Published in final edited form as:
Prostaglandins Leukot Essent Fatty Acids. 2012 July ; 87(1): 11–16. doi:10.1016/j.plefa.2012.04.010.

Serum levels of marine-derived n-3 fatty acids in Icelanders, Japanese, Koreans, and Americans - A descriptive epidemiologic study

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Summary

In the 1990's Iceland and Japan were known as countries with high fish consumption whereas coronary heart disease (CHD) mortality in Iceland was high and that in Japan was low among developed countries. We described recent data fish consumption and CHD mortality from publicly available data. We also measured CHD risk factors and serum levels of marine-derived n-3 and other fatty acids from population-based samples of 1,324 men in Iceland, Japan, South Korea, and the US. CHD mortality in men in Iceland was almost 3 times as high as that in Japan and South Korea. Generally a profile of CHD risk factors in Icelanders compared to Japanese was more favorable. Serum marine-derived n-3 fatty acids in Iceland were significantly lower than in Japan and South Korea but significantly higher than in the US.

Keywords

n-3 fatty acids; eicosapentaenoic acid; docosaehexaenoic acid; coronary heart disease; descriptive epidemiologic study

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Conflict of interest
None declared

Introduction

Since the pioneering work by Bang and Dyerberg, showing low rates of death from coronary heart disease (CHD) among Greenland Eskimos in the 1970's,[1, 2] numerous studies have been carried out on fish, marine-derived n-3 fatty acids, and CHD. An ecological study of 36 countries shows that per capita consumption of fish has a significant inverse association with national CHD mortality, which remains after adjusting for per capita consumption of animal fat, animal protein, alcohol, and cigarette smoking.[3] For assessing per capita consumption of fish, the study used food balance sheets from the Food and Agricultural Organization (FAO). Another ecological study using food balance sheets shows that among 21 countries per capita consumption of fish has a significant inverse association with national CHD mortality.[4] The significant association, however, disappears after adjusting for per capita consumption of dairy products and meat – a proxy for saturated fat intake. Prospective cohort studies and clinical trials have reported that marine-derived n-3 fatty acids reduce the risk of CHD death.[5] Increasing fish intake to two times a week reduces CHD death by 20 to 36%.[6, 7] The reduction in CHD death is attributed to an anti-arrhythmic effect of marine-derived n-3 fatty acids.[6] Further increasing fish intake does not substantially reduce CHD death.[6, 7] In contrast, recent studies in Japan where people eat fish daily and dietary intake of marine-derived n-3 fatty acids is about 1,000 mg/day,[8] as compared to 100 mg/day in a typical Western diet,[8, 9] show that marine-derived n-3 fatty acids contribute to the reduction in non-fatal CHD.[10, 11] The results may indicate an anti-atherogenic effect of marine-derived n-3 fatty acids.[12]

In the late 20th century, Iceland and Japan have been known as countries whose fish consumption is very high whereas both CHD mortality and incidence in Iceland were high and those in Japan were low among developed countries.[13–15] No previous study has compared serum levels of marine-derived n-3 fatty acids between Icelanders and the Japanese.

In this descriptive epidemiological study, we compared recent national data on per capita consumption of fish, fish intake from national nutrition surveys, and CHD mortality in Iceland, Japan, South Korea, and the United States (US). In addition, we described marine-derived serum n-3 fatty acids, total cholesterol, high-density-lipoprotein cholesterol (HDL-C), and other risk factors for CHD among Icelanders, Japanese, Koreans, Japanese Americans, and US whites from our population-based studies.

Materials and Methods

Data on per capita consumption of fish during 2003 to 2005 in Iceland, Japan, South Korea, and the US were obtained from the FAO food balance sheets.[16] Data on fish intake were obtained from national nutrition surveys in Iceland in 2002, Japan in 2002, South Korea in 2007 and the US in 1994–96 and 1998. [17–20] Data on CHD mortality during 2001 to 2004 in Iceland were obtained from the Statistics Iceland (www.statice.is) and those in Japan, South Korea, and the US were obtained from the World Health Organization Statistical Information System (www.who.int/whosis).

Data and stored serum samples from the Risk Evaluation For INfarct Estimates Reykjavik study (REFINE-Reykjavik study) (www.hjarta.is/english/refine)[14, 21] and the Electron-Beam Tomography, Risk Factor Assessment among Japanese and U.S. Men in the Post World War II Birth Cohort (ERA JUMP study)[22–24] were used to compare CHD risk factors and serum fatty acids including marine-derived n-3 fatty acids, respectively. The study was approved by the Institutional Review Boards of each research center.

The REFINE-Reykjavik study is a population-based prospective cohort study on risk factors and etiology of atherosclerotic disease in the homogenic population of Reykjavik city, Iceland. The cohort is a random sample of 9,477 men and women born in 1935–1985 and living in Reykjavik province 1st of December 2005.[14] The rate of participation was 76%.[21] From this study, 97 men were randomly selected.

Venipuncture was performed early in the clinic visit after a 12-hour fast. The samples were stored at −80C°. Serum lipids, i.e., total cholesterol, low-density-lipoprotein cholesterol (LDL-C), HDL-C, and triglycerides were determined with standardized methods according to the International Organization for Standardization (ISO) 15189. Serum glucose was determined using a hexokinase-glucose-6-phosphate-dehydrogenase-enzymatic assay (Roche Diagnostics, Mannheim, Germany).

The ERA JUMP study is a prospective cohort study on risk factors and etiology of subclinical atherosclerosis in population-based samples of men aged 40–49 in Japan, South Korea, and the US.[22–24] During 2002 to 2006, 1,227 men without clinical cardiovascular disease or other sever diseases were randomly selected; 313 Japanese from Kusatsu, Shiga, Japan, 303 Japanese Americans from a representative sample of offspring of fathers who participated in the Honolulu Heart Program,[25] Honolulu, Hawaii, U.S., 301 Koreans from Ansan City, Gyeonggi-Do, Korea, and 310 whites from Allegheny County, Pennsylvania, U.S. The rate of participation in each center was about 50%.[22, 24] For this study we excluded 6 subjects with missing data. Our final samples were 313 Japanese in Japan, 297 Japanese Americans, 301 Koreans, and 307 whites.

Venipuncture was performed early in the clinic visit after a 12-hour fast. The samples were stored at −80C°. Serum lipids were determined with the standardized methods according to the Centers for Disease Control and Prevention (CDC). Serum glucose was determined using a hexokinase-glucose-6-phosphate-dehydrogenase-enzymatic assay, serum insulin using a radio-immuno assay (Linco Research Inc., St. Charles, US),

Determination of serum fatty acids

Serum samples stored at −80°C from REFINE-Reykjavik study and ERA JUMP study were shipped on dry ice to the Heinz Laboratory, University of Pittsburgh. Serum fatty acids were determined using gas chromatography.[22]

The coefficients of variation between runs for major marine-derived n-3 fatty acids, i.e., eicosapentaenoic acid (EPA) (20:5n-3) and docosahexaenoic acid (DHA) (22:6n-3) were 4.5% and 7.2%, respectively. The coefficients of variation for other major fatty acids: palmitic (16:0), stearic (18:0), oleic (18:1n-9), linoleic (LA) (18:2n-6), alpha-linolenic, arachidonic (ARA) (20:4n-6), docosapentaenoic (DPA) (22:5n-3) acids, and total fatty acid amount were 1.2%, 4.0%, 2.3%, 1.6%, 7.9%, 2.8%, 4.5%, and 5.7%, respectively.

Statistical analyses

For age-adjusted mortality from CHD, a new World Health Organization standard was used.[26] Data on body mass index (BMI), systolic blood pressure, total cholesterol, HDL-C, LDL-C, triglycerides, fasting glucose, current smoker and fatty acids were age-adjusted and compared using a general linear model with Bonferroni correction. P values of less than 0.05 were considered to indicate statistical significance. All analyses were performed with the use of PASW statistics 18 (IBM, New York, US).

Results

Per capita consumption of fish and shellfish from the FAO food balance sheets was highest in Iceland, followed by Japan and Korea (Table 1). Consumption in Iceland was more than 40% higher than that in Japan and more than three times higher than in the US. In contrast fish intake from national nutrition surveys was highest in Japan, followed by Korea, and Iceland. Fish intake in Japan was more than 40% higher than that in Iceland and more than 10 times higher than in the US.

Age-adjusted mortality from CHD was highest in the US among the four countries followed by Iceland (Table 2). Age-adjusted mortality from CHD in the US was almost four times higher than that in Japan and Korea and that in Iceland was more than two times higher than that in Japan and Korea.

Table 3 shows the cardiovascular risk factors from the REFINE-Reykjavik study and the ERA JUMP study. Icelanders were similarly obese with Japanese Americans and US whites and had significantly higher levels of BMI than Japanese and Koreans. Icelanders had similar levels of systolic blood pressure with Japanese and Japanese Americans and had higher levels than Koreans and US whites. Generally Icelanders had a more favorable lipid profile as compared to the other groups. Icelanders had significantly lower levels of total cholesterol than Japanese, Japanese Americans and US whites. Icelanders had significantly higher levels of HDL-C than Koreans and US whites. Icelanders had significantly lower levels of triglycerides than the other four groups. As to the rate of current smokers, Icelanders had a significantly lower rate than Japanese and a significantly higher rate than US whites.

Serum levels of total marine-derived n-3 fatty acids in Icelanders were significantly lower than those in Japanese by 36% and Koreans by 30% and significantly higher than that in Japanese Americans by 15% and US whites by 45% (Table 4). Similarly, serum levels of each marine-derived n-3 fatty acid, i.e., EPA, DHA, and DPA, in Icelanders were lower than those in Japanese and Korean but higher than those in Japanese Americans and US whites. One exception was that serum levels of DHA in Icelanders were lower than those in Japanese Americans although the difference did not reach statistical significance. In contrast, serum levels of total n-6 fatty acids in Icelanders were significantly higher than those in Japanese by 5% and Koreans by 9% but significantly lower than those in Japanese Americans by 13% and US whites by 13% (Table 4). Similarly serum levels of LA and ARA in Icelanders were higher than those in Japanese and Koreans and lower than those in Japanese Americans and US whites. One exception was that serum levels of ARA in Icelanders were lower than those in Japanese, although the difference did not reach statistical significance.

Discussion and Conclusions

The results of this study show that serum levels of marine-derived n-3 fatty acids in men in Iceland are significantly lower than in men in Japan and Korea and significantly higher than in Japanese American and US white men. National nutrition surveys indicate that fish intake in Iceland is lower than that in Japan and Korea but is higher than that in the US. Vital statistics show that CHD mortality in men in Iceland is almost three times as high as that in men in Japan and Korea.

The current study shows that per capita consumption of fish from the FAO food balance sheet was highest in Iceland followed by Japan, Korea, and the US whereas fish intake from national nutrition surveys was highest in Japan, followed by Korea, Iceland and the US. Although per capita consumption of fish and shellfish from the FAO food balance sheet has been used in ecological studies not only in cardiovascular disease[3, 4] but also in bipolar disorders,[27] and breast cancer,[28] as well as colon, lung, skin, leukemia and prostate cancers,[29] It has its limitation. Data from the food balance sheet are based on a disappearance model. This model estimates on an annual basis, the total supply of imported and landed seafood converted to raw edible weight, minus exports and other decreases in supply.[16] The error inherent in those statistics is especially large with respect to fish consumption when consumption is only a small fraction of the total amount landed as is the case in Iceland and local consumption is calculated as the difference between two very large numbers.

The current study shows that fish intake from national nutrition surveys was highest in Japan followed by Korea, Iceland and the US. National nutrition surveys assess individual levels of fish intake. Data for fish intake from national nutrition surveys, however, are not directly comparable across countries because methods in assessing dietary intake are not standardized. Additionally, fish intake data from national nutrition survey may not be a good indicator for intake of marine n-3 fatty acids because content of marine-derived n-3 fatty acids in fish differs much from species to species, from season to season, and from wild to farmed fish.

Serum levels of marine n-3 fatty acids are a reasonable indicator of dietary intake of marine n-3 fatty acids.[30] The current study shows that serum levels of marine-derived n-3 fatty acids in men in Iceland are significantly lower than in men in Japan and Korea. Types of fish consumed in each country support the results. Fish intake in Japan is largely from fish rich in marine-derived n-3 fatty acids, e.g., salmon, tuna, saury, mackerel, and yellowtail.[31] Fish intake in Korea is a mixture of oily and lean fish.[32, 33] On the other hand, fish intake in Iceland is dominated by a single lean species, the haddock, which contains relatively small amounts of marine n-3 fatty acids.[34] In Iceland, only about 40% of the total intake of marine n-3 fatty acids in Iceland derives from eating fish whereas 42% originates from cod liver oil,[17] which is commonly taken as a source of vitamin D during the dark winter months in Iceland.[35] Vital statistics in 2001 to 2004 show that age-adjusted mortality from CHD in Iceland is more than two times higher than that in Japan and Korea and that in the US is almost four times higher than that in Japan and Korea. In the past three decades, mortality from CHD has been declining in Iceland, Japan, and the US. [14, 15, 36] The declining trend in CHD mortality is attributed to both risk factor reduction and improvement in medical treatment.[14, 15, 36, 37] As to risk factor reduction, better control of blood pressure and reduction in current smokers especially in men are common in Iceland, Japan, and the US. In striking contrast, serum levels of total cholesterol have been declining in Iceland and the US but have been increasing in Japan. For example, serum levels of total cholesterol in Iceland declined from 232 mg/dL in 1981 to 198 mg/dL in 2006,[14] whereas those in middle-aged men in Japan increased from about 180 mg/dL in 1980 to about 200 mg/dL in 2000.[15] Therefore higher CHD mortality in Iceland and the US as compared to Japan is partly attributed to a cohort effect.

A recent science advisory from the American Heart Association has reported that dietary intake of n-6 fatty acids is protective against CHD and has recommended 5 to 10% of energy from n-6 fatty acids to reduce the risk of CHD.[38] Serum levels of n-6 fatty acids reflect their dietary intake.[30] Our observation that serum levels of total n-6 fatty acids and LA in men in Japan were significantly lower than those in Japanese American and US white men is consistent with the result of dietary data from the International study of micro-nutrients and blood pressure (INTERMAP) study.[8] The INTERMAP study reported that mean dietary intake of n-6 fatty acids (% kcal) among middle-aged men is 4.8 for Japanese, 6.8 for Japanese Americans, and 6.3 for US men. In Iceland, the mean dietary intake of n-3 fatty acids (% kcal) among middle-aged men was 3.6 based on the national nutrition survey.[17]

Our present study shows that serum levels of ARA in men in Iceland, Japan, and Korea were lower than those in Japanese Americans and US whites. ARA is metabolized by cyclooxgenase, lipoxygenase, or cytochrome P450 to generate a wide variety of eicosanoids, e.g. thromboxanes, prostaglandins, leukotrienes, prostacyclins, lipoxins, and cannabinoids, which are potentially associated with various diseases.[38, 39] The INTERMAP study reported that mean dietary intake of ARA (% kcal) among middle-aged Japanese, Japanese American, and US men is similar: 0.07, 0.05, and 0.06, respectively.[8] Although LA is converted to ARA, the rate of conversion of LA to ARA is low, about 0.2%.[40] Thus future research investigating reasons for the population difference in serum levels of ARA is warranted.

The present study had several limitations. The current study is descriptive epidemiology as opposed to analytic epidemiology.[41] Descriptive epidemiology makes use of available data to examine how rates vary according to demographic variables without regards to causal or other hypothesis. Although data from the food balance sheet were collected using standardized methods and can be compared across countries, data from national nutrition surveys were not collected in standardized methods. We believe, however, that data from national nutrition surveys which collect individual data reflect individual fish intake more precisely than data from food balance sheet based on fish import and export as a nation. The rate of participation was 50% in the ERA JUMP Study and the participants of the ERA JUMP Study may be healthier than the general population. Serum marine n-3 fatty acids reflect short-term dietary fat intake and may not reflect long-term dietary intake. A large study in Japan, however, evaluated collected-serum samples twice 6 months apart, and reported that correlations for EPA and DHA were similar in both samples, suggesting that single measurements of serum marine n-3 fatty acids reflect the ranking of habitual intake of marine n-3 fatty acids in Japanese.[42] Official mortality statistics including mortality from CHD are subject to misclassification.[13] Recent studies using the same criteria to diagnose CHD show, however, CHD mortality is much lower in Japan than in Iceland.[14, 43] Comparing cardiovascular risk factors and serum levels of marine-derived n-3 fatty acids, sample size was small and we had data only in men.

Conclusions

Recent statistics show that CHD mortality in men in Iceland was almost 3 times as high as that in Japan and South Korea. Although per capita consumption of fish and shellfish from the food balance sheet is higher in Iceland than in Japan and Korea, national nutrition surveys show fish intake is higher in Japan and Korea than in Iceland. This descriptive study has shown that serum levels of marine-derived n-3 fatty acids, which is a reasonably good indicator of dietary intake of marine n-3 fatty acids, are significantly lower in men in Iceland than in men in Japan and Korea and significantly higher than in Japanese American and US white men.

Acknowledgments

Sources of support

This research was funded by Icelandic Heart Association, Iceland, the Korea Centers for Disease Control and Prevention, Ministry for Health and Welfare 2004-E71001-00, 2005-E71001-00, Korea, R01HL68200, R01HL071561, and N01AG12100, from the National Institutes of Health, USA, B 16790335 and A 13307016 from the Japanese Ministry of Education, Culture, Sports, Science and Technology, Japan, and partly supported by Intramural research program of the National Institutes of Health, National Institute on Aging, USA.

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Table 1

Fish consumption in Iceland, Japan, Korea, and the US based on food balance sheets and national nutrition surveys

	Per capita consumption of fish and shellfish from the food balance sheets [16] (kg/year)	**Fish intake from national nutrition surveys [17–20] (g/day)**
Iceland	90.5	62 *1
Japan	63.2	92–108 *2
Korea	52.6	74 *3
United States	24.2	7 *4

*1 Data were for men aged 40–59;

*2 data were for men aged 40–59;

*3 data were for men aged 50–59:

*4 data were for men aged 45+

Table 2

Trends in age-adjusted mortality from coronary heart disease in men (/100,000)

	Iceland	Japan	Korea	United States
2001	134.7	49.4	49.3	185.6
2002	145.6	48.7	51.7	180.8
2003	121.7	48.2	48.0	172.0
2004	132.1	46.2	47.7	160.0

CHD mortality data in Iceland were obtained from the Statistics Iceland (www.statice.is) and those in Japan, South Korea, and the US were obtained from the World Health Organization Statistical Information System (www.who.int/whosis).

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Table 3

Basic characteristics of subjects from population-based studies

	Icelanders (n=97)	Japanese (n=313)	Japanese Americans (n=297)	Koreans (n=301)	US whites (n=307)
Age (years)	49.6(0.4) [a,b,c,d]	45.1(0.2)[e]	46.1 (0.2)[h,i]	44.8(0.2)	45.0 (0.2)
Body mass index (kg/m^2)	28.1(0.4) [a,c]	23.7(0.2) [e,f,g]	28.0(0.2) [i]	24.8(0.2) [j]	28.0(0.2)
Systolic BP (mmHg)	127.6(1.5) [c,d]	125.2(0.8)[f]	127.4(0.8) [h,i]	122.0(0.8)	122.8(0.8)
Total cholesterol(mmol/L)	4.96(0.09) [a,b,c]	5.64(0.05) [e,f]	5.33(0.05) [h]	4.96(0.05) [j]	5.51(0.05)
HDL-C (mmol/L)	1.37(0.03) [c,d]	1.40(0.01) [e,f,g]	1.18(0.02) [h]	1.31(0.02)	1.24(0.02)
LDL-C (mmol/L)	3.05(0.09) [a,d]	3.43(0.05) [e,f]	3.14(0.05) [i]	3.02(0.05) [j]	3.50(0.05)
Triglycerides (mmo/L)	1.22(0.13) [a,b,c,d]	1.75(0.07) [e]	2.08(0.07) [i]	1.82(0.07)	1.82(0.07)
Fasting glucose (mmol/L)	5.59(0.11) [b]	5.94(0.06) [e,g]	6.22(0.06) [i]	5.73(0.06)	5.66(0.06)
Current smoker (%)	21.0(4.3) [a,d]	49.3(2.3) [e,f,g]	12.8(2.4) [h]	38.0(2.4) [j]	7.8(2.3)

Values were age-adjusted and are expressed as mean (standard error).

BP: blood pressure, HDL-C: high-density-lipoprotein cholesterol, LDL-C: low-density-lipoprotein cholesterol

Significance test was based on general liner model followed by Bonferroni correction.

[a]Significant difference between Icelanders and Japanese, p<0.05

[b]Significant difference between Icelanders and Japanese Americans, p<0.05

[c]Significant difference between Icelanders and Koreans, p<0.05

[d]Significant difference between Icelanders and US whites, p<0.05

[e]Significant difference between Japanese and Japanese Americans, p<0.05

[f]Significant difference between Japanese and Koreans, p<0.05

[g]Significant difference between Japanese and US whites, p<0.05

[h]Significant difference between Japanese Americans and Koreans, p<0.05

[i]Significant difference between Japanese Americans and US whites, p<0.05

[j]Significant difference between Koreans and US whites, p<0.05

Table 4

Serum levels of marine-derived n-3 fatty acids and other fatty acids (%)

	Icelanders (n=97)	Japanese (n=313)	Japanese Americans (n=297)	Koreans (n=301)	US whites (n=307)
Total marine-derived n-3 fatty acids	6.07(0.25)[a,b,c,d]	9.51(0.14)[e,f,g]	5.26 (0.14)[h,i]	8.62(0.14)[j]	4.18 (0.14)
Eicosapentaenoic acids	1.66(0.11) [a,b,d]	2.53(0.06) [e,f,g]	1.00(0.06) [h]	1.97(0.06) [j]	0.81(0.06)
Docosapentaenoic acids	0.72(0.02) [a,c]	0.85(0.01) [e,g]	0.67(0.01) [h]	0.81(0.01) [j]	0.68(0.01)
Docosahexenoic acids	3.04(0.15) [a,c]	5.94(0.08) [e,f,g]	3.15(0.08) [h,i]	4.83(0.08) [j]	2.40(0.08)
Other fatty acids					
Plant derived n-3 fatty acids	0.66(0.05) [a,b,c,d]	0.19(0.03) [e,f]	0.44(0.03) [h,i]	1.01(0.03) [j]	0.29(0.03)
Total n-6 fatty acids	36.6(0.5) [a,b,c,d]	34.8(0.2) [e,f,g]	41.2(0.2) [h,i]	33.3(0.2) [j]	41.3(0.2)
Linoleic fatty acids	28.0(0.4) [a,b,c,d]	26.5(0.2) [e,f,g]	30.0(0.2) [h]	24.7(0.2) [j]	29.8(0.2)
Arachidonic fatty acids	6.32(0.18) [b,d]	6.58(0.10) [e,f,g]	8.90(0.10) [h,i]	6.02(0.10) [j]	9.00(0.10)
Saturated fatty acids	33.2(0.25) [a,b,c,d]	31.7(0.14) [e,f,g]	30.9(0.14) [h]	34.3(0.14) [j]	30.9(0.14)
Monounsaturated fatty acids	20.6(0.34) [a,b,c,d]	19.5(0.18) [e,f]	18.1(0.19) [i]	18.5(0.19)	18.9(0.19)
Trans fatty acids	0.71(0.09) [c,d]	0.57(0.05) [e,f,g]	0.91(0.05) [h]	1.24(0.05) [j]	1.04(0.05)

Values were age-adjusted and are expressed as mean (standard error).

Total marine-derived n-3 fatty acids were defined as the sum of eicosapentaenoic acid (20:5n-3), docosapentaenoic acid (22:5n-3), and docosahexaenoic acid (22:6n-3).

Total n-6 fatty acids were defined as the sum of linoleic acid (18:2n-6), gamma-linoleic acid (18:3n-6), dihomo-gamma-linolenic acid (20:3n-6) and arachidonic acid (20:4n-6).

Saturated fatty acids were defined as the sum of myristic aicd (14:0), palmitic acid (16:0) and stearic acid (18:0).

Monounsaturated fatty acids were defined as the sum of palmitoleic acid (16:1n-7), oleic acid (18:1n-9), and cis-vaccenic acid (18:1n-7).

Trans fatty acids indicate the sum of palmitelaidic acid (16n-7:1t), trans 9-octadecanoic acid (18n-9:1t) and linolelaidic acid (18n-6:2tt).

Significance test was based on general linear model followed by Bonferroni correction.

[a]Significant difference between Icelanders and Japanese, $p<0.05$

[b]Significant difference between Icelanders and Japanese Americans, $p<0.05$

[c]Significant difference between Icelanders and Koreans, $p<0.05$

[d]Significant difference between Icelanders and US whites, $p<0.05$

[e]Significant difference between Japanese and Japanese Americans, $p<0.05$

[f] Significant difference between Japanese and Koreans, $p<0.05$

[g] Significant difference between Japanese and US whites, $p<0.05$

[h] Significant difference between Japanese Americans and Koreans, $p<0.05$

[i] Significant difference between Japanese Americans and US whites, $p<0.05$

[j] Significant difference between Koreans and US whites, $p<0.05$