Cardiovascular and Other Effects of Salt Consumption

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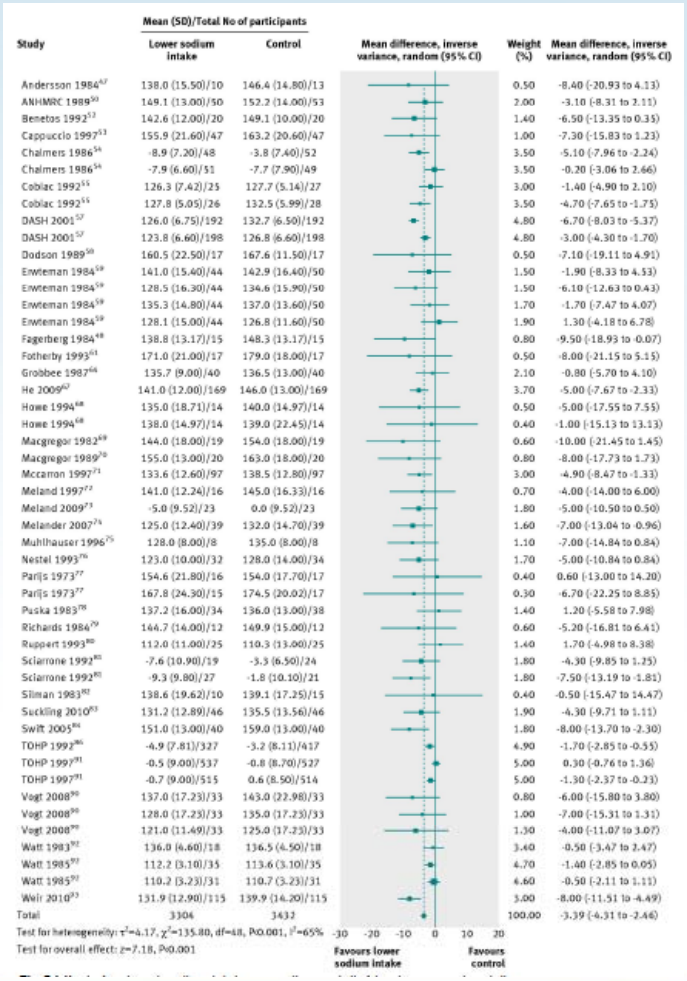
Salt intake and Chronic disease

- Blood pressure
- Cardiovascular outcomes
  - Stroke
  - Congestive Heart Failure
  - Left ventricular hypertrophy
- Renal damage
- Calcium metabolism
  - Hypercalciuria
  - Calcium kidney stones
  - Bone demineralisation / osteoporosis / fractures
- Stomach cancer
- Fluid retention
- Cataract

A reduction in dietary salt intake reduces blood pressure in adults and children



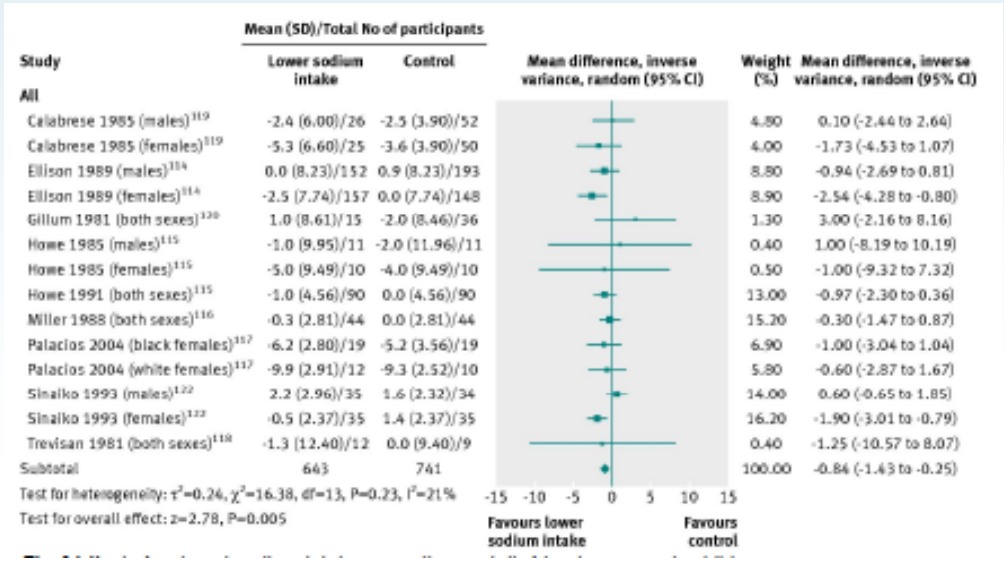
Study	Mean (SD)/Total No of participants: Lower sodium intake	Control	Mean difference, inverse variance, random (95% CI)	Weight (%)	Mean difference, inverse variance, random (95% CI)
Andersson 1984[47]	138.0 (15.50)/10	146.4 (14.80)/13		0.50	-8.40 (-20.93 to 4.13)
ANHMRC 1989[50]	149.1 (13.00)/50	152.2 (14.00)/53		2.00	-3.10 (-8.31 to 2.11)
Benetos 1992[52]	142.6 (12.00)/20	149.1 (10.00)/20		1.40	-6.50 (-13.35 to 0.35)
Cappuccio 1997[53]	155.9 (21.60)/47	163.2 (20.60)/47		1.00	-7.30 (-15.83 to 1.23)
Chalmers 1986[54]	-8.9 (7.20)/48	-3.8 (7.40)/52		3.50	-5.10 (-7.96 to -2.24)
Chalmers 1986[54]	-7.9 (6.60)/51	-7.7 (7.90)/49		3.50	-0.20 (-3.06 to 2.66)
Cobiac 1992[55]	126.3 (7.42)/25	127.7 (5.14)/27		3.00	-1.40 (-4.90 to 2.10)
Cobiac 1992[55]	127.8 (5.05)/26	132.5 (5.99)/28		3.50	-4.70 (-7.65 to -1.75)
DASH 2001[57]	126.0 (6.75)/192	132.7 (6.50)/192		4.80	-6.70 (-8.03 to -5.37)
DASH 2001[57]	123.8 (6.60)/198	126.8 (6.60)/198		4.80	-3.00 (-4.30 to -1.70)
Dodson 1989[59]	160.5 (22.50)/17	167.6 (11.50)/17		0.50	-7.10 (-19.11 to 4.91)
Erwteman 1984[58]	141.0 (15.40)/44	142.9 (16.40)/50		1.50	-1.90 (-8.33 to 4.53)
Erwteman 1984[58]	128.5 (16.30)/44	134.6 (15.90)/50		1.50	-6.10 (-12.63 to 0.43)
Erwteman 1984[58]	135.3 (14.80)/44	137.0 (13.60)/50		1.70	-1.70 (-7.47 to 4.07)
Erwteman 1984[58]	128.1 (15.00)/44	126.8 (11.60)/50		1.90	1.30 (-4.18 to 6.78)
Fagerberg 1984[48]	138.8 (13.17)/15	148.3 (13.17)/15		0.80	-9.50 (-18.93 to -0.07)
Fotherby 1993[61]	171.0 (21.00)/17	179.0 (18.00)/17		0.50	-8.00 (-21.15 to 5.15)
Grobbee 1987[64]	135.7 (9.00)/40	136.5 (13.00)/40		2.10	-0.80 (-5.70 to 4.10)
He 2009[62]	141.0 (12.00)/169	146.0 (13.00)/169		3.70	-5.00 (-7.67 to -2.33)
Howe 1994[68]	135.0 (18.71)/14	140.0 (14.97)/14		0.50	-5.00 (-17.55 to 7.55)
Howe 1994[68]	138.0 (14.97)/14	139.0 (22.45)/14		0.40	-1.00 (-15.13 to 13.13)
Macgregor 1982[69]	144.0 (18.00)/19	154.0 (18.00)/19		0.60	-10.00 (-21.45 to 1.45)
Macgregor 1989[70]	155.0 (13.00)/20	163.0 (18.00)/20		0.80	-8.00 (-17.73 to 1.73)
Mccarron 1997[71]	133.6 (12.60)/97	138.5 (12.80)/97		3.00	-4.90 (-8.47 to -1.33)
Meland 1997[72]	141.0 (12.24)/16	145.0 (16.33)/16		0.70	-4.00 (-14.00 to 6.00)
Meland 2009[73]	-5.0 (9.52)/23	0.0 (9.52)/23		1.80	-5.00 (-10.50 to 0.50)
Melander 2007[74]	125.0 (12.40)/39	132.0 (14.70)/39		1.60	-7.00 (-13.04 to -0.96)
Muhlhauser 1996[75]	128.0 (8.00)/8	135.0 (8.00)/8		1.10	-7.00 (-14.84 to 0.84)
Nestel 1993[76]	123.0 (10.00)/32	128.0 (14.00)/34		1.70	-5.00 (-10.84 to 0.84)
Parijs 1973[77]	154.6 (21.80)/16	154.0 (17.70)/17		0.40	0.60 (-13.00 to 14.20)
Parijs 1973[77]	167.8 (24.30)/15	174.5 (20.02)/17		0.30	-6.70 (-22.25 to 8.85)
Puska 1983[78]	137.2 (16.00)/34	136.0 (13.00)/38		1.40	1.20 (-5.58 to 7.98)
Richards 1984[79]	144.7 (14.00)/12	149.9 (15.00)/13		0.60	-5.20 (-16.81 to 6.41)
Ruppert 1993[80]	112.0 (11.00)/25	110.3 (13.00)/25		1.40	1.70 (-4.98 to 8.38)
Sciarrone 1992[81]	-7.6 (10.90)/19	-3.3 (6.50)/24		1.80	-4.30 (-9.85 to 1.25)
Sciarrone 1992[81]	-9.3 (9.80)/27	-1.8 (10.10)/21		1.80	-7.50 (-13.19 to -1.81)
Silman 1983[82]	138.6 (19.62)/10	139.1 (17.25)/15		0.40	-0.50 (-15.47 to 14.47)
Suckling 2010[83]	131.2 (12.89)/46	135.5 (13.56)/46		1.90	-4.30 (-9.71 to 1.11)
Swift 2005[84]	151.0 (13.00)/40	159.0 (13.00)/40		1.80	-8.00 (-13.70 to -2.30)
TOHP 1992[86]	-4.9 (7.81)/327	-3.2 (8.11)/417		4.90	-1.70 (-2.85 to -0.55)
TOHP 1997[91]	-0.5 (9.00)/537	-0.8 (8.70)/527		5.00	0.30 (-0.76 to 1.36)
TOHP 1997[91]	-0.7 (9.00)/515	0.6 (8.50)/514		5.00	-1.30 (-2.37 to -0.23)
Vogt 2008[90]	137.0 (17.23)/33	143.0 (22.98)/33		0.80	-6.00 (-15.80 to 3.80)
Vogt 2008[90]	128.0 (17.23)/33	135.0 (17.23)/33		1.00	-7.00 (-15.31 to 1.31)
Vogt 2008[90]	121.0 (11.49)/33	125.0 (17.23)/33		1.30	-4.00 (-11.07 to 3.07)
Watt 1983[92]	136.0 (4.60)/18	136.5 (4.50)/18		3.40	-0.50 (-3.47 to 2.47)
Watt 1985[92]	112.2 (3.10)/35	113.6 (3.10)/35		4.70	-1.40 (-2.85 to 0.05)
Watt 1985[92]	110.2 (3.23)/31	110.7 (3.23)/31		4.60	-0.50 (-2.11 to 1.11)
Weir 2010[93]	131.9 (12.90)/115	139.9 (14.20)/115		3.00	-8.00 (-11.51 to -4.49)
Total	3304	3432		100.00	-3.39 (-4.31 to -2.46)

Test for heterogeneity: τ^2=4.17, χ^2=135.80, df=48, P<0.001, I^2=65%

Test for overall effect: z=7.18, P<0.001

-30 -20 -10 0 10 20

Favours lower sodium intake | Favours control



Study	Mean (SD)/Total No of participants: Lower sodium intake	Control	Mean difference, inverse variance, random (95% CI)	Weight (%)	Mean difference, inverse variance, random (95% CI)
All					
Calabrese 1985 (males)[119]	-2.4 (6.00)/26	-2.5 (3.90)/52		4.80	0.10 (-2.44 to 2.64)
Calabrese 1985 (females)[119]	-5.3 (6.60)/25	-3.6 (3.90)/50		4.00	-1.73 (-4.53 to 1.07)
Ellison 1989 (males)[114]	0.0 (8.23)/152	0.9 (8.23)/193		8.80	-0.94 (-2.69 to 0.81)
Ellison 1989 (females)[114]	-2.5 (7.74)/157	0.0 (7.74)/148		8.90	-2.54 (-4.28 to -0.80)
Gillum 1981 (both sexes)[120]	1.0 (8.61)/15	-2.0 (8.46)/36		1.30	3.00 (-2.16 to 8.16)
Howe 1985 (males)[115]	-1.0 (9.95)/11	-2.0 (11.96)/11		0.40	1.00 (-8.19 to 10.19)
Howe 1985 (females)[115]	-5.0 (9.49)/10	-4.0 (9.49)/10		0.50	-1.00 (-9.32 to 7.32)
Howe 1991 (both sexes)[115]	-1.0 (4.56)/90	0.0 (4.56)/90		13.00	-0.97 (-2.30 to 0.36)
Miller 1988 (both sexes)[116]	0.3 (2.81)/44	0.0 (2.81)/44		15.20	0.30 (-1.47 to 0.87)
Palacios 2004 (black females)[117]	-6.2 (2.80)/19	-5.2 (3.56)/19		6.90	-1.00 (-3.04 to 1.04)
Palacios 2004 (white females)[117]	-9.9 (2.91)/12	-9.3 (2.52)/10		5.80	-0.60 (-2.87 to 1.67)
Sinaiko 1993 (males)[122]	2.2 (2.96)/35	1.6 (2.32)/34		14.00	0.60 (-0.65 to 1.85)
Sinaiko 1993 (females)[122]	0.5 (2.37)/35	1.4 (2.37)/35		16.20	-1.90 (-3.01 to -0.79)
Trevisan 1981 (both sexes)[118]	-1.3 (12.40)/12	0.0 (9.40)/9		0.40	-1.25 (-10.57 to 8.07)
Subtotal	643	741		100.00	-0.84 (-1.43 to -0.25)

Test for heterogeneity: τ^2=0.24, χ^2=16.38, df=13, P=0.23, I^2=21%

Test for overall effect: z=2.78, P=0.005

-15 -10 -5 0 5 10 15

Favours lower sodium intake | Favours control

World Health Organization

ESH

Aburto NJ et al. BMJ 2013; 346: f1326

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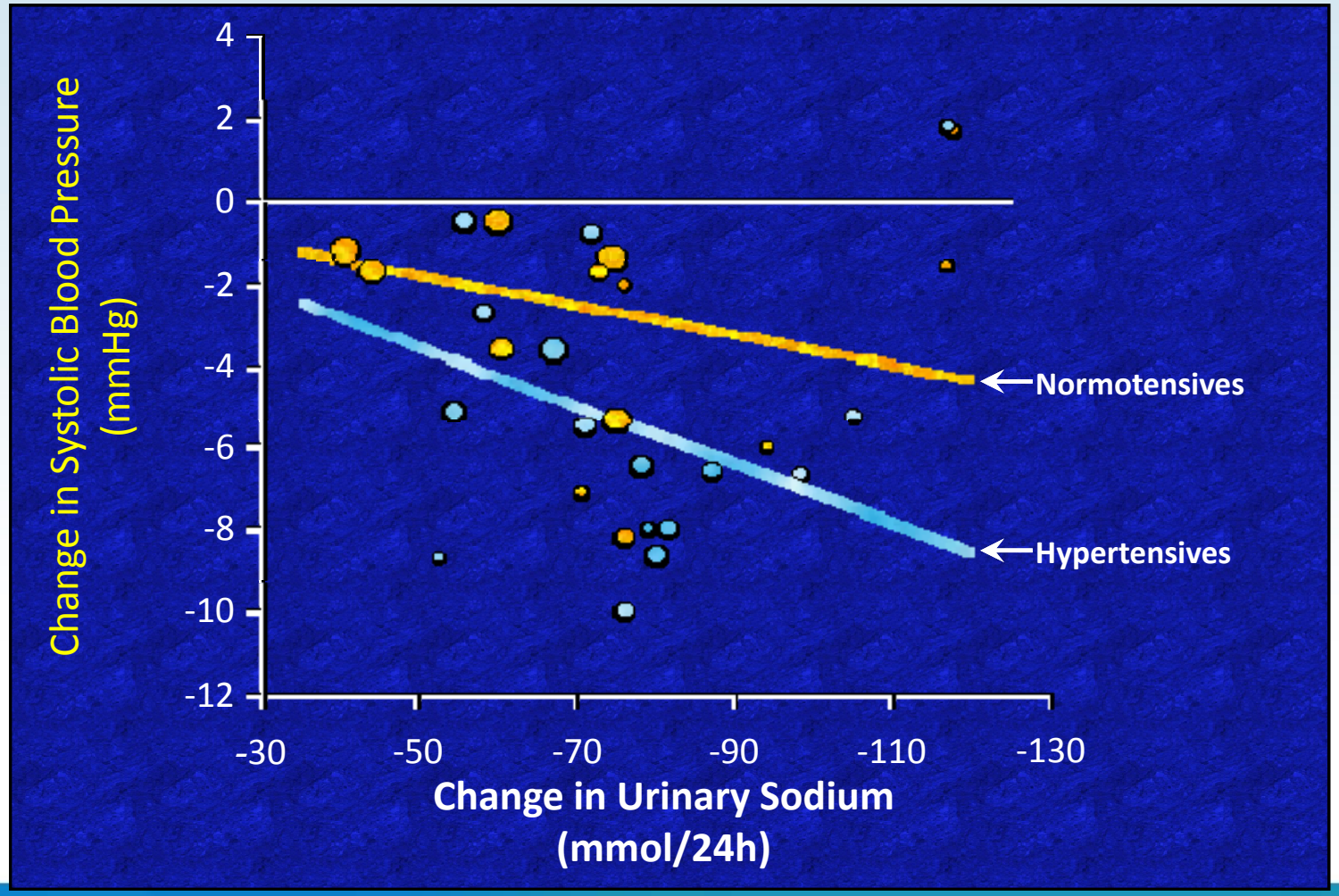
The lower the salt, the lower the blood pressure



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He FJ, & MacGregor GA. J Hum Hypertens. 2002;16:761-70.

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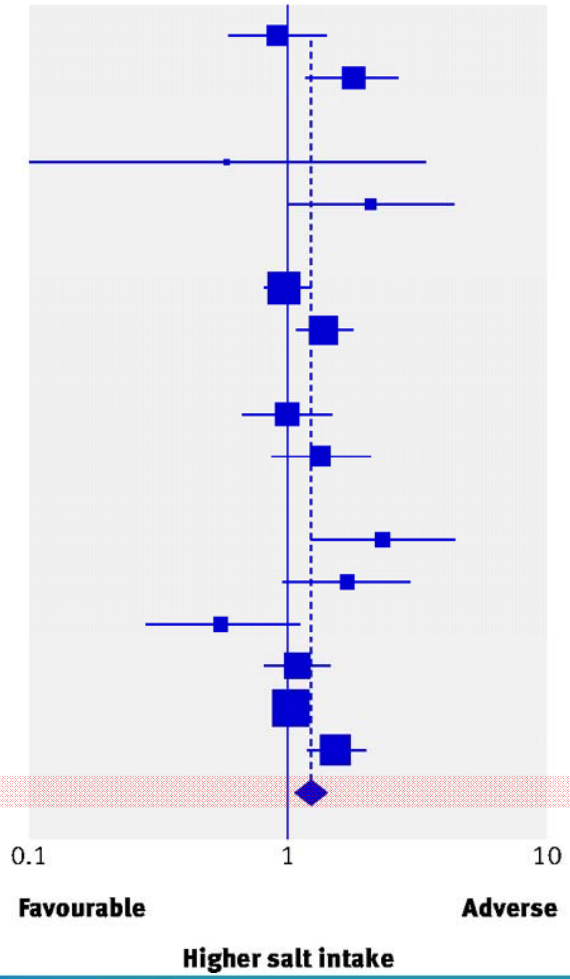
Risk of stroke associated with salt intake in population

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 et al. Br Med J 2009; 339: b4567

Associations between salt intake and CVD risk

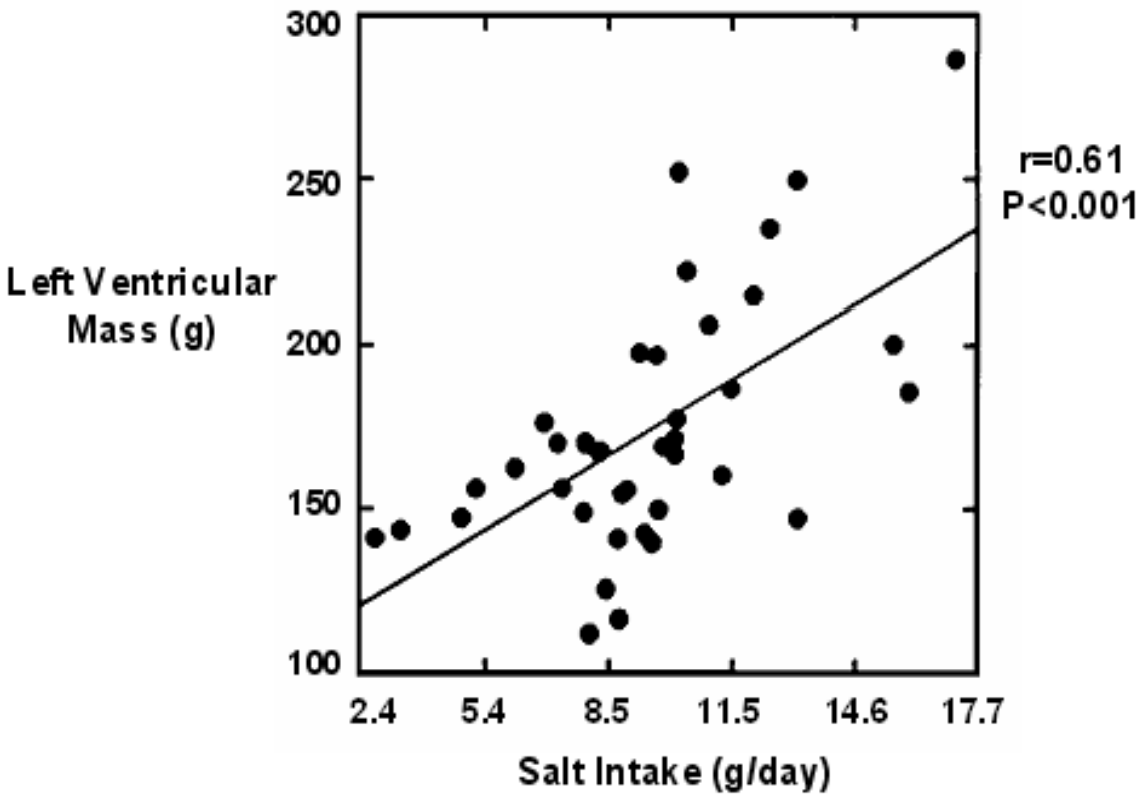
Salt Intake and Blood Pressure Rise with Age (INTERSALT)

Increase in Systolic Blood Pressure with Age (mmHg per y

Salt and Stroke

Deaths From Stroke (per 10^6 per year)

Salt and Left Ventricular Mass



INTERSALT. BMJ 1988;297:319-28

Perry IJ & Beevers DG J Hum Hypert 1992;6:23-5

Schmieder RE et al Circulation 1988;78: 951-6

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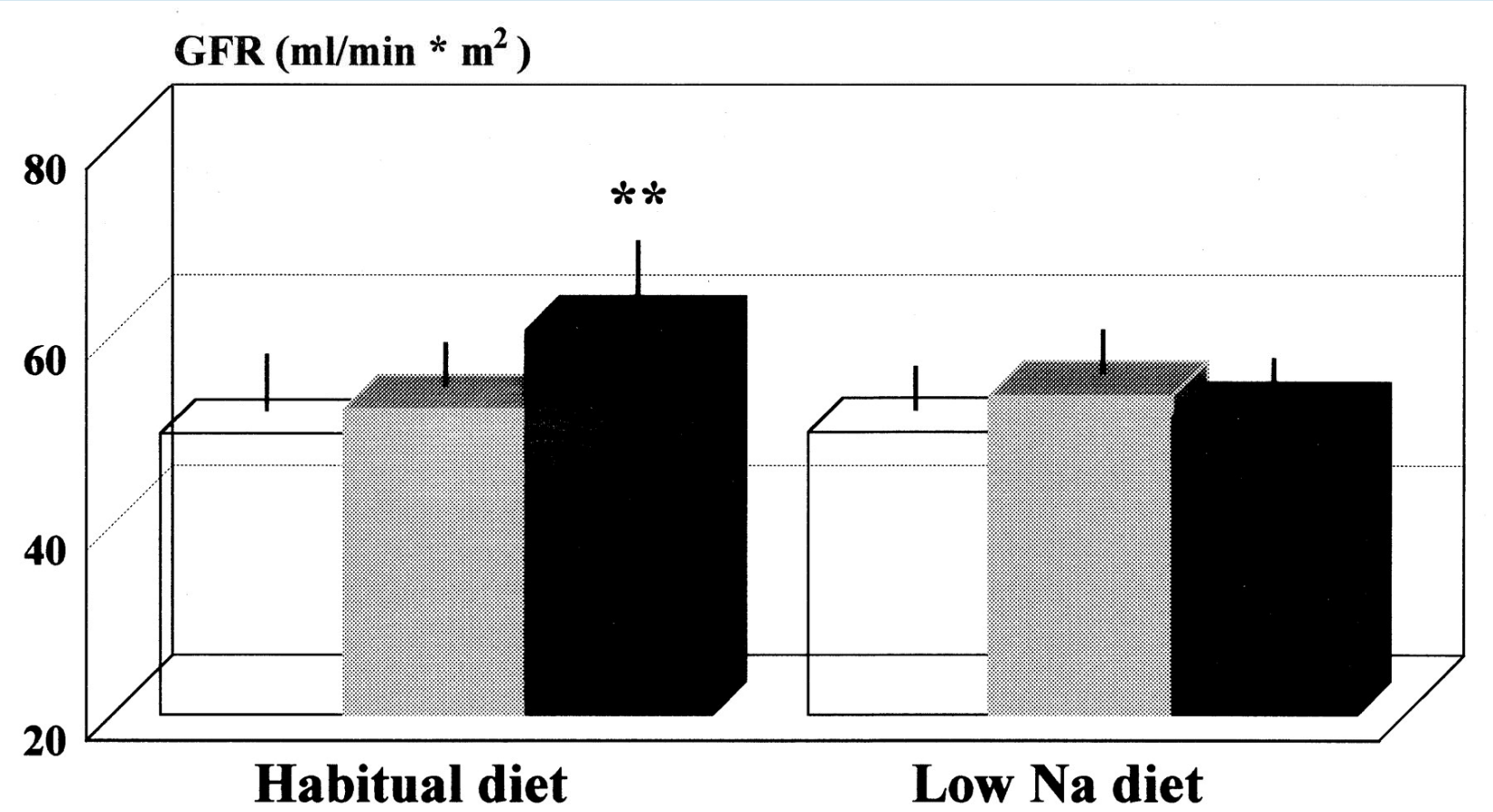
Low salt diet reduces hyperfiltration in salt sensitive normotensive individuals



Barba G et al. Hypertension 1996;27:1160-4

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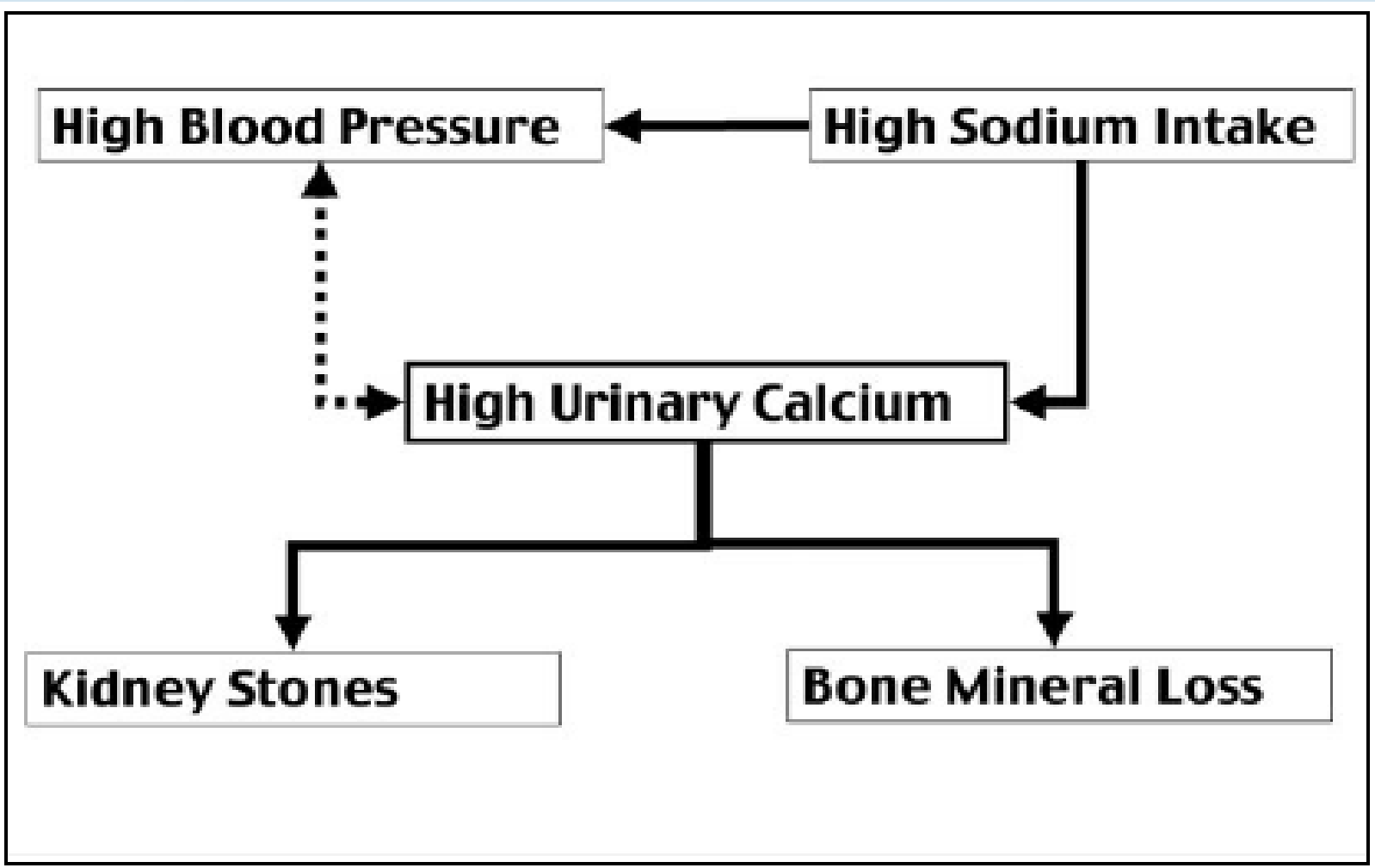
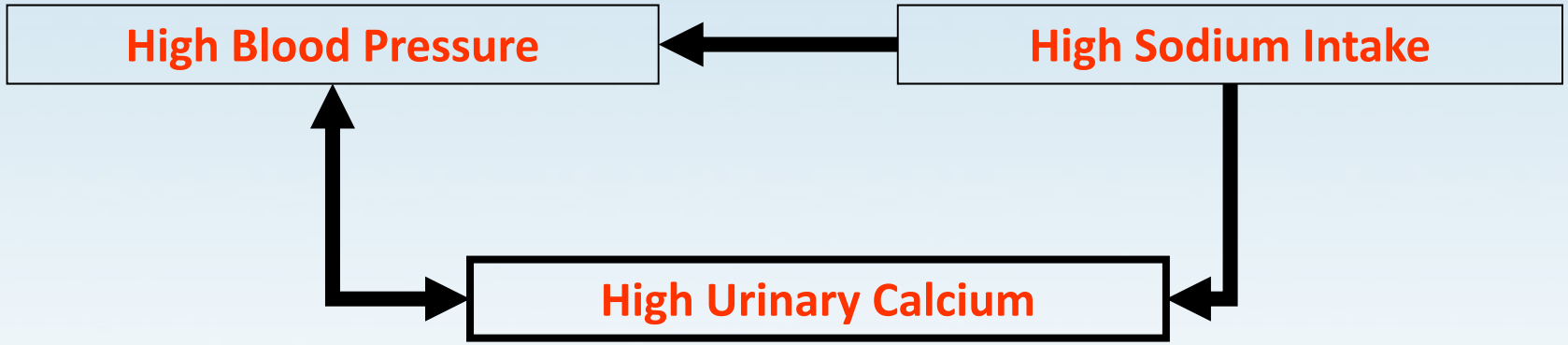
The ‘Four Cornerstones’ hypothesis



Cappuccio FP et al. J Nephrol 2000; 13: 169-77

Sodium intake, urinary calcium and BP



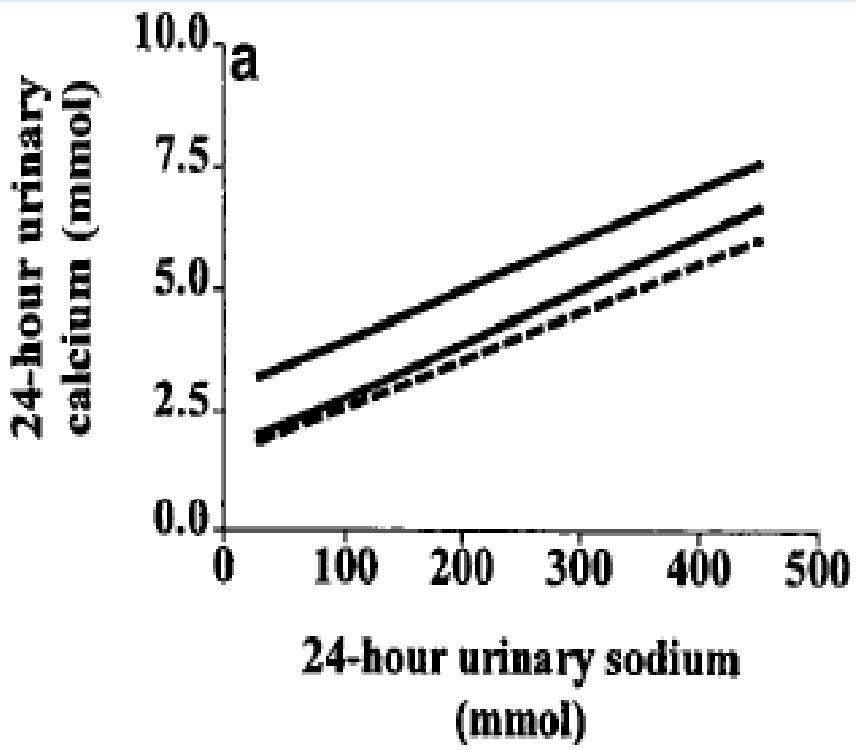
- Animal studies

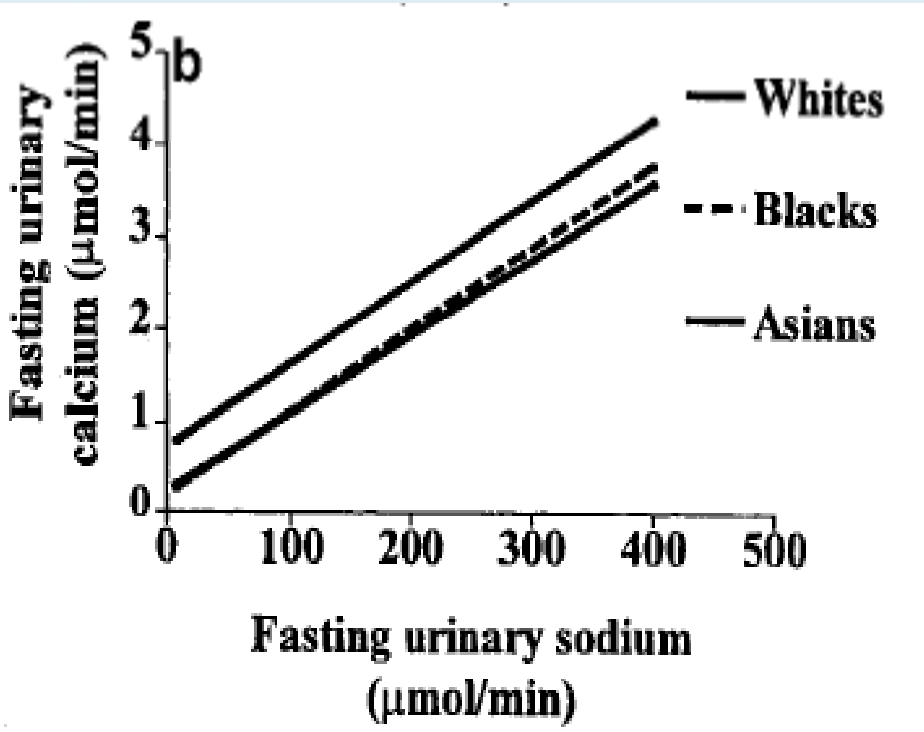
- Population studies: high sodium is associated with high urinary calcium and high blood pressure

- Evidence of independent associations

- Intervention studies: an increase in sodium intake causes an increase in calcium excretion and blood pressure

High salt intake is associated with urinary calcium losses, independent of BP (100 mmol Na ~ 1 mmol Ca)





Blackwood A et al. J Hum Hypert 2001; 15: 229–37

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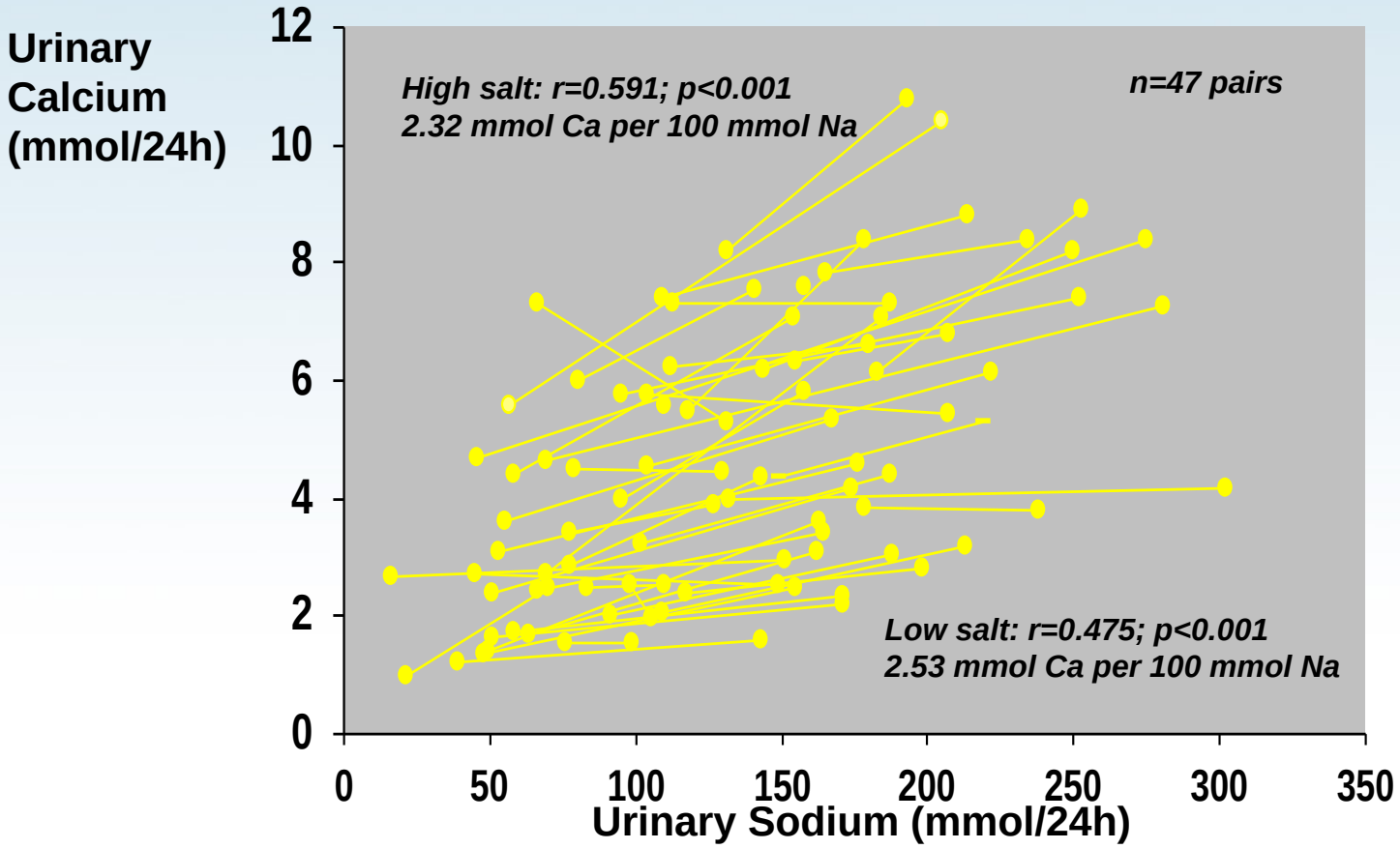
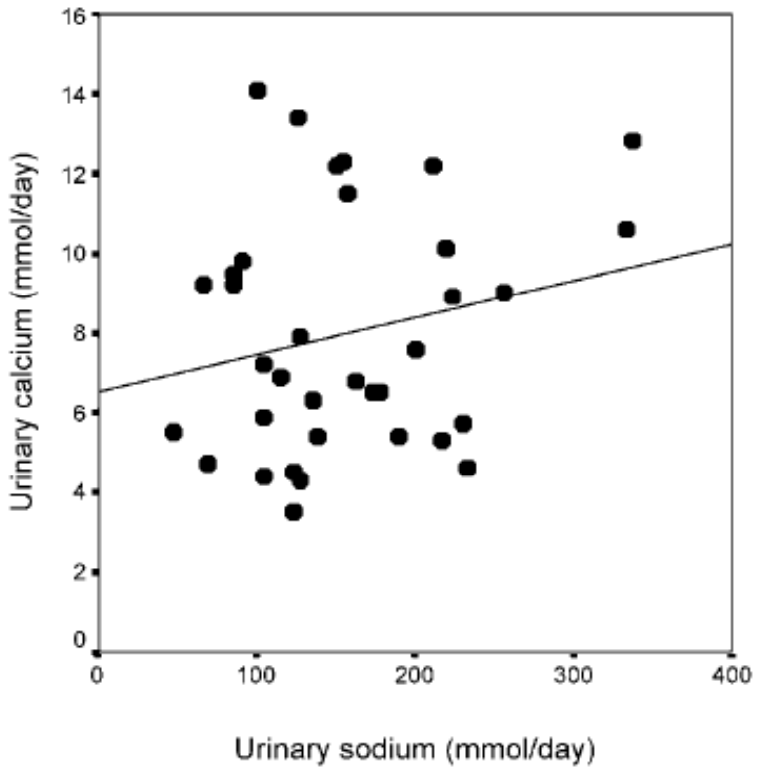
Relationship between sodium and calcium excretion in 47 elderly subjects on a high and a low sodium intake



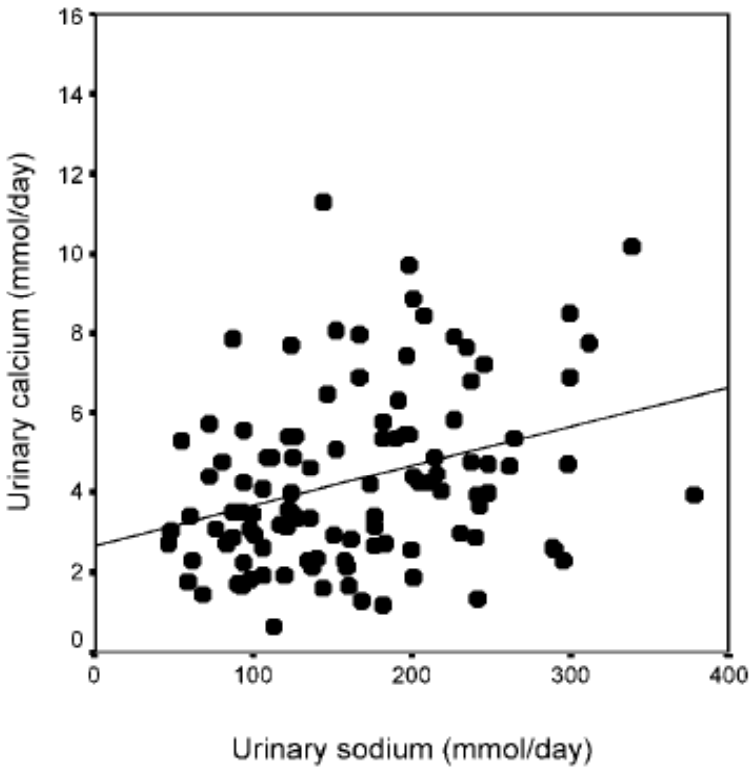
Cappuccio FP et al. J Nephrol 2000; 13: 169-77

Salt intake is the major determinant of urinary calcium excretion

Stone-formers (n=36)
Slope: 0.92 mmol Ca / 100 mmol Na
95% CI: -0.60, 2.40



Population controls (n=108)
Slope: 0.98 mmol Ca / 100 mmol Na
95% CI: 0.40, 1.50



Timio F et al. Blood Pressure 2003; 12: 122-7

Salt intake is the major determinant of urinary calcium excretion

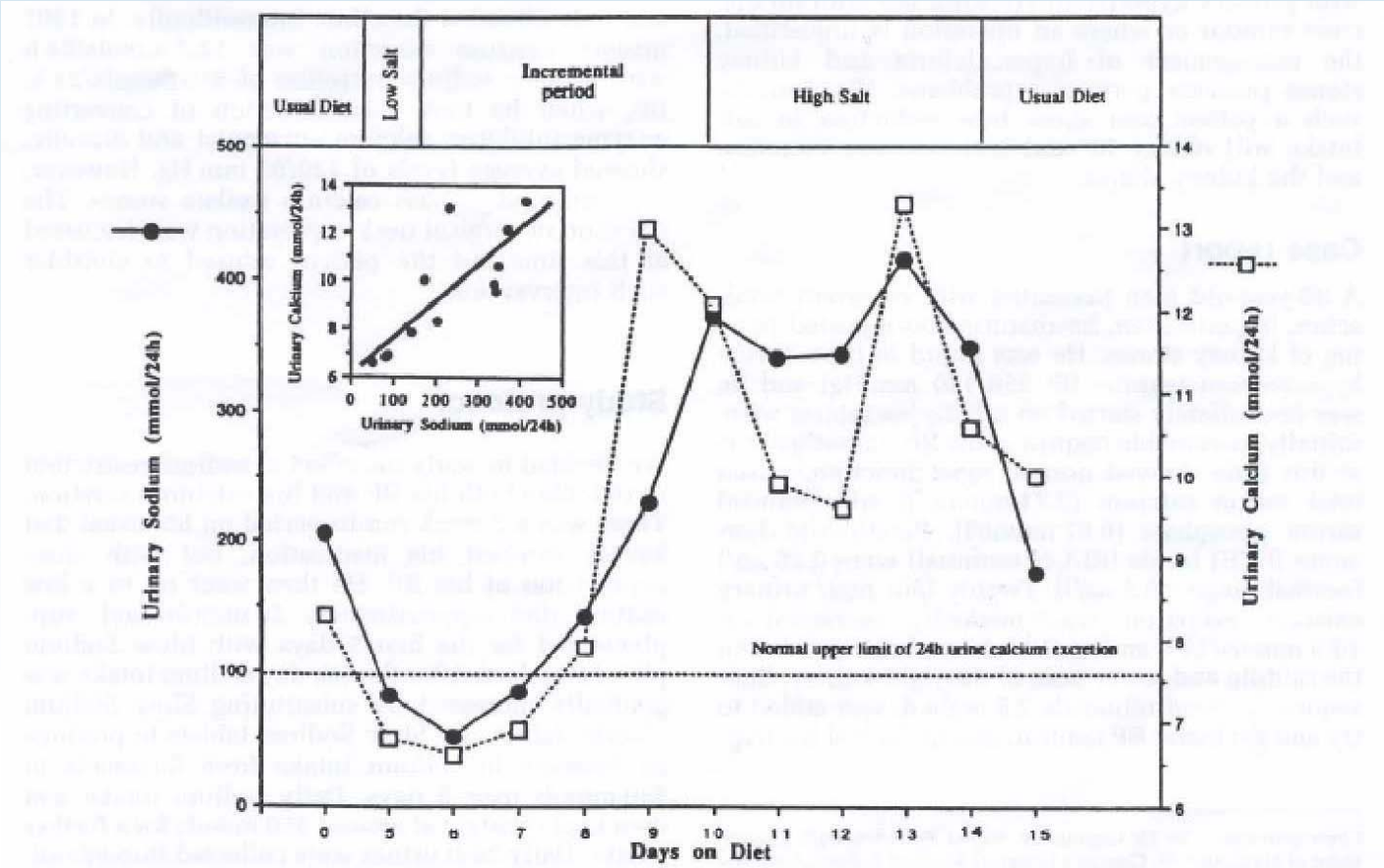
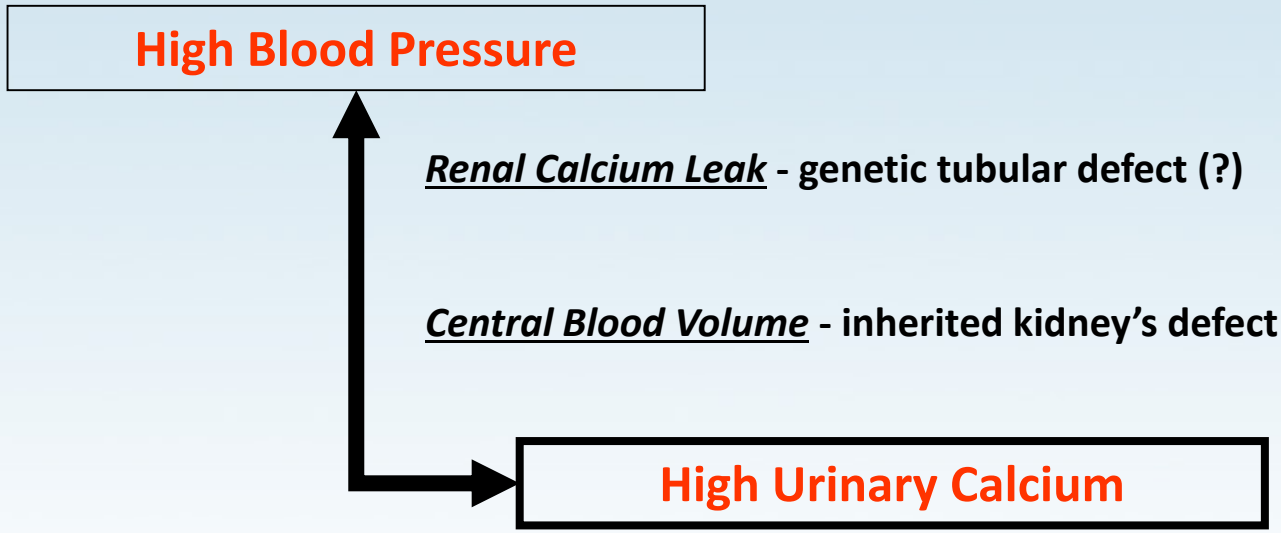


Figure 1 Urinary sodium excretion with associated changes in urinary calcium excretion following dietary alteration. Inset: Correlation between urinary sodium and calcium excretion, including values immediately before and after dietary alteration. $r = 0.81$; $P = 0.001$.

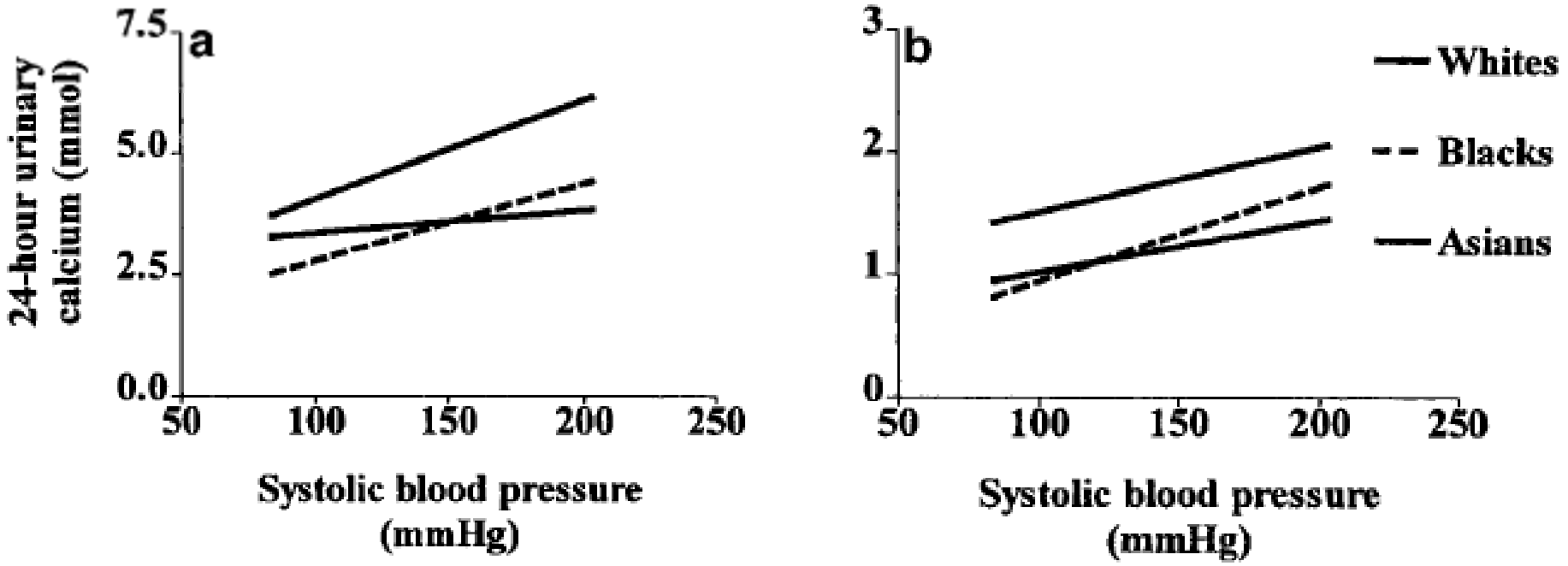
Saggar-Malik AK er al. J Hum Hypert 1996; 10: 811-3

High urinary calcium and blood pressure



- In several animal models of hypertension
- In 11-year old children in the upper quartile of BP distribution
- In hypertensives vs normotensives
- In population-based cross-sectional studies
- Even in fasting conditions

High BP associated with urinary calcium loss, independent of salt intake (10 mmHg ~ 0.2 mmol Ca)



Blackwood A et al. J Hum Hypert 2001; 15: 229–37

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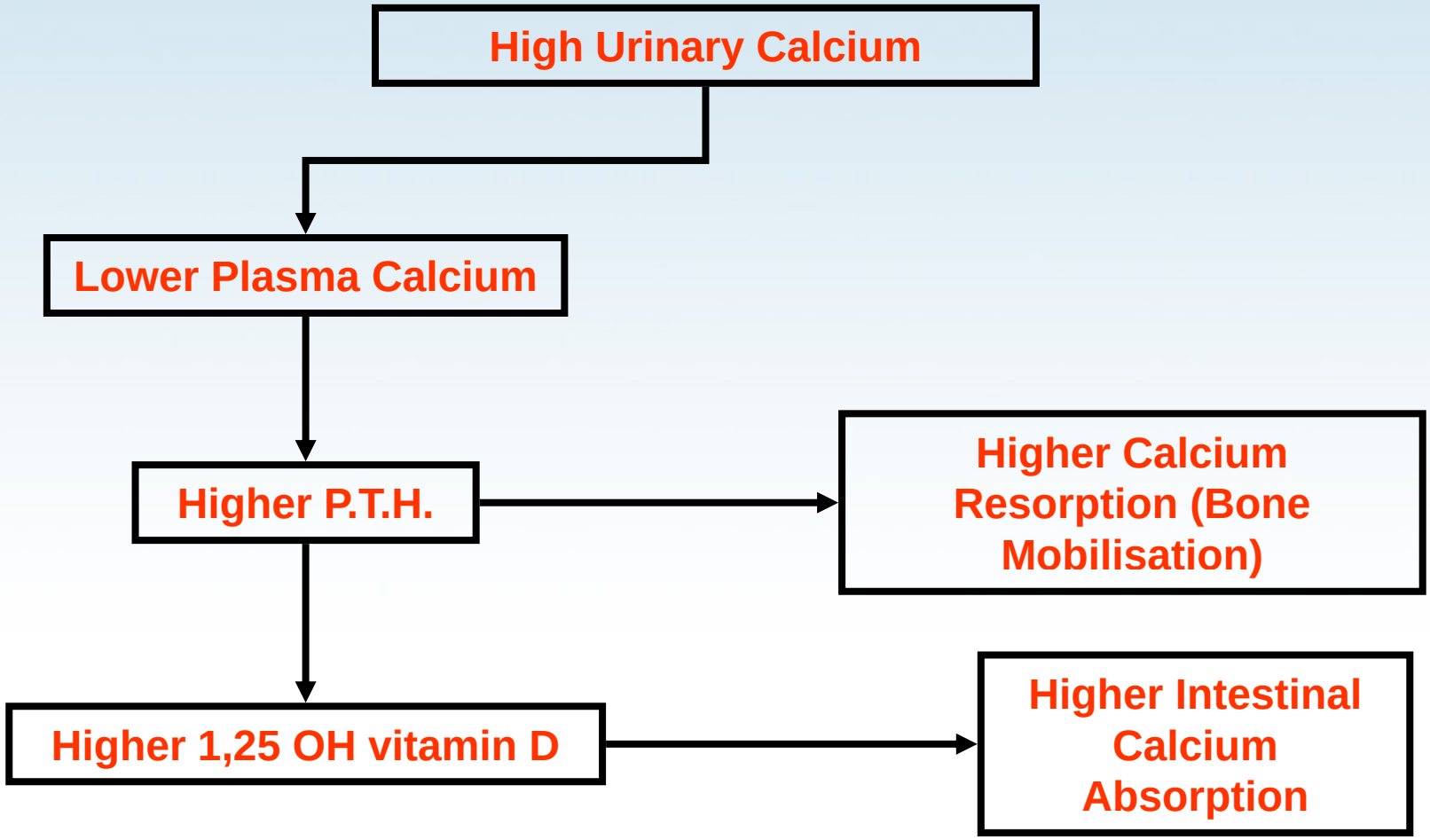
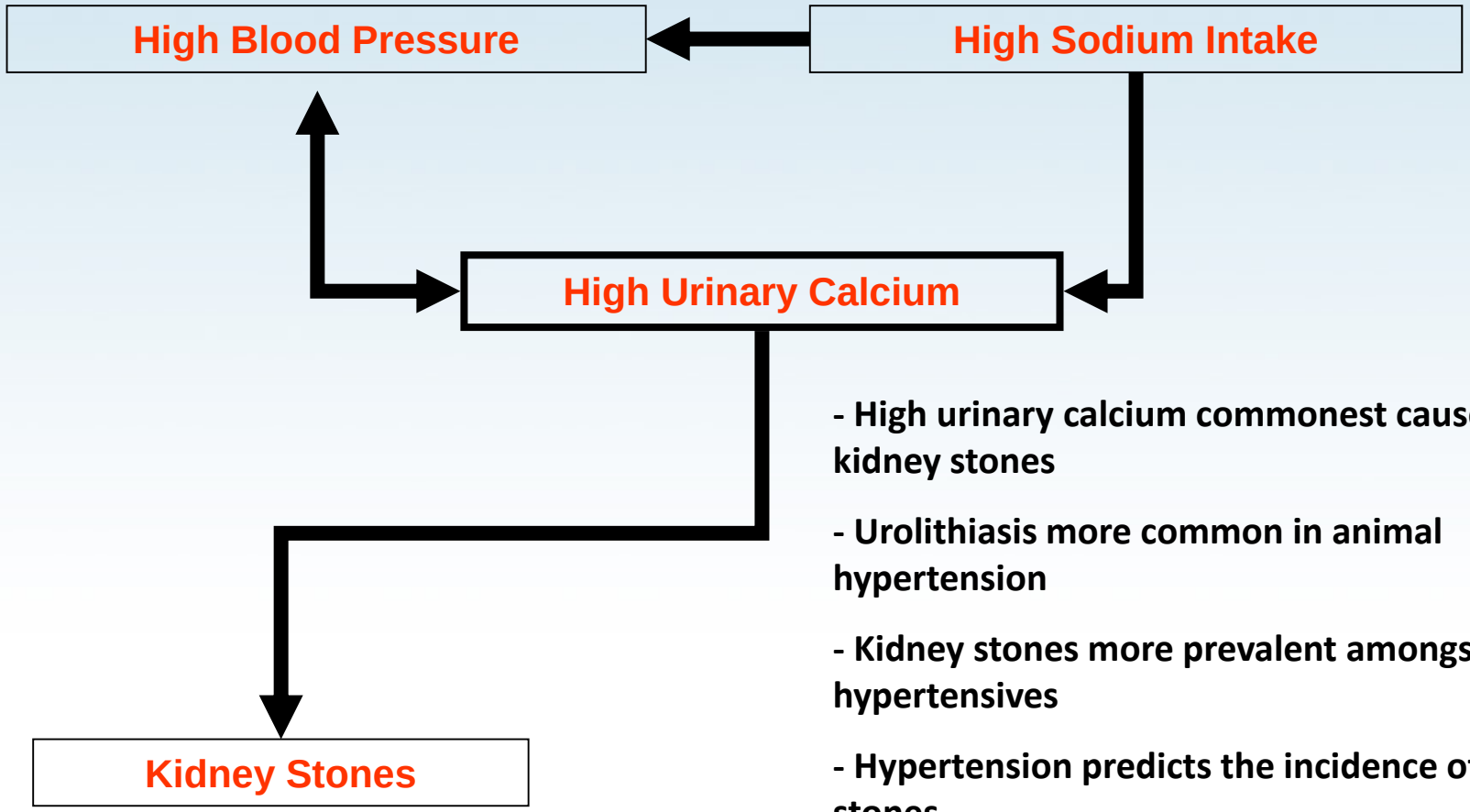
- **High blood pressure is associated with increased urinary calcium excretion**
    - ***experimental hypertension***
    - ***pre-hypertensive children***
    - ***case-control***
    - ***population***
- **The effect is independent of sodium intake, although a high sodium diet increases both urinary calcium excretion and blood pressure**
- **Suggested mechanisms**
    - ***primary renal calcium leak***
    - ***effect of corrected volume expansion***
- **Life-time consequence in hypertension**
    - ***higher incidence of kidney stones***
    - ***greater and faster bone demineralisation***

Metabolic features of hypercalciuria



High urinary calcium and kidney stones



- High urinary calcium commonest cause of kidney stones
- Urolithiasis more common in animal hypertension
- Kidney stones more prevalent amongst hypertensives
- Hypertension predicts the incidence of kidney stones

Hypertension risk factor for kidney stones …
… kidney stones risk factor for hypertension

TABLE I - PROSPECTIVE STUDIES OF HYPERTENSION AND KIDNEYSTONES

Relative risk of kidney stones in hypertensive people

Author	Sex	Cases (%) Hypertensive	Controls (%) Normotensive	Relative Risk	95% CI
Cappuccio (1999)	Men				
all		19/114 (16.7)	33/389 (8.5)	1.89¶	1.12-3.18
untreated only		14/82 (17.1)	33/389 (8.5)	1.94¶	1.10-3.43
Borghi (1999)	Men & Women	19/132 (14.3)	4/135 (2.9)	5.5	1.82-16.7
Madore (1999)	Men	?/10428	?/36990	0.99§	0.82-1.21
Madore (1999)	Women	n/a	n/a	1.01§	0.85-1.20

¶ age-adjusted; § multiple adjustments.

Relative risk of hypertension in stone formers

Author	Sex	Cases (%) Stone-formers	Controls (%) Non stone-formers	Relative Risk	95% CI
Strazzullo (unpub.)	Men	19/58 (32.7)	45/323 (13.9)	1.96¶	1.25-3.07
Madore (1999)	Men	466/2676 (17.4)	4613/35133 (13.1)	1.30¶	1.16-1.45
Madore (1999)	Women	499/2109 (23.7)	12041/65636 (18.3)	1.36¶	1.20-1.43

¶ age-adjusted.

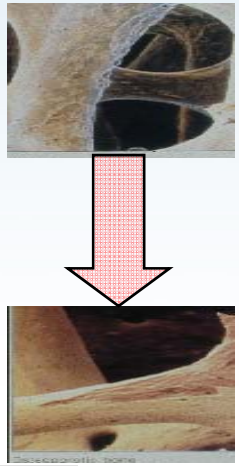
Cappuccio FP et al. J Nephrol 2000; 13: 169-77

Blood pressure and bone mineral density

High Blood Pressure

High Urinary Calcium

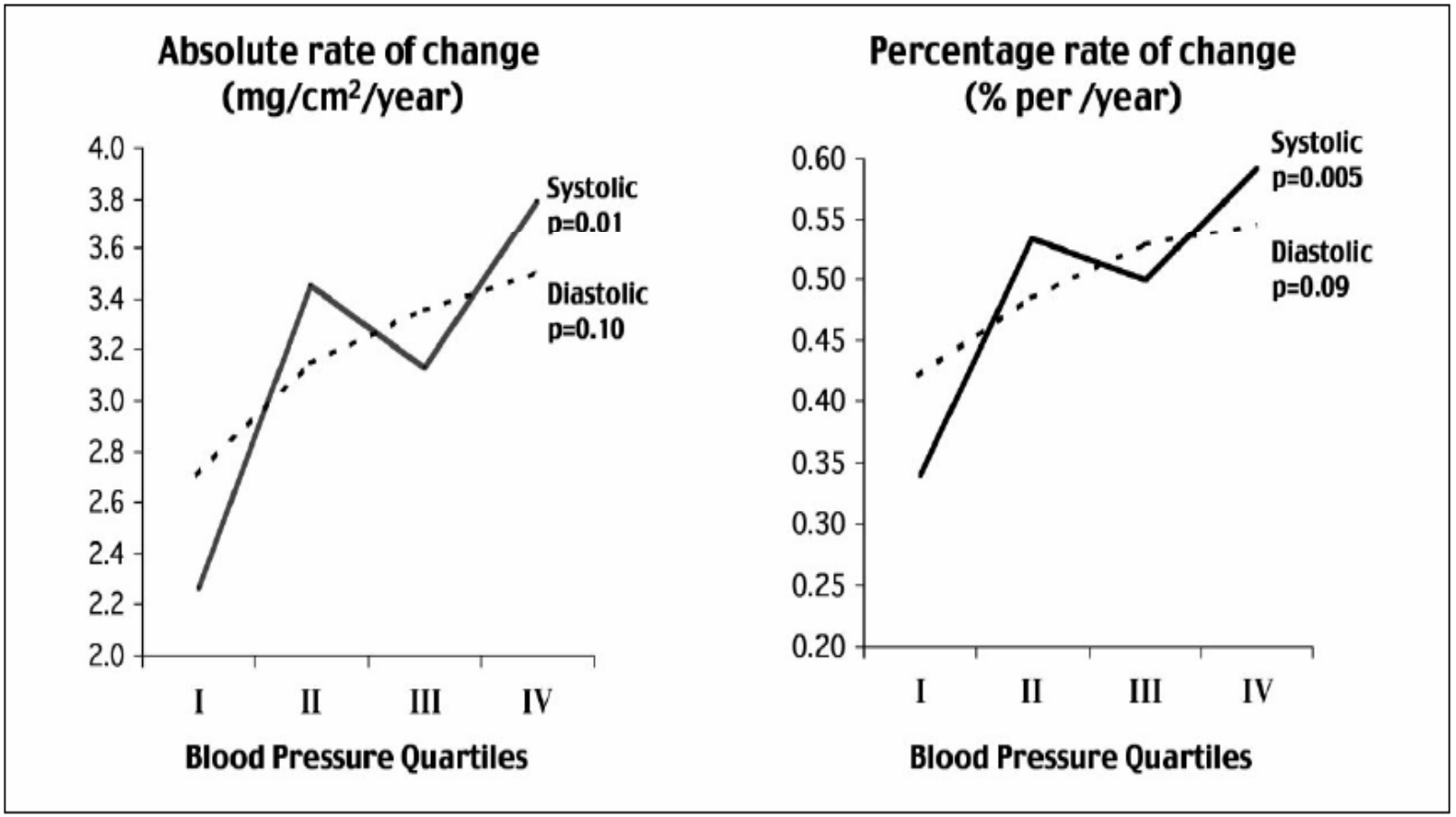
Bone Mineral Loss



- SHR and MSH have high calcium excretion and low bone mineral content

- In elderly women faster bone mineral loss in those with higher blood pressure

High blood pressure is associated with faster loss in femoral-neck bone-mineral density over 3.5 years in 3,676 white women (66-91 yrs) not taking thiazide diuretics



Results are adjusted for age, initial bone-mineral density, body weight, weight change, smoking and use of hormone-replacement therapy.

Cappuccio FP et al. Lancet 1999; 354: 971-5

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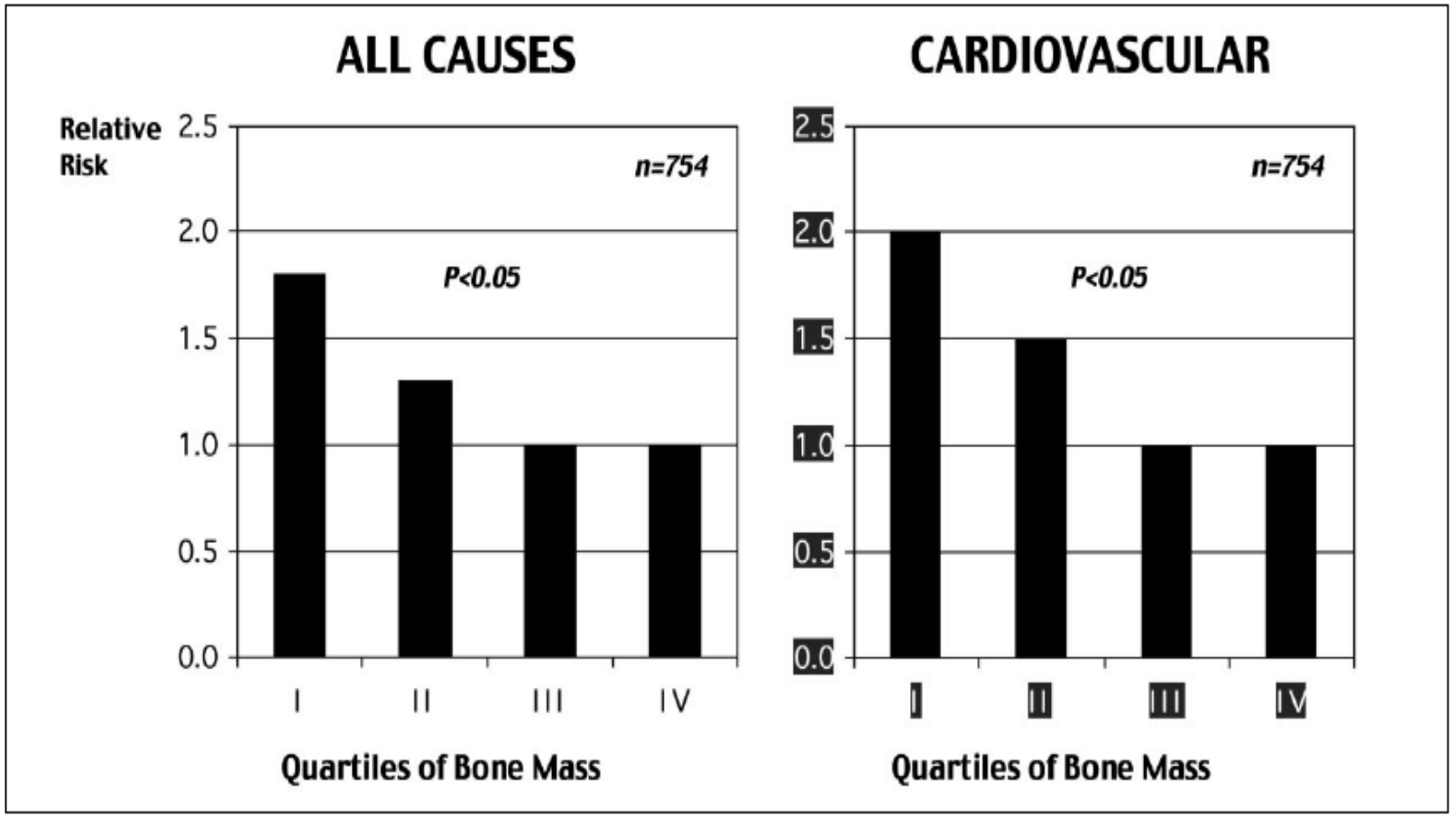
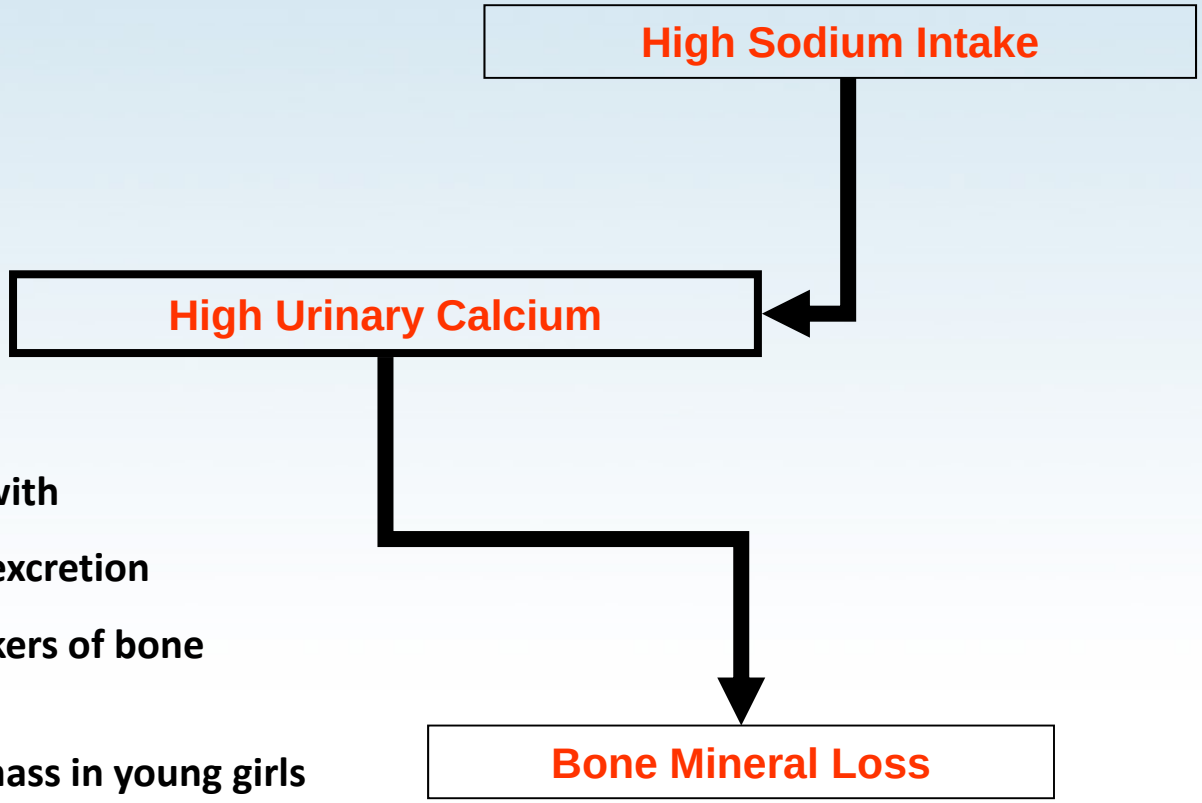
Low bone mineral content of the distal forearm is associated with a higher mortality from CVD in postmenopausal women (>60 yrs)



Von der Recke P et al. Am J Med 1999 ; 106: 273-8

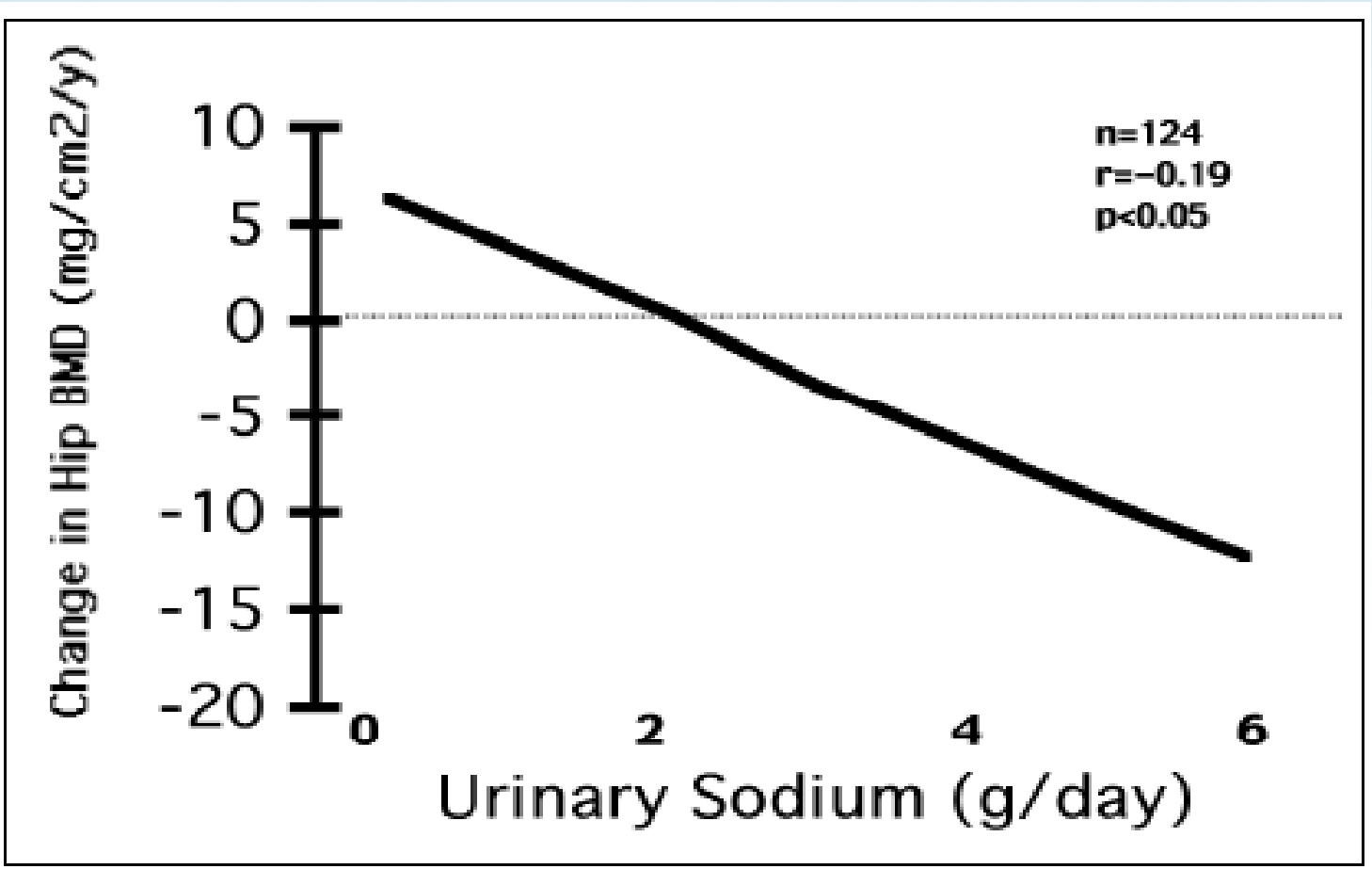
High salt intake and bone mineral density



High salt intake is associated with

- **high hydroxyproline excretion**
- **reduction in bio-markers of bone formation**
- **reduced peak bone mass in young girls**
- **higher rate of bone mineral loss in postmenopausal women**

High salt intake is associated with faster bone mineral density (BMD) loss at the hip in a 2-year follow-up study of postmenopausal women

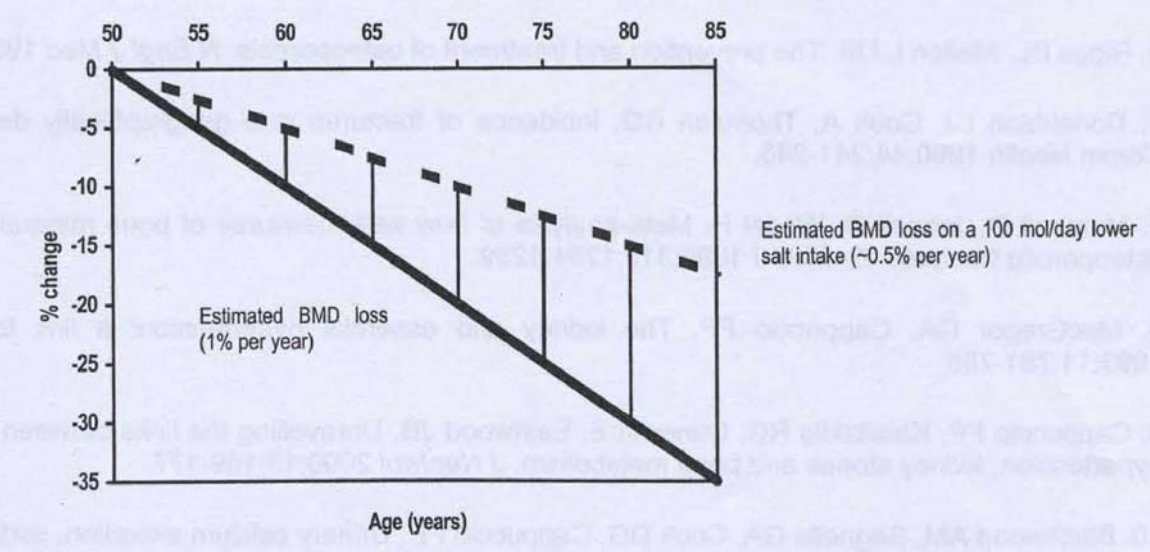


Devine A et al. Am J Clin Nutr 1995; 62: 740-5

Implications

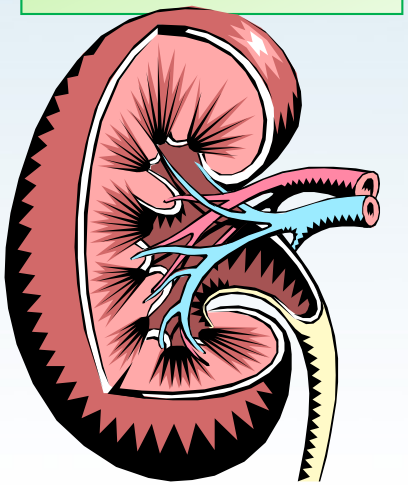
- **The estimated effects on calcium excretion are**
  - ***1 mmol calcium per 100 mmol of sodium change***
  - ***0.2 mmol calcium per 10 mmHg mean BP change***

- **These changes, if sustained over decades, may be responsible for the effects on total body calcium balance**

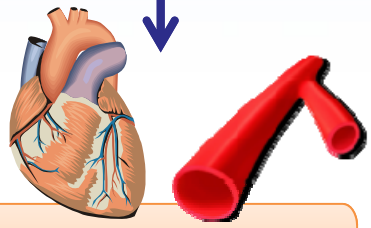


SALT INTAKE

Defect in excreting Na^+



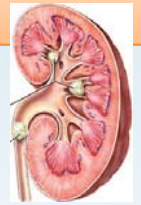
Retention of Na^+ and H_2O



Hypertension

↑ Ca^{++} excretion

Kidney stones



↓ serum Ca^{++}

Compensatory hormonal response (PTH)

↑Bone Ca++ resorption

Bone demineralization Osteoporosis

↑Intestinal Ca^{++} reabsorption

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Re-drawn from:
Cappuccio FP et al. Curr Opinion Nephrol Hypert 1997;6:477-82

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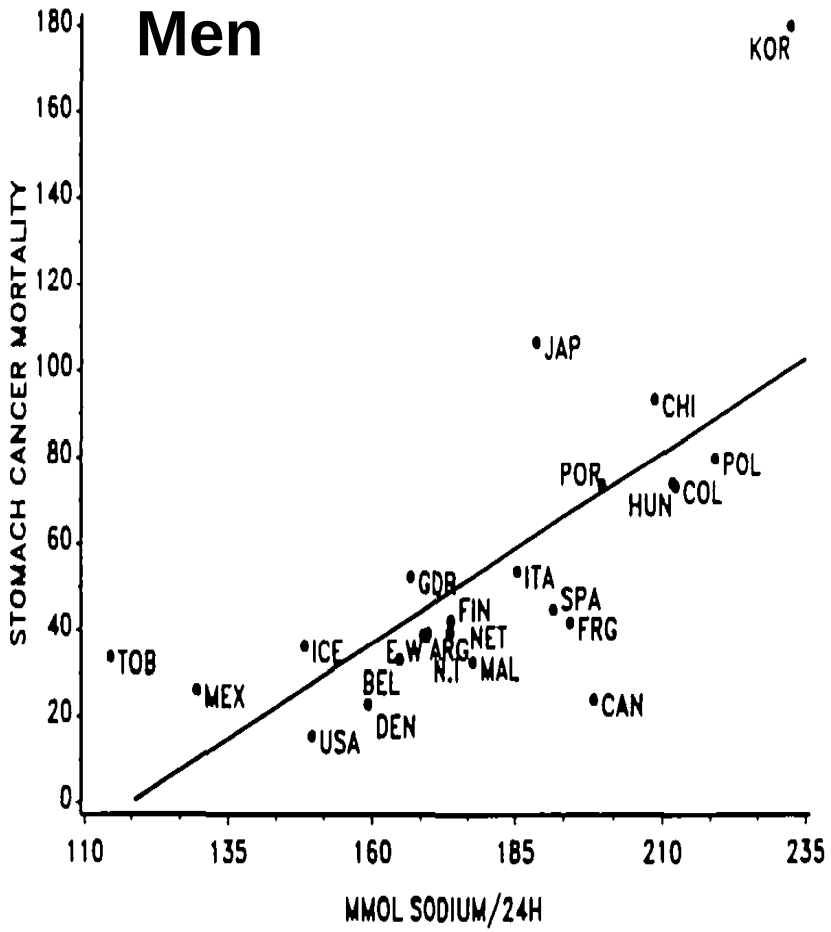
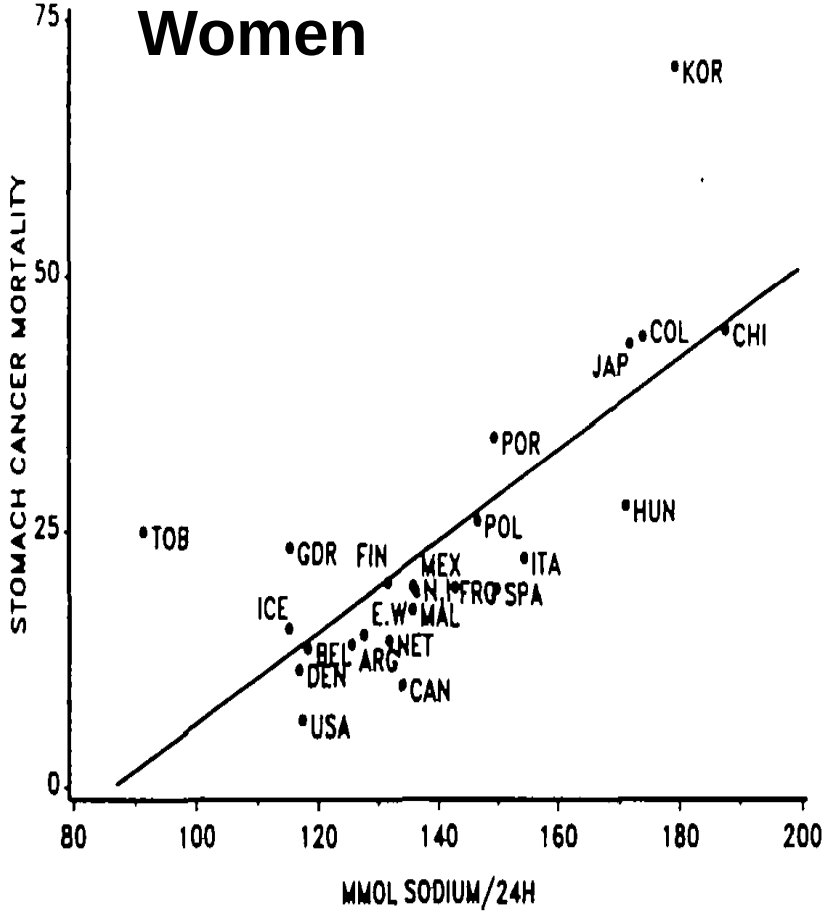
Salt intake and stomach cancer

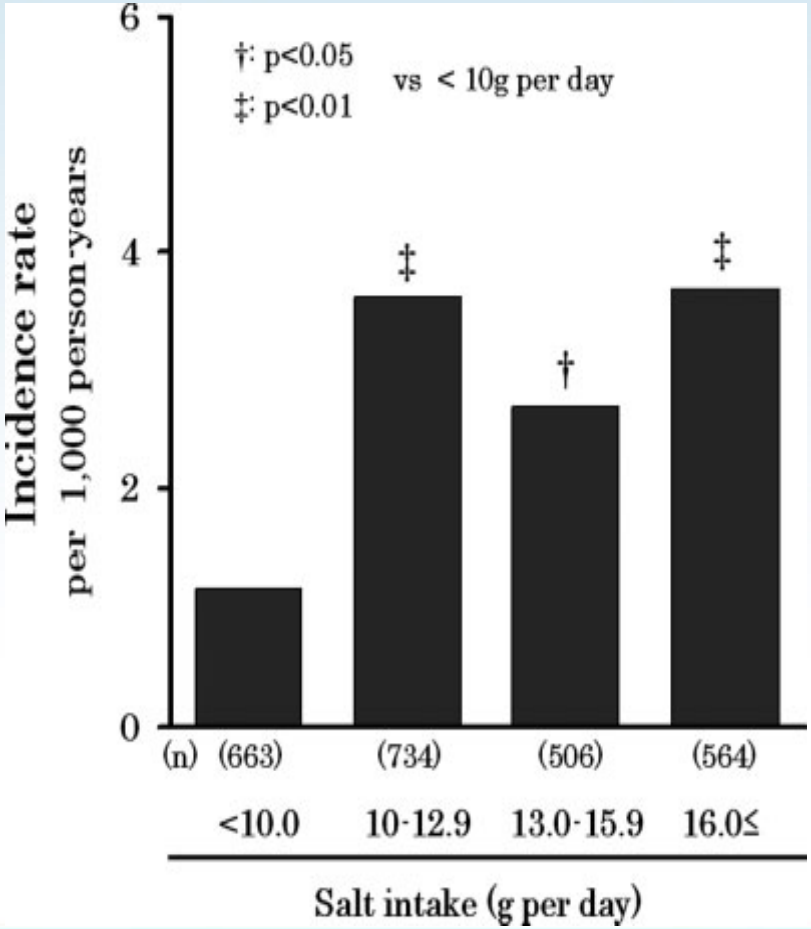




Joossens JV et al. Int J Epidemiol 1996; 25: 494-505

Salt intake and stomach cancer

The Hisayama study (1988-2002)



- Results inconsistent
  - +ve in High risk areas
    Japan, Korea, China
  - -ve in Low risk areas
    Netherlands, Norway
- Synergistic effect
  - Risk greater in those with pre-existing *H. pylori* or atrophic gastritis (HR 2.87; 1.14 to 7.24)

Shikata K et al. Int J Cancer 2006;119:196-201
Br J Cancer 2004;90:128-34
Van den Brandt PA et al. Cancer Causes Cont 2003;14:427-38
Sjodahl K et al. Can Epidemiol Biom Prev 2008;17:1997-2201

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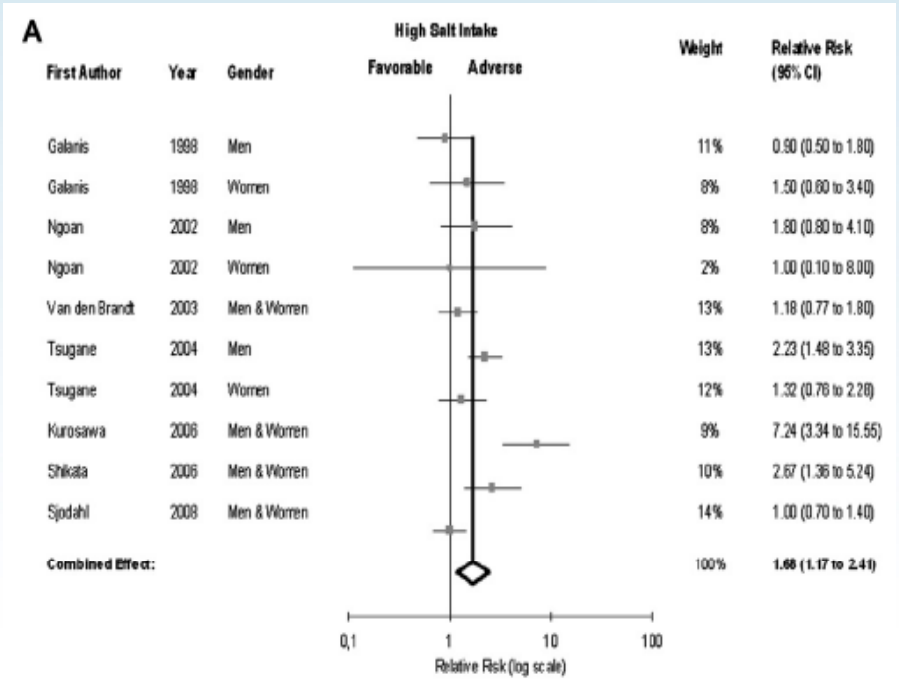
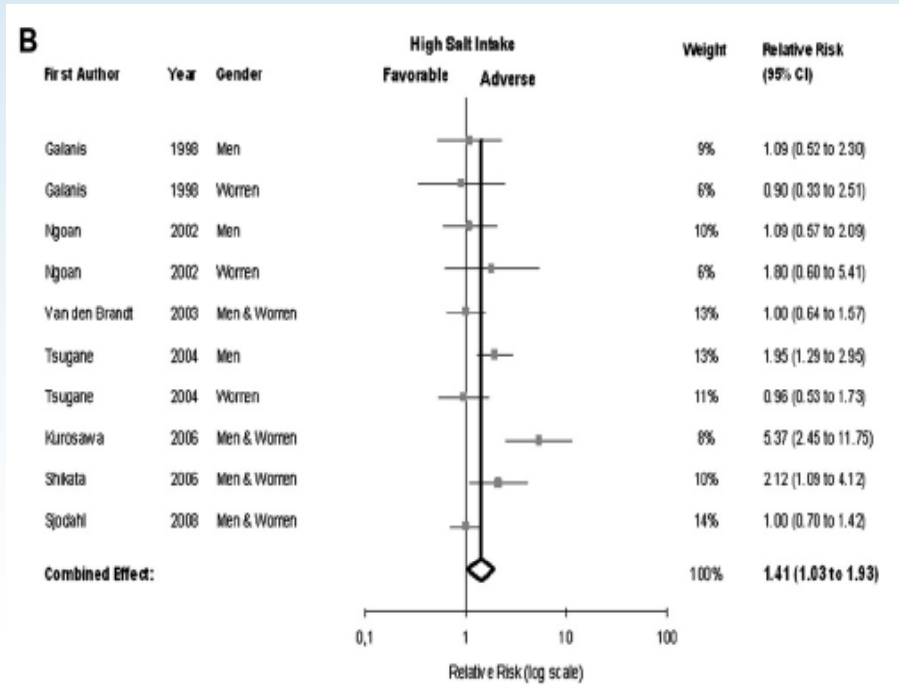
Salt intake and risk of gastric cancer





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D'Elia L et al. Clin Nutr 2012;31:489-98

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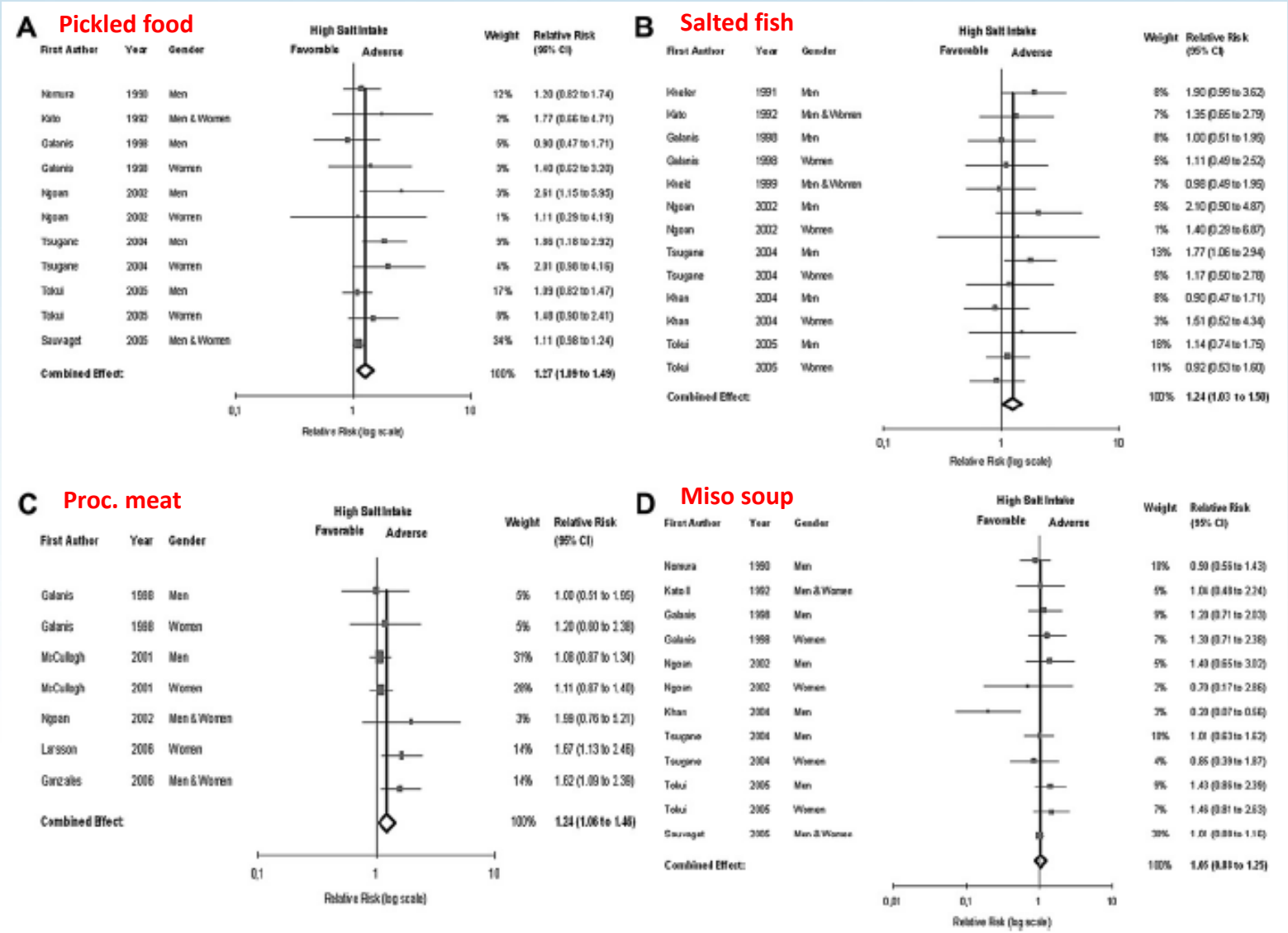

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D'Elia L et al. Clin Nutr 2012;31:489-98

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Salt intake and stomach cancer

- **Potential mechanisms:**
  - High dietary salt alters viscosity of mucous, hence facilitating exposure to carcinogenic agents such as nitrates
  - Persistent inflammation may promote cell proliferation and endogenous mutations
  - In the presence of H. pylori infection and atrophic gastritis, high salt exacerbates mucosal damage

Salt intake and fluid retention

- 'Idiopathic oedema'
  - Treated with diuretic, but rebound sodium and fluid retention – avoided by low salt intake before diuretic is stopped

MacGregor GA et al. Lancet 1975;i:489-91
MacGregor GA et al. Lancet 1979;i:397-400

- Congestive Heart Failure
  - High salt intake may trigger CHF by
    - Pressure overload (increase in BP)
    - Volume overload (extracellular fluid retention)

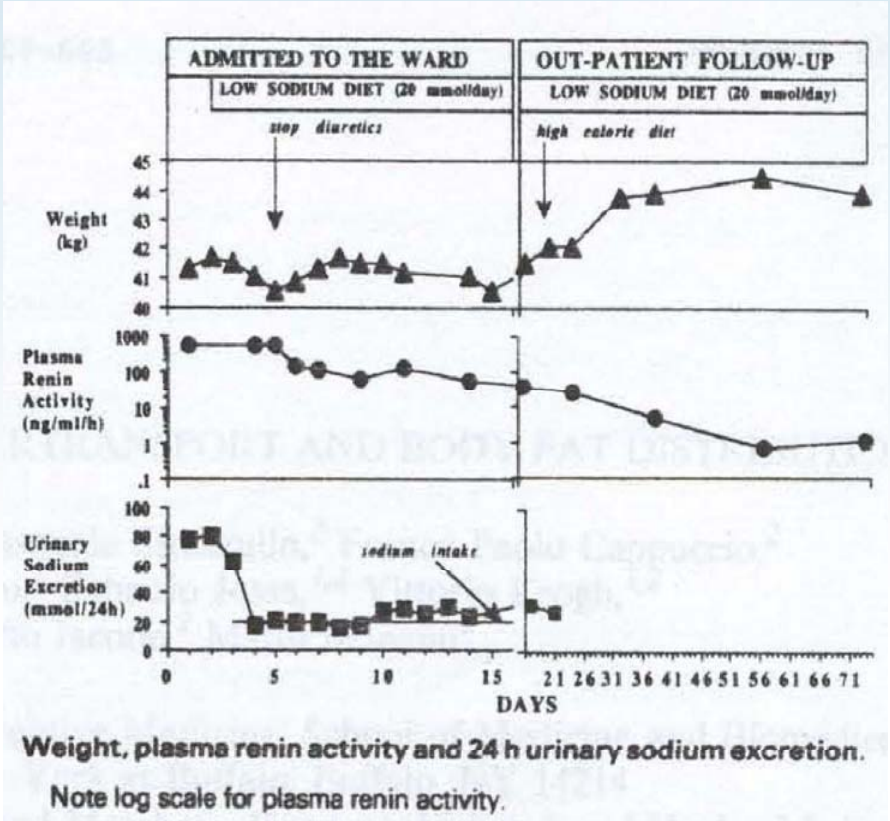
He J et al. Arch Int Med 2002;162:1619-24

- Rebound Fluid retention
  - Anorexia nervosa

Missouris CG et al. Lancet 1992;339:1546

Salt intake and fluid retention

- 21-yr old woman
- 4-y history of anorexia nervosa and diuretic misuse
- Wt 41.3kg; Ht 154.5cm; BMI 17.3kg/m^2
- BP 96/66mmHg ↔ 67/56mmHg ↑
- On frusemide 120mg and bendrofluazide 15mg daily
- SK^+ 1.5mM; $SHCO_3^-$ 37mM; SNa^+ 129mM
- Patient had insight into her condition
- Keen to stop diuretics, bur worried of rebound retention of sodium and water and large gain in weight
- Admitted to a metabolic ward



Weight, plasma renin activity and 24 h urinary sodium excretion.
Note log scale for plasma renin activity.

Missouris CG et al. Lancet 1992;339:1546

Salt intake and cataract

Case-control study

- Milan, Italy 1985-93
- 207 patients (139 men) with cataract extraction
- 796 controls (450 men)
- Median age 62.5 yrs
- Diet by FFQ
- Tertiles of Na intake (OR 95% CI)
  - Low 1
  - Medium 1.7 (1.1 – 2.8)
  - High 2.4 (1.4 – 4.0)

  P<0.01

Cross-sectional study

- Sydney, Australia 1992-94
- 2,873 men and women
- Median age 65 yrs
- Cataract by lens photograph
- Diet by FFQ
- Quintiles of Na intake (OR 95% CI)
  - I (~1,3 g/day) 1
  - II 1.1 (0.6 – 1.9)
  - III 1.2 (0.7 – 2.2)
  - IV 1.2 (0.7 – 2.2)
  - V (~3.2 g/day) 2.0 (1.2 – 3.4)

  P=0.006

Biological plausibility: higher levels of extracellular sodium might make it more difficult for sodium pumps to maintain the low levels of intracellular sodium necessary for lens transparency

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Tavani A et al. Ann Epidemiol 1996;6:41-6
Cumming RG et al. Am J Epidemiol 2000;151:624-6

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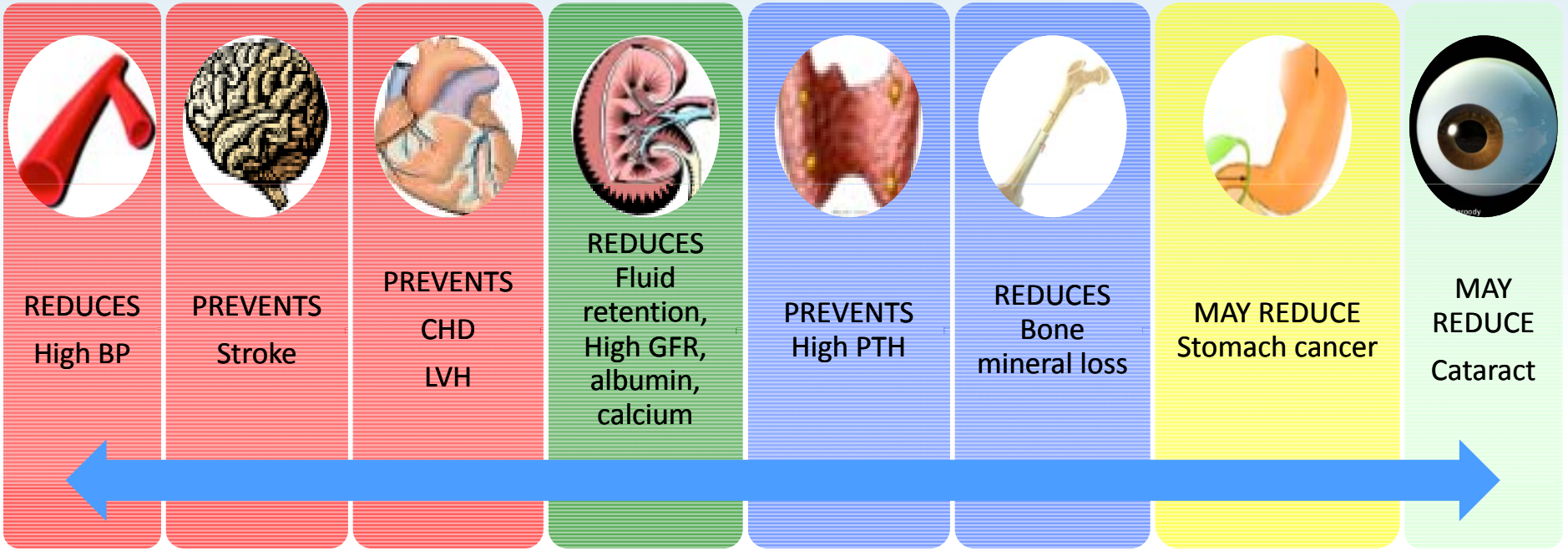
EFFECTS OF A MODERATE REDUCTION IN SALT INTAKE



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