

TABLE 1

Rate ratios (95% CIs) comparing highest versus lowest quantiles for developing pre- and postmenopausal breast cancer and endometrial cancer due to increasing dietary glycemic index or glycemic load

Chronic disease	Glycemic index rate ratio ¹	<i>P</i>	<i>Q</i> ²	<i>P</i> for heterogeneity	Glycemic load rate ratio ¹	<i>P</i>	<i>Q</i> ²	<i>P</i> for heterogeneity
Premenopausal breast cancer								
Cho et al (4) 2003	1.05 (0.83, 1.33)	0.685			1.06 (0.78, 1.45)	0.713		
Holmes et al (5) 2004	1.02 (0.82, 1.28)	0.862			0.99 (0.89, 1.10)	0.852		
Higginbotham et al (6) 2004	1.29 (0.92, 1.81)	0.140			1.27 (0.79, 2.03)	0.321		
Overall	1.08 (0.93, 1.25)	0.316	1.366	0.51	0.99 (0.81, 1.20)	0.880	1.133	0.47
Postmenopausal breast cancer								
Jonas et al (7) 2003	1.03 (0.87, 1.22)	0.732			0.90 (0.76, 1.07)	0.227		
Holmes et al (5) 2004	1.15 (1.02, 1.30)	0.024			1.03 (0.90, 1.17)	0.659		
Higginbotham et al (6) 2004	0.89 (0.67, 1.17)	0.413			0.90 (0.63, 1.31)	0.573		
Overall	1.06 (0.93, 1.20)	0.366	3.183	0.21	0.97 (0.88, 1.08)	0.600	1.696	0.43
Pre- and postmenopausal cancer combined	1.08 (1.00, 1.17)	0.054	4.550	0.47	0.99 (0.92, 1.06)	0.796	3.06	0.69
Endometrial cancer								
Folsom et al (8) 2003	1.05 (0.77, 1.43)	0.757			1.24 (0.90, 1.71)	0.189		
Larsson et al (9) 2006	1.00 (0.77, 1.30)	1.000			1.15 (0.88, 1.51)	0.310		
Overall	1.02 (0.83, 1.25)	0.842	0.056	0.81	1.19 (0.97, 1.46)	0.105	0.124	0.82

¹ Final, fully adjusted random-effects models only.

² Cochran's heterogeneity statistic for fixed-effects models.

different diseases is complex and multifactorial, but we argue that the main pathophysiological mechanism underlying development is the combined metabolic effects of hyperglycemia, hyperinsulinemia, and alterations in insulin sensitivity in different target tissues and organs (13).

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Bold conclusions from inadequate evidence

Dear Sir:

We read with great interest the recent meta-analysis, by Barclay et al (1), of glycemic index (GI), glycemic load (GL), and the risk of chronic disease. The authors made a respectable effort in covering a multitude of outcomes, which—while sparing a good deal of time for a busy reader—resulted in a lack of depth in the dissection.

In our understanding, the very purpose of a meta-analysis is to arrive at a judgment of an association from analyzing a large base of evidence, which usually means several original studies—surely more than a single study, and preferably >2 studies. However, the analysis by Barclay et al of the association of GI and GL with stroke risk, for example, is based on a single study by Oh et al (2). A quick look at Figure 3 (on page 635 of the meta-analysis) suggests that several studies have been summed up, but a closer look reveals that the first point estimate is for lean subjects and the second is for overweight subjects from the study by Oh et al, and that the last 2 figures give fixed- and random-effects estimates based on the first 2 figures.

Heart disease (also in Figure 3) does not fare much better: only 2 studies are referenced (3, 4). Furthermore, although the label “heart disease” is a good approximation of coronary heart disease (3, 4), the label “eye disease” is far too wide a term, as compared with the disease actually studied by Schaumberg et al (5), which was age-related cataract, also evaluated from a single study.

Because there is vigorous discussion, also in the general public, about the possible health effects of GI- and GL-modified diets and about the possible risk effects of a past high-GI or high-GL diet (or both), one should be careful in drawing firm conclusions. This is especially true if the evidence is insufficient and if—as in this case—the risk factor itself is still vague.

Although it is reasonably tempting to draw the big picture, diseases are not equal, and not all of them necessarily have a common background. Therefore, a message such as that given on page 634—“This meta-analysis provides high-level evidence that diets with a high GI, high GL, or both ... increase the risk of chronic lifestyle-related diseases.”—is perhaps an oversimplification.

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Reply to T-P Tuomainen et al

Dear Sir:

Tuomainen et al have suggested that our meta-analysis draws bold conclusions on the basis of inadequate evidence, implying that only 1–2 studies were considered (1). In fact, our conclusions were based on the aggregated findings of 37 prospective studies of various diseases, all of them linked by the hypothesis that glucose and insulin metabolism played a role in the pathogenesis of the diseases. Furthermore, we described the relation as “a modest effect overall” (page 634), but similar in magnitude to that of dietary fiber and whole grains. The effect was most pronounced in type 2 diabetes, for which there were 8 studies altogether and 5 valid studies (correlation coefficients ≥ 0.5 between total carbohydrate intakes from food-frequency questionnaires and other dietary assessment methods), and the rate ratio was 1.40 (95% CI: 1.23, 1.59) for glycemic index (GI) and 1.27 (1.12, 1.45) for glycemic load (GL).

Tuomainen et al correctly state, “[D]iseases are not equal, and not all of them necessarily have a common background.” However, the multiple authors of all 37 studies must have considered the possibility that the combined metabolic effect of postprandial glycemia, insulin resistance, and compensatory hyperinsulinemia may be a mitigating factor, or they would not have bothered to undertake their analyses. Similarly, most nutritionists consider it valid to examine the relation between dietary fiber and whole-grain foods and a wide range of different diseases. If so, then it is equally valid to consider other measures of carbohydrate quality, such as GI and GL. There are recognized limitations to estimating the true GI and GL of a diet, but there are similar uncertainties surrounding the estimation of fiber and whole-grain intake (both, for example, are subject to methodologic variation and problems of definition). Indeed, the assumption that fiber and whole grains are linked to many diseases is based partly on the underlying assumption that they are surrogate measures of the rate of digestion and absorption. In this respect, GI and GL are more likely to reflect the relative extent of postprandial glycemia and insulin response than is a food’s fiber or whole-grain content (2).

A variety of mechanisms may link GI and GL to the risk of certain chronic diseases. With respect to diabetes, postprandial hyperinsulinemia can lead to progressive loss of insulin sensitivity in the muscles, liver, and other organs. In susceptible persons, insulin resistance and defects in insulin secretion eventually lead to the development of type 2 diabetes (3, 4). With respect to coronary heart disease, high blood glucose and insulin concentrations lead to increased protein glycosylation and oxidative stress, chronic low-grade inflammation, impaired fibrinolysis, and poor endothelial function, which combine to produce damage to endothelium of the blood vessels and an increase in the risk of thrombosis (3–5). Finally, high-GI and high-GL diets have been independently associated with higher LDL and C-reactive protein concentrations and lower concentrations of HDL cholesterol (3, 4, 6, 7). The net effect is greater transport of potentially atherogenic cholesterol particles to peripheral tissues and organs and the decreased removal of those particles.

With respect to certain cancers, glucose is a powerful stimulant for insulin release, and insulin itself stimulates an increase in insulin-like growth factor-1 (IGF-1) in target organs. IGF-1 is a structural homologue of insulin; many tissues types have been shown to have receptors for both IGF-1 and insulin, some of which have the capacity to cross-bind insulin and IGF-1 to their mutual receptors (8). Both insulin and IGF-1 are known mitogens, which are necessary for the cell to progress from G1 to the S phase of the cell cycle, then stimulating cell proliferation and inhibiting cell death (apoptosis) (8). In addition, both insulin and IGF-1 stimulate the synthesis of the sex hormones and regulate their bioavailability through the inhibition of the synthesis of