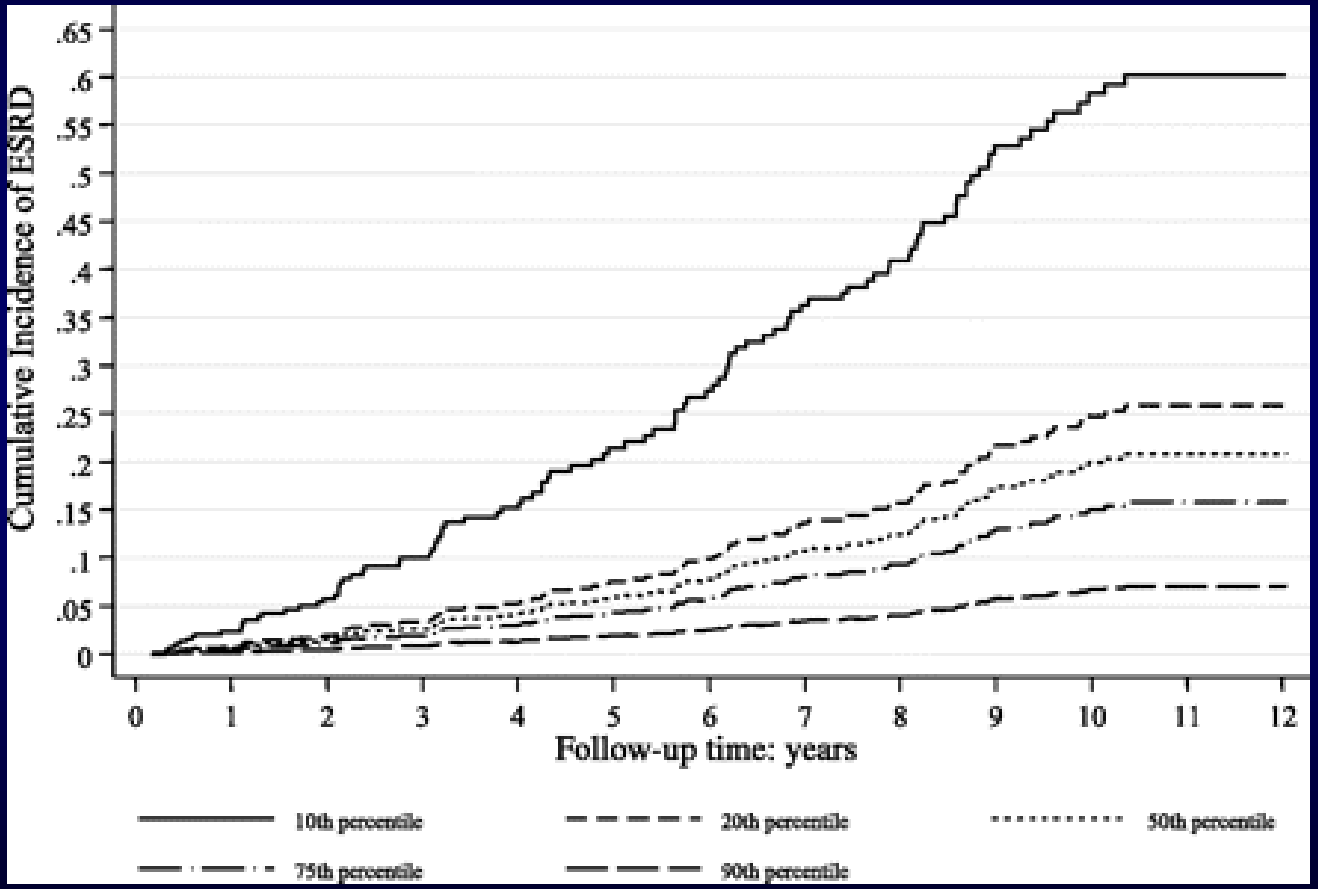
Na intake and mortality in type 1 DM.
The FinnDiane Study



2807 type 1 DM without ESRD

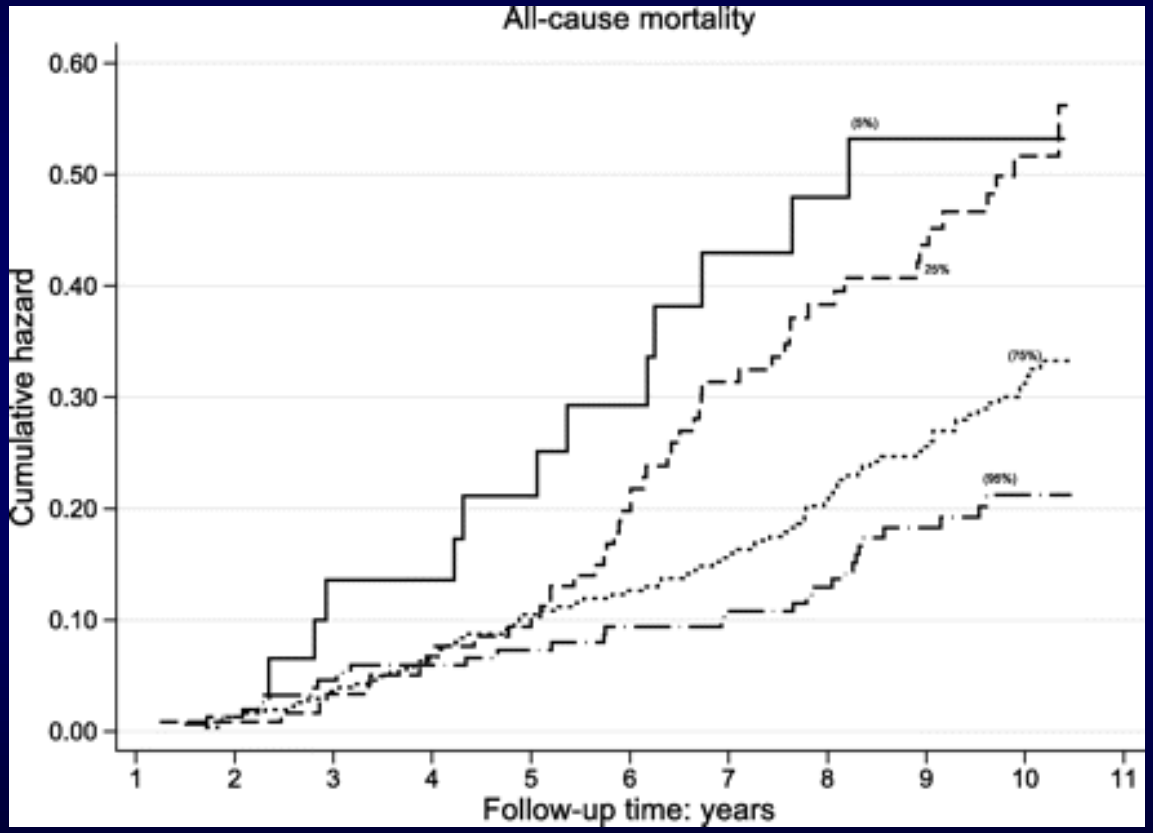
Thomas MC, et al. Diabetes Care 2011

Na intake and development of ESRD in type 1 DM.
The FinnDiane Study



Thomas MC, et al. Diabetes Care 2011

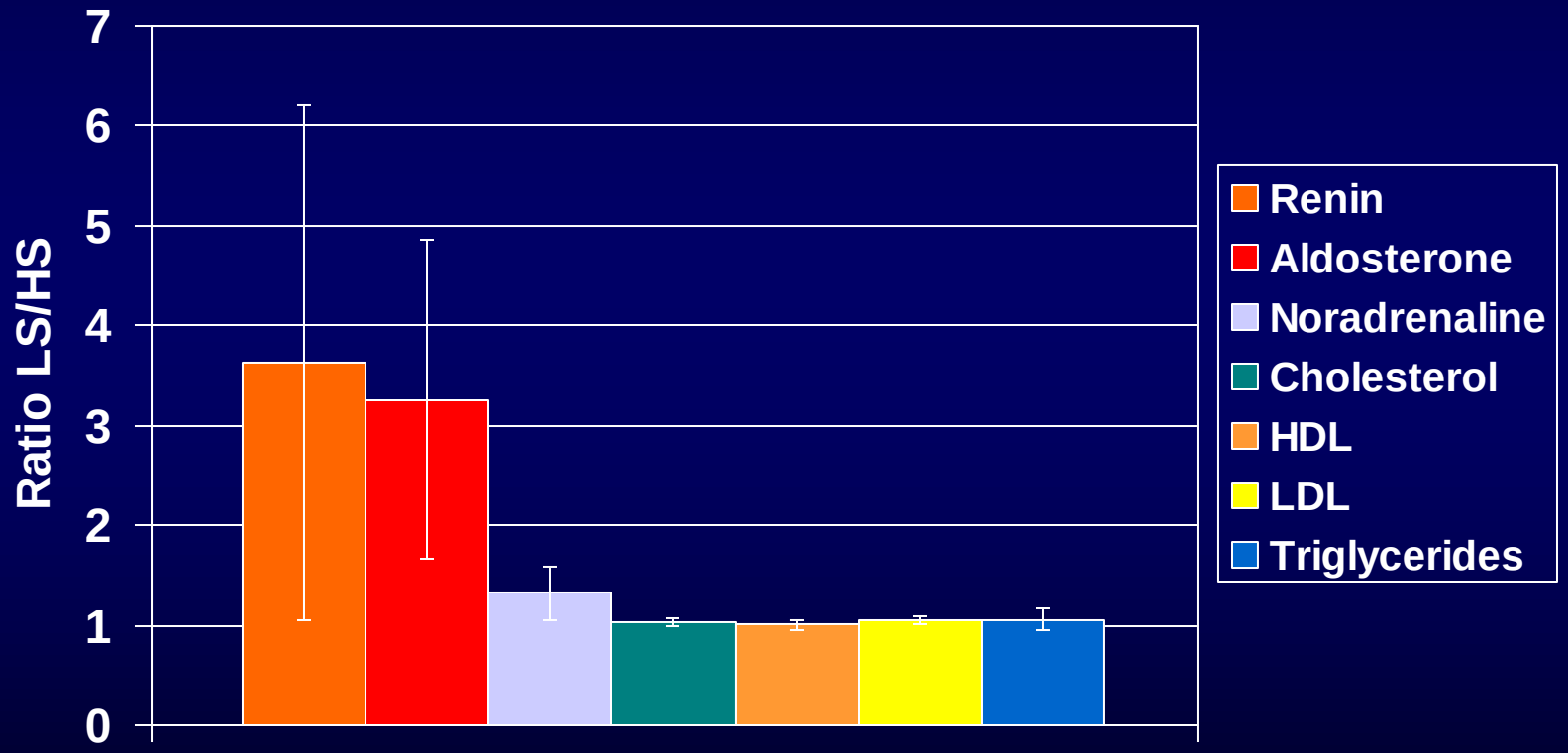
Inverse relationship of Na intake and mortality in type 2 diabetics



638 patients from a single centre in Australia

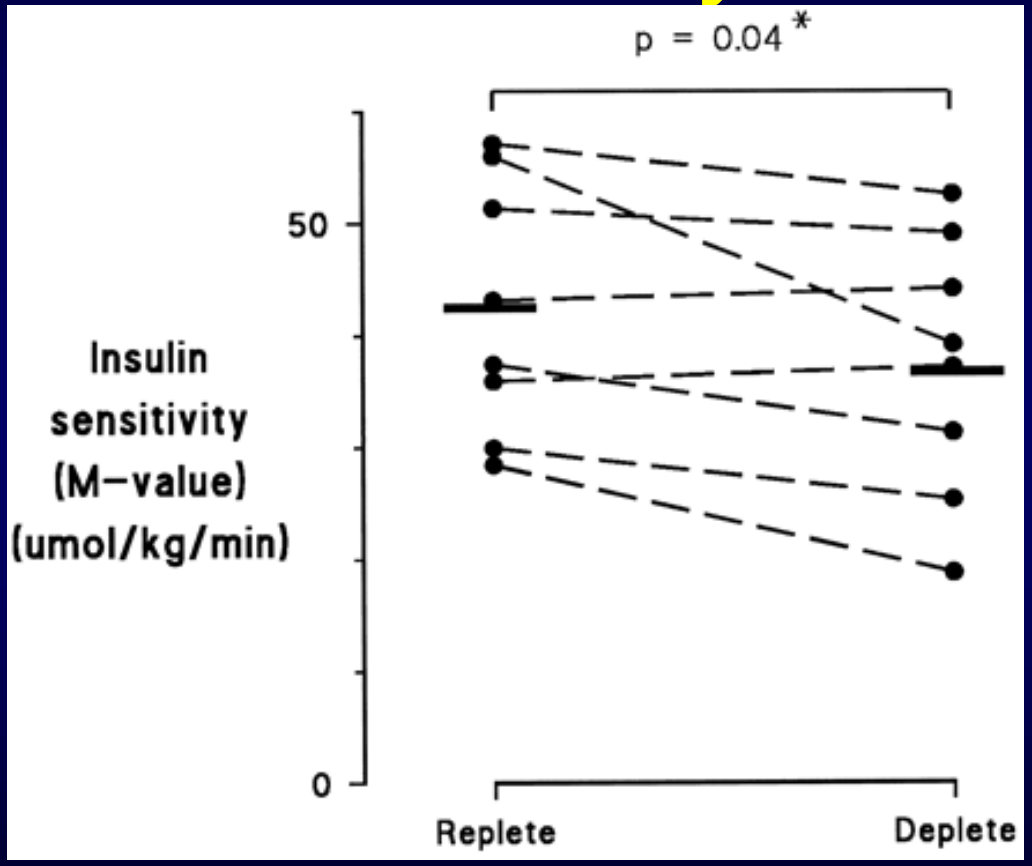
Ekinci EI, et al. Diabetes Care 2011

Effects of Low salt and High salt on lipids and hormones



Graudal NA, et al. JAMA 1998; Graudal NA, et al. AJH 2012

Low-sodium diet reduces insulin sensitivity



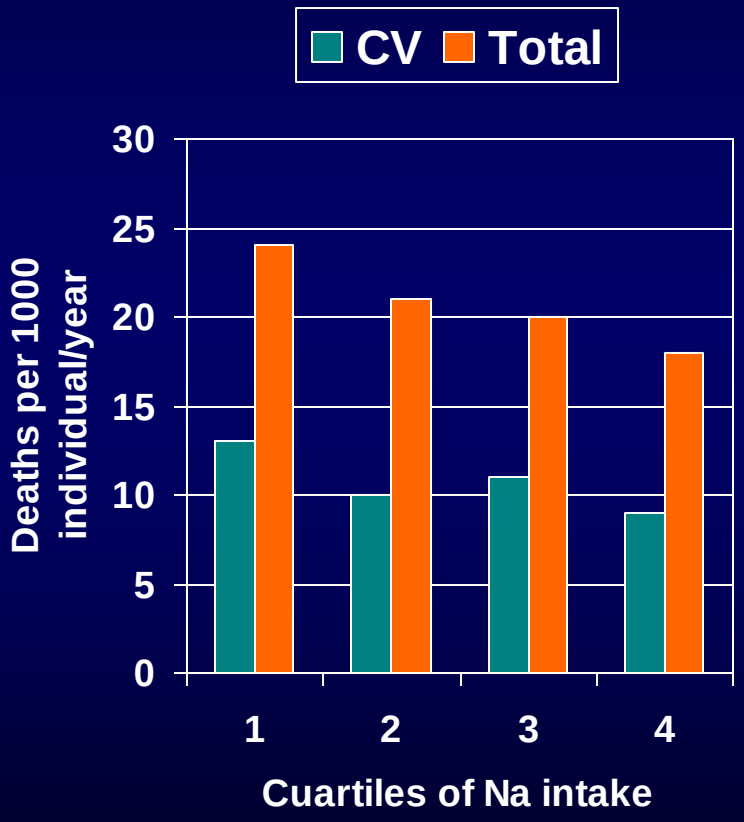
Petrie JR, et al. J Clin Endocrinol Metab 1998

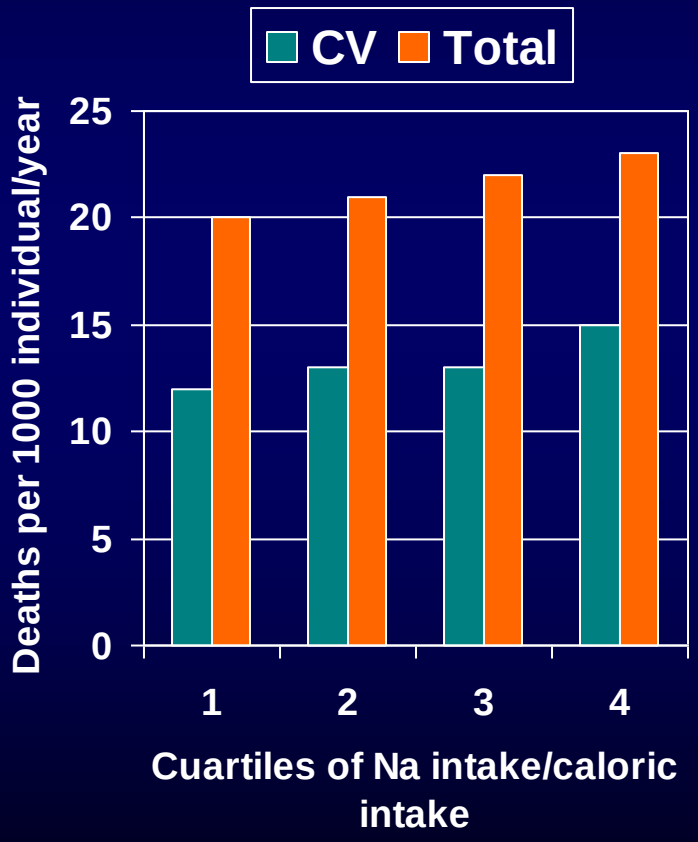
Problems in sodium epidemiology

- Measurement error:
  - Sodium intake varies from one day to another
  - The source of sodium depends on cultural habits (processed food, adding salt when cooking)
  - When compared to 24-h Na urine excretion, all measurements are inaccurate
- Collinearity (confounding factors)
  - Na intake is associated with energy intake, as well as other nutrients (K, Ca, Mg, etc)
- Reverse causality
  - Studies in sick people are more prone to show an association of low Na intake and high mortality (patients are in a more advanced illness state)

Sodium intake and mortality

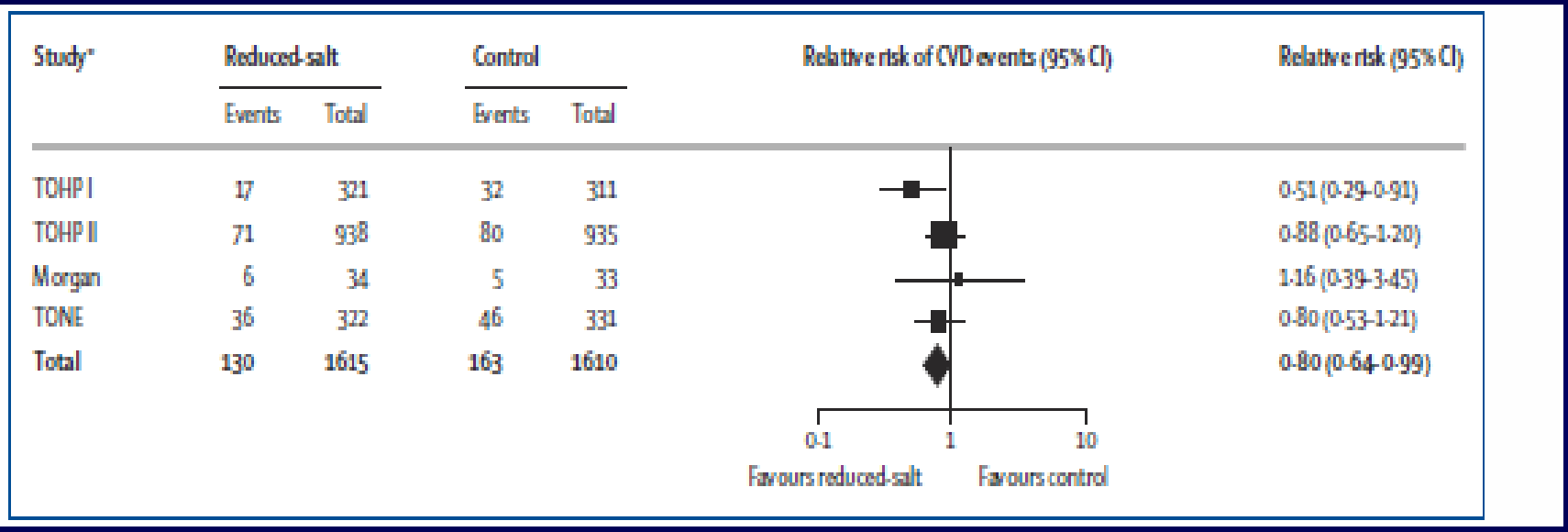
NHANES I





Alderman MH, et al. Lancet 1998

Trials of Na reduction and incidence of CV events



He FJ, et al. Lancet 2011

Beyond blood pressure and cardiovascular disease

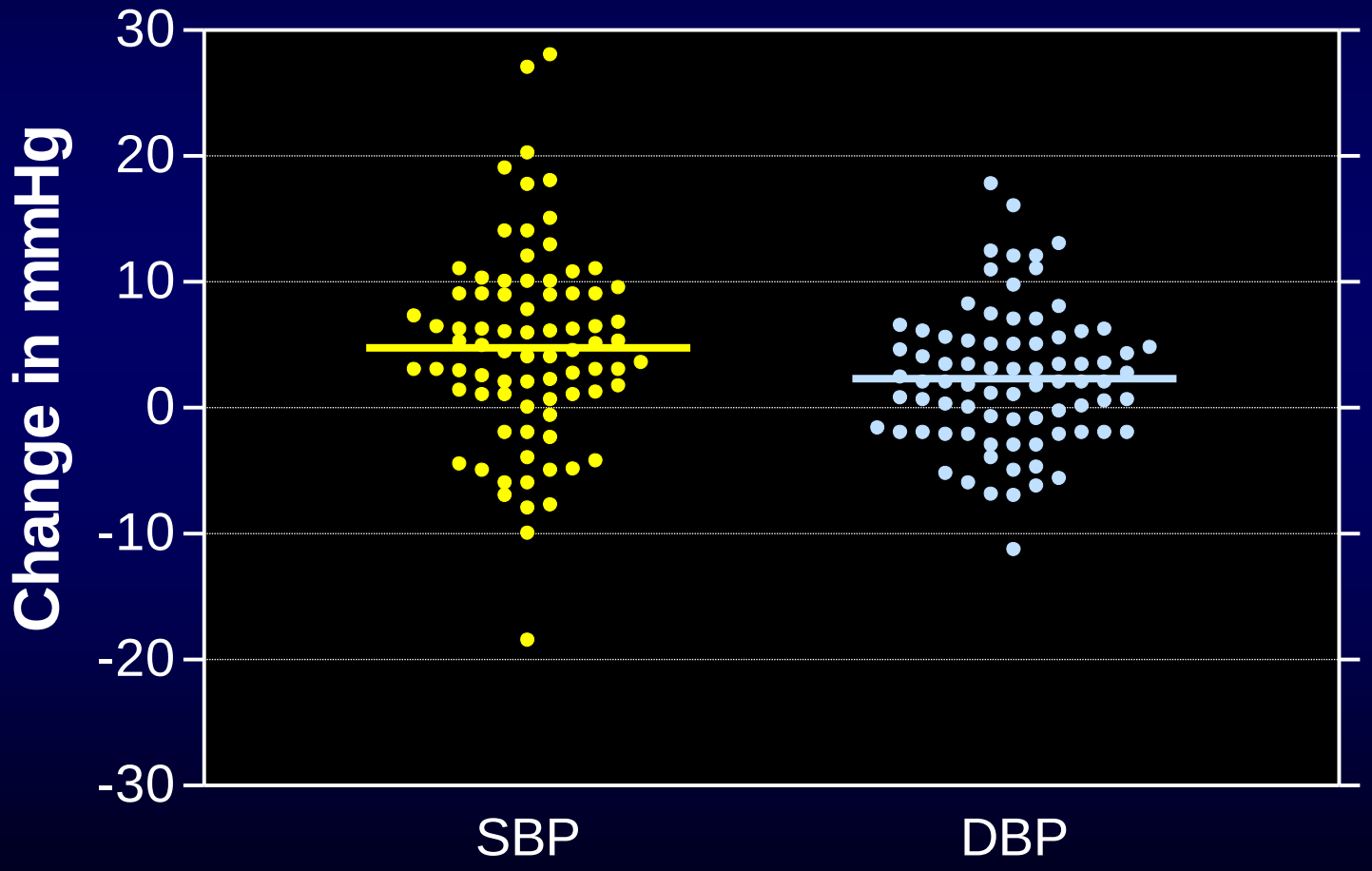
- LVH regression
  - *Jula AM, et al. Circulation 1994*
- Proteinuria reduction
  - *Weir MR, et al. Hypertension 1995*
- Hypercalciuria and kidney stone formation reduction
  - *Sakhaee K, et al. J Urology 1993*
- Osteopenia reduction
  - *Devine A, et al. Am J Clin Nutr 1995*
- Gastric cancer protection
  - *Joossens JV, et al. Int J Epidemiol 1996*
- Antihypertensive drug treatment potentiation (except DHP)
  - *Weir MR, et al. Hypertension 1998*
- Less potassium loss induced by diuretic treatment
  - *Ram CVS, et al. Arch Intern Med 1981*

Sodium, BP and CV prevention

- Salt intake, BP and hypertension
- Salt intake and cardiovascular morbidity/mortality
- Salt sensitivity and BP

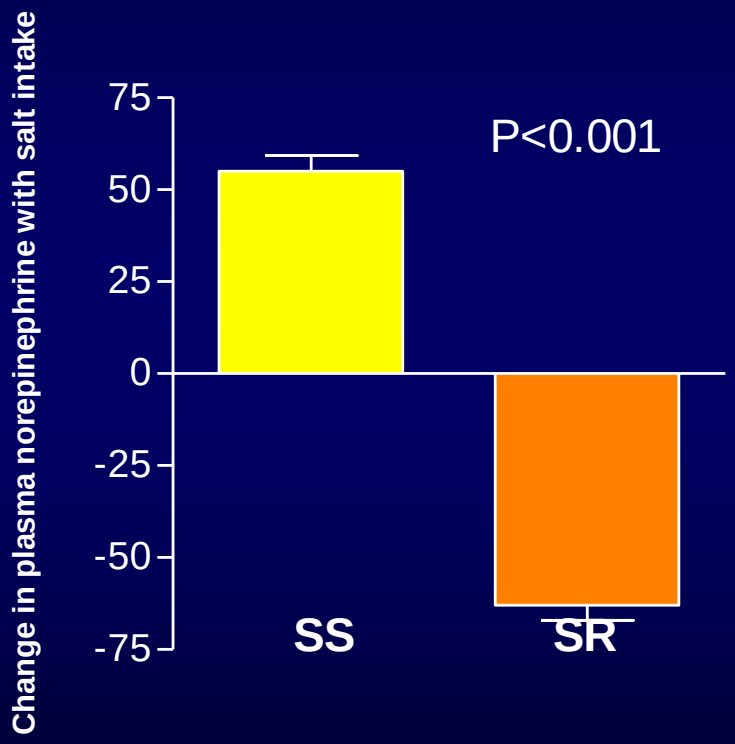
The blood pressure response to salt intake varies among individuals.

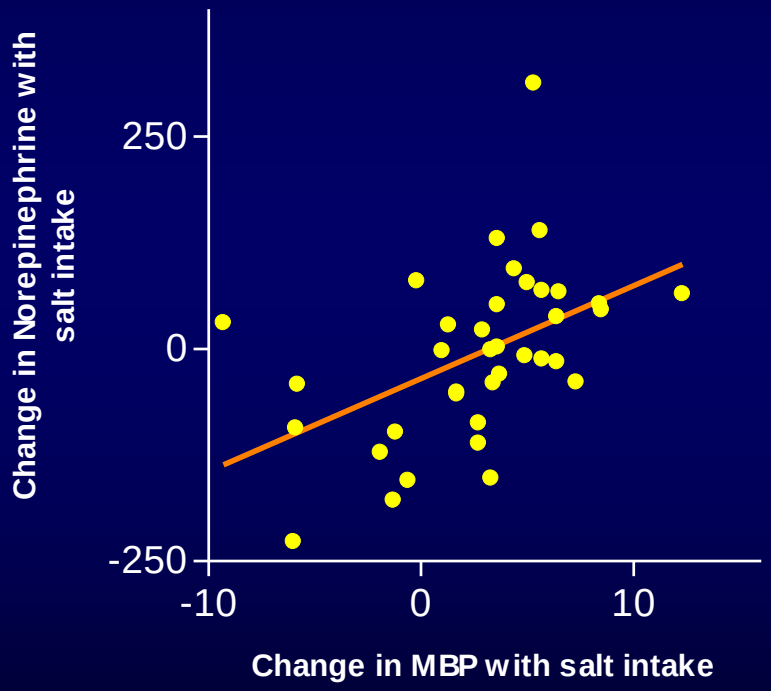
24-hour blood pressure change in 82 hypertensive subjects switching from 20 mmol/day to 260 mmol/day sodium intake



De la Sierra et al AJH 1995

Effect of salt intake on plasma norepinephrine depending on salt sensitivity

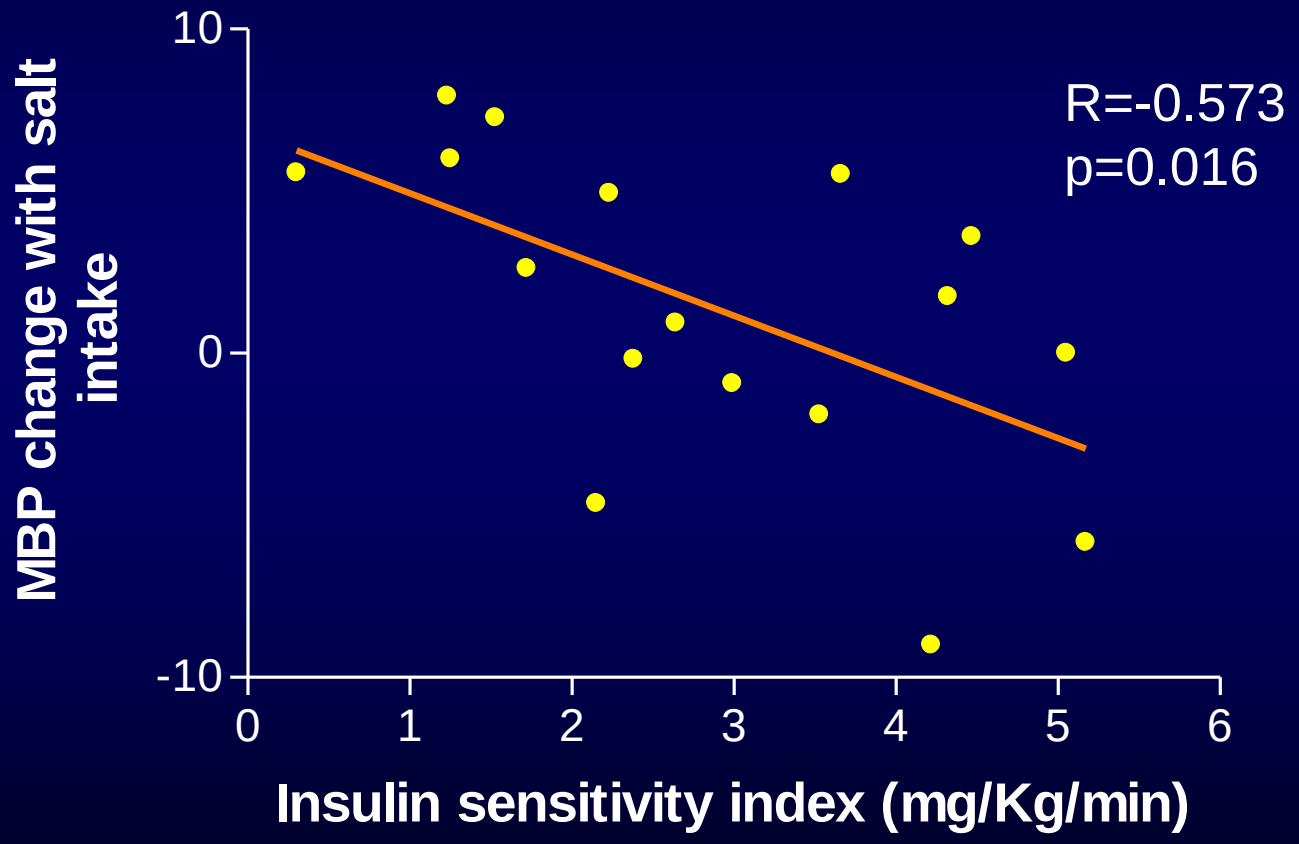




De la Sierra et al. Clin Sci 1996

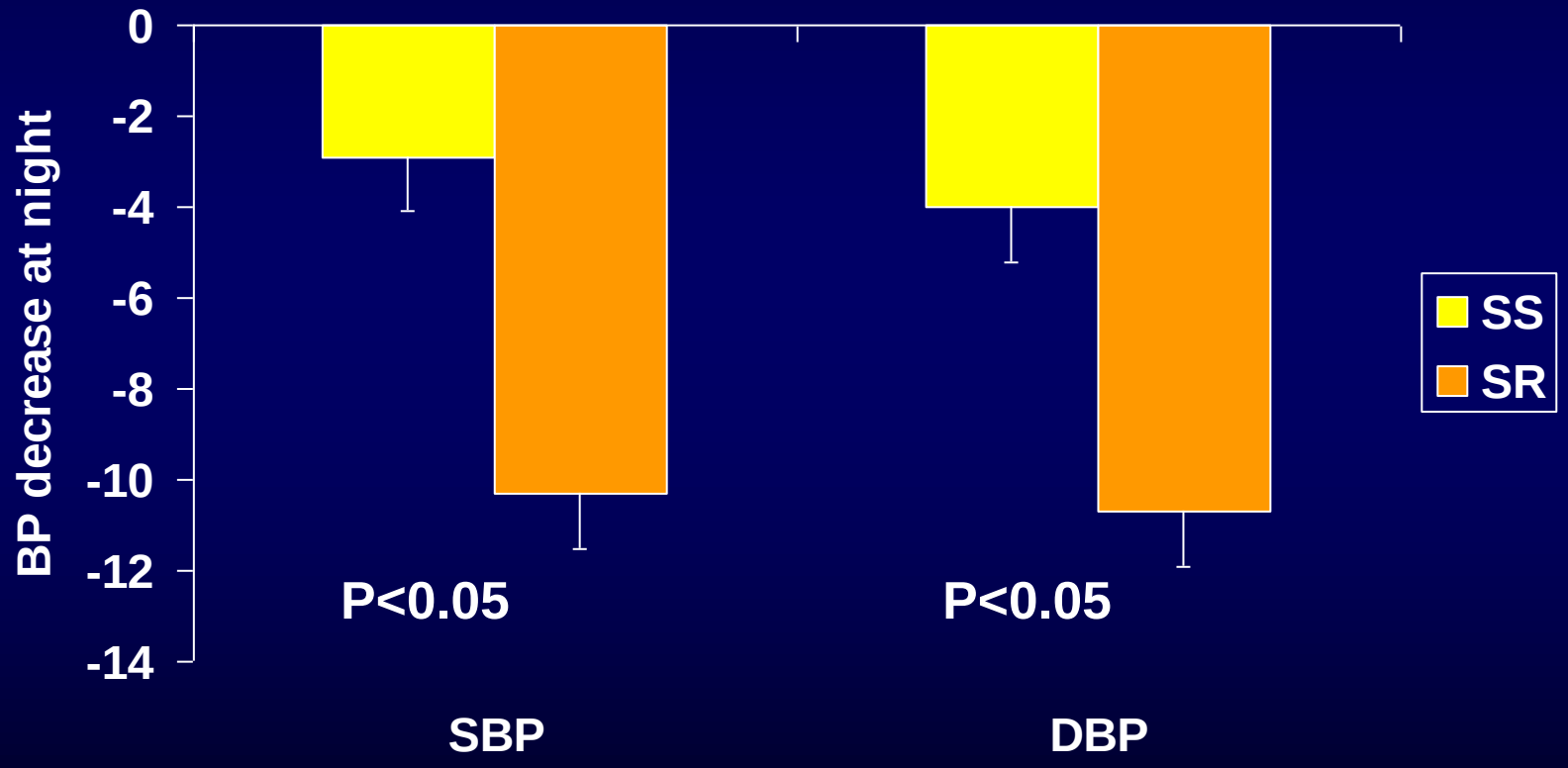
Increased insulin resistance in SS hypertension

Measurement of SS and IR by gold standard methods



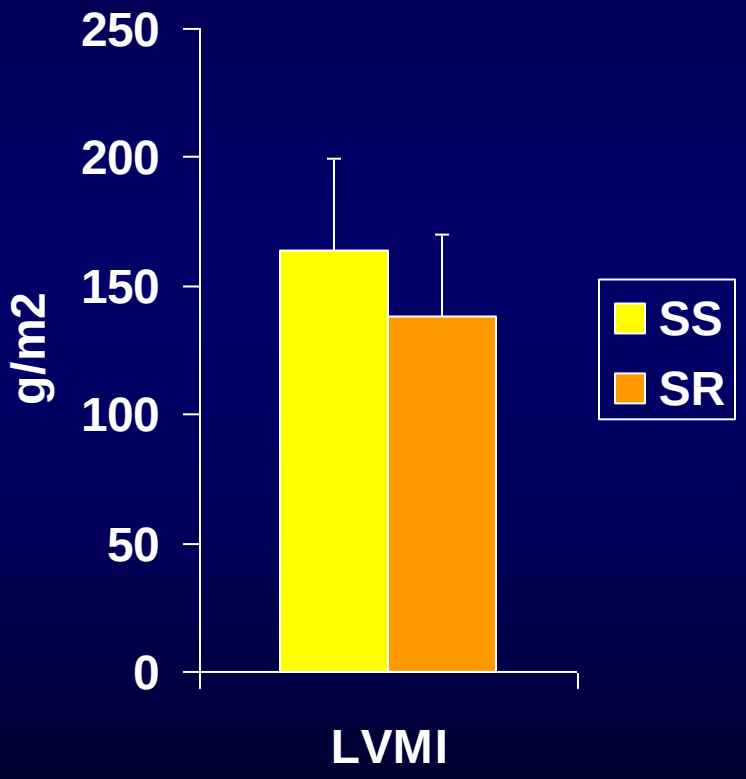
Giner V, et al. J Human Hypertens 2001

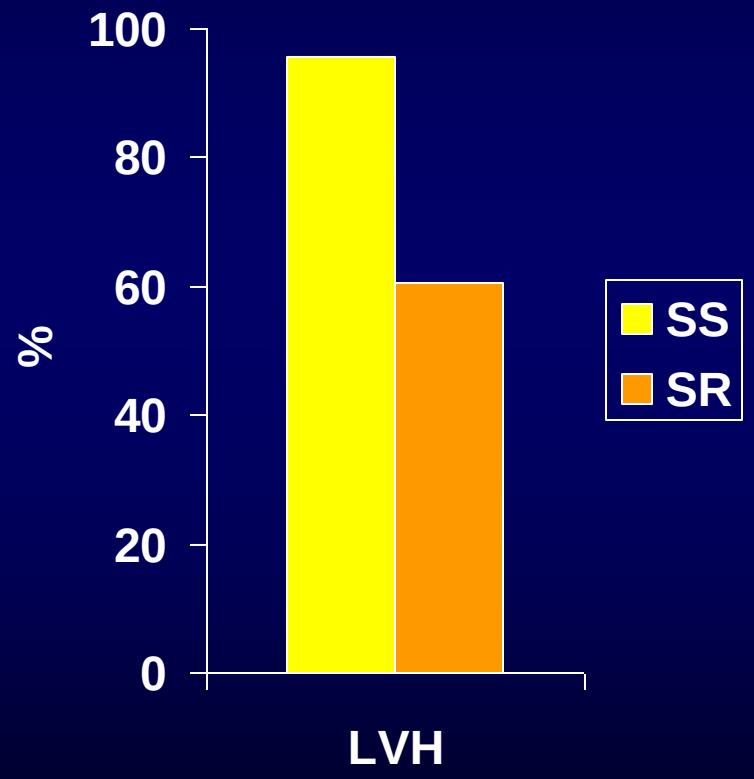
Salt sensitivity and nocturnal fall in BP



De la Sierra et al. Am J Hypertens 1995

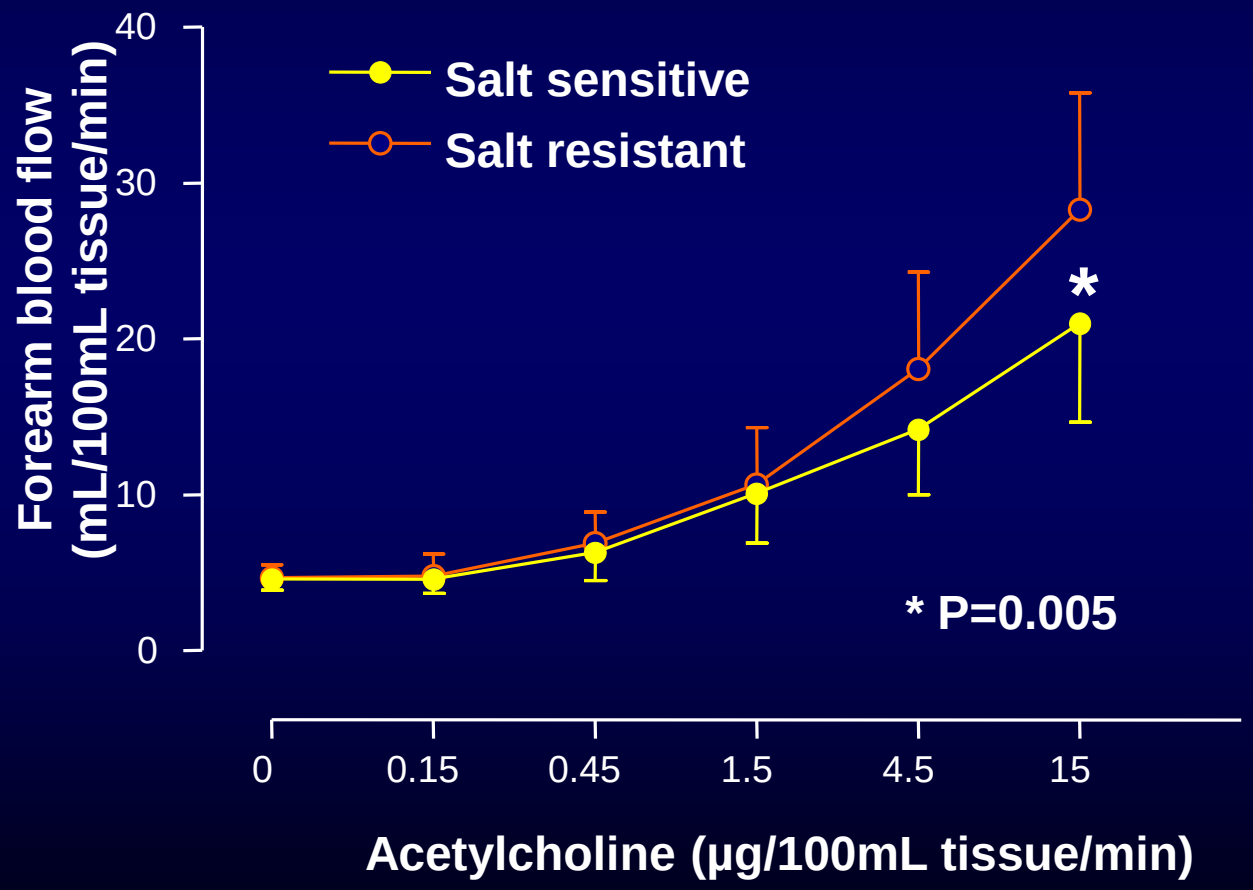
Salt sensitivity and LVH





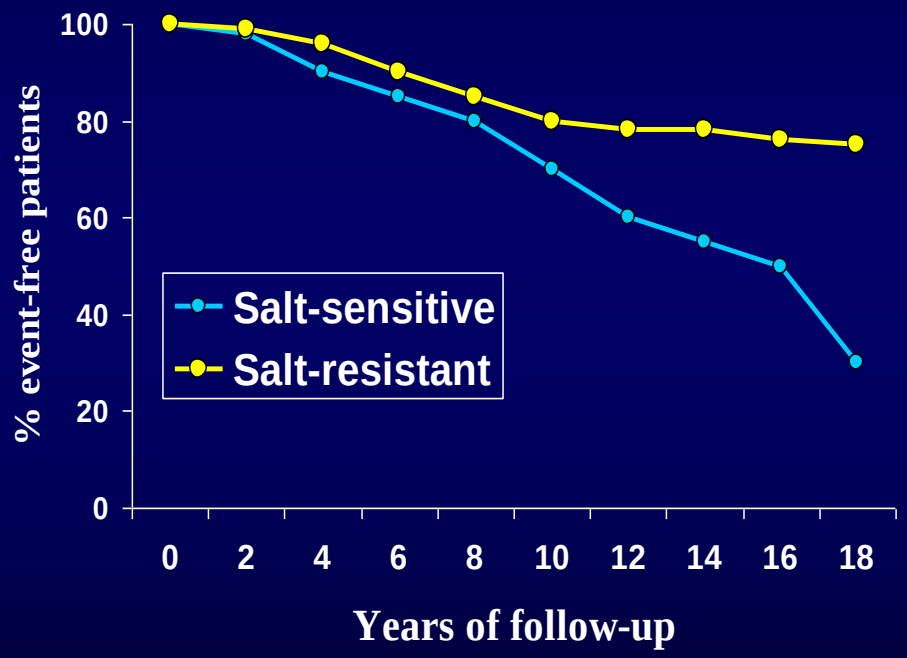
De la Sierra et al. J Human Hypertens 1996

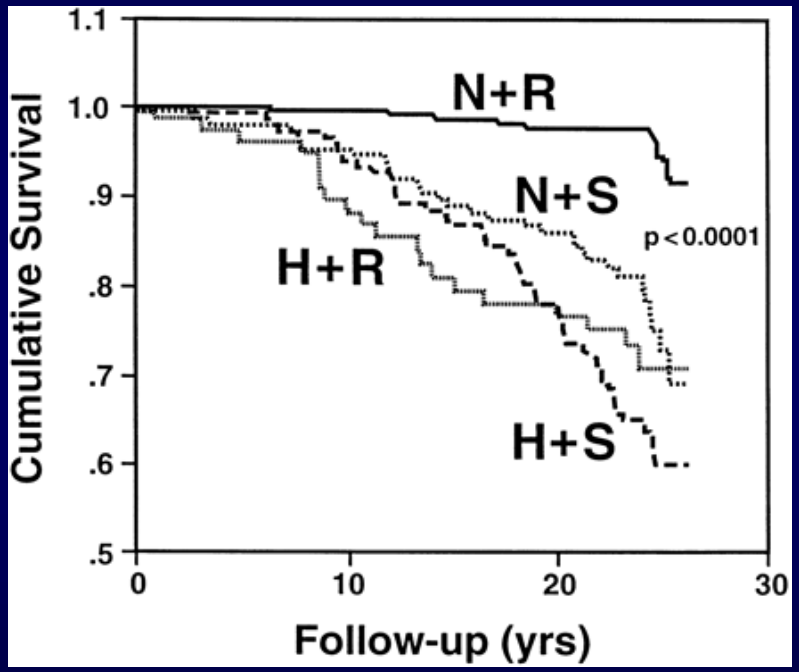
ENDOTHELIUM-DEPENDENT VASODILATION IN SALT-SENSITIVE AND SALT-RESISTANT PATIENTS



Bragulat, De la Sierra et al. Hypertension 2001

CARDIOVASCULAR EVENTS AND MORTALITY IN SALT SENSITIVE AND SALT RESISTANT HYPERTENSIVES





Morimoto. Lancet 1997; 350:1734

Weinberger et al. Hypertension 2001

Closing remarks

- Excessive salt consumption is responsible for BP elevation and hypertension development. Salt restriction reduces BP values. This effect is not blunted in the diabetic population.
- There is some controversy regarding salt consumption and CV (and renal) morbidity/mortality. Methodological problems (accuracy, confounders and reverse causalty) seem to play an importan role in the interpretation of findings.
- The BP response to salt is heterogeneous in the general population. Salt sensitivity is associated with organ damage and blunted (or paradoxal) hormonal responses to salt loading.
- Nutritional advice to reduce sodium intake (if administered as sodium chloride) to less than 1.5 g/day seems to be adequate.