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Association between diabetes, family history of diabetes and risk of nonalcoholic steatohepatitis and fibrosis

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Abstract

Previous studies have shown familial aggregation of insulin resistance and nonalcoholic-fatty-liver-disease (NAFLD). Therefore, we aimed to examine whether family history of diabetes-mellitus (DM) is associated with nonalcoholic steatohepatitis (NASH) and fibrosis in patients with NAFLD. This is a cross-sectional analysis in participants of the NAFLD Database Study and PIVENS Trial who had available data on family history of DM. 1069 patients (63% women) with mean age of 49.6 (± 11.8) years and BMI of 34.2 (± 6.4) kg/m2, were included. 30% had DM and 56% had family history of DM. Both personal history of DM and family history of DM were significantly associated with NASH with an odds ratio (OR) of 1.93 (95% CI, 1.37–2.73; p-value <0.001) and 1.48 (95% CI, 1.11–1.97; P=0.01), and any fibrosis with an OR of 3.31 (95% CI, 2.26–4.85; p-value <0.001) and 1.66 (95% CI, 1.25–2.20; P<0.001), respectively. When the models were adjusted for age, sex, BMI, ethnicity, and metabolic traits, the association between diabetes and family history of DM, with NASH showed an increased adjusted-OR of 1.76 (95% CI, 1.13–2.72, p-value <0.001) and 1.34 (95% CI, 0.99–1.81; P=0.06), respectively, and with any fibrosis with an significant adjusted-OR of 2.57 (95% CI, 1.61–4.11; p-value < 0.0001) and 1.38 (95% CI, 1.02–1.87; P=0.04), respectively. After excluding patients with personal history of

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diabetes, family history of DM was significantly associated with presence of NASH and any fibrosis with adjusted OR of 1.51 (95% CI, 1.01–2.25; P=0.04), and 1.49 (95% CI, 1.01–2.20; P=0.04), respectively. Conclusions: Diabetes is strongly associated with risk of NASH, fibrosis and advanced fibrosis. Family history of diabetes especially among non-diabetics is associated with NASH and fibrosis in NAFLD.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of elevated serum alanine aminotransferase (ALT) in the United States (1). Approximately one in every third American is estimated to have NAFLD (2). Although it is a highly prevalent disease, not all patients with NAFLD develop progressive liver disease. Based upon the current understanding of the natural history of NAFLD, it is well-accepted that only a subset of patients with histologic features of nonalcoholic steatohepatitis (NASH) progress to advanced fibrosis, cirrhosis, and hepatocellular carcinoma (3). Therefore, improved understanding of risk factors that predict increased risk of presence of NASH and fibrosis on liver histology could help in risk stratification of patients with NAFLD (4).

Previous studies have shown that metabolic traits such as diabetes, hypertension, dyslipidemia, and obesity are associated with increased risk of NASH, and advanced fibrosis among patients with NAFLD (5, 6). Metabolic traits are known to have both genetic and environmental influences suggesting a key role of familial risk factors in metabolic diseases (7) including NAFLD and NASH (8, 9). Previous studies have now shown familial clustering of serum gamma-glutamyl transpeptidase (a marker of fatty liver), NAFLD, NASH and advanced fibrosis (7, 10–13). Recent studies have shown that parental obesity is associated with increased odds of suspected NAFLD, and there is strong familial clustering of NAFLD especially in the setting of co-existing insulin resistance (11, 14). Family history is part of routine medical evaluation (15). However, there are limited data on whether family history of diabetes increases the risk of NASH and fibrosis among patients with NAFLD.

We conducted a cross-sectional analysis derived from a prospective, multi-center study of patients with biopsy-proven NAFLD to test the hypothesis that family history of diabetes is associated with increased risk of NASH and fibrosis, after adjusting for multiple metabolic traits as well as personal history of diabetes, in patients with NAFLD who are enrolled in the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) studies.

METHODS

Study Design and Participants

This is a cross-sectional study utilizing prospectively collected data from the participants of the multi-center NAFLD Database Study and PIVENS Trial derived from the Nonalcoholic Steatohepatitis Clinical Research Network studies (NASH-CRN) at the baseline visit (5, 16). The details of the inclusion and exclusion criteria and study designs have been previously published (5, 16, 17). The NASH CRN studies are sponsored by the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK), National Institutes of Health and all patients provided written informed consent before enrolling into these studies.

Derivation of the Cohort and Family History Data

Information on demographic characteristics, anthropomorphic measurements, alcohol consumption, medical history, medication use, clinical tests and liver biopsy results were collected at the baseline visit as previously described (5). There were 1069 participants 18 years or older, enrolled in the above mentioned NASH CRN studies between October 2004

and February 2008 who had available liver biopsies and data on the family history of diabetes in their first degree relatives (parents or children or siblings). Family history of diabetes was based upon patient report during the baseline medical history interview with the clinical coordinator. The exact wording of the question was: "Do any of the patient's first degree relatives (parent, brother, sister, child) have diabetes (Type 1 or Type 2): Yes, No, Don't know." A mix of Interview data and data obtained by a comprehensive chart review was utilized to collect family history data. In addition, family history questions on the baseline form could be answered by interview with the patient, parent, or both and in consultation with the patient's partner, if available. Thus, we utilized all sources to get the most accurate information pertaining to family history. The clinical coordinator and study physician both reviewed and performed a chart review to obtain the most accurate information. All forms were co-signed by the clinical coordinators and the study physician confirming the authenticity of the family history data obtained.

NAFLD Diagnosis

Participants had to meet specific criteria regarding the diagnoses of NAFLD in order to be enrolled in the observational Database Study and the PIVENS Trial. Patients with alcohol consumption of >140 g/ week (>70 g/ week if female) in the 2 years prior to screening, or with suspected alcohol-related liver injury were excluded. In addition, other etiologies of chronic liver disease were carefully excluded. For the purposes of enrollment into the observational Database Study, the diagnosis of NAFLD was based on the histological diagnosis of NAFLD or cryptogenic cirrhosis as described above, or on imaging studies consistent with these (5). However, for this study, only subjects with available liver biopsy were included.

For the purposes of this study, NAFLD was defined based on the following criteria: 1. Histologic diagnosis of NAFLD or histologic diagnosis of cryptogenic cirrhosis; 2. Alcohol use history consistent with NAFLD as defined above; 3. Exclusion of liver disease of other etiologies including viral or autoimmune hepatitis, drug induced liver disease, and cholestatic or metabolic liver disease. These other potential etiologies were carefully investigated based on Database Study specific criteria at screening as previously published (5, 17).

Other Variables

All data used in these analyses were obtained within 6 months of the liver biopsy. Following variables were analyzed: demographic features (age at enrollment (years), gender, race (White or other), ethnicity (Hispanic/Latino)), family history, clinical data (waist circumference, body mass index (kg/ m2), diastolic blood pressure, and systolic blood pressure), laboratory measures (triglyceride, HDL and fasting serum glucose levels) and presence of diabetes.

Diabetes status was based upon either previous history of diabetes based upon patient/ physician report (and/or use of medications to treat diabetes, and/or fasting plasma glucose > 125 mg/dl or a 2 hour glucose >200 mg/dl during an oral glucose tolerance test during the baseline visit). In order to determine whether the association between family history of diabetes and advanced histology in NAFLD in mediated via pre-diabetes, the cohort was further classified into pre-diabetic and normoglycemic participants. Pre-diabetes was defined as fasting glucose between 100–125 mg/dL or hemoglobin A1c between 5.7–6.4%; normoglycemia was defined as fasting glucose<100 mg/dL and hemoglobin A1c less than 5.7%. Patients with discordant results (e.g., glucose<100 mg/dL and hemoglobin A1c>6.4% or patients without diagnosis of diabetes but with discordant one-time laboratory values) were set to missing (N=22). Family history of a condition or disease was self-reported to be

present in a first degree relative (parent, sibling or child). The presence of patatin-like phospholipase domain-containing protein-3 (PNPLA3) rs738409 G allele was determined for each patient as previously described (18), and included in the analysis.

Outcomes

Nonalcoholic Steatohepatitis and fibrosis—Liver biopsy slides stained with hematoxylin and eosin and Masson's trichrome were reviewed and scored centrally by the NASH CRN pathology committee as previously reported (19). Central pathology committee pathologists reviewed biopsies without any knowledge of the local pathology readings or clinical or laboratory values of patients in the study (19, 20).

Fibrosis was graded based on the modified Brunt classification; 0 = no fibrosis, 1a = mild, zone 3 perisinusoidal fibrosis (requires trichrome), 1b = moderate, zone 3 perisinusoidal fibrosis (does not require trichrome), 1c = portal/periportal fibrosis, 2 = zone 3 perisinusoidal or periportal fibrosis or both, 3 = bridging fibrosis, 4 = cirrhosis (19–22). Advanced fibrosis was defined as stages 3–4 and compared with mild or no fibrosis (stages 0–2). Any fibrosis was defined as stages 1–4 and compared with no fibrosis (stage 0). Diagnosis of nonalcoholic steatohepatitis (NASH) was classified as either definite NASH or suspicious for NASH (borderline NASH) based upon central pathology reading as previously defined (19, 20), and compared with no NASH. These categories were defined prior to conducting statistical analyses.

Statistical Analyses

All data were reported as means and standard deviations, numbers and percentages, or odds ratios (OR) and 95% confidence intervals. We first evaluated the baseline characteristics of patients for familial trait using χ^2 and Wilcoxon Rank Sum tests. Based on these results, we assessed the effect of family history of diabetes on two separate outcome measures: NASH and fibrosis (any fibrosis, and then advanced fibrosis, in separate models). Three multiple logistic regression models were run for each of the following outcomes: NASH (definite/borderline vs. none), Any Fibrosis (grades 1–4 vs. grade 0), and Advanced Fibrosis (grades 3–4 vs. grades 0–2). All models included both family history of diabetes and personal history of diabetes as covariates, and the following covariates for adjustment: age at enrollment (years), gender (female vs. male), body mass index (kg/m^2), ethnicity (Hispanic vs. non-Hispanic), waist circumference (cm), triglyceride level (mg/dL), HDL level (mg/dL), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and blood glucose level (mg/dL).

We then conducted sensitivity analyses by excluding patients with personal history of diabetes and examined the association between family history of diabetes and presence of NASH and fibrosis on liver histology using above mentioned logistic regression models. We then utilized *Wald* test for interaction to assess whether there was a significant interaction between personal history of diabetes and family history of diabetes for these histological traits.

Finally, joint effects of personal history of diabetes and family history of diabetes was examined using three separate logistic regression models to analyze the individual effects of personal history of diabetes and family history of diabetes, as well as their combined effect on NASH and fibrosis. Individuals with no family history and personal history of diabetes were used as the control group for all three models. Age at enrollment, gender and BMI were controlled for in these models.

In order to determine whether the association between family history of diabetes and advanced histology in NAFLD in mediated via pre-diabetes, the cohort was further classified into pre-diabetic and normoglycemic participants. We conducted multivariate-adjusted logistic regression analyses to examine the association between family history of diabetes and risk of NASH and any fibrosis by adjusting for diabetes as well as pre-diabetes. In addition, we also examined whether pre-diabetes was independently associated with risk of NASH and any fibrosis in patients with NAFLD in similar models.

All analyses were performed using SAS statistical software (version 9.2). Nominal, two-sided *P* values were used and were considered to be statistically significant if $P \leq 0.05$, a priori.

RESULTS

Baseline characteristics

This study included 1069 patients from the NAFLD Database Study and PIVENS Trial. The mean age and BMI were 49.6 (± 11.8) years and 34.2 (± 6.4) kg/m^2, respectively. Out of these 1069 patients, 596 (56%) reported a family history of diabetes in their first degree relatives, and 30.4% had diabetes. The baseline characteristics of the individuals with a family history of diabetes versus those without a family history of diabetes are shown in Table 1. Those with family history of diabetes were older in age, females, non-White, had higher BMI and higher prevalence of diabetes. On liver histology, patients with family history of diabetes were more likely to have NASH (definite/borderline vs. none), any fibrosis (any vs. none), and advanced fibrosis (stage 3–4 vs. 0–2) as compared to those without family history of diabetes.

Association between family history of diabetes and liver histology

In logistic regression models adjusted for personal history of DM, family history of DM was significantly associated with NASH, and any fibrosis with an adjusted-OR of 1.48 (95% CI, 1.11–1.97; ***P*=0.01**), and 1.66 (95% CI, 1.25–2.20; ***P*<0.001**) respectively, as shown in Table 2. In multiple-logistic regression analyses adjusted for age, sex, BMI, ethnicity, waist circumference, serum triglyceride, HDL, systolic BP, diastolic BP, glucose, and personal history of diabetes, family history of diabetes increased the risk of NASH, and any fibrosis with an adjusted-OR of 1.34 (95% CI, 0.99–1.81; *P*=0.06, not statistically significant) and 1.38 (95% CI, 1.02–1.87; ***P*=0.04**), respectively (Table 2), advanced fibrosis was not statistically significant.

Association between personal history of diabetes and liver histology

Personal history of diabetes was a more robust predictor of NASH, any fibrosis and advanced fibrosis in all models than family history of diabetes as shown in Table 2. When the models were adjusted for age, sex, BMI, ethnicity, metabolic traits and family history of diabetes, the association between personal history of diabetes with NASH, any fibrosis and advanced fibrosis showed an increased adjusted-OR of 1.76 (95% CI, 1.13–2.72, p-value <0.001), 2.57 (95% CI, 1.61 – 4.11; p-value < 0.0001) and 2.39 (95% CI, 1.68 – 3.14; p-value <0.0001), respectively.

Association between family history of diabetes and liver histology after excluding patients with personal history of diabetes

As shown in Table 1. personal history of diabetes in present only in 29.7% of the cohort and family history of diabetes is present in 55.7% of the patients in this cohort. Furthermore, family history of diabetes is not concordant with personal history of diabetes as diabetes

increases with age and aging has little effect in adults with a family history of DM. Thus, family history of diabetes can be used to risk stratify patients who either do not have diabetes or have not yet developed diabetes. Therefore, we performed sensitivity analyses after excluding patients with diabetes to further examine if family history of diabetes increases the risk of NASH or fibrosis in patients with NAFLD. This analysis would assess if presence of family history of diabetes could be utilized in predicting patients at increased risk of advanced NAFLD either before they develop diabetes or independent of their risk of developing diabetes or without the knowledge of whether the patient has diabetes. Using logistic regression models adjusted for age, sex, BMI, ethnicity, and metabolic traits in this subset of patients with NAFLD after excluding individuals with diabetes, we found that family history of diabetes increased the risk of NASH, and any fibrosis with an adjusted-OR of 1.51 (95% CI, 1.01–2.25; P **=0.04**), and 1.49 (95% CI, 1.10–2.20; P **=0.04**), respectively and thus, the results remained consistent.

Interaction between family history and personal history of diabetes

As the association between family history and presence of diabetes is known, we further explored a potential effect modification between family history of diabetes and personal history of diabetes in predicting NASH and fibrosis in Table 3. The *Wald* test did not reveal an interaction between family history and personal history of diabetes in predicting NASH (P = 0.24), any fibrosis (P = 0.58) and advanced fibrosis (P = 0.13).

Joint effects of family and personal history of diabetes

We conducted further analyses to examine the joint effects of presence of diabetes and family history of diabetes on the risk of NASH and fibrosis in patients with NAFLD. The referent group in this analysis was patients with NAFLD with no diabetes and family history of diabetes (Table 3). We found that presence of diabetes increased the risk of NASH, any fibrosis, and advanced fibrosis with an age-sex-BMI-adjusted OR of 2.48 (95% CI, 1.31–4.72, P **=0.01**), 2.94 (95% CI, 1.49–5.81; P **<0.01**) and 6.03 (95% CI, 3.16–11.52, P **<0.0001**), respectively. Consistent with results presented in Table 1, family history of diabetes increased the risk of NASH, any fibrosis, and advanced fibrosis with an adjusted OR of 1.42 (95% CI, 1.02–1.98, P **= 0.04**), 1.40 (95% CI, 1.02–1.94, P **= 0.04**) and 1.24 (95% CI, 0.84–1.82; P **= 0.28**), respectively.

As would be expected, the presence of both diabetes and family history of diabetes increased the risk of NASH, any fibrosis, and advanced fibrosis with an age-sex-BMI-adjusted OR of 2.13 (95% CI, 1.38–3.30, P **<0.001**), 3.43 (95% CI, 2.11–5.56; P **<0.0001**) and 4.76 (95% CI, 2.96–7.64, P **<0.0001**), respectively.

Sensitivity analyses—Association between prediabetes, diabetes, and family history of diabetes: We conducted sensitivity analyses to examine whether the association between family history of diabetes with NASH and any fibrosis was mediated via prediabetes as shown in Table 4. We confirmed that the results remained consistent even after adjusting for prediabetes. Furthermore, prediabetes was not an independent risk factor for worse liver histology in NAFLD.

DISCUSSION

Main findings

The principal findings of this study include that family history of diabetes is associated with presence of NASH and fibrosis in patients with NAFLD. Presence of family history of diabetes may have clinical implications in risk stratification among patients with NAFLD who do not have personal history of diabetes or have not yet developed diabetes. We also

confirmed prior studies by demonstrating robust association between diabetes and presence of NASH, any fibrosis and advanced fibrosis. Furthermore, our results suggest that there was no statistically significant effect modification between diabetes and family history of diabetes in increasing the risk of NASH suggesting that both factors may be increasing the risk of more severe histology among patients with NAFLD via mechanisms that may not be identical and perhaps complementary to each other. Therefore, we propose that family history of diabetes may be utilized in risk stratification of patients with NAFLD (especially among non-diabetics) based upon our results that family history of diabetes is a contributing factor of NASH and fibrosis in patients without diabetes (please see table 3).

Strengths and Limitations

Strengths of the study include the prospective nature of the NASH CRN cohort, and detailed description and blinded analyses of the liver histology by an expert committee of pathologists. As the NASH CRN cohort is a multi-ethnic as well as multi-center study including eight sites across United States, we believe that the results are generalizable to other patients with NAFLD residing in the United States. Finally, the family history data were collected with the help of standardized questionnaire in all the patients enrolled in the NASH CRN cohort using a standard protocol at the baseline visit. However, we acknowledge following limitations of the study: The NASH CRN cohort does not include normal individuals; therefore, these findings may not be generalizable to the general population. However, lack of normal controls, and using non-NASH (milder form of NAFLD) patients as the referent group instead of normal controls would bias the results towards null. Therefore, we believe that the true association at the level of the population may even be stronger. Lastly, family history was based upon self-report as is commonly obtained in cohort studies of single generation.

Interpretation and External Validity

Previous studies have shown that familial factors such as obesity and insulin resistance are associated with suspected NAFLD and/or NASH (7, 11, 23). Willner et al. conducted a retrospective study including 90 patients with biopsy-proven NASH and showed that 9 families had familial clustering of NASH (10). Furthermore, they also observed that obesity, diabetes and insulin resistance were commonly seen in these 9 families (10). Abdelmalek and colleagues conducted a familial aggregation case-control study comparing 20 patients with NAFLD versus 20 controls and showed that insulin resistance and diabetes were more commonly seen in the first-degree relatives of the patients with NAFLD (11). However, these seminal studies provided important insight into the familial associations in NAFLD but were limited by small-sample size, and were single center studies. Previous studies from the NASH CRN cohort and other independent cohorts have consistently shown that diabetes is associated with NASH and advanced fibrosis among patients with NAFLD (4–6, 24). Presence of diabetes has long term prognostic significance in patients with liver disease as it is an independent predictor of cirrhosis and hepatocellular carcinoma (25–27). Family history of diabetes is easily obtainable during a routine clinic visit and can help identify NAFLD patients who may be at increased risk of having NAFLD fibrosis and NASH. As there are no reliable non-invasive biomarkers that can differentiate between NAFLD alone versus NASH, clinical predictors are commonly utilized by clinicians to identify which NAFLD patients should undergo a liver a biopsy (6). Family history of diabetes may be considered one such risk factor in patients with NAFLD. Familial risk factors suggest either a shared genetic and/or environment susceptibility towards NASH. Therefore, it is plausible that common genetic pathways linking insulin resistance and NAFLD may be responsible for fibrosis progression in NAFLD to cirrhosis and perhaps, HCC.

Potential utility and implications of the findings

Since incidence of diabetes is related to increasing age, family history of diabetes could be utilized as a risk factor for NASH or NAFLD fibrosis in patients with NAFLD who are either younger or have not yet developed diabetes. In this NASH CRN cohort with an average age of 50 years, 56% (N= 596) had family history of diabetes but the prevalence of diabetes among those with family history of diabetes was only 38% (please see table 1). Therefore, family history of diabetes without personal history of diabetes was applicable to 62% (N= 367) of individuals. This suggests the potential clinical utility of this observation and at risk population that can be identified by taking family history of diabetes among patients with NAFLD who may be at a higher risk of having NASH or fibrosis on a liver biopsy.

Further studies are needed to develop clinical prediction rules that increase the pre-test probability of finding NASH or fibrosis among patients with NAFLD both in the primary care as well as sub specialty settings.

CONCLUSIONS

Using a large, prospective, clinically and histologically well-charaterized cohort of patients with biopsy-proven NAFLD, we showed that personal history of diabetes and family history of diabetes is associated with presence of NASH and fibrosis among patients with NAFLD. Familial risk factors can help unravel shared genetic and environmental mechanisms underlying to the development of NASH, progression to advanced fibrosis and HCC. Further studies are needed to better understand these mechanistic pathways.

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Abbreviations

NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis

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Table 1

Characteristics of Patients with Nonalcoholic Fatty Liver Disease at Enrollment by Family History of Diabetes Status *

	Family History of Diabetes			
	Yes (N=596)	**No (N=473)**	**Total (N=1069)**	**P†**
Age at enrollment (years)	50.4 ± 11.6	48.6 ± 12.0	49.6 ± 11.8	**0.02**
BMI (kg/m^2)	34.5 ± 6.1	33.9 ± 6.6	34.2 ± 6.4	**0.03**
Gender				**<0.0001**
Male	188 (31.5%)	207 (43.8%)	395 (36.9%)	
Female	408 (68.5%)	266 (56.2%)	674 (63.1%)	
Ethnicity				0.12
Hispanic	73 (12.3%)	44 (9.3%)	117 (10.9%)	
Non-Hispanic	523 (87.7%)	429 (90.7%)	952 (89.1%)	
Race				**0.02**
Whites	498 (86.8%)	419 (91.5%)	917 (88.9%)	
Non-Whites	76 (13.2%)	39 (8.5%)	115 (11.1%)	
Diabetes status‡				**<0.0001**
Diabetes	229 (39.3%)	89 (19.2%)	318 (30.4%)	
Pre-diabetes	188 (32.3%)	183 (39.4%)	371 (35.4%)	
Normoglycemia	166 (28.5%)	192 (41.4%)	358 (34.2%)	
Steatohepatitis				**0.03**
Definite	354 (59.4%)	252 (53.4%)	606 (56.7%)	
Borderline	124 (20.8%)	94 (19.9%)	218 (20.4%)	
None	118 (19.8%)	126 (26.7%)	244 (22.9%)	
Any fibrosis				**<0.001**
Any	472 (79.9%)	330 (70.5%)	802 (75.7%)	
None	119 (20.1%)	138 (29.5%)	257 (24.3%)	
Advanced fibrosis				**<0.01**
Advanced	194 (50.9%)	137 (39.7%)	331 (45.6%)	
Mild/None	187 (49.1%)	208 (60.3%)	395 (54.4%)	
Cirrhosis				0.45
Yes	50 (8.4%)	46 (9.7%)	96 (9.0%)	
No	546 (91.6%)	427 (90.3%)	973 (91.0%)	
PNPLA3, SNP rs738409				0.91
GG	123 (27.3%)	101 (27.7%)	224 (27.5%)	
CC/GC	327 (72.7%)	264 (72.3%)	591 (72.5%)	

*Values are N (%) or means ± SD

†*P* values derived from chi-square for categorical variables and from Wilcoxon Rank Sum test for age at enrollment and BMI

‡Patients were categorized as diabetic based on patient/physician report of diagnosis on the baseline medical history; pre-diabetes was defined as fasting glucose between 100–125 mg/dL or hemoglobin A1c between 5.7–6.4%; normoglycemia was defined as fasting glucose<100 mg/dL and hemoglobin A1c less than 5.7%. Patients with discordant results (e.g., glucose<100 mg/dL and hemoglobin A1c>6.4% or patients without diagnosis of diabetes but with laboratory values in the diabetic range) were set to missing (N=22).

Significant p-values are shown in bold in all tables

Table 2

Association of Family and Personal History of Diabetes with NASH, Fibrosis, and Advanced Fibrosis

Simple Logistic Regression Analyses			
	NASH (N=824/1068)	**Any Fibrosis* (N=802/1059)**	**Advanced Fibrosis* (N=331/1059)**
Family history of diabetes			
Odds ratio	1.48	1.66	1.18
95% CI	1.11 – 1.97	1.25 – 2.20	0.91 – 1.54
P	**0.01**	**<0.001**	0.22
Personal history of diabetes			
Odds ratio	1.93	3.31	3.02
95% CI	1.37 – 2.73	2.26 – 4.85	2.29 – 3.98
P	**<0.001**	**<0.0001**	**<0.0001**
Multiple Logistic Regression Analysis†			
	NASH (N=809/1048)	Fibrosis (N=787/1039)	Advanced Fibrosis (N=324/1039)
Family history of diabetes			
Odds ratio	1.34	1.38	0.92
95% CI	0.99 – 1.81	1.02 – 1.87	0.69 – 1.24
P	0.06	**0.04**	0.60
Personal history of diabetes			
Odds ratio	1.76	2.57	2.39
95% CI	1.13 – 2.72	1.61 – 4.11	1.68 – 3.14
P	**0.01**	**<0.0001**	**<0.0001**

*N is lower for models with any fibrosis and advanced fibrosis as outcomes because the Masson's trichrome stain was not available for some patients.

†Three multiple logistic regression models were run for each of the following outcomes: NASH (definite/borderline vs. none), Any Fibrosis (grades 1–4 vs. grade 0), and Advanced Fibrosis (grades 3–4 vs. grades 0–2). All models included both family history of diabetes and personal history of diabetes as covariates, and the following covariates for adjustment: age at enrollment (years), gender (female vs. male), body mass index (kg/m^2), ethnicity (Hispanic vs. non-Hispanic), waist circumference (cm), triglyceride level (mg/dL), HDL level (mg/dL), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and blood glucose level (mg/dL).

Table 3

Individual and Joint Effects of Personal History of Diabetes and Family History of Diabetes on Histological Traits and Interaction Between Personal and Family History of Diabetes

Diabetes Status*	N†	OR (95% CI) §	P§‡
NASH			
No PH or FH diabetes	270	1.00 (--)	--
PH Diabetes and no FH diabetes	76	2.48 (1.31–4.72)	**0.01**
FH diabetes and no PH diabetes	285	1.42 (1.02–1.98)	**0.04**
PH and FH diabetes	193	2.13 (1.38–3.30)	**<0.001**
Interaction between PH and FH diabetes	--	--	0.24
Any fibrosis			
No PH or FH diabetes	252	1.00 (--)	--
PH Diabetes (yes vs. no)	78	2.94 (1.49–5.81)	**<0.01**
FH diabetes (yes vs. no)	269	1.40 (1.02–1.94)	**0.04**
PH and FH diabetes (yes vs. no)	203	3.43 (2.11–5.56)	**<0.0001**
Interaction between PH and FH diabetes	--	--	0.58
Advanced fibrosis			
No PH or FH diabetes	85	1.00 (--)	--
PH Diabetes (yes vs. no)	52	6.03 (3.16–11.52)	**<0.0001**
FH diabetes (yes vs. no)	92	1.24 (0.84–1.82)	0.28
PH and FH diabetes (yes vs. no)	102	4.76 (2.96–7.64)	**<0.0001**
Interaction between PH and FH diabetes	--	--	0.13

*PH diabetes – Personal history of diabetes; FH diabetes – Family history of diabetes

†N gives the number of patients with the outcome and the diabetes status.

§Odds ratios and P-values corresponding to PH diabetes, FH diabetes, and PH and FH diabetes are obtained from three separate logistic regression models adjusted for age at enrollment, gender and BMI for each outcome. The control group for each model was individuals with no personal history or family history of diabetes.

‡P-values corresponding to interaction between PH and FH diabetes are obtained using *Wald* test.

Table 4

Association Between Prediabetes, Diabetes, and Family History of Diabetes with NASH, Fibrosis, and Advanced Fibrosis

Simple Logistic Regression Analyses			
	NASH (N=805/1046)	**Any Fibrosis* (N=782/1037)**	**Advanced Fibrosis* (N=323/1037)**
Family history of diabetes			
Odds ratio	1.48	1.66	1.18
95% CI	1.11 – 1.97	1.25 – 2.20	0.91 – 1.54
P	**0.01**	**<0.001**	0.22
Personal history of diabetes			
Diabetes vs. normoglycemic			
Odds ratio	1.96	3.77	3.33
95% CI	1.34 – 2.88	2.50 – 5.70	2.39 – 4.65
P	**<0.001**	**<0.0001**	**<0.0001**
Pre-diabetes vs. normoglycemic			
Odds ratio	1.00	1.22	1.16
95% CI	0.72 – 1.39	0.89 – 1.68	0.82 – 1.64
P	0.98	0.22	0.39
Multiple Logistic Regression Analysis†			
	NASH (N=790/1026)	Fibrosis (N=767/1017)	Advanced Fibrosis (N=316/1017)
Family history of diabetes			
Odds ratio	1.35	1.41	0.95
95% CI	0.99 – 1.83	1.04 – 1.91	0.70 – 1.28
P	0.06	**0.03**	0.73
Personal history of diabetes			
Diabetes vs. normoglycemic			
Odds ratio	1.83	2.78	2.33
95% CI	1.09 – 3.05	1.60 – 4.81	1.51 – 3.59
P	**0.02**	**<0.001**	**0.0001**
Pre-diabetes vs. normoglycemic			
Odds ratio	1.00	1.00	0.93
95% CI	0.70 – 1.43	0.71 – 1.43	0.64 – 1.36
P	0.99	0.99	0.72

*N is lower for models with any fibrosis and advanced fibrosis as outcomes because the Masson's trichrome stain was not available for some patients.

†Three multiple logistic regression models were run for each of the following outcomes: NASH (definite/borderline vs. none), Any Fibrosis (stages 1–4 vs. stage 0), and Advanced Fibrosis (grades 3–4 vs. grades 0–2). All models included both family history of diabetes and personal history of diabetes (2 indicator variables for diabetic and pre-diabetic; normoglycemic is the reference group) as covariates, and the following covariates for adjustment: age at enrollment (years), gender (female vs. male), body mass index (kg/m^2), ethnicity (Hispanic vs. non-Hispanic), waist circumference (cm), triglyceride level (mg/dL), HDL level (mg/dL), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and blood glucose level (mg/dL).