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Overview of Evolutionary Aspects of ω3 Fatty Acids in the Diet

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Introduction

The health of the individual and the population in general is the result of interactions between genetics and the environment. This concept was originally articulated by Hippocrates in 480 B.C. as follows:

'Positive health requires a knowledge of man's primary constitution (which today we call genetics) and of the powers of various foods, both those natural to them and those resulting from human skill (today's processed food). But eating alone is not enough for health. There must also be exercise, of which the effects must likewise be known. The combination of these two things makes regimen, when proper attention is given to the season of the year, the changes of the winds, the age of the individual and the situation of his home. If there is any deficiency in food or exercise the body will fall sick'.

Whereas our genetic profile has not changed over the past 40,000 years, major changes have taken place in our food supply and in energy expenditure/physical activity. Our current diet (Western diet) is characterized by an increase in total fat, saturated fat, trans fatty acids and the ω6 essential fatty acids (EFA), but a decrease in the ω3 EFA [1, 2]. The ratio of ω6 to ω3 fatty acids is 10–20/1, whereas during evolution it was 1/1 (table 1; fig. 1) [1–4].

Furthermore, table 2 indicates that vitamin C, calcium and potassium intakes were higher than today's recommended allowances [5]. Wild plants provide higher amounts of both vitamins C and E (fig. 1) [5, 6]. Western societies and other developed countries are characterized by sedentary lifestyles. At the turn of the century, 30% of energy came from muscular work, whereas today it is about 1% [7]. It is evident that today we have an imbalance in ω6 and ω3 EFA and practically a deficiency in ω3 fatty acid intake, as well as a deficiency in energy expenditure/physical activity.

Table 1. Characteristics of hunter-gatherer and Western diet and lifestyles

Characteristic	Diet and lifestyle	
	Hunter-gatherer	Western
Physical Activity Level	high	low
Diet		
Energy-density	low	high
Energy intake	moderate	high
Protein	high	low-moderate
Animal	high	low-moderate
Vegetable	very low	low-moderate
Carbohydrate	low-moderate (slowly absorbed)	moderate (rapidly absorbed)
Fiber	high	low
Fat	low	high
Vegetable	very low	moderate to high
Animal	low	high
	polyunsaturated	saturated
ω6/ω3 ratio	low (2.4)	high (12)
Linolenic and linoleic acids, g fatty acid/person/day	low (3.3)	high (12.3)
Long chain ω6 and ω3 PUFA	high (2.3)	low (0.2)
Vitamins	Paleolithic period	Current US intake
Riboflavin, mg/day	6.49	1.34–2.08
Folate, mg/day	0.357	0.149–0.205
Thiamin, mg/day	3.91	1.08–1.75
Ascorbate, mg/day	604.00	77–109
Carotene, mg/day	5.56	2.05–2.57
(retinol equivalent)	(927.00)	–
Vitamin A, mg/day	17.2	7.02–8.48
(retinol equivalent)	(2,870.00)	(1,170–429)
Vitamin E, mg/day	32.8	7–10

Modified from Simopoulos [4].

The change in the EFA came about because of the indiscriminate recommendation to substitute vegetable oils, i.e. corn oil, safflower, sunflower and cottonseed oil, for saturated fat. These vegetable oils are very high in ω6 fatty acids and very low in ω3 fatty acids. Corn oil has a ratio of ω6/ω3 of 60/1, and safflower oil 77/1. In addition, because animals are grain fed, their carcass

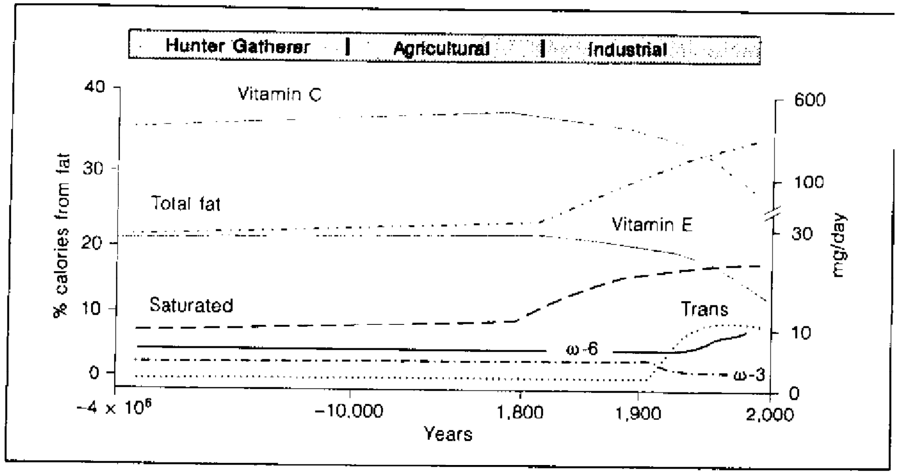

Fig. 1. Hypothetical scheme of fat, fatty acid (ω3, ω6, trans and total) intake (as percent of calories from fat) and intake of vitamins E and C (mg/day). Data were extrapolated from cross-sectional analyses of contemporary hunter-gatherer populations and from longitudinal observations and their putative changes during the preceding 100 years [3].

contains small amounts of ω3 fatty acids but it is high in saturated fats and ω6 fatty acids [8]. Eggs and poultry in agriculture, fish in aquaculture and cultivated plants contain lower amounts of ω3 fatty acids than eggs from chickens that fetch their own food (table 3) [9, 10], fish in the wild [11], and wild plants [1, 5, 12, 13] (table 4). Because of agribusiness and food technology, not only is there an enormous increase in ω6 fatty acids in the food supply, but the hydrogenation process has led to major increases in trans fatty acids. Under natural conditions less than 2% of energy comes from trans fatty acids, whereas today in the US and Canada, 10% of energy comes from trans fatty acids [14]. Trans fatty acids are found in margarines, hydrogenated oils in salad dressings and frying oils, and in ready-made (baking) mixes, crackers, potato chips, pretzels, and other processed foods [15, 16]. The adverse effects of trans fatty acids have been described elsewhere [14].

During evolution, ω3 fatty acids were found in meat, fish and wild plants [2, 6, 8, 11–13, 17]. Recent studies by Cordain et al. [18] on wild animals confirm the original observations of Sinclair et al. [19] (fig. 1).

Over the past 15 years a number of animal experiments, epidemiological investigations and double-blind controlled clinical trials have confirmed the essentiality of ω3 fatty acids, particularly docosahexaenoic acid (DHA) for the normal retina and brain development of the premature infant and the hypotriglyceridemic and inflammatory and antithrombotic aspects of ω3 fatty

Table 2. Late Paleolithic and currently recommended nutrient composition for Americans

	Late Paleolithic	Current recommendations
Total dietary energy, %		
Protein	33	12
Carbohydrate	46	58
Fat	21	30
Alcohol	~0	–
P:S ratio	1.41	1.00
Cholesterol, mg	520	300
Fiber, g	100–150	30–60
Sodium, mg	690	1,100–3,300
Calcium, mg	1,500–2,000	800–1,600
Ascorbic acid, mg	440	60

Modified from Eaton et al. [5].
P:S = Polyunsaturated-to-saturated fat.

acids [20–25]. It therefore became important to investigate the ω3 fatty acid composition of diets that have been shown to be associated with a decreased rate of cardiovascular disease and cancer. Such an opportunity presented itself in the diet of Crete [26].

The population of Crete was one of the populations participating in the Seven Countries Study [27]. The others were the populations of the former Yugoslavia, Italy, Holland (Zutphen), Finland, USA and Japan. The results of the Seven Countries Study are interesting because they showed that the population of Crete had the lowest rate of cardiovascular disease and cancer, followed by the population of Japan. The investigators concluded that the reason must be the high olive oil intake and the low saturated fat intake of the 'Mediterranean diet'. The fact that Crete had a high fat diet, 37% from fat, and Japan had a low fat diet, 11% from fat, was not very much discussed nor were any other fatty acids considered, despite the fact that the people of Crete ate 30 times more fish than the US population. In addition, the people of Crete ate lots of vegetables, fruits, nuts and legumes, all rich sources of folate, calcium, vitamins and minerals.

The traditional Greek diet, including the diet of Crete, includes wild plants. Wild plants are rich sources of ω3 fatty acids and antioxidants [6, 12, 13]. A commonly eaten plant is purslane (table 4). Purslane is rich in α-linolenic

Table 3. Fatty acid levels in chicken egg yolks (mg/g yolk)

Fatty acid	Greek egg	Supermarket egg	Fishmeal egg	Flax egg
Saturates				
14:0	1.1	0.7	1.0	0.6
15:0	–	0.1	0.3	0.2
16:0	77.6	56.7	67.8	58.9
17:0	0.7	0.3	0.8	0.5
18:0	21.3	22.9	23.0	26.7
Total	100.7	80.7	92.9	86.9
Monounsaturates				
16:1ω7	21.7	4.7	5.1	4.4
18:1	120.5	110.0	102.8	94.2
20:1ω9	0.6	0.7	0.9	0.5
24:1ω9	–	–	0.1	–
Total	142.8	115.4	108.9	99.1
ω6 polyunsaturates				
18:2ω6	16.0	26.1	67.8	42.4
18:3ω6	–	0.3	0.3	0.2
20:2ω6	0.2	0.4	0.6	0.4
20:3ω6	0.5	0.5	0.5	0.4
20:4ω6	5.4	5.0	4.4	2.6
22:4ω6	0.7	0.4	0.3	–
22:5ω6	0.3	1.2	0.2	–
Total	23.1	33.9	74.1	46.0
ω3 polyunsaturates				
18:3ω3	6.9	0.5	4.1	21.3
20:3ω3	0.2	–	0.1	0.4
20:5ω3	1.2	–	0.2	0.5
22:5ω3	2.8	0.1	0.4	0.7
22:6ω3	6.6	1.1	6.5	5.1
Total	17.7	1.7	11.3	28.0
P:S ratio	0.4	0.4	0.9	0.9
M:S ratio	1.4	1.4	1.2	1.1
ω6:ω3 ratio	1.3	19.9	6.6	1.3

Modified from Simopoulos and Salem [10].
The eggs were hard-boiled, and their fatty acid composition and lipid content were assessed as described elsewhere. Greek eggs from free-ranging chickens; supermarket eggs = standard US Department of Agriculture eggs found in US supermarkets; fish meal eggs = main source of fatty acids provided by fish meal and whole soybeans; flax eggs = main source of fatty acids provided by flax flour.
P:S = Polyunsaturates:saturates; M:S = monounsaturates:saturates.

Table 4. Fatty acid content of plants (mg/g wet weight)

Fatty acid	Purslane	Spinach	Red leaf lettuce	Buttercrunch lettuce	Mustard
14:0	0.16	0.03	0.03	0.01	0.02
16:0	0.81	0.16	0.10	0.07	0.13
18:0	0.20	0.01	0.01	0.02	0.02
18:1ω9	0.43	0.04	0.01	0.03	0.01
18:2ω6	0.89	0.14	0.12	0.10	0.12
18:3ω3	4.05	0.89	0.31	0.26	0.48
20:5ω3	0.01	0.00	0.00	0.00	0.00
22:6ω3	0.00	0.00	0.002	0.001	0.001
Other	1.95	0.43	0.12	0.11	0.32
Total fatty acid content	8.50	1.70	0.702	0.60	1.101

Adapted from Simopoulos and Salem [9].

acid (LNA; 400 mg/100 g) as well as in vitamin E (12 mg/100 g), vitamin C (27 mg/100 g) and glutathione (15–20 mg/100 g). In one of my trips to Greece, including Crete, I discovered that purslane was eaten fresh in salads, or cooked with poultry, or in soups and omelettes, and during the winter months the dried puslane was also used as a tea for sore throats and earaches. It was highly recommended for pregnant and lactating women and for patients with diabetes.

The purslane study was just the beginning of a series of studies that investigated the ω3 fatty acids in the Greek diet under similar conditions to those prior to 1960. In subsequent studies we examined the composition of eggs from our farm in Ampelistra. In the Greek countryside, chickens wander in the farm, eat grass, purslane, insects, worms, and dried figs, all good sources of ω3 fatty acids. Table 3 shows the composition of the Ampelistra (Greek) egg. It has a ratio of ω6/ω3 fatty acids of 1/3 whereas the US Department of Agriculture egg has a ratio of 19/4.

Similarly, Greek cheeses contain ω3 fatty acids, whereas American cheeses do not (table 5). Noodles made with milk and eggs in Greece also contained ω3 fatty acids. Thus a pattern began to unfold. The diet of Greece, including Crete prior to 1960 contained ω3 fatty acids in every meal – breakfast, lunch, dinner and snacks [26]. Figs stuffed with walnuts are a favorite snack. Both figs and walnuts contain ω3 fatty acids. Contrast this snack with a chocolate chip cookie which contains trans fatty acids and ω6 fatty acids from the

Table 5. Fatty acid content of various cheeses (per 100 g edible portion)

	2% Milk	Cheddar	American	Swiss	Greek myzithra	Greek feta
Total saturated fat, g	1.2	21.00	19.69	16.04	9.30	7.20
12:0, g	>1	0.54	0.48	0.57	–	–
14:0, g	>1	3.33	3.21	2.70	1.90	1.60
16:0, g	>1	9.80	9.10	7.19	5.40	3.90
18:0, g	>1	4.70	3.00	2.60	2.00	1.70
Total monounsaturated fat, g	1	9.99	8.95	7.05	3.90	3.00
Total polyunsaturated						
Fat, g	0.07	0.94	0.99	0.62	0.80	0.58
18:2, g	0.04	0.58	0.61	0.34	0.38	0.29
18:3, g	0.03	0.36	0.38	0.28	0.30	0.20
Arachidonic acid, mg	–	–	–	–	14	10
Eicosapentaenoic acid, mg	–	–	–	–	18	14
Docosapentaenoic acid, mg	–	–	–	–	31	23
Docosahexaenoic acid, mg	–	–	–	–	5.5	5.1
Total fat, g	2.27	31.93	29.63	23.71	14.00	10.78

Milk, cheddar, American and Swiss from US Department of Agriculture Handbook No. 8; Greek myzithra and Greek feta from National Institute on Alcohol Abuse and Alcoholism analyses.

partially hydrogenated oils used in preparation [16]. While these studies were carried out between 1984 to 1986, further analyses of blood specimens from the Seven Countries Study were published in 1993 by Sandker et al. [28] indicating that the serum cholesteryl esters of the population in Crete had three-fold the amount of LNA than the population of Zutphen (table 6). Similar data indicated that the Japanese population also had higher concentrations of ω3 fatty acids than those of Zutphen. Here then was the missing link. It was the higher concentrations of ω3 fatty acids that added protection for cardiovascular disease not only the olive oil, wine, fruits and vegetables of the 'typical Mediterranean diet'.

The two populations with the lowest coronary heart disease in the Seven Countries Study participants had a higher intake of LNA. The Japanese obtained it from canola oil and soybean oil and the population of Crete from purslane, other wild plants, walnuts and figs. Additional studies showed that

Table 6. Mean fatty acid composition of cholesteryl esters in serum of 92 elderly men from Crete and 97 elderly men from Zutphen

Fatty acid	% methylesters		p-value
	Crete	Zutphen	
16:0	11.1 ± 1.0	11.9 ± 1.3	<0.001
16:1	3.2 ± 1.1	2.9 ± 1.6	<0.213
18:0	0.7 ± 0.3	1.1 ± 0.5	<0.001
18:1	31.0 ± 2.7	21.4 ± 3.9	<0.001
18:2ω6	41.9 ± 3.7	53.1 ± 6.5	<0.001
18:3ω3	0.9 ± 0.5	0.3 ± 0.4	<0.001
20:4ω6	6.5 ± 1.6	4.5 ± 1.5	<0.001
Others	4.6 ± 3.3	4.7 ± 3.7	0.891
Ratio 18:2/18:1	1.37 ± 0.20	2.60 ± 0.75	<0.001

Results are expressed as mean % (by weight) methylesters ± SD.
From Sandker et al. [28].

the population of Crete not only had higher serum cholesteryl ester levels of LNA but also lower linoleic acid (18:2ω6; table 6) [28].

Renaud et al. [29] have been working with LNA and have shown that it decreases platelet aggregation. Everything seems now to fall into place in terms of defining the characteristics of the diet of the population of Crete. Their diet was very similar to the paleolithic diet in composition. It was low in saturated fat, balanced in the EFA (ω6 and ω3), very low in trans fatty acids, and high in vitamins E and C. This diet formed the basis of the diet used by Renaud et al. [29–31] in their now famous Lyon study [30]. The Lyon study is a prospective randomized single-blinded secondary prevention trial that compared the effects of a modified Crete diet enriched with LNA to those of a step-I American Heart Association diet. A total of 605 patients were divided into 2 groups, 302 in the experimental group were fed the modified diet of Crete, including 2 g of LNA/day, and 303 in the control group which followed the step-I American Heart Association diet. After a mean follow-up of 27 months, there were 16 cardiac deaths in the control group and 3 in the experimental group; and 17 non-fatal myocardial infarctions in the control and 5 in the experimental group. A risk ratio for these two main end points combined of 0.27 (95% CI 0.12–0.59; $p = 0.001$) after adjustment for prognostic variables. Overall mortality was 20 in the control, 8 in the experimental group, and adjusted risk ratio of 0.30 (95% CI 0.11–0.82; $p = 0.02$).

The study showed a decrease in death rate by 70% in the experimental group and clearly showed that a modified Crete diet enriched with LNA is more efficient than the American Heart Association or similar prudent diets in the secondary prevention of coronary events and death.

Conclusion

Information from archeological findings and studies from modern-day hunter-gatherers suggest that the Paleolithic diet is the diet we evolved on and for which our genetic profile was programmed.

The Paleolithic diet is characterized by lower fat and lower saturated fat intake than Western diets; a balanced intake of ω6 and ω3 EFA; small amounts of trans fatty acids, contributing less than 2% of dietary energy; lots of green leafy vegetables and greens providing higher levels of vitamin E and vitamin C and other antioxidants than today's diet and higher amounts of calcium and potassium but lower in sodium intake.

The characteristics of the traditional Greek diet (the diet prior to 1960) and for that matter, the diet of the people in Crete, consists of high monounsaturated fatty acid intake (olive oil), low saturated fat intake, balanced ω6 and ω3 fatty acids, less than 2% trans fatty acids of total energy intake, and lots of green leafy vegetables and fruits. The Greek-Crete diet is closer to the Paleolithic diet than current Western diets.

The people of Crete participated in the Seven Countries Study and were shown to have the lowest rate of heart disease and cancer, including the highest longevity than the populations of Japan, Yugoslavia, Italy, Holland, Finland, and the US. The people of Crete had the highest amount of 18:3ω3 and the lowest amount of 18:2ω6 in their serum cholesteryl esters than the other six populations. Closer examination of the diet of Crete, or the traditional Greek diet, showed that the ω3 fatty acids were present in every meal the people ate, either as 18:3ω3 or eicosapentaenoic acid and DHA or both. The ω3 fatty acids were present in eggs, milk, cheese, and all products made from milk and eggs, such as noodles and cookies, in wild plants and other green leafy vegetables, and in meat and fish. Because the people of Crete did not use vegetable oils in cooking such as corn oil, safflower, sunflower or cottonseed oils, all rich in ω6 fatty acids, their ω6:ω3 ratio was just over 1, whereas in Western diets this ratio is usually over 10–20:1.

The importance of a balanced ratio of ω6:ω3, a lower saturated fatty acid intake and lower overall fat (30–33%), along with higher intakes of fruits and vegetables leading to increases in vitamin E and C, was tested in the Lyon Heart study. The Lyon study, based on a modified Crete diet, confirmed the importance of ω3 fatty acids from marine and terrestrial sources, and vitamin E and vitamin C, in the secondary prevention of coronary heart disease.

Our current consumption of total fat, saturated fat, ω6 fatty acids and trans fatty acids is not consistent with the evolutionary aspects of diet. Because health as well as disease are the result of the interaction of genes and the environment – in this case, genes and nutrients – our presently constituted food supply is not appropriate for individuals genetically predisposed to chronic diseases such as coronary heart disease, hypertension, diabetes, arthritis, and possibly cancer. The time has come to return the ω3 fatty acids into the food supply. We need both the 18-carbon atom LNA and the 20- to 22-carbon atom eicosapentaenoic acid and DHA.

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References

1 Simopoulos AP: Omega-3 fatty acids in health and disease and in growth and development. Am J Clin Nutr 1991;54:438–463.
2 Eaton SB, Konner M: Paleolithic nutrition. A consideration of its nature and current implications. N Engl J Med 1985;312:283–289.
3 Simopoulos AP: Genetic variation and evolutionary aspects of diet; in Papas A (ed): Antioxidants in Nutrition and Health. In press.
4 Simopoulos AP: Dietary risk factors for hypertension. Compr Ther 1992;18:26–30.
5 Eaton SB, Konner M, Shostak M: Stone agers in the fast lane: Chronic degenerative diseases in evolutionary perspective. Am J Med 1988;84:739–749.
6 Simopoulos AP, Norman HA, Gillaspy JE, Duke JA: Common purslane: A source of omega-3 fatty acids and antioxidants. J Am Coll Nutr 1992;11:374–382.
7 Simopoulos AP: Nutrition and fitness. JAMA 1989;261:2862–2863.
8 Crawford MA: Fatty acid ratios in free-living and domestic animals. Lancet 1968;i:1329–1333.
9 Simopoulos AP, Salem N Jr: n-3 fatty acids in eggs from range-fed Greek chickens (letter). N Engl J Med 1989;321:1412.
10 Simopoulos AP, Salem N Jr: Egg yolk as a source of long-chain polyunsaturated fatty acids in infant feeding. Am J Clin Nutr 1992;55:411–414.
11 van Vliet T, Katan MB: Lower ratio of n-3 to n-6 fatty acids in eggs from range-fed Greek chickens. N Engl J Med 1990;51:1–2.
12 Simopoulos AP, Salem N Jr: Purslane: A terrestrial source of omega-3 fatty acids. N Engl J Med 1986;315:833.
13 Simopoulos AP, Norman HA, Gillaspy JE: Purslane in human nutrition and its potential for world agriculture; in Simopoulos AP (ed): Plants in Human Nutrition. World Rev Nutr Diet. Basel, Karger, 1995, vol 77, pp 47–74.
14 Simopoulos AP: Trans fatty acids; in Spiller GA (ed): Handbook of Lipids in Human Nutrition. Boca Raton, CRC Press, 1995.
15 Dupont J, White PJ, Feldman EB: Saturated and hydrogenated fats in food in relation to health. J Am Coll Nutr 1991;10:577–592.
16 Litin L, Sacks F: Trans-fatty-acid content of common foods. N Engl J Med 1993;329:1969–1970.
17 Guil JL, Torija ME, Gimenez JJ, Rodriguez I: Identification of fatty acids in edible wild plants by gas chromatography. J Chromatogr A 1996;719:229–235.
18 Cordain L, Martin C, Florant G, Watkins BA: The fatty acid composition of muscle, brain, marrow and adipose tissue in elk: Evolutionary implications for human dietary lipid requirements; in Simopoulos A (ed): The return of ω3 fatty acids into the food supply. I. Land-based animal food products and their health effects. World Rev Nutr Diet. Basel, Karger, 1998, vol. 83, p 225.
19 Sinclair AJ, Slattery WJ, O'Dea K: The analysis of polyunsaturated fatty acids in meat by capillary gas-liquid chromatography. J Food Sci Agric 1982;33:771–776.
20 Simopoulos AP, Kifer RE, Martin RR (eds): Health Effects of Polyunsaturated Fatty Acids in Seafoods. Proceedings from the Conference, June 1985. Orlando, Academic Press, 1986.
21 Galli C, Simopoulos AP (eds): Dietary ω3 and ω6 Fatty Acids: Biological Effects and Nutritional Essentiality. New York, Plenum Press, 1989.
22 Simopoulos AP, Kifer RR, Martin RE, Barlow SM (eds): Health Effects of ω3 Polyunsaturated Fatty Acids in Seafoods. World Rev Nutr Diet. Basel, Karger, 1991, vol 66.
23 Galli C, Simopoulos AP, Tremoli E (eds): Effects of Fatty Acids and Lipids in Health and Disease. World Rev Nutr Diet. Basel, Karger, 1994, vol 76.
24 Galli C, Simopoulos AP, Tremoli E (eds): Fatty Acids and Lipids: Biological Aspects. World Rev Nutr Diet. Basel, Karger, 1994, vol 75.
25 Salem N Jr, Simopoulos AP, Galli C, Lagarde M, Knapp H (eds): Proc 2nd Congr ISSFAL on Fatty Acids and Lipids from Cell Biology to Human Disease. Lipids 1996;31(suppl):1–326.
26 Simopoulos AP, Robinson J: The Omega Plan. The Medically Proven Diet that Gives You the Essential Nutrients You Need. New York, Macmillan, 1998.
27 Keys A: Coronary heart disease in seven countries. Circulation 1970;41(suppl):1–211.
28 Sandker GW, Kromhout D, Aravanis C, Bloemberg BPM, Mensink RP, Karalias N, Katan MB: Serum cholesteryl ester fatty acids and their relation with serum lipids in elderly men in Crete and The Netherlands. Eur J Clin Nutr 1993;47:201–208.
29 Renaud S, Godsey F, Dumont E, Thevenon C, Ortchanian E, Martin JL: Influence of long-term diet modification on platelet function and composition in Moselle farmers. A J Clin Nutr 1986;43:136–150.
30 De Lorgeril M, Renaud S, Mamelle N, Salen P, Martin JL, Monjaud I, Guidellet J, Touboul P, Delaye J: Mediterranean alpha-linolenic acid-rich diet in the secondary prevention of coronary heart disease. Lancet 1994;343:1454–1459.
31 Renaud S, de Lorgeril M, Delaye J, Guidollet J, Jacquard F, Mamelle N, Martin JL, Manjaud I, Salen P, Touboul P: Cretan Mediterranean diet for prevention of coronary heart disease. Am J Clin Nutr 1995;61(suppl):1360–1367.

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