Was the Historic Contribution of Spain to the Mexican Gene Pool Partially Responsible for the Higher Prevalence of Type 2 Diabetes in Mexican-Origin Populations?

The Spanish Insulin Resistance Study Group, the San Antonio Heart Study, and the Mexico City Diabetes Study

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OBJECTIVE — Mexican-American populations in San Antonio, Texas (SA-MA) and Mexico have a higher prevalence of type 2 diabetes than non-Hispanic whites in San Antonio (SA-NHW). However, the higher prevalence of type 2 diabetes in Mexican-origin populations might be related, in part, not to Native American genetic admixture but to Spanish genetic admixture.

RESEARCH DESIGN AND METHODS — Four population-based epidemiological surveys conducted with Mexican-origin and European-origin samples provided data relevant to this question. In all four surveys, type 2 diabetes was defined as fasting plasma glucose ≥7.0 mmol/l or 2-h glucose ≥11.1 mmol/l or use of antidiabetic agents.

RESULTS — A comparison of the two Mexican-origin populations showed that the age- and sex-adjusted prevalence of type 2 diabetes was lower in Mexico than in SA-MA (15.1 vs. 17.9%, $P = 0.032$). Between the two European-origin populations, the prevalence of type 2 diabetes was lower in SA-NHW than in Spain (6.2 vs. 9.1%, $P < 0.0001$), but differences were attenuated by adjustment for BMI or after stratification by education. In logistic regression analyses, type 2 diabetes was associated with Mexican ethnic origin after adjusting for age, education, BMI, and waist-to-hip ratio.

CONCLUSIONS — The prevalence of type 2 diabetes in Spain was intermediate between that in Mexican-origin populations and SA-NHW. Although the higher degree of Native American admixture is a major contributor to the higher rates of type 2 diabetes, we cannot completely rule out a partial contribution of Spanish admixture to diabetes susceptibility among Mexican-origin populations.

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Abbreviations: MCDS, Mexico City Diabetes Study; OR, odds ratio; SAHS, San Antonio Heart Study; SA-NHW, non-Hispanic whites in San Antonio; SA-MA, Mexican-Americans in San Antonio; SIRS, Spanish Insulin Resistance Study; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Native American genetic admixture is a major contributor to the higher rates of type 2 diabetes in Mexican-origin populations. However, few comparisons have been performed with data from Spain. The higher prevalence of type 2 diabetes in Mexican-origin populations could be related, in part, not only to Native American genetic admixture but partly to Spanish admixture, as a consequence of its historical contribution to the Mexican gene pool. Mexican-origin communities in Mexico and the U.S. may have similar genetic backgrounds (i.e., Native American genetic admixture) (1,2) but differ in terms of socioeconomic levels and cultural orientation. European-origin communities in the U.S. have distinct genetic backgrounds relative to those of Mexican-origin (i.e., absence of or negligible Native American admixture) and may also differ socioeconomically and/or culturally. Mexican-Americans in San Antonio (SA-MA) and Mexican nationals residing in Mexico have a higher prevalence of type 2 diabetes than non-Hispanic whites in San Antonio (SA-NHW) (3–5). SA-MA and other Hispanics in the U.S. seem to have greater prevalence of type 2 diabetes than Mexican nationals residing in Mexico, which is related, in part, to differences in obesity rates (5,6). Therefore, to the concomitant analysis of studies performed in San Antonio and Mexico City, we added a second European-origin population from Spain with the purpose of comparing the prevalence of type 2 diabetes in these populations.

RESEARCH DESIGN AND METHODS

The San Antonio Heart Study

The San Antonio Heart Study (SAHS) is a population-based study of type 2 diabetes

and cardiovascular disease in Mexican-Americans and non-Hispanic whites in San Antonio, Texas. A person was considered Mexican-American if three or more grandparents were of Mexican origin or if both parents were born in Mexico and his/her self-declared ethnic identity did not specifically rule out Mexican origin. A person was considered non-Hispanic white if three or more grandparents were of non-Hispanic white ethnic background (e.g., Czech, Irish, Italian, Greek) (7). From January 1979 to December 1982 (phase 1) and from January 1984 to December 1988 (phase 2), we randomly selected households from low-income, middle-income, and high-income census tracts (4,8). All men and nonpregnant women aged 25–64 years who resided in the randomly sampled households were eligible to participate. The overall response rate was 65.3%. Detailed descriptions of this study have been published previously (8,9). An 8-year follow-up of the phase 1 cohort was completed between October 1987 and November 1990 (10), and a similar 8-year follow-up of the phase 2 cohort was concluded between October 1991 and October 1996 (11). A total of 3,682 participants were examined in these two follow-up phases and included in the analysis. We have used data from the two SAHS follow-up periods only, because the mean age of participants at that time was closer to the mean ages of those in studies in Mexico City and Spain.

The Mexico City Diabetes Study

The Mexico City Diabetes Study (MCDS) is a population-based study of cardiovascular disease in both diabetic and nondiabetic men and women aged 35–64 years from a low-income area of Mexico City, Mexico. The study site consisted of six low-income neighborhoods, each one corresponding to one census tract. A complete household enumeration was performed in each neighborhood between November 1989 and February 1990, and 3,505 study-eligible individuals (35- to 64-year-old men and nonpregnant women) were identified. Home interviews were conducted with 2,810 subjects, and physical and laboratory examinations were performed on 2,282 individuals (64.7% of the target population). Detailed descriptions of this study have been published previously (5,12,13).

Acquisition of data in San Antonio and Mexico City

Both studies were approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio, and the MCDS was also approved by the Centro de Estudios en Diabetes in Mexico City. All subjects gave informed consent. The SAHS and MCDS used identical protocols with standardized and joint training for medical staff. A metallic tape was used to measure the waist and hip circumferences at the level of the umbilicus and the greater trochanters, respectively (14). Plasma glucose level was measured by a glucose oxidase method. A 75-g oral glucose load (Orangedex; Custom Laboratories, Baltimore, MD) was administered to determine 2-h plasma glucose level.

The Spanish Insulin Resistance Study

The Spanish Insulin Resistance Study (SIRS) was designed as a cross-sectional, population-based study of the prevalence of type 2 diabetes and cardiovascular risk factors. It was conducted in seven towns across Spain (Arévalo, Talavera de la Reina, Guadalajara, La Coruña, Avilés, Vic, Alicante, and Mérida) from March 1995 to April 1998. The overall population of these towns was 831,674 inhabitants; populations of individual towns ranged from 7,359 to 274,577 (15). From a targeted population of 348,980 inhabitants, initial interview was obtained on 3,172 men and nonpregnant women aged 34–69 years. Of those, 121 (3.8%) were excluded because they met one or more of the following criteria: abdominal hernia, overt heart or hepatic failure, surgery during the previous year, weight changes >5 kg within the previous 6 months, or hospitalization. Complete physical examination and fasting blood samples were obtained on 2,949 participants, and 2-h blood specimens were collected from 2,123 participants (66.9% of the target population).

Acquisition of data in Spain

Survey procedures were adapted from the WHO MONICA protocol (16). All participants gave informed consent. One of the SAHS and MCDS investigators (S.H.) was a consultant in the design of the SIRS. The definition of variables and outcomes was identical; however, there was no cross-training of medical staff. Waist and hip circumferences were measured at the level of the umbilicus and greater trochanters, respectively. Blood specimens were obtained after a 12-h fast for determination of plasma glucose (Boehringer, Mannheim, Indianapolis, IN). An oral glucose tolerance test was performed with a 75-g oral glucose load challenge to assess the 2-h plasma glucose concentration.

Definition of variables and outcomes

All of these studies shared definitions for variables and outcomes. Educational attainment was measured as the highest number of years of schooling completed and was treated as a dichotomous variable in the analysis: having versus not having obtained a high school diploma. Overall adiposity was measured by BMI. Upper versus lower body fat pattern was assessed by waist-to-hip ratio (WHR) (12,17). We followed the 1997 "Recommendations from the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus" (18): fasting plasma glucose $\geq$7.0 mmol/l, and/or 2-h postglucose load plasma glucose $\geq$11.1 mmol/l, or use of antidiabetic medications. In nondiabetic subjects, fasting plasma glucose $\geq$6.1 and $<$7.0 mmol/l indicated impaired fasting glucose and 2-h glucose $\geq$7.8 and $<$11.1 mmol/l indicated impaired glucose tolerance.

Statistical methods

Statistical analyses were performed with the SAS statistical software system (SAS Institute, Cary, NC). Descriptive statistics (mean ± SEM) and number/percentage are shown in Table 1. Age- and sex-adjusted differences in continuous variables between the study populations were evaluated by one-way analysis of covariance with the GLM procedure in SAS. Population was used as the grouping variable; the other factors were covariates. Sex, population, and obesity interactions with ethnic origin (Mexican versus European) were also considered. Logistic regression models identified variables independently associated with the prevalence of type 2 diabetes. The Cochran-Armitage trend test was used to assess the relationship of prevalence of type 2 diabetes with BMI categories within each population. All statistical tests used two-sided probabilities.

Table 1—*Sociodemographic characteristics, anthropometric measurements, and age- and sex-adjusted prevalence of type 2 diabetes, impaired glucose tolerance, and impaired fasting glucose in participants from Spain, Mexico City, and San Antonio, Texas (Mexican-Americans and non-Hispanic whites)*

Ethnic origin	Mexican		*P* value	European		*P* value	
Population	Mexico	SA-MA	Mexico versus SA-MA	SA-NHW	Spain	SA-NHW versus Spain	Ethnic origin, *P* value
Sociodemographic characteristics							
Participants (*n*)	2,282	2,343	—	1,339	2,949	—	—
Age (years)	47.3 ± 0.20	51.4 ± 0.20	<0.0001	53.3 ± 0.26	49.3 ± 0.18	<0.0001	<0.0001
Age range (years)	29–67	32–76	—	32–75	34–69	—	—
Men (%)	41.2	41.1	NS	44.3	45.3	NS	0.0003
Education: HSD (%)	7.6	58.1	<0.0001	91.6	18.7	<0.0001	<0.0001
Age- and sex-adjusted anthropometric measurements							
BMI (kg/m^2)	28.2 ± 0.11	29.4 ± 0.10	<0.0001	27.1 ± 0.14	27.9 ± 0.09	<0.0001	<0.0001
WHR (×100)	98.0 ± 0.19	92.6 ± 0.18	<0.0001	89.6 ± 0.24	94.9 ± 0.16	<0.0001	<0.0001
Crude prevalence of type 2 diabetes (%)	14.2	21.9	<0.0001	9.5	10.2	NS	<0.0001
Age- and sex-adjusted prevalence of type 2 diabetes, IGT, and IFG							
Type 2 diabetes (%)	15.1	17.9	0.032	6.2	9.1	0.005	<0.0001
IGT (%)*	14.8	18.0	0.009	11.6	9.4	0.061	<0.0001
IFG (%)*	3.4	4.2	NS	2.0	7.6	<0.0001	<0.0001

Data are means ± SEM unless otherwise indicated. *Results from both, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are shown as percentage of subjects without diabetes. HSD indicates ≥high school diploma.

RESULTS — Mean age, sex distribution, and educational attainment were significantly different among these four populations (Table 1). Overall adiposity was lower in individuals from Mexico than in SA-MA; in contrast, central adiposity was higher in Mexico than in SA-MA. Both parameters of obesity were higher in individuals from Spain than in SA-NHW. The nonadjusted prevalence of type 2 diabetes was 14.2% in Mexico, 21.9% in SA-MA, 9.5% in SA-NHW, and 10.2% in Spain. The age- and sex-adjusted prevalence of type 2 diabetes in Mexico was lower than in SA-MA (15.1 and 17.9%, $P = 0.032$), and the prevalence in SA-NHW was lower than in Spain (6.2 and 9.1%, $P = 0.005$). The age- and sex-adjusted prevalence of impaired glucose tolerance was higher in individuals of Mexican origin than in European-origin populations, and the prevalence of impaired fasting glucose was especially high in Spain relative to the other three populations.

Figure 1 shows the association between the age- and sex-adjusted prevalence of type 2 diabetes and ranked BMI in Mexico ($P = 0.002$), SA-MA ($P < 0.0001$), SA-NHW ($P < 0.0001$), and Spain ($P < 0.0001$). Logistic regression models for the prevalence of type 2 diabetes, which included age, sex, BMI, and WHR as independent variables, were calculated for each one of the populations. The prevalence of type 2 diabetes was no longer associated with BMI in Mexico but with WHR (odds ratio [OR] for 0.1 units

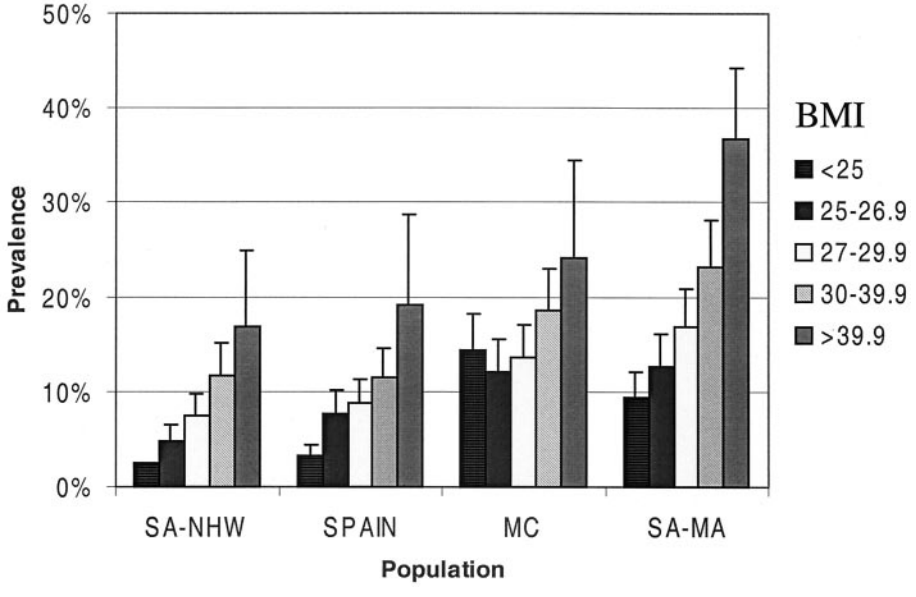

Figure 1—*Age- and sex-adjusted prevalence of type 2 diabetes by BMI categories and population. Cochran-Armitage trend test assessed the relationship between the prevalence of type 2 diabetes and BMI categories by population:* P *< 0.0001 in SA-NHW, Spain, and SA-MA, and* P *= 0.002 in Mexico. MC, Mexican nationals from Mexico City.*

Table 2—*Age- & sex-matched BMI and WHR values and prevalence of type 2 diabetes after stratification by educational attainment*

	Mexican origin			European origin			Mexican versus European
Ethnic origin	Mexico	SA-MA	*P* value	SA-NHW	Spain	*P* value	*P* value
BMI (kg/m^2)							
Without high school diploma	28.3 ± 0.11	30.0 ± 0.16	<0.0001	27.5 ± 0.46	28.3 ± 0.10	0.011	<0.0001
With high school diploma	26.3 ± 0.40	29.0 ± 0.14	<0.0001	27.2 ± 0.15	26.2 ± 0.23	0.0004	<0.0001
Pooled	28.2 ± 0.11	29.4 ± 0.10	<0.0001	27.1 ± 0.14	27.9 ± 0.9	<0.0001	<0.0001
WHR (×100)							
Without high school diploma	98.1 ± 0.16	93.5 ± 0.24	<0.0001	90.7 ± 0.68	95.2 ± 0.15	<0.0001	<0.0001
With high school diploma	93.9 ± 0.84	92.0 ± 0.30	NS	90.0 ± 0.32	93.3 ± 0.47	<0.0001	0.004
Pooled	98.0 ± 0.19	92.6 ± 0.18	<0.0001	89.6 ± 0.24	94.9 ± 0.16	<0.0001	<0.0001
Type 2 diabetes (%)							
Without high school diploma	15.8	20.8	0.003	9.2	9.1	NS	<0.0001
With high school diploma	8.4	15.5	NS	6.2	5.4	NS	<0.0001
Pooled	15.1	17.9	0.032	6.2	9.1	0.005	<0.0001
Pooled & BMI-adjusted	14.6	15.6	NS	6.2	7.9	NS	<0.0001

*Data are means ± SEM unless otherwise indicated.

1.29, 95% CI 1.07–1.55). The OR of 1.29 indicates that, on average, the chances of having type 2 diabetes increases 29% for every 0.1-unit increment in WHR. In the other three populations, the prevalence of type 2 diabetes was associated with both BMI and WHR. For each 5-unit increment of BMI, ORs were as follows: SA-MA, OR 1.39, 95% CI 1.26–1.53; SA-NHW, OR 1.46, 95% CI 1.23–1.74; Spain, OR 1.56, 95% CI 1.33–1.84. For each 0.1-unit increment of WHR, ORs were as follows: SA-MA, OR 1.52, 95% CI 1.29–1.78; SA-NHW, OR 1.80, 95% CI 1.35–2.40; Spain, OR 1.37, 95% CI 1.10–1.70.

As shown in Table 2, a similar trend of association between education and both parameters of obesity was observed in all populations and was significant in six of the eight comparisons. In comparisons between the two Mexican-origin populations, educational attainment did not modify the observed differences in BMI and WHR between cities. However, high school graduates among SA-NHW had higher BMI than those in Mexico ($P = 0.039$) and Spain ($P = 0.0004$) but lower WHR ($P < 0.0001$ for both comparisons). Educational attainment was inversely related to the prevalence of type 2 diabetes; however, this association was statistically significant only in SA-MA ($P = 0.003$) and Spain ($P = 0.045$) and near significance in SA-NHW ($P = 0.071$). After stratification for educational attainment, differences in the age- and sex-adjusted prevalence of type 2 diabetes between SA-NHW and Spain were attenuated, but differences between Mexico and SA-MA actually increased. Adjustment for BMI instead of stratification by education attenuated those differences in comparisons involving both Mexican-origin populations and European-origin populations.

Table 3 shows logistic regression models for the prevalence of type 2 diabetes as a dependent variable with the combined data of all four populations. For the model containing age, sex, and Mexican origin (present versus absent) (model 1), age and Mexican origin were highly statistically significant ($P < 0.0001$). In subsequent models (models 2 through 4), we sequentially added educational attainment, BMI, and WHR. These models demonstrated that Mexican ethnic origin remained significant ($P < 0.0001$). In model 5, we introduced the variable "population" for Mexican origin and observed that the chances of having type 2 diabetes were higher in both Mexican-origin populations than in Spain.

Table 3—*Multiple logistic regression models of prevalence of type 2 diabetes*

	Model 1		Model 2		Model 3		Model 4		Model 5	
	OR*	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age (×10 years)	2.01	1.88–2.16	2.01	1.88–2.15	2.02	1.88–2.17	1.97	1.83–2.11	1.87	1.73–2.02
Male sex	0.99	0.87–1.13	1.00	0.88–1.14	1.12	0.97–1.28	0.97	0.84–1.12	0.95	0.82–1.10
Mexican ethnicity	2.34	2.03–2.69	2.37	2.05–2.73	2.23	1.93–2.59	2.18	1.88–2.52	—	
Education: HSD	—		0.79	0.68–0.91	0.81	0.70–0.93	0.92	0.79–1.07	0.78	0.65–0.94
BMI (×5 units)	—		—		1.49	1.40–1.58	1.41	1.33–1.51	1.37	1.28–1.46
WHR (×0.1 unit)	—		—		—		1.33	1.21–1.44	1.41	1.28–1.55
Population:										
Mexico versus Spain	—		—		—		—		1.74	1.43–2.12
SA-MA versus Spain	—		—		—		—		2.68	2.19–3.28
SA-NHW versus Spain	—		—		—		—		1.12	0.84–1.50

HSD, high school diploma.

CONCLUSIONS — We have previously demonstrated that Native American genetic admixture is a major contributor to the higher rates of type 2 diabetes in Mexican-origin populations. Two of these populations, Mexico and SA-MA, have comparable degree of Native American genetic admixture but different prevalence of type 2 diabetes (1,2), which is partially related to obesity rates (5). The addition of a new epidemiological study from Spain was used to further clarify the relationship between Native American genetic admixture and prevalence of type 2 diabetes. In our analysis, the prevalence of type 2 diabetes was higher in Spain than in SA-NHW and lower than in both Mexican-origin populations. Differences in the prevalence of type 2 diabetes between the two European-origin populations (SA-NHW and Spain), without Native American genetic admixture, were partially associated with differences in the level of obesity and educational attainment.

The adjustment for BMI attenuates differences in the prevalence of type 2 diabetes in all comparisons, and stratification by educational attainment attenuates differences only in comparisons between European-origin populations. However, we encounter some limitations in the comparisons involving educational attainment. Some of these comparisons may lack power to detect differences, because participants with high school diplomas were relatively few in Mexico and Spain and participants without high school diplomas were few in SA-NHW. Completion of high school and susceptibility risk for type 2 diabetes may not have a similar relationship across populations. Moreover, these study populations were not selected to reflect the social composition of their respective general populations. In Spain, the 1997 high school completion rate was 32% for subjects aged 25–64 years (19), and in Mexico, the high school completion rate was 36% for the year 1990 (20). In Texas, the 1994 high school completion rate was 85% in non-Hispanic whites aged 25 years and older and 53% in Mexican-Americans (21). Thus, lifestyle factors related to education other than BMI and WHR may be also important for the prevalence of type 2 diabetes, but their consideration falls outside of the scope of this report.

Other authors have reported that WHR is associated with greater risk for type 2 diabetes among non-Hispanic whites than among Mexican-Americans (22). However, WHR correlates with central fat similarly in Mexican-Americans and in non-Hispanic whites (23). We observed that type 2 diabetes was associated with BMI and WHR in all populations except in Mexico, in which type 2 diabetes was no longer related to BMI after the adjustment for WHR. Therefore, we cannot assess whether ethnic origin has a particular influence on the association between diabetes and both parameters of obesity.

The fact that the prevalence of type 2 diabetes in Spain is intermediate between that in Mexican-origin populations and SA-NHW suggests that Spanish admixture may contribute, to some extent, to the higher susceptibility for diabetes in the Mexican-origin populations, which are a hybrid of Native American and Spanish admixtures. However, the prevalence of type 2 diabetes in Spain was statistically different from the prevalence in both Mexican-origin populations after the adjustment for age, sex, education, BMI, and WHR but was not statistically different from the prevalence in SA-NHW. Because of the inherent limitations of cross-sectional studies, comparisons of the incidence of type 2 diabetes in these populations and/or genetic epidemiological studies are needed to resolve this issue.

We are in agreement with other authors in recommending that the focus of medical intervention for prevention of type 2 diabetes should be placed on weight reduction (24). However, pharmacological and behavioral interventions to achieve weight reduction still fall short of reaching appropriate goals in most individuals. In view of the relationship between type 2 diabetes and education, an important health policy may be improvement of education rates through high school at least in some strata of the society because of its association with lifestyle parameters.

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APPENDIX

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