

# A SUCCESSFUL DIABETES PREVENTION STUDY IN ESKIMOS: THE ALASKA SIBERIA PROJECT

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## ABSTRACT

**Objectives.** To test the efficacy of a simple intervention method to reduce risk factors for type 2 diabetes (DM) and cardiovascular disease (CVD) in Alaskan Eskimos.

**Study Design.** The study consisted of 1) a comprehensive screening for risk factors of 454 individuals in 4 villages, 2) a 4-year intervention and 3) a repetition of the screening in year 5 to test the efficacy of the intervention.

**Methods.** Personal counseling (1hr/year) stressed the consumption of more traditional foods high in  $\omega$ -3 fatty acids and less of certain specific store-bought foods high in palmitic acid, which was identified as being associated with glucose intolerance.

**Results.** The intervention resulted in significant reductions in plasma concentrations of total cholesterol ( $p = 0.0001$ ), LDL cholesterol ( $p = 0.0001$ ), fasting glucose ( $p = 0.0001$ ), diastolic blood pressure ( $p = 0.0007$ ) and improved glucose tolerance ( $p = 0.0006$ ). This occurred without loss of body weight. Sixty percent of the participants had improved glucose tolerance; only one of the 44 originally identified with impaired glucose tolerance (IGT) developed DM during the study.

**Conclusions.** Dramatic improvements of risk factors for DM and CVD were achieved in the intervention by primarily stressing the need for changes in the consumption of specific fats. The results suggest that fat consumption is an important risk factor for DM.

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**Keywords:** cardiovascular disease, Inuit, omega-3 fatty acids, palmitic acid, cholesterol, blood pressure

## INTRODUCTION

Type 2 diabetes (DM) and cardiovascular disease (CVD) are increasing at an alarming rate in Alaskan Eskimos (1-6). The prevalence of DM, that was < 0.4% in 1957 (1), was 9% in 1994 among the Norton Sound Eskimos  $\geq$  45 years of age (2,3). In this region, the death rate from ischemic heart disease (ICD – 9 410-414) is twice the rate of neighboring regions (4). The death rate from heart disease is 30-40% higher among Alaska Natives than among US whites in the age groups 25-54 (5), while the overall death rate from stroke is 50% higher (4). The identification of risk factors in the population and the development of effective intervention and prevention programs have become a priority. Universal risk factors for DM, such as family history of DM (1), obesity (2, 7) and body fat distribution (8), have been identified, in addition to a fatty acid (FA) imbalance (9) that may be ethnic- and geographic- specific.

The reduction of identified risk factors by behavioral modification is an exceptional challenge, as it is known that the rare successful interventions aimed at preventing DM, for example, have required intensive personal counseling (4-7 times/year, 10,11). Sustained weight reduction is rarely obtained (12) and dramatic lifestyle changes, including diet modification and increased physical activity levels, require intensive and, therefore, expensive counseling to yield positive results (13). The question arises as to which intervention and prevention programs can work in an Eskimo population, and what is affordable?

The Diabetes Prevention Program (DPP) of the Alaska Siberia Project (ASP), reported on here, aimed to find a cost-effective, simple method to reduce risk factors. It was based

on the belief that the population was highly amenable to behavioral modification, because 1) DM and CVD had increased so dramatically that the population was fearful of the emerging epidemic, 2) the potential participants have a record of following the advice of the health-care providers and 3) the populations have demonstrated exceptional enthusiasm for research aimed at solving their health problems.

The purpose of this study, the first of its kind among Eskimos, was to use the results as a foundation for future studies and the development of appropriate intervention and prevention programs for this population. The intervention to reduce risk factors for DM and CVD reported on here was based on an initial screening of 454 individuals (240 women, 214 males) in April-May 1994, in order to identify risk factors. This was followed by another screening in 1998. The results of the first screening have been published elsewhere (2, 7-9). The screening revealed the highest prevalence of DM ever recorded in Eskimos (2). The prevalence varied by ethnic group and was approximately two-fold higher in women than in men. The highest prevalence was found in Siberian Yupik Eskimo women  $\geq$  55 years of age, of which 44% had abnormal glucose tolerance, (IGT + DM, DM, 19% +IGT, 25%) The identified associated risk factors were obesity (2, 7, 8) and an imbalance of plasma FAs (9). The plasma concentrations of  $\omega$ -3FAs were lower in participants with IGT and DM than in normoglycemics, suggesting, among other possibilities, an association with a lower consumption of traditional foods. On the other hand, plasma concentrations of palmitic acid (C16:0) were higher than in normoglycemic participants. This saturated fat is in high concentration in butter, shortening and bacon.

Shortening and margarine also contain a large proportion of trans-FAs, especially the trans form of oleic acid, which was also significantly elevated in participants with IGT and DM (9).

Considering that Alaskan Eskimos had a diabetes prevalence of < 0.4% 50 years ago (1, 14), when the consumption of traditional food was high and obesity low, a decision was made to test the hypothesis that the recent increase in DM is not only related to such universal risk factors as obesity, but also to an inadequate consumption of  $\omega$ -3FAs and to an over-consumption of store-bought foods high in palmitic acid and trans-FAs. The intervention was thus designed to encourage the reversal of the trends of acculturation in this ethnic group: more physical activity, more traditional foods and less indiscriminate consumption of store-bought foods high in saturated and trans-FAs. Since the entire study was carried out on a small budget, the intervention was limited to once-a-year personal counseling. Hence, the study was conceptually a pilot study to test community interest and the efficacy of the simplest possible intervention strategies.

The study was approved by the Institutional Review Boards of the University of Alaska and the Indian Health Service in Anchorage. The Norton Sound Health Corporation (NSHC) and village councils support the study enthusiastically.

## MATERIAL AND METHODS

### Study population

This four-year intervention study involved 454 Eskimos from two Siberian Yupik villages on St. Lawrence Island, a Central Yupik village, and an Inupiat village, all in the Bering Strait

region of Alaska (2). Every village resident  $\geq$  25 years of age was invited to participate, but only 50.5% of these ended up participating, as many were away from the villages when the first screening took place (2). Only a week was spent in each village. The participation rate was highest in the older age groups, with 66% of the age-eligible  $\geq$  45 years of age (Fig. 1).

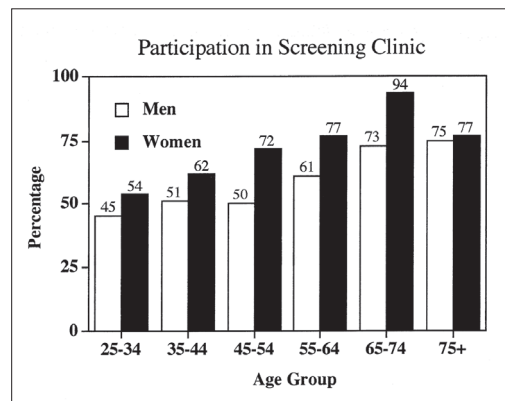


Figure 1. Participation in screening clinic.

The study involved 1) an initial screening to determine the prevalences of impaired glucose tolerance (IGT), DM and CHD, and to identify and characterize risk factors, 2) a 4-year intervention, to test two intervention strategies, and 3) a repeat of the initial screening at the end of the intervention to determine the efficacy of the intervention.

### Initial screening

454 participants  $\geq$  25 years of age, from four villages, were examined using a modified Strong Heart Study protocol (2, 15). The initial screening was conducted during the last 2 weeks of April and the first two weeks of May 1994. The results of the initial screening have been published elsewhere (2, 5, 7, 8, 16). The screening research team was composed of 10 volunteer physicians, nurse practitioners

and technicians. The recruitment was carried out with the PI arriving in the village about a week before the research team. He visited each individual  $\leq 25$  years of age in their homes, in order to explain the study and the consent form. An appointment for the nutritionist's visit and the clinical exam was made at that time. The dietary interview was carried out at the participant's home the day before the screening.

The screenings were carried out in the village health clinic, in the school, or in a church. The examination of 20-25 individuals/day progressed without major problems, although snow storms created some delays and difficulties. The screenings were routinely carried out in a systematic manner, with each participant going from station to station and finally being checked out by a physician, who reviewed the results of the screening with the participant and provided preliminary advice and referrals as needed.

### Screening Protocol

1. Dietary Assessment. An estimate of the nutritional variables was obtained using a 24-hour recall method and a food frequency analysis. These interviews were made the day before blood sampling.

2. Personal Interview. The following information was obtained from personal interview: a) demographic data, including birth date, sex, ethnic identity, quantum of Native blood, birthplace and past and present villages of residence, b) education, c) family history of diabetes and cardiovascular disease, d) tobacco use and alcohol consumption, e) traditional values/culture, f) physical activity, g) medical history, particularly diabetes and CVD history, and h) current medications and dosages.

3. Physical Examination. The physical examination included the following procedures: a) height and weight, using standardized protocols (7, 8), b) waist (abdominal) girth, hip girth and upper arm circumference, c) subscapular, triceps and suprailiac skin-fold thickness, d) blood pressure, following the Strong Heart Study protocol (15, 17), e) examination of heart and lungs, f) palpation of pedal pulses, g) auscultation of femoral and carotid arteries, h) measurement of body composition by electrical impedance measurement (RJL), and j) a resting 12-lead ECG.

4. Laboratory Measurements: A sample of fasting venous blood was obtained and immediately centrifuged, frozen and shipped on dry ice to the Medlantic Research Institute in Washington D C within a week. The chemical analyses included: a) lipids, b) apolipoproteins: ApoB, ApoA-I, Lp(a), ApoE phenotype, c) fasting insulin, d) plasma creatinine, e) fasting glucose, f) glycated hemoglobin (HbA1c), g) glucose tolerance test, including insulin. Blood chemistries were carried out at the Medlantic Research Institute, using published methods (1, 15). This Institute does the blood chemistries for the Strong Heart Study.

Fatty acids were measured, at the University of Alaska Anchorage, on separated plasma that was originally obtained after at least 12 hours fasting. Frozen plasma was stored in EDTA for 2-6 days at  $-10^{\circ}\text{C}$ , then at  $-70^{\circ}\text{C}$  until analysis (9).

### Diagnostic criteria

Diagnostic criteria for DM and impaired glucose tolerance (IGT) were those of the World Health Organization (18): Known Diabetes: If the participant was: a) on insulin

treatment, b) on a hypoglycemic agent and had two prior measurements of elevated blood glucose ( $> 250 \text{ mg}\cdot\text{dl}^{-1}$ ) recorded, c) on renal dialysis, or had kidney transplantation and a history of diabetes by questionnaire, d) a fasting blood glucose  $> 140 \text{ mg}\cdot\text{dl}^{-1}$ , repeated for clinical confirmation. New Diabetes: A fasting blood glucose  $> 140 \text{ mg}\cdot\text{dl}^{-1}$  and repeated for clinical confirmation, or a 2-h blood glucose  $> 200 \text{ mg}\cdot\text{dl}^{-1}$  and no mention of diabetes history in the questionnaire. Impaired Glucose Tolerance (IGT): A fasting blood glucose  $> 140 \text{ mg}\cdot\text{dl}^{-1}$  and a 2-h blood glucose between  $140 \text{ mg}\cdot\text{dl}^{-1}$  and  $199 \text{ mg}/\text{dl}$ . Normal Glucose Tolerance (NGT): fasting blood glucose and 2-h blood glucose  $< 140 \text{ mg}\cdot\text{dl}^{-1}$  and no history of diabetes by questionnaire. Diabetic Status Undetermined: (a) on renal dialysis, or with kidney transplant without mention of diabetes in the medical history by questionnaire (b) results of OGTT were missing (c) participant refused OGTT (d) fasting blood specimen was not sufficient to determine diabetic status.

All of the 69 with abnormal glucose tolerance were monitored by their health-care providers and the Diabetes Prevention Program of the NSHC after the first screening to ascertain glucose tolerance status. Five of those originally considered “new” diabetics after the first screening were not confirmed and were treated as IGT in our follow-up and analysis. All with IGT, or “new DM”, received a warning about the need for changing lifestyle and diet when the results of the first screening were explained to them.

### **Intervention**

For ethical reasons, the study became a comparison of two intervention strategies.

The participants in the two “control villages” (a Siberian Yupik and Central Yupik village) had one personal counseling session after the first screening, during which the test results were explained, followed by an explanation of the handout. The participants in the “intervened” villages (a Siberian Yupik and an Inupiat village) had an additional 30-60 minute counseling session once a year for 3 additional years, during which the handout was reviewed again.

Each participant in the two “control” villages received the same handout once a year by mail. The single page handout listed healthy foods (mostly traditional foods) and fats to be avoided (shortening, butter, margarine, bacon etc). Store managers in all 4 villages provided healthy alternatives to saturated and trans fats, such as olive oil and rapeseed oil (canola). One paragraph in the handout dealt with adequate exercise, and weight reduction when indicated, but specific goals were not provided because of the difficulty in follow-up with only one visit a year. A few were enthusiastic about losing weight and did, but most did not, due to lack of guidance. Exercise bikes were provided in each of the 4 villages at their request, but were not used, because of the lack of supervision. An aerobic exercise video tape, featuring Eskimo girls, was produced and given to authorities in each village, but these were also not used, due to the lack of supervision.

### **Second screening**

At the end of the 4-year intervention, a quasi-random sample of 210 individuals from the four villages were reexamined, using the same methods as in the initial screening. Like the first screening this took place in April-May. A

total of 390 individuals were screened in 1998, of which 210 had been screened in 1994. The low participation resulted from exceptionally bad weather (snow storms), the budget-limited time of the research team in each village, and either participant absence from the village, or an inability to come to the clinical examination. There was no selection of individuals for the exam and only those who were able to show up during the short time that the team was in the village were examined. The sample studied appeared to be representative of the original population screened in 1994: relatively fewer subjects in the 25-44 age group than in the 45-74 age group (about 62% from the original screening were screened in 1998), more women than men, and 55% of those with IGT in the first screening (Fig. 2). All with IGT in the 1994 have been monitored by the Norton Sound Health Corp since then. The results of the two screenings were compared using paired t-tests, comparing before and after intervention values.

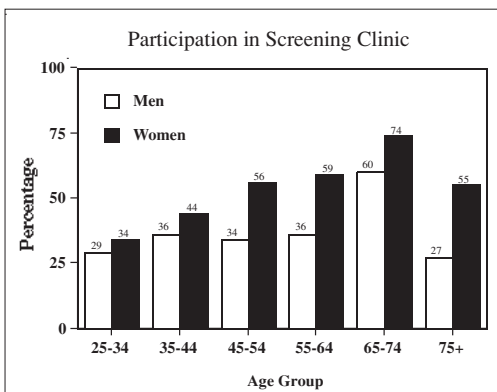


Figure 2. Percentage of 1994 individuals also sampled in 1998.

## RESULTS

### Pre-intervention screening

The results of the first screening revealed the usual risk factors for DM, such as age, family history and obesity. Weight reduction is difficult to achieve in interventions (10-13). Ethnic-specific dietary risk factors related to fat consumption were also discovered (9). Considering the need for meaningful intervention results with a minimal research budget, a decision was made to put emphasis on fat consumption during the intervention. That turned out to be fortuitous, as most participants responded favorably to suggestions related to diet.

The plasma fatty acid profiles obtained during the first screening had revealed several hitherto unrecognized patterns (9). Those with DM and IGT had lower concentrations of  $\omega$ -3 FAs and significantly higher concentrations of oleic acid ( $p = 0.02$ ) and palmitic acid ( $p = 0.03$ ) than normoglycemics. The measured oleic acid included the trans forms. The high plasma concentrations of the saturated palmitic acid (16:0) in those with IGT and DM, compared with the normoglycemic participants, supports the view that the divergence from a traditional diet low in saturated fatty acids may be contributing to the development of DM. These data provided the basis for the design of the intervention.

### Post-intervention screening

The results of the post-intervention screening revealed that 1) repeated health counseling in two "intervention villages" for 30-60 minutes/year, for 4 years, resulted in significantly better glucose tolerance, lower LDL cholesterol levels and lower diastolic blood pressure

than in 2 “control villages” that had only one counseling session the first year (Fig. 3, Table I); 2) those 60% with improved glucose tolerance had significantly higher plasma  $\omega$ -3 FA concentrations ( $p = 0.01$ ) and lower palmitic acid concentrations ( $p = 0.02$ ) than those that had worse glucose tolerance after the intervention, suggesting that the improvement was due to the advocated change in dietary

fat consumption, as there was, on average, no weight loss (Tables II and III) and 3) that this shift in fat consumption appears to have contributed to diabetes prevention, as only 1 person of 44 with IGT in the first screening developed DM during the 4 years of intervention. Unfortunately, we had no physical activity data to relate to the improved glucose tolerance.

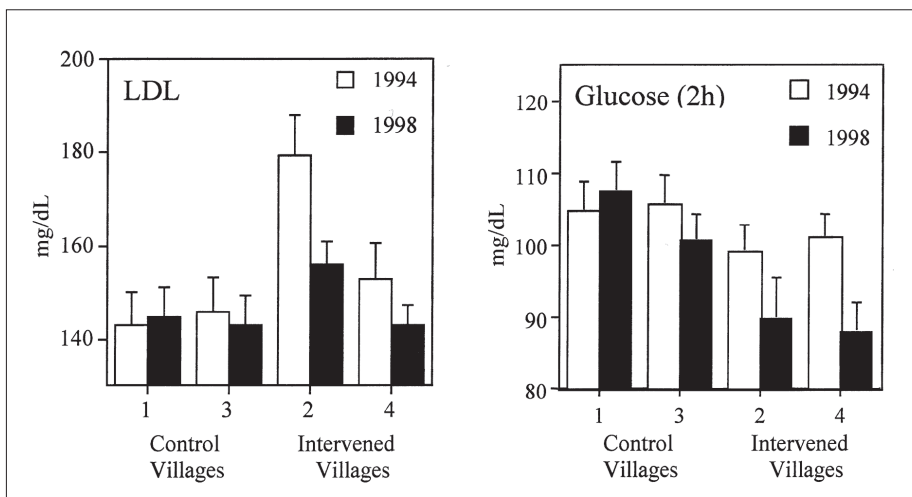


Figure 3. Paired t-test comparison of the effect of two intervention strategies (1 vs 3 counseling sessions).

**Table 1.** Comparison of the effect of two intervention strategies.

	Control Villages				Intervened Villages			
	1994	1998	% change	p*	1994	1998	% change	p*
Subjects	188	88			266	122		
Cholesterol	225±4	219±4	-2.7	0.07	234±4	217±4	-7.3	<0.0001
LDL	145±4	142±4	-2.1	0.28	164±4	150±4	-8.5	<0.0001
HDL	64.8±2	60.6±2	-6.5	0.003	55.2±2	51.4±1	-7.3	0.0004
Triglycerides	70.6±5	78.6±5	+11.3	0.05	72.8±5	78.2±5	+7.4	0.09
Glucose	102±1	97.3±1	-4.9	<0.0001	102±2	96.5±2	-5.4	<0.0001
2-h Glucose	109±3	104±4	-4.6	0.16	95.1±3	86.0±3	-9.6	0.006
Weight	68.3±1	69.6±2	+1.9	0.02	68.8±2	69.9±2	+1.6	0.06
Systolic BP	121±2	123±2	+1.7	0.21	118±2	118±1	0	0.89
Diastolic BP	77.1±1	73.2±1	-5.0	0.003	74.0±1	70.8±1	-4.3	0.0007
Pulse pressure	43.5±2	49.5±2	+13.8	<0.0001	45.0±1	47.2±1	+4.9	0.02

\* paired t-test

**Table II.** Effect of intervention: Comparison of populations with and without improvement of glucose tolerance.

	Improved Glucose Tolerance				Not Improved Glucose Tolerance			
	1994	1998	% change	p*	1994	1998	% change	p*
Subjects	110	110	0		73	73	0	
Cholesterol	228(4.9)	216(3.9)	-5.3	0.0008	237(4.9)	228(4.4)	-3.8	0.0002
LDL	155(4.3)	145(3.8)	-6.5	0.0071	162(5.5)	149(4.4)	-8.0%	0.0008
HDL	59(1.7)	56(1.8)	-5.0	0.0371	59(2.1)	54(2.0)	-8.5	0.0005
Triglyceride	72(3.8)	77(4.0)	+6.9	0.1200	77(6.6)	87(6.9)	+13	0.0225
Glucose	104(1.2)	97(1.0)	-6.7	<0.0001	102(1.4)	97(1.3)	-4.9	0.0054
2-h Glucose	112(3.6)	86(2.6)	-23	<0.0001	89(3.0)	109(3.9)	+22.5	<0.0001
Weight	69(1.4)	70(1.4)	+1.4	0.2017	68(1.7)	70(1.9)	+2.9	0.0071
Systolic BP	121(1.5)	121(1.6)	0	0.9589	120(2.0)	121(1.8)	+0.8	0.7722
Diastolic BP	75(1.1)	71(1.1)	-5.3	<0.0001	76(1.3)	73(1.1)	-3.9	0.0461
Pulse P	45(1.5)	50(1.5)	+11	0.0002	44(1.8)	47(1.6)	+6.8	0.0260

\* paired t-test

**Table III.** Comparison of relative plasma concentrations of fatty acids at the end of intervention in those with and without improvement of glucose tolerance.

	Improved	Not improved	% difference	p*
Subjects	110	73		
% 20:5 $\omega$ -3	5.07 (0.4)	3.83 (0.3)	24	0.03
% 22:6 $\omega$ -3	5.28 (0.2)	4.54 (0.2)	14	0.02
% 20+22 ( $\omega$ -3)	12.00 (0.6)	9.9 (0.5)	18	0.01
% 16:0	17.6 (3.4)	18.8 (0.4)	7	0.03
% 18:0	6.6 (0.1)	6.5 (0.1)	2	0.45

\* Unpaired t-test of results from second screening.

## DISCUSSION

The study succeeded in identifying risk factors for DM and CVD and in reducing some of those risk factors with a simple intervention strategy. This study shows that four years of counseling is better than one. Some participants clearly got the message in the "control" villages with only one counseling session, but repetition improved the results significantly. This is not surprising, considering the published evidence for the need of repetition (10-13). From a public health point of view, it will be important in Alaska to counsel indi-

viduals on a personal basis, in order to ensure comprehension. The villagers were essentially uninformed about risk factors for DM and CHD when this study started.

Several short-comings of the study, including the design, need to be addressed. For ethical reasons and for building enthusiasm for research, a decision was made to invite all villagers to be screened, instead of, for example, to select families at random, which by itself would have created some unwanted diffusion effects. Instead, we chose to compare 2 intervention villages with 2 control villages, measuring changes in test variables of village

residents before and after intervention, using paired t-tests. The selection of villages was not random. Of the two closely related island villages, one served as “control” for one of the “intervention” villages. The other “intervention” village was chosen because the first screening showed a much higher prevalence of risk factors for CHD than the other. It would not have been ethical to carry out an intervention in the village with low prevalence. Nor would it have been so clear from the results whether the intervention had worked. The baseline values for LDL was higher in this intervention village. That this particular village showed a similar improvement during the intervention probably relates to the greater sensitivity of individuals in that village to the intervention message, as they were told of the significance of the high LDL values. The same principle probably holds for those who had high glucose values at baseline, i.e. the more abnormal the baseline value is, the more likely it is that the participant will respond to advice.

The limited budget of this pilot intervention study unfortunately led to several other shortcomings. The protocol for decreasing body weight was inadequate, because, on average, there was no weight reduction. One counseling session/year is not enough. Repetition of counseling with clear goals is needed to achieve significant improvements in weight reduction (10-13). Another weakness in the study was the lack of data on physical activity, which may have served as a confounder. Budget restrictions also prevented more intensive counseling. On the other hand, it became clear early in the study that even minimal counseling on diet was successful. Many heeded our advice, as many enthusiastically told us of “feeling better” following our intervention guide-lines.

Some told us that they “didn’t like the taste” of olive oil, which was new to them, but that they were getting used to it. It should be noted that the traditional seal oil contains 26% oleic acid, a main ingredient in olive oil. The store managers in all four villages told of the change from bacon, shortening and butter to the recommended healthier alternatives. Although we checked the stores in all 4 villages every year, we were not able to discern differences in behavior in the “control” village,s as the visits to those villages were short and casual.

The intervention had a significant impact on glucose tolerance, LDL levels and diastolic blood pressure in the two villages with annual personal counseling sessions. The improved glucose tolerance in 60% of those re-tested in 1998 was a surprisingly good result, considering the minimal intervention. The fact that only one of the 44 with IGT originally developed DM in the 4-year intervention is significant and supports the hypothesis developed after the first screening: FA imbalance appears to contribute to the development of DM (9). This is supported by the improvement of glucose tolerance being associated with higher plasma concentrations of  $\omega$ -3 FAs and lower concentrations of palmitic acid (16:0). It is important to note that the improvement occurred without weight loss, which also would have reduced insulin resistance and glucose intolerance (12, 16, 19).

Historically, the fatty acid imbalance in today’s Alaskan Eskimos appears to related to the changing diet from traditional foods, high in  $\omega$ -3 FAs, to an increased consumption of store-bought foods, high in saturated and trans-FAs (9, 19-22). The four-year intervention study confirmed these observations. Increased consumption of traditional foods rich in  $\omega$ -3

fatty acids (FAs) and a decreased consumption of specific store-bought items high in palmitic acid and trans-FAs, especially shortening, butter, margarine and bacon (9), resulted in a significant decrease in plasma concentrations of glucose and LDL cholesterol ( $p = 0.0001$ ). Those with improved glucose tolerance after the intervention had significantly higher plasma concentrations of  $\omega$ -3 FAs ( $p = 0.01$ ) and lower levels of palmitic acid ( $p = 0.02$ ) than those with worse glucose tolerance after the intervention, indicating that the improvement in glucose tolerance and LDL cholesterol was related to the dietary change advocated in the intervention. The significance of these preliminary findings is that insufficient consumption of  $\omega$ -3 FAs and over-consumption of palmitic acid and trans-FAs may be new risk factors contributing to the high prevalence of CVD and DM, not only among Alaskan Natives, but also in Native American communities, e.g. the Pimas and the Hawaiian Natives.

Although specific dietary saturated fats had not, until our study (9), been recognized as specific risk factors for DM, there is considerable evidence that obesity, high fat and high saturated fat diets contribute to DM and CVD (23-27). Thus, Howard (24) concludes that dyslipidemia originates from an increase in the free FA flux, that results from the central obesity accompanying insulin resistance. Increased total fat consumption in Australian Aborigines (28), Japanese migrant populations (29) and American Indians (24, 30) is associated with an increased prevalence of insulin resistance (IR) and DM. These associations have also been noted in other ethnic groups (25, 26). Total saturated fat consumption has also been correlated with IR and DM (25, 26, 32-36), as have obesity and central obesity

(36). Two studies have also found a correlation between a high consumption of monounsaturated fats and increasing adiposity, a correlate of insulin resistance (25, 37).

Our dietary and FA studies in Alaskan Eskimos appear to corroborate these findings and conclusions (9 and manuscript in preparation). The FA profiles from the 1994 screening showed that total plasma concentrations of FAs (total FAs) were higher (after adjusting for obesity,  $p = 0.03$ ) in those with IGT+DM than in the normoglycemics, as were the concentrations of oleic acid ( $p = 0.03$ ). After adjusting for abnormal glucose tolerance, total FAs and oleic acid concentrations were also significantly higher in the overweight than in those with normal weight ( $p = 0.009$  and  $p = 0.002$ , respectively). Assuming a correlation between plasma FA levels and consumption, these findings fit the results of other studies. It is still too early to make this unqualified assumption, as dietary assessments lack the precision of plasma FA measurements. Nevertheless, our finding of a significant correlation between such estimates provides at least a temporary confidence. Thus, for example, our estimates of dietary consumption of  $\omega$ -3 FAs, obtained by the 24-hour dietary assessment, and the percent plasma  $\omega$ -3 FA content were highly correlated ( $p = 0.003$ ).

### **Omega-3 FAs and diabetes**

Our preliminary FA study revealed that the risk for developing IGT and DM was associated with an imbalance of plasma FA (9). We found lower levels of eicosapentaenoic acid (EPA; 20:5-3) in participants with IGT and DM than in normoglycemic participants. This is suggestive of an inadequate consumption  $\omega$ -3 FAs, or a suppression of FA metabolism by

other fats, such as palmitic acid, or other as yet unidentified factors. The lower C20-C22  $\omega$ -3 FA levels might also be explained by inadequate  $\Delta$ 6-desaturase activity, which initiates the conversion of alpha-linolenic acid to EPA and DHA (9).

Although animal studies suggest that the FA profile of the diet is of primary importance in the development of insulin resistance (35), the data in humans is not conclusive (25-26, 38-40). Feskens *et al.* (40) reported that subjects in the Finnish and Dutch cohorts of the Seven Countries Study who increased their fish intakes between 1970 and 1990 had significantly lower blood glucose levels than those who did not. Studies with fish oil supplementation have been equivocal. Two studies showed modest improvements (38, 39), while two showed no change (41, 42). Our preliminary studies (1) support the concept that  $\omega$ -3 FA consumption is a factor in the development of DM. A strong association between the reported consumption of seal oil and salmon  $\omega$ -3 FAs and the prevalence of glucose intolerance, has been observed in another study from Alaska (43). After adjusting for age, sex, ethnicity and BMI, the odds ratio for IGT+DM was 0.2 (95% CI 0.1-0.8) among consumers of these  $\omega$ -3 FA sources compared to non-consumers. The authors note that "none of the 58 people who consumed both seal oil and salmon on a daily basis developed IGT, or diabetes, compared with 45 of 457 (9.9% [ $p = 0.03$  by  $\chi^2$ ]) who ate neither seal, nor salmon on a daily basis." These observations are consistent with the above-noted connection between the rise in IGT, DM and CHD in the Eskimo populations as they abandon their traditional,  $\omega$ -3 FA-rich, diets in favor of a more Western diet, rich in store-bought items high in saturated and trans-

FA. The question still to be answered in future research is: what component of the imbalance affects which variable among the risk factors.

### **Lipotoxicity and development of DM**

The possibility that the over-consumption of certain specific fats can facilitate the development of DM has emerged only recently. The suggestion comes from three studies: 1) our findings of elevated plasma levels of palmitic acid in participants with IGT and previously undiagnosed DM (9); 2) this intervention study aimed at decreasing palmitic acid consumption; and 3) adult rat pancreatic islet cultures (44). In the latter study, a clear lipotoxic effect of palmitic acid was observed, which involved an increased apoptosis rate, coupled with a reduced proliferation capacity of  $\beta$ -cells and impaired insulin secretion. The deleterious effect of palmitate on  $\beta$ -cell turnover is mediated by the formation of ceramide and the activation of the apoptotic mitochondrial pathway.

The change in diet is less apparent in Greenland, which may account for the low prevalence of disease, while the influence of "American" dietary pressures have clearly affected the health of the Alaskan Eskimos, American Indians and Native Hawaiians. The question is: which specific dietary components contributes most to disease? Some of the answers that have emerged from the studies of Alaskan Eskimos may apply to other ethnic groups as well.

### **Trans fatty acids**

Trans-FAs were not measured in this study, but may partly account for the latter's results, as they were considered in the intervention. Items high in trans-FAs were included in the

list of items to avoid (eg. shortening, margarine etc.). Trans-FAs (TFAs) have not been measured in plasma in cross-sectional studies of DM and CVD, although a growing body of evidence shows an association with increased risks of CHD (45-51) and cardiac arrest (45). However, the data is inconclusive (49). The evidence suggests that the mechanisms involve the reduction in plasma concentrations of HDL (46, 52-54) and increased levels of LDL (52-54), triglycerides (49), Lp(a) (49, 52-56) and platelet aggregation, the latter by altering eicosanoid biosynthesis (49). The reduction in LDL during the intervention described here may be partially due to the advocated decreased consumption of TFAs (52-54). High TFA consumption is also associated with pre-eclampsia (50) and potentiates insulin secretion (56). The role of TFA in the development of DM is however not known, although evidence from the Nurses' Health Study suggests an association (57). The significance of TFAs relates to the known growing consumption of foods with high concentrations of TFAs (45,53). An order of French fries may, alone, contain 7-8 g of TFAs, while the recommended intake is  $> 2.0$  g/day (58). Naturally occurring TFAs in the traditional Cretan diet have been estimated to contribute less than 2.0% of dietary energy (58). We found that Alaskan Eskimos (of all ages) consume an average of more than 4.1 g/day from shortening, butter and margarine alone. Similar over-indulgence is likely among the Pima and Native Hawaiians, but there are no studies to show that in relation to DM, CVD and associated risk factors. We know, from analyzing a small sample ( $n = 20$ ), that the plasma concentrations of C18:1-t9 are about 15% of the total C18:1-9 (9).

### **Diabetes is a risk factor for CHD and stroke**

The prevention of DM in Eskimos is especially important because DM is also a primary risk factor for CHD (59) and stroke (62) as it is in American Indians(60). Other risk factors in Eskimos include high cholesterol levels. In 1994, 36% had total cholesterol levels  $\geq 240$  mg/dl, 18% were  $\geq 265$  and 6%  $\geq 300$  mg/dl that were also improved in this intervention (Fig. 3; (59)). The prevalence of CHD in the cohort studied here is 6% of the population under 55 years of age and 26 % of those over 54 years of age. Stroke is a major health problem among Eskimos and since DM is a major risk factor. In Greenland, the stroke incidence is 2.5 to 3 times higher than in the Danish population (61). The death rates for cerebrovascular disease among Alaskan Natives were about 1.5 times that of the US White rate during 1994-1998 (4). It is known that among Central Yupik Eskimos in Alaska, 79% of the strokes are ischemic (63).

### **The rapid acculturation of Alaskan Natives**

The main reason for the recent increase in CVD and DM among Alaskan Natives may be partially related to their increased lifespan, but it also appears to be 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 televisions. This has resulted in the uninformed purchase of western foods in stores and, for many, the development of a sedentary lifestyle. Where life was once a real struggle, with extensive energy expenditures, the life for many is now more relaxed. The women have been particu-

larly affected, as their energy expenditure has been greatly reduced resulting in a high prevalence of obesity (2, 3, 7, 8, 59).

A study aiming to identify which among the recently introduced foods are harmful to these populations has only begun recently (9). The lack of newspapers and information about healthy food has led many Eskimos to turn away from healthy traditional foods, rich in  $\omega$ -3 fatty acids and low in saturated fats, to store-bought foods high in saturated and trans-FAs (butter, Crisco shortening and margarine (2)). Since 40-45% of their diet was traditionally fat, which comprised their main source of energy, some Eskimos today, in the absence of warnings with respect to their deleterious effects, now consume large amounts of non-traditional fat (9). Thus, ethnic-specific craving for such items as Eskimo Ice Cream (now made from Crisco shortening and berries) has led to a distinct change in fat consumption. The frequently purchased items high in 16:0 and/or trans-18:1-9 FAs are butter, shortening, margarine and bacon. The Eskimos had never heard that these items could be unhealthy if consumed in large amounts. An inquiry in the stores located in a village of 550 inhabitants revealed average monthly sales of approximately 432 pounds (196 kg) of Crisco shortening, 480 pounds (218 kg) of butter and 180 pounds (82 kg) of margarine. Some villagers confirmed that they could consume as much as 1/3 lb/day of Crisco. Since these items are also purchased by mail order, etc., these estimates reflect only a portion of the village consumption. Nevertheless, the village sales of these items alone amount of 286 pounds (180 kg) of palmitic (16:0) and stearic acids (18:0)/month, or 7.9 g/day/person in the village, including infants

and children. To this, one can add 4.1 g/day of trans-FAs just from these sources alone. Many consume other foods rich in trans-FAs, such as potato chips, cookies and French fries. Our screening of 454 Alaskan Eskimos revealed that many exceeded the fat and saturated fat restrictions consistent with the Step 1 NCEP recommendations: 42% of individuals had diets containing  $\geq 10\%$  saturated fat, 61.1% had diets with  $\geq 300$  mg cholesterol, and 81% had diets with  $\geq 30\%$  total fat (19).

Considering that DM and CVD were rare in this population only 30 years ago on a traditional diet (12, 14, 59), it is easy to imagine that the fat consumption in this population contributes to disease. It is also likely, but not yet proven, that other Native Americans have changed their fat consumption. For example, the Pima Indians now also use Crisco shortening in considerable quantities in tortillas and fry bread.

### Summary and significance

This study revealed that health screening, combined with minimal counseling about lifestyle and healthy foods, results in significant improvements of risk factors in this population. The study results suggest that such counseling can lead to the prevention of DM. There is an urgent need to determine to what extent FA imbalance contributes to CVD and DM, especially in Native American populations (60, 64, 65). The evidence strongly suggests that a modest consumption of  $\omega$ -3 FAs protects against arrhythmia, cardiac events and DM (9, 66, 67), and that the larger consumption of C20+C22  $\omega$ -3 FAs in Eskimos is associated with improved glucose tolerance, insulin resistance and components of the metabolic syndrome: HDL, triglycerides and diastolic

blood pressure (68). DM is an important risk factor for CHD and stroke. Omega-3 FAs are important healthy components of traditional diets for many ethnic groups, including Mediterranean and Eskimo populations (58, 68). Evidence is also mounting to indicate the toxic effects of an over-consumption of trans-FAs and specific saturated fats in relation to both CVD and DM (9).

Although the available data suggest that  $\omega$ -3 FAs, palmitic acid and trans-FAs have roles in the development of DM, and thus of CVD, our preliminary data also indicate that variability in desaturase and elongase activities may play a role (9). Future research will no doubt elucidate the significance of those observations.

The significance of these preliminary observations is that we may have found fatty acid imbalance to be an important, hitherto unrecognized, DM risk factor that may be partially responsible for the high prevalence of DM in Native American communities (e.g. the Eskimos, the Pimas, and the Hawaiian Natives), and that the FA imbalance can be reversed fairly easily by a relatively simple intervention. Our results therefore suggest that counseling on specific fat consumption can enhance the intervention and prevention strategies employed in other populations (10, 13, 69).

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