



Minna Similä

Glycemic Index in Epidemiologic Study of Type 2 Diabetes

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ACADEMIC DISSERTATION

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Abstract

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Type 2 diabetes prevalence and costs related to this are on the rise. The carbohydrates inducing a rapid postprandial elevation in blood glucose have been suggested to increase diabetes risk. Glycemic index (GI) classifies foods based on their postprandial blood glucose response compared with the response of reference food (glucose solution or white bread). Glycemic load (GL) is a measure of both quantity and quality of carbohydrates.

The aim here was to investigate the associations between dietary GI, GL, and intake of high-, medium-, and low-GI carbohydrates and the risk of type 2 diabetes and to evaluate the applicability of GI to epidemiologic studies.

In a postprandial study (n=11), variations in glycemic responses and GI values of foods were examined and the effects of methodologic choices on variation compared (capillary and venous sampling, white wheat bread and glucose solution as reference foods, and repeating the reference measurement). Both within-subject and between-subject variation was considerable. The variation was smaller when capillary samples were used and when the reference food was tested at least twice.

The GI database was compiled for dietary GI and GL calculation for the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study participants. The GI values were obtained from the GI measurement laboratory of the National Institute for Health and Welfare and from publications meeting the methodologic criteria.

The ATBC Study cohort comprised 25 943 male smokers, aged 50-69 years, among whom 1098 diabetes cases were identified from the national drug reimbursement register during a 12-year follow-up. Diet was assessed by a validated food frequency questionnaire. The relative risks (RRs) and confidence intervals (CIs) for diabetes were analyzed using Cox proportional hazard modeling, and multivariate nutrient density models were applied to examine the substitutions of macronutrients.

Dietary GI and GL were not associated with diabetes risk: RR (and 95% CI) for the highest versus the lowest quintile in the multivariate model was 0.87 (0.71, 1.07) for GI and 0.88 (0.65, 1.17) for GL. Substitution of low-GI ($GI \leq 55$) carbohydrates for an isoenergetic amount of high-GI ($GI \geq 70$) carbohydrates or low-GI carbohydrates for medium-GI ($55 < GI < 70$) carbohydrates was not associated with diabetes risk. Substitution of medium-GI carbohydrates for high-GI carbohydrates was inversely associated with diabetes risk (RR 0.75 (0.59, 0.96)).

The total carbohydrate intake (as percentage of total energy intake, E%) was inversely associated with the incidence of diabetes, RR 0.78 (0.64, 0.94). Moreover,

a higher intake of medium-GI carbohydrates was associated with a lower diabetes risk, RR 0.69 (0.57, 0.84). Intake of neither high- nor low-GI carbohydrates was associated with diabetes risk.

Total carbohydrate substitutions for total fat and protein were inversely associated with diabetes risk, the multivariate RRs for 2 E% substitution were 0.96 (0.94, 0.99) and 0.85 (0.80, 0.90), respectively. Carbohydrate substitution for saturated plus trans fatty acids, but not unsaturated fatty acids, was inversely associated with diabetes risk. Carbohydrate substitution for total, meat, or milk protein was associated inversely with diabetes risk, independently from GI.

Within-subject and between-subject variations in measured food GI were considerable. In addition, the same total dietary GI and GL result from several different food combinations, thus reflecting different properties of the diet, not only the carbohydrate quality. These factors limit the possibilities of epidemiologic studies to observe reliable associations between glycemic effects of diet and disease risk. In this study population, GI was not associated with diabetes risk. A higher percentage of carbohydrate intake was associated with decreased diabetes risk; the risk was lowered when fat or protein was replaced with carbohydrates.

Key words: carbohydrates, cohort, epidemiology, glycemic index, glycemic load, type 2 diabetes

Tiivistelmä

Minna Similä. Glycemic Index in Epidemiologic Study of Type 2 Diabetes. [Glykeeminen indeksi tyypin 2 diabeteksen epidemiologisessa tutkimuksessa]. National institute for Health and Welfare (THL), Tutkimus 76. 130 sivua. Helsinki 2012. ISBN 978-952-245-612-0 (painettu), ISBN 978-952-245-613-7 (pdf).

Tyypin 2 diabetes on kasvava kansanterveysongelma. On esitetty, että ne hiilihydraatit, jotka suurentavat aterianjälkeistä veren glukoosipitoisuutta nopeasti, lisäävät diabeteksen riskiä. Glykeeminen indeksi (GI) kuvaa ruoan aiheuttamaa aterianjälkeistä glukoosivastetta suhteessa vertailuelintarvikkeen (glukoosiliuos tai vehnäleipä) glukoosivasteeseen. Glykeeminen kuorma (GL) kuvaa sekä hiilihydraattien laatua että määrää.

Tutkimuksen tavoite oli selvittää ruokavalion GI:n, GL:n sekä suuren, keskisuuren ja pienen GI:n hiilihydraattien saannin yhteyttä tyypin 2 diabeteksen riskiin sekä tutkia GI:n soveltuvuutta epidemiologiseen tutkimukseen.

Ateriakokeessa (n=11) tutkittiin ruokien glukoosivasteiden ja GI-arvojen vaihtelua sekä verrattiin menetelmällisten valintojen vaikutusta vaihteluun (kapillaari- vs laskimonäyte, glukoosiliuos vs vehnäleipä vertailuelintarvikkeena sekä vertailuelintarvikkeen toistomittaus). Sekä henkilöidensisäinen että -välinen vaihtelu oli huomattava. Vaihtelu oli pienempi kapillaarinäytteestä sekä silloin, kun vertailuruoka testattiin vähintään kaksi kertaa.

Syövänehkäisyttutkimuksen (SETTI) osallistujien ruokavalion GI:n ja GL:n laskemiseksi koottiin GI-arvot tutkittavien käyttämille ruoille. GI-arvot saatiin Terveyden ja hyvinvoinnin laitoksessa suomalaisille elintarvikkeille tehdyistä määrittelyksistä ja kansainvälisistä menetelmälliset vaatimukset täyttävistä julkaisuista.

Ruokavalion GI:n, GL:n ja hiilihydraattien saannin yhteyttä diabeteksen riskiin tutkittiin SETTI-kohortissa, joka koostui 25 943 tupakoivasta, 50-69-vuotiaasta suomalaismiehestä. Ruoankäyttötiedot kerättiin annoskuvakirja-avusteisella, validoidulla kyselylomakkeella. Diabetestapaukset saatiin Kansaneläkelaitoksen erityiskorvattavien lääkkeiden rekisteristä, yhteensä 1098 tapausta 12 vuoden seuranta-aikana. Diabeteksen riskiä tutkittiin verrannollisten riskitiheyksien mallilla (Coxin regressio) ja monimuuttujaravintotiheysmallia käytettiin tutkittaessa energiaravintoaineiden korvaamista toisillaan.

Ruokavalion GI ja GL eivät olleet yhteydessä diabeteksen riskiin: suhtellinen riski (RR) ja 95% luottamusväli (CI) GI:n ylimmässä kvintiilissä verrattuna alimpaan kvintiiliin oli 0.87 (0.71, 1.07) ja GL:n 0.88 (0.65, 1.17). Suuren GI:n ($GI \geq 70$) tai keskisuuren GI:n ($55 < GI < 70$) hiilihydraattien korvaaminen pienen GI:n ($GI \leq 55$) hiilihydraateilla ei ollut yhteydessä diabetesriskiin. Suuren GI:n hiilihydraattien korvaaminen keskisuuren GI:n hiilihydraateilla oli käänteisessä yhteydessä diabeteksen ilmaantuvuuteen, RR 0.75 (0.59, 0.96).

Hiilihydraattien kokonaissaanti (prosentteina kokonaisenergian saannista, E%) oli käänteisessä yhteydessä diabetesriskiin, RR 0.78 (0.64, 0.94), samoin keskiuuren GI:n hiilihydraattien saanti, RR 0.69 (0.57, 0.84). Suuren GI:n ja pienen GI:n hiilihydraattien saanti ei ollut yhteydessä diabeteksen ilmaantuvuuteen.

Diabetesriski pieneni, kun hiilihydraatit korvasivat 2 E% rasvasta, RR 0.96 (0.94, 0.99), tai proteiinista, RR 0.85 (0.80, 0.90). Diabetesriski pieneni hiilihydraattien korvauksella tyydyttyneitä- ja transrasvahappoja. Proteiinin sekä liha- ja maitoproteiinin korvaaminen hiilihydraateilla oli yhteydessä pienempään diabetesriskiin riippumatta hiilihydraattien GI:stä.

Ruuan GI-mittaustuloksen henkilöidensisäinen ja -välinen vaihtelu on suuri. Lisäksi sama ruokavalion kokonais-GI ja GL voivat muodostua hyvin erilaisten ruokien yhdistelmästä ja siten heijastaa ruokavalion muitakin ominaisuuksia kuin hiilihydraattien laatua. Nämä tekijät heikentävät epidemiologisen tutkimuksen mahdollisuuksia havaita ruokavalion glykeemisen vaikutuksen ja tautiriskin välisiä yhteyksiä. Tässä aineistossa GI ei ollut yhteydessä diabeteksen ilmaantuvuuteen. Suurempi hiilihydraattien saanti oli yhteydessä pienempään diabetesriskiin ja diabetesriski oli pienempi, kun hiilihydraatit korvasivat rasvaa tai proteiinia.

Avainsanat: epidemiologia, glykeeminen indeksi, glykeeminen kuorma, hiilihydraatit, kohortti, tyypin 2 diabetes

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List of original publications

This thesis is based on the following original articles referred to in the text by their Roman numerals.

- I Hätönen KA, Similä ME, Virtamo JR, Eriksson JG, Hannila ML, Sinkko HK, Sundvall JE, Mykkänen HM, Valsta LM. Methodologic considerations in the measurement of glycemic index: glycemic response to rye bread, oatmeal porridge, and mashed potato. *Am J Clin Nutr* 2006;84:1055-61.
- II Similä ME, Valsta LM, Virtanen MJ, Hätönen KA, Virtamo J. Glycaemic index database for the epidemiological Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study. *Br J Nutr* 2009;101:1400-5.
- III Similä ME, Valsta LM, Kontto JP, Albanes D, Virtamo J. Low-, medium- and high-glycaemic index carbohydrates and risk of type 2 diabetes in men. *Br J Nutr* 2011;105:1258-64.
- IV Similä ME, Kontto JP, Valsta LM, Männistö S, Albanes D, Virtamo J. Carbohydrate substitution for fat or protein and risk of type 2 diabetes in male smokers. *Eur J Clin Nutr* 2012 Feb 29. doi:10.1038/ejcn.2012.24 [Epub ahead of print].

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Abbreviations

ATBC Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
BMI	Body mass index
CHO	Carbohydrates
CI	Confidence interval
CV	Coefficient of variation
EPIC	European Prospective Investigation into Cancer and Nutrition
E%	Percentage of total energy intake
FAO	Food and Agriculture Organization
FFQ	Food frequency questionnaire
GI	Glycemic index
GL	Glycemic load
IAUC	Incremental area under curve
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IQR	Interquartile range
MUFA	Monounsaturated fatty acid
PUFA	Polyunsaturated fatty acid
RR	Relative risk
SD	Standard deviation
SFA	Saturated fatty acid
TFA	Trans fatty acid
WHO	World Health Organization
WHR	Waist-hip ratio

1 Introduction

The prevalence of type 2 diabetes is increasing worldwide. An estimated 171 million people globally were afflicted with diabetes in the year 2000, and this figure is projected to increase to 366 million by 2030 (Wild et al. 2004). Diabetes inflicts an expensive burden on society (Straka et al. 2009). The increasing prevalence emphasizes the importance of understanding different risk factors. Obesity, diet, and lifestyle account for the majority of type 2 diabetes risk (Hu et al. 2001), and trials have demonstrated that the risk of type 2 diabetes among high-risk individuals can be halved by changes in lifestyle (Tuomilehto et al. 2001, Knowler et al. 2002).

Carbohydrate-containing foods are commonly and globally used, and carbohydrates are recommended as the major dietary energy source, providing 55-75% of energy intake (WHO 2003). The role of carbohydrates in risk of type 2 diabetes is being intensively investigated, and the optimal proportions of macronutrients are widely debated (Accurso et al. 2008, Micha and Mozaffarian 2010). Attention has been directed to the quality of carbohydrates (Hu 2010). An ecologic assessment in the United States suggested that increasing the intake of refined carbohydrates concomitantly with decreasing the intake of fiber has paralleled the upward trend in the prevalence of type 2 diabetes (Gross et al. 2004). Carbohydrate-containing foods vary in their rate of absorption and the postprandial effects on blood glucose and insulin concentrations. Carbohydrates that induce a rapid elevation in postprandial blood glucose have been suggested to have greater detrimental metabolic effects relative to carbohydrates that elevate blood glucose less and more slowly (Ludwig 2002). A means of quantifying the variation in glucose response of carbohydrates is the glycemic index (GI): a measure that ranks foods on the basis of the blood glucose response that they produce upon ingestion relative to the response of a reference glucose solution or white bread with the same carbohydrate portion (Venn and Green 2007). Glycemic load (GL) takes into account the amount of carbohydrates consumed in addition to GI (Salmeron et al. 1997a).

The GI was proposed in 1981 as a system for classifying carbohydrate-containing foods for improved glycemic control of diabetes (Jenkins et al. 1981). In 1997, the first epidemiologic papers on dietary GI and GL and a disease, type 2 diabetes, were published (Salmeron et al. 1997a, Salmeron et al. 1997b). Several hundred scientific articles and numerous popular diet books (Brand-Miller et al. 2003) have since been published on the topic. However, the clinical significance of the GI remains a subject of debate (Hare-Bruun et al. 2008).

The results from prospective cohort studies on dietary GI and GL and type 2 diabetes have been inconsistent. Some studies showed no associations (Meyer et al. 2000, Stevens et al. 2002, Hodge et al. 2004, Schulz et al. 2006, Mosdøl et al. 2007,

Sahyoun et al. 2008), others reported a positive association for GI, but not for GL (Salmeron et al. 1997a, Schulze et al. 2004, Krishnan et al. 2007), and still others reported positive associations for both GI and GL (Salmeron et al. 1997b, Villegas et al. 2007, Sluijs et al. 2010b). Several methodologic considerations complicate the epidemiologic research on GI and GL and the risk of chronic diseases. Variability in measured GIs of foods, lack of GI values for local carbohydrate-containing foods, and the tendency of the dietary GI, as an average ratio of different combinations of carbohydrate-containing foods, to fall within a narrow range are examples of the difficulties.

The changes in intake of carbohydrates may be related to the intake of other energy-yielding nutrients; in isoenergetic settings, differences in carbohydrate intake reflect substitutions for protein, fat, or alcohol. Thus, the effect of carbohydrates on diabetes risk may be related to the effect of other macronutrients. These relations can be taken into account by using multivariate nutrient density models to examine the isoenergetic substitutions of macronutrients with each other (Willett et al. 1997, Willett 1998). Some studies have evaluated the associations between substitutions of carbohydrates and other macronutrients by each other and the risk of type 2 diabetes (Meyer et al. 2001, Salmeron et al. 2001, Schulze et al. 2008, Sluijs et al. 2010a), but analyses on associations between substitution of lower-GI carbohydrates for higher-GI carbohydrates or substitutions of high-, medium-, and low-GI carbohydrates for other macronutrients and the risk of type 2 diabetes have not been published.

The aim of this study was to examine the associations between dietary GI and GL, intakes of high-, medium-, and low-GI carbohydrates, and risk of type 2 diabetes in the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) cohort. The inconsistent findings from cohort studies on the associations between GI, GL and diabetes risk may, at least partly, result from methodologic weaknesses. Thus, the aim was also to evaluate factors related to application of GI to epidemiologic studies.

2 Review of the literature

2.1 Definition of carbohydrates, glycemic index (GI), and glycemic load (GL)

Carbohydrates

Dietary carbohydrates are derived almost exclusively from food of plant origin and from dairy products (FAO/WHO 1998, Cummings and Stephen 2007). Chemically, carbohydrates are organic molecules containing carbon, hydrogen, and oxygen. The primary classification of dietary carbohydrate is based on chemistry. This divides carbohydrates into sugars, oligosaccharides, and polysaccharides. Sugars comprise monosaccharides (such as glucose, fructose, or galactose), disaccharides (such as sucrose, lactose, or maltose), and sugar alcohols (polyols, such as xylitol and sorbitol). Oligosaccharides comprise e.g. maltodextrin and inulin. Polysaccharides can be divided into starch and non-starch polysaccharides. Starches are polymers of glucose, which are either branched (amylopectin) or non-branched (amylose). Major components of the non-starch polysaccharides are the polysaccharides of the plant cell wall such as cellulose, hemicellulose, and pectin.

In addition to chemical identity of carbohydrates, the food matrix (biological origin and food processing) influences the physicochemical properties of carbohydrate foods (Cummings and Stephen 2007, Englyst et al. 2007). The physiological effects of carbohydrates are dependent, in addition to their primary chemistry, on their physical properties such as water solubility, gel formation, crystallization state, association with other molecules, e.g. proteins or lipids, and aggregation into complex structures of the plant cell wall. The physiology and utilization of carbohydrates depend on their gastrointestinal handling (rate and extent of digestion and absorption), which is affected, in addition to the carbohydrate food properties, by meal and subject factors. A classification based on chemistry does not allow a simple translation into nutritional effects since each class of carbohydrate has overlapping physiological properties and health effects. This dichotomy has led to the use of a number of terms based on physiology to describe carbohydrate in foods, e.g. available and unavailable carbohydrate and glycemic carbohydrate, dietary fiber, and resistant starch.

Carbohydrate that provides glucose for metabolism is referred to as glycemic carbohydrate. Most mono- and disaccharides, some oligosaccharides (maltodextrins), and rapidly or slowly digested starches may be classified as glycemic carbohydrate. Non-starch polysaccharides and resistant starch are considered to be non-glycemic carbohydrates.

GI and GL

The GI is a physiological classification of carbohydrate-containing foods; it is used to classify foods based on the extent to which they postprandially raise blood glucose concentration compared with an equivalent amount of reference carbohydrate (Cummings and Stephen 2007, Venn and Green 2007). The GI is defined as the incremental area under the curve (IAUC) of the blood glucose response elicited by a portion of food containing 50 g of available carbohydrates expressed as a percentage of the response obtained after 50 g of carbohydrates from a reference source (glucose or white bread) were consumed by the same subjects.

To determine the GI of a specific food, subjects are given a test food and a control food on separate days and changes in blood glucose concentration are measured (FAO/WHO 1998). The IAUC of the blood glucose response is calculated for two hours after starting to eat the food. The GI is the IAUC of the test food divided by the corresponding IAUC after the control food, multiplied by 100%, first calculated for each subject and then the GI of the food is the mean of the GIs of the subjects.

GI, as a relative measure of glycemic response to a given amount of carbohydrate, describes the quality of carbohydrate, but does not take into account the quantity of carbohydrates. GL, by contrast, represents the combination of quality and quantity of carbohydrates. The GL of food is GI of food multiplied by the carbohydrate amount of a portion consumed as grams, divided by 100 (Venn and Green 2007).

In addition to individual foods, GI and GL have been applied to whole diets in epidemiologic studies where dietary GI and dietary GL have been examined as possible risk factors for chronic diseases (Salmeron et al. 1997a, Salmeron et al. 1997b, Venn and Green 2007). The dietary GL is calculated by summing the products of the carbohydrate amount of each food multiplied by its GI and divided by 100. The dietary GI is calculated by dividing the dietary GL by the total amount of carbohydrate intake multiplied by 100. The dietary GI has been interpreted as a quantitative indicator of glucose response or insulin demand induced by a given amount of carbohydrate and dietary GL by total carbohydrate amount consumed (Salmeron et al. 1997a, Salmeron et al. 1997b).

The GI and GL of food depend on amount and chemical nature of carbohydrates consumed, such as monosaccharides absorbed (glucose, fructose, galactose) and nature of the starch (amylose, amylopectin, resistant starch), but the GI is also affected by several different factors such as plant variety, storage, processing, and cooking of foods (Liljeberg et al. 1992, Järvi et al. 1995, Soh and Brand-Miller 1999, Östman et al. 2001, Leeman et al. 2005).

2.2 Assessment of dietary carbohydrates, GI, and GL

2.2.1 Measurement of dietary carbohydrate intake, GI, and GL

Commonly used dietary assessment methods are food frequency questionnaire (FFQ), dietary records, and 24-hour dietary recall (Thompson and Byers 1994, Willett 1998). FFQ is a method to assess subjects' past, long-term dietary intake. The FFQ asks respondents to report their usual frequency (and quantity) of consumption of each food from a list of foods for a specific period (e.g. the past 12 month) and is used to rank subjects according to food consumption or nutrient intakes to enable assessment of the relative risk of diseases in epidemiologic studies.

Dietary records and 24-hour dietary recalls measure short-term dietary intake, the consumption of foods on one or more specific days. These methods can also be used to estimate usual long-term intake if a suitable number of recalls or records is collected over a long period. For practical reasons, however, collection of multiple days of intake is rarely feasible in epidemiologic studies, which involve numerous individuals. Because the costs of data collection and processing and the respondent burden are typically much lower for FFQ than for multiple diet records or recalls, the FFQ method is more commonly used to estimate usual dietary intake in large cohort studies.

Dietary records and 24-hour dietary recalls allow more specificity regarding information on foods consumed and may be used to estimate absolute intakes rather than the relative intakes measured with FFQ. As the dietary record method has the potential to provide quantitatively accurate information on food consumption during the recording period, it has been regarded as the gold standard against which other dietary assessment methods are compared. However, food records are not entirely free from misreporting; underreporting may result from incomplete recording and from the impact of the recording process on dietary choices.

Carbohydrate intake has long been a standard variable measured using FFQ and has commonly been included in validation studies (Willett et al. 1985, Pietinen et al. 1988). However, most of the FFQs used in large prospective cohort studies have not been designed to measure dietary GI or GL. Later studies have, nevertheless, validated the assessment of dietary GI or GL using FFQ (Levitan et al. 2007, Barclay et al. 2008a, Du et al. 2009, Barrett and Gibson 2010, Kaartinen et al. 2011).

2.2.2 Measurement of food GI

After launching the GI (Jenkins et al. 1981), GI values for a numerous foods have been determined worldwide and international tables have been published (Foster-Powell and Miller 1995, Foster-Powell et al. 2002, Atkinson et al. 2008).

Several methodologic choices must be made in GI measurement, such as blood sampling method, selection and repetition of the reference food, verification of available carbohydrate content of food, number and type of subjects, and calculation

of the IAUC. Variability in methodology and in GI results has occurred. A standard or proposal for GI-testing methodology was published by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) (FAO/WHO 1998), and the methodology was later discussed in more detail (Brouns et al. 2005, Venn and Green 2007). However, the factors in GI determination that should be controlled and those that are optional have not been studied extensively (Wolever et al. 2008).

Because glycemic responses vary between subjects, the calculation of food GI is intended to control for the differences by dividing the glycemic response to a food by the same subjects's glycemic response to the reference food. The day-to-day within-subject variation in glucose responses is also marked (Vega-Lopez et al. 2007). Thus, current recommendations suggest that the measurement of a reference food be repeated at least three times for each subject, with the mean being more representative of the subject's true glycemic response than the result of a single trial (Wolever et al. 1991, FAO/WHO 1998, Wolever et al. 2003).

Capillary blood sampling rather than venous sampling has been recommended for GI measurement (FAO/WHO 1998, Wolever et al. 2003, Brouns et al. 2005). Venous sampling results in higher within-subject variation, and reducing the within-subject variation has been suggested as the most effective strategy to improve the precision of GI measurement (Wolever et al. 2003). However, the recommendations of use of capillary sampling and repeated reference food measurements have not been systematically followed.

Both glucose solution and white bread are commonly used as reference foods in GI measurement. Because the composition of white bread may vary in different regions, and thus, the glucose response to white bread varies from one experiment to another, comparison of GIs becomes more difficult. Calibrating white bread against glucose solution has therefore been recommended (Brouns et al. 2005).

2.2.3 Assigning food GI values for calculation of dietary GI and GL

Food composition databases are used to convert food consumption data to nutrient intakes. Calculating dietary GI and GL requires measured GI values for foods compatible with those consumed by the study participants. The GI is not a traditional food composition variable, but rather is a physiological classification of carbohydrates, and has not long been a component of standard food composition databases. Descriptions of the compilation of GI or GL databases have recently been published (Flood et al. 2006, Neuhouser et al. 2006, Olendzki et al. 2006, Martin et al. 2008, Schakel et al. 2008, Aston et al. 2010, Kaartinen et al. 2010, Levis et al. 2011).

Most of the GI database publications have reported the numbers and types of linkages between available food GIs and foods consumed in a particular study or measured with a particular method. Some studies have put extra effort into specific methodologic matters such as the GI calculation procedure (Schakel et al. 2008),

documentation of GI values in database according to standardized value documentation vocabularies (Kaartinen et al. 2010), description of confidence level of the GI values (Aston et al. 2010), or updating the GI database (Levis et al. 2011).

A difficulty in developing GI databases has been the lack of tested GI values for foods, especially for local foods in different countries. The GIs measured for foods that are compatible with those consumed by participants of the epidemiologic study are needed because many different food-related factors influence the GI value; GI of a food does not depend only on ingredients or carbohydrate content of food, but also varies due to factors such as plant variety, cooking, or processing (Järvi et al. 1995, Henry et al. 2005, Leeman et al. 2005).

European-specific GI values have been demanded (van Bakel et al. 2009b) because the published international GI tables include mainly American or Australian foods. For Finnish foods, published GI values are scarce (Tahvonen et al. 2006, Hätönen et al. 2011). For some foods, GIs determined anywhere are applicable, i.e. for foods with characters not dependent on local habits, such as sucrose or milk.

2.3 Definition and pathophysiology of type 2 diabetes

2.3.1 Definition and diagnosis of diabetes

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (WHO 1999, WHO 2006, American Diabetes Association 2011). Diabetes, classified based on etiology, comprises type 1 diabetes, type 2 diabetes, other specific types, and gestational diabetes. Type 2 diabetes accounts for approximately 90-95% of those with diabetes. Diabetes is related to substantially increased morbidity and mortality; long-term complications of diabetes include increased risk of macrovascular complications such as ischemic heart disease, stroke and peripheral vascular disease, and microvascular damage such as retinopathy, nephropathy, and neuropathy. Diabetes is associated with reduced life expectancy and diminished quality of life.

The diagnosis of diabetes and other disorders or glycemia is based on blood glucose values in fasting state and after glucose load. The WHO recommendation for the diagnostic criteria for diabetes is fasting plasma glucose ≥ 7.0 mmol/l or venous plasma glucose 2 h after ingestion of 75 g oral glucose load ≥ 11.1 mmol/l (WHO 2006). The American Diabetes Association also includes in their criteria $HbA_{1C} \geq 6.5\%$ (HbA_{1C} is a marker of chronic glycemia) and a random plasma glucose ≥ 11.1 mmol/l in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis (American Diabetes Association 2011). The fasting plasma glucose criterion for diabetes was previously higher, ≥ 7.8 mmol/l (WHO 1985), the lower criterion (7.0 mmol/l) being introduced in the late 1990s (American Diabetes Association 1997, WHO 1999).

Disorders of glycemia also include so-called pre-diabetes stages, i.e. impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). Diagnostic criteria for IGT are fasting plasma glucose <7.0 mmol/l and 2-h venous plasma glucose between 7.8 and 11.1 mmol/l and for IFG fasting plasma glucose 6.1-6.9 mmol/l and 2-h plasma glucose <7.8 mmol/l (WHO 2006). Diabetes and disorders of glucose metabolism are very common; the prevalence of abnormal glucose regulation was found to be 42% among men and 33% among women in 2004-2005 in Finland (Peltonen et al. 2006).

2.3.2 Pathophysiology of type 2 diabetes

Abnormal glucose metabolism is related to inadequate insulin secretion (decreased beta cell function) and impaired insulin function (insulin resistance). Type 2 diabetes may range from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance (WHO 1999, American Diabetes Association 2011).

Several pathogenic processes are involved in development of type 2 diabetes, and the disease develops when beta cells of the pancreas are no longer capable of sustaining sufficient insulin secretion to maintain normal glucose concentrations (Cusi 2010, Yki-Järvinen 2010, Donath and Shoelson 2011). Insulin resistance does not occur only in muscle, which results in decreased glucose uptake, but also in liver and adipose tissue. The liver has an important role in regulating glucose concentrations, and excessive fat accumulation and insulin resistance in the liver contribute to hyperglycemia. Hypertrophic and dysfunctional adipose tissue is related to insulin resistance, β -cell failure, and inflammation, which are involved in pathogenesis of type 2 diabetes. In addition, intestinal hormones, incretins, such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), have biological effects that are related to glucose metabolism (Ranganath 2008). Incretins are released in response to ingestion of nutrients, especially carbohydrates.

The most evident risk factor for type 2 diabetes is obesity and increased body fat, both overall and abdominal (Ford et al. 1997, Wang et al. 2005). Physical inactivity increases the risk for developing diabetes (Fogelholm 2010, Sieverdes et al. 2010) and aging increases the prevalence (Wild et al. 2004). Though poorly understood, diabetes has a strong hereditary component; genetic predisposition increases the risk (McCarthy 2010). Excessive caloric intake is the major cause of obesity and type 2 diabetes, but diet quality has also been suggested to have independent effects (Hu et al. 2001).

2.3.3 High- vs. low-glycemic carbohydrates in pathophysiology of type 2 diabetes

Based on animal and human studies, the carbohydrates that induce rapid and high postprandial blood glucose rise have been postulated to have a role in the pathophysiology of type 2 diabetes (Ludwig 2002). The recurrent high glucose responses after eating high-GI carbohydrates may contribute to insulin resistance and beta cell failure (glucotoxicity). The higher glucose responses stimulate more insulin secretion, and increased insulin concentrations may cause insulin resistance. Both the increased demand for insulin and hyperinsulinemia itself can contribute to beta cell failure. The increased free fatty acid concentration in the late postprandial period after a high-GI meal has been suggested to impair beta cell function (lipotoxicity).

High-GI carbohydrates may also increase diabetes risk by promoting obesity through postprandial insulin-induced hypoglycemia, which may provoke increased hunger and energy intake (Ludwig 2002). In animal studies, increased body fat and decreased lean body mass was observed in rats and mice fed high-GI carbohydrates compared with animals fed low-GI carbohydrates (Pawlak et al. 2004, Scribner et al. 2008). Feeding with carbohydrates that produce high glucose and insulin responses resulted in decreased fat utilization as a source of energy (less fat oxidation), higher plasma triglyceride concentrations, insulin resistance, and disruption of islet-cell architecture. Benefits of low-GI carbohydrates may partly be related to the health effects suggested for unavailable (indigestible) carbohydrates (Englyst et al. 2007, Nilsson et al. 2008).

2.4 Carbohydrates, GI, GL, and risk of type 2 diabetes

2.4.1 Carbohydrate intake

The earliest prospective cohort studies compared carbohydrate intake between subjects with or without diabetes and included only small numbers of subjects. They reported no association (Lundgren et al. 1989, Feskens et al. 1995), a non-significant inverse association (Marshall et al. 1994), or a positive association (Feskens et al. 1991).

Several large prospective follow-up studies evaluating the carbohydrate intake and risk of type 2 diabetes have been published (Table 1). The results from the American cohort of women, the Nurses' Health Study, showed no association in a multivariate-adjusted model between carbohydrate intake and risk of diabetes in subjects aged 30-55 years at baseline (Colditz et al. 1992), in subjects aged 40-65 years (Salmeron et al. 1997b), or in subjects aged 24-44 years (Schulze et al. 2004). These cohorts comprised large numbers of subjects (from 65 173 to 91 249), the follow-up time was 6-8 years, and the number of cases was 702-915. The Nurses'

Health Study II (Schulze et al. 2004), however, reported an inverse association between carbohydrate intake and diabetes risk in an age-adjusted model; the relative risk (RR) and confidence interval (CI) for the highest versus the lowest quintile was 0.43; 95% CI 0.34, 0.56. The other American cohort of women, the Iowa Women's Health Study (Meyer et al. 2000), also reported no association in a multivariate-adjusted model (RR for highest versus lowest quintile 0.93; 95% CI 0.76, 1.13) and an inverse association in an age- and energy-adjusted model (RR for highest versus lowest quintile 0.86 and *p* for trend 0.018). A later result from the Nurses' Health Study, with a 20-year follow-up (number of cases 4670), showed in a multivariate-adjusted model (including e.g. energy, alcohol, protein, and cereal fiber) a positive association between carbohydrate intake and diabetes risk (RR for highest versus lowest quintile 1.26; 95% CI 1.07, 1.49) (Halton et al. 2008). In an age-adjusted model, no association was observed (RR for highest versus lowest quintile 1.04; 95% CI 0.90, 1.20).

In a Chinese cohort of women (Villegas et al. 2007), with rice as the major source of carbohydrates, higher carbohydrate intake was associated with increased diabetes risk (RR for highest versus lowest quintile 1.28; 95% CI 1.09, 1.50). The association was not, however, consistent (RR for increasing quintiles was 1.00, 0.96, 0.87, 1.09, and 1.28).

In the American Health Professionals Follow-up Study (Salmeron et al. 1997a), comprising 42 759 men, no association between carbohydrate intake and diabetes risk was reported in a 6-year follow-up. In the Melbourne Collaborative Cohort Study (Hodge et al. 2004), comprising both women and men and having a relatively short follow-up period (4 years), no association between carbohydrate intake and diabetes risk was reported in a multivariate-adjusted model, including body mass index (BMI) and waist-hip ratio (WHR). An inverse association was reported before adjustment for BMI and WHR (RR for highest versus lowest quintile 0.58; 95% CI 0.36, 0.95). As well, in a German cohort (Schulze et al. 2008), carbohydrate intake was not associated with diabetes risk in a multivariate-adjusted model, but was associated inversely among men before adjustment for BMI and waist circumference (RR for highest versus lowest quintile 0.73; 95% CI 0.54, 0.98). The inverse association was not found among women.

A recent study comprising Dutch women and men reported a positive association between carbohydrate intake and diabetes risk in a multivariate model: RR for a standard deviation (SD) increase was 1.20; 95% CI 1.01, 1.42 (Sluijs et al. 2010b). The model included as adjusting variables e.g. BMI and waist circumference and of nutrient intakes total energy, alcohol, protein, saturated fat, and polyunsaturated fat. An inverse association was reported in a model adjusted only for age and sex (RR for a SD increase 0.92; 95% CI 0.86, 0.98).

Adjusting for BMI might partly represent an over-adjustment since carbohydrate intake may influence body weight and obesity is a major risk factor of diabetes. Moreover, adjusting simultaneously for energy and some of the macronutrients

changes the interpretation of results since in an isoenergetic setting an increase in carbohydrate intake means a simultaneous decrease in intake of other macronutrients (Willett et al. 1997, Willett 1998, Hu et al. 1999).

Summing up, most of the large cohort studies, comprising both female and male subjects, reported no association between carbohydrate intake and diabetes risk in multivariate-adjusted models (Colditz et al. 1992, Salmeron et al. 1997a, Salmeron et al. 1997b, Meyer et al. 2000, Hodge et al. 2004, Schulze et al. 2004, Schulze et al. 2008) and some of them reported an inverse association in the less-adjusted models (Meyer et al. 2000, Hodge et al. 2004, Schulze et al. 2004, Schulze et al. 2008). Of the three recent studies with a positive association between carbohydrate intake and diabetes risk (Villegas et al. 2007, Halton et al. 2008, Sluijs et al. 2010b), two (Halton et al. 2008, Sluijs et al. 2010b) included in the model—in addition to energy intake—most of the other energy-yielding nutrients (both included alcohol and protein, and Sluijs et al. also included saturated and polyunsaturated fat) and fiber intake, which was not typical in the earlier studies. In the less-adjusted models, they reported no association (Halton et al. 2008) or an inverse association (Sluijs et al. 2010b) between carbohydrate intake and diabetes risk.

Thus far, previous studies have not reported separately the associations of high-, medium-, and low-GI carbohydrate intakes and type 2 diabetes risk.

Table 1. Epidemiologic follow-up studies of total carbohydrate intake and type 2 diabetes risk^a

Reference	Cohort	Country	Subjects	Sex	Cases	Follow-up	RR ^b (95% CI)
			n		n	(years)	
Colditz et al. 1992	Nurses' Health Study	USA	84 360	F	702	6	1.31 (0.86, 1.98) ^c
Salmeron et al. 1997b	Nurses' Health Study	USA	65 173	F	915	6	1.13 (0.84, 1.55) ^c
Salmeron et al. 1997a	Health Professionals Follow-up Study	USA	42 759	M	523	6	0.85 (0.62, 1.15)
Meyer et al. 2000	Iowa Women's Health Study	USA	35 988	F	1141	6	0.93 (0.76, 1.13)
Hodge et al. 2004	Melbourne Collaborative Cohort Study	Australia	31 641	F, M	365	4	0.84 (0.51, 1.39)
Schulze et al. 2004	Nurses' Health Study II	USA	91 249	F	741	8	0.89 (0.60, 1.33)
Villegas et al. 2007	Shanghai Women's Health Study	China	64 227	F	1608	4.6	1.28 (1.09, 1.50)
Barclay et al. 2007	Cohort of older Australians	Australia	1833	F, M	138	10	1.14 (0.43, 3.00)
Halton et al. 2008	Nurses' Health Study	USA	85 059	F	4670	20	1.26 (1.07, 1.49)
Schulze et al. 2008	European Prospective Investigation into Cancer and Nutrition-Potsdam	Germany	25 067	F, M	844	7	F: 0.89 (0.62, 1.29) M: 0.91 (0.66, 1.26)
Sluijjs et al. 2010b	European Prospective Investigation into Cancer and Nutrition-Netherlands	Netherlands	37 846	F, M	915	10	1.20 (1.01, 1.42) ^d

^a Abbreviations: F = females, M = males, RR = relative risk, CI = confidence interval; ^b RR for highest vs. lowest category of intake; ^c Subjects with BMI < 29 and BMI ≥ 29, respectively; ^d per standard deviation increase

2.4.2 Carbohydrate substitution for fat or protein

In addition to independent changes in carbohydrate intake, changes may be related to the intake of other energy-yielding nutrients; in isoenergetic settings, differences in carbohydrate intake reflect substitutions for fat and/or protein. Thus, the effect of carbohydrates on diabetes risk may be related to the effects of the other macronutrients. These relations can be taken into account by using multivariate nutrient density models to examine substitutions of macronutrients with each other (Willett et al. 1997, Willett 1998, Hu et al. 1999). In a multivariate nutrient density model studying replacing other macronutrients with carbohydrates, carbohydrate intake is included as nutrient density (as a percentage of total energy intake, E%) as the exposure variable and the model is adjusted for total energy intake and for other energy-yielding nutrients, as E%, except for the nutrient to be replaced. The RR of the model can be interpreted as the effect of replacing the energy-yielding nutrient excluded from the model with carbohydrates. Prospective cohort studies that evaluated the associations of substitutions between carbohydrates and other energy-yielding nutrients with risk of type 2 diabetes are shown in Table 2.

Associations of substituting carbohydrates and fat by each other and the risk of type 2 diabetes were investigated in the Nurses' Health Study (Salmeron et al. 2001) and the European Prospective Investigation into Cancer and Nutrition (EPIC) – Potsdam (Schulze et al. 2008). These studies suggested that substitution of carbohydrates and total fat by each other is not associated with diabetes risk.

Instead, carbohydrate substitution for particular fatty acids may be associated with the risk; increasing trans fatty acid intake at the expense of carbohydrates was associated with increased diabetes risk and increasing polyunsaturated fatty acid intake at the expense of carbohydrates was associated with decreased risk (Salmeron et al. 2001). However, no association between substituting carbohydrates with trans or polyunsaturated fatty acids and diabetes risk has also been published (Meyer et al. 2001). One study reported an inverse association between carbohydrate substitution for polyunsaturated fatty acids and diabetes risk (Schulze et al. 2008), but in this study polyunsaturated fatty acids also contained trans-polyunsaturated fatty acids. Substitutions of carbohydrates and saturated fatty acids by each other or carbohydrates and monounsaturated fatty acids by each other were not associated with diabetes risk (Meyer et al. 2001, Salmeron et al. 2001, Schulze et al. 2008).

Two of the three cohorts examining the substitutions of carbohydrates and fat and diabetes risk consisted of women. In the cohort of both women and men (Schulze et al. 2008), the associations did not differ significantly between the sexes.

Higher carbohydrate intake at the expense of protein was associated with decreased risk in the EPIC-Potsdam study (Schulze et al. 2008) and protein intake at the expense of carbohydrates was associated with increased diabetes risk in the

EPIC-Netherlands study (Sluijs et al. 2010a). The two cohorts comprised both female and male subjects.

Studies on associations between low-carbohydrate diets and diabetes risk suggested that diets higher in animal fat and protein, but not vegetable fat and protein, were associated with increased diabetes risk (Halton et al. 2008, de Koning et al. 2011a). In men, low-carbohydrate diets with high intake of total or animal protein and fat were associated with increased diabetes risk (de Koning et al. 2011a), while those with high vegetable protein and fat showed no such association. In women, lower carbohydrate intake with increased consumption of total or animal protein and fat was associated with increased type 2 diabetes risk when not adjusted for BMI, but not after adjustment (Halton et al. 2008). Among women, low-carbohydrate diets high in vegetable protein and fat were associated inversely with diabetes risk.

Thus far, no studies on associations between high-, medium-, and low-GI carbohydrate substitutions for fat or protein and type 2 diabetes risk have been published.

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Table 2.

A. Epidemiologic follow-up studies of carbohydrate (CHO) substitution for fat or protein and type 2 diabetes risk^a

Reference	Cohort	Country	Subjects	Sex	Case	Follow-up	Substitution	RR (95% CI)
			n		n	(years)		
Schulze et al. 2008	European Prospective Investigation into Cancer and Nutrition-Potsdam	Germany	25 067	F, M	844	7	CHO for protein, 5 E% CHO for fat, 5 E% CHO for SFA, 5 E% CHO for MUFA, 5 E% CHO for PUFA, 5 E%	0.77 (0.64, 0.91) No association No association No association 0.83 (0.70, 0.98)

B. Epidemiologic follow-up studies of fat or protein substitution for carbohydrates (CHO) and type 2 diabetes risk^a

Reference	Cohort	Country	Subjects	Sex	Case	Follow-up	Substitution	RR (95% CI)
			n		n	(years)		
Salmeron et al. 2001	Nurses' Health Study	USA	84 204	F	2507	14	Fat for CHO, 5 E% SFA for CHO, 5 E% MUFA for CHO, 5 E% PUFA for CHO, 5 E% Trans for CHO, 2 E% SFA for CHO ^b Trans for CHO ^b MUFA for CHO ^b PUFA for CHO ^b	0.98 (0.94, 1.02) 0.97 (0.86, 1.10) 1.05 (0.91, 1.20) 0.63 (0.53, 0.76) 1.39 (1.15, 1.67) 0.95 (0.76, 1.19) 0.92 (0.75, 1.11) 1.02 (0.78, 1.34) 0.90 (0.75, 1.07)
Meyer et al. 2001	Iowa Women's Health Study	USA	35 988	F	1890	11	Protein for CHO, 5 E% Animal protein for CHO, 5 E% Vegetable protein for CHO, 5 E%	1.28 (1.01, 1.61) 1.20 (0.97, 1.49) 1.17 (0.73, 1.89)
Sluijs et al. 2010a	European Prospective Investigation into Cancer and Nutrition-Netherlands	Netherlands	38 094	F, M	918	10		

^a Abbreviations: F = females, M = males, RR = relative risk, CI = confidence interval, E% = percentage of total energy intake, SFA = saturated fatty acids, trans = trans fatty acids, MUFA = monounsaturated fatty acids, PUFA = polyunsaturated fatty acids; ^b highest vs. lowest category of intake

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2.4.3 Dietary GI and GL

The first results, in 1997, from large prospective cohort studies showed that high dietary GI in both men and women and high dietary GL in women were significant independent predictors of risk of type 2 diabetes (Table 3) (Salmeron et al. 1997a, Salmeron et al. 1997b). The combination of a high GL and a low cereal fiber intake increased the diabetes risk further compared with a low GL and high cereal fiber intake.

The first positive findings from the American cohorts of the Nurses' Health Study and the Health Professionals Follow-up Study (Salmeron et al. 1997a, Salmeron et al. 1997b) were partially supported by the results from the Nurses' Health Study II (Schulze et al. 2004); a detrimental effect was observed for high GI and low cereal fiber intake, but GL was not associated with diabetes risk. By contrast, in the Iowa Women's Health Study (Meyer et al. 2000) and the Atherosclerosis Risk in Communities Study (Stevens et al. 2002), both American cohorts, cereal fiber and whole grain intake were associated inversely with diabetes risk, but dietary GI or GL were not. In the Australian Melbourne Collaborative Cohort Study (Hodge et al. 2004), higher dietary GI was associated with increased diabetes risk in a model not adjusted for BMI and WHR, but the association was no longer significant after adjustment for these factors. The GL was not associated with diabetes risk.

A meta-analysis of dietary GI, GL, and the risk for chronic diseases, which included studies published through March 2007, found a significant positive association between dietary GI and the risk for type 2 diabetes; the fully adjusted rate ratio of the highest versus the lowest quantile of dietary GI was 1.20 (95% CI 1.04, 1.38) (Barclay et al. 2008b). Further analyses were conducted, including only those studies that applied a dietary assessment method that had been validated in a representative sample and had yielded a correlation coefficient ≥ 0.5 for total carbohydrate; then, the corresponding rate ratio was 1.40 (95% CI 1.23, 1.59). In the further analyses, cohorts not reporting an association between dietary GI, GL, and diabetes risk (Meyer et al. 2000, Stevens et al. 2002, Hodge et al. 2004) were excluded, while a study that did not focus on risk of diabetes (Patel et al. 2007), but presented a positive association between GL and diabetes in a discussion on risk of pancreatic cancer, was included. Some other methodologic choices of the meta-analysis were also later criticized (Mulholland et al. 2008, Tuomainen et al. 2008). In both analyses (for all studies and for studies after the exclusion), the meta-analysis included a study on gestational diabetes among participants in the Nurses' Health Study II (Zhang et al. 2006) in addition to a study reporting results on type 2 diabetes from the same cohort (Schulze et al. 2004). In that study of gestational diabetes, the dietary GL – which is by definition strongly correlated with carbohydrate intake – was adjusted for energy and the energy-yielding nutrients of

protein, alcohol, and saturated, monounsaturated, polyunsaturated, and trans fatty acids. As a result, in the basic model (adjusted for age, parity, and BMI) dietary GL was nonsignificantly inversely associated with risk of gestational diabetes (RR for highest versus lowest quintile 0.84; 95% CI 0.67, 1.05), and in the most adjusted model GL was associated positively with diabetes risk (RR 1.61; 95% CI 1.02, 2.53). Differences in statistical models used in different studies may account for the heterogeneous findings on dietary GL and diabetes risk, and properly interpreting the biological meanings of results from different models is important (Liu and Chou 2010). A similar change in results on dietary GL and diabetes risk was seen in the Black Women's Health Study (Krishnan et al. 2007); in the model adjusted for age, GL was inversely associated with risk of diabetes (RR for highest versus lowest quintile 0.83; 95% CI 0.72, 0.95), but in the fully adjusted model (including e.g. energy, protein, and fat) a nonsignificant positive association was seen (RR for highest versus lowest quintile 1.22; 95% CI 0.98, 1.51). As in the case of carbohydrate intake, an association between dietary GL and diabetes risk may also depend on whether an adjustment is made for BMI, or not, as seen in studies reporting an inverse association between GL and diabetes risk in crude models, but no association in multivariate-adjusted models (Schulze et al. 2004, Krishnan et al. 2007, Mosdøl et al. 2007).

Later results on dietary GI and GL and diabetes risk have also been variable. Between GI and diabetes risk, a positive association (Krishnan et al. 2007, Villegas et al. 2007), a borderline positive association (Sluijs et al. 2010b), and no association (Schulz et al. 2006, Barclay et al. 2007, Mosdøl et al. 2007, Sahyoun et al. 2008) have been reported. Between GL and diabetes risk, some studies reported a positive association (Villegas et al. 2007, Halton et al. 2008, Sluijs et al. 2010b) and others no association (Schulz et al. 2006, Krishnan et al. 2007, Mosdøl et al. 2007, Sahyoun et al. 2008). Hopping et al. (2010) described a positive association among women, but no significant association among men.

Some of the cohorts with no association were of small size (Schulz et al. 2006, Barclay et al. 2007, Sahyoun et al. 2008), but no association was also reported in larger cohorts (Meyer et al. 2000, Stevens et al. 2002, Hodge et al. 2004, Mosdøl et al. 2007). Some of the small-sized cohort studies with no association, draw their conclusions – despite their small number of cases – from stratified analysis of subgroups (Schulz et al. 2006, Barclay et al. 2007), while another study contributed to the understanding of the nutritional correlates of dietary GI and GL (Sahyoun et al. 2008). Although associations stratified by several variables have been reported, only rarely have significant interaction terms been presented. A study reporting results stratified by ethnicity (Hopping et al. 2010) suggested that risk estimates may differ by ethnic group due to differences in commonly consumed foods.

The results from the cohort studies have differed between men and women. Several studies including male subjects suggested no association between GI or GL and diabetes risk, whereas studies including only women suggested a positive

association: Of the six studies reporting a positive association between GI and diabetes risk, four comprised female subjects (Salmeron et al. 1997b, Schulze et al. 2004, Krishnan et al. 2007, Villegas et al. 2007), one mainly (74%) female subjects (Sluijs et al. 2010b), and one only men (Salmeron et al. 1997a). Of the seven studies reporting no association between GI and diabetes risk, six comprised both sexes (Stevens et al. 2002, Hodge et al. 2004, Schulz et al. 2006, Barclay et al. 2007, Mosdøl et al. 2007, Sahyoun et al. 2008) and one contained only female subjects (Meyer et al. 2000). Of the five studies with a positive association between GL and diabetes risk, four consisted of only women (Salmeron et al. 1997b, Villegas et al. 2007, Halton et al. 2008, Hopping et al. 2010) and one mainly (74%) of women (Sluijs et al. 2010b). No association between GL and diabetes risk has been reported among male subjects (Salmeron et al. 1997a, Hopping et al. 2010), among female subjects (Meyer et al. 2000, Schulze et al. 2004, Krishnan et al. 2007), and among both sexes (Stevens et al. 2002, Hodge et al. 2004, Schulz et al. 2006, Mosdøl et al. 2007, Sahyoun et al. 2008).

^A Table 3. Epidemiologic follow-up studies of dietary glycemic index (GI) and glycemic load (GL) and type 2 diabetes risk^a

Reference	Cohort	Country	Subjects	Sex	Cases	Follow-up (years)	RR (95% CI)
			n	n	n		
Salmeron et al. 1997b	Nurses' Health Study	USA	65 173	F	915	6	GI 1.37 (1.09, 1.71) GL 1.47 (1.16, 1.86)
Salmeron et al. 1997a	Health Professionals Follow-up Study	USA	42 759	M	523	6	GI 1.37 (1.02, 1.83) GL 1.25 (0.90, 1.73)
Meyer et al. 2000	Iowa Women's Health Study	USA	35 988	F	1141	6	GI 0.89 (0.72, 1.10) GL 0.95 (0.78, 1.16)
Stevens et al. 2002	Atherosclerosis Risk in Communities	USA	12 251	F, M	1447	9	GI 1.002 (0.990, 1.015) ^c 1.000 (0.982, 1.017) ^c GL 1.10 (0.90, 1.39) ^d 0.97 (0.73, 1.35) ^d
Hodge et al. 2004	Melbourne Collaborative Cohort Study	Australia	31 641	F, M	365	4	GI 1.23 (0.98, 1.54) GL 1.04 (0.68, 1.58)
Schulze et al. 2004	Nurses' Health Study II	USA	91 249	F	741	8	GI 1.59 (1.21, 2.10) GL 1.33 (0.92, 1.91)
Krishnan et al. 2007	Black Women's Health Study	USA	40 078	F	1938	8	GI 1.23 (1.05, 1.44) GL 1.22 (0.98, 1.51)
Schulz et al. 2006	Insulin Resistance Atherosclerosis Study	USA	892	F, M	146	5	GI No association GL No association
Villegas et al. 2007	Shanghai Women's Health Study	China	64 227	F	1608	4.6	GI 1.21 (1.03, 1.43) GL 1.34 (1.13, 1.58)
Mosdøl et al. 2007	Whitehall II Study	UK	5598	M, F	329	13	GI 0.94 (0.71, 1.23) GL 0.80 (0.51, 1.26)
Barclay et al. 2007	Cohort of Older Australians	Australia	1833	F, M	138	10	GI 1.50 (0.95, 2.36)

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Sahyoun et al. 2008	Health, Aging, and Body Composition Study	USA	1898	F, M	99	4	GI 1.0 (0.5, 2.0) GL 1.3 (0.6, 2.7)
Halton et al. 2008	Nurses' Health Study	USA	85 059	F	4670	20	GL 2.47 (1.75, 3.46)
Hopping et al. 2010	Multiethnic Cohort in Hawaii	USA	75 512	F, M	8587	14	GL F: 1.41 (1.15, 1.73) M: 1.16 (0.99, 1.36)
Sluijs et al. 2010b	European Prospective Investigation into Cancer and Nutrition-Netherlands	Netherlands	37 846	F, M	915	10	GI 1.08 (1.00, 1.17) ^e GL 1.27 (1.11, 1.44) ^e

^a Abbreviations: F = females, M = males, RR = relative risk, CI = confidence interval; ^b RR for highest vs. lowest category; ^c Whites and African-Americans, respectively; ^d Whites and African-Americans, respectively; ^e per standard deviation increase

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3 Aims of the study

The main aim was to investigate the associations between dietary GI, GL, intakes of high-, medium-, and low-GI carbohydrates, and risk of type 2 diabetes in a Finnish cohort of male smokers (ATBC Study). For application of GI to epidemiologic research, variation in measured GI values of foods was examined and availability of GI values for foods and the methodologies underlying these values were examined.

Specific aims were as follows:

1. To examine variation in food GI value and factors contributing to this in GI measurement, i.e. capillary vs. venous sampling, glucose solution vs. white bread as a reference food, and repeating reference food measurements (I)
2. To evaluate availability of food GI values and the methodologies used in measurement of the values, and to assign the GI values for epidemiologic study (II)
3. To examine carbohydrate intake, dietary GI and GL, and their relationships with baseline characteristics, food sources, and nutrient intakes among ATBC Study participants (II, III)
4. To examine associations of dietary GI, GL, substitution of lower-GI carbohydrates for higher-GI carbohydrates, and risk of type 2 diabetes (III)
5. To examine associations of total, high-, medium-, and low-GI carbohydrate intake, their substitution for fat or protein, and risk of type 2 diabetes (IV).

4 Materials and methods

4.1 Measurement of food GI (Publication I)

Subjects

Twelve non-smoking volunteers (11 women and one man; mean BMI 21.4 kg/m², range 18.5-24.4) were recruited. One subject dropped out of the study after the fifth visit for personal reasons. At baseline, all subjects had normal fasting plasma glucose (<6.1 mmol/l) as well as normal 2-hour glucose tolerance following a 75-g oral glucose tolerance test (WHO 1999). Exclusion criteria were active gastrointestinal or metabolic disease (e.g. celiac disease), first-degree family history of diabetes, regular medication, and among women pregnancy or lactation. The Ethics Committee of the Hospital District of Helsinki and Uusimaa approved the study protocol, and informed written consent was obtained from all subjects.

Study design (postprandial study)

Each test food, i.e. rye bread, oatmeal porridge, and instant mashed potato, was served once and both reference foods, glucose solution and white bread, three times at one-week intervals in random order to each subject.

Subjects were asked to follow their usual diet throughout the study. They were requested to fast for 12 hours before the study morning, after eating their standardized evening meal. Subjects were asked not to drink alcohol and to avoid vigorous physical activity during the day preceding the tests and to avoid exercise on the morning of the study.

On the study morning, the subject's weight was recorded and a cannula was inserted into a vein in the antecubital fossa. A baseline venous blood sample and a finger-prick capillary blood sample were taken. The subject then consumed the study meal within 10 min, and capillary and venous samples were obtained at 15, 30, 45, 60, 90, 120, and 180 min after the start of the meal.

Study meals

The three test foods were rye bread (Oululainen Ltd., Finland), oatmeal porridge (Elovena, Raisio Group Ltd., Finland), and instant mashed potato (Idahoan Foods, Lewisville, ID, USA). Oatmeal porridge (rolled oats; flake thickness 0.5-0.6 mm) and mashed potato were prepared according to package directions, except that the mashed potato was prepared with water instead of milk, as in the interlaboratory study by Wolever et al. (2003). White bread (Vaasan & Vaasan Ltd., Finland) and glucose solution were used as reference foods. All study meals, except instant mashed potato, were commercially available in Finland. Each of the test foods and

the reference foods were fed as portions providing 50 g of available carbohydrate. They were served with 40 g of cucumber (except oatmeal porridge and glucose solution), and with a drink of the subject's choice, either water or a non-caloric orange drink (the drink of each subject remained the same throughout the study). The total water volume of the meals was standardized to 500 ml, adjusting by the volume of the drink.

The chemical composition of the foods was analyzed by the VTT Technical Research Center of Finland (Helsinki, Finland). Free sugars (glucose, fructose, maltose, maltotriose, sucrose) and enzymatically available starch contents were analyzed, and the available carbohydrate was calculated as the sum of free sugars and enzymatically available starch. In addition, protein, fat, fiber (total, soluble, and insoluble), and moisture were analyzed.

Laboratory analysis of blood samples

Capillary blood glucose was determined by using a HemoCue® Glucose 201 meter (HemoCue Ltd., Ängelholm, Sweden) that applies a modified glucose dehydrogenase method (Bergmeyer 1974, Banauch et al. 1975). The results were automatically transformed to be expressed as plasma values. A quality control solution recommended by HemoCue was measured twice every study morning (28 days), and the coefficient of variation (CV) of these measurements was 1.1%. A fluoride-citrate tube was used to collect a blood sample for determination of venous plasma glucose. The sample was centrifuged for 15 min at 4000 × g at 20°C to separate the plasma. Plasma glucose was analyzed by a hexokinase method (Thermo Electron Ltd., Vantaa, Finland). The inter-assay and intra-assay CV for venous glucose determination were 3.4% and 1.1%, respectively.

Calculation of GI

The IAUC of the glucose response was calculated using the trapezoidal method, ignoring the area under the baseline (FAO/WHO 1998). The GI was defined as the glucose IAUC of a test meal expressed as a percentage of the glucose IAUC of the reference food (or mean IAUC of the repeated reference food). The calculation was carried out first for each subject; the mean of these values was the food GI.

The main results were expressed for the 2-h IAUCs. In addition, GIs were calculated from 3-h IAUC to study the difference with the GIs from 2-h IAUCs. One or two IAUCs of the three IAUCs of reference foods of each subject were selected at random to study the effect of repeating the tests.

The final number of subjects was 11. Some missing values existed, however, due to complications in sampling. When two or more samples on the same test occasion were missing, the IAUC was not calculated. Two subjects had only two eligible IAUC measurements of white bread from venous samples; thus, the number of subjects in venous white bread measurements was 9. When individual samples were missing, they were replaced by estimates from the other values: missing glucose

values (one value for five subjects each) were replaced by estimates from the corresponding average value of the other subjects (rye bread; one value for one subject) or the corresponding average value of the subject's two other reference tests (glucose solution and white bread; one value for four subjects each). The estimate was corrected by the difference between the level of the incomplete curve and the level of the complete curves.

Statistical analysis

The results were expressed as mean and CV ($100\% \times \text{SD}/\text{mean}$). CV was calculated separately for the mean IAUC of the repeated reference measurements of each subject (to express between-subject variation) and for the IAUCs of each subject's repeated reference measurements (to express within-subject variation). Data were analyzed with SAS software (version 8.2; SAS Institute, Cary, NC, USA) and STATA software (version 9, StataCorp, College Station, TX, USA).

4.2 Assigning food GI values for epidemiologic studies (Publication II)

The GI database was compiled for the cohort studies within the ATBC Study: the GI values were assigned for 1097 foods, consumption of which was reported by the ATBC Study participants. The GI values were provided from the following sources: data from the GI-measuring laboratory of the National Institute for Health and Welfare (National Public Health Institute until the end of year 2008), publications reporting measured GIs, GIs from Sydney University published in the international table by Foster-Powell et al. (2002), and GIs for some dairy products from a Finnish manufacturer (Valio Ltd., Helsinki, Finland) (Appendix Table 1).

The GI was assigned relative to the glucose solution standard (GI of glucose solution = 100). When GIs were tested with white bread as the reference food, the values were multiplied by a factor of 0.7 (FAO/WHO 1998). If more than one eligible GI was available for a given food, the mean of the GIs was assigned.

GI values from the laboratory of the National Institute for Health and Welfare

At the laboratory of the National Institute for Health and Welfare, the GI values were measured for common Finnish carbohydrate-containing foods (Appendix Table 1). The methodology followed the recommendations presented internationally (FAO/WHO 1998, Brouns et al. 2005) and was in line with the methodologic GI measurement study described in Section 4.1, with the following methodologic choices: the number of healthy subjects with normal glucose tolerance for each food was at least ten (except for carrot: the number of subjects was six for raw carrot and eight for cooked carrot), glucose solution was used as reference food and was tested

at least twice for each subject, a 50-g available carbohydrate portion was used for test and reference foods, except a 25-g portion was used for foods with low carbohydrate content (carrot, strawberry, beer, and ice cream) and for their reference food. The carbohydrate content (sugars and available starch) of each food was analyzed (AnalyCen, Tampere, Finland), except for information on the carbohydrate content of beer, which was provided by the manufacturer (Oy Sinebrychoff Ab, Kerava, Finland). After overnight fasting, the finger-prick capillary blood sample was obtained and followed by samples at 15, 30, 45, 60, 90, and 120 min after starting to eat the study food. Blood glucose was measured with a glucose meter (HemoCue® Glucose 201 meter). The IAUC was calculated with the trapezoidal method, ignoring the area beneath the fasting concentration (FAO/WHO 1998).

GI values from the literature; the minimum methodologic criteria

Publications providing GI values were reviewed for the quality of the GI determinations. The minimum methodologic criteria were set on the basis of internationally presented recommendations (FAO/WHO 1998, Brouns et al. 2005). Adequate reporting on the methodology was required and the minimum criteria were as follows: 1) The reference food was glucose or white bread, 2) the amount of available carbohydrate of the test and reference foods was the same (50 g or 25 g), 3) the subjects were not treated with insulin, and 4) the number of subjects was ≥ 6 . Some of the methodologic choices in the studies included (number of subjects, amount of available carbohydrate, reference food, number of reference food measurements, and blood sampling type) are described in Appendix Table 1.

Types of linkages between foods and GI values available

For foods that contained no or negligible amounts of carbohydrate (mainly protein- or fat-containing foods, such as meat, inner organs, oil, hard cheese), the GI was set to zero (number of these foods 195). Generally, few reliable GI values existed for roots or vegetables (excluding potatoes and legumes); studies fulfilling the minimum methodologic criteria provided GI values only for carrots. The values for raw and cooked carrots were used for raw and cooked roots and vegetables, respectively, and potatoes and legumes received their own GI values.

The GI of a similar food was available for 130 foods. The foods were considered similar when the GI-tested food and the food consumed by the ATBC Study subjects was the same (e.g. sucrose, milk, fruits, rye porridge) or when there were no reasons to expect substantial differences between the GI values (e.g. wheat bread and wheat roll). If the GI was expected to be affected by processing (e.g. whole-kernel bread compared with milled-flour bread), the assigned GI had to be based on foods similar to those commonly consumed in Finland. The GI from a related food was assigned to 360 foods; the related food was the most similar food for which the GI was available (e.g. the GI of strawberry was assigned to all berries and the GI of wheat bread to wheat flour). The GIs for 412 composite foods were calculated as the

weighted mean of the GIs of the carbohydrate-containing components (FAO/WHO 1998).

Of the foods (n=66) that contributed 90% of the mean carbohydrate intake of the ATBC Study participants, the GI of a similar food was available for 40 foods (61%), of which the GI values for 20 foods were analyzed at the laboratory of the National Institute for Health and Welfare. The GI from a related food was assigned to 10 foods (15%), and the GI was calculated for 16 composite foods (24%).

4.3 Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study (Publications II-IV)

4.3.1 Study design, subjects, and baseline examination

The ATBC Study was a randomized, double-blind, placebo-controlled primary prevention trial testing whether supplementation with α -tocopherol, β -carotene, or both would reduce the incidence of lung cancer and other cancers. The study design and methods have been described in detail elsewhere (The ATBC Cancer Prevention Study Group 1994). The ATBC Study was approved by the institutional review boards of the National Public Health Institute of Finland (Helsinki, Finland) and the United States National Cancer Institute (Bethesda, MD, USA). Each participant provided written informed consent at baseline.

A total of 29 133 male smokers aged 50-69 years were recruited between 1985 and 1988 from southwestern Finland. From the total male population of this age group in the area (n = 290 406), the study participants were recruited after enquiring about their smoking habits and willingness to participate by a mailed questionnaire. Eligibility to the study was assessed during two clinic visits.

At baseline, participants completed an FFQ (also known as a modified diet history questionnaire), and data on demographic, general medical, physical activity, and smoking history were enquired about by questionnaire. Height and weight were measured, and BMI was calculated.

The 27 111 participants (93%) who completed the baseline FFQ satisfactorily were included in the analyses. At study entry, 1168 of the 27 111 participants had a history of physician-diagnosed diabetes. After their exclusion, the final cohort for study of type 2 diabetes comprised 25 943 men.

4.3.2 Dietary assessment

Diet was assessed at baseline with a self-administered FFQ (Pietinen et al. 1988). The questionnaire included 276 food items and mixed dishes. In addition, the subjects could add foods not listed in the questionnaire after each subgroup. Frequencies of consumption were reported as the number of times per day, week, or month during the previous 12 months. The questionnaire was used with a picture

booklet of 122 photographs of foods, each with 3-5 different portion sizes, to estimate the usual portion size of foods. During the first baseline visit each participant received a questionnaire to be completed at home. At the second baseline visit two weeks later, they returned the questionnaires, which were reviewed and completed with the help of a trained nurse.

The dietary method was validated before the ATBC Study among 190 men aged 55-69 years (Pietinen et al. 1988). The energy-adjusted correlations between the dietary questionnaire and food records were 0.55 for total carbohydrates. For starch, the correlation was 0.73, for sucrose 0.50, and for dietary fiber 0.72.

4.3.3 Calculation of nutrient intakes and dietary GI and GL

The foods (n=1097) reported by the participants were encoded; the subjects added 821 food items to the questionnaire in addition to the 276 structured foods.

The nutrient intakes and dietary GI and GL were calculated using the compiled GI database and the food composition database and nutrient intake calculation software of the National Institute for Health and Welfare.

Intakes of the energy-yielding nutrients were calculated as E%. In addition to total carbohydrate intake, the carbohydrate intakes from high-GI foods ($GI \geq 70$), medium-GI foods ($GI 56-69$), and low-GI foods ($GI \leq 55$) were calculated.

The dietary GL was calculated by summing the products of the carbohydrate amount of each food consumed multiplied by its GI and divided by 100, and the dietary GI by dividing the dietary GL by the total amount of carbohydrate multiplied by 100 (Wolever et al. 1991, Wolever et al. 1994, Salmeron et al. 1997a, Venn and Green 2007) as summarized below:

$$\text{Dietary GL: } \sum_{k=1}^n CHO_k \times \frac{GI_k}{100}$$

$$\text{Dietary GI: } \frac{\text{Dietary GL}}{CHO_{tot}} \times 100 = \sum_{k=1}^n \frac{CHO_k}{CHO_{tot}} \times GI_k$$

where CHO_k is the amount of carbohydrate consumed from the k^{th} food (grams), GI_k is the GI of the k^{th} food, and CHO_{tot} is the amount of carbohydrate (grams) in the entire diet.

The main foods contributing to the total carbohydrate intake (90% of total carbohydrate intake) and the main foods contributing to the intake of high-, medium-, and low-GI carbohydrates (foods contributing >0.5% of mean intake of each carbohydrate category) were evaluated. The sources of dietary GL (mathematically same as the sources of dietary GI) were calculated.

4.3.4 Endpoint: type 2 diabetes

Incident diabetes cases were identified from the national registry of reimbursement for costs of diabetes medication. In Finland, patients in need of medical treatment for diabetes are entitled to reimbursement of their medication expenses according to sickness insurance legislation. This necessitates a detailed medical certificate from the attending physician. The certificate is verified to fulfill the diagnostic criteria for diabetes at the Social Insurance Institution (Helsinki, Finland), which maintains a central register of all persons receiving drug reimbursement. The ATBC Study participants were linked to the register through the unique personal identity number assigned to each Finnish citizen. Among the final cohort consisting of 25 943 men, 1098 incident diabetes cases were identified during the 12-year follow-up (until the end of year 1997).

4.3.5 Statistical methods

Dietary GL and the nutrient intake variables, except alcohol and the energy-yielding nutrients when used as E%, were log-transformed and adjusted for energy intake using the residual method (Willett and Stampfer 1986, Willett et al. 1997). Nutrient intakes and baseline characteristics were calculated for incident diabetes cases and for the whole cohort and in quintiles of total, high-, medium-, and low-GI carbohydrate intakes, dietary GI, and GL. The Spearman correlation coefficients between intakes of carbohydrates and the other macronutrients were calculated.

The linear regression model, including age, intervention group, and 33 food ingredient groups, was fit to detect the food ingredient groups that explained most of the interindividual variation in dietary GI. The associations between the foods explaining most of the interindividual variation in dietary GI and diabetes risk were assessed (Cox regression model adjusted for age and intervention group).

Person-time of follow-up was computed from the randomization date to the date of diabetes occurrence or death or end of follow-up (December 1997), whichever came first. Cox regression modeling was used to estimate the RRs and 95% CIs for the incidence of disease. The proportional hazard assumption was tested using Schoenfeld residuals. Potential confounders and main determinants of diabetes were included as covariates in the Cox regression models.

Multivariate nutrient density models (Willett et al. 1997, Willett 1998, Hu et al. 1999) were applied to examine the associations of substitutions of macronutrients with diabetes risk. Carbohydrate intake (as nutrient density, E%) was included as the exposure variable, and the model was adjusted for total energy intake (and for other energy-yielding nutrients, as E%, except for the nutrient to be replaced). The RR of carbohydrates in the model can be interpreted as the effect of carbohydrate substitution for the energy-yielding nutrient(s), that are excluded from the model.

The association between dietary GI, GL, and diabetes risk was studied using the following models: The basic model (model 1) was adjusted for age and intervention

group (supplementation during the original trial). The multivariate models were further adjusted for BMI, smoking (years of smoking and number of cigarettes smoked daily), leisure-time physical activity, and intakes of total energy and alcohol (model 2), and still further for fat and fiber intake and coffee consumption (model 3).

The isoenergetic substitutions of low-GI carbohydrates for medium-GI carbohydrates (A), low-GI carbohydrates for high-GI carbohydrates (B), and medium-GI carbohydrates for high-GI carbohydrates (C) were examined using the following models: The basic model (model 1) was adjusted for age, intervention group, intake of total energy, and intakes of fat, protein, and alcohol, as E%. Furthermore, the basic model for A was adjusted for intake of high-GI carbohydrates, for B for medium-GI carbohydrates, and for C for low-GI carbohydrates, as E% each. The second model (model 2) was further adjusted for BMI, smoking, physical activity, intake of fiber, and consumption of coffee.

The association of total-, high-, medium-, and low-GI carbohydrate intake and diabetes risk was examined using the following models: The basic model (model 1) was adjusted for age and intervention group. The multivariate model (model 2) was further adjusted for total energy intake, BMI, smoking, physical activity, and coffee consumption. The substitutions of carbohydrates for each macronutrient were studied adjusting model 2 further for alcohol and protein (substitution for fat) or fat (substitution for protein). When examining separately high-, medium-, and low-GI carbohydrate substitutions for other macronutrients, the three carbohydrate variables were included in the model, one as an exposure variable and the two others as adjusting variables, in turn. When substitutions for different fatty acids (saturated, trans, monounsaturated, and polyunsaturated) or protein from a particular source (meat, milk, or plant) were studied, the nutrient to be replaced was excluded and the model was adjusted for the other fatty acids or protein groups. The substitution of 2 E% was assessed, except 1 E% for trans fatty acids and plant protein due to their small median intake and less than 2 E% interquartile range (IQR).

Tests for linearity of trend were performed using the Wald test by treating the median values of each quintile as continuous variables. All P-values are two-sided. Analyses were carried out with STATA software (version 9, StataCorp, College Station, TX, USA).

5 Results

5.1 Variation in responses in GI measurement (Publication I)

The mean venous glucose concentrations were lower than capillary glucose concentrations. The difference was small (0.2 mmol/l) in fasting state and largest (1.7 mmol/l) at 45 min after starting to eat the food, decreasing gradually thereafter so that no difference was found at 180 min. The venous glucose decreased to the fasting concentration at 90 min for most foods, whereas the capillary glucose fell to the fasting concentration for most foods between 120 and 180 min. In consequence, the IAUCs were almost double for capillary samples as compared with venous samples (Table 4).

Table 4. Incremental areas under the curve (IAUC) of the glucose response for one or the mean of 2 or 3 tests of glucose solution or white bread of each subject (n=9)

Sampling type	Reference food	IAUC of 3 tests		IAUC of 2 tests		IAUC of 1 test	
		Mean	CV% ^a	Mean	CV% ^a	Mean	CV% ^a
Venous	Glucose	132	46	139	47	132	65
	White bread	92	35	100	49	101	58
Capillary	Glucose	247	32	250	30	244	38
	White bread	181	25	193	27	188	39

^a expresses between-subject variation

Variation in IAUC of glucose solution or white bread was systematically smaller for capillary than for venous samples (both between- and within-subject variations) (Tables 4 and 5). Variation between IAUC of glucose solution and white bread did not differ systematically. The between-subject variation diminished most when IAUC of glucose solution or white bread was measured twice for each subject, as opposed to only one measurement; the third measurement did not diminish the variation as much. The within-subject variation did not differ between measurements conducted twice or three times.

Table 5. Coefficients of variation (CV%) of IAUC of repeated glucose solution or white bread within each subject (n=9)

Sampling type	Reference food	Mean of CV% ^a	Mean of CV% ^a
		of 3 tests	of 2 tests
Venous	Glucose solution	37	38
	Wheat bread	49	32
Capillary	Glucose solution	20	20
	Wheat bread	26	23

^a expresses within-subject variation

Variation in GI was systematically lower for capillary samples than for venous samples, with the exception of the GI of rye bread measured with repeated glucose solution reference (GIs and CVs for rye bread and mashed potato are presented in Table 6). The capillary GI values leveled off with two glucose references, and the variation diminished only a little further with three references. The capillary GIs with white bread as the reference did not differ when tested once, twice, or three times, but the CVs were lower when white bread was tested at least twice. The venous GIs varied least when glucose solution was the reference and was tested twice or three times.

Table 6. Glycemic index (GI) of rye bread and mashed potato from venous and capillary samples (until 120 min) when the reference glucose solution or white bread was tested 1, 2, or 3 times (n=11, except n=9 for venous samples when white bread as the reference)

Food and sampling	No. of reference	GI _{glucose}		GI _{white bread}		GI _{white bread} /GI _{glucose}
		Mean	CV%	Mean	CV%	
Rye bread						
Venous	1	153	120	144	83	0.94
	2	77	21	164	121	2.13
	3	82	22	128	63	1.56
Capillary	1	85	45	99	46	1.16
	2	78	48	96	39	1.23
	3	77	40	102	39	1.32
Mashed potato						
Venous	1	182	135	148	79	0.81
	2	86	41	164	113	1.91
	3	92	44	134	63	1.46
Capillary	1	90	44	108	53	1.20
	2	79	27	102	41	1.29
	3	80	26	108	41	1.35

The mean GI of Finnish white bread was 79 when both white bread and the reference glucose were tested three times from capillary samples. The variation almost halved when white bread was tested twice or three times (CV 24%) instead of only once (CV 43%). However, the GI of white bread, based on three tests of both white bread and glucose solution, varied substantially between the subjects (n=9); it ranged from 42 to 103 (CV 25%) when measured from capillary samples and from 36 to 144 (CV 42%) when measured from venous samples.

The GI of white bread, 79, revealed that white bread as the reference produced GI values 1.27 times as high as did the reference glucose. Approximately this ratio (1.16-1.35) was approached for GIs of the foods when calculated from capillary

samples and the reference food was tested twice or three times, but the ratio was highly variable when calculated from the venous samples.

The late glucose response after the consumption of rye bread differed from the responses after the other study meals; neither capillary nor venous glucose concentrations dropped below the fasting concentration at any time-point. The GI of rye bread, contrary to GIs of the other foods, tended to differ between calculations from samplings until 120 min (GI 78) or until 180 min (GI 84), although the difference was not significant (examined from capillary sampling, when reference tested three times).

5.2 Carbohydrate intake and dietary GI and GL among ATBC Study participants (Publications II-IV)

5.2.1 Carbohydrate intake and dietary GI and GL

The median intake of carbohydrates was 40.4 E% (260 g per day). Over half of the carbohydrate intake came from high-GI foods (21.7 E%), one-quarter from medium-GI foods (9.7 E%), and one-fifth from low-GI foods (8.0 E%). The median dietary GI was 67.3 (IQR 64.8-70.0) and the median energy-adjusted dietary GL 175 (IQR 159-192).

5.2.2 Associations with baseline characteristics and nutrient intakes

Participants with a higher percentage of carbohydrate intake were older, had slightly lower BMI, and were more physically active during leisure-time (Table 7). Similarly, participants with a higher intake of high-, medium-, or low-GI carbohydrates were more physically active (Table 8). Medium-GI carbohydrate intake was associated inversely with BMI, and low-GI carbohydrate intake was associated positively with BMI. Participants with higher dietary GI were younger (Table 9). Physical activity or BMI was not associated with dietary GI. Participants with higher dietary GL were older and more physically active at leisure-time and had lower BMI.

Table 7. Baseline characteristics and nutrient intakes (medians) by quintiles of total carbohydrate intake (n=25 943)^a

	Carbohydrates, E%				
	1	2	3	4	5
	33.4	37.5	40.4	43.3	47.4
Age, years	56.5	56.8	57.0	57.2	57.8
Body mass index, kg/m ²	26.1	26.0	25.9	25.7	25.7
Moderate physical activity, % of subjects ^b	50	56	60	62	66
Energy, MJ/day	10.8	11.0	11.1	10.8	10.6
Fat, E%	44.8	43.2	41.5	39.6	36.1
Protein, E%	14.4	14.4	14.4	14.3	14.1
High-GI carbohydrates, E%	18.3	20.5	21.9	23.3	25.7
Medium-GI carbohydrates, E%	6.8	8.7	9.8	11.3	13.4
Low-GI carbohydrates, E%	7.1	7.9	8.3	8.4	8.4
Alcohol, E%	7.2	4.3	3.0	2.0	0.9
Fiber, g/day ^c	20	23	25	27	30

^a Abbreviations: E% = percentage of total energy intake, GI = glycemic index; ^b Leisure-time physical activity, classified as light or moderate; ^c Energy-adjusted using the residual method

Table 8. Baseline characteristics and nutrient intakes (medians) by quintiles of high-, medium- and low-glycemic index (GI) carbohydrate intake as percentage of total energy intake (E%) (n=25 943)

	High-GI carbohydrates, E%					Medium-GI carbohydrates, E%					Low-GI carbohydrates, E%				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Age, years	15.3	19.0	21.7	24.5	28.8	4.7	7.5	9.7	12.2	16.7	4.6	6.6	8.0	9.5	12.0
BMI ^a , kg/m ²	25.9	25.8	25.9	25.9	26.0	26.7	26.0	25.8	25.7	25.4	25.7	25.8	25.9	26.0	26.1
Moderate physical activity, % of subjects ^b	55	57	60	60	62	54	58	60	62	60	54	58	60	61	61
Energy, MJ/day	10.9	11.1	11.0	10.9	10.5	10.3	10.8	11.0	11.2	11.0	10.9	11.2	11.1	10.8	10.4
Carbohydrates, E%	36.9	38.5	39.9	41.5	44.6	36.6	38.8	40.1	41.7	44.5	39.1	39.7	40.5	40.8	41.7
Fat, E%	42.6	41.9	41.0	39.9	37.6	41.5	41.5	41.0	40.4	38.5	40.6	41.1	40.9	40.5	39.5
Protein, E%	14.4	14.4	14.3	14.3	14.2	15.0	14.6	14.4	14.1	13.5	13.3	13.9	14.3	14.7	15.3
Alcohol, E%	4.3	3.5	3.1	2.6	1.8	5.0	3.5	2.8	2.4	1.8	4.7	3.5	2.9	2.5	2.0
Fiber, g/day ^c	19.4	22.4	24.7	27.3	31.7	25.3	25.2	24.9	24.4	23.5	24.1	24.4	24.7	24.8	25.0

^aBMI = body mass index; ^b Leisure-time physical activity, classified as light or moderate; ^c Energy-adjusted using the residual method

Table 9. Baseline characteristics and nutrient intakes (medians) by quintiles of dietary glyceemic index and glyceemic load (n=25 943)

	Glyceemic index					Glyceemic load ^a				
	1	2	3	4	5	1	2	3	4	5
Age, years	62.6	65.4	67.3	69.3	73.1	144	162	175	188	208
Body mass index, kg/m ²	26.0	25.9	25.9	25.8	25.9	26.2	26.0	25.9	25.8	25.7
Moderate physical activity, % of subjects ^b	58	61	61	60	54	52	57	59	63	63
Energy, MJ/day	10.8	11.0	11.0	11.0	10.5	10.8	11.0	11.0	10.9	10.7
Carbohydrates, g/day ^a	259	264	264	263	248	218	244	261	278	303
Protein, g/day ^a	95	93	92	91	86	95	93	92	91	88
Fat, g/day ^a	121	120	120	118	114	133	126	120	115	105
Alcohol, g/day	7	8	10	12	26	21	14	11	8	5
Fiber, g/day ^a	21	24	26	27	26	20	23	25	27	31

^aEnergy-adjusted using the residual method; ^b Leisure-time physical activity, classified as light or moderate

With increasing carbohydrate intake, the intake of fat and alcohol decreased and the intake of fiber increased (Table 7). Participants with higher high-, medium-, or low-GI carbohydrate intake had lower fat and alcohol intake and higher total carbohydrate intake (Table 8). Intake of protein, by contrast, did not change essentially with increasing high-GI carbohydrate intake, diminished with increasing medium-GI carbohydrate intake, and rose with increasing low-GI carbohydrate intake. Fiber intake associated strongly positively with high-GI carbohydrate intake, inversely with medium-GI carbohydrate intake, and slightly positively with low-GI carbohydrate intake.

With increasing GI, the intake of protein and fat decreased, while the intake of alcohol and fiber increased (Table 9). The GL correlated positively with carbohydrate and fiber intake and negatively with protein, fat, and alcohol intake.

5.2.3 Sources of carbohydrates and dietary GL

The foods that contributed 90% of the mean carbohydrate intake were cereals (45%; wheat 23%, rye 18%, and other 4%), potatoes (11%), sugar and sugar-rich foods (10%), milk (10%), beverages (7%), and fruits, berries, legumes, and vegetables (5%).

The main sources of high-GI carbohydrates were wheat bread and bakery (32%), rye bread (29%), potatoes (17%), and beer (5%), of medium-GI carbohydrates sugar and sugar-rich foods (57%) and wheat bakery (15%), and of low-GI carbohydrates milk (49%) and fruits, berries, legumes, and vegetables (20%).

The main sources of dietary GL were cereals (49%; wheat 24%, rye 21% and other 4%), potatoes (14%), sugar and sweets (12%), milk (7%), and fruits, berries, legumes, and vegetables (6%).

5.2.4 Interindividual variation in dietary GI

Foods that contributed most to interindividual variation in dietary GI were beer (41%) and milk (24%). Other foods explained clearly less of the variation; rye 5% and potatoes, sugars, yoghurt, fruits, and juices 1-2% each. With increasing dietary GI, consumption of milk decreased and consumption of beer increased, especially from the fourth quintile to the fifth quintile (Figure 1).

Consumption of the main contributor foods to the interindividual variation in dietary GI, beer and milk, was associated with diabetes risk: milk directly ($P < 0.001$) and beer marginally inversely ($P 0.08$).

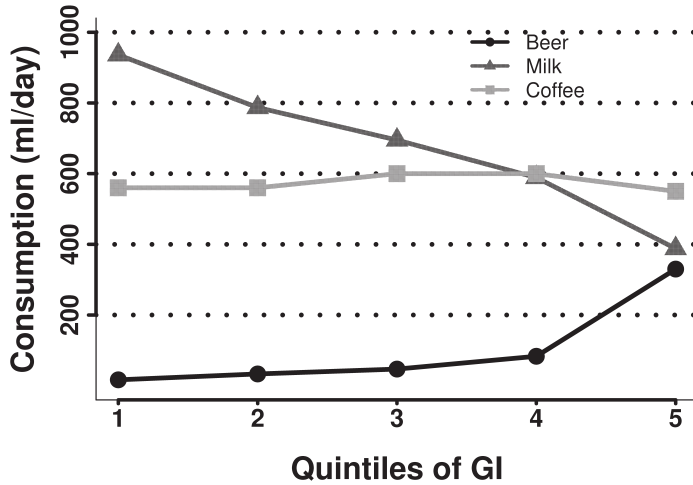


Figure 1. Consumption of beer, milk, and coffee in quintiles of dietary glycemic index (GI).

5.2.5 Correlations of carbohydrates with other macronutrients

The strongest negative correlation was observed for total carbohydrate intake and fat intake (total fat and monounsaturated and saturated fatty acid intake) (Table 10). The strongest positive correlations were found for total carbohydrates and plant protein, high-GI carbohydrates and plant protein, and low-GI carbohydrates and milk protein.

Table 10. Spearman correlation coefficients between intake of total, high-, medium-, and low-glycemic index (GI) carbohydrates (CHO) and the other energy-yielding nutrients as percentage of total energy intake (n = 25 943)^a

	Total CHO	High-GI CHO	Medium-GI CHO	Low-GI CHO
Total protein	-0.07	-0.03	-0.26	0.38
Meat protein	-0.33	-0.18	-0.13	-0.08
Milk protein	-0.05	-0.25	-0.13	0.62
Plant protein	0.59	0.73	-0.04	-0.11
Total fat	-0.57	-0.32	-0.20	-0.08
Saturated fatty acids	-0.32	-0.26	-0.07	0.04
Trans fatty acids	-0.10	-0.02 ^b	-0.04	-0.05
Monounsaturated fatty acids	-0.53	-0.31	-0.15	-0.10
Polyunsaturated fatty acids	-0.02 ^c	0.08	-0.07	-0.05

^a p value for correlations <0.001 with the following exceptions: ^b p=0.001 and ^c p=0.01

5.3 Carbohydrate intake, GI, GL, and risk of type 2 diabetes (Publications III and IV)

5.3.1 Baseline characteristics and dietary intakes among diabetes cases and the whole cohort

The incident diabetes cases had higher BMI and were less physical active relative to the whole cohort (Table 11). Percentages of macronutrient intakes did not differ markedly between cases and the whole cohort.

Table 11. Baseline characteristics and dietary intakes (medians) of incident diabetes cases and whole cohort ^a

	Diabetes cases n = 1098	Cohort n = 25 943
Age, years	56.3	57.0
BMI, kg/m ²	29.7	25.9
Moderate leisure-time physical activity, % of subjects ^b	52.4	58.7
Dietary intakes		
Energy, MJ/day	11.0	10.9
Glycemic index	67.2	67.3
Glycemic load ^c	170	175
Carbohydrates, E%	39.5	40.4
High-GI carbohydrates, E%	21.8	21.7
Medium-GI carbohydrates, E%	8.4	9.7
Low-GI carbohydrates, E%	8.2	8.0
Fat, E%	40.8	40.5
Saturated fatty acids, E%	16.8	17.1
Trans fatty acids, E%	1.0	1.0
Monounsaturated fatty acids, E%	10.9	10.8
Polyunsaturated fatty acids, E%	3.4	3.2
Protein, E%	14.8	14.3
Meat protein, E%	5.4	5.2
Milk protein, E%	4.6	4.4
Plant protein, E%	4.0	3.9
Alcohol, E%	2.8	3.0
Fiber, g/day ^c	24.3	24.6

^a Abbreviations: BMI = body mass index, GI = glycemic index, E% = percentage of total energy intake;

^b Leisure-time physical activity, classified as light or moderate; ^c Energy-adjusted using the residual method

5.3.2 Dietary GI and GL, substitution of lower-GI carbohydrates for higher-GI carbohydrates, and risk of diabetes

Dietary GI was inversely associated with diabetes risk when adjusted for age and intervention group (RR for highest versus lowest quintile 0.79; 95% CI 0.66, 0.94), but in the multivariate model this association was not present (RR for highest versus lowest quintile 0.87; 95% CI 0.71, 1.07) (Figure 2).

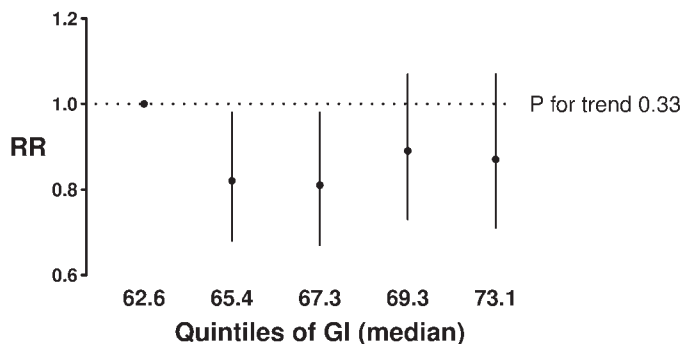


Figure 2. Relative risks (RRs) and 95% confidence intervals of diabetes in quintiles of dietary glycemic index (GI). Adjusted for age, intervention group, body mass index, smoking, physical activity, intakes of total energy, alcohol, fat, and fiber, and consumption of coffee.

Dietary GL was inversely associated with diabetes risk when adjusted for age and intervention group (RR for highest versus lowest quintile 0.63; 95% CI 0.52, 0.76). In the multivariate model, the association was not observed (RR for highest versus lowest quintile 0.88; 95% CI 0.65, 1.17) (Figure 3).

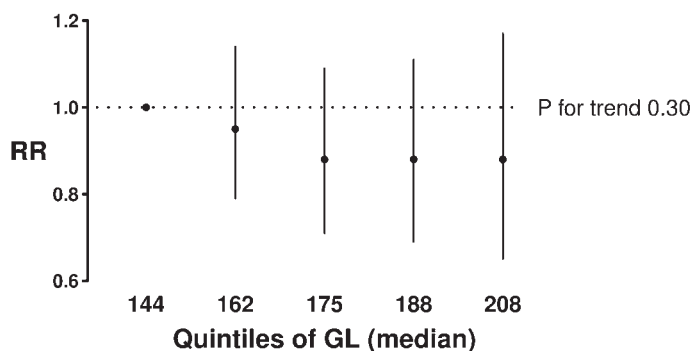


Figure 3. Relative risks (RRs) and 95% confidence intervals of diabetes in quintiles of energy-adjusted dietary glycemic load (GL). Adjusted for age, intervention group, body mass index, smoking, physical activity, intakes of total energy, alcohol, fat, and fiber, and consumption of coffee.

No interaction between fiber intake and the associations of GI or GL and diabetes risk was found (interaction terms non-significant).

The substitution of medium-GI carbohydrates for high-GI carbohydrates was inversely associated with diabetes risk (RR for highest versus lowest quintile 0.75; 95% CI 0.59, 0.96) (Figure 4). The diabetes risk decreased most when the intake of medium-GI carbohydrates substituting for high-GI carbohydrates increased from the lowest to the second lowest quintile (RRs for increasing quintiles were 1.00, 0.83, 0.78, 0.79, and 0.75). Substitution of low-GI carbohydrates for high-GI or medium-GI carbohydrates was not associated with diabetes risk.

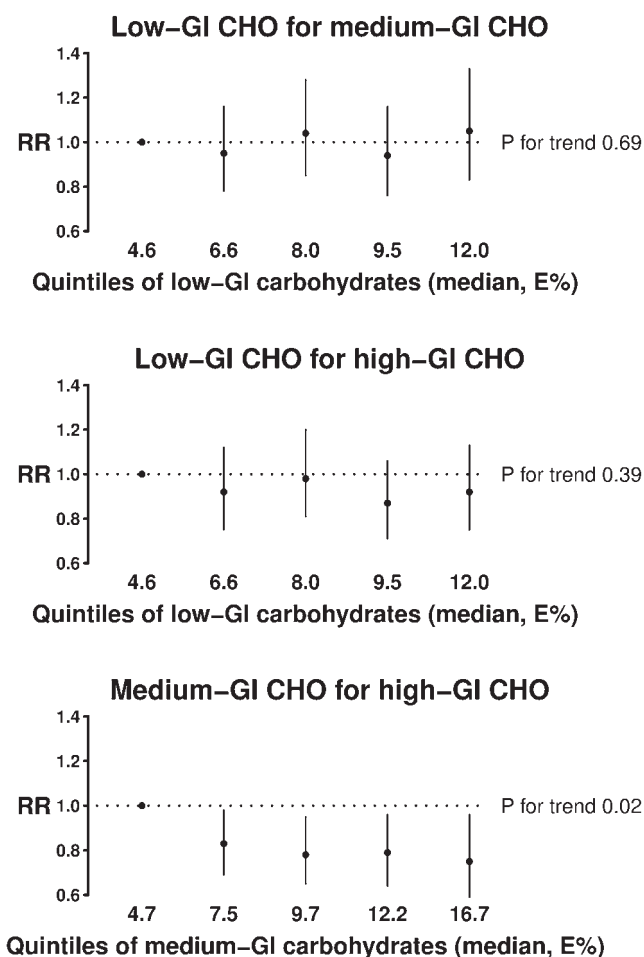


Figure 4. Relative risks (RRs) and 95% confidence intervals of diabetes in quintiles of substitutions of lower-glycemic index (GI) carbohydrates (CHO) for higher-GI carbohydrates. Adjusted for age, intervention group, body mass index, smoking, physical activity, intakes of total energy, alcohol, fat, protein, and the remaining carbohydrate variable as a percentage of total energy intake (E%), coffee consumption, and fiber intake.

No interaction between fiber intake and the associations of substitutions of lower-GI carbohydrates for higher-GI carbohydrates and diabetes risk was found (interaction terms non-significant).

5.3.3 Total, high-, medium-, and low-GI carbohydrate intake

Higher percentage of total carbohydrate intake was associated with decreased incidence of diabetes in the model adjusted for age and intervention group (RR for highest versus lowest quintile 0.62; 95% CI 0.51, 0.75) and in the multivariate model (RR for highest versus lowest quintile 0.78; 95% CI 0.64, 0.94) (Figure 5).

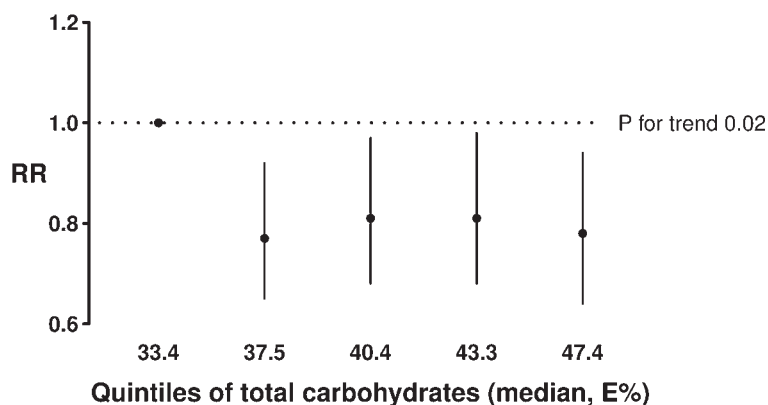


Figure 5. Relative risks (RRs) and 95% confidence intervals of diabetes in quintiles of total carbohydrate intake as a percentage of total energy intake (E%). Adjusted for age, intervention group, body mass index, smoking, physical activity, intake of total energy, and consumption of coffee.

Higher intake of medium-GI carbohydrates was associated with lower diabetes risk in the model adjusted for age and intervention group (RR for highest versus lowest quintile 0.46; 95% CI 0.38, 0.56) and in the multivariate model (RR for highest versus lowest quintile 0.69; 95% CI 0.57, 0.84) (Figure 6). Higher intake of low-GI carbohydrates was associated with increased diabetes risk in the model adjusted for age and intervention group (RR for highest versus lowest quintile 1.19; 95% CI 1.00, 1.44), but not in the multivariate-adjusted model (RR for highest versus lowest quintile 1.10; 95% CI 0.91, 1.33). Intake of high-GI carbohydrates was not associated with diabetes risk.

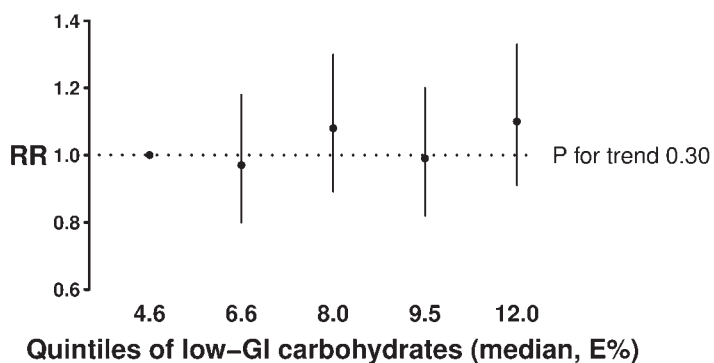
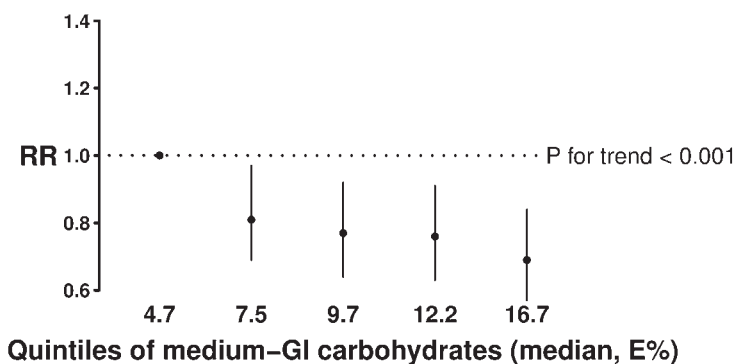
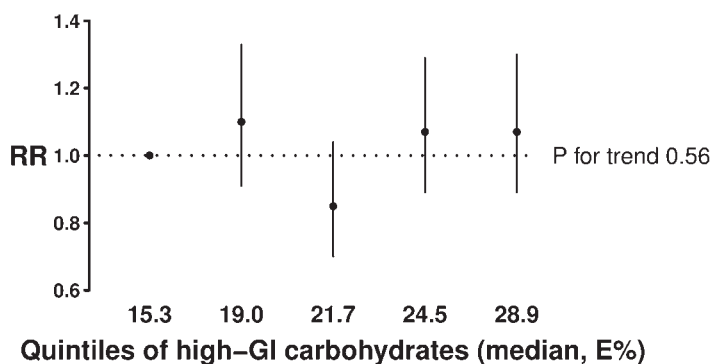


Figure 6. Relative risks (RRs) and 95% confidence intervals of diabetes in quintiles of high-, medium-, and low-glycemic index (GI) carbohydrate intake as a percentage of total energy intake (E%). Adjusted for age, intervention group, body mass index, smoking, physical activity, intake of total energy, and consumption of coffee.

Additional analysis of further adjustment for fiber intake did not alter the associations of total, high-, medium-, or low-GI carbohydrate intakes and diabetes risk. No interaction between fiber intake and the associations of total, high-, medium-, and low-GI carbohydrate intakes and diabetes risk was found (interaction terms non-significant).

5.3.4 Total, high-, medium-, and low-GI carbohydrate substitution for fat or protein

The total carbohydrate substitution for total fat was inversely associated with diabetes risk; the multivariate-adjusted RR for 2 E% substitution was 0.96 (95% CI: 0.94, 0.99) (Table 12). The high- or low-GI carbohydrate substitution for total fat was not associated with diabetes risk, and the medium-GI carbohydrate substitution was inversely associated (RR for 2 E% substitution 0.95; 95% CI: 0.92, 0.98).

Total, high-, medium-, or low-GI carbohydrate substitution for saturated or trans fatty acids was significantly inversely associated with diabetes risk only when total carbohydrates replaced trans fatty acids (multivariate RR for 1 E% substitution 0.81; 95% CI: 0.68, 0.98). Total, high-, medium-, or low-GI carbohydrate substitution for mono- or polyunsaturated fatty acids was not associated with diabetes risk.

Table 12. Relative risks (RRs) and 95% confidence intervals (CIs) of diabetes when carbohydrates replaced total fat or different fatty acids^{a, b}

Substituting nutrient	To be substituted	E% ^c	RR	95% CI
Total carbohydrates	Total fat	2	0.96	0.94, 0.99
High-GI carbohydrates	Total fat	2	0.98	0.95, 1.00
Medium-GI carbohydrates	Total fat	2	0.95	0.92, 0.98
Low-GI carbohydrates	Total fat	2	0.96	0.92, 1.01
Total carbohydrates	SFA	2	0.96	0.91, 1.02
High-GI carbohydrates	SFA	2	0.98	0.92, 1.05
Medium-GI carbohydrates	SFA	2	0.95	0.90, 1.01
Low-GI carbohydrates	SFA	2	0.97	0.89, 1.05
Total carbohydrates	TFA	1	0.81	0.68, 0.98
High-GI carbohydrates	TFA	1	0.89	0.76, 1.05
Medium-GI carbohydrates	TFA	1	0.88	0.75, 1.04
Low-GI carbohydrates	TFA	1	0.88	0.75, 1.04
Total carbohydrates	MUFA	2	0.99	0.87, 1.12
High-GI carbohydrates	MUFA	2	1.01	0.88, 1.15
Medium-GI carbohydrates	MUFA	2	0.98	0.85, 1.12
Low-GI carbohydrates	MUFA	2	0.99	0.87, 1.13
Total carbohydrates	PUFA	2	1.02	0.87, 1.18
High-GI carbohydrates	PUFA	2	1.07	0.92, 1.26
Medium-GI carbohydrates	PUFA	2	1.04	0.89, 1.22
Low-GI carbohydrates	PUFA	2	1.06	0.89, 1.25

^a Abbreviations: GI = glycemic index, SFA = saturated fatty acids, TFA = trans fatty acids, MUFA = monounsaturated fatty acids, PUFA = polyunsaturated fatty acids; ^b Adjusted for age, intervention group, body mass index, smoking, physical activity, coffee consumption, and intakes of total energy and the remaining energy-yielding nutrients; ^c Amount of substitution as a percentage of total energy intake (E%)

When substituting total carbohydrates for combined saturated and trans fatty acids, the substitution was inversely associated with diabetes risk (RR for 2 E% substitution 0.94; 95% CI: 0.89, 0.99). Total carbohydrate substitution for combined mono- and polyunsaturated fatty acids was not associated with diabetes risk.

The substitution of total carbohydrates for total protein was inversely associated with diabetes risk (Table 13); the multivariate-adjusted RR for 2 E% substitution was 0.85 (95% CI: 0.80, 0.90). Substitutions of total, high-, medium-, or low-GI carbohydrates for total, meat, or milk protein were each inversely associated with diabetes risk. Substitution of total carbohydrates for plant protein was inversely associated with diabetes risk, but substitutions of high-, medium- or low-GI carbohydrates for plant protein were not significantly associated with the risk.

Table 13. Relative risks (RRs) and 95% confidence intervals (CIs) of diabetes when carbohydrates replaced protein^{a, b}

Substituting nutrient	To be substituted	E% ^c	RR	95% CI
Total carbohydrates	Total protein	2	0.85	0.80, 0.90
High-GI carbohydrates	Total protein	2	0.87	0.81, 0.94
Medium-GI carbohydrates	Total protein	2	0.85	0.79, 0.90
Low-GI carbohydrates	Total protein	2	0.86	0.78, 0.94
Total carbohydrates	Meat protein	2	0.85	0.79, 0.92
High-GI carbohydrates	Meat protein	2	0.87	0.80, 0.95
Medium-GI carbohydrates	Meat protein	2	0.85	0.79, 0.92
Low-GI carbohydrates	Meat protein	2	0.86	0.79, 0.95
Total carbohydrates	Milk protein	2	0.83	0.77, 0.91
High-GI carbohydrates	Milk protein	2	0.86	0.78, 0.95
Medium-GI carbohydrates	Milk protein	2	0.84	0.77, 0.93
Low-GI carbohydrates	Milk protein	2	0.86	0.75, 0.97
Total carbohydrates	Plant protein	1	0.84	0.77, 0.93
High-GI carbohydrates	Plant protein	1	0.90	0.79, 1.03
Medium-GI carbohydrates	Plant protein	1	0.89	0.79, 1.00
Low-GI carbohydrates	Plant protein	1	0.90	0.79, 1.01

^a Abbreviations: GI = glycemic index; ^b Adjusted for age, intervention group, body mass index, smoking, physical activity, coffee consumption, total energy and the remaining energy-yielding nutrients; ^c Amount of substitution as a percentage of total energy intake (E%)

Additional analysis of further adjustment for fiber intake was conducted. After adjustment for fiber intake, the associations of total, high-, medium-, and low-GI carbohydrate substitutions for total fat, fatty acids, and total, meat, milk, and plant protein remained similar, with the following exceptions: the inverse associations between substitution of medium- and low-GI carbohydrates for plant protein were significant, RR for 1 E% medium-GI carbohydrate substitution for plant protein was

0.86 (95% CI: 0.76, 0.98) and RR for 1 E% low-GI carbohydrate substitution for plant protein 0.87 (95% CI: 0.77, 0.99).

Effect modification by fiber intake in the associations of total carbohydrate substitution for total fat or protein and diabetes risk was not observed (interaction terms non-significant).

6 Discussion

Many methodologic aspects in epidemiologic studies of the association between GI and diabetes risk warrant further consideration. Some of these factors are discussed here, such as variability in food GI value, application of food GI to the whole diet measured with FFQ, and characteristics of dietary GI (an average ratio) and GL (product of GI and carbohydrate amount). Multivariate nutrient density models applied to examine associations between substitution of lower-GI carbohydrates for higher-GI carbohydrates and diabetes risk and between carbohydrate intake at the expense of fat and protein and diabetes risk are discussed.

6.1 Application of food GI to epidemiologic studies

6.1.1 Measurement of food GI and variation in responses

Variation in glycemic responses and GI values of foods was considerable. The variation was smaller when measured from capillary samples than from venous samples and when the reference food (glucose or white bread) was tested at least twice.

The glucose responses measured from capillary samples were higher than those from venous samples, the difference being largest at the highest glucose concentrations. IAUCs were almost twofold from capillary samples than from venous samples. The difference was consistent with previous findings; glucose concentrations in venous samples tend to be lower than those in capillary samples because, as blood flows from the arteries through the capillaries to the veins, peripheral tissues uptake some of the glucose. The rise in blood glucose and insulin after eating stimulates glucose removal by tissues; thus, the difference between capillary and venous glucose concentration is greater postprandially than in fasting state, leading to a smaller glucose rise in venous blood (Coppack et al. 1990). The degree of glucose uptake depends, in addition to glucose and insulin concentrations, on subject's insulin sensitivity. The capillary-venous difference has been found to be largest in insulin-sensitive individuals, e.g. in lean, fit, young athletes, and smallest in insulin-resistant subjects, e.g. diabetic individuals (Marks 1996). In this study, all subjects were non-obese and had normal glucose tolerance at baseline, therefore, the differences in glycemic responses between capillary and venous samples were likely due to glucose uptake by the forearm muscles.

Both the within-subject and between-subject variations in glucose responses and GIs were higher for venous samples than for capillary samples. This result was in line with previous findings (Wolever et al. 2003) and confirmed the recommendation of use of capillary sampling in GI measurement (FAO/WHO 1998).

The GI values measured from venous samples tended to be higher than the values from capillary samples. In the interlaboratory study (Wolever et al. 2003), this tendency was not systematic, but venous samples with a reference measured only once produced high sporadic GI values. In this study, venous sampling occasionally resulted in unreasonably high mean GI values and variation when the reference was measured once or twice. Similar results were published in another study with venous samples and small carbohydrate portions (30 g) (Bucalossi et al. 1990).

The result of no essential difference in accuracy of GI when glucose solution or white bread was used as the reference is in line with previous findings (Wolever et al. 2003). The coefficient between GIs with white bread as the reference compared with GIs with glucose solution as the reference was ~ 1.3 (when using capillary samples; with venous samples, the coefficient was highly variable). Earlier, the GI values obtained using white bread have been presented to be ~ 1.4 times higher than those obtained using glucose (FAO/WHO 1998).

The repetition of reference food measurement influenced the variation; the variation diminished most when the IAUC of glucose solution or white bread was measured twice instead of only once for each subject. A third measurement did not affect the variation as much. The capillary GIs leveled off with two glucose references, and the CV diminished only a little further with three references. The capillary GIs did not differ when white bread as the reference was tested once, twice, or three times, but the CVs were lower when white bread was tested two or three times. Testing the reference food at least three times has been recommended (FAO/WHO 1998); in a later review (Brouns et al. 2005), testing at least twice was advised.

Repeating also the test food measurement lowered the variation in GI estimate. However, repeating measurements adds expenses, and thus, repeating the reference food has been recommended, as it has an influence on the GI of every test food in the series (Brouns et al. 2005).

When GI of white bread was calculated using three measurements of both white bread and glucose solution (supposing low within-subject variation due to repeated test and reference foods), the CV from capillary samples was 25% and from venous samples 42%, and the corresponding GI varied from 42 to 103 and from 36 to 144. The heterogeneity in GI between individuals was in line with a previous finding (Williams et al. 2008). In epidemiologic analysis, the same food GI is assigned to all participants, although the GI calculated for each individual seems to differ substantially. This may attenuate detection of an association between glycemic effects of foods and disease risk.

The GI values were calculated using seven-point sampling for 120 min. This sampling schedule has been shown in subjects without diabetes to provide more valid GI values than other kinds of samplings (Wolever 2004). In this study,

extension of blood sampling to 180 min provided similar GI values, except for the GI of rye bread, which was slightly higher, but the difference was not significant.

The late glucose response after consumption of rye bread differed from the responses of the other foods; although rye bread provided a similar initial blood glucose peak, neither capillary nor venous glucose concentration decreased below the fasting concentration at any sampling point, unlike the other foods. This resulted in a relatively large IAUC for rye bread, and the GI of rye bread (77) was of the same magnitude as that of white bread (79) and instant mashed potato (80). This finding is compatible with previous results showing that although glucose response of rye bread is of the same magnitude as that of white bread, rye bread causes a lower insulin response (Leinonen et al. 1999, Juntunen et al. 2002). The lower insulin response explains, at least partly, the delayed glucose decline. The mechanism behind the lower insulin response of rye bread is unclear. The structure, and not the fiber content, has been suggested to explain the lower insulin response (Juntunen et al. 2003). However, neither fiber content nor amylolysis (dependent on structure) explained the lower insulin response in another study (Rosen et al. 2009).

Beneficial (low and prolonged) postprandial glycemic profile was observed for rye breads in a study that defined the glycemic profile as the duration for the incremental glucose response divided with the incremental peak (Rosen et al. 2009). Postprandial blood glucose profiles and GIs of foods were compared in another study (Brand-Miller et al. 2009); the study suggested that GI provides a good summary of postprandial glycemia. GI as an indicator of postprandial glycemia has been widely applied to epidemiologic studies, while the specific components describing the glycemic profile have not.

6.1.2 Assigning food GI values for epidemiologic studies

The GI database was compiled for the epidemiologic studies of participants in the ATBC Study. The main requirement in compiling a GI database was availability of the measured GI values for foods compatible with those consumed by the participants of the ATBC Study and that the measured GI values were from studies that fulfilled methodologic requirements.

A strength of this study was the possibility to use, for many of the main carbohydrate sources, GI values measured at the laboratory of the National Institute for Health and Welfare. Thus, GI values for relevant local carbohydrate-containing foods were available.

Bread is an example of foods prone to variation in GI depending not only on the ingredients or carbohydrate content of the food, but also on other factors such as processing and structure. For rye bread, high GI value was measured in this study and low or medium GI values have been presented based on some other studies (Foster-Powell et al. 2002). Although the low GI values presented for rye bread (Foster-Powell et al. 2002) referred to breads containing intact kernels (Liljeberg et

al. 1992), some studies did not show low glucose response for rye bread even though it contained whole kernels (Leinonen et al. 1999). In this study, a high GI value was assigned for rye bread produced from milled rye flour.

For some foods, such as beer, a reliable GI value is lacking in the scientific literature. The latest international table of GI and GL values (Atkinson et al. 2008) presented a GI value of 66 for beer, based on an unpublished observation measured using a 10-g carbohydrate portion. However, a carbohydrate portion of at least 25 g has been recommended because a smaller portion may result in an imprecise GI estimate (Brouns et al. 2005, Wolever et al. 2006a). A publication from the brewing industry suggested that the GI of beer is over 100 (Walker 2006). We used for beer a high GI value measured at the laboratory of the National Institute for Health and Welfare. In other GI databases, the GI value for beer has varied widely, from a low 36 (Flood et al. 2006) or a moderate 66 (Neuhouse et al. 2006) to a high 95 (Schulz et al. 2005), and some studies have omitted a value altogether (Hodge et al. 2004).

In compiling the GI database, we reviewed the quality of GI measurements of publications providing GI values and included studies applying internationally recommended methods (FAO/WHO 1998, Brouns et al. 2005). The minimum methodologic criteria were set: the reference food was glucose solution or white bread, the amount of available carbohydrate of the test and the reference foods was the same (50 g or 25 g), the subjects were not treated with insulin, and the number of subjects was ≥ 6 .

In addition to the minimum methodologic criteria, other methodologic factors exist (FAO/WHO 1998, Brouns et al. 2005) that could provide more accurate GI values. Using capillary blood samples rather than venous samples and repeating the reference food measurement could improve the accuracy of GI values (Wolever et al. 2003). However, many studies have not applied these methodologic choices. The total number of publications (or publishers in case of the laboratory of the National Institute for Health and Welfare, a Finnish manufacturer, and the laboratory of Sydney University) used for inclusion of their GI values in the GI database of this study was 41 (Appendix Table 1). Of the 41 publications, 25 (61%) reported use of capillary samples, 16 (39%) reported repeated reference tests, and 12 (29%) reported use of both capillary samples and repeated reference tests. Including only these studies would have severely restricted the availability of GI values, so GI values measured from venous samples and/or calculated using only one reference measurement were also included.

Of the foods ($n=66$) that contributed 90% of the total carbohydrate intake of the ATBC Study participants, GI value determined in the laboratory of the National Institute for Health and Welfare was available for 20 (30%). In measurement of these GI values, the methodology followed the recommendations (FAO/WHO 1998, Brouns et al. 2005), capillary samples were used, and the reference test was repeated.

Although we could not use all criteria known to be useful for the accuracy of GI values, many of the values included in the database were assigned from studies considering more methodologic issues than the minimum criteria. It has not been widely investigated which factors in GI determination should be controlled and which are optional (Wolever et al. 2008).

Many former epidemiologic studies have reported use of the international table of GI values (Foster-Powell et al. 2002), which includes GI values measured with variable methodologic choices. In the later version of the international GI table (Atkinson et al. 2008), GI values were classified according to methodologic choices and variability of results.

6.1.3 Application of GI concept to entire meals and diets assessed using food frequency questionnaire

The GI concept was applied to entire diets of the ATBC Study participants as it has been applied in other epidemiologic studies. Use of the GI concept in epidemiologic studies has, however, been criticized (Pi-Sunyer 2002). GIs are determined for individual foods, while, in practice, people do not eat single foods separately, but in different combinations, and thus, glycemic responses of foods may vary depending on how they are combined with other components. It is not possible to measure glycemic responses for every food in all combinations, and in epidemiologic studies, when diet is assessed using FFQ, frequencies of food consumption are queried without asking about the combinations of foods.

The GI of composite food and entire diet containing several carbohydrate foods was calculated as the weighted mean of the GI values of each component, with the weighting based on the proportion of carbohydrates provided by each component (Wolever and Jenkins 1986, Wolever et al. 1991, FAO/WHO 1998). Mixing pure carbohydrates seems to result in glycemic responses predictable from the responses of the carbohydrate parts, e.g. GI of sucrose (a disaccharide consisting of fructose and glucose) is approximately midway between GI of fructose and glucose (Jenkins et al. 1981, Lee and Wolever 1998). Predicting glycemic responses of meals that also include fat or protein, is, however, more complicated because fat and protein affect (typically lower) glycemic responses (Hätönen et al. 2011). Applicability of food GI to mixed meals has been debated for as long as the GI concept has existed (Coulston et al. 1984, Brand-Miller and Wolever 2005, Flint et al. 2005). Some studies have suggested that the glycemic response to a mixed meal is not predictable from the GI values of foods included in the meal (Coulston et al. 1987, Hollenbeck et al. 1988, Flint et al. 2004), and others have claimed the opposite results, concluding that the GI concept applies well to mixed meals (Wolever and Jenkins 1986, Chew et al. 1988, Wolever et al. 2006b). The latter studies showed that a high correlation exists between observed glucose responses of mixed meals and GIs calculated based on component GIs (Wolever and Jenkins 1986, Chew et al. 1988,

Wolever et al. 2006b). The carbohydrate content and the GI explained 90% of the variation in glycemic responses to meals, and protein and fat had negligible effects (Wolever et al. 2006b).

In this study, carbohydrate intake and dietary GI and GL were measured using FFQ. As in this study, in almost all prospective cohort studies on GI and disease published to date, FFQ has not originally been designed to measure dietary GI and GL. Carbohydrate intake, instead, has long been a standard variable to be measured using FFQ and was included in the validation study for the ATBC Study (Pietinen et al. 1988). Due to variation in food processing practices, the GI values for most foods in epidemiologic studies are at best only estimates of the actual GIs of foods consumed. Even if the method used in collecting the dietary data (dietary recalls or food records) provided more information on different properties of foods consumed, its applicability may be restricted by the lack of GI values for each food type.

Epidemiologic GI studies do not typically examine the health effects of lower GI carbohydrates relative to the effects of higher GI carbohydrates *within* the food groups. The GI concept recommends substitution of low-GI foods for high-GI foods within the same food group (Marsh et al. 2011). The possibility of examining effects of lower GI within food groups is restricted by the limited consumption of foods with variable GIs within food groups.

Applicability of GI to entire diets has been assessed by examining the associations between calculated GI and GL and plasma measures of glycemia; a clinical trial showed that participants with a low-GI diet had lower day-long glucose and insulin profiles than participants with a high-GI diet (McMillan-Price et al. 2006). By contrast, a study comparing dietary GI and GL measured using a validated FFQ with measures of glycemia (fasting glucose, 2-h postprandial glucose, and glycated hemoglobin) called into question the utility of dietary GI and GL since they did not correlate with the plasma measures (Mayer-Davis et al. 2006). The authors suggested that the dietary GI has inadequate utility to capture the true metabolic impact of foods consumed as part of a diet.

6.2 Carbohydrate intake and dietary GI and GL in epidemiologic studies

6.2.1 Carbohydrate intake and dietary GI and GL

The median total carbohydrate intake was 260 g per day and 40.3 E%. The intake as grams measured with the FFQ may be a slight overestimation (Pietinen et al. 1988). However, the carbohydrate intake as E% was low; it was clearly lower than the proportion suggested to prevent chronic diseases (WHO 2003). The carbohydrate intake was somewhat similar than that of men in other cohorts (Salmeron et al. 1997a, Mosdøl et al. 2007, Schulze et al. 2008). In cohorts of women, lower

carbohydrate intakes as grams (Salmeron et al. 1997b, Meyer et al. 2000), but higher intakes as E% (Schulze et al. 2004, Krishnan et al. 2007) have been reported.

Thus far, only a few studies have reported separate high-, medium-, and low-GI carbohydrate intakes (Sieri et al. 2010). In this study, the intake of high-GI carbohydrates was of the same magnitude and the intake of low-GI carbohydrates clearly lower than in the Italian cohort of women and men (Sieri et al. 2010).

The dietary GI in the ATBC Study was higher than reported among men (Mosdøl et al. 2007) or women (Krishnan et al. 2007). The higher dietary GI may be due to higher GI values measured for some foods consumed in Finland, such as the higher GI for rye bread in this study compared with GI values published elsewhere (Foster-Powell et al. 2002). Another reason for the higher dietary GI may be the low consumption of low-GI foods and the high consumption of high-GI foods; among ATBC Study participants, consumption of fruits and vegetables was low (Koushik et al. 2007) and consumption of cereals (prepared mainly from milled flour), potatoes, and beer was high (Park et al. 2005, Genkinger et al. 2009). The dietary GL was higher than in the other cohorts among men (Salmeron et al. 1997a, Mosdøl et al. 2007) or women (Salmeron et al. 1997b, Meyer et al. 2000, Krishnan et al. 2007). However, dietary GI and GL between all cohorts cannot be directly compared since they have been calculated using GI values based on glucose solution reference in some studies and based on white bread reference in others.

6.2.2 Associations with baseline characteristics and nutrient intakes

Participants with higher total carbohydrate intake or higher GL had lower BMI. BMI increased with increasing low-GI carbohydrate intake, decreased with increasing medium-GI carbohydrate intake, and did not alter in quintiles of high-GI carbohydrate intake. The findings are inconsistent with the hypothesis that consumption of higher-GI carbohydrates is associated with obesity (Ludwig 2002).

With increasing carbohydrate intake, both fat and alcohol intakes decreased, in accordance with previous findings (Schulze et al. 2008), but in contrast to the other cohort study, intake of protein did not decrease clearly. With increasing GL, decreasing intakes of protein, fat, and alcohol were found in this and in other studies (Schulze et al. 2004, Villegas et al. 2007, Sahyoun et al. 2008). In this study, dietary GI was associated inversely with protein and fat and positively with alcohol intake. The inverse association between GI and protein intake has been reported by other studies (Salmeron et al. 1997a, Salmeron et al. 1997b, Schulze et al. 2004, Sahyoun et al. 2008), but the intake of fat with increasing dietary GI has varied. Other studies have reported an inverse association between GI and alcohol intake (Salmeron et al. 1997a, Salmeron et al. 1997b, Hodge et al. 2004, Schulze et al. 2004, Krishnan et al. 2007, Mosdøl et al. 2007), while in this study they were correlated positively. The reason for the difference may be the high GI value assigned for beer in this study.

Increasing age and physical activity with increasing carbohydrate intake were in line with previous findings (Schulze et al. 2008), but the increase in physical activity with increasing GL found here has not been consistent in other studies (Schulze et al. 2004, Villegas et al. 2007, Sahyoun et al. 2008).

With increasing total carbohydrate intake and GL, the intake of fiber increased. Intake of fiber increased strongly with increasing high-GI carbohydrate intake, diminished with increasing medium-GI carbohydrate intake, and increased slightly with increasing low-GI carbohydrate intake. Consumption of cereals and potatoes explains the marked increase in fiber intake with increasing high-GI carbohydrates, consumption of sugar explains the decreasing dietary fiber content with increasing medium-GI carbohydrates, and consumption of fruits, berries, legumes, and vegetables explain the slight increase in fiber intake with increasing low-GI carbohydrates. Milk as the main source of low-GI carbohydrates explains the only slight increase in fiber intake. With increasing GI, the intake of fiber increased. Of the cohort studies on GI and diabetes risk, some reported increased cereal fiber intake, but not total fiber intake, with increasing GI (Salmeron et al. 1997a, Salmeron et al. 1997b, Krishnan et al. 2007), while others reported decreased total fiber intake with increasing GI (Schulze et al. 2004, Mosdøl et al. 2007). Increased total and cereal fiber intake has been reported with increasing GL (Schulze et al. 2004, Krishnan et al. 2007, Mosdøl et al. 2007) and with increasing carbohydrate intake (Schulze et al. 2008).

6.2.3 Dietary GI as an average ratio

Dietary GI (calculated as a weighted mean of GIs of all foods consumed) describes the average GI of the carbohydrates consumed. Food GI is a ratio of the glucose response to the investigated food and the glucose response to the reference food, and thus, dietary GI is a (weighted) average ratio. Because subjects eat a wide variety of foods with different GIs, the dietary GI often falls within a narrow range. On the other hand, the same dietary GI can be a result of several different combinations of carbohydrate-containing foods. Dietary GI may reflect different dimensions of the diet, not just the quality of carbohydrates (Schulze et al. 2005).

In this study, the GI quintile medians ranged from 62.6 to 73.1. The range of 10.5 did not differ much from the ranges in other studies reporting a positive association between dietary GI and risk of diabetes; the difference between the highest and lowest GI quintile medians has mostly varied from 11 to 16 (Salmeron et al. 1997a, Salmeron et al. 1997b, Schulze et al. 2004, Krishnan et al. 2007). Being conscious of the inaccuracy in measurement of GIs of foods and in measurement of dietary GI using FFQ, it is debatable whether a range of this magnitude in dietary GI is adequate to reliably rank participants for analysis of the associations with disease risk.

6.2.4 Interindividual variation in dietary GI

The interindividual variation in dietary GI was explained by unexpected foods; the main contributors of the interindividual variation were milk (24%) and beer (41%), explaining as much as 65% of the variation, while the main sources of dietary GI and carbohydrates were cereals and potatoes.

The large contribution of beer and milk in the interindividual variation of GI may be explained by variation in consumption of these foods, and on the other hand, similarity in consumption of the other carbohydrate sources, cereals and potatoes. Another reason for their substantial contribution may be the extreme GI values of milk and beer; GI of milk was one of the lowest GIs and GI of beer was the highest. As a result, consumption of milk decreased strongly with increasing dietary GI, and consumption of beer increased with increasing GI. In the ATBC Study, consumption of milk and beer was high (Cho et al. 2004, Lee et al. 2007, Genkinger et al. 2009). In the literature, there is reliable evidence that the GI of milk is low (Hoyt et al. 2005), but differences between this study and others may arise from the GI assigned to beer. In this study, a high GI value was assigned, whereas in other studies or databases the GI has been low (Flood et al. 2006), medium (Neuhouser et al. 2006), or high (Schulz et al. 2005), and some studies have omitted GIs of alcoholic beverages altogether (Hodge et al. 2004).

Rare studies on the association between dietary GI and diabetes risk have revealed the contributors of the interindividual variation in GI. A study that assigned a high GI value (GI=95) to beer showed similar contributors in men as found here; most of the variation was explained by beer (30%) and milk products (15%) (Schulz et al. 2005). A study using dietary recalls to collect data and assigning a medium GI value of 66 to beer reported bread to be the main contributor of both dietary GL and its interindividual variation (van Bakel et al. 2009a). Because the interindividual variation in a variable is essential in epidemiologic analysis of the relationship between exposure and disease, these results warrant examination of the dimensions of dietary GI in each study population before epidemiologic analysis.

6.2.5 Dietary GL as a measure of quantity and quality of carbohydrates

GL, the product of GIs and grams of carbohydrates consumed, describes both carbohydrate quality and quantity. Thus, GL can be altered by changing GI, amount of carbohydrates, or both. When using dietary GL to analyze disease risk, separating the changes in quality and quantity of carbohydrates is not possible. In practice, a decrease in dietary GL may result from eating low-GI foods instead of high-GI foods or from eating less carbohydrates. In order for dietary GL to be a valid measure, reducing dietary GI should have the same metabolic effects as reducing the amount of carbohydrates in the diet. However, the effects do not seem to be the same (Wolever and Mehling 2003). In addition, changes in the amount of carbohydrates may be related to changes in intake of other energy-yielding nutrients,

protein or fat, and the effect of carbohydrates on diabetes risk may be related to the effects of the other macronutrients.

In this study, the effect of GI was analyzed considering simultaneously carbohydrate quantity; multivariate nutrient density models were applied to examine the associations of substitution of lower-GI carbohydrates for higher-GI carbohydrates with diabetes risk. This was done to better model the use of lower-GI carbohydrates instead of higher-GI carbohydrates when total carbohydrate intake is kept constant. Also, the effect of other macronutrients could be kept constant because the change in carbohydrates with different GIs was adjusted for the other macronutrients.

6.3 Carbohydrates, GI, GL, and risk of type 2 diabetes

6.3.1 Definition of diabetes from registers

The incident diabetes cases were retrieved from a nationwide drug reimbursement register maintained by the Social Insurance Institution. The register does not provide information on the type of diabetes. However, in a Finnish survey, 96% of all diabetic participants diagnosed after the age of 55 years had type 2 diabetes (Laakso and Pyörälä 1985). Since the participants of the ATBC Study were 50-69 years at study entry, the incident cases can be assumed to be primarily type 2 diabetes.

From the register, patients using medication to treat diabetes were extensively identifiable; at the time of the ATBC Study follow-up (result from 1995), the number of persons buying diabetes medication in Finland was only 3% more than the number of persons entitled to reimbursement of their diabetes medication expenses (Reunanen et al. 2008). However, only patients receiving medication for treatment of diabetes are identifiable from the register, not individuals treating their disease with dietary changes. In addition, many diabetic subjects go undiagnosed (Ylihärsilä et al. 2005, Saaristo et al. 2008). Misclassification of participants with undetected diabetes may have attenuated the findings.

During the follow-up period of the ATBC Study the diagnostic criteria at the Social Insurance Institution for reimbursement of costs of diabetes medication differed from the current criteria; the criterion was for venous or capillary sampling fasting whole-blood glucose ≥ 7.0 mmol/l, from repeated measures, while currently diabetes diagnosis is verified with a lower glucose concentration, i.e. fasting whole-blood glucose ≥ 6.1 mmol/l or fasting plasma glucose ≥ 7.0 mmol/l.

6.3.2 Diabetes among ATBC Study participants

The ATBC Study was primarily designed to evaluate the effects of alpha-tocopherol and beta-carotene supplementation on lung cancer and other cancers (The ATBC Cancer Prevention Study Group 1994). The baseline data collection and the register-based follow-up also enable risk factors for other diseases, such as diabetes, to be

investigated. Neither α -tocopherol nor β -carotene supplementation had an impact on diabetes incidence (Kataja-Tuomola et al. 2008).

Because participants comprised male smokers, the results cannot be directly generalized to nonsmokers or females. Smoking is associated with an increased risk of type 2 diabetes (Will et al. 2001), and diabetes has been observed to be more common among men than women (Ylihärsilä et al. 2005, Saaristo et al. 2008).

6.3.3 Dietary GI and GL and risk of diabetes

Dietary GI was not associated with diabetes risk. This result is in line with some previous cohort studies (Meyer et al. 2000, Stevens et al. 2002, Hodge et al. 2004, Schulz et al. 2006, Barclay et al. 2007, Mosdøl et al. 2007, Sahyoun et al. 2008). However, some studies have reported a positive association (Salmeron et al. 1997a, Salmeron et al. 1997b, Schulze et al. 2004, Krishnan et al. 2007, Villegas et al. 2007) or a borderline positive association (Sluijs et al. 2010b). Most studies reporting a positive association consisted of female subjects (Salmeron et al. 1997b, Schulze et al. 2004, Krishnan et al. 2007, Villegas et al. 2007) or mainly women (Sluijs et al. 2010b). Most studies finding no association had both male and female subjects (Stevens et al. 2002, Hodge et al. 2004, Schulz et al. 2006, Barclay et al. 2007, Mosdøl et al. 2007, Sahyoun et al. 2008). The finding of no association among male ATBC Study participants is in line with other studies including men and suggesting no association. This contradicts findings from studies comprising female subjects and suggesting a positive association.

One explanation for the gender difference may be residual confounding. Women may consume more low-GI foods (e.g. fruits) possessing other properties that lower diabetes risk. A gender difference in the foods contributing to dietary GI has been found (Schulz et al. 2005); most of the interindividual variation in dietary GI among men was explained by beer (30%) and milk products (15%) and among women by milk products (28%) and fruits (10%). This highlights the fact that the dietary GI as an average ratio of carbohydrate quality may reflect different dimensions of a diet. The inconsistent findings between dietary GI and diabetes risk may partly be due to different essential carbohydrate sources in different study populations.

Lower diabetes risk has consistently been associated with higher intake of cereal fiber (Salmeron et al. 1997a, Salmeron et al. 1997b, Meyer et al. 2000, Stevens et al. 2002, Schulze et al. 2004, Krishnan et al. 2007) and whole-grain cereals (Liu et al. 2000, Fung et al. 2002, Montonen et al. 2003). A low cereal fiber intake combined with a high GI or GL further increases diabetes risk relative to a low GI or GL and high cereal fiber intake (Salmeron et al. 1997a, Salmeron et al. 1997b, Schulze et al. 2004). In this study, the associations of dietary GI and GL with diabetes risk were unaltered by adjustment for fiber intake, and no interaction with fiber intake was found.

Dietary GL was not associated with diabetes risk in a multivariate-adjusted model. The result is in line with most prospective cohort studies (Salmeron et al. 1997a, Meyer et al. 2000, Stevens et al. 2002, Hodge et al. 2004, Schulze et al. 2004, Schulz et al. 2006, Krishnan et al. 2007, Mosdøl et al. 2007, Sahyoun et al. 2008). However, positive associations have also been reported (Salmeron et al. 1997b, Villegas et al. 2007, Halton et al. 2008, Hopping et al. 2010, Sluijs et al. 2010b). Some of the positive findings were from multivariate models adjusted for most of the energy-yielding nutrients (Sluijs et al. 2010b), with the association not being observed in the less adjusted models. In this study, GL was associated inversely with diabetes risk in models adjusted for age, intervention group, BMI, smoking, leisure-time physical activity, and intakes of energy and alcohol. This finding is in accordance with some previous observations of an inverse association between dietary GL and diabetes risk in models before multivariate adjustment (Schulze et al. 2004, Krishnan et al. 2007, Mosdøl et al. 2007). Because dietary GL is by definition strongly correlated with carbohydrate intake, adjusting for energy and energy-yielding nutrients influences the interpretation of the results (Liu and Chou 2010).

6.3.4 Foods contributing most to interindividual variation in dietary GI

Consumption of the main contributor foods of the interindividual variation in dietary GI, milk and beer, was associated with diabetes risk, not fulfilling expectations based on the GI hypothesis. Consumption of milk, a low-GI food, was positively associated with diabetes risk. Typically, foods that produce a low glucose response also produce a low insulin response (Holt et al. 1997). However, responses of some foods are divergent; although milk produces a low glycemic response, its insulin response is high (Hoyt et al. 2005). Milk protein has been found to be insulinotropic (Nilsson et al. 2004).

Prospective cohort studies have suggested that consumption of dairy products and low-fat dairy, but not high-fat dairy, is inversely associated with risk of type 2 diabetes (Fumeron et al. 2011, Tong et al. 2011). The associations have been independent of GL (Choi et al. 2005, Liu et al. 2006). In the ATBC Study population, which had a high consumption of high-fat milk, the dairy fat may have mitigated the potential benefits of milk.

Consumption of beer, a beverage with a high GI value, was marginally inversely associated with risk of diabetes. This inverse association is in accordance with earlier findings; moderate alcohol consumption has been associated with lower diabetes risk (Conigrave et al. 2001, Baliunas et al. 2009) and lower insulin secretion (Crandall et al. 2009).

The third contributor of interindividual variation in dietary GI in this study was rye bread, although its contribution was minor relative to beer and milk. Rye bread

has been found to produce a high glucose response, but a lower insulin response (Leinonen et al. 1999, Juntunen et al. 2002).

Associations of dietary GI and diseases should be interpreted carefully, also considering other properties of foods because they may affect disease risk in ways unexpected based on glycemic responses to foods.

6.3.5 Substitution of lower- for higher-GI carbohydrates and intake of total, high-, medium-, and low-GI carbohydrates

The substitution of medium-GI carbohydrates for high-GI carbohydrates was inversely associated with diabetes risk. This finding is in line with the hypothesis that carbohydrates that induce a smaller elevation in blood glucose may have beneficial effects on diabetes risk compared with carbohydrates that induce a higher blood glucose response (Ludwig 2002). The inverse association between substitution of medium-GI carbohydrates for high-GI carbohydrates and diabetes risk was not, however, proportional; the largest decrease was found when the substitution increased from the lowest quintile to the second lowest quintile.

Contrary to the GI hypothesis, a decreased diabetes risk was not found when substituting low-GI carbohydrates for medium- or high-GI carbohydrates. One explanation may be the positive association of milk—the major source of low-GI carbohydrates—with diabetes risk. Higher intake of low-GI carbohydrates was associated with increased diabetes risk in a model adjusted for age and intervention group, but the association was not significant in the multivariate-adjusted model.

Intake of high-GI carbohydrates was not associated with diabetes risk. Although consumption of beer, which was associated marginally inversely with diabetes risk, explained most of the interindividual variation in dietary GI, it did not dominate the results on high-GI carbohydrate intake to the same extent since it contributed only 5% to the mean of the high-GI carbohydrate intake. A large proportion of high-GI carbohydrates came from high-fiber cereal rye. This may be one explanation for our result of no association between high-GI carbohydrates and diabetes risk, contrary to the suggested hypothesis (Ludwig 2002); higher intake of cereal fiber or whole-grain cereals has consistently been associated with lower diabetes risk (Salmeron et al. 1997a, Salmeron et al. 1997b, Liu et al. 2000, Meyer et al. 2000, Fung et al. 2002, Stevens et al. 2002, Montonen et al. 2003, Schulze et al. 2004, Krishnan et al. 2007).

Intake of medium-GI carbohydrates was inversely associated with diabetes risk. The main contributor to medium-GI carbohydrates was sugar. Thus, the inverse association between medium-GI carbohydrate intake and diabetes risk is in accord with some cohort studies suggesting inverse association between intake of sugars or sucrose and diabetes risk (Meyer et al. 2000, Hodge et al. 2004). In this study, sugar added to coffee or tea was a considerable source of medium-GI carbohydrates. An inverse association between coffee consumption and diabetes risk has been reported

(Tuomilehto et al. 2004, van Dam et al. 2006, van Dieren et al. 2009). However, adjusting for coffee consumption did not change the inverse association between medium-GI carbohydrates and diabetes risk in this study. On the other hand, growing evidence of a positive association between consumption of sugar-sweetened beverages and risk of obesity, metabolic syndrome, and type 2 diabetes exists (Nissinen et al. 2009, Malik et al. 2010, de Koning et al. 2011b). Associations between consumption of sugar and metabolic states might depend on the magnitude of sugar consumption. In this study, the median sugar intake was 6.7 E%. Metabolic disadvantages of sugars have been reported with higher consumption of added sugar (mean 15.8 E%) (Welsh et al. 2010).

Intake of total carbohydrates was inversely associated with diabetes risk. Most of the previous cohort studies have reported no association between total carbohydrate intake and diabetes risk in multivariate models (Colditz et al. 1992, Salmeron et al. 1997a, Salmeron et al. 1997b, Meyer et al. 2000, Hodge et al. 2004, Schulze et al. 2004, Schulze et al. 2008), and some have reported an inverse association in the less adjusted models (Meyer et al. 2000, Hodge et al. 2004, Schulze et al. 2004). Recently, positive associations have also been reported (Villegas et al. 2007, Halton et al. 2008, Sluijs et al. 2010b), especially in models adjusted for both energy and most energy-yielding nutrients other than carbohydrates (Halton et al. 2008, Sluijs et al. 2010b). In these studies, no association (Halton et al. 2008) or an inverse association (Sluijs et al. 2010b) was seen in crude models. Thus far, apart from this study, no studies have separately reported associations of high-, medium-, or low-GI carbohydrate intake and type 2 diabetes risk.

6.3.6 Total-, high-, medium-, and low-GI carbohydrate substitution for fat or protein

The substitution of total carbohydrates for total fat was inversely associated with diabetes risk. Previous studies have reported no association between the substitution of carbohydrates and fat for each other and diabetes risk (Meyer et al. 2001, Salmeron et al. 2001, Schulze et al. 2008). Instead, the finding of inverse association of carbohydrate substitution for trans fatty acids with diabetes risk was in accordance with a previous result (Salmeron et al. 2001). However, no association has also been reported (Meyer et al. 2001). In this study, the inverse association between carbohydrate substitution for saturated fatty acids and diabetes risk was non-significant. Earlier studies have reported no association between substitution of carbohydrates and saturated fatty acids for each other and risk of diabetes (Meyer et al. 2001, Salmeron et al. 2001, Schulze et al. 2008). In the ATBC Study population, the main source of both saturated and trans fatty acids was dairy products. Because reducing trans fatty acid intake leads to a concomitant decrease in intake of saturated fatty acids, we also analyzed carbohydrate substitution for the combined saturated and trans fatty acids. This substitution was associated inversely with diabetes risk.

The majority of the total fat intake consisted of saturated fatty acid intake, and the intake of trans fatty acids was small (median 1.0 E%). Some authors have suggested that the relevance of trans fatty acids to diabetes incidence is limited because of the low intake (Thompson et al. 2011).

Inconsistent findings have emerged from previous studies between the substitution of carbohydrates and polyunsaturated fatty acids for each other and diabetes risk (Meyer et al. 2001, Salmeron et al. 2001, Schulze et al. 2008). In this study, intake of polyunsaturated fatty acids was low (median 3.2 E%), and no association between carbohydrate substitution for polyunsaturated fatty acids and diabetes risk was found. No association between carbohydrate substitution for monounsaturated fatty acids and diabetes risk was found in this or other studies (Meyer et al. 2001, Salmeron et al. 2001, Schulze et al. 2008).

The results of this study do not support the hypothesis that replacing fat or fatty acids with lower-GI carbohydrates is more beneficial than replacing them with higher-GI carbohydrates.

Substitution of carbohydrates for protein was inversely associated with the incidence of diabetes. This result is in accord with previous findings of prospective cohort studies (Schulze et al. 2008, Sluijs et al. 2010a). Higher consumption of red or processed meat has been associated with increased diabetes risk in several cohorts (Aune et al. 2009, Männistö et al. 2010, Steinbrecher et al. 2011). Studies on an association between low-carbohydrate diet and diabetes risk have reported that diets high in animal fat and protein may increase diabetes risk among men (de Koning et al. 2011a). Diets high in fat and protein from vegetable sources, in turn, have been associated with a decreased diabetes risk among women (Halton et al. 2008). In the present study, substitutions of carbohydrates for protein from meat or milk products were each inversely associated with diabetes risk, and the association did not depend on the GI of the substituting carbohydrates. Substitution of total carbohydrates, but not separately of high-, medium-, or low-GI carbohydrates, for plant protein was inversely associated with diabetes risk. It is noteworthy that the sources of carbohydrates, especially high-GI carbohydrates, and plant protein overlap; sources of both are, for example, cereals and potatoes. Thus, their intake is correlated strongly and positively; the Spearman correlation coefficient for total carbohydrate and plant protein was 0.59 and for high-GI carbohydrates and plant protein 0.73.

In interpretation of substitution results, one should consider that the same amount of replacement means different changes for different nutrients because the mean intakes and ranges differ: e.g. 2 E% change in intake of plant protein corresponds to half of the median intake of plant protein, but only 5% of the median carbohydrate or fat intake. For trans fatty acids and plant protein, we analyzed the substitution of 1 E% instead of 2 E% because of the smaller median intake of these nutrients and an IQR of less than 2 E%.

6.3.7 Strength of evidence from prospective cohort study

One of the strengths of this study was the prospective cohort design, which minimized recall and selection biases. In addition, detailed background and dietary data allowed adjustment for potential confounders. However, despite adjusting for many dietary and non-dietary risk factors of type 2 diabetes, the possibility of residual or unmeasured confounding cannot be ruled out. Data on abdominal obesity (waist circumference or WHR) and family history of diabetes were not available in this study.

The diet was assessed only once, at baseline, and possible changes thereafter were not investigated. Thus, the potential exists for measurement error contributing to a misclassification of exposure. Similarly, data on possible dietary and non-dietary confounders were only from baseline; any changes in these during follow-up may have confounded the associations. These factors might have attenuated the associations towards unity.

Associations detected in prospective cohort study do not necessarily imply causal associations. Nutritional epidemiologic studies provide one category of evidence for evaluating the relation of carbohydrates, GI, and GL to risk of disease. An overall assessment requires consideration of results from clinical randomized controlled trials (RCTs) as well as information regarding underlying disease mechanisms. In interventions, it is possible to observe the effect of the original GI concept of substituting lower-GI foods for higher-GI foods within food groups. However, following subjects until incidence of diseases is rare; influence on risk factors of diseases is often studied (Truswell 2005).

Evidence from RCTs has suggested that a low-GI diet may improve glycemic control in diabetes without compromising hypoglycemic events (Thomas and Elliott 2009). Also benefits of low GI or GL for promoting weight loss and improving lipid profiles among overweight or obese people were suggested (Thomas et al. 2007), but findings have not been consistent (Sichieri et al. 2007). Weak or no evidence from RCTs was reported for benefits of low-GI diets on coronary heart disease and related risk factors (Kelly et al. 2004) or for preventing gestational diabetes (Tieu et al. 2008).

Concerning prevention of diabetes, the strongest evidence from RCTs shows that long-standing lifestyle changes, including dietary changes, according to dietary recommendations, without special attention to GI, can markedly reduce the risk of developing type 2 diabetes among high-risk subjects (Tuomilehto et al. 2001, Knowler et al. 2002). A high-fiber and low-fat diet predicted long-term weight loss and decreased diabetes risk (Lindström et al. 2006).

RCTs have, however, suggested that different carbohydrates, with different postprandial insulin responses, have different effects on the metabolic factors related to metabolic diseases such as alterations in gene expression in adipose tissue and inflammatory status (Kallio et al. 2007, Kallio et al. 2008). Instead, lowering postprandial glucose using medication (a short-acting insulin secretagogue nateglinide,

taken before meals) in addition to a lifestyle modification program did not reduce the incidence of diabetes (Holman et al. 2010).

6.4 Implications for further research

Although an attractive hypothesis, the evidence from epidemiologic cohort studies on associations between dietary GI or GL and diabetes risk is not convincing. Inaccuracy in food GI measurement (including considerable between-subject variation in food GI value) and in dietary GI measurement (application of food GI to whole diet measured using FFQ) and the problematic nature of dietary GI (average ratio; narrow range, unexpected contributor foods) and GL (does not separate GI and amount of carbohydrates of foods) all complicate the capability of dietary GI and GL to capture the true metabolic impacts of carbohydrates consumed as part of the diet. Dietary GI and GL assessed using FFQ may have inadequate utility for evaluating GI concept hypotheses (Mayer-Davis et al. 2006, Mayer-Davis 2007).

Some foods seem to affect diabetes risk in a direction opposite that expected based on glycemic responses. This attenuates the associations towards unity. The nutrient content and diverging health effects of foods should be considered when evaluating the associations of glycemic properties of foods and disease risk. The positive findings from cohort studies on an association between dietary GI and diabetes risk, mostly from cohorts consisting of female subjects, may partly be due to residual confounding related to consumption of some low-GI foods.

Application of multivariate nutrient density models (Willett et al. 1997, Willett 1998) to study associations between substitution of lower-GI carbohydrates for higher-GI carbohydrates would bring new insights by addressing two problems of dietary GI and GL, i.e. the nature of dietary GI to describe only the average quality of dietary carbohydrates and as an average ratio to fall within a narrow range and GL's inability to distinguish changes in carbohydrate quality and quantity. In addition, exploring separately the associations between carbohydrates with different GIs (high-, medium-, and low-GI carbohydrates) and risk of diabetes would clarify the inconsistency between the hypothesis of detrimental effects of high-GI carbohydrates and the finding of many large prospective cohort studies that greater total carbohydrate intake is not associated with increased diabetes risk. Recently, high-protein, low-carbohydrate diets for weight loss have received much attention (Busetto et al. 2011). This study does not offer evidence that higher protein and lower carbohydrate intake result in decreased diabetes risk.

Methodologic progress in GI studies is required to establish the health effects of carbohydrates. Because some of the publications show a positive association between dietary GI and risk of diabetes and others do not, doubt exists about a true association since positive findings tend to become more easily published than null findings (publication bias). On the basis of epidemiologic evidence, it is debatable whether the GI adds anything to the nutritional benefits of fiber-rich cereals, vegetables, legumes, fruits, and berries.

7 Conclusions

Evidence for an association between dietary GI and risk of type 2 diabetes is inconsistent. Methodologic considerations influence the epidemiologic research on associations between GI and diabetes risk.

Specific conclusions are as follows:

1. Within-subject and between-subject variation in glucose responses and GI values of foods was considerable. The variation can be decreased by using capillary blood sampling instead of venous sampling and by testing the reference at least twice.
2. The GI database compiled was feasible for epidemiologic study of dietary GI and type 2 diabetes. However, variability in food GI measurement methodology and the limited availability of food GIs must be considered when assigning and applying a GI database for epidemiologic research.
3. Dietary GI as an average ratio fell within a narrow range, limiting the possibilities to observe associations of dietary GI with disease risk. Dietary GI concealed unexpected dimensions of the diet; the main contributors to the interindividual variation in dietary GI differed substantially from the main contributors to carbohydrate intake. Furthermore, the main contributor foods to the interindividual variation in dietary GI, milk and beer, were associated with diabetes risk in a direction opposite that expected based on their GIs.
4. High dietary GI and GL were not associated with increased diabetes risk. Application of multivariate nutrient density models to epidemiologic studies on GI and diseases allows the GI and the amount of carbohydrates to be considered separately. In this study, substitution of lower-GI carbohydrates for higher-GI carbohydrates was not consistently associated with lower diabetes risk.
5. Higher carbohydrate intake at the expense of fat or protein was associated with decreased diabetes risk. Replacing fat or protein with lower-GI carbohydrates was not consistently more beneficial than replacing it with higher-GI carbohydrates.

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