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Fish Consumption Among Healthy Adults Is Associated With Decreased Levels of Inflammatory Markers Related to Cardiovascular Disease

The ATTICA Study

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OBJECTIVES The aim of this work was to investigate the association between fish consumption and levels of various inflammatory markers among adults without any evidence of cardiovascular disease.

BACKGROUND Fish consumption has been associated with reduced risk of coronary heart disease, but the mechanisms have not been well understood or appreciated.

METHODS The ATTICA study is a cross-sectional survey that enrolled 1,514 men (age 18 to 87 years) and 1,528 women (age 18 to 89 years) from the Attica region, Greece. Of them, 5% of men and 3% of women were excluded due to a history of cardiovascular disease. Among others, C-reactive protein (CRP), interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, serum amyloid A (SAA), and white blood cells (WBC) were measured, and dietary habits (including fish consumption) were evaluated using a validated food frequency questionnaire.

RESULTS A total of 88% of men and 91% of women reported fish consumption at least once a month. Compared to non-fish consumers, those who consumed >300 g of fish per week had on average 33% lower CRP, 33% lower IL-6, 21% lower TNF-alpha, 28% lower SAA levels, and 4% lower WBC counts (all $p < 0.05$). Significant results were also observed when lower quantities (150 to 300 g/week) of fish were consumed. All associations remained significant after various adjustments were made.

CONCLUSIONS Fish consumption was independently associated with lower inflammatory markers levels, among healthy adults. The strength and consistency of this finding has implications for public health and should be explored further. (J Am Coll Cardiol 2005;46:120–4) © 2005 by the American College of Cardiology Foundation

Current scientific evidence suggests that diet plays a significant role in the prevention of cardiovascular diseases, while fish is one of the main components of a healthy diet. Epidemiological studies (1–4) and clinical trials (5,6) underline its beneficial effects in the prevention of coronary artery disease (CAD). On the other hand, low-grade systemic inflammation participates in the pathophysiology of CAD (7). Although there are some metabolic studies and one epidemiological study that observed beneficial effects of fish and its components on inflammatory markers (8–10), there are others that showed no effect (11–13). Therefore, we sought to evaluate the relationship between the amount of fish consumed and the levels of various inflammatory markers in a population-based sample of men and women without any evidence of cardiovascular disease (the ATTICA study) (14,15).

METHODS

Population of the study. During 2001 to 2002, a total of 1,518 men (age 46 ± 13 years) and 1,524 women (age 45 ± 13 years) agreed to participate (75% participation rate). Participants could not exhibit clinical evidence of cardiovascular or atherosclerotic disease or chronic viral infections, and they could not have cold or flu, acute respiratory infection, dental problems, or any type of surgery in the weeks preceding the study (during the sampling none of the participants reported any of the aforementioned conditions during the last 6 to 10 weeks). The study design was approved by the Ethical Committee of the Department of Cardiology of Athens University Medical School.

Dietary assessment. Dietary assessment was based on a validated food frequency questionnaire (FFQ) (16). Consumption of nonrefined cereals and products, vegetables, legumes, fruits, olive oil, dairy products, fish, pulses, nuts, potatoes, eggs, sweets, poultry, red meat and products, and beverages were measured as an average per week during the past year. Based on the FFQ, all participants were also asked their usual average frequency of fish consumption, which was coded as follows: 0 for none or very rare (i.e., <4 U per

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Abbreviations and Acronyms

BMI = body mass index
CAD = coronary artery disease
CRP = C-reactive protein
FFQ = food frequency questionnaire
IL = interleukin
SAA = serum amyloid A
TNF = tumor necrosis factor
WBC = white blood cell

month), 1 for rare (i.e., <4 U or about 150 g/week), 2 for moderate (i.e., 4 to 12 U or 150 g to 300 g/week), and 3 for frequent (i.e., >12 U or >300 g/week). Finally, omega-3 intake was also calculated based on a nutrient database.

Biochemical analyses. During enrollment blood samples were collected after a 12-h overnight fast. C-reactive protein (CRP) and serum amyloid A (SAA) were assayed by immunonephelometry (Date-Behring Marburg GmbH, Marburg, Germany). Interleukin (IL)-6 was measured with high-sensitivity enzyme-linked immunoassay (R & D Systems Europe Ltd., Abingdon, United Kingdom). The intra- and inter-assay coefficient of variation was <5% for CRP and SAA and <10% for IL-6. We used the ELISA method for the quantitative determination of human tumor necrosis factor (TNF)-alpha (Quantikine HS/human TNF-alpha immunoassay kit, R & D Systems, Inc., Minneapolis, Minnesota). We also measured white blood cell (WBC) counts (Medicon analyzer, Medicon Ltd., Athens, Greece).

Demographic, lifestyle, and clinical characteristics. The study's questionnaire also included sociodemographic information about age, gender, average annual income during the past three years, and school-years. Moreover, current smokers were defined as those who smoked daily at least one cigarette, former smokers were defined as those who had stopped smoking more than one year before entry (those who have stopped smoking within one year before enrollment [i.e., 0.7%] were classified as smokers). The rest were defined as nonsmokers. Then cigarette smoking was quantified in number of cigarettes smoked per day, adjusted for a nicotine content of 0.8 mg/cigarette. Physical activity was defined as leisure-time activity of a certain intensity and duration, at least once a week during the past year. The rest of the subjects were defined as sedentary. Body mass index (BMI) was calculated as weight (in kg) divided by standing height (in m^2). Obesity was defined as BMI >29.9 kg/m^2.

Moreover, patients whose average blood pressure levels were ≥140/90 mm Hg, or those under antihypertensive medication, were classified as hypertensive. Hypercholesterolemia was defined as total serum cholesterol levels >200 mg/dl, or use of lipid-lowering agents. Diabetes mellitus was defined as a blood glucose >125 mg/dl, or use of antidiabetic medications.

All participants were informed about the purposes of the study and agreed to participate. Further details about the methodologies used, measurements, and procedures have been presented elsewhere (14,15).

Statistical analysis. Continuous variables are presented as mean values ± SD. Categorical variables are presented as absolute and relative frequencies. Associations between categorical variables were tested by the calculation of the chi-square test. Correlations between inflammatory markers and other cofactors were evaluated by the use of Pearson's or Spearman's correlation coefficient. Comparisons between normally distributed continuous variables and fish-consuming groups were performed by one-way analysis of variance. The Kolmogorov-Smirnov test was applied to assess normality; CRP values were log-transformed due to their skewed distribution. In the case of years of school that could not be transformed to normal distributions, the nonparametric test suggested by Kruskal and Wallis was used. Differences in inflammation markers between subgroups according to fish consumption were tested using post-hoc analysis, after correcting the probability value for multiple comparisons using the Bonferroni rule. Multiple regression models were then applied for all inflammatory markers on fish consumption, whereas fish interaction with potential confounding factors was assessed by likelihood ratio tests. All reported p values were based on two-sided tests. Statistical Package for Social Sciences software version 12.0 (SPSS Inc. 2002, Chicago, Illinois) was used for all the statistical calculations.

RESULTS

Demographic and clinical characteristics of the participants. Eighty-eight percent of men and 91% of women reported that they consume at least one unit of fish per week. Omega-3 fatty acid intake was 0.40 ± 0.31 g/day in men and 0.52 ± 0.29 mg/day in women. Various demographic, clinical, and behavioral characteristics are presented in Table 1. Moreover, consumption of fish was positively correlated with total energy intake and BMI (rho = 0.08, p = 0.01). However, the association between fish intake and BMI was mainly explained by the total daily energy intake (Table 1).

Fish consumption and inflammatory markers. All inflammatory markers showed an inverse dose-response relationship with fish consumption (Table 2). Based on the applied post-hoc analysis, more prominent differences were observed when we compared high fish intake (i.e., >300 g per week) with no consumption. Particularly, compared to non-fish consumers, those who consumed >300 g of fish per week had on average 33% lower CRP, 33% lower IL-6, 21% lower TNF-alpha, 28% lower SAA levels, and 4% lower WBC counts. In addition, omega-3 intake was inversely associated with the levels of CRP ($r = -0.12$, $p < 0.001$), IL-6 ($r = -0.09$, $p = 0.002$), TNF-alpha ($r = -0.11$, $p = 0.01$), SAA ($r = -0.07$, $p = 0.02$), and WBC ($r = -0.08$, $p = 0.03$) (Table 2).

Furthermore, we observed that BMI was positively cor-

Table 1. Participant Demographic, Lifestyle, and Clinical Characteristics

	Fish Consumption				
	No.	**<150 g/week**	**150–300 g/week**	**>300 g/week**	**p Value**
Men (n = 1,514)					
% of Participants	12%	55%	24%	9%	—
Age (yrs)	44 ± 12	49 ± 11*	55 ± 12†	53 ± 12†	0.001
Education status (yrs of school)	13 ± 4	12 ± 2	11 ± 4*	10 ± 4	0.001
Current smokers (%)	50	44	44	48	0.36
Sedentary (%)	60	62	53	52	0.10
Obese (%)	18	22	21	27†	0.03
Energy intake (kcal/day)	1,675 ± 430	1,877 ± 420*	1,974 ± 330†	2,200 ± 330†	0.02
Hypertension (%)	41	43	37*	27†	0.02
Systolic blood pressure (mm Hg)	135 ± 21	128 ± 22	125 ± 35*	124 ± 25†	0.001
Diastolic blood pressure (mm Hg)	81 ± 18	83 ± 21	82 ± 18	79 ± 21	0.12
Hypercholesterolemia (%)	34	37	33	31	0.22
Total cholesterol (mg/dl)	209 ± 41	197 ± 25	193 ± 32	189 ± 43	0.34
HDL cholesterol (mg/dl)	44 ± 11	48 ± 15	49 ± 22	49 ± 13	0.42
Triglycerides (mg/dl)	185 ± 41	168 ± 29	149 ± 32	125 ± 33	0.02
Diabetes mellitus (%)	6	10	10	9	0.25
Women (n = 1,528)					
% of Participants	9%	58%	25%	8%	—
Age (yrs)	44 ± 11	48 ± 12	53 ± 11†	53 ± 14†	0.001
Education status (yrs of school)	12 ± 4	11 ± 3	11 ± 3	9 ± 3†	0.001
Current smokers (%)	35	38	31	30	0.09
Sedentary (%)	73	65	63	58	0.30
Obese (%)	15	18*	18*	25†	0.02
Energy intake (kcal/day)	1,557 ± 410	1,674 ± 290	1,967 ± 390†	2,100 ± 340†	0.01
Hypertension (%)	45	32*	28†	21†	0.02
Systolic blood pressure (mm Hg)	133 ± 20	125 ± 27*	124 ± 25*	121 ± 20†	0.001
Diastolic blood pressure (mm Hg)	79 ± 28	82 ± 22	84 ± 21	78 ± 22	0.21
Hypercholesterolemia (%)	35	38	37	33	0.34
Total cholesterol (mg/dl)	211 ± 40	195 ± 22	190 ± 22	182 ± 33	0.29
HDL cholesterol (mg/dl)	53 ± 13	52 ± 11	51 ± 21	52 ± 16	0.32
Triglycerides (mg/dl)	188 ± 45	171 ± 32	145 ± 33	131 ± 32	0.03
Diabetes mellitus (%)	6	7	7	10	0.13

Data are expressed as mean ± SD or percentages. For the evaluation of the tested hypotheses, we used the chi-square test for categorical variables (i.e., smoking, physical activity status, obesity, hypertension, hypercholesterolemia, and diabetes), the analysis of variance for age, and the Kruskall-Wallis criterion for years of school. *$p < 0.05$ and †$p < 0.01$ (Bonferroni corrected) for the differences between fish consumption groups vs. no consumption. Probability values derived from the analysis of variance.
HDL = high-density lipoprotein.

related with all inflammatory markers (at $p < 0.05$), even after adjusting for physical activity and energy intake, but no differences were observed regarding the effect of fish consumption on the investigated biomarkers when the data were stratified and analyzed by obesity status.

However, several potential confounders may influence the previous associations. Therefore, we applied multiple regression analysis, and adjusted R^2 values were also included to show the explanatory ability of the models. All inflammatory markers were still inversely associated with fish consumption, even after various adjustments were made. Comparing standardized beta coefficients (Table 3), we may see that the strongest associations between fish intake and inflammatory markers were observed in CRP, IL-6, and SAA levels, followed by TNF-alpha and WBC counts (Table 3).

Furthermore, stratified analysis showed that fish and omega-3 fatty acid intake were inversely associated with

Table 2. Inflammatory Markers and Daily Fish Consumption

	Fish Consumption				
	No.	**<150 g/week**	**150–300 g/week**	**>300 g/week**	**p Value**
Number of participants (%)	319 (11%)	1,719 (56%)	745 (24%)	259 (9%)	—
C-reactive protein (mg/l)	2.7 ± 1.2	2.0 ± 1.1†	2.0 ± 2.1†	1.8 ± 1.1†	0.004
Interleukin-6 (ng/ml)	1.5 ± 0.5	1.3 ± 0.6‡	1.2 ± 1.1†	1.0 ± 0.3†	0.03
Tumor necrosis factor-alpha (mg/dl)	5.3 ± 3	5.1 ± 2	4.7 ± 3†	4.2 ± 2†	<0.001
Amyloid A (mg/dl)	6.4 ± 4	5.9 ± 4	5.1 ± 4‡	4.6 ± 3†	0.004
White blood cells (×1,000 counts)	6.8 ± 3	6.7 ± 4	6.5 ± 4‡	6.5 ± 3‡	0.04

No gender differences were observed. *p = values derived from ANOVA that evaluated the associations between inflammatory markers (dependent) and fish intake (independent factor). ‡$p < 0.05$ and †$p < 0.01$ (Bonferroni-corrected) for the differences between fish consumption groups vs. no consumption. Probability values derived from the analysis of variance (ANOVA).

Table 3. Inflammatory Markers and Fish Consumption (in g/Week)

Inflammatory Markers	Standardized Beta Coefficient	Adjusted R^2 With Fish Intake Variable in the Model	Adjusted R^2 Without Fish Intake Variable in the Model	p Value*
C-reactive protein (mg/l)	0.057	0.17	0.10	0.002
Interleukin-6 (ng/ml)	0.051	0.16	0.08	0.008
Amyloid A (mg/dl)	0.044	0.17	0.11	0.02
Tumor necrosis factor-alpha (mg/dl)	0.036	0.11	0.10	0.03
White blood cell (×1,000 counts)	0.009	0.09	0.08	0.04

*p = values derived from multiple linear regression models that evaluated the association of fish consumption (in g/week) on inflammatory markers (dependent), after adjusting for age in years, gender, pack-years of smoking, physical activity status (sedentary, light, moderate, and vigorous), body mass index in kg/m^2, systolic and diastolic blood pressures in mm Hg, total, low-density lipoprotein, and high-density lipoprotein cholesterol, triglycerides levels in mg/dl, the use of medication, and the average weekly frequency of the food groups included food frequency questionnaire.

lower inflammatory markers levels in people with diabetes and hypertension, but not in people with hypercholesterolemia. Particularly, compared to non-fish consumers, diabetic people who ate >300 g of fish per week had on average 10% to 25% lower levels of inflammatory markers (all $p < 0.05$), whereas hypertensive subjects had on average 5% to 15% lower levels (all $p < 0.05$).

Finally, cut-off point analysis showed that omega-3 fatty acid intake of 0.6 g per day was the optimal level that maximized the likelihood of having the levels of the inflammatory markers in the lowest or middle tertile.

DISCUSSION

We studied a population-based sample of 3,042 adult men and women, and we observed a strong inverse relationship between fish consumption and levels of inflammatory markers related to cardiovascular disease, irrespective of other potential confounders. We have also expanded findings from previous works by showing that omega-3 fatty acid intake was inversely associated with inflammatory markers. Moreover, daily consumption of 0.6 g of omega-3 fatty acids seems to be the optimal level that is associated with the maximum reduction in inflammatory markers levels.

The effect of fish and omega-3 fatty acid intake on cardiovascular disease has long been discussed (17–20). The benefits from its intake on the cardiovascular system have been, in part, attributed to their effect on lipoprotein levels, coagulation process, as well as immune response and hypertension status (2). We found that fish intake is associated with decreased levels of proinflammatory markers. It may be hypothesized that fish intake increases IL-6 synthesis, which then affects CRP and SAA production in the liver. Tumor necrosis factor is also involved in the acute-phase protein synthesis, but it has been suggested that only IL-6 can stimulate synthesis of all acute-phase proteins involved in the inflammatory response (21). Therefore, because fish consumption is associated with decreased concentrations of these proinflammatory markers, it is reasonable to suggest that regular fish intake suppresses inflammation and, thus, produces its beneficial actions in human health.

However, metabolic studies gave conflicting results. On the one hand, Ciubotaru et al. (8) suggested that intake of fish oils decreased CRP and IL-6 levels in postmenopausal women. In addition, Trebble et al. (9) observed a decrease in TNF-alpha and IL-6 peripheral blood mononuclear cell production with increasing omega-3 fatty acid intake and also a tendency toward a "U-shaped" dose response with the lowest cytokine production at 1.0 g/day omega-3 fatty acid supplementation. On the other hand, when fish oil supplementation was given in more physiological levels, no statistical differences were found (10–12). In the present work, studying a "free-eating" population, the optimal intake for maximal reduction in the inflammation process was found to be 0.6 g of omega-3 fatty acids per day. We could hypothesize that the benefit is more pronounced if omega-3 fatty acids are consumed in the form of fish rather than in the form of a supplement and that in the metabolic studies, it is easier to detect differences in the sites of production, such as peripheral blood mononuclear cells rather than in plasma.

Some limitations in our study may exist. For example, the design of the study is cross-sectional and, therefore, we cannot make assumptions for causal relationships. The blood sampling was performed only at one visit. Fish intake was evaluated by self-reports through FFQs, and, therefore, information about the amount of fish consumed could be over- or underestimated. Another limitation is the small number of individuals who consumed >300 g/week of fish.

In spite of the lack of causal relationships, based on our findings and those of others, it is reasonable to conclude that fish consumption is associated with reduced inflammatory marker levels and, thus, is of benefit in the prevention of CAD, irrespective of known confounding factors.

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