Institution: King's College London

Unit of Assessment: 3B - Pharmacy and Nutritional Sciences

Title of case study: Dietary fat advice for cardiovascular disease prevention

1. Summary of the impact

Dietary fat plays an important role in the causation of cardiovascular disease (CVD). Using randomized controlled trials of dietary fat modification, King's College London researchers have provided information about the effects of specific fatty acids on CVD risk which the Food Standards Agency have used to inform its policy decisions and future research strategy. The research also contributed to the development of international guidelines on the intakes of specific types of fatty acids and helped the food industry reformulate fats to be low in *trans* fatty acids. This research has also had an impact on dietary advice given by health professionals, the media and patient groups.

2. Underpinning research

Historically, saturated fatty acids (SFA) were regarded as having adverse effects; polyunsaturated fatty acids (PUFA) having positive effects and monounsaturated fatty acids (MUFA) (mainly oleic acid) as being neutral on cardiovascular disease (CVD) risk. However, more recently, emphasis has shifted onto adverse effects of the unsaturated *trans* fatty acids (TFA) and refined carbohydrate. The optimal strategy to replace energy from SFA and TFA is unclear as there is uncertainty to the effects of dietary fat modification on CVD risk factors including clotting factors and vascular function, as well as dyslipidaemia, characterised by raised plasma triglycerides, reduced high density lipoprotein cholesterol (HDL-C) concentration and a predominance of small, dense low-density lipoprotein (sdLDL). In collaboration with the food and pharmaceutical industries, King's College London (KCL) researchers, led by Prof Tom Sanders (1977-present, Professor of Nutrition & Dietetics), Dr Sarah Berry (2004-present, Lecturer) and Prof Phil Chowienczyk (1999-present, Professor of Cardiovascular Pharmacology), have conducted large-scale dietary intervention studies in people at risk of CVD to address important questions about the level and type of fat.

KCL has been at the forefront of evaluating the effects of fats, especially TFAs, on CVD risk including indices of haemostatic function (elevated fibrinogen and factor VII pro-coagulant activity (FVII(c)), decreased fibrinolytic activity and endothelial function) and features of the metabolic syndrome, which is related to CVD risk. In one study using a crossover design, 29 healthy men were fed a TFA-rich diet supplying 10% energy as *trans*-MUFA, followed by diets where TFA were replaced with carbohydrate or oleate, a *cis*-MUFA. This confirmed adverse effects of *trans*-MUFA on HDL-cholesterol concentrations in that when participants were switched from the *trans*-MUFA diet there were falls in the ratio of LDL-C:HDL-C by 11% with carbohydrate and 6% with *cis*-MUFA. However, no specific adverse effects of TFA on haemostatic risk markers for CVD in healthy young men were shown (1). These findings were extended by the five-centre (Reading, Imperial, Surrey, Cambridge, and Kings) RISCK study. This was an important study in that it involved a large group – 548 men and women, 35-70 years – with features of the metabolic syndrome and not just healthy subjects. The 24-week dietary intervention compared a high or low glycaemic index diet, coupled with either a low-fat or high-MUFA component. The study did not find an effect of fat modification on insulin sensitivity but did show that replacing SFAs with MUFA lowered LDL-C:HDL-C compared with replacement with carbohydrate, underpinning advice to replace SFA+TFA with MUFA (2).

Research from KCL, among others, connecting TFA with increased CVD risk led to widespread agreement on the need to minimise intake. TFA produced from partial hydrogenation of vegetable fats were being used to make high melting point fats, key ingredients in the manufacture of some baked goods and margarine. The food industry has sought to replace these TFA by employing a technique called interesterification. This alters the triglyceride structure to increase melting point without changing fatty acid composition. KCL has led on the evaluation of the effects of interesterified fats on CVD risk. Using acute test meal studies (3-5), they showed that stearic acid, an 18 carbon SFA present in high melting point fats, had more favourable effects than *cis*-MUFA or *trans*-MUFA on postprandial lipaemia, a process associated with atherosclerosis, and activation of FVII pro-coagulant activity, a process associated with thrombosis and increased risk of fatal CVD. This refuted previous assertions that stearic acid was thrombogenic. In a chronic feeding study, interesterified fats rich in stearic acid had no effect on LDL-C:HDL-C, insulin sensitivity and blood

pressure, showing that interesterified fats rich in stearic acid are neutral with regard to CVD (5).

KCL research has also contribution to understanding the role of omega-3 or n-3 PUFAs in CVD risk. In the 1980s they showed that high intakes of long-chain n-3 PUFAs decreased plasma triglycerides and hepatic triglyceride synthesis but paradoxically increased LDL apolipoprotein B concentrations, particularly in hypertriglyceridemic individuals. However, in a study in collaboration with Surrey University of 268 men and women aged 50-70, intake of 1-2 portions of oily fish a week, providing about 1.4g/d of a mixture of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), was found to lower both fasting and postprandial triglycerides levels by 11.1% and 7.2% and the proportion of sdLDL by 12.7%, however this did not affect clotting factors or insulin sensitivity (6,7). To investigate whether fish oil could be replaced by a DHA-rich algal oil, which is more sustainable and can be consumed by vegetarians, KCL researchers conducted a randomized control, crossover trial of treatment with 0.7 g purified DHA/d of algal origin for 3 months in 38 healthy men and women (40-65 years). This too showed a 7.1% increase in LDL-C and a 3.4% increase in apolipoprotein B concentration compared with placebo, stimulating public debate as to whether DHA supplements do, in fact, contribute to reduced risk of CVD (8).

3. References to the research (indicative maximum of six references)

1. Sanders TA, Oakley FR, Crook D, Cooper JA, Miller GJ. High intakes of *trans* monounsaturated fatty acids taken for 2 weeks do not influence procoagulant and fibrinolytic risk markers for CHD in young healthy men. Br J Nutr 2003;89(6):767-76. Doi: 10.1079/BJN2003850 (21 Scopus citations)
2. Jebb SA, Lovegrove JA, Griffin BA, Frost GS, Moore CS, Chatfield MD, Bluck LJ, Williams CM, Sanders TAB. Effect of changing the amount and type of fat and carbohydrate on insulin sensitivity and cardiovascular risk: the RISCK (Reading, Imperial, Surrey, Cambridge, and Kings) trial. Am J Clin Nutr 2010;92:748-58. Doi: 10.3945/ajcn.2009.29096 (47 Scopus citations)
3. Sanders TA, de Grassi T, Miller GJ, Morrissey JH. Influence of fatty acid chain length and cis/*trans* isomerization on postprandial lipemia and factor VII in healthy subjects (postprandial lipids and factor VII). Atherosclerosis 2000;149(2):413-20. Doi: 10.1016/S0021-9150(99)00335-4 (47 Scopus citations)
4. Sanders TA, Oakley FR, Cooper JA, Miller GJ. Influence of a stearic acid-rich structured triacylglycerol on postprandial lipemia, factor VII concentrations and fibrinolytic activity in healthy subjects. Am J Clin Nutr 2001;73:715-21. http://ajcn.nutrition.org/content/73/4/715.long (64 Scopus citations)
5. Berry SE, Miller GJ, Sanders TA. The solid fat content of stearic acid-rich fats determines their postprandial effects. Am J Clin Nutr 2007;85:1486-94. Link: http://ajcn.nutrition.org/content/85/6/1486.long (36 Scopus citations)
6. Sanders TA, Lewis F, Slaughter S, Griffin BA, Griffin M, Davies I, Millward DJ, Cooper JA, Miller GJ. Effect of varying the ratio of n-6 to n-3 fatty acids by increasing the dietary intake of alpha-linolenic acid, eicosapentaenoic and docosahexaenoic acid, or both on fibrinogen and clotting factors VII and XII in persons aged 45-70 y: the OPTILIP study. Am J Clin Nutr 2006;84:513-22. Link: http://ajcn.nutrition.org/content/84/3/513.long (34 Scopus citations)
7. Griffin MD, Sanders TA, Davies IG, Morgan LM, Millward DJ, Lewis F, Slaughter S, Cooper JA, Miller GJ, Griffin BA. Effects of altering the ratio of dietary n-6 to n-3 fatty acids on insulin sensitivity, lipoprotein size, and postprandial lipemia in men and postmenopausal women aged 45-70 y: the OPTILIP Study. Am J Clin Nutr 2006;84:1290-8. Link: http://ajcn.nutrition.org/content/84/6/1290.long (75 Scopus citations)
8. Theobald HE, Chowienczyk PJ, Whittall R, Humphries SE, Sanders TA. LDL cholesterol-raising effect of low-dose docosahexaenoic acid in middle-aged men and women. Am J Clin Nutr 2004;79(4):558-63. Link: http://ajcn.nutrition.org/content/79/4/558.long (55 Scopus citations)

Research grants

- 1994-7. Sanders TAB (PI), Miller GJ. The influence of dietary fatty acids on procoagulant and fibrinolytic activity. Ministry of Agriculture Fisheries and Food (MAFF), Diet and Cardiovascular Health Programme: £263,000
- 1997-98. Sanders TAB (PI), Miller GJ. An investigation of the prothrombotic and fibrinolytic effects of SALATRIM in human subjects. Cultor Food Science: £110,000

- 1999-2001. Sanders TAB (PI), Chowienczyk P, Ritter J. Clinical trial of docosahexaenoic acid on endothelial function. Merck Darmstatd: £99,951
- 2000-2003. Sanders (PI). Quantification of the Optimal n-6/n-3 Ratio in the UK diet. MAFF/Food Standards Agency 01-Apr-2000/ 31-Mar-2003 Value to KCL £985,511.
- 2004-7. Sanders TAB. Impact of the amount & composition of dietary fat and carbohydrate on metabolic syndrome & cardiovascular disease risk. Food Standards Agency: £579,876

4. Details of the impact

Cardiovascular disease (CVD) remains a major public health concern. KCL research has contributed to the formulation of dietary fat advice to reduce CVD risk and has had impacts on public health policy and dietary guidelines; on the food industry with regard to reformulation of dietary fats to replace *trans* fatty acids (TFA) and has contributed to public debate and education.

Public health policy and dietary guidelines

In working towards its key strategic aim to reduce diet-related disease, the government's Food Standards Agency (FSA) commissions research into diet, nutrition and CVD. In 2007, the Secretary of State for Health requested advice from the FSA on the evidence in relation to the health effects of TFA so that it could be determined whether current population dietary advice (a maximum of 2% energy) on TFA should be revised. As such, the UK Scientific Advisory Committee on Nutrition (SACN), a group of independent experts who provide advice to Public Health England as well as other government agencies and departments, was tasked to produce an 'Update on *trans* fatty acids and health,' which it published in December 2007. This contained reference to KCL work, including Sanders 2000 and 2003 when discussing postprandial lipemia and haemostatic function (1a). It concluded that TFA intakes were low and SFA reduction was a greater priority. The Scottish Food Standards Agency adopted a similar stance on TFA in February 2008, citing SACN's advice "that the maximum average intake of TFA should be no more than 2% of a person's total food energy" (1b).

Due to his expertise in the area, backed by KCL-led studies, in November 2008 Prof Sanders was invited to be a member of the World Health Organization (WHO)/Food and Agricultural Organization (FAO) Expert Consultation on *Fats and Fatty Acids In Human Nutrition*. This resulted in the publication of a 2009 report that forms the basis for international guidelines on TFA intakes used by both governments and industry (1c). Many of the KCL references detailed above are cited in the report. For instance, they cite Sanders 2001 when discussing how meals high in fat result in postprandial lipemia, with a variable effect of stearic-rich fats. They also utilise this reference, along with Sanders 2006 and Berry 2007, when discussing how meals high in fat, and more particularly MUFA, increase FVIIa. When discussing fish oil and omega-3 fatty acids, they cite Theobald 2004, Sanders 2006 and Griffin 2006. Contrary to the UK report (above), this one concluded that TFA presented a greater CVD risk than SFA and that the elimination of artificial TFA should be a key priority. This guideline recommended that TFA intakes should be no more than 1% energy and as low as possible and noted that stearic acid appeared to be neutral with regard to CVD risk. As such, the Secretary of State for Health changed UK policy by making the elimination of artificial TFA a key target in the *Responsibility Deal* in 2011(1d).

Impacts on Industry

Industrial users (e.g. Unilever PLC, Archer Daniel Midland PLC and Cultor Food Science) were consulted and involved at the planning stage of KCL studies and provided fats and oils for the studies. The impact of policies to eliminate artificial *trans* fats adopted by the Department of Health as part of the *Responsibility Deal* posed a particular challenge for the industry. To replace TFA, they needed to find alternative methods of hardening fats to provide the functionality required to make certain foods. One such technique was interesterification and KCL research on such was of value to industry because it showed none of the adverse effects of *trans* fats with stearic acid-rich interesterified fats. KCL findings were communicated to non-academic users in the food industry by the Food and Drinks Federation Biscuits Cakes and Chocolate Confectionery Alliance in 2009 (2a), Leatherhead Food Research Association in 2010 (2b) and the International Life Science Institute North America in 2012 (2c).

Other impacts on the food industry include that the Greek company D. Genomeres Medical

Research produce a standard meal – called LIPOTEST meal – aimed at healthcare professionals to perform a Fat Tolerance Test on their patients for postprandial triglyceride level determination. The company cites Berry 2007 among the references they used to discuss the fat tolerance test (2d) and in the test patent (2e). On the basis of KCL work, Prof Sanders was also appointed by the Malaysian government to be a member of the Programme Advisory Board of the Malaysian Palm Oil Board (2008-2013) to advise on research on palm oil.

Impacts on public debate and education

The British Nutrition Foundation (BNF) is a charity who advances the education of the public and those involved in training and educating others in nutrition. They also help advance research into nutrition, and dissemination of such, for the public benefit. Prof Sanders is a Trustee and Scientific Governor of the BNF and gave the BNF Annual Lecture in 2009 on the Role of Fat in the Diet in which the results of the research cited was disseminated to the food industry, media and general public (3a). The findings of the RISCK study (Jebb 2010) were also disseminated in the BNF Bulletin and Sanders contributed to a 2008 BBC Radio 4 Case Notes report on the study (3b). HEART UK is charity with an aim to prevent early death caused by high blood cholesterol. Prof Sanders, who is Honorary Nutritional Director and a member of the charity's product approval committee, has communicated the research findings to patient groups at annual meetings (3c). KCL research showing that DHA supplements raised total and LDL cholesterol questioned the value of taking dietary supplements of n-3 long-chain PUFAs as opposed to eating moderate amounts of fish. These findings have contributed to debate in the media (3d: Daily Mail, 15 November 2012), popular science magazines (3e: New Scientist, May 2010) and, further afield, a US website nutraingredients-usa.com (3f).

5. Sources to corroborate the impact

1. Public health policy and dietary guidelines

a. Update on trans fatty acids and health. Position statement by the Scientific Advisory Committee on Nutrition. The Stationery Office. December 2007. ISBN 9780112431176: www.sacn.gov.uk/pdfs/sacn_trans_fatty_acids_report.pdf
b. Scottish Food Standards Agency. http://www.food.gov.uk/scotland/scotnut/satfatenergy/transfat#.Ukgu7SVwaUk
c. WHO/FAO Joint Expert Consultation on Fats and Fatty Acids in Human Nutrition 2008. FAO, Rome 2009. ISBN 978-92-5-106733-8: http://www.fao.org/docrep/013/i1953e/i1953e00.pdf
d. UK Responsibility Deal: https://responsibilitydeal.dh.gov.uk/tag/artifical-trans-fats/
   - http://www.igd.com/our-expertise/Nutrition-food-and-farming/Healthy-balanced-diets/4931/The-Public-Health-Responsibility-Deal/#1

2. Impacts on Industry

a. Talk to the Food and Drinks Federation Biscuits Cakes and Chocolate Confectionery Alliance. 12.2.2009: www.fdf.org.uk/speeches/bccc09_tom_sanders.pdf
b. Talk to the Leatherhead Food Research Association. 23.6.2010: http://www.leatherheadfood.com/nutrition-day-2010
c. International Life Science Institute North America. June 2012: www.youtube.com/watch?v=beTtckdKAa0
d. Lipotest Meal website: http://www.lipotest-meal.com/EN-bibliography.html
e. Lipotest Patent. Triglyceride tolerance test meal EP 2599392 A1. Publication date: 5.6.2013: http://www.google.com/patents/EP2599392A1?cl=en

3. Impacts on public debate and education

a. British Nutritional Foundation: http://www.nutrition.org.uk/
b. BBC Radio 4 Case Notes. 22.1.2008: http://www.bbc.co.uk/radio4/science/casenotes_tr_20080122.shtml
c. Heart UK: http://heartuk.org.uk/
d. Daily Mail. Hooked on fish-oil pills? 13 November 2012: http://www.dailymail.co.uk/health/article-2232022/Fish-oil-pills-Youre-wasting-money-says-nutrition-expert.html
e. Sanjida O'Connell. The Emperor's New Pills. New Scientist, Volume 206, Issue 2760, 12 May 2010, Pages 32-34.
f. Nutraingredients magazine. 28.2.2013: http://www.nutraingredients-usa.com/Research/Should-vegans-and-vegetarians-take-supplements-of-EPA-and-DHA-omega-3s.