Salt substitution and salt-supply restriction for lowering blood pressure in elderly care facilities: a cluster-randomized trial

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Abstract

High quality evidence on effectiveness and safety of salt reduction strategies are few, particularly among older people who have most to benefit and also at higher risk of adverse effects. Here, we conducted a clinical trial in which 48 residential elderly care facilities in China (1612 participants including 1230 men and 382 women, 55 years or older) were cluster-randomized using a 2X2 factorial design to provision of salt substitute (62.5% NaCl and 25%KCl) versus usual salt and to a progressively restricted versus usual supply of salt or salt substitute for 2 years (NCT03290716). Salt substitute compared to usual salt lowered systolic blood pressure (-7.1mmHg, 95% confidence interval (CI) -10.5 to -3.8), meeting the primary outcome of the trial, whereas restricted supply compared to usual supply of salt or salt substitute had no effect on systolic blood pressure. Salt substitute also lowered diastolic blood pressure (-1.9mmHg, 95% CI -3.6 to -0.2) and resulted in fewer cardiovascular events (hazard ratio [HR] 0.60, 95% CI 0.38 to 0.96), but had no effect on total mortality (HR 0.84, 95% CI 0.63 to 1.13). From a safety standpoint, salt substitute, increased mean serum potassium and led to more frequent biochemical hyperkalemia but without adverse clinical outcomes. In contrast, salt restriction had no effect on any study outcome. The results of this trial indicate that use of salt substitute, but not efforts to restrict supply of salt, may achieve blood pressure lowering and deliver health benefits to residents of elderly care facilities in China.

Key words

Randomized trial, salt substitute, blood pressure, cardiovascular events, death, hyperkalemia, hypokalemia, hyponatremia, impaired renal function

High blood pressure is a leading cause of death,[1] and there is clear evidence that lowering dietary sodium intake and increasing dietary potassium intake can reduce blood pressure.[2,3] Sodium consumption in China is high [4] and salt substitution is a proven non-pharmaceutical intervention for blood pressure reduction in China.[5] Studies of salt substitute among older populations, who are at the greatest risk and have most to benefit, are few.[6] In addition, there have been concerns about the risk of hyperkalemia,[7-9] but safety data are limited.[10] Modeling studies projecting effects of salt substitution in China have indicated significant potential benefits for cardiovascular disease and death, [11,12] but data from large trials have been lacking until recently [13].

Progressive reduction in the use of salt for the preparation and seasoning of food is a recommended strategy for reducing dietary sodium consumption.[14] Small, stepwise declines in the sodium content of foods could cumulate to significant decreases, while not being perceived by consumers.[15] In addition, sustained reduction of salt consumption may result in adaptive change in taste preference for a lower salt diet. Some small, short-term trials demonstrated that one-quarter decrease in the sodium content of bread can be delivered unnoticed with gradual reduction.[16] However, strong evidence for the effectiveness and feasibility of this strategy from large-scale, long-term studies remains lacking.

The DECIDE-Salt study aimed to use a factorial design to determine the effectiveness and safety of two practical and scalable sodium reduction intervention strategies in parallel, targeting older adults collectively living in residential elderly care facilities: (1) replacing usual salt with salt substitute and (2) making a stepwise reduction in the quantity of salt/salt substitute supplied to facility kitchens.[17]

Results

Study implementation and baseline characteristics

There were 48 facilities with a total of 1612 eligible participants enrolled from September 29, 2017 to March 28, 2018 (Figure 1). They had a mean age of 71.0 years and mean blood pressure of 137.5/80.5 mmHg; 76.3% were men; 62.1% had a history of hypertension; 29.1% had a history of stroke or coronary artery disease; 19.4% had non-vascular health conditions; 26.2% were apparently healthy; and 8.3% used medications that may elevate serum potassium. All baseline characteristics were balanced across the randomized groups. (Table 1 & Extended Data Table 1).

During follow up, 249 participants died, 131 participants relocated out of the facilities, and 2 facilities with 54 participants (one from the group with no intervention and one from the group with both interventions) dropped out of the study. The deaths, checkouts and dropouts led to a significant reduction in the number of eligible participants for physical and biochemical assessments at follow up visits. In addition, in Xi'an the high proportions of participants who had severe illness or were bedridden, or lacked follow up visits at 6 and 18 months also added to missing data. Among the 1612 eligible participants, 1219 (76%) had a measure for the primary blood pressure outcome made on at least one follow-up visit but all 1612 (100%) had clinical outcomes data available for analyses (**Figure 1**). Participants missing follow-up blood pressure measurements were on average older, more likely to be women, better educated~~,~~ bedridden or severely ill at baseline, and were less likely to smoke, drink, have hypertension or be using anti-hypertension medication (Table S2). These baseline characteristics did not differ between randomized comparisons in those with follow-up measures available (Table S2).

Effects on primary efficacy outcome

Salt substitute compared to usual salt lowered mean systolic blood pressure, the primary outcome, by -7.1mmHg (95% CI -10.5 to -3.8; Bonferroni corrected p<0.0001) (Table 2 and Figure 2). The estimates from the pre-specified sensitivity analyses were -6.9 mmHg (95% CI -10.3 to -3.5) in the per-protocol analysis, -7.0mmHg (95% CI -10.4 to -3.6) with exclusion of facilities from Xi'an, and -6.6 mmHg (95% CI -10.3 to -2.8) with imputation for missing data (Extended Data Table 2). All results were statistically significant after adjustment for multiple comparisons using the Bonferroni method. The effects on systolic blood pressure were greater for women than men and for the less educated compared to the more educated (both p homogeneity< 0.04). Effects also varied by tertiles of baseline systolic blood pressure but with no clear pattern (P homogeneity=0.05), and were not different between the other pre-specified subgroups (all p homogeneity>0.05, Extended Data Fig. 1).

There were no effects on the 2-year overall mean systolic blood pressure of restricted versus usual supply of salt/salt substitute in the primary analysis or any sensitivity analyses, though potential difference were noticed at 24-month (Figure 2, Extended Data Fig. 2).

Effects on secondary efficacy outcomes

The secondary efficacy outcomes were diastolic blood pressure, definite major cardiovascular events and total death. Diastolic blood pressure was -1.9 mmHg (95% CI -3.6 to -0.2; p=0.03) lower in those assigned to salt substitute compared to usual salt, with similar effect estimates in the sensitivity analyses (Figure 2). There were no effects on diastolic blood pressure of restricted versus usual supply of salt/salt substitute.

There were 86 (5.4%) definite and 81 (5.0%) probable major cardiovascular events and 249 (15%) deaths recorded in the two years of study duration. Definite cardiovascular events were reduced with salt substitute compared to usual salt (2.3 versus 3.8 per 100 person years, HR 0.60, 95% CI 0.38 to 0.96;

P=0.03) but no effect on total mortality was found (7.9 versus 9.4 per 100 person years, HR 0.84, 95% CI 0.63 to 1.13; P=0.24) (Figure 3). Exploratory analyses based on all 167 definite or probable cardiovascular events (HR 0.66, 95%CI 0.48 to 0.90; p=0.008) and 117 cardiovascular deaths (HR 0.64, 95%CI 0.44 to 0.92; p = 0.02) suggested benefits for those outcomes with salt substitute (Table 2). There were no effects on cardiovascular events or all-cause mortality for restricted versus usual supply of salt/salt substitute (all p value > 0.24) (Table S5).

Effects on safety outcomes

Safety was assessed among 1086 participants with blood assays during follow-up. Participants without assays were more likely to be older, women, better educated, bedridden, or severely ill (Table S3) but there was no difference in baseline characteristics between randomized groups in those with and without blood assays.

Salt substitute compared to usual salt increased mean serum potassium by 0.26mmol/L (95% CI 0.15 to 0.36; p<0.0001) and decreased mean serum sodium by -0.92mmol/L (95%CI -1.43 to -0.41;p < 0.001). Compared with usual salt the risk of biochemical hyperkalemia was increased with salt substitute (7.0% versus 2.4%, RR 3.29, 95% CI 1.45 to 7.45 P=0.004) with a corresponding fall in the risk of hypokalemia (0.7% versus 3.0%, RR 0.24, 95%CI 0.07 to 0.79 p=0.02), a supplementary safety outcome (Table 3). There was no different effect on the risk of biochemical hyperkalemia by age, sex, health status or hyperkalemia risk at baseline (all p values for interaction > 0.66) (Extended Data Fig. 3).

Among the 51 individuals with biochemical hyperkalemia, two died - one from complications secondary to hip fracture in the intervention group and one from suspected lung cancer in the control group. In addition, amongst these 51 individuals there were none in the intervention group and one in the control group that had a subsequent major cardiovascular event. Persistent biochemical hyperkalemia occurred in only 3 participants, none of whom died or experienced a cardiovascular event.

No effects were observed on risk of incident hyponatremia (RR 1.60, 95% CI 0.48 to 5.41) or renal dysfunction (RR 1.41, 95% CI 0.47 to 4.24) (Table 3).

There were no effects on safety outcomes with restricted supply (all p value > 0.05) (Table S6)

Effects on process indicators

The pre-specified process indicators were 24-hour urinary sodium and potassium excretion and 24-hour urine samples were collected in a subset of participants at 24-months (639 participants). Participants with 24-hour collections were systematically different from those who did not, but there were no differences in baseline characteristics between randomized groups in those with urine specimens (Table S4).

Comparing participants receiving salt substitute versus usual salt, 24-hour urinary potassium excretion was increased by 12.8mmol (95%CI 5.7 to 19.8) but there was no detectable effect on 24-hour urinary sodium excretion (-9.7mmol; 95%CI -28.4 to 9.1). No differences on these urinary outcomes were found for restricted versus usual supply of salt/salt substitute (all p value > 0.46) (Extended Data Table 3). The sensitivity analyses with imputed follow up measurements showed similar results (Extended Data Table 3).

Supplementary analysis of the study salt supply records showed the average consumption of study salt per person per day was 11.0±4.7 grams (equivalent to 36.8mmol potassium, 117.0mmol sodium) in participants using salt substitute and 11.6±3.3 grams (equivalent to 0.0 mmol potassium, 199.6mmol sodium) with usual salt (p for total weight =0.569, p for composition<0.001), 10.5±3.7 grams (equivalent to 17.3 mmol potassium, 145.9mmol sodium) in participants with restricted supply and 12.2 ±4.4 grams (equivalent to 19.5 mmol potassium, 168.9mmol sodium) with usual supply (p for total weight =0.159, p for composition = 0.249).

Changes in urinary electrolytes and efficacy outcomes by randomized groups

Table S7 gives the descriptives on the changes from the baseline to the end of intervention in 24-hour urinary electrolytes and blood pressure as well as the incidence of major cardiovascular events during the 2 years of intervention by randomized groups.

Discussion

The DECIDE-Salt trial showed clear benefits of salt substitute compared to usual salt for blood pressure lowering, as well as protection against cardiovascular events amongst people living in residential elderly care facilities in China. These benefits were accompanied by an increase in frequency of biochemical hyperkalemia but there was no evidence of associated adverse clinical outcomes. In contrast, the efforts to restrict supply of salt/salt substitute was unsuccessful with no detectable effect on blood pressure during the 2 years of intervention and no benefit for cardiovascular outcomes observed.

The effect of salt substitute on blood pressure has been shown previously but mostly in patients with hypertension or high cardiovascular risk [6,13] with few data for older individuals or those living in residential elderly care facilities. In 2013 the Institute of Medicine called for randomized trials to examine the effects of a range of sodium levels among patients in controlled environments, such as the elderly in chronic care facilities.[18] Our trial contributes directly towards this goal with the majority of the study population unable to live independently and affected by multiple diseases, both cardiovascular and non-cardiovascular - 74% had health conditions at baseline and about 5.3 % were bedridden.

This trial showed an effect on blood pressure that was larger than the average effect shown in prior meta-analyses of previous randomized trials of salt substitute among adults with or without hypertension.[19] The effect size on blood pressure was also approximately double that achieved in the recently reported Salt Substitute and Stroke Study (SSaSS)[13] that was done in participants with high

cardiovascular risk with either history of stroke or uncontrolled hypertension but living freely in the community. Implementation of salt substitution in a collective living setting where residents have limited control over the composition of the food they eat and the seasonings they use would be expected to maximize the effect of the intervention. While the uncertainty intervals are wide, the larger blood pressure reduction may explain the apparently greater protection against major cardiovascular events in the DECIDE-Salt trial compared with SSaSS. [13]

The effect on definite cardiovascular events identified in the primary analyses of salt substitute versus regular was consistent for the subsidiary analyses of all events as well as for cardiovascular death and aligns with both the large blood pressure reduction observed in our study and the known strong associations of blood pressure with cardiovascular disease.[20] Prior evidence describing the effects of salt substitute on cardiovascular events and mortality were scarce until the recent report from SSaSS. [13] Our data from DECIDE-Salt extend the SSaSS findings of cardiovascular protection to a broader and older population group with and without health conditions including cardiovascular and non-cardiovascular disease, with and without hypertension. The DECIDE-Salt data also provide additional evidence supporting the use of salt substitute for prevention and control of hypertension and its related cardiovascular consequences.

In contrast to most prior trials of salt substitute, our study sought to manage, rather than exclude, participants at risk of hyperkalemia. Typically, as people age, blood pressure increases and cardiovascular risk rises, but renal function declines. [21,22] Benefits from salt substitute would be expected to accrue from blood pressure reduction but poor renal function might increase the risk of hyperkalemia due to increased dietary potassium intake.[23] For the DECIDE-Salt study, we selected a salt substitute that contained 25% potassium chloride, which is a relatively low potassium content compared to other salt substitutes on the global market, in an effort to maximize benefit and minimize risk.[6] We

also established a safety monitoring plan to closely monitor the risk of clinically important hyperkalemia in participants assigned to the salt substitute. With serial measures of serum potassium and access to clinical outcome data, DECIDE-Salt provided a unique opportunity to assess the safety of salt substitute, among a broad population at elevated risk. Our study showed that salt substitute right-shifts the distribution of serum potassium causing a correspondingly increased frequency of biochemical hyperkalemia and a decreased frequency of biochemical hypokalemia. We did not detect associations of the effect of salt substitute on incidence of biochemical hyperkalemia with baseline risks for hyperkalemia such as health conditions, kidney function or other traits, though statistical power was limited. The absence of adverse clinical outcomes amongst those with biochemical hyperkalemia is a novel observation and provides reassurance about safety. Of note, there was no clinical safety signal despite more than 70% of trial participants reporting significant health problems at baseline, including 6% with renal disease and 8% using medications that may elevate serum potassium. These findings are also aligned with the SSaSS result, which showed no increased risk of clinical hyperkalemia events with use of salt substitute.

The observed increase in mean serum potassium and decrease in serum sodium are indicative of successful implementation and compliance of the salt substitute intervention. Quite unexpected, we found that salt substitute decreased mean level of serum sodium, but increased risk of hyponatremia was not detected. As far as we know, this is the first study reporting the significant serum sodium lowering effect of salt substitute. Simple explanation is that should be reasonably introduced since sodium intake was reduced by the use of salt substitute. Studies have demonstrated that reduction of sodium intake would result in the reduction of serum sodium level, which may cause the blood pressure reduction directly[24]. Further investigation is needed to confirm our findings.

The reasons why efforts to progressively reduce the supply of study salt/salt substitute were unsuccessful could be very complex. First, the premise of the strategy was that it would not be noticed by the participants and that no compensatory actions would be taken against by participants.[25 26] However, site visits and analysis of self-reported data both indicated that participants were able to detect the reduction in salt use and some added non-study table salt to their meals. Second, the successful implementation of the strategy required a well management of salt supply system. We relied on the facility managers and cooks but some of them might not like to take meals with less salt. Third, this strategy is simple and no cost, hence might be also taken by the facilities assigned to usual supply (contamination). The failure of the salt reduction intervention is a potentially important finding, which raises broader doubts about the feasibility of this strategy in real-world settings. In addition, the progressive nature of the intervention strategy, even if well compliant, would take 6 to 12 months to have an effect of more than 20% reduction in salt supply, about half of the target of the intervention. Our current analysis model did not take that nature in account. Further post-hoc analysis with more appropriate model is needed to understand better about and draw lessons from the implementation of this intervention.

The analysis was done separately for each intervention strategy, and since the effect on the restricting salt supply was not significant, the test on the interaction of two interventions was not performed. This analytical strategy differed from the “inside the table” analysis, in which each intervention group would be compared with the ‘pure’ control group. Our reasons included 1) The DECIDE-Salt study aimed primarily to determine the effectiveness and safety of two practical and scalable sodium reduction intervention strategies in parallel. We had no intention to test the effect of the jointly use of both intervention strategies, which is not very meaningful in practice; 2) The use of factorial design could enhance the study efficiency and minimize the study cost. In fact, due to the funding constraint the study was designed in that way and has not enough power to run the analysis in that way; and 3) Many

studies[27,28] used the same strategy of data analysis, which is called "at the margins"[29] analysis. We conducted this analysis under the assumption that the two interventions would act independently. And we operated the study interventions independently too. If there is unrecognized interactions that might distort the results of the "at the margins" analysis, the "inside the table" analysis should be more appropriate but require much larger sample size.

The study has some important strengths. First, the collective living setting enabled a good implementation of the salt substitute intervention and complete follow up for clinical outcome events. Second, this is one of few studies on salt substitute that did not exclude participants at risk of hyperkalemia thus helping to define the safety of salt-substitute among a broader population. DECIDE-Salt also had good statistical power to detect effects on mean serum potassium levels and the frequency of seriously deranged blood potassium levels, and while the capacity to link to adverse clinical outcomes was limited, the clinical safety findings are aligned with those observed a in SSaSS[13]. Besides, as mentioned earlier the use of the factorial design enhanced study efficiency and minimized the study cost by using the 'at the margins'[29] analysis method .

This study also had clear limitations. It was predominantly of men, reflecting the typical resident population in elderly care facilities in China. While the overall effect on blood pressure in DECIDE-Salt was large, the potential population-wide benefits of salt substitution for elderly Chinese may have been under-estimated, because the subgroup analyses indicated a larger effect in women. The collective-living setting enabled implementation and robust testing of the salt substitution intervention but the scale of uptake achieved may not be generalizable to other types of settings. The planned progressive restriction of the supply of salt was not achieved as intended and did not provide a robust evaluation of this intervention strategy. Alternative analysis of the restricted supply of salt intervention, that accommodated the progressive nature of the implementation program may have been a more

appropriate analytic method. Future post-hoc analysis will be taken to explore this possibility. The study also had many missing follow-up measurements for blood pressure, serum potassium, and urinary electrolytes. The missing data predominated in one study site, where high percentages of participants had severe illness (20%) or moved out of the facilities (17%) and where there were difficulties with study staffing. In addition, cultural factors among older Chinese discourage drawing of blood and the storage of urine during specimen collection periods. The 24-hour urine collection was unwelcome also due to the complicated and time-consuming collection process and was refused by many participants. The close comparability of baseline characteristics between randomized comparisons for those who did have complete data provides some reassurance that the relative effects of intervention are unbiased. Besides, our multiple pre-specified sensitivity analyses including imputation, adjustment for co-variates, and per-protocol assessments all produced highly comparable effect estimates. Thus, our results for the primary outcome should be considered robust and reliable. Finally, we did not fully pre-specify statistical adjustment to control for the chance of false positive findings, though our primary results were robust to post hoc Bonferroni testing, and other outcomes were internally consistent and were in line with other reports in this field.[12,13]

In conclusion, salt substitute reduced blood pressure and cardiovascular events in an elderly resident population. It increased the frequency of biochemical hyperkalemia but without adverse clinical outcomes. The DECIDE Trial shows net benefit from the use of salt substitute in line with data from prior trials of salt substitution showing blood pressure lowering effect in diverse populations,[30-32] and results of the recent SSaSS trial showing cardiovascular disease prevention effect. The studies strongly and consistently support the more widespread use of salt substitute for cardiovascular disease prevention. However, efforts to restrict supply of salt failed to achieve the target for blood pressure lowering planned in our study, which requires further analysis to better understand the feasibility and implementation of this intervention.

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Author contributions

YW and AJ designed the study with advices from DL and BN. The Statistical Analysis Plan was finalized by YW, PG and YY prior to the closing of database. YY and AJ analyzed and verified the data analysis. PG, DL, and PE helped on data analysis and interpretation. YY, AJ, BN and YW wrote the first draft with all co-authors participating in the subsequent reviews and revisions. YW had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of Interest Disclosures

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425 Table 1 Baseline characteristics of study participants by randomized group (n=1612)

	Overall (n = 1612)	Salt substitute + restricted supply (n=401)	Restricted supply + usual salt (n=442)	Salt substitute + usual supply (n=406)	Usual supply + usual salt (n=363)
Cluster level					
Number of facilities, n	48	12	12	12	12
Number of study participants per facility, median (IQR)	28.5(23,42.5)	30(19.3,42)	30(22,44)	28(23,39.5)	28(23.8,37.5)
Individual level					
Demographics and anthropometrics					
Age, yrs, mean(SD)	71.0(9.5)	70.9(9.6)	72.2(9.8)	70.8(9.2)	70.1(9.1)
Male, n (%)	1230 (76.3)	301 (75.1)	322 (72.9)	314 (77.3)	293 (80.7)
Study site, n (%)					
Changzhi	489 (30.3)	119(24.3)	110(22.2)	78(23.4)	94(32)
Xi'an	495 (30.7)	160(32.7)	118(23.8)	106(31.7)	58(19.7)
Hohhot	334 (20.7)	96(19.6)	134(27.1)	88(26.4)	88(29.9)
Yangcheng	294 (18.2)	114(23.3)	133(26.9)	62(18.6)	54(18.4)
Education at junior high school or above, n (%)	485 (32.4)	121 (34.8)	149 (35.1)	106 (28.3)	109 (31.1)
Life style					
Current smokers, n (%)	539 (33.4)	128 (31.9)	149 (33.7)	145 (35.7)	117 (32.2)
Current alcohol drinker, n (%)	156 (9.7)	35 (8.7)	44 (10)	41 (10.1)	36 (9.9)
Health status					
Hypertension, n (%)	1001 (62.1)	243 (60.6)	279 (63.1)	251 (61.8)	228(62.8)
Coronary artery disease, n (%)	146 (9.1)	41 (10.2)	38 (8.6)	37 (9.1)	30 (8.3)
Stroke, n (%)	382 (23.7)	78 (19.5)	103 (23.3)	101 (24.9)	100 (27.5)
Diabetes, n (%)	164 (10.2)	44 (11)	40 (9)	46 (11.3)	34 (9.4)
Renal disease, n (%)	88 (5.5)	27 (6.7)	22 (5)	17 (4.2)	22 (6.1)
Bedridden or other severe disease, n (%)	103 (6.4)	26 (6.5)	23 (5.2)	18 (4.4)	36 (9.9)
Any of above	1189 (73.8)	287 (71.6)	324 (73.3)	300 (73.9)	278 (76.6)
Medication use					
Anti-HTN medication n (%)	623 (38.7)	150 (37.4)	187 (42.3)	156 (38.4)	130 (35.8)
Medications that may elevate serum potassium, n (%)	133 (8.3)	30 (7.5)	45 (10.2)	30 (7.4)	28 (7.7)
Serum electrolytes					
Sodium, mmol/L, mean (SD)	142.5(2.5)	142.5(2.7)	142.8(2.3)	142.4(2.4)	142.4(2.4)
Potassium, mmol/L, mean (SD)	4.43(0.50)	4.41(0.52)	4.49(0.48)	4.36(0.49)	4.47(0.49)
Urine electrolytes					
24-hr urinary sodium, mmol, mean (SD)	163.1(82.5)	159.2(89.1)	169.1(78.2)	156.1(82.5)	168.1(79.1)
24-hr urinary potassium, mmol, mean (SD)	26.1(14.5)	22.9(11.5)	27.7(12.9)	25(13.5)	29.1(18.8)
24-hr urinary albumin, mmol, median (Q1,Q3)	3.5(1.8,7.8)	3.2(1.7,7.4)	3.5(1.8,7.8)	3.5(1.8,7.1)	3.7(2.1,9.4)
Blood pressure					
Systolic blood pressure	137.5(21.3)	137.2(20.9)	137.1(20.8)	137(22.8)	139.1(20.6)
Diastolic blood pressure	80.5(11.6)	80.4(11.3)	79.5(11.2)	80.3(12.3)	82.2(11.7)

Baseline data was missing at the baseline for education (n=114) , serum electrolytes (n = 346) and urinary electrolytes (n = 484).Table 2 Effects on cardiovascular events and death for salt substitute versus usual salt

	No. of cases (%)	Salt substitute(N = 807)		Usual salt(N = 805)		Primary model	
		person year	cases (pr-rate)	person year	cases (pr-rate)	HR(95%CI)	P
Cardiovascular events							
Definite	86(5.3%)	1497	34(2.3)	1374	52(3.8)	0.60 (0.38, 0.96)	0.03
Fatal	56(3.5%)	1512	23(1.5)	1387	33(2.4)	0.64 (0.36, 1.14)	0.13
Non-fatal	34(2.1%)	1497	14(0.9)	1374	20(1.5)	0.63 (0.29, 1.36)	0.24
All	167(10.4%)	1485	71(4.8)	1369	96(7)	0.66 (0.48, 0.90)	0.008
Death							
All death	249(15.4%)	1512	119(7.9)	1387	130(9.4)	0.84 (0.63, 1.13)	0.24
CVD	117(7.3%)	1512	48(3.2)	1387	69(5)	0.64 (0.44, 0.92)	0.02
Non-CVD	132(8.2%)	1512	71(4.7)	1387	61(4.4)	1.03 (0.67, 1.6)	0.88

Pr-rate: rate per 100 person years. All cardiovascular events include definite and possible non-fatal acute MI, non-fatal stroke, hospitalization for heart failure, and deaths due to MI, stroke, heart failure and sudden death. Definite cardiovascular events include only definite non-fatal acute MI, non-fatal stroke, hospitalization for heart failure, and deaths due to MI, stroke, and heart failure. Hazard ratios (HRs), 95% CIs and p-values were obtained using frailty survival models with adjustment for clustering by facility. The p value was two-sided and was not adjusted for multiple comparison.

435 TABLE 3 Effects of salt substitute versus usual salt on safety outcomes

Variable	All N = 1086	Salt substitute N = 545	Usual Salt N = 541	Difference (95%CI)	Relative risk (95%CI)	p value
Mean change in serum electrolytes in 2 years[#] (mmol/L, mean(SD))						
Potassium	0.10(0.57)	0.26(0.54)	-0.07(0.54)	0.26(0.15 , 0.36)		<0.001
Sodium	-0.98(2.87)	-1.51(2.76)	-0.44(2.88)	-0.92(-1.43 , -0.41)		<0.001
Incident biochemical hyperkalemia (serum potassium > 5.5 mmol/L, n (%))						
High at 12- or 24-month	51 (4.7%)	38 (7.0%)	13 (2.4%)	4.1 (1.8, 6.4)	3.29 (1.45, 7.45)	0.004
> 6.5 mmol/L	7 (0.6%)	3 (0.6%)	4 (0.7%)	-0.1 (-0.6, 0.4)	0.60 (0.07, 5.47)	0.65
6.0 - 6.5 mmol/L	8 (0.7%)	8 (1.5%)	0	1.2 (0.3, 2.1)	-	-
5.6 – 6.0 mmol/L	36 (3.3%)	27 (5.0%)	9 (1.7%)	3.1 (1.1, 5.1)	3.21 (1.39, 7.41)	0.006
High at 12- & 24-month	3 (-)	2 (-)	1 (-)	-	-	-
Incident biochemical hypokalemia (serum potassium < 3.5 mmol/L, n(%))						
Low at 12- or 24-month	20 (1.8%)	4 (0.7%)	16 (3.0%)	-1.9(-3.4, -0.4)	0.24 (0.07, 0.79)	0.02
Low at 12- & 24-month	0 (-)	0 (-)	0 (-)	-	-	-
Incident chemical hyponatremia (serum sodium < 135 mmol/L, n(%))						
Low at 12- or 24-month	16 (1.5%)	10 (1.8%)	6 (1.1%)	0.5 (-0.7, 1.6)	1.60 (0.48, 5.41)	0.45
Low at 12- & 24-month	0 (-)	0 (-)	0 (-)	-	-	-
Incident renal dysfunction (eGFR< 60ml/min*1.73m^2, n(%))						
eGFR low at 12- or 24-month	47 (4.3%)	25 (4.6%)	22 (4.1%)	0.7 (-1, 2.4)	1.41 (0.47, 4.24)	0.54
eGFR low at 12- & 24-month	14 (1.3%)	9 (1.7%)	5 (0.9%)	0.4 (-0.6, 1.5)	1.72 (0.45, 6.47)	0.43

436 # 149 participants had missing data at baseline and hence were excluded from the analyses, 71 in the salt substitute cohort and
437 78 in the usual salt cohort.
438 * The difference of continuous safety outcomes was calculated using a linear mixed model that accounted for clustering at the
439 facility level. The relative risks of incidence of dichotomous safety outcomes were calculated using a generalized linear mixed
440 model that accounted for clustering at the facility level. The p-value was two-sided and was not adjusted for multiple
441 comparison. For p-values less than .001, we reported them as p<.001, instead of the actual exact p-values.
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Figure legends

FIGURE 1. Patient flow chart. Follow up blood pressure (BP) measurements at 6 (n=903) and 18 (n=799) months are not shown since follow-up visits were not completed in Xi'an at 6 and 18 months.
Drop out of the facility was due to administrative reasons (see Methods).
* Reasons for not participating in the baseline survey: 185 (49.2%) were temporarily absent from the facility, 33(8.8%) were individuals with disabilities, 59(15.7%) were severely ill or bedridden, 32(8.5%) refused the baseline survey, and 67 (17.8%) had unknown reasons.
Reasons for missing follow-up BP measurements: no physical examination was done at 6- and 18-month in Xi'an (29.0%), death (22.9%), permanent (17.0%) or temporary (15.0%) absence from the facility, refusal (5.1%), or unknown reasons (10.9%), among a total of 2841 missing measurements.

FIGURE 2 Effects on blood pressure. Effects of salt substitute versus usual salt (a) and progressively restricted versus continued usual supply of salt or salt substitute (b) on SBP (top) and DBP (bottom) are shown. Data show mean and 95%CI values at baseline and each follow up visit. The mean differences and 95%CI in SBP and DBP between comparison groups are based on blood pressure measurements at four follow up visits and were estimated using a linear mixed model with repeated measurements, accounting for clustering effects and adjusting for baseline values. The p value was two-sided and was not adjusted for multiple comparison. For p-values less than .001, we reported them as p<.001, instead of the actual exact p-values.

FIGURE 3 Effects on cardiovascular events and total mortality. Effects of salt substitute versus usual salt (a) and progressively restricted versus continued usual supply of salt or salt substitute (b) on cardiovascular events (top) and total mortality (bottom).
Hazard ratios, 95% confidence intervals and p values were estimated from the Cox frailty model. The p value was two-sided and was not adjusted for multiple comparison.

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Methods

Project design and oversight

The design of the DECIDE-Salt study has been published previously.[17] Briefly, it was a cluster-randomized, factorial trial that aimed to assess the effects of two salt reduction strategies, salt substitute and a stepwise reduction in salt supply. The rationale for using a cluster design was mainly due to the convenience to implement the interventions at cluster level but the effectiveness should be evaluated at individual level. The trial commenced in September 2017 and was done in 48 residential elderly care facilities, defined as the clusters in the present study, located in four regions in northern China – Xi'an city in Shaanxi province, Hohhot city in Inner Mongolia Autonomous Region, Changzhi county and Yangcheng county in Shanxi province. All regions were selected for their high sodium intake, high prevalence of hypertension, and history of research collaboration. The study was approved by the Peking University Institutional Review Board with a group consent obtained through discussions between the local study investigators, the administrator of each facility, and the government agencies responsible for the facilities. All participants that did the baseline and follow-up surveys provided written informed consent.

Participants

To be eligible for the study, the facilities were required to (1) have 20 or more residents, either men or women determined based on self-report, (2) have staff responsible for salt supply and storage, (3) provide externally sourced food no more than once a week, and (4) provide institutional agreement to participate. Given limited data about the effects of salt substitute on blood pressure in the elderly, the study population for the intervention effects evaluation was limited to residents aged 55 years or older with blood pressure measured at the baseline survey, expected to be resident in the facility for at least 2

572 years with less than one month's absence each year. Residents with physician-confirmed hyperkalemia
573 would be excluded but none met this exclusion criterion at baseline.

574 ## Randomization, study interventions and follow-up

575 Facilities were randomized in a 1:1:1:1 ratio to each of the factorial interventions using a central
576 computerized process, with stratification by region. Random allocation of facilities was done after
577 baseline survey data had been collected and by an independent statistician. Local staff responsible for
578 the intervention implementation were aware of randomized assignment, but the outcome assessment
579 team were masked to the allocation of the facilities.

580 Facilities assigned to the salt substitute group received salt substitute to replace usual salt. The salt
581 substitute, manufactured by the China Salt General Company at Yulin in China, comprised 62.5%
582 (mg/mg) sodium chloride, 25% (mg/mg) potassium chloride, 12.5% (mg/mg) dried food ingredient
583 flavorings (mushroom, lemon, seaweed, hawthorn, wild jujube,) and traces of amino acids. Facilities in
584 the control group received usual salt, 100% sodium chloride, from the same company. Both salt
585 substitute and usual salt were provided free-of-charge every 3 months for the 2-year study period in
586 sufficient quantity to cover all cooking, seasoning and food preservation requirements.

587 The study salt (usual salt or salt substitute) supply to the kitchens in facilities that were allocated to the
588 restricted supply group was reduced step by step, with the goal of achieving a facility-wide reduction of
589 salt supply by 40% by the end of the intervention.[17] Responsible staff were trained to store the salt in a
590 locked room and supply it to the kitchen on a planned schedule, with a target of reduction by 5%-10%
591 every 3 months.[17] During each period, the cooks can use only the salt supplied; if additional salt is
592 requested and delivered, that amount must be documented. At the end of each stage, trained local
593 investigators conducted a site visit to review the records on the amount of salt supplied and stored as
594 well as the number of people living in the facility. The mean salt intake level per person was calculated

periodically to assess whether the planned stepwise target had been achieved. Interviews with staff, cooks, and participants followed to evaluate acceptance by participants. Once the facility successfully achieved the planned target, the next step on the salt reduction target was initiated. Otherwise, the previous planned target was retained for the next step, and the cook and responsible staff for salt supply control were retrained. During the intervention, table salt (usual salt) was allowed to help individuals who had difficulty adjusting to the change. Once the goal of reduction was achieved, it was maintained until the end of the study. At the intervention kick-off event, a health education lecture was given to all residents. The emphasis was on the harms of high sodium intake, the health benefits of lower sodium intake, and the plan for the stepwise salt reduction program. Posters using simple drawings and slogans were put on the walls of dining and living rooms to encourage the residents to support the sodium reduction program. At periodic monitoring visits, the study staff responsible for the intervention component reinforced the implementation messages to ensure the planned targets were achieved. The study salt supply to the kitchens in facilities that were allocated to the usual supply group was not restricted.

Follow-up was scheduled for 6, 12, 18 and 24 months after randomization. Due to the lack of human resources, follow up visits were only done at 12 and 24 months in Xi'an. Two facilities in Xi'an dropped out before the end of study, one from the group with usual supply and usual salt and the other from the group with restricted supply and salt substitute. Both were due to administrative reasons. Local quarantine policy for the control of COVID-19 delayed final follow up in the facilities in Yangcheng county by about 6 months but the randomized interventions were maintained throughout this period. In addition to baseline, blood pressure measurement was sought at all visits, a blood sample at the 12- and 24-month visits and a 24-hour urine sample at the 24-month visit. Inquiry about the occurrence and date of serious adverse events was done at every follow-up visit for all participants. All who were hospitalized or reported possible cardiovascular events had additional information collected for

endpoint adjudication by a central committee masked to the randomized assignment. A similar process was followed for all deaths.

Safety monitoring and management

A safety monitoring and management plan was implemented for hyperkalemia.[17] Any participant with serum potassium > 5.5 mmol/L detected at any time point was referred to a local physician for further investigation and management. Serum potassium was re-checked and an electrocardiogram was done. If a diagnosis of hyperkalemia was made, exposure to salt substitute would be discontinued until normalization of serum potassium or longer as recommended by the responsible clinician. In general, those with serum potassium > 5.5 mmol/L or with eGFR < 30 ml/min./1.73m^2 were considered at higher risk and were placed on a more intensive monitoring plan, which required serum potassium measurements every three months until two consecutive normal measurements were recorded. Participants on salt substitute were screened additionally at 3 and 6 months after the intervention initiation using a questionnaire on hyperkalemia-related signs and symptoms. Serum potassium was tested for those with positive answers to ensure safety, but those data were not used for comparison of the risk of dyskalemia between randomized comparisons.

Outcomes

The primary efficacy outcome was systolic blood pressure, which was taken three times using an OMRON HEM-7136 device following American Heart Association guidelines.[33] Secondary efficacy outcomes were diastolic blood pressure, major cardiovascular events adjudicated as definite (comprising non-fatal stroke, non-fatal myocardial infarction, hospitalized non-fatal heart failure or vascular death) and total mortality. Other pre-specified secondary efficacy outcomes include cost-effectiveness, EQ-5D, food satisfactoriness as well as urinary microalbumin, which will be reported separately. Pre-specified safety outcomes were serum potassium, serum sodium, biochemical

hyperkalemia (defined as serum potassium >5.5mmol/L), biochemical hyponatremia (defined as serum sodium <135mmol/L), and renal dysfunction (defined as eGFR <60ml/min/m^2). Biochemical hypokalemia (defined as serum potassium < 3.5 mmol/L) was analyzed as exploratory safety outcome. The pre-specified process indicators are 24-hour urinary potassium and sodium. We also measured monitoring data on salt supply records as exploratory process indicators of salt reduction interventions.

Both serum and urinary electrolytes were measured with the ion-selective electrode method[34] and serum creatinine was measured using a Roche enzymatic assay.[35] All assays were performed on a Roche Cobas c501 platform.

Sample size and statistical analysis

The study was designed to provide 80% statistical power (with two-sided alpha = 0.05) to detect a minimum difference of 3.0mmHg systolic blood pressure between randomized comparisons.[17] The assumed effect size is conservative according to our previous randomized trials on salt substitute [13], but it is meaningfully large for a population strategy of cardiovascular disease prevention.

The statistical analysis plan was finalized on April 19, 2021 and the database was locked in May 16, 2021. Analyses of effectiveness outcomes followed the intention-to-treat principle. We used a linear mixed model to test the intervention effects on blood pressure, accounting for the clustering effect and adjusting for the baseline value,[36] among eligible participants with at least one blood pressure measurement during follow up (1219 (76%) participants). The analysis was done separately for each intervention strategy in the entire randomized population (Figure 1). It should be noted that the factorial design was employed mainly for efficiency rather than for testing of a possible interaction between interventions. We planned to test the interaction between two strategies only if both strategies were shown effective. Pre-specified sensitivity analyses of the effects on the primary outcome included: (1) a per-protocol analysis (1195 participants, further excluding those from one

facility that discontinued the study and one facility that shifted from salt substitute to usual salt for one month); (2) multiple imputation for missing follow-up values (1612 participants); (3) adjustment for age, sex and region (1219 participants); and (4) exclusion of data from facilities in Xi'an (1019 participants) where more data were missing at follow up than in the other regions (60% in participants from Xi'an versus 9% in participants from the other regions). Significantly more missing follow-up data in Xi'an was due to a high percentage of residents with severe illness (20%), a high proportion moving out of the facilities (17%) and two of four follow-up visits (6 and 18 months) not being implemented for lack of study staff in the local center.

The analyses for cardiovascular events and mortality were based on the first occurrence of each event among the 1612 participants. Rates per 100 person years (100pt-yrs), hazard ratios (HRs), 95% CIs and p-values were obtained using frailty survival models with adjustment for clustering by facility.[37] Those who left the facilities permanently were regarded as censored and the censoring date was the date of the last day of stay. Cumulative event curves were generated using the Kaplan-Meier method.[38] The proportional hazard assumption was tested by Schoenfeld Residuals and was not violated.

Analyses of continuous safety outcomes used a linear mixed model, accounting for the clustering effect and adjusting for the baseline value. Assessment of dichotomous safety outcomes was done by estimation from generalized linear mixed models with adjustment for clustering.[39] The numbers of participants with biochemical hyperkalemia followed by a cardiovascular event or death were quantified by randomized comparison group to better understand the clinical impact of biochemical hyperkalemia. The same approach as for the primary outcome was used to calculate effects on 24-hr urinary potassium, sodium and microalbumin in the 639 participants with measurements.

To estimate the mean salt consumption per person per day in each facility, we first summed up the total salt supply and subtracted the remaining stored product from it, then we divided the difference by the

number of people and further by the total number of days of the intervention period. The average salt consumption per person per day was defined by the sum of the mean salt consumption per person per day in each facility divided by the number of facilities in each comparison group.

The homogeneity of intervention effects on the primary outcome across participant subgroups defined by baseline characteristics (blood pressure, hypertension status, anti-hypertensive medication use, geographic region, sex, age and educational attainment) was tested by including interaction terms in the models and accounting for clustering. The same approach was used to test the homogeneity of intervention effects on the safety outcome across participant subgroups defined by baseline age, sex, and health status as well as hyperkalemia risk status (high risk was defined as having serum potassium > 5.5mmol/l, or history of renal disease, or medications that may elevate serum potassium, which include any of the following medications: ACEI/ARBs, potassium-sparing diuretics, and beta-blockers).

The statistical significance level was 0.05 throughout. P values on the primary study outcomes were corrected using the Bonferroni method, i.e. doubling the original p-values considering that two primary outcomes were tested. But it was not done for secondary outcomes. Instead, we relied on the consistency of all evidence obtained from the study on different outcomes. All analyses were done using SAS version 9.4.

Data availability statement

The availability of anonymized clinical and anthropometric data will be considered based on a proposal review subject to an internal review by the study management committee, completion of a data sharing agreement, and in accordance with the Peking University's institutional review board and institutional guidelines, to ensure that the participants' anonymity and confidentiality are protected. Please submit requests to YW (wuyf@bjmu.edu.cn) copying HL. (pucri_lihj@bjmu.edu.cn). Deidentified participant data and a data dictionary will be made available following approval. A detailed research protocol and statistical analysis plan will be shared as the supplements of this publication.

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