

ESKIMOS HAVE CHD DESPITE HIGH CONSUMPTION OF OMEGA-3 FATTY ACIDS: THE ALASKA SIBERIA PROJECT

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ABSTRACT

Objectives. The thirty-year-old hypothesis that omega-3 fatty acid (FA) may ‘reduce the development of thrombosis and atherosclerosis in the Western World’ still needs to be tested. Dyerberg-Bang based their supposition on casual observations that coronary atherosclerosis in Greenlandic Inuit was ‘almost unknown’ and that they consumed large amounts of ω -3 FAs. However, no association was demonstrated with data.

Study design. Cross-sectional study.

Methods. 454 Alaskan Eskimos were screened for coronary heart disease (CHD), using a protocol that included ECG, medical history, Rose questionnaire, blood chemistries, including plasma FA concentrations, and a 24-hour recall and a food frequency questionnaire assessment of ω -3 FA consumption.

Results. CHD was found in 6 % of the cohort under 55 years of age and in 26 % of those \geq 55 years of age. Eskimos with CHD consume as much ω -3 FAs as those without CHD, and the plasma concentrations confirm that dietary assessment.

Conclusions. Average daily consumption of ω -3 FAs among Eskimos was high, with about 3-4 g/d reported, compared with 1-2 g/d used in intervention studies and the average consumption of 0.2 g/d by the American population. There was no association between current ω -3 FA consumption/blood concentrations and the presence of CHD.

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Keywords: cardiovascular disease, stroke, atherosclerosis, omega-3 fatty acids, prevalence, Inuit

INTRODUCTION

The importance of an adequate consumption of ω -3 fatty acids (FAs) for reducing cardiovascular events, arrhythmias and sudden death are well documented (1-4), but whether they prevent atherosclerosis has not yet been proven. So far, we know that the likely mechanisms for protection involve a reduction in myocardial susceptibility to lethal arrhythmias and the enhancement of plaque stability (5, 6). The basis for the original hypothesis, whereby ω -3 FAs protect against CHD (7, 8), has been challenged recently, because of inconsistencies in the original interpretation of the prevalence data available at the time the hypothesis was first proposed (9). The hypothesis was based on 1) the casual observation, in 1975, that “coronary atherosclerosis is almost unknown among Greenlandic Eskimos living in their own cultural environment“ (7), and 2) that Eskimos consume large amounts of ω -3 FAs from fish and marine mammals (10). They concluded that the “enrichment of tissue lipids with EPA (eicosapentaenoic acid, a 20C ω -3 FA), whether by dietary change, or by supplementation, may reduce the development of thrombosis and atherosclerosis in the Western World”. The published hypothesis was not accompanied by a study showing the correlation of CHD with diet, or ω -3 FA blood concentrations. In fact, to our knowledge, there has never been such a cross-sectional study. Yet, the hypothesis, as now stated in advertisements as facts, clearly gives the intended impression that the consumption of cold-water fish or ω -3 capsules, “prevents heart disease”

and “improves cardiovascular health”. The purpose of the present study was to relate, for the first time, ω -3 FA consumption and plasma concentration with the presence, or absence, of CHD in Eskimos.

Our studies on CHD in Alaskan Eskimos have revealed that, although high concentrations of plasma ω -3 FAs, which are correlated with consumption, are associated with reduced risk factors for CHD (11), they offer no guarantee if other risk factors are present, as shown in the present report. This report deals with the lack of association between ω -3 FA consumption and CHD discovered in a cross-sectional study. Other results from this study (the Alaska Siberia Project) have been published elsewhere: type 2 diabetes (DM; 11-15), obesity (12,16,17), fatty acid imbalance (11) and the prevalence of CHD (18).

MATERIAL AND METHODS

Study population

454 Eskimos (214 males and 240 females) over 24 years of age, from four villages in the Norton Sound Region of Alaska, were screened, over a four-week period in 1994, for DM, CHD and associated risk factors, using the Strong Heart Study protocol, as part of an intervention study for DM (12). One Inupiat, one Central Yupik and two Siberian Yupik villages were represented. All villagers were personally invited to participate by the PI (SE). In general, more women and elderly participated (Fig. 1), but some were absent from the village during the short screening period, which lasted about 6-7 days (12).

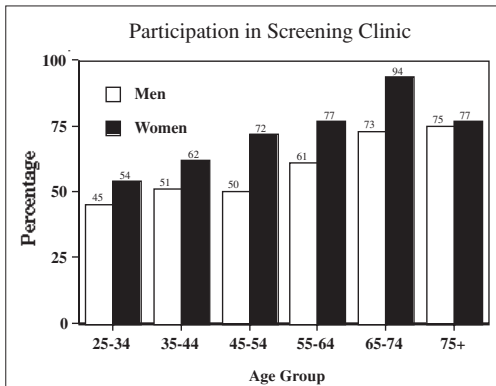


Figure 1. Participants in screening clinic.

Study screening

The screening followed the Strong Heart Study Protocol (12,19) and consisted of a personal interview (including medical history), physical examination (including blood pressure measurements, ECG and a Rose questionnaire), blood sampling and nutritional interviews using 24-h recall and food frequency instruments. The latter were conducted the day before the blood sampling.

Nutritional interviews

Dietary data for this study were collected during house-to-house interviews. Ten interviewers were selected and trained in a week of didactic and practical sessions. Each interviewer was observed by one of the team leaders during the completion of a full interview and the training was completed in the field. Interviewers included two team leaders (dietitians), two additional dietitians and six interviewers; the latter were local to the villages and had no formal nutrition training. Local interviewers conducted several interviews with subjects that spoke only their native language, many of whom were elders.

Included in that interview was a 24-hour recall, which was collected for this project

using the Nutritional Data System (NDS, Version 2.8, Food Database 10A, Nutrient Database 25, University of Minnesota), a software product run on laptop computers (20). The software system prompts the interviewer to complete a short list of foods eaten during the previous 24 hours. The interviewer is then guided by prompts through a series of questions that detail the food brand name, additives, cooking methods, and quantities. These questions match the foods to one of the 160,000 variants of ingredients and/or preparation methods.

The food frequency questionnaire (FFQ) included questions regarding the portion size, quantity, frequency and season of intake of 117 foods. The food list was compiled during formative research in 1992, after which Native foods were added, and infrequently consumed non-Native foods were removed (21-22).

The dietary intake data for both the 24-hour recall and FFQ were translated into nutrient intakes using the NDS System (20-22). Although many Alaskan Native foods were present in the database, twenty-six foods from the subjects' food lists were not on the pre-existing lists. These foods were matched to appropriate foods in the database, as recommended by the University of Minnesota Nutrition Coordinating Center, and were then entered as recommended within the appropriate 24-hour recall. Daily nutrient intakes reported by NDS for each subject were imported into SAS (SAS Institute, Cary, NC) for statistical analysis. Nutrients of interest to this analysis included total energy in kilocalories per day, and ω -3 fatty acids.

For the 7% of interviews where there was no computer availability, or a malfunction (30 of 456), 24-hour recall data were recorded on

paper, using the same procedures, but without the computer-generated prompting of detailed questions. Eighteen Inupiat subjects were excluded from further data analysis, because they were interviewed after a holiday, which was not representative of usual intake. Data was excluded from analyses for five other subjects, due to inconsistencies, or concerns noted by the interviewer, and for eleven more subjects due to missing data. The final sample employed for the analysis thus included 208 men and 225 women.

Plasma FA analysis

The plasma FA analysis was carried out at the University of Alaska Anchorage on plasma that was originally obtained after at least 12 hours fasting (11). Plasma was stored in EDTA for 2-6 days at -10°C , then at -70°C . The analysis of total FA in plasma was carried out as follows (22-24). An aliquot (220 μL) of each plasma sample was added to 2 ml of ethanol, containing 250 μL of 33 % aqueous KOH. An appropriate volume of the internal standard (C17:0) solution was then added. The mixture was incubated at 37°C for 1 hour. After cooling to room temperature, the solution was acidified with HCL and extracted twice with 2 mL of hexane. Boron trifluoride in methanol (1 mL) was added to the tube containing the 4 mL of the hexane extract and the mixture was heated at 100°C for 10 minutes. After cooling to room temperature, 2 mL of water was added to stop the reaction. The solution was then centrifuged and the hexane was separated from the aqueous fraction. The hexane was evaporated to dryness under nitrogen and 250 mL of fresh hexane was added to provide an appropriate concentration for a flame ionization detector (FID) signal. Standard solutions of the corresponding

fatty acids were prepared and analyzed in the same fashion. Analysis was performed on a Hewlett Packard 5890 gas chromatograph equipped with a 30m x 0.32 mm SP2330 capillary column. The temperature program used for the analysis started at 100°C and increased at a rate of $5^{\circ}\text{C}/\text{min}$, up to 250°C .

The concentration of each fatty acid was determined for each sample using regression analysis. The ratio of the area of each fatty acid peak to the internal standard peak was plotted vs. the weight ratio of the fatty acid and the internal standard. The regression equation was used to calculate the concentration of each fatty acid in each sample. Typical correlations were 0.99, or better.

The criteria for coronary heart disease

The Strong Heart Study protocol and procedures (19, 23) were strictly followed for diagnostic purposes. Criteria for definite coronary heart disease (CHD) included definite MI, evidence in the medical record of coronary angioplasty or bypass surgery, thrombolytic therapy, a positive angiogram, or angina pectoris by Rose questionnaire when accompanied by Minnesota Code 4.1, or 5.1, or a verified history of possible MI. Possible CHD included electrocardiographic results with a broad range of Minnesota Codes, angina pectoris by Rose questionnaire, or a history of MI by interview.

The 12-lead electrocardiogram was taken using a Marquette system (MAC-PC, or MAC-12; Marquette Electronics, Milwaukee, Wisconsin). All ECGs were read by staff cardiologists at the Fitzsimons Medical Center and ASP cardiologists. Abnormal ECGs were coded at the Minnesota electrocardiogram center.

Statistical analyses

The ability of each variable to conform to a normal distribution was evaluated by visual examination of histograms, and by the Shapiro-Wilk test. To improve the conformity to a normal distribution, several transformations were used. Generalized Linear Models were constructed with the fatty acid variable as the dependent variable, and age and CHD category as the independent variables. The table shows the age-adjusted means and (standard error) for each variable.

RESULTS

The prevalence of coronary heart disease according to the Strong Heart Study (SHS) criteria (18) is shown in Table I. Definite CHD was found for 5.3% of participants, and possible CHD was found among 8.4%, for a total of 13.7% meeting the criteria for CHD. Of these, the diagnosis of “definite CHD” in

10 individuals was based on confirmed definite MI; in 4 of the individuals, the diagnosis was based on evidence in medical records of coronary angioplasty, or bypass surgery, thrombolytic therapy, or a positive angiogram, and in 10 cases it was based on evidence of angina pectoris by Rose questionnaire and Minnesota Codes 4.1, or 5.1, or verified possible MI. The diagnosis of “possible CHD” was, in 5 cases, made on the basis of the Rose questionnaire and, in the remaining cases (33), on the basis of a variety of Minnesota Codes as defined in the SHS (19). Two cases of self-reported MI that were not confirmed in either the ECG, or the medical charts were not defined as having CHD.

Mean ω -3 FA intakes assessed by FFQ and 24-h recall, and plasma concentrations of ω -3 FAs, are shown in Table II. No differences were found in the consumption of ω -3 FAs between those with and without CHD. A detailed analysis of prevalence and risk factors is presented in a companion article (18).

Table I. Prevalences (per 100) for definite and possible coronary heart disease.

Age (years)	n	Definite CHD n(%)	Possible CHD n(%)	Total CHD n(%)
25-34	108	0 (0.0)	5 (4.6)	5 (4.6)
35-44	116	1 (0.7)	4 (3.4)	5 (4.3)
45-54	72	4 (5.6)	4 (5.6)	8 (11.3)
55-64	75	8 (10.7)	7 (9.3)	15 (20.0)
65-74	52	8 (15.7)	9 (17.6)	17 (33.3)
75+	31	3 (9.7)	9 (29.0)	12 (38.7)
Total	454	24 (5.3)	38 (8.4)	62 (13.7)

Table II. Age-adjusted mean fatty acid data from FFQ and 24-hour recall dietary daily intakes, and plasma concentration.

Variable	No CHD (n=392)	CHD (n=62)	P diff
Food Frequency questionnaire			
ω -3 FAs(g/d)	3.97 (0.240)	3.97 (0.623)	0.9961
ω -3 FAs as percent of total fat	2.86 (0.083)	2.91 (0.216)	0.8258
24-hour recall			
ω 3 FAs (g/d)	3.05 (0.240)	3.77 (0.605)	0.2768
ω -3 FAs as percent of total fat	3.64 (0.173)	4.15 (0.43)	0.2889
Plasma			
ω -3 FAs (% of total FAs)	15.84 (0.299)	17.06 (0.752)	0.1410

DISCUSSION

First, the limitations of this research must be acknowledged. This study data represents a small sample of participants, who were not randomly chosen. Potential bias exists due to the stronger participation of women and elderly village residents. However, as the risk of CHD increases with age, the predominance of elderly participants may have more strongly represented those with CHD than would have been possible with random selection.

Secondly, while these four villages represent Siberian Yupik, Central Yupik and Inupiat ethnic groups, these data may not necessarily be representative of other ethnic groups among Alaskan Natives.

Thirdly, it is also possible that those with CHD had recently increased their consumption of ω -3 FAs, resulting in the similarity to non-CHD participants. This could have resulted from a seasonal feasting on foods rich in ω -3 FAs at the time of the screening. However, there is no data to support that hypothesis.

Finally, as only a single measurement of dietary intake was collected during the Spring (even via two different instruments), potential seasonality and day-to-day variance may not be captured by these methods. However, the strong correlation between the 24-hour dietary data and the serum values strengthens the data with biologic confirmation.

The average daily consumption of ω -3 FAs among the Alaskan Natives (ANs) studied here is about 3-4 g, compared to 1-2 g/d used in intervention studies (2) and the average of 0.2 g/d consumed by the American population (4).

The high prevalence of CHD in Alaskan Eskimos of the Norton Sound region revealed in this study fits the available mortality statistics. The death rate from ischemic heart disease in this region has been reported to be twice that of the adjoining regions (24). This death rate among these Eskimos is much higher than that reported for AN, which includes Aleuts, Athabascan Indians (24, 25). The consensus from several studies is that the death rate from ischemic heart disease in male ANs was about equal to that of the US rate for white men, while the rate for AN women was about 50% of the US White rate in 1994-1998 (26). During this period, death rates from heart disease in the 25-44 age group were 30% higher than in US whites, and the 45-54 age group had a 40% higher mortality; in contrast, the 75+ age group had a 20% lower mortality rate from heart disease than US whites. The death rates from cerebrovascular disease among ANs were about 1.5-fold higher than the US white rate during the same period (25). It cannot be over-emphasized that the data for the ANs include a variety of ethnic groups with widely varying CHD-related death rates (27-29).

The prevalence data obtained in this study confirmed the high prevalence noted in an earlier screening study of one Eskimo village, in which 15% of those \geq 45 years old were diagnosed with CHD using the Strong Heart Study protocol (19).

These findings differ from those made in the 1960s, which showed that CHD was rare in Alaskan Eskimos (27-28), and from those made in the 1980s, that showed a CHD death rate of about 0.5% of the Alaskan non-Native population (25-26). An autopsy study found fewer raised vascular lesions in young

ANs (Eskimos, Aleuts, Athabascan Indians, etc) than in Alaskan non-Natives (29). This finding cannot be interpreted in relation to the prevalence data presented here for Eskimos, because Eskimos were not identified (29).

CHD seems to be increasing in Eskimos (9), who were thought to be relatively immune to CHD by their high consumption of ω -3 fatty acids in fish, seal and whale. One of the emerging questions has become: are those Eskimos developing CHD due to lower consumption of ω -3 FAs, or are other risk factors present that outweigh the effects of ω -3FAs? These data demonstrate that Eskimos with CHD consume amounts of ω -3 FAs similar to those consumed by subjects without CHD.

Relative plasma concentrations of ω -3 FAs clearly reflect and correlate with the dietary data, especially from the 24-hour recall collected the day before the blood draw ($p = 0.003$). Considering that DM, IGT, hypertension and obesity are increasing and are associated with CHD in this study (18), it is clear that such risk factors, and others that have not yet been identified, can also contribute to CHD in this population, despite a high consumption of ω -3 FAs. It would not be expected that ω -3 FAs could absolutely protect an individual from CHD in the presence of other risk factors, such as smoking, obesity, hypertension, or the over-consumption of saturated and trans-FAs.

On the other hand, our finding should not lead to the dismissal of the large body of evidence in support of an adequate consumption of ω -3 FAs. This includes evidence from clinical trials, showing the significant cardiovascular survival benefit of ω -3 FA supplementation among patients surviving a recent myocardial infarction (1, 2), and the reduced

mortality from ischemic heart disease associated with the amount of fish consumed (3,4,30). Additionally, it is well known that ω -3 FA consumption is associated with improved CHD risk factors, such as plasma concentrations of HDL cholesterol and triglyceride (31). ω -3 FAs from fish and marine mammals play important roles in lipoprotein (32) and eicosanoid metabolism (32), and influence a wide variety of physiological processes, including inflammation (33,34), platelet aggregation (35) and blood pressure (36).

What appears as a paradox can be explained, because Dyerberg-Bang hypothesis (7, 8) was not based on adequate scientific data as Alaskan Eskimos, and probably other circumpolar populations, both then and now, develop CHD despite a “large” consumption of ω -3 FAs. The hypothesis, as originally stated, should be replaced with more modest hypotheses based on the information currently available:

- 1) High consumption of ω -3 FAs does not totally protect against the development of CHD, if other risk factors are present.
- 2) Adequate ω -3 FA consumption reduces the risk of arrhythmia and sudden death.
- 3) Adequate ω -3 FA consumption improves some CHD risk factors (31-37), but not others, that lead to CHD.

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