Associations of Glycemic Index and Load With Coronary Heart Disease Events: A Systematic Review and Meta-Analysis of Prospective Cohorts

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Background—Glycemic index (GI) and glycemic load (GL) have been associated with coronary heart disease (CHD) risk in some but not all cohort studies. We therefore assessed the association of GI and GL with CHD risk in prospective cohorts.

Methods and Results—We searched MEDLINE, EMBASE, and CINAHL (through April 5, 2012) and identified all prospective cohorts assessing associations of GI and GL with incidence of CHD. Meta-analysis of observational studies in epidemiology (MOOSE) methodologies were used. Relative measures of risk, comparing the group with the highest exposure (mean GI of cohorts=84.4 Gl units, range 79.9 to 91; mean GL of cohorts=224.8, range 166 to 270) to the reference group (mean GI=72.3 Gl units, range 68.1 to 77; mean GL=135.4, range 83 to 176), were pooled using random-effects models, expressed as relative risk (RR) with heterogeneity assessed by $\chi^2$ and quantified by $I^2$. Subgroups included sex and duration of follow-up. Ten studies (n=240 936) were eligible. Pooled analyses showed an increase in CHD risk for the highest GI quantile compared with the lowest, with RR=1.11 (95% confidence interval [CI] 0.99 to 1.24) and for GL, RR=1.27 (95% CI 1.09 to 1.49), both with evidence of heterogeneity (I$^2$=42%, P<0.07). Subgroup analyses revealed only a significant modification by sex, with the female cohorts showing significance for GI RR=1.26 (95% CI 1.12 to 1.41) and for GL RR=1.55 (95% CI 1.18 to 2.03).

Conclusions—High GI and GL diets were significantly associated with CHD events in women but not in men. Further studies are required to determine the relationship between GI and GL with CHD in men. (J Am Heart Assoc. 2012;1:e000752 doi: 10.1161/JAHA.112.000752)

Key Words: coronary heart disease • glycemic index and load • meta-analysis • nutrition • prospective cohort

High-risk lifestyle and dietary patterns have been proposed to account for more than 80% of all coronary disease events in Western nations. The predominant concern in heart disease prevention has been saturated fatty acid (SFA) reduction, leading to widespread therapeutic adoption of low-total-fat, high-carbohydrate diets as the standard dietary approach for the reduction of coronary heart disease (CHD) risk. However, recent prospective cohort meta-analyses suggest an even greater increase in CHD risk when highly refined and readily absorbed carbohydrates replaced SFAs. In addition, replacement of SFAs with unsaturated fatty acids and complex carbohydrates is associated with favorable changes in CHD risk factors. These findings have intensified the focus on carbohydrates, because diets rich in highly processed carbohydrates can lead to raised triglycerides (TGs), reductions in high-density lipoprotein cholesterol (HDL-C), and increasing CHD risk.

Carbohydrates with differing physical form, particle size, chemical structure, and fiber content alter the rate of starch digestion and their physiological response. The glycemic index (GI) was developed to characterize the rate of digestion...
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Cohort studies have also shown an association between low GI and GL with CHD (including myocardial infarction [MI] or death due to CHD) in adults. Despite the proposed physiological mechanisms, published cohort studies in the last decade have produced mixed results for the associations of GI and GL with CHD. We therefore undertook a systematic review and meta-analysis of prospective cohort studies with healthy populations at baseline to determine whether associations exist between GI and GL with CHD.

Methods

Data Sources and Study Selection

We conducted separate searches for all prospective cohort studies that assessed potential associations between glycemic index or load and primary incidence of CHD (including myocardial infarction [MI] or death due to CHD) in adults. We followed the meta-analysis of observational studies in epidemiology (MOOSE) guidelines for this report. Electronic databases (MEDLINE 1946-March, Week 4, 2012; EMBASE 1980–2012, Week 13; CINAHL 1982–December 2011) were searched by 2 individuals independently; searches were supplemented by manual searches through the reference lists of original publications and review articles. The following search terms were used: [(Glycemic or Glycaemic Index) or (Glycemic or Glycaemic Load)] and (CHD or Cardiovascular Disease or CVD or MI) and (Prospective or Cohort). Titles and abstracts were initially reviewed to identify relevant reports by 2 independent reviewers (A.M., L.C., both investigators); reviewers conducted a subsequent full-text assessment of all studies in which there was uncertainty about the assessment of relevance. Disagreements regarding eligibility were resolved through discussion with 2 additional adjudicators (D.J.A.J/R.J.D.).

Data Extraction

Two reviewers (A.M., L.C.) independently reviewed and extracted relevant data employing a standardized pro forma sheet with the first author and year of publication used as study identifiers for convenience. Data extracted from each cohort included information about sample size, population characteristics (age and sex), country of origin, follow-up duration, method of collecting dietary information, outcome measures, exposure quantification, and analytical methods, including adjustment parameters used for confounding factors. The most complete multivariate adjusted risk estimates from eligible studies assessing GI and GL associations with CHD events with their corresponding confidence intervals (CIs) were extracted to provide the main end points. All authors of eligible reports were contacted to acquire any missing data for each exposure level including number of events, person-years, mean or median dose of GI and GL (all values were converted to bread scale [GI=100] if not already reported as such, as well as risk estimates with corresponding CIs.

Data Synthesis

Data were analyzed using Review Manager (RevMan) 5.1.4 (Cochrane Library software, Oxford, UK) and STATA version 11.0 (StataCorp, College Station, TX). The natural log-transformed relative risks of CHD events (including MI) with corresponding standard errors comparing the highest exposure level with the reference group from each cohort, irrespective of the number of quantile divisions in the original analysis, were pooled in separate analyses for GI and GL. The generic inverse variance method with random-effects models in RevMan were used to allow for heterogeneity assessment. Inter-study heterogeneity was tested by Cochrane’s Q (χ²) and quantified by the I² statistic. Regardless of P value, sensitivity analyses were performed to identify sources of heterogeneity. Potential publication bias was assessed visually by inspecting funnel plots of effect size against the standard error and formally tested using Begg’s and Egger’s tests in STATA. Our a priori stratified analyses included sex and duration of follow-up, that is, whether studies were more or less than 10 years, consistent with the 10-year Framingham Risk Score approach, and analyzed using meta-regression in STATA. Statistical significance was defined as P<0.05 for all comparisons, except for Cochrane’s Q (χ²), where significance was set at <0.10.

Results

Search Results

Figure 1 shows the flow of the literature applying the systematic search and selection strategies. In all, 473 eligible
studies were identified by the search. A total of 10 studies with 12 GI reports28–31,33,35,36,42,43 and 12 GL reports28–31,33–36,42,43 were selected for analyses. Two reports28,34 on the Nurses’ Health Study provided data on the GL exposure; only the report with the larger subject numbers and longer follow-up was included in the GL analyses.34,44

Cohort Characteristics

The study characteristics and their diet compositions are shown in Tables 1 and 2, respectively. Of the 10 studies identified, 12 GI and 12 GL reports with CHD risk estimation were included in our analyses, with a total of 233,65528–31,33,35,36,42,43 and 240,93628–31,33–36,42,43 subjects, respectively. During 6 to 25 years of follow-up, 6,940 coronary events were recorded. All studies used Cox proportional hazard models for CHD risk estimation analyses, except for 1 study43 which used restricted cubic spline models. The most common confounders adjusted for included age, BMI, and cigarette smoking, with full multivariate analyses outlined in Table 1. All cohorts excluded those with documented CHD or major CHD risk factor at time of enrollment, with the exception of 1 that included a population 5% of whom had diabetes35 but adjusted for diabetes status. All analyses were stratified by sex. The majority of the studies (7 of 10) used either a semiquantitative or quantitative Food Frequency Questionnaire (SFFQ or FFQ),28,30,31,33,34,36,42 but 3 used 4- or 7-day diet records or diet history interviews for
| Reference     | N   | Age Range | Country      | Years Range   | Mean Duration of Follow-Up, years | Number of Questionnaires Administered* | Total Number of New Events | Quantile Division | Mean/Median GI (GL) Interquantile Ranges | Method for Reporting Events | Adjustments† |
|---------------|-----|-----------|--------------|---------------|----------------------------------|----------------------------------------|---------------------------|------------------|------------------------------------------|-------------------------------|----------------|
| Liu et al28   | 75  | 38 to 63  | United States | 1984–1994     | 10                               | 3 (SFFQ)                               | 761 CHD                   | Quintiles        | 68.1 to 82.7 (117 to 206)                | Death certificates, medical/autopsy records | Hypertension; hypercholesterolemia; parental history of MI; menopause; use of multivitamins, vitamin E, and ASA; dietary intake of folate, vitamin E, trans fat, PUFA, and total protein |
| van Dam et al29 | 646 | 64 to 84  | Netherlands  | 1985–1995     | 10                               | 1 (Interview)                         | 94 CHD                    | Tertiles         | 77.0 to 85.0 (161 to 230)                | Death and hospital discharge registries           | Prescribed diet (yes/no); dietary intake (g/day) of PUFA and CH2O |
| Levitan et al30 | 36  | 45 to 79  | Sweden       | 1998–2003     | 6                                | 1 (FFQ)                               | 1324 MI                   | Quartiles        | 73.0 to 82.9 (176 to 255)                | Death and hospital discharge registries           | Hypertension; hypercholesterolemia; parental history of MI; living alone; use of ASA; dietary intake of PUFA, total protein, CH2O |
| Beulens et al31 | 15  | 49 to 70  | Netherlands  | 1993–2005     | 9                                | 1 (FFQ)                               | 556 CHD                   | Quartiles        | 68.6 to 81.4 (112 to 174)                | Death and hospital discharge registries           | Hypertension; SBP; menopause; education; use of vitamin E; dietary intake of PUFA, MUFA, total protein |
| Sieri et al33  | 13  | 35 to 64  | Italy        | 1993–2004     | 7.9                              | 1 (SFFQ)                               | 305 CHD                   | Quartiles        | 71.9 to 80.7 (168.6 to 270)             | Death certificates, hospital discharge registries and clinical record | Hypertension; education |
| Sieri et al33  | 30  | 35 to 74  | Italy        | 1993–2004     | 7.9                              | 1 (SFFQ)                               | 158 CHD                   | Quartiles        | 71.9 to 80.9 (175.4 to 265.4)           | Death certificates, hospital discharge registries and clinical record | Hypertension; education |
| Hallton et al34 | 82  | 30 to 55  | United States| 1980–2000     | 20                               | 6 (SFFQ)                               | 1994 CHD                   | Deciles          | GI N/A (83 to 256)                      | Death certificates, medical/autopsy records       | Hypertension; hypercholesterolemia; parental history of MI; menopause; use of multivitamins, vitamin E, and ASA; dietary intake of trans fat, PUFA, MUFA, total protein |

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Table 1. Continued

| Reference     | N   | Age Range | Country       | Years Range | Mean Duration of Follow-Up, years | Number of Questionnaires Administered* | Total Number of New Events | Quantile Division | Mean/Median GI (GL) Interquantile Ranges | Method for Reporting Events | Adjustments† |
|---------------|-----|-----------|---------------|-------------|-----------------------------------|----------------------------------------|--------------------------|------------------|------------------------------------------|---------------------------|--------------|
| Mursu et al³⁵ | 1981 (M) | 42 to 60 | Finland       | 1984-2005   | 16.1                              | 1 (FR)                                 | 376 MI                   | Quartiles       | 70.4 to 89.0 (146.1 to 256.7)           | Hospital discharge registries | Diabetes, SBP, hypertension medications; hypercholesterolemia; TAG; family history of CVD; education; dietary intake of folate, vitamin C, and PUFA |
| Burger et al³⁶ | 8855 (M) | 21 to 64 | Netherlands   | 1993-2008   | 11.9                              | 1 (FFQ)                                | 581 CHD                 | Quartiles       | 72.9 to 85.0 (143.4 to 208.0)           | Municipal administration registries, statistics Netherlands | Hypertension; education; dietary MUFA, PUFA, and energy-adjusted vitamin C, CH₂O, and protein intake; plasma total cholesterol and HDL-C |
| Burger et al³⁶ | 10 753 (W) | 21 to 64 | Netherlands   | 1993-2008   | 11.9                              | 1 (FFQ)                                | 300 CHD                 | Quartiles       | 73.3 to 84.9 (144.7 to 208.3)           | Municipal administration registries, statistics Netherlands | Hypertension; education; dietary MUFA, PUFA, and energy-adjusted vitamin C, CH₂O, and protein intake; plasma total cholesterol and HDL-C |
| Levitan et al⁴² | 36 234 (W) | 48 to 83 | Sweden        | 1998-2006   | 9                                 | 1 (FFQ)                                | 1138 MI                 | Quartiles       | 73.3 to 79.9 (128 to 188)               | Death and hospital discharge registries | Hypertension; hypercholesterolemia; parental history of MI; menopause; education; marital status; use of multivitamin, vitamin E, and ASA; dietary intake of trans fat, PUFA, MUFA, total protein |
| Grau et al⁴³  | 1684 (M) | 30 to 70  | Denmark       | 1974-1999   | 6 to 25                            | 1 (Interview/FR)                      | NR                      | Quintiles       | 75.0 to 91.0 (102 to 220)              | Hospital discharge registries | Education; energy-adjusted intake of fat, total protein, and CH₂O |
| Grau et al⁴³  | 1889 (W) | 30 to 70  | Denmark       | 1974-1999   | 6 to 25                            | 1 (Interview/FR)                      | 114 CHD                 | Quintiles       | 72.0 to 89.0 (84 to 166)               | Hospital discharge registries | Education; energy-adjusted intake of fat, total protein, and CH₂O |

M indicates men; W, women; SFFQ, Semiquantitative Food Frequency Questionnaire (validated); FFQ, Food Frequency Questionnaire (validated); Interview, Diet History Interview, FR, food record; GI, glycemic index; GL, glycemic load; BMI, body mass index; CHD, coronary heart disease; MI, myocardial infarction; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; TAG, triacylglyceride; SBP, systolic blood pressure; ASA, aspirin; PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids; CH₂O, carbohydrate; NR, not reported; N/A, not available.

All studies used Cox proportional hazard models in their CHD risk estimation association analyses with GI and GL, except for Grau et al.⁴³

All studies had a healthy starting population at the beginning of follow-up except for Mursu et al.²⁵ who had a 5% diabetic population at the start.

*Number of Questionnaires Administered denotes number of administered questionnaires at the beginning of and throughout the study.
†All studies adjusted for age, BMI, physical activity, alcohol intake, total energy, saturated fat intake.
‡Dietary fiber intake was adjusted for in all but 1 study.²⁷

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food consumption patterns. All studies used the International Tables of Glycemic Index for assessing the GI of different foods; used the 1995 iteration, and used the 2008 iteration. One study further supplemented the 2002 International GI tables with GI values for 159 local food items.

**Table 2.** Dietary Composition Patterns for Each GL Quantile by Total Energy (E), Percent Energy From Carbohydrates, Protein, and Fat and Types of Fat (SFA, PUFA, MUFA)*

| Reference          | First GL Quantile (CH₂O:Prt:Fat) | Second GL Quantile (CH₂O:Prt:Fat) | Third GL Quantile (CH₂O:Prt:Fat) | Fourth GL Quantile (CH₂O:Prt:Fat) | Fifth GL Quantile (CH₂O:Prt:Fat) |
|--------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Liu et al²⁸ (W)     | E: 1702 kcal/day (34:19:NR)       | E: 1783 kcal/day (38:17:NR)      | E: 1797 kcal/day (41:16:NR)      | E: 1767 kcal/day (45:15:NR)       | E: 1676 kcal/day (54:15:NR)       |
|                    | SFA: 13                          | SFA: 12                          | SFA: 11                          | SFA: 11                          | SFA: 10                          |
|                    | MUFA: 7                          | PUFA: 6                          | PUFA: 6                          | PUFA: 6                          | PUFA: 5                          |
|                    | MUFA: 13                         | MUFA: 12                         | MUFA: 12                         | MUFA: 11                         | MUFA: 10                         |
| Fiber/1000 kcal    | 8.2 g                            | 9.0 g                            | 9.5 g                            | 9.6 g                            | 10.7 g                           |
| van Dam et al²⁹ (M)| E: 2272 kcal/day (40:14:NR)       | E: 2321 kcal/day (42:14:NR)      | E: 2177 kcal/day (45:14:NR)      | —                                | —                                |
|                    | SFA: 17                          | SFA: 17                          | SFA: 18                          | —                                | —                                |
|                    | MUFA: NR                         | MUFA: 9                          | MUFA: 8                          | —                                | —                                |
| Fiber/1000 kcal    | 11.0 g                           | 10.9 g                           | 10.2 g                           | —                                | —                                |
| Levitan et al³⁰ (M)| E: 2703 kcal/day (35:14:NR)       | E: 2728 kcal/day (39:13:NR)      | E: 2710 kcal/day (42:13:NR)      | E: 2705 kcal/day (46:12:NR)      | —                                |
|                    | SFA: 13                          | SFA: 12                          | SFA: 11                          | SFA: 9                            | —                                |
|                    | PUFA: 6                          | PUFA: 3                          | PUFA: 3                          | PUFA: 3                          | —                                |
|                    | MUFA: 9                          | MUFA: 9                          | MUFA: 8                          | MUFA: 7                           | —                                |
| Fiber/1000 kcal    | 5.0 g                            | 6.0 g                            | 6.53 g                           | 7.0 g                            | —                                |
| Beulens et al³¹ (W)| E: 1797 kcal/day (36:16:37)       | E: 1828 kcal/day (41:16:35)      | E: 1819 kcal/day (45:15:34)      | E: 1789 kcal/day (51:15:31)      | —                                |
|                    | SFA: 16                          | SFA: 15                          | SFA: 14                          | SFA: 13                           | —                                |
|                    | PUFA: 7                          | PUFA: 7                          | PUFA: 6                          | PUFA: 6                           | —                                |
|                    | MUFA: 14                         | MUFA: 13                         | MUFA: 12                         | MUFA: 11                          | —                                |
| Fiber/1000 kcal    | 11.1 g                           | 12.0 g                           | 12.6 g                           | 13.4 g                           | —                                |
| Sieri et al³³ (M)  | E: 2562 kcal/day (45:18:40)       | E: 2387 kcal/day (50:17:36)      | E: 2409 kcal/day (54:16:33)      | E: 2677 kcal/day (59:15:29)      | —                                |
|                    | SFA: 14                          | SFA: 12                          | SFA: 11                          | SFA: 10                           | —                                |
|                    | PUFA: 5                          | PUFA: 4                          | PUFA: 4                          | PUFA: 4                           | —                                |
|                    | MUFA: 19                         | MUFA: 17                         | MUFA: 16                         | MUFA: 14                          | —                                |
| Fiber/1000 kcal    | 9.0 g                            | 10.1 g                           | 10.9 g                           | 13.1 g                           | —                                |
| Sieri et al³³ (W)  | E: 2194 kcal/day (42:18:42)       | E: 1998 kcal/day (48:17:38)      | E: 2023 kcal/day (52:16:34)      | E: 2300 kcal/day (58:15:30)      | —                                |
|                    | SFA: 15                          | SFA: 13                          | SFA: 12                          | SFA: 10                           | —                                |
|                    | PUFA: 5                          | PUFA: 4                          | PUFA: 4                          | PUFA: 4                           | —                                |
|                    | MUFA: 20                         | MUFA: 18                         | MUFA: 16                         | MUFA: 14                          | —                                |
| Fiber/1000 kcal    | 9.6 g                            | 10.5 g                           | 11.1 g                           | 12.0 g                           | —                                |
| Halton et al³⁴ (W) | NR                               | NR                               | NR                               | NR                               | NR                               |

*Continued*
that were tested at an academic institution following the International GI table methodologies. The majority of the included reports provided dietary pattern data for GL quantiles. The dietary patterns across the different quantiles of GL were similar between studies, with a trend of increasing carbohydrate and decreasing protein and fat content at higher GL quantiles (Table 2).

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Figure 2 (overall analysis) shows the overall pooled relative risk estimation of GI with CHD events. The CHD incidence rate was increased at the highest level of GI exposure (mean GI of 84.4 GI units, range 79.9 to 91) relative to the lowest (mean GI of 72.3 GI units, range 68.1 to 77), RR=1.11, 95% CI 0.99 to 1.24, and approached significance (P=0.09) but with significant evidence of heterogeneity (I²=45%). Sensitivity analyses identified the Grau et al report on men as the largest contributor to heterogeneity. The removal of this study changed the risk estimate for the association of GI with CHD (RR=1.14 [95% CI 1.02 to 1.26], P=0.02) and also improved the precision of the estimate and eliminated much of the heterogeneity (I²=30%, P=0.16). A priori stratification revealed no significant modification of association

Table 2. Continued

| Reference           | First GL Quantile (CH2O:Prt:Fat) | Second GL Quantile (CH2O:Prt:Fat) | Third GL Quantile (CH2O:Prt:Fat) | Fourth GL Quantile (CH2O:Prt:Fat) | Fifth GL Quantile (CH2O:Prt:Fat) |
|---------------------|----------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|
| Mursu et al35 (M)   | E: 2490 kcal/day (36:16:42)      | E: 2310 kcal/day (42:16:40)       | E: 2306 kcal/day (45:15:37)      | E: 2494 kcal/day (49:15:35)       | NA                               |
|                     | SFA: 20                          | SFA: 18                           | SFA: 17                          | SFA: 16                           | NA                               |
|                     | PUFA: 5                          | PUFA: 5                           | PUFA: 5                          | PUFA: 4                           | NA                               |
|                     | MUFA: 13                         | MUFA: 12                          | MUFA: 11                         | MUFA: 10                          | NA                               |
|                     | Fiber/1000 kcal: 8.8 g           | Fiber/1000 kcal: 10.4 g           | Fiber/1000 kcal: 11.3 g          | Fiber/1000 kcal: 11.2 g           | NA                               |
| Burger et al36 (W)  | NA                               | NA                                | NA                               | NA                                | NA                               |
| Burger et al36 (M)  | NA                               | NA                                | NA                               | NA                                | NA                               |
| Levitan et al42 (W) | E: 1765 kcal/day (41:18:NR)      | E: 1727 kcal/day (47:17:NR)       | E: 1728 kcal/day (50:16:NR)      | E: 1745 kcal/day (55:14:NR)       | NA                               |
|                     | SFA: 17                          | SFA: 15                           | SFA: 13                          | SFA: 11                           | NA                               |
|                     | PUFA: 4                          | PUFA: 4                           | PUFA: 4                          | PUFA: 4                           | NA                               |
|                     | MUFA: NR                         | MUFA: NR                          | MUFA: NR                         | MUFA: NR                          | NA                               |
|                     | Fiber/1000 kcal: 10.8 g          | Fiber/1000 kcal: 12.5 g           | Fiber/1000 kcal: 13.4 g          | Fiber/1000 kcal: 14.0 g           | NA                               |
| Grau et al43 (M)   | E: 2536 kcal/day (29:14:43)      | E: 2608 kcal/day (36:14:43)       | E: 2608 kcal/day (36:14:43)      | E: 2584 kcal/day (45:13:39)       | NA                               |
|                     | SFA: NR                          | SFA: NR                           | SFA: NR                          | SFA: NR                           | NA                               |
|                     | PUFA: NR                         | PUFA: NR                          | PUFA: NR                         | PUFA: NR                          | NA                               |
|                     | MUFA: NR                         | MUFA: NR                          | MUFA: NR                         | MUFA: NR                          | NA                               |
|                     | Fiber/1000 kcal: 5.9 g           | Fiber/1000 kcal: 7.3 g            | Fiber/1000 kcal: 7.3 g           | Fiber/1000 kcal: 8.1 g            | NA                               |
| Grau et al43 (W)   | E: 1818 kcal/day (31:16:46)      | E: 1867 kcal/day (38:15:43)       | E: 1867 kcal/day (38:15:43)      | E: 1842 kcal/day (45:14:39)       | NA                               |
|                     | SFA: NR                          | SFA: NR                           | SFA: NR                          | SFA: NR                           | NA                               |
|                     | PUFA: NR                         | PUFA: NR                          | PUFA: NR                         | PUFA: NR                          | NA                               |
|                     | MUFA: NR                         | MUFA: NR                          | MUFA: NR                         | MUFA: NR                          | NA                               |
|                     | Fiber/1000 kcal: 6.6 g           | Fiber/1000 kcal: 8.0 g            | Fiber/1000 kcal: 8.0 g           | Fiber/1000 kcal: 8.7 g            | NA                               |

GL indicates glycemic load; SFA, saturated fatty acids; PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids; CH2O, carbohydrate; Prt, protein; NR, not reported; NA, author was contacted for data, but data were not available; E, total energy (kcal/day); Fiber, g/1000 kcal; W, women; M, men.

Percent energy for each component in each quantile was calculated from reported intake in grams multiplied by energy per gram (4 kcal/g for protein and CH2O, and 9 kcal/g for fat) and expressed as a percentage of the total energy in the respective quantile.

*Diet composition depicted in percent energy at every exposure level according to glycemic load quantiles.
for the duration of follow-up analysis with cohorts of ≥10 years28,29,30,35,36,43 (RR = 1.08 [95% CI 0.89 to 1.31]) versus those of <10 years30,31,33,42 (RR = 1.13 [95% CI 0.97 to 1.31]) as subsets (β = 0.95 [95% CI 0.71 to 1.26]), both with evidence of heterogeneity (I² > 44% for both, figure not shown). Sex, however, was a significant modifier of the association of GI with CHD (β = 0.77 [95% CI 0.65 to 0.93]; P = 0.004, Figure 2, sex-specific subgroups). The pooled female cohorts28,31,33,36,42,43 showed a larger, statistically significant association (ΔGI between mean of highest exposure and mean of reference = 11.2±1.5 SE, RR = 1.26 [95% CI 1.12 to 1.41]), whereas the male cohorts29,30,33,35,36,43 showed no association (ΔGI between mean of highest exposure and mean of reference = 0.96 [95% CI 0.84 to 1.11]), with no significant evidence of heterogeneity in either subset.

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Figure 3 (overall analysis) shows the overall pooled relative risk estimation of GL with CHD events. The pooled risk estimation showed a significant increase in CHD risk (RR = 1.27 [95% CI 1.09 to 1.49], P = 0.002), with significant heterogeneity (I² = 43%, P = 0.06), for the highest level of GL exposure (mean GL of 224.8 GL units, range 166 to 270) relative to the lowest (mean GL of 135.4 GL units, range 83 to 176). Sensitivity analyses identified the Grau et al43 and Sieri et al33 reports on women as the largest contributors to heterogeneity when removed individually. The removal of Grau et al43 somewhat reduced the estimate of the association of GL with CHD (RR = 1.21 [95% CI 1.05 to 1.38], P = 0.007; I² = 23%, P = 0.23), as did the removal of Sieri et al33 (RR = 1.22 [95% CI 1.06 to 1.40], P = 0.005; I² = 27%, P = 0.19). Similar to the GI analyses, no modification in the association was revealed by the duration of follow-up analysis, ≥10 years29,34–36,43 (RR = 1.26 [95% CI 1.01 to 1.59]) versus <10 years30,31,33,42 (RR = 1.29 [95% CI 1.02 to 1.63]) with β = 0.99 (95% CI 0.68 to 1.44), with evidence of heterogeneity (I² > 47%, figure not shown) for both subgroups. Congruent with the GI analysis, sex was a significant modifier of the association of GL with CHD (β = 0.73 [95% CI 0.56 to 0.96]; P = 0.02, Figure 3, sex-specific subgroups). The female cohorts31,33,34,36,42,43 showed a larger, statistically significant association (ΔGL between mean of highest exposure and mean of reference = 88.4±17.6 SE, RR = 1.55 [95% CI 1.18 to 2.03]), whereas in the male cohorts29,30,33,35,43 the association was not significant (ΔGL between mean of highest exposure and mean of reference = 90.4±9.2 SE, RR = 1.08 [95% CI 0.93 to 1.26]).
There was significant evidence of heterogeneity in the female subset but not in the male subset.

**Publication Bias**

Funnel plots for each of the overall analyses were inspected for presence of publication bias (Figures 4 and 5). Neither Begg’s nor Egger’s tests revealed significant evidence of publication bias in the overall analyses of GI and GL (P=0.115 for all). However, in the visual inspection of the GI funnel plot, the Grau et al study on men appears to be an outlier and in the GL funnel plot, and the Grau et al study on women appears to be an outlier (outside the pseudo 95% confidence limits).

**Discussion**

We believe that this analysis represents the most comprehensive meta-analysis of the data presented as quantiles of GI and/or GL. However, we were unable to include 2 studies in this analysis because of the expression of results as either the substitution of low GI carbohydrates for SFAs, rather than dietary GI analysis, or the incremental association of dietary GI with CHD rather than quantile presentation (ie, CHD risk per 5 GI unit increments). These studies indicated that in Danish and Black American men, positive benefits for cardiovascular events were seen related to consumption of lower GI foods. We demonstrated an overall increased relative risk of CHD of 11% in the comparison of the highest versus lowest quantile of GI and a 27% increased relative risk of CHD for the highest versus the lowest quantile of GL. The effect was seen only in women with 26% increased relative risk of CHD for GI and 55% for GL.

The sex difference in the CHD response to the glycemic index was unexpected and may be the result of the larger total number of subjects in the female cohorts (n=177 887, CHD events=4260) than in the male cohorts (n=63 049, CHD events=2680) and our inability to include 2 studies, 1 from Denmark and 1 from the United States, both of which demonstrated adverse effects of high GI foods or diets on CHD outcomes in men. Furthermore, the 1 study of men in the present analysis that showed a near-significant deleterious effect of low-GI diets was also responsible for the heterogeneity in the analysis. This study differed from the other studies of men in several respects. The proportion (54%) of smokers was almost twice that of the other studies, and BMI was somewhat lower (25.3 versus 26.1 kg/m²); men with lower BMIs have been shown to be less susceptible to the
effects of GI on CHD risk. There may also be another potential explanation for the difference between men and women, possibly a result of differences in diet reporting. For example, if women report more precisely, there would be less measurement error and hence better power. In addition, there may be more homogeneity (insufficient heterogeneity) in the diets of men and therefore a lack of the necessary power to detect potentially important relationships between dietary GI/GL and CHD risk in men.

Despite these reservations there are reasons why women may be potentially more vulnerable to high glycemic index diets. Part of the protection that women have from CHD may be related to their high HDL-C levels. Higher glycemic index diets tend to reduce circulating HDL-C concentrations and thus disproportionately increase CHD risk in women, especially when postmenopausal. At the same time, high-GI diets may raise TG levels, which may also carry more risk for CHD in women than in men.

Other factors that in general may contribute to the increased CHD risk with high-GI diets are blood pressure and CRP, both of which may be raised by high-GI diets. Conversely, acarbose, the α-glucosidase inhibitor that converts dietary carbohydrate to a low glycemic index form, has been shown to prevent hypertension and CHD events in the STOP NIDDM trial.

The link between low GI and GL diets and lower CHD risk is also substantiated by randomized clinical trials (RCTs) assessing the effects of dietary strategies low in GI and GL with low saturated fat content. A systematic review of such RCTs in overweight and obese subjects found that replacing refined carbohydrates with low-GI complex carbohydrates conferred more beneficial effects on CHD lipid risk factors when compared with complex starchy carbohydrates with higher GI. There has also been emerging evidence on the positive effects of low-GI diets on CHD risk factors such as oxidative damage and inflammation in overweight/obese and type 2 diabetic individuals, respectively. In addition, meta-analyses of low-GI RCTs have shown beneficial effects on body weight and lipid profiles in obese and overweight subjects as well as on glycemic control in type 2 diabetic subjects.

The current studies do not suggest a latency effect of GI or GL on CHD risk. Because no studies have a time frame shorter than 6 years, it is not possible to determine whether the effect is early, possibly from alterations in clotting factors, or later due to reduction in the rate of atheroma formation secondary to oxidative damage.

An earlier meta-analysis that assessed the effect of dietary GI on several health outcomes including diabetes, CHD, and cancer also concluded that low-GI diets were protective for diabetes, CHD, and colon and breast cancers. However, only 2 studies were available to assess CHD outcome at the time of that analysis.

In general, the glycemic index and glycemic load data were in agreement, although the magnitude of the CHD risk was greater based on the difference between the extreme quantiles of glycemic load. In the overall GL extreme quantile analysis there was significant heterogeneity that became nonsignificant when either the Grau et al or the Sieri et al reports on women were removed. The Grau et al report was visually an outlier on the publication bias funnel plot, which could potentially be a result of the difference in the analytical
approach, using restricted cubic splines in Grau et al,\textsuperscript{43} compared with the methods of analyses used in other reports. We could not find an explanation for the heterogeneity in the overall GL analysis due to the Sieri et al\textsuperscript{33} report on women.

The weaknesses of the present study include the limited number of studies, the inability to include potentially relevant studies\textsuperscript{44,47} because of lack of necessary data, and the heterogeneity in the overall analyses, especially in the likely underpowered analyses of men. Another inherent limitation of observational analyses is the potential problem for residual confounding as well as the possibility of overadjusting, which remains an area of debate in epidemiology.\textsuperscript{53} Perhaps, the most common limitation in meta-analyses of dietary studies is the combination of dietary data collected using multiple instruments. Although no change was found in our overall conclusions with post hoc sensitivity analyses removing the 4\textsuperscript{29,35,43} reports with food diaries and interviews, because of the time frame of published reports, the GI and GL data were still compiled from various data sources. As such, our findings should be considered with caution, and further studies should be undertaken to allow sufficient power for subgroup analyses of dietary data sources.

Although the reports included men and women from Holland,\textsuperscript{29,31,36} Finland,\textsuperscript{35} Denmark,\textsuperscript{43} Sweden,\textsuperscript{30,42} Italy,\textsuperscript{33} and the United States,\textsuperscript{28,34} the majority of the population was white, limiting the racial diversity of this meta-analysis. However, it is noteworthy that our systematic review captured a report on African American men that, although not included because of lack of necessary data (ie, quantile analyses), showed that a 5-unit increase in GI conferred a 16% increase in CHD risk.\textsuperscript{44} Further studies are required with a wider range of ethnic groups and more racial diversity both in women and especially in men because cohorts of men were likely underpowered.

The strength of our study included the use of random-effects models to allow assessment of heterogeneity to guide the sensitivity analyses. We further believe that our systematic review was strengthened by our efforts to acquire as much data as possible by contacting all study authors to include all relevant studies in our analyses.

**Conclusion**

We conclude that a reduction in the glycemic index and glycemic load may favorably affect CHD outcomes in women. Further studies are required to determine the effect of the glycemic index and load on CHD risk in men.

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