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The association of n-3 fatty acids with serum High Density Cholesterol (HDL) is modulated by sex but not by Inuit ancestry

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ABSTRACT

Objective: To explore the association between dietary n-3 fatty acids and serum lipids in a population with a high intake of marine food. Specifically to test interaction with sex and ethnicity.

Methods: Information was obtained from 2280 Inuit who participated in a countrywide health survey in Greenland in 2005–2009. n-3 intake was estimated from an FFQ and analyses of Red Blood Cell (RBC) membranes. Serum total, HDL and LDL cholesterol and triglyceride were analysed. Obesity was measured. Information on ethnicity, smoking, alcohol consumption, and physical activity was obtained from an interview.

Results: In linear regression models adjusted for age, sex, obesity, ethnicity, alcohol, and smoking serum HDL, LDL and triglyceride were associated with n-3 intake estimated as eicosapentaenoic acid (EPA) in RBC membranes. For HDL the interaction between EPA and sex was significant ($p < 0.001$). No significant interactions were observed for EPA and ethnicity.

Conclusion: A positive association of EPA with serum HDL and LDL and a negative association with triglyceride was observed among both men and women. For HDL, the association was stronger for men. The association of EPA with serum HDL was similar among Inuit with full Inuit ancestry and those with part Inuit ancestry. Diet and overweight are both realistic candidates for a population based intervention against dyslipidemia. Further studies of ethnic differences in the effect of n-3 fatty acids on cardiovascular risk factors are recommended.

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1. Introduction

Many of the scientific studies concerning marine n-3 fatty acids and cardiovascular disease originated in Bang and Dyerberg's original hypothesis [1] which was based on observations from the Inuit in Greenland [2]. These authors observed that concentrations of total cholesterol, β -lipoprotein (LDL), and triglyceride, among others, were low compared with Danish controls, while the concentration of α -lipoprotein (HDL) was high, and hypothesized that this was due to the marine diet of the Inuit and further that this might explain a alleged very low incidence of ischaemic heart disease and the absence of diabetes mellitus. Subsequent research has shown that dietary n-3 fatty acids reduce the risk of cardiovascular mortality especially in patients with previous myocardial infarction, while there is no effect on arrhythmia or all-cause

mortality. Data on their role in primary prevention are inconsistent [3–5]. A recent large study showed no effect of n-3 fatty acid supplementation for 6 years on cardiovascular death or major vascular events in persons with high risk for cardiovascular events [6] while another study showed a significant reduction in major coronary events [7]. The existence of a low mortality from coronary heart disease among the Inuit has since been questioned [8].

A consistent effect of n-3 fatty acids is a lowering of plasma triglyceride concentrations [4]. The effect of n-3 fatty acids on blood lipids further include an increase in Low Density Lipoprotein (LDL) and inconsistently a moderate increase in High Density Lipoprotein (HDL) [9–11] also among Inuit [12,13]. The association between dietary marine n-3 fatty acids and HDL has been shown to be more pronounced among men than among women [14] and to vary among ethnic groups, e.g. Japanese, Koreans and Mongolians [15].

The purpose of the present paper is to explore the association between various dietary n-3 fatty acids and serum lipids (HDL, LDL and triglyceride) in Greenland Inuit, who have an exceptionally high consumption of n-3 fatty acids from marine mammals and fish. We specifically hypothesize that the strength of the associations varies according to sex and degree of Inuit ancestry.

Abbreviations: EPA, eicosapentaenoic acid, C20:5 n-3; DHA, docosahexaenoic acid, C22:6 n-3; HDL, High Density Lipoprotein, High Density Cholesterol; LDL, Low Density Lipoprotein, Low Density Cholesterol; RBC, Red Blood Cells.

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2. Methods

2.1. Sample

Data was collected as part of a countrywide cross sectional health survey in Greenland during 2005–2009. The total population of Greenland is 57,000 of whom 90 percent are ethnic Greenlanders (Inuit). Genetically, Greenlanders are Inuit (Eskimos) with a mixture of European, mainly Scandinavian genes. They are genetically and culturally closely related to the Inuit/Iñupiat in Canada and Alaska and, somewhat more distantly, to the Yupiit of Alaska and Siberia. Questionnaires were developed in Danish language, translated into Greenlandic, back translated and revised. Interviews and self-administered questionnaires gave information about socio-demographic factors, self-rated health and disease, and lifestyle including diet, physical activity, smoking and alcohol use. Interviews were conducted in the language of choice of the participant, most often in Greenlandic, by native Greenlandic speaking interviewers who had been trained in the study procedures.

Fifteen towns and villages in West Greenland (25% of all communities) were selected as study areas to represent different community sizes and geographical locations. From these communities a random population sample was drawn from the central population register. Pregnant women, persons not born in Greenland or Denmark, and persons who had moved out of the study area were excluded from the sample. Ethnicity as Greenlander was determined at enrolment based on the primary language of the participant and self identification. Only one ethnicity was allowed for each participant. Participation rate was 68%. In addition to the interview, clinical testing and sampling of biological media were conducted. A full description of the study methods is available elsewhere [16]. The study comprised a total of 2459 Inuit aged 18–84 years who participated in an interview and took part in a clinical examination with blood sampling. Participants on lipid lowering medication ($n = 91$) and women using oral contraception or hormone replacement therapy ($n = 88$) were excluded leaving a study base of 2280.

2.2. *n*-3 fatty acids and blood lipids

Intake of *n*-3 fatty acids was calculated from an interviewer administered food frequency questionnaire (FFQ) with portion sizes. The FFQ covered 25 local and 43 imported food items [17]. Individuals reporting an average daily intake of less than 3350/2100 kJ (men/women) or more than 17,000/15,000 kJ ($n = 211$) were excluded from the analyses of reported nutrient intake [18].

The composition of phospholipids of erythrocyte membranes was measured after total lipid extraction with chloroform/methanol mixture, phospholipid separation by thin layer chromatography and methylation of fatty acids, followed by capillary GLC using a DB-23 column in an HP-Packard GC chromatograph. The *n*-3 fatty acids comprised C18:3, C18:4, C20:3, C20:4, C20:5 (EPA), C22:3, C22:5 and C22:6 (DHA). The ratio of *n*-3 to *n*-6 fatty acids was calculated. Analyses were performed at the Centre de recherche sur les maladies lipidiques (CRML), Centre hospitalier universitaire de Québec, Canada (CHUQ). Information on *n*-3 fatty acids was missing in nine cases.

Triglyceride, total and High Density Lipoprotein (HDL) were measured in serum by an enzymatic colorimetric tests using Hitachi 917 at Steno Diabetes Centre, Copenhagen, Denmark. Low Density Lipoprotein (LDL) was calculated using Friedewald's formula. Information on HDL was missing in two cases. Information on fasting triglyceride was missing in 78 cases and on LDL in 96 cases.

2.3. Confounders

The following variables were included as confounders in the statistical models as appropriate. Inuit ancestry was estimated from questions about the ethnicity of the grandparents and if this was unknown of the parents. It was recoded as full Inuit ancestry (4 Inuit grandparents) or mixed. Central obesity was estimated from waist circumference measured on the standing participant midway between the iliac crest and the costal margin. Alcohol consumption was estimated from a question about the frequency of alcohol consumption. This information was missing in 335 cases for which values were imputed as medians of 25 nearby cases in the file sorted by smoking, sex, and age. Information on smoking was obtained from the interview and recoded as current smoker vs. previous or non-smoker. Physical activity estimated by the long IPAQ questionnaire [19] was considered for inclusion as a confounder but was not significantly associated with any of the blood lipids and accordingly not included in the statistical models. Sex was coded male = 1, female = 2.

2.4. Statistical methods

Statistical analyses were performed in IBM/SPSS version 19.0. Dependent variables were natural log transformed to obtain better fit to the normal distribution and the results were subsequently back transformed for clarity of presentation. Serum lipids in quintiles of *n*-3 fatty acids were compared by Anova. A linear regression model was constructed with quintiles of EPA in RBC and confounders. The dietary marker and all mentioned confounders were initially included in the models and subsequently removed by backwards selection with $p = 0.05$ as selection criterion for exclusion. Concentrations of HDL according to quintiles of EPA in RBC and adjusted for relevant confounders were estimated by General Linear Models.

2.5. Ethical review

The study was ethically approved by the Commission for Scientific Research in Greenland. Participants gave their written consent after being informed about the study orally and in writing.

3. Results

The study population had a mean age of 44 years and 45% were males. By far the majority (87%) had full Inuit ancestry, i.e. four Inuit grandparents. The calculated intake of *n*-3 fatty acids was high, 4.4 g/day. Serum concentration of High Density Lipoprotein (HDL cholesterol) was high compared with European (Danish) populations (1.67 vs. 1.45 mmol/l), concentration of Low Density Lipoprotein (LDL cholesterol) was also high (3.65 vs. 3.45 mmol/l) while triglyceride concentration was low (1.18 vs 1.30 mmol/l) [20]. More than half of the population had a BMI above 25 kg/m² and 67% of the population was daily smokers of cigarettes (Table 1).

Unadjusted serum concentrations of HDL increased significantly in quintiles of increasing consumption and tissue levels of *n*-3 fatty acids (Table 2). The most pronounced increase from quintile 1 to quintile 5 was for EPA measured in Red Blood Cell (RBC) membranes. Triglyceride showed consistent decrease in quintiles again most prominent for EPA in RBC membranes. LDL increased in quintiles but less prominently than the other two lipids. RBC EPA was used for further analyses. The percentages of EPA in RBC membranes in the quintiles were <0.91, 0.92–1.55, 1.56–2.44, 2.45–3.78, and $\geq 3.79\%$. The average calculated dietary intake of *n*-3 fatty acids in the RBC EPA quintiles was 2.0, 3.3, 4.2, 4.8 and 7.0 g/day.

Table 1
Characteristics of the study population. Population survey in Greenland 2005–2009. $N = 2280$.

Age	44 (18–89)	Years (mean, range)
Males	45.4	%
Full Inuit ancestry	86.7	%
Mixed ancestry	13.3	%
Calculated intake		
n-3 fatty acids (EPA + DHA)	4.3 (4.8)	Mean (SD) g/day
n-3 fatty acids relative to intake of total fat	5.2 (4.9)	Mean % (SD)
Total fat	32.8 (7.0)	Energy % (SD)
Saturated fat	10.6 (2.7)	Energy % (SD)
In RBC membranes		
Total n-3 fatty acids	10.0 (4.3)	Mean % (SD)
EPA	2.4 (1.7)	Mean % (SD)
DHA	5.2 (2.2)	Mean % (SD)
n3/n6 ratio	0.52 (0.28)	Mean (SD)
Overweight (BMI ≥ 25 kg/m ²)	54.2	%
Obesity (BMI ≥ 30 kg/m ²)	23.8	%
Waist circumference	92.1 (13.4)	cm
Alcohol consumption		
Never or rarely	51.7	%
1–2 times per month	28.3	%
1–2 times per week	16.2	%
3 + times per week	3.7	%
Current smoker	66.6	%
Serum High Density Lipoprotein (HDL)	1.67 (0.55)	mmol/l
Serum Low Density Lipoprotein (LDL)	3.65 (1.11)	mmol/l
Serum triglyceride	1.18 (0.70)	mmol/l

In an adjusted linear regression model, EPA in RBC was still positively associated with HDL along with age, female sex, full Inuit ancestry, and consumption of alcohol, while the association with waist circumference was negative (Table 3). The interaction between sex and EPA was statistically significant ($p < 0.001$) while the interaction between Inuit ancestry and EPA was not. In the adjusted model, EPA was still significantly associated with LDL and triglyceride along with age and waist circumference. Triglyceride was also significantly associated with smoking. For LDL and

triglyceride, interactions between sex and EPA or ethnicity and EPA were not significant. R^2 was 0.36 for HDL and lower for LDL and triglyceride. Determined by ΔR^2 the strongest associations were found for waist circumference and age, while weaker associations were found for EPA quintiles and Inuit ancestry.

Based on General Linear Models for men and women separately, Fig. 1 shows that HDL increased with RBC EPA for both men and women but that the difference between men and women diminished and became non-significant ($p < 0.001$ in the lower three quintiles; $p = 0.09$ in the highest quintile) with increasing RBC EPA.

4. Discussion

HDL cholesterol increased with the concentration of EPA in RBC. LDL cholesterol also increased while serum triglyceride decreased. HDL was significantly higher among women than men and higher among participants with full Inuit ancestry. An increase in dietary intake of n-3 fatty acids from 2.0 g/day (in the lowest RBC EPA quintile) to 7.0 g/day (in the highest quintile) was associated with an increased HDL of 0.29 mmol/l among men and 0.22 mmol/l among women. This confirms the observations of Okuda et al. [14] that the association of n-3 fatty acids with HDL was more pronounced among men but contrary to the observations of Okuda et al. there was also a significant association between n-3 fatty acids and HDL for women.

We have confirmed observations that a marine diet is positively associated with HDL and LDL, and negatively with triglyceride [9–13] and that the associations are present through the whole concentration range of n-3 fatty acids. Relative to our hypotheses we found that female sex and Inuit ethnicity were associated with high serum HDL but not with serum LDL or triglyceride. The strength of the association between EPA and HDL was higher for men than for women while there was no interaction for EPA and ethnicity.

Although most studies show an increase in LDL with increased consumption of n-3 fatty acids it should be noted that some studies have shown a reduction in small dense LDL particles and VLDL cholesterol [21,22]. One review concluded furthermore, that while both EPA and DHA reduced triglyceride, only DHA increased HDL

Table 2
Association of n-3 fatty acids with serum lipids in Inuit of Greenland 2005–2009. Unadjusted values.

	Calculated intake of n-3 fatty acids, g/day	RBC sum of n-3 fatty acids, Percent	RBC EPA, Percent	RBC DHA, Percent	RBC n3/n6 ratio, ratio
HDL cholesterol^a					
Quintile 1	1.46	1.56	1.42	1.58	1.46
Quintile 2	1.56	1.46	1.49	1.46	1.45
Quintile 3	1.57	1.53	1.57	1.53	1.56
Quintile 4	1.66	1.65	1.67	1.66	1.67
Quintile 5	1.70	1.79	1.85	1.73	1.84
<i>p</i>	<0.001	<0.001	<0.001	<0.001	<0.001
LDL cholesterol^b					
Quintile 1	3.22	3.49	3.17	3.50	3.20
Quintile 2	3.54	3.27	3.44	3.28	3.46
Quintile 3	3.65	3.49	3.47	3.48	3.48
Quintile 4	3.62	3.57	3.68	3.57	3.66
Quintile 5	3.47	3.60	3.65	3.57	3.63
<i>p</i>	<0.001	<0.001	<0.001	<0.001	<0.001
Triglyceride^c					
Quintile 1	1.14	1.13	1.14	1.10	1.12
Quintile 2	1.10	1.10	1.13	1.11	1.13
Quintile 3	1.06	1.08	1.06	1.09	1.06
Quintile 4	1.03	1.04	1.05	1.02	1.02
Quintile 5	0.96	0.88	0.86	0.92	0.91
<i>p</i>	<0.001	<0.001	<0.001	<0.001	<0.001

^a Fasting and non-fasting subjects. $N = 2067$ for calculated intake; $N = 2271$ for RBC lipids.

^b Fasting subjects. $N = 1984$ for calculated intake; $N = 2178$ for RBC lipids.

^c Fasting subjects. $N = 2001$ for calculated intake; $N = 2196$ for RBC lipids.

Table 3
Linear regression analyses of serum HDL, LDL and triglyceride. Inuit in Greenland 2005–2009. Regression on natural log transformed values, subsequently exponentiated for ease of interpretation.

	Serum HDL <i>N</i> = 2271				Fasting serum LDL <i>N</i> = 2178				Fasting serum triglyceride <i>N</i> = 2196			
	β	95% CI	<i>p</i>		β	95% CI	<i>p</i>		β	95% CI	<i>p</i>	
	$R^2 = 0.36$				$R^2 = 0.33$				$R^2 = 0.20$			
Constant	1.596	1.411	1.804	<0.001	1.747	1.596	1.912	<0.001	0.320	0.278	0.368	<0.001
Age (year)	0.009	0.007	0.010	<0.001	0.006	0.005	0.008	<0.001	0.001	0.001	0.002	<0.001
Sex (female vs. male)	0.352	0.257	0.452	<0.001	Not in model				Not in model			
Waist circumference (cm)	-0.015	-0.016	-0.014	<0.001	0.009	0.008	0.011	<0.001	0.004	0.004	0.005	<0.001
RBC EPA (quintiles)	0.145	0.103	0.187	<0.001	0.027	0.009	0.045	0.003	-0.026	-0.030	-0.022	<0.001
Ethnicity (full Inuit vs. less)	0.276	0.161	0.399	<0.001	Not in model				Not in model			
Alcohol	0.123	0.102	0.145	<0.001	Not in model				Not in model			
Smoker (vs. non-smoker)	Not in model				Not in model				0.021	0.008	0.034	0.001
EPA*sex interaction	-0.050	-0.073	-0.027	<0.001	Not in model				Not in model			
EPA*ethnicity interaction	Not in model				Not in model				Not in model			

and LDL [23]. Although EPA and DHA occur together in the fat of fish and marine mammals this could be of practical importance for dietary supplementation strategies.

From a public health point of view, the association of n-3 fatty acids with HDL is interesting.

For instance, according to our model (Table 3) moving from one quintile of EPA to the next highest which is roughly equivalent to increasing the dietary intake of n-3 fatty acids by 1 g/day, will increase the HDL concentration by 9%. A similar increase is brought about by a decrease in waist circumference of 10 cm according to our model and is similar to an age difference of 17 years. For triglyceride, a reduction in waist circumference of 6 cm is equivalent to moving from one quintile of EPA to the next higher. Given the disappointing effects of weight intervention eating more fish and marine mammals seems to be a relevant alternative in some populations.

The association between n-3 fatty acids and HDL has been observed in several but not all western populations [9–11] and also among Japanese [15] and Inuit [12,13], but not among Koreans and Mongolians [15]. Our study confirmed the association for Inuit of full as well as part Inuit ancestry. The Inuit, Japanese, Korean, and Mongolian populations differ with regard to intake of n-3 fatty acids and several other parameters that could offer an explanation

for the fact that only among the Inuit and the Japanese there is an association between n-3 fatty acids and HDL. Compared with the Japanese and in particular the Inuit, the Koreans and the Mongolians had a low average consumption of n-3 fatty acids which might be part of the explanation. This is substantiated by the finding of an increasing association of EPA with HDL across EPA quintiles in Table 2. Genetic differences may also be present. It is noteworthy that the issue of potential differences among ethnic groups has attracted little interest among researchers. The association of n-3 fatty acids and serum lipids is well established for white people, Japanese and Inuit but not beyond these populations.

It is a weakness of the study that it is cross sectional and therefore cannot establish the direction of a cause-effect relationship from the statistical associations. A person may choose to change his or her diet after being informed about a high serum cholesterol, but health checks for cholesterol do not take place in Greenland to any significant extent, and we excluded participants on lipid lowering medication. It is therefore more plausible that the association between diet and serum lipids is due to an effect of diet on the lipids.

The strengths of the study include its large size in a non-western population with a very high intake of n-3 fatty acids from marine

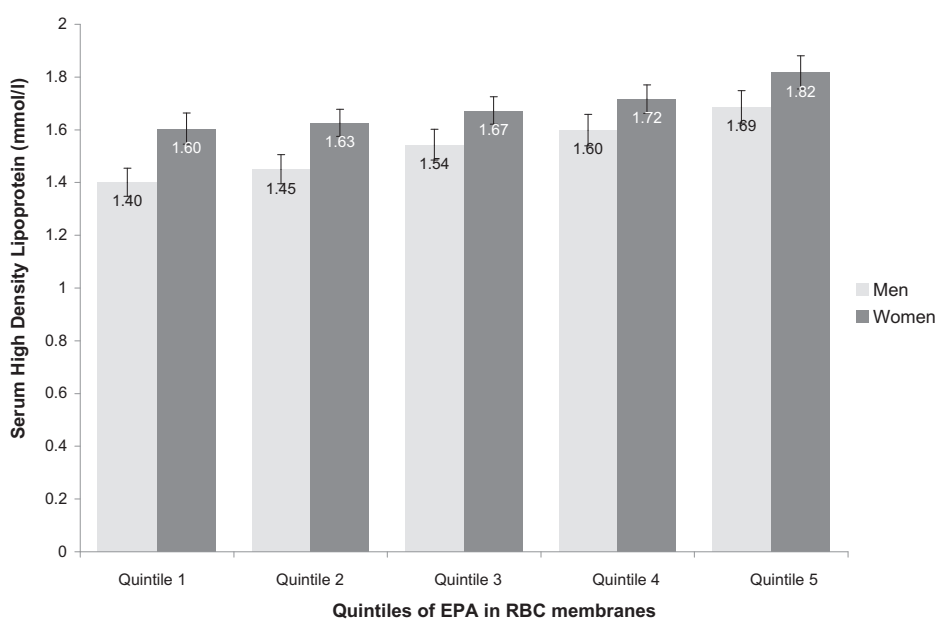


Fig. 1. Serum High Density Lipoprotein (HDL) in Inuit men and women by quintiles of EPA in RBC membranes. Estimated from a general linear model adjusted for age, waist circumference, alcohol consumption, and ethnicity. Greenland 2005–2009; *n* = 2173.

mammals and fish. Even at these high intakes the association between diet and serum lipids was evident. The fact that the study population is drawn from the same ethnic group in which the worldwide interest in the study of “fish oils” originated is a further strength.

5. Conclusion

Dietary n-3 fatty acids were associated with increased serum HDL and LDL and decreased serum triglyceride among Greenlanders, who have an exceptionally high dietary intake. Women had higher HDL cholesterol than men but the association of diet with HDL was more pronounced for men than for women. Participants with full Inuit ancestry had higher HDL than those of mixed Inuit/Danish ancestry but there was no interaction between Inuit ancestry and diet. Diet and overweight, the two preventable risk factors in the model, are both realistic candidates for a population based intervention against dyslipidemia. Studies of ethnic differences in the effect of n-3 fatty acids on cardiovascular risk factors are recommended.

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Conflicts of interest

None.

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