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Dietary Polyunsaturated Fatty Acids and Mortality in the Multiple Risk Factor Intervention Trial (MRFIT)

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Introduction

Dietary polyunsaturated fatty acids (PUFA) have been shown to have effects on biochemical and physiological mechanisms which relate to numerous disease occurrences. Perhaps of greatest concern in PUFA biochemistry is the regulation of eicosanoids, which act in diverse ways to influence biological processes, both positively and adversely. The quality, quantity, and balance of these fatty acids appear to play a significant role in determining their actions [1]. Unfortunately, experimental evidence currently available is not sufficient to even suggest optimal dietary PUFA intake levels. Understanding these relationships as they apply to humans could have profound implications for dietary recommendations aimed at achievement of health promotion and disease prevention.

Given that disease patterns as well as dietary practices differ considerably among populations, the examination of dietary PUFA intakes of large populations would be valuable. Findings from such evaluations in combination with results of experimental studies might help to clarify some of the inconsistencies that currently exist in the literature and provide direction for further research in this very important area.

Among the few large population studies that have estimated dietary intake of specific fatty acids is the Multiple Risk Factor Intervention Trial (MRFIT). This report describes dietary PUFA intakes by middle-aged

American men who participated in this trial from 1973 through early 1982. Estimates of PUFA intakes are available using nutrient data from 24-hour dietary recall interviews obtained during the study. Associations between PUFA intakes and mortality are examined.

Methods

Background, Organization, and Design

A detailed description of the MRFIT is provided elsewhere [2]. Briefly, MRFIT was a multi-center, clinical trial in the primary prevention of coronary heart disease (CHD) supported by the National Heart, Lung, and Blood Institute. The study population included men aged 35–57 years at entry who were determined to be at high risk of developing CHD based upon smoking status, diastolic blood pressure, and serum cholesterol levels. The trial was conducted at 22 clinical centers where the men were followed for 6–8 years. From 361,662 screenees, 12,866 men were selected to be participants during three screening visits. Approximately half were randomized to each of two study groups. The special intervention (SI) group received interventions to reduce smoking, blood pressure, and blood cholesterol, while the usual care (UC) group participants were referred to their usual source of medical care and returned annually for examination at their respective clinical centers.

Principal Dietary Data Collection Method

The principal dietary method chosen for the MRFIT was the 24-hour dietary recall, since it is appropriate for measuring the dietary intake of groups [3]. Highly standardized dietary recall interviews were conducted at the baseline third screen visit for all participants and at follow-up years 1, 2, 3, 5, and 6 for the SI men and at years 1, 2, 3, and 6 for participants in the UC group. Data generated from 24-hour recall interviews have been used to describe the MRFIT population at baseline and to monitor the dietary patterns and food selection trends by both SI and UC groups over the follow-up period [4, 5].

While the 24-hour recall is generally not intended to characterize usual intake by individuals considered desirable when studying diet-disease relationships, multiple recalls on the same individual improve accuracy in terms of establishing more reliable usual intake estimates. On this premise, data from recalls obtained at baseline and at follow-up years were used for this evaluation.

Mortality Ascertainment

Mortality was ascertained from the beginning of the trial and continues to be monitored by the MRFIT coordinating center in Minneapolis, Minnesota. Clinics assumed responsibility for follow-up while the trial was in progress until February 28, 1982 at which time the National Death Index became the primary mortality follow-up method. The data presented include deaths ascertained through December 31, 1985. Cause-specific mortality assignments are based on the 9th revision of the International Classification of Diseases. All death certificates and supporting records have been independently coded by two nosologists without knowledge of treatment group and where differences exist adjudication is achieved by a third.

Statistical Analysis

Only data on the UC group were analyzed for this evaluation to avoid the analytical complexities introduced by the multi-intervention effects on the SI group. MRFIT recalls were reanalyzed in 1985 using the University of Minnesota Nutrition Coordinating Center Food Table version number 11 which contains very complete information on individual fatty acids thereby making possible an evaluation of PUFA intake [6]. Mean values available from recall data analysis at baseline and at the first three follow-up years were calculated for each PUFA estimate under study. PUFA intake estimates in grams were established for total PUFA, 18:2 ω6, 18:3 ω3, 18:4 ω6, 20:4 ω6, 20:5 ω3, 22:5 ω3, 22:6 ω3. The sum of 20:5 ω3, 22:5 ω3, and 22:6 ω3 as well as ratios, 18:3 ω3/18:2 ω6 and total ω3/total ω6, were also calculated for analytic purposes.

Participants were divided into quintiles based on their average intake of each PUFA estimate. Relative risks of mortality were calculated relative to the first quintile using proportional hazards regression analysis. Adjusted relative risks were also determined by including age, race and baseline values of diastolic blood pressure, cigarettes smoked per day, high density lipoprotein-cholesterol, and low density lipoprotein-cholesterol in the model. Each PUFA estimate was also entered into the model as a continuous variable using log transformations as appropriate with the regression coefficient and significance level given. Deaths and documented clinical myocardial infarctions during the first 3 years of follow-up were excluded from the analysis. The mortality categories selected for evaluation are broad, since overall death rates were low. Four groups were established including CHD, all cardiovascular diseases (CVD), all causes, and all cancers.

Results

Dietary Polyunsaturated Fatty Acid Distribution

Table 1 shows the distribution of mean dietary PUFA intake among the MRFIT UC participants based on the average of four 24-hour dietary recall measures. The predominant PUFA was linoleic acid (18:2 ω6) contributing approximaely 87% of the mean total PUFA intake. Linolenic acid (18:3 ω3) contributed about 10%. Stearodonic acid (18:4 ω6) appeared in very low concentrations with 65% of participants reporting no intake of the fatty acid. Mean arachidonic acid (20:4 ω6), the precursor of eisosanoids, was reported to be consumed in relatively low amounts in relation to total PUFA intake. The long-chain ω3 fatty acids found in fish oils – eicosapentaenoic acid (20:5), docosapentaenoic acid (22:5), and docosahexaenoic acid (22:6) – were reported to be consumed in very small quantities with the mean sum equaling about 175 mg/day. It should be noted that the reported intake of these fish fatty acids demonstrated considerable variability and that about 20% of the group reported zero intake. The mean intake ratios of 18:3 ω3/18:2 ω6 and total ω3/total ω6 were approximately 0.12 and 0.13, respectively.

Table 1. Reported dietary polyunsaturated fatty acid (PUFA) intake[1] distributions in grams for usual care participants in the Multiple Risk Factor Intervention Trial (MRFIT)

	Mean	Standard deviation	Quartile 1	Median	Quartile 3	% >0
Total PUFA	16.828	7.663	11.740	15.470	20.420	100
18:2 ω6	14.603	6.957	9.990	13.352	17.868	100
18:3 ω3	1.688	0.736	1.189	1.572	2.028	100
18:4 ω6	0.008	0.027	0.000	0.000	0.005	35
20:4 ω6	0.222	0.107	0.151	0.205	0.272	100
20:5 ω3	0.069	0.155	0.000	0.011	0.070	71
22:5 ω3	0.024	0.057	0.000	0.008	0.021	74
22:6 ω3	0.082	0.193	0.000	0.013	0.089	59
20:5+22:5+22:6	0.175	0.184	0.004	0.043	0.187	79
18:3/18:2	0.122	0.034	0.101	0.119	0.139	100
(18:3+20:5+22:5+22:6)/ (18:2+20:4)	0.133	0.051	0.107	0.127	0.149	100

[1] Mean of baseline, follow-up years 1, 2, and 3 dietary recall nutrient data.

Mortality Findings

Tables 2–6 show the death rates by quintile and the results of proportional hazards regression analyses of selected PUFAs, combined PUFAs, and PUFA ratios on mortality outcome groups including CHD, CVD, all cause, and cancer. Tables 2–4 show findings from analyses of independent variables 18:2 ω6, 18:3 ω3 and sum of 20:5 ω3, 22:5 ω3, and 22:6 ω3 expressed in grams. Tables 5 and 6 display results from analyses for 18:3 ω3/18:2 ω6 and total ω3/total ω6 on the four mortality outcomes.

No significant associations were detected for linoleic acid (18:2 ω6) on any mortality group as shown in table 2. Table 3 presents results using 18:3 ω3 as the independent variable in the analysis. The same negative pattern of adjusted relative risks by quintile of intake was apparent for 18:3 ω3 on CHD, CVD, and all cause mortality. However, the inverse relationship was only significant for all cause mortality and marginally significant for CVD. A weaker association was observed for cancer deaths and was not significant. Analysis of the combined fatty acids predominantly found in fish shown in table 4 demonstrated significant inverse associations with CHD, CVD, and all cause mortality groups but not for cancers. The benefit appeared to be in the largest intake quintile with a mean ingestion of about 664 mg/day.

Table 2. Estimated relative risk for dietary 18:2 ω6 intake and mortality in MRFIT usual care participants from proportional hazards regression analyses[1]

Quintile	Mean, g	n	Deaths	Dead, %		RR	ADJ. RR
CHD mortality							
I	7.037	1,251	44	3.52		1.00	1.00
II	10.646	1,252	31	2.48		0.70	0.74
III	13.387	1,252	27	2.16		0.60	0.65
IV	16.839	1,252	46	3.67		1.04	1.09
V	25.065	1,251	27	2.16		0.61	0.65
					Slope	−0.0150	−0.0128
					Z slope	−1.2610	−1.0909
					p value	0.2077	0.2746
CVD mortality							
I	7.037	1,251	60	4.80		1.00	1.00
II	10.646	1,252	37	2.96		0.61	0.65
III	13.387	1,252	40	3.19		0.65	0.71
IV	16.839	1,252	60	4.79		1.00	1.06
V	25.065	1,251	35	2.80		0.58	0.63
					Slope	−0.0121	−0.0089
					Z slope	−1.1874	−0.8888
					p value	0.2347	0.3737
All cause mortality							
I	7.037	1,251	104	8.31		1.00	1.00
II	10.646	1,252	79	6.31		0.75	0.80
III	13.387	1,252	78	6.23		0.73	0.79
IV	16.839	1,252	105	8.39		1.01	1.10
V	25.065	1,251	73	5.84		0.69	0.77
					Slope	−0.0135	−0.0095
					Z slope	−1.8166	−1.2923
					p value	0.0694	0.1957
Cancer mortality							
I	7.037	1.251	18	1.44		1.00	1.00
II	10.646	1,252	34	2.72		1.87	1.98
III	13.387	1,252	25	2.00		1.36	1.44
IV	16.839	1,252	28	2.24		1.55	1.70
V	25.065	1,251	27	2.16		1.48	1.65
					Slope	−0.0001	0.0033
					Z slope	0.0000	0.2646
					p value	0.9953	0.7876

[1] Mean of baseline, follow-up years 1, 2, and 3 dietary recall nutrient data. Deaths and clinical myocardial infarctions in first 3 years excluded. Adjusted for age, race, and baseline smoking, diastolic blood pressure, high density and low density lipoprotein levels.

Table 3. Estimated relative risk for dietary 18:3 ω3 intake and mortality in MRFIT usual care participants from proportional hazards regression analysis[1]

Quintile	Mean, g	n	Deaths	Dead, %		RR	ADJ. RR
CHD mortality							
I	0.873	1.251	43	3.44		1.00	1.00
II	1.273	1.253	40	3.19		0.93	0.98
III	1.577	1.251	24	1.92		0.55	0.57
IV	1.926	1.251	40	3.20		0.92	0.98
V	2.802	1.252	28	2.24		0.64	0.68
					Slope	−0.1897	−0.1657
					Z slope	−1.6703	−1.4560
					p value	0.0951	0.1458
CVD mortality							
I	0.873	1,251	58	4.64		1.00	1.00
II	1.273	1,253	52	4.15		0.89	0.94
III	1.577	1,251	38	3.04		0.64	0.67
IV	1.926	1,251	49	3.92		0.83	0.90
V	2.802	1,252	35	2.80		0.60	0.63
					Slope	−0.2130	−0.1832
					Z slope	−2.1331	−1.8330
					p value	0.0329	0.0667
All cause mortality							
I	0.873	1,251	105	8.39		1.00	1.00
II	1.273	1,253	99	7.90		0.94	0.96
III	1.577	1,251	73	5.84		0.68	0.69
IV	1.926	1,251	91	7.27		0.86	0.89
V	2.802	1,252	71	5.67		0.67	0.69
					Slope	−0.1982	−0.1784
					Z slope	−2.7514	−2.4556
					p value	0.0059	0.0141
Cancer mortality							
I	0.873	1,251	25	2.00		1.00	1.00
II	1.273	1,253	34	2.71		1.36	1.35
III	1.577	1,251	22	1.76		0.86	0.85
IV	1.926	1,251	29	2.32		1.15	1.14
V	2.802	1,252	22	1.76		0.87	0.87
					Slope	−0.1003	−0.0985
					Z slope	−0.8000	−0.7746
					p value	0.4235	0.4392

[1] Mean of baseline, follow-up years 1, 2, and 3 dietary recall nutrient data. Deaths and clinical myocardial infarctions in first 3 years excluded. Adjusted for age, race, and baseline smoking, diastolic blood pressure, high density and low density lipoprotein levels.

Table 4. Estimated relative risk for sum of dietary 20:5, 22:5, and 22:6 ω3 and mortality in MRFIT usual care participants from proportional hazards regression anaylses[1]

Quintile	Mean, g	n	Deaths	Dead, %		RR	ADJ. RR
CHD mortality							
I	0.000	1,307	42	3.21		1.00	1.00
II	0.009	1,197	39	3.26		1.01	1.08
III	0.046	1,251	35	2.80		0.87	0.91
IV	0.153	1,252	35	2.80		0.87	0.88
V	0.664	1,251	24	1.92		0.59	0.60
					Slope	−0.2803	−0.2877
					Z slope	−2.3707	−2.4310
					p value	0.0178	0.0150
CVD mortality							
I	0.000	1,307	55	4.21		1.00	1.00
II	0.009	1,197	51	4.26		1.01	1.06
III	0.046	1,251	47	3.76		0.90	0.92
IV	0.153	1,252	48	3.83		0.91	0.92
V	0.664	1,251	31	2.48		0.58	0.59
					Slope	−0.2857	−0.2936
					Z slope	−2.7749	−2.8460
					p value	0.0055	0.0044
All cause mortality							
I	0.000	1,307	99	7.57		1.00	1.00
II1	0.009	1,197	96	8.02		1.06	1.09
III	0.046	1,251	93	7.43		0.98	1.02
IV	1.153	1,252	80	6.39		0.84	0.85
V	0.664	1,251	71	5.68		0.74	0.76
					Slope	−0.1799	−0.1826
					Z slope	−2.5338	−2.5671
					p value	0.0113	0.0102
Cancer mortality							
I	0.000	1,307	28	2.14		1.00	1.00
II	0.009	1,197	31	2.59		1.21	1.24
III	0.046	1,251	29	2.32		1.09	1.16
IV	0.153	1,252	19	1.52		0.71	0.73
V	0.664	1,251	25	2.00		0.92	0.97
					Slope	−0.1090	0.0985
					Z slope	−0.8718	0.7874
					p value	0.3836	0.4309

[1] Mean of baseline, follow-up years 1, 2, and 3 dietary recall nutrient data (log +0.1). Deaths and clinical myocardial infarctions in first 3 years excluded. Adjusted for age, race, and baseline smoking, diastolic blood pressure, high density and low density lipoprotein levels.

Table 5. Estimated relative risk for dietary 18:3 ω3/18:2 ω6 intake and mortality in MRFIT usual care participants from proportional hazards regression analyses[1]

Quintile	Mean ratio	n	Deaths	Dead, %		RR	ADJ. RR
CHD mortality							
I	0.080	1,251	41	3.28		1.00	1.00
II	0.105	1,252	29	2.32		0.70	0.70
III	0.120	1,252	32	2.56		0.77	0.81
IV	0.135	1,252	33	2.64		0.79	0.81
V	0.170	1,251	40	3.20		0.97	0.95
					Slope	0.2854	0.1846
					Z slope	0.1414	0.1000
					p value	0.8983	0.9331
CVD mortality							
I	0.080	1,251	56	4.48		1.00	1.00
II	0.105	1,252	40	3.19		0.70	0.70
III	0.120	1,252	42	3.35		0.74	0.77
IV	0.135	1,252	44	3.51		0.77	0.78
V	0.170	1,251	50	4.00		0.89	0.85
					Slope	−0.1776	−0.4419
					Z slope	−0.1000	−0.2236
					p value	0.9278	0.8200
All cause mortality							
I	0.080	1,251	101	8.07		1.00	1.00
II	0.105	1,252	79	6.31		0.77	0.76
III	0.120	1,252	86	6.87		0.84	0.83
IV	0.135	1,252	82	6.55		0.80	0.78
V	0.170	1,251	91	7.27		0.89	0.82
					Slope	−0.2824	−1.0739
					Z slope	−0.2000	−0.7483
					p value	0.8432	0.4539
Cancer mortality							
I	0.080	1,251	31	2.48		1.00	1.00
II	0.105	1,252	26	2.08		0.83	0.81
III	0.120	1,252	27	2.16		0.86	0.81
IV	0.135	1,252	24	1.92		0.76	0.71
V	0.170	1,251	24	1.92		0.77	0.67
					Slope	−4.0296	−5.5186
					Z slope	−1.4595	−1.9824
					p value	0.1442	0.0475

[1] Mean of baseline, follow-up years 1, 2, and 3 dietary recall nutrient data. Deaths and clinical myocardial infarctions in first 3 years excluded. Adjusted for age, race, and baseline smoking, diastolic blood pressure, high density and low density lipoprotein levels.

Table 6. Estimated relative risk for dietary total ω3/ω6 and mortality in MRFIT usual care participants from proportional hazards regression analysis[1]

Quintile	Mean ratio	n	Deaths	Dead, %		RR	ADJ. RR
CHD mortality							
I	0.086	1,251	41	3.28		1.00	1.00
II	0.111	1,252	31	2.48		0.76	0.76
III	0.127	1,252	34	2.72		0.83	0.87
IV	0.145	1,252	31	2.48		0.75	0.76
V	0.199	1,251	38	3.04		0.92	0.89
					Slope	−0.5508	−0.5659
					Z slope	−1.2083	−1.2490
					p value	0.2262	0.2114
CVD mortality							
I	0.086	1,251	55	4.40		1.00	1.00
II	0.111	1,252	45	3.59		0.82	0.82
III	0.127	1,252	43	3.43		0.78	0.81
IV	0.145	1,252	40	3.19		0.72	0.73
V	0.199	1,251	49	3.92		0.89	0.84
					Slope	−0.6571	−0.7062
					Z slope	−1.6492	−1.7776
					p value	0.0091	0.0754
All cause mortality							
I	0.086	1,251	97	7.75		1.00	1.00
II	0.111	1,252	92	7.35		0.95	0.93
III	0.127	1,252	88	7.03		0.90	0.90
IV	0.145	1,252	72	5.75		0.74	0.72
V	0.199	1,251	90	7.19		0.92	0.85
					Slope	−0.3814	−0.5205
					Z slope	−1.3454	−1.8193
					p value	0.1783	0.0690
Cancer mortality							
I	0.086	1,251	31	2.48		1.00	1.00
II	0.111	1,252	33	2.64		1.06	1.02
III	0.127	1,252	26	2.08		0.84	0.80
IV	0.145	1,252	20	1.60		0.64	0.61
V	0.199	1,251	22	1.76		0.70	0.62
					Slope	−0.9513	−1.1848
					Z slope	−1.7664	−2.1726
					p value	0.0771	0.0299

[1] Mean of baseline, follow-up years 1, 2, and 3 dietary recall nutrient data (log +0.1). Deaths and clinical myocardial infarctions in first 3 years excluded. Adjusted for age, race, and baseline smoking, diastolic blood pressure, high density and low density lipoprotein levels.

When compared with zero intake, mortality from CHD, CVD, and all cause mortality was 40, 41 and 24% lower, respectively.

Findings from 18:3 ω3/18:2 ω6 ratios showed no association with CHD, CVD, or all cause mortality but an inverse relationship was observed between the ratio and cancer mortality. 33% less cancer deaths occurred in the highest intake quintile when compared with the lowest. The pattern of relative risk across quintiles generally showed a smooth trend and gradual decline in cancer mortality as the 18:3 ω3/18:2 ω6 ratio increased. An inverse relationship with cancer mortality was also demonstrated when total ω3/total ω6 ratio was the independent variable in the analysis (table 6). A reduction of 38% cancer deaths was apparent when the highest intake quintile was compared with the lowest. Marginally significant inverse associations were observed between the total ω3/total ω6 ratio and mortality from CVD and all cause mortality groups but not for CHD.

Discussion

The mean total PUFA intake of 16.83 g reported by the MRFIT UC group represents approximately 6.5% of the average total kilocalories consumed [5]. This intake is consistent with a reported 6.72% by men in the Lipids Research Clinics Prevalence study conducted from 1972 to 1976 [7]. The MRFIT UC PUFA intake was slightly greater than that reported by men inteviewed during NHANES I (3.92%) from 1971 to 1974 and during NHANES II (4.96%) from 1976 to 1980 [unpublished data].

Information from the Surgeon General's Report estimated an average PUFA intake of 8% total kilocalories for the US population during the late 1980s [8]. It would appear that consumption of PUFA in the US population has increased slightly since the 1970s. Since few reports express PUFA in terms of fatty acids, it is not possible to compare trends in specific PUFA intake among these studies.

Data on Japanese dietary PUFA intake during 1975 show very interesting differences when compared with the MRFIT data [personal communication with Dr. Harumi Okuyama]. The Japanese consumed less total fat but about the same amount of total PUFA as that reported by the MRFIT men. The composition of PUFA, however, was strikingly different. The Japanese consume considerably more fish oil fatty acids (20:5 ω3, 22:5 ω3, 22:6 ω3). While the Japanese intake was approximately 1.5 g/day, MRFIT

UC participants consumed an average of 0.18 g/day. The intake of linoleic acid (18:2 ω6) was about the same for the Japanese comparison with the MRFIT reported intake. Linolenic acid (18:3 ω3) intake was slightly greater for Japanese than MRFIT participants. Overall, the Japanese had a greater ω3 to ω6 fatty acid intake ratio, 0.26 compared with 0.13 in the MRFIT group. Given that the disease patterns between Japan and the US differ considerably, it would seem that dietary PUFA composition may play a role in establishing and changing those patterns over time [9].

The findings of this evaluation which show a protective effect of the long-chain fish fatty acids on CHD, CVD, and all cause mortality are consistent with other reports in the literature [10]. It is known that populations consuming large amounts of marine and seafoods such as the fishing villagers of Japan, Greenland Eskimos and Alaskan natives have remarkably low rates of acute myocardial infarction [11–13]. Moreover, several epidemiologic studies of Western industrialized populations have also reported inverse associations between fish consumption and death especially from coronary heart disease [14, 15].

The inverse associations between ω3/ω6 ratios and cancer mortality are intriguing. Although some evidence exists that ω3 fatty acids have antioncogenic properties, there is a need to evaluate other databases to determine if these results can be duplicated. Interpretation is further complicated by the fact that cancer mortality includes deaths from approximately 30 different forms of cancer, each having its own etiologic factors and pathologic uniqueness. Likewise, interpretation of the negative association between dietary 18:3 ω3 intake and all cause mortality is difficult. Whether the critical factors involved in these complex processes will reveal a benefit from qualitative and/or quantitative changes in the PUFA composition of diets remains to be seen.

Conclusions

The results of this evaluation support the hypothesis that fatty acids found primarily in fish oils protect against cardiovascular disease. They also suggest that the composition and balance of PUFA in the diet may influence mortality from cardiovascular disease and possibly various forms of cancer. Further research is needed to define the optimal level and balance of polyunsaturated fatty acids in the diets of humans to promote health and prevent disease.

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