Dietary Glycemic Load and Index and Risk of Coronary Heart Disease in a Large Italian Cohort

The EPICOR Study

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Background: Dietary glycemic load (GL) and glycemic index (GI) in relation to cardiovascular disease have been investigated in a few prospective studies with inconsistent results, particularly in men. The present EPICOR study investigated the association of GI and GL with coronary heart disease (CHD) in a large and heterogeneous cohort of Italian men and women originally recruited to the European Prospective Investigation into Cancer and Nutrition study.

Methods: We studied 47 749 volunteers (15 171 men and 32 578 women) who completed a dietary questionnaire. Multivariate Cox proportional hazards modeling estimated adjusted relative risks (RRs) of CHD and 95% confidence intervals (CIs).

Results: During a median of 7.9 years of follow-up, 463 CHD cases (158 women and 305 men) were identified. Women in the highest carbohydrate intake quartile had a significantly greater risk of CHD than did those in the lowest quartile (RR, 2.00; 95% CI, 1.16-3.43), with no association found in men ($P = .04$ for interaction). Increasing carbohydrate intake from high-GI foods was also significantly associated with greater risk of CHD in women (RR, 1.68; 95% CI, 1.02-2.75), whereas increasing the intake of low-GI carbohydrates was not. Women in the highest GL quartile had a significantly greater risk of CHD than did those in the lowest quartile (RR, 2.24; 95% CI, 1.26-3.98), with no significant association in men ($P = .03$ for interaction).

Conclusion: In this Italian cohort, high dietary GL and carbohydrate intake from high-GI foods increase the overall risk of CHD in women but not men.

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A DIET WITH HIGH LEVELS OF carbohydrates increases plasma triglyceride levels and reduces high-density lipoprotein (HDL) cholesterol levels,[1-3] in addition to increasing blood glucose and insulin levels,[4] thereby creating a profile expected to increase the risk of cardiovascular disease (CVD). Moreover, postprandial glycemia is now emerging as an independent risk factor for CVD in diabetic and nondiabetic individuals.[5]

Carbohydrates vary in their ability to increase postprandial blood glucose levels. The glycemic index (GI), introduced by Jenkins et al in 1981,[6] is a measure of how much a standard quantity of food raises blood glucose levels compared with a standard quantity of glucose or white bread. The GI is thus an indicator of how quickly a carbohydrate can be absorbed as glucose. Because the amount of carbohydrate in a food (or overall diet) can vary and have a variable influence on the postprandial glycemic response, the glycemic load (GL) measure is also used. The GL is the product of the GI of a food item and the available carbohydrate content of that item.

Short-term intervention studies on overweight and hyperlipidemic subjects show that low-GL diets reduce risk factors for CVD,[7] whereas results from prospective studies suggest that low-GL diets can lower risk factors in healthy subjects.[8,9] With regard to the association between dietary GI/GL and CVD, a recent systematic review on associations between dietary factors and coronary heart disease (CHD) concluded that there was strong evidence of a causal relation between high GI/GL foods and CHD.[10] However, only a few prospective studies have been performed, and these produced inconsistent results, particularly in men. In the Nurses' Health Study, high GI and GL were associated with CHD[8]; a more recent study found that high GI and GL were associated with CVD in Dutch women.[9] In both studies,[8,9] the risk was greater in over-

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weight women. By contrast, neither dietary GI nor GL was associated with CHD in cohort studies on Dutch[11] and Swedish[12] men.

The aim of the present study was to provide further information on the relation of dietary GL and GI to CHD risk in a large and geographically heterogeneous cohort of Italian men and women.

METHODS

SUBJECTS

EPICOR is a prospective investigation into the causes of CVD and is being performed on Italian cohorts recruited from 1993 to 1998 as part of the European Prospective Investigation into Cancer and Nutrition (EPIC).[13,14] A total of 47 749 volunteers (15 171 men and 32 578 women) were recruited to EPICOR from 5 centers, including 2 in northern Italy (Varese [n=12 083] and Turin [n=10 604]), 1 in central Italy (Florence [n=13 597]), and 2 in southern Italy (Ragusa [n=6403] and Naples [n=5062]). Only women were recruited in Naples.[14]

We then excluded 785 subjects with prevalent CVD at recruitment, 670 who were unavailable for follow-up at time 0, 928 who did not complete dietary or lifestyle questionnaires, and 825 in whom the ratio of total energy intake to basal metabolic rate was at either extreme of the distribution (cutoffs, first and half percentiles). We also excluded those who were being treated for diabetes (402 subjects) and those with missing values of confounding variables, including alcohol consumption, body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), smoking, hypertension, physical activity, and education (7 subjects). Thus, analyses were conducted on 44 132 subjects (13 637 men [age range, 35-64 years] and 30495 women [age range, 35-74 years]).

BASELINE MEASUREMENTS

Dietary Information

Diet was assessed with the use of semiquantitative food-frequency questionnaires designed to capture local dietary habits during the previous year. Three questionnaires were developed, including 1 for the northern and central recruitment centers of Varese, Turin, and Florence, 1 for Ragusa, and 1 for Naples. The north-central questionnaire was self-administered; the southern questionnaires were administered by interviewers. All questionnaires were validated.[15] We used specially developed software[16] to estimate the frequency of consumption and average daily consumption of food items from questionnaire responses. These items were then linked to the Italian Food Tables[17] to obtain estimates of nutrient consumption and energy intake.

The GI of food items containing available carbohydrates was estimated by a standardized procedure taking local culinary practices into account and using glucose as the reference food. Briefly, 1123 members (328 men and 795 women) of the Varese EPIC subcohort underwent a 24-hour dietary recall interview,[18] from which 36 436 food items were identified, 16 762 of which contained carbohydrates. After screening for repetitions, 767 carbohydrate-containing food items were identified. The items contributing 95% of total carbohydrate intake were then identified and, in addition, closely similar food items were collapsed to single categories. From literature searches, published GI values of these food categories (or of closely similar foods) were identified, the main sources being the international GI tables[19] and the official Web site of the Glycemic Index of the University of Sydney, Sydney, Australia (http://www.glycemicindex.com). For a total of 159 food items consisting of local commercial foods (eg, biscuits, bread, and pasta) not obtainable from published sources and foods for which the GI varies substantially with preparation method (eg, boiled rice, risotto, and baked rice), GIs were measured directly at the Department of Public Health, Parma University, using a standardized protocol.[20,21] For commercial foods, best-selling brands were analyzed.

The average dietary GI for each volunteer was calculated as the sum of the GIs of each food item consumed, multiplied by the average daily amount consumed and the percentage of carbohydrate content, all divided by the total daily carbohydrate intake. The GL was calculated similarly except that there was no division by total carbohydrate intake.

We also divided carbohydrate intake between high- and low-GI foods, choosing a GI of 57 as the cutoff. Adoption of this cutoff allowed high- and low-GI foods each to contribute 50% to total carbohydrate intake.

For study participants, the main sources of carbohydrates from high-GI foods were bread (60.8%), sugar or honey and jam (9.1%), pizza (5.4%), and rice (3.2%); the main sources of carbohydrates from low-GI foods were pasta (33.3%), fruit (23.5%), and cakes (18.6%).

Additional Variables

A standardized lifestyle questionnaire was completed by each participant to collect detailed information on reproductive and medical history, physical activity, alcohol consumption, smoking, education, and other socioeconomic variables. Weight and height were measured at enrollment. Blood pressure was measured using standardized procedures.[22] Hypertension was defined as a systolic pressure of at least 140 mm Hg or a diastolic pressure of at least 90 mm Hg. Persons taking antihypertensive medication were also considered hypertensive. Persons reporting a history of treatment for diabetes mellitus at baseline were considered diabetic.

MAJOR CARDIOVASCULAR EVENT ASCERTAINMENT AND VERIFICATION

We had access to mortality and hospital discharge databases and performed record linkage to the EPICOR database, mainly via Social Security numbers, after quality control of the database information. For deceased subjects, death certificates were retrieved, which reported specific causes of death and concomitant diseases coded according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*). We also had access to clinical records. At baseline, participants gave informed consent to use clinical data for research.

Suspected coronary deaths were identified from mortality files when *ICD-10* codes I20 through I25, R96, and R98 were reported as the underlying cause of death, and when *ICD-10* codes E10 through E14, I50, and I70 were reported as the underlying cause in association with *ICD-10* codes I20 through I25 as associated conditions. Fatal CHD was assigned after verification against hospital discharge and clinical records.

Persons with suspected CHD were identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* codes 410 through 414 or procedure codes for coronary revascularization (eg, percutaneous transluminal coronary angioplasty and coronary artery bypass surgery) on hospital discharge forms. Clinical records were always retrieved to verify CHD, which was considered verified when acute myocardial infarction, acute coronary syndrome, or coronary revascularization was present, backed up by information on onset symptoms, levels of cardiac enzymes and troponins, and electrocar-

Table 1. Baseline Distribution of Nutrients and Cardiovascular Risk Factors by Quartiles of Energy-Adjusted GL in EPICOR Women[a]

Variable	Quartiles of Energy-Adjusted GL			
	1	2	3	4
No. of subjects	6898	7931	8108	7562
Age, y	49.9 (0.1)	50.4 (0.1)	50.3 (0.1)	50.1 (0.1)
Overall GI	51.7 (0.03)	52.7 (0.03)	53.8 (0.03)	55.4 (0.03)
GL, g/d	122.8 (0.1)	145.5 (0.1)	160.9 (0.1)	185.8 (0.1)
Protein intake, g/d	100.2 (0.3)	85.9 (0.3)	82.7 (0.3)	88.0 (0.3)
Fat intake, g/d	103.0 (0.3)	83.9 (0.3)	77.3 (0.3)	76.3 (0.3)
Saturated fat intake, g/d	37.1 (0.1)	29.8 (0.1)	27.2 (0.1)	26.7 (0.1)
Monounsaturated fat intake, g/d	48.5 (0.1)	39.5 (0.1)	36.2 (0.1)	35.3 (0.1)
Polyunsaturated fat intake, g/d	11.7 (0.1)	9.8 (0.04)	9.4 (0.04)	9.8 (0.04)
Carbohydrate intake, g/d	230.0 (1.0)	239.0 (0.9)	264.9 (0.9)	335.2 (0.9)
Carbohydrates from high-GI food, g/d	95.2 (0.6)	106.7 (0.5)	128.7 (0.5)	189.9 (0.6)
Carbohydrates from low-GI food, g/d	134.8 (0.6)	132.3 (0.6)	136.2 (0.6)	145.2 (0.6)
Starch intake, g/d	127.6 (0.7)	138.0 (0.7)	159.9 (0.7)	220.1 (0.7)
Sugar intake, g/d	102.1 (0.5)	100.8 (0.5)	104.8 (0.5)	114.9 (0.5)
Fiber intake, g/d	21.1 (0.1)	20.9 (0.1)	22.4 (0.1)	27.5 (0.1)
Energy intake, kcal/d[b]	2194 (7)	1998 (7)	2023 (7)	2300 (7)
Alcohol intake, % of subjects				
Abstainers	11.9	15.7	18.8	21.6
≤12 g/d	51.1	59.5	63.2	65.4
>12 to 24 g/d	19.6	16.7	13.0	9.1
>24 g/d	17.5	8.2	5.1	4.0
Hypertension, % of subjects	35.7	36.7	36.8	36.4
BMI	26.0 (0.1)	25.6 (0.1)	25.5 (0.1)	25.6 (0.1)
Physical activity, % of subjects				
Inactive	29.3	32.8	36.4	46.2
Moderately inactive	42.5	41.6	40.4	32.8
Moderately active	16.6	16.0	14.9	12.5
Active	11.6	9.7	8.3	8.6
Education ≥8 y, % of subjects	49.8	52.9	52.5	53.5
Smoking, % of subjects				
Current	27.7	24.4	25.7	27.3
Former	21.7	20.6	19.6	18.8
Never	50.6	55.0	54.8	53.9

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GI, glycemic index; GL, glycemic load.
[a]Unless otherwise indicated, data are expressed as mean (SE). Because of rounding, percentages may not total 100.
[b]Excludes alcohol.

diographic data coded according to the Minnesota Code.[23] Cases were cross-checked with mortality files to identify fatal and nonfatal cases (the later defined as alive 28 days after diagnosis).

Persons with CHD at study entry were identified from the baseline questionnaire, from linkage with hospital discharge records, or by direct examination of clinical records. These cases were excluded. Major CHD prevented recruitment at the Naples center.

FOLLOW-UP

The date of the end of follow-up varied by center because hospital discharge file availability for updating varied as follows: January 1, 2002, for Varese; December 31, 2002, for Ragusa; December 31, 2003, for Florence and Naples; and December 31, 2004, for Turin. Median overall follow-up was 7.9 years (347 465 person-years), and only 181 participants were lost to follow-up.

STATISTICAL ANALYSIS

We used multivariate Cox proportional hazards modeling to estimate the relative risks (RRs) of developing CHD in relation to carbohydrate intake; carbohydrate intake from high- and low-GI foods, starch, and sugar; and dietary GI and GL, with stratification by center to control for center effects (particularly differing follow-up). In all models, age was the primary time variable. Dietary variables were categorized in quartiles defined on the whole cohort and were adjusted for total energy intake using the residual method.[24] The following 2 models are presented: one adjusted only for age, the other (multivariate) also adjusted for non-alcohol energy intake, BMI, fiber intake (in grams per day), hypertension (yes or no), smoking (never, former, or current), education (<8 or ≥8 years), alcohol intake (abstainer, ≤12 g/d, >12 g/d, or >24 g/d), and physical activity (inactive, moderately inactive, moderately active, or active). When the multivariate model was used to examine GL and GI, it was also adjusted for saturated fat intake (in grams per day) to take into account the possible confounding effect of the inverse relation of animal fat to GI/GL. In general, adjustment variables were chosen on the basis of their known associations with dietary GI/GL and a priori knowledge of CVD risk factors.

To test for differences between sexes, we combined men and women and added an interaction term multiplying the sex variable (0 for men and 1 for women) by continuous dietary variables. To assess the significance of the interaction, we used a likelihood ratio test that compared the model that included the multiplication term and the model that did not include it.[25]

To assess the significance of trends, we used the likelihood ratio test between models that included and omitted the quartile variable. We used commercially available statistical software for all computations (Stata, version 7.0; StataCorp, College Station, Texas).

Table 2. Baseline Distribution of Nutrients and Cardiovascular Risk Factors by Quartiles of Energy-Adjusted GL in EPICOR Men[a]

Variable	Quartiles of Energy-Adjusted GL			
	1	2	3	4
No. of subjects	4137	3104	2927	3472
Age, y	49.7 (0.1)	49.6 (0.1)	49.3 (0.1)	49.4 (0.1)
Overall GI	52.2 (0.04)	53.1 (0.1)	53.8 (0.1)	55.2 (0.04)
GL, g/d	118.0 (0.2)	145.3 (0.2)	160.9 (0.3)	189.0 (0.2)
Protein intake, g/d	114.7 (0.5)	100.4 (0.5)	97.6 (0.5)	101.8 (0.5)
Fat intake, g/d	112.6 (0.4)	94.3 (0.5)	88.4 (0.5)	86.9 (0.5)
Saturated fat intake, g/d	39.7 (0.2)	32.6 (0.2)	30.1 (0.2)	28.8 (0.2)
Monounsaturated fat intake, g/d	53.9 (0.2)	45.4 (0.3)	42.6 (0.3)	41.7 (0.2)
Polyunsaturated fat intake, g/d	12.9 (0.1)	11.1 (0.1)	10.7 (0.1)	11.2 (0.1)
Carbohydrate intake, g/d	287.4 (1.5)	300.9 (1.7)	324.5 (1.7)	395.5 (1.6)
Carbohydrates from high-GI food, g/d	127.6 (0.9)	143.0 (1.1)	163.6 (1.1)	228.0 (1.0)
Carbohydrates from low-GI food, g/d	159.9 (1.0)	158.0 (1.1)	160.9 (1.2)	167.5 (1.1)
Starch intake, g/d	182.3 (1.2)	193.3 (1.3)	213.2 (1.4)	271.7 (1.3)
Sugar intake, g/d	104.9 (0.7)	107.4 (0.8)	111.1 (0.8)	123.5 (0.8)
Fiber intake, g/d	23.0 (0.2)	24.0 (0.2)	26.3 (0.2)	35.1 (0.2)
Energy intake, kcal/d[b]	2562 (11)	2387 (12)	2409 (13)	2677 (12)
Alcohol intake, % of subjects				
Abstainers	1.6	2.6	3.8	7.9
≤12 g/d	18.3	32.4	44.5	54.1
>12 to 24 g/d	17.2	24.2	22.5	19.8
>24 g/d	62.9	40.6	29.2	18.2
Hypertension, % of subjects	47.5	42.4	40.8	37.8
BMI	26.9 (0.1)	26.5 (0.1)	26.4 (0.1)	26.4 (0.1)
Physical activity, % of subjects				
Inactive	11.8	13.0	12.2	15.3
Moderately inactive	36.6	36.7	36.0	35.2
Moderately active	24.0	23.5	24.4	22.3
Active	27.7	26.7	27.4	27.2
Education ≥8 y, % of subjects	40.6	40.2	40.5	46.2
Smoking, % of subjects				
Current	28.0	26.6	28.2	30.6
Former	28.9	31.6	30.4	28.6
Never	43.2	41.9	41.4	40.8

Abbreviations: See Table 1.
[a]Unless otherwise indicated, data are expressed as mean (SE). Because of rounding, percentages may not total 100.
[b]Excludes alcohol.

RESULTS

During follow-up, 463 CHD cases (305 men and 158 women) were identified. Incidence of CHD was higher in Turin (161 cases per 87 214 person-years), Varese (96 per 72 804 person-years), and Florence (120 per 104 028 person-years) than the southern centers of Naples (46 per 41 116 person-years) and Ragusa (40 per 42 295 person-years).

Table 1 shows the baseline characteristics of women by quartiles of energy-adjusted dietary GL. Mean dietary GL increased by approximately 50% from the lowest to the highest quartile, whereas mean dietary GI ranged from 51.7 in the lowest to 55.4 in the highest quartile. Women in the highest quartile of dietary GL consumed more carbohydrates (especially more carbohydrates from high-GI foods) and more fiber but less fat and alcohol than did those in the lowest quartile. Women in the highest dietary GL quartile were also more educated.

Table 2 shows baseline characteristics of men by quartiles of energy-adjusted dietary GL. As in women, dietary GL in men increased approximately 50% from the lowest to the highest quartile, whereas mean dietary GI ranged from 52.2 in the lowest to 55.2 in the highest quartile. Men in the highest GL quartile consumed less fat, less alcohol, more carbohydrates (especially from high-GI foods), and more fiber than did those in lower quartiles and were also more educated, smoked more, and a had slightly lower BMI. Men in the highest GL quartile also had hypertension less often, a trend not observed in women.

Table 3 shows age-adjusted and multivariate RRs for CHD in women by quartiles of dietary variables. Women in the highest carbohydrate intake quartile had a significantly greater risk of CHD than did those in the lowest (RR, 2.00; 95% CI, 1.16-3.43, multivariate model; $P=.02$ for trend). We also found that increasing carbohydrate intake from high-GI foods was significantly associated with increasing CHD risk (RR, 1.68; 95% CI, 1.02-2.75 in the highest quartile, multivariate model; $P=.04$ for trend), whereas increasing the carbohydrate intake from low-GI foods was not.

Women in the second quartile of dietary GI had a significantly greater risk of CHD than did those in the lowest quartile, whereas the association was not significant in the other quartiles and there was no dose-response relationship ($P=.46$ for trend). Women in the highest di-

Table 3. Risk of Coronary Heart Disease in Women by Increasing Quartiles of Carbohydrate, High- and Low-GI Carbohydrate, Starch, and Sugar Intake and Dietary GI and GL[a]

	Quartiles				*P* Value for Trend[b]
	1	2	3	4	
Carbohydrates					
No. of cases	20	43	46	49	
Mean intake, g/d	233.9	273.7	299.3	337.8	
Age-adjusted RR (95% CI)	1 [Reference]	1.74 (1.02-2.96)	1.82 (1.08-3.09)	1.95 (1.15-3.33)	.02
Multivariate risk (95% CI)[c]	1 [Reference]	1.79 (1.05-3.05)	1.89 (1.11-3.22)	2.00 (1.16-3.43)	.02
Carbohydrates from high-GI food					
No. of cases	26	39	45	48	
Mean intake, g/d	88.0	124.3	151.0	201.3	
Age-adjusted RR (95% CI)	1 [Reference]	1.29 (0.79-2.12)	1.48 (0.91-2.41)	1.75 (1.07-2.88)	.02
Multivariate risk (95% CI)[c]	1 [Reference]	1.28 (0.77-2.10)	1.44 (0.88-2.35)	1.68 (1.02-2.75)	.04
Carbohydrates from low-GI food					
No. of cases	35	44	39	40	
Mean intake, g/d	101.5	132.7	154.9	192.3	
Age-adjusted RR (95% CI)	1 [Reference]	0.93 (0.60-1.45)	0.81 (0.51-1.27)	0.92 (0.58-1.46)	.61
Multivariate risk (95% CI)[c]	1 [Reference]	0.96 (0.61-1.50)	0.87 (0.55-1.38)	0.99 (0.62-1.57)	.87
Starch					
No. of cases	27	45	47	39	
Mean intake, g/d	120.6	162.4	190.1	237.6	
Age-adjusted RR (95% CI)	1 [Reference]	1.57 (0.98-2.54)	1.67 (1.03-2.69)	1.43 (0.85-2.40)	.19
Multivariate risk (95% CI)[c]	1 [Reference]	1.57 (0.97-2.54)	1.70 (1.05-2.75)	1.40 (0.83-2.35)	.21
Sugars					
No. of cases	33	43	36	46	
Mean intake, g/d	71.5	95.4	114.3	152.1	
Age-adjusted RR (95% CI)	1 [Reference]	0.95 (0.60-1.50)	0.77 (0.48-1.25)	1.02 (0.64-1.62)	.91
Multivariate risk (95% CI)[c]	1 [Reference]	1.01 (0.64-1.60)	0.85 (0.52-1.38)	1.10 (0.69-1.76)	.83
GI					
No. of cases	32	49	31	46	
Mean	49.9	52.6	54.3	57.1	
Age-adjusted RR (95% CI)	1 [Reference]	1.59 (1.01-2.48)	0.98 (0.60-1.61)	1.47 (0.93-2.31)	.37
Multivariate risk (95% CI)[c,d]	1 [Reference]	1.63 (1.04-2.55)	1.00 (0.61-1.65)	1.42 (0.90-2.25)	.46
GL					
No. of cases	21	38	49	50	
Mean, g/d	122.8	145.5	160.9	185.8	
Age-adjusted RR (95% CI)	1 [Reference]	1.51 (0.89-2.57)	1.88 (1.13-3.15)	1.97 (1.17-3.32)	.008
Multivariate risk (95% CI)[c,d]	1 [Reference]	1.63 (0.95-2.81)	2.08 (1.22-3.56)	2.24 (1.26-3.98)	.005

Abbreviations: CI, confidence interval; GI, glycemic index; GL, glycemic load; RR, relative risk.
[a] Energy adjusted by residual method.
[b] By the interquartile test for trend.
[c] Stratified by center and adjusted for nonalcohol energy intake, hypertension (yes or no), smoking (never, former, or current), education (<8 or ≥8 y), categories of alcohol intake (abstainer, ≤12 g/d, >12 g/d, or >24 g/d), body mass index, fiber intake (in grams per day), and physical activity (inactive, moderately inactive, moderately active, or active).
[d] Adjusted also for saturated fat intake.

etary GL quartile had a significantly greater risk of CHD than did those in the lowest quartile (RR, 2.24; 95% CI, 1.26-3.98, multivariate model; $P=.005$ for trend).

Table 4 shows crude and adjusted RRs for CHD in men by quartiles of dietary variables. No significant association of any of these variables with CHD was found.

When we excluded the 2.9% of participants receiving cholesterol-lowering drugs, the results were closely similar to those reported for both sexes (data not shown).

Associations between CHD and dietary GL and carbohydrates differed significantly between men and women ($P=.03$ for interaction for GL; $P=.04$ for interaction for carbohydrates). Interactions of GI and carbohydrates from high- and low-GI foods, starch, and sugars with sex were not significant.

Associations between dietary GL and CHD did not change with BMI category (<25 or ≥25) in either sex (data not shown), although there was insufficient statistical power to detect a supposed interaction.

COMMENT

This is, to our knowledge, the first prospective study to examine the effect of a high glycemic diet on CHD risk in men and women within a single Italian cohort. We found that a high dietary GL was associated with increased CHD risk in women but not men, whereas dietary GI had little or no influence on CHD for either sex. The role of carbohydrates as a risk factor for CHD in women was found to depend on carbohydrate type, with an increased association for carbohydrate intake from high-GI foods but no association for carbohydrate intake from low-GI foods. Thus, a high consumption of car-

Table 4. Risks of Coronary Heart Disease in Men by Increasing Quartiles of Carbohydrate, High- and Low-GI Carbohydrate, Starch, and Sugar Intake and Dietary GI and GL[a]

	Quartile				*P* Value for Trend[b]
	1	2	3	4	
Carbohydrates					
No. of cases	105	59	75	66	
Mean intake, g/d	224.9	273.5	300.0	343.7	
Age-adjusted RR (95% CI)	1 [Reference]	0.80 (0.58-1.11)	1.14 (0.84-1.53)	0.85 (0.62-1.17)	.72
Multivariate risk (95% CI)[c]	1 [Reference]	0.88 (0.63-1.22)	1.24 (0.90-1.70)	0.91 (0.64-1.30)	.91
Carbohydrates from high-GI food					
No. of cases	85	71	72	77	
Mean intake, g/d	82.4	124.3	151.5	209.0	
Age-adjusted RR (95% CI)	1 [Reference]	1.03 (0.75-1.41)	1.05 (0.77-1.44)	1.00 (0.72-1.39)	.95
Multivariate risk (95% CI)[c]	1 [Reference]	1.05 (0.76-1.45)	1.08 (0.78-1.49)	0.97 (0.70-1.36)	.94
Carbohydrates from low-GI food					
No. of cases	109	63	66	67	
Mean intake, g/d	92.2	132.1	154.9	198.1	
Age-adjusted RR (95% CI)	1 [Reference]	0.86 (0.63-1.17)	0.95 (0.70-1.29)	0.84 (0.62-1.15)	.36
Multivariate risk (95% CI)[c]	1 [Reference]	0.88 (0.65-1.21)	1.00 (0.73-1.37)	0.91 (0.65-1.25)	.69
Starch					
No. of cases	78	66	78	83	
Mean intake, g/d	117.5	162.4	191.3	242.9	
Age-adjusted RR (95% CI)	1 [Reference]	0.93 (0.67-1.30)	0.99 (0.72-1.35)	0.89 (0.65-1.23)	.57
Multivariate risk (95% CI)[c]	1 [Reference]	0.98 (0.70-1.36)	1.05 (0.76-1.44)	0.92 (0.66-1.28)	.74
Sugars					
No. of cases	116	71	68	50	
Mean intake, g/d	64.9	94.8	114.0	152.7	
Age-adjusted RR (95% CI)	1 [Reference]	1.00 (0.74-1.34)	1.12 (0.83-1.51)	0.93 (0.67-1.30)	.97
Multivariate risk (95% CI)[c]	1 [Reference]	1.05 (0.78-1.42)	1.20 (0.88-1.63)	0.97 (0.69-1.38)	.75
GI					
No. of cases	78	73	73	81	
Mean	50.0	52.6	54.3	56.9	
Age-adjusted RR (95% CI)	1 [Reference]	0.92 (0.67-1.27)	0.93 (0.68-1.29)	1.00 (0.73-1.37)	.99
Multivariate risk (95% CI)[c,d]	1 [Reference]	0.94 (0.69-1.30)	0.93 (0.68-1.29)	0.96 (0.70-1.33)	.82
GL					
No. of cases	93	80	65	67	
Mean, g/d	118.0	145.3	160.9	189.0	
Age-adjusted RR (95% CI)	1 [Reference]	1.19 (0.88-1.60)	1.05 (0.77-1.45)	0.97 (0.70-1.34)	.79
Multivariate risk (95% CI)[c,d]	1 [Reference]	1.34 (0.97-1.85)	1.22 (0.85-1.76)	1.14 (0.75-1.75)	.59

Abbreviations: CI, confidence interval; GI, glycemic index; GL, glycemic load; RR, relative risk.
[a] Energy adjusted by residual method.
[b] By the interquartile test for trend.
[c] Stratified by center and adjusted for nonalcohol energy intake, hypertension (yes or no), smoking (never, former, or current), education (<8 or ≥8 y), categories of alcohol intake (abstainer, ≤12 g/d, >12 g/d, or >24 g/d), body mass index, fiber intake (in grams per day), and physical activity (inactive, moderately inactive, moderately active, or active).
[d] Adjusted also for saturated fat intake.

bohydrates from high-GI foods, rather than the overall quantity of carbohydrates consumed, appears to influence the risk of developing CHD. Dietary GL is a complex measure that captures the quality and quantity of carbohydrates consumed. The GL can be lowered by reducing total dietary carbohydrate intake or dietary GI. Our finding that only carbohydrates from high-GI foods increased CHD risk, together with the strong effect of increasing GL on CHD risk, suggests that the effect on CHD is conferred not by a diet high in carbohydrates but by a diet rich in rapidly absorbed carbohydrates.

To our knowledge, CHD risk in relation to GL and GI has been examined in 4 previous prospective studies, of which 2 were on women only[8,9] and 2 were on men only.[11,12] Both studies on women found that high dietary GL and GI, but not total carbohydrate intake, were associated with increased CHD risk, particularly in overweight women. These findings are in agreement with ours for dietary GL, whereas we found no evidence that BMI modified the effect of dietary GL on CHD risk. This may have been because our study did not have sufficient statistical power to reveal such an association. Furthermore, women in the EPICOR population consumed considerably more carbohydrates than did the US and Dutch women, which might explain why total carbohydrate intake had no influence on CHD risk in the latter studies. In addition, women in the lowest GI quartile of our cohort had both high GL and high total carbohydrate intake, which might explain why we found no evidence of an adverse effect of dietary GI on CHD.

Regarding men, one cohort study[12] found no association of dietary GI and GL with increased CHD risk, as in our study. The other study[11] examined only dietary GI and again found no association with CHD.

A possible reason for the failure to find an association between a high glycemic diet and CHD among men could be that adverse changes in plasma HDL cholesterol and triglyceride levels, as a result of a high glycemic diet, are stronger risk factors for CVD in women than men,[26-28] as also noted by Levitan et al.[12] Lipoprotein metabolism is about twice as fast in women as men because of the stimulatory effects of estrogen in women and the inhibitory effects of androgen in men.[26] Lipoprotein changes in response to dietary fat and carbohydrates also differ between the sexes, with greater increases in triglyceride levels, decreases in HDL cholesterol and apolipoprotein AI levels, and smaller increases in low-density lipoprotein cholesterol and apolipoprotein B levels in women than men.[26] We had triglyceride and HDL cholesterol level measurements for the Naples subsample of our cohort and found that, as expected, triglyceride levels increased and HDL cholesterol levels decreased as dietary GL increased (Salvatore Panico, MD, oral communication, February 13, 2009). We do not currently have data available for men. High dietary GI and GL have been associated with lower HDL cholesterol and higher triglyceride concentrations in cross-sectional studies on women[3] and also with increased prevalence of the metabolic syndrome.[29]

A high glycemic diet could also affect the risk of CVD by inducing excessive increases in blood glucose and insulin levels. A close correlation between GI and maximum amplitude of glucose excursion has been demonstrated in more than 1000 foods.[30] Postprandial hyperglycemia may increase oxidative stress,[4] whereas hyperinsulinemia has independent effects on blood pressure, serum lipid levels, coagulation factors, inflammatory mediators, and endothelial function,[4] all of which may increase CHD risk.[31]

In a meta-analysis of 38 studies of nondiabetic subjects, increasing glycemia was associated with increasing CVD,[32] more so in women than men and consistent with the similar sex difference seen in diabetic patients.[33] However, the mechanism of this sex difference remains unclear.[34] A meta-analysis of studies on diabetic patients[35] found that the significant difference between men and women for CVD risk disappeared after extensive control for CVD risk factors, suggesting that hyperglycemia in women may be more associated with other CVD risk factors than in men. However, other studies found that adjustment for CVD risk factors did not explain the sex difference and suggested that hyperglycemia may abolish the protective effect of being female on CVD risk.[36]

The strengths of our study include its prospective design and the small number of participants lost to follow-up, limiting the possibility of selection bias. Furthermore, the fact that associations strengthened after adjustment for several recognized risk factors for CVD reduces the possibility of residual confounding. Another study strength, particularly compared with previous cohort studies, is that we used GI values that had mostly been determined on Italian foods. Because the glucose response and probably also the insulin response of a food change with the variety (eg, rice) or the mode of manufacture/preparation (eg, parboiled vs nonparboiled rice and boiled rice vs risotto), the measured GIs of local foods are likely to be more accurate than those derived from international food tables. The validated[15] semiquantitative food-frequency questionnaires were designed to quantify the food items and preparations typically eaten in specific regions of Italy and to enable quantification of the macronutrient content of the diet. However, these questionnaires were not designed to estimate dietary GI and GL, although it was straightforward to apply GI values to the food items consumed. A study by Liu et al[3] on food-frequency questionnaires broadly similar to ours showed that it was possible to accurately estimate dietary GI and GL from questionnaire responses. Another limit of the study is that dietary exposure was based on a single assessment in which participants were asked about eating habits during the preceding year. Some participants may have changed their diet during follow-up, giving rise to some misclassification of exposure that would have weakened diet-disease associations. Furthermore, people do not generally eat single foods but meals in which the GI value of an individual food can vary widely depending on how it is combined with other components, and it is not possible to take such interactions into account using a food-frequency questionnaire. However, strong correlations have been found between observed and calculated GI values of mixed meals based on individual component foods.[37]

In conclusion, in this Italian cohort we found that a high dietary GL and the intake of carbohydrates from high-GI foods increase the overall risk of CHD in women but not men. We tentatively suggest that the adverse effects of a high glycemic diet in women are mediated by sex-related differences in lipoprotein and glucose metabolism, but further prospective studies are required to verify a lack of association of a high dietary GL with CVD in men.

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REFERENCES

1. Ford ES, Liu S. Glycemic index and serum high-density lipoprotein cholesterol concentration among US adults. *Arch Intern Med*. 2001;161(4):572-576.
2. Frost G, Leeds AA, Dore CJ, Madeiros S, Brading S, Dornhorst A. Glycaemic index as a determinant of serum HDL-cholesterol concentration. *Lancet*. 1999; 353(9158):1045-1048.
3. Liu S, Manson JE, Stampfer MJ, et al. Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in postmenopausal women. *Am J Clin Nutr*. 2001;73(3):560-566.
4. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA*. 2002;287(18):2414-2423.
5. Gerich JE. Clinical significance, pathogenesis, and management of postprandial hyperglycemia. *Arch Intern Med*. 2003;163(11):1306-1316.
6. Jenkins DJ, Wolever TM, Taylor RH, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr*. 1981;34(3):362-366.
7. Thomas DE, Elliott EJ, Baur L. Low glycaemic index or low glycaemic load diets for overweight and obesity. *Cochrane Database Syst Rev*. 2007;(3):CD005105.
8. Liu S, Willett WC, Stampfer MJ, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr*. 2000;71(6):1455-1461.
9. Beulens JW, de Bruijne LM, Stolk RP, et al. High dietary glycemic load and glycemic index increase risk of cardiovascular disease among middle-aged women: a population-based follow-up study. *J Am Coll Cardiol*. 2007;50(1):14-21.
10. Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med*. 2009;169(7):659-669.
11. van Dam RM, Visscher AW, Feskens EJ, Verhoef P, Kromhout D. Dietary glycemic index in relation to metabolic risk factors and incidence of coronary heart disease: the Zutphen Elderly Study. *Eur J Clin Nutr*. 2000;54(9):726-731.
12. Levitan EB, Mittleman MA, Hakansson N, Wolk A. Dietary glycemic index, dietary glycemic load, and cardiovascular disease in middle-aged and older Swedish men. *Am J Clin Nutr*. 2007;85(6):1521-1526.
13. Riboli E, Kaaks R. The EPIC Project: rationale and study design: European Prospective Investigation into Cancer and Nutrition. *Int J Epidemiol*. 1997;26 (suppl 1):S6-S14.
14. Palli D, Berrino F, Vineis P, et al; EPIC-Italy. A molecular epidemiology project on diet and cancer: the EPIC-Italy Prospective Study: design and baseline characteristics of participants. *Tumori*. 2003;89(6):586-593.
15. Pisani P, Faggiano F, Krogh V, Palli D, Vineis P, Berrino F. Relative validity and reproducibility of a food frequency dietary questionnaire for use in the Italian EPIC centres. *Int J Epidemiol*. 1997;26(suppl 1):S152-S160.
16. Pala V, Sieri S, Palli D, et al. Diet in the Italian EPIC cohorts: presentation of data and methodological issues. *Tumori*. 2003;89(6):594-607.
17. Salvini S, Parpinel M, Gnagnarella P, Maisonneuve P, Turrini A. *Banca dati di composizione degli alimenti per studi epidemiologici in Italia*. Milano, Italy: Istituto Europeo di Oncologia; 1998.
18. Slimani N, Ferrari P, Ocke M, et al. Standardization of the 24-hour diet recall calibration method used in the European prospective investigation into cancer and nutrition (EPIC): general concepts and preliminary results. *Eur J Clin Nutr*. 2000; 54(12):900-917.
19. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care*. 2008;31(12):2281-2283.
20. Wolever TM, Brand-Miller JC, Abernethy J, et al. Measuring the glycemic index of foods: interlaboratory study. *Am J Clin Nutr*. 2008;87(1):247S-257S.
21. Wolever TM, Vorster HH, Bjorck I, et al. Determination of the glycemic index of foods: interlaboratory study. *Eur J Clin Nutr*. 2003;57(3):475-482.
22. Rose G. Standardisation of observers in blood-pressure measurement. *Lancet*. 1965;1(7387):673-674.
23. Tunstall-Pedoe H, Kuulasmaa K, Tolonen H, et al; WHO MONICA Project. World's largest study of heart disease, stroke, risk factors, and population trends 1979-2002. In: Tunstall-Pedoe H, ed. *MONICA Monograph and Multimedia Sourcebook*. Geneva, Switzerland: World Health Organization; 2003.
24. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol*. 1986;124(1):17-27.
25. Kleinbaum DG, Kupper LL, Nizam A, Muller KE. *Applied Regression Analysis and Multivariable Methods*. New York, NY: Duxburry Press; 1997.
26. Knopp RH, Paramsothy P, Retzlaff BM, et al. Gender differences in lipoprotein metabolism and dietary response: basis in hormonal differences and implications for cardiovascular disease. *Curr Atheroscler Rep*. 2005;7(6):472-479.
27. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. *Circulation*. 1989;79(1):8-15.
28. Reardon MF, Nestel PJ, Craig IH, Harper RW. Lipoprotein predictors of the severity of coronary artery disease in men and women. *Circulation*. 1985;71(5):881-888.
29. Vrolix R, van Meijl LE, Mensink RP. The metabolic syndrome in relation with the glycemic index and the glycemic load. *Physiol Behav*. 2008;94(2):293-299.
30. Brand-Miller JC, Stockmann K, Atkinson F, Petocz P, Denyer G. Glycemic index, postprandial glycemia, and the shape of the curve in healthy subjects: analysis of a database of more than 1000 foods. *Am J Clin Nutr*. 2009;89(1):97-105.
31. Pi-Sunyer FX. Glycemic index and disease. *Am J Clin Nutr*. 2002;76(1):290S-298S.
32. Levitan EB, Song Y, Ford ES, Liu S. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? a meta-analysis of prospective studies. *Arch Intern Med*. 2004;164(19):2147-2155.
33. Lee WL, Cheung AM, Cape D, Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. *Diabetes Care*. 2000;23(7):962-968.
34. Wingard DL, Barrett-Connor EL, Ferrara A. Is insulin really a heart disease risk factor. *Diabetes Care*. 1995;18(9):1299-1304.
35. Kanaya AM, Grady D, Barrett-Connor E. Explaining the sex difference in coronary heart disease mortality among patients with type 2 diabetes mellitus: a meta-analysis. *Arch Intern Med*. 2002;162(15):1737-1745.
36. Hu G; DECODE Study Group. Gender difference in all-cause and cardiovascular mortality related to hyperglycaemia and newly-diagnosed diabetes. *Diabetologia*. 2003;46(5):608-617.
37. Wolever TM, Yang M, Zeng XY, Atkinson F, Brand-Miller JC. Food glycemic index, as given in glycemic index tables, is a significant determinant of glycemic responses elicited by composite breakfast meals. *Am J Clin Nutr*. 2006;83(6): 1306-1312.