Is there a dose-response relation of dietary glycemic load to risk of type 2 diabetes? Meta-analysis of prospective cohort studies[1–3]

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ABSTRACT

Background: Although much is known about the association between dietary glycemic load (GL) and type 2 diabetes (T2D), prospective cohort studies have not consistently shown a positive dose-response relation.

Objective: We performed a comprehensive examination of evidence on the dose response that links GL to T2D and sources of heterogeneity among all prospective cohort studies on healthy adults available in the literature.

Design: We conducted a systematic review of all prospective cohort studies and meta-analyses to quantify the GL-T2D relation both without and with adjustment for covariates.

Results: Among 24 prospective cohort studies identified by August 2012, the GL ranged from ~60 to ~280 g per daily intake of 2000 kcal (8.4 MJ). In a fully adjusted meta-analysis model, the GL was positively associated with RR of T2D of 1.45 (95% CI: 1.31, 1.61) for a 100-g increment in GL ($P < 0.001$; $n = 24$ studies; 7.5 million person-years of follow-up). Sex ($P = 0.03$), dietary instrument validity ($P < 0.001$), and ethnicity (European American compared with other; $P = 0.04$) together explained 97% of the heterogeneity among studies. After adjustment for heterogeneities, we used both funnel and trim-and-fill analyses to identify a negligible publication bias. Multiple influence, cumulative, and forecast analyses indicated that the GL-T2D relation tended to have reached stability and to have been underestimated. The relation was apparent at all doses of GL investigated, although it was statistically significant only at >95 g GL/2000 kcal.

Conclusion: After we accounted for several sources of heterogeneity, findings from prospective cohort studies that related the GL to T2D appear robust and consistently indicate strong and significantly lower T2D risk in persons who consume lower-GL diets. This review was registered at http://www.crd.york.ac.uk/PROSPERO as CRD42011001810. *Am J Clin Nutr* 2013;97:584–96.

INTRODUCTION

Carbohydrate foodstuffs that have a low or lower-than-average glycemic load (GL)[4] or glycemic index (GI) may reduce risk of several chronic diseases, including type 2 diabetes (T2D) (1). Both FAO (2) and WHO (3), along with many diabetes associations, have issues, support, or make recommendations concerning these nutritional concepts. The GL describes the product of the quality of carbohydrate food (GI) and quantity (weight) of carbohydrate ingested. However, it remains uncertain whether there is a positive dose-response relation that links the GL to

T2D, and if so, over what range of GL such a relation exists (1, 4). Because the 2 earliest cohort studies on incident T2D reported a positive relation with GL (5, 6), several studies made less convincing or contradictory observations (7–13), whereas other studies reported strong positive findings (14–17). Reasons for inconsistency in the dose response among these studies have not been examined formally (1, 4) but are of particular interest because an understanding of the reasons could be key to make a decision about the utility of recommending GL (or GI) reduction for lowering T2D risk in apparently healthy individuals.

In the first 2 published studies that prospectively related GL to T2D risk, the positive relation displayed a significant sex difference with a greater magnitude shown in women than in men (5, 6). A subsequent meta-analysis of studies (1) suggested the heterogeneity of findings may have been due in part to the quality of dietary instruments used (food-frequency or diet history questionnaires); those studies that used an instrument reported to have a correlation with food records <0.5 were possibly invalid. Later still, the duration of follow-up was hypothesized as a potential determinant of the strength of a relation between GL and T2D with support from similar observations for coronary heart disease (18). An additional publication indicated that ethnicity was a possible factor that contributes to the strength of the relation between GL and T2D risk (17).

The primary objective of the current study was to determine whether there is a positive dose response that relates GL to incident T2D in apparently healthy adults and, if so, to examine the

range of GL dosages that significantly relate to T2D risk. The secondary objective was to examine the 4 predefined hypotheses as sources of heterogeneity, which we defined as the proportion of male study participants (SEX), energy-adjusted and deattenuated dietary instrument correlation for carbohydrate (CORR), number of follow-up years (FUY), and the proportion of participants of European American ethnicity (ETH). These secondary measures were of changes in RR with changes in values of covariates that represented predefined hypotheses. To meet these objectives, we undertook, in a comprehensive and systematic manner, a dose-response meta-analysis that used data from all available prospective cohort studies in the literature on populations of healthy adults.

METHODS

A comprehensive search and systematic assessment of studies and data extraction were conducted in a stepwise process in accordance with our specific objectives following an a priori defined protocol (http://www.crd.york.ac.uk/PROSPERO; CRD42011001810 at). In brief, our protocol made use of several well-established guidelines, such as the Newcastle-Ottawa Scale (NOS) for observational studies (19, 20), the proposed method for reporting of Meta-analyses Of Observational Studies in Epidemiology (21), the proposed method for Strengthening the Reporting of Observational Studies in Epidemiology (22), the proposed Measurement Tool to Assess Systematic Reviews (23), and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (24).

Search strategies

An electronic search for original publication records was conducted on MEDLINE and EMBASE by using PROQUEST (http://search.proquest.com) via the Royal Society of Medicine, London, United Kingdom (http://www.rsm.ac.uk). Additional searchers were made on the Cochrane Library of Systematic Reviews (http://www.thecochranelibrary.com/view/0/index.html), the Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd), the PROSPERO Register of Systematic Reviews http://www.york.ac.uk/inst/crd/projects/register.htm), the CDC (http://www.cdc.gov), the NIH (http://www.nih.gov), and Google Scholar (http://scholar.google.co.uk) (see "Supplemental data" in the online issue for details of search strategies). Manual searches were also made of full publications that entered the review process (see "Supplemental data" for a list of both excluded and included studies) and of previous key reviews encountered (1, 4, 25–29).

Searches were conducted for the period from 1997 to August 2012 (week 3) inclusive by using medical subject headings (MeSH), titles, and abstracts. Briefly, terms included carbohydrate, glycemic index, glycemic load, blood glucose, diabetes or diabetes mellitus, incidence, risk factor, hazard assessment, risk assessment, follow-up, association, cohort studies, and prospective studies. Records in process or without assigned medical subject headings were also captured from January 2010 to August 2012 (week 3) by using only titles and abstracts. No language restrictions were applied. Electronic searches were limited to records after 1996, which was just before the first relevant publication (6) in 1997.

Eligibility and study selection

At least 2 authors evaluated titles and abstracts of electronic records for potentially relevant studies by selecting for prospective cohort studies that had incident diabetes (T2D) as an endpoint related to GL in adults of any age or sex and from any part of the globe in any language. Full study reports were retrieved for additional examination by ≥2 authors to assess the number of studies included in each publication and whether our inclusion criteria had been met. For the primary analysis, studies had to be *1*) original, *2*) have a prospective-cohort design, *3*) study an eligible (healthy) population, *4*) have an endpoint of T2D either self-reported or clinically confirmed in adults, and *5*) have sufficient dietary and other information to provide a rate of change in RR per unit change in GL for at least one identifiable range of GL. For secondary analysis by using covariates, studies had further *6*) to identify the population sample as men or women or both, *7*) inform directly or indirectly via citation about the validity of the dietary instrument used, *8*) provide FUY, and *9*) identify the ethnicity of participants. All information had to be either reported or calculable from information available in the literature or obtained by author correspondence.

Exclusion criteria, in addition to those in original publications, were not assigned other than studies had to exclude T2D at baseline, and inclusion criteria had to be met (eg, cross-sectional or case-control studies were not included).

Data extraction and process of analysis

The flowchart shown in **Figure 1** illustrates the principle stages and processes of the review undertaken. *See* Tables S1–S4 under "Supplemental data" in the online issue for a list of extracted data. Extraction was undertaken independently by 2 authors (GL and either RT or HL), and discrepancies were resolved jointly. Data were preserved in a Stata11.2 database file (StataCorp LP) from which they were drawn for calculations and statistical analyses.

In particular, we first addressed the primary objective by determining rates of change in RR with rise in GL for each study and combined these rates by using a meta-analysis without covariates. Second, we addressed the secondary objective by meta-analysis with covariates (metaregression) to quantify the hypothesized heterogeneities. Third, we applied various techniques (*see* Study quality and related risk of bias; *see* Statistics) to assess how sound the outcomes shown appeared to be. Fourth, we return to our primary concern to ask over what doses of GL an association with T2D may exist after adjustment for covariates.

Calculations

The primary measure was RR (by combining studies that reported risk ratios and ORs). Values of GL (*see* Table S1 under "Supplemental data" in the online issue) that were based on a white-bread standard were converted to values that were based on the glucose standard (31), which, thus, became smaller. All studies had expressed GL values for given energy intakes, where the energy intakes differed among studies. GL was reexpressed on a common metric with units of grams of GL per 2000 kcal (8.4 MJ). Reported values related to dietary instruments were
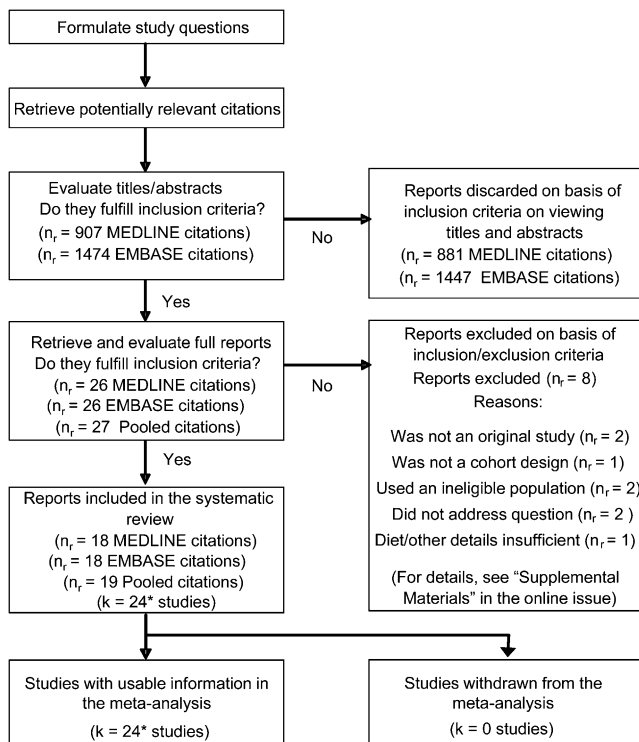
FIGURE 1. Summary of the study methodology, processes of review, and outcomes of inclusion and exclusion criteria. Reasons for exclusion are detailed online (*see* "Supplemental data" in the online issue). *Data from 2 reports from the same study at different times (16, 30) were combined before meta-analysis. Literature searches were conducted in week 3 of August 2012. MEDLINE and EMBASE were searched through PROQUEST (http://search.proquest.com) via the Royal Society of Medicine (http://www.rsm.ac.uk; *see* Search Strategies under "Supplemental data" for details). n_r, number of reports; k, number of studies.

checked against cited validation studies. This check was essential to ensure that energy-adjusted and deattenuated values of the instrument's correlation for carbohydrate were captured for CORR. When this was not possible (3 studies; *see* Table S3), approximate adjustments were made on the basis of average differences between raw and energy-adjusted values and between energy adjusted and deattenuated values imputed from other studies (*see* Table S3). Values of CORR were for validations of single applications of a dietary instrument. When more than one instrument was used in a study, the correlations from each instrument were averaged so that they were comparable with the application of a single instrument (*see* Table S3). For a case-by-case description of required data not reported directly in an original publication but otherwise knowable from related information by calculation, *see* the footnotes to Table S1; such calculations were performed by ≥2 authors independently, with inequalities resolved by discussion. Whenever calculations were considered approximate, the sensitivity of meta-analysis outcomes to approximations was assessed. Authors of original publications were consulted for otherwise unpublished or incalculable information.

Study quality and related risk of bias

Individual studies were assessed independently by 2 authors by using NOS for quality assessment of nonrandomized stud-

ies (19, 32) (*see* "Supplemental data" in the online issue or http://www.crd.york.ac.uk/PROSPEROFILES/1810_PROTOCOL_20111105.pdf for details).

The bias that was due to individual studies retrieved was assessed by the influence of study deletion, and the bias that was due to potential nonretrieved studies was assessed by using funnel plots and trim-and-fill analysis (*see* Statistics). The bias across studies was examined by an analysis of the influence of individual NOS components of selection, outcome, and comparability of studies and other study characteristics related to diet, population, and study progress (*see* Statistics).

Statistics

Interrater agreements on extracted data were determined by using the κ coefficient for dichotomous data (agreed compared with disagreed) and weighted κ for study quality in which ≥2 outcomes were possible (33, 34). Pairwise Pearson's correlations (*pwcorr* version 3.0.13; Stata release 11.2 SE, 2009; StataCorp LP) between variables before meta-analysis with covariates were explored to alert to potential confounders and tested for potential significance by using the 2-tailed *t* test for product-moment correlation (35, 36). In meta-analyses, combined means and trends were obtained by using inverse variance with weighting for both random and fixed effects (37). Random effects were chosen when the variance among studies as a percentage of the total variance (I^2) was >0% (38, 39). The significance of heterogeneity ($I^2 >0\%$) was assessed by using the Q test (38). Associations were assessed for significance by using the asymptotic z test.

In the main analysis, a 2-stage procedure was adopted when findings from cohort studies were assessed. In the first stage, trends for the change of lnRR with the change in energy-adjusted GL (dose-response slope) were obtained for each study separately. Trends were provided or readily calculable for 4 studies in 3 reports (8, 14, 40). All other studies provided several dose-specific RR values relative to a lowest GL referent. For these studies we obtained trends by using the generalized least-squares method for trend estimation of summarized dose-response data as designed for use in meta-analyses of prospective cohort studies (*glst* version 7.0.0; StataCorp LP) (38, 39, 41). In the second stage, trends with GL (dose-response slopes) from each study were combined by using a meta-analysis to obtain the combined mean of trends, both when no covariate was involved (*metan* version 3.03; StataCorp LP) (42–44) and when covariates were fitted by using the method of moments (*metareg* version 2.6.1; StataCorp LP) (45, 46). Covariates were centered and continuous (eg, the validity of a dietary instrument) or centered and dichotomous (eg, European American compared with other ethnicities). The validity of this 2-step approach with these data was assessed by comparison with a one-step *glst* metaregression (38, 39) with virtually identical outcomes (*see* Table S6 under "Supplemental data" in the online issue).

Residuals from meta-analyses with and without covariates were assessed visually for asymmetry by using funnel plots (47) and objectively for size and significance of any asymmetry (interpretable as publication bias) by using the trim-and-fill analysis of Duval and Tweedie (*metatrim* version 1.0.3;

StataCorp LP) (48, 49). The last procedure also provided a nonparametric estimate of the number and location of observations required to both fill a funnel and achieve symmetry.

The sensitivity of a model β coefficient to the dropping of individual studies was assessed graphically by using an influence analysis, in which the change in each jth hypothesized covariate β-coefficient caused by the deletion of each ith study (ie, $\Delta\beta_{ij}$) was expressed as a proportion of the SE of the coefficient (se_{ij}) obtained after the deletion; this yielded a score comparable with the z score for the β coefficient before deletion. This approach was used also to indicate whether the metaregression model was overly complex or not, signified by too large an influence for any study compared with the majority (50). We also expressed the results numerically as the percentage change in the β coefficient that was due to dropping a study from the analysis.

The exploration of the sensitivity of results to a study characteristic or quality item (other than those hypothesized) was by a modification of the influence-analysis procedure. This procedure asked how the β coefficient for each jth hypothesized covariate changed by addition to the metaregression model of a single (vth) explored centered covariable that represented the examined study characteristic or quality item. The change in β (ie, $\Delta\beta_{jv}$) was expressed as a percentage of the β coefficient obtained before addition of the vth variable to the model. An inspection of the influence of individual-study characteristics and quality items was undertaken in preference to assessing the influence of the overall study quality alone (20, 51).

The sensitivity of the overall outcomes to weakness in data was assessed by making alternative assumptions and calculations (see Table S5 under "Supplemental data" in the online issue).

The dose range over which GL remained a positive modifier for incident T2D was assessed by using a graphical display of the trend for the dose response compared with dose. In practice, this was $\Delta lnRR$ per g GL compared with the average dose ($0.5\Delta GL$) over which lnRR could change from each Q_1 to Q_n, where Q_1 referred to the lowest numbered quantile and Q_n to quantiles that had $n > 1$ within each study, pooled across all studies. The trend across the difference ($\Delta lnRR$) compared with the average ($0.5\Delta GL$) plot was obtained by using a metaregression with adjustments for the hypothesized covariates. The possibility of a nonlinear trend with GL was allowed by using a cubic spline (*mksplin* version 1.2.5 with 3 equally dispersed knots; Stata release 11.2 SE, 2009; StataCorp LP).

All analyses were conducted with Stata software (release 11.2 SE, 2009; StataCorp LP) by applying options under *kappa, pwcorr, metan, metatrim, glst, metareg,* and *mksplin* commands (40).

RESULTS

Retrieval and selection of literature

Both MEDLINE and EMBASE returned a similar number of potentially relevant publications (26 each) (Figure 1). On examination of full reports, 18 articles each from MEDLINE and EMBASE were relevant, which together totaled 19 original reports after pooling. Data from 2 reports of the same study, which ostensibly differed only in high numbers of follow-up years (20 and 26 y), were combined prior to meta-analysis (16, 30), and some reports included multiple studies on sexes and ethnicities

separately (8, 17). This process left 24 original studies for meta-analysis. Reasons for exclusion or not meeting inclusion criteria are summarized in Figure 1 (see online materials for details). Two earlier meta-analyses that mistakenly identified studies to include are also detailed in the supplementary materials. All studies that met inclusion and exclusion criteria were retained in meta-analyses, and none of the studies were withdrawn during synthesis of the evidence.

Study quality and other characteristics

Study qualities according to the NOS scale were good to near optimal and ranged from 6 to 8 (mean: 7.6; $n = 24$) for possible scores from 0 to 9 (summarized in **Table 1**; see Table S4 for individual study scores). The preconsultation interrater agreement on NOS between assessors was 97%, which was significantly greater than expected by chance (68%) according to the weighted kappa ($\kappa = 0.87$, $P < 0.0001$ for 10 possible quality scores and $n = 24$ studies). Authors from 16 studies indicated no conflicting interest. Other authors mostly had earlier publication dates and we found no explicit statements (see Table S4). Author affiliations and sources of funding also gave no concern for potential bias.

Correlations among hypothesized factors (SEX, CORR, FUY, and ETH) and various other study characteristics and overall quality were generally low and nonsignificant (monovariate $P >$ 0.05) (Table 1). Some potentially significant correlations did arise. For example, the study average energy intake correlated with the proportion of participants who were men, with intakes in men that were higher than in women ($P = 0.00003$ unadjusted; $P = 0.0006$ after Bonferroni adjustment). Care was taken to assess how much this and other potential correlations (highlighted with asterisks in Table 1) affected the conclusions reached about the hypothesized covariates (see influence analysis in Statistics).

Original articles had RR or trends for RR with GL that had been adjusted for confounding variables. Most commonly, these were (n studies among the 24 studies analyzed); BMI (in kg/m^2) ($n = 21$), physical activity ($n = 21$), age ($n = 15$), smoking ($n =$ 15), level of education ($n = 14$), dietary or cereal fiber intake ($n = 13$), alcohol intake ($n = 11$), and family history of diabetes ($n = 10$). As factors (adjusted = 1; not adjusted = 0), none of these variables correlated significantly with the hypothesized covariates (SEX, CORR, FUY, and ETH). Thus all correlations were <0.25 except for age, which approached a potentially significant correlation with follow-up years (correlation of 0.35; monovariate $P = 0.08$). The variance in age among studies was explored subsequently as a potential confounder in the current meta-analysis with hypothesized covariates.

Glycemic load

Reported GL values reexpressed in a common metric ranged widely, the lowest of which was 62 g/2000 kcal and the highest of which was 279 g/2000 kcal among all study quantiles. Thus, the global range for GL intake spanned at least 217 g/2000 kcal. Within studies, the range for GL was less and spanned on average 81 g/2000 kcal, which was almost one-third of that for the global range of 217 g/2000 kcal. The range of GL intake within a study (region) varied, the lowest of which was 39 g/2000 kcal and the

TABLE 1
Study characteristics in relation to hypothesized sources of heterogeneities, SEX, CORR, FUY, and ETH (n = 24 prospective cohort studies)[1]

Characteristics	Mean	Min	Max	$\kappa \times 10^2$	Pearson's correlations			
					Compared with SEX	Compared with CORR	Compared with FUY	Compared with ETH
Dietary factors								
Range of glycemic load across all studies (g/2000 kcal)[2]	—	62	279	—	—	—	—	—
Study mean glycemic load (g/2000 kcal)[2]	139	93	231	100	0.04	0.19	0.05	−0.40*
Study mean energy intake (kcal/d)	1917	1494	2629	95[3]	0.66*	0.27	0.22	−0.26
Glucose (= 1) or white bread (= 0) reference	0.67	0	1	100	0.20	0.27	0.40	−0.55*
Diet assessments (n)	1.35	1	7	100	−0.31	0.03	0.52*	0.33
Foods in dietary instrument (n)	125	66	276	100	0.31	0.50*	0.17	−0.07
Dietary instrument (CORR) (fractional)	0.62	0.43	0.80	100	0.08	—	0.10	0.07
Applicability within population (yes = 1; doubtful = 0)	0.79	0	1	100	0.09	0.38	0.10	−0.31
Used energy-adjusted intakes (yes = 1; no = 0)	0.91	0	1	100	−0.26	0.05	0.14	0.23
Fiber excluded as confounder (yes = 1; no = 0)	0.96	0	1	100	0.21	−0.18	0.26	0.16
Population factors								
T2D excluded at baseline (yes = 1; no = 0)	1.00	1	1	100	0.00	0.00	0.00	0.00
Population sample analyzed (n)	31,583	1898	124,907	90[4]	−0.33	0.07	−0.05	0.23
ETH (European American = 1; others = 0)	0.38	0	1	100	−0.25	0.07	0.06	—
SEX (M = 1; F = 0)	0.40	0	1	95[5]	—	−0.08	0.03	−0.25
Study average BMI (kg/m^{2})	26	23	29	100	0.04	−0.21	−0.05	−0.18
Age at baseline (y)	54	32	75	82[6]	0.30	0.20	−0.02	−0.26
Progress factors								
Person-years	303,071	7592	2,127,502	90[7]	−0.28	0.04	0.46*	0.27
Total no. of cases in a study	1234	99	6950	100	−0.25	−0.14	0.62*	0.11
FUY	10.1	4	26	100	0.03	0.10	—	0.06
Clinical (= 1) or self-reported (= 0) outcomes	0.79	0	1	100	0.27	0.38	0.36	−0.03
Study quality								
Newcastle-Ottawa Scale (0–9)	7.6	6	8	87[8]	—	—	—	—

[1] CORR was energy adjusted and deattenuated in each case, either as reported in the original studies or the cited validation study or as adjusted and deattenuated subsequently (*see* Table S3 under "Supplemental data" in the online issue). None of the values reported arose from repeated-measures analysis of consecutively used dietary instruments. *Potential to be significant (monovariate $P < 0.05$) according to a 2-tailed t test applicable to the Pearson's product-moment correlation. CORR, energy-adjusted and deattenuated dietary instrument correlation for carbohydrate; ETH, proportion of participants of European American ethnicity; FUY, number of follow-up years; Max, maximum; Min, minimum; SEX, proportion of male study participants; T2D, type 2 diabetes.

[2] Adjusted for energy intake.

[3] κ <100% because of inadvertent selection of a value for men only instead of for men and women combined in one study (40).

[4] κ <100% because of inadvertent selection of the total population investigated (n = 7310) instead of the subsample analyzed (n = 5598) in one study (9) and because of an inadvertent typo in an extracted value from another study (15).

[5] κ <100% because of unequal calculated values between authors after accurate extraction of input data from one study (8).

[6] κ <100% because of unequal calculated values between authors after accurate extraction of input data from one study (52); rounding of 37.8 to 37 instead of to 38 after calculations for one study (53), and extraction error for 1 in 5 numbers used in calculations for study of native Hawaiian men (17).

[7] This value was calculated as the product of $\kappa \times 10^2$ shown for the population sample analyzed and FUY extracted.

[8] κ in this row is weighted for 10 possible scores (0–9).

highest of which was 143 g/2000 kcal. Overall, the mean of study GL intakes was 139 g/2000 kcal (Table 1).

Combined studies: meta-analysis without covariates

Observations made in this and the next section were of central importance. Differences were found among studies for the rise in RR for T2D per 100-g rise in GL (**Figure 2**). Thus, the inconsistency among all studies (heterogeneity) was high (I^2 = 48%) and significant (P = 0.005). Each sex subgroup (males, females, and mixed sexes) contributed heterogeneity ($I^2 > 0\%$). By using this approach to analysis, there was only a clearly significant association of T2D

with GL in women ($P < 0.001$ for females, P = 0.060 for mixed sexes, and P = 0.132 for males). Nevertheless, the random-effects meta-analysis provided strong evidence that RR for T2D was significant ($P < 0.001$) over all studies at 1.27 (95% CI: 1.15, 1.40) for a 100-g rise in GL.

With visual inspection (Figure 2), the inconsistency among studies within each sex subgroup appeared possibly related to the validity of the dietary instrument used (CORR; tested below, *see* Strength, stability, and significance of covariates). This possibility confounded attempts to use a subgroup analysis without covariates to assess differences between sexes. Similar observations were made when the rate of change in lnRR per 100 g
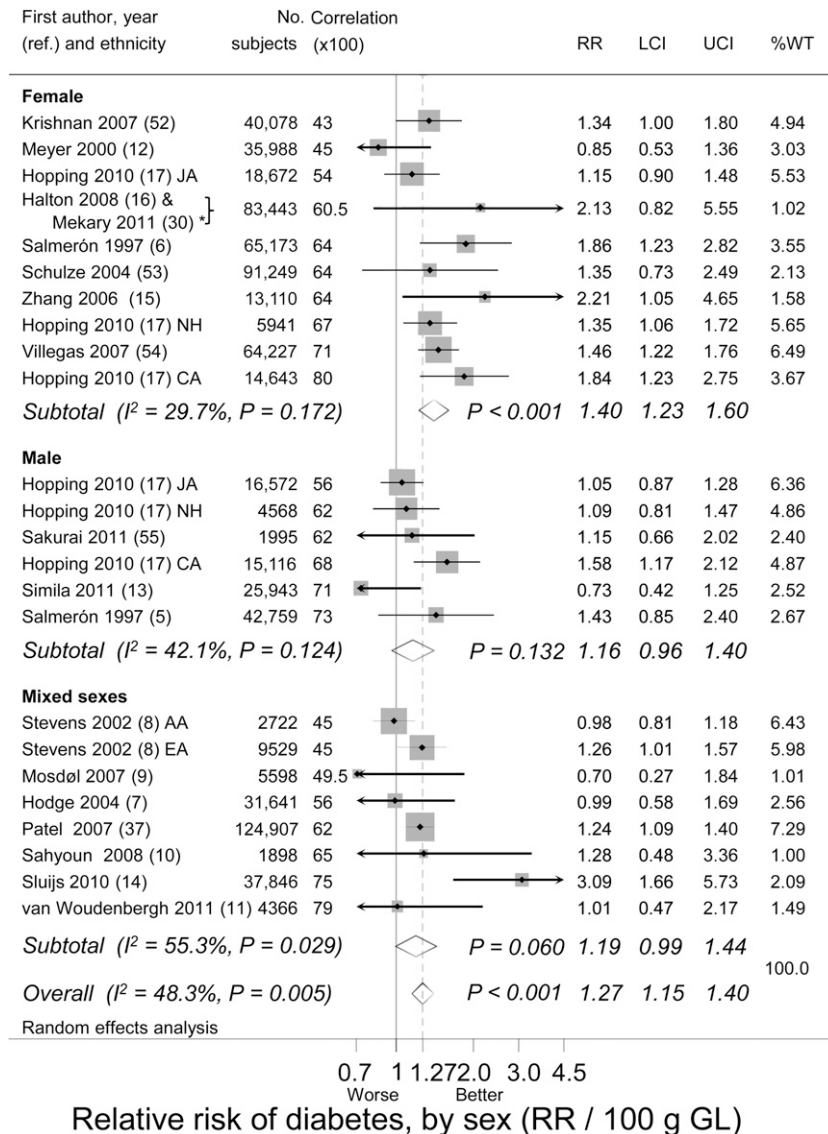
First author, year (ref.) and ethnicity	No. subjects	Correlation (x100)	RR	LCI	UCI	%WT
Female						
Krishnan 2007 (52)	40,078	43	1.34	1.00	1.80	4.94
Meyer 2000 (12)	35,988	45	0.85	0.53	1.36	3.03
Hopping 2010 (17) JA	18,672	54	1.15	0.90	1.48	5.53
Halton 2008 (16) & Mekary 2011 (30) *]	83,443	60.5	2.13	0.82	5.55	1.02
Salmerón 1997 (6)	65,173	64	1.86	1.23	2.82	3.55
Schulze 2004 (53)	91,249	64	1.35	0.73	2.49	2.13
Zhang 2006 (15)	13,110	64	2.21	1.05	4.65	1.58
Hopping 2010 (17) NH	5941	67	1.35	1.06	1.72	5.65
Villegas 2007 (54)	64,227	71	1.46	1.22	1.76	6.49
Hopping 2010 (17) CA	14,643	80	1.84	1.23	2.75	3.67
Subtotal (I² = 29.7%, P = 0.172)			P < 0.001	1.40	1.23	1.60
Male						
Hopping 2010 (17) JA	16,572	56	1.05	0.87	1.28	6.36
Hopping 2010 (17) NH	4568	62	1.09	0.81	1.47	4.86
Sakurai 2011 (55)	1995	62	1.15	0.66	2.02	2.40
Hopping 2010 (17) CA	15,116	68	1.58	1.17	2.12	4.87
Simila 2011 (13)	25,943	71	0.73	0.42	1.25	2.52
Salmerón 1997 (5)	42,759	73	1.43	0.85	2.40	2.67
Subtotal (I² = 42.1%, P = 0.124)			P = 0.132	1.16	0.96	1.40
Mixed sexes						
Stevens 2002 (8) AA	2722	45	0.98	0.81	1.18	6.43
Stevens 2002 (8) EA	9529	45	1.26	1.01	1.57	5.98
Mosdøl 2007 (9)	5598	49.5	0.70	0.27	1.84	1.01
Hodge 2004 (7)	31,641	56	0.99	0.58	1.69	2.56
Patel 2007 (37)	124,907	62	1.24	1.09	1.40	7.29
Sahyoun 2008 (10)	1898	65	1.28	0.48	3.36	1.00
Sluijs 2010 (14)	37,846	75	3.09	1.66	5.73	2.09
van Woudenbergh 2011 (11)	4366	79	1.01	0.47	2.17	1.49
Subtotal (I² = 55.3%, P = 0.029)			P = 0.060	1.19	0.99	1.44
						100.0
Overall (I² = 48.3%, P = 0.005)			P < 0.001	1.27	1.15	1.40
Random effects analysis						

0.7 1 1.272.0 3.0 4.5
Worse   Better

Relative risk of diabetes, by sex (RR / 100 g GL)

FIGURE 2. Meta-analysis without covariates that relates RR of type 2 diabetes to GL by sex group. Study means are denoted by gray boxes (larger points have greater weight). Horizontal lines denote 95% CIs. Arrowheads indicate truncations. Diamonds show combined-study means and corresponding 95% CIs. The scale is logarithmic with RR and 95% CIs shown untransformed. Individual studies are identified by first author, date, and citation. P values were calculated by using the z test for RR and the Q test for I^2. *Data from the same study reported at different follow-up durations (20 and 26 y) (16, 30) were combined before meta-analysis. AA, African American; CA, Caucasian American; EA, European American; GL, glycemic load; I^2, variance among studies as a percentage of the total variance; JA, Japanese American; LCI, lower CI; NH, Native Hawaiian; ref., reference; UCI, upper CI; %WT, weight based on random effects.

GL (ie, dose-response) was replaced in each study with the absolute rise in lnRR from the lowest to highest quantile of GL in each study (*see* Figure S1 under "Supplemental data" in the online issue).

Combined studies: meta-analysis with covariates

Without covariate adjustments, the all-studies combined-mean incremented RR per 100-g GL was 1.27 (95% CI: 1.15, 1.40) as summarized in **Table 2** (model 1) ($P < 0.001$). This relation became progressively stronger while remaining significant after adjustment for SEX, CORR, and ETH but not FUY and reached 1.45 (95% CI: 1.31, 1.61) in the fully adjusted model applied to all studies (Table 2, model 5).

The progressive inclusion of covariates in the model, in which, eg, model 2 included the same covariates as in model 1 plus the

covariate for SEX, and model 3 included the same covariates as in model 2 plus the covariate for CORR (Table 2), progressively accounted for heterogeneity (inconsistency among studies) with exception for FUY. This effect was indicated by the progressive fall in heterogeneity (I^2) from 48% to 2% (models 1–5).

R^2 (Table 2) is a measure of the variance among studies that was fully explained by the covariates. Model 1 was without covariates as explanatory variables, and therefore, had $R^2 = 0\%$ (the model explained none of the between-study variance). R^2 increased progressively to 97% (model 5) because of the inclusion of hypothesized covariates that were due to associations with SEX, CORR, and ETH (but not FUY) so that 3 of the 4 hypothesized covariates explained virtually all variability among studies.

Altogether, cohorts of healthy adults who consumed diets with a high GL appeared to be at 45% greater risk of developing T2D

TABLE 2
RR of T2D when energy-adjusted glycemic load was 100 g higher than the point of reference (RR = 1) for 24 prospective cohort studies[1]

Model	Covariates used in the model	RR (95% CI)	P	R²	I²	P for I²
				%	%	
1	None	1.27 (1.15, 1.40)	<0.001	0	48	0.005
2	SEX	1.24 (1.12, 1.36)	<0.001	18	42	0.016
3	SEX, CORR	1.39 (1.24, 1.54)	<0.001	72	20	0.20
4	SEX, CORR, FUY	1.39 (1.24, 1.56)	<0.001	64	23	0.16
5	SEX, CORR, FUY, ETH	1.45 (1.31, 1.61)	<0.001	97	2	0.43

[1] Values of RR were untransformed after analysis of the ln form (lnRR). Model 1 was a meta-analysis without covariates, Model 2 was adjusted for sex (to 50% male and 50% female). Model 3 was adjusted as for model 2 and for dietary instrument validity (CORR centered on 0.7, which was the approximate middle value for generally acceptable correlations (correlations >0.5). Model 4 was adjusted as for model 3 and for FUY (centered on 10 y, which was the approximate mean for these studies). Model 5 was adjusted as for model 4 and for ETH (centered on 50% European Americans and 50% other ethnicities). Model 5 was also called the fully adjusted model. P values were calculated by using the z test for RR and the Q test for I². CORR, energy-adjusted and deattenuated dietary instrument correlation for carbohydrate; ETH, proportion of participants of European American ethnicity; FUY, number of follow-up years; I², heterogeneity that remained after adjustment for covariates; R², heterogeneity accounted for by adjustments for covariates; SEX, proportion of male study participants; T2D, type 2 diabetes.

than were cohorts of adults who consumed a diet lower in GL by 100 g (Table 2, model 5).

Sensitivity of RR to retention of FUY in the model

A model that excluded the nonsignificant FUY as covariate exhibited relations for RR that were essentially no different to those in model 5, which included FUY, and thus, RR remained at 1.45 (95% CI: 1.31, 1.61) for a 100-g increment in GL. Meanwhile the among-studies variance remained essentially completely explained by SEX, CORR, and ETH ($I^2 = 1\%$, $R^2 = 99\%$).

Sensitivity of RR to study deletions

In the fully adjusted model (model 5), the combined-study mean incremental RR for T2D stabilized at ~0.45 (95% CI: 0.31, 0.61) for a 100-g increase in GL. The deletion of any individual study from the analysis affected this increment by <8%; the increments ranged from 0.42 (95% CI: 0.26, 0.60; $P < 0.001$, $I^2 = 4\%$) after deletion of a study from Hopping et al (17) to 0.48 (95% CI: 0.34, 0.65; $P < 0.001$, $I^2 = 0\%$) after deletion of the study from Krishnan et al (52).

Sensitivity of RR to study quality items

Adjustments to RR, additional to those in model 5, by individual NOS study quality items were negligible and affected the combined study incremental RR by <4% (range: −4% to +4%) (see Table S6). The quality items fell under 3 headings of participant-selection criteria, outcome criteria, and comparability criteria. Sensitivity to these and to individual quality items were assessed. Individual quality items were: whether the sample populations were truly or somewhat truly representative of the average adult population or sex subgroup in the communities; whether subcohorts (by quantile) were selected from the same community; whether exposure to GL was ascertained securely; whether the outcome of interest was absent at the start of the study; whether few subjects were lost to follow-up or the losses were adequately explained; whether the analysis of the study had adjusted for nonnutrient risk factors (smoking, physical activity, and BMI); whether there had been adequate adjustments for nutritional factors (energy, fiber, fat, and alcohol intakes); whether the outcome was assessed adequately; and whether the follow-up was sufficiently long for the outcome to occur (≥4y) (see Table S7 under "Supplemental data" in the online issue for results on individual items).

Sensitivity of RR to other study characteristics

Adjustments to RR, additional to those in model 5, were explored for other study characteristics but were also negligible, each of which affected the combined study incremental RR by ≤10% (range: −4% to +10%). These variables included the study mean GL, the study mean energy intake, whether GL had been expressed on a glucose or a bread standard in the original study, the number of dietary assessments made during the follow-up period, the number of food items in the dietary instrument, whether or not the dietary instrument had been validated within the population studied, whether or not the validation was for energy adjusted intakes, or not dietary (or cereal) fiber had been excluded as a confounder or covariate, the size of the study population sample, the study average BMI, the study average age of participants at baseline, the number of person-years captured in the study, the total number of incident T2D cases captured in the study, and the case ascertainment (ie, self-report compared with a clinical report) (see Table S7 for results on individual items).

Sensitivity of RR to data weaknesses

Weaknesses in data used in the meta-analysis were explored by making a range of alternative assumptions and simulations. Details are provide online (see Table S5) and concerned approximations that were assumed to exist or were introduced by calculations when information was not reported (or not provided in correspondence) directly or indirectly for GL, energy intake, cases by quantile, noncases by quantile, person-years by quantile, and CORR. CORR was the only hypothesized covariable

that had been derived in previous experimental work by using estimation procedures. When the assumptions for CORR were varied, RR for a 100-g increment in GL stayed within the range from 1.45 (95% CI: 1.31, 1.61) to 1.49 (95% CI: 1.33, 1.67) compared with 1.45 (95% CI: 1.31, 1.61) as reported in Table 2 (model 5). A lower value was found only when an additional random error for GL was simulated, at which point model 5 yielded, on average for 10 simulations, a consistently lower RR ($P < 0.001$; t test) of 1.42 (95% CI: 1.28, 1.58) for an increment in GL of $100 \pm$ SD of 10 g. Altogether, the sensitivity analyses (*see* Table S5) provided confirmation that the assumptions we made introduced either a negligible error or resulted in conservative estimates for the RR-T2D relation with GL.

Publication bias

Asymmetry in a funnel plot (*see* Figure S2 under "Supplemental data" in the online issue) according to trim-and-fill analysis indicated a 0.00 (95% CI: –0.06, +0.06; $P > 0.99$) bias in the incremental RR over 100 g GL in the fully adjusted model (model 5). The analysis also provided the location and precision of hypothetical points needed to achieve symmetry and eliminate bias and that represented studies potentially missed by the literature search, but the analysis returned no studies as potentially missing.

Range of GL associated with T2D risk

To assess the range over which GL associated with T2D, one-step pooled metaregression analysis was performed on sub-cohorts ($n = 24$ studies; including 24 referent and 79 nonreferent cohorts) (**Figure 3**). The analysis made adjustments for SEX, CORR, FUY, and ETH as in model 5 but allowed the increment in RR from referent to nonreferent cohort to vary with the dose for GL. The dose for GL was the average GL between the referent Q_1 and the higher nonreferent Q_n, and curvature was permitted by fitting the dose as a cubic spline. The fitted dose-response (trend) was imperfectly linear (horizontal) with a loss of this imperfection when the study of Meyer et al (12) was dropped from the analysis. Nevertheless, when all studies were retained, the GL was significantly related to risk of T2D at all doses >95 g/2000 kcal.

Model forecasts

We compared our model forecasts with combined estimates of RR related to GL obtained as other authors have done before us (1, 4, 26) by using only lowest and highest quantiles in the meta-analysis without covariates. In this last scenario, the current data set yielded RR of 1.20 (95% CI: 1.11, 1.30) and corresponded to an average range for GL across regions of 81 g from the lowest (Q_1) to the highest (Q_{max}) quantile (*see* Figure S1 under "Supplemental data" in the online issue).

In model 5 (Table 2), RR after adjustment for SEX, ETH, and CORR equal to 0.7 indicated the higher value for RR of 1.45 (95% CI: 1.31, 1.61) for a 100-g rise in GL (Table 2). The same adjustments with CORR equal to 1.0 (ie, the unattainable ideal) forecasted RR of 2.05 (95% CI: 1.55, 2.65), which was 5 times stronger than the RR of 1.20. With consideration that, globally, a significant association was indicated for GL between $\sim$100 and 279 g (Figure 3), the same model forecasted RR of 3.56 (95% CI:
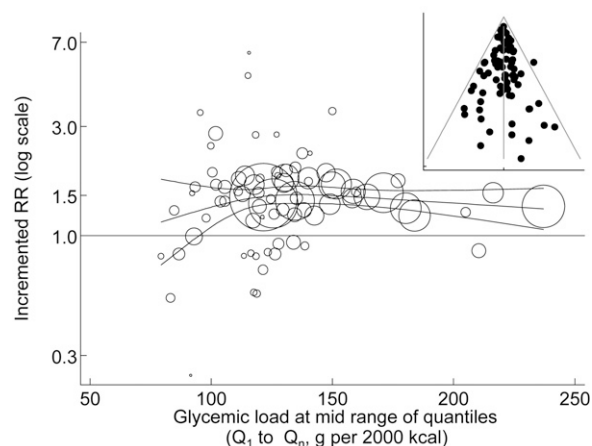

FIGURE 3. Range over which GL and RR of type 2 diabetes are related. Data points are bubbles and show RRs per 100 g GL for study quantiles from the lowest quantile (Q_1) to each higher quantile (Q_n) after adjustment for the 4 hypothesized covariates. Bubbles increase in size with increase in weight of the data point. Curvilinearity of the trend and 95% CIs for the adjusted RR per 100 g GL was permitted by fitting a one-step pooled cubic-spline metaregression with 3 equally dispersed knots to the lnRR. Larger bubbles have greater precision and weight. The inset shows the corresponding funnel plot for model residuals. GL, glycemic load.

2.06, 5.75) over this range for GL, which spanned 179 g GL. This RR (3.56) was 12 times stronger than that obtained by using only the lowest and highest quantiles in the meta-analysis without covariates. Although such forecasts should be considered cautiously and have wide 95% CIs, they provide evidence that a meta-analysis that is without consideration of dose and covariates can substantially underestimate the importance of the GL in affecting T2D incidence both regionally and, more so, globally.

Strength, stability, and significance of covariates

In Model forecasts, the only critical uncertainty about the covariates was the strength (and significance) of the relation between RR and CORR. Without study deletions, RR increased to 2.05 (95% CI: 0.6, 4.7) per unit of CORR (1.0) with $P = 0.0005$ (**Table 3**). Any single study deletion from the analysis left CORR significant at $P \le 0.007$. Largest deviations occurred after deletion of observations from Meyer et al (12) and Krishnan et al (52), which left the RR-CORR association between 11% lower and 19% higher, respectively. However, after deletion of both studies, the RR-CORR association was 2.3 (95% CI: 0.7, 5.4), which remained both significant ($P = 0.001$) and no less strong than when these studies were retained in the analysis.

The RR-CORR association also remained stable to possible adjustments for any other study characteristic or study quality items explored as centered covariates additional to those hypothesized (*see* Table S7). Each item had only a minor influence (–10 to +19%) on the size of the RR-CORR association, but this association always remained significant ($P < 0.03$).

Relations for RR-SEX, RR-ETH, and RR-FUY together with RR-CORR are also shown graphically online (*see* Figure S3 under "Supplemental data" in the online issue) and are summarized in Table 3. Even after consideration of multiple covariances (and

TABLE 3
Association of hypothesized determinants with the RR of T2D ($n = 24$ studies)[1]

		P-trend				
	Increment in RR[2]	Unadjusted	Adjusted[3]	R^2	I^2	P for I^2
SEX (F > M)						
Single covariate model	0.24 (−0.01, 0.57)	0.065	—	17	43	0.02
Bi-covariate model (model 3)[4]	0.23 (0.01, 0.47)	0.036	0.036	72	14	0.20
Fully adjusted (model 5)[5]	0.22 (0.02, 0.46)	0.031	0.031	97	2	0.43
CORR (over the maximum range, 0.0–1.0)						
Single-covariate model	2.19 (0.5, 6.0)	0.004	—	53	30	0.09
Bi-covariate model (model 3)[4]	2.15 (0.5, 5.5)	0.002	0.004	72	14	0.20
Fully adjusted model (model 5)[5]	2.05 (0.6, 4.7)	0.0005	0.001	97	2	0.43
FUY (/10 y)						
Single-covariate model	−0.01 (−0.28, 0.26)	0.92	—	−9	49	0.01
Fully adjusted (model 5)[5]	0.00 (−0.19, 0.20)	0.96	>0.99	97	2	0.43
ETH (European American > other ethnicities combined)						
Single-covariate model	0.24 (0.01, 0.52)	0.041	—	18	43	0.016
Fully adjusted model (model 5)[5]	0.22 (0.05, 0.41)	0.011	0.044	97	2	0.43

[1] RR of T2D was for an energy-adjusted glycemic load 100 g higher than in the referent quantile. P values were calculated by using the z test for RR and the Q test for I^2. CORR, energy-adjusted and deattenuated dietary instrument correlation for carbohydrate; ETH, proportion of participants of European American ethnicity; FUY, number of follow-up years; I^2, heterogeneity that remained after adjustment for covariates; R^2, heterogeneity accounted for by adjustments for covariates; SEX, proportion of male study participants; T2D, type 2 diabetes.

[2] All values are trends; 95% CIs in parentheses. Trends and 95% CIs are shown untransformed. RR was analyzed as the ln.

[3] Adjusted for 2 or more covariances according to Bonferroni (see footnote 1 of Table 2). The following are listed in order of priority: $1 \times P$ for the first hypothesized determinant (SEX), $2 \times P$ for the second hypothesized determinant (CORR), $3 \times P$ for the third hypothesized determinant (FUY), and $4 \times P$ for the fourth hypothesized determinant (ETH).

[4] Inclusive of the first 2 hypothesized covariates (ie, SEX and CORR).

[5] Inclusive of all 4 hypothesized covariates (ie, SEX, CORR, FUY, and ETH).

the hierarchy of hypotheses), the relation for RR-SEX was significant ($P < 0.031$) and that for RR-ETH was significant ($P < 0.011$) or borderline significant after multiple covariances were accounted for ($P = 0.044$) (Table 3). Sensitivity analysis shown graphically (*see* Figure S4 under "Supplemental data" in the online issue) indicated that no one study compared with any other had an unduly large influence on the size of β coefficients for covariates, which was also an indication that model 5 was not unduly complex. Also, neither the RR-SEX nor the RR-ETH association was modified by greater than –23% to +19% when adjusted for an additional (v^{th}) covariate that represented any study quality items and any other study characteristics, none of which were themselves significant (z score <2; $P > 0.05$) (*see* Table S7).

The exclusion of the hypothesized but nonsignificant variable FUY from model 5 (Tables 2 and 3) also had a negligible influence on the size of the remaining but significant hypothesized covariables. Increments in RR that were due to a 100-g increment in GL after exclusion of FUY were: for SEX, 0.21 (95% CI: 0.02, 0.42) higher in women than in men, which compared with 0.22 (95% CI: 0.03, 0.46) when FUY was included; for ETH, the value was 0.21 (95% CI: 0.04, 040) higher in European Americans than in other ethnicities combined compared with 0.22 (95% CI: 0.05, 0.41) when FUY was included; and for CORR, the values was higher by 2.01 (95% CI: 0.64, 4.6) per unit increase in CORR compared with 2.05 (95% CI: 0.6, 0.47) when FUY was included. Meanwhile, the variance among studies was still essentially fully explained ($I^2 = 1\%$, $R^2 = 99\%$).

We concluded that the T2D-GL relation had significant covariates (SEX, CORR, and ETH) that were neither highly sensitive to observations for individual studies nor attributable to an inadequate account of other study characteristics or study quality items or data weaknesses explored.

Cumulative meta-analysis with covariates

Additional evidence on the stability of variable estimates comes from the cumulative meta-analysis (*see* Figure S5 under "Supplemental data" in the online issue). All cumulative RR values obtained remained positive (RR >1) and stabilized at 1.45. Covariates SEX, CORR, and ETH each approached stability, although with less precision than for RR. By contrast, the cumulative information on FUY was unstable. A positive and seemingly significant association between RR and FUY emerged with the observations of Halton et al (16), who reported results of a 20-y follow-up study (16). However, any relation with FUY was lost progressively when subsequent studies were included in the analysis and was not evident by the time of the study of Mekary et al (30) that reported on 26-y follow-up.

DISCUSSION

Our meta-analysis of 24-prospective cohort studies had 7.5 million person-years of follow-up and revealed a significant and strongly positive relation between GL and T2D risk across a wide range of GL values. Also shown was that the relation was

significantly affected by several main sources of heterogeneity. These sources included sex, ethnicity, and the quality of the dietary assessment, although not the duration of follow-up, and explained essentially all of the variance in RR among studies. After adjustment for heterogeneities, the RR stabilized at 1.45 (95% CI: 1.31, 1.61) for a rise in GL of 100 g/2000 kcal. That is, over this dose range, the risk of T2D increased by 45%.

The associations we found with covariates were generally supportive of 3 of the 4 hypotheses addressed and that originated elsewhere (1, 5, 6, 17). The positive dose-dependent GL-T2D relation was stronger in women than in men (SEX), stronger when the dietary instrument had greater validity (CORR), and stronger in European Americans than in the other ethnicities examined as a single group. The duration of follow-up (FUY), which may reflect the duration of exposure to GL or time to develop clinical disease had an unstable relation with RR for T2D, and over all studies, our analysis was unable to confirm that this factor had importance. The positive GL-T2D relation in the current meta-analysis was coherent with meta-analyses of human interventions that showed, for the first time to our knowledge, that both GL (and GI) and fasting blood glucose (and glycated protein) interrelate independently of dietary fiber intake while dependent on the severity of dysglycemia (56, 57).

Our meta-analysis with covariates had several strengths. It combined many studies, small to large cohorts, and few to many cases and, thus, allowed reasonably precise variable estimations, power to detect significant relations, and precise assessment of asymmetric biases. The publication bias was both far from significant and negligible, whereas the sensitivity of each main outcome to each individual study was relatively small. In addition, the main outcomes proved relatively insensitive to surrogacy or confounding by many other study characteristics or quality items assessed. Notably too, we provided an account of essentially all heterogeneity among studies. A major strength was that our 4 hypothesized covariates had been suggested previously, although at a time when only very limited evidence was available. In the current study, 3 of the 4 hypotheses were far from refuted, although only CORR was highly significant over all studies, and SEX and ETH were weakly significant ($P < 0.05$ after multiple covariates were accounted for). Additional studies are needed to better define how the GL-T2D relation changes with the duration of follow-up because studies with 10–20 y of follow-up are low in number.

A good balance of men, women, and mixed-sex studies have provided us with a reasonable representation of each sex and a postori power to detect a significant effect. Our observation of a sex difference was strengthened by avoiding errors made (1, 26) when data from Patel et al (40) were extracted during a previous meta-analysis of fewer studies. Although the sex difference may be genetic, it could also reflect a sex-related behavior (eg, greater alcohol consumption in men than in women) recently reported as a determinate in women (30, 58). Moreover, the sex difference shown in the current study had an evidence level that was no better than the narrative grade of the original studies (ie, grade B compared with grade A for interventional studies) (59, 60).

Dietary instruments in the reviewed studies had a broad range of validities for the assessment of carbohydrate intake (CORR), which facilitated a precision and power to detect a significant influence. A possible weakness is that CORR is an instrument variable rather than an exposure variable and, thus, had a potential to hide an unidentified exposure. However, in the absence of such an identification, a bias because of inadvertent adjustment for an instrument variable is not thought to present a major threat (61). An additional weakness was that few studies used dietary instruments that had been specifically validated for GL. However, instrumental estimates of carbohydrate and GL intakes appeared highly correlated (30, 62) or yielded similar values for CORR (63). An implication of CORR for the prediction of the size of the GL-T2D relation is that all combined means from a meta-analysis without appropriate covariates will underestimate the importance of GL in the contribution of risk of T2D. Moreover, whenever GL is shown to have a negligible positive effect in observational studies, a low validity for the dietary instrument used needs to be excluded as a possible artifact. Whether an inconsistent association between RR for other chronic diseases and carbohydrate intake (12, 14, 16, 54, 64) would be resolved by examining evidence along lines used here for GL remains to be examined when sufficient observations accumulate.

It has been understood that GI compares favorably with GL in terms of predicting chronic disease risk generally (1), which is a view that has been refuted (4) and affirmed (65) for T2D. However, such comparisons depend on an understanding of the causes of heterogeneity in results for both GI and GL. Furthermore, that the GL-T2D relation depends on CORR raises the interesting question of whether similar results might arise for other chronic diseases, including cancers associated with T2D (66, 67).

The current study is limited in its ability to describe the effect of ethnicity on the relation between GL and T2D. Many ethnic groups have not yet been researched, and other ethnic groups have limited representation. European Americans formed the largest group, and the simplest assessment possible was for a 2-group comparison with a similar number of studies that represented all other ethnicities. Clearly, a distinction between these groups will eventually depend on representation among all other ethnicities. For the present, the data simply support rather than refute differences in RR in defined groups of people. That the strength of the GL-T2D relation was found to depend on ethnicity does not automatically mean GL has less importance in some ethnic groups; this is because, in some instances, it might be due to an overall higher ethnic susceptibility to the incidence of T2D unrelated to GL.

In several important aspects, our meta-analysis went beyond previous work (1, 4, 25–29). First, we applied a dose-response meta-analysis and considered the range of GL that showed significant association. Second, our analyses were much more systematic and comprehensive with an in-depth quantification of heterogeneities. Third, cumulative analyses were conducted with adjustments for several significant covariates. A model that permits adjustment for 4 possible covariates may seem overly complex with ≤24 prospective studies. However, the significant covariates had higher levels of significance when applied simultaneously than singly. Moreover, our cumulative analysis reached toward stable means and trends for RR and significant covariates before the last 10 studies were includes in the analysis. Furthermore, a low sensitivity to the deletion of individual studies was a direct indication that the fully adjusted model (model 5) was not unduly complex.

We showed that the GL-T2D relation operated over a wide range of GL values and was especially significant when the GL

was >95 g/2000 kcal. A target of 100 g GL would, in theory, be reached by consuming 100 g carbohydrates with a GI of 100, by 130 g carbohydrates [the US Recommended Dietary Allowance (RDA) for adults (68)] with a GI of 77, or by 200 g carbohydrates with GI of 50, or by 250 g carbohydrates with a GI of 40. The 200–250-g carbohydrate intake approximates the median for Western diets in adults (69). Numerous examples of highly palatable foods have a GI ≤40 (70), which allows for achievement of all these possibilities. Thus, up to and immediately above the carbohydrate RDA for adults, the replacement of high-GI foods with low-GI foods would allow the target to be met. However, when carbohydrate intake is >250 g, high-GI foods would need to be consumed at a lower frequency or by increasing elimination from the diet. At 300 g carbohydrates (60% of energy), the GI would need to be 33 and would be achievable by combining foods with a GI <50.

Nutritionists are likely to be interested in the limitations that the current evidence placed on the contribution to GL and carbohydrate intake that can be made by sugars. With an assumption of a GI of 68 for sucrose (31), 147 g alone would contribute a GL of 100 g in a 2000-kcal/d diet, and at 4 kcal/g sucrose, this would be 29% of energy. These amounts already exceed both the RDA of 130 g carbohydrate/d and the upper intake for sugars of 25% of energy intake in the United States (68) [and 10% elsewhere (70)]. Therefore the target of a 100-g GL in a 2000 kcal/d diet would not pose a more stringent limitation on sucrose intake than would either the RDA for carbohydrate or upper intake for sugars. Similar considerations hold for pure fructose and high-fructose corn syrup. Therefore, the current evidence is consistent with a view that, for carbohydrate nutrition in general, with regard to GL, sugars can be treated as just another carbohydrate together with starches. For both types of carbohydrates, the measure of grams of GL per 2000 kcal becomes a factor (aside from energy intake) that explains the risk of T2D. However, an intake of 100 g pure fructose/d (equivalent to 20% of 2000 kcal) has been recommended by the American Heart Association as an upper limit for normal to borderline hypertriglyceridemic individuals (71).

Weaknesses exist in these approaches to target a 100-g GL in 2000 kcal and in the underpinning meta-analyses and were inherent to the reviewed studies. These weaknesses are that the methodology for the assessment of the GI of foods is imprecise (72, 73) and varies with ripeness, processing, and chewing, and in observational studies foods are reported rather than provided. However, with 7.5 million years of follow-up, the use of energy-adjusted nutrient values, deattenuated correlations, multiple dietary assessments in studies of longer follow-up, and precision for GL expressed and recorded per grams of fresh-weight food, such weaknesses appeared not to be as great as often envisaged (58, 74–77).

In conclusion, the prospective association between GL and T2D risk is moderate to strong, depends on the prevailing circumstance, and appears to have greater importance globally than regionally. The relation appears stronger in studies that use dietary instruments of greater validity (as defined in the current study), women, and European Americans. Persons who consume diets >100 g GL/2000 kcal appear at progressively greater risk of T2D with greater GL intake. Altogether, our meta-analysis supports that GL is an important and underestimated dietary characteristic that, among others, contributes significantly to the incidence of T2D.

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