All-Cause and Cardiovascular Mortality Among Diabetic Participants in the San Antonio Heart Study

Evidence against the "Hispanic Paradox"

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OBJECTIVE — The observation that Hispanics have lower all-cause and cardiovascular mortality, despite increased diabetes and obesity, lower socioeconomic status (SES), and barriers to health care, has been termed the "Hispanic Paradox." We examined the relationship between ethnicity and all-cause and cardiovascular mortality in Mexican Americans (MAs) and non-Hispanic whites (NHWs) with diabetes.

RESEARCH DESIGN AND METHODS — In the San Antonio Heart Study, a prospective cohort, we compared the mortality in 554 U.S.-born MAs, 95 Mexico-born MAs, and 178 NHW participants with diabetes aged 25–72 years. Over an average of 10.4 years, 188 deaths occurred: 115 from cardiovascular disease (CVD) [death certificate ICD-9 codes 401–414 or 420–447 (excluding 427.5)]. Because of potential differences between migrants and nonmigrants, hazard ratios (HRs) were calculated comparing U.S.-born MAs and Mexico-born MAs with NHWs.

RESULTS — The age- and sex-adjusted HR for all-cause mortality comparing U.S.-born MAs with NHWs was 1.66 (95% CI 1.15–2.40), while comparing Mexico-born MAs with NHWs was 1.14 (95% CI 0.63–2.06). Cardiovascular mortality HRs were 1.66 (95% CI 1.04–2.65) and 0.89 (95% CI 0.40–2.01), respectively. After adjusting for possible confounders, such as fasting glucose and diabetes duration, the hazard of all-cause and cardiovascular mortality (although not statistically significant) appeared higher in U.S.-born MAs than in the other two groups.

CONCLUSIONS — We found it important to differentiate MAs by birthplace. Among diabetic participants, contrary to the prediction of the "Hispanic Paradox," compared with NHWs, U.S.-born MAs were at greater risk of all-cause and cardiovascular mortality, while Mexico-born MAs appeared to be at similar risk.

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In the year 2000 there were an estimated 35.3 million Hispanics in the U.S., representing the largest and fastest growing minority group in the nation. Despite their higher rates of diabetes and obesity, lower socioeconomic status (SES), and barriers to health care, several studies have suggested that Hispanics have lower all-cause and cardiovascular mortality rates than non-Hispanic whites (NHWs) (1–8). Sociocultural factors have been invoked to explain this paradox; however, ethnic misclassification and differential ascertainment of deaths by ethnicity are alternative explanations (9,10).

Of the Hispanics residing in the U.S., Mexican Americans (MAs) represent the largest ethnically distinct subgroup. Moreover, their incidence of diabetes is two- to threefold higher than among NHWs, and individuals with diabetes have twice the hazard of death as those with normal glucose tolerance (11,12). Hence, if the "Hispanic Paradox" were true for MAs, because diabetes is an established cardiovascular disease (CVD) risk factor, a strong predictor of death, and more common in MAs than in NHWs, one would expect diabetic MAs to have fewer all-cause and CVD deaths than diabetic NHWs. We examined the relationship between ethnicity, stratified by birthplace for MAs, and mortality (all-cause and cardiovascular) in 827 diabetic individuals in the San Antonio Heart Study (SAHS) cohort.

RESEARCH DESIGN AND METHODS

The SAHS design and population

The SAHS cohort consists of 5,158 participants recruited at baseline in two phases: phase 1 between 1979 and 1982, and phase 2 between 1984 and 1988. Households were randomly sampled in three types of San Antonio neighborhoods: low-income, inner city—essentially 100% MA neighborhoods ("barrios"); middle-income, transitional neighborhoods; and high-income suburbs. Men and nonpregnant women between the ages of 25 and 64 years residing in the selected households were eligible and invited to participate. The combined response rate for both phases of the study was 65.3%. Of the 5,096 surviving partic-

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Abbreviations: BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; MA, Mexican American; NHW, non-Hispanic white; SAHS, San Antonio Heart Study; SEI, socioeconomic index; SES, socioeconomic status.

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

ipants, ~7.7 years after their initial clinic examination, 72% of MA and 73% of NHW participants returned for a follow-up examination. Details of the study design have been previously published (6,13,14). The Institutional Review Board of the University of Texas Health Science Center at San Antonio approved the study, and all subjects gave informed consent.

SAHS cohort examinations

The baseline and follow-up SAHS cohort examinations were standardized across the exams and included interviews, blood pressure measurements, anthropometry, a fasting venipuncture, and an oral glucose tolerance test. At baseline, trained interviewers obtained information on demographic variables. At both baseline and follow-up, trained interviewers obtained information on medical history, medication use, and smoking status.

Ethnicity was defined by a validated algorithm that considered parental surnames and birthplaces, stated ethnicity of grandparents, and participant's preferred ethnic identity when a distinct national origin was indicated (13). SES was assessed with the Duncan socioeconomic index (SEI) (15,16). Participants were asked to fast for 12 h prior to their examination. Measurement of blood pressure (BP), BMI, total and HDL cholesterol, triglycerides, and plasma glucose (fasting and 2 h after a standardized oral glucose load) have been previously described (14,17).

Prevalent Rose angina was ascertained using the London School of Hygiene Chest Pain Questionnaire (18). Prevalent heart disease, stroke, cancer, and gall bladder disease were defined based on self-reported physician diagnoses. A history of CVD was defined as having had a heart attack, stroke, or Rose angina. A history of poor health was defined as having a history of CVD, cancer, or gall bladder disease. Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or current treatment with antihypertensive medication. Low HDL cholesterol was defined ≤0.91 mmol/l in men and ≤1.17 mmol/l in women.

Diabetes was defined as a fasting plasma glucose ≥7.0 mmol/l and/or 2-h postload glucose ≥11.1 mmol/l (19). Participants who did not meet these criteria, but who self-reported physician-diagnosed diabetes, and who reported current therapy with diabetes medication (either oral or insulin) were also considered to have diabetes. Based on self-reported medication use, diabetic participants were further classified into those using insulin, those using oral agents but not insulin, and those not using medication for diabetes.

Study design, follow-up, and events

Analyses were limited to 830 individuals who were first identified as diabetic at either their SAHS baseline (n = 528) or follow-up (n = 302) examination. Participant characteristics were assessed at the examination when their diabetes was first recognized, now referred to as their index examination. Information for the present analyses corresponds to information collected at the time of a positive diabetes diagnosis, and follow-up time corresponds to time elapsed since a positive diabetes diagnosis.

In 1999, a vital status follow-up of the SAHS cohort was initiated to determine all-cause and cause-specific mortality. Vital status was determined by annual mailed questionnaires, completed by a participant or their next of kin. In cases of nonresponse, telephone interviews, home visits, voting records, driver registration, address information from the Retail Merchants' Association, and the National Death Index were used to determine a participant's vital status. Among the 830 participants in this study, only 5 people had incomplete vital status ascertainment through 1 January 1999 (2 Mexico-born MAs and 3 U.S.-born MAs; ascertainment rate = 99.4%).

Information on cause of death was abstracted from death certificates (with names and ethnic identifiers suppressed) and sent to a certified nosologist (Medical Coding and Consultation Services, Rolesville, NC) for coding according to the ICD-9. Cardiovascular mortality was defined as deaths with mention anywhere on the death certificate of ICD-9 codes 401–405 (hypertensive), 410–414 (ischemic), 420–429 (other) with the exception of 427.5 (cardiac arrest), 430–439 (stroke), or 440–447 (arteries, etc.). ICD-9 code 427.5 was not included as a cardiovascular death because cardiac arrest is often included as a non-underlying cause of death when the death is not due to CVD. Ten deaths with the mention of ICD-9 code 427.5 were classified as non-cardiovascular (three NHWs, six U.S.-born MAs, and one Mexico-born MA). Two deceased individuals without cause of death information were excluded from the cardiovascular mortality analyses.

Statistical analyses

Prospective analyses were carried out by determining a person's exposure status based on ethnicity and birthplace. Two indicator variables defined the three ethnicity/birthplace categories: U.S.-born NHW, U.S.-born MA, and Mexico-born MA. One NHW born outside the U.S. and two MAs without information on birthplace were excluded from all analyses. All-cause and cardiovascular mortality were the studied outcomes.

Covariates included age, sex, diabetic medications (none, oral antidiabetic agents, and/or insulin), duration of diabetes, BP levels including antihypertensive medication, current smoking status, history of poor health, history of CVD, BMI, lipid levels (total cholesterol, HDL cholesterol, and level of triglycerides), fasting glucose, 2-h glucose, and Duncan SEI. Age- and sex-adjusted means and proportions were determined for covariates at a participant's index examination in U.S.-born NHWs, U.S.-born MAs, and Mexico-born MAs (20). For the three ethnicity/birthplace categories, all-cause and cardiovascular Kaplan-Meier survival estimates were graphed over the follow-up period, and Poisson regression was used to determine age- and sex-adjusted mortality rates (per 1,000 person-years).

Cox proportional hazard models were used to calculate hazard ratios (HRs) for all-cause and cardiovascular mortality in relation to ethnicity/birthplace status. The association between ethnicity/birthplace status and all-cause and cardiovascular mortality was then assessed after controlling for covariates. Age, BMI, blood pressure (systolic and diastolic), glucose (fasting and 2-h), and the natural logarithm of triglycerides were modeled as linear in the log (hazard) scale, while total and HDL cholesterol levels were modeled as dichotomous traits. For each outcome, models with and without the appropriate interaction terms were compared to identify interactions between significant covariates and ethnicity/birthplace status. A P value of 0.05 was used as a nominal value for statistically significant interactions. For each outcome, the assumption of proportional hazards was evaluated for significant covariates and the main exposure variable

Table 1—*Characteristics of the study population stratified by ethnicity and birthplace*

	U.S.-born NHWs (n = 178)	U.S.-born MAs (n = 554)	Mexico-born MAs (n = 95)
Unadjusted			
Age (years)	55.0	53.2	51.6
Male [% (n)]	47.8 (85)	39.4 (218)	39.0 (37)
Decreased before 1 January 1999 [% (n)]	20.8 (37)	24.4 (135)	16.8 (16)
Cardiovascular mortality [% (n)]	12.9 (23)	15.2 (84)	8.4 (8)
Adjusted for age and sex			
Diabetic medication			
Using any medication (%)	22.1 (16.6–28.9)	33.7 (29.9–37.8)	27.3 (19.2–37.3)
Insulin use (%)	10.5 (6.7–16.0)	10.6 (8.3–13.5)	3.1 (1.0–9.2)
Hypertension (%)	39.1 (32.0–46.8)	39.9 (35.8–44.3)	30.4 (21.6–40.9)
Current smoker (%)	22.6 (16.9–29.5)	28.1 (24.4–32.2)	22.3 (15.0–31.9)
Poor health (%)	34.2 (27.2–42.0)	36.1 (32.0–40.5)	24.5 (16.6–34.6)
Heart attack (%)	7.2 (4.1–12.5)	7.2 (5.0–10.2)	2.4 (0.6–9.5)
Stroke (%)	4.7 (2.4–9.2)	3.7 (2.3–5.8)	3.6 (1.2–10.8)
Rose angina (%)	5.6 (3.0–10.1)	9.6 (7.4–12.4)	7.6 (3.7–15.2)
Cancer (%)	13.4 (8.5–20.5)	2.8 (1.7–4.8)	3.3 (1.0–10.1)
Gallbladder disease (%)	12.4 (7.9–19.0)	22.6 (18.3–27.7)	14.8 (8.5–24.9)
CVD history (%)	15.3 (10.7–21.5)	17.1 (14.9–20.7)	13.5 (7.8–22.4)
Duncan SEI (scale: 0 to 100)	57.9 (54.8–60.9)	39.0 (37.2–40.7)	34.4 (30.1–38.6)
BMI (kg/m^2)	30.4 (29.5–31.3)	31.6 (31.1–32.1)	30.7 (29.5–31.9)
Fasting glucose (mg/dl)	145 (136–154)	163 (158–169)	156 (144–168)
2-h glucose (mg/dl)	260 (245–275)	300 (292–308)	291 (271–312)
Duration of diabetes (years)	2.46 (1.51–3.40)	3.62 (3.09–4.15)	2.73 (1.45–4.00)
Systolic BP (mmHg)	127 (124–129)	130 (128–131)	129 (126–132)
Diastolic BP (mmHg)	74.3 (72.8–75.7)	75.0 (74.2–75.8)	75.4 (73.4–77.4)
Total cholesterol (mg/dl)	220 (212–228)	217 (213–222)	223 (213–234)
HDL cholesterol (mg/dl)	46.3 (44.2–48.4)	43.1 (41.9–44.3)	43.9 (41.0–46.7)
Triglycerides (mg/dl)	237 (208–266)	230 (214–247)	211 (171–250)

Data are means or proportions (95% CI) unless otherwise indicated. Poor health was defined as having had CVD, cancer, or gall bladder disease; a history of CVD was defined as having had a heart attack, stroke, or Rose angina; Variables for which >1% of the population was missing information follow (number missing): history of cancer (9), history of a heart attack (12), Duncan SEI (18), fasting glucose (9), 2-h glucose (79), total cholesterol (12), HDL cholesterol (23), and triglycerides (12).

by testing for interaction with a continuous time variable.

Finally, sensitivity analyses were conducted for the outcomes of interest, assuming that missing information supported the "Hispanic Paradox," i.e., assuming the five MAs not reported at follow-up were living as of 1 January 1999; the deceased NHW with missing cause of death information had died a cardiovascular death; and the deceased MA with missing cause of death information had died a noncardiovascular death.

RESULTS — The study population included 827 diabetic SAHS participants with information on birthplace and ethnicity: 178 U.S.-born NHWs, 554 U.S.-born MAs, and 95 Mexico-born MAs. Participants identified as diabetic at their baseline SAHS examination were followed for 12.8 years on average, while participants identified as diabetic at their follow-up SAHS examination were followed for 6.2 years on average. Before 1 January 1999, 188 deaths were reported, 115 having CVD listed on their death certificate.

Using information from a participant's index examination, and compared with U.S.-born MAs, U.S.-born NHWs were older, were less likely to be using medications for diabetes, but equally likely to be using insulin, were more recently diagnosed with diabetes, and had lower fasting and 2-h glucose levels (Table 1).

For each ethnicity/birthplace stratum, all-cause and cardiovascular unadjusted Kaplan-Meier survival estimates are illustrated for the follow-up period, as well as age- and sex-adjusted mortality rates (Fig. 1). Although not always statistically significant, point estimates for age- and sex-adjusted rates of all-cause and cardiovascular mortality were higher in U.S.-born MAs than in either U.S.-born NHWs or Mexico-born MAs.

The age- and sex-adjusted HR for all-cause mortality comparing U.S.-born MAs with NHWs was 1.66 (95% CI 1.15–2.40), while the HR comparing Mexico-born MAs with NHWs was 1.14 (95% CI 0.63–2.06) (Table 2: Model 1a). Diabetes medications, total cholesterol, HDL cholesterol, and smoking status were independent predictors of all-cause mortality. After controlling for these covariates, as well as age, sex, and systolic blood pressure, the HR comparing U.S.-born MAs with NHWs remained statistically significant, and the point estimate comparing Mexico-born MAs with NHWs remained above 1 (Table 2: Model 2a). Adjusting for fasting glucose and duration of diabetes, markers of disease severity that were in-

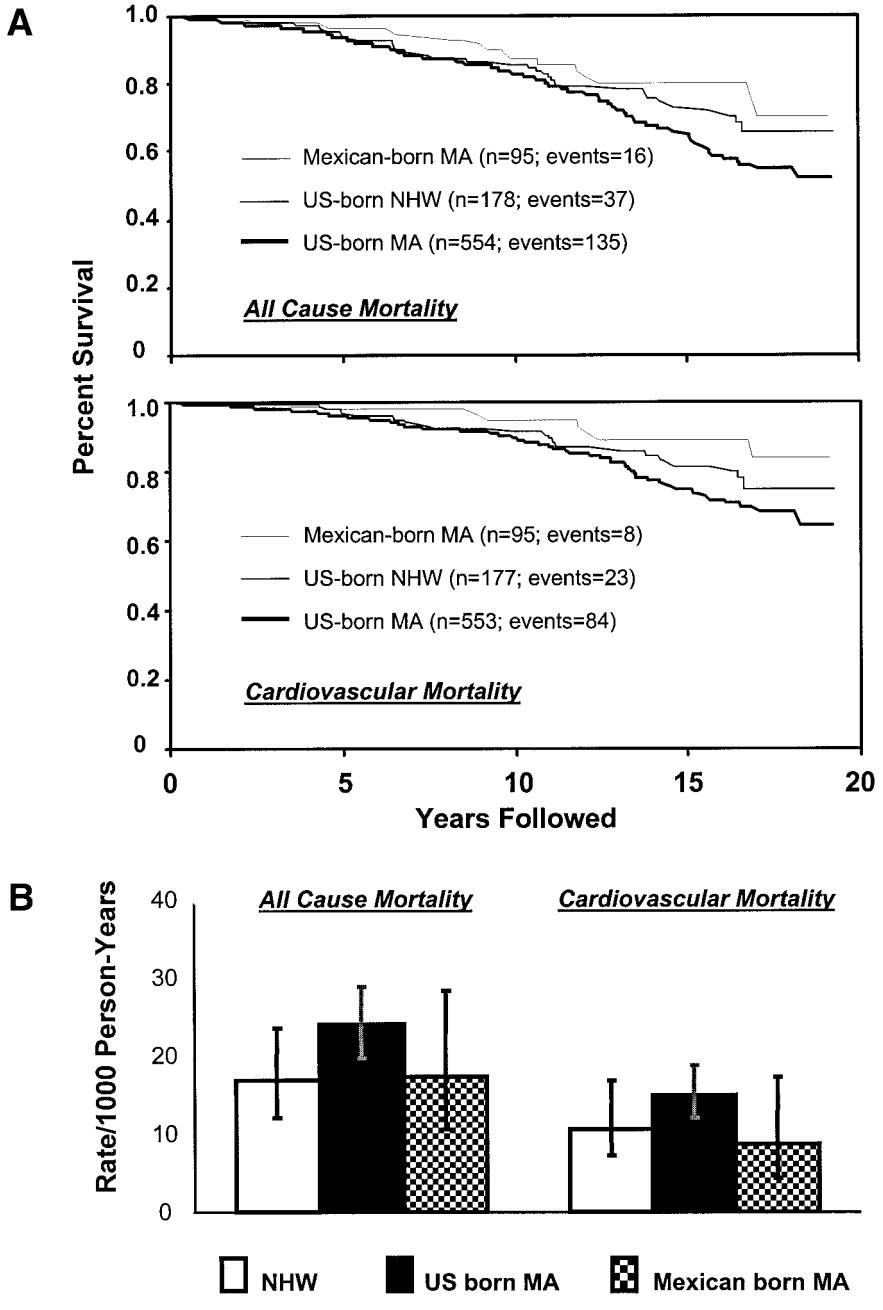

Figure 1—A*: Kaplan-Meier all-cause and cardiovascular survival estimates for the three ethnicity/birthplace stratum (unadjusted).* B*: All-cause and cardiovascular mortality rates (rates/1,000 person-years and 95% confidence intervals) adjusted for age and sex.*

dependent predictors of all-cause mortality further attenuated these associations. However, the point estimate comparing U.S.-born MAs with NHWs remained above 1 (Table 2: Model 3a). Finally, after restricting the population to U.S.-born of middle or high SES, (n = 372) and including Duncan SEI, neighborhood, and markers of disease severity (fasting glucose and duration of diabetes) as well as the other previously included covariates, the HR for all-cause mortality comparing MAs with NHWs was essentially 1 [HR = 1.04 (95% CI 0.61–1.79)].

The age- and sex-adjusted HR for cardiovascular mortality comparing U.S.-born MAs with NHWs was 1.66 (95% CI 1.04–2.65), while the HR comparing Mexico-born MAs with NHWs was 0.89 (95% CI 0.40–2.01) (Table 2: Model 1b). Diabetes medications, history of CVD, total cholesterol, HDL cholesterol, and systolic blood pressure levels (but not hypertensive status) were independent predictors of cardiovascular mortality. After controlling for these covariates as well as age, sex, and smoking status, the HRs comparing U.S.-born MAs and Mexico-born MAs with NHWs were attenuated (Table 2: Model 2b). Adjusting for fasting glucose and duration of diabetes, markers of disease severity that were independent predictors of cardiovascular mortality, further attenuated these associations. However, the point estimate comparing U.S.-born MAs with NHWs remained above 1 (Table 2: Model 3b). Finally, after restricting the population to U.S.-born of middle or high SES (n = 371) and including Duncan SEI, neighborhood, and markers of disease severity (fasting glucose and duration of diabetes) as well as the other previously included covariates, the HR for cardiovascular mortality comparing MAs with NHWs remained above one [HR = 1.30 (95% CI 0.65–2.60)].

There was no evidence that significant covariates, including age and sex, were effect modifiers of the associations between ethnicity/birthplace and either outcomes. Further, with the exception of a history of CVD being a stronger predictor of cardiovascular mortality during the first 6 years of the study than in the remaining years of the study, there was no evidence that the assumption of proportional hazards was violated. Finally, in the sensitivity analysis (data not shown) the age- and sex-adjusted HRs for all-cause mortality (Table 2: Model 1a) were reduced by <3%, while those for cardiovascular mortality (Table 2: Model 1b) were reduced by <5%.

CONCLUSIONS — The observation that Hispanics have lower all-cause and cardiovascular mortality rates despite increased diabetes and obesity, lower SES, and barriers to health care has been termed the "Hispanic Paradox." Sociocultural factors have been used to explain this paradox. However, ethnic misclassification and incomplete ascertainment of deaths could also explain these findings (9,10). Unlike our study, which focuses on diabetic individuals, most prior studies of the "Hispanic Paradox" focused on the general population. These studies typically used denominator information from the U.S. census with vital status in-

Table 2—*Adjusted hazard rate ratios (and 95% CIs) from multivariate Cox models for a given difference in risk factor level for all-cause and cardiovascular mortality*

	Model 1a (n = 827)		Model 2a (n = 799)		Model 3a (n = 795)	
All-cause mortality	HR	95% CI	HR	95% CI	HR	95% CI
Age (1-year increase)	1.08	(1.06–1.10)	1.08	(1.05–1.10)	1.08	(1.05–1.10)
Sex (M vs. F)	1.43	(1.07–1.90)	1.45	(1.07–1.97)	1.44	(1.06–1.96)
Ethnicity and birthplace						
U.S.-born MAs vs. NHWs	1.66	(1.15–2.40)	1.52	(1.02–2.27)	1.35	(0.90–2.03)
Mexico-born MAs vs. NHWs	1.14	(0.63–2.06)	1.08	(0.58–2.01)	0.97	(0.52–1.81)
Diabetic medication						
Insulin vs. none	—	—	2.63	(1.76–3.94)	1.69	(1.05–2.73)
Oral antidiabetic agents alone versus none	—	—	1.26	(0.88–1.81)	1.04	(0.71–1.52)
Current smoker versus others	—	—	1.53	(1.11–2.11)	1.43	(1.04–1.98)
Total cholesterol (high vs. low)*	—	—	1.45	(1.05–2.00)	1.36	(0.98–1.88)
HDL cholesterol (low vs. high)†	—	—	1.39	(1.02–1.89)	1.22	(0.89–1.68)
Systolic blood pressure (an increase of 10 mmHg)	—	—	1.05	(0.96–1.16)	1.09	(0.99–1.19)
Duration of diabetes (an increase of 1 year)	—	—	—	—	1.03	(1.01–1.05)
Fasting glucose (an increase of 10 mg/dl)	—	—	—	—	1.05	(1.03–1.08)
	Model 1b (n = 825)		Model 2b (n = 797)		Model 3b (n = 793)	
Cardiovascular mortality	HR	95% CI	HR	95% CI	HR	95% CI
Age (1-year increase)	1.07	(1.04–1.09)	1.06	(1.03–1.09)	1.06	(1.03–1.09)
Sex (M vs. F)	1.45	(1.01–2.10)	1.64	(1.11–2.42)	1.67	(1.12–2.47)
Ethnicity and birthplace						
U.S.-born MAs vs. NHWs	1.66	(1.04–2.65)	1.47	(0.87–2.47)	1.29	(0.76–2.17)
Mexico-born MAs vs. NHWs	0.89	(0.40–2.01)	0.90	(0.39–2.09)	0.83	(0.36–1.91)
Diabetic medication						
Insulin vs. none	—	—	3.31	(2.02–5.40)	1.83	(1.01–3.32)
Oral antidiabetic agents alone versus none	—	—	1.27	(0.78–2.04)	0.97	(0.58–1.60)
History of CVD at index visit (yes versus no)	—	—	1.65	(1.07–2.54)	1.93	(1.25–2.99)
Current smoker versus others	—	—	1.44	(0.95–2.17)	1.30	(0.86–1.98)
Total cholesterol (high vs. low)*	—	—	1.81	(1.21–2.71)	1.72	(1.15–2.58)
HDL cholesterol (low vs. high)†	—	—	1.61	(1.09–2.40)	1.40	(0.94–2.10)
Systolic blood pressure (an increase of 10 mmHg)	—	—	1.13	(1.00–1.27)	1.17	(1.04–1.31)
Duration of diabetes (an increase of 1 year)	—	—	—	—	1.04	(1.01–1.06)
Fasting glucose (an increase of 10 mg/dl)	—	—	—	—	1.06	(1.03–1.09)

*High total cholesterol was defined as ≥240 mg/dl (6.22 mmol/l); †low HDL cholesterol was defined as 35 mg/dl (0.91 mmol/l) or less in men and 45 mg/dl (1.17 mmol/l) or less in women.

formation supplied from a state bureau of vital statistics or used the NDI to follow individuals participating in national surveys (1,2,4,5,8). Thus, they are limited by potential biases affecting both the numerator and denominator. For example, ethnic misclassification may be differential with respect to the population base and observed deaths within that population. Further, studies that rely on follow-up information from a state bureau of vital statistics or the NDI may suffer from incomplete ascertainment of deaths, differential with respect to ethnicity and birthplace. For example, migration of ill individuals back to their country of origin differentially affects mortality rates with respect to ethnicity and birthplace. Finally, cause-specific mortality may be influenced by higher rates of ill-defined cause of death (ICD-9: 780–799 and including code 798, sudden death) in minority populations (9,21,22).

More recently, three additional study populations have been used to examine this paradox: the SAHS, the San Luis Valley Diabetes Study, and the Corpus Christi Heart Project (6,7,23–26). In the SAHS, the baseline prevalence of coronary heart disease (CHD) was lower in MA men when compared with NHW men, but slightly elevated in MA women when compared with NHW women (6). In the San Luis Valley Diabetes Study, in nondiabetic participants, MAs and NHWs were at equal risk of incident CHD, while in diabetic participants, NHWs were at a higher risk than MAs of incident CHD (7). In contrast, a community-based surveillance project, the Corpus Christi Heart Project, has reported a higher incidence of hospitalized CHD among MAs than NHWs (23), a higher CHD fatality rate among MAs than NHWs (24,26), and higher community-wide CHD mortality (both in and out of the hospital) in MAs than NHWs (25).

There are several possible explanations for the "Hispanic Paradox" other than ethnic misclassification and differential ascertainment of deaths. The above-

cited findings from the SAHS were based on prevalence, not incidence: if MAs were less likely to survive a heart attack compared with NHWs, CHD prevalence could be lower despite similar or higher incidence levels. Second, some groups of Native Americans have been shown to have a lower prevalence of CHD despite high–risk factor levels (27); hence, admixture between MA and Native American populations is one argument for a lower incidence of CHD in MAs compared with NHWs. However, in contrast to some groups of Native Americans who have a favorable lipid profile when compared with NHWs, in our study population MAs and NHWs had similar lipid profiles. Third, most prior studies did not differentiate between U.S.-born MAs and MAs who immigrated to the U.S. Fourth, because earlier studies consistently reported the "Hispanic Paradox," while more recent studies generally report similar or greater CVD risk in Hispanics compared with NHWs, one could postulate an upward secular trend in cardiovascular mortality among Hispanics. Available data, however, suggest that among Hispanics, as in the general U.S. population, cardiovascular mortality has been declining (4,8). Finally, the different definitions of cardiovascular mortality across studies as well as the considerable heterogeneity of the U.S. Hispanic population, and hence the Hispanic populations studied, could explain some of the differences between studies. Strictly speaking, our results apply only to Hispanics of Mexican origin, the principal Hispanic subgroup in San Antonio.

The "healthy migrant effect" is one possible explanation for differences between U.S.-born MAs and MAs who immigrated to the U.S. Individuals able to leave one country and enter another are on average likely to be healthier than the population from which they emigrate, and as a result their death rates might be lower (28). Other explanations include differences in genetic and environmental exposures. If Native American genetic admixture was higher in Mexico-born MAs compared with U.S.-born MAs, one might expect protective Native American influences to be stronger in the former; however, in a study in Mexico City we found Native American genetic admixture to be similar to that in San Antonio MAs (29). Differences in environmental exposures during childhood, such as dietary patterns and physical activity, could be an alternative explanation. Finally, because Mexico-born MAs on average have a lower SES and are less likely to speak English than U.S.-born MAs, it is unlikely that superior access to health care explains their more favorable outcomes.

At the baseline SAHS examination, the age- and sex-adjusted prevalence of diabetes was 4.9% in U.S.-born NHWs, 14.0% in U.S.-born MAs, and 12.1% in Mexico-born MAs, while cumulative incidence of diabetes between the baseline and follow-up examinations was 5.1, 12.5, and 8.0%, respectively. Markers of disease severity, including fasting glucose levels, 2-h glucose levels, and use of diabetes medications, indicate that on average, diabetes in MAs is more severe than in NHWs (30). Hence, the increased incidence and the increased severity indicate that with respect to diabetes risks, U.S.-born MAs are in "double jeopardy" when compared with NHWs.

This study is one of the first population-based cohort studies to follow MA and NHW diabetic individuals for all-cause and cardiovascular mortality. The study population is representative of individuals from each of the three types of neighborhoods from which it was selected. Because we defined a participant's ethnicity at baseline using a validated algorithm, the potential for ethnic misclassification is minimized. Additionally, because the nosologist was masked to ethnicity, potential cause of death misclassification differential with respect to ethnicity was limited to the filling out of the death certificate. The high vital status ascertainment rates and the results of the sensitivity analysis, combined with the other strengths, make it unlikely that differential bias with respect to either exposure or outcome could explain our findings. On the other hand, the response rates at baseline (65.3%) and follow-up (72–73%) do not rule out the potential for selection bias that may influence external validity.

In summary, our study provides evidence against the "Hispanic Paradox" in a population of diabetic individuals. On the whole, studies that established and support the "Hispanic Paradox" fail to differentiate between Mexico-born and U.S.-born MAs. Because of potential differences between migrants and nonmigrants, we made this distinction. In contrast to the paradox, which indicates that despite an unfavorable risk-factor profile MAs would have lower all-cause and cardiovascular mortality, age- and sex-adjusted HRs indicate that U.S.-born diabetic MAs have a 66% greater risk of all-cause mortality and a 66% greater risk of cardiovascular mortality than diabetic NHWs. Further adjustment for biomedical risk factors, as well as SES, indicated that these factors accounted for the increased risk of all-cause mortality and partially accounted for the increased risk of cardiovascular mortality in US-born MAs. Furthermore, Mexico-born MAs appeared to be at similar risk of all-cause and cardiovascular mortality when compared with U.S.-born NHWs.

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