# Is complying with the recommendations of sodium intake beneficial for health in individuals at high cardiovascular risk? Findings from the PREDIMED study[1–5]

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**ABSTRACT**

**Background:** Excess sodium intake is associated with high blood pressure, a major risk factor for cardiovascular disease (CVD). It is unknown whether decreasing sodium intake to <2300 mg/d has an effect on CVD or all-cause mortality.

**Objective:** The objective was to assess whether reductions in sodium intake to <2300 mg/d were associated with either an increased or a decreased risk of fatal and nonfatal CVD and all-cause mortality.

**Design:** This observational prospective study of the PREvención con DIeta MEDiterránea (PREDIMED) trial included 3982 participants at high CVD risk. Sodium intake was evaluated with a validated food-frequency questionnaire and categorized as low (<1500 mg/d), intermediate (≥1500 to ≤2300 mg/d), high (>2300 to ≤3400 mg/d), or very high (>3400 mg/d). Subsequently, 1-y and 3-y changes in sodium intake were calculated. Multivariate relative risks were assessed by using Cox proportional hazards ratios. Marginal structural models with inverse probability weighting were used to test the effect of changes in sodium intake and the Mediterranean diet (MedDiet).

**Results:** We documented 125 CVD events and 131 deaths after a 4.8-y median follow-up. Sodium intake <2300 mg/d was associated with a lower risk of all-cause mortality: 48% (HR: 0.52; 95% CI: 0.30, 0.91; $P = 0.02$) and 49% (HR: 0.51; 95% CI: 0.26, 0.98; $P = 0.04$) after 1 and 3 y, respectively. Increasing sodium intake after 1 y was associated with a 72% (HR: 1.72; 95% CI: 1.01, 2.91; $P = 0.04$) higher risk of CVD events. The incidence rate of CVD was reduced for those who reduced their sodium intake and were randomly assigned to MedDiet interventions [4.1/10,000 (95% CI: 3.1, 8.0) compared with 4.4/10,000 (95% CI: 2.7, 12.4) person-years; $P = 0.002$].

**Conclusions:** Decreasing sodium intake to <2300 mg/d was associated with a reduced risk of all-cause mortality, whereas increasing the intake to >2300 mg/d was associated with a higher risk of CVD. Our observational data suggest that sodium intake <2300 mg/d was associated with an enhanced beneficial effect of the MedDiet on CVD. These results should be interpreted with caution, and other confirmatory studies are necessary. This study was registered at controlled-trials.com as 35739639. *Am J Clin Nutr* 2015;101:440–8.

**Keywords** cardiovascular disease, Mediterranean diet, mortality, PREDIMED study, sodium intake

## INTRODUCTION

Increased sodium intake is associated with higher blood pressure (1). Raised blood pressure and hypertension are major

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[3] Supplemental Table 1 is available from the "Supplemental data" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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risk factors for cardiovascular disease (CVD)[6] and are estimated to contribute to almost half of CVD deaths (2). Adults in the United States consume an average of 3400 mg sodium/d (3); a similar intake had been reported in Spanish Mediterranean hypertensive individuals and those at high risk for CVD, whose intake ranged between 2900 and 3100 mg/d (4). The 2010 Dietary Guidelines for Americans recommended a sodium intake <2300 mg/d (equivalent to <1 teaspoon salt/d) in the general population, with a further reduction in intake to 1500 mg/d among persons aged >51 y, individuals of African ethnicity, and those with hypertension, diabetes, or chronic kidney disease (5). This amount of sodium can be achieved by following a low-sodium diet such as the Dietary Approaches to Stop Hypertension. However, no specific advice on salt intake has been stated in the recommendations based on the Mediterranean dietary pattern, which is usually low in sodium because it is rich in fresh and unprocessed food (6).

Some scientific evidence suggests that low-sodium diets are associated with adverse health outcomes (7–11). A meta-analysis of 7 clinical trials originally designed to test the effectiveness of sodium reduction on blood pressure found nonsignificant associations between sodium reduction and lower CVD risk and total mortality after ≥6 mo of follow-up (12). No consistent associations between sodium intake and CVD have been reported in observational studies ranging from inverse (8) or J-shaped (13) to positive associations (14, 15). In this context, the recent Institute of Medicine report (16) explicitly concluded that studies on health outcomes are inconsistent in quality and insufficient in quantity to determine that sodium intake <2300 mg/d may increase or decrease the risk of heart disease, stroke, or all-cause mortality.

The present analysis was conducted as an observational cohort study nested within the PREDIMED trial. We aimed to investigate the associations between changing sodium intake to >2300 or <2300 mg/d and a composite of fatal and nonfatal cardiovascular events (myocardial infarction, stroke, and cardiovascular mortality) and all-cause mortality in a Mediterranean population at high risk for CVD. In addition, we investigated whether reducing sodium intake to <2300 mg/d was associated with benefits of the intervention with a Mediterranean diet (MedDiet) on CVD and all-cause mortality.

## METHODS

### Study population

The present study was conducted as an observational cohort nested within the PREDIMED trial, whose design has been described in detail elsewhere (17). Briefly, the PREDIMED study is a large, multicenter, parallel-group, randomized trial for the primary prevention of CVD (http://www.predimed.es). We assigned 7447 participants (men aged 55–80 y and women aged 60–80 y) to one of 3 interventions of dietary advice: a MedDiet supplemented with extra-virgin olive oil (EVOO), a MedDiet supplemented with mixed nuts, or advice on a low-fat diet (control diet). The main results of the trial on the primary cardiovascular endpoint have been published elsewhere (18). Participants had no CVD at enrollment, but they were at high risk of CVD because of the presence of type 2 diabetes or at least 3 of the following risk factors: current smoking, hypertension, high LDL cholesterol, low HDL cholesterol, overweight or obesity, and family history of premature CVD. Exclusion criteria were the presence of any severe chronic illness, alcohol or drug abuse, BMI (in kg/m$^2$) ≥40, and allergy or intolerance to olive oil or nuts. The study was registered at controlled-trials.com as 35739639 (19). The institutional review board of each recruiting center approved the study protocol, and all participants provided written informed consent.

### Assessment of sodium intake and other covariates

At baseline and yearly during the follow-up, trained dietitians completed a 137-item semiquantitative food-frequency questionnaire in a face-to-face interview with the participants; this questionnaire has been validated before in a population from Spain at high risk of CVD (20). We used Spanish food composition tables to estimate energy and nutrient intake (21). At baseline and yearly, a questionnaire about lifestyle variables, educational achievement, history of illnesses, and medication use was administered. Physical activity was assessed by using the validated Spanish version of the Minnesota Leisure-Time Physical Activity questionnaire (22). Participants were considered diabetic, hypercholesterolemic, or hypertensive if they had been diagnosed as such or were being treated with antidiabetic, cholesterol-lowering, or antihypertensive agents, respectively. Anthropometric and blood pressure measurements were taken by trained personnel. We used calibrated scales and a wall-mounted stadiometer to measure weight and height, respectively, with participants in light clothing and no shoes; waist circumference was measured midway between the lowest rib and the iliac crest with an anthropometric tape. We used a validated oscillometer (Omron HEM705CP) to measure blood pressure, in triplicate, with a 5-min interval between each measurement, and we recorded the mean of these 3 values.

### Ascertainment of CVD and mortality

For the present analysis and according to the *International Classification of Diseases, 10th Revision*, we used the following 3 endpoints: *1*) a composite of cardiovascular events [myocardial infarction (I21), ischemic or hemorrhagic stroke (I64), and death from cardiovascular causes], *2*) cardiovascular death, and *3*) all-cause mortality. For the purpose of this study, cardiovascular death included the following causes of death: coronary artery disease (CAD) deaths [i.e., acute myocardial infarction (I21, I22), unstable angina pectoris (I20), chronic ischemic heart disease (I25), and other forms of chronic ischemic heart disease (I24)], stroke (I60–I69), atrial fibrillation (I48), other cardiac arrhythmias (I49), congestive heart failure (I50), pulmonary embolism (I26), pulmonary edema (I50.1), and aortic aneurysm (I71). Total mortality includes all causes of death, including cardiovascular and noncardiovascular causes. Detailed information on the endpoints was published before (18). The endpoint adjudication committee, whose members were blinded to treatment allocation, updated information on these endpoints once a year. The committee used different sources of

[6]Abbreviations used: CAD, coronary artery disease; CVD, cardiovascular disease; EVOO, extra-virgin olive oil; MedDiet, Mediterranean Diet.

information: *1*) yearly questionnaires and examinations for all participants, *2*) family physicians, *3*) yearly review of medical records, and *4*) linkage to the National Death Index. Medical records of deceased participants were requested, and the endpoint adjudication committee determined the cause of death and confirmed major events.

### Statistical analyses

Follow-up time was calculated as the interval between the date of the cardiovascular event, death, or end of follow-up (the date of the last visit or the last recorded clinical event in which the participant was still alive), whichever came first, and the date of randomization. Extremes of total energy intake (>4000 or <800 kcal/d in men and >3500 or <500 kcal/d in women) were excluded from the present analysis. Baseline characteristics of the studied population are presented according to 1-y changes in dietary sodium intake, as means ± SDs for quantitative variables, and percentage (*n*) for categorical variables. Multivariate Cox proportional hazard models were used to assess the association between changes in sodium intake of the whole cohort, regardless of the intervention group, and the risk of CVD, cardiovascular mortality, and all-cause mortality through the study follow-up. In addition, myocardial infarction and stroke were used as secondary outcomes of the analysis. The exposure in these models was calculated to analyze the effects on CVD and mortality of changing sodium intake < or >2300 mg/d. Sodium intake at baseline, 1 y, and 3 y was assessed by the food-frequency questionnaire and categorized as *1*) low (<1500 mg/d), *2*) intermediate (≥1500 to ≤2300 mg/d), *3*) high (>2300 to ≤3400 mg/d), or *4*) very high (>3400 mg/d) (23). These categories were used to recode the changes in sodium intake in 3 categories: *1*) decrease sodium intake (for those individuals who reported a high or very high intake of sodium at baseline and decreased their sodium intake to <2300 mg/d after 1 and 3 y of follow-up), *2*) maintain sodium intake, and *3*) increase sodium to >2300 mg/d (for those who reported a low or intermediate sodium intake at baseline and exceeded the 2300 mg/d after 1 and 3 y of follow-up). We have calculated changes in sodium intake from baseline to 1 y of follow-up and subsequently the change in sodium intake from baseline to 3 y of follow-up. We have not analyzed the associations after longer follow-up because of lack of statistical power of the outcomes at that time. All analyses were stratified by the recruitment center. Results are expressed as HRs with 95% CIs. Multivariable model 1 was adjusted for lifestyle and medication covariates: age in years (quintiles), sex, intervention group, BMI in kg/m$^2$, systolic blood pressure in mm Hg, diastolic blood pressure in mm Hg, smoking status (never, former, or current smoker), educational level (primary education, secondary education, or academic/graduate), leisure-time physical activity in metabolic equivalent tasks per minute per day (continuous), prevalence of diabetes (yes or no), prevalence of hypertension (yes or no), prevalence of hypercholesterolemia (yes or no), family history of CAD (no, yes before age 55 y, or yes after age 55 y), medication (use of hypocholesterolemic drugs, aspirin, antihypertensive medication, or oral antiadiabetic drugs), alcohol intake in g/d (continuous, adding a quadratic term), and total energy intake in kcal/d. Model 2 was further adjusted for 1- and 3-y changes in BMI (kg/m$^2$), systolic blood pressure in mm Hg, diastolic blood pressure in mm Hg, leisure-time physical activity in metabolic equivalent task per minute per day (continuous), alcohol intake (g/d), total energy intake (kcal/d), total carbohydrates (g/d), total protein (g/d), monounsaturated fat (g/d), polyunsaturated fat (g/d), saturated fat (g/d), marine omega-3 (ω-3) intake (g/d), total dietary fiber (g/d), dietary calcium intake (mg/d), and dietary potassium intake (mg/d). Because blood pressure and prevalence of hypertension are potential mediators of the associations among sodium consumption, CVD, and mortality, an additional model was conducted without including systolic and diastolic blood pressure and prevalence of hypertension.

As a supplementary analysis, we evaluated the association between baseline sodium intake categories (<1500 mg/d, ≥1500 to ≤2300 mg/d, >2300 to ≤3400 mg/d, and >3400 mg/d), all-cause mortality, and major CVD by using the same previously described models.

We also applied marginal structural models with inverse probability weighting as an alternative and complementary analytic approach (24, 25). The conditional probabilities of reducing sodium intake after 1 and 3 y were estimated by using logistic regression models with the dichotomous dependent variable of the respective actual sodium change and the following independent predictors: intervention group, age, sex, educational level, BMI, smoking status, family history of CAD, baseline hypertension, diabetes, hypercholesterolemia, use of statins, use of antihypertensive drugs, use of oral antidiabetic medication, aspirin use, total energy intake, alcohol intake, and physical activity.

To test the effect of the intervention group (MedDiet + EVOO, MedDiet + nuts, or control group) on CVD by using marginal structural models with inverse probability weighting, we used the reduction below 2300 mg/d in sodium intake to build a joint classification with the intervention group.

Sensitivity analyses were conducted with multiple imputation (*mi*) procedures for missing values (including participants who lacked sodium intake change after 1 y) by using multivariable normal imputation methods implemented in Stata 12.1 (StataCorp LP) and with 20 imputations.

The level of significance for all statistical tests was $P < 0.05$ for a bilateral contrast. To avoid multiple comparison bias and as a sensitivity analysis, we applied Benjamini-Hochberg correction when assessing the outcome variables. Analyses were done with SPSS statistical software, version 19 (SPSS Inc.) and Stata 12.1 (StataCorp LP).

## RESULTS

After exclusion of individuals with extreme values of total energy intake (*n* = 153) and those with incomplete baseline dietary data (*n* = 78), a total of 7216 participants had sodium intake measurements at baseline. In total, 3982 participants had data on changes in sodium intake after 1 y and 3123 after 3 y of follow-up (**Figure 1**). There were no significant differences in sex, age, BMI, and body weight between those individuals who had sodium intake data at baseline (*n* = 7216) and those for whom sodium intake changes were calculated (*n* = 3982). The baseline characteristics of the participants according to 1-y changes in dietary sodium intake are described in **Table 1**. Changes in sodium intake after 1 y of follow-up were −1090 ± 664 mg/d in the decrease category, +25 ± 338 mg/d in the

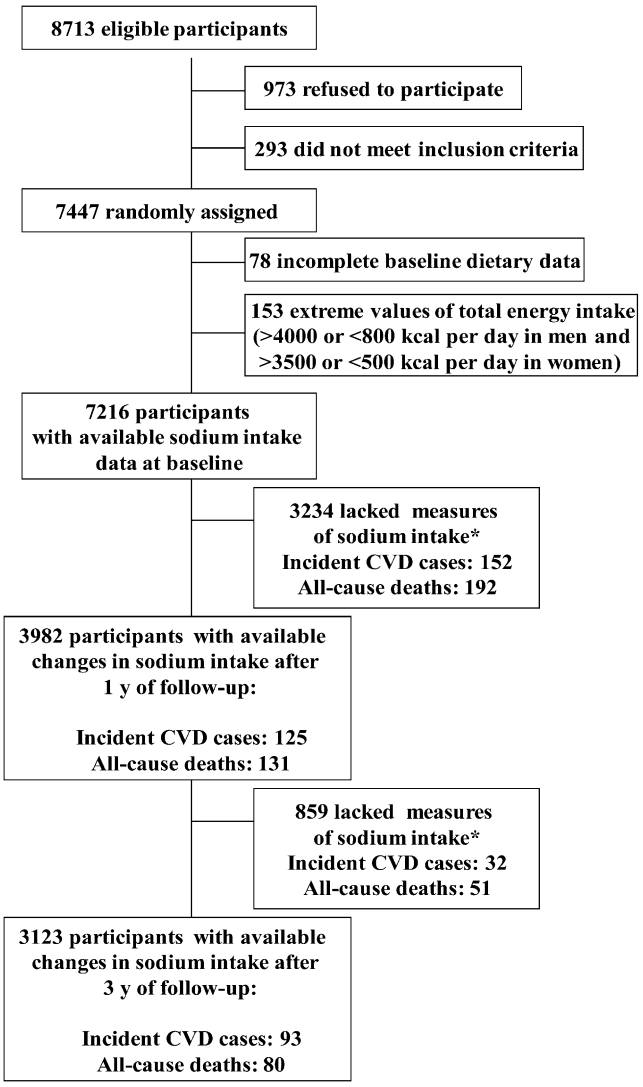


**FIGURE 1** *Lacked measures of sodium intake because of end of follow-up or missing information on the food-frequency questionnaire. CVD, cardiovascular disease.

no-change category, and +968 ± 616 mg/d in the increase category. The respective changes in sodium intake after 3 y were −1138 ± 644, −32 ± 362, and +966 ± 608 mg/d (**Table 2**). There were no significant differences between categories of sodium intake changes after 1 y and baseline age, sex, BMI, weight, blood pressure, prevalence of diseases, and medication use (Table 1). Those participants who decreased their sodium intake to <2300 mg/d after 1 y had higher baseline total energy, alcohol, dietary fiber, and marine ω-3 fatty acid intake (Table 1). Because of the strong correlation between sodium and energy intake ($r$ = 0.8, $P < 0.001$), the fully adjusted models were adjusted for changes in energy intake. During a median follow-up of 4.8 y, we documented 125 incident cases of major cardiovascular events, 34 cardiovascular deaths, and 131 all-cause deaths among 3982 participants with available data on 1-y sodium changes. Table 2 shows HRs and 95% CIs for all-cause mortality according to changes in sodium intake categories. After adjustment for potential confounders (model 2), participants who decreased their sodium intake to <2300 mg/d after the first and third years of follow-up had an inverse association with the risk of all-cause mortality by 48% (HR: 0.52; 95% CI: 0.30, 0.91; $P$ = 0.02) and 49% (HR: 0.51; 95% CI: 0.26, 0.98; $P$ = 0.04), respectively, compared with those who did not change their baseline sodium intake category. **Table 3** shows the HRs and 95% CIs for cardiovascular events according to changes in sodium intake categories. In the fully adjusted models, we observed that individuals who increased their sodium intake to >2300 mg/d after 1 and 3 y of follow-up, had respectively a 72% (HR: 1.72; 95% CI: 1.01, 2.91; $P$ = 0.04) and a 14% (HR: 1.14; 95% CI: 0.61, 2.16; $P$ = 0.67) increased risk of having a major cardiovascular event. The HRs for cardiovascular mortality were 2.23 (95% CI: 0.75, 6.59; $P$ = 0.14) and 2.25 (95% CI: 0.59, 8.55; $P$ = 0.23) after 1 and 3 y of follow-up in those participants increasing their sodium intake to >2300 mg/d compared with those who did not change with respect to their baseline intake.

Because blood pressure and hypertension are potential mediators of CVD and mortality, additional models without including systolic and diastolic blood pressure and prevalence of hypertension were performed. Compared with those who did not change their sodium intake, increasing sodium intake after 1 y of follow-up was associated with an increased risk of CVD (HR: 1.66; 95% CI: 1.00, 2.78; $P$ = 0.05), and decreasing sodium intake after 1 y of follow-up was inversely associated with all-cause mortality (HR: 0.57; 95% CI: 0.34, 0.97; $P$ = 0.03).

When myocardial infarction and stroke were analyzed separately as secondary endpoints, the associations between 1-y and 3-y changes in sodium intake and the aforementioned endpoints were not statistically significant (data not shown).

At baseline, sodium intake between 2300 and 3400 mg/d was associated with a 38% (HR: 0.62; 95% CI: 0.39, 0.97; $P$ = 0.03) lower risk of all-cause mortality compared with those in the very low category of baseline sodium intake (<1500 mg/d) (**Supplemental Table 1**). However, no associations were found when the model was adjusted for dietary variables. A similar trend was found for cardiovascular events in this category, but the associations were not statistically significant in any model. The associations between other categories of sodium intake at baseline, all-cause mortality, and major cardiovascular events were also nonsignificant (Supplemental Table 1).

By using the inverse probability weighting and marginal structural models, we found that, compared with those participants in the control group who did not reduce their sodium intake after 1 y of follow-up, those in the MedDiet + EVOO group and in the MedDiet + nuts group who reduced their sodium consumption had a reduced risk in all-cause mortality [HR: 0.46 (95% CI: 0.26, 0.83); $P$ = 0.01 and HR: 0.51 (95% CI: 0.25, 1.03); $P$ = 0.06, respectively]. After 3 y of follow-up, the inverse association with all-cause mortality was significant for both MedDiet groups [HR: 0.35 (95% CI: 0.10, 0.63); $P < 0.01$ and HR: 0.35 (95% CI: 0.18, 0.70); $P < 0.01$, respectively].

A similar but mostly nonsignificant trend was found for CVD events for those who were simultaneously in the MedDiet + EVOO group and reduced their sodium intake after 1 and 3 y, respectively [HR: 0.72 (95% CI: 0.37, 1.41); $P$ = 0.34 and HR: 0.41 (95% CI: 0.19, 0.88); $P$ = 0.02] and for those in the MedDiet + nuts group who also reduced their sodium intake [HR: 0.65 (95% CI: 0.32, 1.30); $P$ = 0.22 and HR: 0.55 (95% CI: 0.26, 1.17); $P$ = 0.11].

**TABLE 1**
Baseline characteristics of study participants according to 1-y changes in sodium intake[1]

| Variable | 1-y changes in dietary sodium intake | | | *P* value |
|---|---|---|---|---|
| | 2 (decrease in category) (*n* = 1199) | 1 (no change in category) (*n* = 2016) | 3 (increase in category) (*n* = 767) | |
| Median sodium intake, mg/d | 2759 | 2194 | 1899 | |
| Age, y | 66 ± 6[2] | 67 ± 6 | 67 ± 6 | 0.237 |
| Men, % (*n*) | 44 (534) | 42 (848) | 40 (308) | 0.141 |
| BMI, kg/m$^2$ | 30.0 ± 3.9 | 29.8 ± 3.8 | 29.9 ± 3.9 | 0.141 |
| Weight, kg | 77.1 ± 12.1 | 76.1 ± 11.9 | 76.5 ± 12.7 | 0.067 |
| Systolic blood pressure, mm Hg | 149 ± 21 | 150 ± 20 | 148 ± 20 | 0.081 |
| Diastolic blood pressure, mm Hg | 83 ± 11 | 83 ± 11 | 82 ± 11 | 0.292 |
| Leisure-time energy expenditure in physical activity, MET[3]-min/d | 239.9 ± 238.0 | 251.8 ± 261.3 | 220.1 ± 220.9 | 0.010 |
| Smoking status, % (*n*) | | | | 0.050 |
| Never | 59.9 (718) | 63.7 (1284) | 61.4 (471) | |
| Current | 14.8 (178) | 11.8 (237) | 14.9 (114) | |
| Former | 25.3 (303) | 24.6 (495) | 23.7 (182) | |
| Educational level, % (*n*) | | | | 0.147 |
| Primary education | 75.8 (909) | 77.8 (1569) | 75.7 (581) | |
| Secondary education | 15.3 (184) | 14.9 (300) | 17.6 (135) | |
| Academic/graduate | 8.8 (106) | 7.3 (147) | 6.6 (51) | |
| Prevalence of diabetes, % (*n*) | 46.1 (553) | 46.6 (939) | 48.0 (368) | 0.713 |
| Prevalence of hypertension, % (*n*) | 82.4 (988) | 82.6 (1665) | 83.3 (639) | 0.865 |
| Prevalence of hypercholesterolemia, % (*n*) | 73.2 (881) | 73.2 (1475) | 72.6 (557) | 0.916 |
| Family history of myocardial infarction, % (*n*) | 24.5 (294) | 22.9 (462) | 24.6 (189) | 0.472 |
| Medication use, % (*n*) | | | | |
| Aspirin | 22.4 (268) | 21.3 (430) | 22.2 (170) | 0.765 |
| Oral antidiabetic drugs | 30.8 (369) | 31.7 (640) | 32.2 (255) | 0.517 |
| Antihypertensive drugs | 72.0 (863) | 71.8 (1447) | 72.2 (554) | 0.971 |
| Statins | 40.3 (483) | 41.8 (842) | 40.9 (314) | 0.704 |
| Total energy intake, kcal/d | 2523 (427) | 2229 (427) | 1976 (383) | <0.001 |
| Sodium intake, mg/d | 2912 (569) | 2275 (496) | 1847 (328) | <0.001 |
| Alcohol intake, g/d | 9.73 (14.53) | 8.49 (14.35) | 6.80 (11.43) | <0.001 |
| Total protein, g/d | 102.05 (17.27) | 91.51 (17.53) | 82.14 (15.61) | <0.001 |
| Total carbohydrates, g/d | 273.84 (70.50) | 231.68 (58.93) | 199.95 (50.81) | <0.001 |
| Total fat, g/d | 105.75 (25.68) | 97.40 (25.11) | 88.92 (24.07) | <0.001 |
| Saturated fat, g/d | 27.59 (8.05) | 24.51 (7.15) | 22.28 (6.76) | <0.001 |
| Monounsaturated fat, g/d | 51.47 (14.43) | 48.49 (14.24) | 44.78 (13.82) | <0.001 |
| Polyunsaturated fat, g/d | 17.10 (6.47) | 15.67 (6.25) | 14.16 (5.98) | <0.001 |
| Marine ω-3 fatty acid, mg/d | 859 (476) | 815 (492) | 765 (433) | <0.001 |
| Total fiber, g/d | 27.97 (9.16) | 25.36 (8.31) | 22.85 (7.77) | <0.001 |
| Calcium intake, mg/d | 1134 (359) | 1041 (322) | 948 (313) | <0.001 |
| Potassium intake, mg/d | 4651 (1002) | 4348 (1003) | 3963 (937) | <0.001 |

[1]*P* values are for comparisons across baseline sodium intake categories (Pearson $\chi^2$ test for categorical variables or 1-way ANOVA for continuous variables) as appropriate. Categories are changes in dietary sodium intake (mg/d) from baseline to 1 y. Categories at baseline and after 1 y were defined according to the Institute of Medicine recommendations: low (<1500 mg/d), intermediate (≥1500 to ≤2300 mg/d), high (>2300 to ≤3400 mg/d), and very high (>3400 mg/d). According to these categories, we calculated the change in sodium intake.
[2]Mean ± SD (all such values).
[3]MET, metabolic equivalent task.

The adjusted incidence rate/10,000 persons-years of CVD after 3 y of follow-up was lower for individuals randomly allocated to both merged MedDiet group interventions who reduced their sodium intake to <2300 mg/d compared with those in the control group [4.1/10,000 (95% CI: 3.1, 8.0) and 4.4/10,000 (95% CI: 2.7, 12.4) person-years, respectively; $P = 0.002$] (**Figure 2**).

Findings of the primary analysis were consistent with the sensitivity analyses that used marginal structural models and imputed changes in sodium intake. After 1 y, the relative risk estimates of all-cause mortality were 0.48 (95% CI: 0.26, 0.88; $P = 0.01$) and 0.53 (95% CI: 0.26, 1.08; $P = 0.08$) for those in the MedDiet + EVOO and MedDiet + nuts groups who also reduced their sodium intake, respectively. However, when applying the multiple-comparison tests as a sensitivity analysis, the associations did not remain statistically significant in fully-adjusted models.

## DISCUSSION

In this observational prospective study of individuals at high risk of CVD, which aimed to assess whether sodium intake <2300 mg/d was associated with either an increased or

**TABLE 2**
HRs and 95% CIs for all-cause mortality according to changes in categories of sodium intake[1]

| | All-cause mortality | | |
|---|---|---|---|
| | 2 (decrease in category) | 1 (no change in category) | 3 (increase in category) |
| 1-y changes in categories of dietary sodium intake, *n* | 1199 | 2016 | 767 |
| Dietary sodium intake variation, mg/d | −1090 ± 664[2] | −25 ± 338 | 968 ± 616 |
| Total cases, % (*n*) | 2.7 (32) | 3.5 (70) | 3.8 (29) |
| Crude model | 0.76 (0.50, 1.15) | 1 (Reference) | 1.08 (0.70, 1.66) |
| Multivariate model 1 | 0.72 (0.45, 1.13) | 1 (Reference) | 1.17 (0.73, 1.88) |
| Multivariate model 2 | 0.52 (0.30, 0.91) | 1 (Reference) | 1.39 (0.83, 2.34) |
| 3-y changes in categories of dietary sodium intake, *n* | 1104 | 1388 | 631 |
| Dietary sodium intake variation, mg/d | −1138 ± 644 | −32 ± 362 | 966 ± 608 |
| Total cases, % (*n*) | 2.1 (23) | 2.7 (38) | 3.0 (19) |
| Crude model | 0.78 (0.46, 1.31) | 1 (Reference) | 1.03 (0.59, 1.79) |
| Multivariate model 1 | 0.51 (0.28, 0.92) | 1 (Reference) | 1.10 (0.59, 2.07) |
| Multivariate model 2 | 0.51 (0.26, 0.98) | 1 (Reference) | 1.33 (0.68, 2.61) |

[1]Values are reported as HRs (95% CIs) unless otherwise indicated. Cox regression models were used to assess the risk of all-cause mortality by changes in the categories of dietary sodium intake (mg/d). Categories were defined according to the Institute of Medicine recommendations: low (<1500 mg/d), intermediate (≥1500 to ≤2300 mg/d), high (>2300 to ≤3400 mg/d), and very high (>3400 mg/d). Multivariable model 1 was adjusted for age in years (quintiles), sex, intervention group, BMI (in kg/m$^2$), systolic blood pressure (in mm Hg), diastolic blood pressure (in mm Hg), smoking status (never, former, or current smoker), educational level (primary education, secondary education, or academic/graduate), leisure-time physical activity (in MET-min/d) (continuous), prevalence of diabetes (yes or no), prevalence of hypertension (yes or no), prevalence of hypercholesterolemia (yes or no), family history of coronary artery disease (no, yes before age 55 y, or yes after age 55 y), use of aspirin (yes or no), use of antihypertensive medication (yes or no), use of oral antidiabetic medication (yes or no), use of hypocholesterolemic medication (yes or no), alcohol intake (in g/d) (continuous, adding a quadratic term), and total energy intake (in kcal/d). Model 2 was further adjusted for 1- and 3-y changes in BMI, systolic blood pressure, diastolic blood pressure, leisure-time physical activity (continuous), alcohol intake (g/d), total energy intake (kcal/d), total carbohydrates (g/d), total protein (g/d), monounsaturated fat (g/d), polyunsaturated fat (g/d), saturated fat (g/d), marine ω-3 fatty acid intake (g/d), total dietary fiber (g/d), dietary calcium intake (mg/d), and dietary potassium intake (mg/d). All models were stratified by recruitment center. Extremes of total energy intake were excluded. MET, metabolic equivalent task.

[2]Mean ± SD (all such values).

a decreased risk of CVD and mortality, we observed that decreasing sodium intake to <2300 mg/d after 1 and 3 y of follow-up was associated with a 48% and 49% reduction in the risk of all-cause mortality, respectively. Increasing sodium intake to >2300 mg/d after 1 y was associated with a higher risk of CVD but not with a higher risk of all-cause mortality.

**TABLE 3**
HRs and 95% CIs for cardiovascular events according to changes in categories of sodium intake[1]

| | Major cardiovascular event | | |
|---|---|---|---|
| | 2 (decrease in category) | 1 (no change in category) | 3 (increase in category) |
| 1-y changes in categories of dietary sodium intake, *n* | 1199 | 2016 | 767 |
| Dietary sodium intake variation, mg/d | −1090 ± 664[2] | −25 ± 338 | 968 ± 616 |
| Total cases, % (*n*) | 2.8 (33) | 3.1 (62) | 3.9 (30) |
| Crude model | 0.90 (0.59, 1.37) | 1 (Reference) | 1.25 (0.81, 1.94) |
| Multivariate model 1 | 0.89 (0.56, 1.41) | 1 (Reference) | 1.40 (0.87, 2.25) |
| Multivariate model 2 | 0.66 (0.38, 1.15) | 1 (Reference) | 1.72 (1.01, 2.91) |
| 3-y changes in categories of dietary sodium intake, *n* | 1104 | 1388 | 631 |
| Dietary sodium intake variation, mg/d | −1138 ± 644 | −32 ± 362 | 966 ± 608 |
| Total cases, % (*n*) | 2.9 (32) | 3.1 (43) | 2.9 (18) |
| Crude model | 0.95 (0.60, 1.50) | 1 (Reference) | 0.87 (0.50, 1.51) |
| Multivariate model 1 | 1.01 (0.61, 1.68) | 1 (Reference) | 0.93 (0.52, 1.67) |
| Multivariate model 2 | 0.97 (0.54, 1.74) | 1 (Reference) | 1.14 (0.61, 2.16) |

[1]Values are reported as HRs (95% CIs) unless otherwise indicated. Cox regression models were used to assess the risk of major cardiovascular event (myocardial infarction, stroke, or cardiovascular death) by changes in the categories of dietary sodium intake (mg/d). Categories were defined according to the Institute of Medicine recommendations: low (<1500 mg/d), intermediate (≥1500 to ≤2300 mg/d), high (>2300 to ≤3400 mg/d), and very high (>3400 mg/d). Multivariable model 1 was adjusted for age in years (quintiles), sex, intervention group, BMI (in kg/m$^2$), systolic blood pressure (in mm Hg), diastolic blood pressure (in mm Hg), smoking status (never, former, or current smoker), educational level (primary education, secondary education, or academic/graduate), leisure time physical activity (in MET-min/d) (continuous), prevalence of diabetes (yes or no), prevalence of hypertension (yes or no), prevalence of hypercholesterolemia (yes or no), family history of coronary artery disease (no, yes before age 55 y, or yes after age 55 y), use of aspirin (yes or no), use of antihypertensive medication (yes or no), use of oral antidiabetic medication (yes or no), use of hypocholesterolemic medication (yes or no), alcohol intake (in g/d) (continuous, adding a quadratic term), and total energy intake (in kcal/d). Model 2 was further adjusted for 1- and 3-y changes in BMI, systolic blood pressure, diastolic blood pressure, leisure-time physical activity (continuous), alcohol intake, total energy intake, total carbohydrates (g/d), total protein (g/d), monounsaturated fat (g/d), polyunsaturated fat (g/d), saturated fat (g/d), marine ω-3 fatty acid intake (g/d), total dietary fiber (g/d), dietary calcium intake (mg/d), and dietary potassium intake (mg/d). All models were stratified by recruitment center. Extremes of total energy intake were excluded. MET, metabolic equivalent task.

[2]Mean ± SD (all such values).

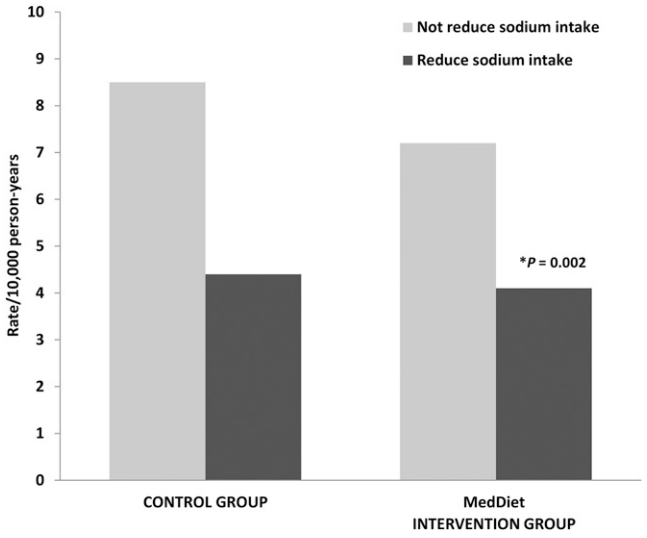


**FIGURE 2** Adjusted incidence rate per 10,000 person-years of cardiovascular disease. Incidence-adjusted rate per 10,000 person-years with inverse probability weighting of the cardiovascular event for the control group and MedDiet groups combined (extra-virgin olive oil and nuts group) according to sodium intake reduction after 3 y of follow-up. Light gray columns represent individuals who reduced sodium intake after 3 y of follow-up, and black columns represent those who did not reduce sodium intake. *$P$ value for the comparison between reduction in sodium intake in the control group and reduction in sodium intake in the MedDiet group [4.1/10,000 (95% CI: 3.1, 8.0) and 4.4/10,000 (95% CI: 2.7, 12.4) person-years, respectively; $P = 0.002$]. Adjusted for intervention group, age, sex, educational level, BMI, smoking status, family history of coronary artery disease, baseline hypertension, diabetes, hypercholesterolemia, medication (use of hypocholesterolemic drugs, aspirin, or antihypertensive and oral antidiabetic drugs), total energy intake, alcohol intake, and physical activity. Reduction in sodium intake in the control group ($n$ = 289): 4.4/10,000 (95% CI: 2.7, 12.4) person-years. Reduction in sodium intake in the MedDiet group ($n$ = 816): 4.1/10,000 (95% CI: 3.1, 8.0) person-years. No reduction in sodium intake in the control group ($n$ = 2094): 8.5/10,000 (95% CI: 6.7, 10.8) person-years. No reduction in sodium intake in the MedDiet group ($n$ = 4017): 7.7/10,000 (95% CI: 6.2, 8.8) person-years. MedDiet, Mediterranean diet.

Some previous scientific evidence suggests that a higher adherence to a MedDiet and reduced salt consumption could be beneficial in the prevention of stroke (26), but the association between the MedDiet and reduced sodium consumption to <2300 mg/d on the risk of CVD and all-cause mortality has not been elucidated. Findings of the present study showed a lower incidence-adjusted rate of CVD for those individuals who were randomly allocated to a MedDiet and reduced their sodium intake to <2300 mg/d. There were 30 fewer incident events per 10,000 person-years in those in the MedDiet group compared with those who reduced sodium intake to <2300 mg/d but were randomly allocated to the control group. This apparently small number of prevented cardiovascular events may be translated to a decreased burden for the health care system when recommending a reduction in sodium intake to <2300 mg/d. As advocated by professional and policy-making organizations, the pandemic of blood pressure–related CVD warrants a comprehensive approach in both healthy adults and populations at high risk that addresses the underlying causes of elevated blood pressure (27, 28). Adopting a healthy lifestyle is considered a cornerstone for the prevention and treatment of hypertension and consequently a decrease in the risk of CVD and mortality (29). Previous results of the PREDIMED trial have demonstrated that adherence to the MedDiet reduces the incidence of major CVD by 30%, including stroke, a condition known to be highly dependent on blood pressure (18). However, in the present study, we did not find associations between changes in sodium intake and specific cardiovascular outcomes (stroke or myocardial infarction). The nonsignificant associations may be due to the lack of statistical power for these outcomes. A recent report of the PREDIMED cohort concluded that both MedDiets and a low-fat diet exerted beneficial effects on systolic and diastolic blood pressure (30). The reduction achieved in blood pressure (~4 mm Hg) is similar to the effects that have been observed by the Dietary Approaches to Stop Hypertension study, which has been one of the most recommended dietary patterns for the prevention and treatment of hypertension (31). It has been estimated that a 2–mm Hg reduction in diastolic blood pressure results in a 17% decrease in the prevalence of hypertension, a 6% decrease in the risk of CAD, and a 15% decrease in the risk of stroke (32). Because blood pressure and hypertension are potential mediators of the relation between sodium intake, CVD, and mortality, we repeated the statistical models excluding these variables. After 1 y, increasing sodium intake to >2300 mg/d was associated with a 66% increased risk of all-cause mortality. In contrast, decreasing sodium intake was related to a 43% reduced risk.

The present study focused on answering the key question stated by the Institute of Medicine regarding whether reducing sodium intake <2300 mg/d has any impact on CVD and mortality, which has not been elucidated. Nevertheless, in baseline multivariate models of sodium intake, we observed that sodium intake between 2300 and 3400 mg/d was associated with a 38% lower risk of all-cause mortality compared with very low sodium intake (<1500 mg/d). A similar nonsignificant trend was found for cardiovascular events in the same category of baseline sodium intake. These findings may suggest a J-shaped association between baseline sodium intake and mortality, but this was apparent in only one of the multivariable models, among many multiple tests. A J-shaped association was also reported in an observational study including >28,000 patients with established CVD, individuals who may be more vulnerable to the extremes of sodium intake (11). Previous studies have suggested that the J-shaped or inverse relation reflects a causal relation (i.e., a very low sodium intake is a consequence of disease). A more plausible explanation is that such findings resulted from methodologic limitations of the studies, the most important of which were inaccurate measurement of sodium intake in free-living individuals and the potential for reverse causality (33–35). The gold standard for estimating dietary sodium intake is measuring 24-h urinary sodium excretion in multiple collections (36). A significant linear 17% increase in the risk of CVD and death per a 1000-mg/d increase of 24-h urine sodium excretion was observed among 2275 subjects with prehypertension (14). In line, higher 24-h urinary sodium excretion was associated only with an increased CAD risk among high-risk individuals (i.e., subjects with increased intravascular volume or with hypertension) in the Prevention of Renal and Vascular Endstage Disease (PREVEND) study (15).

Some limitations of our study deserve attention. First, the estimation of sodium intake by using a food-frequency questionnaire must be recognized as a potential limitation. Second, there is the possibility of reverse causality. The correlation between sodium and calorie intake is extremely high ($r$ = 0.8 in our

study), and for this reason, we adjusted for total energy and excluded individuals with extreme calorie intake in the analysis. Third, our analyses were extensively adjusted for a wide range of nutrients and CVD risk factors, but because of the observational nature of the study, residual confounding remains a possibility, and a cause-effect relation cannot be established. In addition, the lower number of incident cases in some of the studied categories attenuated the statistical power of our analysis, and thus our results should be interpreted with caution and as a probable hypothesis-generating study. Our study population included older Mediterranean individuals at high risk of CVD with high blood pressure, and therefore our findings may not be generalizable to other populations with lower levels of blood pressure. Nonetheless, our study adds evidence to support that sodium reduction may be beneficial for individuals at high risk with high blood pressure. In addition, it is unknown when during the 1-y or 3-y interval the change in sodium intake occurred in the participants.

The strengths of the present study are its prospective design, repeated assessment of diet and lifestyle variables, and long duration of follow-up. The analyses have been conducted in a high-risk population, most of them hypertensive, allowing a better assessment of the association between sodium intake and CVD events and cardiovascular and total mortality.

In conclusion, despite substantial evidence demonstrating the health benefits of reducing sodium intake, some studies have raised concerns that population-wide sodium reduction strategies may increase the risk of CVD events and have adverse effects on some health outcomes. Our findings indicated that decreasing sodium intake to <2300 mg/d was associated with a reduced risk of all-cause mortality, and a positive association was found between increasing sodium intake to >2300 mg/d, CVD, and mortality in a population at high risk of CVD. We also observed that reducing sodium intake to <2300 mg/d could be associated with an enhanced beneficial effect of the MedDiet on CVD in comparison with those who did not reduce sodium intake. Caution should be taken when interpreting the present results, but they are helpful as new insights in dietary strategies for CVD prevention, especially in those patients at increased risk of CVD.

The authors' responsibilities were as follows—MAM-G, DC, RE, MF, ER, FA, EG-G, MM, JL, LS-M, MAM, XP, and JS-S: designed research; JM, MG-F, MAM-G, DC, RE, MF, ER, FA, MB, EG-G, MM, JL, LS-M, CR, PB-C, JVS, MAM, XP, LM, and JS-S: conducted the research; JM, M-GF, CR, MAM-G, and JS-S: analyzed the data; JM, MG-F, and JS-S: wrote the manuscript; MAM-G, DC, RE, ER, MF, JL, LS-M, MAM, XP, and JS-S: were the coordinators of subject recruitment at the outpatient clinics; and MG-F and JS-S: had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors revised the manuscript for important intellectual content and read and approved the final manuscript. The authors reported no potential conflicts of interest relevant to this article. None of the funding sources played a role in the design, collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

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