CARDIOVASCULAR DISEASE AND RISK FACTORS IN THREE ALASKAN ESKIMO POPULATIONS: THE ALASKA-SIBERIA PROJECT

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ABSTRACT

Objectives. To determine the prevalence of CVD and to identify and characterize associated risk factors in three distinct Eskimo populations.

Study Design. Cross-sectional.

Methods. A slightly modified Strong Heart Study protocol was followed to examine 454 participants, aged 25-91, from four villages.

Results. Overall, 6% of the participants under 55 years of age and 26% of those ≥ 55 years of age showed evidence of CHD by ECG, or in patient records. The prevalence of “definite coronary heart disease” (CHD) in women with glucose intolerance (GI) was 21.0%, compared to 2.4% in those with normal glucose tolerance (NGT). Men had comparable values of 26.7% and 6.3%. In addition, comparable values for “possible CHD” were 29.7% vs 6.0% for women and 21.4% vs 8.0% for men. GI was associated with relatively higher prevalences of CHD in women than in men (prevalence ratio = 8.5 vs 4.3). CHD was significantly related to age, glucose intolerance and insulin. Hypertension and obesity were significantly associated with CHD only in some ethnic groups. The prevalence of current smokers was 56%.

Conclusions. Recent changes in lifestyle and diet of Alaskan Eskimos, leading to obesity, hypertension, insulin resistance and DM, contribute to an increased risk for cardiovascular disease. (Int J Circumpolar Health 2005; 64(4):365-386.)

Keywords: diabetes, insulin, omega-3 fatty acids, stroke, Inuit, prevalence
INTRODUCTION

Although the prevalence of coronary heart disease (CHD), type 2 diabetes (DM) and associated risk factors are well known in American Indians (1), little is known about these diseases in the genetically distinct Alaska Natives (2). This is particularly disconcerting because of the magnitude of the problem and the uniqueness of these ethnic groups.

Cardiovascular disease (CVD) mortality rates among Alaska Natives (ANs) were extremely low only 35 years ago (3), but are increasing rapidly and are now (1994-8) 30% and 40% higher in the age groups 25-44 and 45-54, respectively, than in the US White population (4). The death rates for heart disease and stroke in the US White population have decreased by 32% and 31%, respectively, from 1979 to 1998 (4). During this period, mortality from cerebrovascular disease increased by 17% among ANs, while the overall mortality rate from heart disease remained the same. These rates reflect the average of all AN ethnic groups (Eskimos, Aleuts, Athabascan Indians etc.) that differ genetically, and by their lifestyle and food consumption habits. Mortality rates are not known for each ethnic group, but regional differences have been noted. For example, the age-adjusted mortality rates for CVD in the Norton Sound region were recently reported to be twice those of neighboring regions (5, 6).

The reasons for the exceptionally high incidence of stroke and the high prevalence of cerebrovascular disease (CD) among Eskimos in all circumpolar regions are not known (4, 7, 8), although it is known that DM is an important risk factor (9). In a 1990-1998 study of Central Yupik Eskimos, Trimble et al. (10) found that 79% of the strokes were ischemic, 12% hemorrhagic, 5% were by subarachnoid hemorrhage, and 4% were classed as unknown. Death rates for cerebrovascular disease among ANs were about 1.5 times higher than that of the US White rate during 1994-1998 (4). Greenlandic Eskimos, with a three-fold higher incidence of stroke than Danes, have, until recently, experienced exceptionally low prevalences of CHD and DM (8, 11), while Alaskan Eskimos currently experience an increase of DM, obesity, hypertension and hypercholesterolemia (12-18).

The need for systematic cross-sectional studies to determine the prevalence of CVD and to identify associated risk factors in specific ethnic groups have become critical for the initiation of meaningful intervention and prevention studies. This became clear when a pilot screening of one Eskimo village in 1992 revealed prevalences of 15% for CHD and 9% for DM (≥ 45 years of age; 15). That study led to a screening, in 1994, of 454 individuals from four villages of three Eskimo ethnic groups which is reported here. Some of the data related to DM have been presented elsewhere (12-18), but the data on CVD have not. The high prevalence of DM in one ethnic group was particularly disconcerting. The 1994 screening of this ethnic group revealed that 44% of the women ≥55 years of age had abnormal glucose tolerance (AGT: DM, 19%, impaired glucose tolerance (IGT), 25%). The concern is for another Pima Indian-type epidemic, where the prevalence of diabetes among Indians over 35 years of age increased from 3.2% in the 1950’s (19; all ages), to 50% in the 1980s (20). DM is an important risk factor for CVD (21). The Pima diabetes epidemic has also led to a rapid rise in CVD (21,22).
The data published so far about Eskimos have, for the first time, begun to reveal hitherto unknown ethnic-specific risk factors associated with DM in this population (23). The findings presented below elucidate further the uniqueness of this population and the important role of DM in the development of CHD in Eskimos.

Alaskan Natives have, until recently, been neglected by medical researchers interested in chronic diseases. One reason for this has been that public health statistics on causes of death had predicted no alarming trends (24-26). Another reason for the neglect has been the perception that their high consumption of ω-3 FAs protects the Eskimos from CHD (27-30). Yet, physicians’ anecdotal reports indicate that stroke, coronary heart disease, diabetes, obesity, hypertension and hypercholesterolemia, rare only a few years ago, are rapidly becoming major health problems among Alaskan Natives. Heart disease currently accounts for 55% of all deaths among ANs (4).

Here, we report a summary of the CVD data collected during our initial 1994 screening of four Eskimo villages comprising three ethnic groups, Inupiat, Central and Siberian Yupik, for a diabetes prevention study, the Alaska Siberia Project (ASP). One purpose was to determine whether health profiles and risk factors varied in these ethnic groups. Just as the Strong Heart Study revealed different causal effects of obesity vs. family history of DM in different American Indian tribes (1,31), the three Eskimo tribes we studied were also found to differ significantly from one another.

### MATERIAL AND METHODS

**Study population and design**

The population for the ASP screening examination in April-May of 1994 included 454 participants aged 25-91 years, living in four villages in the Norton Sound region of Alaska. Of these participants, 240 were women and 214 men (see Table I), residing in one Inupiat, one Central Yupik and two Siberian Yupik villages. The study design, survey methods and laboratory techniques of the Alaska Siberia Project (ASP) were based on the Strong Heart Study (SHS) protocol and have been reported previously (13).

**Recruitment and follow-up**

Every village resident ≥ 25 years of age was invited to participate by the PI (SE), who visited every home in the four villages. Consent forms were explained and signed at this time.

### Table I. The Alaskan-Siberia Project: Study population by village and sex.

| Ethnic Group       | Gender | no. | Mean age (yrs) | SD  | Range  |
|--------------------|--------|-----|----------------|-----|--------|
| Central Yupik      | Women  | 54  | 50             | 17  | 25-88  |
|                    | Men    | 52  | 45             | 13  | 28-81  |
| Inupiaq            | Women  | 59  | 48             | 15  | 25-78  |
|                    | Men    | 50  | 47             | 15  | 25-79  |
| Siberian Yupik     | Women  | 127 | 49             | 16  | 25-88  |
|                    | Men    | 112 | 47             | 15  | 25-91  |
| All                | Women  | 240 | 49             | 16  | 25-88  |
|                    | Men    | 214 | 46             | 15  | 25-91  |
Individual results of the screening were also later returned to each participant and explained by the PI. Figure 1 clearly shows that the older age groups were better represented than the younger and that females were more likely to be screened than the more physically active men, who were busy whale-hunting etc. The examination team only spent one week in each village, which meant that some potential study participants were away from the village that week.

Between 10-25 clinical examinations were carried out between 8 AM and 1 PM each day, with participants going from station to station. The clinical examination and diagnostic criteria were identical to those described for the Strong Heart Study (31). The clinical examination consisted of a personal interview and a physical examination.

Biochemical analysis
The procedure followed that described by Howard et al. (1) in the SHS. Participants reported in the morning, after at least a 12-hour overnight fast. Fasting blood samples were obtained for measurement of lipids and lipoproteins (total cholesterol and triglyceride; low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol, APOE phenotype, insulin, plasma creatinine and glycated hemoglobin (1,32-37). A 75-g oral glucose tolerance test was performed on all participants, except for diabetic persons being treated with insulin, or oral hypoglycemic agents, or participants with a fasting glucose level greater than, or equal to, 225 mg/dl, as determined by an Accu-Check II (Baxter Healthcare Corporation, Grand Prairie, Texas). A morning urine specimen was obtained from each participant. Micro-albuminuria was defined as a ratio of urinary albumin (mg/ml) to creatinine (g·ml⁻¹) of 30-299 mg·g⁻¹, and macro-albuminuria as a ratio greater than 300 mg·g⁻¹(37). The chemistry analyses were carried out at the Medlantic Research Institute, Washington D.C., where the Strong Heart Study chemistries are also done.

Anthropometrics
Anthropometric measurements were collected as in the Strong Heart Study (31) and have
been published (16,17). These measurements included weight, height, waist and hip circumferences and 4 skin-fold measurements. Percentage of body fat was estimated with an RJL impedance meter (model B14101; RJL bioelectrical Equipment Company, Detroit, Michigan), using an equation based on total body water (M. Singer, RJL Equipment Company). Overweight was defined as a body mass index (BMI) (weight in kg/height in m$^2$) greater than 27.0, and obesity as a BMI greater than 31.1 for men and greater than 32.3 for women (16).

**Blood pressure**

Blood pressure measurements used for the analysis were the means of the last two of three measurements after being seated for 5 minutes. Persons were considered hypertensive if they had a systolic blood pressure greater than 140 mm Hg, or a diastolic blood pressure greater than 90 mm Hg, or if they were currently taking anti-hypertensive medication (38).

**Interview questions**

Interview questions provided demographic information, family health history, lifestyle and medical history. The Rose questionnaire provided an assessment of angina pectoris (39). Percentage of Eskimo heritage was computed from the reported degree of Eskimo heritage (to the nearest quarter) for each parent and grandparent. DM and hypertension therapy were assessed by personal interview, with individuals having been asked to bring all medications to the examination site.

**Definition of cardiovascular disease**

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 (G.E. and W.D.). Abnormal, and a small number of normal, ECGs were coded at the Minnesota electrocardiogram center (40).

Criteria used to define prevalent disease are summarized in table II. Definite myocardial infarction (MI) was determined by Minnesota-Coded electrocardiogram, or by a history of definite MI verified by chart review and confirmed by ASP cardiologists (GE, WDG). Possible MI included electrocardiographic results with a broader range of Minnesota Codes, or a history of possible MI verified by chart review and confirmed by an ASP cardiologist (MS). 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 (40).

**Definition of glucose intolerance**

Diagnostic criteria for DM and impaired glucose tolerance (IGT) were those of the World Health Organization (41). These included Known Diabetes, if the participant: a) was known to have diabetes by the Alaska Native Medical Center, Indian Health Service, b) was taking insulin, c) was using a hypoglycemic agent and had two prior recorded measurements of elevated blood glucose (> 250 mg/dl),
d) was treated by renal dialysis, or had kidney transplantation and a history of diabetes by questionnaire, e) had a fasting blood glucose > 140 mg/dl, repeated for clinical confirmation; New Diabetes if the participant had a fasting blood glucose > 140 mg/dl, or a 2-h blood glucose > 200 mg/dl and no mention of diabetes history in the questionnaire; Impaired Glucose Tolerance (IGT) if the participant had a fasting blood glucose > 140 mg/dl and a 2-h blood glucose between 140 mg/dl and 199 mg/dl; Previous Impaired Glucose Tolerance if the participant had previously met the criteria for impaired glucose tolerance (above) according to records of the Alaska Native Medical Center, Indian Health Service, but now glucose met the criteria for either normal, or again impaired; Normal Glucose Tolerance (NGT) if the participant had a fasting blood glucose and 2-h blood glucose < 140 mg/dl and no history of diabetes by questionnaire; Diabetic Status Undetermined if (a) the participant was on renal dialysis, or had a kidney transplant without mention of diabetes in the medical history by questionnaire, (b) results of OGTT were missing, (c) the participant refused OGTT, (d) the fasting blood specimen was not sufficient to determine the participant's diabetic status.

**Statistics**

Statistical analyses were identical to those in the SHS (1,31). Prevalence per 100 was computed for various measures of CHD by sex, ethnic group and diabetes status. Due to the high rates of impaired glucose tolerance (IGT) and DM among ANs, the prevalences of the various indices of CHD were computed separately for persons with and without abnormal glucose tolerance (AGT = IGT + DM). This was done because AGT is associated with altered rates of CHD in virtually all populations studied (1).

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**Table II. Diagnostic criteria for coronary heart disease.**

| Criterion | Definition |
|-----------|------------|
| Definite myocardial infarction | Minnesota Codes 1.1 and 1.2, except 1.26 and no Code 7.1, or 7.4; or verified history of definite myocardial infarction |
| Possible myocardial infarction | Minnesota Codes 1.3, 126, and 1.28 and no Code 7.1, or 7.4; or verified history of possible myocardial infarction |
| Definite coronary heart disease | Definite myocardial infarction; or history of coronary artery bypass graft, angiogram showing occlusion, percutaneous transluminal coronary angioplasty, or thrombolytic therapy; or angina pectoris by Rose questionnaire if accompanied by Minnesota Code 4.1, or 5.1, or a verified history of possible myocardial infarction |
| Possible coronary heart disease | Minnesota Codes 1.3, 1.26, 1.28, 4.1, 4.2, 5.2, 7.1, and 7.4; or angina pectoris by Rose questionnaire; or history of myocardial infarction by interview |
The statistical significance of ethnic-specific differences was evaluated by analysis of variance. The prevalence ratios and 95 percent confidence intervals were computed to evaluate the relative differences in rates between normo-glycemic (NGT) and AGT participants, or between men and women. Univariate assessment of associations of risk factors and CHD was performed by computing prevalence ratios and 95 percent confidence intervals for variables stratified either by tertiles, or by specific diagnostic criteria. In the former case, prevalence ratios compared persons in the first and third tertiles. Multiple logistic regression was used for computing standardized regression coefficients. A forward step-wise procedure was employed to explore which variables entered the model for all CHD, using \( p = 0.05 \) as the cutoff point for inclusion. All of these variables, plus sex and ethnic group, were then used in a final model for all and definite CHD, and for the examination of all CHD by ethnic group.

**Referrals**

The preliminary individual results of the screening were provided to each participant in the form of a letter, that was explained personally by the PI. Copies of the letters were provided to the village staff physician, in addition to referrals generated at the time of screening related to abnormal ECGs, blood pressure etc. Since many had not had a physical examination, or seen a physician, for a long time, an unexpected large number of abnormal findings were made and reported, not only to the participants and their health-care providers, but also to the Board of the Norton Sound Health Corporation, which initiated a Diabetes Prevention Program to improve the monitoring and education of the population. The new abnormal data included those with newly diagnosed diabetes and IGT, new hypertensive subjects (20%), participants with total cholesterol levels \( \geq 240 \text{ mg/dl} \) (36%; 18% had \( \geq 265 \) and 6% had \( \geq 300 \text{ mg/dl} \)). 37% were overweight (BMI \( \geq 27 \)) and 56% were current smokers.

**RESULTS**

The number of participants and their mean ages are presented by ethnic group and sex in Table I. The women were, on average, slightly older than the men (49 vs 46) and more women than men participated in the screening (Fig 1). Among those \( \geq 45 \) years of age, 76% of the women and 56% of the men participated. The prevalence of CHD is shown in Fig. 2.

![Figure 2. CHD prevalence (n = 452); Strong Heart Study definitions.](image)

CHD risk factors differed in the three ethnic groups, although not often significantly because of the small number (Tables III, IV). Prevalences for CHD, using the two Strong Heart Study definitions of CHD from table II, are shown in table III. The population
### Table III. Prevalences (per 100) for indices for cardiovascular disease, by gender, ethnic group and diabetes status, in the Alaska Study.

|                      | Prevalence Ratio | Abnormal Glucose Tolerance | Abnormal (IGT + DM) : Normal (NGT) |
|----------------------|------------------|-----------------------------|-----------------------------------|
|                      | Normal Glucose   | Abnormal Glucose Tolerance  |                                   |
|                      | Women            | Men                         | Women                             |
|                      | n %              | n %                         | n %                               |
| **Definite CHD**     |                  |                             |                                   |
| Central Yupik        | 0 0.00           | 2 4.65                      | 0 0.00                            |
| Inupiaq              | 1 2.13           | 3 8.33                      | 1 25.00                           |
| Siberian Yupik       | 3 3.80           | 5 6.17                      | 6 27.00                           |
| All                  | 4 2.48           | 10 6.25                     | 7 21.00                           |
|                      | 8.5 3.2 - 23.1   | 4.3 1.5 - 11.9              |                                   |
| p (ethnic group)     | 0.477 0.796      | 0.301 0.455                 |                                   |
| **Possible CHD**     |                  |                             |                                   |
| Central Yupik        | 4 10.26          | 1 2.38                      | 5 41.67                           |
| Inupiaq              | 1 2.13           | 4 10.81                     | 3 50.00                           |
| Siberian Yupik       | 5 8.17           | 8 9.52                      | 3 50.00                           |
| All                  | 10 5.99          | 13 7.98                     | 11 29.73                          |
|                      | 5.0 2.4 - 10.3   | 2.7 0.8 - 8.5               |                                   |
| p (ethnic group)     | 0.285 0.291      | 0.162 0.588                 |                                   |
| **Stroke**           |                  |                             |                                   |
| Central Yupik        | 2 5.41           | 4 8.89                      | 1 12.50                           |
| Inupiaq              | 4 8.00           | 6 15.38                     | 0 0.00                            |
| Siberian Yupik       | 13 14.61         | 12 13.64                    | 5 23.81                           |
| All                  | 19 10.80         | 22 12.79                    | 6 18.75                           |
|                      | 1.7 0.7 - 4.1    | 0.6 0.1 - 4.2               |                                   |
| p (ethnic group)     | 0.239 0.636      | 0.635 0.580                 |                                   |
| **Rose Ang Pect**    |                  |                             |                                   |
| Central Yupik        | 1 2.44           | 0 0.00                      | 0 0.00                            |
| Inupiaq              | 1 1.92           | 2 4.35                      | 1 14.29                           |
| Siberian Yupik       | 3 3.09           | 2 1.98                      | 1 3.33                            |
| All                  | 5 2.63           | 4 2.05                      | 2 4.00                            |
|                      | 1.5 0.3 - 7.6    | 2.6 0.3 - 20.8              |                                   |
| p (ethnic group)     | 0.510 0.330      | 0.286 0.691                 |                                   |
| **Rose Int Claud**   |                  |                             |                                   |
| Central Yupik        | 0 0.00           | 0 0.00                      | 0 0.00                            |
| Inupiaq              | 2 3.85           | 1 2.17                      | 1 14.29                           |
| Siberian Yupik       | 1 1.03           | 0 0.00                      | 0 0.00                            |
| All                  | 3 1.58           | 1 0.51                      | 2 2.00                            |
|                      | 1.3 0.1 - 11.9   | 20.5 3.8 - 109.6            |                                   |
| p (ethnic group)     | 0.277 0.196      | 0.044 0.444                 |                                   |
Table IV. Prevalences (per 100) for indices for coronary heart disease (“definite” plus “possible”), according to physiologic variables in the Alaska Study.

| Table IV continues to next page |
|---------------------------------|

has been stratified by diabetes and by gender. Due to the small numbers, IGT and DM were combined as AGT for the statistical treatment. Overall, 6% of the participants over 55 years of age, and 26% of those ≥ 55 years of age, showed evidence of CHD by ECG, or in patient records (Strong Heart Study definitions of “definite” plus “possible” CHD). The prevalence of “definite CHD” in women with AGT was 21.0%, compared to 2.4% in those with NGT. Men had comparable values of 26.7% and 6.3%. Comparable values for “possible” CHD were...
29.7% vs 6.0% for women, and 21.4% vs 8.0% for men. Evidence of previous stroke was found in 10.8% of the normoglycemic women and in 12.8% of the normoglycemic men, and in 18.8% of the women and 8.33% of the men with abnormal glucose tolerance. Prevalences of heart disease were lowest among Central Yupiks and similar among Siberian Yupiks and Inupiats, but the differences were not statistically significant.
Table V. Prevalences (per 100) for indices for coronary heart disease (“definite” plus “possible”), according to plasma lipoprotein levels and ethnicity in the Alaska Study.

| Village and variable | Women |         |         |         | Men |         |         |         |
|----------------------|-------|---------|---------|---------|-----|---------|---------|---------|
|                      | Prev  | Prev Ratio | 95 % CI | p      | Prev  | Prev Ratio | 95 % CI | p       |
| Central Yupik        |       |          |         |        |      |         |         |         |
| Total cholesterol (mg/dl) |     |          |         |        |      |         |         |         |
| < 200                | 20.00 | 0.00     | 0.00    | 0.00   | 14.29| 0.099   |         |         |
| > 240                | 15.79 | 0.8      | 0.2-4.1 | 0.775  |      |         |         |         |
| LDL chol (mg/dl)     |       |          |         |        |      |         |         |         |
| < 130                | 20.00 | 0.00     | 0.00    |        |      |         |         |         |
| > 160                | 12.50 | 0.6      | 0.1-3.3 | 0.570  | 8.38 | 0.169   |         |         |
| HDL chol (mg/dl)     |       |          |         |        |      |         |         |         |
| > 50                 | 19.57 | 0.488    | 10.26   | 0.501  |      |         |         |         |
| < 35 (women)         | 0.00  |          | 0.00    |        |      |         |         |         |
| < 45 (men)           | 0.00  |          | 0.00    |        |      |         |         |         |
| Triglycerides (mg/dl)|       |          |         |        |      |         |         |         |
| < 125, dm+igt; < 100, ngt | 19.18 | 9.52    |         |        |      |         |         |         |
| >250, dm + igt; >200, ngt | 0.00  | 0.417   | 0.00    | 0.746  |      |         |         |         |
| % of Eskimo Heritage | 100   | 16.28    | 0.451   | 7.50   | 0.570|         |         |         |
| < 75                 | 33.33 | 0.00     |         |        |      |         |         |         |
| Inupiaq              |       |          |         |        |      |         |         |         |
| Total cholesterol (mg/dl) |     |          |         |        |      |         |         |         |
| < 200                | 11.11 | 1.1      | 0.1-10.0| 0.910  |      | 0.262   |         |         |
| > 240                | 12.50 |          |         |        | 20.83|         |         |         |
| LDL chol (mg/dl)     |       |          |         |        |      |         |         |         |
| < 130                | 14.29 | 0.8      | 0.1-6.2 | 0.811  |      | 0.430   |         |         |
| > 160                | 11.11 |          |         |        | 24.14|         |         |         |
| HDL chol (mg/dl)     |       |          |         |        |      |         |         |         |
| > 50                 | 10.71 | 0.401    | 30.77   | 6.5    | 1.1-39.5| 0.037  |         |         |
| < 35 (women)         | 0.00  |          |         |        |      |         |         |         |
| < 45 (men)           | 4.76  |          |         |        |      |         |         |         |
| Triglycerides (mg/dl)|       |          |         |        |      |         |         |         |
| < 125, dm+igt; <100, ngt | 10.26 | 25.00  |         |        |      |         |         |         |
| > 250, dm + igt; >200, ngt | 0.00  | 0.634   | 0.00    | 0.419  |      |         |         |         |
| % of Eskimo heritage | 100   | 8.33     | 0.548   | 20.00  | 0.482|         |         |         |
| < 75                 | 0.00  |          |         |        |      |         |         |         |
| Siberian Yupik       |       |          |         |        |      |         |         |         |
| Total cholesterol (mg/dl) |     |          |         |        |      |         |         |         |
| < 200                | 8.82  | 3.2      | 1.0-9.8 | 0.042  | 12.50| 0.522   |         |         |
| > 240                | 28.13 |          |         |        | 18.52|         |         |         |
| LDL chol (mg/dl)     |       |          |         |        |      |         |         |         |
| < 130                | 5.88  | 3.8      | 1.0-14.5| 0.051  | 14.81| 0.567   |         |         |
| > 160                | 22.22 |          |         |        | 20.00|         |         |         |
| HDL chol (mg/dl)     |       |          |         |        |      |         |         |         |
| > 50                 | 13.68 | 0.430    | 19.61   | 1.3    | 0.5-3.3| 0.646  |         |         |
| < 35 (women)         | 0.00  |          |         |        |      |         |         |         |
| < 45 (men)           | 15.63 |          |         |        |      |         |         |         |
| Triglycerides (mg/dl)|       |          |         |        |      |         |         |         |
| < 125, dm+igt; < 100, ngt | 13.40 | 15.87  |         |        |      |         |         |         |
| > 250, dm + igt; >200, ngt | 33.33 | 3.0   | 2.0     | 0.3-12.2| 0.460|         |         |         |
| % of Eskimo heritage | 100   | 15.46    | 0.934   | 19.10  | 0.334|         |         |         |
| < 75                 | 14.29 | 0.00     |         |        |      |         |         |         |

Prevalence ratio: higher:lower values
| Ethnic group and variable | Abnormal Glucose Tolerance | Normal Glucose Tolerance |
|---------------------------|---------------------------|-------------------------|
|                           | Prevalence | Ratio | 95% Cl | p   | Prevalence | Ratio | 95% Cl | p   |
| **Central Yupik**         |            |       |        |     |            |       |        |     |
| Albuminuria               | Absent     | 30.77 | 7.69   | 0.337 | Present    | 20.00 | 2.6   | 0.915 |
|                          | Present    | 20.00 | 2.6   | 0.915 |
| Insulin                   | Lowest tertile | 33.33 | 1.000 | 0.000 | Highest tertile | 60.00 | 1.8   | 0.376 |
|                          |              | 3.85 | 0.4   | 0.480 |
| HbA1c                     | Lowest tertile | 50.00 | 1.000 | 0.045 | Highest tertile | 50.00 | 1.000 | 0.045 |
|                          |              | 1.000 | 0.045 |
| **Inupiaq**               | Absent     | 50.00 | 9.41   | 0.891 | Present    | 0.00  | 0.838 | 0.179 |
|                          | Present    | 0.00  | 0.838 | 0.179 |
| Insulin                   | Lowest tertile | 33.33 | 1.000 | 0.000 | Highest tertile | 33.33 | 1.000 | 0.000 |
|                          |              | 5.26  | 0.26  | 0.533 |
| HbA1c                     | Lowest tertile | 50.00 | 1.000 | 0.045 | Highest tertile | 50.00 | 1.000 | 0.045 |
|                          |              | 13.79 | 0.045 |
| **Siberian Yupik**        | Absent     | 36.36 | 12.43  | 0.000 | Present    | 100.00 | 2.8   | 0.452 |
|                          | Present    | 100.00 | 2.8   | 0.452 |
| Insulin                   | Lowest tertile | 20.00 | 0.74  | 0.000 | Highest tertile | 60.00 | 3.0   | 0.291 |
|                          |              | 13.73 | 1.9   | 0.291 |
| HbA1c                     | Lowest tertile | 40.00 | 0.6   | 0.000 | Highest tertile | 22.22 | 0.6   | 0.000 |
|                          |              | 22.00 | 4.5   | 0.000 |

Albuminuria absent: < 30 or =30; present: > 300, dm + igt, > 30, ngt.

Relationships between risk factors and CHD prevalence in the three ethnic groups were first evaluated by univariate comparisons of the rate of CHD within strata of the potential risk factors (Tables IV and V). These comparisons were made within each ethnic group, for each sex. The combination of “definite” and “possible” CHD (All CHD) are shown. Since the mean ages of the men and women were very similar in all ethnic groups (Table II), the data were not age-adjusted; thus, actual rates by the various risk factor strata are shown.

Obesity (Table IV), as evaluated by Second National Health and Nutrition Examination Survey (NHANES II) criteria for body mass index (BMI), or by
first and third tertials of body fat, appeared to be a significant correlate of CHD among Central Yupik men only, although the prevalence of obesity and measures of body fat in those with CHD were higher for men and women in all ethnic groups. Waist:hip ratios also showed a similar relationship to CHD, but was only statistically significant in Siberian Yupik women. The prevalence of overweight was higher in women and varied significantly between villages (Figs. 3 and 4).

Hypertension (Table IV) was associated with CHD in men and women of all ethnic groups, but reached statistical significance only among Central Yupik women, and Siberian Yupik men and women. The prevalence of hypertension was higher in women than men, a difference that increased with age (Fig. 5) and BMI (Fig. 6).

Plasma lipids (Table V) showed no significant associations with CHD, except for total cholesterol in Siberian Yupik women (p = 0.042) and HDL in Inupiaq men (p = 0.037). There was a significant ethnic difference in allele frequency of Apo E4 (Fig. 7), although there was no significant association with CHD.

The smoking prevalence was exceptionally high among individuals aged 25-54, but was
not significantly associated with CHD (Fig. 8; Tables IV and VII), probably because most of the CHD in this population was identified in those over 54 years of age (Fig. 2).

The relationships between CHD prevalence and albuminuria, insulin and hemoglobin A1c concentrations are shown in Table VI. There were no associations between CHD and albuminuria. Concentrations of hemoglobin A1c were significantly associated with CHD in Inupiat and Siberian Yupik normoglycemics.

The percentage of Eskimo heritage (Table V) was not statistically related to CHD in any of the ethnic groups.

Logistic regression analysis (Table VII) was used to test the independence of the association of various risk factors with indices of CHD. Forward step-wise regression was first performed, using “definite” plus “possible” CHD as the dependent variable. The final model indicates that age, AGT and insulin were independently related to the prevalence of CHD. There was no significant difference in the prevalence of CHD between ethnic groups. Other variables did not reach statistical significance, because of the relatively small actual number of participants with CHD.

![Figure 7. Percentages of apoE alleles in 4 Eskimo villages.](image)

![Figure 8. Smoking prevalence.](image)

**Table VII.** Logistic regression coefficients and prevalence ratios for indices of coronary heart disease in Alaskan Indians in the Alaskan Study: results from step-wise logistic regression.

|                      | All coronary heart disease | Definite coronary heart disease |
|----------------------|----------------------------|---------------------------------|
|                      | Coeff  | SE      | p       | Prev OR | Coeff  | SE      | p       | Prev OR |
| Age (years) - (prev OR: 67 vs 32, mean of 3rd vs 1st tertiles) | 0.0531 | 0.0113  | 0.0001  | 8.414   | 0.0501 | 0.0168  | 0.0029  | 5.775   |
| Diabetes mellitus (dm + igt = 1, ngt = 0)                   | 0.9322 | 0.3617  | 0.0100  | 2.540   | 1.0334 | 0.5146  | 0.0446  | 2.811   |
| Smoking (cur smoker = 1, ex + nev smoker = 0)                | -0.7534| 0.3443  | 0.0286  | 0.471   | -1.1542| 0.5592  | 0.0890  | 0.315   |
| Insulin (prev OR 12 vs, mean of 3rd vs 1st tertiles)        | 0.0338 | 0.0349  | 0.3397  | 1.849   | 0.0926 | 0.0460  | 0.0441  | 2.301   |

*Other variables in the model, but not reaching the significance level: sex, % of body fat, hypertension, HDL cholesterol, % micro-ethnic group, % of Eskimo heritage, triglycerides, LDL cholesterol, waist to hip ratio and glycated hemoglobin.
DISCUSSION

This study shows that, contrary to common belief, there is a high prevalence of cardiovascular disease (CVD) in Alaskan Eskimos (Figure 2). The belief that Eskimos have a low prevalence of CHD is based on observations suggesting that a high consumption of ω-3 fatty acids (FAs) protects against CHD (27, 28). There is also the local belief that the high HDL/LDL ratio in this population affords a sense of non-urgency. Yet, the high prevalence of CHD shown here, added to the known death rates from CHD and stroke, warrants a careful examination of the available prevalence data and risk factors.

First, the mortality and morbidity data. Clinical evidence suggests an almost total absence of cardiovascular disease among ANs before 1950 (42), but this may partially reflect their relatively short life-span. During the period 1955-65, the heart disease mortality rate (not counting acute rheumatic fever) of ANs aged 40 years and older was approximately 50% lower than the corresponding rates in the US (3). The mortality rate for Eskimos aged 40-64 was significantly lower than those of other AN ethnic groups. While the heart disease mortality rate of US Whites decreased by 32% during the period 1979-1998, there was no significant change in the overall heart disease mortality rate of ANs (4). During the period 1994-1998, ANs in the age groups 25-44 and 45-54 had 30% and 40% higher mortality rates, respectively, than US Whites, while those in the 75+ age group had 20% lower mortality rate from heart disease (4). When one adds that the death rate for cerebrovascular disease among ANs was about 1.5 times that of the US White rate during the period 1994-1998 (4), it becomes clear that the overall mortality rate for CVD among ANs is greater than in the US White population. The time has come to intervene both by studies to identify and characterize risk factors, and through the development of intervention and prevention programs.

The published mortality rates of Eskimos in Canada and Greenland are somewhat more difficult to interpret, because of how the data were collected and interpreted (43). In Greenland, some early reports (1975) indicated that CHD was rare (27) and that “coronary atherosclerosis is almost unknown among Greenlandic Eskimos when living in their own cultural environment” (27). Others, at the same time, reported that coronary heart death rates in Greenlandic Eskimos were higher than in Denmark (44). Bjerregaard and coworkers concluded that the early evidence for negligible CHD among the Greenlandic Eskimos is weak and that recent mortality rates for ischemic heart disease is now slightly greater than in the Danish population (ratio 1.09:43). The death rate for cerebrovascular disease is now 2.69 times greater than in the Danish population (43).

In Canada, the heart disease mortality rate of the Inuits is not statistically different from the all-Canadian rate (43). However, there appears to be some statistical evidence for a lower rate of ischemic heart disease and a higher rate for stroke in the Inuit population compared to the all-Canadian death rates.

The overall CHD prevalence in the Strong Heart Study of 21% (1; “definite” plus “possible” CHD) among American Indians, aged 45-74, was approximately the same as that reported here for Alaskan Eskimos in the same age group (19%). The data in both studies
were collected during approximately the same period (SHS: 1989-1992; ASP: 1994).

In summary, the overall mortality rates for CVD in Alaskan, Canadian and Greenlandic Eskimos are increasing and are now greater in some regions than in the white populations. Figure 2 shows the increasing prevalence of CHD with age observed in the present study.

**The ω-3 fatty acid hypothesis**

It is well documented that CHD and DM were rare in Eskimos only 30 years ago (45, 46). From those data, and from dietary fat studies in Greenland, emerged the now universally accepted hypothesis that the consumption of ω-3 FA (from fish oils) protects against CHD (27, 28). The ω-3 hypothesis started with the casual observation by Bang and Dyerberg (27) that ischemic heart disease in Greenlandic Eskimos appeared to be rare (no screenings were done) and that Eskimos consumed larger quantities of ω-3 FAs than Danes. Although the hypothesis has not been tested as originally envisioned, there is compelling evidence that the consumption of ω-3 FAs is beneficial for the reduction of arrhythmia and adverse cardiac events (47). In the GISSI Prevention study (47), supplements of 0.85 g of marine ω-3 FA (eicosapentaenoic and docosahexaenoic acids, EPA and DHA) resulted in a 15% decrease in major adverse cardiac events, a 20% decrease in overall mortality and a 45% reduction in sudden death. All reductions were statistically significant. Thus, a relatively small amount of marine ω-3 FA, which is easily consumed in the traditional Eskimo diet, proved to be cardio-protective in CHD patients with, or without, DM. One would therefore expect that Eskimos in the Norton Sound Region would be similarly protected, but that appears not to be the case. The question now is: does a high consumption of ω-3 FAs protect against atherosclerosis as the original hypothesis states? ω-3 FAs are known to reduce some risk factors but not others (48). A preliminary analysis of plasma fatty acid profiles of the participants in this study revealed that Eskimos with CHD had the same consumption and plasma levels of ω-3 FAs as non-CHD participants (48). This preliminary analysis, coupled with the high prevalence of CHD shown here, suggests that a high consumption of ω-3 FAs does not necessarily protect against CVD if other risk factors are present.

**Diabetes**

Logistic regression analysis (Table VII) revealed that CHD was significantly and independently associated with age, AGT (DM+IGT) and plasma concentrations of fasting insulin. Glucose intolerance in Eskimos is, in turn, associated with age (p = 0.0001) family history of DM (p = 0.0009), obesity (p = 0.03) (13), low plasma concentrations of ω-3 FAs (23) and high plasma levels of palmitic acid (23).

Diabetes is known to be a major risk factor for CVD (1, 21) and is shown here to be very strongly associated with both “definite” and “possible” CHD in Eskimos, as is the case for American Indians (1). For both men and women, individuals with AGT (DM+IGT) had higher prevalences of “definite” and possible” CHD (Tables III, VIII). As for American Indians (1), gender differences were more pronounced among the normoglycemics than among those with AGT. The higher prevalence associated with AGT was more pronounced in women than in men. This has been observed in some (51, 52), but not all (53), studies of whites. Differences in CHD preva-
ience between the three ethnic groups was not statistically significant, as in the cases of IGT, DM and obesity (13, 16, 17). This cannot be explained at this time. Environmental and genetic differences may, some day, account for the differences.

Diabetes is an important risk factor for stroke and CHD (50). Considering that DM has increased from being rare among the Norton Sound Eskimos in 1970 (11,54), to reach frequencies of 8.8% females and 4.2% males (25-91 years of age) in 1992-4 (12, 13), DM has now become a serious health problem in this population. This is especially true for women, when one considers that the prevalence of DM among the latter was approximately twice that observed among in men, e.g., of the Siberian Yupik women ≥ 55 years of age, 44% had abnormal glucose tolerance (DM, 19% + IGT, 25%). The relatively high IGT prevalence and earlier assessment (12) support the conclusion that DM is rapidly increasing in this population.

We also know from the work of Schraer et al. (50) that the incidence of confirmed myocardial infarction (MI) per person year of DM was significant. The incidence of confirmed stroke per person year of DM in Alaska Natives was significantly higher than in American Indians and than the incidence of MI per person year of DM (50). The prevalence of stroke victims among our female participants with AGT was almost twice that of those with NGT (18.8% vs 10.8%).

Lipotoxicity and DM
The possibility that certain specific fats can facilitate the development of DM has emerged recently. The suggestion comes from four studies: 1) our findings of elevated palmitic acid plasma levels in participants with IGT and previously undiagnosed DM (23); 2) our intervention study aimed at decreasing the consumption of palmitic acid, in which only 1 out of 44 participants with IGT developed DM during the 4-year intervention (55); 3) the 60% with improved glucose tolerance, who had significantly lower plasma palmitic acid levels (P = 0.02) after the intervention than those that did not improve; and 4) from experiments in which adult rat pancreatic islets were cultured on plates (56). In the latter experiment, a clear lipotoxic effect of palmitic acid was observed, which involved an increased apoptosis rate coupled with a reduced proliferation capacity of β-cells and an impaired insulin secretion. The deleterious effect of palmitate on β-cell turnover is mediated via the formation of ceramide and the activation of the apoptotic mitochondrial pathway.

Considering that an fatty acid imbalance in the diet appears to contribute to DM among Eskimos, and hence to stroke and CHD, the focus on future characterizations of risk factors and intervention will be to determine the roles of specific FAs in either the development, or the prevention of these diseases among Eskimos. The extent to which FA imbalance in this context is ethnic-specific or universal, requires further studies.

Fasting insulin
Fasting plasma insulin concentrations were significantly and independently associated with definite CHD in this cross-sectional study, but this is not unique to this population, and is comparable to the observations of Liu et al. (57), who compared ECG abnormalities to plasma insulin concentrations in Pima Indians. Howard et al. (1) found an association between
plasma insulin levels and “all CHD”. Fasting concentrations of serum insulin are directly correlated with the risk of atherosclerosis, peripheral vascular disease, hypertension, dyslipidemia and central obesity in several populations (58-60). Insulin may be a central link among these degenerative conditions, but it is unclear if it is causal.

**Obesity**

Obesity is an important risk factor for DM and CVD in all studies, including those of Eskimos (1, 13, 61). In this study, obesity among Central Yupik men, was significantly associated with CHD ($P = 0.02$; Table IV) and, among Siberian Yupik women, the waist/hip ratio was significantly associated with CHD ($P = 0.005$; Table IV). There is a consistent trend for all measures of obesity to be associated with CHD, but the small numbers probably prevent the attainment of significance. Without reference to CHD, the data in this study (16,17) revealed that both Eskimo men and women were proportionally more overweight, or severely overweight, than U.S. citizens of all races, but still less so than the dramatic proportion documented among Native Americans from other States. Upper body obesity for Alaskan Eskimo men (1.01 versus 0.91, $p < 0.01$) and, especially, women (0.92 versus 0.79, $p < 0.01$), as measured by WHR, was significantly higher than in the U.S. (all races). Concomitantly, Alaskan Eskimos had less subcutaneous fat. Upper and central body fat is associated with high risks of hypertension, heart disease and diabetes in other populations. This is especially true of central non-subcutaneous fat and visceral abdominal fat. Alaskan Eskimos exhibit alarming body fat patterns that clearly reflect a high risk of IGT, DM and CHD.

**Hypertension and CVD**

Although Alaskan Eskimos traditionally have relatively low blood pressures (15), hypertension in Eskimos is a growing concern, because of its impact on stroke and CVD. Decreased physical activity and increased obesity appear to be the most important new risk factors for Alaskan Eskimos. Our cross-sectional studies show that the prevalence of hypertension (SBP $\geq 140$, or DBP $\geq 90$) was 34% in the sample $\geq 55$ years (Fig. 5). Females had a significantly higher prevalence than males. Both DBP and SBP were associated with body weight (see Fig. 6). Prevalence varied between ethnic groups and was significantly higher among Central Siberian Yupik women and Siberian Yupik men with CHD, than in those without. The Strong Heart Study also found that hypertension was significantly associated with CHD in persons with and without DM (1). In that study, step-wise logistic regression analysis showed significant associations of hypertension with age, ethnic group, current smoking, DM and triglycerides.

**Plasma lipids**

Eskimos in this study had significantly higher levels of total, LDL and HDL cholesterol than American Indians and other US races. The important relationship between cholesterol and CHD is well established (48), but not in Eskimos. Plasma lipids (Table V) showed no significant associations with CHD, except for total cholesterol in Siberian Yupik women ($P = 0.042$) and HDL in Inupiaq men ($P = 0.037$). There was a significant ethnic difference in allele frequency of Apo E4 (Fig. 7), but there was no association with CHD.

The lack of significance may reflect the small numbers in this study. The high LDL
levels no doubt partially reflect the high allele frequency of APOE 4 in one of the villages (Fig. 7). The question remains as to whether the notoriously high LDL levels in Eskimos (14,48) are protected by the high HDL levels. Lipid measurements, especially total cholesterol and HDL cholesterol, are usually important predictors of CVD (62), but the unique fat diet of this population, including the consumption of large quantities of ω-3 FAs, may change the dynamics of fat metabolism and make cholesterol measures less predictive. While somewhat more controversial, triglyceride concentrations, especially in relationship to HDL cholesterol, comprise an important factor in assessing the risk of CHD in a population/individual. Both HDL and triglyceride levels have been associated with ω-3 FA consumption (49,63). High consumption of ω-3 FAs may improve these variables and other risk factors for CVD (49,63).

Unfortunately, HDL subclasses have not been studied in Alaskan Eskimos, although it is well known that the HDL levels in the latter are significantly higher than those found in other ethnic groups (14). The questions to be answered are: which subclass is elevated and which is protective in this population? The HDL fraction is heterogeneous, composed of particles of differing density and apolipoprotein content. We have previously found high levels of HDL in Eskimos, especially in women (14). It is important to determine whether one subfraction predominates. In general, CHD risk is inversely proportional to HDL concentration (64), and lower HDL3 levels are stronger predictors of CHD than HDL2 (65,66).

**Albuminuria**
Albuminuria was more frequently found in association with CHD in normoglycemic Central Yupik and Inupiat males and in glucose intolerant (DM+IGT) Siberian Yupic Eskimos, but the numbers did not reach statistical significance. Albuminuria was, however, found in 100% of Siberian Yupiks with CHD. This is the first report of such associations in Eskimos. An increased concentration of albumin in the urine of diabetic individuals is a strong and independent predictor of all-cause and coronary heart disease mortality (67).

**Smoking**
Smoking is a universal risk factor for CVD and, as in the American Indian population (1), the rates are significantly higher than other US rates. In our study, 56% of the participants are current smokers. Of particular concern is the high rate among the young (Fig. 8). As for the American Indians, more Eskimo men than women smoke. The statistical analysis of our data on smoking suggests an inverse association with CHD. That finding should not be interpreted as smoking being protective, but rather a statistical fluke that can be explained by the fact that mostly the aged, with the low prevalence of smoking (Fig. 8), have CHD (Fig. 2).

**Conclusion**
In the broader context, it appears that the increase in CVD, DM and associated risk factors are related to acculturation and, possibly, to the increase of the mean age of the population. It is clear that we only have a partial understanding of what the risk factors
are and how to prevent the aggravation of those risk factors. Paradoxically, the main reason for the recent increase in DM, CVD, obesity and hypertension in Alaska Natives appears related to the improving economy over the past 25 years. With Alaskan statehood came considerable wealth, including cash for store-bought foods, four-wheelers, snow machines and television. This has resulted in the uninformed purchase of western foods in stores and, for many, the development of a sedentary lifestyle. Where daily life was once a struggle with extensive energy expenditures, the activities of daily living have now become more sedentary in nature. The women have been particularly affected, as their energy expenditure has been greatly reduced, and their prevalences of DM and obesity are twice those of the males studied (12,13).

Most Alaskan Natives live in very isolated villages, only recently reachable by airplane. Each of the 250 villages has, over thousands of years, developed a unique genetic homogeneity, lifestyle and food sources. For example, one tribe in our sample depends to a great extent on whale meat and fat, while the other villages have no access to such food. Such variability may explain tribal differences in both the prevalences of disease and their risk factors.

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REFERENCES

1. Howard BV, Lee ET, Cowan LD, et al. Coronary heart disease prevalence and its relation to risk factors in American Indians. The Strong Heart Study. Am J Epidemiol 1995; 142:254-68.
2. Shields GF, Schmiechen AM, Frazier BL, et al. Mitochondrial DNA sequences suggest a recent evolutionary divergence for Beringian and Northern North American populations. Amer J Hum Genet 1993; 53:549-562.
3. Maynard JE, Harnes LM, Kester FE. Mortality due to heart disease among Alaskan Natives 1955-65. Public Health Reports 1967; 82:714-20.
4. Lanier AP, Ehrsam G, Sandidge J. Alaska Native Mortality 1989-1999. Office of Alaska Native Health Research, Division of Community Health Services, Alaska Native Tribal Health Consortium, July, 2002.
5. Davidson M, Bulkow LR, Gellin BG. Cardiac mortality in Alaska's indigenous and non-native residents. Int J Epidemiology 1993; 22:62-71.
6. Middaugh JP. Cardiovascular deaths among Alaskan natives 1980-86. Am J Public Health 1990; 80:282-85.
7. Kristensen MO. Increased incidence of bleeding intracranial aneurysms in Greenlandic Eskimos. Acta Neurochirurgica 1983 67:37-43.
8. Bjerregaard P. Geographic variations of mortality in Greenland. Arctic Med Res 1990; 49:16-24.
9. Schraer CD, Adler AL, Mayer AM, Halderson KR, Trimble BA. Diabetes complications and mortality among Alaska Natives: 8 years of observation. Diabetes Care 1997; 20:314-321.
10. Trimble B, Wainwright K, Lanier AP, Stroke in Yup'ik Eskimos. Presented at the American Academy of Neurology, Scientific Session on Neuroepidemiology of Stroke, Toronto, Canada, April 1999.
11. Young TK, Schraer CD, Shubnikoff EV, et al. Prevalence of diagnosed diabetes in circumpolar indigenous populations. Int J Epidem 1992; 21:730-736.
12. Schraer CD, Ebbesson SOE, Adler A, Cohen JS, Boyko EJ, Nobmann ED. Glucose tolerance and insulin-resistance syndrome among St. Lawrence Island Eskimos: The Alaska-Siberia Project. Proc. X International Congress Circumpolar Health 1997; 348-354.
13. Ebbesson SOE, Schraer CD, Risica PM, et al. Diabetes mellitus and impaired glucose tolerance in three Alaskan Eskimo populations: The Alaska-Siberia Project. Diabetes Care 1998;21:563-569.
14. Ebbesson SOE, Schraer DC, Nobmann ED, Ebbesson LOE. Lipoprotein profiles in Alaskan-Siberia project. Arctic Med Res 1996; 55:165-173.
15. Schraer CD, Ebbesson SOE, Boyko EJ, Nobmann ED, Adler A, Cohen JS. Hypertension and diabetes among Siberian Yupik Eskimos of St. Lawrence Island, Alaska. Public Health Reports 1996; Vol II, Supplement 42-44.

16. Risica PM, Schraer C, Ebbesson SO, Nobmann ED, Caballero B. Overweight and Obesity Among Alaskan Eskimos of the Bering Straits Region: the Alaska Siberia Project. Int J Obes Relat Metab Disord 2000; 24(8):939-44.

17. Risica PM, Ebbesson SO, Schraer CD, Nobmann ED, Caballero BH. Body Fat Distribution in Alaskan Eskimos of the Bering Straits Region: the Alaskan Siberia Project. Int J Obes Relat Metab Disord 2000; 24(2):171-9.

18. Schraer CD, Risica PM, Ebbesson SOE, Go OT, Howard BV. Low fasting insulin levels in Eskimos compared to American Indians: Are Eskimos less insulin resistant? Int J Circumpolar Health 1999; 58: 272-280.

19. Bennett PH, Miller PH. Diabetes mellitus in Indians of the southwestern United States. In Proc of the VII Congress of the International Diabetes Federation. Amsterdam, Excerpta Medica Foundation 1970: 318-324.

20. Knowler WC, Pettitt DJ, Savage PJ, Bennett PH. Diabetes incidence in Pima Indians: Contributions of obesity and parental diabetes. Am J Epidemiol 1981; 113:144-156.

21. Howard BV, Lee ET, Cowan LD, Fabsitz RR, Howard WJ, Oopik JJ, Robbins DC, Savage PJ, Yok JL, Welty TK. Coronary heart disease prevalence and its relation to risk factors in American Indians. Am J Epid 1995; 142:254-268.

22. Howard BV, Lee ET, Cowan LD. Rising Tide of Cardiovascular Disease in American Indians, The Strong Heart Study. Circulation 1999; 99:2389-95.

23. Ebbesson SOE, Kennish J, Ebbesson LOE, Go O, Yeh J. Diabetes is related to fatty acid imbalance in Eskimos. Int J Circumpolar Health 1999; 58:108-119.

24. Welty TK, Coulehan JL. Cardiovascular disease among American Indians and Alaska Natives. Diabetes Care 1993; 16: (Suppl 1):277-283.

25. Bjerregaard P, Mulvad G, Pedersen HS. Cardiovascular risk factors in Inuit of Greenland. Int J Epid 1997; 126:1182-1190.

26. Bjerregaard P. Rapid sociocultural change and health in the Arctic. Int J Circumpolar Health 2001; 60:102-111.

27. Dyerberg J, Bang HO, Hjorne N. Fatty acid composition of the plasma lipids in Greenland Eskimos. Am J Clin Nutr 1975; 28:958-66.

28. Ulbricht TLV, Southgate DAT. Coronary heart disease: seven dietary factors. Lancet 1991; 338:985-92.

29. Dyerberg J, Bang HO. Hemostatic function and platelet polynsaturated fatty acids in Eskimos. Lancet 1979; 2:433-435.

30. Newman WP, Middaugh JP, Guzman MA, Propst MT, Rogers DR. Comparison of atherosclerosis in Alaska Natives and non-Natives. Arch Pathol Lab Med 1997; 121:1069-75.

31. Lee ET, Welty TK, Fabitz R, et al. The Strong Heart Study--a study of cardiovascular disease in American Indians: design and methods. Amer J Epidem 1990; 132:1141-55.

32. Lipid Research Clinics Program. Manual of laboratory operations. Vol I. Washington, DC: US Department of Health Education, and Welfare, 1975. (DHFW publication no. 75-628).

33. Morgan C, Lazarow A. Immunoassay of insulin: two-antibody system. Plasma insulin levels in normal, sub diabetic and diabetic rats. Diabetes 1963; 12:115-26.

34. Little RA, England JD, Wiedmeyer HM, et al. Inter-laboratory standardization of glyceded hemoglobin determinations. Clin Chem 1986; 32:358-60.

35. Vasquez B, Flock EV, Savage PJ, et al. Sustained reduction of proteinuria in Type 2 (non-insulin-dependent) diabetes following diet-induced reduction of hyperglycemia. Diabetologia 1984; 26:127-33.

36. Chasson AL, Grady HJ, Stanley MA. Determination of creatinine by means of automatic chemical analyzer. Tech Bull Regist Med Technol. 30:207-12(1960).

37. Bakker AJ. Detection of microalbuminuria. Receiver operating characteristic curve analysis favors albumin-to-creatinine ratio over albumin concentration. Diabetes Care 1999; Feb;22(2):307-13.

38. National Heart, Lung, and Blood Institute. Fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, MD: National Heart, Lung, and Blood Institute, 1993. (NIH publication no. 1088).

39. Rose GA, Blackburn H. Cardiovascular survey methods. 2nd ed. Geneva, Switzerland: World Health Organization, 1982. (WHO Monograph Series no. 56G).

40. Prineas Rj, Crow RS, Blackburn H. The Minnesota Code manual of electrocardiographic findings. Littleton, MA: John Wright PSC, 1982.

41. World Health Organization. WHO Expert Committee on diabetes Mellitus: second report. Geneva, Switzerland: World Health Organization, 1980. (WHO Technical Report Series no. 646).

42. Wilber CG, Levine VE. Fat metabolism in Alaskan Eskimos. Exp Med Surg 1949; 3:422-5.

43. Bjerregaard P, Young TK, Hegele RA. Low incidence of cardiovascular disease among the Inuit-what is the evidence? Atherosclerosis 2003; 166:351-357.

44. Clausen J. an epidemiological and demographic study of the coronary heart deaths in Denmark, the Faroes and Greenland. Nordic Council Arctic Med Res Rep 1974; 11:13-28.

45. Scott EM, Griffith IV. Diabetes mellitus in Eskimos. Metabolism,1957; 6:320-32.

46. Young TK, Schraer CD, Shubnikoff EV, et al. Prevalence of diagnosed diabetes in circumpolar indigenous populations. Int J Epidem 1992; 21:730-736.

47. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-prevenzione trial. Lancet 1999; 354:447-55.

48. Dawailly E, Blanchet C, Lemieux S, et al. n-3 Fatty acids and cardiovascular disease risk factors among the Inuit of Nunavik. Am J Clin Nutr 2001; 74(4):464-73.
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49. Ebbesson SOE, Risica PM, Ebbesson LOE, Kennish JM, Tejero ME. Omega-3 fatty acids improve glucose tolerance and components of the metabolic syndrome in Alaskan Eskimos: The Alaska Siberia project. Int J Circumpolar Health 2005; 64(4):396-408.

50. Schraer CD, Adler AL, Mayer AM, Halderson KR, Trimble BA. Diabetes complications and mortality among Alaska Natives: 8 years of observations. Diabetes Care 1997; 20:314-321.

51. Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: The Framingham Study. Diabetes Care 1979; 2:120-6.

52. Heyden S, Heiss G, Bartel AF, et al. Sex differences in coronary mortality among diabetics in Evans County, Georgia. J Chronic Dis 1980; 33:265-73.

53. Butler WJ, Ostrander LD Jr, Carman WJ, et al. Mortality from coronary heart disease in the Tecumseh Study: long-term effect of diabetes mellitus, glucose tolerance and other risk factors. Am J Epidemiol 1985; 121:541-7.

54. Scott EM, Griffith IV. Diabetes mellitus in Eskimos. Metabolism 1957; 6:320-325.

55. Ebbesson SOE, Ebbesson LOE, Swenson M, Kennish JM, Robbins DC. A successful diabetes prevention study in Eskimos: The Alaska Siberia project. Int J Circumpolar Health 2005; 64(4):409-424.

56. Maedler K, Spinas GA, Dyntar D, Moritz W, Kaiser N, Donath MY. Distinct effects of saturated and monounsaturated fatty acids on B-cell turnover and function. Diabetes 2001; 50: 69-76.

57. Liu QZ, Knowler WC, Nelson RG, et al. Insulin treatment, endogenous insulin concentration, and ECG abnormalities in diabetic Pima Indians: cross-sectional and prospective analyses. Diabetes 1992; 41:1141-50.

58. Lamarche B, Tchernof A, Mauriege P, Cantin B, Dagenais GR, Lupien PJ, Despres JP. Fasting insulin and apolipoprotein B levels and low-density lipoprotein particle size as risk factors for ischemic heart disease. JAMA 1998; 279:1955-61.

59. Despres JP, Lamarche B, Mauriege P, Cantin B, Dagenais GR, Moirjani S, Lupien PJ. Hyperinsulinemia as an independent risk factor for ischemic heart disease. N Engl J Med 1996; 334:952-7.

60. Pyorala K. Hyperinsulinemia as predictor of atherosclerotic vascular disease: epidemiological evidence. Diabetes Metab 1991; 17:87-92.

61. Hubert HB, Feinleib M, McNamara PM, et al. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation 1983; 67:968-77.

62. Kannel WB, Wilson PW. Efficacy of lipid profiles in prediction of coronary disease. Am Heart J 1992; 124:786-94.

63. Ebbesson SOE, Risica PM, Ebbesson LOE, Kennish JM. Eskimos have CHD despite high consumption of omega-3 fatty acids: The Alaska Siberia project. Int J Circumpolar Health 2005; 64(4):387-395.

64. Manninen V, Tenkanen L, Koskinen P, et al.: Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: implications for treatment. Circulation 1992; 85:37.

65. Sweetnam PM, Bolton CH, Yarnell JW, et al. Associations of HDL2 and HDL3 cholesterol subfractions with the development of ischemic heart disease in British men. The Caerphilly and Speedwell Collaborative Heart Disease Studies. Circulation 1994; 90: 769.

66. Gotto AM Jr. Hypertriglyceridemia: risks and perspectives. Am J Cardiol 1992; 14:19H-25H.

67. Neil A, Hawkins M, Potok, Thorogood M, Cohen D, Mann J. A prospective population-based study of microalbuminuria as a predictor of mortality in NIDDM. Diabetes Care 1993; 16:996-207.

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