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Adding salt to foods and hazard of premature mortality

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INTRODUCTION

The relationship between dietary salt intake and health remains a subject of longstanding debate. A recent ecological study has rekindled this controversy by reporting that sodium intake was inversely associated with risk of all-cause mortality and positively associated with healthy life expectancy in 181 countries worldwide[1]. Notably, previous studies investigating the association between sodium intake and risk of mortality have produced conflicting results, showing positively linear [2-4], J-shaped [5, 6], or inversely linear associations[7-9].

The low accuracy of sodium measurement is an important reason for the inconsistent results related to sodium intake and disease outcomes in previous studies[10, 11]. Sodium intake varies widely from day to day. However, the majority of previous studies have largely relied on a single day's urine collection or dietary survey for estimating the sodium intake, which is inadequate to assess an individual's usual consumption levels[10, 12]. Moreover, it is difficult to separate contributions of intakes of sodium and potassium to health based on current methods for measuring dietary sodium and dietary potassium[2, 5, 13, 14], since both the dietary intake and metabolism of sodium in the kidneys are closely related to potassium[15-17]. Notably, such two essential cations have opposite biological effects on the human health[17-20], thus their collinearity may confound the association between sodium intake and health outcomes. The hypothesis that the high-potassium intake may attenuate the adverse association of high-sodium intake with health outcomes has been proposed for many years[3, 21], whereas the studies particularly assessing interaction between sodium intake and potassium intake on the risk of mortality are scarce[14].

Adding salt to foods (usually at the table) is a common eating behavior directly related to

individual's long-term preference to salty taste foods and habitual salt intake[22, 23]. Indeed, in western diet, adding salt at the table accounts for 6-20% of total salt intake[24, 25]. In addition, the commonly used table salt contains 97 to 99% sodium chloride, minimizing the potential confounding effects of other dietary factors including potassium. Therefore, adding salt to foods provides a unique assessment to evaluate the association between habitual sodium intake and mortality. However, very few studies have investigated the association between the frequency of adding salt to foods and mortality[26].

In this study, we analyzed association between the frequency of adding salt to foods and hazard of premature mortality and life expectancy.

METHODS

Study population

The UK Biobank study is a population-based cohort study; the study design and methods have been described in detail previously[27]. In brief, more than 0.5 million participants (5.5% response rate) were recruited in the baseline survey at 22 assessment centers throughout England, Wales, and Scotland from 2006 to 2010. Individuals were invited to participate on a voluntary basis if they lived within 25 miles of a UK Biobank assessment center and were registered with the UK National Health Service (NHS). Data from 502,505 participants were available for our study, we excluded 1126 participants with incomplete data on the frequency of adding salt to foods, a total of 501,379 participants were included in the main analysis. All participants provided written informed consent, and the study was approved by the North West Multi-Centre Research Ethics Committee and the Tulane University (New Orleans, LA) Biomedical Committee Institutional Review Board.

Exposure Assessment

Participants were asked "Do you add salt to your foods? (Do not include salt used in cooking)" through a touch-screen questionnaire at baseline (2006-2010). Participants selected one answer from five options: 1) never/rarely; 2) sometimes; 3) usually; 4) always; 5) Prefer not to answer. Those prefer not to answer were assigned to missing value.

In addition, participants were also asked "Have you made any major changes to your diet in the last 5 years" through the questionnaire at baseline. Participants selected one answer from five options: 1) No; 2) Yes, because of illness; 3) Yes, because of other reasons; 4) Prefer not to answer.

Urine samples (a random urinary spot) were collected at baseline (481,565 participants were available for our study). Urinary sodium and potassium were measured in stored urine samples by the Ion Selective Electrode method (potentiometric method) using Beckman Coulter AU5400, UK Ltd. Details of assays and quality control information for the urinary sodium and potassium are available elsewhere (https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/urine_assay.pdf). Concentrations of spot urinary sodium and potassium were log transformed to normalize the distribution of the data. The 24-h sodium excretion was estimated from the casual (spot) urinary concentration values based on the sex-specific INTERSALT equations[28, 29].

Participants were also invited to complete the 24-h dietary recalls conducted using the Oxford WebQ between 2009 and 2012. The Oxford WebQ asks about the consumption of >200 types of foods and >30 types of drinks during the previous 24 h. The detailed description and accuracy of the dietary assessment have been described elsewhere[30, 31]. Of 210,999 participants

who completed at least one dietary recall (1-5 times), we included 189,266 participants who had both complete data on the frequency of adding salt to foods at baseline and complete data on dietary information and had realistic total energy intake (e.g., 500–3,500 kcal/day in women and 800–4,000 kcal/day in men)[32]. We excluded 24-h dietary assessments where participants indicated that their diet for that day was not typical because of illness, fasting or other reasons. The mean values of total energy, red meat, processed meat, fish, vegetable and fruit were used in this study.

Ascertainment of premature mortality and life expectancy

Information on death and death date was obtained by reviewing the death certificates held by the National Health Service Information Centre for participants in England and Wales and the National Health Service Central Register Scotland for participants from Scotland. Person-years at risk was calculated from the date of assessment center attended until the date of lose to follow-up, the date of death or February 14, 2018, whichever came first. Deaths that occurred at ages younger than 75 were defined as premature[33]. Detailed information on causes of deaths described in the **Supplementary method**.

To calculate the life expectancy of participants with distinct frequency of adding salt to foods, we used life table[34, 35]. We built the life tables starting at age 45 years and ending at age 100 years with the following 3 estimates to calculate the cumulative survival from 45 years onward: (1) the sex- and age-specific population mortality rate from the Office for National Statistics (https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/singleyearlifetablesuk1980to2018/singleyearlifetablesuk); (2) the sex-specific hazard ratios (HRs) of all-cause mortality in each exposure group (frequency of adding salt to

foods) versus the reference; (3) the sex-specific prevalence of each frequency of adding salt to foods. The estimated lower survival time (years) due to high due to high frequency of adding salt to foods was estimated as difference in the life expectancy at any given age between the reference group and each of the exposure group. Details of the methods used for estimating the difference in expected survival time have been described in **supplemental materials**.

Statistical Analysis

We used general linear models to evaluate the associations between frequency of adding salt to foods and concentrations of spot urinary sodium, spot urinary potassium or estimated 24-h sodium excretion. Rate estimates for all-cause premature mortality were expressed as HRs with 95% confidence interval (CI) and calculated by using Cox proportional hazards models with the follow-up time as the time scale. The proportional hazards assumption was tested by Kaplan-Meier method and Schoenfeld residuals method. Several potential confounders were adjusted in these models, including age, sex, race, Townsend deprivation index, body mass index (BMI), smoking status, moderate drinking, regular physical activity, diabetes, high cholesterol, chronic kidney disease (CKD), cardiovascular diseases, cancer and dietary factors (red meat intake, processed meat intake, fish intake, vegetable intake, fruit intake and total energy). Details of the assessment of covariates are described in **supplemental materials**. For analyses about estimated 24-h sodium excretion, because the sex-specific INTERSALT equations included age and BMI, we did not adjust for age and BMI in the model.

We performed stratified analyses by following factors[10, 36, 37]: sex (women or men), age (<60 or ≥ 60 years), race/ethnicity (whites or non-whites), Townsend deprivation index (<median or ≥ median), BMI (<25, 25-30 or ≥30 kg/m^2), regular physical activity (<150 min/week or ≥150

min/week), smoking (never, past, current), moderate drinking (yes or no), hypertension (yes or no) and high cholesterol (yes or no), total energy (tertiles), total vegetables and fruits intake (tertiles), vegetables intake (tertiles), fruits intake (tertiles) and urinary potassium (quintiles 1, quintiles 2-4 or quintiles 5). To evaluate interactions between the frequency of adding salt to foods and these factors, multiplicative interaction was assessed by adding interaction terms to the Cox models.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc) and R version 3.6.1. We used Monte Carlo simulation (parametric bootstrapping) with 10 000 runs to calculate the CIs of the life expectancy estimation with boot R package. All statistical tests were two sided, and we considered $P<0.05$ to be statistically significant.

RESULTS

Basic characteristics of participants according to the frequency of adding salt to foods

Basic characteristics of participants according to the frequency of adding salt to foods are shown in **Table 1**. Compared with participants with lower frequency of adding salt to foods, participants with higher frequency were more likely to be male; non-white; and to have a higher BMI and Townsend deprivation index; they were less likely have a healthy lifestyle (moderate drinking, non-current smoking, regular physical activity); and had higher a prevalence of diabetes and cardiovascular diseases but a lower prevalence of hypertension and CKD. For dietary factors, higher frequency of adding salt to foods was associated with higher intake of red meat and processed meat but lower intake of vegetable, fruit and fish.

Association of the frequency of adding salt to foods with concentrations of urinary sodium

and potassium

Figure 1A shows the concentrations of urinary sodium and urinary potassium according to the frequency of adding salt to foods. Urinary sodium and potassium were highly correlated, with a person correlation of 0.46. After adjustment for covariates, we found a graded relationship between higher frequency of self-reported adding salt to foods and higher concentrations of spot urinary sodium. The concentrations of spot log-urinary sodium were 1.86 (95% CI 1.86-1.87), 1.90 (1.89-1.90), 1.92 (1.91-1.92) and 1.94 (1.94-1.95) mmol/L, in "never/rarely", "sometimes", "usually" and "always" groups, respectively (*P*-trend <0.001). In contrast, an inverse relationship between frequency of adding salt to foods and concentrations of spot urinary potassium was observed **(Figure 1A)**, the corresponding concentrations of spot log-urinary potassium were 1.68 (95% CI 1.68-1.68), 1.67 (1.67-1.67), 1.66 (1.66-1.67) and 1.65 (1.64-1.65) mmol/L across groups (*P*-trend <0.001).

Similar with results of spot urinary sodium, we found a significantly positive association between the frequency of adding salt to foods and the estimated 24-h sodium excretion. The estimated 24-h sodium excretion were 3.34 (3.33-3.35), 3.41 (3.40-3.42), 3.45 (3.44-3.46) and 3.50 g (3.49-3.51) **(Figure 1B)**.

Association between the frequency of adding salt to foods and hazard of premature mortality

Table 2 shows association between the frequency of adding salt to foods and hazard of all-cause premature mortality. During a median follow-up of 9.0 years, we documented 18,474 incident cases of all-cause premature death. After adjustment for sex, age, race, smoking, moderate drinking, BMI, physical activity, Townsend deprivation index, high cholesterol, CKD,

diabetes, cardiovascular disease and cancer, we found the hazard of all-cause premature mortality increased monotonously with increasing frequency of adding salt to foods. The adjusted HRs were 1 (reference), 1.02 (95% CI 0.99-1.06), 1.07 (1.02-1.11) and 1.28 (1.20-1.35) across groups, respectively (*P*-trend <0.001). These results did not change appreciably after further adjustment for hypertension, or urinary potassium; or dietary factors (vegetable, fruit, fish, red meat, processed meat intake and total energy); or excluding participants with CKD, diabetes, cardiovascular disease or cancer at baseline; or excluding participants who had changed their diet in last 5 years due to illness or other reasons. In addition, the results did not change appreciably if attained age was used as the time scale in the Cox proportional hazards model.

For cause-specific mortality, we found that higher frequency of adding salt to foods was significantly associated with higher hazard of premature cardiovascular disease mortality and cancer mortality (*P*-trend <0.001 and *P*-trend <0.001, respectively) **(Supplementary Table 1)**, but not for dementia mortality or respiratory mortality (*P*-trend =0.98 and *P*-trend =0.07, respectively). For the subtypes of cardiovascular disease mortality, we found that higher frequency of adding salt to foods was significantly associated with higher hazard of stroke-mortality but not coronary heart disease mortality (*P*-trend=0.002 and *P*-trend=0.25, respectively) **(Supplementary Table 1)**.

Association between the frequency of adding salt to foods and hazard of premature mortality stratified by potential risk factors

We also conducted stratified analyses according to the potential risk factors including sex, age, race, BMI, Townsend deprivation index, regular physical activity, smoking, moderate

drinking, hypertension, high cholesterol, levels of urinary potassium, total energy and high potassium foods (vegetable and fruit) **(Table 3)**. Interestingly, we found the positive association of adding salt to foods with hazard of all-cause premature mortality appeared to be attenuated with increasing levels of total vegetables and fruits intake (*P*-interaction =0.02). Higher frequency of adding salt to foods was significantly associated with higher hazard of premature mortality in participants with low level of total vegetables and fruits (*P*-trend =0.02), whereas the association was not significant in those with high level total vegetables and fruits (*P*-trend =0.90). Similar interaction patterns were also observed for fruits intake and urinary potassium (*P*-interaction =0.02 and =0.01, respectively). The joint associations between the frequency of adding salt to foods and total fruits and vegetables intake or urinary potassium in relation to hazard of premature mortality are also shown in **Figure 2**.

We also found the positive association between the frequency of adding salt to foods and hazard of all-cause premature mortality appeared to be attenuated with increasing BMI level (*P*-interaction <0.001), and the association was not significant in obese participants (BMI $\geqslant$ 30 kg/m^2). Notably, the observed significant interaction between BMI and the frequency of adding salt to foods was abolished after excluding ever-smokers **(Supplementary Table 2).** We did not find significant interactions between other potential confounders and the frequency of adding salt to foods on hazard of all-cause premature mortality.

Association between the frequency of adding salt to foods and estimated life expectancy

We estimated the lower survival time (years) due to the high frequency of adding salt to foods. At age 50, women who always adding salt to food had an average 1.50 (95% CI 0.72-2.30) lower years of life expectancy, and men who always adding salt had an average 2.28 (95% CI

1.66-2.90) lower years of life expectancy, as compared with their counterparts who never/rarely adding salt to foods **(Figure 3)**. The corresponding lower years of life expectancy at the age of 60 years were 1.37 (95% CI 0.66-2.09) and 2.04 (95% CI 1.48-2.59) years in women and men, respectively.

DISCUSSION

In this prospective study of 501,379 participants from UK Biobank, we found that higher frequency of adding salt to foods was significantly associated with a higher hazard of premature mortality and lower life expectancy, independent of diet, lifestyle, socioeconomic level and pre-existing diseases. We found that the positive association appeared to be attenuated with increasing intakes of high-potassium foods (vegetables and fruits) (Graphical Abstract).

Our study provides novel evidence to show the adverse relation between sodium intake and mortality. In western diet, it is difficult to estimate sodium intake using traditional dietary assessment methods because of the most sodium is typically hidden in processed foods and vary from brand to brand[11]. The 24-hour urine collections are the recommended method for monitoring population sodium intake. However, such methods are not sufficient to assess an individual's usual salt intake because of the large day-to-day variability in sodium consumption and salt excretion[12, 38-40]. Relying on data measured in a single day lead to considerable random errors in sodium assessment, which may severely confound or even alter the direction of association between sodium intake and health outcomes[10, 41] In this study, instead of assessing the amount of sodium intake, we provided a unique perspective to evaluate the association between salt usage behaviors and mortality. The frequency of adding salt to foods reflects a

person's long-term salt taste preference, and it is less likely to be affected by the large day-to-day variations in sodium intake[22, 23]. Indeed, there were strong positive correlations between adding salt and concentrations of objective measured urinary sodium, evidenced by the observations in our study. We found higher frequency of adding salt to foods was significantly associated with a higher hazard of all-cause premature mortality. Very few previous studies have examined the relationship between the frequency of adding salt to foods and health outcomes. Our findings are consistent with the results reported in an Australian elderly male community population, in which higher frequency of adding salt to foods were associated with higher risk of all-cause mortality[26]. Moreover, for the first time, we reported that always adding salt to foods was associated with the lower life expectancy at age 50 years by 1.50 (95% CI 0.72-2.30) and 2.28 (95% CI 1.66-2.90) years for women and men, respectively, compared with participants who never or rarely added salt to foods.

Our results on the premature cause-specific mortality indicate that the increased hazard of all-cause mortality associated with more frequent addition of salt to foods could be partly attributed to cardiovascular disease and cancer-specific mortality. Such observations are consistent with previous evidence linking salt intake with various conditions including cardiovascular disease and cancer[42]. Evidence from experimental and epidemiological studies have shown that excessive sodium intake was related to gastric cancer[43, 44], liver cancer[45], lung cancer[46] and renal cell cancer[47]. Moreover, for the subtypes of cardiovascular disease mortality, we found that higher frequency of adding salt to foods were significantly associated with higher hazard of stroke mortality but not coronary heart disease mortality. These observations were supported by the results from the Salt Substitute and Stroke Study, in which the use of salt

substitute has a significant benefit on stroke mortality but not for coronary heart disease mortality[37]. Future investigations are warranted to explore the association of high salt intake with various cardiovascular disease subtypes.

The present findings may have several public health implications. First, the evidence is complementary to those on the quantity of salt intakes. The frequency of adding salt to foods is easily assessed in clinical and public settings, and may be useful for future dietary interventions, especially in western diet in which most of the salt intake comes from processed foods. Second, the evidence may inform the recommendations on behavioral changes regarding salt intakes. Third, the amounts of discretionary sodium intake (the salt used at the table or in home cooking) have been largely overlooked in previous studies, even though adding salt to foods accounts for a considerably proportion of total sodium intake (6-20%) in western diet[24, 25]. Our findings also support the notion that even a modest reduction in sodium intake is likely to result in substantial health benefits, especially when it is achieved in the general population[48-50].

Moreover, because the high-sodium foods is usually accompanied by high-potassium foods (i.e., taco, a typical salty food, also contains many vegetables)[15, 16], the highly positive correlation between dietary sodium and potassium intake and their opposite effects on health may be another important reason for the previous inconsistent results relating sodium intake with health outcomes[10]. Intriguingly, different from the salt already contained in foods, we found that the frequency of adding salt to foods was slightly and inversely associated with high-potassium foods intake (vegetables and fruits) and concentrations of urinary potassium. Additional adjustment for urinary potassium or high-potassium foods intake did not materially

alter the results, suggesting the observed positive association between adding salt to food and mortality was mainly driven by high sodium intake, rather than low potassium intake. Moreover, we found that the positive association between adding salt to foods and all-cause premature mortality tended to be attenuated with increasing levels of high-potassium foods intake (vegetables and fruits) or urinary potassium, lending support to the hypothesis that a high potassium intake can attenuate the adverse associations of high sodium intake with health outcomes[3, 14, 21].

The finding in subgroup analyses suggested that the positive association between the frequency of adding salt to foods and hazard of mortality appeared to be attenuated with increasing BMI level. Caution should be taken in interpreting the observations, especially given that obese persons might have higher salt sensitivity than their normal weight counterparts[51, 52]. Notably, smoking would be considered when investigating the interaction between BMI and the frequency of adding salt to foods on the hazard of mortality, because smoking is associated with a lower BMI but a higher liking for salty taste[53, 54]. The observed significant interaction between BMI and the frequency of adding salt to foods was abolished after excluding ever-smokers, suggesting that the interaction between BMI and the frequency of adding salt to foods on the hazard of mortality was at least partly driven by smoking.

The strengths of our study include large sample size, the multiple repeated measurements of dietary data and the consistent results in several sensitivity and subgroup analyses. Several potential limitations should be carefully considered in this study. Firstly, we could not exclude the possibility that high frequency of adding salt to foods is a marker for an unhealthy lifestyle or a lower socioeconomic level. However, subgroup analyses indicated that the positive

association between the frequency of adding salt to foods and hazard of mortality were consistent across the subgroups of lifestyle factors and socioeconomic level. Secondly, the frequency of adding salt to foods was unable to provide quantitative information on total sodium intake; however, the dose-response relationship between the frequency of adding salt to foods and concentrations of objectively measured urinary sodium (both spot urinary sodium and estimated 24-h sodium excretion) indicated it could reflect individual's long-term salt taste preference. Thirdly, adding salt might be related to total energy intake and other dietary components; and the residual confounding due to the collinearity with other dietary factors might still exist in this study. Fourthly, an important limitation of this study is that the UK Biobank is not representative of the general population due to the voluntary participation[27]. Further studies are needed to confirm our findings, especially in populations which are more representative of the UK population.

In conclusion, our study indicates that the higher frequency of adding salt to foods is associated with a higher hazard of all-cause premature mortality and lower life expectancy. High intakes of potassium-rich foods, such as vegetables and fruits, may attenuate the association between adding salt to foods and mortality. Further clinical trials are warranted to validate these findings.

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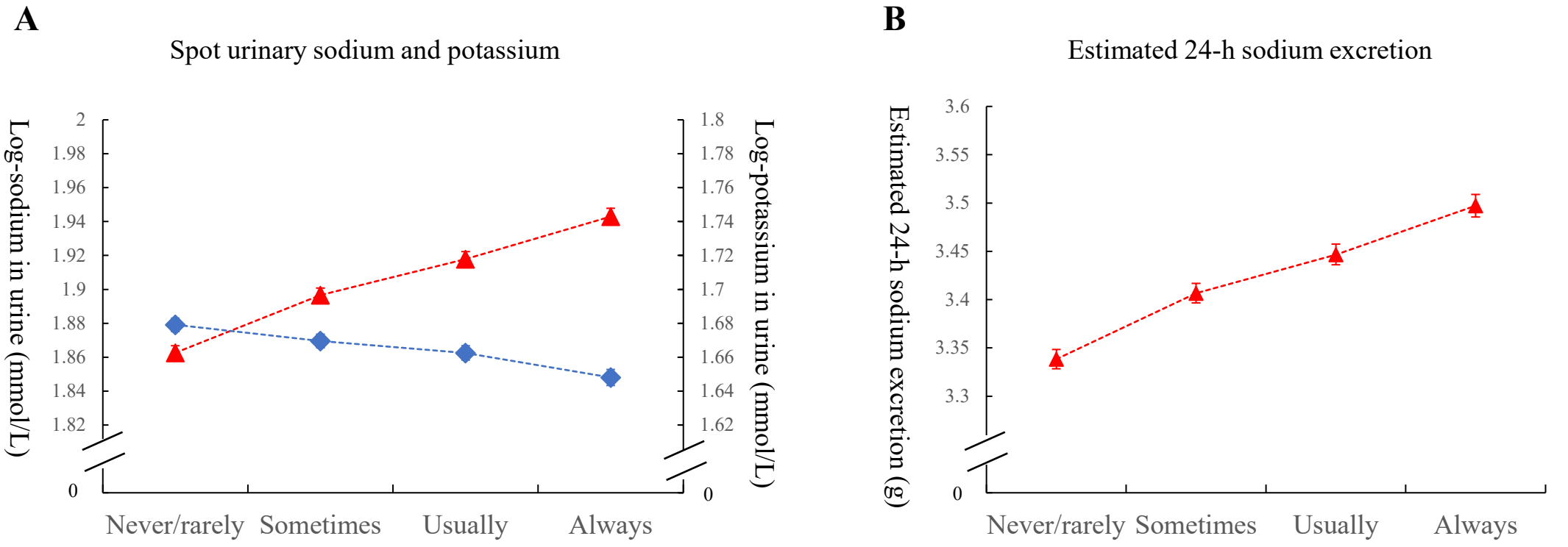
Figure 1. Concentrations of spot urinary sodium, spot urinary potassium and estimated 24-h sodium excretion by the frequency of adding salt to foods.

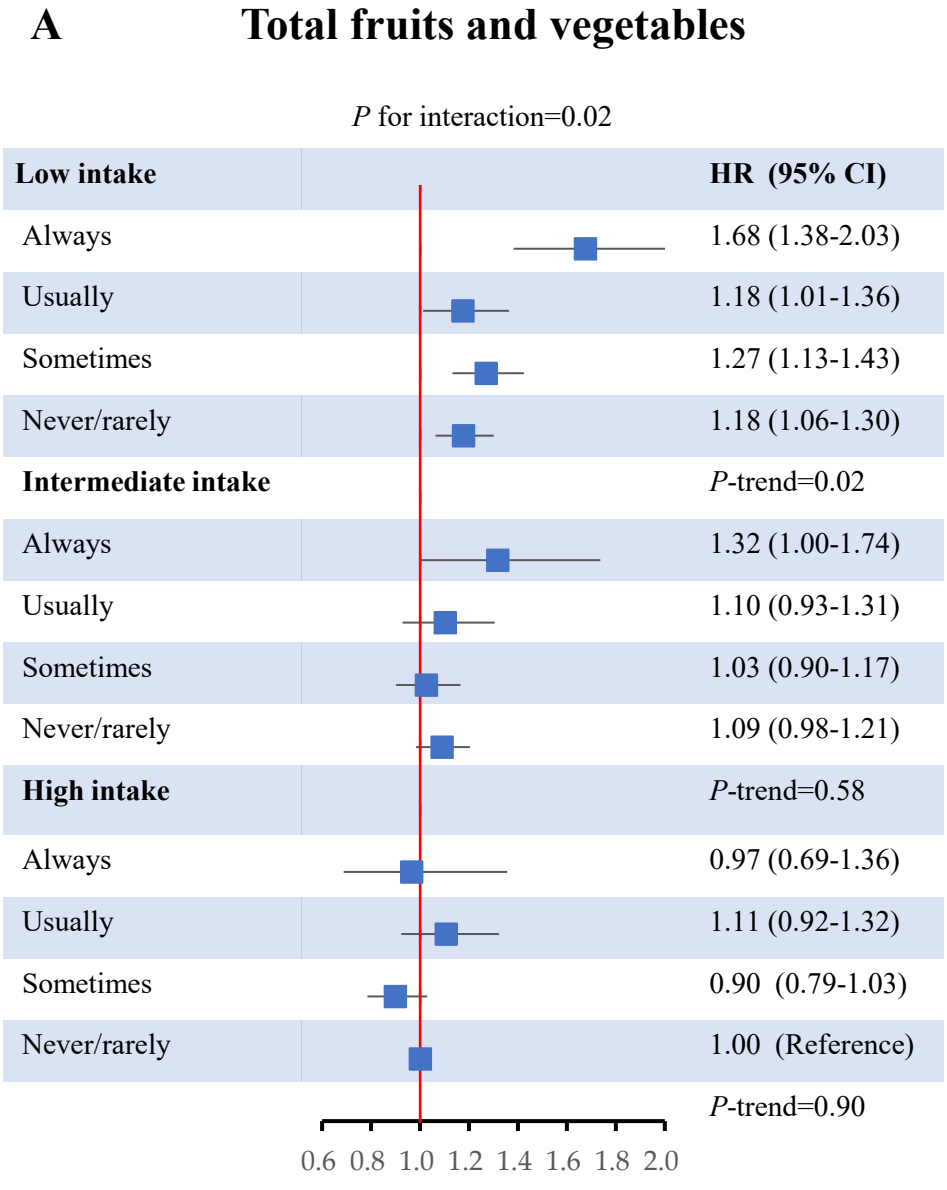
Figure 1A adjusted for sex, age, race, smoking, moderate drinking, BMI, regular physical activity, Townsend deprivation index, hypertension, high cholesterol, CKD, diabetes, cardiovascular disease and cancer, spot urinary sodium (only for analysis of potassium) and spot urinary potassium (only for analysis of sodium).
Figure 1B adjusted for sex, race, smoking, moderate drinking, physical activity, TDI, hypertension, high cholesterol, CKD, diabetes, cardiovascular disease and cancer.

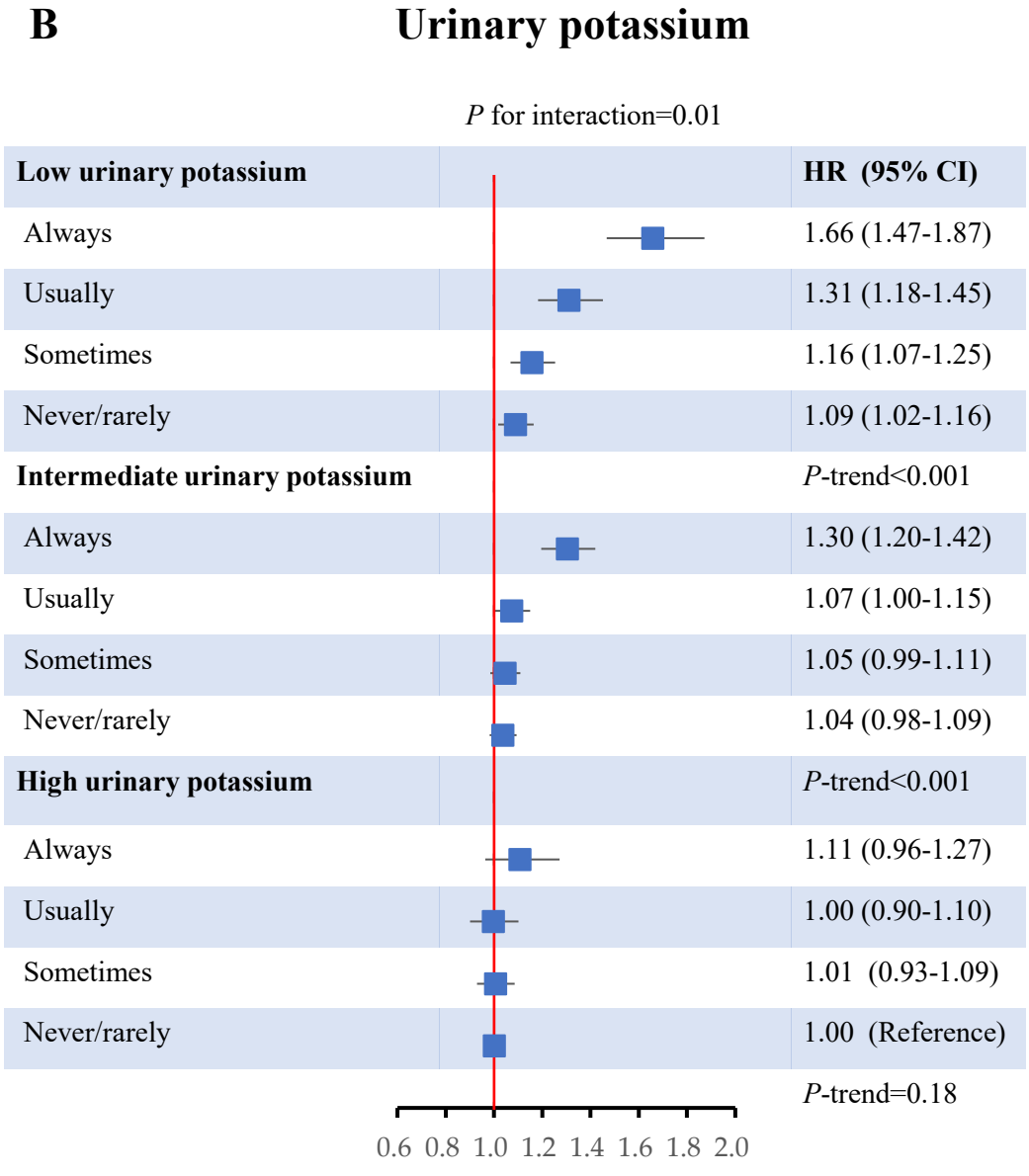
Figure 2. Joint association between total vegetables and fruits intake or urinary potassium and the frequency of adding salt to foods in relation to hazard of all-cause premature mortality.

Results were adjusted for sex, age, race, smoking, moderate drinking, BMI, physical activity, TDI, high cholesterol, CKD, diabetes, cardiovascular disease, cancer, total energy (only for Figure 2A) and dietary intake (fish intake, processes meat and red meat intake) (only for Figure 2A).

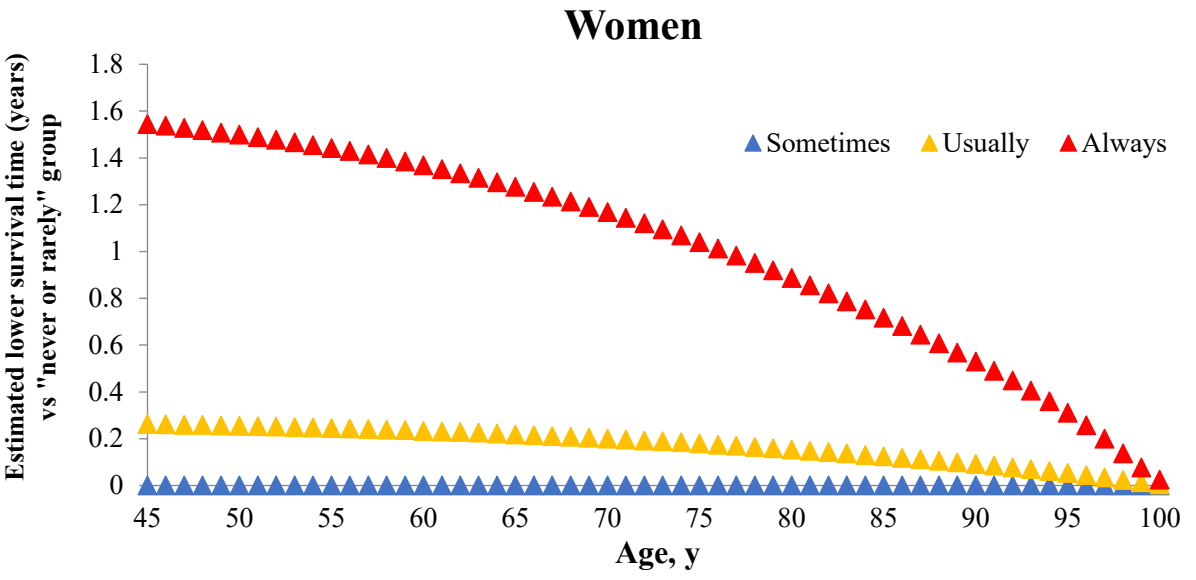
Figure 3. The estimates of cumulative survival time from 45 years of age onward among participants with distinct frequency of adding salt to foods.


A
Spot urinary sodium and potassium
Log-sodium in urine (mmol/L)
2
1.98
1.96
1.94
1.92
1.9
1.88
1.86
1.84
1.82
0
Log-potassium in urine (mmol/L)
1.8
1.78
1.76
1.74
1.72
1.7
1.68
1.66
1.64
1.62
0
Never/rarely
Sometimes
Usually
Always
B
Estimated 24-h sodium excretion
Estimated 24-h sodium excretion (g)
3.6
3.55
3.5
3.45
3.4
3.35
3.3
0
Never/rarely
Sometimes
Usually
Always


A
Total fruits and vegetables
P for interaction=0.02
Low intake
HR (95% CI)
Always
1.68 (1.38-2.03)
Usually
1.18 (1.01-1.36)
Sometimes
1.27 (1.13-1.43)
Never/rarely
1.18 (1.06-1.30)
Intermediate intake
P-trend=0.02
Always
1.32 (1.00-1.74)
Usually
1.10 (0.93-1.31)
Sometimes
1.03 (0.90-1.17)
Never/rarely
1.09 (0.98-1.21)
High intake
P-trend=0.58
Always
0.97 (0.69-1.36)
Usually
1.11 (0.92-1.32)
Sometimes
0.90 (0.79-1.03)
Never/rarely
1.00 (Reference)
P-trend=0.90
0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0


B
Urinary potassium
P for interaction=0.01
Low urinary potassium
HR (95% CI)
Always
1.66 (1.47-1.87)
Usually
1.31 (1.18-1.45)
Sometimes
1.16 (1.07-1.25)
Never/rarely
1.09 (1.02-1.16)
Intermediate urinary potassium
P-trend<0.001
Always
1.30 (1.20-1.42)
Usually
1.07 (1.00-1.15)
Sometimes
1.05 (0.99-1.11)
Never/rarely
1.04 (0.98-1.09)
High urinary potassium
P-trend<0.001
Always
1.11 (0.96-1.27)
Usually
1.00 (0.90-1.10)
Sometimes
1.01 (0.93-1.09)
Never/rarely
1.00 (Reference)
P-trend=0.18
0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0

A


Women
Estimated lower survival time (years) vs "never or rarely" group
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Sometimes
Usually
Always
45
50
55
60
65
70
75
80
85
90
95
100
Age, y

B

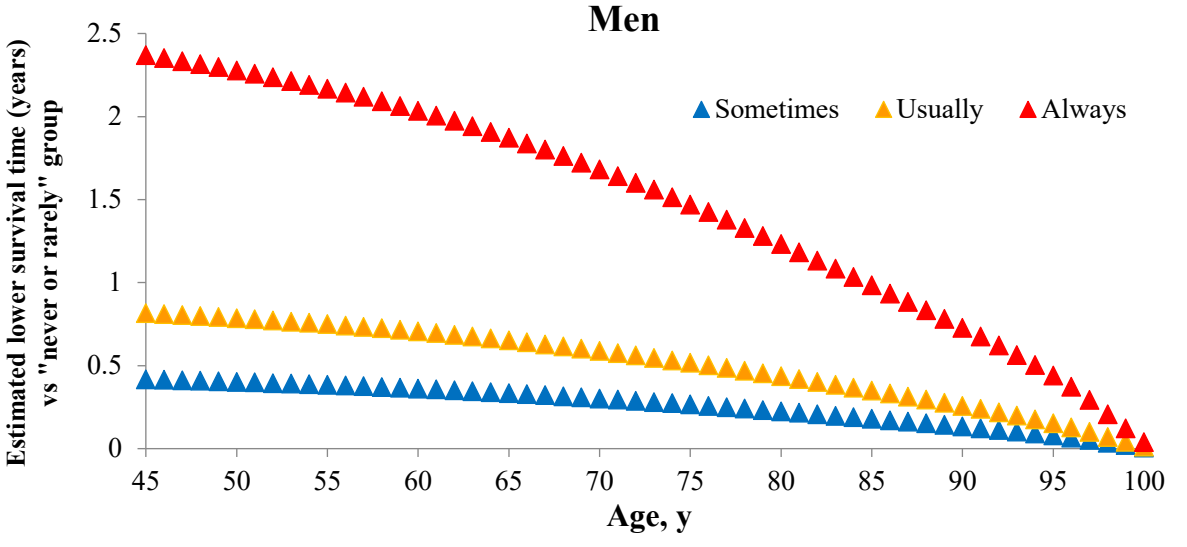

Men
Estimated lower survival time (years) vs "never or rarely" group
2.5
2
1.5
1
0.5
0
Sometimes
Usually
Always
45
50
55
60
65
70
75
80
85
90
95
100
Age, y

Table 1. Baseline characteristics according to the frequency of adding salt to foods.

	Total	***Never/rarely***	***Sometimes***	***Usually***	***Always***
Number of participants	501,379	277,931	140,618	58,399	24,431
Age, years (SD)	56.5 (8.1)	56.5 (8.1)	56.4 (8.1)	57.0 (8.0)	55.9 (8.3)
Male (%)	45.6	43.9	46.0	51.2	48.6
Whites (%)	94.3	95.5	93.4	93.4	87.6
BMI	27.4 (4.8)	27.2 (4.7)	27.7 (4.8)	27.8 (4.8)	28.1 (5.1)
Townsend deprivation index	-1.3 (3.1)	-1.5 (3.0)	-1.2 (3.1)	-1.1 (3.2)	-0.2 (3.5)
Moderate drinking (%)	45.6	47.7	45.3	41.4	33.7
Current smoking (%)	10.6	8.0	11.3	15.3	23.7
Regular physical activity (%)	60.3	61.2	60.3	58.6	54.9
Hypertension (%)	55.5	56.1	54.5	55.2	54.6
High cholesterol (%)	18.7	18.9	18.2	18.9	18.3
Diabetes (%)	5.3	5.2	5.4	5.3	5.6
CKD (%)	1.3	1.4	1.2	1.2	1.2
CVD (%)	7.1	6.9	6.9	7.5	8.8
Cancer (%)	8.8	8.7	8.8	9.2	8.8
Total energy intake, kcal/d (SD) [a]	2055.9 (555.1)	2036.8 (543.2)	2076.3 (560.5)	2101.0 (580.8)	2087.5 (617.8)
Vegetables (SVs/d, SD) [a]	4.7 (3.7)	4.8 (3.7)	4.5 (3.7)	4.4 (3.6)	4.1 (3.8)
Fruits (SVs/d, SD) [a]	3.3 (2.6)	3.5 (2.7)	3.2 (2.6)	3.0 (2.6)	2.7 (2.7)
Fish (SVs/d, SD) [a]	0.49 (0.72)	0.51 (0.73)	0.47 (0.71)	0.45 (0.71)	0.40 (0.71)
Red meats (SVs/d, SD) [a]	0.52 (0.69)	0.51 (0.68)	0.53 (0.69)	0.56 (0.72)	0.58 (0.76)
Processed meats (SVs/d, SD) [a]	0.84 (1.32)	0.80 (1.28)	0.87 (1.35)	0.93 (1.42)	0.90 (1.46)

[a] A total of 189,266 participants were available.
SVs/week: servings/week

Table 2. Hazard ratios and 95% confidence interval for the frequency of adding salt to foods with the hazard of premature all-cause mortality.

	Never/rarely	*Sometimes*	*Usually*	*Always*	*P-trend*
Case, n	9345	5188	2573	1368	
Person-Years	2,476,365.2	1,252,906.4	519,167.1	215,970.0	
Sex and age adjusted	1(reference)	1.09 (1.06-1.13)	1.22 (1.17-1.27)	1.69 (1.59-1.78)	<0.001
Multivariable adjusted [a]	1(reference)	1.02 (0.99-1.06)	1.07 (1.02-1.11)	1.28 (1.20-1.35)	<0.001
Multivariable adjusted [a]+ hypertension	1(reference)	1.02 (0.99-1.06)	1.07 (1.03-1.12)	1.29 (1.21-1.36)	<0.001
Multivariable adjusted [a]+ spot urinary potassium b	1(reference)	1.02 (0.98-1.06)	1.06 (1.01-1.11)	1.28 (1.21-1.36)	<0.001
Multivariable adjusted [a]+ dietary factors [c]	1(reference)	0.99 (0.92-1.06)	1.03 (0.93-1.13)	1.26 (1.09-1.45)	0.04
Excluding participants with CKD, diabetes, CVD or Cancer	1(reference)	1.04 (0.99-1.09)	1.08 (1.02-1.14)	1.35 (1.25-1.46)	<0.001
Excluding participants who changed their diet in last 5 years	1(reference)	1.04 (0.99-1.09)	1.07 (1.01-1.13)	1.31 (1.21-1.41)	<0.001
Using attained age as the time scale [d]	1(reference)	1.02 (0.99-1.06)	1.06 (1.02-1.11)	1.28 (1.20-1.35)	<0.001

[a] adjusted for sex, age, race, smoking, moderate drinking, BMI, physical activity, Townsend deprivation index, high cholesterol, chronic kidney disease (CKD), diabetes, cardiovascular disease and cancer at baseline.

[b] A total of 481,565 participants were available.

[c] Dietary factors including total energy intake, red meat intake, processed meat intake, fish intake, vegetable intake and fruit intake. A total of 189,266 participants were available.

[d] adjusted for sex, race, smoking, moderate drinking, BMI, physical activity, Townsend deprivation index, high cholesterol, chronic kidney disease (CKD), diabetes, cardiovascular disease and cancer at baseline.

Table 3. Stratified analyses for association between frequency of adding salt to food and hazard of all-cause premature mortality.

	Frequency of adding salt to food					
Age	***Never/rarely***	***Sometimes***	***Usually***	***Always***	***P-trend***	***P for interaction***
< 60 years old	1(reference)	1.02 (0.96-1.08)	1.10 (1.02-1.19)	1.31 (1.19-1.44)	<0.001	0.75
⩾60 years old	1(reference)	1.03 (0.99-1.07)	1.07 (1.01-1.13)	1.26 (1.17-1.35)	<0.001	
Sex	***Never/rarely***	***Sometimes***	***Usually***	***Always***	***P-trend***	
women	1(reference)	0.99 (0.94-1.05)	1.04 (0.97-1.12)	1.21 (1.10-1.34)	0.004	0.12
men	1(reference)	1.04 (0.99-1.09)	1.08 (1.02-1.14)	1.31 (1.22-1.41)	<0.001	
Race	***Never/rarely***	***Sometimes***	***Usually***	***Always***	***P-trend***	
Non-whites	1(reference)	1.08 (0.90-1.30)	1.07 (0.84-1.36)	1.41 (1.09-1.81)	0.02	0.93
Whites	1(reference)	1.02 (0.98-1.05)	1.07 (1.02-1.12)	1.27 (1.20-1.35)	<0.001	
BMI	***Never/rarely***	***Sometimes***	***Usually***	***Always***	***P-trend***	
<25 kg/m^2	1(reference)	1.01 (0.95-1.08)	1.16 (1.06-1.26)	1.53 (1.38-1.69)	<0.001	<0.001
25-29.9 kg/m^2	1(reference)	1.05 (1.00-1.11)	1.01 (0.94-1.08)	1.26 (1.15-1.38)	<0.001	
⩾30 kg/m^2	1(reference)	0.99 (0.93-1.05)	1.06 (0.98-1.14)	1.06 (0.95-1.18)	0.18	
Townsend deprivation index	***Never/rarely***	***Sometimes***	***Usually***	***Always***	***P-trend***	
< median	1(reference)	1.01 (0.95-1.06)	1.02 (0.96-1.10)	1.26 (1.13-1.39)	0.003	0.08
⩾median	1(reference)	1.03 (0.99-1.08)	1.10 (1.04-1.16)	1.30 (1.21-1.39)	<0.001	
Regular physical activity	***Never/rarely***	***Sometimes***	***Usually***	***Always***	***P-trend***	
<150 minutes/week	1(reference)	1.00 (0.95-1.05)	1.05 (0.98-1.12)	1.28 (1.18-1.40)	<0.001	0.82
≥150 minutes/week	1(reference)	1.03 (0.98-1.08)	1.08 (1.02-1.15)	1.27 (1.18-1.39)	<0.001	
Smoking status	***Never/rarely***	***Sometimes***	***Usually***	***Always***	***P-trend***	
never	1(reference)	1.00 (0.94-1.06)	1.04 (0.96-1.13)	1.15 (1.02-1.30)	0.06	0.39
ever	1(reference)	1.02 (0.96-1.07)	1.06 (1.00-1.14)	1.25 (1.14-1.38)	<0.001	
current	1(reference)	1.05 (0.97-1.13)	1.08 (0.99-1.19)	1.33 (1.21-1.47)	<0.001	
Moderate drinking	***Never/rarely***	***Sometimes***	***Usually***	***Always***	***P-trend***	
No	1(reference)	1.02 (0.98-1.07)	1.07 (1.01-1.13)	1.32 (1.24-1.42)	<0.001	0.11
Yes	1(reference)	1.01 (0.96-1.07)	1.05 (0.98-1.13)	1.15 (1.03-1.28)	0.02	
Hypertension	***Never/rarely***	***Sometimes***	***Usually***	***Always***	***P-trend***	
No	1(reference)	0.98 (0.92-1.04)	1.05 (0.97-1.14)	1.27 (1.15-1.42)	<0.001	0.39
Yes	1(reference)	1.04 (1.00-1.09)	1.09 (1.04-1.15)	1.31 (1.23-1.40)	<0.001	
High cholesterol	***Never/rarely***	***Sometimes***	***Usually***	***Always***	***P-trend***	
No	1(reference)	1.03 (0.99-1.07)	1.07 (1.01-1.13)	1.33 (1.25-1.43)	<0.001	0.59
Yes	1(reference)	1.01 (0.95-1.07)	1.09 (1.01-1.18)	1.21 (1.09-1.34)	<0.001	
Energy [a]	***Never/rarely***	***Sometimes***	***Usually***	***Always***	***P-trend***	
Low (T1)	1(reference)	0.97 (0.86-1.09)	0.94 (0.80-1.10)	1.29 (1.01-1.64)	0.61	0.59

Intermediate (T2)	1(reference)	1.06 (0.94-1.20)	1.13 (0.96-1.33)	1.22 (0.94-1.58)	0.048	
High (T3)	1(reference)	0.97 (0.86-1.10)	1.10 (0.94-1.29)	1.42 (1.13-1.79)	0.02	
Total vegetables and fruits intake [b]	***Never/rarely***	***Sometimes***	***Usually***	***Always***	***P-trend***	
Low (T1)	1(reference)	1.08 (0.97-1.20)	0.99 (0.86-1.15)	1.41 (1.17-1.70)	0.02	0.02
Intermediate (T2)	1(reference)	0.94 (0.83-1.07)	1.02 (0.86-1.20)	1.20 (0.91-1.59)	0.58	
High (T3)	1(reference)	0.90 (0.78-1.03)	1.11 (0.93-1.33)	0.97 (0.69-1.37)	0.90	
Total vegetables intake [b]	***Never/rarely***	***Sometimes***	***Usually***	***Always***	***P-trend***	
Low (T1)	1(reference)	1.11 (0.99-1.24)	1.05 (0.91-1.22)	1.34 (1.09-1.65)	0.02	0.10
Intermediate (T2)	1(reference)	0.91 (0.80-1.03)	0.98 (0.83-1.16)	1.24 (0.96-1.61)	0.73	
High (T3)	1(reference)	0.92 (0.81-1.05)	1.06 (0.88-1.26)	1.16 (0.86-1.56)	0.60	
Total fruits intake [b]	***Never/rarely***	***Sometimes***	***Usually***	***Always***	***P-trend***	0.02
Low (T1)	1(reference)	1.05 (0.95-1.16)	0.99 (0.87-1.14)	1.36 (1.14-1.62)	0.03	
Intermediate (T2)	1(reference)	1.00 (0.86-1.17)	0.95 (0.76-1.18)	1.29 (0.92-1.83)	0.63	
High (T3)	1(reference)	0.88 (0.78-1.00)	1.13 (0.96-1.34)	0.97 (0.70-1.34)	0.84	
Urinary potassium [c]	***Never/rarely***	***Sometimes***	***Usually***	***Always***	***P-trend***	
Low (Q1)	1(reference)	1.05 (0.97-1.14)	1.17 (1.06-1.30)	1.43 (1.26-1.62)	<0.001	0.01
Intermediate (Q2-Q4)	1(reference)	1.01 (0.97-1.06)	1.04 (0.98-1.10)	1.27 (1.18-1.37)	<0.001	
High (Q5)	1(reference)	1.02 (0.94-1.10)	1.01 (0.92-1.12)	1.14 (0.99-1.31)	0.18	

Results were adjusted for sex, age, race, smoking, moderate drinking, BMI, physical activity, Townsend Index, high cholesterol chronic kidney disease (CKD), diabetes, cardiovascular disease and cancer at baseline.

[a] Results were restricted to 189,266 participants who completed at least one dietary recall (1-5 times) during the follow-up period (2009–2012).Results were further adjusted for red meat intake, processed meat intake, fish intake, vegetable intake and fruit intake.

[b] Results were further adjusted for red meat intake, processed meat intake, fish intake, vegetable intake (if applicable) and fruit intake (if applicable).

[c] A total of 481,565 participants were available.

Supplementary method

Cause-specific mortality: The leading causes of death in UK were selected: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/articles/leadingcausesofdeathuk/2001to2018**.** Causes of deaths were classified as cardiovascular disease (CVD) with ICD-10 code of I00-I99, CHD with code of I20-I25, stroke with code I60-I69, cancer with code of C00-D48, respiratory diseases with code J09-J18 and J40-J47, dementia with code F00-F03, F051, F106, G30, G310, G311, G318, A810 and I673.

Potential confounders: A touch-screen questionnaire was used to assesses the potential confounders at baseline, including age, sex, Townsend deprivation index (a composite measure of deprivation based on unemployment, non-car ownership, non-home ownership, and household overcrowding; a negative value represents high socioeconomic status)[1], smoking status (never, past and current), physical activity, moderate drinking.

Regular physical activity was defined as physical activity as ≧150 minutes of moderate intensity activity per week or ≧75 minutes of vigorous activity per week or an equivalent combination per week. Moderate drinking was defined as the following criterion (women: >0 and ≤14g/day, men: >0 and ≤28g/day, https://health.gov/dietaryguidelines/2015/guidelines/appendix-9/)).

Height was measured by a Seca 202 height measure. Weight was measured to the nearest 0.1 kg by the Tanita BC-418 MA body composition analyzer. Body mass index (BMI) (calculated as weight (kg) divided by height in meters squared (m^2)). Hypertension was defined as a self-reported history of hypertension or a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mm Hg or taking antihypertensive medications. High cholesterol was defined as a self-reported history of high cholesterol or taking medications. Diabetes was evaluated by UK biobank algorism for the diagnosis of diabetes[2]. Cardiovascular disease was defined as self-reported history of coronary heart disease or stroke. Cancer was defined as self-reported history of any cancer. CKD was defined as International Classification of Diseases, 10th Revision (ICD-10) (N18), 9th Revision (ICD-9) (5859) or self-reported.

References

1 Townsend P. Deprivation. J Soc Policy 1987;16:125.

2 Eastwood SV, Mathur R, Atkinson M, Brophy S, Sudlow C, Flaig R, et al. Algorithms for the capture and adjudication of prevalent and incident diabetes in UK Biobank. PLoS One 2016;11:e0162388.

Statistical method used for estimating the difference in expected survival time

We combined information from three sources within the same population to estimate lower survival time associated with the frequency of adding salt to food (henceforth "exposure groups").

(1) Sex- and age- specific population mortality rate from the Office for National Statistics;

(2) The sex-specific HRs of all-cause mortality in each exposure group (frequency of adding salt to food) versus the reference in UK biobank;

(3) The sex-specific prevalence of each frequency of adding salt to food in UK biobank.

The sex-specific lifetables for each of the 4 exposure groups were built on the above-mentioned three estimates. Population all-cause mortality rates per 100,000 per sex and per single-year age group were obtained from the Office for National Statistics. We used sex-specific Cox regression models to evaluate the associations between frequency of adding salt to food and risk of all-cause mortality. Several potential confounders were adjusted in these models, including age, sex, race, Townsend deprivation index, BMI, smoking status, moderate drinking, regular physical activity, diabetes, hypertension, high cholesterol, chronic kidney disease (CKD), cardiovascular diseases and cancer. Then we applied the sex- specific HRs to estimate the life expectancy at different age of women and men, separately.

We built the life table starting at age 45 years and ending at 100 years by single-year age intervals. Survival probability was set of 1 at age 45 years and probability of survival between ages x and x + 1 was calculated based on probability of dying (mortality rate) between ages x

and x+1 assuming that survivor function declines linearly between ages x and x + 1.[1,2] The life expectancy at any given age was derived by dividing the total person-years that would be lived beyond age x by the number of persons who survived to that age interval.[1]

We inferred the age-specific mortality rates appropriate for our reference group IR_{a0} as:[3]

$$IR_{a0=} = \frac{IR_a}{(p_{a0} + \sum^{3}_{j=} p_{aj} \times RR_{aj})}$$

Where IR_a is the population mortality rate for age group a, p_{aj} is the prevalence of exposure group j, and RR_{aj} is the hazard ratio in comparison of exposure group j versus reference group ($j = 0$). The age-specific mortality rates in each of the non-reference exposure groups were then inferred in turn by multiplying the age-specific mortality rate for the reference group IR_{a0} by the hazard ratios RR_{aj}.

Finally, the estimated lower survival time (years) due to high frequency of adding salt to food was calculated as the difference in the life expectancy at any given age between the reference group and each of the exposure group.

Supplemental References

1.Arias E. United States life tables, 2008. Natl Vital Stat Rep. 2012 Sep 24;61(3):1-63.

2.Chiang CL, World Health Organization. Life table and mortality analysis. 1979. Publisher: Geneva : World Health Organization.

3. Woloshin S, Schwartz LM, Welch HG. The risk of death by age, sex, and smoking status in the United States: putting health risks in context. J Natl Cancer Inst 2008;100(12):845-53.

Supplementary Table 1. The association between the frequency of adding salt to food and hazard of cause-specific premature mortality

Total CVD mortality [a]					
	Never/rarely	***Sometimes***	***Usually***	***Always***	***P-trend***
Case, n	2,047	1,189	609	327	
Person-Years	2,309,919.0	1,169,707.0	481,746.9	197,772.3	
Sex and age adjusted	1(reference)	1.13 (1.05-1.22)	1.28 (1.17-1.40)	1.84 (1645-2.07)	<0.001
Multivariable adjusted	1(reference)	1.04 (0.96-1.11)	1.10 (1.00-1.20)	1.34 (1.19-1.51)	<0.001
Multivariable adjusted + hypertension	1(reference)	1.05 (0.97-1.12)	1.11 (1.01-1.22)	1.36 (1.21-1.54)	<0.001
Stroke mortality [b]					
	Never/rarely	***Sometimes***	***Usually***	***Always***	***P-trend***
Case, n	489	273	139	84	
Person-Years	2,437,007.0	1,233,742.0	510,583.0	211,668.8	
Sex and age adjusted	1(reference)	1.10 (0.95-1.28)	1.26 (1.04-1.52)	2.01 (1.59-2.53)	<0.001
Multivariable adjusted	1(reference)	1.03 (0.89-1.20)	1.13 (0.93-1.36)	1.53 (1.21-1.94)	0.002
Multivariable adjusted + hypertension	1(reference)	1.04 (0.90-1.21)	1.14 (0.94-1.38)	1.55 (1.23-1.97)	0.001
CHD mortality [c]					
	Never/rarely	***Sometimes***	***Usually***	***Always***	***P-trend***
Case, n	894	515	246	144	
Person-Years	2,346,980.0	1,187,429.0	489,184.4	201,351.4	
Sex and age adjusted	1(reference)	1.11 (1.00-1.24)	1.15 (1.00-1.32)	1.80 (1.51-2.15)	<0.001
Multivariable adjusted [a]	1(reference)	1.00 (0.89-1.12)	0.95 (0.83-1.10)	1.24 (1.03-1.48)	0.25
Multivariable adjusted + hypertension	1(reference)	1.01 (0.91-1.13)	0.97 (0.84-1.12)	1.26 (1.05-1.50)	0.15
Cancer mortality [d]					
	Never/rarely	***Sometimes***	***Usually***	***Always***	***P-trend***
Case, n	4,001	2,195	1,088	563	
Person-Years	2,268,920.0	1,147,378.0	473,628.8	197,826.1	
Sex and age adjusted	1(reference)	1.08 (1.03-1.14)	1.22 (1.14-1.30)	1.64 (1.50-1.79)	<0.001

Multivariable adjusted	1(reference)	1.01 (0.96-1.07)	1.06 (0.99-1.14)	1.26 (1.15-1.38)	<0.001

Results adjusted for sex, age, race, smoking, moderate drinking, BMI, regular physical activity, Townsend deprivation index, high cholesterol, chronic kidney disease (CKD), diabetes, cardiovascular disease and cancer at baseline.

[a] excluding participants with CVD at baseline.

[b] excluding participants with CHD at baseline.

[b] excluding participants with stroke at baseline.

[d] excluding participants with cancer baseline.

Supplementary table 2. The association between the frequency of adding salt to foods and hazard of all-cause premature mortality by BMI levels (after excluding ever smokers).

BMI	*Never/rarely*	*Sometimes*	*Usually*	*Always*	*P-trend*	*P-interaction*
<25 kg/m^2	1(reference)	0.97 (0.87-1.07)	1.16 (1.00-1.34)	1.20 (0.93-1.54)	0.09	0.18
25-29.9kg/m^2	1(reference)	1.02 (0.94-1.11)	0.94 (0.83-1.07)	1.25 (1.04-1.50)	0.34	
⩾30 kg/m^2	1(reference)	1.02 (0.92-1.13)	1.11 (0.97-1.28)	1.04 (0.84-1.28)	0.25	

Results were adjusted for sex, age, race, moderate drinking, BMI, regular physical activity, Townsend deprivation Index, high cholesterol chronic kidney disease (CKD), diabetes, cardiovascular disease and cancer at baseline.