European Journal of Clinical Nutrition (2010) 64, S1–S13
 0954-3007/10
www.nature.com/ejcn

REVIEW

Essential fats for future health. Proceedings of the 9th Unilever Nutrition Symposium, 26–27 May 2010

PC Calder[1], AD Dangour[2], C Diekman[3], A Eilander[4], B Koletzko[5], GW Meijer[4], D Mozaffarian[6,7,8], H Niinikoski[9], SJM Osendarp[4], P Pietinen[10], J Schuit[11,12] and R Uauy[2,13]

[1]*Institute of Human Nutrition, School of Medicine, University of Southampton, Southampton, UK;* [2]*Department of Nutrition and Public Health Intervention Research, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK;* [3]*Washington University, St Louis, MO, USA;* [4]*Unilever R&D Vlaardingen, Vlaardingen, The Netherlands;* [5]*Dr von Hauner Children's Hospital, University of Munich Medical Centre, Munich, Germany;* [6]*Division of Cardiovascular Medicine and Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA;* [7]*Department of Epidemiology, Harvard School of Public Health; Boston, MA, USA;* [8]*Department of Nutrition, Harvard School of Public Health; Boston, MA, USA;* [9]*Turku University Hospital, Turku, Finland;* [10]*National Institute for Health and Welfare, Helsinki, Finland;* [11]*National Institute for Public Health and the Environment, Bilthoven, The Netherlands;* [12]*Department of Health Sciences and EMGO Institute for Health and Care Research, VU University, Amsterdam, The Netherlands and* [13]*INTA, Universidad de Chile, Santiago, Chile*

The 9th Unilever Nutrition Symposium entitled 'Essential fats for future health', held on 26–27 May 2010, aimed to review the dietary recommendations for essential fatty acids (EFA); discuss the scientific evidence for the roles of EFA in cognition, immune function and cardiovascular health; and to identify opportunities for joint efforts by industry, academia, governmental and non-governmental organizations to effectively improve health behaviour. This paper summarizes the main conclusions of the presentations given at the symposium. Linoleic acid (LA) and α-linolenic acid (ALA) are EFA that cannot by synthesized by the human body. Docosahexaenoic acid (DHA) is considered as conditionally essential because of its limited formation from ALA in the human body and its critical role in early normal retinal and brain development and, jointly with eicosapentaenoic acid (EPA), in prevention of cardiovascular disease (CVD). Some evidence for possible beneficial roles of *n*-3 fatty acids for immune function and adult cognitive function is emerging. A higher consumption of polyunsaturated fatty acids (PUFA; >10%E), including LA, ALA and at least 250–500 mg per day of EPA + DHA, is recommended for prevention of coronary heart disease (CHD). Two dietary interventions suggest that EFA may affect CVD risk factors in children similarly as in adults. To ensure an adequate EFA intake of the population, including children, public health authorities should develop clear messages based on current science; ensure availability of healthy, palatable foods; and collaborate with scientists, the food industry, schools, hospitals, health-care providers and communities to encourage consumers to make healthy choices.
European Journal of Clinical Nutrition (2010) **64,** S1–S13; doi:10.1038/ejcn.2010.242

Keywords: essential fatty acids; cognition; immune function; heart health; public health

Introduction

Fatty acids that cannot be synthesized by humans, that is, necessary to be obtained from the diet, are referred to as 'essential' fatty acids (EFA). These include the polyunsaturated fatty acids (PUFA), *n*-6 linoleic acid (LA, 18:2*n*-6) from vegetable oils and *n*-3 α-linolenic acid (ALA, 18:3*n*-3) from plant sources (flaxseed, rapeseed oil, walnuts, soybean oil). The *n*-3 PUFA, found in fish and shellfish, eicosapentaenoic acid (EPA, 20:5*n*-3) and docosahexaenoic acid (DHA, 22:6*n*-3) can be synthesized from ALA and thus formally are not 'essential' fatty acids. However, synthesis of EPA and especially DHA is extremely limited in humans (<5–6 and <0.1% conversion from ALA, respectively; Harris *et al.*, 2009a) and the rate of conversion is further reduced in a substantial portion of the populations that carries genetic variants of the fatty acid desaturase gene cluster (Glaser *et al.*, 2010; Lattka *et al.*, 2010a). At present, it remains unclear whether this endogenous conversion of parent EFA to their long-chain metabolites is sufficient for optimal health. Thus, EPA and especially DHA may be considered to be conditionally essential, that is, necessary to obtain from the diet.

Correspondence: Dr A Eilander, Unilever R&D Vlaardingen, Olivier van Noortlaan 120, Vlaardingen 3133 AT, The Netherlands.
E-mail: ans.eilander@unilever.com

Sufficient intakes of PUFA during childhood are required for optimal growth and development and for prevention of the onset of chronic disease in later life. Consumption of a healthy diet that includes PUFA throughout the life is important to maintain cardiovascular and possibly also cognitive and immune health (WHO/FAO, 2003). In most populations, current intakes of PUFA and especially *n*-3 PUFA are insufficient for optimal health (Elmadfa and Kornsteiner, 2009). Therefore, researchers, policy-makers and the food industry must work together in translating the science and dietary guidelines for PUFA into practical coherent dietary recommendations and high-quality products that allow people to improve the fat quality of their diets and benefit their health.

The 9th Unilever Nutrition Symposium entitled 'Essential fats for future health' was held on 26–27 May 2010, with objectives of (1) reviewing the health effects of *n*-3 and *n*-6 PUFA in children and adults, including cognitive development and performance, immune function, and cardiovascular health; (2) addressing gaps in PUFA intakes versus recommendations for different age groups; and (3) identifying opportunities for joint efforts by academia, industry, governmental and non-governmental organizations to effectively improve health behaviour with regard to a sustained, desirable intake of PUFA including EFA.

The symposium consisted of three sessions, including (1) Requirements and recommendations; (2) Benefits of essential fats for future health; and (3) Joint solutions for future health. This paper summarises the main conclusions of the presentations given at the symposium.

Session 1. Requirements and Recommendations

The first session was an introductory session aiming to clarify the roles of PUFA including EFA in the body, which was presented by Professor Ricardo Uauy. In addition, an overview on the latest fatty acid recommendations for prevention of cardiovascular disease (CVD) was provided by Dr Dariush Mozaffarian.

EFA requirements: how much do we really need—Professor Ricardo Uauy

Fats have traditionally been considered a necessary part of the dietary energy supply. Until recently, the main focus of research has been on the total amount of fat that can be tolerated and digested by infants and young children, although the composition of dietary fat had received relatively less attention. Interest in the quality of dietary fat supply in early life as a major determinant of growth, infant development and long-term health is presently growing. Indeed, the selection of dietary fat and fatty acid sources during the first years of life is now considered to be of critical importance. Fats enhance the taste and acceptability of foods; fat components determine, in large part, the texture, flavour and aroma of foods. In addition, fats slow gastric emptying and intestinal motility, thereby affecting satiety. Dietary fats provide EFA and facilitate the absorption of fat-soluble vitamins. Fats are the main energy source in the infant diet and are therefore necessary for normal growth and physical activity. Indeed, fats provide around half of the energy in human milk and in most infant formulas. Finally, fat also constitutes the major energy store in the body; the energy content of adipose tissue on a wet weight basis is 7–8-fold higher than that of tissue containing glycogen or protein.

EFA deficiency, synthesis and metabolism

In 1929, George and Mildred Burr (Burr and Burr, 1973) introduced the concept that specific components of fat may be necessary for normal growth and development of animals and possibly humans. They proposed that three specific fatty acids be considered as essential: LA, arachidonic acid (AA, 20:4*n*-6) and ALA. Despite this important early work, EFA largely ignored in human nutrition until the 1960s, when signs of clinical deficiency were first noted in infants fed skim milk-based formula and in neonates given fat-free parenteral nutrition. These seminal observations firmly established that LA is essential for normal infant nutrition. Hansen *et al*. (1963) observed dryness, desquamation and thickening of the skin, and growth faltering as clinical manifestations of LA deficiency in young infants. More subtle symptoms appeared in *n*-3 EFA deficiency including skin changes unresponsive to LA supplementation, abnormal visual function and peripheral neuropathy; these have been reported in subjects receiving high *n*-6, low *n*-3 fat sources as part of their intravenous nutrition supply (Holman *et al*., 1982).

Humans can synthesize saturated and monounsaturated fatty acids, but not the *n*-3 and the *n*-6 families of PUFA. Thus, the parent EFA, ALA and LA, respectively, must be present in the diet. The essentiality of EFA for humans is best explained by the inability of animal tissues to introduce double bonds in positions proximal to carbon 9, counting from the methyl or N-terminus. Moreover, the respective *n*-3 and *n*-6 EFA cannot be interconverted, thereby making both essential. ALA and LA can be converted to longer chain PUFA (LCPUFA) through enzymatic chain elongation and desaturation. ALA is converted to EPA and then to DHA, whereas LA is converted to AA. DHA is a critical component of cell membranes, especially relevant for the functioning of retina and brain. The high DHA relative content of cerebral cortex and retinal phospholipids supports an essential role of this *n*-3 fatty acid for brain and visual functions (Uauy and Hoffman, 1991), and it is also possible that nervous system manifestations of *n*-3 deficit may result from DHA deficit. AA is both a membrane component and a precursor to potent signalling molecules, the prostaglandins and leukotrienes.

The chain elongation/desaturation enzymes are shared by the *n*-3 and *n*-6 fatty acids leading to competition between substrates. However, synthesis of *n*-6 LCPUFA from LA in early life seems to be more efficient than that of *n*-3 fatty acids.

Typically, cell membranes from animal or human tissues deficient in *n*-3 fatty acids have decreased levels of DHA and increased levels of the end product of *n*-6 metabolism, *n*-6 docosapentaenoic acid (DPA, 22:5*n*-6). Within the subcellular organelles, synaptosomes and mitochondria seem to be the most sensitive to a low dietary *n*-3 supply, as evidenced by the relative abundance of DHA in these organelles and their response to dietary deprivation.

Human neonates as young as 28 weeks gestation weighing 900 g are able to synthesize LCPUFA from their precursors. However, this conversion is quite limited (3–5% of a tracer dose of labelled precursors was found to be converted to LCPUFA over a 96 h period), and the overall evidence indicates that in early life, ALA is not sufficiently converted to DHA to allow for biochemical and functional normalcy (Salem *et al*., 1996). Moreover, recent studies of genetic polymorphisms in genes responsible for fatty acid desaturation suggest that variability in biochemical responses and functional central nervous system effects to changes in diet are partly explained by single-nucleotide polymorphisms affecting a large proportion of the population (Caspi *et al.*, 2007).

The uniqueness of the biological effects of feeding human milk on EFA metabolism is based on the direct supply of preformed LCPUFA, bypassing the regulatory step of both the delta-6 and delta-5 desaturases. Excess dietary LA associated with some vegetable oils, particularly safflower, sunflower and corn oil, may decrease the formation of DHA from ALA because the delta-6 desaturase is inhibited by excess *n*-6 substrates. In addition, on a relative basis, AA formation is lower when excess LA is provided. The inhibitory effect of EPA on delta-5 desaturase activity has been considered responsible for the lower membrane and plasma AA content observed when marine oil is consumed. Excess LA, as seen in infants receiving corn oil or safflower oil as the predominant fatty acid supply, will inhibit the elongation and desaturation of the parent EFA and thus lower the LCPUFA supply available for membrane synthesis. Human milk and LCPUFA from most non-marine food sources provide minimal preformed DHA.

LA and ALA should be considered essential and indispensable as they cannot be synthesized by humans. Although DHA and AA can be synthesized from ALA and LA, respectively, they should be considered non-essential though a dietary supply may be necessary for long-term health. However, given the limited and highly variable formation of DHA from ALA (1–5%) and because of its critical role in normal retinal and brain development in the human, DHA should be considered conditionally essential during early development. Similarly, EPA + DHA might be considered conditionally essential for life-long health considering intakes required for the prevention of CVD.

Essential fats for prevention of CVD—Dr Dariush Mozaffarian

Setting fatty acid guidelines

Inconsistencies across different dietary fatty acid guidelines appear related to the absence of transparent and consistent methods for evaluating scientific evidence (Smit *et al*., 2009). Several types of evidence are available, including that from the randomized controlled trials (RCTs), prospective cohort studies, retrospective case-control studies, ecological studies, cross-sectional studies, case series or reports and animal studies. For setting dietary guidelines, it is essential that strengths and limitations of the different study designs be explicitly considered when determining whether these are optimal for setting dietary guidelines.

As previously reviewed, these different study designs each have unique strengths and limitations (Smit *et al*., 2009). Animal experiments, cross-sectional studies and ecological studies are useful for hypothesis generation. RCTs of physiological measures (intermediate end points or risk factors for disease) are important for supporting evidence. Prospective cohort studies and RCTs of disease outcomes provide the most direct evidence for effects of dietary fatty acids on chronic disease. Prospective cohort studies have many strengths, but a major potential limitation is the inability to exclude residual confounding. In contrast, the major strength of properly executed RCTs is minimization of confounding, but many other study design limitations can limit the utility of the results. A comparison of the strengths and limitations of RCTs versus prospective cohorts demonstrates their complementary nature; thus, inference regarding health effects of specific dietary factors can be considered strongest when both types of designs provide concordant results. When RCTs of disease outcomes are not available, RCTs of physiological measures can provide concordant evidence with prospective cohorts studies for effects on disease risk.

Convincing evidence for setting dietary fatty acid requirements is derived from concordant evidence from well-conducted RCTs of disease outcomes, prospective cohort studies of disease outcomes and RCTs of physiological measures. Given the challenges of performing well-conducted dietary trials of chronic disease outcomes, convincing evidence can also be derived from concordant evidence from well-conducted prospective cohort studies of disease outcomes and RCTs of physiological measures, when there is overall consistency and little evidence to the contrary. This framework is consistent with evidence statements from the World Health Organization (WHO; WHO/FAO, 2003) and the World Cancer Research Fund/American Institute for Cancer Research (2007).

The scientific evidence for cardiovascular effects of the seafood-derived *n*-3 fatty acids, EPA + DHA, and the plant-derived *n*-3 and *n*-6 fatty acids is described below.

Seafood-derived n-*3 PUFA*

RCTs demonstrate clear benefits of EPA + DHA on heart rate, blood pressure and triglyceride levels and also the likely

benefits on myocardial relaxation and efficiency, inflammatory responses, endothelial function, autonomic tone and urine proteinuria (Mozaffarian and Rimm, 2006; Mozaffarian, 2007; Peoples *et al*., 2008). Animal experiments, including non-human primates, also demonstrate clear anti-arrhythmic effects (McLennan, 2001), although small trials of prevention of recurrent ventricular tachyarrhythmia in patients with implantable cardiodefibrillators have been inconsistent (Brouwer *et al*., 2009). Large prospective cohort studies and RCTs provide more direct evidence for effects on clinical end points. Nearly 20 prospective cohort studies have reported on fish consumption and cardiac death, and five RCTs have evaluated effects of fish or fish oil consumption on cardiovascular events. Meta-analyses of observational data consistently indicate that *n*-3 LCPUFAs are associated with lower incidence of fatal coronary heart disease (CHD; Mozaffarian and Rimm, 2006; Wang *et al*., 2006; Mente *et al*., 2009; Harris *et al*., 2009a). Additionally, four of five large RCTs of fish or fish oil intake have demonstrated significant reductions in CHD events (Harris *et al*., 2009a). In a meta-analysis of RCTs that included mostly high-risk populations, EPA + DHA supplementation reduced total mortality by 17% (relative risk (RR) = 0.83, 95% confidence interval (CI) = 0.68–1.00; $P < 0.05$); reductions in total mortality would be more modest in populations at lower risk of ischemia-induced arrhythmic death (Mozaffarian and Rimm, 2006). The dose response for preventing CHD death appears non-linear, with 36% risk reduction ($P < 0.001$) at ~250 mg per day EPA + DHA and then decreasing benefits thereafter (Mozaffarian and Rimm, 2006). Benefits for other end points such as non-fatal myocardial infarction, ischemic stroke and atrial fibrillation are suggested by observational studies but are not yet clearly established from RCTs (Mozaffarian and Rimm, 2006; Wang *et al*., 2006; Harris *et al*., 2009a). Because most studies have assessed combined intakes of EPA + DHA, insufficient evidence exists to make recommendations about EPA versus DHA separately. Overall, the evidence is convincing that modest consumption of fish or fish oil reduces CHD death, and may favorably affect other clinical outcomes.

Plant-derived n-*3 PUFA*

Consumption of the plant-derived *n*-3 fatty acid ALA may also reduce cardiovascular risk, but the evidence is not yet as strong or convincing as for EPA + DHA. In a handful of RCTs, ALA consumption has favourably affected some cardiovascular risk markers, for example, related to platelet function, inflammation, endothelial function and arterial compliance (Mozaffarian, 2005). A meta-analysis of 14 trials of ALA supplementation found improvements in fibrinogen and fasting glucose (Wendland *et al*., 2006). Whether such effects are caused directly by ALA or by its (limited) conversion to EPA is unclear. Ecological studies suggest benefits of increasing ALA intake in populations with low overall *n*-3 PUFA consumption (Zatonski *et al*., 2008). Results of prospective cohort studies of ALA and CVD have been mixed, with some individual studies observing inverse associations with CHD events but meta-analyses showing no significant overall relationship (Brouwer *et al*., 2004; Mozaffarian, 2005; Wang *et al*., 2006; Mente *et al*., 2009). Only one RCT of ALA supplementation and CHD events has been completed: no significant effects were seen, but follow-up was limited to only 1 year (Mozaffarian, 2005). Overall, there is currently only possible evidence that ALA consumption prevents CVD. Because ALA is an accessible and inexpensive source of *n*-3 PUFA, further investigation of these effects is essential, and several trials are planned or are ongoing.

n-*6 PUFA*

LA is the major dietary PUFA, typically comprising >90% of dietary PUFA. RCTs demonstrate clear benefits of LA on blood lipid concentrations, including lowering the levels of low-density lipoprotein (LDL) cholesterol and triglycerides, the total/high-density lipoprotein (HDL) cholesterol ratio, and increasing the level of HDL cholesterol (Mensink *et al*., 2003). Some trials suggest that LA may also be anti-inflammatory or improve insulin resistance, but findings have been mixed (Galgani *et al*., 2008; Riserus *et al*., 2009; Harris *et al*., 2009b). In a pooled analysis of 11 prospective cohorts, greater PUFA intake in place of saturated fat was associated with significantly lower incidence of CHD (for each 5%E, RR = 0.87, 95% CI = 0.77–0.97; Jakobsen *et al*., 2009). Consistent with this, a meta-analysis of RCTs demonstrated similar reduction in CHD events when PUFA replaced saturated fat (for each 5%E, RR = 0.90, 95% CI = 0.83–0.97; Mozaffarian *et al*., 2010). PUFA intake has also been associated with lower CHD risk when replacing carbohydrate (Oh *et al*., 2005). These different lines of research provide strong concordant evidence that LA consumption lowers CHD risk, whether in place of saturated fat or carbohydrate. Because both *n*-3 and *n*-6 PUFA are beneficial, the ratio of *n*-6 to *n*-3 fatty acids is not a useful metric of health effects (Mozaffarian, 2005; Griffin, 2008; Harris *et al*., 2009b).

On the basis of this evidence for health effects of *n*-3 and *n*-6 PUFA, current recommendations for an upper limit of PUFA consumption at 10% energy need to be revisited, and policy measures should prioritize higher consumption of both EPA + DHA and LA (and probably ALA) in the population.

Session 2. Benefits of essential fats for future health

The second session focused on the current state of the scientific evidence for specific health effects of not only EFA LA and ALA but also their long-chain derivates, including AA, EPA and DHA. The session started with a presentation by Professor Berthold Koletzko who evaluated the data on the

importance of fatty acid intake during pregnancy and lactation for infant growth and development. Dr Alan Dangour reviewed the evidence on the effects of *n*-3 fatty acids for improving cognition in children and older people, and Professor Philip Calder continued with the evidence of fatty acids in relation to immune function. The session ended with an overview on the effects of EFA intake during childhood on the development of cardiovascular health later in life by Dr Saskia Osendarp, which was illustrated with a presentation by Dr Harry Niinikoski on the results of the Special Turku coronary Risk factor Intervention Project (STRIP).

The role of long-chain omega 3 fatty acids in pregnancy, lactation and infancy—Professor Berthold Koletzko

Intrauterine and postnatal growth requires a high supply of essential *n*-6 and *n*-3 PUFA. These are precursors of LCPUFA, in particular AA, EPA and DHA. Endogenous LCPUFA synthesis by mothers, fetuses and infants is limited. Moreover, common polymorphisms in the *FADS* gene cluster have strong effects on LCPUFA synthesis, therefore, some individuals have a lower ability than others to form LCPUFA from dietary precursors supplied with vegetable oils (Lattka *et al*., 2010a, 2010b). DHA is rapidly deposited in brain and retina during early growth. Meta-analyses of randomized trials providing pregnant women with placebo or with oils providing DHA or EPA + DHA showed a reduction by 31% in premature births <34 weeks in the total population, and by 61% in at-risk pregnancies (Cetin and Koletzko, 2008). No relevant adverse effects were found at up to 1 g DHA per day, 2.7 g *n*-3 LCPUFA per day or 5 g fish oil per day. Perinatal DHA supply was also associated with benefits for infant development. In utero, the human fetus is supplied with preformed DHA by preferential placental transfer mediated by specific fatty acid transfer proteins. Maternal DHA supply enhances the DHA content of infant cord blood at birth and of human breast milk, which is associated with DHA accretion in infant brain and other tissues, and functional outcomes. Several observational and controlled intervention studies associated the degree of DHA supply to pregnant and lactating women, and to infants, to the child's visual development, fine motor function, social skill scores, language discrimination and verbal intelligent quotient up to school age (Cetin and Koletzko, 2008; Koletzko *et al*., 2008). Maternal DHA supply during pregnancy also appears to modulate the infant's immune response and to lower the allergy risk (Krauss-Etschmann *et al*., 2008). Recent evidence-based consensus recommendations on dietary fat supply for pregnant and lactating women, developed with support from the European Commission and endorsed by several international scientific organizations, concluded that pregnant and lactating women should aim at achieving an average DHA intake of at least 200 mg DHA per day (Koletzko *et al*., 2007). This level of intake can usually be reached by 1–2 meals of ocean fish per week if fatty fish is included (for example, herring, mackerel, salmon, sardines). Women who do not achieve this level of regular fish consumption should consider using DHA supplements or DHA-enriched foods. The acceptable intake in pregnancy and lactation was defined by the European Food Safety Authority as 100–200 mg DHA in addition to the general adult acceptable intake of 250 mg *n*-3 LCPUFA (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2010).

Essential fats for future cognitive health—Dr Alan Dangour

n-3 and *n*-6 PUFA have crucial roles in brain development in utero and in early infancy (Uauy and Dangour, 2006). Some epidemiological evidence from early childhood, such as that from the Avon Longitudinal Study of Parents and Children, suggests that fish consumption by mothers during pregnancy is associated with enhanced behaviour and cognitive function in children (Hibbeln *et al*., 2007). However, the evidence from RCTs is inconsistent. Maternal supplementation with 803 mg EPA + 1183 mg DHA from 18 weeks of gestation to 3 months postpartum was associated with improved child cognitive function at 4 years, but not at 3 , 6 months or 7 years (Helland *et al*., 2001, 2003, 2008), and supplementation of 8–10-year-old children with 200 mg EPA + 83 mg DHA for 16 weeks had no effect on cognitive function (Kirby *et al*., 2010). Even among 6–10-year-old children potentially at-risk of poor nutrition living in urban Jakarta, supplementation for 12 months with 22 mg EPA + 88 mg DHA was not effective in enhancing cognitive function (Osendarp *et al*., 2007). Of late, supplementation of 8–10-year-old boys with DHA (400 mg or 1.2 g per day for 8 weeks) was found to significantly increase activation of the dorsolateral prefrontal cortex, although the significance of this effect for cognitive function remains unclear (McNamara *et al*., 2010).

In adults, *n*-3 LCPUFA have long been thought to be important for the prevention of cognitive decline and dementia, and there is a growing body of mechanistic evidence to suggest an important role of DHA in neuronal health (Bazan, 2006; Cole and Frautschy, 2010). Several, although not all, longitudinal studies have identified positive associations between fish or *n*-3 LCPUFA consumption and cognitive health (Barberger-Gateau *et al*., 2002; Schaefer *et al*., 2006; Albanese *et al*., 2009). A Cochrane review published in 2006 was unable to identify a single RCT evaluating the effect of EPA or DHA supplementation on cognitive function in older people (Lim *et al*., 2006). Recently, however, two RCTs have been published. Van de Rest *et al*. (2008) identified no benefits to cognitive function of supplementation with low-dose (400 mg EPA + DHA per day) or high-dose (1.8 g EPA + DHA per day) EPA + DHA for 6 months. In a significantly larger study, Dangour *et al*. (2010) randomized 867 cognitively healthy participants aged

70–79 years at baseline to either 200 mg EPA + 500 mg DHA or olive oil placebo for 24 months. Despite significant differences in *n*-3 PUFA composition of plasma lipids between study arms at the end of the study, intervention with EPA + DHA had no effect on cognitive function.

It is possible that supplementation with *n*-3 PUFA does not improve cognitive function in childhood or benefit cognitive health in later life. However, there are also other possible reasons for the lack of a positive effect of supplementation from the few available RCTs. The existing trials could be too short to show benefit, the individuals supplemented may be replete in *n*-3 fatty acids such that extra supplementation may not be of benefit, and it may be that any effect may be limited to individuals with particular variants of the genes that encode enzymes involved in the metabolism of PUFA, such as the fatty acid desaturases (Tanaka *et al*., 2009). It is estimated that by 2040, 81 million people worldwide will suffer from dementia (Ferri *et al*., 2005); further studies investigating the factors determining the effectiveness of *n*-3 fatty acids in preserving cognitive health in later life remains a worthwhile endeavour.

Essential fats for future immune health—Professor Philip Calder

The immune system acts to protect the host from pathogens and from other environmental insults. It has four key activities: being a barrier to pathogen entry; identification of 'non-self'/tolerance of 'self'; elimination of 'non-self'; and memory (Cummings *et al*., 2004). The immune system includes many different cell types each with their own specific functions and roles and which act in a coordinated and integrated manner (Cummings *et al*., 2004). A breakdown or dysfunction in one (or more) of the key activities of the immune system can result in disease. Inflammation is often a feature of such disease and can be damaging to the host (Calder *et al*., 2009). The complexity of the immune response, the large number of cells and functions involved, and the redundancies that exist mean that there is no single marker of the 'immune response' or of 'immune function' (Albers *et al*., 2005). This has made it difficult to identify with certainty the effects of fatty acids on the immune response, although many effects of fatty acids have been reported upon specific components of the response. It is known that EFA deficiency impairs cellular aspects of the immune response (Harbige, 2003). Incorporation of certain fatty acids into immune cell membranes can affect membrane structure and function including raft formation and signalling processes leading to gene expression, and can alter the profile of lipid mediators being produced (Shaikh and Edidin, 2006; Yaqoob and Calder, 2007; Calder, 2008; Kim *et al*., 2010). These events have been most thoroughly studied in the context of marine *n*-3 fatty acids. Effects of fatty acids, especially marine *n*-3 fatty acids, on phagocytosis, respiratory burst, antigen presentation, T-cell reactivity, immunoglobulin production, cytokine production and lipid-mediator production have all been demonstrated (Calder, 2001, 2007; Calder *et al*., 2002). However, it is not always clear how these effects might translate into a more or less robust immune response *in vivo* and into an altered risk of infectious or inflammatory disease. Data from the Physician's Health Study showed a protective effect of increased intake of either LA or ALA towards community-acquired pneumonia; there was no significant effect of marine *n*-3 fatty acid intake (Merchant *et al*., 2005). An intervention study with marine *n*-3 fatty acids in Thai schoolchildren found a reduction in infectious illness, mainly upper respiratory tract infections (Thienprasert *et al*., 2009). Studies with marine *n*-3 fatty acids in pregnancy or infancy demonstrate some immune effects (Dunstan *et al*., 2003a, 2003b; Denburg *et al*., 2005; Damsgaard *et al*., 2007) and there is substantial literature suggesting an association between early fish or marine *n*-3 fatty acid exposure and reduced risk of allergic disease in children (Kremmyda *et al*., 2009). The role of the *n*-6 fatty acid AA as a precursor for inflammatory eicosanoids suggests that *n*-6 fatty acids are likely to be pro-inflammatory, whereas *n*-3 fatty acids, which act to antagonize AA metabolism (Calder, 2006), are likely to be anti-inflammatory. However, this seems to be an oversimplification as some studies find inverse associations between both *n*-6 and *n*-3 fatty acid intake or status and circulating inflammatory marker concentrations (Fernandez-Real *et al*., 2003; Lopez-Garcia *et al*., 2004; Ferrucci *et al*., 2006). An intervention study increasing LA intake from 7.7 to 12.6% energy found a limited effect of inflammatory markers (Zhao *et al*., 2004), whereas increasing ALA intake can lower inflammatory marker concentrations and the response of inflammatory cells to stimulation (Burdge and Calder, 2006). Two studies that demonstrate an anti-inflammatory effect of high intakes of ALA (Caughey *et al*., 1996; Zhao *et al*., 2004) suggest that the effect is likely due to conversion of ALA to the more biologically active EPA. Marine *n*-3 fatty acids have been shown to have anti-inflammatory effects, although these are variable between studies (Calder, 2006; Sijben and Calder, 2007). Reasons for such variation likely include differences in the dose of *n*-3 fatty acids administered, duration of administration, characteristics of subjects studied including genetic differences, sample size, and relative amounts of EPA and DHA provided. Fish oil, which is rich in marine *n*-3 fatty acids, is effective in rheumatoid arthritis (Calder *et al*., 2009). Overall it appears that a balanced supply of *n*-6 and *n*-3 fatty acids and an appropriate supply of marine *n*-3 fatty acids are important for the immune system to respond appropriately. However, at the present time, it is not possible to state the amounts of different fatty acids that are required for an optimal immune response.

Essential fats for future cardiovascular health—Dr Saskia Osendarp

CVD risk factors, such as obesity, unfavourable blood lipid profiles and high blood pressure, are now increasingly being

observed in children. Globally in 2010, an estimated 42 million children under the age of 5 years were classified overweight or obese and more than 75% of these children were living in low- and middle-income countries (World Health Organization, 2010). High total and LDL cholesterol and triglyceride levels, and high blood pressure have been observed in cohorts in the US, Finland and Chile in children from as early as 4 years of age (Viikari *et al*., 1988; Berenson *et al*., 1998; McGill *et al*., 2001; Ford *et al*., 2009; Corvalan *et al*., 2010).

In children, like in adults, CVD risk factors are associated with the extent of atherosclerosis: in autopsy data from children with multiple CVD risk factors, a larger percentage of the intimal surface was covered by fibrous plaques compared with children with no CVD risk factors (Berenson *et al*., 1998). Overall, 50% of children had fatty streaks and 8% had fibrous-plaque lesions in the coronary arteries (Berenson *et al*., 1998).

Data from longitudinal cohort studies suggest that CVD risk factors tend to track from childhood into adulthood (Webber *et al*., 1991; Chen and Wang, 2008; Raghuveer, 2010). However, the strength of evidence and predictive value seem to depend on the type and severity of CVD risk factor. In a recent analysis, data from three major studies were combined to estimate the predictive values of childhood metabolic syndrome for metabolic syndrome and type 2 diabetes during adulthood. The negative, but not positive, predictive value of childhood metabolic syndrome was strong for type 2 diabetes and adult metabolic syndrome. The authors suggested that measurements of metabolic syndrome during childhood may therefore be particularly useful to identify children not at risk (Schubert *et al*., 2009).

Positive associations are observed between childhood CVD risk factors and carotid intima–media thickness and arterial stiffness in adulthood (Davis *et al*., 2001; Li *et al*., 2003, 2004). Evidence from a limited number of cases in one longitudinal cohort (Morrison *et al*., 2007) suggests that pediatric metabolic syndrome, defined as $\geqslant 3$ abnormal CVD risk factors during childhood, is predictive for adult CVD events (odds ratio = 14.6; 95% CI = 4.8–45.3).

Role of fatty acids on CVD risk factors in children

Similar to adults, dietary saturated fatty acid (SAFA) intake has also been found to be positively associated with plasma cholesterol concentrations in infants and children (Akerblom *et al*., 1985; Ohlund *et al*., 2008).

Two studies have investigated the effect of dietary fatty acids on CVD risk factors in children through dietary counselling aimed at reducing SAFA and increasing PUFA intakes. The Dietary Intervention Study in Schoolchildren included 663 8–10-year-old children with moderately elevated LDL-cholesterol levels at baseline. The intervention group received a series of group and individual sessions of dietary counselling for a diet low in total fat (28%E), SAFA (8%E) and high in PUFA (up to 9%E), whereas the control group received general dietary information only. The intervention diet resulted in significantly lower LDL cholesterol after 3 years, but not after 5 years of follow-up. The authors suggested that the latter may have been because of difficulties in adherence to the diet in the intervention group (Obarzanek *et al*., 2001).

The STRIP study aimed to reduce SAFA intake (<10%E) and increase PUFA intake (>10%E) by dietary counselling from infancy onwards, and demonstrated that at 14 years of age and compared with the control group, children (both boys and girls) with a low-saturated-fat diet had lower LDL-cholesterol levels and lower blood pressure whereas lower serum triglyceride levels occurred only in boys (Niinikoski *et al*., 2007, 2009).

A review of dietary surveys and population studies of fat and fatty acid intakes in children and adolescents worldwide found data for 28 countries; mainly from Europe, North America, Australia and New Zealand, with data for only four countries from other regions (Harika *et al*.,submitted for publication). Mean SAFA intakes were higher (>10%E) in 26 out of 28 countries and PUFA intakes were lower (<6%E) in 21 out of 28 countries, than the population-based nutrient intake goals recommended by WHO for prevention of chronic diseases (WHO/FAO, 2003). In particular ALA, DHA and EPA intakes were lower than that recommended for the prevention of CVD. Overall, these data suggest that the intakes of fatty acids in children and adolescents are not in line with recommendations for future cardiovascular health.

Future research from long-term follow-up studies is required to determine whether childhood interventions and specific EFA intakes in early childhood impact ultimate disease risk at adult age. In this regard, it would be useful to identify and validate surrogate markers for clinical disease end points in children. More research is required on the most effective timing of interventions during childhood. Recent evidence suggests that perhaps the most critical window for interventions aiming at prevention of chronic diseases is in early infancy and in utero (Uauy *et al*., 2009), supporting the importance of a life-course perspective on prevention of future cardiometabolic diseases.

Essential fats for future health: a case study—Dr Harri Niinikoski

Individuals with high total- and LDL-cholesterol concentrations are predisposed to early atherosclerotic changes in aorta and large arteries already in childhood and adolescence. As fat quality greatly contributes to serum cholesterol levels at all ages, efforts should be made to improve fat quality from early years onwards. The Special Turku coronary Risk factor Intervention Project (STRIP) is a randomized intervention trial which was launched in 1990 to investigate whether atherosclerosis risk factors could be prevented in childhood by means of supervised dietary and lifestyle counselling (Simell *et al*., 2009). The STRIP counselling aims

at decreasing the intake of saturated fat while increasing the intake of unsaturated fat, that is, improving the fat quality. Thus, STRIP provides detailed data on the influences of low-saturated-fat diet on dietary intakes, serum cholesterol concentration, and growth and development in healthy children and adolescents. The intervention and control groups consist of 540 and 522 children, respectively. After 1 year of age, the intervention children were advised to use skim or 1% fat milk and other low-fat dairy products and to add 2–3 teaspoons of vegetable oil (mainly low-erucic acid rapeseed oil) to their daily food. They were also advised to use vegetable oil and margarine in food preparation, on bread and so on. Compared with controls, the intervention children had ~2E% lower saturated fat intake ($P<0.001$) and 0.1–0.2 mmol/l lower LDL-cholesterol values ($P<0.001$), whereas HDL-cholesterol values did not differ between the study groups (Niinikoski *et al*., 2007). HDL-to-total cholesterol ratio was higher in the intervention children than in controls. The intervention had more effects on cholesterol concentrations in boys than in girls. The intervention did not influence growth or pubertal development in either sex (Niinikoski *et al*., 1997, 2007), but the intervention children had ~1 mm Hg lower blood pressure throughout childhood than controls (Niinikoski *et al*., 2009). Detailed cognitive tests performed at the age of 5 years showed no differences between the two study groups (Rask-Nissila *et al*., 2000). Thus, the STRIP data support the safety of supervised low-saturated-fat diet in children.

Session 3. Joint solutions for future health

The third session was convened to discuss how public health policies are developed to improve the fat quality of the diet in children and adults. Professor Jantine Schuit provided a general overview on the challenges to translate scientific developments into public health strategies, with a specific focus on the work of the National Institute for Public Health and the Environment in the Netherlands. This topic was further illustrated by a presentation by Professor Pirjo Pietinen on the nutrition policies for prevention of CVD in Finland. Drs Leendert Wesdorp and Andy Porteous discussed the technological difficulties in designing healthy products containing a high PUFA content and the marketing opportunities for these products. The session ended with a call from Connie Diekman to unite academia, public health authorities and industry to effectively improve the public's health.

Translating scientific developments into public health strategies—Professor Jantine Schuit

The research, including monitoring, modelling and risk assessment, of the National Institute for Public Health and the Environment (RIVM) is used to support policy and practice in public health, food, safety and the environment. The task is to ensure that decision making in policy and practice is well informed by the best available (scientific) evidence.

In translating knowledge into policy and practice, it is important to understand the role of the actors and factors involved in the process and to take the context (political, public opinion, health care and so on) into account. Not only the question 'what is effective' but also questions such as 'why, how and under what circumstances is it working' should be answered. This could lead to improved effectiveness of innovations in public health and health care (Oxman *et al*., 2009). Furthermore, it is important to recognize that (scientific) knowledge is only part of the policy decision-making process (Armstrong *et al*., 2006). Other kinds of knowledge, such as values and policy context, resources, habits and culture, influence of lobbyist and pressure groups, experience and expertise have a role.

The likelihood of research being used by policymakers is increased when there is interaction between researchers and policymakers or professionals. Furthermore, the policy maker should have a positive attitude towards the relevance of research evidence. This may be difficult because the context in which policy makers or professionals operate is very different from a researcher. Whereas a policy maker has to deal with complex problems which need quick answers, has to be accountable for different parties and works in a dynamic world, the scientist usually investigates one problem very conscientiously, which takes time and often does not yield clear-cut answers. The uptake of knowledge can be enhanced by making knowledge more accessible and fit for purpose. This can be improved by closer interaction during the process of the identification of the research question, the research itself and the timing of the communication of key outcomes (Lomas, 2007). Clear messages are needed that translate the research outcome for policy and practice, for example, can we relate the international experience to the local context, what is the feasibility (political, technical, costs and legal, community acceptance) of introducing innovations in the health system. However, during the process of interaction, the researcher has to retain independence, which sometimes may be challenging. To support evidence-informed policy and practice, the RIVM uses various approaches and strategies, including websites, knowledge brokering, appraisal systems, competence building and close collaboration with policy makers, health professionals and stakeholders during the research process. The challenge for institutes like the RIVM is to develop knowledge that is valid and robust, fitting the need, translatable, feasible and acceptable, and developed in close interaction with the policy makers, health professionals and other stakeholders, with a mutual goal and commitment.

Translating science into nutrition policy: Finland as an example—Professor Pirjo Pietinen

Finland has a long history of nutrition policy aiming at preventing CVD. The North Karelia Project, which was

a community-based project in the early 1970s, was the starting point and a pilot project testing population-based strategies, which have then spread to the whole country involving the media, primary health care, food industry, catering and so on, to make healthy choices easy for the consumer, and building a monitoring system.

The National Institute for Health and Welfare, THL (former KTL) is responsible for CVD risk factor surveys (FINRISK surveys) carried out every 5 years in large cross-sectional population samples in several areas since 1972 (Vartiainen *et al*., 2010). In addition, an annual postal survey covering the whole country focuses on health behaviour. Dietary surveys (FINDIET surveys) have been carried out in connection with FINRISK Surveys since 1982. A separate, large population survey carried out by the National Insurance Institution in the early 1970s gives information on diet from that time.

Since the early 1970s, the Finnish diet has changed dramatically: the majority of people use skim or low-fat milk, oils for cooking and low-fat margarines on bread instead of butter and high-fat milk, and vegetable consumption has tripled. The most important oil used in the margarine industry as well as at home is rapeseed oil, which is also locally produced. The most often used margarines are now low-fat margarines, which have 30–60% fat content. Margarines with plant sterols or stanols have also gained popularity, one reason being that one brand has been developed in Finland. Skim milk is the most popular milk among women and over 90% of milk consumed has a fat content between 0.5–1.5%.

These changes are reflected in the fatty acid composition of the Finnish diet. The share of SAFA has decreased from 20 to 13%E, and that of PUFA has increased from 3 to 6%E. The share of monounsaturated fatty acids has remained about the same. The intake of total fat has decreased from about 38 to 33%E. Mean serum cholesterol has decreased from close to 7 mmol/l in North Karelian men in 1972 to 5.4 mmol/l in the same area. The differences between areas have diminished.

How much the dietary changes explain the decline in serum cholesterol has been analyzed from 1982 to 2007 (Valsta *et al*., 2010). Predicted changes in serum cholesterol were calculated by the Keys' equation assuming the effect of *trans*-fatty acids to be similar to SAFA. The effect of medication was estimated based on the information on use of lipid-lowering medication among survey participants. Changes in dietary fat quality and cholesterol intake explain 0.70 mmol/l (65%) of the decrease in serum cholesterol in men and 0.65 mmol/l (60%) in women. Decline in SAFA intake is the main explanatory factor (47% in men and 41% in women) for the changes. The impact of lipid-lowering medication on observed cholesterol levels was found to be 16% among men and 7% among women.

Risk factor changes (decrease in serum cholesterol and blood pressure, and in the prevalence of smoking) explain about 60% of the reduction in coronary mortality over the period 1972–2007, although the observed reduction has been 80%. The most important risk factor in this analysis was clearly serum cholesterol. Thus, the favourable dietary changes have been the most important factor in this development.

This success story has been possible, thanks to good cooperation between the many stakeholders involved. Non-governmental organizations have been important, particularly the Finnish Heart Association and the Finnish Diabetes Association, which have together launched the Heart Symbol to be used on front of pack labelling. The symbol tells the consumer at a glance that the product marked with this symbol is a better choice in its product category. The right to use the Heart Symbol can be given in several different food categories and the criteria is concerned with the quantity and quality of fat, sodium, cholesterol, sugars, and fiber as is applicable in the product category. A group of professionals grants the rights upon application from the manufacturers and subsequent review. About 80% of the consumers recognize the symbol and 52% say that the symbol has influenced their purchases.

The catering sector, which offers a hot lunch from daycare to schools and worksites, has also had an important role. The National Nutrition Council, which gives dietary recommendations, also gives recommendations for the catering sector. On the basis of recent research, children in daycare have a healthier diet than children at home, and school lunch is the healthiest meal in the diet of 13-year olds.

The role of food industry has been very important, and healthier products such as low-fat cheeses and other dairy products, good quality margarines and so on have become increasingly available.

Translating scientific developments into sustainable consumer solutions—Dr Leendert Wesdorp and Andy Porteous

Even today, in essence, food culture remains quite traditional. Therefore, it is difficult to convince people to change their dietary habits to improve the quality of their diet. Fortification of foods is an effective strategy to improve the intakes of nutrients and usually does not have a large impact on food texture, such as iodized salt (Lotfi *et al*., 1996). However, improving fat quality by replacing SAFA with PUFA in a product will dramatically change its properties. Whereas SAFA provide texture and palatability to a food, PUFA are liquid and easily give rancid off-flavours due to oxidation. Thus, developing attractive healthy foods with a high PUFA content has created a significant technical challenge for the food industry.

In margarines, the SAFA content can be reduced by re-arrangement of palm stearin and palm kernel-oil and use of a combination of long and medium chain fatty acids which give very small fat crystals that provide a similar texture with half the amount of SAFA (Dickinson and

McClements, 1996). To prevent oxidation of PUFA, vegetable oils are purified to remove oxidized components, their precursors and pro-oxidative trace metals from oil and processing equipment (Fe, Cu). This can be realized by scavenging trace metals in the products using chelation with proteins and EDTA; addition of antioxidants such as vitamin C, vitamin E and herbal extracts; and by physical separation of pro-oxidants and PUFA in the product. To completely remove the remaining fat oxidation flavours, small amounts of low PUFA fat sources are selectively pre-oxidized before these are added to the product (de Deckere and Verschuren, 2000).

Marketing of healthy products is directed to help people to make healthier choices within their current diet. The benefits of these products should be communicated through different media and communication channels and to different target audiences, including consumers, health-care professionals and scientists. In addition, positive endorsement of recognized public health authorities and clear regulation of health claims are required.

Achieving optimal intakes of EFAs—Connie Diekman

Healthy eating involves choosing healthier fats in place of less healthy fats but research shows that most consumers continue to be confused about fat. A global study, done in 2007 and 2008, as a part of the International Experts Movement, found that fat is misunderstood by the majority of consumers (Diekman and Malcolm, 2009). The study was composed of 3200 subjects who were the main grocery shoppers for their families. The subjects were asked about information on fat and a majority, 57%, indicated that they felt the information on fat and health was contradictory. In addition, 52% did not know which fats were more healthful than others. This confusion among consumers makes it difficult for them to change behaviours and generally results in staying with the fat choices they are more comfortable with.

The food industry is working to provide more options for the consumer but faces challenges associated with palatability and performance of different fat sources, the cost of developing new products and how consumers will view a change or higher cost, and identifying which products are the right products. As health-care providers work to educate people about healthier fats, changes in science require ongoing education, which often isn't feasible given the time constraints on many health-care providers. Staying on top of new products is also difficult for health-care providers, making collaborative efforts the only way to improve understanding of fatty acids and the use of healthier fats.

Developing a plan for collaboration requires identification of the main players with some of the potentials being the food industry, schools, hospitals, health-care providers and communities. Working together these groups can agree on nutrition messages that are based on science, develop practical tips for consumers, change messages as science changes but with a message that conveys the science behind the change and finally, the important message of lifestyle eating patterns. A few examples of programs that are the result of a collaborative effort include the National Dairy Council, The National Football League and the US Department of Agriculture's Fuel Up to Play 60 program which focuses on nutrition and activity goals for school age children. Another program is the new Let's Move campaign started by United States First lady Michelle Obama. This program includes chefs through the Chef's Move to Schools segment, food companies, schools and community organizations. The American Dietetic Association Foundation, along with PE4Life and the American Council for Fitness and Nutrition started a Healthy Schools partnership in Kansas City, Missouri with a goal of changing eating and activity behaviours. Outcomes show an increase in knowledge, vegetable consumption and small changes in weight.

Making changes in fat intake requires collaboration from all segments on clear messages related to fat in a healthy diet. Understanding the process of change will also be important as new food products take time to develop and changing taste palates takes time. Continuing to study fats in terms of healthfulness, developing ways to change fat in foods that consumers love and the importance of smaller portions are important steps in achieving optimal fatty acid consumption. Finally, these collaborative steps will help consumers understand the role and value of fat in a healthful eating plan.

Conflict of interest

PCC, CD, BK, DM, HN and RU received an honorarium for their contributions to the symposium and the current paper from Unilever Netherlands BV. AE, GWM and SJMO are employees of Unilever. DM reports receiving research grants from GlaxoSmithKline, Sigma Tau, Pronova, and the National Institutes of Health for an investigator-initiated, not-for-profit clinical trial; travel reimbursement, honoraria, or consulting fees from the International Life Sciences Institute, Aramark, Unilever, SPRIM, and Nutrition Impact; and royalties from UpToDate for an online chapter. BK is the recipient of a Freedom to Discover Award of the Bristol Myers Squibb Foundation, New York, NY, USA. The other authors declare no other conflict of interest.

References

Akerblom HK, Viikari J, Uhari M, Rasanen L, Byckling T, Louhivuori K *et al.* (1985). Atherosclerosis precursors in Finnish children and adolescents. I. General description of the cross-sectional study of 1980, and an account of the children's and families' state of health. *Acta Paediatr Scand Suppl* **318**, 49–63.

Albanese E, Dangour AD, Uauy R, Acosta D, Guerra M, Guerra SS *et al*. (2009). Dietary fish and meat intake and dementia in Latin America, China, and India: A 10/66 Dementia Research Group population-based study. *Am J Clin Nutr* **90**, 392–400.

Albers R, Antoine JM, Bourdet-Sicard R, Calder PC, Gleeson M, Lesourd B *et al*. (2005). Markers to measure immunomodulation in human nutrition intervention studies. *Br J Nutr* **94**, 452–481.

Armstrong R, Doyle J, Lamb C, Waters E (2006). Multi-sectoral health promotion and public health: the role of evidence. *J Public Health (Oxf)* **28**, 168–172.

Barberger-Gateau P, Letenneur L, Deschamps V, Peres K, Dartigues JF, Renaud S (2002). Fish, meat, and risk of dementia: cohort study. *BMJ* **325**, 932–933.

Bazan NG (2006). Cell survival matters: docosahexaenoic acid signaling, neuroprotection and photoreceptors. *Trends Neurosci* **29**, 263–271.

Berenson GS, Srinivasan SR, Bao W, Newman III WP, Tracy RE, Wattigney WA (1998). Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med* **338**, 1650–1656.

Brouwer IA, Katan MB, Zock PL (2004). Dietary alpha-linolenic acid is associated with reduced risk of fatal coronary heart disease, but increased prostate cancer risk: a meta-analysis. *J Nutr* **134**, 919–922.

Brouwer IA, Raitt MH, Dullemeijer C, Kraemer DF, Zock PL, Morris C *et al*. (2009). Effect of fish oil on ventricular tachyarrhythmia in three studies in patients with implantable cardioverter defibrillators. *Eur Heart J* **30**, 820–826.

Burdge GC, Calder PC (2006). Dietary alpha-linolenic acid and health-related outcomes: a metabolic perspective. *Nutr Res Rev* **19**, 26–52.

Burr GO, Burr MM (1973). Nutrition classics from the journal of biological chemistry 82:345-67, 1929. A new deficiency disease produced by the rigid exclusion of fat from the diet. *Nutr Rev* **31**, 248–249.

Calder PC (2001). Polyunsaturated fatty acids, inflammation, and immunity. *Lipids* **36**, 1007–1024.

Calder PC (2006). N-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *Am J Clin Nutr* **83**, 1505S–1519S.

Calder PC (2007). Immunomodulation by omega-3 fatty acids. *Prostaglandins Leukot Essent Fatty Acids* **77**, 327–335.

Calder PC (2008). The relationship between the fatty acid composition of immune cells and their function. *Prostaglandins Leukot Essent Fatty Acids* **79**, 101–108.

Calder PC, Albers R, Antoine JM, Blum S, Bourdet-Sicard R, Ferns GA *et al*. (2009). Inflammatory disease processes and interactions with nutrition. *Br J Nutr* **101** (Suppl 1), S1–S45.

Calder PC, Yaqoob P, Thies F, Wallace FA, Miles EA (2002). Fatty acids and lymphocyte functions. *Br J Nutr* **87** (Suppl 1), S31–S48.

Caspi A, Williams B, Kim-Cohen J, Craig IW, Milne BJ, Poulton R *et al*. (2007). Moderation of breastfeeding effects on the IQ by genetic variation in fatty acid metabolism. *Proc Natl Acad Sci USA* **104**, 18860–18865.

Caughey GE, Mantzioris E, Gibson RA, Cleland LG, James MJ (1996). The effect on human tumor necrosis factor alpha and interleukin 1 beta production of diets enriched in n-3 fatty acids from vegetable oil or fish oil. *Am J Clin Nutr* **63**, 116–122.

Cetin I, Koletzko B (2008). Long-chain omega-3 fatty acid supply in pregnancy and lactation. *Curr Opin Clin Nutr Metab Care* **11**, 297–302.

Chen X, Wang Y (2008). Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. *Circulation* **117**, 3171–3180.

Cole GM, Frautschy SA (2010). DHA may prevent age-related dementia. *J Nutr* **140**, 869–874.

Corvalan C, Uauy R, Kain J, Martorell R (2010). Obesity indicators and cardiometabolic status in 4-y-old children. *Am J Clin Nutr* **91**, 166–174.

Cummings JH, Antoine JM, Azpiroz F, Bourdet-Sicard R, Brandtzaeg P, Calder PC *et al*. (2004). PASSCLAIM—gut health and immunity. *Eur J Nutr* **43** (Suppl 2), II118–II173.

Damsgaard CT, Lauritzen L, Kjaer TM, Holm PM, Fruekilde MB, Michaelsen KF *et al*. (2007). Fish oil supplementation modulates immune function in healthy infants. *J Nutr* **137**, 1031–1036.

Dangour AD, Allen E, Elbourne D, Fasey N, Fletcher AE, Hardy P *et al*. (2010). Effect of 2-y n-3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. *Am J Clin Nutr* **91**, 1725–1732.

Davis PH, Dawson JD, Riley WA, Lauer RM (2001). Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: the Muscatine Study. *Circulation* **104**, 2815–2819.

de Deckere EAM, Verschuren PM (2000). Functional fats and spreads. In: GR Gibson and CM Williams (eds). *Functional Foods: Concept to Product*. CRC press: Cambridge.

Denburg JA, Hatfield HM, Cyr MM, Hayes L, Holt PG, Sehmi R *et al*. (2005). Fish oil supplementation in pregnancy modifies neonatal progenitors at birth in infants at risk of atopy. *Pediatr Res* **57**, 276–281.

Dickinson E, McClements DJ (1996). *Advances in Food Colloids*. Blackie Academic and Professional: Glasgow.

Diekman C, Malcolm K (2009). Consumer perception and insights on fats and fatty acids: knowledge on the quality of diet fat. *Ann Nutr Metab* **54** (Suppl 1), 25–32.

Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG *et al*. (2003a). Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. *J Allergy Clin Immunol* **112**, 1178–1184.

Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG *et al*. (2003b). Maternal fish oil supplementation in pregnancy reduces interleukin-13 levels in cord blood of infants at high risk of atopy. *Clin Exp Allergy* **33**, 442–448.

EFSA Panel on Dietetic Products, Nutrition and Allergies (2010). Scientific opinion on dietary reference values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, *trans* fatty acids, and cholesterol. EFSA-Q-2008-466. *EFSA J* **8**, 1461.

Elmadfa I, Kornsteiner M (2009). Dietary fat intake—a global perspective. *Ann Nutr Metab* **54** (Suppl 1), 8–14.

Fernandez-Real JM, Broch M, Vendrell J, Ricart W (2003). Insulin resistance, inflammation, and serum fatty acid composition. *Diabetes Care* **26**, 1362–1368.

Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M *et al*. (2005). Global prevalence of dementia: a delphi consensus study. *Lancet* **366**, 2112–2117.

Ferrucci L, Cherubini A, Bandinelli S, Bartali B, Corsi A, Lauretani F *et al*. (2006). Relationship of plasma polyunsaturated fatty acids to circulating inflammatory markers. *J Clin Endocrinol Metab* **91**, 439–446.

Ford ES, Li C, Zhao G, Mokdad AH (2009). Concentrations of low-density lipoprotein cholesterol and total cholesterol among children and adolescents in the United States. *Circulation* **119**, 1108–1115.

Galgani JE, Uauy RD, Aguirre CA, Diaz EO (2008). Effect of the dietary fat quality on insulin sensitivity. *Br J Nutr* **100**, 471–479.

Glaser C, Heinrich J, Koletzko B (2010). Role of FADS1 and FADS2 polymorphisms in polyunsaturated fatty acid metabolism. *Metabolism* **59**, 993–999.

Griffin BA (2008). How relevant is the ratio of dietary n-6 to n-3 polyunsaturated fatty acids to cardiovascular disease risk? Evidence from the OPTILIP study. *Curr Opin Lipidol* **19**, 57–62.

Hansen AE, Wiese HF, Boelsche AN, Haggard ME, Adam DJD, Davis H (1963). Role of linoleic acid in infant nutrition: clinical and chemical study of 428 infants fed on milk mixtures varying in kind and amount of fat. *Pediatrics* **31**, 171–192.

Harbige LS (2003). Fatty acids, the immune response, and autoimmunity: a question of n-6 essentiality and the balance between n-6 and n-3. *Lipids* **38**, 323–341.

Harika RK, Cosgrove MC, Osendarp SJ, Verhoef P, Zock PL: Fatty acid intakes of children and adolescents are not in line with the dietary intake recommendations for future cardiovascular health: a review of dietary intake data from 28 countries. (Submitted for publication).

Harris WS, Mozaffarian D, Lefevre M, Toner CD, Colombo J, Cunnane SC *et al*. (2009a). Towards establishing dietary reference intakes for eicosapentaenoic and docosahexaenoic acids. *J Nutr* **139**, 804S–819S.

Harris WS, Mozaffarian D, Rimm E, Kris-Etherton P, Rudel LL, Appel LJ *et al*. (2009b). Omega-6 fatty acids and risk for cardiovascular disease: a science advisory from the American heart association nutrition subcommittee of the council on nutrition, physical activity, and metabolism; council on cardiovascular nursing; and council on epidemiology and prevention. *Circulation* **119**, 902–907.

Helland IB, Saugstad OD, Smith L, Saarem K, Solvoll K, Ganes T *et al*. (2001). Similar effects on infants of n-3 and n-6 fatty acids supplementation to pregnant and lactating women. *Pediatrics* **108**, art-e82.

Helland IB, Smith L, Blomen B, Saarem K, Saugstad OD, Drevon CA (2008). Effect of supplementing pregnant and lactating mothers with n-3 very-long-chain fatty acids on children's IQ and body mass index at 7 years of age. *Pediatrics* **122**, e472–e479.

Helland IB, Smith L, Saarem K, Saugstad OD, Drevon CA (2003). Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. *Pediatrics* **111**, art-e39.

Hibbeln JR, Davis JM, Steer C, Emmett P, Rogers I, Williams C *et al*. (2007). Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. *Lancet* **369**, 578–585.

Holman RT, Johnson SB, Hatch TF (1982). A case of human linolenic acid deficiency involving neurological abnormalities. *Am J Clin Nutr* **35**, 617–623.

Jakobsen MU, O'Reilly EJ, Heitmann BL, Pereira MA, Balter K, Fraser GE *et al*. (2009). Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. *Am J Clin Nutr* **89**, 1425–1432.

Kim W, Khan NA, McMurray DN, Prior IA, Wang N, Chapkin RS (2010). Regulatory activity of polyunsaturated fatty acids in T-cell signaling. *Prog Lipid Res* **49**, 250–261.

Kirby A, Woodward A, Jackson S, Wang Y, Crawford MA (2010). A double-blind, placebo-controlled study investigating the effects of omega-3 supplementation in children aged 8–10 years from a mainstream school population. *Res Dev Disabil* **31**, 718–730.

Koletzko B, Cetin I, Brenna JT (2007). Dietary fat intakes for pregnant and lactating women. *Br J Nutr* **98**, 873–877.

Koletzko B, Lien E, Agostoni C, Bohles H, Campoy C, Cetin I *et al*. (2008). The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and consensus recommendations. *J Perinat Med* **36**, 5–14.

Krauss-Etschmann S, Hartl D, Rzehak P, Heinrich J, Shadid R, Del CR-T *et al*. (2008). Decreased cord blood IL-4, IL-13, and CCR4 and increased TGF-beta levels after fish oil supplementation of pregnant women. *J Allergy Clin Immunol* **121**, 464–470.

Kremmyda LS, Vlachava M, Noakes PS, Diaper ND, Miles EA, Calder PC (2009). Atopy risk in infants and children in relation to early exposure to fish, oily fish, or long-chain omega-3 fatty acids: a systematic review. *Clin Rev Allergy Immunol* (DOI:10.1007/S21016-009-8186-2).

Lattka E, Illig T, Heinrich J, Koletzko B (2010a). Do FADS genotypes enhance our knowledge about fatty acid related phenotypes? *Clin Nutr* **29**, 277–287.

Lattka E, Illig T, Koletzko B, Heinrich J (2010b). Genetic variants of the FADS1 FADS2 gene cluster as related to essential fatty acid metabolism. *Curr Opin Lipidol* **21**, 64–69.

Li S, Chen W, Srinivasan SR, Berenson GS (2004). Childhood blood pressure as a predictor of arterial stiffness in young adults: the Bogalusa heart study. *Hypertension* **43**, 541–546.

Li S, Chen W, Srinivasan SR, Bond MG, Tang R, Urbina EM *et al*. (2003). Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa heart study. *JAMA* **290**, 2271–2276.

Lim WS, Gammack JK, Van NJ, Dangour AD (2006). Omega 3 fatty acid for the prevention of dementia. *Cochrane Database Syst Rev*, CD 005379.

Lomas J (2007). The in-between world of knowledge brokering. *BMJ* **334**, 129–132.

Lopez-Garcia E, Schulze MB, Manson JE, Meigs JB, Albert CM, Rifai N *et al*. (2004). Consumption of (n-3) fatty acids is related to plasma biomarkers of inflammation and endothelial activation in women. *J Nutr* **134**, 1806–1811.

Lotfi M, Mannar MGV, Merx RJHM, Naber-Van den Heuvel P (1996). *Micronutrient Fortification of Foods. Current Practices, Research, and Opportunities*. The Micronutrient Initiative/International Development Research Centre/International Agricultural Centre: Ottawa.

McGill HC, McMahan CA, Zieske AW, Malcom GT, Tracy RE, Strong JP (2001). Effect of nonlipid risk factors on atherosclerosis in youth with favorable lipoprotein profile. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Circulation* **103**, 1546–1550.

McLennan PL (2001). Myocardial membrane fatty acids and the antiarrhythmic actions of dietary fish oil in animal models. *Lipids* **36** (Suppl), S111–S114.

McNamara RK, Able J, Jandacek R, Rider T, Tso P, Eliassen JC *et al*. (2010). Docosahexaenoic acid supplementation increases prefrontal cortex activation during sustained attention in healthy boys: A placebo-controlled, dose-ranging, functional magnetic resonance imaging study. *Am J Clin Nutr* **91**, 1060–1067.

Mensink RP, Zock PL, Kester AD, Katan MB (2003). Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr* **77**, 1146–1155.

Mente A, de KL, Shannon HS, Anand SS (2009). A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med* **169**, 659–669.

Merchant AT, Curhan GC, Rimm EB, Willett WC, Fawzi WW (2005). Intake of n-6 and n-3 fatty acids and fish and risk of community-acquired pneumonia in US men. *Am J Clin Nutr* **82**, 668–674.

Morrison JA, Friedman LA, Gray-McGuire C (2007). Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the Princeton lipid research clinics follow-up study. *Pediatrics* **120**, 340–345.

Mozaffarian D (2005). Does alpha-linolenic acid intake reduce the risk of coronary heart disease? A review of the evidence. *Altern Ther Health Med* **11**, 24–30.

Mozaffarian D (2007). Fish, n-3 fatty acids, and cardiovascular haemodynamics. *J Cardiovasc Med (Hagerstown)* **8** (Suppl 1), S23–S26.

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.

Mozaffarian D, Rimm EB (2006). Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA* **296**, 1885–1899.

Niinikoski H, Jula A, Viikari J, Ronnemaa T, Heino P, Lagstrom H *et al*. (2009). Blood pressure is lower in children and adolescents with a low-saturated-fat diet since infancy: the special turku coronary risk factor intervention project. *Hypertension* **53**, 918–924.

Niinikoski H, Lagstrom H, Jokinen E, Siltala M, Ronnemaa T, Viikari J *et al*. (2007). Impact of repeated dietary counseling between infancy and 14 years of age on dietary intakes and serum lipids and lipoproteins: the STRIP study. *Circulation* **116**, 1032–1040.

Niinikoski H, Viikari J, Ronnemaa T, Helenius H, Jokinen E, Lapinleimu H *et al*. (1997). Regulation of growth of 7- to 36-month-old children by energy and fat intake in the prospective, randomized STRIP baby trial. *Pediatrics* **100**, 810–816.

Obarzanek E, Kimm SY, Barton BA, Van Horn LL, Kwiterovich Jr PO, Simons-Morton DG *et al*. (2001). Long-term safety and efficacy of a cholesterol-lowering diet in children with elevated low-density lipoprotein cholesterol: seven-year results of the Dietary Intervention Study in Children (DISC). *Pediatrics* **107**, 256–264.

Oh K, Hu FB, Manson JE, Stampfer MJ, Willett WC (2005). Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the nurses' health study. *Am J Epidemiol* **161**, 672–679.

Ohlund I, Hornell A, Lind T, Hernell O (2008). Dietary fat in infancy should be more focused on quality than on quantity. *Eur J Clin Nutr* **62**, 1058–1064.

Osendarp SJ, Baghurst KI, Bryan J, Calvaresi E, Hughes D, Hussaini M *et al*. (2007). Effect of a 12-mo micronutrient intervention on learning and memory in well-nourished and marginally nourished school-aged children: 2 parallel, randomized, placebo-controlled studies in Australia and Indonesia. *Am J Clin Nutr* **86**, 1082–1093.

Oxman AD, Lavis JN, Lewis S, Fretheim A (2009). Support tools for evidence informed policy making. *Health Res Policy Syst* **16**, S1.

Peoples GE, McLennan PL, Howe PR, Groeller H (2008). Fish oil reduces heart rate and oxygen consumption during exercise. *J Cardiovasc Pharmacol* **52**, 540–547.

Raghuveer G (2010). Lifetime cardiovascular risk of childhood obesity. *Am J Clin Nutr* **91**, 1514S–1519S.

Rask-Nissila L, Jokinen E, Terho P, Tammi A, Lapinleimu H, Ronnemaa T *et al*. (2000). Neurological development of 5-year-old children receiving a low-saturated fat, low-cholesterol diet since infancy: a randomized controlled trial. *JAMA* **284**, 993–1000.

Riserus U, Willett WC, Hu FB (2009). Dietary fats and prevention of type 2 diabetes. *Prog Lipid Res* **48**, 44–51.

Salem Jr N, Wegher B, Mena P, Uauy R (1996). Arachidonic and docosahexaenoic acids are biosynthesized from their 18-carbon precursors in human infants. *Proc Natl Acad Sci USA* **93**, 49–54.

Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, Au R *et al*. (2006). Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham heart study. *Arch Neurol* **63**, 1545–1550.

Schubert CM, Sun SS, Burns TL, Morrison JA, Huang TT (2009). Predictive ability of childhood metabolic components for adult metabolic syndrome and type 2 diabetes. *J Pediatr* **155**, S6–S7.

Shaikh SR, Edidin M (2006). Polyunsaturated fatty acids, membrane organization, T cells, and antigen presentation. *Am J Clin Nutr* **84**, 1277–1289.

Sijben JW, Calder PC (2007). Differential immunomodulation with long-chain n-3 PUFA in health and chronic disease. *Proc Nutr Soc* **66**, 237–259.

Simell O, Niinikoski H, Ronnemaa T, Raitakari OT, Lagstrom H, Laurinen M *et al*. (2009). Cohort Profile: the STRIP Study (Special Turku Coronary Risk Factor Intervention Project), an Infancy-onset Dietary and Life-style Intervention Trial. *Int J Epidemiol* **38**, 650–655.

Smit LA, Mozaffarian D, Willett W (2009). Review of fat and fatty acid requirements and criteria for developing dietary guidelines. *Ann Nutr Metab* **55**, 44–55.

Tanaka T, Shen J, Abecasis GR, Kisialiou A, Ordovas JM, Guralnik JM *et al*. (2009). Genome-wide association study of plasma polyunsaturated fatty acids in the InCHIANTI Study. *PLoS Genet* **5**, e1000338.

Thienprasert A, Samuhaseneetoo S, Popplestone K, West AL, Miles EA, Calder PC (2009). Fish oil n-3 polyunsaturated fatty acids selectively affect plasma cytokines and decrease illness in Thai schoolchildren: a randomized, double-blind, placebo-controlled intervention trial. *J Pediatr* **154**, 391–395.

Uauy R, Corvalan C, Dangour AD (2009). Conference on 'Multidisciplinary approaches to nutritional problems'. Rank Prize Lecture Global nutrition challenges for optimal health and well-being. *Proc Nutr Soc* **68**, 34–42.

Uauy R, Dangour AD (2006). Nutrition in brain development and aging: role of essential fatty acids. *Nutr Rev* **64**, S24–S33.

Uauy R, Hoffman DR (1991). Essential fatty acid requirements for normal eye and brain development. *Semin Perinatol* **15**, 449–455.

Valsta LM, Tapanainen H, Sundvall J, Laatikainen T, Mannisto S, Pietinen P *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**, 932–938.

van de Rest O, Geleijnse JM, Kok FJ, van Staveren WA, Dullemeijer C, Olderikkert MG *et al*. (2008). Effect of fish oil on cognitive performance in older subjects: a randomized, controlled trial. *Neurology* **71**, 430–438.

Vartiainen E, Laatikainen T, Peltonen M, Juolevi A, Mannisto S, Sundvall J *et al*. (2010). Thirty-five-year trends in cardiovascular risk factors in Finland. *Int J Epidemiol* **39**, 504–518.

Viikari J, Akerblom HK, Seppanen A, Marniemi J, Sarna S (1988). Atherosclerosis precursors in Finnish children and adolescents—serum lipids, tracking of serum lipids, and preliminary results from cluster analyses of risk factors. *Prog Clin Biol Res* **255**, 81–87.

Wang C, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B *et al*. (2006). n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am J Clin Nutr* **84**, 5–17.

Webber LS, Srinivasan SR, Wattigney WA, Berenson GS (1991). Tracking of serum lipids and lipoproteins from childhood to adulthood. The Bogalusa heart study. *Am J Epidemiol* **133**, 884–899.

Wendland E, Farmer A, Glasziou P, Neil A (2006). Effect of alpha linolenic acid on cardiovascular risk markers: a systematic review. *Heart* **92**, 166–169.

WHO/FAO (2003). *Diet, Nutrition and the Prevention of Chronic Diseases: Report of a Joint WHO/FAO Expert Consultation. WHO Technical Report Series No. 916*. World Health Organization: Geneva.

World Cancer Research Fund/American Institute for Cancer Research (2007). *Food, Nutrition, Physical Activity and the Prevention of Cancer*. AICR: Washington DC.

World Health Organization (2010). *Population-Based Strategies for Childhood Obesity: Report of the WHO Forum and Technical Meeting, Geneva, 15-17 December 2009*. WHO: Geneva.

Yaqoob P, Calder PC (2007). Fatty acids and immune function: new insights into mechanisms. *Br J Nutr* **98** (Suppl 1), S41–S45.

Zatonski W, Campos H, Willett W (2008). Rapid declines in coronary heart disease mortality in Eastern Europe are associated with increased consumption of oils rich in alpha-linolenic acid. *Eur J Epidemiol* **23**, 3–10.

Zhao G, Etherton TD, Martin KR, West SG, Gillies PJ, Kris-Etherton PM (2004). Dietary alpha-linolenic acid reduces inflammatory and lipid cardiovascular risk factors in hypercholesterolemic men and women. *J Nutr* **134**, 2991–2997.