HHS Public Access

Author manuscript

J Am Coll Nutr. Author manuscript; available in PMC 2016 October 13.

Published in final edited form as:

J Am Coll Nutr. 2009 April ; 28(2): 150–158.

Dietary Carbohydrates and Cardiovascular Disease Risk Factors in the Framingham Offspring Cohort

Nicola M. McKeown, PhD, **James B. Meigs, MD, MPH**, **Simin Liu, MD, ScD**, **Gail Rogers, MA**, **Makiko Yoshida**, **Edward Saltzman, MD**, and **Paul F. Jacques, ScD**

Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University (N.M.M., G.R., M.Y., E.S., P.F.J.), General Medicine Division and Department of Medicine, Massachusetts General Hospital and Harvard Medical School (J.B.M.), Boston, Massachusetts, Departments of Epidemiology and Medicine, UCLA (S.L.), Los Angeles, California

Abstract

Objective—Evidence from observational studies has suggested that carbohydrate quality rather than absolute intake is associated with greater risk of chronic diseases. The aim of this study was to examine the relationship between carbohydrate intake and dietary glycemic index and several cardiovascular disease risk factors.

Methods—We examined cross-sectional associations between total carbohydrate and dietary glycemic index (GI) intakes and several cardiovascular disease risk factors (CVD) in a sample of 2,941 Framingham Offspring Participants. CVD risk factors included waist, blood pressure, lipids, fasting insulin, fasting glucose, and the insulin sensitivity index ($ISI_{0,120}$). Dietary intake was assessed by a food frequency questionnaire (FFQ) and categorized by quintiles of dietary intake.

Results—After adjustment for potential confounding factors, dietary GI was positively associated with fasting triglycerides (mean: 115mg/dL in the lowest and 127 mg/dL in the highest quintile of intake; *P* for trend < 0.001), fasting insulin (26.8 and 28.9 μu/mL, respectively, *P* for trend < 0.0001), and inversely associated with HDL cholesterol (49 and 47 mg/dL, respectively, *P* for trend 0.003) and $ISI_{0,120}$ (26.8 and 25.1, *P* for trend < 0.001). There was no significant relationship between dietary GI and waist circumference, total cholesterol, LDL cholesterol and fasting glucose. Intakes of total carbohydrate were inversely associated with waist circumference and HDL cholesterol, and positively associated with fasting triglycerides.

Conclusion—These cross-sectional findings support the hypothesis that a high GI diet unfavorably affects CVD risk factors and therefore, substitution of high with low GI dietary carbohydrates may have reduce the risk of CVD.

Address correspondence to: Nicola McKeown, Nutrition Epidemiology Program, Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, 711 Washington Street Boston, MA 02111. nicola.mckeown@tufts.edu.

Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the views of the U.S. Department of Agriculture.

The results were presented at Experimental Biology, 2004

Keywords

dietary glycemic index; CVD risk factors; diet

INTRODUCTION

Observational studies have recently identified post-challenge hyperglycemia as an independent risk factor for CVD [1–3]. By decreasing post-prandial blood glucose levels, acar-bose - a α-glucosidase inhibitor, improved several CVD risk factors [4,5] and significantly reduce CVD risk among patients with impaired glucose tolerance [6]. In diabetic patients, acarabose improved glycemic control in a dose-responsive manner [7]. The GI is a measure that ranks foods on the basis of the incremental glucose response of a test food relative to a reference food (white bread or glucose) for a given amount of carbohydrate [8,9]. Dietary carbohydrates that produce low post-prandial glucose response, as reflected by their low glycemic index (a qualitative indicator of carbohydrates ability to raise blood glucose), have been hypothesized to improve glucose and insulin control and reduce type 2 diabetes risk. In observational studies, carbohydrate diets with a high glycemic index (GI) have been associated with decreased concentrations of HDL cholesterol [10–12] and c-reactive protein [13], increased triacylglycerol concentrations [14] and greater insulin resistance [12,15].

Evidence from animal [16,17] to human subjects [18–22] appears to support the role of low GI carbohydrates influencing insulin sensitivity. Two intervention studies found that insulin sensitivity improved in both healthy individuals [19] and patients with coronary heart disease [20] following 4 weeks on a low GI diet. In rats, the long term feeding of high GI foods causes an increase in postprandial glucose and insulin profiles and elevated insulin response to an intravenous glucose tolerance test [17]. Other intervention studies [18,19,21–23], but not all [24,25] support the hypothesis that reducing the GI of the diet improves insulin sensitivity. However, evidence linking dietary GI to reduced diabetes risk is also inconsistent with some [26–29], but not all [30,31] finding that individuals who habitually consume high GI diets have a greater risk of developing type 2 DM.

We recently reported that a high dietary GI was associated with a higher prevalence of the metabolic syndrome in the Framingham Offspring Cohort [15], while neither total carbohydrate intake nor dietary GL were associated with this syndrome [15]. The purpose of this study was to examine the relationship between total carbohydrate intake and dietary GI, and individual CVD risk factors, and our hypothesis was that higher dietary GI diets were unfavorably associated with several CVD factors.

SUBJECTS AND METHODS

Study Population

The Framingham Offspring Study is a longitudinal community-based study of cardiovascular disease among the offspring of the original participants of the Framingham Heart Study Cohort and their spouses [32]. In 1971, 5,124 participants were enrolled into the

study [33] and since then, the cohort has been examined every 3 to 4 years. Between 1991 and 1995 during the fifth examination cycle of the Framingham Offspring Study, 3799 participants (81% of those alive at the time of the exam) underwent a standardized medical history and physical examination. Valid food frequency questionnaire (FFQ) data were available for 3,418 participants. Dietary information was judged as valid if reported energy intakes were ≥ 2.51 MJ/d (600 kcal) for men and women or < 16.74MJ/d (4000 kcal/d) for women and < 17.57 (4200 kcal/d) for men, respectively, or if fewer than 13 food items were left blank. Participants were excluded from these analyses if they had previously diagnosed diabetes (n = 122) based on use of insulin or oral hypoglycemic medication or if they were taking cholesterol-lowering medication (n = 229). Furthermore, we excluded participants with missing covariate or dietary information (n = 108), reducing the final sample to 2941 (1338 men and 1603 women, mean BMI 27.2 kg/m^2). Because of missing laboratory measures, the numbers of subjects across quintiles of nutrient intake differs according to the CVD risk factor (numbers range from 2479 to 2939) as reflected in the Tables presented in the results section. Excluding participants with previously undiagnosed diabetes (n = 118) based on either a fasting blood glucose level (≥ 7.0 mmol/L) or 2 hour post challenge plasma glucose (2-hr plasma glucose level ≥ 11.1 mmol/L) did not alter the findings of the present study and therefore these participants were included in the analyses. The Institutional Review Board for Human Research at Boston University and the Human Investigation Research Committee of Tufts-New England Medical Center approved the protocol.

Assessment of Dietary Intake

Usual dietary intake for the previous year was assessed at the 5th cycle using a semi-quantitative 126-item FFQ [34]. The questionnaires were mailed to the participants before the examination and the participants were asked to bring the completed questionnaire with them to their appointment. The FFQ consisted of a list of foods with a standard serving size and a selection of 9 frequency categories ranging from never or < 1 serving/month to > 6 servings/day. Participants were asked to report their frequency of consumption of each food item during the last year. Separate questions about use of vitamin and mineral supplements and type of breakfast cereal most commonly consumed were also included in the FFQ. Nutrient intakes were calculated by multiplying the frequency of consumption of each unit of food from the FFQ by the nutrient content of the specified portion. The relative-validity of this FFQ has been examined in several populations for both nutrients and foods [34–36]. The exposures of interest, total carbohydrate, dietary GL and GI, were energy-adjusted by using the residual method [37]. The correlation coefficients between the FFQ and multiple diet records in previous validation studies were moderately correlated for total carbohydrate, with correlation coefficients of 0.69 and 0.45 for men and women respectively.

GI values for foods in the FFQ were obtained either from analyzed published values (~53%) [38] or imputed when necessary by matching similar foods based on calories, carbohydrate, sucrose, fat and dietary fiber content (~28%). The remaining foods included on the FFQ (19%) do not have GI values because these foods contain little or no carbohydrate and thus these were assigned a zero. In addition for cereals, whenever possible, the method of processing was taken into account. An average dietary GI, which represents the overall quality of carbohydrate intake for each participant, was calculated as follows:

$$\left\{\sum\left[(\text{Frequency of food per day})\times(\text{carbohydrate content of the food})\times(GI)\right]\right\}/\text{total carbohydrate in the diet}$$

Thus the dietary GI can be interpreted as the weighted average of the GI values of all carbohydrate-containing foods, with the weight being the amount of carbohydrate consumed from each food item. The correlation between dietary glycemic index and total carbohydrate is low (r = 0.16). A related concept, the dietary GL is similar to that of the dietary GI, but rather than dividing by the total amount of carbohydrate, this is divided by 100. The dietary GL is considered a measure of carbohydrate quality and quantity. The main foods that contributed to the overall dietary glycemic load included potatoes, cold cereal, white bread, pizza, pasta, dark bread, orange juice, bananas, English muffin/bagel and white rice. In this study, the dietary GL was highly correlated with total carbohydrate intake (r = 0.92) and largely reflected carbohydrate intake. We did not, therefore, present the results for dietary GL and CVD risk factors.

Laboratory Methods

Blood samples were obtained from subjects who had fasted for at least 8 h and stored at −70°C. Fasting plasma glucose was measured in fresh specimens with a hexokinase reagent kit. Glucose assays were run in duplicate and the intra-assay coefficient of variation (CV) was < 3%. Fasting plasma insulin levels were determined using the Coat-A-Count ^{125}I radioimmunoassay (Diagnostic Products, Los Angeles, CA). This assay has cross-reactivity with proinsulin at the mid-curve of 40%, and a intra- and interassay CVs of 5.0 to 10% and a lower limit of sensitivity of 1.1 μU/mL (7.9 pmol/L). A standard 75-g oral glucose tolerance test post glucose challenge was administered according to the World Health Organization (WHO) standards [39] among patients without known diagnosed diabetes, and 2-h post challenge glucose and insulin concentrations were measured. The insulin sensitivity index ($ISI_{0,120}$) [40] was calculated using the following formula:

$$\frac{75,000+(\text{fasting glucose}-2\text{- h glucose})\times 0.19\times\text{body weight}\,(kg)/120}{log\,(\text{fasting insulin}+2\text{- h insulin})/2} \quad (1)$$

The $ISI_{0,120}$ is highly correlated with the euglycemic hyper-insulinemic clamp and is a measure of peripheral insulin sensitivity. A lower $ISI_{0,120}$ is indicative of greater insulin resistance. Serum lipid profiles included enzymatic measurement of total cholesterol (Total-C) and triacylglycerol concentrations [41], and the measurement of the HDL cholesterol (HDL-C) fraction after precipitation of LDL and VLDL cholesterol with dextran sulfate-magnesium [42]. LDL-cholesterol (LDL-C) concentrations were calculated using the Friedewald equation [43] for individuals with triacylglycerol concentrations less than 400mg/dL.

Lifestyle Variables

Height, weight, waist and hip circumferences were measured with the subject standing. Body mass index (BMI) was calculated as weight kg/height $(m)^2$. Additional covariate

information included age, smoking dose (cigarettes per day, none, 1–15, 16–25, ≥ 25), alcohol intake (g/d), total calories (kcal/d), current multivitamin use (y/n), physical activity score [44], treatment for hypertension (y/n), saturated fat (SFA)(% of energy) and polyunsaturated fat (PUFA) (% of energy) and dietary fiber (g/day).

Statistical Methods

SAS statistical software (release 8.0, SAS institute, Cary, NC) was used for all statistical analyses. Dependent variables include LDL-C and the natural logarithms of BMI, waist circumference, total-C, HDL-C fasting glucose, 2-h post challenge plasma glucose, fasting insulin, 2-hour post glucose challenge plasma insulin and triacylglycerols. For the blood pressure analyses, subjects were excluded if they were being treated for hypertension. To express transformed variables in their natural scale, geometric means and standard errors were computed by exponentiation of adjusted least squares means. Interactions between sex and the carbohydrate measures were examined to determine if associations were similar between men and women. We tested for potential interactions between BMI and the carbohydrate measures with BMI as a continuous variable. There were no statistically significant interactions with sex or BMI on any of the associations between the carbohydrate measures and CVD risk factors (> 0.05 for all interactions tested).

To examine the associations between carbohydrate intake and dietary GI, we determined age- and sex- adjusted geometric means for lifestyle and age-, sex- and energy-adjusted geometric means for dietary characteristics across increasing quintiles of dietary intake using SAS PROC GLM. We assessed statistical significance (defined as a two-tailed *P*-value < 0.05) of linear trends across categories of dietary intake by assigning each participant the median value for the category and modeling this value as a continuous variable.

We used a similar approach to model the association between the carbohydrate measures and CVD risk factors. For these analyses we used multivariable models including sex, age (y), BMI, waist circumference, energy intake (kcal/d), multivitamin supplementation use (y/n), alcohol intake (g/d), blood pressure medication (y/n), current cigarette smoking (categorical), physical activity score (continuous), percentage intakes of SFA and PUFA, and dietary fiber (g/day).

RESULTS

The characteristics of the Framingham Offspring Cohort according to energy-adjusted carbohydrate and dietary GI in-takes are shown in Table 1. Individuals with a higher intake of total carbohydrates were older, less likely to smoke and more likely to take multivitamins. A higher intake of carbohydrate was related to a lower intake of saturated and polyunsaturated fat, higher total energy, dietary fiber and magnesium intakes. Individuals whose dietary GI was higher were more likely to have hypertension and less likely to take multivitamins, have higher carbohydrate intakes and lower intakes of saturated fat, dietary fiber, alcohol and dietary magnesium.

CVD risk factors across quintile categories of energy adjusted total carbohydrate intake are shown in Table 2. Median energy adjusted total carbohydrate ranged from 179 in the lowest

to 272 in the highest quintile of energy-adjusted carbohydrate intake. After multivariate adjustment, a significant inverse association was observed between total carbohydrate intake and waist circumference (94 versus 89 cms, lowest versus the highest quintile of intake, p for trend < 0.0001) and HDL cholesterol concentrations (50 versus 46 mg/dL, p for trend 0.01) and a significant positively associated with fasting triacylglycerol (110 mg/dL versus 127 mg/dL, p for trend < 0.01). Energy-adjusted carbohydrate intake was not significantly associated with total-C, LDL-C, fasting insulin and glucose, and $ISI_{0,120}$. The associations between dietary GL and CVD risk factors were similar to those of total carbohydrate and CVD risk factors.

CVD risk factors across quintile categories of energy adjusted dietary GI intake are shown in Table 3. Median energy-adjusted dietary GI ranged from 72 in the lowest to 84 in the highest quintile category of intake. After multivariate adjustment, energy-adjusted dietary GI was positively associated with fasting triacylglycerol (115 mg/dL vs 127 mg/dL; p for trend, < 0.001) and inversely associated with HDL cholesterol (49 mg/dL versus 47 mg/dL, p for trend < 0.001). Dietary GI was significantly associated with all of the glucose related risk factors, including fasting insulin (26.8 vs 28.9 μu/mL, p for trend, < 0.001) and $ISI_{0,120}$ (26.8 versus 25.1, p for trend < 0.001). No significant association was found between dietary GI and waist circumference, total-C, LDL-C or fasting glucose. The associations between dietary GI and these CVD risk factors remained independent after adjustment for total carbohydrate intake. Furthermore, the associations between dietary GI and CVD risk factors did not vary by degree of overweight status.

DISCUSSION

In this middle-aged cohort, dietary GI was significantly associated with several CVD risk factors, including triacylglycerol concentrations and low HDL cholesterol concentrations. Furthermore, dietary GI was the only carbohydrate measure significantly associated with fasting insulin and the insulin sensitivity index ($ISI_{0,120}$,), an index that reflects β-cell dysfunction and increased hepatic glucose production. By definition, the GI ranks foods according to their effect on postprandial glycemia, and thereby, provides a measure of carbohydrate quality rather that quantity [8]. These findings suggest that individuals consuming higher GI diets need to secrete more insulin to dispose of the glucose load compared to those who consumed a lower dietary GI diet - as indicated by a lower ISI. In contrast, there was no significant association between total carbohydrate intake and fasting insulin and the ISI.

Previous cross-sectional studies on the relationship between dietary GI and measures of insulin sensitivity have been mixed. Sahyoun and colleagues [45] found that higher dietary GI intakes were positively associated with 2 hr post challenge plasma glucose levels in elderly men and women (>70 y), however, 2-h insulin concentrations were not measured in this study. In contrast, dietary GI was unrelated to 2 hr post challenge plasma glucose and insulin glucose concentrations in 394 elderly Dutch men [46]. Similarly, there was no relationship between dietary GI and 2-hr post glucose plasma in middle-aged individuals with varying degrees of glucose tolerance status [47]. The evidence from cross-sectional studies on the relationship between dietary GI and surrogate measures of insulin resistance

(fasting insulin, HOMA-IR) have also been inconsistent, with some reporting a positive association [12,45,48], while others finding no association [46,49,50]. Using a more direct measure of insulin sensitivity, the frequently sampled intravenous glucose-tolerance test (FSIVGT), neither digestible carbohydrate intake nor dietary GI were related to insulin secretion or sensitivity in 979 middle-aged adults [50]. Some short-term intervention studies have found that a low GI diet, as opposed to a high GI diet, improved insulin sensitivity [20,21] while others have found the reverse [51], or no effect on insulin sensitivity [52–54]. Low GI diets may have different effects on glucose and insulin homeostasis in individuals with different metabolic syndrome risk factors, which may, in part, explain the inconsistencies between studies.

High carbohydrate diets have consistently been found to elevate fasting triacylglycerol concentrations, primarily by enhancing hepatic synthesis of VLDL, and reduce HDL cholesterol concentrations [55]. In the present study, total carbohydrate, dietary GI and dietary GL were all inversely related to HDL cholesterol and positively associated triacylglycerol concentrations. Three cross-sectional studies found that dietary GI and GL were positively associated with triacylglycerol in women [12,14,56], while one study observed no association between dietary GI and fasting triacylglycerol in elderly men [46]. High GI diets have been adversely associated with fasting HDL cholesterol concentrations in some [11,12,57], but not all cross-sectional studies [46,56]. Short-term dietary intervention studies in individuals predisposed to developing type 2 DM (i.e. those with glucose intolerance, hyperlipidemia, overweight individuals or patients with CHD,) have found no effects of low GI diets on HDL-cholesterol [20,22,52,58], although triglyceride concentrations improved in some of these intervention studies [22,58]. Consolidating the findings from intervention studies is difficult, because they differ with respect to study population and different dietary interventions of varying durations.

Findings from controlled feeding studies suggest that low GI foods compared to high may increase satiety, delayed the return of hunger or decreased ad libitum food intake thereby impacting body weight [59]. We therefore expected to observe a positive relationship between dietary GI and waist circumference. Surprisingly, there was no relationship between dietary GI and waist circumference, yet both dietary GL and total carbohydrate intakes were inversely associated with waist circumference in this study. In other studies, neither dietary GI nor GL have reportedly been associated with waist circumference in middle-aged adults [50] or young children [48]. In older adults using DEXA to measure visceral abdominal fat, no association was observed between either dietary GI or GL and visceral abdominal fat in women, but dietary GL was inversely associated with visceral abdominal fat in men [45]. In contrast, one prospective study found that a high GI diet was related to greater gains in body weight and waist circumference in women, but not in men, and the relationship in women was strongest among those women who were sedentary [60]. Other observational studies have reported a positive relationship between dietary GI, but not GL, and BMI [56,61]. It remains to be established, in longitudinal studies and primary prevention studies in healthy middle aged adults, whether dietary carbohydrates mediate weight change.

There is considerable debate over the use and interpretation of the dietary GI and GL in observational studies [62,63]. For instance, the calculation of dietary GI and GL differ

between studies, with some using available (total carbohydrate minus dietary fiber) [45,50] rather than total carbohydrate [14,15] in the calculation of dietary GI and GL. Neuhouser and colleagues [64] recently developed a GI and GL database, and reported very little difference in the GL values for those estimated using available vs. total carbohydrate, even for foods with moderate fiber content such as whole-wheat breads and select fruits. The calculation of GI in mixed meals is another controversy, with some studies indicating that the carbohydrate content and GI of individual foods does not predict the glycemic and insulinemic effects of mixed meals [65,66], which vary in fat, protein, and carbohydrate content. Other studies however demonstrate that the dietary GI of individual foods is predictive of the glycemic effect of mixed meals [9,67,68]. Finally, most observational studies relating dietary GI to type 2 DM risk were based on estimates derived from a FFQ, which in the past, have been criticized for its calculation of the dietary GI [63].

In order to correctly interpret these results, some potential study limitations warrant consideration. First, the cross-sectional design of this study prohibits any assessment of the antecedent-consequence nature of these associations. Although we have adjusted for many other dietary and lifestyle characteristics, it is possible that errors in assessing these covariates, such as physical activity and smoking, may have lead to residual confounding. Thus, the natural history between dietary carbohydrate measures and CVD risk factors remains uncertain. In addition to error in measuring potential confounding variables, a second limitation we face is potential confounding caused by unrecognized factors. Third, a higher dietary glycemic index is reflective of a dietary pattern that is characterized by higher sugar and soda consumption, lower in fiber rich foods such as whole-grains, fruits and vegetables (McKeown et al., unpublished data). Thus the dietary pattern associated with a high GI is one that encompasses several aspects of diet that may independently affect glucose and insulin. Finally, the FFQ has limitations with respect to the assessment of dietary GI and GL [63], which may result in some misclassification of subjects. This misclassification may have underestimated some associations between aspects of carbohydrates nutrition and CVD risk factors. Despite this potential misclassification, we observed significant associations between dietary GI and several measures of insulin and glucose homeostasis. Strengths of the study include the large sample size and the availability of several CVD risk factors.

CONCLUSION

Based on the current study we confirm that a high dietary GI is associated with surrogate measures of insulin resistance, and other key components of the metabolic syndrome, including elevated blood pressure and triacylglycerol concentrations, and low HDL cholesterol concentrations. While these cross-sectional studies suggest that dietary GI is unfavorably associated with CVD risk factors, the fact that there are so many inconsistencies between intervention and observational studies, raises concerns. Health professionals should concentrate on encouraging the public to eat their recommended intakes of vegetables, legumes, and fruits (which generally have a low GI). In the meantime, evidence from both long-term intervention studies and longitudinal studies on the metabolic consequence of lower GI diets is clearly needed before specific recommendations can be made surrounding the GI.

Acknowledgments

Financial support: Supported in part by the U.S. Department of Agriculture, under agreement No. 58-1950-7-707 and support from the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health (Contract No. N01-HC-25195): Dr Meigs is supported by an American Diabetes Association Career Development Award. Dr. McKeown is supported in part by a scientist development award from the American Heart Association.

REFERENCES

1. de Vegt F, Dekker JM, Ruhe HG, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ. Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. Diabetologia. 1999; 42:926–931. [PubMed: 10491751]
2. Smith NL, Barzilay JI, Shaffer D, Savage PJ, Heckbert SR, Kuller LH, Kronmal RA, Resnick HE, Psaty BM. Fasting and 2-hour postchallenge serum glucose measures and risk of incident cardiovascular events in the elderly: the Cardiovascular Health Study. Arch Intern Med. 2002; 162:209–216. [PubMed: 11802755]
3. Meigs JB, Nathan DM, D'Agostino RB Sr, Wilson PW. Fasting and postchallenge glycemia and cardiovascular disease risk: the Framingham Offspring Study. Diabetes Care. 2002; 25:1845–1850. [PubMed: 12351489]
4. Chiasson JL. The effect of acarbose on insulin sensitivity in subjects with impaired glucose tolerance. Diabet Med. 1996; 13:S23–S24.
5. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA. 2003; 290:486–494. [PubMed: 12876091]
6. National Heart, Lung and Blood Institute. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. U.S. Department of Health and Human Services; Washington DC: 1998.
7. Coniff RF, Shapiro JA, Robbins D, Kleinfield R, Seaton TB, Beisswenger P, McGill JB. Reduction of glycosylated hemoglobin and postprandial hyperglycemia by acarbose in patients with NIDDM. A placebo-controlled dose-comparison study. Diabetes Care. 1995; 18:817–824. [PubMed: 7555508]
8. 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; 34:362–366. [PubMed: 6259925]
9. Wolever TM, Jenkins DJ, Jenkins AL, Josse RG. The glycemic index: methodology and clinical implications. Am J Clin Nutr. 1991; 54:846–854. [PubMed: 1951155]
10. Frost G, Leeds AA, Dore CJ, Madeiros S, Brading S, Dornhorst A. Glycaemic index as a determinant of serum HDL-cholesterol concentration. Lancet. 1999; 353:1045–1048. [PubMed: 10199351]
11. Ford ES, Liu S. Glycemic index and serum high-density lipoprotein cholesterol concentration among us adults. Arch Intern Med. 2001; 161:572–576. [PubMed: 11252117]
12. 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; 58:1472–1478. [PubMed: 15127092]
13. Liu S, Manson JE, Buring JE, Stampfer MJ, Willett WC, Ridker PM. Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity C-reactive protein in middle-aged women. Am J Clin Nutr. 2002; 75:492–498. [PubMed: 11864854]
14. Liu S, Manson JE, Stampfer MJ, Holmes MD, Hu FB, Hankinson SE, Willett WC. Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in post-menopausal women. Am J Clin Nutr. 2001; 73:560–566. [PubMed: 11237932]
15. McKeown NM, Meigs JB, Liu S, Saltzman E, Wilson PW, Jacques PF. Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort. Diabetes Care. 2004; 27:538–546. [PubMed: 14747241]

16. Pawlak DB, Bryson JM, Denyer GS, Brand-Miller JC. High glycemic index starch promotes hypersecretion of insulin and higher body fat in rats without affecting insulin sensitivity. J Nutr. 2001; 131:99–104. [PubMed: 11208944]
17. Byrnes SE, Miller JC, Denyer GS. Amylopectin starch promotes the development of insulin resistance in rats. J Nutr. 1995; 125:1430–1437. [PubMed: 7782895]
18. Rizkalla SW, Taghrid L, Laromiguiere M, Huet D, Boillot J, Rigoir A, Elgrably F, Slama G. Improved plasma glucose control, whole-body glucose utilization, and lipid profile on a lowglycemic index diet in type 2 diabetic men: a randomized controlled trial. Diabetes Care. 2004; 27:1866–1872. [PubMed: 15277409]
19. Goff LM, Frost GS, Hamilton G, Thomas EL, Dhillo WS, Dornhorst A, Bell JD. Carbohydrate-induced manipulation of insulin sensitivity independently of intramyocellular lipids. Br J Nutr. 2003; 89:365–374. [PubMed: 12628032]
20. Frost G, Keogh B, Smith D, Akinsanya K, Leeds A. The effect of low-glycemic carbohydrate on insulin and glucose response in vivo and in vitro in patients with coronary heart disease. Metabolism. 1996; 45:669–672. [PubMed: 8637438]
21. Slabber M, Barnard HC, Kuyl JM, Dannhauser A, Schall R. Effects of a low-insulin-response, energy-restricted diet on weight loss and plasma insulin concentrations in hyperinsulinemic obese females. Am J Clin Nutr. 1994; 60:48–53. [PubMed: 8017337]
22. Dumesnil JG, Turgeon J, Tremblay A, Poirier P, Gilbert M, Gagnon L, St-Pierre S, Garneau C, Lemieux I, Pascot A, Bergeron J, Despres JP. Effect of a low-glycaemic index--low-fat--high protein diet on the atherogenic metabolic risk profile of abdominally obese men. Br J Nutr. 2001; 86:557–568. [PubMed: 11737954]
23. Jarvi AE, Karlstrom BE, Granfeldt YE, Bjorck IE, Asp NG, Vessby BO. Improved glycemic control and lipid profile and normalized fibrinolytic activity on a low-glycemic index diet in type 2 diabetic patients. Diabetes Care. 1999; 22:10–18. [PubMed: 10333897]
24. Wolever TM, Mehling C. High-carbohydrate-low-glycaemic index dietary advice improves glucose disposition index in subjects with impaired glucose tolerance. Br J Nutr. 2002; 87:477–487. [PubMed: 12010586]
25. Sloth B, Krog-Mikkelsen I, Flint A, Tetens I, Bjorck I, Vinoy S, Elmstahl H, Astrup A, Lang V, Raben A. No difference in body weight decrease between a low-glycemic-index and a high-glycemic-index diet but reduced LDL cholesterol after 10-wk ad libitum intake of the low-glycemic-index diet. Am J Clin Nutr. 2004; 80:337–347. [PubMed: 15277154]
26. Salmeron 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; 20:545–550. [PubMed: 9096978]
27. 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 [see comments]. JAMA. 1997; 277:472–477. [PubMed: 9020271]
28. Hodge AM, English DR, O'Dea K, Giles GG. Glycemic index and dietary fiber and the risk of type 2 diabetes. Diabetes Care. 2004; 27:2701–2706. [PubMed: 15505008]
29. 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; 80:348–356. [PubMed: 15277155]
30. 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; 71:921–930. [PubMed: 10731498]
31. 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; 25:1715–1721. [PubMed: 12351467]
32. Dawber T, Meadors G, Moore FJ. Epidemiological approaches to heart disease: The Framingham Study. Am J Public Health. 1951; 41:279–286.
33. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham Offspring Study. Design and preliminary data. Prev Med. 1975; 4:518–525. [PubMed: 1208363]

34. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol. 1992; 135:1114–1126. discussion 1127–1136. [PubMed: 1632423]
35. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol. 1985; 122:51–65. [PubMed: 4014201]
36. Salvini S, Hunter DJ, Sampson L, Stampfer MJ, Colditz GA, Rosner B, Willett WC. Food-based validation of a dietary questionnaire: the effects of week- to-week variation in food consumption. Int J Epidemiol. 1989; 18:858–867. [PubMed: 2621022]
37. Willett W, Stampfer MJ. Total energy intake: Implications for epidemiologic analyses. Am J Epidemiol. 1986; 124:17–27. [PubMed: 3521261]
38. 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. [PubMed: 12081815]
39. Organization WH. WHO Expert Committee on Diabetes mellitus: Second Report. Geneva, World Health Organisation. Tech. Rep. Ser. no. 646:1980.
40. Gutt M, Davis CL, Spitzer SB, Llabre MM, Kumar M, Czarnecki EM, Schneiderman N, Skyler JS, Marks JB. Validation of the insulin sensitivity index (ISI(0,120)): comparison with other measures. Diabetes Res Clin Pract. 2000; 47:177–184. [PubMed: 10741566]
41. McNamara JR, Schaefer EJ. Automated enzymatic standardized lipid analyses for plasma and lipoprotein fractions. Clin Chim Acta. 1987; 166:1–8. [PubMed: 3608193]
42. Warnick GR, Benderson J, Albers JJ. Dextran sulfate-Mg2[H11001] precipitation procedure for quantitation of high-density-lipoprotein cholesterol. Clin Chem. 1982; 28:1379–1388. [PubMed: 7074948]
43. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18:499–502. [PubMed: 4337382]
44. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. Am J Epidemiol. 1979; 110:281–290. [PubMed: 474565]
45. Sahyoun NR, Anderson AL, Kanaya AM, Koh-Banerjee P, Kritchevsky SB, de Rekeneire N, Tylavsky FA, Schwartz AV, Lee JS, Harris TB. Dietary glycemic index and load, measures of glucose metabolism, and body fat distribution in older adults. Am J Clin Nutr. 2005; 82:547–552. [PubMed: 16155266]
46. van Dam RM, Visscher AW, Feskens EJ, Verhoef P, Kromhout D. Dietary glycemic index in relation to metabolic risk factors and incidence of coronary heart disease: the Zutphen Elderly Study. Eur J Clin Nutr. 2000; 54:726–731. [PubMed: 11002385]
47. 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. [PubMed: 16469159]
48. Scaglioni S, Stival G, Giovannini M. Dietary glycemic load, overall glycemic index, and serum insulin concentrations in healthy schoolchildren. Am J Clin Nutr. 2004; 79:339–340. [PubMed: 14749248]
49. Lau C, Faerch K, Glumer C, Tetens I, Pedersen O, Carstensen B, Jorgensen T, Borch-Johnsen K. Dietary glycemic index, glycemic load, fiber, simple sugars, and insulin resistance: the Inter99 study. Diabetes Care. 2005; 28:1397–1403. [PubMed: 15920058]
50. Liese AD, Schulz M, Fang F, Wolever TM, D'Agostino RB Jr, Sparks KC, Mayer-Davis EJ. 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; 28:2832–2838. [PubMed: 16306541]
51. Kiens B, Richter EA. Types of carbohydrate in an ordinary diet affect insulin action and muscle substrates in humans. Am J Clin Nutr. 1996; 63:47–53. [PubMed: 8604670]

52. Bouche C, Rizkalla SW, Luo J, Vidal H, Veronese A, Pacher N, Fouquet C, Lang V, Slama G. Five-week, low-glycemic index diet decreases total fat mass and improves plasma lipid profile in moderately overweight nondiabetic men. Diabetes Care. 2002; 25:822–828. [PubMed: 11978675]

53. Frost GS, Brynes AE, Bovill-Taylor C, Dornhorst A. A prospective randomised trial to determine the efficacy of a low glycaemic index diet given in addition to healthy eating and weight loss advice in patients with coronary heart disease. Eur J Clin Nutr. 2004; 58:121–127. [PubMed: 14679377]

54. Wolever TM. Carbohydrate and the regulation of blood glucose and metabolism. Nutr Rev. 2003; 61:S40–48. [PubMed: 12828191]

55. Parks EJ, Hellerstein MK. Carbohydrate-induced hypertriacylglycerolemia: historical perspective and review of biological mechanisms. Am J Clin Nutr. 2000; 71:412–433. [PubMed: 10648253]

56. Murakami K, Sasaki S, Takahashi Y, Okubo H, Hosoi Y, Horiguchi H, Oguma E, Kayama F. Dietary glycemic index and load in relation to metabolic risk factors in Japanese female farmers with traditional dietary habits. Am J Clin Nutr. 2006; 83:1161–1169. [PubMed: 16685061]

57. Buyken AE, Toeller M, Heitkamp G, Karamanos B, Rottiers R, Muggeo M, Fuller JH. Glycemic index in the diet of European outpatients with type 1 diabetes: relations to glycated hemoglobin and serum lipids. Am J Clin Nutr. 2001; 73:574–581. [PubMed: 11237934]

58. Jenkins DJ, Wolever TM, Kalmusky J, Guidici S, Giordano C, Patten R, Wong GS, Bird JN, Hall M, Buckley G, et al. Lowglycemic index diet in hyperlipidemia: use of traditional starchy foods. Am J Clin Nutr. 1987; 46:66–71. [PubMed: 3300252]

59. Ludwig DS. Dietary glycemic index and obesity. J Nutr. 2000; 130:280S–283S. [PubMed: 10721888]

60. Hare-Bruun H, Flint A, Heitmann BL. Glycemic index and glycemic load in relation to changes in body weight, body fat distribution, and body composition in adult Danes. Am J Clin Nutr. 2006; 84:871–879. quiz 952–873. [PubMed: 17023715]

61. Ma Y, Olendzki B, Chiriboga D, Hebert JR, Li Y, Li W, Campbell M, Gendreau K, Ockene IS. Association between dietary carbohydrates and body weight. Am J Epidemiol. 2005; 161:359–367. [PubMed: 15692080]

62. Willett W, Manson J, Liu S. Glycemic index, glycemic load, and risk of type 2 diabetes. Am J Clin Nutr. 2002; 76:274S–280S. [PubMed: 12081851]

63. Pi-Sunyer FX. Glycemic index and disease. Am J Clin Nutr. 2002; 76:290S–298S. [PubMed: 12081854]

64. Neuhouser ML, Tinker LF, Thomson C, Caan B, Horn LV, Snetselaar L, Parker LM, Patterson RE, Robinson-O'Brien R, Beresford SA, Shikany JM. Development of a glycemic index database for food frequency questionnaires used in epidemiologic studies. J Nutr. 2006; 136:1604–1609. [PubMed: 16702328]

65. Coulston AM, Hollenbeck CB, Swislocki AL, Reaven GM. Effect of source of dietary carbohydrate on plasma glucose and insulin responses to mixed meals in subjects with NIDDM. Diabetes Care. 1987; 10:395–400. [PubMed: 3304893]

66. Hollenbeck CB, Coulston AM. The clinical utility of the glycemic index and its application to mixed meals. Can J Physiol Pharmacol. 1991; 69:100–107. [PubMed: 2036591]

67. Wolever TM, Jenkins DJ. The use of the glycemic index in predicting the blood glucose response to mixed meals. Am J Clin Nutr. 1986; 43:167–172. [PubMed: 3942088]

68. Wolever TM, Yang M, Zeng XY, Atkinson F, Brand-Miller JC. Food glycemic index, as given in glycemic index tables, is a significant determinant of glycemic responses elicited by composite breakfast meals. Am J Clin Nutr. 2006; 83:1306–1312. [PubMed: 16762941]

Table 1

Characteristics of the Framingham Offspring Cohort according to Quintiles of Energy Adjusted Total Carbohydrate Intake and Dietary Glycemic Index[1]

Characteristic	Quintiles of dietary carbohydrate			Quintiles of dietary glycemic index		
	1	3	5	1	3	5
Age (y)	53	53	56	53	54	55
Female (%)	45	56	61	55	51	55
Current smoker (%)	31	15	14	21	17	21
Multivitamin use (%)	27	30	34	34	27	25
Hypertension (%)	20	18	19	16	17	20
Physical Activity Score	35.0	34.6	35.5	35.1	35.3	34.4
Nutrients (daily intakes)[2]						
Total Energy (kcal)	1745	1787	1789	1751	1825	1730
Total carbohydrate (g)	172	225	276	209	222	235
Saturated fat (g)	24	21	15	20	21	19
Polyunsaturated fat (g)	12	11	9	11	11	11
Dietary fiber (g)	13	17	19	17	17	15
Alcohol (g)	11	5	2	7	4	2
Magnesium (mg)	268	286	299	321	285	248
Dietary glycemic index	76	78	79	71	78	84

[1] All lifestyle characteristics were adjusted for age and sex. Reported nutrient and food intakes are adjusted for age, sex and total energy intake. Tests for trend (based on ordinal variables containing median values for each quintile) were all significant ($P < 0.01$), except for hypertension use and physical activity (for total carbohydrate intake), polyunsaturated fat intake (dietary glycemic index), age, waist circumference, physical activity score, percentage female and current smokers and total energy intake (dietary glycemic index).

[2] Geometric mean.

Table 2

Cardiovascular Disease Risk Factors by Energy-Adjusted Quintiles of Total Carbohydrate Intake

Median Intake	Quintile of total carbohydrate intake					*P* for trend[4]
	179	207	227	244	272	
Metabolic Risk Factors						
Waist Circumference (cm) (n = 2939)[1]	94	93	91	90	89	<0.0001
Total Cholesterol (mg/dL) (n = 2,939)[2]	200	202	198	201	202	0.70
LDL Cholesteorl (mg/dL) (n = 2,939)[2]	124	126	123	125	127	0.51
HDL Cholesterol (mg/dL) (n = 2939)[2]	50	48	48	48	46	<0.01
Triglycerides (mg/dL) (n = 2939)[2]	110	123	120	124	127	<0.01
Fasting glucose (mg/dL) (n = 2937)[2]	97	96	96	96	96	0.44
Fasting insulin (μu/mL) (n = 2831)[2]	27.5	27.7	27.2	28.1	29.0	0.06
Insulin Sensitivity Index ($ISI_{0,120}$)[2] (n = 2739)	25.9	26.3	26.3	25.6	25.7	0.47

[3] Excluded individuals on treatment for hypertension.

[1] Adjusted for age, sex, smoking dose, total energy intake, alcohol intake, physical activity score, multivitamin use, treatment for hypertension, %SFA, %PUFA and dietary fiber.

[2] Adjusted for age, sex, body mass index, smoking dose, total energy intake, alcohol intake, physical activity score, multivitamin use, treatment for hypertension, %SFA, %PUFA, dietary fiber and waist circumference.

[4] Test for linear trend used median value in each quintile as a continuous variable in linear regression.

Table 3

Cardiovascular Disease Risk Factors by Energy-Adjusted Quintiles of Dietary GI Intake

Median	Quintile of dietary glycemic index intake					*P* for trend[4]
	72	76	78	80	84	
Metabolic risk factors						
Waist Circumference (cm) (n = 2939)[1]	92	91	91	91	92	0.83
Total Cholesterol (mg/dL) (n = 2,939)[2]	200	201	201	201	200	0.98
LDL Cholesterol (mg/dL) (n = 2,939)[2]	125	125	125	125	124	0.68
HDL Cholesterol (mg/dL) (n = 2939)[2]	49	48	49	48	47	0.003
Triglycerides (mg/dL) (n = 2939)[2]	115	118	120	123	127	<0.001
Fasting glucose (mg/dL) (n = 2937)[2]	96	96	97	97	95	0.86
Fasting insulin (μu/mL) (n = 2831)[2]	26.8	27.9	27.8	28.1	28.9	<0.0001
Insulin Sensitivity Index ($ISI_{0,120}$)[2] (n = 2739)	26.8	26.2	25.9	25.7	25.1	<0.001

[3] Excluded individuals on treatment for hypertension.

[1] Adjusted for age, sex, smoking dose, total energy intake, alcohol intake, physical activity score, multivitamin use, treatment for hypertension, %SFA, %PUFA and dietary fiber.

[2] Adjusted for age, sex, body mass index, smoking dose, total energy intake, alcohol intake, physical activity score, multivitamin use, treatment for hypertension, %SFA, %PUFA, dietary fiber and waist circumference.

[4] Test for linear trend used median value in each quintile as a continuous variable in linear regression.