ORIGINAL ARTICLE

Glycemic Index, Glycemic Load, and Cardiovascular Disease and Mortality

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ABSTRACT

BACKGROUND
Most data regarding the association between the glycemic index and cardiovascular disease come from high-income Western populations, with little information from non-Western countries with low or middle incomes. To fill this gap, data are needed from a large, geographically diverse population.

METHODS
This analysis includes 137,851 participants between the ages of 35 and 70 years living on five continents, with a median follow-up of 9.5 years. We used country-specific food-frequency questionnaires to determine dietary intake and estimated the glycemic index and glycemic load on the basis of the consumption of seven categories of carbohydrate foods. We calculated hazard ratios using multivariable Cox frailty models. The primary outcome was a composite of a major cardiovascular event (cardiovascular death, nonfatal myocardial infarction, stroke, and heart failure) or death from any cause.

RESULTS
In the study population, 8780 deaths and 8252 major cardiovascular events occurred during the follow-up period. After performing extensive adjustments comparing the lowest and highest glycemic-index quintiles, we found that a diet with a high glycemic index was associated with an increased risk of a major cardiovascular event or death, both among participants with preexisting cardiovascular disease (hazard ratio, 1.51; 95% confidence interval [CI], 1.25 to 1.82) and among those without such disease (hazard ratio, 1.21; 95% CI, 1.11 to 1.34). Among the components of the primary outcome, a high glycemic index was also associated with an increased risk of death from cardiovascular causes. The results with respect to glycemic load were similar to the findings regarding the glycemic index among the participants with cardiovascular disease at baseline, but the association was not significant among those without preexisting cardiovascular disease.

CONCLUSIONS
In this study, a diet with a high glycemic index was associated with an increased risk of cardiovascular disease and death. (Funded by the Population Health Research Institute and others.)

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*A complete list of investigators in the PURE study is provided in the Supplementary Appendix, available at NEJM.org.

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Concern over the health effects of poor-quality carbohydrate foods and beverages has increased the popularity of so-called low-carbohydrate diets.[1-3] Poor-quality carbohydrate foods include those that contain a low amount of fiber, a higher percentage of refined grains than whole grains, and a high glycemic index (a measure of how much 50 g of carbohydrate from a specific food raises the blood glucose level). There is broad agreement on the value of whole-grain and high-fiber foods for the prevention of chronic disease.[4-8] Although many studies support the consumption of a diet with a low glycemic index in the prevention and treatment of diabetes,[9,10] data regarding the association between a diet with a low glycemic index and a reduction in cardiovascular risk have been more mixed.[5,11,12] In addition, most data regarding the association between the glycemic index and cardiovascular disease have been collected in high-income Western populations, with little data provided for non-Western countries with low or middle incomes.

We have assessed the association between the glycemic index and cardiovascular disease and all-cause mortality in the large, international Prospective Urban Rural Epidemiology (PURE) study involving participants with a broad range of carbohydrate intakes and diverse dietary patterns.[13-15] We hypothesized that such a study would be most likely to indicate the extent to which the glycemic index has any value as a marker of carbohydrate quality related to chronic disease in general and to cardiovascular disease in particular.

METHODS

STUDY DESIGN AND PARTICIPANTS

The design and methods of the present study have been described previously,[13-15] as detailed in the Methods section and in Tables S1 through S7 in the Supplementary Appendix (available with the full text of this article at NEJM.org). In brief, our study included 137,851 participants between the ages of 35 and 70 years from 20 countries on five continents. The countries included 4 high-income countries (Canada, Sweden, Saudi Arabia, and the United Arab Emirates), 11 middle-income countries (Argentina, Brazil, Chile, China, Colombia, Iran, Malaysia, Palestinian territory, Poland, South Africa, and Turkey), and 5 low-income countries (Bangladesh, India, Pakistan, Tanzania, and Zimbabwe). Income designations were based on gross national income per capita from the World Bank classification for 2006, the year in which the study was initiated. The participants were further classified according to seven ethnocultural regions: Europe and North America, South America, Africa, Middle East, South Asia, Southeast Asia, and China. The sampling and recruitment strategies that we used are described in detail in previous articles[13-15] and in the Supplementary Appendix.

PROCEDURES

We used standardized questionnaires to collect information about demographic factors, socioeconomic status (education, income, and employment), lifestyle (smoking, physical activity, and alcohol intake), health history, and medication use. Physical assessments included weight, height, waist and hip circumference, and blood pressure. Standard case-report forms were used to record data regarding major cardiovascular events and death during follow-up, findings that were adjudicated centrally in each country with the use of standard definitions.[16,17] In the final analysis, we included all outcome events that had occurred as of June 30, 2019. Data were available for more than 98% of the participants regarding vital status and for 95% regarding cardiovascular disease.

FOOD-FREQUENCY QUESTIONNAIRES

At baseline, we recorded details regarding the habitual food intake of participants (i.e., food frequency) using 28 questionnaires, including 19 that were specific to individual countries and 9 that were specific to regions in India. The food-frequency questionnaires covered a total of 3200 food items, with a range of 98 to 220 items per questionnaire.

For each food, a commonly used unit or portion size was specified. Participants were asked how often on average during the previous year they had consumed that unit of food. Nine responses were possible, ranging from "never" to "six or more times per day." We calculated the daily intake of foods and 45 nutrients by multiplying the frequency of consumption of each unit of food by the nutrient content using both the U.S. Department of Agriculture food-composition database (release 18 and 21) and culturespecific food-composition tables for local dishes. Details regarding the development and assessment of the food-frequency questionnaire for each country are provided in the text in the Supplementary Appendix and in Tables S4 and S5. Participants were excluded from the study if their baseline energy intake as recorded on their food-frequency questionnaire was considered to be implausible (<800 or >4200 kcal per day for men or <500 or >3500 kcal per day for women).[8]

OUTCOMES

The primary outcome was a composite of a major cardiovascular event (cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) or death from any cause. Secondary outcomes were each of the components of the composite outcome plus death from noncardiovascular causes, as adjudicated in previous studies (see the Supplementary Methods section and Table S3).[16] In the primary analysis, participants were categorized according to the presence or absence of preexisting cardiovascular disease and were grouped into quintiles of glycemic index and glycemic load (Fig. S1).

ESTIMATION OF GLYCEMIC INDEX AND GLYCEMIC LOAD

We obtained the glycemic index for carbohydrate foods that were identified in the 28 food-frequency questionnaires from international glycemic-index tables and from databases of certain tropical foods.[18] Glycemic-index values were ascribed to all foods that had a combined occurrence of four or more times as recorded on the food-frequency questionnaires (Table S8). Where possible, we used the mean of more than two studies of the same food. We used the so-called bread scale, which is based on a glycemic index of 100 for white bread (as compared with the glucose scale, on which 100 indicates the glycemic index for glucose). If no data were found, the glycemic-index value for a similar food was used. A glycemic index was ascribed to each of seven categories of carbohydrate-containing foods as follows: legumes, 42; nonlegume starchy foods, 93; nonstarchy vegetables, 54; fruit, 69; fruit juice, 68; dairy, 38; and sugar-sweetened beverages, 87 (Table S8). These values were derived from the individual foods in that category, which were calculated as a weighted mean according to their frequency of occurrence in the food-frequency questionnaires (Tables S9 and S10). The glycemic indexes of the seven carbohydrate categories were then weighted according to the net carbohydrate consumed in each food category to obtain the participant's mean glycemic index.

The participant's glycemic load was calculated by multiplying the mean net carbohydrate intake (as measured in grams per day) by the glycemic index and then dividing by 100.[19] We had previously compared our food-category approach to the glycemic-index calculation with the conventional individual-food approach using 204 7-day food records from a previously published clinical trial.[20] The mean glycemic index as calculated by the conventional method was 77, as compared with a glycemic index of 81 as calculated by our method (r=0.69). The seven-category approach captured 92.5% of the net carbohydrate in the participants' diets.

STATISTICAL ANALYSIS

Continuous variables are expressed as means (±SD) and categorical variables as percentages. The methods for classifying education, smoking status, exercise status, and other covariates are provided in the Supplementary Appendix. We used restricted cubic-spline plots with three knots to explore the shape of the association between the glycemic index and the risk of the primary composite outcome (death or major cardiovascular events).[21] We used a multivariable Cox frailty model to calculate hazard ratios; estimates of hazard ratios and 95% confidence intervals are presented for each quintile of glycemic index and glycemic load. Minimally adjusted models were adjusted for age, sex, and study center as a random effect. Maximally adjusted models were further adjusted for urban or rural location, country income category (economic region), education level, smoking status, physical activity, waist-to-hip ratio, history of diabetes, statin use, use of blood-pressure medication, total daily energy intake, consumption of dietary fiber, and consumption of whole-grain cereals (grams per day). We verified the proportional-hazards assumption of the Cox model by visual assessment of linearity in plots of the log of the negative log of the estimated survival function against the log of time.

In subgroup analyses, we assessed the association between the glycemic index and the primary composite outcome according to economic region, geographic region (Asian or non-Asian countries), sex, body-mass index (BMI, the weight in kilograms divided by the square of the height in meters, of <25 or ≥25), and smoking and exercise status. To determine whether the associations differed among subgroups, the significance of the interaction between groups was assessed for both the glycemic index and glycemic load as a categorical variable. Tests of heterogeneity comparing the estimates of association across different subgroups were conducted with the use of the I^2 statistic. A P value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with Stata software, version 15, or SAS software, version 9.4.

RESULTS

HIGH GLYCEMIC VALUES AND CARDIOVASCULAR EVENTS

Overall, the consumption of diets and specific foods with a high glycemic index was highest in China, followed by Africa and Southeast Asia. The consumption of diets with a high glycemic load was highest in South Asia, followed by Africa and China (Table 1 and Table S11).

During a median of 9.5 years of follow-up (range, 3.2 to 11.9 years), data regarding the primary composite outcome were available for 119,575 participants; data regarding major cardiovascular events were available for 119,572 participants. During this period, the primary composite outcome occurred in 14,075 participants and included 8780 deaths (3229 definite or possible cardiovascular deaths and 5551 noncardiovascular deaths) (Table 2 and Table S12). An additional 649 injury-related deaths were not included with the noncardiovascular deaths because of their unlikely association with diet.[7] During the same period, 8252 participants had at least one major cardiovascular event (3579 with myocardial infarction, 3840 with stroke, and 923 with heart failure).

ASSOCIATION BETWEEN HEALTH OUTCOMES AND GLYCEMIC MEASURES

Data regarding the association between health outcomes and the glycemic index are reported according to the presence or absence of cardiovascular disease at baseline and in the total population (Table 2). The median values for the glycemic index were as follows: quintile 1, 76 (interquartile range [IQR], 74 to 78); quintile 2, 81 (IQR, 80 to 83); quintile 3, 86 (IQR, 85 to 87); quintile 4, 89 (IQR, 88 to 89), and quintile 5, 91 (IQR, 90 to 91). In comparing highest versus lowest quintiles of glycemic index in the fully adjusted model, we observed a positive association with the primary composite outcome in all three groups, including among participants with no preexisting cardiovascular disease (hazard ratio, 1.21; 95% confidence interval [CI], 1.11 to 1.34), in those with preexisting cardiovascular disease (hazard ratio, 1.51; 95% CI, 1.25 to 1.82), and in the total population (hazard ratio, 1.25; 95% CI, 1.15 to 1.37). Similar associations were seen for cardiovascular death, major cardiovascular events, and stroke. The glycemic index was also associated with the risk of death from any cause and from noncardiovascular causes (Table S12). A significant positive nonlinear relationship was found between the glycemic index and total mortality and major cardiovascular disease (Fig. S2).

A similar pattern for the total population was also seen for the glycemic load, although the effects were less marked. (Details regarding outcomes and individual quintiles of glycemic load are provided in Table 3.) However, for major cardiovascular events and death from any cause, a significant association with glycemic load was seen only among participants with preexisting cardiovascular disease (Table S12).

EFFECT OF BMI, EXERCISE, AND SMOKING

The association between the glycemic index and the primary composite outcome was significantly stronger among participants with a higher BMI (≥25) than among those with a lower BMI (<25) (P=0.01) (Fig. 1). There was no significant association between the glycemic index and the primary composite outcome according to exercise status (heavy or light), smoking status, or the use of blood-pressure medications or statins (Table S13).

REGIONAL EFFECTS

The association between the glycemic index or glycemic load and the primary composite outcome varied slightly according to geographic region (Fig. S3). Among the 44,845 Chinese participants (the largest subgroup), a significant effect was seen for the top quintile of the glycemic index as compared with the bottom quintile

Table 1. Characteristics of the Participants at Baseline, According to Region.*

Characteristic	Europe and North America (N=15,045)	South America (N=22,496)	Africa (N=5,759)	Middle East (N=13,405)	South Asia (N=27,216)	Southeast Asia (N=9,085)	China (N=44,845)	Total (N=137,851)
Demographic								
Age (yr)	53.5±9.3	51.5±9.7	49.9±10.7	48.8±9.4	48.5±10.3	51.6±10.0	51.0±9.7	50.6±9.9
Male sex (%)	45.6	39.2	31.1	46.4	44.4	43.5	42.1	42.5
Urban residence (%)	70.1	57.1	48.7	59.1	48.2	49.1	48.4	53.1
Current smoker (%)	15.2	20.6	24.6	18.3	23.2	16.1	22.6	20.8
Daily energy intake (kcal)	2173±717	2114±670	1882±748	2192±700	2056±709	2191±767	1949±628	2059±690
Daily servings of seven categories of carbohydrate foods								
Dairy	4.0±3.1	1.6±1.5	0.4±0.5	2.3±1.5	0.7±1.0	0.9±1.1	0.5±0.6	1.3±1.8
Fruit	1.8±1.4	1.9±1.7	1.8±2.6	4.1±3.0	0.9±1.2	1.5±1.8	0.8±0.7	1.5±1.8
Fruit juice†	0.4±0.5	0.7±1.0	0.0±0.2	0.1±0.2	0.1±0.2	0.1±0.2	NA	0.3±0.7
Vegetables	6.4±5.7	3.7±2.3	2.0±2.2	2.9±1.9	1.7±1.4	2.5±2.9	1.6±0.5	2.7±2.9
Starchy foods	5.1±3.6	5.1±2.4	5.2±2.4	4.3±1.9	7.4±3.2	5.8±3.0	7.4±3.4	6.3±3.3
Legumes	0.5±0.7	0.6±0.8	0.6±0.4	0.4±0.4	1.5±2.4	0.4±0.5	0.6±0.6	0.7±1.3
Soft drinks	0.4±0.7	0.5±1.1	0.2±0.4	0.1±0.2	0.0±0.1	0.1±0.3	0.01±0.04	0.2±0.6
Glycemic index‡	76.7±4.4	79.7±4.8	85.3±4.0	77.9±3.9	83.3±5.2	85.4±3.8	86.2±2.8	82.6±5.4
Glycemic load (g/day)§	183.8±69.5	254.6±99.3	314.0±165.0	194.5±70.1	350.0±186.0	267.3±99.0	311.6±116.0	280.8±137.0

* Plus–minus values are means ±SD. NA denotes not applicable.
† The daily intake of fruit juice was not measured in China and Bangladesh; data for the latter country are included under South Asia.
‡ The glycemic index is the measure of how much 50 g of carbohydrate from a specific food raises the blood glucose level.
§ The glycemic load was calculated by multiplying the mean net carbohydrate intake (as measured in grams per day) by the glycemic index and then dividing by 100.

Table 2. Association between Clinical Outcomes and Glycemic Index, According to Cardiovascular Disease (CVD) Status.*

Variable	Events					Hazard Ratio (95% CI)			
	Q1	Q2	Q3	Q4	Q5	Q2 vs. Q1	Q3 vs. Q1	Q4 vs. Q1	Q5 vs. Q1
	no. with event (%)								
All participants									
No. of participants	27,571	27,570	27,570	27,570	27,570				
Primary composite outcome	2,279 (8.3)	2,308 (8.4)	2,760 (10.0)	3,118 (11.3)	3,610 (13.1)	1.04 (0.97–1.11)	1.14 (1.05–1.22)	1.23 (1.13–1.33)	1.25 (1.15–1.37)
Major cardiovascular event	1,439 (5.2)	1,345 (4.9)	1,617 (5.9)	1,835 (6.7)	2,016 (7.3)	0.97 (0.89–1.05)	1.08 (0.98–1.19)	1.14 (1.03–1.27)	1.14 (1.02–1.27)
Cardiovascular death	504 (1.8)	486 (1.8)	611 (2.2)	741 (2.7)	887 (3.2)	0.95 (0.82–1.10)	1.01 (0.87–1.19)	1.20 (1.01–1.42)	1.25 (1.05–1.49)
Stroke	486 (1.8)	509 (1.8)	752 (2.7)	996 (3.6)	1097 (4.0)	1.03 (0.89–1.18)	1.12 (0.96–1.31)	1.23 (1.04–1.45)	1.28 (1.08–1.51)
No CVD at baseline									
No. of participants	24,935	25,164	25,359	25,713	25,845				
Primary composite outcome	1,777 (7.1)	1,835 (7.3)	2,271 (9.0)	2,651 (10.3)	3,132 (12.1)	1.03 (0.96–1.11)	1.12 (1.03–1.22)	1.20 (1.10–1.31)	1.21 (1.11–1.34)
Major cardiovascular event	1,050 (4.2)	1,011 (4.0)	1,246 (4.9)	1,484 (5.8)	1,654 (6.4)	0.97 (0.88–1.07)	1.04 (0.93–1.16)	1.11 (0.99–1.25)	1.10 (0.99–1.24)
Cardiovascular death	340 (1.4)	374 (1.5)	471 (1.9)	592 (2.3)	712 (2.8)	1.07 (0.90–1.28)	1.10 (0.91–1.33)	1.31 (1.07–1.59)	1.32 (1.08–1.61)
Stroke	356 (1.4)	382 (1.5)	600 (2.4)	806 (3.1)	925 (3.6)	1.02 (0.86–1.21)	1.14 (0.95–1.36)	1.20 (0.99–1.45)	1.24 (1.02–1.50)
CVD at baseline									
No. of participants	2,636	2,406	2,211	1,857	1,725				
Primary composite outcome	502 (19.0)	473 (19.7)	489 (22.1)	467 (25.1)	478 (27.7)	1.05 (0.91–1.21)	1.20 (1.03–1.41)	1.39 (1.16–1.66)	1.51 (1.25–1.82)
Major cardiovascular event	389 (14.8)	334 (13.9)	371 (16.8)	351 (18.9)	362 (21.0)	0.95 (0.81–1.12)	1.19 (0.99–1.43)	1.33 (1.08–1.63)	1.49 (1.20–1.85)
Cardiovascular death	164 (6.2)	112 (4.7)	140 (6.3)	149 (8.0)	175 (10.1)	0.69 (0.53–0.90)	0.84 (0.64–1.12)	1.03 (0.75–1.39)	1.25 (0.90–1.71)
Stroke	130 (4.9)	127 (5.3)	152 (6.9)	190 (10.2)	172 (10.0)	1.04 (0.80–1.36)	1.11 (0.82–1.50)	1.51 (1.10–2.07)	1.71 (1.21–2.40)

* The primary composite outcome was a major cardiovascular event (cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) or death from any cause. Data are shown for the primary composite outcome and for the overall category of major cardiovascular events, plus two of its components (cardiovascular death and stroke). The values are reported according to the quintile (Q) of the median glycemic index and range from 76 in Q1 to 91 in Q5. Models have been adjusted for age, sex, study center, urban or rural location, country income category (economic region), education level, smoking status, physical activity, waist-to-hip ratio, history of diabetes, statin use, use of blood-pressure medication, total daily energy intake, consumption of dietary fiber, and consumption of whole-grain cereals (grams per day).

Table 3. Association between Clinical Outcomes and Glycemic Load, According to CVD Status.*

Variable	Events					Hazard Ratio (95% CI)			
	Q1	Q2	Q3	Q4	Q5	Q2 vs. Q1	Q3 vs. Q1	Q4 vs. Q1	Q5 vs. Q1
	no. with event (%)								
All participants									
No. of participants	27,571	27,570	27,570	27,570	27,570				
Primary composite outcome	2,580 (9.4)	2,530 (9.2)	2,604 (9.4)	2,941 (10.7)	3,420 (12.4)	1.00 (0.94–1.07)	1.05 (0.97–1.12)	1.12 (1.04–1.22)	1.07 (0.97–1.18)
Major cardiovascular event	1,526 (5.5)	1,541 (5.6)	1,590 (5.8)	1,772 (6.4)	1,823 (6.6)	1.00 (0.92–1.08)	1.03 (0.94–1.13)	1.09 (0.99–1.21)	1.07 (0.94–1.21)
Cardiovascular death	602 (2.2)	528 (1.9)	554 (2.0)	741 (2.7)	804 (2.9)	0.97 (0.84–1.12)	1.00 (0.86–1.17)	1.27 (1.07–1.50)	1.16 (0.95–1.42)
Stroke	573 (2.1)	666 (2.4)	783 (2.8)	900 (3.3)	918 (3.3)	0.98 (0.86–1.11)	1.06 (0.93–1.22)	1.16 (1.00–1.35)	1.21 (1.00–1.46)
No CVD at baseline									
No. of participants	25,110	25,112	25,136	25,552	26,106				
Primary composite outcome	2,061 (8.2)	2,030 (8.1)	2,066 (8.2)	2,472 (9.7)	3,037 (11.6)	1.00 (0.93–1.07)	1.01 (0.94–1.10)	1.08 (0.99–1.19)	1.02 (0.91–1.13)
Major cardiovascular event	1,130 (4.5)	1,172 (4.7)	1,191 (4.7)	1,405 (5.5)	1,547 (5.9)	1.02 (0.92–1.12)	1.00 (0.90–1.11)	1.05 (0.93–1.19)	1.02 (0.89–1.18)
Cardiovascular death	442 (1.8)	389 (1.5)	413 (1.6)	581 (2.3)	664 (2.5)	0.97 (0.82–1.15)	1.02 (0.85–1.22)	1.24 (1.02–1.50)	1.09 (0.86–1.37)
Stroke	429 (1.7)	517 (2.1)	585 (2.3)	735 (2.9)	803 (3.1)	1.00 (0.87–1.16)	1.02 (0.87–1.19)	1.14 (0.96–1.36)	1.20 (0.97–1.47)
CVD at baseline									
No. of participants	2,461	2,458	2,434	2,018	1,464				
Primary composite outcome	519 (21.1)	500 (20.3)	538 (22.1)	469 (23.2)	383 (26.2)	1.00 (0.87–1.15)	1.14 (0.97–1.33)	1.25 (1.05–1.50)	1.34 (1.08–1.67)
Major cardiovascular event	396 (16.1)	369 (15.0)	399 (16.4)	367 (18.2)	276 (18.9)	0.96 (0.82–1.13)	1.11 (0.93–1.32)	1.26 (1.02–1.54)	1.31 (1.02–1.69)
Cardiovascular death	160 (6.5)	139 (5.7)	141 (5.8)	160 (7.9)	140 (9.6)	0.93 (0.72–1.21)	0.94 (0.71–1.24)	1.26 (0.93–1.71)	1.46 (1.01–2.10)
Stroke	144 (5.9)	149 (6.1)	198 (8.1)	165 (8.2)	115 (7.9)	0.96 (0.74, 1.24)	1.27 (0.97–1.67)	1.33 (0.97–1.83)	1.45 (0.98–2.14)

* Values are shown according to the quintile (Q) of the median glycemic load as follows: Q1, 136 g per day (interquartile range, 111 to 155); Q2, 202 g per day (interquartile range, 187 to 218); Q3, 262 g per day (interquartile range, 248 to 278); Q4, 339 g per day (interquartile range, 316 to 365); and Q5, 468 g per day (interquartile range, 418 to 548).

(hazard ratio, 1.76; 95% CI, 1.23 to 2.53); a similar direction of effect was found among participants in the Middle East (hazard ratio, 3.22; 95% CI, 1.02 to 10.19). Among the participants in South America, a significant association was seen for glycemic load only (hazard ratio, 1.38; 95% CI, 1.03 to 1.84) (Table S14). In the analysis that compared participants in Asia with those not in Asia, the effect was seen only in the non-Asian region (Fig. S4), probably because of the greater range of glycemic-index values in non-Asian countries (Fig. S5). In comparisons of economic regions, a gradation was seen for glycemic load, with the highest economic regions tending to have the strongest association with the primary composite outcome in the total population (hazard ratio, 1.93; 95% CI, 1.05 to 3.53) (Table S15).

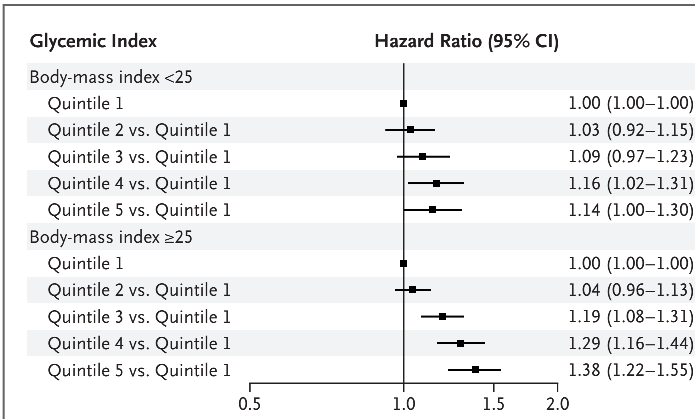

Figure 1. Association between the Primary Composite Outcome and the Glycemic Index in the Study Participants, According to Body-Mass Index.
Shown is the risk of the primary composite outcome of a major cardiovascular event (cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) or death from any cause among the study participants, according to the quintile of the median glycemic index (ranging from 76 in quintile 1 to 91 in quintile 5) and the category of body-mass index (<25 or ≥25).

Discussion

In this study, we found that across multiple countries and geographic and economic regions, diets with a high glycemic index were associated with a higher risk of cardiovascular disease and death than diets with a low glycemic index. The cultural and socioeconomic diversity of this study permits an examination of the association between glycemic index and glycemic load with events across a very broad range of dietary patterns. The assessment of outcomes among participants according to the presence or absence of preexisting cardiovascular disease allowed for the exploration of associations with implications for both primary and secondary prevention strategies.

As expected, a higher glycemic index was associated with an increased risk of adverse effects among the participants with a higher BMI, as reported previously.[8] Persons with a high BMI are at increased risk for diabetes, cardiovascular disease, and certain cancers. Although the glycemic index of foods is independent of glucose-tolerance status,[12] the overall postprandial glycemic response to diet increases as the BMI increases.[22] Thus, diets with a high glycemic index can be expected to interact with the insulin resistance associated with increased BMI to produce an even higher postprandial glycemic response, thus increasing the negative consequences of consumption of a diet with a high glycemic index.

Diets with a low glycemic index have been associated with lower postprandial glycemic levels, lower levels of serum cholesterol and C-reactive protein, and lower blood pressure.[4,23] Such diets have been associated with a reduced incidence of diabetes and cardiovascular disease,[8,12] conditions that may increase the risk of death from other causes, possibly including coronavirus disease 2019 (Covid-19).[24]

Our study has some potential limitations. First, carbohydrate foods were grouped into seven categories, which may have resulted in less precision in calculations than the method of calculating values for individual foods. However, because standard glycemic-index values were not available for many foods and dishes that were listed on the 28 food-frequency questionnaires, such values had to be imputed on the basis of the values of similar foods. Thus, although the approach that we used in this study may dilute real associations with particular foods, it is likely to be more readily applicable to very diverse dietary intakes and has shown a reasonable correlation with glycemic-index values generated by the individual-food method.

Second, the inclusion of many different populations could limit uniform conclusions; however, the diversity also increases the range of differences that may be helpful in establishing associations, and when effects are seen, they are likely to be robust and meaningful.

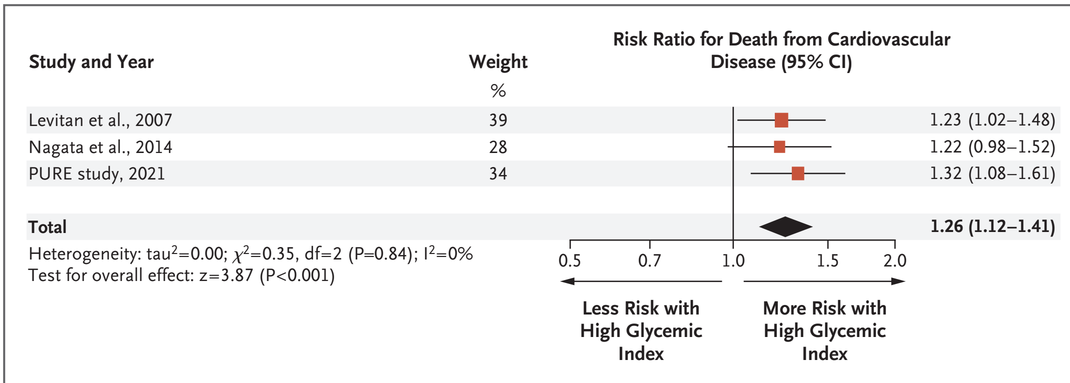

Figure 2. Association between the Glycemic Index and the Risk of Death from Cardiovascular Disease in Three Studies.

Shown in the forest plot is the risk of death from cardiovascular disease associated with a diet with a high glycemic index in two key studies, as compared with the findings in the PURE study. The data were identified by Reynolds et al.[5] in 2019 from two cohort studies (by Levitan et al.[27] and Nagata et al.[28]) that formed the basis for one of the series of meta-analysis commissioned by the World Health Organization and to which the corresponding data from the current study were added. In their meta-analysis, Reynolds et al. used the less adjusted model for the study by Levitan et al. to avoid overadjustment and combined men and women in the study by Nagata et al. The weighting of the analysis according to the inclusion of data from each study is indicated as a percentage. The size of the squares corresponds to the number of participants in the study; the diamond represents the pooled risk estimate. All results are presented as risk ratios and 95% confidence intervals on the basis of a random-effects model. CI denotes confidence interval, df degrees of freedom, and I^2 the percentage of total variation that is due to heterogeneity rather than chance.

Third, we were interested in learning how different regions and countries may be affected differently by diets with a high glycemic index. Unfortunately, the numbers of participants, although large overall, were not large enough to allow meaningful analyses according to geographic region. Furthermore, the diets with a high glycemic index that are common to Asian nations may have limited the range of exposure required to establish associations with outcomes. In our study, such associations were seen in our non-Asian subgroup and have also been reported in studies involving Western populations.[8,11]

Fourth, we could not correct for measurement errors in covariates, especially in dietary variables, although the elimination of dietary covariates made little difference to the outcome (Table S16). And fifth, our reliance on one baseline measure of dietary intake may not reflect current patterns in the various countries. For example, we began recruiting participants in China at a time when carbohydrate intakes were higher than they are now.[25] More rapid changes in dietary patterns are likely to be seen in populations, such as those in China, that have had rapid economic growth. Moreover, the differing rates of change of diets over time in different countries are likely to reduce the ability to show associations between glycemic index and cardiovascular disease. Nevertheless, the data from the present study have proved sufficiently consistent to show dietary associations with disease outcomes.[13,14,17]

The present study has several strengths. It is large and includes participants from diverse economic regions and many low-income countries that have been little studied. We have used country-specific food-frequency questionnaires to assess dietary intake. The study design has allowed us to compare the effect of glycemic index and glycemic load among participants according to the presence or absence of preexisting cardiovascular disease. We were able to show significant associations between the glycemic index and the incidence of death and major cardiovascular disease with a positive dose–response relationship that was not seen in a recent meta-analysis that had a smaller sample size.[26] The addition of our data to a recent meta-analysis that was commissioned by the World Health Organization strengthened the association between glycemic index and death from cardiovascular disease (Fig. 2).[27,28] Furthermore, we were able to perform adjustments using detailed covariates, a major strength of the study. We also determined that the glycemic index and glycemic load are relevant measures of carbohydrate quality in the analysis of a wide range of different dietary patterns according to their association with adverse health outcomes.

Our study showed that in a diverse population of participants, those who consumed a diet with a low glycemic index and a low glycemic load had a lower risk of cardiovascular disease and death than participants who consumed a diet with a higher glycemic index and glycemic load.

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APPENDIX

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