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Original Research Article

Pleiotropic Effects on Subclasses of HDL, Adiposity, and Glucose Metabolism in Adult Alaskan Eskimos

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ABSTRACT The aim of this study was to analyze the heritability and the presence of pleiotropic effects on subfractions of high-density lipoproteins (HDLs) as measured by nuclear magnetic resonance (NMR), parameters for adiposity, and glucose metabolism in adult Alaskan Eskimos. The present family study included 1,214 adult Alaskan Eskimos (537 male/677 female). Body weight, height, circumferences, selected skinfolds, and blood pressure were measured in all participants. Blood samples were collected under fasting conditions for the isolation of plasma. Glucose, insulin, subclasses and size of lipoproteins, triglycerides, total, and HDL cholesterol and lipoprotein (a) were measured in plasma. HbA1c was measured in total blood. Univariate and bivariate quantitative genetic analyses were conducted between HDL subclasses and size and the anthropometric and biochemical measures using the variance decomposition approach. Variation in all the analyzed traits exhibits a significant genetic component. Heritabilities ranged between 0.18 ± 0.11 for LDL_2 (intermediate) and 0.89 ± 0.07 for small HDL. No common genetic effects were found on the HDL subclasses (small, intermediate, and large). Small HDL particles were genetically correlated with LDL particles and HbA1c. Negative genetic correlations were observed between intermediate and large HDL subfractions, HDL size and measures of adiposity, and LDL and parameters for glucose metabolism (HbA1, insulin). These observations confirm the presence of possible pleiotropic effects on HDL, adiposity, and cardiovascular risk factors and provide novel insight on the relationship between HDL subclasses, adiposity, and glucose regulation. Am. J. Hum. Biol. 22:444–448, 2010.

During 1955–1965, Alaska natives had lower mortality rates from cardiovascular disease (CVD) than Caucasian men and women living in the same environment. Since then, an increase in this chronic condition has been documented among Alaskan Eskimos (Maynard et al., 1967). A study by Bjerregaard et al. in 2004 reported that Inuit subjects, living in Denmark and West Greenland, differ little from western populations, and levels of cholesterol and triglycerides varied in association with westernization, diet, alcohol consumption, and smoking.

A number of studies across different populations have shown that levels of cholesterol bound to high-density lipoproteins (HDL-C) are associated with the risk for coronary artery disease (Marcil et al., 2004). HDLs seem to have a complex function. They are thought to mediate the uptake of peripheral cholesterol and exchange core lipids with other lipoproteins. These lipoproteins may modulate vasomotor function thrombosis, cell-adhesion molecule expression, platelet function, nitric oxide release, endothelial cell apoptosis, and proliferation (Morgan et al., 2004). Prospective studies have demonstrated that low-HDL levels are strong predictors for CVD, independently of low-density lipoprotein (LDL) levels (Marcil et al., 2004; Rashid et al., 2007). The HDLs are composed of particles of diverse size, each with different capacity to confer protection. The large particles, known as HDL_2, are less dense, cholesterol, and phospholipid enriched and seem to be more protective than the denser, smaller, and relatively protein rich HDL_3 (Castelli et al., 1986; Freedman et al., 2003; Rashid et al., 2007; Rosenson et al., 2002; von Eckardstein and Assmann, 2001). Obesity is frequently associated with low concentrations and adverse distribution of HDL particles. Metabolic abnormalities present in obese subjects such as hypertriglyceridemia are frequently associated with reduced HDL levels and insulin resistance (Rashid et al., 2007, Ginsberg, 2000).

Findings of previous genetic studies on the components of the metabolic syndrome have identified the presence of pleiotropy or shared genetic effects, indicating that some phenotypes may be influenced by the same gene or suite of genes (Kissebah et al., 2000; Martin et al., 2004). The extent of pleiotropy is expressed in terms of genetic correlations between pairs of phenotypes (Martin et al., 2004).

The aim of this study was to explore the extent of pleiotropy on subfractions of HDL and risk factors for CVD, including body fat amount and distribution, and parameters of glucose metabolism in adult Alaska Eskimos.

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MATERIALS AND METHODS

Study design

The Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) is focused on the genetic determinants of CVD and its associated risk factors. A sample of 1,214 men and women, 18 years and older, was recruited from nine villages located at the Norton Sound region. In seven of the nine villages, an average of 82.6% of the eligible residents participated (Ebbesson et al., 2006). Screenings were terminated early in an additional village, when it was determined that the village was not able to support the data collection due to absent villagers for the fishing season, and, in Nome, the study reached its total recruitment goal. Participants belonged primarily to the following groups: 75.8% Inupiat, 9.4% mixed Eskimos, 7.7% Yupik Eskimos, and 2.8% Aleutians. Other participants were identified as Siberian Yupik Eskimos, mixed Alaskan Natives, and other Native American groups. All family members, at least 18 years of age, were recruited, and most of them are members of a large extended pedigree. All participants signed an informed consent form describing the procedures. A clinical history was obtained from each participant. Details on the design and methods have been published elsewhere (Howard et al., 2005; Nobmann et al., 2005).

Collection of phenotypes

Plasma samples were stored at -70°C. Measurements included a lipid panel by conventional enzymatic chemistry analyzer as well as a detailed lipoprotein subclass type, size, and concentration by nuclear magnetic resonance (NMR) spectroscopy (Otvos et al., 2002). Fractions were analyzed as follows: subclasses 1 and 2 are considered small particles, fraction 3 is intermediate, and fractions 4 and 5 correspond to large particles. Laboratory determinations included assays for glucose, lipids, hemoglobin A1c (HbA1c), lipoprotein (a) (Lp (a)), and lipoprotein subfraction levels. All measurements were performed by reference methods. LDL subfractions were measured by NMR and reported as described by Otvos et al. (2002).

Body composition was analyzed by bioelectrical impedance analysis using a RJL bioelectric impedance meter Model No. B1A101. As recommended by the manufacturer, body composition was estimated using the following equation:

$$\text{Fat-free tissue (FFT)} = 13.74 + 0.25 \times (\text{height squared}/\text{resistance}) + 0.30 \times (\text{weight}) - 0.14 \times (\text{age}) + 6.18 \times (\text{sex})$$

where height is in cm, weight in kg, age in years, and sex (0 = female, 1 = male).

Fat mass was estimated by subtracting FFT from body weight, and percent of body fat was calculated as follows:

$$\text{Percent of fat} = (\text{FM}/\text{weight}) \times 100$$

Anthropometric measurements included weight, height, waist, and hip circumferences. Weight was measured on a calibrated balance scale, with the subject wearing a scrub suit or light clothing. Results were recorded to the nearest pound. The participant was instructed to stand as straight as possible, and height was recorded to the nearest inch. Supine waist girth was measured at the level of the umbilicus with the subject supine. Erect hip girth was measured at the level of maximal protrusion of the gluteal muscles. Triceps and subscapular skinfolds were measured according to techniques described by Lohman et al. (1988). Skinfold measurements were read to the nearest 1 mm. Blood pressure was measured in the resting state using the peak of three measurements with a Baum mercury sphygmomanometer, with the means of the last two measurements used for analyses. All measurements were performed on the right side of the body by trained personnel.

Statistical analysis

Quantitative genetic analyses were conducted using a maximum likelihood-based, variance decomposition approach implemented in SOLAR (Almasy and Blangero, 1998). Univariate analyses were conducted to estimate the heritability of the analyzed variables and included age, sex, and their interaction, use of lipid lowering medication, and smoking as covariates. The use of lipid-lowering medication was reported during the initial interview as current user or not user. Smoking was classified as a dichotomous variable as well, coded as current smoker, or noncurrent smoker. Heritability can be calculated as the proportion of the trait variance that results from the additive genetic effects ($h^2 = \sigma^2_G/\sigma^2_P$). The likelihood of the model is estimated and compared with the likelihood of a model in which the effect is absent (heritability of zero). The asymptotical distribution is a [1/2]:[1/2] mixture of a χ^2 variable with one degree of freedom and a point mass at zero. Significance of the residual heritability estimates was assessed by likelihood ratio (Self and Lian, 1987).

To investigate shared genetic effects (pleiotropy) between pairs of phenotypes, bivariate analyses were performed. For this analysis, the phenotypic variance (σ^2_P) was divided into two major components, the additive genetic (σ^2_G) and nongenetic (σ^2_E), or environmental components:

$$\rho_P = \rho_G \sqrt{h_1^2}\sqrt{h_2^2} + \rho_E \sqrt{(1-h_1^2)}\sqrt{(1-h_2^2)}$$

where h_1^2 and h_2^2 are heritabilities of the two studied phenotypes, ρ_P is the phenotypic correlation, ρ_G is the genetic correlation, and ρ_E represents the environmental correlation (i.e., residual correlation). Evidence of pleiotropy is indicated by additive genetic correlations that are significantly different from zero (Williams-Blangero et al., 1993).

RESULTS

Information on the measured traits in this study was available for 1,214 participants. Table 1 provides descriptive data of the analyzed variables according to sex and provides the heritabilities of each trait. Mean values of blood pressure, glucose, LDL, HDL, triglycerides, and the proteins assayed in this study were within the normal range. The mean values for body mass index (BMI) and waist circumference indicate the presence of overweight and central adiposity among the studied sample. According to the recommended cut-off points for overweight (BMI $>$ 25 and $<$30) and obesity (BMI $\geq$ 30), 29.1% of women and 3.4% of men in this study were overweight and 39.2% of women and 20.9% of men were obese. The prevalence of abdominal obesity defined as waist circumference $>$90 cm for men and $>$80% for women was 36.8%

TABLE 1. Descriptive data (Mean ± SD) and heritability of the analyzed phenotypes

Variable	Male (N = 537)	Female (N = 677)	h^2	S.E.	P
Age (years)	30.5 ± 20.2	30.0 ± 21.1			
Weight (kg)	76.2 ± 14.8	71.1 ± 15.9	0.56	0.09	5.5E-11
BMI	26.4 ± 4.6	28.6 ± 5.9	0.51	0.09	2.5E-10
Waist (cm)	87.7 ± 12.0	88.7 ± 13.4	0.49	0.09	4.5E-09
% body fat	31.5 ± 6.5	43.2 ± 5.7	0.55	0.09	3.70E-013
WHR	0.87 ± 0.07	0.84 ± 0.06	0.34	0.09	3.2E-05
Tricipital skinfold (mm)	12.8 ± 6.1	21.7 ± 7.7	0.48	0.09	4.5E-10
Subscapular skinfold (mm)	14.6 ± 7.3	20.8 ± 8.9	0.57	0.09	9.1E-13
Systolic blood pressure (mm Hg)	121.2 ± 13.1	117.7 ± 15.9	0.46	0.09	1.1E-08
Diastolic blood pressure (mm Hg)	77.8 ± 9.3	74.1 ± 9.1	0.45	0.09	1.0E-07
Glucose (mmol/l)	5.1 ± 0.5	5.0 ± 0.5	0.31	0.09	2.7E-05
Insulin	9.4 ± 8.3	11.2 ± 7.9	0.24	0.09	0.002
HbA1c	5.5 ± 0.4	5.4 ± 0.4	0.47	0.09	4.5E-09
Total cholesterol (mmol/l)	5.06 ± 1.0	5.20 ± 1.0	0.45	0.09	2.90E-008
HDL (mmol/l)	1.4 ± 0.4	1.6 ± 0.4	0.57	0.09	7.90E-008
LDL_1 (mmol/l)	0.27 ± 0.25	6.6 ± 8.4	0.34	0.12	0.008
LDL_2 (mmol/l)	0.56 ± 0.46	0.45 ± 0.48	0.18	0.11	0.049
LDL_3 (mmol/l)	1.69 ± 0.82	1.97 ± 0.86	0.18	0.09	0.023
LDL total (mmol/l)	3.03 ± 0.92	2.97 ± 0.90	0.35	0.09	1.6E-05
LDL particle (nmol/l)	1054.2 ± 250.2	1027.4 ± 241.0	0.44	0.09	3.9E-08
LDL size (nm)	21.2 ± 0.5	21.4 ± 0.5	0.40	0.11	0.000016
Triglycerides (mmol/l)	1.37 ± 0.66	1.39 ± 0.65	0.56	0.04	2.7E-09
HDL large (mg/dl)	0.54 ± 0.34	0.74 ± 0.38	0.39	0.10	1.5E-07
HDL intermediate (mg/dl)	0.11 ± 0.10	0.12 ± 0.12	0.43	0.10	7.0E-07
HDL small (mg/dl)	0.51 ± 0.11	0.52 ± 0.12	0.20	0.10	0.007
HDL size (nm)	9.0 ± 0.5	9.2 ± 0.5	0.89	0.07	9.0E-07
Lp (a) (mg/dl)	0.49 ± 0.48	0.39 ± 0.56	0.89	0.07	1.2E-22

TABLE 2. Genetic correlations between small, intermediate and large HDL and cardiovascular risk factors in Alaskan Eskimos

	Small HDL		Intermediate HDL		Large HDL	
	ρ Genetic ± SE	P	ρ Genetic ± SE	P	ρ Genetic ± SE	P
Weight	0.05 ± 0.14	0.67	**0.36 ± 0.15**	**0.02**	−0.07 ± 0.15	0.63
BMI	0.04 ± 0.15	0.28	**0.40 ± 0.16**	**0.01**	−0.18 ± 0.13	0.17
% Body fat	0.03 ± 0.14	0.81	**0.39 ± 0.15**	**0.01**	**−0.36 ± 0.11**	**0.003**
Waist	0.05 ± 0.14	0.70	**0.35 ± 0.16**	**0.03**	−0.19 ± 0.11	0.14
WHR	−0.03 ± 0.17	0.85	0.27 ± 0.18	0.14	−0.16 ± 0.13	0.22
Tricipital S	−0.11 ± 0.17	0.44	**0.50 ± 0.18**	**0.005**	**−0.49 ± 0.12**	**0.0008**
Subscapular S	−0.04 ± 0.14	0.90	**0.56 ± 0.15**	**0.0003**	**−0.31 ± 0.14**	**0.04**
Systolic BP	−0.25 ± 0.20	0.17	**0.46 ± 0.16**	**0.008**	**−0.30 ± 0.12**	**0.02**
Diastolic BP	−0.02 ± 0.17	0.90	**0.57 ± 0.15**	**0.0006**	0.08 ± 0.15	0.60
Glucose	0.18 ± 0.20	0.37	−0.15 ± 0.21	0.49	−0.19 ± 0.14	0.16
Insulin	0.34 ± 0.19	0.10	−0.08 ± 0.23	0.70	**−0.29 ± 0.19**	**0.04**
HbA1c	**0.35 ± 0.17**	**0.03**	−0.12 ± 0.17	0.47	**−0.41 ± 0.17**	**0.02**
Totcholesterol	**0.41 ± 0.15**	**0.01**	−0.15 ± 0.13	0.25	**−0.28 ± 0.13**	**0.05**
LDL1	0.14 ± 0.23	0.52	−0.14 ± 0.18	0.43	**−0.67 ± 0.11**	**0.0001**
LDL 2	0.16 ± 0.19	0.38	−0.14 ± 0.18	0.43	**0.42 ± 0.12**	**0.003**
LDL 3	**0.31 ± 0.15**	**0.05**	−0.14 ± 0.11	0.42	**−0.39 ± 0.12**	**0.006**
LDL	0.22 ± 0.16	0.16	−0.14 ± 0.18	0.42	**−0.43 ± 0.17**	**0.03**
LDL particles	**0.45 ± 0.15**	**0.006**	0.04 ± 0.28	0.80	0.17 ± 0.10	0.11
LDL size	0.12 ± 0.16	0.45	**−0.58 ± 0.13**	**0.0007**	**−0.35 ± 0.11**	**0.005**
Triglycerides	0.29 ± 0.15	0.07	0.23 ± 0.13	0.16	0.06 ± 0.14	0.69
HDL large	0.01 ± 0.19	0.95	−0.28 ± 0.15	0.08		
Lp (a)	−0.07 ± 0.15	0.63	−0.22 ± 0.14	0.10	**0.52 ± 0.10**	**0.01**

P values < 0.05 in bold.

and 70%, respectively. The present sample included 721 smokers and 69 participants using lipid-lowering medication. As observed, all phenotypes had a significant genetic component after adjustment for sex, age, use of lipid lowering medication, and smoking, with heritabilities ranging from 0.18 to 0.89.

Small HDLs represent the sum of fractions 1 and 2 measured by NMR (Table 2). These HDL subtypes were not correlated with any anthropometric parameter. This HDL fraction had significant genetic correlation with HbA1c, LDL particle concentration, and LDL_3 levels. No association was found between the small subfraction and other HDL types. Intermediate size HDL corresponds to fraction 3 of HDL as measured by NMR. This HDL form had positive significant genetic correlations with parameters for adiposity including body weight, BMI, waist circumference, percentage of body fat, and skinfolds. In our study, we found significant genetic correlation (ρ_G) values between intermediate HDL and blood pressure measurements. Significant negative genetic correlations were observed between this HDL subclass and LDL size, suggesting the presence of genetic effects on both traits.

Large HDL is the sum of fractions 4 and 5 as measured by NMR. As observed in Table 2, there are significant inverse genetic correlations with parameters of body fat, levels of insulin, HbA1c, LDL subclasses, and size. A positive genetic correlation was found with Lp(a) levels as well.

Genetic correlations between HDL size and the studied phenotypes are summarized in Table 2. This phenotype had inverse genetic correlations with BMI, percentage of body fat, and subscapular skinfold. Insulin, HbA1c, and LDL measurements were inversely correlated with HDL size. Circulating levels of total HDL were genetically correlated with subscapular skinfold and glucose levels.

DISCUSSION

Mean values for BMI, waist circumference, HDL-C, and total cholesterol in this study resemble findings in previous investigations among Inuit in three countries (United States, Canada, and Greenland) reported by Young et al. (2007). These investigators used the term Inuit as a collective term encompassing various regional groups, including the Central and Siberian Yupik and Inupiat in Alaska, Canadian Inuit, and Greenlanders (Young et al., 2007). The sample studied in the present investigation had a high-obesity rate when compared with data published for the region. According to the Alaska Division of Public Health, about 55% of men and 38% of women living in the rural region of Alaska are overweight and 16% and 24%, respectively, are obese (Alaska Division of Public Health, 2003).

Lipoproteins are believed to be determined by the interaction between numerous modest and occasionally large genetic effects and environmental factors (Pollex and Hegele, 2007). Significant heritability has been found in our study for cardiovascular risk factors such as body weight, BMI, glucose, lipoproteins, and triglycerides across different populations and investigation models (Edwards et al., 1999; North et al., 2003; Rainwater et al., 1997; Velasquez-Melendez et al., 2007), implying that a significant proportion of the variation in these traits is due to genetic factors. In this study, small HDL had the highest heritability, indicating that 89% of its variation is attributable to additive genetic effects, as opposed to large HDL with only 43%.

In the past, it was difficult to accurately quantify the lipoprotein subclasses, but the use of NMR has made this process more efficient and specific. Although there is a high degree of correlation between chemically measured and NMR-derived lipid levels, it must be stressed that the NMR values come from direct measurement of the lipoprotein particles carrying the lipids and not from an actual lipid measurement (Freedman et al., 2003; Garvey et al., 2003; Otvos et al., 2002).

Earlier studies addressed the relationship between obesity and low-HDL levels, with HDL-C associated with both the degree and distribution of adiposity. Decreased HDL levels in obesity have been attributed to diverse mechanisms (Rashid and Genest, 2007). Interestingly, negative correlations between large HDL and BMI or other indicators of adiposity have been found previous investigations (Bertiere et al., 1988; Willliams et al., 1995). It has been proposed that the elevation of very low-density triglycerides and increased glycemia may cause the decrease in large HDL particles, indicating the presence of insulin resistance, decreased lipolysis, and defective transfer of surface elements to small HDL in obese subjects (Williams et al., 1995). A study by Garvey et al. (2003), using NMR for measurement of lipoproteins, found a correlation between large HDL ($r = 0.28$, $P < 0.0001$) and HDL size ($r = 0.41$, $P = 0.003$) with glucose disposal rate after the adjustment for sex, age, race, and BMI in a sample of unrelated subjects. Studies in different populations have identified significant genetic components in circulating levels of HDL in humans (North et al., 2003; Pollin et al., 2004; Rainwater et al., 1997; Velásquez-Meléndez et al., 2007). According to our results, these observations may have a genetic background, with the same group of genes influencing the variation of traits such as adiposity, large HDL, and parameters of glucose metabolism. To the best of our knowledge, this is the first genetic analysis using measurements by NMR.

Analyses conducted in the same Alaskan Eskimo population found that subclasses of LDLs have significant genetic correlations with parameters of adiposity (Voruganti et al., 2006). Small and medium LDL had positive genetic correlations with body weight, BMI, and skinfolds. In this analysis, levels of large HDL were inversely correlated with parameters reflective of obesity such as body fat percentage and skinfolds (Voruganti et al., 2006). A recent investigation by Arya et al. (2003) identified a quantitative trait locus with pleiotropic effects influencing BMI and HDL-C near marker *D6S1009*, indicating that this region on chromosome 6 may harbor a major gene influencing these traits.

Genetic studies of glucose metabolism and CVD have demonstrated pleiotropy on diabetes-related traits and vascular risk across different human populations (Hokanson et al., 2003; North et al., 2003). In this study, levels of HbA1c were used as a marker of plasma glucose regulation in the previous 3 months. Significant genetic correlations were found between small HDL ($\rho_G = 0.33$, $P = 0.03$) and large HDL ($\rho_G = -0.41$, $P = 0.02$) subclasses, and levels of HbA1c. Large HDL particles and HDL size were correlated with fasting insulin levels and total HDL and glucose. Together, these genetic correlations indicate that a common set of genes has an effect on HDL particles and glucose metabolism, and these effects seem to be contrary for small and large subfractions. Previous studies have found genetic correlations between insulin levels and HDL and anthropometric measurements in Mexican-Americans (Mitchel et al., 1996).

The coupling of low-HDL concentrations and elevated triglycerides has been shown in other investigations and is believed to jointly increase the risk for CVD (Mitchel et al., 1996). No significant genetic correlation between total HDL or their subfractions and triglycerides was found in this study.

Lp(a) is considered an independent risk factor for coronary atherosclerosis and has been associated with the severity of this condition (Boroumand et al., 2007; Zlatohlavek et al., 2008). In our study, this phenotype was genetically correlated with large HDL, HDL size, and HDL-C, which are considered protective against CVD. These correlations indicate that a significant proportion of variation in each pair of traits is regulated by common genes. It is paradoxical that the increase in HDL and their size is related to an increase of Lp(a).

Collectively, our findings indicate that the association between adiposity, lipoprotein, and glucose metabolism

has a genetic component. Results in this study indicate that each HDL subfraction may be influenced by different genes, because no genetic correlation was found between HDL particles of different size. The HDL subfractions were genetically correlated with different sets of variables. Overall, pleiotropy was found on subclasses of HDL and measurements of adiposity, subclasses of LDL, and parameters for glucose metabolism. In particular, the protective large HDL subfractions were inversely correlated with the measurements of adiposity. Observations from this study of Alaskan Eskimos are consistent with observations in other populations and suggest that the size of the HDL particle is a highly important factor to be assessed for the risk of CVD. Further studies are needed to identify the location of specific genes that determine the size of the HDL subclasses.

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