Original research

Salt restriction and risk of adverse outcomes in heart failure with preserved ejection fraction

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2022-321167).

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Received 26 March 2022
Accepted 24 May 2022

To cite: Li J, Zhen Z, Huang P, *et al*. *Heart* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/heartjnl-2022-321167

ABSTRACT

Background The optimal salt restriction in patients with heart failure (HF), especially patients with heart failure with preserved ejection fraction (HFpEF), remains controversial.

Objective To investigate the associations of cooking salt restriction with risks of clinical outcomes in patients with HFpEF.

Methods Cox proportional hazards model and subdistribution hazards model were used in this secondary analysis in 1713 participants with HFpEF from the Americas in the TOPCAT trial. Cooking salt score was the sum of self-reported salt added during homemade food preparation. The primary endpoint was a composite of cardiovascular death, HF hospitalisation and aborted cardiac arrest, and secondary outcomes were all-cause death, cardiovascular death and HF hospitalisation.

Results Compared with patients with cooking salt score 0, patients with cooking salt score >0 had significantly lower risks of the primary endpoint (HR=0.760, 95% CI 0.638 to 0.906, p=0.002) and HF hospitalisation (HR=0.737, 95% CI 0.603 to 0.900, p=0.003), but not all-cause (HR=0.838, 95% CI 0.684 to 1.027, p=0.088) or cardiovascular death (HR=0.782, 95% CI 0.598 to 1.020, p=0.071). Sensitivity analyses using propensity score matching baseline characteristics and in patients who prepared meals mostly at home yielded similar results. Subgroup analysis suggested that the association between overstrict salt restriction and poor outcomes was more predominant in patients aged ≤70 years and of non-white race.

Conclusion Overstrict cooking salt intake restriction was associated with worse prognosis in patients with HFpEF, and the association seemed to be more predominant in younger and non-white patients. Clinicians should be prudent when giving salt restriction advice to patients with HFpEF.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

⇒ Salt restriction is commonly recommended in heart failure guidelines, but the optimal restriction range and its effect on patients with heart failure with preserved ejection fraction (HFpEF) remained poorly understood.

WHAT THIS STUDY ADDS?

⇒ In this post hoc analysis of TOPCAT trial data, we found that patients with overstrict cooking salt restriction (nearly no salt added when preparing meals) was associated with worse outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY?

⇒ The results suggest, that as with the SODIUM-HF trial, physicians should reconsider the practice of recommending salt restriction to patients with HFpEF (not just as little as possible), and high-quality trials to investigate the optimal salt restriction range for patients with HFpEF are needed.

INTRODUCTION

The prevalence of heart failure (HF) is increasing globally, and heart failure with preserved ejection fraction (HFpEF) has gradually accounted for a higher proportion of the HF population.[1] Salt intake restriction in HF guidelines to reduce sodium intake, recommends ranges from <1.5 to <3 g/day (approaching <4 to <8 g/day salt intake).[2 3] However, these recommendations are based on the observational data that dietary sodium intake could lead to fluid retention and risk of hospitalisation,[4 5] and there is a lack of high-quality evidence to support salt intake restriction in patients with HF. Of note, two randomised controlled trials conducted by Paterna *et al* suggested that low sodium intake might be harmful in patients with compensated HF, and might cause detrimental renal and neurohormonal effects.[6 7] Another randomised controlled trial by Parrinello *et al* even showed a counterintuitive result that diuretic response in patients with compensated HF was improved by increasing sodium intake and limiting fluid intake, and associated with lower readmission and death/readmission rates.[8] The most recent SODIUM-HF trial also reported that reducing dietary sodium intake did not benefit clinical outcomes.[9]

Although some observational studies and randomised controlled trials have focused on sodium intake in patients with HF, patients with HFpEF were frequently excluded in these studies.[10] Similar to patients with HF with reduced ejection fraction (HFrEF), patients with HFpEF have HF symptoms and high mortality rate, but patients with HFpEF have a normal or near-normal cardiac function on echocardiography.[11] Moreover, patients with HFpEF have a different response to treatment and volume status than those with HFrEF.[11 12] As salt intake could significantly affect volume status and neurohormonal status, which might play a role

in the response to treatment in HFpEF, we aimed to explore the effect of cooking salt restriction in patients with HFpEF with data from the TOPCAT trial.

METHODS

Study population

The TOPCAT trial is a phase III, randomised, double-blind, placebo-controlled study, and its design and results have been published previously.[13 14] Briefly, this trial was designed to determine the therapeutic role of spironolactone in patients with symptomatic HFpEF. Patients with HF, aged ≥50 years with a left ventricular ejection fraction (LVEF) ≥45%, were included in the trial. Patients with an expected life expectancy of <3 years were excluded. The original study protocol was approved by the institutional review board at each participating site. All subjects had signed informed consent forms before participation in the trial. We acquired the data of the TOPCAT trial from Biologic Specimen and Data Repositories Information Coordinating Centre of National Heart, Lung, and Blood Institute (https://biolincc.nhlbi.nih.gov/) via reasonable application. The application and the present study have been approved by the medical ethics commission of First Affiliated Hospital of Sun Yat-sen University. No patients or the public were involved in the present study.

Data from Russia and Georgia were excluded in our study, because of concerns about the representativeness of patients with HFpEF in these two countries.[15] Twenty-one patients without cooking salt score records, 3 without New York Heart Association class, 1 without information on baseline drug use, 12 without a baseline serum chloronium result, 1 without a blood pressure result and 16 without plasma volume status were excluded. Finally, a total of 1713 patients were included in the present study.

Cooking salt score

Cooking salt score was collected using case report forms by the question, "How much salt does the subject add during cooking to the following homemade foods per serving?" Cooking salt scores of staple food (eg, rice, pasta, potatoes, etc), soup, meat and vegetables were collected separately, with 0 point for 'NONE', 1 point for '1/8 tsp', 2 points for '1/4 tsp' and 3 points for '1/2+tsp'. A final cooking salt score was the sum of the above four cooking salt scores of different kinds of foods.

Plasma volume status

Plasma volume status (PVS) was calculated following the method described by Grodin *et al*.[16] Briefly, actual plasma volume (aPV), ideal plasma volume (iPV) and PVS estimates were calculated using the following formulas:

1. aPV = (1–haematocrit) × (a + (b×weight in kg)), haematocrit as a proportion, a=1530 and b=41 for men while a=864 and b=47.9 for women,
2. iPV=c × wt (kg), c=39 for men while c=40 for women,
3. PVS = ((aPV–iPV)/iPV)×100%.

Outcomes of interest

The primary endpoint was a composite of cardiovascular death, HF hospitalisation and aborted cardiac arrest. Other outcomes of interest were all-cause death, cardiovascular death and HF hospitalisation.

Statistical analysis

Continuous variables following normal distribution were presented as mean±SD, those not following normal distribution were presented as median and IQR, and categorical variables were presented as number and percentage. Between-group comparisons were performed using Student's t-test for normally distributed continuous variables, Wilcoxon tests for non-normally distributed continuous variables and X^2 tests for categorical variables. The correlations between cooking salt score and blood pressure, serum sodium, chloronium and PVS were obtained using Spearman correlation analysis. Kaplan-Meier curves with log-rank test (for primary endpoint and all-cause death) and estimated cumulative incidence functions with Grey's test (for cardiovascular death and HF hospitalisation) were performed to explore the difference in outcomes of interest between patients with cooking salt score 0 and >0. A Cox proportional hazards model (for primary endpoint and all-cause death) and subdistribution hazards model for competing risk (for cardiovascular death and HF hospitalisation) were used for survival analyses, and HR and 95% CI were reported. In the above-mentioned analyses, the competing risk of cardiovascular death was non-cardiovascular death while the competing risk of HF hospitalisation was death.

In multivariable adjustment, model 1 included randomisation group, age, gender and race, and model 2 additionally included previous HF hospitalisation, diuretics use, estimated glomerular filtration rate, LVEF and serum sodium for adjustment. To explore the potential non-linear relation between cooking salt score and outcomes, restricted cubic spline analyses were performed, and three knots were located at the 10th, 50th and 90th centiles following Harrell's suggestion.[17] Based on the significant differences in baseline characteristics between patients with cooking salt score 0 and >0, survival analyses were performed after propensity score matching (nearest method, calliper=0.2, matching continuous variables: age, diastolic blood pressure, estimated glomerular filtration rate, LVEF and haemoglobin; and categorical variables: gender, white race or not, previous HF hospitalisation and diabetes mellitus) as sensitivity analysis 1 (n=1530). Additionally, as some patients did not prepare meals at home, in sensitivity analysis 2, we included only those who prepared almost all noon and evening meals at home (n=1081). In a subgroup analysis, we divided participants according to age (≤70 or>70), gender (male or female), race (white or non-white), previous HF hospitalisation history (yes or no) and diuretic use (yes or no). Survival analyses were performed in each subgroup, and multivariate adjustment was the same as that in the main analysis. Interaction terms of binary cooking salt score (0 or >0) and subgroups were created and p values for interaction were calculated by the likelihood-ratio test. Statistical analyses were performed using R 4.0.2 (packages *tableone, cmprsk, survival, rms* and *MatchIt*) and GraphPad Prism 8. A two-tailed value of p<0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Comparisons of baseline characteristics of patients with cooking salt score 0 and >0 are summarised in table 1. Approximately half of the patients (816/1713) included in this study had a cooking salt score of o, in other words, with extremely strict cooking salt restriction. More patients with cooking salt score 0 were male (56.4% vs 44.7%, p<0.001) and white race (80.8% vs 76.9%, p=0.013). Patients with cooking salt score 0 were significantly heavier (97.34±25.81 kg vs 91.08±23.76 kg, p<0.001) and had a lower diastolic blood pressure (70.20±11.28 mm Hg vs 72.35±11.61 mm Hg, p<0.001) than those with score

Table 1 Baseline characteristics of patients with cooking salt score 0 and >0

Characteristics	Cooking salt score 0 (n=816)	Cooking salt score >0 (n=897)	P value
Cooking salt score	0	4 (3–7)	–
Randomised to spironolactone	413, 50.6%	452, 50.4%	0.965
Demographic characteristics			
Age (years)	72 (63–79)	73 (64–79)	0.290
Male	460, 56.4%	401, 44.7%	**<0.001**
Race			**0.013**
White	659, 80.8%	690, 76.9%	
Black	132, 16.2%	154, 17.2%	
Others	25, 3.1%	53, 5.9%	
Physical examinations			
NYHA class	297, 36.4%	299, 33.3%	0.201
Weight (kg)	97.34±25.81	91.08±23.76	**<0.001**
Heart rate (bpm)	69.50±11.25	68.62±11.20	0.105
Systolic BP (mm Hg)	127.21±15.64	127.81±16.14	0.434
Diastolic BP (mm Hg)	70.20±11.28	72.35±11.61	**<0.001**
Medical history			
Previous HF hospitalisation	511, 62.6%	494, 55.1%	**0.002**
Myocardial infarction	180, 22.1%	174, 19.4%	0.194
Stroke	72, 8.8%	82, 9.1%	0.885
COPD	142, 17.4%	139, 15.5%	0.318
Hypertension	734, 90.0%	809, 90.2%	0.933
Diabetes mellitus	388, 47.5%	376, 41.9%	**0.022**
Medications			
ACEI/ARBs	643, 78.8%	708, 78.9%	0.995
β Blockers	672, 82.4%	676, 75.4%	**0.001**
CCBs	319, 39.1%	342, 38.1%	0.719
Diuretics	752, 92.2%	779, 86.8%	**<0.001**
Ancillary examinations			
LVEF (%)	57 (51–61)	60 (53–65)	**0.002**
eGFR	62.51±20.80	66.06±21.88	**0.001**
Sodium (mmol/L)	139.48±3.13	139.88±3.11	**0.009**
Potassium (mmol/L)	4.15±0.43	4.22±0.43	**0.001**
Chloronium (mmol/L)	101.97±3.84	102.39±4.02	**0.027**
Haematocrit (%)	38.39±4.90	38.91±4.70	**0.024**
Haemoglobin (g/dL)	12.77±1.69	12.93±1.65	**0.038**
Plasma volume status (%)	−11.0((−16.4) −(−4.8))	−10.7((−16.0) −(−5.0))	0.566

Values are presented as n, %, mean±SD or median (IQR), as appropriate.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

>0, but had a similar systolic blood pressure (127.21±15.64 mm Hg vs 127.81±16.14 mm Hg, p=0.434). With regards to medical history and medications, patients with cooking salt score 0 had higher proportions of previous HF hospitalisation, diabetes mellitus and use of β blockers and diuretics. For ancillary examinations, patients with cooking salt score 0 had significantly lower LVEF, estimated glomerular filtration rate, serum sodium, serum potassium, serum chloronium, haematocrit and haemoglobin.

Correlation between cooking salt score and baseline parameters

Result of Spearman correlation analyses showed that cooking salt score (included as continuous variable, ranging from 0 to 12) correlated significantly with systolic and diastolic blood pressure, serum sodium and chloronium levels positively (online supplemental table 1), suggesting that cooking salt score could at least partially reflect salt intake of these patients. However, cooking salt score did not correlate significantly with PVS.

Cooking salt score and outcomes

Figure 1 shows Kaplan-Meier curves and estimated cumulative incidence functions for patients with cooking salt score 0 and >0 for different outcomes during a median follow-up of 2.93 years. It was found that patients with cooking salt score >0 had significantly better survival than those with cooking salt score 0 for the outcomes primary endpoint (p=0.002) and HF hospitalisation (p=0.003), but no significantly better survival was found in patients with cooking salt score >0 for the outcomes all-cause death (p=0.087) and cardiovascular death (p=0.081). In Cox proportional hazards models and subdistribution hazards models, similar results were found: patients with cooking salt score >0 had significantly lower risks of the primary endpoint (HR=0.760, 95% CI 0.638 to 0.906, p=0.002) and HF hospitalisation (HR=0.737, 95% CI 0.603 to 0.900, p=0.003), but not all-cause (HR=0.838, 95% CI 0.684 to 1.027, p=0.088) or cardiovascular death (HR=0.782, 95% CI 0.598 to 1.020, p=0.071). Results in multivariate models adjusted for potential confounders were similar to those in univariate models (table 2).

When we included cooking salt score as a continuous variable in Cox proportional hazards models and subdistribution hazards models, similar results were found in univariate and multivariate model 1. However, in multivariate model 2, no significant association was found between cooking salt score and outcomes of interest (online supplemental table 2). High cooking salt might lead to poor prognosis, and along with the above results, the potentially non-linear relationship between cooking salt score and outcomes was explored. In restricted cubic spline analyses, we found that when the cooking salt score was >6, risks of the primary endpoint and all-cause death did not continue to decrease and the risk of cardiovascular death even shown a tendency to increase, while the risk of HF hospitalisation still showed a tendency to continue to decrease (online supplemental figure 1).

Sensitivity analysis

After propensity score matching, baseline characteristics in patients with cooking salt score 0 and >0 were generally comparable (online supplemental table 3). Survival analyses yielded the same results that patients with cooking salt score >0 had significantly lower event risks of the primary endpoint and HF hospitalisation, but not all-cause or cardiovascular death, both in univariate and multivariate analysis (table 3).

In patients who prepared almost all noon and evening meals at home, similar results were found in univariate analyses and adjusted model 1 (table 3). Surprisingly, patients with cooking salt score >0 also had a significantly lower risk of cardiovascular death in univariate analysis. However, in adjusted model 2 (fully adjusted), patients with cooking salt score >0 were only associated with a lower risk of the primary endpoint but not HF hospitalisation or cardiovascular death.

Subgroup analysis

Results of subgroup analysis are summarised briefly in figure 2 and in more detail in online supplemental table 4. Of note, patients aged ≤70 years significantly benefited more from adding cooking salt compared with those >70 years old for the primary endpoint and HF hospitalisation. Additionally, patients of non-white race seemed to benefit more from adding cooking

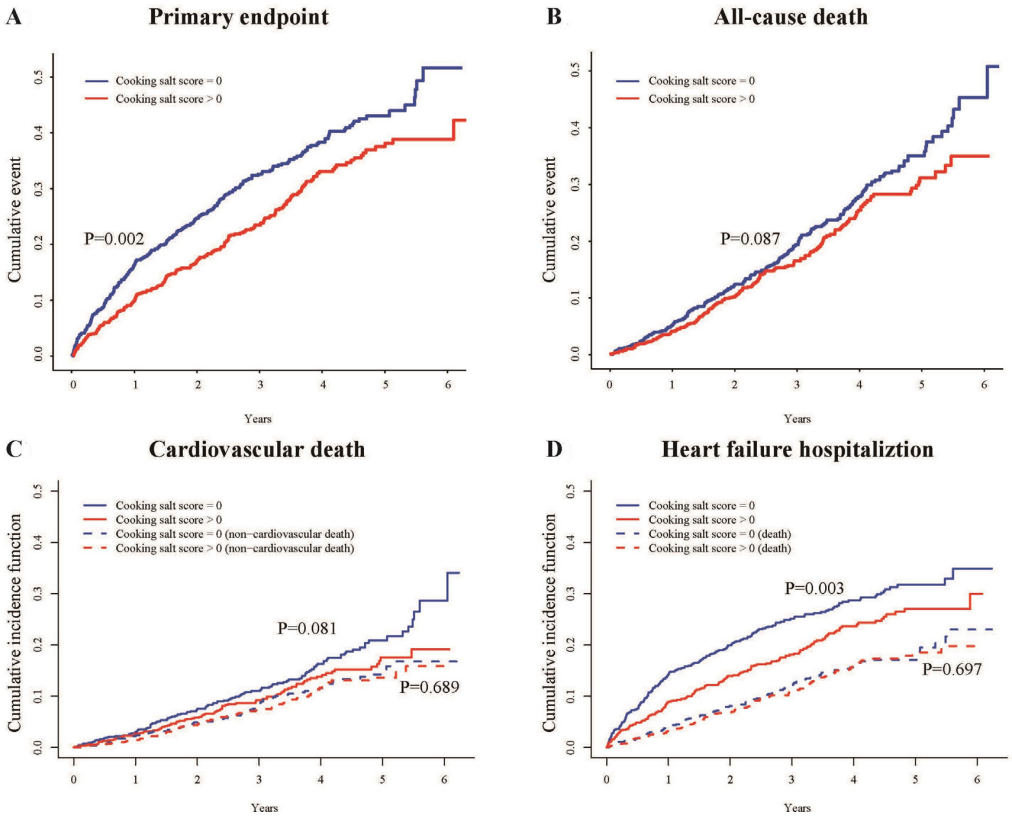

Figure 1 Kaplan-Meier curves with log-rank test for (A) primary endpoint and (B) all-cause death, and estimated cumulative incidence functions with Grey's test for (C) cardiovascular death and (D) heart failure hospitalisation, grouped by patients with cooking salt score >0 versus 0.

salt regarding the primary endpoint, although p for interaction did not reach statistical significance (figure 2), which might be due to the relatively small number of non-white participants. No significant difference in the association of cooking salt score and risks of outcomes was found between gender, previous HF hospitalisation and diuretics use subgroups (online supplemental table 4).

DISCUSSION

Results of the present study suggested that an overstrict cooking salt restriction was significantly associated with higher risks of the composite primary endpoint of cardiovascular death, HF hospitalisation and aborted cardiac arrest in patients with HFpEF. Additionally, an overstrict cooking salt restriction was also significantly associated with a higher risk of HF hospitalisation but not cardiovascular or all-cause mortality. Subgroup analysis indicated that the association of overstrict cooking salt restriction and poor prognosis was probably more predominant in patients aged ≤70 years and of non-white race.

Lower sodium intake is associated with lower blood pressure and a lower risk of cardiovascular disease in the general population and in those with hypertension, and is thought to be achieved by reducing fluid retention and alleviating renin-angiotensin-aldosterone system (RAAS) activation.[18] However, in the setting of HF, the effect of sodium intake restriction is complicated. Low sodium intake may lead to intravascular volume contraction, which could in turn reduce congestion and diuretic requirement, leading to HF compensation.[10] However, the results in our study showed that PVS had no significant relationship with cooking salt score, suggesting that low sodium intake did not have an intravascular volume contraction effect on patients with HFpEF.

Table 2 Cooking salt score >0 versus 0 and outcomes in survival analyses

	Unadjusted			Adjusted model 1*			Adjusted model 2†		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Primary endpoint	0.760	0.638 to 0.906	**0.002**	0.757	0.635 to 0.903	**0.002**	0.834	0.698 to 0.997	**0.046**
All-cause death	0.838	0.684 to 1.027	0.088	0.853	0.696 to 1.047	0.128	0.944	0.768 to 1.160	0.583
Cardiovascular death	0.782	0.598 to 1.020	0.071	0.791	0.604 to 1.035	0.088	0.872	0.664 to 1.145	0.320
Heart failure hospitalisation	0.737	0.603 to 0.900	**0.003**	0.726	0.593 to 0.888	**0.002**	0.791	0.645 to 0.970	**0.024**

*Adjusted for randomisation group, age, gender and race.
†Adjusted for randomisation group, age, gender, race, previous heart failure hospitalisation, diuretics use, estimated glomerular filtration rate, left ventricular ejection fraction and serum sodium.
HR, hazard ratio.;

Table 3 Sensitivity analyses for cooking salt score >0 versus 0 and outcomes

	Unadjusted			Adjusted model 1*			Adjusted model 2†		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Patients after propensity score matching (n=1530)									
Primary endpoint	0.791	0.658 to 0.951	**0.013**	0.786	0.654 to 0.945	**0.011**	0.822	0.683 to 0.989	**0.038**
All-cause death	0.915	0.739 to 1.134	0.418	0.920	0.743 to 1.140	0.447	0.960	0.774 to 1.191	0.711
Cardiovascular death	0.812	0.613 to 1.080	0.150	0.814	0.614 to 1.080	0.150	0.849	0.640 to 1.127	0.260
Heart failure hospitalisation	0.776	0.629 to 0.958	**0.018**	0.767	0.621 to 0.947	**0.013**	0.799	0.647 to 0.987	**0.037**
Patients almost prepared all noon and evening meals at home (n=1081)									
Primary endpoint	0.735	0.586 to 0.921	**0.007**	0.713	0.568 to 0.896	**0.004**	0.790	0.627 to 0.996	**0.046**
All-cause death	0.842	0.651 to 1.088	0.189	0.854	0.659 to 1.105	0.229	0.935	0.720 to 1.214	0.615
Cardiovascular death	0.705	0.502 to 0.990	**0.043**	0.714	0.508 to 1.004	0.053	0.774	0.549 to 1.091	0.140
Heart failure hospitalisation	0.753	0.582 to 0.975	**0.032**	0.722	0.555 to 0.940	**0.016**	0.800	0.613 to 1.040	0.100

*Adjusted for randomisation group, age, gender and race.
†Adjusted for randomisation group, age, gender, race, previous heart failure hospitalisation, diuretics usage, estimated glomerular filtration rate, left ventricular ejection fraction and serum sodium.
HR, hazard ratio.;

Additionally, previous randomised controlled trials have yielded counterintuitive results showing that reduced dietary sodium intake was associated with worse survival and higher readmission rate in patients with HF,[6–8] and this association was reinforced in a recent meta-analysis including 3545 patients.[19] The most recent randomised controlled trial, the SODIUM-HF trial, which recruited 806 patients with HF and assigned them to either a low sodium diet (<1.5 g/day) or usual care group, also reported that dietary sodium intake restriction did not benefit 1-year clinical outcomes.[9] A possible explanation of these results is that low sodium intake might actually result in neurohormonal activation and subsequently aggravate HF, which has been observed in two randomised controlled trials.[6 7] Additionally, it has been reported that dietary sodium restriction significantly lowers cardiac output, increases peripheral resistance and activates RAAS in rabbits.[20] Although the neurohormonal activation effect could be ameliorated by the use of RAAS inhibitors, a higher plasma renin activity is still an independent predictor of poor prognosis.[21] The low cardiac output and stroke volume, as well as increased epinephrine and vascular resistance, could result in deteriorated haemodynamic status of patients with HF, and subsequently lead to poor prognosis.[10] Results in the present study also showed that patients with cooking salt score 0 had significantly lower LVEF, indicating lower cardiac output in these patients.

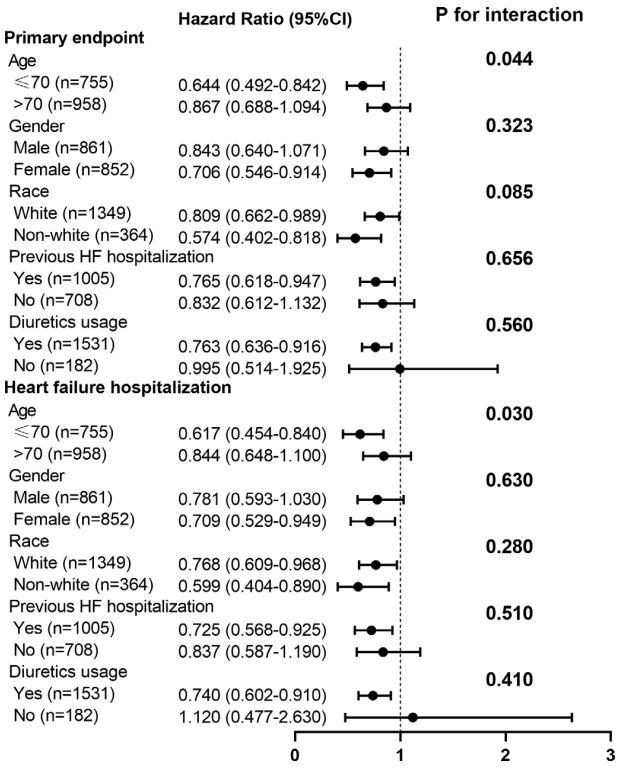

Figure 2 Forest plot summarising subgroup analyses in age, gender, race, previous heart failure (HF) hospitalisation, and diuretics use subgroups.

Of note, consistent with the results of randomised controlled trials showing that low sodium intake could cause a detrimental renal effect,[6 7] patients with cooking salt score 0 had significantly lower estimated glomerular filtration rate in our study. It is a consensus that worse renal function is associated with worse HF prognosis,[22] and the harmful renal effect of overstrict dietary salt restriction might play a role in the worse prognosis of these patients. It is worth noting that the significant differences in baseline characteristics between patients with cooking salt score 0 and >0 might lead to a reverse causation (ie, patients with worse health had worse prognosis and consumed less salt because of loss of appetite and/or physician advice) when interpreting our results. We tried to rule out this reverse causation using propensity score matching to balance between-group baseline characteristics in sensitivity analysis, and the results showed that patients with cooking salt score 0 consistently had a higher risk of worse prognosis.

Optimal salt intake in patients with HF has been studied for decades and many published articles have focused on this topic,[23] but unfortunately, patients with HFpEF were excluded in most of these studies.[10] Even in those not excluding patients with HFpEF, as well as the recently published SODIUM-HF trial, patients with HFpEF were not independently analysed.[9 10] As a result, the effect of salt intake restriction in patients with HFpEF is underexplored. Another study showed that aggressive sodium restriction together with fluid restriction did not lead to improved symptoms or prognosis in patients with HFpEF, but in that study the number of enrolled patients was small (53 patients in total).[24] Our present study including 1713 patients further demonstrates that overstrict salt restriction could be

harmful to patients with HFpEF. It is also worth mentioning that most studies of salt intake in patients with HF were carried out in the white race, but there is a significant difference in RAAS physiology among racial groups, which could lead to a different response to salt restriction.[10] Consistently, subgroup analysis in the present study suggested that overstrict cooking salt restriction leading to poor prognosis was seemingly more predominant in non-white patients. Future studies should pay more attention to the optimal salt intake range in patients with HFpEF, as well as patients with HFpEF of different races.

The present study has some limitations. First, no urinary sodium excretion data are available in the TOPCAT trial, and the cooking salt score was self-reported, which might lead to recall bias. Additionally, haemodynamic parameters were seldom acquired in the TOPCAT trial, and thus the effect on hemodynamics of cooking salt restriction could not be thoroughly investigated. Last, but not least, a reverse causation between low dietary sodium intake and worse HF might still exist even though we performed a propensity score matching sensitivity analysis, because patients might have worse underlying health that was not shown by baseline characteristics. Future randomised controlled trials are needed to disclose the beneficial salt intake range in patients with HFpEF.

CONCLUSION

Overstrict dietary salt intake restriction could harm patients with HFpEF and is associated with worse prognosis. Physicians should reconsider giving this advice to patients with HFpEF. High-quality trials are needed to determine the optimal salt intake range for patients with HFpEF.

Acknowledgements We much appreciate TOPCAT investigators and participants for their efforts and time. We also thank NHLBI for establishing BioLINCC to share the data for analysis.

Contributors Conception and study design: WL and PH, analysis and manuscript drafting: JL and ZZ manuscript revision and supervision: YD, CL and WL. WL is responsible for the overall content as guarantor.

Funding This study was funded by the National Natural Science Foundation of China (No. 81770392, 81770394, 81970340, 82000260), Guangdong Natural Science Foundation (No. 2021A1515010755) and China Postdoctoral Science Foundation (No. 2019TQ0380, 2019 M660229, 2021 M693615).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants but the medical ethics commission of First Affiliated Hospital of Sun Yat-sen University (No. [2021]454) exempted this study. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data of the TOPCAT trial can be acquired via reasonable request to BioLINCC (https://biolincc.nhlbi.nih.gov/)

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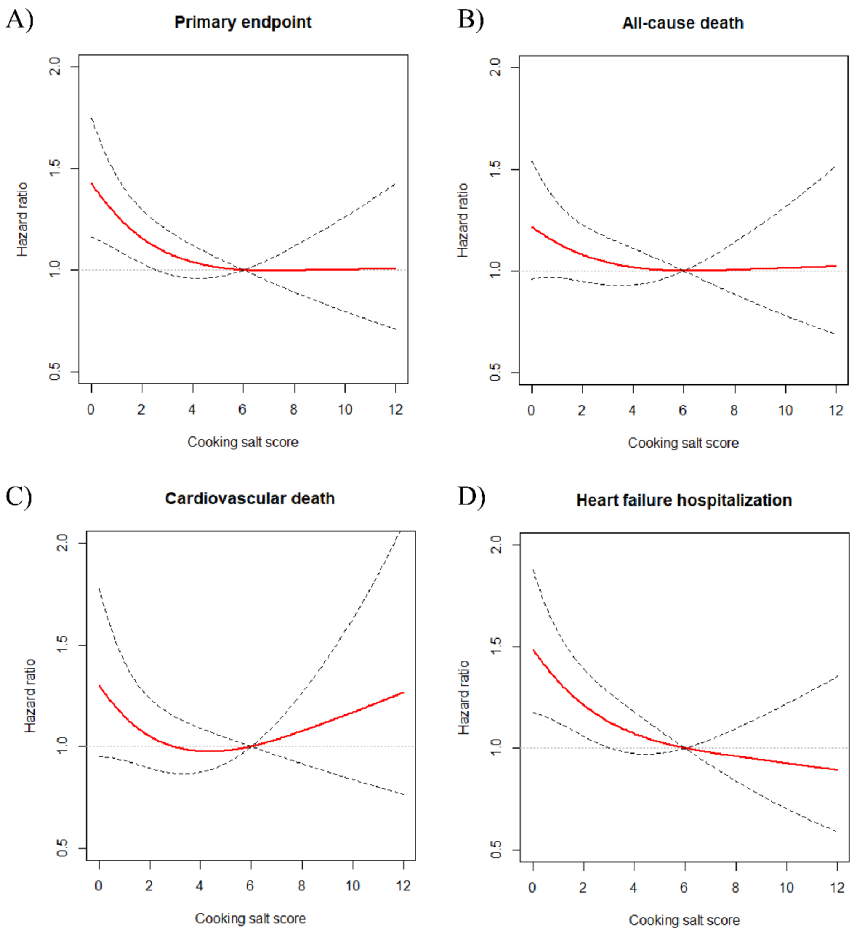
Supplement figure 1. Restrict cubic spline analyses using cooking salt score as continuous variable for outcomes A) primary endpoint, B) all-cause death, C) cardiovascular death and D) heart failure hospitalization.



Supplement table 1. Correlation between cooking salt score and blood pressure, serum sodium, chloronium and plasma volume status.

Variable	Correlation coefficient	P
Systolic blood pressure	0.054	**0.026**
Diastolic blood pressure	0.119	**<0.001**
Serum sodium	0.059	**0.014**
Serum chloronium	0.070	**0.004**
Plasma volume status	0.013	0.591

Supplement table 2. Cooking salt score as continuous variable and outcomes in survival analyses.

	Unadjusted			Adjusted model 1*			Adjusted model 2**		
	HR	95%CI	P	HR	95%CI	P	HR	95%CI	P
Total study population (n=1713)									
Primary endpoint	0.958	0.931-0.986	**0.003**	0.958	0.931-0.986	**0.004**	0.977	0.942-1.014	0.223
All-cause death	0.978	0.947-1.010	0.171	0.983	0.952-1.016	0.304	0.985	0.945-1.026	0.457
Cardiovascular death	0.982	0.940-1.030	0.420	0.986	0.943-1.031	0.550	0.976	0.920-1.035	0.410
Heart failure hospitalization	0.948	0.916-0.981	**0.002**	0.946	0.913-0.981	**0.002**	0.971	0.930-1.014	0.180
Patients after propensity score matching (n=1530)									
Primary endpoint	0.965	0.936-0.995	**0.022**	0.965	0.936-0.996	**0.025**	0.974	0.945-1.005	0.094
All-cause death	0.986	0.952-1.020	0.406	0.988	0.955-1.023	0.502	0.996	0.963-1.031	0.840
Cardiovascular death	0.985	0.939-1.030	0.520	0.987	0.942-1.040	0.600	0.997	0.951-1.045	0.890
Heart failure hospitalization	0.961	0.927-0.997	**0.033**	0.961	0.926-0.997	**0.033**	0.968	0.934-1.004	0.084
Patients almost prepared all noon and evening meals at home (n=1081)									
Primary endpoint	0.961	0.928-0.997	**0.031**	0.958	0.924-0.994	**0.022**	0.977	0.942-1.014	0.223
All-cause death	0.966	0.927-1.006	0.093	0.972	0.933-1.013	0.176	0.985	0.945-1.026	0.457
Cardiovascular death	0.953	0.900-1.010	0.100	0.958	0.904-1.016	0.150	0.976	0.920-1.035	0.410
Heart failure hospitalization	0.959	0.920-1.000	**0.050**	0.953	0.912-0.995	**0.030**	0.971	0.930-1.014	0.180

HR: hazard ratio, CI: confidence interval.

*Adjusted for randomization group, age, gender and race.

**Adjusted for randomization group, age, gender, race, previous heart failure hospitalization, diuretics usage, estimated glomerular filtration rate, left ventricular ejection fraction and serum sodium.

Supplement Table 3. Baseline characteristics of patients after PSM.

	Cooking salt score = 0 (n = 765)	Cooking salt score > 0 (n = 765)	P
Cooking salt score	0	4 (3-7)	-
Randomized to spirolactone	382, 49.9%	383, 50.1%	1.000
Demographic characteristics			
Age (years)	72 (64-79)	73 (64-79)	0.375
Male	411, 53.7%	382, 49.9%	0.152
Race			0.056
White	611, 79.9%	603, 78.8%	
Black	129, 16.9%	118, 15.4%	
Others	25, 3.3%	44, 5.8%	
Physical examinations			
NYHA class	277, 36.2%	262, 34.2%	0.454
Weight (kg)	96.48±25.76	92.29±24.21	**0.001**
Heart rate (bpm)	69.48±11.28	68.41±11.05	0.060
Systolic BP (mmHg)	127.55±15.61	126.85±16.22	0.393
Diastolic BP (mmHg)	70.66±11.10	71.28±11.39	0.279
Medical history			
Previous HF hospitalization	465, 60.8%	433, 56.5%	0.107
Myocardial infarction	160, 20.9%	157, 20.5%	0.900
Stroke	70, 9.2%	75, 9.8%	0.727
COPD	134, 17.5%	124, 16.2%	0.539
Hypertension	688, 89.9%	683, 89.3%	0.738
Diabetes mellitus	352, 46.0%	339, 44.3%	0.538
Medications			
ACEI/ARBs	598, 78.2%	600, 78.4%	0.951
Beta blockers	625, 81.7%	578, 75.6%	**0.004**
CCBs	301, 39.3%	283, 37.0%	0.371
Diuretics	701, 91.6%	668, 87.3%	**0.008**
Ancillary examinations			
LVEF (%)	58 (53-62)	58 (52-64)	0.380
eGFR	63.31±20.89	64.28±19.72	0.349
Sodium (mmol/L)	139.48±3.09	139.78±3.13	0.058
Potassium (mmol/L)	4.15±0.42	4.22±0.44	**0.001**
Chloronium (mmol/L)	101.95±3.88	102.29±4.07	0.097
Hematocrit (%)	38.51±4.91	38.74±4.70	0.350
Hemoglobin (g/dL)	12.80±1.68	12.89±1.66	0.347
Plasma volume status (%)	-10.9 [(-16.4) -(-4.6)]	-10.6 [(-16.0) -(-4.8)]	0.370

Values were presented as *n, %*, *mean ± SD* or *median (interquartile range)*, as appropriate.

NYHA: New York heart association, BP: blood pressure, LVEF: left ventricular ejection fraction, HF: heart failure, COPD: chronic obstructive pulmonary disease, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, CCB: calcium channel blocker, eGFR: estimated glomerular filtration rate.

Supplement table 4. Detailed subgroup analysis results for cooking salt score > 0 versus = 0 and outcomes.

	Unadjusted			Adjusted model 1*			Adjusted model 2**		
	HR	95%CI	P	HR	95%CI	P	HR	95%CI	P
Primary endpoint									
Age			**0.044**[#]			0.067[#]			0.136[#]
≤70 (n=755)	0.644	0.492-0.842	0.001	0.631	0.481-0.828	0.001	0.716	0.542-0.946	0.019
>70 (n=958)	0.867	0.688-1.094	0.229	0.877	0.695-1.108	0.271	0.941	0.744-1.190	0.612
Gender			0.323[#]			0.392[#]			0.489[#]
Male (n=861)	0.843	0.640-1.071	0.163	0.802	0.630-1.020	0.072	0.869	0.681-1.109	0.259
Female (n=852)	0.706	0.546-0.914	0.008	0.695	0.537-0.901	0.006	0.767	0.589-0.998	0.048
Race			0.085[#]			0.094[#]			0.115[#]
White (n=1349)	0.809	0.662-0.989	0.039	0.819	0.668-1.002	0.053	0.904	0.737-1.108	0.330
Non-white (n=364)	0.574	0.402-0.818	0.002	0.589	0.408-0.849	0.005	0.612	0.421-0.890	0.010
Previous HF hospitalization			0.656[#]			0.643[#]			0.614[#]
Yes (n=1005)	0.765	0.618-0.947	0.014	0.756	0.609-0.939	0.012	0.805	0.647-0.002	0.052
No (n=708)	0.832	0.612-1.132	0.242	0.835	0.613-1.137	0.252	0.895	0.656-1.222	0.486
Diuretics usage			0.560[#]			0.661[#]			0.542[#]
Yes (n=1531)	0.763	0.636-0.916	0.004	0.765	0.637-0.919	0.004	0.819	0.681-0.986	0.034
No (n=182)	0.995	0.514-1.925	0.987	0.860	0.427-1.733	0.674	1.063	0.514-2.196	0.869
All-cause death									
Age			0.606[#]			0.447[#]			0.255[#]
≤70 (n=755)	0.856	0.598-1.226	0.396	0.878	0.610-1.263	0.482	1.045	0.719-1.519	0.816
>70 (n=958)	0.820	0.640-1.049	0.114	0.840	0.655-1.076	0.167	0.904	0.704-1.160	0.426
Gender			0.057[#]			0.129[#]			0.153[#]
Male (n=861)	1.026	0.783-1.343	0.853	0.963	0.734-1.263	0.785	1.088	0.826-1.434	0.547
Female (n=852)	0.690	0.507-0.940	0.019	0.708	0.519-0.965	0.029	0.777	0.568-1.064	0.116

Race			0.410#			0.482#			0.312#
White (n=1349)	0.806	0.643-1.009	0.060	0.823	0.656-1.032	0.092	0.904	0.720-1.136	0.388
Non-white (n=364)	1.003	0.620-1.622	0.991	0.924	0.557-1.532	0.758	1.117	0.670-1.863	0.670
Previous HF hospitalization			0.923#			0.850#			0.853#
Yes (n=1005)	0.869	0.673-1.121	0.280	0.909	0.702-1.177	0.469	0.968	0.747-1.256	0.808
No (n=708)	0.838	0.598-1.175	0.306	0.831	0.592-1.166	0.284	0.901	0.640-1.267	0.547
Diuretics usage			0.489#			0.489#			0.551#
Yes (n=1531)	0.869	0.703-1.075	0.196	0.887	0.717-1.098	0.271	0.957	0.772-1.187	0.690
No (n=182)	0.707	0.348-1.435	0.337	0.822	0.392-1.724	0.603	0.954	0.446-2.041	0.904
Cardiovascular death									
Age			0.980#			0.850#			0.640#
≤70 (n=755)	0.801	0.518-1.240	0.320	0.805	0.515-1.260	0.340	0.971	0.614-1.536	0.900
>70 (n=958)	0.770	0.549-1.080	0.130	0.790	0.563-1.109	0.170	0.841	0.596-1.186	0.320
Gender			0.460#			0.600#			0.620#
Male (n=861)	0.877	0.613-1.260	0.470	0.842	0.585-1.210	0.360	0.931	0.643-1.349	0.710
Female (n=852)	0.710	0.476-1.060	0.093	0.721	0.483-1.080	0.110	0.797	0.528-1.200	0.280
Race			0.520#			0.550#			0.700#
White (n=1349)	0.813	0.604-1.090	0.170	0.825	0.612-1.110	0.210	0.902	0.667-1.220	0.500
Non-white (n=364)	0.658	0.360-1.200	0.170	0.656	0.352-1.220	0.180	0.712	0.369-1.370	0.310
Previous HF hospitalization			0.840#			0.880#			0.930#
Yes (n=1005)	0.791	0.567-1.100	0.170	0.812	0.580-1.140	0.220	0.869	0.619-1.221	0.420
No (n=708)	0.836	0.531-1.320	0.440	0.821	0.518-1.300	0.400	0.867	0.552-1.360	0.540
Diuretics usage			0.790#			0.830#			0.810#
Yes (n=1531)	0.783	0.592-1.040	0.087	0.795	0.600-1.050	0.110	0.857	0.645-1.140	0.290
No (n=182)	0.944	0.371-2.400	0.900	0.957	0.344-2.660	0.930	1.071	0.376-3.049	0.900
Heart failure hospitalization									

Age			**0.030**[#]			**0.044**[#]			0.086[#]
≤70 (n=755)	0.617	0.454-0.840	0.002	0.606	0.444-0.827	0.002	0.677	0.490-0.935	0.018
>70 (n=958)	0.844	0.648-1.100	0.210	0.844	0.646-1.100	0.210	0.893	0.683-1.170	0.410
Gender			0.630[#]			0.680[#]			0.770[#]
Male (n=861)	0.781	0.593-1.030	0.077	0.746	0.566-0.984	0.038	0.799	0.605-1.056	0.110
Female (n=852)	0.709	0.529-0.949	0.021	0.693	0.516-0.930	0.015	0.770	0.567-1.050	0.094
Race			0.280[#]			0.320[#]			0.400[#]
White (n=1349)	0.768	0.609-0.968	0.025	0.768	0.607-0.972	0.028	0.833	0.657-1.057	0.130
Non-white (n=364)	0.599	0.404-0.890	0.011	0.615	0.414-0.913	0.016	0.654	0.435-0.985	0.042
Previous HF hospitalization			0.510[#]			0.510[#]			0.480[#]
Yes (n=1005)	0.725	0.568-0.925	0.010	0.708	0.552-0.907	0.006	0.745	0.581-0.955	0.020
No (n=708)	0.837	0.587-1.190	0.320	0.831	0.583-1.180	0.310	0.894	0.624-1.280	0.540
Diuretics usage			0.410[#]			0.460[#]			0.440[#]
Yes (n=1531)	0.740	0.602-0.910	0.004	0.733	0.595-0.903	0.003	0.778	0.631-0.959	0.019
No (n=182)	1.120	0.477-2.630	0.790	0.844	0.310-2.300	0.740	0.966	0.318-2.934	0.950

HR: hazard ratio, CI: confidence interval, HF: heart failure.

*Adjusted for randomization group, age, gender and race.

**Adjusted for randomization group, age, gender, race, previous heart failure hospitalization, diuretics usage, estimated glomerular filtration rate, left ventricular ejection fraction and serum sodium.

[#]P for interaction, age was included as continuous variable here.