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Carbohydrate quality changes and concurrent changes in cardiovascular risk factors: a longitudinal analysis in the PREDIMED-Plus randomized trial

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ABSTRACT

Background: Overall quality of dietary carbohydrate intake rather than total carbohydrate intake may determine the risk of cardiovascular disease (CVD).

Objective: We examined 6- and 12-mo changes in carbohydrate quality index (CQI) and concurrent changes in several CVD risk factors in a multicenter, randomized, primary-prevention trial (PREDIMED-Plus) based on an intensive weight-loss lifestyle intervention program.

Methods: Prospective analysis of 5373 overweight/obese Spanish adults (aged 55–75 y) with metabolic syndrome (MetS). Dietary intake information obtained from a validated 143-item

semiquantitative food-frequency questionnaire was used to calculate 6- and 12-mo changes in CQI (categorized in quintiles), based on 4 criteria (total dietary fiber intake, glycemic index, whole grain/total grain ratio, and solid carbohydrate/total carbohydrate ratio). The outcomes were changes in intermediate markers of CVD.

Results: During the 12-mo follow-up, the majority of participants improved their CQI by increasing their consumption of fruits, vegetables, legumes, fish, and nuts and decreasing their consumption of refined cereals, added sugars, and sugar-sweetened beverages. After 6 mo, body weight, waist circumference (WC), systolic and diastolic blood pressure (BP), fasting blood glucose, glycated hemoglobin (HbA1c), triglyceride levels, triglycerides and glucose (TyG) index, and TyG-WC decreased across successive quintiles of improvement in the CQI. After 12 mo, improvements were additionally observed for HDL cholesterol and for the ratio of total to HDL cholesterol. Favorable improvements (expressed in common units of SD and 95% CI) for quintile 5 compared with quintile 1 of CQI change were observed for most risk factors, including TyG-WC (SD −0.20; 95% CI −0.26, −0.15), HbA1c (SD −0.16; 95% CI −0.23, −0.10), weight (SD −0.12; 95% CI −0.14, −0.09), systolic BP (SD −0.11; 95% CI −0.19, −0.02) and diastolic BP (SD −0.11; 95% CI −0.19, −0.04).

Conclusions: Improvements in CQI were strongly associated with concurrent favorable CVD risk factor changes maintained over time in overweight/obese adults with MetS. This trial was registered as ISRCTN 89898870. *Am J Clin Nutr* 2020;111:291–306.

Keywords: PREDIMED-Plus, carbohydrate, cardiovascular disease, fiber, glycemic index, carbohydrate quality index, obesity, randomized controlled trials

Introduction

The prevalence of chronic conditions is increasing worldwide and represents a public health concern. Approximately 60% of US adults and over one-third of Europeans have at least one chronic condition (1, 2). Among chronic conditions, cardiovascular disease (CVD) is the leading cause of disease burden in the world as well as an important economic burden for individuals, families, and healthcare systems (3). In recent decades, efforts to prevent CVD have focused on reducing certain risk factors and promoting healthy lifestyle behaviors, particularly eating habits (4–7). In this regard, a large body of evidence has demonstrated that improving quality of dietary carbohydrates, rather than modifying their quantity, may have a greater impact on reducing the risk of CVD (8–11). In fact, the authors of a recent series of systematic reviews and meta-analyses of multiple prospective studies and clinical trials concluded that quality of dietary carbohydrates, rather than quantity, is a major determinant of CVD and all-cause mortality (12).

Most of the current evidence in the field has been obtained by assessment of the relation between quality of dietary carbohydrates and CVD using isolated dimensions such as fiber intake (13–15), whole-grain consumption (16, 17), glycemic index, or glycemic load (18, 19). To date, there is no clear multidimensional and integrated definition of carbohydrate quality. Only a few studies (20–24) have used a combined carbohydrate quality index (CQI) integrating several dimensions in a single score to account for multiple quality components. These studies have examined the association of CQI at baseline with subsequent outcomes, but have not assessed its dynamic changes throughout time. Thus, we examined 6- and 12-mo changes in a multidimensional, integrated CQI and assessed the effect of its changes on multiple traditional and novel intermediate markers of CVD risk in overweight/obese adults with metabolic syndrome (MetS) who are at high cardiovascular risk.

Subjects and Methods

Study design

This is a prospective analysis of data from the PREDIMED-Plus (PREvención con DIeta MEDiterránea Plus), a 6-y parallel-group, multicenter lifestyle intervention study involving 6874 participants. The design and methods of the PREDIMED-Plus randomized trial have been previously described in detail elsewhere (25, 26). Briefly, the trial aims to assess the effects of an intensive lifestyle intervention based on an energy-reduced Mediterranean diet (MedDiet), physical activity promotion, and behavioral support for weight loss [intervention group (IG)] on primary prevention of CVD events in comparison with a control group (CG) receiving usual care with an unrestricted energy MedDiet (total energy intake is ad libitum) and without physical activity recommendations or specific goals for weight loss. Physical activity promotion consists of regular counseling to gradually increase participant levels of physical activity in order to meet the WHO guidelines (27). Recommendations include

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MAM-G and CIF-L contributed equally to this work.

Supplemental Tables 1–5 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: BP, blood pressure; CG, control group; CQI, carbohydrate quality index; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; IG, intervention group; MedDiet, Mediterranean Diet; MetS, metabolic syndrome; SFFQ, semiquantitative food-frequency questionnaire; TC, total cholesterol; TyG index, triglycerides and glucose index; TyG-WC, product of triglycerides and glucose index and waist circumference; WC, waist circumference.

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TABLE 1 Criteria used to calculate the CQI[1]

Components of CQI	Index range (points)[2]	Criterion for minimum index	Criterion for maximum index
Dietary fiber intake, g/d	1–5	Minimum intake (Q1)	Maximum intake (Q5)
Glycemic index (reverse quintiles)	1–5	Maximum value (Q5)	Minimum value (Q1)
Ratio of whole-grain to total-grain carbohydrates[3]	1–5	Minimum value (Q1)	Maximum value (Q5)
Ratio of solid carbohydrates to solid + liquid carbohydrates[4]	1–5	Minimum value (Q1)	Maximum value (Q5)
Total index (range)	4–20		

[1]CQI, carbohydrate quality index; Q, quintile.
[2]Proportional dietary indices were computed for intakes ranging between the maximum and minimum criteria.
[3]Ratio of whole grains/(whole grains + refined grains or their products).
[4]Ratio of solid carbohydrates/(solid carbohydrates + liquid carbohydrates).

aerobic activities, such as gentle walking or equivalent activities of moderate intensity, and resistance training. Further details about the physical activity intervention in the PREDIMED-Plus trial have been reported elsewhere (28). Likewise, all participants receive behavioral and motivational support group sessions in which dietitians address different strategies to make suitable dietary and lifestyle changes. Each of the Institutional Review Boards of the participating centers approved the study protocol. The trial was registered in 2014 as ISRCTN 89898870.

Participants, recruitment, and randomization

Between September 2013 and December 2016, potential participants were screened in 23 Spanish centers for eligibility assessment. Community-dwelling men (aged 55–75 y) and women (60–75 y), with overweight or obesity (BMI 27–40 kg/m^2) and without a baseline history of CVD, who met at least 3 components of MetS (29), were considered eligible for inclusion in the study. More specific details of recruitment, inclusion/exclusion criteria, and the internet-based randomization process have been described elsewhere (25, 26). Participants were randomly assigned in a 1:1 ratio to either the CG or IG by using a computer-generated random allocation stratified by sex, age (<65, 65–70, >70 y), and center. Couples who wished to belong to the same group were randomly assigned as a unit (this was the case for 618 participants, i.e., 309 couples). The internet-based randomization sequence was concealed to all staff members and principal investigators.

Dietary assessment and quality carbohydrate index

Trained dietitians collected participant information about dietary intake through face-to-face interviews at baseline and follow-up visits using the Spanish version of the validated 143-item semiquantitative food-frequency questionnaire (SFFQ) (30–32). Participants specified their average frequency of food consumption (from "never" to "more than 6 times per day") in common portion or serving sizes. Spanish food composition tables were used to calculate energy and nutrient intakes for each subject (33). Additionally, we assessed adherence to the MedDiet using the 14-point scale of adherence (with total energy intake ad libitum) previously applied in PREDIMED (34) and the new 17-point scale of adherence to an energy-reduced MedDiet (25) used as the intervention tool in PREDIMED-Plus (which aimed to obtain energy reduction and weight loss). The 17-item energy-reduced MedDiet score was based on the previously validated questionnaire used in the PREDIMED trial (34). This questionnaire includes a few additional items to better capture the potential caloric reduction that should be applied to a Mediterranean dietary pattern as a means for weight loss.

Dietary intake information obtained from the SFFQs was used to calculate the CQI. This index has been used in previous studies (20–24) to evaluate quality of carbohydrates and is constructed based on the following 4 dimensions: total dietary fiber intake (g/d), glycemic index, whole-grain/total grain ratio, and solid carbohydrate/total carbohydrate ratio. To estimate total grains, we included whole grains, refined grains, and their derived products. Liquid carbohydrate intake was estimated as sugar-sweetened beverages and fruit juice consumption, while solid carbohydrate intake included the rest of the carbohydrates contained in solid foods. Further details of these calculations can be found elsewhere (20–23).

To determine the CQI, we categorized participants into quintiles for each of the 4 components (fiber intake, glycemic index, whole grains/total grains ratio, and solid carbohydrates/total carbohydrates ratio). We assigned values ranging from 1 point for the first quintile to 5 points for the fifth quintile, except for the glycemic index component, which was inversely weighted (1 point for the fifth quintile and 5 points for the first quintile). Then, all the values were added to calculate the CQI (score index ranging from 4 to 20), with higher values representing better carbohydrate quality (**Table 1**).

Outcomes and assessments

The primary outcome of the current study was weight change at 6 and 12 mo of follow-up according to changes in the quality of carbohydrate intake. The secondary outcomes at 6 and 12 mo were changes in waist circumferences (WCs), blood pressure (BP), blood glucose variables, and lipid profiles.

Participants provided updated information at each follow-up visit throughout several questionnaires regarding sociodemographic characteristics, physical activity (35, 36), lifestyles, medication use, and personal and family history of disease. For each visit, height, weight, and WC were measured in duplicate by registered nurses using standardized techniques, calibrated scales, and wall-mounted stadiometers, respectively. BP was measured in triplicate using a validated semiautomatic oscillometer (Omron HEM 297 705C). Measurement averages were calculated later for analysis purposes. Blood samples

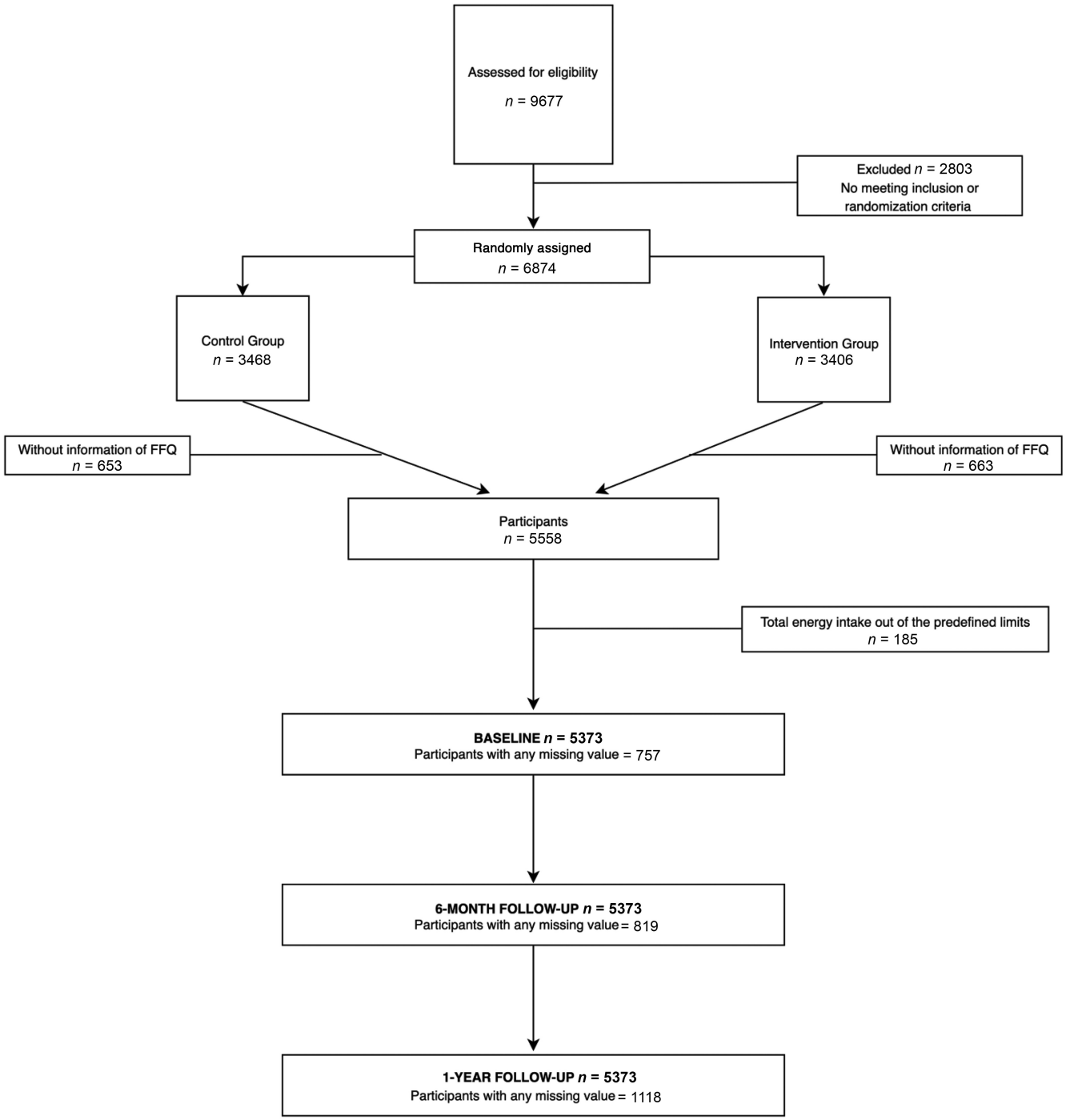

FIGURE 1 Flow chart of the participants. The PREDIMED-Plus trial.

were also obtained after an overnight fast to determine levels of fasting blood glucose, glycated hemoglobin (HbA1c), total cholesterol (TC), LDL cholesterol, HDL cholesterol, and triglycerides using standard enzymatic methods. Furthermore, we calculated the total cholesterol ratio the ratio of TC to HDL cholesterol, the triglycerides and glucose index (TyG index) [Ln(triglycerides × fasting glucose/2)], and the product of the TyG index and WC (TyG-WC) (37, 38).

Statistical analysis

All analyses were performed using Stata software, version 15.0 (StataCorp LP) using the PREDIMED-Plus database updated in October, 2018. Missing data were imputed with regression equations to predict missing outcomes. Imputations represented <5% of missing outcomes (**Supplemental Table 1**).

Baseline characteristics of study participants were described according to quintiles of CQI change from baseline to 12-mo

TABLE 2 Baseline characteristics of study participants and changes from baseline in dietary sources according to quintiles of carbohydrate quality index change after 12 mo of follow-up[1]

	Quintiles of change in CQI from baseline to 12-mo follow-up				
Characteristics	Q1	Q2	Q3	Q4	Q5
n (frequency)	1243	1119	1183	834	994
CQI change range	−12 to −3	−2 to −1	0 to 1	2 to 3	4 to 12
Intervention group	424 (34%)	447 (40%)	597 (50%)	492 (59%)	700 (70%)
Age, y	65.2 ± 4.9	65.2 ± 4.8	65.1 ± 4.8	65.2 ± 4.9	64.8 ± 4.9
Sex, men	571 (46%)	545 (49%)	634 (54%)	457 (55%)	575 (58%)
BMI at baseline, kg/m^2	32.6 ± 3.5	32.4 ± 3.4	32.5 ± 3.5	32.4 ± 3.3	32.5 ± 3.5
Physical activity at baseline, METs-h/week	42 ± 38	42 ± 39	41 ± 38	43 ± 39	40 ± 39
Smoking status at baseline					
Current	150 (12%)	123 (11%)	142 (12%)	99 (12%)	139 (14%)
Former	510 (41%)	478 (43%)	514 (43%)	358 (43%)	451 (45%)
Never	583 (47%)	518 (46%)	527 (45%)	377 (45%)	404 (41%)
Marital status, married	937 (75%)	870 (78%)	933 (79%)	651 (78%)	758 (76%)
Attained education					
College/university	271 (22%)	227 (20%)	279 (24%)	169 (20%)	189 (19%)
Secondary	351 (28%)	321 (29%)	341 (29%)	249 (30%)	301 (30%)
Primary or less	621 (50%)	571 (51%)	563 (48%)	416 (50%)	504 (51%)
Self-reported diabetes at baseline	332 (27%)	285 (25%)	338 (29%)	231 (28%)	284 (29%)
Medications at baseline					
Antihypertensive therapy	967 (78%)	873 (78%)	931 (79%)	654 (78%)	776 (78%)
Lipid-lowering therapy	635 (51%)	587 (52%)	589 (50%)	420 (50%)	510 (51%)
Insulin	61 (5%)	53 (5%)	51 (4%)	43 (5%)	36 (4%)
Metformin	270 (22%)	236 (21%)	271 (23%)	195 (23%)	235 (24%)
Other antidiabetic agents	224 (18%)	202 (18%)	247 (21%)	156 (19%)	198 (20%)
Cardiovascular risk factors at baseline					
Weight, kg	86.2 ± 12.9	85.6 ± 13.0	86.2 ± 12.9	86.4 ± 12.7	87.3 ± 12.9
Waist circumference, cm	107 ± 10	107 ± 9	107 ± 10	107 ± 9	108 ± 10
Systolic BP, mmHg	139 ± 17	139 ± 16	140 ± 17	141 ± 17	141 ± 17
Diastolic BP, mmHg	81 ± 10	80 ± 10	81 ± 10	81 ± 10	81 ± 10
Fasting blood glucose, mg/dL	113 ± 28	112 ± 27	114 ± 31	113 ± 29	115 ± 29
HbA1c, %	6.1 ± 0.9	6.1 ± 0.9	6.1 ± 0.9	6.1 ± 0.9	6.1 ± 0.9
Total cholesterol, mg/dL	199 ± 38	199 ± 38	197 ± 38	194 ± 37	196 ± 38
LDL cholesterol, mg/dL	122 ± 33	123 ± 34	121 ± 33	119 ± 32	119 ± 32
HDL cholesterol, mg/dL	49 ± 12	49 ± 12	48 ± 12	48 ± 11	47 ± 12
Ratio of TC to HDL cholesterol (×100)	426 ± 104	428 ± 116	428 ± 106	421 ± 102	433 ± 111
Triglycerides, mg/dL	150 ± 77	153 ± 78	151 ± 77	147 ± 67	156 ± 80
TyG index	8.9 ± 0.5	8.9 ± 0.5	8.9 ± 0.5	8.9 ± 0.5	9.0 ± 0.5
TyG-WC	959 ± 108	955 ± 109	958 ± 108	957 ± 101	970 ± 110
Foods, daily consumption, g					
Fruits	410 ± 221	374 ± 214	346 ± 205	336 ± 192	309 ± 164
Change from baseline	−43 ± 238	18 ± 213	60 ± 212	102 ± 201	142 ± 203
Vegetables	358 ± 148	343 ± 137	325 ± 136	314 ± 132	293 ± 116
Change from baseline	−34 ± 144	13 ± 137	39 ± 140	73 ± 148	109 ± 147
Legumes	23 ± 13	21 ± 11	20 ± 10	20 ± 10	19 ± 9
Fish	105 ± 47	104 ± 47	104 ± 47	97 ± 45	99 ± 45
Meat, meat products	150 ± 61	147 ± 56	146 ± 54	146 ± 58	150 ± 59
Dairy products	338 ± 201	340 ± 186	347 ± 200	362 ± 215	345 ± 205
Total nuts	18 ± 20	16 ± 18	15 ± 16	13 ± 16	12 ± 14
Olive oil	40 ± 17	40 ± 17	40 ± 17	40 ± 17	41 ± 17
Refined olive oil	7.4 ± 14	8.3 ± 15	8.8 ± 16	8.9 ± 16	7.6 ± 15
Extra-virgin olive oil	33 ± 20	32 ± 21	32 ± 21	31 ± 21	34 ± 21
Cereals	145 ± 77	152 ± 79	150 ± 78	151 ± 79	160 ± 78
Change from baseline	−17 ± 82	−19 ± 82	−21 ± 81	−25 ± 89	−33 ± 86
White bread	59 ± 78	82 ± 86	88 ± 84	103 ± 85	131 ± 83
Change from baseline	7 ± 73	−19 ± 73	−39 ± 73	−67 ± 91	−117 ± 86
Brown bread	62 ± 71	45 ± 65	39 ± 63	25 ± 52	8.8 ± 29
Change from baseline	−24 ± 67	2 ± 55	16 ± 62	39 ± 63	79 ± 70
Alcohol	9 ± 13	11 ± 15	12 ± 16	12 ± 16	12 ± 16
Change from baseline	−0 ± 10	−1 ± 11	−2 ± 12	−1 ± 11	−2 ± 12
Sweetened drinks	15 ± 43	16 ± 39	22 ± 61	24 ± 70	33 ± 90
Change from baseline	3 ± 72	−2 ± 52	−12 ± 61	−16 ± 68	−28 ± 90

(*Continued*)

TABLE 2 (*Continued*)

Characteristics	Quintiles of change in CQI from baseline to 12-mo follow-up				
	Q1	Q2	Q3	Q4	Q5
Dietary pattern, total energy, and nutrient intake					
17-item energy-reduced MedDiet score	9.0 ± 2.6	8.7 ± 2.6	8.5 ± 2.8	8.3 ± 2.7	7.9 ± 2.5
Total energy intake, kcal/d	2414 ± 552	2385 ± 549	2334 ± 529	2326 ± 541	2352 ± 544
Carbohydrate intake, % E	40.3 ± 6.6	40.6 ± 6.9	40.1 ± 7.0	40.7 ± 7.0	40.6 ± 6.6
Change from baseline	−2.4 ± 6.7	−2.8 ± 6.4	−3.0 ± 6.9	−3.3 ± 7.1	−4.2 ± 7.1
Solid carbohydrates, g/d	223 ± 67	220 ± 69	211 ± 67	212 ± 68	213 ± 65
Change from baseline	−35 ± 68	−25 ± 65	−21 ± 66	−19 ± 73	−26 ± 67
Liquid carbohydrates, g/d	21.2 ± 16.6	22.8 ± 15.1	24.1 ± 15.9	25.9 ± 17.5	27.0 ± 17.7
Change from baseline	2.6 ± 17.2	−1.5 ± 14.2	−4.8 ± 16.9	−6.9 ± 17.1	−11.1 ± 17.7
Fiber intake, g/d	30.0 ± 8.7	27.4 ± 8.9	25.6 ± 8.8	24.1 ± 8.0	21.9 ± 5.9
Change from baseline	−3.6 ± 8.3	1.4 ± 7.0	4.3 ± 7.3	7.9 ± 7.8	12.6 ± 7.5
Protein intake, g/d	16.9 ± 2.8	16.8 ± 2.7	16.9 ± 2.9	16.7 ± 2.9	16.5 ± 2.7
Animal protein, g/d	66.4 ± 18.4	65.3 ± 17.0	65.2 ± 16.8	64.3 ± 17.3	64.8 ± 17.7
Plant protein, g/d	34.4 ± 9.4	33.4 ± 9.6	31.8 ± 9.2	31.5 ± 9.3	31.0 ± 8.5
Fat intake, % E	40.1 ± 6.2	39.6 ± 6.3	39.7 ± 6.8	39.3 ± 6.8	39.4 ± 6.5
MUFA	20.9 ± 4.7	20.6 ± 4.5	20.6 ± 4.8	20.4 ± 4.7	20.5 ± 4.5
PUFA	6.6 ± 1.9	6.4 ± 1.8	6.3 ± 1.9	6.2 ± 1.8	6.2 ± 1.7
SFA	10.0 ± 2.0	9.9 ± 1.9	9.9 ± 2.0	9.9 ± 2.1	9.9 ± 1.9
α-Linolenic acid, g/d	1.6 ± 0.7	1.5 ± 0.7	1.4 ± 0.7	1.4 ± 0.7	1.4 ± 0.7
Marine n-3 fatty acids, g/d	0.7 ± 0.4	0.7 ± 0.4	0.7 ± 0.4	0.6 ± 0.4	0.7 ± 0.4

[1] Values are means ± SDs or numbers of participants (percentages) unless otherwise indicated. BP, blood pressure; CQI, carbohydrate quality index; E, energy; HbA1c, glycated hemoglobin; MedDiet, Mediterranean diet; MET, metabolic equivalent; TC, total cholesterol; TyG index, triglycerides and glucose index; TyG-WC, product of triglycerides and glucose index and waist circumference.

follow-up. We used crude and multivariate linear regression models to study the relation between CQI and changes in CVD risk factors. Risk factor differences (from baseline to 6- and 12-mo follow-up visits) were expressed as mean changes and 95% CIs. Adjustments were made for the following baseline covariates: age, sex, IG/CG, level of attained studies (primary education, secondary education, college/university), energy intake (kcal/d, continuous), BMI (kg/m^2, continuous), smoking (current smokers, former smokers, never smokers), alcohol intake (g/d, continuous), physical activity (metabolic equivalent hours per week, continuous), changes from baseline in fatty acid subtype intake as percentage of total energy (MUFA, PUFA, SFA, all continuous), changes in animal protein intake and in plant protein (both continuous), changes in physical activity (continuous), changes in smoking status, and changes in alcohol intake (continuous). We performed tests of linear trends across successive quintiles of CQI and risk factors, assigning the median value to each quintile category and treating the variables as continuous. We additionally assessed interactions between CQI and the IG of the trial in adjusted models to address significant subgroup differences. When we assessed the interaction with the randomized IG, we used robust variance estimators to account for intracluster correlations in all regression models, considering as clusters the members of the same household (n = 309 couples). We used linear mixed-effects models to compare changes in CVD risk factors over time (0 compared with 6 and 12 mo) by changes in the CQI. In these models, we tested for the potential interactions of CQI changes with time, after adjusting for the variables mentioned above. To test the robustness of our findings, sensitivity analyses were performed among completers (including only participants with no missing data) and completers stratified by self-reported diabetes.

Results

Among the 9677 candidates assessed for eligibility, 6874 participants met the inclusion criteria and were randomly allocated either to the CG or IG. We excluded 1316 subjects who did not complete the SFFQ at baseline or after 6 or 12 mo of follow-up. We additionally excluded 185 participants with energy intakes outside of predefined limits (<500 or >3500 kcal/d for women and <800 or >4000 kcal/d for men) according to published recommendations (39). The remaining 5373 participants comprised the sample of the study. There were neither withdrawals nor losses to follow-up before the study completion (**Figure 1**).

Foods, nutrients, diet, and energy intake

Baseline characteristics of the subjects of the study according to quintiles of change in CQI after 12 mo of follow-up are shown in **Table 2**. The majority of participants improved their CQI by increasing their consumption of fruits, vegetables, and other noncarbohydrate food sources such as legumes, fish, and nuts, main components of the MedDiet, and decreasing their consumption of refined cereals and sugar-sweetened beverages (Table 2 and **Table 3**). Consumption of white bread, a frequently consumed staple highly rooted in the Spanish culinary culture, also decreased in favor of increased consumption of whole-grain bread (less common in Spain). Hence, an increase in the overall fiber intake and a decrease in the total consumption of rapid carbohydrates (solid and liquid) were observed among the participants during the follow-up. Participants less adherent to the MedDiet at baseline showed the largest improvements in the CQI during the 12-mo intervention. Lastly, total energy intake remained fairly similar across quintiles of CQI change.

TABLE 3 Changes in noncarbohydrate dietary sources according to quintiles of CQI change after 6 and 12 mo of follow-up[1]

	Quintiles of change in CQI from baseline		
Characteristics	Q1	Q5	*r*
Foods, daily consumption, g			
Fish			
6-mo changes	−0.7 ± 47.8	21.1 ± 51.6	0.155
12-mo changes	0.1 ± 50.0	21.4 ± 49.5	0.157
Meat, meat products			
6-mo changes	−15.5 ± 51.4	−13.9 ± 55.4	0.012
12-mo changes	−16.1 ± 55.6	−18.9 ± 61.1	−0.014
Dairy products			
6-mo changes	5.0 ± 189.3	−19.5 ± 204.5	−0.045
12-mo changes	1.2 ± 192.2	−33.1 ± 207.6	−0.070
Legumes			
6-mo changes	−1.1 ± 13.1	9.0 ± 13.7	0.261
12-mo changes	−1.3 ± 13.2	9.0 ± 13.1	0.275
Total nuts			
6-mo changes	5.5 ± 21.6	22.9 ± 23.3	0.262
12-mo changes	6.8 ± 22.0	22.7 ± 23.2	0.241
Olive oil			
6-mo changes	3.6 ± 19.3	3.7 ± 19.2	−0.007
12-mo changes	6.4 ± 19.3	4.7 ± 19.9	−0.033
Refined olive oil			
6-mo changes	−4.4 ± 15.3	−5.9 ± 15.6	−0.041
12-mo changes	−4.7 ± 14.6	−5.5 ± 14.9	−0.032
Extra-virgin olive oil			
6-mo changes	7.8 ± 22.1	9.5 ± 22.7	0.024
12-mo changes	11.2 ± 22.6	10.2 ± 22.7	−0.006
Nutrient intake			
Protein intake, % E			
6-mo changes	0.3 ± 2.7	1.5 ± 2.8	0.158
12-mo changes	0.1 ± 2.9	1.3 ± 2.9	0.137
Animal protein, g/d			
6-mo changes	–4.1 ± 16.6	–0.7 ± 17.8	0.074
12-mo changes	–4.1 ± 17.9	–2.2 ± 18.5	0.039
Plant protein, g/d			
6-mo changes	–2.8 ± 9.4	5.0 ± 10.4	0.258
12-mo– changes	–2.9 ± 9.7	4.4 ± 10.0	0.252
Fat intake, % E			
6-mo changes	1.4 ± 6.9	3.0 ± 7.1	0.069
12-mo changes	2.2 ± 6.7	3.2 ± 7.1	0.047
MUFA			
6-mo changes	2.1 ± 5.5	3.8 ± 5.5	0.102
12-mo changes	3.0 ± 5.5	4.2 ± 5.5	0.071
PUFA			
6-mo changes	0.6 ± 2.2	1.7 ± 2.3	0.171
12-mo changes	0.6 ± 2.1	1.6 ± 2.2	0.171
SFA			
6-mo changes	−0.6 ± 2.0	−1.2 ± 2.1	−0.096
12-mo changes	−0.5 ± 2.0	−1.1 ± 2.0	−0.120
α-Linolenic acid, g/d			
6-mo changes	0.03 ± 0.84	0.43 ± 0.86	0.162
12-mo changes	0.03 ± 0.81	0.38 ± 0.83	0.146
Marine n-3 fatty acids, g/d			
6-mo changes	0.02 ± 0.40	0.21 ± 0.44	0.156
12-mo changes	0.03 ± 0.41	0.21 ± 0.42	0.157

[1] Values are means ± SDs unless otherwise indicated. CQI, carbohydrate quality index; E, energy; Q, quintile.

Last column (*r*): Pearson product–moment correlation coefficient between changes in CQI and foods or nutrients.

CQI and CVD risk factors

The primary outcome of the present study was weight change, whereas the secondary outcomes were changes in BP, lipids, and glycemic control variables. Crude and adjusted changes in CVD risk according to quintiles of changes in CQI from baseline to the 6-mo assessment are shown in **Table 4**. Overall, the greater the increase in the CQI, the greater the reduction in body weight, WC, and systolic and diastolic BP. Fasting blood glucose and HbA1c concentrations also monotonically decreased across successive quintiles of improvements in CQI. Regarding the lipid risk factors, reductions in triglyceride levels, TyG index, and TyG-WC were observed for subjects with greater increases in the CQI during the first 6 mo. CQI changes were not significantly associated with differences in TC, LDL or HDL cholesterol, or the ratio of TC to HDL cholesterol during the first 6 mo.

TABLE 4 Crude and multivariate linear regression models of 6-mo changes in risk factors by quintiles of change in CQI in the overall cohort of the PREDIMED-Plus Trial ($n = 5373$)[1]

	Quintiles of change in CQI from baseline to 6-mo follow-up						
Characteristics	Q1	Q2	Q3	Q4	Q5	*P*-trend[2]	*P*-interaction[3]
n (frequency)	1193	1179	1202	861	938		
CQI range	−13 to −3	−2 to −1	0 to 1	2 to 3	4 to 13		
Weight change, kg	−1.07 (−1.24, −0.89)	−1.44 (−1.62, −1.25)	−1.78 (−1.97, −1.60)	−2.68 (−2.92, −2.44)	−3.76 (−4.01, −3.51)		
vs. Q1 (MV-adjusted)	0 (ref.)	−0.22 (−0.48, 0.03)	−0.47 (−0.73, −0.22)	−0.98 (−1.26, −0.69)	−1.64 (−1.93, −1.35)	<0.001	<0.001
Waist circumference change, cm	−1.31 (−1.57, −1.06)	−1.97 (−2.21, −1.72)	−2.18 (−2.41, −1.94)	−2.87 (−3.19, −2.54)	−4.05 (−4.38, −3.73)		
vs. Q1 (MV-adjusted)	0 (ref.)	−0.49 (−0.84, −0.14)	−0.62 (−0.97, −0.26)	−0.89 (−1.28, −0.49)	−1.64 (−2.04, −1.24)	<0.001	0.086
Systolic BP change, mmHg	−1.31 (−2.16, −0.46)	−1.60 (−2.47, −0.73)	−2.25 (−3.12, −1.39)	−3.40 (−4.41, −2.39)	−4.16 (−5.18, −3.14)		
vs. Q1 (MV-adjusted)	0 (ref.)	−0.26 (−1.50, 0.97)	−0.92 (−2.17, 0.34)	−1.73 (−3.12, −0.34)	−2.27 (−3.69, −0.86)	<0.001	0.015
Diastolic BP change, mmHg	−0.86 (−1.33, −0.40)	−1.03 (−1.51, −0.54)	−1.02 (−1.49, −0.55)	−1.77 (−2.34, −1.21)	−2.54 (−3.07, −2.02)		
vs. Q1 (MV-adjusted)	0 (ref.)	−0.14 (−0.81, 0.54)	−0.09 (−0.77, 0.59)	−0.68 (−1.44, 0.07)	−1.26 (−2.03, −0.48)	<0.001	0.143
Fasting blood glucose change, mg/dL	−0.59 (−1.87, 0.69)	−1.40 (−2.62, −0.18)	−3.21 (−4.33, −2.09)	−3.47 (−5.05, −1.90)	−4.92 (−6.19, −3.64)		
vs. Q1 (MV-adjusted)	0 (ref.)	−0.90 (−2.63, 0.84)	−2.71 (−4.46, −0.96)	−2.69 (−4.63, −0.75)	−3.83 (−5.81, −1.84)	<0.001	0.679
HbA1c change, %	−0.01 (−0.05, 0.02)	−0.05 (−0.09, −0.01)	−0.07 (−0.10, −0.04)	−0.10 (−0.14, −0.06)	−0.17 (−0.21, −0.13)		
vs. Q1 (MV-adjusted)	0 (ref.)	−0.03 (−0.08, 0.02)	−0.05 (−0.10, −0.00)	−0.07 (−0.12, −0.01)	−0.11 (−0.17, −0.05)	<0.001	0.913
TC change, mg/dL	−1.62 (−3.26, 0.03)	−0.06 (−1.81, 1.70)	0.20 (−1.53, 1.92)	−1.79 (−3.73, 0.16)	−3.05 (−5.04, −1.06)		
vs. Q1 (MV-adjusted)	0 (ref.)	1.66 (−0.78, 4.11)	2.10 (−0.37, 4.57)	0.46 (−2.28, 3.19)	−0.44 (−3.24, 2.36)	0.616	0.196
LDL cholesterol change, mg/dL	−2.14 (−3.64, −0.63)	−1.34 (−2.92, 0.23)	−0.53 (−2.10, 1.05)	−2.09 (−3.89, −0.29)	−2.10 (−3.83, −0.37)		
vs. Q1 (MV-adjusted)	0 (ref.)	0.94 (−1.27, 3.16)	1.87 (−0.37, 4.10)	0.49 (−1.97, 2.96)	0.76 (−1.76, 3.28)	0.657	0.359
HDL cholesterol change, mg/dL	1.05 (0.58, 1.52)	1.42 (0.94, 1.89)	1.20 (0.77, 1.63)	1.86 (1.38, 2.34)	1.97 (1.49, 2.46)		
vs. Q1 (MV-adjusted)	0 (ref.)	0.29 (−0.35, 0.92)	0.01 (−0.63, 0.66)	0.55 (−0.16, 1.26)	0.51 (−0.22, 1.24)	0.118	0.625
Ratio of TC to HDL cholesterol change (×100)	−11.64 (−15.92, −7.36)	−11.44 (−16.13, −6.74)	−11.70 (−16.54, −6.87)	−19.06 (−24.15, −13.96)	−23.87 (−29.39, −18.35)		
vs. Q1 (MV-adjusted)	0 (ref.)	1.15 (−5.42, 7.72)	1.94 (−4.69, 8.58)	−3.70 (−11.05, 3.65)	−6.09 (−13.61, 1.43)	0.063	0.223
Triglycerides change, mg/dL	−7.12 (−10.69, −3.55)	−3.64 (−7.51, 0.23)	−6.91 (−10.77, −3.04)	−9.52 (−13.46, −5.57)	−17.90 (−22.34, −13.47)		
vs. Q1 (MV-adjusted)	0 (ref.)	4.04 (−1.30, 9.37)	1.40 (−4.00, 6.79)	0.20 (−5.77, 6.17)	−6.51 (−12.61, −0.40)	0.027	0.063
TyG index change	−0.05 (−0.07, −0.03)	−0.04 (−0.06, −0.01)	−0.08 (−0.10, −0.06)	−0.12 (−0.14, −0.09)	−0.16 (−0.19, −0.14)		
vs. Q1 (MV-adjusted)	0 (ref.)	0.02 (−0.01, 0.05)	−0.02 (−0.05, 0.01)	−0.04 (−0.08, −0.00)	−0.08 (−0.11, −0.04)	<0.001	0.094
TyG-WC change	−16.03 (−19.67, −12.38)	−20.66 (−24.29, −17.03)	−26.90 (−30.36, −23.43)	−36.57 (−41.14, −32.01)	−53.26 (−57.83, −48.69)		
vs. Q1 (MV-adjusted)	0 (ref.)	−2.70 (−7.81, 2.41)	−7.82 (−12.98, −2.66)	−12.48 (−18.20, −6.76)	−23.94 (−29.79, −18.10)	<0.001	0.029

[1] Values are means (95% CIs) unless otherwise indicated. Multivariable-adjusted model for baseline covariates age, sex, group, level of attained studies, energy intake, BMI, smoking, alcohol intake, physical activity, and changes from baseline in MUFA, PUFA, SFA, animal protein, plant protein, physical activity, smoking status, and alcohol intake. BP, blood pressure; CQI, carbohydrate quality index; HbA1c, glycated hemoglobin; MV, multivariate; ref., reference value; Q, quintile; TC, total cholesterol; TyG index, triglycerides and glucose index; TyG-WC, product of triglycerides and glucose index and waist circumference.

[2] *P* value for linear trend.

[3] *P* value for interaction between CQI and intervention group (control group compared with intervention group).

At 12-mo follow-up, improvements in CVD risk factors in association with improvements in the CQI remained significant for body weight, WC, systolic and diastolic BP, fasting glucose, HbA1c, triglyceride levels, TyG index, and TyG-WC. Significant reductions were also observed for the ratio of TC to HDL cholesterol. Additionally, HDL cholesterol levels exhibited progressive significant elevations across successive quintiles of changes in CQI from baseline to 12 mo. Changes in LDL cholesterol and TC levels remained not significantly associated with changes in CQI at 12 mo (**Table 5**).

Improvements in the respective baseline risk factor values found in the highest compared with the lowest quintiles of change in the CQI (quintile 5 compared with quintile 1) after 6 and 12 mo are displayed in **Figure 2**. At 12-mo follow-up, TyG-WC (−0.20 SD; 95% CI −0.26, −0.15), TyG index (−0.17 SD; 95% CI −0.25, −0.10), HbA1c (−0.16 SD; 95% CI −0.23, −0.10), WC (−0.15 SD; 95% CI −0.20, −0.11), fasting blood glucose (−0.13 SD; 95% CI −0.19, −0.06), triglycerides (−0.12 SD; 95% CI −0.20, −0.04), weight (−0.12 SD; 95% CI −0.14, −0.09), systolic BP (−0.11 SD; 95% CI −0.19, −0.02), diastolic BP (−0.11 SD; 95% CI −0.19, −0.04), and the ratio of TC and HDL cholesterol (−0.10 SD; 95% CI −0.17, −0.02) represented the largest observed improvements in risk factors.

Interaction between CQI and the CG and IG

We tested the interaction (effect modification) between the randomized intervention and the observed changes in CQI with regard to changes in risk factors at the 6-mo (Table 4, last column) and 12-mo visits (Table 5, last column). The presence of a significant *P*-interaction indicates that the association between longitudinal changes in CQI and changes in risk factors differs depending on the intervention arm of the trial (CG compared with IG). To better appraise the effect and direction of these significant interactions, we graphically represented them for both the 6-mo (**Figure 3**) and 12-mo visits (**Figure 4**). The results indicated that the effects of the changes in CQI on changes in weight, systolic BP, and TyG-WC at 6 mo, and on weight, WC, fasting blood glucose, HbA1c, and TyG-WC at 12 mo, were stronger in the IG than in the CG. As can be deduced from Figures 3 and 4, differences in risk factor changes between the IG and the CG were wider when the improvements in CQI were greater.

Interaction between CQI and time

We graphically compared changes in CVD risk factors at 6 and 12 mo to examine if these changes over time differed across categories of changes in CQI. Moreover, we tested the interactions between time and changes in CQI in multivariable-adjusted mixed linear models. For this purpose, we categorized the changes in the CQI into 3 groups by merging the 3 intermediate quintiles and thus building only 3 categories of changes in CQI (quintile 1, quintiles 2–4, and quintile 5). This merging was performed to better capture the contrast between extreme categories. As shown in **Figure 5**, most of the changes in risk factors associated with changes in the CQI were apparent over time, with steeper inverse slopes for groups with higher improvements in carbohydrate quality. A significant interaction between time and CQI was observed for most of the CVD risk factors under study.

Sensitivity analyses

The association of CQI changes with improvements in risk factors at 6-mo (**Supplemental Table 2**) and 12-mo follow-up (**Supplemental Table 3**) were consistent with our previous findings, after we adopted different assumptions. Moreover, when we stratified completers by self-reported diabetes at baseline, observed associations with HbA1c improvements remained favorable for better CQI (**Supplemental Table 4** and **Supplemental Table 5**).

Discussion

The present study examined the PREDIMED-Plus trial as a longitudinal, observational cohort to evaluate changes in quality of carbohydrates and their effects on changes in CVD risk factors in community-dwelling adults at high risk. We used a multidimensional index to simultaneously account for several dimensions of dietary carbohydrates to capture their quality in a comprehensive manner. Our findings support the premise that quality of dietary carbohydrates is likely to play a major role as a determinant of numerous cardiometabolic health outcomes. We found significant associations between improvements in CQI and reductions in most traditional and novel CVD risk factors under study. The greatest improvements were observed for TyG-WC, TyG index, HbA1c, WC, fasting blood glucose, triglycerides, weight, systolic BP, diastolic BP, the ratio of TC and HDL cholesterol, and HDL cholesterol. These benefits associated with changes in the CQI became apparent over time and showed slightly stronger associations within the IG. However, the magnitude of the interaction between IG and CQI change was of a small size from a clinical point of view, which suggests that favorable effects of CQI on CVD did not substantially vary depending on the group of the trial.

After the disappointing results of low-fat diets in preventing CVD (6, 40), carbohydrates have become the focus of intense interest in nutritional epidemiology. The question of whether the quality of carbohydrates in the diet, rather than their relative quantity, can positively impact population health outcomes has become very relevant. In this respect, a number of quality markers have been used to investigate the relation between carbohydrate quality and health improvements. For instance, some studies have provided strong evidence that dietary fiber has beneficial effects to reduce levels of CVD events (15), risk factors (13, 14), and mortality (41, 42). Similarly, a higher consumption of whole grains has demonstrated protective effects against CVD (16) and has been associated with reductions in all-cause mortality (43, 44). Low glycemic index and low glycemic load diets have also been associated with a decreased risk for certain chronic diseases (18, 45). Despite the multiple studies performed, no evidence was available to measure the predictive potential of changes in a multidimensional quality indicator on chronic conditions and their usefulness for nutritional guidelines. To address this gap in the literature, Reynolds et al. (12) reviewed 185 prospective studies and 58 clinical trials and

TABLE 5 Crude and multivariate linear regression models of 12-mo changes in risk factors by quintiles of change in CQI in the overall cohort of the PREDIMED-Plus Trial ($n = 5373$) [1]

	Quintiles of change in CQI from baseline to 12-mo follow-up						
Characteristics	Q1	Q2	Q3	Q4	Q5	*P*-trend[2]	*P*-interaction[3]
n (frequency)	1243	1119	1183	834	994		
CQI range	−12 to −3	−2 to −1	0 to 1	2 to 3	4 to 12		
Weight change, kg	−1.28 (−1.49, −1.07)	−1.58 (−1.79, −1.37)	−2.17 (−2.39, −1.96)	−3.27 (−3.57, −2.96)	−3.99 (−4.27, −3.70)		
vs. Q1 (MV-adjusted)	0 (ref.)	−0.19 (−0.49, 0.11)	−0.40 (−0.70, −0.10)	−1.20 (−1.53, −0.86)	−1.51 (−1.84, −1.18)	<0.001	<0.001
Waist circumference change, cm	−1.69 (−1.96, −1.43)	−1.92 (−2.20, −1.64)	−2.71 (−3.00, −2.43)	−3.47 (−3.82, −3.12)	−4.48 (−4.83, −4.13)		
vs. Q1 (MV-adjusted)	0 (ref.)	−0.05 (−0.44, 0.34)	−0.47 (−0.85, −0.08)	−0.89 (−1.33, −0.46)	−1.45 (−1.88, −1.03)	<0.001	0.015
Systolic BP change, mmHg	−2.01 (−2.89, −1.14)	−3.11 (−3.99, −2.24)	−3.65 (−4.51, −2.78)	−3.75 (−4.78, −2.71)	−4.39 (−5.34, −3.44)		
vs. Q1 (MV-adjusted)	0 (ref.)	−1.06 (−2.31, 0.18)	−1.38 (−2.63, −0.13)	−1.35 (−2.74, 0.05)	−1.76 (−3.14, −0.39)	0.013	0.300
Diastolic BP change, mmHg	−1.23 (−1.72, −0.74)	−1.83 (−2.31, −1.36)	−2.23 (−2.71, −1.76)	−1.76 (−2.30, −1.22)	−2.68 (−3.19, −2.17)		
vs. Q1 (MV-adjusted)	0 (ref.)	−0.59 (−1.27, 0.08)	−0.84 (−1.52, −0.17)	−0.29 (−1.05, 0.47)	−1.13 (−1.87, −0.38)	0.011	0.261
Fasting blood glucose change, mg/dL	−2.23 (−3.39, −1.07)	0.12 (−1.24, 1.48)	−2.16 (−3.44, −0.88)	−3.51 (−4.91, −2.12)	−6.20 (−7.53, −4.88)		
vs. Q1 (MV-adjusted)	0 (ref.)	2.04 (0.27, 3.81)	0.16 (−1.62, 1.93)	−1.15 (−3.13, 0.83)	−3.65 (−5.61, −1.70)	<0.001	0.004
HbA1c change, %	−0.03 (−0.07, 0.00)	−0.01 (−0.05, 0.02)	−0.06 (−0.10, −0.02)	−0.14 (−0.18, −0.10)	−0.21 (−0.25, −0.17)		
vs. Q1 (MV-adjusted)	0 (ref.)	0.02 (−0.04, 0.07)	−0.02 (−0.07, 0.04)	−0.08 (−0.14, −0.02)	−0.14 (−0.20, −0.09)	<0.001	0.014
TC change, mg/dL	−1.29 (−3.31, 0.73)	−3.84 (−5.76, −1.92)	−3.10 (−4.98, −1.22)	−1.17 (−3.21, 0.88)	−2.91 (−4.86, −0.97)		
vs. Q1 (MV-adjusted)	0 (ref.)	−2.86 (−5.55, −0.17)	−1.92 (−4.62, 0.77)	−0.24 (−3.26, 2.78)	−1.87 (−4.85, 1.11)	0.459	0.380
LDL-cholesterol change, mg/dL	−1.57 (−3.52, 0.38)	−5.02 (−6.80, −3.24)	−3.39 (−5.06, −1.72)	−2.04 (−3.89, −0.18)	−3.11 (−4.84, −1.37)		
vs. Q1 (MV-adjusted)	0 (ref.)	−3.86 (−6.34, −1.37)	−2.25 (−4.73, 0.24)	−1.20 (−3.96, 1.57)	−2.36 (−5.10, 0.38)	0.245	0.125
HDL-cholesterol change, mg/dL	1.03 (0.60, 1.45)	1.25 (0.77, 1.74)	1.32 (0.90, 1.75)	2.20 (1.71, 2.70)	2.20 (1.74, 2.66)		
vs. Q1 (MV-adjusted)	0 (ref.)	0.24 (−0.38, 0.86)	0.15 (−0.47, 0.77)	0.92 (0.22, 1.61)	0.75 (0.07, 1.43)	0.009	0.539
Ratio of TC to HDL cholesterol change (×100)	−11.58 (−16.56, −6.60)	−17.67 (−23.45, −11.88)	−18.03 (−22.73, −13.32)	−21.10 (−26.43, −15.77)	−25.42 (−30.51, −20.34)		
vs. Q1 (MV-adjusted)	0 (ref.)	−6.91 (−13.95, 0.13)	−5.25 (−12.31, 1.81)	−7.86 (−15.76, 0.04)	−10.36 (−18.15, −2.57)	0.010	0.551
Triglycerides change, mg/dL	−2.25 (−5.86, 1.36)	−2.98 (−7.67, 1.71)	−9.59 (−13.19, −5.99)	−12.47 (−16.51, −8.43)	−15.99 (−20.71, −11.26)		
vs. Q1I (MV-adjusted)	0 (ref.)	−0.53 (−6.15, 5.10)	−5.25 (−10.89, 0.38)	−7.39 (−13.69, −1.08)	−9.07 (−15.29, −2.85)	0.001	0.697
TyG index change	−0.04 (−0.06, −0.02)	−0.03 (−0.05, −0.00)	−0.07 (−0.10, −0.05)	−0.12 (−0.15, −0.09)	−0.16 (−0.19, −0.14)		
vs. Q1 (MV-adjusted)	0 (ref.)	0.01 (−0.02, 0.05)	−0.02 (−0.05, 0.02)	−0.06 (−0.10, −0.02)	−0.09 (−0.13, −0.05)	<0.001	0.335
TyG-WC change	−18.78 (−22.61, −14.96)	−18.27 (−22.41, −14.13)	−31.26 (−35.23, −27.29)	−43.56 (−48.49, −38.64)	−56.91 (−61.72, −52.10)		
vs. Q1 (MV-adjusted)	0 (ref.)	1.99 (−3.59, 7.57)	−6.16 (−11.75, −0.57)	−15.03 (−21.28, −8.77)	−23.01 (−29.18, −16.84)	<0.001	0.008

[1] Values are means (95% CIs) unless otherwise indicated. MV-adjusted model for baseline covariates age, sex, group, level of education, energy intake, BMI, smoking, alcohol intake, physical activity, and changes from baseline in MUFA, PUFA, SFA, animal protein, plant protein, physical activity, smoking status, and alcohol intake. BP, blood pressure; CQI, carbohydrate quality index; HbA1c, glycated hemoglobin; mv, multivariate; Q, quintile; ref., reference value; TC, total cholesterol; TyG index, triglycerides and glucose index; TyG-WC, product of triglycerides and glucose index and waist circumference.

[2] *P* value for linear trend.

[3] *P* value for interaction between CQI and intervention group (control group vs intervention group).

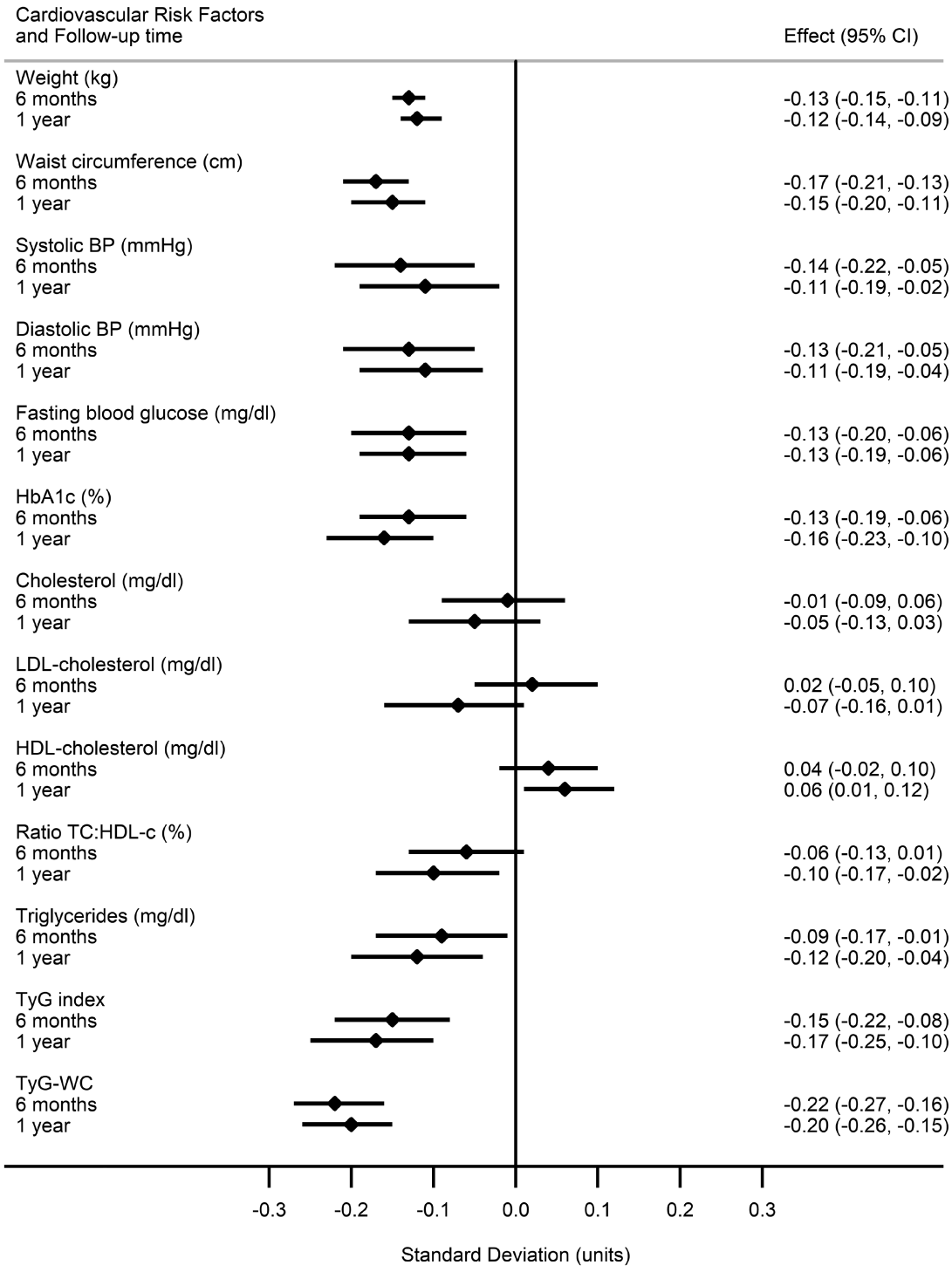

FIGURE 2 Mean multivariable-adjusted differences (95% CI) for changes in cardiovascular risk factors between the highest and the lowest quintile of CQI changes after 6- and 12-mo follow-up, expressed in common units of baseline SDs, in the overall cohort of the PREDIMED-Plus Trial, $n = 5373$. Model adjusted for baseline age, sex, group, level of attained studies, energy intake, BMI, smoking, alcohol intake, physical activity, and changes from baseline in MUFA, PUFA, SFA, animal protein, plant protein, physical activity, smoking status, and alcohol intake. BP, blood pressure; CQI, carbohydrate quality index; HbA1c, glycated hemoglobin; TyG index, triglycerides and glucose index; TyG-WC, product of triglycerides and glucose index and waist circumference.

evaluated the relation between the most widely used indicators of carbohydrate quality (dietary fiber, whole grain, and dietary glycemic index) and incidence of, and mortality from, a wide range of chronic conditions. The authors concluded that higher intakes of dietary fiber or whole grains were associated with reduced incidence of cardiometabolic diseases, type 2 diabetes, colorectal, breast, and esophageal cancer, as well as all-cause and cardiovascular-related mortality. However, the authors only

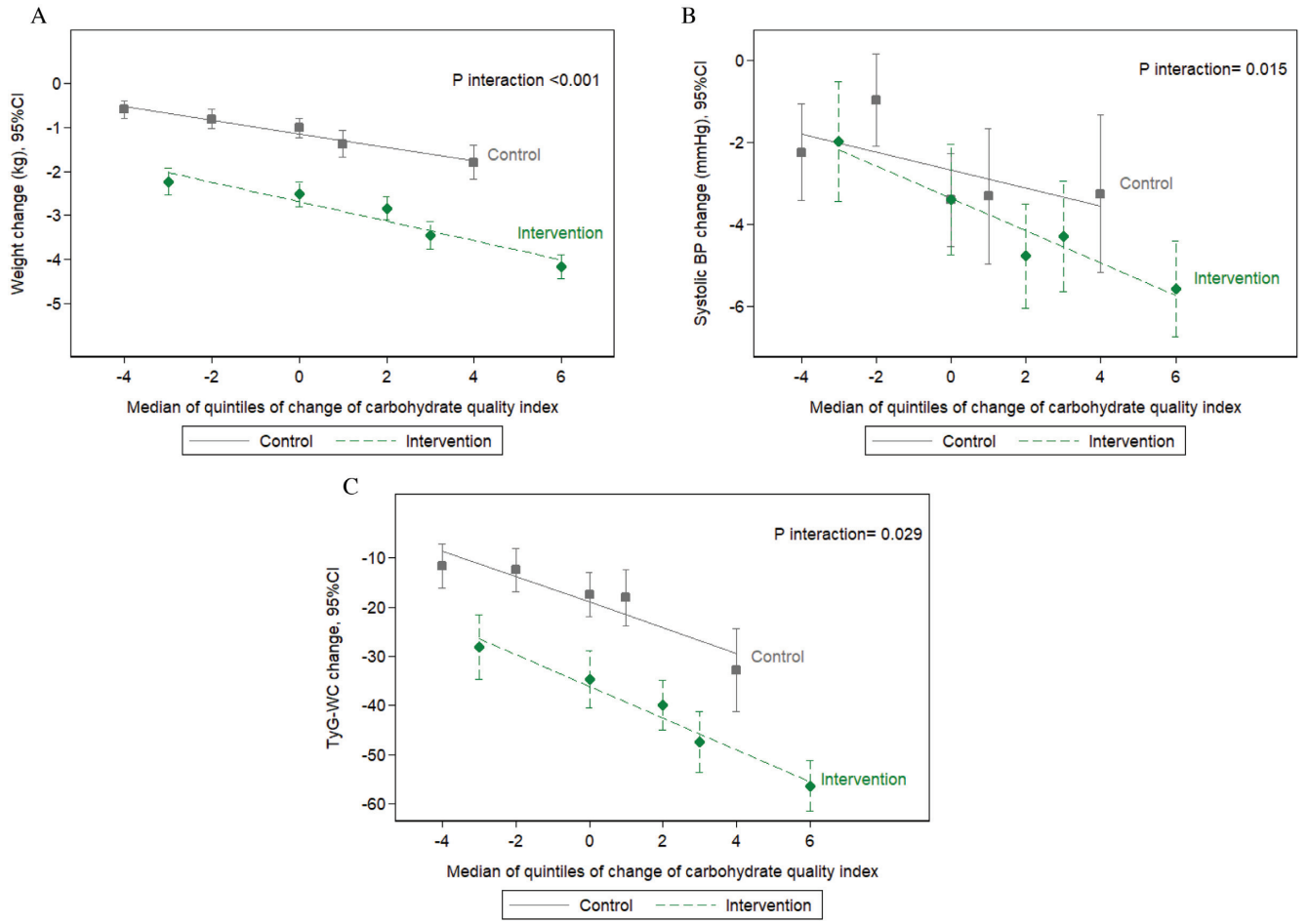

FIGURE 3 Subgroup analyses of interactions between changes in the CQI and randomized trial arms (control, $n = 2713$, compared with intervention, $n = 2660$), synergy on 6-mo changes in (A) weight in kilograms, (B) systolic BP in millimeters of mercury, and (C) TyG-WC. Model adjusted for baseline age, sex, group, level of attained studies, energy intake, BMI, smoking, alcohol intake, physical activity, and changes from baseline in MUFA, PUFA, SFA, animal protein, plant protein, physical activity, smoking status, and alcohol intake. BP, blood pressure; CQI, carbohydrate quality index; TyG-WC, product of triglycerides and glucose index and waist circumference.

focused on single isolated quality markers and did not include any multidimensional index (i.e., markers composed by several single indicators). We have also considered an additional dimension that was not assessed by Reynolds et al., namely, the preference for solid as opposed to liquid carbohydrates as an additional quality criterion, because it is well known that liquid carbohydrates are less likely to produce satiety and their extra calories are not fully compensated (46).

Carbohydrate quality has been broadly defined by 4 major dimensions or domains—low glycemic index/load, high dietary fiber, preference for whole grains, and avoidance of liquid carbohydrates. Therefore, a broad, multidimensional food-based approach emphasizing specific carbohydrate-containing foods (whole grains, pulses, and fruit), avoiding liquid carbohydrates, and reducing added sugars may have important effects in clinical practice (47). In contrast, it might be overly optimistic to expect an accurate measure of quality carbohydrate when using only a single domain. For example, whole-grain rice is a fiber-rich food but it does also contain a mid-to-high glycemic index, whereas nuts are a high-fiber but a low-glycemic food. Analogous to the food synergy tenet (48, 49), the combined effects of quality domains may probably lead to interactive or synergistic actions of health effects, which, a priori, probably cannot be well captured by a single quality indicator. Moreover, the potential effects of interactions and correlations between domains may be difficult to evaluate when using isolated quality dimensions.

In this line of thought, it seems essential to consider multiple aspects of carbohydrate quality when evaluating the role of carbohydrates in human health or when conducting nutritional interventions in clinical practice (50). Consequently, multidimensional indices to appraise the associations between carbohydrate quality, nutritional adequacy, and risk factors have been recently adopted. The results of these previous studies are consistent with our findings. Higher CQI was associated with better micronutrient intake adequacy (20, 23), lower prevalence of obesity/overweight (22) and hypertension (24), and lower incidence of CVD (21). Contrary to our study, the design of previous studies did not allow evaluation of whether changes in CQI are associated with favorable changes in CVD risk factors and whether these improvements can be maintained over time.

Based on our findings, recommending diets with high carbohydrate quality may represent an effective approach to improve

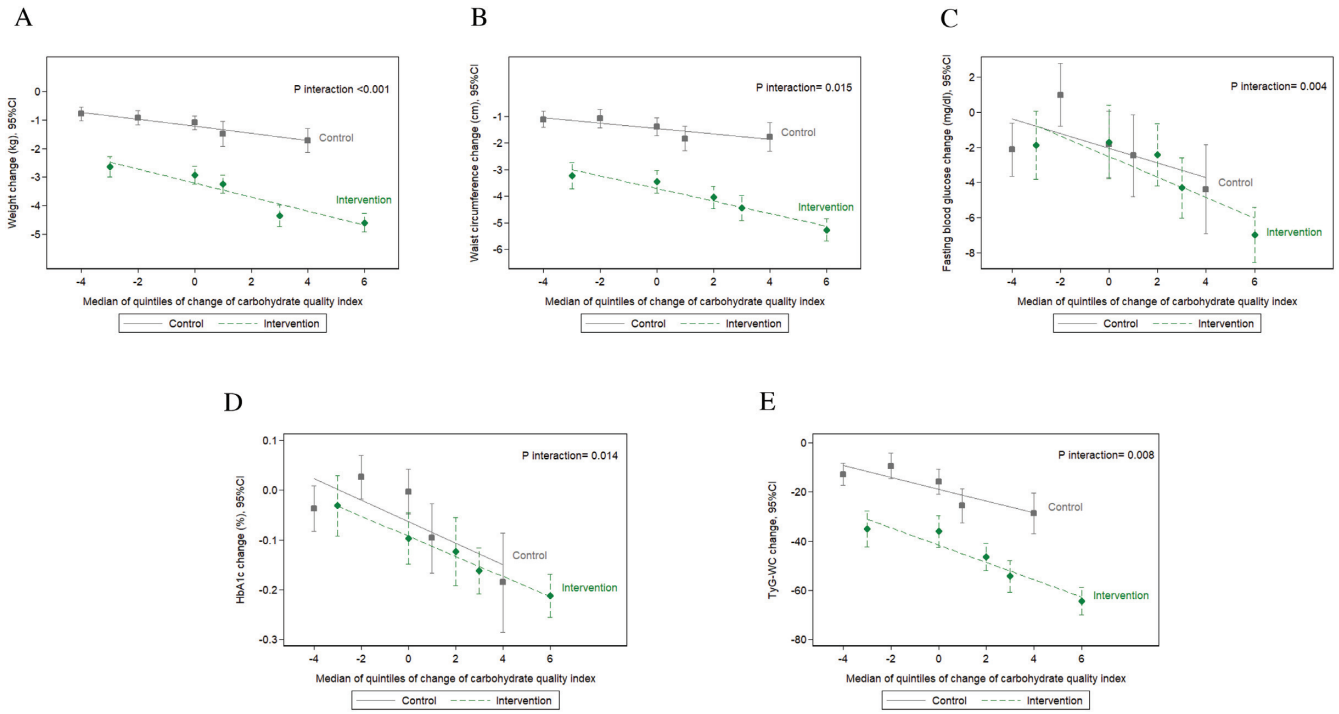

FIGURE 4 Subgroup analyses of interaction between changes in the CQI and randomized trial arms (control, $n = 2713$, compared with intervention, $n = 2660$), on 12-mo changes in (A) weight in kilograms, (B) waist circumference in centimeters, (C) fasting blood glucose in milligrams per deciliter, (D) HbA1c percentage, and (E) TyG-WC. Model adjusted for baseline age, sex, group, level of attained studies, energy intake, BMI, smoking, alcohol intake, physical activity, and changes from baseline in MUFA, PUFA, SFA, animal protein, plant protein, physical activity, smoking status, and alcohol intake. CQI, carbohydrate quality index; HbA1c, glycated hemoglobin; TyG-WC, product of triglycerides and glucose index and waist circumference.

population outcomes. In other words, fostering dietary patterns such as the MedDiet, which features fiber, fish, vegetables, and fruits and minimizes soda and sugar-sweetened beverages, would presumably result in a far greater impact on health than any other intervention. The additional precaution suggested by our results in subjects with MetS is reduction of the consumption of white bread and other refined grains (despite their traditional inclusion in Mediterranean-type diets) because of their suboptimal carbohydrate quality.

The current study has some limitations. First, the population of community-dwelling men and women with overweight/obesity and MetS included in the study is not representative of the general population; however, populations at high risk of CVD represent an important proportion of current Western societies. Second, although the SFFQ has been widely used in nutritional studies (30–32), self-reporting questionnaires are subject to some degree of measurement error. However, we excluded participants with energy intakes outside predefined limits (39). Despite these limitations, the strengths of our study are reflected in the assessment of an intervention specifically focused on improving the quality of carbohydrates in a sample size that was considerably larger than that of most previous trials. The use of a novel multidimensional CQI that seems able to dynamically capture changes in risk factors provides a more comprehensive approach than previous research on this topic. Also, the inclusion of multiple traditional and emerging CVD risk factors, and the considerable amount of nutritional information, with 3 repeated measurements used to calculate changes in the CQI, are advantages and novelties of our study.

In conclusion, our study adds to the extensive literature on carbohydrates, reporting that positive changes in the quality of carbohydrates lead to short-term improvements in CVD risk factors and these improvements are maintained or even enhanced over time. These results emphasize the need to focus on carbohydrate quality over quantity to avoid outdated paradigms. A greater effort to educate the general population is crucial to better help consumers to appraise the differences between foods and beverages with high-quality and low-quality carbohydrates.

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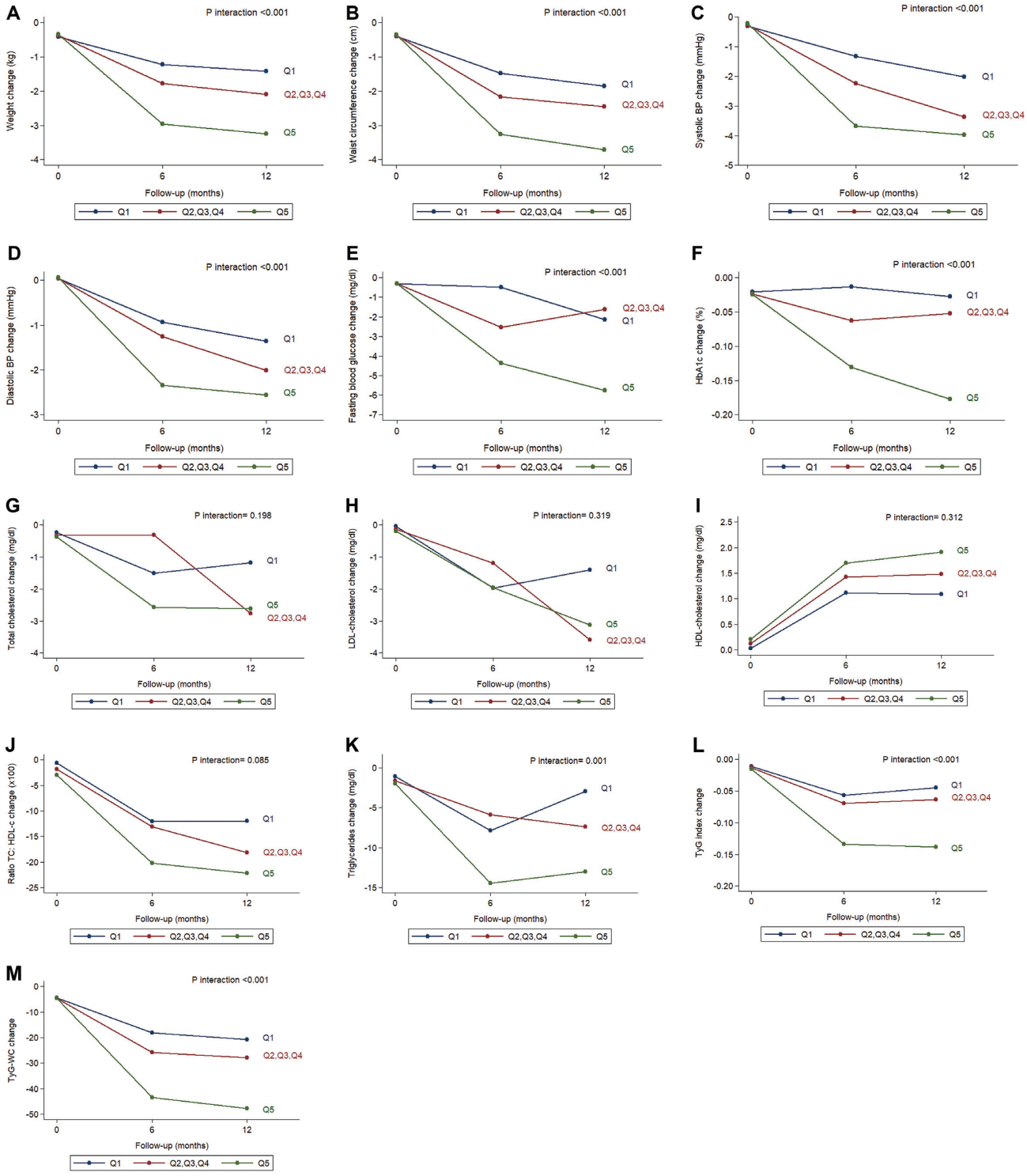

FIGURE 5 Analysis of changes in cardiovascular risk factors over time by changes in carbohydrate quality in the linear mixed-effects models. Carbohydrate quality changes were categorized into 3 groups by merging the 3 intermediate quintiles as follows: quintile 1, $n = 1243$, compared with quintiles 2, 3, and 4, $n = 3242$, compared with quintile 5, $n = 994$. The outcomes (dependent variables) were changes in the following risk factors: (A) weight in kilograms, (B) waist circumference in centimeters, (C) systolic BP in millimeters of mercury, (D) diastolic BP in millimeters of mercury, (E) fasting blood glucose in milligrams per deciliter, (F) HbA1c percentage, (G) total cholesterol in milligrams per deciliter, (H) LDL cholesterol in milligrams per deciliter, (I) HDL cholesterol in milligrams per deciliter, (J) ratio of TC to HDL cholesterol × 100, (K) triglycerides in milligrams per deciliter, (L) TyG index, and (M) TyG-WC. Linear mixed-effects model adjusted for baseline covariates for baseline age, sex, group, level of attained studies, energy intake, BMI, smoking, alcohol intake, physical activity, and changes from baseline in MUFA, PUFA, SFA, animal protein, plant protein, physical activity, smoking status, and alcohol intake. *P*-interaction for interaction between CQI and time. BP, blood pressure; HbA1c, glycated hemoglobin; Q, quintile; TC, total cholesterol; TyG index, triglycerides and glucose index; TyG-WC, product of triglycerides and glucose index and waist circumference.

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