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Dietary Fat Quality for Optimal Health and Well-Being: Overview of Recommendations

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Abstract
A century ago, dietary fat was mainly seen as a source of energy. In 1929, George and Mildred Burr introduced the concept of essential fats: certain fats, i.e. linoleic acid and α-linolenic acid, need to be provided by the diet to prevent deficiencies. Although essential fats were initially considered of marginal nutritional importance for humans, clinical deficiency symptoms were recorded for the first time in the 1960s. Beyond the fact that essential fats can prevent deficiencies, research over the past decades has shown that they also play a major role in preventing chronic conditions such as cardiovascular diseases. This has resulted in an increased interest in the quality of the dietary lipid supply as a major determinant of long-term health and well-being, which is also reflected in recent diet guidelines. This paper will give an overview of key aspects of present recommendations on dietary fats.

Introduction

Fats were traditionally considered part of dietary energy needs until George and Mildred Burr in 1929 introduced the concept that fat might be necessary for the proper growth and development of animals and possibly humans. They proposed that linoleic acid (LA; 18:2 n–6), arachidonic acid (20:4 n–6) and α-LA (ALA; 18:3 n–3) be considered essential fatty acids (EFAs) [1]. These were considered of marginal nutritional importance for humans until the 1960s, when signs of clinical n–6 (omega–6) EFA deficiency were first identified in infants given skimmed milk with added coconut oil, providing limited or absent EFAs, and later recorded in children and adults given fat-free parenteral nutrition [2, 3]. More subtle symptoms appear in n–3 (omega–3) EFA deficiency including skin changes unresponsive to LA supplementation, abnormal visual function and peripheral neuropathy in subjects receiving high n–6, low n–3 fat sources in their intravenous nutrition supply [4].

Over the past decades, the focus of lipid nutrition research has shifted beyond the study of their role as essential nutrients for growth and skin health to encompass the role of specific fatty acids (FAs) on cholesterol, lipoprotein and glucose metabolism [5, 6]. It is now well

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established that the plasma concentration of low-density-lipoprotein (LDL), very-low-density-lipoprotein and high-density-lipoprotein (HDL) cholesterol and triglyceride levels are related to the type and amount of FA intake [7, 8]. More recently, evidence on the effect of FAs on insulin sensitivity and glucose metabolism has emerged [9]. The recognition that n–6 and n–3 EFA are precursors to the formation of prostanoids, thromboxanes, leukotrienes and neuroprotectins, which in turn regulate key physiologic functions (blood pressure, vessel stiffness/relaxation, thrombocyte aggregation, fibrinolytic activity, inflammatory responses and leukocyte migration) has added a further dimension to the potential consequences of FAs for human health. Inflammation, vasoconstriction, vasodilatation, blood pressure, bronchial constriction, uterine contractility and reperfusion oxidative damage have been demonstrated to be affected and potentially regulated by n–3 and n–6 EFA or their endogenous metabolic products [10–12].

Interest in the quality of dietary lipid supply as a major determinant of long-term health and well-being is presently growing. We clearly have to go beyond the traditional saturated and polyunsaturated classification that yielded the polyunsaturated/saturated ratio or vegetable versus animal fat division suggesting that animal fat was bad and vegetable fats were good. The role of specific fats which define fat quality and impact health must presently be considered by examining the effects of individual FAs. The key descriptors for fat quality presently include: saturated FAs (SFAs: lauric, myristic, palmitic and stearic acids); monounsaturated FAs (oleic); polyunsaturated FAs [(PUFAs) of the n–6 (LA and arachidonic acid) and n–3 (ALA, eicosapentaenoic acid, EPA, and docosahexaenoic acid, DHA) series] and trans FAs (TFAs, elaidic and conjugated trans LA). Thus recent national/international dietary fat and FA recommendations consider the need to satisfy EFA needs, promote neurodevelopment and cardiovascular health and prevent degenerative diseases at all stages of the life course. The World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) have provided international recommendations for fats in human health in 1978 and 1994 [13, 14]; additionally, the WHO/FAO expert group that met in 2002 to address nutrition and the prevention of chronic diseases considered fat quality as an important aspect of the preventive strategies (Technical Report Series 916) [15, 16]. The WHO recently produced an update on TFAs in human nutrition [17], and a new report on fat and FAs in human nutrition based on expert consultation conducted late in 2008 is being edited and will be published in the near future. The Barcelona International Expert Meeting used existing national and international recommendations for its deliberations.

Overview of the Present Knowledge and Recommendations

Essential Fatty Acids

Present knowledge establishes a clear need for essential fats; these are the essential PUFAs, LAs and ALAs. These should be considered essential and indispensable since they cannot be synthesized by humans and must be provided by the diet. Since DHA (22:6 n–3) and arachidonic acid (20:4 n–6) can be synthesized from ALA and LA, respectively, they should be considered dispensable, although a dietary supply may be necessary for long-term health [11, 18]. 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 (as provided by human milk) should be considered conditionally essential during early development [19–22]. Similarly, DHA might be considered necessary for life-long health considering intakes required for the prevention of cardiovascular (CVDs) and other chronic diseases [10, 11]. Moreover, considering new knowledge on the role of genetic polymorphisms [(rs174575) FADS2 gene responsible for δ6 desaturase activity] – that might explain the variability in the capacity to form DHA from dietary ALA by humans – it is recommended that preformed long-chain n–3 PUFAs (EPA + DHA) be provided for optimal health at all stages of the life course [23, 24]. Infants and children from conception to birth and throughout the life course need sufficient essential fats of the n–6 and n–3 series in their diet to meet their needs [11, 25]. Breast milk as consumed normally provides adequate amounts of these essential fats and adequate amounts of DHA for normal development. After breast feeding is completed, all children and adults should secure an adequate intake of EFAs not only to meet needs for normal growth and development but also sufficient to promote optimal health and well-being. There is limited and inconclusive evidence of the effect of fish oil (a good source of EPA and DHA) on learning ability and behavior among school-age children; studies are mostly limited to children with neurodevelopmental disorders. Research is needed to determine potential age-specific effects of n–3 PUFAs on depression, aggressiveness, mood swings, attentiveness and learning of school children. The potential impact on learning/behavior in school is of great social,

public health and economic interest [Koletzko et al., pers. commun.].

Fat Intake and Weight Maintenance

Ecological studies, including the recent publication by Marantz et al. [26], show that emphasis on low-fat diets has not resulted in a decreased trend of obesity. The effect of the total fat content of the diet on health is mediated by the quality of fat consumed rather than by the quantity of fat consumed. Consumption of excess energy beyond energy needed for maintenance, growth and physical activity is responsible for excess body fat accumulation independent of whether the energy is derived from fat or carbohydrates. In addition, the fat and water contents of foods are the main determinants of the energy density of the diet. A lower consumption of energy-dense (i.e. high-fat, high-sugars and high-starch) foods and energy-dense (i.e. high free sugars) drinks contributes to a reduction in total energy intake. Conversely, a high intake of energy-dilute foods (i.e. vegetables and fruits) and foods high in non-starch polysaccharide, e.g. wholegrain cereals, contributes to a reduction in total energy intake. It should be noted, that very active groups who have diets high in vegetables, legumes, fruits and wholegrain cereals may sustain a total fat intake of up to 35–40% without the risk of unhealthy weight gain. Despite the role of fat in increasing energy density of diets, the long-term effect of energy density in defining unhealthy weight gain is not well established. Women's Healthy Eating & Living Trial and Women's Health Initiative, two very large and long-term randomized, double-blind, placebo-controlled trials (RCTs) of low fat, both showed minimal effects on weight [27, 28]. Multiple well-controlled RCTs of equal intensity interventions show greater weight loss on high-fat diets [29, 30]. However, recent data [31] suggest that weight loss is attained mainly by achieving a sustained reduction in energy intake independent of the fat, protein or carbohydrate composition of the diet. The recommendations for total fat are usually formulated to include countries where the usual fat intake is typically above 30% as well as those where the usual intake may be very low, for example <15%. Total fat energy of at least 20% is consistent with good health [15, 32]. Highly active groups with diets rich in vegetables, legumes, fruits and wholegrain cereals may, however, sustain a total fat intake of up to 35% without the risk of unhealthy weight gain. For women of reproductive age at least 20% has been recommended by the Joint FAO/WHO Expert Consultation on Fats and Oils in Human Nutrition [13] and confirmed in the WHO Technical Report Series 916 on Diet, Nutrition and the Prevention of Chronic Diseases [15]. The concern for low-fat diets in women from developing countries relates to the high prevalence of young women with low body mass index, especially in the Indian subcontinent, since this condition is associated with low birth weight and a high prevalence of stunted children [32].

Fats, Fatty Acids and Cholesterol, and Risk of Cardiovascular Diseases

The study of the relationship between dietary fats and CVDs, especially coronary heart disease (CHD), with evidence accrued from animal experiments, observational studies, clinical trials and metabolic studies conducted in diverse human populations, reveals strong and consistent associations between diet and CHD [5, 6, 33, 34]. The potential mechanisms have also been well studied focusing mainly on the effect of diet on plasma lipoprotein cholesterol fractions. SFAs raise total and LDL cholesterol, but individual FAs within this group have different effects. Myristic and palmitic acids have the greatest LDL raising effect and are abundant in diets rich in dairy products and meat [7, 8]. Stearic acid has not been reported to elevate blood cholesterol and has been shown to be rapidly converted to oleic acid in vivo, thus it is considered neutral in terms of the plasma cholesterol effect [35, 36]; less is known on other potential adverse effects of stearic acid on the CVD risk [37, 38]. TFAs are similar to SFAs in their effect on LDL, but additionally they lower the protective HDL cholesterol and increase lipoprotein(a), which further increases the CHD risk. TFAs are the geometrical isomers of cis-unsaturated FAs produced in the rumen of ruminant animals or by partial hydrogenation; this process creates TFAs and also removes the critical unsaturated bonds present in EFAs and essential for their action. Metabolic studies have demonstrated that TFAs of natural or as products of partial hydrogenation render the plasma lipid profile even more atherogenic than SFAs, not only by elevating LDL cholesterol to similar levels but also by decreasing HDL cholesterol [7, 39–41]. Several large cohort studies have found that intake of TFAs increases the risk of CHD [42–44]. The most effective replacement for SFAs and TFAs in terms of reducing CHD as an outcome are PUFAs; oils with both LA and ALA predominantly present have been shown to be effective in decreasing LDL cholesterol, CHD events and deaths. This is now supported by the results of several large randomized clinical trials, in which replacement of SFAs and TFAs by vegetable oils rich in essential PUFAs lowered the CHD risk. A recent pooled analysis of 11 large prospective cohort RCTs confirms this statement [45]. TFAs

are presently being reduced or eliminated from retail fats and margarines and spreads in many parts of the world, however deep-fried fast foods and baked goods remain a major source of TFAs [17, 44]. The very-long-chain PUFA of the n–3 series, EPA and DHA, powerfully lower serum triglycerides, but do not modify or may even raise serum LDL cholesterol [45–49]. Most of the epidemiological evidence related to the protective effects of n–3 PUFAs is derived from studies of fish consumption in populations or interventions involving fish oils administered in clinical trials [50–54].

Cholesterol in the blood and tissues is derived from two sources: diet and endogenous synthesis, the former commonly contributes 20–30% to the total body cholesterol pool, thus the regulation of endogenous synthesis plays a key role in the control of plasma levels [55]. Although dietary cholesterol mildly raises plasma cholesterol levels when intake is very high (>400 mg/day), an increase in intake of 100 mg/day would be expected to increase serum cholesterol by approximately 4 mg/dl [56]; epidemiological evidence for an association of dietary cholesterol intake with CVD is contradictory [56–58].

Conclusions

CHD rates can be significantly reduced by dietary changes, which is achieved by replacing saturated fat and trans fats with cis-unsaturated FAs. Advice about dietary fat should focus on the replacement of SFAs and TFAs with PUFA-rich vegetable oils, including sources of n–3 FAs. Replacement of SFAs by carbohydrates provides no benefit in terms of the CHD risk [45]. The food industry should take advantage of the costs and effort of reformulation to make healthier products, avoiding replacing trans and saturated animal fats with vegetable oils rich in palmitic acid (palm oil) and lauric acid (coconut oil). Emphasis should be placed on the need to reduce overall energy intake and increase physical activity rather than recommendations to lower percent energy from fat and reduce fat or 'fatty foods' as a way to lose weight.

The following recommendations on the quality of fat in the diet are made for optimal health across the life course worldwide, from an age of about 2 years onwards:

- fat may provide up to 30–35% of the daily energy intake;
- saturated fat should provide no more than 10% of the daily energy intake;
- essential PUFA (n–6 and n–3) should contribute 6–10% of the daily energy intake;
- trans fats should be less than 1% of the daily energy intake, and
- the remaining of the energy from fat can be provided by monounsaturated fats (based on Technical Report Series 916) [15].

Disclosure Statement

Ricardo Uauy is President of the IUNS, the IUNS has a private public partnership (PPP) agreement with UNILEVER that has as an objective the dissemination of up-to-date scientific information on diet and nutrition, including dietary fat quality. The PPP is in the public domain and is available at www.iuns.org. R.U. has no personal financial gain linked to this PPP or to his participation in this International Expert Meeting.

References

1 Burr GO, Burr MM: 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 1973;31:248–249.
2 Hansen AE, Wiese HF, Boelsche AN, Haggard ME, Adam DJD, Davis H: 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 1963;31:171–192.
3 Paulsrud JR, Pensler L, Whitten CF, Holman RT: Essential fatty acid deficiency in infants induced by fat-free intravenous feeding. Am J Clin Nutr 1972;25:897–904.
4 Holman RT, Johnson SB, Hatch TF: A case of human linolenic acid deficiency involving neurological abnormalities. Am J Clin Nutr 1982;35:617–623.
5 Hegsted DM, McGandy RB, Myers ML, Stare FJ: Quantitative effects of dietary fat on serum cholesterol in man. Am J Clin Nutr 1965;17:281–295.
6 Keys A, Menotti A, Karvonen MJ, Aravanis C, Blackburn H, Buzina R, Djordjevic BS, Dontas AS, Fidanza F, Keys MH, et al: The diet and 15-year death rate in the seven countries study. Am J Epidemiol 1986;124:903–915.
7 Katan MJ, Zock PL, Mensink RP: Dietary oils, serum lipoproteins and coronary heart disease. Am J Clin Nutr 1995;61(suppl 6):1368–1373.
8 Mensink RP, Zock PL, Kester AD, Katan MB: 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 2003;77:1146–1155.
9 Intake of a diet high in trans monounsaturated fatty acids or saturated fatty acids. Effects on postprandial insulinemia and glycemia in obese patients with NIDDM. Diabetes Care 1997;20:881–887.

10 Simopoulos AP: Omega–3 fatty acids in health and disease and in growth and development. Am J Clin Nutr 1991;54:438–463.
11 Uauy R, Mena P, Valenzuela A: Essential fatty acids as determinants of lipid requirements in infants, children and adults. Eur J Clin Nutr 1999;53(suppl 1):S66–S77.
12 Calder PC: n–3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. Am J Clin Nutr 2006;83:1505S–1519S.
13 FAO: Dietary fats and oils in human nutrition. Report of a Joint FAO/WHO Expert Consultation. FAO Food and Nutrition Paper No 3. Rome, FAO, 1978.
14 FAO/WHO: Fats and oils in human nutrition: FAO Food and Nutrition Paper No 57. Rome, FAO, 1994.
15 WHO: Diet, nutrition and the prevention of chronic diseases. Report of a Joint WHO/FAO Expert Consultation. WHO Technical Report Series No 916. Geneva, WHO, 2003.
16 WHO: Global strategy on diet, physical activity and health. Resolution of the World Health Assembly. WHA57.17. Geneva, WHO, 2004.
17 Uauy R, Aro A, Clarke R, Ghafoorunissa, L'Abbe M, Mozaffarian D, Willett WC, Skeaff M, Stender S, Tavella M: WHO scientific update on trans fatty acids: summary and conclusions. Eur J Clin Nutr 2009, in press.
18 Salem N Jr, Wegher B, Mena P, Uauy R: Arachidonic and docosahexaenoic acids are biosynthesized from their 18-carbon precursors in human infants. Proc Natl Acad Sci USA 1996;93:49–54.
19 Neuringer M, Connor WE, Van Petten C, Barstad L: Dietary omega–3 fatty acid deficiency and visual loss in infant rhesus monkeys. J Clin Invest 1984;73:272–276.
20 Uauy RD, Birch DG, Birch EE, Tyson JE, Hoffman DR: Effect of dietary omega–3 fatty acids on retinal function of very-low-birthweight neonates. Pediatr Res 1990;28:485–492.
21 Yuhas R, Pramuk K, Lien EL: Human milk fatty acid composition from nine countries varies most in DHA. Lipids 2006;41:851–858.
22 Eilander A, Hundscheid DC, Osendarp SJ, Transler C, Zock PL: Effects of n-3 long chain polyunsaturated fatty acid supplementation on visual and cognitive development throughout childhood: a review of human studies. Prostaglandins Leukot Essent Fatty Acids 2007;76:189–203.
23 Schaeffer L, Gohlke H, Muller M, Heid IM, Palmer LJ, Kompauer I, Demmelmair H, Illig T, Koletzko B, Heinrich J: Common genetic variants of the FADS1 FADS2 gene cluster and their reconstructed haplotypes are associated with the fatty acid composition in phospholipids. Hum Mol Genet 2006;15:1745–1756.
24 Xie L, Innis SM: Genetic variants of the FADS1 FADS2 gene cluster are associated with altered (n–6) and (n–3) essential fatty acids in plasma and erythrocyte phospholipids in women during pregnancy and in breast milk during lactation. J Nutr 2008;138:2222–2228.
25 Koletzko B, Lien E, Agostoni C, Böhles H, Campoy C, Cetin I, Decsi T, Dudenhausen JW, Dupont C, Forsyth S, Hoesli I, Holzgreve W, Lapillonne A, Putet G, Secher NJ, Symonds M, Szajewska H, Willatts P, Uauy R, World Association of Perinatal Medicine Dietary Guidelines Working Group: The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and consensus recommendations. J Perinat Med 2008;36:5–14
26 Marantz PR, Bird ED, Alderman MH: A call for higher standards of evidence for dietary guidelines. Am J Prev Med 2008;34:234–240.
27 Thomson CA, Rock CL, Giuliano AR, Newton TR, Cui H, Reid PM, Green TL, Alberts DS, Women's Healthy Eating & Living Study Group: Longitudinal changes in body weight and body composition among women previously treated for breast cancer consuming a high-vegetable, fruit and fiber, low-fat diet. Eur J Nutr 2005;44:18–25.
28 Kuller LH, Simkin-Silverman LR, Wing RR, Meilahn EN, Ives DG: Women's Healthy Lifestyle Project: a randomized clinical trial: results at 54 months. Circulation 2001;103:32–37.
29 Gardner CD, Kiazand A, Alhassan S, Kim S, Stafford RS, Balise RR, Kraemer HC, King AC: Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. JAMA 2007;297:969–977.
30 Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, Golan R, Fraser D, Bolotin A, Vardi H, Tangi-Rozental O, Zuk-Ramot R, Sarusi B, Brickner D, Schwartz Z, Sheiner E, Marko R, Katorza E, Thiery J, Fiedler GM, Blüher M, Stumvoll M, Stampfer MJ; Dietary Intervention Randomized Controlled Trial (DIRECT) Group: Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med 2008;359:229–241.
31 Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, McManus K, Champagne CM, Bishop LM, Laranjo N, Leboff MS, Rood JC, de Jonge L, Greenway FL, Loria CM, Obarzanek E, Williamson DA: Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009;360:859–873.
32 Beare-Rogers J, Ghafoorunissa A, Korver O, Rocquelin G, Sundram K, Uauy R: Dietary fat in developing countries. Food Nutr Bull 1998;19:251–266.
33 Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, Willett WC: Dietary fat and risk of coronary heart disease in men: cohort follow-up study in the United States. BMJ 1996;313:84–90.
34 Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, Hennekens CH, Willett WC: Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med 1997;337:1491–1499.
35 Grundy SM, Vega GL: Plasma cholesterol responsiveness to saturated fatty acids. Am J Clin Nutr 1988;47:822–824.
36 Grundy SM: Comparison of monounsaturated fatty acids and carbohydrates for lowering plasma cholesterol. N Engl J Med 1986;314:745–748.
37 Sanders TA, Berry SE, Miller GJ: Influence of triacylglycerol structure on the postprandial response of factor VII to stearic acid-rich fats. Am J Clin Nutr 2003;77:777–782.
38 Sanders TA, Berry SE: Influence of stearic acid on postprandial lipemia and hemostatic function. Lipids 2005;40:1221–1227.
39 Lichtenstein AH, Ausman LM, Jalbert SM, Schaefer EJ: Effects of different forms of dietary hydrogenated fats on serum lipoprotein cholesterol levels. N Engl J Med 1999;340:1933–1940.
40 Mozaffarian D, Rimm EB: Fish intake, contaminants, and human health: evaluating the risks and the benefits. JAMA 2006;296:1885–1899.
41 Chardigny JM, Destaillats F, Malpuech-Brugere C, Moulin J, Bauman DE, Lock AL, Barbano DM, Mensink RP, Bezelgues JB, Chaumont P, Combe N, Cristiani I, Joffre F, German JB, Dionisi F, Boirie Y, Sebedio JL: Do trans fatty acids from industrially produced sources and from natural sources have the same effect on cardiovascular disease risk factors in healthy subjects? Results of the trans Fatty Acids Collaboration (TRANSFACT) study. Am J Clin Nutr 2008;87:558–566.
42 Oh K, Hu FB, Manson JE, Stampfer MJ, Willett WC: Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the nurses' health study. Am J Epidemiol 2005;161:672–679.
43 Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC: Trans fatty acids and cardiovascular disease. N Engl J Med 2006;354:1601–1613.
44 Mozaffarian D, Aro A, Willett W: Health effects of trans fatty acids: experimental and observational evidence. Eur J Clin Nutr, in press.
45 Jakobsen MU, O'Reilly EJ, Heitmann BL, Pereira MA, Bälter K, Fraser GE, Goldbourt U, Hallmans G, Knekt P, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett WC, Ascherio A: Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. Am J Clin Nutr 2009;89:1425–1432.

46 L'Abbe M, Ghafoorunissa R, Tavella M, Stender S, Skeaff M: Assessing approaches to removing trans fats in the food supply in industrialized and developing countries. Eur J Clin Nutr, in press.
47 Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. Lancet 1999;354:447–455.
48 GISSI-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G: Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008; 372:1223–1230.
49 Uauy R, Valenzuela A: Marine oils: the health benefits of n-3 fatty acids. Nutrition 2000;16: 680–684.
50 He K, Liu K, Daviglus ML, Mayer-Davis E, Jenny NS, Jiang R, Ouyang P, Steffen LM, Siscovick D, Wu C, Barr RG, Tsai M, Burke GL: Intakes of long-chain n-3 polyunsaturated fatty acids and fish in relation to measurements of subclinical atherosclerosis. Am J Clin Nutr 2008;88:1111–1118.
51 Hu FB, Bronner L, Willett WC, Stampfer MJ, Rexrode KM, Albert CM, Hunter D, Manson JE: Fish and omega–3 fatty acid intake and risk of coronary heart disease in women. JAMA 2002;287:1815–1821.
52 Albert CM, Hennekens CH, O'Donnell CJ, Ajani UA, Carey VJ, Willett WC, Ruskin JN, Manson JE: Fish consumption and risk of sudden cardiac death. JAMA 1998;279:23–28.
53 Wang C, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B, Jordan HS, Lau J: 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 2006;84:5–17.
54 Mozaffarian D, Rimm EB: Fish intake, contaminants, and human health: evaluating the risks and the benefits. JAMA 2006;296: 1885–1899.
55 Brown MS, Kovanen PT, Goldstein JL: Regulation of plasma cholesterol by lipoprotein receptors. Science 1981;212:628–635.
56 Hegsted DM: Serum-cholesterol response to dietary cholesterol: a re-evaluation. Am J Clin Nutr 1986;44:299–305.
57 Hopkins PN: Effects of dietary cholesterol on serum cholesterol: a meta-analysis and review. Am J Clin Nutr 1992;55:1060–1070.
58 Hu FB, Stampfer MJ, Rimm EB, Manson JE, Ascherio A, Colditz GA, Rosner BA, Spiegelman D, Speizer FE, Sacks FM, Hennekens CH, Willett WC: A prospective study of egg consumption and risk of cardiovascular disease in men and women. JAMA 1999;281: 1387–1394.