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DIETARY SODIUM CONTENT, MORTALITY, AND RISK FOR CARDIOVASCULAR EVENTS IN OLDER ADULTS

BY

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Degree to be awarded: M.P.H.
Career MPH

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An abstract of a Thesis submitted to the Faculty of the Rollins School of Public Health of Emory University in partial fulfillment of the requirements of the degree of Master of Public Health in the Career MPH program 2013

Abstract

DIETARY SODIUM CONTENT, MORTALITY, AND RISK FOR CARDIOVASCULAR EVENTS IN OLDER ADULTS

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Andreas P. Kalogeropoulos

Excess dietary sodium intake is associated with risk factors for cardiovascular disease (CVD) and heart failure (HF), mainly elevated blood pressure and adverse vascular effects. Therefore, limiting sodium intake at the population level might reduce risk for CVD and HF. However, the optimal level of sodium restriction is currently unclear. Although simulation studies have projected significant benefits with strict sodium control, low sodium intake may exert unfavorable effects on certain factors predisposing to CVD and HF. Recently published findings from large cohorts have disputed the current recommendations (≤2300 mg daily for the general population, ≤1500 mg for high risk groups, including older adults). Specifically for older adults, concerns with strict sodium control include inadequate caloric intake and interaction with medications. For example, experimental evidence suggests that combining renin-angiotensin system blockade with low sodium impairs cardiomyocyte contractility. Moreover, dose-response data on sodium intake and outcomes are scarce in older adults. Therefore, evaluating the association of dietary sodium with key outcomes in older adults using data from well-designed cohort studies is a crucial step to inform design of much needed outcome trials. In this work, we examine the association between sodium intake, as assessed with a food frequency questionnaire, and risk for mortality, CVD, and HF in older adults. For this purpose, we evaluated 10-year follow-up data from the NIH-funded Health, Aging, and Body Composition (Health ABC) Study, a population-based cohort of 3075 well-functioning, community-dwelling participants aged 70 to 79 years at inception (1997-1998) from Pittsburgh, PA, and Memphis, TN. We evaluated the functional form of association (linear vs. nonlinear) between sodium intake and outcomes and considered the competing risk of non-cardiovascular mortality for incident CVD and HF using appropriate statistical models. In multivariable models, we adjusted for risk factors previously linked to mortality and incident CVD and HF in this cohort. Finally, we examined for modification effects of gender, race, and baseline hypertensive status on the association between dietary sodium intake and 10-year cardiovascular outcomes.

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Dietary Sodium Content, Mortality, and Risk for Cardiovascular Events in Older Adults

Andreas P. Kalogeropoulos, MD PhD

CMPH Candidate Fall 2013

1. Introduction

1.1. Project Objective

The purpose of this work is to investigate the association between dietary sodium intake, as assessed with a food frequency questionnaire (FFQ), and risk for (1) all-cause mortality; (2) incident cardiovascular disease (CVD); and (3) incident heart failure (HF) in older adults. For this purpose, we will use 10-year follow-up data from the NIH-funded Health, Aging, and Body Composition (Health ABC) Study. Briefly, the Health ABC Study is a population-based cohort of 3075 well-functioning, community-dwelling men and women aged 70 to 79 years at inception (1997-1998) from Pittsburgh, PA, and Memphis, TN. Specifically, we will investigate whether a J-or U-shape association exists and what are the breaking points of this association (e.g. whether there is evidence of harm below or above a certain sodium intake level). In secondary analyses, we will evaluate this association in gender and race groups, and in participants with vs. without hypertension at baseline.

1.2. The Burden of Heart Failure in Older Adults as a Public Health Problem

Heart Failure as Public Health Problem

Improved therapies and outcomes of acute cardiac conditions, aging of the population, increasing prevalence of lifestyle-related risk factors, and advances in HF therapy, all have led to an ever-increasing prevalence of HF. Because of these trends, HF is considered an "epidemic" and a public health priority in developed countries[1-3] and is emerging as major non-communicable syndrome in developing regions.[4, 5] The lack of prevention strategies specific to HF compounds the problem. In the United States, the population prevalence of HF is projected to increase by 23% in the next 20 years.[3]

Heart failure has a high lifetime incidence and serious prognosis, especially after a hospitalization for decompensation. For a middle-aged person, the lifetime risk for HF is estimated at 20% to 30%.[6-8] In recent registries, 1-year mortality after a hospitalization for HF ranges between 25% and 35% and is remarkably consistent across healthcare systems.[1, 2, 9, 10] Among outpatients, 5-year survival is 50% to 75%.[7, 11-13] Heart failure affects quality of life adversely also.[14] From a public health perspective, beyond the direct impact on survival and

quality of life, the burgeoning burden imposed on health care systems in terms of resources and costs is another major consideration. The total direct cost of HF in the United States is projected to increase from $21 billion in 2012 to $53 billion in 2030.[3]

Aging and Heart Failure

Age is a major determinant of incidence and prevalence of HF and, therefore, the aging of the population worldwide is expected to have a dramatic impact on the burden of HF. Based on 2007-2010 NHANES data (**Figure 1**), it is estimated that 5.1 million Americans aged ≥20 years have HF[15] and the population prevalence for 2012 is estimated at 2.4%.[3] By year 2030, the population prevalence of HF in US is projected to reach 3.0%.[3]

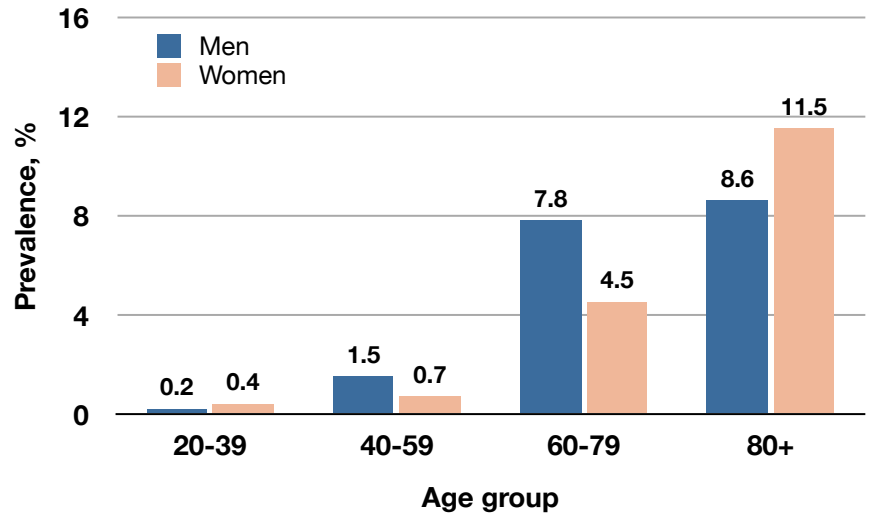


Figure 1. Prevalence of heart failure by gender and age in the United States (Source: National Health and Nutrition Examination Survey: 2007–2010).

In a recent study of approximately 12,000 new HF cases identified between 2005 and 2008 among adults enrolled in a major healthcare plan in the United States, 46% of cases were women and 73% were over age 65.[16] Of note, 52% of cases had preserved (≥50%) ejection fraction (EF), and these patients were more likely to be women and over age 65. Less than 25% of new HF cases had previous acute coronary syndrome or history of revascularization; however, over 20% had cerebrovascular disease and 30% had atrial fibrillation or flutter. Hypertension was present in 75% and diabetes mellitus in 19%, whereas 35% had concomitant chronic lung disease. Renal dysfunction (estimated glomerular filtration rate <60 ml/min/1.73m^2) and anemia (hemoglobin <13g/L in men and <12g/L in women) were present in over 40% and 30% of cases, respectively. Depression and dementia were present in 16% and 7% of cases, respectively.[16]

These data demonstrate a shift from a model where HF was mainly a consequence of coronary artery disease with male preponderance towards a condition of older adults that equally affects both sexes and is accompanied by a complex medical profile.

Among 360,000 adults enrolled in a large, managed-care organization in Georgia, United States, the population incidence of HF as determined by administrative data from 2000 to 2005 was 3.9 cases per 1,000 patient-years.[17] Incidence was higher in men compared to women (4.2 versus 3.7 per 1,000 patient-years); however, among the 4,000 new cases, >50% were women. Incidence increased dramatically with age, with men demonstrating higher rates before age 75; however, sex-based differences were no longer evident in the ≥75-year age group, **Figure 2A**.[17]

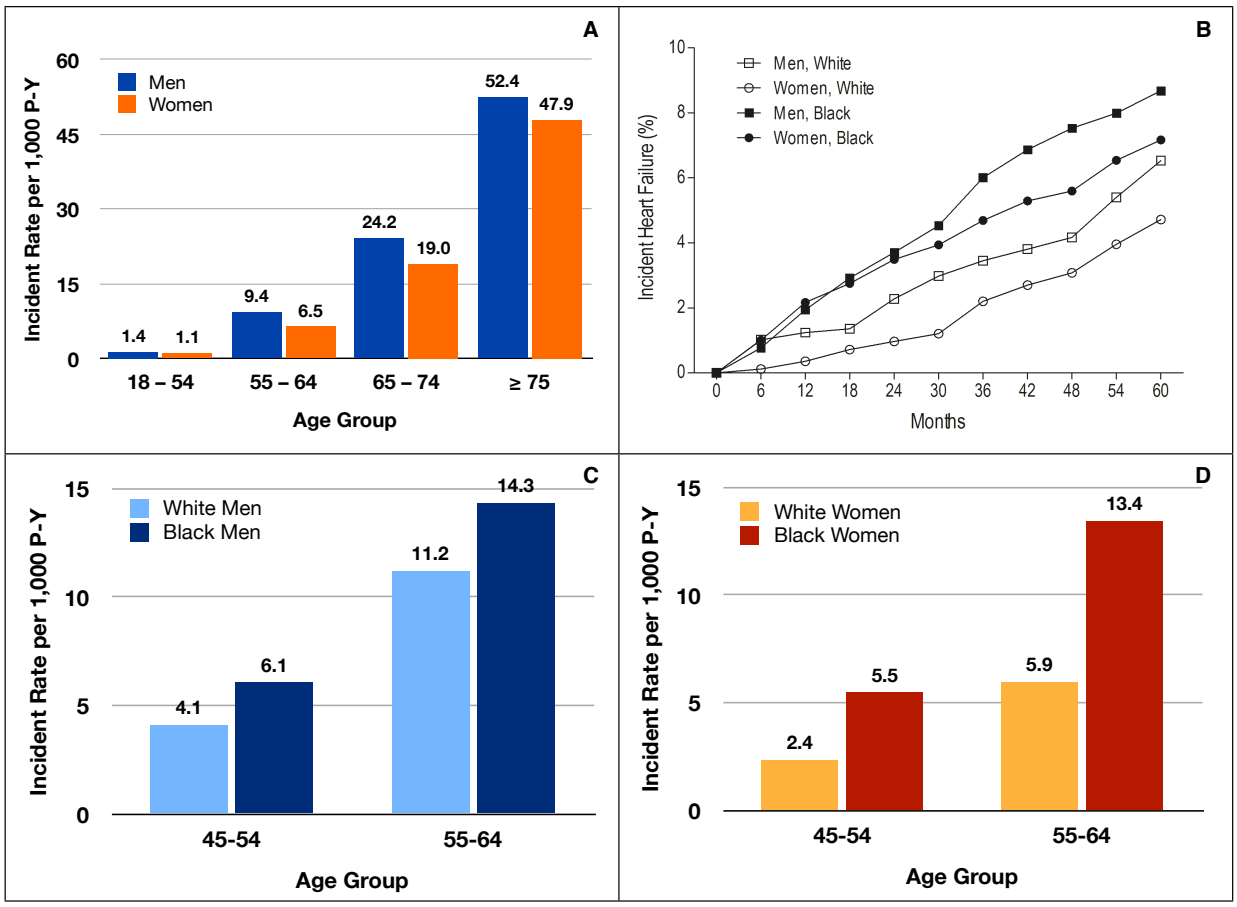


Figure 2. A: Heart failure incidence among adults enrolled in a managed-care organization in Georgia, United States. (Data from Goyal A et al *Circ Heart Fail* 2010; 3:698-705, and personal communication with Dr. Abhinav Goyal). B: Incident heart failure by sex and race in the Health, Aging, and Body Composition Study cohort. (Source: Kalogeropoulos et al, *Arch Intern Med* 2009; 169:708-15). C & D: Heart failure incidence by sex, race, and age

in the Atherosclerosis Risk in Communities (ARIC) cohort. (Data from Loehr et al, *Am J Cardiol* 2008; 101:1016-22). P-Y: person-years.

In the Health, Aging, and Body Composition (Health ABC) Study, which enrolled over 3,000 well-functioning participants aged 70 to 79 years between 1997 and 1998, the incidence of HF over 7 years of follow-up was 15.8 and 11.7 per 1,000 person-years in men and women, respectively,[18] reflecting the effect of age on HF incidence. Men and black participants were more likely to develop HF (**Figure 2B**). In the Atherosclerosis Risk in Communities (ARIC), a population-based study that recruited over 15,000 participants aged 45 to 64 years between 1987 and 1989, the age-adjusted incidence of new HF hospitalizations was 5.7 per 1,000 person-years between 1987 and 2002.[19]Although incidence rates were greater for blacks (men, 9.1; women, 8.1) than whites (6.0 and 3.4, respectively), **Figure 2C & 2D**, adjustment for confounders attenuated the difference; hence, the greater HF incidence in blacks could be largely explained by the higher prevalence of risk factors among blacks at cohort inception.[19] Of note, because surveillance for new HF cases was based on hospitalization in both studies, the incidence of HF was likely underestimated in ARIC and Health ABC. In the Rotterdam Study (Netherlands), which included surveillance data from outpatient records in addition to hospital discharge records, HF incidence after 7.1 years of follow up was considerably higher: 17.6 per 1,000 in men and 12.5 per 1,000 in women, despite a younger population (age ≥55).[7]

Contemporary Outcomes and Trends in Patients with Heart Failure

Despite relative improvement in HF outcomes over the past 20 years, the absolute mortality and morbidity rates remain unacceptably high. In a longitudinal analysis from Canada, adjusted 1-year mortality decreased from 17.7% in 1997 to 16.2% in 2007 for outpatients.[2] In a study from a single U.S. center, among patients referred for advanced systolic HF, the unadjusted mortality decreased from 20.6% in 1993-98 to 17.8% in 2005-10.[20] Importantly, increasing rates of death from progressive HF have offset reductions in sudden death rates, whereas the rates for heart transplants and mechanical circulatory support increased during the same time.[20] In the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF) registry, which included data from 167 outpatient cardiology practices in the United States, 2-year mortality was 22.1% among 11,600 patients with available vital status data.[21]

Limited data exist on long-term outcomes among ambulatory HF patients. The majority of evidence suggests that, depending on underlying demographics and comorbid conditions, 50% to 75% of HF outpatients are alive by 5 years.[11-13]

1.3. Study Rationale: The Conundrum of Dietary Sodium Intake and Risk for Cardiovascular Disease and Heart Failure

Excess dietary sodium intake is associated with several risk factors for CVD and HF, most prominently with elevated blood pressure,[22-24] but also with worse renal function,[25-27] left ventricular hypertrophy,[28-31] and increased arterial stiffness. [32-34] Therefore, limiting dietary sodium intake might be an important preventive intervention at the population level to reduce risk for CVD and HF. However, although there is little ambiguity as to whether limiting dietary sodium intake is beneficial, the optimal level of dietary sodium restriction is currently unclear.

Americans consume approximately 3700 mg/day of sodium on average,[35] whereas the United States Department of Agriculture (USDA) and the Department of Health and Human Services recommend 2300 mg/day for the general population, with a stricter recommendation of 1500 mg/day for those over age 50, African-Americans, or those with hypertension, diabetes, or chronic kidney disease.[36] According to a recent report from the National Health and Nutrition Examination Survey (NHANES), although 47.6% of persons aged ≥2 years meet the criteria to limit daily sodium intake to 1500 mg, the usual intake for 98.6% of those persons was >1500 mg[37]; in 88.2% of the remaining population, daily intake was greater than the recommended 2300 mg.[37] This report highlights the tremendous efforts that would be required at the industry, community, interpersonal, and individual level to achieve this level of dietary sodium intake. In turn, such dramatic efforts should be ideally backed by firm evidence of benefit. Of note, the American Heart Association in 2010 recommended dietary sodium intake of 1500 mg/day for all Americans.[38] However, USDA upheld the previous 2300-mg/day recommendations on the basis of inadequate evidence to support the stricter level of 1500 mg/day.

Based on the effects of sodium reduction on blood pressure and current levels of dietary sodium intake in the population, two simulation studies have projected substantial benefits on outcomes with stricter dietary sodium control (1500mg).[39, 40] These projections were based on extrapolation from small studies with higher sodium intake (>3000 mg/day) at baseline and assumed no or beneficial, effects on other risk factors. However, sodium restriction may exert

unfavorable effects on insulin resistance, [41, 42] serum lipids,[43] and neurohormonal activation,[43-45] factors that predispose to CVD and HF. The uncertain net effect of these opposing forces on outcomes (mortality, CVD, and HF) is highlighted by two recently published studies. In a large European cohort study investigating the genetic background of hypertension,[46] middle-aged persons in the lower sodium stratum had higher cardiovascular mortality despite lower blood pressure. Also, in a post-hoc analysis from two large randomized trials with telmisartan, a blood pressure-lowering medication, the association between urine sodium excretion (a close correlate of dietary sodium consumption) and CVD events was J-shaped[47]; compared with a baseline sodium excretion of 4 to 5.99 g per day, excretion of greater than 7 g per day was associated with an increased risk of CVD, and excretion of less than 3 g per day was associated with increased risk of CV mortality and HF.[47]

In addition to the concerns raised by these recent reports, there are additional concerns with strict dietary sodium restriction in older adults, the population segment with the highest incidence and prevalence of CVD and HF. These concerns include inadequate caloric intake and interaction with medications.[48, 49] Data on the effects of sodium restriction are scarce for older adults, especially for those with blood pressure at target. Also, achieving 1500 mg/day sodium intake is difficult, particularly in older adults with long-held dietary habits.[28] Therefore, the incremental benefit of recommending lowering dietary sodium to 1500 vs. 2300 mg/day needs to be prospectively evaluated. In a recent report from the Institute of Medicine (2013), committed from the Centers for Disease Control and Prevention (CDC), the evidence from studies on direct health outcomes was considered "insufficient and inconsistent regarding an association between sodium intake below 2300 mg per day and benefit or risk of CVD or all-cause mortality in the general population".[50] In addition, the committee concluded that the evidence on direct health outcomes does not support recommendations to lower sodium intake within previously considered "high-risk" subgroups to, or even below, 1500 mg per day. (Previously "high-risk" subgroups included persons over age 50). The committee called therefore for further rigorous research to strengthen the evidence base on the association between lower (1500 to 2300 mg) levels of sodium and health outcomes in the general population and population subgroups.

In this direction, evaluating the dose-response association of dietary sodium with key cardiovascular outcomes in older adults using data from well-designed cohort studies is a crucial step to inform design of outcome trials.

1.4. Research Questions

Question #1:

a. Is sodium intake associated with all-cause mortality in older (age ≥70) adults?

b. Is this association dependent on gender, race, adequate blood pressure control at baseline evaluation, and preexisting CVD and HF?

Question #2:

a. Is sodium intake associated with risk for CVD in older adults?

b. Is this association dependent of gender, race, and blood pressure control at baseline?

c. Does dietary sodium intake add risk stratification information for CVD when added to an established CVD risk score (the Framingham CVD risk profile)? [Do we need to account for sodium intake when assessing risk for future cardiovascular events in older adults?]

Question #3:

a. Is sodium intake associated with risk for heart failure in older adults?

b. Is this association dependent of gender, race, and blood pressure control at baseline?

c. Does dietary sodium intake add risk stratification information for HF when added to an established HF risk score (the Health ABC HF Risk Score)? [Do we need to take sodium consumption into account when assessing risk for future heart failure in older adults?]

For (a) sub-questions, we will first examine whether there is an association at all at first place. Then, using appropriate analytic methods, we will define the shape of the association (linear, curvilinear, J-shape, U-shape, inverse U-shape etc.) and then reach any reasonable thresholds from a practical perspective (i.e. for policy making suggestions).

Additional rationale for (b) sub-questions: most of the harm attributed to increased dietary sodium intake is thought to be mediated by increases in blood pressure, especially in those with uncontrolled (=high) blood pressure. Also, African-Americans appear to be more sensitive to the blood pressure-increasing effects of sodium. Data are mixed for gender-specific vulnerability, so I think it is reasonable to explore any interaction with gender.

1.5. Project Assumptions and Contextual Considerations

The overarching underlying assumption is that dietary sodium intake is associated with future mortality, CVD, and HF in older adults. However, a host of factors may modify or confound this association (**Figure 3**). Based on previous clinical and mechanistic studies, we have opted to test for modifying effects of race, gender, and baseline systolic blood pressure. Although age might be an effect modifier in a different population, this is a homogeneous population of older adults and thus we do not expect significant interactions with age; we will, however, consider age as a confounder and include in the adjustment model. Also, if no interaction is detected for gender, race, and blood pressure, in which case we will present separate analyses for these subgroups, we will consider these variables as potential confounders and include in the adjustment model.

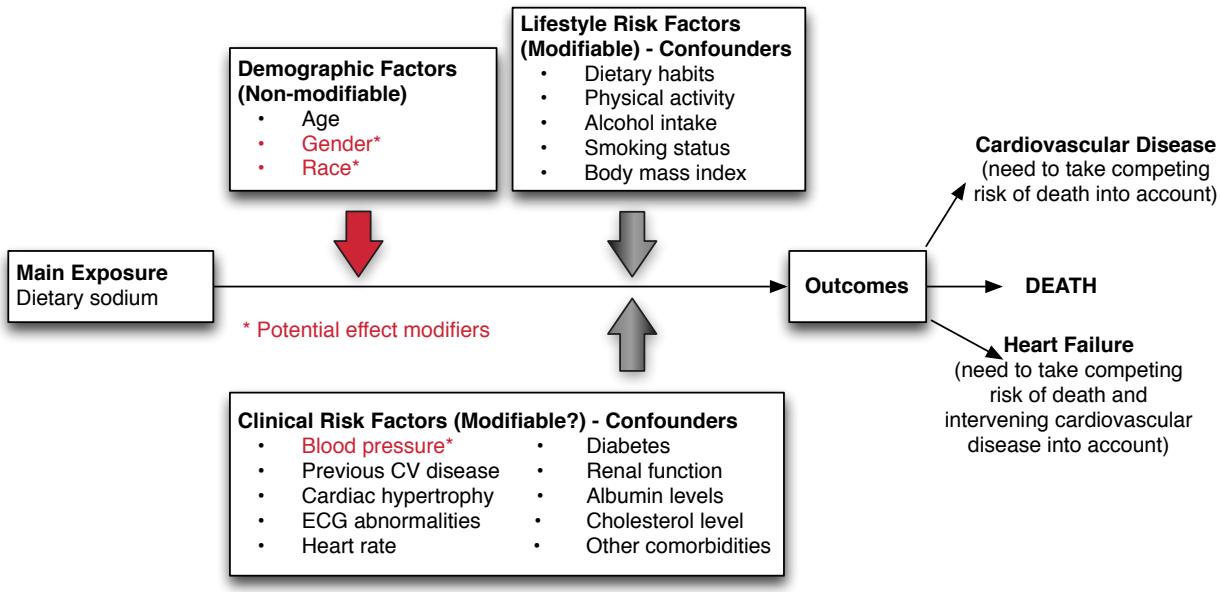


Figure 3. Conceptual model for the proposed project. Dietary sodium is considered as a modifiable risk factor in this context. CV: cardiovascular. ECG: electrocardiography

We have classified the confounding factors into three categories: (1) demographic risk factors, generally considered as non-modifiable; (2) lifestyle-related risk factors for mortality and cardiovascular disease, generally considered as modifiable and (3) clinical risk factors. Previous work has shown that adequate control with therapy may attenuate the effects of some clinical risk factors, such as blood pressure, diabetes, cholesterol level etc.; however, the increased risk associated with these factors cannot be completely abolished. Also, some clinical risk factors are

difficult to modify once present, e.g. previous cardiovascular disease or electrocardiographic (ECG) abnormalities. Therefore, we have classified clinical risk factors separately.

The rationale for classification of confounders into categories based on amenability to modification is that, from a public health perspective, it might be important to know what fraction (if any) of the increased risk for these outcomes can be attributed to dietary sodium intake versus other modifiable factors. In other words, it might be useful to know what is the relative importance of modifiable factors for future events so that we can prioritize policies [18]. Dietary sodium intake is considered a modifiable factor in this framework.

2. Literature Review

2.1. Dietary Sodium Intake and Mortality

There is no consistent evidence to support an association between sodium intake and either a beneficial or adverse effect on most direct health outcomes. Also, most studies were conducted in populations consuming much higher levels of sodium than those consumed in the United States. The evidence linking dietary sodium intake with cardiovascular and all-cause mortality is conflicting and inconsistent. The data on older adults are scarce and come mostly from post-hoc subgroup analyses from cohort studies. We summarize here the evidence for general population from the most rigorous and large sample-size studies

Using data from the National Health and Nutrition Examination Survey (NHANES) II, Cohen and colleagues examined the association of dietary sodium intake on risk of CVD and all-cause mortality over a mean of 13.7 years of follow-up in 7154 participants 30-74 years of age.[51] Individuals with self-reported preexisting disease, as well as those who reported being on a low-sodium diet for hypertension were excluded. Dietary sodium intake was assessed from a 24-hour dietary recall administered in the NHANES survey and was categorized as <2,300 mg (n=3443) or ≥2,300 mg (n=3711]. Sodium intake was adjusted for calories and the highest and lowest one percent of the calorie intake range was excluded from the analysis. Compared to ≥2300 mg per day, lower sodium intake was significantly associated with increased risk of all-cause mortality. Models of sodium density, expressed as a sodium/calorie ratio, showed an inverse association with all-cause mortality (HR=0.89; CI: 0.79, 1.00; p=0.05). For sodium intake measured as a

continuous variable, a significant inverse relationship was found between sodium intake and CVD mortality whether expressed as sodium per mg (HR=0.89; CI: 0.80, 0.99; p=0.03) or as sodium per calorie (HR=0.80; CI: 0.68, 0.94; p=0.008). Although data were not shown, the authors reported that they found no evidence of interactions by age, race, or prevalence of diabetes or hypertension. The same authors observed similar trends in NHANES III.[52]

In a combined analysis from two population-based prospective cohort studies (the Flemish Study on Environment, Genes, and Health Outcomes and the European Project on Genes in Hypertension), which included 2,856 participants recruited from a random sample of households in several European countries grouped into 20-39, 40-59, and 60+ years of age, Stolarz-Skrzypek and colleagues examined the association between 24-h urinary sodium excretion, changes in blood pressure, and risk of CVD mortality and all-cause mortality over a median of 7.9 years.[46] The 24-h urine samples were collected 1 week following blood pressure measurements and analyzed for sodium and potassium. Sodium excretion was categorized into tertiles of low (1150-2900 mg for women; 1150-3630 mg for men); medium (2920-4070 mg for women; 3660-5080 mg for men); and high (4090-9200 mg for women; 5,100-9200 mg for men). After adjusting for sex, age, blood pressure level, body mass index, alcohol use, antihypertensive drugs, urinary potassium excretion, education, smoking status, total cholesterol, and diabetes, the authors found that lower sodium intake was associated with higher risk of CVD mortality. In the low, medium, and high tertiles of sodium excretion the % of events were 4.1% (CI: 3.5%, 4.7%); 1.9% (CI: 1.5%, 2.3%); and 0.8% (CI: 0.5%, 1.1%) events, respectively. CVD mortality was statistically significantly higher in the low vs. the high tertile (HR=1.56; CI: 1.02, 2.36; p=0.04) with a significant trend over tertiles (p=0.02). All-cause mortality showed a trend similar to that of CVD mortality although it was not statistically significant.

Using data from the third NHANES cohort, Yang and colleagues linked sodium intake, potassium intake, and sodium/potassium ratio from 12,267 adults 20 years of age and older with CVD and all-cause mortality data from the National Death Index over an average of 14.8 years.[53] Estimates of dietary sodium intake were derived from the NHANES 24-hour dietary recall. Within-person variability was calculated using 7% of individuals and was used to adjust the sodium intake. Sodium intake levels were categorized into quartiles from lowest to highest: Q1=2176; Q2=3040; Q3=3864; and Q4=5135 mg per day, using the lowest intake as reference. Nutrient-disease associations were estimated as continuous variables for all-cause and CVD

mortality. After multivariable adjustment, higher usual sodium intake was found to be directly associated with all-cause mortality (HR=1.20; CI: 1.03, 1.41 per 1,000 mg per day), but not with CVD mortality. However, the investigators opted not to adjust for blood pressure or anti-hypertensive treatment, arguing that these factors may be in the causal pathway linking dietary sodium to health outcomes. Although not reported, the authors found no evidence of interactions by age, race, or prevalence of diabetes or hypertension.

As previously discussed, data specifically for older adults are scarce. Geleijnse and colleagues examined a subset of participants in the Rotterdam prospective cohort study that included 1448 randomly selected participants ≥55 years old living in the Netherlands.[54] This case-cohort design examined the relationships between sodium and potassium intake and incidence of myocardial infarction, stroke, CVD mortality and all-cause mortality. Participants were followed for a median of 5.5 years. Urinary sodium, potassium, and creatinine excretion were estimated from a single overnight urine sample collected at home. Quartile levels were 1520, 2420, and 3470 mg per day. Adjustments were made for total energy, alcohol intake, saturated fat intake, and 24-hour urinary potassium. Baseline blood pressure for the cohort was 140±22 mmHg systolic and 74±11 mmHg diastolic; and 37% had a diagnosis of hypertension. Adjustments were made for age, sex, 24-hour urinary creatinine, BMI, smoking status, diabetes, use of diuretics, and education. The authors found no significant association between urinary sodium level and risk of CVD mortality or all-cause mortality. However, there was an inverse association with CVD mortality that was of borderline significance (RR=0.77; CI: 0.60, 1.01 per 1 SD). After excluding participants with a history of CVD or hypertension, the difference was attenuated and non-significant. Several other studies in the general population listed analyzed data on health outcomes by age and found no interaction.[51-53]

2.2. Dietary Sodium Intake and Cardiovascular Disease

In the combined analysis from the Flemish Study on Environment, Genes, and Health Outcomes and the European Project on Genes in Hypertension, Stolarz-Skrzypek and colleagues reported no significant effect of dietary sodium intake on total CVD incidence.[46]

Gardener and colleagues analyzed data from the Northern Manhattan Study (n=2657) who had no previous diagnosis of stroke, were older than 40 years of age (mean 69±10 years) and were ethnically diverse. Dietary sodium intake was estimated using the Block National

Cancer Institute FFQ. Sodium intake was calculated from self-reported data and categorized into tertiles of ≤1500, 1501-3999, and ≥4000 mg per day. This study found that sodium intake was positively associated with increased risk of stroke. Using sodium as a continuous variable, stroke risk increased 17% for each 500 mg per day higher sodium intake (HR=1.17; CI: 1.07, 1.27). However, the authors noted that the relationship did not appear linear. Participants consuming ≥ 4000 mg sodium daily had a 2.5-fold increase in risk of stroke compared to those who consumed less than 1500 mg per day (HR=2.50; CI: 1.23, 5.07). This difference persisted after adjustment for vascular risk factors. Those who consumed more than 1500, but less than 4000 mg of sodium daily had an ~30% increased risk, though this was not statistically significant. Consumption of ≥ 4000 mg per day also was associated with an increased risk of combined vascular events, while the results were less consistent for lower levels of sodium consumption and CVD events. The authors found no evidence of interactions by age, race, or prevalence of diabetes or hypertension.

Takachi and colleagues examined data from the Japan Public Health Center-based Prospective Study, conducted in two cohorts. Cohort I and II participants were 40-59 and 40-69 years of age, respectively. Those with a history of cancer or coronary heart disease were excluded, leaving a final study population of 77,500 (35,730 men and 41,770 women). Dietary sodium intake data were determined from a 138-item FFQ that included cooking salt, soy sauce, table salt, and other salty condiments. Energy-adjusted sodium intake per day was categorized by quintile: medians were 3080, 4,000, 4710, 5500, and 6840 mg per day for Q1 through Q5, respectively. Thus, the average sodium intake in the United States would be close to the lowest quintile of this study. Cardiovascular outcomes included diagnosis of myocardial infarction and diagnosis of stroke confirmed by computer tomography scan and/or magnetic resonance imaging from medical records. Adjustment variables were sex and age, with additional adjustment for body mass index, smoking status, alcohol consumption, physical activity, and quintiles of energy, potassium, and calcium. Multivariable analysis found a significant positive association between sodium consumption at the highest compared to the lowest quintile and risk of stroke (HR=1.21; CI: 1.01, 1.43; p for trend=0.03). The risk of the composite CVD endpoint was elevated in the highest quintile of sodium (HR=1.19; CI: 1.01, 1.40; p for trend=0.06). The results also showed correlation with other variables, such as dried and salted fish, although the impact of those variables on the outcomes is unknown.

2.3. Dietary Sodium Intake and Heart Failure

Data on sodium intake and HF risk are limited and derived primarily from younger populations[55] whereas most new HF cases are encountered in older adults. In the first National Health and Nutrition Examination Survey (NHANES) Follow-up Study, risk for HF increased by 43% in persons consuming ~2600 mg sodium compared to <1155 mg.[55] However, this association was only observed in overweight individuals.[55] A direct association between sodium intake and HF risk in older adults has yet to be demonstrated. High sodium intake can lead to HF through multiple pathways since excessive intake has been associated with increased left ventricular (LV) mass [29-31, 56] and LV diastolic dysfunction[57-59] independent of BP. Excess sodium is associated with worsening renal function, urinary protein excretion,[25-27] and impaired arterial stiffness.[32-34] All these alterations in turn predispose to HF.[60-66] However, the effect of sodium restriction on physiological endpoints related to HF has not been studied in older adults. Specifically for normotensive older adults, data are scarce and the effect on left ventricular mass is unknown.

2.4. Summary

The evidence linking dietary sodium intake and CVD, HF, and mortality both in the general population and specifically among older adults is scarce and conflicting. Moreover, in older adults, inadequate nutrient intake[48] and interaction with medications[49] are additional concerns with strict sodium restriction. For example, experimental evidence suggests that combined renin-angiotensin system blockade and sodium restriction impairs cardiomyocyte contractility.[67] Therefore, assessing efficacy and safety of sodium restriction is important before generalizing such recommendations in older adults, in whom long-standing eating habits would render very low sodium diets especially difficult to implement and may affect quality of life. Towards this direction, evaluating the dose-response association of dietary sodium with key cardiovascular outcomes in older adults using data from well-designed cohort studies is a crucial step to inform design of outcome trials. Our purpose is therefore to investigate the association between dietary sodium intake, as assessed with a FFQ, and risk for (1) all-cause mortality; (2) incident CVD; and (3) incident HF in older adults.

3. Design and Methodology

3.1. Study Design Overview

The study is using data from a prospective cohort study. Although the prospective cohort design is considered a strong design, and the deriving evidence comes second only to that resulting from randomized controlled trials, there are several weaknesses associated with cohort studies as well. We briefly outline here strengths and weaknesses of the prospective cohort design and discuss the application of these issues in the Health ABC Study.

Basic Design of Cohort Studies

In a cohort study, a group of individuals exposed to a risk factor (or to various levels of a risk factor in the case of sodium intake) are followed over time to determine incidence of disease. The incidence of disease in the exposed group is compared with the incidence of disease in the. Levels of exposure (e.g. level of daily sodium intake) are measured at baseline and/or assessed at intervals during follow-up. Exposure data may be obtained from a number of sources including medical records, standardized questionnaires, interviews, or physical examination. Outcome data may be obtained from various sources, including routine surveillance, death certificates, medical records, or directly from the participant. The follow-up in a cohort study is a major challenge. A great deal of cost and time is required to ensure follow-up and update measures of exposures and confounders, in addition to monitoring outcomes.

Potential Sources of Bias in Cohort Studies

A major source of potential bias in cohort studies is loss to follow-up. Cohort members may die, migrate, or refuse to continue to participate. In addition, losses to follow-up may be related to the exposure, outcome or both. For example, individuals developing the outcome may be less likely to continue to participate in the study. Loss to follow-up associated with the exposure and/or the outcome introduces bias in the measures of effect of exposure. In the Health ABC Study, only participants planning to remain in the designated geographic areas for ≥3 years were included and surveillance was very rigorous (telephone contact every 6 months and annual physical visit). As a result, follow up status was complete after 10 years for >99% of participants and vital status was obtained and available practically for every patient.

Another source of potential bias in cohort studies arises from the degree of accuracy with which subjects have been classified with respect to their exposure or disease status at baseline. Differential misclassification can lead to an over- or under-estimate of the effect of the exposure on the outcome. We discuss these issues in the "measurement of main exposure of interest" and "baseline disease status classification" sections below.

Selection bias may be introduced not only when the completeness of follow-up or case ascertainment differs between exposure categories, but also when selection of participants is not representative of the intended population. In the Health ABC Study, selection bias was present by design, because the study enrolled only older adults reporting no difficulty walking a quarter of a mile, climbing one flight of stairs without resting, or performing basic activities of daily living. Persons who required an assistive device, such as a cane or walker, were excluded. The findings of the study should therefore be interpreted in the context of well-functioning older adults and cannot be extrapolated to the general population of older adults.

Strengths and Weaknesses of Cohort Studies

We summarize here briefly the strengths and weaknesses of the cohort study design in the context of the research question and the current cohort study:

Strengths:

- Multiple outcomes can be measured.
- We can look at multiple exposures (although not directly applicable to the research question, it allows to account for potential important exposure covariates).
- Exposure has been measured before the onset of disease.
- We can measure incidence and prevalence of the desired outcomes.

Weaknesses:

- Cohort designs are prone to confounding.
- Participants may move between exposure categories (regression dilution).
- Knowledge of exposure status may bias classification of the outcome.
- Being in the study may have altered participant's behavior.
- Classification of individuals (exposure or outcome status) might have been affected by differences in diagnostic procedures.

3.2. Measurement of Main Exposure of Interest

Dietary sodium intake was calculated from an FFQ administered during the first annual follow-up visit (year 2 visit) of the Health ABC Study. This 108-item FFQ was designed specifically for the Health ABC Study by Block Dietary Data Systems (Berkeley, CA), based on reported intakes of non-Hispanic white and black residents of the Northeast and South older than age 65 years in NHANES III. The FFQ reference period was the preceding year. A trained dietary interviewer administered the FFQ, and interviews were periodically monitored to assure quality and consistency. Wood blocks, real food models, and flash cards were used to help participants estimate portion sizes. Block Dietary Data Systems determined nutrient and food group intakes.

Several FFQs have been validated for sodium intake estimation demonstrating that these tools are generally less accurate than prospective food diaries (when compared to biochemical gold standards), partially because of recall bias, but useful for large epidemiological studies. In a study validating a 7-day food diary (7DD) and a FFQ against biomarkers of intake in urine (nitrogen, potassium, and sodium) in 123 healthy middle-aged men and women in the United Kingdom, correlations between 24-h urinary sodium excretion and dietary intake were stronger for 7DD (r=0.48) compared to FFQ (r=0.18-0.20).[68] In a study of 123 individuals who completed a FFQ and a 7-day diary (7DD) on 2 occasions separated by approximately 12 months, the error variances for nitrogen, potassium and sodium was more than twice as great with the FFQ than the 7DD; (2) there was substantial correlation (0.46-0.58) between the error of both the FFQ and the 7DD completed on different occasions; (3) there was moderate correlation (0.24-0.29) between the error in the FFQ and the error in the 7DD for each nutrient; (4) the correlation between errors in different nutrients was higher for the FFQ (0.77-0.80) than for 7DD (0.52-0.70). The investigators concluded that regression dilution with the FFQ is considerably greater than with the 7DD. [69] In 264 participants of a health screening program in Denmark [70], a FFQ was validated against a 28-days' diet history, a 24-h urine collection, and a fasting blood sample. Spearman's rank correlation coefficients between the two dietary methods was 0.31; however, the proportion of individuals classified in the same or adjacent quintiles were, on average, 72% for men and 69% for women. Gross misclassification was found on average in 2%. The authors concluded that the FFQ provides acceptable classification of individuals according to their dietary intakes and gives a good quantitative measurement of key dietary components.

3.3. Baseline Disease Status Classification

Baseline data for the cohort participants (inception period) were collected from April 1997 to June 1998. Cardiovascular disease status at baseline, including prevalent CVD and HF, was based on self-reported history, use of selected drugs, and the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes as reported by Medicare and Medicaid Services from 1995 through 1998. Prevalent CVD was defined as (1) prevalent coronary heart disease (history of myocardial infarction, angina treated with medications, or coronary revascularization); (2) prevalent cerebrovascular disease (history of stroke, transient ischemic attack, or carotid endarterectomy), or (3) prevalent peripheral vascular disease (history of intermittent claudication or vascular bypass or angioplasty). Prevalent HF was defined as physician diagnosis of HF followed by treatment for HF (i.e., a current prescription for a diuretic agent and either digitalis or a vasodilator).[18]

3.4. Event Surveillance Methods

In the Health ABC Study, surveillance was conducted by in-person examination alternating with a telephone interview every 6 months. Participants were asked to report any hospitalizations and were also asked direct questions regarding incident CVD and HF events and during the planned telephone interviews and in-person examinations. Medical records for overnight hospitalizations were reviewed at each site by local adjudicators. Using algorithms mirroring those of the Cardiovascular Health Study, [71] a panel of clinicians verified diagnoses and caused of death based on interview, review of all hospital records, and death certificates. It is important to stress that physicians, subsequently adjudicated all events captured through patient self-report, using copies of hospital records and other source documents. Therefore, the Health ABC Study is not relying on self-reported elements for adjudication; self-report is used only for event surveillance.

4. Data Collection, Analysis, and Results:

4.1. Description of the Data Sources

The Health ABC) study was designed to assess the relationship between body composition, long-term conditions, and incident mobility limitation in an initially well-functioning older adult cohort. From March 1997 to April 1998, the study enrolled 3075 people aged 70 to 79 years, of

whom 1584 (52%) were women and 1281 (42%) were black. Potential participants were recruited from a random sample of white and all black Medicare beneficiaries residing in designated ZIP code areas in Pittsburgh, PA, and Memphis, TN, with a mailed invitation followed by a telephone screening interview to determine eligibility. Race was defined by self-report. Eligible participants reported no difficulty walking a quarter of a mile, climbing one flight of stairs without resting, or performing basic activities of daily living. Persons with plans to leave the area within 3 years; who required an assistive device, such as a cane or walker; who reported being actively treated for cancer; or who were participating in a clinical trial were excluded. Eligible participants were scheduled for a home interview during which eligibility was confirmed, consent was obtained, and a comprehensive interview was conducted followed by a clinic examination that included assessment of mobility. The protocol was approved by the institutional review boards at the 2 field centers and the coordinating center. All participants gave written informed consent. At year 2, participants were asked to complete an FFQ. Data on sodium intake were available for 2713 participants. This analysis, however, includes data on 2642 participants; we excluded 63 participants with manifest HF at year 2 and 8 participants because of implausibly low dietary sodium content values by FFQ (<300 mg/d). For outcomes, we used adjudicated 10-year follow up data.

4.2. Identification of the Critical Dependent and Independent Variables

The main independent variable (main exposure of interest) in the proposed project is dietary sodium intake at year 2, derived from a food frequency questionnaire (FFQ). This is expressed as mg/day. The dependent variables (outcomes) of interest are:

- Mortality at 10 years

- Cardiovascular disease at 10 years

- Heart failure at 10 years

Because mortality rates in older adults can be substantially higher than the rates of incident cardiovascular disease and heart failure, especially in the higher risk strata, and hence lead to overestimation of absolute risks,[72, 73] we will adjust for the competing risk of death in analyses looking at the association between sodium intake and CVD and HF. For this purpose, we will use extended Cox proportional hazards models (details will be provided in the statistical analysis

section).[72, 73] Finally, although both CVD and HF can lead to death, we will use all-cause mortality in our primary analysis.

As previously discussed in Section 1 (Figure 3), there is a host of risk factors that can modify or confound the association between the exposure of interest (dietary sodium) and outcomes. These risk factors have been identified from previous work done in the Health ABC Study and other large cohort studies. In the current study, these risk factors will be expressed through the covariates presented in **Table 1**.

4.3. Definition of the Proposed Outcome Measures

Outcome #1 – Mortality

The Health ABC Diagnosis and Disease Ascertainment Committee reviewed all deaths. For this purpose, the Committee reviewed hospital records, death certificates, and informant interviews.

Outcome #2 - Incident Cardiovascular Disease

Incident CVD events were identified and adjudicated using the standard Health ABC Study surveillance and adjudication process described above. Incident CVD was defined as (1) incident coronary heart disease (myocardial infarction, angina, or coronary revascularization); (2) incident cerebrovascular disease (stroke, transient ischemic attack, or symptomatic carotid artery disease); (3) incident peripheral arterial disease; or (4) death due to cardiovascular causes.

Outcome #3 - Incident Heart Failure

All first admissions with an overnight stay that was confirmed as related to HF, based on symptoms, signs, chest radiograph results, and echocardiographic findings, using criteria similar to those used in the Cardiovascular Health Study, were designated as incident HF event.[71] The criteria required HF diagnosis by a physician and treatment for HF.[74] Briefly, an HF event was confirmed if, in addition to a physician diagnosis, there was documentation in the medical record of (1) symptoms (e.g., shortness of breath, fatigue) and physical signs (e.g., edema and rales), (2) supporting clinical findings (e.g., pulmonary edema on chest x-ray), and (3) treatment, including diuretics, digitalis, angiotensin-converting enzyme inhibitors or β- blockers. Information from echocardiography was not required but was taken into account whenever available.

4.4. Analysis Plan

Descriptive Statistics

To describe baseline characteristics and adjust for these characteristics in multivariable models, we will use values from the year 2 visit where available to be consistent with the time of baseline sodium intake assessment (year 2); the remaining values will be carried over from year 1. We summarize the source if the covariates in **Table 1:**

Table 1. Derivation of covariates for multivariable analysis

Covariates	Most recent year available
Age, race, gender	Year 2 (static variables)
Left ventricular hypertrophy (by EKG)	Year 1
Prevalent cardiovascular (coronary artery, cerebro-vascular, peripheral vascular) disease variables	Year 2
Diabetes mellitus	Year 2
Pulmonary disease	Year 2
Hypertension	Year 2
Depression	Year 2
Smoking status, alcohol consumption	Year 1
Blood pressure, heart rate, body mass index	Year 2
Lipid panel	Year 2
Fasting glucose	Year 2
Medication variables	Year 2
Dietary variables from food frequency questionnaire	Year 2
Physical activity variables	Year 1
Ankle-brachial index	Year 1
Creatinine, albumin	Year 2

We have opted to present the baseline characteristics (covariates) according to categories of sodium intake, i.e. <1500, 1500-2300, and >2300 mg/day, based on the current recommendations from the American Heart Association (≤1500 mg/d) and USDA (≤2300 mg) in order to facilitate clinical and public health interpretation. We will also use the non-parametric test for trend to examine trends of characteristics across sodium categories. This is an important step to build a

multivariable model for the outcomes of interest: if a covariate is associated with the exposure of interest (=sodium intake), we will include this covariate in multivariable models.

Inferential Statistics

We will examine sodium intake and association with outcomes (mortality, incident CVD, and incident HF) using two different approaches for sodium:

(1) Entering sodium intake as a clinically predefined categorical variable using recommendation level cut-off points, i.e. <1500, 1500-2300, and >2300 mg/day and
(2) Entering sodium intake as a continuous variable, where we will examine for nonlinear associations with the event of interest using fractional polynomial functions and restricted cubic splines as introduced by Royston and coworkers. [75 76]

To graphically present crude survival and incidence of CVD and HF according to sodium intake category at baseline, we will plot appropriate 10-year Kaplan-Meier curves and provide 10-year Kaplan-Meier estimates for survival and incidence of CVD and HF. We will compare the crude curves using the log-rank chi-square statistic.

To examine the association between baseline sodium and 10-year mortality, we will use the Cox proportional hazards regression models. For sodium entered as a continuous variable, we will fist examine the appropriate functional form for sodium (linear vs. nonlinear forms) using fractional polynomials and restricted cubic splines as described by Royston, Sauerbrei, and associates.[75] We will then evaluate the proportional hazards assumption using the Schoenfeld residuals and interactions tests with time as appropriate. In multivariable analyses, we will adjust for clinical risk factors previously associated with mortality in the Health ABC Study[77] and any additional covariates (i.e., baseline characteristics) from **Table 1** associated with the exposure of interest (sodium intake). To examine for significant modification effects, we will introduce interaction terms in univariate models and verify in the multivariable model. We will only keep interaction terms if these retain significance in multivariable models.

To examine the association between baseline sodium and CVD, we will use the Fine and Grey extension of the Cox proportional hazards model.[78] This model allows taking into account the competing risk of non-cardiovascular death (since cardiovascular death is included in the CVD endpoint), which is considerable in older adults and may inflate estimates especially for

higher-risk patients. For this analysis, we excluded participants with CVD at baseline. In multivariable analyses, we will adjust for clinical CVD risk factors previously identified in the Health ABC Study[77, 79] and any additional covariates associated with sodium intake. We will follow the same approach for sodium intake and risk for HF, with all-cause mortality as a competing risk. We will adjust for clinical risk factors previously identified as HF risk predictors in the Health ABC Study[80] and any additional covariates associated with sodium intake. All analyses were performed with STATA version 12 (StataCorp LP, College Station, TX).

4.5. Results

Descriptive Statistics

Data on sodium intake were available for 2713 participants, based on the FFQ completed at the year 2 visit. After excluding (1) 63 participants with manifest (prevalent) HF at year 2 and (2) eight participants because of implausibly low dietary sodium values by FFQ (<300 mg/d), the final analysis dataset included data on 2642 participants. For incident CVD, because of exclusion of participants with prevalent CVD at baseline, the analysis was restricted to 1981 participants.

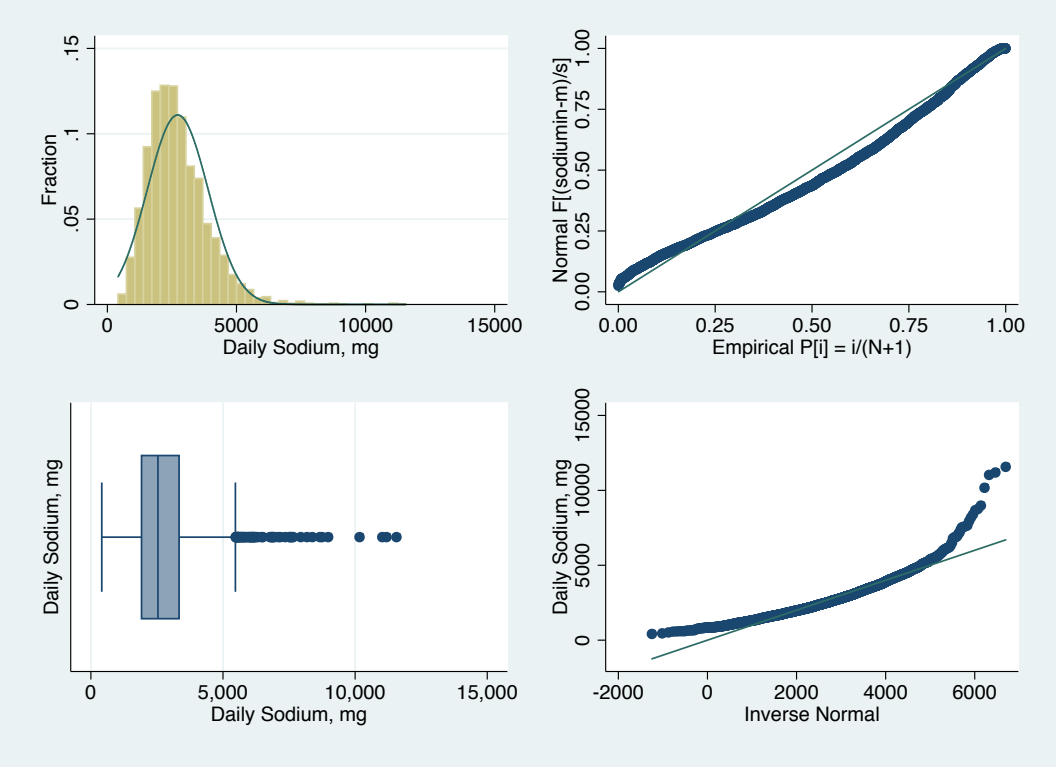


Figure 4. Distribution of daily sodium intake at baseline in the Health ABC Study (N=2642)

Main Exposure

The distribution of daily sodium intake at year 2 (i.e., the baseline assessment for this study) is presented in **Figure 4**. Median intake was 2540 mg (interquartile range [IQR], 1920 to 3340).

Baseline Characteristics

Table 2 summarizes the baseline characteristics of these participants according to sodium intake category, i.e. <1500, 1500-2300, and >2300 mg/day, at year 2.

Table 2. Baseline participant characteristics according to sodium intake at year 2

	<1500 mg/day	**1500-2300 mg/d**	**>2300 mg/d**	**P value***
N	**291**	**779**	**1572**	
Age, years	74.4 (2.9)	74.6 (2.9)	74.6 (2.9)	0.17
Male sex, %	88 (30.2)	315 (40.4)	887 (56.4)	<0.001
Race				0.028
Blacks, %	137 (47.1)	285 (36.6)	590 (37.5)	
Whites, %	154 (52.9)	494 (63.4)	982 (62.5)	
Body mass index, kg/m^2	27.7 (5.0)	27.2 (4.8)	27.1 (4.8)	0.14
Smoking				0.91
Current smokers, %	32 (11.0)	65 (8.3)	149 (9.5)	
Past smokers, %	131 (45.0)	359 (46.1)	728 (46.3)	
Physical activity, kcal/kg/week	64.8 (39.8, 101.8)	68.0 (39.7, 107.8)	66.1 (39.4, 110.0)	0.42
Coronary heart disease, %	55 (18.9)	140 (18.0)	284 (18.1)	0.81
Cerebrovascular disease, %	27 (9.3)	61 (7.8)	103 (6.6)	0.069
Peripheral vascular disease, %	17 (5.8)	35 (4.5)	78 (5.0)	0.79
Any cardiovascular disease, %	74 (25.4)	203 (26.1)	384 (24.4)	0.49
Pulmonary disease, %	39 (13.4)	81 (10.4)	180 (11.5)	0.69
Diabetes mellitus, %	38 (13.1)	138 (17.7)	297 (18.9)	0.028
Hypertension, %	167 (57.4)	427 (54.8)	803 (51.1)	0.019
Depression, %	31 (10.7)	75 (9.6)	163 (10.4)	0.88
Systolic blood pressure, mmHg	136.1 (22.3)	133.3 (19.9)	133.6 (20.8)	0.36
Diastolic blood pressure, mmHg	71.0 (12.4)	70.2 (11.1)	70.3 (11.9)	0.43
Heart rate, beats/min	64.7 (9.5)	64.7 (10.9)	64.9 (11.1)	0.98
ECG – major abnormalities, † %	56 (19.2)	172 (22.1)	326 (20.7)	0.96

ECG – minor abnormalities, ‡ %	57 (19.7)	129 (16.6)	260 (16.6)	0.30
Glucose, mg/dl	97.8 (23.8)	102.3 (31.3)	103.0 (29.6)	0.019
Albumin, g/dl	3.96 (0.30)	3.98 (0.32)	4.00 (0.31)	0.042
Creatinine, mg/dl	1.04 (0.37)	1.04 (0.40)	1.05 (0.37)	0.007
Total cholesterol, mg/dl	211.9 (37.8)	208.2 (39.2)	203.6 (38.3)	<0.001

Continuous variables are presented as mean (standard deviation) or median (25th percentile, 75th percentile); categorical variables are presented as number (%). ECG: electrocardiogram. * Nonparametric test for trend. † Major Q or QS abnormality, major ST or T wave abnormality, left ventricular hypertrophy, or ventricular conduction defects. ‡ Minor Q or QS abnormality or ST or T wave abnormalities.

As evident from Table 2, men, whites, and participants with diabetes are more likely to consume larger amounts of sodium. On the other hand, participants with hypertension are more likely to consume smaller amounts of sodium. Lower sodium intake was associated with lower glucose, albumin, and creatinine levels and also with higher total cholesterol levels.

Outcomes

After 10 years of follow up, 881 of 2642 (33.3%) of patients died. The annualized mortality was 3.9% (95% CI, 3.7% to 4.2%) and the Kaplan-Meier estimate for 10-year mortality was 33.7% (95% CI, 31.9% to 35.5%). Among the 1981 participants without CVD at baseline, 572 (28.9%) developed CVD during follow up. The annualized CVD incidence was 3.7% (95% CI, 3.4% to 4.0%) and the Kaplan-Meier estimate for 10-year CVD incidence was 31.7% (95% CI, 29.6% to 34.0%). By design, no patient with HF at baseline was included. Among the 2642 participants, 398 (15.1%) developed HF during follow up. The annualized HF incidence was 1.9% (95% CI, 1.7% to 2.0%) and the Kaplan-Meier estimate for 10-year HF incidence was 17.4% (95% CI, 15.9% to 19.0%).

Univariate Association of Sodium Intake with Outcomes

Mortality – Sodium Intake as Continuous Predictor

We first examined sodium intake as a continuous exposure variable. The first step was to assess the appropriate functional form in Cox models, i.e. to decide whether sodium can be reasonably treated as a linear predictor or a nonlinear form would me more appropriate. We tested both with restricted cubic splines and with fractional polynomials in Cox models with mortality as the outcome of interest. The restricted cubic spline model (**Figure 5**) with 3 knots had a likelihood ratio (LR) of 12.33 with 4 d.f. (P=0.015). The Bayesian information criterion (BIC) was 13545.

The fractional polynomial model that optimized mortality prediction was the (3, 3) model (**Figure 6**). This model had a LR of 12.21 with 2 d.f. (P=0.002) and a BIC of 13532 and was therefore considered superior to the restricted cubic spline model.

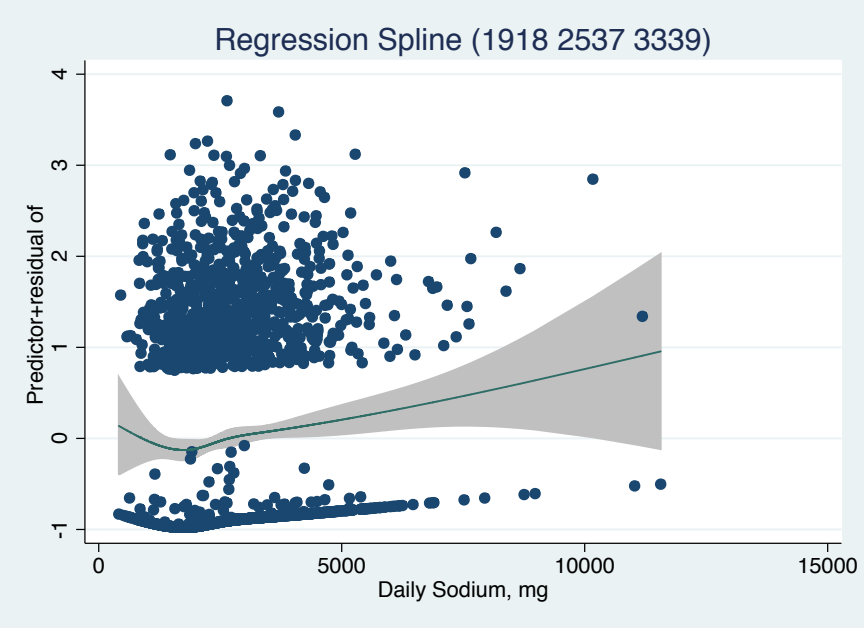


Figure 5. Residual plot of restricted cubic spline model with sodium intake as a univariate predictor for mortality.

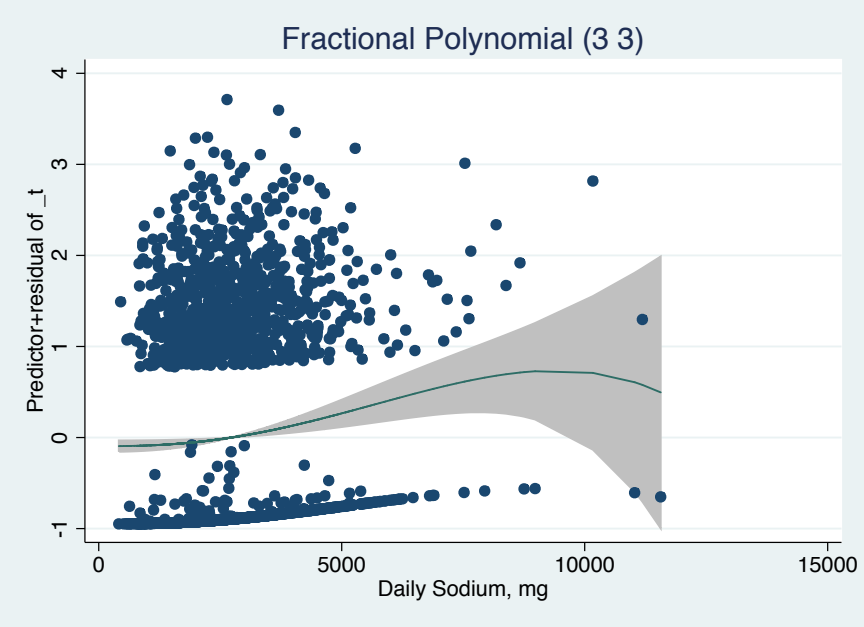


Figure 6. Residual plot of fractional polynomial model with sodium intake as a univariate predictor for mortality.

However, the added complexity of these two nonlinear models was not adequately justified by the incremental fit for prediction of mortality. The simple linear model had a LR of 10.71 with 1 d.f. (P=0.001) and a BIC of 13527 and was therefore considered superior to nonlinear models.

After concluding that it is reasonable to assume a linear association between daily sodium intake and relative risk for mortality, we calculated the corresponding hazard ratio (HR). In order to produce sensible estimates, we estimated the HR per 1,000 mg (=1g) of sodium. The crude (i.e., univariate or unadjusted) HR per 1g of sodium intake was 1.09 (95% confidence interval [CI], 1.04 to 1.15; P=0.001), that is, each 1 g of sodium intake at baseline was associated with 9% (95% CI, 4% to 15%) higher mortality. The Schoenfeld residuals test for non-proportional hazards was nonsignificant (P=0.41). The interaction term with time was nonsignificant also (P=0.41). We therefore concluded that the proportional hazards assumption was satisfied.

Incident CVD – Sodium Intake as Continuous Predictor

Similar to mortality, the linear form best represented the association between baseline dietary sodium intake and CVD. Taking the competing risk of death into account, the crude HR for CVD per 1g of sodium intake was 1.09 (95% CI, 1.01 to 1.16; P=0.023), that is, each 1 g of sodium intake at baseline was associated with 9% (95% CI, 1% to 16%) higher CVD incidence. Because the Schoenfeld residuals test is not appropriate for competing risks (i.e., Fine & Grey) models, we relied on the interaction with time to detect non-proportionality. The term was nonsignificant (P=0.17); we thus concluded that the proportional hazards assumption was satisfied.

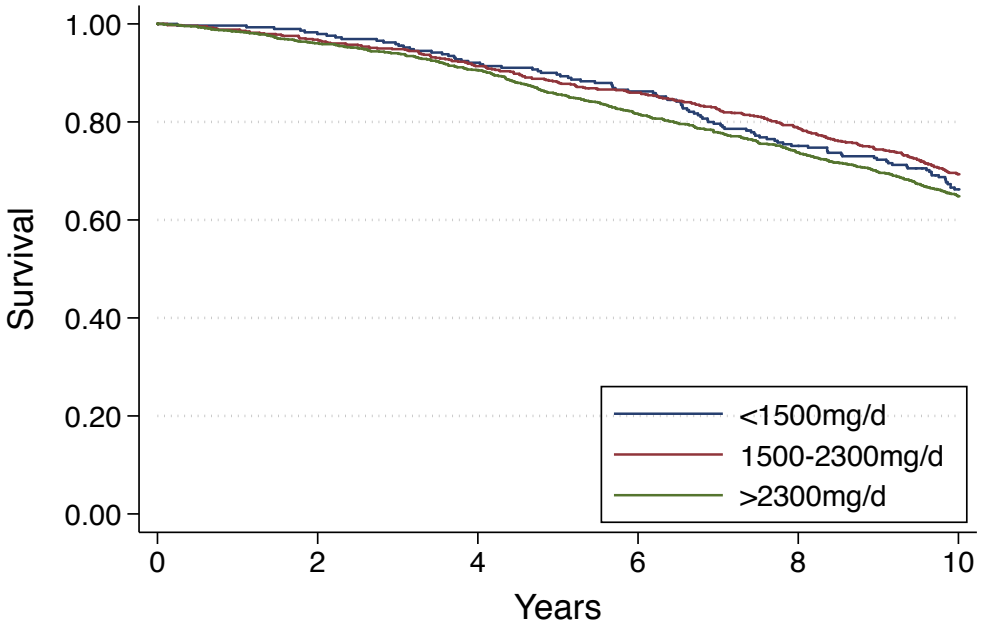
Incident HF – Sodium Intake as Continuous Predictor

The linear form best represented the association between baseline dietary sodium intake and HF. Taking the competing risk of death into account, the crude HR for HF per 1g of sodium intake was 1.03 (95% CI, 0.95 to 1.12; P=0.50). Thus, we concluded that sodium intake was not associated with incident HF. The interaction term with time was nonsignificant (P=0.14); we therefore concluded that the proportional hazards assumption was satisfied.

Mortality – Sodium Intake as Categorical Predictor

Figure 7 presents the unadjusted Kaplan-Meier curves for 10-year survival according to baseline sodium consumption. The 10-year Kaplan-Meier survival was 66.2%, 69.3%, and 64.8% for participants consuming <1500, 1500-2300, and >2300 mg sodium daily, respectively (chi-square

5.22 with d.f. =2; P=0.074 for the log-rank test). We therefore conclude that overall survival differed only minimally between the sodium consumption categories.



Number at risk

<1500mg/d	291	285	267	250	214	185
1500-2300mg/d	779	752	709	665	604	518
>2300mg/d	1572	1508	1418	1276	1148	988

Figure 7. Unadjusted Kaplan-Meier survival according to baseline sodium consumption.

Using the 1500-2300 mg as reference (lowest mortality), the HR for <1500 mg intake was 1.11 (95% CI, 0.88 to 1.41; P=0.38) and the HR for >2300 mg intake was 1.19 (95% CI, 1.02 to 1.39; P=0.023). We concluded that the main difference in survival was between the 1500-2300 and >2300 mg groups, which also exhibited some separation in Figure 7. The Schoenfeld residuals test for non-proportional hazards was nonsignificant (P=0.26).

Incident CVD – Sodium Intake as Categorical Predictor

Figure 8 presents the cumulative incidence of CVD over 10 years, accounting for the competing risk of death. The 10-year CVD incidence was 28.5%, 28.2%, and 29.7% for participants consuming <1500, 1500-2300, and >2300 mg sodium daily, respectively. Using the 1500-2300

mg as reference (lowest incidence), the subhazard ratio[1] (sHR) for <1500 mg intake was 1.01 (95% CI, 0.76 to 1.35; P=0.92) and for >2300 mg was 1.06 (95% CI, 0.88 to 1.28; P=0.52).

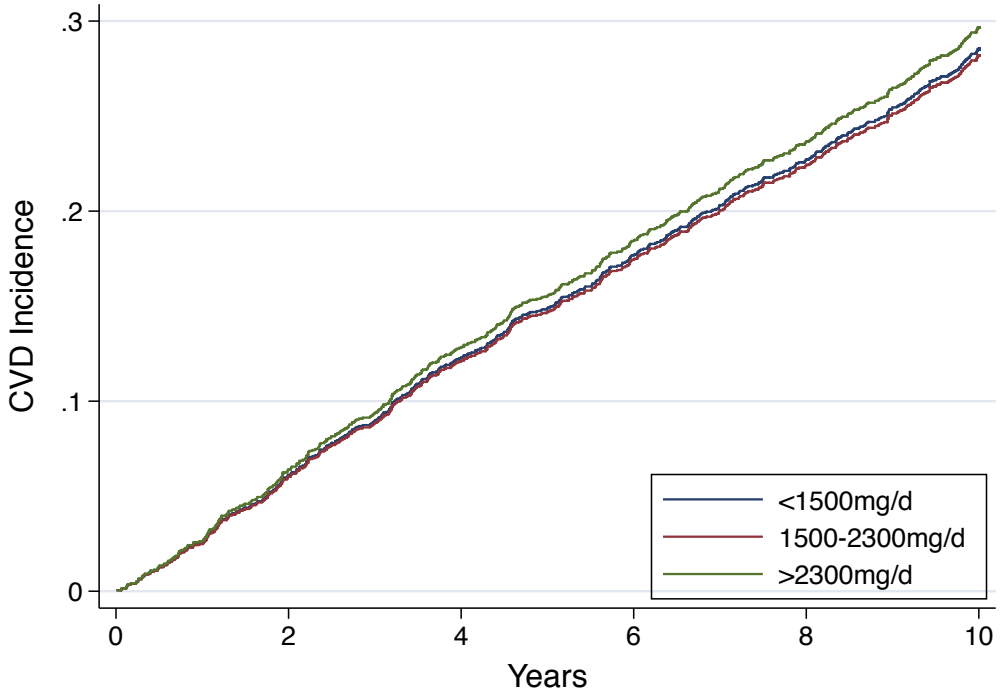


Figure 8. Unadjusted cumulative CVD incidence (accounting for competing mortality) according to baseline sodium consumption.

We concluded that there is no difference in the 10-year CVD incidence between the baseline sodium intake groups. The interaction terms with time was significant for the <1500 mg category (P=0.019) but not the >2300 mg category (P=0.65).

Incident HF – Sodium Intake as Categorical Predictor

Figure 9 presents the cumulative incidence of HF over 10 years, accounting for the competing risk of death. The 10-year HF cumulative incidence was 15.7%, 14.3%, and 15.5% for participants consuming <1500, 1500-2300, and >2300 mg sodium daily, respectively. Using the 1500-2300 mg category as reference (lowest incidence), the HF sHR for <1500 mg intake was 1.10 (95% CI, 0.78 to 1.56; P=0.58) and the sHR for >2300 mg intake was 1.09 (95% CI, 0.87 to 1.36; P=0.74). We concluded that there is no difference in the 10-year HF incidence between the

[1] This term is used in competing-risks models instead of the hazard ratio to underline that the hazard ratio of interest is conditional to the distribution of the competing risk.

baseline sodium intake groups. The interaction terms with time were not significant for either the <1500 mg (P=0.37) or the >2300 mg (P=0.68) category.

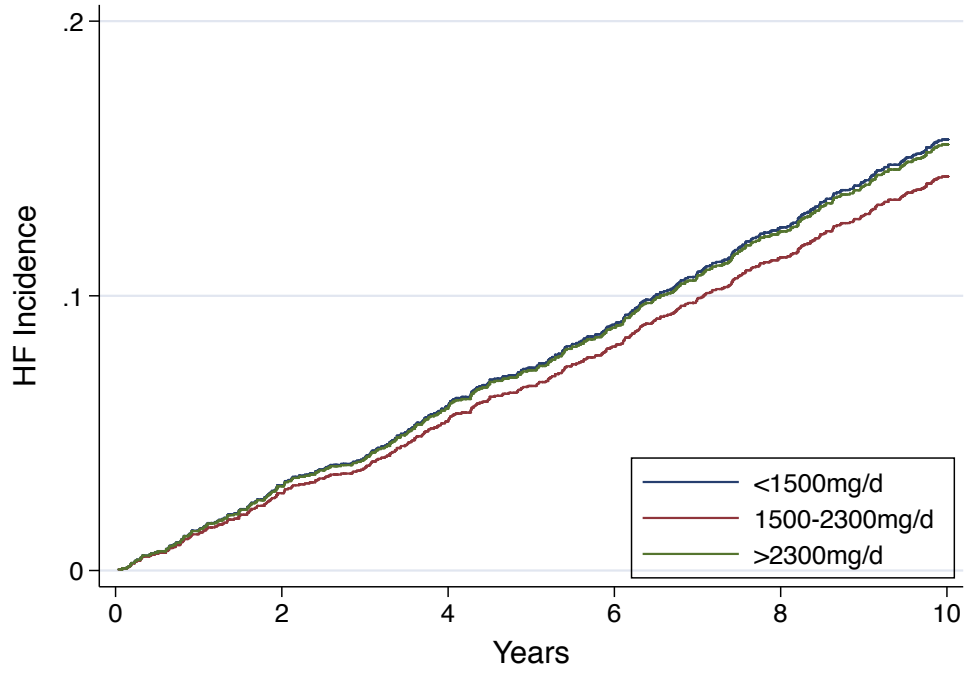


Figure 9. Unadjusted cumulative HF incidence (accounting for competing mortality) according to baseline sodium consumption.

Interactions with the Main Modifiers of Interest

In the table below (**Table 3**), we summarize the direction and significance of the interaction terms between the main modifiers of interest (gender, race, hypertensive status at baseline), as outlined in our objectives, and sodium intake for outcomes. We retained the continuous nature of the main exposure for this analysis to maximize power to detect any significant interactions.

Table 3. Interactions of sodium intake with gender, race, and hypertensive status

Interaction Term (per 1 g sodium)	Mortality		Incident CVD		Incident HF	
	HR (95% CI)	P	sHR (95% CI)	P	sHR (95% CI)	P
Black vs. White	1.01 (0.91-1.12)	0.91	1.00 (0.87-1.16)	0.97	0.95 (0.80-1.12)	0.51
Female vs. Male	1.12 (0.99-1.26)	0.065	1.08 (0.92-1.27)	0.33	0.99 (0.83-1.19)	0.95
Hypertensive vs. Non-hypertensive	0.91 (0.82-1.02)	0.094	0.95 (0.82-1.09)	0.45	0.94 (0.80-1.12)	0.51

CI: confidence interval; CVD: cardiovascular disease; HF: heart failure; HR: hazard ratio; sHR: subhazard ratio

From the table, we conclude that there is no significant interaction between dietary sodium intake at baseline with race, gender, and hypertensive status at baseline for 10-year outcomes.

Univariate Analyses – Summary and Subgroups

In the table below, we summarize the findings from the univariate analyses (categorical):

Table 4. Univariate association of dietary sodium intake categories and 10-year outcomes

	Mortality		Incident CVD		Incident HF	
Group	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
All	**N=2642**		**N=1981**		**N=2642**	
<1500 mg	1.11 (0.88-1.41)	0.38	1.01 (0.76-1.35)	0.92	1.10 (0.78-1.56)	0.58
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.19 (1.02-1.39)	0.023	1.06 (0.88-1.28)	0.52	1.09 (0.87-1.36)	0.46
Men	**N=1290**		**N=900**		**N=1290**	
<1500 mg	1.11 (0.78-1.59)	0.57	1.02 (0.65-1.59)	0.94	1.32 (0.76-2.27)	0.32
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	0.95 (0.78-1.17)	0.66	0.88 (0.68-1.14)	0.34	0.99 (0.72-1.37)	0.97
Women	**N=1352**		**N=1081**		**N=1352**	
<1500 mg	1.25 (0.91-1.72)	0.17	1.10 (0.76-1.60)	0.61	1.04 (0.66-1.64)	0.87
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.33 (1.05-1.67)	0.017	1.09 (0.83-1.43)	0.53	1.12 (0.82-1.55)	0.47
Whites	**N=1630**		**N=1217**		**N=1630**	
<1500 mg	0.85 (0.60-1.21)	0.36	1.19 (0.83-1.71)	0.35	0.88 (0.53-1.47)	0.64
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.12 (0.92-1.36)	0.26	1.18 (0.93-1.50)	0.17	1.04 (0.78-1.38)	0.81
Blacks	**N=1012**		**N=764**		**N=1012**	
<1500 mg	1.36 (0.98-1.89)	0.066	0.80 (0.51-1.26)	0.34	1.32 (0.81-2.16)	0.27
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.31 (1.03-1.67)	0.029	0.89 (0.66-1.19)	0.43	1.17 (0.82-1.67)	0.39
Hypertension	**N=1397**		**N=951**		**N=1397**	
<1500 mg	1.29 (0.97-1.72)	0.085	0.89 (0.6-1.32)	0.56	1.11 (0.73-1.69)	0.61
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.14 (0.93-1.39)	0.20	1.03 (0.80-1.33)	0.80	1.05 (0.8-1.39)	0.72
No hypertension	**N=1245**		**N=1030**		**N=1245**	
<1500 mg	0.83 (0.54-1.27)	0.39	1.18 (0.78-1.78)	0.44	1.03 (0.55-1.94)	0.92
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.30 (1.02-1.65)	0.034	1.12 (0.85-1.48)	0.43	1.22 (0.83-1.78)	0.32

CI: confidence interval; CVD: cardiovascular disease; HF: heart failure; HR: hazard ratio; sHR: subhazard ratio

In all, we observe that only daily sodium intake >2300 mg shows a weak association with mortality. This association appears to be driven by women, black participants, and patients without hypertension at baseline. However, it is striking that no association was observed with incident CVD and HF, implying that the increased mortality in the >2300-mg group may not be driven by higher risk for CVD and HF. Also, we did not observe any significant interaction in **Table 3** and thus the differences in association with mortality between subgroups should be interpreted with caution. For completeness, we summarize the results for subgroups from the continuous-sodium analysis below also:

Table 5. Univariate association of dietary sodium intake (continuous) and 10-year outcomes

	Mortality		Incident CVD		Incident HF	
Group	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
All	**N=2642**		**N=1981**		**N=2642**	
Sodium, per 1g	1.09 (1.04-1.15)	0.001	1.09 (1.01-1.16)	0.023	1.03 (0.95-1.12)	0.50
Men	**N=1290**		**N=900**		**N=1290**	
Sodium, per 1g	1.01 (0.95-1.08)	0.73	1.01 (0.92-1.11)	0.90	1.01 (0.91-1.12)	0.87
Women	**N=1352**		**N=1081**		**N=1352**	
Sodium, per 1g	1.13 (1.03-1.25)	0.012	1.09 (0.96-1.24)	0.20	1.00 (0.86-1.16)	0.97
Whites	**N=1630**		**N=1217**		**N=1630**	
Sodium, per 1g	1.08 (1.00-1.17)	0.042	1.08 (0.98-1.19)	0.10	1.05 (0.94-1.19)	0.38
Blacks	**N=1012**		**N=764**		**N=1012**	
Sodium, per 1g	1.09 (1.02-1.17)	0.015	1.09 (0.98-1.21)	0.11	1.00 (0.89-1.12)	0.98
Hypertension	**N=1397**		**N=951**		**N=1397**	
Sodium, per 1g	1.05 (0.98-1.13)	0.13	1.06 (0.97-1.16)	0.20	1.01 (0.92-1.12)	0.83
No hypertension	**N=1245**		**N=1030**		**N=1245**	
Sodium, per 1g	1.15 (1.07-1.25)	<0.001	1.12 (1.00-1.26)	0.041	1.07 (0.93-1.23)	0.34

CI: confidence interval; CVD: cardiovascular disease; HF: heart failure; HR: hazard ratio; sHR: subhazard ratio

As evident from **Table 5**, there is a signal towards more prominent association with mortality in women and participants without hypertension, whereas the association with mortality appears to be similar for whites and blacks. Therefore, the higher mortality observed in the >2300-mg group among blacks should be interpreted with caution.

Multivariable Association of Sodium Intake with Outcomes

Evaluation for Interactions (Modification Effects)

In the multivariable setting, we first examined for important interactions of the main exposure (sodium intake) with the covariates of interest (**Tables 1 & 2**). Using the same approach as in **Table 3**, we present below a matrix of interaction terms of sodium as a continuous variable with each covariate for the specific outcome of interest:

Table 6. Interactions of sodium intake with covariates for 10-year outcomes

Interaction Term (per 1 g sodium)	Mortality		Incident CVD		Incident HF	
	HR (95% CI)	P	sHR (95% CI)	P	sHR (95% CI)	P
Age, per year	0.99 (0.97-1.01)	0.41	1.00 (0.98-1.03)	0.90	1.00 (0.97-1.03)	0.83
Body mass index, per kg/m^2	1.00 (0.99-1.01)	0.62	1.00 (0.98-1.01)	0.50	1.00 (0.99-1.02)	0.89
Active smoker (vs. Nonsmoker)	0.87 (0.74-1.02)	0.091	1.09 (0.88-1.35)	0.45	1.34 (1.05-1.72)	0.019
Former smoker (vs. Nonsmoker)	0.92 (0.81-1.04)	0.18	1.02 (0.88-1.19)	0.79	1.20 (1.00-1.43)	0.048
Physical activity, 100 kcal/kg/week	1.07 (0.99-1.15)	0.078	1.01 (0.93-1.10)	0.76	1.02 (0.92-1.13)	0.72
Coronary heart disease	0.98 (0.87-1.11)	0.80	-	-	1.06 (0.90-1.26)	0.49
Cerebrovascular disease	0.99 (0.82-1.19)	0.92	-	-	0.78 (0.56-1.07)	0.12
Peripheral vascular disease	0.89 (0.81-1.18)	0.85	-	-	1.28 (1.03-1.60)	0.028
Any CVD	1.00 (0.89-1.11)	0.95	-	-	1.06 (0.90-1.25)	0.47
Pulmonary disease	1.06 (0.93-1.20)	0.37	1.29 (1.12-1.48)	0.001	0.99 (0.78-1.25)	0.94
Diabetes mellitus	0.96 (0.85-1.10)	0.56	0.88 (0.74-1.04)	0.14	0.87 (0.72-1.05)	0.14
Depression	0.95 (0.79-1.15)	0.63	0.80 (0.59-1.08)	0.15	1.01 (0.76-1.34)	0.94
Systolic BP, per 10 mmHg	0.99 (0.97-1.01)	0.36	1.01 (0.98-1.04)	0.59	1.00 (0.96-1.04)	1.00
Diastolic BP, per 10 mmHg	1.02 (0.98-1.07)	0.37	1.01 (0.95-1.07)	0.70	1.05 (0.98-1.12)	0.14
Heart rate, per 10 beats/min	0.99 (0.94-1.03)	0.55	0.97 (0.92-1.03)	0.36	0.94 (0.88-1.01)	0.10
ECG – major abnormalities	0.93 (0.83-1.05)	0.24	1.03 (0.87-1.21)	0.76	0.94 (0.79-1.11)	0.46
ECG – minor abnormalities	0.95 (0.84-1.06)	0.34	0.93 (0.78-1.11)	0.40	1.07 (0.92-1.25)	0.40
Glucose, per 10 mg/dl	0.99 (0.98-1.01)	0.45	0.99 (0.97-1.01)	0.49	1.00 (0.98-1.01)	0.73
Albumin, per g/dl	1.02 (0.86-1.21)	0.85	0.99 (0.79-1.24)	0.93	0.94 (0.75-1.18)	0.58

Creatinine, per mg/dl	1.06 (0.89-1.27)	0.49	0.89 (0.66-1.20)	0.45	0.85 (0.41-1.26)	0.41
Total cholesterol, per 100 mg/dl	1.05 (0.90-1.22)	0.52	1.08 (0.89-1.32)	0.42	0.97 (0.78-1.21)	0.78

BP: blood pressure; CI: confidence interval; CVD: cardiovascular disease; ECG: electrocardiogram; HF: heart failure; HR: hazard ratio; sHR: subhazard ratio

As evident from this table, there are no consistent interactions of sodium intake with covariates. Smoking (active and quitted) and history of peripheral vascular disease appear to increase the risk associated with sodium intake for incident HF. Similarly, a history of pulmonary disease increases the risk associated with sodium intake for incident CVD. Because of multiple testing and inconsistent findings, we will confirm these interactions in multivariable models also.

Mortality

We present the results of the multivariable Cox regression model for 10-year mortality below, with sodium as a continuous predictor first. Because prevalent CVD is defines as prevalent coronary heart, peripheral vascular, or cerebrovascular disease, and hence there is structural collinearity, we only kept prevalent CVD in the starting mortality model.

Table 7. Multivariable Cox model for 10-year mortality - sodium intake continuous

Variable	HR	SE	z	P	95% CI	
Sodium, per 1 gr	**1.04**	**0.03**	**1.29**	**0.20**	**0.98**	**1.09**
Male gender	1.31	0.10	3.45	0.001	1.12	1.52
Black race	1.24	0.09	2.93	0.003	1.07	1.43
Hypertensive	1.22	0.09	2.66	0.008	1.05	1.4
Age, per year	1.10	0.01	7.74	<0.001	1.07	1.12
Body mass index, per kg/m^2	0.96	0.01	-4.43	<0.001	0.95	0.98
Active smoker (vs. Nonsmoker)	1.91	0.22	5.74	<0.001	1.53	2.38
Former smoker (vs. Nonsmoker)	1.31	0.10	3.48	0.001	1.13	1.53
Physical activity, 100 kcal/kg/week	0.81	0.05	-3.72	<0.001	0.72	0.90
Any cardiovascular disease	1.21	0.09	2.44	0.015	1.04	1.4
Pulmonary disease	1.36	0.13	3.20	0.001	1.13	1.64
Diabetes mellitus	1.23	0.11	2.37	0.018	1.04	1.46
Heart rate, per 10 beats/min	1.20	0.04	5.96	<0.001	1.13	1.27
ECG – major abnormalities	1.30	0.10	3.34	0.001	1.12	1.52
ECG – minor abnormalities	1.16	0.10	1.76	0.078	0.98	1.38
Albumin, per g/dl	0.71	0.08	-3.01	0.003	0.57	0.89
Creatinine, per mg/dl	1.42	0.07	7.06	<0.001	1.29	1.57
Total cholesterol, per 100 mg/dl	0.81	0.08	-2.17	0.030	0.67	0.98

CI: confidence interval; ECG: electrocardiogram; HR: hazard ratio; SE: standard error

In backwards-stepwise approach, we removed history of depression, glucose levels (probably because diabetic status is a stronger predictor), and systolic and diastolic blood pressure (again, hypertensive status probably captures adequately the risk associated with elevated blood pressure) based on significance and the 10% rule (estimate for the main exposure did not change more than ±10% in the reduced model versus the full model). From the model, we conclude that sodium intake at baseline was not an independent predictor of mortality in the Health ABC Study population. We repeated the modeling process with sodium in take as a categorical predictor.

Table 8. Multivariable Cox model for 10-year mortality - sodium intake categorical

Variable	HR	SE	z	P	95% CI	
Sodium, <1500 mg (vs. 1500-2300)	**1.13**	**0.14**	**0.98**	**0.33**	**0.89**	**1.43**
Sodium, >2300 mg (vs. 1500-2300)	**1.15**	**0.09**	**1.81**	**0.070**	**0.99**	**1.35**
Male gender	1.31	0.10	3.53	<0.001	1.13	1.53
Black race	1.24	0.09	2.98	0.003	1.08	1.43
Hypertensive	1.22	0.09	2.68	0.007	1.05	1.41
Age, per year	1.10	0.01	7.76	<0.001	1.07	1.12
Body mass index, per kg/m^2	0.96	0.01	-4.43	<0.001	0.95	0.98
Active smoker (vs. Nonsmoker)	1.92	0.22	5.77	<0.001	1.54	2.39
Former smoker (vs. Nonsmoker)	1.31	0.10	3.5	<0.001	1.13	1.53
Physical activity, 100 kcal/kg/week	0.81	0.05	-3.67	<0.001	0.72	0.91
Any cardiovascular disease	1.21	0.09	2.46	0.014	1.04	1.40
Pulmonary disease	1.36	0.13	3.20	0.001	1.13	1.64
Diabetes mellitus	1.23	0.11	2.41	0.016	1.04	1.46
Heart rate, per 10 beats/min	1.20	0.04	6.02	<0.001	1.13	1.27
ECG – major abnormalities	1.31	0.10	3.43	0.001	1.12	1.53
ECG – minor abnormalities	1.16	0.10	1.75	0.079	0.98	1.38
Albumin, per g/dl	0.71	0.08	-3.02	0.003	0.57	0.89
Creatinine, per mg/dl	1.42	0.07	7.08	<0.001	1.29	1.57
Total cholesterol, per 100 mg/dl	0.82	0.08	-2.12	0.034	0.68	0.99

CI: confidence interval; ECG: electrocardiogram; HR: hazard ratio; SE: standard error

We conclude that dietary sodium intake >2300 mg daily has a borderline association with 10-year mortality in the multivariable setting, with a 15% higher risk compared to daily intake 1500-2300 mg but a wide confidence interval (-1% to 35%; P=0.070). Therefore, we cannot draw a firm conclusion about the independent association of dietary sodium intake with mortality.

Incident CVD

We present the results of the multivariable Fine and Gray (competing-risks) regression model for 10-year incident CVD below, with sodium as a continuous predictor first. Prevalent CVD and its components (prevalent coronary heart, peripheral vascular, or cerebrovascular disease) are not considered in this model, since participants with prevalent CVD are excluded from this analysis.

We first examined for significant interaction of baseline sodium intake with history of pulmonary disease in the multivariable setting, to confirm our previous finding in **Table 6**. We confirmed that the interaction was significant in the full model; sHR for the interaction (per 1 g of sodium intake) was 1.27 (95% CI 1.09-1.48) and this was significant at the P=0.002 level. Therefore, we proceeded with separate incident CVD models for patients with versus without history of pulmonary disease at baseline.

For patients without history of pulmonary disease (N=1771), we did not remove any variables from the full model because of potential bias (the estimate for sodium intake changed more than 10% compared to the full model). From the model, we conclude that sodium intake at baseline was not an independent predictor of incident CVD in Health ABC Study participants without a history of pulmonary disease at baseline.

Table 9. Multivariable Fine and Gray (competing-risks) model for 10-year incident CVD - sodium intake continuous – participants without history of pulmonary disease (N=1771)

Variable	sHR	rSE	z	P	95% CI	
Sodium, per 1 gr	**0.99**	**0.04**	**-0.16**	**0.87**	**0.92**	**1.07**
Male gender	1.66	0.18	4.59	<0.001	1.34	2.06
Black race	0.84	0.08	-1.75	0.080	0.69	1.02
Hypertensive	1.20	0.12	1.78	0.075	0.98	1.46
Age, per year	1.03	0.02	1.89	0.058	1.00	1.07
Body mass index, per kg/m^2	1.01	0.01	1.05	0.29	0.99	1.03
Active smoker (vs. Nonsmoker)	1.45	0.24	2.26	0.024	1.05	2.00
Former smoker (vs. Nonsmoker)	1.15	0.11	1.40	0.16	0.95	1.40
Physical activity, 100 kcal/kg/week	0.98	0.06	-0.32	0.75	0.87	1.11
Diabetes mellitus	1.16	0.17	0.99	0.32	0.87	1.55
Depression	0.65	0.13	-2.20	0.028	0.44	0.95
Systolic BP, per 10 mmHg	1.09	0.03	3.23	0.001	1.03	1.15
Diastolic BP, per 10 mmHg	0.90	0.04	-2.23	0.026	0.83	0.99
Heart rate, per 10 beats/min	1.08	0.05	1.95	0.052	1.00	1.18
ECG – major abnormalities	1.36	0.16	2.69	0.007	1.09	1.70

ECG – minor abnormalities	1.22	0.15	1.63	0.10	0.96	1.54
Glucose, per 10 mg/dl	1.04	0.02	2.01	0.044	1.00	1.08
Albumin, per g/dl	0.45	0.07	-5.21	<0.001	0.33	0.61
Creatinine, per mg/dl	1.10	0.09	1.13	0.26	0.93	1.30
Total cholesterol, per 100 mg/dl	1.32	0.17	2.16	0.031	1.03	1.70

CI: confidence interval; ECG: electrocardiogram; rSE: robust standard error; sHR: subhazard ratio

For patients with history of pulmonary disease (N=210) we were able to reach a parsimonious model that did not introduce bias (compared to the full model) and provided stable estimates for all covariates, to compensate for the mall N of participants and events, **Table 10**.

Table 10. Multivariable Fine and Gray (competing-risks) model for 10-year incident CVD - sodium intake continuous – participants with history of pulmonary disease (N=210)

Variable	sHR	rSE	z	P	95% CI	
Sodium, per 1 gr	1.31	0.09	3.81	<0.001	1.14	1.50
Black race	0.49	0.14	-2.56	0.010	0.28	0.85
Active smoker (vs. Nonsmoker)	2.17	0.88	1.92	0.054	0.99	4.80
Former smoker (vs. Nonsmoker)	2.46	0.83	2.68	0.007	1.27	4.75
Systolic BP, per 10 mmHg	1.13	0.07	2.08	0.038	1.01	1.28
Glucose, per 10 mg/dl	1.11	0.05	2.24	0.025	1.01	1.22
Creatinine, per mg/dl	2.82	1.59	1.84	0.066	0.93	8.51

CI: confidence interval; rSE: robust standard error; sHR: subhazard ratio

From the model, we conclude that sodium intake at baseline is an independent predictor of incident CVD in Health ABC Study participants with a history of pulmonary disease. Because of the small N of participants and events, however, this finding will need confirmation in other studies. We present the data for categorical sodium intake analysis below.

Table 11. Multivariable Fine and Gray (competing-risks) model for 10-year incident CVD - sodium intake categorical – participants without history of pulmonary disease (N=1771)

Variable	sHR	rSE	z	P	95% CI	
Sodium, <1500 mg (vs. 1500-2300)	**0.91**	**0.14**	**-0.59**	**0.56**	**0.67**	**1.24**
Sodium, >2300 mg (vs. 1500-2300)	**0.94**	**0.14**	**-0.41**	**0.68**	**0.71**	**1.25**
Male gender	1.60	0.17	4.41	<0.001	1.30	1.97
Black race	0.85	0.08	-1.66	0.097	0.70	1.03
Hypertensive	1.22	0.12	1.96	0.049	1.00	1.48
Age, per year	1.03	0.02	1.94	0.053	1.00	1.07
Body mass index, per kg/m^2	1.01	0.01	0.88	0.38	0.99	1.03
Active smoker (vs. Nonsmoker)	1.41	0.23	2.11	0.035	1.02	1.94
Former smoker (vs. Nonsmoker)	1.14	0.11	1.32	0.19	0.94	1.38

Physical activity, 100 kcal/kg/week	0.98	0.06	-0.39	0.69	0.86	1.10
Diabetes mellitus	1.14	0.17	0.91	0.36	0.86	1.52
Depression	0.63	0.13	-2.30	0.022	0.43	0.94
Systolic BP, per 10 mmHg	1.08	0.03	2.83	0.005	1.02	1.13
Diastolic BP, per 10 mmHg	0.91	0.04	-2.17	0.030	0.83	0.99
Heart rate, per 10 beats/min	1.09	0.05	2.02	0.043	1.00	1.18
ECG – major abnormalities	1.42	0.16	3.15	0.002	1.14	1.77
ECG – minor abnormalities	1.27	0.15	2.01	0.044	1.01	1.59
Glucose, per 10 mg/dl	1.04	0.02	2.22	0.026	1.00	1.08
Albumin, per g/dl	0.43	0.07	-5.48	<0.001	0.32	0.58
Creatinine, per mg/dl	1.12	0.09	1.43	0.15	0.96	1.32
Total cholesterol, per 100 mg/dl	1.30	0.17	2.05	0.040	1.01	1.67

CI: confidence interval; ECG: electrocardiogram; rSE: robust standard error; sHR: subhazard ratio

From **Table 11**, we confirm the lack of association between dietary sodium intake and incident CVD in participants without pulmonary disease at baseline.

Table 12. Multivariable Fine and Gray (competing-risks) model for 10-year incident CVD - sodium intake continuous – participants with history of pulmonary disease (N=210)

Variable	sHR	rSE	z	P	95% CI	
Sodium, <1500 mg (vs. 1500-2300)	**0.98**	**0.37**	**-0.05**	**0.96**	**0.47**	**2.05**
Sodium, >2300 mg (vs. 1500-2300)	**1.09**	**0.38**	**0.25**	**0.80**	**0.55**	**2.17**
Black race	0.54	0.16	-2.12	0.034	0.31	0.95
Active smoker (vs. Nonsmoker)	2.14	0.88	1.85	0.064	0.96	4.78
Former smoker (vs. Nonsmoker)	2.56	0.84	2.86	0.004	1.34	4.87
Systolic BP, per 10 mmHg	1.13	0.07	1.87	0.062	0.99	1.28
Glucose, per 10 mg/dl	1.1	0.05	2.14	0.033	1.01	1.21
Creatinine, per mg/dl	3.38	1.91	2.15	0.031	1.12	10.26

CI: confidence interval; rSE: robust standard error; sHR: subhazard ratio

The results in **Table 12**, however, contradict our findings in **Table 10**. In a further exploration (not shown here), it appears that most of the association between sodium intake and incident CVD in participants with pulmonary disease at baseline relies on data points (events) above 2300 mg. In any case, the findings in this subgroup will need further confirmation

Incident HF

Because we have previously detected potential interactions of sodium intake with history of peripheral arterial disease and smoking status for incident HF, we first examined whether these interactions are present in the multivariable setting. For peripheral arterial disease, the interaction

was not significant in models with (P=0.22) or without (P=26) history of cardiovascular disease included. We therefore did not pursue separate analyses based on history of peripheral arterial disease. The interaction of sodium intake with active smoker status was significant in the multi-variable setting (P=0.010 for the interaction term), but not the interaction with former smoker status (P=0.11). Because of (1) the small N of participants with active smoking status (N=246) and (2) the borderline significance of the joint interaction terms (P=0.034), we opted not to pursue separate regression analysis for each smoking status category and only included smoking status as a covariate in subsequent models.

We present below the results of the multivariable competing-risks analysis for incident HF with sodium intake entered as a continuous (**Table 13**) and a categorical (**Table 14**) variable. Race and history of depression did not any information in the models and thus we were able to remove these variables and reach a more parsimonious model without introducing bias.

Table 13. Multivariable Fine and Gray (competing-risks) model for 10-year incident HF - sodium intake as continuous variable

Variable	sHR	rSE	z	P	95% CI	
Sodium, per 1 gr	**0.99**	**0.04**	**-0.16**	**0.87**	**0.92**	**1.08**
Male gender	1.08	0.13	0.63	0.53	0.85	1.36
Hypertensive	1.11	0.13	0.86	0.39	0.88	1.39
Age, per year	1.04	0.02	2.16	0.031	1.00	1.08
Body mass index, per kg/m^2	1.03	0.01	2.51	0.012	1.01	1.05
Active smoker (vs. Nonsmoker)	1.48	0.28	2.09	0.036	1.03	2.14
Former smoker (vs. Nonsmoker)	1.25	0.14	1.93	0.054	1.00	1.56
Physical activity, 100 kcal/kg/week	1.12	0.08	1.61	0.11	0.98	1.28
Any cardiovascular disease	1.84	0.20	5.46	<0.001	1.48	2.28
Pulmonary disease	1.16	0.18	0.92	0.36	0.85	1.57
Diabetes mellitus	1.13	0.17	0.78	0.44	0.83	1.52
Systolic BP, per 10 mmHg	1.15	0.03	4.96	<0.001	1.09	1.21
Diastolic BP, per 10 mmHg	0.85	0.04	-3.63	<0.001	0.77	0.93
Heart rate, per 10 beats/min	1.20	0.06	3.80	<0.001	1.09	1.32
ECG – major abnormalities	1.79	0.20	5.17	<0.001	1.44	2.23
ECG – minor abnormalities	1.46	0.18	3.10	0.002	1.15	1.85
Glucose, per 10 mg/dl	1.02	0.02	0.74	0.46	0.97	1.06
Albumin, per g/dl	0.77	0.13	-1.54	0.12	0.55	1.07
Creatinine, per mg/dl	1.30	0.11	3.07	0.002	1.10	1.54
Total cholesterol, per 100 mg/dl	0.82	0.12	-1.32	0.19	0.62	1.10

CI: confidence interval; ECG: electrocardiogram; rSE: robust standard error; sHR: subhazard ratio

As evident from these tables, we did not observe any association between dietary sodium intake and risk for incident HF.

Table 14. Multivariable Fine and Gray (competing-risks) model for 10-year incident HF - sodium intake as categorical variable

Variable	sHR	rSE	z	P	95% CI	
Sodium, <1500 mg (vs. 1500-2300)	**0.88**	**0.17**	**-0.65**	**0.51**	**0.61**	**1.28**
Sodium, >2300 mg (vs. 1500-2300)	**0.95**	**0.17**	**-0.27**	**0.79**	**0.68**	**1.35**
Male gender	1.06	0.13	0.52	0.60	0.84	1.35
Hypertensive	1.11	0.13	0.88	0.38	0.88	1.40
Age, per year	1.04	0.02	2.23	0.026	1.01	1.08
Body mass index, per kg/m^2	1.03	0.01	2.60	0.009	1.01	1.05
Active smoker (vs. Nonsmoker)	1.53	0.28	2.27	0.023	1.06	2.20
Former smoker (vs. Nonsmoker)	1.25	0.14	1.98	0.048	1.00	1.57
Physical activity, 100 kcal/kg/week	1.12	0.08	1.62	0.11	0.98	1.28
Any cardiovascular disease	1.85	0.21	5.55	<0.001	1.49	2.30
Pulmonary disease	1.15	0.18	0.87	0.39	0.84	1.56
Diabetes mellitus	1.15	0.18	0.91	0.36	0.85	1.55
Systolic BP, per 10 mmHg	1.15	0.03	4.93	<0.001	1.09	1.21
Diastolic BP, per 10 mmHg	0.84	0.04	-3.74	<0.001	0.77	0.92
Heart rate, per 10 beats/min	1.20	0.06	3.77	<0.001	1.09	1.32
ECG – major abnormalities	1.79	0.20	5.16	<0.001	1.43	2.23
ECG – minor abnormalities	1.44	0.18	3.03	0.002	1.14	1.83
Glucose, per 10 mg/dl	1.01	0.02	0.68	0.50	0.97	1.06
Albumin, per g/dl	0.77	0.13	-1.57	0.12	0.55	1.07
Creatinine, per mg/dl	1.31	0.11	3.18	0.001	1.11	1.55
Total cholesterol, per 100 mg/dl	0.82	0.12	-1.34	0.18	0.62	1.10

CI: confidence interval; CVD: cardiovascular disease; ECG: electrocardiogram; rSE: robust standard error; sHR: subhazard ratio

Multivariable Analyses – Summary and Subgroups

In the tables below, we summarize the findings from the multivariable analysis with sodium as a continuous (**Table 15**) and as a categorical (**Table 16**) variable. Because the number of patients with pulmonary disease was small, we did not stratify into presence or absence of pulmonary disease for incident CVD analysis in these tables.

Table 15. Multivariable association of sodium intake (continuous) with 10-year outcomes

	Mortality		Incident CVD		Incident HF	
Group	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
All	**N=2642**		**N=1981**		**N=2642**	
Sodium, per 1g	1.04 (0.98-1.09)	0.20	1.03 (0.95-1.11)	0.46	0.99 (0.92-1.08)	0.87
Men	**N=1290**		**N=900**		**N=1290**	
Sodium, per 1g	1.02 (0.95-1.09)	0.56	0.98 (0.89-1.08)	0.73	1.00 (0.91-1.11)	0.99
Women	**N=1352**		**N=1081**		**N=1352**	
Sodium, per 1g	1.06 (0.97-1.16)	0.22	1.12 (0.98-1.28)	0.094	0.99 (0.87-1.13)	0.86
Whites	**N=1630**		**N=1217**		**N=1630**	
Sodium, per 1g	1.03 (0.95-1.12)	0.42	0.98 (0.88-1.09)	0.72	1.00 (0.89-1.13)	0.99
Blacks	**N=1012**		**N=764**		**N=1012**	
Sodium, per 1g	1.04 (0.97-1.12)	0.24	1.08 (0.97-1.20)	0.17	1.00 (0.89-1.13)	0.94
Hypertension	**N=1397**		**N=951**		**N=1397**	
Sodium, per 1g	1.01 (0.94-1.08)	0.81	1.02 (0.93-1.12)	0.68	0.98 (0.89-1.08)	0.72
No hypertension	**N=1245**		**N=1030**		**N=1245**	
Sodium, per 1g	1.07 (0.99-1.17)	0.099	1.06 (0.93-1.20)	0.40	1.02 (0.89-1.18)	0.74

CI: confidence interval; CVD: cardiovascular disease; HF: heart failure; HR: hazard ratio; sHR: subhazard ratio

From the continuous-variable analysis, no consistent association appears to exist between dietary sodium intake and outcomes (mortality, incident CVD, and incident HF).

Table 16. Multivariable association of sodium intake categories with 10-year outcomes

	Mortality		Incident CVD		Incident HF	
Group	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
All	**N=2642**		**N=1981**		**N=2642**	
<1500 mg	1.13 (0.89-1.43)	0.33	0.92 (0.69-1.22)	0.56	0.88 (0.61-1.28)	0.51
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.15 (0.99-1.35)	0.070	0.95 (0.73-1.24)	0.71	0.95 (0.68-1.35)	0.79
Men	**N=1290**		**N=900**		**N=1290**	
<1500 mg	1.12 (0.78-1.61)	0.55	0.88 (0.56-1.36)	0.56	0.66 (0.37-1.18)	0.16
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.07 (0.87-1.32)	0.52	0.79 (0.53-1.19)	0.26	0.73 (0.43-1.23)	0.23
Women	**N=1352**		**N=1081**		**N=1352**	
<1500 mg	1.16 (0.83-1.61)	0.38	0.90 (0.62-1.32)	0.60	1.08 (0.67-1.75)	0.76
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.23 (0.97-1.57)	0.083	1.04 (0.74-1.47)	0.83	1.19 (0.76-1.87)	0.45
Whites	**N=1630**		**N=1217**		**N=1630**	
<1500 mg	0.88 (0.62-1.27)	0.50	0.85 (0.59-1.22)	0.37	1.25 (0.74-2.13)	0.41
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.08 (0.88-1.32)	0.46	0.87 (0.62-1.22)	0.42	1.19 (0.71-1.98)	0.51
Blacks	**N=1012**		**N=764**		**N=1012**	
<1500 mg	1.40 (0.99-1.96)	0.054	1.12 (0.72-1.75)	0.62	0.61 (0.36-1.04)	0.072
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.31 (1.02-1.67)	0.036	1.09 (0.72-1.65)	0.68	0.81 (0.51-1.29)	0.38
Hypertension	**N=1397**		**N=951**		**N=1397**	
<1500 mg	1.25 (0.93-1.68)	0.14	1.03 (0.69-1.53)	0.89	0.91 (0.58-1.43)	0.69
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.10 (0.90-1.34)	0.37	1.09 (0.76-1.57)	0.65	0.92 (0.60-1.40)	0.70
No hypertension	**N=1245**		**N=1030**		**N=1245**	
<1500 mg	0.86 (0.56-1.32)	0.49	0.82 (0.55-1.22)	0.33	0.91 (0.47-1.77)	0.79
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.20 (0.94-1.55)	0.15	0.83 (0.57-1.20)	0.32	1.06 (0.57-1.96)	0.85

CI: confidence interval; CVD: cardiovascular disease; HF: heart failure; HR: hazard ratio; sHR: subhazard ratio

From the categorical-variable analysis, no consistent association (either in terms of direction or strength) appears to exist between dietary sodium intake and outcomes (mortality, incident CVD, and incident HF). We did observe, nevertheless, a higher risk with >2300-mg daily sodium intake in blacks (HR 1.31; 95% CI 1.02-1.67; P=0.036). However, considering the multiple post-hoc testing and the borderline association, this finding needs further confirmation.

5. Journal Article

5.1. Introduction

Excess dietary sodium intake is associated with several risk factors for cardiovascular disease (CVD) and heart failure (HF), most prominently with elevated blood pressure,[22-24] but also with worse renal function,[25-27] left ventricular hypertrophy,[28-31] and increased arterial stiffness.[32-34] Therefore, limiting sodium intake might be an important potential intervention to reduce risk for CVD and HF. However, the optimal level of dietary sodium restriction is currently unclear.

Americans consume approximately 3700 mg/day of sodium on average,[35] whereas the United States Department of Agriculture and the Department of Health and Human Services recommend 2300 mg/day for the general population, with a stricter recommendation of 1500 mg/day for those over age 50, African-Americans, or those with hypertension, diabetes, or chronic kidney disease.[81] According to a recent report from the National Health and Nutrition Examination Survey, although 47.6% of persons aged ≥2 years meet the criteria to limit daily sodium intake to 1500 mg, the usual intake for 98.6% of those persons was >1500 mg; in 88.2% of the remaining population, daily intake was greater than the recommended 2300 mg.[37] Of note, the American Heart Association now recommends sodium intake of 1500 mg/day for all Americans[38]; similar to the recommendation by the Institute of Medicine.[82]

Based on the effects of sodium reduction on blood pressure and the current levels of sodium intake in the population, simulation studies have projected substantial benefits on outcomes with stricter dietary sodium control (1500mg).[39, 40] These projections are based on extrapolation from small studies with higher baseline sodium intake (>3000 mg/day) and assume no or beneficial, effects on other risk factors. However, sodium restriction may exert unfavorable effects on insulin resistance,[41, 42] serum lipids,[43] and neurohormonal activation,[43, 44] factors that predispose to CVD and HF. The uncertain net effect of these opposing forces is highlighted by two recently published studies. In a large European cohort study investigating the genetic background of hypertension,[46] middle-aged persons in the lower sodium stratum had higher cardiovascular mortality despite lower blood pressure. Also, in a post-hoc analysis from two large randomized trials with telmisartan, the association between urine sodium excretion and cardiovascular (CV) events was J-shaped[47]; compared with baseline sodium excretion of 4 to

5.99 g per day, excretion of greater than 7 g per day was associated with an increased risk of CVD, and excretion of <3 g per day was associated with increased risk of CV mortality and HF.

In addition to the concerns raised by these recent reports, inadequate caloric intake and interaction with medications are additional concerns with very low sodium intake in older adults.[48, 49] Data on the effects of sodium restriction are scarce in this population, especially for those with blood pressure at target. Also, achieving 1500 mg/day sodium intake is difficult, particularly in older adults with long-held dietary habits.[28] Thus, the incremental benefit of lowering sodium to 1500 vs. 2300 mg/day needs to be prospectively evaluated. In this direction, evaluating the dose-response association of dietary sodium with key CV outcomes in older adults using data from well-designed cohort studies is a crucial step to inform design of outcome trials.

In this study, we investigate the association between dietary sodium intake, as assessed in year 2 with the food frequency questionnaire (FFQ), and risk for (1) all-cause mortality; (2) incident CVD; and (3) incident HF in the Health ABC Study using 10-year follow-up data. In secondary analyses, we will evaluate this association in gender and race subgroups and in participants with vs. with without hypertension.

5.2. Methods

Study Population

The Health ABC Study enrolled 3075 well-functioning, community dwelling individuals aged 70 to 79 years between April 1997 and June 1998. Participants were identified from a random sample of white Medicare beneficiaries and all age eligible black community residents in designated zip code areas surrounding Pittsburgh and Memphis. Exclusion criteria included difficulties with activities of daily living, obvious cognitive impairment, inability to communicate, anticipated move within 3 years, or participation in a trial involving lifestyle intervention. At year 2, participants were asked to complete an FFQ. Data on sodium intake were available for 2713 participants. This analysis includes data on 2642 participants; we excluded 63 participants with manifest HF at year 2 and 8 participants because of implausibly low dietary sodium content values by FFQ (<300 mg/d). For this analysis, adjudicated 10-year follow up data were used.

Assessment of Dietary Sodium Intake

Food intake was measured during year 2 of the Health ABC Study, at the first annual follow-up visit, with a 108-item FFQ designed specifically for the Health ABC Study by Block Dietary Data Systems (Berkeley, CA), based on reported intakes of non-Hispanic white and black residents of the Northeast and South older than age 65 years in the 3rd National Health and Nutrition Examination Survey. The FFQ reference period was the preceding year. A trained dietary interviewer administered the FFQ, and interviews were periodically monitored to assure quality and consistency. Wood blocks, real food models, and flash cards were used to help participants estimate portion sizes. Block Dietary Data Systems determined nutrient and food group intakes.

Study Definitions

Race was self-defined by the participant. Diabetes mellitus was considered present if the participant reported a positive history or use of anti-hyperglycemic medication. Smoking was defined as current, past (≥100 lifetime cigarettes), or never. Physical activity was ascertained using a standardized questionnaire designed by the Health ABC study. Kilocalories per week expended in common exercise activities (e.g., walking for exercise, exercise classes, weightlifting) and lifestyle activities (e.g., gardening, housework, yard work, non-exercise walking) were collected and a summary variable of kcal/week was derived. Major ECG abnormalities included: (1) atrioventricular conduction defect; (2) ventricular conduction defect; (3) rhythm irregularity; (4) left ventricular hypertrophy; (5) Q-wave; and (6) major T-wave and ST-segment abnormalities.

Prevalent CVD was defined as prevalent: (1) coronary heart disease (history of myocardial infarction, angina treated with medications, or coronary revascularization); (2) cerebrovascular disease (history of stroke, transient ischemic attack, or carotid endarterectomy); or (3) peripheral vascular disease (history of intermittent claudication or vascular bypass or angioplasty) at year 2. These definitions follow the definitions used in previous Health ABC Study publications.[77, 83] Incident CVD was defined as (1) incident coronary heart disease (myocardial infarction, angina, or coronary revascularization); (2) incident cerebrovascular disease (stroke, transient ischemic attack, or symptomatic carotid artery disease); (3) incident peripheral arterial disease; or (4) death due to cardiovascular causes.

Study Outcomes

Participants were asked to report any hospitalizations and were also asked direct questions regarding incident CVD and HF events and during the planned telephone interviews and in-person examinations. Medical records for overnight hospitalizations were reviewed at each site by local adjudicators; using algorithms mirroring those of the Cardiovascular Health Study, a panel of clinicians verified diagnoses and caused of death based on interview, review of all hospital records, and death certificates. All first admissions with an overnight stay that was confirmed as related to HF, based on symptoms, signs, chest radiograph results, and echocardiographic findings, using criteria similar to those used in the Cardiovascular Health Study, were designated as incident HF event.[71] The criteria required HF diagnosis by a physician and treatment for HF.[74] Incident CVD events were identified and adjudicated using the standard Health ABC Study surveillance and adjudication process described above. The Health ABC Diagnosis and Disease Ascertainment Committee reviewed all deaths.

Statistical Analysis

We examined sodium intake both as a continuous variable and as categorical variable using a clinically predefined (recommendation based) cut-off points, i.e. <1500, 1500-2300, and >2300 mg/day. In continuous-variable analysis, we examined for nonlinear associations with the event of interest using restricted cubic splines.[76] To describe baseline characteristics, we used values from the year 2 visit where available; the remaining values were carried over from year 1. We used the non-parametric test for trend to examine trends of characteristics across sodium categories. To examine the association between baseline sodium and 10-year mortality, we used Cox regression models; in multivariable analyses, we adjusted for clinical risk factors previously associated with mortality in the Health ABC Study.[77] To examine for significant modification effects, we introduced appropriate interaction terms. For incident CVD, we used the Fine and Grey competing-risks extension of the Cox model. The competing-risks model allows accounting for the competing risk of non-cardiovascular death (because cardiovascular death is included in the CVD endpoint), which is considerable in older adults. In multivariable analyses, we adjusted for clinical risk factors previously identified as CVD risk predictors in the Health ABC Study.[77, 79] We followed the same approach for sodium intake and HF risk (with death as a competing risk) and adjusted for clinical risk factors previously identified as HF risk predictors in the

Health ABC Study.[80] All analyses were performed with STATA version 12 (StataCorp LP, College Station, TX).

5.3. Results

Baseline Characteristics

The mean age of participants (N=2642) was 74.4±2.9 years; 50% were women; and 50 were black and 40% were white. Median sodium intake at baseline was 2540 mg (interquartile range [IQR], 1920 to 3340). **Table 1** summarizes the baseline characteristics of these participants according to sodium intake category, i.e. <1500, 1500-2300, and >2300 mg/day. Men, whites, and participants with diabetes were more likely to consume larger amounts of sodium. In contrast, participants with hypertension are more likely to consume smaller amounts of sodium. Lower sodium intake was associated with lower glucose, albumin, and creatinine levels and also with higher total cholesterol levels.

Outcomes

After 10 years of follow up, 881 of 2642 (33.3%) of patients died. The annualized mortality was 3.9% (95% CI, 3.7% to 4.2%) and the Kaplan-Meier estimate for 10-year mortality was 33.7% (95% CI, 31.9% to 35.5%). Among the 1981 participants without CVD at baseline, 572 (28.9%) developed CVD during follow up. The annualized CVD incidence was 3.7% (95% CI, 3.4% to 4.0%) and the Kaplan-Meier estimate for 10-year CVD incidence was 31.7% (95% CI, 29.6% to 34.0%). By design, no patient with HF at baseline was included. Among the 2642 participants, 398 (15.1%) developed HF during follow up. The annualized HF incidence was 1.9% (95% CI, 1.7% to 2.0%) and the Kaplan-Meier estimate for 10-year HF incidence was 17.4% (95% CI, 15.9% to 19.0%).

Sodium Intake and Outcomes

Mortality

In Cox models using restricted cubic splines and fractional polynomials to model sodium intake, complex models did not demonstrate superior performance compared to the simple linear model. The unadjusted HR per 1g of sodium intake was 1.09 (95% CI, 1.04 to 1.15; P=0.001), **Table 2**. However, this association was substantially attenuated in multivariable models (HR 1.04; 95% CI, 0.98 to 1.09; P=0.20, **Table 3**. In univariate analysis with sodium intake as a categorical

predictor, the 10-year Kaplan-Meier survival was 66.2%, 69.3%, and 64.8% for participants consuming <1500, 1500-2300, and >2300 mg sodium daily, respectively (chi-square 5.22 with d.f. =2; P=0.074 for the log-rank test), **Figure 1.** Using the 1500-2300 mg as reference (lowest mortality), the HR for <1500 mg intake was 1.11 (95% CI, 0.88 to 1.41; P=0.38) and for >2300 mg intake was 1.19 (95% CI, 1.02 to 1.39; P=0.023), **Table 2**. Again, these associations were attenuated in multivariable models; the HR for <1500 mg intake was 1.13 (95% CI, 0.89 to 1.43; P=0.33) and for >2300 mg intake was 1.15 (95% CI, 0.99 to 1.35; P=0.070), **Table 3**.

In subgroup analyses, sodium intake demonstrated a continuous (linear) association with mortality most pronounced in women and those without a history of hypertension, as well as in both white and black participants (**Table 2**). However, these gender-, race- and hypertensive status-specific associations were attenuated to nonsignificant levels in multivariable models (**Table 4**).

Incident Cardiovascular Disease

Similar to mortality, the linear form best represented the association between baseline dietary sodium intake and CVD. Taking the competing risk of death into account, the crude HR for CVD per 1g of sodium intake was 1.09 (95% CI, 1.01-1.16; P=0.023). This association was attenuated in multivariable models (sHR 1.03; 95% CI, 0.95-1.11; P=0.46). However, we observed a significant interaction between baseline sodium intake and history of pulmonary disease for the CVD outcome, which was confirmed in the multivariable models. In participants with history of pulmonary disease, sHR per 1 g sodium was 1.31 (95% CI, 1.14-1.50; P<0.001) versus 0.99 (95% CI, 0.92 -1.7; P=0.87) participants without a history of pulmonary disease. The interaction term was significant at the P=0.002 level. This finding will need additional confirmation in other studies because of the small N of participants with pulmonary disease and corresponding events.

The 10-year CVD incidence was 28.5%, 28.2%, and 29.7% for participants consuming <1500, 1500-2300, and >2300 mg sodium daily, respectively. Using the 1500-2300 mg as reference (lowest incidence), the subhazard ratio (sHR) for <1500 mg intake was 1.01 (95% CI, 0.76 to 1.35; P=0.92) and for >2300 mg was 1.06 (95% CI, 0.88 to 1.28; P=0.52). The lack of association of sodium intake with incident CVD was confirmed in multivariable models and was consistent across all subgroups of interest (gender, race, and hypertensive status), **Tables 2-4**.

Incident Heart Failure

The linear form best represented the association between baseline dietary sodium intake and CVD. Taking the competing risk of death into account, the crude HR for HF per 1g of sodium intake was 1.03 (95% CI, 0.95 to 1.12; P=0.50). The 10-year HF cumulative incidence was 15.7%, 14.3%, and 15.5% for participants consuming <1500, 1500-2300, and >2300 mg sodium daily, respectively. Using the 1500-2300 mg category as reference (lowest incidence), the HF sHR for <1500 mg intake was 1.10 (95% CI, 0.78 to 1.56; P=0.58) and the sHR for >2300 mg intake was 1.09 (95% CI, 0.87 to 1.36; P=0.74). The lack of association of sodium intake with incident HF was confirmed in multivariable models and was consistent across all subgroups of interest (gender, race, and hypertensive status), **Tables 2-4**.

5.4. Discussion

In our study, we did not observe a strong association between dietary sodium intake, estimated from an FFQ, and mortality or cardiovascular outcomes among the older adults participating in the Health ABC Study. Compared with baseline sodium intake of 1500-2300-mg daily, there was no signal of benefit with <1500 mg daily sodium. The signal for potential harm with >2300-mg daily sodium intake was weak and only for all-cause mortality. The latter was more pronounced among black participants, but this finding needs further confirmation because of borderline significance and multiple subgroup testing. Also, there was no signal for association of sodium intake with incident CVD and HF in this older adult population.

A recent meta-analysis of 13 prospective studies reported that a 2-g increase in sodium was associated with a 14% increase in risk for CVD.[84] The estimates in our study were more conservative (approximately 6% increase in risk per 2-g increase in sodium intake) and did not reach statistical significance. However, the Health ABC Study included only older adults age 70 years or older at the time of inception and the average sodium intake was much lower compared to that meta-analysis, emphasizing the importance of the population under investigation and the absolute levels of sodium intake where the potential treatment effect is estimated. This is further underlined by a recent observational analysis from the ONTARGET and TRANSCEND trials (N=28,880) where a significant association between sodium urinary excretion and CVD was not observed until sodium excretion exceeded 6.5 g per day, a threshold that is much higher than that recommended by national guidelines (2.3 to 1.5 g/d depending on concomitant risk factors).

A number of trials have found that by reducing sodium excretion to levels consistent with current guidelines, blood pressure was reduced in participants with and without hypertension.[85-87] However, trials in younger patients with high-normal blood pressure, did not report a difference in CVD risk events on initial follow-up, and only during an extended observational follow-up of 10 to 15 years a nonsignificant benefit was reported, which became statistically significant only after multivariable adjustment.[88] Therefore, these studies are suggestive but not conclusive of a benefit from sodium reduction to very low intake targets in a primary prevention population.

In line with our findings, a recent Cochrane review of randomized controlled trials evaluating reduced sodium intake did not detect a significant reduction in cardiovascular mortality or morbidity.[89] In this direction, it is interesting that in some observational studies the reductions in blood pressure achieved by dietary means did not translate into CVD prevention.[90] In another meta-analysis including exclusively trials of primary prevention, a marginally significant reduction in CVD events in the group randomized to reduced sodium intake was reported.[91] However, in contrast with these populations, our study population included older adults who are inherently at higher risk for CVD and HF and therefore the effect of sodium intake, especially around the usual consumption zone (3.5g), may be more difficult to ascertain.

Previous individual prospective cohort studies have either reported a positive association, no association, or an inverse relationship between sodium intake and mortality.[46, 89, 92] Discrepant findings of previous studies are likely due to differences in ranges of sodium intake, study populations, methods of measurement, and failure to explore nonlinear associations.[47] It becomes evident from these discrepancies that large randomized controlled trials evaluating the effect of reduced sodium intake in primary and secondary prevention populations on cardiovascular outcomes are needed urgently. However, considering the special case of older adults, in whom inadequate caloric intake and interaction with medications are additional concerns with very low sodium intake,[48, 49] the effect of sodium restriction should probably be tested explicitly in this population. In the interim, a more cautious approach to policy on sodium intake restriction may be appropriate, especially for older adults.

Our study has a number of limitations. First, the accuracy of FFQ for estimation of sodium intake, albeit adequate from an epidemiological perspective, it is probably less accurate at the individual participant level compared to mother methods such urinary sodium excretion.

Therefore, we have likely underestimated sodium intake. However, it is unlikely that we have differentially underestimate sodium intake in patients with higher vs. lower consumption and hence the overall association is likely to be valid. Second, Health ABC Study participants were selected on the basis of voluntary participation and good functional capacity. This sample may therefore not fully reflect the general older adult population including those who declined participation or have limited functional capacity. In addition, our older population is at higher risk of CVD and HF and therefore our results may not apply to a lower-risk population. Third, confounders not included in our study may have affected mortality and incident CVD and HF. Although we comprehensively adjusted in our models for factors previously identified in this cohort, we cannot exclude the possibility of unobserved confounding.

In conclusion, we observed that sodium intake was not associated with mortality or risk for CVD and HF in a cohort of adults 70 years or older. These findings extended to gender- and race-based subgroups and in patients with and without hypertension at baseline. Also, some individual signals in subgroups were inconsistent and subject to further confirmation. Our data emphasizes the need for evidence from rigorous randomized controlled trials before applying a policy of further sodium restriction beyond the current recommendation for the general adult population (2.3 g) in older adults.

5.5. Tables

Table 1. Participant characteristics according to sodium intake at baseline

	<1500 mg/day	1500-2300 mg/d	>2300 mg/d	P value*
N	**291**	**779**	**1572**	
Age, years	74.4 (2.9)	74.6 (2.9)	74.6 (2.9)	0.17
Male sex, %	88 (30.2)	315 (40.4)	887 (56.4)	<0.001
Race				0.028
Blacks, %	137 (47.1)	285 (36.6)	590 (37.5)	
Whites, %	154 (52.9)	494 (63.4)	982 (62.5)	
Body mass index, kg/m^2	27.7 (5.0)	27.2 (4.8)	27.1 (4.8)	0.14
Smoking				0.91
Current smokers, %	32 (11.0)	65 (8.3)	149 (9.5)	
Past smokers, %	131 (45.0)	359 (46.1)	728 (46.3)	
Physical activity, kcal/kg/week	64.8 (39.8, 101.8)	68.0 (39.7, 107.8)	66.1 (39.4, 110.0)	0.42
Coronary heart disease, %	55 (18.9)	140 (18.0)	284 (18.1)	0.81
Cerebrovascular disease, %	27 (9.3)	61 (7.8)	103 (6.6)	0.069
Peripheral vascular disease, %	17 (5.8)	35 (4.5)	78 (5.0)	0.79
Any cardiovascular disease, %	74 (25.4)	203 (26.1)	384 (24.4)	0.49
Pulmonary disease, %	39 (13.4)	81 (10.4)	180 (11.5)	0.69
Diabetes mellitus, %	38 (13.1)	138 (17.7)	297 (18.9)	0.028
Hypertension, %	167 (57.4)	427 (54.8)	803 (51.1)	0.019
Depression, %	31 (10.7)	75 (9.6)	163 (10.4)	0.88
Systolic blood pressure, mmHg	136.1 (22.3)	133.3 (19.9)	133.6 (20.8)	0.36
Diastolic blood pressure, mmHg	71.0 (12.4)	70.2 (11.1)	70.3 (11.9)	0.43
Heart rate, beats/min	64.7 (9.5)	64.7 (10.9)	64.9 (11.1)	0.98
ECG – major abnormalities, † %	56 (19.2)	172 (22.1)	326 (20.7)	0.96
ECG – minor abnormalities, ‡ %	57 (19.7)	129 (16.6)	260 (16.6)	0.30
Glucose, mg/dl	97.8 (23.8)	102.3 (31.3)	103.0 (29.6)	0.019
Albumin, g/dl	3.96 (0.30)	3.98 (0.32)	4.00 (0.31)	0.042
Creatinine, mg/dl	1.04 (0.37)	1.04 (0.40)	1.05 (0.37)	0.007
Total cholesterol, mg/dl	211.9 (37.8)	208.2 (39.2)	203.6 (38.3)	<0.001

Continuous variables are presented as mean (standard deviation) or median (25th percentile, 75th percentile); categorical variables are presented as number (%). ECG: electrocardiogram. * Nonparametric test for trend. † Major

Q or QS abnormality, major ST or T wave abnormality, left ventricular hypertrophy, or ventricular conduction defects. ‡ Minor Q or QS abnormality or ST or T wave abnormalities.

Table 2. Univariate association of dietary sodium intake (continuous) and 10-year outcomes

	Mortality		Incident CVD		Incident HF	
Group	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
All	**N=2642**		**N=1981**		**N=2642**	
Sodium, per 1g	1.09 (1.04-1.15)	0.001	1.09 (1.01-1.16)	0.023	1.03 (0.95-1.12)	0.50
Men	**N=1290**		**N=900**		**N=1290**	
Sodium, per 1g	1.01 (0.95-1.08)	0.73	1.01 (0.92-1.11)	0.90	1.01 (0.91-1.12)	0.87
Women	**N=1352**		**N=1081**		**N=1352**	
Sodium, per 1g	1.13 (1.03-1.25)	0.012	1.09 (0.96-1.24)	0.20	1.00 (0.86-1.16)	0.97
Whites	**N=1630**		**N=1217**		**N=1630**	
Sodium, per 1g	1.08 (1.00-1.17)	0.042	1.08 (0.98-1.19)	0.10	1.05 (0.94-1.19)	0.38
Blacks	**N=1012**		**N=764**		**N=1012**	
Sodium, per 1g	1.09 (1.02-1.17)	0.015	1.09 (0.98-1.21)	0.11	1.00 (0.89-1.12)	0.98
Hypertension	**N=1397**		**N=951**		**N=1397**	
Sodium, per 1g	1.05 (0.98-1.13)	0.13	1.06 (0.97-1.16)	0.20	1.01 (0.92-1.12)	0.83
No hypertension	**N=1245**		**N=1030**		**N=1245**	
Sodium, per 1g	1.15 (1.07-1.25)	<0.001	1.12 (1.00-1.26)	0.041	1.07 (0.93-1.23)	0.34

CI: confidence interval; CVD: cardiovascular disease; HF: heart failure; HR: hazard ratio; sHR: subhazard ratio

Table 3. Univariate association of dietary sodium intake categories and 10-year outcomes

	Mortality		Incident CVD		Incident HF	
Group	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
All	**N=2642**		**N=1981**		**N=2642**	
<1500 mg	1.11 (0.88-1.41)	0.38	1.01 (0.76-1.35)	0.92	1.10 (0.78-1.56)	0.58
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.19 (1.02-1.39)	0.023	1.06 (0.88-1.28)	0.52	1.09 (0.87-1.36)	0.46
Men	**N=1290**		**N=900**		**N=1290**	
<1500 mg	1.11 (0.78-1.59)	0.57	1.02 (0.65-1.59)	0.94	1.32 (0.76-2.27)	0.32
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	0.95 (0.78-1.17)	0.66	0.88 (0.68-1.14)	0.34	0.99 (0.72-1.37)	0.97
Women	**N=1352**		**N=1081**		**N=1352**	
<1500 mg	1.25 (0.91-1.72)	0.17	1.10 (0.76-1.60)	0.61	1.04 (0.66-1.64)	0.87
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.33 (1.05-1.67)	0.017	1.09 (0.83-1.43)	0.53	1.12 (0.82-1.55)	0.47
Whites	**N=1630**		**N=1217**		**N=1630**	
<1500 mg	0.85 (0.60-1.21)	0.36	1.19 (0.83-1.71)	0.35	0.88 (0.53-1.47)	0.64
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.12 (0.92-1.36)	0.26	1.18 (0.93-1.50)	0.17	1.04 (0.78-1.38)	0.81
Blacks	**N=1012**		**N=764**		**N=1012**	
<1500 mg	1.36 (0.98-1.89)	0.066	0.80 (0.51-1.26)	0.34	1.32 (0.81-2.16)	0.27
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.31 (1.03-1.67)	0.029	0.89 (0.66-1.19)	0.43	1.17 (0.82-1.67)	0.39
Hypertension	**N=1397**		**N=951**		**N=1397**	
<1500 mg	1.29 (0.97-1.72)	0.085	0.89 (0.6-1.32)	0.56	1.11 (0.73-1.69)	0.61
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.14 (0.93-1.39)	0.20	1.03 (0.80-1.33)	0.80	1.05 (0.8-1.39)	0.72
No hypertension	**N=1245**		**N=1030**		**N=1245**	
<1500 mg	0.83 (0.54-1.27)	0.39	1.18 (0.78-1.78)	0.44	1.03 (0.55-1.94)	0.92
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.30 (1.02-1.65)	0.034	1.12 (0.85-1.48)	0.43	1.22 (0.83-1.78)	0.32

CI: confidence interval; CVD: cardiovascular disease; HF: heart failure; HR: hazard ratio; sHR: subhazard ratio

Table 4. Multivariable association of sodium intake (continuous) with 10-year outcomes

	Mortality		Incident CVD		Incident HF	
Group	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
All	**N=2642**		**N=1981**		**N=2642**	
Sodium, per 1g	1.04 (0.98-1.09)	0.20	1.03 (0.95-1.11)	0.46	0.99 (0.92-1.08)	0.87
Men	**N=1290**		**N=900**		**N=1290**	
Sodium, per 1g	1.02 (0.95-1.09)	0.56	0.98 (0.89-1.08)	0.73	1.00 (0.91-1.11)	0.99
Women	**N=1352**		**N=1081**		**N=1352**	
Sodium, per 1g	1.06 (0.97-1.16)	0.22	1.12 (0.98-1.28)	0.094	0.99 (0.87-1.13)	0.86
Whites	**N=1630**		**N=1217**		**N=1630**	
Sodium, per 1g	1.03 (0.95-1.12)	0.42	0.98 (0.88-1.09)	0.72	1.00 (0.89-1.13)	0.99
Blacks	**N=1012**		**N=764**		**N=1012**	
Sodium, per 1g	1.04 (0.97-1.12)	0.24	1.08 (0.97-1.20)	0.17	1.00 (0.89-1.13)	0.94
Hypertension	**N=1397**		**N=951**		**N=1397**	
Sodium, per 1g	1.01 (0.94-1.08)	0.81	1.02 (0.93-1.12)	0.68	0.98 (0.89-1.08)	0.72
No hypertension	**N=1245**		**N=1030**		**N=1245**	
Sodium, per 1g	1.07 (0.99-1.17)	0.099	1.06 (0.93-1.20)	0.40	1.02 (0.89-1.18)	0.74

CI: confidence interval; CVD: cardiovascular disease; HF: heart failure; HR: hazard ratio; sHR: subhazard ratio

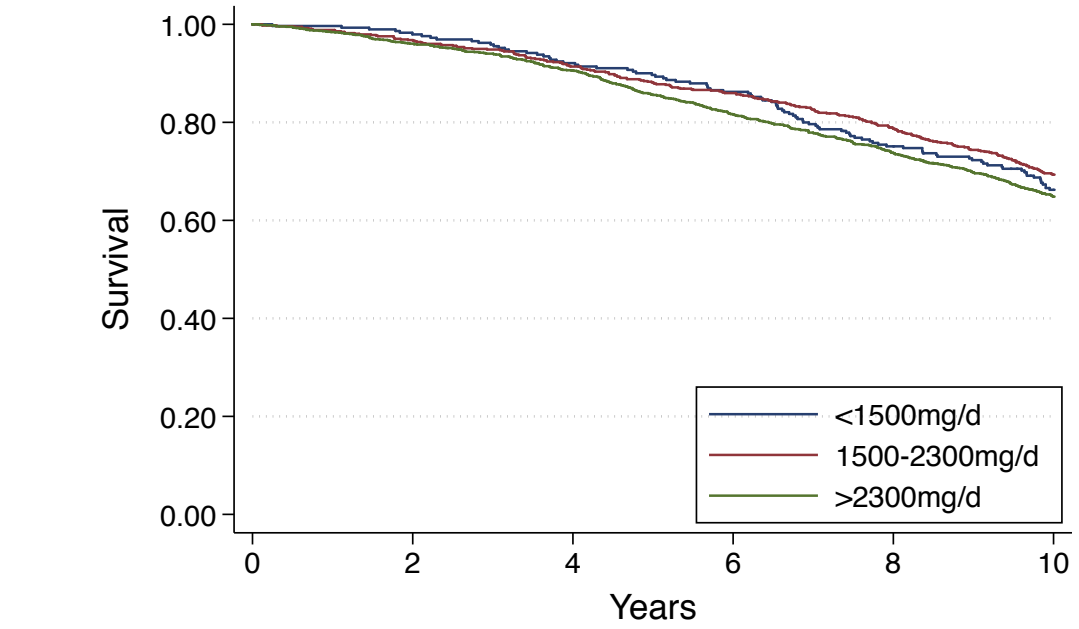
From the continuous-variable analysis, no consistent association appears to exist between dietary sodium intake and outcomes (mortality, incident CVD, and incident HF).

Table 5. Multivariable association of sodium intake categories with 10-year outcomes

	Mortality		Incident CVD		Incident HF	
Group	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
All	**N=2642**		**N=1981**		**N=2642**	
<1500 mg	1.13 (0.89-1.43)	0.33	0.92 (0.69-1.22)	0.56	0.88 (0.61-1.28)	0.51
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.15 (0.99-1.35)	0.070	0.95 (0.73-1.24)	0.71	0.95 (0.68-1.35)	0.79
Men	**N=1290**		**N=900**		**N=1290**	
<1500 mg	1.12 (0.78-1.61)	0.55	0.88 (0.56-1.36)	0.56	0.66 (0.37-1.18)	0.16
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.07 (0.87-1.32)	0.52	0.79 (0.53-1.19)	0.26	0.73 (0.43-1.23)	0.23
Women	**N=1352**		**N=1081**		**N=1352**	
<1500 mg	1.16 (0.83-1.61)	0.38	0.90 (0.62-1.32)	0.60	1.08 (0.67-1.75)	0.76
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.23 (0.97-1.57)	0.083	1.04 (0.74-1.47)	0.83	1.19 (0.76-1.87)	0.45
Whites	**N=1630**		**N=1217**		**N=1630**	
<1500 mg	0.88 (0.62-1.27)	0.50	0.85 (0.59-1.22)	0.37	1.25 (0.74-2.13)	0.41
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.08 (0.88-1.32)	0.46	0.87 (0.62-1.22)	0.42	1.19 (0.71-1.98)	0.51
Blacks	**N=1012**		**N=764**		**N=1012**	
<1500 mg	1.40 (0.99-1.96)	0.054	1.12 (0.72-1.75)	0.62	0.61 (0.36-1.04)	0.072
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.31 (1.02-1.67)	0.036	1.09 (0.72-1.65)	0.68	0.81 (0.51-1.29)	0.38
Hypertension	**N=1397**		**N=951**		**N=1397**	
<1500 mg	1.25 (0.93-1.68)	0.14	1.03 (0.69-1.53)	0.89	0.91 (0.58-1.43)	0.69
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.10 (0.90-1.34)	0.37	1.09 (0.76-1.57)	0.65	0.92 (0.60-1.40)	0.70
No hypertension	**N=1245**		**N=1030**		**N=1245**	
<1500 mg	0.86 (0.56-1.32)	0.49	0.82 (0.55-1.22)	0.33	0.91 (0.47-1.77)	0.79
1500-2300 mg	1.00	Ref.	1.00	Ref.	1.00	Ref.
>2300 mg	1.20 (0.94-1.55)	0.15	0.83 (0.57-1.20)	0.32	1.06 (0.57-1.96)	0.85

CI: confidence interval; CVD: cardiovascular disease; HF: heart failure; HR: hazard ratio; sHR: subhazard ratio

5.6. Figures



Number at risk						
<1500mg/d	291	285	267	250	214	185
1500-2300mg/d	779	752	709	665	604	518
>2300mg/d	1572	1508	1418	1276	1148	988

Figure 1. Unadjusted Kaplan-Meier survival according to baseline sodium consumption.

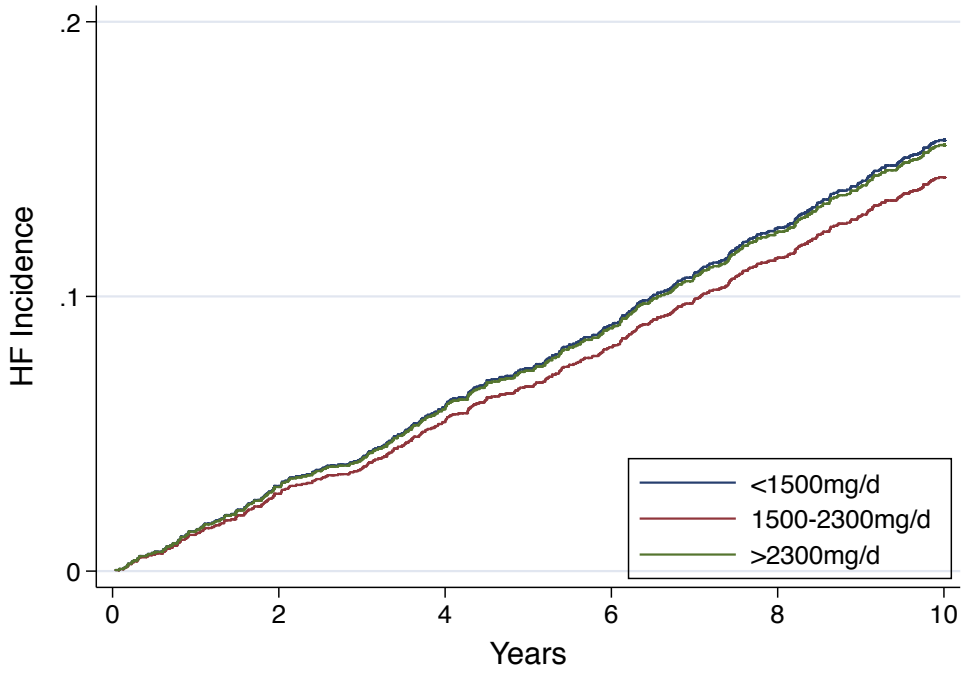


Figure 2. Unadjusted cumulative HF incidence (accounting for competing mortality) according to baseline sodium consumption.

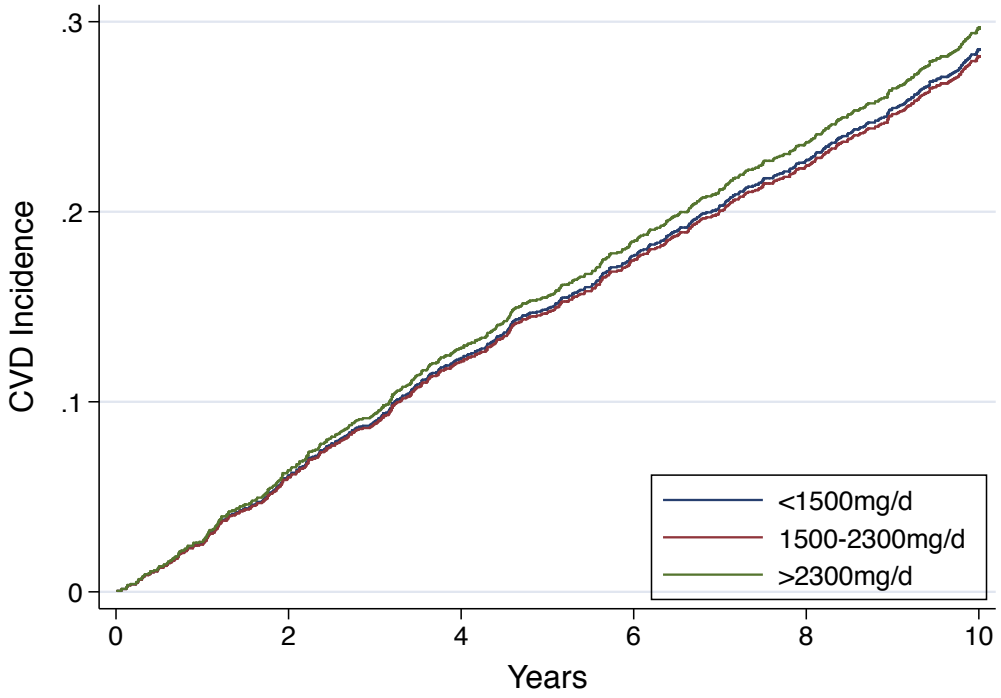


Figure 3. Unadjusted cumulative CVD incidence (accounting for competing mortality) according to baseline sodium consumption.

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