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Dietary Glycemic Index, Glycemic Load, and Digestible Carbohydrate Intake Are Not Associated with Risk of Type 2 Diabetes in Eight European Countries[1–3]

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Abstract

The association of glycemic index (GI) and glycemic load (GL) with the risk of type 2 diabetes remains unclear. We investigated associations of dietary GI, GL, and digestible carbohydrate with incident type 2 diabetes. We performed a case-cohort study nested within the European Prospective Investigation into Cancer and Nutrition Study, including a random subcohort (n = 16,835) and incident type 2 diabetes cases (n = 12,403). The median follow-up time was 12 y. Baseline dietary intakes were assessed using country-specific dietary questionnaires. Country-specific HR were calculated and pooled using random effects meta-analysis. Dietary GI, GL, and digestible carbohydrate in the subcohort were (mean ± SD) 56 ± 4, 127 ± 23, and 226 ± 36 g/d, respectively. After adjustment for confounders, GI and GL were not associated with incident diabetes [HR highest vs. lowest quartile (HR_{Q4}) for GI: 1.05 (95% CI = 0.96, 1.16); HR_{Q4} for GL: 1.07 (95% CI = 0.95, 1.20)]. Digestible carbohydrate intake was not associated with incident diabetes [HR_{Q4}: 0.98 (95% CI = 0.86, 1.10)]. In additional analyses, we found that discrepancies in the GI value assignment to foods possibly explain differences in GI associations with diabetes within the same study population. In conclusion, an expansion of the GI tables and systematic GI value assignment to foods may be needed to improve the validity of GI values derived in such studies, after which GI associations may need reevaluation. Our study shows that digestible carbohydrate intake is not associated with diabetes risk and suggests that diabetes risk with high-GI and -GL diets may be more modest than initial studies suggested. J. Nutr. 143: 93–99, 2013.

Introduction

Carbohydrate-rich diets are known to produce high postprandial glucose concentrations and have therefore been expected to increase diabetes risk (1,2). However, prospective studies have generally found no association of carbohydrate intake with risk of diabetes (3–5). Dietary carbohydrate content may not fully represent glycemic response, because other aspects of the diet,

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such as fat content and cooking methods, can also influence glycemic response. The glycemic index (GI)[31] was introduced, which classifies carbohydrate-containing foods according to their glycemic response (1). High-GI foods cause high postprandial glucose concentrations that decline rapidly, whereas low-GI foods cause lower postprandial glucose concentrations that decline more gradually (1,2). The GI represents carbohydrate quality. The glycemic load (GL) is the product of the GI and the amount of carbohydrate in a food and represents both carbohydrate quantity and quality (5).

High-GI diets have been suggested to contribute to diabetes development by rapidly increasing postprandial glucose concentrations, thereby increasing insulin demand and leading to pancreatic exhaustion. High-GI diets are also suggested to increase postprandial FFA release, which can directly increase insulin resistance (6,7). Current evidence regarding the prospective associations of dietary GI and GL with diabetes is still somewhat mixed, with some studies reporting harmful associations (4,5,8–16) and others reporting no association (8,9,12–14,17–23). Three recent meta-analyses of prospective, predominantly American studies reported increased diabetes risk in the highest GI and GL categories, ranging from an increased risk of 16% (GI) and 20% (GL) to 58% (both GI and GL) (24–26).

Although GI and GL are generally not implemented in dietary guidelines, the GI concept can be applied in practice, as shown in Australia, where GI symbols are put on food labels (27).

Recently, van Bakel et al. (28) reported that food patterns underlying the GI and GL of the diet, and dietary GI and GL levels, vary substantially among European regions. Wide variation in dietary GI and GL can improve the ability to detect potential effects of GI and GL on diabetes risk. The European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct study (29) is a large, prospective, case-cohort study with contributions from 8 European countries and provides an excellent opportunity to investigate dietary GI and GL at wide varying intakes, derived from different underlying food patterns. Therefore, we investigated the association of GI, GL, and digestible carbohydrate with the risk of diabetes in the InterAct-EPIC study.

Participants and Methods

Study design and population. We used a nested case-cohort design, including incident type 2 diabetes cases (n = 12,403) and a representative subcohort (n = 16,835, including 778 incident type 2 diabetes cases), selected randomly from the EPIC cohort (29). EPIC is a multi-center, prospective, cohort study with 519,978 participants designed to investigate the relationships among food habits, nutritional status, lifestyle and environmental factors, and the incidence of cancer and other chronic diseases. The current analysis used the case cohort-only data from 8 European countries [Denmark (n = 4037; 2055 cases), France (n = 867; 288 cases), Germany (n = 3578; 1584 cases), Italy (n = 3393; 1437 cases), The Netherlands (n = 2290; 828 cases), Spain (n = 5889; 2564 cases), Sweden (n = 5401; 2622 cases), and the United Kingdom (UK) (n = 2324; 1025 cases)], with a total of 26 centers (**Supplemental Table 1**). The majority of study participants were aged 35–70 y and were recruited between 1991 and 2000, mainly from the general population. Exceptions were the French cohort, which included female members of a health insurance scheme for school and university employees, and the Spanish and Italian centers, which included blood donors. In addition, the Utrecht cohort (The Netherlands) and the Florence cohort (Italy) included women attending a breast cancer screening program. Most of the Oxford cohort (UK) consisted of vegetarian and health-conscious volunteers. All participants gave written informed consent and the study was approved by the local ethics committee in the participating countries and the Internal Review Board of the International Agency for Research on Cancer. The full rationale and methods and detailed descriptions of the study populations of the EPIC study were reported elsewhere (29,30).

We excluded prevalent diabetes cases (n = 548), participants with unknown diabetes status (n = 133), and participants with abnormal energy intake (in the top 1% and bottom 1% of the distribution of the ratio of reported energy intake over estimated energy requirement, assessed by basal metabolic rate; n = 619). Furthermore, we excluded participants with missing information on nutritional intake (n = 117) or other covariables (n = 955), leaving a total of 26,088 (11,559 cases, 15,258 subcohort participants, including 729 cases in the subcohort) for the present analysis.

Dietary intake. The EPIC dietary data were assessed at baseline by means of a quantitative dietary questionnaire with individual portion sizes (in France, Spain, The Netherlands, Germany, and Italy, except Naples) or semiquantitative FFQs (in Denmark, Naples, Sweden, and the UK), which were developed and validated locally (31,32). Correlation coefficients for the relative validity for carbohydrate measured with FFQ against 24-h recalls or weighted food records varied from 0.40 in Denmark to 0.84 in Spain for men and from 0.46 in Malmo (Sweden) to 0.78 in Spain for women (32). Detailed descriptions of the usual dietary intake were described elsewhere (33).

GI values, with glucose as a reference scale, were assigned to food items reported in the dietary questionnaires in a standardized manner as described in detail elsewhere (34). In brief, foods reported in the dietary questionnaires were selected on the basis of the GI value of the food while considering aspects of the food that might influence GI (e.g., cooking method, preservation method, sugar content, and country-specific types of food). GI values obtained from the Foster-Powel table (35), British values (36), internet updates (37), and some communicated from GI experts (J. Brand-Miller, University of Sydney and T. Wolever, University of Toronto, personal communication) were then assigned to individual food items. No value was assigned to food items that contained no or a negligible amount of carbohydrate or foods that do not increase blood glucose concentrations (primarily meat, fish, fats, and eggs). GI values were updated in 2009 using the recently published table by Atkinson et al. (38). Mean dietary GL was calculated by adding the products of digestible carbohydrate for each food (quantity per day) and its GI. Mean dietary GI was calculated as GL and then divided by the total amount of digestible carbohydrate consumed in 1 d.

Measurement of other baseline characteristics. Baseline information on lifestyle and medical history were obtained from self-administered questionnaires. Weight, height, and waist circumference were recorded by trained health professionals during a visit to a study center. Exceptions to this were that in Oxford (UK) and France a restricted number had waist circumference and/or height and weight measured. In Umea (Sweden) only weight and height were measured (39). Information on coronary heart disease, angina, and stroke at baseline was obtained from self-reported diagnosis or hospital discharge registries. Presence of hypertension and hyperlipidemia were based on self-reported diagnosis and/ or use of

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[3] Supplemental Tables 1–3 are available from the ''Online Supporting Material'' link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.

[31] Abbreviations used: EPIC, European Prospective Investigation into Cancer and Nutrition; GI, glycemic index; GL, glycemic load; HR_{Q4}, HR highest vs. lowest quartile.

medication. Physical activity was assessed by questionnaire and classified into inactive, moderately inactive, moderately active, and active according to the Cambridge Physical Activity Index (40).

Diabetes. Ascertainment and verification of incident diabetes has been described in detail elsewhere (29). In short, incident diabetes cases were identified on the basis of self-report, linkage to primary care registers, secondary care registers, medication use, and hospital admissions and mortality data. Identified cases were verified with further evidence, including individual medical record reviews. Participants were followed-up for occurrence of diabetes until the December 31, 2007.

Data analysis. Daily dietary GI, GL, and digestible carbohydrate (and its subtypes sugar and starch) (all g/d, except GI) were adjusted for total energy intake using the residual method (41) and were divided into quartiles on the basis of the distributions in the subcohort. Baseline characteristics and dietary intakes in the subcohort were examined by quartiles of GI and GL and presented as mean ± SD or median (IQR) for continuous variables and *n* (%) for categorical variables. Tests for linear trend were performed by including the median GI and GL intakes per quartile as continuous variables in linear (for continuous variables) or logistic (for categorical variables) regression models. Differences in baseline characteristics between quartiles of GI or GL were evaluated using a chi-square test (for categorical variables), 1-way ANOVA, or Kruskal-Wallis test (for continuous variables). Correlations among GI, GL, and digestible carbohydrate were estimated using a Pearson correlation. Country-specific HR (95% CI) for associations of GI, GL, and digestible carbohydrate (and its subtypes sugar and starch) with incident type 2 diabetes were calculated and random effects meta-analyses were performed to calculate a pooled HR. Modified Cox regression models that accounted for the case-cohort design [Prentice-weighted method (42)] were used to estimate associations. Age was used as underlying time variable in the Cox models, with age at recruitment as entry time and exit time as the age at diagnosis of diabetes, death, loss to follow-up, or censoring at the end of the follow-up, whichever came first. Covariables that were entered into the models were center (categorical), sex (men, women), BMI (continuous), education (none, primary school completed, technical or professional school, secondary school, longer education), physical activity (inactive, moderately inactive, moderately active, active), menopausal status (premenopausal, perimenopausal, postmenopausal), smoking status (never, former, current), alcohol consumption (≤10, 11–25, 26–50, ≥51 g/d), and dietary intakes of total energy, protein, polyunsaturated:saturated fat ratio, and fiber [all energy adjusted using the residual method (41) and continuous]. The estimates obtained for GL and digestible carbohydrate from this model can be interpreted as a substitution of GL or digestible carbohydrate for fat. The polyunsaturated:saturated fat ratio included in the model allows the absolute amount of fat to vary while the fat quality is kept constant. Tests for linear trend were performed by including median values of each quartile of intake for GI, GL, and digestible carbohydrate in the Cox regression models. We quantified the percentage of heterogeneity (I^2) between countries for quartile comparisons of GI, GL, and digestible carbohydrate using a multivariate meta-analysis approach. This approach takes into account the correlation between the variable estimates of all quartile comparisons.

Sensitivity analyses were done by excluding participants diagnosed with diabetes within the first 2 y of follow-up and those with baseline chronic diseases (coronary heart disease, angina, stroke, hyperlipidemia, and/or hypertension). Moreover, analyses were repeated after adding waist circumference to the multivariable-adjusted model; as a consequence, the Umea center (Sweden, *n* = 1734) was excluded, because waist circumference was not collected in this center. Interactions of GI,

TABLE 1 Baseline characteristics of the subcohort by quartiles of daily dietary GI and GL (EPIC-InterAct Study)[1,2]

	GI					GL				
	Q1 (lowest) ≤53.6	Q2 53.7–56.0	Q3 56.1–58.5	Q4 (highest) ≥58.6	*P*-trend	Q1 (lowest) ≤111 g/d	Q2 112–126	Q3 127–141	Q4 (highest) ≥142 g/d	*P*-trend
n	3815	3814	3815	3814		3815	3814	3815	3814	
Men, *n (%)*	1173 (31)	1380 (36)	1553 (41)	1668 (44)	<0.001	1562 (41)	1442 (38)	1343 (35)	1427 (37)	<0.001
Age, *y*	52 ± 9	53 ± 9	53 ± 9	52 ± 9	0.08	52 ± 8	52 ± 9	53 ± 9	52 ± 10	0.01
High education, *n (%)*	920 (24)	875 (23)	798 (21)	568 (15)	<0.001	908 (24)	841 (22)	745 (20)	667 (17)	<0.001
Waist circumference, *cm*	86 ± 13	86 ± 13	87 ± 13	87 ± 13	<0.001	88 ± 13	87 ± 13	86 ± 12	85 ± 12	<0.001
BMI, *kg/m²*	26.2 ± 4.3	26.0 ± 4.1	26.0 ± 4.2	26.1 ± 4.2	0.19	26.5 ± 4.2	26.1 ± 4.2	26.0 ± 4.2	25.6 ± 4.1	<0.001
Current smoker, *n (%)*	906 (24)	885 (23)	979 (26)	1195 (31)	<0.001	1248 (33)	1040 (27)	875 (23)	802 (21)	
Postmenopausal,[3] *n (%)*	1300 (49)	1260 (52)	1190 (53)	1070 (50)	0.44	1040 (46)	1180 (50)	1320 (53)	1270 (53)	<0.001
Physically inactive, *n (%)*	814 (21)	815 (21)	889 (23)	1090 (28)	<0.001	909 (24)	804 (21)	872 (23)	1020 (27)	0.001
Hypertension, *n (%)*	757 (20)	731 (19)	677 (18)	660 (17)	0.002	724 (19)	701 (18)	724 (19)	676 (18)	0.22
Dietary intake[2]										
Energy, *kcal/d*	2120 ± 640	2170 ± 620	2160 ± 620	2110 ± 650	0.70	2130 ± 650	2160 ± 630	2130 ± 620	2140 ± 650	0.80
Digestible carbohydrate, *g/d*	218 ± 38	225 ± 34	229 ± 35	233 ± 37	<0.001	183 ± 22	216 ± 14	237 ± 15	268 ± 22	<0.001
Starch, *g/d*	100 ± 25	117 ± 25	127 ± 27	146 ± 33	<0.001	96 ± 21	115 ± 20	128 ± 23	150 ± 35	<0.001
Sugar, *g/d*	114 ± 34	103 ± 30	99 ± 30	86 ± 31	<0.001	83 ± 26	97 ± 27	106 ± 29	116 ± 39	<0.001
Total fiber, *g/d*	23 ± 6	23 ± 6	22 ± 6	22 ± 6	<0.001	20 ± 5	22 ± 6	23 ± 6	24 ± 7	<0.001
Cereal fiber, *g/d*	7 ± 4	9 ± 4	9 ± 4	9 ± 4	<0.001	6 ± 4	8 ± 4	9 ± 4	10 ± 5	<0.001
Protein, *g/d*	90 ± 17	87 ± 15	86 ± 14	86 ± 15	<0.001	95 ± 16	89 ± 15	86 ± 14	80 ± 13	<0.001
SFA, *g/d*	31 ± 8	31 ± 7	31 ± 8	29 ± 8	<0.001	33 ± 9	32 ± 8	30 ± 7	26 ± 6	<0.001
MUFA, *g/d*	31 ± 9	30 ± 7	30 ± 7	30 ± 7	<0.001	35 ± 9	31 ± 7	29 ± 6	26 ± 6	<0.001
PUFA, *g/d*	13 ± 5	13 ± 4	13 ± 4	13 ± 4	0.24	14 ± 5	13 ± 4	13 ± 4	11 ± 4	<0.001
PUFA:SFA ratio	0.4 ± 0.2	0.4 ± 0.2	0.5 ± 0.2	0.5 ± 0.2	<0.001	0.5 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.5 ± 0.2	0.32
Alcohol, *g/d*	7 (1, 18)	7 (1, 17)	6 (1, 16)	5 (1, 16)	<0.001	15 (4, 32)	8 (2, 18)	5 (1, 13)	2 (0, 8)	<0.001

[1] Values are mean ± SD, *n* (%), or median (IQR), *n* = 15,258. *P* values for differences between quartiles (using chi-square test, 1-way ANOVA, or Kruskal-Wallis test) were all <0.001, except for BMI (0.05 for quartiles of GI), total energy intake (0.18 for quartiles of GI), monounsaturated fat intake (0.13 for quartiles of GI), and hypertension (0.01 for quartiles of GI; 0.44 for quartiles of GL). EPIC, European Prospective Investigation into Cancer and Nutrition study; GI, glycemic index; GL, glycemic load.

[2] Energy-adjusted intake, using residual method (41).

[3] Among women only, *n* = 9484.

TABLE 2 Association of quartiles of dietary GI, GL, digestible carbohydrate, sugar, and starch and risk of type 2 diabetes (EPIC-InterAct Study)[1,2]

	Quartile 1 (lowest)	Quartile 2	Quartile 3	Quartile 4 (highest)	*P*-trend
GI					
Median intake	52	55	57	60	
Incident type 2 diabetes cases, *n*	2757	2713	3050	3039	
Model 1: age, sex, center[3]	1	0.94 (0.87, 1.01)	1.04 (0.92, 1.16)	1.02 (0.91, 1.15)	0.65
Model 2: diabetes risk factors[4]	1	0.96 (0.87, 1.05)	1.05 (0.96, 1.15)	1.04 (0.94, 1.14)	0.17
Model 3: dietary factors[5]	1	0.97 (0.89, 1.07)	1.07 (0.97, 1.17)	1.05 (0.96, 1.16)	0.11
GL					
Median intake, *g/d*	101	119	133	153	
Incident type 2 diabetes cases, *n*	3051	2886	2800	2822	
Model 1: age, sex, center[3]	1	0.94 (0.88, 1.01)	0.91 (0.84, 0.98)*	0.87 (0.79, 0.96)*	0.003
Model 2: diabetes risk factors[4]	1	0.98 (0.89, 1.07)	0.94 (0.85, 1.03)	0.96 (0.87, 1.06)	0.40
Model 3: dietary factors[5]	1	1.02 (0.93, 1.13)	1.01 (0.90, 1.14)	1.07 (0.95, 1.20)	0.26
Digestible carbohydrate					
Median intake, *g/d*	185	215	238	267	
Incident type 2 diabetes cases, *n*	3230	2825	2760	2744	
Model 1: age, sex, center[3]	1	0.88 (0.82, 0.95)*	0.86 (0.80, 0.92)**	0.81 (0.72, 0.90)**	<0.001
Model 2: diabetes risk factors[4]	1	0.92 (0.83, 1.03)	0.90 (0.82, 0.99)*	0.88 (0.79, 0.98)*	0.01
Model 3: dietary factors[5]	1	0.98 (0.86, 1.11)	0.96 (0.86, 1.06)	0.98 (0.86, 1.10)	0.51
Sugar					
Median intake, *g/d*	65	88	108	137	
Incident type 2 diabetes cases, *n*	3251	2872	2741	2695	
Model 1: age, sex, center[3]	1	0.86 (0.76, 0.96)*	0.81 (0.71, 0.92)*	0.76 (0.62, 0.93)*	0.01
Model 2: diabetes risk factors[4]	1	0.95 (0.84, 1.08)	0.86 (0.78, 0.94)*	0.90 (0.80, 1.03)	0.04
Model 3: dietary factors[5]	1	0.98 (0.86, 1.11)	0.89 (0.81, 0.99)*	0.96 (0.86, 1.07)	0.31
Starch					
Median intake, *g/d*	88	110	130	159	
Incident type 2 diabetes cases, *n*	3020	2804	2825	2910	
Model 1: age, sex, center[3]	1	0.93 (0.85, 1.01)	0.94 (0.84, 1.06)	0.94 (0.83, 1.08)	0.30
Model 2: diabetes risk factors[4]	1	0.92 (0.81, 1.05)	0.93 (0.84, 1.05)	0.99 (0.89, 1.09)	0.90
Model 3: dietary factors[5]	1	0.96 (0.83, 1.10)	1.00 (0.88, 1.14)	1.05 (0.94, 1.18)	0.25

[1] Values are pooled HR (95% CI) derived from random effects meta-analyses, n = 26,088. *$P < 0.05$; **$P < 0.001$. EPIC, European Prospective Investigation into Cancer and Nutrition study; GI, glycemic index; GL, glycemic load.
[2] Energy-adjusted intake using the residual method (41).
[3] Model 1: adjusted for center, age (as underlying timescale), and sex.
[4] Model 2: adjusted for variables in model 1 + education, physical activity, BMI, menopausal status, smoking status, and alcohol consumption.
[5] Model 3: adjusted for variables in model 2 + energy intake, dietary protein, polyunsaturated:saturated fat ratio, and fiber (all energy adjusted).

GL, or digestible carbohydrate with BMI, fiber intake, sex, and physical activity and between digestible carbohydrate and GI were tested within each country by including interaction terms in the multivariable models. Country-specific estimates were pooled as described above. All results are presented for men and women together, because no evidence for an interaction with sex was present. The proportional hazard assumption was visually checked in the subcohort using log-minus-log plots, with no deviation detected. Analyses were performed using Stata, version 10.1 (Stata Corp). The significance level was set 2-sided at α 0.05.

Results

Estimated intakes of GI, GL, and digestible carbohydrate in the subcohort were (mean ± SD) 56 ± 4, 127 ± 23, and 226 ± 36 g/d, respectively. Approximately 55% of digestible carbohydrate was derived from starch and 45% from sugar (mono- and disaccharides). The highest dietary GI was reported in The Netherlands (men) and Sweden (women) and the lowest in Germany. The highest dietary GL was reported in Sweden and the lowest in Spain. Women reported less dietary GI and greater sugar consumption than men did (**Supplemental Table 2**). Correlations were 0.52 between GI and GL, 0.18 between GI and digestible carbohydrate, and 0.93 between GL and digestible carbohydrate.

Dietary GI was inversely associated with the percentage of those with a higher education and prevalent hypertension, whereas it was positively associated with the percentage of men. Dietary intakes of total digestible carbohydrates and its subtype starch associated directly with dietary GI, whereas the intake of sugar associated inversely with dietary GI. Dietary GL was inversely associated with waist circumference and BMI and the percentage of men, those with a higher education, and current smokers. Dietary GL associated directly with dietary intakes of total digestible carbohydrates and its subtypes sugar and starch, whereas intakes of protein, fats, and alcohol were inversely associated with GL (**Table 1**).

During a median (IQR) follow-up of 12 y (11, 13), 11,559 participants had developed incident diabetes. After adjustment for sex, established diabetes risk factors, and dietary factors, dietary GI was not associated with the risk of diabetes [HR_{Q4}: 1.05 (95% CI: 0.96, 1.16)]. Dietary GL was inversely associated

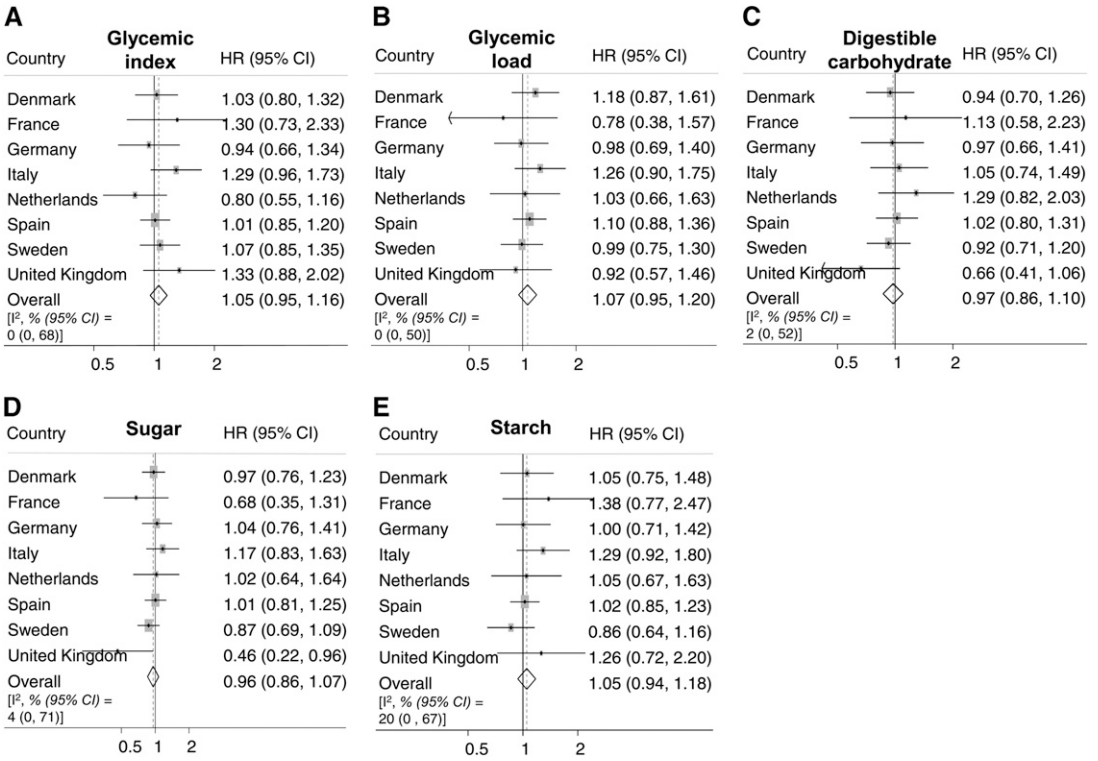

FIGURE 1 Association of GI (*A*), GL (*B*), digestible carbohydrate (*C*), sugar (*D*), and starch (*E*) with diabetes risk (quartile 4 vs. quartile 1) and I^2 for the proportion of heterogeneity between countries. Values are HR (95% CI) per country and pooled. The pooled estimate is based on random effects meta-analysis. I^2 values are based on multivariate meta-analysis. All estimates are adjusted for center, age (as underlying timescale), sex, education, physical activity, BMI, menopausal status, smoking status, alcohol consumption, dietary intake of total energy, protein, polyunsaturated:saturated fat ratio, and fiber. All dietary variables are adjusted for total energy intake using the residual method (41). GI, glycemic index; GL, glycemic load; I^2, percentage of heterogeneity between countries.

with risk of diabetes, with a HR_{Q4} of 0.87 (95% CI: 0.79, 0.96) in age- and sex-adjusted analysis and was nonsignificantly associated with increased risk of diabetes in an analysis adjusted for confounders [HR highest vs. lowest quartile (HR_{Q4}): 1.07 (95% CI: 0.95, 1.20)]. Digestible carbohydrate was not associated with risk of diabetes in adjusted analysis [HR_{Q4}: 0.98 (95% CI: 0.86, 1.06)]. In addition, neither of the digestible carbohydrate subtypes, sugar or starch, was associated with incident diabetes in the multivariable-adjusted model [HR_{Q4} for sugar: 0.96 (95% CI: 0.86, 1.07); starch: 1.05 (95% CI: 0.94, 1.18)] (**Table 2**).

The estimates for (pooled) country-specific multivariable HR_{Q4} and corresponding I^2 for heterogeneity between countries are presented in **Figure 1**. Heterogeneity between countries was low to moderate, with I^2 ranging from 0 to 20% for HR_{Q4} (Fig. 1) and from 0 to 57% for the second and third quartile vs. the first quartile (data not shown).

The exclusion of participants diagnosed with diabetes within the first 2 y of follow-up (n = 975) did not alter our findings [HR_{Q4} for GI: 1.05 (95% CI: 0.95, 1.16); GL: 1.06 (95% CI: 0.94, 1.19)] and neither did exclusion of participants with chronic diseases at baseline [myocardial infarction, stroke, angina, hyperlipidemia, hypertension, n = 9864; HR_{Q4} for GI: 1.06 (95% CI: 0.92, 1.22); GL: 1.06 (95% CI: 0.91, 1.24)]. Analyses with additional corrections for waist circumference did not affect the associations with GI [HR_{Q4}: 1.06 (95% CI: 0.96, 1.18)] and GL [HR_{Q4}: 1.08 (95% CI: 0.96, 1.22)].

No significant interactions of GI and GL with sex, total fiber intake, BMI, or physical activity level were found. We found no interaction between digestible carbohydrate and GI.

Discussion

In this European, prospective, case-cohort study with a large number of diabetes cases, dietary GI, GL, and digestible carbohydrate were not associated with risk of diabetes.

Strengths of this study include its prospective, large-scale, and multi-center design, the use of verified incident diabetes cases, and long follow-up. Several limitations need to be addressed. First, GI and GL were measured by FFQs, which were not specifically designed to assess GI and GL. However, relative validity for carbohydrate measured with FFQs was generally reported to be moderate to good in each country or center that contributed to the EPIC cohort (32). In addition, great efforts were made to assign GI values to food items in FFQs; assignment was done centrally, separately for each country, using the best available information (34). This yielded optimal comparability of GI values between countries within our study. However, comparability with other studies may still be limited by subjective decisions involved in assignment of GI values. Second, we assigned GI values to single foods, because dietary intake data were collected on the level of individual foods. The GI of foods in mixed meals may be affected by other dietary aspects, such as co-ingestion of fat or protein (2), which is not taken into account when assigning GI values to single foods. However, it was shown earlier that the glycemic response to mixed meals can be predicted by adding the weighted GI values for each meal component (2). Another concern is that a potential misclassification of individuals with undiagnosed diabetes as nondiabetic individuals may be present in our study (43). However, such misclassification can only have attenuated our findings.

In this study, higher dietary GI, GL, and digestible carbohydrate were not associated with risk of diabetes. The null-association of digestible carbohydrate with diabetes is consistent with previous evidence (3–5). Current evidence regarding the association of GI and GL with diabetes is still somewhat mixed but tends toward an increased risk of diabetes with higher GI and/or GL (4,5,9,11,12,14–16). Increased diabetes risks, up to 59% for the highest compared with the lowest quintile of GI in the Nurses Health Study II (14) and up to 47% in the highest compared with the lowest quintile of GL in the Nurses Health Study I (5), have been reported. However, others reported no association with GL and/or GI (8,9,12–14,17–23). A meta-analysis of 4 (GL) and 5 (GI) prospective studies, including one study on gestational diabetes, reported 40 and 27% increased diabetes risk in the highest categories of GI and GL, respectively (26). Another meta-analyses of 13 cohort studies reported a 58% increased risk of diabetes in the highest compared with the lowest category of GL (25). This finding seems largely driven by one study that contributed relatively high HRs (44), possibly because this HR represents diabetes risk in the highest compared with the lowest decile of GL, whereas other studies included in the meta-analysis used fewer GL categories. However, our findings did not materially change when we used deciles instead of quartiles (data not shown). The most recent meta-analysis of 13 studies suggested more modest associations of 16% (GI) and 20% (GL) increased diabetes risk (24).

The Dutch EPIC cohort, also part of the InterAct study, previously reported increased diabetes risk with higher GI [HR per SD increase: 1.08 (95% CI: 1.00, 1.17)] (15), whereas our country-specific analyses showed a HR_{Q4} of 0.80 (95% CI: 0.55, 1.16) for GI among the Dutch participants. In an attempt to determine the reason for this discrepancy, we carefully evaluated possible differences between the 2 studies. First, exclusion criteria applied in both studies were largely similar and case ascertainment and verification were identical, so these factors likely do not explain the discrepancies. Moreover, our findings did not materially change after including covariables in the multivariable model similar to those applied in the Dutch EPIC cohort or when GI was scaled, as in the Dutch EPIC cohort, per SD increase (**Supplemental Table 3**). When we reanalyzed the Dutch EPIC data with only those participants included in the InterAct study, this also did not largely change the findings (Supplemental Table 3). Both studies used similar GI tables for GI assignment, but GI values were separately assigned in the Dutch EPIC cohort and the InterAct study. When comparing quartile ranking of participants according to GI values of both studies, the agreement turned out to be moderate ($\kappa = 0.51$). This discrepancy was previously reported and was to a large extent explained by differences in the assignments of GI values to milk products and potatoes (34), which are important contributors to the Dutch diet. Due to the narrow ranges of GI, even small discrepancies in assigned GI values can affect the ranking of participants for GI (34). Especially in Europe, difficulties in the application of GI values may exist, because current GI tables predominantly contain values for Australian and American food products. Our data indicate that those GI tables cannot be plainly extrapolated to studies in other countries and highlight the need for an expansion of the GI tables and a systematic assignment of GI values. After these improvements, associations of GI with disease outcomes need to be reevaluated before firm conclusions can be drawn. However, our findings need first to be confirmed in other countries with few country-specific GI data available. Discrepancies in GI value assignment may have contributed to the differences in findings between InterAct and the Dutch EPIC cohort. Discrepancies in GI value assignment may to some extent also have contributed to inconsistencies between previous studies, although other explanations such as differences in populations and range of dietary GI and GL should also be considered.

Country-specific analyses showed an inverse association of sugar with risk of diabetes in the UK, which may be due to greater underreporting of sugar intake in this country. The percentage of energy-underreporters [energy intake (assessed by FFQ) vs. basal metabolic rate (based on height, weight, age, and sex) < 1.14, according to Goldberg cutoffs (45)] was relatively high in the UK (26 vs. 22% mean of all countries). However, excluding energy underreporters did not change our finding (data not shown).

GI and GL are currently not implemented in dietary guidelines. Yet their applicability in practice has been shown in Australia and the UK, where GI symbols are put on food labels and media exposure about the GI concept is high (27). Consumer awareness and understanding of GI are keen in these countries (27). This suggests that when consumers are broadly exposed to the GI concept, GI and GL could be used to indicate food choices in other Western countries as well. However, it is still questionable if guidelines should be specified given the results of the present and other studies.

In conclusion, our data indicate that currently available GI tables, largely based on Australian and U.S. GI data, cannot plainly be extrapolated to studies in other countries. An expansion of the GI tables and a systematic GI value assignment to foods may be needed to improve the validity of GI values derived in such studies, after which GI associations may need reevaluation. Our study shows that digestible carbohydrate intake is not associated with diabetes risk and suggests that diabetes risk with high-GI and -GL diets may be more modest than initial studies suggested.

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Literature Cited

1. Jenkins DJ, Wolever TM, Taylor RH, Barker H, Fielden H, Baldwin JM, Bowling AC, Newman HC, Jenkins AL, Goff DV. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr. 1981;34:362–6.
2. Sheard NF, Clark NG, Brand-Miller JC, Franz MJ, Pi-Sunyer FX, Mayer-Davis E, Kulkarni K, Geil P. Dietary carbohydrate (amount and type) in the prevention and management of diabetes: a statement by the American Diabetes Association. Diabetes Care. 2004;27:2266–71.

3. Schulze MB, Schulz M, Heidemann C, Schienkiewitz A, Hoffmann K, Boeing H. Carbohydrate intake and incidence of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Br J Nutr. 2008;99:1107–16.
4. Salmerón J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, Stampfer MJ, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of NIDDM in men. Diabetes Care. 1997;20:545–50.
5. Salmerón J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. JAMA. 1997;277:472–7.
6. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. JAMA. 2002;287:2414–23.
7. Willett W, Manson J, Liu S. Glycemic index, glycemic load, and risk of type 2 diabetes. Am J Clin Nutr. 2002;76:S274–80.
8. Barclay AW, Flood VM, Rochtchina E, Mitchell P, Brand-Miller JC. Glycemic index, dietary fiber, and risk of type 2 diabetes in a cohort of older Australians. Diabetes Care. 2007;30:2811–3.
9. Hodge AM, English DR, O'Dea K, Giles GG. Glycemic index and dietary fiber and the risk of type 2 diabetes. Diabetes Care. 2004; 27:2701–6.
10. Hopping BN, Erber E, Grandinetti A, Verheus M, Kolonel LN, Maskarinec G. Dietary fiber, magnesium, and glycemic load alter risk of type 2 diabetes in a multiethnic cohort in Hawaii. J Nutr. 2010; 140:68–74.
11. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med. 2001;345:790–7.
12. Krishnan S, Rosenberg L, Singer M, Hu FB, Djousse L, Cupples LA, Palmer JR. Glycemic index, glycemic load, and cereal fiber intake and risk of type 2 diabetes in US black women. Arch Intern Med. 2007;167:2304–9.
13. Sakurai M, Nakamura K, Miura K, Takamura T, Yoshita K, Morikawa Y, Ishizaki M, Kido T, Naruse Y, Suwazono Y, et al. Dietary glycemic index and risk of type 2 diabetes mellitus in middle-aged Japanese men. Metabolism. 2012;61:47–55.
14. Schulze MB, Liu S, Rimm EB, Manson JE, Willett WC, Hu FB. Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. Am J Clin Nutr. 2004;80:348–56.
15. Sluijs I, van der Schouw YT, van der A DL, Spijkerman AM, Hu FB, Grobbee DE, Beulens JW. Carbohydrate quantity and quality and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) study. Am J Clin Nutr. 2010; 92:905–11.
16. Villegas R, Liu S, Gao YT, Yang G, Li H, Zheng W, Shu XO. Prospective study of dietary carbohydrates, glycemic index, glycemic load, and incidence of type 2 diabetes mellitus in middle-aged Chinese women. Arch Intern Med. 2007;167:2310–6.
17. Meyer KA, Kushi LH, Jacobs DR Jr, Slavin J, Sellers TA, Folsom AR. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. Am J Clin Nutr. 2000;71:921–30.
18. Mosdøl A, Witte DR, Frost G, Marmot MG, Brunner EJ. Dietary glycemic index and glycemic load are associated with high-density-lipoprotein cholesterol at baseline but not with increased risk of diabetes in the Whitehall II study. Am J Clin Nutr. 2007;86:988–94.
19. Sahyoun NR, Anderson AL, Tylavsky FA, Lee JS, Sellmeyer DE, Harris TB. Dietary glycemic index and glycemic load and the risk of type 2 diabetes in older adults. Am J Clin Nutr. 2008;87:126–31.
20. Schulz M, Liese AD, Fang F, Gilliard TS, Karter AJ. Is the association between dietary glycemic index and type 2 diabetes modified by waist circumference? Diabetes Care. 2006;29:1102–4.
21. Stevens J, Ahn K, Juhaeri, Houston D, Steffan L, Couper D. Dietary fiber intake and glycemic index and incidence of diabetes in African-American and white adults: the ARIC study. Diabetes Care. 2002; 25:1715–21.
22. Similä ME, Valsta LM, Kontto JP, Albanes D, Virtamo J. Low-, medium- and high-glycaemic index carbohydrates and risk of type 2 diabetes in men. Br J Nutr. 2011;105:1258–64.
23. van Woudenbergh GJ, Kuijsten A, Sijbrands EJ, Hofman A, Witteman JC, Feskens EJ. Glycemic index and glycemic load and their association with C-reactive protein and incident type 2 diabetes. J Nutr Metab. 2011;2011:623076.
24. Dong JY, Zhang L, Zhang YH, Qin LQ. Dietary glycaemic index and glycaemic load in relation to the risk of type 2 diabetes: a meta-analysis of prospective cohort studies. Br J Nutr. 2011;106:1649–54.
25. Liu S, Chou EL. Dietary glycemic load and type 2 diabetes: modeling the glucose-raising potential of carbohydrates for prevention. Am J Clin Nutr. 2010;92:675–7.
26. Barclay AW, Petocz P, Millan-Price J, Flood VM, Prvan T, Mitchell P, Brand-Miller JC. Glycemic index, glycemic load, and chronic disease risk: a meta-analysis of observational studies. Am J Clin Nutr. 2008; 87:627–37.
27. Mitchell HL. The glycemic index concept in action. Am J Clin Nutr. 2008;87:S244–6.
28. van Bakel MM, Kaaks R, Feskens EJ, Rohrmann S, Welch AA, Pala V, Avloniti K, van der Schouw YT, van der A DL, Du H, et al. Dietary glycaemic index and glycaemic load in the European Prospective Investigation into Cancer and Nutrition. Eur J Clin Nutr. 2009;63:S188–205.
29. InterAct consortium. Design and cohort description of the InterAct Project: an examination of the interaction of genetic and lifestyle factors on the incidence of type 2 diabetes in the EPIC Study. Diabetologia. 2011;54:2272–82.
30. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, Charrondiere UR, Hemon B, Casagrande C, Vignat J, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr. 2002;5:1113–24.
31. Bingham SA, Gill C, Welch A, Day K, Cassidy A, Khaw KT, Sneyd MJ, Key TJ, Roe L, Day NE. Comparison of dietary assessment methods in nutritional epidemiology: weighed records v. 24 h recalls, food-frequency questionnaires and estimated-diet records. Br J Nutr. 1994;72:619–43.
32. Margetts BM, Pietinen P. European Prospective Investigation into Cancer and Nutrition: validity studies on dietary assessment methods. Int J Epidemiol. 1997;26:S1–5.
33. Slimani N, Kaaks R, Ferrari P, Casagrande C, Clavel-Chapelon F, Lotze G, Kroke A, Trichopoulos D, Trichopoulou A, Lauria C, et al. European Prospective Investigation into Cancer and Nutrition (EPIC) calibration study: rationale, design and population characteristics. Public Health Nutr. 2002;5:1125–45.
34. van Bakel MM, Slimani N, Feskens EJ, Du H, Beulens JW, van der Schouw YT, Brighenti F, Halkjaer J, Cust AE, Ferrari P, et al. Methodological challenges in the application of the glycemic index in epidemiological studies using data from the European Prospective Investigation into Cancer and Nutrition. J Nutr. 2009;139:568–75.
35. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. Am J Clin Nutr. 2002;76:5–56.
36. Henry CJ, Lightowler HJ, Strik CM, Storey M. Glycaemic index values for commercially available potatoes in Great Britain. Br J Nutr. 2005;94:917–21.
37. The University of Sydney home of the glycemic index. [cited 2009 Dec 10]. Available from: http://www.glycemicindex.com.
38. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. Diabetes Care. 2008;31:2281–3.
39. Haftenberger M, Lahmann PH, Panico S, Gonzalez CA, Seidell JC, Boeing H, Giurdanella MC, Krogh V, Bueno-De-Mesquita HB, Peeters PH, et al. Overweight, obesity and fat distribution in 50- to 64-year-old participants in the European Prospective Investigation into Cancer and Nutrition (EPIC). Public Health Nutr. 2002;5:1147–62.
40. Wareham NJ, Jakes RW, Rennie KL, Schuit J, Mitchell J, Hennings S, Day NE. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Public Health Nutr. 2003;6:407–13.
41. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr. 1997;65:S1220–8.
42. Prentice RL. A case-cohort design for epidemiologic cohort studies and disease prevention trials. Biometrika. 1986;73:1–11.
43. Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4–7 yr before clinical diagnosis. Diabetes Care. 1992;15:815–9.
44. Halton TL, Liu S, Manson JE, Hu FB. Low-carbohydrate-diet score and risk of type 2 diabetes in women. Am J Clin Nutr. 2008;87:339–46.
45. Goldberg GR, Black AE, Jebb SA, Cole TJ, Murgatroyd PR, Coward WA, Prentice AM. Critical evaluation of energy intake data using fundamental principles of energy physiology: 1. Derivation of cut-off limits to identify under-recording. Eur J Clin Nutr. 1991;45:569–81.