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Letter to the Editor

Further response from Hoenselaar

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I wish to thank Pedersen *et al.* for their comments[1] in response to my letter to the editor[2]. The articles they refer to may indeed cast some doubt on the use of HDL-cholesterol as a predictor of CHD. The authors then continue their letter by summarising the evidence linking SFA to CHD risk. However, their conclusions may not in all cases be a valid representation of the scientific literature.

The authors provide evidence that SFA intake decreased and PUFA intake increased in the USA and state that there are also reports of declining SFA intake concomitant with the reduction in CHD mortality in several other populations, referring to five articles[3–7]. However, the link between SFA intake and CHD mortality was not examined in the articles referred to; what these articles actually described were trends in fat intake over different time periods for three different populations. Two reports described fat intake in the USA[3,4]. The changes in SFA and PUFA intake were accompanied by a decrease in MUFA intake[4]. Since these three changes were of equal size and took place at the same time, it will take other data to put them in perspective before they can be possibly directly linked to CHD. Two other reports described fat intake in Nordic countries, with an emphasis on Finland[5,6]. Again, changes in SFA and PUFA intake took place in the same time frame. This time, these changes were accompanied by a decrease in *trans*-fat (TFA) intake. The New Zealand report is the only article which might suggest a direct link between SFA and CHD[7]. It shows a trend in decreased CHD rates over time, and (in another part of the text) it is mentioned that SFA consumption decreased over time. However, no direct correlation was examined.

At least one fairly recent report is available though, which allows ecological data to be directly correlated. In 2008, the European Cardiovascular Disease Statistics were published. The report provided data about per-capita SFA intake in 1998 and annual CHD death rates from 1972 to 2005 for adults aged 0–64 years[8]. Based on these data, SFA intake in 1998 was inversely correlated to CHD mortality in 1998 among males for all countries with available data for this year (n 41) using SPSS statistical software package version 17.0 (IBM corporation). Results are shown in Fig. 1 (Pearson correlation $-0{\cdot}58$; $P<0{\cdot}01$). Findings were similar for women and for both CHD and stroke endpoints (P for all $<0{\cdot}01$).

Most ecological studies examine data from the second half of the 20th century, but correlations may be different if a longer time frame is considered. In the USA, age-standardised mortality from diseases of the heart gradually increased from 1900 to 1950 and then gradually decreased until 1996 when it reached approximately the same level as in 1900[9]. No low-fat products existed over a century ago.

Pedersen *et al.* state that the randomised controlled trials included in the meta-analysis by Mozaffarian *et al.*[10] were designed to test the hypothesis that lowering blood cholesterol concentration by diets low in SFA and high in PUFA would reduce the risk in CHD. They concluded that the results showed that replacement of SFA by PUFA did indeed reduce CHD. This conclusion does not do justice to the large amount of dietary and non-dietary changes which actually took place in these trials. In all trials included in the meta-analysis by Mozaffarian *et al.*, SFA, TFA and dietary cholesterol were replaced by PUFA. In the St Thomas' Atherosclerosis Regression Study (STARS) trial, the experimental group consumed more fruits, vegetables and EPA and DHA[11]. In addition, overweight patients were put on a 1000–1200 kcal/d (4184–5021 kJ/d) diet and 'suitable foodstuffs' were given to participants in the experimental groups who did not achieve/maintain the desired serum cholesterol reductions[12]. In the Oslo Diet-Heart Study (ODHS), the experimental group consumed more vegetables, fruits, nuts, fish and whole grains[13]. In the Los Angeles Veterans Study, the control group was distinctly deficient in vitamin E[14]. All these dietary variables have been linked to CHD in prospective studies[15]. Also in the STARS trial, all three patients in the control group who died of sudden death had severe CHD at entry[12]. And according to Ramsden *et al.*[13], in the Finnish Mental Hospital Study (FMHS), the drug thioridazine was used more abundantly in the control group. This drug is strongly associated with risk of sudden death and electrocardiogram changes.

Results from the trials included in the meta-analysis by Mozaffarian *et al.* can be seen in Table 1. Trials are entered by decreasing risk reduction and potential confounders are indicated. Significant protective effects were found in two trials only: the FMHS and the ODHS. The largest effect size was found in the STARS trial. It is doubtful if any of these three trials should have been included in the meta-analysis. In the FMHS, participants were not randomly assigned on an individual basis. Instead, one hospital was put on a diet, while another hospital functioned as the control. In the STARS and ODHS trials the complete dietary pattern was

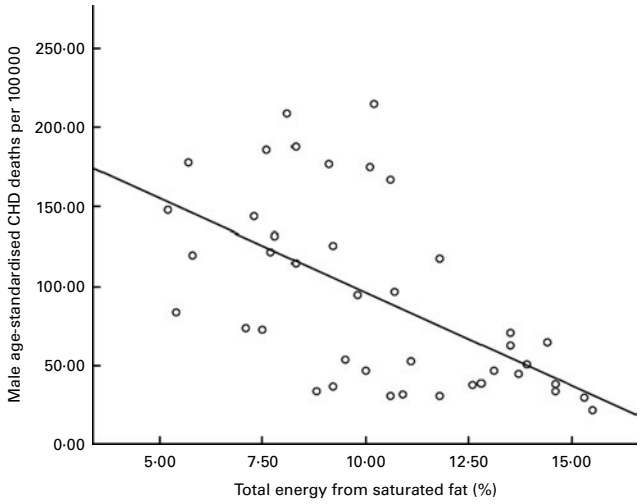

Fig. 1. Saturated fat intake and CHD mortality in Europe (1998). R^2 linear = 0·339.

changed, making it impossible to assess the specific effects from substitution of dietary fats. High consumption of vegetables, fruits, nuts, fish, whole grains and dietary vitamin E has all been linked to relative risk (RR) of 0·70–0·81 in prospective cohort studies and TFA increased risk with an RR of 1·32[15]. Decreased consumption of SFA was only related to decreased CHD when they were replaced by PUFA[16]. No direct association between SFA and CHD was found consistently[15,17,18]. Therefore, it seems that the best dietary fit to explain the effects from randomised trials would be the decrease of TFA and concomitant increases of PUFA and fruits, vegetables, fish, whole grains and nuts where appropriate, rather than the decrease of SFA.

Pedersen *et al.* find that the reduction of CHD risk by replacing SFA by linoleic acid in randomised trials compares well with the predicted change in total/HDL-cholesterol and with the fall in risk observed in the pooled analysis by Jakobsen *et al.*[16]. Therefore, they find no further explanation necessary. Predicted changes in total/HDL-cholesterol would suggest that the replacement of SFA by carbohydrates does not influence CHD and that replacement by MUFA decreases CHD[19]. However, Jakobsen *et al.* showed that the replacement of SFA by either carbohydrate or MUFA actually increased CHD risk, though the effect from MUFA was of borderline significance. Ramsden *et al.* show that only one of the randomised trials (Minnesota Coronary Survey) included in the meta-analysis by Mozaffarian *et al.* examined the effect of replacing SFA specifically by *n*-6 PUFA (linoleic acid). The DART study did not provide data about the *n*-6 and *n*-3 PUFA composition of the diets used and the other four trials included a mixed *n*-6 and *n*-3 PUFA experimental diet. In the experimental group of the Minnesota Coronary Survey, serum cholesterol fell by 13·8% compared to the control group; the corresponding RR for CHD was 1·08.

Fig. 2 shows the decreases in serum total cholesterol concentration for the experimental groups *v.* the control groups in six studies from Table 1 plotted against the RR for CHD. No significant correlation was found (Pearson correlation −0·13). In addition, subgroup analyses within the trials show that changes in cholesterol did not always correspond to predicted effects on CHD[14,20,21].

In conclusion, Pedersen *et al.* provide some ecological data describing changes in SFA intake over time and no correlations with CHD were made in any of the articles referred to. Further, intakes of SFA correlated well with intakes of other types of fat. Other ecological correlations show that European countries with the highest SFA intake have the lowest mortality rates from CHD. US mortality rates from diseases of the heart in 1996 were approximately the same as those that prevailed a century earlier, long before statin use or dietary advice. Systematic reviews of prospective

Table 1. Confounding variables in the trials included in the meta-analysis by Mozaffarian *et al.*[10]
(Relative risks (RR) and 95 % confidence intervals)

Clinical trial	Confounders in experimental group	Confounders in control group	RR according to Mozaffarian *et al.*	95 % CI according to Mozaffarian *et al.*
STARS	Higher consumption of fruits, vegetables, oats and EPA + DHA Overweight patients were put on a 1000–1200 kcal/d (4184–5021 kJ/d) diet	All sudden deaths had severe CHD at entry	0·41	0·09, 1·96
Finnish Mental Hospital	Not a randomised trial	Disproportional use of thioridazine	Men: 0·55 Women: 0·64	Men: 0·34, 0·88 Women: 0·41, 1·00
LA Veterans		Distinct deficiency in vitamin E	0·74	0·53, 1·03
Oslo Diet Heart	Higher consumption of fruits, vegetables, nuts, fish, whole grains and vitamin D		0·75	0·57, 0·99
MRC Soy			0·86	0·61, 1·22
DART			0·91	0·73, 1·14
Minnesota CS			1·08	0·84, 1·37
Pooled estimate			0·81	0·70, 0·95
			0·87 after exclusion of The Finnish Mental Hospital Study	0·76, 1·00 after exclusion of The Finnish Mental Hospital Study

STARS, St Thomas' Atherosclerosis Regression Study; LA, Los Angeles; MRC, Medical Research Council; DART, Diet and Reinfarction Trial; CS, Coronary Survey.

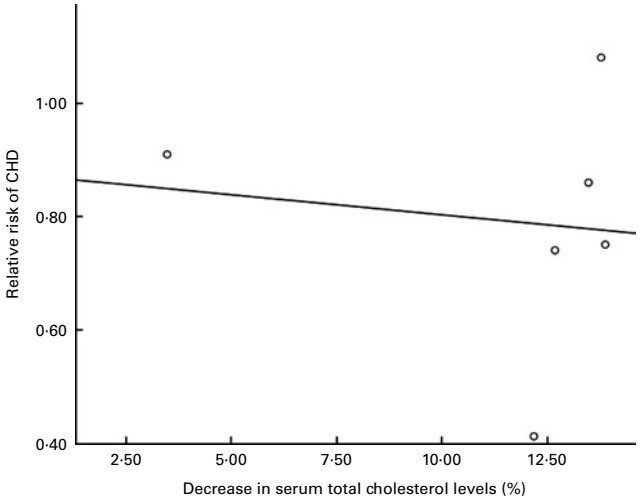

Fig. 2. Changes in serum total cholesterol and CHD risk in randomised trials. Experimental group *v.* control group. R^2 linear = 0·016.

cohort studies show a consistent lack of an association between SFA and CHD. These reviews also show that replacing SFA with PUFA may decrease CHD risk and that replacing SFA with MUFA or carbohydrates might even increase CHD risk. Randomised trials substituting dietary fats suggest a strong correlation between the effect size and the possibility of confounding by other – mostly dietary – variables. Results from prospective cohort studies show that the effects from these dietary variables on CHD may fully explain the effects observed in the randomised trials. Finally, results from both prospective cohort and randomised trials show that changes in serum cholesterol, caused by dietary changes, do not predict effects on CHD in a reliable way.

Pedersen *et al.* seem to interpret epidemiological research and clinical trials from the perspective that SFA increases cholesterol and that cholesterol increases CHD, and so therefore, SFA increases CHD. But if we omit the effects on cholesterol when judging the evidence for an association between SFA and CHD, none of the different types of studies seem to be able to provide reliable evidence that SFA increases CHD. Convincing evidence for an association would mean that all different lines of evidence show an association between SFA and CHD, preferably beyond any level of doubt. Clearly, an overview of the scientific evidence shows suggestive evidence for an association at most.

R. H. is a student at the High School of Arnhem and Nijmegen (The Netherlands). There is no conflict of interest. The research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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