ETHNIC DIFFERENCES IN FISH AND OTHER SOURCES OF OMEGA-3 FATTY ACIDS AND MORTALITY FROM CORONARY HEART DISEASE, STROKE, AND HYPERTENSION IN A MULTIEHNIC COHORT

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Dedication

To the memory of Shihao Meng who passed away from heart disease and had been encouraging my quest of research;

To Dingzhen Xiao, Alen Wei, Kevin Wei, and Howard Wei

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Abstract

Background: Fish and other sources for omega-3 fatty acids (ω3) were found to be protective against cardiovascular diseases (CVD). However, little is known regarding whether the levels of benefit differ by food sources or by ethnicity. This research studied how sources of ω3 contribute to its effects on coronary heart disease (CHD), stroke, and hypertension mortality among African-Americans, Caucasians, Japanese, Native Hawaiians, and Latinos in the Multiethnic Cohort. These groups have varying sources of ω3 and CVD mortality rates.

Methods: Using data from over 180,000 adults aged 45-75, residing in Hawaii and Los Angeles County, relative risks (RR) of mortality due to CHD and stroke overall by sex and ethnicity were computed by Cox regression for ω3 sources, adjusting for known risk factors.

Results: Fish, vegetable oils, and soy products were major ω3 sources. There were 4,516 CHD deaths and 1,789 stroke deaths during an average of 11.9 years of follow-up through the end of 2005. ω3 was inversely associated with CHD mortality (5^{th} vs. 1^{st} quintile: RR=0.77, 95% Confidence Intervals=0.60-0.98) in men, but the trend was unclear in women. Whereas fried fish was positively related to CHD risk, baked, boiled or raw fish had an inverse relation in men. Salted and dried fish intake was positively related to CHD risk, while oils, shoyu and tofu had inverse relations in both sexes. Canned tuna was inversely associated with stroke mortality, as were ω3 and oils. Fried fish was positively related to stroke risk in men, while total fish had an inverse relation in women. Baked, boiled and raw fish was inversely related to stroke risk, except among Japanese men (p=0.0014 for interaction). Salted and dried fish was positively related to hemorrhagic but not ischemic stroke mortality.

Conclusions: The findings suggest a cardiovascular protective effect of ω3 that varied by source and preparation method. Fresh fish, soy products, and vegetable oils may be protective, while fried, salted, or dried fish may be detrimental, especially leading to the high hemorrhagic stroke mortality in Japanese men, presumably due to their respective high level of trans fat or sodium.

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List of Abbreviations

Abbreviations	Terms
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
ALA	alpha-linolenic acid
AMI	acute myocardial infarction
ANOVA	analysis of variance
ANCOVA	analysis of covariance
ATP III	Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults
BMI	body mass index
CHD	coronary heart disease
CI	confidence intervals
CRCH	Cancer Research Center of Hawaii
CVD	cardiovascular disease
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
EPCs	Evidence-based Practice Centers
ICD	International Classification of Diseases
JPHC	Japan Public Health Center-based study cohort
LDL	low-density lipoprotein
MDR	minimal detectable relative risks
MEC	Multiethnic/Minority Cohort (MEC) Study
MRFIT	Multiple Risk Factor Intervention Trial
NDI	National Death Index
NHANES III	Third National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
ODS	Office of Dietary Supplements
PUFA	polyunsaturated fatty acid
ω3	omega-3 fatty acids
ω6	omega-6 fatty acids
RR	relative risk
QFFQ	quantitative food frequency questionnaire
SCD	sudden cardiac death
Tufts-NEMC	Tufts-New England Medical Center
USDA	U.S. Department of Agriculture

Chapter 1. Research Proposal

1.1 OBJECTIVES

The aim of this research project was to estimate the association between fish and plant sources of dietary omega-3 fatty acids and the risks of coronary heart disease (CHD), stroke, and hypertension mortality from a large population-based cohort study in the U.S. and to provide evidence for appropriate dietary intervention messages for different populations. The hypothesis was that fish and plant sources of omega-3 fatty acids vary among ethnic groups and that the direction and magnitude of the relations between these food sources to CHD, stroke, and hypertension mortality vary among ethnic groups. That is, different food sources may be protective against CHD but detrimental for stroke or hypertension in different ethnic groups.

1.2 SPECIFIC AIMS

The primary specific aim was:

- to evaluate the possible relationship of dietary omega-3 fatty acids and its fish and plant sources to the relative risk of CHD, stroke, and hypertension mortality among ethnic groups, overall and for men and women, while controlling for the known risk factors. Food sources of omega-3 fatty acids included fish, soy products, vegetable oils, and ethnic traditional dishes. Fish intake was considered overall and by type and by preparation method (e.g., frying, shoyu use). Adjustment variables included body mass index, baseline hypertension, diabetes, smoking, alcohol consumption, amount of vigorous physical activity, educational level, energy intake, percent energy from saturated fat, and for women, type and age at menopause and hormone replacement therapy use.

The secondary aims were

- to describe sources of dietary omega-3 and omega-6 fatty acids in a large population-based sample of 215,000 adults from five ethnic groups in U.S.;
- to evaluate the relationship of total dietary omega-6 fatty acids and the ratio of dietary omega-6 to omega-3 fatty acid intake to the CHD, stroke, or hypertension mortality;
- to evaluate the association of the dietary omega-3 fatty acids to CHD risk on the high risk groups with hypertension, diabetic history, and obesity;
- to evaluate the association of the dietary omega-3 fatty acids to acute myocardial infarction (AMI) mortality or sudden cardiac death (SCD).

1.3 BACKGROUND

According to the National Center for Health Statistics, heart disease (mainly CHD) has been the leading cause of death for both men and women in the United States for over 90 years. In 2005, heart disease and cerebrovascular disease accounted for 652,091 and 143,579 deaths respectively, comprising 26.6% and 5.9% of all U.S. deaths.[1] CHD and stroke are not prevented by vaccines, nor do they just disappear in several courses of treatment. To a large degree, health-damaging behaviors, in particular, lack of control of high blood pressure and high cholesterol, tobacco use, lack of physical activity, obesity, and poor nutrition are major contributors to CHD and stroke.[2] It is the most prevalent, costly[3], but preventable disease or condition among all health problems.

The CHD and stroke mortality rates are not uniform among racial and ethnic groups. On one hand, the age-adjusted death rates of CHD for the largest US ethnic groups were, respectively, 193.9 and 130.0 per 100,000 for Latino men and women, 146.5 and 96.1 for Asian and Pacific Islander men and women, 342.1 and 236.5 for African American men and women, and 268.7 and 175.1 for Caucasian men and women in 2004.[1] On the other hand, the age-adjusted death rates for stroke were, respectively, 15.0 and 17.9 per 100,000 for Latino men and women, 24.3 and 27.0 for Asian and Pacific Islander men and women, 41.5 and 51.9 for African American men and women, and 41.8 and 65.3 for Caucasian men and women in 2004.[1] Asian and Pacific Islander had a lower incidence of CHD deaths but a higher rate of stroke deaths than Latinos. In a recent report from a population-based cohort study, the mortality rates from cardiovascular diseases (CVD), after the adjustment for known risk factors, were ranked from the lowest to the highest among ethnic groups: Japanese-American, Latino American, Caucasian, Native Hawaiian, and African American.[4] The reasons for these disparities, after accounting for known risk factors for cardiovascular disease, are not fully understood. This suggests that genetic or other environmental factors may contribute to the association of ethnicity with cardiovascular diseases risk.

There are also very large differences in the risk for CHD and stroke between migrant populations and the populations in their places of origin, such as blacks in Africa and those in the US, or Japanese in Japan and those in Hawaii and California.[5-8] CHD mortality in Japan is about half of that in the United States, while stroke death in Japan is more than double. Japanese-American men experience stroke incidence that is lower than men in Japan, but higher than other ethnic groups in Hawaii.[5,6] This indicates that certain environmental factors may be protective against CHD but risk factors for stroke. According to the 2005 report by the Office of Health Status Monitoring of the Hawaii State Department of Health, the age-adjusted mortality rate of CHD among Japanese Americans in Hawaii was 66.6 as compared to 80.4 among Caucasians. However, the Japanese age-adjusted stroke mortality rate was 48.2 as compared to 32.1 for Caucasians.[9] These epidemiological data in the same geographic region further suggest that lifestyle factors or genetic susceptibility may play a crucial role contributing to the ethnic differences in cardiovascular disease risks. Diet is a modifiable risk factor that changes upon migration but remains somewhat distinct between ethnic groups. In addition, there is substantial evidence that diet has an influence on the progression of CHD and stroke, and it is estimated that over $42 billion in direct and indirect medical costs due to CHD and stroke can be attributed to diet.[10] We believe that the comparison of diet and other modifiable risk factors and the risks of CHD and stroke among racial and ethnic groups is a powerful approach to study genetic susceptibility and lifestyle interactions.

It has been noted that Japanese have markedly higher fish and soy product intakes with a lower incidence and mortality from CHD but a higher incidence and mortality from stroke than other ethnic groups in Hawaii.[8] Both Japanese and Hawaiians have high fish consumption but Japanese have much lower CHD risk than Hawaiians after controlling known risk factors. The differences in risk of CHD related to fish consumption factors could be due to differences in fish preparation methods and fish types. Japanese often use shoyu and stir-frying in food preparation, while other ethnic groups may deep fry their fish. Other dietary components may influence risk, such as the trans fat content of fried food and the sodium content of shoyu, particularly on the risk of hypertension and stroke.

Different food sources of omega-3 fatty acids contain different specific types of ω3, which could influence risk of disease. Fish and fish oils contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), omega-3 long-chain polyunsaturated fatty acids (PUFA); and soybeans and other plant sources contain alpha-linolenic acid (ALA), omega-3 short-chain PUFA. EPA, DHA, and ALA are a group of bioactive food components.[11] Omega-3 fatty acids in fish and fish oil supplements have been reported to have a variety of beneficial effects on cardiovascular disease in observational studies and clinical studies.[12-19] Results of these studies suggest that omega-3 fatty acid intake is associated with reduced risk of cardiovascular disease, although causality has not been determined. The mechanisms underlying the cardiovascular protective effects from omega-3 fatty acids are probably multifactorial and may collectively modulate the processes of atherothrombogenesis, as observed in numerous animal experiments and some clinical human studies.[20,21] Omega-3 fatty acids may prevent arrhythmias, lower heart rate and blood pressure, decrease platelet aggregation, and lower triglyceride levels by decreased production of hepatic triglycerides and increased clearance of plasma triglycerides.[22-25]

Omega-3 fatty acids and omega-6 fatty acids are essential fatty acids that are important components of all cell membranes, but they are not interconvertable. The biological actions of their metabolites are particularly interesting. Eicosanoids derived from omega-6 fatty acids are pro-inflammatory and pro-aggregatory agonists, whereas those derived from omega-3 fatty acids tend to inhibit platelet aggregation and be anti-inflammatory.[24,25] The ratio between omega-6 to omega-3 fatty acids, rather than the absolute amounts of omega-3 fatty acids in the diet, may be critical for disease prevention, due to the competition between these two essential polyunsaturated fatty acids in the elongation and desaturation pathways, leading to the synthesis of their respective eicosanoids.[26] A high ratio of omega-6 to omega-3 fatty acids tends to accentuate a dietary deficit in EPA[27], while low ratios increase endogenous production of EPA.

1.4 KNOWLEDGE GAPS

The National Institutes of Health's (NIH) Office of Dietary Supplements (ODS) commissioned the U.S. Agency for Healthcare Research and Quality (AHRQ) to provide evidence-based reports on the role of omega-3 fatty acids in various health conditions and diseases using all available scientific literature in 2002. AHRQ subsequently contracted with three of its Evidence-based Practice Centers (EPCs): Tufts-New England Medical Center (Tufts-NEMC); the University of Ottawa EPC; and the RAND Southern California EPC—to provide 11 evidence-based reports. The ODS and the NIH's National Heart, Lung, and Blood Institute (NHLBI) collaborated to request the evidence-based reports on CVD. The EPCs screened over 7,464 abstracts published up to 2003 and selected 39 unique studies, including 12 randomized clinical trials, 22 prospective cohort studies, 4 case-control studies, and 1 cross-sectional study, reporting cardiovascular outcomes with follow-up duration of 1 year or longer.[28] Due to the huge differences in study populations, settings, and measurement, no meta-analysis was possible using these studies.

In 2004, ODS in collaboration with NHLBI, facilitated a Working Group[29] meeting to review the evidence-based reports on omega-3 fatty acids in relation to cardiovascular diseases, to cardiovascular risk factors, and to biomarkers of cardiovascular disease in order to determine the future clinical research directions on omega-3 fatty acids and cardiovascular disease. A placebo-controlled randomized intervention trial of well-measured and highly controlled supplements was suggested on primary and secondary prevention populations with a large sample size. Additional observational studies were not recommended because the AHRQ evidence report was based on 22 prospective cohort studies with up to 223,000 participants. However, the following knowledge gaps were recognized: none of the large trials on omega-3 fatty acids in relation to cardiovascular disease was conducted in the U.S., thus leaving open the question of their applicability to the U.S. population of which only about 25% reported any daily fish consumption according to the Third National Health and Nutrition Examination Survey (NHANES III) data[29]; the influence of the ratio of omega-6 to omega-3 fatty acids on outcomes has not been well-studied; most studies of fish intake did not report the type of fish or methods of preparation. Plant sources for omega-3 fatty acids such as vegetable oil use in cooking and soy products including tofu and shoyu used in fish preparation has been little studied.

1.5 RATIONALE FOR USING MULTIETHNIC COHORT DATA

This unique project will fill gaps in knowledge by exploring the effects of total dietary omega-3 fatty acids and its food sources, including tofu, shoyu use, methods of preparation, types of fish, oils in cooking, and certain traditional ethnic dishes on CHD, stroke, and hypertension outcomes in an existing large population-based long-term follow-up study in the U.S. The prospective Multiethnic Cohort (MEC) Study of diet and cancer was initially established in Hawaii and Los Angeles County in 1993 to 1996, recruiting 215,251 men and women, aged between 45 to 75 years in 1993 and primarily of five major ethnicities.[30] Extensive information was collected at baseline on demographics, diet, smoking status, medical conditions (those relevant to CVD are heart attack, angina, hypertension, stroke and diabetes) and reproductive history for women.

Although the cohort study was established to explore the relationships of diet and other lifestyle factors to cancer risks within and among ethnic groups, the nature of the data offers the opportunity to study the ethnic-specific associations of dietary factors and CHD, stroke, and hypertersion mortality risk. Deaths were identified by computer-linkage to death certificates in Hawaii and Los Angeles, and to the National Death Index for individuals who moved out of state. After an average of 11.9 years of follow-up till the end of 2005, over 7,500 cases of CHD, stroke, and hypertension deaths were identifed. This rich data source provides the opportunities to examine:

- overall possible dose-response relationship of total dietary omega-3 fatty acids, fish, and other food sources to CHD, stroke, and hypertension mortality in a U.S. population with high statistical power;
- the relationship of omega-6 fatty acids and the ratio of dietary omega-6 fatty acids to omega-3 fatty acids to CHD, stroke, or hypertension mortality;

These data have already been useful in the study of the risk of CVD. Past MEC researchers found that while adjustment for established risk factors led to attenuation, ethnic differences in CVD mortality remained[4] and found that omega-3 fatty acid intake was protective against AMI incidence in African Americans and Latinos (not yet published). Further analyses of the outcomes of AMI mortality and SCD as well as subgroup analyses in CHD and stroke risks by the status of baseline hypertension, obesity, and diabetes could provide more insights into the mechanisms of the effects from omega-3 fatty acids and its food sources on CVD risk.

Several aspects of the MEC data[4,30] support the feasibility of this study. First, variations in dietary exposure and mortality rates among ethnic groups should improve the ability to detect an association between omega-3 fatty acids exposure or food sources and death from cardiovascular disease. In 2000, the baseline characteristics of the cohort population were reported.[30] Both within and among ethnic groups, the questionnaire data show substantial variations in dietary intakes (nutrients as well as foods) and in the distributions of non-dietary risk factors, including smoking, alcohol consumption, obesity, and physical activity.

Table 1.1. Intake of Fish and Other Sources of Omega-3 Fatty Acids from the Quantitative Food Frequency Questionnaire by Sex among the Main Ethnic Groups in the Cohort, Hawaii and Los Angeles, 1993-1996

Food*	Caucasian	African-American	Native Hawaiian	Japanese-American	Latino
Men					
Fish	25.1	20.6	39.4	32.9	17.2
Legumes#	34.4	38.9	27.4	24.2	96.4
Tofu	7.4	1.9	14.7	22.0	2.9
Shoyu use	1.61	0.51	4.79	4.86	0.58
Oils in cooking	1.7	1.9	3.5	2.7	2.5
Women					
Fish	17.6	18.6	32.0	23.5	14.0
Legumes#	26.5	31.6	24.5	20.4	67.4
Tofu	5.4	1.7	16.1	23.9	3.0
Shoyu use	1.04	0.34	3.69	3.89	0.56
Oils in cooking	1.2	1.4	2.8	2.2	2.1

*Mean daily intake (g), standardized to the overall cohort age distribution.
#Legumes excluding tofu.

Table 1.1 displays the variations of fish and plant sources of omega-3 fatty acids consumption among ethnic groups. Japanese Americans and Native

Hawaiians had much higher intake of fish, tofu, shoyu, and vegetable oils in cooking than the other ethnic groups. These dietary variations support the approach to study ethnic differences in dietary omega-3 fatty acid intake associated with cardiovascular disease risks. Whether the type of fish, the preparation methods of fish, and plant sources of the dietary omega-3 fatty acid intake to prevent CVD vary among ethnic groups will be explored.

Another positive aspect of the MEC for this research is the large number of cases. Through 2005, there are nearly 7,500 cases of CHD, stroke, and hypertension death.

Table 1.2. Omega-3 and Omega-6 Fatty Acids from the Quantitative Food Frequency Questionnaire by Sex among the Main Ethnic Groups in the Cohort, Hawaii and Los Angeles, 1993-1996

Fatty Acids	Caucasian	African-American	Native Hawaiian	Japanese-American	Latino
Men					
ω3 (g/d)	2.0	2.0	2.5	2.0	2.3
ω6 (g/d)	17.6	18.0	21.4	16.9	19.6
ω6/ω3	9.1	9.1	8.5	8.5	8.7
Women					
ω3 (g/d)	1.5	1.7	2.2	1.7	1.9
ω6 (g/d)	13.6	15.5	18.8	13.9	16.3
ω6/ω3	8.8	9.0	8.4	8.9	8.6

Also, much of ethnic differences in mortality rates due to cardiovascular disease were not fully explained by known risk factors.[4] The focus of this dissertation was the excess risk in Native Hawaiians and African Americans and the lower risk in Japanese Americans for CHD mortality, and the higher stroke and hypertension mortality risk in Japanese Americans compared to Caucasians.[5,6] Table 1.2 displays that Japanese and Hawaiians had similar means for dietary omega-3 fatty acids and the ratio of omega-6 to omega-3 fatty acids. The effect of omega-3 fatty acids may vary by ethnic group, possibly due to different food sources, preparation methods of fish, or genetic susceptibility. The latter would imply that requirements and the potential health benefits from dietary interventions would vary across ethnicities. The data also allowed us to explore the interaction of omega-3 fatty acid intake and ethnicity so that the unexplained ethnic disparities in cardiovascular mortality could possibly be understood further.

In summary, this research project had several advantages for answering questions on the effects from dietary omega-3 fatty acids and their food sources and the risk of CHD, stroke, and hypertension death. The project was economical and time-saving by using existing cohort data; it was based on representative sample of the five ethnic groups; the extensive dietary data were of good quality; the method of death case ascertainment was validated; and results could be applicable to the U.S. population. This study will produce scientific data to fill gaps in our knowledge of the effect of fish and other sources of omega-3 fatty acids to promote health in U.S. populations.

1.6 EXPERIMENTAL APPROACH

1.6.1 Study Design

This research used a prospective cohort study and Cox regression to compare the risk of CHD, stroke, and hypertension mortality from omega-3 fatty acids and its food sources, overall and by ethnic group in men and women. The Multiethnic Cohort (MEC) is a large prospective population-based study that enrolled, between 1993 and 1996, 215,251 men and women in Hawaii and Los Angeles County, aged 45-75 in 1993 and primarily of five major ethnicities. Ethnicity was self-defined. The cohort consisted of individuals of African-American (16.3%), Latino (22.0%), Japanese-American (26.4%), Native Hawaiian (6.5%), Caucasian (22.9%), and other (5.8%) ancestry. The MEC sampling frame for the cohort included the Hawaii and Los Angeles driver's license files, the Hawaii voters registration file and the California Health Care Financing

Administration (Medicare) files. Out-migration rates after ten years were low (< 5 percent). Additional details are discussed in another report.[30]

A 26-page self-administered mail questionnaire was completed by each cohort member that included a 17-page quantitative food frequency questionnaire (1st QFFQ), as well as demographic, medical, and lifestyle information. A calibration substudy collected multiple 24-hour diet recalls on more than 2,000 of the participants, evenly distributed by sex-ethnic subgroup, to permit correction of nutrient intake estimates for measurement error.[31] A brief follow-up questionnaire (2nd QX) to update selected dietary and non-dietary baseline information was completed by more than 80% of the participants after about five years of follow-up; in the current period 2003-2008, the baseline dietary questionnaire is being repeated (3rd QX or repeat QFFQ).

1.6.2 Dietary Assessment

The development of the QFFQ was described in the another report.[31] In brief, three-day measured dietary records from 60 men and 60 women of each ethnic group served as the basis for the selection of food items for the QFFQ. A minimum set of food items contributing at least 85% to the intake of nutrients of interest for each ethnic group were selected and complemented by the inclusion of traditional food items in the diet of a particular ethnic group, irrespective of their nutrient contributions.

The QFFQ enquires about the usual intake frequency, based on 8-9 categories ranging from ‘Never or hardly ever’ to ‘2 or more times a day’, and the amount of food consumed, based on a photographs showing a choice of three portion sizes for many food items on the QFFQ. The reference portion sizes were derived from the three-day measured dietary records. Usual dietary intake over the previous 12 months was assessed. The QFFQ was designed for self-administration and optical scanning. For analyzing dietary intake data, a QFFQ-specific food composition table was developed at the Cancer Research Center of

Hawaii (CRCH), based largely on USDA data[32], and supplemented with information from Japan, Canada and the United Kingdom, as well as locally analyzed foods. The CRCH food composition table includes information on 1500 foods, many unique to the multiethnic population under study, and 700 recipes.

1.7 PLANNED STATISTICAL ANALYSIS

1.7.1 Core Analyses

The baseline characteristics and exposures of interest were summarized descriptively, overall and by ethnicity, in men and women. Continuous variables were summarized in terms of sample size, mean, standard deviation, minimum, and maximum. Categorical variables were summarized in count and percentage overall and for cases separately. Death rates from CHD, stroke, stroke subtype, and hypertension by sex and ethnicity were calculated adjusting for age using the US 2000 standard population.

For the primary objectives, Cox regression (proportional hazards model) was used to calculate relative risks (RR) for men and women and 95% confidence intervals (95% CI) of CHD, stroke, or hypertension mortality overall and among ethnic groups. Age was used as the time metric to calculate relative risks. Follow-up began at the date of cohort entry, defined as questionnaire completion or as the date when the participant turned 45 years old (for the few individuals younger than 45 when they completed the baseline questionnaire). Follow-up ended at the earliest of the date of death, or December 31st 2005, the closure date for the study. Events included only individuals whose cause of death was due to the specific cause of interest among CHD, stroke, and hypertension. A base model had been built for CHD, stroke, and hypertension mortality in the MEC that accounted for the strong risk factor of smoking: the final model included smoking status (never, former, current) and duration of smoking in years as a time-dependent variable.[33] Modeling this strong risk factor well should minimize the chance of residual confounding. Other covariates for adjustment included body mass index, hypertension, diabetes, alcohol consumption, amount of vigorous physical activity, educational level, log-transformed daily calories, and percent calories from saturated fats; and for women, type and age at menopause and hormone replacement therapy use. The risk factors of interest included intake of omega-3 fatty acids and its food sources. These variables were entered into the model as indicator variables representing quantiles, using the lowest quantile as reference. Quintiles were generally applied, although other groupings, such as tertiles, were used when appropriate for the distribution. Dose-response were tested by inclusion of a trend variable, assigned the median value for the appropriate quantile by ethnicity. The risk factors were studied overall and by sex-ethnic groups. Interactions were tested by likelihood ratio tests comparing models with cross-product terms between ethnicity and risk factors and main effects models. Subgroup analysis was performed by smoking status (informing the possibility of residual confounding), and history of hypertension, diabetes, and obesity.

For the secondary objectives, the Cox regressions were repeated to model the CHD, stroke, and hypertension mortality with omega-6 fatty acid intake and the ratio of omega-6 to omega-3 fatty acids, adjusting for the same covariates in the primary analysis. In order to examine the correlation between risk factors for CHD risk and omega-3 fatty acid intake, logistic models were applied to regress the history of hypertension, diabetes, or obesity separately on the intake of omega-3 fatty acids, adjusting for the same covariates. The primary proportional hazards model was compared with a similar model excluding either history of hypertension or diabetes, in order to examine mediation. These two analyses could shed light on whether the underlying mechanisms of the effect of omega-3 fatty acids are mediated through an association with hypertension and diabetes.

Supporting analyses were performed: 1) to repeat the primary model with CHD risk for the cohort members at high risk for heart disease, defined by being hypertensive, diabetic, and/or obese; 2) to repeat the primary model with acute myocardial infarction or sudden cardiac deaths.

In the primary analysis, the missingness patterns of information on diet, smoking, diabetes, hypertension, physical activity, weight, height, educational level, alcohol consumption, aspirin use, and menopausal status and the use of hormone therapy in women were examined. If the variables are missing completely at random, then the missing data would not bias the results. Examination of the missingness pattern was done by comparing the risk of cardiovascular disease within sex, ethnic and age group, among cohort members with missing data and those with no missing data. In addition, multiple imputation techniques were used, where imputation was based on sampling from a distribution conditional on relevant covariates of age, sex, and ethnicity. If the multiple imputation methods validated our main findings, the findings using individuals with no missing data were presented.

Based on the analysis, a dietary intervention recommendation could be generated to display the amount of daily food items for omega-3 fatty acids that confers protection, based on sex-specific or sex-ethnic specific risk estimates as needed. These values could be used to plan an intervention study to test the causal effect of changing dietary fatty acid consumption of omega-3, overall and by source.

1.7.2 Limitations

The accuracy of the exposure measurement was limited by the original QFFQ design and the possible dietary changes over time. On one hand, the first QFFQ did not collect information on fish oil supplement use as it was not widely used during that time. However, preliminary analysis of the data from the readministration of the MEC QFFQ in 2003-2008 found that 15% of cohort members reported taking fish oil at least once a week. Therefore, the exposure of the omega-3 fatty acids could be somewhat underestimated. Moreover, cohort members with healthier lifestyles were more likely to use dietary supplements.[34] This might cause difficulties to separate the effects of true omega-3 fatty acid intake from other lifestyle factors protective for cardiovascular risk.

On the other hand, the assumption to examine the relationship of food sources of omega-3 fatty acid intake to CHD, stroke, and hypertension mortality was that individuals maintain their dietary patterns for a long period of time. However, cohort memebrs who were diagnosed of CHD, stroke, or hypertension between the 1st QFFQ and the repeat QFFQ might have modified their dietary pattern over the period, as during that period the American Heart Association Nutrition Committee, the Adult Treatment Panel III, and the year 2000 Dietary Guidelines Advisory Committee published a series of dietary recommendations. Cohort members who were free of heart disease and are health conscious might have modified their dietary pattern as well.

1.7.3 Validation Analyses

In order to address the limitations and verify the asumption that individuals had steady dietary patterns, the change in diet exposures between the first QFFQ and the repeat QFFQ will be examined. Only subjects with the repeat QFFQ completed will be included in this analysis. Change in the following diet exposures from the first QFFQ to the repeat QFFQ will be examined: total omega-3 fatty acids; major contributors for total omega-3 fatty acids; vegetable intake; fruit intake; grain intake; meat intake excluding fish and tofu; diary product intake. The analysis of covariance (ANCOVA) will be used to estimate the change in diet exposures from the first QFFQ to the repeat QFFQ, adjusting for covariates of ethnicity, baseline diet, age, sex, energy, whether omega-3 supplements were taken at the repeat QFFQ. Comparisons of the changes in the diet will be performed among ethnic groups. The difference in change in total omega-3 fatty acid consumption between omega-3 fatty acids supplement users and non-users will be estimated. If the changes in dietary patterns are modest over time, the primary analysis should be considered valid. If the dietary pattern changes are marked, a repeat analysis using the repeat QFFQ data will be conducted, albeit the number of events occurring after the repeat QFFQ will be small.

Another cross validation will be conducted using the level of erythrocyte membrane omega-3 fatty acids. Erythrocyte membrane fatty acid composition is a valid biomarker of relative dietary levels of fatty acids and reflects usual diet over a period of months. In a case-control study of prostate cancer nested within the MEC, about 1,100 cases with fasting blood specimens collected before diagnosis and 2,200 controls had omega-3 and omega-6 fatty acids measured in the erythrocyte membrane by the method of Godley et al.[35] For subjects in this substudy, the relationship between the erythrocyte omega-3 fatty acids and intake of omega-3 fatty acids from food at the repeat QFFQ will be graphically displayed by all age-ethnic subgroups. Linear regression will be used to determine prediction equations of erythrocyte levels of omega-3. Separate equations will be determined by age-ethnic group if necessary. If the goodness-of-fit statistics are reasonable, these equations will be applied to the baseline intake of omega-3 fatty acids to estimate erythrocyte levels for all male subjects. The Cox regression for the primary analysis will be repeated replacing the exposure of interest with the predicted erythroid omega-3 fatty acids. If the predicted biomarker results are similar to main findings, it implies that findings are robust. If the predicted biomarker results are different from main findings, a repeat analysis using the second QFFQ data will be performed.

1.8 CHANGES TO PLANNED STATISTICAL ANALYSIS

Since the repeat QFFQ data was not available during the project time frame, no formal validation analyses was conducted. We calculated the correlation between the dietary omega-3 fatty acids from the first QFFQ and the level of erythrocyte membrane omega-3 fatty acids in the prostate cancer substudy. However, the data collection time would be much closer to the repeated QFFQ than the first QFFQ.

All analyses in the research were performed using SAS version 9.1.3.[36]

1.9 STRUCTURE OF DISSERTATION

The dissertation is structured as a series of manuscripts, followed by results from additional analyses. Chapter 2 presents a manuscript on the food sources of omega-3 and omega-6 fatty acids among the ethnic groups in the MEC. Chapter 3 presents a manuscript on the association between CHD death and omega-3 fatty acid intake and its food sources. Chapter 4 presents a similar manuscript for the outcome of stroke death. Chapters 5-7 present additional analysis: Chapter 5 for the outcome of hypertension death, Chapter 6 for other outcomes, such as death from acute myocardial infarction and sudden cardiac death, Chapter 7 for the role of omega-6 fatty acid intake. Chapter 8 presents sensitivity analysis to test data assumptions, and Chapter 9 gives a summary of results, nutritional message, and future research.

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Chapter 2. Sources of Omega-3 and Omega-6 Fatty Acids: the Multiethnic Cohort

2.1 ABSTRACT

Objective: To describe sources of dietary omega-3 and omega-6 fatty acids in a large sample of over 215,000 individuals from five ethnic groups.

Design: Cohort study designed to examine associations between diet and chronic diseases.

Setting: The Multiethnic Cohort includes representative population samples of the five ethnic groups located in Hawaii and Los Angeles, California USA.

Subjects: Over 215,000 adults aged 45-75 from five ethnic groups: African American, Japanese American, Native Hawaiian, Latino and Caucasian, who completed the extensive quantitative food frequency questionnaire in 1993-1996.

Results: The top sources for omega-3 fatty acids were regular salad dressings, canned tuna fish, macaroni or potato salad, mayonnaise in sandwiches, and vegetable oils in cooking. These are also the top sources for omega-6 fatty acids with the addition of peanuts and other nuts. All ethnic groups consumed substantial amounts of omega-3 and omega-6 fatty acids from typical Western foods. However, for select ethnic groups, traditional food sources, including tofu, miso soup, Mexican and Spanish rice, and refined beans, were major contributors to dietary omega-3 fatty acid intake but not to dietary omega-6 fatty acid intake.

Conclusion: Our data highlight the need for nutrition interventions involving dietary omega-3 fatty acids to be tailored specifically to each population because of traditional variations in eating patterns. The differing sources may also influence associations between dietary omega-3 and omega-6 fatty acids and chronic diseases observed across the five ethnic groups.

2.2 INTRODUCTION

According to the National Center for Health Statistics, heart disease (mainly coronary heart disease) has been the leading cause of death for both women and men in the United States for over 90 years. In 2005, heart disease and stroke claimed 652,091 and 143,579 lives respectively, comprising 26.6% and 5.9% of all U.S. deaths.[1]

The intake of the omega-3 polyunsaturated fatty acids (PUFA), particularly in fish and fish oil supplements, has been reported to have a variety of beneficial effects on CHD and stroke in observational studies and clinical studies.[2] Omega-3 fatty acids may prevent arrhythmias, lower heart rate and blood pressure, decrease platelet aggregation, and lower triglyceride levels by decreased production of hepatic triglycerides and increased clearance of plasma triglycerides.[3,4] This evidence has prompted the American Heart Association (AHA) Nutrition Committee[5,6] and the National Cholesterol Education Program Adult Treatment Panel III (ATP III) to make recommendations for fish consumption and omega-3 fatty acid intake for adults.[7]

The association of the omega-6 PUFA and heart disease risk appears to be more complicated. A large body of data from randomized trials, observational studies, and animal feeding experiments indicate that the consumption of omega-6 fatty acids reduces the risk of CHD. However, a high ratio of omega-6 to omega-3 fatty acids has been associated to an increased risk of CHD.[8] The AHA recommends an omega-6 fatty acid intake contributing between 5% to 10% of energy. To reduce omega-6 fatty acid intake from the recommended levels would be more likely to increase rather than to decrease the risk for CHD.[9] Because the Western diet usually contains sufficient amounts of omega-6 fatty acids, emphasis has been on increasing dietary omega-3 fatty acid intake as prevention against cardiovascular diseases.

In the US, the major food sources of omega-3 fatty acids are fatty fish and oils of soybean, canola, and flaxseed, and walnuts and of omega-6 fatty acids are walnuts and soybean according to the USDA food composition database. Although there is a large body of scientific literature studying fish and omega-3 fatty acids and chronic disease outcomes, we have found no large studies examining other food sources of omega-3 and omega-6 fatty acids for different ethnic groups in U.S. The CHD and stroke mortality rates vary among racial and ethnic groups, with death rates for CHD (age-adjusted to the 2000 U.S. standard population) ranging from 146.5 and 96.1 for Asian and Pacific Islander men and women respectively to 342.1 and 236.5 for African American men and women in 2004.[10] Age-adjusted death rates for stroke ranged from 15.0 and 17.9 per 100,000 for Latino men and women to 41.8 and 65.3 for Caucasian men and women in 2004.[10] Understanding the different food sources of dietary omega-3 and omega-6 fatty acids may be very important to the interpretation of the association of these fatty acids with CHD and stroke in multiethnic populations.

The aims of this paper are to use data from the large Multiethnic Cohort from a common Quantitative Food Frequency Questionnaire (QFFQ) to describe the food sources of omega-3 and omega-6 fatty acids in a large representative sample of five ethnic groups.

2.3 METHODS

The Multiethnic Cohort has been detailed elsewhere.[11,12] Briefly, the Multiethnic Cohort includes over 215,000 members from representative population samples of five ethnic groups: African Americans, Latinos, Japanese Americans, Native Hawaiians and Caucasians in Hawaii and Los Angeles (LA). Ethnicity was self-reported. Participants (aged 45-75 years at recruitment) completed a mailed self-administered questionnaire at baseline in 1993-1996. The 26-page questionnaire included a 17 page QFFQ which was developed specifically for the study population based on 3-day measured food records from approximately 60 men and 60 women from each ethnic group. A minimum list of foods that contributed greater than 85% of the intake of fat, dietary fiber, vitamin A, carotenoids and vitamin C for each ethnic group was identified for inclusion on the QFFQ. Traditional foods of each ethnic group were also included irrespective of their contribution to the diet. The QFFQ includes over 180 items, with eight frequency categories for foods and nine for drinks, and with three portion sizes, many displayed by photograph. Usual dietary intake over the previous 12 months was assessed. The reference portion sizes were derived from the three-day measured dietary records. For analyzing dietary intake data, a food composition table was developed at the Cancer Research Center of Hawaii (CRCH), based largely on USDA data, and supplemented with information from Japan, Canada and the UK, as well as locally analyzed foods. The CRCH food composition table includes a large recipe database and many unique foods consumed by the multiethnic population. Correspondence between fatty acids measured from the questionnaire and multiple 24-hour recalls for the ethnic groups was acceptable in a calibration substudy of over 2000 individuals, with correlations, adjusting for energy intake, ranging from 0.25 to 0.70 for omega 3 fatty acids and from 0.27 to 0.79 for omega 6 fatty acids.[12] For omega-3 fatty acids in men, African-Americans had the highest correlation at 0.55, followed by Caucasians at 0.51, Latinos at 0.40, Native Hawaiians at 0.26, and Japanese at 0.25; for omega-3 fatty acids in women, Caucasians had the highest correlation at 0.70, followed by Japanese at 0.49, Native Hawaiians at 0.36, African-Americans at 0.35, and Latinas at 0.25. For omega-6 fatty acids in men, Latinos had the highest correlation at 0.79, followed by African-Americans at 0.73, Japanese at 0.56, and Caucasians at 0.53, and Native Hawaiians at 0.27; for omega-6 fatty acids in women, Caucasians had the highest correlation at 0.61, followed by Japanese at 0.54, African-Americans at 0.52, Latinas at 0.48, and Native Hawaiians at 0.35.

Individuals with implausible diets were excluded.[13] Individuals of other ethnicities (n=11,381) were excluded as the QFFQ was not designed for these groups. After exclusions, our analysis included 33,349 African Americans, 13,890

Native Hawaiians, 54,890 Japanese Americans, 45,615 Latinos, and 47,554 Caucasians.

Statistical Analysis

Daily intake of omega-3 and omega-6 fatty acids was considered in absolute amount as grams per day and as densities as grams per day per 1,000 calories. The ratio of omega-6 to omega-3 fatty acids was also computed. The ratio variable was set to missing if the value of omega-3 fatty acids was zero. The means for these quantities were estimated by sex and sex-ethnicity using analysis of covariance adjusting for age at cohort entry. The correlation between omega-3 and omega-6 fatty acids was calculated by Spearman's Rho by sex and sex-ethnicity. The percentage contribution to overall omega-3 and omega-6 fatty acid intake was computed for each QFFQ food item, for sex and sex-ethnic groups. The daily grams of each fatty acid were computed for each item for each cohort member. The intake was then summed across people for each item is then divided by the total intake, to obtain the contribution.

2.4 RESULTS

The overall means for daily intake of dietary omega-3 and omega-6 fatty acids are displayed by sex and sex-ethnic group in Table 2.1. In general, men had higher omega-3 and omega-6 fatty acid intake than women, as well as a larger ratio of omega-6 to omega-3 fatty acids. The correlation between the two fatty acids was very high at 0.95 for both men and women. The energy adjusted densities for omega-3 and omega-6 fatty acids were more similar between men and women. Native Hawaiians had the highest dietary omega-3 and omega-6 fatty acid intakes, followed by Latinos, African Americans, Japanese Americans, and Caucasians. However, Native Hawaiians had the lowest ratio of omega-6 to omega-3 fatty acids, followed by Japanese Americans, Latinos, Caucasians, and African Americans. Whereas Native Hawaiian and Japanese men consumed relatively more of their calories from omega-3 than from omega-6 fatty acids, men in other groups consumed relatively more from omega-6 fatty acids. The patterns by ethnic group for women were similar.

Table 2.2 shows the ten major sources for dietary omega-3 fatty acids in men. Overall, regular salad dressings, canned tuna fish, macaroni or potato salad, and mayonnaise in sandwiches were the top 4 contributors in men, and were among the top 10 sources for omega-3 fatty acids for each ethnic group. Macaroni or potato salad and regular salad dressings were the top 2 contributors in all male groups, except among Latinos for whom soybean or corn oil in cooking was a stronger contributor than regular salad dressings. The major omega-3 contributors for African Americans and Caucasian men were similar, although Caucasian men consumed relatively more omega-3 fatty acids from canned tuna fish and African Americans consumed relatively more from fried chicken with skin and chicken wings with skin. Japanese-American (3.7%) and Native Hawaiian (3.5%) men frequently used canola oil in cooking but soybean and corn oil was used more frequently among African-Americans (3.0%) and Latinos (3.7%). All fish items, including canned tuna fish, fried fish, and baked, broiled, and raw fish, accounted for 10.3% of the dietary omega-3 fatty acid intake in Japanese men and 12.3% in Native Hawaiian men, but lower amounts in the other groups. Japanese men consumed the largest relative amount (40%) of their omega-3 fatty acid intake from their top 10 contributors, followed by Native Hawaiians (39%), Caucasians (34%), African Americans (33%), and Latin Americans (27%). Traditional foods were major contributors for Japanese and Latinos. The soy products tofu and miso soup, components of a typical Japanese diet, only appeared in the top ten contributors for Japanese men at 6.1%. Likewise, Mexican or Spanish rice, refined beans, tacos and tostadas, and whole milk appeared only for Latinos.

Table 2.3 shows the ten major sources for dietary omega-3 fatty acids in women. Although women had the same 4 common top sources for omega-3 fatty acids as men, women consumed relatively less of their intake from macaroni and potato salad than men (4.3% versus 5.5%). Women showed similar ethnic differences in fish consumption patterns as the men. Coleslaw contributed about 2% for all women except for Japanese, while this food was only in a major contributor among men for Caucasians. Foods that were among the top 10 sources for women but not men included coleslaw for African Americans, coleslaw and tofu for Native Hawaiians, stir fried chicken with vegetables for Japanese Americans, enchiladas with cheese and coleslaw for Latinas, and low-calorie dressings and baked, broiled, and raw fish for Caucasians. The traditional foods that were important contributors in men were observed for women as well.

Table 2.4 shows the top 10 foods contributing to dietary omega-6 fatty acids in men. Regular salad dressings, macaroni or potato salad, peanuts and other nuts, and canned tuna fish were the top 4 sources for omega-6 fatty acids overall. These foods were the top 4 contributors in Caucasian and Japanese male groups only; soybean and corn oil in cooking was a major contributor for Latinos (where it was the top source), African Americans, and Native Hawaiians; and mayonnaise in sandwiches was a major contributor for Native Hawaiians. The comparison of omega-6 fatty acids sources by ethnic group mirrored the findings for omega-3 fatty acids.

Table 2.5 shows the top 10 foods contributing to dietary omega-6 fatty acids in women. The top 4 sources for women overall were the same as for men. Women, compared to men, consumed relatively more of their omega-6 fatty acid intake from popcorn (3.4% versus 2.4%) and canned tuna fish (4.0% versus 3.7%) and relatively less from eggs. Women showed similar patterns as the men for each ethnic group.

Comparing sources for omega-3 and omega-6 fatty acids, peanuts and other nuts, along with peanut butter added to bread, were top sources for omega-6 fatty acids only. The percentage of total intake accounted for by the top 10 sources was similar for the two polyunsaturated fatty acids at about 30% to 40%.

Traditional foods seem to play an important role in some ethnic foods. Although they may be modest contributors for the overall population, they are among the top contributors for omega-3 and omega-6 fatty acids within ethnic groups. Japanese foods such as tuna fish, tofu, and miso soup were major omega-3 fatty acid contributors for Japanese. Latino foods such as Mexican or Spanish rice and refined beans were major omega-3 fatty acid contributors, and corn tortilla bread was a major omega-6 fatty acid contributor for Latinos. Furthermore, tuna fish, tofu, miso soup, Mexican or Spanish rice, and refined beans were stronger contributors to omega-3 than omega-6 fatty acids.

2.5 DISCUSSION

Our results describe the overall intake and major food sources of omega-3 and omega-6 fatty acid intake in five ethnic groups in Hawaii and California. Japanese Americans had lower intakes of these polyunsaturated fatty acids than other groups, derived a higher percentage of their intake from the top 10 sources, and had the lowest ratio of omega-6 to omega-3 fatty acids. We have shown that traditional Japanese and Latino foods contribute to dietary omega-3 fatty acid intake more than to dietary omega-6 fatty acid intake, while the contribution for typical Western foods to the intake of the fatty acids was similar.

The percentage of the US population from Non-White ethnic backgrounds is increasing. In 2002, about 38 million (13.1%) of the total US population were estimated to be Black, 39 million (13.4%) were estimated to be of Hispanic origin, and 13 million (4.4%) were estimated to be Asians or Pacific Islanders.[14] Our data highlight the need for cardiovascular nutrition interventions involving omega-3 and omega-6 fatty acids to be tailored specifically to each population because of variations in their eating patterns. It has been reported that ethnic minority groups are more likely to participate and continue in interventions based on acceptable traditional foods.[15] Many ethnic minority groups are adopting the prevailing Western diet, which is typically lower in dietary omega-3 fatty acids than many traditional diets. We have illustrated this with our Japanese population, as sources from a traditional Japanese diet, such as tuna fish, tofu, and miso soup, were better contributors to omega-3 fatty acid intake than to omega-6 fatty acid intake. In addition, sources from a traditional Latino diet, including Mexican or Spanish rice and refined beans, were better contributors to omega-3 fatty acid intake. To promote consumption of omega-3 fatty acids, all ethnic groups could be encouraged to add these foods to their diets.

In conclusion, we have provided for the first time comparable data on the food sources of dietary omega-3 and omega-6 fatty acids in a large multiethnic population. These observations will help guide the interpretation of the associations of dietary omega-3 and omega-6 fatty acids and chronic disease risk in the five ethnic groups. Such data are not only valuable for guiding nutrition education programs and interventions, but also for providing a more practical nutrition intervention messages on dietary omega-3 and omega-6 fatty acid intake to protect against cardiovascular diseases.

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Table 2.1. Omega-3 and omega-6 fatty acid intake by sex-ethnic group in the multiethnic cohort, Hawaii and Los Angeles, 1993-1996.

Mean Intake*	All (n=88,218)	Caucasians (n=22,004)	African Americans (n=12,216)	Native Hawaiians (n=6,051)	Japanese Americans (n=25,948)	Latinos (n=21,999)
Men						
ω3 (g/day)	2.1	1.9	2.0	2.5	2.0	2.3
Density of ω3 (g/1000kcal/d)	3.0	2.8	3.2	3.1	3.1	2.9
ω6 (g/day)	18.7	17.5	18.2	21.0	17.1	19.7
Density of ω6 (g/1000kcal/d)	3.1	3.0	3.4	3.0	3.0	3.0
ω6/ω3	8.8	9.0	9.1	8.4	8.5	8.7
Rho between ω3 and ω6**	0.96	0.95	0.97	0.96	0.95	0.97
Women	(n=107,080)	(n=25,550)	(n=21,133)	(n=7,839)	(n=28,942)	(n=23,616)
ω3 (g/day)	1.8	1.5	1.7	2.2	1.7	1.9
Density of ω3 (g/1000kcal/d)	3.1	2.7	3.2	3.3	3.2	2.9
ω6 (g/day)	15.5	13.5	15.7	18.3	14.0	16.3
Density of ω6 (g/1000kcal/d)	3.0	2.8	3.4	3.1	3.0	2.8
ω6/ω3	8.6	8.8	9.0	8.4	8.4	8.6
Rho between ω3 and ω6**	0.95	0.95	0.97	0.96	0.94	0.97

*Aga-adjusted means from ANCOVA
** Spearman’s Rho reflecting the correlation between omega-3 and omega-6 fatty acid intake

Table 2.2. Ten major food sources of omega-3 fatty acid intake for each ethnic group in men

	All		Caucasian		African Americans		Native Hawaiians		Japanese Americans		Latinos	
Food Item	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%
Regular Salad Dressings	1	6.5	1	7.9	2	5.4	2	6.7	1	8.1	3	3.5
Macaroni or Potato Salad	2	5.5	2	5.4	1	6.2	1	7.4	2	5.8	1	4.3
Canned Tunafish	3	4.3	3	4.7	3	3.4	3	5.8	3	5.2	5	2.7
Mayonnaise in Sandwiches	4	3.2	4	4.0	4	3.2	4	4.4	8	2.9	6	2.4
Soybn/Corn Oil in cooking	5	2.8			6	3.0	6	2.6	6	3.0	2	3.7
Canola Oil in cooking	6	2.4	7	1.8			5	3.5	4	3.7		
Cookies/Fruit Bars	7	1.8	5	2.5	10	2.0					9	1.8
Fried Fish	8	1.8					8	2.2	9	2.9		
Fried Chicken (with skin)	9	1.7			5	3.1	10	1.9				
Eggs, Cooked or Raw	10	1.6										
Baked/Broiled/Raw Fish	11	1.5					9	1.9	10	2.2		
Ice Cream	12	1.5	9	1.7	9	2.1						
Coleslaw	13	1.5	8	1.7								
Popcorn	14	1.4	6	2.3	8	2.1						
Tofu	19	1.2							5	3.1		
Other Canned Fish	20	1.2					7	2.4				
Miso Soup	21	1.2							7	3.0		
Whole Milk	22	1.1									8	1.9
Pizza	24	1.1	10	1.7								
Chicken Wings (with skin)	25	1.1			7	2.6						
Mexican or Spanish Rice	30	1.0									4	3.0
Tacos/Tostadas (beef/pork)	36	0.8									10	1.7
Refried Beans	42	0.7									7	2.3
Total contribution from top 10 items				33.6		33.1		38.9		39.8		27.3

Table 2.3. Ten major food sources of omega-3 fatty acid intake for each ethnic group in women

	All		Caucasians		African Americans		Native Hawaiians		Japanese Americans		Latinos	
Food Item	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%
Regular Salad Dressings	1	7.1	1	8.2	1	5.9	1	7.7	1	9.3	2	4.2
Canned Tunafish	2	4.5	2	5.2	3	4.1	2	5.9	2	5.0	4	3.2
Macaroni or Potato Salad	3	4.3	4	3.8	2	5.3	3	5.1	4	3.9	1	4.3
Mayonnaise in Sandwiches	4	3.1	3	4.0	6	2.9	4	4.0	7	3.0	6	2.3
Canola Oil in cooking	5	2.6	9	1.8			5	3.5	3	4.3	8	1.9
Soybn/Corn Oil in cooking	6	2.3			8	2.4	7	2.3	9	2.4	3	3.4
Popcorn	7	2.0	5	2.7	4	3.4						
Coleslaw	8	1.9	8	2.1	9	2.1	8	2.0			9	1.8
Cookies/Fruit Bars	9	1.7	6	2.5								
Low-Calorie Dressings	10	1.5	7	2.2								
Stir-Fried Chicken/Vegs	11	1.5							10	2.2		
Fried Fish	12	1.5					9	1.9	8	2.5		
Stick Margarine on bread	13	1.4			10	2.0						
Baked/Broiled/Raw Fish	14	1.4	10	1.6								
Tofu	15	1.4					10	1.8	5	3.7		
Fried Chicken (with skin)	18	1.2			7	2.7						
Other Canned Fish	20	1.2					6	2.3				
Chicken Wings (with skin)	21	1.2			5	3.3						
Miso Soup	23	1.1							6	3.1		
Mexican or Spanish Rice	29	0.9									5	3.1
Enchiladas with Cheese	46	0.7									7	1.9
Refried Beans	57	0.6									10	1.8
Total contribution from top 10 items				34.1		34.0		36.6		39.4		27.9

Table 2.4. Ten major food sources of omega-6 fatty acid intake for each ethnic group in men

	All		Caucasians		African Americans		Native Hawaiians		Japanese Americans		Latinos	
Food Item	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%
Regular Salad Dressings	1	5.9	1	6.9	3	4.7	2	6.4	1	7.8	4	3.2
Macaroni or Potato Salad	2	5.0	3	4.8	1	5.4	1	7.1	2	5.5	2	3.9
Peanuts and Other Nuts	3	4.6	2	5.3	2	5.1	5	3.9	3	5.1	3	3.3
Canned Tunafish	4	3.7	4	4.0	8	2.8	3	5.2	4	4.7	6	2.3
Soybn/Corn Oil in cooking	5	3.3			4	3.4	6	3.2	5	3.8	1	4.4
Mayonnaise in Sandwiches	6	2.9	6	3.5	9	2.8	4	4.2	7	2.8	7	2.2
Popcorn	7	2.4	5	3.7	5	3.3					10	2.0
Eggs, Cooked or Raw	8	2.1			10	2.2	7	2.3	10	2.1	9	2.0
Chips-Pot./Corn/Tort.	9	2.0	7	2.6								
Fried Chicken (with skin)	10	1.9			7	3.1	9	2.1				
Peanut Butter Added-Bread	11	1.8	9	2.3			8	2.3	8	2.3		
Cookies/Fruit Bars	12	1.8	8	2.4								
Reg Tub Margarine on bread	13	1.7	10	2.0			10	2.0				
Stir-Fried Chicken/Vegs	14	1.6							9	2.2		
Chicken Wings (with skin)	16	1.4			6	3.2						
Tofu	26	1.1							6	2.9		
Mexican or Spanish Rice	35	0.9									5	2.8
Latinos:Corn Tortilla/brd	54	0.5									8	2.1
Total contribution from top 10 items				37.5		36.1		38.7		39.2		28.2

Table 2.5. Ten major food sources of omega-6 fatty acid intake for each ethnic group in women

	All		Caucasians		African Americans		Native Hawaiians		Japanese Americans		Latinos	
Food Item	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	%
Regular Salad Dressings	1	6.5	1	7.4	2	5.1	1	7.3	1	9.0	3	3.8
Macaroni or Potato Salad	2	4.0	6	3.4	3	4.7	3	4.8	4	3.8	2	4.0
Canned Tunafish	3	4.0	3	4.5	6	3.4	2	5.4	2	4.6	5	2.8
Peanuts and Other Nuts	4	3.9	4	4.3	4	4.6	5	3.4	3	4.4	7	2.4
Popcorn	5	3.4	2	4.5	1	5.5	7	2.7			6	2.5
Mayonnaise in Sandwiches	6	2.9	5	3.6	9	2.5	4	3.9	7	2.9	9	2.1
Soybn/Corn Oil in cooking	7	2.8			8	2.7	6	2.9	6	3.0	1	4.1
Reg Tub Margarine on bread	8	1.9	9	2.1			8	2.3				
Stir-Fried Chicken/Vegs	9	1.8					10	1.9	8	2.8		
Chips-Pot./Corn/Tort.	10	1.8	8	2.2								
Cookies/Fruit Bars	11	1.8	7	2.5								
Stick Margarine on bread	14	1.6			10	2.2						
Peanut Butter Added-Bread	15	1.6					9	2.0	9	2.3		
Chicken Wings (with skin)	16	1.5			5	4.1						
Low-Calorie Dressings	17	1.4	10	1.9								
Fried Chicken (with skin)	18	1.3			7	2.8						
Stir-Fried Beef/Pork/Vegs	19	1.3							10	2.1		
Tofu	21	1.2							5	3.5		
Rolls/Buns/Biscuits	22	1.2									10	2.0
Mexican or Spanish Rice	35	0.9									4	2.9
Latinos:Corn Tortilla/brd	61	0.5									8	2.2
Total contribution from top 10 items				36.3		37.5		36.6		38.6		28.8

Chapter 3. Association of Fish and Other Sources of Omega-3 Fatty Acids with Mortality from Coronary Heart Disease: the Multiethnic Cohort

3.1 ABSTRACT

Background: Evidence indicates that omega-3 fatty acid (ω3) intake from fish and other foods reduces the risk of coronary heart disease (CHD). However, little is known regarding whether the food sources of ω3 have different associations with risk. That the ethnic groups of the Multiethnic Cohort (MEC) have varying diets, with different sources of ω3, provides a unique opportunity to study this question.

Methods: We examined associations between consumption of fish, prepared in different ways, and other sources of ω3, such as soy products and vegetable oils, and risk of coronary heart disease (CHD) mortality in 82,243 men and 103,884 women of African-American (AA), Caucasian, Japanese (JA), Native Hawaiian (NH), and Latino descent, aged 45-75 at recruitment, residing in Hawaii and Los Angeles and free of a history of angina or heart attack at cohort entry between 1993 and 1996. We identified deaths due to CHD through the end of 2005 by linkage of the cohort with state and national death files. Using Cox regression with age as the time metric, we calculated relative risks (RRs) of CHD mortality in men and women, overall and by ethnicity, for ω3 sources, adjusting for known risk factors.

Results: There were 4,516 CHD deaths during an average of 11.9 years of follow-up. For men, ω3 intake was inversely associated with overall CHD mortality (5^{th} vs. lowest quintile: RR = 0.77, 95% confidence interval (CI) = 0.60-0.98). For women, the protective effect of ω3 was present, but the trend was not monotonic. The trend was mainly observed in Caucasians, JA, and Latinos. Whereas fried fish intake was positively related to CHD death, baked, boiled or raw fish intake was inversely related to CHD mortality in men. Salted and dried

fish intake was positively related to CHD death, while vegetable oil use (5^{th} vs. lowest quintile: RR = 0.82, 95%CI = 0.74-0.91) and shoyu and tofu intake was inversely associated with CHD mortality in men and women.

<u>Conclusion:</u> The findings suggest a cardioprotective effect of ω3 intake from fish and plant sources. Observed differences by food source may reflect the effects of different preparation methods. Omega-3 sources of fresh fish, soy products, and oil use appeared to be protective, but intake of foods rich in ω3 and nutrients associated with the risk of CHD, such as trans fats and reduced ω3 in fried fish and sodium in salted or dried fish, could be detrimental.

3.2 INTRODUCTION

According to the National Center for Health Statistics, heart disease (mainly coronary heart disease (CHD)) has been the leading cause of death for both women and men in the United States for over 90 years. However, the CHD mortality rates are not uniform among racial and ethnic groups. The age-adjusted death rates for CHD for the largest US ethnic groups in 2004 were, respectively, 193.9 and 130.0 per 100,000 for Latino men and women, 146.5 and 96.1 for Asian and Pacific Islander men and women, 342.1 and 236.5 for African American men and women, and 268.7 and 175.1 for Caucasian men and women.[1] The risk of CHD mortality was found to vary within Asian/Pacific islander groups in Hawaii in 2005, with rates of 135.4 for Native Hawaiians, 66.4 for Chinese, 128.3 for Filipinos, and 66.6 for Japanese.[2] The reasons for these disparities, after accounting for known risk factors, are not fully understood.[3]

Omega-3 fatty acid intake from fish and fish oil supplements has been reported to have a variety of beneficial effects on cardiovascular disease risk in observational studies and clinical studies.[11-18] Results of these studies suggest that omega-3 fatty acid intake is associated with reduced risk of cardiovascular disease, although causality has not been determined. Omega-3 fatty acids may prevent arrhythmias, lower heart rate and blood pressure, decrease platelet aggregation, and lower triglyceride levels by decreasing the production of hepatic triglycerides and increasing the clearance of plasma triglycerides.[9-10] In 2002, the National Institutes of Health’s (NIH) Office of Dietary Supplements (ODS) commissioned the U.S. Agency for Healthcare Research and Quality (AHRQ) to provide evidence-based reports on the role of dietary omega-3 fatty acids in various health conditions and diseases using all available scientific literature up to year 2003. While it was recognized that none of the large trials were conducted in the U.S. population where only about 25% of individuals reported daily fish consumption according to NHANES III data, the review concluded that intake of omega-3 fatty acids reduces cardiovascular diseases but that a definitive trial was needed.[19]

There are differences in the levels of omega-3 fatty acids consumption among ethnic groups. In addition, the contributing food sources vary. Common food sources for all ethnic groups include vegetable oils and canned tuna fish. However, the fish preparation method, such as frying versus baking, varies among ethnic groups. Also, the intake of soy products was a major contributor among Japanese, as were Mexican dishes including beans and tortillas among Latinos. Studying the association of food sources of omega-3 fatty acids and CHD within a multiethnic population with a wide variation in consumption patterns may lead to a better understanding of the protective role of omega-3 fatty acids. In particular, the type of omega-3 fatty acids present varies by food source: fish contains eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), long-chain omega-3 PUFA; and soybeans contain alpha-linolenic acid (ALA), short-chain omega-3 PUFA.[8] Little is known regarding which food source of omega-3 fatty acids or which method of preparation for fish is most beneficial.

The prospective Multiethnic Cohort (MEC) Study was initially established in Hawaii and Los Angeles in 1993 to 1996. Extensive information on diet and other lifestyle factors was collected at study entry. Past research established that known risk factors only partially accounted for the ethnic differences in CVD mortality[3] and that ω-3 was protective against AMI risk in African Americans and Latinos (not yet published). We now use the MEC data to study the food sources of omega-3 fatty acid intake and CHD mortality risk.

3.3 METHODS

Study design

The association of sources of omega-3 fatty acids and the risk of CHD mortality was studied using a prospective design and the MEC data in men and women overall and by ethnic group. The sampling frame for the MEC included adults aged 45-75 in 1993 from the Hawaii and Los Angeles driver's license files, the Hawaii voters registration file and the California Health Care Financing Adminstration (Medicare) files; details are discussed in another report.[20] The cohort consisted of 215,251 men and women of African-American (16.3%), Latino (22.0%), Japanese-American (26.4%), Native Hawaiian (6.5%), Caucasian (22.9%), and other (5.8%) ancestry.[20] At cohort entry, participants completed a 26-page self-administered mail questionnaire that included a 17-page quantitative food frequency questionnaire (1st QFFQ), as well as sections on demographic, medical, and other lifestyle information. For this study, only the 82,243 men and 103,884 women who were from the five major ethnic groups and were free of a history of heart attack and angina at cohort entry were included.

Dietary assessment

The development of the QFFQ was described in the another report.[21] In brief, three-day measured dietary records from 60 men and 60 women of each ethnic group served as the basis for the selection of food items for the QFFQ. A minimum set of food items contributing at least 85% to the intake of nutrients of interest for each ethnic group were selected and complemented by the inclusion of traditional food items that were common in the diet of a particular ethnic group, irrespective of their nutrient contribution. The QFFQ enquires, for the past year, about the usual intake frequency, based on 8-9 categories ranging from 'Never or hardly ever' to '2 or more times a day', and the amount of food consumed, based on a choice of three portion sizes specific for each food item listed on the QFFQ. The reference portion sizes were derived from the three-day measured dietary records.

A food composition database created for the MEC QFFQ was used to convert food intakes into nutrients. The food composition table was developed at the Cancer Research Center of Hawaii (CRCH), based largely on USDA data, and supplemented with information from Japan, Canada, Mexico and the UK, as well as unique locally consumed analyzed foods. Omega-3 fatty acid intake in grams per day was considered in this analysis. The QFFQ was found to adequately measure diet when compared with multiple 24-hour diet recalls collected on over 2,000 MEC participants, evenly distributed by sex-ethnic subgroup in a calibration study[21]; the correlation, adjusted for energy intake, between instruments for omega-3 fatty acid intake ranged from 0.25 to 0.70 for the 10 sex-ethnic groups. For men, African-Americans had the highest correlation at 0.55, followed by Caucasians at 0.51, Latinos at 0.40, Native Hawaiians at 0.26, and Japanese at 0.25; for women, Caucasians had the highest correlation at 0.70, followed by Japanese at 0.49, Native Hawaiians at 0.36, African-Americans at 0.35, and Latinas at 0.25. Daily grams of food groups were computed by summing relevant food items and portions of recipes. The following food groups were found to be major contributors to omega-3 fatty acid intake in at least one ethnic group and are included in this analysis: fish (excluding shellfish) in total and by type: canned fish, baked, boiled, and raw fish, fried fish, dried and salted fish; legumes, tofu, and shoyu; and vegetable oils in cooking, regular salad dressing, macaroni or potato salad, mayonnaise in sandwiches; and Mexican dishes.

Case Ascertainment

Deaths are ascertained annually by linkage between the MEC participants to the state death files for Hawaii and California. Cohort members who have moved out of these areas are linked to the National Death Index file periodically. The vital status was ascertained through December 31, 2005 for this analysis, resulting in 4,516 CHD deaths during an average of 11.9 years of follow-up. The underlying cause of death was obtained from the death certificate. Coronary heart disease deaths included deaths with ICD9 codes of 410 to 414 or ICD10 codes of I20-I25.9 for acute myocardial infarction, ischemic heart disease, and angina pectoris; and ICD9 codes of 425 to 429 or ICD10 codes of I30-I51.9 for cardiomyopathy, unspecified cardiovascular disease, cardiomegaly, congestive heart failure, myocardial degeneration, and myocarditis.

Statistical analysis

We used Cox regression (proportional hazards model), with age as the time metric, to calculate relative risks (RR) and 95% confidence intervals (95% CI) of CHD mortality, overall and among subgroups defined by sex and ethnicity. Follow-up began at the date of cohort entry, defined as questionnaire completion or as the date when the participant turned 45 years old (for the few individuals younger than 45 when they completed the baseline questionnaire) and ended at the earliest of the date of death, or December 31st 2005, the closure date for the study. Only individuals whose cause of death was CHD as defined above were counted as events; all other deaths were censored. To ensure that the strong risk factor of smoking was adjusted for, a base model for smoking was developed. We started with the extensive model built for lung cancer in the MEC[22] and used the likelihood ratio test to determine the most parsimonious model needed for CHD death. The final smoking model included indicator variables for smoking status (never, former, current) and a continuous variable for pack-years at baseline. Other adjustment variables included ethnicity (when appropriate), body mass index (weight in kg / height in m^2), log transformed daily energy intake, hypertension history, diabetes history, daily alcohol consumption, amount of vigorous physical activity (hours per day), educational level, percent of energy from saturated fat, and for women, type and age at menopause and hormone replacement therapy use. The risk factors of interest included omega-3 fatty acid intake and its food sources. Indicator variables were created to represent the quantiles, using the lowest quantile as reference. Quintiles were generally used, although quartiles, tertiles, or binary variables were used when appropriate. Dose-response was tested by inclusion of a trend variable, assigned the median value for the appropriate quantiles within sex and ethnicity groups. Interactions were tested by likelihood ratio tests comparing models with cross-product terms between ethnicity and the risk factor of interest and main effects models.

3.4 RESULTS

CHD mortality rates and means for the risk factors of interest are presented by ethnic group for men and women in Table 3.1. African American men had the highest CHD mortality rate, whereas Japanese American men had the lowest CHD death rate. Women had a lower CHD mortality rates as compared to men overall and for each ethnic group. For both men and women, Native Hawaiians and Japanese Americans had higher intakes of fish (total and type-specific), oils use in cooking, and tofu than other ethnic groups. Interestingly, the means for omega-3 fatty acid intake were similar among ethnic groups, although slightly higher for Native Hawaiian.

The relative risk for CHD mortality and 95% confidence intervals from omega-3 fatty acids and its sources are displayed in Table 3.2 for men by ethnicity. Omega-3 fatty acid intake had a dose-response inverse association with CHD mortality (5^{th} vs. lowest quintile: RR = 0.77, 95%CI = 0.60-0.98), after adjustment for known CHD risk factors as shown in Figure 1; however, the trend variable was not significant (p=0.15). This association was not consistent across ethnic groups (p for interaction=0.017). The trend was mainly observed in JA (5^{th} vs. lowest quintile: RR = 0.60, 95%CI = 0.35-1.01) and Latinos (5^{th} vs. lowest quintile: RR = 0.61, 95%CI = 0.37-1.00). A risk reduction was also found among Caucasian but was not statistically significant. No trend was observed for total fish or canned fish overall; however, the association for canned tuna fish was not consistent across ethnic groups (p for interaction=0.0015). Canned fish intake was positively related to CHD death for Japanese men and inversely related to CHD death for African American men.

The relative risks of CHD mortality and 95% confidence intervals for women by ethnicity are displayed in Table 3.3. Omega-3 fatty acid intake in the second, third and fourth quintiles were inversely associated with CHD mortality, but the RR for the fifth quintile was null, making the trend not monotonic. Interactions between omega-3 fatty acids and ethnicity existed in women as well (p=0.039), with a suggestion of a protective effect in Caucasians and Japanese.

Similar to men, no trend was observed for total fish or canned fish overall; however, the association for total fish intake was not consistent across ethnic groups (p for interaction=0.027), with a suggested inverse association in Caucasian women and a positive association in Latinas.

There are observed differences in fish preparation methods overall and by sex in Table 3.4. Baked, boiled, and raw fish intake was inversely related to CHD death with RR of 0.90 (95% CI=0.82-0.99) as compared to non-consumers in men with a p of 0.15 for interaction by sex. When using tertile indicators in the model, a clear inverse trend with the p-value for trend of 0.02 was observed in Caucasian men who baked and boiled their fish. Salted or dried fish consumption was positively related to CHD mortality with an RR of 1.15 and a p-value of 0.021 for men and women combined.

The relative risks of CHD for vegetable oil used in cooking and fried fish are displayed in Table 3.5. Although there was not a significant interaction between ethnicity and fried fish intake, fried fish appeared to be a protective factor for Japanese with a p of 0.088 for the interaction of Japanese versus non-Japanese. When excluding Japanese who often used stir frying rather than deep frying, greater than 6 grams of fried fish intake per day resulted in a 12% (95%CI=1.01-1.23) higher risk of dying from CHD. Vegetable oil use in cooking demonstrates a clear inverse dose-response relationship with CHD risk with a p-value for trend of 0.0002. The 5^{th} quintile of oil use was inversely related to CHD death as compared to the first quintile with an RR of 0.82 (0.74-0.91). No differences in effect were observed across ethnic groups.

The association of soy product intake and CHD death is shown in Table 3.6. Tofu intake was inversely related to CHD death for the 2^{nd} to the 5^{th} quintiles as compared to the lowest quintiles for both sexes and all ethnic groups. There were no differences in effect for tofu intake by ethnicity. However, tofu had a relatively stronger protective trend in women than in men with the RR of 0.71

(95%CI=0.56-0.91) for the highest quintile as compared to the lowest quintile, and the p-value for the interaction of tofu intake and sex was 0.033. Surprisingly, shoyu or teriyaki sauce added at the table seemed protective against the risk of CHD mortality. For women, the 3rd tertile of shoyu intake had an RR of 0.84 (95%CI=0.72-1.00) compared to non-users with a p-value for trend of 0.017. The inverse trend with CHD death was consistently seen for Caucasian, Native Hawaiian, Japanese, and Latino women (data not shown).

We examined the role of other omega-3 fatty acid food sources, such as mayonnaise, fried chicken with skin, and Latino foods including legumes and tortillas. No clear associations were found for mayonnaise use, fried chicken with skin, and legumes. Latino dishes with tortillas was found to be positively associated with risk of CHD with an RR of 1.11 (95%CI=1.01-1.22) at the 3rd tertile as compared with non-eaters.

3.5 DISCUSSION

Dietary omega-3 fatty acids demonstrated a protective effect against CHD death that varied by sex and ethnicity. Among men, omega-3 fatty acid intake had a dose-response relationship with risk after adjusting for known CHD risk factors. The trend for women was not as clear as for men. However, for men and women combined, the result confirmed that total dietary omega-3 fatty acids have an overall protective effect as reported in other literature.[11-18]

The inverse association of omega-3 fatty acid intake and CHD death was apparent in JA, Latinos and Caucasian men as well as in Caucasian and Japanese women. The protective effect appeared stronger for Japanese than Caucasians. This result suggests that either genetic variations are differentially affecting omega-3 fatty acids metabolism or that the food sources contributing omega-3 fatty acids for Japanese confer a stronger cardioprotective effect.[23,24]

Although our data did not show that total fish consumption was beneficial to CHD mortality, this result is consistent with the Physician's Health Study, a cohort with 4 years of follow-up on 21,185 US male physicians, that reported an RR for myocardial infarction death of 1.2 (95% CI=0.6-2.2) for at least 5 fish meals/week using < 1 meal/week as the referent group, with a p for trend of 0.34.[22] In the present study, ethnic differences were found for fish intake among women, where a positive association was found among Latinas, with an RR of 1.67 (95% CI 1.0-2.7) for the highest compared to the lowest quintile.

We observed different associations with CHD death by type and preparation method of fish. The association with canned fish varied by ethnicity for men, with a suggested protective effect in Japanese men and a suggested deleterious effect in African Americans. Perhaps the choices of type of canned fish and the ways canned fish were consumed differed among these ethnic groups. Baked, boiled, and raw fish had an inverse relation in men whereas fried fish had a positive relation to CHD mortality, suggesting that the preparation methods may greatly affect the fatty acids composition in fish. Frying can often markedly increase the ratio of omega-6 to omega-3 fatty acids that has been shown to be a positive risk factor.[25] Furthermore, negative health effects from trans-fatty acids and lipid oxidation products in the frying fats and oils[26-28] may increase cardiovascular risk[29,30] by raising levels of LDL cholesterol and lowering levels of HDL cholesterol.[31] The population-based prospective Cardiovascular Health Study with 3,910 members and an average of 9.3 years of follow-up reported an RR for ischemic heart disease death of 0.47 (95% CI=0.27-0.82) associated with at least 3 tuna and other broiled or baked fish meals/week using < 1 meal/month as the reference group, with a p for trend of 0.002, after adjusting for known risk factors. But in the same study, fried fish and fish burger consumption had trends toward higher risk.[30] Interestingly, fried fish was inversely related to CHD risk for Japanese in our study. A review of the 24-hour recall data from the MEC revealed that Japanese often stir fried fish while other ethnic groups mostly deep fried fish. Pan frying or stir frying may have introduced less trans-fats by using a lower temperature as compared to deep frying and therefore may be viewed as a more protective preparation method like baking or boiling.

Salted or dried fish consumption was found to be related to an increased risk of CHD death in our study. Each serving of salted or dried fish contains at least 60% of the daily recommended intake of salt intake, and therefore, its effect may be mediated through hypertension caused by the high sodium content.[32] Substantial evidence indicates that at least 3-4 grams per day of omega-3 fatty acid intake can reduce blood pressure but the relationship between blood pressure and salt use is likely to be much stronger.[33]

The protective effects of soy products such as tofu[34,35] on CHD mortality, as well as their stronger protective role in women than in men[36,37], that were found in our study were consistent with other observational studies. In the Seven Countries Study including 12,763 middle-aged men belonging to 16 cohorts in seven countries (USA, Finland, The Netherlands, Italy, former Yugoslavia, Greece and Japan) who entered the cohort study between 1958 and 1964, significant negative correlation coefficients were shown for legumes (R = 0.822) with CHD death rates.[35] The Japan Public Health Center-based (JPHC) study cohort I followed 40,462 Japanese, initially free of cardiovascular disease, from 1990-1992 until 2002. An RR of 0.31 (95%CI=0.13 to 0.74) was reported among women for cardiovascular disease mortality associated with soy intake of at least 5 times per week versus 0 to 2 times per week; however, no significant association of dietary intake of soy products, miso soup, beans or isoflavones with cardiovascular mortality was found in men.[37]

The phytoestrogen content of shoyu and tofu might be a reason that tofu and shoyu had a stronger cardioprotective effect in women than men, possibly because women benefited more from the estrogenic effects of soy than men.[38] Shoyu is a unique product containing plant omega-3 fatty acids, salt, and other active ingredients such as phytoestrogens. Adding shoyu at the table increases omega-3 fatty acid intake but also increases salt intake that is associated with risk for hypertension. The different effects from salt and phytoestrogen components might explain the sex differences in the association between shoyu and CHD mortality. However, as shoyu use is correlated to healthy behaviors, such as maintaining a BMI lower than 25 and engaging in moderate and vigorous physical activities, shoyu use may be an indicator reflecting health consciousness.

It has been proposed that alpha-linolenic acids (ALA), the plant omega-3 fatty acids, have a similar mechanism related to CVD risk as long-chain fatty acids.[39-41] A prospective, randomized single-blinded secondary prevention trial with a mean follow up of 27 months comparing a Mediterranean alpha-linolenic acid-rich diet (n=302) to the usual post-infarct prudent diet (n=303) found an RR for the composite endpoint of cardiac death and non-fatal myocardial infarction of 0.27 (95% CI 0.12-0.59, p = 0.001) after adjustment for prognostic variables.[40] In another more recent randomized trial of 1,000 patients with angina pectoris, myocardial infarction, or surrogate risk factors for coronary artery disease in India, 499 patients were allocated to a Mediterranean style diet rich in alpha-linolenic acid and 501 controls to a prudent diet. Total cardiac endpoints were significantly fewer in the intervention group as compared to the control group (39 versus 76 events, p<0.001), with a corresponding reduction in serum cholesterol.[41] The strong protective effect for vegetable oil use in cooking that we observed across ethnicities supports the hypothesis of a protective effect for ALAs, as vegetable oils are major sources for ALA and omega-3 fatty acids in our cohort. For the U.S. population with low fish consumptions, vegetable oils used in cooking may provide an alternative food source of omega-3 fatty acids for cardiovascular disease prevention.

There are strengths and limitations of our study that need to be considered. The strengths include the large number of CHD events and the representative samples across major ethnic groups in the U.S. Limitations include that although we focused on omega-3 fatty acid intake, its strong correlation with omega-6 intake makes it difficult to separate their effects. Also, omega-3 fatty acid intake may have been underestimated. First, only exposure data at baseline was considered, and the baseline collection was almost one decade before the AHA recommendations for omega-3 fatty acid consumption.[42-44] Second, fish oil supplement use was not collected in the baseline QFFQ. However, data from a repeat QFFQ administered from 2003 to 2008 found that 15% of individuals reported omega-3 supplement use. This underestimation is likely to attenuate the association between CHD mortality and omega-3 fatty acid intake.

In conclusion, our findings provide evidence for a protective effect for CHD mortality of total dietary omega-3 fatty acid intake from fish and other sources that varies by sex and ethnicity. The ethnic differences may be due to variations in sample sizes, sources of omega-3 fatty acids, methods of fish preparation, or genetic susceptibility. Baked or boiled fish intake was associated with a lower risk of coronary heart disease mortality, while fried, salted or dried fish intake was positively associated. These opposite effects resulted in an overall null effect for total fish intake. Intake of vegetable oils, shoyu, and tofu was inversely related to risk. The soy products that contain plant omega-3 fatty acids and isoflavones may have a stronger protective effect for women than fish sources. Additional studies on plant sources need to be done to confirm these results and to clarify their possible mechanisms.

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Table 3.1. Risk of CHD Death and Intake of Food Sources of Omega-3 Fatty Acids at Baseline by Sex

Men	All (n=82,243)	Caucasian (n=20,568)	African American (n=11,151)	Native Hawaiian (n=5,658)	Japanese American (n=24,389)	Latinos (n=20,477)
CHD death (rate*)	2,604 (348.9)	561 (343.9)	659 (541.3)	191 (506.6)	526 (228.6)	667 (386.2)
Mean (g/d)						
Total fish	20.7	19.2	15.6	35.8	27.9	12.1
Canned fish	9.4	9.4	8.0	17.8	15.4	6.0
Canned tuna	7.6	8.2	5.9	13.2	8.9	5.0
Tofu	8.7	4.2	0.5	12.7	21.9	0.6
Shoyu use	2.4	1.6	0.5	4.9	4.9	0.6
Fried fish	4.9	3.2	3.9	7.5	7.7	3.1
Baked, boiled, raw fish	6.2	6.5	3.7	10.0	9.1	2.9
Salted, dried fish	0.1	0	0	0.5	0.3	0
Omega-3 Fatty Acids	2.1	2	2	2.5	2	2.3
Oils in cooking	2.4	1.7	1.9	3.5	2.7	2.5
Women	**All (n=103,884)**	**Caucasian (n=25,224)**	**African American (n=19,475)**	**Native Hawaiian (n=7,630)**	**Japanese American (n=28,989)**	**Latinos (n=22,566)**
CHD death (rate*)	1,912 (201.9)	340 (156.2)	774 (366.2)	136 (311.3)	295 (106.0)	367 (212.6)
Mean (g/d)						
Total fish	16.5	14.6	14.4	28.8	21.2	10.4
Canned fish	8.3	7.9	7.9	15.3	8.9	5.9
Canned tuna	6.8	6.9	6.1	11.5	7.3	5.2
Tofu	8.4	3.5	0.5	14.4	22.1	0.7
Shoyu use	1.8	1.0	0.3	3.7	3.9	0.6
Fried fish	3.4	1.7	2.9	5.6	5.5	2.1
Baked, boiled, raw fish	4.8	5.0	3.6	7.6	6.6	2.4
Salted, dried fish	0.1	0	0	0.3	0.2	0
Omega-3 Fatty Acids	1.7	1.5	1.7	2.2	1.7	1.9
Oils in cooking	1.8	1.2	1.4	2.8	2.2	2.1

* Age-adjusted rate using the US 2000 standard population

Table 3.2. Relative Risks (95% CI) of CHD Mortality and Omega-3 Fatty Acids and Fish Intake among Men in the Multiethnic Cohort Study, 1993-2005

	All (n=70,837)	Caucasian (n=18,376)	African American (n=9,056)	Native Hawaiian (n=5,073)	Japanese American (n=2,1953)	Latinos (n=16,379)
CHD Deaths	2,198	492	516	171	466	553
Omega-3 Fatty Acids (g/day)						
-< 1.1	1.00	1.00	1.00	1.00	1.00	1.00
1.1 <- 1.4	0.86 (0.74-1.00)	0.95 (0.68-1.31)	0.87 (0.64-1.19)	1.14 (0.59-2.20)	0.93 (0.67-1.30)	0.72 (0.53-0.97)
1.4 <- 1.9	0.80 (0.68-0.95)	0.96 (0.67-1.36)	0.80 (0.56-1.16)	1.16 (0.59-2.29)	0.80 (0.56-1.15)	0.60 (0.43-0.86)
1.9 <- 2.6	0.75 (0.62-0.91)	0.78 (0.51-1.18)	0.85 (0.56-1.28)	1.28 (0.61-2.68)	0.68 (0.45-1.02)	0.63 (0.43-0.93)
> 2.6	0.77 (0.60-0.98)	0.82 (0.49-1.38)	1.10 (0.66-1.84)	1.20 (0.49-2.94)	0.60 (0.35-1.01)	0.61 (0.37-1.00)
p for trend	0.15	0.39	0.19	0.89	0.032	0.39
p for interaction with ethnicity	0.017					
Canned Tuna Fish (g/day)						
0	1.00	1.00	1.00	1.00	1.00	1.00
0<-3.0	0.97 (0.86-1.08)	0.93 (0.73-1.19)	0.88 (0.70-1.12)	0.97 (0.58-1.62)	0.81 (0.62-1.06)	1.18 (0.96-1.44)
3.0<-7.4	1.00 (0.89-1.12)	0.85 (0.67-1.09)	1.24 (0.98-1.57)	0.85 (0.51-1.39)	0.85 (0.65-1.10)	1.03 (0.81-1.30)
>7.4	1.00 (0.88-1.14)	1.09 (0.84-1.42)	1.43 (1.09-1.86)	0.95 (0.58-1.56)	0.74 (0.55-0.98)	0.80 (0.59-1.08)
p for trend	0.79	0.64	0.0005	0.96	0.082	0.12
p for interaction with ethnicity	0.0015					
Other Canned Fish						
Non-Consumers	1.00	1.00	1.00	1.00	1.00	1.00
Consumers	1.03 (0.94-1.12)	0.97 (0.80-1.19)	1.18 (0.99-1.41)	1.13 (0.81-1.57)	0.80 (0.67-0.97)	1.14 (0.94-1.39)
p-value	0.59	0.80	0.066	0.48	0.024	0.18
p for interaction with ethnicity	0.91					
Total Fish Excluding Shell Fish (g/day)						
-< 4.7	1.00	1.00	1.00	1.00	1.00	1.00
4.7 <- 9.6	0.97 (0.84-1.11)	0.90 (0.68-1.19)	0.91 (0.69-1.20)	1.13 (0.54-2.33)	0.90 (0.60-1.35)	1.05 (0.84-1.32)
9.6 <-15.9	1.04 (0.91-1.20)	1.01 (0.77-1.33)	1.22 (0.93-1.60)	1.03 (0.51-2.08)	0.84 (0.57-1.24)	1.04 (0.81-1.34)
15.9 <-27.0	1.01 (0.88-1.16)	0.88 (0.66-1.17)	1.22 (0.91-1.62)	0.84 (0.42-1.67)	0.93 (0.64-1.34)	1.01 (0.76-1.34)
> 27.0	1.04 (0.89-1.20)	0.92 (0.67-1.24)	1.47 (1.08-1.99)	1.00 (0.51-1.98)	0.76 (0.51-1.11)	1.19 (0.87-1.63)
p for trend	0.58	0.60	0.0034	0.97	0.14	0.35
p for interaction with ethnicity	0.32					

Table 3.3. Relative Risks (95% CI) of CHD Mortality and Omega-3 Fatty Acids and Fish Intake among Women in the Multiethnic Cohort Study, 1993-2005

	All (n=86,266)	Caucasian (n=21,950)	African American (n=15,324)	Native Hawaiian (n=6,593)	Japanese American (n=25,542)	Latinos (n=16,857)
CHD Deaths	1,491	297	573	100	240	281
Omega-3 Fatty Acids (g/day)						
-< 1.1	1.00	1.00	1.00	1.00	1.00	1.00
1.1 <- 1.4	0.74 (0.63-0.88)	0.90 (0.64-1.27)	0.65 (0.49-0.87)	1.18 (0.56-2.51)	0.69 (0.47-1.04)	0.72 (0.47-1.10)
1.4 <- 1.9	0.85 (0.70-1.04)	0.92 (0.60-1.40)	0.85 (0.61-1.17)	1.00 (0.44-2.29)	0.72 (0.45-1.16)	0.97 (0.60-1.56)
1.9 <- 2.6	0.79 (0.62-0.99)	0.67 (0.40-1.13)	0.82 (0.55-1.20)	0.85 (0.33-2.15)	0.55 (0.30-0.99)	1.36 (0.79-2.35)
> 2.6	0.94 (0.70-1.27)	0.56 (0.27-1.18)	1.06 (0.66-1.71)	1.10 (0.35-3.48)	0.86 (0.41-1.81)	1.34 (0.65-2.76)
p for trend	0.35	0.080	0.10	0.88	0.93	0.096
p for interaction with ethnicity	0.039					
Canned Tuna Fish (g/day)						
0	1.00	1.00	1.00	1.00	1.00	1.00
0 <- 3.0	0.95 (0.82-1.09)	0.96 (0.70-1.30)	0.81 (0.65-1.01)	1.29 (0.60-2.77)	1.17 (0.79-1.73)	1.05 (0.78-1.41)
3.0 <- 7.4	0.97 (0.84-1.12)	0.86 (0.63-1.19)	0.95 (0.76-1.18)	1.59 (0.77-3.28)	1.01 (0.68-1.51)	1.07 (0.77-1.50)
> 7.4	0.95 (0.80-1.12)	0.96 (0.66-1.39)	0.79 (0.60-1.04)	1.18 (0.55-2.52)	0.97 (0.61-1.54)	1.41 (0.97-2.06)
p for trend	0.28	0.69	0.20	0.97	0.51	0.066
p for interaction with ethnicity	0.32					
Other Canned Fish						
Non-Consumers	1.00	1.00	1.00	1.00	1.00	1.00
Consumers	1.05 (0.94-1.18)	1.17 (0.90-1.51)	1.02 (0.86-1.21)	1.06 (0.69-1.63)	1.02 (0.78-1.33)	1.17 (0.85-1.61)
p-value	0.36	0.25	0.81	0.79	0.91	0.34
p for interaction with ethnicity	0.37					
Total Fish Excluding Shell Fish (g/day)						
-< 2.1	1.00	1.00	1.00	1.00	1.00	1.00
2.1 <- 7.1	1.06 (0.91-1.23)	0.82 (0.60-1.12)	1.02 (0.80-1.31)	2.74 (0.91-8.23)	1.30 (0.80-2.12)	1.20 (0.88-1.62)
7.1 <- 12.4	1.09 (0.93-1.28)	0.90 (0.65-1.25)	1.06 (0.82-1.37)	2.33 (0.78-7.00)	1.23 (0.76-2.01)	1.45 (1.00-2.10)
12.4 <- 20.4	1.06 (0.89-1.26)	0.80 (0.55-1.18)	1.03 (0.78-1.36)	2.37 (0.80-7.05)	1.09 (0.66-1.81)	1.68 (1.11-2.54)
> 20.4	1.04 (0.86-1.26)	0.76 (0.48-1.18)	1.01 (0.75-1.37)	2.58 (0.85-7.77)	0.95 (0.55-1.65)	1.67 (1.04-2.68)
p for trend	0.67	0.39	0.98	0.49	0.34	0.0070
p for interaction with ethnicity	0.027					

Table 3.4. Relative Risks (95% CIs) of CHD Mortality and Selected Fish Preparation Methods, Men and Women

	All (n=157,103)	Men (n=70,837)	Women (n=86,266)
Baked, Boiled, Raw Fish (g/d)			
Non-Consumers	1.00	1.00	1.00
Consumers	0.96 (0.89-1.03)	0.90 (0.82-0.99)	1.04 (0.93-1.16)
p for interaction with ethnicity	0.28	0.28	0.43
Salted or Dried Fish			
Non-Consumers	1.00	1.00	1.00
Consumers	1.15 (1.02-1.29)	1.08 (0.94-1.25)	1.26 (1.03-1.55)
p for interaction with ethnicity	0.30	0.52	0.26

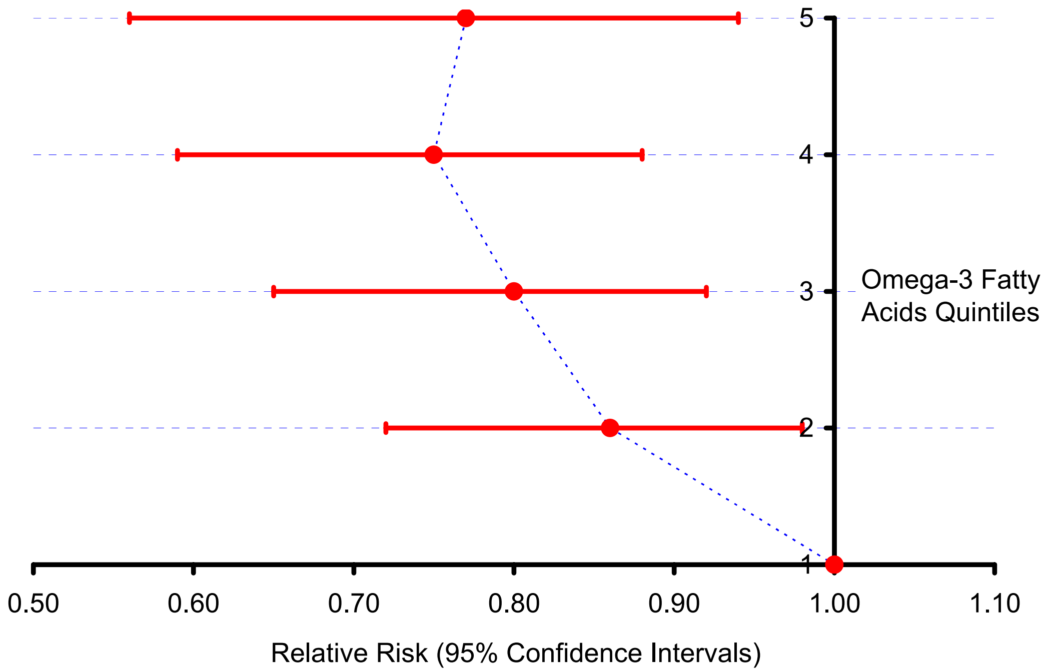
Table 3.5. Relative Risks (95% CI) of CHD Mortality and Oil Use in Cooking by Ethnicity, Men and Women Combined

	All (n=157,103)	Caucasian (n=40,326)	African American (n=24,380)	Native Hawaiian (n=11,666)	Japanese American (n=47,495)	Latinos (n=33,236)
Fried Fish (g/day)						
0	1.00	1.00	1.00	1.00	1.00	1.00
0 <- 6.2	1.01 (0.93-1.09)	0.98 (0.83-1.16)	1.02 (0.88-1.18)	1.18 (0.85-1.62)	0.85 (0.69-1.04)	1.11 (0.95-1.29)
>6.2	1.06 (0.97-1.16)	0.97 (0.79-1.19)	1.22 (1.04-1.42)	1.10 (0.79-1.54)	0.85 (0.69-1.04)	1.23 (1.00-1.51)
p for trend	0.16	0.64	0.018	0.78	0.33	0.081
p for interaction with ethnicity	0.52					
Vegetable Oils in Cooking (g/day)						
0	1.00	1.00	1.00	1.00	1.00	1.00
0 <- 0.5	0.99 (0.90-1.10)	0.84 (0.67-1.05)	1.04 (0.87-1.24)	0.80 (0.49-1.32)	1.07 (0.82-1.40)	1.08 (0.88-1.33)
0.5 <- 1.2	0.88 (0.80-0.97)	0.91 (0.75-1.10)	0.96 (0.80-1.14)	0.85 (0.56-1.29)	0.75 (0.58-0.97)	0.92 (0.74-1.13)
1.2 <- 3.7	0.85 (0.76-0.94)	0.73 (0.59-0.91)	0.85 (0.70-1.03)	0.93 (0.62-1.42)	0.82 (0.64-1.06)	0.93 (0.75-1.15)
> 3.7	0.82 (0.74-0.91)	0.73 (0.58-0.93)	0.93 (0.76-1.14)	0.95 (0.63-1.41)	0.76 (0.58-0.99)	0.82 (0.67-1.01)
p for trend	0.0002	0.0063	0.24	0.68	0.077	0.030
p for interaction with ethnicity	0.51					

Table 3.6. Relative Risks (95% CI) of CHD Mortality and Tofu or Shoyu Use by Sex

Shoyu (g/d)	Men	Women	Tofu (g/d)	Men	Women
0	1.00	1.00	-< 0.4	1.00	1.00
0<-1.1	0.90 (0.80-1.01)	0.96 (0.85-1.10)	0.4 <-1.7	0.84 (0.74-0.95)	0.88 (0.76-1.01)
>1.1	0.99 (0.88-1.11)	0.84 (0.72-1.00)	1.7 <-5.3	0.82 (0.72-0.94)	0.79 (0.67-0.92)
			5.3 <-14.9	0.87 (0.74-1.02)	0.88 (0.72-1.08)
			> 14.9	0.85 (0.71-1.02)	0.71 (0.56-0.91)
p for trend	0.31	0.13		0.54	0.017
p for interaction with ethnicity	0.15	0.28		0.52	0.78

Figure 3.1. Relative Risks of CHD Mortality with Omega-3 Fatty Acids in Men



Chapter 4. Association of Fish and Other Sources of Omega-3 Fatty Acids with Stroke Mortality: the Multiethnic Cohort Study

4.1 ABSTRACT

Background: Fish and other sources for omega-3 fatty acids (ω3) have been found to be protective against cardiovascular disease (CVD) in some studies. However, Japanese, whose diets are rich in these components, have a relatively low heart disease rate but a high stroke incidence compared to other ethnic groups. Comparing the effects of ω3 on risk of CVD by ethnic group provides a unique opportunity to try to uncover more information on mechanisms.

Methods: We used the Multiethnic Cohort to examine the relationship of ω3 and its food sources to the risk of stroke mortality, overall and by subtype, among African-Americans, Caucasians, Japanese, Native Hawaiians, and Latinos. We included deaths through the end of 2005 in 89,052 men and 109,090 women aged 45-75, residing in Hawaii and Los Angeles and with no history of stroke at recruitment between 1993 and 1996. Using Cox regression with age as the time metric, we calculated relative risks (RRs) of stroke mortality, overall and by sex and ethnicity, for the intake of total dietary ω3 fatty acids, fish, vegetable oils, and soy products, as well as by methods of preparation for fish, adjusting for known risk factors.

Results: There were 1,789 cerebrovascular deaths during an average of 11.9 years of follow-up. For men and women combined, intake of total dietary ω3 was inversely associated with stroke mortality (4^{th} vs. lowest quintile: RR=0.74, 95%CI=0.58-0.94), as was intake of canned tuna fish (4^{th} vs. lowest quartile: RR=0.84, 95%CI=0.71-0.99) and vegetable oils in cooking (4^{th} vs. lowest quintile: RR=0.81, 95%CI=0.69-0.95). Intake of baked, boiled and raw fish was inversely

related to stroke deaths in non-Japanese (3rd vs. lowest tertile overall: RR=0.84, 95%CI=0.72-0.97), and the ethnic interaction between Japanese men and others was significant at a p-value of 0.0014. Salted and dried fish intake was positively associated with hemorrhagic but not ischemic stroke mortality (consumers vs. non-consumers: RR=1.41, 95%CI=1.06-1.87). Among men, although no effect from total fish consumption was observed, fried fish (consumers vs. non-consumers: RR=1.18, 95%CI=1.00-1.38) and legume intake (5th vs. lowest quintile: RR=1.34, 95%CI=1.01-1.78) were positively associated with stroke risk. Among women, total fish consumption (4th vs. lowest quintile: RR=0.75, 95%CI=0.58-0.98) was inversely associated with stroke death, as was legume intake, but only in postmenopausal women (3rd vs. lowest quintile: RR=0.68, 95%CI=0.49-0.95).

Conclusions: These findings suggest that dietary ω3 from fish and plant sources may be protective against mortality from stroke. Consumption of fish with high salt content was related to a higher risk of stroke, especially hemorrhagic stroke. The difference in the association of baked, boiled or raw fish consumption between Japanese and others requires more study. It could be that Japanese do not exhibit the protective effect because they more often choose fish, such as sashimi, to which they add salt or shoyu. Reasons for possible sex differences in the effects of legume intake require further study.

4.2 INTRODUCTION

The coronary heart disease (CHD) and stroke mortality rates are not uniform among racial and ethnic groups. On one hand, the age-adjusted death rates for CHD for the largest US ethnic groups were, respectively, 193.9 and 130.0 per 100,000 for Latino men and women, 146.5 and 96.1 for Asian and Pacific Islander men and women, 342.1 and 236.5 for African American men and women, and 268.7 and 175.1 for Caucasian men and women in 2004.[1] On the other hand, the age-adjusted death rates for stroke were, respectively, 15.0 and

17.9 per 100,000 for Latino men and women, 24.3 and 27.0 for Asian and Pacific Islander men and women, 41.5 and 51.9 for African American men and women, and 41.8 and 65.3 for Caucasian men and women in 2004.[1] Asian and Pacific Islanders had a lower incidence of CHD death but a higher incidence of stroke death than Latinos. The rate of CHD mortality in Japan is about half that in the United States, while the rate of stroke death is double in Japan. Japanese-American men experience lower stroke incidence than men in Japan, but higher than other ethnic groups in Hawaii.[4,5,10-13] The reasons for these disparities, after accounting for known risk factors, are not fully understood.[2] This suggests that certain environmental factors may be protective for CHD but not for stroke.

Omega-3 fatty acids from fish and fish oil supplements and plant sources have been reported to have a variety of beneficial effects on heart disease, stroke, and hypertension in observational studies and clinical studies.[2-9] Omega-3 fatty acids may prevent arrhythmias, lower heart rate and blood pressure, decrease platelet aggregation, and lower triglyceride levels by decreasing the production of hepatic triglycerides and increasing the clearance of plasma triglycerides.[8-10] The level of intake of omega-3 fatty acids and its food sources vary across ethnic groups, making it a potential factor in the differences in stroke mortality. In particular, the traditional diets of Japanese are rich in foods containing omega-3 fatty acids, suggesting that there might be ethnic-specific food sources or preparation methods that are protective against heart disease but not against stroke. Also, the type of omega-3 fatty acids present varies by food source: fish contains eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), long-chain omega-3 fatty acids; and soybeans contain alpha-linolenic acid (ALA), short-chain omega-3 fatty acids.

The prospective Multiethnic Cohort (MEC) Study of over 200,000 individuals aged 45-75, primarily from five ethnic groups -- African-American, Latino, Japanese-American, Native Hawaiian, Caucasian – was established in Hawaii and Los Angeles in 1993 to 1996. An extensive food frequency questionnaire was administered at cohort entry and deaths are ascertained by linkage to vital status files. This data provides a unique opportunity to address the role of omega-3 fatty acids and their food sources on the risk of stroke death among a diverse population, with varying rates of disease and exposure.

4.3 METHODS

Study design

The association of sources of omega-3 fatty acids and the risk of stroke mortality was studied using a prospective design and the MEC data in men and women overall and by ethnic group. The MEC sampling frame included adults aged 45-75 in 1993 from the Hawaii and Los Angeles driver's license files, the Hawaii voters registration file and the California Health Care Financing Adminstration (Medicare) files; details are discussed in another report.[14] The cohort consisted of 215,251 men and women of African-American (16.3%), Latino (22.0%), Japanese-American (26.4%), Native Hawaiian (6.5%), Caucasian (22.9%), and other (5.8%) ancestry. At cohort entry, participants completed a 26-page self-administered mail questionnaire that included a 17-page quantitative food frequency questionnaire (1st QFFQ), as well as sections on demographic, medical, and other lifestyle information. For this study, only the 89,052 men and 109,090 women who were from the five major ethnic groups and were free of a history of stroke at cohort entry were included.

Dietary assessment

The development of the QFFQ was described in another report.[15] In brief, three-day measured dietary records from 60 men and 60 women of each ethnic group served as the basis for the selection of food items for the QFFQ. A minimum set of food items contributing at least 85% to the intake of nutrients of interest for each ethnic group were selected and complemented by the inclusion of traditional food items that were common in the diet of a particular ethnic group, irrespective of their nutrient contributions. The QFFQ enquires, for the past year, about the usual intake frequency, based on 8-9 categories ranging from 'Never or hardly ever' to '2 or more times a day', and the amount of food consumed, based on a choice of three portion sizes specific for each food item listed on the QFFQ. The reference portion sizes were derived from the three-day measured dietary records.

A food composition database created for the MEC QFFQ was used to convert food intakes into nutrients. The food composition table was developed at the Cancer Research Center of Hawaii (CRCH), based largely on USDA data, and supplemented with information from Japan, Canada and the UK, as well as unique locally consumed analyzed foods. The overall Cancer Research Center of Hawaii food composition database includes over 1,500 foods and 700 recipes. Omega-3 fatty acid intake in grams per day was considered in this analysis. The QFFQ was found to adequately measure diet when compared with multiple 24-hour diet recalls collected on over 2,000 MEC participants, evenly distributed by sex-ethnic subgroup in a calibration study[15]; the correlation, adjusted for energy intake, between instruments for omega-3 fatty acid intake ranged from 0.25 to 0.70 for the 10 sex-ethnic groups. For men, African-Americans had the highest correlation at 0.55, followed by Caucasians at 0.51, Latinos at 0.40, Native Hawaiians at 0.26, and Japanese at 0.25; for women, Caucasians had the highest correlation at 0.70, followed by Japanese at 0.49, Native Hawaiians at 0.36, African-Americans at 0.35, and Latinas at 0.25. Daily grams of food groups or food items were computed by summing relevant food items and portions of recipes. The following food groups were found to be major contributors to omega-3 fatty acid intake and are included in this analysis: fish (excluding shellfish) in total and by type: canned fish, baked, boiled, and raw fish, fried fish, dried and salted fish; legume, tofu, and shoyu; and oil, regular salad dressing, macaroni or potato salad, mayonnaise in sandwiches, and Mexican dishes.

Case ascertainment

Deaths are ascertained annually by the linkage between the MEC participants to the state death files for Hawaii and California. Cohort members who have moved out of these areas are linked to the National Death Index file periodically. The vital status was ascertained through December 31, 2005 for this analysis. The underlying cause of death was obtained from the death certificate. Stroke deaths included those with ICD9 codes of 430, 431, 434, and 436 or ICD10 codes of I60-I69 for stroke. Hemorrhagic stroke included ICD9 codes of 430, 431, 432 or ICD10 codes of I61 and I62, and ischemic stroke included ICD9 codes of 433, 434, 435, 436, 437.0, 437.1 or ICD10 codes of I63, I65, I66, I67.2 and I67.8.

Statistical analysis

We used the Cox regression (proportional hazards model), with age as the time metric, to calculate relative risks (RR) and 95% confidence intervals (95% CI) of stroke mortality overall and among subgroups defined by sex and ethnicity. Follow-up began at the date of cohort entry, defined as questionnaire completion or as the date when the participant turned 45 years old (for the few individuals younger than 45 when they completed the baseline questionnaire) and ended at the earliest of the date of death, or December 31st 2005, the closure date for the study. Only individuals whose cause of death was stroke as defined above were counted as events; all other deaths were censored. Analysis was repeated for the stroke subtypes; for the hemorrhagic stroke analysis, ischemic stroke deaths were censored, and vice-versa. To ensure that the strong risk factor of smoking was adjusted for, a base model for smoking was developed. We started with the extensive model built for lung cancer in the MEC[16] and used the likelihood ratio test to determine the most parsimonious model needed for stroke death. The final smoking model included indicator variables for smoking status (never, former, current) and a continuous variable for pack-years at baseline. Other adjustment variables included ethnicity (where appropriate), body mass index(weight in kg / height in m^2), log transformed daily energy intake, hypertension history, diabetes history, daily alcohol consumption, amount of vigorous physical activity, educational level, percent of energy from saturated fat, and for women, type and age at menopause and hormone replacement therapy use. The risk factor of interest included omega-3 fatty acid intake and its food sources. Indicator variables were created to represent the quantiles, using the lowest quantile as reference. Quintiles were used when possible. Dose-response was tested by inclusion of a trend variable, assigned the median value for the appropriate quantiles within sex and ethnicity groups. Interactions were tested by likelihood ratio tests comparing models with cross-product terms between ethnicity and the risk factor of interest, and main effects models.

4.4 RESULTS

There were 89,052 men and 109,090 women of the five major ethnic groups of Caucasian, African American, Native Hawaiians, Japanese-American, and Latino who were free of stroke at study entry. By the end of 2005, there were 1,789 deaths due to strokes, including 530 deaths due to hemorrhagic stroke and 314 deaths due to ischemic stroke, during an average of 11.9 years of follow-up. The stroke mortality rates and mean intakes for omega-3 fatty acids and its sources by ethnic groups are presented for males in Table 4.1. Native Hawaiians had the highest age-adjusted stroke death rate at 105.6 per 100,000, and followed by Japanese Americans at 92.6, African Americans at 77.5, Latinos at 66.6, and Caucasians at 51.1. Consistent with the literatures, Japanese men had the highest mortality rate of hemorrhagic stroke (64.3), but the lowest ischemic stroke mortality (2.7) among all ethnic groups. Caucasian men experienced a hemorrhagic stroke mortality rate (32.7) half of that of Japanese and an ischemic stroke mortality rate (8.6) about three times higher. Native Hawaiians and Japanese Americans had higher mean intakes of total fish, tofu, and vegetable oils in cooking than other ethnic groups. While Japanese had the highest tofu inake and Latinos had the highest legume consumption.

The death rates due to stroke and the means for the intakes of interest are presented for women in Table 4.2. Latinas had the highest stroke mortality rate at 160.8, followed by African Americans at 57.5, Caucasians at 54.9, Japanese

Americans at 35.4, and Native Hawaiians at 22.5. Latinas had the highest mortality rates due to hemorrhagic stroke and ischemic stroke among the ethnic groups. Among women with history of hypertension, there were about 9% fewer Latinas (56.3%) using hypertension medications to control the condition than women of other ethnic groups (65.5%). Although the intake amounts were smaller, women had a similar pattern across ethnic groups as men for the intake of omega-3 fatty acids, fish, and other omega-3 fatty acid sources.

The relative risk (RR) and 95% confidence intervals for stroke mortality and omega 3 fatty acid intake and its sources for men and women are selectively displayed in Table 4.3. Men and women were combined when the results were similar between sexes. Overall, omega-3 fatty acid intake for the second to fourth quintile showed an inverse relation to stroke mortality compared to the lowest quintile (RR of 0.74 (95%CI=0.58-0.92) at the fourth quintile vs the first quintile). However, the trend was not monotonic. Intake of canned tuna fish (4^{th} vs. lowest quartile: RR=0.84, 95%CI=0.71-0.99) and vegetable oils in cooking (4^{th} vs. lowest quintile: RR=0.81, 95%CI=0.69-0.95) also showed an inverse relation to stroke mortality, although the trends were not significant. No trend was observed for total fish for men, but for women, an inverse relation to stroke death was suggested with an RR at the 4^{th} quintile of 0.75 (95%CI=0.58-0.98) compared to the lowest quintile; however, the trend was not monotonic.

The effects of preparation methods for fish on stroke mortality are shown in Table 4.4. There was a significant difference in effect between Japanese men and other men (p for interaction=0.0014). Overall, excluding Japanese men, baked, boiled and raw fish was inversely related to stroke death (3^{rd} vs. lowest tertile: RR = 0.84, 95%CI = 0.72-0.97) with the p-value for trend of 0.038. In contrast, baked, boiled and raw fish intake was positively associated to stroke death among Japanese men (3^{rd} vs lowest tertile: RR=1.82, 95%CI=1.20-2.76) and the p-value for trend was 0.0021. For men, fried fish consumption was associated with an 18% significant increase in the risk of stroke death, when compared to no consumption (p=0.048), especially in African American men (RR=1.25, 95%CI=1.02-1.54). But this finding was not observed in women.

Table 4.5 displays the RRs of mortality by stroke subtype for selected risk factors. Although not significant, a protective effect was suggested with increasing dietary omega-3 fatty acid intake for both hemorrhagic and ischemic stroke; a similar result for hemorrhagic but not ischemic stroke was found with total fish intake in women. Vegetable oils used in cooking were inversely associated to ischemic (p for trend of 0.049) but not hemorrhagic stroke mortality.

Different preparation methods for fish showed different effects on mortality by stroke subtype and by ethnicity. Japanese men had a higher risk for hemorrhagic stroke with a higher intake of baked, boiled and raw fish (RR =2.25; 95%CI=1.05-4.80 for the 3rd tertile vs. the lowest tertile), whereas Japanese women did not (RR=0.81; 95%CI=0.42-1.56). In contrast, Japanese of both sexes had an increased risk of ischemic stroke with a higher intake of baked, boiled and raw fish; this relationship was stronger for Japanese men (RR of 9.13; 95%CI=1.21-68.6 for the 3rd vs. the lowest tertile) than for Japanese women (RR=1.57; 95%CI=0.47-5.29). As expected, salted and dried fish intake was positively associated with hemorrhagic stroke mortality (consumers vs. non-consumers: RR=1.41, 95%CI=1.06-1.87), but not ischemic stroke, and this was particularly apparent in Japanese women (RR=1.73, 95% CI=1.02-2.92).

There were suggested differences in the effects for legume intake including soy products by sex (p=0.12 for interaction of legume intake and sex) for stroke mortality in Table 4.6. Legume intake (5th vs. lowest quintile: RR=1.34, 95%CI=1.01-1.78) was a risk factor for stroke mortality among men. In contrast, although not significant, the relative risks for legume intake were in a protective direction for the top four quintiles among women. Among postmenopausal women, the inverse association to stroke death from legumes was suggested in quintiles above the first (3rd vs. lowest quintile: RR = 0.68, 95%CI = 0.49-0.95), but there was no dose-response relation. The protective effects from legume intake varied by stroke subtype in post-menopausal women as shown in Tables 4.7. No clear association of legume intake was found for hemorrhagic stroke, whereas the protective effect for ischemic stroke was strong with an RR of 0.17 in the 5th quintile (>60.7 grams of legume per day) and a p for trend of 0.0035. However, the effects from soy products were less clear. Tofu intake did not demonstrate any significant inverse association with hemorrhagic or ischemic stroke death, although the RRs for the 2nd to 5th quintiles were less than 1. Less than 1.1 grams of shoyu per day seemed inversely related to hemorrhagic stroke death among all cohort members and in women, but not related to ischemic stroke.

4.5 DISCUSSION

This study generally found inverse associations between intake of omega-3 fatty acids and its sources and stroke death. However, the effects were often not very strong and not significant. Total fish consumption did show a significant inverse association with stroke mortality among women but not among men. Food sources for omega-3 fatty acids broadly had similar effects for stroke mortality as for CHD mortality in the MEC.[17] Consistent with the findings in other observational studies and clinical studies[3,8,18-24,] our data suggested that total dietary omega-3 fatty acid intake was protective against all stroke mortality and against ischemic stroke mortality.

Varying methods of preparation for fish had different effects on stroke death, overall and by subtypes. Fried fish intake was positively associated with stroke mortality in men; this could be caused by deep frying increasing the ratio of omega-6 to omega-3 fatty acids[25]. Furthermore, negative health effects from trans-fatty acids and lipid oxidation products in the fried fats and oils[26-28] may increase cardiovascular risk[29,30] by raising levels of LDL cholesterol, lowering levels of HDL cholesterol, and increasing the chance of blood clots.[31]

Salted and dried fish intake was positively related to hemorrhagic but not to ischemic stroke mortality. The positive association between high intake of salt or salted food and stroke mortality has been well documented.[32] In a meta-analysis including 19 independent cohort studies, with 177,025 participants and a follow-up 3.5-19 years, higher salt intake (5 grams of salt per day) was associated with a greater risk of stroke with a pooled relative risk of 1.23 (95% CI=1.06-1.43) and a p-value of 0.007 with no significant evidence of publication bias. Epidemiologic evidence from the Japanese and Yugoslavian cohorts of the Seven Countries Study suggested that increased salt intake was associated with a quicker rise in blood pressure levels and arterial stiffness during aging.[33] The positive association of salted fish intake and the risk of hemorrhagic stroke further supports the hypothesis that high salt intake increases the likelihood of developing hypertension, which is an important risk factor for hemorrhagic stroke.[34]

Baked, boiled, and raw fish intake was protective for stroke, overall and by subtype, in men after excluding Japanese. Furthermore, baked, boiled, and raw fish intake was strongly related in a positive direction to both hemorrhagic stroke and ischemic stroke mortality in Japanese men. On one hand, Japanese often use shoyu in food preparation which could have led to a high salt intake with baked, boiled and raw fish that might explain the higher risk of hemorrhagic stroke and ischemic stroke in Japanese men than in other groups.[34,35] On the other hand, an association between intracranial hemorrhage and the combination of high blood pressure and low serum cholesterol level for middle-aged men in the Multiple Risk Factor Intervention Trial was reported.[36] This association may be related to high level of omega-3 fatty acids in the diet, because there is evidence to suggest that these fatty acids can reduce platelet aggregation that would lead to lowering of cholesterol.[37] Several recent observational studies showed that high total cholesterol was inversely associated with stroke mortality.[38-40] In addition, exploratory research based on clinical data from the Honolulu Heart Program suggested that stroke is more likely due to lesions in the small intracerebral arteries and appears to be related to low levels of serum cholesterol, high alcohol intake, and some aspect of a traditional Oriental diet in Japanese-Americans.[41] In our cohort, Japanese men had a 10% higher prevalence of hypertension at study entry and a 36% higher fish intake than the overall study population. In future studies, raw fish consumption should be separated from baked and boiled fish intake, as sashimi is traditionally consumed with sake, shoyu, and pickles.

There were distinct opposite effects for legumes between men and women for overall stroke mortality. There was a suggested inverse relationship between legume intake and stroke mortality in women, and that was more marked in postmenopausal women. Among women, the protective effects from the 5th quintile legume for ischemic but not hemorrhagic stroke largely contributed to the overall protective effect on stroke. This suggests that legumes confer different protective mechanisms between the stroke subtypes. This result repeats the findings recently reported from the Japan Public Health Center-Based Study Cohort I and the Shanghai Women's Health Study Cohort.[42,43] The Japan Public Health Center-Based Cohort study recruited 40,462 Japanese aged 40 to 59 years old and free of cardiovascular disease or cancer at cohort entry from 1990 to 1992 and followed them through the end of year 2002. Women who had soy intake more than 5 times per week had an RR of 0.64 (95% CI=0.43 - 0.95) for stroke mortality as compared to women consumed 0 to 2 times per week. The RR for the highest versus the lowest quintiles of isoflavones in women was 0.35 (0.21 to 0.59) for stroke mortality. The inverse association between isoflavone intake and risk of stroke was observed primarily among postmenopausal women but not in men.[42] This finding had generally been reported only for Japanese, but with confirmation in the entire MEC population, may be more broadly generalizable to the U.S. population.

Surprisingly, our data showed that legume intake was a significant risk factor for stroke mortality in men. Legumes including soy are the major source of isoflavones in food that can act like estrogen agonists to prevent the development of atherosclerosis[44] and slow down the formation of LDL.[45] Soy protein was concluded to reduce total serum cholesterol in a meta-analysis of 38 controlled clinical studies.[46] The isofavone genistein has a high affinity to beta-estrogen receptors, found in the brain and endothelium cells[47], and protects against pro-inflammatory factor-induced vascular endothelial barrier dysfunction and inhibits leukocyte-endothelium interaction, thereby modulating vascular inflammation, a major event in the pathogenesis of atherosclerosis.[48] Sex differences in beta estrogen receptor distribution were reported.[49] The hypothesis that the total serum cholesterol lowering and estrogen-like effects from legumes are sex-dependent requires further study.

Whereas tofu intake was not observed to have strong protective effects on stroke mortality, moderate shoyu use at the table was protective for hemorrhagic but not ischemic stroke mortality. The protective effects from the moderate intake of legume and soy products against hemorrhagic stroke are possibly because of their cholesterol-lowering effects, along with the increasing use of lower salt content shoyu in preparations. In contrast, the stronger protective effect from high intake of legumes against ischemic stroke in post-menopausal women is possibly because this group naturally has more estrogen receptors than men, and this could enhance the benefit from isoflavones that act as estrogens by slightly lowering blood cholesterol and preventing the development of atherosclerosis.[44,48]

One could hypothesize a possible U shaped relationship for fish and plant sources of omega-3 fatty acids to stroke mortality, due to their serum cholesterol lowering effects. Both low and high serum cholesterol levels could be associated with a higher risk of stroke death, while the moderate serum cholesterol at the bottom of the U shape would be related to the low risk of stroke mortality. Perhaps relatively low serum cholesterol is the reason for the paradox of the high risk of stroke in male Japanese-Americans who are at low CHD risk. Since the 1970's, several Japanese epidemiologic studies of hemorrhagic stroke indicated an increased risk at lower levels of blood cholesterol.[11] The finding that a low blood cholesterol level was associated with the increased risk of intracerebral hemorrhage has been confirmed in several Japanese populations, Japanese Americans and Caucasian Americans, and was replicated by the Honolulu Heart Study in migrants from Japan, as well as in the MRFIT Screening Study.[36,50] It was also noted that elderly people in Japan, as observed in the Seven Countries Study, had far lower serum total cholesterol levels in midlife, i.e., around 160 mg/dL in the 1960s, compared to Caucasians with about 240mg/dL in the U.S.[51-52] In recent decades, with increasing blood cholesterol, the CHD mortality remained stable in Japan, while stroke mortality declined.[53] Pathological research revealed that the relationship between blood cholesterol and arterial lesions is inverse for arteriolosclerosis and positive for atherosclerosis. The role of blood cholesterol is opposite for hemorrhagic and nonhemorrhagic stroke.[50] Therefore, increased dietary omega-3 fatty acids and legume intake might have reduced the total cholesterol to a level that could increase the risk of stroke death in men.

There are several strengths and limitations that need to be considered in the interpretation of our findings. The strengths include the large number of stroke mortality events and the representative samples across major ethnic groups in the U.S. Limitations include that although we focused on omega-3 fatty acid intake, its strong correlation with omega-6 intake (r=0.95) makes it difficult to separate their effects. Also, omega-3 fatty acid intake may have been underestimated. First, only exposure data at baseline was considered, and the baseline collection was almost one decade before the AHA recommendations for omega-3 fatty acid consumption. Second, fish oil supplement use was not collected in the baseline QFFQ. Fish oil supplementation was little used at the start of the MEC study. However, data from a repeat QFFQ administered from 2003-2008 found that 15% of individuals reported omega-3 supplement use. This underestimation is likely to attenuate the association between CHD mortality and omega-3 fatty acid intake. Another limitation is the lack of detailed information on raw fish intake in our food frequency questionnaire to verify whether raw fish but not boiled and baked fish intake was associated with the increased risk of stroke mortality in Japanese-American men.

To our knowledge, there has been limited prospective cohort data on the dietary aspects of fish and plant sources of omega-3 fatty acids and the risk of stroke mortality in Japanese men at low CHD risk in the U.S. population. The examination of stroke mortality and omega-3 fatty acid food sources, including fish and plants, provided evidence for the possible underlying mechanisms. The findings suggest a protective effect of ω3 intake against stroke mortality. High salt use in the preparation methods of baked, boiled, and raw fish and the high sodium content of salted or dried fish, as well as a possible sex differences in the effect of legume intake, may explain the higher risk of stroke mortality, especially hemorrhagic stroke deaths, in Japanese men than in other groups. The serum cholesterol lowering effects of various sources of omega-3 fatty acids may have confounded its protective effect on stroke risk by lowering cholesterol to a level that confers risk. Possible sex differences in the effects from legumes and soy products on stroke mortality and stroke subtype warrant further study. In general, intake of omega-3 fatty acids from baked or boiled fish and tofu may reduce the risk of stroke mortality.

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Table 4.1. Baseline Sources of Omega-3 Fatty Acids in Men in the Multiethnic Cohort, 1993-2005

	All (n=89,052)	Caucasian (n=22,362)	African American (n=12,160)	Native Hawaiian (n=6,136)	Japanese American (n=26,077)	Latinos (n=22,317)
Stroke death (rate*)	872 (68.7)	164 (51.1)	202 (77.5)	50 (105.6)	265 (92.6)	191 (66.6)
Hemorrhagic stroke death (rate*)	276 (41.8)	52 (32.7)	46 (46.0)	12 (46.4)	97 (64.3)	69 (36.5)
Ischemic stroke death (rate*)	153 (14.0)	31 (8.6)	41 (13.1)	12 (43.7)	36 (2.7)	33 (22.2)
Diagnosed hypertension (n)	34,828	6,792	6,435	2,868	11,127	7,606
Hypertensive medication use (%)	57.4	58.8	58.9	54.7	60.4	51.4
Mean (g/d)						
Total fish	20.8	19.2	15.7	35.8	28.4	12.3
Canned fish	9.5	9.5	8	17.7	11.1	6.1
Canned tuna	7.7	8.1	5.9	13.1	9.1	5.1
Tofu	8.7	4.2	0.5	12.9	22.1	0.6
Shoyu	2.4	1.6	0.5	4.8	4.9	0.6
Legume	52.4	32	33.4	34.9	41	101
Fried fish	4.9	3.2	3.9	7.5	7.8	3.1
Baked, boiled, raw fish	6.3	6.5	3.8	10.2	9.2	3.1
Salted, dried fish	0.1	0	0	0.5	0.3	0
Omega-3 Fatty Acids	2.1	2	2	2.5	2	2.3
Vegetable oils in cooking	2.7	1.7	1.9	3.5	2.7	2.5

* Age-adjusted for 2000 US standard population

Table 4.2. Baseline Sources of Omega-3 Fatty Acids in Women in the Multiethnic Cohort, 1993-2005

	All (n=109,090)	Caucasian (n=26,152)	African American (n=21,264)	Native Hawaiian (n=7,953)	Japanese American (n=29,531)	Latinos (n=24,190)
Stroke death (rate*)	917 (50.9)	177 (54.9)	298 (57.5)	61 (22.5)	204 (35.4)	177(160.8)
Hemorrhagic stroke death (rate*)	254 (25.9)	45 (45.3)	60 (23.9)	21 (9.9)	78 (10.7)	50 (68.0)
Ischemic stroke death (rate*)	872 (10.4)	164 (2.3)	202 (10.8)	50 (4.0)	265 (1.6)	191 (57.6)
Diagnosed hypertension (n)	41,202	7,010	11,768	3,337	10,636	4,756
Hypertensive medication use (%)	63.6	65.3	66.2	62.1	66.0	56.3
Mean (g/d)						
Total fish	16.5	14.6	14.4	29.1	21.3	10.4
Canned fish	8.3	7.9	7.9	15.5	8.9	5.9
Canned tuna	6.8	6.9	6.1	11.6	7.3	5.2
Tofu	8.2	3.5	0.5	14.4	22.1	0.8
Shoyu use	1.8	1	0.3	3.7	3.9	0.6
Legume	41.9	26.6	27.5	34.5	38	78.2
Fried fish	3.4	1.7	2.9	5.7	5.6	2.1
Baked, boiled, raw fish	4.8	4.9	3.6	7.7	6.6	2.4
Salted, dried fish	0.1	0	0	0.3	0.2	0
Omega-3 Fatty Acids	1.7	1.5	1.7	2.2	1.7	1.9
Vegetable oils in cooking	1.8	1.2	1.4	2.8	2.2	2.1

* Age-adjusted for 2000 US standard population

Table 4.3. Relative Risks (95% CI) of Stroke Mortality with Fish, Omega-3 Fatty Acids, and Vegetable Oils, Men and Women

Total Fish (g/day)	Men	Women	Canned Tuna (g/day)	All	Omega-3 Fatty Acids (g/day)	All	Vegetable Oils in Cooking (g/day)	All
-< 4.7	1.00	1.00	0	1.00	-< 1.1	1.00	0	1.00
4.7 <- 9.6	1.02 (0.81-1.30)	1.00 (0.81-1.23)	0<-3.0	0.94(0.82-1.08)	1.1 <- 1.4	0.81 (0.68-0.96)	0 <- 0.5	1.02 (0.87-1.19)
9.6 <- 15.9	0.94 (0.73-1.20)	0.99 (0.79-1.24)	3.0<-7.4	0.93(0.81-1.08)	1.4 <- 1.9	0.82 (0.68-1.00)	0.5 <- 1.2	0.83 (0.71-0.97)
15.9 <- 27.0	1.08 (0.84-1.37)	0.75 (0.58-0.98)	>7.4	0.84(0.71-0.99)	1.9 <- 2.6	0.73 (0.58-0.92)	1.2 <- 3.7	0.81 (0.69-0.95)
> 27.0	1.07 (0.83-1.39)	1.03 (0.79-1.34)			> 2.6	0.82 (0.61-1.10)	> 3.7	0.94 (0.80-1.11)
p for trend	0.45	0.40		0.13		0.81		0.72
p factor-by-ethnicity	0.048	0.11		0.56		0.96		0.77

Table 4.4. Relative Risks (95% CI) of Stroke Mortality and Fish Preparation Methods, Men and Women

Baked, Boiled, Raw Fish (g/day)	Non-Japanese Men	Japanese Men	Fried Fish	Men	Women
0	1.00	1.00	Non-Consumer	1.00	1.00
0 <- 6.2	0.85 (0.74-0.98)	1.04 (0.66-1.64)	Consumer	1.18 (1.00-1.38)	1.01 (0.87-1.19)
> 6.2	0.84 (0.72-0.97)	1.82 (1.20-2.76)			
p for trend	0.038	0.0021		0.048	0.86
p method-by-ethnicity		0.0014		0.11	0.55

Table 4.5. Relative Risks (95% CI) of Mortality by Stroke Subtype with Selected Sources of Omega-3 Fatty Acids, Men and Women

Omega-3 Fatty Acids (g/day)	All	Baked, Boiled, Raw Fish (g/day)	Non-Japanese Men	Japanese Men	Salted or Dried Fish vs. None	Total Fish (g/day)	Women	Vegetable oils in cooking (g/day)	All
				HEMORRHAGIC STROKE					
-< 1.1	1.00	0	1.00	1.00	1.00	-< 4.7	1.00	0	1.00
1.1 <- 1.4	0.90		0.75	1.28	1.40		0.82	0 <- 0.5	1.17
	(0.65-1.25)	0 <- 6.2	(0.58-0.99)	(0.56-2.89)	(1.06-1.87)	4.7 <- 9.6	(0.55-1.23)		(0.86-1.59)
1.4 <- 1.9	0.76		0.86	2.25			0.65	0.5 <- 1.2	0.99
	(0.52-1.13)	> 6.2	(0.65-1.13)	(1.05-4.80)		9.6 <-15.9	(0.41-1.02)		(0.74-1.33)
1.9 <- 2.6	0.96						0.70	1.2 <- 3.7	0.90
	(0.62-1.48)					15.9 <- 27.0	(0.44-1.13)		(0.66-1.23)
> 2.6	0.87						1.06	> 3.7	1.15
	(0.50-1.53)					> 27.0	(0.65-1.71)		(0.85-1.57)
p for trend	0.94		0.60	0.0096	0.020		0.64		0.61
p factor-by-ethnicity	0.10			0.14	0.88		0.32		0.61
				ISCHEMIC STROKE					
-< 1.1	1.00	0	1.00	1.00	1.00	-< 4.7	1.00	0	1.00
1.1 <- 1.4	0.76		0.87	3.47	1.05		1.59	0 <- 0.5	1.09
	(0.50-1.17)	0 <- 6.2	(0.62-1.22)	(0.43-28.3)	(0.67-1.64)	4.7 <- 9.6	(0.92-2.76)		(0.76-1.56)
1.4 <- 1.9	0.74		0.68	9.13			1.62	0.5 <- 1.2	0.79
	(0.45-1.20)	> 6.2	(0.46-1.00)	(1.21-68.6)		9.6 <- 15.9	(0.91-2.87)		(0.55-1.13)
1.9 <- 2.6	0.64						1.18	1.2 <- 3.7	0.61
	(0.36-1.15)					15.9 <- 27.0	(0.62-2.25)		(0.41-0.92)
> 2.6	0.59						1.25	> 3.7	0.71
	(0.28-1.26)					> 27.0	(0.63-2.46)		(0.47-1.06)
p for trend	0.56		0.15	0.0059	0.84		0.87		0.049
p factor-by-ethnicity	0.03			0.10	0.84		0.82		0.73

Table 4.6. Relative Risks (95% CIs) of All Stoke Mortality and Legume Intake, Men and Women

Quintiles (g/d)	Men	Women	Post-Menopausal Women
-< 11.1	1.00	1.00	1.00
11.1 <- 20.5	1.32 (1.02-1.70)	0.95 (0.77-1.18)	0.81 (0.60-1.11)
20.5 <- 33.2	1.35 (1.04-1.74)	0.84 (0.67-1.06)	0.68 (0.49-0.95)
33.2 <- 60.7	1.25 (0.96-1.63)	0.91 (0.71-1.16)	0.87 (0.62-1.22)
> 60.7	1.34 (1.01-1.78)	0.89 (0.67-1.18)	0.86 (0.59-1.27)
p for trend	0.51	0.50	0.85
p legume-by-ethnicity	0.49	0.35	0.79

Table 4.7. Relative Risks (95% CIs) of Mortality by Stroke Subtype with Legume and Soy Product Intake, Men and Women

Legume Quintiles (g/d)	Women	Post-Menopausal Women	Tofu Quintiles (g/d)	All	Shoyu Tertiles (g/d)	All	Women
			HEMORRHAGIC STROKE				
-< 11.1	1.00	1.00	-< 0.4	1.00	0	1.00	1.00
11.1 <- 20.5	0.80 (0.54-1.20)	0.52 (0.28-0.95)	0.4 <-1.7	0.89 (0.66-1.19)	0<-1.1	0.77 (0.59-1.01)	0.70 (0.48-1.03)
20.5 <- 33.2	0.56 (0.35-0.89)	0.31 (0.15-0.66)	1.7 <-5.3	0.86 (0.63-1.19)	>1.1	0.91 (0.70-1.19)	0.88 (0.60-1.30)
33.2 <- 60.7	0.78 (0.49-1.24)	0.58 (0.30-1.11)	5.3 <-14.9	0.82 (0.57-1.20)			
> 60.7	1.16 (0.71-1.89)	1.15 (0.60-2.19)	> 14.9	0.88 (0.58-1.32)			
p for trend	0.21	0.14		0.078		0.78	0.11
p factor-by-ethnicity	0.92	0.38		0.059		0.80	0.063
			ISCHEMIC STROKE				
-< 11.1	1.00	1.00	-< 0.4	1.00	0	1.00	1.00
11.1 <- 20.5	1.19 (0.72-1.95)	1.17 (0.59-2.32)	0.4 <-1.7	0.93 (0.65-1.32)	0<-1.1	1.04 (0.76-1.43)	1.28 (0.84-1.97)
20.5 <- 33.2	0.91 (0.52-1.57)	0.68 (0.31-1.53)	1.7 <-5.3	0.88 (0.59-1.31)	>1.1	1.12 (0.78-1.60)	1.10 (0.65-1.86)
33.2 <- 60.7	0.92 (0.52-1.64)	0.65 (0.27-1.52)	5.3 <-14.9	0.86 (0.53-1.40)			
> 60.7	0.45 (0.21-0.97)	0.17 (0.05-0.68)	> 14.9	0.93 (0.54-1.61)			
p for trend	0.0062	0.0035		0.89		0.78	0.26
p factor-by-ethnicity	0.073	0.93		0.77		0.41	0.13

Chapter 5. Fish and Other Sources of Omega-3 Fatty acids and Hypertension Mortality

The sex-ethnic hypertension mortality statistics in cohort members with no history of stroke are shown in Table 5.1. Deaths with ICD9 codes of 401.x or ICD10 codes of I10-I13 and I15 for hypertension were included. By the end of 2005, there were 307 hypertensive deaths after an average of 11.9 years of follow-up. In men, Latinos had the highest age-adjusted hypertension mortality rate at 54.7 per 100,000, followed by African Americans at 16.8, Native Hawaiians at 4.3, Japanese Americans at 1.7, and Caucasians at 1.3. African American women had the highest hypertension mortality rate at 26.1, while all other groups had rates less than 3.2.

Table 5.1. Hypertension Death Rate in the Multiethnic Cohort, 1993-2005

Men	Total (n=89,052)	Caucasian (n=22,362)	African American (n=12,160)	Native Hawaiian (n=6,136)	Japanese American (n=26,077)	Latinos (n=22,317)
Deaths (Rate*)	150 (11.4)	14 (1.3)	61 (16.8)	13 (4.3)	28 (1.7)	34 (54.7)
Women	Total (n=109,090)	Caucasian (n=26,152)	African American (n=21,264)	Native Hawaiian (n=7,953)	Japanese American (n=29,531)	Latina (n=24,190)
Deaths (Rate*)	157 (9.7)	21 (1.6)	69 (26.1)	10 (2.9)	21 (1.2)	36 (3.2)

*Age-adjusted rate using the US 2000 standard population

The possible hypertension-risk lowering effects of omega-3 fatty acids and its food sources are displayed in Table 5.2. The 2nd to the 5th quintiles for tofu intake as compared to the lowest quintiles for both sexes and all ethnic groups were all less than one and the RR at the 3rd quintile was significant. There was no interaction between tofu intake and ethnicity. The relative risks for omega-3 fatty acid intake was generally in an inverse direction with hypertension mortality risk in men and women but were not statistically significant. A more pronounced inverse association for omega-3 fatty acids was observed in subjects not taking hypertension medications with a p-value for trend of 0.065. Increased baked, boiled, or raw fish intake was inversely related to hypertension mortality with an RR of 0.66 (95%CI=0.46-0.95) at the highest tertile, and a p-value for trend of 0.012. This effect was not consistent across ethnic groups (p for interaction=0.0013) and the fish prepared in this way seemed to be a risk fatcor for hypertension death in Japanese with RR of 1.04 (95%CI = 1.01-1.06) and a p-value for trend of 0.0015.

Table 5.2. Relative Risk* (95% CI) of Hypertension Mortality and Intake of Omega-3 Fatty Acid and Its Food Sources for Men and Women

Baked, Boiled, or Raw Fish (g/day)	All	Omega-3 Fatty Acids (g/day)	All	All Not On Hypertension Medications	Tofu (g/day)	All
0	1.00	-< 1.1	1.00	1.00	-< 0.4	1.00
0 <- 6.2	0.80 (0.58-1.11)	1.1 <- 1.4	1.04 (0.64-1.70)	1.19 (0.64-2.24)	0.4 <-1.7	0.80 (0.56-1.13)
> 6.2	0.66 (0.46-0.95)	1.4 <- 1.9	0.75 (0.39-1.43)	0.75 (0.33-1.71)	1.7 <-5.3	0.63 (0.41-0.96)
		1.9 <- 2.6	0.66 (0.28-1.56)	0.50 (0.17-1.50)	5.3 <-14.9	0.64 (0.38-1.09)
		> 2.6	0.59 (0.16-2.18)	0.31 (0.06-1.70)	> 14.9	0.57 (0.30-1.08)
p for trend**	0.012		0.38	0.065		0.15
p (factor-by-ethnicity)***	0.0013		0.15	0.054		0.17

*Adjusting for sex, ethnicity, body mass index, daily energy intake, hypertension history, baseline hypertension medication use (when applicable), water pill use, diabetes history, daily alcohol consumption, amount of vigorous physical activity, educational level, percent calories from saturated fat, and for women, type and age at menopause and hormone replacement therapy use
** Inclusion of a trend variable assigned the median value for the quintiles, quartiles, or tertiles within sex and ethnicity groups
*** Inclusion of a cross-product terms between ethnicity and the risk factor of interest

Total dietary omega-3 fatty acids appear to be protective against hypertensive mortality. However, the limited number of deaths from hypertension did not provide sufficient power for a definitive analysis. Increasing intake of omega-3 fatty acids from baked, boiled or raw fish and tofu may reduce the risk of hypertension mortality. Consistent with the findings for CHD and stroke mortality in Japanese, baked, boiled, or raw fish intake seemed to increase risk for hypertension death.

Chapter 6. Association of Omega-3 Fatty Acids with Acute Myocardial Infarction Death, Sudden Cardiac Death, and Prevalence of Diabetes, Hypertension, and Obesity

6.1 RISK OF ACUTE MYOCARDIAL INFARCTION OR SUDDEN CARDIAC DEATH WITH DIETARY OMEGA-3 FATTY ACIDS IN MEN AND WOMEN

Deaths with ICD9 codes of 140 or ICD10 codes of I21 were classified as actue myocardial infarction deaths; and deaths with ICD9 codes of 427.5 and ICD10 codes of I46 were classified as sudden cardiac deaths. Relative risks (95% confidence intervals) of acute myocardial infarction mortality and sudden cardiac death with omega-3 fatty acids are shown in Table 6.1 for men and women combined. Whereas no association was found between omega-3 fatty acids and acute myocardial infarction death, there was a clear inverse dose-response relationship between sudden cardiac death and increased dietary omega-3 fatty acids. Similar to the effect of omega-3 fatty acids on CHD mortality risk, the protective effect for sudden cardiac death from omega-3 fatty acids was clearer in men than in women. The protective effect from omega-3 fatty acid intake for sudden cardiac death was even stronger than the effect for CHD death, overall and in men.

Table 6.1. Relative Risks (95% CIs) of AMI Mortality or Sudden Cardiac Death with Omega-3 Fatty Acids in Men and Women

Omega-3 Fatty Acids (g/day)	AMI in All	SCD in All	SCD in Men	SCD in Women
-< 1.1	1.00	1.00	1.00	1.00
1.1 <- 1.4	0.96 (0.77-1.20)	0.75 (0.51-1.11)	0.59 (0.35-0.98)	1.17 (0.63-2.16)
1.4 <- 1.9	1.03 (0.80-1.33)	0.66 (0.43-1.03)	0.59 (0.35-1.01)	0.79 (0.36-1.74)
1.9 <- 2.6	0.79 (0.58-1.08)	0.58 (0.35-0.97)	0.42 (0.23-0.78)	1.16 (0.48-2.79)
> 2.6	1.01 (0.69-1.48)	0.47 (0.24-0.90)	0.36 (0.16-0.79)	0.68 (0.19-2.37)
p for trend	0.11	0.022	0.025	0.66
p omega-3-by-ethnicity	0.056	0.22	0.20	0.96

The overall cardioprotective effect from omega-3 fatty acids seemed to be driven by the reduction of sudden cardiac death in the MEC cohort after an average of 11.9 years of follow-up. This finding supports the anti-arrhythmia effect of omega-3 fatty acids, as heart rate variability is the major underlying cause of sudden cardiac death.

6.2 RISK OF CHD WITH OMEGA-3 FATTY ACIDS IN MEN WITH DIABETES, HYPERTENSION, AND OBESITY

The inverse relationship between omega-3 fatty acid intake and CHD mortality in men is further examined for mediation factors. Women are not included as no overall association of ω3 was seen for them. The associations between baseline omega-3 fatty acids and the prevalence of diabetes, hypertension, or obesity conditions are shown as odds ratios in Table 6.2 for men only. These factors are considered to be risk factors for CHD mortality that are potentially modifiable or controllable. Obesity was defined as body mass index greater than 30 kg/m^2. There were clear dose-response inverse associations between omega-3 fatty acid intake and baseline diabetes, hypertension, or obesity conditions.

Table 6.2. Odds Ratio (95% CIs) of Hypertension, Diabetes, or Obesity with Omega-3 Fatty Acids at Cohort Entry, in Men

Omega-3 Fatty Acids (g/day)	Diabetes	Hypertension	Obesity
-< 1.1	1.00	1.00	1.00
1.1 <- 1.4	0.88 (0.81-0.97)	0.96 (0.90-1.02)	0.91 (0.83-1.00)
1.4 <- 1.9	0.84 (0.76-0.93)	0.94 (0.88-1.01)	0.89 (0.81-0.99)
1.9 <- 2.6	0.72 (0.64-0.80)	0.93 (0.86-1.00)	0.80 (0.72-0.89)
> 2.6	0.57 (0.50-0.66)	0.89 (0.81-0.97)	0.64 (0.56-0.73)

Relative risks (95% CIs) of CHD mortality with omega-3 fatty acids in men with hypertensive, diabetic, and obese conditions at baseline are shown in Table 6.3. Omega-3 fatty acids seemed protective in men with these high risk conditions for CHD death. Although the results among diabetics or hypertensives did not reach statistical significance, the protective trend is significant in men with both hypertension and diabetes with a p-value for trend of 0.0036. The significant interaction with p-value of 0.039 between the combination of hypertension and diabetes conditions and omega-3 fatty acid intake suggests the protective effect from omega-3 fatty acids was different between subjects with these combined conditions and without.

Table 6.3. Relative Risks (95% CIs) of CHD Mortality and Omega-3 Fatty Acids in Hypertensive, Diabetic, or Obese Men

Omega-3 Fatty Acids (g/day)	Diabetes	Hypertension	Hypertension and Diabetes	Obesity
-< 1.1	1.00	1.00	1.00	1.00
1.1 <- 1.4	1.14 (0.85-1.54)	0.91 (0.75-1.12)	1.11 (0.78-1.58)	0.92 (0.61-1.38)
1.4 <- 1.9	0.90 (0.64-1.27)	0.84 (0.67-1.05)	0.86 (0.57-1.29)	0.61 (0.38-0.97)
1.9 <- 2.6	0.89 (0.61-1.31)	0.82 (0.63-1.06)	0.81 (0.51-1.29)	0.93 (0.57-1.52)
> 2.6	0.75 (0.46-1.22)	0.78 (0.56-1.08)	0.51 (0.28-0.93)	0.73 (0.39-1.37)
p for trend	0.070	0.21	0.0036	0.51
p* (condition-by-omega-3)	0.91	0.92	0.039	0.29

* p-value from a model with all men and interactions between condition and no condition.

Table 6.4. Relative Risks (95% CIs) of CHD Mortality and Omega-3 Fatty Acids Excluding Hypertension, Diabetes, or Obesity at Baseline as Covariates from the Primary Model in Men

Omega-3 Fatty Acids (g/day)	Primary Model	Primary Model - Diabetes	Primary Model - Hypertension	Primary Model - Obesity
-< 1.1	1.00	1.00	1.00	1.00
1.1 <- 1.4	0.86 (0.74-1.00)	0.87 (0.75-1.01)	0.87 (0.74-1.01)	0.85 (0.73-0.99)
1.4 <- 1.9	0.80 (0.68-0.95)	0.82 (0.69-0.97)	0.82 (0.69-0.97)	0.80 (0.67-0.95)
1.9 <- 2.6	0.75 (0.62-0.91)	0.78 (0.64-0.95)	0.76 (0.63-0.92)	0.74 (0.61-0.90)
> 2.6	0.77 (0.60-0.98)	0.83 (0.65-1.06)	0.78 (0.61-1.00)	0.76 (0.59-0.97)

The relative risks of CHD mortality with omega-3 fatty acids are shown in Table 6.4, after exclusion as covariates of either diabetes, hypertension, or obesity at baseline from the primary model. In these models, all individuals without missing data on the excluded covariate were included. Removing diabetes from the primary model noticeably attenuated the relative risks of CHD for the 2nd to 5th quintiles of omega-3 fatty acids by 1%, 2%, 3%, and 6%, respectively, in a dose response manner. This finding suggests that the protective effects from omega-3 fatty acids may be partially mediated through diabetes in men.

Chapter 7. Role of Omega-6 and Ratio of Omega-6 to Omega-3 Fatty Acids in Mortality from CHD, Stroke, Hypertension

7.1 RISK OF CHD MORTALITY WITH OMEGA-6 FATTY ACIDS OR RATIO OF OMEGA-6/OMEGA-3 FATTY ACIDS IN MEN AND WOMEN

Relative risks (95% CI) of CHD mortality with intake of omega-6 fatty acids or the ratio of omega-6 to omega-3 fatty acids are displayed in Table 7.1. For men and women combined, moderate omega-6 fatty acid intake between 8.9 and 22.6 grams per day was inversely associated with CHD mortality (2^{nd}, 3^{rd}, and 4^{th} quintiles versus the lowest quintiles: RRs were 0.87, 0.84, and 0.88 with p-values of 0.0151, 0.0062, and 0.075, respectively). However, the fifth quintile was not significant. There was a significant interaction between omega-6 fatty acid intake and ethnicity with a p-value of 0.025. Japanese Americans experienced a clearer protective dose-response effect from omega-6 fatty acids with a p-value for trend of 0.031 than did the other ethnic groups.

Table 7.1. Relative Risks (95% CIs) of CHD Mortality with Omega-6 Fatty Acids or Ratio of Omega-6 to Omega-3 Fatty Acids, Men and Women in the Multiethnic Cohort

Omega-6 Fatty Acid Quintiles (g/d)	All	Omega-6/-3 Fatty Acids Quintiles	All
-<8.9	1.00	-<7.7	1.00
8.9<-12.4	0.87 (0.78-0.97)	7.7<-8.3	1.21 (1.08-1.35)
12.4<-16.4	0.84 (0.74-0.95)	8.3<-8.9	1.15 (1.03-1.29)
16.4<-22.6	0.88 (0.76-1.01)	8.9<-9.6	1.10 (0.98-1.23)
>22.6	0.90 (0.75-1.09)	>9.6	1.09 (0.98-1.22)
p for trend	0.81	p for trend	0.68
p omega-6-by-ethnicity	0.025	p ratio-by-ethnicity	0.19

A ratio of omega-6 to omega-3 fatty acids above 7.7 was positively related to CHD mortality, as observed in the 2^{nd} to 5^{th} quintiles versus the lowest quintile with RRs ranging from 1.21 to 1.09. However, there was no monotonic trend in risk.

7.2 RISK OF STROKE MORTALITY WITH OMEGA-6 FATTY ACIDS OR RATIO OF OMEGA-6/OMEGA-3 FATTY ACIDS IN MEN AND WOMEN

Table 7.2 shows the relative risks and 95% confidence intervals of stroke mortality with dietary omega-6 fatty acid intake and the ratio of omega-6 to omega-3 fatty acids. An inverse dose-response relationship between omega-6 fatty acid intake and stroke mortality risk was observed, that seemed stronger than the association of omega-6 fatty acids with CHD mortality. The ratio of omega-6 to omega-3 fatty acids did not show any obvious effects on stroke mortality risk.

Table 7.2. Relative Risks (95% CIs) of Stoke Mortality with Omega-6 Fatty Acids or Ratio of Omega-6/Omega-3 Fatty Acids, Men and Women in the Multiethnic Cohort

Omega-6 Fatty Acids Quintiles (g/d)	All	Omega-6/-3 Fatty Acids Quintiles	All
-<8.9	1.00	-<7.7	1.00
8.9<-12.4	0.78 (0.66-0.93)	7.7<-8.3	0.91 (0.77-1.08)
12.4<-16.4	0.76 (0.62-0.92)	8.3<-8.9	1.08 (0.92-1.27)
16.4<-22.6	0.69 (0.55-0.87)	8.9<-9.6	0.99 (0.84-1.17)
>22.6	0.72 (0.54-0.97)	>9.6	1.06 (0.90-1.25)
p for trend	0.26	p for trend	0.83
p omega-6-by-ethnicity	0.51	p ratio-by-ethnicity	0.81

7.3 RISK OF HYPERTENSION DEATH WITH OMEGA-6 FATTY ACIDS OR RATIO OF OMEGA-6/OMEGA-3 FATTY ACIDS IN MEN AND WOMEN

Table 7.3 shows the relative risks and 95% confidence intervals for hypertension mortality from dietary omega-6 fatty acids and the ratio of omega-6 to omega-3 fatty acids. An inverse relationship between omega-6 fatty acid intake above 12.4 g/day and hypertension mortality risk was observed, with a dose-response trend up to the 4th quintile. The protective effect of omega-6 fatty acids for hypertension death seems stronger than for CHD mortality. The ratio of omega-6 to omega-3 fatty acids did not show any clear effects on the risk of hypertension deaths.

Table 7.3. Relative Risks (95% CIs) of Hypertension Mortality with Omega-6 Fatty Acids or Ratio of Omega-6/Omega-3 Fatty Acids, Men and Women in the Multiethnic Cohort

Omega-6 Fatty Acids Quintiles (g/d)	All	Omega-6/-3 Fatty Acids Quintiles	All
-<8.9	1.00	-<7.7	1.00
8.9<-12.4	1.00 (0.67-1.51)	7.7<-8.3	0.83 (0.56-1.24)
12.4<-16.4	0.73 (0.45-1.18)	8.3<-8.9	0.91 (0.62-1.34)
16.4<-22.6	0.48 (0.27-0.85)	8.9<-9.6	0.72 (0.48-1.09)
>22.6	0.58 (0.28-1.18)	>9.6	0.75 (0.50-1.11)
p for trend	0.091	p for trend	0.13
p omega-6-by-ethnicity	0.23	p ratio-by-ethnicity	0.53

7.4 RISK OF CHD, STROKE, AND HYPERTENSION DEATH WITH PEANUTS AND OTHER NUTS IN MEN AND WOMEN

Since peanuts and other nuts were identified as the highest omega-6 fatty acid contributor that was not highly correlated with dietary omega-3 fatty acid intake, the relative risks of CHD, stroke, and hypertension mortality with intake of peanuts and other nuts were examined in order to differentiate the effect between omega-6 fatty acids and omega-3 fatty acids to these diseases. In Table 7.4, a clear inverse dose-response relation was observed between increasing nut intake and CHD risk, overall and across ethnicities. An inverse dose-response relation was also evident for the risk of hypertension death. An inverse association with stroke mortality was also observed at a higher intake of nuts but the trend was not significant. Therefore, it is possible that the observed inverse association of omega-3 fatty acids and CHD mortality was due to consumption of polyunsaturated fatty acids generally. However, the stronger inverse trend for

CHD death risk with nuts than with total dietary omega-6 fatty acids suggests that nut consumers were possibly a group practicing other healthy behaviors that had manifested the lower CHD risk, as compared to non-consumers. Also, the sex-specific findings for omega-3 fatty acids and CHD death were not replicated for omega-6 fatty acids (see Section 7.5).

Table 7.4. Relative Risks (95% CIs) of CHD, Stroke, and Hypertension Mortality with Peanuts and Other Nuts, Men and Women in the Multiethnic Cohort

Peanuts and other nuts Tertiles (g/d)	CHD	Stroke	Hypertension
0	1.00	1.00	1.00
0<- 2.9	0.82 (0.76-0.88)	0.92 (0.82-1.04)	0.83 (0.63-1.10)
> 2.9	0.69 (0.63-0.75)	0.86 (0.74-0.99)	0.61 (0.43-0.88)
p for trend	<0.0001	0.16	0.024
p nuts-by-ethnicity	0.73	0.45	0.75

7.5 RISK OF CHD MORTALITY WITH OMEGA-6 FATTY ACIDS BY SEX

The relative risks of CHD mortality for omega-6 fatty acids by sex and ethnicity are displayed in Table 7.5. Inverse associations between omega-6 fatty acids and CHD death were observed for men and women, although the RRs were not strong and generally not significant. No sex difference in the effect from omega-6 fatty acids was found (p-value for interaction=0.95). This does not agree with the findings for omega-3 fatty acids where men had a much clearer inverse association than women, implying that the two fatty acids may not be interchangeable.

The effect of omega-6 fatty acids varied by ethnicity in men, with a clear dose-responsive inverse association for Japanese men. Ethnic variation of effects was suggested in women, with a strong dose-responsive positive association for Latinas.

Table 7.5. Relative Risks (95% CI) of CHD Mortality with Omega-6 Fatty Acids by Sex in the Multiethnic Cohort Study, 1993-2005

Men	All (n=70,837)	Caucasian (n=18,376)	African American (n=9,056)	Native Hawaiian (n=5,073)	Japanese American (n=2,1953)	Latinos (n=16,379)
CHD Deaths	2,198	492	516	171	466	553
-<8.9	1.00	1.00	1.00	1.00	1.00	1.00
8.9<-12.4	0.91 (0.78-1.07)	0.92 (0.65-1.29)	0.80 (0.59-1.09)	1.52 (0.79-2.92)	1.04 (0.75-1.43)	0.85 (0.62-1.17)
12.4<-16.4	0.84 (0.71-1.00)	0.99 (0.69-1.41)	0.66 (0.46-0.94)	1.61 (0.82-3.13)	0.73 (0.51-1.06)	0.87 (0.61-1.23)
16.4<-22.6	0.87 (0.72-1.05)	0.90 (0.60-1.35)	0.79 (0.53-1.18)	1.47 (0.70-3.09)	0.74 (0.49-1.11)	0.93 (0.63-1.37)
>22.6	0.88 (0.69-1.13)	0.87 (0.52-1.45)	0.85 (0.51-1.40)	1.90 (0.77-4.67)	0.60 (0.35-1.01)	1.06 (0.65-1.74)
p for trend	0.78	0.60	0.68	0.35	0.031	0.29
p for interaction with ethnicity	0.086					
Women	**All (n=86,266)**	**Caucasian (n=21,950)**	**African American (n=15,324)**	**Native Hawaiian (n=6,593)**	**Japanese American (n=25,542)**	**Latinos (n=16,857)**
CHD Deaths	1,491	297	573	100	240	281
-<8.9	1.00	1.00	1.00	1.00	1.00	1.00
8.9<-12.4	0.82 (0.70-0.97)	0.93 (0.66-1.31)	0.77 (0.58-1.02)	1.18 (0.57-2.44)	0.73 (0.49-1.08)	0.88 (0.58-1.35)
12.4<-16.4	0.83 (0.68-1.01)	0.91 (0.60-1.36)	0.77 (0.55-1.07)	0.80 (0.34-1.86)	0.63 (0.39-1.02)	1.27 (0.79-2.03)
16.4<-22.6	0.89 (0.71-1.12)	0.83 (0.50-1.36)	0.86 (0.59-1.26)	0.93 (0.37-2.30)	0.55 (0.30-1.02)	1.67 (0.97-2.88)
>22.6	0.94 (0.70-1.27)	0.54 (0.27-1.08)	0.94 (0.58-1.52)	0.68 (0.21-2.22)	0.78 (0.36-1.68)	2.11 (1.05-4.24)
p for trend	0.48	0.085	0.44	0.38	0.67	0.0058
p for interaction with ethnicity	0.14					
p for interaction with sex	0.95					

Chapter 8. Study Assumption Validation

8.1 MISSING PATTERN EXAMINATION

Risk factors included in the base model appear to be missing at a modest level, with all missing rates less than 5%. Missing data rates of omega-3 fatty acids were similar across ethnic groups, with 4.2% for Caucasian, 4.6% for African American, 4.2% for Native Hawaiian, 3.9% for Japanese, and 3.8% for Latino.

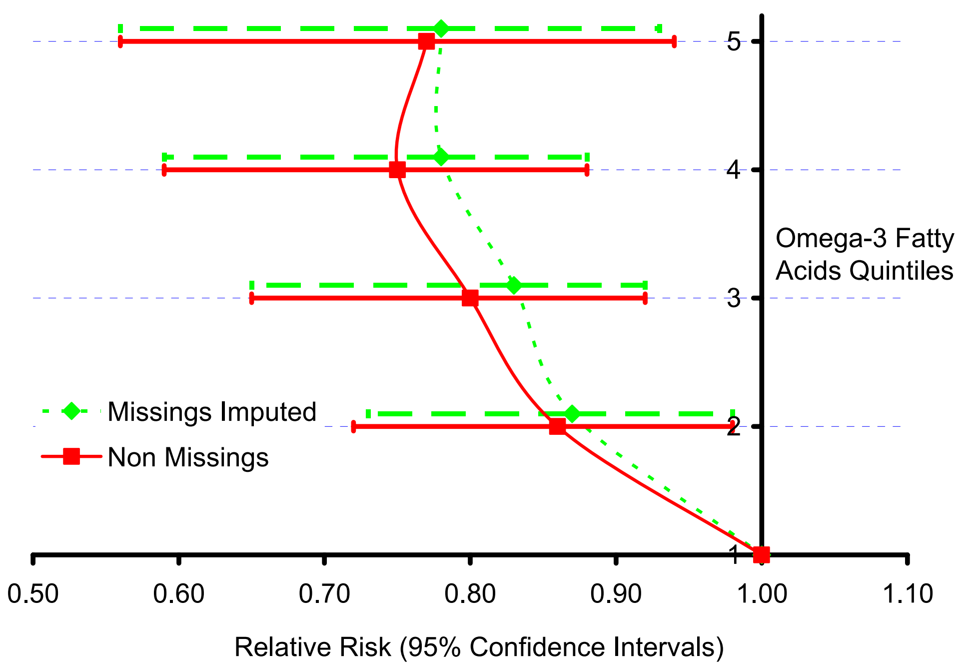
CHD, stroke, or hypertension mortality rates within sex, ethnic, and age groups are higher in cohort members with missing data than those without missing data. Men and African Americans had higher death rates in subjects with missing data than did other groups. Missing data of each of the risk factors in the primary model were imputed, conditioning on age at cohort entry, sex, and ethnicity, for a single instance as a sensitivity analysis. Table 8.1 displays the number of deaths and observations available for analysis before and after imputation. After single imputation, there were 267 additional cases (18%) of CHD deaths and 10.2% more observations available for the primary model for men, and 217 additional cases (9.9%) of CHD deaths and 5.8% more observations available for the analyses in women.

The relative risks and 95% confidence intervals for CHD mortality with imputed omega-3 fatty acids were calculated for men and women, adjusting for other imputed covariates. The robustness of the primary model for omega-3 fatty acids in men was validated as displayed graphically in Figure 2. The inverse relationship between CHD mortality and omega-3 fatty acids from the imputed data was similar to the result from non-missing data model. Therefore results of non-missing data were used.

Table 8.1. Distribution of CHD Deaths and Obervations Avaliable for the Primary Model Before and After Imputing Missing Risk Factors

Sex	Death/ Observations	Total	Caucasian	African American	Native Hawaiian	Japanese American	Latino
Men	No Imputation	2,198/ 70,837	492/ 18,376	516/ 9,056	171/ 5,073	466/ 21,953	553/ 16,379
	Imputed	2,415/ 74,951	533/ 19,193	590/ 9,939	179/ 5,270	503/ 22,835	610/ 17,714
Women	No Imputation	1,491/ 86,266	297/ 21,950	573/ 15,324	100/ 6,593	240/ 25,542	281/ 16,857
	Imputed	1,758/ 95,076	329/ 23,658	701/ 17,685	120/ 7,068	282/ 27,345	326/ 19,320

Figure 8.1. Graphical Comparisons of Relative Risks of CHD with Omega-3 Fatty Acids between Non Missing Data and Missing Data Imputed in Men



Chapter 9. Summary

9.1 CONCLUSIONS

- There were large differences in food sources for dietary omega-3 fatty acids among ethnic groups. The top sources for omega-3 fatty acids were regular salad dressings, canned tuna fish, macaroni or potato salad, mayonnaise in sandwiches, and vegetable oils in cooking. The ethnic differences in the contribution of these typical Western sources to dietary omega-3 and omega-6 fatty acid intake were small. However, there are larger ethnic differences in traditional sources for dietary omega-3 fatty acids such as tofu, miso soup, Mexican and Spanish rice, and refined beans. There is a need for nutrition interventions involving dietary omega-3 fatty acids to be tailored specifically to each population because of traditional variations in eating patterns.
- The findings suggested a protective effect of omega-3 fatty acids from fish and plant sources on CHD death. Observed differences by food source may reflect the effects of different preparation methods. Omega-3 fatty acid sources of fresh fish, soy products, and oil use may reduce CHD mortality risk, but intake of foods rich in omega-3 fatty acids and other nutrients associated with the risk of CHD, such as trans fats and reduced ω3 in fried fish and sodium in salted/dried fish, may increase CHD risk.
- The data also suggested that dietary omega-3 fatty acids from fish and plant sources may be protective against mortality from stroke. Consumption of fish with high salt content (e.g., salted and dried fish) was related to a higher risk of stroke mortality, especially hemorrhagic stroke for Japanese men. Perhaps use of shoyu in fish preparation, with its high salt content, led to the Japanese men not exhibiting the protective effect for fish seen in other groups. Reasons for possible sex differences in the effects of legume intake require further study.

- The strong inverse association of omega-3 fatty acid intake with the risk for sudden cardiac death supported their purported anti-arrhythmias effect as heart rate variability is the major underlying cause of sudden cardiac death. The cardioprotective effect of dietary omega-3 fatty acids may be mediated through diabetes.
- The findings also suggested that omega-6 fatty acids may be protective against CHD, stroke, and hypertension death. This is further supported by the protective effect of nut intake, a source of omega-6 but not omega-3 fatty acids. The effect was stronger against stroke and hypertension mortality. A high ratio of omega-6 to omega-3 fatty acids may be related to CHD mortality risk, but not to stroke and hypertension death. A well-controlled trial is needed to identify the most protective ratio of omega-6 to omega-3 fatty acids.
- The primary model in this research was considered robust given that imputation of missing data among the risk factors and adjustment variables did not alter the results.
- This research has filled gaps in knowledge by studying: 1) the role of the ratio of omega-6 to omega-3 fatty acids on CVD mortality outcomes; 2) the effect of different methods of preparation for fish, with those having the smallest introduction of trans fat and salt content being protective; 3) vegetable oil use in cooking, a relevant food sources for omega-3 fatty acids in the U.S., that may be protective against CHD and stroke mortality; and 4) tofu and shoyu intake that may be protective against CHD and stroke death.

9.2 CARDIOPROTECIVE NUTRITION INTERVENTION MESSAGES

- The findings suggest an increased daily intake of omega-3 fatty acids might be beneficial to cardiovascular prevention. The median intake of omega-3 fatty acids was 1.8 grams per day in our cohort. We observed protective relative risks at the 4th quintile (median of 2.2 grams/day) and the 5th quintile of omega-3 fatty acid intake for CHD death, but only found the protection against stroke death up to the 4th quintile of omega-3 fatty acids. Therefore, moderately increased dietary omega-3 fatty acid intake seems appropriate for the prevention of cardiovascular disease in the U.S. population.

- For Americans who do not have easy access to fresh fish or who are allergic to fish, increased vegetable oils in cooking could be an option. The median vegetable oil use in cooking was 0.7 gram per day in our data. The 5th quintile was 3.7 grams per day in our data and intake above this level was found to be protective against the risk of CHD as well as ischemic stroke, as was the 4th quintile (1.2-3.7 grams/day) for overall stroke death. Although the cardiovascular protective mechanism from vegetable oil has not been determined, increasing vegetable oil use to salads and in non-deep-fry cooking seems to be a reasonable recommendation.
- To gain benefits from fish consumption, good choices need to be made regarding type and preparation methods. For instance, canned tuna fish and baked, boiled and raw fish are preferable to fried and salted fish. Also, as soy product intake also seemed to be protective, preparing fish with sauce of low salt content, such as low sodium shoyu, could be recommended.
- Tofu could be considered as an alternative for nutrition intervention against cardiovascular diseases, particularly for women.

9.3 FUTURE RESEARCH

The following research questions could be followed up from this research:

- What is the optimum range of the ratio of omega-6 to omega-3 fatty acids for dietary cardiovascular prevention? Although we found < 7.7 (the referent) has a lower risk than other higher quintiles, the range of this ratio from 1 to 7.7 is too wide and some levels may be associated with risk.

Perhaps further analysis for this range could be done when more cases are ascertained after a longer term of follow-up.

- Whether ALA in vegetable oils has a stronger cardioprotective effect than EPA from fish? The specific effects of EPA, DHA, and ALA on the mortality risk of CHD, stroke, and hypertension could be explored in this cohort.
- Is high salt use in the preparation of baked, boiled, and raw fish the primary risk factor for the high stroke mortality rate in Japanese?
- What is the determinant for the sex differences in the effects from legumes and soy products on stroke mortality, overall and by subtype? Does the effect of legume intake on stroke mortality vary by preparation methods among ethnic groups?
- Omega-3 fatty acid intake is correlated with other healthy dietary intakes, making it difficult to definitively separate the effects on CVD mortality. The examination of dietary patterns may further elucidate the role of diet on risk.

Appendixes

Appendix 1. Characteristics of Men Free of Heart Attack or Angina at Baseline

The study population for the CHD risk investigation included 82,243 men and 103,884 women of the five major ethnic groups of Caucasian, African American, Native Hawaiian, Japanese, and Latino who were free of angina and heart attack at study entry. By the end of 2005, there were 4,516 CHD deaths during an average of 11.9 years of follow-up. Distribution of cohort males free of heart attack or angina, baseline characteristics, their median intake of fish, omega-3 fatty acids, tofu, shoyu, fish preparation methods, and numbers of CHD deaths are shown by ethnicity in Table A1.1 to 6. African Americans had the highest CHD age-adjusted death rate at 541.3, whereas Japanese Americans had the lowest CHD death rate at 228.6. Native Hawaiians and Japanese Americans had higher median total fish and tofu intake than other ethnic groups, respectively of 24.6 and 20.2 grams of fish per day and 7.4 and 14.9 grams of tofu per day. The median tofu intake for other ethnic groups were zero. Interestingly, the median omega-3 fatty acid intake of about 1.8 gram/day were similar among ethnic groups, except slightly higher for Native Hawaiians.

Only 5.1% Japanese were obese with a BMI greater than 30, but other ethnic groups had at least double. More Native Hawaiians, African Americans, and Latinos had diabetes history (>14.7%) than other ethnic groups, whereas Caucasian men had the lowest at only 5.6%. More African Americans and Native Hawaiians had hypertension history, at 51.3% and 45.2% respectively, than other ethnic groups, but Caucasians had the lowest at 28.6%. African Americans had the highest proportion of current smokers and Caucasians had the largest proportion of heavy drinkers (>24 g/day) among all the ethnic groups. Caucasians had the highest proportion with some colleague education while Latinos had the least. Japanese had the lowest median calories from saturated fat per day while Latinos had the highest. More African Americans and Japanese did not have any vigorous physical activities than other ethnic groups.

Table A1.1. Descriptive Statistics of Baseline Characteristics as Known Risk Factors and Deaths of CHD in Men Free of Heat Attack or Angina by Ethnicity

	Statistics (N)	Total (82,243)	Caucasian (20,568)	African American (11,151)	Native Hawaiian (5,658)	Japanese American (24,389)	Latinos (20,477)
CHD death	n	2,604	561	659	191	526	667
(rate)	(rate*)	(348.9)	(343.9)	(541.3)	(506.6)	(228.6)	(386.2)
Age (years)	Mean	59.8	58.5	61.7	56.4	60.8	59.9
	S.D.	8.86	9.04	8.96	8.56	9.24	7.72
	Median	60	58	63	55	62	60
	Minimum	45	45	45	45	45	45
	Maximum	78	77	78	78	77	77
Body Mass Index							
<23	n (%)	17194 (20.9%)	4429 (21.5%)	1880 (16.9%)	628 (11.1%)	7599 (31.2%)	2658 (13.0%)
23-	n (%)	18190 (22.1%)	4898 (23.8%)	2081 (18.7%)	790 (14.0%)	6521 (26.7%)	3900 (19.0%)
25-	n (%)	34903 (42.4%)	8463 (41.1%)	4863 (43.6%)	2419 (42.8%)	8777 (36.0%)	10381 (50.7%)
30-	n (%)	8749 (10.6%)	2116 (10.3%)	1520 (13.6%)	1174 (20.7%)	1237 (5.1%)	2702 (13.2%)
35-	n (%)	2581 (3.1%)	616 (3.0%)	432 (3.9%)	620 (11.0%)	223 (0.9%)	690 (3.4%)
Hypertension	n (%)	30915 (37.6%)	5881 (28.6%)	5720 (51.3%)	2556 (45.2%)	10186 (41.8%)	6572 (32.1%)
Diabetes	n (%)	9386 (11.4%)	1152 (5.6%)	1640 (14.7%)	839 (14.8%)	2710 (11.1%)	3045 (14.9%)
Smoking							
Never	n (%)	25034 (30.4%)	6764 (32.9%)	2787 (25.0%)	1790 (31.6%)	7213 (29.6%)	6480 (31.6%)
Past <=20 pkyrs	n (%)	29557 (35.9%)	6577 (32.0%)	4063 (36.4%)	1749 (30.9%)	8877 (36.4%)	8291 (40.5%)
Past >20 pkyrs	n (%)	11545 (14.0%)	3659 (17.8%)	1203 (10.8%)	789 (13.9%)	4348 (17.8%)	1546 (7.5%)
Current <=20 pkyrs	n (%)	7312 (8.9%)	1117 (5.4%)	1751 (15.7%)	509 (9.0%)	1464 (6.0%)	2471 (12.1%)
Current >20 pkyrs	n (%)	7791 (9.5%)	2294 (11.2%)	1182 (10.6%)	766 (13.5%)	2321 (9.5%)	1228 (6.0%)
Education							
<=High School	n (%)	33838 (41.1%)	4491 (21.8%)	4616 (41.4%)	2808 (49.6%)	8977 (36.8%)	12946 (63.2%)
Further Educ	n (%)	23462 (28.5%)	5918 (28.8%)	3880 (34.8%)	1722 (30.4%)	7255 (29.7%)	4687 (22.9%)
=>College	n (%)	24014 (29.2%)	10006 (48.6%)	2479 (22.2%)	1070 (18.9%)	7993 (32.8%)	2466 (12.0%)

Table A1.2. Descriptive Statistics of Baseline Energy-Related Characteristics as Known Risk Factors and Deaths of CHD in Men Free of Heart Attack or Angina by Ethnicity

	Statistics (N)	Total (82,243)	Caucasian (20,568)	African American (11,151)	Native Hawaiian (5,658)	Japanese American (24,389)	Latinos (20,477)
Alcohol (g/day)							
0	n (%)	29493 (35.9%)	5418 (26.3%)	4642 (41.6%)	2196 (38.8%)	10313 (42.3%)	6924 (33.8%)
>0 – 12	n (%)	25615 (31.1%)	6260 (30.4%)	3359 (30.1%)	1584 (28.0%)	6857 (28.1%)	7555 (36.9%)
>12 - 24	n (%)	8687 (10.6%)	2625 (12.8%)	957 (8.6%)	579 (10.2%)	2444 (10.0%)	2082 (10.2%)
>24	n (%)	15232 (18.5%)	5437 (26.4%)	1699 (15.2%)	1070 (18.9%)	3852 (15.8%)	3174 (15.5%)
Vigorous Work (hrs/day)							
0	n (%)	32790 (39.9%)	7604 (37.0%)	5233 (46.9%)	1426 (25.2%)	10488 (43.0%)	8039 (39.3%)
>0 - 1.5	n (%)	39728 (48.3%)	10613 (51.6%)	4602 (41.3%)	3430 (60.6%)	11768 (48.3%)	9315 (45.5%)
>1.5 - 5.0	n (%)	5327 (6.5%)	1463 (7.1%)	487 (4.4%)	593 (10.5%)	1154 (4.7%)	1630 (8.0%)
Daily Calories							
	n	79027	19740	10657	5429	23466	19735
	Mean	2386.6	2298.5	2192.8	2788.4	2269	2608.7
	S.D.	1101.07	900.91	1163.24	1338.16	834.62	1361.38
	Median	2164.4	2137.9	1934.6	2499.6	2130	2306.8
	Minimum	475.4	763.6	475.4	731.4	803.3	604.1
	Maximum	8434.2	5713.5	7217.7	8390.9	5408.1	8434.2
Calories from Saturated Fat per Day							
	n	79027	19740	10657	5429	23466	19735
	Mean	220.8	221.7	223.8	247.4	175.8	264.3
	S.D.	131.08	113.76	138.39	146.73	88.84	160.36
	Median	189.6	198.6	190.1	212.2	157.9	225.8
	Minimum	21.8	32.3	24.9	32.9	21.8	26.4
	Maximum	1328.9	971.2	1047.9	1042.7	723.9	1328.9

Table A1.3. Descriptive Statistics of Baseline Fish and Fish Preparation Methods in Men Free of Heart Attack or Angina by Ethnicity

	Statistics (N)	Total (82,243)	Caucasian (20,568)	African American (11,151)	Native Hawaiian (5,658)	Japanese American (24,389)	Latinos (20,477)
Total Fish Excluding Shell Fish (g/day)							
	n	79027	19740	10657	5429	23466	19735
	Mean	20.7	19.2	15.6	35.8	27.9	12.1
	S.D.	25.5	22.34	20.29	40.07	27.52	18.01
	Median	13.7	13	10.2	24.6	20.2	7.1
	Minimum	0	0	0	0	0	0
	Maximum	644	360	393.2	644	394.1	459.7
<4.7	n (%)	14272 (17.4%)	3451 (16.8%)	2342 (21.0%)	315 (5.6%)	1559 (6.4%)	6605 (32.3%)
4.7-<9.6	n (%)	13832 (16.8%)	3640 (17.7%)	2302 (20.6%)	510 (9.0%)	2976 (12.2%)	4404 (21.5%)
9.6-<15.9	n (%)	15364 (18.7%)	4179 (20.3%)	2223 (19.9%)	836 (14.8%)	4477 (18.4%)	3649 (17.8%)
15.9-<27.0	n (%)	17071 (20.8%)	4316 (21.0%)	2035 (18.2%)	1386 (24.5%)	6475 (26.5%)	2859 (14.0%)
27.0-	n (%)	18488 (22.5%)	4154 (20.2%)	1755 (15.7%)	2382 (42.1%)	7979 (32.7%)	2218 (10.8%)
Fried Fish (g/day)							
	n	79027	19740	10657	5429	23466	19735
	Mean	4.9	3.2	3.9	7.5	7.7	3.1
	S.D.	8.74	6.58	7.37	11.97	10.53	6.67
	Median	2.8	0	0.9	4.7	4.7	0.9
	Minimum	0	0	0	0	0	0
	Maximum	284	142	101.4	170	142	284
0	n (%)	30970 (37.7%)	10490 (51.0%)	5114 (45.9%)	1233 (21.8%)	4489 (18.4%)	9644 (47.1%)
0 <-6.2	n (%)	24636 (30.0%)	5417 (26.3%)	3003 (26.9%)	1923 (34.0%)	7675 (31.5%)	6618 (32.3%)
> 6.2	n (%)	23421 (28.5%)	3833 (18.6%)	2540 (22.8%)	2273 (40.2%)	11302 (46.3%)	3473 (17.0%)
Baked, Boiled or Raw Fish (g/day)							
	n	79027	19740	10657	5429	23466	19735
	Mean	6.2	6.5	3.7	10	9.1	2.9
	S.D.	11.6	10.87	8.48	16.69	13.74	7.28
	Median	2.8	2.8	0	7	7	0
	Minimum	0	0	0	0	0	0
	Maximum	284	284	170	284	284	142
0	n (%)	28830 (35.1%)	6567 (31.9%)	5934 (53.2%)	936 (16.5%)	3799 (15.6%)	11594 (56.6%)
0 <-6.2	n (%)	22510 (27.4%)	5721 (27.8%)	2419 (21.7%)	1721 (30.4%)	7694 (31.5%)	4955 (24.2%)
> 6.2	n (%)	27687 (33.7%)	7452 (36.2%)	2304 (20.7%)	2772 (49.0%)	11973 (49.1%)	3186 (15.6%)

Table A1.4. Descriptive Statistics of Baseline Canned Fish by Type, Salted/Dried Fish, and Fried Chicken in Men Free of Heart Attack or Angina by Ethnicity

	Statistics (N)	Total (82,243)	Caucasian (20,568)	African American (11,151)	Native Hawaiian (5,658)	Japanese American (24,389)	Latinos (20,477)
Canned Tuna Fish (g/day)							
	n	79027	19740	10657	5429	23466	19735
	Mean	7.6	8.2	5.9	13.2	8.9	5
	S.D.	13.78	14.06	12.59	20.62	13.87	10.59
	Median	3	3	3	7.4	5.9	3
	Minimum	0	0	0	0	0	0
	Maximum	360	360	360	360	180	360
0		21707	5241	3620	712	4229	7905
	n (%)	(26.4%)	(25.5%)	(32.5%)	(12.6%)	(17.3%)	(38.6%)
0<-3.0		20595	4862	2999	1050	6367	5317
	n (%)	(25.0%)	(23.6%)	(26.9%)	(18.6%)	(26.1%)	(26.0%)
3.0<-7.4		19632	5007	2382	1520	6867	3856
	n (%)	(23.9%)	(24.3%)	(21.4%)	(26.9%)	(28.2%)	(18.8%)
>7.4		17093	4630	1656	2147	6003	2657
	n (%)	(20.8%)	(22.5%)	(14.9%)	(37.9%)	(24.6%)	(13.0%)
Other Canned Fish (g/day)							
	n	79027	19740	10657	5429	23466	19735
	Mean	1.8	1.3	2.1	4.5	2	1
	S.D.	4.97	4.24	6	9.28	4.28	3.6
	Median	0	0	0	2.5	0	0
	Minimum	0	0	0	0	0	0
	Maximum	300	150	300	150	150	150
		28192	5007	4238	3339	10999	4609
Consumers	n (%)	(34.3%)	(24.3%)	(38.0%)	(59.0%)	(45.1%)	(22.5%)
Non-		50835	14733	6419	2090	12467	15126
consumers	n (%)	(61.8%)	(71.6%)	(57.6%)	(36.9%)	(51.1%)	(73.9%)
Salted and Dried Fish (g/day)							
	n	79027	19740	10657	5429	23466	19735
	Mean	0.1	0	0	0.5	0.3	0
	S.D.	0.73	0.33	0.24	1.61	0.94	0.38
	Median	0	0	0	0	0	0
	Minimum	0	0	0	0	0	0
	Maximum	30	10.7	10.7	30	30	30
		12087	1199	257	2024	7671	936
Consumers	n (%)	(14.7%)	(5.8%)	(2.3%)	(35.8%)	(31.5%)	(4.6%)
Non-		66940	18541	10400	3405	15795	18799
consumers	n (%)	(81.4%)	(90.1%)	(93.3%)	(60.2%)	(64.8%)	(91.8%)
Fried Chicken with Skin (g/d)							
	n	79027	19740	10657	5429	23466	19735
	Mean	5.8	3.8	9.6	7.8	6	5.1
	S.D.	12.45	9.35	18.07	14.79	10.85	11.99
	Median	1	0	4.3	4.3	2.1	0
	Minimum	0	0	0	0	0	0
	Maximum	265	189.2	265	265	265	265
		43948	8312	7397	3737	14735	9767
Consumers	n (%)	(53.4%)	(40.4%)	(66.3%)	(66.0%)	(60.4%)	(47.7%)
Non-		35079	11428	3260	1692	8731	9968
consumers	n (%)	(42.7%)	(55.6%)	(29.2%)	(29.9%)	(35.8%)	(48.7%)

Table A1.5. Descriptive Statistics of Baseline Soy Products and Omega-3 Fatty Acids in Men Free of Heart Attack or Angina by Ethnicity

	Statistics (N)	Total (82,243)	Caucasian (20,568)	African American (11,151)	Native Hawaiian (5,658)	Japanese American (24,389)	Latinos (20,477)
Tofu (g/day)							
	n	79027	19740	10657	5429	23466	19735
	Mean	8.7	4.2	0.5	12.7	21.9	0.6
	S.D.	21.89	14.38	5.95	26.98	30.57	7.07
	Median	0	0	0	7.4	14.9	0
	Minimum	0	0	0	0	0	0
	Maximum	450	450	225	450	450	450
-< 0.4		14747	4758	4652	185	306	4846
	n (%)	(17.9%)	(23.1%)	(41.7%)	(3.3%)	(1.3%)	(23.7%)
0.4 <-1.7		15728	5236	3347	442	601	6102
	n (%)	(19.1%)	(25.5%)	(30.0%)	(7.8%)	(2.5%)	(29.8%)
1.7 <-5.3		16326	4931	1903	1220	2715	5557
	n (%)	(19.9%)	(24.0%)	(17.1%)	(21.6%)	(11.1%)	(27.1%)
5.3 <-14.9		16018	3009	601	1955	7798	2655
	n (%)	(19.5%)	(14.6%)	(5.4%)	(34.6%)	(32.0%)	(13.0%)
> 14.9		16208	1806	154	1627	12046	575
	n (%)	(19.7%)	(8.8%)	(1.4%)	(28.8%)	(49.4%)	(2.8%)
Shoyu (g/day)							
	n	79027	19740	10657	5429	23466	19735
	Mean	2.4	1.6	0.5	4.9	4.9	0.6
	S.D.	4.1	3.01	1.55	5.64	5.03	1.86
	Median	0.3	0.3	0	3.6	3.6	0
	Minimum	0	0	0	0	0	0
	Maximum	20	20	20	20	20	20
	n (%)	31032	7617	6957	919	2734	12805
0		(37.7%)	(37.0%)	(62.4%)	(16.2%)	(11.2%)	(62.5%)
	n (%)	18124	5658	2656	1095	4036	4679
0 <-1.1		(22.0%)	(27.5%)	(23.8%)	(19.4%)	(16.5%)	(22.9%)
	n (%)	29871	6465	1044	3415	16696	2251
> 1.1		(36.3%)	(31.4%)	(9.4%)	(60.4%)	(68.5%)	(11.0%)
Omega 3 Fatty Acids (g/day)							
	n	79027	19740	10657	5429	23466	19735
	Mean	2.1	2	2	2.5	2	2.3
	S.D.	1.14	0.95	1.17	1.45	0.94	1.34
	Median	1.8	1.8	1.7	2.2	1.8	1.9
	Minimum	0.1	0.2	0.1	0.4	0.2	0.2
	Maximum	11.2	8.7	8.6	11.2	7.8	10.1
-< 1.1	n (%)	11370	2830	2175	500	2960	2905
		(13.8%)	(13.8%)	(19.5%)	(8.8%)	(12.1%)	(14.2%)
1.1 <- 1.4	n (%)	13874	3785	1980	678	4313	3118
		(16.9%)	(18.4%)	(17.8%)	(12.0%)	(17.7%)	(15.2%)
1.4 <- 1.9	n (%)	15882	4354	1982	918	5147	3481
		(19.3%)	(21.2%)	(17.8%)	(16.2%)	(21.1%)	(17.0%)
1.9 <- 2.6	n (%)	17770	4572	2054	1251	5748	4145
		(21.6%)	(22.2%)	(18.4%)	(22.1%)	(23.6%)	(20.2%)
> 2.6	n (%)	20131	4199	2466	2082	5298	6086
		(24.5%)	(20.4%)	(22.1%)	(36.8%)	(21.7%)	(29.7%)

Table A1.6. Descriptive Statistics of Baseline Major Sources for Omega-3 Fatty Acids in Men Free of Heart Attack or Angina by Ethnicity

	Statistics (N)	Total (82,243)	Caucasian (20,568)	African American (11,151)	Native Hawaiian (5,658)	Japanese American (24,389)	Latinos (20,477)
Oils in cooking (g/day)							
	n	79027	19740	10657	5429	23466	19735
	Mean	2.4	1.7	1.9	3.5	2.7	2.5
	S.D.	3.22	2.46	2.8	4.18	3.15	3.67
	Median	1	0.7	0.7	1.6	1.6	0.9
	Minimum	0	0	0	0	0	0
	Maximum	22.7	22.7	22.7	22.7	22.7	22.7
0		16140	5595	2453	675	2455	4962
	n (%)	(19.6%)	(27.2%)	(22.0%)	(11.9%)	(10.1%)	(24.2%)
0 <- 0.5		10133	2515	1694	508 (	2572	2844
	n (%)	(12.3%)	(12.2%)	(15.2%)	9.0%)	(10.5%)	(13.9%)
0.5 <- 1.2		17983	4653	2581	1194	5913	3642
	n (%)	(21.9%)	(22.6%)	(23.1%)	(21.1%)	(24.2%)	(17.8%)
1.2 <- 3.7		16259	3781	2003	1149	5978	3348
	n (%)	(19.8%)	(18.4%)	(18.0%)	(20.3%)	(24.5%)	(16.4%)
> 3.7		18512	3196	1926	1903	6548	4939
	n (%)	(22.5%)	(15.5%)	(17.3%)	(33.6%)	(26.8%)	(24.1%)
Mayonnaise use (g/d)							
	n	79027	19740	10657	5429	23466	19735
	Mean	18.7	19.2	19.6	24.4	14.8	20.9
	S.D.	29.54	24.93	30.24	49.3	21.17	33.84
	Median	10.2	11.7	10.9	11.1	8.4	11
	Minimum	0	0	0	0	0	0
	Maximum	1085.8	581.7	555.8	1085.8	574.5	738.3
0<-4.5		19387	3666	2552	1415	6748	5006
	n (%)	(23.6%)	(17.8%)	(22.9%)	(25.0%)	(27.7%)	(24.4%)
4.5 <- 8.9		15763	3944	2096	890	5290	3543
	n (%)	(19.2%)	(19.2%)	(18.8%)	(15.7%)	(21.7%)	(17.3%)
8.9 <- 15.2		15977	4282	2231	943	4615	3906
	n (%)	(19.4%)	(20.8%)	(20.0%)	(16.7%)	(18.9%)	(19.1%)
15.2 <- 29.0		15174	4321	2010	1038	4112	3693
	n (%)	(18.5%)	(21.0%)	(18.0%)	(18.3%)	(16.9%)	(18.0%)
> 29.0		12726	3527	1768	1143	2701	3587
	n (%)	(15.5%)	(17.1%)	(15.9%)	(20.2%)	(11.1%)	(17.5%)
Mexican dishes with Tortilla Bread (g/d)							
	n	79027	19740	10657	5429	23466	19735
	Mean	36	26.1	27.7	12.4	11.1	86.4
	S.D.	71.49	40.29	49.1	31.77	24.1	114.02
	Median	12.2	12.7	10.5	0	0	53
	Minimum	0	0	0	0	0	0
	Maximum	2100.8	869.9	1040	987.3	798.1	2100.8
0		30439	6893	3963	3379	14234	1970 (
	n (%)	(37.0%)	(33.5%)	(35.5%)	(59.7%)	(58.4%)	9.6%)
0 <- 26.2		20354	6240	3236	1224	5890	3764
	n (%)	(24.7%)	(30.3%)	(29.0%)	(21.6%)	(24.2%)	(18.4%)
> 26.2		28234	6607	3458	826	3342	14001
	n (%)	(34.3%)	(32.1%)	(31.0%)	(14.6%)	(13.7%)	(68.4%)

Appendix 2. Characteristics of Women Free of Heart Attack or Angina at Baseline

Similar distribution of these characteristics were observed in women as shown in Table A2.1 to 7. Distribution of cohort females free of heart attack or angina, baseline characteristics, their median intake of fish, omega-3 fatty acids, tofu, shoyu, fish preparation methods, and numbers of CHD are shown by ethnicity in Table 13 to 18. African Americans had the highest CHD death rate at 366.2, whereas Japanese Americans had the lowest CHD death rate at 106.0. Native Hawaiians and Japanese Americans had higher median total fish and tofu intake than other ethnic groups, respectively of 19.3 and 15.5 grams of fish per day and 7.8 and 14.9 grams of tofu per day. The median tofu intake for other ethnic groups were also zero. The median omega-3 fatty acid intake of about 1.5 gram/day were similar among ethnic groups, except slightly high for Native Hawaiians.

Among women, only 4.9% Japanese were obese with a BMI greater than 30, but other ethnic groups had at least triple. African Americans, Latinos, and Native Hawaiians had relatively high diabetes history of at least 13%, whereas Caucasian had the lowest at only 4.8%. More African Americans and Native Hawaiians had hypertension history, at 53.2% and 40.7% respectively, than other ethnic groups, whereas Caucasians had the lowest at 25.6%. African Americans and Native Hawaiians had the most current smokers and Caucasians had the most heavy drinkers (>24 g/day) among all the ethnic groups. Caucasians also had the highest proportion with some colleague education while Latinas had the least among ethnic groups. Japanese had the lowest median percent calories from saturated fat per day while Latinas had the highest. Similarly to men, more African American and Japanese women did not report any vigorous physical activities than other ethnic groups. Japanese women had the oldest age at natural menopause. In addition, Japanese and Caucasians reported more hormonal use than other ethnic groups.

Table A2.1. Descriptive Statistics of Baseline Characteristics as Known Risk Factors and Deaths of CHD in Women Free of Heart Attack or Angina by Ethnicity

	Statistics (N)	Total (103,884)	Caucasian (25,224)	African American (19,475)	Native Hawaiian (7,630)	Japanese American (28,989)	Latinos (22,566)
CHD death	n	367	340	774	136	295	367
	(Rate)	(212.6)	(156.2)	(366.2)	(311.3)	(106.0)	(212.6)
Age (years)	Mean	59.5	58.7	60.6	56	60.8	59.1
	S.D.	8.83	8.99	9.18	8.64	8.95	7.73
	Median	60	58	61	54	62	59
	Minimum	45	45	45	45	45	45
	Maximum	78	77	78	78	78	77
Body Mass Index							
<23	n (%)	35,114 (33.8%)	10,233 (40.6%)	3,026 (15.5%)	1,636 (21.4%)	15,890 (54.8%)	4,329 (19.2%)
23-	n (%)	16,584 (15.9%)	4,246 (16.8%)	2,576 (13.2%)	1,038 (13.6%)	5,062 (17.5%)	3,662 (16.2%)
25-	n (%)	31,192 (30.0%)	6,756 (26.8%)	6,966 (35.8%)	2,468 (32.3%)	6,131 (21.1%)	8,871 (39.3%)
30-	n (%)	12,242 (11.8%)	2,425 (9.6%)	3,687 (18.9%)	1,337 (17.5%)	1,138 (3.9%)	3,655 (16.2%)
35-	n (%)	6,908 (6.6%)	1,427 (5.7%)	2,436 (12.5%)	1,035 (13.6%)	284 (1.0%)	1,726 (7.6%)
Hypertension	n (%)	37,619 (36.2%)	6,462 (25.6%)	10,367 (53.2%)	3,102 (40.7%)	10,291 (35.5%)	7,397 (32.8%)
Diabetes	n (%)	10,429 (10.0%)	1,208 (4.8%)	2,652 (13.6%)	1,003 (13.1%)	2,539 (8.8%)	3,027 (13.4%)
Smoking							
Never	n (%)	57,403 (55.2%)	11,240 (44.6%)	8,869 (45.5%)	3,422 (44.8%)	19,771 (68.2%)	1,4101 (62.5%)
Past <=20 pkyrs	n (%)	24,902 (23.9%)	7,192 (28.5%)	5,588 (28.7%)	1,915 (25.1%)	5,397 (18.6%)	4,810 (21.3%)
Past >20 pkyrs	n (%)	4,899 (4.7%)	2,363 (9.4%)	864 (4.4%)	457 (6.0%)	855 (2.9%)	360 (1.6%)
Current <=20 pkyrs	n (%)	9,210 (8.9%)	1,777 (7.0%)	2,852 (14.6%)	1,090 (14.3%)	1,676 (5.8%)	1,815 (8.0%)
Current >20 pkyrs	n (%)	5,410 (5.2%)	2,408 (9.5%)	981 (5.0%)	657 (8.6%)	931 (3.2%)	433 (1.9%)
Education							
<=High School	n (%)	47,432 (45.6%)	7,437 (29.5%)	7,742 (39.8%)	4,148 (54.4%)	12,195 (42.1%)	15,910 (70.5%)
Further Educ	n (%)	30,252 (29.1%)	8,381 (33.2%)	7,046 (36.2%)	2,187 (28.7%)	8,354 (28.8%)	4,284 (19.0%)
=>College	n (%)	24,876 (23.9%)	9,183 (36.4%)	4,370 (22.4%)	1,223 (16.0%)	8,185 (28.2%)	1,915 (8.5%)

Table A2.2. Descriptive Statistics of Baseline Energy-Related Characteristics as Known Risk Factors and Deaths of CHD in Women Free of Heart Attack or Angina by Ethnicity

	Statistics (N)	Total (103,884)	Caucasian (25,224)	African American (19,475)	Native Hawaiian (7,630)	Japanese American (28,989)	Latinos (22,566)
Alcohol (g/day)							
0	n (%)	61,330 (59.0%)	9,633 (38.2%)	11,506 (59.1%)	4,573 (59.9%)	21,674 (74.8%)	13,944 (61.8%)
>0 – 12	n (%)	28,665 (27.6%)	9,262 (36.7%)	5,454 (28.0%)	2,052 (26.9%)	5,326 (18.4%)	6,571 (29.1%)
>12 - 24	n (%)	4,562 (4.4%)	2,335 (9.3%)	757 (3.9%)	344 (4.5%)	521 (1.8%)	605 (2.7%)
>24	n (%)	5,162 (5.0%)	2,996 (11.9%)	892 (4.6%)	336 (4.4%)	432 (1.5%)	506 (2.2%)
Vigorous Work (hrs/day)							
0	n (%)	70,635 (67.9%)	16,247 (64.4%)	13,804 (70.9%)	3,993 (52.3%)	21,932 (75.7%)	14,659 (65.0%)
>0 - 1.5	n (%)	22,991 (22.1%)	6,805 (27.0%)	3,233 (16.6%)	2,978 (39.0%)	5,290 (18.2%)	4,685 (20.8%)
>1.5 - 5.0	n (%)	1,152 (1.1%)	359 (1.4%)	136 (0.7%)	204 (2.7%)	145 (0.5%)	308 (1.4%)
Daily Calories							
	n	99,719	24,226	18,609	7,305	27,953	21,626
	Mean	1942.6	1810.1	1877.8	2362.8	1810.4	2175.9
	S.D.	939.11	704.3	992.61	1260.08	679.24	1170.73
	Median	1741.5	1686.3	1648.8	2065.7	1692.5	1896.3
	Minimum	417.3	608.8	417.3	575.5	641.3	487.4
	Maximum	7659.2	4511.5	6111.5	7659.2	4361.2	7211.3
Calories from Saturated Fat per Day							
	n	99,719	24,226	18,609	7,305	27,953	21,626
	Mean	176	169.1	184	210.9	137.6	214.9
	S.D.	109.88	88.2	117.07	135.16	69.94	136.84
	Median	148.9	149.8	155	176.4	123.4	180.3
	Minimum	18.6	23.2	21	26.7	20.5	18.6
	Maximum	1108.7	757.5	912.6	1108.7	590.8	1090.3

Table A2.3. Descriptive Statistics of Type and Age at Menopause and Hormone Replacement Therapy Use in Women Free of Heart Attack or Angina by Ethnicity

	Statistics (N)	Total (103,884)	Caucasian (25,224)	African American (19,475)	Native Hawaiian (7,630)	Japanese American (28,989)	Latinos (22,566)
Age at Natural Menopause							
<45	n (%)	8,181 (7.9%)	1,826 (7.2%)	1,597 (8.2%)	655 (8.6%)	1,713 (5.9%)	2,390 (10.6%)
45-49	n (%)	15,909 (15.3%)	4,224 (16.7%)	2,450 (12.6%)	1,040 (13.6%)	4227 (14.6%)	3,968 (17.6%)
50-54	n (%)	20,646 (19.9%)	4,995 (19.8%)	2,817 (14.5%)	1,129 (14.8%)	7,339 (25.3%)	4,366 (19.3%)
>=55	n (%)	5,409 (5.2%)	1,211 (4.8%)	878 (4.5%)	327 (4.3%)	2,001 (6.9%)	992 (4.4%)
Age at Oophorectomy							
<45	n (%)	2,121 (8.4%)	2,013 (10.3%)	623 (8.2%)	1,903 (6.6%)	1,471 (6.5%)	8,131 (7.8%)
45-49	n (%)	1,028 (4.1%)	750 (3.9%)	291 (3.8%)	1,288 (4.4%)	680 (3.0%)	4,037 (3.9%)
50-54	n (%)	435 (1.7%)	273 (1.4%)	114 (1.5%)	614 (2.1%)	329 (1.5%)	1,765 (1.7%)
>=55	n (%)	97 (0.4%)	56 (0.3%)	24 (0.3%)	107 (0.4%)	44 (0.2%)	328 (0.3%)
Age at Hysterectomy							
<45	n (%)	11,397 (11.0%)	2,836 (11.2%)	3,250 (16.7%)	731 (9.6%)	1,922 (6.6%)	2,658 (11.8%)
45-49	n (%)	2,606 (2.5%)	618 (2.5%)	627 (3.2%)	177 (2.3%)	597 (2.1%)	587 (2.6%)
50-54	n (%)	889 (0.9%)	190 (0.8%)	164 (0.8%)	52 (0.7%)	268 (0.9%)	215 (1.0%)
>=55	n (%)	176 (0.2%)	28 (0.1%)	54 (0.3%)	16 (0.2%)	43 (0.1%)	35 (0.2%)
Hormonal Use							
Never	n (%)	17,920 (17.2%)	3,337 (13.2%)	4,160 (21.4%)	1,277 (16.7%)	3,954 (13.6%)	5,192 (23.0%)
Past ET	n (%)	10,871 (10.5%)	2,567 (10.2%)	2,835 (14.6%)	682 (8.9%)	2,411 (8.3%)	2,376 (10.5%)
Past PT	n (%)	537 (0.5%)	144 (0.6%)	93 (0.5%)	52 (0.7%)	138 (0.5%)	110 (0.5%)
Past EPT	n (%)	5,298 (5.1%)	1,569 (6.2%)	798 (4.1%)	357 (4.7%)	1,302 (4.5%)	1,272 (5.6%)
Current ET	n (%)	16,861 (16.2%)	5,164 (20.5%)	2473 (12.7%)	1043 (13.7%)	5,015 (17.3%)	3,166 (14.0%)
Current PT	n (%)	777 (0.7%)	198 (0.8%)	90 (0.5%)	61 (0.8%)	267 (0.9%)	161 (0.7%)

Table A2.4. Descriptive Statistics of Baseline Fish and Fish Preparation Methods in Women Free of Heart Attack or Angina by Ethnicity

	Statistics (N)	Total (103,884)	Caucasian (25,224)	African American (19,475)	Native Hawaiian (7,630)	Japanese American (28,989)	Latinos (22,566)
Total Fish Excluding Shell Fish (g/day)							
	n	99,719	24,226	18,609	7,305	27,953	21,626
	Mean	16.5	14.6	14.4	28.8	21.2	10.4
	S.D.	20.8	16.5	18.62	34.57	21.52	16.25
	Median	10.7	10.2	9.6	19.3	15.5	5.8
	Minimum	0	0	0	0	0	0
	Maximum	667	384.7	340	667	378.9	350
<4.7	n (%)	22,262 (21.4%)	5,649 (22.4%)	4,562 (23.4%)	623 (8.2%)	2,836 (9.8%)	8,592 (38.1%)
4.7-<9.6	n (%)	22,338 (21.5%)	5,919 (23.5%)	4,426 (22.7%)	1,089 (14.3%)	5,484 (18.9%)	5,420 (24.0%)
9.6-<15.9	n (%)	20,539 (19.7%)	5,245 (20.8%)	3,873 (19.9%)	1,348 (17.7%)	6,713 (23.2%)	3,360 (14.9%)
15.9-<27.0	n (%)	18,644 (17.9%)	4,326 (17.2%)	3,162 (16.2%)	1,832 (24.0%)	6,913 (23.8%)	2,411 (10.7%)
27.0-	n (%)	15,936 (15.3%)	3,087 (12.2%)	2,586 (13.3%)	2,413 (31.6%)	6,007 (20.7%)	1,843 (8.2%)
Fried Fish (g/day)							
	n	99,719	24,226	18,609	7,305	27,953	21,626
	Mean	3.4	1.7	2.9	5.6	5.5	2.1
	S.D.	7.04	4.1	6.13	10.49	8.57	5.71
	Median	0.9	0	0	2.8	2.8	0
	Minimum	0	0	0	0	0	0
	Maximum	284	101.4	170	284	170	284
0	n (%)	47,861 (46.0%)	15,902 (63.0%)	10,388 (53.3%)	2,093 (27.4%)	6,806 (23.5%)	12,672 (56.2%)
0 <-6.2	n (%)	30,328 (29.2%)	5,643 (22.4%)	4,835 (24.8%)	2,692 (35.3%)	10,642 (36.7%)	6,516 (28.9%)
> 6.2	n (%)	21,530 (20.7%)	2,681 (10.6%)	3,386 (17.4%)	2,520 (33.0%)	10,505 (36.2%)	2,438 (10.8%)
Baked, Boiled or Raw Fish (g/day)							
	n	99,719	24,226	18,609	7,305	27,953	21,626
	Mean	4.8	5	3.6	7.6	6.6	2.4
	S.D.	9.43	8.49	8.63	12.81	10.91	6.51
	Median	2.3	2.8	0	2.8	2.8	0
	Minimum	0	0	0	0	0	0
	Maximum	284	167.2	284	170	284	170
0	n (%)	39,979 (38.4%)	9,094 (36.1%)	10,356 (53.2%)	1,596 (20.9%)	5,694 (19.6%)	13,239 (58.7%)
0 <-6.2	n (%)	30,530 (29.4%)	7,466 (29.6%)	4,274 (21.9%)	2,511 (32.9%)	10,871 (37.5%)	5,408 (24.0%)
> 6.2	n (%)	29,210 (28.1%)	7,666 (30.4%)	3,979 (20.4%)	3,198 (41.9%)	11,388 (39.3%)	2,979 (13.2%)

Table A2.5. Descriptive Statistics of Baseline Canned Fish by Type, Salted/Dried Fish, and Fried Chicken in Women Free of Heart Attack or Angina by Ethnicity

	Statistics (N)	Total (103,884)	Caucasian (25,224)	African American (19,475)	Native Hawaiian (7,630)	Japanese American (28,989)	Latinos (22,566)
Canned Tuna Fish (g/day)							
	n	99,719	24,226	18,609	7,305	27,953	21,626
	Mean	6.8	6.9	6.1	11.5	7.3	5.2
	S.D.	11.45	10.62	10.58	18.53	10.9	10.08
	Median	3	3	3	7.4	3.7	3
	Minimum	0	0	0	0	0	0
	Maximum	360	180	180	360	360	180
0	n (%)	23,967 (23.0%)	5,644 (22.4%)	5,224 (26.8%)	920 (12.1%)	4,694 (16.2%)	7,485 (33.2%)
0<-3.0	n (%)	29,134 (28.0%)	6,913 (27.4%)	5,877 (30.2%)	1,646 (21.6%)	8,270 (28.5%)	6,428 (28.5%)
3.0<-7.4	n (%)	28,479 (27.4%)	7,010 (27.8%)	4,710 (24.2%)	2,367 (31.0%)	9,606 (33.1%)	4,786 (21.2%)
>7.4	n (%)	18,139 (17.4%)	4,659 (18.5%)	2,798 (14.4%)	2,372 (31.1%)	5,383 (18.6%)	2,927 (13.0%)
Other Canned Fish (g/day)							
	n	99,719	24,226	18,609	7,305	27,953	21,626
	Mean	1.4	0.9	1.9	3.8	1.6	0.7
	S.D.	4.26	2.99	4.79	8.88	3.45	3.02
	Median	0	0	0	1.2	0	0
	Minimum	0	0	0	0	0	0
	Maximum	300	107.1	150	300	107.1	150
Consumers	n (%)	33,411 (32.1%)	5,551 (22.0%)	7,240 (37.2%)	4,310 (56.5%)	12,705 (43.8%)	3,605 (16.0%)
Non-consumers	n (%)	66,308 (63.8%)	18,675 (74.0%)	11,369 (58.4%)	2,995 (39.3%)	15,248 (52.6%)	18,021 (79.9%)
Salted and Dried Fish (g/day)							
	n	99,719	24,226	18,609	7,305	27,953	21,626
	Mean	0.1	0	0	0.3	0.2	0
	S.D.	0.63	0.17	0.21	1.27	0.94	0.25
	Median	0	0	0	0	0	0
	Minimum	0	0	0	0	0	0
	Maximum	60	10.7	21.4	30	60	20
Consumers	n (%)	9,883 (9.5%)	602 (2.4%)	268 (1.4%)	1,930 (25.3%)	6,326 (21.8%)	757 (3.4%)
Non-Consumers	n (%)	89,836 (86.4%)	23,624 (93.7%)	18,341 (94.2%)	5,375 (70.4%)	21,627 (74.6%)	20,869 (92.5%)
Fried Chicken with Skin (g/d)							
	n	99719	24226	18609	7305	27953	21626
	Mean	3.4	1.6	7.3	4.7	2.4	2.7
	S.D.	10.17	5.44	17.65	10.04	5.8	8.92
	Median	0	0	2.1	2	0	0
	Minimum	0	0	0	0	0	0
	Maximum	530	189.2	530	189.2	189.2	260
Consumers	n (%)	42795 (41.1%)	6781 (26.9%)	12356 (63.4%)	4188 (54.9%)	11620 (40.1%)	7850 (34.8%)
Non-Consumers	n (%)	56924 (54.7%)	17445 (69.2%)	6253 (32.1%)	3117 (40.9%)	16333 (56.3%)	13776 (61.0%)

Table A2.6. Descriptive Statistics of Baseline Soy Products and Omega-3 Fatty Acids in Women Free of Heart Attack or Angina by Ethnicity

	Statistics (N)	Total (103,884)	Caucasian (25,224)	African American (19,475)	Native Hawaiian (7,630)	Japanese American (28,989)	Latinos (22,566)
Tofu (g/day)							
	n	99,719	24,226	18,609	7,305	27,953	21,626
	Mean	8.4	3.5	0.5	14.4	22.1	0.7
	S.D.	20.93	12.38	4.7	29	29.47	5.41
	Median	0	0	0	7.8	14.9	0
	Minimum	0	0	0	0	0	0
	Maximum	450	225	160.6	450	450	210
-< 0.4		21,618	6,995	8,359	251	227	5,786
	n (%)	(20.8%)	(27.7%)	(42.9%)	(3.3%)	(0.8%)	(25.6%)
0.4 <-1.7		20,210	6,606	5,682	600	521	6,801
	n (%)	(19.4%)	(26.2%)	(29.2%)	(7.9%)	(1.8%)	(30.1%)
1.7 <-5.3		18,806	5,531	3,266	1,548	2,812	5,649
	n (%)	(18.1%)	(21.9%)	(16.8%)	(20.3%)	(9.7%)	(25.0%)
5.3 <-14.9		19,170	3,290	1,014	2,573	9,557	2,736
	n (%)	(18.4%)	(13.0%)	(5.2%)	(33.7%)	(33.0%)	(12.1%)
> 14.9		19,915	1,804	288	2,333	14,836	654
	n (%)	(19.1%)	(7.2%)	(1.5%)	(30.6%)	(51.2%)	(2.9%)
Shoyu (g/day)							
	n	99,719	24,226	18,609	7,305	27,953	21,626
	Mean	1.8	1	0.3	3.7	3.9	0.6
	S.D.	3.53	2.29	1.16	5.06	4.63	1.78
	Median	0.3	0.3	0	1.4	1.4	0
	Minimum	0	0	0	0	0	0
	Maximum	20	20	20	20	20	20
	n (%)	46,599	11,880	13,122	1,901	5,336	14,360
0		(44.8%)	(47.1%)	(67.4%)	(24.9%)	(18.4%)	(63.6%)
	n (%)	23,804	7,031	4,333	1,669	5,761	5,010
0 <-1.1		(22.9%)	(27.9%)	(22.2%)	(21.9%)	(19.9%)	(22.2%)
	n (%)	29,316	5,315	1,154	3735	16,856	2,256
> 1.1		(28.2%)	(21.1%)	(5.9%)	(49.0%)	(58.1%)	(10.0%)
Omega 3 Fatty Acids (g/day)							
	n	99,719	24,226	18,609	7,305	27,953	21,626
	Mean	1.7	1.5	1.7	2.2	1.7	1.9
	S.D.	0.98	0.74	1.03	1.33	0.78	1.17
	Median	1.5	1.4	1.5	1.9	1.5	1.6
	Minimum	0.1	0.2	0.1	0.3	0.2	0.2
	Maximum	12	6.9	10.8	11.9	7.2	12
-< 1.1	n (%)	24,035	6,736	5,160	1,084	6,029	5,026
		(23.1%)	(26.7%)	(26.5%)	(14.2%)	(20.8%)	(22.3%)
1.1 <- 1.4	n (%)	22,088	6,139	3,951	1,162	6,657	4,179
		(21.2%)	(24.3%)	(20.3%)	(15.2%)	(23.0%)	(18.5%)
1.4 <- 1.9	n (%)	20,274	5,079	3,367	1,365	6,504	3,959
		(19.5%)	(20.1%)	(17.3%)	(17.9%)	(22.4%)	(17.5%)
1.9 <- 2.6	n (%)	18,210	4,066	3,166	1,583	5,459	3,936
		(17.5%)	(16.1%)	(16.3%)	(20.7%)	(18.8%)	(17.4%)
> 2.6	n (%)	15,112	2,206	2,965	2,111	3,304	4,526
		(14.5%)	(8.7%)	(15.2%)	(27.7%)	(11.4%)	(20.1%)

Table A2.7. Descriptive Statistics of Baseline Major Sources for Omega-3 Fatty Acids in Women Free of Heart Attack or Angina by Ethnicity

	Statistics (N)	Total (103,884)	Caucasian (25,224)	African American (19,475)	Native Hawaiian (7,630)	Japanese American (28,989)	Latinos (22,566)
Oils in cooking (g/day)							
	n	99719	24226	18609	7305	27953	21626
	Mean	1.8	1.2	1.4	2.8	2.2	2.1
	S.D.	2.63	1.89	2.22	3.5	2.52	3.18
	Median	0.7	0.5	0.6	1.2	1	0.6
	Minimum	0	0	0	0	0	0
	Maximum	22.7	22.7	22.7	22.7	22.7	22.7
0		23920	7985	5166	1094	3241	6434
	n (%)	(23.0%)	(31.7%)	(26.5%)	(14.3%)	(11.2%)	(28.5%)
0 <- 0.5		17535	4545	4062	948	4496	3484
	n (%)	(16.9%)	(18.0%)	(20.9%)	(12.4%)	(15.5%)	(15.4%)
0.5 <- 1.2		21472	5517	4168	1610	6809	3368
	n (%)	(20.6%)	(21.9%)	(21.4%)	(21.1%)	(23.5%)	(14.9%)
1.2 <- 3.7		19615	3911	3013	1560	7460	3671
	n (%)	(18.9%)	(15.5%)	(15.5%)	(20.4%)	(25.7%)	(16.3%)
> 3.7		17177	2268 (	2200	2093	5947	4669
	n (%)	(16.5%)	9.0%)	(11.3%)	(27.4%)	(20.5%)	(20.7%)
Mayonnaise use (g/d)							
	n	99719	24226	18609	7305	27953	21626
	Mean	24.4	23.6	25.7	32.7	20.6	26.5
	S.D.	37.84	30.7	39.58	66.73	27.6	40.74
	Median	12.9	13.8	13.2	14.5	11.7	13.2
	Minimum	0	0	0	0	0	0
	Maximum	1278	1128.8	582.5	1278	545.8	601.8
0<-4.5		18098	3834	3373	1335	5370	4186
	n (%)	(17.4%)	(15.2%)	(17.3%)	(17.5%)	(18.5%)	(18.6%)
4.5 <- 8.9		18224	4374	3326	1188	5782	3554
	n (%)	(17.5%)	(17.3%)	(17.1%)	(15.6%)	(19.9%)	(15.7%)
8.9 <- 15.2		19855	4836	3742	1217	5849	4211
	n (%)	(19.1%)	(19.2%)	(19.2%)	(16.0%)	(20.2%)	(18.7%)
15.2 <- 29.0		20647	5454	3827	1512	5465	4389
	n (%)	(19.9%)	(21.6%)	(19.7%)	(19.8%)	(18.9%)	(19.4%)
> 29.0		22895	5728	4341	2053	5487	5286
	n (%)	(22.0%)	(22.7%)	(22.3%)	(26.9%)	(18.9%)	(23.4%)
Mexican dishes with Tortilla Bread (g/d)							
	n	99719	24226	18609	7305	27953	21626
	Mean	28.4	23	26.3	14.2	9	66.3
	S.D.	55.94	34.3	47.89	29.23	18.29	91.56
	Median	10.5	12.3	12.3	3	0	39.5
	Minimum	0	0	0	0	0	0
	Maximum	1610.3	852.6	1096.4	800	543.9	1610.3
0		34751	7218	6173	3648	15350	2362
	n (%)	(33.4%)	(28.6%)	(31.7%)	(47.8%)	(53.0%)	(10.5%)
0 <- 26.2		34031	9767	6585	2420	9676	5583
	n (%)	(32.7%)	(38.7%)	(33.8%)	(31.7%)	(33.4%)	(24.7%)
> 26.2		30937	7241	5851	1237	2927	13681
	n (%)	(29.7%)	(28.7%)	(30.0%)	(16.2%)	(10.1%)	(60.6%)

Appendix 3. Relative Risks (95% CI) of CHD Mortality and Omega-3 Fatty Acids with Other Risk Factors Overall and by Ethnicity

Table A3.1. Relative Risks (95% CI) of CHD Mortality and Selected Major Sources of Omega-3 Fatty Acids Overall and by Ethnicity

RR*	All (n=157,103)	Caucasian (n=40,326)	African American (n=24,380)	Native Hawaiian (n=11,666)	Japanese American (n=47,495)	Latinos (n=33,236)
Mexican Dishes with Tortillas (g/day)						
0	1.00	1.00	1.00	1.00	1.00	1.00
0 <- 26.2	1.00 (0.92-1.08)	0.81 (0.68-0.96)	1.00 (0.86-1.16)	1.14 (0.85-1.52)	1.08 (0.90-1.30)	1.00 (0.77-1.30)
> 26.2	1.11 (1.01-1.22)	0.90 (0.75-1.08)	1.13 (0.97-1.33)	0.80 (0.52-1.22)	1.67 (1.32-2.10)	1.08 (0.84-1.39)
p for trend**	0.22	0.22	0.11	0.36	<0.0001	0.71
p for interaction with ethnicity***	0.34					
Mayonnaise Use (g/day)						
0<-4.5	1.00	1.00	1.00	1.00	1.00	1.00
4.5 <- 8.9	0.87 (0.79-0.96)	1.07 (0.86-1.33)	0.81 (0.66-0.98)	1.43 (0.97-2.09)	0.85 (0.68-1.06)	0.74 (0.60-0.91)
8.9 <- 15.2	0.89 (0.80-0.98)	0.89 (0.71-1.12)	0.79 (0.65-0.95)	1.11 (0.74-1.67)	1.15 (0.93-1.42)	0.82 (0.67-1.00)
15.2 <- 29.0	0.92 (0.83-1.02)	1.05 (0.84-1.31)	0.91 (0.75-1.10)	1.36 (0.92-1.99)	0.94 (0.74-1.19)	0.79 (0.64-0.98)
> 29.0	0.93 (0.83-1.03)	0.98 (0.77-1.24)	1.08 (0.89-1.31)	1.47 (1.00-2.17)	0.92 (0.71-1.20)	0.63 (0.50-0.80)
p for trend**	0.84	0.87	0.016	0.11	0.60	0.0013
p for interaction with ethnicity***	0.0002					
Fried Chicken with Skin						
Non-Consumers	1.00	1.00	1.00	1.00	1.00	1.00
Consumers	1.06 (0.99-1.14)	1.12 (0.96-1.31)	0.95 (0.83-1.08)	1.08 (0.82-1.40)	1.01 (0.86-1.19)	1.17 (1.01-1.36)
p for trend**	0.11	0.17	0.41	0.59	0.87	0.035
p for interaction with ethnicity***	0.74					

Table A3.2. Relative Risks (95% CI) of CHD Mortality and Omega-3 Fatty Acids with Known Risk Factors Overall and by Ethnicity

RR*	All (n=157,103)	Caucasian (n=40,326)	African American (n=24,380)	Native Hawaiian (n=11,666)	Japanese American (n=47,495)	Latinos (n=33,236)
Body Mass Index						
< 23	1.00	1.00	1.00	1.00	1.00	1.00
23-<25	0.79 (0.71-0.88)	0.72 (0.57-0.89)	0.68 (0.56-0.84)	0.93 (0.58-1.50)	0.87 (0.71-1.06)	0.83 (0.66-1.04)
25-<30	0.80 (0.73-0.87)	0.85 (0.71-1.02)	0.63 (0.53-0.74)	0.99 (0.67-1.46)	0.94 (0.78-1.14)	0.77 (0.63-0.93)
30-<35	0.84 (0.74-0.94)	0.84 (0.65-1.09)	0.75 (0.62-0.92)	0.99 (0.63-1.54)	1.14 (0.80-1.64)	0.66 (0.51-0.86)
>35	1.16 (1.01-1.34)	1.44 (1.06-1.96)	0.95 (0.75-1.20)	1.00 (0.61-1.63)	1.58 (0.80-3.10)	1.10 (0.80-1.50)
Smoking						
Never Smoker	1.00	1.00	1.00	1.00	1.00	1.00
Ex-Smoker	1.04 (0.95-1.14)	0.99 (0.80-1.21)	1.12 (0.94-1.32)	0.96 (0.68-1.35)	1.04 (0.84-1.29)	1.09 (0.91-1.30)
Current-Smoker	1.96 (1.76-2.19)	2.05 (1.59-2.65)	1.85 (1.53-2.25)	1.57 (1.03-2.40)	2.52 (1.92-3.30)	1.87 (1.50-2.34)
Increase by 1 pack-yr	1.01 (1.01-1.01)	1.01 (1.01-1.02)	1.01 (1.00-1.01)	1.01 (1.00-1.02)	1.01 (1.00-1.01)	1.01 (1.00-1.01)
Hours Vigorous Exercise per Week						
0	1.00	1.00	1.00	1.00	1.00	1.00
0<-1.5	0.80 (0.74-0.87)	0.75 (0.64-0.89)	0.89 (0.77-1.03)	0.78 (0.60-1.01)	0.77 (0.65-0.91)	0.82 (0.70-0.96)
1.5<-5.0	0.87 (0.72-1.05)	0.75 (0.50-1.12)	0.63 (0.38-1.06)	0.84 (0.50-1.43)	1.04 (0.66-1.65)	1.07 (0.77-1.49)
High Blood Pressure History						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	1.87 (1.75-2.01)	1.98 (1.71-2.30)	1.71 (1.50-1.95)	1.91 (1.46-2.49)	1.86 (1.59-2.18)	1.92 (1.67-2.21)
Diabetes History						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	2.70 (2.51-2.91)	2.61 (2.15-3.17)	2.34 (2.04-2.68)	3.40 (2.62-4.40)	2.92 (2.47-3.44)	2.92 (2.52-3.38)
Education						
<=High School	1.00	1.00	1.00	1.00	1.00	1.00
Further Educ	0.91 (0.85-0.99)	0.80 (0.68-0.95)	0.80 (0.70-0.92)	0.91 (0.69-1.22)	1.15 (0.96-1.37)	1.01 (0.85-1.20)
=>College	0.77 (0.70-0.85)	0.69 (0.58-0.82)	0.83 (0.71-0.98)	0.55 (0.35-0.86)	0.91 (0.74-1.13)	0.63 (0.47-0.85)

*RRs in Tables A3.2, A3.3, and A3.4 were from the same primary model.

Table A3.3. Relative Risks (95% CI) of CHD Mortality and Omega-3 Fatty Acids with Known Reproductive Risk Factors Overall and by Ethnicity

RR*	All (n=157,103)	Caucasian (n=40,326)	African American (n=24,380)	Native Hawaiian (n=11,666)	Japanese American (n=47,495)	Latinos (n=33,236)
Hormonal Therapy						
None	1.00	1.00	1.00	1.00	1.00	1.00
Past ET	0.75 (0.63-0.89)	0.77 (0.53-1.13)	0.78 (0.59-1.01)	0.82 (0.40-1.68)	0.71 (0.46-1.12)	0.73 (0.49-1.07)
Past PT	0.59 (0.22-1.58)	0.63 (0.09-4.55)	1.30 (0.42-4.10)	0.00 (0.00- .)	0.00 (0.00-****)	0.00 (0.00-****)
Past EPT	0.66 (0.51-0.87)	0.62 (0.36-1.07)	0.82 (0.53-1.27)	0.53 (0.16-1.78)	0.67 (0.34-1.32)	0.53 (0.27-1.06)
Current ET	0.48 (0.39-0.59)	0.54 (0.35-0.83)	0.59 (0.42-0.83)	0.31 (0.11-0.87)	0.36 (0.21-0.60)	0.47 (0.29-0.76)
Current PT	0.47 (0.21-1.06)	0.35 (0.05-2.54)	0.31 (0.04-2.25)	0.00 (0.00- .)	1.23 (0.44-3.42)	0.00 (0.00-****)
Age at Oophorectomy						
Never	1.00	1.00	1.00	1.00	1.00	1.00
45-49	0.85 (0.61-1.17)	0.58 (0.29-1.17)	0.94 (0.56-1.58)	3.43 (0.76-15.4)	1.10 (0.49-2.46)	0.56 (0.23-1.38)
50-54	0.78 (0.49-1.22)	0.37 (0.11-1.18)	1.27 (0.66-2.41)	0.00 (0.00- .)	0.82 (0.27-2.46)	0.69 (0.24-1.98)
=>55	0.86 (0.40-1.85)	0.40 (0.05-2.91)	0.84 (0.21-3.46)	0.00 (0.00- .)	1.63 (0.37-7.16)	1.50 (0.35-6.36)
Age at Hysterectomy						
Never	1.00	1.00	1.00	1.00	1.00	1.00
45-49	0.99 (0.72-1.36)	1.04 (0.45-2.41)	0.74 (0.44-1.24)	1.64 (0.57-4.75)	1.14 0.50-2.63)	1.35 (0.66-2.75)
50-54	1.06 (0.65-1.75)	0.47 (0.06-3.49)	1.57 (0.82-3.01)	0.00 (0.00- .)	0.92 (0.27-3.12)	1.13 (0.35-3.70)
>=55	1.50 (0.71-3.20)	0.00 (0.00-****)	1.36 (0.43-4.29)	7.12 (1.50-33.8)	0.00 (0.00-****)	2.13 (0.51-8.92)
Age at Natural Menopause						
Never	1.00	1.00	1.00	1.00	1.00	1.00
45-49	0.85 (0.70-1.03)	0.81 (0.52-1.27)	1.14 (0.80-1.62)	0.95 (0.47-1.92)	0.87 (0.53-1.45)	0.59 (0.39-0.88)
50-54	0.75 0.62-0.92)	0.77 (0.50-1.20)	1.04 (0.73-1.48)	0.71 (0.35-1.46)	0.65 (0.40-1.06)	0.61 (0.41-0.91)
>=55	0.69 (0.52-0.90)	1.00 (0.57-1.76)	0.83 (0.52-1.34)	0.58 (0.21-1.65)	0.54 (0.28-1.05)	0.52 (0.27-1.00)

*RRs in Tables A3.2, A3.3, and A3.4 were from the same primary model.

Table A3.4. Relative Risks (95% CI) of CHD Mortality and Omega-3 Fatty Acids with Known Diet Risk Factors Overall and by Ethnicity

RR*	All (n=157,103)	Caucasian (n=40,326)	African American (n=24,380)	Native Hawaiian (n=11,666)	Japanese American (n=47,495)	Latinos (n=33,236)
Alcohol Intake g per day						
0	1.00	1.00	1.00	1.00	1.00	1.00
>0 - 12	0.81 (0.74-0.87)	0.89 (0.75-1.05)	0.85 (0.73-0.98)	0.71 (0.52-0.98)	0.74 (0.61-0.90)	0.75 (0.63-0.88)
>12 - 24	0.70 (0.61-0.81)	0.68 (0.52-0.88)	0.87 (0.67-1.14)	0.99 (0.63-1.56)	0.52 (0.36-0.77)	0.59 (0.42-0.83)
>24	0.81 (0.73-0.91)	0.71 (0.57-0.87)	1.07 (0.87-1.32)	0.67 (0.43-1.03)	0.77 (0.58-1.01)	0.84 (0.66-1.08)
0	1.00	1.00	1.00	1.00	1.00	1.00
Log Transformed Calories per day						
Log (1 cal/day)	1.09 (0.95-1.24)	1.22 (0.89-1.68)	1.09 (0.87-1.38)	0.79 (0.51-1.24)	1.26 (0.89-1.77)	0.87 (0.66-1.15)
Percent Calories from Saturated Fat						
<6.6	1.00	1.00	1.00	1.00	1.00	1.00
6.6<-8.2	1.06 (0.94-1.19)	0.96 (0.72-1.27)	1.04 (0.81-1.33)	1.05 (0.69-1.59)	1.15 (0.94-1.40)	1.00 (0.74-1.35)
8.2<-9.5	1.20 (1.07-1.35)	1.13 (0.86-1.47)	1.21 (0.95-1.53)	1.05 (0.69-1.61)	1.24 (1.00-1.55)	1.15 (0.86-1.53)
9.5<-11.1	1.27 (1.13-1.43)	1.38 (1.07-1.78)	1.12 (0.88-1.42)	1.49 (0.98-2.24)	1.37 (1.06-1.77)	1.11 (0.84-1.47)
>11.1	1.42 (1.26-1.60)	1.62 (1.25-2.08)	1.24 (0.99-1.57)	1.47 (0.94-2.32)	1.53 (1.11-2.11)	1.25 (0.95-1.66)
Omega 3 Fatty Acids						
-< 1.1	1.00	1.00	1.00	1.00	1.00	1.00
1.1 <- 1.4	0.80 (0.72-0.90)	0.92 (0.73-1.16)	0.74 (0.60-0.92)	1.15 (0.70-1.89)	0.81 (0.63-1.04)	0.71 (0.55-0.90)
1.4 <- 1.9	0.82 (0.72-0.93)	0.91 (0.70-1.20)	0.82 (0.65-1.05)	1.11 (0.66-1.86)	0.75 (0.57-1.00)	0.71 (0.53-0.94)
1.9 <- 2.6	0.76 (0.66-0.88)	0.73 (0.52-1.00)	0.82 (0.62-1.09)	1.11 (0.63-1.96)	0.62 (0.44-0.87)	0.80 (0.58-1.09)
> 2.6	0.83 (0.68-1.00)	0.76 (0.50-1.14)	1.07 (0.75-1.51)	1.17 (0.58-2.36)	0.65 (0.43-0.99)	0.80 (0.53-1.20)
p for trend	0.62	0.13	0.042	0.80	0.086	0.73
Ethnicity						
Caucasian as referent		1.00	1.37 (1.24-1.51)	1.14 (0.98-1.31)	0.57 (0.51-0.64)	0.98 (0.88-1.09)

*RRs in Tables A3.2, A3.3, and A3.4 were from the same primary model.

Appendix 4. Relative Risks (95% CI) of Mortality for Omega-3 Fatty Acids and Omega-6 Fatty Acids

Table A4.1. Relative Risks (95% CI) of CHD Mortality with Omega-3 and Omega-6 Fatty Acids

RR*	All (n=157,103)	Caucasian (n=40,326)	African American (n=24,380)	Native Hawaiian (n=11,666)	Japanese American (n=47,495)	Latinos (n=33,236)
Omega-3 Fatty Acids						
-< 1.1	1.00	1.00	1.00	1.00	1.00	1.00
1.1 <- 1.4	0.81	0.92	0.80	0.85	0.85	0.61
	(0.70-0.93)	(0.69-1.23)	(0.61-1.06)	(0.43-1.68)	(0.62-1.16)	(0.44-0.85)
1.4 <- 1.9	0.81	0.87	0.93	0.80	0.90	0.47
	(0.67-0.97)	(0.60-1.26)	(0.65-1.33)	(0.36-1.78)	(0.61-1.33)	(0.31-0.72)
1.9 <- 2.6	0.70	0.69	0.89	0.82	0.75	0.44
	(0.57-0.88)	(0.44-1.07)	(0.58-1.37)	(0.34-2.03)	(0.47-1.21)	(0.27-0.72)
> 2.6	0.77	0.78	1.30	0.87	0.82	0.36
	(0.59-1.00)	(0.45-1.37)	(0.78-2.16)	(0.32-2.40)	(0.46-1.45)	(0.20-0.66)
p for trend	0.33	0.39	0.036	0.96	0.59	0.027
Omega-6 Fatty Acids						
-<8.9	1.00	1.00	1.00	1.00	1.00	1.00
8.9<-12.4	0.99	0.96	0.92	1.57	0.95	1.17
	(0.86-1.15)	(0.72-1.29)	(0.70-1.20)	(0.79-3.09)	(0.70-1.30)	(0.85-1.62)
12.4<-16.4	1.00	1.04	0.81	1.49	0.74	1.70
	(0.83-1.20)	(0.73-1.50)	(0.56-1.16)	(0.67-3.34)	(0.50-1.10)	(1.11-2.59)
16.4<-22.6	1.12	1.07	0.91	1.45	0.79	2.11
	(0.90-1.39)	(0.70-1.65)	(0.60-1.38)	(0.59-3.56)	(0.49-1.27)	(1.28-3.45)
>22.6	1.09	0.94	0.75	1.49	0.71	2.75
	(0.83-1.42)	(0.54-1.62)	(0.45-1.25)	(0.54-4.13)	(0.39-1.28)	(1.54-4.93)
p for trend	0.39	0.75	0.33	0.84	0.30	0.0007

*Omega-3 and -6 were included in the same primary model in the subpopulation free of angina pectoris and heart attacks at baseline.

Table A4.2. Relative Risks (95% CI) of Stroke Mortality with Omega-3 and Omega-6 Fatty Acids

RR*	All (n=166,784)	Caucasian (n=42,650)	African American (n=26,507)	Native Hawaiian (n=12,348)	Japanese American (n=49,495)	Latinos (n=35,784)
Omega-3 Fatty Acids						
-< 1.1	1.00	1.00	1.00	1.00	1.00	1.00
1.1 <- 1.4	0.92	1.10	0.96	0.37	1.00	0.82
	(0.74-1.15)	(0.70-1.73)	(0.62-1.51)	(0.14-1.00)	(0.66-1.51)	(0.46-1.46)
1.4 <- 1.9	1.00	1.39	1.04	0.25	1.08	0.92
	(0.75-1.32)	(0.77-2.51)	(0.59-1.83)	(0.07-0.83)	(0.64-1.82)	(0.44-1.90)
1.9 <- 2.6	0.92	1.91	0.64	0.24	1.12	0.82
	(0.65-1.30)	(0.93-3.93)	(0.32-1.30)	(0.06-1.03)	(0.61-2.09)	(0.35-1.92)
> 2.6	1.05	1.50	1.27	0.57	0.91	0.85
	(0.69-1.60)	(0.57-3.93)	(0.54-2.98)	(0.11-3.01)	(0.43-1.94)	(0.31-2.38)
p for trend	0.43	0.32	0.31	0.92	0.79	0.98
Omega-6 Fatty Acids						
-<8.9	1.00	1.00	1.00	1.00	1.00	1.00
8.9<-12.4	0.82	0.83	0.77	1.23	0.87	0.86
	(0.66-1.02)	(0.53-1.30)	(0.49-1.20)	(0.47-3.24)	(0.58-1.32)	(0.49-1.53)
12.4<-16.4	0.77	0.66	0.83	0.89	0.72	1.14
	(0.58-1.03)	(0.37-1.17)	(0.48-1.46)	(0.26-3.09)	(0.42-1.21)	(0.55-2.36)
16.4<-22.6	0.72	0.45	0.74	0.48	0.93	1.12
	(0.51-1.01)	(0.22-0.92)	(0.38-1.44)	(0.11-2.21)	(0.50-1.72)	(0.48-2.60)
>22.6	0.70	0.52	0.57	0.29	0.98	1.39
	(0.46-1.06)	(0.21-1.28)	(0.24-1.34)	(0.05-1.67)	(0.46-2.11)	(0.51-3.80)
p for trend	0.18	0.16	0.14	0.12	0.71	0.37

*Omega-3 and -6 were included in the same primary model in the subpopulation free of stroke at baseline.

Table A4.3. Relative Risks (95% CI) of Hypertension Mortality with Omega-3 and Omega-6 Fatty Acids

RR*	All (n=166,784)	Caucasian (n=42,650)	African American (n=26,507)	Native Hawaiian (n=12,348)	Japanese American (n=49,495)	Latinos (n=35,784)
Omega-3 Fatty Acids						
-< 1.1	1.00	1.00	1.00	1.00	1.00	1.00
1.1 <- 1.4	1.29	1.73	1.82	0.42	0.63	1.79
	(0.73-2.30)	(0.39-7.68)	(0.71-4.65)	(0.02-8.26)	(0.17-2.33)	(0.54-5.95)
1.4 <- 1.9	1.24	0.75	1.66	0.52	0.32	3.04
	(0.59-2.59)	(0.07-7.59)	(0.47-5.92)	(0.02-13.9)	(0.06-1.74)	(0.69-13.4)
1.9 <- 2.6	1.58	4.09	2.46	0.00	0.94	1.51
	(0.65-3.82)	(0.34-48.5)	(0.54-11.2)	(0.00- .)	(0.15-5.93)	(0.23-9.82)
> 2.6	1.39	2.83	2.79	0.18	1.44	1.14
	(0.46-4.16)	(0.15-54.6)	(0.44-17.6)	(0.00- 169)	(0.12-16.7)	(0.11-11.6)
p for trend	0.86	0.68	0.36	0.30	0.52	0.79
Omega-6 Fatty Acids						
-<8.9	1.00	1.00	1.00	1.00	1.00	1.00
8.9<-12.4	0.86	1.19	0.63	1.11	1.58	0.75
	(0.49-1.52)	(0.27-5.22)	(0.25-1.59)	(0.06-21.1)	(0.42-5.98)	(0.24-2.40)
12.4<-16.4	0.67	0.77	0.41	2.26	2.26	0.36
	(0.33-1.38)	(0.10-5.75)	(0.12-1.38)	(0.09-58.3)	(0.41-12.3)	(0.08-1.57)
16.4<-22.6	0.41	0.54	0.32	0.00	0.55	0.49
	(0.17-1.00)	(0.04-6.71)	(0.07-1.42)	(0.00- .)	(0.07-4.56)	(0.09-2.72)
>22.6	0.59	1.40	0.34	0.89	0.38	0.80
	(0.20-1.69)	(0.09-23.0)	(0.06-1.99)	(0.00- 836)	(0.03-5.73)	(0.09-6.80)
p for trend	0.48	0.54	0.38	0.97	0.27	0.89

*Omega-3 and -6 were included in the same primary model in the subpopulation free of stroke at baseline.

Appendix 5. Hypertension Medication Use in Subjects Free of Stroke but Having History of Hypertension

In Tables 4.2, Latina experienced a much higher rate of total stroke and subtype stroke than women in other ethnic groups. The following table showed that there were about 9% fewer Latinas use hypertenstion medications to control the condition.

Men	All (n=34,828)	Caucasian (n=6,792)	African American (n=6,435)	Native Hawaiian (n=2,868)	Japanese American (n=11,127)	Latinos (n=7,606)
Users	19,985 (57.4%)	3,991 (58.8%)	3,792 (58.9%)	1,568 (54.7%)	6,721 (60.4%)	3,913 (51.4%)
Women	All (n=41,202)	Caucasian (n=7,010)	African American (n=11,768)	Native Hawaiian (n=3,337)	Japanese American (n=10,636)	Latina (n=8,451)
Users	26,213 (63.6%)	4,581 (65.3%)	7,790 (66.2%)	2,071 (62.1%)	7,015 (66.0%)	4,756 (56.3%)