Glycemic index and glycemic load in relation to food and nutrient intake and metabolic risk factors in a Dutch population

Huaidong Du, Daphne L van der A, Marit ME van Bakel, Carla JH van der Kallen, Ellen E Blaak, Marleen MJ van Greevenbroek, Eugène HJM Jansen, Giel Nijpels, Coen DA Stehouwer, Jacqueline M Dekker, and Edith JM Feskens

ABSTRACT
Background: Previous studies on the glycemic index (GI) and glycemic load (GL) reported inconsistent findings on their association with metabolic risk factors. This may partly have been due to differences in underlying dietary patterns.

Objective: We aimed to examine the association of GI and GL with food and nutrient intake and with metabolic risk factors including blood glucose, insulin, lipids, and high-sensitivity C-reactive protein (CRP).

Design: The study entailed cross-sectional analyses of data from 2 joint observational studies, the CoDAM Study and the Hoorn Study.

Results: In total, 974 subjects aged 42–87 y were included in the study. The mean (±SD) GI was 57 ± 4 and the mean GL was 130 ± 39. Dairy products, potatoes and other tubers, cereal products, and fruit were the main predictive food groups for GI. GL was closely correlated with intake of total carbohydrates (r = 0.97), which explained >95% of the variation in GL. After adjustment for potential confounders, GI was significantly inversely associated with HDL cholesterol and positively associated with fasting insulin, the homeostasis model assessment index of insulin resistance, the ratio of total to HDL cholesterol, and CRP. No association was observed between GL and any of the metabolic risk factors, except for a borderline significant positive association with CRP.

Conclusions: In this population, a low-GI diet, which is high in dairy and fruit but low in potatoes and cereals, is associated with improved insulin sensitivity and lipid metabolism and reduced chronic inflammation. GL is highly correlated with carbohydrate intake and is not clearly associated with the investigated metabolic risk factors.

KEY WORDS Glycemic index, GI, glycemic load, GL, metabolic risk factor, glycemic control, insulin resistance, lipid metabolism, systematic chronic inflammation

INTRODUCTION

The glycemic index (GI), an indicator ranking carbohydrates according to their effects on the body’s postprandial glycemic response, was introduced >2 decades ago to facilitate glycemic control in patients with diabetes (1). It was described as the percentage incremental area under the 2-h blood glucose response curve of a test food divided by the corresponding area of a reference food containing the same amount of available carbohydrates. The glycemic load (GL) was introduced more recently and is a product of GI with the amount of total available carbohydrates (2). Since then, research has been extended to the role of GI and GL in the prevention and management of overweight and obesity (3), cardiovascular disease (4), cancer (5), and many other health problems, such as age-related macular degeneration (6). However, findings are not always consistent, and consensus regarding the incorporation of the GI and GL concepts into dietary guidelines has not yet been reached (7, 8).

Liu et al (9, 10) observed that GI and GL are inversely associated with the concentration of HDL cholesterol and positively associated with triacylglycerol and high-sensitivity C-reactive protein (CRP) concentrations in US women. Frost et al (11) showed that GI is associated with serum HDL-cholesterol concentrations in middle-aged British men and women. These associations, however, were not detected by van Dam et al (12) in Dutch elderly men. In a Danish prospective study, Oxlund et al (13) found only weak associations between GI, GL, and changes in serum lipids.

Although GI and GL are based on the different influences of carbohydrates on glucose and insulin responses, findings from epidemiologic studies on their associations with markers of glycemic control and insulin sensitivity are conflicting (14). For example, a positive association between GI and the insulin resistance index was found in the Framingham Offspring Cohort (15), but not in the Insulin Resistance Atherosclerosis Study (16). Evidence from observational studies and clinical trials supports the positive association between GI and glycated hemoglobin (HbA1c) in diabetic patients (17–19), but findings in general populations are contradictory (20, 21).

1 From the National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands (HD, DLvdA, and EHJM); the Department of Human Biology, Nutrition and Toxicology Research Institute of Maastricht (NUTRIM) (HD and EEB) and Department of Internal Medicine, Cardiovascular Research Institute of Maastricht (CARIM) (CJHvdK, MMJvG, and CDAS), Maastricht University, Maastricht, Netherlands; the Nutrition and Hormones Group, International Agency for Research on Cancer (IARC), Lyon, France (MMEvB); the Institute for Research in Extramural Medicine, VU University Medical Center Amsterdam, Netherlands (JMD and GN); and the Division of Human Nutrition, Wageningen University, Wageningen, Netherlands (EIJMF).
2 Supported by the DiOGenes project. DiOGenes is the acronym of the project “Diet, Obesity and Genes” supported by the European Community (contract no. FOOD-CT-2005-513946). Internet: http://www.diongenes-eu.org/.
3 Reprints not available. Address correspondence to H Du, National Institute for Public Health and the Environment (RIVM), The Netherlands, PO Box 1 3720 BA, Bilthoven, Netherlands. E-mail: huaidong.du@rivm.nl.

Received August 8, 2007.
Accepted for publication October 8, 2007.
One of the practical concerns about whether a low-GI diet should be recommended is that low-GI or -GL diets may limit food choices and increase fat intake (22). Therefore, understanding the relation of GI and GL with food and nutrient intakes is important. This may also provide further insight into the underlying reasons for the diverse findings in the associations between GI and GL and health-related outcomes.

Under the joint efforts of the EPIC (European Prospective Investigation into Cancer and Nutrition) and the DiOGenes Study, an extensive GI database was recently developed to be used to investigate the association of GI and GL with cancer, obesity, and other health indicators (23). For European studies, this incorporates the best knowledge in the field so far. Using this database, we conducted the current study to investigate the relation of GI and GL with food and nutrient intakes and to explore their association with metabolic risk factors, including markers of glycemic control, insulin sensitivity, lipid metabolism, and systematic chronic inflammation, in a combined population consisting of subjects from 2 ongoing observational studies in the Netherlands.

SUBJECTS AND METHODS

Subjects

The study population included participants of the CoDAM Study (Cohort study Diabetes and Atherosclerosis Maastricht) (24) and subjects taking part in the follow-up examination of the Hoorn Study (25). Supported by a common grant, both studies were carried out jointly and followed a similar research protocol to investigate the behavioral and genetics associates of obesity, diabetes, and atherosclerosis.

The CoDAM Study started in 1999–2000 and is a population-based cohort study designed to investigate the effects of glucose metabolism, blood lipids, lifestyle, and genetic factors on cardiovascular disease morbidity and mortality (24). Subjects were invited after a screening oral-glucose-tolerance test in a high-risk population on the basis of the following inclusion criteria: white, aged 40–70 y old, not using medication that affects glucose metabolism, and having any of the following: a body mass index (BMI; in kg/m²) > 25, a family history of type 2 diabetes mellitus, a history of gestational diabetes, use of antihypertensive medication, a postprandial blood glucose concentration >6.0 mmol/L, or glucosuria. In total, 574 subjects were recruited. The study protocol was approved by the Medical Ethical Review Committee of Maastricht University, and written informed consent was obtained from all participants before the start of the study.

The Hoorn Study, which started in 1989, is a population-based cohort study investigating glucose tolerance status and cardiovascular disease risk factors among a sample of the general population in Hoorn, Netherlands (25). In 2000–2001, a follow-up examination was conducted in a selected group of 903 subjects consisting of all subjects with type 2 diabetes and a random sample of the survival cohort with normal or impaired glucose metabolism. Details of the study population have been described previously (26). The Ethical Review Committee of the VU University Medical Center Amsterdam approved the study, and written informed consent was obtained from all participants before participation.

We excluded a priori subjects to whom any of the following applied: >10% missing items on the food-frequency questionnaire (FFQ), ratio of total energy intake overpredicted resting energy expenditure in the top and bottom 1%, implausible energy intake (<800 or >4200 kcal/d for men and <500 or >3500 kcal/d for women), self-reported diabetes, following a specific diet (ie, weight-loss or cholesterol-lowering diet), and using cholesterol-lowering medication. The current study population consisted of 974 subjects, 517 men and 457 women, of whom 321 originated from the CoDAM Study and 653 from the Hoorn Study.

Dietary assessments

Both studies used the same validated FFQ to assess the subjects’ habitual dietary intake. This FFQ was developed for Dutch cohorts of the EPIC Study, and details of the FFQ have been described previously (27, 28). In brief, it is a self-administered, quantitative FFQ. Its relative validity against multiple 24-h recalls in terms of total energy, carbohydrates, fiber, breads and pasta, potatoes, fruit, dairy products, sugar, and sweet products was relatively high [Spearman correlation coefficients (r): 0.51–0.79]. Food items from the FFQ were collapsed into 17 food groups following the same classification method applied by the EPIC study (29). Intakes of energy and nutrients were calculated according to the extended version of the Dutch food-composition table (NEVO) 1996 (30). Dietary GI and GL were calculated according to the formulas below:

\[
GI = \frac{\sum (GI_i \times CHO_i)}{\sum CHO_i} \quad (1)
\]

\[
GL = \frac{\sum (GI_i \times CHO_i)}{100} \quad (2)
\]

where GI and GL are the GI value of food \(i\) from the GI database. The source of the GI values used to compile this GI database has been described before (23). In brief, published GI values (31–33) derived from 50 g glucose as the reference food and 2-h testing periods. For generic items in the FFQ, the 24-h dietary recall values were used to weigh the mean GI values based on the frequency of consumption. CHO is the amount of available carbohydrates from food \(i\) calculated by the amount of food consumed (g/d) multiplied by the carbohydrate content from NEVO (g/g), and \(n\) is the number of foods eaten per day. In the current analysis, foods involved in calculating the GI and GL provided \(\approx 98\%\) of the total available carbohydrate intake.

Biochemical measurements

During the subjects’ first visit to the research units, venous blood samples were drawn from all participants after they had fasted overnight (>12 h). Serum and plasma were immediately separated after centrifugation (3000 x g for 15 min at 4 °C) and were stored at −70 °C until the assays were performed.

A standard 75-g oral-glucose-tolerance test was performed. Fasting and 2-h postprandial plasma glucose concentrations were measured by using enzymatic methods (G6PDase method, ABX Diagnostics Glucose HK 125, Montpellier, France, for the CoDAM Study; hexokinase method, Roche Diagnostics GmbH, Mannheim, Germany, for the Hoorn Study). Glucose metabolic
status was evaluated according to the WHO 1999 criteria (34). HbaA₁c was analyzed by using ion-exchange HPLC (HPLC, Bio-Rad, Veenendaal, The Netherlands). Insulin was measured by using a paired monoclonal antibody-based two-site immunoradiometric assay (Medgenix Diagnostics, Fleurus, Belgium). HOMA-IR (insulin resistance index of homeostatic model assessment) was calculated by using a Microsoft EXCEL-based HOMA 2 calculator (35). Total cholesterol (TC), HDL cholesterol, and triacylglycerol were measured by using enzymatic techniques (Roche Diagnostics, Mannheim, Germany), and LDL cholesterol was calculated by using the Friedewald formula (36). High-sensitivity CRP was measured in serum samples with a Hitachi-912 auto-analyzer (Roche Diagnostics, Mannheim, Germany) in the CoDAM Study and in EDTA-plasma samples with a high-sensitivity in-house sandwich enzyme immunoassay (Dako, Copenhagen, Denmark, and Sigma Chemical Co, St Louis, MO) in the Hoorn Study. All measurements had inter- and intra-assay CVs <8%.

Anthropometric and other measurements

A self-administered questionnaire was used to collect information on demographic characteristics, lifestyle habits, and health and disease status. The validated SQUASH (Short Questionnaire to Assess Health-enhancing Physical Activity) questionnaire was used to measure physical activity levels (37).

At the time of the research unit visit, body weight, height, and waist circumference were measured without shoes and in light clothing to the nearest 100 g and 1 cm, respectively. Body mass index (BMI, in kg/m²) was calculated as weight divided by height squared.

Statistical methods

Stepwise regression analyses were carried out to investigate the contribution of food groups to the interindividual variation in GI and GL. For those food groups contributing at least 1% variation, multiple linear regression analyses were performed with only those predictive food groups plus total energy as explanatory variables and GI or GL as the response variable. Associations of energy, macronutrients, and their components with GI and GL were investigated through Spearman correlation analyses with and without adjustment for total energy intake.

Metabolic risk factors were log-transformed to improve their distribution toward normal. Multiple linear regression analyses were performed to explore the associations of GI and GL with the metabolic risk factors. These analyses were adjusted for potential confounders including age, sex, current smoking status (yes or no), physical activity (inactive, moderately active, highly active and unknown), cohort (CoDAM or Hoorn), and the intake of total energy, alcohol, fiber, cholesterol, animal- and plant-based protein, and saturated fatty acids. For GI, we additionally adjusted for monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), polysaccharides, and mono- and disaccharides. Total energy intake was adjusted for by using the residual method (38).

Interaction of GI and GL with age, sex, smoking, physical activity, and cohort was explored by adding interaction terms to the models. In none of the analyses did the interaction term with cohort reach statistical significance, which indicates that pooling of the data was justified. All analyses were performed with the SAS statistical software package (version 9.1; SAS Institute Inc, Cary, NC). $P < 0.05$ was considered significant.

RESULTS

The study population consisted of 517 men and 457 women; 30% of them had newly diagnosed type 2 diabetes and 23% had intermediate hyperglycemia (including impaired glucose tolerance and impaired fasting glycaemia) (Table 1). The subjects were on average 65 ± 9 (mean ± SD) y old (range: 42–87 y), with a mean GI of 57 ± 4 and a mean GL of 130 ± 39. Compared with the subjects from the CoDAM Study, the Hoorn population was on average older (68 compared with 58 y), included slightly fewer men (50% compared with 60%), included more patients with newly diagnosed type 2 diabetes (39% compared with 12%), and was less physically active (3.4 compared with 5.3 h/d).

The dairy products group was inversely associated with GI and it contributed most (30%) to the interindividual variation in GI. The fruit group was also inversely associated with GI and predicted 6% of the variation in GI. The group of potatoes and other tubers and the group of cereals and cereal products were positively associated with GI, and they respectively accounted for 17% and 7% of the variation in GI (Table 2). In total, these 4 groups accounted for 61% of the variation in GI. GL was positively associated with all 17 food groups except vegetables. Six carbohydrate-rich food groups explained in total 85% of the variation in GL. The most predictive food group was cereal products, which explained 43% of the variation, followed by sugar and confectionery (23%).

Both GI and GL were positively associated with total energy intake ($r_g = 0.17$ and 0.82, respectively; Table 3). In crude analyses, GI was positively associated with most of the nutrients but inversely associated with the intake of mono- and disaccharides, animal protein, and alcohol; GL was positively associated with all nutrients under investigation. After adjustment for total energy intake by partial regression analysis, GI was strongly and positively associated with polysaccharides ($r_g = 0.61$), plant protein ($r_g = 0.32$), total fat ($r_g = 0.17$), PUFAs ($r_g = 0.20$), and MUFAs ($r_g = 0.15$) but inversely associated with mono- and disaccharides ($r_g = -0.38$), animal protein ($r_g = -0.26$), alcohol ($r_g = -0.18$), and total protein ($r_g = -0.16$). Total carbohydrates and fiber were only weakly associated with GI, and the association of GI with saturated fat and cholesterol was not statistically significant. GL was positively associated with the intake of total carbohydrates ($r_g = 0.92$), polysaccharides ($r_g = 0.63$), mono- and disaccharides ($r_g = 0.49$), plant protein ($r_g = 0.43$), and fiber ($r_g = 0.38$) but inversely associated with the other nutrients (Table 3).

GI was positively associated with insulin resistance, as indicated by both the concentration of fasting insulin and the HOMA-IR level (Table 4). A 10-unit GI increment, which corresponds to the difference between the lowest and the highest quintile, was significantly associated with a 23% increase in markers of insulin resistance. The association of GI with HDL cholesterol (inverse) and CRP (positive) concentration and the ratio of total to HDL cholesterol (positive) was also statistically significant. A 10-unit increase in GI was associated with a 7% decrease in the HDL-cholesterol concentration, a 10% increase in the ratio of total to HDL cholesterol, and a 29% increase in the CRP concentration. In addition, this amount of GI increase was also associated with a 10% increase in triacylglycerol concentration, although this association was not statistically significant. In contrast, GL was not significantly associated with any of the
TABLE 1  
Population characteristics by study (n = 974)  

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>CoDAM Study (n = 321)</th>
<th>Hoorn Study (n = 653)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>65 ± 9</td>
<td>58 ± 7</td>
<td>68 ± 7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex [n (% of men)]</td>
<td>517 (53)</td>
<td>192 (60)</td>
<td>325 (50)</td>
<td>0.003</td>
</tr>
<tr>
<td>Glycemic index</td>
<td>57 ± 4</td>
<td>59 ± 3</td>
<td>56 ± 3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glycemic load</td>
<td>130 ± 39</td>
<td>143 ± 41</td>
<td>123 ± 36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking [n (% of current smokers)]</td>
<td>166 (17)</td>
<td>56 (17)</td>
<td>110 (17)</td>
<td>0.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.8 ± 4.2</td>
<td>28.0 ± 4.1</td>
<td>27.6 ± 4.3</td>
<td>0.05</td>
</tr>
<tr>
<td>Physical activity (h/d)</td>
<td>4.0 ± 3.0</td>
<td>5.3 ± 3.3</td>
<td>3.4 ± 2.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose metabolic status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal [n (%)]</td>
<td>456 (47)</td>
<td>212 (66)</td>
<td>244 (38)</td>
<td></td>
</tr>
<tr>
<td>IHG [n (%)]</td>
<td>218 (23)</td>
<td>72 (22)</td>
<td>146 (23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Newly diagnosed T2DM</td>
<td>288 (30)</td>
<td>37 (12)</td>
<td>251 (39)</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.8 (5.3–6.6)</td>
<td>5.4 (5.1–5.9)</td>
<td>6.0 (5.5–7.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2-h Glucose (mmol/L)</td>
<td>6.5 (5.2–8.3)</td>
<td>6.4 (5.1–8.1)</td>
<td>6.6 (5.4–8.3)</td>
<td>0.3</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.8 (5.5–6.2)</td>
<td>5.7 (5.4–6.0)</td>
<td>5.9 (5.6–6.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>56 (42–82)</td>
<td>54 (43–74)</td>
<td>57 (41–84)</td>
<td>0.3</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.1 (0.8–1.6)</td>
<td>1.0 (0.8–1.4)</td>
<td>1.1 (0.8–1.7)</td>
<td>0.1</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.6 (4.9–6.3)</td>
<td>5.2 (4.7–5.8)</td>
<td>5.8 (5.1–6.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.3 (1.1–1.6)</td>
<td>1.2 (1.0–1.4)</td>
<td>1.3 (1.1–1.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TC:HDLC</td>
<td>4.3 (3.5–5.4)</td>
<td>4.4 (3.6–5.9)</td>
<td>4.3 (3.5–5.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>3.6 (3.0–4.2)</td>
<td>3.3 (2.8–3.9)</td>
<td>3.7 (3.1–4.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerol (mmol/L)</td>
<td>1.4 (1.0–1.9)</td>
<td>1.4 (1.0–1.9)</td>
<td>1.4 (1.0–1.9)</td>
<td>0.5</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>2.0 (1.2–3.6)</td>
<td>2.2 (1.3–3.5)</td>
<td>2.0 (1.1–3.6)</td>
<td>0.6</td>
</tr>
<tr>
<td>Total energy intake (MJ/d)</td>
<td>8.6 ± 2.3</td>
<td>9.4 ± 2.5</td>
<td>8.2 ± 2.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Carbohydrate intake (% of energy)</td>
<td>45.5 ± 6.6</td>
<td>44.5 ± 6.1</td>
<td>46.0 ± 6.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Protein intake (% of energy)</td>
<td>15.4 ± 2.3</td>
<td>15.2 ± 2.0</td>
<td>15.5 ± 2.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Fat intake (% of energy)</td>
<td>34.8 ± 5.2</td>
<td>35.8 ± 4.8</td>
<td>34.3 ± 5.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fiber intake (g/MJ)</td>
<td>2.9 ± 0.7</td>
<td>2.9 ± 0.6</td>
<td>2.9 ± 0.7</td>
<td></td>
</tr>
</tbody>
</table>

1 IHG, intermediate hyperglycemia; T2DM, type 2 diabetes mellitus; HbA1c, glycated hemoglobin A1c; HOMA-IR, homeostasis model assessment insulin resistance index; TC, total cholesterol; CRP, high-sensitivity C-reactive protein. Comparison between the 2 studies was conducted by Wilcoxon rank-sum test for continuous variables or chi-square test for categorical variables.

2 ± SD (all such values).

3 Based on GI of glucose = 100 scale.

4 Median, interquartile range in parentheses (all such values).

5 Those with CRP > 10 mg/L were excluded from the calculation.

...metabolic risk factors, except for a borderline positive association with CRP.

Neither GI nor GL was significantly associated with BMI or waist circumference after adjustment for age, sex, and physical activity level (data not shown). The only significant interaction was between GI and smoking in the association with fasting glucose (P = 0.02), fasting insulin (P = 0.04), and HOMA-IR (P = 0.04). Additional stratified analyses showed that the positive associations between GI and these metabolic factors were confined to nonsmokers and were absent in current smokers (data not shown).

**DISCUSSION**

In this study population, a low-GI diet was characterized by a high dairy and fruit intake and a low potato and cereal intake. GI was inversely associated with HDL cholesterol and was positively associated with fasting insulin, HOMA-IR, the ratio of total to HDL cholesterol, and CRP. In nonsmokers, it was also associated with fasting glucose. By contrast, GL was not clearly associated with any of these risk factors.

Previous studies on GI and GL and risk factors showed inconsistencies (9, 12). We used a newly developed GI database that for European studies incorporates the best knowledge in the field so far (23). This enabled us to study the association with metabolic risk factors in a more optimal way. We acknowledge the difficulties and inaccuracy in assessing GI and GL by use of FFQs (39). However, the validity of our FFQ in terms of estimating carbohydrate intake is comparable with that of the FFQ used in the Nurses’ Health Study (40) and is for example higher than that of the FFQ used in the Insulin Resistance Atherosclerosis Study (16). Moreover, GI values were assigned to foods providing 98% of the total available carbohydrate consumption, which was slightly higher than in previous reports (13, 41, 42).

We analyzed the pooled data of 2 Dutch cohort studies to increase the statistical power. Although baseline characteristics differed mainly because of the age and sex differences between the 2 studies, pooling the data was justified, because statistical analyses of interaction terms in the regression models showed no evidence of effect modification. In addition, in both studies, a common examination protocol was used, the general questionnaires and FFQ were the same, and biochemical measurements were mostly done in the same laboratory, which ensures a lack of bias. Analyses of metabolic factors were adjusted for an extended...
set of potential confounders, including age, sex, smoking, physical activity, cohort, total energy, dietary fiber, alcohol, and cholesterol intake. For GI, additional adjustment was made for fatty acids, plant- and animal-based protein, polysaccharides, and mono- and disaccharides. Therefore, the observed associations are not likely to be explained by a different dietary composition. For GL, additional adjustment was made for animal- and plant-based protein and saturated fatty acids, but not for MUFA and PUFA. Thus, the observed associations represented substituting unsaturated fatty acids (PUFA and MUFA) with GI. In a post hoc analysis, models substituting either animal protein or plant protein with GL yielded essentially the same results. Thus, in this population, a low GI diet is not significantly different from a high-unsaturated-fat or high-protein diet in its associations with metabolic risk factors.

The concern that low-GI diets may limit food choices and increase fat intake (22) was not supported by our findings. Actually, we found a moderate positive association between GI and fat intake, both unadjusted and adjusted for total energy. At the food level, GI was positively associated with the intake of meats, fats, and oils but was inversely associated with the intake of vegetables, legumes, fruit, and fish. These findings imply that a low-GI diet may be a marker of healthy eating habits. The positive association between GI and foods containing negligible amounts of carbohydrates, including meats and fats and oils, was also found in a previously published US study (43). An explanation may be that these foods are usually consumed in combination with high-GI foods such as potatoes and cereals.

The association between GI and dairy products was consistent with previous findings among Dutch elderly men (12) and in a US population (43). Unexpectedly, GI and GL in our study were positively, not inversely, associated with total dietary fiber intake. This supports the notion that low-GI and -GL diets are not necessarily high in fiber, and attributing the health effects of low-GI and -GL diets to higher fiber content may be imprecise. Separating soluble and insoluble fiber may shed more light on this issue but was currently not possible because of a lack of information in the Dutch food-composition table.

### TABLE 2

<table>
<thead>
<tr>
<th>Food groups</th>
<th>GI</th>
<th>GL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dairy products</td>
<td>−0.66 (0.03)</td>
<td>−0.60 (0.07)</td>
</tr>
<tr>
<td>Potatoes and other tubers</td>
<td>1.84 (0.11)</td>
<td>1.83 (0.11)</td>
</tr>
<tr>
<td>Cereals and cereal products</td>
<td>1.43 (0.11)</td>
<td>1.37 (0.11)</td>
</tr>
<tr>
<td>Fruit</td>
<td>−0.69 (0.06)</td>
<td>−0.70 (0.06)</td>
</tr>
<tr>
<td>Cereals and cereal products</td>
<td>19.96 (0.70)</td>
<td>19.96 (0.70)</td>
</tr>
<tr>
<td>Sugars and confectionery</td>
<td>42.04 (1.71)</td>
<td>42.04 (1.71)</td>
</tr>
<tr>
<td>Potatoes and other tubers</td>
<td>13.04 (0.64)</td>
<td>13.04 (0.64)</td>
</tr>
<tr>
<td>Cakes</td>
<td>27.12 (1.74)</td>
<td>27.12 (1.74)</td>
</tr>
<tr>
<td>Fruit</td>
<td>4.13 (0.33)</td>
<td>4.13 (0.33)</td>
</tr>
<tr>
<td>Dairy products</td>
<td>0.72 (0.18)</td>
<td>0.72 (0.18)</td>
</tr>
</tbody>
</table>

1. Stepwise regression analysis with 17 food groups as explanatory variables and GI or GL as response variable; only those food groups that contributed ≥1% of the variation are listed.

2. Models with listed variables and total energy as the explanatory variables and GI or GL as the response variable; regression coefficients mean the change of GI or GL with a 100-g increase of each food group.

### TABLE 3

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>GI</th>
<th>GL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total energy (MJ/d)</td>
<td>0.17²</td>
<td>0.82²</td>
</tr>
<tr>
<td>Total carbohydrate (g/d)</td>
<td>0.18²</td>
<td>0.06²</td>
</tr>
<tr>
<td>Total fat (g/d)</td>
<td>0.23²</td>
<td>0.17²</td>
</tr>
<tr>
<td>Total protein (g/d)</td>
<td>0.05</td>
<td>0.16²</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids (g/d)</td>
<td>0.51²</td>
<td>0.61²</td>
</tr>
<tr>
<td>Monounsaturated fat (g/d)</td>
<td>0.22²</td>
<td>0.15²</td>
</tr>
<tr>
<td>Animal protein (g/d)</td>
<td>−0.09²</td>
<td>−0.26²</td>
</tr>
<tr>
<td>Plant protein (g/d)</td>
<td>0.33²</td>
<td>0.32²</td>
</tr>
<tr>
<td>Fiber intake (g/d)</td>
<td>0.17²</td>
<td>0.08²</td>
</tr>
<tr>
<td>Cholesterol (mg/d)</td>
<td>0.12²</td>
<td>0.02</td>
</tr>
<tr>
<td>Alcohol (g/d)</td>
<td>−0.10²</td>
<td>−0.18²</td>
</tr>
</tbody>
</table>

1. \( r_s \), Spearman correlation coefficient; \( r_{s \_adj} \), partial Spearman correlation coefficient (adjusted for total energy intake).

2. \( P < 0.05 \).

Regarding alcohol, some found an inverse association with GI (40, 44), whereas others found the opposite (43). In the present study, we found a modest inverse association between GI and GL and alcohol intake. Different approaches used to assign GI values to alcoholic beverages might be, at least in part, the explanation for these dissimilar findings. In our study, the GI values of most alcoholic drinks, except beer, liqueurs, and cocktails (GI = 61 versus glucose), were 0, whereas Schulz et al (43) assigned an estimated GI value of 95 to beer and a value of 61 to wine and other alcoholic beverages. More information on the GI values of alcoholic beverages in different countries may be needed.

GL was strongly associated with the intake of total carbohydrates \( (r_s = 0.97) \) but was only moderately associated with GI \( (r_s = 0.41) \). More than 95% of the variation in GI was explained by total carbohydrates and only ≈4% by GL. Compared with what was shown by Brand-Miller et al (45), GL in our study depended more heavily (95% compared with 68%) on carbohydrate intake. This might be secondary to the smaller variation in GI than in carbohydrate intake. Previous epidemiologic studies showing similar variation of GI, however, did not report the relation of GL with carbohydrates (10, 16, 42).

Mechanisms involved in the association of GI and GL with blood glucose, insulin, and lipid concentrations have been reviewed before (14). In addition to the significant inverse association between GI and HDL cholesterol, we also observed a positive association between GI and the ratio of total to HDL cholesterol. The ratio of total to HDL cholesterol is considered the best predictor of ischemic heart diseases because it takes into account both the cardioprotective effect of HDL cholesterol and the atherogenic effect of LDL and VLDL cholesterol (46). Although small, the significant association of GI with HDL cholesterol and the ratio of total to HDL cholesterol suggests a protective role of low-GI diets on lipid metabolism disorders and cardiovascular disease.

Potential mechanisms underlying the association between GI, GL, and chronic systematic inflammation were recently summarized in detail (47). Hyperglycemia, dyslipidemia, insulin resistance, and weight change may all be involved in this pathway. A
positive relation between GI, GL, and CRP was found previously in 2 US studies (10, 48). Although the association was of only borderline significance for GL, a 29% decrease in CRP by a 10-unit decrease in GI seems promising for decreasing the risk of metabolic syndrome and cardiovascular disease (49).

Low-GI diets showed significant benefits on fasting glucose and insulin sensitivity among nonsmokers. None of the previous studies on GI and GL reported this effect modification. It may be that the independent adverse effects of cigarette smoking on glucose and insulin metabolism leaves little room for the main exposure variables, as in a study on β-carotene (50), although this is rather unlikely in comparison with stronger determinants of glucose metabolism, such as BMI and waist circumference. Further investigation of the potential effects of smoking on nutrient (carbohydrates) partitioning may be needed.

It should also be noted that the current findings resulted from analyses that included both polysaccharides and mono- and disaccharides as covariates. This was because GI in our study, as also in a US study (43), was positively associated with polysaccharides but inversely associated with mono- and disaccharides. When we adjusted for total carbohydrate instead, GI was not significantly associated with fasting insulin and HOMA-IR, whereas the association with lipids and CRP remained essentially the same. This suggests that low-GI diets may benefit insulin sensitivity by replacing high-GI polysaccharides with low-GI polysaccharides but not by replacing polysaccharides with mono- and disaccharides.

In this study, neither GI nor GL was associated with HbA1C, a marker of long-term glycemic control. Although more than one-half of the subjects had type 2 diabetes or intermediate hyperglycemia, HbA1C was on average in the low diabetic and normal range. Subgroup analyses among type 2 diabetes patients (n = 288), subjects with either type 2 diabetes or intermediate hyperglycemia (n = 506), and subjects with a high HbA1C level (7%, n = 78) also failed to detect any statistically significant association.

In conclusion, in this Dutch population, a low-GI diet is high in dairy products and fruit but low in potatoes and cereals. Even though cross-sectional studies do not prove a causal relation, the findings of this current study support a beneficial role of low-GI diets in optimizing insulin sensitivity, lipid metabolism, chronic inflammation, and, in nonsmokers, fasting glucose. GL was highly correlated with total carbohydrates and marginally associated with CRP but not with other metabolic risk factors under investigation. Large, prospective cohort studies and clinical trials are warranted to ascertain the beneficial effects cast on low-GI diets.

We thank JC Brand-Miller from the University of Sydney and TMS Wolever from the University of Toronto for their advice in the processes of assigning GI values to items.

The contributions of the authors were as follows—HD: designed the study, performed the statistical analyses, and drafted the manuscript; DLvdA and EMF: supervised this work; MMEvB: was responsible for the GI database; EEB, CJHvdK, MMvG, CDAS, EHJMJ, JMD, GN, and EJMF: contributed to data collection and study organization. All authors reviewed and commented on the manuscript. None of the authors had a conflict of interest to declare.

REFERENCES

7. Food and Agriculture Organization of the United Nations, The World


