Glycemic index, glycemic load, and chronic disease risk—a meta-analysis of observational studies[1,2]

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ABSTRACT

Background: Inconsistent findings from observational studies have prolonged the controversy over the effects of dietary glycemic index (GI) and glycemic load (GL) on the risk of certain chronic diseases.

Objective: The objective was to evaluate the association between GI, GL, and chronic disease risk with the use of meta-analysis techniques.

Design: A systematic review of published reports identified a total of 37 prospective cohort studies of GI and GL and chronic disease risk. Studies were stratified further according to the validity of the tools used to assess dietary intake. Rate ratios (RRs) were estimated in a Cox proportional hazards model and combined by using a random-effects model.

Results: From 4 to 20 y of follow-up across studies, a total of 40 129 incident cases were identified. For the comparison between the highest and lowest quantiles of GI and GL, significant positive associations were found in fully adjusted models of validated studies for type 2 diabetes (GI RR = 1.40, 95% CI: 1.23, 1.59; GL RR = 1.27, 95% CI: 1.12, 1.45), coronary heart disease (GI RR = 1.25, 95% CI: 1.00, 1.56), gallbladder disease (GI RR = 1.26, 95% CI: 1.13, 1.40; GL RR = 1.41, 95% CI: 1.25, 1.60), breast cancer (GI RR = 1.08, 95% CI: 1.02, 1.16), and all diseases combined (GI RR = 1.14, 95% CI: 1.09, 1.19; GL RR = 1.09, 95% CI: 1.04, 1.15).

Conclusions: Low-GI and/or low-GL diets are independently associated with a reduced risk of certain chronic diseases. In diabetes and heart disease, the protection is comparable with that seen for whole grain and high fiber intakes. The findings support the hypothesis that higher postprandial glycemia is a universal mechanism for disease progression. *Am J Clin Nutr* 2008;87:627–37.

KEY WORDS Glycemic index, glycemic load, dietary carbohydrates, epidemiology

INTRODUCTION

Worldwide, chronic diseases such as diabetes, cardiovascular disease, stroke, and cancer contribute to ≈60% of all deaths, and the proportion is predicted to increase to 75% by the year 2020 (1, 2). Habitual diet is the major modifiable risk factor, and the identification of simple, cost-effective strategies for prevention and management is a matter of urgency.

Although changes in the quantity and quality of fat have received considerable attention, the role of carbohydrates is less clear (2). Increases in refined sugar intake have been accompanied by more subtle changes in starchy foods, eg, processed cereal products have replaced more traditionally processed grains. Because carbohydrate is the main dietary component affecting insulin secretion and postprandial glycemia (3), it is implicated in the etiology of many chronic diseases. Both the amount and type of carbohydrate consumed have an effect on both insulin secretion and postprandial glycemia, with differences not explained by glucose chain length (4). In 1981, the concept of the glycemic index (GI) was introduced by Jenkins et al (5) to quantify the glycemic response to carbohydrates in different foods. Glycemic load (GL), the mathematical product of the GI of a food and its carbohydrate content, has been proposed as a global indicator of the glucose response and insulin demand induced by a serving of food (6).

The results of studies that investigated the association between overall dietary GI, GL, and disease risk have been inconsistent. With respect to diabetes, a positive association was documented in 6 large cohort studies (6–11), but no association was seen in 2 others (12, 13). In cardiovascular disease, 2 studies reported a positive association (14, 15), whereas 1 found no relation (16). Most of the studies that have investigated cancer risk have reported no associations (11, 17–29), but there are notable exceptions (30–37). Two studies that investigated the risk of gallbladder disease showed positive associations (38, 39). Finally, 2 studies (40, 41) reported an association with eye disease, whereas a third found no association (42).

Of concern, 5 (13%) (22, 25, 27, 31, 33) of the 37 prospective studies that investigated the relation between dietary carbohydrates, GI, GL, and chronic disease risk did not validate carbohydrate intake, and an additional 5 (13%) (12, 13, 20, 36, 37) showed correlation coefficients for total carbohydrate of <0.5. Another 2 (5%) studies (29, 32) appear to have been validated, but the validation study has not been published, and 2 others (5%)

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were validated in a population markedly different from the cohort under investigation (8, 21).

To help resolve these inconsistencies, we used meta-analysis techniques to evaluate the association between GI, GL, and risk of certain chronic diseases by reanalyzing the primary data. In the first instance, we examined all prospective cohort studies and then reanalyzed only those studies that were appropriately validated in a comparable population.

SUBJECTS AND METHODS

Study selection

We conducted a literature search of the MEDLINE, EMBASE, CINAHL, and Cochrane Library databases from January 1981 through March 2007 using the Medical Subject Heading Glycemic Index and the terms *glycaemic index* or *glyc(a)emic load*. The search was restricted to human studies. There were no language restrictions. We also performed a manual search of references cited by the published original studies and relevant review articles and contacted experts in the area who may have known of prospective cohort studies nearing completion.

The contents of 274 abstracts or full-text manuscripts identified through the literature search were reviewed independently by 2 investigators (AWB, JM-P) in duplicate to determine whether they met the eligibility criteria for inclusion. Studies were eligible for inclusion if the design was that of a prospective cohort study and the final outcome was occurrence of a chronic disease, but not its risk factors. The flow of studies in this analysis is depicted in **Figure 1**. We included a total of 37 prospective cohort studies representing data from 1 950 198 participants (6–42). All of these prospective cohort studies were conducted in free-living individuals with no history of the disease under investigation.

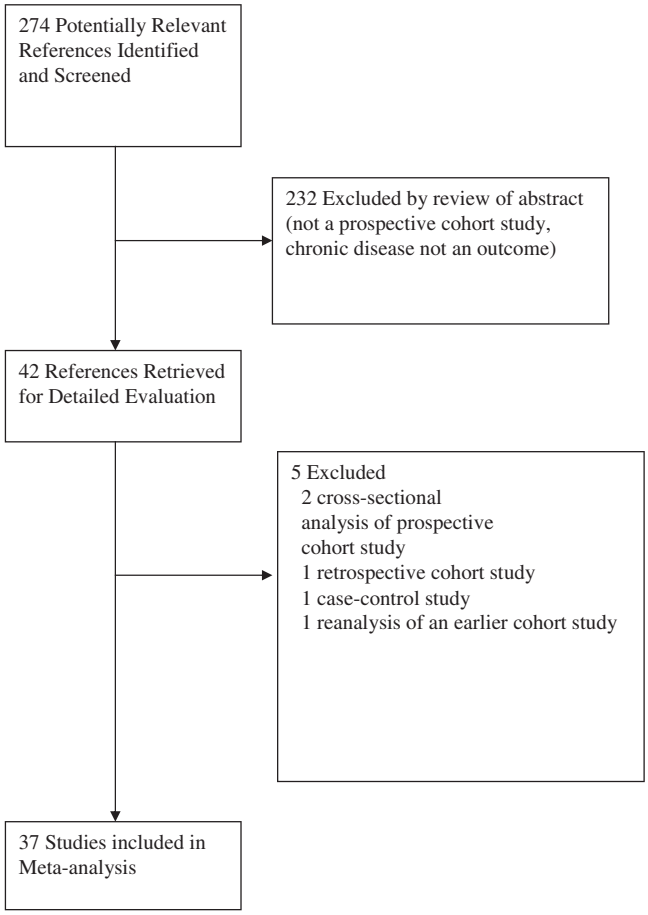

FIGURE 1. Study selection process.

Data extraction

All data were independently abstracted in duplicate by 2 investigators (AWB and JM-P) using a custom-built database. Discrepancies were resolved by verbal discussion. When necessary, the original authors were contacted for additional information. The study characteristics recorded were as follows: surname of first author; year of publication; source of publication; country of origin; language; funding source; disease outcome; method of diagnosis; mean age and range; sex; ethnicity; education levels; mean body mass index (BMI) of group; response rate; dietary assessment tool and number of items; mode of administration of dietary assessment tool; validation method and result; number of dietary intake assessments; duration of follow-up; source of GI values; method of segregation according to GI (tertiles, quartiles, quintiles, deciles, and other); adjustments for potential confounders in basic, intermediate and final models; and macronutrient intakes.

Statistical analysis

Some studies included in our meta-analysis differed in the units used to report levels of GI and GL (glucose = 100 versus bread = 100). We therefore converted those using the bread scale to the glucose = 100 scale, using a conversion rate of 0.71 (ie, bread Scale × 0.71 = glucose scale).

Rate ratios (RRs) for a comparison of the highest with the lowest quantiles were used as the measure of association between GI, GL, and risk of developing a chronic disease. Statistical testing for heterogeneity indicated that there was significantly different variability between studies; hence, although both fixed- and random-effects models yielded similar findings in many cases, results from the random-effects models are presented here. This also takes into account the different disease conditions, study duration, and dietary GIs and GLs that were reported from the original prospective cohort studies. To assess the potential for publication bias, we constructed funnel plots for each outcome in which the log RR was plotted against their SE (43). We also conducted a sensitivity analysis in which each prospective cohort study was excluded in turn to evaluate the influence of that prospective cohort study on the estimate. All analyses were conducted in parallel by 2 investigators (PP and TP) using 2 different meta-analysis packages: Comprehensive Meta Analysis version 2.2 (Biostat, Englewood, NJ; Internet: http://www.meta-analysis.com/) and R version 2.4.1 with its contributed package rmeta version 2.14 (R Foundation for Statistical Computing, Vienna, Austria; Internet: http://cran-rproject.org/).

Most studies included in our meta-analysis reported correlation coefficients for total carbohydrates, and, occasionally, additional carbohydrate fractions, to assess the ability of their food-frequency questionnaire (FFQ) to rank individuals according to GI and GL. Brunner et al (44) suggests that correlation coefficients above ". . . 0.5 for most nutrients and 0.8 for alcohol between methods is good evidence that the FFQ has the ability to rank individuals . . . according to nutrient intake." Because the

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TABLE 1
Baseline characteristics of participants in 37 prospective cohort studies of glycemic index or glycemic load and chronic disease risk

Study	No. of subjects	Age[1]	Sex	Country of residence	BMI	Disease outcome	Method of diagnosis
		y			*kg/m²*		
Salmeron et al (6) 1997	65 173	52 (40–65)	Female	USA	27.5	Type 2 diabetes	Biochemical test[2]
Salmeron et al (7) 1997	42 759	57 (40–75)	Male	USA	25.5	Type 2 diabetes	Biochemical test[2]
Meyer et al (12) 2000	35 988	(55–69)	Female	USA	26.8	Type 2 diabetes	Self-report
Stevens et al (13) 2002[3]	9 529	54 (45–64)	Both	USA	26.5	Type 2 diabetes	Biochemical test[2]
Stevens et al (13) 2002[4]	2 722	53 (45–64)	Both	USA	28.9	Type 2 diabetes	Biochemical test[2]
Hodge et al (8) 2004	36 787	54 (40–69)	Both	Australia	25.9	Type 2 diabetes	Self-report
Schulze et al (9) 2004	91 249	36 (24–44)	Female	USA	24.6	Type 2 diabetes	Biochemical test[2]
Zhang et al (10) 2006	13 110	32 (24–44)	Female	USA	23.5	Type 2 diabetes	Self-report
Patel et al (11) 2007	124 907	63 (50–74)	Female	USA	26.1	Type 2 diabetes	Medical records
Liu et al (14) 2000	75 521	(38–63)	Female	USA	25	Heart disease	Medical records
van Dam et al (16) 2000	646	71 (67–75)	Male	Netherlands	25.5	Heart disease	Medical records
Oh et al (15) 2005	78 779	46 (30–55)	Female	USA	24	Stroke	Medical records
Jonas et al (17) 2003	63 307	62 (50–74)	Female	USA		Breast cancer	Medical records
Cho et al (18) 2003	90 665	36 (26–46)	Female	USA	25	Breast cancer	Medical records
Holmes et al (30) 2004	88 678	56 (30–55)	Female	USA	25.8	Breast cancer	Medical records
Higginbotham et al (19) 2004	38 446	54 (45+)	Female	USA	26.1	Breast cancer	Medical records
Silvera et al (31) 2005	49 111	48 (40–59)	Female	Canada	24.7	Breast cancer	Medical records
Nielsen et al (20) 2005	23 870	57 (50–64)	Female	Denmark	25	Breast cancer	Medical records
Giles et al (21) 2006	12 273	54 (40–69)	Female	Australia	25.9	Breast cancer	Medical records
Terry et al (22) 2003	49 124	61 (40–59)	Female	Canada	23.9	Colorectal cancer	Medical records
Oh et al (23) 2004	34 428	59 (30–55)	Female	USA	24.45	Colorectal cancer	Physical examination
Higginbotham et al (34) 2004	38 451	54 (≥45)	Female	USA	26.1	Colorectal cancer	Physical examination
Michaud et al (35) 2005[5]	83 927	47 (30–55)	Female	USA	24	Colorectal cancer	Medical records
Michaud et al (35) 2005[6]	47 422	54	Male	USA	26	Colorectal cancer	Medical records
McCarl et al (36) 2006	35 197	62 (55–69)	Female	USA		Colorectal cancer	Medical records
Larsson et al (29) 2006	61 433	(40–76)	Female	Sweden	24.7	Colorectal cancer	Medical records
Michaud et al (37) 2002	88 802	47 (30–55)	Female	USA	23.7	Pancreatic cancer	Medical records
Johnson et al (24) 2005	33 551	(55–69)	Female	USA		Pancreatic cancer	Medical records
Silvera et al (25) 2005	49 613	(40–59)	Female	Canada	24.8	Pancreatic cancer	Medical records
Patel et al (11) 2007	124 907	63 (50–74)	Female	USA	26.1	Pancreatic cancer	Medical records
Folsom et al (26) 2003	23 335	(55–69)	Female	USA		Endometrial cancer	Medical records
Silvera et al (27) 2005	49 613	(40–59)	Female	Canada		Endometrial cancer	Medical records
Larsson et al (32) 2007	61 226	54	Female	Sweden	24.8	Endometrial cancer	Medical records
Silvera et al (33) 2007	49 613	49 (40–59)	Female	Canada	25	Ovarian cancer	Medical records
Larsson et al (28) 2006	61 433	54	Female	Sweden	24.7	Gastric cancer	Medical records
Tsai et al (39) 2005	44 525	(40–75)	Male	USA	24.9	Gallbladder disease	Self-report
Tsai et al (38) 2005	70 408	48 (35–61)	Female	USA	24.9	Gallbladder disease	Self-report
Schaumberg et al (41) 2004[6]	51 529	(40–75)	Male	USA	25.6	Eye disease	Medical records
Schaumberg et al (41) 2004[5]	71 919	(30–55)	Female	USA	25.1	Eye disease	Medical records
Chiu et al (42) 2005	603	61 (53–73)	Female	USA	24.1	Eye disease	Physical examination
Chiu et al (40) 2006	526	63 (53–73)	Female	USA	24.9	Eye disease	Physical examination

[1] All values are means; range in parentheses.
[2] Biochemical test = fasting plasma glucose or oral-glucose-tolerance test.
[3] White Americans.
[4] Black Americans.
[5] Women.
[6] Men.

GI is a characteristic of the carbohydrate in different foods, we hypothesized that the studies with low correlation coefficients for total carbohydrate and/or carbohydrate fractions would most likely be unable to rank individuals according to GI and/or GL. As a consequence, we conducted additional analyses, which included only those studies with correlation coefficients for total carbohydrate ≥0.5, in validation studies that had been conducted in representative samples.

P values <0.05 were considered to indicate statistical significance. RR and 95% CIs are shown. We conformed as much as practicable to MOOSE (Meta-analyses of Observational Studies in Epidemiology) guidelines in the report of this meta-analysis (45).

RESULTS

The characteristics of the participants and study design are presented in **Table 1** and **Table 2**, respectively. Of the 37 prospective cohort studies, 25 were conducted in the United States, 5 in Canada, 2 in Australia, and 5 in European countries. The

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TABLE 2
Design characteristics of 37 prospective cohort studies of glycemic index or glycemic load and chronic disease risk[1]

Study	Disease outcome	Dietary assessment method	FFQ items	Validation of nutrients	Correlation with WFR	Validated in study population	Number of times assessed	Assessment interval	Total duration of follow-up
								y	*y*
Salmeron et al (6) 1997	Type 2 diabetes	FFQ	134	Correlation	0.69	Yes	Baseline only	—	6
Salmeron et al (7) 1997	Type 2 diabetes	FFQ	131	Correlation	0.69	Yes	Baseline only	—	6
Meyer et al (12) 2000	Type 2 diabetes	FFQ	127	Correlation	0.45	Yes	Baseline only	—	6
Stevens et al (13) 2002	Type 2 diabetes	FFQ	66	Correlation	0.45	No	Baseline only	—	9
Hodge et al (8) 2004	Type 2 diabetes	FFQ	121	Correlation	0.78	No	Baseline only	—	4
Schulze et al (9) 2004	Type 2 diabetes	FFQ	133	Correlation	0.64	Yes	Twice	4	8
Zhang et al (10) 2006	Type 2 diabetes	FFQ	133	Correlation	0.64	Yes	Twice	4	8
Patel et al (11) 2007	Type 2 diabetes	FFQ	68	Correlation	0.73	Yes	Baseline only	—	9
Liu et al (14) 2000	Heart disease	FFQ	126	Correlation	0.73	Yes	3	—	6
van Dam et al (16) 2000	Heart disease	Diet history (2–4 wk)	—	Attenuation factor	0.85	Yes	Twice	5	5
Oh et al (15) 2005	Stroke	FFQ	116	Correlation	0.61	Yes	5	4	18
Jonas et al (17) 2003	Breast cancer	FFQ	68	Correlation	0.51	Yes	Twice	5	5
Cho et al (18) 2003	Breast cancer	FFQ	133	Correlation	0.61	Yes	Twice	4	8
Higginbotham (19) 2004	Breast cancer	FFQ	131	Correlation	0.73	Yes	Baseline only	—	6.8
Holmes et al (30) 2004	Breast cancer	FFQ	134	Correlation	0.61	Yes	5	4	18
Nielsen et al (20) 2005	Breast cancer	FFQ	192	Correlation	0.47	Yes	Baseline only	—	6.6
Silvera et al (31) 2005	Breast cancer	FFQ	86	CHO not validated	—	N/a	Baseline only	—	16.6
Giles et al (21) 2006	Breast cancer	FFQ	121	Correlation	0.78	No	Twice	2	4
Terry et al (22) 2003	Colorectal cancer	FFQ	86	CHO not validated	—	N/a	Baseline only	—	16.5
Oh et al (23) 2004	Colorectal cancer	FFQ	116	Correlation	0.61	Yes	5	4	18
Higginbotham et al (34) 2004	Colorectal cancer	FFQ	131	Correlation	0.73	Yes	Baseline only	—	7.9
Michaud et al (35) 2005[2]	Colorectal cancer	FFQ	131	Correlation	0.73	Yes	4	4	14
Michaud et al (35) 2005[3]	Colorectal cancer	FFQ	116	Correlation	0.61	Yes	5	4	20
McCarl et al (36) 2006	Colorectal cancer	FFQ	127	Correlation	0.45	Yes	Baseline only	—	15
Larsson et al (29) 2007	Colorectal cancer	FFQ	67	Correlation	0.53	Yes	Twice	8	15.7
Michaud et al (37) 2002	Pancreatic cancer	FFQ	61	Correlation	0.45	Yes	3	4	18
Silvera et al (25) 2005	Pancreatic cancer	FFQ	86	CHO not validated	—	N/a	Baseline only	—	16.5
Johnson et al (24) 2005	Pancreatic cancer	FFQ	126	Correlation	0.61	Yes	Baseline only	—	15
Patel et al (11) 2007	Pancreatic cancer	FFQ	68	Correlation	0.73	Yes	Baseline only	—	9
Folsom et al (26) 2003	Endometrial cancer	FFQ	126	Correlation	0.61	Yes	Baseline only	—	15
Silvera et al (27) 2005	Endometrial cancer	FFQ	86	CHO not validated	—	N/a	Baseline only	—	16.4
Larsson et al (32) 2006	Endometrial cancer	FFQ	67	Correlation	0.53	Yes	Twice	8	15.6
Silvera et al (33) 2007	Ovarian cancer	FFQ	86	CHO not validated	—	N/a	Baseline only	—	16.4
Larsson et al (28) 2006	Gastric cancer	FFQ	67	Correlation	0.53	Yes	Twice	7	17
Tsai et al (39) 2005	Gallbladder disease	FFQ	131	Correlation	0.73	Yes	3	4	12
Tsai et al (38) 2005	Gallbladder disease	FFQ	116	Correlation	0.61	Yes	5	4	16
Schaumberg et al (41) 2004[2]	Eye disease	FFQ	126	Correlation	0.73	Yes	3	4	12
Schaumberg et al (41) 2004[3]	Eye disease	FFQ	126	Correlation	0.69	Yes	4	4	14
Chiu et al (42) 2005	Eye disease	FFQ	126	Correlation	0.73	Yes	5	4	14
Chiu et al (40) 2006	Eye disease	FFQ	126	Correlation	0.61	Yes	4	4	10

[1] WFR, weighed food record; FFQ, food-frequency questionnaire; CHO, carbohydrate.
[2] Men.
[3] Women.

number of participants ranged from 526 in the study by Chiu et al (40) to 124 907 in the Cancer Society Cancer Prevention Study II reported by Patel et al (11). Most of the participants in the studies were women (90.4%). Of the 37 studies, 7 reported diabetes events, 7 reported breast cancer events, 6 reported colorectal cancer events, 3 reported cardiovascular disease events, 3 reported eye disease events, 4 reported pancreatic cancer events, 3 reported endometrial cancer events, 2 reported gallbladder disease events, 1 reported ovarian cancer events, and 1 reported gastric cancer events. Diagnosis was primarily through the assessment of the participant's medical records (65%) or biochemical (eg, fasting plasma glucose or oral glucose tolerance) tests

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(11%). However, diagnosis was based on self-report in 5 of the studies and on physical examination in 4. The participants ranged in age from 24 to 76 y, and their average BMI (kg/m^2) ranged from 23.5 to 29.0. The median dietary GI of the groups was 54 (glucose = 100; range: 50–61), and the median dietary GL was 112 units (range: 80–140 units). The median GI value for the highest quantile was 58 and for the lowest quantile was 49. The median GL value in the highest quantile was 142 and in the lowest quantile was 92. FFQs were used in all studies, except for in the study by van Dam et al (16), who used the diet history method for assessing typical food and nutrient intakes. Correlation coefficients for total carbohydrates between the FFQs and weighed food records ranged from a low of 0.45 in the study by Stevens et al (13) to a high of 0.78 in the studies by Hodge et al (8) and Giles et al (21). However, the validation studies of Hodge et al (8), Giles et al (21), and Stevens et al (13) were not conducted in a population representative of their cohorts (46, 47), and for the purposes of this meta-analysis, were not considered to be valid estimates. No study directly assessed the ability of their FFQ to measure GI or GL. The greater proportion (46%) of studies only assessed food and nutrient intakes at baseline, although a reasonable proportion assessed intakes twice (20%) and 5 times (16%) and the remainder from 3 (10%) to 4 (8%) times throughout the duration of the study. The duration of follow-up ranged from 4 to 20 y.

Most of the studies used basic models, controlling for age and sex only, and then used increasingly complex models (3 levels of complexity per study, on average), adjusting for either known chronic disease risk factors or those determined through the authors independent analysis of their data. We performed the meta-analysis on both the basic and fully adjusted models (age; sex, when appropriate; family history of disease; BMI; smoking; alcohol consumption; physical activity; dietary fiber; and medication and dietary supplement use). However, the results presented are for the fully adjusted data only, because these were reported as the main findings in the original articles.

Listed in **Table 3** are the RRs and 95% CIs for the fully adjusted random-effects models that investigated the association between GI and GL and the risk of developing type 2 diabetes, heart disease, stroke, breast cancer, colorectal cancer, pancreatic cancer, endometrial cancer, gastric cancer, gallbladder disease, eye disease, and all diseases combined. When all of the studies were analyzed, there were significant positive associations between GI or GL and RR for type 2 diabetes (GI RR = 1.20, 95% CI: 1. 04, 1.38; GL RR = 1.16, 95% CI: 1.04, 1.28), heart disease (GI RR = 1.25; 95% CI: 1.00, 1.56), colorectal cancer (GI RR = 1.10; 95% CI: 1.00, 1.21), endometrial cancer (GL RR = 1.40; 95% CI: 1.05, 1.87), gallbladder disease (GI RR = 1.26, 95% CI: 1.13, 1.40; GL RR = 1.42, 95% CI: 1.25, 1.60), and all diseases combined (GI RR = 1.12, 95% CI: 1.08, 1.17; GL RR = 1.09, 95% CI: 1.05, 1.14). In an analysis stratified by the 2 major chronic disease groups, cancer and cardiovascular disease, there were significant positive associations between GI and risk of all cancers (RR = 1.08; 95% CI: 1.02, 1.14) and between GL and risk of all cardiovascular diseases (RR = 1.41; 95% CI: 1.18, 1.69).

In an analysis stratified by the type of chronic disease (type 2 diabetes, heart disease, stroke, breast cancer, colorectal cancer, pancreatic cancer, endometrial cancer, gastric cancer, gallbladder disease, or eye disease) and validity of the study FFQ (correlation for total carbohydrate with a weighed food record ≥0.5 in a group representative of the cohort; **Table 4**), there were significant positive associations between GI or GL and risk of type 2 diabetes (GI RR = 1.40, 95% CI: 1. 23, 1.59; GL RR = 1.27, 95% CI: 1.12, 1.45), heart disease (GI RR = 1.25; 95% CI: 1.00, 1.56), gallbladder disease (GI RR = 1.26, 95% CI: 1.13, 1.40; GL RR = 1.41, 95% CI: 1.25, 1.60), breast cancer (GI RR = 1.08, 95% CI: 1.02, 1.16), and for all diseases combined (GI RR = 1.14, 95% CI: 1.09, 1.19; GL RR = 1.09, 95% CI: 1.04, 1.15). There was a nonsignificant positive association between GI and colorectal cancer (RR = 1.11; 95% CI: 0.99, 1.24; P = 0.059). Results are shown in **Figure 2** and **Figure 3** for GI and GL, respectively. When stratified by the 2 major chronic disease groups and validity of study FFQ, significant positive associations remained between GI and risk of all cancers (GI RR = 1.08; 95% CI: 1.03, 1.14) and GL and risk of all cardiovascular diseases (RR = 1.41; 95% CI: 1.00, 1.97). When the 5 studies that relied on self-diagnosis were removed from the analysis, the RR remained essentially the same for GI (RR = 1.12; 95% CI: 1.05, 1.16; $P < 0.0001$), but increased slightly for GL (RR = 1.11; 95% CI: 1.05, 1.17; $P < 0.0001$).

In sensitivity analyses, exclusion of any single prospective cohort study from the analysis did not alter the overall findings of a positive association of GI or GL and chronic disease risk. There was no evidence of publication bias in funnel plots ($P < 0.0001$). The overall results obtained are credible at the 95% level, according to the Bayesian method of Matthews (48) based on the critical prior interval, as long as prior experience indicates that odds ratios >1.035 are reasonable.

DISCUSSION

In a meta-analysis of 37 prospective observational studies, we found that diets with a high GI or GL independently increased the risk of type 2 diabetes (GI RR = 1.40; GL RR = 1.27), heart disease (GI RR = 1.25), gallbladder disease (GI RR = 1.26; GL RR = 1.41), breast cancer (GI RR = 1.08), and all diseases combined (GI RR = 1.14; GL RR = 1.09). Overall, there were more positive associations of greater magnitude between GI and chronic disease than between GL and chronic disease. The findings indicate that the protection offered by low GI or GL diets is similar or higher than that seen for whole grains or fiber on the risk of type 2 diabetes (49), coronary heart disease (50, 51), or colorectal cancer (52). Habitual intake of whole grains, for example, produces a 20–40% reduction in the risk of coronary heart disease (50) and a 20–30% reduction in risk of diabetes (49) compared with rare consumption.

This meta-analysis has notable strengths. There were many large studies with a correspondingly high number of incident cases, which improved the statistical power to detect significant differences. We found no evidence of publication bias on testing, and our sensitivity analysis showed minimal influence on the combined results for any single study: the heterogeneity of variance between studies was allowed for by using random-effects models. A limitation, however, was that 90% of participants were female; therefore, the findings may not be generalizable to men. We made an a priori assumption that validation of carbohydrate intake was an important attribute of more reliable studies on GI and GL. A significant limitation, however, was the fact that no study actually validated the assessment of GI or GL using another dietary method or against an objective standard. The assignment of GI values to

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TABLE 3
Rate ratios (and 95% CIs) for the comparison of the highest with the lowest quantile for developing chronic disease because of increasing glycemic index or glycemic load in 37 prospective cohort studies

Chronic disease	Glycemic index rate ratio[1]	*P*	Glycemic load rate ratio[1]	*P*
Type 2 diabetes				
Salmeron et al (6) 1997	1.37 (1.02, 1.84)	0.035	1.25 (0.90, 1.73)	0.181
Salmeron et al (7) 1997	1.37 (1.09, 1.72)	0.006	1.47 (1.16, 1.86)	0.001
Meyer et al (12) 2000	0.89 (0.72, 1.10)	0.281	0.95 (0.78, 1.16)	0.612
Stevens et al (13) 2002[2]	1.03 (0.86, 1.23)	0.746	1.10 (0.89, 1.37)	0.386
Stevens et al (13) 2002[3]	1.00 (0.77, 1.30)	1.000	0.97 (0.71, 1.32)	0.847
Hodge et al (8) 2004	1.36 (0.95, 1.95)	0.094	0.91 (0.52, 1.59)	0.739
Schulze et al (9) 2004	1.590 (1.21, 2.10)	0.001	1.33 (0.92, 1.92)	0.126
Zhang et al (10) 2006	1.30 (1.00, 1.69)	0.047	1.61 (1.02, 2.54)	0.040
Patel et al (11) 2007	—	—	1.15 (1.06, 1.25)	0.001
Overall	1.20 (1.04, 1.38)	0.014	1.16 (1.04, 1.28)	0.006
Heart disease				
Liu et al (14) 2000	1.28 (1.00, 1.64)	0.050	1.98 (1.41, 2.78)	0.000
van Dam et al (16) 2000	1.11 (0.66, 1.87)	0.694	1.33 (0.92, 1.92)	0.126
Overall	1.25 (1.00, 1.56)	0.050	1.57 (0.87, 2.84)	0.140
Stroke				
Oh et al (15) 2005[4]	0.90 (0.67, 1.18)	0.370	1.03 (0.76, 1.39)	0.846
Oh et al (15) 2005[5]	1.12 (0.83, 1.52)	0.463	1.61 (1.15, 2.26)	0.006
Overall	1.00 (0.81, 1.24)	0.979	1.28 (0.83, 1.98)	0.272
Breast cancer				
Jonas et al (17) 2003	1.03 (0.87, 1.22)	0.732	0.90 (0.76, 1.07)	0.240
Cho et al (18) 2003	1.05 (0.83, 1.33)	0.685	1.06 (0.78, 1.45)	0.713
Holmes et al (30) 2004	1.08 (0.97, 1.20)	0.156	0.99 (0.89, 1.10)	0.852
Holmes et al (30) 2004	1.15 (1.02, 1.30)	0.024	1.03 (0.90, 1.17)	0.659
Higginbotham et al (19) 2004	1.03 (0.83, 1.27)	0.783	1.01 (0.76, 1.35)	0.946
Nielsen et al (20) 2005	0.94 (0.80, 1.10)	0.446	1.04 (0.90, 1.20)	0.582
Silvera et al (31) 2005	1.87 (1.18, 2.97)	0.008	1.08 (0.82, 1.42)	0.578
Giles et al (21) 2006	0.98 (0.88, 1.10)	0.740	1.19 (0.93, 1.52)	0.170
Overall	1.06 (0.98, 1.15)	0.156	0.99 (0.94, 1.06)	0.970
Colorectal cancer				
Terry et al (22) 2003	—	—	1.05 (0.73, 1.52)	0.796
Oh et al (23) 2004	1.11 (0.94, 1.32)	0.228	0.92 (0.76, 1.11)	0.388
Higginbotham et al (34) 2004	1.71 (0.98, 2.98)	0.059	2.85 (1.40, 5.80)	0.004
Michaud et al (35) 2005[6]	1.08 (0.87, 1.34)	0.485	0.89 (0.71, 1.11)	0.307
Michaud et al (35) 2005[7]	1.14 (0.88, 1.48)	0.323	1.32 (0.98, 1.78)	0.071
McCarl et al (36) 2006	1.08 (0.88, 1.32)	0.457	1.09 (0.88, 1.35)	0.430
Larsson et al (29) 2007	1.00 (0.75, 1.33)	1.000	1.06 (0.81, 1.39)	0.672
Overall	1.10 (1.00, 1.21)	0.044	1.08 (0.92, 1.26)	0.352
Pancreatic cancer				
Michaud et al (37) 2002	1.16 (0.69, 1.96)	0.579	1.53 (0.96, 2.44)	0.075
Silvera et al (25) 2005	1.43 (0.56, 3.65)	0.454	0.80 (0.45, 1.42)	0.444
Johnson et al (24) 2005	1.08 (0.74, 1.58)	0.691	0.87 (0.56, 1.35)	0.532
Patel et al (11) 2007[7]	0.80 (0.53, 1.20)	0.284	1.10 (0.73, 1.65)	0.644
Patel et al (11) 2007[6]	1.11 (0.71, 1.74)	0.648	0.89 (0.56, 1.41)	0.621
Overall	1.03 (0.83, 1.27)	0.785	1.02 (0.82, 1.27)	0.843
Endometrial cancer				
Folsom et al (26) 2003	1.05 (0.77, 1.43)	0.757	1.24 (0.90, 1.71)	0.193
Silvera et al (27) 2005	1.47 (0.90, 2.41)	0.125	1.36 (1.01, 1.84)	0.044
Larsson et al (32) 2006	1.73 (0.72, 4.16)	0.221	2.99 (1.17, 7.66)	0.022
Overall	1.20 (0.93, 1.55)	0.168	1.40 (1.05, 1.87)	0.023
Ovarian cancer				
Silvera et al (33) 2007	1.27 (0.65, 2.48)	0.483	1.72 (1.13, 2.62)	0.011
Overall	1.27 (0.65, 2.48)	0.483	1.72 (1.13, 2.62)	0.011
Gastric cancer				
Larsson et al (28) 2006	0.77 (0.46, 1.29)	0.320	0.76 (0.46, 1.25)	0.282
Overall	0.77 (0.46, 1.29)	0.320	0.76 (0.46, 1.25)	0.282
Gallbladder disease				
Tsai et al (39) 2005	1.17 (0.99, 1.37)	0.056	1.46 (1.14, 1.87)	0.003
Tsai et al (38) 2005	1.31 (1.18, 1.45)	<0.0001	1.40 (1.22, 1.61)	<0.0001
Overall	1.26 (1.13, 1.40)	<0.0001	1.42 (1.25, 1.60)	<0.0001

(Continued)

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TABLE 3 (*Continued*)

Chronic disease	Glycemic index rate ratio[1]	*P*	Glycemic load rate ratio[1]	*P*
Eye disease				
Schaumberg et al (41) 2004[6]	1.11 (0.99, 1.25)	0.079	1.01 (0.83, 1.23)	0.921
Schaumberg et al (41) 2004[7]	0.95 (0.81, 1.11)	0.523	0.86 (0.65, 1.13)	0.285
Chiu et al (42) 2005[8]	1.09 (0.61, 1.94)	0.770	—	—
Chiu et al (42) 2005[9]	1.15 (0.63, 2.10)	0.649	—	—
Chiu et al (40) 2006	2.71 (1.24, 5.93)	0.013	—	—
Overall	1.10 (0.91, 1.31)	0.323	0.96 (0.82, 1.12)	0.590
All diseases (6–42)				
Overall	1.13 (1.08, 1.19)	<0.0001	1.10 (1.06, 1.15)	<0.0001

[1] Final fully adjusted models only.
[2] White Americans.
[3] Black Americans.
[4] BMI < 25 kg/m^2.
[5] BMI ≥ 25 kg/m^2.
[6] Women.
[7] Men.
[8] Cortical opacity.
[9] Nuclear opacity.

foods in a nutrient database is to some extent subjective and may be unreliable when extrapolating from one country to another. It is likely in any case that any misclassification of GI or GL would lead to a bias toward the null hypothesis and diminish the observed effect size. Despite comprehensive measurement and adjustment strategies, the uncontrolled or residual confounding in observational studies of dietary intake is always a concern. Healthy lifestyle effects associated with dietary intake cannot be completely adjusted for in observational studies. Therefore, a meta-analysis of intervention studies looking at "hard" clinical endpoints, not chronic-disease risk factors, may be warranted, when sufficient data have accumulated.

Our findings support the hypothesis that postprandial hyperglycemia, in individuals without diabetes, contributes to chronic disease. Higher glucose concentrations are thought to play a direct pathogenic role in the disease process. The DECODE study, a meta-analysis of 13 studies involving 25 000 individuals, found an almost 2-fold increased risk of all-cause mortality in individuals with an elevated 2-h postchallenge blood glucose (53). Similarly, a meta-analysis of 38 studies involving 194 000 individuals found a progressive relation between hyperglycemia and cardiovascular disease risk (54). Cancer risk is also elevated in those with preexisting hyperglycemia. Larsson et al (55) reported a 30% increase in risk of colorectal cancer in a meta-analyses of persons with type 2 diabetes; similarly, Huxley et al (56) found an 82% increase in risk of pancreatic cancer.

There are plausible mechanisms linking the development of certain chronic diseases with high-GI diets. Specifically, 2 major pathways have been proposed to explain the association with type 2 diabetes risk (57). First, the same amount of carbohydrate from high-GI foods produces higher blood glucose concentrations and a greater demand for insulin. The chronically increased insulin demand may eventually result in pancreatic β cell failure, and, as a consequence, impaired glucose tolerance. Second, there is evidence that high-GI diets may directly increase insulin resistance through their effect on glycemia, free fatty acids, and counter-regulatory hormone secretion. High glucose and insulin concentrations are associated with increased risk profiles for cardiovascular disease, including decreased concentrations of

TABLE 4
Rate ratios (and 95% CIs) for the comparison of the highest with the lowest quantile for developing chronic disease because of increasing glycemic index or glycemic load in 27 prospective cohort studies meeting a priori exclusion criteria (correlation between food-frequency questionnaire and weighed food records/24-h dietary recall ≥ 0.5 in representative subgroups)

Chronic disease	Glycemic index rate ratio[1]	*P*	Glycemic load rate ratio[1]	*P*
Type 2 diabetes (6–11)	1.40 (1.23, 1.59)	<0.0001	1.27 (1.12, 1.45)	<0.0001
Heart disease (14, 16)	1.25 (1.00, 1.56)	0.050	1.57 (0.87, 2.84)	0.140
Stroke (15)	1.02 (0.86, 1.21)	0.805	1.28 (0.83, 1.98)	0.270
Breast cancer (17–19, 21, 30)	1.09 (1.02, 1.16)	0.015	0.99 (0.92, 1.06)	0.797
Colorectal cancer (23, 29, 34, 35)	1.11 (0.99, 1.24)	0.059	1.11 (0.88, 1.40)	0.385
Pancreatic cancer (11, 24)	0.98 (0.78, 1.25)	0.896	0.96 (0.75, 1.23)	0.733
Endometrial cancer (26, 32)	1.13 (0.80, 1.60)	0.489	1.72 (0.75, 3.95)	0.204
Gastric cancer (28)	0.77 (0.46, 1.29)	0.320	0.76 (0.46, 1.25)	0.282
Gallbladder disease (38, 39)	1.26 (1.13, 1.40)	<0.0001	1.41 (1.25, 1.60)	<0.0001
Eye disease (40–42)	1.10 (0.91, 1.31)	0.323	0.96 (0.82, 1.12)	0.590
All diseases (6–11, 14–19, 21, 23, 24, 26, 28–30, 32, 34, 35, 38–42)	1.14 (1.09, 1.19)	<0.0001	1.09 (1.04, 1.15)	<0.0001

[1] Final fully adjusted models only.

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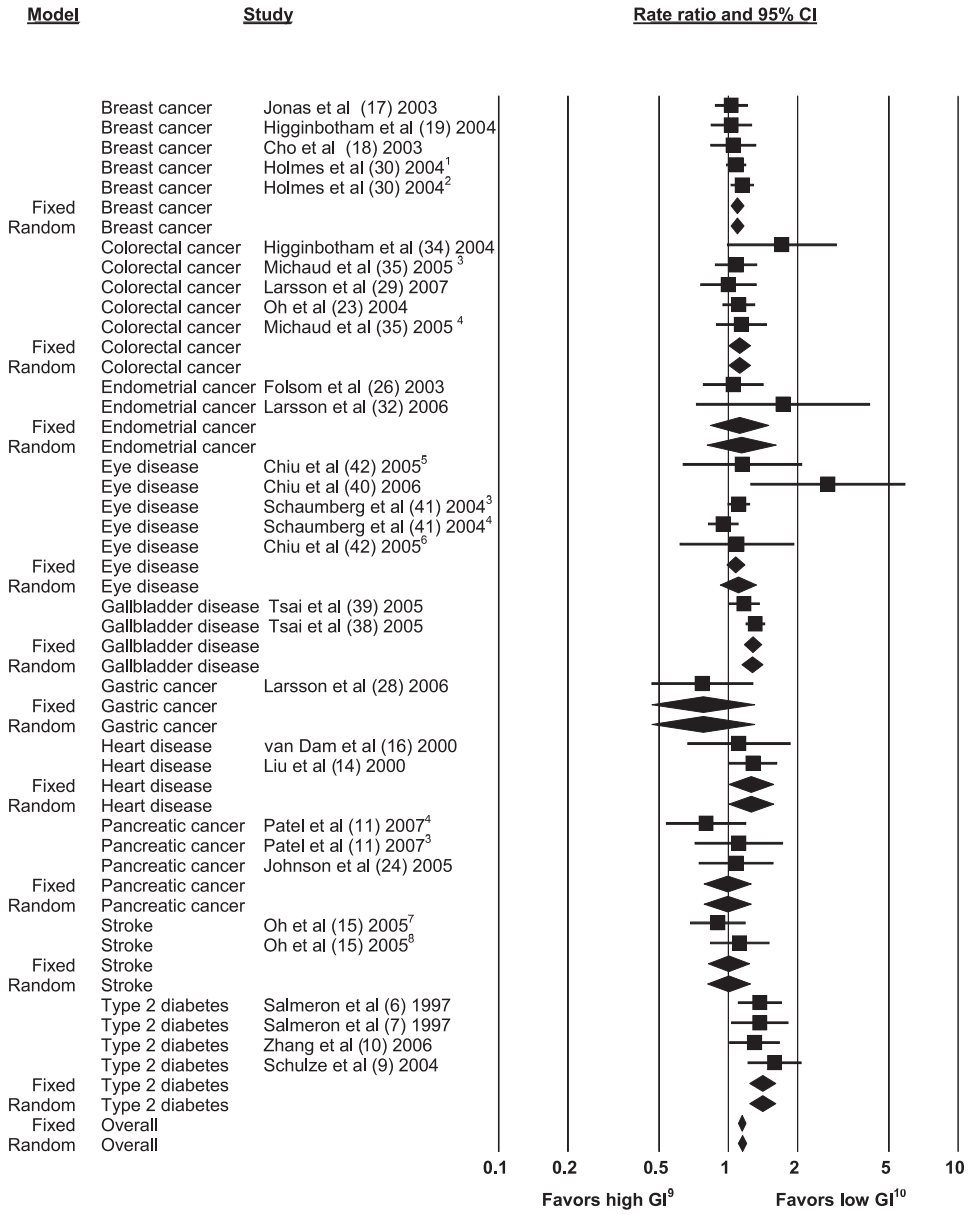

FIGURE 2. Rate ratios and 95% CIs for fully adjusted fixed- and random-effects models that investigated the association between glycemic index (GI) and risk of developing type 2 diabetes, heart disease, stroke, breast cancer, colorectal cancer, pancreatic cancer, endometrial cancer, gastric cancer, gallbladder disease, eye disease, and all diseases combined. Data apply to validated studies only, in order of follow-up. [1]Premenopausal women. [2]Postmenopausal women. [3]Women. [4]Men. [5]Nuclear opacity. [6]Cortical opacity. [7]BMI < 25 kg/m^2. [8]BMI ≥ 25 kg/m^2. [9]Diets with a high GI reduce chronic disease risk. [10]Diets with a low GI reduce chronic disease risk.

HDL cholesterol, increased glycosylated proteins, oxidative status, hemostatic variables, and poor endothelial function (58). The mitogenic action of insulin-like growth factors suggests a role in the etiology of various cancers. Insulin itself stimulates a rise in free insulin-like growth factors, which are necessary for the cell to progress from the G1 to the S phase of the cell cycle (58).

The reason that low-GI diets may offer greater protection than low-GL diets may be due to the fact that low-GL diets are more heterogeneous and can include either low-GI, high-carbohydrate foods or low-carbohydrate foods (eg, meat and cheese) (59). Although both diets will reduce postprandial glycemia, it is likely that the 2 dietary patterns will have very different metabolic effects, including differences in β cell function (60), triacylglycerol concentrations (60), free fatty acid concentrations (61), and effects on satiety (62). These factors would, in turn, affect the risk of developing chronic disease in genetically susceptible individuals.

This meta-analysis provides high-level evidence that diets with a high GI, high GL, or both, independently of known confounders, including fiber intake, increase the risk of chronic lifestyle-related diseases. The effect was modest overall (GI RR = 1.14; GL RR = 1.09) but more pronounced for type 2 diabetes (GI RR = 1.40; GL RR = 1.27), heart disease (GI RR = 1.25), and gallbladder disease (GI RR = 1.26; GL RR = 1.41). Overall,

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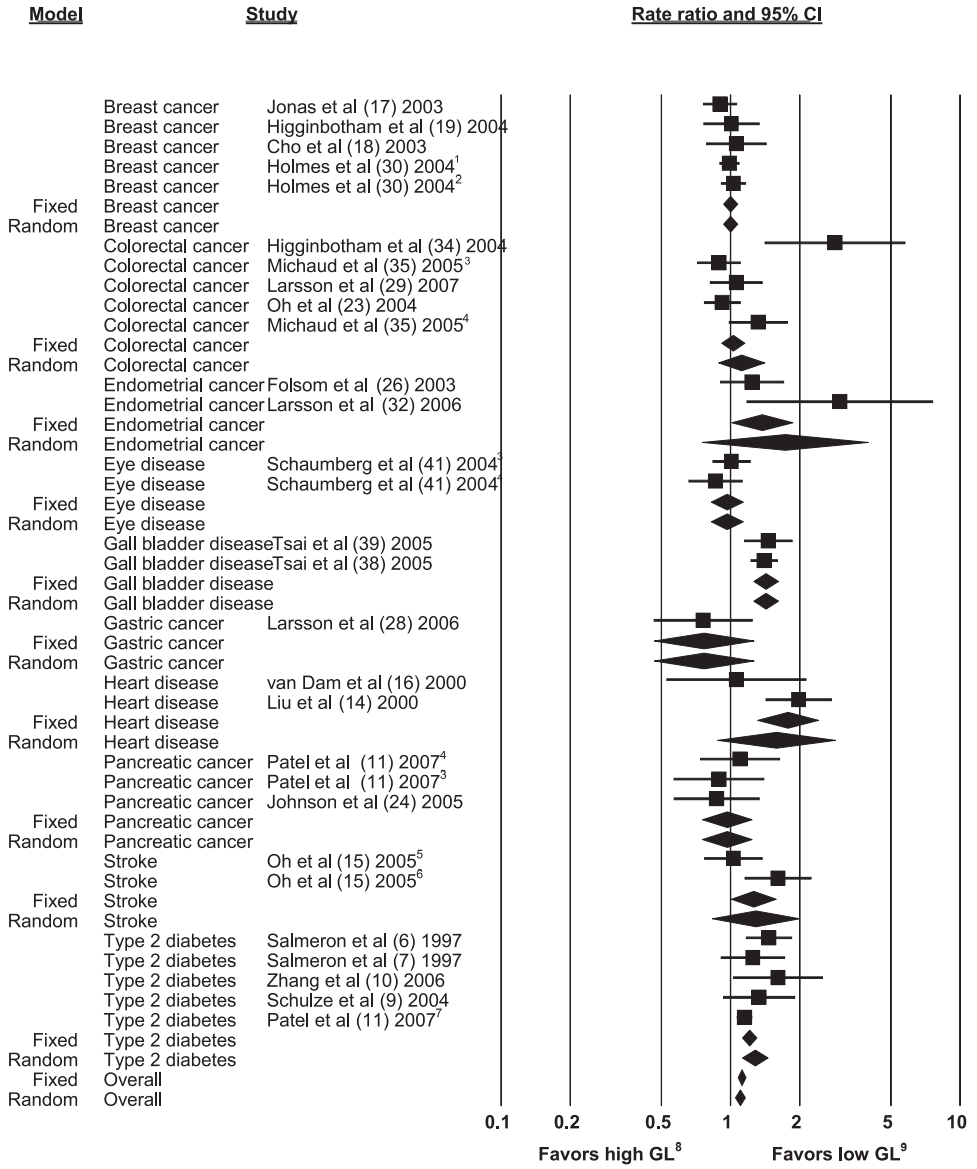

FIGURE 3. Rate ratios and 95% CIs for fully adjusted fixed- and random-effects models that investigated the association between glycemic load (GL) and risk of developing type 2 diabetes, heart disease, stroke, breast cancer, colorectal cancer, pancreatic cancer, endometrial cancer, gastric cancer, gallbladder disease, eye disease, and all diseases combined. Data apply to validated studies only, in order of follow-up. [1]Premenopausal women. [2]Postmenopausal women. [3]Women. [4]Men. [5]BMI < 25 kg/m^2. [6]BMI ≥ 25 kg/m^2. [7]Women and men. [8]Diets with a high GL reduce chronic disease risk. [9]Diets with a low GL reduce chronic disease risk.

the GI had a more powerful effect than did the GL (the product of carbohydrate and GI), with more positive associations between GI and chronic disease risk, and associations of greater magnitude, which suggests that, irrespective of the level of carbohydrate intake, the GI of contributing carbohydrate foods is important. The findings indicate that the judicious choice of low-GI foods offers a similar or higher level of protection as whole-grain foods or high fiber intake in the prevention of chronic lifestyle-related disease. The observation that a subgroup (the lowest quantile) of people in developed countries self-selects a low-GI or a low-GL diet is evidence that such diets can be sustained over the longer term. Because most participants were women, there is a need to confirm the findings in men.

The authors' responsibilities were as follows—JCB-M, AWB, PP, and VMF: conceived the study; AWB and JM-P: conducted the literature search and data input; PP and TP: conducted the statistical analyses; and AWB: prepared the first draft of the manuscript. All authors contributed to the writing, editing, and proofing of the final manuscript. JCB-M is a coauthor of *The New Glucose Revolution* book series (Hodder and Stoughton, London; Marlowe and Co, NY; Hodder Headline, Sydney; and elsewhere), is the Director of a not-for-profit GI-based food endorsement program in Australia, and manages the University of Sydney GI testing service. AWB is a coauthor of one of these books (the *Diabetes & Pre-diabetes Handbook*) and is a consultant to a not-for-profit GI-based food endorsement program in Australia. JM-P is a coauthor of 2 of these books, including *The Low GI Diet*. None of the other authors had a conflict of interest to disclose.

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