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Elevated liver enzymes in individuals with undiagnosed diabetes in the U.S.

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Abstract

Objective—We investigated the association of diabetes diagnosis and medication type with liver injury in individuals with clinical diabetes.

Methods—We analyzed 2,426 patients with clinical diabetes in the National Health and Nutrition Examination Survey conducted from 1999 to 2008. Elevated alanine transaminase (ALT) and aspartate transaminase (AST) levels were used as markers of liver injury. Participants were categorized into one of three categories: 1) clinical diabetes without physician's diagnosis or diabetes medication; 2) diagnosed diabetes without diabetes medication; or 3) diagnosed diabetes with diabetes medication, further divided by classes of diabetes medications prescribed. We conducted logistic regression analysis to examine the relationship between diabetes diagnosis and medication type and elevated ALT and AST, adjusting for race/ethnicity, education, health insurance status, BMI category, alcohol consumption, physical activity, antihyperlipidemic agents, glycohemoglobin, C-reactive protein, viral hepatitis and liver disease.

Results—Participants with undiagnosed diabetes were more likely to have elevated ALT and AST levels (OR = 1.82, 95% CI 1.47, 2.42; OR = 1.99, 95% CI 1.46, 2.71, respectively). In contrast, there was no association between specific diabetes medication (i.e., sulfonylureas, biguanides/thiazolidinediones) and elevated ALT or AST levels among the treated. Our findings were confirmed in sensitivity analyses employing a lower threshold for ALT, and excluding individuals with viral hepatitis or liver disease.

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Author contributions

CYJ was responsible for conception of the study, the analysis, and the first draft of the manuscript. CYJ, CKR, CMC, ZFZ contributed to interpretation of the results and critical revision of the manuscript.

Conclusion—We found that undiagnosed diabetes is associated with liver injury, compared to diagnosed diabetes with treatment. The effect of diabetes treatment on liver injury in individuals with diabetes remains uncertain.

Keywords

diabetes mellitus; alanine transaminase; aspartate transaminase; liver injury; biguanides

Introduction

Chronic liver disease and cirrhosis are leading causes of death due to digestive diseases in the U.S. (1) and entails considerable direct and indirect costs to patients and their family (1, 2). A common cause of chronic liver disease is non-alcoholic fatty liver disease (NAFLD), which is associated with higher risk of mortality, especially in the presence of cirrhosis and impaired glucose control (3). Risk factors for NAFLD include diabetes, obesity and hyperlipidemia (4). In individuals without diabetes, NAFLD and higher levels of alanine transaminase and gamma-glutamyl transpeptidase, were found to predict incident diabetes and insulin resistance (5–9). Based on the association, it has been proposed that liver enzymes and NAFLD may serve as useful biomarkers for diabetes (10).

Although no pharmacological agent has been approved specifically for treatment of NAFLD, some insulin-sensitizing agents for diabetic or pre-diabetic conditions show beneficial effects. For example, in the Diabetes Prevention Program, metformin treatment was found to lower alanine transaminase (ALT) levels, an indicator of hepatobiliary injury (11). Furthermore thiazolidinediones, another class of insulin sensitizing agent, was found to be associated with decreased hepatic steatosis and lower ALT levels (12). In addition, sustained reduction of ALT, independent of insulin resistance, was achieved in a trial of metformin and thiazolidinediones therapy (13). While the mechanism of the impact of insulin sensitizing agents is still unclear, it was hypothesized that part of the effect is mediated by weight loss, as demonstrated in the Diabetes Prevention Program (11). This is plausible, given that increased adiposity is associated with higher ALT levels (14, 15).

In light of the potential benefit of diabetes management on prevention of liver injury, we investigated the association between diabetes diagnosis status and liver injury, as measured by ALT and aspartate transaminase (AST), and how liver injury varies by type of diabetes medication in a representative sample of the U.S. population with clinical diabetes. We also conducted sub-group analyses to examine if the associations of diabetes diagnosis and medication and liver injury varied by overweight/obese status.

Methods

Study population

The National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC) has been conducting an ongoing series of cross-sectional surveys known as the National Health and Nutrition Examination Survey (NHANES) (16) to assess the health and nutritional status of adults and children in the United States. Recruited participants are interviewed and physically examined, and blood samples are collected for laboratory tests. For this study, we analyzed a sub-sample of the population surveyed between 1999 and 2008, who were 20 years of age or older and who met the clinical definition of diabetes at the time of the interview.

Diabetes

Following current guidelines set forth by the American Diabetes Association, diabetes was defined as a fasting blood glucose of ≥ 126 mg/dL, blood glucose level of ≥ 200 mg/dL by oral glucose tolerance testing, or a hemoglobin A1c (HbA1c) level of $\geq 6.5\%$ (17). Because oral glucose tolerance test was not available for the years 1999–2003, we defined diabetes based on fasting blood glucose and HbA1c for these years. Plasma glucose levels were determined by the hexokinase enzymatic method at the Diabetes Diagnostic Laboratory at the University of Missouri-Columbia. HbA1c was measured also at the Diabetes Diagnostic Laboratory at the University of Missouri-Columbia using Primus CLC330 and Primus CLC 385 (Primus Corporation, Kansas City, MO) for years 1999–2004, Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer for years 2005–2006 and Tosoh A1c G7 HPLC Glycohemoglobin Analyzer for years 2007–2008 (Tosoh Medics, San Francisco, CA). The administration of diabetes medication was determined through an in-home interview, which included an inventory of the participants' medicine cabinet. Those with clinical diabetes were categorized into one of the following groups: 1) clinical diabetes without physician's diagnosis of diabetes or diabetes medication, 2) diagnosed diabetes without diabetes medication, or 3) diagnosed diabetes treated with diabetes medication. Individuals with clinical diabetes who did not report physician's diagnosis of diabetes but reported use of diabetes drugs were considered to have diagnosed diabetes. Participants treated for diabetes were further grouped by class of diabetes medications: 1) sulfonylureas only, 2) biguanides or thiazolidinediones only, 3) any combination of sulfonylureas, biguanides, thiazolidinediones, 4) other diabetes medications (e.g. alpha-glucosidase inhibitors) and 5) insulin.

Liver function enzymes

We considered two indicators of liver injury in the NHANES data: ALT and AST. From 2003 to 2008, both indicators were measured using a Beckman Synchron LX20 and Beckman UniCel Dx C800 Synchron (Beckman Coulter, Brea, CA). For samples collected in 1999–2002 the Hitachi Model 704 multichannel analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN) was used. Following the NHANES III Laboratory Procedure, we defined elevated ALT levels as >40 U/L for males and >31 U/L for females, and elevated AST levels as >37 U/L for males and >31 U/L for females (18).

Covariates

We considered the following as potential confounders: age, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic and other race), education level (11th grade or less, high school, some college or above), current health insurance status, HbA1c level, body mass index (BMI), C-reactive protein, hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, alcohol intake (<12 drinks/year, 12 drinks/yr to 1 drink/day, >1 drink/day), physical activity for leisure or for commute, use of anti-hyperlipidemic agents, and self-report of physician-diagnosed liver disease. C-reactive protein was measured by latex-enhanced nephelometry. Infection with HBV was defined as testing positive for antibody to HBV surface antigen by the AUSZYME Monoclonal Test (Abbott Diagnostics, Lake Forest, IL) and infection with HCV was defined as testing positive to HCV RNA by COBAS Amplicor HCV Monitor Test (Roche, Pleasanton, CA).

Statistical Analyses

Differences in the distribution of categorical covariates among diabetes diagnosis and treatment groups (diagnosed with medication, diagnosed without medication, undiagnosed) were assessed using chi-square tests, and pairwise differences in distributions of continuous covariates were assessed using the Wilcoxon rank-sum test. Differences in ALT and AST

distribution by diabetes medication type were examined using Kruskal Wallis analysis of variance. The bivariate associations of diabetes diagnosis and medication category and other variables with the outcomes elevated ALT and elevated AST status were assessed using logistic regression unadjusted for other variables. To assess for confounder-independent association between diabetes diagnosis and medication category and liver injury, we conducted multivariate logistic regression adjusting for all potential confounders listed above. We performed two sets of logistic regression analyses, comparing diagnosed diabetes without medication and undiagnosed diabetes to diagnosed diabetes with medication as the referent group, and separately comparing diabetes treated with non-insulin diabetes drugs (i.e. sulfonylureas, insulin sensitizers) to insulin-treated diabetes as the referent group. We also conducted stratified analyses by BMI categories of $<25 \text{ kg/m}^2$, $25\text{--}30 \text{ kg/m}^2$ and 30 kg/m^2 . We performed sensitivity analyses for ALT using a threshold of $>29 \text{ U/L}$ for males and $>22 \text{ U/L}$ for females following a recent finding that these cutoffs yield maximum correct classification of individuals at high risk for liver disease (19). We also performed sensitivity analysis excluding individuals with HBV/HCV infection and those with liver disease, who are expected to have considerable liver injury. Significance of associations was interpreted at P-value of less than 0.05. All statistical analyses were conducted with SAS version 9.2 (SAS Institute, Cary, NC).

Results

A total of 51,623 individuals were interviewed for NHANES between years 1999 and 2008. Of these, 26,246 were 20 years of age or older, 2,758 had diabetes and 2,426 had complete data on liver enzymes and other variables used in analyses; the latter group constituted the analytic sample. The age and sex distribution of individuals excluded due to missing data was not different from that of individuals included in the analyses.

Among participants with glucose or glycohemoglobin levels indicative of diabetes, 818 were undiagnosed, 251 were diagnosed but were not taking any diabetes medications, and 1,357 were taking at least 1 diabetes medication. Median ALT and AST levels were higher in those with undiagnosed diabetes compared to participants with diagnosed diabetes, either with or without medication (P-values < 0.0001 , Table 1). Median ALT and AST levels were similar between people with diagnosed diabetes with and without medication. Those with undiagnosed diabetes or diabetes without medication were younger, more likely to be male, less likely to be insured, drank more alcohol and were less likely to be on anti-hyperlipidemic agents compared to those with diabetes with medication (Table 1). Among those on anti-diabetic medication, 267 (20%) were taking a sulfonylurea agent only, 305 (21%) were taking a biguanide agent or thiazolidinedione agent only, 341 (27%) were taking a combination of sulfonylurea, biguanide and/or thiazolidinedione agents, 91 (7%) were taking other diabetes drugs and 353 (26%) were on insulin. Median ALT and AST levels did not vary by diabetes treatment type (P=0.13 for ALT, p=0.73 for AST by Kruskal Wallis analysis of variance).

ALT and AST levels were elevated in 407 (17%) and 312 (13%) of the analytic sample, respectively. In bivariate analysis (Table 2), those with undiagnosed diabetes were more likely to have elevated ALT levels (OR = 1.74, 95% CI 1.39, 2.18) and AST levels (OR = 1.75, 95% CI 1.37, 2.25) compared to those who were taking diabetes medications. Proportions of elevated ALT and AST were not different in those who were treated with insulin-sensitizers (biguanide or a thiazolidinedione) compared to those treated with insulin. Younger individuals, Hispanics, those with higher alcohol intake, and those with HBV/HCV infection or liver disease were more likely to have elevated ALT levels, while insured individuals and those taking antihyperlipidemic agents were less likely to have elevated ALT levels. Associations with elevated AST levels yielded similar results; younger

individuals, those who commute by walking or biking, those with higher alcohol intake, and those with HBV/HCV infection or liver disease were more likely to have elevated AST levels, while insured individuals and those taking antihyperlipidemic agents were less likely to have elevated AST levels. Higher BMI was associated with both elevated ALT and elevated AST levels (Table 2).

When adjusted for potential confounders, the associations between undiagnosed diabetes and elevated ALT and AST levels remained significant (OR = 1.82, 95% CI 1.47, 2.42 for ALT, OR = 1.99, 95% CI 1.46, 2.71 for AST) (Table 3). Adjusting for all potential confounders considered, those treated with insulin sensitizers (biguanides and/or thiazolidinediones), sulfonylureas, or a combination of these frequently-prescribed diabetes drugs were not more or less likely to have higher levels of ALT or AST compared to insulin-treated individuals. (Table 3) Multivariate analysis was not conducted for those treated with other diabetes drugs due to small sample size. Sensitivity analysis using a lower cut-off for ALT levels confirmed our finding for undiagnosed diabetes (OR = 1.98, 95% CI 1.59, 2.46), as well as the null findings for insulin-sensitizers and sulfonylureas. A second sensitivity analysis excluding HBV or HCV infected individuals and those with liver disease also confirmed our findings for association of undiagnosed diabetes with elevated ALT levels (OR = 2.11, 95% CI 1.56, 2.84) and with elevated AST levels (OR = 2.49, 95% CI 1.78, 3.48).

When we conducted stratified analyses by BMI categories of <25, 25–29, ≥30 kg/m², corresponding to normal weight, overweight and obese, we found a similar association for elevated ALT and AST levels with undiagnosed diabetes among obese individuals (OR = 1.83, 95% CI 1.28, 2.61 for ALT, OR = 1.87, 95% CI 1.25, 2.80 for AST) (Table 4). While the associations were not statistically significant for individuals in the normal and overweight categories, there were trends towards positive associations and a test for heterogeneity of the effect by BMI level was insignificant (p=0.86 for ALT, p=0.99 for AST).

Discussion

In this study of liver injury among individuals with clinical diabetes in a nationally representative sample of U.S. population, we found that those with undiagnosed diabetes were more likely to have elevated levels of ALT and AST compared to those who were taking diabetes medication. Elevated ALT and AST levels are strong laboratory-based indications of NAFLD (4). Insulin resistance in individuals with undiagnosed diabetes could drive accumulation of lipids in hepatocytes, causing NAFLD (4), which increases vulnerability to cirrhosis and resulting mortality (3). The association may also be driven by the effect of liver injury or NAFLD on incident diabetes, which has been reported in previous observational studies (5–9). We were unable to attribute the association to the lack of medication for diabetes, as those with diagnosed diabetes without medication exhibited similar levels of ALT and AST as those treated with diabetes medication. Associations with ALT and AST levels were not attenuated after adjustment for other factors associated with liver function, including alcohol consumption, insurance status, BMI, HBV or HCV infection and liver disease, or factors related to diabetes, such as physical activity and glycohemoglobin. This suggests that variables other than these known risk factors of liver disease influence liver enzyme levels in those with undiagnosed diabetes. Possible contributors may include continuity of care that would influence detection and management of diabetes (20, 21) and related liver conditions. People with undiagnosed diabetes may have higher allostatic load, or physiological responses to environmental stress, which is linked to accumulation of fat, inflammation, and oxidative stress that can negatively impact liver health (22).

Regarding the effect of diabetes medications on liver enzyme levels, our findings stand in contrast to that of previous studies that found that treatment with biguanides or thiazolidinediones was associated with reduced ALT levels among individuals at risk for diabetes (11–13). Variability in results may arise from different methodologies or study populations. Our study was a cross-sectional study of a representative sample of people with diabetes in the U.S. while other studies were of randomized controlled design recruiting more homogenous group of participants with pre-diabetic conditions or hepatic steatosis (11–13). While our study is more vulnerable to confounding bias, it is possible that the effect on ALT is less pronounced in those who already have diabetes, while more apparent in those who are en route to developing diabetes as examined in previous trials (11, 13). As demonstrated in this study, those with undiagnosed diabetes appeared particularly at risk for elevated levels of ALT compared to those who were already diagnosed, despite lower levels of glycohemoglobin in the undiagnosed. The discordant results may also be due to differences in the referent groups. The referent group in our study sample of people with diabetes consisted of insulin treated individuals and diabetic regimen was not randomly assigned. Previous studies on insulin sensitizers and hepatic injury were conducted in people without diabetes and comparison groups were randomly assigned to either no treatment or placebo (11, 13). Thus, the non-random distribution of diabetic regimens may have introduced unmeasured confounding in our study. However, randomized placebo-controlled trials are not feasible in people with diabetes, who are recommended to take oral medications or insulin by consensus guidelines. Given that insulin resistance is correlated with higher ALT levels (23), we expected that people who took insulin-sensitizers would show more favorable ALT levels compared to those who took insulin or sulfonylureas that increase systemic levels of insulin. However, there was no clear difference in liver enzyme levels across all classifications of diabetes drugs. It is possible that the effect of the hypoglycemic agents were diluted due to non-adherence to treatment regimen.

Taking the findings from our study and together with those from other studies demonstrating higher levels of ALT in undiagnosed diabetes compared to those with impaired fasting glucose or normoglycemic individuals (15, 24), we conclude that in the continuum of progression from no diabetes to insulin-dependent diabetes, vulnerability to liver injury is highest in those with undiagnosed diabetes.

Our study was limited in that it employed cross-sectional data, and therefore could not examine the longitudinal effect of diabetes diagnosis and treatment on liver injury. Prospective studies with repeated measures of liver function enzymes would be particularly informative considering that effects of diabetes treatment take time to manifest and that liver enzymes are subject to temporal variation, especially in the presence of co-morbid conditions that require hemodialysis (25). In addition, the number of people taking each type of anti-diabetic medication may not have been large enough to detect nuanced differences in prevalence of elevated liver enzyme levels. There was also sparse data on specific liver disease conditions, such as non-alcoholic steatohepatitis or fatty liver disease that would better serve as definitive markers of liver injury. The study lacked detailed data on healthcare utilization and environmental stress that could have been correlated with diabetes diagnosis status and linked to liver health and may have thus confounded the relationship between undiagnosed diabetes and liver injury. It is also possible that those with diagnosed diabetes could have received better clinical follow-up with treatment for reversible causes that has positive effects on the liver. Finally, part of the NHANES data (1999–2003) lacked information on oral glucose tolerance testing, through which we may have missed those with true diabetes, but did not meet the definition of diabetes by fasting blood glucose or hemoglobin A1c. This decreased our sample size of people with diabetes, limiting the power of the study.

Despite the limitations, our study has a number of strengths. We employed a dataset representative of non-institutionalized people residing in the U.S. and thus our findings are generalizable to the US adult population living with diabetes. Also, we were able to consider multiple potential confounders relevant to liver health, including alcohol consumption and hepatitis B and C infection. Furthermore, systematic data on fasting blood glucose and glycohemoglobin permitted us to identify those who had undiagnosed diabetes.

In sum, we found that undiagnosed diabetes is associated with liver injury, as indicated by elevated levels of ALT and AST, compared to diagnosed diabetes with medication. Treatment with insulin-sensitizers was not associated with better liver enzyme levels compared to insulin treatment. Our findings suggest that early detection and treatment of diabetes might improve liver health, while further studies are needed to compare the effects of different diabetes medications on liver injury.

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Table 1

Sample characteristics of individuals with clinical diabetes mellitus by diabetes diagnosis and treatment status, NHANES 1999–2008

Variable	Treated DM	Diagnosed DM not treated	P-value (vs. treated)	Undiagnosed DM	P-value (vs. undiagnosed DM)	P-value (vs. treated DM)
Total N	1357	251		818		
Liver enzyme levels						
Alanine transaminase (U/L)	21 (17, 28)	22 (17, 29)	0.45	25 (19, 36)	<0.0001	<0.0001
Aspartate transaminase (U/L)	22 (18, 27)	22 (18, 28)	0.95	24 (20, 31)	<0.0001	<0.0001
Age group (yrs)			0.15		0.42	0.003
20–39	73 (5.4%)	17 (6.8%)		72 (8.8%)		
40–59	392 (29%)	85 (34%)		249 (30%)		
60+	892 (66%)	149 (59%)		497 (61%)		
Male sex	670 (49%)	138 (55%)	0.10	468 (57%)	0.53	0.0004
Race / ethnicity			0.62		0.008	0.0002
Non-Hispanic Black	371 (27%)	67 (27%)		170 (21%)		
Hispanic	436 (32%)	89 (35%)		234 (30%)		
Other	39 (2.9%)	9 (2.6%)		25 (3.1%)		
Non-Hispanic White	511 (38%)	86 (34%)		380 (46%)		
Years of school completed			0.08		0.003	0.09
11 th grade or less	617 (45%)	132 (53%)		335 (41%)		
High school / GED	299 (22%)	43 (17%)		205 (25%)		
Some college or above	441 (33%)	76 (30%)		278 (34%)		
Current health insurance	1207 (89%)	196 (78%)	<0.0001	554 (81%)	0.26	<0.0001
Body mass index			0.003		0.02	0.79
<25.0 kg/m ²	188 (14%)	52 (21%)		117 (14%)		
25.0–29.9 kg/m ²	427 (31%)	87 (35%)		266 (33%)		
30.0 kg/m ²	742 (55%)	112 (45%)		435 (53%)		
Alcohol intake			0.03		0.02	<0.0001

Variable	Treated DM	Diagnosed DM not treated	P-value (vs. treated)	Undiagnosed DM	P-value (vs. untreated diagnosed DM)	P-value (vs. treated DM)
	N (%) or median (IQR)	N (%) or median (IQR)		N (%) or median (IQR)		
0 – 12 drinks in the past year	577 (43%)	90 (36%)		237 (29%)		
>12 drinks/year to 1 drink/day	478 (35%)	94 (37%)		294 (36%)		
2–4 drinks/day	231 (17%)	43 (17%)		215 (26%)		
> 4 drinks / day	71 (5.2%)	24 (9.6%)		72 (8.8%)		
Leisure activity in the past 30 days			0.11		0.39	0.47
None	809 (60%)	154 (61%)		502 (61%)		
Moderate	391 (29%)	59 (24%)		216 (26%)		
Vigorous	157 (12%)	38 (15%)		100 (12%)		
Commute by walking or biking			0.88		0.37	0.08
238 (18%)	45 (18%)			168 (21%)		
Use of antihyperlipidemic agents			<0.0001		0.79	<0.0001
628 (46%)	61 (24%)			192 (23%)		
Glycohemoglobin (%)			0.005		<0.0001	<0.0001
7.5 (6.9, 8.7)	7.4 (6.7, 9.2)			6.5 (5.9, 7.1)		
<7.0%	380 (28%)	87 (35%)		464 (70%)		
7–8.9%	679 (50%)	98 (39%)		155 (19%)		
9.0%	295 (22%)	66 (26%)		76 (11%)		
C-reactive protein (mg/L)			0.06		0.0006	0.01
3.4 (1.5, 7.6)	3.1 (1.3, 8.4)			4.1 (1.8, 8.4)		
HBV or HCV infection			0.45		0.90	0.31
32 (2.4%)	4 (1.6%)			14 (1.7%)		
Liver disease			0.90		0.90	1.00
73 (5.4%)	13 (5.2%)			44 (5.4%)		

DM = diabetes mellitus; IQR = interquartile range; HBV = hepatitis B virus, HCV = hepatitis C virus

P-values obtained by chi-square tests (categorical variables) or Wilcoxon rank-sum test (continuous variables).

Table 2

Bivariate logistic regression results for the outcomes ALT elevation and AST elevation among individuals with clinical diabetes, NHANES 1999–2008

Explanatory variable	Elevated ALT (N=407) n (%) or median (IQR)	Not elevated ALT (N=2019) n (%) or median (IQR)	Unadjusted OR for elevated ALT (95% CI)	p-value	Elevated AST (N=312) n (%) or median (IQR)	Not elevated AST (N=2114) n (%) or median (IQR)	Unadjusted OR for elevated AST (95% CI)	p-value
Analysis of all individuals (N = 2,426)								
Diabetes category								
Undiagnosed diabetes	181 (44%)	637 (32%)	1.74 (1.39, 2.18)	<0.0001	143 (46%)	675 (32%)	1.75 (1.37, 2.25)	<0.0001
Diagnosed untreated diabetes	37 (9.1%)	214 (11%)	1.07 (0.73, 1.56)	0.74	24 (7.7%)	227 (11%)	0.88 (0.56, 1.39)	0.59
Treated diabetes	189 (46%)	1168 (58%)	Ref		145 (46%)	1212 (57%)	Ref	
Age group (yrs)								
20–39	50 (12%)	112 (5.6%)	3.56 (2.46, 5.15)	<0.0001	36 (12%)	126 (6.0%)	2.51 (1.67, 3.76)	<0.0001
40–59	185 (45%)	541 (27%)	2.73 (2.16, 3.43)	<0.0001	118 (38%)	608 (29%)	1.70 (1.32, 2.20)	<0.0001
60+	172 (42%)	1366 (68%)	Ref		158 (51%)	1380 (65%)	Ref	
Sex								
Male	216 (53%)	1060 (53%)	1.02 (0.82, 1.26)	0.83	148 (47%)	1128 (53%)	0.78 (0.62, 0.99)	0.044
Female	20191 (47%)	959 (48%)	Ref		164 (53%)	986 (47%)	Ref	
Race / ethnicity								
Non-Hispanic Black	61 (15%)	547 (27%)	0.55 (0.40, 0.75)	0.0002	53 (17%)	555 (26%)	0.63 (0.45, 0.89)	0.007
Hispanic	167 (41%)	601 (30%)	1.38 (1.08, 1.75)	0.009	120 (38%)	648 (31%)	1.23 (0.94, 1.61)	0.13
Other	15 (3.7%)	58 (2.9%)	1.28 (0.71, 2.32)	0.41	11 (3.5%)	62 (2.9%)	1.18 (0.60, 2.29)	0.63
Non-Hispanic White	164 (40%)	813 (40%)	Ref		128 (41%)	849 (40%)	Ref	
Years of school completed								
11 th grade or less	911 (45%)	173 (43%)	0.89 (0.70, 1.14)	0.37	141 (45%)	943 (45%)	1.11 (0.84, 1.47)	0.47
High school / GED	452 (22%)	95 (23%)	0.99 (0.75, 1.33)	0.97	77 (25%)	470 (22%)	1.22 (0.89, 1.69)	0.22
Some college or above	2656 (32%)	139 (34%)	Ref		94 (30%)	701 (33%)	Ref	
Covered by health insurance at the time of survey								
Insured	306 (75%)	1762 (87%)	0.44 (0.34, 0.57)	<0.0001	241 (77%)	1827 (86%)	0.53 (0.40, 0.71)	<0.0001
Uninsured	101 (25%)	257 (13%)	Ref		71 (23%)	287 (14%)	Ref	
Body mass index (kg/m²)								
<25.0 kg/m ²	32 (28, 37)	30 (27, 35)	1.04 (1.02, 1.05)	<0.0001	31 (27, 37)	30 (27, 35)	1.02 (1.00, 1.04)	0.02
25.0 – 29.9 kg/m ²	36 (8.9%)	321 (16%)	Ref		36 (12%)	321 (15%)	Ref	
30.0 – 34.9 kg/m ²	112 (28%)	668 (33%)	1.49 (1.00, 2.22)	0.05	93 (30%)	687 (33%)	1.20 (0.80, 1.81)	0.37

Explanatory variable	Elevated ALT (N=407) n (%) or median (IQR)	Not elevated ALT (N=2019) n (%) or median (IQR)	Unadjusted OR for elevated ALT (95% CI)	p-value	Elevated AST (N=312) n (%) or median (IQR)	Not elevated AST (N=2114) n (%) or median (IQR)	Unadjusted OR for elevated AST (95% CI)	p-value
>=30.0 kg/m ²	259 (64%)	1030 (51%)	2.23 (1.54, 3.23)	<0.0001	183 (59%)	1106 (52%)	1.47 (1.00, 2.14)	0.048
Alcohol intake								
0–12 drinks in the past year	129 (32%)	775 (38%)	Ref		97 (31%)	807 (38%)	Ref	
>12 drinks/year to 1 drink/day	118 (29%)	748 (37%)	0.94 (0.72, 1.23)	0.64	107 (34%)	759 (36%)	1.16 (0.87, 1.55)	0.32
2–4 drinks/day	111 (27%)	378 (19%)	1.76 (1.33, 2.34)	<0.0001	73 (23%)	416 (20%)	1.46 (1.05, 2.02)	0.02
> 4 drinks / day	49 (12%)	118 (5.8%)	2.49 (1.70, 3.65)	<0.0001	35 (11%)	132 (6.2%)	2.20 (1.43, 3.38)	0.0003
Leisure activity in the past 30 days								
None	236 (58%)	1229 (61%)	Ref		198 (63%)	1267 (60%)	Ref	
Moderate	115 (28%)	551 (27%)	1.09 (0.85, 1.39)	0.50	76 (24%)	590 (28%)	0.83 (0.62, 1.10)	0.19
Vigorous	56 (14%)	239 (12%)	1.22 (0.89, 1.69)	0.22	38 (12%)	257 (12%)	0.95 (0.65, 1.38)	0.78
Commute								
Walking or biking	87 (21%)	1655 (82%)	1.24 (0.95, 1.61)	0.11	241 (77%)	1735 (82%)	1.38 (1.04, 1.83)	0.03
Other	320 (79%)	264 (18%)	Ref		72 (23%)	379 (18%)	Ref	
Use of antihyperlipidemic agents								
Yes	114 (28%)	1252 (62%)	0.63 (0.50, 0.80)	0.0001	215 (69%)	1330 (63%)	0.76 (0.59, 0.98)	0.04
No	23 293 (72%)	767 (38%)	Ref		97 (31%)	784 (38%)	Ref	
Glycohemoglobin (%)								
<7.0%	159 (39%)	883 (44%)	Ref		128 (41%)	914 (43%)	Ref	
7–8.9%	158 (39%)	774 (38%)	1.13 (0.89, 1.44)	0.31	119 (38%)	813 (39%)	1.05 (0.80, 1.37)	0.75
>=9.0%	89 (22%)	359 (18%)	1.38 (1.03, 1.84)	0.029	64 (21%)	384 (18%)	1.19 (0.86, 1.64)	0.29
C-reactive protein (mg/L)	4.1 (1.9, 8.6)	3.5 (1.5, 7.6)	1.006 (1.000, 1.013)	0.07	4.3 (1.6, 9.2)	3.5 (1.5, 7.6)	0.992 (0.978, 1.006)	0.43
HBV or HCV infection								
Infected	28 (6.9%)	22 (1.1%)	6.71 (3.80, 11.9)	<0.0001	27 (8.7%)	23 (1.1%)	8.63 (4.88, 15.3)	<0.0001
Uninfected	384 (94%)	2002 (99%)	Ref		290 (93%)	2096 (99%)	Ref	
Liver disease								
Liver disease	63 (15%)	67 (3.3%)	5.34 (3.72, 7.68)	<0.0001	58 (19%)	72 (3.4%)	6.49 (4.49, 9.40)	<0.0001
No liver disease	344 (85%)	1952 (97%)	Ref		254 (81%)	2042 (97%)	Ref	
Analysis of individuals with treated diabetes (N = 1,357)								
Treatment groups								

Explanatory variable	Elevated ALT (N=407) n (%) or median (IQR)	Not elevated ALT (N=2019) n (%) or median (IQR)	Unadjusted OR for elevated ALT (95% CI)	p-value	Elevated AST (N=312) n (%) or median (IQR)	Not elevated AST (N=2114) n (%) or median (IQR)	Unadjusted OR for elevated AST (95% CI)	p-value
Sulfonylureas	36 (19%)	231 (20%)	0.99 (0.62, 1.58)	0.97	22 (15%)	245 (20%)	0.77 (0.44, 1.33)	0.35
Biguanide/Thiazolidinediones	40 (19%)	265 (20%)	0.96 (0.61, 1.51)	0.86	31 (21%)	273 (22%)	0.97 (0.58, 1.60)	0.89
Combination	51 (27%)	290 (25%)	1.12 (0.73, 1.71)	0.61	45 (31%)	296 (24%)	1.30 (0.82, 2.06)	0.27
Other drug	14 (7.4%)	77 (6.6%)	NE	NE	10 (6.9%)	81 (6.7%)	NE	NE
Insulin	48 (25%)	305 (26%)	Ref	Ref	37 (26%)	316 (26%)	Ref	Ref

CI = confidence interval, HBV = hepatitis B virus, HCV = hepatitis C virus, NE = not estimated due to low sample size

Table 3

Results of multivariate logistic regression analyses for the outcomes ALT elevation and AST elevation among individuals with clinical diabetes, NHANES 1999–2008

Variable	Adjusted OR for elevated AST	p-value	Adjusted OR for elevated AST	p-value
Analysis of all individuals (N = 2,426)				
Diabetes category				
Undiagnosed diabetes	1.82 (1.37, 2.42)	<0.0001	1.99 (1.46, 2.71)	0.0001
Diagnosed untreated diabetes	1.04 (0.69, 1.59)	0.84	0.89 (0.55, 1.45)	0.64
Treated diabetes	Ref		Ref	
Analysis of individuals with treated diabetes (N = 1,357)				
Diabetes medication type				
Sulfonylureas	1.12 (0.66, 1.90)	0.68	0.80 (0.43, 1.51)	0.50
Biguanide/Thiazolidinediones	1.05 (0.64, 1.73)	0.84	1.12 (0.64, 1.95)	0.69
Combination	1.08 (0.67, 1.74)	0.84	1.32 (0.79, 2.22)	0.29
Insulin	Ref		Ref	

Each analysis was adjusted for all variables listed in Table 2.

Table 4

Results of multivariate logistic regression analyses for the outcomes ALT elevation and AST elevation among individuals with clinical diabetes, NHANES 1999–2008, stratified by BMI categories

Variable	Adjusted OR for elevated ALT	p-value	Adjusted OR for elevated AST	p-value
Analysis of normal weight (n=357)				
Diabetes category				
Undiagnosed diabetes	2.40 (0.86, 6.68)	0.095	2.27 (0.81, 6.41)	0.12
Diagnosed untreated diabetes	1.33 (0.42, 4.19)	0.63	0.17 (0.02, 1.49)	0.11
Treated diabetes	Ref		Ref	
Analysis of overweight (n=780)				
Diabetes category				
Undiagnosed diabetes	1.50 (0.88, 2.55)	0.13	1.89 (1.09, 2.30)	0.02
Diagnosed untreated diabetes	1.08 (0.51, 2.27)	0.84	0.81 (0.33, 2.02)	0.66
Treated diabetes	Ref		Ref	
Analysis of obese (n=1289)				
Diabetes category				
Undiagnosed diabetes	1.83 (1.28, 2.61)	0.001	1.87 (1.25, 2.80)	0.002
Diagnosed untreated diabetes	1.01 (0.56, 1.81)	0.98	1.28 (0.67, 2.43)	0.45
Treated diabetes	Ref		Ref	

Each analysis was adjusted for all variables listed in Table 2.