The George Institute for Global Health

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Effects of reduced-sodium, added-potassium salt substitute on stroke – the salt substitute and stroke study (SSaSS)

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Sodium, potassium and salt substitute

- Both higher sodium consumption and lower potassium consumption are associated with higher BP levels.
- Randomised trials show clear BP lowering effects with reduced dietary sodium or added dietary potassium.
- Salt substitutes combine the two effects with clear benefits for BP in randomised trials.

But

- Effects of salt substitutes on cardiovascular events unproven
- Salt substitution carries a theoretical risk of hyperkalaemia
- Concerns raised about reducing dietary sodium intake

Salt Substitute and Stroke Study (SSaSS)

The primary aim was to define the effect of salt substitute versus regular salt on stroke

- The secondary aims were to define the effects on:
  - Major adverse cardiovascular events
  - Total mortality
- The safety outcome was hyperkalaemia

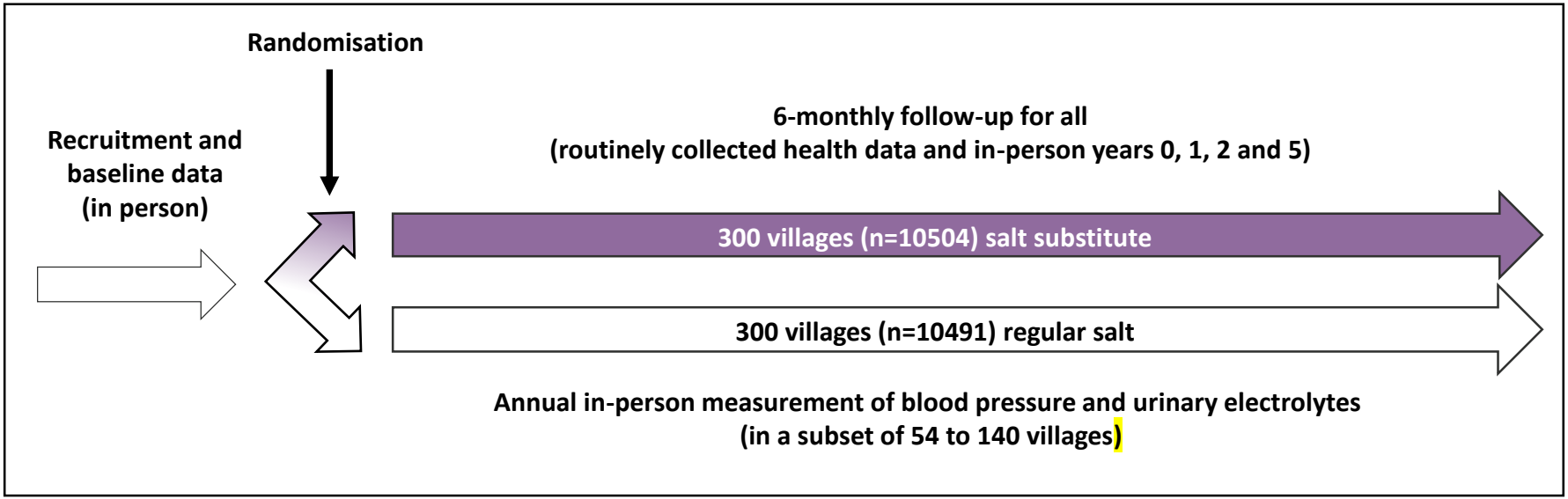
Endpoint adjudication masked to treatment allocation for all outcomes

Participants and recruitment

- 600 villages and about 35 participants from each village
- Adults with history of stroke, or
- Age 60+ years with poorly controlled BP
- No self-reported history of severe kidney disease, use of potassium supplements or use of potassium sparing diuretics
- No blood test for renal function or serum potassium

Design

- Pragmatic, large-scale (n=20,995), open, cluster randomised trial
- Salt substitute (75%NaCl, 25%KCl) versus regular salt (100%NaCl)



Statistical power and analysis

- 90% power (p=0.05) to detect a 13% lower risk of stroke with salt substitute compared to regular salt. Assumptions:
  - 3.0mmHg BP lowering
  - 3.5% p.a. primary outcome event rate
  - Cluster randomisation of 600 villages in 1:1 ratio
  - Intra-cluster correlation coefficient =0.04
- Primary analysis using Poisson regression, adjusted for clustering by village with rate ratios, 95%CIs and p-values calculated
- Control for multiple testing across primary and secondary outcomes was done using the Benjamini-Hochberg approach
- The Kaplan Meier method used to generate cumulative event curves

Participant characteristics

	Salt substitute	Regular salt
Age (years), mean	65	65
Women, %	50	49
Education beyond primary, %	28	27
History of stroke, %	73	72
Uncontrolled blood pressure, %	59	59
Diabetes, %	11	11
Hypertension, %	89	88
ACE/ARB, %	23	23
Calcium antagonist, %	43	41
Any antihypertensive, %	80	79
Mean blood pressure, mmHg	154/89	154/89
Mean 24-hour urinary sodium, mmol (g)*	191 (4.4)	182 (4.2)
Mean 24-hour urinary potassium, mmol (g)*	36 (1.4)	36 (1.4)

*calculated from subset of 539 individuals with complete baseline 24-hour urine collections.

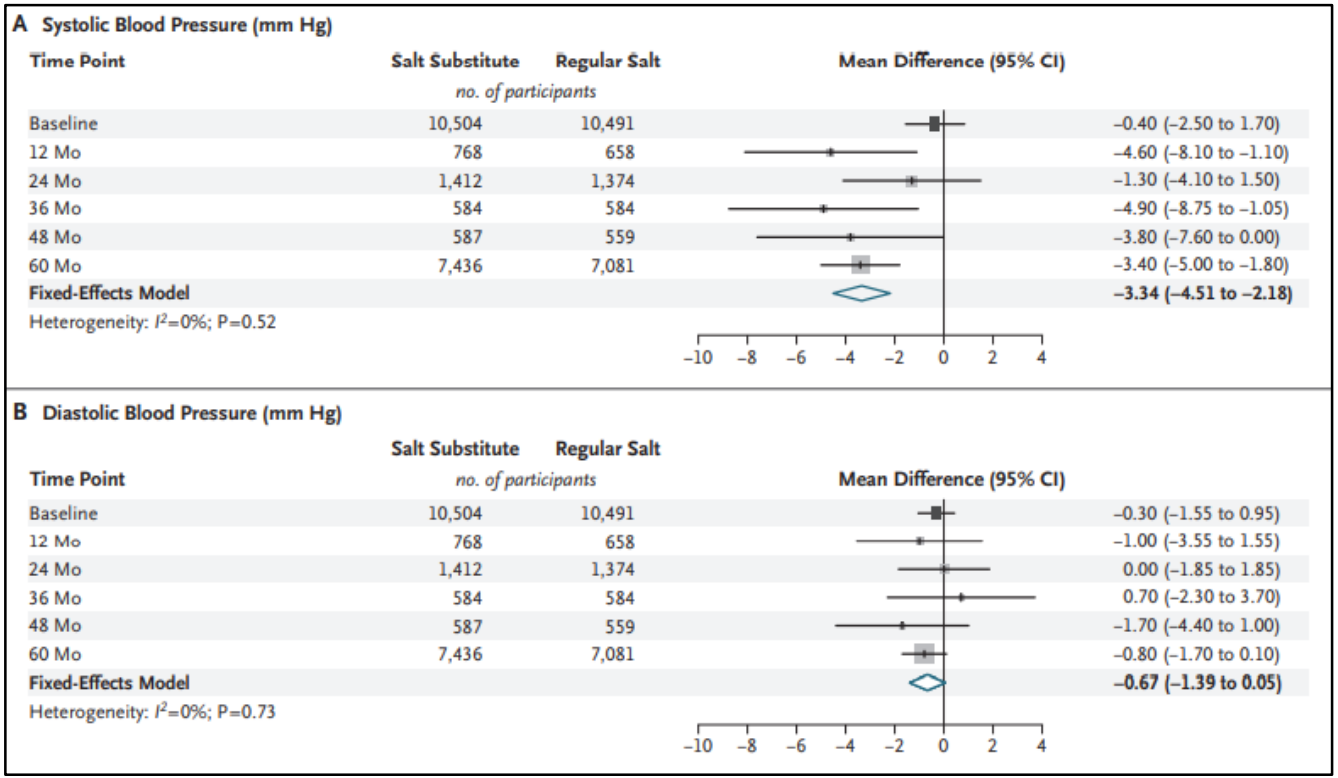
Source: Neal, Am Heart J 2017

Follow-up and adherence

Follow-up

- Mean follow-up 4.74 years
- 100% vital status for all participants
- 99.9% complete follow-up for non-fatal outcomes
- At 5 years, 92% intervention group still using salt substitute and 6% control group started using salt substitute

Effects on blood pressure

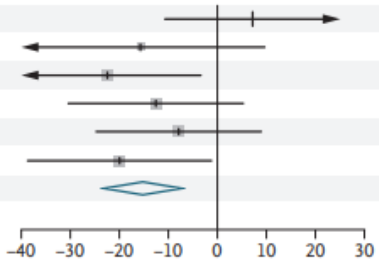


Effects on urinary electrolytes

C 24-Hr Urinary Sodium Excretion (mmol)

Time Point	Salt Substitute (no. of participants)	Regular Salt (no. of participants)	Mean Difference (95% CI)
Baseline	276	268	9.96 (–12.39 to 32.32)
12 Mo	577	445	–15.69 (–41.05 to 9.66)
24 Mo	1,047	939	–22.45 (–41.52 to –3.37)
36 Mo	428	392	–12.55 (–30.41 to 5.31)
48 Mo	444	383	–7.89 (–24.73 to 8.95)
60 Mo	424	358	–19.95 (–38.71 to –1.20)
Fixed-Effects Model			**–15.21 (–23.72 to –6.70)**

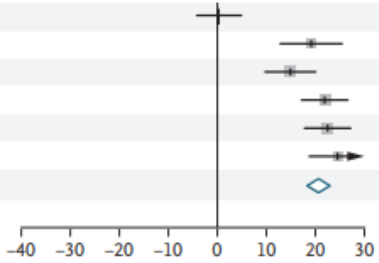
Heterogeneity: I^2=0%; P=0.81



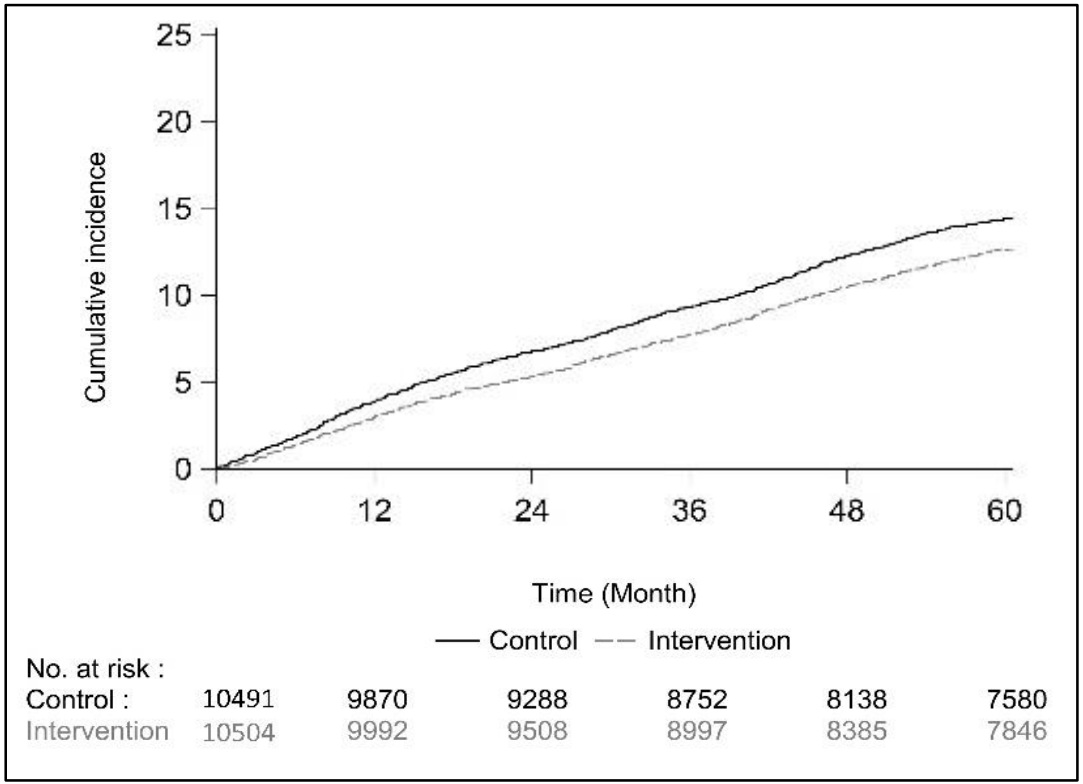
D 24-Hr Urinary Potassium Excretion (mmol)

Time Point	Salt Substitute (no. of participants)	Regular Salt (no. of participants)	Mean Difference (95% CI)
Baseline	276	268	0.63 (–3.36 to 4.62)
12 Mo	577	445	19.13 (12.82 to 25.45)
24 Mo	1,047	939	14.88 (9.73 to 20.03)
36 Mo	428	392	21.87 (17.15 to 26.60)
48 Mo	444	383	22.48 (17.78 to 27.18)
60 Mo	424	358	24.52 (18.74 to 30.30)
Fixed-Effects Model			**20.64 (18.30 to 22.98)**

Heterogeneity: I^2=47.4%; P=0.11



Stroke



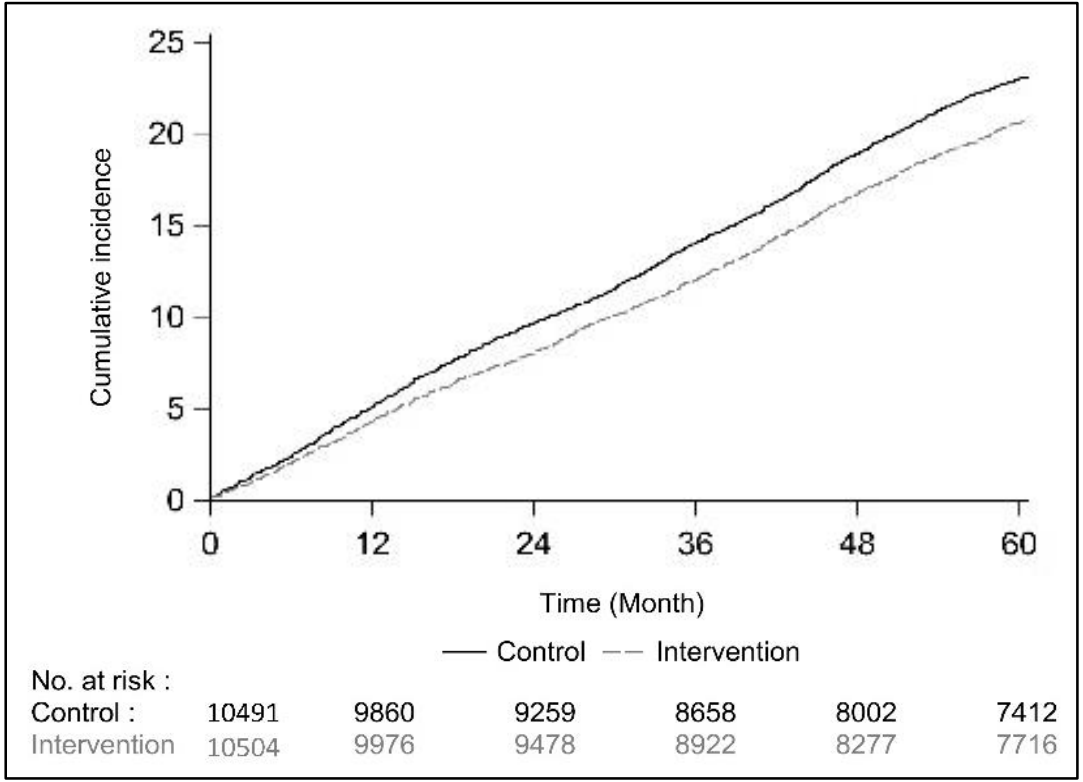
Total events = 3123

Participants with event = 2678

Rate ratio = 0.86 (0.77 to 0.96)

P value = 0.006

Major adverse cardiovascular events



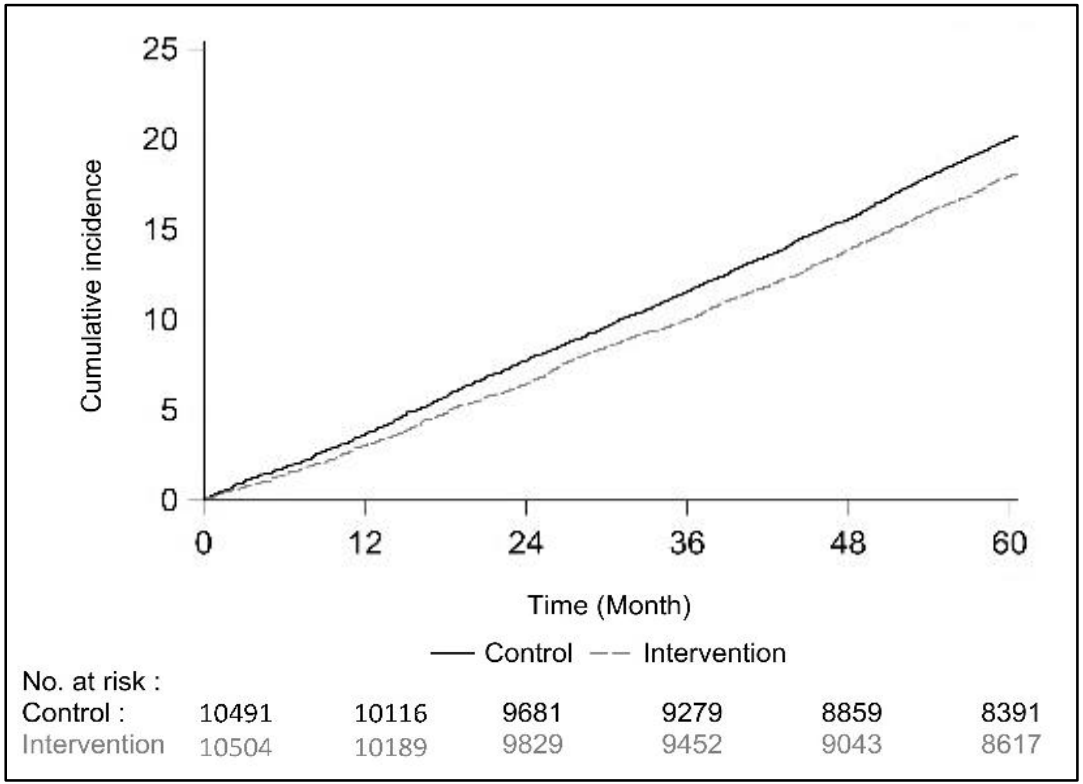
Total events = 5241

Participants with event = 4499

Rate ratio = 0.87 (0.80 to 0.94)

P value <0.001

Total mortality



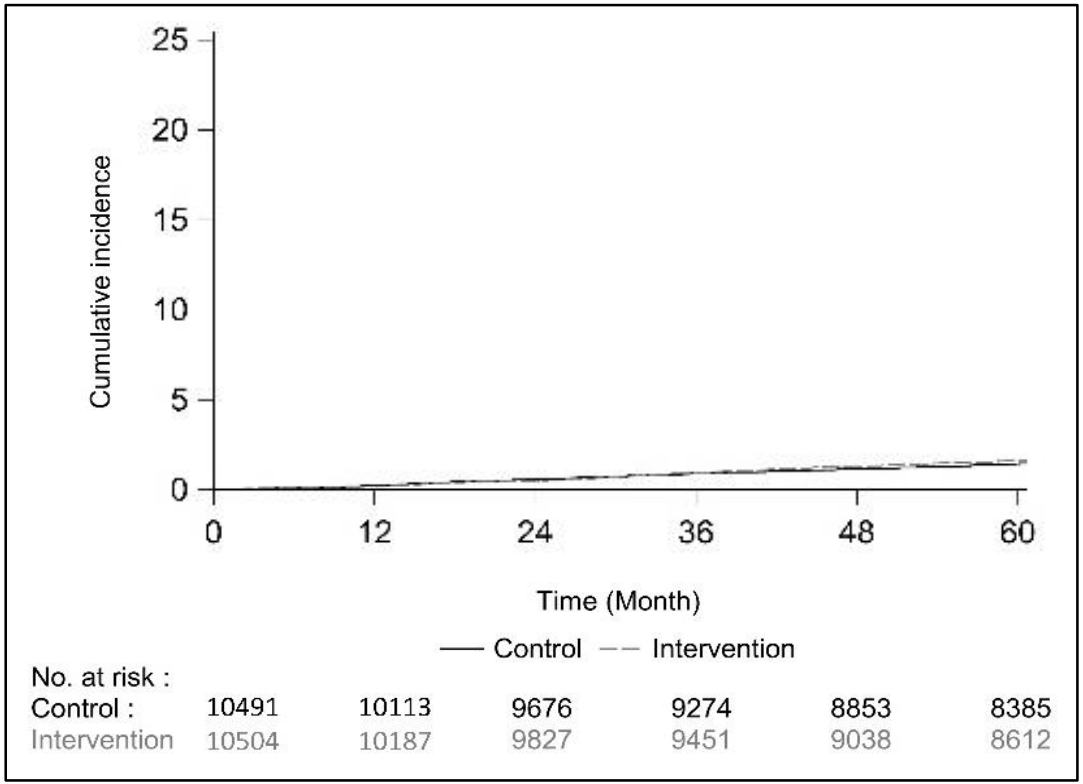
Total events = 4172

Participants with event = 4172

Rate ratio = 0.88 (0.82 to 0.95)

P value <0.001

Hyperkalaemia



Total events = 331

Participants with event = 315

Rate ratio = 1.04 (0.80 to 1.37)

P value = 0.76

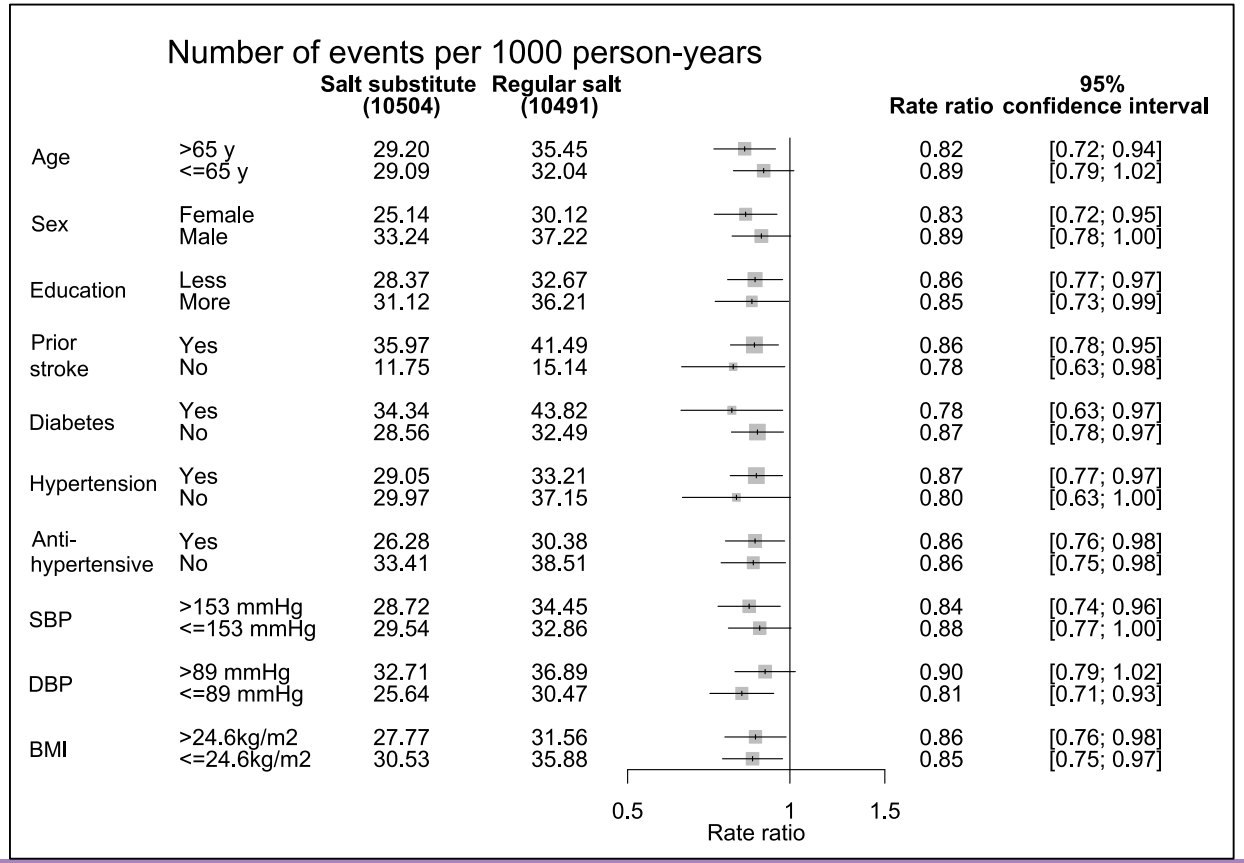
Effects on stroke subtypes

Outcome	Salt Substitute	Regular Salt	Rate Ratio (95% CI)
	no. of events per 1000 person-years		
Stroke	29.14	33.65	0.86 (0.77–0.96)
Fatal	6.78	8.79	0.77 (0.65–0.91)
Nonfatal	22.36	24.86	0.90 (0.80–1.01)
Ischemic	21.36	22.90	0.93 (0.82–1.05)
Hemorrhagic	4.37	6.30	0.69 (0.56–0.85)
Undetermined	3.41	4.45	0.76 (0.61–0.96)
Fatal or disabling	12.71	15.04	0.84 (0.73–0.97)
Nonfatal and nondisabling	9.14	9.33	0.99 (0.82–1.91)
Nonfatal and unknown severity	7.30	9.27	0.79 (0.67–0.92)
Definite	9.43	11.62	0.81 (0.70–0.94)
Probable	19.71	22.03	0.89 (0.78–1.02)
Possible	95.60	103.41	0.92 (0.85–0.99)
Nonfatal acute coronary syndrome	3.79	5.12	0.70 (0.52–0.93)

Effects on causes of death

Outcome	Salt Substitute	Regular Salt	Rate Ratio (95% CI)
	no. of events per 1000 person-years		
Death from any cause	39.28	44.61	0.88 (0.82–0.95)
Undetermined	8.58	9.58	0.89 (0.75–1.06)
Nonvascular	7.76	8.73	0.89 (0.77–1.03)
Vascular	22.94	26.30	0.87 (0.79–0.96)
Fatal ischemic stroke	1.78	2.23	0.77 (0.55–1.07)
Fatal hemorrhagic stroke	2.55	3.38	0.75 (0.58–0.98)
Fatal undetermined type of stroke	2.45	3.18	0.77 (0.58–1.01)
Death from acute coronary syndrome	2.53	2.53	1.00 (0.75–1.32)
Fatal heart failure	1.10	1.30	0.88 (0.55–1.43)
Kidney-related death	0.32	0.34	0.97 (0.24–3.94)
Other known vascular causes	1.20	1.58	0.72 (0.45–1.14)
Sudden death from presumed vascular causes	11.01	11.76	0.94 (0.82–1.07)

Effects on stroke in subgroups



- All p homogeneity >0.20

Strengths and weaknesses

- Large-scale, long term, definitive outcomes
- Pragmatic risk screening
- Scalable and low-cost intervention
- Good power for key subgroups

- Population selected to be amenable to salt substitution
- Record linkage was likely imperfect
- Did not replace all dietary sodium
- No potassium measurement only clinical hyperkalaemia
- No assays of kidney function
- Done in a single country

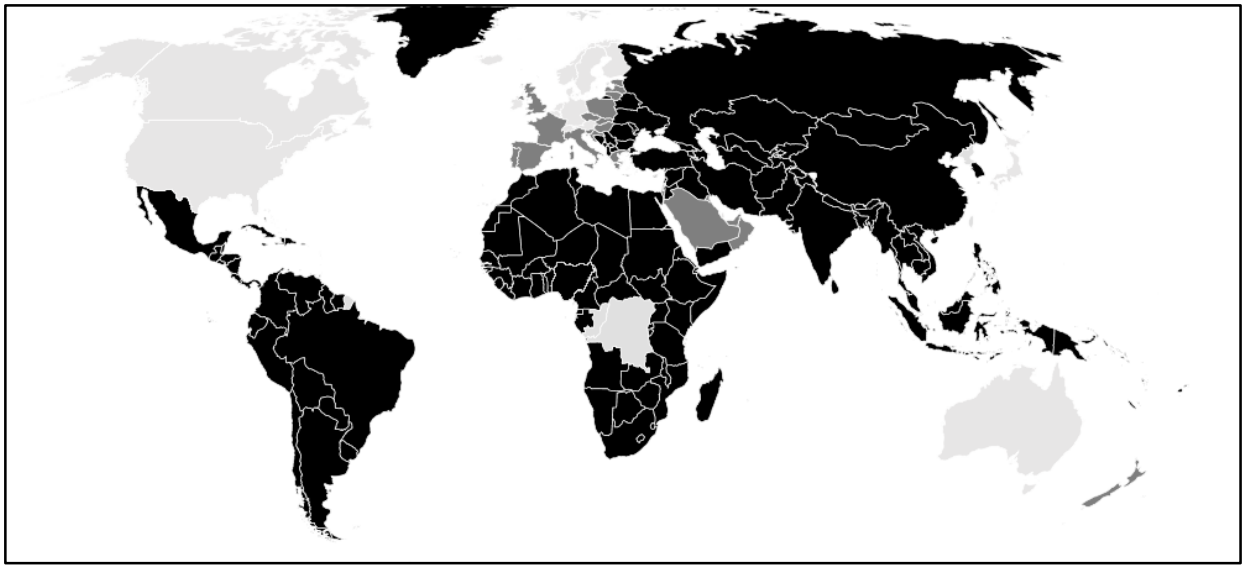
Benefits and risks - potential health impact in China

- Comparative risk assessment modelling
- Nationwide implementation of salt substitution in China

	Current events in China (000s)	Events averted	
		In 000s	% of current
Cardiovascular deaths	4201	461	10.9
Non-fatal strokes	4022	365	9.1
Non-fatal heart attacks	1546	147	9.5
TOTAL	**9769**	**973**	**10.0**

Source: Marklund, BMJ 2020

Generalisability - potential health impact worldwide



- >50% dietary sodium consumed as discretionary salt
- 25-50% dietary sodium consumed as discretionary salt
- <25% dietary sodium consumed as discretionary salt

- Relevant to everyone that eats salt
- Most relevant to the >5 billion people consuming most of their dietary sodium as 'discretionary' salt

Source: Bhat, Adv Nutr 2020

Conclusions and potential implications

SSaSS provides a definitive result - salt substitute is effective for the prevention of stroke, major cardiovascular events and premature death with no evidence of harm

Implementation strategies

- *Salt manufacturers and retailers* worldwide could switch to producing and marketing salt substitute at scale
- *Food processing industry* worldwide could reformulate products to lower sodium and higher potassium compositions
- *Governments* worldwide could design polices to promote salt substitute and discourage regular salt use
- *Consumers* worldwide could cook, season and preserve foods with salt substitute not regular salt

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Journal publication

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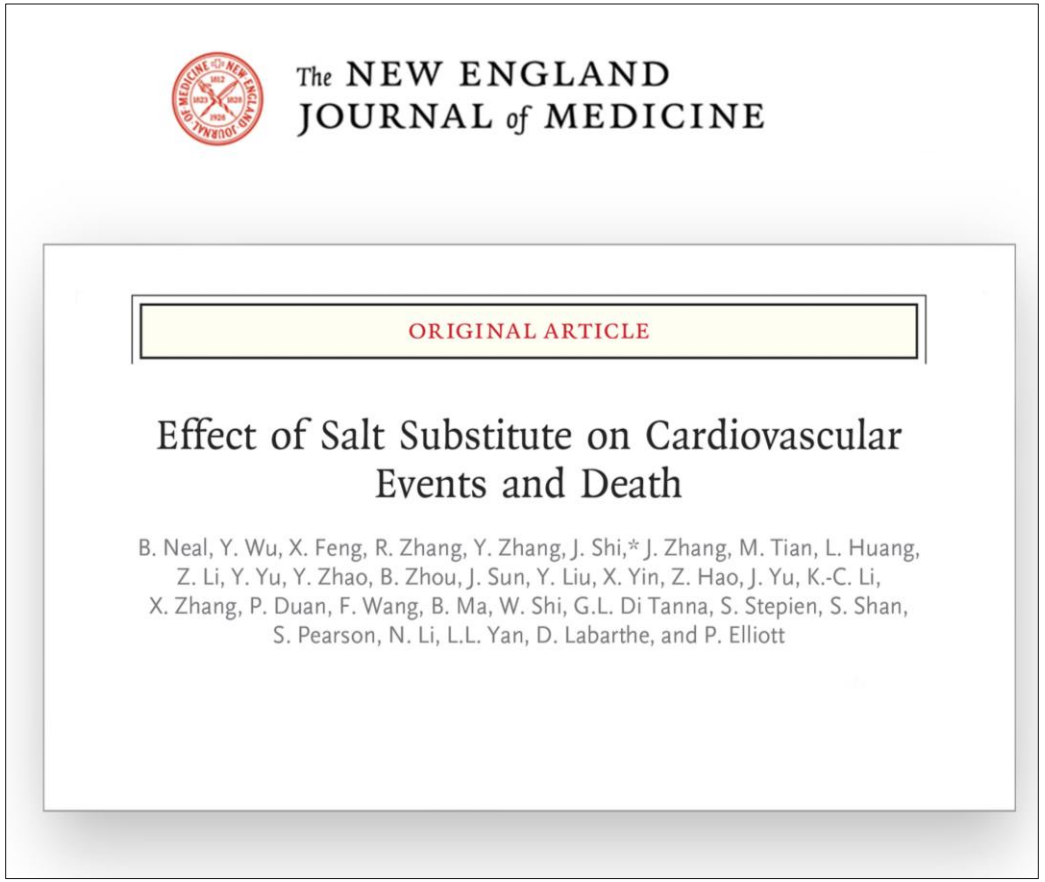

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