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Carbohydrate quality index and mortality risk in older adults at high cardiovascular risk

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Carbohydrate quality may influence long-term health, but its relationship with mortality in older adults remains unclear. We examined the association between carbohydrate quality and all-cause and cause-specific mortality in 7210 older adults at high cardiovascular disease risk from the PREDIMED trial. Carbohydrate quality was assessed using a cumulative average carbohydrate quality index (CQI), combining glycemic index, dietary fiber intake, whole-grain-to-total grain ratio, and solid carbohydrate-to-total carbohydrate ratio, derived from repeated validated food frequency questionnaires. During a median follow-up of 6 years, 425 deaths occurred, including 103 cardiovascular, 169 cancer, and 153 other-cause deaths. In multivariable-adjusted Cox regression models, higher CQI was associated with lower cancer mortality, while participants in the lowest CQI quintile had higher risks of all-cause and cancer mortality compared with those with higher CQI scores. Dietary fiber and whole-grain intake appeared to be the main CQI components driving these associations. These findings suggest that improving carbohydrate quality, particularly through higher intake of fiber-rich and whole-grain foods, may contribute to lower mortality risk in older adults at high cardiovascular risk.

1. Introduction

Carbohydrates are a fundamental component of diets worldwide, yet the significance of carbohydrate quality in the prevention and management of chronic diseases associated with increased mortality rates remains an area of ongoing scientific debate.[1] A 2019 World Health Organization (WHO)-sponsored report advocated for the inclusion of high-fiber and whole-grain carbohydrate foods in chronic disease management.[2] While it emphasized the benefits of these foods for reducing disease risk and mortality, it did not consider glycemic index (GI) or the proportion of carbohydrates derived from solid *versus* total sources.[3] Although WHO guidelines generally recommend limiting free sugars to <10% (ideally <5%) of total energy intake, which tends to largely target sugars from sugar-sweetened beverages, this approach implicitly addresses the balance between liquid and solid carbohydrate sources but does not operationalize it as a continuous dietary metric.[4,5]

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However, emerging evidence suggests that carbohydrate quality, including GI, may be as important as, or even more important than, total carbohydrate intake in influencing morbidity and mortality.[6,7] This highlights a significant gap in the existing research, as limitations in the study design and data presented have been identified, raising questions about the strength and clarity of evidence supporting these dietary recommendations.[6]

Understanding the influence of carbohydrate quality on health outcomes could provide valuable insights into how diet can be tailored to reduce mortality rates.[8] A recent systematic review and meta-analysis emphasized the need for research investigating the relationship between holistic indicators of dietary carbohydrate quality and mortality.[9] The Carbohydrate Quality Index (CQI) has been proposed as a multidimensional scoring system, extending the examination beyond individual aspects of carbohydrate quality.[10] This index integrates four dimensions of carbohydrate quality: GI, dietary fiber content, the proportion of whole-grain carbohydrates, and the proportion of solid carbohydrates to all carbohydrates. By integrating these components, the CQI is thought to provide a comprehensive measure that accounts for potential additive and synergistic effects on health outcomes.[11]

To date, evidence on the relationship between CQI and mortality is limited, with existing research primarily focused on middle-aged adults. No studies have specifically examined this association in older adults, a population with inherently higher mortality rates.[12] Within the PREDIMED (Prevención con Dieta Mediterránea) cohort, which comprises older adults, a low dietary CQI has been previously associated with intermediary outcomes associated with higher cardiovascular disease (CVD) risk, potentially driving mortality.[13] However, the relationship between dietary CQI and mortality remains unknown. Therefore, the present study aimed to evaluate the association between CQI and all-cause and specific-cause mortality within the PREDIMED cohort.

2. Materials and methods

2.1 Study design

This prospective cohort study was performed under the framework of the PREDIMED trial, a multicenter, randomized clinical trial testing the efficacy of two Mediterranean diet (MedDiet) interventions compared to a control diet, for primary prevention of CVD. Further details regarding the trial protocol can be accessed at https://www.predimed.es/ and in previously published sources.[13,14] The Research Ethics Committees of all recruitment centres approved the overall PREDIMED trial design according to the ethical guidelines of the Declaration of Helsinki. All participants provided informed consent and signed a written consent form. The trial was registered at the International Standard Randomized Controlled Trial registry [ISRCT; https://www.isrctn.com/ISRCTN35739639].

2.2 Participants

The PREDIMED trial enrolled 7447 community-dwelling older adults. Eligible participants were men (55 to 80 years of age) or women (60 to 80 years of age) with no CVD at enrollment, who had either type 2 diabetes or at least three of the following major CVD risk factors: smoking, hypertension, elevated low-density lipoprotein cholesterol levels, low high-density lipoprotein cholesterol levels, overweight or obesity, or a family history of premature coronary heart disease. The recruitment took place between October 2003 and June 2009. The trial was completed by July 22, 2011;[15] while endpoints for the present analysis were based on an extended follow-up of mortality until June 2012. Participants were randomly assigned in a 1 : 1 : 1 ratio to either an intervention group receiving the MedDiet enriched with extra-virgin olive oil or mixed nuts, or the control group receiving low-fat diet recommendations as previously reported.[15] For the purposes of the present study, we excluded participants who did not complete the baseline food frequency questionnaire (FFQ) or provided incomplete information, reported energy intakes outside predefined limits (<800 to ≥4000 kcal d^{-1} for men, <500 to ≥3500 kcal d^{-1} for women),[16] or those without follow-up data. A total of 7210 participants were finally included for the main analyses in the present study (Fig. 1).

2.3 Exposure: carbohydrate quality index (CQI) and individual quality dimensions

Dietary intake at baseline and at each annual visit over the subsequent follow-up were assessed with a semi-quantitative 137-item FFQ repeatedly validated in Spain. The reproducibility and relative validity of the FFQ is reported elsewhere.[17] In terms of reproducibility of the FFQ, the intraclass correlation coefficient for carbohydrates was 0.71 (unadjusted) and 0.67 (energy-adjusted).[17] The validity of the carbohydrate assessment of the FFQ was also determined in relation to four 3-day dietary records with intraclass correlation coefficients of 0.55 (unadjusted) and 0.71 (energy-adjusted) indicating moderate and moderate-to-strong agreement, respectively.[17] Nutrient and energy intakes were calculated using Spanish food composition tables.[18] The GI value for each relevant food item was obtained from International Tables of GI values with glucose as the reference.[1] For foods that were not in the tables, the mean was calculated for similar foods that were present in the FFQ.

Details about the construction of the CQI have been described elsewhere,[11,19] and the individual quality dimensions are presented in the SI methods. Briefly, the CQI score, proposed by Zazpe *et al.*,[11] is a composite measure of carbohydrate quality aligned with previously assessments of carbohydrate quality applied in epidemiological studies to facilitate comparability.[11,19–21] The CQI comprises four dimension: dietary GI, total dietary fiber intake (g d^{-1}), the ratio of carbohydrates from whole grains to total grains (whole grains + refined grains or their products), and the ratio of carbohydrates from solid foods to total carbohydrates (*i.e.*, solid carbohydrates + liquid carbohydrates), selected based on evi-

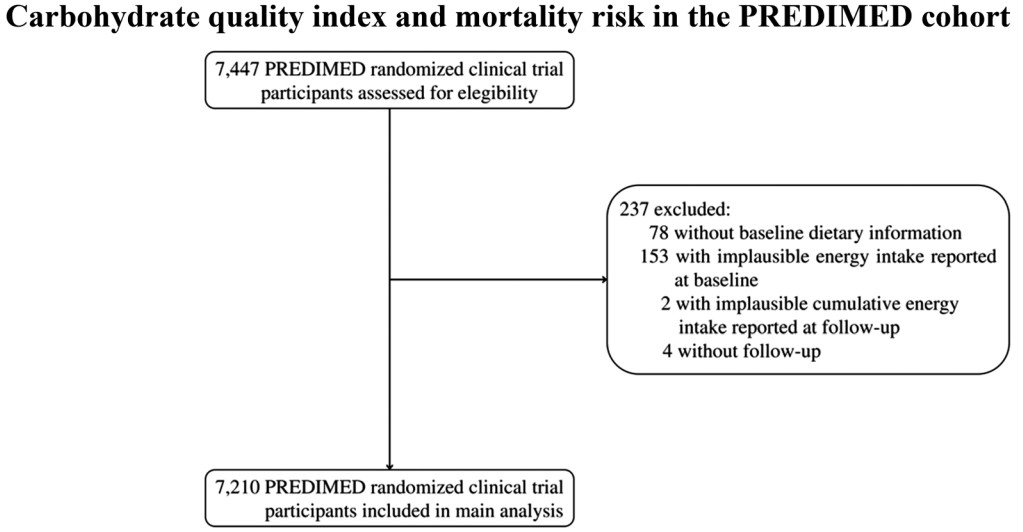

Fig. 1 Flow chart of the study participants. PREDIMED, Prevención con Dieta Mediterránea.

dence linking each to cardiometabolic health through distinct physiological pathways.[2,22] To determine the CQI, participants were categorized into quintiles for each component. A score of 1 (lowest quality) to 5 (highest quality) was assigned to each quintile for dietary fiber intake (sex-specific quintiles), whole-grain-to-total-grain carbohydrate ratio, and solid-to-total carbohydrate ratio. The GI quintiles were inversely scored, with participants in the fifth quintile receiving 1 point and those in the first quintile receiving 5 points. The final CQI score was calculated by summing the scores across all four dimensions, ranging from 4 (lowest carbohydrate quality) to 20 points (highest carbohydrate quality).

CQI scores were calculated for all participants at baseline and cumulatively. A single time-averaged cumulative average of the CQI score and its individual components were calculated for each individual using all available FFQ data until their participation in the PREDIMED trial ended, accounting for intra-individual variation,[23] to better represent long-term intake, reduce within-person variation and measurement errors. By incorporating repeated dietary assessments over time, this approach provides a more stable estimate of habitual diet than a single baseline measurement and minimizes the impact of short-term fluctuations in intake. The cumulative average scores were further categorized into quintiles, comparing low intake (lowest quintile) *vs.* high intake (the four upper quintiles merged, as a reference category).[23]

2.4 Outcome: mortality

For the present study, the following outcomes were assessed: (1) all-cause mortality, (2) CVD mortality, (3) cancer mortality, and (4) other causes of mortality as ascertained in PREDIMED and as previously described.[24] All information on mortality in PREDIMED has been updated until June 2012. Mortality data were systematically updated on an annual basis by an endpoint adjudication committee that was blinded to participants' dietary intake and intervention group allocation. Mortality ascertainment was based on multiple sources: annual participant questionnaires and clinical assessments, direct communication with primary care physicians, annual reviews of medical records, and data linkage with the Spanish National Death Index. Therefore, follow-up outcome data for mortality can be assumed to be complete for the noted time frame. Follow-up time was calculated as the interval between the date of mortality event or the end of follow-up (the date of the last visit or the last recorded clinical event of participants still alive) and the date of randomization.

2.5 Covariate assessments

Sociodemographic and lifestyle information regarding age, sex, education level, and smoking status was collected through administered questionnaires. Anthropometric variables, such as weight and height, were assessed using calibrated scales and wall-mounted stadiometers, respectively. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Physical activity was estimated using a validated Spanish version of the Minnesota Leisure Time Physical Activity Questionnaire.[25] Dietary variables were obtained using the previously mentioned FFQ at baseline and collected annually during the follow-up. Personal medical history, encompassing conditions such as obesity, type 2 diabetes, hypertension, and hypercholesterolemia, as well as medication usage, were either self-reported or extracted from medical records.

2.6 Statistical analyses

The normality of the variables was evaluated using the Shapiro–Wilk test and complementary visual inspection of histograms, Q–Q plots, and box plots. According to these criteria, all variables were deemed to approximate a normal distribution sufficiently. Baseline characteristics of the study cohort was stratified and compared by the quintiles of cumulative average CQI calculated over the follow up. For this preliminary analysis, continuous variables were presented as means ± stan-

dard deviations (SDs), and as counts (percentages) for categorical variables. One-way analysis of variance (ANOVA) and chi-square tests were employed to compare continuous and categorical variables, respectively.

The main analysis used multivariate Cox proportional hazard regression models stratified by recruiting center to assess the associations between cumulative average CQI (the average of baseline information and updated information from each year) with the risk of all-cause and specific causes of mortality. This analysis was also applied to each of the four individual carbohydrate quality components.

Exposures of interest were analyzed both as continuous variables and categorized into quintiles. We focused our analyses on assessing the potential detrimental effect of a low quality intake by using the 4 upper quintiles as the reference category and assessed hazard ratios (HRs) with their 95% confidence interval (CI) for the lowest quintile. Given the relatively narrow distribution of CQI in this cohort, this approach was intended to explore the possibility of a threshold effect rather than assuming a strictly linear dose–response relationship.[23] Moreover, tests of linear trend were applied for the evaluation of dose–response relationships across quintiles, assigning to each category of the total intake its quintile-specific median and using the resulting variable as continuous. Model 1 was adjusted for age (years), sex (male or female), and randomized intervention group (control, MedDiet + extra virgin olive oil, or MedDiet + nuts). Model 2 was additionally adjusted for educational level (primary education or less, secondary, or college/graduate), baseline physical activity (metabolic equivalent task units in min day^{-1}), smoking status (never, current, or former), cumulative average dietary alcohol intake (using the linear term and adding a quadratic term, g day^{-1}), baseline BMI (kg m^{-2}), prevalent type 2 diabetes (yes or no) or medication (yes or no), prevalent hypertension (yes or no) or medication (yes or no), and prevalent hypercholesterolemia (yes or no) or medication (yes or no). Model 3 was additionally adjusted for cumulative average dietary energy intake (kcal day^{-1}). Model 4 was additionally adjusted for cumulative average dietary protein intake (g day^{-1}), dietary saturated fatty acids intake (g day^{-1}), dietary monounsaturated fatty acids intake (g day^{-1}), and dietary polyunsaturated fatty acids intake (g day^{-1}). In the case of CVD and cancer mortality, family history of such diseases were included as covariates. Results were expressed as HRs with 95% CIs. A supplementary model was also performed to account for overadjustment by using baseline CQI score as the exposure in models similar to the ones previously described.

No imputation was performed for missing outcome data as the information was complete. At baseline, among the continuous covariates used in the modelling, 2 participants had missing physical activity data, which were not imputed. For the categorical covariates, 9 participants (*i.e.*, <0.5% of the total population) had insufficient data on education; missing data was replaced by cohort mode (primary education).

Sensitivity analyses were conducted excluding early cases of mortality defined by less than one year of follow-up. By including interaction terms between the cumulative CQI intake (low (quintile) *vs.* high (other quintiles)) and potential effect modifiers (baseline categories of age (<70 or ≥70 years), sex (male or female), intervention group (control, or MedDiet + extra virgin olive oil, or MedDiet + nuts), obesity defined by a BMI ≥30 kg m^{-2} (yes or no), type 2 diabetes status (yes or no), and total carbohydrate intake (<median or ≥ median)) within multivariable-adjusted models, we tested for possible interactions using a likelihood ratio test. Additionally, stratified analysis by levels of each of these factors were tested and visually inspected.

All statistical analyses and plotted graphs were conducted with Stata/SE version 14.2 (StataCorp LLC, College Station, TX, USA). Statistical significance was defined as a two-tailed *P* value <0.05.

3. Results

Table 1 shows the baseline characteristics of included PREDIMED participants according to quintiles of baseline CQI. A total of 7210 participants (4143 [57.5%] women) were included in the present analyses. The mean age was 67.0 (6.2) years, and the median follow-up was 6.0 years (IQR 4.4–7.3). Overall, during follow-up, 425 (5.9% of total population) total deaths were documented, including 103 (1.4%) deaths from CVD disease, 169 (2.3%) deaths from cancer, and 153 (2.1%) from other causes. Information regarding baseline dietary intake by quintiles of baseline CQI is available in Table 2. Baseline characteristics and cumulative average dietary intake of PREDIMED participants according to cumulative average CQI are additionally shown in Tables S1 and S2, respectively.

Table 3 and Fig. 2 presents the relationship between cumulative average CQI either as a continuous or categorical variable by low *vs.* high intake and all-cause and specific-cause mortality. After adjusting for multiple covariates (Model 4), every one point increase in cumulative average CQI was associated with a 6% lower risk of cancer mortality (HR: 0.94; 95% CI: 0.89 to 0.99). When cumulative average CQI was categorized into low *vs.* high intake, participants with low CQI intake had a 28% higher risk of all-cause mortality (HR: 1.28; 95% CI: 1.03 to 1.59), and a 48% higher risk of cancer mortality (HR: 1.48; 95% CI: 1.04 to 2.10), compared to those with higher quality intake. In the fully adjusted models, an "L-shaped association" but no significant dose–response relationship was observed (all *P*-trend ≥ 0.09). This lack of dose–response relationship within the range of exposures observed in this cohort is seen in the supplementary analysis by individual cumulative average CQI quintiles (Table S3). Risk reductions in all-cause and cancer mortality were attenuated when excluding early cases of mortality defined by occurrence within less than one year of follow-up (Table S4). However, the lowest quintile of cumulative average CQI intake had a significantly higher incidence of CVD mortality. Additional information regarding the prospective relationship between baseline CQI either as a continuous or categorical variable by low *vs.* higher quality

Table 1 Baseline characteristics of the PREDIMED participants by baseline carbohydrate quality index

	Quintiles						
Characteristic[a]	1	2	3	4	5	Total	*P* value[b]
Participants, no. (%)	2184 (30.3%)	885 (12.3%)	1489 (20.7%)	1532 (21.2%)	1120 (15.5%)	7210 (100.0%)	
Age, mean (SD), years	67.1 (6.4)	66.9 (6.1)	67.2 (6.3)	66.9 (6.1)	66.9 (6.0)	67.0 (6.2)	0.415
Women, no. (%)	1180 (54.0%)	444 (50.2%)	809 (54.3%)	974 (63.6%)	736 (65.7%)	4143 (57.5%)	**<0.001**
Intervention group, no. (%)							
MedDiet + EVOO	744 (34.1%)	288 (32.5%)	507 (34.0%)	530 (34.6%)	404 (36.1%)	2473 (34.3%)	0.143
MedDiet + nuts	695 (31.8%)	311 (35.1%)	510 (34.3%)	470 (30.7%)	373 (33.3%)	2359 (32.7%)	
Low fat diet	745 (34.1%)	286 (32.3%)	472 (31.7%)	532 (34.7%)	343 (30.6%)	2378 (33.0%)	
Educational level, no. (%)							
Primary education or less	1718 (78.7%)	671 (75.8%)	1147 (77.0%)	1183 (77.2%)	882 (78.8%)	5601 (77.7%)	0.361
Secondary	315 (14.4%)	158 (17.9%)	228 (15.3%)	231 (15.1%)	163 (14.6%)	1095 (15.2%)	
College	151 (6.9%)	56 (6.3%)	114 (7.7%)	118 (7.7%)	75 (6.7%)	514 (7.1%)	
Smoking status, no. (%)							
Never smoked	1280 (58.6%)	516 (58.3%)	882 (59.2%)	1008 (65.8%)	749 (66.9%)	4435 (61.5%)	**<0.001**
Former smoker	539 (24.7%)	241 (27.2%)	394 (26.5%)	352 (23.0%)	246 (22.0%)	1772 (24.6%)	
Current smoker	365 (16.7%)	128 (14.5%)	213 (14.3%)	172 (11.2%)	125 (11.2%)	1003 (13.9%)	
Physical activity, mean (SD), MET min^{-1} d^{-1}	213.5 (229.5)	226.6 (233.3)	244.8 (240.6)	237.9 (259.7)	260.0 (277.2)	234.0 (247.2)	**<0.001**
BMI, mean (SD), kg m^{-2}	30.1 (3.8)	30.0 (3.8)	29.9 (3.8)	29.9 (3.8)	30.0 (4.1)	30.0 (3.9)	0.326
Obesity, no. (%)	1070 (49.0%)	409 (46.2%)	689 (46.3%)	696 (45.4%)	519 (46.3%)	3383 (46.9%)	0.222
Type 2 diabetes, no. (%)	1015 (46.5%)	413 (46.7%)	761 (51.1%)	734 (47.9%)	603 (53.8%)	3526 (48.9%)	**<0.001**
Waist circumference, mean (SD), cm	100.9 (10.4)	101.3 (10.2)	100.9 (10.1)	99.5 (10.3)	99.6 (10.6)	100.5 (10.3)	**<0.001**
Systolic blood pressure, mean (SD), mm Hg	146.5 (20.9)	147.2 (19.1)	145.8 (18.8)	144.6 (20.6)	143.8 (20.4)	145.5 (20.1)	**0.024**
Diastolic blood pressure, mean (SD), mm Hg	82.3 (10.7)	82.6 (10.0)	82.1 (10.4)	80.7 (10.6)	81.7 (29.7)	81.8 (15.5)	0.168
Blood parameters, mean (SD), mg dL^{-1}							
Glucose	140.6 (424.2)	121.6 (38.5)	138.0 (365.3)	137.9 (362.5)	126.7 (49.8)	135.0 (332.5)	0.559
Total cholesterol	219.1 (298.5)	212.4 (37.8)	216.3 (256.4)	225.3 (357.1)	210.3 (36.8)	217.6 (260.9)	0.615
Low-density lipoprotein	134.1 (17.6)	134.0 (17.7)	132.9 (18.3)	133.2 (18.9)	133.5 (19.7)	133.6 (18.4)	0.271
High-density lipoprotein	52.9 (7.8)	52.8 (7.3)	53.2 (8.6)	53.1 (8.2)	53.2 (8.2)	53.1 (8.1)	0.651
Triglycerides	144.3 (73.5)	157.9 (94.7)	137.0 (63.0)	141.7 (69.8)	139.0 (69.8)	142.8 (72.9)	**0.004**

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided 2 by height in meters squared); CVD, cardiovascular disease; EVOO, extra virgin olive oil; MedDiet, Mediterranean diet; METs, metabolic equivalents; PREDIMED = Prevención con Dieta Mediterránea. [a] Data are presented as no. (%) or mean (SD) for categorical and continuous variables, respectively. [b] *P* values for intergroup differences by quintiles of carbohydrate quality index in the overall population were calculated with the Pearson χ^2 test or univariate ANOVA, as appropriate. Significance was set at *P* values less than 0.05 and boldfaced.

intake and all-cause and specific-cause mortality is shown in Table S5.

The relationship between the cumulative average of each individual dimension of the CQI with all-cause and specific-cause mortality was also assessed (Tables S6–S9). After adjusting for multiple covariates (Model 4), and compared to participants with high intake, participants with low intake had a 51% higher risk of all-cause mortality (HR: 1.51; 95% CI: 1.16 to 1.97; *P*-trend = 0.002) and a 72% higher risk of cancer mortality (HR: 1.72; 95% CI: 1.13 to 2.62; *P*-trend = 0.012) for cumulative average dietary fiber (Table S7), a 53% higher risk of all-cause mortality (HR: 1.51; 95% CI: 1.24 to 1.90) and a 71% higher risk of cancer mortality (HR: 1.71; 95% CI: 1.22 to 2.40) for whole-grain-to-total grain ratio (Table S8), and a 51% higher risk of cancer mortality (HR: 1.51; 95% CI: 1.03 to 2.21) for cumulative average solid to all carbohydrates ratio (Table S9). No significant associations were observed for cumulative average GI (Table S6).

Regarding the *post hoc* interactions observed for all-cause mortality, significant interactions were found between cumulative average CQI and baseline type 2 diabetes status (*P* = 0.007). While among participants without diabetes at baseline a lower cumulative average CQI was associated with higher risk of all-cause mortality (HR (95% CI) for lowest *vs.* rest of quintiles: 1.81 (1.29 to 2.55)), this was not significant in those who had diabetes at baseline 0.98 (0.74 to 1.31). No significant interactions were observed for the remaining variables (Fig. S1).

4. Discussion

The present findings suggest that carbohydrate quality, as measured continuously by the CQI, is inversely associated with cancer mortality. Moreover, categorically, participants in the lowest quintile of carbohydrate quality had significantly higher risks of all-cause and cancer mortality compared to those with higher CQI scores. Of note, except for the GI, the rest of components of the CQI (*i.e.*, dietary fiber, whole grain-to-total grain ratio, and solid-to-all carbohydrates ratio) independently showed associations with mortality in the expected direction. The lack of association with some mortality outcomes may be

Table 2 Dietary intake[a] by baseline carbohydrate quality index categories

Characteristic[b]	Quintiles					Total	*P* value[c]
	1	2	3	4	5		
Participants, no. (%)	2184 (30.3%)	885 (12.3%)	1489 (20.7%)	1532 (21.2%)	1120 (15.5%)	7210 (100.0%)	
Carbohydrate quality index	7.1 (1.0)	9.0 (0.0)	10.4 (0.5)	13.0 (0.8)	15.9 (0.9)	10.6 (3.2)	**<0.001**
Glycemic index	57.0 (4.0)	55.0 (5.0)	52.0 (6.0)	52.0 (5.0)	49.0 (5.0)	54.0 (6.0)	**<0.001**
Fiber, g day^{-1}	19.2 (4.5)	23.1 (5.5)	25.1 (7.1)	28.9 (8.8)	33.8 (8.9)	25.2 (8.7)	**<0.001**
Whole-grain-to-total grain ratio	0.0 (0.0)	0.0 (0.1)	0.0 (0.1)	0.4 (0.3)	0.7 (0.3)	0.2 (0.3)	**<0.001**
Solid to total carbohydrates ratio	0.96 (0.08)	0.97 (0.07)	0.98 (0.06)	0.99 (0.05)	0.99 (0.04)	0.98 (0.07)	**<0.001**
Energy, kcal day^{-1}	2163 (514)	2293 (549)	2276 (572)	2245 (568)	2263 (503)	2235 (543)	**<0.001**
Carbohydrates, %	42.2 (6.9)	41.9 (7.6)	41.0 (07.3)	41.6 (7.0)	42.0 (6.9)	41.8 (7.1)	**<0.001**
Protein, %	16.1 (2.7)	16.4 (2.7)	16.6 (2.9)	16.9 (2.9)	17.3 (2.7)	16.6 (2.8)	**<0.001**
Fat, %	39.0 (6.6)	39.0 (6.8)	39.7 (6.9)	39.4 (6.8)	38.9 (6.9)	39.2 (6.8)	**0.014**
Alcohol, g day–	9.1 (15.4)	9.5 (14.9)	9.3 (14.4)	7.3 (12.9)	6.0 (11.1)	8.3 (14.1)	**<0.001**
Cereals, g day^{-1}	239.8 (97.0)	240.5 (114.6)	212.1 (107.7)	216.0 (105.2)	214.3 (82.7)	225.1 (102.1)	**<0.001**
Fruits, g day^{-1}	272.1 (137.0)	366.7 (168.0)	407.3 (209.5)	409.5 (222.2)	449.5 (217.7)	368.4 (201.4)	**<0.001**
Vegetables, g day^{-1}	261.7 (100.6)	317.0 (108.3)	358.9 (141.6)	366.4 (167.2)	411.2 (164.2)	334.0 (147.2)	**<0.001**
Legumes, g day^{-1}	16.8 (7.9)	19.6 (8.9)	21.6 (13.9)	22.5 (17.7)	24.7 (16.0)	20.6 (13.5)	**<0.001**
Nuts, g day^{-1}	7.0 (10.3)	9.7 (12.1)	11.2 (15.0)	11.5 (14.7)	13.3 (15.8)	10.1 (13.6)	**<0.001**
Dairy products, g day^{-1}	331.4 (198.5)	375.3 (212.9)	389.5 (222.3)	399.2 (224.1)	441.8 (239.7)	380.3 (220.7)	**<0.001**
Meat, g day^{-1}	131.7 (53.6)	136.2 (58.0)	135.9 (59.3)	127.4 (56.3)	124.1 (56.1)	131.0 (56.5)	**<0.001**
Red meat, g day^{-1}	89.5 (48.1)	92.0 (49.7)	91.1 (51.7)	81.4 (47.4)	75.3 (46.1)	86.2 (49.0)	**<0.001**
Eggs, g day^{-1}	20.1 (11.4)	20.6 (11.1)	20.1 (11.1)	19.9 (10.3)	19.5 (11.7)	20.0 (11.1)	0.303
Fish, g day^{-1}	91.4 (44.3)	99.7 (45.1)	101.0 (50.5)	103.5 (49.9)	106.0 (63.1)	99.2 (50.5)	**<0.001**
Olive oil, ml day^{-1}	38.7 (17.2)	39.8 (16.7)	39.3 (17.5)	39.2 (18.5)	38.5 (18.9)	39.0 (17.8)	0.423
Sugar and honey, g day^{-1}	8.8 (12.7)	8.2 (12.1)	7.7 (12.8)	7.4 (12.0)	5.9 (10.4)	7.8 (12.2)	**<0.001**
Cookies, g day^{-1}	23.7 (28.5)	24.3 (30.2)	22.3 (28.4)	21.0 (28.8)	14.4 (20.1)	21.5 (27.8)	**<0.001**
Sugar-sweetened beverages, g day^{-1}	54.3 (108.4)	28.5 (70.2)	27.8 (80.1)	32.5 (75.7)	21.9 (57.9)	36.0 (85.9)	**<0.001**
Coffee and tea, mL day^{-1}	37.7 (52.1)	36.6 (54.2)	34.8 (50.9)	34.1 (50.5)	33.2 (53.9)	35.5 (52.1)	0.093
Adherence to MedDiet, points	5.1 (4.2)	5.5 (4.3)	6.1 (4.3)	6.0 (4.4)	6.5 (4.5)	5.8 (4.4)	**<0.001**

Abbreviations: MedDiet, Mediterranean diet. [a] Dietary intakes are calculated as cumulative average of all available dietary data for individual participants. [b] Data are presented as no. (%) or mean (SD) for categorical and continuous variables, respectively. [c] *P* values for intergroup differences by quintiles of carbohydrate quality index in the overall population were calculated with the Pearson χ^2 test or univariate ANOVA, as appropriate. Significance was set at *P* values less than 0.05 and boldfaced.

due to narrower range of variation in carbohydrate quality indicators within the cohort compared to the general population, as our participants were advised, during the follow-up, to adhere to a healthy dietary pattern associated with high carbohydrate quality, justifying the comparison of the lowest quintile with the rest of the quintiles.[26] For instance, among the components of the CQI, dietary GI was not significantly associated with all-cause or cause specific mortality in the present cohort. However, this may have been due to the cumulative average GI only ranging between 50–56 across quintiles, with the 6-unit difference observed between the extreme quintiles falling short of clinical relevance ascribed to a 10-unit difference.[27]

Interestingly, in the present cohort, among participants without diabetes at baseline, low cumulative average CQI was associated with approximately a 80% higher risk of all-cause mortality (HR: 1.81; 95% CI: 1.29–2.55), whereas no significant association was observed among those with diabetes (HR: 0.98; 95% CI: 0.74–1.31). Notably, mean (SD) CQI values were similar in the two groups, at 11.6 (3.3) among participants without diabetes and 11.9 (3.4) among those with diabetes. This finding suggests that the impact of carbohydrate quality on health may be more pronounced in individuals without type 2 diabetes, whose metabolic response to carbohydrate intake may be less impaired.[28] Additionally, stronger associations were observed between the CQI and mortality outcomes when cumulative average measures were used, highlighting the importance of long-term dietary patterns over short-term intake, despite participants were enrolled in an intervention to improve dietary patterns.[29]

Most research examining this relationship between carbohydrate quality and mortality have typically assessed carbohydrate quality using single-dimensional indicators.[10] Specifically, higher consumption of whole grains and fiber has been consistently associated with a lower risk of mortality, whereas the evidence for GI is more limited and the quality of evidence has often been considered weaker,[30] suggesting a need for further research related to this dimension. In terms of CQI, since it integrates multiple dimensions of dietary carbohydrate quality, it has been proposed as a useful tool for nutritional counseling,[31] yet its association with mortality is examined in only two studies to date.[12,32] In a prospective cohort study of 19 083 middle-aged Mediterranean adults followed for a median of 12.2 years, during which 440 deaths occurred, participants in the highest *versus* lowest category of CQI score, assessed using a validated 136-item FFQ, had a 30% lower risk of all-cause mortality. Notably, none of the four individual CQI components was significantly associated with all-cause mortality when analyzed separately.[12] Similarly, in a cohort of 101 694 middle-aged and older US adults followed

Table 3 Relationship between cumulative average carbohydrate quality index and all-cause and specific-cause mortality in the PREDIMED cohort[d]

		Models			
	No. deaths (%)	Model 1[e]	Model 2[f]	Model 3[g]	Model 4[h]
All-cause mortality					
Continuous[a] (n = 7210)	425 (5.9%)	**0.96 [0.94 to 0.99]**	0.97 [0.94 to 1.00]	0.97 [0.94 to 1.00]	0.98 [0.94 to 1.01]
Category[b]					
High (n = 5231)	270 (5.2%)	Reference	Reference	Reference	Reference
Low (n = 1979)	155 (7.8%)	**1.40 [1.14 to 1.72]**	**1.33 [1.08 to 1.64]**	**1.33 [1.08 to 1.64]**	**1.28 [1.03 to 1.59]**
P-Trend[c]		**0.013**	**0.028**	**0.035**	0.094
CVD mortality					
Continuous[a] (n = 7210)	103 (1.4%)	0.95 [0.89 to 1.02]	0.97 [0.91 to 1.04]	0.97 [0.90 to 1.04]	0.97 [0.90 to 1.03]
Category[b]					
High (n = 5231)	62 (1.2%)	Reference	Reference	Reference	Reference
Low (n = 1979)	41 (2.0%)	**1.57 [1.03 to 2.38]**	1.43 [0.92 to 2.21]	1.48 [0.96 to 2.28]	1.48 [0.99 to 2.24]
P-Trend[c]		0.091	0.187	0.157	0.213
Cancer mortality					
Continuous[a] (n = 7210)	169 (2.3%)	**0.93 [0.88 to 0.98]**	**0.94 [0.89 to 0.99]**	**0.93 [0.89 to 0.98]**	**0.94 [0.89 to 0.99]**
Category[b]					
High (n = 5231)	102 (1.9%)	Reference	Reference	Reference	Reference
Low (n = 1979)	67 (3.4%)	**1.64 [1.18 to 2.27]**	**1.57 [1.13 to 2.18]**	**1.55 [1.11 to 2.15]**	**1.48 [1.04 to 2.10]**
P-Trend[c]		0.109	0.133	0.176	0.269
Other causes of mortality					
Continuous[a] (n = 7210)	153 (2.1%)	1.02 [0.96 to 1.07]	1.01 [0.96 to 1.07]	1.01 [0.96 to 1.07]	1.03 [0.97 to 1.09]
Category[b]					
High (n = 5231)	106 (2.0%)	Reference	Reference	Reference	Reference
Low (n = 1979)	47 (2.4%)	1.05 [0.74 to 1.50]	1.03 [0.72 to 1.47]	1.03 [0.72 to 1.47]	0.97 [0.69 to 1.40]
P-Trend[c]		0.306	0.418	0.451	0.666

Abbreviations: CI – confidence interval, CQI – carbohydrate quality index, CVD – cardiovascular disease, PREDIMED – Prevención con Dieta Mediterránea. [a] Cox regression calculated per unit increase in CQI score with a posible score range of 4–20. [b] Cumulative average carbohydrate quality index treated as a categorical variable by low intake (lowest quintile) *vs.* high intake (the four upper quintiles merged, as a reference category). [c] Tests of linear trend were applied for the evaluation of dose–response relationships across quintiles, assigning to each category of the total intake its quintile-specific median and using the resulting variable as continuous. [d] Multivariable Cox regression models stratified by recruiting centre with robust standard errors to account for small deviations from individual randomization. Results are expressed as Hazard Ratios (HR) and 95% Confidence Intervals (95% CI). [e] Extremes of total energy intake (≥4000 or <800 kcal day^{-1} in men and ≥3500 or in women) were excluded. Significance was set at P values less than 0.05 and boldfaced. The exposure as continuous is presented per 1 unit increase. Model 1: adjusted for age (years), sex (male or female), intervention group (control, Mediterranean diet + extra virgin olive oil, Mediterranean diet + nuts). [f] Model 2: additionally adjusted for educational level (primary education or less, secondary education, or college/graduate), baseline physical activity (metabolic equivalent task units in min day^{-1}), smoking status (never, current, or former), cumulative average dietary alcohol intake (using the linear term and adding a quadratic term, g day^{-1}), baseline body mass index (kg m^{-2}), prevalent type 2 diabetes (yes or no) or medication (yes or no), prevalent hypertension (yes or no) or medication (yes or no), prevalent hypercholesterolemia (yes or no) or medication (yes or no). [g] Model 3: additionally adjusted for cumulative average dietary energy intake (kcal day^{-1}). [h] Model 4: additionally adjusted for cumulative average dietary protein intake (g day^{-1}), dietary saturated fatty acids intake (g day^{-1}), dietary monounsaturated fatty acids intake (g day^{-1}), and dietary polyunsaturated fatty acids intake (g day^{-1}). In the case of CVD and cancer mortality, family history of such diseases were included as covariates.

for a mean of 8.8 years, during which 311 colorectal cancer deaths were documented, participants in the highest *versus* lowest quartile of CQI score, assessed using a validated 137-item FFQ questionnaire, had a 39% lower risk of colorectal cancer mortality.[32]

Mechanistically, there are several reasons why higher CQI may be associated with greater longevity. Individuals with higher CQI scores typically eat more fruits, vegetables, legumes, nuts, and whole grains, while consuming fewer refined grains, sweets, and sugar-sweetened beverages.[33,34] Of note, in our study, whole grains accounted for approximately 10% of total dietary fibre, whereas fruits and vegetables each contributed about 25%. It is likely that these dietary factors in combination exert a synergistic effect in lowering the risk of all-cause and cause-specific mortality.[35] Carbohydrate quality aspects may also impact cardiometabolic health, which could influence the development and progression of chronic diseases, which are among the leading causes of mortality worldwide.[8]

The findings of carbohydrate quality studies require careful interpretation as variations in effect estimates across populations may be attributed to differences in dietary sources of carbohydrates and methodological approaches used for the exposure assessment.[36] In informing the public, dietary guidelines, for example, have increasingly highlighted the importance of whole grain food sources and dietary fiber in reducing the risk of chronic disease; however, guidelines often neglect that these categories encompass a variety of foods with different compositions and health impacts. Although this study focuses on carbohydrate quality, consideration of carbohydrate quantity is also warranted, as these dimensions are inherently interrelated.

Unlike dietary patterns in several other regions in the world where the percentage energy contribution from carbohydrates range between 55–70%, carbohydrates contributed to approximately 40% of dietary energy in the present cohort. PREDIMED participants especially consumed relatively low

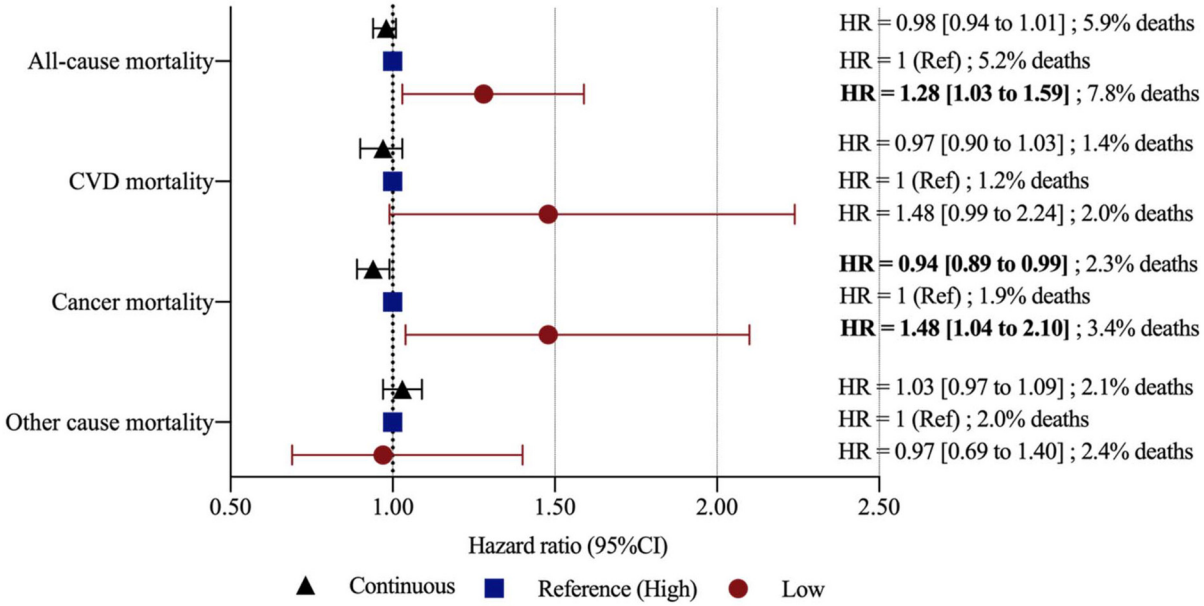

Fig. 2 Relationship between cumulative average carbohydrate quality index and all cause and specific cause mortality in the PREDIMED cohort. Cumulative average carbohydrate quality index was treated as continuous per unit increase in CQI score with a posible score range of 4 to 20. Cumulative average carbohydrate quality inde was also treated as a categorical variable by low intake (lowest quintile) *vs*. high intake (the four upper quintiles merged, as a reference category). The % of deaths represent the proportion of participants that presented mortality. Abbreviations: CI – confidence interval, CVD – cardiovascular disease.

quantities of high-quality carbohydrates as indicated by the overall low GI and high fiber intake,[13,37] suggesting that the results are defined by the lower intake of carbohydrate quantity with high quality. The 'optimal' proportion of carbohydrates, fats, and proteins remains a topic of ongoing debate.[38] Evidence suggests that the relationship between the quantity of carbohydrate intake and mortality follows a U-shaped pattern, with the lowest mortality risk observed when carbohydrate intakes contribute 50%–60% of total energy[39] and both low-carbohydrate diets (<40% of energy) and high-carbohydrate diets (>70% of energy) have been associated with increased mortality risk.[40] Of note, higher consumption of carbohydrates from nutrient-dense, unrefined plant-based sources has been linked to lower all-cause mortality, highlighting the greater importance of carbohydrate quality in addition to quantity in relation to mortality risk.[7,41] Our findings suggest that improving carbohydrate quality may be independently beneficial irrespective of macronutrient composition and energy intake (*i.e.*, carbohydrate quantity). Moreover, from a public health perspective, our findings agree with the argument that it is prudent for dietary guidelines to incorporate and enhance recommendations related to carbohydrate quality in addition to those on carbohydrate quantity.[12] The CQI provides a practical framework to operationalize this concept by integrating complementary dimensions of carbohydrate intake, including dietary fiber, whole grain consumption, glycemic response, and carbohydrate form (solid *vs.* liquid). This multidimensional construct aligns with current recommendations that promote higher intake of whole grains and fiber while limiting refined and free sugars.[2] As such, the CQI may facilitate the translation of complex nutritional evidence into coherent, pattern-based dietary guidance. Nonetheless, further validation across diverse populations is needed to support its broader application in dietary policy and practice.

Several limitations of this study should be acknowledged. Its observational design precludes the establishment of causal relationships. Of note, residual confounding from unmeasured socioeconomic factors or overall dietary patterns cannot be discounted. Moreover, the PREDIMED trial was aimed at reducing CVD risk,[15] which may have limited the statistical power to detect associations between CQI and CVD mortality. Additionally, we acknowledge that the time-to-event (6 years) in this analysis may have been insufficient given that the average age of participants was 67.0 (6.2) years and the high life expectancy.[42] Furthermore, the FFQ and therefore the CQI may not fully capture all aspects of carbohydrate quality. The available food items and intake ranges of this population may limit the precision and generalizability of the findings. Additionally, the FFQ does not discern cooking methods or processing (*e.g.*, al dente or parboiled).[35] Of note, differences in food composition or preparation methods may differentially influence postprandial glycemic response, potentially impacting the internal validity of the findings. Additionally, self-reported dietary data is subject to measurement errors.[43] However, multiple strategies were employed to enhance data accuracy: the FFQ had been previously validated in a Spanish population;[17] trained dietitians conducted repeated face-to-face interviews to administer the questionnaire; participants with implausible total energy intake values were excluded from

analyses.[16] This approach was intended to minimize the influence of substantial misreporting and measurement error, as these extreme values are unlikely to represent usual dietary intake. This study also has notable strengths, including its prospective multicenter design and robust control for a wide range of relevant confounding factors and usage of a multidimensional quality index to better capture the interactive relationships of food components on health outcomes. Other strengths include the verification of cases of mortality by medical records or consultation of the National Death Index, use of validated methods, utilization of repeated dietary measurements, and numerous sensitivity analyses to confirm the robustness of our findings.

5. Conclusion

In conclusion, our findings reveal low carbohydrate quality consumption as measured by the CQI to be associated with increased risk of all-cause and cancer mortality in older adults. Of note, several individual components of the CQI including dietary fiber, whole grains, and solid to total carbohydrate ratio were associated with mortality outcomes. This suggests that multipronged strategies to improve carbohydrate quality through greater efforts to increase intakes of fiber, whole grain and reduce sugar-sweetened beverage consumption may be beneficial. Such efforts may be particularly pertinent for individuals without diabetes. Further research in larger and more diverse populations is warranted to better understand the role of CQI in relation to all-cause and cause-specific mortality. Clarifying these associations could further inform the development of more targeted dietary strategies aimed at reducing mortality risk.

Author contributions

All the principal PREDIMED investigators contributed to the study concept and design and to data extraction from the PREDIMED participants. SKN and JSS contributed to the concept and design of the present study. HVL and SS wrote the first draft and performed the statistical analyses, respectively, under the supervision of SKN and JSS. HVL, SS, and JSS are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed the manuscript for important intellectual content and approved the final version to be published.

Conflicts of interest

JSS has had his travel accommodation expenses covered for lectures in Congresses by the International Nut and Dried Fruit Foundation and reports receiving honoraria as the Member of the Spain Institute Danone Advisory Board. JSS is also Honorary Member of the Scientific Committee of Danone Institute International and the International Nut and Dried Fruit Foundation World Forum for Nutrition Research and Dissemination. Patrimonio Comunal Olivarero provided olive oil free of cost to PREDIMED-Plus participants, coordinated by JSS. JSS's institution has received research grants from the International Nut and Dried Fruit Foundation.

Ethics approval and consent to participate

The Research Ethics Committees of all recruitment centres approved the overall PREDIMED trial design according to the ethical guidelines of the Declaration of Helsinki. All participants provided informed consent and signed a written consent form.

Data availability

Data described in the manuscript, codebook, and analytic code will be made available upon request pending application and approval of the PREDIMED Steering Committee. There are restrictions on the availability of data for the PREDIMED trial due to the signed consent agreements around data sharing, which only allow access to external researchers for studies following the project purposes. Requestors wishing to access the PREDIMED trial data used in this study can make a request to the PREDIMED trial Steering Committee chair: jordi.salas@urv.cat. The request will then be passed to members of the PREDIMED Steering Committee for deliberation.

Supplementary information (SI) is available. See DOI: https://doi.org/10.1039/d5fo04430h.

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