Diabetes risk assessment in Mexicans and Mexican-Americans: Effects of Parental History of Diabetes are Modified by Adiposity Level.

Hector E. Velasco Mondragon, MD, MSc, PhD
R. William Charlton, MD, MAS
Tasha Peart, DrPH
Ana I B Garcia, MD, PhD
Mauricio Hernandez-Avila, MD, MPH
Wen-Chi Hsueh, MPH, PhD

1Morgan State University, Baltimore, MD; 2University of California, San Francisco, CA, USA; 3National Institute of Public Health, Cuernavaca, Morelos, Mexico

*H.E.V.M. and R.W.C. Contributed equally to the manuscript

Corresponding author:
Wen-Chi Hsueh, MPH, PhD
Email: wen-chi.hsueh@ucsf.edu

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Background: Parental diabetes history is a well-known risk factor for type 2 diabetes and considered strong evidence for a genetic basis of type 2 diabetes. Whether this relationship is affected by other known risk factors, specifically obesity, remains unclear, possibly due to a relative paucity of lean diabetes patients.

Methods: This issue was investigated using data from a high-risk population from Mexico (National Health Survey 2000, n = 27,349), with observations replicated using United States citizens of Mexican descent from the NHANES 2001-2002, 2003-2004 (n = 1,568).

Results: As expected, positive parental diabetes was a significant risk factor for type 2 diabetes, regardless of age, gender, or adiposity level. However, positive parental diabetes conferred greater risk in leaner individuals than in their overweight peers (P = 0.001). In other words, the effect of BMI on type 2 diabetes risk was smaller in the presence of parental diabetes history.

Conclusions: These findings suggest that parental diabetes is a stronger risk factor for type 2 diabetes in the absence of obesity. Thus lean diabetes patients could help identify type 2 diabetes susceptibility genes. This study reinforces the concept that parental diabetes and body mass index are independent type 2 diabetes risk factors, and suggests that glycemic screening may be helpful in assessing type 2 diabetes risk in individuals with parental diabetes history, regardless of their overweight status.

Type 2 diabetes is an important public health priority because of escalating prevalence, its association with other health conditions, and associated costs. An estimated 24 million Americans suffer from type 2 diabetes, with one quarter of them unaware of their disease, incurring societal costs estimated at $174 billion annually (1). Because the incidence rate of type 2 diabetes can be reduced as much as 58% by exercise and moderate weight reduction (2), improving risk assessment could decrease its morbidity and cost.

Well described risk factors for type 2 diabetes include obesity, family history of diabetes, age, race, and physical inactivity. Of these, adiposity is considered the principal risk factor. Genetic factors, estimated using family history, are also known to contribute substantially to risk. However, little is known about how these important risk factors may interact with each other. Multiple genetic variations are associated with type 2 diabetes, but family history remains the only feasible measure of “genetic load” that can be used on a population level. Family history of diabetes is independently associated with type 2 diabetes prevalence (3). Also, the Centers for Disease Control recommend its use in prevention and screening programs (4). Although not itself a modifiable risk factor, use of family history in risk assessment can lead to targeted interventions and increased patient awareness of risk (5). Because obesity is the primary risk factor for type 2 diabetes, genetic influences on
type 2 diabetes risk may be masked. Moreover, type 2 diabetes and obesity may share genetic risk factors, confounding identification of susceptibility variants for type 2 diabetes (6). Therefore, the goals of our study were to: (1) evaluate whether the risk for type 2 diabetes conferred by a family history of diabetes varies by level of adiposity, (2) evaluate the relative influence of maternal versus paternal diabetes in a population at high risk for type 2 diabetes and (3) contribute information to the standardization of a family history definition by comparing our risk estimates based on parental diabetes history to those of previous studies using more extensive measures of family history.

RESEARCH DESIGN AND METHODS
To address these objectives, a large dataset from the national health survey in Mexico (Encuesta Nacional de Salud 2000, or ENSA 2000) was utilized. Degree of genetic load was assessed by self-reported parental diabetes history and the level of adiposity was measured by body mass index (BMI). Findings were replicated using U.S. nationals of Mexican descent, hereafter referred to as the Mexican-American subgroup, from the United States National Health and Nutrition Examination Surveys (NHANES).

This cross-sectional study design aimed at evaluating relationships between parental diabetes history, adiposity, age, and risk of type 2 diabetes in a population at high risk for type 2 diabetes. Specifically, the interaction between adiposity and parental diabetes history was evaluated to determine if non-overweight diabetes patients have a higher contribution of risk from parental diabetes history than do their overweight peers.

Moreover, type 2 diabetes and obesity. The primary study population was from the Mexican National Health Survey conducted in 2000 (Encuesta Nacional de Salud 2000, or ENSA 2000). ENSA 2000 is a nationally representative population sample, and has been previously described (7; 8). Weighted samples of participants with age ≥30 years represent a population of 28,041,807. ENSA 2000 obtained informed consent and approval from Mexico's National Institute of Public Health Internal Review Board, in accordance with stipulations of the Mexican Statistical and Geographic information law (Ley de Información Estadística y Geográfica. Diario Oficial de la Federación. Estados Unidos Mexicanos, 1980).

For comparison, the Mexican-American subgroup of NHANES 2001-2002 and 2003-2004 was used. To accrue a larger sample size, both survey datasets were appended (2001-2004) and analyzed using new weights recommended by NHANES. (http://www.cdc.gov/nchs/nhanes/nhanes2003-2004/analytical_guidelines.htm).

Both surveys used consistent definitions and measurements. Similar to ENSA, NHANES employed a complex multistage probability sampling design. Overall response rates were 80%. Weighted samples of participants with age ≥30 years represent a combined population size of 153,700,000 for NHANES Mexican-American subgroup. NHANES obtained informed consent and performed interviews and examinations per standardized protocols. Approval was obtained by the Committee on Human Research at University of California, San Francisco.

In both the ENSA and NHANES surveys, trained personnel used standardized questionnaires to record demographic
data and medical history. Information obtained included sex, age, residential region (ENSA), and parental diabetes history. A daily-calibrated balance measured height to the nearest 5mm and weight to the nearest 0.1kg, with the subjects in light clothing without shoes. Body mass index (BMI) was calculated as weight(kg) divided by height squared(m\(^2\)). Capillary glucose measurements were performed by the glucose oxidase technique on random samples (Accutrend Sensor Comfort; Roche Diagnostic Corporation, Indianapolis, IN). Overweight status was defined as having a BMI ≥25kg/m\(^2\).

Diabetes status was determined by self report based on a physician diagnosis, or by using the American Diabetes Association criteria (9). Family history of diabetes was defined by the self-reported diabetes status of the parents. This definition correlated well with the results of studies using a wider array of relatives (5). Also, it avoids the potential differential bias inherent in trying to compare different family structures (i.e. risks of subjects with diabetic siblings relative to subjects without siblings).

Among the ENSA participants, fasting glucose levels were obtained from a subsample reporting a fasting period of 9 to 12h. 4.9% of our subjects were fasting; approximately 4.8% of non-diabetic participants and 5.7% of diabetic participants. This subset has been previously described (8). ENSA 2000 collected information on 41,126 individuals. NHANES 2001-2004 contains data on 2,066 Mexican-Americans. Unknown diabetes status caused exclusion from analysis. Incomplete parental diabetes history, or missing values from any of the above mentioned covariates, also caused exclusion. Inclusion was limited to age ≥30 years to minimize inclusion of younger participants with less accurate classification of their own and their parents’ diabetes status. Consequently, our final analysis included 27,349 ENSA 2000 subjects and 1,568 NHANES subjects. Furthermore, subjects with diabetes diagnosis made at the time of the survey (n = 823) were excluded from analyses related to age at diabetes diagnosis.

Risk for type 2 diabetes was estimated using logistic regression models. Initially, BMI was treated as a continuous variable. It was then dichotomized at 25kg/m\(^2\), stratified by the clinical definition of overweight. To investigate differential effects of maternal versus paternal diabetes, participants were first classified as having both parents, mother only, father only, or no parents with diabetes. When no significant parent-of-origin effect was observed, parental diabetes history was treated as an ordinal variable, with participants classified as having two parents, one parent, or no parents with diabetes. To assess whether effects of positive parental diabetes history vary by BMI, a multiplicative interaction term (parental diabetes history × BMI) was included in the statistical model, in addition to their main effects. Significance of the interaction effect was evaluated using likelihood ratio tests; comparing the likelihood of a full model with both the main effects of BMI and positive parental diabetes history and a joint effect to that of a nested model in which only the two main effects were estimated. The effect of this interaction term was significant in both the NHANES (P = 0.037) and ENSA (P = 0.01) groups. A similar modeling approach for linear regression analyses was used to evaluate whether these factors affected the age at diabetes diagnosis. Age and sex were included in
all regression models. Effects of geographical regions and the ability to speak Native American dialects were evaluated and were found not to be significant covariates.

Because samples were differentially weighted to represent nationwide populations, analyses were conditioned on population weights and cluster sampling for both ENSA 2000 and NHANES 01-04. Analyses were performed on both the ENSA 2000 and the NHANES 01-04 data using Stata version 10.0 (College Station, TX), with statistical significance defined as a two-tailed p-value <0.05. The SVY module was used to account for the complex survey sampling variance estimation.

RESULTS

Of the 27,349 individuals aged ≥30 years in the ENSA 2000 sample, the mean age was 46.2 years (SD 13.3), 10.4% had diabetes, and 53% were female (Table 1). The average BMI was 28.0 kg/m² (SD 5.4), and 70.9% of participants were overweight. Among people with diabetes diagnosed after age 30, the mean age at diabetes diagnosis was 48.5 years (SD 10.7). In the NHANES sample, participants were slightly more overweight (77%). However, other characteristics were comparable between populations.

Parental diabetes history was significantly positively associated with type 2 diabetes (Table 2). This relationship was consistent regardless of overweight status, after adjusting for the effects of age, sex, and BMI (Table 3). Overall, there was no significant difference in maternal versus paternal influence on type 2 diabetes risk. In the overweight ENSA subgroup, maternal influence on type 2 diabetes risk appeared larger compared to paternal effects with borderline significance; OR = 2.16, 95% CI: 1.85 – 2.52 compared to OR = 1.30, 95% CI: 1.02 – 1.67. No such difference was seen in the non-overweight subgroup. The effect of parental diabetes history was log additive if both parents had diabetes. Estimates were similar in the smaller NHANES sample, although there was no difference between effects of maternal versus paternal diabetes history regardless of subjects’ overweight status.

In the ENSA sample, when risk was estimated based on weight status, the ORs for type 2 diabetes by parental diabetes history appeared higher in the non-overweight group compared to the overweight group (Table 3) (P for trend < 0.05). In the non-overweight group, individuals with either a mother or father having diabetes respectively had about 3.3 and 3.4 times the risk of having diabetes compared to those without any diabetic parents, whereas in the overweight group, the OR estimates were lower (1.3 – 2.2). Similarly, bilineal parental history conferred nearly twice the risk in non-overweight (OR = 7.9, 95% CI: 3.15 – 19.6) versus overweight participants (OR = 3.9, 95% CI: 2.81 – 5.33). Estimates were comparable when parental history was coded as an ordinal variable (0, 1, or 2 parents with diabetes) (data not shown). When adiposity level was assessed by BMI and modeled as a quantitative trait, there was a significant interaction effect between BMI and the parental diabetes history, after adjusting for age and sex. Having one diabetic parent was associated with an increased diabetes risk (OR = 5.0, 95% CI: 3.0 – 8.5), and diabetes risk associated with a one unit increase in BMI showed OR = 1.04, 95% CI: 1.03 – 1.06. Interestingly, the interaction between BMI and parental history was significant but negative (β = -0.03, P = 0.001). In other words, it
supported the patterns observed in Table 3 that the effects of a positive parental diabetes history were stronger among subjects with lower BMI. Analyses of age at diabetes diagnosis revealed that parental diabetes history was associated with earlier age at diabetes diagnosis overall. Mean age was comparable across BMI categories, and there was no apparent parent-of-origin effect (Table 4). Subjects with two diabetic parents had earlier age at diabetes diagnosis than those with one diabetic parent. This pattern persisted across all subgroups except in the lean NHANES subgroup, in which the estimate is considered unstable due to a small sample size (n = 36). Among all diabetic participants in ENSA 2000, mean age at diagnosis was 50.6 (SD, 11.0) years for subjects with no parental history, 46.5 (SD, 9.3) years for those with maternal history, 47.2 (SD, 10.8) years for those with paternal history, and 41.3 (SD, 8.2) years for those with bilineal history. Not all of the regression coefficients for parental diabetes history and age were significant when stratified by parent-of-origin, but direction and magnitude of point estimates were consistent across all subgroups (Table 5). Observations were similar in both populations, but NHANES estimates may not be stable due to smaller sample sizes.

CONCLUSIONS
One of the major strengths of the primary study population is that ENSA 2000 is the largest dataset available to test the aforementioned hypotheses in a population at high risk for type 2 diabetes. Findings showed that parental diabetes history was a significant risk factor for type 2 diabetes, and that adiposity negatively modified the relationship of parental diabetes history and diabetes risk. In other words, it appears that parental diabetes history plays a greater role in type 2 diabetes risk assessment in individuals with lower levels of adiposity compared to those with higher levels. Previous research describes risk estimates of type 2 diabetes increasing from two to six-fold with a positive family history of diabetes. Consistency of these estimates across several ethnic groups and study designs, independent of risk factors including age, BMI, and smoking, has been summarized by Harrison et al. (5). Results of this study are similar to these previous estimates, and are consistent with the additive models described in the Framingham Offspring Study and the Pima Indians (10; 11). In the ENSA cohort, risk estimates ranged from approximately 2 – 6 in the non-overweight group, and 1 – 2.5 in the overweight group. ORs were approximately double in participants with two diabetic parents (Table 3). Risk estimates based on the NHANES data were similar, although the estimates from the NHANES sample were less stable due to smaller sample size (~6% of the ENSA sample).

Regarding the findings of a significant interaction between BMI and parental diabetes history, direct comparisons were not readily available in the current literature. In our analysis, BMI was treated as a quantitative trait, and its effect on T2D was weaker in the presence of parental history ($\beta = 0.97$, $P = 0.001$). Therefore, it appears that parental history is more important in assessing diabetes risk in non-overweight individuals than in their overweight counterparts. In contrast, Sargeant et al. reported a positive interaction between parental diabetes history and BMI, but this finding was only significant in subjects with BMI $\geq 27.5$kg/m$^2$ (12). Morris
et al. also reported a positive interaction between family history of diabetes and BMI, but their subjects were all overweight (and female only) (13). For the sake of comparison, the authors repeated the interaction analysis, including only subjects with BMI $\geq 27.5\text{kg/m}^2$. Findings did not change in this subgroup; there remained a significant negative interaction.

The association of parental diabetes history and earlier age at diabetes diagnosis in these populations was consistent with previous research. Compared to ENSA 2000 subjects with no parental diabetes history, those with one diabetic parent were diagnosed an average of three and a half years earlier, while those with two diabetic parents were diagnosed an average of nine years earlier. Annis et al. reported a similar relationship in NHANES 1999-2002 participants, and Molyneaux in an Australian cohort (4; 14).

Regarding parent-of-origin effect, no significant difference in maternal versus paternal influence was found. Some early studies reported an excess in maternal transmission (15; 16). However, much has been written about potential biases that could have affected these results (17-19), including Thorand et al.’s suggestion that this phenomenon may result from misclassification due to unknown paternal history. In fact, examination of the confidence intervals reported in several papers supporting maternal transmission corroborate our results; point estimates for type 2 diabetes risk were higher in subjects with maternal history, but the estimates do not reach statistical significance (16; 20). In their evaluation of maternal transmission of type 2 diabetes, Karter et al. report that the proportion of their participants who knew only parental history of diabetes was over twice that of those who knew only paternal history. Although they found a borderline significant difference between maternal and paternal transmission overall, this difference did not retain statistical significance in any racial sub-groups (even though the Hispanic subgroup represented 2,354 families).

One last point of interest was whether limiting our definition of family history to include only parents might limit risk assessment. Across multiple ethnic groups of varying risk levels, similar risk estimates result whether family history is limited to parents, or expanded to include first or even second degree relatives (5). Therefore, because the correct diabetes status of more distant or younger relatives are more difficult to ascertain, and sibling risk contribution cannot be ascertained in singletons, defining family history using only parental information may be recommended.

Overall, we interpret these findings in light of the “multiple hit’ model of diabetes. Current understanding of type 2 diabetes risk purports that underlying genetic risk is compounded by other factors until the threshold of clinical disease is reached. It follows that those with a greater genetic risk would require smaller proportions of other risk factors, including adiposity and age. This theory may explain the results of the interaction analysis: among those with greater genetic risk (using positive parental diabetes history as a proxy), relatively less adiposity is required to manifest clinical disease. Similarly, it explains why subjects with greater genetic risk of diabetes (higher value of parental history) had significantly earlier age at diagnosis than those without parental history, regardless of adiposity status. Age, BMI, and family history are independent risk factors for type 2
diabetes. An increased proportion of any one risk factor allows for a relative decrease in others. Limitations of this study include the fact that multiple definitions of type 2 diabetes were used, including one random glucose measure, one fasting glucose value, and self reported physician diagnosis. Therefore, risk assessment precision could be diminished by non-differential misclassifications of type 2 diabetes status. There are also potential biases regarding age at diagnosis, including recall bias associated with self-reporting. Knowledge of positive parental history may lead to early screening, diagnosis, or even protective behaviors (reverse causation) (21-24), but this potential bias strengthens the argument for screening all patients for parental diabetes history. Additionally, in patients with type 2 diabetes, BMI was measured after diabetes onset, so we were unable to account for ways in which the pathophysiology or treatment of type 2 diabetes affects BMI. Unidentified cases of parental diabetes were also unaccounted for. These could falsely lower the apparent influence of parental history in the models, decreasing the magnitude of resulting risk estimates. Lastly, the datasets do not provide clear information regarding type of diabetes. Subjects diagnosed prior to age 30 years were excluded, in an attempt to eliminate participants with type 1 diabetes. However, any unidentified Maturity Onset Diabetes of the Young (MODY) lineages could falsely increase risk estimates. Finally, our comments regarding the definition of family history are based on comparisons to external data (multiple cohorts), as we were unable to compare estimates based on parental versus extended family history in our primary study population.

In conclusion, findings from these large datasets in a high-risk population support a log additive risk model of parental transmission of type 2 diabetes, with maternal and paternal history conferring epidemiologically similar effects. One novel and important observation is the significant interaction effect between adiposity and parental diabetes history on type 2 diabetes risk, which suggests that parental diabetes history confers greater risk in non-overweight versus overweight individuals. There are two important implications of this finding. First, it may be more cost-effective to study non-overweight individuals to search for type 2 diabetes susceptibility genes. Second, from a public health perspective, universal screening for family history of diabetes, as well as reconsideration of glycemic screening in lean individuals, may be recommended. Currently, the American Diabetes Association recommends testing for glycemic control in patients with family history of diabetes only in the context of overweight (BMI $\geq 25\text{kg/m}^2$) (25). However, family history is an independent risk factor for type 2 diabetes, and these findings suggest that using it as a criteria for glycemic testing could help identify high-risk, not-yet diagnosed patients as well as undiagnosed diabetic patients. Potential prevention of new cases as well as complications of undiagnosed type 2 diabetes could be an important public health improvement.

Author contributions: EV researched data, reviewed/edited manuscript, contributed to discussion. WC wrote manuscript, contributed to the discussion. TP analyzed data, reviewed/edited manuscript. AB researched data. MH researched data. WH designed the study.
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Table 1. Selected Characteristics of Participants by Survey and Diabetes, ENSA, Mexico, 2000, and NHANES, United States, 2001-2004

|                        | ENSA 2000 (n = 27,349) | NHANES 01-04 Mexican-American (n = 1,568) |
|------------------------|------------------------|-------------------------------------------|
|                        | Diabetic (n = 3,057)   | Non-diabetic (n = 24,292) | P | Diabetic (n = 266) | Non-diabetic (n = 1,302) | P |
| Age, years – Mean (SD) | 54.7 (12.8)            | 45.2 (13.0) | <0.001 | 55.8 (27.5) | 43.6 (19.9) | <0.001 |
| Female sex (%)         | 53 NS                  | NS            |          | 48 NS          | NS            |          |
| BMI, kg/m² – Mean (SD) | 28.0 (5.4)             | NS            |          | 29.0 (9.8)     | NS            |          |
| BMI <25 kg/m² (%)      | 29.1                   | <0.001        |          | 23.0           | 0.02          |
| Diabetes prevalence (%)| 22.2                   | 30.0          | <0.001   | 16.1           | 23.8          | 0.02    |
| Parental diabetes history (%) | <0.001    | <0.001       |          | <0.001         | <0.001       |
| None                   | 58.9                   | 72.0          |          | 43.1           | 65.6          |
| Mother only            | 22.9                   | 14.9          |          | 27.9           | 17.9          |
| Father only            | 9.2                    | 9.5           |          | 13.9           | 11.1          |
| Both                   | 9.0                    | 3.6           |          | 15.1           | 5.4           |
| Age at diabetes diagnosis – Mean (SD) | 48.5 (10.7) | 47.7 (28.1) |

Abbreviations: SD, standard deviation; BMI, body mass index
Table 2. Association of Parental Diabetes History and Type 2 Diabetes, by Adiposity Status, ENSA, Mexico, 2000, and NHANES, United States, 2001-2004*

|                    | ENSA 2000          | NHANES 01-04       |
|--------------------|--------------------|--------------------|
|                    | All BMI < 25 BMI ≥ 25 | All BMI < 25 BMI ≥ 25 |
| Parental diabetes  | Diabetes OR (95% CI) | Diabetes OR (95% CI) |
| history            |                    |                    |
| Mother only        | 2.38 (2.00, 2.83)  | 2.16 (1.85, 2.52)  |
|                    | (2.13, 6.00)‡     | (1.45, 4.41)‡      |
| Father only        | 1.60 (1.22, 2.13)  | 1.30 (1.02, 1.67)† |
|                    | (2.07, 5.49)‡     | (1.37, 5.15)‡      |
| Both parents       | 4.46 (3.13, 6.36)  | 3.87 (2.81, 5.33)‡ |
|                    | (3.15, 19.60)‡    | (2.74, 11.20)‡     |

Reference group: Individuals without parental diabetes history

† P <0.05
‡ P <0.001

Table 3. Regression Coefficients for Parental Diabetes History and Age at Diabetes Diagnosis, in Years, Stratified by Adiposity Status, ENSA, Mexico, 2000, and NHANES, United States 2001-2004 *

|                    | ENSA 2000 BMI < 25 (n = 445) | BMI ≥ 25 (n = 1,541) |
|--------------------|-------------------------------|----------------------|
| Parental diabetes  | Age (yrs) Mean ± SD β (95% CI) | Age (yrs) Mean ± SD β (95% CI) |
| None               | 51.1 ± 11.8                  | -5.48 (-8.5, -2.5)‡ |
| Mother             | 45.5 ± 9.5                   | 47.0 ± 9.7           |
|                    | -5.48 (-8.5, -2.5)‡          | -3.39 (-5.1, -1.7)‡ |
| Father             | 49.0 ± 12.7                  | 46.6 ± 9.9           |
|                    | -1.96 (-8.1, 4.2)            | -3.75 (-6.0, -1.5)† |
| Both               | 42.3 ± 8.5                   | 41.0 ± 8.4           |
|                    | -8.62 (-14.2, -3.0)‡         | -9.41 (-12.2, -6.6)‡ |

|                    | NHANES Mexican-American BMI < 25 (n = 36) | BMI ≥ 25 (n = 179) |
|--------------------|-------------------------------------------|-------------------|
| Parental diabetes  | Age (yrs) Mean ± SD β (95% CI)             | Age (yrs) Mean ± SD β (95% CI) |
| None               | 51.9 ± 36.0                               | 50.7 ± 25.4       |
| Mother             | 45.4 ± 22.6                               | 47.2 ± 29.6       |
|                    | -6.86 (-18.7, 4.9)                        | -4.05 (-10.0, 1.9) |
| Father             | 42.0 ± 16.9                               | 43.9 ± 18.8       |
|                    | -10.04 (-23.2, 3.1)                      | -7.11 (-12.5, -1.7)† |
| Both               | 45.6 ± 16.1                               | 41.7 ± 9.4        |
|                    | -5.95 (-16.8, 6.2)                       | -8.62 (-13.9, -3.3)† |

† P <0.05
‡ P <0.001

Abbreviations: CI, Confidence Interval
Reference group: Individuals without parental diabetes history adjusted for gender