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Comparison of the ketogenic ratio of macronutrients with the low-carbohydrate diet score and their association with risk of type 2 diabetes in postmenopausal women: A secondary analysis of the women's health initiative

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Abstract

Background: Previous attempts to identify low-carbohydrate diets (LCDs) in epidemiological studies relied on the LCD score, which is unable to identify ketogenic dieters. Ketogenic ratios of macronutrients are clinical equations proposed to predict ketogenic diets; however, their utility in epidemiological studies is unknown.

Objective: To determine the number of participants consuming a ketogenic diet, compare ketogenic ratios to the LCD score, and evaluate their association with type 2 diabetes mellitus (T2DM).

Design: Secondary analysis of the Women's Health Initiative (WHI) with 17.9 ± 6.03 years of follow-up. Baseline food frequency questionnaires were used to calculate the ketogenic ratio as follows: (0.9*grams fat + 0.46*grams protein) divided by (0.1*grams fat + 0.58*grams protein + grams net carbohydrate), a value ≥1.5 is the minimum threshold for a ketogenic diet.

Participants/Setting: 125,982 postmenopausal women without diabetes (age 50–79 years) enrolled in the multicenter WHI observational study and clinical trials were included.

Main outcome measures: Risk of self-reported incident T2DM.

Statistical Analysis Performed: Cox proportional hazards models, adjusted for age, race, ethnicity, education, income, health insurance, relationship status, geographic region, WHI study component, female hormone use, smoking status, alcohol use, recreational physical activity, total energy intake, diet quality, body mass index, hyperlipidemia, and hypertension, were used to

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compare hazard ratios (HRs) and 95% confidence intervals (CIs) for T2DM between quintiles of the ketogenic ratio.

Results: 18,775 incident cases of T2DM occurred. The median ketogenic ratio was 0.35 (interquartile range 0.28–0.42) and 15 individuals (0.01%) exceeded the threshold for a ketogenic diet. Higher ketogenic ratio quintiles were associated with increased risk of T2DM in a dose-dependent manner. Comparing extreme quintiles of the ketogenic ratio, the HR and 95% CI for diabetes was 1.24 (1.18–1.31; $P_{trend} < 0.001$) in fully adjusted models. Similarly, comparing extreme quintiles, the HR (95% CI) for diabetes was 1.36 (1.29–1.43; $P_{trend} < 0.001$) for the LCD score and 1.13 (1.07–1.19; $P_{trend} < 0.001$) for the simplified ketogenic ratio in fully adjusted models.

Conclusion: Increasing ketogenic ratio values are associated with increased risk of T2DM and align well with LCD scores; however, too few participants consumed a ketogenic diet to determine its association with T2DM.

Keywords

ketogenic diet; ketogenic ratio; low-carbohydrate diet score; diabetes; postmenopausal women; nutritional epidemiology

INTRODUCTION

The ketogenic diet has attracted wide attention among dieters and researchers alike; however, scientific evidence regarding the long-term effects of the ketogenic diet is limited.[1] The ketogenic diet is a very-low-carbohydrate, high-fat diet that displaces energy intake from carbohydrates with energy from dietary fat in order to achieve nutritional ketosis,[2] defined as plasma β-hydroxybutyrate levels of 0.5–3.0 mmol/L.[3] Typical recommendations for the ketogenic diet are to restrict net carbohydrate intake to 20–50 grams per day (<10% energy), consume moderate protein, and consume the remaining 70–80% of daily energy requirements in the form of fat.

Carbohydrate restriction triggers gluconeogenesis and ketogenesis in the liver. Once endogenous glucose production is depleted via gluconeogenesis, the production of ketone bodies from fatty acids replaces glucose as the primary fuel source.[4] This process lowers glucose and insulin levels in the blood, which further limits the storage of glucose in the body. Therefore, the ketogenic diet has been proposed as a therapeutic diet in the clinical management of obesity and type 2 diabetes mellitus (T2DM). Two recent meta-analyses of randomized controlled trials found the ketogenic diet to be associated with short-term (3 to 12 months) improvements in glycemic, weight, and blood lipid control among T2DM patients.[5, 6] A recent scientific statement by the American Heart Association indicates that very-low carbohydrate (i.e. ketogenic) diets may be an appropriate short term dietary approach for reduction of triglycerides, glucose, weight, and diabetes medication use among people with T2DM.[7]

However, the long-term outcomes of ketogenic diets are not well understood. Mouse studies have observed increased insulin resistance following the ketogenic diet.[8, 9] Furthermore, a meta-analysis of long-term observational studies with 3.5 to 20 years follow-up found a

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marginally increased risk of T2DM for low-carbohydrate diets (LCDs).[10] These findings raise concern that a long-term risk of a ketogenic diet among apparently healthy individuals might include an increased risk of T2DM. Additional concerns of micronutrient deficiencies and cardiovascular risk factors[11] further necessitate the need for evaluation of long-term risks of the ketogenic diet.

Previous attempts to identify low-carbohydrate dietary patterns in epidemiological studies have relied on the LCD score;[12] however, the LCD score is unable to predict a diet likely of inducing nutritional ketosis. In clinical nutrition practice, ratios of macronutrients are used to identify diets predictive of inducing nutritional ketosis.[13, 14] The ketogenic ratio and simplified ketogenic ratio of macronutrients have historically been used for implementing a therapeutic ketogenic diet for people with epilepsy;[15] however, the utility of these ratios of macronutrients for assessing the risk of long-term health outcomes of ketogenic diets in epidemiological studies remains unknown. The objectives of this study were to evaluate the utility of ketogenic ratios in epidemiological studies by 1) determining the number of participants who consume a ketogenic diet, 2) comparing them to the LCD score, and 3) examine the association of ketogenic ratios of macronutrients with risk of T2DM in the Women's Health Initiative (WHI) cohort of postmenopausal women.

METHODS

Study Population

The WHI design has been described in detail elsewhere.[16–18] Briefly, between 1993 and 1998, the WHI recruited 161,808 postmenopausal women ages 50–79 years into one or more of three clinical trials or into an observational study. When the first phase of WHI ended in 2005, participants were invited to join subsequent WHI extension studies that are ongoing to date. Informed consent was obtained from all participants and the studies were approved by all local institutional review boards.[19] Macronutrients used to calculate ketogenic ratios were obtained from baseline food frequency questionnaires (FFQs) developed and validated specifically for the WHI.[20, 21] The FFQs were analyzed using the Nutrition Data System for Research, 2005 version (Nutrition Coordinating Center, Minneapolis, MN, USA).[22] Because the WHI dietary modification trial excluded participants with high fat intake, post-intervention FFQs at year one were used in this analysis for participants in the control arm of the dietary modification trial as recommended by WHI analytical guidelines.[23] Participants enrolled in the control arm of the dietary modification trial were also excluded if they reported a new instance of T2DM between baseline and the FFQ collected at year one. Participants with missing dietary intake data, those enrolled in the intervention arm of the dietary modification trial, those with prevalent or missing information on T2DM at baseline, and implausible energy intakes (<600 kcal/day or >5,000 kcal/day) were excluded from this analysis. Furthermore, based on the visual inspection of box and QQ plots, outliers of ketogenic ratio values were excluded resulting in a final analytical sample of 125,982 women (Supplementary Figure 1). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology-nutritional epidemiology (STROBE-nut) reporting guidelines.[24]

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Exposure Assessment

To evaluate dietary patterns that are predictive of achieving nutritional ketosis, both the ketogenic ratio empirically based on the proportion of macronutrients that are ketogenic and antiketogenic and the simplified ketogenic ratio that is more commonly used in the clinical setting were calculated. The ketogenic ratio of macronutrients was calculated using the equation by Withrow.[15] Briefly, the ketogenic ratio was calculated as (0.9*grams fat + 0.46*grams protein) divided by (0.1*grams fat + 0.58*grams protein + grams net carbohydrate), which ranges from 0 to 9. Similarly, the simplified ketogenic ratio was calculated for each participant as grams fat divided by (grams protein + grams net carbohydrate), which ranges from 0 to a diet dependent value. Higher ketogenic ratio and simplified ketogenic ratio values represent diets with higher likelihood of inducing nutritional ketosis. A calculated ketogenic ratio value of 1.5 and simplified ketogenic ratio value of 3.0 are the minimum thresholds at which a diet may be considered ketogenic.[13, 14] Values below these thresholds are considered antiketogenic.[13, 14]

The LCD score[12] was also calculated for each participant to compare the ketogenic ratios to an established score. Briefly, participants were divided into 11 strata for percent of energy from each protein, fat, and carbohydrate. For percent of energy from fat and protein, participants in the highest stratum received 10 points and those in the lowest stratum received 0 points. Percent energy from carbohydrate was reverse scored, where participants in the highest stratum received 0 points and those in the lowest stratum received 10 points. The points for the 3 macronutrients were then summed to create the overall LCD score, which ranges from 0 to 30.

Outcome Ascertainment

WHI participants were asked if a physician had ever told them they had “sugar diabetes or high blood sugar” when they were not pregnant, and about treatment with insulin or oral antidiabetic medications. T2DM was defined as an affirmative answer to any of the queries; thus, only self-reported physician diagnosed incident T2DM was ascertained in this study. The accuracy of self-reported T2DM in the WHI has been found to be highly valid and reliable.[25]

Potential Confounders

Demographic, socioeconomic, lifestyle, and medical history risk factors for diabetes were controlled for in various models. At baseline, participants self-reported the following information in questionnaires: demographic and socioeconomic characteristics (age, race, ethnicity, education, annual income, relationship status, health insurance), lifestyle factors (smoking status, physical activity, alcohol intake, total energy intake, overall diet quality), and medical history (hyperlipidemia, family history of diabetes, female hormone therapy). The simple scoring algorithm for individuals was used to calculate the 2015 healthy eating index (HEI), where a higher score indicates better diet quality defined by higher alignment to the 2015 Dietary Guidelines for Americans.[26] Metabolic equivalent task hours per week of recreational physical activity for each participant were calculated for moderate to vigorous intensity recreational physical activity.[18, 27] Anthropometrics including weight, height, and systolic and diastolic blood pressure were measured during

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clinic visits proximate to self-reported T2DM using standard methods and were used to calculate time-varying BMI as weight (in kilograms) divided by height (in meters squared)[28] and hypertension status defined as systolic ≥ 130 mmHg or diastolic ≥ 80 mmHg.

Statistical Analysis

Chi-square tests and analysis of variance (ANOVA) were used to compare baseline categorical variables and continuous variables, respectively. Spearman's rank correlation coefficients were calculated between the ketogenic ratio, simplified ketogenic ratio, and LCD score to assess the correlation between diet scores.

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between ketogenic ratio, simplified ketogenic ratio, or LCD score quintiles and risk of T2DM. In addition, ketogenic ratios and simplified ketogenic ratios values were dichotomized as above or below respective ketogenic thresholds (1.5 and 3.0, respectively) and estimated HRs and 95% CIs for associations with risk of T2DM. Follow-up time was calculated as the number of days from FFQ collection to the first instance of self-reported T2DM, death, or loss-to-follow-up through September 2020. Covariates in fully adjusted models included age as a continuous variable and BMI, hypertension, hyperlipidemia, educational attainment, income, relationship status, health insurance, race, ethnicity, smoking status, alcohol use, family history of T2DM, female hormone therapy, total energy intake quartiles, 2015 HEI quartiles, recreational physical activity, geographic region, and WHI study component as categorical variables. Missing values for categorical variables were grouped into a 'missing' category. To assess linear trends across exposure quintiles, continuous exposure values were fit in models.

To evaluate effect modification from other well-known nutritional risk factors for T2DM, interaction and stratified analyses by obesity status, total energy intake, and diet quality were conducted. To limit bias due to sub-clinical diabetes at baseline, a sensitivity analysis was conducted excluding participants who developed T2DM within the first 2 years of follow-up. To limit bias due to missing information, a sensitivity analysis was conducted excluding participants with missing covariate information.

All analyses were conducted with 2-sided tests (α=0.05) in SAS version 9.4.[29]

RESULTS

During 17.9 ± 6.03 years of follow-up, there were 18,775 incident cases of T2DM. The median ketogenic ratio was 0.35 (interquartile range [IQR] 0.28–0.42). Only 15 individuals (0.01% of the total sample) exceeded the ketogenic ratio threshold while none exceeded the simplified ketogenic ratio threshold for a ketogenic diet. Participants with higher ketogenic ratio values were more likely to be married, heavy alcohol consumers, current smokers, enrolled in the WHI clinical trials, have lower education levels, lower income, have a higher BMI, lower female hormone use, a family history of T2DM, and hypertension (Table 1). In addition, participants with higher ketogenic ratio values were less likely to be physically active, from the northeast geographical region, have health insurance, and hyperlipidemia. Furthermore, participants with higher ketogenic ratio values had higher intake of total

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energy and lower diet quality (Table 2). The ketogenic ratio (r_s = 0.94) and simplified ketogenic ratio (r_s = 0.79) were highly correlated with the LCD score (P < 0.001 for both) and inversely correlated with HEI scores (P < 0.001 for all, Supplementary Table 3).

In models adjusted for age, race, and ethnicity, each ketogenic ratio quintile was associated with increased risk of T2DM (Table 4). Comparing the highest to the lowest ketogenic ratio quintile, the adjusted HR (95% CI) for T2DM was 1.47 (1.40–1.53; P_{trend} < 0.001). The association remained significant after additional adjustment for education, income, marital status, health insurance, family history of T2DM, WHI component, and geographical region with an adjusted HR (95% CI) for T2DM of 1.36 (1.30–1.43; P_{trend} < 0.001). With further addition of several lifestyle covariates including smoking status, recreational physical activity, total energy intake, female hormone therapy, and alcohol use, the adjusted HR (95% CI) for T2DM was 1.29 (1.23–1.36; P_{trend} < 0.001). Finally, the association remained significant after further adjustment for BMI, comorbidities, and diet quality with an adjusted HR (95% CI) of 1.20 (1.14–1.26; P_{trend} < 0.001).

The results from the analysis with simplified ketogenic ratio or LCD score quintiles as the exposure were similar to the primary ketogenic ratio analysis (Table 4). In age, race, and ethnicity adjusted models the HR (95% CI) for T2DM between the highest and the lowest simplified ketogenic ratio quintile was 1.40 (1.34–1.46; P_{trend} < 0.001). This association remained significant in all models with a HR (95% CI) for T2DM of 1.13 (1.07–1.19; P_{trend} < 0.001) in the fully adjusted model that includes BMI. For the LCD score, the HR (95% CI) for T2DM between the highest and lowest quintile was 1.57 (1.50–1.65; P_{trend} < 0.001) in age, race, and ethnicity adjusted models. In the fully adjusted model that includes BMI, the HR (95% CI) for T2DM remained significant 1.28 (1.22–1.35; P_{trend} < 0.001).

Sensitivity analyses excluding participants who were diagnosed with T2DM within 2 years of study enrollment or excluding participants with missing covariate information yielded results that were similar to the primary analysis for the ketogenic ratio (Supplementary Tables 5–6). Similarly, analyses stratified by diet quality (Table 7), total energy intake, and obesity status (Supplementary Tables 8–9) did not differ from the primary analysis for the ketogenic ratio.

DISCUSSION

Increasing ketogenic ratio, simplified ketogenic ratio, and LCD score values were associated with higher risk of T2DM among postmenopausal women. The associations remained significant after adjustment for major risk factors of T2DM, such as demographic, socioeconomic, and lifestyle factors.

Historically, ketogenic ratios were utilized clinically to evaluate ketogenic diets used for treatment of epilepsy;[15] however, to date no known observational studies have evaluated the ketogenic ratio (or simplified ketogenic ratio) for its association with any outcomes among healthy adults. Based on its linear distribution, the strong correlation with the LCD score, and the striking similarity of the results compared to the LCD score, the results of this study provide robust validation of the ketogenic ratio against the LCD score and suggest that

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the ketogenic ratio may be a useful method to evaluate diet in observational studies. It is important to note that this study sample contained information only on the habitual diet of postmenopausal women, so even in the fifth quintile of the ketogenic ratio, the percent of energy from fat was about half and the total carbohydrate intake was over three times higher than the typical recommendations for a ketogenic diet.

A proposed benefit to either of the ketogenic ratios is that they are theoretically capable of identify ketogenic dieters, whereas the LCD score is unable to identify a ketogenic dieter. However, due to the small number of participants who exceeded the threshold for a ketogenic diet of ≥1.5 (n = 15), this study lacked power to determine the association of the ketogenic diet with T2DM risk. An even larger sample size or a cohort containing information specifically on ketogenic dieters is needed to determine the association of ketogenic ratio and simplified ketogenic ratio values indicative of a ketogenic diet with risk of T2DM or other health outcomes.

Previous attempts to identify low-carbohydrate dieters in epidemiological studies have relied on the LCD score, in which fat and protein are scored higher for higher percent of energy and carbohydrates are scored higher for lower percent of energy of intake.[12, 30, 31] Similar to the results of the present study, a meta-analysis of observational studies found an association between higher LCD scores and higher risk of T2DM.[10] An analysis of the Health Professionals Follow-Up Study observed a HR (95% CI) for T2DM of 1.31 (1.14–1.49) comparing the highest to lowest quintile of LCD score.[31] In addition, an analysis of the Nurses' Health Study I found that the relative risk (RR; 95% CI) for T2DM was 1.40 (1.21–1.61) comparing the highest to the lowest decile of LCD scores; however, this association was completely attenuated and no longer statistically significant by the inclusion of BMI in the model.[12] Among women with a history of gestational diabetes enrolled in the Nurses' Health Study II, the HR (95% CI) for T2DM was 1.36 (1.04–1.78) comparing the highest to lowest quintiles of the LCD score.[30] Of note, all three of these studies observed that this association was only significant among LCDs, high in animal-derived protein and fat and was absent among LCDs high in plant-derived protein and fat when stratified by diet quality.[12, 30, 31] The consistency among these three cohorts emphasizes the importance of evaluating diet quality in LCD score epidemiologic studies. Calculating 'healthy' and 'unhealthy' ketogenic ratios is not possible with the ketogenic ratio as it is with the LCD score as the ketogenic potential of a diet is dependent on total macronutrient composition. However, in the present study the results from the stratified by HEI tertiles were consistent in each model suggesting that the association of higher ketogenic ratio values with T2DM risk is independent of diet quality.

Strengths of this study include the consistent results across analyses, and the prospective study design, long-term follow-up, and the large sample size of the WHI that contains comprehensive demographic, socioeconomic, and lifestyle information, allowing for the ability to evaluate the association between the ketogenic ratio and T2DM independent of several confounding variables. There are also several limitations to the present study. First, the ketogenic ratio and simplified ketogenic ratio have not previously been used in cohort studies to identify ketogenic dieters and the cutoffs for ketogenic diets are estimates based on clinical studies;[13, 14] therefore, it is unclear how sensitive these thresholds are

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in observational studies for identifying ketogenic dieters. Second, the ketogenic ratio and simplified ketogenic ratio do not reflect diet quality or the specific foods included in each individual's diet that may be associated risk of T2DM. For example, intake of olive oil is associated with lower risk of T2DM;[32] however, a high intake of olive oil would lead to higher ketogenic ratio values. Because specific foods and diet quality are important predictors of T2DM risk, information on the 2015 HEI was included as a covariate in models to address this issue. Third, due to the small number of participants who exceeded the ketogenic threshold, the association of the ketogenic diet (as a binary variable) with T2DM risk was not evaluated due to insufficient power. Fourth, it is important to note that the WHI FFQ was only collected at baseline and not designed to evaluate ketogenic dieters which limits these results. Finally, as in all observational studies, residual confounding may be unaccounted due to other confounders not collected in the WHI or included in models.

CONCLUSION

The results of this study indicate that increasing ketogenic ratios are associated with risk of T2DM and align well with the LCD score; however, this study lacked power necessary for the interpretation of these results regarding the long-term risks of a ketogenic diet. The ketogenic ratio may be a useful measure to evaluate LCDs in observational studies, but extremely large sample size or ketogenic diet specific study samples are needed to identify a sufficient sample of ketogenic dieters to have power. Further investigations are needed to replicate these findings and better understand the utility of the ketogenic ratio for identifying ketogenic dieters in observational studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Sharing:

The data described in the manuscript are available from https://www.whi.org/.

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RESEARCH SNAPSHOT

Research Questions:

Are ketogenic ratio values useful for identifying ketogenic dieters in observational studies and are they associated with type 2 diabetes mellitus (T2DM) among postmenopausal women?

Key Findings:

Among 125,982 postmenopausal women without T2DM, only 15 women were identified as ketogenic dieters; therefore, the association of the ketogenic diet with risk of T2DM was unable to be determined. However, increasing ketogenic ratio values were associated with increased risk for T2DM. Based on the strong correlation with and the similar results compared to the low-carbohydrate diet score, this study suggests that the ketogenic ratio may be useful.

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Table 1.

Baseline demographic characteristics of 125,982 postmenopausal women without diabetes stratified by ketogenic ratio of macronutrient quintiles.[a]

	Ketogenic ratio quintiles					
Variables	**Q1 (<0.27)**	**Q2 (0.27–0.32)**	**Q3 (0.32–0.37)**	**Q4 (0.37–0.44)**	**Q5 (>0.44)**	**P-value**
Number participants	25196	25197	25196	25197	25196	
Age at baseline, years (mean ± SD)	63.3 ± 7.4	63.4 ± 7.3	63.5 ± 7.3	63.5 ± 7.2	63.0 ± 7.1	<0.001
Race, (%)						
American Indian/Alaska Native	0.27	0.23	0.24	0.22	0.30	<0.001
Asian	3.45	2.71	2.31	2.10	1.58	
Native Hawaiian/Other Pacific Islander	0.06	0.06	0.04	0.09	0.10	
Black	7.62	6.64	6.30	7.00	8.01	
White	85.6	87.6	88.5	87.9	87.1	
More than one race	1.20	1.07	0.89	0.98	1.21	
Unknown/Not reported	1.85	1.69	1.69	1.75	1.74	
Ethnicity, (%)						<0.001
Not Hispanic/Latino	95.0	95.3	95.4	95.3	95.1	
Hispanic/Latino	4.10	3.93	3.93	4.05	4.29	
Unknown/Not reported	0.93	0.81	0.66	0.61	0.58	
Education, (%)						
High school or less	17.4	18.5	20.2	23.3	27.3	<0.001
Some college	34.7	36.0	36.9	38.3	39.4	
College	11.9	11.9	11.7	11.1	10.0	
Postgraduate or professional	35.1	32.9	30.4	26.7	22.5	
Missing	0.8	0.7	0.8	0.7	0.8	
Family income, (%)						
<$20,000	13.4	13.2	13.9	15.1	16.9	<0.001
$20,000-$50,000	39.3	40.9	41.5	43.3	43.6	
>$50,000	40.3	39.2	38.0	35.0	33.0	
Missing	7.0	6.7	6.6	6.6	6.5	
Alcohol, (%)						
Non-drinker	31.1	27.0	26.0	26.1	26.0	<0.001
Moderate	59.1	61.5	60.6	59.1	56.4	
Heavy	9.2	10.9	12.8	14.3	17.1	
Missing	0.7	0.6	0.6	0.5	0.6	
WHI component, (%)						
Clinical trials	19.4	26.5	34.3	41.0	43.6	<0.001
Observational study	80.6	73.6	65.7	59.0	56.5	
Smoking status, (%)						
Never	52.4	51.4	51.2	50.2	45.5	<0.001
Past	42.5	42.9	41.9	40.9	41.0	
Current	3.8	4.4	5.7	7.6	12.3	

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Variables	Ketogenic ratio quintiles					P-value
	Q1 (<0.27)	Q2 (0.27–0.32)	Q3 (0.32–0.37)	Q4 (0.37–0.44)	Q5 (>0.44)	
Missing	1.3	1.3	1.2	1.3	1.2	
Health Insurance, (%)						
No	3.4	3.4	3.7	4.2	6.0	<0.001
Yes	95.7	95.7	95.3	94.9	93.1	
Missing	1.0	0.9	0.9	0.9	1.0	
Hyperlipidemia, (%)[b]						
No	80.0	81.6	82.4	82.9	84.7	<0.001
Yes	16.3	14.2	12.5	11.5	9.6	
Missing	3.7	4.3	5.1	5.6	5.7	
Hypertension, (%)[c]						
No	55.0	54.8	55.0	54.0	52.9	<0.001
Yes	45.1	45.2	45.0	46.0	47.1	
BMI category, kg/m^2 (%)[d]						
<18.5	1.6	1.0	1.0	1.0	1.0	<0.001
18.5–24.9	43.4	37.5	34.7	31.0	27.2	
25.0–29.9	33.6	35.5	36.0	35.6	33.7	
≥30.0	21.2	25.6	28.0	32.1	37.6	
Missing	0.3	0.3	0.4	0.4	0.5	
Female hormone therapy, (%)						
Never	31.7	31.0	31.0	32.0	33.5	<0.001
Past	22.1	22.3	22.5	23.1	23.8	
Current	43.5	44.0	43.7	42.2	40.4	
Missing	2.6	2.7	2.8	2.7	2.4	
Geographical region, (%)						
Northeast	25.5	25.4	23.4	21.3	19.5	<0.001
South	26.2	24.8	24.7	24.7	25.3	
Midwest	19.6	21.4	23.0	24.2	24.3	
West	28.8	28.5	28.9	29.8	30.9	
Family history of diabetes, (%)						
no	66.4	65.4	65.4	65.2	62.9	<0.001
yes	28.8	30.1	30.0	30.1	31.5	
missing	4.9	4.5	4.6	4.7	5.6	
Relationship status, (%)						
Single	5.1	4.6	4.2	4.3	3.8	<0.001
Divorced, widowed, or separated	34.8	32.3	31.5	31.2	31.9	
Married or marriage-like relationship	59.6	62.7	64.0	64.1	63.9	
Missing	0.5	0.4	0.4	0.5	0.5	
Recreational physical activity (MET-h/wk), (%)[e]						
<10	37.6	44.5	49.7	55.4	61.8	<0.001
≥10	59.9	52.2	46.4	40.1	33.7	

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	Ketogenic ratio quintiles					
Variables	**Q1 (<0.27)**	**Q2 (0.27–0.32)**	**Q3 (0.32–0.37)**	**Q4 (0.37–0.44)**	**Q5 (>0.44)**	**P-value**
Missing	2.6	3.2	3.9	4.5	4.4	

[a]Abbreviations: BMI, body mass index; MET, metabolic equivalent of task; SD, standard deviation; WHI, women's health initiative.

[b]Defined by self-reported physician diagnosis.

[c]Defined as systolic ≥ 130 mmHg or diastolic ≥ 80 mmHg.

[d]Based on CDC cutoffs.[28]

[e]Determined by WHI physical activity questionnaire.

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Table 2.

Baseline dietary intake of 125,982 postmenopausal women without diabetes stratified by ketogenic ratio of macronutrient quintiles.[a,b]

	Ketogenic ratio quintiles					
Variables	**Q1 (<0.27)**	**Q2 (0.27–0.32)**	**Q3 (0.32–0.37)**	**Q4 (0.37–0.44)**	**Q5 (>0.44)**	**P-value**
Ketogenic ratio	0.23 ± 0.03	0.30 ± 0.01	0.35 ± 0.02	0.41 ± 0.02	0.53 ± 0.09	<0.001
Simplified ketogenic ratio	0.12 ± 0.02	0.17 ± 0.01	0.21 ± 0.01	0.27 ± 0.02	0.37 ± 0.07	<0.001
LCD score	6.09 ± 3.10	11.1 ± 2.49	15.2 ± 2.47	19.2 ± 2.71	23.4 ± 3.24	<0.001
LCD (%)[d]	0.1	0.2	0.8	3.4	50.0	<0.001
Total energy intake (kcal)	1406 ± 494	1515 ± 534	1587 ± 574	1659 ± 625	1742 ± 697	<0.001
Total carbohydrate (grams)	225.1 ± 79.0	213.2 ± 75.8	204.1 ± 74.7	193.1 ± 74.1	169.8 ± 71.9	<0.001
Energy from carbohydrate (%)	64.3 ± 5.4	56.3 ± 3.1	51.4 ± 3.0	46.5 ± 3.0	38.9 ± 5.0	<0.001
Total protein (grams)	56.4 ± 22.6	63.7 ± 24.5	67.5 ± 26.1	69.8 ± 27.8	74.1 ± 31.5	<0.001
Energy from protein (%)	16.0 ± 3.2	16.9 ± 3.1	17.1 ± 3.2	17.0 ± 3.2	17.2 ± 3.4	<0.001
Total fat (grams)	32.3 ± 14.2	45.3 ± 17.8	54.7 ± 21.9	65.8 ± 27.1	82.1 ± 36.1	<0.001
Energy from fat (%)	20.5 ± 4.3	26.8 ± 3.3	30.9 ± 3.5	35.5 ± 3.7	42.1 ± 5.2	<0.001
Total fiber (grams)	18.9 ± 7.5	17.4 ± 6.8	16.3 ± 6.5	15.0 ± 6.2	13.1 ± 5.7	<0.001
HEI-2015	71.7 ± 9.1	69.9 ± 9.2	67.3 ± 9.4	63.6 ± 9.4	58.9 ± 9.0	<0.001

[a] Data are shown as mean ± SD.

[b] Diet information collected at baseline using WHI block food frequency questionnaires.[20, 21]

[c] Abbreviations: LCD, low-carbohydrate diet; HEI, healthy eating index; kcal, kilocalories.

[d] Defined as <40% energy from carbohydrate.

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Table 4.

Association of ketogenic ratio of macronutrients and risk of incident type 2 diabetes mellitus among 125,982 postmenopausal women.[a]

	Ketogenic ratio quintiles					
	Q1 (<0.27)	**Q2 (0.27–0.32)**	**Q3 (0.32–0.37)**	**Q4 (0.37–0.44)**	**Q5 (>0.44)**	**P_{trend}**
No. cases/ non-cases	3253/21943	3524/21673	3691/21505	3997/21200	4310/20886	
Model 1[b]	1 (reference)	1.11 (1.06–1.17)	1.19 (1.14–1.25)	1.33 (1.27–1.39)	1.47 (1.40–1.53)	<0.001
Model 2[c]	1 (reference)	1.09 (1.04–1.14)	1.15 (1.10–1.21)	1.26 (1.20–1.32)	1.36 (1.30–1.43)	<0.001
Model 3[d]	1 (reference)	1.07 (1.02–1.13)	1.12 (1.07–1.18)	1.21 (1.16–1.27)	1.29 (1.23–1.36)	<0.001
Model 4[e]	1 (reference)	1.05 (1.00–1.10)	1.09 (1.04–1.14)	1.15 (1.10–1.21)	1.20 (1.14–1.26)	<0.001
	Simplified ketogenic ratio quintiles					
	Q1 (<0.15)	**Q2 (0.15–0.19)**	**Q3 (0.19–0.24)**	**Q4 (0.24–0.30)**	**Q5 (>0.30)**	**P_{trend}**
No. cases/ non-cases	3333/21863	3571/21626	3582/21614	4032/21165	4257/20939	
Model 1[b]	1 (reference)	1.09 (1.04–1.14)	1.12 (1.06–1.17)	1.30 (1.24–1.36)	1.40 (1.34–1.46)	<0.001
Model 2[c]	1 (reference)	1.07 (1.02–1.12)	1.07 (1.02–1.12)	1.22 (1.16–1.28)	1.29 (1.23–1.35)	<0.001
Model 3[d]	1 (reference)	1.04 (0.99–1.09)	1.03 (0.98–1.08)	1.16 (1.10–1.21)	1.20 (1.14–1.26)	<0.001
Model 4[e]	1 (reference)	1.02 (0.97–1.07)	1.00 (0.95–1.05)	1.11 (1.05–1.17)	1.13 (1.07–1.19)	<0.001
	Low-carbohydrate diet score quintiles					
	Q1 (<8.0)	**Q2 (9.0–13.0)**	**Q3 (14.0–17.0)**	**Q4 (18.0–21.0)**	**Q5 (>22.0)**	**P_{trend}**
No. cases/ non-cases	2987/20250	3978/25377	3851/22045	3819/20742	4140/18793	
Model 1[b]	1 (reference)	1.10 (1.05–1.15)	1.23 (1.17–1.29)	1.32 (1.25–1.38)	1.57 (1.50–1.65)	<0.001
Model 2[c]	1 (reference)	1.09 (1.04–1.14)	1.20 (1.14–1.26)	1.26 (1.20–1.32)	1.47 (1.41–1.55)	<0.001
Model 3[d]	1 (reference)	1.08 (1.03–1.13)	1.17 (1.12–1.23)	1.22 (1.16–1.28)	1.40 (1.33–1.47)	<0.001
Model 4[e]	1 (reference)	1.06 (1.01–1.11)	1.13 (1.08–1.19)	1.15 (1.09–1.21)	1.28 (1.22–1.35)	<0.001

[a]Data are hazard ratios (95% CIs) unless otherwise indicated.

[b]Model 1: adjusted for age (years), race (American Indian/Alaska Native, Asian, Native Hawaiian/Other Pacific Islander, Black, White, More than one race, Unknown/not reported), and ethnicity (Not Hispanic/Latino, Hispanic/Latino, Unknown/not reported).

[c]Model 2: adjusted for all factors in Model 1 plus education (High school or less, some college, college, postgraduate or professional, missing), income (<$20,000, $20,000-$50,000, >$50,000, missing), health insurance (no, yes, missing), relationship status (single, separated, married, missing), family history of diabetes (no, yes, missing), and WHI region (northeast, south, Midwest, west), and WHI component.

[d]Model 3: adjusted for all factors in Model 2 plus female hormone use (never, past, current, missing), smoking status (never, past, current, missing), alcohol use (non-drinker, moderate, heavy, missing), recreational physical activity MET-hr/wk (<10, ≥10, missing), and total energy intake (quartiles).

[e]Model 4: adjusted for all factors in Model 3 plus body mass index proximate to T2DM (<18.5, 18.5–24.9, 25.0–29.9, ≥30, missing), hyperlipidemia at baseline (no, yes, missing), hypertension proximate to T2DM (no, yes, missing), and 2015-healthy eating index (quartiles).

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Table 7.

Association of ketogenic ratio of macronutrients and type 2 diabetes mellitus risk among postmenopausal women stratified by HEI tertiles.[a,b,c]

	Ketogenic ratio quintiles						
HEI tertile	**Q1 (<0.27)**	**Q2 (0.27–0.32)**	**Q3 (0.32–0.37)**	**Q4 (0.37–0.44)**	**Q5 (>0.44)**	**P_{trend}**	**$P_{interaction}$**
No. cases / non-cases	556/3101	738/4078	1127/5741	1831/8670	2912/13240		
T1 (n=41994)	1 (reference)	1.01 (0.91–1.13)	1.10 (1.00–1.22)	1.17 (1.06–1.29)	1.20 (1.10–1.32)	<0.001	0.24
No. cases / non-cases	1047/6430	1192/7274	1398/8092	1432/8139	1107/5883		
T2 (n=41994)	1 (reference)	0.99 (0.91–1.08)	1.05 (0.96–1.14)	1.07 (0.99–1.17)	1.14 (1.05–1.25)	<0.001	
No. cases / non-cases	1650/12412	1594/10321	1166/7672	734/4391	291/1763		
T3 (n = 41994)	1 (reference)	1.13 (1.05–1.21)	1.10 (1.02–1.19)	1.22 (1.12–1.34)	1.21 (1.07–1.38)	<0.001	

[a] Data are hazard ratios (95% CIs) unless otherwise indicated.

[b] Models are adjusted for all factors in Model 4 except for HEI.

[c] Abbreviations: HEI, healthy eating index.