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Significant inverse association of marine n-3 fatty acids with plasma fibrinogen levels in Japanese in Japan but not in whites or Japanese Americans

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Abstract

Background—Numerous studies reported beneficial effects of marine n-3 fatty acids (n-3 FAs) on cardiovascular disease (CVD) and its risk factors. However, the association of marine n-3 FAs with plasma fibrinogen, a risk factor for CVD, remains uncertain.

Methods—In a population-based, cross-sectional study of 795 men aged 40-49 without CVD (262 whites in Allegheny County, Pennsylvania, US, 302 Japanese in Kusatsu, Japan, and 229 Japanese Americans in Honolulu, Hawaii, US), we examined the association of marine n-3 FAs with plasma fibrinogen. Serum FAs were measured by capillary gas-liquid chromatography. Marine n-3 FAs were defined as the sum of docosahexaenoic, eicosapentaenoic, and docosapentaenoic acids. Plasma fibrinogen was measured by an automated clot-rate assay. Multiple linear regression analyses were performed to assess the association.

Results—White, Japanese, and Japanese American men had mean marine n-3 FAs levels of 3.47%, 8.78%, and 4.46%, respectively. Japanese men had a significant inverse association of marine n-3 FAs with fibrinogen (standardized regression coefficient of -0.11, p=0.049), after adjusting for age, body-mass index, and current smoking. The significant inverse association

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remained after further adjusting for diabetes, C-reactive protein, triglycerides and other variables. White or Japanese American men did not show a significant association.

Conclusion—We observed the significant inverse association of marine n-3 FAs with fibrinogen in Japanese, but not in whites or Japanese Americans. The observation suggests that marine n-3 FAs at very high levels, as seen in the Japanese, may decrease plasma fibrinogen levels.

Keywords

fibrinogen; marine n-3 fatty acids; epidemiology; Japanese

Introduction

Since the 1970's when the relationship between marine n-3 fatty acids (n-3 FAs) and cardiovascular disease (CVD) was first reported in the Inuit studies (Bang et al 1971, Dyerberg et al 1975), numerous studies have reported the effect of marine n-3 fatty acids (n-3 FAs) on CVD and its risk factors.(Balk et al 2004, Balk et al 2006a, Harris et al 2008, He et al 2002, Mozaffarian and Rimm 2006) These studies have found that marine n-3 FAs reduce coronary heart disease (CHD) death and all cause mortality, and may have beneficial effects on other CVD outcomes, such as heart failure and stroke.(Balk et al 2004, Marchioli et al 2009, Wang et al 2006)

Other studies have examined effects of marine n-3 FAs on individual CVD risk factors. The inverse relationship between marine n-3 FAs and triglycerides has been the strongest and most consistent finding.(Balk et al 2004) Marine n-3 FAs are associated with a 10 to 33% decrease in triglycerides in a dose-dependent manner. Additionally, marine n-3 FAs are associated with a small but significant decrease in blood pressure as well as with an increase in heart rate variability in survivors of myocardial infarction.(Balk et al 2004) However, the relationships between marine n-3 FAs and other CVD risk factors, including low-density lipoprotein cholesterol (LDL-C), glucose, insulin, and C-reactive protein (CRP), are inconclusive.(Balk et al 2004, Balk et al 2006b) One such risk factor is fibrinogen.(Balk et al 2004)

Fibrinogen levels have been established as a risk factor for both CHD and stroke.(Bots et al 2002) Fibrinogen plays a major role in thrombosis, the formation of blood clots, which is a central mechanism in stroke and myocardial infarction. The Fibrinogen Studies Collaboration found that the adjusted hazard ratio per 1-g/L increase in usual fibrinogen levels for CHD and stroke was 1.8, and concluded that the associations of fibrinogen level with CHD or stroke did not differ substantially according to sex, smoking, blood pressure or blood lipid levels.(Danesh et al 2005)

No previous study has examined the association of fibrinogen with serum levels of marine n-3 FAs among populations with wide range of fish consumption. Fish consumption in Japan is one of the highest in the world whereas fish consumption in Western countries is generally low.(Zhang et al 1999) Based on the data by the Food and Agriculture Organization, percent energy from fish is 6.5% in Japan, 0.81 % in Australia, 0.71% in the US and 0.70% in the UK. The International Study of Macro- and Micro-Nutrients and Blood

Pressure,(Stamler et al 2003b) which provides the most comprehensive dietary data across Japan, China, the UK and the US, shows that mean dietary intake of marine n-3 FAs for men aged 40-59 is 1.32 g/day in Japan, 0.03 g/day in China, 0.43 g/day in the UK, and 0.21 g/day in the US.(Stamler et al 2003a)

In this study we examine the association of serum marine n-3 FAs with plasma fibrinogen levels, analyzing data from the 'Electron-Beam Tomography, Risk Factor Assessment among Japanese and U.S. Men in the Post-World War II Birth Cohort' (ERA-JUMP) study, a population-based cross-sectional study of Japanese, white, and Japanese American men aged 40-49.(Sekikawa et al 2008)

Subjects and Methods

Subjects and basic measurements

During 2002 to 2006, 926 men aged 40-49 were randomly selected: 310 whites from Allegheny County, Pennsylvania, U.S.,(Abbott et al 2007, Sekikawa et al 2007, Sekikawa et al 2008) 313 Japanese from Kusatsu, Shiga, Japan, and 303 Japanese Americans from offspring of fathers who participated in the Honolulu Heart Program (Kagan et al 1974), Honolulu, Hawaii, U.S. These offspring were the third or fourth generation of Japanese Americans without ethnic admixture. (Abbott et al 2007) All participants were without clinical cardiovascular disease, type 1 diabetes, or other severe diseases.(Sekikawa et al 2007) Additionally, the current study excluded subjects who were taking lipid-lowering medications. Our final sample was 262 whites, 302 Japanese, and 229 Japanese Americans. Informed consent was obtained from all participants. The study was approved by the Institutional Review Boards of University of Pittsburgh, Pittsburgh, U.S., Shiga University of Medical Science, Otsu, Japan, and Kuakini Medical Center, Honolulu, U.S.

All participants underwent a physical examination, lifestyle questionnaire, and laboratory assessment as described previously.(Abbott et al 2007, Sekikawa et al 2007, Sekikawa et al 2008) Body weight and height were measured while the participant was wearing light clothing without shoes. Body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m^2). Blood pressure was measured in the right arm of the seated participant after the participant emptied his bladder and sat quietly for 5 minutes, using an automated sphygmomanometer (BP-8800; Colin Medical Technology, Komaki, Japan) with an appropriate-sized cuff. The average of two measurements was used.

Venipuncture was performed early in the clinic visit after a 12-hour fast. Serum samples were stored at -80°C and shipped on dry ice to the University of Pittsburgh. Serum lipids, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides, were analyzed using the standardized methods according to the Centers for Disease Control and Prevention. LDL-C was subsequently determined using the Friedewald equation.(Sekikawa et al 2007) LDL-C was directly measured by an automated spectrophotometric assay (Equal Diagnostics, Exton, PA) when the levels of triglycerides exceeded 10.7 mmol/L. CRP was determined using a calorimetric-competitive-enzyme-linked-immunosorbent assay. Plasma fibrinogen was determined using an automated-clot-rate assay (Diagnostica Stago, Parsippany, New Jersey).

Serum fatty acids were analyzed by capillary-gas-liquid chromatography (PerkinElmer Clarus 500).(Sekikawa et al 2008) Marine n-3 FAs were defined as the sum of eicosapentaenoic acid (EPA) (20:5n-3), docosapentaenoic acid (DPA) (22:5n-3), and docosahexaenoic acid (DHA) (22:6n-3). The coefficients of variation for EPA, DPA, and DHA were 2.5 %, 2.5%, 7.0%, respectively. Fatty acids were expressed as a percent of total serum fatty acids.

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure 90 mmHg, or use of anti-hypertensive medications. Diabetes mellitus was defined as fasting serum glucose level ≥7 mmol/L or use of anti-diabetic medications.

A self-administered questionnaire was used to obtain information on demography, smoking habits, alcohol drinking, and other factors. Alcohol drinking was assessed as whether the participant drank beer, wine, liquor, sake (Japanese rice wine), or other alcoholic beverages, with quantity and frequency. Ethanol consumption per day was estimated, assuming that concentrations of alcohol were 5 percent for beer, 12 percent for wine, 40 percent for liquor, and 16 percent for sake.

Statistical Analyses

To compare risk factors among populations, analysis of variance for continuous variables except for triglycerides, CRP and ethanol or the Mantel-Haenszel test for categorical variables were used. To compare triglycerides, CRP, and ethanol which had skewed distributions among populations, the Kruskal-Wallis test was used. To examine correlation between fibrinogen and each of continuous risk factors, Spearman correlation test was used. To examine associations of serum marine-derived n-3 FAs with fibrinogen, we conducted multivariable-adjusted linear regression analyses for each of the three populations. In model I, we adjusted for age, BMI, current smoking, which are commonly reported as confounders of fibrinogen and are major determinants of fibrinogen.(The Fibrinogen Studies Collaboration 2007) In model II we further adjusted for diabetes, triglycerides, HDL-C, LDL-C and CRP, which are reported as strong confounders of fibrinogen but may not be necessarily causally related to fibrinogen.(The Fibrinogen Studies Collaboration 2007) In model III we further adjusted for hypertension and ethanol. Triglycerides, CRP, and ethanol were log-transformed in these multiple regression models. Statistical significance was considered to be $P<0.05$. All statistical analyses were performed with PSAW Statistics 18 (Release 18.0.0, IBM Corporation, New York).

Results

Table 1 describes the baseline characteristics of the three population samples. It should be noted that fibrinogen levels were significantly different among the three groups ($p<0.05$); Japanese and Japanese-American men had the lowest and highest levels, respectively. Additionally, BMI varied significantly among the three groups. While the percentage of current smokers did not differ significantly between whites (8.0%) and Japanese-Americans (13.7%), the difference between both groups and Japanese men (49.3%) was striking.

Marine n-3 FAs in the Japanese was about twice as high as those in whites or Japanese Americans and overlapped little between the Japanese and the other two samples. Mean ± standard deviation was 9.31 ± 2.96 % for the Japanese, 3.85 ± 1.78 % for whites, and 5.39 ± 2.37 % for Japanese Americans. The lower 25 percentile of the Japanese (5.86%) was higher than the upper 25 percentiles of whites (4.53%) and Japanese Americans (5.94%). Levels of total fatty acids were not significantly different among the three population samples (mean ± standard deviation was 239 ± 52 mg/dL for whites, 244 ± 52 for the Japanese in Japan and 236 ± 81 mg/dL for Japanese Americans).

Fibrinogen had associations with various risk factors. Fibrinogen had significant positive correlations with each of BMI and CRP in each sample population (Table 2). Fibrinogen had positive correlations with systolic BP, LDL-C, and triglycerides and had negative correlations with HDL-C in all sample population (Table 2). Fibrinogen was significantly higher among current smokers than non-smokers in the Japanese. Mean ± standard deviation was 7.79 ± 1.94 μmol/L for current smokers (n=149) and 7.23 ± 1.91 μmol/L for non smokers (n=153) (p=0.010). Fibrinogen was higher in current smokers than in non smokers in the other two population samples, but the difference did not reach statistical significance (data not shown). Similarly, fibrinogen was significantly higher in those with hypertension than those without hypertension and in those with diabetes than those without diabetes in the Japanese. Mean ± standard deviation was 8.00 ± 1.76 μmol/L for those with hypertension (n=77) and 7.53 ± 1.97 μmol/L for those without hypertension (n=225) (p=0.011). Likewise, mean ± standard deviation was 8.41 ± 1.97 μmol/L for those with diabetes (n=17) and 7.47 ± 1.94 μmol/L for those without diabetes (n=285) (p=0.048). Fibrinogen was higher in those with hypertension or diabetes than in those without hypertension or diabetes, respectively in the other two population samples, but the difference did not reach statistical significance (data not shown).

Age-adjusted analyses show that fibrinogen was inversely associated with marine n-3 FAs in the Japanese (Table 3). The inverse association became significant after further adjusting for current smoking and BMI (model I). The significant inverse association remained after further adjusting for diabetes, triglycerides, HDL-C, LDL-C, and CPR (model II) as well as hypertension and ethanol(model III). However, fibrinogen had no significant associations with marine n-3 FAs in either the whites or Japanese-Americans.

Discussion

A significant inverse association between serum marine n-3 FAs and plasma fibrinogen was observed only in Japanese men, whose serum marine n-3 levels were about twice as high as white and Japanese American men. This population-based study is the first study reporting that the association of serum n-3 FAs and fibrinogen is different by the background level of marine n-3 FAs.

We observed that levels of fibrinogen differ across population groups. The observation that Japanese men in Japan had lower levels of fibrinogen than the other two groups is consistent with the results from previous studies.(Iso et al 1993, Miura et al 2006) We also observed that levels of fibrinogen are significantly higher in Japanese American than white men. This

observation is inconsistent with the results from a few previous studies. Elderly Japanese American men had lower levels of fibrinogen than elderly white men (Yano et al 1999) and middle-aged Japanese American women had lower levels of fibrinogen than middle-aged white women.(Matthews et al 2005) This discrepancy may be due to differences in confounders of fibrinogen.(The Fibrinogen Studies Collaboration 2007) For example, our study of men shows that BMI, a significant confounder of fibrinogen, is similar between Japanese Americans and whites whereas the study of women shows that Japanese Americans have lower BMI than whites by 4 units.(Matthews et al 2005)

We observed that fibrinogen was positively associated with BMI and CRP in each population group and that fibrinogen was higher in smokers as well as those with diabetes. These observations are consistent with previous studies.(The Fibrinogen Studies Collaboration 2007) Although some of the associations in our study did not reach statistical significance, this is likely to be due to a small sample size.

Results from epidemiological studies on the association of fibrinogen with intake of either fish or marine n-3 FAs are conflicting. The Atherosclerosis Risk in Communities (ARIC) Study reported that fibrinogen has a significant inverse association with fish intake after adjusting for age, race, BMI, smoking, diabetes, alcohol and other factors.(Shahar et al 1993) In contrast, the Coronary Artery Risk Development in Young Adults (CARDIA) Study reported that fish intake or dietary intake of marine n-3 FAs does not have a significant association with fibrinogen.(Archer et al 1998) The discrepancy may be partly due to the difference in intake of EPA and DHA: mean intake of EPA + DHA in the ARIC Study is 0.27 g/day whereas that in the CARDIA Study ranges from 0.09 to 0.18 g/day depending on race and sex. These data are not inconsistent with our results. One study comparing the association of fish intake with fibrinogen between Japanese and white men and women reported that total fish intake has a significant inverse association with fibrinogen only in white men but not white women or Japanese men or women.(Iso et al 1993) However, the study did not adjust for potential confounders, and the sample size, i.e., 150 whites and 150 Japanese, is much smaller than the current study.

Although results from randomized clinical trials of marine n-3 FAs on fibrinogen are conflicting, this may be partly due to the small number and short duration of these studies. A recent review of 22 trials reported that only 4 trials show a statistically significant difference in fibrinogen levels between n-3 FAs group and control group.(Balk et al 2004) Three of these studies show significant decrease of fibrinogen whereas one study shows a significant increase. Another study suggested that lower doses of marine n-3 FAs are ineffective in lowering fibrinogen; Radack et al. found that dyslipidemic subjects given 2.2 g of EPA and DHA daily for 20 weeks had a statistically significant net reduction in fibrinogen, whereas subjects who took 1.1 g of EPA and DHA had no effect.(Radack et al 1989) However, other studies using much higher doses of EPA and DHA did not show a significant reduction in fibrinogen.(Grundt et al 1999, Hansen et al 1993, Nordoy et al 2000, Toft et al 1997) These randomized clinical trials are small in numbers, e.g., 15 to 40, and short in duration, e.g., 2 weeks to 2 years, either of which may have attenuated existing effects. In fact, a study of marine n-3 FAs on fibrinogen of 365 subjects for 7 years showed a significant reduction in fibrinogen in a time-dependent manner.(Saynor and Gillott 1992)

Marine n-3 FAs can reduce fibrinogen through several mechanisms. Marine n-3 FAs reduce thrombin generation, which is causally associated with fibrinogen.(Vanschoonbeek et al 2004) In mice, marine n-3 FAs can downregulate the hepatic expression of the peroxisome proliferator-activated receptor-α,(Takahashi et al 2002) which controls fibrinogen levels in human.(Gervois et al 2001)

The differences in the association of serum n-3 FAs with fibrinogen we observed among white, Japanese, and Japanese American men could also be related to the method of marine n-3 FAs consumption rather than amount. Cobiac et al. conducted a small study comparing equal fish oil intake through fish consumption and supplements in healthy men. After 3 weeks, the fish group showed a significant decrease in fibrinogen by 0.13 g/L as compared to the control group. In contrast, the fish oil group showed a non-significant increase in fibrinogen by 0.38 g/L. The authors suggest that complementary compounds in fish flesh may be required for the decrease in fibrinogen.(Cobiac et al 1991)

We excluded subjects taking statin because statins have variable effects on fibrinogen. (Rosenson and Tangney 1998) Some studies reported an increase and some a decrease in fibrinogen by statin, whereas other studies showed no change. When we analyzed the data including those with lipid lowering medications, the significant inverse association of marine n-3 FAs with plasma fibrinogen remained in Japanese men. After adjusting for age, BMI, current smoking, diabetes, triglycerides, HDL-C, LDL-C, CRP and lipid-lowering medications, standardized beta for marine n-3 was -0.11 ($p=0.034$). After further adjusting for hypertension and ethanol standardized beta for marine n-3 was -0.10 ($p=0.0499$).

Strengths of our study include that having the Japanese in Japan whose fish consumption is one of the highest in the world allowed us to analyze the association of a wide range of marine n-3 FAs with fibrinogen. We would also like to acknowledge several limitations. The sample size is relatively small. Serum marine n-3 FAs reflect short-term dietary intake and may not reflect long-term dietary intake. However, because the variation in serum marine n-3 FAs occurs randomly, the actual association of marine n-3 FAs with fibrinogen is likely to be stronger than was observed in the current study. Our study examined only men aged 40-49 and the results are not generalizable to women or other age groups. The study is observational and we cannot exclude the possibility of residual or unmeasured confounding, i.e., other dietary factors and total energy intake.(Miura et al 2006, Willett et al 1997)

In conclusion, we observed the significant inverse association of marine n-3 FAs with fibrinogen in Japanese, but not in Japanese Americans or Whites. This observation suggests that marine n-3 FAs at very high levels, as seen in the Japanese, may decrease plasma fibrinogen levels.

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References

Abbott RD, Ueshima H, Rodriguez BL, Kadowaki T, Masaki KH, Willcox BJ, et al. Coronary artery calcification in Japanese men in Japan and Hawaii. Am J Epidemiol. 2007; 166:1280–1287. [PubMed: 17728270]

Archer SL, Green D, Chamberlain M, Dyer AR, Liu K. Association of Dietary Fish and n-3 Fatty Acid Intake With Hemostatic Factors in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Arterioscler Thromb Vasc Biol. 1998; 18:1119–1123. [PubMed: 9672072]

Balk E, Chung M, Lichtenstein A, Chew P, Kupelnick B, Lawrence A, et al. Effects of omega-3 fatty acids on cardiovascular risk factors and intermediate markers of cardiovascular disease. Evid Rep Technol Assess (Summ). 2004:1–6.

Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J. Effects of omega-3 fatty acids on coronary restenosis, intima-media thickness, and exercise tolerance: a systematic review. Atherosclerosis. 2006a; 184:237–246. [PubMed: 16084516]

Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. Atherosclerosis. 2006b; 189:19–30. [PubMed: 16530201]

Bang HO, Dyerberg J, Nielsen AB. Plasma lipid and lipoprotein pattern in Greenlandic West-coast Eskimos. Lancet. 1971; 1:1143–1145. [PubMed: 4102857]

Bots ML, Elwood PC, Salonen JT, Freire de Concalves A, Sivenius J, Di Carlo A, et al. Level of fibrinogen and risk of fatal and non-fatal stroke. EUROSTROKE: a collaborative study among research centres in Europe. J Epidemiol Community Health. 2002; 56(Suppl 1):i14–18. [PubMed: 11815639]

Cobiac L, Clifton PM, Abbey M, Belling GB, Nestel PJ. Lipid, lipoprotein, and hemostatic effects of fish vs fish-oil n-3 fatty acids in mildly hyperlipidemic males. Am J Clin Nutr. 1991; 53:1210–1216. [PubMed: 1826986]

Danesh J, Lewington S, Thompson SG, Lowe GD, Collins R, Kostis JB, et al. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. JAMA. 2005; 294:1799–1809. [PubMed: 16219884]

Dyerberg J, Bang HO, Hjorne N. Fatty acid composition of the plasma lipids in Greenland Eskimos. Am J Clin Nutr. 1975; 28:958–966. [PubMed: 1163480]

Gervois P, Vu-Dac N, Kleemann R, Kockx M, Dubois G, Laine B, et al. Negative Regulation of Human Fibrinogen Gene Expression by Peroxisome Proliferator-activated Receptor α Agonists via Inhibition of CCAAT Box/Enhancer-binding Protein β. Journal of Biological Chemistry. 2001; 276:33471–33477. [PubMed: 11418615]

Grundt H, Nilsen DW, Hetland O, Mansoor MA, Aarsland T, Woie L. Atherothrombogenic risk modulation by n-3 fatty acids was not associated with changes in homocysteine in subjects with combined hyperlipidaemia. Thromb Haemost. 1999; 81:561–565. [PubMed: 10235439]

Hansen JB, Olsen JO, Wilsgard L, Lyngmo V, Svensson B. Comparative effects of prolonged intake of highly purified fish oils as ethyl ester or triglyceride on lipids, haemostasis and platelet function in normolipaemic men. Eur J Clin Nutr. 1993; 47:497–507. [PubMed: 8404785]

Harris WS, Miller M, Tighe AP, Davidson MH, Schaefer EJ. Omega-3 fatty acids and coronary heart disease risk: Clinical and mechanistic perspectives. Atherosclerosis. 2008; 197:12–24. [PubMed: 18160071]

He K, Rimm EB, Merchant A, Rosner BA, Stampfer MJ, Willett WC, et al. Fish Consumption and Risk of Stroke in Men. JAMA. 2002; 288:3130–3136. [PubMed: 12495393]

Iso H, Folsom AR, Sato S, Wu KK, Shimamoto T, Koike K, et al. Plasma fibrinogen and its correlates in Japanese and US population samples. Arterioscler Thromb. 1993; 13:783–790. [PubMed: 8499398]

Kagan A, Harris BR, Winkelstein W Jr, Johnson KG, Kato H, Syme SL, et al. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: demographic, physical, dietary and biochemical characteristics. J Chronic Dis. 1974; 27:345–364. [PubMed: 4436426]

Marchioli R, Levantesi G, Silletta MG, Barlera S, Bernardinangeli M, Carbonieri E, et al. Effect of n-3 polyunsaturated fatty acids and rosuvastatin in patients with heart failure: results of the GISSI-HF trial. Expert Rev Cardiovasc Ther. 2009; 7:735–748. [PubMed: 19589110]

Matthews KA, Sowers MF, Derby CA, Stein E, Miracle-McMahill H, Crawford SL, et al. Ethnic differences in cardiovascular risk factor burden among middle-aged women: Study of Women's Health Across the Nation (SWAN). American Heart Journal. 2005; 149:1066–1073. [PubMed: 15976790]

Miura K, Nakagawa H, Ueshima H, Okayama A, Saitoh S, Curb JD, et al. Dietary Factors Related to Higher Plasma Fibrinogen Levels of Japanese-Americans in Hawaii Compared With Japanese in Japan. Arterioscler Thromb Vasc Biol. 2006; 26:1674–1679. [PubMed: 16675719]

Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. JAMA. 2006; 296:1885–1899. [PubMed: 17047219]

Nordoy A, Bonaa KH, Sandset PM, Hansen J-B, Nilsen H. Effect of {omega}-3 Fatty Acids and Simvastatin on Hemostatic Risk Factors and Postprandial Hyperlipemia in Patients With Combined Hyperlipemia. Arterioscler Thromb Vasc Biol. 2000; 20:259–265. [PubMed: 10634827]

Radack K, Deck C, Huster G. Dietary supplementation with low-dose fish oils lowers fibrinogen levels: a randomized, double-blind controlled study. Ann Intern Med. 1989; 111:757–758. [PubMed: 2802434]

Rosenson RS, Tangney CC. Antiatherothrombotic Properties of Statins: Implications for Cardiovascular Event Reduction. JAMA. 1998; 279:1643–1650. [PubMed: 9613915]

Saynor R, Gillott T. Changes in blood lipids and fibrinogen with a note on safety in a long term study on the effects of n-3 fatty acids in subjects receiving fish oil supplements and followed for seven years. Lipids. 1992; 27:533–538. [PubMed: 1453884]

Sekikawa A, Ueshima H, Kadowaki T, El-Saed A, Okamura T, Takamiya T, et al. Less subclinical atherosclerosis in Japanese men in Japan than in White men in the United States in the post-World War II birth cohort. Am J Epidemiol. 2007; 165:617–624. [PubMed: 17244636]

Sekikawa A, Curb JD, Ueshima H, El-Saed A, Kadowaki T, Abbott RD, et al. Marine-derived n-3 fatty acids and atherosclerosis in Japanese, Japanese-American, and white men: a cross-sectional study. Journal of the American College of Cardiology. 2008; 52:417–424. [PubMed: 18672160]

Shahar E, Folsom AR, Wu KK, Dennis BH, Shimakawa T, Conlan MG, et al. Associations of fish intake and dietary n-3 polyunsaturated fatty acids with a hypocoagulable profile. The Atherosclerosis Risk in Communities (ARIC) Study. Arterioscler Thromb. 1993; 13:1205–1212. [PubMed: 8343495]

Stamler J, Elliott P, Chan Q. for the INTERMAP Research Group. INTERMAP APPENDIX TABLES. Journal of Human Hypertension. 2003a; 17:665–775. [PubMed: 14504623]

Stamler J, Elliott P, Dennis B, Dyer AR, Kesteloot H, Liu K, et al. INTERMAP: background, aims, design, methods, and descriptive statistics (nondietary). J Hum Hypertension. 2003b; 17:591–608.

Takahashi M, Tsuboyama-Kasaoka N, Nakatani T, Ishii M, Tsutsumi S, Aburatani H, et al. Fish oil feeding alters liver gene expressions to defend against PPARalpha activation and ROS production. Am J Physiol Gastrointest Liver Physiol. 2002; 282:G338–348. [PubMed: 11804856]

The Fibrinogen Studies Collaboration. Associations of Plasma Fibrinogen Levels with Established Cardiovascular Disease Risk Factors, Inflammatory Markers, and Other Characteristics: Individual Participant Meta-Analysis of 154,211 Adults in 31 Prospective Studies: The Fibrinogen Studies Collaboration. Am J Epidemiol. 2007; 166:867–879. [PubMed: 17785713]

Toft I, Bonaa KH, Ingebretsen OC, Nordoy A, Jenssen T. Fibrinolytic Function After Dietary Supplementation With {omega}3 Polyunsaturated Fatty Acids. Arterioscler Thromb Vasc Biol. 1997; 17:814–819. [PubMed: 9157942]

Vanschoonbeek K, Feijge MAH, Paquay M, Rosing J, Saris W, Kluft C, et al. Variable Hypocoagulant Effect of Fish Oil Intake in Humans: Modulation of Fibrinogen Level and Thrombin Generation. Arterioscler Thromb Vasc Biol. 2004; 24:1734–1740. [PubMed: 15217806]

Wang C, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B, et al. 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. [PubMed: 16825676]

Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr. 1997; 65:1220S–1228. [PubMed: 9094926]

Yano K, Kodama K, Shimizu Y, Chyou P-H, Sharp DS, Tracy RP, et al. Plasma Fibrinogen and Its Correlates in Elderly Japanese Men Living in Japan and Hawaii. Journal of Clinical Epidemiology. 1999; 52:1201–1206. [PubMed: 10580783]

Zhang J, Sasaki S, Amano K, Kesteloot H. Fish consumption and mortality from all causes, ischemic heart disease, and stroke: an ecological study. Prev Med. 1999; 28:520–529. [PubMed: 10329343]

Table 1

Baseline characteristics of the study participants in 2002 - 2006

	Whites (n=262)	Japanese (n=302)	Japanese Americans (n=229)
Population characteristics			
Age (years)	44.9 ± 2.8	45.1 ± 2.8	46.0 ± 2.9 †‡
Body-mass index (kg/m^2)	27.8 ± 4.3	23.7 ± 3.1	27.4 ± 4.2 *‡
Systolic blood pressure (mmHg)	122.9 ± 11.4	124.6 ± 15.8	126.6 ± 12.1 †
Diastolic blood pressure (mmHg)	73.2 ± 8.8	76.3 ± 11.9	76.9 ± 8.7 *†
Low-density-lipoprotein cholesterol (mmol/L)	3.54 ± 0.85	3.41 ± 0.93	3.31 ± 0.84 †‡
High-density-lipoprotein cholesterol (mmol/L)	1,24 ± 0.34	1.40 ± 0.35	1.31 ± 0.32 *†‡
Triglycerides (mmol/L)	1.42 (1.04, 2.11)	1.53 (1.15, 2.03)	1.57 (1.04, 2.48) †‡
Fibrinogen (μmol/L)	8.47 ± 2.10	7.29 ± 2.68	9.08 ± 2.26 *†‡
C-reactive protein (mg/L)	0.95 (0.50, 1,85)	0.31 (0.15, 0.68)	0.61 (0.31, 1.32) *†
Current smoker (%)	8.1%	49.3%	13.7% *‡
Ethanol (g/day)	4.9 (1.0, 16.5)	14.1 (2.4, 42.0)	1.0 (0.0, 24.7) *†‡
Hypertension (%)	13.6%	25.5%	24.0% *†
Diabetes (%)	3.3%	5.6%	8.2% †

Values are expressed as mean ± standard deviation, median (inter-quartile range), or %.

*p<0.017 between the Japanese and white men.

†p<0.017 between white and Japanese-American men.

‡p<0.017 between the Japanese and Japanese-American men.

Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or use of anti-hypertensive medications. Diabetes mellitus was defined as fasting serum glucose level ≥7 mmol/L or use of anti-diabetic medications.

Table 2

Spearman correlation between plasma fibrinogen and cardiovascular risk factors of the study participants in 2002 – 2006

	Whites (n=262)	Japanese (n=302)	Japanese Americans (n=229)
Population characteristics			
Age	.116 †	.184 ‡	-.016
Body-mass index	.246 ‡	.112 †	.199 ‡
Systolic blood pressure	.142 †	.087	.055
Low-density-lipoprotein cholesterol	.025	.180 ‡	.039 †
High-density-lipoprotein cholesterol	-.151 ‡	-.081	-.194 ‡
Triglycerides	.096	.137 †	.124 †
C-reactive protein	.298 ‡	.367 ‡	.467 ‡
Ethanol	-.067	.012	-.117 †

† $p<0.05$,

‡ $p<0.01$

Table 3

Multivariate regression coefficients (standardized beta) of marine n-3 fatty acids with plasma fibrinogen in whites, Japanese, and Japanese Americans in 2002 - 2006

	Whites (n=262)	Japanese (n=302)	Japanese Americans (n=229)
Age adjusted	0.03 (p=0.647)	-0.11 (p=0.069)	-0.02 (p=0.783)
Model I	0.08 (p=0.212)	-0.11 (p=0.049)	0.01 (p=0.853)
Model II	0.11 (p=0.095)	-0.12 (p=0.039)	0.08 (p=0.146)
Model III	0.10 (p=0.110)	-0.11 (p=0.041)	0.10 (p=0.088)

Model I was adjusted for age, current smoking, and body mass index.

Model II was further adjusted for diabetes, triglycerides, high-density-lipoprotein cholesterol, low-density-lipoprotein cholesterol, and C-reactive protein.

Model III was further adjusted for hypertension and ethanol.