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Lipoprotein Particle Distribution and Size, Insulin Resistance, and Metabolic Syndrome in Alaska Eskimos: The GOCADAN Study

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Abstract

Background—Metabolic syndrome (MS) is associated with dyslipidemia, and insulin resistance (IR) may be a main determinant of this dyslipidemia.

Objective—To determine how lipoprotein particle concentration and size are related to MS and IR in a population based-sample of Alaska Eskimos.

Design—Participants underwent a physical exam, personal interview, collection of biological specimens, and diagnostic tests.

Setting—This study was conducted in the Norton Sound Region of Alaska.

Participants—1,158 Inupiat Eskimo adults (women = 653, men = 505).

Main Outcome Measures—Lipoprotein particle profile was evaluated by nuclear magnetic resonance (NMR) and related to presence of MS and level of IR.

Results—Participants with MS (women = 105, men = 52) had a) significantly higher concentrations of all VLDLs and a larger VLDL size (women, $p = 0.007$; men, $p = 0.0001$); b) higher concentrations of small LDL (women, $p < 0.0001$; men, $p = 0.09$) and lower concentrations of large LDL (women, $p < 0.0001$), leading to a smaller overall LDL size (women, $p < 0.0001$; men, $p < 0.05$); c) significantly lower concentrations of large HDL (both genders, $p < 0.0001$) and an increase in intermediate (women, $p < 0.05$) and small HDL (women, $p < 0.0001$; men, $p < 0.004$). Lipoprotein profile with increasing HOMA-IR resembled that of individuals with MS.

Conclusions—In this population MS is characterized by lipoprotein distribution and size abnormalities independent of obesity, age, and other cardiovascular risk factors, including lipid concentration. IR seems the major determinant.

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Keywords

lipoprotein particle distribution; insulin resistance; metabolic syndrome; GOCADAN Study; Alaska Eskimos

INTRODUCTION

Metabolic syndrome (MS) is associated with dyslipidemia characterized by increased triglycerides, low HDL-cholesterol (C), and small LDL particles (1–2). Insulin resistance (IR) may be a main determinant of these lipid abnormalities (3). Each lipoprotein class consists of a continuous spectrum of particles with different size, density, metabolism, and atherogenic impact (4). The relationship of MS and particularly IR to the size and density of lipoprotein particles has been only partly investigated. Although some data relate MS and IR to LDL subfractions (5–7), more information is needed concerning VLDL and HDL subfractions in individuals with MS or IR. Previous studies were limited by small sample sizes, because the usual laboratory methods to measure lipoprotein subclasses require large sample volumes, are laborious, time-consuming (8–9), and unsuitable for large population samples.

Proton nuclear magnetic resonance (NMR), a new, rapid, cost-effective method (10–11) that measures the full spectrum of lipoprotein subfraction distribution and size at the same time on a small fresh or frozen sample, is suitable for use in large cohorts. In the current study, this method was used to investigate, for the first time, how the full spectrum of lipoprotein subclass distribution and size is related to MS and IR in a population based-sample age 18 and older. This study was undertaken to elucidate the role of MS and IR in cardiovascular disease, a topic of much debate (12).

METHODS

Study population

A total of 1,214 predominantly Inupiat Eskimos (537 men and 677 women) ≥ 18 years old from nine villages (including the town of Nome) in the Norton Sound Region of Alaska were examined in 2000–2004 for cardiovascular disease (CVD) and associated risk factors as part of the Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) study (13). Recruitment was conducted by family. In seven of the nine villages, an average of 82.6% of residents > 18 years participated.

Each participant underwent a physical examination, personal interview, collection of biological specimens, and other diagnostic tests. Data on blood measures were available for 1,160 participants. Of these participants, 3.3% (n = 32) had diabetes according to 1998 World Health Organization criteria (14) and were excluded from the analyses, for a cohort of 636 women and 524 men. Permission was granted by each community to conduct the study; written informed consent was obtained from all participants.

Physical and metabolic measurements

Anthropometry (height, weight, BMI, waist circumference) was performed with participants fasting, according to standard procedures. Abdominal obesity was defined using Adult Treatment Panel III (ATP III) criteria (1). Seated blood pressure was measured three times under standard conditions, with the mean value used as the final measure. Smoking and alcohol intake habits were evaluated via questionnaire; participants were categorized as current, former, and never-smokers (13).

Samples of whole blood, plasma, serum, and urine were collected from each participant and stored at −80° C. All laboratory methods have been published (13). LDL-C was calculated by the Friedewald formula (15).

Definitions of metabolic syndrome and IR

MS was defined according to ATP III criteria (1) as meeting three or more of the following criteria: waist circumference 102 cm for men, 88 cm for women; triglycerides ≥ 150 mg/dL (0.59 mmol/L); HDL-C < 40 mg/dL (1.30 mmol/L) for men, < 50 mg/dL (1.04 mmol/L) for women; arterial hypertension (systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg); fasting glucose ≥ 100 mg/dL (5.56 mmol/L).

Insulin resistance was estimated by HOMA index calculated as follows:

*Fasting plasma glucose (mmol/L)*fasting plasma insulin (mU/L)/22.5* (16).

Lipoprotein subfraction profile

Detailed lipoprotein subclassification (type, size, and concentration) was performed on plasma isolated by centrifuge (3,000 rpm, 10 min, 4° C) and stored at −80° C for the NMR spectroscopy (10), using a rapid, automated, commercially available assay (LipoScience Inc., Raleigh, NC, USA). Details of the NMR methodology have been published (10–11).

The data are presented as molar particle concentrations, because the focus of the study is on the occurrence of lipoprotein subclasses and their distribution rather than abnormal lipid composition.

To simplify the data evaluation, the 15 NMR lipoprotein subfractions (V1–V6, IDL, L1–L3, H1–H5) were grouped into three size groups (large, intermediate, and small) for each lipoprotein class. This resulted in the following spectra: large VLDL (V5 + V6, 60–220 nm), intermediate VLDL (V3 + V4, 35–60 nm), and small VLDL (V1 + V2, 27–35 nm); large LDL (L3, 21.3–22.7 nm), intermediate LDL (L2, 19.8–21.2 nm) and small LDL (L1, 18.3–19.7 nm); and large HDL (H4 + H5, 8.8–13 nm), intermediate HDL (H3, 8.2–8.8 nm), and small HDL (H1 + H2, 7.3–8.2 nm) (11). Data on IDL particles (25 nm) are not reported in this study.

Statistical analysis

All data are expressed as mean ± SD. The natural log transformation was applied to variables which were highly skewed. The means of the actual measured data are shown in the tables and figures. However, the transformed variables have been used in all comparisons, analysis of variance (ANOVA), regressions, and correlation analyses. Comparisons between groups were evaluated by Student's *t*-test and ANOVA. The p-values were adjusted for the variables known to influence lipid metabolism (age, BMI, systolic blood pressure [SBP], smoking habits) and corrected by the Bonferroni method for multiple comparisons. Data on VLDL particle concentrations were adjusted also for triglyceride levels and data on LDL and HDL particle concentrations were adjusted for LDL-C and HDL-C levels, respectively. Relationships between HOMA-IR index and lipoprotein subclass concentration and size were evaluated using Pearson's correlation analysis, adjusted for the same covariates as above. All probability values were 2-tailed, and values less than 0.05 were considered statistically significant.

RESULTS

Characteristics of the population are shown (Table 1). Average age was 43 for women and 42 for men, and 18% had impaired glucose regulation (mainly IFG). A large percentage of the population were smokers (63% of the men and 57% of the women were current smokers).

Women were significantly more overweight and insulin resistant than the men. However, the women had lower blood pressure levels and higher HDL-C concentrations.

Gender significantly influenced lipoprotein particle concentration and size (Table 2); women, although more overweight and more insulin resistant than men, had significantly greater concentrations of large LDL particles (550 ± 187 vs 494 ± 175 nmol, $p < 0.0001$), significantly lower concentrations of intermediate and small LDL particles ($p < 0.0001$ for both), and a larger LDL size ($p < 0.0001$). Women also had greater concentrations of large and intermediate HDL particles ($p < 0.0001$ and $p < 0.006$, respectively) and a larger HDL size ($p < 0.0001$).

Lipoprotein subfraction concentrations and particle sizes were compared in men and women with (n = 159) and without (n = 969) MS (Figure 1a). All comparisons were adjusted for the covariates described above. The concentrations of all VLDL-C subfractions were higher in women and men with MS; in these subjects, more VLDL were large or intermediate in size (34.5%) compared with individuals without MS (in which 28% of the VLDL were large or intermediate in size). Consequently, VLDL size was greater in both women and men with MS ($p = 0.007$, $p = 0.0001$, respectively). LDL particle concentrations were also higher in women and men with MS (Figure 1b) but, in this case, there was a shift in the distribution: large subfractions were lower (women, $p < 0.0001$; men, $p = 0.12$), the intermediate and, particularly, the small particles were higher (almost doubled) (women, $p < 0.0001$; men, $p = 0.09$); thus, there was a significant reduction of LDL size (women, $p < 0.0001$; men, $p = 0.05$). HDL particle concentrations, as a whole, did not differ in those with and without MS; however, there was a different HDL subfraction distribution in those with MS that was characterized by a decrease in the largest particles (both genders, $p < 0.0001$), an increase in the intermediate particles ($p = 0.05$ only for women), and a tendency toward increased small particles (women, $p = 0.06$; men, $p = 0.09$ for men) (Figure 1c). This particle distribution was reflected in a significant decrease in HDL size in individuals with MS (women, $p < 0.0001$; men, $p = 0.004$) (Figure 1c). Adjusting for alcohol intake did not change the results.

To evaluate whether the abnormalities in lipoprotein subfraction distribution and size in individuals with MS could be linked to the IR typical of this syndrome, the population was stratified by tertile of HOMA-IR index (< 1.47, 1.47–2.40, > 2.40). Differences in lipoprotein subfraction concentration and size were evaluated separately by gender, adjusted as reported before (Table 3 and Table 4). Increasing tertiles of HOMA-IR in women were characterized by the same pattern of lipoprotein particle distribution and size observed in both genders with MS (Table 3). In men, the trend was similar, but statistical significance was reached for differences in small VLDL ($p < 0.05$), VLDL size ($p = 0.0002$), and large and intermediate HDL ($p = 0.01$ for both). Comparisons of lipoprotein subfractions by tertile of IR were repeated in those without MS and similar changes were seen (data not shown).

Correlations among HOMA-IR index and lipoprotein particle concentration and size were also evaluated adjusting for the same variables as before (Table 5). There was a significant direct correlation between HOMA-IR index, large VLDL concentration, and VLDL size, while intermediate and small VLDL were inversely related to IR. For LDL there was a significant direct correlation with both intermediate and small particles, while for HDL, HOMA-IR index was significantly and positively correlated only with the concentration of intermediate-size HDL ($p < 0.006$). Adjusting for alcohol intake did not change the results.

DISCUSSION

In this study we have evaluated the impact of MS and IR on plasma lipoprotein subclass distribution and size. To our knowledge, this has been the first demonstration in a large population-based sample and independent of confounding factors (i.e., age, BMI, systolic

blood pressure, and smoking habits) that MS is associated with a spectrum of lipoprotein distribution and size abnormalities, as measured by NMR spectroscopy. This relationship is also independent of plasma lipid concentrations and, therefore, these abnormalities may represent an additive cardiovascular risk for individuals with MS. Because similar relations were observed with IR, our results suggest that IR may be a major determinant of these lipoprotein abnormalities.

These results extend and reinforce on a larger scale data obtained by previous studies using traditional methods for lipoprotein fractionation. It is known that MS is associated with an increase in plasma triglycerides, low HDL-C concentration, and increased levels of small, dense LDL (2).

Less information is available on other lipoprotein subclass alterations. Our data have shown that in both genders there is an increase in all VLDL particle concentrations and in VLDL size, probably due to an increase of the largest particles. These changes may contribute to the higher cardiovascular risk of individuals with MS. According to Colhoun et al. (17), a larger VLDL size was significantly associated with coronary calcification in nondiabetic individuals. Also in a prospective study (18), large VLDL were positively associated with coronary artery disease (CAD) severity, independently of plasma triglyceride levels.

The current study shows that in both genders MS is associated with a decrease in large and an increase in small LDL subfraction concentrations, with a subsequent reduction in LDL size, independent of LDL-C levels. The relevance of an increase in small LDL as a cardiovascular risk factor has been supported by cross-sectional (19–23) and prospective studies (24–26).

Data on HDL subclass distribution show that individuals with MS have fewer large and more intermediate and small HDL particles. In our population, differences in HDL subfraction distribution seem less prominent in men but this finding may have been influenced by the sample: fewer men in this sample had MS. These HDL particle abnormalities may also contribute to the high cardiovascular risk of people with MS. An association between small HDL particles and severity of coronary disease has been reported (27–29). Moreover, both small HDL particles and larger VLDL size were found to be significant predictors of type 2 diabetes in the IRAS study (7), reinforcing the role of these lipoprotein abnormalities from a pathophysiologic and clinical point of view.

The other main finding of our study is the relationship between IR and abnormalities in lipoprotein distribution and size. Previous studies support the relationship between IR and LDL particle concentration and size (6–7,30). Less information exists on the relationship between IR and VLDL/HDL particles. In our study, increasing IR was associated with VLDL and HDL particle concentrations and size abnormalities similar to the ones observed in subjects with MS, with a shift toward a worse profile in terms of cardiovascular risk. A similar relationship was also seen in those with IR but no MS. These results are similar to those of other studies using traditional methods (31) or NMR (30). The present study extends these observations to a larger population-based sample.

Our data also provide additional information on gender differences in lipoprotein distribution. Women in our study, although more obese and insulin resistant than the men, had lower levels of small LDL. This gender difference in atherogenic LDL subclass profile has been shown by Freedman et al. (32) in the Framingham Offspring Study using NMR and in other smaller studies (23,33–34). Changes in lipoprotein profile with MS and IR were greater in women than in men. This may be due to the higher percentage of women in our sample with MS and IR.

This study was limited by the following factors. The population studied was all Alaska Eskimos; the homogeneity of this population is an advantage for examining metabolic

relationships. This population has high levels of cardiovascular disease, and the lipoprotein subclass distribution abnormalities found in this population may explain, at least in part, this increased risk. However, these observations must be confirmed in other populations. This study was also limited by its cross sectional design. Relations between MS and lipoprotein subfractions need to be examined in a longitudinal analysis, which will be possible after the second GOCADAN exam is completed. Finally, the data were obtained using NMR methodology. This method has the advantage of quickly providing simultaneously a quantification of both size and concentration of different lipoprotein subclasses without requiring physical separation. Lipoprotein subclass profile determined by NMR and established methods have been shown to correspond well (10–11,35–36).

In conclusion, our data show that MS is characterized by a spectrum of VLDL, LDL, and HDL distribution and size abnormalities, independent of age, BMI, SBP, smoking, lipid concentrations, and that IR may be a major determinant of these lipoprotein subfraction abnormalities. These abnormalities may explain the high cardiovascular risk of people with MS beyond the traditional cardiovascular risk factors, which include abnormalities in lipid concentrations. Measures are needed in this and other populations to prevent and reverse the lifestyle changes that lead to these abnormalities and subsequent cardiovascular disease.

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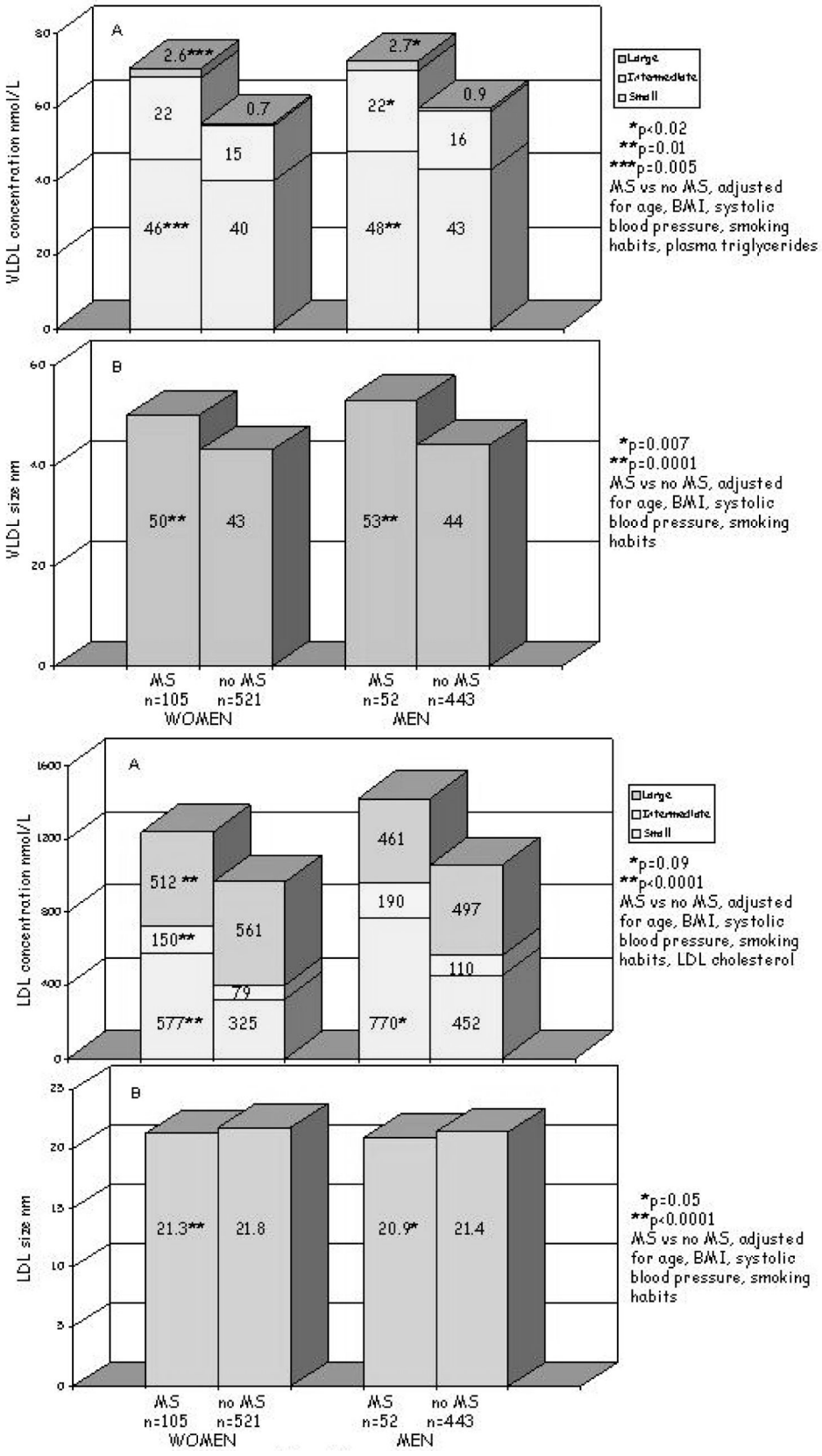

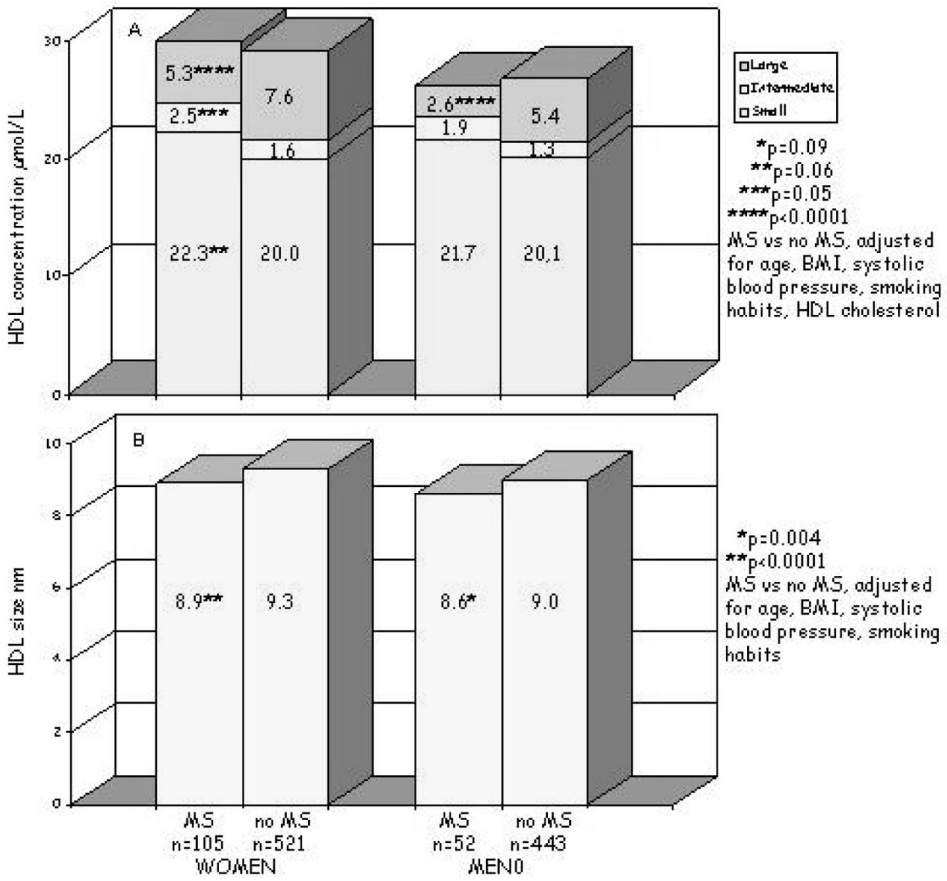

Figure 1.

Figure 1a. Plasma VLDL particle concentrations (A) and size (B) in individuals with metabolic syndrome (MS) and without metabolic syndrome (no MS), by gender. P adjusted for age, BMI, systolic blood pressure, smoking habits, and plasma triglycerides.

Figure 1b. Plasma LDL particle concentrations (A) and size (B) in individuals with metabolic syndrome (MS) and without metabolic syndrome (no MS), by gender. P adjusted for age, BMI, systolic blood pressure, smoking habits, and LDL cholesterol.

Figure 1c. Plasma HDL particle concentrations (A) and size (B) in individuals with metabolic syndrome (MS) and without metabolic syndrome (no MS), by gender. P adjusted for age, BMI, systolic blood pressure, smoking habits, and HDL cholesterol.

Table 1

Characteristics of the GOCADAN population, by gender and MS status, N = 1,160

	Women (n = 636)			Men (n = 524)		
	Without MS	**With MS**	**P value**	**Without MS**	**With MS**	**P value**
Age (years)	40.6±15.50	47.7±14.85	<.0001	40.9±15.36	47.4±15.79	0.0037
BMI (kg/m^2)	27.1±5.41	34.7±5.67	<.0001	25.6±4.08	33.7±5.34	<.0001
Waist circumference (cm)	84.7±12.20	102.6±12.02	<.0001	84.9±10.02	105.3±11.54	<.0001
Systolic blood pressure (mmHg)	114.4±13.44	128.4±17.79	<.0001	120.1±12.40	129.8±11.18	<.0001
Diastolic blood pressure (mmHg)	73.2±8.62	79.9±9.88	<.0001	77.5±9.14	82.6±8.31	<.0001
Plasma insulin (pmol/L)	67.0±39.23	111.3±79.41	<.0001	56.2±39.44	111.3±61.69	<.0001
HOMA-IR index	2.2±1.57	4.0±3.26	<.0001	1.9±1.51	4.0±2.22	<.0001
Plasma glucose (mmol/L)	5.0±0.50	5.5±0.59	<.0001	5.1±0.55	5.6±0.52	<.0001
Plasma cholesterol (mmol/L)	5.2±1.06	5.5±1.00	0.0054	5.1±1.04	5.3±1.06	0.0769
Plasma triglycerides (mmol/L)	1.2±0.66	2.3±0.94	<.0001	1.3±0.74	2.5±1.05	<.0001
LDL cholesterol (mmol/L)	3.0±0.93	3.1±0.91	0.0785	3.0±0.93	3.2±1.00	0.2941
HDL cholesterol (mmol/L)	1.7±0.45	1.4±0.42	<.0001	1.5±0.46	1.1±0.29	<.0001
Use of antihypertensive drugs (%)	7.1	33.3	<0.001	8.6	35.1	<0.001
Use of hypolipidemic drugs (%)	3.0	9.8	.0041	2.4	17.5	<0.001
Current smokers (%)	60.9	48.0	.0210	65.6	45.6	.0057
Former smokers (%)	19.2	32.4	.0052	17.3	36.9	.0011
Never smokers (%)	19.9	19.6	1.000	17.1	17.5	.8534

Notes. Data are mean ± SD. The GOCADAN population consists of Alaska Eskimos of the Norton Sound Region. Data are from the baseline exam.

Table 2

Plasma lipoprotein particle concentrations and size, (Alaska Eskimos ages ≥ 18 years, N = 1,128)

	Women (n = 623)	Men (n = 505)	P-Value
Total VLDL particles (nmol/L)	58.8 ± 27.2	61.5 ± 28.3	0.10
Large (nmol/L)	1.6 ± 2.2	1.7 ± 2.1	0.40
Intermediate (nmol/L)	15.8 ± 11.6	16.3 ± 12.1	0.52
Small (nmol/L)	41.3 ± 18.7	43.5 ± 19.3	0.05
VLDL size (nm)	45.4 ± 9.0	45.7 ± 9.6	0.82
Total LDL particles (nmol/L)	1,036 ± 298	1,118 ± 336	<0.0001
Large (nmol/L)	550 ± 187	494 ± 175	<0.0001
Intermediate (nmol/L)	92 ± 65	119 ± 70	<0.0001
Small (nmol/L)	371 ± 245	486 ± 269	<0.0001
LDL size (nm)	21.7 ± 0.64	21.4 ± 0.60	<0.0001
Total HDL particles (μmol/L)	29.6 ± 6.6	27.1 ± 5.7	<0.0001
Large (μmol/L)	7.2 ± 3.9	5.1 ± 3.7	<0.0001
Intermediate (μmol/L)	2.1 ± 3.1	1.8 ± 2.9	0.006
Small (μmol/L)	20.4 ± 5.2	20.2 ± 4.7	0.60
HDL size (nm)	9.2 ± 0.5	9.0 ± 0.5	<0.0001

Data are mean ± SD.

Table 3

Lipoprotein particle concentrations and size in women (Alaska Eskimos ages ≥ 18 years), by tertile of HOMA–IR

	HOMA-IR			
	< 1.47 (n = 207)	**1.47–2.40 (n = 208)**	**> 2.40 (n = 208)**	**P Adjusted***
VLDL (nmol/L)				
Large	0.6 ± 1.4	0.8 ± 1.5	1.6 ± 2.3	0.003
Intermediate	13.8 ± 11.7	15.5 ± 10.9	17.8 ± 12.1	0.62
Small	38.8 ± 17.9	41.0 ± 19.5	43.9 ± 18.9	0.18
VLDL size (nm)	42.3 ± 7.1	44.1 ± 9.6	47.2 ± 8.9	<0.001
LDL (nmol/L)				
Large	558 ± 178	565 ± 187	535 ± 193	0.02
Intermediate	74 ± 52	82 ± 51	117 ± 77	0.0001
Small	310 ± 199	332 ± 201	459 ± 289	0.0006
LDL size (nm)	21.8 ± 0.6	21.8 ± 0.6	21.5 ± 0.7	0.01
HDL (μmol/L)				
Large	8.0 ± 3.9	7.5 ± 3.8	6.2 ± 3.6	0.0005
Intermediate	1.8 ± 3.1	1.4 ± 2.7	2.1 ± 3.4	0.91
Small	19.2 ± 4.8	20.3 ± 5.3	21.6 ± 5.3	0.02
HDL size (nm)	9.4 ± 0.5	9.3 ± 0.4	9.0 ± 0.5	0.0002

Data are mean ± SD.

*Adjusted for age, BMI, systolic blood pressure, smoking habits, plasma triglycerides (VLDL subfractions), LDL-cholesterol (LDL subfractions), and HDL-cholesterol (HDL subfractions).

Lipoprotein particles were measured using nuclear magnetic resonance.

Table 4

Lipoprotein particle concentrations and size in men (Alaska Eskimos ages ≥ 18 years), by tertile of HOMA–IR

	HOMA-IR Index			
	< 1.47 (n = 168)	**1.47–2.40 (n = 168)**	**> 2.40 (n = 169)**	**P Adjusted***
VLDL (nmol/L)				
Large	0.7 ± 1.6	1.0 ± 1.8	1.4 ± 2.7	0.28
Intermediate	13.4 ± 11.1	17.0 ± 13.1	18.4 ± 12.0	0.21
Small	40.5 ± 17.9	44.7 ± 20.3	45.6 ± 18.9	0.05
VLDL size (nm)	41.9 ± 8.5	45.9 ± 9.4	47.3 ± 10.1	<0.0002
LDL (nmol/L)				
Large	489 ± 162	511 ±175	479 ± 187	0.36
Intermediate	99 ± 50	112 ± 65	146 ± 82	0.06
Small	410 ± 208	465 ± 260	583 ± 307	0.37
LDL size (nm)	21.5 ± 0.5	21.4 ± 0.6	21.2 ± 0.6	0.42
HDL (μmol/L)				
Large	6.2 ± 3.9	4.8 ± 3.4	4.3 ± 3.2	0.01
Intermediate	1.2 ± 3.1	1.3 ± 2.4	1.7 ± 3.0	0.01
Small	19.7 ± 4.6	20.2 ± 4.2	20.7 ± 5.1	0.79
HDL size (nm)	9.1 ± 0.5	8.9 ± 0.5	8.8 ± 0.5	0.33

Data are mean ± SD.

*Adjusted for age, BMI, systolic blood pressure, smoking habits, plasma triglycerides (VLDL subfracions), LDL-cholesterol (LDL subfractions), and HDL-cholesterol (HDL subfractions).

Lipoprotein particles were measured using nuclear magnetic resonance.

Table 5

Pearson's coefficient between HOMA-IR index and nuclear magnetic resonance lipoprotein subfractions

	r*	P
VLDL (nmol/L)		
Large	0.10	0.006
Intermediate	−0.09	0.02
Small	−0.l7	<0.0001
VLDL size (nm)	0.20	<0.0001
LDL (nmol/L)		
Large	−0.05	0.07
Intermediate	0.12	<0.0001
Small	0.10	0.001
LDL size (nm)	−0.05	0.09
HDL (μmol/L)		
Large	−0.005	0.89
Intermediate	0.10	0.006
Small	−0.04	0.25
HDL size (nm)	−0.04	0.34

*Partial Pearson's coefficients were calculated adjusting for age, BMI, systolic blood pressure, smoking habits, plasma triglycerides (VLDL subfractions), LDL-cholesterol (LDL subfractions), and HDL-cholesterol (HDL subfractions).