

Dietary Glycemic Index, Glycemic Load, Fiber, Simple Sugars, and Insulin Resistance

The Inter99 study

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OBJECTIVE — To examine the relationship between daily glycemic index, daily glycemic load, simple sugars, dietary fiber, and the prevalence of a measure of insulin resistance in 30- to 60-year-old nondiabetic Danish men and women.

RESEARCH DESIGN AND METHODS — The Inter99 study is a nonpharmacological intervention study. We used baseline data and examined cross-sectional associations between carbohydrate-related dietary factors and an estimate of insulin resistance in 5,675 subjects at 30–60 years. The dietary intake was estimated from a self-administered food frequency questionnaire, and insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR). Multiple regressions were performed with HOMA-IR as the dependent variable and carbohydrate-related factors as explanatory variables. All models were adjusted for age, sex, smoking, physical activity, total energy intake, BMI, and waist circumference.

RESULTS — Intake of lactose was positively associated with HOMA-IR ($P < 0.0001$), whereas daily glycemic load and intake of glucose, fructose, dietary fiber, total carbohydrate, fruit, and vegetables were inversely associated with HOMA-IR ($P < 0.05$). Intake of dietary fiber explained the associations with daily glycemic load and total carbohydrate and attenuated the association with fruit and vegetables. No significant associations were observed for daily glycemic index or sucrose.

CONCLUSIONS — Habitual intake of diets with a high glycemic index and high glycemic load or diets with a high content of total carbohydrate including simple sugars was not associated with the probability of having insulin resistance. Furthermore, intake of dietary fiber was inversely associated with the probability of having insulin resistance.

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Abbreviations: 2-h PG, 2-h postchallenge plasma glucose; FFQ, food frequency questionnaire; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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The rising prevalence of disorders associated with insulin resistance, including type 2 diabetes, cardiovascular disease, and the metabolic syndrome, is commonly attributed to changes over time in dietary patterns and physical activity levels (1–4). Preventive strategies against these disorders, therefore, often incorporate dietary recommendations. However, only few observational studies have investigated the independent effects of carbohydrate-related dietary factors and obesity on the degree of insulin resistance. The official carbohydrate-related recommendations are high intake of fiber-rich carbohydrates (>55 E% [energy percent] carbohydrate, 25–35 g fiber), low consumption of sugar (<10 E% sugar), and five to six servings of fruit and vegetables per day (5–7). No official recommendations exist regarding the glycemic index and glycemic load of the diet.

One observational study involving 2,834 subjects has examined the glycemic index and glycemic load of the diet in relation to a measure of insulin resistance (8). This study suggests that diets with a high glycemic index and glycemic load are positively associated with the prevalence of insulin resistance. Few observational studies have examined the intake of simple sugars in relation to insulin resistance, and in general no associations have been observed (9,10). Most observational studies have not found significant associations between intake of total carbohydrate and estimates of insulin resistance (8,10–12). Observational studies have consistently suggested that foods rich in different types of dietary fiber are associated with a reduced probability of developing insulin resistance (8,11,13–15).

Whereas observational studies suggest that intake of dietary fiber has an important role in determining insulin resistance, the precise nature of the relationships between glycemic index, glycemic load, simple sugars, total carbohydrate, and insulin resistance is uncertain. The

dietary recommendations given may therefore not be in favor of the prevention of insulin resistance in particular. The influence of carbohydrate-related dietary factors on insulin resistance thus needs further attention.

The purpose of the present study was to examine the relationship between daily glycemic index, daily glycemic load, simple sugars, dietary fiber, and the prevalence of insulin resistance estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) in 30- to 60-year-old nondiabetic Danish men and women participating in the Inter99 study.

RESEARCH DESIGN AND METHODS

This study used baseline data from the Danish population-based Inter99 study, which is an intervention study on diet, physical activity, and smoking with the aim to decrease the incidence of cardiovascular diseases. The overall aim, data collection methods, and nondietary baseline results of the Inter99 study have been reported elsewhere (16,17).

In 1999, the study population comprised 61,301 individuals born in 1939–1940, 1944–1945, 1949–1950, 1954–1955, 1959–1960, 1964–1965, and 1969–1970, resident in 11 municipalities in the southwestern part of Copenhagen County. All individuals were drawn from the Civil Registration System. An age- and sex-stratified random sample of 13,016 individuals was drawn from the study population and 12,934 were eligible for further examination. All these individuals were invited for a health survey at the Research Centre for Prevention and Health in Glostrup. Baseline data were collected in 1999 and 2000, and 6,784 (52.5%) agreed to participate.

We excluded individuals who did not fill in the food frequency questionnaire (FFQ) ($n = 149$) and who had missing information on BMI ($n = 1$), waist circumference measures ($n = 8$), and fasting circulating levels of glucose or insulin ($n = 38$). Participants with hemolyzed fasting serum insulin samples ($n = 518$), previously undiagnosed diabetes (defined as a fasting plasma glucose [FPG] concentration ≥ 7.0 mmol/l or a 2-h postchallenge plasma glucose [2-h PG] concentration ≥ 11.1 mmol/l [18]), or known diabetes were also excluded ($n = 395$). Thus, 5,675 individuals qualified for the present analyses.

All participants gave a written consent before taking part in the Inter99 study. The protocol was in accordance with the Helsinki Declaration and approved by the local ethical committee.

Dietary data

The participants completed a self-administered FFQ during their first visit to the Research Centre. They were asked to report their dietary intake during the month before examination. The FFQ included 198 questions on food items and beverages with additional questions regarding portion sizes of some selected food items. Where no portion size was specified, a standard portion size for women and men, respectively, was used (19). The consumed quantity of food was obtained by multiplying the portion size with the corresponding consumption frequency. All food items in the FFQ were linked to a food item in the Danish Food Composition Databank (20). The amount of macronutrients and simple sugars was calculated as energy percentages (E%). In addition, the intake of total carbohydrate and simple sugars was calculated as grams per day (g/day). The reported intake from dietary fiber, fruit, and vegetables was also estimated in grams per day (g/day). A detailed description of the questionnaire and estimation of the dietary intake of the population is published elsewhere (21).

The glycemic index for carbohydrate-containing food items was estimated using average glycemic index values from the glycemic index table by Foster-Powell et al. (22), with white bread as the reference food. Whenever possible, the method of preparation was taken into account. The daily glycemic index for an individual was calculated by summing the products of the absolute available carbohydrate content in each food item eaten per day and the glycemic index for each food item, divided by the total amount of available carbohydrate eaten (23–25). The daily glycemic load was the sum of available carbohydrates in grams \times glycemic index for each food item, divided by 100 (26). The calculation of daily glycemic index and daily glycemic load was based on 57 different glycemic index values ranging from 16 to 147.

Physical activity and smoking

Information on physical activity and smoking was obtained by a self-administered general questionnaire com-

pleted in advance of the first visit. Based on answers about physical activity level during work and leisure time (27), all individuals were categorized as either being “physically active” or “physically inactive.” The group of “physically inactive” was either not physically active at work and during leisure time, only minor physically active at work (sitting/walking) combined with no activity during leisure time, or physically inactive at work combined with minor activity during leisure time (sitting/walking/cycling). Those categorized as “physically active” did at least minor physical activity both at work and during leisure or did moderate amounts of physical activity at work (walking stairways/heavy work) or during leisure time (sport/competitive sport).

Smoking status was categorized as “daily and occasional smokers,” “ex-smokers,” and “never-smokers.” Missing values of physical activity ($n = 65$) and smoking status ($n = 41$) were classified in separate categories and included in the analyses as such.

Anthropometric data

Waist circumference was measured once with a tape measure under the clothes and midway between the lowest point of the costal margin and highest point of the iliac crest with the participant in the standing position. Weight was measured to the nearest 0.1 kg using either an electronic or mechanical standard weight (Seca 707, Seca 710) with the participant wearing light indoor clothes without shoes. Height was measured to the nearest 0.5 cm with the participant wearing no shoes. BMI was calculated as weight in kilograms divided by the square of height in meters.

Blood samples

A standard 75-g oral glucose tolerance test was undertaken in the fasting state in participants without known diabetes. Blood samples for analysis of venous plasma glucose were taken before glucose ingestion and after 120 min in a tube containing sodium fluoride. The blood samples were put on ice immediately and centrifuged within 60 min in a cool centrifuge. The plasma glucose was analyzed using the hexokinase/G6P-DH technique (Boehringer Mannheim, Mannheim, Germany). Blood samples for analysis of serum insulin were also taken before glucose ingestion. Serum-specific insulin was analyzed using fluoro-immunoassay

Table 1—Characteristics of 5,675 nondiabetic subjects in the Inter99 study grouped into quartiles of HOMA-IR

	Quartiles				P*
	0.12 to <0.79	0.79 to <1.15	1.15 to <1.76	1.76 to 14.74	
Participants (n)	1,425	1,418	1,421	1,411	
Men (%)	41.7	45.9	47.9	57.8	0.000
Physically inactive (%)	29.6	30.1	37.8	40.2	0.000
Smokers (%)	47.3	42.5	37.0	30.5	0.000
Normal glucose tolerant (%)†	91.0	85.8	80.0	58.8	0.000
Impaired fasting glucose (%)†	01.8	06.1	09.9	17.7	0.000
Impaired glucose tolerant (%)†	07.2	08.1	10.2	23.5	0.000
Age (years)	45.1 (40.0–50.1)	45.0 (39.9–50.2)	45.0 (40.0–50.2)	45.1 (40.0–50.3)	0.067
BMI (kg/m ²)	23.3 (21.5–25.2)	24.7 (22.8–26.8)	26.1 (23.9–28.5)	28.9 (26.0–32.2)	0.000
Waist (cm)	78.0 (71.0–86.0)	83.0 (75.0–91.0)	87.0 (78.0–95.0)	95.0 (87.0–104.0)	0.000
Energy (kcal)	2,448 (1,965–3,042)	2,359 (1,873–2,983)	2,432 (1,925–3,037)	2,377 (1,918–2,976)	0.000
Fat (E%)	32.6 (27.5–39.0)	33.3 (28.3–39.7)	33.6 (28.0–40.2)	33.3 (28.2–40.2)	0.454
Protein (E%)	14.3 (12.7–16.3)	14.5 (12.8–16.4)	14.5 (12.8–16.4)	14.8 (12.9–16.7)	0.001
Alcohol (E%)	02.9 (01.1–06.5)	02.7 (01.0–05.5)	02.6 (00.9–05.4)	02.5 (00.8–05.7)	0.000
Carbohydrate (E%)	47.1 (40.7–53.1)	46.7 (40.8–52.4)	46.9 (40.4–52.4)	46.2 (39.9–51.9)	0.986
Carbohydrate (g/day)	275 (220–354)	270 (209–348)	271 (214–339)	270 (214–337)	0.000
Sucrose (g/day)	31.7 (18.9–48.6)	31.4 (18.9–48.9)	30.6 (19.1–48.3)	29.3 (18.3–48.0)	0.044
Glucose (g/day)	10.6 (5.9–19.2)	9.6 (5.7–18.1)	9.3 (5.5–17.4)	9.2 (5.3–17.3)	0.063
Fructose (g/day)	9.2 (5.0–18.3)	8.6 (4.7–17.2)	8.4 (4.7–16.5)	8.1 (4.4–16.3)	0.065
Lactose (g/day)	11.3 (5.3–22.3)	11.5 (5.1–23.1)	11.9 (5.7–23.3)	12.1 (5.6–25.6)	0.004

Data are medians and interquartile range (25th to 75th percentile) unless otherwise indicated. *P values for trend are analyzed in regression models with HOMA-IR as the continuous explanatory variable and sex as the categorical explanatory variable. †Percentages are based on individuals where both fasting and 2-h plasma glucose values were available.

technique (Code Number K6219; Dako Diagnostics, Ely, U.K.).

Classification of glucose tolerance status

By use of the FPG and the 2-h PG values from the oral glucose tolerance test, the participants were classified into categories of glucose tolerance according to the 1999 World Health Organization criteria (18). Normal glucose tolerance was defined as an FPG concentration <6.1 mmol/l and a 2-h PG <7.8 mmol/l. Impaired fasting glycemia was defined as FPG between 6.1 and 6.9 mmol/l and a 2-h PG <7.8 mmol/l, and impaired glucose tolerance was defined as FPG <7.0 mmol/l and 2-h PG between 7.8 and 11.0 mmol/l.

Assessment of insulin resistance

HOMA-IR was used to estimate the degree of insulin resistance. HOMA-IR was estimated from fasting plasma glucose and serum insulin concentrations using the following:

$$\text{HOMA-IR} = (\text{fasting plasma glucose [mmol/l]} \times \text{fasting serum insulin [mU/l]}) / 22.5 \text{ (28,29).}$$

Statistical analysis

Baseline characteristics of the participants were computed across quartiles of the HOMA-IR. Linear regression was used to test for linear trend between the explanatory variable HOMA-IR and each selected continuous variable (age, BMI, waist circumference, intake of energy, fat, protein, alcohol, carbohydrate, and simple sugars). For categorical variables (sex, physical activity, smoking, and glucose tolerance status), logistic regression was applied.

To examine the relation between the explanatory carbohydrate-related dietary factors and the dependent variable, HOMA-IR simple (univariate) and multiple linear regression models were used. The assumption of normality of the residuals was not fulfilled for the HOMA-IR. Transformation with the natural logarithm rendered the residuals normally distributed, and analyses were performed on the transformed HOMA-IR variable. As a consequence of the log-transformation of the HOMA-IR, the associations reported are calculated by taking the exponential of the estimated coefficients estimated from the regression analysis for

each carbohydrate-related variable. The reported associations with the carbohydrate-related variables are relative changes in the continuous variable HOMA-IR expressed as HOMA ratios with corresponding 95% CIs. The changes in HOMA-IR are thus a result of a specific increase in the carbohydrate-related factor under study.

Sex, age, BMI, waist circumference, smoking, and physical activity were included in the multiple regression models as confounders. Furthermore, adjustment for total energy intake was made in all multiple analyses. In this way, the increase in the carbohydrate-related factor under study is at the expense of the same amount of energy from other unspecified dietary factors.

All analyses were conducted using PROC GENMOD from the SAS 9.1 (SAS Institute, Cary, NC), and a P value of 0.05 was considered significant.

RESULTS— Characteristics of the study population are given in Table 1. The highest quartile of HOMA-IR included a higher fraction of men and physically inactive individuals as well as a higher frac-

Table 2—Associations between carbohydrate-related dietary factors and HOMA-IR in 5,675 nondiabetic subjects in the Inter99 cohort

	Dependent variable			
	HOMA ratio* (95% CI)	P	HOMA ratio† (95% CI)	P
Explanatory variables				
Daily glycemic index (per 10 units)	1.02 (0.99–1.04)	0.230	1.01 (0.99–1.03)	0.315
Daily glycemic load (per 30 units)	0.99 (0.99–1.00)	0.021	0.99 (0.99–1.00)	0.047
Carbohydrate (per 3 E%)	1.00 (0.99–1.00)	0.058	0.99 (0.99–1.00)	0.011
Sucrose (per 1 E%)	1.00 (0.98–1.00)	0.147	1.00 (1.00–1.00)	0.444
Glucose (per 1 E%)	0.99 (0.98–1.00)	0.020	0.98 (0.97–0.99)	0.001
Fructose (per 1 E%)	0.99 (0.98–1.00)	0.020	0.98 (0.97–0.99)	0.002
Lactose (per 1 E%)	1.02 (1.01–1.03)	0.000	1.02 (1.01–1.02)	0.000
Dietary fiber (per 10 g/day)	0.97 (0.96–0.99)	0.000	0.97 (0.96–0.99)	0.001
Fruit and vegetables (per 100 g/day)	0.99 (0.98–0.99)	0.000	0.99 (0.98–0.99)	0.000

*Univariate analyses. †Adjusted for age, sex, smoking, physical activity, total energy intake, BMI, and waist circumference. Values >1 indicate a positive association, and values <1 indicate an inverse association.

tion of individuals with impaired fasting glycemia and impaired glucose tolerance, but a lower fraction of smokers and individuals with normal glucose tolerance compared with the other quartiles. Individuals in the highest quartile of HOMA-IR had higher BMI, waist circumference, and intake of protein (E%) and lactose (g/day), but lower intake of energy (kcal), alcohol (E%), carbohydrate (g/day), and sucrose (g/day). The large data sample may explain why some of the very small absolute differences across the quartiles of HOMA-IR result in very small *P* values. No difference in age and carbohydrate (E%) and fat (E%) or glucose (g/day) and fructose (g/day) intake across the quartiles of HOMA-IR was found.

The associations between the different carbohydrate-related dietary factors and HOMA-IR are presented in Table 2. Intake of lactose was positively associated with HOMA-IR both in the univariate analyses and after adjustment for potential confounders. The increase in daily glycemic load and in the intake of glucose, fructose, dietary fiber, fruit, and vegetables was inversely associated with HOMA-IR both before and after adjustment for potential confounders. Carbohydrate was inversely associated with HOMA-IR after adjustment for potential confounders. No associations were observed for daily glycemic index or sucrose.

In addition to the results presented in Table 2, a correlation between daily glycemic load and carbohydrate (g/day) was observed ($r^2 = 0.97799$). Furthermore, the multiple regression models with daily glycemic index, daily glycemic load, carbohydrate, fruit, and vegetables were ad-

justed for dietary fiber intake. Inclusion of dietary fiber intake in the model rendered the effects of daily glycemic load (*P* = 0.51) and carbohydrate (*P* = 0.41) insignificant. It attenuated the association with fruit and vegetables (*P* = 0.02), but did not change the association observed for daily glycemic index.

CONCLUSIONS— We found no associations between daily glycemic index, daily glycemic load, and insulin resistance after adjustment for confounders including dietary fiber. Based on evidence from a recent observational study involving 2,834 subjects (8), we had expected to find an inverse association between daily glycemic index, daily glycemic load, and insulin resistance. However, within the few observational studies published examining associations between glycemic index, glycemic load, and risk of type 2 diabetes (23,24,26,30), inconsistency also exists. The inconsistency may be due to inaccurate estimation of daily glycemic index (31). The glycemic effect of foods in an individual varies depending on individual food composition, preparation methods, and the composition of the total meal. It is not possible to register these factors in an FFQ. Furthermore, the available carbohydrate content in the same kind of food can vary for instance according to country and season, which also may contribute to imprecise estimates of daily glycemic index. It is therefore questionable whether the estimated daily glycemic index values reported in observational studies reflect the physiological responses measured in experimental meal studies of glucose metabolism (9,32,33). It may

thus be inappropriate to examine associations between daily glycemic index and disease in large population-based surveys, where the dietary data collection methods have not been developed with the purpose of glycemic index estimation. More valid data should be available before we can suggest that values regarding daily glycemic index can be recommended. With respect to daily glycemic load, the present study indicates, because of the high correlation between daily glycemic load and carbohydrate (g/day), that an association observed between intake of carbohydrates and HOMA-IR may reflect an association between daily glycemic load and HOMA-IR. This was evident from the analysis in the present study. Development of recommendations regarding daily glycemic load may therefore not be as important as recommendations for daily glycemic index, since recommendations for total carbohydrate intake to a large extent will cover values recommended for daily glycemic load.

With respect to simple sugars, the present study suggests that intake of total sucrose does not affect insulin sensitivity as estimated by the HOMA-IR method. This is consistent with findings from another observational study involving 173 subjects (10). The lack of association between intake of total sucrose and HOMA-IR is probably caused by the fact that sugar (glycemic index_{sucrose} = 68) is often ingested as part of mixed meals, where the glycemic index of the meal may be relatively high because of the starch content (glycemic index_{white bread} = 100). Therefore, intake of sucrose rarely results in a high glycemic postprandial response

(25,34). The association between dietary intake of total sucrose and HOMA-IR may also have been underestimated, because the participants' glucose tolerance status was not taken into consideration (9).

No studies have examined the association between intake of lactose and HOMA-IR. A protective effect of lactose on glucose metabolism was expected, because dietary lactose elicits a relatively low glycemic response in clinical studies (34). The adverse effect on insulin sensitivity may, however, be a result of the relationship between milk products and lactose, because milk and dairy products comprise not only lactose but also saturated fat, which is strongly associated with increased insulin resistance (35,36). Adjustment for saturated fat did not, however, change the observed significant association between lactose and HOMA-IR in the present study (data not shown). It is therefore still questionable whether lactose is associated with higher HOMA-IR values in itself or whether the association is due to other confounding factors.

No other studies have analyzed the association between intake of glucose or fructose and insulin resistance in a cross-sectional setting. Fructose has a low glycemic index (22), which physiologically supports the observed inverse association for fructose in the present study. Furthermore, both glucose and fructose are present in fruits and vegetables (37). Accordingly, beneficial components in fruit and vegetables (e.g., fiber) could be responsible for the observed inverse associations with fructose and glucose. This reasoning is supported by the inverse association observed for fruit and vegetables, which to some extent was explained by intake of dietary fiber in this study.

Any change in the carbohydrate composition of the diet will produce reciprocal changes in other parts of the diet. A concomitant decrease in fat consumption may therefore explain the inverse association between total carbohydrate intake and insulin resistance observed from the multiple regression analysis, as well as it explains findings from other studies (11). The additional analyses with adjustment for dietary fiber indicate, however, that the inverse association between carbohydrate and HOMA-IR is likely to be caused by a concomitant intake of dietary fiber, which is in agreement with the inverse association for dietary fiber in the present

study. Other cross-sectional (8,11,13,14) and prospective studies (12,15), which have used various measures of insulin resistance, support our finding regarding dietary fiber. Only one study has not observed any association between intake of dietary fiber and insulin resistance (10). Taken together, our study and most other studies support that high-carbohydrate diets do not adversely affect insulin sensitivity.

Studies examining dietary intake in relation to insulin resistance are difficult to compare. It must be considered that a gene-environment interaction may be of importance (38,39). This study and other studies analyzing associations between carbohydrate-related dietary factors and estimates of insulin resistance have not taken into account the genetic predisposition for obesity and type 2 diabetes. However, genetic heterogeneity likely affects the associations between habitual dietary intake and insulin resistance. As more genetic information emerges on insulin resistance, this new information should be incorporated into future nutritional studies.

Furthermore, several methodological issues may affect the results. First, the FFQ used in the Inter99 study did not include specific questions regarding intake of soft drinks, juice, selected sweet products, and some of the relatively new products, such as low-fat and fructose-rich products. In addition, only a limited number of questions regarding fruit and vegetables were included. This may all together have resulted in an underestimation in the intake of macronutrients from these products. We assume, however, that these factors have not affected the direction of the observed associations due to the systematic properties of these errors. Second, selection bias may have occurred. Individuals who were obese and overweight or had an unhealthy lifestyle were more likely to participate in the intervention program for lifestyle modification than those who considered themselves living relatively healthy (17). Hence, the precision (interquartile range) of the observed associations in the present study may have been affected, but the direction of the associations will not be any different for individuals not participating in the study. Finally, we recognize that recall bias is an issue for which to consider using an FFQ (40). However, as a study of the relation between insulin resistance and intake of carbohydrate-related fac-

tors, our study has two strengths: 1) We investigated the associations in a relatively large population and used an FFQ, which is a feasible way to evaluate dietary intakes in large populations (41). The FFQ is designed to minimize random within-person variation by assessing the average long-term diet (41), and this is important when dietary data are used to assess diet-disease associations. 2) We analyzed the carbohydrate-related dietary factors and the response variable for insulin resistance as continuous variables in an attempt to minimize the otherwise population-specific effect that do result in studies analyzing the variables as categorical variables.

The present study does not support the hypothesis that habitual intake of diets with a high glycemic index and high glycemic load is associated with increased probability of having insulin resistance as estimated by HOMA-IR. Furthermore, our findings indicate that intake of simple sugars in itself is not associated with an increased probability of having insulin resistance. Intake of dietary fiber explained the observed inverse associations with daily glycemic load and carbohydrates and attenuated the association with fruit and vegetables. These data are consistent with the hypothesis that intake of dietary fiber independent of obesity is important in prevention of insulin resistance. Our findings therefore support the existing recommendations regarding increased intakes of fiber-rich carbohydrates, also with respect to prevention of insulin resistance.

Our findings with respect to the daily glycemic index, daily glycemic load, and simple sugars should be confirmed in large observational prospective studies before any recommendations can be formulated. Future studies should furthermore consider gene-environment interactions.

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APPENDIX— The Inter99 Steering Committee includes the following: Torben Jørgensen (Principal Investigator), Knut Borch-Johnsen (Principal Investigator, diabetes part), Troels Thomsen, and Hans Ibsen.

References

- King H, Aubert RE, Herman WH: Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care* 21:1414–1431, 1998
- Drivsholm T, Ibsen H, Schroll M, Davidsson M, Borch-Johnsen K: Increasing prevalence of diabetes mellitus and impaired glucose tolerance among 60-year-old Danes. *Diabet Med* 18:126–132, 2001
- Dunstan DW, Zimmet PZ, Welborn TA, De-Court, Cameron AJ, Sicree RA, Dwyer T, Colagiuri S, Jolley D, Knuiman M, Atkins R, Shaw JE: The rising prevalence of diabetes and impaired glucose tolerance: the Australian Diabetes, Obesity and Lifestyle Study. *Diabetes Care* 25:829–834, 2002
- Watkins LO: Epidemiology and burden of cardiovascular disease. *Clin Cardiol* 27: 2–6, 2004
- Alexander J, Andersen SA, Aro A, Becker W, Fogelholm M, Lyhne N, Meltzer HM, Pedersen AN, Pórsdóttir I, Pedersen JI: Planning diets for groups. In *Nordic Nutrient Recommendations 2004. Integrating Nutrition and Physical Activity*. 4th ed. Copenhagen, Denmark, Nordic Council of Ministers, 2005, p. 13–22
- Dietary Guidelines for Americans 2005: Key Recommendations for the General Population (online), 2005. Available from <http://www.health.gov/dietaryguidelines/dga2005/recommendations.htm>. Accessed 13 January 2005
- Trolle E, Fagt S, Ovesen L: *Fruit and Vegetables: Recommended Intakes*. Søborg, Denmark, The Danish Ministry of Food, Agriculture and Fisheries, 1998
- McKeown NM, Meigs JB, Liu S, Saltzman E, Wilson PWF, Jacques PF: Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort. *Diabetes Care* 27:538–546, 2004
- Daly M: Sugars, insulin sensitivity, and the postprandial state. *Am J Clin Nutr* 78 (Suppl. 4):865S–872S, 2003
- Sevak L, McKeigue PM, Marmot MG: Relationship of hyperinsulinemia to dietary intake in south Asian and European men. *Am J Clin Nutr* 59:1069–1074, 1994
- Feskens EJ, Loeber JG, Kromhout D: Diet and physical activity as determinants of hyperinsulinemia: the Zutphen Elderly Study. *Am J Epidemiol* 140:350–360, 1994
- Marshall JA, Bessesen DH, Hamman RF: High saturated fat and low starch and fiber are associated with hyperinsulinaemia in a non-diabetic population: the San Luis Valley Diabetes Study. *Diabetologia* 40: 430–438, 1997
- Lovejoy J, DiGirolamo M: Habitual dietary intake and insulin sensitivity in lean and obese adults. *Am J Clin Nutr* 55:1174–1179, 1992
- Liese AD, Roach AK, Sparks KC, Marquart L, D'Agostino RB Jr, Mayer-Davis EJ: Whole-grain intake and insulin sensitivity: the Insulin Resistance Atherosclerosis Study. *Am J Clin Nutr* 78:965–971, 2003
- Ludwig DS, Pereira MA, Kroenke CH, Hilner JE, Van Horn L, Slattery ML, Jacobs DR: Dietary fiber, weight gain, and cardiovascular disease risk factors in young adults. *JAMA* 282:1539–1546, 1999
- Glümer C, Jørgensen T, Borch-Johnsen K: Prevalences of diabetes and impaired glucose regulation in a Danish population: the Inter99 study. *Diabetes Care* 26:2335–2340, 2003
- Jørgensen T, Borch-Johnsen K, Thomsen TF, Ibsen H, Glümer C, Pisinger C: A randomized non-pharmacological intervention study for prevention of ischaemic heart disease: baseline results Inter99. *Eur J Cardiovasc Prev Rehabil* 10:377–386, 2003
- World Health Organization: *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva, World Health Org., 1999
- Haraldsdóttir J, Seppänen R, Steinrímsdóttir L, Tryggv K, Hagman U: *Portion Sizes: Nordic Standard Portions of Food and Foodstuffs*. Copenhagen, Denmark, Nordic Council and Council of Ministers, 1998
- Møller A, Saxholt E, Christensen AT, Hartkopp HB: Danish Food Composition Databank version 5.0 (Fødevaredatabanken V 5.0). Available from http://www.foodcomp.dk/fvdb_default.htm. Danish Institute for Food and Veterinary Research, Ministry of Food, Fisheries and Agriculture 2002. Accessed 1 October 2002
- Lau C, Færch K, Glümer C, Toft U, Tetens I, Borch-Johnsen K, Jørgensen T: Evaluation of dietary intake in a Danish population: the Inter99 study. *Scan J Nutr* 48: 136–143, 2004
- Foster-Powell K, Holt SHA, Brand-Miller JC: International table of glycemic index and glycemic load values: 2002. *Am J Clin Nutr* 76:5–56, 2002
- 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* 20:545–550, 1997
- 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* 277:472–477, 1997
- Wolever TM, Nguyen PM, Chiasson JL, Hunt JA, Josse RG, Palmason C, Rodger NW, Ross SA, Ryan EA, Tan MH: Determinants of diet glycemic index calculated retrospectively from diet records of 342 individuals with non-insulin-dependent diabetes mellitus. *Am J Clin Nutr* 59:1265–1269, 1994
- Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, Hennekens CH, Manson JE: A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr* 71:1455–1461, 2000
- Saltin B, Grimby G: Physiological analysis of middle-aged and old former athletes: comparison with still active athletes of the same ages. *Circulation* 38:1104–1115, 1968
- Albareda M, Rodriguez-Espinosa J, Murugo M, de Leiva A, Corcoy R: Assessment of insulin sensitivity and beta-cell function from measurements in the fasting state and during an oral glucose tolerance test. *Diabetologia* 43:1507–1511, 2000
- Tripathy D, Carlsson M, Almgren P, Iso-maa B, Taskinen M, Tuomi T, Groop LC: Insulin secretion and insulin sensitivity in relation to glucose tolerance: lessons from the Botnia Study. *Diabetes* 49:975–980, 2000
- 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* 71:921–930, 2000
- Pi-Sunyer FX: Glycemic index and disease. *Am J Clin Nutr* 76:290S–298S, 2002
- Willett W, Manson J, Liu SM: Glycemic index, glycemic load, and risk of type 2 diabetes. *Am J Clin Nutr* 76 (Suppl.): 274S–280S, 2002
- Ludwig DDS: The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA* 287:2414–2423, 2002
- Wolever TM, Miller JB: Sugars and blood glucose control. *Am J Clin Nutr* 62 (Suppl. 1):212S–221S, 1995
- Storlien LH, Kriketos AD, Jenkins AB, Baur LA, Pan DA, Tapsell LC, Calvert GD: Does dietary fat influence insulin action?

- Ann N Y Acad Sci* 827:287–301, 1997
36. Lovejoy JC: The influence of dietary fat on insulin resistance. *Curr Diab Rep* 2:435–440, 2002
 37. Gray J: *Carbohydrates: Nutritional and Health Aspects*. Astrup A, Eds. Brussels, Belgium, International Life Sciences Institute, 2003
 38. McCarthy MI: Progress in defining the molecular basis of type 2 diabetes mellitus through susceptibility-gene identification. *Hum Mol Genet* 13:33R–41R, 2004
 39. Snyder EE, Walts B, Pérusse L, Hagnon YC, Eisinger SJ, Rankinen T, Bouchard C: The human obesity gene map: the 2003 update. *Obes Res* 12:369–439, 2004
 40. Dwyer J: Dietary assessment. In *Modern Nutrition in Health and Disease*. Shills ME, Olson JA, Shike M, Ross AC, Eds. Philadelphia, Lippincott Williams and Wilkins, 1999, p. 937–959
 41. Gibson RS: Food consumption of individuals. In *Principles of Nutritional Assessment*. New York, Oxford University Press, 1990, p. 37–54