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, “Diseases 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
sex hormone–binding globulin (SHBG) (8). Elevated insulin, IGF-1, sex hormones, or decreased concentrations of SHBG (or all 4) have been associated with a greater risk of a range of cancers, including premenopausal breast (9) and colorectal (8, 10) cancer.

Therefore, dietary patterns that stimulate postprandial elevations in blood glucose and insulin concentrations, such as those with a high GI and GL, may potentially increase the risk of a range of diseases, including type 2 diabetes, cardiovascular disease, and some cancers.

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Folic acid supplements are good (not bad) for rheumatoid arthritis patients treated with low-dose methotrexate

Dear Sir:

The interesting and provocative commentary on folic acid fortification and supplementation by Smith et al (1) seems to contain a conceptual error in the “thought experiment” involving folic acid supplements and the use of methotrexate (MTX) in the treatment of autoimmune disease such as rheumatoid arthritis (RA) and psoriasis. Folic acid supplements are routinely used to reduce the toxicity of low-dose MTX (usually to the gastrointestinal system, liver, and bone marrow) in the treatment of autoimmune disease such that the patient may experience the efficacy of this drug without its toxicity (ie, an increase in the therapeutic index) (2). A major reason for stopping low-dose MTX therapy is drug toxicity, not a lack of efficacy (3). Thus, it is unethical to continue to use MTX to treat RA patients who develop conditions such as stomatitis, elevated concentrations of liver function enzymes, and cytopenias, even though their joint disease is greatly reduced. In addition, many nonsteroidal anti-inflammatory drugs (NSAIDs) are used in high doses with MTX in RA therapy, and many NSAIDs also have antifolate activities (4).

There is no evidence that food folate fortification has resulted in increased MTX doses or greater degrees of toxicity (5). However, on the other hand, there is a large group of patients with RA who have better-controlled disease because folic acid supplements have maintained their joint disease is greatly reduced. In addition, many nonsteroidal anti-inflammatory drugs (NSAIDs) are used in high doses with MTX in RA therapy, and many NSAIDs also have antifolate activities (4).

Medical emergencies have been reported in patients taking MTX in combination with other antifolates (5). Because of its remarkable efficacy, MTX is the “gold standard” drug for RA therapy and an anchor drug to which other drugs or biologicals are added (6, 7). Over the past few decades, rheumatologists have become more confident in the use of MTX, especially because its associated toxicity is manageable with folic acid supplements; therefore, it is more widely used at higher doses to achieve better responses. Confidence in the use of higher doses has likely occurred at the same time as folic acid fortification; therefore, higher doses cannot necessarily be attributed only to folate fortification (8).

The post hoc analysis of the 2 randomized trials that found that patients who were taking folic acid had a poor clinical response to MTX (9) has been criticized because of I) differences in the patient’s baseline characteristics, 2) the lack of a placebo group in the European Study, 3) the post hoc data interpretation, 4) differences in mean disease duration between the patients in the European and American trials, 5) a larger proportion of patients receiving NSAIDs in the European study, and 6) the similarity in response rates in the European and American studies at 2 y. Therefore, we suggest caution in using this as a piece of confirmatory data (10).

There is no evidence that food folate fortification has resulted in an increase in the incidence or severity of RA in the United States; however, on the other hand, there is a large group of patients with RA who have better-controlled disease because folic acid supplements allow them to tolerate MTX therapy. Although we agree that folic acid supplements may have exposed the general population to certain risks, it is generally accepted that modest amounts of this vitamin are beneficial to patients chronically treated with low-dose MTX.

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