Exploring Differences in Adiposity in Two US Hispanic Populations of Mexican Origin Using Social, Behavioral, Physiologic and Genetic Markers: The IRAS Family Study

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Objective: The census classification of Hispanic origin is used in epidemiological studies to group individuals, even though there is geographical, cultural, and genetic diversity within Hispanic Americans of purportedly similar backgrounds. We observed differences in our measures of adiposity between our two Mexican American populations, and examined whether these differences were attributed to social, behavioral, physiologic or genetic differences between the two populations.

Research Design and Methods: In the IRAS Family Study, we examined 478 Hispanics from San Antonio, Texas and 447 Hispanics from the San Luis Valley, Colorado. Associations with body mass index (BMI), visceral adipose tissue area (VAT), and subcutaneous adipose tissue area (SAT) using social, behavioral, physiologic and genetic variables were examined.

Results: Hispanics of Mexican origin in our clinic population in San Antonio had significantly higher mean BMI (31.09 vs 28.35 kg/m^2), VAT (126.3 vs 105.5 cm^2), and SAT (391.6 vs 336.9 cm^2), than Hispanics of Mexican origin in the San Luis Valley. The amount of variation in adiposity explained by clinic population was 4.5% for BMI, 2.8% for VAT, and 2.7% for SAT. After adjustment, clinic population was no longer associated with VAT and SAT, but remained associated with BMI, although the amount of variation explained by population was substantially less (1.0% for BMI).

Conclusion: Adiposity differences within this population of Mexican origin can be largely explained by social, behavioral, physiologic and genetic differences. (*Ethn Dis.* 2012;22(1):65–71)

Key Words: Hispanics, Adiposity, Admixture, Environmental Differences, Social Factors, Behavior, Genetics

Introduction

Hispanic Americans are the fastest growing subpopulation within the United States[1] and have an increased prevalence of obesity in children, adolescents and adults compared to non-Hispanic Whites.[2,3] The census defines individuals as being of Hispanic origin if they report their ethnic origin as Mexican American, Chicano, Mexican, Mexicano, Puerto Rican, Cuban, Central or South American, or other Hispanic. This definition is used in many epidemiological studies to classify individuals, even though there are known ancestral and cultural differences between Cuban, Mexican, Puerto Rican and Central/South American populations in the United States.[4] There may also be differences within Hispanic groups of similar origin (ie, Mexican-Americans living in different regions of the United States). Within Hispanics, differences in risk factors among subgroups are associated with differences in prevalence of disease.[5] One study found that varying amounts of Spanish ancestry in a Spanish population, Mexican population and Mexican American population may explain part of the difference in rates of disease between these groups.[6]

Previous studies have examined single ethnic groups from different geographic locations and lifestyles in order to disentangle behavioral, social and genetic influences on disease. Differences in traditional risk factors for coronary artery disease could not explain all of the differences in disease rates between non-Hispanic Whites of the Old Order Amish and study participants from Minnesota.[7] Studies examining genetically similar Pima Indians living in Arizona and Mexico found that geographic location and behavioral differences are important factors in disease risk.[8,9] While some of these studies have looked within populations,[7–9] and others looked across Hispanics of different origin,[5,6] none have looked at whether differences in risk factors within Hispanics of similar origin living in different regions in the United States can explain differences in disease outcomes.

The unique design of the Insulin Resistance Atherosclerosis Study (IRAS) Family Study allows us to learn more about the etiology of adiposity by exploring the reasons for differences in adiposity between two well-characterized populations of Hispanics of Mexican origin living in distinct geographic areas. Hispanic Americans in the IRAS Family Study were recruited from two sites: the San Luis Valley, Colorado and San Antonio, Texas. While both populations are considered Mexican American, published admixture analysis indicates that the San Luis Valley Hispanic population is approximately 63% European and 34% Native American,[10] and that the San Antonio Hispanic

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population is approximately 16% European and 80% Native American.[11] In addition to the genetic variation, there are known differences in vitamin D levels[12] in the two populations, and social and behavioral differences most likely exist considering the rural/urban distinction and the amount of in-migration between the two locations. Since identical protocols were used in assessing outcomes and risk factors in both of these populations, we postulated that any phenotypic differences in adiposity between clinic sites could be explained by social, behavioral, physiologic and genetic differences.

MATERIALS AND METHODS

The IRAS Family Study was designed to explore genetic and epidemiologic contributions to abdominal adiposity and glucose homeostasis traits among Hispanic and African Americans using a family-based design.[13] Families were ascertained through participants in the IRAS cohort,[14] and recruitment was based on family size, not on phenotype. Hispanic families were recruited from San Antonio, Texas, and the San Luis Valley, Colorado. African American families were recruited from Los Angeles, California, but are not the subject of these analyses. Data from the follow-up examination (2005–2007) were used in these analyses because this exam alone obtained a dietary assessment. The institutional review boards at the respective institutions approved the protocol and informed consent was given by each participant.

We postulated that any phenotypic differences in adiposity between clinic sites could be explained by social, behavioral, physiologic and genetic differences.

Adiposity Phenotypes

Height and weight were measured to the nearest .5 cm and .1 kg, respectively. Body mass index (BMI) was calculated as weight(kg)/height(m^2). Abdominal fat mass was measured at the L4/L5 vertebral regions by computed tomography (CT) under a common protocol at each of the three sites and read centrally at the University of Colorado Denver using IDL Version 6.3 software (Research Systems, Inc, Boulder, Colo). The areas of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were calculated.

Physiological Measures

We examined two physiologic parameters that are associated with adiposity: type 2 diabetes status and plasma vitamin D levels. Type 2 diabetes was determined by a fasting glucose of 126 mg/dL or more, or a participant report of taking insulin injections or diabetes pills. Those with a history of gestational diabetes only were not classified as having type 2 diabetes.

Levels of 25[OH]D were measured by a 2-step process involving rapid extraction of 25[OH]D and other hydroxylated metabolites from fasting plasma and chemiluminescent immunoassay with a 25[OH]D-specific antibody (DiaSorin, Stillwater, Minn) with interassay CVs $<15\%$. Ninety blinded duplicate samples were tested; the intraclass correlation coefficient between duplicates was .98 (95% CI .97–.99).

Behavioral and Social Measures

We selected a panel of social and behavioral factors that had previously been associated with adiposity. These included: smoking habits, marital status, employment and education level, diet, physical activity, and sleep. An estimate of usual frequency of participation in vigorous physical activities was recorded with a defined response set ranging from rarely or never to 5 or more times per week. The variable, hours of sleep per day, was collected by the question, "On average, about how many hours of sleep do you get a night?"

Data on smoking habits, marital status, employment, and education level were gathered by standardized questionnaire.[13] Dietary variables were derived from a Block Brief 2000 food frequency questionnaire (FFQ) (Block 1990) that was administered by interview at the follow-up visit. The questionnaire contains a 70-item food list, developed from the NHANES III dietary recall data, and is designed to provide estimates of usual and customary dietary intake. The nutrient database was developed from the USDA Nutrient Database for Standard Reference. Individual portion size was asked, and pictures were provided in a standardized manner. The FFQs were edited initially at the clinical sites and additional editing and quality control checks, including internal consistency and range, were conducted by NutritionQuest using the Block/DietSys edit check program. We examined the following variables: total calories, and % of calories from fat, carbohydrates and protein. Usual consumption of beer, wine, and liquor in the past year was assessed by self-report.

Genetic Measures

In order to obtain an estimate of admixture in these populations, a principal component analysis was conducted using a set of 80 ancestry informative markers for Hispanic Americans. The principal component that explained genetic variation along the Hispanic ancestry axis in terms of amount of European admixture (lower value = greater European admixture) was used as a covariate to account for admixture.

In addition, we selected variants in genes that had been previously associated with adiposity traits in the entire Hispanic IRAS Family Study cohort in order to study whether differences in

frequency of these variants explained differences in adiposity across the two Hispanic populations. Single nucleotide polymorphism (SNP) selection for the *FTO, SOCS3, INSIG2, NGEF* and *RGS6* genes has been described previously.[15–18] Within each gene, we selected the single most significantly and consistently associated SNP across the adiposity phenotypes for this analysis (*FTO* rs1421085, *SOCS3* rs7221341, *INSIG2* rs17047718, *RGS6* rs6574069, and *NGEF* rs6745724). We also calculated a genetic risk score based on these SNPs, by summing the number of at-risk alleles for SNPs that followed an additive model and by counting alleles as either 0 (for 0/0 and 0/1) or 1 (for 1/1) for SNPs that followed a recessive model.

Maximum likelihood estimates of allele frequencies were computed using the largest set of unrelated Hispanic American individuals; the genotypes were also tested for departure from Hardy-Weinberg equilibrium expectations using a chi square goodness-of-fit test, and no evidence for departure was found.[15–18] Each pedigree has previously been examined for consistency of stated family structure.[15]

Statistical Methods

The analysis dataset consisted of 925 Hispanic individuals with measured BMI. Of these, 842 had CT measures of VAT and SAT. Variance component analysis implemented in SOLAR (Texas Biomedical Research Institute, San Antonio, Tex.) was used to examine associations while accounting for the correlations among family members in pedigrees of arbitrary size and complexity.[19] To best approximate the test's distributional assumptions of conditional normality and homogeneity of variance, we natural-log transformed BMI, and square-root transformed VAT and SAT. Univariate analyses were initially run to describe phenotypic, social, behavioral, physiological and genetic differences between the Hispanic populations from our two recruitment sites, San Antonio and the San Luis Valley.

The primary goal of our analyses was to explore whether clinic population (San Antonio and San Luis Valley) remained a significant predictor of adiposity phenotypes after accounting for other measured differences between the populations. For reference, a model was run for each adiposity trait using clinic site only to determine how much of the variance of each trait was explained by clinic site when it was in the model by itself. All multivariate models were adjusted for age and sex. Additional variables were included in the model if they were statistically significantly associated with the adiposity trait, as assessed by the likelihood ratio test. The best model for each adiposity phenotype was built based on proportion of variance in the overall trait explained, and then the variable indicating the clinic population (San Antonio vs San Luis Valley) was included in the model to determine if it was still a significant predictor of the adiposity trait. The proportion of the variance in adiposity phenotype explained by the overall model and that additionally explained by clinic population was calculated.

Given that we have family data, we were able to calculate the residual heritability of the adiposity phenotypes, which quantifies the proportion of variation in our adiposity phenotypes attributable to genetic variation after adjustment for the social, behavioral and physiologic factors in the model. After building the best model using demographic and behavioral factors, we added the admixture variable (admixture) and select adiposity-associated SNPs in the IRAS Family Study Hispanic cohort, as described above. Based on the findings of the original genetic association studies, additive models were run for *FTO, INSIG2* and *RGS6*; recessive models were run for *SOCS3* and *NGEF*. In addition, in a separate set of models, we tested whether a genetic risk score based on these SNPs was associated with adiposity phenotypes.

RESULTS

Descriptive characteristics of the Hispanic Americans in IRAS Family Study are listed in Table 1. The clinic population in San Antonio had a higher mean BMI, VAT and SAT, and a higher prevalence of type 2 diabetes than the clinic population in the San Luis Valley. The San Antonio population had a lower proportion of current smokers, reported less sleep per day, reported less physical activity, reported a diet with a lower proportion of fat and higher proportion of protein, had lower plasma 25[OH]D and had more non-European admixture than the clinic population in the San Luis Valley. The San Antonio population had a higher frequency of the risk allele of *FTO* rs1421085 and lower frequency of the risk allele of *NGEF* rs6745724 than those in the San Luis Valley.

Univariately, clinic population was significantly associated with the adiposity phenotypes, accounting for 4.5% of the variance in BMI (P=7.6e-06), 2.8% of the variance in VAT (P=.0009), and 2.7% of the variance in SAT (P=.0006) (Table 2). Our first strategy using multivariate linear models indicated that higher BMI was associated with younger age, having diabetes, not being a current smoker, spending fewer hours sleeping, a lower frequency of vigorous activity, and having lower 25[OH]D levels (Table 2). We then included the variable, clinic population, into this model and found that being from San Antonio (compared with the San Luis Valley) was still significantly associated with higher BMI (P=.004), although it explained a substantially smaller amount of the variance than before the adjustment for social, behavioral, and physiologic factors (1.4% vs 4.5%).

Table 1. Characteristics of the IRAS Family Study Hispanic Americans from San Antonio and San Luis Valley

	San Antonio *N*=478	San Luis Valley *N*=447	*P*
BMI, kg/m^2 mean ± SD	31.09 ± 6.32	28.35 ± 5.73	<.0001
VAT[a], cm^2 mean ± SD	126.3 ± 63.5	105.5 ± 56.9	<.0001
SAT[a], cm^2 mean ± SD	391.6 ± 162.2	336.9 ± 149. 2	<.0001
Age, years mean ± SD	47.82 ± 14.85	47.63 ± 13.80	.84
25[OH]D, ng/mL mean ± SD	19.06 ± 8.39	21.09 ± 8.32	.0002
Type 2 diabetes, *n* (%)	94 (19.7)	59 (13.2)	.008
Female, *n* (%)	302 (63.2)	272 (60.9)	.47
Current smokers, *n* (%)	72 (15.0)	117 (26.2)	<.0001
High school or higher, *n* (%)	246 (51.5)	162 (36.2)	<.0001
Currently employed, *n* (%)	431 (90.2)	389 (86.0)	.13
Currently married, *n* (%)	272 (56.9)	254 (56.8)	.98
Number of people living in household, mean ± SD	3.10 ± 1.59	3.05 ± 1.42	.62
Hours of sleep per day, mean ± SD	6.72 ± 1.28	6.97 ± 1.41	.005
Height, cm mean ± SD	163.3 ± 8.53	163.30 ± 9.24	.91
Frequency of vigorous physical activity, *n* (%)			
Rarely/never	166 (34.7)	36 (8.1)	
1–3 times/month	103 (21.6)	94 (21.0)	<.0001
1 time/week	62 (13.0)	69 (15.4)	
2–4 times/week	114 (23.8)	172 (38.5)	
≥5 times/week	33 (6.9)	76 (17.0)	
Energy intake (Kcal), mean ± SD	1769.2 ± 888.2	1862.0 ± 1000.2	.14
% calories from fat	36.3	37.5	.001
% calories from protein	17.0	16.2	.0004
% calories from carbohydrates	46.2	46.7	.28
Non-European admixture, mean ± SD	.60 ± .15	.51 ± .10	<.0001
FTO rs1421085, T/C MAF%	25.5	12.5	<.0001
INSIG2 rs17047718, A/G MAF%	7.4	6.2	.37
SOCS3 rs7221341, A/G MAF%	25.5	27.1	.42
RGS6 rs6574069, C/T MAF%	26.6	27.1	.86
NGEF rs6745724, A/G MAF%	30.9	43.8	<.0001
Number of at-risk alleles, mean ± SD	1.61 ± 1.04	1.87 ± 1.16	.0007

BMI, body mass index; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; 25[OH]D, 25-hydroxyvitamin D.
[a] There were 430 in SA and 412 in SLV with VAT and SAT measures.

Higher VAT was associated with older age, being male, having diabetes, a lower frequency of vigorous activity, lower 25[OH]D levels, and greater height (Table 2). After adjusting for these factors, being from San Antonio remained significantly associated with higher VAT (*P*=.01), although substantially less of the variance of VAT was explained by clinic population than before adjustment for social, behavioral, and physiologic factors (.8% vs 2.8%).

Higher SAT was associated with younger age, being female, having diabetes, not being a current smoker, spending less hours in sleep, a lower frequency of vigorous physical activity, lower plasma 25[OH]D, consuming a higher percent of calories from fat, and greater height (Table 2). After controlling for these factors, being from the San Antonio population was significantly associated with higher SAT (*P*=.03), although substantially less of the SAT variance was explained by clinic population than before adjustment for social, behavioral, and physiologic factors (.6% vs 2.7%).

In order to explore whether any of the contribution of the clinic population variable to adiposity was due to genetic differences between the Hispanic populations in San Antonio and the San Luis Valley, we calculated the residual heritability, which quantifies the proportion of variation in the adiposity phenotypes attributable to genetic variation after adjustment for the social, behavioral, and physiological factors shown in Table 2. We observed that additional adjustment for clinic population reduced the residual heritability of BMI from .438 to .391, the residual heritability of VAT .278 to .246, and the residual heritability of SAT from .439 to .430, indicating that clinic population may, indeed, explain some of the heritability. This led us to explore whether differences in selected genetic variants (*FTO* rs1421085, *SOCS3* rs7221341, *INSIG2* rs17047718, *RGS6* rs6574069, and *NGEF* rs6745724) and non-European admixture, explained the clinic population differences in adiposity phenotypes. With the addition of all of these SNPs as covariates to multivariate models of adiposity that were presented in Table 2, clinic population remained significantly associated with BMI (*P*=.02), but was no longer associated

Table 2. Multivariate associations between social, behavioral and physiologic factors and adiposity phenotypes in Hispanics from the IRAS Family Study[a]

	Adiposity phenotype		
	BMI β ± SE; *P* *N*=925	**VAT** β ± SE; *P* *N*=842	**SAT** β ± SE; *P* *N*=842
Age, years	−.002 ± .0005; *P*=.0003	.064 ± .006; *P*<.0001	−.029 ± .010; *P*=.004
Female sex	.002 ± .013; *P*=.89	−1.114 ± .245; *P*<.0001	3.783 ± .382; *P*<.0001
Diabetes	.080 ± .018; *P*<.0001	1.455 ± .232; *P*<.0001	.844 ± .360; P=.02
Current smoker	−.073 ± .015; *P*<.0001	[b]	−1.370 ± .303; *P*<.0001
Hours of sleep	−.013 ± .004; *P*=.003	[b]	−.203 ± .086; *P*=.02
Frequency of vigorous activity	−.017 ± .005; *P*=.0008	−.221 ± .065; *P*=.0007	−.286 ± .099; *P*=.004
25[OH]D, ng/mL	−.005 ± .0008; *P*<.0001	−.073 ± .010; *P*<.0001	−.097 ± .015; *P*<.0001
% calories from fat	[b]	[b]	.045 ± .020; *P*=.03
Height, cm	[b]	.039 ± .014; *P*=.005	.066 ± .022; *P*=.003
Clinic population, SLV vs SA	−.054 ± .018; *P*=.004	−.516 ± .204; *P*=.01	−.801 ± .365; *P*=.03
Proportion of variance explained by clinic population univariately	.045	.028	.027
Proportion of variance explained by adjusted model	.182	.358	.294
Proportion of variance explained by clinic population in adjusted model	.014	.008	.006

SLV, San Luis Valley; SA, San Antonio

[a] All models were adjusted for age and sex regardless of statistical significance. Additional variables were added based on statistical significance. The clinic population variable was then added to determine the amount of remaining variance in adiposity that is explained by being in the San Antonio population compared with San Luis Valley after accounting for environmental and behavioral characteristics.

[b] Not included in model because it was not statistically significant.

with VAT (*P*=.06) and SAT (*P*=.17), suggesting that these social, behavioral, physiological and genetic variables explain most of the differences in adiposity between the San Antonio and San Luis Valley clinic populations of the IRAS Family Study, as evidenced by the further reduction in the amount of variance explained by clinic population (Table 3). The genetic risk score was not significantly associated with any adiposity phenotype (data not shown).

DISCUSSION

Our objective was to learn more about the etiology of adiposity by exploring the reasons for differences in adiposity between two well-characterized populations of Hispanics of Mexican origin living in distinct geographic areas. Previous studies have attempted to account for phenotypic differences between ethnicities in various ways: by accounting for social and behavioral differences;[20] by examining social, behavioral and geographic differences in groups of purportedly the same genetic background, (ie, Pima Indians living in Arizona and Mexico);[7] and by looking at admixture and differences in social and behavioral factors in Spanish, Mexican, and Mexican Americans.[6] Almost all of the variation across our two Mexican origin populations could be accounted for by extensive covariate adjustment, suggesting that the observed adiposity differences can largely be explained by social, behavioral, physiologic and genetic characteristics.

Our data suggest that the clinic population variable may reflect, in part, genetic differences across the two populations. While our admixture variable did not account for the population differences in adiposity, the adiposity candidate gene SNPs did, to a moderate extent. We chose SNPs that had been associated with adiposity in our population,[15–18] and acknowledge that we did not adjust for all the known (and, certainly, the unknown) adiposity genes in this analysis; it is possible that the small remaining population differences in adiposity phenotypes could be accounted for by the inclusion of additional adiposity genetic variants to the model.

The social, behavioral, and physiological factors that we measured may represent downstream characteristics of the more obvious differences between the two populations, which include self-identity, time of migration to the United States, and urban/rural environment. Those in the San Luis Valley self-identify as Spanish rather than Mexican, having settled in the San Luis Valley before Mexico was a country, and having remained in one location for generations with little in-migration. San Antonio has more recent Mexican origins, with more continuous in-migration than the San Luis Valley, which could result in differences in social factors that the IRAS Family Study did not measure. The San Luis Valley is a rural community surrounded on three sides by mountain ranges, with an average altitude of 7100 feet above sea

Table 3. Associations between genetic factors[a] and adiposity phenotypes in Hispanics from the IRAS Family Study, adjusting for social, behavioral and physiologic factors[b]

	Adiposity phenotype		
	BMI β ± SE; *P* *N*=918	**VAT β ± SE; *P* *N*=822**	**SAT β ± SE; *P* *N*=822**
FTO rs1421085[c]	.029 ± .010; *P*=.009	.220 ± .144; *P*=.13	.446 ± .226; *P*=.04
INSIG2 rs17047718[d]	−.114 ± .060; *P*=.06	−1.782 ± .798; *P*=.03	−3.194 ± 1.205; *P*=.008
SOCS3 rs7221341[d]	−.043 ± .024; *P*=.08	−1.059 ± .324; *P*=.001	−.953 ± .501; *P*=.06
RGS6 rs6574069[c]	.016 ± .010; *P*=.12	−.037 ± .134; *P*=.78	.157 ± .211; *P*=.46
NGEF rs6745724[c]	−.037 ± .011; *P*=.0006	−.201 ± .134; *P*=.14	−.705 ± .211; *P*=.0009
Admixture	−.019 ± .059; *P*=.75	.241 ± .712; *P*=.74	.574 ± 1.164; *P*=.62
Clinic population (SLV vs SA)	−.046 ± .019; *P*=.02	−.402 ± .215; *P*=.06	−.520 ± .378; *P*=.17
Proportion of variance explained by adjusted model	.209	.359	.312
Proportion of variance explained by clinic population in adjusted model	.010	.005	.002

SLV, San Luis Valley; SA, San Antonio
[a] Genetic variants that had been found to be significantly associated with adiposity phenotypes in Hispanics in the IRAS Family Study.[15–18]
[b] Best models from table 2 were used as the base models for these analyses.
[c] Additive model.
[d] Recessive model.

level. San Antonio is a more urban community, with an average altitude of 770 feet. In addition to the urban/rural and altitude differences, there are most likely social factors such as stress, prejudice and social support, and life course differences, including where an individual's parents were born, which we did not specifically measure. And finally, while our physical activity and diet questionnaires are validated and thorough, there still may be unmeasured variation, resulting in inadequate adjustment.

The census classification of Hispanic American is used in many epidemiological studies to categorize individuals into similar groups, even though there are known ancestral and cultural differences between Hispanic populations, even within Hispanic groups of purportedly similar background (ie, Mexican Americans).[4] Our results indicate that while these differences exist in populations of Mexican origin, they can largely be explained by measured social, behavioral, physiologic and genetic differences.

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