Associations of Calibrated Dietary Sodium and Potassium Intakes with the Risk of Heart Failure and its Subtypes in Postmenopausal Women: the Women's Health Initiative

By

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Thesis

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Heart Failure (HF), with an annual incidence of 915,000 cases, affects more than 5.7 million Americans including a large proportion of women and the elderly.[1,2] While the incidence of most cardiovascular diseases (CVD) is decreasing, it remains the leading cause of morbidity and mortality in the US. Additionally, rates for HF have remained stable in the past few decades.[2,3] High hospital readmissions, an estimated cost of over 30 billion dollars and the 50% 5-year mortality rate further indicate substantial burden of HF.[3-5] In epidemiologic cohorts, 40-70% of incident HF occurs as HF with preserved ejection fraction (HFpEF), which is more common in women.[2,6] Yet, strategies to control HFpEF are less well established than for HF with reduced ejection fraction (HFrEF).[7,8]

Although history of hypertension and coronary disease account for sizable proportions of HF risk,[6,9,10] understanding how modifiable factors such as dietary sodium reduction contributing to HF incidence and its subtypes could improve HF prevention strategies, especially in older women who are understudied. In both observational prospective studies and clinical trials, high dietary sodium intake, as well as low dietary potassium intake, have been consistently linked to higher blood pressure and the risk of myocardial infarction (MI), which are strong predictors of HF.[11-19] Results on calibrated sodium/potassium intake and the incidence of CVD, including HF have been published.[20] However, evidence on the association between dietary sodium/potassium intake and the HF subtypes, is still limited. The dose-response relationship between dietary sodium intake and the risk of HF also remains uncertain.[21-25] While the effect of restricting dietary sodium on controlling blood pressure and progression of HF has been acknowledged by clinical guidelines, more evidence that direct link and dose-response relationship between dietary sodium intake and the onset of clinically diagnosed HF and its subtypes is needed to inform clinical practice and primary prevention strategies.[7,12,26-34] Towards this end, biomarker calibrated measures of dietary sodium and potassium were used to investigate their associations with the incident hospitalized HF, HFpEF and HFrEF up to 22 years' follow-up of a cohort of postmenopausal women enrolled in the Women's Health Initiative (WHI).

METHODS

Study population

The Women's Health Initiative recruited 161,808 women aged 50-79 years from 40 clinical centers across the country between 1993-1998 with the detailed study design of the WHI described elsewhere.[35-39] In our analysis, we included participants from the Observational Study (OS), the comparison group of the Dietary Modification Trial (DM), and both intervention and control groups of the Hormone Therapy Trials (HT). The dietary data used for this analysis was from the baseline for OS, intervention and control arms of HT, and 1-year follow-up data or the comparison arm of DM due to potential changes in diet related to participating in the DM.[35] Women who reported a history of HF at baseline (n=1,701), had FFQ energy intake <600 kcal/day or >5,000 kcal/day (n=4,701), were underweight (BMI ≤18.5 kg/m2) (n=1,223), or had missing FFQ data (n=16,582) were excluded from our study sample (Supplemental figure 1). The end of follow-up for this study is January 13, 2015. The analysis on HF and HF subtypes had different sample sizes: the final study population for the analysis on HF included 118,060 women; the sample size for analyses on HF subtypes was 29,232 because the subtypes of HF were adjudicated in a subset of WHI, including all HT and black and Hispanic participants of the OS.

Exposure and covariates measurements

At baseline, self-administrated questionnaires collected information on race/ethnicity, age, income, education, geographic region, marital status, dietary supplements use, recreational physical activity, histories of hypertension, MI, atrial fibrillation (AF) and diabetes. Also at baseline, dietary intake in the past 3 months was collected by Food Frequency Questionnaire (WHI FFQ).[40] Nutrient and energy values were derived based on the Nutrition Data Systems for Research food and nutrient database (NDS-R®, version 2005, University of Minnesota Nutrition Coordinating Center).[40] We calculated uncalibrated mean daily dietary sodium and potassium intake, total energy intake and other nutrient intakes by multiplying the frequency of item consumptions in the WHI FFQ by their nutrient contents and summing up the products across all foods. Detailed information of the WHI FFQ can be found elsewhere.[40] To measure overall dietary pattern, we used the modified Alternative Healthy Eating Index 2010 (AHEI-2010), which includes 10 components (vegetables, whole fruit, whole grains, sugar-sweetened beverages, nuts, red and processed meat, eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA), polyunsaturated fat, trans fat and alcoholic drinks, with the component score for sodium intake excluded) that characterizes a healthy diet and strongly predicts the risk of major chronic disease.[41]

Body height, body weight, and blood pressure were measured using standard methods during physical examination at WHI clinics.[42] Body mass index (BMI) was calculated as body weight (kg) divided by body height (m) squared (kg/m^2). Baseline fasting blood draw were used to estimate the glomerular filtration rate (eGFR) by calculating the CKD Epidemiology Collaboration (CKD-EPI) equation based on each participant's serum creatinine concentration, age, sex and races in a limited sub-sample (n=15,846).[43] Detailed information about serum creatinine measurement in WHI was published previously.[44]

Outcome measurements

Self-reported HF hospitalization information was abstracted from medical records of WHI participants. These records were obtained annually and all diagnoses were confirmed by trained adjudicators. The abstracted HF cases were then centrally adjudicated for HT participants and locally adjudicated on all non-HT CT and OS participants by using the standardized methodology as previously described.[45] Hospitalized HF requiring and/or occurring during hospitalization required physician diagnosis of new-onset or worsened congestive HF on the reported hospital admission based upon symptoms, physical exam, chest X-ray and imaging of systolic or diastolic dysfunction. The agreement rate (k) between locally and centrally adjudicated HF was 79%.[45,46]

A sub-cohort of all participants randomized to HT and all Black and Hispanic participants enrolled in WHI with HF diagnosis by the above described adjudication process were re-adjudicated using an epidemiology algorithm that allowed adjudicators to further define definite and possible acute

HF, chronic HF, and unclassifiable or unknown event (no HF) and for acute HF to define HF with preserved ejection fraction (HFpEF, ejection fraction ≥45%), HF with reduced ejection fraction (HFrEF, ejection fraction <45%) and unknown ejection fraction HF (HFuEF).[46,47] This adjudication allowed this sub-cohort to be followed through 2015.

Statistical Analysis

Person-years of follow-up were calculated from the baseline questionnaire, until the earliest time of onset of HF, death, date of last contact, or the end of follow-up. For analyses on HF subtypes, we also censored subtypes of HF other than the outcome of interest over the follow-up. We used previously published biomarker calibration equations to calibrate dietary sodium and potassium intakes according to 24-hour urinary excretion data that were generated from a subpopulation of 994 WHI participants.[20,48-50] Details of the calibration equations are given in Supplemental Method I.

Cox proportional hazards models with adjustment for multiple covariates (detailed covariate list can be found in the footnotes of Table 2) were used to estimate hazard ratios (HRs) for HF, HFpEF and HFrEF, and their 95% confidence intervals (CIs). We modeled the intake levels continuously (HR per 1 SD) and categorically (HR comparing higher to the lowest quintile). To quantify a linear trend, we assigned the median within each quintile as an ordinal variable and modeled the variable continuously. The Wald test was used to evaluate statistical significance. For the analysis within WHI OS, the Cox model was stratified on age, and within WHI CT, it was additionally stratified on intervention group assignments. To explore potential non-linear dose-response relationships between sodium intake and the risk of HF and its subtypes, we used restricted cubic spline cox regression with 3 knots.[51] We also evaluated the associations between calibrated sodium intakes of the risk of HF in the subgroups defined by baseline histories of hypertension, myocardial infarction (MI), diabetes, atrial fibrillation (AF) (all yes or no), eGFR (<60, ≥60 ml/min), and BMI (<30, ≥30 kg/m^2) in secondary analyses. The interactions between calibrated sodium intake and the variables of stratification were tested using the Wald test with 1 degree of freedom. In a sensitivity analysis, we adjusted for several potential mediating factors, including baseline hypertension, diabetes, MI, AF and BMI. All the analyses were conducted in OS and CT separately. An inverse-variance-weighted, fixed-effect meta-analysis was used to combine the results across OS and CT. All analyses were performed using SAS software (Version 9.4) at a 2-sided P value of 0.05.

RESULTS

Among the total study population (n=118,060), the mean baseline age was 63.4 years and 84.3% of the participants were white, 7.8% were African American, 3.8% were Hispanic and 4.1% were other race/ethnicity groups. The median of calibrated dietary sodium intake was 2385 mg/day (IQR: 2236-2576 mg/day) and median of dietary potassium intake was 2238 mg/day (IQR: 1971-2486 mg/day) (Table 1). White participants had higher dietary potassium intake, whereas the intake levels of African American participants were relatively lower. Participants with higher calibrated sodium intake had higher BMI, lower alcohol intake, less recreational physical activity, higher prevalence of diabetes, lower prevalence of MI and AF than those with lower sodium intake.

During 1,731,518 person-years of follow-up, 3,347 (2.8%) participants developed HF. For the analysis on HFpEF, there were 738 (2.6%) cases developed over 394,659 person-years of follow-up. For the analysis on HFrEF, 432 (1.5%) cases developed over 390,865 person-years of follow-up (Table 2). In the main model (Model 2), every 1-SD increment in calibrated sodium intake was significantly associated with 1.35 (95% CI: 1.29-1.42), 1.40 (95% CI: 1.26-1.55) and 1.22 (95% CI: 1.06-1.39) times the risk of developing incident HF, HFpEF and HFrEF, respectively. Comparing the extreme quintiles, a significant positive association was observed between calibrated dietary sodium intake and the incidence of HF ($HR_{Q5 \text{ vs. } Q1}$ =2.36, 95% CI: 2.05-2.72, P-trend <0.001). When comparing to participants in the lowest quintile, participants in the highest quintile of calibrated dietary sodium intake had significantly higher risk of developing HFpEF ($HR_{Q5 \text{ vs. } Q1}$ =2.72, 95% CI: 2.01-3.68, P-trend<0.001). For HFrEF, the comparison between the highest and the lowest quintile of calibrated sodium intake was associated with a HR of 1.78

Table 1. Basic characteristics of the study population according to calibrated intake levels

	Calibrated Dietary Sodium Intake			Calibrated Dietary Potassium Intake			Calibrated Sodium/ Potassium Ratio		
	Q1	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**
n	23612	23612	23612	23612	23612	23612	23612	23612	23612
Calibrated Sodium Intake (mg/day) [2]	2155±182	2409±186	2693±273	2432±319	2421±268	2395±239	2213±190	2405±216	2639±299
Age	68.2±6.7	62.9±6.8	59.5±6.2	64.3±7.5	64.1±7.1	60.8±6.8	65.7±7.3	63.2±7.2	61.6±7.0
Income	4.3±2.0	4.4±1.8	4.0±1.7	3.9±2.0	4.4±1.8	4.3±1.8	4.3±2.0	4.4±1.8	3.9±1.8
BMI	24.4±3.5	26.8±4.4	32.9±7.3	29.2±6.4	27.5±5.6	26.6±5.4	24.3±3.4	27.1±4.6	32.4±7.2
Alcohol Intake	7.8±14.9	5.5±10.1	3.3±7.8	4.1±11.1	6.2±11.2	5.1±9.9	7.3±13.5	5.8±10.8	3.0±8.3
Modified AHEI-2010 [1]	48.4±11.4	49.9±11.5	48.5±11.6	43.7±10.7	49.4±11.0	54.6±11.1	52.0±11.4	50.3±11.3	44.3±10.7
Leisure-time physical activity (MET-hours/week)	14.1±14.3	13.9±14.4	10.6±12.8	9.5±12.3	13.1±13.6	17.3±16.0	17.0±15.6	13.6±13.9	8.7±11.7
Calibrated Dietary Energy (kcal)	1939±148	2159±165	2444±282	2127±279	2166±252	2235±240	2028±181	2169±216	2328±322
Ethnicity*									
Whites	18047(76.4)	20660(87.5)	19819(83.9)	9116(38.6)	22778(96.5)	23487(99.5)	22500(95.3)	21470(90.9)	13366(56.6)
African American	1392(5.9)	1670(7.1)	2615(11.1)	8049(34.1)	162(0.7)	7(0.0)	65(0.3)	493(2.1)	6921(29.3)
Hispanic	825(3.5)	861(3.7)	1000(4.2)	2834(12.0)	366(1.6)	44(0.2)	207(0.9)	556(2.4)	2259(9.6)
Other	3280(13.9)	365(1.6)	132(0.6)	3571(15.1)	238(1.0)	17(0.1)	761(3.2)	1025(4.3)	1018(4.3)
Education*									
<High school	533(2.3)	956(4.1)	2358(10.0)	3267(13.8)	693(2.9)	211(0.9)	114(0.5)	590(2.5)	3640(15.4)
High school	1079(4.6)	2931(12.4)	9118(38.6)	5877(24.9)	4018(17.0)	1580(6.7)	358(1.5)	2836(12.0)	9387(39.8)
School after high school	11065(46.9)	8965(38.0)	5897(25.0)	7580(32.1)	8856(37.5)	9609(40.7)	10783(45.7)	9454(40.0)	5436(23.0)
College degree or higher	10897(46.2)	10620(45.0)	5821(24.7)	6568(27.8)	9871(41.8)	12131(51.4)	12346(52.3)	10611(44.9)	4687(19.9)
Smoking*									
Never	11092(47.0)	12351(52.3)	12263(51.9)	12631(53.5)	11699(49.6)	11788(49.9)	11155(47.2)	12090(51.2)	12683(53.7)
Past smoker	8240(34.9)	10122(42.9)	10843(45.9)	8447(35.8)	10312(43.7)	10694(45.3)	9399(39.8)	10180(43.1)	9692(41.1)
Current smoker	4155(17.6)	1025(4.3)	389(1.7)	2400(10.2)	1474(6.2)	1023(4.3)	2933(12.4)	1229(5.2)	1106(4.7)
Hypertension									
Yes	9224(39.1)	7160(30.3)	7639(32.4)	11532(48.8)	7595(32.2)	4153(17.6)	6254(26.5)	7298(30.9)	10427(44.2)
No	14388(60.9)	16452(69.7)	15973(67.7)	12080(51.2)	16017(67.8)	19459(82.4)	17358(73.5)	16314(69.1)	13185(55.8)
MI									
Yes	804(3.4)	562(2.4)	556(2.4)	588(2.5)	678(2.9)	471(2.0)	654(2.8)	610(2.6)	553(2.3)
No	22808(96.6)	23050(97.6)	23056(97.7)	23024(97.5)	22934(97.1)	23141(98.0)	22958(97.2)	23002(97.4)	23059(97.7)
Diabetes									
Yes	615(2.6)	761(3.2)	1685(7.1)	1785(7.6)	798(3.4)	554(2.4)	419(1.8)	739(3.1)	2028(8.6)
No	22997(97.4)	22851(96.8)	21927(92.9)	21827(92.4)	22814(96.6)	23058(97.7)	23193(98.2)	22873(96.9)	21584(91.4)
Atrial fibrillation									
Yes	1245(5.3)	910(3.9)	783(3.3)	1110(4.7)	1027(4.4)	730(3.1)	1081(4.6)	947(4.0)	950(4.0)
No	22367(94.7)	22702(96.2)	22829(96.7)	22502(95.3)	22585(95.7)	22882(96.9)	22531(95.4)	22665(96.0)	22662(96.0)

Abbreviations: BMI, Body Mass Index; AHEI, Alternate Healthy Eating Index; MET, metabolic equivalent; GED, General Educational Development; MI, myocardial infarction.
For continuous variables, the values are mean ± SD; for categorical variables, the values are n (%).

[*] Does not include participants for whom data was not reported

[1] AHEI-2010 component score for sodium was excluded

[2] Sodium intake was standardized according to total energy intake of 2000kcal/day

Table 2. Associations of calibrated sodium and calibrated potassium intakes with incident heart failure, HFpEF and HFrEF [1]

	Quintile of Calibrated Intake [2]					P for trend	HR per sd (95% CI)
	Q1	Q2	Q3	Q4	Q5		
Heart Failure							
Dietary sodium							
Cases/Person-years	902/316755	635/347602	572/357079	545/358983	693/351099		
Model 1 [3]	1.00	0.90 (0.81, 1.00)	1.03 (0.93, 1.15)	1.18 (1.06, 1.32)	1.91 (1.71, 2.13)	<0.001	1.25 (1.21, 1.30)
Model 2 [4]	1.00	1.03 (0.92, 1.15)	1.21 (1.07, 1.37)	1.43 (1.26, 1.63)	2.36 (2.05, 2.72)	<0.001	1.35 (1.29, 1.42)
Dietary potassium							
Cases/Person-years	869/298637	801/334145	673/353499	572/365062	432/380174		
Model 1	1.00	0.83 (0.76, 0.92)	0.73 (0.66, 0.81)	0.66 (0.60, 0.74)	0.58 (0.52, 0.66)	<0.001	0.83 (0.80, 0.86)
Model 2	1.00	0.94 (0.84, 1.06)	0.84 (0.74, 0.96)	0.76 (0.66, 0.88)	0.66 (0.56, 0.78)	<0.001	0.86 (0.82, 0.91)
Sodium:potassium ratio							
Cases/Person-years	688/349671	588/360535	592/356409	647/346178	832/318726		
Model 1	1.00	1.03 (0.92, 1.15)	1.12 (1.00, 1.25)	1.34 (1.20, 1.50)	2.03 (1.83, 2.25)	<0.001	1.29 (1.25, 1.34)
Model 2	1.00	1.11 (0.99, 1.25)	1.25 (1.11, 1.41)	1.51 (1.34, 1.71)	2.20 (1.91, 2.54)	<0.001	1.32 (1.26, 1.38)
HFpEF							
Dietary sodium							
Cases/Person-years	192/74151	153/79329	126/81469	113/80358	154/79352		
Model 1	1.00	0.91 (0.73, 1.13)	0.94 (0.74, 1.18)	0.99 (0.78, 1.26)	1.81 (1.44, 2.29)	<0.001	1.21 (1.12, 1.31)
Model 2	1.00	1.11 (0.88, 1.40)	1.21 (0.94, 1.57)	1.39 (1.05, 1.84)	2.72 (2.01, 3.68)	<0.001	1.40 (1.26, 1.55)
Dietary potassium							
Cases/Person-years	127/71016	175/76447	163/79716	155/82066	118/85413		
Model 1	1.00	1.10 (0.87, 1.39)	0.96 (0.75, 1.23)	0.96 (0.75, 1.22)	0.85 (0.65, 1.11)	0.14	0.94 (0.86, 1.02)
Model 2	1.00	1.15 (0.87, 1.53)	1.05 (0.77, 1.44)	1.06 (0.76, 1.49)	1.01 (0.69, 1.48)	0.76	0.98 (0.87, 1.11)
Sodium:potassium ratio							
Cases/Person-years	164/80329	153/81591	145/80387	131/78073	145/74277		
Model 1	1.00	1.05 (0.84, 1.31)	1.09 (0.87, 1.36)	1.15 (0.91, 1.45)	1.66 (1.31, 2.10)	<0.001	1.19 (1.10, 1.28)
Model 2	1.00	1.12 (0.89, 1.41)	1.23 (0.97, 1.57)	1.40 (1.06, 1.83)	2.20 (1.60, 3.04)	<0.001	1.32 (1.18, 1.47)
HFrEF							
Dietary sodium							
Cases/Person-years	106/73533	86/78636	84/80488	75/79437	81/78771		
Model 1	1.00	0.91 (0.68, 1.21)	1.05 (0.78, 1.42)	1.07 (0.78, 1.46)	1.40 (1.02, 1.93)	0.03	1.13 (1.01, 1.25)
Model 2	1.00	1.10 (0.81, 1.50)	1.27 (0.91, 1.78)	1.32 (0.91, 1.90)	1.78 (1.19, 2.69)	0.005	1.22 (1.06, 1.39)
Dietary potassium							
Cases/Person-years	102/70234	94/75716	91/78865	86/81327	59/84725		
Model 1	1.00	0.76 (0.57, 1.02)	0.72 (0.53, 0.97)	0.71 (0.52, 0.95)	0.55 (0.39, 0.77)	<0.001	0.83 (0.75, 0.92)
Model 2	1.00	0.81 (0.57, 1.16)	0.82 (0.55, 1.20)	0.89 (0.59, 1.35)	0.71 (0.44, 1.14)	0.13	0.90 (0.77, 1.05)
Sodium:potassium ratio							
Cases/Person-times	88/79741	87/80691	88/79625	76/77266	93/73543		
Model 1	1.00	1.09 (0.81, 1.46)	1.18 (0.88, 1.59)	1.15 (0.84, 1.57)	1.69 (1.24, 2.31)	0.001	1.18 (1.07, 1.31)
Model 2	1.00	1.12 (0.82, 1.52)	1.20 (0.87, 1.65)	1.11 (0.78, 1.60)	1.57 (1.03, 2.40)	0.06	1.15 (1.00, 1.32)

Abbreviations: HFpEF, Heart Failure with preserved ejection fraction; HFrEF, Heart Failure with reduced ejection fraction.
[1] Results for WHI-OS and WHI-CT from the multivariable model were combined using the fixed-effects model.

[2] Intake levels measured by FFQ were calibrated by urinary excretion level according to the following characteristics: dietary self-report, age, BMI, race, dietary supplementation, smoking status, education and family income.
[3] Model 1 was stratified on age in WHI-OS or on age and intervention group assignments in WHI-CT.
[4] Model 2 was stratified on age in WHI-OS or on age and intervention group assignments in WHI-CT, and adjusted for race, alcohol intake, smoking status, family income, education, leisure-time physical activity score, region, marital status, and modified AHEI-2010.

(95% CI: 1.19-2.69, P-trend=0.005). Also in the main model, every 1-SD increment in calibrated potassium intake was significantly associated with 0.86 (95% CI: 0.82-0.91) times the risk of developing incident HF. Participants in the highest quintile of calibrated potassium intake had significantly lower risk of developing HF ($HR_{Q5\ vs.\ Q1}$ =0.66, 95% CI: 0.56-0.78, P-trend<0.001), when comparing to participants in the lowest quintile. Additionally, we found a significantly positive association between sodium/potassium ratio and HF ($HR_{Q5\ vs.\ Q1}$: 2.20, 95% CI: 1.91-2.54, P-trend<0.001). Participants in the highest quintile of calibrated sodium/potassium ratio had a 120% higher risk of having HFpEF, when comparing to those in the lowest quintile ($HR_{Q5\ vs.\ Q1}$: 2.20, 95% CI: 1.60-3.04, P-trend<0.001). Although calibrated sodium/potassium ratio was significantly associated with a 57% higher risk of incident HFrEF comparing extreme quintiles, a significant linear trend was not observed across quintiles (95% CI: 1.03-2.40, P-trend=0.06) (Table 2). We did not observe significant association of calibrated potassium intake with HFpEF and HFrEF.

In the restricted cubic spline modeling, we observed non-linear dose-response relationship between calibrated sodium intake and the risk of HF and HFpEF, with an accelerated increasing trend in HR at higher intake levels (P-curve <0.001 for HF and HFpEF) (Figure 1, Supplemental figure 2). We found linear dose-response relationships of calibrated sodium intake with the risk of HFrEF (P-linear =0.002) (Supplemental figure 3).

We observed significantly positive association between calibrated sodium intakes and the risk of HF in different subgroups defined by baseline histories of hypertension, MI, diabetes, AF, eGFR levels and obesity, while stronger associations were observed for participants with baseline hypertension, diabetes and obesity (all $P_{\text{interaction}}$ <0.05) (Supplemental Table 5, 6 and Figure 2). In general, we observed attenuation of all the associations between calibrated intakes and the risk of HF, HFpEF and HFrEF, after further adjusting for the potential mediating factors and BMI (Supplemental Table 4). The associations between calibrated sodium intake and the risk of HF remained strongly significant (P-trend<0.001). The results for uncalibrated intakes were consistent with that for calibrated intakes in terms of the direction of association, but the associations for uncalibrated intakes were weaker in magnitude (Supplemental Table

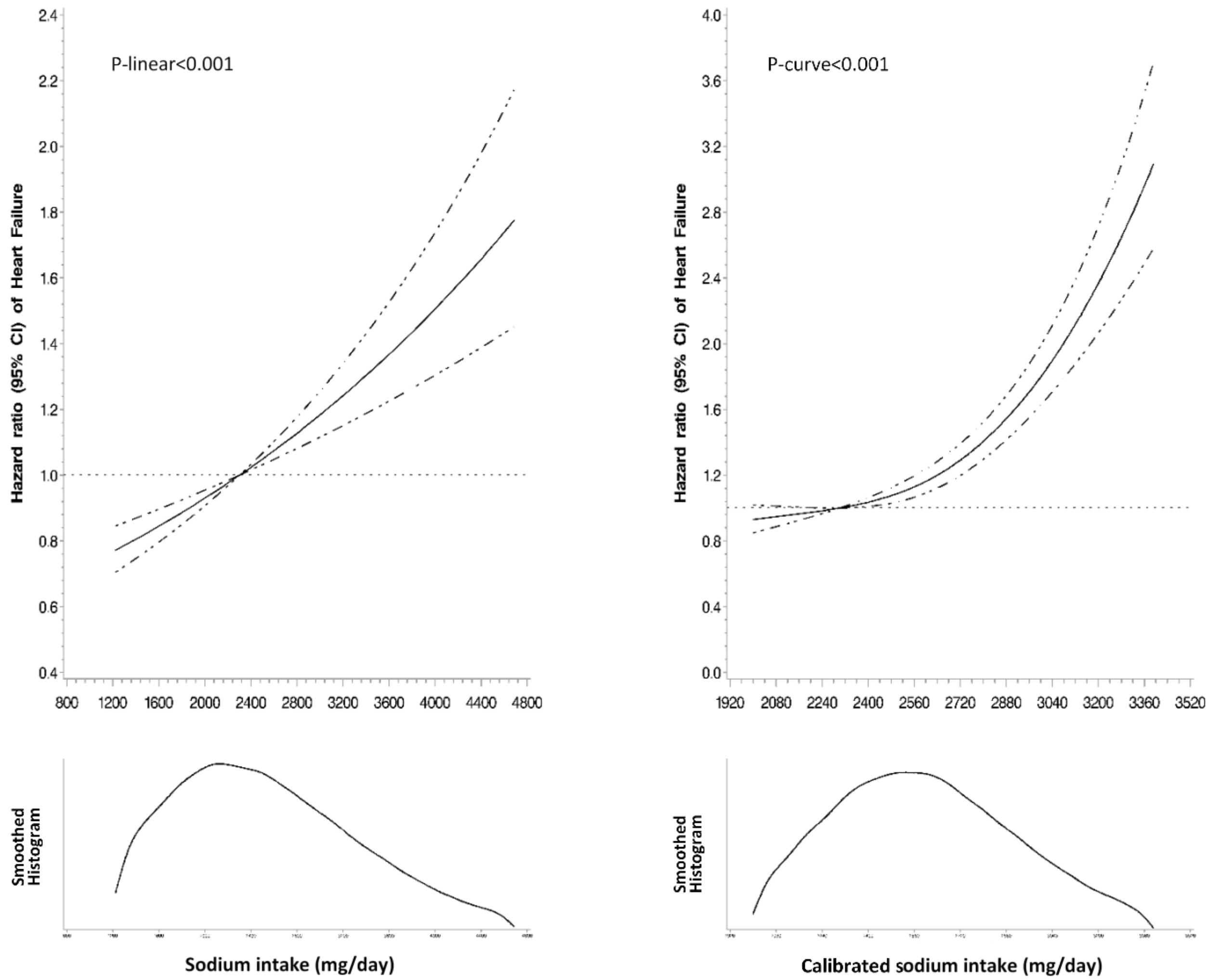


Figure 1. Dose response relationship between sodium intake and risk of heart failure

The model was stratified on age and intervention group assignments, and adjusted for race, alcohol intake, smoking status, family income, education, leisure-time physical activity score, region, marital status, and modified AHEI-2010.
The dose response relationship was estimated using restricted cubic spline cox regression with 3 knots; tests for curvature used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms.
Intake levels measured by FFQ were calibrated by urinary excretion level according to the following characteristics: dietary self-report, age, BMI, race, dietary supplementation, smoking status, education and family income.

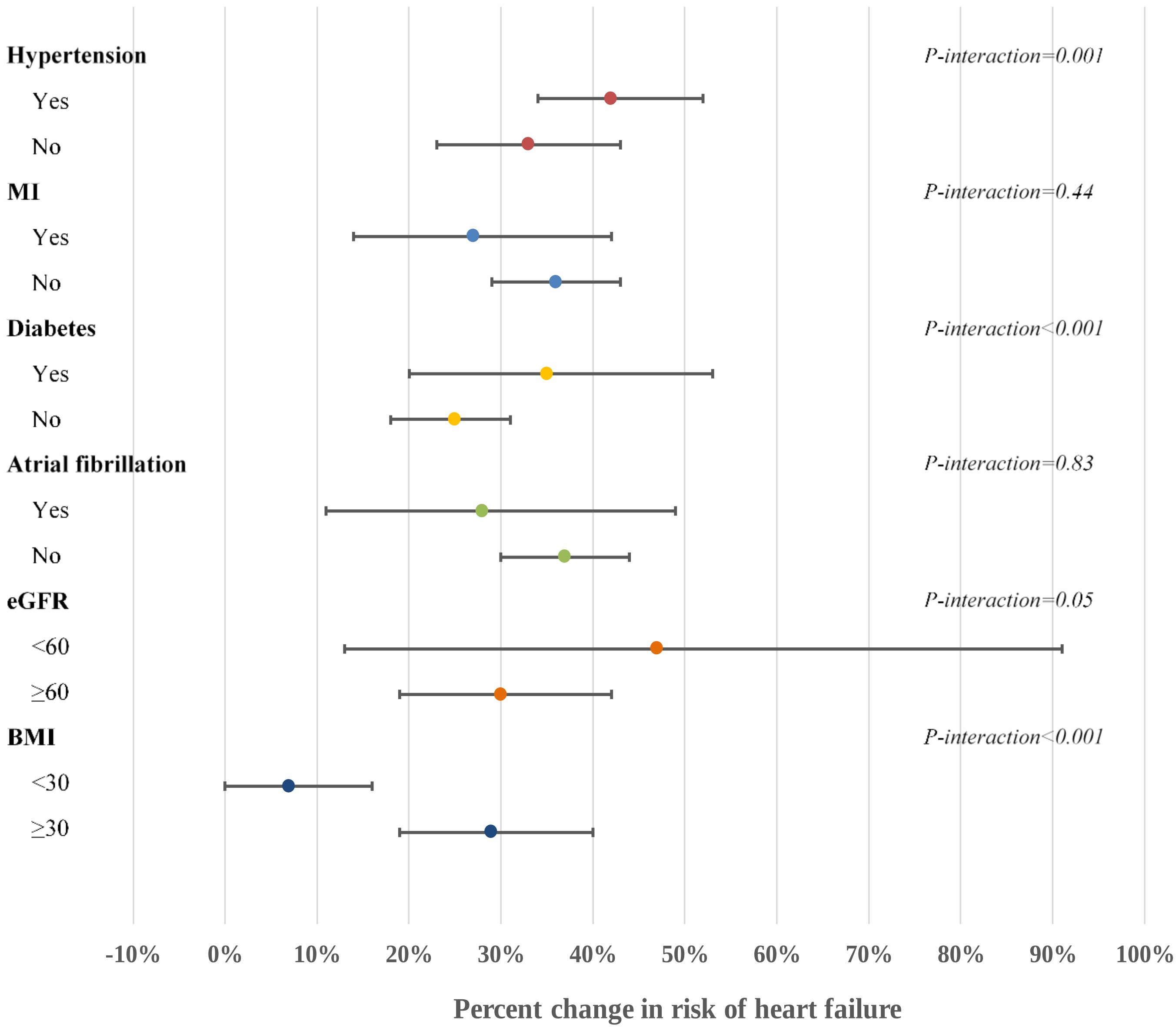


Figure 2. Hazard ratio of heart failure associated with 1 sd increment in sodium intake in subgroups defined by select baseline characteristics

Abbreviations: MI, myocardial infarction; eGFR, estimated glomerular filtration rate.

The model was stratified on age in WHI-OS or on age and intervention group assignments in WHI-CT, and adjusted for race, alcohol intake, smoking status, family income, education, leisure-time physical activity score, region, marital status, and modified AHEI-2010.

P-interaction were estimated from the Wald test of the product term between sodium intake and the variable of stratification.

Intake levels measured by FFQ were calibrated by urinary excretion level according to the following characteristics: dietary self-report, age, BMI, race, dietary supplementation, smoking status, education and family income.

3). Finally, the results were generally consistent between analyses conducted using the OS and CT cohorts separately (Supplemental Table 2).

DISCUSSION

In postmenopausal women, calibrated sodium intake and sodium/potassium ratio were positively associated with HF and its major subtypes, HFpEF and HFrEF. A stronger association was observed for HFpEF than for HFrEF. The dose-response relationship between sodium intake and the risks of HF, HFpEF and HFrEF appeared to be monotonically increasing. We also observed inverse associations between calibrated potassium and the risk of HF. The observed significant interactions of calibrated sodium intake with hypertension, diabetes, and BMI pointed to their potential mediating effects in the association between sodium intake and the risk of HF.

Our observation of stronger association between calibrated sodium and the risk of HFpEF than that of HFrEF could possibly be explained by the difference in pathophysiology between the two major HF subtypes. HFpEF is complex and associated with older age, neuroendocrine dysfunction, low grade systemic inflammation, autonomic dysfunction, both LV diastolic and systolic dysfunction, RV dysfunction, pulmonary and renal dysfunction, chronotropic incompetence, vascular dysfunction, skeletal muscle dysfunction, and multiple co-morbidities including hypertension, diabetes and obesity.[57,58] However, what remains common to eventually all patients with HFpEF is volume overload.[52] High sodium intake produces a rise in cardiac output by increasing LV preload which influences LV diastolic filling.[53,54] Therefore, HFpEF patients are particularly sensitive to the change in blood volume or fluid homoeostasis. In contrast to HFpEF, systolic dysfunction associated with left ventricular chamber dilation and remodeling is the main characteristic of HFrEF.[55] Its etiology is linked to a variety of reasons including to a large extent coronary heart disease but also other myopathies. Common on a functional basis is that in chronic, compensated HFrEF, stroke volume is typically similar to normal. In this context, HFrEF and HFpEF display markedly different left ventricular end systolic pressure volume relationships or end-systolic elastance.[56] HfpEF patients exhibit a stiffer myocardium which is why HFrEF individuals respond better to arterial vasodilators or preload changes leading to smaller changes blood pressure. As a result, the observed association between sodium and HFrEF was relatively weakened. Previous evidence regarding the impact of high sodium intake on the risk of HFpEF and HFrEF is sparse.[7,57,58] Our study, for the first time, showed that increased risks of incident HFpEF and HFrEF associated with high sodium intake with differing magnitude of associations.

For the first time, our study identified the inverse association between calibrated potassium intake and the risk of HF in a large population. This association could be largely explained by potassium's protective effect against the risk of hypertension, possibly through a series of pathways including promoting natriuresis, vascular smooth muscle relaxation, endothelial dependent vasodilation, and nitric oxide release.[19,59,60] Previous studies also showed that fruit and vegetable intakes, which are major food sources of dietary potassium, have strong protective effect on the risk of CVD.[61,62] It is possible that this association may due to the correlation between potassium and other beneficial constituents in fruits and vegetables, such as dietary fibers, vitamins, phenolic and phytochemicals.[63] However, such correlation cannot entirely explain our findings because our statistical model adjusted for fruit and vegetable intakes as components of AHEI-2010. Moreover, the positive association between sodium/potassium ratio and the risk of HF was similar to existing findings on the risk of hypertension or CVD.[64-66] Considering the strong positive association between sodium intake and HF risk and the inverse association between potassium intake and HF risk, our significant result on sodium/potassium ratio was expected.

Our study in baseline healthy postmenopausal women had relatively higher generalizability than previous studies conducted in chronic kidney disease patients and in overweight population.[25,67] Moreover, with the use of biomarker calibrated sodium, our study has the advantage of reduced measurement error over previous study measuring dietary sodium intake with one-day 24-hour recall.[67] The stronger association observed in our study is also an indication of reduced random measurement error after applying the biomarker calibration methods. Another previous study used a calibration equation developed in a Japanese population based on spot urinary sample collection to calibrate the dietary sodium intake of a European population, making the results hard to interpret.[68] Therefore, our study in a relative homogenous and well-characterized population using validated calibration equation developed from the same study population provided more reliable evidence. In addition, our findings were generally consistent across various subgroups except those defined by hypertension, diabetes, and BMI, showing the robustness of our data and analyses. The different associations between sodium intake and HF across hypertensive and non-hypertensive groups were possibly due to the mediating effect of increasing blood pressure. Finally, the significant interaction between BMI and sodium intake could be explained by the correlation between high sodium intake and energy imbalance, a major cause of body adiposity and diabetes risk. The attenuation observed in Model 3 and Model 4 in the sensitivity analyses could also be explained by these mediating effects (Supplemental Table 4).

Our findings based on the application of biomarker calibration of sodium and potassium intake are informative for strengthening the evidence base of the clinical guidelines for HF, especially making specialized recommendations for different subtypes of HF. One explanation of the discrepancies existed in previous study findings regarding dietary sodium intake and CVD risks is the measurement error in self-reported dietary intake collected by questionnaires, and similarly for potassium.[21,22,25,69,70] Twenty-four-hour urinary sodium excretion, as a recovery biomarker of sodium intake, would eliminate some of the measurement errors in dietary self-report.[69,71] However, due to its high cost and participant burden, it is not common to utilize 24-hour urinary excretion in large epidemiological studies. The biomarker calibration equations approach used in this analysis enabled us to examine associations between sodium and potassium intakes and disease outcomes while partially taking into account systematically biased measurement errors from the self-reported FFQ dietary data.[20,50] Moreover, our study included a large population with long follow-up period, and therefore had sufficient statistical power to detect the associations of interest. Finally, our findings stem from a geographically and ethnically diverse population with high generalizability.

There are some limitations in our study. First, our single sex population limited the extrapolation of findings to men. Second, out-patient diagnosed HF or its subtypes were not included, leading to potential selection bias. However, with the severity and fast progression of HF, such missing only occupied a small portion of all the HF cases. Moreover, potential misclassification bias existed because 30.1% of the HF outcomes had missing in ejection fraction. Finally, to ensure the power of our analyses in HF subtypes, we redefined HFrEF with ejection fraction of <45%, instead of <40%, which is the stricter criteria.

CONCLUSION

This study showed a strong positive association of dietary sodium and an inverse association of dietary potassium with the incidence of HF in a very large population of postmenopausal women. For the first time, this study linked sodium intake to 2 major subtypes of HF with different pathophysiological basis. The increasing prevalence, as well as the impairment of life expectancy and quality after the onset of HF are urgently calling effective population approaches for primary prevention, among which dietary recommendation is a core approach. Our findings support current dietary and clinical recommendations on sodium reduction for HF prevention.

SUPPLEMENTAL MATERIALS:

Supplemental Table 1. Basic characteristics of the study population according to uncalibrated intake levels

	Uncalibrated Dietary Sodium Intake			Uncalibrated Dietary Potassium Intake			Uncalibrated Sodium/ Potassium Ratio		
	Q1	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**
n	23612	23612	23612	23612	23612	23612	23612	23612	23612
Uncalibrated Sodium Intake (mg/day) [2]	2604±299	3346±100	4187±434	3208±579	3394±589	3462±628	3424±749	3360±180	3418±836
Age	63.1±7.4	63.6±7.3	63.4±7.2	62.2±7.3	63.5±7.2	64.3±7.2	63.4±7.3	63.4±7.3	63.5±7.3
Income	4.2±1.9	4.3±1.8	4.3±1.9	3.9±1.9	4.4±1.8	4.4±1.8	4.3±1.9	4.2±1.8	4.3±1.8
BMI	27.5±5.8	27.4±5.6	28.4±6.1	29.3±6.5	27.3±5.5	26.9±5.3	27.6±5.8	27.7±5.8	27.6±5.6
Alcohol Intake	9.4±17.9	4.6±8.3	3.7±7.2	5.2±12.5	5.8±10.8	5.2±10.5	6.2±12.7	4.4±8.3	6.8±13.5
Modified AHEI-2010 [1]	45.7±11.5	48.6±11.0	54.1±11.4	41.8±9.7	49.2±10.6	56.9±10.7	49.4±10.3	49.0±12.0	50.2±11.7
Leisure-time physical activity (MET-hours/week)	12.2±14.0	13.0±13.8	14.6±14.9	8.6±11.7	13.2±13.6	17.8±16.1	13.4±14.1	12.9±14.1	13.5±14.0
Uncalibrated Dietary Energy (kcal)	1781±661	1424±533	1759±647	1737±759	1465±537	1728±550	1598±612	1535±596	1627±609
Ethnicity*									
Whites	19242(81.5)	19892(84.3)	20342(86.2)	16557(70.1)	20524(86.9)	21568(91.3)	20219(85.6)	19273(81.6)	20434(86.5)
African American	2285(9.7)	1771(7.5)	1534(6.5)	3903(16.5)	1323(5.6)	894(3.8)	1540(6.5)	2199(9.3)	1473(6.2)
Hispanic	1201(5.1)	796(3.4)	793(3.4)	1641(7.0)	753(3.2)	490(2.1)	859(3.6)	936(4.0)	838(3.6)
Other	825(3.5)	1088(4.6)	891(3.8)	1439(6.1)	953(4.0)	607(2.6)	931(3.9)	1150(4.9)	815(3.5)
Education*									
<High school	1374(5.8)	1127(4.8)	1151(4.9)	2272(9.6)	975(4.1)	553(2.3)	1167(4.9)	1279(5.4)	1017(4.3)
High school	4170(17.7)	4030(17.1)	3484(14.8)	5349(22.7)	3825(16.2)	2778(11.8)	3794(16.1)	4081(17.3)	3728(15.8)
School after high school	8789(37.2)	8778(37.2)	8593(36.4)	9077(38.4)	8759(37.1)	8094(34.3)	8722(36.9)	8680(36.8)	8799(37.3)
College degree or higher	9091(38.5)	9478(40.1)	10200(43.2)	6675(28.3)	9885(41.9)	12018(50.9)	9754(41.3)	9363(39.7)	9904(41.9)
Smoking*									
Never	11649(49.3)	12401(52.5)	11567(49.0)	11730(49.7)	11978(50.7)	12277(52.0)	11937(50.6)	12376(52.4)	11626(49.2)
Past smoker	9659(40.9)	9649(40.9)	10602(44.9)	9047(38.3)	10120(42.9)	10318(43.7)	10129(42.9)	9521(40.3)	10247(43.4)
Current smoker	2201(9.3)	1445(6.1)	1309(5.5)	2727(11.6)	1402(5.9)	883(3.7)	1420(6.0)	1607(6.8)	1627(6.9)
Hypertension									
Yes	7341(31.1)	7680(32.5)	8335(35.3)	8693(36.8)	7480(31.7)	7265(30.8)	7701(32.6)	7842(33.2)	7660(32.4)
No	16271(68.9)	15932(67.5)	15277(64.7)	14919(63.2)	16132(68.3)	16347(69.2)	15911(67.4)	15770(66.8)	15952(67.6)
MI									
Yes	544(2.3)	648(2.7)	705(3.0)	642(2.7)	614(2.6)	624(2.6)	585(2.5)	628(2.7)	616(2.6)
No	23068(97.7)	22964(97.3)	22907(97.0)	22970(97.3)	22998(97.4)	22988(97.4)	23027(97.5)	22984(97.3)	22996(97.4)
Diabetes									
Yes	535(2.3)	859(3.6)	1609(6.8)	1167(4.9)	900(3.8)	845(3.6)	1090(4.6)	892(3.8)	959(4.1)
No	23077(97.7)	22753(96.4)	22003(93.2)	22445(95.1)	22712(96.2)	22767(96.4)	22522(95.4)	22720(96.2)	22653(95.9)
Atrial fibrillation									

Yes	1002(4.2)	997(4.2)	976(4.1)	998(4.2)	949(4.0)	1002(4.2)	967(4.1)	977(4.1)	975(4.1)
No	22610(95.8)	22615(95.8)	22636(95.9)	22614(95.8)	22663(96.0)	22610(95.8)	22645(95.9)	22635(95.9)	22637(95.9)

Abbreviations: BMI, Body Mass Index; AHEI, Alternate Healthy Eating Index; MET, metabolic equivalent; GED, General Educational Development; MI, myocardial infarction. For continuous variables, the values are mean ± SD; for categorical variables, the values are n (%).

[*] Does not include participants for whom data was not reported.

[1] AHEI-2010 component score for sodium was excluded.

[2] Sodium intake was standardized according to total energy intake of 2000kcal/day

Supplemental Table 2. Associations of calibrated sodium and calibrated potassium intakes with incident heart failure, HFpEF and HFrEF in WHI-OS and WHI-CT

	Quintile of Calibrated Intake [1]					P for trend	HR per sd (95% CI)
	Q1	Q2	Q3	Q4	Q5		
Heart Failure							
Dietary sodium							
OS							
Cases/Person-years	544/233729	363/257462	308/265010	335/266584	416/258772		
Model 1 [2]	1.00	0.87 (0.76, 1.00)	0.95 (0.83, 1.10)	1.26 (1.09, 1.45)	2.02 (1.76, 2.33)	<0.001	1.29 (1.23, 1.35)
Model 2 [3]	1.00	1.01 (0.87, 1.17)	1.11 (0.94, 1.30)	1.53 (1.29, 1.80)	2.45 (2.05, 2.94)	<0.001	1.38 (1.30, 1.47)
CT							
Cases/Person-years	358/83026	272/90140	264/92069	210/92399	277/92327		
Model 1	1.00	0.94 (0.80, 1.11)	1.15 (0.98, 1.36)	1.07 (0.89, 1.27)	1.75 (1.48, 2.08)	<0.001	1.20 (1.13, 1.27)
Model 2	1.00	1.06 (0.89, 1.26)	1.36 (1.13, 1.64)	1.30 (1.05, 1.60)	2.24 (1.79, 2.80)	<0.001	1.31 (1.21, 1.41)
Dietary potassium							
OS							
Cases/Person-years	540/217684	495/246865	395/262257	318/271317	218/283433		
Model 1	1.00	0.84 (0.74, 0.95)	0.71 (0.63, 0.81)	0.63 (0.55, 0.73)	0.53 (0.45, 0.62)	<0.001	0.81 (0.77, 0.84)
Model 2	1.00	0.98 (0.85, 1.14)	0.83 (0.70, 0.99)	0.74 (0.61, 0.90)	0.62 (0.50, 0.77)	<0.001	0.84 (0.79, 0.90)
CT							
Cases/Person-years	329/80953	306/87280	278/91242	254/93745	214/96741		
Model 1	1.00	0.83 (0.71, 0.97)	0.76 (0.65, 0.89)	0.71 (0.61, 0.84)	0.66 (0.55, 0.79)	<0.001	0.87 (0.82, 0.91)
Model 2	1.00	0.88 (0.73, 1.07)	0.85 (0.69, 1.05)	0.79 (0.63, 0.99)	0.72 (0.56, 0.93)	0.008	0.90 (0.83, 0.97)
Sodium:potassium ratio							
OS							
Cases/Person-years	385/260178	325/267674	334/264669	407/255994	515/233042		
Model 1	1.00	1.00 (0.86, 1.16)	1.11 (0.96, 1.28)	1.46 (1.27, 1.68)	2.14 (1.87, 2.44)	<0.001	1.33 (1.28, 1.39)
Model 2	1.00	1.09 (0.93, 1.27)	1.24 (1.06, 1.46)	1.68 (1.43, 1.97)	2.28 (1.90, 2.74)	<0.001	1.35 (1.27, 1.43)
CT							
Cases/Person-years	303/89493	263/92861	258/91740	240/90184	317/85684		
Model 1	1.00	1.08 (0.91, 1.27)	1.14 (0.96, 1.34)	1.18 (0.99, 1.40)	1.88 (1.60, 2.21)	<0.001	1.24 (1.17, 1.30)
Model 2	1.00	1.14 (0.96, 1.36)	1.26 (1.06, 1.51)	1.30 (1.06, 1.58)	2.09 (1.67, 2.62)	<0.001	1.28 (1.18, 1.38)
HFpEF							
Dietary sodium							
OS							
Cases/Person-years	25/22554	29/23458	22/23770	19/22875	30/21778		
Model 1	1.00	1.38 (0.81, 2.37)	1.26 (0.70, 2.26)	1.37 (0.74, 2.55)	2.78 (1.57, 4.93)	0.001	1.38 (1.14, 1.66)
Model 2	1.00	1.57 (0.88, 2.77)	1.48 (0.78, 2.80)	1.72 (0.85, 3.46)	3.29 (1.62, 6.70)	0.002	1.46 (1.15, 1.84)
CT							
Cases/Person-years	167/51597	124/55871	104/57699	94/57483	124/57574		
Model 1	1.00	0.84 (0.66, 1.06)	0.89 (0.69, 1.14)	0.94 (0.72, 1.22)	1.67 (1.29, 2.15)	<0.001	1.18 (1.08, 1.29)
Model 2	1.00	1.03 (0.80, 1.33)	1.17 (0.88, 1.55)	1.33 (0.98, 1.81)	2.61 (1.87, 3.64)	<0.001	1.39 (1.24, 1.55)
Dietary potassium							
OS							
Cases/Person-years	30/20945	31/22574	23/23020	24/23579	17/24315		

Model 1	1.00	1.10 (0.66, 1.82)	0.82 (0.47, 1.42)	0.87 (0.51, 1.51)	0.67 (0.36, 1.23)	0.14	0.87 (0.72, 1.05)
Model 2	1.00	1.16 (0.67, 2.02)	0.98 (0.53, 1.81)	1.04 (0.53, 2.03)	0.99 (0.45, 2.21)	0.90	0.98 (0.76, 1.27)
CT							
Cases/Person-years	97/50071	144/53873	140/56696	131/58487	101/61098		
Model 1	1.00	1.10 (0.84, 1.44)	1.00 (0.76, 1.31)	0.98 (0.74, 1.29)	0.90 (0.67, 1.21)	0.29	0.95 (0.87, 1.04)
Model 2	1.00	1.15 (0.83, 1.60)	1.08 (0.75, 1.55)	1.07 (0.73, 1.59)	1.02 (0.66, 1.56)	0.79	0.98 (0.86, 1.12)
Sodium:potassium ratio							
OS							
Cases/Person-years	27/24020	18/23440	24/23314	19/22381	37/21279		
Model 1	1.00	0.75 (0.41, 1.36)	1.02 (0.59, 1.77)	0.93 (0.51, 1.67)	2.06 (1.25, 3.40)	0.002	1.33 (1.11, 1.58)
Model 2	1.00	0.76 (0.41, 1.42)	1.06 (0.58, 1.94)	0.99 (0.50, 1.95)	2.27 (1.14, 4.52)	0.008	1.38 (1.09, 1.75)
CT							
Cases/Person-years	137/56309	135/58151	121/57073	112/55692	108/52998		
Model 1	1.00	1.11 (0.87, 1.41)	1.10 (0.86, 1.41)	1.20 (0.93, 1.55)	1.56 (1.19, 2.03)	0.001	1.15 (1.06, 1.26)
Model 2	1.00	1.19 (0.93, 1.52)	1.27 (0.97, 1.65)	1.49 (1.11, 2.01)	2.19 (1.52, 3.14)	<0.001	1.30 (1.15, 1.47)
			HFrEF				
Dietary sodium							
OS							
Cases/Person-years	23/22415	14/23342	10/23606	21/22736	14/21699		
Model 1	1.00	0.71 (0.36, 1.38)	0.59 (0.27, 1.25)	1.49 (0.79, 2.80)	1.19 (0.58, 2.45)	0.27	1.14 (0.90, 1.45)
Model 2	1.00	0.95 (0.46, 1.93)	0.82 (0.36, 1.87)	2.26 (1.07, 4.79)	1.85 (0.76, 4.49)	0.05	1.33 (0.99, 1.77)
CT							
Cases/Person-years	83/51118	72/55294	74/56882	54/56701	67/57072		
Model 1	1.00	0.96 (0.70, 1.33)	1.17 (0.85, 1.62)	0.96 (0.67, 1.38)	1.46 (1.03, 2.08)	0.06	1.12 (1.00, 1.26)
Model 2	1.00	1.14 (0.81, 1.61)	1.39 (0.96, 2.00)	1.11 (0.72, 1.69)	1.77 (1.11, 2.80)	0.03	1.19 (1.02, 1.38)
Dietary potassium							
OS							
Cases/Person-years	26/20793	12/22472	14/22882	16/23456	14/24197		
Model 1	1.00	0.47 (0.24, 0.93)	0.57 (0.29, 1.09)	0.66 (0.35, 1.24)	0.64 (0.32, 1.25)	0.28	0.88 (0.70, 1.11)
Model 2	1.00	0.57 (0.28, 1.17)	0.78 (0.38, 1.62)	1.11 (0.51, 2.43)	1.13 (0.45, 2.84)	0.57	1.09 (0.80, 1.50)
CT							
Cases/Person-years	76/49441	82/53244	77/55983	70/57871	45/60528		
Model 1	1.00	0.85 (0.62, 1.18)	0.77 (0.55, 1.07)	0.72 (0.51, 1.02)	0.53 (0.36, 0.78)	<0.001	0.82 (0.73, 0.92)
Model 2	1.00	0.91 (0.61, 1.36)	0.83 (0.53, 1.31)	0.82 (0.50, 1.34)	0.59 (0.34, 1.04)	0.06	0.85 (0.71, 1.01)
Sodium:potassium ratio							
OS							
Cases/Person-years	17/23886	19/23303	15/23229	13/22244	18/21137		
Model 1	1.00	1.23 (0.64, 2.37)	0.98 (0.49, 1.96)	0.96 (0.47, 1.99)	1.50 (0.77, 2.93)	0.37	1.11 (0.89, 1.38)
Model 2	1.00	1.14 (0.57, 2.26)	0.88 (0.41, 1.87)	0.88 (0.39, 2.00)	1.22 (0.50, 2.96)	0.78	1.04 (0.78, 1.40)
CT							
Cases/Person-years	71/55855	68/57388	73/56396	63/55022	75/52406		
Model 1	1.00	1.05 (0.75, 1.47)	1.23 (0.89, 1.72)	1.19 (0.84, 1.69)	1.75 (1.23, 2.48)	0.001	1.21 (1.08, 1.35)
Model 2	1.00	1.11 (0.79, 1.57)	1.28 (0.90, 1.83)	1.18 (0.79, 1.77)	1.69 (1.05, 2.74)	0.04	1.18 (1.01, 1.39)

Abbreviations: HFpEF, Heart Failure with preserved ejection fraction; HFrEF, Heart Failure with reduced ejection fraction.

[1] Intake levels measured by FFQ were calibrated by urinary excretion level according to the following characteristics: dietary self-report, age, BMI, race, dietary supplementation, smoking status, education and family income.
[2] Model 1 was stratified on age in WHI-OS or on age and intervention group assignments in WHI-CT.
[3] Model 2 was stratified on age in WHI-OS or on age and intervention group assignments in WHI-CT, and adjusted for race, alcohol intake, smoking status, family income, education, leisure-time physical activity score, region, marital status, and modified AHEI-2010.

Supplemental Table 3. Associations of uncalibrated sodium and uncalibrated potassium intakes with incident heart failure, HFpEF and HFrEF in WHI-OS and WHI-CT

	Quintile of Uncalibrated Intake					P for trend	HR per sd (95% CI)
	Q1	**Q2**	**Q3**	**Q4**	**Q5**		
			Heart Failure				
Dietary sodium							
OS							
Cases/Person-years	359/252901	372/256414	382/256620	394/258782	459/256840		
Model 1 [2]	1.00	1.00 (0.86, 1.15)	1.03 (0.89, 1.19)	1.07 (0.93, 1.23)	1.28 (1.11, 1.47)	<0.001	1.09 (1.04, 1.14)
Model 2 [3]	1.00	1.10 (0.95, 1.28)	1.19 (1.02, 1.38)	1.23 (1.06, 1.43)	1.50 (1.29, 1.74)	<0.001	1.14 (1.09, 1.20)
CT							
Cases/Person-years	268/89611	240/90439	254/89851	297/90384	322/89677		
Model 1	1.00	0.86 (0.72, 1.03)	0.93 (0.78, 1.10)	1.09 (0.92, 1.28)	1.15 (0.98, 1.35)	0.008	1.07 (1.02, 1.13)
Model 2	1.00	0.91 (0.76, 1.09)	1.01 (0.84, 1.21)	1.21 (1.01, 1.44)	1.26 (1.06, 1.49)	<0.001	1.11 (1.05, 1.17)
Pooled [1]							
Cases/Person-years	627/342512	612/346853	636/346471	691/349166	781/346517		
Model 1	1.00	0.94 (0.84, 1.05)	0.99 (0.88, 1.10)	1.08 (0.97, 1.20)	1.22 (1.10, 1.36)	<0.001	1.08 (1.05, 1.12)
Model 2	1.00	1.02 (0.91, 1.15)	1.11 (0.99, 1.25)	1.22 (1.09, 1.37)	1.39 (1.24, 1.56)	<0.001	1.13 (1.09, 1.17)
Dietary potassium							
OS							
Cases/Person-years	449/237192	378/251851	384/261399	395/264146	360/266969		
Model 1	1.00	0.74 (0.65, 0.85)	0.73 (0.64, 0.84)	0.72 (0.63, 0.82)	0.63 (0.55, 0.73)	<0.001	0.87 (0.83, 0.91)
Model 2	1.00	0.94 (0.81, 1.09)	1.04 (0.90, 1.21)	1.08 (0.92, 1.26)	1.01 (0.86, 1.20)	0.48	1.02 (0.97, 1.07)
CT							
Cases/Person-years	268/86125	260/88481	260/91150	277/91693	316/92513		
Model 1	1.00	0.87 (0.73, 1.03)	0.79 (0.67, 0.94)	0.76 (0.65, 0.91)	0.74 (0.63, 0.87)	<0.001	0.91 (0.86, 0.96)
Model 2	1.00	1.02 (0.86, 1.22)	0.96 (0.80, 1.16)	1.02 (0.84, 1.22)	1.02 (0.84, 1.24)	0.82	1.01 (0.95, 1.07)
Pooled							
Cases/Person-years	717/323317	638/340332	644/352549	672/355839	676/359482		
Model 1	1.00	0.79 (0.71, 0.88)	0.76 (0.68, 0.84)	0.74 (0.66, 0.82)	0.67 (0.61, 0.75)	<0.001	0.89 (0.86, 0.92)
Model 2	1.00	0.97 (0.87, 1.09)	1.01 (0.90, 1.14)	1.05 (0.93, 1.19)	1.02 (0.90, 1.15)	0.49	1.01 (0.97, 1.06)
Sodium:potassium ratio							
OS							
Cases/Person-years	387/258073	417/255716	376/254202	388/254889	398/258675		
Model 1	1.00	1.06 (0.92, 1.22)	0.97 (0.84, 1.12)	1.01 (0.88, 1.16)	1.02 (0.89, 1.17)	0.90	1.00 (0.96, 1.05)
Model 2	1.00	1.05 (0.91, 1.21)	0.94 (0.81, 1.09)	0.98 (0.85, 1.13)	1.03 (0.90, 1.19)	0.80	1.01 (0.96, 1.05)
CT							
Cases/Person-years	286/90797	260/90077	285/89590	283/89484	267/90013		
Model 1	1.00	0.89 (0.75, 1.05)	0.95 (0.81, 1.12)	0.98 (0.83, 1.15)	0.91 (0.77, 1.08)	0.44	0.98 (0.93, 1.03)
Model 2	1.00	0.90 (0.75, 1.06)	0.98 (0.83, 1.16)	0.99 (0.84, 1.18)	0.93 (0.78, 1.10)	0.55	0.98 (0.93, 1.04)
Pooled							
Cases/Person-years	673/348870	677/345793	661/343792	671/344373	665/348688		
Model 1	1.00	0.99 (0.89, 1.10)	0.96 (0.86, 1.07)	1.00 (0.90, 1.11)	0.98 (0.88, 1.09)	0.68	0.99 (0.96, 1.03)
Model 2	1.00	0.98 (0.88, 1.09)	0.96 (0.86, 1.07)	0.98 (0.88, 1.10)	0.99 (0.88, 1.10)	0.84	1.00 (0.96, 1.03)

			HFpEF				
Dietary sodium							
OS							
Cases/Person-years	18/22432	19/23030	27/23301	35/23332	26/22339		
Model 1	1.00	0.91 (0.48, 1.73)	1.30 (0.72, 2.37)	1.70 (0.96, 3.00)	1.26 (0.69, 2.30)	0.16	1.14 (0.95, 1.36)
Model 2	1.00	1.18 (0.60, 2.34)	1.66 (0.87, 3.17)	2.07 (1.11, 3.86)	1.36 (0.70, 2.62)	0.18	1.14 (0.94, 1.37)
CT							
Cases/Person-years	125/55442	97/56181	125/55809	138/56445	128/56348		
Model 1	1.00	0.71 (0.54, 0.92)	0.91 (0.71, 1.17)	1.00 (0.78, 1.27)	0.95 (0.74, 1.21)	0.57	1.02 (0.94, 1.11)
Model 2	1.00	0.76 (0.58, 1.00)	0.99 (0.76, 1.29)	1.10 (0.85, 1.42)	1.04 (0.80, 1.35)	0.25	1.05 (0.97, 1.15)
Pooled							
Cases/Person-years	143/77874	116/79211	152/79110	173/79777	154/78687		
Model 1	1.00	0.73 (0.57, 0.94)	0.96 (0.76, 1.21)	1.08 (0.87, 1.35)	0.99 (0.79, 1.24)	0.26	1.04 (0.97, 1.12)
Model 2	1.00	0.81 (0.63, 1.05)	1.07 (0.84, 1.36)	1.21 (0.95, 1.53)	1.08 (0.84, 1.38)	0.11	1.07 (0.99, 1.15)
Dietary potassium							
OS							
Cases/Person-years	22/21717	26/22518	18/22979	29/23497	30/23723		
Model 1	1.00	1.05 (0.59, 1.85)	0.66 (0.35, 1.23)	1.04 (0.60, 1.81)	0.97 (0.56, 1.69)	0.96	1.00 (0.84, 1.20)
Model 2	1.00	1.20 (0.65, 2.21)	0.80 (0.40, 1.58)	1.41 (0.75, 2.64)	1.58 (0.82, 3.06)	0.11	1.19 (0.96, 1.47)
CT							
Cases/Person-years	106/52698	115/55035	123/56439	129/57678	140/58373		
Model 1	1.00	0.86 (0.66, 1.12)	0.85 (0.66, 1.11)	0.83 (0.64, 1.07)	0.83 (0.64, 1.07)	0.20	0.95 (0.87, 1.03)
Model 2	1.00	0.96 (0.73, 1.27)	0.98 (0.74, 1.29)	1.06 (0.79, 1.41)	1.12 (0.83, 1.52)	0.31	1.05 (0.95, 1.16)
Pooled							
Cases/Person-years	128/74415	141/77553	141/79418	158/81175	170/82096		
Model 1	1.00	0.89 (0.70, 1.14)	0.82 (0.64, 1.05)	0.86 (0.68, 1.09)	0.85 (0.68, 1.08)	0.25	0.96 (0.89, 1.03)
Model 2	1.00	1.00 (0.78, 1.29)	0.95 (0.73, 1.23)	1.11 (0.86, 1.44)	1.19 (0.91, 1.57)	0.12	1.07 (0.98, 1.17)
Sodium:potassium ratio							
OS							
Cases/Person-years	19/22815	31/22724	33/23298	17/23154	25/22444		
Model 1	1.00	1.64 (0.93, 2.91)	1.70 (0.97, 2.99)	0.90 (0.47, 1.74)	1.33 (0.73, 2.42)	0.68	1.04 (0.87, 1.24)
Model 2	1.00	1.87 (1.02, 3.45)	2.17 (1.18, 3.99)	1.12 (0.56, 2.24)	1.58 (0.84, 3.00)	0.36	1.09 (0.91, 1.30)
CT							
Cases/Person-years	119/56677	112/56291	135/55709	123/55665	124/55882		
Model 1	1.00	0.93 (0.72, 1.21)	1.13 (0.88, 1.44)	1.08 (0.84, 1.40)	1.05 (0.82, 1.35)	0.51	1.03 (0.95, 1.11)
Model 2	1.00	0.97 (0.74, 1.26)	1.19 (0.93, 1.54)	1.08 (0.83, 1.40)	1.06 (0.82, 1.38)	0.52	1.03 (0.95, 1.11)
Pooled							
Cases/Person-years	138/79492	143/79015	168/79007	140/78819	149/78326		
Model 1	1.00	1.03 (0.81, 1.30)	1.20 (0.96, 1.51)	1.06 (0.84, 1.34)	1.09 (0.86, 1.38)	0.44	1.03 (0.96, 1.11)
Model 2	1.00	1.07 (0.84, 1.37)	1.30 (1.03, 1.65)	1.09 (0.85, 1.39)	1.13 (0.89, 1.43)	0.33	1.04 (0.96, 1.12)
			HFrEF				
Dietary sodium							
OS							
Cases/Person-years	15/22278	17/22897	14/23206	15/23264	21/22155		

Model 1	1.00	1.02 (0.51, 2.04)	0.85 (0.41, 1.76)	0.89 (0.43, 1.81)	1.29 (0.67, 2.52)	0.50	1.08 (0.87, 1.35)
Model 2	1.00	1.32 (0.63, 2.75)	1.10 (0.51, 2.38)	1.19 (0.55, 2.57)	1.68 (0.83, 3.41)	0.19	1.16 (0.93, 1.46)
CT							
Cases/Person-years	59/54918	81/55317	65/55225	70/55853	75/55753		
Model 1	1.00	1.28 (0.91, 1.79)	1.03 (0.72, 1.47)	1.10 (0.78, 1.56)	1.19 (0.84, 1.67)	0.57	1.03 (0.93, 1.15)
Model 2	1.00	1.31 (0.93, 1.86)	1.11 (0.77, 1.60)	1.19 (0.83, 1.72)	1.32 (0.92, 1.90)	0.23	1.07 (0.96, 1.20)
Pooled							
Cases/Person-years	74/77196	98/78214	79/78431	85/79117	96/77908		
Model 1	1.00	1.22 (0.90, 1.65)	0.99 (0.72, 1.37)	1.06 (0.78, 1.45)	1.21 (0.89, 1.64)	0.42	1.04 (0.95, 1.14)
Model 2	1.00	1.31 (0.96, 1.80)	1.11 (0.79, 1.54)	1.19 (0.86, 1.66)	1.39 (1.01, 1.92)	0.10	1.09 (0.98, 1.20)
Dietary potassium							
OS							
Cases/Person-years	13/21606	18/22371	22/22834	11/23395	18/23594		
Model 1	1.00	1.24 (0.61, 2.53)	1.39 (0.70, 2.77)	0.70 (0.31, 1.56)	1.04 (0.50, 2.12)	0.58	0.94 (0.75, 1.17)
Model 2	1.00	1.78 (0.84, 3.75)	2.46 (1.16, 5.19)	1.38 (0.57, 3.32)	1.91 (0.81, 4.53)	0.31	1.15 (0.88, 1.49)
CT							
Cases/Person-years	73/52069	72/54299	80/55737	61/57149	64/57813		
Model 1	1.00	0.84 (0.61, 1.17)	0.88 (0.64, 1.22)	0.63 (0.44, 0.88)	0.61 (0.43, 0.86)	0.001	0.84 (0.75, 0.93)
Model 2	1.00	0.93 (0.66, 1.31)	1.01 (0.72, 1.43)	0.77 (0.53, 1.13)	0.78 (0.52, 1.16)	0.15	0.91 (0.80, 1.03)
Pooled							
Cases/Person-years	86/73675	90/76670	102/78571	72/80544	82/81407		
Model 1	1.00	0.90 (0.67, 1.21)	0.96 (0.71, 1.28)	0.64 (0.46, 0.87)	0.68 (0.50, 0.92)	0.002	0.86 (0.78, 0.94)
Model 2	1.00	1.04 (0.76, 1.42)	1.19 (0.87, 1.62)	0.85 (0.60, 1.20)	0.91 (0.63, 1.31)	0.37	0.95 (0.85, 1.07)
Sodium:potassium ratio							
OS							
Cases/Person-years	24/22621	15/22629	14/23220	12/23033	17/22296		
Model 1	1.00	0.63 (0.33, 1.21)	0.57 (0.30, 1.10)	0.50 (0.25, 1.01)	0.71 (0.38, 1.32)	0.18	0.86 (0.69, 1.07)
Model 2	1.00	0.56 (0.29, 1.08)	0.53 (0.27, 1.04)	0.46 (0.23, 0.92)	0.71 (0.38, 1.34)	0.19	0.86 (0.69, 1.08)
CT	24/22621	15/22629	14/23220	12/23033	17/22296		
Cases/Person-years	75/55949	71/55724	70/55109	67/54978	67/55307		
Model 1	1.00	0.93 (0.67, 1.29)	0.94 (0.68, 1.30)	0.93 (0.67, 1.29)	0.90 (0.65, 1.25)	0.53	0.97 (0.87, 1.07)
Model 2	1.00	0.94 (0.67, 1.31)	0.96 (0.69, 1.35)	0.98 (0.70, 1.38)	0.94 (0.67, 1.32)	0.78	0.98 (0.88, 1.10)
Pooled							
Cases/Person-years	99/78570	86/78353	84/78329	79/78011	84/77603		
Model 1	1.00	0.86 (0.65, 1.15)	0.85 (0.64, 1.14)	0.83 (0.62, 1.12)	0.85 (0.64, 1.14)	0.24	0.95 (0.86, 1.04)
Model 2	1.00	0.84 (0.63, 1.14)	0.85 (0.63, 1.15)	0.85 (0.63, 1.16)	0.88 (0.66, 1.19)	0.40	0.96 (0.87, 1.06)

Abbreviations: HFpEF, Heart Failure with preserved ejection fraction; HFrEF, Heart Failure with reduced ejection fraction.

[1] Results for WHI-OS and WHI-CT from the multivariable model were combined using the fixed-effects model.

[2] Model 1 was stratified on age in WHI-OS or on age and intervention group assignments in WHI-CT.

[3] Model 2 was stratified on age in WHI-OS or on age and intervention group assignments in WHI-CT, and adjusted for race, energy intake, alcohol intake, smoking status, family income, education, leisure-time physical activity score, region, marital status, and modified AHEI-2010.

Supplemental Table 4. Associations of calibrated sodium and calibrated potassium intakes with incident heart failure, HFpEF and HFrEF in the sensitivity analysis further adjust for intermediating covariates [1]

	Quintile of Calibrated Intake [2]					P for trend	HR per sd (95% CI)
	Q1	**Q2**	**Q3**	**Q4**	**Q5**		
Heart Failure							
Dietary sodium							
Cases/Person-years	902/316755	635/347602	572/357079	545/358983	693/351099		
Model 3 [3]	1.00	1.02 (0.92, 1.14)	1.20 (1.07, 1.36)	1.38 (1.21, 1.57)	2.04 (1.77, 2.35)	<0.001	1.29 (1.23, 1.35)
Model 4 [4]	1.00	0.97 (0.86, 1.08)	1.09 (0.96, 1.24)	1.19 (1.03, 1.38)	1.65 (1.40, 1.94)	<0.001	1.20 (1.14, 1.27)
Dietary potassium							
Cases/Person-years	869/298637	801/334145	673/353499	572/365062	432/380174		
Model 3	1.00	1.02 (0.91, 1.15)	1.00 (0.87, 1.14)	0.96 (0.83, 1.11)	0.92 (0.78, 1.09)	0.29	0.97 (0.92, 1.02)
Model 4	1.00	1.03 (0.91, 1.16)	1.01 (0.89, 1.16)	0.98 (0.85, 1.14)	0.96 (0.81, 1.14)	0.58	0.98 (0.93, 1.04)
Sodium:potassium ratio							
Cases/Person-years	688/349671	588/360535	592/356409	647/346178	832/318726		
Model 3	1.00	1.03 (0.92, 1.16)	1.09 (0.97, 1.22)	1.21 (1.07, 1.37)	1.63 (1.41, 1.89)	<0.001	1.19 (1.13, 1.25)
Model 4	1.00	0.99 (0.88, 1.11)	0.99 (0.88, 1.12)	1.05 (0.92, 1.20)	1.30 (1.11, 1.52)	<0.001	1.10 (1.04, 1.16)
HFpEF							
Dietary sodium							
Cases/Person-years	192/74151	153/79329	126/81469	113/80358	154/79352		
Model 3	1.00	1.17 (0.93, 1.47)	1.20 (0.93, 1.56)	1.38 (1.04, 1.84)	2.30 (1.69, 3.12)	<0.001	1.32 (1.19, 1.46)
Model 4	1.00	1.02 (0.80, 1.29)	0.97 (0.74, 1.28)	1.02 (0.75, 1.40)	1.51 (1.06, 2.15)	0.03	1.15 (1.02, 1.29)
Dietary potassium							
Cases/Person-years	127/71016	175/76447	163/79716	155/82066	118/85413		
Model 3	1.00	1.25 (0.93, 1.68)	1.26 (0.91, 1.74)	1.36 (0.96, 1.93)	1.41 (0.95, 2.10)	0.10	1.11 (0.98, 1.25)
Model 4	1.00	1.23 (0.92, 1.65)	1.23 (0.89, 1.70)	1.35 (0.95, 1.92)	1.45 (0.98, 2.15)	0.08	1.12 (0.99, 1.27)
Sodium:potassium ratio							
Cases/Person-years	164/80329	153/81591	145/80387	131/78073	145/74277		
Model 3	1.00	1.04 (0.82, 1.31)	1.05 (0.82, 1.35)	1.14 (0.86, 1.49)	1.75 (1.26, 2.43)	<0.001	1.21 (1.08, 1.35)
Model 4	1.00	0.93 (0.73, 1.17)	0.86 (0.66, 1.11)	0.86 (0.64, 1.15)	1.14 (0.80, 1.63)	0.39	1.05 (0.93, 1.19)
HFrEF							
Dietary sodium							
Cases/Person-years	106/73533	86/78636	84/80488	75/79437	81/78771		
Model 3	1.00	1.16 (0.85, 1.59)	1.17 (0.83, 1.64)	1.32 (0.90, 1.94)	1.46 (0.96, 2.23)	0.07	1.13 (0.99, 1.30)
Model 4	1.00	1.15 (0.83, 1.59)	1.15 (0.80, 1.65)	1.31 (0.86, 1.99)	1.43 (0.88, 2.34)	0.15	1.13 (0.96, 1.33)
Dietary potassium							
Cases/Person-years	102/70234	94/75716	91/78865	86/81327	59/84725		
Model 3	1.00	0.87 (0.60, 1.26)	0.89 (0.59, 1.36)	0.97 (0.62, 1.52)	0.83 (0.49, 1.39)	0.42	0.95 (0.81, 1.12)
Model 4	1.00	0.86 (0.59, 1.25)	0.89 (0.59, 1.35)	0.98 (0.63, 1.52)	0.84 (0.50, 1.40)	0.45	0.96 (0.81, 1.13)
Sodium:potassium ratio							
Cases/Person-times	88/79741	87/80691	88/79625	76/77266	93/73543		
Model 3	1.00	0.91 (0.66, 1.24)	1.01 (0.72, 1.40)	0.90 (0.62, 1.31)	1.15 (0.74, 1.80)	0.53	1.05 (0.91, 1.22)
Model 4	1.00	0.89 (0.65, 1.23)	0.97 (0.69, 1.37)	0.85 (0.57, 1.27)	1.05 (0.65, 1.71)	0.82	1.02 (0.87, 1.20)

Abbreviations: HFpEF, Heart Failure with preserved ejection fraction; HFrEF, Heart Failure with reduced ejection fraction.

[1] Results for WHI-OS and WHI-CT from the multivariable model were combined using the fixed-effects model.
[2] Intake levels measured by FFQ were calibrated by urinary excretion level according to the following characteristics: dietary self-report, age, BMI, race, dietary supplementation, smoking status, education and family income.
[3] Model 3 was stratified on age in WHI-OS or on age and intervention group assignments in WHI-CT, and adjusted for race, alcohol intake, smoking status, family income, education, leisure-time physical activity score, region, marital status, modified AHEI-2010, baseline hypertension, baseline diabetes, baseline myocardial infarction and baseline atrial fibrillation.
[4] Model 4 was additionally adjusted for BMI.

Supplemental Table 5. Associations of calibrated sodium intakes with incident heart failure, HFpEF and HFrEF stratified by baseline hypertension [1 2]

	Hypertension			
	Yes		No	
	Cases	**HR (95% CI) [3]**	**Cases**	**HR (95% CI) [3]**
Heart Failure				
Q1	509	1.00	393	1.00
Q2	338	1.05 (0.90, 1.21)	297	1.10 (0.93, 1.29)
Q3	283	1.18 (1.00, 1.40)	289	1.38 (1.16, 1.65)
Q4	311	1.68 (1.42, 2.00)	234	1.37 (1.12, 1.67)
Q5	406	2.65 (2.20, 3.20)	287	2.34 (1.88, 2.90)
P for trend		<0.001		<0.001
HFpEF				
Q1	109	1.00	83	1.00
Q2	74	1.00 (0.72, 1.38)	79	1.38 (0.98, 1.94)
Q3	65	1.18 (0.83, 1.68)	61	1.38 (0.93, 2.05)
Q4	64	1.52 (1.04, 2.22)	49	1.48 (0.96, 2.28)
Q5	83	2.62 (1.74, 3.94)	71	3.51 (2.23, 5.52)
P for trend		<0.001		<0.001
HFrEF				
Q1	59	1.00	47	1.00
Q2	43	1.05 (0.68, 1.61)	43	1.34 (0.85, 2.11)
Q3	33	0.90 (0.55, 1.48)	51	1.95 (1.22, 3.12)
Q4	49	1.83 (1.12, 2.99)	26	1.01 (0.56, 1.82)
Q5	40	1.71 (0.97, 3.04)	41	2.33 (1.28, 4.25)
P for trend		0.02		0.03

Abbreviations: HFpEF, Heart Failure with preserved ejection fraction; HFrEF, Heart Failure with reduced ejection fraction.
[1] Results for WHI-OS and WHI-CT from the multivariable model were combined using the fixed-effects model.
[2] Intake levels measured by FFQ were calibrated by urinary excretion level according to the following characteristics: dietary self-report, age, BMI, race, dietary supplementation, smoking status, education and family income.
[3] The model was stratified on age in WHI-OS or on age and intervention group assignments in WHI-CT, and adjusted for race, alcohol intake, smoking status, family income, education, leisure-time physical activity score, region, marital status, and modified AHEI-2010.

Supplemental Table 6. Hazard ratio of heart failure per 1 sd increment in calibrated sodium intake stratified by hypertension, MI, diabetes, atrial fibrillation, eGFR and BMI [1]

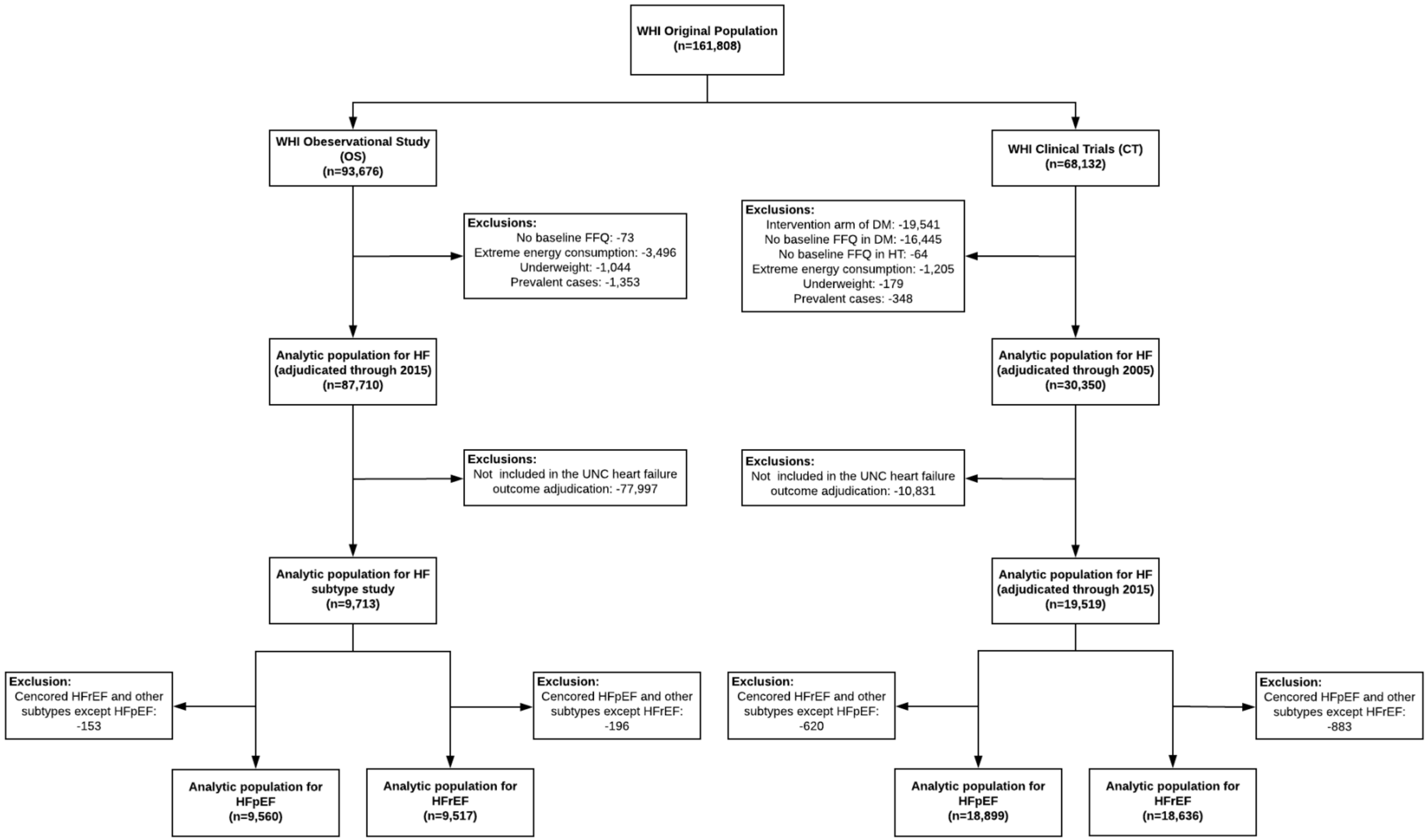
	Pooled	
	HR (95% CI) [2]	**P-value**
Hypertension		
Yes	1.42 (1.34, 1.52)	<0.001
No	1.33 (1.23, 1.43)	<0.001
P-interaction [3]	0.001	
MI		
Yes	1.27 (1.14, 1.42)	<0.001
No	1.36 (1.29, 1.43)	<0.001
P-interaction [2]	0.44	
Diabetes		
Yes	1.35 (1.20, 1.53)	<0.001
No	1.25 (1.18, 1.31)	<0.001
P-interaction [2]	<0.001	
Atrial fibrillation		
Yes	1.28 (1.11, 1.49)	<0.001
No	1.37 (1.30, 1.44)	<0.001
P-interaction [2]	0.83	
eGFR		
<60	1.47 (1.13, 1.91)	0.004
≥60	1.30 (1.19, 1.42)	<0.001
P-interaction [2]	0.05	
BMI		
<30	1.07 (1.00, 1.16)	0.06
≥30	1.29 (1.19, 1.40)	<0.001
P-interaction [2]	<0.001	

Abbreviations: MI, myocardial infarction; eGFR, estimated glomerular filtration rate.

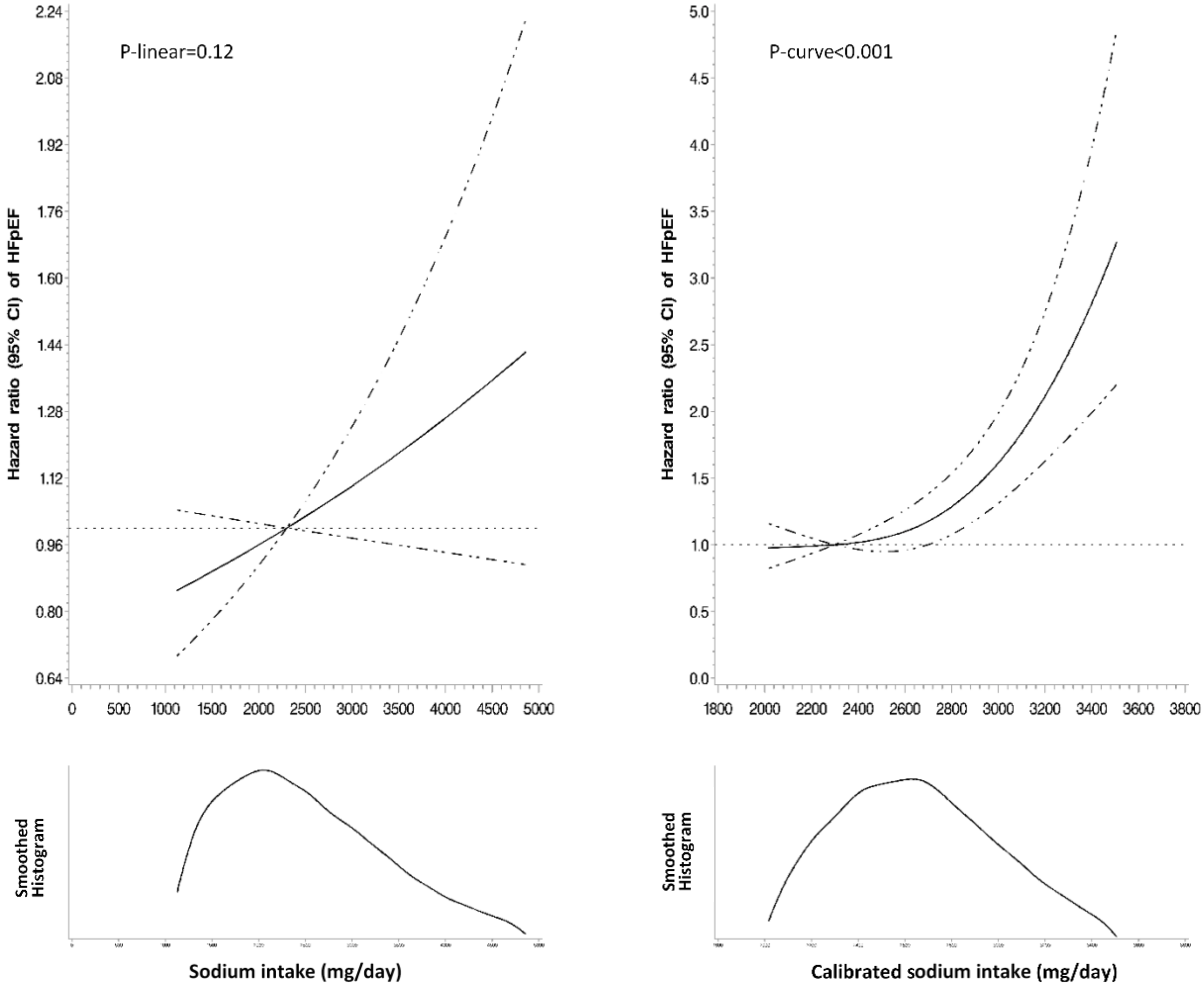
[1] Intake levels measured by FFQ were calibrated by urinary excretion level according to the following characteristics: dietary self-report, age, BMI, race, dietary supplementation, smoking status, education and family income.

[2] The model was stratified on age in WHI-OS or on age and intervention group assignments in WHI-CT, and adjusted for race, alcohol intake, smoking status, family income, education, leisure-time physical activity score, region, marital status, and modified AHEI-2010.

[3] P-interaction were estimated from the Wald test of the product term between sodium intake and the variable of stratification.



Supplemental Figure 1. Analytical populations and number of participants excluded

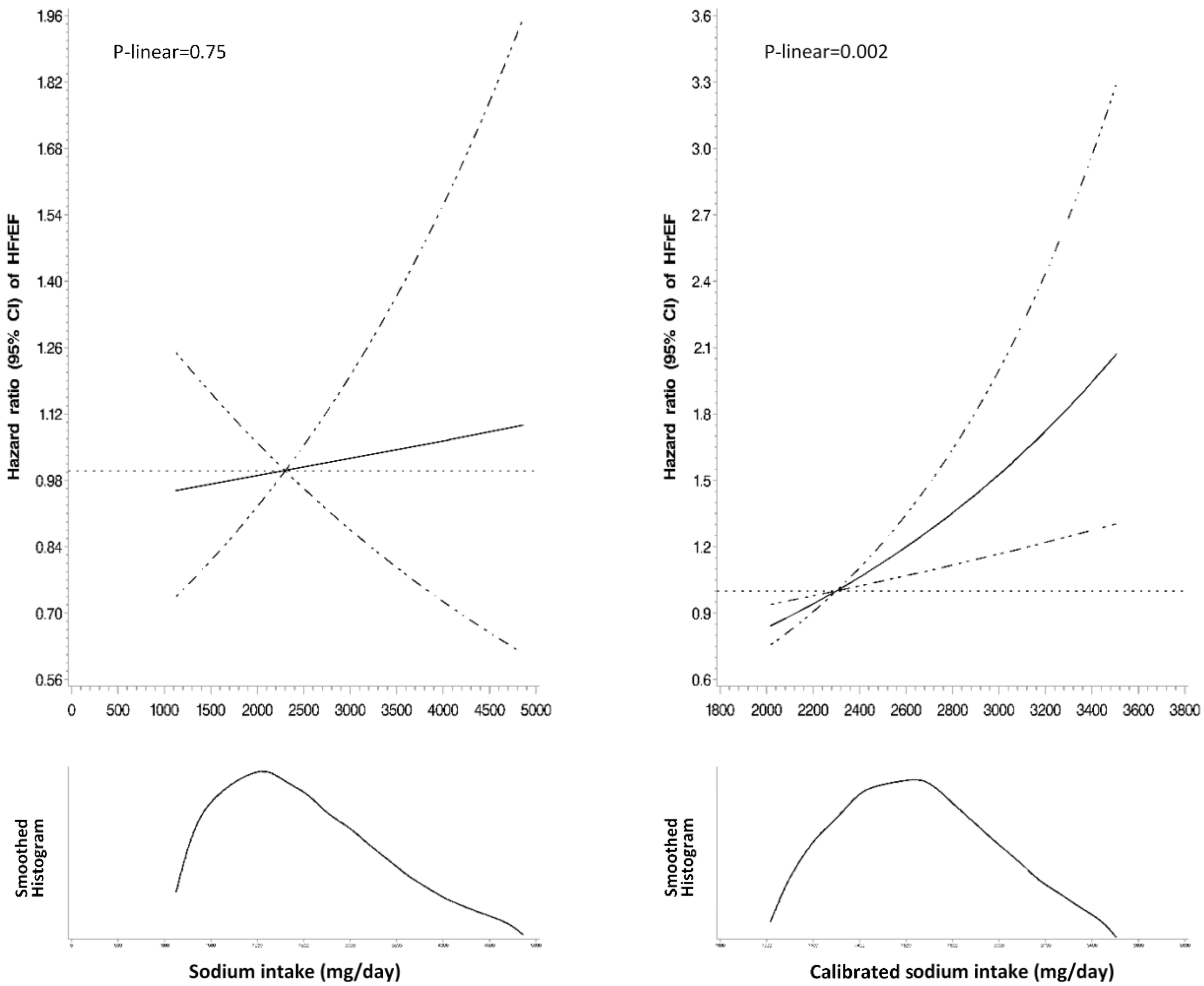


Supplemental Figure 2. Dose response relationship between sodium intake and risk of HFpEF

The model was stratified on age in WHI-OS or on age and intervention group assignments in WHI-CT, and adjusted for race, alcohol intake, smoking status, family income, education, leisure-time physical activity score, region, marital status, and modified AHEI-2010.

The dose response relationship was estimated using restricted cubic spline cox regression with 3 knots; tests for curvature used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms.

Intake levels measured by FFQ were calibrated by urinary excretion level according to the following characteristics: dietary self-report, age, BMI, race, dietary supplementation, smoking status, education and family income.



Supplemental Figure 3. Dose response relationship between sodium intake and risk of HFrEF

The model was stratified on age in WHI-OS or on age and intervention group assignments in WHI-CT, and adjusted for race, alcohol intake, smoking status, family income, education, leisure-time physical activity score, region, marital status, and modified AHEI-2010.

The dose response relationship was estimated using restricted cubic spline cox regression with 3 knots; tests for curvature used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms.

Intake levels measured by FFQ were calibrated by urinary excretion level according to the following characteristics: dietary self-report, age, BMI, race, dietary supplementation, smoking status, education and family income.

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