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[1–3]

Annhild Mosdøl, Daniel R Witte, Gary Frost, Michael G Marmot, and Eric J Brunner

ABSTRACT

Background: Findings of the effect of dietary glycemic index (GI) and glycemic load (GL) on the risk of incident diabetes are inconsistent.

Objective: We examined the associations of dietary GI and GL with clinical variables at baseline and the incidence of diabetes.

Design: The 7321 white Whitehall II participants (71% men) attending screening in 1991–1993, free of diabetes at baseline, and with food-frequency questionnaire data were followed for 13 y.

Results: At baseline, dietary GI and GL were associated inversely with HDL cholesterol, and GI was associated directly with triacylglycerols. Dietary GI and GL were related inversely to fasting glucose and directly to 2-h postload glucose, but only the association between GI and 2-h postload glucose was robust to statistical adjustments for employment grade, physical activity, smoking status, and intakes of alcohol, fiber, and carbohydrates. High-dietary GI was not associated with increased risk of incident diabetes. Hazard ratios (HRs) across sex-specific tertiles of dietary GI were 1.00, 0.95 (95% CI: 0.73, 1.24), and 0.94 (95% CI: 0.72, 1.22) (adjusted for sex, age, and energy misreporting; P for trend = 0.64). Corresponding HRs across tertiles of dietary GL were 1.00, 0.92 (95% CI: 0.71, 1.19), and 0.70 (95% CI: 0.54, 0.92) (P for trend = 0.01). The protective effect on diabetes risk remained significant after adjustment for employment grade, smoking, and alcohol intake but not after further adjustment for carbohydrate and fiber intakes.

Conclusion: The proposed protective effect of low-dietary GI and GL diets on diabetes risk could not be confirmed in this study. *Am J Clin Nutr* 2007;86:988–94.

KEY WORDS Glycemic index, carbohydrate, diabetes, glycemia, lipids

INTRODUCTION

The prevalence of type 2 diabetes mellitus is increasing rapidly in many parts of the world, and prevention of the disease has become one of the main challenges facing public health (1–3). Healthy eating patterns were associated with lower risk of diabetes in cohort studies (4–6), and there is considerable interest in the extent to which the reduced risk is attributable to the quality and quantity of carbohydrates eaten.

Variations in the blood glucose-raising effect of foods are extensively documented (7). The glycemic index (GI) was first introduced by Jenkins et al (8) as a dietary management tool for diabetic patients. It measures the glycemic response to ingestion of a fixed amount of available carbohydrate in a test food compared with the same amount of available carbohydrate in a reference food (glucose or white bread) by the same subject. The glycemic load (GL) takes into account the differences in carbohydrate content of foods and is the product of the GI and the proportion of carbohydrate in a food. GI and GL are also used to assess the glycemic response of meals or habitual dietary intakes. In these instances, the dietary GI is calculated as the average of the GI values of all foods consumed weighted for their relative proportion of available carbohydrate, whereas the dietary GL is the sum of GL values for all foods eaten (9, 10).

Meals with a large amount of high-GI carbohydrates give higher insulin secretion than do equicaloric diets with low-GI carbohydrates. It is thought that frequent episodes of hyperinsulinemia may contribute to development of insulin resistance (11). The carbohydrate-insulin-disease hypothesis is supported by 4 cohort studies that relate high-dietary GI or GL or both with increased risk of incident diabetes (9, 10, 12, 13) but not by 2 other studies (14, 15).

In our study population, a healthy eating pattern was associated with a 30% reduction in the incidence of type 2 diabetes after controlling for socioeconomic position, smoking history, and physical activity levels (PALs) (EJ Brunner et al, unpublished observations, 1991–2006). The aim of this paper was to examine whether dietary GI and GL are associated with clinical risk factors at baseline and with incident type 2 diabetes mellitus in a healthy cohort of middle-aged men and women.

[1] From the International Institute for Society and Health, Department of Epidemiology and Public Health, University College London, United Kingdom (AM, DRW, MGM, and EJB), and the School of Biomedical and Molecular Sciences, Surrey University, Surrey, United Kingdom (GF).

[2] Supported by grants from the Medical Research Council; Economic and Social Research Council; British Heart Foundation; Health and Safety Executive; Department of Health; National Institutes of Health, National Heart, Lung, and Blood Institute (HL36310): National Institute on Aging (AG13196); NIH Agency for Health Care Policy Research (HS06516); and the John D and Catherine T MacArthur Foundation Research Networks on Successful Midlife Development and Socioeconomic Status and Health. MM is supported by a Medical Research Council (MRC) Research Professorship.

[3] Reprints not available. Address correspondence to A Mosdøl, Section for Food Studies and Public Nutrition, Akershus University College, PO Box 423, 2001 Lillestrøm, Norway. E-mail: annhild.mosdol@hiak.no.

Received November 21, 2006.

Accepted for publication June 8, 2007.

SUBJECTS AND METHODS

Study population

Participants were recruited to the Whitehall II study in 1985–1988 (phase 1) from 20 civil service departments in London. After the initial clinical examination, the 10 308 participants (69% men) were followed up with postal questionnaires at 2.5-y intervals (phases 2–7) and further clinical examinations in 1991–1994 (phase 3), 1997–1999 (phase 5), and 2003–2004 (phase 7) (16). Detailed dietary information was first collected during phase 3 (baseline in the present analyses). At phase 3, 86% of the cohort ($n = 8826$) completed a questionnaire, attended the research clinic, or both (17). The 7321 white participants (71% men) with complete food-frequency questionnaire (FFQ) data were included if they had no history or diagnosis of diabetes at the phase 3 screening. Ethnic minority participants were excluded because the FFQ was designed for Western diets.

The study was approved by the University College London Medical School Committee on the Ethics of Human Research. Informed consent was obtained at baseline and renewed at each contact.

Dietary assessment

The relative validity of the 127-item FFQ used was determined against a 7-d diary and biomarkers (18). For each FFQ item, participants were asked to report their frequency of eating a common unit or portion during the previous year. Energy and nutrient intakes were calculated with the use of the 4th and 5th editions of McCance and Widdowson's *The Composition of Foods* and supplementary tables (19, 20). Supplementary tables included in these publications are as follows: Cereals and Cereal Products, 1988; Milk Products and Eggs, 1989; Vegetables, Herbs, and Spices, 1991; Fruits and Nuts, 1992; Vegetable Dishes, 1992; Fish and Fish Products, 1993; Miscellaneous Foods, 1994; Meat, Poultry, and Game, 1995. The GI values for each food item in the questionnaire were taken from the 2002 international table of GI values of foods (7). Average dietary GI was calculated by adding the product of the carbohydrate content of each food item multiplied by the assigned portion size, the frequency of use, and the GI value of the food item and then dividing this sum by the total carbohydrate intake. The GL was calculated as the total carbohydrate intake multiplied by dietary GI divided by 100.

Evaluation of energy intake

The reported energy intake (EI) was evaluated against estimated energy expenditure (EE) to account for energy misreporting (21). For a weight stable person the ratio of EI to EE (EI:EE) is 1 if there is no energy misreporting, <1 if there is underreporting, and >1 if intake is overreported. EE was based on estimated basal metabolic rate (BMR) (22) and a minimum assumed PAL of 1.55 × BMR (sedentary) in this cohort of office workers, plus the estimated energy cost of self-reported weekly hours of moderate and vigorous leisure-time activity. The energy cost was estimated with the use of metabolic equivalent (MET) values. One MET is the metabolic EE of lying quietly and is equivalent to 1 kcal · kg body weight^{-1} · h^{-1} (23). A MET score of 3 was used for hours of moderate activity and 5 MET/h was used for vigorous activity. Weight was missing for 261 men and 149 women, who were assigned either the average of the weights recorded at phases 1 and 5 ($n = 133$) or weight at phase 1 ($n = 244$), depending on availability of data. Mean calculated PAL based on EE/BMR was 1.63 (range: 1.55–2.99) and mean EI:EE was 0.79 (range: 0.14–3.40). Participants with a log EI:EE value outside 3 SDs of the log mean were excluded ($n = 80$). Participants were not excluded based on intakes below fixed energy values, because heavy or physically active persons have a lower likelihood of being identified as energy underreporters (21).

Blood collection and analysis

Blood samples were collected after either an 8-h fast (participants presenting to the clinic in the morning) or at least 4 h after a light fat-free breakfast (participants presenting in the afternoon). After the initial blood sample, participants drank 389 mL Lucozade (equivalent to 75 g anhydrous glucose; GlaxoSmithKline UK, Brentford, United Kingdom) over 5 min. A second blood sample was taken 2 h later. Venepuncture of the left antecubital vein was performed with tourniquet. Blood was collected into plain and fluoride Sarstedt (Neumbrecht, Germany) monovettes. Centrifugation differed somewhat in each phase: in phase 3, the blood was left for 15–30 min and then spun for 10 min at 3000 RPM at room temperature; in phase 5, the blood was left for 15 min and then spun for 15 min at the same speed and temperature; and in phase 7, the blood was left for 30 min and then spun for 10 min at the same speed and temperature (CL3 ThermoIEC centrifuge; Thermo Life Sciences, Waltham, MA used for all procedures). After centrifugation, samples were immediately frozen at −80 °C, and serum for lipids was refrigerated at −4 °C for analysis on the following working day. Glucose was measured in fluoride plasma by an electrochemical glucose oxidase method. Serum insulin was measured by radioimmunoassay with the use of a polyclonal guinea pig antiserum. Cholesterol and triacylglycerols were measured with the use of a Cobas Fara centrifugal analyzer (Roche Diagnostics System, Nutley, NJ). HDL cholesterol was measured by precipitating non-HDL cholesterol with dextran sulfate-magnesium chloride with the use of a centrifuge and measuring cholesterol in the supernatant fluid.

Employment grade and other covariates

Employment grade within the civil service was used as the measure of adult socioeconomic position (6 levels). Annual salary range at 1 August 1992 was from £6483 to £87 620. Weight was measured to the nearest 0.1 kg with the use of an electronic scale with participants dressed in a gown. Height was measured to the nearest centimeter, and waist (narrowest point between lower rib and upper trochanter) and hip circumferences (most lateral point on the greater trochanter) were measured to the nearest 0.1 cm. Smoking habits (never, exsmoker, current) and leisure-time physical activity (hours of moderate and vigorous activity per week) were self-reported.

Outcome ascertainment

Incident cases of diabetes were identified by self-report of doctor's diagnosis and diabetic medication at phase 1 and subsequent study phases and by 2-h oral glucose tolerance test (2-h postload glucose) at phases 3, 5, and 7. Incident diabetes was dated at the day of study visit for participants first identified through the 2-h postload glucose. For participants identified by self-report, the midpoint between the first instance of self-reported diabetes and the previous phase was used. Person-time of exposure was censored at the midpoint between the last known visit and the first missing visit for participants lost to follow-up. Participants with an intermediate missing phase were assumed to

TABLE 1
Baseline characteristics according to tertiles of energy-adjusted average glycemic index (GI) and glycemic load (GL) among Whitehall II participants aged 39–63 y (n = 5175 men, n = 2146 women)[1]

	GI tertile				GL tertile			
	Low	Medium	High	P for trend[2]	Low	Medium	High	P for trend[2]
Age (y)								
Men	48.9 ± 6.0[3]	49.2 ± 6.1	49.3 ± 5.9	0.003	48.6 ± 5.8	49.1 ± 6.0	49.6 ± 6.1	<0.001
Women	50.1 ± 6.1	50.1 ± 6.2	50.9 ± 6.3		50.0 ± 6.1	50.3 ± 6.2	50.8 ± 6.3	
Administrative grade (%)								
Men	54.4	54.9	45.4	<0.001	54.0	53.0	47.7	<0.001
Women	22.6	20.1	11.4		22.8	18.8	12.6	
Current smokers (%)								
Men	10.1	10.9	15.6	0.002	14.9	11.9	9.8	<0.001
Women	16.4	14.9	25.3		22.0	17.7	17.0	
Physically active (%)[4]								
Men	58.8	60.0	53.4	<0.001	57.4	57.5	57.3	0.84
Women	38.0	36.6	32.4		35.9	35.0	36.1	
BMI (kg/m^2)								
Men	25.5 ± 3.2	25.0 ± 3.1	24.8 ± 3.1	<0.001	25.6 ± 3.2	25.1 ± 3.1	24.5 ± 3.1	<0.001[5]
Women	25.7 ± 4.5	25.2 ± 4.5	25.2 ± 4.5		25.7 ± 4.7	25.2 ± 4.3	25.1 ± 4.6	0.012[5]
WHR								
Men	0.91 ± 0.06	0.90 ± 0.06	0.90 ± 0.06	0.02	0.91 ± 0.06	0.90 ± 0.06	0.89 ± 0.06	<0.001[5]
Women	0.77 ± 0.07	0.76 ± 0.07	0.77 ± 0.07		0.77 ± 0.07	0.77 ± 0.06	0.77 ± 0.07	0.16[5]
Carbohydrate intake (g/d)[6]								
Men	265 ± 37	272 ± 35	276 ± 34	<0.001[5]	236 ± 25	272 ± 15	305 ± 22	<0.001[5]
Women	234 ± 34	237 ± 32	240 ± 32	<0.001[5]	206 ± 24	238 ± 14	267 ± 23	<0.001[5]
Fiber intake (g/d)[6]								
Men	26.6 ± 7.4	26.4 ± 7.4	25.0 ± 7.0	<0.001[5]	22.9 ± 6.3	26.1 ± 6.4	29.0 ± 7.8	<0.001
Women	26.2 ± 9.0	25.0 ± 7.5	23.5 ± 6.7	<0.001[5]	21.7 ± 7.3	25.2 ± 6.9	27.8 ± 8.2	
Alcohol intake (g/d)[6]								
Men	19.1 ± 17.9	14.6 ± 15.2	11.3 ± 13.0	<0.001[5]	25.3 ± 19.5	12.9 ± 11.6	6.8 ± 7.7	<0.001[5]
Women	9.1 ± 11.2	8.1 ± 10.5	6.2 ± 9.5	<0.001[5]	12.9 ± 14.0	6.8 ± 8.0	3.6 ± 5.1	<0.001[5]
Total fat intake (g/d)[6]								
Men	80.7 ± 13.5	82.4 ± 12.8	83.7 ± 12.7	<0.001	87.8 ± 13.9	83.4 ± 10.5	75.6 ± 11.5	<0.001[5]
Women	69.6 ± 13.6	70.9 ± 12.0	72.5 ± 12.3		77.9 ± 13.2	71.2 ± 9.3	63.9 ± 11.0	<0.001[5]
EI:EE								
Men	0.75 ± 0.22	0.79 ± 0.22	0.76 ± 0.20	0.09	0.78 ± 0.22	0.74 ± 0.21	0.79 ± 0.21	0.07[5]
Women	0.84 ± 0.27	0.88 ± 0.26	0.85 ± 0.26		0.89 ± 0.27	0.80 ± 0.24	0.87 ± 0.26	0.17[5]

[1] Mean (range) GI tertiles for men were 52.3 (42.5–54.6), 56.0 (54.6–57.3), and 59.5 (57.3–68.4) and for women were 50.3 (38.4–52.9), 54.5 (53.0–56.0), and 58.8 (56.0–72.5); GL tertiles for men were 127 (45–143), 152 (143–161), and 176 (161–259) and for women were 108 (19–121), 129 (121–137), and 152 (137–281). Data were incomplete for administrative grade (54 men, 20 women), smoking status (145 men, 85 women), physical activity (52 men, 21 women), BMI (244 men, 140 women), and WHR (313 men, 152 women). WHR, waist-to-hip ratio; EI:EE, ratio of reported energy intake to estimated energy expenditure.
[2] Analyzed for sexes combined with sex as covariate. The effect of sex was significant in all models, $P < 0.05$.
[3] $\bar{x}$ ± SD (all such values).
[4] Moderate and vigorous activity ≥ 2.5 h/wk.
[5] Significant sex interaction (sex × tertiles of GI or sex × tertiles of GL, respectively), $P < 0.05$. P for trend presented separately by sex.
[6] Energy-adjusted values obtained by using the residuals method.

have continuous follow-up time. For participants who had not developed diabetes up to phase 7, follow-up was censored on 30 September 2004 (phase 7 closing date).

Statistical methods

All nutrient intakes, dietary GI, and GL were adjusted for energy with the use of the residuals method (24), and values are presented in **Table 1** as the sum of the residual and the sex-specific mean. Participants were ranked and divided into sex-specific tertiles of dietary GI and GL, respectively. The distributions of HDL, triacylglycerols, fasting glucose and insulin, and 2-h postload glucose were all positively skewed, and their lns were used in analyses. In **Table 2**, the mean values of the clinical measures were age-adjusted with age groups as a covariate (5-y bands), and the resulting mean logarithmic terms of the clinical measures were exponentiated.

Linear trends were analyzed with the use of univariate analyses of variance (Tables 1 and 2) for continuous variables and chi-square linear-by-linear association for trends in proportions (administrative grade, smokers, physically active). The univariate analyses of variance were repeated with interaction terms (sex × tertiles of GI or sex × tertiles of GL, respectively). If the interaction term was significant ($P < 0.05$), P values for trend were presented for each sex separately, otherwise trends were analyzed for the whole sample with sex as a covariate in Table 1 and sex and age as covariates in Table 2.

Linear regression models were used to examine associations between dietary GI and GL, respectively, and the clinical

TABLE 2
Age-adjusted geometric mean of HDL cholesterol, triacylglycerols, fasting glucose, fasting insulin, and 2-h postload glucose across tertiles of energy-adjusted dietary glycemic index (GI) and glycemic load (GL) at baseline[1]

		GI				GL			
	Subjects	Low	Medium	High	*P* for trend[2]	Low	Medium	High	*P* for trend[2]
	n								
HDL (mmol/L)									
Men	4888	1.31 ± 0.36[3]	1.27 ± 0.34	1.26 ± 0.34	<0.001	1.34 ± 0.38	1.26 ± 0.33	1.24 ± 0.33	<0.001
Women	1985	1.68 ± 0.43	1.65 ± 0.42	1.61 ± 0.43		1.70 ± 0.44	1.65 ± 0.42	1.59 ± 0.41	
Triacylglycerols (mmol/L)									
Men	4907	1.31 ± 1.18	1.33 ± 1.18	1.36 ± 1.24	0.011	1.33 ± 1.20	1.36 ± 1.19	1.30 ± 1.21	0.21[4]
Women	1986	1.03 ± 0.71	1.01 ± 0.64	1.10 ± 0.83		1.01 ± 0.67	1.05 ± 0.74	1.08 ± 0.78	0.12[4]
Fasting glucose (mmol/L)									
Men	4632	5.27 ± 0.47	5.24 ± 0.44	5.21 ± 0.44	<0.001[4]	5.28 ± 0.45	5.25 ± 0.46	5.19 ± 0.44	<0.001
Women	1874	5.01 ± 0.48	5.04 ± 0.47	5.03 ± 0.46	0.71[4]	5.05 ± 0.49	5.03 ± 0.46	5.00 ± 0.45	
Fasting insulin (IU)									
Men	4359	5.41 ± 6.25	5.27 ± 5.07	5.38 ± 4.91	0.43	5.54 ± 6.13	5.40 ± 5.27	5.13 ± 4.83	0.002
Women	1706	4.83 ± 5.23	4.73 ± 4.50	5.25 ± 6.14		4.98 ± 5.36	4.93 ± 5.58	4.87 ± 5.04	
2-H glucose (mmol/L)									
Men	4723	5.10 ± 1.53	5.11 ± 1.53	5.22 ± 1.59	0.005	5.02 ± 1.54	5.19 ± 1.59	5.22 ± 1.52	0.006
Women	1902	5.30 ± 1.56	5.45 ± 1.54	5.46 ± 1.54		5.37 ± 1.54	5.47 ± 1.53	5.38 ± 1.58	

[1] Mean (range) GI tertiles for men were 52.3 (42.5–54.6), 56.0 (54.6–57.3), and 59.5 (57.3–68.4) and for women were 50.3 (38.4–52.9), 54.5 (53.0–56.0), and 58.8 (56.0–72.5); GL tertiles for men were 127 (45–143), 152 (143–161), and 176 (161–259) and for women were 108 (19–121), 129 (121–137), and 152 (137–281). The geometric mean was analyzed with the ln of the clinical variables with age groups as a covariate (5-y bands) and exponentiating the resulting mean logarithmic term. The SD was of the untransformed variable with age groups as a covariate.

[2] Analyzed for sexes combined with age groups and sex as covariates. The effect of sex was significant in all models, $P < 0.05$.

[3] $\bar{x} \pm$ SD (all such values).

[4] Significant sex interaction (sex × tertiles of GI or sex × tertiles of GL, respectively), $P < 0.05$. *P* for trend presented separately by sex, with age groups as a covariate.

measures with the base model were adjusted for sex, age (4 age bands), and energy misreporting (EI:EE values). In 3 further models, the associations were adjusted for employment grade (6 levels); physical activity (3 levels); smoking status (current, exsmoker, or never); alcohol, carbohydrate, and fiber intakes; body mass index (BMI; in kg/m^2); and waist-to-hip ratio (WHR). A main effect of sex was observed in all models ($P < 0.01$). All models were repeated to test for sex interactions (data not shown).

STATA software (version 9.0; Stata Corporation, College Station, TX) was used to fit Cox proportional hazards regression models with follow-up time as the underlying time variable. The base models adjusted for age and energy misreporting. Further adjustments were made by fitting models with the same factors as in the linear regression models. In Table 4, both sexes were analyzed in the same model, using sex-specific tertiles of the exposure variables. This was justified by fitting logistic regression models with disease outcome as the dependent variable and with sex, the glycemic measures, and an interaction term as independent variables. The log-likelihood test comparing models with and without the interaction term indicated no sex interaction. Similar hazard ratios were obtained in analyses for each sex separately. In tables involving serial adjustments (**Tables 3** and **4**), observations with incomplete covariates were excluded from the analyses.

RESULTS

Descriptive characteristics of the study participants across sex-specific tertiles of energy-adjusted dietary GI and GL are presented in Table 1. Energy misreporting, based on EI:EE, did not vary systematically across tertiles of dietary GI and GL. Dietary GI was weakly associated with total carbohydrate and fat intakes and negatively with fiber and alcohol intakes. GL was strongly associated with total carbohydrate and fiber intakes and inversely with total fat intake. Participants with a high-dietary GI were more likely to be current smokers and less likely to be physically active and have an administrative grade (high grade). High GL was associated with a lower proportion of smokers and a lower proportion with an administrative grade. BMI was inversely related to dietary GI and GL. Slight inverse trends in WHR were observed across tertiles of dietary GI and GL.

Table 2 shows age-adjusted mean fasting HDL, triacylglycerols, glucose, and insulin and 2-h postload glucose in participants with low-, medium-, and high-dietary GI and GL, respectively. Significant inverse trends were observed for HDL with higher values of dietary GI and GL. A significant increasing trend in triacylglycerols with higher GI was observed, whereas no association was present across tertiles of GL. Lower fasting glucose concentrations and higher 2-h postload glucose values were observed with increasing dietary GI and GL, apart from dietary GI and fasting glucose among women. Fasting insulin was inversely related to dietary GL only.

In linear regression models (Table 3), the significant inverse association between both GI and GL with HDL remained after adjustment for employment grade, physical activity, smoking status, and alcohol intake but were notably attenuated after adjustments for fiber and carbohydrate intakes (model 3). Further adjustment for fat intake and fat fractions barely attenuated the estimates (data not shown). In models that examined triacylglycerols, the direct

TABLE 3
Linear regression models with clinical measures as outcome variables according to 10-unit increments in energy-adjusted dietary glycemic index (GI) and glycemic load (GL) among Whitehall II participants[1]

	HDL cholesterol (n = 6581)		Triacylglycerols (n = 6600)		Fasting glucose (n = 6262)		Fasting insulin (n = 5832)		Postload glucose (n = 6371)	
	β	SE	β	SE	β	SE	β	SE	β	SE
	mmol/L		*mmol/L*		*mmol/L*		*IU*		*mmol/L*	
GI										
Model 1[2]	−0.068[3]	0.009	0.081[3]	0.018	−0.010[4]	0.003	0.014	0.024	0.028[4]	0.010
Model 2[5]	−0.027[4]	0.009	0.063[3]	0.019	−0.004	0.003	0.0004	0.025	0.023[6]	0.010
Model 3[7]	−0.018	0.009	0.039[6]	0.019	−0.004	0.003	−0.012	0.026	0.022[6]	0.011
Model 4[8]	−0.035[3]	0.008	0.074[3]	0.017	−0.001	0.003	0.054[6]	0.023	0.028[4]	0.010
GL										
Model 1[2]	−0.016[3]	0.001	−0.002	0.003	−0.003[3]	0.001	−0.014[3]	0.004	0.006[3]	0.002
Model 2[5]	−0.005[4]	0.002	0.005	0.003	−0.001	0.001	−0.018[3]	0.005	0.002	0.002
Model 3[7]	−0.003	0.004	0.012	0.007	−0.002	0.001	−0.010	0.010	0.007	0.004
Model 4[8]	−0.009[4]	0.003	0.026[3]	0.007	0.0004	0.001	0.016	0.009	0.009[6]	0.004

[1] Linear regression models were analyzed with the ln of the clinical variables. Interaction terms (sex × GI or sex × GL, respectively) were significant ($P < 0.05$) when included in base models (model 1) that examined dietary GI and fasting glucose, dietary GL and triacylglycerols, and dietary GL and fasting glucose ($P < 0.05$). The interaction terms were not significant in the adjusted models (models 2–4).
[2] Adjusted for sex, age group, and ratio of reported energy intake to estimated energy expenditure (EI:EE).
[3] $P < 0.001$.
[4] $P < 0.01$.
[5] Adjusted for sex, age group, EI:EE, employment grade, physical activity, smoking, and alcohol intake.
[6] $P < 0.05$.
[7] Adjusted for sex, age group, EI:EE, employment grade, physical activity, smoking, and intakes of alcohol, fiber, and carbohydrates.
[8] Adjusted for sex; age group; EI:EE; employment grade; physical activity; smoking; intakes of alcohol, fiber, and carbohydrates; baseline BMI; and waist-to-hip ratio.

association with dietary GI remained significant also in model 3 with adjustments for fiber and carbohydrate intakes. Further adjustment for BMI and WHR strengthened the associations between the dietary GI and GL with both HDL and triacylglycerols.

Few of the associations between dietary GI or GL, respectively, and measures of glycemia were robust to statistical adjustments. Only the relation between dietary GI and 2-h postload glucose remained significantly in all the models tested. The weak inverse associations between fasting glucose and both GI and GL and between fasting insulin and GL were not significant in multiple adjusted models.

After 65 774 person-years of follow-up, 329 incident cases of diabetes were identified among participants with dietary assessment (Table 4). Dietary GI was not associated with the risk of incident diabetes. Further adjustment for employment grade; physical activity; smoking status; intake of alcohol, fiber, and carbohydrates; WHR; and BMI did not alter the findings (models 2–4). Hazard ratios across tertiles of GL showed an inverse

TABLE 4
Hazard ratios (and 95% CIs) of incident diabetes across sex-specific tertiles of dietary glycemic index (GI) and glycemic load (GL) in 5598 Whitehall II participants[1]

	GI tertile			P for trend	GL tertile			P for trend
	Low	Medium	High		Low	Medium	High	
n	1872	1897	1829		1840	1872	1886	
Cases	113	110	106		119	117	93	
Person-years	21 885	22 447	21 443		21 340	22 075	22 359	
Model 1[2]	1	0.95 (0.73, 1.24)[3]	0.94 (0.72, 1.22)	0.64	1	0.92 (0.71, 1.19)	0.70 (0.54, 0.92)	0.011
Model 2[4]	1	0.94 (0.72, 1.23)	0.86 (0.65, 1.22)	0.26	1	0.88 (0.67, 1.15)	0.65 (0.48, 0.88)	0.005
Model 3[5]	1	0.95 (0.73, 1.24)	0.87 (0.66, 1.14)	0.30	1	0.92 (0.67, 1.25)	0.70 (0.45, 1.10)	0.13
Model 4[6]	1	1.00 (0.77, 1.31)	0.94 (0.71, 1.23)	0.65	1	1.05 (0.76, 1.44)	0.80 (0.51, 1.26)	0.34

[1] Men were 70.9% of the participants. Mean GI tertiles for men were 52.3, 56.0, and 59.5 and for women were 50.3, 54.5, and 58.8; GL tertiles for men were 127, 152, and 176 and for women were 108, 129, and 152.
[2] Adjusted for sex, age group, and ratio of reported energy intake to estimated energy expenditure (EI:EE).
[3] Hazard ratios; 95% CI in parentheses (all such values).
[4] Adjusted for sex, age group, EI:EE, employment grade, physical activity, smoking, and alcohol intake.
[5] Adjusted for sex, age group, EI:EE, employment grade, physical activity, smoking, and intakes of alcohol, fiber, and carbohydrates.
[6] Adjusted for sex; age group; EI:EE; employment grade; physical activity; smoking; intakes of alcohol, fiber, and carbohydrates; baseline BMI; and waist-to-hip ratio.

association with diabetes risk in the base model (P for trend = 0.011). The weak protective effect of high GL remained after adjustment for employment grade, physical activity, smoking status, and alcohol intake, but it was not significant after further adjustment for carbohydrate and fiber intakes (model 3) and in a model additionally adjusted for BMI and WHR (model 4).

DISCUSSION

Higher dietary GI and GL were not associated with an increased risk of incident diabetes in this population after 13 y of follow-up. On the contrary, high-dietary GL was associated with decreased risk of diabetes. This protective effect remained after adjustments for employment grade, smoking, and alcohol intake and the attenuation by adjustment for total carbohydrate and fiber intakes was moderate. These findings are consistent with a possible protective role of dietary factors on disease risk, but they do not support the hypothesis that high-dietary GI and GL may be a risk factor for type 2 diabetes. In this population, participants with high-dietary GI and GL had slightly lower BMIs, but this did not appear to mask a possible increased risk of diabetes associated with such diets.

Assessment of incident diabetes in our cohort was based on both 2-h postload glucose tests at 5-y intervals and self-reports of doctors' diagnosis and medication. Diabetes assessment with the use of self-reported diagnosis only may be selective for severe cases. We were able to exclude both known and previously undiagnosed diabetes at baseline, producing results based entirely on incident disease. The participants are well characterized for socioeconomic position and health behaviors. A particular strength of the Whitehall II study is the full ascertainment of clinical risk factors at baseline which confirmed that the dietary GI and GL scores based on FFQ data were related to HDL and triacylglycerols. Dietary GI was associated with 2-h postload glucose, but dietary GI and GL were not associated with fasting glucose and insulin in a coherent way. The FFQ method is prone to measurement error, but we found that our questionnaire performed relatively well in our cohort, in comparison with biomarkers of intake and a 7-d food diary (18). We excluded few participants with extreme energy misreporting (using EI:EE). The use of alternative less-extreme cutoffs excluding a higher proportion of participants did not change the findings (data not shown).

The studies published so far provide conflicting evidence on the possible role of dietary GI and GL on diabetes risk (9, 10, 12–15). The 3 studies showing the strongest association between dietary GI or GL and diabetes risk are based on large cohorts, considerable follow-up time, and similar dietary assessment tools (9, 10, 13), but they differ about the effects of GI or GL. One showed an increase in disease risk for both dietary GI and GL (9), whereas the others showed increased risk associated with dietary GL only (10, 13). In the first 2 analyses (9, 10) the association between dietary GL and diabetes risk appeared when it was coupled with cereal fiber. Those studies also include complex statistical models with adjustments for several other dietary factors, including total carbohydrate intake. Singling out the effect of specific nutrients is generally difficult because dietary factors are often strongly correlated. In our sample, the correlation between energy-adjusted dietary GL and total carbohydrate intake was 0.93, making separation of these 2 effects impossible with the use of statistical modeling.

Dietary GI was associated with 2-h postload glucose but not with fasting glucose and insulin concentrations. If a high-GI or high-GL diet increases the risk of diabetes, it might be expected that these measures would be associated with poorer glucose tolerance at baseline. A lack of coherent associations between dietary GI and GL with measures of glycemia was observed in other population studies (25, 26). Evidence from randomized controlled trials has, however, shown that low-GI diets can improve insulin sensitivity (27–29).

Mayer-Davis et al (26) suggest that divergent findings between trials and observational studies could be due to dietary GI and GL scores being unable to capture the metabolic effect of foods consumed as part of a habitual diet. This explanation is plausible, but it is contradicted by the associations between dietary GI and GL with HDL cholesterol and triacylglycerols, respectively, as seen in several studies (30–33). Dietary GL is closely related to total carbohydrate intake, and, consequently, it is inversely related to total fat intake. A low-fat and high-carbohydrate diet is known to decrease HDL cholesterol and to increase triacylglycerols (34, 35). In this study, the relation of dietary GI and GL with HDL cholesterol and triacylglycerols was attenuated by adjustments for carbohydrate and fiber intakes. Still, some of the associations remained in the fully adjusted models. These associations indicate that dietary GI and GL capture some physiologically relevant qualities of the diet.

Although randomized controlled trials of low-GI diets offer good control of the changes made, such dietary manipulations may be confounded by other nutrients or bioactive substances. Low-GI trial diets are often based on foods thought to be protective of diabetes in their own right, particularly whole-grain cereals (36). The concordance with conventionally healthy eating patterns is likely to be high, whereas this may not be so in cohort studies observing self-selected diets. Schultz et al (37) described that dietary GI is associated with intake of white bread, beer, meats, and fries or fried potatoes and is inversely associated with fruit and low-fat dairy products in a multiethnic American population. In addition, their study showed that dietary GI, less so than the GL, is associated with a number of other foods with low-carbohydrate content and with noncarbohydrate nutrients. It could be that there is more variation in the underlying food base at any given value of dietary GI or GL in data from observational studies than there is in dietary trials. If this were the case, different dietary patterns with the same overall dietary GI and GL values might explain the divergent health effects of carbohydrate quality observed in trials as opposed to cohort studies.

Dietary GI and GL are global measures of a physiologic response that are determined both by the rate of glucose uptake as well as the removal of glucose from the bloodstream. Important factors contributing to the GI of foods are *1*) intact structures slowing down digestion, *2*) the fructose content, *3*) viscous polysaccharides slowing down gastric emptying and enzymatic hydrolysis, *4*) concomitant fat intake slowing down gastric emptying, and *5*) high-protein content stimulating insulin secretion (38). Those factors may differ in their effects on disease pathways. Intake of some fiber fractions and resistant starch appears to improve insulin sensitivity, increase satiety, and reduce fat storage (39, 40). Fructose intake, however, triggers endocrine mechanisms that may favor positive energy balance and hyperlipidemia (41).

Our study could not confirm that high-dietary GI or GL diets are associated with increased risk of type 2 diabetes mellitus, despite the expected link with a higher risk lipoprotein profile. The ascertainment of incident diabetes mellitus is exceptionally

good in this screened population. The growing number of studies with null findings casts further doubt on whether dietary GI and GL contribute to our understanding of the diabetes epidemic. There are good reasons to believe that dietary modifications can alter diabetes risk, but whether the multifactorial concept of GI is useful in studies of carbohydrate metabolism and its significance for disease remain uncertain.

We thank all participating civil service departments and their welfare, personnel, and establishment officers; the Occupational Health and Safety Agency; the Council of Civil Service Unions; all participating civil servants in the Whitehall II study; and all members of the Whitehall II study team.

The author's responsibilities were as follows—AM: prepared data, analyzed statistics, wrote manuscript; DRW: prepared data (diabetes), contributed to analyses and discussion; GF: prepared data (glycemic index and glycemic load), contributed to analyses and discussion; MGM (principal investigator): contributed to analyses and discussion; EJB: prepared data, contributed to analyses and discussion; and all authors: contributed to the study design and critiqued the manuscript. All of the authors declared that they had no competing interests.

REFERENCES

1. Seidell JC. Obesity, insulin resistance and diabetes–a worldwide epidemic. Br J Nutr 2000;83(suppl):S5–S8.
2. Yach D, Stuckler D, Brownell KD. Epidemiologic and economic consequences of the global epidemics of obesity and diabetes. Nat Med 2006;12:62–6.
3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–53.
4. Fung TT, Schulze M, Manson JE, Willett WC, Hu FB. Dietary patterns, meat intake, and the risk of type 2 diabetes in women. Arch Intern Med 2004;164:2235–40.
5. Heidemann C, Hoffmann K, Spranger J, et al. A dietary pattern protective against type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study cohort. Diabetologia 2005;48:1126–34.
6. Montonen J, Knekt P, Harkanen T, et al. Dietary patterns and the incidence of type 2 diabetes. Am J Epidemiol 2005;161:219–27.
7. 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.
8. Jenkins DJ, Wolever TM, Taylor RH, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr 1981;34:362–6.
9. Salmeron J, Ascherio A, Rimm EB, et al. Dietary fiber, glycemic load, and risk of NIDDM in men. Diabetes Care 1997;20:545–50.
10. Salmeron 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.
11. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. JAMA 2002;287:2414–23.
12. 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.
13. 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.
14. Meyer KA, Kushi LH, Jacobs DR, 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.
15. 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.
16. Marmot MG, Brunner EJ. Cohort Profile: the Whitehall II study. Int J Epidemiol 2005;34:251–6.
17. Brunner EJ, Marmot MG, Nanchahal K, et al. Social inequality in coronary risk: central obesity and the metabolic syndrome. Evidence from the Whitehall II study. Diabetologia 1997;40:1341–9.
18. Brunner EJ, Stallone D, Juneja M, Bingham S, Marmot M. Dietary assessment in Whitehall II: comparison of 7 d diet diary and food frequency questionnaire and validity against biomarkers. Br J Nutr 2001;86:405–14.
19. Paul AA, Southgate DAT. McCance and Widdowson's the composition of foods. 4th ed. London, United Kingdom: HMSO, 1978.
20. Holland B, Welch AA, Unwin ID, Bus DH, Paul AA, Southgate DAT. McCance and Widdowson's the composition of foods. 5th ed. Cambridge, United Kingdom: Royal Society of Chemistry, 1991.
21. Black AE. Critical evaluation of energy intake using the Goldberg cut-off for energy intake: basal metabolic rate. A practical guide to its calculation, use and limitations. Int J Obes Relat Metab Disord 2000;24:1119–30.
22. Schofield WN, Schofield C, James WPT. Basal metabolic rate. Hum Nutr Clin Nutr 1985;39C(suppl):1–96.
23. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sport Ex 1993;25:71–80 (abstr).
24. Willett WC, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27.
25. Liese AD, Schulz M, Fang F, et al. Dietary glycemic index and glycemic load, carbohydrate and fiber intake, and measures of insulin sensitivity, secretion, and adiposity in the Insulin Resistance Atherosclerosis Study. Diabetes Care 2005;28:2832–8.
26. Mayer-Davis EJ, Dhawan A, Liese AD, Teff K, Schulz M. Towards understanding of glycaemic index and glycaemic load in habitual diet: associations with measures of glycaemia in the Insulin Resistance Atherosclerosis Study. Br J Nutr 2006;95:397–405.
27. Frost G, Leeds A, Trew G, Margara R, Dornhorst A. Insulin sensitivity in women at risk of coronary heart disease and the effect of a low glycemic diet. Metabolism 1998;47:1245–51.
28. Laaksonen DE, Toppinen LK, Juntunen KS, et al. Dietary carbohydrate modification enhances insulin secretion in persons with the metabolic syndrome. Am J Clin Nutr 2005;82:1218–27.
29. Ostman EM, Frid AH, Groop LC, Bjorck IM. A dietary exchange of common bread for tailored bread of low glycaemic index and rich in dietary fibre improved insulin economy in young women with impaired glucose tolerance. Eur J Clin Nutr 2006;60:334–41.
30. Frost G, Leeds AA, Dore CJ, Madeiros S, Brading S, Dornhorst A. Glycaemic index as a determinant of serum HDL-cholesterol concentration. Lancet 1999;353:1045–8.
31. Liu S, Manson JE, Stampfer MJ, et al. Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in postmenopausal women. Am J Clin Nutr 2001;73:560–6.
32. Amano Y, Kawakubo K, Lee JS, Tang AC, Sugiyama M, Mori K. Correlation between dietary glycemic index and cardiovascular disease risk factors among Japanese women. Eur J Clin Nutr 2004;58:1472–8.
33. Slyper A, Jurva J, Pleuss J, Hoffmann R, Gutterman D. Influence of glycemic load on HDL cholesterol in youth. Am J Clin Nutr 2005;81:376–9.
34. Grundy SM. Comparison of monounsaturated fatty acids and carbohydrates for lowering plasma cholesterol. N Engl J Med 1986;314:745–8.
35. Mensink RP, Katan MB. Effect of dietary trans fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects. N Engl J Med 1990;323:439–44.
36. Venn BJ, Mann JI. Cereal grains, legumes and diabetes. Eur J Clin Nutr 2004;58:1443–61.
37. Schulz M, Liese AD, Mayer-Davis EJ, et al. Nutritional correlates of dietary glycaemic index: new aspects from a population perspective. Br J Nutr 2005;94:397–406.
38. Englyst KN, Englyst HN. Carbohydrate bioavailability. Br J Nutr 2005;94:1–11.
39. Robertson MD, Bickerton AS, Dennis AL, Vidal H, Frayn KN. Insulin-sensitizing effects of dietary resistant starch and effects on skeletal muscle and adipose tissue metabolism. Am J Clin Nutr 2005;82:559–67.
40. Brighenti F, Benini L, Del RD, et al. Colonic fermentation of indigestible carbohydrates contributes to the second-meal effect. Am J Clin Nutr 2006;83:817–22.
41. Elliott SS, Keim NL, Stern JS, Teff K, Havel PJ. Fructose, weight gain, and the insulin resistance syndrome. Am J Clin Nutr 2002;76:911–22.