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Clinical Research Article

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Meal Timing of Subtypes of Macronutrients Consumption With Cardiovascular Diseases: NHANES, 2003 to 2016

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Abbreviations:BMI, body mass index; CVD, cardiovascular disease; HOMA-IR, homeostasis model assessment of insulin resistance; NHANES, US National Health and Nutrition Examination Survey; OR, odds ratio; SFA, saturated fatty acid; USFA, unsaturated fatty acid.

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Abstract

Context: Emerging evidence suggests that not only the quantity but also the quality and food sources of macronutrients plays an important role in CVD. However, limited studies have examined the association of meal timing of different quality of macronutrients with CVD risk.

Objective: This study aimed to examine the association of subtypes of macronutrient consumption at dinner vs breakfast with cardiovascular diseases (CVD).

Methods: A total of 27 911 participants from the National Health and Nutrition Examination Survey (2003-2016) were included. The differences of subtypes of macronutrients at dinner vs breakfast (Δratio) were categorized into quintiles. Multiple logistic regression models and isocaloric substitution effects of subtypes were performed.

Results: After adjustment of a variety of covariates, participants in the highest quintile of the Δratio of low-quality carbohydrates had a higher risk of angina (odds ratio [OR] = 1.63; 95% CI, 1.16-2.29) ($P_{\text{for trend}}$ = .007) and heart attack (OR = 1.47; 95% CI, 1.13-1.93) ($P_{\text{for trend}}$ = .068) compared with the lowest quintile. The highest quintile of the Δratio of animal protein had a higher risk of coronary heart disease (OR = 1.44; 95% CI, 1.06-1.95) ($P_{\text{for trend}}$ = .014) and angina (OR = 1.44; 95% CI, 1.01-2.07) ($P_{\text{for trend}}$ = .047). For the Δratio of unsaturated fatty acid (USFA), the highest quintile of the Δratio of USFA was related to lower stroke risk (OR = 0.76; 95% CI, 0.58-0.99) ($P_{\text{for trend}}$ = .049). Isocaloric substitution of low-quality carbohydrates/animal protein by high-quality carbohydrates/plant protein at dinner reduced CVD risk by around 10%.

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Conclusion: This study indicated that overconsumption of low-quality carbohydrates and animal protein at dinner rather than breakfast was significantly associated with higher CVD risk and USFA consumption at dinner related to lower CVD risk among US adults. Substitution of low-quality carbohydrates or animal protein by high-quality carbohydrates or plant protein at dinner could reduce CVD risk.

Key Words: subtypes, macronutrients, meal timing, cardiovascular diseases

Cardiovascular disease (CVD) is the main cause of mortality regardless of race, ethnicity, or sex, and almost 46% of noncommunicable disease deaths are attributable to CVD around the globe (1, 2). Diet plays a critical role in the prevention and treatment of CVD (3). Emerging evidence suggests that not only the quantity but also the quality and food sources of macronutrients is a relevant aspect of nutrition and plays an important role in human health (4-7). However, limited studies have examined the association of meal timing of different quality of macronutrients with CVD risk.

Nowadays it appears that meal timing has major effects on metabolic and physiological parameters (8). For example, breakfast skipping (9, 10), late lunch eating (11), and high energy intake at dinner (12-15) were related to a higher risk of obesity, as well as lower overall diet quality and poorer cognitive performance. Late-night eating has been related to a higher risk of poor cardiometabolic health in several observational studies (12, 14, 16). Further, it has been reported that dietary patterns with higher energy load in the evening may lead to metabolic syndrome by the deterioration of postprandial glucose and insulin (17). On the other hand, a high-energy breakfast with a reduced dinner was suggested to be beneficial and considered to be a useful alternative for the management of obesity and metabolic syndrome (18). Meanwhile, a large number of studies have indicated that time-restricted feeding is beneficial for a variety of metabolic responses, reducing insulin resistance, and increasing glucose tolerance (19-22). During the past 2 decades, the overall macronutrient consumption has remained unchanged among US adults, but subtypes of macronutrients obviously changed (23). However, to the best of our knowledge, no studies have examined the association of macronutrients with CVD risk by considering subtypes and meal timing of macronutrients.

In the present study, we classified subtypes of macronutrients based on the food sources using data from the US National Health and Nutrition Examination Survey (NHANES) and examined the association of subtypes consumption at dinner vs breakfast with CVD risk.

Materials and Methods

Study Population

The NHANES is a stratified, multistage study using a nationally representative sample of the population in the United States (24). Detailed information has been provided elsewhere (23). The present study included adults who were older than 20 years and finished at least 1 valid dietary recall during the 7 cycles of NHANES (2003-2016). We excluded participants with extreme energy intake (< 500 kcal/day or > 3500 kcal/day for women and < 800 kcal/day or > 4200 kcal/day for men), pregnant women, and individuals with missing information on current drinking, current smoking, and body mass index (BMI). Ultimately a total of 27 911 participants were included.

The NHANES protocol was approved by the National Center for Health Statistics Research Ethics Review Board, and all participants provided informed consent.

Dietary Assessment

Participants' food consumption for 2 nonconsecutive days through 24-hour dietary recall interviews were collected. The first 24-hour dietary recall was conducted in person and the second was conducted 3 to 10 days later by telephone. Dietary nutrients and energy intake were estimated using the US Department of Agriculture's (USDA's) Food and Nutrient Database for Dietary Studies. We calculated the mean values of nutrient consumption for the 2-day, 24-hour dietary recall.

Based on the MyPyramid Equivalents Database 2.0 for USDA Survey Foods (MPED 2.0), the dietary intake component of the NHANES was integrated into 37 MyPyramid major groups. Similar kinds of food were combined into one subtype in the present study. A total of 6 subtypes of macronutrients were derived, which were high-quality carbohydrates including whole grains, legumes, whole fruits, tomatoes, dark-green vegetables, and other red/orange vegetables; low-quality carbohydrates including refined grains, fruit juice, potatoes, other starchy vegetables, and added sugars; animal protein including unprocessed red meat, processed meat, poultry, seafood, dairy, and eggs; plant protein including whole grains, refined grains, legumes, nuts, and soy; saturated fatty acid (SFA); and unsaturated fatty acid (USFA). Food sources of fat were not examined because they are similar to protein food sources, and existing evidence on fat mostly focuses on types of fatty acids rather than food sources (25). The definitions and serving sizes for each subtype are presented in Supplementary Table 1 (26).

Main Exposure

The main exposure variable in this study was the ratio of breakfast, the ratio of dinner, and the difference in the ratio of subtypes of macronutrient consumption at dinner vs breakfast throughout the day (Δratio). For example, we calculated the ratio of breakfast of high-quality carbohydrates : high-quality carbohydrates consumption at breakfast/total high-quality carbohydrates; the ratio of dinner of high-quality carbohydrates : high-quality carbohydrates consumption at dinner/total high-quality carbohydrates; the Δratio of high-quality carbohydrates : the ratio of dinner of high-quality carbohydrates—the ratio of breakfast of high-quality carbohydrates. The Δratio of macronutrients examined in this study included high-quality carbohydrates, low-quality carbohydrates, SFA, USFA, animal protein, and plant protein.

Main Outcome

Our outcomes were cardiovascular diseases including congestive heart failure, coronary heart disease, angina, heart attack, and stroke. CVD was defined as a positive answer to the question "Have you ever been told you had congestive heart failure/coronary heart disease/angina/heart attack/stroke?" A further detailed description of examination protocol, quality control, and safety procedures are available in the anthropometry procedures manual via the NHANES website.

Assessment of Covariates

Potential covariates were age (years), sex (male/female), race/ethnicity (non-Hispanic White/non-Hispanic Black/Mexican American/other), education level (< 9th grade/9-11th grade/high school graduate/General Educational Development or equivalent/some college or associate of arts degree/college graduate or above), annual household income (< $20 000/$20 000-$45 000/$45 000-$75 000/> $100 000), exercise regularly (yes/no), current smoker (yes/no), current drinker (yes/no), BMI, medicine use for lower blood sugar, medicine use for hypertension, medicine use for cholesterol; total intake of energy (kcal/day), SFA (g/day), high-quality carbohydrates (serving/day), animal protein (serving/day), dietary supplements use (yes/no), breakfast skipping (yes/no), and diet quality calculated by the Alternative Healthy Eating Index (27).

Statistical Analyses

All analyses incorporated the dietary sample weights, stratification, and clustering of the complex sampling design to ensure nationally representative estimates according to the NHANES analytic guidelines. To correct for measurement error, the absolute intakes of foods per day were adjusted for total energy intake by the residual method in dietary estimates (28).

The Δratio, the ratio of breakfast, and the ratio of dinner of subtypes of macronutrients were categorized into quintiles. Demographic characteristics, dietary intake, and anthropometric measurements were presented as means (95% CIs) for continuous variables and weighted percentages (95% CIs) for categorical variables. Characteristics across the NHANES cycle were tested using general linear models adjusting for age and chi-square test for continuous and categorical variables, respectively. Differences in total macronutrient consumption during the day across CVD patients were tested by general linear models adjusting for age.

Multiple logistic regression models were developed to examine the association between the Δratio, the ratio of breakfast, the ratio of dinner and CVD. Odds ratios (ORs) and 95% CIs were provided. To test for linear trend, we modeled categorical variables as continuous by assigning the median value to each quintile. Models were adjusted for age, sex, ethnicity, education level, annual household income, regular exercise, current smoker, current drinker, BMI, the medicine used for lower blood sugar, the medicine used for hypertension, the medicine used for cholesterol, total intake of energy, SFA, high-quality carbohydrates, and animal protein, dietary supplements use, breakfast skipping, and Alternative Healthy Eating Index.

We further explored the isocaloric substitution effects with a one-serving decrease of low-quality carbohydrates or animal protein food and simultaneous one-serving increase of high-quality carbohydrates or plant protein food at dinner with CVD. The low-quality carbohydrates and high-quality carbohydrates consumption at dinner were all included in the same multivariable models as continuous variables. For each isocaloric substitution of low-quality carbohydrates by high-quality carbohydrates, we used the difference between the β coefficients of the 2 variables to estimate the OR, and we used the variances and covariance of the 2 variables to estimate the 95% CI (29). A similar method was performed for the isocaloric substitution effect of animal protein by plant protein. The differences in the estimates statistically predict the isocaloric substitution effects on the risk of CVD.

Sensitivity Analyses

Two sensitivity analyses were performed. The first sensitivity analysis was performed in participants without breakfast skipping, which plays a critical role in the development of CVD (16, 30). Another sensitivity analysis was performed to examine the association of Δprotein foods (Δanimal protein = food consumption at dinner—food consumption at breakfast) with CVD. It is well known that some foods containing animal protein show different associations with CVD, for example, seafood and processed meat (31, 32). We examined the association between the Δratio of animal protein and CVD further adjusted for Δseafood. A 2-sided *P* value less than .05 was considered statistically significant. All analyses were performed by R 3.6.1.

Results

Participant Characteristics

Table 1 illustrates the characteristics of participants across the NHANES cycle (N = 27 911). No significant difference was observed for age, sex, ethnicity, energy, dietary supplementary use, CVD status across the survey cycle ($P \geq .05$). Other variables show significant differences across years ($P < .05$).

Differences in Total Macronutrient Consumption During the Day Across Cardiovascular Disease Patients

Table 2 illustrates the differences in total macronutrient consumption during the day across CVD patients. Total macronutrient consumption shows significant differences across groups of CVD patients. High-quality carbohydrates, low-quality carbohydrates, SFA, USFA, and plant protein consumption during the day show significant differences between congestive heart failure patients (all $P < .05$). High-quality carbohydrates, SFA, and plant protein show significant differences between coronary heart disease patients (all $P < .05$). High-quality carbohydrates, low-quality carbohydrates, SFA, and USFA show significant differences between angina and heart attack (all $P < .05$). High-quality carbohydrates, low-quality carbohydrates, SFA, USFA, and plant protein show significant differences between stroke patients (all $P < .05$).

Association of ΔRatio, Ratio of Breakfast, and Ratio of Dinner of Subtypes of Macronutrients With Cardiovascular Disease

The association of the Δratio of subtypes of macronutrients with CVD is shown in Table 3. After adjustment of a variety of covariates, participants in the highest quintile of the Δratio of low-quality carbohydrates had a higher risk of angina (OR = 1.63; 95% CI, 1.16-2.29) ($P_{\text{for trend}}$ = .007) and heart attack (OR = 1.47; 95% CI, 1.13-1.93) ($P_{\text{for trend}}$ = .068) compared with the lowest quintile. A similar association was found for the Δratio of animal protein, the highest quintile was associated with a higher risk of coronary heart disease (OR = 1.44; 95% CI, 1.06-1.95) ($P_{\text{for trend}}$ = .014) and angina (OR = 1.44; 95% CI, 1.01-2.07) ($P_{\text{for trend}}$ = .047). For the Δratio of USFA, the highest quintile of the Δratio of USFA was related to lower stroke risk (OR = 0.76; 95% CI, 0.58-0.99) ($P_{\text{for trend}}$ = .049). No significant association was found for the Δratio of high-quality carbohydrates, SFA, and plant protein.

The association of ratio of subtypes of macronutrients at breakfast with CVD is shown in Supplementary Table 2 (26). As indicated by the ORs and 95% CIs, the highest quintile of the ratio of USFA at breakfast was significantly associated with a decreased risk of coronary heart disease (OR = 0.62; 95% CI, 0.41-0.92) ($P_{\text{for trend}}$ = .030). Also, the highest quintile of the ratio of animal protein at breakfast was significant associated with a decreased risk of coronary heart disease (OR = 0.59; 95% CI, 0.45-0.77) ($P_{\text{for trend}}$ = .002).

The association of ratio of subtypes of macronutrients at dinner with CVD is shown in Supplementary Table 3 (26). The results illustrate that the highest quintile of the ratio of low-quality carbohydrates and animal protein at dinner was significantly associated with angina ([$OR_{\text{low-quality carbohydrates}}$ 1.54; 95% CI, 1.13-2.10] [$P_{\text{for trend}}$ = .007]; [$OR_{\text{animal protein}}$ = 1.43; 95% CI, 1.01-2.02] [$P_{\text{for trend}}$ = .088]).

Isocaloric Substitution Effects With Subtypes of Carbohydrate and Protein at Dinner With Cardiovascular Disease

Isocaloric substitution effects with the one-serving decrease of low-quality carbohydrates or animal protein food and a simultaneous one-serving increase of high-quality carbohydrates or plant protein food at dinner with CVD are shown in Table 4. Overall, we found the one-serving decrease of low-quality carbohydrates consumption with the simultaneous one-serving increase of high-quality carbohydrates at dinner could reduce the risk of congestive heart failure by 10% (OR 0.90; 95%CI 0.82–0.98) and stroke by 12% (OR 0.88; 95%CI 0.81–0.96). Similarly, one serving decrease of animal protein consumption with simultaneously one serving increase plant protein at dinner could reduce the risk of congestive heart failure by 10% (OR = 0.90; 95% CI, 0.83-0.98) and heart attack by 8% (OR = 0.92; 95% CI 0.86-0.99).

Sensitivity Analyses

After excluding participants who skipped breakfast, the association of Δratio of subtypes of macronutrients with CVD and isocaloric substitution effects was consistent with those from the primary analyses of the total number of participants (Supplementary Tables 4

Table 1. Characteristics of participants across the US National Health and Nutrition Examination Survey cycle, 2003 to 2016

Characteristics	2003-2004 (N = 3572)	2005-2006 (N = 3493)	2007-2008 (N = 4242)	2009-2010 (N = 4596)	2011-2012 (N = 3983)	2013-2014 (N = 4140)	2015-2016 (N = 3885)	*P*
Age, y	47.01 (45.99-48.04)	47.46 (45.84-49.09)	47.71 (46.78-48.65)	47.83 (46.76-48.91)	48.06 (46.39-49.74)	47.87 (47.03-48.70)	48.99 (47.72-50.26)	.451
Female, %	52.30 (50.48-54.11)	52.85 (51.36-54.33)	53.02 (51.40-54.64)	53.03 (51.88-54.17)	52.60 (50.97-54.23)	52.91 (51.00-54.82)	52.36 (50.86-53.86)	.988
Non-Hispanic White, %	73.99 (67.06-79.90)	74.27 (68.45-79.33)	72.08 (65.12-78.12)	70.41 (63.38-76.58)	68.93 (61.27-75.67)	67.57 (60.77-73.70)	67.68 (59.78-74.69)	.890
BMI	28.25 (27.88-28.62)	28.67 (28.16-29.17)	28.62 (28.26-28.98)	28.73 (28.47-28.99)	28.84 (28.41-29.27)	29.11 (28.73-29.48)	29.47 (28.91-30.04)	.013
College graduate or above, %	24.47 (21.07-28.23)	27.46 (23.22-32.14)	27.01 (22.83-31.64)	29.90 (27.34-32.60)	32.49 (27.70-37.69)	32.23 (28.40-36.33)	34.27 (28.07-41.05)	.003
> $100 000 annual household income, %	–	–	18.90 (15.33-23.07)	21.83 (19.70-24.13)	24.17 (18.86-30.42)	26.68 (22.32-31.55)	26.86 (21.58-32.90)	< .001
Exercise regularly, %	17.26 (15.20-19.25)	16.21 (14.59-17.97)	21.41 (18.95-24.09)	20.54 (18.35-22.56)	24.03 (21.93-26.26)	33.61 (31.01-36.32)	21.14 (18.30–24.30)	< .001
Current smoker, %	28.13 (25.50-30.91)	26.17 (23.66-28.85)	25.26 (22.63-28.08)	21.95 (20.25-23.75)	22.15 (19.98-24.49)	19.74 (17.41-22.29)	19.84 (17.34-22.60)	< .001
Current drinker, %	68.67 (64.68-72.40)	71.84 (67.49-75.81)	71.60 (68.61-74.41)	73.26 (70.66-75.70)	76.32 (74.11-78.40)	75.69 (70.81-79.98)	73.67 (70.50-76.62)	.001
Medicine use for lower blood sugar, %	5.23 (4.14-6.59)	5.89 (4.91-7.04)	7.07 (5.73-8.70)	6.79 (6.08-7.57)	7.35 (6.34-8.51)	7.37 (6.56-8.27)	9.01 (7.79-10.40)	< .001
Medicine use for hypertension, %	20.93 (18.57-23.50)	22.03 (19.82-24.41)	23.92 (22.00-25.95)	24.29 (21.41-27.43)	24.14 (21.51-26.98)	24.97 (23.14-26.89)	24.80 (22.64-27.10)	.013
Medicine use for cholesterol, %	17.15 (15.03-19.50)	17.95 (15.52-20.67)	21.28 (19.70-22.95)	19.96 (18.32-21.70)	23.45 (21.29-25.76)	25.36 (23.40-27.42)	26.16 (23.98-28.46)	< .001
Total energy, kcal/d	2100.94 (2067.50-2134.39)	2081.53 (2042.14-2120.92)	2040.53 (1996.73-2084.33)	2043.95 (2010.41-2077.49)	2071.38 (2030.13-2112.63)	2034.06 (2007.56-2060.56)	2043.81 (2007.32-2080.30)	.057
High-quality carbohydrate, serving/d	2.69 (2.50-2.88)	2.60 (2.45-2.76)	2.64 (2.44-2.83)	2.90 (2.80-3.00)	3.02 (2.86-3.19)	2.88 (2.77-2.98)	2.87 (2.69-3.05)	.003
Low-quality carbohydrate, serving/d	23.19 (22.21-24.16)	22.69 (21.96-23.41)	22.82 (21.66-23.98)	22.07 (21.59-22.55)	21.71 (20.99-22.43)	21.43 (20.73-22.12)	20.75 (19.95-21.55)	.002
SFA, g/d	26.29 (25.53-27.05)	26.45 (25.73-27.18)	25.52 (24.66-26.38)	24.86 (24.11-25.61)	24.93 (24.17-25.69)	25.33 (24.81-25.84)	26.64 (25.94-27.34)	.001
USFA, g/d	47.07 (45.79-48.35)	46.17 (44.83-47.52)	45.36 (44.14-46.59)	44.48 (43.57-45.40)	46.51 (45.39-47.63)	45.81 (44.87-46.74)	47.26 (46.10-48.42)	.006
Animal protein, serving/d	4.51 (4.37-4.65)	4.67 (4.59-4.76)	4.68 (4.62-4.74)	4.77 (4.68-4.87)	4.55 (4.49-4.61)	4.78 (4.70-4.85)	3.29 (3.21-3.37)	< .001
Plant protein, serving/d	7.02 (6.84-7.19)	6.90 (6.79-7.01)	6.89 (6.67-7.11)	7.09 (6.99-7.20)	7.22 (7.05-7.39)	7.14 (7.03-7.26)	7.12 (6.96-7.28)	.016
AHEI	55.04 (54.30-55.79)	53.86 (53.11-54.62)	53.34 (52.45-54.22)	53.95 (53.37-54.52)	54.03 (53.22-54.85)	53.15 (52.57-53.73)	59.34 (58.51-60.17)	< .001
Dietary supplement use, %	55.04 (51.81-58.22)	55.79 (53.46-58.10)	52.50 (49.09-55.90)	51.64 (49.35-53.91)	53.63 (51.02-56.23)	55.77 (52.37-59.11)	57.83 (53.84-61.72)	.256
Congestive heart failure, %	2.40 (1.84-3.13)	2.23 (1.83-2.73)	2.31 (1.80-2.95)	1.83 (1.39-2.40)	2.40 (1.77-3.25)	2.25 (1.88-2.67)	2.02 (1.68-2.42)	.681
Coronary heart disease, %	4.12 (3.29-5.13)	3.33 (2.67-4.14)	3.45 (2.91-4.09)	3.39 (2.75-4.17)	2.96 (2.16-4.05)	3.73 (2.92-4.76)	3.61 (2.82-4.62)	.600
Angina, %	3.20 (2.30-4.43)	2.45 (1.98-3.03)	2.08 (1.56-2.77)	2.03 (1.53-2.71)	2.06 (1.58-2.68)	2.10 (1.64-2.67)	1.94 (1.51-2.48)	.074
Heart attack, %	4.07 (3.37-4.92)	3.31 (2.48-4.42)	3.42 (2.87-4.05)	3.08 (2.43-3.91)	3.38 (2.83-4.02)	3.02 (2.57-3.54)	3.27 (2.67-4.00)	.460
Stroke, %	2.50 (1.94-3.20)	2.54 (1.93-3.35)	3.26 (2.39-4.43)	2.48 (2.07-2.97)	2.31 (1.84-2.89)	2.75 (2.34-3.24)	2.48 (1.94-3.18)	.464

All data analyses in the present study were based on weighted estimates with sample weights provided by the US National Health and Nutrition Examination Survey (NHANES). Continuous variables were presented as weighted means (95% CIs). Categorical variables were presented as weighted percentages (95% CIs). *P* values were calculated by a general linear model for continuous variables adjusting for age and the chi-square test for categorical variables.

Abbreviations: AHEI, Alternative Healthy Eating Index; BMI, body mass index; SFA, saturated fatty acid; USFA, unsaturated fatty acid.

Table 2. Differences of total macronutrients consumption during the day across cardiovascular disease patients

Total macronutrient consumption	NHANES, 2003 to 2016														
	Congestive heart failure (N = 848)	Non–congestive heart failure (N = 27 063)	*P*	Coronary heart disease (N = 1182)	Non–coronary heart disease (N = 26 729)	*P*	Angina (N = 778)	Non-angina (N = 27 133)	*P*	Heart attack (N = 1203)	Non–heart attack (N = 26 708)	*P*	Stroke (N = 971)	Non-stroke (N = 26 940)	*P*
High-quality carbohydrates, serving/d	2.41 (2.24-2.57)	2.81 (2.75-2.88)	< .001	2.65 (2.49-2.81)	2.81 (2.75-2.87)	.037	2.56 (2.37-2.74)	2.81 (2.75-2.87)	.005	2.42 (2.27-2.57)	2.82 (2.75-2.88)	< .001	2.32 (2.17-2.47)	2.82 (2.75-2.88)	< .001
Low-quality carbohydrates, serving/d	23.68 (22.77-24.59)	22.03 (21.71-22.35)	< .001	22.76 (21.92-23.61)	22.04 (21.72-22.36)	.068	23.62 (22.64-24.61)	22.03 (21.71-22.35)	.001	23.58 (22.60-24.56)	22.01 (21.69-22.33)	.001	24.80 (23.88-25.73)	21.99 21.67-22.31)	< .001
SFA, g/d	24.26 (23.24-25.27)	25.74 (25.46-26.02)	.004	25.20 (24.33-26.08)	25.73 (25.44-26.02)	< .001	24.14 (22.80-25.48)	25.75 (25.47-26.02)	.014	24.71 (23.74-25.68)	25.75 (25.47-26.03)	.033	24.33 (23.34-25.31)	25.75 (25.47-26.03)	.004
USFA, g/d	43.05 (41.14-44.96)	46.17 (45.73-46.61)	.001	45.70 (44.19-47.22)	46.12 (45.66-46.57)	.606	43.52 (41.15-45.89)	46.16 (45.71-46.61)	.033	44.08 (42.58-45.57)	46.17 (45.73-46.62)	.007	41.35 (39.83-42.86)	46.23 (45.79-46.66)	< .001
Animal protein, serving/d	4.54 (4.40-4.68)	4.46 (4.42-4.49)	.255	4.39 (4.25-4.53)	4.46 (4.42-4.50)	.339	4.35 (4.20-4.50)	4.46 (4.42-4.50)	.159	4.53 (4.39-4.67)	4.46 (4.42-4.49)	.309	4.46 (4.30-4.62)	4.46 (4.42-4.50)	.970
Plant protein, serving/d	6.84 (6.64-7.05)	7.06 (7.00-7.12)	.037	7.29 (7.07-7.51)	7.05 (6.99-7.11)	.034	7.18 (6.96-7.40)	7.06 (7.00-7.12)	.275	6.99 (6.80-7.19)	7.06 (7.00-7.12)	.491	6.84 (6.64-7.04)	7.06 (7.00-7.12)	.024

All data analyses in the present study were based on weighted estimates with sample weights provided by the NHANES. Continuous variables were presented as weighted means (95% CIs). *P* values were calculated by general linear models adjusting for age.

Abbreviations: AHEI, Alternative Healthy Eating Index; BMI, body mass index; NHANES, US National Health and Nutrition Examination Survey; SFA, saturated fatty acid; USFA, unsaturated fatty acid.

Table 3. Association of Δ ratio of subtypes of macronutrients with cardiovascular diseases

Δ Ratio	Congestive heart failure	Coronary heart disease	Angina	Heart attack	Stroke
High-quality carbohydrates					
Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	0.95 (0.67-1.34)	1.04 (0.79-1.37)	0.88 (0.63-1.22)	0.93 (0.72-1.21)	0.81 (0.60-1.11)
Q3	0.75 (0.54-1.04)	1.03 (0.80-1.32)	0.90 (0.67-1.20)	0.98 (0.73-1.32)	0.68 (0.51-0.90)
Q4	0.78 (0.56-1.08)	1.02 (0.74-1.39)	0.95 (0.70-1.29)	0.95 (0.74-1.22)	0.90 (0.67-1.21)
$P_{\text{for trend}}$	.078	.921	.848	.825	.483
Low-quality carbohydrates					
Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	1.12 (0.84-1.50)	1.19 (0.87-1.63)	1.74 (1.26-2.41)	1.75 (1.37-2.24)	1.00 (0.77-1.31)
Q3	1.04 (0.77-1.42)	1.39 (1.06-1.83)	1.85 (1.31-2.62)	1.30 (1.01-1.68)	0.99 (0.76-1.29)
Q4	1.02 (0.75-1.39)	1.21 (0.91-1.61)	1.63 (1.16-2.29)	1.47 (1.13-1.93)	1.13 (0.86-1.49)
$P_{\text{for trend}}$	.992	.144	.007	.068	.396
SFA					
Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	0.89 (0.62-1.26)	1.13 (0.87-1.48)	1.08 (0.77-1.51)	0.91 (0.71-1.16)	0.77 (0.60-1.00)
Q3	0.88 (0.61-1.27)	1.05 (0.78-1.42)	1.21 (0.82-1.80)	0.87 (0.65-1.16)	0.79 (0.60-1.03)
Q4	0.80 (0.56-1.14)	1.11 (0.83-1.49)	1.13 (0.83-1.55)	1.07 (0.82-1.40)	0.76(0.57-1.01)
$P_{\text{for trend}}$	.239	.593	.378	.544	.108
USFA					
Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	1.04 (0.72-1.50)	0.94 (0.73-1.21)	1.16 (0.83-1.63)	1.07 (0.83-1.39)	0.88 (0.69-1.13)
Q3	1.04 (0.79-1.36)	1.14 (0.84-1.56)	1.06 (0.76-1.47)	1.09 (0.85-1.40)	0.86 (0.65-1.13)
Q4	0.87 (0.63-1.21)	1.16 (0.86-1.54)	1.14 (0.85-1.53)	1.07 (0.82-1.39)	0.76 (0.58-0.99)
$P_{\text{for trend}}$	.389	.191	.508	.6	.049
Animal protein					
Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	0.85 (0.64-1.14)	1.24 (0.95-1.62)	1.22 (0.89-1.68)	0.98 (0.77-1.23)	1.04 (0.79-1.36)
Q3	1.08 (0.81-1.43)	1.44 (1.12-1.87)	1.31 (0.93-1.84)	1.03 (0.78-1.34)	0.96 (0.76-1.21)
Q4	1.03 (0.77-1.38)	1.44 (1.06-1.95)	1.44 (1.01-2.07)	1.13 (0.88-1.46)	0.93 (0.68-1.26)
$P_{\text{for trend}}$	.496	.014	.047	.266	.511
Plant protein					
Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	1.30 (0.99-1.71)	1.22 (0.93-1.60)	1.11 (0.83-1.47)	1.12 (0.89-1.40)	1.50 (1.18-1.91)
Q3	0.94 (0.68-1.29)	1.18 (0.92-1.50)	0.98 (0.74-1.31)	1.03 (0.80-1.34)	1.23 (0.96-1.58)
Q4	0.74 (0.52-1.07)	1.34 (0.97-1.84)	1.20 (0.90-1.60)	1.19 (0.91-1.56)	1.05 (0.82-1.34)
$P_{\text{for trend}}$	.056	.084	.323	.276	.894

Adjustments included age, sex, ethnicity, income, education, exercise, smoke, alcohol intake, supplement use, BMI, medication use for lower blood sugar, medication use for hypertension, medication use for cholesterol, and total intake of energy, high-quality carbohydrates, SFA, animal protein, AHEI, and breakfast skipping.
Abbreviations: AHEI, Alternative Healthy Eating Index; BMI, body mass index; SFA, saturated fatty acid; Q, quintile.

and 5 [26]). Further, we found that Δseafood was related to reduced CVD risk, whereas Δprocessed meat showed no significant association. When additionally adjusted for Δseafood, the highest quintile of the Δratio of animal protein foods was still associated with coronary heart disease and angina, independent of Δseafood (Supplementary Tables 6 and 7 [26]).

Discussion

In this nationally representative sample of US adults, this study demonstrated that excessive consumption of low-quality carbohydrates and animal protein at dinner rather than breakfast throughout the day was associated with an increased risk of CVD, and USFA consumption at dinner was related to reduced CVD risk. Furthermore, the substitution effects with a one-serving decrease of low-quality carbohydrate or animal protein and a simultaneous one-serving increase of high-quality carbohydrates or plant protein could reduce CVD risk.

To the best of our knowledge, this is the first study that reports the association of macronutrients and CVD by considering subtypes and meal timing simultaneously based on national-scale representative data. The major finding of the present study was that overconsumption of low-quality carbohydrates and animal protein at dinner rather

Table 4. Isocaloric substitution effects with one-serving decrease of low-quality carbohydrate or animal protein food and simultaneous one-serving increase of high-quality carbohydrate or plant protein food at dinner with cardiovascular diseases

Isocaloric substitution effect	Congestive heart failure	Coronary heart disease	Angina	Heart attack	Stroke
Substitution with low-quality carbohydrate by high-quality carbohydrate	0.90 (0.82-0.98)	0.95 (0.89-1.01)	0.93 (0.86-1.01)	0.95 (0.89-1.01)	0.88 (0.81-0.96)
Substitution with animal protein by plant protein	0.90 (0.83-0.98)	1.06 (0.99-1.15)	0.99 (0.92-1.06)	0.92 (0.86-0.99)	1.03 (0.95-1.11)

Adjustments included age, sex, ethnicity, income, education, exercise, smoke, alcohol intake, supplement use, BMI, medication use for lower blood sugar, medication use for hypertension, medication use for cholesterol, and total intake of energy, high-quality carbohydrate, SFA, animal protein, AHEI, and breakfast skipping.
Abbreviations: AHEI, Alternative Healthy Eating Index; BMI, body mass index; SFA, saturated fatty acid.

than breakfast was significantly associated with a higher CVD risk, and USFA consumption at dinner was related to a lower CVD risk independent of a variety of classical CVD risk factors, in particular, breakfast skipping and diet quality (16, 33). Observational studies reported a positive association between evening high-energy intake and BMI (14, 34, 35), all-cause, and disease-specific mortality (36), which is consistent with findings in the present study. On the other hand, a series of studies have supported that total energy consumption at breakfast reduced weight gain and CVD risk factors, such as elevated serum low-density lipoprotein cholesterol, decreased serum high-density lipoprotein cholesterol, and hypertension (9, 37, 38). These were consistent with our findings; in particular, the ratio of low-quality carbohydrates and animal protein at breakfast was associated with a reduced CVD risk. However, the ratio of low-quality carbohydrates and animal protein at dinner was related to higher CVD risk. The evidence suggests that meal timing plays a critical role in metabolic regulation and that the circadian clock interacts with metabolic functions (39). Furthermore, the efficient secretion of insulin and incretins with low-quality carbohydrates after breakfast would be expected to attenuate postprandial glycemic responses and decrease insulin requirements after lunch and dinner (40, 41). This would decrease insulin resistance and hyperinsulinemia, the 2 major mechanisms leading to atherosclerosis and CVD (42). Therefore, low-quality carbohydrate consumption at breakfast may benefit the metabolic and incretin systems with respect to subsequent meals, thereby improving glucose tolerance during the day (43). Angina is the predominant and subsequent presentation of coronary heart disease; it has been reported that high-carbohydrate meals could lead to angina through a greater increase in sympathetic nervous activity and the release of vasoactive gastrointestinal peptides, which is likely a possible mechanism response for the association between low-quality carbohydrates and angina (44). On the other hand, many components of animal protein, including heme iron, cholesterol, advanced glycation, and lipoxidation end products, probably lead to type 2 diabetes, which is a significant CVD risk factor (45). A recent study showed that protein consumption at breakfast is inversely associated with blood pressure and positively associated with high-density lipoprotein cholesterol, whereas protein at dinner is positively associated with the homeostasis model assessment of insulin resistance (HOMA-IR) and insulin concentrations (46). In particular, participants were most insulin sensitive during the morning, which may contribute to the inverse association between protein consumption at breakfast and HOMA-IR and insulin concentrations (46). It appears that consuming more protein early in the day could align with circadian peaks in energy and macronutrient metabolism, which were related to better cardiometabolic health (47). Animal studies also have shown that mice fed a high-fat diet at the end of the active phase had higher body weight and decreased glucose tolerance, compared to mice fed the same diet at the beginning of the active phase (48). All the aforementioned evidence was consistent with our finding of the harmful effect of overconsumption of low-quality carbohydrates and animal protein at dinner with regard to CVD risk.

Furthermore, substitution effects with a one-serving decrease of low-quality carbohydrates or animal protein food and a simultaneous one-serving increase of high-quality carbohydrates or plant protein food at dinner reduced CVD risk. After 2000, dietary guidelines suggested the benefits of healthy fats and plant sources of protein and the harms of low-quality carbohydrates (49). Studies have reported that low-quality carbohydrates, such as refined grains and added sugars with a high glycemic load, could be associated with higher postprandial glucose and insulin, inflammation, insulin resistance, and dyslipidemia, which provide limited nutritional value and increase CVD risk (50-53). It appears that high glycemic index and glycemic load carbohydrates have been considered to exacerbate postprandial hypertriglyceridemia, which has been highlighted in the pathogenesis of CVD (54). Meanwhile, evidence has been documented that USFA is considered an ideal dietary pattern with cardioprotective effects, especially polyunsaturated fatty acids (55). Similar findings were observed for protein: Evidence supports that CVD risk can be reduced by a dietary pattern that provides more plant sources of protein compared with the classic American diet (56). The accumulated findings in the present study suggest the harmful effect of overconsumption of low-quality carbohydrates and animal protein and the benefits of USFA at dinner. The food sources of high-quality carbohydrates, plant protein, and USFA including whole grains, nonstarchy vegetables, whole fruits, and nuts, which contain fiber, vitamins, minerals, and phytochemicals, may be involved in the beneficial association with CVD risk (57, 58). Overall, nutritional guidelines should emphasize the importance of diet quality and meal timing throughout the day. It appears that people should eat fewer low-quality carbohydrates and less animal protein at dinner.

Strengths and Limitations

Our study has several strengths. First, this was the first study that reported the association of macronutrients and CVD by considering subtypes and meal timing simultaneously based on national-scale representative data from a well-designed study (NHANES). Second, the association remained robust when considering breakfast skipping and dietary quality, which were classic dietary confounders. Of course, there are several limitations to this study. First, this study was a cross-sectional study and could not establish causal inferences. Second, a series of confounders were considered, but residual confounding still likely existed. Third, individuals with missing information on current smoking, current drinking, or BMI were excluded, which may affect the generalizability of our findings.

Conclusions

This study indicated that overconsumption of low-quality carbohydrates and animal protein at dinner rather than breakfast was significantly associated with higher CVD risk, and USFA consumption at dinner had a lower CVD risk among US adults. Substitution of low-quality carbohydrates or animal protein by high-quality carbohydrates or plant protein at dinner could reduce CVD risk.

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