Racial differences in the interaction between family history and risk factors associated with diabetes in the National Health and Nutritional Examination Survey, 1999–2004

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Purpose: We sought to determine whether the association between family history, a surrogate for genetic predisposition, and diabetes was modified by any known diabetes risk factors and if these relationships were constant across different ethnic groups. **Methods:** We examined 10,899 adults from the National Health and Nutrition Examination Survey (1999–2004) to identify interactions between family history and clinical, demographic, and lifestyle variables for the outcome of diabetes using logistic regression analysis in racial/ethnic subgroups. **Results:** There was significant heterogeneity by race/ethnicity in the interaction between covariates and family history in relation to diabetes. In black ($P = 0.0001$) and Hispanic ($P = 0.013$), but not white ($P = 0.75$) subgroups, high-familial risk was a strong risk factor for diabetes among lean individuals but less so among overweight or obese subjects. Among blacks, high-familial risk conferred a 20-fold increased odds of diabetes among lean subjects and only a sixfold increased odds among obese individuals. **Conclusions:** These findings suggest possible race/ethnic-specific differences in gene by environment interaction and identify body mass index as an important effect modifier of familial risk in diabetes in non-white populations. These findings may help guide future genetic studies and improve the utility of family history as a public health screening tool. *Genet Med* 2009;11(7):542–547.

Key Words: family history, gene environment interaction, diabetes

Approximately 7.0% of the US population have diabetes mellitus, and for the past 2 decades, the prevalence has been steadily increasing.^{1–3} Type 2 diabetes mellitus, which accounts for over 90% of all diagnosed cases, is a multifactorial disease with primary established risk factors including older age, physical inactivity, obesity, and family history of diabetes. Racial/ethnic differences exist as well: diabetes rates among Hispanic subjects are 1.7-times higher and among blacks 1.8-times higher when compared to whites.¹

Recent advances in genomic technologies have resulted in the identification of a number of new genetic risk factors yielding robust associations with type 2 diabetes.^{4–10} Despite their high level of statistical significance, most of the genetic variants

identified to date have weak effects (small odds ratios, ORs), making their clinical utility for predicting risk of diabetes less compelling. Interestingly, although the initial discoveries have been made primarily in white populations, the few published studies that have attempted to replicate these associations in non-white populations have in large part failed to do so.^{11–14} Nonetheless, full consideration has not been given to the possible modifying effect of important diabetes covariates on genetic risk factors, and whether ethnic differences in the distribution or effect of these risk factors would improve our ability to find genes underlying diabetes or enhance their generalizability or clinical utility once found.

In this study, we sought to identify covariates that broadly influence genetic susceptibility to diabetes, using family history as a surrogate, in the National Health and Nutrition Examination Surveys (NHANES) conducted from 1999 to 2004. Furthermore, we sought to determine whether there were racial/ethnic differences in these relationships that might explain some of the ethnic disparities in the prevalence of type 2 diabetes as well as the failure to replicate novel white genetic risk factors in black and Hispanic ethnic groups.

METHODS

Study Population

The NHANES is a sequential series of cross-sectional, nationally representative health examination surveys of the US civilian noninstitutionalized population. The surveys are conducted annually by the National Center for Health Statistics of the Centers for Disease Control and Prevention. Data for NHANES are from US households and are obtained using two methods: an in-home interview and a physical health examination. The institutional review board at the Centers for Disease Control and Prevention approved the study, and written informed consent was obtained from each participant. NHANES documentation and codebooks are available elsewhere.¹⁵

We merged three survey cycles to create an NHANES 1999–2004 data set ($N = 31,126$). The analyses were conducted using data for all participants who completed both the in-home interview and the physical health examination ($n = 29,402$). We excluded individuals who were <30 years of age at screening ($n = 17,832$), who developed diabetes before the age of 30 ($n = 195$), and who were pregnant ($n = 903$). Of the remaining 11,142 eligible persons, four were excluded from analysis because of missing or indeterminate self-reported diabetes status, and 239 were excluded for missing or indeterminate family history information. The final analytical sample consisted of 10,899 participants.

Data Collection

Our main outcome of interest, diabetes status, was based on self-report by asking whether a doctor or health professional

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had told the participant that he/she had diabetes or “sugar diabetes” other than during pregnancy (for female respondents). Measures of fasting glucose were available on a subset of the cohort and used in conjunction with self-reported family history as a confirmatory measure. For this definition, diabetes cases were those who either self-reported or had a fasting glucose measure of ≥ 126 mg/dL at enrollment. For family history, we assigned a stratified family history risk profile used by others and based on which relatives of a participant had diabetes.^{16–19} Individuals were classified as having a high-familial risk if at least two first-degree relatives had diabetes or if one first-degree relative and two second-degree relatives from the same lineage had diabetes. Individuals were classified as having a moderate familial risk if one first-degree relative had diabetes, and the number of second-degree relatives in the same lineage was less than two. Individuals were also assigned a moderate familial risk if no first-degree relatives had diabetes, but two second-degree relatives from the same lineage had diabetes. Individuals were classified as having an average familial risk if they did not have a family history of diabetes, if one second-degree relative had diabetes, or if the relative with diabetes was not a first-degree or a second-degree relative.

Several biologically relevant covariates were evaluated for their joint effect on diabetes outcome. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Mexican-American/Hispanic, and Other. Physical activity was categorized as ever/never based on questioning participants as to whether, over the past 30 days, they did any vigorous or moderate activities for at least 10 minutes. Vigorous activities were those that caused heavy sweating, or large increases in breathing or heart rate. Moderate activities were those that caused light sweating or a slight to moderate increase in breathing or heart rate. Hypertension was based on the interview and the medical exam. For the exam, blood pressure was measured three to four times. We discarded the first measurement and averaged the remaining measurements. We defined hypertension as having a diastolic pressure greater than or equal to 90 mm Hg, having a systolic pressure greater than or equal to 140 mm Hg, or indicating the use of a blood pressure medication.

High density lipoprotein (HDL) cholesterol and fasting triglycerides (collected on a random subset of individuals) were measured according to standard procedures¹⁵ and log transformed for analysis. Waist circumference was categorized (<102 cm in men or <88 cm in women) to define abdominal obesity. Body mass index (BMI, kg/m^2) was classified as normal (BMI <25), overweight (BMI between 25 and 29.9), and obese (BMI ≥ 30). Dietary intake variables included saturated fatty acids (g) and total food energy (kcal), obtained from a 24-hour dietary recall.²⁰

Statistical Analysis

All analyses were performed using the statistical package SAS, version 9.1 (SAS Institute Inc., Cary, NC). The ggplot2 package from the R statistical language was used to construct plots.^{21,22} To account for the complex, stratified, multistage probability cluster sampling design of NHANES, SAS Survey Procedures were used. These procedures incorporate statistical weights determined by the survey design. Exam weights were used if the analysis incorporated covariates obtained from the medical exam, and fasting weights were used for triglycerides, which is part of the fasting subsample. Four-year weights for the first two cycles were multiplied by 2/3, and 2-year weights from the last cycle were multiplied by 1/3 so that the merged data represented an average year within the 6 years under study. To confirm results, we incorporated fasting glucose levels to model the prevalence of total diabetes. The subset with fasting glucose is

considerably smaller. In addition, 403 individuals were excluded because they fasted <8 hours or >23 hours. Six-year fasting weights were formed in the same manner as 6-year exam weights. A combined weight was then used: 6-year exam weights were used for individuals with self-reported diabetes, and 6-year fasting weights were used for individuals with valid fasting glucose levels.

Comparisons between different groups were performed using *F* test based on design-adjusted Rao-Scott χ^2 for categorical variables and analysis of variance for continuous variables. Crude and adjusted odd ratios (ORs) and corresponding 95% confidence intervals (CI) were calculated using logistic regression analysis. Potential confounders were determined by adding covariates individually to a logistic regression model and retaining those that changed the ORs by 10% or more. These included age, sex, education, income, insurance, access to care, physical activity, total energy intake, total saturated fatty acids, HDL cholesterol, triglycerides, abdominal obesity (waist), history of hypertension and BMI. Next, we examined interaction between family history and selected biologically relevant covariates including age, sex, physical activity, total energy intake, total saturated fatty acids, HDL cholesterol, triglycerides, abdominal obesity (waist), history of hypertension, and BMI. First, we tested the three-way interaction between family history, the covariate, and race. If the three-way interaction was significant, we conducted race-specific analyses and calculated ORs comparing family history at different levels of the covariate. If the three-way interaction was not significant, we dropped it from the model and constructed models to test two-way interactions between family history and the covariate for the entire analytical sample (races combined).

RESULTS

The estimated weighted prevalence of self-reported diabetes in the study population was 7.6% (95% CI: 7.0–8.3). A high-familial risk was found in 27% of diabetic subjects and 7% of nondiabetic subjects (Table 1), resulting in an unadjusted OR for having diabetes of 7.5 (95% CI: 6.3–8.9) relative to an average familial risk. Moderate familial risk was found in 37% of diabetic subjects and 23% of nondiabetic subjects, yielding an unadjusted OR of 3.1 (95% CI: 2.5–3.8) relative to having an average familial risk. Considering a range of diabetes covariates, only BMI and waist circumference were determined to be confounders of the relationship between family history and type 2 diabetes, as they each changed the OR for family history association with diabetes by $>10\%$. We included only BMI as a confounder in the multiple regression models along with age, sex, and race. Addition of waist circumference did not change risk estimates further. The adjusted model resulted in only a slight attenuation of effect, producing ORs of 6.6 (95% CI: 5.4–8.0) for the high-familial risk group and 3.1 (95% CI: 2.5–3.8) for the moderate familial risk group. There were some differences in the magnitude of association between family history and diabetes by race (Table 2), with Hispanic subjects showing a stronger effect of family history than black or white subjects, but these differences were not statistically significant (family history by race interaction raw $P = 0.11$).

To analyze the modifying effect of covariates on family history and examine race-specific effects, we began by testing three-way interactions between family history, race and each covariate (Table 3). We found significant three-way interactions between family history, race, and three different covariates: HDL cholesterol, triglycerides, and BMI (Bonferroni adjusted $P < 0.05$). Stratified by race, the familial risk by BMI interac-

Table 1. Descriptive characteristics for demographic and risk factors of study participants with and without self-reported diabetes, adults aged 30 years and older, United States, 1999–2004

Characteristic	Total (N = 10,899)	No diabetes (n = 9692)	Diabetes (n = 1207)	P ^a
Age (yr)	51.3 (0.26)	50.5 (0.26)	61.0 (0.55)	<0.0001
HDL cholesterol (mmol/L)	1.36 (0.007)	1.37 (0.008)	1.21 (0.012)	<0.0001
Triglycerides (mmol/L)	1.73 (0.04)	1.69 (0.04)	2.26 (0.10)	<0.0001
Total energy intake (kcal/day)	2145 (14.1)	2171 (14.3)	1833 (33.6)	<0.0001
Total saturated fatty acids (g/day)	26.6 (0.21)	26.8 (0.22)	23.1 (0.62)	<0.0001
Sex				0.57
Male (%)	5390 (48)	4787 (48)	603 (49)	
Female (%)	5509 (52)	4905 (52)	604 (51)	
Race/ethnicity				0.0001
Non-Hispanic White (%)	5653 (74)	5184 (75)	469 (65)	
Mexican-American/Hispanic (%)	2784 (11)	2380 (11)	404 (14)	
Non-Hispanic Black (%)	2120 (10)	1824 (10)	296 (16)	
Other (%)	342 (4)	304 (4)	38 (5)	
Physical activity				<0.0001
Ever (%)	5669 (60)	5170 (61)	499 (48)	
Never (%)	5227 (40)	4519 (39)	708 (52)	
BMI				<0.0001
Normal (%)	3108 (32)	2919 (33.3)	189 (16)	
Overweight (%)	3929 (36)	3534 (36.3)	395 (29)	
Obese (%)	3459 (32)	2906 (30.4)	553 (55)	
Abdominal obesity				<0.0001
Normal (%)	4595 (47)	4314 (49)	281 (22)	
Obese (%)	5730 (53)	4896 (51)	834 (78)	
History of hypertension				<0.0001
Normal (%)	5586 (62)	5272 (65)	314 (30)	
Hypertension (%)	4826 (38)	3970 (35)	856 (70)	
Family history of diabetes				<0.0001
Average (%)	6992 (67)	6574 (70)	418 (36)	
Moderate (%)	2766 (25)	2328 (23)	438 (37)	
High (%)	1141 (8)	790 (7)	351 (27)	

^aP values for categorical variables are from *F* tests based on design adjusted Rao-Scott χ^2 . Results are weighted using appropriate NHANES sampling weights to account for unequal selection probabilities and nonrandom sampling design. Results are expressed as mean (SE) or number (%).

tions were significant in both black (raw *P* = 0.0001) and Hispanic (raw *P* = 0.013) subpopulations. In these groups, the effect of family history was strongest in subjects with BMI in the normal range (Fig. 1). To test whether these results were driven by sibling effects alone, we constructed a variable representing sibling history and tested whether BMI modified its effect on diabetes. There was no evidence suggesting a strong sibling effect: *P* = 0.052 in blacks and *P* = 0.63 in Hispanics. In whites, the risk associated with familial history was constant across different BMI groups, with no evidence of interaction (*P* = 0.75). The significant three-way interactions with lipids

were examined next. When stratified by race, the family history-HDL cholesterol and family history-triglyceride interactions were confined to the small group of subjects defined by "Other." Because this is a heterogeneous category including persons of multiracial, missing, or other racial background, these results were not considered further.

The above results for diagnosed diabetes are based on self-report because incorporating fasting glucose to capture undiagnosed cases (3% of the population) resulted in a 50% reduction in sample size. Using fasting glucose to define total diabetes—diagnosed and undiagnosed diabetes—we observe an attenuated

Table 2. Estimated adjusted and unadjusted odds ratios with 95% confidence intervals for the association between familial risk and self-reported diabetes in the NHANES population, 1999–2004, by race

	Unadjusted high-familial risk	Moderate familial risk	Adjusted ^a high-familial risk	Moderate familial risk
All races	7.5 (6.3–8.9)	3.1 (2.5–3.8)	6.6 (5.4–8.0)	3.1 (2.5–3.8)
Whites	7.4 (5.8–9.5)	2.9 (2.2–3.8)	7.0 (5.3–9.0)	2.9 (2.1–3.8)
Hispanics	9.0 (6.4–12.6)	4.1 (2.9–5.8)	8.4 (5.6–12.7)	4.1 (3.0–5.8)
Blacks	5.6 (3.7–8.3)	2.9 (1.9–4.3)	5.0 (3.1–7.9)	2.8 (1.8–4.4)

^aAdjusted for age, sex, and BMI. All odds ratios are relative to the average familial risk category.

Table 3. *P* values for interaction between family history of diabetes and selected covariates with respect to self-reported diabetes in the NHANES population, 1999–2004

	<i>P</i> , Three way	<i>P</i> , All	<i>P</i> , Hispanic	<i>P</i> , Black	<i>P</i> , White
Age	0.38	0.63	—	—	—
HDL cholesterol	0.0001	—	0.10	0.49	0.13
Triglycerides	0.0013	—	0.64	0.41	0.27
Total energy	0.039	0.81	—	—	—
Fatty acids	0.044	0.25	—	—	—
Sex	0.19	0.67	—	—	—
Race/ethnicity	—	0.11	—	—	—
Physical inactivity	0.89	0.59	—	—	—
BMI	<0.0001	—	0.013	0.0001	0.75
Abdominal obesity	0.086	0.15	—	—	—
Hypertension	0.72	0.65	—	—	—

^aAll models were adjusted for age, sex, and BMI. The three-way *P* value is represents the race, family history, and covariate interaction. Pooled model *P* values are for two-way interactions between family history and the covariate in all races together, adjusting for race. *P* values for each race are for two-way interactions between family history and covariates in each race stratum.

tion of each OR, but the interaction remained borderline significant in blacks (*P* = 0.06), despite the much reduced sample size. In this subset, ORs for having a high-familial risk were as follows: in black subjects whose BMIs were defined as normal weight, overweight or obese, the ORs for the highest familial risk were 20.4 (95% CI: 6.5–64.5), 5.2 (95% CI: 2.2–12.3), and 5.0 (95% CI: 2.5–10.3), respectively. Among Hispanics, the stratified ORs showed a similar trend to self-reported diabetes, but the interaction was no longer significant. ORs for the highest familial risk in normal weight, overweight, and obese Hispanic subjects were 14.0 (95% CI: 3.4–58.0), 5.6 (95% CI: 1.8–17.3), and 8.5 (95% CI: 3.8–19.4), respectively. The differences between ORs for diagnosed diabetes and total diabetes could result from an observed differential misclassification of diabetes between familial risk groups. We calculated the weighted percentage of individuals who reported that they are not diabetic but had fasting glucose values >126 mg/dL. These frequencies differed by familial risk groups, where we observed misclassification rates of 2.6%, 4.1%, and 7.2% for average, moderate, and high-familial risk groups, respectively.

DISCUSSION

In this study, we confirmed the strong relationship between family history and the prevalence of type 2 diabetes, consistent

with numerous other studies, including a previous report in the NHANES population.^{19,23–36} However, we also found that the magnitude of association between family history and diabetes varied depending on the presence of other risk factors and that these relationships, in turn, varied by race/ethnicity. Among blacks in particular, a high-familial risk was a much stronger risk factor for diabetes among subjects with a normal BMI, increasing the odds approximately 20-fold relative to subjects with an average family history. Similar, but less striking effects were seen in Hispanics, but among whites the modifying effect of BMI on familial risk was absent. Overall, our research suggests that the impact of family history is modified by BMI, and that this relationship varies significantly by race/ethnicity.

Ours is not the first study to explore interaction between family history and other risk factors for diabetes. However, few other studies examined risk factors besides obesity and sex, or racial/ethnic groups other than whites. There are numerous published studies addressing the interaction between obesity and family history on risk of type 2 diabetes, but the findings are inconsistent.^{29–32,37–43} Five studies (four among whites and one among Pima Indians) found that a combination of family history and increased body mass were most strongly associated with diabetes.^{30–32,37,39} However, only three of these formally tested interaction, resulting in interaction p-values between 0.01 and 0.05.^{30,37,39} In contrast, five studies (three in white, one in

Fig. 1. Odds ratios (and 95% confidence bars) for familial risk of self-reported diabetes for different categories of body mass index (BMI) in the three major race/ethnicity subgroups. Odds ratios compare high and moderate risks to the average familial risk and are adjusted for age and sex.

Japanese, and one in Pima Indian populations) reported that the combination of lean body mass and family history of diabetes conferred a greater risk of diabetes than having family history and a higher body mass, which agrees with our findings. But only two of these studies conducted a formal test of interaction: one in whites and one in Pima Indians.^{38,40–43} The study by Boer et al.⁴⁴ in the elderly Dutch male cohort formally tested, but found no evidence of, interaction between obesity and family history, which is consistent with our finding of no effect in whites. To our knowledge, ours is the only published study to examine family history by obesity interaction among US Hispanic or black populations. In terms of other risk factors, we did not see a trend of a stronger relationship between family history and diabetes in men compared with women as noted in other studies, but it remains possible that three and four-way interactions that include sex are present.^{26,31,33}

The main strength of this study is the use of a large, ethnically diverse population-based sample, and the formal analysis of interaction between covariates. Many of the other studies were carried out in individuals selected based on having diabetes or being overweight, introducing possible selection bias. Furthermore, a number of the studies failed to provide statistical support for reported interactions. One caveat of our study is the use of self-reported diabetes, which fails to take into account undiagnosed diabetes. We chose to use self-reported diabetes because inclusion of fasting glucose or other biometrics of diabetes reduced our sample size in half. Importantly, when we tested the association among the subset with fasting glucose, it showed that the resulting misclassification bias may have overestimated the effect sizes, so caution should be taken when

interpreting the data based on self-reported diabetes status. Nonetheless, the interaction between BMI and family history in blacks remained significant.

Another drawback of using self-reported diabetes status is that knowledge of diabetes status could be influenced by family history of the disease and thus, differential misclassification of diabetes status is a possibility. Similarly, with respect to family history, previous studies have shown that persons with diabetes are more likely to recall a family member with diabetes than persons without the disease.⁴⁵ In addition, both participant self-report of diabetes and family history variables did not differentiate between cases of type 1 and type 2 diabetes. However, we limited our analysis to subjects with age of onset of diabetes >30 years to minimize this bias.

The findings of our study have implications both for the design of genetic epidemiology studies and the use of family history as a risk predictor in clinical practice. If we believe family history to be a good surrogate of genetic risk, then studies aimed at discovering genes underlying type 2 diabetes would benefit from considering BMI levels of participants to enrich for subpopulations having a greater genetic predisposition. Specifically, in non-white populations, nonobese diabetic subjects may carry a higher genetic load than obese-diabetic subjects, and including this information may provide a useful strategy for finding genes of stronger effect. Similarly, once a gene is discovered, studies that determine the generalizability and utility of diabetes risk alleles should consider these important effect modifiers and race/ethnicity group differences in their effect. Of note, the few studies in African American, Hispanic, or Pima Indian populations that have tried to replicate previously identified diabetes risk alleles discovered in genome-wide association studies have failed to replicate many of these associations.^{11,13,14,46} Formal tests of genotype by obesity interaction or stratified association analysis based on obesity status would help to clarify this.

Finally, family history and other variables are used as risk predictors in clinical practice, but little consideration has been given to the interplay of family history with additional risk factors, nor to differences between race/ethnicity groups. Practically speaking, the results of our study suggest that perhaps in non-white populations, a high-familial risk of diabetes should be given much more weight in the absence of obesity. More research in this area is required to realize the potential clinical utility of both family history and newly discovered genetic markers of diabetes susceptibility.

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