Family History and Prevalence of Diabetes in the U.S. Population

The 6-year results from the National Health and Nutrition Examination Survey (1999–2004)

RODOLFO VALDEZ, PHD, MSC
PAULA W. YOON, SCD, MPH

TIEBIN LIU, MSPH
MUIN J. KHOURY, MD, PHD

OBJECTIVE — We sought to test the association between stratified levels of familial risk of diabetes and the prevalence of the disease in the U.S. population.

RESEARCH DESIGN AND METHODS — This study includes 16,388 adults interviewed for the National Health and Nutrition Examination Survey between 1999 and 2004. Fasting glucose was available for a subsample of 6,004 participants. Familial risk of diabetes was classified as average, moderate, or high. The prevalence and the odds of having diabetes were estimated for each risk class after accounting for other risk factors.

RESULTS — Overall, 69.8% of the U.S. adults were in the average, 22.7% in the moderate, and 7.5% in the high familial risk for diabetes. The crude prevalence of diabetes for each risk class was 5.9, 14.8, and 30%, respectively. The graded association between familial risk and prevalence of diabetes remained even after accounting for sex, race/ethnicity, age, BMI, hypertension, income, and education. Versus people in the average risk class, independently of other risk factors considered, the odds of having diabetes for people in the moderate and high familial risk categories were, respectively, 2.3 and 5.5 times higher.

CONCLUSIONS — In the U.S. population, family history of diabetes has a significant, independent, and graded association with the prevalence of diabetes. This association not only highlights the importance of shared genes and environment in diabetes but also opens the possibility of formally adding family history to public health strategies aimed at detecting and preventing the disease.

Diabetes Care **30:**2517–2522, 2007

Diabetes is a complex metabolic disease characterized by persistently elevated concentrations of glucose in the blood caused by the autoimmune destruction of the pancreatic β-cells (type 1) or by insulin resistance coupled with relative insulin deficiency (type 2). From 90 to 95% of all cases of diabetes are type 2, and between 5 and 10% are type 1 (1). There are ~21 million people with diabetes in the U.S. and about one-third of them are unaware they have the disease (2). Its microvascular complications include damage to the eyes, kidneys, and nerves, whereas macrovascular complications include atherosclerosis and other cardiovascular conditions (3). The total cost of diabetes in the U.S. for 2002 was estimated at $132 billion (4).

Environments with plentiful food and scarce opportunities for physical activity are well suited for the development of obesity and ultimately type 2 diabetes. Nevertheless, the development of type 2 diabetes in such environments also requires a permissive genetic component. In this regard, several genetic variants related to the risk for diabetes have been reported, but their use to estimate diabetes risk in populations is limited (5–7). Even so, the accumulation of genetic information relative to diabetes has the potential to become a very effective public health tool in the near future. Meanwhile, we must rely on the use of family history as a basic approach that clearly hints at such public health potential (8,9). Family history is relatively easy to obtain and conveniently conveys information on genes and environment shared by close relatives (10).

The association between family history of diabetes and risk for the disease has been well documented (9,11,12). Recent studies have shown the graded and independent contribution of a positive family history to the increasing risk for diabetes in the U.S. population (13–15). Questions remain, however, on the public health applications of this knowledge: *1*) What is the best way to incorporate family history into the already populated list of risk factors for diabetes? *2*) Can family history be used effectively to improve the detection and prevention of diabetes in the U.S. population? The answers to these questions would benefit greatly from a thorough analysis of the association between family history and the prevalence of diabetes using a large representative sample of the U.S. population.

In this study, we provide a brief but detailed analysis of the association between family history of diabetes and the prevalence of the disease in the U.S. adult population. Our objective is to test the relative strength and independence of this association after accounting for well-known risk factors for diabetes. In particular, we examine the effect of family history on the prevalence of diabetes along a broad range of variation of two well-established risk factors: age and BMI.

Table 1—*Crude prevalence of diabetes according to diagnosis status and selected variables (NHANES, 1999–2004)*

		Prevalence (%)		
	n (%)	Diagnosed (n = 16,388)*	Undiagnosed (n = 6,004)†	Total (n = 7,540)‡
Sex				
Male	8,086 (49.3)	6.7 (6.1–7.5)	3.7 (3.0–4.5)	10.2 (9.2–11.2)
Female	8,302 (50.7)	6.8 (6.2–7.5)	2.1 (1.7–2.7)	8.8 (8.0–9.6)
Race/ethnicity				
Non-Hispanic white	7,980 (52.6)	6.1 (5.5–6.9)	2.9 (2.4–3.5)	8.8 (8.0–9.6)
Non-Hispanic black	3,367 (22.2)	9.9 (8.8–11.1)	3.0 (2.2–4.2)	12.7 (11.2–14.2)
Mexican American	3,833 (25.3)	6.6 (5.7–7.5)	2.2 (1.3–3.5)	8.7 (7.2–10.5)
Age (years)				
18–34	5,265 (32.1)	1.1 (0.7–1.6)	0.4 (0.1–0.9)	1.4 (0.9–2.2)
35–44	2,481 (15.1)	3.7 (3.0–4.6)	1.5 (0.7–3.3)	5.1 (3.9–6.7)
45–54	2,266 (13.8)	7.5 (6.3–8.8)	3.5 (2.2–5.6)	10.8 (9.1–12.9)
55–64	2,031 (12.4)	12.4 (10.9–14.1)	5.9 (4.3–8.1)	16.4 (14.2–18.7)
≥65	4,345 (26.5)	16.5 (15.0–18.2)	7.1 (5.5–9.3)	23.1 (20.7–25.7)
BMI (kg/m^2)				
<18.5	300 (2.0)	0.7 (0.2–2.5)	0.4 (0.1–3.1)	1.1 (0.4–3.2)
18.5–24.9	4,860 (33.0)	3.2 (2.5–4.2)	1.0 (0.7–1.6)	4.0 (3.1–5.0)
25–29.9	5,066 (34.4)	5.7 (4.9–6.6)	2.8 (2.2–3.7)	8.0 (7.0–9.1)
≥30	4,484 (30.5)	11.7 (10.6–13.0)	5.1 (4.0–6.3)	15.7 (14.1–17.3)
Hypertension				
Yes	6,250 (41.4)	13.9 (12.8–14.9)	5.9 (4.8–7.3)	18.4 (17.0–20.0)
No	8,840 (58.6)	3.1 (2.6–3.6)	1.4 (1.0–1.9)	4.2 (3.6–4.9)
Education				
Less than high school	5,704 (34.8)	10.9 (9.8–12.1)	4.6 (3.7–5.8)	15.0 (13.6–16.6)
High school	4,013 (24.5)	6.5 (5.7–7.4)	2.8 (2.0–3.9)	9.0 (7.7–10.5)
More than high school	6,614 (40.4)	5.3 (4.5–6.1)	2.2 (1.6–3.1)	7.3 (6.4–8.3)
Unknown	57 (0.3)	3.6 (1.5–8.5)	13.5 (2.0–54.9)	17.3 (3.7–53.1)
Household income				
<$35,000	7,238 (44.2)	9.2 (8.3–10.2)	4.1 (3.1–5.4)	13.0 (11.7–14.5)
$35,000 to $54,999	2,767 (16.9)	6.8 (5.5–8.4)	2.7 (1.7–4.2)	9.6 (7.9–11.5)
≥$55,000	4,340 (26.5)	4.0 (3.5–4.7)	1.8 (1.3–2.5)	5.5 (4.7–6.4)
Unknown	2,043 (12.5)	8.0 (6.3–10.1)	3.2 (1.8–5.7)	11.9 (9.3–15.0)
Familial risk				
Average	9,938 (67.5)	3.8 (3.4–4.3)	2.2 (1.8–2.7)	5.9 (5.4–6.6)
Moderate	3,437 (23.4)	11.2 (9.9–12.6)	4.1 (3.1–5.4)	14.8 (13.1–16.7)
High	1,340 (9.1)	24.3 (21.8–27.0)	8.2 (5.6–11.9)	30.0 (26.6–33.6)
Overall	16,388	6.8 (6.2–7.4)	2.9 (2.4–3.4)	9.4 (8.7–10.2)

*Number of adults (aged ≥18 years) interviewed. †Number of adults examined in the morning under fasting condition. ‡Combined number of adults examined in the morning and adults previously diagnosed with diabetes (see RESEARCH DESIGN AND METHODS for explanation).

RESEARCH DESIGN AND METHODS

Survey

The National Health and Nutrition Examination Survey (NHANES) is an annual survey that uses a complex multistage sampling scheme designed to obtain a sample that is statistically representative of the U.S. population. People selected for the survey are invited to a home interview and those who complete the interview are then invited to a mobile clinic for a series of physical and laboratory examinations (assignment to morning or afternoon visits to the clinic is random) (16).

Sample and study population

This study included a 6-year (1999–2004) sample of adults (aged ≥18 years, n = 17,061). Most of them (n = 15,781) also received a physical examination, 42.8% (n = 6,755) of whom were examined in the morning. The morning sample is important for conditions such as diabetes, for which assessment requires an overnight fasting period. The design of the study, through the use of sample weights, allows for the calculation of national estimates from both the entire interview sample and the morning sample. These estimates are for a typical year within the 6-year period.

Main variables

Diabetes cases were classified as diagnosed (participant reported receiving a diagnosis of diabetes from a health care professional) or undiagnosed (examination from NHANES revealed a fasting glucose ≥126 mg/dl in people who reported no previous diagnosis of diabetes) (1). The diabetes status of women who reported just a previous diagnosis of gestational diabetes was determined by their blood fasting glucose. The total number of cases of diabetes was calculated by adding the previously diagnosed cases to the newly detected cases from the morning sample. There were no attempts to distinguish be-

Table 2—*Percent prevalence of diabetes (95% CI) according to three risk levels of family history of diabetes and selected variables (NHANES, 1999–2004)*

	Diagnosed			Undiagnosed			Diagnosed plus undiagnosed		
	Average	Moderate	High	Average	Moderate	High	Average	Moderate	High
Sex									
Male	4.2 (3.7–4.8)	10.7 (9.0–12.8)	26.4 (22.3–30.9)	3.2 (2.5–4.0)	4.7 (3.1–6.9)	9.5 (5.1–17.0)	7.3 (6.4–8.3)	14.7 (12.2–17.6)	32.3 (26.3–38.9)
Female	3.5 (3.0–4.0)	11.6 (9.9–13.5)	22.8 (19.7–26.3)	1.2 (0.8–1.9)	3.6 (2.4–5.3)	7.3 (4.5–11.7)	4.6 (4.0–5.3)	14.9 (12.8–17.4)	28.3 (24.0–33.0)
Race/ethnicity									
Non-Hispanic white	3.7 (3.2–4.2)	10.2 (8.7–12.0)	23.1 (19.9–26.6)	2.3 (1.9–3.0)	3.9 (2.7–5.7)	8.4 (5.0–13.9)	5.9 (5.3–6.6)	13.6 (11.7–15.7)	28.4 (23.8–33.5)
Non-Hispanic black	5.4 (4.4–6.6)	14.6 (12.3–17.2)	28.1 (23.8–32.9)	1.5 (0.7–3.0)	6.2 (3.7–10.2)	7.8 (3.8–15.3)	6.8 (5.5–8.3)	20.4 (16.8–24.5)	33.4 (27.9–39.3)
Mexican American	3.4 (2.7–4.2)	9.6 (7.6–12.1)	22.6 (18.4–27.5)	1.0 (0.5–2.3)	1.9 (1.2–2.8)	12.8 (5.8–26.1)	4.4 (3.3–6.0)	11.3 (9.0–14.3)	32.1 (24.0–41.4)
Age (years)									
18–34	0.7 (0.4–1.1)	2.0 (1.2–3.6)	6.2 (2.4–15.0)	0.2 (0.0–1.2)	0.9 (0.3–3.2)	1.0 (0.1–7.4)	0.9 (0.5–1.8)	3.0 (1.7–5.1)	5.9 (2.4–13.6)
35–44	1.6 (1.0–2.5)	7.5 (5.4–10.3)	11.3 (7.4–16.8)	0.7 (0.3–1.8)	3.2 (1.5–6.9)	5.0 (1.5–15.8)	2.2 (1.4–3.5)	10.8 (7.7–15.0)	17.4 (11.1–26.2)
45–54	3.6 (2.6–5.1)	10.5 (7.7–14.1)	25.7 (20.7–31.3)	2.8 (1.6–4.8)	3.0 (1.2–7.2)	11.0 (4.9–23.1)	6.4 (5.0–8.2)	13.4 (9.8–18.1)	33.4 (25.3–42.6)
55–64	7.5 (6.3–9.0)	16.9 (13.0–21.6)	31.4 (24.0–39.9)	4.3 (2.6–7.1)	8.1 (5.0–13.0)	12.1 (6.1–22.7)	10.8 (8.6–13.5)	21.6 (16.6–27.6)	37.6 (28.2–48.1)
≥65	10.4 (9.3–11.7)	24.3 (20.8–28.2)	42.2 (36.6–48.0)	6.2 (4.5–8.4)	8.4 (4.8–14.5)	14.0 (6.8–26.6)	16.4 (14.3–18.7)	31.5 (26.5–37.1)	50.7 (41.5–59.8)
BMI (kg/m²)									
<18.5	0.3 (0.1–1.2)	4.1 (0.8–18.8)	—	0.6 (0.1–4.2)	—	—	0.8 (0.2–3.6)	3.6 (0.7–16.3)	—
18.5–24.9	1.6 (1.2–2.2)	7.0 (5.0–9.6)	18.3 (12.5–26.2)	0.8 (0.4–1.6)	1.5 (0.7–3.3)	4.0 (1.6–9.6)	2.3 (1.7–3.1)	8.0 (5.8–10.9)	17.7 (12.0–25.4)
25–29.9	3.5 (2.9–4.2)	8.6 (6.5–11.4)	19.3 (14.6–25.0)	2.5 (1.7–3.5)	3.9 (2.4–6.5)	4.4 (2.0–9.4)	5.6 (4.6–6.8)	11.9 (9.5–14.7)	21.1 (15.0–28.9)
≥30	7.0 (5.7–8.5)	16.2 (13.6–19.0)	30.0 (26.6–33.7)	3.4 (2.4–4.7)	6.6 (4.5–9.4)	15.3 (9.3–24.1)	9.9 (8.2–11.8)	20.5 (17.2–24.2)	41.2 (34.3–48.6)
Hypertension									
Yes	8.5 (7.6–9.5)	18.6 (16.4–21.1)	36.0 (32.1–40.1)	4.8 (3.5–6.6)	6.8 (4.8–9.5)	13.0 (8.5–19.4)	12.5 (10.9–14.4)	23.4 (20.5–26.7)	43.7 (38.7–48.8)
No	1.6 (1.3–2.1)	6.0 (4.7–7.6)	13.0 (9.4–17.7)	1.0 (0.6–1.6)	2.1 (1.1–4.0)	5.1 (2.3–10.6)	2.5 (2.0–3.2)	7.8 (6.1–9.9)	16.1 (11.9–21.2)
Education									
Less than high school	6.5 (5.6–7.6)	17.1 (14.6–19.9)	29.6 (24.6–35.1)	3.9 (2.8–5.4)	6.3 (3.8–10.4)	10.2 (5.7–17.6)	10.2 (8.9–11.7)	22.5 (18.7–26.8)	37.3 (29.2–46.1)
High school	3.6 (2.9–4.4)	10.3 (7.8–13.5)	23.8 (19.2–29.0)	2.2 (1.4–3.6)	2.7 (1.3–5.6)	11.6 (5.9–21.6)	5.7 (4.7–7.0)	12.8 (9.0–17.8)	34.0 (26.6–42.3)
More than high school	3.0 (2.6–3.6)	9.0 (7.1–11.3)	20.7 (15.8–26.7)	1.5 (1.0–2.3)	3.9 (2.3–6.4)	5.3 (2.4–11.5)	4.5 (3.8–5.4)	12.5 (10.2–15.2)	22.8 (17.3–29.4)
Household income									
<$35,000	5.8 (5.1–6.6)	13.0 (11.0–15.2)	30.7 (26.5–35.3)	3.6 (2.5–5.2)	4.6 (3.2–6.7)	9.9 (5.4–17.7)	9.4 (8.0–10.9)	16.8 (14.2–19.9)	36.3 (30.5–42.5)
$35,000 to $54,999	3.3 (2.4–4.6)	11.3 (8.7–14.7)	25.8 (18.6–34.5)	1.3 (0.6–3.0)	5.6 (2.8–10.8)	9.1 (3.9–19.8)	4.7 (3.5–6.4)	16.8 (12.7–21.9)	32.9 (24.2–43.0)
≥$55,000	2.1 (1.6–2.6)	7.9 (5.9–10.6)	15.1 (11.1–20.4)	2.8 (1.4–5.6)	5.7 (2.3–13.5)	3.2 (2.6–4.0)	4.9 (3.2–7.3)	10.2 (7.5–13.8)	18.9 (13.7–25.4)
Unknown	4.6 (3.2–6.7)	15.7 (11.7–20.8)	21.9 (14.0–32.6)	2.7 (1.2–6.0)	4.0 (1.5–10.6)	8.8 (3.7–19.2)	7.3 (5.0–10.5)	20.7 (14.8–28.1)	32.2 (22.1–44.3)
Overall	3.8 (3.4–4.3)	11.2 (9.9–12.6)	24.3 (21.8–27.0)	2.2 (1.8–2.7)	4.1 (3.1–5.4)	8.2 (5.6–11.9)	5.9 (5.4–6.6)	14.8 (13.1–16.7)	30.0 (26.6–33.6)
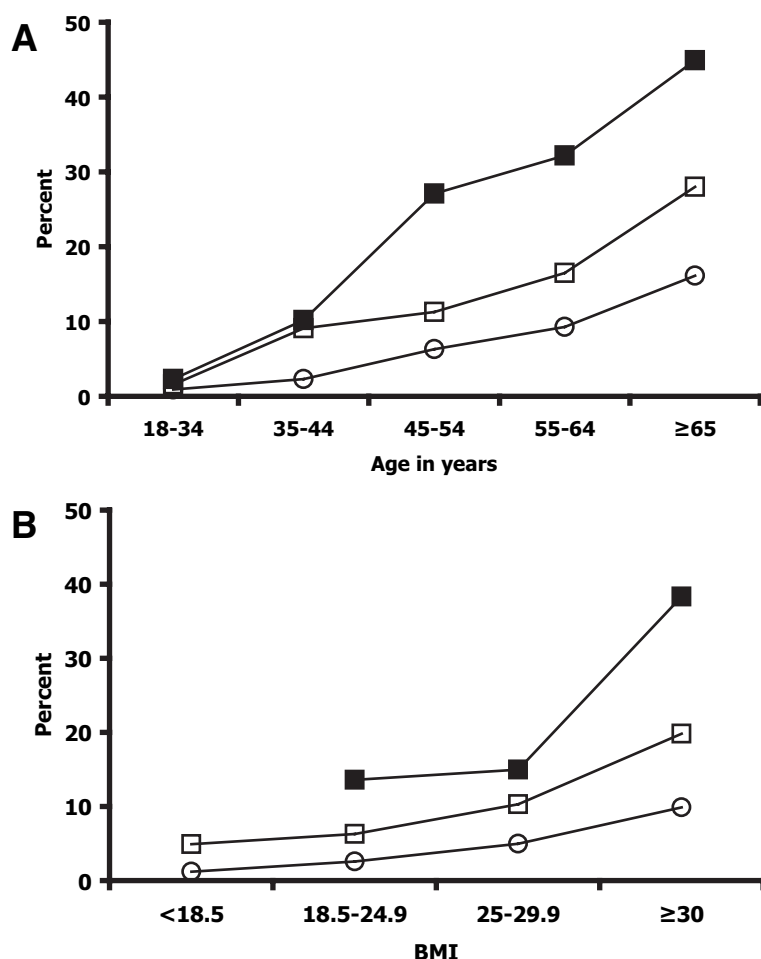
Figure 1—*Adjusted prevalence (predicted marginals) for diagnosed or undiagnosed diabetes by age (A: controlling for BMI, sex, ethnicity, and education) and BMI (B: controlling for age, sex, ethnicity, and education) (NHANES, 1999–2004). There were no participants in the lowest BMI category with a high familial risk. ■, High familial risk; □, moderate familial risk; ○, average familial risk (see text for statistical significance).*

pertension was defined as a diastolic blood pressure ≥90 mmHg or a systolic blood pressure ≥140 mmHg or the acknowledgment of treatment for high blood pressure (18).

This study reports the prevalence of diabetes for five age-groups: 18–34, 35–44, 45–54, 55–64, and ≥65 years; four BMI categories: <18.5, 18.5 to 24.9, 25–29.9, and ≥30 kg/m^2; three ethnic/racial groups: non-Hispanic white, non-Hispanic black, and Mexican American (the only Hispanic group nationally represented in NHANES); four levels of education: less than high school, high school, more than high school, and unknown; four family income levels: <$35,000, $35,000 to $54,999, ≥$55,000, and unknown; and two categories for blood pressure: hypertensive and nonhypertensive.

Exclusions
In addition to excluding participants younger than 18 years, we excluded people with the following characteristics: pregnant, unknown diabetes status, unmeasured height or weight, fasting period under 8 h or over 24 h, or a missing family history of diabetes. The net sample for this study was of 16,388 adults with valid data from the interview, among whom there were 6,004 participants with valid glucose data from the morning physical examination.

Analyses
The data were handled using SAS version 9.1 (19), and the analyses were performed using SUDAAN version 9 (20). All analyses followed a methodology that was specific for complex surveys. In complex surveys like NHANES, participants are selected at random, but the probability of selection is not the same for all participants. To account for the differences in the probability of selection and the design of the survey, each participant is assigned a statistical weight that must be included in all analyses to obtain unbiased estimates. In this study, the prevalence of diagnosed diabetes was estimated among all participants with an assigned interview weight; the prevalence of undiagnosed diabetes was estimated only among participants with assigned morning weights; and the total prevalence of diabetes was estimated by combining participants with diagnosed diabetes (interview weights) and all participants in the morning sample whose diabetes status was assessed at the Mobile Exam Center under fasting conditions (morning weights).

Adjusted odd ratios were obtained by multiple logistic regression models.

tween type 1 and type 2 diabetes, but the sample was restricted to adults; therefore, our results apply mostly to type 2 diabetes.

Family history of diabetes was determined with the following question: including living and deceased, were any of your biological relatives, that is, blood relatives, including grandparents, parents, brothers, and sisters, ever told by a health professional that they had diabetes? If the answer was "yes," then they were asked, which family member? The possible answers by multiple-choice were mother, father, mother's mother, mother's father, father's mother, father's father, brother, sister, other, refused, or don't know. The risk of diabetes according to family history was stratified in three levels as follows: *1*) high: at least two first-degree relatives or one first-degree and at least two second-degree relatives with diabetes from the same lineage; *2*) moderate: just

one first-degree and one second-degree relative with diabetes, or only one first-degree relative with diabetes, or at least two second-degree relatives with diabetes from the same maternal or paternal line; or *3*) average: no family history of diabetes or, at most, one second-degree relative with diabetes (17).

Covariates
Standing height was measured, to the nearest millimeter, with a fixed stadiometer. Weight was measured in pounds with a digital scale and converted to kilograms. BMI was calculated as weight in kilograms divided by height in meters squared. Blood pressure (systolic or diastolic) was measured three and sometimes four times, after a 5-min rest. The first reading was ignored and the average of the last two or three determinations was recorded as the blood pressure (16). Hy-

Adjusted prevalence data were obtained by predicted marginals (multivariate-adjusted rates expressed as a percentage) (21). Age and BMI were included in all regression models as continuous variables.

RESULTS — The crude prevalence of diabetes (diagnosed, undiagnosed, and combined) is shown in Table 1 by several demographic and socioeconomic variables, BMI, hypertension, and familial risk of diabetes. In each category, the crude prevalence of diabetes displayed well-established trends: It increased with age, it showed minor sex differences and major racial/ethnic differences (non-Hispanic whites and Mexican Americans showed similar prevalence, but the latter were a much younger population), it decreased as education and income increased, it increased with BMI, and it was much more prevalent among the hypertensive.

Overall, the weighted distribution of the U.S. population according to familial risk of diabetes was as follows: 22.7% were in the moderate and 7.5% in the high familial risk category. The rest were in the average familial risk category (not shown in tables). These weighted proportions varied slightly for adult non-Hispanic whites: 22.1% in the moderate and 6.3% in the high-risk category. These proportions increased to 25.4% for moderate and 11.5% for high familial risk in adult non-Hispanic blacks and to 25.7% for moderate and 10.3% for high familial risk among adult Mexican Americans. Thus, there was a high familial risk in 1 of 16 non-Hispanic white adults and in 1 of 10 non-Hispanic black or Mexican American adults.

The crude prevalence of diabetes is shown in Table 2 across the same variables included in Table 1, but this time, each category of diabetes status was subdivided into the three categories for familial risk. Except for a few instances of no data in the low BMI category, probably due to the small number of participants, the prevalence of diabetes increased with familial risk within each stratum for each variable. Overall, the crude prevalence of diagnosed diabetes was 3.8% in the group with average risk, but it increased to 24.3% in the group with high risk. Similarly, the crude total prevalence of diabetes (diagnosed or undiagnosed) increased from 5.9 to 30.0% from the first to the third level of family risk.

Given the strong influences of age and
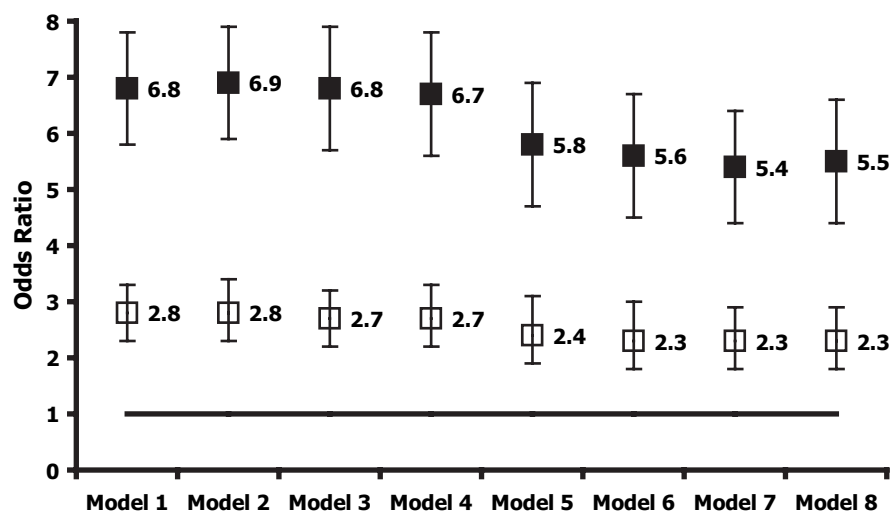
Figure 2—*Adjusted odds ratios for diabetes (diagnosed or undiagnosed) according to familial risk level of diabetes (NHANES, 1999–2004). The models are (adjusted for): Model 1 (unadjusted); Model 2 (sex); Model 3 (sex, race/ethnicity); Model 4 (sex, race/ethnicity, age); Model 5 (sex, race/ethnicity, age, BMI); Model 6 (sex, race/ethnicity, age, BMI, hypertension); Model 7 (sex, race/ethnicity, age, BMI, hypertension, education); Model 8 (sex, race/ethnicity, age, BMI, hypertension, household income).* ■, *High familial risk;* □, *moderate familial risk; continuous line, average familial risk (reference).*

BMI on the prevalence of diabetes, we tested separately the influence of familial risk stratification on the prevalence of diabetes across commonly used age and BMI categories, while controlling for other key variables (Fig. 1). In virtually every stratum of age (Fig. 1*A*) and BMI (Fig. 1*B*), there was a clear stratification of risk for diabetes according to family history. Versus the average-risk category, the adjusted overall prevalence of diabetes in each case was significantly higher for the high and the moderate familial risk categories ($P < 0.0001$, *t* statistic).

Finally, unadjusted and sequentially adjusted odd ratios for diabetes are shown in Fig. 2. According to this figure, people with moderate familial risk, independently of several important covariates, had between two and three times the odds of having diabetes as did people whose familial risk was average. In contrast, depending on the factors accounted for, people with high familial risk had five to seven times the odds of having diabetes as people with average familial risk.

CONCLUSIONS — This study has shown in detail that family history of diabetes has a graded association with the prevalence of diabetes in the U.S. population and that this association is detectable within strata of several well-established risk factors for diabetes. Moreover, the risk of diabetes imposed by family history is evident along a broad range of adult ages and BMI, even

after adjusting for relevant covariates. With these results, this study provides *1*) definitive evidence of the independence and significance of the association between family history and the prevalence of diabetes in the U.S. population and *2*) reliable estimates of the prevalence of familial risk of diabetes in the U.S. population: about 1 of every 3 adults has a moderate to high risk and about 1 of every 13 adults has a high risk as determined by the algorithm we used (14,15,17). Incidentally, this algorithm could be expanded to include other first- and second-degree relatives (sons, daughters, aunts, and uncles).

Previous studies have indicated that, versus people without a family history of diabetes, those who have a family history of diabetes are two to six times as likely to have type 2 diabetes (9). More specifically, a recent study based on NHANES data found that *1*) family history of diabetes was significantly and independently associated with diabetes in U.S. adults (based on self-reports) and *2*) the strength of the association was related to the type and number of relatives involved (13). Even though the definitions of family history are not comparable, our study is in agreement with this previous study. Our results add the information that a stratified familial risk of diabetes can be linked not only to the prevalence of diabetes detected from self-reports, but also to the prevalence of undiagnosed and diagnosed

diabetes, separately or combined. This suggests that the association between family history of diabetes and the prevalence is not due to recall bias among those who already know that they have the disease. It cannot be proven because NHANES contains no information on whether or not the knowledge of family history preceded the diagnosis of diabetes. However, our results (Table 1) indicate that family history might influence the knowledge of having diabetes. Overall, undiagnosed cases constituted about one-third of the total cases of diabetes. This proportion diminished to about one-fourth among the moderate and high familial risk categories. In other words, people with diabetes are more likely to know that they have the disease when they are at an elevated familial risk.

A previous NHANES-based study anticipated the findings of the present study (14), but this earlier study was not designed to be a direct test of the independence of the association between family history and prevalence of diabetes. Rather, it was designed to test the use of family history and BMI as screening tools for undiagnosed diabetes in the U.S. population. Nevertheless, with the same risk stratification, this previous study showed that the prevalence of diabetes (diagnosed or undiagnosed) is positively associated with familial risk. Our study has confirmed these results and has provided a detailed account of the strength and independence of the association between familial risk and the prevalence of diabetes (diagnosed, undiagnosed, and combined) in the U.S. population.

In conclusion, having demonstrated that family history of diabetes is indeed a powerful independent risk factor for the disease, our efforts should now be directed toward translating this knowledge for use in public health programs designed to detect and prevent diabetes. For that translation to occur, however, further research is needed to give the use of family history a place as a public health strategy against diabetes: First, the use of family history as a predictor should be tested more often in large prospective studies, just to be certain that the ascertainment of the familial risk actually precedes the disease status. Second, family history of diabetes should be considered not as a dichotomous variable (present/absent) but rather as a variable whose influence on the disease is graded. Third, a universally agreed-upon definition of family history of diabetes that is also simple to collect would be necessary to establish and compare familial risk across a variety of populations. Fourth, our results show that stratified familial risk, combined with other readily available indicators of diabetes risk, could be a great tool to identify segments of the population at high risk for the disease. The incorporation of family history into screening and prevention programs for diabetes, however, needs to be accomplished as rigorously as possible. That is, the value added by family history to these programs must be evaluated and found to be significant and cost-effective (8,22).

References

1. American Diabetes Association: Diagnosis and classification of diabetes mellitus. *Diabetes Care* 30:S42–S47, 2007
2. Centers for Disease Control and Prevention: National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2005. Atlanta, GA, U.S. Department of Health and Human Services, 2005
3. Reusch JEB: Diabetes, microvascular complications, and cardiovascular complications: what is it about glucose? *J Clin Invest* 112:986–988, 2003
4. American Diabetes Association: Economic costs of diabetes in the U.S. in 2002. *Diabetes Care* 26:917–932, 2003
5. Permutt MA, Wasson J, Cox N: Genetic epidemiology of diabetes. *J Clin Invest* 115:1431–1439, 2005
6. Weedon MN, McCarthy MI, Hitman G, Walker M, Groves CJ, Zeggini E, Rayner NW, Shields B, Owen KR, Hattersley AT, Frayling TM: Combining information from common type 2 diabetes risk polymorphisms improves disease prediction. *PLoS Med* 3:e374, 2006
7. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, Boutin P, Vincent D, Belisle A, Hadjadj S, Balkau B, Heude B, Charpentier G, Hudson TJ, Montpetit A, Pshezhetsky AV, Prentki M, Posner BI, Balding DJ, Meyre D, Polychronakos C, Froguel P: A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* 445:881–885, 2007
8. Yoon PW, Scheuner MT, Peterson-Oehlke KL, Gwinn M, Faucett A, Khoury MJ: Can family history be used as a tool for public health and preventive medicine? *Genet Med* 4:304–310, 2002
9. Harrison TA, Hindorff LA, Kim H, Wines RC, Bowen DJ, McGrath BB, Edwards KL: Family history of diabetes as a potential public health tool. *Am J Prev Med* 24:152–159, 2003
10. Guttmacher AE, Collins FS, Carmona RH: The family history: more important than ever. *N Engl J Med* 351:2333–2336, 2004
11. Meigs JB, Cupples LA, Wilson PW: Parental transmission of type 2 diabetes: the Framingham Offspring Study. *Diabetes* 49:2201–2207, 2000
12. Goldfine AB, Bouche C, Parker RA, Kim C, Kerivan A, Soeldner JS, Martin BC, Warram JH, Kahn CR: Insulin resistance is a poor predictor of type 2 diabetes in individuals with no family history of disease. *Proc Natl Acad Sci U S A* 100:2724–2729, 2003
13. Annis AM, Caulder MS, Cook ML, Duquette D: Family history, diabetes, and other demographic and risk factors among participants of the National Health and Nutrition Examination Survey 1999–2002. *Prev Chronic Dis* 2:A19, 2005
14. Hariri S, Yoon PW, Moonesinghe R, Valdez R, Khoury MJ: Evaluation of family history as a risk factor and screening tool for detecting undiagnosed diabetes in a nationally representative survey population. *Genet Med* 8:752–759, 2006
15. Hariri S, Yoon PW, Qureshi N, Valdez R, Scheuner MT, Khoury MJ: Family history of type 2 diabetes: a population-based screening tool for prevention? *Genet Med* 8:102–108, 2006
16. Centers for Disease Control and Prevention: National Center for Health Statistics. http://www.cdc.gov/nchs/nhanes.htm. Accessed 10 April 2007
17. Scheuner MT, Wang SJ, Raffel LJ, Larabell SK, Rotter JI: Family history: a comprehensive genetic risk assessment method for the chronic conditions of adulthood. *Am J Med Genet* 71:315–324, 1997
18. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ: The Seventh Report of the Joint National Committee on Prevention, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report. *JAMA* 289:2560–2571, 2003
19. SAS Institute: *Base SAS 9.1.3 Procedures Guide.* 2nd ed. Vol. 1–4. Cary, NC, SAS Institute, 2006
20. Research Triangle Institute: *SUDAAN Language Manual.* Release 9.0. Research Triangle Park, NC, Research Triangle Institute, 2004
21. Graubard BI, Korn EL: Predictive margins with survey data. *Biometrics* 55:652–659, 1999
22. Yoon PW, Scheuner MT, Khoury MJ: Research priorities for evaluating family history in the prevention of common chronic diseases. *Am J Prev Med* 24:128–135, 2003