ORIGINAL RESEARCH

Low-Carbohydrate Diets and Risk of Incident Atrial Fibrillation: A Prospective Cohort Study

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***Background*—**The influences of low-carbohydrate diets in cardiovascular disease are controversial. Few studies have examined the relationship of carbohydrate intake and risk of incident atrial fibrillation (AF). We aimed to evaluate the association between carbohydrate intake and the risk of incident AF in the ARIC (Atherosclerosis Risk in Communities) Study.

***Methods and Results*—**We included 13 385 participants (age, 54.2±5.8 years; 45.1% men and 74.7% white) who completed a dietary questionnaire at baseline (1987–1989) in the ARIC Study. The primary outcome was incident AF, which was identified by ECG performed during study examinations, hospital discharge codes, and death certificates. We used multivariable Cox hazard regression models to assess the association between carbohydrate intake and incident AF. We further explored the effects of specific food source (animal versus plant based) used to replace carbohydrate intake in the low-carbohydrate intake setting. During a median follow-up of 22.4 years, 1808 cases (13.5%) of AF occurred. The hazard ratio for incident AF associated with a 1-SD (9.4%) increase in carbohydrate intake as a percentage of energy intake was 0.82 (95% CI, 0.72–0.94), after adjustment for traditional AF risk factors and other diets factors. Results were similar when individuals were categorized by carbohydrate intake quartiles (hazard ratio, 0.64; 95% CI, 0.49–0.84; comparing extreme quartiles). No association was found between the type of protein or fat used to replace the carbohydrate and risk of incident AF.

***Conclusions*—**Low-carbohydrate diets were associated with increased risk of incident AF, regardless of the type of protein or fat used to replace the carbohydrate. **(*J Am Heart Assoc*. 2019;8:e011955. DOI: 10.1161/JAHA.119.011955.)**

Key Words: atrial fibrillation • diet • epidemiology • risk factor

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, with an estimated lifetime risk of 25%.[1,2] As AF is related to substantial increased morbidity, mortality, and economic costs,[3] it is important to recognize modifiable risk factors, such as dietary factors, as a step to provide preventive strategies for this disease.

Low-carbohydrate diets, which restrict carbohydrate intake, in favor of increased protein or fat intake, have gained substantial popularity because of their ability to induce short-term weight loss.[4,5] Nevertheless, the long-term effect of carbohydrate restriction is still controversial, especially in the influence on cardiovascular disease.[6–9] Recently, the 2017 PURE (Prospective Urban-Rural Epidemiology) Study, of 135 335 participants from 18 countries across 5 continents, reported that higher carbohydrate intake was associated with an increased risk of total mortality but not with the risk of cardiovascular disease (myocardial infarction, stroke, and heart failure) or cardiovascular disease mortality.[10] Another recent study of a large cohort, the ARIC (Atherosclerosis Risk in Communities) Study, reported a U-shaped association between carbohydrate intake and total mortality, whereas no association was found with cardiovascular mortality.[5] However, to the best of our knowledge, no study has examined the relationship of carbohydrate intake and risk of incident

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Clinical Perspective

What Is New?

- In this large, prospective, community-based cohort study with a long-term follow-up, we were the first to evaluate the association of carbohydrate intake with incident atrial fibrillation and found that people with a low-carbohydrate diet may have had a higher risk of incident atrial fibrillation, regardless of the type of protein or fat used to replace the carbohydrate.

What Are the Clinical Implications?

- Low-carbohydrate diets are associated with increased risk of incident atrial fibrillation, indicating that this popular weight control method, by restricting carbohydrate intake, should be recommended cautiously and more studies should be conducted to evaluate the effect.

AF. As a result, we analyzed the ARIC Study data set to assess the association of carbohydrate intake and incident AF.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because of human subjects' restrictions. However, interested investigators can contact the ARIC Study Coordinating Center at the University of North Carolina–Chapel Hill to request overall access to ARIC Study data.[11]

Study Populations

The ARIC Study is a population-based, prospective, cohort study of cardiovascular risk factors in 4 US communities (Forsyth County, North Carolina; Jackson, MD; suburbs of Minneapolis, MN; and Washington County, Maryland), initially consisting of 15 792 participants, aged 45 to 64 years, recruited between 1987 and 1989 (visit 1). Four subsequent study visits were conducted: visit 2 (1990–1992), visit 3 (1993–1995), visit 4 (1996–1998), and visit 5 (2011–2013). Participants are being followed up by annual or semiannual telephone interviews and active surveillance of ARIC Study community hospitals. Further details about the study design have been previously described.[12] The ARIC Study has been approved by institutional review boards at all participating institutions, and all participants provided written informed consent. In the present analysis, of 15 792 participants at baseline (visit 1), we excluded participants who had race other than white or black (n=103), participants with prevalent AF or missing data of AF (n=243), participants with missing dietary information or with extreme caloric intake (defined as <600 or >4200 kcal/d for men and <500 or >3600 kcal/d for women) (n=327), and participants missing other covariates (n=1734). The final sample size was 13 385 (Figure 1).

Dietary Assessment

At visits 1 and 3, participants completed an interview that included a 66-item semiquantitative food frequency questionnaire, a modified version of the 61-item instrument developed by Willett et al.[13] Participants reported the frequency of particular foods and beverages consumed on a 9-category scale, ranging from never or <1 time per month to ≥6 times per day. Standard portion sizes were provided as a reference based on picture and food models. Foods were grouped into dairy foods, fruits, vegetables, meats, sweets, baked goods, cereals, miscellaneous, beverages, and other dietary items. In addition, detailed information about alcohol intake was ascertained on a separate interview form. Nutrient intakes were derived from the food frequency questionnaire responses using the Harvard Nutrient Database. The macronutrients (carbohydrate, fat, and protein) were expressed as percentage of energy, calculated as the daily calories of the macronutrient divided by the total number of calories for the day.[13]

AF Ascertainment

Detailed ascertainment of AF, including both AF proper and atrial flutter, has been described previously.[14] Incident AF was identified by ECGs performed during study examinations, hospital discharge codes, and death certificates. At each study visit, a 12-lead ECG was performed with the participant lying in a supine position. Electrocardiographic data were transmitted electronically to a reading center (EpiCare, Wake Forest University, Winston-Salem, NC), reviewed, and analyzed using the GE Marquette 12-SL program (GE Marquette, Milwaukee, WI). ECGs automatically coded as AF or atrial flutter were visually checked and confirmed by a cardiologist.

Hospitalizations during follow-up were identified through annual telephone calls and surveillance of local hospitals. Trained abstractors collected information from all participants' hospitalizations, including all *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), codes for diagnoses. AF was considered to be present if the *ICD-9-CM* code 427.31 (AF) or 427.32 (atrial flutter) was present in any hospitalization. AF events associated with open cardiac surgery were excluded. Besides, AF was also defined if *ICD-9-CM* code 427.31 or 427.32 was listed as a cause of death.

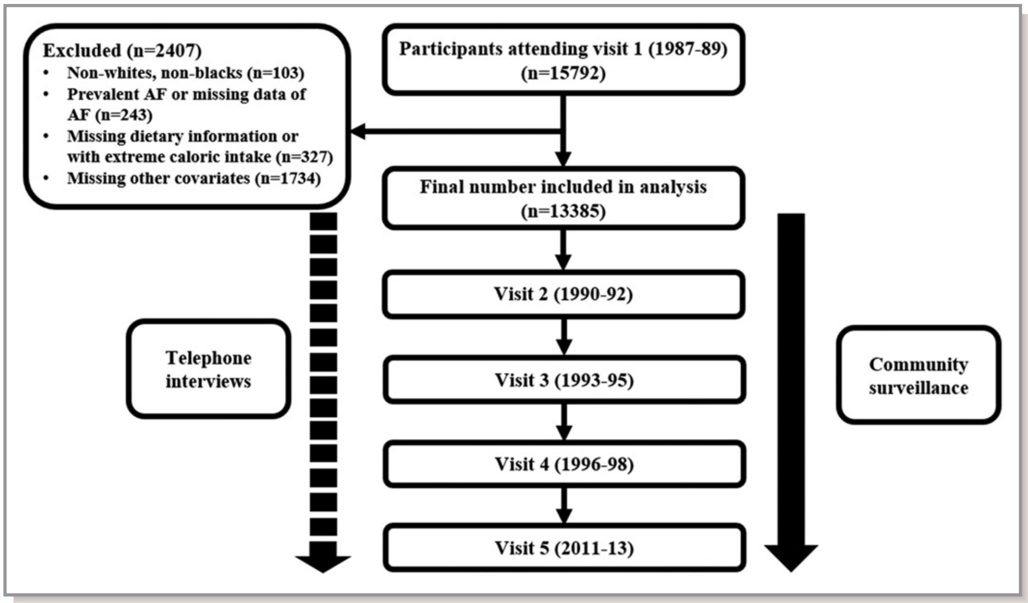

Figure 1. Flow diagram of participants in the ARIC (Atherosclerosis Risk in Communities) Study. AF indicates atrial fibrillation.

Measurement of Other Covariates

All covariates were assessed at visit 1, except for body mass index, which was also a measure at visits 2 and 3. Race, age, sex, education level, smoking, and alcohol consumption status were self-reported. Height and weight were measured with the participant wearing light clothes, and body mass index was calculated as weight (in kilograms) divided by squared height (in meters). Body surface area was calculated according to the Mosteller formula as the square root of [height (cm)×weight (kg)/3600]. Sport and physical activity during leisure time was accessed using the validated Baecke questionnaire. Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, or blood pressure medicine use in the past 2 weeks. Diabetes mellitus was defined if the participants had fasting blood glucose ≥126 mg/dL, nonfasting blood glucose ≥200 mg/dL, use of antidiabetic medicines, or self-reported physician diagnosis of diabetes mellitus. Stroke was identified by 6 associated symptoms (speech, vision, double vision, numbness, paralysis, and dizziness) corresponding to the specific artery. Prevalent coronary heart disease and heart failure were defined as previously described.[15,16] Total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured using standardized enzymatic assays, and low-density lipoprotein cholesterols were than calculated on the basis of the Friedewald formula.[17] Creatinine was measured using a modified kinetic Jaffe method, and uric acid was measured by the method of Haeckel.[12]

Statistical Analysis

We primarily modeled carbohydrate intake as a continuous variable, and we rescaled the data by dividing by the SD (1 SD=9.4%). Then, we categorized carbohydrate intake into quartiles based on the sample distribution. Baseline characteristics of participants were compared between groups using the 1-way ANOVA test, the χ^2 test, and the Kruskal-Wallis test, as appropriate. We used multivariable Cox hazard regression models to assess the association between baseline carbohydrate intake and incident AF. Time of follow-up was defined as time from visit 1 (baseline) to incident of AF, loss to follow-up, death, or December 31, 2012, whichever occurred first. We also used a restricted cubic spline with 4 knots to express the dose-response association between total energy from carbohydrate intake and incident AF. The initial model adjusted for age, sex, and race. A second model additionally adjusted for total energy intake, total fat intake as a percentage of energy, animal fat intake as a percentage of energy, total protein intake as a percentage of energy, animal protein intake as a percentage of energy, dietary fiber intake, glycemic index, and glycemic load. In a final model, we further adjusted for body mass index, body surface area, smoking, drinking, education level, sport, physical activity, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, creatinine, uric acid, hypertension, stroke, diabetes mellitus, prevalent coronary artery disease, and prevalent heart failure. We did a time-varying sensitivity analysis for participants who were identified with incident AF, loss to follow-up, or death before visit 3;

carbohydrate intake was calculated on the basis of responses from the baseline (visit 1) food frequency questionnaire. From visit 3 onwards, the carbohydrate intake was calculated on the basis of the mean of visit 1 and visit 3 food frequency questionnaire responses. Carbohydrate exposures were not updated for participants who developed heart disease, diabetes mellitus, or stroke before visit 3 for reducing potential confounding from changes in diet that could arise from the diagnosis. For the missing of dietary information at visit 3 in 2743 participants, we did a further sensitivity analysis: we excluded the missing data in the first analysis, and in the second we used dietary information in visit 1 to replace missing data. In addition, we performed prespecified subgroup analysis by age, sex, and race and tested for potential interactions of these covariates with carbohydrate intake separately. To minimize the potential of reverse causation, we did a sensitivity analysis whereby individuals with prevalent coronary artery disease, heart failure, stroke, or diabetes mellitus at baseline were excluded from the analysis. Because of the high rate of hypertension at the baseline, we also did a subgroup analysis of participants with or without hypertension and tested for interaction of hypertension and carbohydrate intake.

To further explore the effects of specific food sources (animal versus plant based) that are used to replace carbohydrate intake in the low-carbohydrate intake setting, we created animal- and plant-based low-carbohydrate diet scores, as previously described.[8] Either animal- or plant-based fat and protein and carbohydrate intake as a percentage of energy were divided into deciles. For carbohydrate, participants got 10 points in the lowest decile and 0 points in the highest decile. The order was reversed for animal- or plant-based fat and protein. Animal-based low-carbohydrate diet scores were calculated by summing up the points for carbohydrate, animal-based fat, and animal-based protein. Plant-based low-carbohydrate diet scores were calculated by summing up the points for carbohydrate, plant-based fat, and plant-based protein (Table S1). As a result, the highest score represented low-carbohydrate and high animal- or plant-based fat and protein intake. We used the Cox hazard regression model to determine the association of incident AF with animal- or plant-based low-carbohydrate scores.

Results

Baseline characteristics are shown in Table 1. The mean value of carbohydrate intake as a percentage of energy for 13 384 participants was 44.8±9.4%. The average age was 54.2±5.8 years, and 45.1% of participants were men. Participants with a relatively low percentage of energy from carbohydrate were more likely to be young, men, white, smokers, and ever drinkers; and to have diabetes mellitus, a high education level, a high high-density lipoprotein cholesterol level, a high uric acid level, high total fat intake, high animal fat intake, high total protein intake, high animal protein intake, low plant protein intake, low dietary fiber intake, a low glycemic index, and a low glycemic load. Total energy intake or plant fat intake had reverse U-shaped relationship across carbohydrate intake quartiles: participants in both the first and fourth quartiles had lower total energy intake and plant fat intake than those in the intermediate quartiles. There was no significant difference in change in body mass index at the time points of 3 and 6 years from baseline across carbohydrate quartiles. The prevalence of hypertension, stroke, coronary artery disease, and heart failure was similar across carbohydrate quartiles (Table 1).

During a median follow-up of 22.4 years, 1808 cases (13.5%) of AF occurred. In the model that measured carbohydrate intake as a continuous variable, an increase of 9.4% in carbohydrate intake (corresponding to 1 SD) was associated with an 18% lower rate of incident AF (hazard ratio, 0.82; 95% CI, 0.72–0.94), after adjusting for all covariates (Table 2). Results were similar when we categorized individuals by carbohydrate intake quartiles: the highest risk of incident AF was observed in the lowest carbohydrate intake subgroup, in both unadjusted and adjusted models ($P<0.001$, Table 2). In the final model, the hazard ratios for incident AF comparing the second, third, and fourth quartiles of carbohydrate intake as a percentage of energy with the first quartile were 0.79 (95% CI, 0.68–0.92), 0.77 (95% CI, 0.64–0.93), and 0.64 (95% CI, 0.49–0.84) separately (Table 2, Figure 2). Figure 3 shows the restricted cubic splines of the risk of incident AF across levels of carbohydrate intake as a percentage of energy intake. Consistent with the analysis using quartiles of sample distribution, the risk of incident AF increased in participants with a lower carbohydrate intake. However, there was no significant difference for risk of incident AF in participants with carbohydrate intake as a percentage of energy >62%, compared with the reference level of 50% (Figure 3).

There were similar results in the time-varying sensitivity analysis (Tables S2 and S3). When stratified by age, sex, race, and presence of hypertension, the associations between carbohydrate intake and incident AF were stronger in white participants, women, older participants, and participants with hypertension; however, all interactions were not statistically significant ($P>0.05$ for all interactions, Tables S4 through S7). In sensitivity analysis, the association between carbohydrate intake and incident AF persisted after excluding participants with prevalent coronary artery disease, prevalent heart failure, prevalent stroke, or diabetes mellitus at baseline (Table S8).

To further explore the effects of source of fat and protein alternatives to low-carbohydrate intake, we analyzed the association of animal- or plant-based low-carbohydrate diet

Table 1. Baseline Characteristics of Study Participants by Quartiles of Carbohydrate Intake as a Percentage of Energy

Characteristic	Total (n=13 384)	Quartile 1 (n=3344)	Quartile 2 (n=3345)	Quartile 3 (n=3349)	Quartile 4 (n=3347)	*P* Value
Carbohydrate, % of energy	48.8±9.4	37.2±4.7	45.8±1.7	51.5±1.8	60.8±5.3	<0.001
Age, y	54.2±5.8	53.9±5.7	54.2±5.8	54.3±5.8	54.3±5.8	0.018
Sex						<0.001
Men	6036 (45.1)	1772 (53.0)	1547 (46.2)	1477 (44.1)	1240 (37.0)	
Women	7349 (54.9)	1572 (47.0)	1798 (53.8)	1872 (55.9)	2107 (63.0)	
Race						<0.001
Black	3393 (25.3)	730 (21.8)	814 (24.3)	879 (26.2)	970 (29.0)	
White	9992 (74.7)	2614 (78.2)	2531 (75.7)	2470 (73.8)	2377 (71.0)	
BMI, kg/m^2	27.6±5.3	27.8±5.1	27.8±5.3	27.5±5.3	27.3±5.5	<0.001
Change in BMI, kg/m^2						
3-y Change	0.36±1.7	0.35±1.7	0.34±1.7	0.33±1.7	0.42±1.7	0.127
6-y Change	0.93±2.1	0.91±2.3	0.92±2.2	0.92±2.1	0.96±2.1	0.812
BSA, m^2	1.91±0.2	1.94±0.2	1.92±0.2	1.90±0.2	1.87±0.2	<0.001
Hypertension	4750 (34.1)	1116 (33.4)	1118 (33.4)	1136 (33.9)	1200 (35.9)	0.108
Stroke	625 (4.7)	160 (4.8)	151 (4.5)	159 (4.7)	155 (4.6)	0.953
Diabetes mellitus	1239 (9.3)	356 (10.6)	334 (10.0)	278 (8.3)	271 (8.1)	<0.001
Coronary artery disease	643 (4.8)	151 (4.5)	155 (4.6)	151 (4.5)	186 (5.6)	0.132
Heart failure	607 (4.5)	144 (4.3)	137 (4.1)	147 (4.4)	179 (5.3)	0.067
Smoking						<0.001
Current smoker	3504 (26.2)	1056 (31.6)	897 (26.8)	785 (23.4)	766 (22.9)	
Former smoker	4377 (32.7)	1191 (35.6)	1100 (32.9)	1105 (33.0)	981 (29.3)	
Never smoker	5504 (41.1)	1097 (32.8)	1348 (40.3)	1459 (43.6)	1600 (47.8)	
Drinking						<0.001
Current drinker	7650 (57.2)	2379 (71.1)	2034 (60.8)	1801 (53.8)	1436 (42.9)	
Former drinker	2488 (18.6)	480 (14.4)	575 (17.2)	625 (18.7)	808 (24.1)	
Never drinker	3247 (24.3)	485 (14.5)	736 (22.0)	923 (27.6)	1103 (33.0)	
Education level						<0.001
Basic or 0 y	3048 (22.8)	662 (19.8)	730 (21.8)	780 (23.3)	876 (26.2)	
Intermediate	5492 (41.0)	1319 (39.4)	1319 (39.4)	1369 (40.9)	1404 (41.9)	
Advanced	4845 (36.2)	1363 (40.8)	1246 (37.2)	1165 (34.8)	1071 (32.0)	
Sport	2.3 (1.8–3.0)	2.3 (1.8–3.0)	2.3 (1.8–3.0)	2.3 (1.8–3.0)	2.3 (1.8–3.0)	0.003
Physical activity	2.3 (2.0–2.8)	2.3 (2.0–2.8)	2.3 (2.0–2.8)	2.3 (2.0–2.8)	2.3 (2.0–2.8)	<0.001
Total cholesterol, mmol/L	5.5±1.1	5.5±1.1	5.5±1.1	5.5±1.1	5.6±1.1	0.266
HDL-C, mmol/L	1.3±0.4	1.4±0.5	1.3±0.4	1.3±0.4	1.3±0.4	<0.001
LDL-C, mmol/L	3.6±1.0	3.5±1.0	3.6±1.0	3.5±1.0	3.6±1.0	0.042
Lg triglycerides, lg(mmol/L)	0.099±0.21	0.097±0.21	0.096±0.21	0.099±0.21	0.104±0.21	0.345
Creatinine, mg/dL	1.1±0.4	1.1±0.4	1.1±0.5	1.1±0.3	1.1±0.3	0.007
Uric acid, mg/dL	6.0±1.6	6.2±1.6	6.0±1.6	6.0±1.5	6.0±1.6	<0.001
Total energy intake, kcal	1623.4±609.0	1592.9±604.2	1660.0±601.5	1656.3±596.3	1584.6±629.9	<0.001
Total fat, % of energy	32.9±6.8	38.4±6.3	35.1±4.5	31.9±4.0	26.1±4.8	<0.001
Animal fat, % of energy	19.9±6.2	25.6±5.9	21.4±4.4	18.5±3.9	14.3±4.0	<0.001

Continued

Table 1. Continued

Characteristic	Total (n=13 384)	Quartile 1 (n=3344)	Quartile 2 (n=3345)	Quartile 3 (n=3349)	Quartile 4 (n=3347)	*P* Value
Plant fat, % of energy	13.0±5.1	12.9±5.4	13.8±5.1	13.4±4.8	11.8±4.6	<0.001
Total protein, % of energy	17.9±4.2	20.3±4.3	18.6±3.5	17.5±3.4	15.3±3.6	<0.001
Animal protein, % of energy	13.5±4.3	16.4±4.5	14.2±3.6	12.9±3.4	10.6±3.3	<0.001
Plant protein, % of energy	4.4±1.2	4.0±1.1	4.4±1.1	4.6±1.2	4.7±1.5	<0.001
Dietary fiber, g	17.2±8.2	14.0±6.7	17.0±7.2	18.4±7.7	19.6±9.8	<0.001
Glycemic index	588.6±263.3	447.7±196.6	574.8±226.6	641.8±259.4	689.9±294.7	<0.001
Glycemic load	10 439±4673	7532±3189	9928±3661	11 295±4168	12 995±5516	<0.001

Data are median (interquartile range), mean±SD, or number (percentage), unless otherwise indicated. Baseline characteristics are from the study population (n=13 384) at baseline visit 1, according to quartiles of carbohydrate intake as a percentage of energy intake. BMI indicates body mass index; BSA, body surface area; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

scores with incident AF using Cox hazard regression analysis. However, no significant relationship could be found (Tables S9 and S10).

Discussion

In this large, prospective, cohort study with a long-term follow-up of >20 years, we found that low-carbohydrate intake as a percentage of energy was associated with a higher risk of incident AF, which was independent of other well-known risk factors for incident AF. The association was consistently observed in several sensitivity analyses (Tables S2 through S8). No relationship was found in the further exploration of the effects of source of fat and protein alternatives to low-carbohydrate intake. To the best of our knowledge, it is the first large prospective cohort study to assess the relationship of carbohydrate intake with risk of incident AF.

Previous assessments of dietary exposures in relation to AF mostly focused on the effect of omega-3 fatty acid from fish, although with controversial conclusions.[18–24] In the PREDIMED (Prevención con Dieta Mediterránea) trial,[25] Martinez-Gonzalez et al found that extravirgin olive oil in the context of a Mediterranean dietary pattern may reduce the risk of AF. Other studies[26–28] also found inconsistent associations between chocolate, coffee, and AF. Similarly, our study also evaluated the relationship between diet factors and incident AF. The adverse association of carbohydrate intake with incident AF found in our study supplemented the relationship of macronutrient and risk of AF.

A low-carbohydrate diet, with the reduction of carbohydrate intake and thereby encouragement of high protein or fat intake, is now widely recommended for weight control, for the effect of significant weight loss in the short-term without feeling hungery.[29] However, the long-term effectiveness and safety of low-carbohydrate diets remain controversial. Several studies reported that the weight loss effect of a low-carbohydrate diet was observed for 6 months only and was no longer significant after 12 months, compared with the energy-restricted low-fat diet.[30–32] The effect of weight loss

Table 2. Risk of Incident AF for Carbohydrate Intake as a Percentage of Energy

Carbohydrate Intake (% of Energy)	Model 1*		Model 2†		Model 3‡	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Quartiles						
1 (≤42.70)	1.00 (Reference)	···	1.00 (Reference)	···	1.00 (Reference)	···
2 (42.71–48.55)	0.84 (0.74–0.95)	0.007	0.77 (0.67–0.90)	0.001	0.79 (0.68–0.92)	0.002
3 (48.56–54.74)	0.84 (0.74–0.96)	0.008	0.73 (0.61–0.88)	0.001	0.77 (0.64–0.93)	0.007
4 (≥54.75)	0.79 (0.69–0.90)	<0.001	0.62 (0.48–0.81)	<0.001	0.64 (0.49–0.84)	0.001
Per 1 SD (9.4%)	0.93 (0.89–0.98)	0.003	0.79 (0.70–0.91)	0.001	0.82 (0.72–0.94)	0.005

AF indicates atrial fibrillation; HR, hazard ratio.
*Adjusted for age, sex, and race.
†Further adjusted for total energy intake, total fat intake as a percentage of energy, animal fat intake as a percentage of energy, total protein intake as a percentage of energy, animal protein intake as a percentage of energy, dietary fiber intake, glycemic index, and glycemic load.
‡Further adjusted for body mass index, body surface area, smoking, drinking, education level, sport, physical activity, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, creatinine, uric acid, hypertension, stroke, diabetes mellitus, coronary artery disease, and heart failure.

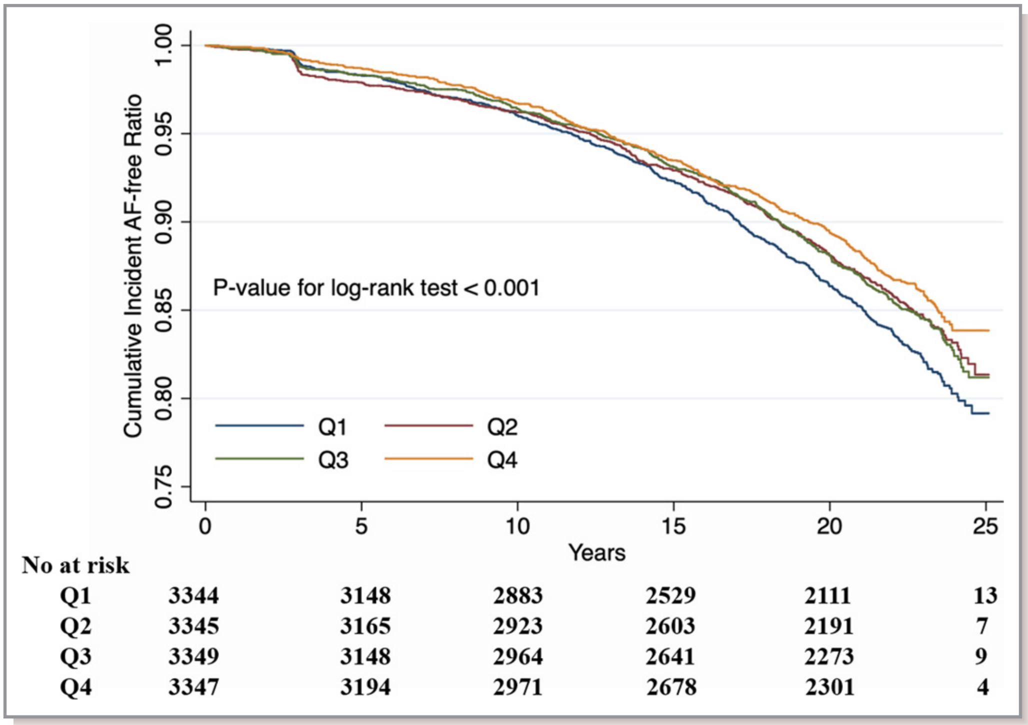

Figure 2. Kaplan-Meier curve of incident atrial fibrillation (AF) by quartiles of carbohydrate intake as a percentage of energy.

might be attributable to excretion of bound water; decreased energy intake, by appetite suppression or satiation; and increased energy expenditure.[29,33] For the safety of a low-carbohydrate diet, previous studies reported inconsistent conclusions. In the study by Lagiou et al,[9] low-carbohydrate–high-protein diets were associated with increased risk of cardiovascular disease. On the contrary, Bazzano et al[6] reported the reduction of cardiovascular risk factors in a low-carbohydrate diet; and in the study by Halton et al,[8] a lower-carbohydrate diet was not associated with increased risk of coronary artery disease. Two recent studies for 2 large prospective cohorts (the PURE and ARIC Studies), combined with a meta-analysis study of several previous studies, reported a U-shaped association of carbohydrate intake and total mortality, whereas no association was found between carbohydrate intake and risk of cardiovascular disease (myocardial infarction, stroke, and heart failure) or cardiovascular mortality.[5,10] However, none of these studies assessed the potential relationship between carbohydrate intake and incident AF, which is also a common cardiovascular disease in clinical practice, with high mortality. Interestingly, our study, for the first time, discovered the adverse effect of a low-carbohydrate diet to AF, which provided a novel potential risk factor for the primary prevention of AF. In view of the different effect of food source used to replace carbohydrate to the risk of total mortality, as the previous study described,[5] we further explored the association of animal- or plant-based low-carbohydrate diet scores with incident AF; no association could be found, which suggests that the increased risk of AF caused by a low-carbohydrate intake was not related to the source of food used to replace carbohydrate.

Several potential mechanisms may explain the observed inverse association. First, a low-carbohydrate diet may lead to lower intake of vegetables, fruits, and grain, as well as the vitamins they contain, which may reduce their anti-inflammatory effects[34] and stimulate inflammatory pathways. As the association between a proinflammatory state and incidence of AF has been extensively demonstrated,[25,35] reducing intake of these anti-inflammatory foods may be one of the important mechanisms for the risk of incident AF. Second, a low-carbohydrate diet with increased protein and fat consumption may stimulate oxidative stress,[36] which was also demonstrated to be associated with incident AF.[37] Finally, the effect could result from the increased risk of other cardiovascular disease during the follow-up, which is a known risk factor for AF.[38] Nevertheless, the effect of a low-carbohydrate intake on other cardiovascular disease is still controversial, as mentioned above.

Strengths and Limitations

Our analysis has important strengths. We used a large community-based biracial cohort with a long follow-up duration and adequate AF events to test our hypotheses.

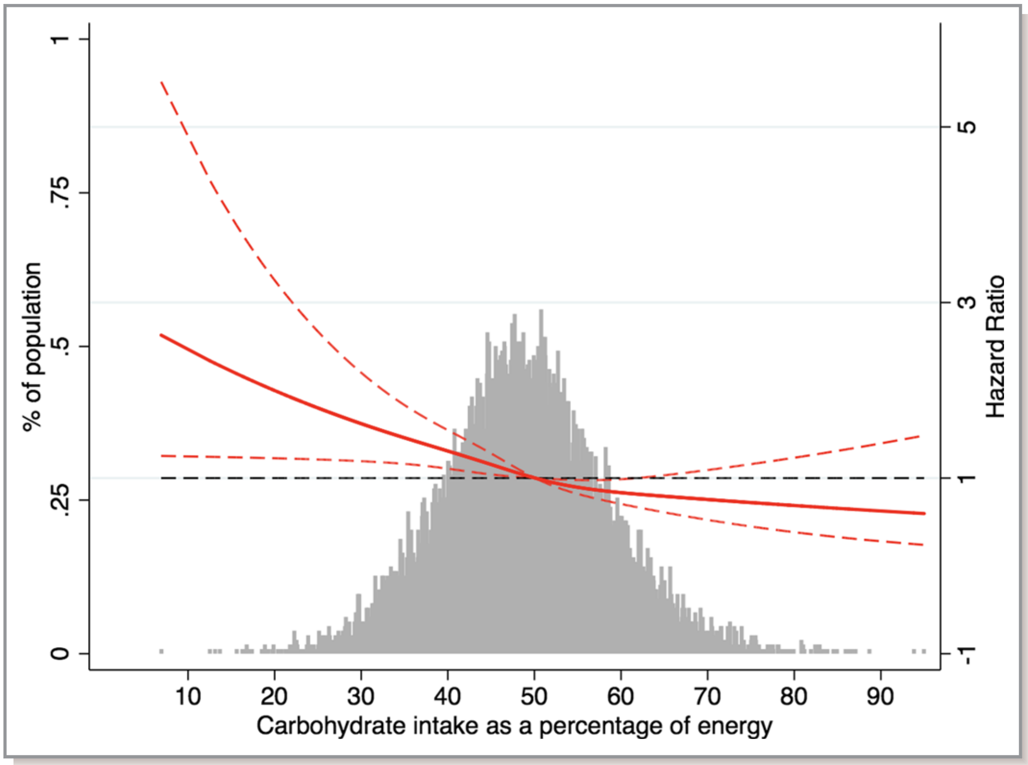

Figure 3. Adjusted hazard ratios of atrial fibrillation by baseline carbohydrate intake as a percentage of energy. Each hazard ratio was computed with a carbohydrate intake level of 50% as the reference. The hazard ratio was adjusted for age, race, total energy intake, total fat intake as a percentage of energy, animal fat intake as a percentage of energy, total protein intake as a percentage of energy, animal protein intake as a percentage of energy, dietary fiber intake, glycemic index, glycemic load, body mass index, smoking, drinking, education level, sport, physical activity, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, creatine, uric acid, hypertension, stroke, diabetes mellitus, coronary artery disease, and heart failure. Red solid line represents the hazard ratio of carbohydrate intake across the whole range. Red dotted lines represent the 95% CI. Black dotted lines is the reference line as hazard ratio =1. Histograms represent the frequency distribution of carbohydrate intake as a percentage of energy at baseline.

The ARIC Study's design, with the extensive and rigorous measurement of covariates, allows us to perform comprehensive statistical adjustment and reduce confounding as much as possible. AF incidence in the ARIC Study is consistent with other population-based studies, and the use of hospital discharge records for the AF ascertainment has been previously validated in the ARIC Study.[14,39–41] There are also some limitations to consider. First, in the method of AF ascertainment, most AF events were found through hospital discharge codes. As a result, individuals with asymptomatic AF or those managed in an outpatient setting, not requiring hospital admission, were unable to be identified. Second, we are unable to classify AF type (paroxysmal, persistent, or permanent AF) accurately in the ARIC Study, so the relationship between carbohydrate intake and incident AF we found was not detailed enough. Third, our study was based on the diet information at the baseline, and dietary patterns could change during >20 years of follow-up. We conducted a time-varying sensitivity analysis spanning 6 years to minimize the bias as possible, and the result was similar, although the change after 6 years could not be assessed because of the unavailable data in the ARIC Study. Fourth, some degree of measurement error is unavoidable for the dietary assessment methods. As a result, the interpretation of absolute intakes should be cautious. Last, as it is an observational study, we could not exclude residual confounding, despite the fact that we adjusted for potential covariates as much as possible. More randomized controlled trials, with rigorously controlled food types and alternative energy sources, are needed to confirm this hypothesis, although it is difficult because of the long duration of study required.

In conclusion, we found that a low-carbohydrate intake was associated with increased risk of incident AF, regardless of the type of protein and fat used to replace the carbohydrate. A low-carbohydrate diet, a way to control weight, should be cautiously recommended, especially considering the potential influence on arrhythmia.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1 Criteria for determining the low-carbohydrate-diet scores.

Points	Carbohydrate Intake	Animal-Protein Intake	Animal-Fat Intake	Vegetable-Protein Intake	Vegetable-Fat Intake
	percentage of energy				
0	>61.3	≤8.2	≤12.0	≤3.0	≤6.6
1	57.1-61.3	8.2-9.7	12.0-14.3	3.0-3.4	6.6-8.3
2	54.0-57.1	9.7-10.8	14.3-16.0	3.4-3.7	8.3-9.7
3	51.7-54.0	10.8-11.8	16.0-17.6	3.7-3.9	9.7-10.9
4	49.6-51.7	11.8-12.7	17.6-19.0	3.9-4.2	10.9-12.0
5	47.6-49.6	12.7-13.6	19.0-20.3	4.2-4.4	12.0-13.1
6	45.6-47.6	13.6-14.6	20.3-21.8	4.4-4.7	13.1-14.3
7	43.3-45.6	14.6-15.7	21.8-23.4	4.7-5.1	14.3-15.6
8	40.6-43.3	15.7-17.0	23.4-25.3	5.1-5.5	15.6-17.3
9	36.6-40.6	17.0-19.2	25.3-28.4	5.5-6.1	17.3-19.8
10	≤36.6	>19.2	>28.4	>6.1	>19.8

Table S2 Time varying sensitivity analysis for risk of incident AF for carbohydrate intake as a percentage of energy, excluding participants with missing dietary data in visit 3.

Carbohydrate intake (% of energy)	Model 1* HR (95% CI)	Model 1* *P*	Model 2† HR (95% CI)	Model 2† *P*	Model 3‡ HR (95% CI)	Model 3‡ *P*
Quartiles						
Q1 (≤43.90)	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Q2 (43.90-49.15)	0.83 (0.73-0.96)	0.011	0.80 (0.69-0.93)	0.003	0.86 (0.74-0.99)	0.040
Q3 (49.15-54.47)	0.77 (0.67-0.89)	<0.001	0.72 (0.61-0.85)	<0.001	0.78 (0.66-0.93)	0.005
Q4 (≥54.47)	0.74 (0.64-0.85)	<0.001	0.66 (0.53-0.81)	<0.001	0.73 (0.60-0.90)	0.004
Per 1 SD (8.2%)	0.90 (0.87-0.95)	<0.001	0.86 (0.79-0.93)	<0.001	0.90 (0.83-0.98)	0.018

*Adjusted for age, sex, race.

†Further adjusted for total energy intake, total fat intake as a percentage of energy, animal fat intake as a percentage of energy, total protein intake as a percentage of energy, animal protein intake as a percentage of energy, dietary fiber intake, glycemic index, glycemic load.

‡Further adjusted for BMI, smoking, drinking, education level, sport, physical activity, total cholesterol,

HDL-c, LDL-c, total triglycerides, creatinine, uric acid, hypertension, stroke, diabetes, coronary artery disease, heart failure.

AF = atrial fibrillation

Table S3 Time varying sensitivity analysis for risk of incident AF for carbohydrate intake as a percentage of energy, replacing missing dietary information in visit 3 by data from visit 1.

Carbohydrate intake (% of energy)	Model 1*		Model 2†		Model 3‡	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Quartiles						
Q1 (≤43.69)	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Q2 (43.69-49.03)	0.85 (0.75-0.97)	0.014	0.81 (0.71-0.93)	0.003	0.88 (0.77-1.01)	0.070
Q3 (49.03-54.58)	0.80 (0.71-0.91)	0.001	0.74 (0.63-0.87)	<0.001	0.83 (0.71-0.97)	0.017
Q4 (≥54.58)	0.76 (0.67-0.87)	<0.001	0.67 (0.56-0.82)	<0.001	0.75 (0.62-0.92)	0.006
Per 1 SD (8.6%)	0.91 (0.87-0.96)	<0.001	0.86 (0.79-0.93)	<0.001	0.90 (0.83-0.98)	0.017

*Adjusted for age, sex, race.

†Further adjusted for total energy intake, total fat intake as a percentage of energy, animal fat intake as a percentage of energy, total protein intake as a percentage of energy, animal protein intake as a percentage of energy, dietary fiber intake, glycemic index, glycemic load.

‡Further adjusted for BMI, smoking, drinking, education level, sport, physical activity, total cholesterol,

HDL-c, LDL-c, total triglycerides, creatinine, uric acid, hypertension, stroke, diabetes, coronary artery disease, heart failure.

AF = atrial fibrillation

Table S4 Risk of incident AF for carbohydrate intake as a percentage of energy, stratified by race

Carbohydrate intake (% of energy)	Model 1[†] HR (95% CI)	Model 1[†] *P*	Model 2[‡] HR (95% CI)	Model 2[‡] *P*	Model 3[§] HR (95% CI)	Model 3[§] *P*
Black						
Quartiles						
Q1 (≤42.70)	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Q2 (42.71-48.55)	0.83 (0.61-1.13)	0.24	0.77 (0.53-1.11)	0.16	0.79 (0.55-1.15)	0.79
Q3 (48.56-54.74)	0.94 (0.70-1.26)	0.68	0.84 (0.54-1.32)	0.45	0.89 (0.57-1.41)	0.62
Q4 (≥54.75)	0.73 (0.54-0.99)	0.04	0.60 (0.32-1.14)	0.12	0.67 (0.34-1.29)	0.23
While						
Quartiles						
Q1 (≤42.70)	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Q2 (42.71-48.55)	0.84 (0.73-0.97)	0.015	0.77 (0.65-0.91)	0.002	0.79 (0.67-0.93)	0.005
Q3	0.82	0.007	0.71	0.001	0.74	0.005

(48.56-54.74)	(0.72-0.95)		(0.58-0.87)		(0.60-0.91)	
Q4 (⩾54.75)	0.81 (0.70-0.94)	0.004	0.63 (0.47-0.83)	0.001	0.64 (0.48-0.85)	0.003
P for interaction	0.628		0.643		0.735	

†Adjusted for age, sex.

‡Further adjusted for total energy intake, total fat intake as a percentage of energy, animal fat intake as a percentage of energy, total protein intake as a percentage of energy, animal protein intake as a percentage of energy, dietary fiber intake, glycemic index, glycemic load.

§Further adjusted for BMI, smoking, drinking, education level, sport, physical activity, total cholesterol, HDL-c, LDL-c, triglycerides, creatinine, uric acid, hypertension, stroke, diabetes, coronary artery disease, heart failure.

AF = atrial fibrillation

Table S5 Risk of incident AF for coronary intake as a percentage of energy, stratified by sex

Carbohydrate intake (% of energy)	Model 1† HR (95% CI)	Model 1† *P*	Model 2‡ HR (95% CI)	Model 2‡ *P*	Model 3§ HR (95% CI)	Model 3§ *P*
female						
Quartiles						
Q1 (≤42.70)	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Q2 (42.71-48.55)	0.73 (0.60-0.90)	0.003	0.67 (0.53-0.85)	0.001	0.67 (0.53-0.85)	0.001
Q3 (48.56-54.74)	0.87 (0.71-1.05)	0.137	0.74 (0.52-0.97)	0.030	0.76 (0.57-1.00)	0.050
Q4 (≥54.75)	0.78 (0.64-0.94)	0.010	0.59 (0.40-0.86)	0.007	0.59 (0.40-0.88)	0.010
male						
Quartiles						
Q1 (≤42.70)	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Q2 (42.71-48.55)	0.92 (0.78-1.09)	0.335	0.86 (0.70-1.04)	0.116	0.88 (0.73-1.08)	0.223
Q3	0.82	0.023	0.72	0.010	0.75	0.027

(48.56-54.74)	(0.69-0.97)		(0.56-0.92)		(0.58-0.97)	
Q4 (≥54.75)	0.79 (0.66-0.95)	0.013	0.64 (0.45-0.91)	0.013	0.65 (0.45-0.94)	0.022
P for interaction	0.162		0.154		0.075	

†Adjusted for age, race.

‡Further adjusted for total energy intake, total fat intake as a percentage of energy, animal fat intake as a percentage of energy, total protein intake as a percentage of energy, animal protein intake as a percentage of energy, dietary fiber intake, glycemic index, glycemic load.

§Further adjusted for BMI, smoking, drinking, education level, sport, physical activity, total cholesterol, HDL-c, LDL-c, triglycerides, creatinine, uric acid, hypertension, stroke, diabetes, coronary artery disease, heart failure.

AF = atrial fibrillation

Table S6 Risk of incident AF for coronary intake as a percentage of energy, stratified by age

Carbohydrate intake (% of energy)	Model 1† HR (95% CI)	Model 1† *P*	Model 2‡ HR (95% CI)	Model 2‡ *P*	Model 3§ HR (95% CI)	Model 3§ *P*
Age <51						
Quartiles						
Q1 (⩽42.70)	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Q2 (42.71-48.55)	0.88 (0.64-1.21)	0.43	0.90 (0.62-1.31)	0.58	0.94 (0.64-1.38)	0.74
Q3 (48.56-54.74)	0.96 (0.71-1.31)	0.80	1.04 (0.65-1.65)	0.88	1.09 (0.67-1.77)	0.73
Q4 (⩾54.75)	0.84 (0.61-1.17)	0.30	1.00 (0.52-1.94)	1.00	0.97 (0.49-1.91)	0.92
51 ⩽ Age <57						
Quartiles						
Q1 ⩽ 42.70	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Q2 42.71-48.55	0.84 (0.66-1.07)	0.158	0.86 (0.65-1.15)	0.314	0.85 (0.64-1.13)	0.267
Q3 48.56-	0.97 (0.77-	0.798	1.03 (0.73-	0.850	1.12 (0.79-	0.522

54.74		1.23)			1.46)			1.59)	
Q4 ≥ 54.75		0.81 (0.63-1.03)		0.087	0.86 (0.53-1.42)		0.562	0.95 (0.57-1.58)	0.841
Age ≥ 57									
Quartiles									
Q1 (≤42.70)		1.00 (reference)		-	1.00 (reference)		-	1.00 (reference)	-
Q2 (42.71-48.55)		0.84 (0.71-1.00)		0.043	0.70 (0.58-0.86)		<0.001	0.73 (0.60-0.89)	0.002
Q3 (48.56-54.74)		0.78 (0.66-0.93)		0.005	0.58 (0.45-0.73)		<0.001	0.59 (0.46-0.76)	<0.001
Q4 (≥54.75)		0.78 (0.65-0.93)		0.005	0.47 (0.33-0.66)		<0.001	0.47 (0.33-0.67)	<0.001
P for interaction		0.778			0.777			0.578	

†Adjusted for gender, race.

‡Further adjusted for total energy intake, total fat intake as a percentage of energy, animal fat intake as a percentage of energy, total protein intake as a percentage of energy, animal protein intake as a percentage of energy, dietary fiber intake, glycemic index, glycemic load.

§Further adjusted for BMI, smoking, drinking, education level, sport, physical activity, total cholesterol, HDL-c, LDL-c, triglycerides, creatinine, uric acid, hypertension, stroke, diabetes, coronary artery disease, heart failure.

AF = atrial fibrillation

Table S7 Risk of incident AF for coronary intake as a percentage of energy, stratified by hypertension.

Carbohydrate intake (% of energy)	Model 1† HR (95% CI)	Model 1† *P*	Model 2‡ HR (95% CI)	Model 2‡ *P*	Model 3§ HR (95% CI)	Model 3§ *P*
Hypertension						
Quartiles						
Q1 (≤42.70)	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Q2 (42.71-48.55)	0.88 (0.73-1.06)	0.17	0.80 (0.64-0.99)	0.043	0.76 (0.61-0.96)	0.018
Q3 (48.56-54.74)	0.77 (0.64-0.94)	0.009	0.66 (0.50-0.87)	0.003	0.64 (0.48-0.85)	0.002
Q4 (≥54.75)	0.69 (0.56-0.83)	<0.001	0.52 (0.35-0.78)	0.001	0.49 (0.33-0.73)	<0.001
Free from hypertension						
Quartiles						
Q1 (≤42.70)	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Q2 (42.71-48.55)	0.82 (0.68-0.97)	0.022	0.77 (0.63-0.94)	0.012	0.79 (0.65-0.97)	0.026
Q3	0.90	0.250	0.83	0.135	0.89	0.367

(48.56-54.74)	(0.76-1.07)		(0.65-1.00)		(0.69-1.15)	
Q4 (≥54.75)	0.87 (0.73-1.04)	0.134	0.76 (0.54-1.08)	0.121	0.82 (0.57-1.17)	0.261
P for interaction	0.098		0.098		0.094	

†Adjusted for gender, race, age

‡Further adjusted for total energy intake, total fat intake as a percentage of energy, animal fat intake as a percentage of energy, total protein intake as a percentage of energy, animal protein intake as a percentage of energy, dietary fiber intake, glycemic index, glycemic load.

§Further adjusted for BMI, smoking, drinking, education level, sport, physical activity, total cholesterol, HDL-c, LDL-c, triglycerides, creatinine, uric acid, stroke, diabetes, coronary artery disease, heart failure.

AF = atrial fibrillation

Table S8 Risk of incident AF for carbohydrate intake as a percentage of energy, excluded of patients with cardiovascular disease or diabetes.

Carbohydrate intake (% of energy)	Model 1[†] HR (95% CI)	Model 1[†] *P*	Model 2[‡] HR (95% CI)	Model 2[‡] *P*	Model 3[§] HR (95% CI)	Model 3[§] *P*
Quartiles						
Q1 (≤42.70)	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Q2 (42.71-48.55)	0.84 (0.72-0.97)	0.021	0.77 (0.65-0.92)	0.003	0.79 (0.66-0.94)	0.009
Q3 (48.56-54.74)	0.84 (0.72-0.98)	0.024	0.73 (0.59-0.91)	0.005	0.76 (0.61-0.94)	0.013
Q4 (≥54.75)	0.78 (0.67-0.91)	0.002	0.61 (0.45-0.83)	0.002	0.64 (0.46-0.87)	0.005
Per 1 SD (9.3%)	0.92 (0.87-0.98)	0.006	0.77 (0.66-0.89)	0.001	0.79 (0.68-0.93)	0.005

[†]Adjusted for age, sex, race.

[‡]Further adjusted for total energy intake, total fat intake as a percentage of energy, animal fat intake as a percentage of energy, total protein intake as a percentage of energy, animal protein intake as a percentage of energy, dietary fiber intake, glycemic index, glycemic load.

[§]Further adjusted for BMI, smoking, drinking, education level, sport, physical activity, total cholesterol, HDL-c, LDL-c, triglycerides, creatinine, uric acid, hypertension.

AF = atrial fibrillation

Table S9 Risk of incident AF for animal-based low-carbohydrate diet scores

Low-carbohydrate diet scores	Model 1[†]		Model 2[‡]		Model 3[§]	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Quartiles						
Q1 (≤9)	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Q2 (10-15)	1.05 (0.92-1.19)	0.472	1.04 (0.89-1.22)	0.631	1.05 (0.89-1.24)	0.563
Q3 (16-21)	0.94 (0.82-1.07)	0.340	0.93 (0.75-1.16)	0.531	0.94 (0.76-1.16)	0.543
Q4 (22-30)	1.18 (1.04-1.33)	0.011	1.17 (0.87-1.58)	0.295	1.17 (0.87-1.58)	0.302
Continuous	1.01 (1.00-1.01)	0.051	1.01 (0.98-1.04)	0.984	1.01 (0.99-1.04)	0.442

[†]Adjusted for age, sex, race.

[‡]Further adjusted for total energy intake, total fat intake as a percentage of energy, animal fat intake as a percentage of energy, total protein intake as a percentage of energy, animal protein intake as a percentage of energy, dietary fiber intake, glycemic index, glycemic load.

[§]Further adjusted for BMI, smoking, drinking, education level, sport, physical activity, total cholesterol, HDL-c, LDL-c, triglycerides, creatinine, uric acid, hypertension.

AF = atrial fibrillation

Table S10 Risk of incident AF for plant-based low-carbohydrate diet scores

Low-carbohydrate diet scores	Model 1†		Model 2‡		Model 3§	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Quartiles						
Q1 (≤11)	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Q2 (12-15)	0.95 (0.83-1.09)	0.460	0.91 (0.77-1.06)	0.220	0.92 (0.79-1.08)	0.319
Q3 (16-19)	1.05 (0.93-1.20)	0.437	0.99 (0.82-1.20)	0.939	1.01 (0.83-1.22)	0.949
Q4 (20-30)	1.14 (1.00-1.30)	0.049	1.05 (0.81-1.37)	0.700	1.04 (0.80-1.35)	0.792
Continuous	1.01 (1.00-1.01)	0.026	1.00 (0.97-1.03)	0.987	1.00 (0.98-1.03)	0.772

†Adjusted for age, sex, race.

‡Further adjusted for total energy intake, carbohydrate intake as a percentage of energy, total fat intake as a percentage of energy, animal fat intake as a percentage of energy, total protein intake as a percentage of energy, animal protein intake as a percentage of energy, dietary fiber intake, glycemic index, glycemic load.

§Further adjusted for BMI, smoking, drinking, education level, sport, physical activity, total cholesterol, HDL-c, LDL-c, triglycerides, creatinine, uric acid, hypertension.

AF = atrial fibrillation