Journal of the American Heart Association

ORIGINAL RESEARCH

Mediterranean Diet Score, Dietary Patterns, and Risk of Sudden Cardiac Death in the REGARDS Study

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BACKGROUND: Sudden cardiac death (SCD) is a common cause of death in the United States. Few previous studies have investigated the associations of diet scores and dietary patterns with risk of SCD. We investigated the associations of the Mediterranean diet score and various dietary patterns with risk of SCD in participants in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study cohort.

METHODS AND RESULTS: Diet was assessed with a food frequency questionnaire administered at baseline in REGARDS. The Mediterranean diet score was derived based on the consumption of specific food groups considered beneficial or detrimental components of that diet. Dietary patterns were derived previously using factor analysis, and adherence to each pattern was scored. SCD events were ascertained through regular contacts. Cox proportional hazards regression was used to examine the risk of SCD events associated with the Mediterranean diet score and adherence to each of the 5 dietary patterns overall and stratifying on history of coronary heart disease at baseline. The analytic sample included 21 069 participants with a mean 9.8±3.8 years of follow-up. The Mediterranean diet score showed a trend toward an inverse association with risk of SCD after multivariable adjustment (hazard ratio [HR] comparing highest with lowest group, 0.74; 95% CI, 0.55–1.01; P_{trend}=0.07). There was a trend toward a positive association of the Southern dietary pattern with risk of SCD (HR comparing highest with lowest quartile of adherence, 1.46; 95% CI, 1.02–2.10; P_{trend}=0.06).

CONCLUSIONS: In REGARDS participants, we identified trends toward an inverse association of the Mediterranean diet score and a positive association of adherence to the Southern dietary pattern with risk of SCD.

Key Words: dietary patterns ■ epidemiology ■ follow-up studies ■ nutrition ■ sudden cardiac death

Sudden cardiac death (SCD) usually is defined as death attributable to cardiac causes occurring within 1 hour of the onset of symptoms.[1] While coronary heart disease (CHD) is the most common underlying cause of SCD in the West, responsible for 75% to 80% of cases, other causes include cardiomyopathies, inherited channelopathies, heart failure, and valve disease.[2] SCD is a common cause of death, mentioned in ≈1 of every 7.5 deaths in the United States in 2016 (a total of nearly 367 000 deaths).[3]

The Mediterranean diet has been associated with reduced risk of disease incidence and mortality in various populations.[4] A limited number of previous studies have investigated the possible association of the Mediterranean diet with risk of SCD, although most have included only women and few Black participants. For example, an analysis from the Women's Health Initiative demonstrated that a higher Mediterranean diet score was associated with lower risk of SCD in women.[5] The alternate Mediterranean diet score also

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Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.019158

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- REGARDS (Reasons for Geographic and Racial Differences in Stroke) study participants who adhered more closely to a traditional Mediterranean diet showed a trend toward a lower risk of sudden cardiac death than those with lower adherence to this diet.
- REGARDS study participants who adhered more closely to a Southern dietary pattern showed a trend toward a higher risk of sudden cardiac death than those with lower adherence to this dietary pattern.

What Are the Clinical Implications?

- Although observational in nature, these data suggest that diet may be a modifiable risk factor for sudden cardiac death and should be discussed with patients.

Nonstandard Abbreviations and Acronyms

FFQ	food frequency questionnaire
REGARDS	Reasons for Geographic and Racial Differences in Stroke
SCD	sudden cardiac death

was inversely associated with risk of SCD in women in the US Nurses' Health Study.[6]

While individual foods and nutrients (eg, fish and n-3 fatty acids) have been studied in relation to SCD risk,[7] the association of overall diet with risk of SCD may be more informative because foods typically are eaten in combination, not in isolation.[8] Empirically deriving dietary patterns with cluster or factor analysis has facilitated investigations into the role overall diet may play in the etiology of multiple diseases.[9,10] Factor analysis, a data-driven exploratory method, assesses eating patterns in specified groups without preconceived judgments about which foods commonly are consumed together. Investigations of the possible association of dietary patterns with SCD are lacking.

In previous work, we derived dietary patterns within the REGARDS (Reasons for Geographic and Racial Differences in Stroke) cohort with factor analysis[11] and investigated associations of these dietary patterns with CHD events.[12,13] In the first study, after multivariable adjustment, highest adherers to the so-called Southern dietary pattern (characterized by added fats, fried food, eggs, organ and processed meats, and sugar-sweetened beverages) experienced a 56% higher risk of incident acute CHD compared with lowest consumers of this dietary pattern.[12] In a subsequent analysis, our group investigated the associations of these same dietary patterns plus the Mediterranean diet score with recurrent CHD events and all-cause mortality in REGARDS participants with documented CHD at baseline.[13] In multivariable-adjusted models, the Mediterranean diet score was inversely associated with risk of recurrent CHD events, the Southern dietary pattern was adversely associated with risk of all-cause mortality, and the Mediterranean diet score was inversely associated with risk of all-cause mortality.

In the current study, we sought to further our analyses and address a notable gap in the published literature by investigating the possible associations of the Mediterranean diet score and various dietary patterns with risk of SCD in the REGARDS cohort. We hypothesized that the Mediterranean diet score and adherence to the plant-based dietary pattern would be inversely associated with risk of SCD, while adherence to the convenience and Southern dietary patterns would be positively associated. In addition, we made an a priori decision to further investigate the association of the diet score and dietary patterns with risk of SCD in participants with and without a history of CHD at baseline, since the risk factor profile can vary greatly according to CHD status. In addition to including men, women, Blacks, and Whites, a strength of the REGARDS study is that it includes adjudicated SCD events, obviating the often-unreliable data on SCD obtained solely from death certificates.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

Details on the design and methods of REGARDS have been published.[14] Briefly, REGARDS is a national, population-based, longitudinal cohort of 30 239 community-dwelling Black and White women and men aged ≥45 years, identified via mail and telephone using commercially available lists of US residents, enrolled from 2003 to 2007. The sampling scheme included 30% of participants from the stroke belt (North Carolina, South Carolina, Georgia, Tennessee, Alabama, Mississippi, Arkansas, and Louisiana), 20% from the stroke buckle (the coastal plain of North Carolina, South Carolina, and Georgia), and 50% from elsewhere in the continental United States. The baseline cohort was 42% Black and 55% women. Exclusion criteria included race other than Black or White, active treatment for cancer, chronic medical conditions precluding long-term participation, cognitive impairment, current or impending residence in a nursing home, or inability to communicate in English. The study was approved by the institutional review boards at all participating institutions, and all participants provided written informed consent.

An initial telephone interview was conducted to survey participants and determine eligibility. Following verbal consent, demographic information (age, sex, race, education, income, and residence), lifestyle information (smoking history and physical activity), and medical history (history of hypertension, dyslipidemia, and diabetes mellitus) was collected by computer-assisted telephone interviewing. An in-home examination was conducted to perform various physical measurements (blood pressure, body weight, height, and waist circumference), medication inventory (including use of angiotensin-converting enzyme inhibitors, beta-blockers, statins, and aspirin [to reduce the chance of a heart attack or stroke]), Physical Component Summary-12 (a physical health summary scale), ECG, phlebotomy (from which blood lipid and glucose concentrations were determined), and urine collection.

Dietary Assessment

Diet was assessed at baseline with the Block 98 food frequency questionnaire (FFQ), a validated semi-quantitative FFQ that assessed usual dietary intake of 110 food items (NutritionQuest, Berkeley, CA).[15,16] For each line item on the FFQ, participants were asked how often, on average, they consumed the food (or group of foods) during the previous year, as well as the usual quantity of the food consumed. The FFQ also included adjustment questions (eg, inquiring about the type of milk consumed—low-fat, non-fat, etc) to further refine intake data. The FFQs were self-administered after the in-home visit and mailed to the REGARDS Operations Center, where they were reviewed for completeness, scanned, and forwarded to NutritionQuest for processing and analysis. Amounts of each food on the FFQ consumed by a participant were calculated by multiplying the frequency of consumption of that food by the usual amount consumed. A total of 56 food groups, on which dietary patterns were based, were derived using the 110 individual food variables on the FFQ using methods previously published.[11]

Dietary Patterns

Split sample replication was used to (1) derive the dietary patterns using exploratory factor analysis, and (2) test the patterns using confirmatory factor analysis.[17] Three separate analyses were conducted: (1) by sex (men/women); (2) by race (Black/White); and (3) by region (Southeastern US stroke belt/non-belt). Coefficients of congruence were determined for each stratification pair. The final number of factors retained was based on the eigenvalue (scree plot) and the solution providing the optimal congruence across sex, race, and region. Because congruence between sex, race, and region was high, final factor loadings were calculated using factor analysis with varimax rotation of 5 factors on the full sample. Patterns were named based on the major factor loadings of each pattern. Factor 1 loaded heavily on mixed dishes, pasta dishes, pizza, Mexican food, and Chinese food and was designated the "Convenience" pattern. Factor 2 had high factor loadings for vegetables, fruits, fruit juice, cereal, beans, fish, poultry, and yogurt and was named the "Plant-based" pattern. Factor 3 loaded on added sugars, desserts, chocolate, candy, and sweetened breakfast foods and was named the "Sweets" pattern. Factor 4 loaded heavily on added fats, fried food, eggs and egg dishes, organ meats, processed meats, and sugar-sweetened beverages, reflecting a culinary pattern observed in the Southeastern United States, and was named the "Southern" pattern. Factor 5 loaded highly on beer, wine, liquor, green leafy vegetables, tomatoes, and salad dressing and was designated the "Alcohol and Salad" pattern.

Mediterranean Diet Score

The Mediterranean diet score was derived according to previously published methods used in REGARDS,[18] based on the method of Trichopoulou and colleagues.[19] In brief, food group contributors to the Mediterranean diet score included those designated as "beneficial" (vegetables, fruits, legumes, cereals, fish), and "detrimental" (meat, dairy). One point was assigned for consumption that exceeded the sex-specific median for the "beneficial" groups or was below the median for "detrimental" food groups. For fat intake (eighth food category), the ratio of daily consumption (in grams) of monounsaturated lipids to saturated lipids was used, and the median was calculated separately for each sex. Participants with ratios at or above the sex-specific median were assigned a value of 1, and those with ratios below the sex-specific median were assigned a value of 0. Moderate alcohol consumption (ninth food category) was defined as >0 and ≤ 7 drinks per week for women and >0 and ≤ 14 drinks per week for men. More-than-moderate consumption was defined as >7 drinks per week for women and >14 drinks per week for men. Participants were assigned a score of 1 for moderate consumption and a score of 0 for the other 2 categories (zero and more-than-moderate consumption). Summing scores for the 9 food groups resulted in a possible range of scores of 0 to 9, with a higher score reflecting higher adherence to the Mediterranean diet.

Covariates

Physically active was defined as ≥4 days of exercise (enough to work up a sweat) per week. Hypertension was defined as systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥80 mm Hg or self-reported current use of medication to control blood pressure. Dyslipidemia was defined as total cholesterol ≥240 mg/dL and/or low-density lipoprotein cholesterol ≥160 mg/dL and/or high-density lipoprotein cholesterol ≤40 mg/dL or self-reported current use of medication to control cholesterol. Diabetes mellitus was defined as fasting glucose ≥126 mg/dL and/or non-fasting glucose ≥200 mg/dL or self-reported current use of medication to control blood sugar.

Outcome Ascertainment

To assess for cardiovascular disease events and deaths during follow-up, REGARDS participants or their next of kin were contacted by telephone in regular, 6-month intervals. Deaths also were identified through receipt of a letter from a proxy stating that the participant had died or through a search of the Social Security Death Index. Once a death was identified, an exit interview with the next of kin was conducted and, if possible, medical records were obtained, including those from the last hospitalization before death. These data, as well as baseline REGARDS data and data on cardiovascular disease events during follow-up, were reviewed by 2 trained adjudicators to assign a cause of death. Disagreements between adjudicators on cause of death were resolved by an adjudication committee.

The definition of SCD was consistent with that proposed by the National Heart, Lung, and Blood Institute-sponsored expert panel: (1) unexpected death without an obvious extracardiac cause occurring with a rapid witnessed collapse; and (2) for unwitnessed events, SCD is defined as an event that occurs within 1 hour after symptom onset or an unexpected death without obvious extracardiac cause that occurred within the previous 24 hours.[20] Deaths occurring in the emergency department could have been adjudicated as SCD, but not those occurring as a consequence of acute trauma, intoxications, or the culmination of a terminal illness (eg, cancer or end-stage lung disease).[21] It is important to note that simply having a death certificate with cardiac arrest as the cause of death was not sufficient to assign SCD as the cause of death.

Statistical Analysis

Of 30 239 REGARDS participants at baseline, we excluded 56 participants missing baseline information, 440 participants who were lost to follow-up, and 8674 participants who were missing information required for the calculation of Mediterranean diet score or derivation of dietary patterns (ie, missing FFQ data altogether, had >15% missing data on the FFQ, or had implausible reported energy intakes [<800 or >5000 kcal/day in men and <500 or >4500 kcal/day in women]). This resulted in a final sample of 21 069 (Figure 1).

We categorized adherence to the 5 dietary patterns into quartiles, with quartile 1 representing the lowest adherence to each pattern and quartile 4 representing

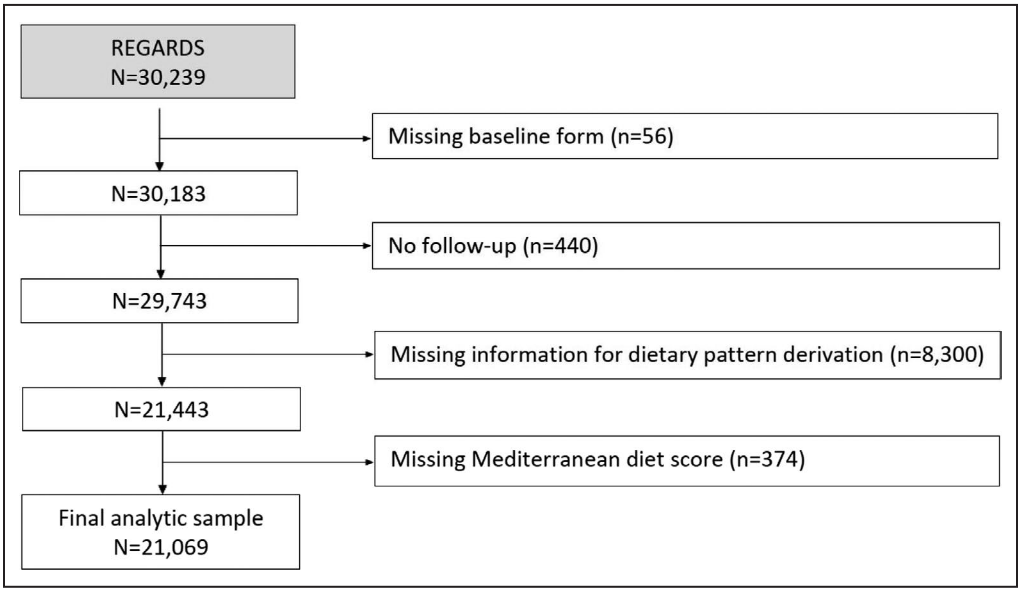

Figure Participant exclusion cascade.
REGARDS indicates Reasons for Geographic and Racial Differences in Stroke study.

the highest adherence to the pattern. We categorized the Mediterranean diet score into 3 groups representing lowest to highest adherence to the Mediterranean diet. Quartiles proved not to be appropriate for analyses of the Mediterranean diet score. Specifically, attempting to categorize Mediterranean diet scores (originally on a scale of 0–9 to assess adherence) into 4 somewhat uniform groups was not possible because of the distribution of the scores—this would have resulted in at least 1 category with a small number compared with the other groups. Therefore, 3 groups that were more equal were created based on the scores: 0 to 3, 4 to 5, and 6 to 9.

We calculated descriptive statistics (including proportions and measures of central tendency) for demographic, socioeconomic, lifestyle, anthropometric, medical history, and medication variables at the baseline assessment according to SCD status using the Chi-square test (for categorical variables) and analysis of variance (for continuous variables). We used Cox proportional hazards regression to examine the risk of SCD events associated with the Mediterranean diet score and adherence to each of the 5 dietary patterns, using the lowest group/quartile of adherence (ie, group 1/quartile 1) as the referent group/quartile throughout. Years since study entry was the time metric, with participants censored at the date of an SCD event, date of withdrawal from the study, date of death from other cause, or December 31, 2017, whichever came first. We examined Schoenfeld residuals and confirmed that proportional hazards assumptions were met. The base model (model 1) included age, sex, and race. The multivariable-adjusted model (model 2) included factors in model 1 plus socioeconomic factors (education, household income), region, lifestyle factors (smoking, physical activity), total energy intake, anthropometric factors (waist circumference, body mass index), systolic blood pressure, medical history (CHD at baseline, adjudicated CHD events during follow-up, hypertension, dyslipidemia, diabetes mellitus), medication use (use of angiotensin-converting enzyme inhibitors, beta-blockers, statins, aspirin [to reduce the chance of a heart attack or stroke]), and the Physical Component Summary-12.

In an a priori-determined analysis, we conducted the analyses above separately in participants with and without a history of CHD at baseline—self-reported myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or ECG evidence of myocardial infarction. As a sensitivity analysis, we examined the possible interaction by CHD event during follow-up on the associations of the Mediterranean diet score and dietary patterns with risk of SCD.

A total of 2276 participants (10.8% of the 21 069 participants) were missing information for at least 1 covariate of interest. Variables with the largest proportion of missing data included Physical Component Summary-12 (3.9%), diabetes mellitus status (3.4%), dyslipidemia status (3.3%), and physical activity (1.3%). All other characteristics had ≤1% missing data. We repeated the analyses using the multiply imputed data derived from chained equations and with fully conditional specification.

We performed analyses using SAS statistical software, version 9.4 (SAS Institute, Cary, NC) and Stata, version 14.2 (StataCorp, College Station, TX). A *P* value of <0.05 was considered statistically significant.

RESULTS

Participant characteristics overall and stratified by SCD status are presented in Table 1. Over a mean±SD follow-up of 9.8±3.8 years, there were 401 SCD events (1.9% of the analytic sample). At enrollment, participants who did not experience SCD were significantly younger, more likely to be women, more likely to have at least a high school education, and less likely to have an annual household income <$20 000/year compared with those experiencing an SCD event. They also were less likely to be current smokers and had significantly lower mean waist circumference, body mass index, and systolic blood pressure. Participants who did not experience SCD also were less likely to have CHD at baseline, an adjudicated CHD event during follow-up, or history of hypertension, dyslipidemia, and diabetes mellitus, and less likely to be current users of angiotensin-converting enzyme inhibitors, beta-blockers, statins, and aspirin (to reduce the chance of heart attack or stroke) compared with those with an SCD event. Finally, participants without SCD had significantly higher scores on the Physical Component Summary-12 compared with those with SCD.

In the model adjusted for only age, sex, and race, the Mediterranean diet score was inversely associated with risk of SCD, comparing group 3 (highest scores) with group 1 (lowest scores): hazard ratio (HR), 0.59 (95% CI, 0.45–0.78; P_{trend}=0.0001) (Table 2). In the fully adjusted model, the association was attenuated, but there was a trend toward an inverse association: HR, 0.74 (95% CI, 0.55–1.01; P_{trend}=0.07).

In the minimally adjusted model, the Southern dietary pattern was positively associated with the risk of SCD, comparing quartile 4 (highest adherence) with quartile 1 (lowest adherence): HR, 2.22 (95% CI, 1.61–3.05; P_{trend}<0.0001) (Table 3). In the fully adjusted model, the association was attenuated, but there was a trend toward a positive association: HR, 1.46 (95% CI, 1.02–2.10; P_{trend}=0.06). No other

Table 1. Characteristics of Study Participants Overall and According to SCD Status

Characteristic	Total, N=21 069	No SCD, n=20 668	SCD, n=401	$P_{difference}$
Age, y	64.9±9.3	64.8±9.2	69.1±9.4	<0.001
Sex, women	11 794 (56.0)	11 650 (56.4)	144 (35.9)	<0.001
Race, Black	6999 (33.2)	6859 (33.2)	140 (34.9)	0.47
Education, < high school graduate	2020 (9.6)	1965 (9.5)	55 (13.8)	0.0043
Household income <$20 000/y	3316 (15.7)	3228 (15.6)	88 (21.9)	<0.001
Residence in US Southeast	11 865 (56.3)	11 629 (56.3)	236 (58.9)	0.30
Current smoker	2845 (13.6)	2772 (13.5)	73 (18.3)	0.0056
Physically active*	6322 (30.4)	6207 (30.4)	115 (29.1)	0.57
Total energy intake, kcal/d	1707±710	1707±710	1753±745	0.20
Waist circumference, cm	95.4±15.5	95.3±15.5	102.6±16.4	<0.001
Body mass index, kg/m^2	29.1±6.1	29.0±6.1	30.0±6.6	0.0012
Systolic blood pressure, mm Hg	126.8±16.3	126.7±16.2	132.1±17.8	<0.001
Hypertension†	15 147 (72.1)	14 801 (71.8)	346 (86.7)	<0.001
Dyslipidemia‡	12 117 (59.5)	11 847 (59.3)	270 (69.1)	<0.001
Diabetes mellitus§	3856 (18.9)	3724 (18.7)	132 (33.8)	<0.001
ACE inhibitor use	4583 (21.8)	4428 (21.4)	155 (38.7)	<0.001
Beta-blocker use	4615 (21.9)	4470 (21.6)	145 (36.2)	<0.001
Statin use	6731 (31.9)	6564 (31.8)	167 (41.6)	<0.001
Aspirin use‖	8449 (40.1)	8227 (39.8)	222 (55.4)	<0.001
Physical Component Summary-12	46.9±10.4	46.9±10.4	43.0±11.0	<0.001
CHD at baseline¶	3585 (17.0)	3405 (16.5)	180 (44.9)	<0.001
Adjudicated CHD event during follow-up	2231 (10.6)	2145 (10.4)	86 (21.5)	<0.001

Data are presented as mean±SD or frequency (percent). ACE indicates angiotensin-converting enzyme; CHD, coronary heart disease; SCD, sudden cardiac death.

*Physically active defined as ≥4 days of exercise (enough to work up a sweat) per week.

†Hypertension defined as systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥80 mm Hg or self-reported current use of medication to control blood pressure.

‡Dyslipidemia defined as total cholesterol ≥240 mg/dL and/or low-density lipoprotein cholesterol ≥160 mg/dL and/or high-density lipoprotein cholesterol ≤40 mg/dL or self-reported current use of medication to control cholesterol.

§Diabetes mellitus defined as fasting glucose ≥126 mg/dL and/or non-fasting glucose ≥200 mg/dL or self-reported current use of medication to control blood sugar.

‖To reduce the chance of a heart attack or stroke.

¶CHD defined as self-reported myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or ECG evidence of myocardial infarction.

dietary patterns were significantly associated with risk of SCD.

In an a priori-defined analysis, when stratifying results according to history of CHD at baseline ($P_{interaction}$=0.20), in participants with no history of CHD at baseline, the Mediterranean diet score was inversely associated with risk of SCD, comparing group 3 with group 1, in the minimally adjusted model: HR, 0.49 (95% CI, 0.34–0.71; P_{trend}=0.0022) (Table 4). A 41% lower risk of SCD was demonstrated, comparing group 3 of the Mediterranean diet score with group 1, in the fully adjusted model: HR, 0.59 (95% CI, 0.40–0.89; P_{trend}=0.0363). There was no association of the Mediterranean diet score with risk of SCD in participants with a history of CHD at baseline.

Results of the a priori-defined analysis of the association of adherence to the various dietary patterns with risk of SCD stratified by history of CHD at baseline ($P_{interaction}$=0.12–0.87) are presented in Table 5. In participants with no history of CHD at baseline, adherence to the Southern dietary pattern was positively associated with risk of SCD, comparing quartile 4 with quartile 1, in the minimally adjusted model: HR, 2.34 (95% CI, 1.51–3.64; P_{trend}=0.0004); however, the association was attenuated and no longer statistically significant in the fully adjusted model, although in the same range as in the model using the whole cohort: HR, 1.48 (95% CI, 0.90–2.45; P_{trend}=0.26). There were no associations with any of the other dietary patterns and risk of SCD in

Table 2. Risk of Sudden Cardiac Death by Mediterranean Diet Score Group

Diet Score	Model	Group 1 (Score 0–3)	Group 2 (Score 4–5)	Group 3 (Score 6–9)	P_{trend}
Mediterranean		n=6725 (140*)	n=8873 (175)	n=5471 (86)	
		22.0†	20.1	15.6	
	1‡	1 (referent)	0.82 (0.66–1.03)	0.59 (0.45–0.78)	0.0001
	2§	1 (referent)	0.97 (0.76–1.23)	0.74 (0.55–1.01)	0.07

Data are presented as hazard ratio (95% CI), unless stated otherwise.
*Number of events.
†Crude rate of sudden cardiac death events per 10 000 person-years.
‡Model 1 adjusts for age, sex, and race.
§Model 2 adjusts for age, sex, race, education, household income, region, smoking, physical activity, total energy intake, waist circumference, body mass index, systolic blood pressure, coronary heart disease at baseline, adjudicated coronary heart disease events during follow-up, hypertension, dyslipidemia, diabetes mellitus, angiotensin-converting enzyme inhibitor use, beta-blocker use, statin use, aspirin use (to reduce the chance of a heart attack or stroke), and Physical Component Summary-12.

multivariable-adjusted analyses in participants with no history of CHD at baseline.

In participants with a history of CHD at baseline, adherence to the convenience pattern was positively associated with risk of SCD, comparing quartile 4 with quartile 1, in the minimally adjusted model: HR, 1.63 (95% CI, 1.07–2.48; P_{trend}=0.0463). This association was of the same magnitude but no longer statistically significant in the fully adjusted model: HR, 1.64 (95% CI, 0.98–2.73; P_{trend}=0.12). Conversely, adherence to the sweets pattern was inversely associated with risk of SCD, comparing quartile 4 with quartile 1, in the fully adjusted model: HR, 0.49 (95% CI, 0.28–0.88; P_{trend}=0.0093). The Southern dietary pattern was positively associated with risk of SCD, comparing quartile 4 with quartile, 1 in the minimally adjusted model: HR, 1.97 (95% CI, 1.24–3.13; P_{trend}=0.0011). The association was attenuated and was no longer statistically

Table 3. Risk of Sudden Cardiac Death by Quartile of Adherence to the Various Dietary Patterns

Dietary Pattern	Model	Quartile 1 (Lowest Adherence)	Quartile 2	Quartile 3	Quartile 4 (Highest Adherence)	P_{trend}
Convenience		n=5265 (103*)	n=5247 (98)	n=5286 (93)	n=5271 (107)	
		20.9†	19.3	17.8	20.1	
	1‡	1 (referent)	1.02 (0.77–1.34)	0.95 (0.72–1.27)	1.19 (0.89–1.57)	0.34
	2§	1 (referent)	1.05 (0.77–1.43)	1.14 (0.83–1.57)	1.32 (0.93–1.86)	0.11
Plant-based		n=5257 (90)	n=5259 (115)	n=5283 (98)	n=5270 (98)	
		17.8	22.4	18.9	18.8	
	1	1 (referent)	1.12 (0.85–1.48)	0.95 (0.71–1.26)	0.95 (0.71–1.27)	0.46
	2	1 (referent)	1.16 (0.86–1.57)	1.01 (0.73–1.40)	1.19 (0.85–1.67)	0.51
Sweets		n=5260 (98)	n=5270 (117)	n=5272 (92)	n=5267 (94)	
		19.0	22.7	17.8	18.5	
	1	1 (referent)	1.13 (0.87–1.48)	0.87 (0.65–1.16)	0.93 (0.70–1.23)	0.27
	2	1 (referent)	1.14 (0.85–1.53)	0.83 (0.60–1.16)	0.81 (0.56–1.17)	0.11
Southern		n=5277 (65)	n=5282 (91)	n=5259 (106)	n=5251 (139)	
		11.9	17.4	21.0	28.6	
	1	1 (referent)	1.42 (1.03–1.96)	1.62 (1.18–2.22)	2.22 (1.61–3.05)	<0.0001
	2	1 (referent)	1.18 (0.84–1.66)	1.13 (0.80–1.60)	1.46 (1.02–2.10)	0.06
Alcohol and salad		n=5264 (100)	n=5263 (105)	n=5272 (96)	n=5270 (100)	
		20.1	20.7	18.5	18.8	
	1	1 (referent)	1.10 (0.84–1.45)	1.01 (0.76–1.34)	1.06 (0.80–1.42)	0.84
	2	1 (referent)	1.02 (0.76–1.38)	0.94 (0.69–1.28)	0.94 (0.68–1.30)	0.61

Data are presented as hazard ratio (95% CI), unless stated otherwise.
*Number of events.
†Crude rate of sudden cardiac death events per 10 000 person-years.
‡Model 1 adjusts for age, sex, and race.
§Model 2 adjusts for age, sex, race, education, household income, region, smoking, physical activity, total energy intake, waist circumference, body mass index, systolic blood pressure, coronary heart disease at baseline, adjudicated coronary heart disease events during follow-up, hypertension, dyslipidemia, diabetes mellitus, angiotensin-converting enzyme inhibitor use, beta-blocker use, statin use, aspirin use (to reduce the chance of a heart attack or stroke), and Physical Component Summary-12.

Table 4. Risk of Sudden Cardiac Death by Mediterranean Diet Score Group According to Coronary Heart Disease Status at Baseline

Diet Score	Model	Group 1 (Score 0–3)	Group 2 (Score 4–5)	Group 3 (Score 6–9)	P_{trend}
No history of coronary heart disease at baseline					
Mediterranean		n=5572 (85*)	n=7364 (93)	n=4548 (43)	
		15.8†	12.6	9.2	
	1‡	1 (referent)	0.72 (0.54–0.97)	0.49 (0.34–0.71)	0.0022
	2§	1 (referent)	0.80 (0.58–1.10)	0.59 (0.40–0.89)	0.0363
History of coronary heart disease at baseline					
Mediterranean		n=1153 (55)	n=1509 (82)	n=923 (43)	
		56.4	61.9	49.5	
	1	1 (referent)	1.02 (0.72–1.43)	0.77 (0.52–1.15)	0.13
	2	1 (referent)	1.25 (0.85–1.83)	1.00 (0.63–1.59)	0.48

Data are presented as hazard ratio (95% CI), unless stated otherwise.
*Number of events.
†Crude rate of sudden cardiac death events per 10 000 person-years.
‡Model 1 adjusts for age, sex, and race.
§Model 2 adjusts for age, sex, race, education, household income, region, smoking, physical activity, total energy intake, waist circumference, body mass index, systolic blood pressure, adjudicated coronary heart disease events during follow-up, hypertension, dyslipidemia, diabetes mellitus, angiotensin-converting enzyme inhibitor use, beta-blocker use, statin use, aspirin use (to reduce the chance of a heart attack or stroke), and Physical Component Summary-12.

significant in the fully adjusted model but was of a similar magnitude as the overall fully adjusted result as well as the result for participants without a history of CHD at baseline: HR, 1.37 (95% CI, 0.81–2.31; P_{trend}=0.18). No other dietary patterns were associated with risk of SCD in multivariable-adjusted analyses in participants with a history of CHD at baseline.

As a sensitivity analysis, we examined the possible interaction by CHD event during follow-up, and none of the heterogeneous *P* values were >0.10. Further, the direction of association was similar, although slightly but not statistically significantly stronger in those with no CHD in follow-up, across strata of CHD during follow-up (Tables S1 and S2). Finally, the results including imputed values for missing exposure and covariate information were not appreciably different from the results without imputation (data not shown).

DISCUSSION

In this analysis of participants in the ongoing REGARDS study, we observed a trend toward an inverse association of the Mediterranean diet score and risk of SCD overall after ≈10 years of follow-up. Further analysis revealed that this association was evident only in participants with no history of CHD at baseline. The Southern dietary pattern showed a trend toward a positive association with risk of SCD overall, but although the results were of similar magnitude, they were not statistically significant in the stratified analyses. In participants with a history of CHD at baseline, the sweets pattern was inversely associated with risk of SCD.

Few published analyses have reported on the possible association of the Mediterranean diet and the risk of SCD, and they did not include men or sizable proportions of Black participants, as the present study did. In agreement with the inverse association of the Mediterranean diet score and risk of SCD in the current analysis, in the Women's Health Initiative, participants in the highest quintile of Mediterranean diet score experienced a 36% lower risk of SCD compared with participants in the lowest quintile after multivariable adjustment.[5] Likewise, the alternate Mediterranean diet score was inversely associated with risk of SCD in the Nurses' Health Study.[6]

We know of no published studies investigating the possible associations of dietary patterns with risk of SCD. However, previous studies have investigated possible associations between individual foods and risk of SCD. For example, the risk of SCD was 47% lower in men who consumed nuts ≥2 times per week compared with men who rarely or never consumed nuts after controlling for known cardiac risk factors and other dietary factors in the US Physicians' Health Study.[22] In addition to the non-marine n-3 fatty acid α-linolenic acid, other potential antiarrhythmic components of nuts include magnesium, potassium, and vitamin E.

Fish consumption has been associated with a reduced risk of SCD in previous studies, with n-3 fatty acids, abundant in fatty fish, as the nutrient purported to be responsible for this protective association.[7] Potential mechanisms through which n-3 fatty acids might influence SCD risk include effects on resting heart rate, systolic and diastolic blood pressure, systemic arteriolar resistance and left ventricular diastolic filling, vascular endothelial function, circulating triglyceride concentrations, inflammatory pathways, and

Table 5. Risk of Sudden Cardiac Death by Quartile of Adherence to the Various Dietary Patterns According to Coronary Heart Disease Status at Baseline

Dietary Pattern	Model	Quartile 1 (Lowest Adherence)	Quartile 2	Quartile 3	Quartile 4 (Highest Adherence)	P_{trend}
No history of coronary heart disease at baseline						
Convenience		n=4255 (60*)	n=4334 (53)	n=4423 (56)	n=4472 (52)	
		14.7[†]	12.4	12.5	11.3	
	1[‡]	1 (referent)	0.95 (0.66–1.38)	1.00 (0.69–1.45)	0.99 (0.67–1.46)	0.98
	2[§]	1 (referent)	0.92 (0.61–1.39)	1.17 (0.78–1.75)	1.06 (0.66–1.70)	0.56
Plant-based		n=4373 (54)	n=4323 (64)	n=4393 (49)	n=4395 (54)	
		12.6	14.9	11.1	12.2	
	1	1 (referent)	1.04 (0.72–1.50)	0.77 (0.52–1.15)	0.86 (0.59–1.27)	0.23
	2	1 (referent)	1.10 (0.74–1.64)	0.88 (0.57–1.35)	1.09 (0.70–1.70)	1.00
Sweets		n=4416 (52)	n=4359 (62)	n=4362 (48)	n=4347 (59)	
		11.8	14.3	11.0	13.7	
	1	1 (referent)	1.19 (0.82–1.73)	0.92 (0.62–1.36)	1.18 (0.81–1.72)	0.71
	2	1 (referent)	1.25 (0.83–1.87)	0.95 (0.61–1.48)	1.18 (0.72–1.93)	0.80
Southern		n=4472 (33)	n=4375 (54)	n=4307 (52)	n=4330 (82)	
		7.1	12.2	12.3	19.9	
	1	1 (referent)	1.62 (1.05–2.51)	1.50 (0.96–2.35)	2.34 (1.51–3.64)	0.0004
	2	1 (referent)	1.45 (0.91–2.31)	1.17 (0.72–1.89)	1.48 (0.90–2.45)	0.26
Alcohol and salad		n=4310 (63)	n=4329 (54)	n=4383 (51)	n=4462 (53)	
		15.1	12.7	11.5	11.6	
	1	1 (referent)	0.93 (0.65–1.34)	0.88 (0.60–1.28)	0.93 (0.64–1.37)	0.65
	2	1 (referent)	0.81 (0.55–1.20)	0.80 (0.53–1.20)	0.79 (0.52–1.22)	0.28
History of coronary heart disease at baseline						
Convenience		n=1010 (43)	n=913 (45)	n=863 (37)	n=799 (55)	
		50.2	56.0	47.9	74.9	
	1	1 (referent)	1.18 (0.77–1.80)	1.00 (0.64–1.57)	1.63 (1.07–2.48)	0.0463
	2	1 (referent)	1.25 (0.78–1.98)	1.04 (0.62–1.73)	1.64 (0.98–2.73)	0.12
Plant-based		n=884 (36)	n=936 (51)	n=890 (49)	n=875 (44)	
		47.5	61.6	62.5	55.0	
	1	1 (referent)	1.22 (0.79–1.87)	1.22 (0.79–1.89)	1.07 (0.68–1.68)	0.83
	2	1 (referent)	1.34 (0.83–2.14)	1.28 (0.78–2.11)	1.40 (0.83–2.37)	0.27
Sweets		n=844 (46)	n=911 (55)	n=910 (44)	n=920 (35)	
		61.0	68.3	54.0	44.1	
	1	1 (referent)	1.06 (0.72–1.58)	0.84 (0.55–1.28)	0.69 (0.44–1.07)	0.05
	2	1 (referent)	1.05 (0.68–1.63)	0.72 (0.45–1.17)	0.49 (0.28–0.88)	0.0093
Southern		n=805 (32)	n=907 (37)	n=952 (54)	n=921 (57)	
		41.5	45.4	65.2	75.5	
	1	1 (referent)	1.14 (0.71–1.83)	1.63 (1.05–2.54)	1.97 (1.24–3.13)	0.0011
	2	1 (referent)	0.87 (0.52–1.47)	1.05 (0.64–1.72)	1.37 (0.81–2.31)	0.18
Alcohol and salad		n=954 (37)	n=934 (51)	n=889 (45)	n=808 (47)	
		45.1	62.3	57.8	62.7	
	1	1 (referent)	1.39 (0.91–2.13)	1.34 (0.86–2.10)	1.42 (0.91–2.22)	0.17
	2	1 (referent)	1.39 (0.88–2.22)	1.20 (0.74–1.94)	1.14 (0.68–1.90)	0.78

Data are presented as hazard ratio (95% CI), unless stated otherwise.
*Number of events.
[†]Crude rate of sudden cardiac death events per 10 000 person-years.
[‡]Model 1 adjusts for age, sex, and race.
[§]Model 2 adjusts for age, sex, race, education, household income, region, smoking, physical activity, total energy intake, waist circumference, body mass index, systolic blood pressure, adjudicated coronary heart disease events during follow-up, hypertension, dyslipidemia, diabetes mellitus, angiotensin-converting enzyme inhibitor use, beta-blocker use, statin use, aspirin use (to reduce the chance of a heart attack or stroke), and Physical Component Summary-12.

autonomic activity.[7] Laboratory and animal studies indicate that n-3 fatty acids have strong antiarrhythmic properties.[23] Fish consumption was inversely associated with risk of SCD in the Physicians' Health Study, with an apparent threshold effect at a consumption level of 1 fish meal per week.[24] Consumption of fatty, but not lean, fish was inversely associated with risk of SCD in the Zutphen Study.[25] Both α-linolenic acid and marine n-3 fatty acids (eicosapentanoic acid and docosahexanoic acid) were significantly inversely associated with risk of SCD in the Nurses' Health Study.[26,27]

The Mediterranean diet prominently features foods such as nuts and fish, which could account for some of the inverse association of this diet with risk of SCD. Conversely, the Southern dietary pattern in our study did not load heavily on these foods, and generally loaded heavily on foods with a higher saturated and lower n-3 (polyunsaturated) fatty acid content, which could have contributed to the trend toward a positive association of this dietary pattern with risk of SCD that was observed.

It is interesting to note that when we stratified our results on history of CHD at baseline, we observed a significant inverse association of the Mediterranean diet score with risk of SCD in participants with no history of CHD at baseline, but observed no association in those with a history of CHD at baseline, which was somewhat unexpected since the Mediterranean diet score was shown to be inversely associated with recurrent CHD events and mortality in patients with CHD in our previous work.[13] One possible explanation of this was that diet was rendered less important by other, more powerful, risk factors for SCD in those with a history of CHD. However, the convenience dietary pattern showed a trend toward a positive association with risk of SCD in those with a history of CHD, but not in those with no history of CHD at baseline. Another possible explanation is that individuals may change their diets in response to a diagnosis of CHD, so actually may have been following the Mediterranean or similar healthy diet for only a limited time before their SCD event, after consuming a less heart-healthy diet for most of their adult lives. More follow-up time may be needed to observe an association with risk of SCD resulting from such change in diet. We have no viable explanation for the inverse association of the sweets dietary pattern with risk of SCD in those with a history of CHD at baseline. We again point out that there were no statistically significant interactions by baseline CHD status of the associations of the Mediterranean diet score or various dietary patterns with risk of SCD, likely because of limited statistical power. The decision to present results stratified on baseline CHD status was an a priori decision attributable to possible differences in the risk factor profile depending on CHD status.

Strengths of this study included the large, population-based sample with sociodemographic and regional diversity, including the large proportion of Black participants; a comprehensive assessment of diet with a recognized instrument; derivation of dietary patterns using a rigorous method—factor analysis—based on the actual dietary data collected in the population of interest rather than dietary patterns created a priori based on the authors' opinions on what defines various dietary patterns; and expert adjudication of study end points.

It should be noted that the Block 98 FFQ has not been validated in the REGARDS population. Measurement error is a potential limitation in any study relying on recall of dietary intake, including using an FFQ. It is possible that inaccuracies in reporting dietary intake may have resulted in misclassification. However, this would tend to bias results toward the null, potentially reducing the magnitude of the associations that were observed in this analysis. Unfortunately, correction for potential measurement error was not possible. In addition, diet was assessed at only one time point, so potential changes in diet could not be accounted for. While those who did not provide a completed FFQ showed no differences in sex compared with those who completed the FFQ, they were more likely to be Black race, less educated, and have a lower income. Non-completers also were slightly more likely to be current smokers and inactive and had a slightly lower body mass index, compared with those who completed the FFQ. The presence of CHD at baseline was based partially on self-report, which could have introduced bias. It is possible that selection bias may have resulted from using commercially available lists for recruitment, as not all people have listed telephone numbers and/or a mailing address. Finally, the results may not be generalizable to groups other than White and Black race in the United States.

In conclusion, in REGARDS participants with no history of CHD at baseline, a higher Mediterranean diet score was associated with a lower risk of SCD. Adherence to the Southern dietary pattern showed a trend toward a positive association with risk of SCD in the overall cohort, while adherence to the sweets pattern was inversely associated with risk of SCD in participants with a history of CHD at baseline.

ARTICLE INFORMATION

Received October 27, 2020; accepted April 29, 2021.

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Acknowledgments

The authors thank the other investigators, the staff, and the participants of the REGARDS study for their valuable contributions. A full list of participating

REGARDS investigators and institutions can be found at: https://www.uab.edu/soph/regardsstudy/.

Sources of Funding

This research project is supported by cooperative agreement U01 NS041588 co-funded by the National Institute of Neurological Disorders and Stroke and the National Institute on Aging, National Institutes of Health, Department of Health and Human Services. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke or the National Institute on Aging. Representatives of the National Institute of Neurological Disorders and Stroke were involved in the review of the manuscript but were not directly involved in the collection, management, analysis, or interpretation of the data. Additional funding was provided by National Heart, Lung, and Blood Institute (grant number 5F31HL129701). Representatives of the National Heart Lung, and Blood Institute did not have any role in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, or the preparation or approval of the manuscript. General Mills Bell Institute of Health and Nutrition generously supported the scanning and analysis of the dietary questionnaires used in this study.

Disclosures

None.

Supplementary Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Risk of Sudden Cardiac Death by Mediterranean Diet Score Group According to Coronary Heart Disease Status during Follow-up.

Diet score	Model	Group 1 (score 0-3)	Group 2 (score 4-5)	Group 3 (score 6-9)	P_{trend}
Without a non-fatal coronary heart disease event during follow-up					
Mediterranean		n = 5957 (107*)	n = 7925 (145)	n = 4956 (63)	
		19.2[†]	18.8	12.6	
	1[‡]	1 (referent)	0.89 (0.69-1.14)	0.55 (0.41-0.76)	0.0003
	2[§]	1 (referent)	1.01 (0.77-1.34)	0.69 (0.49-0.99)	0.06
With a non-fatal coronary heart disease event during follow-up					
Mediterranean		n = 768 (33)	n = 948 (30)	n = 515 (23)	
		42.7	30.8	42.7	
	1[‡]	1 (referent)	0.66 (0.40-1.08)	0.85 (0.50-1.45)	0.46
	2[§]	1 (referent)	0.74 (0.43-1.26)	0.92 (0.50-1.70)	0.70

Data are presented as hazard ratio (95% confidence interval), unless stated otherwise.

[*]Number of events.

[†]Crude rate of sudden cardiac death events per 10,000 person-years.

[‡]Model 1 adjusts for age, sex, and race.

[§]Model 2 adjusts for age, sex, race, education, household income, region, smoking, physical activity, total energy intake, waist circumference, body mass index, systolic blood pressure, coronary heart disease at baseline, hypertension, dyslipidemia, diabetes mellitus, angiotensin-converting enzyme inhibitor use, beta-blocker use, statin use, aspirin use (to reduce the chance of a heart attack or stroke), and Physical Component Summary-12.

Table S2. Risk of Sudden Cardiac Death by Quartile of Adherence to the Various Dietary Patterns According to Coronary Heart Disease Status during Follow-up.

Dietary pattern	Model	Quartile 1 (lowest adherence)	Quartile 2	Quartile 3	Quartile 4 (highest adherence)	P_{trend}
Without a non-fatal CHD event during follow-up						
Convenience		n = 4675 (83*)	n = 4715 (74)	n = 4737 (75)	n = 4711 (83)	
		19.0†	16.3	16.1	17.5	
	1‡	1 (referent)	0.96 (0.70-1.32)	0.97 (0.70-1.33)	1.15 (0.83-1.58)	0.43
	2§	1 (referent)	0.98 (0.69-1.39)	1.09 (0.76-1.55)	1.24 (0.84-1.84)	0.25
Plant-based		n = 4656 (72)	n = 4695 (91)	n = 4729 (76)	n = 4758 (76)	
		16.3	20.0	16.4	16.2	
	1	1 (referent)	1.09 (0.80-1.49)	0.91 (0.65-1.26)	0.91 (0.66-1.26)	0.34
	2	1 (referent)	1.13 (0.80-1.59)	0.99 (0.69-1.44)	1.17 (0.80-1.72)	0.60
Sweets		n = 4783 (76)	n = 4693 (93)	n = 4686 (73)	n = 4676 (73)	
		16.3	20.4	16.0	16.2	

	1	1 (referent)	1.20 (0.88-1.63)	0.92 (0.66-1.27)	0.95 (0.69-1.32)	0.40
	2	1 (referent)	1.19 (0.85-1.67)	0.88 (0.61-1.27)	0.82 (0.54-1.26)	0.21
Southern		n = 4774 (49)	n = 4744 (70)	n = 4654 (82)	n = 4666 (114)	
		10.0	15.0	18.5	26.7	
	1	1 (referent)	1.45 (1.00-2.09)	1.68 (1.17-2.41)	2.41 (1.68-3.47)	<.0001
	2	1 (referent)	1.21 (0.81-1.81)	1.23 (0.83-1.84)	1.67 (1.11-2.53)	0.02
Alcohol and Salad		n = 4737 (78)	n = 4713 (82)	n = 4691 (77)	n = 4697 (78)	
		17.5	18.1	16.8	16.6	
	1	1 (referent)	1.13 (0.83-1.54)	1.08 (0.78-1.49)	1.11 (0.80-1.54)	0.60
	2	1 (referent)	1.05 (0.75-1.47)	0.99 (0.70-1.40)	0.92 (0.63-1.33)	0.61
With a non-fatal CHD event during follow-up						
Convenience		n = 590 (20)	n = 532 (24)	n = 549 (18)	n = 560 (24)	
		34.7	44.6	31.4	40.0	
	1	1 (referent)	1.36 (0.75-2.47)	0.98 (0.51-1.88)	1.35 (0.73-2.52)	0.55
	2	1 (referent)	1.42 (0.74-2.73)	1.33 (0.66-2.67)	1.67 (0.79-3.51)	0.22
Plant-based		n = 601 (18)	n = 564 (24)	n = 554 (22)	n = 512 (22)	

		28.9	41.6	39.6	41.3	
	1	1 (referent)	1.30 (0.70-2.40)	1.20 (0.64-2.26)	1.21 (0.64-2.29)	0.65
	2	1 (referent)	1.32 (0.69-2.54)	1.10 (0.55-2.21)	1.28 (0.62-2.66)	0.66
Sweets		n = 477 (22)	n = 577 (24)	n = 586 (19)	n = 591 (21)	
		44.0	41.0	31.5	35.1	
	1	1 (referent)	0.88 (0.49-1.57)	0.68 (0.37-1.27)	0.80 (0.44-1.47)	0.36
	2	1 (referent)	0.92 (0.48-1.76)	0.68 (0.34-1.38)	0.74 (0.33-1.62)	0.32
Southern		n = 503 (16)	n = 538 (21)	n = 605 (24)	n = 585 (25)	
		30.2	38.3	38.9	42.3	
	1	1 (referent)	1.30 (0.67-2.49)	1.30 (0.68-2.47)	1.42 (0.73-2.78)	0.33
	2	1 (referent)	1.09 (0.56-2.14)	0.80 (0.40-1.60)	0.85 (0.39-1.83)	0.50
Alcohol and Salad		n = 527 (22)	n = 550 (23)	n = 581 (19)	n = 573 (22)	
		41.9	42.7	31.3	35.8	
	1	1 (referent)	1.05 (0.58-1.89)	0.78 (0.41-1.46)	0.89 (0.48-1.65)	0.52
	2	1 (referent)	0.97 (0.51-1.86)	0.76 (0.38-1.52)	1.00 (0.50-1.99)	0.82

Data are presented as hazard ratio (95% confidence interval), unless stated otherwise.

[*]Number of events.

[†]Crude rate of sudden cardiac death events per 10,000 person-years.

[‡]Model 1 adjusts for age, sex, and race.

[§]Model 2 adjusts for age, sex, race, education, household income, region, smoking, physical activity, total energy intake, waist circumference, body mass index, systolic blood pressure, coronary heart disease at baseline, hypertension, dyslipidemia, diabetes mellitus, angiotensin-converting enzyme inhibitor use, beta-blocker use, statin use, aspirin use (to reduce the chance of a heart attack or stroke), and Physical Component Summary-12.