Appendix

Estimated population-wide benefits and risks in China of lowering sodium through potassium enriched salt substitution: modelling study

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Appendix 1. Effect of salt substitutes on blood pressure

We considered several sources of evidence for estimating the effect of salt substitution on systolic blood pressure (SBP). To date, three meta-analyses on the blood pressure effects of salt substitutes have been published.[1-3] First, Peng and coworkers presented their findings based on six comparisons (five in Chinese and one in Dutch participants) and reported an average 4.91 (95% confidence interval: 2.54 to7.29) mm Hg lower SBP and 1.52 (0.32 to 2.73) mm Hg lower diastolic blood pressure (DBP) in the salt substitute groups compared to controls (consuming regular salt).[1] When stratified by hypertension status (defined as SBP⩾140 mm Hg or DBP⩾90 mm Hg), the reduction in SBP and DBP were only significant among hypertensives, although potential differences in blood pressure effects between normotensives and hypertensives were not statistically tested.[1] Newberry and colleagues conducted an updated meta-analysis for the Agency for Healthcare Research and Quality (AHRQ) that included 14 comparisons from 13 trials conducted in China (n=6), UK (n=2), Brazil, Finland, Italy, Netherlands, and South Africa (each n=1).[2] Compared to controls (consuming regular salt), the participants in the salt substitute group had on average 5.58 (4.09 to 7.08) mm Hg lower SBP and 2.88 (1.83 to 3.93) mm Hg lower DBP. The authors concluded that the findings suggest that potassium-containing salt substitute has a significant beneficial effect on blood pressure, and that the evidence is insufficient to draw conclusions regarding the moderating effects of sex, age, or hypertension status.[2] Recently, Hernandez and colleagues conducted a systematic review and meta-analyses of the effects of low-sodium salt substitutes on blood pressure, hypertension prevalence and urinary excretion of potassium and sodium. [3] The meta-analysis of trials (n=16 comparisons [n=7 in Chinese populations], total n= 1,933) evaluating the blood pressure effects of salt substitutes estimated salt substitutes to lower SBP by −7.81 mm Hg (95% CI −9.47 to –6.15). Moderating effects of sex, age, or blood pressure status on the effects of salt substitutes on SBP were not evident. In the same report, the effects of the salt substitute intervention on urinary potassium excretion were estimated by meta-analysis of salt substitute trials (n=10 comparisons [n=4 in Chinese populations], total n= 870), and suggested an average increase in 24-h urinary potassium excretion by 11.5 mmol/d (95% CI: 8.4 to 14.6).[3] Given that the large heterogeneity in study settings of included studies in the three meta-analyses could influence the translation of effect estimates to a population-wide salt substitute intervention in China, we also evaluated the effect on systolic blood pressure (SBP) from our ongoing Salt Substitute and Stroke Study (SSaSS), which is an open, large-scale, cluster-randomized controlled trial currently conducted in 600 villages across 5 provinces in rural areas of Northern China.[4] The primary objective of the trial is to determine the effects of sodium reduction through salt replacement with potassium-containing salt substitutes on stroke risk. Salt substitutes containing 30±10% KCl are provided free-of-charge to participants in villages assigned to the intervention group and are accompanied by advice to use the salt substitutes instead of regular salt for all cooking, seasoning, and food preservation purposes. In addition, participants in the intervention villages are advised to use the salt substitutes sparingly and not more frequently than when they consumed regular salt. Participants in control villages continue their usual practice and received general advice about stroke prevention including recommendations to reduce salt intake at the initiation of the trial. Evaluation of data from interim measurements (1-3 y after baseline) of >4,500 individuals in SSaSS, revealed that the use of salt substitutes lowered SBP with greater reductions at older ages; the SBP effect of -2.82 (-4.75, -0.89; P=0.004) mmHg at age 65 y increased and decreased by 0.13 (-0.02; 0.27; P=0.085) mm Hg for each year of age below and above 65 y, respectively (eTable 2). Thus the estimated mean intervention effect on SBP at age 75 y would be -4.12 mmHg while only -1.52 mmHg in 55-year-olds. The point estimate of SBP effect was numerically greater in hypertensives compared to normotensives (2.96 vs. 2.40 mm Hg), but there was no significant difference between the two groups (P=0.92). We compared the effect estimates from SSaSS and the most recent meta-analysis on salt substitute trials with our previous meta-analysis on blood pressure effects of sodium reduction (eTable 3).[5] When standardized to the age and observed reduction in sodium excretion in SSaSS, the effect on SBP was numerically lower in the sodium reduction trials compared to SSaSS and the other salt substitute trials. However, the confidence/uncertainty intervals were greatly overlapping and it has been suggested that reductions in sodium intake in salt substitute trials are not necessarily reflected in sodium excretion.[2]

Appendix 2. Intervention impact on CVD outcomes and incident CKD in the whole adult population through BP reduction

For the primary model, we used estimates of the intervention effect on SBP from the ongoing SSaSS, including the main effect of the salt substitute and the interaction effect of salt substitute and age. We adjusted the

intervention effect for age but given the limited number of participants in SSaSS aged <40 y or >80 y (<3%), we truncated the age-adjustment so that the intervention effect increased with age only in the interval 40-80y, The post-intervention SBP mean in each stratum was calculated by summing the pre-intervention SBP mean [6] with the age-adjusted intervention effect for the same strata. We assumed that the salt substitute will not increase SBP and truncated intervention effects at zero (i.e., model estimates suggesting increased blood pressure from salt substitutes were replaced with zero). Based on age and-sex specific SBP distributions estimated in over 500,000 Chinese,[7] we assumed the standard deviation of SBP in each stratum was equal to 15% of the mean for that specific stratum. We assumed both pre- and post-intervention follow gamma distributions, based on visual inspection of SBP exposure data from NHANES [6], and derived gamma parameters from mean and standard deviation in each stratum. We used estimates of the SBP effect on CVD outcomes and incident CKD from the Global Burden of Disease (GBD) Study,[6 8] except for hypertensive heart disease for which we used estimates from our previous meta-analysis.[9]

The PIF for each CVD outcome (o) is defined as

$$\mathrm{PIF}_{oas} = \frac{\int_{x=0}^{m} RR_{oa}(x)P_{as}(x)dx - \int_{x=0}^{m} RR_{oa}(x)P'_{as}(x)dx}{\int_{x=0}^{m} RR_{oa}(x)P_{as}(x)dx} \quad \text{Eq. 1}$$

$RR_{oa}(x)$ is the relative risk as a function of SBP (x), outcome (o), and age (a). $P_{as}(x)$ is the pre-intervention SBP distribution in age group (a) and sex (s). $P'_{as}(x)$ is the post-intervention SBP distribution in age group (a) and sex (s). The $RR_{oa}(x)$ is defined as

$$RR_{oa}(x) = e^{\left(\frac{\ln RR^{M}_{oa}\,(x-TMREL)}{10}\right)} \quad \text{Eq 2.}$$

$\ln RR^{M}_{oa}$ is the increase in the natural logarithm of the relative risk of outcome (o) in age (a) per 10 mm Hg SBP increase, derived from previous meta-analyses. [6 9] TMREL is the theoretical-minimum-risk exposure level. The PIF for each outcome and stratum was calculated by numerical integration. The averted number of CVD events were computed by multiplying an age-, sex-, and cause-specific PIF by the estimated current number of CVD events for the same stratum. Total numbers of current and averted events were calculated as the sum of estimates over all strata.

Averted CVD deaths (CVM_{asc}) in CKD patients (c) were modelled in each sex (s) and age (a) stratum as

$$CVM_{asc} = \frac{P_{asc} \times CVM_{as}}{(P_{asc} + ((1 - P_{asc})/\mathrm{HR}_{ac}))} \quad \text{Eq 3.}$$

$P_{asc}$is the prevalence of CKD (i.e., estimated glomerular filtration rate [eGFR]<60 mL/min per 1.73 m^2) in age group (a) and sex (s), CVM_{as} is the total number of CVD deaths in age group (a) and sex (s), and HR_{ac} is the hazard ratio of CVD mortality among CKD patients (c) compared to others in age group (a). Age-and sex-specific CKD prevalence of CKD was based on the China National Survey of CKD, where CKD prevalence was presented in eight sex-and age-groups (18-39 y, 40-59y, 60-69 y, and ⩾70 y).[10] We plotted these estimates against the midpoint age of each age-group and used piecewise linear regression to estimate the prevalence in each of the 24 age- and sex-groups of our model. The 95% CI of CKD prevalence was estimated in a similar fashion. The upper and lower 95% CI boundaries for the eight sex-and age-groups presented for the China National Survey of CKD were plotted against the midpoint ages and we used piecewise linear regression to estimate the 95% CI boundaries for each of the 24 age- and sex-groups of our model. Hazard ratios of CVD mortality among CKD patients compared to others in the same age group were derived from an individual-level meta-analysis of >2 million participants conducted within the CKD Prognosis Consortium, where multivariable-adjusted HRs of CVD mortality comparing eGFR 50 vs 80 mL/min per 1.73m^2 were presented for four age-groups (18-54 y, 55-64y, 65-74 y, and ⩾75 y).[11] We plotted the natural logarithm of the HR against the midpoint age of each age group and conducted linear extra- and interpolation to estimate logHRs in 5-year age intervals. To minimize overestimation of benefits in CKD patients, averted deaths were expressed as a percentage of pre-intervention CVD deaths (calculated in a similar manner) after summing estimates from all strata.

Uncertainties of modelled estimates were quantified using Monte Carlo simulations (n=1000).[12] For each simulation, a draw was made from the distributions of a) current mean SBP for the specific age-sex stratum, b) the TMREL, c) the salt substitute treatment effect on SBP, d) the age-salt substitute treatment interaction effect

on SBP, e) the effects of SBP on each CVD outcome, f) the current number of events (e.g., deaths) for each CVD outcome, g) CKD prevalence in each stratum, and h) hazard ratio of CVD mortality among CKD patients compared to others in the same age group. To include the uncertainty in the TMREL, 1000 random draws from the uniform distribution of the interval 110-115 mm Hg were taken. [6] Each set of draws was used to calculate PIF and averted events of each CVD outcome for each age-sex stratum. We present the 50th and 2.5-97.5th percentiles of the distribution of the intervention effects (e.g., averted deaths) estimated across all 1000 simulations as the central estimate and 95% uncertainty intervals (UI) for each stratum, respectively.

Appendix 2. Effect of salt substitutes on potassium intake

In SSaSS, the 24h urinary potassium excretion was 0.66 g (95% CI: 0.52 to 0.80) greater in individuals consuming salt substitutes compared to controls.[13] We multiplied the increase in urinary potassium excretion by a factor 1.3 to estimate the corresponding increase in potassium intake.[14]

Appendix 4. Intervention impact on hyperkalemia-related CVD mortality in the CKD population

In order to estimate the increase in potassium intake, we used the increase in 24-h urinary potassium excretion observed in SSaSS and multiplied it by a factor 1.3.[14] We defined CKD stages (i.e., G1, G2, G3a, G3b, G4, G5) by eGFR level.[15]

For each CKD stage (*e*), we modelled the current CVD mortality M_e as

$$M_e = M \times P_e \times HR_e \frac{\sum_{e=1}^{n} P_e}{\sum_{e=1}^{n} P_e \times HR_e} \quad \text{Eq 4.}$$

where M is the total CVD mortality in the adult Chinese population, P_e is the prevalence of CKD stage e, and HR_e is the crude hazard ratio for CVD mortality in CKD stage e compared to the reference level (eGFR=100 mL/min per 1.73 m^2).

We assumed that alterations in serum potassium concentrations due to changes in potassium intake are restricted to patients with moderate to severe CKD (i.e., CKD stages ≥3a; eGFR<60 mL/min per 1.73 m^2). We used data from our unpublished randomized controlled trial on blood pressure effects from potassium supplementation in patients with moderate CKD to estimate the dose-response relationship between dietary and serum potassium in patients with CKD stage 3a (clinicaltrials.gov, number: NCT00949585). The 2-period crossover trial included 29 CKD stage G3a patients (mean eGFR= 54.5 mL/min per 1.73 m^2) who were fed 100 and 40 mmol K per day in two 4-weeks periods. We used data from serum potassium measurements conducted one week after initiation of each feeding period. Serum potassium concentration was 0.55 (0.38 to 0.72) mmol/L greater at the higher dose compared to the lower dose, which translate to 0.23 (0.08 to 0.38) mmol/L greater serum potassium per additional g/d of dietary potassium. In our primary model, we assumed that this dose-response relationship doubles for each progressing stage of CKD (i.e, 3b, 4, and 5).

Pre-intervention serum potassium levels were derived from an individual-level meta-analysis of >1.2 million participants conducted within the CKD Prognosis Consortium, where mean and standard deviations of serum potassium concentration were estimated separately in two groups of individuals with CKD (i.e., stage G3 and stage ≥G4).[16] We plotted the means and standard deviations of serum potassium of these groups against the stage-specific eGFR midpoints and conducted linear extra- and interpolations to estimate means and standard deviations for stages G3a, G3b, G4, and G5. The post-intervention serum potassium mean was calculated by summing the pre-intervention mean with the product of the estimated increase in potassium intake and the dose-response effect estimate of dietary and serum potassium. The post-intervention standard deviation of serum potassium was assumed to increase proportionally with the mean. We computed PIF for CVD mortality for each CKD stage (*e*) as

$$\text{PIF}_e = \frac{\sum_{x=0}^{m} RR(x) P_e(x) - \sum_{x=0}^{m} RR(x) P'_e(x)}{\sum_{x=0}^{m} RR(x) P_e(x)} \quad \text{Eq 5.}$$

where *RR (x)* is the relative risk of CVD mortality at serum potassium concentration (*x*), estimated in a pooled analysis of 27 international cohorts (including >1.2 M individuals) and presented for each 0.05 mmol/L increment in the interval 2.5-6.5 mmol/L with 4.2 mmol/L as the reference concentration. [16] Compared to serum potassium concentration 4.2 mmol/L, lower levels (i.e., <4.2 mmol/L) are not associated with CVD mortality, [16] thus we truncated RR(x) to 1 at concentrations <4.2 mmol/L and we assumed *RR(>6.5) = RR(6.5). $P_e(x)$* is the

pre-intervention distribution of serum potassium in CKD stage *e*. $P'_e(x)$ is the post-intervention distribution of serum potassium in CKD stage *e* . We assumed that both $P_e(x)$ and $P'_e(x)$ follow normal distribution based on visual inspection of serum potassium data from the CKD-PC.[16]

Additional CVD deaths due to increased potassium intake were computed per stratum by multiplying the negative stratum-specific PIF by the estimated current number of CVD deaths for the same stratum. Total numbers of current and additional deaths were calculated as the sum of estimates over all strata.

Uncertainties of modelled estimates were quantified using Monte Carlo simulations (n=1000).[12] For each simulation, a draw was made from the adult population's distributions of a) increased potassium intake, b) total CVD mortality, c) stage-specific CKD prevalence, and d) the relative risk of serum potassium with CVD mortality. Likewise, draws were made for the stratum-specific distributions of e) CVD mortality risk, f) diet-serum relationship of potassium, g) and serum potassium level. The 50th and 2.5-97.5th percentiles of the distribution of the additional CVD deaths across all 1000 simulations for each stratum were then interpreted as the central estimate and 95% UI for each stratum.

Appendix 5: Net effect of the intervention

For each of 1000 simulations, we calculated the intervention net effect on CVD mortality by subtracting the averted deaths due to blood pressure reduction from the additional deaths due to elevated serum potassium levels. The net effect, expressed both as absolute number of deaths and as percentage of current number of CVD deaths, was calculated for the whole population and specifically for CKD patients. We also calculated the benefit-to-risk ratio for each of 1000 simulations by dividing averted deaths by additional deaths. The 50th and 2.5-97.5th percentiles of the distributions of net effects and benefit-to-risk ratios estimated across all 1000 simulations were then interpreted as the central estimates and 95% UI.

Appendix 6: Sensitivity analyses

The robustness of the primary model was evaluated in several sensitivity analyses. In the SSaSS, 97.5% of participants randomized to the intervention arm reported use of salt substitute (unpublished data), However, we do not know the extent (the frequency and amount) to which participants used the salt substitutes or the proportion of regular salt replaced. Therefore, we modelled evaluated the impact of intervention coverage assuming that the extent to which participants used the salt substitutes was 50% less and 50% more than what was observed in SSaSS. We assumed corresponding proportional effects on SBP and potassium intake, given that blood pressure effects increases with salt substitutes use (as indicated by achieved sodium reductions).[3] We estimated the net impact on CVD mortality assuming that all CKD patients aware of their diagnosis (around 14% of CKD patients with stages ≥3a)[10 17] would avoid salt substitutes; for this sensitivity analysis we used published data on CKD prevalence[10] and awareness[17] in China, and assumed neither benefits nor risks of the intervention among the proportion of CKD patients aware of their diagnosis. Awareness reported for CKD stages G3 and ≥G4 with and without albminuria[17] was used together with prevalence of CKD and albuminuria[10] to derive mean and standard errors of awareness for each of four individual CKD stages (i.e., G3a, G3b, G4, and G5) by inter- and extrapolation using stage-specific eGFR midpoints. We varied the impact of potassium-enriched salt substitutes on BP by using alternative effects from each of three meta-analyses of salt substitute trials.[1 2 3]Hernandez et al. also evaluated the effect of salt substitutes on urinary potassium excretion (11.5 mmol/d; 95% CI: 8.4 to 14.6) and we used this to vary the potassium intake simultaneously with the SBP effect from the same study.[3] As in the primary model, we calculated potassium intake as 130% of 24h urinary potassium excretion.[14] While sodium reduction lowers SBP among normotensives,[5] there is more limited evidence on the SBP effects of salt substitutes in normotensives.[1 2] Thus, we conducted a sensitivity analysis assuming no effect of salt substitution on SBP among normotensive individuals based on hypertension prevalence by age and sex from a recent survey of 1.7 million Chinese.[18] Age- and sex-specific hypertension prevalence for ages 25-29, 30-34, 75-79, and ≥80 y were extrapolated from prevalence reported for 5-y intervals in the range 35-74y.[18] We evaluated the impact of stronger and weaker dose-response relationships between dietary and serum potassium by assuming serum response to potassium dose to increase exponentially and linearly, respectively, with decreasing eGFR; and investigated the impact of assuming the same serum response to potassium dose in CKD stages G3b, G4, and G5 as estimated in stage G3a. We varied the standard deviation of SBP in each age-sex-stratum (10% and 20% of the mean). Finally, we evaluated the impact on additional CVD deaths in the CKD population of 1) proportions (10-100%) of discretionary salt replaced by salt substitutes, and 2) potassium chloride content (10% or 25%) of salt substitutes.

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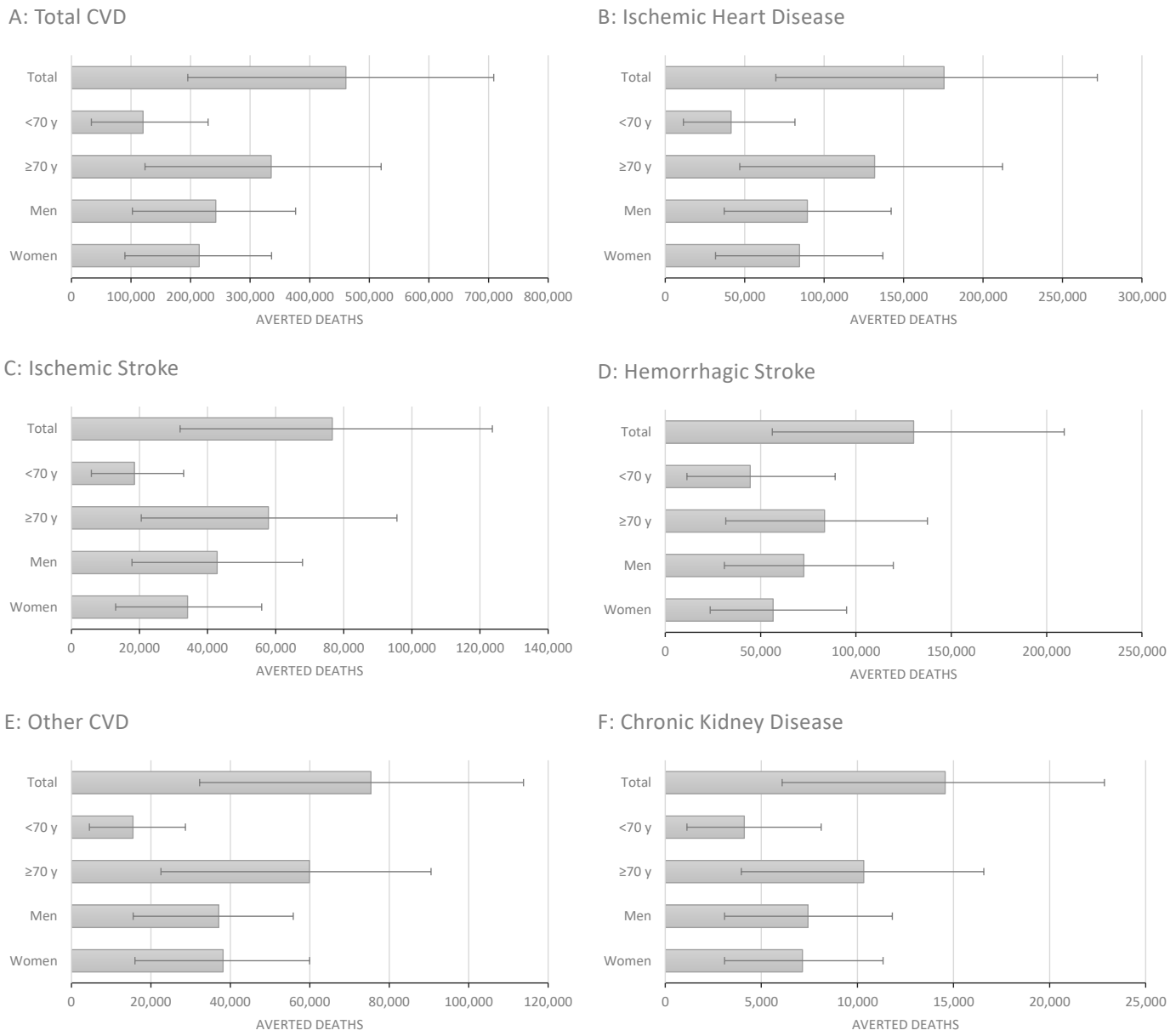
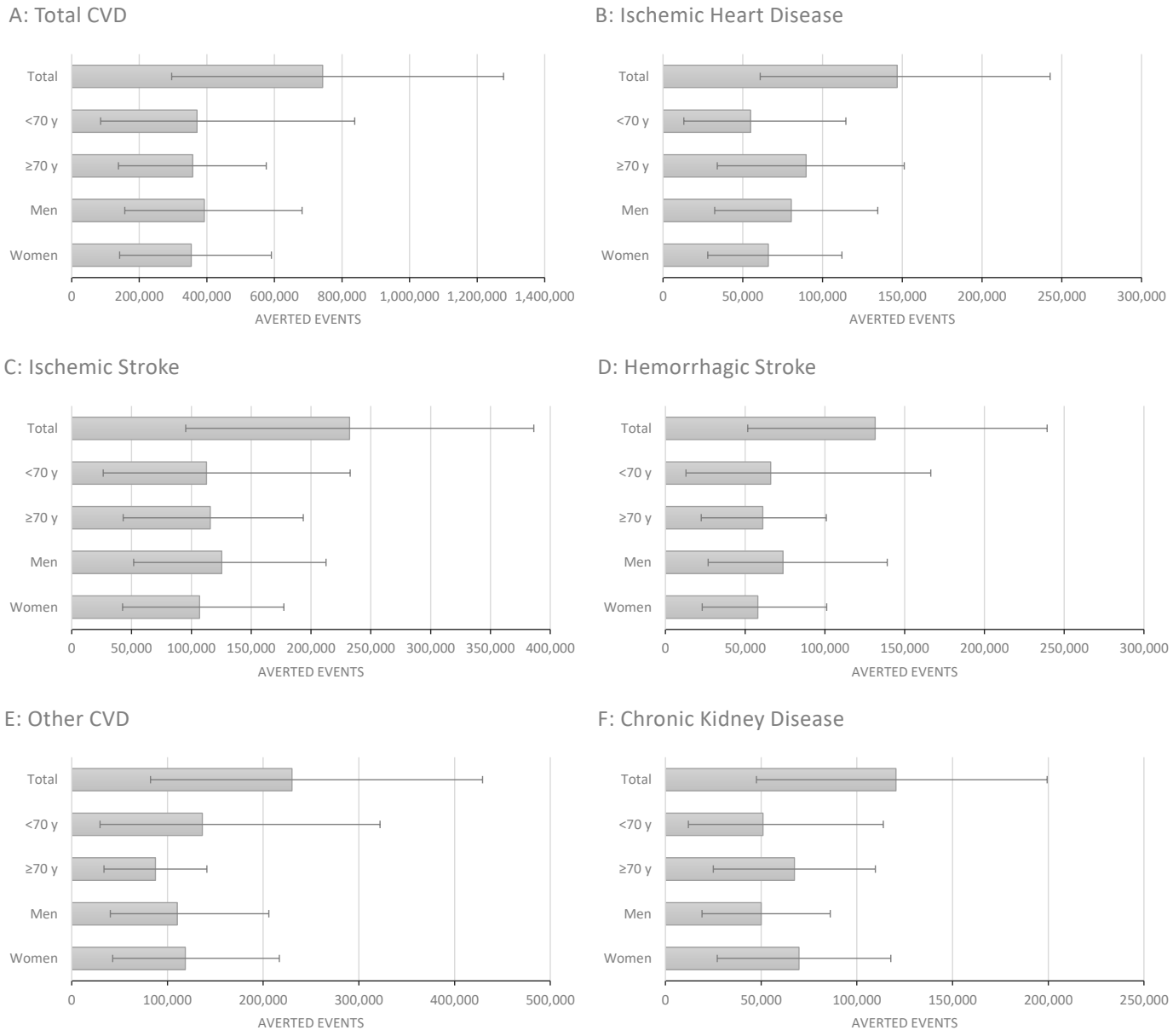
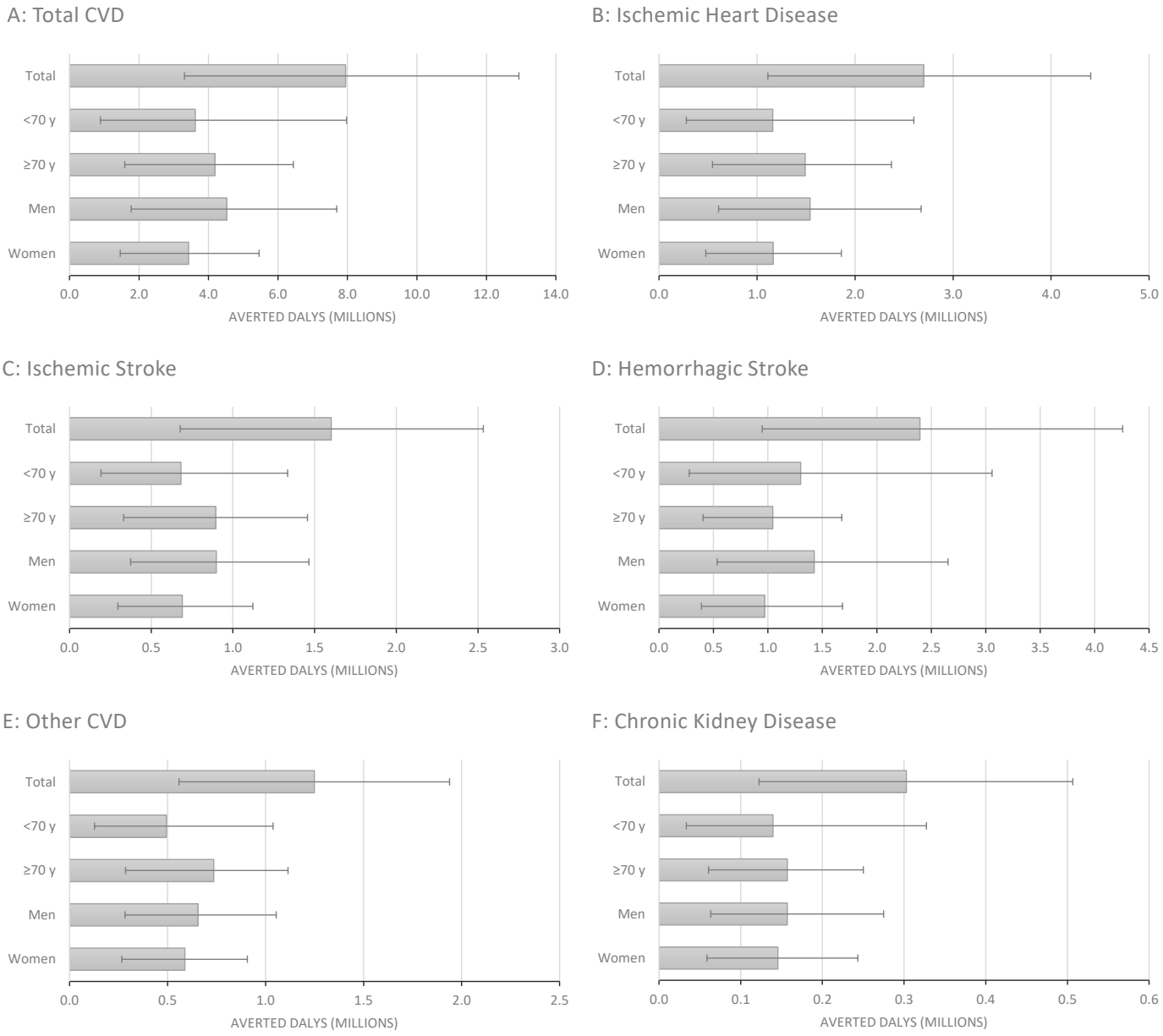


eFigure 1. Age-and sex-specific effects from blood pressure reductions by salt substitution on mortality from A) total CVD, B) IHD, C) ischemic stroke, D) haemorrhagic stroke, E) other CVD, and F) CKD. Error bars represent 95% uncertainty intervals defined as 2.5 and 97.5 percentiles of model estimates from n=1000 simulations.

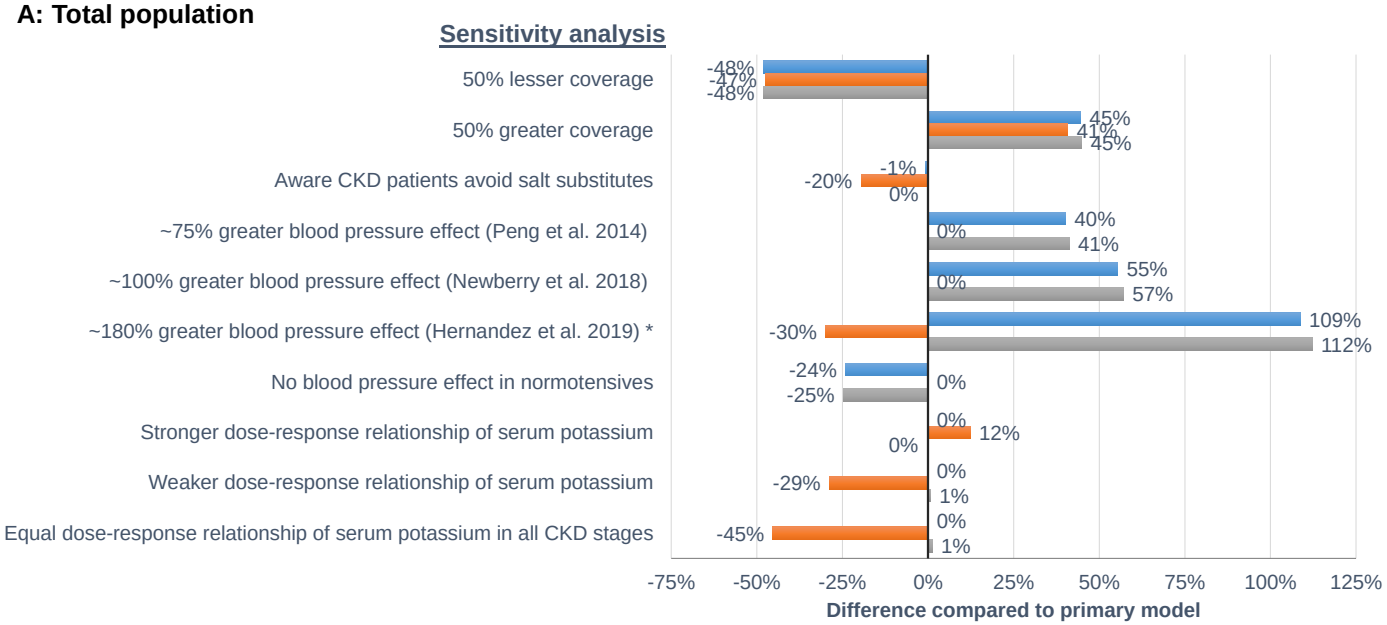


eFigure 2. Age-and sex-specific effects from blood pressure reductions by salt substitution on events of A) total CVD, B) IHD, C) ischemic stroke, D) haemorrhagic stroke, E) other CVD, and F) CKD. Error bars represent 95% uncertainty intervals defined as 2.5 and 97.5 percentiles of model estimates from n=1000 simulations. Panels B-D only include first events.

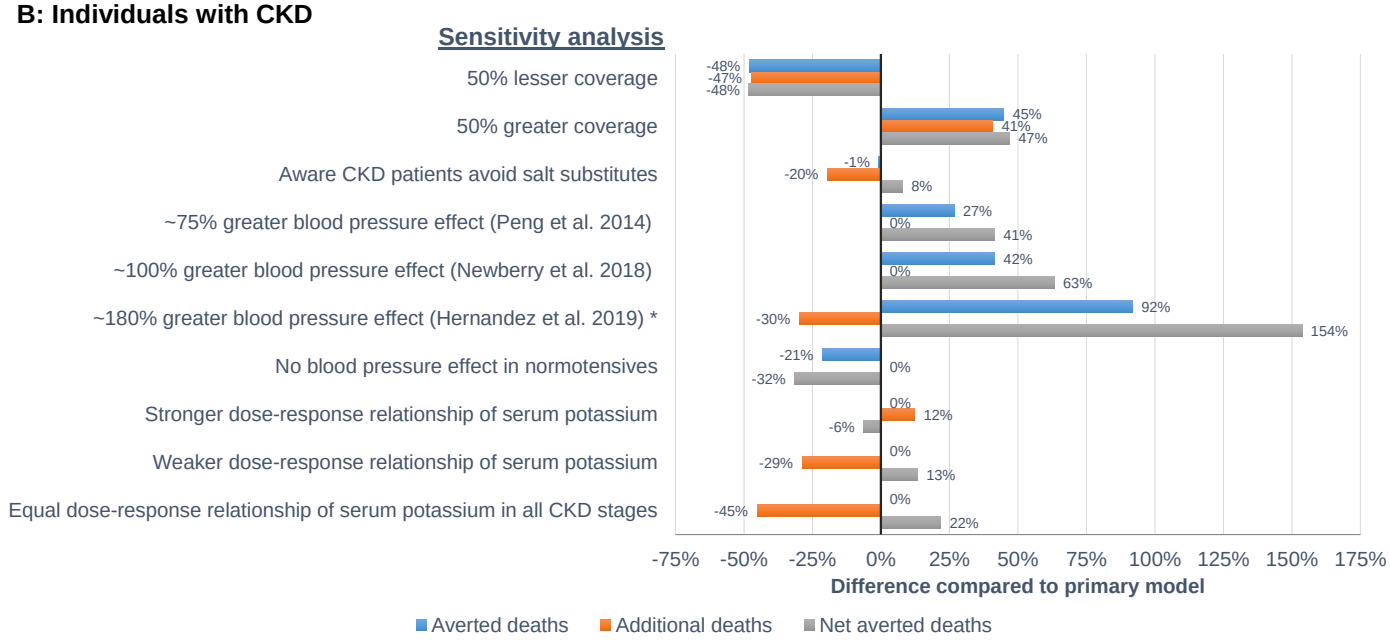


eFigure 3. Age-and sex-specific effects from blood pressure reductions by salt substitution on disability-adjusted life years (DALYs) due to A) total CVD, B) IHD, C) ischemic stroke, D) haemorrhagic stroke, E) other CVD, and F) CKD. Error bars represent 95% uncertainty intervals defined as 2.5 and 97.5 percentiles of model estimates from n=1000 simulations.

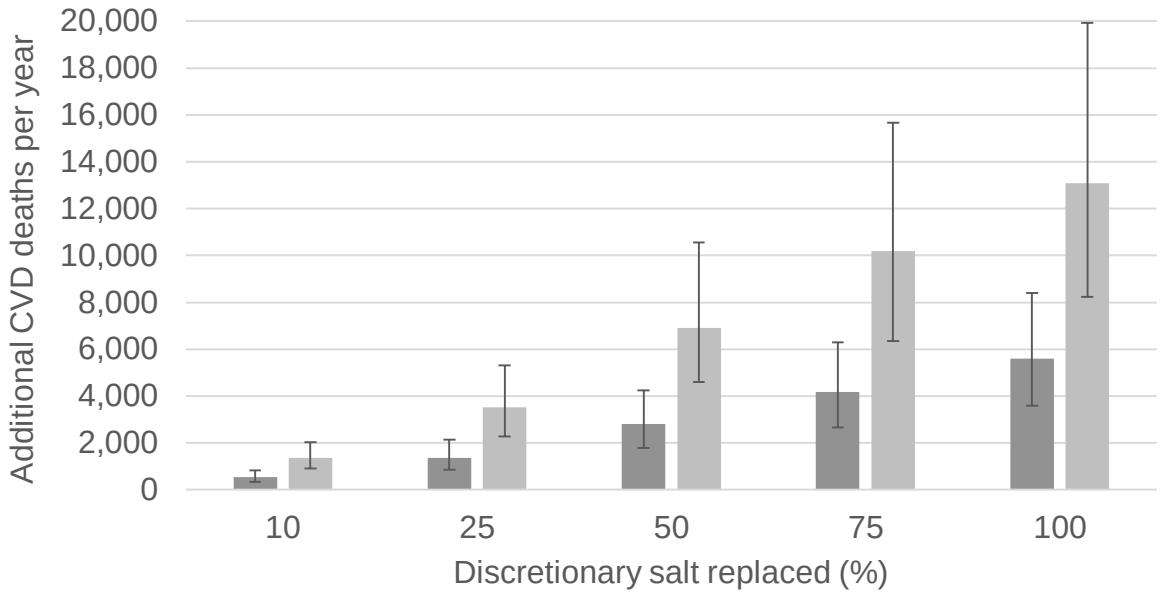
A: Total population



B: Individuals with CKD



eFigure 4. Relative change in point estimates from sensitivity analyses compared to primary model. Estimates of total averted deaths due to blood pressure reduction (blue), additional deaths due to hyperkalemia among individuals with CKD (orange), and net averted deaths including both total averted and additional deaths (grey) in the total population (A) and in individuals with CKD (B). *



eFigure 5. Estimated additional CVD deaths due to elevated serum K in CKD patients from proportional replacement of discretionary salt using salt substitutes containing 10% (dark grey) and 25% (light grey) potassium chloride (KCl). All estimates were generated assuming the same mean and standard error of discretionary salt, 8.4 (0.1) g/d,[19] in all strata. The presented estimates represent the central estimates of n=1000 simulations and error bars represent 95% uncertainty intervals.

eTable 1. Pre-intervention characteristics (systolic blood pressure and prevalence of hypertension and CKD) and CVD mortality risk in individuals with CKD, stratified by age.

	Systolic blood pressure, mmHg*		Hypertension prevalence, %†		CKD Prevalence, %‡		Hazard ratio of CVD mortality in CKD§
Age, y	Men	Women	Men	Women	Men	Women	
25 to 29	122.9 (121.9 to 124.0)	115.5 (114.5 to 116.6)	8	<1	0.2 (0.0 to 3.2)	0.8 (0.1 to 3.2)	3.05
30 to 34	126.5 (125.5 to 127.6)	117.5 (116.5 to 118.5)	16	<1	0.5 (0.1 to 3.0)	1.1 (0.1 to 3.0)	2.91
35 to 39	127.8 (126.9 to 128.8)	119.7 (118.7 to 120.7)	25	13	0.7 (0.1 to 2.8)	1.4 (0.1 to 2.8)	2.77
40 to 44	129.2 (128.2 to 130.2)	122.9 (121.8 to 123.9)	30	20	0.9 (0.1 to 2.6)	1.7 (0.1 to 2.6)	2.65
45 to 49	130.7 (129.6 to 131.7)	126.7 (125.6 to 127.7)	37	29	1.2 (0.1 to 2.4)	2.0 (0.1 to 2.4)	2.53
50 to 54	132.5 (131.4 to 133.5)	130.5 (129.4 to 131.6)	44	40	1.6 (0.1 to 2.3)	2.7 (0.2 to 2.3)	2.41
55 to 59	135.6 (134.6 to 136.6)	133.9 (132.8 to 135.0)	49	48	2.1 (0.2 to 2.1)	3.9 (0.2 to 2.1)	2.30
60 to 64	137.6 (136.4 to 138.6)	137.3 (136.1 to 138.5)	54	55	2.7 (0.3 to 2.0)	5.2 (0.3 to 2.0)	2.20
65 to 69	140.3 (139.1 to 141.5)	141.9 (140.8 to 143.2)	59	61	3.4 (0.3 to 1.8)	6.0 (0.4 to 1.8)	2.10
70 to 74	141.2 (140.0 to 142.4)	143.7 (142.5 to 144.9)	61	66	4.3 (0.4 to 1.7)	6.4 (0.4 to 1.7)	2.00
75 to 79	142.3 (141.2 to 143.5)	142.9 (141.5 to 144.3)	65	72	5.1 (0.4 to 1.6)	6.8 (0.5 to 1.6)	1.91
80+	142.5 (141.3 to 143.9)	143.7 (142.4 to 145.1)	70	81	6.5 (0.5 to 1.4)	7.5 (0.5 to 1.4)	1.77

*2015 blood pressure levels by age and sex were extracted from the GBD Study 2015 (GBD 2015) Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm HG 1990-2015. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2017. † Sex-specific mean prevalence of hypertension in ages (35-75 y) were extrapolated in ages 25-34y and >75y (eTable 1), based on estimates from 1.7 million adult Chinese (Lu et al., Lancet 2017).[18] ‡ Age- and sex-specific prevalence of CKD (i.e., eGFR<60 mL mL/min per 1.73m2) were estimated through inter- and extrapolation based on piecewise linear regression of age-specific CKD prevalence in four age-groups (18-39 y, 40-59y, 60-69 y, and ⩾70 y; Zhang et al. 2012)[10] plotted against midpoint age of each age group. Similarly, 95% CI of CKD prevalence were estimated through inter- and extrapolation based on piecewise linear regression of upper and lower 95% CI boundaries. §Age-specific (18-54 y, 55-64y, 65-74 y, and ⩾75 y) HRs comparing eGFR 50 vs 80 mL/min per 1.73m2 were assessed by Hallan et al. in individual-level meta-analysis of >2 million participants.[11] We conducted linear extra- and interpolation of natural logarithms of the multivariable-adjusted HR plotted against the midpoint ages of the age groups evaluated by Hallan et al, to estimate HRs in 5-year age intervals.

eTable 2. Effects of salt substitute on systolic blood pressure (SBP) by hypertension status in interim measurements of the Salt Substitute and Stroke Study (SSaSS)**.**

	All participants (n= 4,705)		Hypertensives (n= 3,577)		Normotensives (n= 1,128)	
Covariate	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Baseline SBP	0.42 (0.39 to 0.44)	<0.001	0.40 (0.37 to 0.44)	<0.001	0.39 (0.27 to 0.49)	<0.001
Treatment	-2.82 (-4.75 to -0.89)	0.004	-2.96 (-5.06 to -0.86)	0.006	-2.40 (-5.22 to 0.44)	0.097
Age	0.09 (-0.01 to 0.19)	0.087	0.06 (-0.06 to 0.19)	0.339	0.15 (-0.03 to 0.33)	0.095
Treatment × age	-0.13 (-0.27 to 0.02)	0.085	-0.17 (-0.35 to 0.00)	0.053	0.03 (-0.23 to 0.28)	0.842

Assessed in mixed effects models including SBP at last measurement as dependent variable, village nested within province as random effects, and baseline SBP, age (years above 65), treatment (salt substitute or regular salt), and the interaction between age and treatment as fixed effects.

eTable 3. Comparison of blood pressure effects in salt substitute and sodium reduction trials

	The Salt Substitute and Stroke Study (SSaSS)	Mozaffarian et al., NEJM, 2014[5]	Newberry et al., AHRQ 2018[2]	Hernandez et al., Heart, 2019[3]
Descriptives				
Study description	Open, cluster randomized controlled trial in 600 Chinese villages.	Meta-analysis and –regression of sodium reduction trials.	Meta-analysis of salt substitution trials.	Meta-analysis of salt substitution trials.
Comparisons, n	1	107	14	16
Total sample size, n	4,705	6,970	5,310	1,933
Mean age, y	65	47	53[*]	52[*]
Hypertension, %	76	65	71[*]	72[*]
Mean achieved Na, mmol/d	-15[†]	-99	-22[*]	-36
Mean achieved K, mmol/d	17[†]	n/a	14[*]	11
Observed effects				
Observed mean difference in SBP (95% CI), mmHg	-3.08 (-4.49 to -1.66)[‡]	n/a	-5.58 (-7.08 to -4.09)[¶]	-7.81 (-9.47 to -6.15)[§]
Salt substitute effect on SBP in 65-y-old normotensives, mmHg	-2.71 (-5.60 to 0.19)[‡]	n/a	-4.52 (-9.35 to 0.30)[‖]	-8.35 (-11.92 to -4.77)[**]
Salt substitute and age interaction, mmHg per year	-0.13 (-0.27 to 0.02)[††]	n/a	-0.12 (-0.39 to 0.14)[‖]	-0.03 (-0.16 to 0.10)[**]
Salt substitute and hypertension interaction, mmHg	-0.15 (-2.99, 2.69)[††]	n/a	-2.14 (-7.86, 3.58)[‖]	0.18 (-4.41 to 4.76)[**]
Na reduction effect on SBP in 50-y-old normotensive whites per 100mmol/d Na reduction, mmHg	n/a	-3.74 (-5.18 to -2.29)[‡‡]	n/a	n/a
Na reduction and age interaction, mmHg per year	n/a	-0.11 (-0.16 to -0.05)[‡‡]	n/a	n/a
Na reduction and hypertension interaction, mmHg	n/a	-1.87 (-3.63 to -0.12)[‡‡]	n/a	n/a
Standardized effects				
Mean difference per 15 mmol/d achieved Na in 65 y old normotensives	-2.40 (-5.23 to 0.44)[§§]	-0.80 (-1.05 to -0.56)[¶¶]	-1.22 (-2.29 to -1.15)[‖‖]	-1.90 (-3.20 to -0.60)[***]
Mean difference per 15 mmol/d achieved Na in 65 y old hypertensives	-2.96 (-5.06 to -0.86)[§§]	-1.07 (-1.43 to -0.73)[††]	-2.33 (-2.94 to -1.73)[‖‖]	-2.63 (-3.83 to -1.42)[***]

[*]Weighted mean where each study is weighted by the effect size weight in the random meta-analysis of mean difference in systolic blood pressure. [†]Huang et al., Spot urine samples compared to 24-hour urine samples for estimating changes in urinary sodium and potassium excretion in the China Salt Substitute and Stroke Study. International Journal of Epidemiology, 2018.[13] [‡]Mean difference in change from baseline assessed by unpaired t-test. When assessed in mixed models including province and village (nested in province) as random effects and treatment as fixed effect, the difference was -3.24 (-5.70; -0.79) mm Hg. [¶]Evaluated by random effect meta-analysis without consideration of sodium reduction, n=14 comparisons. [§]Evaluated by random effect meta-analysis without consideration of sodium reduction, n=16 comparisons. [‖]Assessed by meta-regression of 12 comparisons in Newberry et al., reporting participant age and hypertension prevalence. [**]Assessed by meta-regression of 16 comparisons in Hernandez et al., reporting participant age and hypertension prevalence. [††]Assessed in a mixed model including SBP at last measurement as dependent variable, village nested within province as random effects, and baseline SBP, age (years above 65), treatment (SS or regular salt), hypertension status, and two interaction terms (1: age and treatment; 2; hypertension and treatment) as fixed effects. [‡‡]Assessed by meta-regression of mean difference per 100 mmol/d sodium reduction. Models include age (years over 50), hypertension status, and race. [§§]Assessed in hypertension-stratified mixed models including SBP at last measurement as dependent variable, village nested within province as random effects, and baseline SBP, age (years above 65), treatment (SS or regular salt), and an age-treatment interaction terms fixed effects. [¶¶]Calculated as 0.15 × (main effect + (65-50) × age-treatment interaction effect). Values represent median (2.5th and 97.5th percentiles) of 1000 iterations, each with unique draws of main and interaction effects. [‖‖]Assessed in meta-regression of 6 comparisons in Newberry et al., reporting participant age, hypertension prevalence, and a negative point estimate in urinary sodium excretion. Mean difference and standard errors of each comparison were standardized to 15mmol/d sodium reduction. [***]Assessed in meta-regression of 8 comparisons in Hernandez et al., reporting participant age, hypertension prevalence, and a negative point estimate in urinary sodium excretion. Mean difference and standard errors of each comparison were standardized to 15mmol/d sodium reduction. [††]Calculated as 0.15 × (main effect + (65-50) × age-treatment interaction effect + hypertension-treatment interaction effect). Values represent median (2.5th and 97.5th percentiles) of 1000 iterations, each with unique draws of main and interaction effects.

eTable 4. Relative risk of CVD subtypes, stratified by age.

	Relative risk (95% CI)							
Age (y)	Ischemic heart disease*	Ischemic stroke*	Hemorrhagic stroke*	Hypertensive heart disease†	Aortic aneurysm*	Rheumatic heart disease*	Endocarditis*	Other cardiovascular diseases*
25 to 29	1.97 (1.44 to 2.71)	1.85 (1.39 to 2.47)	2.13 (1.55 to 2.93)	3.29 (3.00 to 3.60)	1.54 (1.26 to 1.90)	1.63 (1.17 to 2.27)	1.76 (1.26 to 2.43)	1.74 (1.34 to 2.27)
30 to 34	1.82 (1.46 to 2.27)	1.77 (1.43 to 2.21)	2.05 (1.59 to 2.64)	3.29 (3.00 to 3.60)	1.47 (1.29 to 1.67)	1.47 (1.17 to 1.86)	1.61 (1.29 to 2.00)	1.62 (1.38 to 1.91)
35 to 39	1.66 (1.46 to 1.90)	1.69 (1.40 to 2.04)	1.97 (1.59 to 2.43)	2.86 (2.67 to 3.06)	1.39 (1.30 to 1.50)	1.32 (1.14 to 1.52)	1.46 (1.28 to 1.66)	1.50 (1.41 to 1.61)
40 to 44	1.57 (1.40 to 1.76)	1.63 (1.35 to 1.96)	1.87 (1.49 to 2.36)	2.86 (2.67 to 3.06)	1.34 (1.23 to 1.48)	1.23 (1.09 to 1.39)	1.37 (1.23 to 1.52)	1.43 (1.35 to 1.50)
45 to 49	1.53 (1.39 to 1.67)	1.57 (1.36 to 1.82)	1.78 (1.48 to 2.13)	2.49 (2.37 to 2.61)	1.32 (1.23 to 1.42)	1.21 (1.10 to 1.33)	1.34 (1.22 to 1.46)	1.39 (1.34 to 1.46)
50 to 54	1.49 (1.38 to 1.60)	1.52 (1.36 to 1.70)	1.68 (1.45 to 1.94)	2.49 (2.37 to 2.61)	1.30 (1.23 to 1.37)	1.19 (1.11 to 1.29)	1.31 (1.22 to 1.40)	1.36 (1.32 to 1.41)
55 to 59	1.45 (1.37 to 1.53)	1.47 (1.34 to 1.60)	1.58 (1.40 to 1.78)	2.16 (2.09 to 2.24)	1.27 (1.22 to 1.33)	1.18 (1.10 to 1.25)	1.28 (1.21 to 1.34)	1.33 (1.30 to 1.36)
60 to 64	1.41 (1.33 to 1.48)	1.41 (1.30 to 1.54)	1.48 (1.33 to 1.64)	2.16 (2.09 to 2.24)	1.25 (1.19 to 1.31)	1.16 (1.09 to 1.23)	1.25 (1.18 to 1.32)	1.30 (1.27 to 1.33)
65 to 69	1.36 (1.26 to 1.48)	1.36 (1.21 to 1.53)	1.38 (1.21 to 1.58)	1.88 (1.82 to 1.94)	1.22 (1.16 to 1.29)	1.14 (1.05 to 1.23)	1.22 (1.13 to 1.31)	1.26 (1.23 to 1.30)
70 to 74	1.33 (1.22 to 1.45)	1.32 (1.17 to 1.49)	1.32 (1.16 to 1.51)	1.88 (1.82 to 1.94)	1.20 (1.14 to 1.27)	1.13 (1.05 to 1.21)	1.19 (1.12 to 1.28)	1.23 (1.20 to 1.27)
75 to 79	1.30 (1.22 to 1.39)	1.28 (1.18 to 1.40)	1.31 (1.19 to 1.44)	1.63 (1.56 to 1.71)	1.18 (1.13 to 1.23)	1.12 (1.06 to 1.18)	1.18 (1.12 to 1.23)	1.21 (1.18 to 1.24)
80+	1.27 (1.13 to 1.41)	1.20 (1.11 to 1.30)	1.28 (1.13 to 1.45)	1.63 (1.56 to 1.71)	1.12 (1.07 to 1.17)	1.10 (1.04 to 1.17)	1.13 (1.07 to 1.19)	1.14 (1.09 to 1.18)

*Extracted from the GBD Study 2015 (GBD 2015) Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm HG 1990-2015. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2017. †Singh et al. (2013). PLOS ONE 8(7): e65174.

eTable 5. Assumptions and restrictions of models estimating health benefits and risk of salt substitutes in China

Model	Assumption/Restriction	Note*
Both	The estimated health benefits and harms accounts only for cardiovascular disease and chronic kidney diseases.	We did not consider potential associations of sodium intake and stomach cancer or other non-cardiovascular diseases.[12]
	The effects of the intervention is not different between provinces.	Current availability of province-specific input data does not allow stratification by province.
Blood pressure	All beneficial effects on CVD from replacing regular salt with salt substitutes are mediated through blood pressure.	We did not consider potential benefits on cardiovascular health independent of blood pressure (e.g., reduced vascular stiffness and fibrosis from reduced sodium intake)[12]
	The effects of the salt substitute intervention on blood pressure were assumed to be the same as observed in the ongoing Salt Substitute and Stroke Study (SSaSS).	Sensitivity analyses assuming alternative estimates of intervention coverage and blood pressure effects were conducted.
	The blood pressure effect of the intervention increases with age in the age interval 40-80y.	The SSaSS (where age-treatment interaction was assessed) includes almost exclusively participants aged 40-80 y at baseline.[4]
	The relationship of blood pressure and cardiovascular disease follows a log-linear dose-response until a systolic blood pressure level of 110 mm Hg, below which no further lowering of risk was assumed.	Consistent with the approach of the Global Burden of Disease study.[6]
	Rheumatic heart disease, endocarditis, and myocarditis were included in the modelling of CVD mortality but not incident CVD or CVD-attributed DALYs.	Although these CVD subtypes are caused by infection or autoimmune responses, high SBP has been associated with an increasing risk of fatal heart failure which is considered an intermediate cause of death. [9]
	The benefits on blood pressure and cardiovascular disease were assumed to be concurrent.	Consistent with the approach of Webb et al., 2017. [12]
	The effects of salt substitutes on blood pressure and blood pressure on CVD were the same in CKD patients as in the whole adult population	Sodium reduction lowers blood pressure in CKD. [20]
	CKD awareness (i.e., proportion of individuals with CKD aware of their condition) varies by CKD stage, but was assumed to be equal over age-sex strata: 14% (95% uncertainty interval: 12 to 16).	Age and sex were not associated with CKD awareness in the China national survey of CKD.[17]
Potassium	The daily intake of potassium was calculated as 1.3 times the 24h urinary potassium excretion.	As described by Aburto et al, 2013.[14]
	No difference between CKD patients and the whole population in potassium intake.	Generally low potassium intake and low awareness of CKD in China.[17 21]
	All harms of dietary K on CVD mortality are mediated through serum K.	Increased potassium has no adverse effects on blood lipid concentrations, catecholamine concentrations, and renal function.[14]
	The increase in dietary K from salt substitutes has no effect on serum K in individuals with eGFR≥ 60 mL/min per 1.73 m^2.	In general, no clinically relevant effects of increased potassium intake on serum potassium in individuals with eGFR≥60 mL/min per 1·73 m^2.[22 23]
	The relationship of dietary K and serum K is assumed to be 2 × in CKD stage G3b (eGFR 30-44) compared to stage G3a (eGFR 45 to 59). Stage-specific estimates are presented in Table 1.	In lack of reliable data, we assumed that the same increase in intake will result in 100% greater increase in serum potassium compared to CKD stage 3a (eGFR 45 to 59).
	The relationship of dietary K and serum K is assumed to be 4 × in CKD stage G4 (eGFR 15-29) compared to CKD stage G3a (eGFR 45 to 59). Stage-specific estimates are presented in Table 1.	In lack of reliable data, we assumed that the same increase in intake will result in 300% greater increase in serum potassium compared to CKD stage 3a (eGFR 45 to 59).
	The relationship of dietary K and serum K is assumed to be 8 × in CKD stage G5 (eGFR<15) compared to CKD stage G3a (eGFR 45 to 59). Stage-specific estimates are presented in Table 1.	In lack of reliable data, we assumed that the same increase in intake will result in 700% greater increase in serum potassium compared to CKD stage 3a (eGFR 45 to 59).
	Within each CKD stage, no difference in serum K between Chinese and other nationalities.	No evidence of between-country differences in serum K concentration.[16]
	Linear relationship between eGFR level and serum K concentration.	As suggested by Kovesdy et al., 2018.[16]
	No difference between CKD stages in the association of serum K and CV mortality	No evidence of strata-specific associations.[16]
	Hazard ratios of serum K >6.5 mmol/L are assumed to be equal to that of serum K = 6.5 mmol/L.	Kovesdy et al., did not report HR for serum K>6.5 mmol/L.[16]
	Hazard ratios of serum K <4.2 mmol/L are assumed to be equal to that of serum K = 4.2 mmol/L.	Kovesdy et al., reported no significant increased risk of CV mortality at serum K<4.2 mmol/L compared to 4·2 mmol/L.[16]
	The increases on serum K concentration and hyperkalemia-related CV mortality were assumed to be concurrent.	

*See reference section for cited publications.

eTable 6. Model inputs and assumptions in 1-way deterministic sensitivity analyses.

Parameter	Assumption	Reference*	Model input
Intervention coverage			
Base model	The effects of the salt substitute intervention on blood pressure and potassium intake were assumed to be the same as observed in the Salt Substitute and Stroke Study (SSaSS), an open, large-scale, cluster-randomized controlled trial currently conducted in 600 villages across 5 provinces in rural areas of Northern China. Salt substitutes containing 30±10% KCl are provided free-of-charge to participants in villages assigned to the intervention group and are accompanied by advice to use the salt substitutes instead of regular salt for all cooking, seasoning, and food preservation purposes. In addition, participants in the intervention villages are advised to use the salt substitutes sparingly and not more frequently than when they consumed regular salt. Participants in control villages continue their usual practice and received general advice about stroke prevention including recommendations to reduce salt intake at the initiation of the trial. Salt substitute use was reported by 97.5% of participants in intervention villages, vut the extent of use (i.e., amount and frequency) and proportion of regular salt replaced is unknown.	SSaSS *(unpubl.)*†	100% of effects on blood pressure and potassium intake observed in SSaSS.
Sensitivity analyses			
Greater use of salt substitutes	Assuming that the usage of salt substitutes would be 50% greater than in SSaSS, leading to 50% greater effects on blood pressure and potassium intake.	SSaSS *(unpubl.)*†	150% of effects on blood pressure and potassium intake observed in SSaSS.
Lower use of salt substitutes	Assuming that the usage of salt substitutes would be 50% lower than in SSaSS, leading to 50% lower effects on blood pressure and potassium intake.	SSaSS *(unpubl.)*†	50% of effects on blood pressure and potassium intake observed in SSaSS.
CKD awareness			
Base model	Awareness of CKD diagnosis was not considered (i.e., all adults consume salt substitutes) as most (86%) Chinese with eGFR<60 mL/min per 1.73m^2 are unaware of their CKD status.		All individuals with CKD consume salt substitutes.
Sensitivity analyses			
All CKD patients aware of diagnosis avoid salt substitutes	We assumed CKD patients aware of diagnosis avoid salt substitutes (i.e., no effects on blood pressure and potassium intake). Proportions of CKD patients aware of diagnosis were estimated from CKD prevalence and awareness among CKD patients		Awareness per CKD stage: G3a: 9.7 % (95% CI: 9.1, 10.1) G3b: 17.6 % (95% CI: 13.1, 22.1) G4: 26.8 % (95% CI: 15.2, 37.9) G5: 48.6 % (95% CI: 27.6, 72.6)
Blood pressure effects			
Base model	The effects of the salt substitute intervention on blood pressure and potassium intake were assumed to be the same as observed in the ongoing SSaSS, where salt substitutes were promoted and provided free of charge. Evaluation of data from interim measurements (1-3 y after baseline) of n=4,705 individuals in SSaSS, revealed that the use of salt substitutes lowered systolic blood pressure with greater reductions at older ages.	SSaSS *(unpubl.)*†	-2.82 (-4.75 to -0.89) mmHg at age 65 y, with 0.13 (-0.02 to 0.27) mmHg lesser or greater reduction for each year of age below or above 65 y, respectively.
Sensitivity analyses			
Meta-analysis by Peng et al.	The effects of the salt substitute intervention on systolic blood pressure was assumed to be the same as estimated in a meta-analysis of trials (n=6 comparisons [n=5 in Chinese populations], total n= 1,974 [n=1,874 Chinese]) evaluating the blood pressure effects of salt substitutes. Moderating effects of sex or age on the effects of salt substitutes on systolic BP were not evaluated. When stratified by hypertension status, significant reduction in systolic blood pressure was only observed among hypertensives.	[1]	-4.91 (-7.29 to -2.54) mmHg, with no age-treatment interaction evaluated.
Meta-analysis by Newburry et al. (n=13 comparisons; total n= 5,310)	The effects of the salt substitute intervention on systolic blood pressure was assumed to be the same as estimated in a meta-analysis of trials (n=13 comparisons [n=5 in Chinese populations], total n= 5,310 [n=4,491 Chinese]) evaluating the blood pressure effects of potassium-enriched salt substitutes. The authors stated that evidence was insufficient to draw conclusions regarding the moderating effects of sex, age, or blood pressure status on the effects of salt substitutes on systolic BP.	[2]	-5.58 (-7.08; -4.09) mmHg, with no evident age-treatment interaction.
Meta-analysis by Hernandez et al.	The effects of the salt substitute intervention on systolic blood pressure was assumed to be the same as estimated in a meta-analysis of trials (n=16 comparisons [n=7 in Chinese populations], total n= 1,933 [n=1,553 Chinese]) evaluating the blood pressure effects of salt substitutes. Moderating effects of sex, age, or blood pressure status on the effects of salt substitutes on systolic BP were not evident. In the same report, the effects of the salt substitute intervention on urinary potassium excretion were estimated by meta-analysis of salt substitute trials (n=10 comparisons [n=4 in Chinese populations], total n= 870 [n=372 Chinese]). In line with our base	[2]	Systolic blood pressure: -7.81 (-9.47; -6.15) mmHg, with no evident age-treatment interaction. Potassium intake: 0.45 (0.33, 0.57) g/d

	model, we multiplied the increase in 24h urinary potassium excretion (11.5 mmol/d [95% CI: 8.4, 14.6]) by a factor 1.3 to estimate the corresponding increase in potassium intake.		
No effect in normotensives	The effects of the salt substitute intervention on blood pressure and potassium intake were assumed to be only present in hypertensives not among normotensives. When stratified by hypertension status, salt substitutes in SSaSS lowered systolic blood pressure significantly in hypertensives, but not in normotensives. Sex-specific mean prevalence of hypertension in ages (35-75 y) were extrapolated in ages 25-34y and >75y (eTable 1), based on estimates from 1.7 million adult Chinese (Lu et al., Lancet 2017).	SSaSS *(unpubl.)*†	Hypertensives: -2.96 (-5.06 to -0.86) mmHg at age 65 y, with 0.17 (0.00 to 0.35) mmHg lesser or greater reduction for each year of age below or above 65 y, respectively. Normotensives: 0 mmHg.
Potassium diet-serum relationship			
Base model	The effects on serum potassium of increased dietary potassium in individuals with CKD stage G3a is assumed to be equal to the effect observed in a randomized clinical trial with cross-over design where CKD patients were randomized to a sequence of diets high or low in potassium. The effects in more advanced stages of CKD (i.e., G3b, G4, and G5) were assumed to be doubled by each stage due to reduced kidney function.	Turban (*unpubl.*) ‡	G3a: 0.23 (0.16 to 0.30) mmol/L per g/d G3b : 0.47 (0.33 to 0.61) mmol/L per g/d G4: 0.93 (0.66 to 1.21) mmol/L per g/d G5: 1.87 (1.33 to 2.41) mmol/L per g/d
Sensitivity analyses			
Weaker	The serum response to dietary potassium load was assumed to increase linearly with decreasing kidney function (i.e., eGFR level). Serum potassium responses to potassium dose in CKD stages G3b, G4, and G5 were estimated by extrapolating a linear regression of serum responses in G3a patients (0.23 [95% CI: 0.16 to 0.30] mmol/L per g/d) and in individuals without impaired kidney function (0.08 [95% CI: 0.05 to 0.11] mmol/L per g/d) regressed against eGFR 54.5 (i.e., mean in trial on G3a patients) and 75 mL/min per 1.73 m^2, respectively. Standard error of the mean serum potassium response was assumed to increase proportionally with the mean.	Turban (*unpubl.*)‡ [24]	G3a: 0.23 (0.16 to 0.30) mmol/L per g/d G3b: 0.36 (0.25 to 0.47) mmol/L per g/d G4: 0.47 (0.33 to 0.61) mmol/L per g/d G5: 0.59 (0.41 to 0.76) mmol/L per g/d
Stronger	The serum response to dietary potassium load was assumed to increase exponentially with decreasing kidney function (i.e., eGFR level). Serum potassium responses to potassium dose in CKD stages G3b, G4, and G5 were estimated by extrapolating an exponential regression of serum responses in G3a patients (0.23 [95% CI: 0.16 to 0.30] mmol/L per g/d) and in individuals without impaired kidney function (0.08 [95% CI: 0.05 to 0.11] mmol/L per g/d) regressed against eGFR 54.5 (i.e., mean in trial on G3a patients) and 75 mL/min per 1.73 m^2, respectively. Standard error of the mean serum potassium response was assumed to increase proportionally with the mean.	Turban (*unpubl.*) ‡ [24]	G3a: 0.23 (0.16 to 0.30) mmol/L per g/d G3b: 0.57 (0.41 to 0.74) mmol/L per g/d G4: 1.25 (0.89 to 1.61) mmol/L per g/d G5: 2.73 (1.94 to 3.52) mmol/L per g/d
Equal in CKD stages G3a-5	The same serum response to dietary potassium load estimated in CKD stages G3a (0.23 [95% CI: 0.16 to 0.30] mmol/L per g/d) was assumed for stages G3b, G4, and G5.	Turban (*unpubl.*) ‡	G3a: 0.23 (0.16 to 0.30) mmol/L per g/d G3b: 0.23 (0.16 to 0.30) mmol/L per g/d G4: 0.23 (0.16 to 0.30) mmol/L per g/d G5: 0.23 (0.16 to 0.30) mmol/L per g/d
Standard deviation of systolic blood pressure			
Base model	Based on age and-sex specific SBP distributions estimated in over 500,000 Chinese,[7] we assumed the standard deviation of systolic blood pressure in each stratum was equal to 15% of the mean for that specific stratum.	[7]	15%
Sensitivity analyses			
Smaller standard deviation	We assumed the standard deviation of systolic blood pressure in each stratum was equal to 10% of the mean for that specific stratum.	n/a	10%
Larger standard deviation	We assumed the standard deviation of systolic blood pressure in each stratum was equal to 20% of the mean for that specific stratum.	n/a	20%

eTable 7. Estimated intervention effects on cardiovascular mortality by CKD stage from a nation-wide salt-substitute intervention where discretionary salts (i.e., salt used at table and in cooking) are replaced with potassium-enriched salt substitutes. *,†,-‡

CKD Stage	G3-5	G3a	G3b	G4	G5
eGFR, mL/min per 1·73 m2	<60	45-59	30-44	15-29	<15
Prevalence in thousands (95% UI)	17,193 (14,564 to 19,659)	13,909 (11,928 to 15,944)	1,949 (1,036 to 2,977)	999 (342 to 1,720)	298 (100 to 495)
Current CVD deaths (95% UI)[§]	286,124 (204,675 to 386,141)	185,946 (123,147 to 279,885)	44,708 (20,719 to 87,250)	32,511 (10,066 to 68,802)	16,854 (4,911 to 38,025)
Additional CVD deaths (95% UI)	10,583 (6,422 to 16,562)	3,616 (1,996 to 6,218)	1,984 (820 to 4,344)	2,689 (773 to 6,326)	1,740 (277 to 5,185)
Total averted CVD deaths (95% UI)	32,192 (54,453 to 12,261)	n/a[¶]	n/a[¶]	n/a[¶]	n/a[¶]
Net averted CVD deaths (95% UI)	21,425 (1,928 to 42,926)	n/a[¶]	n/a[¶]	n/a[¶]	n/a[¶]

[*]See table 1 and eTable 1-5 for information on input data and model assumptions. [†]The effect of disease burden (i.e., events and deaths) from the intervention was estimated by calculation of the potential impact factor (PIF) each stratum. [‡]Uncertainty was quantified using Monte Carlo simulation (n=1000). For each simulation, a draw was made from the input data. Each draw was used to calculate for each eGFR stratum both the PIF and the additional number of deaths. The uncertainty intervals for each stratum then represent the 2.5-97.5 percentiles of the distribution of the intervention effects estimated across all 1000 simulations for that stratum. [§]Estimated from CKD prevalence, crude hazard ratio of cardiovascular mortality by eGFR level, and current (2015) CV mortality in the adult Chinese population. [¶]Stage-specific CKD prevalence was not available for age-sex groups and thus averted and net CVD deaths were not modelled per CKD stage but only for total CKD patients (i.e., eGFR<60 mL/min per 1.73 m^2).