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Quality and quantity of macronutrients, and their joint associations with the incidence of type 2 diabetes over a nine-year follow-up

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Abstract

Background The association between macronutrient consumption and the risk of type 2 diabetes (T2D) remains equivocal. Here, we investigated whether the quantity and quality of macronutrient intake are associated with T2D incidence in a West Asian population.

Methods T2D-free adults ($n=2457$, mean age 38.5 ± 13.6 years, 54.2% women) who participated in the third examination cycle (2005–2008) of the Tehran Lipid and Glucose Study were followed for a median of 8.6 years. We estimated the macronutrient quality index (MQI), its individual sub-indices (carbohydrate quality index (CQI), fat quality index (FQI), and healthy plate protein quality index (HPPQI)), as well as the macronutrient quantity. The risk of T2D in relation to macronutrient quantity, quality, and their combined effects was examined using Cox proportional hazard models adjusted for known risk factors for T2D.

Results During the study follow-up, 257 incident cases of T2D were documented. Individuals in the highest tertiles of MQI and CQI had a 27% (HR = 0.73, 95% CI = 0.54, 0.98) and 29% (HR = 0.71, 95% CI = 0.51–0.99) lower T2D risk than those in the lowest tertiles. The T2D incidence was 35% lower in the middle HPPQI tertile than in the lowest (HR = 0.65, 95% CI = 0.47, 0.89). The multivariable adjusted model showed that individuals in the middle and highest tertiles of carbohydrate intake had 32% (HR = 0.68, 95% CI = 0.49–0.95) and 26% (HR = 0.74, 95% CI = 0.55–1.00) lower risks of T2D than individuals in the lowest tertile. A high-quantity, high-quality carbohydrate diet (≥ 58.5% of energy from carbohydrate with a CQI ≥ 13) and a low-glycemic index (GI), high-fiber diet (GI < 55 and fiber ≥ 25 g/d) were related to a reduced risk of T2D by 34% (HR = 0.66, 95% CI = 0.47, 0.93) and 42% (HR = 0.58, 95% CI = 0.38, 0.90), respectively.

Conclusion A diet with a higher carbohydrate quality may be associated with a lower T2D incidence, particularly when the carbohydrate quantity is also high.

Keywords Carbohydrates, Carbohydrate quality index, Fat quality index, Protein quality index, Fiber, Glycemic index

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Background

The dramatic increase in diabetes prevalence over the past few decades has made it one of the main global health challenges [1]. The International Diabetes Federation predicts that the number of adults with diabetes will reach 783 million by 2045 [2]. Type 2 diabetes (T2D) affects over 90% of individuals with diabetes, increases the risk of premature death, and threatens public health [3]. Changes in diet and physical activity as a result of accelerated urbanization and development have led to this dramatic increase in T2D incidence [4].

Dietary macronutrients are postulated to be the determinants of T2D. However, previous prospective studies on the associations between macronutrients and T2D have produced inconsistent results, depending on the macronutrient sources and study populations [5–7]. For carbohydrates, the majority of studies conducted in Western populations found no association, whereas studies conducted in Asian populations found an increased risk of T2D with higher carbohydrate consumption [7]. Studies on carbohydrate quality have demonstrated an inverse association between dietary fiber and whole grains and the risk of T2D. However, there is insufficient data supporting the hypothesis that a lower compared with a higher glycemic index (GI) reduces T2D risk, indicating that additional research is required [8, 9]. There are fewer studies on the quality and quantity of fats and proteins in relation to T2D than those on carbohydrates. For fats, previous studies have reported no association between total dietary fats and T2D risk, but certain types of fats have been demonstrated to have beneficial effects, depending on the study population [5]. A meta-analysis of prospective studies has linked total protein and animal protein to an increased risk of developing T2D [6]. However, all studies, with the exception of one [10], have been conducted in Western populations. It is therefore unclear whether these associations also apply to non-Western populations [6].

Recently, the macronutrient quality index (MQI) was proposed to evaluate the overall macronutrient quality of a diet by simultaneously considering the qualities of all three macronutrients [11]. The carbohydrate quality index (CQI), fat quality index (FQI), and healthy plate protein quality index (HPPQI) are three sub-indices of the MQI used to assess the quality of each macronutrient [11]. To our knowledge, no previous studies have examined the association between the MQI, FQI, and HPPQI and the risk of T2D, and only one prospective study has examined the association between the CQI and T2D [12]. Therefore, we aimed to investigate the association of the MQI and its sub-indexes with the incidence of T2D in an adult population over a median follow-up of 8.6 years. The associations of macronutrient quantity and the joint associations of quality and quantity of macronutrients with T2D were also investigated.

Methods

Participants

The Tehran Lipid and Glucose Study (TLGS) is a longitudinal population-based investigation of non-communicable disease risk factors and outcomes that began in 1999 with 15,005 participants aged 3 to 69 years recruited from district 13 in Tehran, Iran [13]. During the follow-up examinations, participants' information was updated approximately every three years after the baseline examination. The Food Frequency Questionnaire (FFQ) has been used to capture dietary data since the third examination cycle (2005–2008), which served as the baseline for current analyses. Of 3687 participants in the third examination cycle who had dietary data, we excluded participants aged < 18 years ($n=569$), those with T2D ($n=219$) or an unclear state of diabetes at baseline ($n=28$), and pregnant women at baseline ($n=21$), as well as those who did not attend the follow-up ($n=206$), and those who had missing information to define T2D at follow-up ($n=33$). After further exclusion of participants with missing covariates ($n=106$) and unrealistic energy intake based on sex-specific percentiles 1 and 99 ($n=48$), 2457 participants free of T2D at baseline were followed till the sixth examination cycle (2016–2018; Supplemental Fig. 1). The study was carried out in compliance with the principles outlined in the Declaration of Helsinki. The study's design was granted approval by the research ethics committees of the Research Institute for Endocrine Sciences at Shahid Beheshti University of Medical Sciences. Everyone who participated in the study provided informed consent.

Dietary assessment

An FFQ was first administered to assess dietary intakes at the third examination cycle and every 3 years thereafter. Participants were asked about the quantity and frequency of 168 food items consumed in the previous year. The daily intakes of each item were estimated, and then energy and nutrient intakes were calculated using the Iranian and United States Department of Agriculture food composition tables. Previous studies have demonstrated the reliability and validity of the FFQ in measuring dietary intakes [14, 15]. The FFQ's validity against twelve 24-hour dietary recalls was demonstrated by Pearson correlation coefficients of 0.38 for carbohydrate, 0.62 for fat, and 0.64 for protein in men, 0.47 for carbohydrate, 0.40 for fat, and 0.48 for protein in women [15].

The quality of the dietary carbohydrate was assessed by the calculation of the CQI. The CQI was computed using the four components: GI, fiber, the ratio of carbohydrates from solids to total carbohydrates, and the ratio of carbohydrates from whole grains to total grains. These four components were categorized into quartiles, scored between 1 (the first quartile) and 4 (the fourth quartile), and then summed. GI was scored reversely between 1 (the highest quartile) and 4 (the lowest quartile). The range of the CQI was between 4 and 20 [16]. The GI was determined using the international table of GI and a list of the GI of Iranian foods [17, 18]. Liquid carbohydrates were determined by adding the consumption of sugar-sweetened beverages and fruit juices (four items), whereas solid carbohydrates were calculated by adding the carbohydrate content of the remaining carbohydrate-containing foods. Four food items corresponding to whole breads, rye, and bulgur were used to determine consumption of whole grains, while fourteen food items, including white rice, pasta, and bread or other bakery products derived from refined grains, were used to determine consumption of refined grains. The quality of dietary fat and protein was determined by computing FQI and HPPQI using the following ratios [11]:

FQI = (monounsaturated fatty acids+polyunsaturated fatty acids) / (saturated fatty acids+trans fatty acids).
HPPQI = (seafood+poultry+pulses+nuts) / (red and processed meats+cheese).

Combining the CQI, FQI, and HPPQI yields the MQI, which represents the overall quality of macronutrients. The three components were grouped into quintiles, scored between 1 (the first quintile) and 5 (the fifth quintile), and then added together. The range of MQI scores was from 3 to 15 [11].

Dietary indices were calculated for each examination cycle, and their average values from the third examination to the examination before the onset of T2D or the last follow-up were used in analyses to figure out long-term dietary exposure.

For macronutrient quantities, the percentage of total energy intake from each macronutrient was calculated for each macronutrient (nutrient density method) [19]. In the statistical analyses, the average intake of each macronutrient throughout the study was used.

Demographic, lifestyle, and anthropometric assessment

Participants were asked via questionnaire about their demographic characteristics, medical history, and medications. Based on their smoking history at baseline, we divided participants into three categories: never-smokers, current smokers, or former smokers. We classified the baseline education status as low (less than 6 years), middle (6–12 years), and high (more than 12 years). Based on their marital status, we divided the participants into two categories: married and single (unmarried, divorced, and widowed).

Physical activity during leisure, work, and household tasks was measured with a Persian translation of the Modifiable Activity Questionnaire (MAQ) and calculated as metabolic equivalent of task (MET) minutes per week. For statistical purposes, participants were divided into two groups: less than 600 and equal to or greater than 600 Met-min/week [20].

Body weight and height were measured while the subject was standing, barefoot, and wearing light clothes. The body mass index (BMI) was computed by dividing weight (kg) by height squared (m^2). A non-stretched tape was used to measure the waist circumference at the narrowest position between the iliac crest and the lowest rib. No pressure was applied to the surface of the body. Using the residual method, the waist circumference adjusted for BMI (WC_{BMI}) was determined [21].

A mercury sphygmomanometer (Riester, Jungingen, Germany) was used to measure the systolic (SBP) and diastolic (DBP) blood pressures on the right arm while the subject was seated after 15 min of rest. The participant's blood pressure was determined by averaging the results of two blood pressure measures taken at 30-second intervals.

Details of the biochemical measurements in the TLGS samples have been described [22]. In brief, after a 12- to 14-hour overnight fast, blood sampling was done, and biochemical variables, including serum glucose, triglycerides, and high-density lipoprotein cholesterol (HDL-C), were measured at baseline and in all subsequent examinations.

Definition of T2D

According to the American Diabetes Association, T2D was diagnosed if fasting serum glucose was ≥126 mg/dL, 2-h serum glucose was ≥200 mg/dL or glucose-lowering medication was used [23].

Statistical analysis

The characteristics of the participants were examined across the MQI tertiles using analysis of variance (ANOVA) for continuous variables and chi-square for categorical variables.

The person-years for each participant were estimated from the baseline to the date of the T2D incidence, the date of the last follow-up, or the end date of the study. The event date of the occurrence of T2D was defined as the midpoint between the data of the follow-up examination during which the events were found for the first time and the most recent follow-up examination prior to diagnosis. The hazard ratio (HR) and 95% confidence interval (CI) for incident T2D were determined across the tertiles of the MQI, CQI, FQI, HPPQI, and macronutrient quantity using the Cox proportional hazards regression, with the first tertile serving as the reference group. The test for linear trend across the tertiles was performed by treating the median values of the tertiles as the continuous variable. In addition, the associations between dietary exposures as continuous variables and T2D were investigated. Age, sex, BMI, WC_{BMI}, family history of diabetes, education, smoking, physical activity, marital status, and anti-hypertensive medications were considered potential covariates according to the literature and known risk factors for T2D. The covariates were included in the statistical analysis if their associations with outcomes in the univariate model had a p-value < 0.2. Three statistical models were reported: unadjusted, sex- and BMI-adjusted, and multivariable-adjusted. The multivariable model accounted for sex, BMI (continuous), WC_{BMI}, family history of diabetes (yes/no), education (low, middle, and high), physical activity (< 600 and ≥ 600 Met-minute/week), energy intake (continuous), fasting glucose (continuous), triglycerides-to-HDL-C ratio (continuous), and antihypertensive medication (yes/no). Age was defined as a time scale. The Schoenfeld residual test verified the proportionality assumption for the main exposures.

The joint associations were investigated by joint classifications of the median of each macronutrient's quantity and quality into four levels of categorical variables. The HR (95% CI) was estimated for the four groups after adjusting for all potential covariates and using the low quantity, low quality group as the reference. Moreover, we performed a joint analysis by joint classification of fiber (median) and GI (median), defining the low-fiber, high-GI group as a reference. We also conducted a joint analysis by joint classification of fiber (< 25 and ≥ 25 g/d) and GI (≤ 55 and > 55) based on the literature [8, 24]. We determined *p-value* for interaction by including interaction terms in the multivariable model.

The SPSS statistical software (version 20; IBM Corp., Armonk, NY, USA) was used to perform the statistical analysis, and *p-vlaue* ≤ 0.05 was defined as statistically significant.

Results

Characteristics of the participants

The mean ± standard deviation for the baseline age of the participants was 38.5 ± 13.6 years, and 54.2% were women. Table 1 shows the characteristics of the participants based on the tertiles of the MQI. Age, BMI, waist circumference, energy, and protein proportion were significantly higher from tertile 1 to tertile 3. Furthermore, fasting glucose, SBP, DBP, and carbohydrate proportion were significantly higher in those within tertile 3, while fat proportion was lower than in tertiles 1 and 2. The education and marital status of the participants were also significantly different according to the tertiles.

Quality of macronutrients and risk of T2D

During a median follow-up of 8.6 years (interquartile range = 6.5, 9.5), 257 incidences of T2D occurred. Table 2 shows the associations between macronutrient quality indices and T2D incidence. Compared to the first tertile, the incidence of T2D was 27% (HR = 0.73, 95% CI = 0.54, 0.98) lower in the highest tertile of MQI after accounting for all covariates. MQI as a continuous variable demonstrated a marginally significant inverse association with T2D (HR = 0.96, 95% CI = 0.92, 1.00). After adjusting for all potential covariates, the risk of T2D was 29% (HR = 0.71, 95% CI = 0.51, 0.99) lower in those within tertile 3 of the CQI than in those in tertile 1. One unit increase in the CQI as a continuous variable was also associated with a lower risk of T2D in the fully adjusted model (HR = 0.96, 95% CI = 0.93, 1.00). Moreover, the risk of T2D was significantly lower in the second tertile of HPPQI compared to the first tertile in the unadjusted model and after adjusting for potential covariates. As a continuous variable, HPPQI was unrelated to T2D. No significant association was observed between FQI and T2D.

Supplemental Table 1 presents associations between the tertiles of the CQI components and T2D incidence. The incidence of T2D was 36% higher in participants at the highest tertile of GI compared with those at the lowest tertile (HR = 1.36, 95% CI = 1.01, 1.82) after accounting for sex and BMI. The association remained significant in the multivariable adjusted model (HR = 1.38, 95% CI = 1.02, 1.86). Furthermore, the hazard of T2D decreased significantly across the tertiles of fiber (p-trend = 0.001) in the multivariable adjusted model. The incidence of T2D was 33% lower (HR = 0.67, 95% CI = 0.48, 0.92) in the second tertile and 50% lower (HR = 0.50, 95% CI = 0.34, 0.75) in the third tertile compared to the first tertile of fiber intake. The ratio of carbohydrates from solid to total and the ratio of carbohydrates from whole grains to total grains were not significantly related to T2D.

Quantity of macronutrients and risk of T2D

Table 3 displays the T2D incidence according to the proportion of macronutrients. In the unadjusted model, those in the second and third categories of dietary carbohydrate intake had a lower incidence of T2D, with respective HRs of 0.57 (95% CI = 0.41, 0.78) and 0.68 (95% CI = 0.51, 0.91). After adjusting for all potential covariates, the inverse association became marginally significant for tertile 3 (HR = 0.74; 95% CI = 0.55, 1.00). Moreover, each 5% increase in the proportion of energy from carbohydrate intake was associated with a 10% (HR = 0.90, 95% CI = 0.82, 0.99) reduced risk of T2D in

Table 1 Baseline characteristics and macronutrient composition of the diet of the participants according to tertiles of the macronutrient quality index [1]

	Tertiles			*P*-value
	1	**2**	**3**	
Range	≤ 8	9–10	≥ 11	
No. of participants	1133	620	704	
Baseline characteristics				
Age, years	36.9 ± 13.6	38.0 ± 13.1	41.4 ± 13.5	< 0.001
Women, %	51.9	54.7	57.5	0.060
BMI, kg/m^2	26.3 ± 4.67	26.9 ± 4.83	27.5 ± 4.99	< 0.001
Waist circumference, Cm	87.8 ± 13.1	89.2 ± 13.6	90.5 ± 13.1	< 0.001
Smoking status, %	77.3	79.8	80.5	0.323
Never	13.9	12.6	10.8	
Current	8.8	7.6	8.7	
Former				
Education, %	11.7	13.1	17.0	0.023
Low	61.5	61.3	58.9	
Middle	26.8	25.6	24.0	
High				
Marital status	70.7	72.4	77.0	0.012
Married	29.3	27.6	23.0	
Single				
Physical activity < 600 Met-min/week	41.0	38.4	35.7	0.068
Family history type 2 diabetes, %	31.7	34.8	34.5	0.292
Fasting blood glucose, mg/dL	86.37 ± 8.54	86.7 ± 8.05	87.6 ± 9.20	0.052
Triglycerides-to-HDL-C ratio	1.51 ± 1.25	1.65 ± 1.32	1.60 ± 1.13	0.062
Systolic blood pressure, mmHg	110 ± 15.2	110 ± 15.7	113 ± 16.6	< 0.001
Diastolic blood pressure, mmHg	72.8 ± 10.2	72.8 ± 10.6	74.0 ± 10.8	0.043
Anti-hypertensive mediation, %	2.4	1.6	3.4	0.106
Dietary characteristics[2]				
Total energy intake, Kcal/d	2331 ± 752	2448 ± 780	2552 ± 798	< 0.001
Carbohydrate intake, % of energy	57.7 ± 6.00	58.0 ± 5.91	59.0 ± 6.68	< 0.001
Fat intake, % of energy	30.9 ± 5.59	30. 8 ± 5.91	30.0 ± 6.19	0.007
Protein intake, % of energy	13.9 ± 2.00	14.1 ± 2.28	14.7 ± 2.85	< 0.001

[1] Data are reported as mean ± standard deviation for continuous variable and as percentages for categorical variables. [2] Cumulative average intake.

the unadjusted model; however, this association was no longer significant after adjusting for potential covariates. The proportion of energy from protein and fat was not related to the T2D incident.

Joint associations of quality and quantity of macronutrients with T2D risk

When the joint associations of quantity and quality of macronutrients were analyzed (Table 4), participants with a high dietary proportion of carbohydrates (carbohydrate ≥ 58.5% of energy) and a high dietary carbohydrate quality (CQI ≥ 13) had a significantly lower incidence of T2D compared to those with a low quantity (carbohydrate < 58.5% of energy) and low quality (CQI ≤ 12) of dietary carbohydrate (HR = 0.66, 95% CI: 0.47, 0.93; p for interaction = 0.122).

The combined association of fiber and GI also showed that the incidence of T2D was significantly lower in those participants with a high fiber, low GI diet (fiber ≥ 21.4 g/d and GI ≥ 60.7), compared to those with a low-fiber, high-GI diet (HR = 0.70, 95% CI = 0.49, 1.00), but the interaction between the two variables was not significant (p for interaction = 0.803). The association was more evident when we defined high fiber and low GI based on dietary fiber intake ≥ 25 and GI ≤ 55. Based on the categorization, the hazard of T2D was 0.58 (95% CI = 0.38, 0.90) in participants with a high-fiber, low-GI diet than in those with a low-fiber, high-GI diet.

Discussion

In this prospective study, participants with the highest MQI scores had a 27% lower incidence of T2D compared to those with the lowest scores, after controlling for all potential confounding factors. Furthermore, among the MQI components, tertile 3 of the CQI and the middle tertile of the HPPQI exhibited 29% and 35% reduced incidences of T2D compared to the first tertile, respectively.

The MQI was introduced in 2022 to assess the overall quality of macronutrients in a diet by assigning equal weight to the quality of all three macronutrients [11].

Table 2 Hazard ratios and 95% confidence intervals for type 2 diabetes according to carbohydrate quality index, fat quality index, and healthy plate protein quality index [1, 2]

	Tertiles				Continuous	*P* value
	1	2	3	*P* trend		
Macronutrient quality index						
Median (range)	7 (≤ 8)	9 (9–10)	12 (≥ 11)			
Cases/populations	108/1133	69/620	80/704		257/2457	
Person-years	8788	4896	5557		19,241	
Incidence, per 1000	12.3	14.1	14.4		13.4	
Unadjusted	1.00	1.12 (0.83, 1.52)	0.88 (0.66, 1.18)	0.373	0.99 (0.95, 1.03)	0.675
Sex and BMI-adjusted	1.00	1.04 (0.77, 1.41)	0.75 (0.56, 1.01)	0.050	0.81 (0.62, 1.05)	0.109
Multivariable adjusted [2]	1.00	1.06 (0.78, 1.44)	0.73 (0.54, 0.98)	0.031	0.96 (0.92, 1.00)	0.058
Carbohydrate quality index range						
Median (range)	9 (≤ 10)	12 (11–14)	16 (≥ 15)			
Cases/populations	81/830	102/1030	74/597		257/2457	
Person-years	6355	8122	4764		19,241	
Incidence, per 1000	12.7	12.6	15.5		13.4	
Unadjusted	1.00	0.92 (0.69, 1.23)	0.87 (0.64, 1.20)	0.407	0.98 (0.95, 1.02)	0.270
Sex and BMI-adjusted	1.00	0.91 (0.68, 1.22)	0.80 (0.58, 1.10)	0.169	0.97 (0.94, 1.01)	0.127
Multivariable adjusted	1.00	0.88 (0.65, 1.18)	0.71 (0.51, 0.99)	0.042	0.96 (0.93, 1.00)	0.028
Fat quality index range						
Median (range)	1.19 (≤ 1.34)	1.46 (1.35–1.62)	1.84 (≥ 1.63)			
Cases/populations	81/818	81/819	95/820		257/2457	
Person-years	6417	6550	6274		19,241	
Incidence, per 1000	12.6	12.4	15.1		13.4	
Unadjusted	1.00	0.97 (0.71, 1.32)	1.01 (0.75, 1.36)	0.810	1.22 (0.89, 1.65)	0.213
Sex and BMI-adjusted	1.00	0.87 (0.64, 1.19)	0.88 (0.65, 1.19)	0.447	1.04 (0.76, 1.42)	0.831
Multivariable adjusted	1.00	0.88 (0.64, 1.20)	0.86 (0.63, 1.16)	0.363	1.04 (0.75, 1.44)	0.820
Healthy plate protein quality index						
Median (range)	0.76 (≤ 1.07)	1.38 (1.08–1.77)	2.44 (≥ 1.78)			
Cases/populations	94/819	67/819	96/819		257/2457	
Person-years	6155	6660	6425		19,241	
Incidence, per 1000	15.3	10.1	14.9		13.4	
Unadjusted	1.00	0.69 (0.50, 0.94)	0.83 (0.63, 1.11)	0.373	1.02 (1.00, 1.04)	0.066
Sex and BMI-adjusted	1.00	0.66 (0.48, 0.90)	0.74 (0.56, 1.00)	0.111	1.00 (0.98, 1.03)	0.764
Multivariable adjusted	1.00	0.65 (0.47, 0.89)	0.78 (0.58, 1.04)	0.211	1.01 (0.99, 1.03)	0.227

[1] Data are reported as hazard ratio (95% confidence interval). [2] Adjusted for sex, BMI (continuous), waist circumference adjusted for baseline BMI (continuous), family history diabetes (yes/no), education (<6, 6–12, and ≥12 years of education), physical activity (<600 and ≥600 metabolic equivalent task minutes/week), energy intake (continuous), fasting serum glucose (continuous), triglycerides to HDL-C ratio (continuous), and antihypertensive medication (yes/no). Age is considered as a time scale

The association of the MQI with T2D has not been previously investigated. The CQI reflects the overall quality of dietary carbohydrates by incorporating four distinct carbohydrate quality indicators [16]. To date, two investigations have examined the relationship between the CQI and T2D [12, 25]. A cross-sectional study of Korean adults revealed that the odds of T2D were not significantly different across quintiles of the CQI [25]. A prospective study in Chinese adults also found no significant association between the CQI and incident T2D in all the study participants, but age (p-value for interaction = 0.03) and education (p-value for interaction = 0.007) were suggested to modify the association. In that study, a 37% lower (95% CI = 20, 50%) incidence of T2D was reported for participants aged < 60 within the highest quintile than those in the lowest (p-trend = 0.001) over a mean follow-up of 10 years. The risk of T2D was also 54% lower (95% CI = 36, 66%) in quintile 5 of the CQI than quintile 1 in the strata of participants with middle school or above education (p-trend < 0.0001) [12]. In our study, despite the overall diabetes risk reduction in the middle and upper tertiles of the CQI (p-trend = 0.042), the reduction was only significant in those within the highest CQI (CQI ≥ 15).

When we examined the associations between the individual components of the CQI and T2D, we found that GI and fiber had significant associations. In the multivariable adjusted model, a 38% higher incidence of T2D was observed in the highest GI group (GI ≥ 63.5) than in the lowest GI group (GI ≤ 57.8). Also, the risk of T2D

Table 3 Hazard ratios and 95% confidences intervals for type 2 diabetes according to macronutrient content of diet using nutrient density model [1, 2]

	Tertiles				Per 5%	*P*-value
	1	2	3	*P* trend		
Carbohydrate (% of energy)						
Median (range)	52.7 (< 56)	58.4 (56-60.6)	63.5 (≥ 60.6)			
Case/population	96/819	62/819	99/819		257/2457	
Person-years	6334	6621	6286		19,241	
Incidence, per 1000	15.2	9.36	15.7		13.4	
Unadjusted	1.00	0.57 (0.41, 0.78)	0.68 (0.51, 0.91)	0.010	0.90 (0.82, 0.99)	0.027
Sex and BMI-adjusted	1.00	0.60 (0.43, 0.83)	0.72 (0.54, 0.96)	0.029	0.91 (0.83, 1.00)	0.061
Multivariable adjusted	1.00	0.68 (0.49, 0.95)	0.74 (0.55, 1.00)	0.050	0.98 (0.96, 1.00)	0.067
Fat (% of energy)						
Median	25.2 (≤ 28)	30.2 (28.1–32.5)	35.9 (≥ 32.5)			
Case/population	101/819	72/818	84/820		257/2457	
Person-years	6243	6683	6315		19,241	
Incidence, per 1000	16.2	10.8	13.3		257	
Unadjusted	1.00	0.98 (0.72, 1.32)	1.29 (0.96, 1.73)	0.095	1.07 (0.97, 1.19)	0.164
Sex and BMI-adjusted	1.00	0.99 (0.73, 1.34)	1.22 (0.91, 1.64)	0.202	1.06 (0.96, 1.17)	0.270
Multivariable adjusted	1.00	1.07 (0.79, 1.46)	1.15 (0.84, 1.56)	0.387	1.01 (0.99, 1.03)	0.262
Protein (% of energy)						
Median	12.2 (≤ 13.2)	14.0 (13.3–14.7)	15.9 (≥ 14.8)			
Case/population	72/818	82/820	103/819		257/2457	
Person-years	6270	6584	6386		19,241	
Incidence, per 1000	11.5	12.5	16.1		13.4	
Unadjusted	1.00	1.01 (0.73, 1.38)	1.28 (0.94, 1.72)	0.096	1.28 (1.00, 1.65)	0.050
Sex and BMI-adjusted	1.00	0.96 (0.70, 1.61)	1.19 (0.88, 1.61)	0.220	1.22 (0.95, 1.57)	0.126
Multivariable adjusted	1.00	1.05 (0.76, 1.45)	1.21 (0.89, 1.64)	0.210	1.03 (0.98, 1.09)	0.215

[1] Data are reported as hazard ratio (95% confidence interval). [2] Adjusted for sex, BMI (continuous), waist circumference adjusted for baseline BMI (continuous), family history diabetes (yes/no), education (<6, 6–12, and ≥12 years of education), physical activity (<600 and ≥600 metabolic equivalent task minutes/week), energy intake (continuous), fasting serum glucose (continuous), triglycerides to HDL-C ratio (continuous), and antihypertensive medication (yes/no). Age is considered as a time scale

Table 4 Joint association of quantity and quality of macronutrients in relation to the risk of type 2 diabetes [1]

	Hazard ratio (95% confidence interval)				*P* for interaction
	Low quantity-low quality	Low quantity-high quality	High quantity-low quality	High quantity-high quality	
Carbohydrate					
Case /population	72/734	56/494	63/631	66/598	
Multivariable adjusted [2]	1.00	0.82 (0.57, 1.18)	0.82 (0.58, 1.15)	0.66 (0.47, 0.93)	0.122
Fat					
Case /population	61/650	69/579	53/578	74/650	
Multivariable adjusted	1.00	0.93 (0.66, 1.31)	1.30 (0.89, 1.89)	1.12 (0.79, 1.60)	0.135
Protein					
Case /population	65/702	49/526	64/527	79/702	
Multivariable adjusted	1.00	0.93 (0.64, 1.35)	1.40 (0.99, 1.99)	0.93 (0.66, 1.29)	0.761
Fiber and glycemic index	**Low fiber-high GI**	**low fiber-low GI**	**High fiber-high GI**	**High fiber-low GI**	
Case /population	81/775	54/453	44/453	78/776	
Multivariable adjusted	1.00	1.04 (0.73, 1.48)	0.86 (0.57, 1.30)	0.70 (0.49, 1.00)	0.803
Case /population [3]	150/1419	24/209	54/553	29/276	
Multivariable adjusted	1.00	0.85 (0.54, 1.31)	0.73 (0.50, 1.08)	0.58 (0.38, 0.90)	

[1] Categorizations were made based on the median values of the variables in the study population as follows: carbohydrate ≥ 58.5% of energy (high carbohydrate quantity), CQI ≥ 13 (high carbohydrate quality), fat ≥ 30.2% of energy (high fat quantity), FQI ≥ 1.47 (high fat quality), protein ≥ 14% of energy (high protein quantity), HPPQI ≥ 1.39 (high protein quality), GI ≥ 60.7 (high GI diet), and fiber ≥ 21.4 g/d (high fiber diet). [2] Adjusted for sex, BMI (continuous), waist circumference adjusted for baseline BMI (continuous), family history diabetes (yes/no), education (< 6, 6–12, and ≥ 12 years of education), physical activity (< 600 and ≥ 600 metabolic equivalent task minutes/week), energy intake (continuous), fasting blood glucose (continuous), triglycerides to HDL-c ratio (continuous), and antihypertensive medication (yes/no). Age is considered as a time scale. [3] Categorization based on intake of ≥ 25 g/d fiber for high fiber and value of < 55 for low GI diet

was 33% (95% CI=8, 52%) lower in the middle tertile of fiber intake compared to the lowest tertile and 50% (95% CI=25, 66%) lower in the upper tertile of fiber intake compared to the middle tertile (p-trend=0.001). Meta-analyses revealed a positive association between GI and T2D; however, the certainty of the evidence was rated as low to very low, indicating that additional research is required [8, 9]. On the basis of 13 prospective studies, it has been estimated that those with the highest GI diets have a 13% (95% CI=3, 24%) higher incidence of T2D than those with the lowest GI diets. In addition, meta-analyses provided evidence of moderate certainty that a reduction in the incidence of T2D is associated with higher intakes of total dietary fiber [8, 9]. The risk of T2D was estimated to be 16% (95% CI=10, 22%) lower in participants with the highest dietary fiber intake than those with the lowest intake, using data from 17 prospective studies [8]. The risk reduction was also estimated to be 9% (95% CI=4, 13%) per 10 g/d total fiber intake [9]. According to a meta-analysis, the protective association of dietary fiber is observed when daily fiber intake is at least 25–29 g, and higher intakes might confer greater benefits [8]. In our study, the inverse association was observed in the second fiber tertile with a median fiber intake of 21.4 g, whereas the lowest risk was in the highest fiber tertile with a median fiber intake of 31 g/d. In addition to the amount of fiber consumed, its dietary sources may also be important. Evidence strongly supports the inverse association between cereal fiber and T2D, whereas fruit fiber and vegetable fiber were not significantly associated with the disease [9]. A joint analysis of fiber and GI in our study showed that the beneficial association of a high-fiber diet is greatest when the GI of the diet is low. This joint association between fiber and GI became more apparent when we categorized fiber and GI based on dietary intakes of 25 g and 55, respectively. The incidence of T2D was 42% (95% CI=10, 62%) lower in participants with a high fiber (fiber≥25 g/d), low GI diet (<55) than those with a low fiber, high GI diet.

Meta-analyses on clinical trials demonstrated that higher compared to lower intakes of dietary fiber decreased body weight (mean difference (95% CI) = -0.37 (-0.63, -0.11) kg, n=27 studies; high certainty), total cholesterol (-0.15 (-0.22, -0.07) mmol/L, n=36 studies; moderate certainty), and systolic blood pressure (-1.27 (-2.5, -0.04) mm Hg, n=15 studies; moderate certainty); the risk factors for cardio-metabolic diseases [8]. Although the reported effect sizes for mean differences between higher and lower dietary intakes are smaller than the minimal clinically significant estimates [26], the combined beneficial effects of dietary fiber on various cardiometabolic risk factors may reduce the incidence of T2D.

In this study, we could not find a significant association between the ratio of carbohydrates from whole grains/total grains, although the hazard of T2D was lower in tertiles 2 (HR=0.77) and 3 (HR=0.86). A previous prospective investigation in the TLGS participants found a decreased risk of T2D (HR=0.80, 95% CI=0.69, 0.93) when replacing refined grains with whole grains in an isocaloric diet [27]. A meta-analysis using data from 8 prospective studies revealed a lower risk of T2D in those with the highest versus lowest categories of whole cereals (HR=0.67, 95% CI=0.58, 0.78); however, the evidence was of low certainty [8]. However, an umbrella review including data from 12 studies suggests a 13% (95% CI=7, 18%) reduction in the risk of T2D per 30 g/d intake of whole grains with the high certainty of the evidence [9]. The differences between the extreme tertiles of whole grains/total grains may not be high enough in our study population to observe a significant association.

In the present study, participants within the middle tertiles of carbohydrate proportion had a 32% (95% CI=5, 51%) lower incidence of T2D than those within the lowest proportion. The T2D incidence was also lower in tertile 3 compared to tertile 1, but the association became marginally significant in the multivariable adjusted model. The most recent meta-analysis on the association between carbohydrates and the development of T2D reported no significant findings based on extreme quantile analysis and a 10% increase in carbohydrates. However, a dose-response meta-analysis of 13 prospective studies revealed a J-shaped association between percentage of carbohydrate and risk of T2D, with the lowest risk at 50% and an increasing risk at more than 70%. Nonetheless, significant variations in risk estimation were observed based on geographic location. In western populations, carbohydrate proportions showed no significant association with T2D, whereas in Asian populations, the risk increased substantially when carbohydrate proportions exceeded 70% [7]. Differences in the quantity and quality of dietary carbohydrates can account for variations in the association between carbohydrates and the risk of T2D across populations.

Our study found that fat quantity and quality were not significantly associated with T2D. Furthermore, total protein intakes were not significantly related to T2D, while those within the second tertile of HPPQI had a significantly lower hazard of T2D than those with the lowest. In addition, no significant association was observed for the combined effects of quantity and quality for fat and protein. In accordance with our findings, an umbrella review indicated no significant associations between total fat intakes and their different subtypes, including saturated fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids [9]. Previous research on the relationship between dietary protein and T2D has focused on total protein intake as well as protein from animal and plant sources. In contrast to our findings, a meta-analysis published in 2019 suggested, respectively, 9% (95% CI=4, 13%) and 12% (95% CI=8, 17%) higher T2D incidents per 5% increase in total protein and animal protein intake. However, all but one of the studies were conducted on Western populations; therefore, it is uncertain whether the association holds true for non-Western populations [6]. HPPQI is developed according to international dietary guidelines for dietary protein quality, and the healthy protein group consists of both animal (seafood and poultry) and plant (nuts and pulses) protein sources [11]. Since HPPQI indicates the quality of dietary protein extends beyond animal and plant sources [28], more studies are necessary to examine the association between HPPQI and the development of T2D.

The present study's strengths include a prospective investigation with a relatively long follow-up period, repeated dietary assessments using a reliable FFQ, identification of T2D based on biochemical measurements, and consideration of both the quantity and quality of macronutrients. The study's limitations include its limited generalizability to other populations, the possibility of reporting bias for dietary assessments due to recall bias and social desire [29], and concern for residual and unmeasured confounding factors despite adjusting for multiple known and suspected T2D risk factors.

Conclusions

In this study, participants in the highest tertile of MQI and CQI, as well as those in the middle tertile of HPPQI, had a lower incidence of T2D than those in the lowest tertile. Among the CQI components, GI and fiber were significantly related to the T2D incidence. The T2D incidence was significantly lower in the middle tertile of carbohydrates than in the first. The hazard for T2D was significantly lower in participants on the high fiber (≥25 g), low GI diet (≤55) versus participants on the low fiber, high GI diet, and in participants on the high quantity (≥58.5% of energy) and high quality (≥13) of dietary carbohydrates than in those with a low quantity, low quality of dietary carbohydrates.

Abbreviations

T2D	Type 2 Diabetes
MQI	Macronutrient Quality Index
CQI	Carbohydrate Quality Index
FQI	Fat Quality Index
HPPQI	Healthy Plate Protein Quality Index
TLGS	Tehran Lipid and Glucose Study
FFQ	Food Frequency Questionnaire
GI	Glycemic Index
BMI	Body Mass Index
WC_{BMI}	Waist Circumference adjusted for BMI
SBP	Systolic Blood Pressures
DBP	Diaystolic Blood Pressures
HDL-C	High Density Lipoprotein Cholesterol
ANOVA	Analysis of Variance
HR	Hazard Ratio
CI	Confidence Interval

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

NM: contributed to the conception and design of the study, conducted statistical analyses, and drafted the manuscript. ZK and ZB: Contributed to the conception and design of the study and helped in interpretation and preparation of the manuscript. PM and FA: Conceptual design of the study and contributed to the critical revision of the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study's design was granted approval by the research ethics committees of the Research Institute for Endocrine Sciences at Shahid Beheshti University of Medical Sciences. Everyone who participated in the study provided informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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