Resilience:
Wat is het en hoe begrenst het onze mineraalhuishouding en zuur-base evenwicht?

Frits A.J. Muskiet

Laboratorium Geneeskunde UMCG

We're a little concerned about your potassium levels

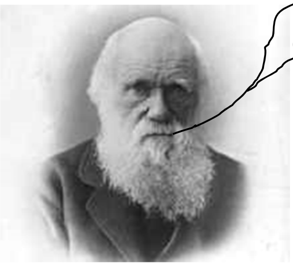
Allostasis

That is: maintaining stability, or homeostasis, through change

Aim: adjust to predictable and unpredictable events

Mediators: e.g. cortisol, adrenaline

McEwen, Ann Acad Sci 2004; Wingfield, Animal Behav 2003

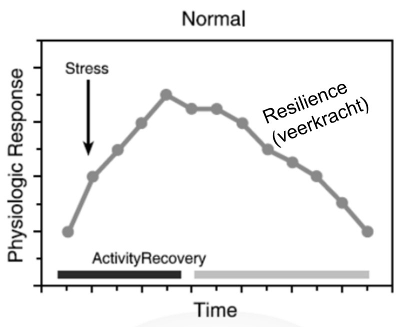


Charles Robert Darwin, (1809-1882)

***On the Origin of Species,* 1859**

"Adaptation to the conditions of existence"

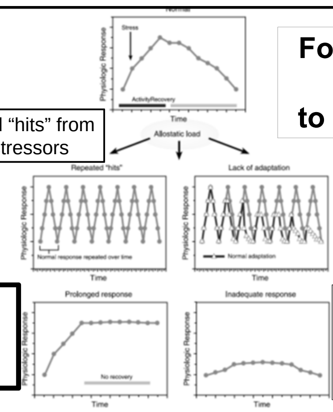
- In the long run (speciation) we adapt by **mutation/selection**.
- In the intermediate (up to several generations) and short run (individual) we adapt by **epigenetics**.
- In the short run (individual) we adapt through **sensors**, e.g. transcription activators/repressors like PPARs, Nrf2, etc



Normal allostatic response. A response is initiated by a stressor, sustained for an appropriate interval, and then turned off

McEwen, Physiol Rev 2007

Four conditions leading to allostatic load



Repeated "hits" from multiple stressors

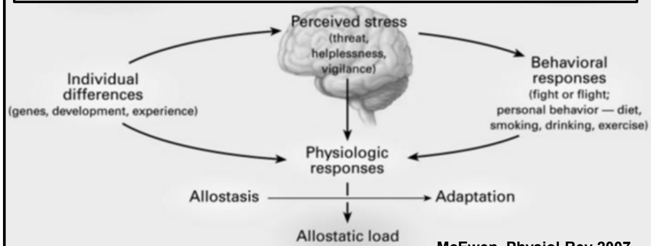
Lack of adaptation

Prolonged response due to delayed shut down

Inadequate response that leads to compensatory hyperactivity of other mediators (e.g., inadequate secretion of glucocorticoid, resulting in increased levels of cytokines that are normally counterregulated by glucocorticoids)

McEwen, Physiol Rev 2007

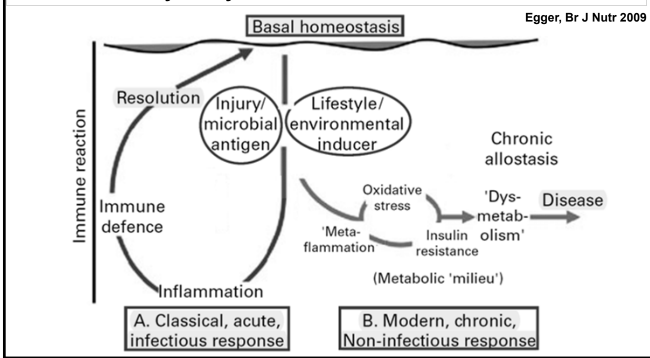
Central role of the brain in allostasis and the behavioral and physiological response to stressors



McEwen, Physiol Rev 2007

The difference between classical inflammation initiated by a microbial antigen or injury, and metaflammation caused by lifestyle or environmental inducers

Egger, Br J Nutr 2009

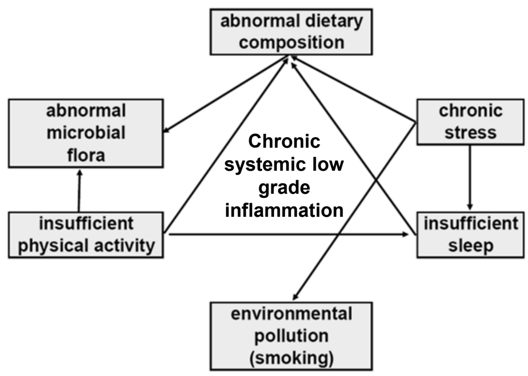


Inflammation and metabolism are intimately related

Hotamisligil, Nat Rev Immunol 2008

We reside in a pro-inflammatory state

Lifestyle factors exhibit interaction



Metabolic syndrome

The deadly quartet

1. Too high body mass
2. Disturbed glucose metabolism
3. High blood pressure
4. Disturbed lipid metabolism

~~Metabolic syndrome~~

Insulin resistance syndrome

Western lifestyle

↓

Chronic systemic low grade inflammation

↓

Insulin resistance ++ → aim: Energy reallocation; Modulate immune response; Tissue repair

↓ time

Metabolic syndrome

↓ time

Metabolic syndrome related diseases

Muskiet, NTKC 2011

Ruiz, J Nutr Biochem 2013

Dietary characteristics changed by the agricultural and industrial revolutions

- Macronutrient composition
- Fiber content
- Na-K ratio
- Acid-base balance
- Micronutrient density
- Glycemic load
- Fatty acid composition

Cordain AJCN 2005

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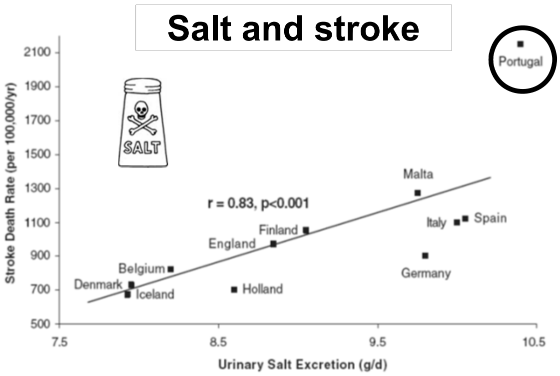
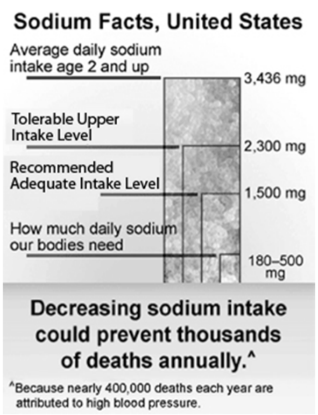
Too high sodium-intake associated with:

1. **Hypertension**
2. **Cardiovascular disease (ischemic, stroke, heart failure)**
3. **Kidney disease**
4. **Kidney stones**
5. **Osteoporosis**
6. **Stomach cancer**

Salt and stroke



O'Shaughnessy Ann Rev Nutr 2006



Recommendations (mg per day)

<1,500=AI (IOM, AHA)

<2,000 (WHO)

<2,300=UL (IOM, 2010 Guidelines Americans)

<2,400 (NL VoedingsCentrum)

(=6 g salt/day)

1,500 mg for: African Americans, people 51 years of age, and older people who have hypertension, diabetes, or chronic kidney disease.

IOM dropped <1,500 mg/day in May 2013

20 Year stroke, ischemic heart disease and mortality reduction in NL by reducing salt intake together with gain of life expectancy and DALE (Disablity Adjusted Life Expectancy)

	Stroke	Ischemic HD	Mortality
30% salt reduction	33,100	48,600	29,900
5 grams/day (WHO)	50,000	75,600	46,100

	20 years (M/F)	60 years (M/F)
Life Expectancy	+0.4/0.2 %	+0.2/0.2 %
DAL Expectancy	+0.6/0.2 %	+0.4/0.2 %

Hendriksen, PLoS ONE 2015

Contents

Salt and cardiovascular disease

Taylor, Cochrane Database Syst Rev 2011; Taylor, Am J Hypertens 2011

Meta-analysis 7 RCTs (>6 months) reduction salt intake vs. mortality, CAD mortality and events:

"Cutting down on the amount of salt has no clear benefits in terms of likelihood of dying or experiencing cardiovascular disease".
"Cutting down on salt does not reduce your chance of dying"

Critics:
- One study not to be included (heart failure, also aggressive diuretic therapy), remaining 6 consistent decrease, but not significant
- hypertensives and normotensives separately analysed (loss of power)

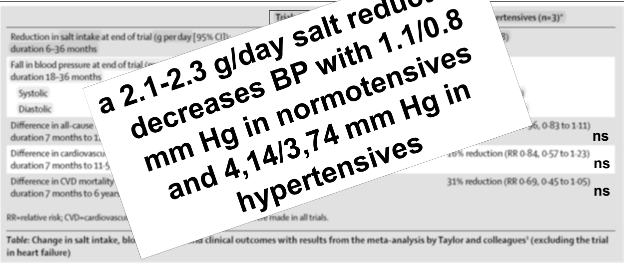
He, MacGregor, Lancet 2011

We found no strong evidence that salt reduction reduced all-cause mortality in normotensives or hypertensives

Taylor, Cochrane Database Syst Rev 2011

July 6, 2011

Change in salt intake, blood pressure, and clinical outcomes with results from the meta-analysis by Taylor and colleagues (6 trials, that is, excluding the trial in heart failure included by Taylor): a 2 g/day salt reduction hardly decreases BP (1.1/0.8 mm Hg) in normotensives



Little change in BP and no significant risk!

He, MacGregor, Lancet 2011

Salt and cardiovascular disease only significant if normotensives and hypertensives are combined

<u>If hypertensives and normotensives combined (6 studies):</u>

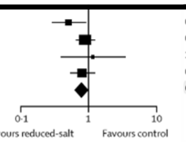
For a reduction of salt intake by 2.0-2.3 g/day:

1) 20% reduction CAD events (significant)

2) 5-7% reduction all cause mortality (not significant)

Relative risk of cardiovascular disease (CVD) events in our meta-analysis of outcome trials of salt reduction at longest follow-up combining hypertensive and normotensive individuals

Study*	Reduced-salt		Control		Relative risk of CVD events (95% CI)	Relative risk (95% CI)
	Events	Total	Events	Total		
TOHP I	17	321	32	311		0·51 (0·29–0·91)
TOHP II	71	938	80	935		0·88 (0·65–1·20)
Morgan	6	34	5	33		1·16 (0·39–3·45)
TONE	36	322	46	331		0·80 (0·53–1·21)
Total	130	1615	163	1610		0·80 (0·64–0·99)



He, MacGregor, Lancet 2011

Cochrane: Reduced dietary salt for the prevention of cardiovascular disease

(updates meta-analysis of 2011)

Trials fulfilled the following criteria: (1) randomised, follow-up of at least six months, (2) intervention was reduced dietary salt (through advice to reduce salt intake or low-sodium salt substitution), (3) adults and (4) mortality or cardiovascular morbidity data were available. Eight RCTs met the inclusion criteria: 3 in normotensives (n=3,518) and 5 in hypertensives or mixed populations of normo and hypertensives (n=3,766). End of trial follow-up ranged from 6-36 and the longest observational follow-up (after trial end) was 12.7 years.
Dietary advice and salt substitution did reduce the amount of salt eaten, which led to a small reduction in blood pressure by six months.
There was weak evidence of benefit for cardiovascular events, but these findings were inconclusive and were driven by a single trial among retirement home residents, which reduced salt intake in the kitchens of the homes.

There is insufficient power to confirm clinically important effects of dietary advice and salt substitution on cardiovascular mortality in normotensive or hypertensive populations. Our estimates of the clinical benefits from advice to reduce dietary salt are imprecise, but are larger than would be predicted from the small blood pressure reductions achieved.

Adler, Taylor, Cochrane Database Syst Rev 2014

Alburto: sodium, blood pressure, risk: 14 cohorts and 5 RCTs

Study selection Randomised controlled trials and prospective cohort studies in non-acutely ill adults and children assessing the relations between sodium intake and blood pressure, renal function, blood lipids, and catecholamine levels, and in non-acutely ill adults all cause mortality, cardiovascular disease, stroke, and coronary heart disease.

Conclusions High quality evidence in non-acutely ill adults shows that reduced sodium intake reduces blood pressure and has no adverse effect on blood lipids, catecholamine levels, or renal function, and moderate quality evidence in children shows that a reduction in sodium intake reduces blood pressure. Lower sodium intake is also associated with a reduced risk of stroke and fatal coronary heart disease in adults. The totality of evidence suggests that most people will likely benefit from reducing sodium intake.

Alburto BMJ 2013

Current guidelines are based on the following assumptions

(i) Any elevation in systolic blood pressure above 115 mm Hg is associated with increasing CVD risk

(ii) Measures of sodium intake are positively associated with elevated BP

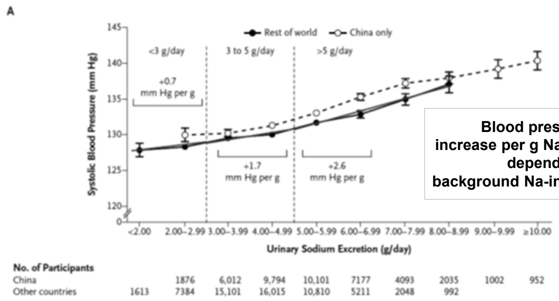
(iii) Reducing sodium intake will reduce BP irrespective of the level of sodium intake or BP level

(iv) Reducing sodium must therefore reduce CVD

Smyth, O'Donnell, Mente, Curr Hypertens Rep 2015

PURE study: Na and hypertension

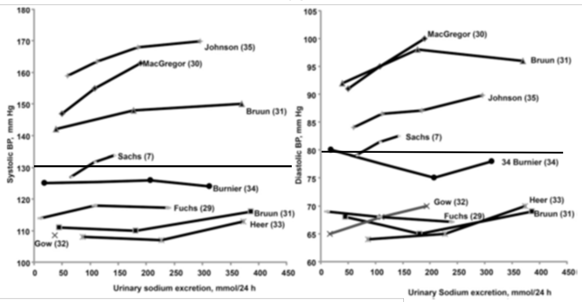
102,216 subjects general population, 35-70 years, 18 countries, 5 continents



Blood pressure increase per g Na/day depends on background Na-intake

Mente, O'Donnell, NEJM 2014

Individual study diastolic and systolic BP response to increasing changes in sodium urinary excretion in otherwise healthy normotensive and hypertensive individuals



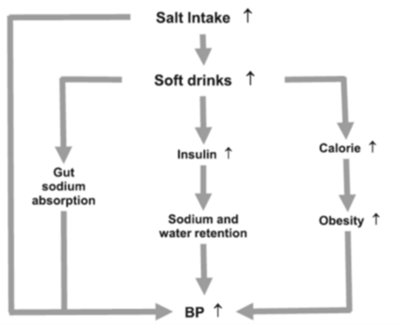
There is no relation between sodium dose and BP in subjects whose BP is <130/80 mm Hg.

Graudal, Adv Nutr 2015

Blood pressure change per gram sodium increase/decrease depends on:

1. **Background sodium intake**
2. **Background blood pressure**
3. **Age**
4. **Race/ ethnicity**

Mechanism for the links between salt intake, sugar-sweetened soft drink consumption, and blood pressure (BP)



He, MacGregor, Am J Cardiol 2014

Dietary sugars influence blood pressure and serum lipids.

The effect of sugar intake on blood pressure was greatest in trials ≥ 8 wk in duration [mean difference: 6.9 mm Hg (95% CI: 3.4, 10.3 mm Hg; P , 0.001) for systolic blood pressure and 5.6 mm Hg (95% CI: 2.5, 8.8 mm Hg; P = 0.0005) for diastolic blood pressure].

Te Morenga AJCN 2014

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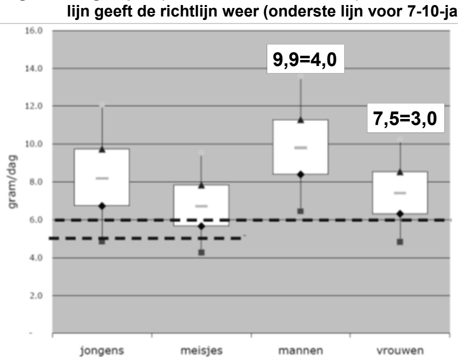
Gebruikelijke consumptie van zout voor vier leeftijds- en geslachtsgroepen (VCP 2007-2010, n = 3.819). De blauwe onderbroken lijn geeft de richtlijn weer (onderste lijn voor 7-10-jarigen)

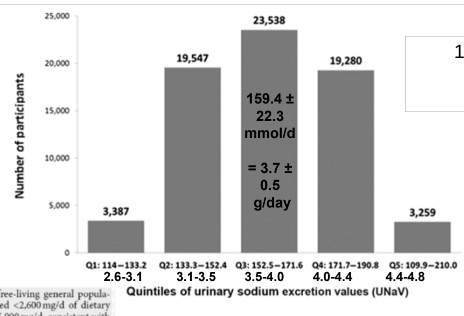


Gemiddelde volwassenen: (g/dag)

8,7 zout
3,5 natrium

Van Rossum, RIVM rapport 2012

Population's normal distribution of sodium intake by quintiles of 24-hour urinary sodium excretion (UNaV)



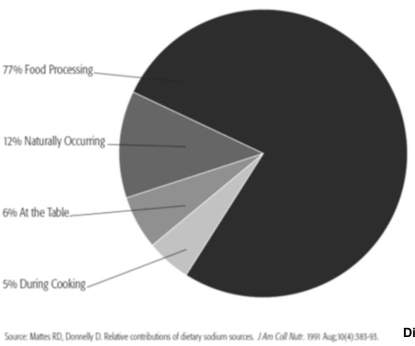
129 surveys, 50,060 participants

mmol/day
g/day.

<1% of the free-living general population consumed <2,600 mg/d of dietary sodium or >5,000 mg/d, consistent with physiologic regulation within a defined and limited range. This scientifically

McCarron, Am J Hypertension 2013

Our current sodium intake



Source: Mattes RD, Donnelly D. Relative contributions of dietary sodium sources. J Am Coll Nutr. 1991 Aug;10(4):383-95.

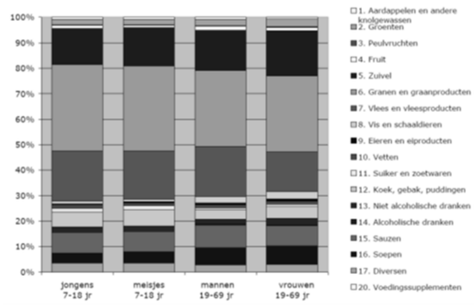
NL 1995-1997 intake:
3.9 g Na /d
(9.8 g NaCl/d)

NL advice 2006:
2.4 g Na/d
(6 g NaCl/d)

US DRIs:
AI = 1.5 g Na/d (3.8)
UL = 2.3 g Na/d (5.8)

Dietary Guidelines for Americans 2005

Gemiddelde bijdrage* van voedingsmiddelengroepen (EPICSoft) aan zoutconsumptie voor vier leeftijds- en geslachtsgroepen* (VCP 2007-2010; n=3.819).**



De belangrijkste bronnen waren **brood (26%), vlees-producten (15%) en kaas (10%), samen 51%.**

De bronnen verschilden nauwelijks over de vier leeftijds- en geslachts-groepen

Van Rossum RIVM rapport 2012, Zoutconsumptie van …

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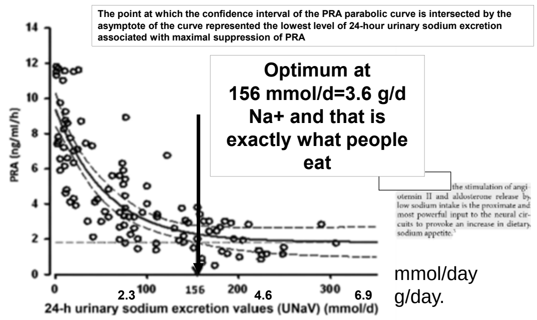
Physiologic relationship of 24-hour urinary sodium excretion (UNaV) to plasma renin activity (PRA) predicts mean sodium intake



McCarron, Am J Hypertension 2013

Dietary salt restriction increases plasma lipoprotein and inflammatory marker concentrations in hypertensive patients

Low-salt (60 mmol/day=1.380 mg/day), 3 weeks, non-obese untreated hypertensive adults

<u>Increase of:</u>
Fasting triglycerides
Chylomicron-cholesterol
hsCRP
TNF-alfa
IL-6
Renine activity
Aldosteron
Insuline
HOMA-IR

<u>Lowering of:</u>
Blood pressure
Free fatty acids

<u>After fat-rich meal increase of AUC of:</u>
Triglycerides
Chylomicron-cholesterol
apoB
Cholesterol/apo B ratio

<u>And decrease of AUC of:</u>
Free fatty acids

This study shows that various markers of the metabolic syndrome increase upon salt reduction

Nakandakare, Atherosclerosis 2008

Low salt causes insulin resistance and this is not dependent on baseline salt sensitivity

389 subjects (44% women; 16% blacks; body mass index, 28.5±4.2 kg/m2)
1 week of high salt (200 mmol/day sodium=4.600 mg/d) and 1 week of low salt (10 mmo/day sodium=230 mg/d)

Salt restriction is emphasized for the hypertensive population as part of a healthy lifestyle. The rationale for salt restriction is lower blood pressure that should improve cardiovascular outcomes.

However, salt restriction has no significant effect on blood pressure in salt-resistant individuals and is associated with increase in IR in both salt-sensitive and salt-resistant individuals. Although the importance of increase in IR in the setting of LS diet is not known, IR in other settings is an established CVD risk factor.

Therefore, salt restriction in salt-resistant individuals seems to offer no advantage, whereas its benefits in salt-sensitive individuals need to be considered in the context of increase in IR.

Garg, Hypertension 2014

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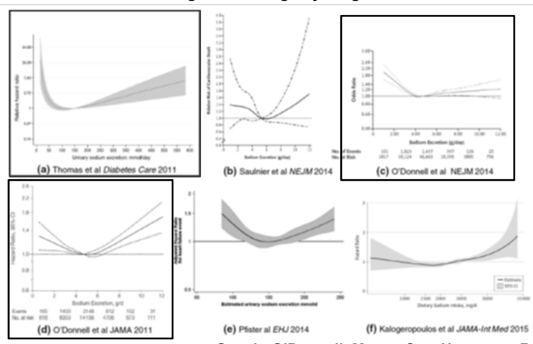
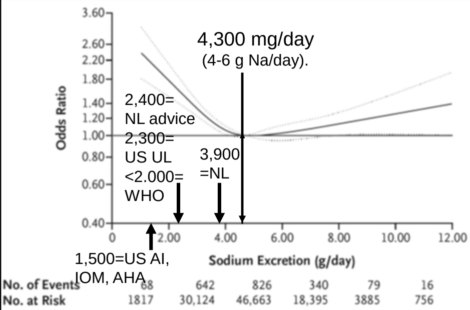
At least five independent prospective cohort studies have indicated a J-shaped association between sodium intake and CVD, with the lowest event rates occurring in the 3–5 g/day range of sodium intake



Smyth, O'Donnell, Mente, Curr Hypertens Rep 2015

U-shaped relation of Estimated Sodium Excretion and Risk of Death from Any Cause

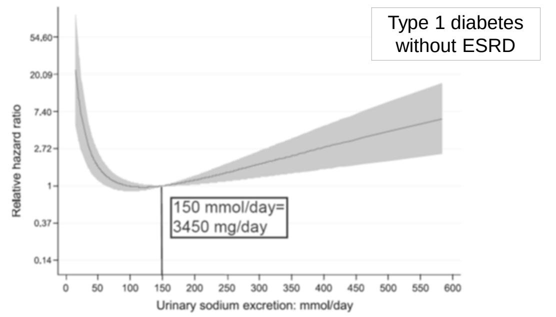
(ibid: death of CAD and major CAD events)



De PURE (Prospective Urban Rural Epidemiology) studie is een grote epidemiologische cohort studie die bestaat uit 156.424 personen van 35-70 jaar. Ze wonen in stads en platteland gemeenschappen in 17 landen met laag-, middel- en hoog inkomen. De getoonde gegevens tonen de relatie tussen de geschatte urine Na-excretie en risico op overlijden aan alle oorzaken voor 101.945 personen gedurende een gemiddelde follow-up van 3,7 jaar. Het schijnbaar laagste risico trad op bij een Na-uitscheiding van ongeveer 4.300 mg/dag (4-6 g Na/dag).

O'Donnell NEJM 2014

The association between 24-h urinary sodium excretion and all-cause mortality



Thomas, Diabetes Care 2011

Contents

Salt sensitivity (no consensus)

A change in blood pressure (office measurement) of 5-10% or at least 5 mm Hg, in response to a change in NaCl intake.

An increase in mean arterial blood pressure (MAP) of at least 4 mm Hg (24-h ambulatory blood pressure monitoring) with an increase in NaCl intake.

Felder, Curr Opin Nephrol Hypertens 2013

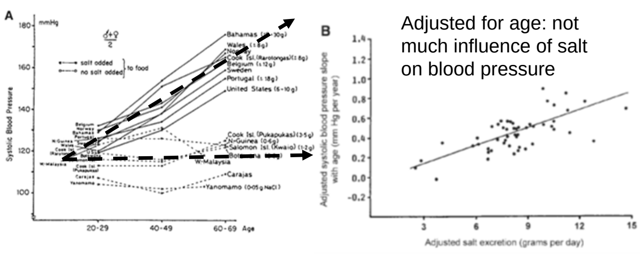
Salt Sensitivity in Various Groups*

Salt Resistant	Salt Sensitive
Young	Aged
Middle-aged	Hypertensive
Normotensive	African American
Caucasian	Chronic kidney disease
	History of pre-eclampsia
	Low birth weight

*Data derived from Weinberger et al. (4), de Bier et al. (9), Koomans et al. (10), Martillotti et al. (11), Weinberger (12,13), and Weinberger et al. (14)

Farquhar, J Am Coll Cardiol 2015

Blood pressure increases with age in Western countries. Cause: insulin resistance + high salt intake?

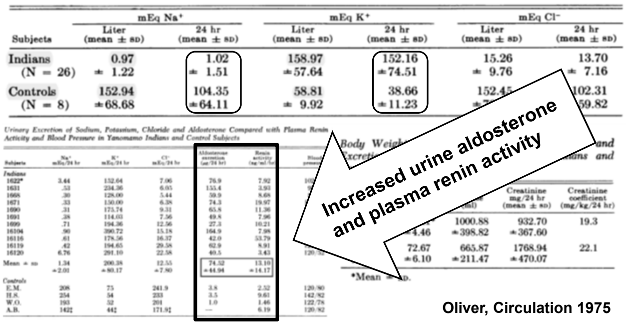


Meneton, Phys Rev 2005

Yanomamo Indians: a "no-salt" culture

Sodium	23 mg/day
	2,392 mg/day

Potassium	5,928 mg/day
	1,505 mg/day



Urinary Excretion of Sodium, Potassium and Chloride in Yanomamo Indians and Control Subjects

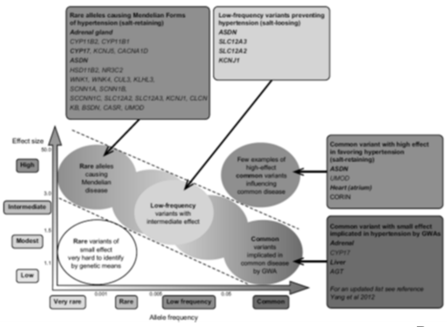
Subjects	mEq Na⁺ Liter (mean ± SD)	mEq Na⁺ 24 hr (mean ± SD)	mEq K⁺ Liter (mean ± SD)	mEq K⁺ 24 hr (mean ± SD)	mEq Cl⁻ Liter (mean ± SD)	mEq Cl⁻ 24 hr (mean ± SD)
Indians (N = 26)	0.97 ± 1.22	1.02 ± 1.51	158.97 ±57.64	152.16 ±74.51	15.26 ± 9.76	13.70 ± 7.16
Controls (N = 8)	152.94 ±68.68	104.35 ±64.11	58.81 ± 9.92	38.66 ±11.23	152.45 [illegible]	102.31 ±59.82

Oliver, Circulation 1975

Mineral intakes by humans
(in mg/day)

	Konner, Eaton, 2010 Paleolithic	Sebastian 2006 Paleolithic	Adrogue 2014 Hunter-gatherers	NL VCP 2007-2010 19-69 years (range of medians)	IOM	EFSA 2015	NL GR	WHO 2014
Sodium	<1000		460	3453	<1500/ <2300		<2400	
Potassium	7000	15600	>5850	2796-3997	4700 (AI)		=IOM	3510
Magnesium	1223			285-402	310/420	300/350	250/300	
Calcium	1000-1500			910-1136	1000/ 1200		1000/ 1100	
kcal	3000			1849-2753				

Spectrum of allele frequency and effect size in the genetics of hypertension



Identifying genetic variants by risk allele frequency (*x*-axis) and strength of genetic effect (odds ratio) (effect size) on the *y*-axis.

The genes identified in the control of blood pressure are indicated in boxes corresponding to four categories of variants.

Two genes (UMOD and CYP 17, in red) are linked to diseases with either Mendelian or non-Mendelian transmission.

Low-frequency variants of SLC12A3, SLC12A1, and KCNJ1 (yellow) are protective against cardiovascular disease in the general population. Rare alleles of the same genes cause severe salt-losing syndromes.
A list of common variants identified by GWAs can be found in Ref. 348.
[Adapted from Manolio et al. (212).

Rossier, Physiol Rev 2015

Percentage gene variants associated with salt sensitivity in different populations (ALL: general population; AFR: Africans; AMR: Americans; ASN: Asians; EUR: Europeans. Data are from 1,000 genome project)

GENE SYMBOL	ALL	AFRICANS	AMERICANS	ASIANS	EUROPEANS
ACE	38%	17%	40%	31%	56%
ADD1	27%	17%	19%	50%	20%
ADRB1	30%	40%	21%	21%	34%
AGT	66%	88%	64%	83%	41%
AGTR1	16%	3%	23%	7%	27%
CYP11B2	36%	17%	43%	31%	49%
GNB3	48%	79%	42%	47%	31%
NOS3	26%	50%	50%	20%	50%

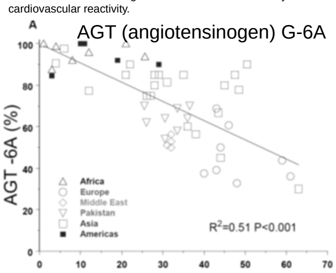
Salt sensitivity genes, genetics table of salt sensitivity gene-prevalence across populations_Internet GB Health Watch

The Association of Absolute Latitude with the Functional Genotypes in Five Genes Involved in Blood Pressure Regulation among the 53 Populations of the CEPH HGDP Cell Line Panel

alleles that were adaptive in our ancestral environment are maladaptive in the current one

Functional alleles in five genes that affect volume avidity and cardiovascular reactivity.

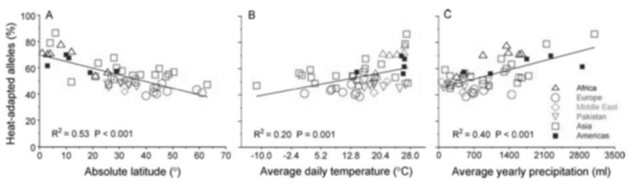
AGT (angiotensinogen) G-6A



Originating in Africa some 100,000 to 200,000 y ago, our species has since expanded out of Africa to inhabit the rest of the world. As populations expanded out of Africa, the primary thermodynamic requirement shifted from heat dissipation to heat conservation and selection for salt and water avidity, and cardiovascular reactivity lessened.

Young, PLoS ONE 2005

Heat Adaptation Is Strongly Associated with Absolute Latitude, Temperature, and Precipitation among the 53 Populations of the CEPH HGDP Cell Line Panel



heat adaptation as defined by prevalence of the allele that increases volume avidity or cardiovascular reactivity.

Young, PLoS ONE 2005

Hypertension susceptibility is ancestral

Young, PLoS ONE 2005

Hot Africa; low Na- and high K/Mg- availability
↓
Heat adaptation: sweating (up to 2 L/h)
↓
Loss of water and salt
↓
Efficient renal water- and Na- reabsorption
↓
Susceptibility to hypertension at high Na- and low K/Mg- intakes

Insulin resistance

(equals: SNS over-activation, reduced RAAS suppression)

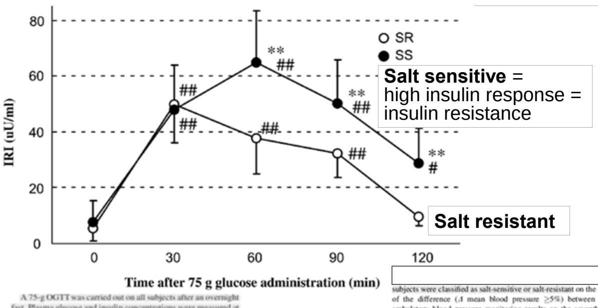
≡

Salt sensitive

(equals: salt and fluid retention)

Yatabe, AJCN 2010

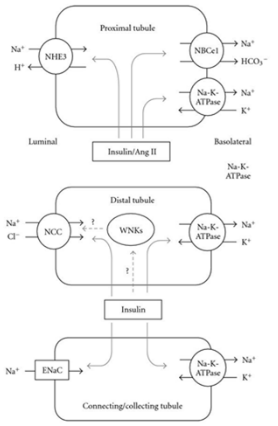
Mean (SEM) changes in serum immunoreactive insulin (IRI) after an oral administration of glucose (75 g) in salt-resistant (SR) subjects (n = 14, white circles) and salt-sensitive (SS) subjects (n = 10, black circles) with essential hypertension



A 75-g OGTT was carried out on all subjects after an overnight fast. Plasma glucose and insulin concentrations were measured at 0, 30, 60, 90, and 120 min after oral glucose ingestion, and the area under the curve of insulin was calculated during the 120-min study period.

subjects were classified as salt-sensitive or salt-resistant on the basis of the difference (Δ mean blood pressure ≥5%) between 24-h ambulatory blood pressure monitoring results on the seventh day of low-salt (34 mmol/d) and high-salt (252 mmol/d) diets.

Yatabe, AJCN 2010



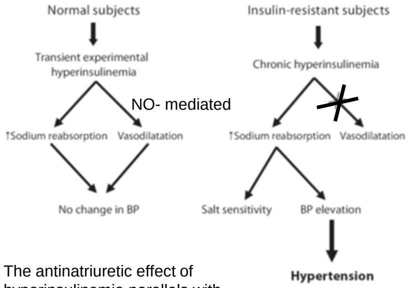
Insulin acts on almost all the nephron segments and is a strong enhancer of sodium reabsorption

The main sodium transporters and regulators in the proximal tubule and distal and connecting/collecting tubules. In the proximal tubule, insulin and Ang II stimulate NHE3 at the luminal side, NBCe1, and Na-K-ATPase at the basolateral side. In the distal and connecting/collecting tubules, insulin stimulates ENaC and NCC in the luminal side, Na-K-ATPase at the basolateral side. Insulin may also indirectly stimulate NCC via WNK kinases

Horita, Int J Hypertens 2011

Chronic hyperinsulinemia causes hypertension

development of salt sensitivity and uric acid retention



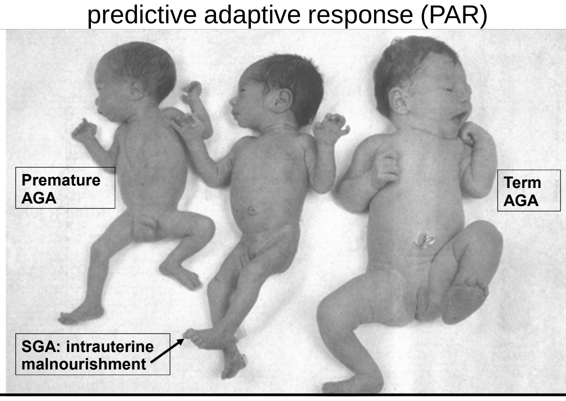
Insulin is reno- and vaso- active!

Hyperinsulinemia in insulin resistant subjects is characterized by fully preserved (or increased) antinatriuretic effect of insulin together with impaired insulin-mediated direct vasodilating effects secondary to nitric oxide increases

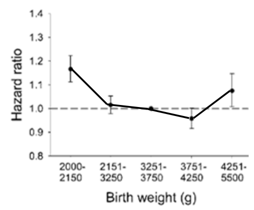
The antinatriuretic effect of hyperinsulinemia parallels with decreased uric acid excretion

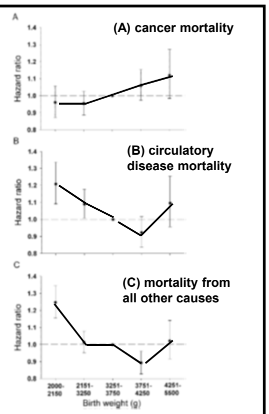
Sarafidis, Am J Nephrol 2007

Barker hypothesis, programming, thrifty phenotype, predictive adaptive response (PAR)



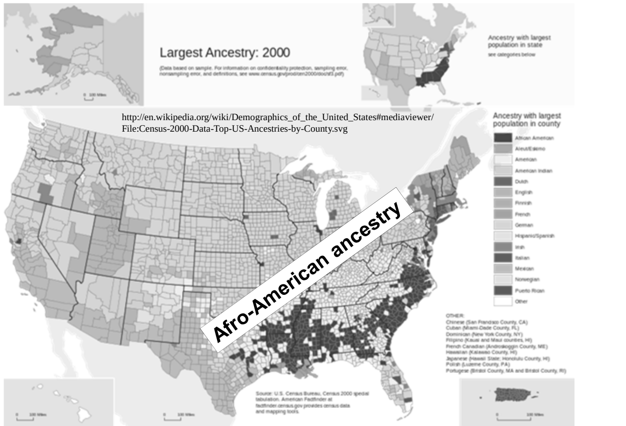
Mortality of 216,000+ Danish men and women according to birth weight





U-shaped association between birth weight and all-cause mortality:
both low and high birth weights are associated with a significantly elevated risk

Baker, Epidemiology 2008



USA prematurity 2011

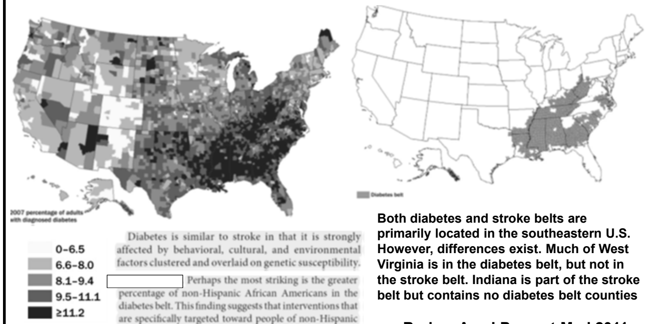
USA obesity 2011

USA stroke belt

U.S. Department of Health and Human Services, National Heart, Lung, and Blood Institute: Data fact sheet. The stroke belt. Bethesda, MD, October 1989.

Siegel, Publ Health Rep 1992

Estimates of prevalence of **diagnosed diabetes**, by county, 2007 (left) and the diabetes belt (>11% right)

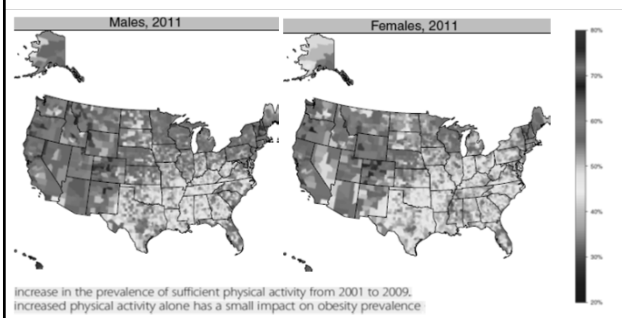


Diabetes is similar to stroke in that it is strongly affected by behavioral, cultural, and environmental factors clustered and overlaid on genetic susceptibility. Perhaps the most striking is the greater percentage of non-Hispanic African Americans in the diabetes belt. This finding suggests that interventions that are specifically targeted toward people of non-Hispanic African-American ancestry should be considered in appropriate locations within the diabetes belt.

Both diabetes and stroke belts are primarily located in the southeastern U.S. However, differences exist. Much of West Virginia is in the diabetes belt, but not in the stroke belt. Indiana is part of the stroke belt but contains no diabetes belt counties

Barker, Am J Prevent Med 2011

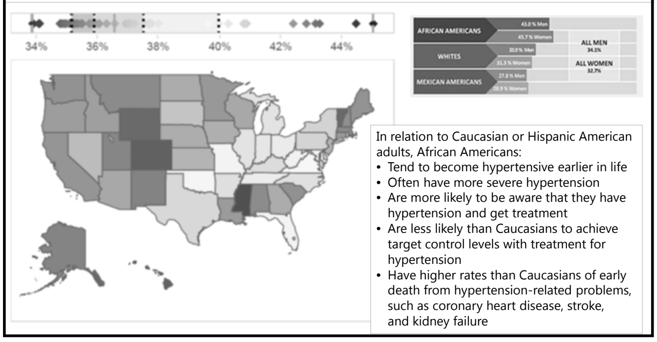
Age-standardized prevalence of reporting **sufficient activity** by sex among adults age 20 and older, 2011



increase in the prevalence of sufficient physical activity from 2001 to 2009.
increased physical activity alone has a small impact on obesity prevalence

Dwyer-Lindgren Pop Health Metr 2013

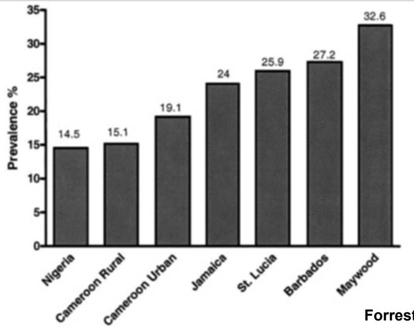
Prevalence of Hypertension in United States, 2001-2009



In relation to Caucasian or Hispanic American adults, African Americans:

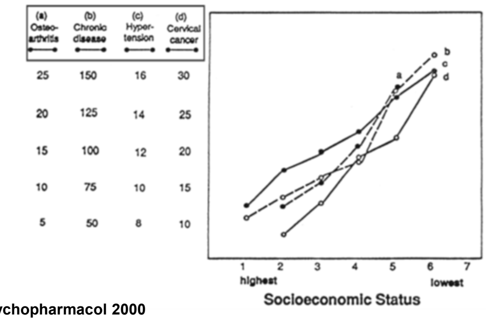
- Tend to become hypertensive earlier in life
- Often have more severe hypertension
- Are more likely to be aware that they have hypertension and get treatment
- Are less likely than Caucasians to achieve target control levels with treatment for hypertension
- Have higher rates than Caucasians of early death from hypertension-related problems, such as coronary heart disease, stroke, and kidney failure

Age/sex adjusted prevalence of hypertension (≥140/90) among seven populations of West African origin



Forrester, J Nutr 2004

Prevalence of osteoarthritis, chronic disease, hypertension and cervical cancer as a function of socioeconomic status



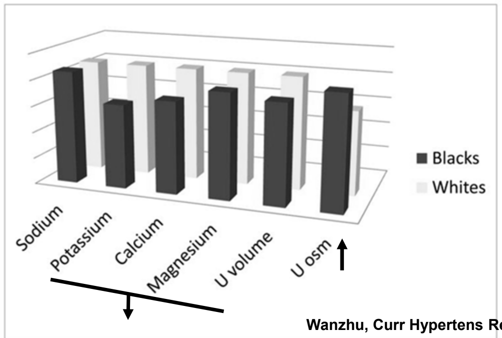
McEwen,
Neuropsychopharmacol 2000

Racial and economical predictors of adverse birth outcomes

- Income
- Education
- Access to prenatal care
- Exposure to racial discrimination
- Neighborhood-level poverty

Kuzawa, Am J Hum Biol 2009

A comparative depiction of average urinary excretion rates of cations (Na, K, Ca and Mg), urine volumes and urine osmolalities in blacks and whites



Wanzhu, Curr Hypertens Rep 2013

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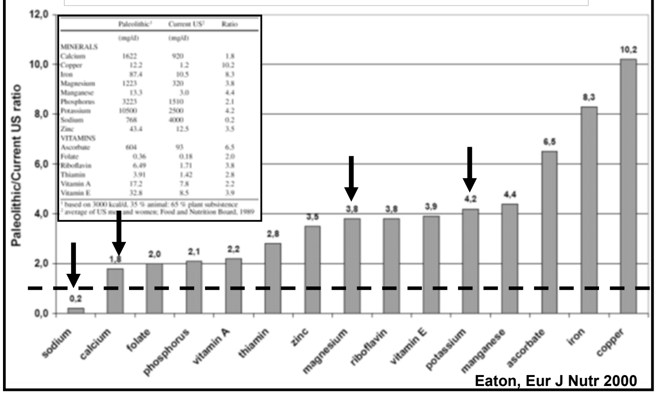
Micronutrients in the Paleolithic diet

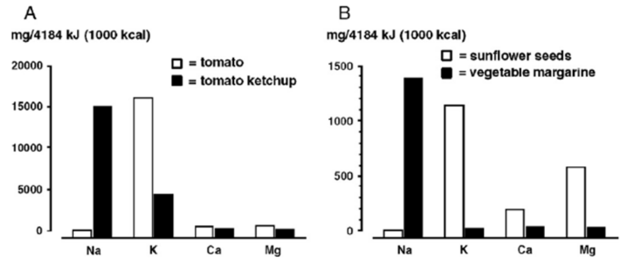


	Paleolithic[1]	Current US[2]	Ratio
	(mg/d)	(mg/d)	
MINERALS			
Calcium	1622	920	1.8
Copper	12.2	1.2	10.2
Iron	87.4	10.5	8.3
Magnesium	1223	320	3.8
Manganese	13.3	3.0	4.4
Phosphorus	3223	1510	2.1
Potassium	10500	2500	4.2
Sodium	768	4000	0.2
Zinc	43.4	12.5	3.5
VITAMINS			
Ascorbate	604	93	6.5
Folate	0.36	0.18	2.0
Riboflavin	6.49	1.71	3.8
Thiamin	3.91	1.42	2.8
Vitamin A	17.2	7.8	2.2
Vitamin E	32.8	8.5	3.9

[1] based on 3000 kcal/d, 35 % animal: 65 % plant subsistence
[2] average of US men and women; Food and Nutrition Board, 1989

Eaton, Eur J Nutr 2000

The questionable role of industry:
tomato vs. tomato ketchup; sunflower vs. vegetable margarine



Karppanen Prog Cardiovasc Dis 2006

Transcellulaire elektrolyt gradiënten

	Extracellulair (mmol/L)	Intracellulair (mmol/L)	Extra/Intra (mol/mol)
Kalium	4,5	150	0,03 (33)
Magnesium	1	3	0,33 (3)
Natrium	145	11	13
Calcium	2,5	0,0001	25.000

Schroll, 1998

Het lichaam investeert veel energie in de actief-transport processen die deze gradiënten in stand houden. Een voorbeeld is de Na^+-K^+-ATPase. Naar schatting wordt 20% van ons basaal metabolisme verbruikt door deze Na^+-K^+-ATPase en gaat 50-70% van het energieverbruik van onze hersenen en nieren hieraan op (155)

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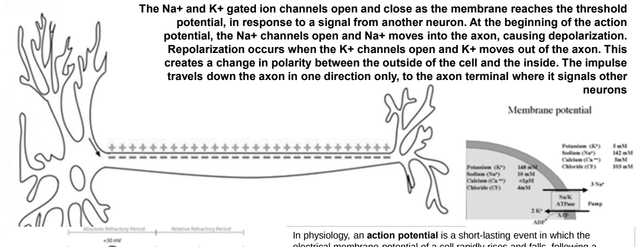
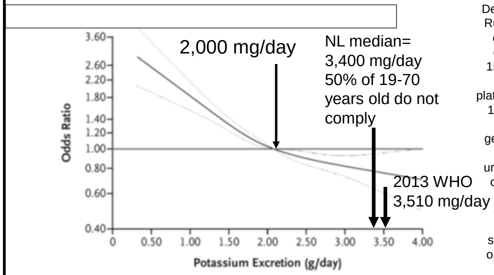
Action potential travelling down the axon

The Na+ and K+ gated ion channels open and close as the membrane reaches the threshold potential, in response to a signal from another neuron. At the beginning of the action potential, the Na+ channels open and Na+ moves into the axon, causing depolarization. Repolarization occurs when the K+ channels open and K+ moves out of the axon. This creates a change in polarity between the outside of the cell and the inside. The impulse travels down the axon in one direction only, to the axon terminal where it signals other neurons



In physiology, an **action potential** is a short-lasting event in which the electrical membrane potential of a cell rapidly rises and falls, following a consistent trajectory. Action potentials occur in several types of animal cells, called excitable cells, which include <u>**neurons, muscle cells, and endocrine cells**</u>, as well as in some plant cells. In neurons, they play a central role in cell-to-cell communication. In other types of cells, their main function is to activate intracellular processes. In muscle cells, for example, an action potential is the first step in the chain of events leading to contraction. In beta cells of the pancreas, they provoke release of insulin. Action potentials in neurons are also known as "**nerve impulses**" or "spikes", and the temporal sequence of action potentials generated by a neuron is called its "**spike train**". A neuron that emits an action potential is often said to "fire".

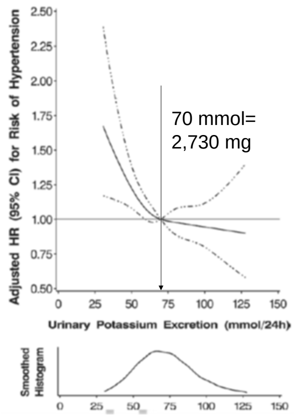
Inverse relation of Estimated Potassium Excretion and Risk of Death from Any Cause
(ibid: risk death of CAD, and risk major CAD events)



No. of Events	0	75	362	641	537	261	71	24
No. at Risk	6	1730	12,526	31,466	30,956	17,171	6128	1507

De PURE (Prospective Urban Rural Epidemiology) studie is een grote epidemiologische cohort studie die bestaat uit 156.424 personen van 35-70 jaar. Ze wonen in stads en platteland gemeenschappen in 17 landen met laag-, middel- en hoog inkomen. De getoonde gegevens tonen de relatie tussen de geschatte urine Na-excretie en risico op overlijden aan alle oorzaken voor 101.945 personen gedurende een gemiddelde follow-up van 3,7 jaar. Het schijnbaar laagste risico trad op bij een K-uitscheiding van ongeveer 2.000 mg/dag.

O'Donnell NEJM 2014



Association between urinary potassium excretion and risk of hypertension

Kieneker, Joosten Hypertension 2014

Alburto study: Effect Potassium on blood pressure and CVD

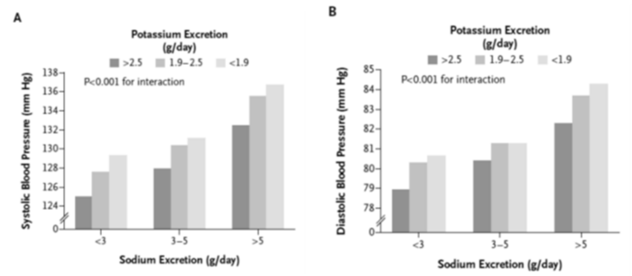
22 RCTs + 11 cohorts

Conclusions High quality evidence shows that increased potassium intake reduces blood pressure in people with hypertension and has no adverse effect on blood lipid concentrations, catecholamine concentrations, or renal function in adults. Higher potassium intake was associated with a 24% lower risk of stroke (moderate quality evidence). These results suggest that increased potassium intake is potentially beneficial to most people without impaired renal handling of potassium for the prevention and control of elevated blood pressure and stroke.

Aburto, BMJ 2013

PURE study Na and K hypertension:

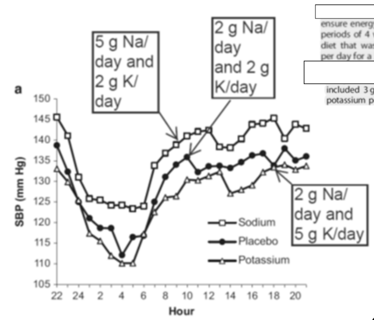
high K-intake blunts the blood pressure increasing effect of Na-intake (at all intakes)



Mente, NEJM 2014

Unadjusted mean ambulatory systolic blood pressure for each hour over 24 h after 4-week supplementation with sodium, potassium or placebo in 36 untreated (pre)hypertensive adults.

During the 1-week run-in (to ensure energy balance and reach basal BP) and 3 consecutive intervention periods of 4 weeks (not separated by washout) each subject consumed a diet that was targeted to provide 2 g of sodium and 2 g of potassium per day for a 2500 kcal intake. Treatments included 3 g of added sodium (equals 7.5 g salt) per day, 3 g of added potassium per day or placebo. Subjects



NL recomm=2400 mg Na/day NL eats 4000 mg Na/day (male) and 3000 mg Na/day (women)

The WHO recommendation is 3510 mg K/day, NL eats median 3400 mg K/day

Gijsbers, J Hum Hypertens 2015

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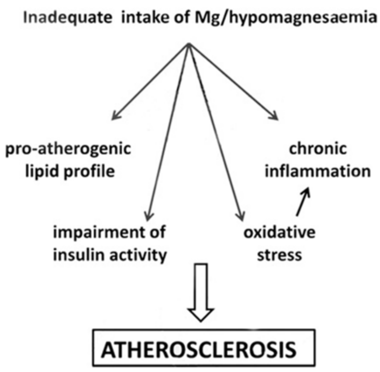


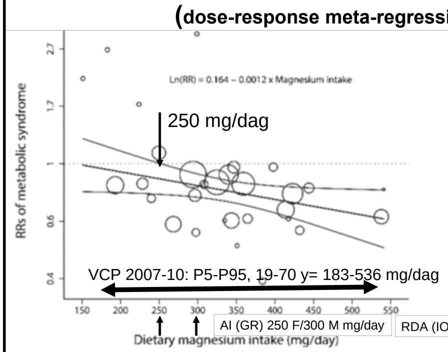
How low Mg intake and/or hypomagnesaemia contribute to atherogenesis: a summary from human studies

Human studies indicate that low Mg intake and/or hypomagnesaemia promote inflammation, oxidative stress, insulin resistance and hyperlipaemia, all known risk factors for atherosclerosis.

Maier, Clin Sci 2012

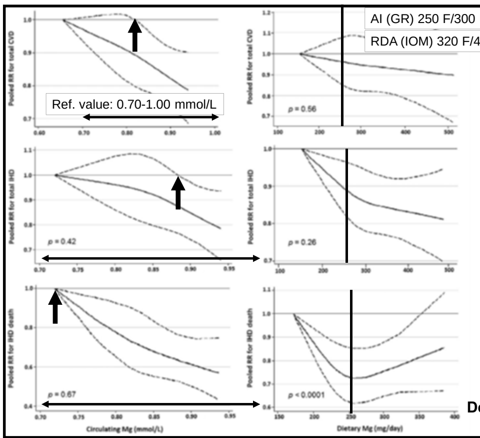
Inverse relation between risk of metabolic syndrome and dietary magnesium intake

(dose-response meta-regression)



Meta-analyse van 8 cross-sectionele studies en 2 prospectieve cohort studies die aangeeft dat het relatieve risico (RR) op metabool syndroom met 12% afneemt per inname van 150 mg Mg/dag. Vanaf een Mg-inname van 250 mg/dag was het risico significant verlaagd. De grootte van de cirkels zijn proportioneel met de precisie van het relatieve risico (RR)

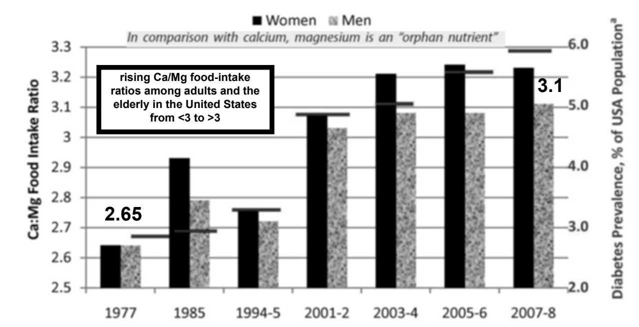
Ju et al., Nutrients 2014



Associations between circulating and dietary magnesium across their usual physiologic ranges and CVD risk.

Del Gobbo, Mozaffarian AJCN 2013

Dietary calcium-to-magnesium (Ca:Mg) intake ratio from foods for US adults, along with prevalence of diabetes



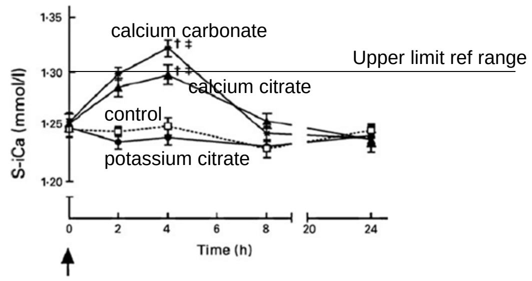
Rosanoff, Nutr Rev 2012

Meta-analysis for treatment of 1,000 older adults for 5-years with calcium monotherapy

14 more	**myocardial infarctions**
10 more	**strokes**
13 more	**deaths**
26 less	**fractures**

Reid IR, Bolland MJ. Calcium supplements: bad for the heart? Heart. 2012

Changes in serum ionized calcium concentration following administration of control (squares), calcium citrate (triangles), calcium carbonate (asterisks), or potassium citrate (circles). The calcium doses were both 1 g.



Reid, Bolland, Osteoporos Int 2011, uit Karp Br J Nutr 2009

Association between intakes of magnesium, potassium, and calcium and risk of stroke

Prospective studies:
Nurses Health Study and meta analysis of all prospective studies

	Nurses Health Studies I+II					Meta-analysis	
	intake lowest mg/day	intake highest mg/day	**RR highest vs lowest quintiles** total stroke	ischemic stroke	hemorrhagic stroke	RR total stroke	For a:
Magnesium			**0.87**			**0,87**	100 mg increase
Potassium			**0.89**			**0.91**	1000 mg increase
Calcium			0.97			0.98	300 mg increase
Mg+K+Ca			**0.72**	**0.78**	0.80		

NHSI=86,149, 30 y; NHSII=94,715, 22 y

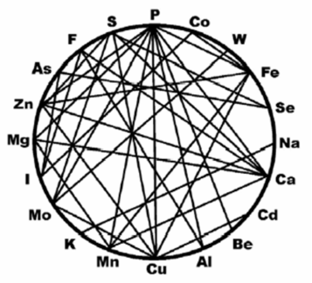
significant

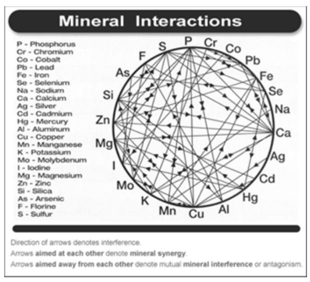
Relative risk reduction is higher for the sum of Mg+K+Ca, compared with the risk reductions of the individual minerals

Adebamowo, AJCN 2015

Mineral Interactions (mineral wheel)

Minerals interact with each other in the body. The many interactions can result in mineral elements' tying up or making other mineral elements unavailable for essential body functions.





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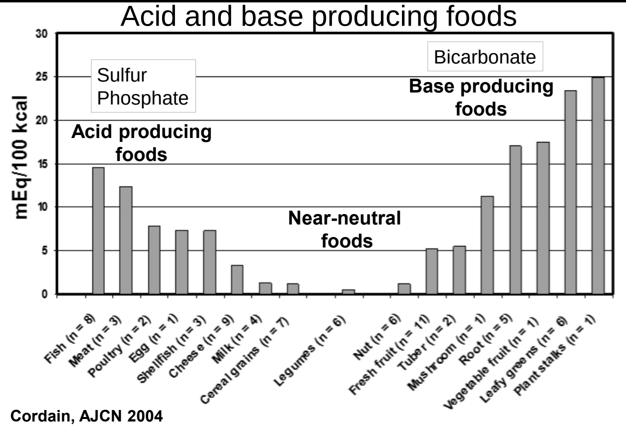
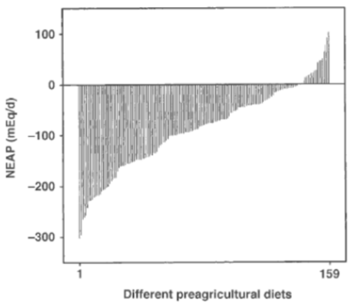
Acid and base producing foods



Cordain, AJCN 2004

Effect of 159 different retrojected ancestral preagricultural diets on Net Endogenous Acid Production (NEAP)



The mean NEAP for 159 retrojected preagricultural diets was:
-88±82 mEq/d;
87% were
net base-producing.

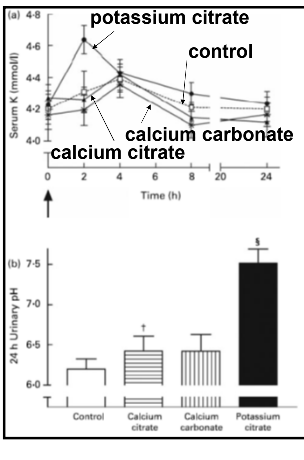
Today's Western (USA) diet has NEAP of
48 mEq/d.

Sebastian, AJCN 2002

Hoge consumptie van vlees met lage consumptie van groente/fruit veroorzaakt chronische toestand van lage graad metabole acidose die gerelateerd is aan:

- Lage urine pH (binnen "ref gebied")
- Osteoporose (o.a. Ca-verlies, botmarkers)
- Sarcopenie (negatieve N-balans)
- Nierstenen (Ca-oxalaat in zure urine)
- Verlies nierfunctie (trial Goraya, 2014)
- Hypertensie (CAD)

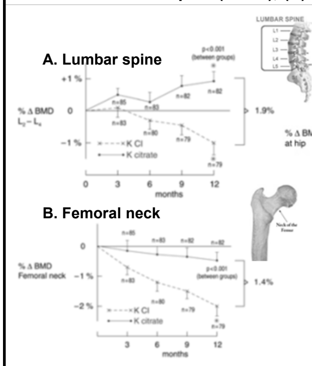
Frassetto, Eur J Nutr 2001



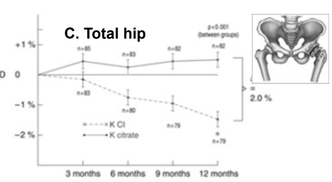
Changes in serum K concentration and urine pH during the four study sessions: control; calcium citrate; calcium carbonate; potassium citrate

Karp, Br J Nutr 2009

Effect of potassium citrate (K-citrate) treatment (30 mEq/day) vs. KCl on the percentage change in bone mineral density (BMD) measured by DEXA at (A) lumbar spine (L2-L4), (B) femoral neck and (C) total hip



Women in the treatment group significantly increased their bone mineral density at lumbar spine, femoral neck and total hip by 1% to 2% after 1 year

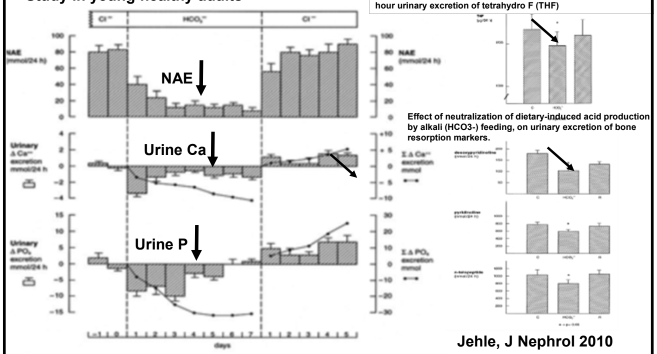


160 postmenopausal women with osteopenia who were randomized to daily alkali treatment with 30 mEq of potassium citrate for 12 months and compared with women ingesting an equimolar amount of potassium chloride.

Jehle, J Nephrol 2010

Effect of neutralization of dietary-induced acid production by alkali (HCO3-) feeding, on urinary calcium and phosphorus excretion

Study in young healthy adults



Effect of neutralization of dietary-induced acid production by alkali (HCO3-) feeding, on glucocorticoid activity. Twenty-four-hour urinary excretion of tetrahydro F (THF)

Effect of neutralization of dietary-induced acid production by alkali (HCO3-) feeding, on urinary excretion of bone resorption markers.

Jehle, J Nephrol 2010

Decrease in urinary nitrogen excretion only during the period when the diet in these normal postmenopausal women is supplemented with sufficient base to lower their net acid excretion to near zero

Frassetto, Eur J Nutr 2001

Renal generation of new bicarbonate by catabolism of glutamine, excretion of ammonia and secretion of bicarbonate

Chronic acidosis causes sarcopenia

Nitrogen comes from amino acids

Negative Nitrogen balance and muscle waisting, sarcopenia

The amount of NH4+ excreted in the urine is proportional to the amount of alkali added to the body.

Poupin, Clin Nutr 2012

Influence of Chronic Metabolic Acidosis in sham-operated or OVX rats on mean cortical thickness (A) and muscle cross section of the tibia muscle group (B): Loss of cortical and trabecular bone and skeletal muscle

Sham

Metabolic acidosis was induced by oral administration of NH4Cl (15 mEq/kg body wt, twice a day) by gavage for 6 and 10 wk.

Gasser, Am J Physiol Renal Physiol 2014

Contents

Wat u doet en wat u denkt dat u doet

De meeste Nederlanders denken dat ze niet alleen lekker maar ook <u>goed eten</u>

Groente: 10% denkt te weinig groente te eten; in werkelijkheid is dat 80%

Fruit: 33% denkt onvoldoende fruit te eten; in werkelijkheid is dat 60%

NHS; Eten naar hartelust, januari 2010