Diabetes and Hypertension in Mexican American Families: Relation to Cardiovascular Risk

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There is a strong familial predisposition to type 2 diabetes, hypertension, and cardiovascular disease. The authors evaluated the association between a family history of these diseases and a large panel of cardiovascular risk factors in 1,431 Mexican American subjects who were enrolled in the San Antonio Family Heart Study in San Antonio, Texas. The baseline phase of the study covered 1992–1996. Diabetes and hypertension were diagnosed according to standard clinical criteria, while cardiovascular disease was defined as a history of heart attack or heart surgery. The prevalence of diabetes, hypertension, and cardiovascular disease in this population was 15%, 12%, and 3%, respectively. For each unaffected subject, the authors computed a family history score based on the presence or absence of disease in parents and older siblings, and correlations between cardiovascular risk factors and family history scores were estimated by using likelihood-based variance component methods. Diabetes family history score was significantly correlated with a broad panel of cardiovascular risk factors, including glucose and insulin, obesity, blood pressure, triglycerides, and total cholesterol. Hypertension family history score was significantly correlated with glucose, blood pressure, body mass index, waist circumference, total cholesterol, and triglycerides. These results support the idea that genes that confer a risk for diabetes, and to a lesser extent hypertension, adversely alter the cardiovascular risk profile long before the manifestation of clinical disease.


Cardiovascular disease is the leading cause of death among adults in the United States and is a major cause of morbidity (1). A family history of early heart disease is an important risk factor for cardiovascular disease, and relatives of patients with diabetes and hypertension are also at increased risk, partly because these relatives tend to have elevated glucose and blood pressure levels. However, a family history of diabetes and/or hypertension may also be associated with other alterations in the cardiovascular risk profile. For example, numerous studies have reported that relatives of diabetic subjects tend to be more insulin resistant than control subjects (2–8), and insulin resistance has been reported in nonhypertensive offspring of subjects with essential hypertension (9–12). Moreover, prospective studies have established that an atherogenic cardiovascular risk profile, including elevations in body mass index, triglyceride concentrations, and blood pressure, begins to emerge long before the onset of clinical diabetes (13, 14). This pattern of risk factor clustering is commonly referred to as the multiple metabolic syndrome, or syndrome X. Clustering of these risk factors is consistent with the idea that genes associated with diabetes and/or hypertension may have pleiotropic effects on cardiovascular risk that are independent of the secondary changes that occur as a consequence of the diabetic (and/or hypertensive) state.

The goal of this study was to evaluate the relation between a family history of diabetes, hypertension, and cardiovascular disease and a broad panel of cardiovascular risk factors, including measures of adiposity, lipids and lipoproteins, and blood pressure. The study population consisted of persons with large, multigenerational pedigrees. A unique feature of this population is that the families represented a population-based sample, which were not selected for any particular disease or phenotype.

MATERIALS AND METHODS

The San Antonio Family Heart Study was designed to investigate the genetics of heart disease and its determinants in Mexican American families from San...
Antonio, Texas. Probands for the study were identified, without regard to health status or family health history, from low-income neighborhoods, and all first-, second-, and third-degree relatives of the proband and spouse aged 16 years or older were invited to participate. A total of 1,431 persons from 42 extended families were recruited into the baseline phase of the study, which was conducted between 1992 and 1996. Details of the sampling design and recruitment procedures have been described previously (15).

Probands and participating family members received a medical examination in our clinic. Pregnant women were not eligible to participate; women who reported that they were pregnant were recontacted following their pregnancies to reschedule the examination. Examinations took place in the morning following a 12-hour fast. An anthropometric assessment was conducted that included measurement of height and weight, skinfold thicknesses, and waist and hip circumferences. Systolic (first phase) and diastolic (fifth phase) blood pressures were measured to the nearest even digit by using a random-zero sphygmomanometer (Hawksley-Gelman, London, England) on the right arm of the seated participant. Three readings were recorded for each person, whose blood pressure was defined as the average of the second and third readings.

A 75 g glucose equivalent load was also administered, and glucose and insulin levels were determined from a blood sample obtained 2 hours following the glucose challenge. Plasma glucose was measured by using an Abbott V/P Analyzer (Diagnostic Products Corp., Los Angeles, California) and serum insulin and leptin by radioimmunoassay. Lipid and lipoprotein concentrations were determined from fasting blood samples by using methods described previously (15). Low density lipoprotein (LDL) size was measured by using nondenaturing gradient gel electrophoresis in laboratory-made gels (16). LDL cholesterol was stained with Sudan black B; median diameter, the laboratory diameter that splits the LDL absorbance profile in two, was determined as described by Rainwater et al. (17). Median diameter is similar to LDL particle score as measured by other laboratories (18, 19).

Diabetes was diagnosed according to the plasma glucose criteria of the World Health Organization (20). Subjects were also considered to have diabetes if they were currently taking antidiabetic medications. Hypertension was defined as a systolic blood pressure of $\geq 160$ mmHg, a diastolic blood pressure of $\geq 95$ mmHg, or current use of antihypertensive medications. Overt heart disease was defined as a self-reported history of heart attack (“Have you ever been told by a doctor that you had a heart attack?”) or a history of heart surgery (“Have you ever had surgery on your heart?”).

A medical history interview was administered, in which information was obtained on a variety of other factors potentially related to diabetes, hypertension, and heart disease. These variables included years of education, current smoking status, alcohol consumption (converted to g/day), menopausal status, oral contraceptive use, and postmenopausal estrogen use. Women were considered postmenopausal if they reported having had both ovaries removed or if at least 12 months had elapsed since their last menstrual period. These variables were used as covariates in the regression analyses.

The extent to which diabetes, hypertension, and overt heart disease clustered in study subjects was evaluated by comparing the prevalence of each disorder in those with and without a second disorder. For example, we compared the prevalence of hypertension and overt heart disease in those subjects with and without diabetes. These analyses were performed for men and women separately. Odds ratios were computed by using multiple logistic regression to describe the association between each pair of disorders while adjusting for the effects of age.

In a preliminary analysis, we compared mean levels of cardiovascular risk factors between subjects with and without a parental history of diabetes, hypertension, and overt heart disease. Only unaffected subjects were included in these analyses. For example, we compared cardiovascular risk factors between nondiabetic offspring of diabetic parents and nondiabetic offspring of nondiabetic parents (and between nonhypertensive offspring of hypertensive parents and nonhypertensive offspring of nonhypertensive parents). Parental history was considered positive if either parent was affected and negative if both parents were examined and found to be unaffected. Offspring of one unaffected parent were not included in this analysis if the other parent was not examined. Age-adjusted means for the cardiovascular risk factors were computed by using the analysis of variance procedure in SYSTAT (SPSS Inc., Chicago, Illinois). This analytic approach was deemed preliminary because it makes only limited use of the known information about disease status in ancestors (i.e., parental disease status is dichotomized, and information about other relatives is not considered). In addition, the analysis does not take into account the nonindependence of offspring within sibships and between related sibships.

To incorporate into the analysis information about whether additional family members were affected, we computed a family history score for each participant and estimated its effect on each quantitatively distributed risk factor. The family history score was designed to summarize the burden of disease (diabetes, hyper-
tension, and heart disease) in each participant's immediate family members. Scores were calculated by adding 1 for each affected parent and older sibling and -1 for each unaffected parent and older sibling. Unexamined family members did not contribute any information to the family history score. Thus, although they were excluded from the preliminary “parental history” analysis, subjects who had one examined unaffected parent and one unexamined parent could be included in this analysis. This scoring is analogous to that described by Bonney in his class D regressive models, in which each subject's phenotype is dependent on the phenotype of his or her parents and all older siblings (21). In the context of our study, a significant effect of this family history score occurs only when the familial correlation between the discrete trait and the quantitative risk factor does not equal 0.

A virtue of this scoring function is that the scores are influenced largely by the “density” of disease in a family, since information from both affected and unaffected relatives is included. In contrast, scores based on the numbers of affected relatives only are heavily dependent on family size; larger families may include more affected persons than smaller families do merely because of their size. The problem is not remedied simply by considering the proportion of affected persons in the family. This approach introduces the problem that scores generated from small families may be highly variable but will be assigned weights equal to those scores generated from large families. Our scoring function places more weight on larger families, because extremely high (or extremely low) scores cannot be generated from small, and less informative, families. Obviously, the scores among siblings are correlated, but these familial correlations are accounted for in the analysis by conditioning on the pedigree structures, described below.

We modeled each risk factor as a function of age, age squared, sex, and family history score. The following covariates were also included in the model: years of education, alcohol consumption (g/day), current smoking (yes/no), menopausal status (postmenopausal vs. other), oral contraceptive use (current use vs. other), and postmenopausal estrogen use (current use vs. other). Although genetic influences shared among relatives can also be incorporated as an additional component of variance, we chose not to model them because we hypothesized that any associations between the cardiovascular risk factor and a family history of disease are largely due to the transmission of genes from parents to offspring. In fact, we demonstrated previously that genetic factors account for much more of the phenotypic variability in cardiovascular risk factors in this population than do environmental influences shared among relatives (15). Maximum likelihood estimates of the means and variances were obtained by using the FISHER software program (22), which conditions parameter estimations on the family relationships.

We accounted for nonindependence among siblings by conditioning the analysis on the pedigree data. Briefly, we used FISHER software to compute the likelihood of the pedigree data in models that both included and excluded the family history score. The significance of the family history score was assessed by using the likelihood ratio test, which compares the likelihood of a full model (e.g., age, sex, covariates, and family history score) with that of a nested model (e.g., age, sex, and covariates only). The likelihood ratio statistic is distributed asymptotically as a chi-square statistic with degrees of freedom equal to the difference in the numbers of parameters included in the two models being compared (23). No adjustment was made for multiple comparisons, in part because we hypothesized that many of the outcomes were interdependent.

We tested for the presence of interactions between sex and family history score by estimating the effect of family history score independently for men and women. The sex interaction term was interpreted as statistically significant if the likelihood of this model with sex-specific regression coefficients was significantly larger than that of the nested model, in which the sex correlations were constrained to be identical.

Persons who were currently taking antilipid medications were excluded from the analyses involving lipid and lipoprotein concentrations, and diabetic persons were excluded from analyses involving insulin. Insulin, triglyceride, and lipoprotein(a) (Lp(a)) concentrations were logarithm-transformed prior to analysis to remove skewness, and the distribution of LDL sizes was transformed by using the reciprocal of the square root.

**RESULTS**

The mean age (standard deviation) of the 1,431 persons examined in this study was 39.3 (16.8) years. The prevalence of diabetes, hypertension, and self-reported heart disease, according to age and sex, is shown in table 1. More than 20 percent of the men and women had at least one of these three conditions. The overall prevalence of diabetes was 14.0 and 15.7 percent in men and women, respectively. Approximately 57 percent of the diabetic subjects were currently taking antidiabetic medications (either insulin or oral agents). Hypertension was present in 9.0 percent of the men and 14.0 percent of the women. Of those affected, 79.0 percent reported that they were currently taking anti-
hypertensive medications (82.4 percent of the men and 77.6 percent of the women). A total of 4.4 percent of the men and 2.0 percent of the women reported that they had previously been told by a physician that they had had a heart attack or that they had undergone heart surgery in the past.

The prevalence of hypertension and heart disease in men and women, according to diabetes status, is shown in figure 1. Hypertension was present in 33.3 and 5.1 percent of diabetic and nondiabetic men, respectively, and in 42.0 and 8.7 percent of diabetic and nondiabetic women, respectively. Heart disease was present in 13.8 and 2.9 percent of diabetic and nondiabetic men, respectively, and in 6.2 and 1.3 percent of diabetic and nondiabetic women, respectively. After adjustment for age, the association between diabetes and hypertension was highly significant in both men (adjusted odds ratio (OR) = 4.00, \( p < 0.001 \)) and women (adjusted OR = 2.78, \( p < 0.001 \)). The association between diabetes and heart disease was statistically significant in men (adjusted OR = 2.76, \( p < 0.05 \)) but not women (adjusted OR = 1.52, \( p = 0.46 \)). The prevalence of heart disease was higher in hypertensives than in nonhypertensives, but the association was not statis-
tically significant in either men (adjusted OR = 2.25, p = 0.11) or women (adjusted OR = 2.19, p = 0.16).

The distribution of cardiovascular risk factors in nondiabetic subjects, according to a parental history of diabetes, is shown in Table 2. In men, those with a parental history of diabetes had a significantly higher body mass index and subscapular-triceps ratio, a significantly larger waist circumference, and significantly higher serum leptin concentrations and triglyceride levels (p < 0.05 for each comparison). In women, a parental history of diabetes was associated with significantly higher levels of fasting (p < 0.01) and 2-hour (p < 0.001) glucose, fasting (p < 0.05) and 2-hour (p < 0.01) insulin, and triglycerides (p < 0.01); a significantly higher body mass index (p < 0.001) and waist-hip ratio (p < 0.01); a significantly larger waist circumference (p < 0.001); a significantly smaller LDL size (p < 0.05); and significantly lower concentrations of Lp(a) (p < 0.01).

The distribution of cardiovascular risk factors in nonhypertensive subjects with and without a parental history of hypertension is shown in Table 3. Men who had a parental history of hypertension had significantly higher concentrations of leptin (p < 0.05), while women with a parental history of hypertension had significantly higher systolic blood pressure (p < 0.01) and triglyceride levels (p < 0.05). Two-hour insulin concentrations were also significantly lower in women with a parental history of hypertension than in those without such a history (p < 0.05).

The distribution of cardiovascular risk factors in subjects free of overt heart disease, with and without a parental history of heart disease, is shown in Table 4. For men, fasting insulin and apolipoprotein B concentrations were significantly lower in those with a positive parental history compared with those without such a history; for women, those with a positive parental history had significantly higher levels of fasting insulin (p < 0.05), a significantly higher body mass index (p < 0.001), a significantly larger waist circumference (p < 0.05), and significantly lower concentrations of Lp(a) (p < 0.01).

The results of the variance component analyses are shown in Table 5. The family history scores ranged from -11 to 5 for diabetes, -13 to 3 for hypertension, and -13 to 2 for heart disease. Diabetes family history score was significantly correlated with fasting and 2-hour glucose (p < 0.001 for both), fasting (p < 0.05) and 2-hour (p < 0.001) insulin, and several different measures of obesity, including body mass index (p < 0.01), waist circumference (p < 0.01), leptin concentrations (p < 0.05), and waist-hip ratio (p < 0.05). Diabetes family history score was also significantly correlated with both systolic and diastolic blood pressure (p < 0.05), higher concentrations of total cholesterol (p < 0.05) and triglycerides (p < 0.01), and lower

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**TABLE 2. Age-adjusted levels of cardiovascular risk factors in nondiabetic subjects with and without a parental history of diabetes, the San Antonio Family Heart Study, San Antonio, Texas, 1992–1996**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Men</th>
<th>Women</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No parental history (n = 82)</td>
<td>Confirmed parental history (n = 137)</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>85.8</td>
<td>88.6</td>
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<tr>
<td>2-hour glucose (mg/dl)</td>
<td>89.8</td>
<td>94.7</td>
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<tr>
<td>In (fasting insulin (μU/ml))</td>
<td>2.31</td>
<td>2.29</td>
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<tr>
<td>In (2-hour insulin (μU/ml))</td>
<td>3.56</td>
<td>3.68</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>7.3</td>
<td>10.0*</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>25.8</td>
<td>27.8*</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>89.0</td>
<td>93.3*</td>
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<tr>
<td>Waist-hip ratio</td>
<td>0.903</td>
<td>0.917*</td>
</tr>
<tr>
<td>Subscapular-triceps ratio</td>
<td>1.705</td>
<td>1.909*</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>117.2</td>
<td>118.0</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>69.3</td>
<td>71.0</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>175.6</td>
<td>182.2</td>
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<tr>
<td>HDL† cholesterol (mg/dl)</td>
<td>48.4</td>
<td>45.3</td>
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<tr>
<td>Apolipoprotein A-I (mg/dl)</td>
<td>136.9</td>
<td>134.8</td>
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<tr>
<td>Apolipoprotein A-II (mg/dl)</td>
<td>57.6</td>
<td>57.7</td>
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<tr>
<td>Apolipoprotein B (mg/dl)</td>
<td>105.2</td>
<td>111.4</td>
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<tr>
<td>In (triglycerides (mg/dl))</td>
<td>4.66</td>
<td>4.85*</td>
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<tr>
<td>In (lipoprotein(a) (mg/dl))</td>
<td>1.94</td>
<td>2.00</td>
</tr>
<tr>
<td>Median LDL† size (nm)</td>
<td>26.68</td>
<td>26.52</td>
</tr>
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</table>

* p < 0.05; ** p < 0.01; *** p < 0.001.
† HDL, high density lipoprotein; LDL, low density lipoprotein.

*Am J Epidemiol* Vol. 149, No. 11, 1999
TABLE 3. Age-adjusted levels of cardiovascular risk factors in nonhypertensive subjects with and without a parental history of hypertension, the San Antonio Family Heart Study, San Antonio, Texas, 1992–1996

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Fasting glucose (mg/dl)</th>
<th>2-hour glucose (mg/dl)</th>
<th>In (fasting insulin (μU/ml))</th>
<th>In (2-hour insulin (μU/ml))</th>
<th>Leptin (ng/ml)</th>
<th>Body mass index (kg/m²)</th>
<th>Waist circumference (cm)</th>
<th>Waist-hip ratio</th>
<th>Subscapular-triceps ratio</th>
<th>Systolic blood pressure (mmHg)</th>
<th>Diastolic blood pressure (mmHg)</th>
<th>Total cholesterol (mg/dl)</th>
<th>HDLf cholesterol (mg/dl)</th>
<th>Apolipoprotein A-I (mg/dl)</th>
<th>Apolipoprotein A-II (mg/dl)</th>
<th>Apolipoprotein B (mg/dl)</th>
<th>In (triglycerides (mg/dl))</th>
<th>In (lipoprotein(a) (mg/dl))</th>
<th>Median LDLf size (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No parental history</td>
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<tr>
<td>(n = 124)</td>
<td>96.0</td>
<td>112.0</td>
<td>2.24</td>
<td>3.56</td>
<td>7.6</td>
<td>26.7</td>
<td>91.3</td>
<td>0.918</td>
<td>1.750</td>
<td>117.0</td>
<td>70.2</td>
<td>182.2</td>
<td>59.0</td>
<td>117.0</td>
<td>136.9</td>
<td>110.4</td>
<td>4.82</td>
<td>26.58</td>
<td></td>
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<tr>
<td>Confirmed parental history</td>
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<tr>
<td>(n = 116)</td>
<td>98.2</td>
<td>106.3</td>
<td>2.34</td>
<td>3.58</td>
<td>10.3*</td>
<td>29.0</td>
<td>94.0</td>
<td>0.916</td>
<td>1.899</td>
<td>112.0</td>
<td>71.6</td>
<td>185.4</td>
<td>57.3</td>
<td>120.0</td>
<td>139.0</td>
<td>113.7</td>
<td>4.80</td>
<td>26.59</td>
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</table>
| * \( p < 0.05; \) ** \( p < 0.01. \)

† HDL, high density lipoprotein; LDL, low density lipoprotein.

TABLE 4. Age-adjusted levels of cardiovascular risk factors in subjects free of overt heart disease, with and without a parental history of overt heart disease, the San Antonio Family Heart Study, San Antonio, Texas, 1992–1996

| Risk factor                        | Fasting glucose (mg/dl) | 2-hour glucose (mg/dl) | In (fasting insulin (μU/ml)) | In (2-hour insulin (μU/ml)) | Leptin (ng/ml) | Body mass index (kg/m²) | Waist circumference (cm) | Waist-hip ratio | Subscapular-triceps ratio | Systolic blood pressure (mmHg) | Diastolic blood pressure (mmHg) | Total cholesterol (mg/dl) | HDLt cholesterol (mg/dl) | Apolipoprotein A-I (mg/dl) | Apolipoprotein A-II (mg/dl) | Apolipoprotein B (mg/dl) | Median LDLt size (nm) |
|-----------------------------------|-------------------------|------------------------|-----------------------------|-----------------------------|-----------------|--------------------------|---------------------------|----------------|--------------------------|-----------------------------|----------------------------|---------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|-----------------------------|
| No parental history               |                         |                        |                             |                             |                 |                          |                            |                |                          |                             |                            |                          |                          |                          |                          |                          |                          |                          |                          |
| (n = 161)                         | 96.9                    | 110.5                  | 2.36                        | 3.58                        | 9.3             | 27.4                     | 93.0                       | 0.916          | 1.819                    | 117.0                       | 70.2                       | 182.2                     | 59.0                      | 117.0                    | 136.9                    | 110.4                    | 4.82                      | 26.58                     |
| Confirmed parental history        |                         |                        |                             |                             |                 |                          |                            |                |                          |                             |                            |                          |                          |                          |                          |                          |                          |                          |                          |
| (n = 38)                          | 98.9                    | 112.3                  | 2.04*                       | 3.33                        | 8.6             | 27.5                     | 90.4                       | 0.897          | 1.728                    | 119.6                       | 71.6                       | 185.4                     | 57.3                      | 123.0                    | 140.0                    | 113.7                    | 4.61                      | 26.82                     |
| * \( p < 0.05; \) ** \( p < 0.01. \)  

† HDL, high density lipoprotein; LDL, low density lipoprotein.
concentrations of Lp(a) ($p < 0.05$). Hypertension family history score was significantly correlated with higher concentrations of fasting and 2-hour glucose, serum total cholesterol, and triglycerides ($p < 0.05$ for each); higher systolic and diastolic blood pressure ($p < 0.01$) and body mass index ($p < 0.05$); a larger waist circumference ($p < 0.05$); and lower concentrations of Lp(a) ($p < 0.05$). For none of these variables was there any evidence of an interaction between sex and family history score.

**DISCUSSION**

A major conclusion of this study is that a family history of type 2 diabetes, and to a lesser extent hypertension, is associated with an atherogenic cardiovascular risk profile, as reflected by greater adiposity, higher triglyceride and total cholesterol concentrations, and elevated blood pressure. This atherogenic profile is apparent even for unaffected persons in the pedigree, only some of whom will presumably develop overt diabetes and/or hypertension. These results are not unexpected, since many previous studies have shown that nondiabetic relatives of diabetics are insulin resistant (2–8). Indeed, the associations that we found probably can be considered a manifestation of the multiple metabolic syndrome. However, few studies have demonstrated the extent of the atherogenic changes that we observed, nor have they evaluated the impact of the multiple metabolic syndrome within a population-based sample of families.

The heritability of the cardiovascular risk factors that we analyzed in this study is moderately high (15, 24). In a previous study of this Mexican American population, we estimated that the additive effects of genes (i.e., polygenes) accounted for 18–46 percent of the phenotypic variance in glucose, insulin, blood pressure, adiposity, and concentrations of various lipid and lipoprotein measures; in contrast, age, sex, and other covariates accounted for generally less than 5 percent of the total variance in these traits (15). In the present study, the associations we observed between a family history of diabetes and many of these risk factors are consistent with the commonly held idea that the genes that influence variation in cardiovascular risk factors ultimately influence the risk for overt disease. If true, then identification of such genes may lead to insights about future directions for therapy and disease prevention.
An elevated body mass index and a parental history of diabetes have long been recognized as important risk factors for type 2 diabetes. The independent contributions of these two risk factors to diabetes risk were definitively demonstrated by Knowler et al., who showed that diabetes incidence in Pima Indians increased with increasing levels of body mass index independently of whether one or both parents were affected and, conversely, that at any given level of body mass index, diabetes incidence increased with an increasing number of diabetic parents (from 0 to 1 to 2) (25). The one exception to this trend was that body mass index was not associated with diabetes incidence in subjects who did not have a parental history of diabetes. More recently, Hanson et al. observed that diabetes prevalence was higher in offspring of lean diabetics than in offspring of heavy diabetics, and they hypothesized that a higher genetic load was required for a lean person to become diabetic (26). Many have used these observations to reinforce the belief that body mass index and a family history of diabetes are etiologically distinct risk factors. However, this interpretation may be at least partially incorrect, since common genes may predispose to both diabetes and obesity. In other words, obesity should be regarded as part of the pathogenic process of diabetes, and it may be equally as valid to consider that persons become obese because they have inherited diabetes susceptibility genes as it is to consider that they become diabetic because they get fat.

Because it is largely unknown which genes influence both obesity and diabetes risk, it is difficult to project the relative importance of pleiotropic genes in the etiology of these disorders. However, recent results from the Pima Diabetes Genes Group suggest that some pleiotropic genes may have relatively major effects on both traits. In a genome-wide screen to identify genes for susceptibility to diabetes and related traits, these investigators have used linkage analysis to map a locus to the long arm of chromosome 11 that influences both susceptibility to diabetes and, in non-diabetic persons, variation in body mass index (27).

In our data, a family history of hypertension was highly correlated with systolic and diastolic blood pressure but only weakly correlated with (a few) other cardiovascular risk factors. We interpret this finding to indicate that the pleiotropic effects of hypertension susceptibility genes on other cardiovascular risk factors are relatively weak. Supporting this interpretation is the fact that the epidemiologic evidence for an association between hypertension and insulin resistance, at least in Mexican Americans and Pima Indians, is relatively weak (28–30). Moreover, we previously reported from our own study that the genetic correlation (which reflects the degree of pleiotropy) for insulin concentrations with body mass index, high density lipoprotein cholesterol, and triglyceride concentrations is much higher than it is for insulin concentrations with blood pressure (31).

The association of a family history of cardiovascular disease with cardiovascular risk factors was not strong in our study. The most likely explanation is that we used a relatively crude definition of cardiovascular disease that relied on a self-reported history of heart attack and/or heart surgery, and we were unable to verify disease endpoints. Furthermore, the sensitivity of our case definition was low, further reducing our power to detect associations. It is possible that additional associations would have been identified had we broadened our case definition to include subclinical measures of atherosclerotic vessel disease, such as those obtained from ultrasonography of the carotid arteries or electron-beam computed tomography of the coronary arteries.

The inverse association between diabetes family history score and Lp(a) agrees with our earlier studies that reported significantly lower Lp(a) concentrations in diabetic subjects (32, 33). More recently, we found that Lp(a) concentrations are inversely correlated with serum insulin concentrations (34). However, the observation that Lp(a) concentrations were inversely correlated with family history scores for cardiovascular disease was unexpected, since most studies report a positive association between Lp(a) and cardiovascular disease (35, 36) or no association at all (37, 38). However, the frequency of insulin resistance is high in this population, and the inverse association between Lp(a) and a family history of heart disease may be secondary to insulin resistance. Supporting this interpretation is the fact that in this population, 2-hour insulin concentrations were also inversely associated with family history score for heart disease.

The impact of diabetes on cardiovascular risk is disproportionately worse for diabetic women than for diabetic men; the risk for cardiovascular mortality is increased threefold to fourfold in diabetic women but only twofold in diabetic men (39). In a longitudinal study of Mexican Americans also from San Antonio, Haffner et al. extended these observations to show that prediabetic women have a relatively more atherogenic cardiovascular risk profile than prediabetic men do, as reflected by their concentrations of fasting insulin, triglycerides, and high density lipoprotein cholesterol and by their diastolic blood pressure (40). However, our study found no evidence that a family history of diabetes was more strongly correlated with cardiovascular risk in women than in men.

The prevalence of type 2 diabetes is increasing rapidly in the United States, particularly in low-income

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ethnic populations such as Mexican Americans (41). The cause of this rapid increase has been attributed to behavioral changes, including an increase in sedentary lifestyle, with diabetes risk accentuated in those who have an underlying genetic susceptibility (42). An overlooked consequence of this diabetes epidemic may be an accompanying increase in cardiovascular risk that will occur even in many who will never develop overt diabetes. Although some studies have observed a paradoxical lower prevalence of cardiovascular disease in Mexican Americans (in whom diabetes and obesity occur relatively frequently) compared with non-Hispanic Whites (43), other studies have suggested that the burden of cardiovascular disease actually may be higher in Mexican Americans. For example, in the Corpus Christi Heart Project, the incidence of persons hospitalized with myocardial infarction was 1.5 and 1.3 times higher in Mexican American women and men, respectively, than in their non-Hispanic White counterparts (44). The discrepancy between the results of these prevalence and incidence studies is possibly explained by a lower survival rate among Mexican Americans with cardiovascular disease, as suggested by the observation that 28-day case fatality among those in the Corpus Christi Heart Project who were hospitalized for a definite or possible myocardial infarction was 1.5 times higher in Mexican Americans than in non-Hispanic Whites (45).

In summary, we detected significant associations between a family history of diabetes, and to a lesser extent hypertension, and a range of cardiovascular risk factors. These associations probably reflect the pleiotropic effects of genes that are transmitted from affected persons to their offspring. In populations such as Mexican Americans, in whom the incidence of diabetes is increasing rapidly, there is likely to be an accompanying increase in cardiovascular risk.

ACKNOWLEDGMENTS

This work was supported by grant PO1-HL45522 from the National Institutes of Health.

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