

# Coronary Heart Disease and Dietary Carbohydrate, Glycemic Index, and Glycemic Load: Dose-Response Meta-analyses of Prospective Cohort Studies

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## Abstract

**Objective:** To clarify the role of dietary carbohydrate, glycemic index (GI), and glycemic load (GL) in progression from health to coronary heart disease (CHD) by determining disease-nutrient risk relation (RR) values needed for intake ranges within jurisdictions and across the globe.

**Methods:** We performed a literature search of MEDLINE and EMBASE for prospective cohort studies that used truly valid dietary instruments in healthy adults published from January 1, 2000, to June 5, 2018. Relevant observations were extracted by 2 reviewers independently. We used dose-response meta-analysis accounting for nonindependence of results within studies. Bradford-Hill criteria were used to assess causality.

**Results:** Eligible studies had a mean follow-up of 11 years (range, 5-19 years), were conducted in North America, Europe, and East Asia, and yielded combined RRs of 1.44 (95% CI, 1.25-1.65) per 65 g/d GL (11 studies) and 1.24 (95% CI, 1.12-1.38) per 10 U GI (10 studies) (glucose scale). The CHD-carbohydrate RR on GI was 1.66 (95% CI, 1.23-2.25) per 98 g/d of carbohydrates per 10 units GI. The 65 g/d GL, 10 U GI, and 98 g/d carbohydrate values corresponded to oral intakes from the 10th to the 90th percentiles within sampled populations. Inconsistencies were minor ( $I^2 \leq 20\%$ ), as were small-study effects ( $P = .61$  for GL and  $P = .26$  for GI). Funnel plots were symmetric. Cubic spline dose-response meta-analysis yielded RRs as follows: across the global range for GL (55-290 g/d), 5.5 (95% CI, 3.1-9.8) ( $I^2 = 0$ ); for GI (47-82 U), 2.71 (95% CI, 1.47-4.40) ( $I^2 = 0$ ); and for the CHD-carbohydrate dependence on GI (50-80 U), 4.57 (95% CI, 1.86-11.4) ( $I^2 = 16\%$ ). Bradford-Hill criteria indicated that these relations were probably causal.

**Conclusion:** Strong and probably causal CHD-GL and GI RRs exist within populations. The RRs were remarkably higher across global exposures. The results support the consideration of these markers of carbohydrate food quality in dietary guidelines for general populations.

**Trial Registration:** PROSPERO Identifier: CRD42013004504

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Cardiovascular disease (CVD) is recognized as the number one cause of morbidity and mortality globally, with coronary heart disease (CHD) being the major contributor. This issue is of growing concern in low- and middle-income countries<sup>1,2</sup> in addition to wealthy Western countries, where it has long been recognized that diet and lifestyle contribute to 80% of CHD.<sup>3</sup> However, the role of dietary carbohydrate is unclear, it may not even be mentioned in major articles<sup>4</sup> or media,<sup>2</sup> and it may be concluded to have negligible impact<sup>5</sup> even when considering

the glycemic index (GI) and glycemic load (GL).<sup>6</sup> Meanwhile, Halton et al<sup>7</sup> reported a modest increase in incident CHD of 22% from the 10th to the 90th percentile of carbohydrate intake in women nurses in the United States. Dwarfing this finding, they reported a 90% higher risk for CHD from GL, strong enough to suggest a role for this marker in carbohydrate food quality.

Whether the risk relations (RR) between CHD and dietary GL and GI are sufficiently strong (threshold RR >1.20 with a lower bound >1.10) to support risk reduction via nutrition

guidance is unclear. Methodological problems in original studies and existing systematic and meta-analytic reviews prevent an understanding of whether this threshold is met. Therefore, we reexamined the available evidence, aiming to avoid pitfalls in the existing literature.

A number of extreme-quantile meta-analyses (EQMs) have supported that a higher risk for CHD arises among women consuming diets of higher GL, by 69% in 5 studies,<sup>8</sup> 55% in 6 studies,<sup>9</sup> and 49% in 5 studies while representing 1 study of high RR twice.<sup>10</sup> Each meta-analysis combined mostly the same studies, and they reported CHD-GI RRs approximately half that for GL and that RRs were lower in men than women. Unfortunately, each meta-analysis combined results having different definitions for GL or GI (across tertile or quartile or quintile ranges) and with different ranges per quantile. Also, none of the studies adjusted GL to a common energy intake before analysis. None asked whether the size of these RRs was dependent on the quality of the dietary instrument or selected to use only those studies using truly validated dietary instruments to assess GI and GL intakes. Also not addressed was whether the RRs were independent of macronutrient intakes.

Another EQM with problems similar to those noted previously had additionally undertaken dose-response meta-analyses (DRMs) combining studies on men and women.<sup>10</sup> Dose-response meta-analysis helps to avoid combining studies of different definitions of exposure. However, DRM depends on the dietary assessment systems not resulting in overdispersion of the exposure variable, which results in bias toward the null.<sup>11</sup> The authors of the EQM<sup>10</sup> tabulated the CHD RR to be higher by only 5% per 50-U increment in GL (11 studies), which is hard to reconcile with results from other EQMs.<sup>8-10</sup> Moreover, a graphical presentation in their article shows a pattern of confidence intervals inconsistent with the method of DRM indicated.

Mente et al<sup>12</sup> reported evidence supporting a causal link between dietary factors and CHD, indicating a 32% greater risk among persons consuming higher GI and GL diets, a combined value as if the risk was the same from GI and GL. The approach to assessment of causality was that of Bradford-Hill,<sup>13</sup> although only the first 4 of the 9 criteria were used, and for GI and GL, none of the criteria were independent of

the prospective cohort studies analyzed. Micha et al<sup>14</sup> reported some evidence on the CHD-GL RR, although they did address all Bradford-Hill criteria. However, although they reported use of an appropriate DRM, the value for the CHD-GL RR they provided was from an earlier publication,<sup>9</sup> which was based on EQM having the problems noted previously.

Usually, relevant studies have assessed the CHD-GL and GI RRs in prospective cohort studies as noted previously. Notably, Jakobsen et al<sup>15</sup> adopted a different approach by investigating the CHD-carbohydrate RR, finding this relation was “dependent” on the GI of the carbohydrate, although they did not quantify the “dependence.” Others have also provided estimates of the CHD-carbohydrate RR for dietary carbohydrate of known mean GI.<sup>16-20</sup> To our knowledge, there are no published meta-analyses of these data, which we provide. Also to our knowledge, there is no published quantitative DRM of the CHD-GL and GI RRs across the global (worldwide) range of dietary GL and GI intakes as large as 235 g/d GL and 30 U GI, and just one exists for half these ranges,<sup>10</sup> with the attendant problems noted. We aimed to rectify this absence since observations are now available to cover the wider ranges.<sup>16,17,19-24</sup> We further explored whether the size of the CHD-GL and GI RRs depends on the absence of study-level adjustments for each specific macronutrient. Finally, in discussion, we address causality.

## METHODS

### Protocol and Guidelines

The study protocol was registered with PROSPERO (CRD42013004504). It was to investigate CHD-GI and GL and type 2 diabetes—GL and GI RRs with control for the validity of the dietary instrument, potential sex differences, and macronutrient adjustments (among others). The present article concerns CHD only.

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)<sup>25</sup> and MOOSE (Meta-analyses of Observational Studies in Epidemiology)<sup>26</sup> guidelines for reporting were used.

### Literature Searches and Sources

MEDLINE and EMBASE were searched simultaneously using ProQuest LLC via the Royal

Society of Medicine, London, United Kingdom. A highly efficient protocol was developed in collaboration with the Royal Society of Medicine LitSearch and adapted to CHD. The search period was January 1, 2000, to June 5, 2018 (Supplemental Figure S1a, available online at <http://mcpiqjournal.org>). The search included identification of Cochrane studies and was for prospective cohort studies (the most reliable epidemiological design) that investigated the association of CHD (first incidence and deaths) with GI and/or GL and carbohydrate characterized by GI in ostensibly healthy adult populations without selection by age, sex, race/ethnicity, or region.

### Inclusion and Exclusion Criteria

For inclusion in our analyses, studies had to meet the following criteria: (1) prospective cohort study, (2) relevant to adult public health, (3) investigated the association between confirmed first nonfatal myocardial infarction (MI) or fatal CHD (collectively, CHD) and GI and/or GL, (4) used at least 2 defined categories of exposure (by quantiles and/or range such as standard deviation of intakes) and (5) included estimates of relative risk (risk ratio, hazard ratio, odds ratios, relative risk) with (6) measures of uncertainty (standard errors or confidence intervals) (7) relative to a referent exposure, (8) used study-level adjustments for major confounding factors, (9) had a follow-up duration of 4 or more years (when there were multiple publications from a study, the longest duration of follow-up was used unless there was a prohibitive reason [eg, insufficient information]), (10) ascertained MI or CHD by clinical record, (11) reported the sex of the participants, and (12) used either food records or a dietary instrument with validation for the investigated population. Validity was accepted by us when the instrumental measure of carbohydrate (or carbohydrate food) intakes correlated ( $>0.55$ ) with intakes obtained using objective food records (see Exclusions). Adults of any age, sex, race/ethnicity from any region worldwide in a report published at any time during the study parameters were included without language restriction. External to the registered protocol, we included observations on the CHD-carbohydrate RR when the GI of the carbohydrate was reported.

Studies were excluded if they (1) were not observational, longitudinal, or prospective studies, (2) used self-reported disease ascertainment only, (3) included patients with MI, CHD, or type 2 diabetes at baseline, (4) reported observations other than from fully adjusted models, (5) reported observations including stroke or other CVD, and (6) used invalid dietary instruments (defined as those with energy-adjusted correlation coefficients [Corr] of 0.55 or less for carbohydrate or carbohydrate foods vs objective food records<sup>27-29</sup> unless there was reason to do otherwise).

### Data Extraction and Calculation

Data were extracted by 2 reviewers independently (G.L., H.L.), and disparities were resolved by agreement. Data included the following: (1) carbohydrate, GI, and GL by quantiles (means, medians), (2) the reference standard used (glucose or white bread)—to adjust to a common glucose metric (GI glucose = 100, GI white bread = 70), (3) relative risks for first incidence of MI and CHD deaths (risk ratios, hazard ratios, or odds ratios) and their 95% confidence limits by quantiles or by linear relations if not provided by quantiles, (4) energy intake by quantiles and the intake of energy to which GL, GI, and carbohydrate were adjusted, (5) cohort average alcohol intakes, (6) whether RR had received study-level adjustments for intakes of energy, carbohydrate, fat (or fats), protein, fiber, folate, supplemental multivitamins, and alcohol, (7) whether RR had received study-level adjustments for nonnutrient factors—baseline hypertension, hypercholesterolemia, menopausal state and related hormone use, level of education, body mass index, age, physical activity, family history of MI or diabetes, smoking, occupation, income, and marital status, (8) whether studies had excluded CVD other than (in addition to) MI and CHD at baseline, (9) population region, (10) participants' sex (fraction of men), (11) population race/ethnicity, (12) the number of followed up participants, cases, and person-years of follow-up, (13) follow-up in years, (14) attrition rates during follow-up, (15) whether the dietary instrument was validated and the level of validity, and (16) the method used for ascertainment of MI or CHD. Information not reported directly was calculated when possible or sought from corresponding dietary instrument validation publications (for validity),

related publications with dietary details, or correspondence with authors (Supplemental Tables S1, S2, and S3, available online at <http://mcpiqjournal.org>).

### Study Quality

The Newcastle-Ottawa Quality Assessment score for prospective cohort studies was used to generate a score from 0 to 9 “stars” based on criteria for selection of participants, comparability of subcohorts, and study-level outcomes.<sup>30</sup> We deducted one star from comparability for those studies using a dietary instrument with an energy-adjusted carbohydrate correlation of 0.55 or less.

### Meta-analyses/Synthesis

Analyses used Stata/SE statistical software, version 11.2 (StataCorp) with “mais” (Meta-Analysis in Stata) installation.<sup>31</sup> Two-step meta-analysis was used for quantitative DRM for doses within jurisdictions or nationwide exposures. Step 1 used the generalized least squares method for trend estimation of summarized dose-response data of Geenland and Longnecker<sup>32</sup> as implemented by Osini et al<sup>33</sup> (*gls* v9.2), which provided individual study dose-response RR values. Step 2 combined the RR values by meta-analysis without covariates (*metan* v3.03) or with covariates—meta-regression (*metareg* v6.1) using method of moments and random effects,<sup>34</sup> which resolved to fixed effects when results from different studies were consistent ( $I^2=0$ ). Eligible studies providing only extreme quantile RR values or providing dose-response results directly were introduced at step 2.

Global DRM examined the dose response across the global population (sampled worldwide exposures) and used cubic spline (nonlinear) meta-regression analysis placing knots at the 10th, 50th, and 90th percentile of global exposures. For this purpose, the procedure of Geenland and Longnecker<sup>32</sup> was used to combine eligible studies in one repeating step (from the second to the last study) using at each repeat the pooling procedure with random effects.<sup>33</sup> The repeating steps introduced studies one at a time beginning with the study with the lowest referent exposure to enable prediction from prior studies of the graphical location of the subsequently added study observations. Each study introduced resulted in a third error term equal to the forecast standard error ( $\sigma_{fi}$ )

for the placement of results from each additional study, the combined square of which ( $\sigma_f^2$ ) was additive with heterogeneity ( $\tau^2$ ) and the combined within-study variance estimate ( $\sigma^2$ ). Thus, the usual  $\tau^2 + \sigma^2$  for random effects became  $\tau^2 + \sigma^2 + \sigma_f^2$  in the global analysis (only), in which  $\tau^2$  was zero for fixed effects.  $I^2$  was calculated as  $100 \cdot \tau^2/(\tau^2 + \sigma^2 + \sigma_f^2)$ , although it was also calculated as  $100 \cdot \tau^2/(\tau^2 + \sigma^2)$  to assess whether inclusion of  $\sigma_f^2$  made an important difference.

### Additional Analyses

Small-study effects were assessed by nonparametric trim-and-fill funnel plots (*metatrim* in Stata) and by a Galbraith-like regression (Log  $RR_i \cdot N_i$  on  $N_i$ , where  $RR_i$  was the study-level dose-response RR and  $N_i$  was the number of persons followed up).<sup>35,36</sup>

Because epidemiological studies have potential to generate precise but spurious results, the possibility of an outlying result ( $P < .05$ ) was examined by meta-regression using an indicator variable for a suspected study (one for which confidence intervals were not overlapping the combined studies mean RR).

Difference in RR between two subgroups was assessed using meta-regression using an indicator variable for one of the subgroups.

### Statistical Tests

The  $z$  test was used for combined means, covariates, and outliers, the  $t$  test for small-study effects, and the  $\chi^2$  test for heterogeneity.  $I^2$  can be interpreted only approximately.<sup>37</sup>

### Bradford-Hill Rating

All 9 Bradford-Hill criteria<sup>38</sup> were used. We limited the ratings to either probable or less than probable for each criterion, with total possible scores of 0 to 9. This procedure involved less subjectivity in decision making (G. Livesey, R. Taylor, H. Livesey, et al, unpublished data, 2018) than 3 categories per criterion.<sup>39</sup>

## RESULTS

### Search Outcomes

The search of MEDLINE and EMBASE (including Cochrane studies) for prospective cohort studies on the CHD-GL and GI RRs (Supplemental Figure S1a) identified 176 potentially relevant

records without duplicates. After examination of titles and abstracts, 30 were potentially relevant and were retrieved (Supplemental Figure S1a). On examination of the full publications, 16 did not meet the inclusion criteria: an early commentary<sup>40</sup>; a narrative review on diet and CHD<sup>41</sup>; a systematic review of randomized controlled trials (RCTs)<sup>42</sup>; 2 systematic reviews of potentially relevant studies<sup>10</sup>; 2 cross-sectional studies<sup>43,44</sup>; 1 case-control study<sup>45</sup>; 4 prospective cohort studies examining dietary factors other than GI or GL<sup>5,46-48</sup>; a prospective cohort study on nondietary factors<sup>49</sup>; a conference report of an otherwise later study report<sup>50</sup>; a prospective cohort study that focused on the CHD-carbohydrate score RR and reported on relations with GI and GL but without quantitative information on exposures by categories of exposure<sup>7</sup>; and a conference report of CHD-GI and GL RRs, again with too little quantitative information on GI and GL.<sup>51</sup>

Among the retrieved publications, 14 included prospective cohort studies reporting on one or more of either the CHD-GL or CHD-GI or the CHD-carbohydrate RRs. Thirteen reported on the CHD-GL RR<sup>16-24,52-55</sup> including 19 studies. Twelve reported on the CHD-GI risk RR<sup>16-24,52,53,55</sup> including 17 studies. Six reported on the CHD-carbohydrate RR for carbohydrate with specified GI values<sup>15-20</sup> including 12 studies (Supplemental Figure S1a).

Among the 19 studies on the CHD-GL RR, 7 studies from 4 publications<sup>18,53-55</sup> were not eligible because they had invalid dietary instruments by our criterion (Supplemental Figure S1b). Similarly, among the 17 studies on the CHD-GI RR, 5 studies from 3 publications<sup>18,53,55</sup> were not eligible because of invalid dietary instruments by our criterion (Supplemental Figure S1c). Among the 12 studies on the CHD-carbohydrate RR with known GI, 5 studies from 2 publications<sup>15,18</sup> were not eligible because of invalid dietary instruments by our criterion (Supplemental Figure S1d). This left 12, 12, and 7 studies eligible for DRM of the CHD-GL, CHD-GI, and CHD-carbohydrate characterized by GI. These inclusions were provided that results would not prove to be significant outliers ( $P < .05$ ) (Supplemental Figure S1a-d).

### Characteristics of the Study Participants

Eligible studies included only men (6 studies) or only women (6 studies). They included adults

with a mean  $\pm$  SD age at baseline of  $51 \pm 12$  years (range, 26-71 years) and mean  $\pm$  SD body mass index (calculated as weight in kilograms divided by height in meters squared) of  $25 \pm 1.0$  kg/m<sup>2</sup> (range, 23-26 kg/m<sup>2</sup>). All were ostensibly healthy persons free of prior MI (or CHD) and diabetes at baseline. Participants lived in the United States (1 study), Europe (9 studies), and China (2 studies). Occupations were considered representative of these populations in 8 studies, and 1 study focused on nurses. Urban dwelling was included in 2 studies, and smokers were included in 1. Race/ethnicities were largely European/white (9 studies), European American (1 study), and East Asian (2 studies).

### Nutritional Characteristics

Nutritional characteristics were collected for the 12 studies that used valid dietary instruments by our criterion. Population mean  $\pm$  SD values were as follows: energy intake,  $2367 \pm 280$  kcal/d (range, 1930-2617 kcal/d) (1 kcal = 4.184 kJ) in men (6 studies) and  $1792 \pm 120$  kcal/d (range, 1674-1984 kcal/d) in women (6 studies); alcohol consumption (reported in 11 of the 12 eligible studies),  $12.5 \pm 7$  g/d (range, 2-24 g/d) in men (5 studies) and  $6.2 \pm 2$  g/d (range, 2-9 g/d) in women (6 studies); dietary fiber intake (or cereal fiber in 2 studies) (reported in 10 of 12 eligible studies),  $24 \pm 3.6$  g/d (range, 19-29 g/d) in men (5 studies) and  $20 \pm 3.6$  g/d (range, 15-23 g/d) in women (5 studies); protein intake (reported in 10 of the 12 eligible studies),  $69 \pm 8$  g/2000 kcal (range, 57-79 g/2000 kcal) in men (5 studies) and  $79 \pm 5$  g/2000 kcal (range, 73-86 g/2000 kcal) in women (5 studies); carbohydrate intake (reported in 12 of 12 eligible studies),  $236 \pm 66$  g/2000 kcal (range, 185-366 g/2000 kcal) in men (6 studies) and  $271 \pm 58$  g/2000 kcal (range, 190-369 g/2000 kcal) in women (6 studies); GI (reported in all 12 eligible studies),  $62 \pm 19$  on the glucose scale (range, 55-82) in men (6 studies) and  $59 \pm 10$  (range, 47-82) on same scale in women (6 studies); GL (reported in all 12 eligible studies),  $166 \pm 63$  g/2000 kcal (range, 119-290 g/2000 kcal) in men (6 studies) and  $170 \pm 59$  g/2000 kcal (range, 125-286 g/2000 kcal) in women (6 studies).

The 10th to 90th percentile range of carbohydrate intakes in populations of men and women combined and relevant to the CHD-carbohydrate

RR was  $98 \pm 24$  g/d (range 78-144 g/d) (adjusted to 2000 kcal/d) (11 studies). That relevant to the CHD-GL RR was  $65 \pm 13$  g/d (range, 46-83 g/d) (adjusted to 2000 kcal/d) (12 studies), and that relevant to the CHD-GI RR was  $10 \pm 3.2$  (range, 5.7-13.8) (glucose scale) (12 studies).

### Study Quality

Newcastle-Ottawa quality scores (from 0-9) for the CHD-GL RRs were 8.1 (range, 7-9) for inlying studies with valid dietary instrument (correlation  $>0.55$ ), 7 for an outlying study,<sup>54</sup> and 7.3 (range, 6-8) for those studies with a correlation of 0.55 or less (Supplemental Figure S2, available online at <http://mcpiojournal.org>). Corresponding scores for the CHD-GI RR were 8.1 (range, 7-9), 7.5 (range, 7-8),<sup>24,54</sup> and 7.0 (range, 6-8) (Supplemental Figure S3, available online at <http://mcpiojournal.org>). For the CHD-carbohydrate RR, corresponding results were 8.3 (range, 8-9), 7 (range, 7-7), and 7.4 (range, 7-8) (Supplemental Figure S4, available online at <http://mcpiojournal.org>).

### Study Characteristics

Study characteristics were collected for the 12 studies that used valid dietary instruments by our criterion. Dietary intakes were mostly assessed using food frequency questionnaires (9 studies); 1 study each used a combination of food records and diet history interview, food records, and diet history questionnaire.

Studies using food frequency questionnaires as their dietary instrument were validated using energy-adjusted Pearson (otherwise Spearman) Corr comparing the dietary instrument values with food records for carbohydrate (9 studies) or for high-carbohydrate foods (1 study). Studies using food records directly (2 studies) were assigned an arbitrary but high value for Corr of 0.8. The mean Corr value for the 12 eligible studies was 0.72 (range, 0.64-0.80). The mean  $\pm$  SD value was  $0.71 \pm 0.05$  (range, 0.64-0.8) in men (6 studies) and  $0.73 \pm 0.05$  (range, 0.66-0.8) in women (6 studies).

Categories of intakes were presented by tertiles in 1 study, quartiles in 5 studies, and quintiles in 6 studies. The mean  $\pm$  SD follow-up duration for the 12 studies was  $11.4 \pm 4.6$  years (range, 5-19 years). The median study size was 22,400 persons (range, 646-75,521 persons), and the total number of persons entering the

studies was 350,000. The median number of events per study (cases) of first MI and CHD deaths was 614 (range, 114-4379), totaling 10,400 events. Excluded at baseline were MI, CHD, and type 2 diabetes in all 12 studies. All 12 studies ascertained cases from medical records.

The 12 eligible studies made study-level adjustments to relative risks for variance in nutrient intakes: energy (12 studies), alcohol (12 studies), dietary fiber (5 studies, including 1 for cereal fiber alone), protein (9 studies), fat or individual groups of fats (saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids) (10 studies), and carbohydrate for the CHD-GI RRs only (7 studies).

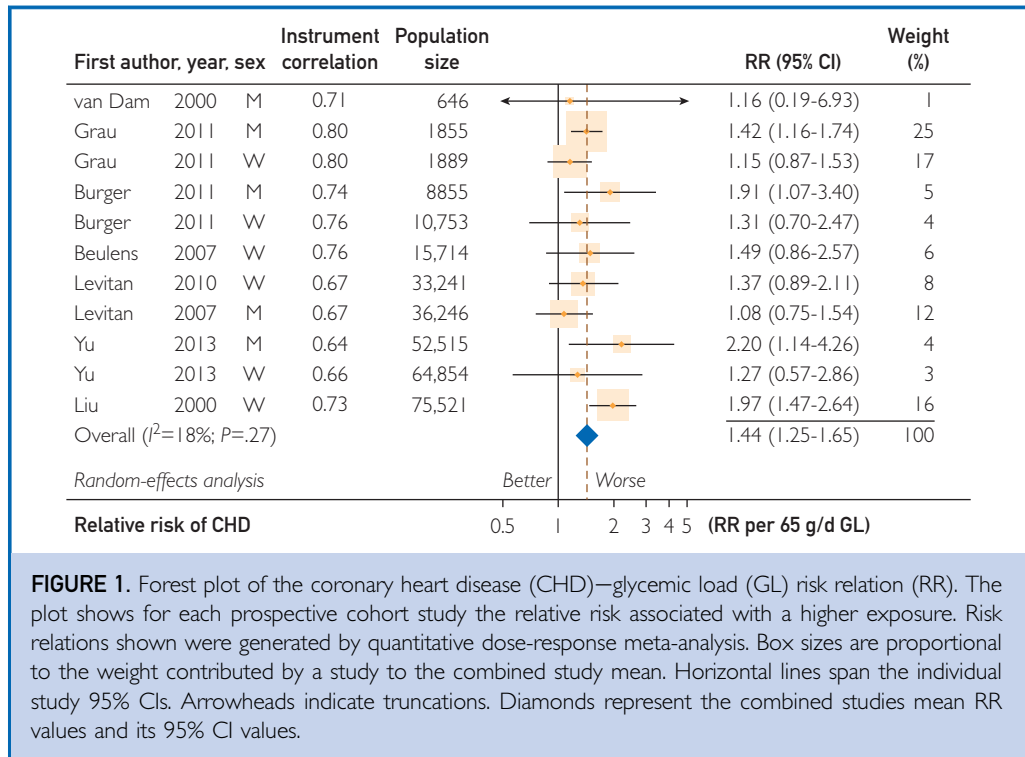
Study-level adjustments made for nonnutritive factors were as follows: smoking (12 studies), body mass index (12 studies), age of participants (12 studies), physical activity (12 studies), history of hypertension (8 studies) and systolic blood pressure (2 studies), level of education (8 studies), hypercholesterolemia (total cholesterol or high-density lipoprotein [HDL] cholesterol) (6 studies), family history of MI or CHD (12 studies), aspirin use (3 studies), income (2 studies), marital status (2 studies), multivitamin use (1 study), and menopausal state and related hormone use in women (3 studies).

### Risk of Bias Assessment

All 12 studies were judged to have adequate dietary assessment tools (Corr  $>0.55$ ), had objective outcome assessment (medical records), had adequate follow-up ( $>4$  years), had been reported with no competing interests, generally had low attrition rates (1%-8% in 9 studies, 20% in 1 study,<sup>17</sup> and not reported but seemingly  $<1\%$  in 2 studies<sup>22,23</sup>), and had probable adequate adjustment for confounding (nutrient and nonnutrient factors). From the outset, therefore, there was no appreciable evidence of study-level risk of bias other than what may arise from confounding factors (see [Sensitivity of RRs to Study-Level Adjustments](#) section, subsections Macronutrient and Folate Intakes and Nonnutrient Factors) and occurrence of small-study effects (see subsequent results).

### Coronary Heart Disease—Glycemic Load RR

Of 19 studies on the CHD-GL RR, 12 were eligible with dietary instruments having a



**FIGURE 1.** Forest plot of the coronary heart disease (CHD)—glycemic load (GL) risk relation (RR). The plot shows for each prospective cohort study the relative risk associated with a higher exposure. Risk relations shown were generated by quantitative dose-response meta-analysis. Box sizes are proportional to the weight contributed by a study to the combined study mean. Horizontal lines span the individual study 95% CIs. Arrowheads indicate truncations. Diamonds represent the combined studies mean RR values and its 95% CI values.

correlation for carbohydrate greater than 0.55 (Supplemental Figure S1b). Meta-analysis of these valid studies yielded a combined dose-response RR (relative to the lowest dose) that increased in 11 studies by 1.44 (95% CI, 1.25-1.65;  $P<.001$ ) per 65 g/d GL (adjusted to 2000 kcal/d) with nonsignificant inconsistency among studies ( $I^2=18\%$ ;  $P=.27$ ) (Figure 1). The study of Similä et al<sup>52</sup> in men was dropped from the meta-analysis as a significant outlier ( $P=.005$ ) and remained significantly outlying among the subgroup of men ( $P=.02$ ).

As expected, studies that were less reliable because they used dietary instruments that performed less well (Corr  $\leq 0.55$ )<sup>18,56-58</sup> gave a lower mean relative risk of 1.30 (95% CI, 1.13-1.50) ( $P<.001$ ) per 65 g/d GL (adjusted to 2000 kcal/d) (Table 1).

The CHD-GL RR was not different in men and women for studies with Corr greater than 0.55 (Table 1). In women-only studies, it was 1.44 (95% CI, 1.17-1.78) (6 studies;  $P<.001$ ) with nonsignificant inconsistency ( $I^2=30\%$ ;  $P=.21$ ), while in men it was 1.43 (95% CI, 1.15-1.78) (5 studies;  $P=.001$ ) with nonsignificant inconsistency ( $I^2=21\%$ ;  $P=.28$ ).

Potentially, the low RR in the study of men by Similä et al<sup>52</sup> may in part be due to relatively higher alcohol consumption. The population alcohol consumption in studies with a mean of less than 15 g/d was known in 9 studies with Corr greater than 0.55 (from 8 publications).<sup>16,17,19-23,52</sup> Meta-regression using alcohol as a continuous covariate in the low to moderate range of intakes ( $<15$  g/d or approximately 1 drink per day) indicated that at the lowest level of consumption (2 g/d for the present studies), the CHD-GL RR was 1.90 (95% CI, 1.25-2.89;  $P=.003$ ). By contrast, at a higher level of alcohol consumption (10.9 g/d), this RR was only 1.09 (95% CI, 0.88-1.36;  $P=.44$ ). Thus, alcohol may significantly attenuate the CHD-GL RR (9 studies;  $P=.04$ ). However, meta-regression analysis with only 9 studies should be regarded cautiously. Inconsistency was not absent, although it was nonsignificant ( $I^2=27\%$ ;  $P=.20$ ). From this model perspective, the study of Similä et al<sup>52</sup> ceased to be significantly outlying ( $P=.14$ ).

The men and women combined studies RR of 1.44 (95% CI, 1.25-1.65) (11 studies;  $P<.001$ ) (Figure 1) was sensitive to individual studies. The lowest combined RR of 1.34

**TABLE 1. Sensitivity of the CHD-GL and GI Risk Relations to Dietary Instrument Correlation for Carbohydrate and to Sex of the Study Population<sup>a,b</sup>**

Variable	n	Risk relation		I <sup>2</sup> (%)	τ <sup>c</sup>	P value
		Mean (95% CI)	P value			
Corr ≤0.55 (low or nonvalid studies), <sup>d</sup> men and women combined						
Glycemic load <sup>e</sup>	7	1.30 (1.13-1.50)	<.001	0	0	.66
Glycemic index <sup>f</sup>	5	1.18 (1.03-1.34)	.016	0	0	.64
Corr >0.55 (valid studies), <sup>c</sup> men and women combined						
Glycemic load <sup>e</sup>	11	1.44 (1.25-1.65)	<.001	18	0.10	.27
Glycemic index <sup>f</sup>	10	1.24 (1.12-1.38)	<.001	10	0.05	.35
Men, Corr >0.55 <sup>d</sup>						
Glycemic load <sup>e</sup>	5	1.43 (1.15-1.78)	.001	21	0.12	.28
Glycemic index <sup>f</sup>	4	1.04 (0.88-1.23)	.62	0	0	.96
Women, Corr >0.55 <sup>d</sup>						
Glycemic load <sup>e</sup>	6	1.44 (1.17-1.78)	<.001	30	0.14	.21
Glycemic index <sup>f</sup>	6	1.35 (1.20-1.52)	<.001	0	0	.62

<sup>a</sup>CHD = coronary heart disease morbidity (myocardial infarction) and mortality; GI = glycemic index; GL = glycemic load; I<sup>2</sup> = inconsistency among study-level risk relation values, ie, the variance among studies expressed as a percentage of the sum of the variance within and among studies; n = number of prospective cohort studies; P = probability values for risk relation, τ, and I<sup>2</sup>; τ<sup>2</sup> = heterogeneity, ie, the variance among studies.

<sup>b</sup>Risk relations obtained by random-effects dose-response meta-analysis.

<sup>c</sup>τ, the square root of τ<sup>2</sup>, is the standard error among studies and has the same units as risk relation (footnotes e and f).

<sup>d</sup>Corr, dietary instrument correlation for carbohydrate intake (energy adjusted and deattenuated) measured by food frequency questionnaire vs diet records; values ≤0.55 were deemed invalid instruments.

<sup>e</sup>Units: higher risk relation per 65 g/d GL adjusted to 2000 kcal (8400 kJ) of energy intake per day.

<sup>f</sup>Units: higher risk relation per 10 U dietary GI.

(95% CI, 1.18-1.51; P<.001) (I<sup>2</sup>=0%; P=.06) arose when dropping the study in women by Liu et al,<sup>16</sup> and the highest RR of 1.48 (95% CI, 1.29-1.68; I<sup>2</sup>=4%; P=.40) arose when the study in women by Grau et al<sup>24</sup> was dropped.

The Egger test indicated no significant small-study effects (11 studies; P=.61). Trim-and-fill analysis funnel plots indicated symmetry (ie, no trimming or filling to attain this state) (Supplemental Figure S5, available online at <http://mcpiqjournal.org>).

For eligible studies across the globe, GL intakes ranged from 55 to 290 g/d (span 235 g/d), which was more than 3 times wider than the study average range of intakes (65 g/d GL) and reached higher RR values (Figure 2 Inset). The CHD-GL relative risk across the lowest 65 g/d GL range of intakes was 1.32 (1.21-1.45) (Figure 2 and Table 2, row 9). The CHD-GL relative risk across the sampled Western populations range of GL intakes (110 g/d) was 1.78 (1.57-2.02), and across the full range of GL intakes (235 g/d) was 5.5 (3.1-9.8). Heterogeneity and inconsistency among study RR values was absent (I<sup>2</sup>

and τ = 0 by each method of derivation (see Methods section).

### Coronary Heart Disease—Glycemic Index RR

Of 17 studies reporting on the CHD-GI RRs, 12 were eligible with dietary instruments correlation for carbohydrate greater than 0.55 (Supplemental Figure S1c), of which 2 proved to be outliers (see subsequent discussion). Meta-analysis gave a combined studies mean CHD-GI RR of 1.24 (95% CI, 1.12-1.38) (P<.001) per 10 U GI (Figure 3). Inconsistency of results among studies was nonsignificant (10 studies; I<sup>2</sup>=10%; P=.35). As expected, studies that were less reliable because they used a dietary instrument with Corr of 0.55 or less<sup>18,53,55</sup> gave a lower RR of 1.18 (95% CI, 1.03-1.34) (P=.02) per 10 U GI (5 studies; I<sup>2</sup>=0%; P=.64) (Table 1).

The CHD-GI RR was higher in women than in men (4 studies; P=.01) for studies with Corr of greater than .55 (Figure 3 and Table 1). In women-only studies, RR was 1.35 (95% CI, 1.20-1.52) (P<.001) with no inconsistency



TABLE 2. Summary of the CHD-Carbohydrate, Glycemic Load, and Glycemic Index Risk Relations in Men and Women Combined<sup>a,b</sup>

Variable	n	Risk relation (95% CI) and unit of measurement		P value	I <sup>2</sup> (%)	P value
CHD-carbohydrate risk relation by GI <sup>c</sup>						
1 Over eligible studies, <sup>d</sup> GI = 50 U	11 <sup>b</sup>	1.11 (0.86-1.42)	Per 98 g CHO	.42	18	.28
2 Over eligible studies, <sup>d</sup> GI = 80 U		5.10 (2.39-10.9)	Per 98 g CHO	<.001		
CHD-GI risk relation derived from CHD-carbohydrate risk relations per 98 g/d carbohydrate at different glycemic indices (thus avoiding attenuation due to study-level adjustment for carbohydrate intake) <sup>e</sup>						
3 Over eligible studies <sup>d</sup>	11	1.66 (1.23-2.25)	Per 10 U GI	<.001	16	.30
4 Over the 50-80 U GI <sup>d</sup>	11	4.57 (1.86-11.4)	Per 30 U GI	<.001	16	.30
CHD-glycemic index risk relations (not avoiding potential attenuation due to study-level adjustment for carbohydrate intake)						
5 Over eligible studies <sup>f</sup>	10	1.24 (1.12-1.38)	Per 10 U GI	<.001	10	.35
6 Lowest range of GI values <sup>g</sup>	10 <sup>b</sup>	1.26 (1.15-1.38)	Over 10 U GI	<.001	0	.98
7 Full range of GI values <sup>g</sup>		2.71 (1.47-4.40)	Over 35 U GI	<.001		
CHD-glycemic load risk relations (avoiding attenuation due to study-level adjustment for carbohydrate)						
8 Over eligible studies <sup>h</sup>	11	1.44 (1.25-1.65)	Per 65 g/d GL	<.001	18	.27
9 Lowest range of GL values <sup>i</sup>	11 <sup>b</sup>	1.32 (1.21-1.45)	Over 65 g/d GL	<.001	0	.41
10 Full range of GL values <sup>i</sup>		5.5 (3.1-9.8)	Over 235 g/d GL	<.001		

<sup>a</sup>CHD = coronary heart disease; CHO = carbohydrates; DRM = dose-response meta-analysis; GI = glycemic index; GL = glycemic load; I<sup>2</sup> = inconsistency; n = number of prospective cohort studies; P = probability values for risk relation and  $\tau$  (and I<sup>2</sup>); RR = risk relation.  
<sup>b</sup>Adjacent rows sharing common values for n, I<sup>2</sup> (and its P-value) shared common inputs and common meta-regression models of analysis but differed in the outputs for the relative risk dependent on the question asked related to GL, GI, and CHO and to the level of exposure or range of exposures addressed.  
<sup>c</sup>Two-stage quantitative DRM, obtained by centering GI at 50 U and 80 U, respectively, rather than using the noncentered GI as in Figure 7.  
<sup>d</sup>Excluding one outlying study (P<.001).  
<sup>e</sup>Two-stage quantitative DRM: estimating RR per 98 g/d CHO (adjusted to 2000 kcal) followed by meta-regression (Figure 7).  
<sup>f</sup>Two-stage quantitative DRM: estimating RR per 10 U GI followed by meta-analysis without covariates (Figure 3).  
<sup>g</sup>One-stage cubic-spline pool-first quantitative DRM (Figure 4).  
<sup>h</sup>Two-stage quantitative DRM: estimating RR per 65 g/d GL intake (adjusted to 2000 kcal/d), followed by meta-analysis (Figure 1).  
<sup>i</sup>One-stage cubic-spline pool-first quantitative global DRM (Figure 2).

(6 studies; I<sup>2</sup>=0%; P=.62). However, in men-only studies, this relation was small and nonsignificant at 1.04 (95% CI, 0.88-1.23) (P=.62) (4 studies; I<sup>2</sup>=0%; P=.96). This difference should be regarded cautiously because it may not be an inherent sex difference.

Among studies with Corr greater than 0.55, the men-only study of Grau et al<sup>24</sup> was a significantly low outlier (P<.001) and therefore not included. Among the remaining studies, the men-only study of Similä et al<sup>52</sup> was also a significant outlier (P<.001). Low values of RR for men were therefore not due to these low outlying studies, although they may be related to alcohol consumption.

Meta-regression with population average alcohol intake as a covariate in the low to moderate range of intakes (<15 g/d or approximately 1 drink per day) indicated that at low consumption (2 g/d) the CHD-GI RR was 1.51 (95% CI, 1.17-1.94) (10 studies; P=.001) (I<sup>2</sup>=10%; P=.35). By contrast, at the higher population average alcohol consumption (10.9 g/d), a

CHD-GI RR was not evident because RR was 0.95 (95% CI, 0.86-1.06) (10 studies; P=.38) (I<sup>2</sup>=10%; P=.35). The study of Similä et al<sup>52</sup> remained outlying (P=.02) even with alcohol as a covariate, while the study of women from Grau et al<sup>24</sup> became outlyingly high (P=.01).

The men and women combined studies RR without covariates of 1.24 (95% CI, 1.12-1.38) (10 studies; P<.001) (Figure 3) was sensitive to dropping of individual studies. The lowest combined RR of 1.18 (95% CI, 1.07-1.32) (9 studies; P=.002) (I<sup>2</sup>=0%; P=.70) arose when the study in women from Grau et al<sup>24</sup> was dropped, and a highest RR of 1.30 (95% CI, 1.17-1.44) (9 studies; P<.001) (I<sup>2</sup>=0%; P=.64) arose when the study in men by Levitan et al<sup>23</sup> was dropped.

A Galbraith-type plot with Egger test indicated no significant small-study effects (10 studies; P=.26). Trim-and-fill analysis of the funnel plot indicated symmetry (no trimming or filling to attain this state) (Supplemental Figure S6, available online at <http://mcpqjournal.org>).

Across the globe, the range of GI values in men and women was 47 to 82 U GI (glucose scale), which covered a range more than 3 times wider than the average range of 10 U GI within study population samples. By global DRM (Figure 4 Inset), the CHD-GI RR over the lowest 10 units range of GI (from 47-57 GI) was 1.26 (95% CI, 1.15-1.38) (Table 2, row 6). Across the sampled Western populations range of GI intakes (lowest 16 U GI), the RR was 1.44 (95% CI, 1.28-1.63), and across sampled global population range of GI intakes (35 U GI), the RR was 2.71 (95% CI, 1.47-4.40). No inconsistency or heterogeneity was evident ( $I^2$  and  $\tau = 0$ ), and these relations were significant ( $P < .001$ ).

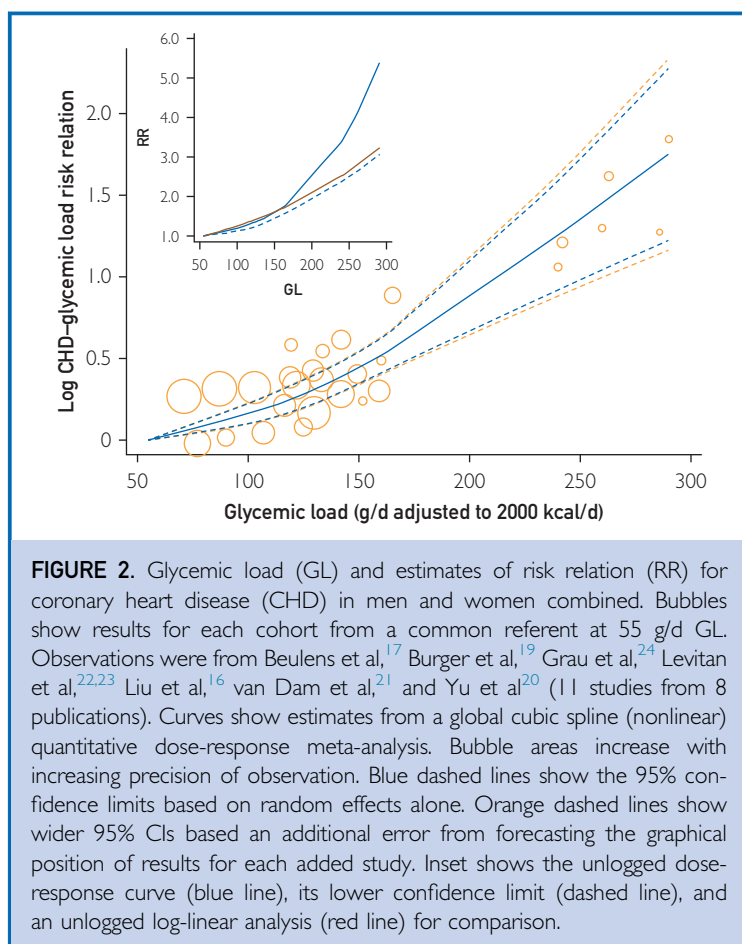
In women (Figure 5 Inset), the global DRM for the CHD-GI RR across the lowest range of 10 U GI (47-57 U GI) was 1.35 (95% CI, 1.21-1.50) per 10 U GI. Across the sampled Western populations range of GI intakes (lowest 16 U GI), the RR was 1.64 (95% CI, 1.38-1.94), and across the sampled global population range of GI intakes (35 U GI), the RR was 3.78 (95% CI, 1.51-9.42). No inconsistency or heterogeneity among observations was evident ( $I^2$  and  $\tau = 0$ ), and all 3 RRs were statistically significant ( $P < .001$ ).

### Sensitivity of RRs to Study-Level Adjustments

**Macronutrient and Folate Intakes.** Where study-level adjustments had been made for intakes of energy, alcohol, fiber, protein, fats, or folate, the CHD-GL RR in men and women combined remained greater than 1.20 with a lower confidence limit (LCL) greater than 1.10. Prudently, no study adjusted for carbohydrate intake (Supplemental Table S4, available online at <http://mcpiqjournal.org>).

To avoid possible confounding by an apparently low risk in men (Table 1), the CHD-GI RR was examined for women alone. Where study-level adjustments had been made for intakes of the aforementioned factors and carbohydrate or folate, the CHD-GI RR also remained greater than 1.20 with a LCL greater than 1.10 (Supplemental Table S4, available online at <http://mcpiqjournal.org>).

**Nonnutrient Factors.** Where study-level adjustments had been made to the CHD-GL and

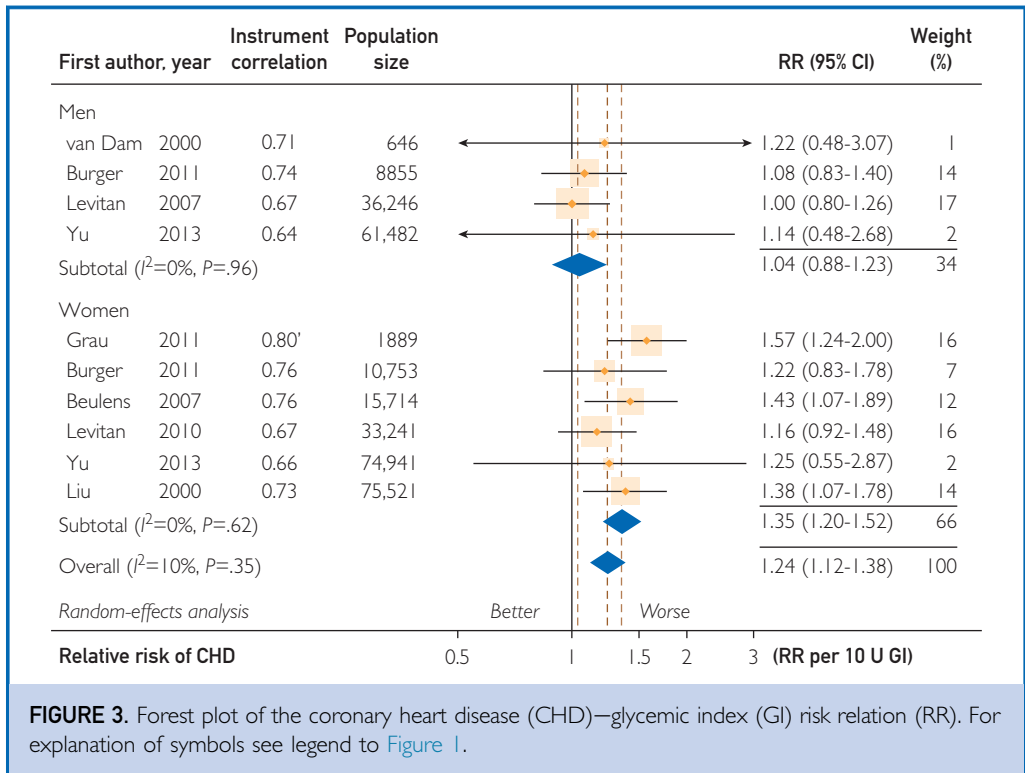


**FIGURE 2.** Glycemic load (GL) and estimates of risk relation (RR) for coronary heart disease (CHD) in men and women combined. Bubbles show results for each cohort from a common referent at 55 g/d GL. Observations were from Beulens et al,<sup>17</sup> Burger et al,<sup>19</sup> Grau et al,<sup>24</sup> Levitan et al,<sup>22,23</sup> Liu et al,<sup>16</sup> van Dam et al,<sup>21</sup> and Yu et al<sup>20</sup> (11 studies from 8 publications). Curves show estimates from a global cubic spline (nonlinear) quantitative dose-response meta-analysis. Bubble areas increase with increasing precision of observation. Blue dashed lines show the 95% confidence limits based on random effects alone. Orange dashed lines show wider 95% CIs based on an additional error from forecasting the graphical position of results for each added study. Inset shows the unlogged dose-response curve (blue line), its lower confidence limit (dashed line), and an unlogged log-linear analysis (red line) for comparison.

GI RRs for smoking, body mass index, age of participants, physical activity, family history of MI, diabetes status, hypertension, hypercholesterolemia, menopausal state and related hormone use (in women), level of education, and exclusion of other CVD in addition to MI or CHD at baseline, these relations remained greater than 1.20 with an LCL greater than 1.10 (Supplemental Table S4). Aspirin use was associated with variable results. Potentially, it lowered the CHD-GI RR, although nonsignificantly ( $P = .26$ ), and the RR remained greater than 1.20 for both GL and GI but with an LCL of less than 1.10 for GI (Supplemental Table S5).

### Coronary Heart Disease—Carbohydrate RR

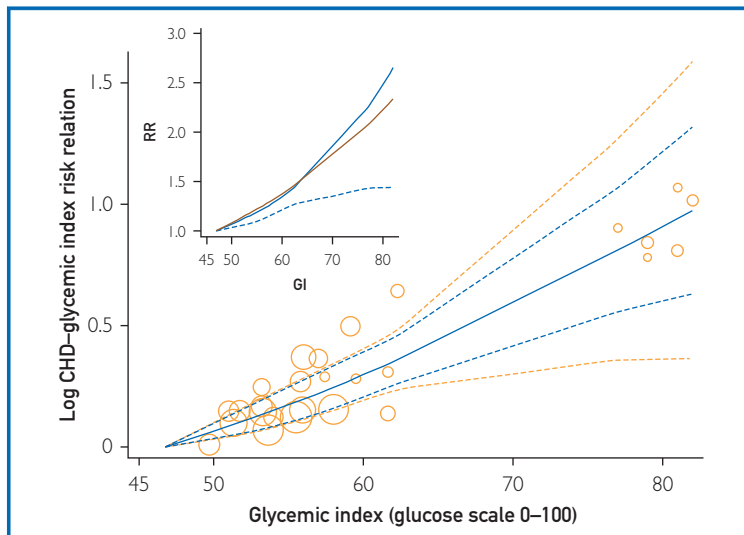
The CHD-carbohydrate RR when using valid dietary instruments ( $\text{Corr} > 0.55$ ) was reported in 6 single-sex studies with apparent inconsistency ( $I^2 = 47\%$ ;  $P = .09$ ) (Figure 6). No study reported on this RR for a GI of less than 50 U on



the glucose scale. Carbohydrate with GI of less than 56 U showed no clear association, while at the highest GI, the RR was high at 4.46 (95% CI,

1.53-12.9) per 98 g/d carbohydrate (adjusted to 2000 kcal diet).

Meta-regression requires more than the 6 studies presented in Figure 6. Therefore, we reintroduced the 3 studies by Jakobsen et al<sup>15</sup> and the 2 studies by Sieri et al<sup>18</sup> with Corr of 0.55 or less to assess the rate of change in RR with GI (Figure 7). The RR was high at 1.66 (95% CI, 1.23-2.25) per 10 U GI on the glucose scale ( $P<.001$ ) (Table 2, row 6). Inconsistency was low ( $I^2=16\%$ ;  $P=.30$ ). While the funnel plot for studies in Figure 6 was asymmetrical (Supplemental Figure S7), adjustment for differences in GI (Figure 7) removed 85% of the inconsistency and resulted in a symmetrical funnel plot (Supplemental Figure S8, available online at <http://mcpiqjournal.org>). Among these studies, the observations from Similä et al<sup>52</sup> were excluded as statistically significant outliers ( $P<.001$ ) both for high and medium GI categories of carbohydrate.



**FIGURE 4.** Glycemic index (GI) and estimates of the risk relation (RR) for coronary heart disease (CHD) in men and women. Bubbles show results for each cohort from a common referent at 47 U GI. Observations were from Beulens et al,<sup>17</sup> Burger et al,<sup>19</sup> Grau et al,<sup>24</sup> Levitan et al,<sup>22,23</sup> Liu et al,<sup>16</sup> van Dam et al,<sup>21</sup> and Yu et al<sup>20</sup> (10 studies from 8 publications). For explanation of symbols see legend to Figure 2.

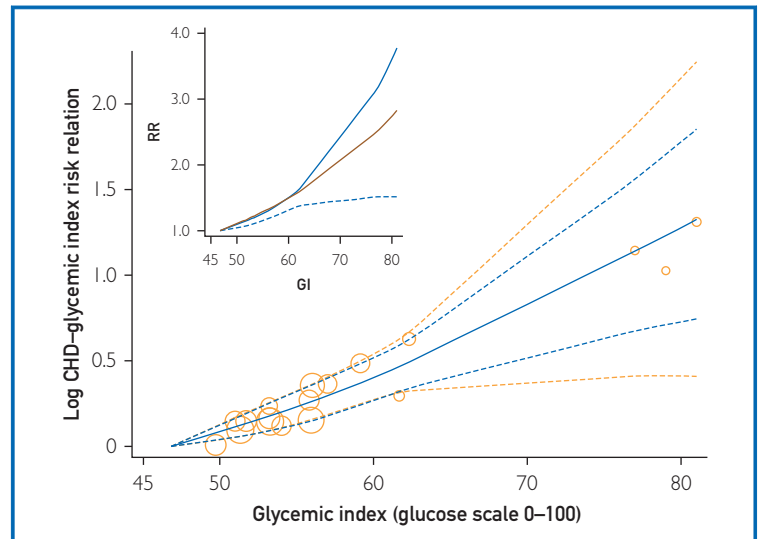
## DISCUSSION

### Risk Relations

To our knowledge no prior meta-analysis on the dependence of the CHD-carbohydrate RR on GI has been undertaken. Carbohydrate

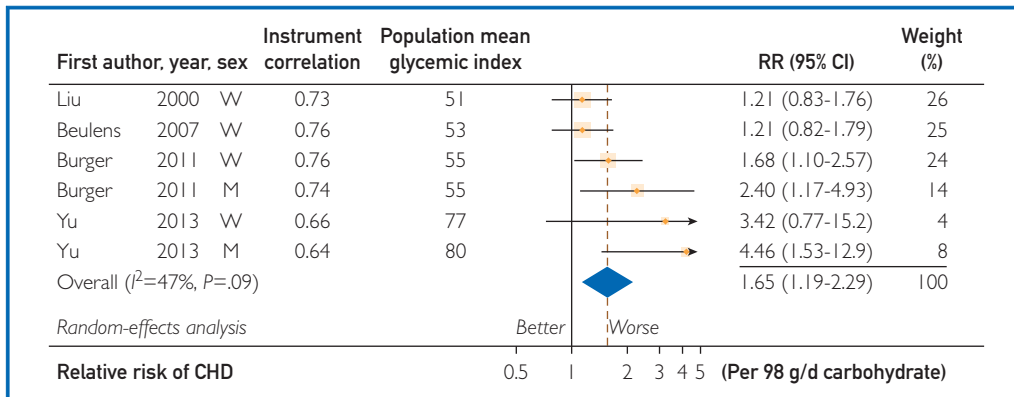
with a GI of greater than 50 U on the glucose scale was a strong risk factor for CHD and reached 4.46 (95% CI, 1.53-12.9) (Figure 6) and 5.1 (95% CI, 2.39-10.9) (Figure 7) each per 98 g/d carbohydrate, increasing by 1.66 (95% CI, 1.23-2.25) per 10 U GI. The quantities 98 g/d carbohydrate and 10 U GI each were combined studies mean ranges of intake, from the 10th to the 90th percentile of the study populations. To put this into further context, the ranges of GI values within major food categories (eg, whole-grain, vegetable, fruit) are approximately 60 U for each category.<sup>56</sup> This implies that “healthy foods” of extreme high GI for their food category might be a 20 times greater risk to heart health than foods of extreme low GI from the same food category when assuming the increment remains truly log-linear, ie,  $\exp(\ln[1.66] \cdot 60/10) = 21$ . This strong RR on the global scale was supported by high RR values for GL at 5.5 (95% CI, 3.1-9.8) (Figure 2 Inset; Table 2, row 10) and for GI at 2.71 (95% CI, 1.47-4.40) (Figure 4 Inset; Table 2, row 7). It seems worrisome, therefore, that the general public receives little authoritative guidance leading toward the consumption of lower rather than higher GI carbohydrate foods within food groups.

Whether addressing GI or GL of carbohydrate characterized by GI, all 3 associated strongly globally for a nutrient relation with CHD risk. In general, however, harmful RRs greater than 1.20 with a lower 95% CL greater than 1.10 within sample population ranges of

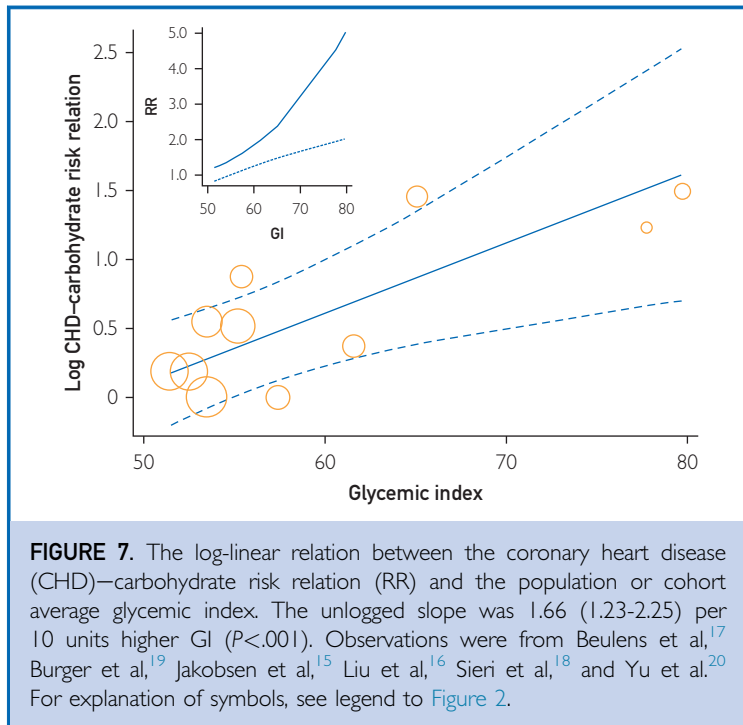


**FIGURE 5.** Glycemic index (GI) and estimates of the risk relation (RR) for coronary heart disease (CHD) in women. Bubbles show results for each cohort from a common referent at 47 U GI. Observations were from Beulens et al,<sup>17</sup> Burger et al,<sup>19</sup> Grau et al,<sup>24</sup> Levitan et al,<sup>22</sup> Liu et al,<sup>16</sup> and Yu et al<sup>20</sup> (6 studies from 6 publications). For explanation of symbols, see legend to Figure 2.

intakes have been regarded as sufficient to consider a nutrient for inclusion in nutrition guidance<sup>12</sup> (G. Livesey, R. Taylor, H. Livesey, et al, unpublished data, 2018) when sufficiently supported by an assessment such as Bradford-Hill ratings<sup>12</sup> (G. Livesey, R. Taylor, H. Livesey, et al, unpublished data, 2018). These within-population RR criteria were clearly met, both for all eligible studies on GL combined (Table 2, row 8) and over the lowest 65 g/d GL



**FIGURE 6.** Forest plot of the coronary heart disease (CHD)—carbohydrate risk relation (RR) by population sample mean glycemic index. Observations were from Liu et al,<sup>16</sup> Beulens et al,<sup>17</sup> Burger et al,<sup>19</sup> and Yu et al.<sup>20</sup> For explanation of symbols, see legend to Figure 1.



range within the global range of GL (Table 2, row 9). These criteria were less clearly met by the CHD–GI RR for all eligible studies (Table 2, row 5) and for the lowest 10 units range of GI within the global range (Table 2, row 6). Avoiding possible attenuation by adjustment for carbohydrate, this RR was possibly stronger (Table 2, RRs in row 3 vs rows 5 or 6).

A strength of our analyses was that eligible studies showed no significant study-level risk of bias (see the Results section, Risk of Bias Assessment). Newcastle-Ottawa study quality scores were high (see Results section, Study Quality), and only studies applying truly valid dietary instruments were used, as first suggested,<sup>27</sup> first used in relation to GI and GL,<sup>28</sup> and first shown to be a significant determinant of the type 2 diabetes–GL RR.<sup>29</sup> A further strength was that we used DRM, which makes use of more of the available observational information than is used by EQM, accounts for different definitions of exposure in respect to the number of quantiles reported, and allows global DRM to be undertaken. In addition, for carbohydrate and GL, which are adjusted within the original studies to different energy intakes, we readjusted to a common energy intake of 2000 kcal/d for each study. Another

strength was that DRM as performed obtains efficient estimates of RR by accounting for nonindependence of observations within studies<sup>32</sup> and in global DRM additionally took account of the error introduced by the placement of observations graphically. A further strength is that none of the primary relations (Figures 1, 3, and 7 and Table 2, rows 3, 5, and 8) had significant Egger test results for small-study effects (eg, publication bias) or had asymmetric funnel plots (Supplemental Figures S5, S6, and S8, available online at <http://mcpqjournal.org>). Further still, all primary RRs had low levels of inconsistency ( $I^2<20%$ ), which for GI and GL were reduced to zero when accounting for curvature in the global dose-response analysis ( $I^2=0%$ ).

A weakness of our study is that residual confounding can never be excluded. Also, weaknesses existed in original reporting of results for eligible studies at the study level. In particular, some studies did not report values of exposure, energy intakes to which exposures were adjusted, number of cases, and number of persons followed up, each by categories of exposure. However, sufficient information was available from related publications, by correspondence with the authors, by calculation from related published data (exposures and energy intakes for exposure adjustments), or approximated (number of persons and cases per quantile) as described study by study (footnotes to Supplemental Tables S1, S2, and S3). For the present purpose, the approximated values contribute negligible error (<3%) to an individual study's estimated log dose-response RR (see Supplemental Table S1 footnotes d and e).

### Bradford-Hill Ratings

Bradford-Hill ratings aim to assess the probability of RRs being causal.<sup>38</sup> The ratings fall under 9 headings or viewpoints: *strength* of association (from meta-analyses when possible), *consistency* of association, *specificity*, *temporality*, *biological gradient* (dose dependency), *plausibility*, *experimental evidence*, *analogy*, and *coherence* with the natural history and biology of disease. Ratings increase from 0 to 9 with increasing probability of causality. The ratings provide guidance in the absence of convincing proof from large long-term RCTs or when RCTs might be judged to be unrepresentative

of real-world circumstances assessed within prospective cohort studies.

**1. Strength of Association.** This factor is important for public health when RR is greater than 1.20 and its lower confidence limit is greater than 1.10 from the 10th to 90th percentile of nutrient intake<sup>12</sup> (G. Livesey, R. Taylor, H. Livesey, et al, unpublished data, 2018). This criterion was met for the CHD-carbohydrate RR for high GI carbohydrate, the CHD-GL RR, and the CHD-GI RR for men and women combined (Table 2). The last two were examined for the influence of alcohol, finding stronger relations when population average alcohol intake was small (2 g/d), RR then being 1.90 (95% CI, 1.25-2.89) per 65 g/d GL and 1.51 (95% CI, 1.17-1.94) per 10 U GI (see Results section, [Coronary Heart Disease—Glycemic Load RR](#), paragraph 4, and [Coronary Heart Disease—Glycemic Index RR](#), paragraph 4).

**2. Consistency of Association.** This criterion refers to inconsistency ( $I^2 < 50\%$ )<sup>57</sup> when the lower confidence limit is greater than 1.10 for a harmful relation<sup>12</sup> (G. Livesey, R. Taylor, H. Livesey, et al, unpublished data, 2018). National (or local) DRM (Figures 1, 3, and 7) indicated little inconsistency in these relations ( $I^2 \leq 20\%$ ), in part attributable to differences in alcohol consumption and/or a sex difference in study-level results and to curvature in the dose responses (when in the latter,  $I^2 = 0\%$ ). The direction of these relations was the same in 100% of eligible studies on GL (Figure 1), 90% of studies on GI (Figure 3), and 80% of studies on the CHD-carbohydrate on GI RR (Figure 7). Thus, all 3 relations met the consistency criterion for men and women combined.

**3. Specificity.** Diverse health effects of nutrients are possible (see [Coherence](#) section) so that the original definition for this criterion (relating to a single specified disease<sup>38</sup>) is not possible. To meet this criterion, therefore, the specified association for the disease incidence must be related to the exposure variable hypothesized. Potentially confounding risk factors (see below), both dietary and nondietary, must therefore be adjusted for at the study level or assessed by relevant sensitivity analysis during meta-analyses—finding, RR greater than 1.20 with LCL greater than 1.10 for harmful relations where

adjustments were made. This criterion was met for adjustments for energy, fiber, alcohol, protein, and fats or fats and folate for both GI and GL (Supplemental Table S4) and for hypertension, hypercholesterolemia, menopausal state (in women), educational status, and exclusion of other CVD at baseline for both GL and GI (Supplemental Table S5). Other adjustments made at the study level for all eligible studies were smoking, body mass index, age of participants, physical activity, family history of MI, and diabetes status (in addition to exclusion of diabetes at baseline). When these adjustments were made, the CHD-GL and GI RRs were greater than 1.20 with LCL greater than 1.10. An exception was for aspirin consumption (Supplemental Table S5) when the LCL greater than 1.10 criterion was met for neither GL nor GI; however, differences in RR with vs without aspirin use were not statistically significant ( $P = .78$  and  $P = .16$ , respectively) (Supplemental Table S5).

**4. Temporality.** Exposure must precede incidence of disease. This criterion is met by design in all prospective cohort studies (see also [Experimental](#) and [Analogy](#) sections, which refer to intervention studies).

**5. Biological Gradient (Dose Response).** In prospective cohort studies, this criterion is met when the combined studies dose-response RR is statistically significant, as was the case for GL (Figures 1 and 2), GI (Figures 2 and 4), and carbohydrate meta-regressed on GI (Figures 6 and 7).

**6. Plausibility.** This criterion is met when at least one credible mechanism can explain the association. The GL and GI are major food and dietary markers predictive of a food's (or diet's) ability once ingested to both elevate postprandial blood glucose<sup>58</sup> and determine longer-term fasting blood glucose and HbA<sub>1c</sub> concentrations in the nondiabetic and diabetic states.<sup>59</sup> Elevated HbA<sub>1c</sub> and blood glucose concentrations, including postprandial glucose, each are major risk factors for CVD,<sup>60,61</sup> for which CHD is the major contributor.<sup>2,62</sup> This includes elevation of glucose and HbA<sub>1c</sub> in the normal range in addition to the elevation that occurs in diabetes.<sup>60,61,63-65</sup> Further, observations in the general population have shown that HbA<sub>1c</sub> and

blood glucose are better markers of cardiovascular and CHD risk than either HDL cholesterol or total cholesterol<sup>66,67</sup> (see also [Experimental](#) section).

**7. Experimental.** Intervention trials that show either reduction of the specified disease incidence or reduction in markers of disease are needed to meet this criterion. (For trials, see [Analogy](#) section.) Several pathogenic pathways from high GI and GL lead to a conclusion that “modern dietary guidelines for patients at risk of CHD should reflect...[the] danger of consuming a HGL [high GL] diet.”<sup>68</sup> Further evidence comes from a primary care setting. A study by Unwin et al<sup>69,70</sup> found that lowering the GL of the diet by advice to avoid high GI foods for 13 months in 69 at-risk persons with either prediabetes or diabetes lowered several parameters, including body weight (−9 kg;  $P<.001$ ), waist circumference (−15 cm;  $P<.001$ ), HbA<sub>1c</sub> (−19%;  $P<.001$ ), total cholesterol (−6%;  $P<.001$ ), and cholesterol to HDL cholesterol ratio (−9%;  $P=.001$ ). The study concluded that this dietary approach was a practical alternative to drug therapy (for prediabetes and diabetes, ie, patients at risk for CHD) and had considerable cost savings for general medical practice. Consistently, the present analyses support high GI carbohydrate as a major nutritional risk factor for CHD among general populations.

**8. Analogy.** Lower GI and GL diets can be achieved using inhibitors of carbohydrate digestion.<sup>71</sup> Treatment with acarbose (an  $\alpha$ -glucosidase inhibitor) has the same pattern of effect on markers of metabolic disease as does treatment with lower GI or lower GL diets.<sup>58</sup> Further, reducing the GI and GL of the diet by use of acarbose has reduced the incidence of any cardiovascular event by 49% (5%-72%) and CHD (as MI) by 91% (28%-99%).<sup>71</sup>

**9. Coherence.** To meet this criterion, a disease-exposure association should not conflict with the natural history of disease. Evidence of coherence arises in part from the interventional studies supporting plausibility, experimental, and analogy criteria (see preceding sections). Further evidence comes from the association of one disease with another, each of which is linked to higher blood glucose and insulin concentrations; thus,

excess body weight<sup>72</sup> and CHD, diabetes, and certain cancers.<sup>73,74</sup> Meta-analysis has revealed that lower GL diets, achieved using lower GI carbohydrate foods, result in a dose-dependent reduction in body weight among persons with varied glycemic control from normal to the diabetic state.<sup>59</sup> Further, avoidance of high GI foods to achieve a lower GL diet has proved effective in improving body weight and glycemic and lipidemic parameters over a mean of 13 months in prediabetic and diabetic patients.<sup>69,70</sup> Beneficial effects of low GI and GL have become evident in long-term primary prevention of obesity-associated diseases.<sup>75</sup> In longitudinal trials, lower GI and GL due to ingestion of  $\alpha$ -glucosidase inhibitors lowers not only the risk of CHD<sup>72</sup> but also the risk of diabetes<sup>76-78</sup> and colorectal cancer.<sup>79</sup> Likewise, lower GI and GL diets also prospectively associate with a lower risk for type 2 diabetes,<sup>28,29,80-82</sup> a disease that increases the risk of subsequent CHD<sup>83-85</sup> and subsequent diagnosis of colon cancer.<sup>58</sup>

In summary, all 9 of Bradford-Hill's criteria for probable causality were met in our study. In application of GI and GL to food and dietary guidance, it should be noted that food group-based dietary guidelines would be insufficient because each food group contains foods having a very wide range of GI and GL values<sup>56,86</sup> and that prospective cohort studies have shown that even within beneficial food patterns, such as the Mediterranean diet and the healthy or vegetarian diet in the United Kingdom, there was evidence of added benefits of lower GI and GL.<sup>87-89</sup>

## CONCLUSION

Among healthy persons from Europe, North America, and East Asia, strong (RR >1.20, LCL >1.10 within jurisdictions) and probably causal (Bradford-Hill ratings) RRs occur between incident CHD and dietary GI and GL. The CHD-carbohydrate of high GI, the CHD-GL, and the CHD-GI RRs each are markedly greater across the globe than within jurisdictions. The evidence presented supports the use of these markers of carbohydrate food quality in dietary guidelines for general populations.

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### SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://mcpiqjournal.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

**Abbreviations and Acronyms:** CHD = coronary heart disease; **Corr** = correlation coefficients; **CVD** = cardiovascular disease; **DRM** = dose-response meta-analysis; **EQM** = extreme-quantile meta-analysis; **GI** = glycemic index; **GL** = glycemic load; **HDL** = high-density lipoprotein; **LCL** = lower confidence limit; **MI** = myocardial infarction; **RCT** = randomized controlled trial; **RR** = risk relation

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