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Letter to the Editor

n-6 Fatty acids and risk for CHD: consider all the evidence

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Ramsden *et al.* have recently confirmed what many other studies have shown: that consumption of vegetable oils rich in *n*-6 PUFA lowers the risk of CHD[1]. These authors performed a meta-analysis of randomised controlled trials which evaluated the effects of increased consumption of such oils, largely in place of animal fats, on CHD outcomes. The key difference from a similar meta-analysis[2] was that here the authors stratified studies by whether the vegetable oil intervention included any *n*-3 PUFA or not, i.e. soyabean oil (which contains small amounts of α-linolenic acid (ALA)) or maize oil (which contains little to no ALA). The former group also included one trial that encouraged cod liver oil consumption. In the four trials utilising soyabean oil, CHD events were reduced by 22 % (relative risk (RR) 0·78 (95 % CI 0·65, 0·93); $P=0·005$); these results were robust in various sensitivity analyses. This is a welcomed observation, as these authors had previously worried that soyabean oil, with its 'high' *n*-6:*n*-3 PUFA ratio, would increase CHD risk[3]. Here, based on their own estimates from the soyabean oil trials in which *n*-6 PUFA consumption was often raised to very high levels (far exceeding the currently recommended 5–10 % energy from PUFA and producing, in three trials, *n*-6:*n*-3 PUFA ratios ranging from 7 to 21), they demonstrated CHD benefit, not detriment. Thus, these results directly contradict widely cited but unsupported hypotheses that high *n*-6 PUFA intakes or 'high' *n*-6:*n*-3 PUFA ratios, increase the risk of CHD.

In the two trials utilising maize oil, no significant effect on CHD events was seen (RR 1·13 (95 % CI 0·84, 1·53); $P=0·43$). Because of its limited statistical power, this two-trial analysis provides insufficient evidence to reject the null hypothesis that consumption of maize oil reduces (or increases) CHD events, and it clearly cannot support the authors' statement that 'advice to specifically increase *n*-6 PUFA intake is unlikely to provide the intended benefits, and may actually increase the risk of CHD and death'.

As pointed out in our own previous studies[2,4], each of these fat/oil-substitution randomised trials had important potential limitations, such as lack of double-blinding, non-compliance, somewhat variable dietary interventions, and limited statistical power due to small sample sizes or few events. In the setting of such limitations, performing stratified analyses is interesting for hypothesis generation but is insufficient for deriving meaningful conclusions. Accordingly, evidence from these types of trials, although helpful and relevant, should be interpreted cautiously and – more importantly – in the context of supporting (or contradictory) evidence from other types of studies in human subjects.

This last critical point appears wholly forgotten by Ramsden *et al.*[1]. Metabolic feeding trials demonstrate clear benefits of *n*-6 PUFA consumption on blood lipid levels[5] and large prospective observational cohorts demonstrate significant inverse associations between *n*-6 PUFA or total PUFA consumption and risk of CHD events[6,7]. The magnitudes of both the expected lower risk from blood lipid changes and the observed lower risk in cohort studies are remarkably consistent with the risk reduction demonstrated by Ramsden *et al.*[1] in the soyabean oil trials and in prior meta-analyses of all PUFA trials[2]. The total body of evidence continues to support the view that higher consumption of *n*-6 PUFA lowers the risk of CHD. Based on these findings, and together with emerging evidence on cardiovascular benefits of ALA[8], it would be reasonable to recommend (as the American Heart Association has done[4,9]) increased consumption of both forms of PUFA – *n*-6 and *n*-3 both plant- and fish-derived.

Conflicts of interest

W. S. H. has been a speaker for GlaxoSmithKline and a consultant to several other companies with interests in *n*-3 fatty acids, including Monsanto, Acasti Pharma, Unilever and Omthera. In addition, he is the owner of OmegaQuant, LLC which provides blood fatty acid testing to researchers and clinicians.

I. A. B. was employed by Wageningen University and posted to the Wageningen Centre for Food Sciences (WCFS) for 100 % of her time from 1999 to 2005. The WCFS is a partnership which receives funding from the Netherlands Ministry of Economic Affairs, five research organisations (University of Groningen, Wageningen University and Research Centre, Maastricht University, NIZO Food Research, and TNO Quality of Life) and six Dutch food industries. In 2006 she moved to VU University but continued with the WCFS and its successor Top Institute (TI) Food and Nutrition for 40 % of her time in 2006 and for 10 % in 2007 and the first half of 2008. Her research involved B vitamins and *n*-3 fatty acids. As from August 2008 she has no conflicts of interest to report.

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