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Viva la Familia Study: genetic and environmental contributions to childhood obesity and its comorbidities in the Hispanic population¹⁻⁴

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ABSTRACT

Background: Genetic and environmental contributions to childhood obesity are poorly delineated.

Objective: The Viva la Familia Study was designed to genetically map childhood obesity and its comorbidities in the Hispanic population. The objectives of this report were to describe the study design and to summarize genetic and environmental contributions to the phenotypic variation in obesity and risk factors for metabolic diseases in Hispanic children.

Design: The Viva la Familia cohort consisted of 1030 children from 319 families selected based on an overweight proband between the ages of 4 and 19 y. In-depth phenotyping to characterize the overweight children and their siblings included anthropometric and body-composition traits by dual-energy X-ray absorptiometry and assessments of diet by 24-h recalls, physical activity by accelerometry, and risk factors for metabolic diseases by standard biochemical methods. Univariate quantitative genetic analysis was used to partition phenotypic variance into additive genetic and environmental components by using the computer program SOLAR.

Results: Sex, age, and environmental covariates explained 1–91% of the phenotypic variance. Heritabilities of anthropometric indexes ranged from 0.24 to 0.75. Heritability coefficients for the body-composition traits ranged from 0.18 to 0.35. Diet and physical activity presented heritabilities of 0.32 to 0.69. Risk factors for metabolic diseases were heritable with coefficients ranging from 0.25 to 0.73. Significant genetic correlations between obesity traits and risk factors for metabolic diseases substantiated pleiotropy between traits.

Conclusion: The Viva la Familia Study provides evidence of a strong genetic contribution to the high prevalence of obesity and its comorbidities in Hispanic children. *Am J Clin Nutr* 2006;84:646–54.

KEY WORDS Obesity, genetics, environment, insulin resistance, dyslipidemia, hypertension

INTRODUCTION

Childhood obesity in the United States has steadily increased in the past 2 decades according to National Health and Nutrition Examination Surveys (NHANES), especially among Hispanic children (1, 2). The prevalence of overweight, defined as a body mass index (BMI) \geq 95th percentile, was $>20\%$ among Mexican

American children. Childhood obesity is associated with several metabolic and endocrine derangements—including glucose intolerance, hypertension, and dyslipidemia—that predispose to early development of cardiovascular disease (CVD), type 2 diabetes, and nonalcoholic fatty liver disease (3, 4).

Obesity is a complex disease influenced by genetic and environmental factors and their interactions. The current surge in childhood obesity in the United States is attributable to an interaction between a genetic predisposition toward efficient energy storage and a permissive environment of readily available food and sedentary behaviors. Genetic predisposition to obesity is expressed consequent to the induction of a positive energy balance due to changes in energy intake, energy expenditure, and partitioning of energy to adipose tissue. Obesity, in turn, is a major risk factor for metabolic diseases, each of which is influenced by their own specific genes and environmental factors.

The genetic architecture of childhood obesity has not been studied thoroughly, particularly in the Hispanic population. Although corroboration is often observed, heritabilities are not necessarily transferable from one population to another or from adults to children, even in the same population, because genetic expression and environmental influences may vary with age, time, and place. In genetic studies of childhood obesity, the phenotypic description of the obese child has been largely limited to anthropometric measures. A few pediatric studies have addressed the heritability of fat mass (FM) by using skinfold thicknesses (5–7) or bioimpedance analysis (5). In 41 monozygotic and 25 dizygotic twin pairs aged 3–17 y, the heritability for %FM was 0.75 (5). A genetic correlation was observed between BMI

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and %FM ($\rho_G = 0.74$); however, 62.5% of the total genetic variation in %FM was attributable to genes independent of BMI. Studies on the heritability of the mediators of childhood obesity, food intake and physical activity, are limited in children.

In the present study, in-depth phenotyping was performed to characterize the overweight child and included anthropometric and body-composition traits and assessments of diet, physical activity, and risk factors for metabolic diseases. The overweight proband was selected on the basis of BMI and FM. Given the central role of FM in the pathophysiology of obesity, a direct measure of FM may be a superior phenotype in the search of genes involved in childhood obesity. Herein, we present a quantitative genetic analysis of the Viva la Familia Study, which was designed to genetically map childhood obesity and its comorbidities in the Hispanic population with the use of a genome scan. The objectives of this report were 2-fold: to describe the basic design of the Viva la Familia Study and to summarize the genetic and environmental contributions to phenotypic variation in obesity and risk factors for metabolic diseases in a large cohort of Hispanic children.

SUBJECTS AND METHODS

Subject recruitment and study design

Genetic and environmental factors affecting obesity and its comorbidities were investigated in 1030 children from 319 families enrolled in the Viva la Familia Study between November 2000 and August 2004 in Houston, TX. Recruitment was conducted through local television and radio stations and community outreach efforts. Each family was selected from an overweight proband between the ages of 4 to 19 y with the use of a bivariate ascertainment scheme, ie, overweight ≥ 95 th percentile for BMI (8) and ≥ 85 th percentile for FM (9, 10). In addition, families were required to have ≥ 3 children between the ages of 4 and 19 y. Related families were also recruited to expand the relative pair types. Once identified, the overweight proband and all siblings aged 4–19 y and their parents were invited to the US Department of Agriculture/Agricultural Research Service (USDA/ARS) Children's Nutrition Research Center (CNRC) at Baylor College of Medicine for a tour and full explanation of the study. All enrolled children and parents gave written informed consent or assent. The protocol was approved by the Institutional Review Boards for Human Subject Research at Baylor College of Medicine and Affiliated Hospitals and at the Southwest Foundation for Biomedical Research.

Phenotypic assessments were conducted at the CNRC over the course of 3 study visits. At the first visit, interviews were conducted with the parents, in Spanish if necessary, to obtain family pedigree information, sociodemographic data, lifestyle data, and medical histories. The Hazuda Acculturation and Assimilation Scales (11) were completed by the fathers and mothers (scales A1, A2, A3, and S2) and children (scales A1, A2, A3, and S1). The USDA 6-item Household Food Security Survey was completed by the mother (12). Clinical signs and anthropometric and body-composition traits were performed in the children and their parents. The children's diet and physical fitness (data not reported) were assessed. At the second visit, 24-h calorimetry, followed by observations of eating behavior, were performed in the children only (data not reported). On awakening in the room calorimeter, a 12-h fasting blood sample was obtained between

0700 and 0800 for the analysis of DNA and other biochemistries. Children were discharged from the CNRC equipped with an accelerometer to measure free-living physical activity. At the third visit, scheduled 1 y later, anthropometric and body-composition traits were repeated in the children only (data not reported).

Phenotypic and covariate data

Clinical signs

Blood pressure, heart rate, and temperature were taken in triplicate with a DINAMAP Vital Signs Monitor (8100T; Critikon Inc, Tampa, FL). The child was seated quietly for ≥ 5 min before measurement. The arm was supported at heart level, and the appropriate cuff size used. Tanner stages of sexual maturation based on pubic hair and breast and penis development illustrated with drawings were self-reported (13, 14).

Anthropometric and body-composition traits

Body weight was measured with a digital balance to the nearest 0.1 kg, and height was measured to the nearest 1 mm with a stadiometer. Body composition was determined by dual-energy X-ray absorptiometry with a Delphi-A whole-body scanner (Hologic Inc, Waltham, MA). Total body and regional estimates of FM and fat-free mass (FFM) were obtained by using the manufacturer's software (version 11.2).

Dietary intake

A multiple-pass 24-h dietary recall was recorded on 2 occasions, 2–4 wk apart, at the CNRC by a registered dietitian using Nutrition Data System software on a laptop computer (15). This system automates interviewing, editing, and coding of dietary intake data. The multiple-pass 24-h dietary recall method uses 3 distinct passes to garner information about a subject's food intake during the preceding 24 h. Children aged < 7 y were assisted by their mothers.

Fasting blood biochemistries

A fasting blood sample was drawn for biochemical determinations. Serum samples were obtained from whole blood after clotting. Fasting serum concentrations of glucose, triacylglycerol, total cholesterol, and HDL were measured by enzymatic-colorimetric techniques with the GM7 Analyzer (Analox Instruments, Lundeburg, MA) and Microquant Platereader (Biotek Instruments, Winooski, VT). Glucose was assayed by using glucose oxidase. Triacylglycerols were assayed enzymatically by using lipase, glycerol kinase, glycerol phosphate oxidase, and peroxidase supplied by Thermo Electron (Louisville, CO). Total cholesterol and HDL were determined by using cholesterol esterase, cholesterol oxidase, and peroxidase supplied by Thermo Electron (16, 17). Serum insulin was measured by radioimmunoassay (Linco Research Inc, St Charles, MO). Serum alanine aminotransferase (ALT) was determined according to standard enzymatic assay procedures with a SPECTRAMaxPLUS spectrophotometer (Molecular Devices Corp, Sunnyvale, CA) and reagents from ThermoDMA (Arlington, TX).

Physical activity

Actiwatch accelerometers (Mini Mitter Co, Inc, Bend, OR) were used to measure the frequency, duration, and intensity of



physical activity on 3 consecutive days. The percentage of awake time spent in sedentary, light, moderate, and vigorous physical activity was computed from thresholds established for children with the use of a room respiration calorimetry, as described in our previous publication (18).

Analytic methods

Database management and descriptive statistical analysis

ACCESS (version 9; Microsoft Corp, Seattle, WA) was used for database management. STATA (version 8.2; STATA Corp, College Station, TX) and SPSS (version 13; SPSS Inc, Chicago, IL) were used for statistical analyses. Data are summarized as means \pm SEs. If the data were not normally distributed (kurtosis > 1.9), a log transformation was performed and used in further analyses (19). Descriptive statistics, generalized estimating equations, and general least-squares regression were performed. Statistical significance was set at $P < 0.05$.

Quantitative genetic analysis

Variance component analysis was used to partition the total phenotypic variance (σ_P^2) of the traits into additive genetic (σ_G^2) and environmental (σ_E^2) components:

$$\sigma_P^2 = \sigma_G^2 + \sigma_E^2 \quad (1)$$

The environmental component includes factors such as socioeconomic status and acculturation, measurement errors, and any genetic factor that is not additive. The additive heritability (h^2) of a trait represents the portion of the total phenotypic variance accounted for by the additive genetic variance:

$$h^2 = \sigma_G^2 / \sigma_P^2 \quad (2)$$

Heritability was expressed as a proportion of the residual phenotypic variance. To determine the significance of the heritability, a null model in which the additive genetic variance (σ_G^2) for the trait equals zero is compared with another model, where σ_G^2 is estimated by using the maximum likelihood method (20).

Bivariate analyses were conducted to partition the phenotypic relations (ρ_P) between 2 traits into genetic (ρ_G) and environmental correlations (ρ_E)

$$\rho_P = \rho_G \sqrt{h_1^2 h_2^2} + \rho_E \sqrt{(1 - h_1^2)(1 - h_2^2)} \quad (3)$$

In this equation, h_1^2 and h_2^2 correspond to the heritabilities of the 2 traits. The bivariate phenotype is considered a linear function of the individual's phenotypic values, the population means, the additive genetic values, and the environmental effects (21). A model with the genetic correlation constrained to zero is compared with another model in which all parameters are estimated. To test for complete pleiotropy, a model in which the genetic correlation is constrained to 1.0 is compared with an alternative model in which all parameters are estimated. Twice the difference of logarithm likelihood of the 2 models asymptotically yields a distribution of χ^2 with 1 df. Evidence of pleiotropy (a common set of genes influencing more than one trait) is indicated by a genetic correlation significantly different from 0.

These genetic analyses have been implemented in the computer program SOLAR 2.0 (Southwest Foundation for Biomedical Research, San Antonio, TX) (22). Age, sex, age², and the interactions of age \times sex and age² \times sex were simultaneously

estimated in these analyses. Some potentially important covariates were excluded because they may be genetically mediated, and their inclusion could substantially reduce the h^2 if pleiotropic genes affecting both covariates and risk factors exist.

Because our cohort was selected on the basis of a proband who was an overweight child, an ascertainment correction was required and was performed in SOLAR to obtain unbiased parameter estimates in the variance components model. In the variance components method, ascertainment corrections condition on the trait value of the proband (23).

RESULTS

The Viva la Familia Study cohort is composed of 319 families with 631 parents and 1030 children. Most (82%) of the children participating in the Viva la Familia Study are second-generation Americans of Mexican and Central American descent. Most of the parents were from Mexico (71%); the remainder were from Central America (11%), South America (3%), and the United States (15%). The mean duration of residing in the United States for foreign-born parents was 14.3 ± 0.4 y. The mean strata for the Hazuda Acculturation Scales (range: 1–4) were similar for fathers and mothers, respectively: 1.2 ± 0.02 and 1.3 ± 0.03 for childhood experience with the English compared with the Spanish language (A1), 2.5 ± 0.03 and 2.5 ± 0.03 for adult proficiency in English (A2), and 1.7 ± 0.03 and 1.7 ± 0.03 for a pattern of English compared with Spanish language usage (A3), and 2.0 ± 0.02 and 2.0 ± 0.02 for adult interaction with members of the mainstream society (S2). Ninety-four percent of fathers were employed for an average of 9.7 ± 0.2 h/d, and 50% of mothers were employed for 7.1 ± 0.2 h/d. The highest level of education attained by the parents was 8th grade or less in 42% and 35%, some high school or high school graduate in 38% and 43%, and some college or college graduate in 19% and 22% of the fathers and mothers, respectively. Total household income before taxes was $< \$19,999$ in 22%, $\$20,000$ – $29,999$ in 34%, $\$30,000$ – $39,999$ in 25%, and $> \$40,000$ in 19% of families. The average family size was 5.3 (range: 2–10). On the basis of the mothers' responses to the USDA Household Food Security Survey, 51% of families were food secure, 33% were insecure with no hunger, and 16% were insecure with hunger. Federal food-assistance programs were used by 23% (Special Supplemental Nutrition Program for Women, Infants and Children) and 14% (Food Stamps) of households.

A high degree of obesity was present in these families. Most of the parents were either overweight (34%) or obese (57%). The mean (\pm SE) BMIs of the fathers and mothers were 30.8 ± 0.2 and 33.5 ± 0.2 , respectively. The mean (\pm SE) %FMs of the fathers and mothers were $27 \pm 0.3\%$ and $41 \pm 0.3\%$, and the mean waist-hip ratios were 0.95 ± 0.003 and 0.83 ± 0.004 , respectively. A family history of diabetes (68%), CVD (60%), and hypertension (78%) in the parents or grandparents were reported.

In the variance components models for the obesity-related phenotypes and the risk factors for metabolic diseases, age, Tanner stage, and other covariates were significant. Birth order ranged from the first to the eighth born, with a preponderance of first- (30%), second- (30%), third- (27%), and fourth-born (9%) children enrolled in the study. Exposure to gestational diabetes mellitus was reported in 12.8% of cases. With respect to infant feeding practices, the predominant milk source was human milk



in 34% of the cases (median duration: of 8.2 ± 0.4 mo). Mixed feeding of human milk and formula was used in 24% of cases. Formula only was used in 42% of cases for a median duration of 10.4 ± 0.2 mo. Solid foods were introduced at a mean (\pm SE) of 5.1 ± 0.1 mo for all cases.

At the time of the study, the mean (\pm SE) age was 11.2 ± 0.2 y for the boys and 10.7 ± 0.2 y for the girls; the age distribution was 14%, 45%, and 41% in the age brackets 4–5 y, 6–11 y, and 12–19 y, respectively. The median Tanner stage was 1.5; 51%, 14%, 16%, 12%, and 7% of the children were at Tanner stages 1, 2, 3, 4, and 5, respectively. Most of the children were healthy. The most common medical condition in the children was allergies (14%). Asthma was reported for 6.6% of the children, with no significant differences by sex or overweight status. Seven cases of attention-deficit hyperactivity disorder, 4 cases of type 2 diabetes, 1 case of type 1 diabetes, 2 cases each of visually impairment and cerebral palsy, and 1 case each of autism, Asperger disease, and myasthenia gravis were reported. Smoking was indicated in <1% of cases. Twenty-four percent of children reported dieting in the past year, and 26% reported current dieting; dieting practices were reported more frequently among the overweight children (30–40%; $P = 0.001$), but similarly among boys and girls.

The mean (\pm SE) acculturation strata were similar for boys and girls, respectively, and were slightly higher than those of their parents: 1.8 ± 0.05 and 1.8 ± 0.05 for childhood experience with the English compared with the Spanish language (A1), 3.1 ± 0.04 and 3.0 ± 0.04 for adult proficiency in English (A2), and 3.2 ± 0.10 and 3.4 ± 0.10 for a pattern of English compared with Spanish language usage (A3), and 2.2 ± 0.04 and 2.0 ± 0.04 for the child's interaction with members of mainstream society (S1). The BMI z score was negatively correlated with stratum A3 ($P = 0.03$).

As for reported physical activity, most (78%) of the children participated in physical education classes at school for a mean (\pm SE) of 2.8 ± 0.09 h/wk. Parents rated their children's level of physical activity as inactive with no regular physical activity (19%), moderate with sporadic recreational activities (59%), heavy with 30–60 min recreational activities ≥ 3 times/wk (18%), or vigorous with >60 min in physical activity >3 times/wk (4%); the boys and nonoverweight children were rated more often in the active and very active categories. The parents estimated that their children watched television, played videos, or used the computer for 3.0 ± 0.05 h/d. The children were involved in a mean (\pm SE) of 1.2 ± 0.04 sports outside of school and participated $\approx 12.3 \pm 0.3$ times/mo for 1.3 ± 0.03 h/occasion.

The obesity-related phenotypes—anthropometric and body-composition traits, diet, and physical activity—are summarized in **Table 1**. Eighteen percent of the children were at risk of overweight (85th \leq BMI <95th percentile). Fifty-one percent of the children were classified as overweight. Of the overweight children, 47% were above the 99.0th BMI percentile; the z scores ranged from 2.3 to 4.5. The boys were heavier and taller than the girls but had a lower %FM ($P = 0.001$). On the basis of the 24-h dietary recalls, the mean energy intake of the boys was significantly higher than that of the girls ($P = 0.001$). There were no sex differences in the macronutrient composition of the diets. Physical activity counts measured by accelerometry were higher in the boys than in the girls ($P = 0.001$). The percentage of awake time partitioned into light and moderate activities also differed by sex.

TABLE 1

Obesity-related phenotypes: anthropometric and body-composition traits, dietary intakes, and physical activity in the boys and girls in the Viva la Familia Study¹

	Boys (n = 510)	Girls (n = 520)
Anthropometric and body-composition traits		
Weight (kg)	58.6 \pm 1.3	50.3 \pm 1.1 ²
Height (m)	1.46 \pm 0.01	1.39 \pm 0.01 ²
BMI (kg/m ²)	25.9 \pm 0.4	24.3 \pm 0.3 ²
Fat-free mass (kg)	38.2 \pm 0.7	31.1 \pm 0.6 ²
Fat mass (kg)	19.0 \pm 0.6	18.9 \pm 0.5
Truncal fat mass (kg)	8.1 \pm 0.8	8.5 \pm 0.7
Waist circumference (cm)	79.0 \pm 0.8	72.1 \pm 0.7 ²
Hip circumference (cm)	89.0 \pm 0.9	86.5 \pm 0.9 ²
Dietary intake		
Energy (kcal/d)	2184 \pm 32	1829 \pm 26 ²
Protein (% of energy)	14.3 \pm 0.1	13.9 \pm 0.1
Fat (% of energy)	33.9 \pm 0.3	33.9 \pm 0.3
Carbohydrate (% of energy)	53.0 \pm 0.3	53.4 \pm 0.3
Physical activity		
Activity counts ($\times 10^{-4}$ /d)	23.6 \pm 0.4	21.6 \pm 0.4 ²
Sedentary (% of awake time)	38.0 \pm 0.6	37.5 \pm 0.6
Light (% of awake time)	51.7 \pm 0.5	53.9 \pm 0.5 ²
Moderate (% of awake time)	10.0 \pm 0.3	8.4 \pm 0.3 ²
Vigorous (% of awake time)	0.4 \pm 0.03	0.2 \pm 0.02

¹ All values are $\bar{x} \pm$ SE.

² Significantly different from boys, $P < 0.05$ (general estimating equations).

The risk factors for metabolic diseases are presented in **Table 2**. Systolic blood pressure (SBP) was significantly higher in the boys ($P = 0.001$). Diastolic blood pressure (DBP) was within normal limits for all children. Fasting serum glucose and ALT were higher in the boys than in the girls ($P = 0.01$ – 0.001).

Heritabilities of the obesity-related phenotypes and risk factors for metabolic diseases are shown in **Table 3**. In the first model, age, sex, age², age \times sex, and age² \times sex were included. In the second model, birth order (rank), Tanner stage, child's acculturation, parents' education, family income, food security,

TABLE 2

Quantitative risk factors for metabolic diseases in the boys and girls in the Viva la Familia Study¹

	Boys (n = 510)	Girls (n = 520)
Systolic blood pressure (mm Hg)	110.2 \pm 0.5	105.7 \pm 0.4 ²
Diastolic blood pressure (mm Hg)	51.1 \pm 0.3	50.8 \pm 0.3
Glucose (mg/dL)	92.9 \pm 0.4	91.7 \pm 0.7 ²
Insulin (μ U/mL)	22.0 \pm 0.8	23.0 \pm 0.8
Triacylglycerol (mg/dL)	107.7 \pm 2.8	102.6 \pm 2.3
Total cholesterol (mg/dL)	172.5 \pm 1.6	170.9 \pm 1.5
HDL (mg/dL)	46.6 \pm 0.5	46.9 \pm 0.5
Alanine aminotransferase (U/L)	26.6 \pm 1.2	21.8 \pm 1.0 ²

¹ All values are $\bar{x} \pm$ SE.

² Significantly different from boys, $P < 0.05$ (general estimating equations).

TABLE 3
Heritabilities (h^2) of the obesity-related phenotypes and risk factors for metabolic diseases¹

Trait	Age	Sex	Age × sex	Age ² × sex	Age ² × sex	Rank	Tanner stage	Acculturation	Education	Income	Food security	Gestational diabetes	Breastfeeding	Age at solid food introduction	Asthma	Physical education	Family size	Adjusted h^2 of trait ²	Adjusted h^2 of trait ³	P	Variance by covariates	
Anthropometric and body composition																						%
Weight	+	-	-	-	-	-	+	+	-	-	-	-	-	-	-	+	-	0.36 ± 0.08	0.24 ± 0.08	7 × 10 ⁻⁴	61	
Height	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	+	-	0.71 ± 0.08	0.75 ± 0.08	2 × 10 ⁻²⁸	91	
BMI	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	+	-	0.39 ± 0.08	0.24 ± 0.08	7 × 10 ⁻⁴	32	
FFM	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	+	-	0.40 ± 0.08	0.32 ± 0.08	4 × 10 ⁻⁶	79	
FM	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	+	-	0.33 ± 0.07	0.18 ± 0.08	6 × 10 ⁻³	38	
Truncal FM	+	+	-	+	-	-	+	-	-	-	-	-	-	-	-	+	-	0.31 ± 0.08	0.28 ± 0.09	1 × 10 ⁻⁴	33	
Waist circumference	+	-	-	-	-	-	+	-	-	-	+	-	-	-	-	+	-	0.43 ± 0.08	0.26 ± 0.08	3 × 10 ⁻⁴	41	
Hip circumference	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	+	-	0.48 ± 0.08	0.35 ± 0.08	3 × 10 ⁻⁶	59	
Dietary intake																						
Energy	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	0.53 ± 0.08	0.54 ± 0.08	3 × 10 ⁻¹⁴	22	
Protein																		0.59 ± 0.08	0.61 ± 0.08	3 × 10 ⁻¹⁵	1	
Fat																		0.69 ± 0.08	0.69 ± 0.08	6 × 10 ⁻²¹	1	
Carbohydrate																		0.56 ± 0.08	0.58 ± 0.09	3 × 10 ⁻¹³	1	
Physical activity																						
Activity counts	-	-	-	+	+	+	+	+	-	-	-	-	-	-	-	-	-	0.60 ± 0.08	0.57 ± 0.09	3 × 10 ⁻¹³	29	
Sedentary	+	-	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	0.66 ± 0.08	0.60 ± 0.09	5 × 10 ⁻¹⁴	37	
Light																		0.54 ± 0.08	0.39 ± 0.11	3 × 10 ⁻⁵	21	
Moderate	-	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	0.52 ± 0.08	0.50 ± 0.08	3 × 10 ⁻¹¹	31	
Vigorous	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.32 ± 0.11	0.32 ± 0.11	1 × 10 ⁻³	8	
Risk factors																						
Systolic BP	+	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	0.32 ± 0.07	0.33 ± 0.08	2 × 10 ⁻⁶	39	
Diastolic BP	+	-	-	-	-	-	+	+	-	-	-	-	-	+	-	-	-	0.34 ± 0.07	0.32 ± 0.08	4 × 10 ⁻⁶	9	
Insulin	+	+	-	-	-	-	-	+	-	-	-	-	-	-	-	+	-	0.40 ± 0.08	0.34 ± 0.09	1 × 10 ⁻⁵	26	
Glucose	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	0.57 ± 0.08	0.52 ± 0.08	3 × 10 ⁻¹²	2	
Triacylglycerol	+	-	-	-	-	-	+	-	-	-	-	-	-	+	-	+	-	0.52 ± 0.08	0.52 ± 0.08	1 × 10 ⁻¹⁴	15	
Total cholesterol	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	0.71 ± 0.08	0.73 ± 0.08	5 × 10 ⁻²³	3	
HDL																		0.63 ± 0.07	0.66 ± 0.07	7 × 10 ⁻²³	6	
ALT	+	-	-	+	+	+	-	-	-	+	+	-	-	-	-	-	-	0.29 ± 0.08	0.25 ± 0.08	3 × 10 ⁻⁴	1	

¹ $n = 1030$. Data indicate significant ($P < 0.05$) positive and negative coefficients for the covariates in the model. FFM, fat-free mass; FM, fat mass; BP, blood pressure; ALT, alanine aminotransferase.

² Adjusted for age, sex, age², age × sex, age² × sex.

³ Adjusted for age, sex, age², age × sex, age² × sex, and all other covariates.

TABLE 4

Additive genetic correlations (ρ_G) between the obesity-related phenotypes and risk factors for metabolic diseases, adjusted for age, sex, age², age \times sex, and age² \times sex¹

Obesity-related trait	BMI	Weight	Height	FFM	FM	Waist circumference
Energy intake	0.08 (0.14)	0.19 (0.14)	0.24 (0.10) ²	0.26 (0.13)	0.0005 (0.15)	0.11 (0.13)
Fat	0.25 (0.12) ²	0.30 (0.12) ²	0.25 (0.10) ²	0.27 (0.12) ²	0.18 (0.13)	-0.02 (0.13)
Carbohydrate	-0.29 (0.13) ²	-0.30 (0.13) ²	-0.20 (0.10)	-0.19 (0.13)	-0.21 (0.14)	-0.23 (0.13)
Sedentary activity	0.32 (0.12) ²	0.30 (0.12) ²	0.04 (0.10)	0.15 (0.12)	0.35 (0.12) ²	0.26 (0.12) ²
Light activity	-0.38 (0.12) ²	-0.33 (0.13) ²	-0.06 (0.11)	-0.14 (0.13)	-0.32 (0.13) ²	-0.32 (0.12) ²
Insulin	0.67 (0.08) ²	0.57 (0.10) ²	0.17 (0.12)	0.47 (0.11) ²	0.61 (0.10) ²	0.72 (0.08) ²
Total cholesterol	-0.08 (0.12)	-0.22 (0.13)	-0.33 (0.09) ²	-0.19 (0.12)	-0.15 (0.13)	-0.18 (0.12)
HDL	-0.13 (0.11)	-0.17 (0.12)	-0.27 (0.09) ²	-0.20 (0.11)	-0.15 (0.12)	-0.16 (0.11)
ALT	0.35 (0.14) ²	0.12 (0.17)	-0.33 (0.13) ²	0.05 (0.17)	0.31 (0.14) ²	0.26 (0.15)

¹ All values are $\bar{x} \pm SE$; $n = 1030$. FFM, fat-free mass; FM, fat mass; ALT; alanine aminotransferase. Additive genetic correlations provide evidence of pleiotropy (a common set of genes that influence more than one trait).

² $P < 0.05$.

exposure to gestational diabetes mellitus, exposure to breastfeeding, age at introduction of solid foods, asthma, physical education classes, and family size were also included. For anthropometric and body-composition traits, these covariates explained 32–91% of the phenotypic variance. With respect to diet, $\approx 20\%$ of the phenotypic variation in total energy intake and only 1% of the variation in macronutrient composition were accounted for by the covariates. The covariates explained 8–37% of the variance in the physical activity traits. Expression of the comorbidity risk factors (blood pressure, insulin, and triacylglycerol) were also attributable to these covariates (range: 15–39%). In contrast, glucose, total cholesterol, HDL, and ALT concentrations were only marginally affected by these covariates. After control for these important covariates, significant additive genetic effects were detected in all these traits. The heritabilities of anthropometric indexes ranged from 0.24 to 0.75. The heritability coefficients for body composition ranged from 0.18 to 0.35. Dietary intakes presented an average heritability of ≈ 0.60 , whereas the heritabilities of physical activities ranged from 0.32 to 0.60. The risk factors for metabolic diseases were heritable; the coefficients ranged from 0.25 to 0.73.

The additive genetic correlations between obesity traits and risk factors for metabolic diseases, where significant, are shown in **Table 4**. The genetic correlations (ρ_G) among the anthropometric and body-composition traits (body weight, BMI, FFM, FM, truncal FM, and waist and hip circumferences) were highly significant, with a mean genetic correlation of 0.80 (data not shown). Height had a lower genetic correlation with other body size traits (mean $\rho_G = 0.3$). The dietary intake and physical activity traits also showed positive genetic correlations with the anthropometric and body-composition traits. Bivariate analysis of total energy intake and height indicated the sharing of common genes in their expression ($\rho_G = 0.24 \pm 0.10$, $P = 0.03$). Percentage fat intake was genetically associated with BMI, weight, height, and FFM; ρ_G values were 0.25, 0.30, 0.25, and 0.27, respectively ($P < 0.05$). The percentage carbohydrate intake showed negative genetic relations with BMI and weight ($\rho_G = -0.29$ and -0.30 , respectively; $P < 0.05$). The percentage awake time spent in sedentary and light activities showed the same pattern; ρ_G values were significant for BMI, weight, FM, and waist circumference; however, the opposite pattern was seen for the percentage awake time in

light activity because of the inverse relation between sedentary and light activities.

The diabetes risk factors showed positive genetic correlations with several anthropometric and body-composition traits. Insulin was genetically correlated with all the studied traits of body size and composition, except for height. The tightly regulated fasting serum glucose showed no genetic correlations with any of the phenotypes of body size or composition. The positive genetic correlation of ALT with BMI and FM may have contributed to these children's risk of nonalcoholic fatty liver disease. Height shared genetic influences with fasting serum concentrations of total cholesterol, HDL, and ALT. The negative genetic correlations between height and ALT and cholesterol implied that a set of genes with a positive influence on height may exhibit negative effects on cholesterol and ALT concentrations in children.

DISCUSSION

The Viva la Familia Study was designed to genetically map childhood obesity and its comorbidities in the Hispanic population. By design, our Viva la Familia cohort is enriched for genes and behaviors related to obesity; therefore, it is genetically informative with respect to the development of childhood obesity and its metabolic consequences. Most (51%) of the children were overweight, and 24% were above the 99th BMI percentile. A strong family history of obesity, diabetes, CVD, and hypertension in the parents or grandparents was reported for these Hispanic children. The ascertainment of our cohort was based on an overweight proband, which theoretically could introduce bias into our estimate of heritability. However, we routinely correct for ascertainment bias in all our genetic analyses; therefore, these estimates of heritability are generalizable to Hispanic children. Although it is clear that genetic variation is responsible for a large proportion of the phenotypic variation in childhood obesity and its comorbidities, it is also equally clear that expression of the genotype will depend on the environment.

Epidemiologic studies have identified several risk factors for childhood obesity, each with their own genetic and environmental determinants. The effect of socioeconomic factors on childhood obesity varies across populations. In westernized countries and societies in transition, obesity is usually more prevalent in

areas of social deprivation and poverty (24). In the United States, the relation between socioeconomic status and overweight is weaker and less consistent (25). In NHANES III, the prevalence of overweight among Mexican American and black children and adolescents was not related to family income; however, an inverse relation was seen for white adolescents. In general, >13 y of parental education was associated with the lowest prevalence of childhood overweight.

Parental obesity increases the risk of obesity in the offspring (26–29). Childhood-onset obesity has been associated with an increased relative risk (2.14) of obesity in first-degree relatives, which suggests a higher genetic loading and familial aggregation (30). In fact, quantitative genetic analyses of obesity-related phenotypes have consistently found significant heritabilities, which suggests that there is an additive or oligogenic component to obesity (31–34). Results from twin studies in children (35, 36) and adolescents (37, 38) show heritabilities for BMI in the range of 70–90% (39). Family studies report estimates of parent-offspring and sibling correlations in agreement with heritabilities for BMI of 20–80%. Although genetic variation is responsible for a large proportion of the variation in BMI, it is equally clear that expression of the genotype will depend on the environment. Individual nonshared environments rather than familial shared environments seem responsible for the nongenetic differences in BMI (7, 40–42).

Early life experiences can also affect later childhood obesity. Infant feeding practices may play a critical role in the entrainment of eating behaviors later in life as suggested by a meta-analysis showing that breastfeeding reduced the risk of childhood obesity significantly with an adjusted odds ratio of 0.78 (43). Another such meta-analysis failed to find a significant protective effect of breastfeeding (44). Rapid maturation during puberty may predispose to the development of obesity. The Amsterdam Growth and Health Study showed that persons who matured rapidly in adolescence were generally more obese than were those who matured slowly (45). A study in Finnish twin and singleton adolescents suggested sex-specific effects of genes on BMI, most likely as a result of differences in pubertal development (39).


Familial resemblance has been observed for dietary intake (46). In the Framingham Children's Study, parents and children reported similar nutrient intakes. In the Quebec Family Study, aggregation for energy and macronutrient intakes was primarily accounted for by environmental factors. The heritability observed for carbohydrate and fat intakes was 0.20. Evidence of genetic influences on habitual physical activity is limited (47). In a Finnish twin study (48), the heritability for leisure-time physical activity was estimated to be 0.62. In the Quebec Family Study, most of the variation in habitual physical activity was accounted for by environmental factors: 71% for habitual physical activity and 88% for exercise participation (49). Additive genetic effects only accounted for 29% of the variance in habitual physical activity.

In our analysis, h^2 was defined in the narrow sense as the proportion of the residual variance attributed to the additive genetic effects only; other genetic effects were subsumed under environmental factors. Thus, these h^2 estimates are conservative if dominance and epistasis exist for the studied traits. From our estimations, the additive genes explained from 0.18 to 0.75 of the variance in traits of interest. The remainder (0.25 to 0.72) of the

total phenotypic variation was derived from dominance, epistasis, maternal imprinting, environmental factors, and measurement errors. In one study that used structural equation modeling, genetic factors accounted for 67% of the variance in BMI, of which 50% was due to dominance and 50% to additive genetic effects (35).

In our study, the residual heritabilities for body size and composition were significant, ranging from 0.18 to 0.75. The heritability for diet and physical activity were in the range of 0.32 to 0.69. Heritabilities for the metabolic risk factors were from 0.25 to 0.73. The covariates accounted for 1 to 91% of the phenotypic variation in our measured traits. All heritabilities were significantly greater than zero, and for most traits large enough to warrant a search for single major genes with relatively large effects. Although direct comparison of heritability estimates across studies is problematic since they depend on study design, ascertainment, methods of parameter estimation, and environmental contributions, the heritabilities for body size and composition, and risk factors for metabolic diseases from this study are in the range of commonly reported estimates from other populations. In the San Antonio Family Heart Study (SAFHS) in Mexican Americans, genes accounted for 15–40% of phenotypic variation in lipids, glucose, insulin, adiposity, and blood pressure (50, 51). In the SAFHS, familial relations accounted for a low proportion of the variance in physical activity (0.09) and nutrient intakes (0.13–0.26) (52). In 38 dizygotic and 62 monozygotic twin pairs aged 4–10 y, familial resemblance in physical activity was explained predominantly by shared environmental factors, not genes (53). In the Strong Heart Family Study in American Indians, heritabilities for the obesity phenotypes were >40% (54). In the Northern Manhattan Family Study in Caribbean-Hispanic families, heritabilities for the components of the metabolic syndrome ranged from 0.16 for SBP to 0.60 for HDL (55). In the Hong Kong Family Diabetes Study, significant heritabilities were seen for BMI (0.60), glucose (0.28), and insulin (0.62); significant genetic correlations between BMI, glucose, insulin and lipids suggested that pleiotropy (a common set of genes influencing more than one trait) contributed to the clustering of metabolic diseases (56).

Pleiotropy was seen between several of our obesity-related traits. Dietary intake and physical activity showed positive genetic correlations with the anthropometric and body-composition traits. Pleiotropy was also evident between the metabolic risk factors and anthropometric and body-composition traits. The positive genetic correlations indicate that shared genes that augment adiposity also increase fasting serum insulin and ALT. The negative genetic correlations with height implies that the genes influencing height have opposite effects on ALT and cholesterol.

In conclusion, obesity in Hispanic children arises as a result of complex interactions between genetic and environmental factors. Given the significant heritability for the obesity-related traits in this cohort, the Viva la Familia Study should prove valuable for identifying major genes with relatively large effects on the development of childhood obesity and its comorbidities in the Hispanic population. The Viva la Familia Study has provided evidence for a strong genetic contribution to the high prevalence of obesity and its comorbidities in Hispanic children. 

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