British Journal of Nutrition (2012), **107**, 452–454

Letter to the Editor

Response to Hoenselaar from Pedersen *et al.*

(First published online 13 December 2011)

We thank R. Hoenselaar for his comments[1] in response to our Editorial[2]. He wonders why we concentrate on the effects of SFA on LDL-cholesterol and not also on HDL-cholesterol. The evidence that interventions which change HDL levels affect CHD risk is distinctly weaker than that for LDL. High HDL levels clearly predict lower CHD risk[3], but the question whether the association is causal has not been settled.

People with mutations that cause life-long elevated LDL levels have higher risks of CHD, but mutations that lower HDL levels do not cause such excess risk of CHD[4].

Moreover, randomised trials of statins have demonstrated that substantial reductions in LDL of about 2 mmol/l are associated with about a halving in the risk of CHD and ischaemic stroke[5]. Other drugs and surgical intervention to lower LDL also reduce the incidence of CHD. In contrast, recent trials of drugs that raise HDL failed to reduce the risk of atherosclerosis and CHD[6] (http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=2792), and a recent meta-analysis of 108 randomised lipid-lowering trials could not document that altering HDL-cholesterol by drugs or diet influences the risk of CHD[7]. Several other ongoing large-scale trials are currently assessing whether raising HDL will reduce the risk of CHD and ischaemic stroke. Pending the results from these ongoing HDL-raising trials, the available evidence is still consistent with HDL levels being a marker of CHD rather than being causally related to CHD. Although the drug intervention trials do not, of course, provide a definitive answer on the impact of lifestyles, including diet, on HDL metabolism and the risk of atherosclerotic vascular diseases known to associate with low HDL levels, they currently do not provide strong support for interventions to raise HDL.

Consequently, the primary target for risk reduction by dietary fat should still be LDL- or total cholesterol[7], thus reinforcing the overwhelming importance of reducing the intakes of SFA. PUFA might be a preferred replacement for SFA because it lowers LDL more and has less of an effect on HDL than carbohydrate.

Hoenselaar expresses doubt if a reduction in SFA intake has occurred concurrent with the decline in CHD mortality in developed populations[1]. This is illustrated by citing the small relative reduction of SFA intake in the US population during the period 1990–5/6. It may, however, be more relevant to look at the changes that occurred during earlier decades when the CHD mortality started to decline and before statins were available and complicating the interpretation of causal factors. During several decades before the turn of the 20th century, SFA intake declined and PUFA intake increased[8,9] in the USA. There are also reports of declining SFA intake concomitant with the reduction in CHD mortality in several other populations. In all Nordic countries, SFA intake has decreased compared to the levels in the 1960s[10]. The decline has been particularly noticeable in the Finnish population that has experienced the most rapid fall in CHD mortality in the world. Thus, total fat declined from around 40 percentage of energy (E%) in the 1960s to close to 30 E% in 2007 and SFA intake decreased from 18 to 13 E% among men and to 12 E% among women[11]. At the same time, PUFA increased from 4·3 to 5·9 E% in men and to 5·6 E% in women. These changes came about as a result of active public health programmes. New Zealand may be cited as another example. In 1977, SFA provided 20 E% in males and females. In 1997, SFA was reduced to 15·1 E% in men and to 14·7 E% in women concurrent with reduced CHD mortality[12]. Cholesterol levels declined in most developed countries before the 'statin era' and the major part of this decline can be explained by dietary changes with an important reduction in SFA[13].

Hoenselaar wonders why we did not discuss the confounding role of *trans* fatty acids (TFA)[1]. This was simply because the aim of our editorial was to stress the importance of reducing SFA in public health strategies to prevent CHD. The risk associated with TFA is well accepted and we approve of measures to eliminate these fatty acids from the food chain. However, TFA intake cannot explain the CHD epidemic. The best example is again Finland with originally the highest CHD mortality in the world but with very low intakes of TFA (< 1·5 E%) largely derived from dairy fat[11].

The randomised controlled trials included in the meta-analysis by Mozaffarian *et al.*[14] were designed to test the hypothesis that reducing cholesterol by diets low in SFA and high in PUFA would reduce the risk of CHD. The results showed that replacement of SFA by PUFA indeed reduced CHD. To use these results for evaluating the effects of replacing TFA by other fatty acids may be questionable and tentative only. A comparison[15] of the risk reduction by replacing 5 E% of SFA by linoleic acid in these trials with the predicted change in total/HDL-cholesterol as well as with the fall in risk observed in the meta-analysis by Jacobsen *et al.*[16] suggests that the results of the trials are largely explained by changes in blood lipids and that no further explanation is necessary. The amount of TFA replaced in the trials was much smaller than the amount of SFA, and therefore only a minor part of the fall in total- and LDL-cholesterol and in CHD risk could have been due to TFA.

Hoenselaar finally states that Siri-Tarino *et al.*[17] already responded to our criticisms of their meta-analysis of the prospective cohort studies. That is not correct. Siri-Tarino *et al.*[18] only addressed the issue of over-adjustment for serum cholesterol levels. It can be deduced from their response that studies which over-adjusted by including serum cholesterol in the model showed less of an effect of saturated fat on CHD than studies which did not. The lack of statistical significance for the difference between the two types of studies proves little; absence of proof does not equal proof of absence. In the studies included in this analysis, SFA were replaced by non-specific macronutrients. Thus, in addition to what was said before[2], the results from this meta-analysis do not allow a clear interpretation.

Hoenselaar's questions reflect some of the difficult problems in evaluating the multiple contributors to the complex processes underlying CVD, and CHD in particular. This was highlighted in a previous editorial which illustrates that an understanding of the CHD epidemic requires that all forms of evidence have to be taken into account[19]. This also includes multiple consistent ecological data relating to well-documented diets and CHD rates in many countries. This evidence should not be set aside in analyses. Dietary behaviour is complex and trials that select aspects of diet in isolation are fraught with difficulties of interpretation in a public-health context. As one component of diet changes very often, other aspects also change; imputing causality to only one of these changes can be difficult. Although we do realise the weaknesses of the ecological studies and their possibility of bias, they do provide important insights into population trends in diet and disease patterns over time, and provide a national perspective of the potential impact of multiple changes and prevailing dietary patterns in a societal context, which is the key perspective required in public health.

Jan I. Pedersen
Kaare R. Norum
Department of Nutrition
Institute of Basic Medical Sciences
University of Oslo
POB 1046 Blindern
0316 Oslo
Norway
email j.i.pedersen@medisin.uio.no

Philip T. James
London School of Hygiene and Tropical Medicine
London
UK

Ingeborg A. Brouwer
Martijn B. Katan
Department of Health Sciences
VU University
1081 HV Amsterdam
The Netherlands

Robert Clarke
Clinical Trial Service Unit
University of Oxford
Oxford
UK

Ibrahim Elmadfa
Institute of Nutritional Sciences
University of Vienna
1090 Vienna
Austria

Penny M. Kris-Etherton
Department of Nutritional Sciences
Penn State University
University Park
PA 16802
USA

Daan Kromhout
Division of Human Nutrition
Wageningen University
6700 EV Wageningen
The Netherlands

Barrie M. Margetts
School of Medicine
University of Southampton
Southampton General Hospital
Southampton
UK

Ronald P. Mensink
Department of Human Biology
School for Nutrition
Toxicology and Metabolism
Maastricht University
Maastricht
The Netherlands

Mike Rayner
British Heart Foundation Health
Promotion Research Group
Department of Public Health
University of Oxford
Oxford
UK

Matti Uusitupa
Institute of Public Health and Clinical Nutrition
Clinical Nutrition
Kuopio Campus

British Journal of Nutrition

University of Eastern Finland
Kuopio
Finland

doi:10.1017/S0007114511006593

References

1. Hoenselaar R (2012) The importance of reducing SFA intake to limit CHD risk. *Br J Nutr* **107**, 450–451.
2. Pedersen JI, James PT, Brouwer IA, *et al.* (2011) The importance of reducing SFA to limit CHD. *Br J Nutr* **106**, 961–963.
3. The Emerging Risk Factors Collaboration (2009) Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* **302**, 1993–2000.
4. Teslovich TM, Musunuru K, Smith AV, *et al.* (2010) Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* **466**, 707–713.
5. Cholesterol Treatment Trialists' (CTT) Collaboration (2010) Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* **376**, 1670–1681.
6. Barter PJ, Caulfield M, Eriksson M, *et al.* (2007) Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* **357**, 2109–2122.
7. Briel M, Ferreira-Gonzalez I, You JJ, *et al.* (2009) Association between change in high density lipoprotein cholesterol and cardiovascular disease morbidity and mortality: systematic review and meta-regression analysis. *BMJ* **338**, b92.
8. Committee on Diet and Health (1989) Dietary Intake and Nutritional Status: Trends and Assessment. Chapter 3 in: Diet and Health. Implications for Reducing Chronic Disease Risk, pp. 41–84. Washington, DC: National Research Council, National Academy Press.
9. Stephen AM & Wald NJ (1990) Trends in individual consumption of dietary fat in the United States, 1920–1984. *Am J Clin Nutr* **52**, 457–469.
10. The Project Group: Food Consumption in the Nordic Countries (2001) *National, Annual Food Balance Sheets (in Swedish) TemaNord 2001:527*. Copenhagen: Nordic Council of Ministers.
11. Valsta LM, Tapanainen H, Sundvall J, *et al.* (2010) Explaining the 25-year decline of serum cholesterol by dietary changes and use of lipid-lowering medication in Finland. *Public Health Nutr* **13**, 932–838.
12. Ministry of Health and the University of Auckland (2003) *Nutrition and the Burden of Disease: New Zealand 1997–2011. Public Health Intelligence Occasional Bulletin No 17*. Wellington: Ministry of Health. http://www.moh.govt.nz
13. Capewell & Ford ES (2011) Why have total cholesterol levels declined in most developed countries? *BMC Public Health* **11**, 641. http://www.biomedcentral.com/1471-2458/11/641
14. Mozaffarian D, Micha R & Wallace S (2010) Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med* **7**, e1000252.
15. Katan MB (2009) Omega-6 polyunsaturated fatty acids and coronary heart disease. *Am J Clin Nutr* **89**, 1283–1284.
16. Jacobsen MU, O'Reilly EJ, Heitmann BL, *et al.* (2009) Major types of dietary fat and risk of coronary heart disease: a pooled analysis off 11 cohort studies. *Am J Clin Nutr* **89**, 1425–1432.
17. Siri-Tarino PW, Sun Q, Hu FB, *et al.* (2010) Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *Am J Clin Nutr* **91**, 535–546.
18. Siri-Tarino PW, Sun Q, Hu FB, *et al.* (2011) Reply to P Scarborough. *Am J Clin Nutr* **92**, 459.
19. Stamler J (2010) Diet-heart: a problematic revisit. *Am J Clin Nutr* **91**, 497–499.

British Journal of Nutrition