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## Association of dietary omega-3 fatty acids with prevalence of metabolic syndrome: The National Heart, Lung, and Blood Institute Family Heart Study

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### Abstract

**Background & Aims**—Metabolic syndrome (MetS), characterized by abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, and insulin resistance is a major public health concern in the United States. Omega-3 fatty acids have been relatively well studied in relation to many individual cardiovascular risk factors; however, their effects on MetS are not well established.

**Methods**—We conducted a cross-sectional study consisting of 4,941 participants from the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study to assess the relation of dietary omega-3 fatty acids with the prevalence of MetS. Omega-3 intake was assessed using a food frequency questionnaire and we used generalized estimating equations to estimate adjusted odds ratios for prevalent MetS.

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**Conflict of Interest Statement:**

None of the authors has any conflict of interest to declare.

**Results**—Our study population had a mean age (SD) of 52.1 (13.9) years and 45.9% were men. The mean (SD) of dietary omega-3 fatty acids was 0.25g/day (0.27). From the lowest to the highest quintile of dietary omega-3 fatty acids, multivariable adjusted ORs (95% CI) for MetS were 1.00 (ref), 0.90 (0.72–1.13), 1.03 (0.82–1.28), 0.94 (0.74–1.18), and 0.99 (0.77–1.25), respectively. In a secondary analysis, neither fish consumption nor dietary alpha-linolenic acid was associated with MetS.

**Conclusions**—Our findings do not support an association between dietary omega-3 fatty acids and MetS in a large US population.

### Keywords

Omega-3 fatty acids; fish; dietary alpha-linolenic acid (ALA); metabolic syndrome

## Introduction

Metabolic syndrome (MetS) has been a major public health concern in the United States for the past few decades and its prevalence has been increasing due to rising rates of obesity. The third National Health and Nutrition Examination Survey (NHANES) showed that approximately one-fourth of the United States' adult population has MetS.<sup>1</sup> The National Cholesterol Education Program's Adult Treatment Panel III (ATP III) has identified components of MetS such as abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance (with or without glucose intolerance), proinflammatory state, and prothrombotic state as a multiplex risk factor for cardiovascular disease (CVD).<sup>2</sup>

Past research and treatments have aimed to reduce the risk of heart disease and diabetes by weight loss, physical activity,<sup>3</sup> increasing high-density lipoprotein (HDL) cholesterol<sup>4</sup> and lowering triglycerides (TG)<sup>5</sup> in individuals with MetS. During the past 30 years, there has also been a renewed interest in health benefits of omega-3 fatty acids (FA), a class of polyunsaturated fatty acids (PUFA), that has been shown to favorably improve triglycerides and reduce risk of CVD.<sup>6,7</sup> Fish and fish oils are major sources of long-chain omega-3 FA [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)], whereas intermediate chain alpha-linolenic acid (ALA) is mostly provided by walnuts, soybeans, and flaxseed oils. The American Heart Association (AHA) recommends that all adults should eat fish at least two times a week, and for patients with documented coronary heart disease, approximately 1g of EPA and DHA per day.<sup>8</sup> The guidelines also suggested that two to four grams of EPA and DHA per day might be useful in patients with hypertriglyceridemia.

There is no extensive research on the association between consumption of omega-3 fatty acids and the prevalence of MetS. Hence, we sought to assess whether dietary omega-3 fatty acids assessed by food questionnaires are associated with prevalent MetS in the NHLBI Family Heart Study.

## Materials and Methods

In a cross-sectional study design, we analyzed data on 4,941 subjects from the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study. The original cohort consisted of 5,975 subjects; however because of missing data for omega-3, ALA, or fish consumption, metabolic syndrome criteria or covariates, 4,941 subjects were used in analysis. MetS was defined using the ATP III guidelines (having three or more of the following conditions: systolic blood pressure greater than 130 mm Hg and diastolic blood pressure greater than 85 mm Hg; triglycerides  $\geq$  150 mg/dL; fasting glucose  $\geq$  110 mg/dL; waist circumference  $>$  102 cm for men and 88 cm for women; and HDL cholesterol less than 40 mg/dL for men and 50 mg/dL for women<sup>2</sup>). A Willett food frequency questionnaire

(FFQ)<sup>9</sup> was used to obtain dietary omega-3 fatty acids as well as other nutrients using Harvard University nutrient database supplemented by manufacturers' information (see previous papers for details).<sup>10</sup> The validity of FFQ has been reported elsewhere.<sup>11, 12</sup> Information on cigarette smoking and alcohol intake was obtained by interview during clinic visits. Frequency of fish intake, energy intake, multivitamin intake, fruit and vegetable consumption were obtained from the FFQ. The level of physical activity, which includes the amount of exercise and TV watching were obtained through self-reports. CHD was assessed from the medical history, defined as a self-reported history of myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft.

### Statistical Analysis

We created quintiles of dietary omega-3 FA and used the lowest group as the reference. Since fish is a major source of long-chain omega-3 FA, we also examined whether frequency of fish consumption (classified as 0, 1, 2, or 3 or more servings per week) was related to MetS.

To correct for familial clustering, we used generalized estimating equations (GEE) to calculate the prevalence odds ratios for the presence of metabolic syndrome across quintiles of omega-3 fatty acids. GEE accounts for correlation matrix among related individuals. We assessed confounding by age, gender (male/female), race (Caucasian/African American/other), current drinker (yes/no), current smoker (yes/no), exercise (continuous), television watching (quartiles based on self reported number of hours), energy intake (continuous), fruit and vegetable intake (continuous), fiber intake (continuous), multivitamin use (yes/no), and risk group (high risk/random/other). We obtained a p-value for linear trend by creating a new variable that was assigned the median value of the corresponding exposure in each quintile, and then used the new variable in the generalized estimating equations. Interaction of omega-3 FA with gender was tested and not found to be significant.

In a secondary analysis, we repeated above analyses for fish consumption and separated marine (EPA/DHA) from plant-based (ALA) omega-3 fatty acids. As a sensitivity analysis, we restricted analysis to Caucasians. All p-values were two-tailed and significance level was set at an alpha of 0.05. All analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

### Results

A full description of the NHLBI Family Heart Study has been published previously.<sup>13</sup> The mean age (SD) was 52.1 (13.9) years and the prevalence of MetS was 21.0%. Table 1 presents baseline characteristics according to quintiles of dietary omega-3 fatty acids. Higher omega-3 FA was associated with older age, hypertension and history of CHD.

As shown in Table 2, dietary omega-3 FAs were not associated with prevalent MetS (p for trend=0.97). Adjustment for age, gender, race, alcohol consumption, smoking, exercise, TV watching, energy intake, multivitamin use, fruits, vegetable, fiber intake and risk group did not alter results. In secondary analysis, findings were not altered when we excluded African-Americans (n=228): from the lowest to highest quintile of dietary omega-3 FA, adjusted odds ratios (95% CI) were 1.00 (ref), 0.91 (0.73–1.14), 1.03 (0.82–1.28), 0.95 (0.75–1.20), and 0.97 (0.75–1.24), respectively, p for trend=0.83.

In secondary analyses, neither fish consumption nor dietary ALA was associated with prevalent MetS (Table 3).

## Discussion

### Dietary Omega-3 FA & MetS

Our data did not show an association of dietary omega-3 with prevalent MetS. The effects of omega-3 have been relatively well studied in relation to cardiovascular risk factors, results of which have led the US Food and Drug Administration (FDA) to approve EPA/DHA use to treat hypertriglyceridemia. This recommendation is also consistent with the AHA dietary guidelines, recommending at least two servings of fish per week (particularly fatty fish).<sup>14, 15</sup> However, the association of omega-3 FA and major cardiovascular end points is still controversial as a recent systematic review and meta-analysis revealed that omega-3 supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke.<sup>16</sup> An important predictor of cardiovascular disease is obesity, which is one of the major causal factors of the rapidly increasing prevalence of MetS. Diabetes mellitus and insulin resistance are part of phenotypes used to define MetS. In a meta-analysis, Wu et al. reported that omega-3 FA were not related to the onset of diabetes mellitus.<sup>17</sup> In another meta-analysis, investigators reported that increment of each serving per week in fish consumption was associated with a slight increase in developing type 2 diabetes mellitus in a US population.<sup>18</sup> However, the effects of omega-3 FA on risk of MetS are not well established.

In our cross-sectional study, we did not find any association between dietary omega-3 FA and prevalent MetS. Our findings are consistent with data from other studies. Mauno et al reported no significant association between omega-3 PUFA and the incidence of MetS in a longitudinal, population-based study over a 6.4-year follow up.<sup>19</sup> In addition, one Italian retrospective study showed no significant association of omega-3 FA with the risk of MetS.<sup>20</sup>

### Fish intake, dietary ALA, & MetS

Neither fish consumption nor ALA intake was associated with MetS in our study. Our findings are consistent with a French study that reported no relation between higher fish consumption and MetS.<sup>21</sup> In contrast, a population-based prospective cohort study of Koreans found that high consumption of fish was significantly associated with a lower risk of MetS among men.<sup>22</sup> Three observational studies showed that ALA intake or plasma ALA levels were not associated with cardiovascular risk factors.<sup>23, 24, 25</sup> A meta-analysis of randomized controlled trials also showed that ALA did not significantly reduce total cholesterol, triglycerides, body mass index, LDL, or diastolic and systolic blood pressure.<sup>26</sup>

In several other studies, a significant lowering of TG was observed with increased consumption of fish.<sup>27, 28</sup> However, in our data, higher intake of fish was related to higher plasma TG (155.82 mg/dl) compared to no fish consumption (144.64 mg/dl). It is possible that subjects with elevated TG were advised to consume more fish given established TG-lowering effects of marine omega-3 FA (EPA/DHA) and our observation of paradoxical elevated TG in the group with highest fish consumption may reflect confounding by indication. We had no information on the cooking method for fish in this population for further analyses. It is possible that some of the naturally occurring unsaturated fatty acids in fish may have been altered by partial hydrogenation, and thus converted to deleterious trans-isomers during the high-temperature heating process.<sup>29, 30</sup>

### Study Limitations & Strengths

One of our study limitations is the inability to determine causal relation between dietary omega-3 FA and MetS because of the cross-sectional study design. Information on omega-3 FA was based on a self-reported questionnaire, which might have led to an overestimation or

underestimation of dietary omega-3 FAs. Another limitation is the use of a single FFQ, which may not fully capture dietary habits over time. The use of a single assessment of physical activity via self-report prevented us to control for changes in physical activity over time in this study. Our subjects were predominantly non-Hispanic whites, which might limit the generalizability of our findings to non-white populations. However, to date, this is the largest multi-center, population-based study assessing the relationship between dietary omega-3 FA, fish consumption, and ALA with prevalent MetS. The availability of information on several covariates including physical activity, smoking, alcohol use, etc. is a strength of this study.

## Conclusion

Our findings do not support an association between dietary omega-3 FA and MetS in this multi-center population-based study of US men and women.

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**Table 1**  
Baseline characteristics of 4,941 subjects in the NHLBI Family Heart Study by dietary omega-3 fatty acids

Variables	Quintiles of dietary omega-3 fatty acids (g/d) [0.00–5.65]				
	Q1 [0.00–0.07] (n=970)	Q2 [0.08–0.14] (n=1070)	Q3 [0.15–0.21] (n=918)	Q4 [0.22–0.37] (n=1009)	Q5 [0.38–5.65] (n=974)
Age (y)	50.3±14.1	51.2±14.0	52.7±13.9	53.1±13.5	53.4±13.7
Body mass index (kg/m <sup>2</sup> )	27.2±5.3	27.4±5.7	28.03±5.6	27.5±5.2	28.1±5.7
Waist Circumference (cm)	96.0±15.3	96.6±15.5	98.4±15.6	97.1±14.5	98.3±15.5
TG (mg/dL)	144.2±100.1	148.9±110.8	151.7±98.9	151.4±111.9	148.0±112.8
LDL (mg/dL)	124.6±35.7	124.2±33.4	124.3±35.1	126.0±35.5	125.8±36.8
HDL (mg/dL)	50.0±14.8	50.3±14.7	49.9±15.3	50.7±15.3	51.0±16.2
Exercise (min/day)	22.7±33.7	26.8±37.9	30.4±38.2	33.6±41.3	33.1±38.3
Omega-3 fatty acids (g/day)	0.04 ± 0.02	0.11 ± 0.02	0.18 ± 0.02	0.28 ± 0.05	0.64 ± 0.37
Fish intake (servings/week)	0.41 ± 0.62	0.85 ± 0.94	1.18 ± 1.15	1.58 ± 1.20	2.41 ± 1.83
Alpha-linolenic acid (g/day)	0.65 ± 0.33	0.72 ± 0.34	0.74 ± 0.34	0.80 ± 0.38	0.93 ± 0.62
Males (%)	44.6	45.9	45.3	50.5	43.0
Race & Ethnicity (%)					
Non-Hispanic White	97.9	97.8	96.1	93.9	88.9
African American	1.8	1.9	3.1	5.9	10.7
Others	0.3	0.4	0.9	0.3	0.4
Hypertension (%)	24.0	26.5	28.9	31.1	34.4
Diabetes (%)	5.2	5.1	8.2	6.5	8.2
Coronary Heart Disease (%)	8.1	9.3	11.8	12.3	14.2
Current Smoker (%)	16.2	15.3	14.1	12.9	16.6
Current Drinker (%)	49.0	53.2	54.8	57.2	54.9
Regular Vitamin Intake (%)	39.2	41.5	41.9	42.6	47.6

\* Data are presented as means (±) SD or percentages



**Table 2**

Prevalence odds ratios (95% confidence intervals) of metabolic syndrome according to dietary omega-3 FA

Dietary omega-3 fatty acids (Quintiles)	MetS cases / N	Crude	Adjusted Model *
Q1 (0.00, 0.07)	210/970	1.00 (ref)	1.00 (ref)
Q2 (0.08, 0.14)	212/1070	0.89 (0.72–1.11)	0.90 (0.72–1.13)
Q3 (0.15, 0.21)	203/918	1.03 (0.83–1.27)	1.03 (0.82–1.28)
Q4 (0.22, 0.37)	203/1009	0.91 (0.73–1.13)	0.94 (0.74–1.18)
Q5 (0.38, 5.65)	207/974	0.98 (0.78–1.22)	0.99 (0.77–1.25)
P-value for linear trend		0.97	0.90

\* Adjusted for age, gender, race, alcohol intake (yes/no), smoking (yes/no), exercise (min/day), TV watching (hours/weekday), energy intake, multivitamin use, fruits and vegetables intake, fiber intake, and risk group (random vs. high risk) using generalized estimating equations (GEE)

**Table 3**

Prevalence odds ratios (95% confidence intervals) of metabolic syndrome according to fish consumption in the NHLBI Family Heart Study

Number of fish servings/ week	MetS cases / N	Crude	Model 1*
0	271/1341	1.00 (ref)	1.00 (ref)
1	454/2183	1.04 (0.88–1.23)	1.00 (0.84–1.18)
2	162/794	1.01 (0.82–1.26)	1.00 (0.80–1.26)
3	148/623	1.23 (0.97–1.56)	1.30 (1.00–1.68)

\* Adjusted for age, gender, race, alcohol intake (yes/no), smoking (yes/no), exercise (min/day), TV watching (hours/weekday), energy intake, multivitamin use, fruits and vegetables intake, fiber intake, and risk group (random vs. high risk) using generalized estimating equations (GEE)