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ORIGINAL RESEARCH

Effects of Low-Carbohydrate and Low-Fat Diets on Morbidity and Mortality of COPD

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Purpose: Although low-carbohydrate and low-fat diets improve weight loss, cardiovascular disease, and diabetes, the relationship between these dietary patterns, highlighting macronutrient sources, and chronic obstructive pulmonary disease (COPD) remains unclear. This study aimed to assess the association between low-carbohydrate diets (LCDs) and low-fat diets (LFDs) and the odds of COPD and mortality among people with COPD in the National Health and Nutrition Examination Survey.

Patients and Methods: Clinical data were extracted from the 2007–2008, 2009–2010, and 2011–2012 National Health and Nutrition Examination Survey (NHANES) cycles that met the inclusion criteria. Multivariable logistic regression was used to evaluate the associations between LCD and LFD scores and COPD, and multivariable Cox proportional hazards regression and restricted cubic spline (RCS) regression were used to assess the relationship between all-cause mortality and LCD and LFD scores.

Results: Comparing extreme tertiles, multivariable-adjusted odds ratio (OR) were 1 (reference), 1.09 (95% CI, 0.77–1.55), 1.84 (95% CI, 1.09–3.09) ($P = 0.045$ for trend) for unhealthy LFD scores. After multivariate adjustment, a per 5-point increase in unhealthy LCD score was associated with a 21% higher risk of total mortality (hazard ratio, 1.21; 95% CI, 1.03–1.43); while a per 5-point increase in healthy LFD scores was associated with a 21% lower risk of total mortality (HR, 0.79; 95% CI, 0.67–0.94).

Conclusion: Higher unhealthy LFD score was associated with an increased odds of COPD. Unhealthy LCD scores were significantly associated with higher total mortality, whereas healthy LFD scores were associated with lower total mortality in patients with COPD.

Keywords: low-carbohydrate diet, low-fat diet, chronic obstructive pulmonary disease, mortality, NHANES

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by chronic respiratory symptoms and progressive airflow obstruction owing to airway and/or alveolar abnormalities. It is now consensually agreed that the prevalence of COPD in people aged 30–79 years is 10.3% worldwide, with 14.1% in men and 6.5% in women.[1] Chronic respiratory diseases are the third leading cause of deaths from non-communicable diseases, of which COPD is the most prominent cause of mortality and disability.[2] The genetic factor and environmental exposures, such as tobacco smoking, particulate matter, outdoor air pollution, are in combination with social factors lead to COPD.[3] Non-pharmacological treatments for COPD are a crucial part of the treatments including vaccinations, smoking cessation, avoidance of exposures and active lifestyle and so on. Although diet is a modifiable lifestyle factor, there are no approved dietary modifications to prevent or manage these diseases.

Diet, a modifiable lifestyle factor, is beneficial in intervention strategies for obesity and other chronic diseases. Previous studies have indicated that obesity has a protective effect against mortality in patients with COPD.[4,5] The effect of nutrition on COPD is a potential research topic. The Western-style dietary pattern, characterised by high intake of saturated fat, processed red meats, refined grains, and sweets, is related to an increased risk of development and progression of COPD.[6] A randomized trial reported that COPD patients following a diet rich in fruits and vegetables showed an increase in FEV1 compared with the control group. While dietary management in COPD treatment has yet to

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be defined.[7] In recent years, attention has been paid to low-carbohydrate diets (LCDs) and low-fat diets (LFDs), with lower intake of energy from carbohydrate and fat. Halton et al created overall, healthy, and unhealthy LCD scores based on the sources and relative levels of carbohydrate, protein, and fat intake. A similar approach has been used to create LFD scores.[8,9] As reported, LCDs and/or LFDs with chronic liver disease, prediabetes, and cognitive performance are closely related. Several studies have revealed that unhealthy LCDs and LFDs are associated with a higher risk of mortality, and healthy LCDs and LFDs are associated with a lower risk of mortality in the general population.[10–12] But little is known about the effect of low-carbohydrate and low-fat diets on morbidity and mortality in COPD.

Here, we used data from the US National Health and Nutrition Examination Survey (NHANES) 2007–2012 cycle, in which spirometry was performed on a nationally representative sample, to assess the impact of LCD and LFD scores on the risk of developing COPD and mortality from COPD.

Materials and Methods

Subject Population

NHANES was performed by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) to assess the health and nutritional status of the American population. The NHANES study protocol was approved by the research ethics review board of the NCHS, and written informed consent was obtained from all participants. After being reviewed by the Institutional Review Board of the First Affiliated Hospital of Xi'an Jiaotong University, it was determined that ethical approval is exempted since the study does not contain any data which can identify individual. We enrolled 30442 participants from three cycles (2007–2008, 2009–2010 and 2011–2012) of the NHANES. After merging the databases, we excluded individuals with missing spirometry information (n = 28,878), missing dietary information (n = 59), or age < 18 years (n = 401), with implausible total energy intake (n = 84; < 800 or > 4200 kcal for men and < 600 or > 3500 kcal for women), Ultimately, 1020 adults were included in the final analysis, and 456 participants had COPD (Figure S1). Details of the NHANES are available on the CDC website (https://www.cdc.gov/nchs/nhanes/index.htm).

Ascertainment of Mortality

All-cause mortality data were obtained from the public-use mortality file linked to the National Death Index for the NHANES through December 31, 2019. Follow-up time was defined as the interval from the date of interview to the date of death for individuals who had died or to December 31, 2019, for participants who were censored.

Assessments of LCD and LFD Scores

In the NHANES, diet was assessed using a 24-hour dietary recall. Nutrients were estimated based on cycle-specific versions of the US Department of Agriculture (USDA) Food and Nutrition Database for Dietary Studies (FNDDS). To assess the intake of major food groups, USDA Food Patterns Equivalents Database and the MyPyramid Equivalents Database were harmonized during the survey cycles. We used the percentage of energy from each macronutrient rather than the absolute energy to represent the dietary components and reduce bias due to the underreporting of food consumption (Tables S1 and S2). The participants were divided into 11 sex-specific strata based on the percentage of energy derived from fats, proteins, and carbohydrates. For fat and protein, individuals in the highest stratum received 10 points and those in the lowest stratum received 0. For carbohydrates, the order of the strata was reversed. The scores for the three macronutrients were then summed to create the total LCD score, which ranged from 0 to 30. Therefore, the higher the score, the closer the participant's diet is to the overall pattern of LCDs. Furthermore, carbohydrate, fat, and protein subtypes were analyzed. High-quality carbohydrates were defined as carbohydrates from whole grains, whole fruits, legumes, and non-starchy vegetables, whereas low-quality carbohydrates were defined as those from refined grains, fruit juice, added sugar, potatoes, other starchy vegetables, and other sources. Animal proteins include those from red and processed meat, fish and seafood, poultry, dairy products, eggs, and other animal sources. Plant proteins are defined as proteins from whole grains, refined grains, nuts, legumes, soy, and other sources. Fat was divided into saturated fatty acids (SFAs) and unsaturated fatty acids (UFAs). An unhealthy LCD score was created based on the

percentage of energy from high-quality carbohydrates, animal proteins, and saturated fats, while a healthy LCD score was calculated based on the percentage of energy from low-quality carbohydrates, plant proteins, and unsaturated fats. A similar approach was used to create the overall, unhealthy, and healthy LFD scores.

Ascertainment of COPD

Spirometry data were collected from participants aged > 18 years, who met the strict inclusion criteria detailed in the NHANES Survey. The best forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) were selected for analysis. COPD was defined as individuals with FEV1/FVC < 0.70 (post-bronchodilation).[3]

Assessments of Demographic and Covariates

Information on age, sex, race/ethnicity, educational level, income, and smoking status was collected during household interviews using standardized questionnaires. Body weight, height, and alcohol consumption data were obtained from the participants who underwent physical examinations at a mobile examination center. Participants reported their race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other Hispanics, or other). (Other Hispanic groups were combined to create another group) according to the categories provided by the NCHS. Three educational levels were categorized (less than a high school graduate, high school graduate, or more than a high school graduate). Family income was classified as the ratio of family income to poverty (PIR) and categorized into three levels (< 1.3, 1.3–3.49, ≥ 3.5). For missing data on family income (n = 67), median values were imputed. Smokers were defined as individuals who reported smoking at least 100 cigarettes during their lifetime, and drinkers were defined as participants who drank a minimum of 12 drinks in any given year. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Comorbidity conditions (cancer, heart disease, stroke, diabetes, and hypertension) were defined as participants reporting that they had been told by a health professional that they had such conditions and/or that they took prescribed medications because of these conditions. Laboratory test data, including white blood cell (WBC) count, lymphocyte percentage, monocyte percentage, segmented neutrophil percentage, eosinophil percentage, basophil percentage, triglyceride level, and total cholesterol level, were collected from participants who provided blood samples at recruitment.

Statistical Analysis

A multivariable logistic regression model was used to estimate the odds ratios (ORs) and 95% confidence intervals (CI) for COPD prevalence associated with the LCD and LFD scores. The 6 LCD and LFD scores were categorized into tertiles. Model 1 was adjusted for age. Model 2 was further adjusted for sex, race/Hispanic origin, BMI, education, ratio of family income to poverty, smoking, total energy intake, history of cancer, hypertension, and history of heart disease. We presented the ORs and percentage changes by tertile category and per five-point increases for each dietary pattern. A test for linear trends was performed by treating each diet score as a continuous variable in the model.

The multivariable Cox proportional hazards regression model was used to assess the hazard ratios (HRs) and 95% CIs of mortality associated with the LCD and LFD scores. Person-years were calculated from the date of the interview to the date of death or end of follow-up, whichever occurred first. Model 1 was adjusted for age. In multivariate analyses, we further adjusted for sex, race/Hispanic origin, BMI, education, ratio of family income to poverty, smoking, total energy intake, history of cancer, hypertension, and history of heart disease. Trends were estimated by treating the dietary score as a continuous variable. A 5-point increase in each score was used to estimate the HRs for all-cause mortality.

We further performed a stratification analysis for the associations between dietary scores and all-cause mortality according to several potential confounding factors at baseline. We also examined the interactions between diet scores and subgroup variables to evaluate potential modifications by subgroups. Several sensitivity analyses were conducted to test the robustness of the results. First, we further adjusted for lymphocyte, monocyte, segmented neutrophil, eosinophil, and basophil percentages at the baseline. Second, patients with heart disease or cancer at the baseline were excluded. Third, participants who died during the first year of follow-up were excluded. All statistical analyses were conducted using R statistical software (version 4.3.0; R Core Team), and a two-sided P value of < 0.05, was set to indicate statistical significance.

Results

Characteristics of Individuals

In the present study, after reviewing the inclusion and exclusion criteria, a total of 1020 adults (median [IQR] age: 52.0 [35.0, 64.0] years) were confirmed to meet the conditions for further analysis, of which 456 individuals had COPD. The crude COPD rate was 44.71%. During 4360 person-years of follow-up, 89 deaths occurred. The baseline characteristics of the study participants according to tertiles of the LCD and LFD scores are shown in Table 1. Participants with a higher overall LCD score were more likely to be older; have higher BMI, educational level, income level, and monocyte percentage; have lower lymphocyte percentage and triglycerides; and have higher comorbidities (diabetes and hypertension). Similar results were observed for healthy LCD scores. In contrast, participants with higher unhealthy LCD scores tended to be younger, smokers, have higher white blood cell and lymphocyte percentages, and were unlikely to have complications. Conversely, those with higher LFD scores tended to be non-smokers, had lower BMI, educational level, and incidence of complications, and had higher triglyceride levels. With increasing overall and unhealthy LFD scores, a greater proportion of participants had lower income levels and monocyte percentages. Overall, participants with higher LCD scores tended to have a higher energy intake, whereas those with higher LFD scores showed the opposite trend. Pearson correlation coefficients were 0.18 between the healthy LCD and LFD scores, −0.03 between the unhealthy LCD and LFD scores, −0.70 between the healthy LFD score and unhealthy LCD score, and −0.67 between the unhealthy LFD score and healthy LCD score (Table S3).

LCD, LFD Scores, and COPD

Neither the overall nor healthy LCD scores were associated with the odds of COPD (Table 2). A higher unhealthy LCD score was associated with a higher odds of developing COPD. The age-adjusted ORs were 1 (reference), 1.26 (95% CI, 0.90–1.77), 1.60 (95% CI, 1.05–2.42) (P = 0.028 for trend). The multivariable-adjusted ORs were 1 (reference), 1.24 (95% CI, 0.87–1.78), 1.29 (95% CI, 0.83–2.01) (P = 0.233 for trend). The overall and healthy LFD scores were not associated with the odds of COPD. A higher unhealthy LFD score was associated with an increased odds of developing COPD comparing extreme tertiles, multivariable-adjusted OR were 1 (reference), 1.09 (95% CI, 0.77–1.55), 1.84 (95% CI, 1.09–3.09) (P = 0.045 for trend).

The overall and unhealthy LFD scores were not associated with all-cause mortality (Table 3). Healthy LFD score was negatively associated with all-cause mortality in COPD patients. The multivariable-adjusted HRs of total mortality from the lowest to highest tertiles of healthy LFD score were 1 (reference), 0.70 (95% CI, 0.43–1.12), 0.47 (95% CI, 0.24–0.90) (P = 0.019 for trend). A per 5-point increase in healthy LFD score was associated with 21% lower risk of all-cause mortality (HR, 0.79; 95% CI, 0.67–0.94) after multivariate adjustment.

Figure 1 shows the dose–response relationships of healthy LCD and LFD scores with all-cause mortality. After adjusting for age, unhealthy LCD and LFD scores were associated with all-cause mortality (both P for overall < 0.05). After multivariable adjustment, unhealthy LCD scores were still associated with a higher risk of all-cause mortality (overall P = 0.01), and the inflection point of the unhealthy LCD score was 16.03.

Subgroup and Sensitivity Analyses

In the subgroup survival analysis, the associations remained persistent in most subgroups (Figures 2, 3, and S2). However, the results were not always statistically significant, possibly due to the small sample size. After multiple testing corrections, a statistically significant interaction on all-cause mortality was detected between healthy LCD score and PIR (P = 0.014 for interaction); the HRs per 5-point increase were 1.20 (95% CI, 0.96–1.50) among participants with PIR < 2.5 vs 0.75 (95% CI, 0.57–0.99) among participants with PIR ≥ 2.5. When we further adjusted for lymphocyte percentage, monocyte percentage, segmented neutrophil percentage, eosinophil percentage, and basophil percentage at baseline, associations per 5-point increase remained statistically significant in the unhealthy LCD and healthy LFD scores (Table 4).

Table 1 Characteristics of Participants by Tertiles of Low-Carbohydrate-Diet and Low-Fat-Diet Scores

level	OLCD		ULCD		HLCD		OLFD		ULFD		HLFD	
	Tertile 1	Tertile 3	Tertile 1	Tertile 3	Tertile 1	Tertile 3	Tertile 1	Tertile 3	Tertile 1	Tertile 3	Tertile 1	Tertile 3
n	267	334	256	216	233	261	291	173	253	133	266	236
Age(y) (median [IQR])	49.00 [32.00, 62.00]	53.00 [36.00, 65.00]	54.00 [36.00, 66.00]	50.50 [35.00, 64.00]	46.00 [32.00, 62.00]	55.00 [39.00, 66.00]	53.00 [39.00, 63.00]	51.00 [35.00, 67.00]	55.00 [39.00, 65.00]	46.00 [30.00, 62.00]	52.00 [35.00, 63.75]	55.00 [36.00, 67.00]
Family income to poverty ratio (%)												
<1.3	95 (35.6)	80 (24.0)	71 (27.7)	73 (33.8)	84 (36.1)	59 (22.6)	75 (25.8)	50 (28.9)	60 (23.7)	46 (34.6)	86 (32.3)	61 (25.8)
1.3 to <3.5	113 (42.3)	114 (34.1)	99 (38.7)	68 (31.5)	97 (41.6)	84 (32.2)	95 (32.6)	74 (42.8)	86 (34.0)	54 (40.6)	88 (33.1)	87 (36.9)
≥3.5	59 (22.1)	140 (41.9)	86 (33.6)	75 (34.7)	52 (22.3)	118 (45.2)	121 (41.6)	49 (28.3)	107 (42.3)	33 (24.8)	92 (34.6)	88 (37.3)
BMI (%)												
<18.5	8 (3.0)	2 (0.6)	4 (1.6)	4 (1.9)	10 (4.3)	2 (0.8)	4 (1.4)	3 (1.7)	3 (1.2)	3 (2.3)	6 (2.3)	2 (0.8)
18.5 to <25	109 (40.8)	107 (32.1)	96 (37.5)	70 (32.4)	92 (39.5)	81 (31.3)	101 (34.9)	66 (38.2)	91 (36.0)	49 (36.8)	94 (35.3)	79 (33.5)
25 to <30	83 (31.1)	122 (36.6)	91 (35.5)	77 (35.6)	75 (32.2)	99 (38.2)	107 (37.0)	62 (35.8)	95 (37.5)	53 (39.8)	92 (34.6)	88 (37.3)
≥30	67 (25.1)	102 (30.6)	65 (25.4)	65 (30.1)	56 (24.0)	77 (29.7)	77 (26.6)	42 (24.3)	64 (25.3)	28 (21.1)	74 (27.8)	67 (28.4)
Sex (%)												
Males	155 (58.1)	228 (68.3)	160 (62.5)	151 (69.9)	138 (59.2)	174 (66.7)	190 (65.3)	94 (54.3)	158 (62.5)	83 (62.4)	172 (64.7)	148 (62.7)
Females	112 (41.9)	106 (31.7)	96 (37.5)	65 (30.1)	95 (40.8)	87 (33.3)	101 (34.7)	79 (45.7)	95 (37.5)	50 (37.6)	94 (35.3)	88 (37.3)
Race/ethnicity (%)												
Non-Hispanic white	144 (53.9)	210 (62.9)	144 (56.2)	141 (65.3)	135 (57.9)	162 (62.1)	186 (63.9)	83 (48.0)	156 (61.7)	74 (55.6)	172 (64.7)	120 (50.8)
Non-Hispanic black	48 (18.0)	63 (18.9)	36 (14.1)	43 (19.9)	43 (18.5)	46 (17.6)	52 (17.9)	21 (12.1)	50 (19.8)	22 (16.5)	50 (18.8)	35 (14.8)
Mexican American	36 (13.5)	29 (8.7)	30 (11.7)	16 (7.4)	23 (9.9)	20 (7.7)	17 (5.8)	30 (17.3)	16 (6.3)	16 (12.0)	17 (6.4)	32 (13.6)
Other races	39 (14.6)	32 (9.6)	46 (18.0)	16 (7.4)	32 (13.7)	33 (12.6)	36 (12.4)	39 (22.5)	31 (12.3)	21 (15.8)	27 (10.2)	49 (20.8)
Nonsmoker (%)	83 (32.4)	106 (33.3)	98 (39.4)	54 (26.2)	68 (30.5)	100 (39.7)	79 (28.1)	71 (43.0)	79 (32.1)	41 (33.3)	56 (21.9)	107 (47.3)
Educational level (%)												
≤12th grade	83 (31.1)	80 (24.0)	71 (27.7)	64 (29.6)	70 (30.0)	51 (19.5)	57 (19.6)	59 (34.1)	47 (18.6)	43 (32.3)	67 (25.2)	60 (25.4)
High school graduate	73 (27.3)	79 (23.7)	55 (21.5)	54 (25.0)	63 (27.0)	63 (24.1)	79 (27.1)	31 (17.9)	66 (26.1)	31 (23.3)	74 (27.8)	40 (16.9)
More than high school	111 (41.6)	175 (52.4)	130 (50.8)	98 (45.4)	100 (42.9)	147 (56.3)	155 (53.3)	83 (48.0)	140 (55.3)	59 (44.4)	125 (47.0)	136 (57.6)
Nondrinker (%)	57 (23.1)	50 (15.8)	49 (20.4)	33 (16.3)	48 (22.4)	39 (15.6)	41 (14.9)	48 (30.2)	44 (18.0)	32 (26.7)	41 (16.3)	49 (22.2)
History of stroke (%)	11 (4.3)	7 (2.2)	8 (3.2)	5 (2.4)	10 (4.5)	5 (2.0)	4 (1.4)	7 (4.2)	6 (2.4)	4 (3.3)	5 (2.0)	6 (2.7)
History of cancer (%)	27 (10.5)	40 (12.6)	29 (11.6)	22 (10.7)	27 (12.1)	32 (12.7)	33 (11.8)	21 (12.7)	38 (15.5)	21 (17.1)	32 (12.5)	31 (13.7)
Diabetes (%)	12 (4.5)	48 (14.4)	19 (7.4)	28 (13.0)	11 (4.7)	38 (14.6)	34 (11.7)	14 (8.1)	37 (14.6)	10 (7.5)	28 (10.5)	24 (10.2)
Hypertension (%)	70 (26.2)	115 (34.4)	91 (35.5)	69 (31.9)	61 (26.2)	94 (36.0)	97 (33.3)	52 (30.1)	93 (36.8)	35 (26.3)	81 (30.5)	84 (35.6)
History of heart disease (%)	11 (4.3)	27 (8.5)	18 (7.3)	14 (6.8)	13 (5.9)	18 (7.2)	17 (6.1)	7 (4.2)	14 (5.7)	6 (4.9)	15 (5.9)	20 (8.9)
Total energy, kcal/d (median [IQR])	1919.00 [1416.00, 2565.50]	2069.00 [1545.75, 2647.25]	1867.50 [1468.75, 2497.25]	2164.00 [1598.75, 2712.00]	1886.00 [1318.00, 2582.00]	1999.00 [1565.00, 2648.00]	2326.00 [1701.50, 2917.50]	1650.00 [1247.00, 2205.00]	2063.00 [1568.00, 2798.00]	1935.00 [1432.00, 2494.00]	2207.50 [1568.75, 2798.00]	1841.00 [1382.75, 2349.50]
WBC (median [IQR])	7.10 [5.90, 8.60]	6.90 [5.60, 8.20]	6.90 [5.70, 8.38]	7.20 [6.00, 8.70]	7.25 [6.10, 8.65]	6.90 [5.50, 8.10]	7.10 [5.60, 8.20]	6.80 [5.80, 8.10]	6.90 [5.50, 8.10]	7.30 [6.10, 8.65]	7.30 [5.97, 8.72]	6.80 [5.75, 8.00]
Lymphocyte percent (%) (median [IQR])	30.00 [25.75, 35.55]	28.50 [23.10, 33.90]	28.85 [24.68, 34.95]	29.30 [23.20, 34.30]	30.00 [24.92, 36.38]	28.55 [23.72, 33.88]	29.10 [23.30, 34.70]	29.30 [25.10, 35.00]	29.05 [23.72, 34.30]	27.70 [24.10, 33.15]	29.60 [23.95, 35.25]	28.10 [24.45, 34.10]

(*Continued*)

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Table 1 (Continued).

level	OLCD		ULCD		HLCD		OLFD		ULFD		HLFD	
	Tertile 1	Tertile 3	Tertile 1	Tertile 3	Tertile 1	Tertile 3	Tertile 1	Tertile 3	Tertile 1	Tertile 3	Tertile 1	Tertile 3
Monocyte percent (%) (median [IQR])	7.20 [5.90, 8.65]	7.85 [6.50, 9.30]	7.60 [6.10, 8.90]	7.70 [6.30, 9.10]	7.30 [5.90, 8.90]	7.80 [6.40, 9.30]	8.00 [6.40, 9.30]	7.40 [6.10, 8.90]	8.00 [6.40, 9.40]	6.90 [5.60, 8.65]	7.60 [6.30, 9.05]	7.70 [6.30, 8.95]
Segmented neutrophils percent (%) (median [IQR])	58.80 [53.15, 63.80]	60.45 [53.80, 65.97]	59.50 [53.40, 64.90]	59.50 [53.90, 65.90]	58.80 [52.13, 64.82]	60.40 [53.92, 65.60]	59.70 [53.10, 64.70]	58.50 [53.20, 63.60]	59.70 [51.82, 64.62]	61.70 [55.30, 66.10]	59.30 [52.60, 65.05]	59.30 [53.60, 65.55]
Eosinophils percent (%) (median [IQR])	2.60 [1.70, 3.70]	2.70 [1.70, 4.10]	2.55 [1.70, 3.60]	2.40 [1.70, 4.00]	2.55 [1.60, 3.80]	2.70 [1.70, 4.10]	2.80 [1.80, 4.10]	2.50 [1.60, 3.70]	2.65 [1.70, 3.98]	2.30 [1.55, 3.55]	2.50 [1.70, 3.80]	2.50 [1.70, 3.80]
Cholesterol (mg/dL) (median [IQR])	189.50 [166.00, 215.75]	189.00 [161.00, 219.00]	191.00 [165.75, 217.25]	190.00 [164.00, 220.00]	188.00 [163.25, 216.00]	193.00 [165.00, 222.00]	191.00 [163.00, 221.00]	187.00 [162.25, 212.00]	192.50 [164.00, 217.75]	191.50 [162.00, 214.75]	196.00 [167.50, 223.00]	187.00 [160.75, 216.00]
Triglycerides (mg/dL) (median [IQR])	125.00 [86.00, 188.25]	113.00 [79.00, 166.00]	132.00 [85.00, 201.00]	114.00 [80.00, 169.00]	127.50 [89.00, 207.50]	115.00 [79.00, 175.25]	109.00 [76.00, 158.00]	125.50 [89.50, 201.00]	107.50 [72.00, 155.00]	122.50 [86.25, 210.50]	114.00 [80.00, 171.00]	126.00 [83.00, 202.25]

Abbreviations: OLCD, overall low-carbohydrate-diet score; ULCD, unhealthy low-carbohydrate-diet score; HLCD, healthy low-carbohydrate-diet score; OLFD, overall low-fat-diet score; ULFD, unhealthy low-fat-diet score; HLFD, healthy low-fat-diet score; BMI, body mass index; WBC, white blood cell count; IQR, interquartile range.

Table 2 Associations of LCD and LFD Scores with COPD[a]

	Tertile 1	Tertile 2	Tertile 3	Per 5-Point Increase	*P*-trend
Overall LCD					
Model 1[b]	Reference	1.23 (0.86–1.76, *P* = 0.247)	1.38 (0.96–2.01, *P* = 0.086)	1.07 (0.97–1.17, *P* = 0.179)	0.087
Model 2[c]	Reference	1.32 (0.90–1.92, *P* = 0.152)	1.27 (0.85–1.88, *P* = 0.238)	1.03 (0.93–1.14, *P* = 0.544)	0.255
Unhealthful LCD					
Model 1[b]	Reference	1.26 (0.90–1.77, *P* = 0.181)	1.60 (1.05–2.42, *P* = 0.028)	1.18 (1.05–1.32, *P* = 0.004)	0.028
Model 2[c]	Reference	1.24 (0.87–1.78, *P* = 0.236)	1.29 (0.83–2.01, *P* = 0.251)	1.11 (0.99–1.25, *P* = 0.068)	0.233
Healthful LCD					
Model 1[b]	Reference	1.05 (0.73–1.50, *P* = 0.803)	1.08 (0.72–1.63, *P* = 0.694)	0.99 (0.89–1.10, *P* = 0.834)	0.694
Model 2[c]	Reference	1.06 (0.72–1.54, *P* = 0.779)	1.10 (0.71–1.69, *P* = 0.677)	0.99 (0.88–1.11, *P* = 0.826)	0.676
Overall LFD					
Model 1[b]	Reference	0.80 (0.58–1.10, *P* = 0.165)	0.67 (0.44–1.03, *P* = 0.070)	0.92 (0.82–1.03, *P* = 0.144)	0.059
Model 2[c]	Reference	0.86 (0.61–1.21, *P* = 0.398)	0.92 (0.58–1.46, *P* = 0.723)	0.98 (0.86–1.11, *P* = 0.719)	0.633
Unhealthful LFD					
Model 1[b]	Reference	1.08 (0.78–1.50, *P* = 0.647)	1.79 (1.10–2.93, *P* = 0.019)	1.10 (0.97–1.25, *P* = 0.135)	0.043
Model 2[c]	Reference	1.09 (0.77–1.55, *P* = 0.621)	1.84 (1.09–3.09, *P* = 0.022)	1.11 (0.97–1.27, *P* = 0.128)	0.045
Healthful LFD					
Model 1[b]	Reference	1.22 (0.87–1.71, *P* = 0.245)	0.72 (0.48–1.07, *P* = 0.107)	0.93 (0.84–1.03, *P* = 0.177)	0.211
Model 2[c]	Reference	1.45 (1.02–2.09, *P* = 0.041)	0.93 (0.60–1.44, *P* = 0.737)	1.00 (0.89–1.12, *P* = 0.994)	0.916

Notes: [a]: Logistic regression models were used to estimate the ORs and 95% CI for COPD according to tertiles of LCD and LFD scores. [b]: Model 1 was adjusted for age. [c]: Model 2 was further adjusted for sex, race/ethnicity, BMI, family income to poverty ratio, smoking, education, history of cancer, hypertension, history of heart disease, and total calorie intake.
Abbreviations: LCD, low-carbohydrate diet; LFD, low-fat diet.

Table 3 Associations of LCD and LFD Scores with All-Cause Mortality Among People with COPD[a]

	Tertile 1	Tertile 2	Tertile 3	Per 5-Point Increase	*P*-trend
Overall LCD					
Model 1[b]	Reference	0.82 (0.47–1.42, *P* = 0.481)	1.20 (0.70–2.05, *P* = 0.514)	1.10 (0.95–1.27, *P* = 0.192)	0.423
Model 2[c]	Reference	0.94 (0.53–1.66, *P* = 0.828)	1.30 (0.74–2.27, *P* = 0.360)	1.12 (0.97–1.30, *P* = 0.119)	0.313
Unhealthful LCD					
Model 1[b]	Reference	1.43 (0.80–2.53, *P* = 0.226)	2.18 (1.28–3.73, *P* = 0.004)	1.24 (1.06–1.46, *P* = 0.009)	0.003
Model 2[c]	Reference	1.55 (0.87–2.76, *P* = 0.138)	2.30 (1.23–4.31, *P* = 0.009)	1.21 (1.03–1.43, *P* = 0.021)	0.009
Healthful LCD					
Model 1[b]	Reference	0.86 (0.51–1.46, *P* = 0.588)	0.68 (0.36–1.29, *P* = 0.243)	0.97 (0.82–1.15, *P* = 0.737)	0.244
Model 2[c]	Reference	0.99 (0.57–1.73, *P* = 0.976)	0.91 (0.46–1.77, *P* = 0.770)	1.04 (0.87–1.24, *P* = 0.659)	0.777
Overall LFD					
Model 1[b]	Reference	0.92 (0.58–1.48, *P* = 0.745)	0.72 (0.37–1.41, *P* = 0.341)	0.94 (0.79–1.13, *P* = 0.520)	0.356
Model 2[c]	Reference	0.86 (0.52–1.41, *P* = 0.543)	0.70 (0.34–1.41, *P* = 0.312)	0.92 (0.76–1.10, *P* = 0.360)	0.307
Unhealthful LFD					
Model 1[b]	Reference	1.14 (0.69–1.89, *P* = 0.601)	1.19 (0.56–2.54, *P* = 0.645)	1.06 (0.88–1.29, *P* = 0.529)	0.584
Model 2[c]	Reference	1.09 (0.66–1.81, *P* = 0.736)	1.11 (0.52–2.40, *P* = 0.784)	1.02 (0.83–1.24, *P* = 0.867)	0.739
Healthful LFD					
Model 1[b]	Reference	0.64 (0.40–1.01, *P* = 0.056)	0.43 (0.23–0.80, *P* = 0.008)	0.77 (0.65–0.90, *P* = 0.001)	0.005
Model 2[c]	Reference	0.70 (0.43–1.12, *P* = 0.134)	0.47 (0.24–0.90, *P* = 0.023)	0.79 (0.67–0.94, *P* = 0.006)	0.019

Notes: [a]: Cox proportional hazards models were used to estimate the HRs and 95% CIs of all-cause mortality according to tertiles of LCD and LFD scores. [b]: Model 1 was adjusted for age. [c]: Model 2 was further adjusted for sex, race/ethnicity, BMI, family income to poverty ratio, smoking, education, history of cancer, hypertension, history of heart disease, and total calorie intake.
Abbreviations: LCD, low-carbohydrate diet; LFD, low-fat diet.

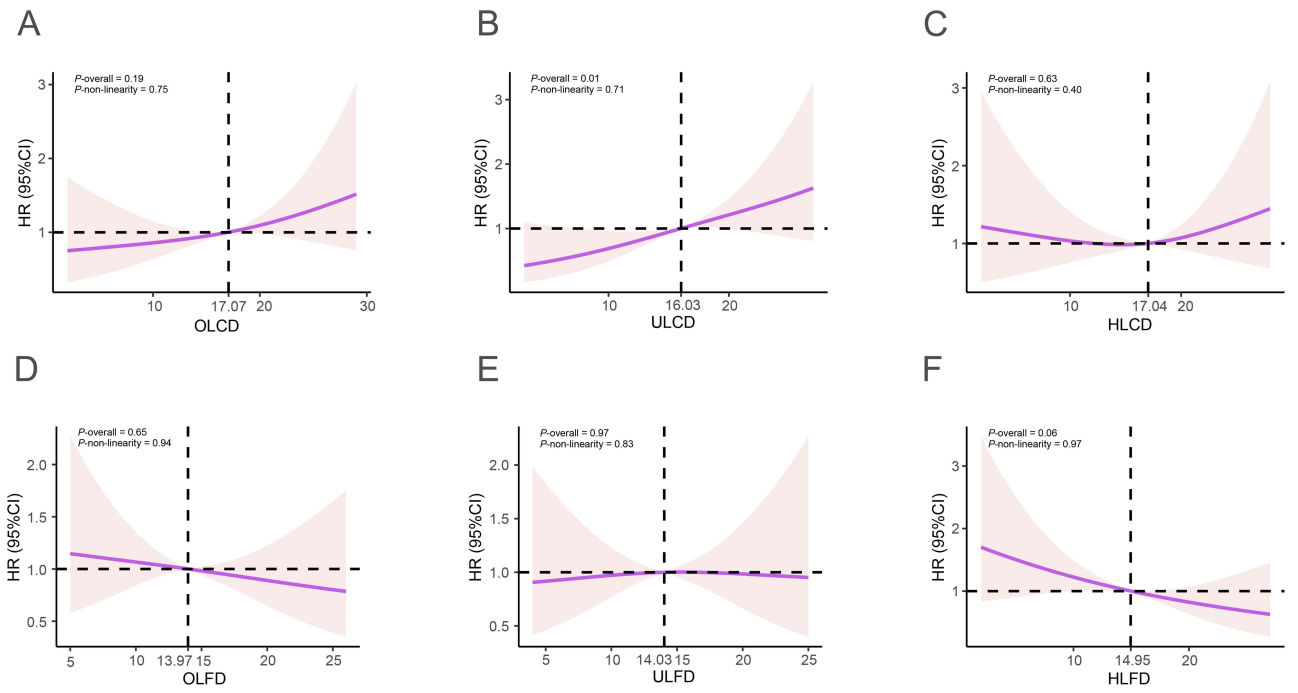

Figure 1 Associations of low-carbohydrate diet (**A**–**C**) and low-fat diet (**D**–**F**) scores with all-cause mortality among people with COPD.

Notes: A restricted cubic spline regression model was used to estimate the dose–response relationship between LCD and LFD scores and all-cause mortality. The covariates adjusted in the models were the same as those in Model 2 in Table 2. Solid purple lines indicate estimates and pink areas represent 95% CI. All *P*-non-linearity > 0.05.

Abbreviations: OLCD, overall low-carbohydrate diet score; ULCD, unhealthy low-carbohydrate diet score; HLCD, healthy low-carbohydrate diet score; OLFD, overall low-fat diet score; ULFD, unhealthy low-fat diet score; HLFD, healthy low-fat diet score; HR, hazard ratio.

Discussion

In this study, the overall LCD and LFD scores were not associated with the odds of COPD or the risk of total mortality in the COPD population. However, unhealthy LCD and LFD scores were positively associated with COPD risk. Unhealthy LCD score was associated with a higher total mortality, whereas healthy LFD scores were associated with a lower total mortality.

We observed that an unhealthy LFD diet was associated with an increased prevalence of COPD, and a healthy LFD score was inversely associated with the total mortality of people with COPD, indicating the remarkable health benefits of saturated fat reduction and unsaturated fat increase for the development and progression of COPD. Previous studies have shown that high fat diet can change the composition of gut microbes, which can affect the development of gastrointestinal diseases, metabolic dysfunction, and cognitive impairment.[13–16] David et al have confirmed that high fat diet, which was composed of dietary fat 69.5 ± 0.4% kcal and dietary protein 30.1 ± 0.5% kcal, can increase the abundance of bile-tolerant microorganisms, such as Bilophila, Alistipes, and Bacteroides; and reduce the level of saccharolytic microbes (Roseburia, E. rectale and Faecalibacterium prausnitzii), which may contribute to the development of inflammatory bowel disease.[14] The consumption of polyunsaturated fatty acids increased SCFA-producing bacteria, such as Bifidobacterium in humans.[17] It is now well established that SCFAs play an important role in promoting an anti-inflammatory environment, strengthening immunomodulatory functions and improving barrier homeostasis.[18–20] Furthermore, the high fat and high fructose diet induced alveolar and interstitial inflammation in the lung.[21] Microbial structure was associated with increased emergence of airway diseases such as asthma in childhood.[22,23] However, there is no definitive evidence whether dietary macronutrients are able to affect chronic respiratory diseases via change of gut microbiota so far.

The adverse impact of fat, especially unsaturated fat, on health has been widely recognized, and low- or no-fat products have become more popular. However, high carbohydrate intake, inevitable in low-fat dietary patterns, induced obesity and promoted abnormal metabolic features.[24,25] Previous trials have reported that a high-carbohydrate diet was

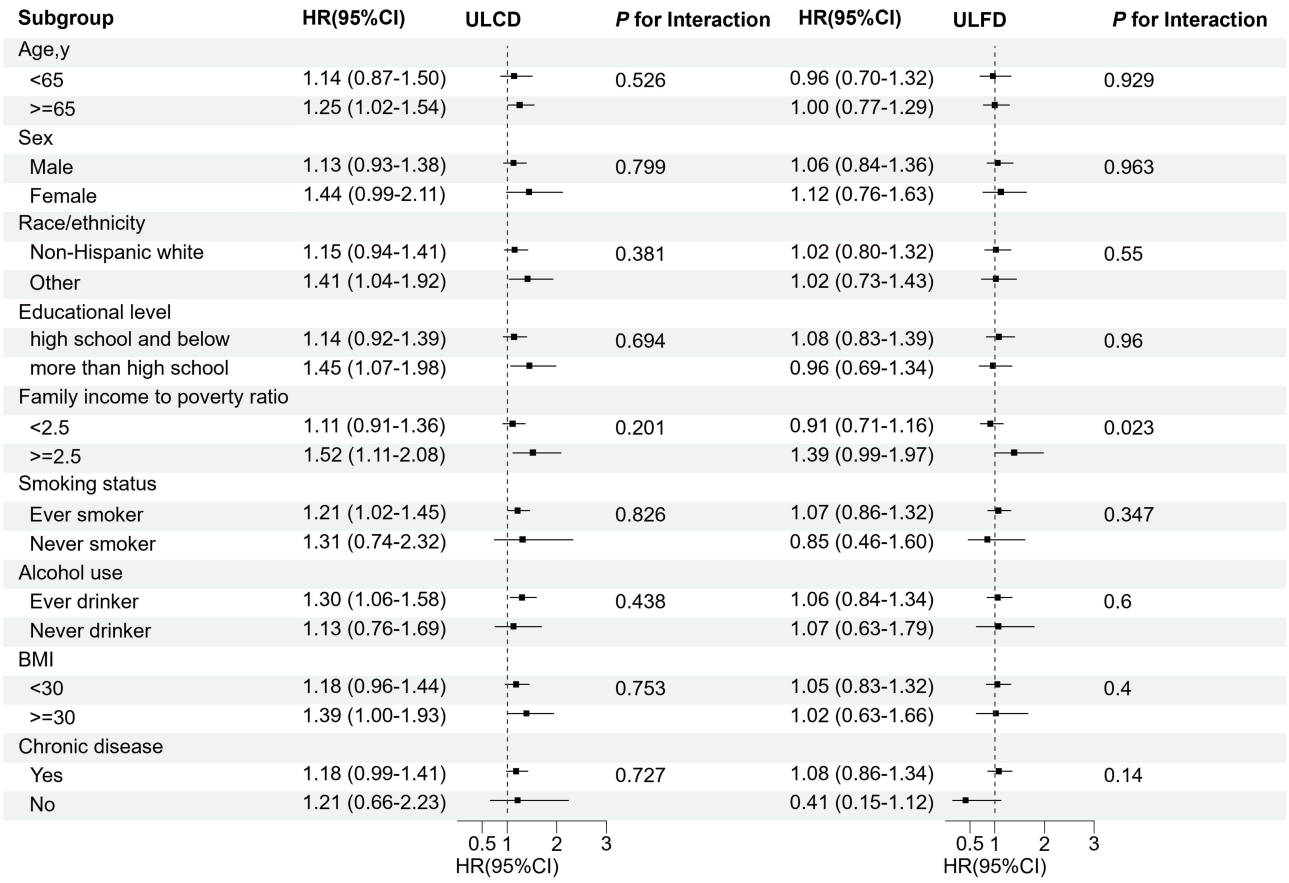

Figure 2 Hazard ratios (HRs) of total mortality per 5-point increase in unhealthy low-carbohydrate-diet and low-fat-diet scores by subgroups.
Notes: Results were adjusted for age, sex, race/ethnicity, BMI, family income to poverty ratio, Smoking, Education, History of cancer, Hypertension, History of heart disease, and total calories.
Abbreviations: ULCD, unhealthy low-carbohydrate diet score; ULFD, unhealthy low-fat diet score; HR, hazard ratio; 95% CI, 95% Confidence interval.

related to higher glycemic load and greater postprandial glucose and insulin levels.[21] Hyperinsulinemia and hyperglycemia produced systemic inflammation associated with the development of several chronic diseases, including diabetes, cardiovascular disease, and cancer.[26,27] In a large cohort study in Chinese adults, carbohydrates and free sugars were consumed more frequently in patients with nonalcoholic fatty liver disease (NAFLD) than in participants without NAFLD.[28] Additionally, previous studies have suggested that high consumption of simple sugars, resulting in the intestinal formation of pro-inflammatory products, was associated with asthma.[27] While complex carbohydrate consumption typical of a Mediterranean diet indicated a protective role against childhood asthma.[29] These conclusions have highlighted that the quality and composition of carbohydrate intake should be a more meaningful determinant of health outcomes than its quantity. On the other hand, due to the different respiratory quotients (RQs) of carbohydrates, proteins, and fats, low carbohydrate/high fat is more suitable for COPD patients who cannot excrete CO2 adequately because of their expiratory flow obstruction and loss of elastic recoil.[30–32] A case-control study also indicated that a low-carbohydrate diet was inversely associated with the odds of COPD.[33] An unhealthy LCD score was positively associated with the prevalence of COPD and with higher total mortality in COPD patients.

Data on the association between low-carbohydrate and low-fat diets and COPD are scarce. To the best of our knowledge, this study is the first to explore the association between different types of LCD and LFD scores with morbidity and mortality in COPD. Consistent with our conclusion, among the general US population, the conclusions of recent cross-sectional study revealed that no association between overall LCD and LFD with total mortality, however positive association between unhealthy LCD and LFD with total mortality, whereas healthy LCD and LFD scores were associated with lower total mortality.[9] In addition, another observational research indicated that a higher Dietary

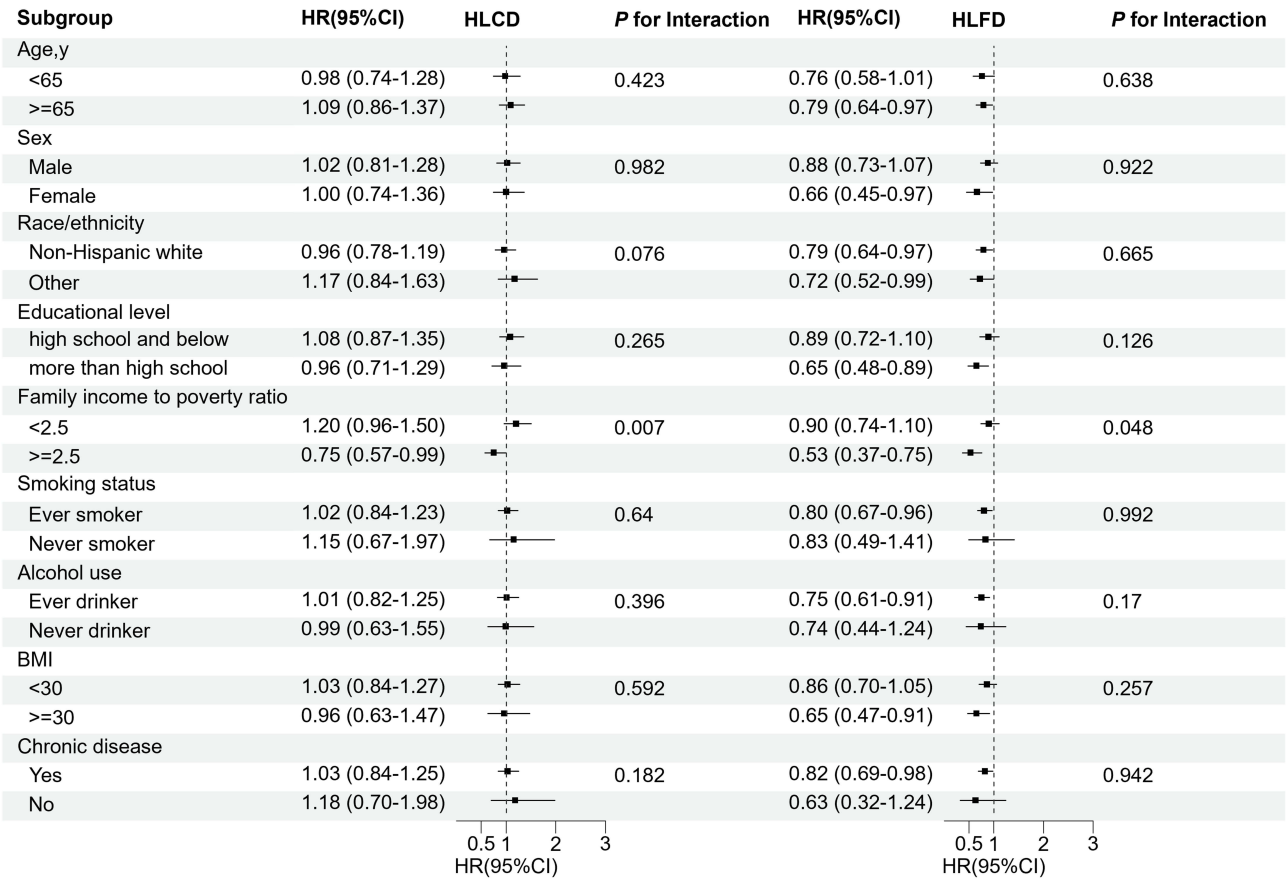

Figure 3 Hazard ratios (HRs) of total mortality per 5-point increase in healthy ow-carbohydrate-diet and low-fat-diet scores by subgroups.
Notes: The results were adjusted for age, sex, race/ethnicity, BMI, family income to poverty ratio, smoking, education, history of cancer, hypertension, history of heart disease, and total calories, excluding the corresponding subgroup variates.
Abbreviations: HLCD, healthy low-carbohydrate diet; HLFD, healthy low-fat diet.

Inflammatory Index (DII) score, meaning a higher intake of a pro-inflammatory diet, contributed to an increased risk of early COPD and lower lung function.[34] What potential mechanisms might explain the observed associations was that food sources of the micronutrients of LCD and LFD. The healthy dietary scores in this study emphasized high-quality carbohydrates, plant proteins, and unsaturated fats, which have been associated with immune system regulation and have benefits in improving gut microbiota and reducing inflammation and metabolic risk factors.[35,36] To provide specific evidence on different macronutrients, we further conducted statistical subgroup analyses. We identified a stronger inverse association between healthy LCD and mortality in low-income individuals than in high-income individuals. A possible

Table 4 HRs and 95% CI of All-Cause Mortality per 5-Point Increase in LCD and LFD Scores

	Model 1	Model 2	Model 3
Overall LCD	1.11 (0.95–1.30, *P* = 0.178)	1.18 (0.99–1.41, *P* = 0.069)	1.14 (0.98–1.32, *P* = 0.098)
Unhealthful LCD	1.21 (1.01–1.44, *P* = 0.036)	1.34 (1.09–1.66, *P* = 0.007)	1.19 (1.01–1.41, *P* = 0.040)
Healthful LCD	1.03 (0.86–1.23, *P* = 0.753)	1.11 (0.89–1.38, *P* = 0.344)	1.08 (0.90–1.29, *P* = 0.408)
Overall LFD	0.92 (0.75–1.11, *P* = 0.380)	0.89 (0.71–1.11, *P* = 0.294)	0.91 (0.75–1.10, *P* = 0.314)
Unhealthful LFD	1.03 (0.84–1.27, *P* = 0.790)	0.93 (0.74–1.18, *P* = 0.573)	0.99 (0.81–1.21, *P* = 0.917)
Healthful LFD	0.80 (0.67–0.95, *P* = 0.011)	0.72 (0.58–0.89, *P* = 0.003)	0.81 (0.69–0.96, *P* = 0.015)

Notes: Model 1: Further adjusted for the lymphocyte, monocyte, segmented neutrophil, eosinophil, and basophil percentages at baseline. Model 2: Exclude patients with heart disease and cancer at baseline. Model 3: Exclude deaths during first-year follow-up.
Abbreviations: LCD, low-carbohydrate diet score; LFD, low-fat diet score; HRs, hazard ratios.

explanation is that low-income families tend to concentrate their intake on low-cost, high-energy-dense, and limited variety in their diet, which makes them vulnerable to chronic diseases.[37]

The strengths of this study are the nationally representative cohort, reliable spirometry data for COPD diagnosis, and the use of validated measures to collect dietary data, providing a foundation for subsequent longitudinal studies to assess macronutrients as a modifiable dietary risk factor in the development of inflammatory airway diseases. However, our study had several limitations. First, diet and other lifestyle factors were self-reported and a 24-hour dietary recall may not represent long-term dietary habits, although the NHANES design used the multiple-pass method and dietary sample weights to improve the estimates of dietary intake and reduce measurement errors, and therefore are prone to have several biases. Second, due to the missing of spirometry data in the NHANES database from 2007 to 2012, the sample size was limited. Third, a cross-sectional study design was used to measure the association between dietary macronutrients and the odds of COPD, but no causal relationships were identified.

Conclusion

In conclusion, unhealthy LCD and LFD may increase the risk of developing COPD. In individuals with COPD, an unhealthy LCD increases the risk of mortality, whereas a healthy LFD may improve the survival rate of patients. Therefore, the importance of quality and food sources of macronutrients should be emphasized.

Data Sharing Statement

Publicly available datasets were analyzed in this study. The data are available at https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

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Disclosure

The authors report no conflicts of interest in this work.

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