

Salt

Too much of a good thing?





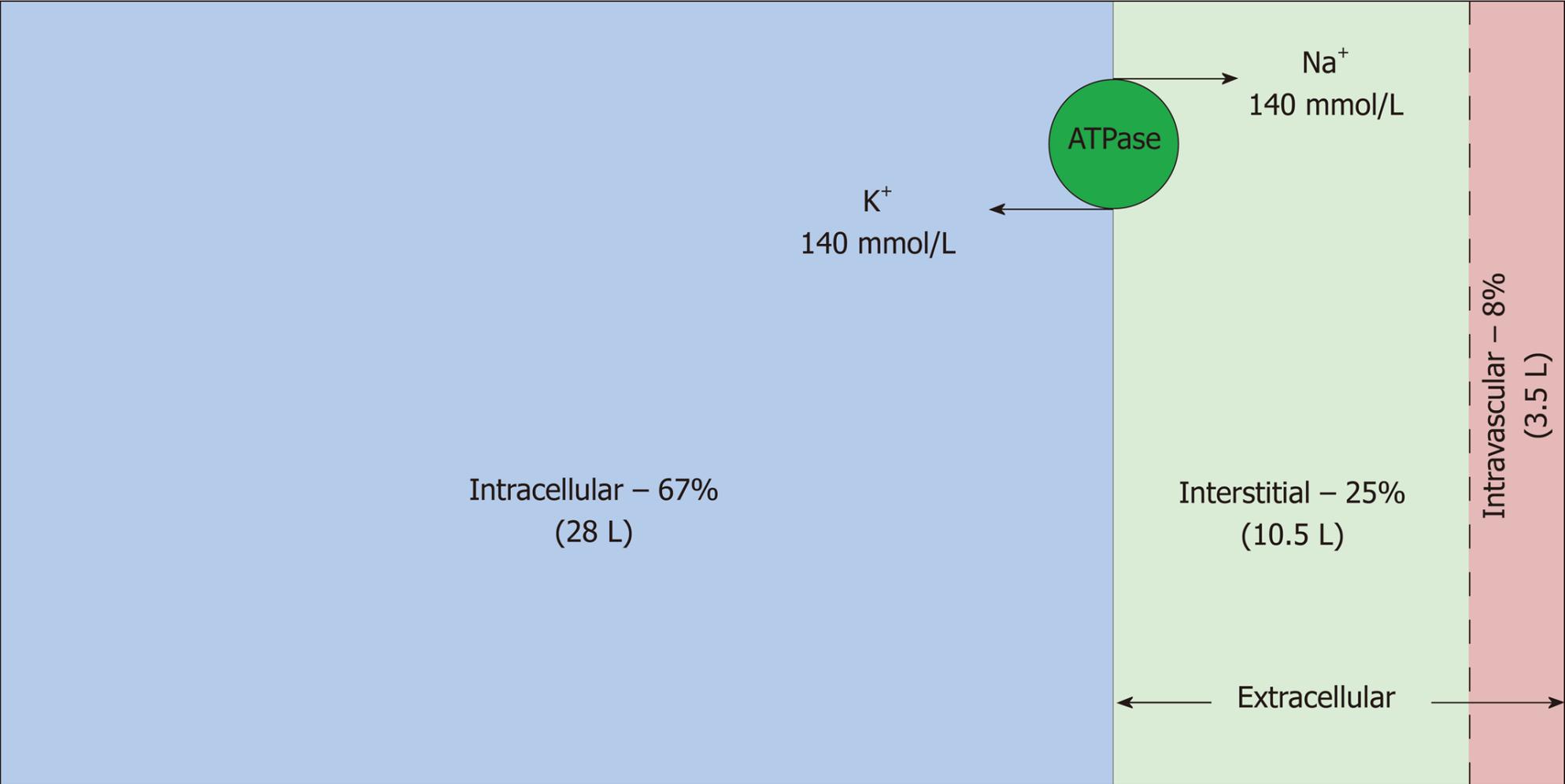
Neil Shubin holding the **Tiktaalik fossil** in the Canadian Arctic.

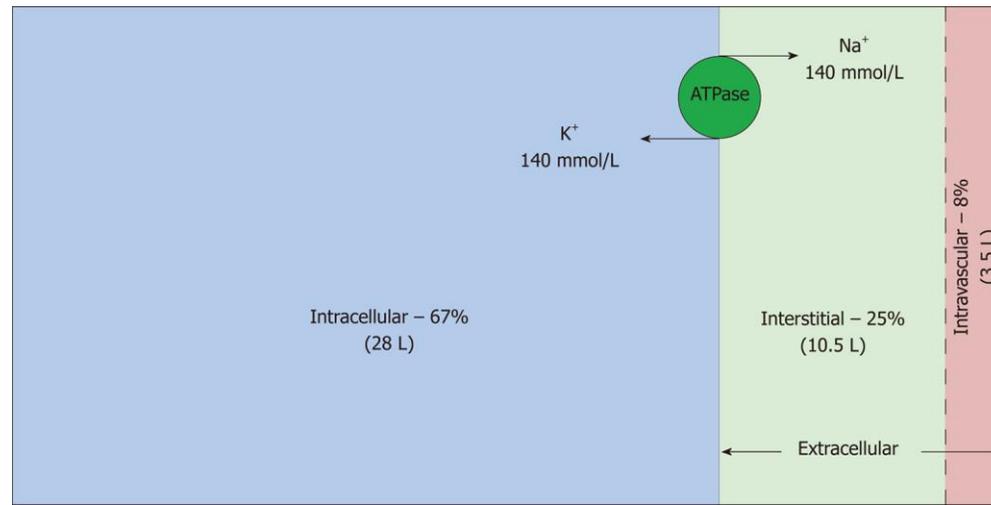
Eukaryotic cell-based life evolved all the way to vertebrate animals (ancient fish) in an aqueous environment, vertebrates had to bring the ocean inside them as they emerged from the deep to begin the terrestrial phase of vertebrate development.



TIKO

The volume of our extracellular fluid, the “internal ocean”, is determined by the amount of sodium in our body.





The Serum sodium concentration is not dependent on total body sodium content.

Abnormalities of serum sodium concentration indicate dysfunction of osmoregulation

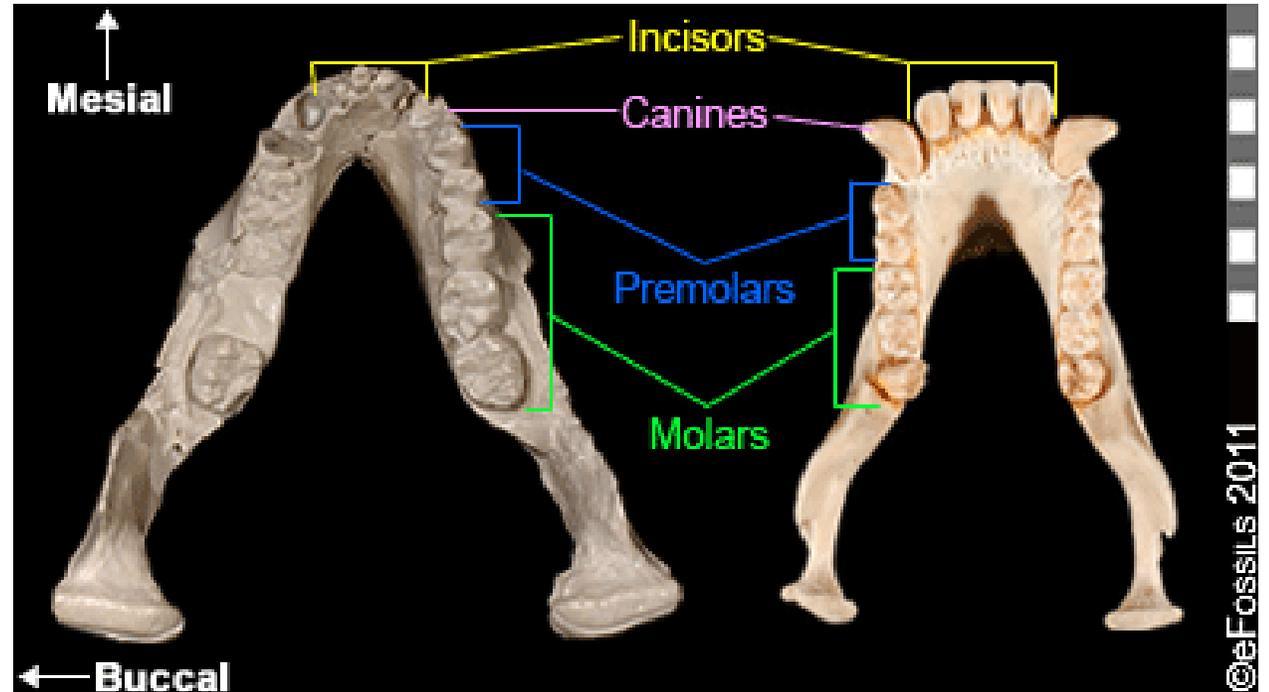
In order to maintain this internal ocean of extracellular fluid, we need to minimize losses of salt and water, and balance unavoidable losses with dietary sodium and water intake

Our capacity to conserve salt is especially crucial in environments where dietary sources of salt are scarce

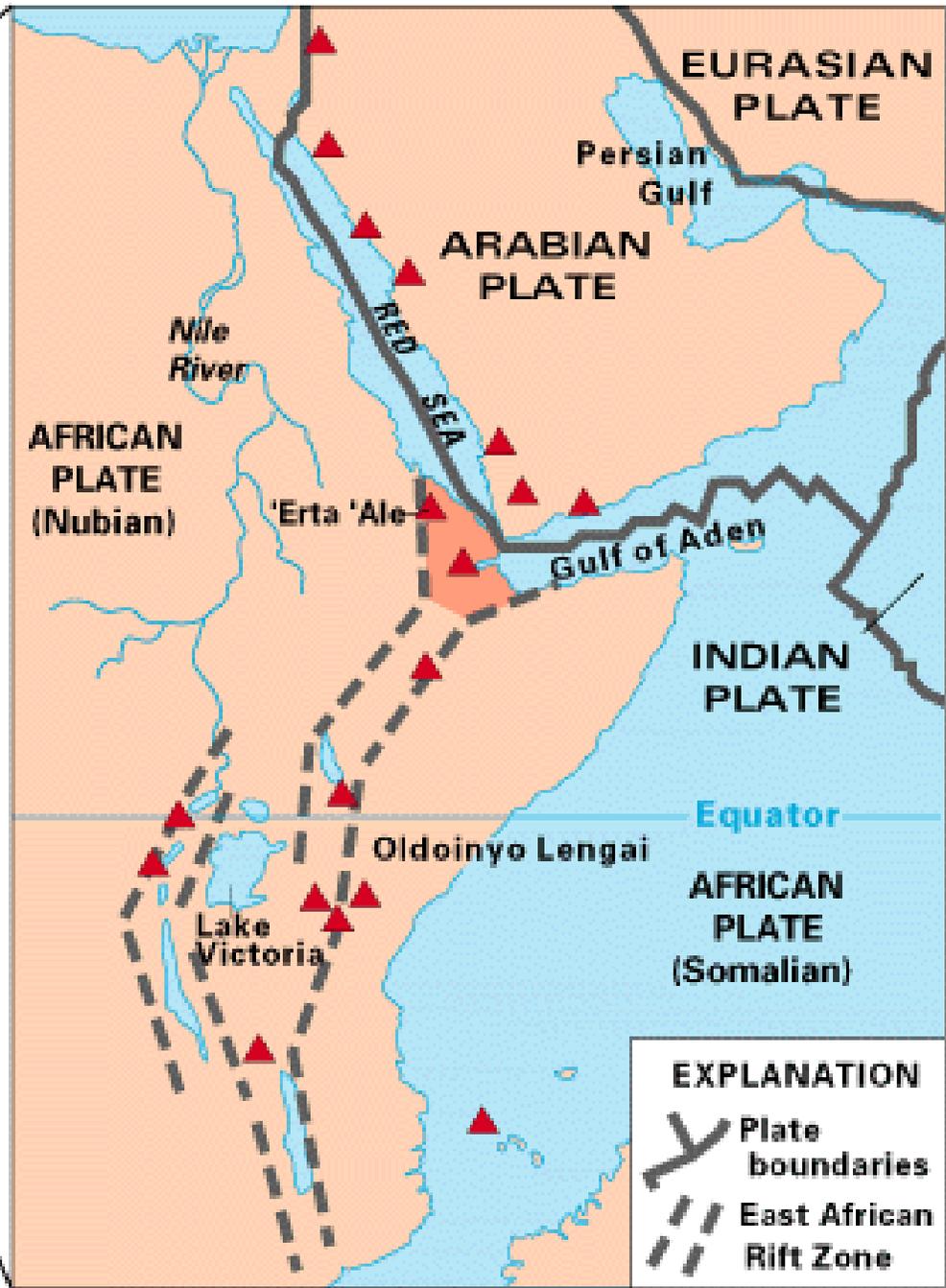
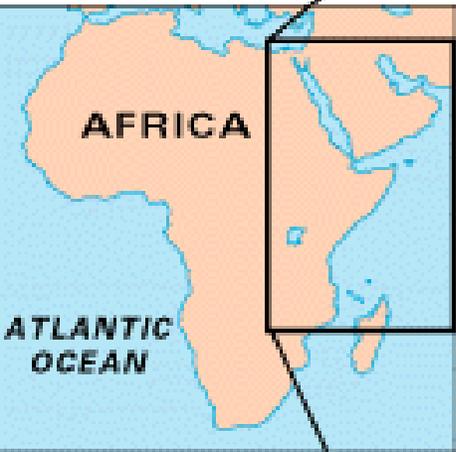
Which brings us to central Africa, the so-called “cradle of humanity”



Picture of modern day East Africa with open grasslands and a lake, perhaps similar to the habitat that Lucy occupied 3.2 million years ago.



Comparison of Lucy's mandible with that of a male chimpanzee. Both male and female chimpanzee's have relatively larger canines than that seen in *A. afarensis*. Images to scale.





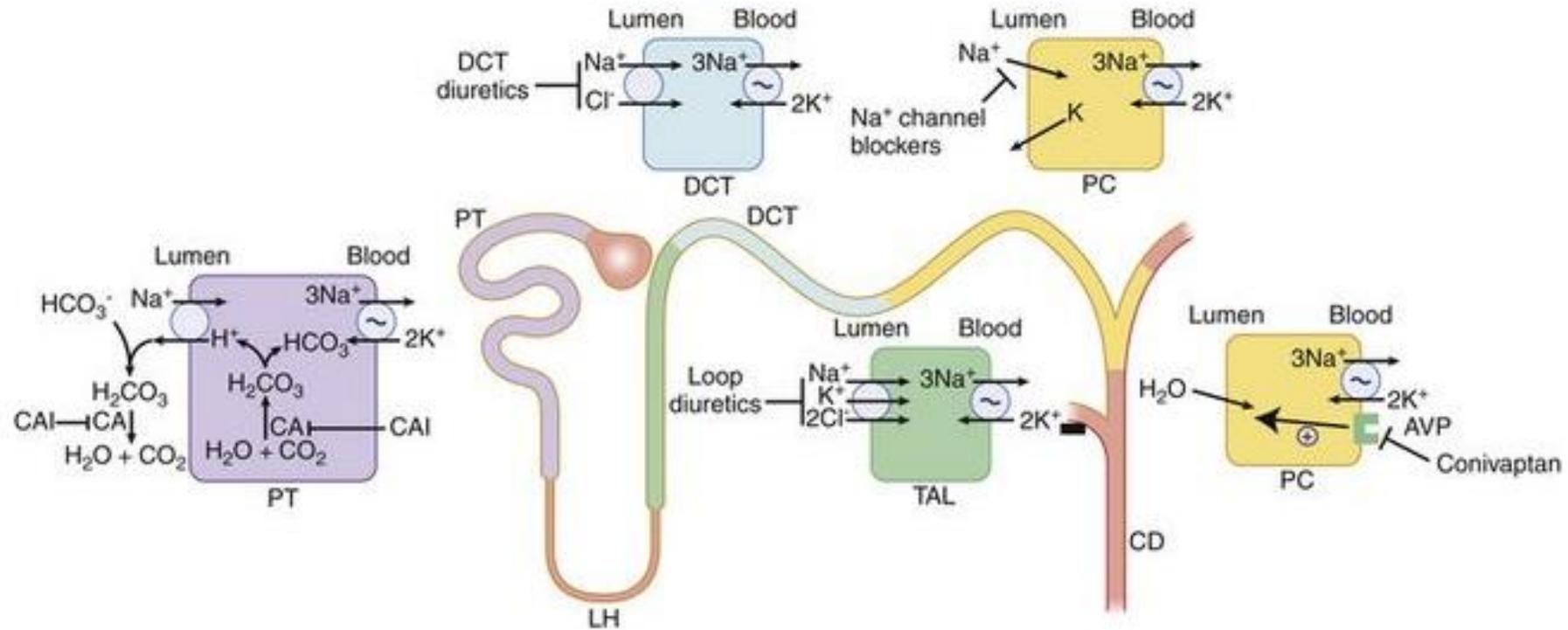


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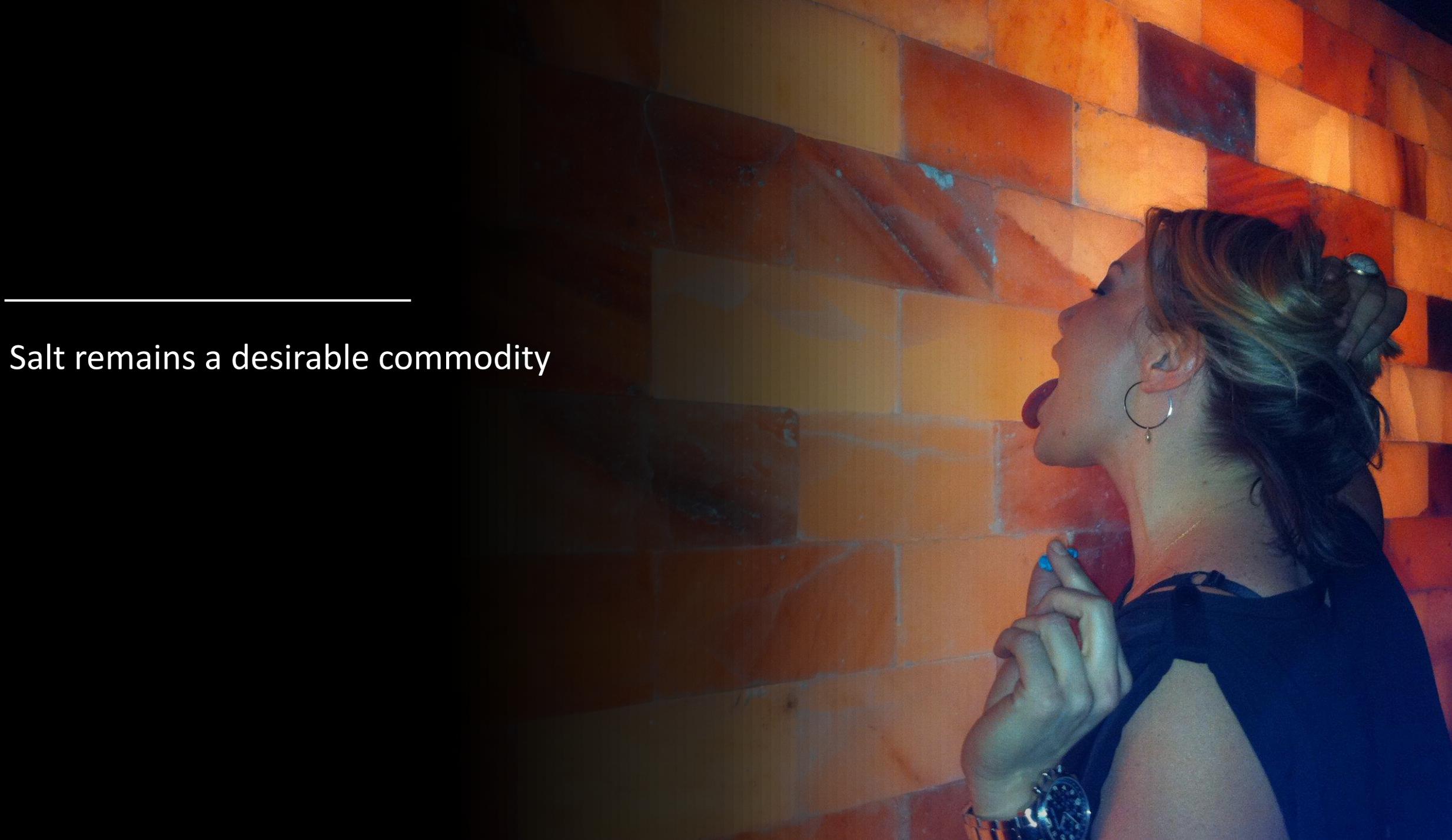
SALT WAY
Broughton
Stratford

2³/₄
31

The kidney has multiple sites of sodium reabsorption, with the capacity to practically exclude sodium from the final urine.



Salt remains a desirable commodity



Humans developed in areas where salt was extremely difficult to obtain.

This almost certainly explains why our kidneys are extremely good at holding on to salt , and quite possibly also explains why we have developed an appetite for salt

In more recent human history, technologies were developed to obtain salt from mining or evaporation. In the resulting era of salt abundance, salt remains a very desirable component of our diet and there is a practically unlimited supply

There is increasing evidence that this unnecessarily large intake of salt has important adverse health consequences

Salt sensitivity on an individual level

Increase in salt intake causes increased BP in populations

Salt sensitivity can be demonstrated in studies in individuals:

26% of normotensive people

51% of hypertensive people

In some people, especially those with elevated BP, sodium balance is achieved at higher levels of BP

Time to consider Guyton's hypothesis

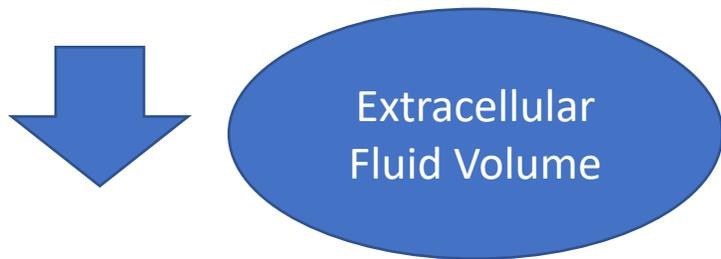
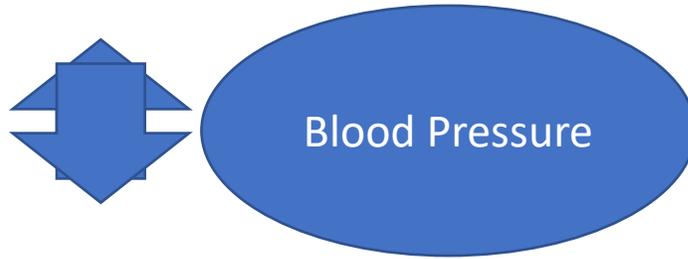
Arthur C Guyton



Guyton's pressure natriuresis
hypothesis

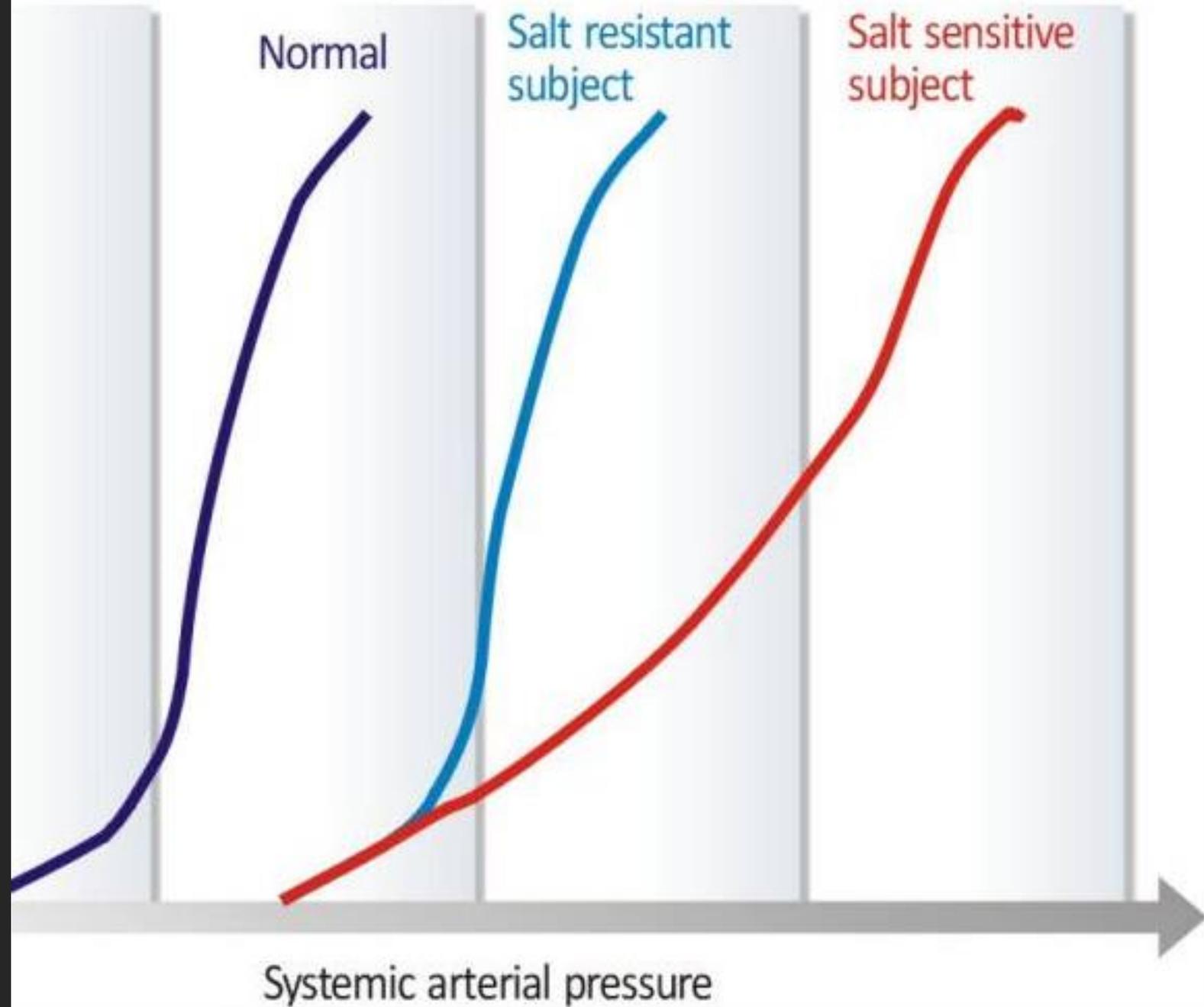
Pressure natriuresis

A physiological negative feedback system whereby increases in blood pressure result in increased sodium excretion by the kidney, causing a reduction in extracellular fluid volume which in turn results in reduced blood pressure



The pressure natriuresis relationship is altered in salt sensitive hypertension

Sodium excretion in the urine



Enough theory

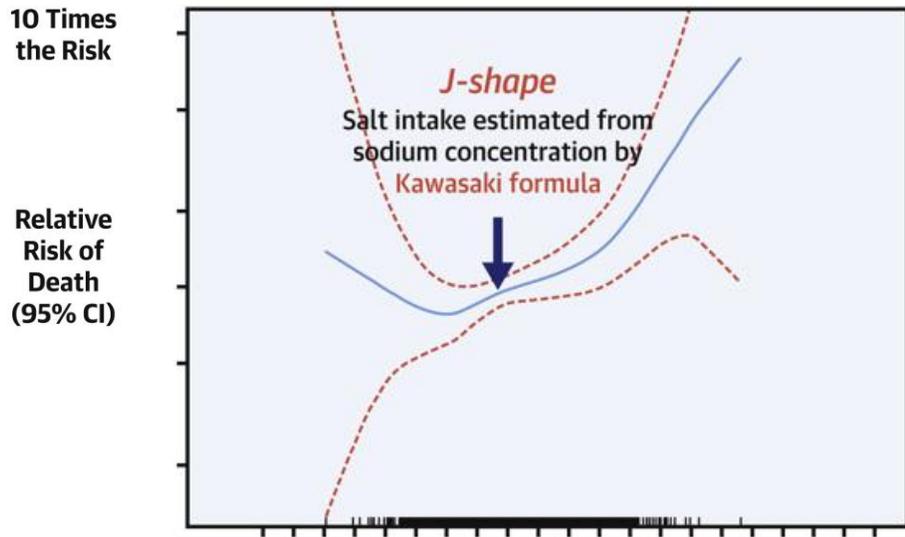
What's the evidence that increased salt intake is bad for us?

- **Sodium and Health: Old Myths and a Controversy Based on Denial**

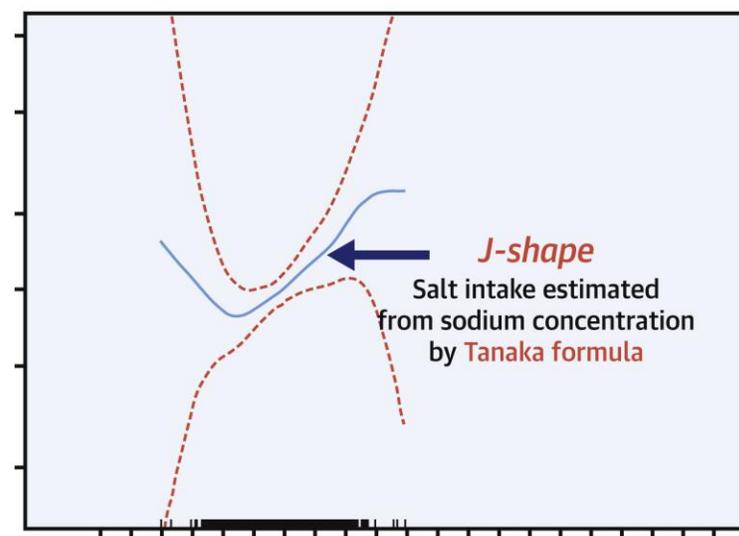
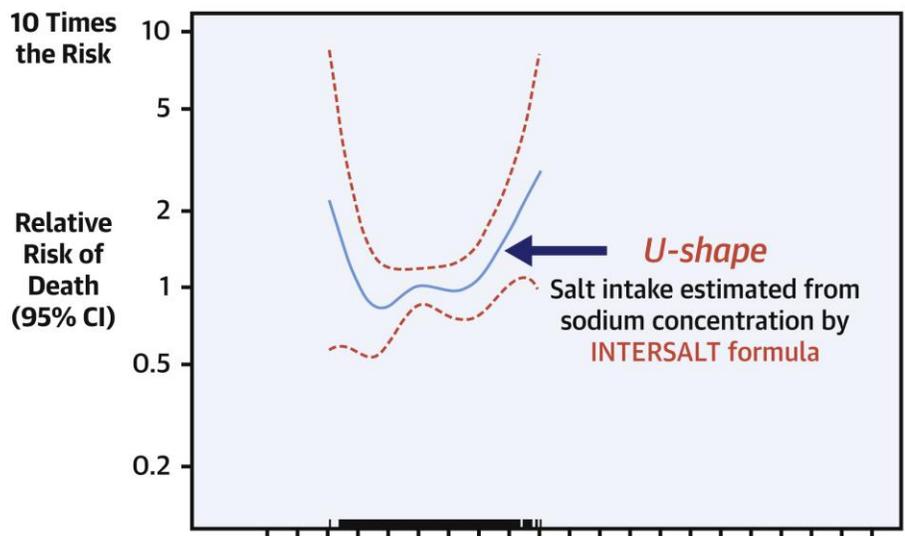
- **Francesco P. Cappuccio¹ · Norm R. C. Campbell² · Feng J. He³ · Michael F. Jacobson⁴ · Graham A. MacGregor³ · Elliott Antman⁵ · Lawrence J. Appel⁶ · JoAnne Arcand⁷ · Adriana Blanco-Metzler⁸ · Nancy R. Cook⁵ · Juliet R. Guichon² · Mary R. L'Abbè⁹ · Daniel T. Lackland¹⁰ · Tim Lang¹¹ · Rachael M. McLean¹² · Marius Miglinas¹³ · Ian Mitchell² · Frank M. Sacks¹⁴ · Peter S. Sever¹⁵ · Meir Stampfer¹⁴ · Pasquale Strazzullo¹⁶ · Wayne Sunman¹⁷ · Jacqui Webster¹⁸ · Paul K. Whelton¹⁹ · Walter Willett¹⁴**

- **Current Nutrition Reports, Published online, February 2022**

“Evidence supporting population-wide reduction in sodium intake is consistent, robust, and endorsed by such major health authorities as the WHO [16] and NASEM [8••]. A comprehensive public health approach to reduce sodium in the food supply is underway to prevent millions of unnecessary deaths and billions in health-care costs. This important work aims literally to save lives. It should not be impeded or derailed by fatally flawed research [168]. “



All these risk calculations were based on extrapolating dietary salt intake from random urine samples



Sodium Intake (mg/d) 1,000 2,500 4,000 5,500 7,000 8,500 10,000
Salt Intake (g/d) 2.50 6.25 10.00 13.75 17.50 21.25 25.00

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When salt intake is measured accurately, there really isn't a J-shaped curve with respect to cardiovascular risk

24-Hour Urinary Sodium and Potassium Excretion and Cardiovascular Risk

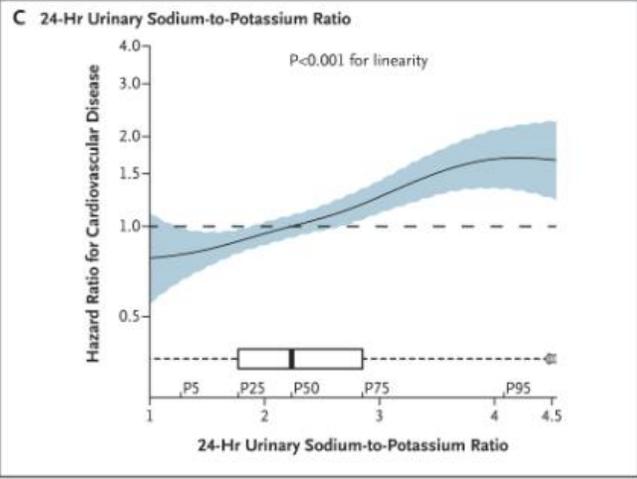
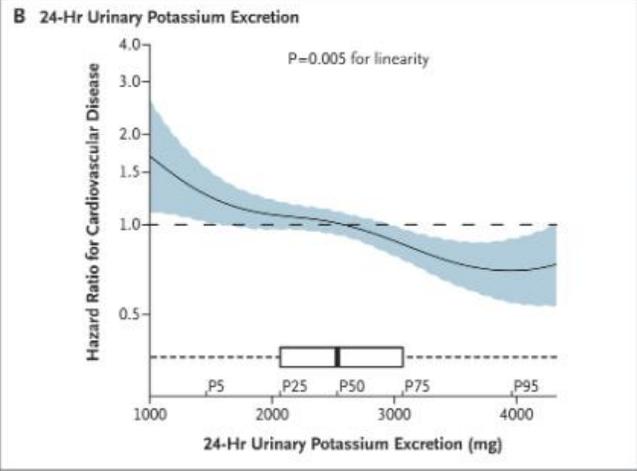
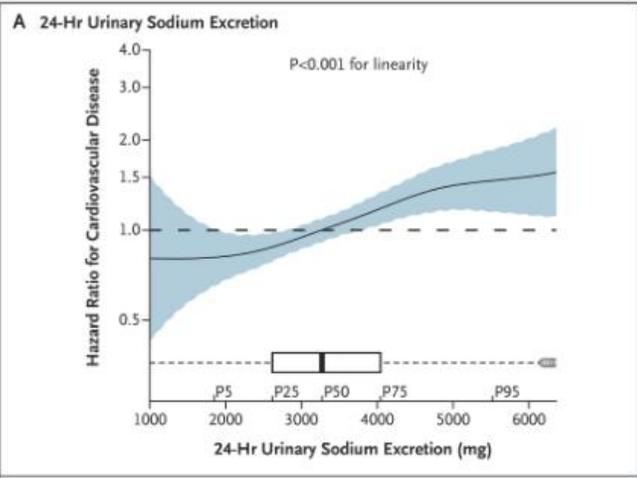
Yuan Ma, Ph.D., et. A.;

January 20, 2022

N Engl J Med 2022; 386:252-263

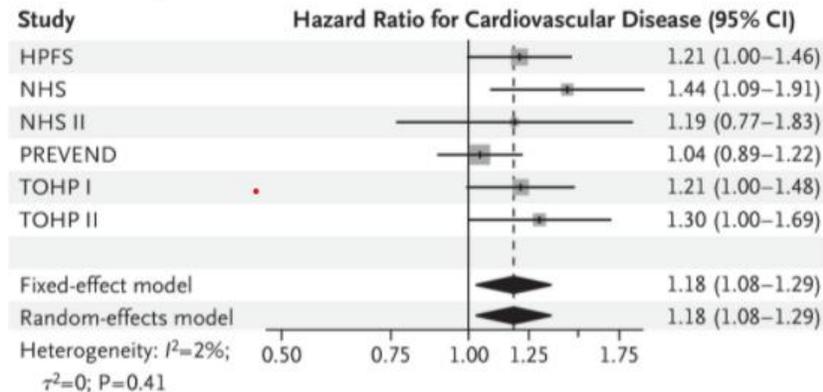
The important aspects of this meta-analysis of six prospective cohorts:

- **Studying generally healthy populations**, reduced confounding and potential reverse-causation bias
- **Repeated 24 hr urine sodium.** Projections from spot urines are extremely unreliable and subject to confounding (Age, gender, weight etc)

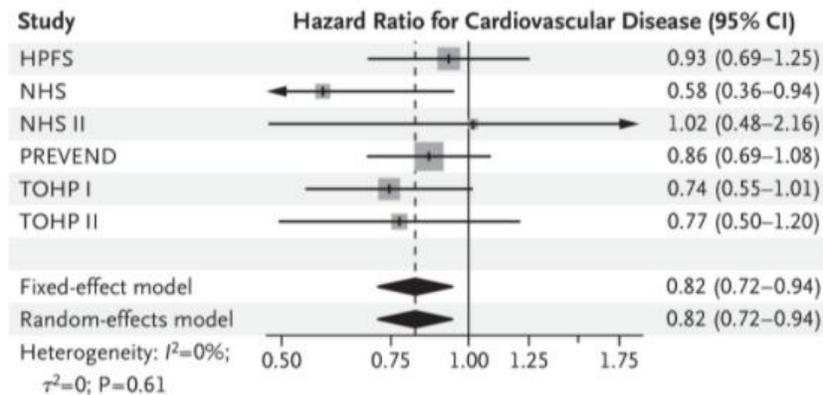


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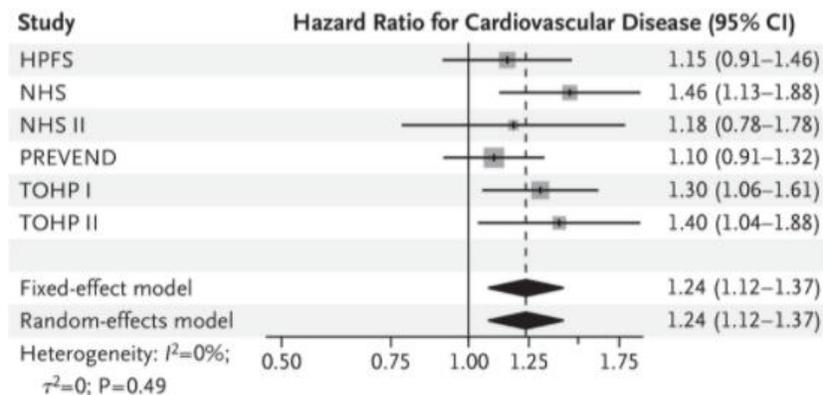
A Per 1000-mg Increase in 24-Hr Urinary Sodium Excretion

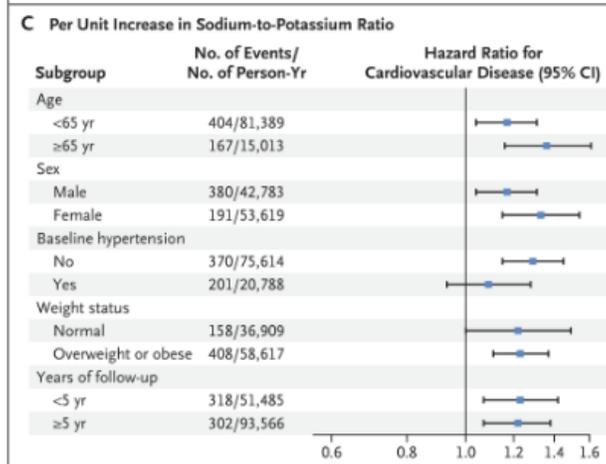
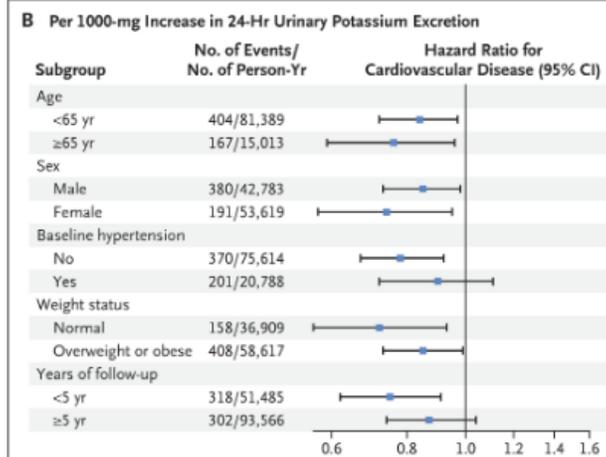
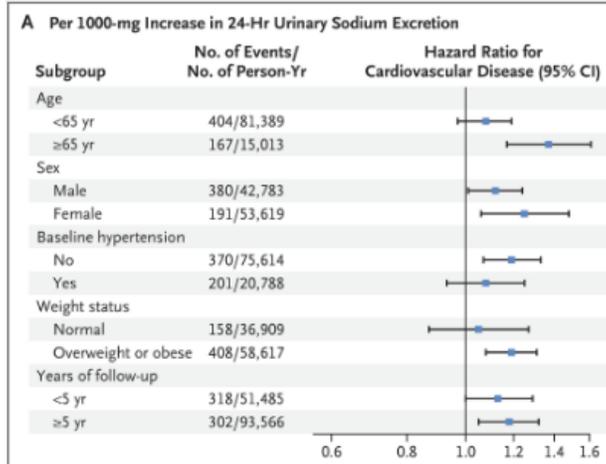


B Per 1000-mg Increase in 24-Hr Urinary Potassium Excretion



C Per Unit Increase in Sodium-to-Potassium Ratio





How much salt should we eat?

- The percentage of U.S. adults with sodium intake above the Chronic Disease Risk Reduction target of 2300mg (100mmol) was 87.0% during 2003–2004 and 86.7% during 2015–2016
- The lowest recommended sodium intake is around 500 mg per day, which is about 20 mmol
- Salt intake in rural areas in some developing countries can be as low as 100 mg a day, roughly 5 mmol.
- A healthy human subjected to stringent sodium restriction can reduce urinary sodium excretion to less than 10 mmol per 24 hours

Hence, we generally eat much more salt than we need, driven by our salt appetite and the food industry

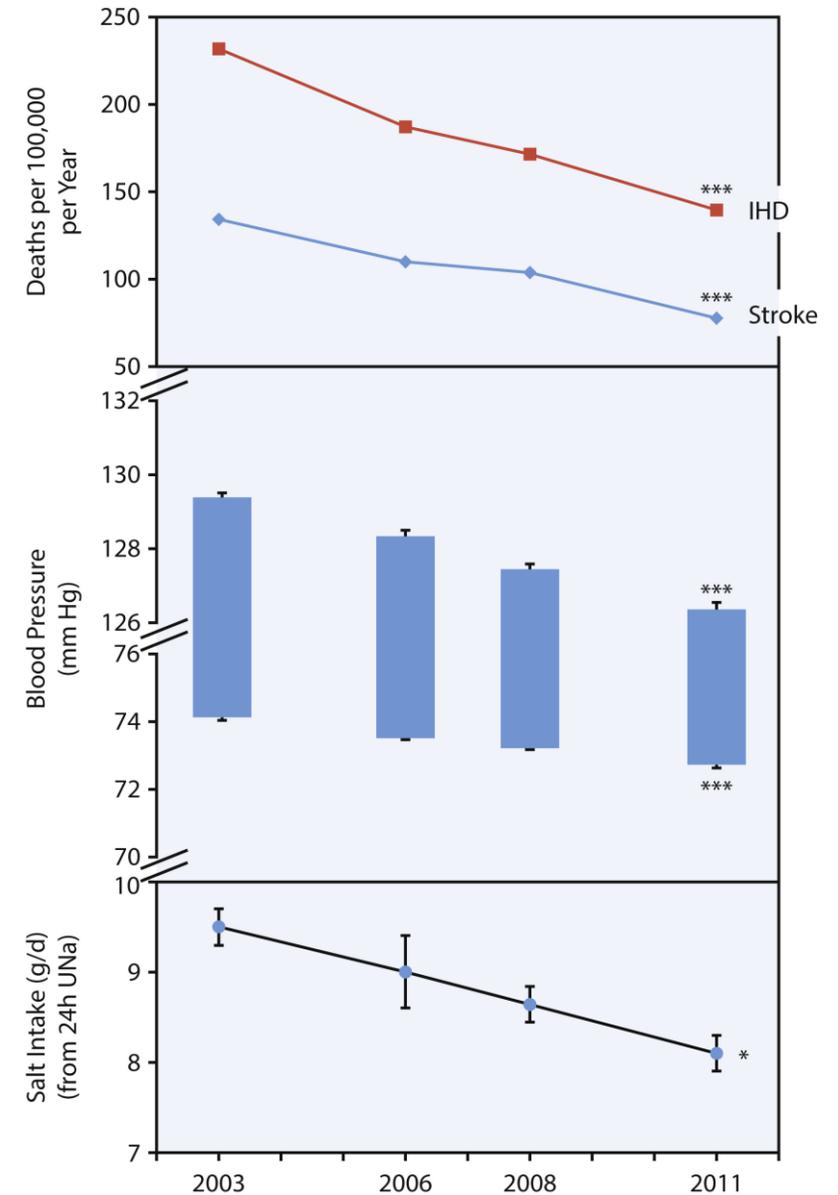
Note that only 10-20% of the sodium in our diets is derived from salt we personally add to our food, the rest is largely the consequence of food processing

Perhaps as consequence of our tendency to hang on to sodium, this excessive intake results in harm through multiple pathways

What is the impact of lowering salt intake on cardiovascular risk?

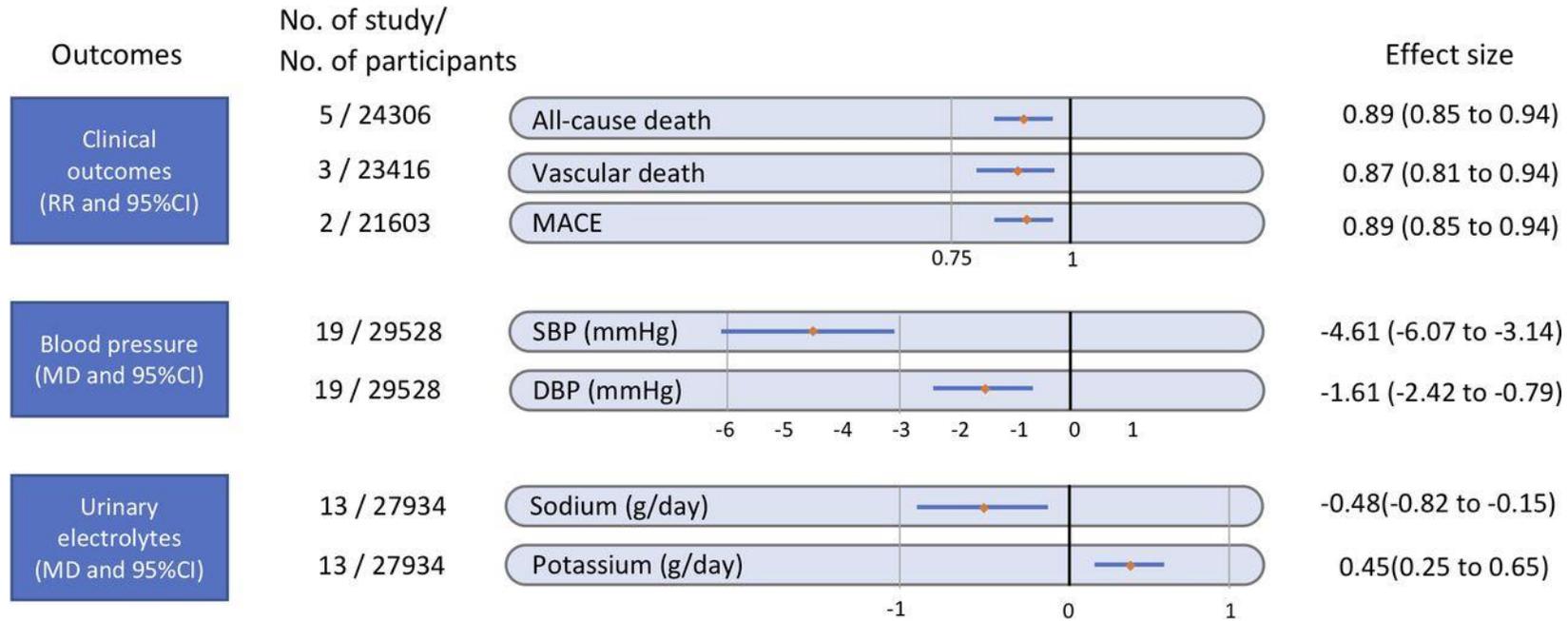
F.J. He, S. Pombo-Rodrigues, G.A. MacGregor

Salt reduction in England from 2003 to 2011: its relationship to blood pressure, stroke and ischaemic heart disease mortality



Salt substitution with potassium chloride, shows promise as a powerful intervention to reduce dietary sodium intake on a population level, with the added advantage of increasing potassium intake.

Summary of impact of salt substitutes on outcomes of interest.

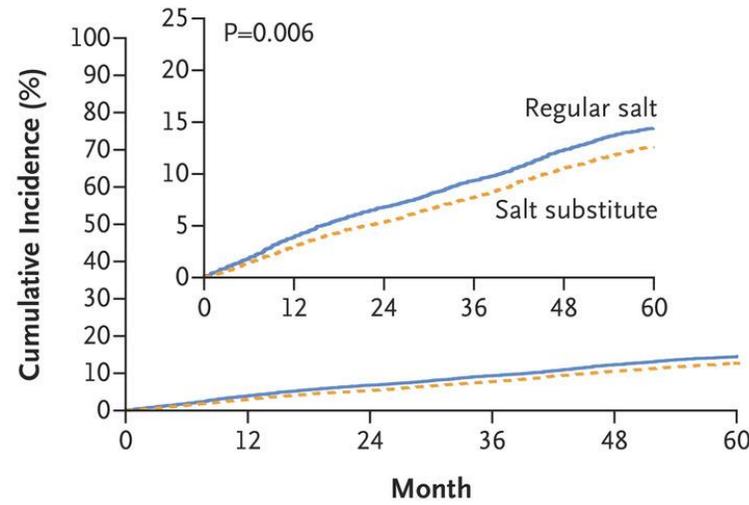


Xuejun Yin et al. Heart doi:10.1136/heartjnl-2022-321332



Effects of Salt Substitution on Trial Outcomes

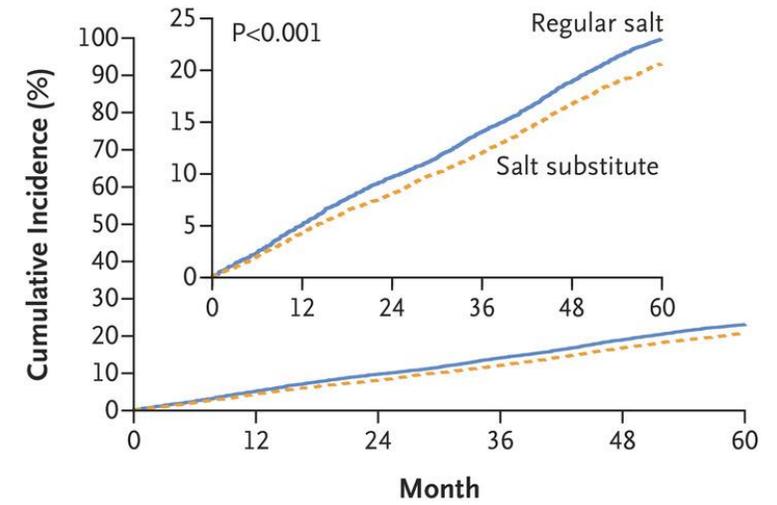
A Stroke



No. at Risk

Regular salt	10,491	9870	9288	8752	8138	7580
Salt substitute	10,504	9992	9508	8997	8385	7846

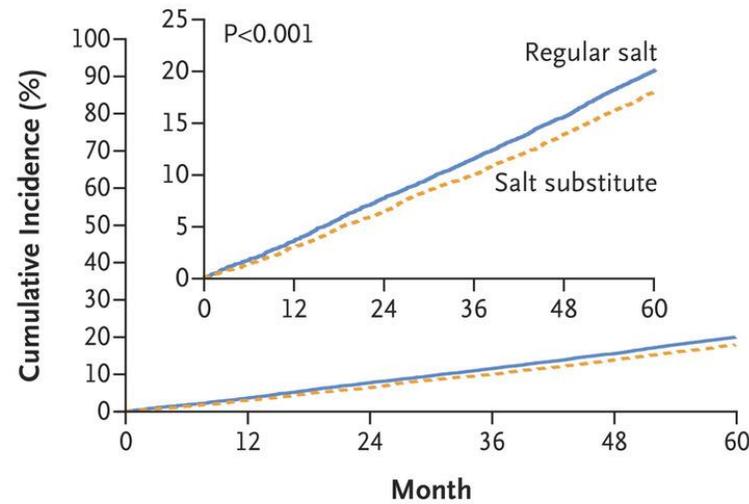
B Major Adverse Cardiovascular Events



No. at Risk

Regular salt	10,491	9860	9259	8658	8002	7412
Salt substitute	10,504	9976	9478	8922	8277	7716

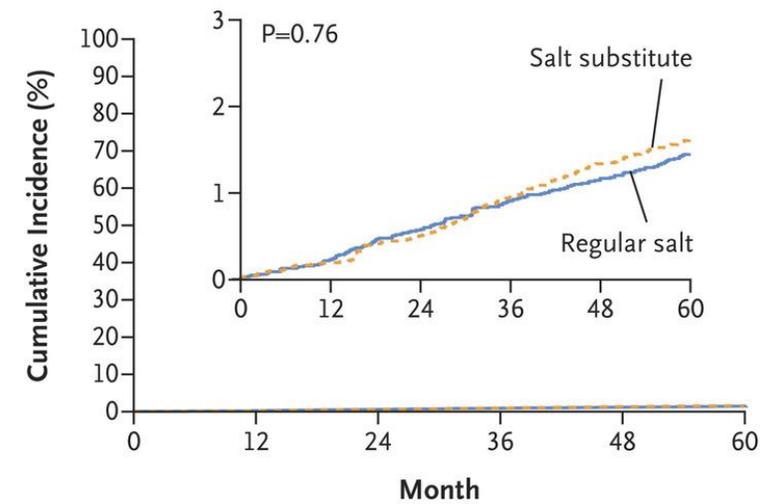
C Death from Any Cause



No. at Risk

Regular salt	10,491	10,116	9681	9279	8859	8391
Salt substitute	10,504	10,189	9829	9452	9043	8617

D Hyperkalemia

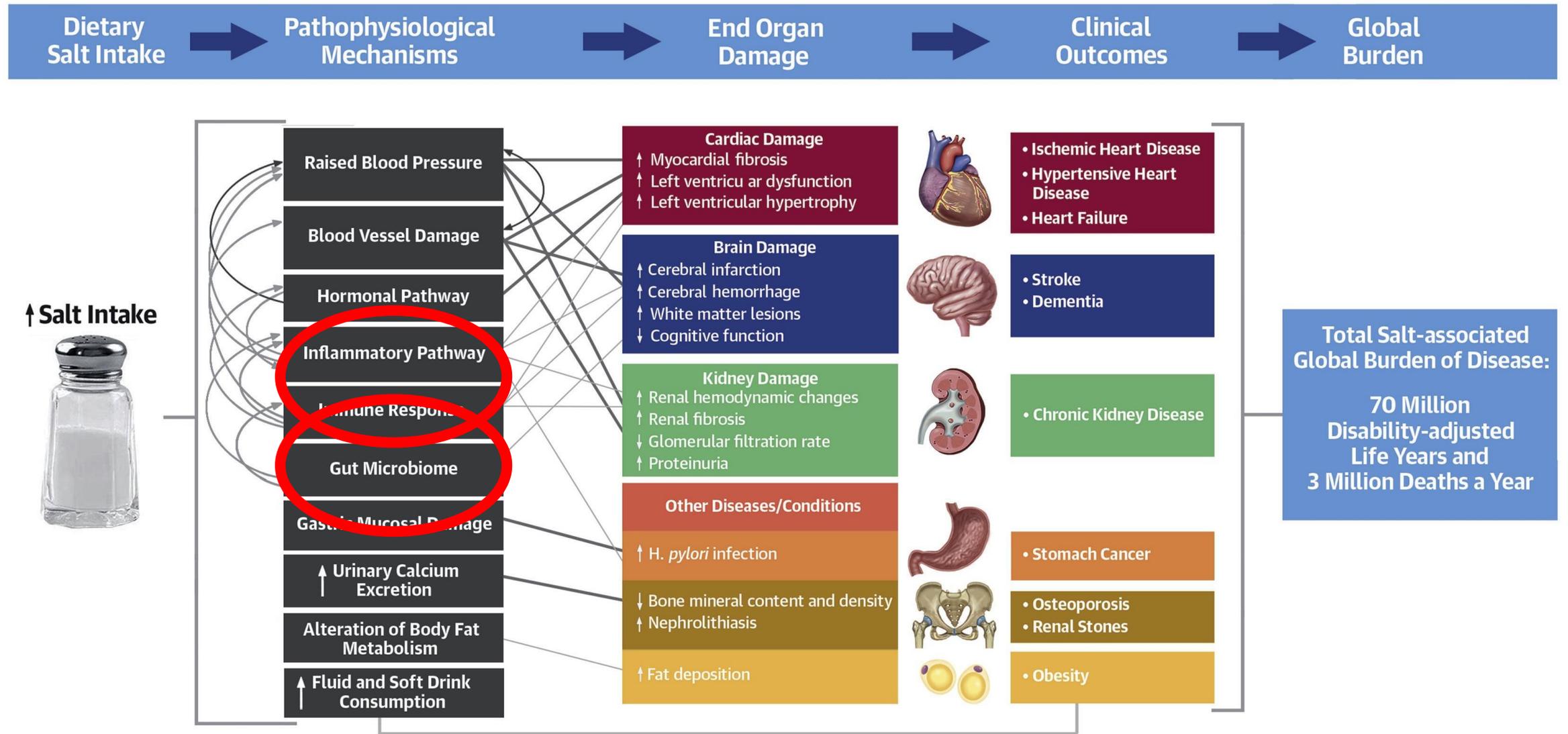


No. at Risk

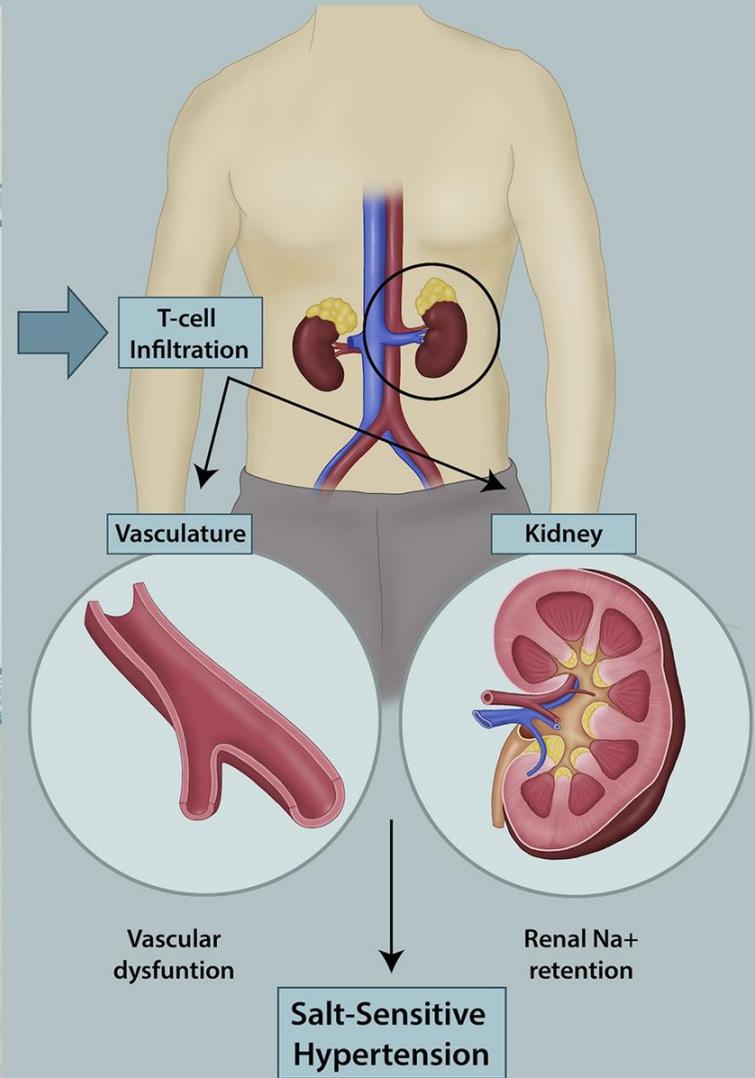
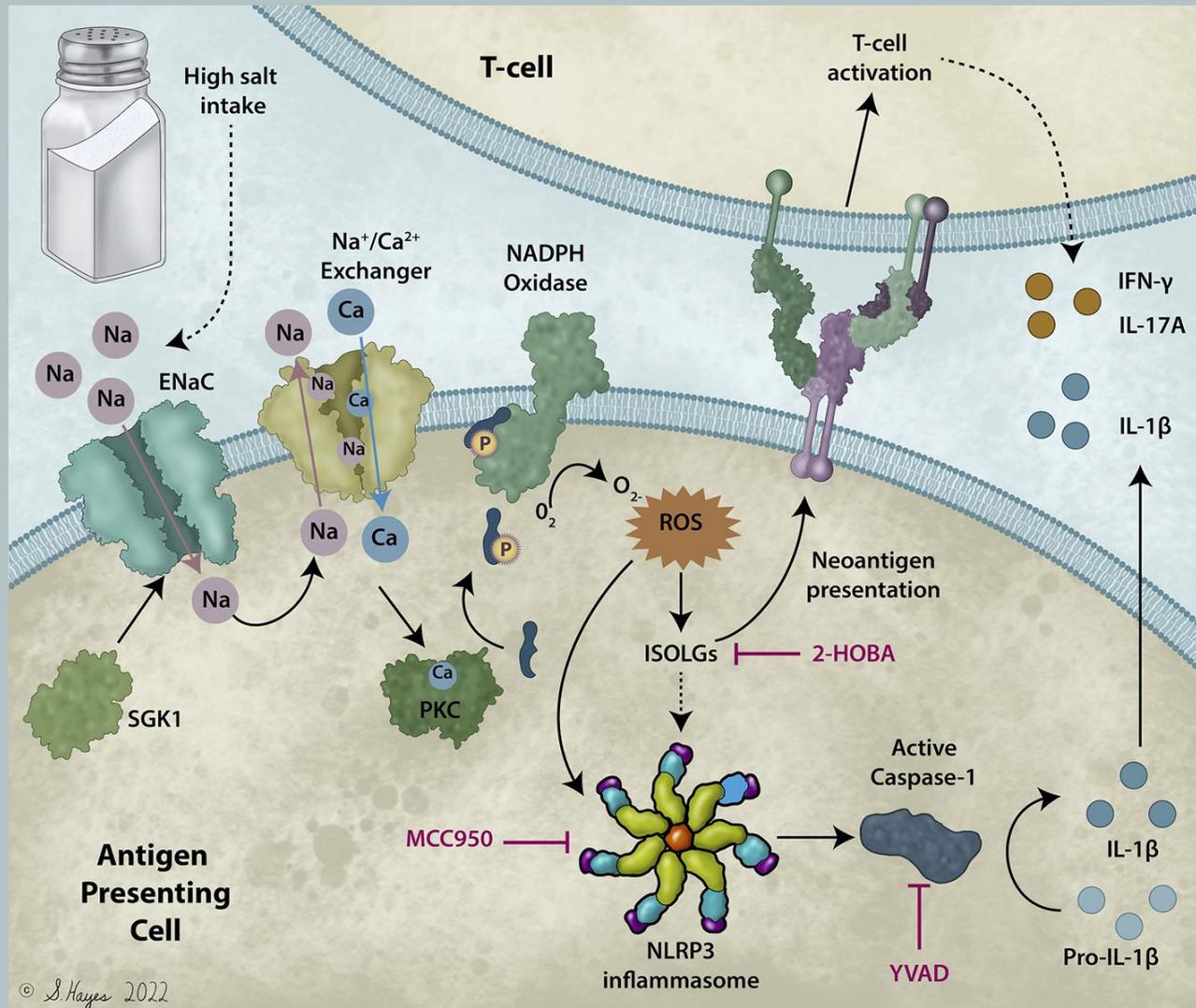
Regular salt	10,491	10,113	9676	9274	8853	8385
Salt substitute	10,504	10,187	9827	9451	9038	8612

The harmful effects of increased salt intake may not result solely from changes in extracellular fluid volume and arterial pressure, and are not confined to the cardiovascular system

CENTRAL ILLUSTRATION: Salt and Health

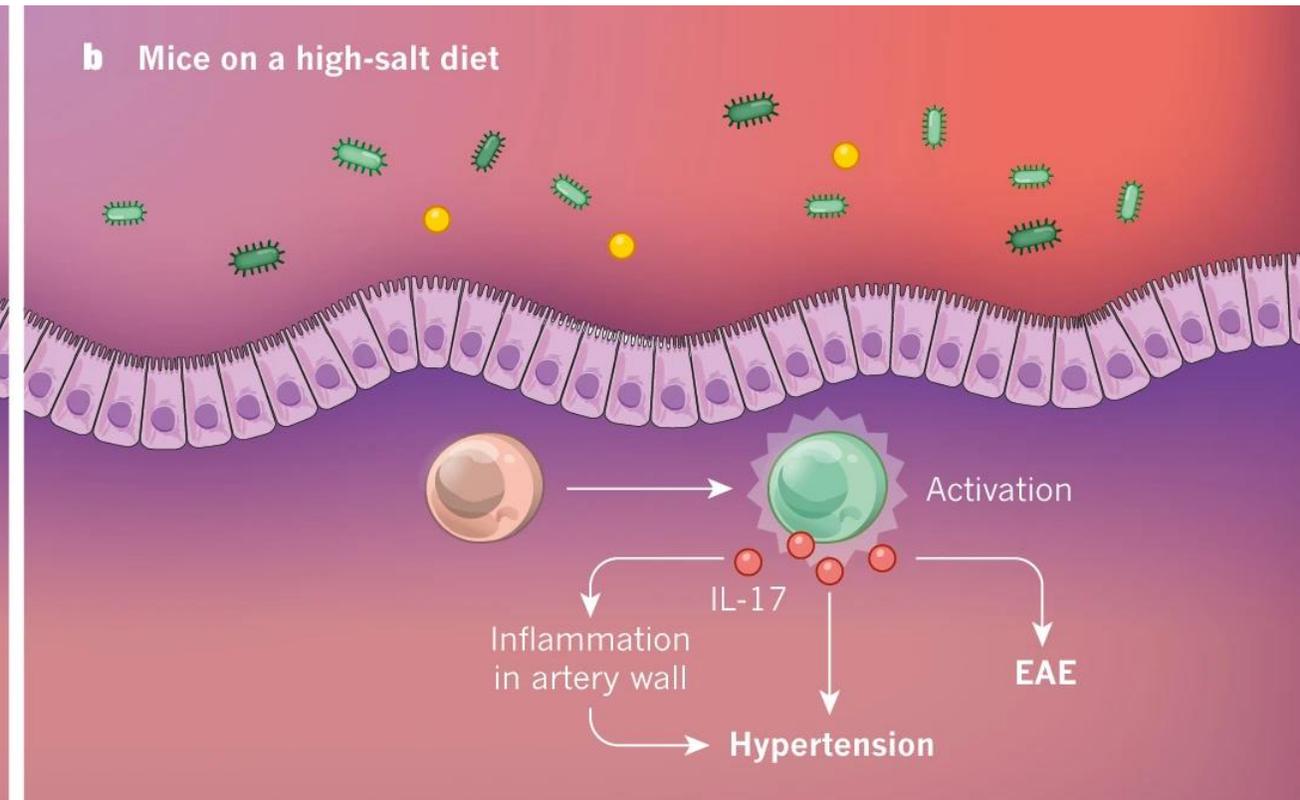
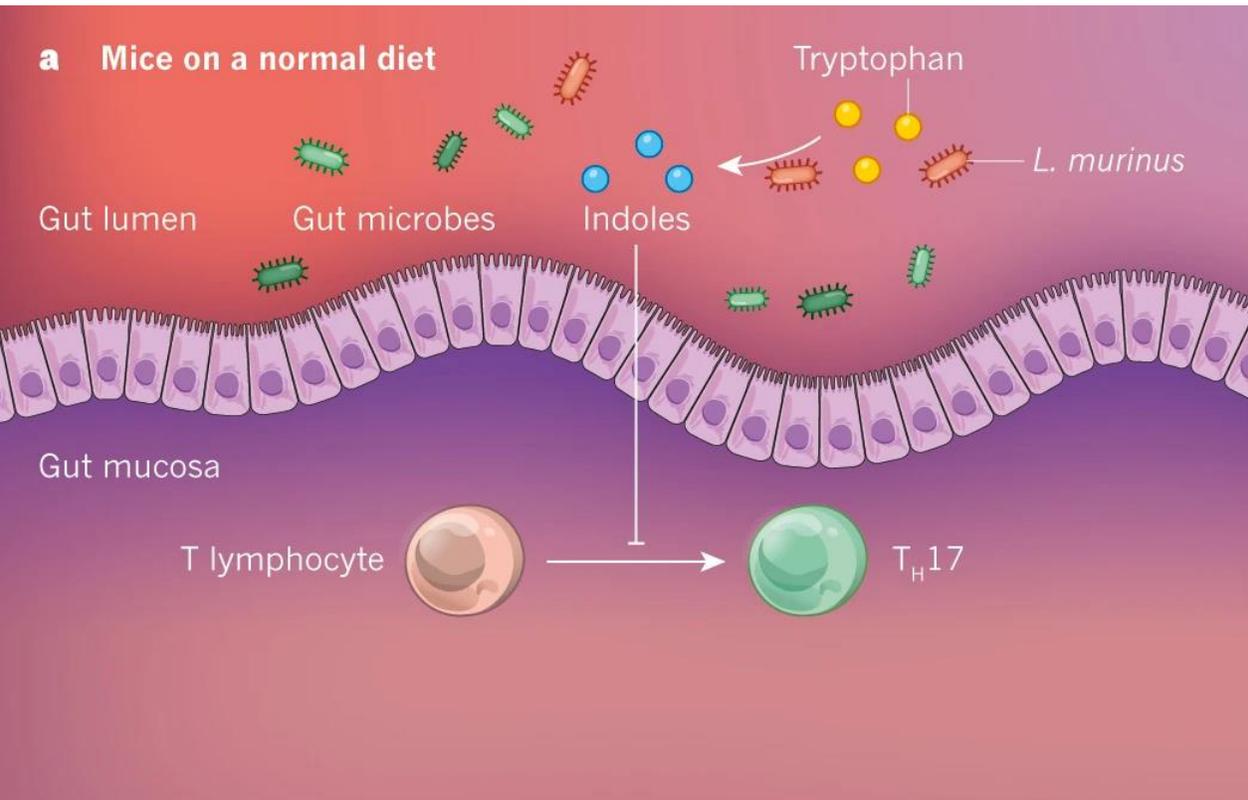


He, F.J. et al. J Am Coll Cardiol. 2020;75(6):632-47.

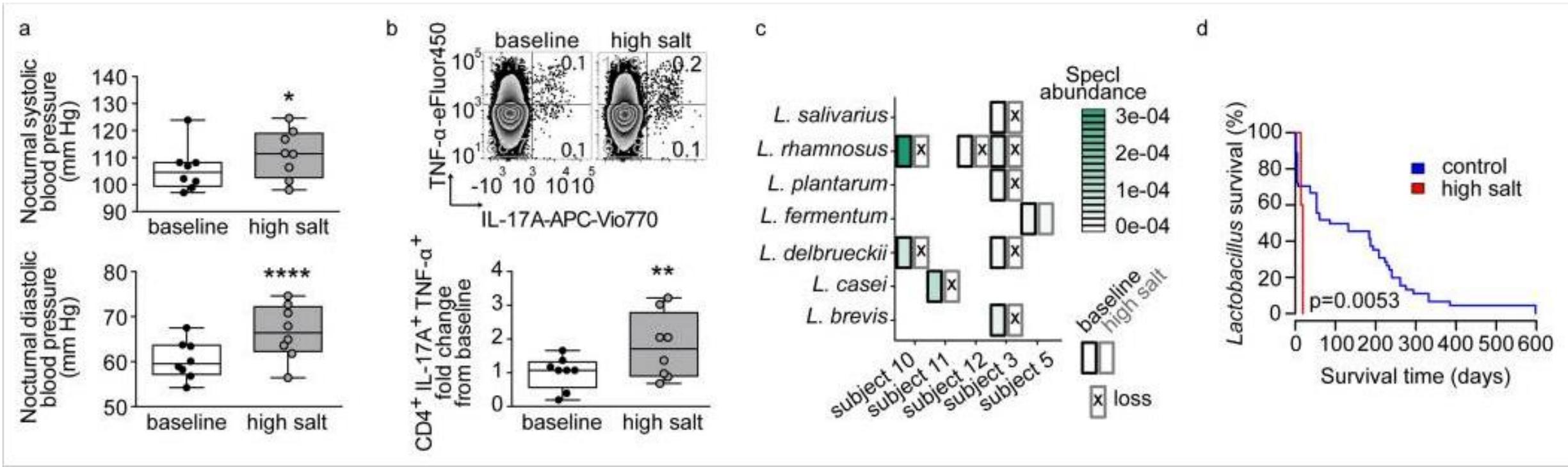


Ashley Pitzer. *Circulation Research*. DC ENaC-Dependent Inflammasome Activation Contributes to Salt-Sensitive Hypertension, Volume: 131, Issue: 4, Pages: 328-344, DOI: (10.1161/CIRCRESAHA.122.320818)

Dietary salt, the gut microbiome and hypertension

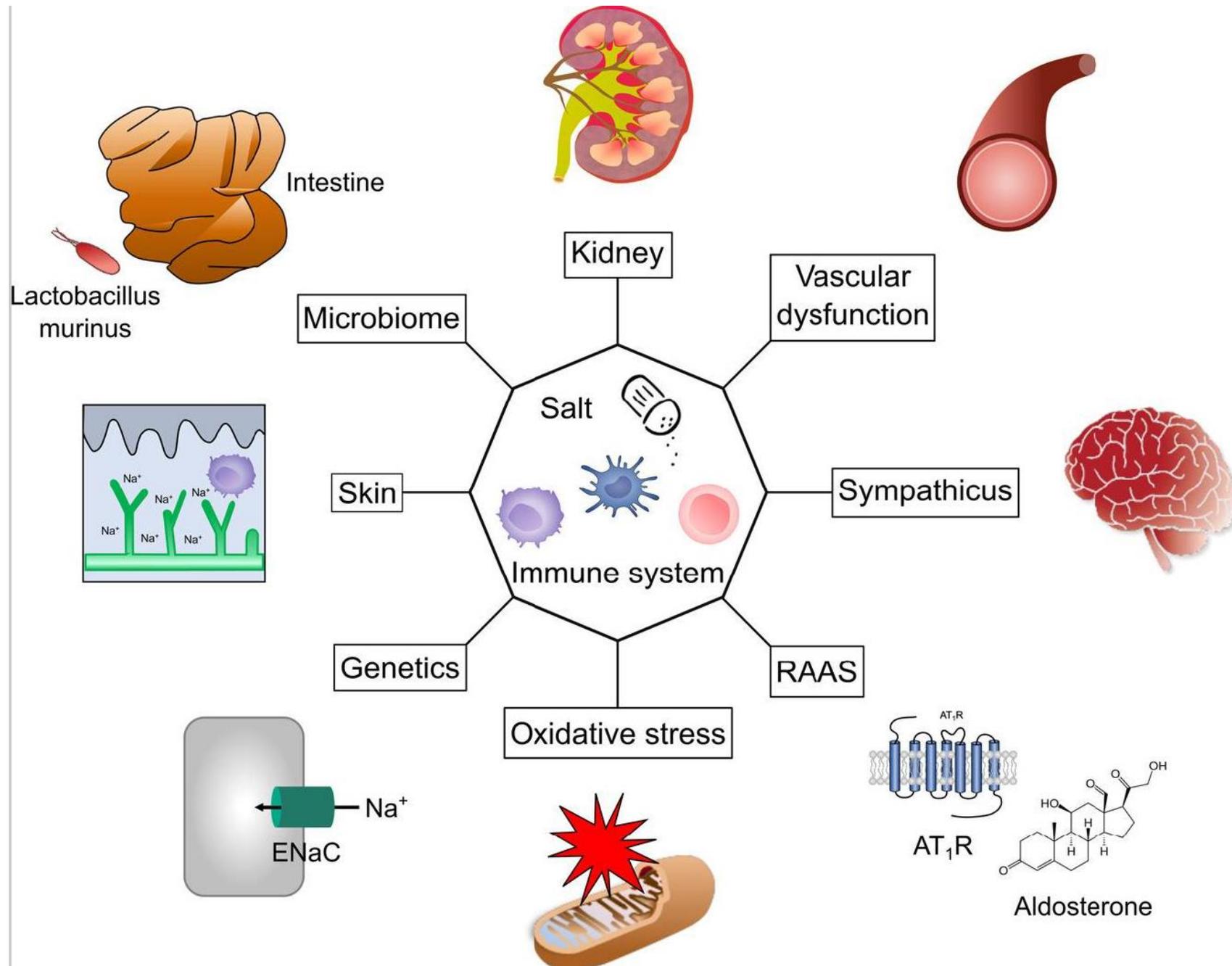


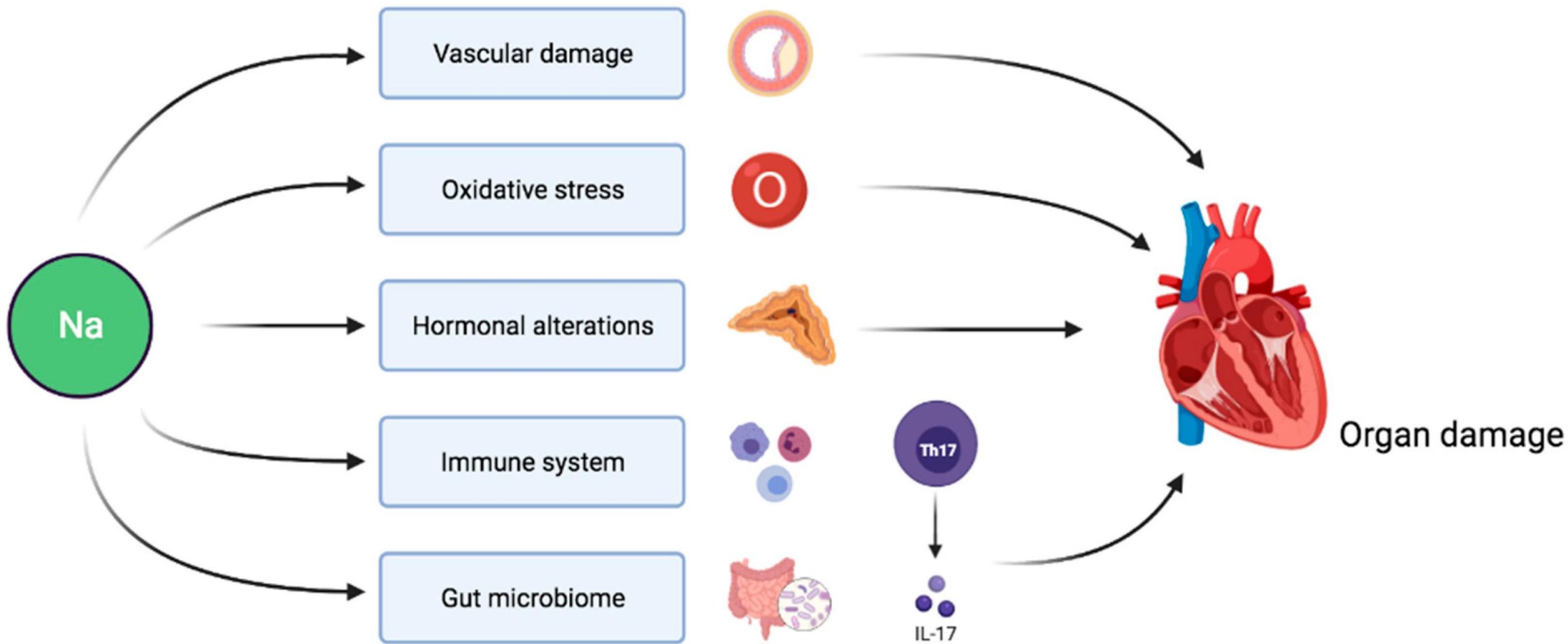
High salt intake induces expansion of T_H17 positive T lymphocytes (T-helper cells) and reduces survival of lactobacillus species in human feces.



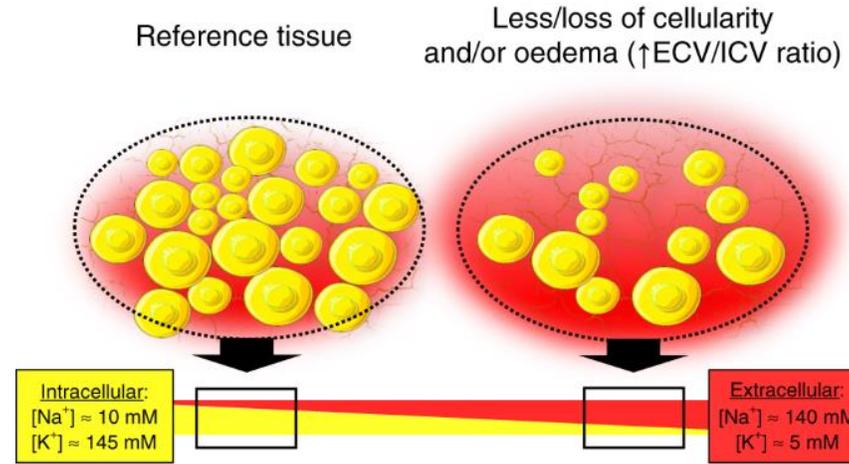
Summary

- Salt is an essential component of our diet
- We have evolved to manage perfectly well with very low dietary salt intake
- The typical Western diet leads to the ingestion of as much as 40 times the minimum required intake of sodium
- Excessive sodium intake leads to injury to multiple organ systems via multiple pathways
- In addition to the classical effects of salt intake on blood pressure, there is increasing evidence that high salt intake leads to organ damage through immune mechanisms and alterations in the microbiome
- Relatively simple measures can promote significantly reduced intake of salt at population level
- Even relatively modest reductions in population salt intake lead to significant health benefits

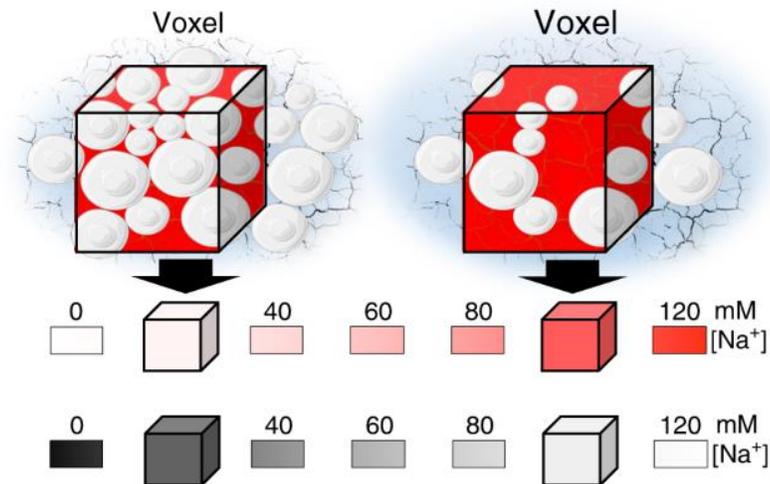




(HISTO) Chemical analysis — $[\text{Na}^+]$ and $[\text{K}^+]$

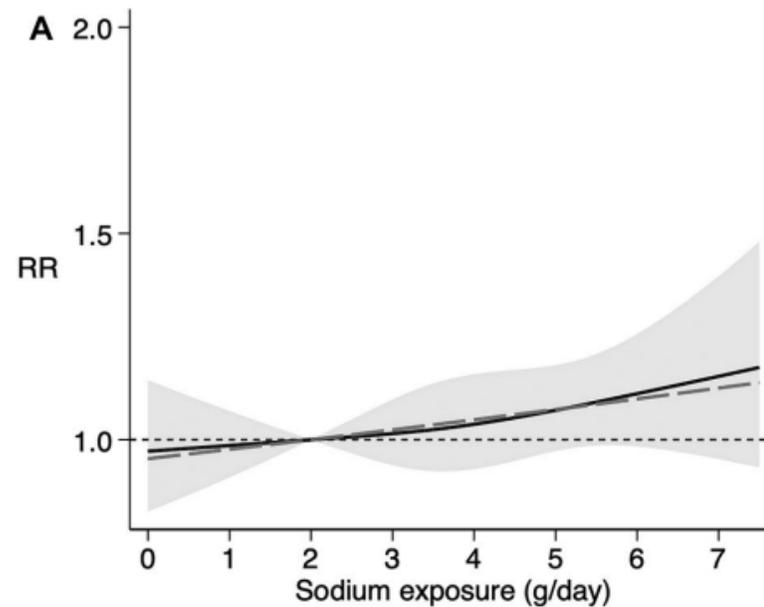


^{23}Na Magnetic resonance imaging

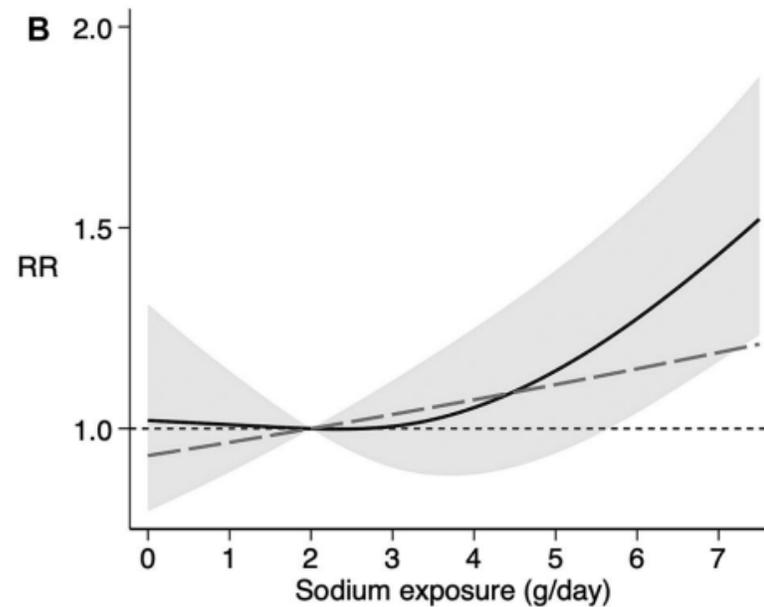


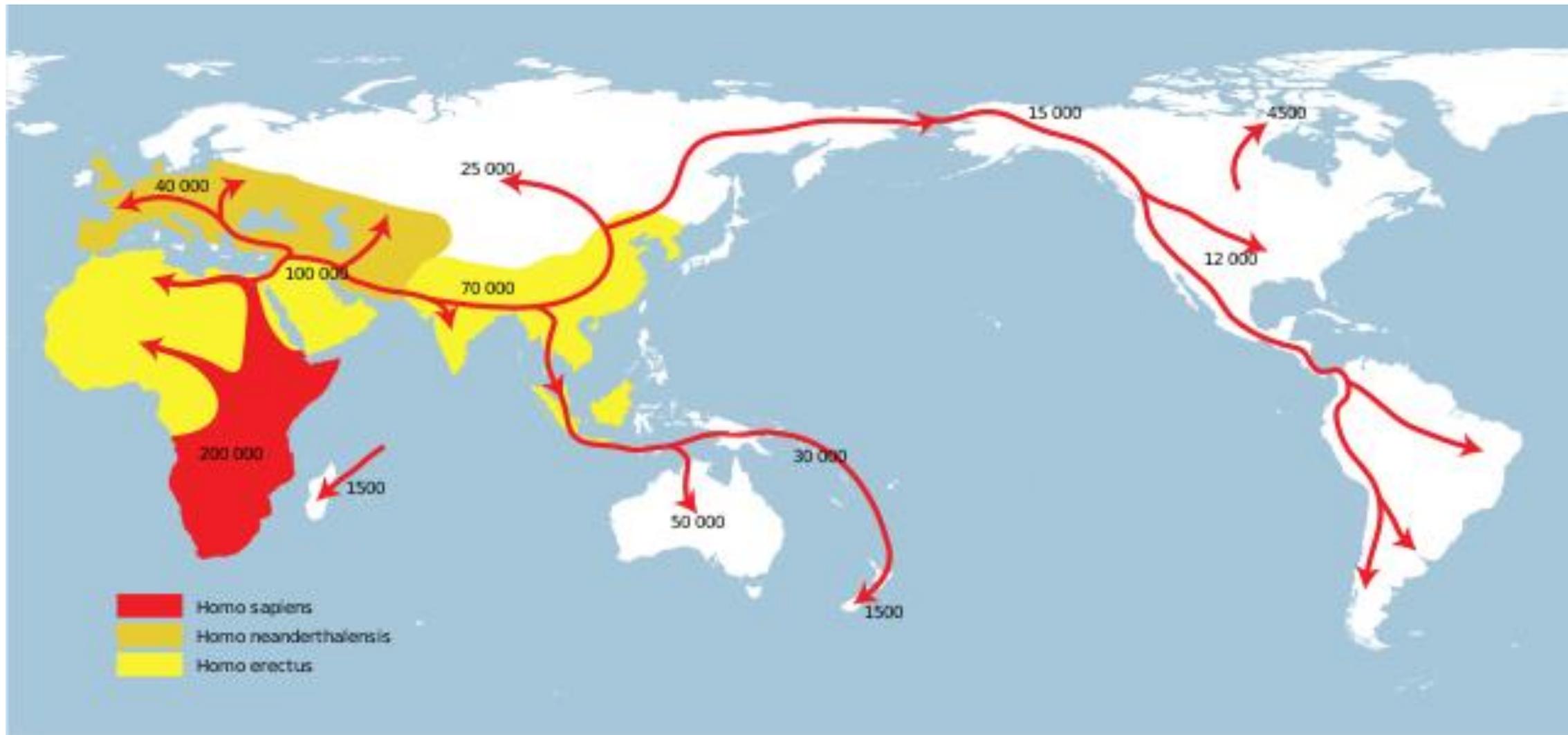
The controversy

24 hr urine sodium



Spot or dietary estimate





It is important to note that the sodium concentration in our extracellular fluid is not determined by the amount of sodium in our body, but rather by the amount of water relative to sodium.