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# Adherence to a Mediterranean diet and prediction of incident stroke

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## Abstract

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There are no conflicts of interest to disclose.

**Contributor’s statement**

Georgios Tsivgoulis had the idea for the paper and data analyses and wrote the first version of the manuscript
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Virginia G. Wadley: contributed to editing of the manuscript
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**Context—**There are limited data regarding the potential association of adherence to Mediterranean Diet (MeD) with incident stroke in non-Mediterranean populations.

**Objective—**We sought to assess the longitudinal association between greater adherence to MeD and lower risk of incident stroke both with and without adjustment for factors that are independently related to stroke burden by capitalizing on the large, sample of the REasons for Geographic And Racial Differences in Stroke (REGARDS) subjects.

**Design, Setting and Participants—**Prospective, population-based, cohort of 30,239 individuals enrolled in REGARDS Study 2003–2007, excluding participants with stroke history, missing demographic data and Food Frequency Questionnaires and unavailable follow-up information. Adherence to MeD was categorized using dichotomization and trichotomization of MeD-score.

**Main Outcome Measures—**Incident stroke diagnosed by expert panel review of medical records using clinical and neuroimaging data during a mean follow-up period of 6.5 years.

**Results—**Incident stroke was identified in 565 participants (2.8%; 497 cases of ischemic and 68 cases of hemorrhagic stroke) out of 20,197 individuals fulfilling the inclusion criteria. Low (HR versus high adherence: 1.28; 95%CI:1.00–1.63) and moderate (HR versus high adherence: 1.32; 95%CI:1.05–1.66) adherence to MeD were associated with higher risk of incident ischemic stroke (IS) in initial univariate analysis. After adjusting for demographics, vascular risk factors, blood pressure levels, and antihypertensive medications use, low adherence to MeD (MeD-score: 0–3) tended to be associated with a higher risk of incident IS [HR versus high adherence (MeD-score: 6–9): 1.29; 95%CI:0.99–1.67]. A similar relationship was documented for moderate adherence to MeD (MeD score: 4–5; HR versus high adherence: 1.25; 95%CI:0.98–1.58). After dichotomization of MeD-score, low adherence to MeD (MeD-score: 0–4) was independently associated with higher incidence of IS in multivariable analyses (HR: 1.27;95%CI:1.04–1.54). We documented no association ($p>0.5$) of dichotomized or trichotomized MeD-score with incident hemorrhagic stroke. There was no interaction of race ($p=0.38$) on the association of adherence to MeD with incident IS.

**Conclusions—**Low adherence to MeD appears to be associated with a higher risk of incident IS independent of numerous potential confounders. Adherence to MeD is not related to the risk of incident hemorrhagic stroke.

### Keywords

Mediterranean diet; stroke; ischemic; hemorrhagic; adherence; predictor

## Introduction

Recent data from American Heart Association (AHA) indicates that every year, more than 795,000 individuals in the United States (US) have a stroke, with cerebrovascular diseases accounting for almost 1 of every 18 deaths in the US.[1–3] On average, every 40 seconds, someone in the US has a stroke and every four minutes one American dies from stroke.[1,2] Stroke is a major cause of disability in the US and stroke-related costs are estimated to reach $34 billions each year.[1] By 2050, the incidence of stroke is estimated to more than double,

with particularly large increases in the elderly and in minority groups (particularly Hispanics).[4] Despite recent advances in acute stroke treatment, effective primary stroke prevention, by means of improved control of vascular risk factors, has the greatest potential to reduce its burden.[5] Epidemiological studies have identified hypertension, diabetes, atrial fibrillation, transient ischemic attack, hypercholesterolemia, smoking and carotid stenosis as risk factors for stroke.[6] However, only up to three quarters of all strokes can be attributed to these recognized risk factors.[5,7] In recent years, several dietary factors including salt or high saturated fatty acids intake, dietary fiber, olive oil, fresh fruit/vegetable intake and moderate alcohol consumption have been shown to exhibit harmful or protective effects on the risk and mortality from stroke.[6,8–10]

The traditional Mediterranean diet (MeD) is a dietary pattern characterized by high consumption of plant foods (vegetables, fruits, legumes and cereals), high intake of olive oil as principal source of monounsaturated fat, low intake of saturated fat with limited consumption of meat and dairy products and moderate intake of fish and alcohol.[11] It has recently received increased attention since high adherence to MeD has been associated with longer survival, reduced risk of cardiovascular or cancer mortality and lower likelihood of neurodegenerative disorders including Alzheimer's Disease.[12–15] Moreover, higher adherence to MeD was recently reported to be associated with a lower likelihood of incident cognitive impairment in the the REasons for Geographic And Racial Differences in Stroke (REGARDS) study.[16] This association was attenuated by incident stroke and was moderated by the presence of diabetes mellitus. Furthermore, a systematic review ranked the Mediterranean-style diet as the most likely dietary model to provide protection against coronary heart disease.[17] There are limited prospective data[18–21] investigating the potential relationship of adherence to MeD with incident stroke and these are mainly in Caucasian populations[18,19], while blacks have been under-represented in a single North-American study.[21]

The present study aims to extend previous research by capitalizing on the large, geographically dispersed, black-white race- and sex-balanced sample of REGARDS subjects. Acknowledging the fact that collection of data on numerous potential confounders or moderators of the relationship between adherence to a healthy dietary pattern such as MeD and incident stroke (vascular risk factors, health behaviors including exercise and smoking, demographic characteristics, depressive symptoms and cognitive status) have been included in the design of REGARDS, we sought to determine longitudinally the potential association between higher adherence to MeD and lower risk of stroke before and after controlling for factors that are independently related to cerebrovascular disease burden.[22] Moreover, we also investigated potential relationships of MeD patterns with specific stroke subtypes including ischemic and hemorrhagic stroke by capitalizating on the validated REGARDS protocol for verification of incident stroke and specific stroke subtypes.[22] Finally, we aimed to evaluate the potential interaction of race (blacks vs. whites) on the association of adherence to MeD with incident stroke (as well as stroke subtypes).

## Subjects and Methods

### Study Design

REGARDS is a national, population-based, longitudinal cohort study with oversampling from the Stroke Belt region of the US, an area that has stroke mortality rates higher than the rest of the US.[22] From January 2003 – October 2007, a total of 30,239 individuals 45 years or older were enrolled; the cohort is followed by telephone twice a year for incident stroke. By design, the sample includes 21% from the "buckle" of the Stroke Belt (coastal plain region of North Carolina, South Carolina, and Georgia), 35% from the Stroke Belt states (remainder of North Carolina, South Carolina, and Georgia, plus Alabama, Mississippi, Tennessee, Arkansas, and Louisiana), and the remaining 44% from the other 40 contiguous states and the District of Columbia. Methodological details are available elsewhere.[22–25]

### Standard Protocol Approvals, Registration and Consents

The study methods have been reviewed and approved by the Institutional Review Boards of all participating institutions. Written informed consent was obtained from all participants involved in the study.

### Data collection and definitions

Data variables were gathered at baseline via a computer-assisted telephone interview followed by a home visit 3–4 weeks later during which blood, urine, blood pressure, ECG, medication audit, and anthropometric data were collected. Self-administered questionnaires (including a food frequency questionnaire) were left with the participant to gather information and mail back. Variables included in the present analysis are: age, race, sex, region of residence, height, weight, BMI, waist circumference, income, education, smoking status, alcohol use, sedentary behavior (more than 4 hours of screen time and no physical activity), myocardial infarction, diabetes mellitus, atrial fibrillation (by self report or centrally read electrocardiogram), systolic blood pressure (SBP), diastolic blood pressure (DBP), high cholesterol, antihypertensive regimen (specific drug classes), and perceived general health status. Additional details regarding definitions of data variables are available elsewhere.[16,22–25]

### Dietary assessment and MeD

Average food consumption information at baseline was obtained using the self-administered Block 98 Food Frequency Questionnaire,[26] which was left with each participant during the in-person visit with instructions for completion and a stamped envelope in which to return the questionnaire. For construction of MeD-score, we followed the most commonly described method that has been previously used by our group as well as other investigators.[14–16] First, we identified the nine food groups considered to be part of the Mediterranean-type Diet Score: (i) vegetables, (ii) fruits, (iii) legumes, (iv) cereals (including bread, pasta and rice), (v) fish; (vi) meat; (vii) dairy products; (viii) fat intake and (ix) alcohol intake. Second, we regressed caloric intake (kilocalories) and calculated the derived residuals of daily gram intake for 7 food categories (vegetables, fruits, legumes, cereals, fish, meat and dairy products). Individuals were assigned a value of 1 (i) for each

beneficial component (fruits, vegetables, legumes, cereals and fish) whose consumption was at or above the median and (ii) for each detrimental component (meat and dairy products) whose consumption was below the median. For fat intake (eighth food category) we used the ratio of daily consumption (in grams) of monounsaturated lipids to saturated lipids[14–16] and we calculated the median separately for each sex. Individuals with ratios at or above the sex-specific median were assigned a value of 1.

Alcohol intake was analyzed according to the National Institute on Alcohol Abuse and Alcoholism recommendations.[14–16] Moderate consumption was defined as between 1 and 7 drinks per week for women and between 1 and 14 drinks per week for men. More-than-moderate consumption was defined as more than 7 drinks per week for women and more than 14 drinks per week for men. Individuals were assigned a score of 1 (lower risk for cardiovascular disorders or dementia) for moderate consumption (different cut-offs for men and women) and a score of 0 for the other two categories (zero and more-than-moderate consumption).[14–16] The MeD score was computed as the sum of scores in the nine food categories (range 0–9) with a higher score indicating a higher adherence to MeD.[14–16,27–29] Adherence to MeD was categorized as high, moderate and low using MeD-score tertiles (MeD-score: 6–9, 4–5 & 0–3 respectively).[14–16] The diet score was also analyzed in a median split (low adherence range: 0–4; high adherence range: 5–9).[14–16] Adherence to MeD was assessed using both trichotomization and dichotomization of MeD-score in order to yield comparable results to previous studies evaluating potential associations of adherence to MeD with incident neurological disorders[14–16] and to be consistent with the findings of a recent meta-analysis that assessed the relationship of MeD with the risk of cerebrovascular diseases by dichotomizating and trichotomizating MeD-score[29].

## Stroke Ascertainment

REGARDS participants were contacted via telephone for every 6 months to ascertain vital status and to obtain information on reasons for hospitalization, including stroke, transient ischemic attack, and stroke symptoms. Medical records were pursued if the participant reported seeking medical care for stroke or transient ischemic attack or was hospitalized for stroke symptoms or unknown reason. Once a medical record was received, it was reviewed by a committee of clinicians to verify that a stroke occurred and to provide stroke subtying as haemorrhage versus infarction. Stroke was defined either according to the World Health Organization definition of focal neurological deficit lasting >24 hours or as a nonfocal neurological symptoms with imaging consistent with stroke as previously described.[27,28] The National Death Index was also queried annually to identify stroke deaths that might not have been hospitalized.[28] For the present analysis, strokes occurring through September 1, 2012, were included.

## Statistical analyses

The 2-tailed Pearson $^2$ test for categorical variables and ANOVA (Analysis of Variance) or Kruskal-Wallis test for continuous variables were used to assess intergroup differences between participants with high, moderate and low adherence to MeD. The relationship between adherence to MeD (trichotomized and dichotomized MeD-score) and incident ischemic as well as hemorrhagic stroke was evaluated separately in a set of incremental Cox

proportional hazards models with high adherence to MeD as reference group. First, crude associations were estimated followed by subsequent adjustment for: (1) age, race (whites vs. blacks), age-race interaction, region (Stroke Belt/Stroke Buckle vs. Remainder of Continental US), sex (male vs. female); Model I; (2) age, race, age-race interaction, region, sex, income (categorized as ≥$75.000, $35.000-$74.000, $20.000-$34.000 and <$20.000), education (categorized as less than high school, high school graduate, some college, or college graduate); Model II; (3) variables in Model II plus total energy (calories from food or beverages analyzed by Nutrition Quest), smoking status (current smoking vs. no smoking or prior smoker, sedentary behavior (watching more than 4 hours of television and no physical activity); Model III; (4) variables in Model III plus self-reported history of heart disease, atrial fibrillation, obesity (defined as a body mass index>30kg/$m^2$), waist circumference, diabetes (defined as fasting glucose levels >126 ml/dL, nonfasting glucose >200 ml/dL, or self-reported use of diabetes medications), hypertension, hypertension medication use, systolic and diastolic blood pressure levels; Model IV. We also evaluated the presence of interactions between race, stroke region and vascular risk factors with the association of adherence to MeD and risk of incident stroke. Since there were fewer events for hemorrhagic stroke, the final model included only age, race, age-race interaction, sex, region, systolic blood pressure, and hypertension medication use. In our prespecified analyses adherence to MeD was categorized both by dichotomization and trichotomization of MeD-score as previously described.[16] Analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

## Results

A total of 30,239 individuals were included in REGARDS. After excluding participants with history of stroke (n=2,088), incomplete dietary data (n=7,738) and missing follow-up (n=216), the sample of 20,197 (67%) individuals included in the present analyses had a mean age of 65±9 years, 33% were black (n=6,670), 44% were male (n=8,853) and 56% (n=11,368) were from the stroke belt region. The MeD-score ranged from 0 to 9 with a bell-shaped (i.e., approximately normal) distribution with 42% of participants (n=8354) having a score of 4 or 5. The mean MeD-score was 4.4±1.7. A total of 9181 individuals (53%) had a low adherence to MeD (MeD-score 0–4). Demographic characteristics, environmental and vascular risk factors in participants with low, moderate and high adherence to MeD are presented in Table 1. MeD adherence was greater among males, black race, residents of regions other than the stroke belt, and non-smokers, and was lower among those with hypertension, diabetes mellitus, obesity and sedentary life style.

During a mean follow-up period of 6.5±2.2 years, incident stroke was identified in 565 participants (2.8%). Ischemic stroke was documented in 497 participants (88% of all strokes), while hemorrhagic stroke occurred in the remaining 68 participants (12% of all strokes). Results of incremental Cox proportional hazards models estimating the association of adherence to MeD (stratified by MeD tertiles) with incident ischemic stroke appear in Table 2. Low adherence to MeD was associated with higher risk of incident ischemic stroke in initial univariate analyses (HR versus high adherence: 1.28; 95%CI:1.00–1.63; p=0.047). Moderate adherence to MeD was also related to incident IS (HR versus high adherence: 1.32; 95%CI:1.05–1.66; p=0.020). After adjusting for demographics, environmental and

vascular risk factors, blood pressure levels, and antihypertensive medications use (Model 4), low adherence to MeD tended to be associated with a higher risk of incident IS (HR versus high adherence: 1.29; 95%CI:0.99–1.67; p=0.057). A similar relationship was documented for moderate adherence to MeD (HR versus high adherence: 1.25; 95%CI:0.98–1.58; p=0.079). When MeD was evaluated in Cox proportional hazards models as a continuous variable, a 1-point increase in MeD-score was independently associated with a 5% reduction in the risk of incident (95%CI: 0%-11%) after adjustment for all potential confounders (Model IV). There was no interaction of age (p=0.46), sex (p=0.76), race (p=0.38), stroke-belt region (p=0.67), atrial fibrillation (p=0.47), history of heart disease (p=0.42), diabetes mellitus (p=0.85), hypertension (p=0.90) and systolic blood pressure levels (p=0.67) on the association of adherence to MeD with incident ischemic stroke.

Results of incremental Cox proportional hazards models estimating the association of adherence to MeD (stratified by MeD tertiles) with incident hemorrhagic stroke are shown in Table 3. We documented no association of high or moderate adherence to MeD with incident hemorrhagic stroke both in the initial univariate and multivariate analyses adjusting for potential confounders (Model II; p for the association of high adherence to MeD with incident hemorrhagic stroke: 0.16; p for the association of moderate adherence to MeD with incident hemorrhagic stroke 0.53). There was no interaction of age (p=0.28), sex (p=0.21), race (p=0.38), stroke-belt region (p=0.67) and systolic blood pressure levels (p=0.39) on the association of adherence to MeD with incident hemorrhagic stroke.

All analyses were repeated after dichotomizing MeD-score. Table 4 presents the findings of incremental Cox proportional hazards models evaluating the association of adherence to MeD with incident IS. Low adherence to MeD was independently associated with a higher risk of incident IS (HR: 1.27;95%CI:1.04–1.54; p=0.0164) after adjusting for multiple confounders including demographics, environmental and vascular risk factors, blood pressure levels, and antihypertensive medications use. Table 5 shows the results of incremental Cox proportional hazards models investigating the association of adherence to MeD with incident hemorrhagic stroke. High adherence to MeD was not associated with the risk of hemorrhagic stroke in either the unadjusted or adjusted Cox proportional hazards models (HR= 0.93; 95%CI: 0.57–1.51; p=0.7621).

## Comment

Our longitudinal study showed that low adherence to MeD was associated with a higher risk of incident ischemic stroke in a large population-based sample of U.S. black and white adults during a mean-follow-up period of 6.5 years. This relationship persisted after adjustment for numerous potential confounders including demographic characteristics, health behaviors, educational level, income, physical activity, vascular risk factors, blood pressure levels and antihypertensive medications. Moreover, we found no evidence for interaction between race, sex, or region of residence and the relationship of adherence to MeD and incident ischemic stroke. Finally, we failed to document any association between adherence to MeD and risk of hemorrhagic stroke.

Our findings are in line with the results of a recent meta-analysis that quantitatively synthesized all studies evaluating the association between adherence to MeD and risk of stroke, depression, cognitive impairment, and Parkinson disease.[29] The protective association of high adherence to MeD with likelihood or risk of incident stroke has been replicated in both case-control (2 studies; OR: 0.20; 95%CI: 0.10–0.41) and longitudinal cohort (5 studies; OR: 0.84; 95%CI: 0.74–0.95) studies that were published till October 31st, 2012. In addition, the former association was detected also in studies conducted in non-Mediterranean countries (OR: 0.80; 95%CI: 0.66–0.97). Our study puts more insight in the examined relation for US populations, notably concerning both races. Interestingly, when stroke subtypes were separately examined, the meta-analysis detected no association between moderate or high adherence to MeD and likelihood of hemorrhagic stroke both in case-control (n=1) and cohort studies (n=2). In contrast, high adherence to MeD was strongly related with a lower likelihood of ischemic stroke in case-control studies (2 studies; OR: 0.19; 95%CI: 0.08–0.46), while a non-significant trend was documented between high adherence to MeD and lower risk of incident ischemic stroke in longitudinal cohort studies (3 studies; OR: 0.88; 95%CI: 0.70–1.12). Notably, the prior three cohort studies[18,20,21] that investigated the potential association of dietary patterns with risk of cerebrovascular diseases, had a lower statistical power to identify effects on specific stroke subtypes and the relationship of high or moderate adherence to MeD with the incidence of ischemic stroke did not reach the level of statistical significance. Consequently, our study expands the preliminary findings of the prior cohort studies[18,20,21] and comprehensive meta-analysis[29] that detected a trend towards lower incidence of ischemic stroke in persons with higher adherence to MeD.

Our observations are consistent with the mounting literature underscoring a potential beneficial role of a healthy dietary pattern such as MeD in cerebrovascular disease protection. More specifically, a detailed analysis within the Nurses' Health Study showed that 70% of incident stroke (both ischemic and hemorrhagic) could be avoided by healthy food choices that are consistent with the traditional MeD in combination with regular physical exercise and smoking abstinence.[30] Similarly, a systematic review ranked the MeD as the most likely dietary model to provide protection against cardiovascular diseases.[31] Finally, the results of a recent randomized controlled trial provided additional evidence that among persons at high cardiovascular risk, a MeD supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events, with comparisons of stroke risk being the only component of the primary endpoint that reached statistical significance in secondary analyses.[32] More specifically, the incidence of stroke was reduced by 34% (95%CI: 3%-54%) and 49% (95%CI: 21%-67%) in individuals who were randomized to MeD with extra-virgin olive oil and nuts respectively in comparison to the control group. In contrast, MeD was not associated with a reduction in myocardial infarction, cardiovascular and all-cause mortality. In view of the former considerations, it may be postulated that high adherence to MeD appears to be effective in terms of primary stroke prevention.

The association of high adherence to MeD with lower incidence of ischemic but not hemorrhagic stroke is intriguing. Neuroimaging studies have provided preliminary evidence demonstrating protective relation between MeD and white matter hyperintensities[33] as well as infarcts detected in brain Magnetic Resonance Imaging[34]. However, high adherence to

MeD was not cross-sectionally or longitudinally related to a lower risk of cerebral microbleeds or intracerebral hemorrrhages.[33,34] These observations are suggestive of a vascular protective component of this diet that may preferentially reduce the risk of cerebral ischemia. Another plausible explanation may be related to the fact that MeD has been shown to exert salutary effects in risk factors that are associated with a high risk of ischemic (but not hemorrhagic) stroke including diabetes mellitus[35] and metabolic syndrome[36]. Interestingly, Esposito et al recently provided randomized trial data indicating that MeD is associated with a higher rate of regression as well as a lower rate of progression of common carotid artery intima-media thickness (CCA-IMT) in patients with diabetes mellitus in comparison to a standard low-fat diet.[37,38] CCA-IMT has been repeatedly shown to be strongly associated with the risk of ischemic (but not hemorrhagic) stroke both cross-sectionally[39,40] and longitudinally[41,42]. However, it should be noted that the incidence of hemorrhagic stroke was lower than that of ischemic stroke (consistent with national estimates) and power may have been limited.

The findings of the present study are subject to certain limitations. For one, methodological shortcomings related to the construction of Mediterranean-type Diet Score (equal weighting of underlying food categories and underestimation of total food and caloric intake) need to be acknowledged. Moreover, the assessment of dietary intake was performed only at baseline and thus we were unable to capture potential changes in dietary patterns during the follow-up period that may have affected the reported associations. Additionally, it should be noted that the dietary assessment was self-administered and subject to differential return by participants and this may have resulted in selection or recall biases. Moreover, the observational design of the present study cannot rule out the possibility of residual confounding by unknown risk factors, such as general healthier lifestyle or higher adherence to medication intake of individuals adhering to a MeD. Lastly, it should be kept in mind that REGARDS findings focus on black/white disparities in stroke risk and fail to examine other racial/ethnic groups

In conclusion, greater adherence to MeD was associated with lower risk of incident IS in REGARDS dataset independent of potential confounders. The former association was not reproduced for hemorrhagic stroke, while we detected no evidence for race, sex or region interactions in the relationship of adherence to MeD with incident cerebrovascular events (both ischemic and hemorrhagic). Our findings lend support to the accruing data indicating that dietary habits are critical to effective primary stroke prevention and highlighting that the beneficial effects of a healthy dietary pattern in reducing the risk of stroke appear to apply to different racial subgroups and different regions across the US.

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## Table 1

Baseline Characteristics by Tertile of Mediterranean Diet Score in the REasons for Geographic and Racial Differences in Stroke (REGARDS) Study

| Variables | Mediterranean Diet Score | | | |
|---|---|---|---|---|
| | 6–9 N=5211 | 4–5 N=8354 | 0–3 N=6632 | p |
| *Demographics* | | | | |
| Male (%) | 2465 (47) | 3614 (43) | 2774 (42) | <0.001 |
| Black (%) | 1780 (34) | 2820 (34) | 2070 (31) | <0.001 |
| Age <65 years (%) | 4225 (51) | 3675 (55) | 2462 (47) | <0.001 |
| Mean age, years (SD) | 66 (9) | 65 (9) | 64 (9) | <0.001 |
| Residence in the Stroke Belt (%) | 2721 (52) | 4800 (57) | 3847 (58) | <0.001 |
| Income over $75,000 (%) | 1168 (22) | 1488 (18) | 902 (14) | <0.001 |
| College graduate (%) | 2517 (48) | 3277 (39) | 1891 (29) | <0.001 |
| *Co-morbid Conditions* | | | | |
| Diabetes mellitus (%) | 771 (15) | 1531 (18) | 1250 (19) | <0.001 |
| Heart Disease (%) | 842 (16) | 1331 (16) | 1057 (16) | 0.947 |
| Hypertension (%) | 2426 (47) | 4075 (49) | 3225 (49) | 0.019 |
| Atrial Fibrillation (%) | 409 (8) | 685 (8) | 540 (8) | 0.733 |
| Obesity (%) | 1559 (30) | 3071 (37) | 2687 (41) | <0.001 |
| *Lifestyle Factors* | | | | |
| Sedentary (%) | 376 (7) | 994 (12) | 1087 (16) | <0.001 |
| Current smoking (%) | 428 (8) | 1034 (12) | 1246 (19) | <0.001 |
| *Blood pressure levels* | | | | |
| Mean systolic blood pressure, mmHg (SD) | 126 (16) | 126 (16) | 127 (16) | 0.001 |
| Mean diastolic blood pressure, mmHg (SD) | 76 (9) | 76 (9) | 77 (10) | 0.006 |

## Table 2

Association of adherence to Mediterranean Diet (MeD) stratified by tertiles of MeD-score with incident ischemic stroke on incremental Cox proportional hazards models.

| Association | Mediterranean Diet Score | | |
|---|---|---|---|
| | **6–9 N=5211** | **4–5 N=8354** | **0–3 N=6632** |
| | $N_{strokes}$=108 | $N_{strokes}$=222 | $N_{strokes}$=167 |
| Crude | Reference | HR=1.32 (95%CI: 1.05, 1.66) p=0.020 | HR=1.28 (95%CI:1.00,1.63) p=0.047 |
| Model 1 | Reference | HR=1.37 (95%CI: 1.09, 1.73) p=0.007 | HR=1.46 (95%CI:1.14, 1.86) p=0.003 |
| Model 2 | Reference | HR=1.33 (95%CI: 1.05, 1.67) p=0.016 | HR=1.36 (95%CI: 1.07, 1.74) p=0.013 |
| Model 3 | Reference | HR=1.31 (95%CI: 1.04, 1.65) p=0.023 | HR=1.31 (95%CI: 1.02, 1.68) p=0.034 |
| Model 4 | Reference | HR=1.24 (95%CI:0.98, 1.58) p=0.079 | HR=1.29 (95%CI: 0.99, 1.67) p=0.057 |

Model 1 adjusts for age, race, age-race interaction, region, sex

Model 2 adjusts for age, race, age-race interaction, region, sex, income, education

Model 3 adjusts for age, race, age-race interaction, region, sex, income, education, total energy, smoking status, sedentary behavior

Model 4 adjusts for age, race, age-race interaction, region, sex, income, education, total energy, smoking status, sedentary behavior, history of heart disease, atrial fibrillation, BMI, waist circumference, diabetes, hypertension, hypertension medication use, systolic and diastolic blood pressure levels

## Table 3

Association of adherence to Mediterranean Diet (MeD) stratified by tertiles of MeD-score with incident hemorrhagic stroke on incremental Cox proportional hazards models.

| **Association** | **Mediterranean Diet Score** | | |
|---|---|---|---|
| | **6–9 N=5211** | **4–5 N=8354** | **0–3 N=6632** |
| | $N_{strokes}$=23 | $N_{strokes}$=29 | $N_{strokes}$=16 |
| Crude | Reference | HR=0.80 (95%CI: 0.46, 1.39) p=0.80 | HR=0.57 (95%CI:0.30,1.08) p=0.08 |
| Model 1 | Reference | HR=0.85 (95%CI: 0.49, 1.48) p=0.57 | HR=0.65 (95%CI:0.34, 1.24) p=0.19 |
| Model 2 | Reference | HR=0.84 (95%CI: 0.49, 1.46) p=0.53 | HR=0.64 (95%CI: 0.34, 1.21) p=0.16 |

Model 1 adjusts for age, race, age-race interaction, region, sex

Model 2 adjusts for age, race, age-race interaction, region, sex, hypertension medication use, systolic blood pressure levels

## Table 4

Association of adherence to Mediterranean Diet (MeD) stratified by dichotomization of MeD-score with incident ischemic stroke on incremental Cox proportional hazards models.

| Association | Mediterranean Diet Score | |
|---|---|---|
| | **5–9 N=9234** | **0–4 N=10889** |
| | $N_{strokes}$=208 | $N_{strokes}$=284 |
| Crude | Reference | HR= 1.20 (95%CI: 1.00, 1.43) p=0.0460 |
| Model 1 | Reference | HR=1.31 (95%CI: 1.10, 1.57) p=0.0030 |
| Model 2 | Reference | HR=1.25 (95%CI: 1.05, 1.50) p=0.0140 |
| Model 3 | Reference | HR=1.22 (95%CI: 1.02, 1.46) p=0.0336 |
| Model 4 | Reference | HR=1.27 (95%CI: 1.04, 1.54) p=0.0164 |

Model 1 adjusts for age, race, age-race interaction, region, sex

Model 2 adjusts for age, race, age-race interaction, region, sex, income, education

Model 3 adjusts for age, race, age-race interaction, region, sex, income, education, total energy, smoking status, sedentary behavior

Model 4 adjusts for age, race, age-race interaction, region, sex, income, education, total energy, smoking status, sedentary behavior, history of heart disease, atrial fibrillation, BMI, waist circumference, diabetes, hypertension, hypertension medication use, systolic and diastolic blood pressure levels

## Table 5

Association of adherence to Mediterranean Diet (MeD) stratified by dichotomization of MeD-score with incident hemorrhagic stroke on incremental Cox proportional hazards models.

| Association | Mediterranean Diet Score | |
|---|---|---|
| | **5–9 N=9234** | **0–4 N=10889** |
| | $N_{strokes}$=35 | $N_{strokes}$=33 |
| Crude | Reference | HR= 0.82 (95%CI: 0.51, 1.32) p=0.4182 |
| Model 1 | Reference | HR=0.91 (95%CI: 0.56, 1.46) p=0.6853 |
| Model 2 | Reference | HR= 0.93 (95%CI: 0.57, 1.51) p=0.7621 |

Model 1 adjusts for age, race, age-race interaction, region, sex

Model 2 adjusts for age, race, age-race interaction, region, hypertension medication use, systolic blood pressure levels