Dear Sir:

Oomen et al (1) reported on the lack of association between α-linolenic acid (ALA, 18:3n−3) consumption and the incidence of coronary artery disease in a 10-y follow-up. We believe that 2 major limitations of this study might have affected its outcome and led to the wrong conclusions. First, this study did not control for plasma concentrations of α-linolenic acid; it is thus difficult to establish a causal relation between actual plasma concentrations of α-linolenic acid—and of its elongation products eicosapentaenoic acid (22:5n−3) and docosahexaenoic acid (22:6n−3)—and the incidence of coronary artery disease. In contrast, the only clinical study of α-linolenic acid carried out thus far, the Lyon Diet Heart Study (2, 3), proved that supplementation with adequate and controlled amounts of ALA increases plasma concentrations of this fatty acid, which was the only fatty acid significantly associated with an improved prognosis (3). Second, the amounts of ALA consumed by the subjects in the Zutphen Elderly Study were estimated only on the basis of food tables and dietary recollection data. Although food composition tables may provide acceptable estimates of the intakes of major fatty acids, it is questionable whether such tables provide acceptable estimates of the intakes of minor fatty acids such as ALA that are present in amounts rarely exceeding 1 g/kg. Conversely, in the Lyon Diet Heart Study, patients were provided with known amounts of margarine enriched in ALA so that the daily intake of this fatty acid in the experimental and control groups was reliably determined to be =2 g and 0.69 g, respectively. These differential intakes resulted in a 2-fold increase in the plasma concentrations of ALA in the experimental group (2). In conclusion, despite growing evidence that suggests health effects of ALA (4), we believe that because of the absence of reliable quantitative data, no definitive conclusions should be drawn regarding the health effects of ALA in terms of either plasma concentrations or daily intake.

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REFERENCES


Reply to F Visioli and C Galli

Dear Sir:

Visioli and Galli offer 2 major comments on our article (1) on the intake of α-linolenic acid and the incidence of coronary artery disease (CAD). First, they suggest that we should have controlled for plasma concentrations of α-linolenic acid. However, to have done so would have resulted in an overadjustment of the results, thus yielding an invalid estimate. We agree that information on plasma α-linolenic acid would have been useful, but not as a variable to be controlled for but instead as one to be studied in separate research on the association between plasma α-linolenic acid and CAD risk. In our opinion, the association between dietary α-linolenic acid and CAD risk is an interesting research question in itself (1).

In addition, note that the analysis of plasma fatty acids in relation to endpoints in the Lyon Diet Heart Study (2) is not clearly described in terms of adjustments for other dietary changes that were introduced in the trial. Therefore, as mentioned in our Discussion (1), we maintain that on the basis of this trial it cannot be concluded that the protective effect against CAD was solely due to α-linolenic acid.

Visioli and Galli’s second comment on our article refers to the quality of our dietary intake data. In reply to their criticism of our method of estimating intakes, we point out that we used the crosscheck dietary history method adapted to the Dutch population (1); this method is acknowledged to be valid in epidemiologic settings (1, 3). In addition, we carefully constructed an extensive table on the α-linolenic acid content of the foods consumed.
The mechanisms involved indicate that the protective effect of α-linolenic acid in the experimental and control margarines in that study was known (7), information on the amount of margarine consumed daily, as well as on the consumption of other sources of α-linolenic acid, was gained by methods similar to ours, as more extensively described by Renaud et al (8).

Therefore, we agree with the comment that no definite conclusions should be drawn from our data, but the same holds in general for all the results of other individual studies on this topic. We observed no beneficial association. We conclude that the methodologic limitations of our study and of other prospective studies, including trials, and the limited evidence on the mechanisms involved indicate that the protective effect of α-linolenic acid has not yet been proven.

References


Vitamins, diet, and cancer prevention

Dear Sir:

In recent letters to the Journal by Horrobin (1) and Zeisel (2), the unexpected failure of β-carotene in clinical trials of lung cancer (3) was explained by the fact that free radicals may be involved both in the elimination of cancer cells and in the generation of mutations that help to initiate cancer. Although the cancer-preventive effects of β-carotene appear to originate mainly in its strong free radical scavenging activity against DNA damage, β-carotene has also been shown to modulate cell proliferation and differentiation through antiproliferative effects on human lung cancer cells (4) and through the enhancement of gap junctional intercellular communication (5). When these effects are taken into account, β-carotene does not appear to promote lung cancer by free radical elimination.

Recently, it was reported that, despite its possible procarcinogenic action as indicated in an editorial by van der Vliet (6), β-carotene acts as an antioxidant rather than as a tumor promoter in a 2-stage model of skin carcinogenesis (7). We speculate that the reason for β-carotene’s failure in the lung cancer trials can be explained by multistage carcinogenesis. Most of the elderly persons with long-term smoking habits who participated in the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study (3) were likely to have mutated genes or premalignant lesions before starting the β-carotene supplementation. Because β-carotene is believed to be most effective in the initiation and promotion stages of carcinogenesis, it may not have shown beneficial effects in the progression stage. Therefore, we believe that β-carotene does not prevent cancer.

However, we do not recommend β-carotene as a dietary supplement to prevent cancer, either. A recent study showed an inverse relation between plasma vitamin C and mortality due to cancer (8). Similar results of lower cancer mortality were obtained in another study that examined daily fruit consumption (9). Recently, we reported that most of the antioxidant and antiproliferative activities of apples result not from vitamin C but mainly from the synergistic effects of phytochemicals (nonvitamins) (10). These results suggest that the cancer-preventive effects of vegetables and fruit may result from phytochemicals rather than from β-carotene, vitamin C, and vitamin E. Therefore, we suggest that balanced diets high in phytochemicals and vitamins may be more advantageous than dietary supplements of single vitamins alone.

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Dear Sir:

In a recent issue of the Journal, Garaulet et al (1) report that adipose tissue from the perivisceral depot (surrounding the gallbladder) has a relatively high saturated fatty acid content and a relatively low monounsaturated fatty acid content compared with fat from other abdominal depots. They also report that there were no correlations between fasting serum insulin values and the fatty acid composition of the abdominal adipose tissue samples. However, the interpretation of these findings might be complicated by the authors' method of selecting their study subjects.

All of the 84 subjects in their study were patients admitted to a hospital for abdominal laparoscopy or laparotomy, but the sites of adipose tissue sampling depended on the patient's type of surgery and surgical diagnosis (specifically gallbladder, ulcer, or umbilical hernia). Assuming that the subjects providing perivisceral tissue (n = 57) and those providing omental tissue (n = 24) were generally distinct from one another, these site-specific tissue specimens were probably taken from patient groups with different medical conditions. The perivisceral tissue probably was sampled from patients with gallbladder disease, whereas the omental tissue probably came from patients with ulcer or hernia. If this is true, then any differences observed in the fatty acid compositions could reflect the subject's medical condition rather than the anatomic site of the adipose tissue specimen. Persons with gallbladder disease tend to have a higher weight and higher glucose and insulin concentrations (2, 3). Because these conditions are also characteristic of the insulin resistance syndrome, it could be important to learn whether the adipose tissue from patients with gallbladder disease (regardless of anatomic site) has a relatively higher concentration of saturated fatty acids.

Fasting serum insulin concentrations are useful in estimating insulin resistance in nondiabetic populations (4) but serve less well in estimating insulin resistance among subjects with impaired glucose tolerance or diabetes (5), ie, persons with diminished insulin production. In Garaulet et al's study, the potential association between insulin resistance and fatty acid composition in tissue might have been obscured by undiagnosed diabetes among the subjects. Despite the investigators' intention to exclude patients with diabetes, many of their subjects had impaired fasting glucose or type 2 diabetes as evidenced by their relatively high mean fasting glucose concentrations (x ± SD: men, 6.9 ± 3.8 mmol/L; women, 6.2 ± 2.7 mmol/L). The threshold value for diagnosing impaired fasting glucose is 6.1 mmol/L and for provisionally diagnosing diabetes is 7.0 mmol/L. Thus, many of Garaulet et al's subjects had some degree of pancreatic insufficiency. Given their heterogeneous study population, perhaps Garaulet et al could use alternative analytic approaches to determine whether the fatty acid composition of adipose tissue is associated with insulin resistance. This would be of interest because previous studies have reported an association between the fatty acid composition of a person's diet and an elevated risk of type 2 diabetes (6, 7).

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REFERENCES
Reply to HS Kahn and R Valdez

Dear Sir:

We read with interest the comments made by Khan and Valdez in reference to our article “Site-specific differences in the fatty acid composition of abdominal adipose tissue in an obese population from a Mediterranean area: relation with dietary fatty acids, plasma lipid profile, serum insulin, and central obesity” (1). They make 2 main points: 1) the differences we found in the fatty acid composition of perivisceral adipose tissue and other intraabdominal depots might be due to the medical condition of the patients from whom the samples were taken and 2) the potential association between insulin resistance and the fatty acid composition of adipose tissue might be obscured by undiagnosed diabetes among our subjects.

As regards the first point, the statistical analysis to establish possible differences in the fatty acid composition of the different types of adipose tissue was only carried out in those patients for whom we had obtained adipose tissue samples from the 3 regions studied (subcutaneous, perivisceral, and omental). In these subjects, a two-way (subject and fatty acid) analysis of variance was applied. For this group, then, it is safe to say that the perivisceral fat was significantly more saturated than were the other fats. We are sorry that this aspect was not clear in our article.

However, when we reanalyzed our patients with insulin resistance as a variable, as suggested by Khan and Valdez, we found some interesting results. The obese population studied was divided into 2 groups according to the degree of insulin resistance, as determined by the HOMA index (homeostasis model assessment; 2). Those with a HOMA index ≥3.8 were designated as being insulin resistant (n = 29), and those with a HOMA index <3.8 were designated as non–insulin resistant (n = 55) (3). We found no significant association between the fatty acid composition of subcutaneous fat and plasma insulin concentrations in either group. The correlation in perivisceral fat was only significant in the non-insulin-resistant group: 22:6n−3 (r = 0.37, P = 0.032) and 20:4n−6 (r = 0.39, P = 0.019). The metabolic significance of these findings is unclear, and perhaps other studies are necessary. However, there were strongly significant associations between the composition of omental fat and insulin values in both groups: 18:3n−3 (r = 0.75, P = 0.021), 18:0 (r = 0.83, P = 0.006), and total saturated fatty acids (r = 0.76, P = 0.018) were positively correlated and 18:1n−9 (r = −0.75, P = 0.019) and total monounsaturated fatty acids (r = −0.82, P = 0.008) were negatively correlated with insulin concentrations in the insulin-resistant group. A negative and significant correlation was also found between 18:1n−9 (r = −0.59, P = 0.02) and insulin concentrations in the non-insulin-resistant group. In reference to dietary composition, we found a significant correlation between 18:3n−3 (r = −0.43, P = 0.028), total polyunsaturated n−3 fatty acids (r = −0.41, P = 0.036), and insulin only in the insulin-resistant group. These findings confirm that the correlation between insulin and the fatty acid composition both in the diet and in adipose tissue differ depending on whether patients are studied as a whole or divided into groups on the basis of their insulin resistance, as Khan and Valdez suggested.

In conclusion, as mentioned in our article, the fatty acid composition of perivisceral, omental, and subcutaneous abdominal tissue is different. Our results after the use of insulin resistance as a variable lend weight to our original finding that the higher 18:1n−9 and polyunsaturated fatty acid contents and the lower saturated fatty acid content of the diet and adipose tissue of the Mediterranean population than of the non-Mediterranean population may mitigate the harmful effects of obesity.

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REFERENCES
Erratum

Four of the values in Table 2 on page 583 are transposed: those for the correlation of restriction with restriction, of pressure with restriction, and of total fat mass with restriction and pressure. The discussion of Table 2 in the right column of page 583 is correct. The corrected table appears below.

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\textsuperscript{1}P < 0.001.  
\textsuperscript{2}P < 0.01.