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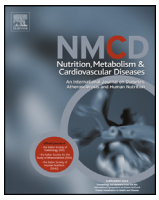

CONSENSUS

# Glycemic index, glycemic load and glycemic response: An International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC)☆

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**KEYWORDS**
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**Abstract** *Background and aims:* The positive and negative health effects of dietary carbohydrates are of interest to both researchers and consumers.
*Methods:* International experts on carbohydrate research held a scientific summit in Stresa, Italy, in June 2013 to discuss controversies surrounding the utility of the glycemic index (GI), glycemic load (GL) and glycemic response (GR).
*Results:* The outcome was a scientific consensus statement which recognized the importance of postprandial glycemia in overall health, and the GI as a valid and reproducible method of

☆ Based on the meeting "Glycemic Index, Glycemic Load and Glycemic Response: an International Scientific Consensus Summit" held in Stresa (Italy) on June 6–7th, 2013.

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classifying carbohydrate foods for this purpose. There was consensus that diets low in GI and GL were relevant to the prevention and management of diabetes and coronary heart disease, and probably obesity. Moderate to weak associations were observed for selected cancers. The group affirmed that diets low in GI and GL should always be considered in the context of diets otherwise understood as healthy, complementing additional ways of characterizing carbohydrate foods, such as fiber and whole grain content. Diets of low GI and GL were considered particularly important in individuals with insulin resistance.
*Conclusions:* Given the high prevalence of diabetes and pre-diabetes worldwide and the consistency of the scientific evidence reviewed, the expert panel confirmed an urgent need to communicate information on GI and GL to the general public and health professionals, through channels such as national dietary guidelines, food composition tables and food labels.


## Introduction

Dietary carbohydrates have received negative publicity in the last decade following the popularity of high protein diets for weight loss, and the more recent finds that carbohydrates may be 'worse than saturated fats' for cardiovascular disease (CVD) risk [1,2]. These landscape changes have raised questions about the amount and type of carbohydrate to be recommended in healthy diets. Now the majority of carbohydrate-containing foods consumed in industrialized nations are of poor quality (e.g. higher in GI and GL as well as low in dietary fiber and calorie-dense). Generally foods are now of the kind that are quickly digested, absorbed and give rise to high blood glucose and insulin 'spikes'. As overweight, obesity and insulin resistance have become more prevalent, concerns for the amount and type of carbohydrate consumed has increased because of the changed view that carbohydrate nutrition can increase rather than (as originally perceived) only decrease cardiometabolic risk. Thus evidence has supported that some carbohydrate sources can be beneficial, while others are not, depending on both their glycemic index and fiber content [2–6]. Accordingly a meeting was organized in Stresa (Italy) titled "Glycemic Index (GI), Glycemic Load (GL) and Glycemic Response (GR): an International Scientific Consensus Summit". The purpose of the summit was to bring together international experts in the field of carbohydrates, glycemic index, fiber and health in order to present and discuss the issues related to the role of the dietary GI, GL and GR in the prevention and management of chronic diseases. Discussion points addressed areas of agreement, areas of further investigation, and areas that should be communicated to the public.

Over two days and eight sessions, the expert group discussed the relevance of dietary carbohydrates and postprandial glycemia to health, covering historical perspectives, analytical issues, chronic disease, metabolism, body weight, novel health effects, health claims and future research. Two sessions were devoted to food industry concerns. The program specifically addressed the following issues:

- Postprandial glycemia: should it be lowered?
- If yes, how should it be achieved?
- What does the GI measure?
- GI methodology
- Strengths and weakness of the terms GI, GL and GR
- Testing foods, meals or the overall diet
- Simple sugars, fructose and low GI diets
- Different ways of lowering GI and GL
- GI and GL in diabetes prevention and management
- GI and GL in CHD risk
- GI and GL in cancer risk
- GI and GL and satiety
- GI and GL in overweight and obesity
- GI and GL and chronic inflammation
- GI and GL in childhood and adolescence
- GI and GL in different dietary patterns
- Low GI diets in the context of a healthy Mediterranean diet
- The appropriateness of GI in national/international nutrition guidelines
- Consensus: what can we agree upon?
- Looking to the future and planning new research

The outcome of this first international summit was a consensus statement comprising 20 points of agreement that could be utilized by scientists, industry, health agencies and governmental bodies. In addition, the International Carbohydrate Quality Consortium (ICQC) was officially formed with intention to meet on a bi-annual basis both to bring clarity to the controversy surrounding the health effects of carbohydrates and to increase awareness of healthy carbohydrate choices.

## Definitions

Basic definitions are given to clarify terminology used at present: GR is the post-prandial blood glucose response (change in concentration) elicited when a food or meal that contains carbohydrate is ingested. Available carbohydrate is the carbohydrate in foods that is digested, absorbed and metabolized as carbohydrate and it is sometimes referred to as net carbohydrate or glycemic carbohydrate (expressed as the monosaccharide equivalent for optimal comparability between carbohydrates) [7]. The GI is conceptually the GR elicited by a portion of food

containing 50 g (or in some cases 25 g) of available carbohydrate and is expressed as a percentage of the GR elicited by 50 g (or 25 g) of the reference carbohydrate (i.e. either a glucose solution or white wheat bread, defined respectively as the glucose scale or the bread scale). GI is precisely defined by the ISO (International Organization for Standardization) method 26642:2010 (http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=43633). The GI is therefore both a standardized GR (based on an equal amount of available carbohydrate) and a relative GR (relative to a referent food). It is a property of the food itself, an index or percentage representing a quality of carbohydrate foods. Foods having carbohydrate that is digested, absorbed and metabolized quickly are considered high GI foods (GI $\geq$ 70 on the glucose scale) whereas those that are digested, absorbed and metabolized slowly are considered low GI foods (GI $\leq$ 55 on the glucose scale). The GL is the product of GI and the total available carbohydrate content in a given amount of food (GL = GI $\times$ available carbohydrate/given amount of food). Available carbohydrates can have different modes of expression, for example: gram (g) per serving, g per 100 g food, g per day's intake, and g per 1000 kJ or 1000 kcal (1 kcal = 4.184 kJ). Thus depending on the context in which GL is used, the GL has corresponding units of g per serving, g per 100 g food, and g per 1000 kJ or 1000 kcal.

## Presentations summaries

### *Glycemic index: history and clinical implications*[5]

One of the major dietary changes from the ancient to the modern world has been the increased consumption of fiber-depleted processed carbohydrate foods, coincident with rising rates of obesity and diabetes [8,9] and with great concern for increasing CHD risk. Pharmacological approaches to improve glycemic control in type 2 diabetes (T2DM) in large clinical trials have been shown useful but additional improvements in diabetes control have been demonstrated when diets of lower rather than higher GI are eaten [10–13]. Moreover, tight pharmacologic glycemic control has to date failed to show the anticipated clear benefits for CHD among T2DM patients, hence pharmacotherapy may represent only a partial solution [14]. These findings suggest that certain dietary approaches that both improve blood glucose control and reduce CHD risk and risk factors should also be emphasized. One of these approaches may include reducing the rate of digestion, absorption and metabolism of carbohydrate by the low GI of foods. The relevance of the GI continues to be debated. Since the first GI publication in 1981 [15], there has been a growing body of evidence suggesting the potential importance of GI/GL in diabetes, CVD, cancer and body weight management. International GI tables were developed in 1995 and later updated in 2002 and 2008 [16] with the GL concept first introduced by Walter Willett and colleagues in 1997 [17]. Large epidemiological investigations have shown that the combination of low GL and high cereal fiber intake reduced T2DM risk by 2-fold in men and women [17,18]. More recently these trends have been confirmed in both men and women, with greater risk reduction in women [19]. CHD risk was also reduced with low GL [6] and with low GI diets [20] again shown clearly in women, as well as risk of certain cancers, mainly breast and colorectal although not all studies have demonstrated these benefits [11,21–23]. There are also studies linking modification of risk factors for these diseases to differences in dietary GI. Meta-analyses demonstrated that low GI diets significantly improved glycemic control [13] and LDL-cholesterol [24], and in single studies, risk factors such as plasminogen activator inhibitor-1 [25,26], and c-reactive protein, particularly at higher BMI (>25 kg/m$^2$), both in epidemiological investigations [27] and in clinical trials [28,29]. The mechanism responsible for these beneficial effects may relate to the slow absorption of carbohydrate typically seen with the use of low GI foods, viscous fibers and Acarbose, the alpha-glucoside hydrolase inhibitor. Acarbose through its inhibition of pancreatic amylase and brush border sucrase-isomaltase inhibits both starch digestion and the uptake of sugar and di- and trisaccharide products of starch digestion thus reducing postprandial glycemia. It therefore transforms the diet into a low GI diet [30]. Acarbose in combination with a habitual diet in the STOP NIDDM trial has been shown to reduce new cases of diabetes (−36%), CVD (−49%) and hypertension (−34%) [31,32]. A meta-analysis of 7 clinical trials using acarbose confirmed the reduction in cardiovascular events and risk factors, including triglycerides, blood pressure and body weight [33]. Other alpha-glucoside hydrolase inhibitors have been tested and have confirmed the postprandial blood glucose lowering effect and diabetes risk reduction [34,35]. Notably, these studies with inhibitors are unconfounded by fiber or other components of food and collectively represent strong evidence supporting a possible role of low GI diets on hard end points, i.e. CHD and T2D, even in people without diabetes at baseline.

Questions remain as to the applicability of the GI for general use. A key issue is what characteristics of the individual will make them more susceptible to differences in the GI/GL of the diet. A pattern has been emerging in the last 15 years of GI research that those with increased insulin resistance, assessed as high postprandial insulin, greater BMI, or specifically waist circumference as a marker of central adiposity, especially in the presence of diabetes, are likely to benefit most. In particular those with diabetes and indicators of the metabolic syndrome such as raised systolic blood pressure [36], are most likely to have benefits from a low GI/GL diet in terms of weight reduction, diabetes control and CHD risk reduction [36–39]. Should we be designing diets for overweight people? The Nurses' Health Study [38] showed increased risk of CHD with higher GL but only in those with a higher BMI. When comparing conventional low fat diets to low GL diets those individuals who had low insulin levels lost body weight

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regardless of diet, but those with higher insulin levels only lost weight on the low GL diet [37]. Many cases of cirrhosis nowadays are a consequence of excess body weight and it was shown that the prevalence of non-alcoholic fatty liver was significantly greater in people with high GI diets but only in insulin resistant subjects [39].

Further support comes from a meta-analysis of diets for the treatment of diabetes, where the effective diets to reduce CHD risk in diabetes included the low GI diets [40]. Given the high prevalence of diabetes, obesity and the metabolic syndrome worldwide, including a low GI/GL dietary component within the context of a healthy diet offers the prospect of reducing chronic disease and its complications.

### *GI/GL/GR: methodology and issues*[6]

GI is an index that was designed as a measure to assess the blood glucose raising potential of the available carbohydrate in high carbohydrate foods, and recognizes that equivalent amounts of carbohydrate from different foods elicit GRs which vary over a 4–5-fold range. Due to poor interpretation of the evidence GI has been controversial ever since it was introduced in 1981 [15]. Recent criticisms cast doubt upon the validity of GI, asserting that: GI does not predict GRs, GI methodology is inaccurate and imprecise [41–43], the calculated GI of mixed meals does not predict their measured GI [44–46], and that many factors influence the results. Most current criticisms are not valid but do reflect a failure of knowledge translation [47–49]. Many criticisms (eg. the GI of subjects changes from day to day) are based on inappropriate use of the term "GI" as if it were synonymous with "GR". "GI" is not "GR" and so care must be taken to use terms correctly. The core methodology used to measure GI back in 1981 has not changed, but a number of additional procedures and checks have been added to improve accuracy and precision (15). If used correctly, the GI method is precise enough to distinguish between high-GI (GI $\geq$ 70, glucose scale) and low-GI (GI $\leq$ 55, glucose scale) foods with 95% certainty [49]. GI values that are not based on use of correct methodology should not be termed "GI". Alternate terms include "GR" or "relative GR". The calculated GI of mixed meals is not necessarily expected to predict their GR because the glycemic impact of a mixed meal depends not only on its GI, but also on the amounts and types of fat, protein and carbohydrate the diet contains. GI is a property of high carbohydrate foods, thus it is not appropriate to measure the GI of mixed meals. The GI of mixed meals needs to be calculated from the GI of the carbohydrate foods or ingredients in the meal and calculated in the same way as we calculate the average GI of a diet. A number of critics have raised the objection that many factors, such as variety, processing and cooking, influence the GI of a food. Indeed they do; but it is difficult to see how this is an argument against the use of the GI of foods; rather it is a reason why GI is useful – how else to quantify the impact of variety, processing and cooking? However, that GI values of the "same" food as given in the International GI Tables may vary widely for some foods is a problem because it is impossible to know the GI value of the specific food you, your client or your research subject is actually eating. This makes clinical use of GI less accurate than it could be, which is problematic because it may introduce bias into study data. Further progress on GI will be difficult unless nutrition scientists and health professionals eliminate confusing abuse of GI and agree on the actual state of knowledge about GI. To use GI effectively, ways to provide consumers and health professionals with accurate and reliable information about the GI of foods need to be developed; at the very least this will involve the standardization and accreditation of laboratories involved in measuring GI.

### *Postprandial glycemia: should we keep it low? If yes, how?*[7]

The epidemiological evidence suggests a direct relationship between postprandial glycemia and CVD or total mortality in people with T2DM [50,51] or without diabetes [52,53]. Controlling postprandial glycemia results in greater CVD benefits than controlling fasting hyperglycemia for the same percent reduction in HbA1c levels [54]. In healthy people glycemia has been shown to fluctuate during the 24 h between 70 and 140 mg/dL (3.8–7.6 mmol/L) [55]. However in the study by Ferrannini et al. [56] it is clearly shown that already at the upper end of the normal post-challenge blood glucose ranges (120–140 ng/mL or 6.6–7.6 mmol/L) beta-cell function drops significantly by 60% and this seems to occur equally in lean as well as in obese individuals. Insulin resistance and altered insulin secretion are early signs of progressive beta cell dysfunction leading eventually to T2DM. Insulin resistance starts with impaired secretion of first phase insulin which is the insulin required for controlling diet-derived blood glucose. The consequence is postprandial hyperglycemia. We spend most of our lives in the postprandial state since the true fasting state occurs only in the last 2 h of a regular night sleep [57]. Eating is followed by a surge of acetyl CoA which combines with oxygen in the mitochondria resulting in the generation of ATP molecules and charged particles called free radicals. When the system is overloaded with acetyl CoA (e.g. from over-nutrition) a larger number of free radical products escape the mitochondria. It is suggested that this excessive oxidative stress may be the pathogenic mechanism underlying insulin resistance, diabetes and CVD [58,59]. Hyperglycemia activates many pathways which lead to endothelial dysfunction and hence to diabetes complications [60–62] while antioxidants such as vitamin C and E have been shown to counterbalance the endothelial dysfunction [62] and glutathione to normalize blood pressure [63]. These studies support the oxidative stress hypothesis. Managing postprandial hyperglycemia reduced oxidative stress [64], endothelial dysfunction [65],

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thrombosis-related factors [66] and low density lipoprotein oxidation [67]. Particularly, larger blood glucose fluctuations have been found to induce greater oxidative stress than constant high blood glucose levels [68]. Lower GI foods therefore should induce smaller blood glucose fluctuations than higher GI foods over the day. The relationship between the dietary GI and GR was examined in a study of free-living people with T2DM and obesity using a continuous glucose monitoring device and a simultaneous 3-day food record. The dietary GI was positively related to blood glucose area under the curve, to mean glucose and to the hyperglycemic ranges, while it was negatively related to the euglycemic ranges [69]. In this study the GI resulted as the strongest and the most consistent independent predictor of glycemic fluctuations. These data lend support to the ecologic validity of the GI in free-living people. Benefits of low GI diets were seen also within hypocaloric diets where the low GI component resulted in improved endothelial function and reduced glycemic variability in obese people without diabetes [70]. All together these findings support the need for an optimal postprandial blood glucose management in people with and without diabetes. The International Diabetes Federation recognized the relevance of prandial glucose regulation and the need for moderating the acute surges in plasma glucose levels following meals by making mandatory the targeting of postprandial hyperglycemia to achieve HbA1c targets and by developing specific guidelines on post-meal glucose management which include the GI concept [71].

### *Is GI/GL of the diet important in diabetes prevention and management?*[8]

Traditional societies consumed largely unprocessed plant based diets that were high in fiber and included whole grains, legumes and nuts as staples. These diets were low GI and low GL. The shift away from traditional diets to western highly processed diets has paralleled a dramatic rise in the prevalence of diabetes, obesity and CVD. Epidemiological studies indicate that the consumption of plant-based diets reduce risk of T2DM and CHD [72,73]. The "fiber hypothesis" suggested that this was a direct effect of fiber [74]. The GI concept is an extension of the fiber hypothesis suggesting that fiber would reduce the rate of nutrient influx from the gut [75]. It has particular relevance to those chronic Western diseases associated with central obesity and insulin resistance [76].

Low GI diets have been shown in clinical studies to improve glycemic control in people with diabetes, to improve serum lipids and other cardiovascular risk factors and possibly to promote weight loss [4,13,77,78]. In large epidemiological studies, consumption of low GI diets has been associated with decreased risk of diabetes, CHD and certain cancers [11,20,22]. Findings from recently completed clinical trials provide further support for the utility of the GI and GL [40,77]. In these studies, a low GI diet significantly improved glycemic control and decreased CVD risk factors in T2DM and a low GL diet was found to improve glycemic control and blood lipids [36].

Legumes are a good source of slowly digestible carbohydrate and fiber, making them a valuable means for lowering the glycemic-index of the diet [77,79]. Nuts have a healthy macronutrient profile, being high in mono- and polyunsaturated fatty acids, vegetable protein and fiber and low in available carbohydrate, making them a useful way to lower the GL of the diet. Recent findings from clinical studies indicate that dietary approaches that include legumes and other low GI carbohydrates, and nuts improve glycemic control in T2DM [80]. In addition, these dietary approaches improve cardiovascular risk factors and markers associated with the metabolic syndrome and contribute to CHD prevention [81,82]. These results have been partly attributed to the slow absorption of the carbohydrate component of low GI foods as proved by the acarbose pharmacological approach [31,32].

### *GI and GL and risk of diabetes and CVD: an epidemiologic perspective*[9]

The relation of GI and GL to risk of T2DM has now been examined in many prospective studies [11,17,18,83,84]. Although positive associations have not been seen in every study [84], dietary GI has been associated with greater risk in the three largest studies and in a meta-analysis combining them [85]. One of the strengths of epidemiological investigations is that the variability in GI values between different samples of the same foods is averaged out over time in large populations. However it is still possible to fail to detect true associations due to insufficient sample sizes, resulting in wide confidence intervals [86]. Strong supportive evidence for the benefit of low GI diets has been provided by the acarbose randomized trial, in which an inhibitor of starch conversion to glucose, which thus mimics a low GI diet, reduced the incidence of T2DM by 36% in high risk individuals [31]. These findings are also consistent with randomized trials among patients with diabetes documenting physiologically significant reductions of HbA1c levels with lower GI diets [87] and with experiments in animals in which high GI carbohydrates showed damage to pancreatic islet cells [88]. GL has also been directly associated with risk of T2DM, although not as strongly as GI [85]. GL is associated with greater incidence of CHD [6,38], although probably not among lean and active persons with low insulin resistance, which probably explains in part why populations in physically active agrarian countries could, until recently, tolerate high GL diets. In the acarbose trial described above, risk of CVD was also reduced by 49% [32]. Overall, the dietary GI seems to be the strongest risk factor for T2DM while GL for heart disease. BMI, however as a surrogate for insulin resistance, makes a substantial difference in how we respond to carbohydrate quality and quantity. Furthermore, there is a third dimension to carbohydrates beyond quality and quantity, i.e. the liquid form, which results in higher GI

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**Table 1** Relative risk (RR) and 95% confidence interval (CI) for the highest versus the lowest quantile of dietary glycemic index (GI) and glycemic load (GL) by cancer site [23].

| Cancer site | GI | | | GL | | |
|---|---|---|---|---|---|---|
| | No. of studies | RR (95% CI) | $I^2$ (%) | No. of studies | RR (95% CI) | $I^2$ (%) |
| Breast | 19 | 1.05 (0.99, 1.11) | 52 | 18 | 1.07 (0.98, 1.16) | 68 |
| Colon-rectum | 15 | 1.16 (1.07, 1.25) | 59 | 15 | 1.10 (0.97, 1.25) | 75 |
| Endometrium | 10 | 1.13 (0.98, 1.32) | 60 | 11 | 1.17 (1.00, 1.37) | 60 |
| Esophageal | 4 | 1.46 (0.90, 2.38) | 83 | 4 | 1.25 (0.45, 3.48) | 95 |
| Liver | 4 | 1.11 (0.80, 1.53) | 62 | 6 | 1.14 (0.78, 1.67) | 70 |
| Ovary | 5 | 1.11 (0.85, 1.46) | 74 | 5 | 1.19 (0.85, 1.68) | 79 |
| Pancreas | 10 | 1.10 (0.99, 1.22) | 0 | 11 | 1.01 (0.85, 1.19) | 51 |
| Prostate | 6 | 1.06 (0.96, 1.18) | 70 | 5 | 1.04 (0.91, 1.18) | 67 |
| Stomach | 6 | 1.17 (0.83, 1.66) | 81 | 6 | 1.10 (0.85, 1.42) | 44 |

values, reduced satiety and overconsumption, and is associated with greater T2DM risk [89]. Given essentially conclusive evidence that high GI/GL diets contribute to risk of T2DM and CVD, reduction in GI and GL should be a public health priority. One important approach would be to replace refined starches (e.g. grains and potatoes) with whole grains, mainly intact; this also incorporates the benefits of higher amounts of fiber, minerals and vitamins. The concept of GI is valuable in understanding the effects of diet on risk of chronic disease. Whether this should be explicitly part of widespread dietary advice and included in food labeling is less clear. Although we should avoid overly focusing on a single attribute of any food, some information on carbohydrate quality is essential for the public to make optimal dietary choices.

### *GI/GL and risk of major cancers: what can we conclude based on epidemiological evidence?*[10]

Dietary carbohydrates increase blood glucose and insulin concentrations at different rates and levels depending on their GI [15]. A direct association has long been found between diabetes and cancer [90] and hyperinsulinemia/hyperglycemia may be a contributing factor in this relationship [91,92], while some anti-hyperglycemic medications (i.e. metformin) seem to beneficially alter it [93]. Insulin acts as a growth factor increasing the bioactivity of the cancer-promoting insulin-like growth factor-1 (IGF-1) which has proliferatory, angiogenic, anti-apoptotic and estrogen-stimulating properties [94,95]. It has been proposed that low GI foods by virtue of their lower glucose rises and overall insulin economy may beneficially influence cancer risk compared to high GI foods [96]. Systematic reviews and meta-analyses indicate that the dietary GI is moderately and directly associated with breast and colorectal cancer risk with pooled relative risk (RR) of 1.1–1.2 for the highest versus the lowest GI level, and less consistent associations were found with endometrial cancer [11,21,97].

We have therefore updated a previous meta-analysis [97] to January 2015 with available data on GI and GL and all cancer sites, in both cohort and case–control studies, using random effects models [23]. The pooled RRs were above unity for all cancer sites. The RR for the highest versus the lowest GI and GL quantiles were respectively: 1.16 (significant) and 1.10 for colorectal, 1.05 and 1.07 for breast, 1.13 and 1.17 for endometrial cancer, 1.06 and 1.04 for prostate cancer (see Table 1 for all results). There was significant heterogeneity among studies which was not explained by publication bias.

If real, such associations would be explained by the higher impact of high GI/GL foods on glycemia, insulinemia and insulin-like growth factors which may promote tumor growth [98]. These associations would be of relevance on a prevention and public health level, considering the high incidence of several of these neoplasms. There are however uncertainties in interpreting these results, considering the moderate associations, the heterogeneity across studies and study design (cohort versus case–control) and possible inadequate allowance for confounding or interactions with other aspects of diet and carbohydrate composition, including body weight and metabolic syndrome. Moreover, in general, interpretation of any RR from observational studies (cohort and case–control) of the order of 1.1–1.2 requires due caution.

### *Dietary carbohydrates and metabolic outcomes: assessing the totality, consistency and quality of epidemiologic observations and clinical interventions*[11]

Nutrition is a complex issue with many factors and variables exerting an influence on metabolic health and incidence of disease. Regardless of whether studies are interventional or observational, heterogeneities abound in nutritional studies of health outcomes. These heterogeneities are measured with standard meta-analytical methods. The simplest of meta-analyses assume that all studies in the meta-analysis share one true effect size (fixed effects), but this rarely occurs. Two approaches that assess determinants of heterogeneity are subgroup analysis and meta-regression. The former is useful to distinguish between influential factors (e.g. men versus women) whereas the latter is better for continuous variables (e.g. age, BMI, severity of disease). Care should be taken when

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using subgroup analysis for the assessment of dose–response or severity of a metabolic perturbation, which is not uncommon, because can be misleading about the position on the continuum that any effect is evident. Furthermore, factoring sexes as subgroups may be difficult or suboptimal when many studies are of mixed gender and of varying proportion of each sex. However, sex proportion is a variable that is assessable in meta-regression. Meta-regression also has potential for the building of models to explain how key variables relate to one another. Recent use of meta-analytical methods has been illuminating in understanding the role of GI/GL/GR in the development and management of key metabolic diseases, especially when the number of original studies is large enough to provide sufficient statistical power. We discuss herein some examples concerning T2DM and CHD. A comprehensive systematic meta-regression analysis of published prospective cohort studies of the T2DM-GL risk relation has explained 97% of heterogeneity among studies [19,99]. Women [19] and men [99] each have a significantly higher risk of T2DM when consuming diets of high GL across a wide range of GL values above 95 g GL/2000 kcal diet, with women at higher risk than men. The findings are sufficient to realize that in the lower reaches of GL this risk can be reduced by choosing lower GI foods. For the higher reaches of GL, as attained across populations worldwide, aiming for a target of 100 g GL/2000 kcal would need also a reduction in the amount of carbohydrate in the diet, which is an energy source that appears to elevate the risk less than does GL [100]. Together with gender, other explanations of heterogeneity found were ethnicity (European-Americans versus all other ethnicities combined), the number and validity of the dietary instrument used to assess the amount of carbohydrate eaten, length of follow-up, and type of T2DM assessments. The validity of the dietary assessment approach has demonstrated a marked underestimation of the role of GI/GL/GR in relation to risk of T2DM in many studies.

Turning to meta-regression of controlled intervention trials (mostly randomized controlled trials), lower GL diets achieved by reducing GI have reduced (improved) both fasting blood glucose and glycated proteins in patients with T2DM [12]. These effects are additional to improvements obtained by glucose controlling drugs. Heterogeneity in these studies was explained by the severity with which blood glucose control was impaired, and by differences for incidental amounts of dietary fiber ingested between the treatment and control arms within studies. These benefits, of lower GL and higher fiber intake, and of lower GI and higher fiber intake were additive. This find is consistent with the original similar finds for incident T2DM in prospective cohort studies for both men [17] and women [18]. Together these meta-regression analyses show risk reduction among populations of both healthy persons and patients diagnosed with T2DM, with sources of heterogeneity mostly explained. An additional, central plank for diabetes prevention and management is body weight control management [101,102]. Meanwhile early meta-regression analyses have indicated body weight reduction can occur with GL reduction progressively given time and sufficiently large GL reduction [12,103], determinants of heterogeneity that are not best assessed by subgroup analysis. CHD is prevalent among populations and especially T2DM patients. To date meta-analyses indicate, as for T2DM, a stronger beneficial relation between CHD and lower GI/GL/GR in non-diabetic women more than in men among prospective cohort studies [6,20,104]. Reasons for difference between men and women in respect of both incident T2DM and incident CHD remain to be elucidated. When undertaking original epidemiological studies and subsequent meta-analyses, much due attention still needs to be given to the use and reporting of the adequacy of dietary instruments used to assess food intakes [11,19,105]. Outside the context of instrument validation, whether men are less accurate than women when reporting food they eat is unclear. If it is true that the assessment is less accurate for men, then it would result in underestimation of the risk among men and might be responsible for gender difference in the effects of GI/GL/GR on T2DM and CHD.

Foods low in GI/GL/GR need to be eaten in the context of a healthy diet. In this context there is little need to be concerned about the fructose content of compliant diets. However, it cannot be assumed that current food-based healthy eating advice will improve or optimize the GI/GL/GR of foods eaten both because these values are very heterogenous among food groups advised and because current compositional advice emphasizes the quantity, rather than the quality of carbohydrates. Indeed, it is possible to select a vast number of high GI foods and still be compliant with advice; this even when the advice arises from national authorities or from hitherto lifestyle intervention studies of T2DM. Therefore, there is a need to reconsider or revise current dietary recommendations with an emphasis on GI/GL/GR.

### *Fructose the low-GI sugar: is there cause for concern?*[12]

There was initially an interest in fructose as an alternative sweetener in people with diabetes owing to its low-GI [15]. Other molecular mechanisms were subsequently described, whereby low-doses of fructose were shown to improve the metabolic handling of glucose through the induction of glucokinase resulting in increases in glycogen synthesis and decreased hepatic glucose output [106–108]. Translation of these findings in the acute clinical setting has shown that small so called ‘catalytic’ fructose doses ($\leq$10 g/meal) can reduce the postprandial GRs to high-glycemic index meals from 15 to 30% [109–111]. The interest in fructose, however, has recently focused on its harm. Over the past decade, fructose has become a focus of intense concern regarding its role in the epidemics of obesity, diabetes, and their cardiometabolic complications. There have been dozens of editorials, commentaries, and letters in the scientific literature and numerous pieces in the lay media calling for efforts to restrict its intake. Ecological observations which have linked increasing fructose intake with increasing obesity and diabetes rates along with animal models and

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select human trials of fructose overfeeding at levels of exposure far beyond actual population levels of intake have driven this debate [112–116]. To address the uncertainties in extrapolating from these data and to support international diabetes and heart association guidelines, a series of systematic reviews and meta-analyses of the highest level of evidence from prospective cohort studies (clinicaltrials.gov identifier, NCT01608620) and controlled feeding trials (Clinicaltrials.gov identifier, NCT01363791) [117] has been undertaken. Although large prospective cohorts studies have shown significant positive associations with incident obesity, diabetes, gout, CHD, and stroke when comparing the highest with the lowest levels of intake of sugar-sweetened beverages, these associations do not hold true at moderate levels of intake or when modeling total fructose (with the exception of gout) [118]. Similarly, the evidence from controlled feeding trials shows that there is a reasonable body of consistent evidence from controlled feeding trials that fructose in isocaloric exchange for other sources of carbohydrate at low-to-moderate doses near the average U.S. intake of fructose (~10% total energy) [119] does not have adverse effects [79,120–125]. There may even be benefits for blood pressure [122] and glycemic control [121], especially at low doses ('catalytic' doses, ≤10 g/meal) which are equivalent to levels obtainable from fruit [126]. There is, however, an emerging body of consistent evidence that fructose providing excess energy (+18–97% excess energy) at extreme doses (>100-g/day) well above the 95th-percentile for U.S. intake (7) may promote weight gain, dyslipidemia, raised uric acid levels, and non-alcoholic fatty liver disease (NAFLD), effects which may be more attributable to excess energy than fructose [120,123–125,127]. Taken together, higher level evidence in humans does not support the view that fructose is harmful at typical intakes. Low doses of fructose (≤10 g/meal) at levels obtainable from fruit may even have advantages for glycemic control and blood pressure and be a useful way for lowering the glycemic index of some foods. The shorter duration, poor quality and unexplained inter-study heterogeneity among the available trials indicate the need for larger, longer-term feeding trials to guide our understanding of the effect of fructose on cardiometabolic risk. There is also a need for true ad libitum trials to assess whether fructose when freely replaced with other sources of energy likely to replace it in the diet leads to differences in energy intake, weight gain, and downstream cardiometabolic risk.

### *Effects of GI/GL on satiety and body weight*[13]

Should future nutritional recommendations for the general population take into account the notion of GI? This question is all the more legitimate as the glycemic response to foods seems to be a factor that affects satiety and could therefore affect food intake. Consumption of low GL foods is expected to result in a reduced postprandial rise of insulin [75], thus altering availability of metabolic fuels after a meal [3,76,128]. After a high GI/high GL meal, blood glucose and insulin levels initially rise much higher than after a low GI/low GL meal, leading therefore to stimulation of cellular nutrient uptake, inhibition of hepatic glucose production, and suppression of lipolysis. Subsequent declines in blood glucose concentration induced by the relative hyperinsulinemia of a high GI diet have been proposed to induce excessive hunger and overeating. High GI diets have therefore been hypothesized to promote excessive weight gain. Several studies in adults [76,128,129], in children and in adolescents reported decreased hunger, increased satiety, and decreased voluntary food intake in response to low GI/low GL meals in acute conditions. Ludwig et al. [128] reported higher ratings of hunger and greater energy intake after a high GI meal in a randomized crossover study comparing high GI to low GI meals in 12 adolescent boys. Ball et al. [129] reported a 48-min prolongation of satiety after a low GI versus a high GI supplement in a similar crossover study of 16 adolescents, but found no differences in hunger ratings or changes in actual energy intake. Such crossover meal studies have the advantages of a within-subjects design that controls for many extraneous factors that may complicate human studies. Short-term treatment studies have described beneficial effects of low GI or GL diets on body weight and composition. Slabber et al. [130] reported greater weight loss after 3 months among obese women who were counseled to eat low GI foods compared with those who did not receive this advice. Bouche et al. [131] found that fat mass decreased more in overweight men after 5 weeks on a low GI compared with a high GI diet. In overweight subjects with increased insulin secretion, 18 months of a low GI diet also increased weight loss [37]. A modest increase in protein content together with a low GI-hypocaloric diet for 4 weeks, decreased adipocyte size, a phenotype of adiposity, and tended to decrease body weight and fat mass [133]. A significant weight loss was achieved after 12 weeks on such a diet [134]. Additionally, "DIOGenes" (diet, obesity and genes) randomized clinical trial from eight European countries [78], a diet moderately high in protein and low GI prevented weight regain and reduced body fat mass following a weight loss program. The low GI was an independent contributor. Long term dietary weight loss programs using low GI diets succeeded to induce a decrease in fat mass albeit not always in body weight. However, a low GI diet may decrease body weight in some special cases, in gestational women and in subjects with higher postprandial insulin secretion. Importantly, the demonstration of the efficacy of a low GI diet combined with high protein to prevent weight regain over the long term could have major public health significance.

### GI and GL during childhood and adolescence and its relevance for metabolic outcomes[14]

Evidence from cohort studies in children and adolescents regarding the role of a lower dietary GI/GL in the prevention of overweight is presently inconclusive. In

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prospective analyses of data from German participants of the DONALD Study, a lack of association was observed both between dietary GI/GL and BMI/body fat and between changes in dietary GI/GL and changes in BMI/body fat during three time windows (childhood, adolescence, from puberty to adulthood, n = 215–380) [136–138]. Similarly, changes in GI or GL during a 2-year follow-up were not associated with changes in adiposity measures in a group of 85 overweight US American adolescents of Latin-American origin [139]. Conversely, among 279 Australian adolescent girls an increase in dietary GL during the 5-year follow-up was related to concurrent increases in BMI and waist circumference [140]. With respect to the role of low GI/GL diets in the treatment of obesity, initial evidence from a small pilot [141] and a retrospective study [132] suggested a superiority of low GL diets for weight loss in obese children and adolescents. However, this was not confirmed by recent intervention studies (duration 3–24 months) performed on larger pediatric samples [135,142,143]. Nonetheless, in the DiOGenes study the combination of GI and protein intake was related to a decrease in overweight or obesity rates among children on a diet higher in protein and lower in GI [135]. Thus, data available to date does not support a strong role of GI or GL in the prevention or treatment of childhood obesity, yet the relevance of a lower dietary GI in combination with higher protein content should be further elucidated in observational and intervention studies.

Evidence on the relevance of GI/GL for risk markers of T2DM and CVD in children and adolescents is still emerging. Smaller intervention studies suggest some benefits of low GI/GL diets specifically for insulin resistance [141,144,145]. However, in a recent 2-year intervention on 113 obese Hispanic children the examined diets did not differ in their effect on changes in insulin resistance or markers of the metabolic syndrome [142]. Similarly, in a sub-sample of 253 children and adolescents participating in the DiOGenes study, dietary GI did not affect cardiovascular risk markers [146]. Conversely, prospective cohort studies suggest long-term adverse health consequences of a habitually higher GI or GL during adolescence. In an Australian adolescent cohort, increases in dietary GI and GL between age 12 and 17 years were related to substantial concurrent increases in systolic blood pressure among 278 girls [147]. In a sample of 226 healthy German adolescents, a habitually higher dietary GI during puberty was the only feature of carbohydrate nutrition that was consistently related to higher insulin resistance and higher markers of hepatic steatosis in younger adulthood [148]. In addition, in the same cohort higher intakes of carbohydrate from high GI sources during puberty were prospectively associated with higher adult levels of IL-6 [149].

Consideration of the GI in the diet of children and adolescents is of long-term relevance, since nutritional behaviors are shaped during childhood and adolescence. Of note, analysis of dietary GI in a representative sample of Australian children and adolescents revealed that a preferred selection of carbohydrates from low GI sources may indeed confer benefits for overall nutrient adequacy [150]. By contrast, adherence to the current recommendations to increase whole grain consumption and/or reduce intake of sugary foods cannot be expected to translate into a lower dietary GI/GL. Associations of dietary GI to dietary fiber are neither strong nor uniform across pediatric populations [151,152]. In the DONALD cohort, 76% of the whole grains consumed by healthy adolescents came from sources with a higher dietary GI (GI $\geq$ 55) [149], which reflects the fact that many whole grain products have a relatively high GI [16]. Also, contrary to the popular belief a higher dietary sugar intake is not related to a higher dietary GI [153], because all common sugars, except glucose, are of moderate (sucrose) or low GI (fructose and lactose) [16]. Since dietary GI is not closely related to dietary fiber or dietary sugar intake it needs to be addressed as a separate entity in nutritional recommendations given to children and adolescents. Efforts to reduce the dietary GI and GL in children and adolescents should best be targeted to energy-dense starchy food, since these make a considerable contribution to total dietary GL in children and adolescents [151,152].

### *GI/GL/GR: are all methods of reducing postprandial glycemic responses equally beneficial?*[15]

There are multiple dietary strategies that reduce postprandial glycemia, including 1) reducing the carbohydrate intake as a percentage of energy, 2) increasing the intake of nutrients that slow gastric emptying (e.g. fat, protein, viscous fiber and acidity), 3) incorporating nutrients that increase insulin secretion (e.g. protein, specific amino acids and fat), 4) reducing the GI of the main carbohydrate foods (by reducing starch gelatinization, increasing viscous fiber or fructose content) or 5) using pre-loads (e.g. small amount of alcohol, fructose or protein), or a combination of these approaches. Not all of these approaches are associated with beneficial effects. Indeed, striving for the lowest level of postprandial glycemia possible may not be desirable.

In practice, energy-standardized GL is a good predictor of the level of postprandial glycemia associated with a particular food or diet [154]. In cohort studies, GL, but not carbohydrate content, has been frequently linked to reduced risk of T2DM [19] and CVD [11]. In randomized controlled trials, diets with a reduced GL, including higher protein/moderate carbohydrate diets [78], Mediterranean diets [155] and low GI diets [134], have been linked to improved weight control and risk factors for T2DM and CVD. Very low carbohydrate-high protein diets also have beneficial effects on weight control and some cardiovascular risk factors (not LDL-cholesterol) in the short term, but are associated with increased mortality in long term cohort studies [156]. In practice such diets include large amounts of animal protein and/or red meat, both of which have been linked to increased risk of T2DM [100].

Hence, at the present time, aiming for a moderate reduction in postprandial glycemia using low GI, Mediterranean-style and higher protein-moderate

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carbohydrate diets is safe and helpful. Some whole grains or minimally processed grain foods (e.g. steel-cut oats, quinoa or pumpernickel bread) as well as viscous fibers (psyllium, beta-glucans, and PGX™) also reduce postprandial glycemia, but the majority of whole grain foods do not. The lowest level of postprandial glycemia is achieved using very low carbohydrate-high protein diets, but these cannot be recommended for long term use.

### *GI as affected by the presence of proteins/amino acids*[16]

Recent research has highlighted the importance of dietary protein in satiety and weight maintenance. Thus, a diet characterized by a slightly lower GI and a moderately higher protein content was more efficient in counteracting weight gain after a period of energy restriction and weight loss [78]. Also, high protein diets consumed ad lib improved metabolic risk markers in children of overweight parents [146]. However, the current knowledge regarding the metabolic impact of the type of protein is scarce. Of interest in this respect are reports indicating that dairy proteins, by virtue of increasing satiety and promoting skeletal muscle growth, have advantageous effect on metabolic health [157]. In particular, whey protein appears to induce benefits on risk factors associated with the metabolic syndrome [158]. Consistent with a protective role of dairy proteins, an increase in dairy intake significantly attenuated markers of oxidative and inflammatory stress in subjects with the metabolic syndrome [159]. It cannot be excluded that other milk components beyond protein may play a role e.g. vitamin D and calcium. However, a possible explanation for the improved metabolic variables could be the capacity of certain proteins to lower the postprandial glycemic responses.

The presence of certain proteins, and/or amino acids (AA) reduce postprandial glycemia to glucose, or composite meals in healthy subjects. When comparing lactose equivalent amounts of meals containing different proteins, whey in particular was found to stimulate insulin response and reduce postprandial glycemia [160]. Whey ingestion promoted higher levels of the AA's lysine, threonine, valine, iso-leucine and leucine, and the effects of whey on glycemia and insulinaemia following a carbohydrate challenge could essentially be mimicked by oral ingestion of a protein equivalent mixture of these five AA's provided in a ratio as appeared in postprandial blood following ingestion of whey protein [161]. Similar effects of whey protein on glycemia and insulinemia to an oral glucose challenge in healthy subjects has been reported also by others, and appeared to be unaffected by the fasting insulinemic state [162]. A dose–response relationship was established, such that each gram of added whey protein decreased blood glucose incremental area under curve (0–120 min) by 3.8 mmol min/L [163]. Also certain plant proteins e.g. soy, may reduce glycemia to a carbohydrate challenge in healthy subjects. Whey proteins favorably affect acute glycemia of composite meals also in people with T2DM [165], and longer term dietary supplementation with essential AA's improved markers of metabolic control in diabetes. Consequently, in poorly controlled T2DM oral supplementation with essential AA's, improved a measure of insulin resistance (HOMA IR) and decreased HbA1c compared with placebo [166]. Recent studies further indicate that timing of protein ingestion may be of importance. A "pre-meal" load of whey protein supplemented with leucine, iso-leucine, valine, threonine and lysine, stimulated an early GLP-1 response and reduced blood glucose after a composite carbohydrate rich meal in healthy subjects in the absence of differences in postprandial peak insulin or overall incremental insulin responses compared with the same meal ingested with water [164]. Whey intake with the meal or as a "pre-meal" load prior to a composite meal, significantly reduced glycemic response in people with T2DM compared with a reference meal without whey [167]. The pre-meal load in particular induced higher GLP-1 responses in the postprandial period compared with the reference meal, indicating an incretin effect also in people with diabetes.

Suggested mechanisms for benefits on acute glycemia following co-ingestion of carbohydrates with proteins and/or amino acids may include insulinogenic effects of certain AA and/or stimulation of incretins [160], reduced gastric emptying rate [167], decreased hepatic insulin extraction, increased C-peptide clearance [162] or improved insulin sensitivity [168].

It is concluded, that in addition to the GI characteristics of carbohydrates in foods/meals, the glucose regulatory properties of co-ingested proteins may also influence postprandial glycemia. The potential of low GI/high protein diets should be further evaluated in relation to weight regulation, glycemic regulation and risk factors for the metabolic syndrome, with attention paid to the quality of different food proteins. Also, different food proteins and/or AA-mixtures may be exploited to lower postprandial glycemia in healthy subjects and in T2DM.

### *Mediterranean diet, GL and diabetes: evidence from EPIC-Greece*[17]

An EPIC-wide study, based on 24-h recalls, indicated that population groups from Mediterranean regions, the diet of whom tends to conform more closely to the traditional Mediterranean diet, tend to also be of lower GL, although the pattern was not without exceptions. Moreover, in a study based on food frequency questionnaires administered to more than 20,000 participants in the Greek EPIC cohort, the association between conformity to the Mediterranean diet and GL, although positive, was rather weak, so that the GL of diets with high conformity to the Mediterranean diet was 27% higher in comparison to diets with low conformity to the Mediterranean diet [169]. This indicates that it is quite feasible to envisage dietary patterns compatible with the traditional Mediterranean diet and yet be characterized by low GL.

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Indeed, the contribution of olive oil to the energy intake in the Greek traditional Mediterranean diet (around 20%) allows the identification of a relevant dietary pattern. We have therefore evaluated the association of high conformity to the Mediterranean diet/low GL dietary pattern with certain chronic diseases, e.g. T2DM. The results showed that a high adherence to the Mediterranean diet was inversely associated with T2DM risk (OR = 0.88, CI: 0.77–0.99, p trend = 0.021) while combining it with low GL the association became stronger (OR = 0.82, CI: 0.71–0.95). These results suggest that a low GL combined with a traditional Mediterranean diet conveys 18% protection against the occurrence of T2DM [169] suggesting that even within an overall healthy diet there may be benefits of lowering the dietary GL.

### *An update on the health claims in Europe and some considerations about reducing GI/GL in the context of European diets*[18]

Postprandial glycemia can influence a number of physiological responses linked to long-term health maintenance and/or disease risk, and has been advocated as a useful parameter describing the quality of dietary carbohydrates. In Europe, the European Food Safety Authority (EFSA) is the independent body acting as the scientific support to risk managers of the EU government and member states. An intense activity has been performed in the last few years by the EFSA Dietetic products, Nutrition and Allergies (NDA) panel for the authorization of health claims made on foods. According to the NDA panel, the criteria that should be taken into consideration to demonstrate a health effect of foods or food ingredients are rather straightforward: the indicated effect must be a beneficial physiological effect; the active ingredient to which the effect is related should be clearly identified and characterized; if this is the case, the effect of displacing unhealthy components must be assessed; the amount of the ingredient required to elicit the claimed effect must be compatible with a balanced diet and, finally, there must be sufficient scientific evidence to support it. A specific guidance was issued by EFSA in 2012 about the requirements for health claims related to blood glucose concentrations [170]. Regarding the first criterion, reduction of post-prandial glycemic response (PGR) was considered a beneficial physiological effect, provided insulin is not disproportionally increased. A number of well characterized food ingredients including sugar replacers, resistant starch and some fibers, have been authorized to bear the PGR reduction claim (for reference, please consult the EU register of authorized health claims http://ec.europa.eu/nuhclaims/).

Among available carbohydrates, fructose has gained positive opinion, as EFSA found it effective in reducing PGR when replacing at least 30% of sucrose and/or glucose (i.e. a comparative claim) [171]. On the contrary, no claims were allowed for 14 other carbohydrate foods which were related to their GI or GR. The general impression is that the GI methodology was not considered by the competent authorities solid enough to represent a benchmark for food characterization. A likely next step from the food industry may be to use the PGR of carbohydrate foods comparatively to equi-carbohydrate amounts of glucose, as already accepted for fructose. This however may increase confusion among consumers since without a standard comparator no properranking of the foods is possible. Indeed, the importance of considering food classification based on GI/GL in food selection is little if none endorsed by the bodies issuing dietary recommendations in the European Union and the member countries.

In 2010 EFSA issued the European Dietary Reference Values (DRV) document for carbohydrate [172]. The panel found the evidence for GI and GL inconclusive, and therefore made no specific recommendations. Other European countries have taken the GI into consideration when preparing national DRV documents with contrasting results (Table 2) [173,174].

**Table 2** Glycemic index (GI) in European dietary reference values (DRVs).

| EU country | DRV on GI |
|---|---|
| France | The 2004 document from the French Agency ANSES concluded that the level of evidence is insufficient to provide indications on GI based on health benefits for the general population and prohibited the use of GI labeling or any derived measures [173]. |
| Germany | The recently issued German Nutrition Society DRV document reports that: "*to date there is only possible evidence regarding a risk-increasing effect of high Glycaemic Index on some nutrition-related diseases. Therefore, no recommendations are made in that respect*" [174]. |
| Nordic Countries | Nordic Nutrition Recommendations 2012 conclude that "*There is not enough evidence that choosing foods with low Glycaemic Index will decrease the risk of chronic diseases in the population overall. However, there is suggestive evidence that ranking food based on their Glycaemic Index might be of use for overweight and obese individuals*" [175]. |
| Italy | The recently issued DRVs from the Italian Society of Human Nutrition, included under "*Suggested Dietary Targets*" generic qualitative indications on preference for low-Glycemic Index foods when intakes of carbohydrates approach the upper limit of intake, i.e. 60% energy. They also specified the need of preferentially selecting low GI foods provided the GI was not reduced by adding fructose and/or fat [176]. |
| UK | The Scientific Advisory Committee on Nutrition (SACN) has recently attempted a comprehensive opinion on carbohydrate and health. The document, a compromise between DRVs and Food-Based dietary Guidelines for the UK population, was published for public consultation at the end of June 2014 [177]. The Committee concludes that "*it is not possible to assign cause-effect relationships for outcomes based on variation in diet Glycaemic Index or Load, as higher or lower GI and GL diets differ in many ways other than just the carbohydrate fraction*". |

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Despite the current lack of DRVs consensus, some consideration must be achieved before dismissing the contribution of low GII foods to a healthy diet. First of all we should acknowledge that a growing proportion of the European population, though apparently healthy, presents conditions that may significantly affect glucose metabolism, such as aging, sedentary lifestyle and overweight and thus could especially benefit from a reduction of postprandial glucose response. Although EFSA requires the target population to be "healthy", given the high prevalence of metabolic conditions it is indeed advisable to test GI/GL in studies which do not exclude these high risk individuals. Moreover, we must recognize that differences among diets consumed in different European countries exist and are quite large. This heterogeneity might very well represent a benefit in nutrition research since it may help to clarify the role of GI on health. Indeed, there are large regional differences in the proportion of energy derived from carbohydrates [178] and in the characteristics of the carbohydrate foods. Therefore there may be a need to have country-specific GI databases which would help assess with more precision both GI exposures and disease risk. It is plausible that the determinants of the dietary GI and GL between populations may differ and that specific country-based GI databases might help to evaluate with more precision the exposure and hence disease risk [179].

Finally, we should not forget that in Europe, as well as in other continents, dietary habits are constantly evolving in the light of rapidly changing factors such as demography, commodity supply, product innovation, regulations, consumers' beliefs and the overall economy of the different countries. Traditional ways to identify dietary patterns, such as country-specific diets, might also evolve according to such factors. Therefore, additional efforts are required in order to properly update the information on European diets, interpreting existing data and designing future studies to assess the relationships between diet and health and their determinants.

### *GI claims on foods: the Australian experience*[19]

Rates of overweight/obesity, T2DM and their sequelae are increasing around the globe in both developed and developing nations [180]. Healthy low GI foods and drinks can be incorporated into prevention and/or management plans for many of these conditions, helping to reduce the global disease burden [11,78,181,182]. Availability of healthy low GI foods and drinks for purchase is often cited as a barrier to recommending the use of the GI [183]. Even when they are available, easy identification of healthy low GI choices amongst the many thousands of food choices available within an average supermarket is another potential barrier. Few nations regulate the use of GI claims on food and drink labels [184]. However, most food purchasing decisions are made at the point of sale [185], so having the GI on labels may help people make healthier food choices, helping them prevent/manage weight, diabetes, CVD and certain cancers [11,78,181,182].

As well as including nutrition information like GI values in Nutrition Facts/Nutrition Information Panels, there is growing interest globally in the development of front-of-pack labeling schemes to assist consumers with healthy food purchasing decisions [186].

The GI Symbol is a front-of-pack labeling scheme that also includes the requirement to include a GI value in the Nutrition Facts/Nutrition Information Panel. It was registered as a Certification Trademark (CTM) in Australia—New Zealand, North America, the EU, and Asian nations between 2002 and 2015. In order to utilize the CTM (GI Symbol), foods must be low GI according to ISO 26642:2010 [187] and also meet stringent nutrient criteria for energy (kJ or kcal), carbohydrate, saturated fat, sodium, and in certain foods fiber and calcium [188]. Nutrient criteria are in line with international dietary guidelines [189].

The GI Symbol was launched in Australia in 2002 [190]. Market research was conducted in Australia by Newspoll prior to the launch [191], and then annually until 2007, and then again in 2012 [192]. Survey participants were 490–1502 main grocery buyers representative of the Australian adult (aged 18+ years) population and living in the 5 mainland capital cities (Adelaide, Brisbane, Melbourne, Perth and Sydney) of Australia.

In 2002, 5 foods carried the GI Symbol and this increased to over 150 foods by 2013 [190]. In 2002, 28% of respondents ($n = 490$) were aware of the GI [190]. This increased to 86% of respondents ($n = 458$) by 2005, and has remained approximately the same from that point in time onwards [191]. Awareness of the GI Symbol was 2% at baseline [190], and increased to 37% by 2012 ($n = 1502$) [191]. Most (94%) consumers who were aware of the GI looked for the GI Symbol when shopping [191]. The majority (80%) believe that the GI Symbol indicates that foods that carry it are "healthy, wholesome and a good choice", "scientifically tested" and "provide sustained energy/glucose release" [191].

In conclusion, the GI Symbol program is a simple front-of-pack labeling tool that helps people to identify healthy low GI foods when shopping. Awareness of both the GI and the GI Symbol increased rapidly upon introduction of the tool into the Australian food environment. It is envisaged that a similar uptake will be achievable in other nations when the GI Symbol Program is progressively rolled out.

### *Do low GI/GL diets improve traditional and novel cardiovascular risk factors including chronic inflammation?*[20]

In many epidemiological studies low GI/GL diets have been found to be associated with a lower risk of cardiovascular events. This association could be mediated by a favorable impact of this type of diet on cardiovascular risk factors. As a matter of fact, this hypothesis is plausible since observational studies have consistently shown that in people

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having a habitual diet with a lower GI/GL, most cardiovascular risk factors are reduced; this holds true also after taking into account the overall composition of the diet [193].

In order to validate this association, intervention trials are needed. The majority of these studies are focused on blood glucose and plasma lipids. In general they are concordant in showing a beneficial effect of low GI/GL diets on plasma glucose values (particularly during the post-prandial period) and on plasma (LDL) cholesterol levels; this applies both to people with diabetes and without [24,194,195]. The favorable impact on plasma total and LDL cholesterol seems to be much more relevant when the low GI/GL diet is also fiber rich [196]. As for other lipid classes, the studies indicate that lowering the GL but not the GI of the habitual diet is able to reduce plasma triglyceride levels and to increase plasma concentrations of HDL [24,197]. In this respect, it may be relevant to consider that a favorable impact of a low GI/GL diet on plasma triglycerides may be attenuated if this diet includes a high proportion of low GI foods and beverages rich in sucrose/fructose, since it has been reported that a high fructose or sucrose intake predisposes to triglyceride elevations and to HDL decrease [198]. In addition, the impact of different foods on plasma insulin levels could also modulate their effects on plasma triglycerides and on HDL, especially in obese individuals, and this could also explain some inconsistencies of the relationship between dietary GI/GL and plasma lipid levels [199]. It has been suggested that race/ethnicity and body mass index may have an effect on these associations, however, this needs to be confirmed in larger studies. Also markers of subclinical inflammation (c-reactive protein, CRP) are consistently reduced by a low GI diet; data on the effects of low GL are, instead, less concordant [29]. However, so far this aspect has only been evaluated in a small number of studies. Among other features of the metabolic syndrome, there is no effect of GI/GL on blood pressure in healthy subjects although Acarbose as a pharmacological model of low GI, reduces incidence of hypertension in individuals with impaired glucose tolerance [32], while there is a modest but reproducible influence on body weight; the data on insulin sensitivity are few and not always concordant but, overall, they indicate a beneficial effect [200].

A new area of interest for intervention studies on GI/GL diets is the evaluation of post-prandial lipemia; there are many epidemiological and pathophysiological studies indicating that elevations of plasma triglyceride levels (and excessive increases of triglyceride rich lipoproteins) after a meal are associated with an increased predisposition to atherosclerosis. The impact of low GI/GL diets on post-prandial metabolism is the background evidence of many intervention trials aiming at evaluating the influence of diet on metabolic abnormalities in the post-prandial period. They have clearly shown that in patients with diabetes a low GL diet improves the overall metabolic response in the postprandial period by reducing: plasma glucose levels, plasma insulin values, glycemic variability, hypoglycemic events and plasma concentrations of triglyceride-rich lipoproteins; further studies are needed in non-diabetic people [195,196,201].

## Conclusions

The scientific summit on the health effect of carbohydrate quality reached a consensus on all the points summarized in Table 3. The panel recognized postprandial glycemia as a relevant factor in overall health and considers dietary approaches that slow carbohydrate absorption to be useful tools in lowering the risk of major chronic diseases and related risk factors. One of these tools is represented by the low GI aspect of carbohydrate foods and the panel recognized that the GI methodology is reproducible and valid to express the glycemic response of foods in a standardized fashion (Table 3). The panel found strong evidence from clinical trials that low GI diets moderately improved glycemic control in type 1 and 2 diabetes, with evidence for benefits in blood lipids and inflammatory markers in people with and without diabetes (Tables 3 and 4). The panel recognized a strong association between lower dietary GI/GL in reducing the risk of developing T2DM in men and women and CHD risk mainly in women (Tables 3 and 4). These health advantages may be of greater relevance in individuals who are sedentary, overweight and in those with the insulin resistance condition (Tables 3 and 4). Despite the lack of clinical trials investigating the role of low GI in reducing the risk of developing T2DM and heart disease, the experience with alpha-glucosidase inhibitors, which convert meals into low GI meals, suggests a potential role of low GI in disease risk reduction end points (Table 4). The evidence was found to be moderate to weak for a possible protective role of low GI/GL diets in cancer risk (Table 4) and in metabolic outcomes in childhood and adolescence although some benefits may be seen in individuals with insulin resistance. However, low GI diets may have health advantages in youth since they related to overall improvements in nutrient profiles. The panel recognized a probable role of low GI and GL diets in body weight management. In adults, low GI diets tended to have a greater impact on reducing body fat mass than body weight while weight loss was mainly observed in overweight people with high insulin levels. However, after weight loss, the combination of low GI and higher protein may prevent weight regain. Despite the indication of the effect of low GI and GL foods in reducing postprandial glucose response which is considered a beneficial physiological effect by EFSA, very little consensus was found within the European DRV documents for the use of low GI. Only Scandinavian countries and Italy suggested the use of low GI diets but in selected groups, i.e. in overweight and obese people and in those whose dietary carbohydrate intakes reach 60% of total calories, with a warning regarding foods where low GI is a consequence of high levels of fructose or fats. However the concern that the low GI sugar fructose may adversely affect metabolic makers when in substitution for equivalent amounts of other sources of carbohydrate likely to replace it (mainly refined starch, glucose, or sucrose) was not supported by the

**Table 3** Consensus: scientific statements [1–14] and future recommendations [15–20].

1. Carbohydrates present in different foods have distinct physiological effects, including effects on postprandial glycemia, also known as the glycemic response (GR), with different implications for health.
2. Reducing postprandial glycemia is recognized as a beneficial physiological effect [52,53,202,203].
3. Ways to reduce postprandial glycemia include slowing carbohydrate absorption by consuming low glycemic index (GI) and low glycemic load (GL) foods to reduce the dietary GI and GL [15,18].
4. The GI methodology is a sufficiently valid and reproducible method for differentiating foods based on their GR [49,204].
5. The GI quantifies specific physiological properties of carbohydrate-containing foods as influenced by the food matrix. These characteristics extend beyond the chemical composition of the foods and include delaying gastric emptying and reducing the rate of digestion and small intestinal absorption.
6. When considering the macronutrient composition, the GL/1000 kJ (the product of GI and available carbohydrate content) is the single best predictor of the GR of foods [154].
7. There is convincing evidence from meta-analyses of controlled dietary trials that diets low in GI improve glycemic control in people with type 2 and type 1 diabetes [12,13,77,87,194].
8. There is convincing evidence from meta-analyses of prospective cohort studies that low GI/GL diets reduce the risk of type 2 diabetes [11,19].
9. There is convincing evidence from a large body of prospective cohort studies that low GI/GL diets reduce the risk of coronary heart disease [6,38,205].
10. The proof of principle for the concept of slowing carbohydrate absorption is the use of alpha-glucosidase inhibitors (acarbose etc.) to reduce progression to type 2 diabetes and coronary heart disease [31,32].
11. The quality of carbohydrate rich foods as defined by GI/GL is particularly important for individuals who are sedentary, overweight and at increased risk of type 2 diabetes [3,18].
12. Potential mechanisms for reduction of type 2 diabetes include evidence that low GI/GL diets improve insulin sensitivity and beta-cell function in people with type 2 diabetes and those at risk for type 2 diabetes [206,207].
13. Potential mechanisms for reduction of coronary heart disease include evidence that low GI/GL diets improve blood lipids and inflammatory markers including C-reactive protein [24,27–29,193,208,209].
14. Probable evidence exists for low GI/GL diets in reducing total body fat mass and in weight management [37,78,131,134,210].
15. The GI complements other ways of characterizing carbohydrate-foods, such as fiber and whole grain content [201,211].
16. Low GI and low GL should be considered in the context of a healthy diet.
17. Given the rapid rise in diabetes and obesity there is a need to communicate information on GI/GL to the general public and health professionals.
18. This should be supported by inclusion of GI/GL in dietary guidelines and in food composition tables.
19. In addition package labels and low GI/GL symbols on healthy foods should be considered.
20. More comprehensive high-quality food composition tables need to be developed for GI/GL at the national level.

scientific evidence particularly if the quantity of fructose is moderate. The panel supports the use of the dietary GI and GL labeling in the context of a healthy diet complementing other healthy dietary attributes (e.g. high fiber) as with the Australian GI Symbol. A front-of-pack label could be used that also requires foods to meet healthy nutrient criteria in line with international dietary guidelines. In light of the epidemic of conditions affecting glucose metabolism, the panel strongly believes that the dietary GI and GL should be communicated to the general public and health professionals through dietary guidelines, country-specific GI databases, food composition tables and food labels (Table 3).

## Conflicts of interest

Arne Astrup is currently an ad hoc consultant for clients of Gerson Lehrman Group, and consultant/member of advisory boards for Global Dairy Platform, USA; Jenny Craig, USA; McCain Foods Limited, USA; McDonald's, USA.

Livia Augustin has received an honorarium from the Nutrition Foundation of Italy (NFI) and is the wife of Meal Garden CEO.

Sara Baer-Sinnott is the president of Oldways is a nonprofit food and nutrition organization. We receive support from a wide variety of organizations – foundations, government entities and companies. We were also the co-organizer of the Glycemic Index, Glycemic Load and Glycemic Response Summit.

Alan Barclay is Vice President and consultant to the Glycemic Index Foundation, an international not-for-profit organization which endorses healthy low GI food products by means of a certified GI symbol. He is a co-author of lay books about the glycemic index of foods and sweeteners.

Jennie Brand-Miller is President of the Glycemic Index Foundation, an international not-for-profit organization which endorses healthy low GI food products by means of a certified GI symbol. She manages a glycemic index testing service at the University of Sydney and is the co-author of lay books about the glycemic index of foods.

Furio Brighenti is affiliated to a department of the University of Parma that does Glycemic index analysis as a service to third parties.

David Jenkins reported serving on the Scientific Advisory Board of Unilever, Sanitarium Company, California Strawberry Commission, Loblaw Supermarket, Herbal Life International, Nutritional Fundamental for Health, Pacific Health Laboratories, Metagenics, Bayer Consumer Care, Orafti, Dean Foods, Kellogg's, Quaker Oats, Procter & Gamble, Coca-Cola, NuVal Griffin Hospital, Abbott, Pulse Canada, Saskatchewan Pulse Growers, and Canola Council of Canada; receiving honoraria for scientific advice from the Almond Board of California, International Tree Nut Council Nutrition Research and Education Foundation, Barilla, Unilever Canada, Solae, Oldways, Kellogg's, Quaker Oats, Procter & Gamble, Coca-Cola, NuVal Griffin Hospital, Abbott, Canola Council of Canada, Dean Foods, California Strawberry Commission, Haine Celestial, and Alpro Foundation; being on the speakers panel for the Almond Board of California; receiving research grants from Loblaw

**Table 4** Disease risk and metabolic effects of low GI and GL diets and of alpha-glucosidase inhibitors.

| | Low GI[a] | Low GL[a] | Alpha glucosidase inhibitors[b] |
|---|---|---|---|
| T2D risk | ↓↓↓[c] | ↓↓↓[c] | ↓↓↓ |
| CHD risk | ↓↓[c,d] | ↓↓↓[c,d] | ↓↓↓ |
| Colorectal cancer risk | ↓↓ | – | ? |
| Breast cancer risk | ↓ | – | ? |
| Endometrial cancer risk | – | ↓ | ? |
| HbA1c in diabetes | ↓↓ | ↓↓ | ↓↓ |
| Postprandial glycemia | ↓↓↓[e] | ↓↓↓[e] | ↓↓↓[e] |
| Postprandial insulinemia | ↓↓↓ | ↓↓↓ | ↓↓↓ |
| Insulin resistance | ↓↓ | ↓↓ | ↓ |
| LDL-cholesterol | ↓ | – | – |
| HDL-cholesterol | ? | ↑ | ↑ |
| Triglycerides | ↓ | ↓↓ | ↓↓ |
| CRP | ↓↓ | ↓ | ↓ |
| Blood pressure | ? | ? | ↓ |
| Body weight | ↓[f] | ↓↓[f] | ↓↓ |
| Body fat mass | ↓↓[f] | ↓↓[f] | ? |

↓↓↓ Strong reduction; ↓↓ moderate reduction; ↓ weak reduction; – no effect; ? either not enough evidence or no evidence available; CRP, C-reactive protein; GI, glycemic index, GL, glycemic load; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; GI, glycemic index, GL, glycemic load; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein.

[a] Low GI compared to high GI and low GL compared to high GL.

[b] Acarbose/voglibose compared to placebo: they reduce the rate of carbohydrate absorption mimicking a low GI diet.

[c] Evidence for risk markers of T2DM and CVD in children and adolescents is still emerging.

[d] Demonstrated particularly in those with higher body weight and in women, not clearly demonstrated in men.

[e] Reduction is more marked in people with diabetes or impaired glucose regulation.

[f] Studies among children and adolescents suggest only a minor role of GI/GL in prevention or treatment of childhood obesity.

Brands Ltd, Unilever, Barilla, Almond Board of California, Solae, Haine Celestial, Sanitarium Company, Orafti, International Tree Nut Council, and Peanut Institute; and receiving travel support to meetings from the Almond Board of California, Unilever, Alpro Foundation, and International Tree Nut Council, Canadian Institutes for Health Research, Canada Foundation for Innovation, Ontario Research Fund. Dr. Jenkins receives salary support as a Canada Research Chair from the federal government of Canada. Dr Jenkins' wife is a director of Glycemic Index Laboratories, Toronto, Ontario, Canada.

Cyril Kendall has received research grants, travel funding, consultant fees, honoraria, or has served on the scientific advisory board for Abbott Laboratories, Advanced Food Materials Network, Agrifoods and Agriculture Canada (AAFC), Almond Board of California, American Peanut Council, American Pistachio Growers, Barilla, California Strawberry Commission, Calorie Control Council, Canadian Institutes of Health Research (CIHR), Canola Council of Canada, The Coca Cola Company (investigator initiated, unrestricted), Danone, General Mills, Hain Celestial, International Tree Nut Council, Kellogg, Kraft, Loblaw Brands Ltd, Nutrition Foundation of Italy, Oldways Preservation Trust, Orafti, Paramount Farms, Peanut Institute, Pepsi-Co, Pulse Canada, Saskatchewan Pulse Growers, Solae, Sun-Maid, Tate & Lyle and Unilever.

Carlo La Vecchia is member of the Advisory Board of the Nutrition Foundation of Italy (NFI, honorary) and received honoraria from Ferrero.

Geoffrey Livesey holds shares in Independent Nutrition Logic Ltd, which is an independent consultancy that takes commissions from many organizations, a full list of which is shown at www.inlogic.co.uk.

Simin Liu received consulting fees from Stanford University, Fred Hutchinson Cancer Research Center, honoraria from General Mills Co, and royalty payment from UpToDate, Inc.

Andrea Poli is the scientific director of the Nutrition Foundation of Italy (NFI), a non-profit organization, which was a co-organizer of the Glycemic Index, Glycemic Load and Glycemic Response Summit.

Gabriele Riccardi is a member of the scientific advisory board of Barilla Center for Food and Nutrition.

John L Sievenpiper has received research support from the Canadian Institutes of Health Research (CIHR), Calorie Control Council, The Coca-Cola Company (investigator initiated, unrestricted grant), Pulse Canada, and The International Tree Nut Council Nutrition Research & Education Foundation. He has received travel funding, speaker fees, and/or honoraria from the American Heart Association (AHA), American College of Physicians (ACP), American Society for Nutrition (ASN), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), Canadian Diabetes Association (CDA), Canadian Nutrition Society (CNS), University of South Carolina, Calorie Control Council, Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD), International Life Sciences Institute (ILSI) North America, International Life Sciences Institute (ILSI) Brazil, Abbott Laboratories, Pulse Canada, Canadian Sugar Institute, Dr. Pepper Snapple Group, and The Coca-Cola Company. He is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of both the Canadian Diabetes Association (CDA) and European Association for the study of Diabetes (EASD), as well as being on the American Society for Nutrition (ASN) writing panel for a scientific statement on the metabolic and nutritional effects of fructose, sucrose and high fructose corn syrup. He is an unpaid scientific advisor for the International Life Sciences Institute (ILSI) North America, Food, Nutrition, and Safety Program (FNSP). His wife is an employee of Unilever Canada.

Thomas Wolever is a part owner and receives payment as the President and Medical Director of Glycemic Index Laboratories, Inc. (GI Labs, a contract research organization) and Glycaemic Index Testing, Inc. (GI Testing, which supplies services to GI Labs) Toronto, Canada. He has authored or co-authored several books on the glycemic index for which has received royalties from Philippa Sandall Publishing Services and CABI Publishers. He has received research support, consultant fees or honoraria from or served on the scientific advisory board for

Canadian Institutes of Health Research, Canadian Diabetes Association, Dairy Farmers of Canada, Agriculture Agri-Food Canada, Public Health Agency of Canada, GI Labs, GI Testing, Abbott, Proctor and Gamble, Mars Foods, McCain Foods, Bunge, Temasek Polytechnic Singapore, Northwestern University, Royal Society of London, Glycemic Index Symbol program, CreaNutrition AG, McMaster University, University of Manitoba, University of Alberta, Canadian Society for Nutritional Sciences, National Sports and Conditioning Association, Faculty of Public Health and Nutrition—Autonomous University of Nuevo Leon, Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes (EASD). His wife is part owner of Glycemic Index Laboratories, Inc., and Glycaemic Index Testing, Inc., and receives payment as chief financial officer of both corporations.

Antonio Ceriello declares the following conflicts of interest. Advisory Board membership: Bayer Healthcare (Basel, Switzerland and/or Milan, Italy), Bristol Myers Squibb (Rome, Italy), Danone (Amsterdam, The Netherlands), DOC Generici (Milan, Italy), Eli Lilly (Indianapolis, USA, and/or Madrid, Spain and/or Sesto Fiorentino, Italy), Janssen (Amsterdam, the Netherlands, and/or Milan, Italy), Medtronic (Milan, Italy), Merck Sharp & Dome (Rome, Italy), Novartis (Origgio, Italy), Novo Nordisk (Copenhagen, Denmark), OM Pharma (Basel, Switzerland), Roche Diagnostics (Milan, Italy), Sanofi (Milan, Italy), Takeda (Rome, Italy) and Unilever (Amsterdam, The Netherlands). Consultancy: Bayer Pharma (Milan, Italy), Lifescan (Milan, Italy), Mendor (Helsinki, Finland), Novartis (Origgio, Italy) and Roche Diagnostics (Milan, Italy). Lectures: Astra Zeneca (Milan, Italy), Bayer Healthcare (Basel, Switzerland and/or Milan, Italy), Bayer Pharma (Milan, Italy), Boehringer Ingelheim (Milan, Italy), Bristol Myers Squibb (Rome, Italy), Eli Lilly (Indianapolis, USA, and/or Madrid, Spain and/or Sesto Fiorentino, Italy), Merck Sharp & Dome (Rome, Italy), Mitsubishi (Tokyo, Japan), Novartis (Origgio, Italy), Novo Nordisk (Copenhagen, Denmark), Nutricia (Amsterdam, The Netherlands), Sanofi (Paris, France and/or Barcelona, Spain and/or Milan, Italy), Servier (Paris, France) and Takeda (Rome, Italy). Research Grants: Mitsubishi (Tokyo, Japan), Novartis (Origgio, Italy), and Novo Nordisk (Copenhagen, Denmark).

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