The beneficial effect of α-linolenic acid in coronary artery disease is not questionable

Dear Sir:

In a recent prospective study of 667 men in Zutphen (Netherlands) and of 98 cases of coronary artery disease (CAD), Oomen et al (1) concluded that the protective effect of dietary α-linolenic acid (ALA) against CAD is questionable. However, recently confirmed positive effects of ALA (2) were reported in several large studies.

The first prospective study showing a beneficial effect of ALA on CAD was conducted in 6250 middle-aged men of the usual care group of the Multiple Risk Factor Intervention Trial (3). After 10.5 y of follow-up, 175 deaths from CAD occurred in that group. ALA intake, as evaluated by dietary recall interviews at 5 different periods, was significantly inversely related to mortality from CAD ($P < 0.04$) and from all causes ($P < 0.02$). The intake of ALA in the highest quintile was 3.2-fold that in the lowest quintile.

More recently, 2 large prospective studies in 76 283 nurses (4) and 43 757 health professionals (5) showed that ALA was the only fatty acid that protected against cardiac death (4) and against nonfatal myocardial infarction (5), independently of other dietary or nondietary factors. In both studies, the intake of ALA in the highest quintile was 1.9-fold that in the lowest quintile.

In the Lyon intervention trial in 600 patients with coronary heart disease (6, 7), both fatal and nonfatal myocardial infarctions were lowered by >70%. Statistical analysis has indicated that most of the beneficial effects are attributable to plasma ALA concentrations. The experimental group had an ALA intake 2.9-fold that of the control group.

In a double-blind, placebo-controlled study in India, the effects of ALA (supplied by mustard oil) in 120 patients with suspected acute myocardial infarction were compared with those of a placebo in 98 control subjects (8). After 1 y of follow-up, both cardiac death and nonfatal myocardial infarction were significantly lower in the group treated with mustard oil. ALA intake in the treated patients was 3.6-fold that in the placebo group.

Finally, the most recent results of the effects of linolenic acid (mostly ALA) on CAD are from a cross-sectional study in 4406 participants of the National Heart, Lung, and Blood Institute Family Heart Study (2). The intake of ALA was significantly inversely related to the prevalence (485 cases) of CAD, in both women and men.

Concordant with the results mentioned above are those of a dietary intervention study conducted in the entire country of Finland over the past 25 y (9). During that period, CAD mortality was reduced overall by >65% and by 80% in 40–50-y-old men. Canola oil rich in ALA is now the main oil used for cooking and to make margarines in Finland.

Thus, ≥7 human studies (3 prospective, 1 cross-sectional, and 3 intervention studies) have reported significant protective effects of a diet enriched in ALA on CAD morbidity, mortality, or both, whereas negative results have only been reported in the Zutphen Elderly Study (1). Because of the suspected key role of ALA in the prevention of CAD, it may be important to unravel the possible explanation (other than the small sample size) for the discrepant results of the Zutphen Elderly Study.

Possible confounding factors in the Zutphen Elderly Study include the following. First, the intake of ALA was strongly associated with that of *trans* fatty acids, which are known for their positive association with CAD (10). When the statistical analysis was performed only with ALA sources without *trans* fatty acids, the positive association between the intake of ALA and CAD was no longer observed. In the Nurses Health Study (4), the intake of *trans* fatty acids also inhibited the inverse relation between ALA and fatal CAD, but not to the extent of the Zutphen Elderly Study. The ratio of *trans* fatty acids to ALA in the group with the highest intake of ALA in the Nurses Health Study (4) was 2.86 and in the Zutphen Elderly Study was 8.65. Thus, the high intake of *trans* fatty acids may be the main reason for the discrepant results of the Zutphen Elderly Study. Even when the relation of food without *trans* fatty acids was evaluated, a residual confounding was probably not totally excluded. Second, an additional factor may be the difference in the intake of ALA between the experimental group or the highest tertile (or quintile) and the control group or the lowest tertile (or quintile). In the Indian intervention trial (8), the intake of ALA in the experimental group was 3.6-fold that in the control group; it was 2.9-fold that in the Lyon study (6). The intake of ALA in the highest quintile or tertile was 3.2-fold that in the lowest quintile or tertile in the prospective Multiple Risk Factor Intervention Trial (3), 2.15-fold that in the men and 2.05-fold that in the women in the Family Heart Study (2), 1.9-fold that in the Nurses Health Study (4) and the Health Professionals Follow-up Study (5), and 1.68-fold that in the Zutphen Elderly Study (1). Thus, it seems that an intake 1.9-fold that of the control group may be required to observe a positive effect of ALA.

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Reply to SC Renaud and D Lanzmann-Petithory

Dear Sir:

In their letter, Renaud and Lanzmann-Petithory question the validity of our conclusion concerning the available evidence on the association between α-linolenic acid intakes and the risk of coronary artery disease (CAD) (1). We agree that our questionable conclusion may have been too firm, but we would like to point out that we arrived at this conclusion not only on the basis of our cohort results but also on our review of previous studies. Therefore, we believe that the issue is still open to question.

One of Renaud and Lanzmann-Petithory's comments relates to confounding by a concomitant intake of *trans* fatty acids. The largest contribution to the intake of α-linolenic acid in our study was provided by foods that also contained *trans* fatty acid (margarines and meat). We observed a nonsignificant increased CAD risk with high α-linolenic acid intakes [relative risk (RR): 1.68] as well as with high α-linolenic acid intake from sources with *trans* fatty acids (RR: 1.51) but a nonsignificant smaller RR with α-linolenic acid intakes from sources without *trans* fatty acids (RR: 1.15). As we indicated in our discussion, modification with *trans* fatty acids, residual confounding, or both may have played a role in our study as well as in others; therefore, Renaud and Lanzmann-Petithory seem to agree with us.

However, the main controversy seems to be the interpretation of the results of former studies. We respectfully disagree with the author's optimistic review. We commented on each former individual study in our article, and the findings are far less consistent than suggested. A summary of the cohort and trial results is therefore presented in **Table 1**. The strongest association was observed in the Nurses' Health Study (6), because the association was not modified by other risk or dietary factors. In the other cohorts, however, the results were less clear and only in a few instances were they statistically significant. The results were strongly affected by adjustments for other dietary factors. In the Health Professionals Follow-up Study (4), the adjusted RR was strengthened after adjustment for total fat. In the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, the RR for the fifth quintile was reduced from 0.99 to 0.75 after additional adjustment for *trans*-

TABLE 1
Summary of the effect of dietary α-linolenic acid (ALA) intake on fatal coronary artery disease (CAD) and fatal plus nonfatal CAD reported in prospective studies[1]

Population	Comparison	Difference in ALA intake	Fatal CAD			Fatal plus nonfatal CAD		
			Crude RR (95% CI)	Adjusted RR[2] (95% CI)	*P* for trend[2]	Crude RR (95% CI)	Adjusted RR[2] (95% CI)	*P* for trend[2]
		g/d						
Cohort studies								
MRFIT (2)	Q5 and Q1	1.9	0.64 (0.40, 1.03)[3]	0.66	0.15	NR	NR	NR
MRFIT (3)[4]	Q5 and Q1	0.56	NR	0.58	<0.05	NR	NR	NR
HPFS (4)	Q5 and Q1	0.7	1.07 (0.70, 1.03)[3]	1.03 (0.66, 1.59)	0.76	0.88 (0.69, 1.12)[3]	0.80 (0.63, 1.03)	0.07
	Continuous	2.2	1.08 (0.46, 2.54)[5]	0.57 (0.18, 1.79)	—	0.65 (0.38, 1.14)[5]	0.41 (0.21, 0.80)	—
ATBC Prevention Study (5)	Q5 and Q1	1.6	0.73 (0.57, 0.93)[3]	0.75 (0.52, 1.10)	0.05	0.85 (0.72, 1.00)[3]	0.96 (0.80, 1.14)	0.91
Nurses' Health Study (6)	Q5 and Q1	0.7	0.79 (0.52, 1.20)[3]	0.55 (0.32, 0.94)	0.01	0.87 (0.67, 1.12)[3]	0.75 (0.56, 1.00)	0.05
Zutphen Elderly Study (1)	T3 and T1	0.8	1.97 (0.97, 3.98)	1.59 (0.62, 4.10)	0.25	2.24 (1.33, 3.77)	1.68 (0.86, 3.29)	0.17
Trials								
Lyon Diet Heart Study (7)	E and C	1.1[6]	0.30 (0.12, 0.75)[3]	0.35 (0.15, 0.83)	—	0.23 (0.11, 0.48)	0.28 (0.15, 0.53)	—
IEIS-4 (8)	E and C	2.9	0.60 (0.23, 1.40)	NR	—	0.81 (0.30, 1.12)	NR	—

[1] RR, relative risk; Q, quintile; T, tertile; NR, not reported; E, experimental group; C, control group; MRFIT, Multiple Risk Factor Intervention Trial; HPFS, Health Professionals Follow-up Study; ATBC, Alpha-Tocopherol Beta-Carotene Cancer; IEIS-4, Indian Experiment of Infarct Survival-4.
[2] For each study, the fully adjusted model is presented here. For details refer to the original papers.
[3] Crude RRs and 95% CIs could be calculated by using the number of cases and person-years of each category (Q1 and Q5 or E and C).
[4] ALA intake expressed as a percentage of energy and with additional adjustment for alcohol when compared with the results presented in reference 2.
[5] Adjusted for age.
[6] Simultaneous changes in other dietary factors.

and *cis*-monounsaturated and saturated fatty acids (5). In the Multiple Risk Factor Intervention Trial, the association may have been confounded by dietary factors other than energy and alcohol use, because such adjustments were not made (3). Second, there was no suggestion of a linear dose-response relation in data from the Health Professionals Follow-up Study because there was no reduced risk of fatal CAD in the highest quintile and a nonsignificant reduction in the risk of fatal plus nonfatal CAD. Finally, a recent cross-sectional study reported an inverse significant association between α-linolenic acid intake and CAD risk (9). However, because of the cross-sectional design, subjects with CAD may have changed their dietary habits (including α-linolenic acid intake) after diagnosis. Because this could have affected the RRs, the results of this study have to be interpreted with caution.

Concerning the intervention studies that suggest beneficial effects of α-linolenic acid, we note that the analysis of plasma fatty acids in relation to endpoints in the Lyon Diet Heart Study (7) is not clearly described in terms of adjustments for other dietary changes that were introduced in the trial. In the Indian mustard-oil trial, the intervention and control groups differed in important characteristics such as smoking, which were not taken into account in the data analyses (8). Therefore, as mentioned in our discussion, we maintain our conclusion that on the basis of this trial it cannot be concluded that the protective effect was solely due to α-linolenic acid.

A final issue is the difference in α-linolenic acid intakes in our study compared with those in the studies described in Table 1. In our article the median intake varied from 0.40% of energy in the lowest tertile to 0.67% of energy in the highest tertile, a 1.7-fold increase. This finding agrees with an absolute difference in intakes between the extreme categories of 0.8 g α-linolenic acid/d, which we think is a better indication of the range of exposure. Other studies reported α-linolenic acid intakes as energy-adjusted grams per day. The lowest differences in intake were observed in the Nurses' Health Study (6) and the Health Professional Follow-up Study (4), 0.7 g/d (a 1.9-fold increase), which is comparable with the range in intake of 0.8 g/d in the Zutphen Elderly Study. Thus, of the 3 prospective studies with a similar range in α-linolenic acid intakes (1, 4, 6), only 1 study observed a significant inverse association (6). Therefore, the suggestion by Renaud and Lanzmann-Petithory that a 1.9-fold difference seems at least necessary to observe a beneficial effect is unwarranted.

In summary, we observed no beneficial effect of α-linolenic acid on the risk of CAD. We conclude that the methodologic limitations of our study and of other prospective studies, including trials, and the limited evidence on the responsible mechanisms, indicate that the protective effect of α-linolenic acid on CAD has not yet been proven.

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Reply to SC Renaud and D Lanzmann-Petithory

Dear Sir:

Evidence from several prospective studies suggests that n−3 fatty acids play an important role in preventing fatal coronary artery disease (CAD). Specifically, α-linolenic acid (ALA) has been inversely related with fatal and nonfatal coronary events (1–3). In a recent article published in the Journal, Oomen et al (4) reported a positive association between ALA and CAD; a comparison of the highest with the lowest tertile of ALA intakes showed the adjusted relative risk of CAD to be 1.68 (95% CI: 0.8, 3.29).

Contrary to the findings of that study, Hu et al (5) reported a 45% reduction in incident fatal myocardial infarction when the highest and the lowest quintiles of ALA intake were compared in the Nurses' Health Study. Other prospective studies showed that a lower risk of CAD was associated with higher ALA intakes (1–3). We reported earlier—in a cross-sectional design—that the prevalence of CAD among men in the highest quintile of total linolenic acid intake was 40% lower than it was among men in the lowest quintile (6).

The discrepancy between the findings of Oomen et al (4) and of other studies merits comment. In the Zutphen Elderly Study (4),

tertiles of ALA intake were created based on the percentage of energy intake. With this approach, 2 subjects with the same absolute ALA intakes will belong to the same quantile of ALA intake only if their energy intakes are similar. However, if one subject consumes more energy than the other, the subject with the lower energy intake will be placed in a higher quantile, whereas the subject with the higher energy intake might be classified into a lower quantile. Thus, assessment of the effects of ALA under these circumstances is obscured and could bias the estimate of the effect. Furthermore, intake of more energy implies consumption of other nutrients, which may or may not affect the outcome of interest. Therefore, it is not surprising that in the Zutphen Elderly Study (4), subjects in the highest tertile of ALA intake also had higher intakes of *trans* fatty acids and total fat. The percentage of energy from ALA does not reflect the absolute amount of ALA consumed. If adjustment for total energy is considered desirable, an unbiased assessment of the effect of ALA would involve a comparison of categories of ALA intakes among subjects with comparable energy intakes.

Furthermore, the rate of conversion of ALA to long-chain fatty acids is dependent on the concentration of linolenic acid (7). A higher ratio of n−6 to n−3 fatty acids may influence the rate of ALA conversion to long-chain fatty acids. Unfortunately, the data reported by Oomen et al (4) do not permit an exact computation of the ratio of n−6 to n−3 fatty acids.

The main results in the Zutphen Elderly Study (4) may have been driven by *trans* fatty acids among subjects in the highest tertile of ALA intake, because the median difference in the percentage of energy from ALA between the highest and the lowest tertiles of ALA intake was only 0.04% in subjects whose ALA intakes were derived from sources that did not contain *trans* fatty acids. This finding suggests that the reported increased risk in CAD observed in the highest tertile of ALA intake is probably related to other nutrients.

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