ORIGINAL RESEARCH

Nonalcoholic Fatty Liver Disease Is Associated With QT Prolongation in the General Population

Chi-Sheng Hung, MD;* Ping-Huei Tseng, MD, PhD;* Chia-Hung Tu, MD, MSc; Chien-Chuan Chen, MD; Wei-Chih Liao, MD, PhD; Yi-Chia Lee, MD, PhD; Han-Mo Chiu, MD, PhD; Hung-Ju Lin, MD; Yi-Lwun Ho, MD, PhD; Wei-Shiung Yang, MD, PhD; Ming-Shiang Wu, MD, PhD;† Ming-Fong Chen, MD, PhD†

***Background*—**Nonalcoholic fatty liver disease (NAFLD) is independently associated with QT prolongation among patients with diabetes. It has not yet been determined whether this association remains valid in the general population. We designed an observational study to explore this association.

***Methods and Results*—**We conducted a cross-sectional analysis of 31 116 consecutive participants in our health management program. Heart rate–corrected QT (QTc) interval was derived from 12-lead electrocardiography and by Bazett's formula. NAFLD was diagnosed by abdominal ultrasonography and classified as *none, mild, moderate*, or *severe*, according to the ultrasonographic criteria. A multivariable linear regression model was fitted for the association between QTc interval and potential predictors (including demographic, anthropometric, biochemical factors, and comorbidities). Multivariable logistic regression analyses were fitted to assess the association between the severity of NAFLD and QTc prolongation, with the adjustment of significant predictors derived from multivariable linear regression. The mean QTc interval was 421.3 ms (SD 45.4 ms). In the multivariable linear regression analyses, mild, moderate, and severe NAFLD were associated with increases of 2.55, 6.59, and 12.13 ms, respectively, in QTc interval compared with no NAFLD (all $P<0.001$). In the multivariable logistic regression analyses, mild, moderate, and severe NAFLD were associated with an increased risk for QTc prolongation, with odds ratios of 1.11 (95% CI: 1.01 to 1.21, $P<0.05$), 1.61 (95% CI: 1.36 to 1.9, $P<0.001$), and 1.31 (95% CI: 1.16 to 2.24, $P<0.01$), respectively, in women, and 1.11 (95% CI: 1.01 to 1.21, $P<0.05$), 1.39 (95% CI: 1.22 to 1.59, $P<0.001$), and 1.87 (95% CI: 1.16 to 2.24, $P<0.001$), respectively, in men, after adjusting for predictors known to be associated with the QTc interval. The association remained significant among subgroups with or without diabetes.

***Conclusions*—**The severity of NAFLD was associated with a higher risk for QTc prolongation in the general population with and without diabetes. **(*J Am Heart Assoc*. 2015;4:e001820 doi: 10.1161/JAHA.115.001820)**

Key Words: diabetes • general population • nonalcoholic fatty liver disease • QT prolongation

Nonalcoholic fatty liver disease (NAFLD) has become the most common hepatic disorder in the Western world.[1,2] In the United States, approximately one-third of adults have NAFLD.[3] NAFLD is defined as the presence of macrovesicular steatosis occurring in >5% of hepatocytes, excluding the effects of alcohol and viral hepatitis. NAFLD is a complex metabolic disease and is frequently associated with insulin resistance, dyslipidemia, and obesity.[2] It is estimated that NAFLD will replace viral hepatitis as the leading cause of end-stage liver disease by 2020 in the United States.[4,5] Recently, NAFLD has also been associated with higher rates of cardiovascular complications, atrial fibrillation, QT prolongation, and mortality.[6,7]

The QT interval represents the duration of electrical depolarization and repolarization of the ventricle. A prolonged QT interval reflects a lengthening of this vulnerable period and increases the risk of malignant arrhythmias.[8] Extreme prolongation of the QT interval is also associated with sudden cardiac death. Moreover, the duration of the QT interval, even within a reference range, is a predictor for cardiovascular death in the general population.[9–12] The QT interval has been shown to be related to cardiac and metabolic disorders including hypertension, diabetes, obesity, and coronary artery disease.[10,13] In a recent report of 400 patients with type 2 diabetes, the presence

From the Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan (C.-S.H., P.-H.T., C.-H.T., C.-C.C., W.-C.L., Y.-C.L., H.-M.C., H.-J.L., Y.-L.H., W.-S.Y., M.-S.W., M.-F.C.); Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan (C.-S.H., P.-H.T., C.-H.T., W.-S.Y.).

*Dr Hung and Dr Tseng contributed equally to the work.

†Dr Wu and Dr Chen contributed eqaully to the work.

Correspondence to: Ming-Fong Chen, MD, PhD, Department of Internal Medicine, National Taiwan University Hospital, No 7 Chung-Shan South Road, Taipei, Taiwan. E-mail: mfchen@ntuh.gov.tw

Received January 22, 2015; accepted May 28, 2015.

of NAFLD was associated with QT prolongation after adjustment for established confounders.[14]

The association between QT prolongation and NAFLD among patients without diabetes has not been demonstrated. Because diabetes per se has been associated with QT prolongation,[13] it is not clear whether the association between QT prolongation and NAFLD remains valid among patients without diabetes. Consequently, we designed this cross-sectional study to elucidate the association between NAFLD and QT prolongation among the general population with or without diabetes.

Methods

Ethics Statement

This cross-sectional study was approved by the institutional review board at National Taiwan University Hospital to analyze the deidentified data. This study complied with the Declaration of Helsinki.

Patients

We recruited persons who attended health examinations at National Taiwan University Hospital, Taipei, Taiwan, between January 2005 and December 2011. Attendees of the health examinations at our center were recruited through advertised messages for health-promotion purposes, as described previously.[15] Attendees did not belong to any particular socioeconomic group or employment type. Attendees were enrolled if they attended the examination for the first time and did not meet exclusion criteria. Participants were categorized into 4 groups according to the severity of NAFLD on abdominal ultrasonography: (1) no NAFLD (the reference group), (2) mild NAFLD, (3) moderate NAFLD, and (4) severe NAFLD. Grading for the severity of NAFLD is described in detail under "Abdominal Ultrasonography" in the Methods section.

Exclusion Criteria

Persons with the following conditions were excluded from our study: (1) aged <20 years; (2) estimated alcohol consumption >20 g/day for men and >10 g/day for women; (3) history of viral hepatitis or seropositivity for hepatitis B virus surface antigen or anti–hepatitis C antibody; (4) history of liver cirrhosis; (5) incomplete results of abdominal ultrasonography; (6) 12-lead ECG findings including atrial fibrillation, atrial flutter, complete left or right bundle-branch block, or pacemaker rhythm; and (7) taking antiarrhythmic medications.

Protocol of the Health Examinations

On the day of the health examination, a standard questionnaire was administered by a trained nurse to obtain data on the demographic characteristics, medical history, and health habits of the participants. Cigarette smoking was categorized into current smokers and nonsmokers. Significant alcohol consumption was defined as alcohol intake >20 g/day for men and >10 g/day for women. Blood pressures were measured at 8 to 9 AM before taking any medication. Systolic and diastolic blood pressures were measured in both arms in the sitting position using a mercury sphygmomanometer, with the arm supported at heart level after the subject sat quietly for 10 minutes. The higher reading for the 2 arms was used in the analysis.

Anthropometric Measurements

Body height was measured to the nearest 0.1 cm. Body weight was measured with an electronic scale to the nearest 0.1 kg with participants wearing a hospital gown. Waist circumferences were measured according to the method of the World Health Organization and the International Diabetes Federation to the nearest 0.1 cm.[16] Body mass index was calculated based on the body weight in kilograms divided by the square of the body height in meters.

Blood Chemistry

All participants received blood biochemistry tests after an overnight 12-hour fast. Blood glucose concentration was measured by the hexokinase method (Roche Diagnostic GmbH). Plasma hemoglobin A1c was measured using an automatic analyzer (HLC-723 G7 HPLC system; Tosoh Corporation). The hemoglobin A1c assay was certified by the National Glycohemoglobin Standardization Program[17] and standardized to the Diabetes Control and Complications Trial reference assay. Hepatitis B surface antigen and hepatitis C virus antibody were measured by the AxSYM system (Abbott Laboratories). The laboratory is qualified by an external quality-assurance program of the Taiwan Society of Laboratory Medicine twice a year.

Definitions

Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or a reported history of hypertension. Central obesity was defined as waist circumference ≥90 cm in men and ≥80 cm in women. Metabolic syndrome was diagnosed using the criteria defined in the Adult Treatment Panel III, with a modification of waist circumference, as appropriate for Asian participants.[18] Participants were diagnosed as having metabolic syndrome if they met ≥3 of the following 5 criteria: (1) high blood pressure, defined as systolic and/or diastolic blood pressure ≥130/85 mm Hg or taking blood pressure–lowering

medications; (2) hyperglycemia, defined as fasting plasma glucose concentration ≥100 mg/dL (5.6 mmol/L) or taking glucose-lowering medications; (3) hypertriglyceridemia, defined as fasting plasma triglyceride concentration ≥150 mg/dL (1.69 mmol/L); (4) high-density lipoprotein cholesterol concentration <40 mg/dL in men and <50 mg/dL in women; (5) waist circumference ≥90 cm in men and ≥80 cm in women.[19] Diabetes was diagnosed according to the American Diabetes Association 2014 recommendations (hemoglobin A1c concentration ≥6.5% [48 mmol/mol], fasting plasma glucose concentration ≥126 mg/dL, or 2-hour plasma glucose concentration ≥200 mg/dL). Diabetes was also diagnosed if participants took medication for diabetes with any level of glycemic parameters. Because we did not perform the standard 75-g oral glucose tolerance test, we used the 2-hour postprandial glucose level as a substitute for the standard criteria.

ECG and QT Interval

A 12-lead ECG was recorded by a trained nurse for 10 seconds with the participant in the supine position on the morning of the same day as the health examination. ECGs were performed using a MAC 3500 resting ECG machine (GE Healthcare). ECGs were analyzed with computerized automated analysis software imbedded in the ECG machine and then were confirmed by a physician. The QT interval was defined as being from the first deflection from the isoelectric line of the QRS complex to the end of the T wave. The corrected QT (QTc) interval was derived from Bazett's formula (QTc equals the QT interval divided by the square root of the RR interval) to correct the QT interval for heart rate.[20] A linear QT correction formula proposed by Hodges et al (QTc Hodges=QT interval+105×[1/RR interval−1]) was also used as an alternative method of QT correction. QTc by Hodges' formula was used as the dependent variable in the multivariable logistic regression analysis after adjustment, as a sensitivity analysis.[21] Resting heart rates were obtained from ECG readings. The diagnosis of left ventricular hypertrophy on ECG was based on Sokolow's voltage criteria. Complete left bundle-branch block was defined as a QRS duration of ≥120 ms with wide S wave or rS in V1 and wide terminal R wave in I, aVL, and V5 to V6, without the presence of a Q wave in the same lead. Complete left bundle-branch block was defined as a QRS duration ≥120 ms with wide terminal R in V1 and wide terminal S in I, aVL, and V5 to V6. The diagnosis of atrial fibrillation was defined as an irregular rhythm occurring irregularly with a range of RR intervals >15% of average RR intervals and RR intervals not organized. Atrial flutter was diagnosed if an atrial rate of 200 to 350 beats per minute was detected.

Abdominal Ultrasonography

Abdominal ultrasonography was performed on the same day as the health examination by experienced gastrointestinal specialists with high-resolution ultrasonography (Aplio XG SSA-790A; Toshiba) using a 3.5-MHz linear transducer. The ultrasound diagnostic criterion for NAFLD was increased parenchymal brightness compared with the right renal cortex. The level of brightness was graded as *mild, moderate*, or *severe*, according to the criteria described by Needleman et al.[22] Briefly, mild NAFLD consisted of an increased hepatic brightness with slight decreased definition of portal venule walls. Severe NAFLD was characterized by an increased hepatic brightness with only the main portal vein walls able to be visualized and all smaller portal venule walls absent. Moderate NAFLD showed results between mild and severe NAFLD.

Statistical Analyses

Sample size was calculated to detect a mean difference of 5 ms in QTc interval among the 4 study groups: no NAFLD, mild NAFLD, moderate NAFLD, and severe NAFLD. Power analysis revealed a minimum of 757 participants per group for a power of 90% at a significance level <0.05 for a 2-sided test to detect a difference in mean QTc of 5 ms between the 4 study groups by 1-way ANOVA. Normally distributed continuous data are presented as mean±SD. Categorical data were reported as numbers and percentages. The continuous variables among the 4 study groups were compared with 1-way ANOVA for heterogeneity, with each of the continuous variables as the outcome variable and the 4 study groups as the categorical variables. A generalized linear model was used to test the trend of each continuous variable across 4 study groups. The continuous variables reported included demographic data (age), anthropometric measures (body mass index, waist circumference), systolic and diastolic blood pressures, biochemical data, and QT and QTc intervals. The categorical variables among the 4 study groups were compared with Pearson's chi-square test for heterogeneity and with the Cochran-Armitage test for trend. Multivariable linear regression analyses were performed to examine the relationship between QTc interval and predictors including age, sex, the severity of NAFLD, and other cardiometabolic risk factors. The significant predictors (age, sex, diabetes, hypertension, cholesterol, body mass index, left ventricular hypertrophy, history of coronary artery disease, hypokalemia, and estimated glomerular filtration rate) were adjusted in the later multivariate logistic regression analyses and subsequent sensitivity analyses.

QTc prolongation was defined as QTc interval >440 ms in men and women. Multivariate logistic regression analyses

were performed to examine the relationship between the presence of QTc prolongation and the severity of NAFLD in men or women. In these analyses, we set the group without NAFLD as the reference group to determine the existence of a dose-dependent relationship. Subgroup analyses were performed among different age groups (by tertiles), status of diabetes (with or without), status of hypertension (with or without), status of metabolic syndrome (with or without), status of left ventricular hypertrophy (with or without), and body mass index groups (by tertiles). Sensitivity analyses were performed using 3 different cutoff points for QTc prolongation and 2 different definitions for alcohol consumption to exclude participants with alcoholic fatty liver disease. The 3 alternative cutoffs for QTc prolongation were (1) QTc ≥440 ms (men) or ≥450 ms (women), (2) QTc ≥440 ms (men) or ≥460 ms (women), and (3) QTc ≥470 ms. The 2 alternative definitions for alcohol consumption were (1) estimated alcohol consumption <10 g per week and (2) no alcohol consumption. Sensitivity analysis using an alternative QT correction formula, Hodges' formula, for multivariable logistic regression with full adjustment was also performed among all participants. The same set of predictors was adjusted in the sensitivity analyses.

A 2-tailed *P* value <0.05 was considered to demonstrate statistical significance for all analyses. Listwise deletion was used to account for missing data. Statistical analyses were performed using the Stata version 11.0 software package (StataCorp LP).

Results

A total of 31 116 patients were enrolled in this study. The mean age was 50.1 years (SD 12.1 years), and men represented 16 014 (51.5%) of the participants. The mean QTc interval of all participants was 421.3 ms (SD 45.4 ms). A total of 9781 participants (31.4%) had a QTc interval of >440 ms. The baseline characteristics of the participants stratified by the severity of NAFLD are shown in Table 1. An increase in the severity of NAFLD was associated with an increase in the severity of anthropometric and metabolic parameters, including body mass index, blood pressure, cholesterol, triglycerides, and glycemic parameters. The QT and QTc intervals increased progressively with increased severity of NAFLD (Figure). The QTc derived from Hodges' formula was shorter than QTc derived from Bazett's formula (Table 1). The QTc intervals derived from these 2 formulas were highly correlated in our participants (correlation coefficient 0.980, *P*<0.05).

Table 2 shows the independent predictors for the QTc interval in a multivariable linear regression model including age, glycemic parameters, lipid profile, electrolytes, past history of cardiovascular disease, presence of metabolic syndrome, and medications. The severity of NAFLD was positively associated with the QTc interval by Bazett's formula (in women, β coefficient: mild 1.46 [95% CI −0.52 to 3.44, *P*=0.148], moderate 7.60 [95% CI 3.97 to 11.22, *P*<0.001], and severe 11.84 [95% CI 5.12 to 18.55, *P*=0.001]; in men, β coefficient: mild 3.29 [95% CI 1.50 to 5.08, *P*<0.001], moderate 6.40 [95% CI 3.74 to 9.05, *P*<0.001], and severe 13.71 [95% CI 9.16 to 18.25, *P*<0.001]) for mild, moderate, and severe NAFLD compared with no NAFLD. The results were similar if analyzed by Hodges' formula (Table 2).

Table 3 shows the odds ratios for the severity of NAFLD to predict the presence of QTc prolongation >440 ms. In the fully adjusted model, the severity of NAFLD was significantly associated with a higher risk for QTc prolongation according to the following odds ratios. For mild, moderate, and severe NAFLD in women, odds ratios were 1.11 (95% CI 1.01 to 1.21, *P*<0.05), 1.61 (95% CI 1.36 to 1.90, *P*<0.001), and 1.31 (95% CI 1.16 to 2.24, *P*<0.01), respectively, compared with no NAFLD. In men, odds ratios were 1.11 (95% CI 1.01 to 1.21, *P*<0.05), 1.39 (95% CI 1.22 to 1.59, *P*<0.001), and 1.87 (95% CI 1.51 to 2.31, *P*<0.001) for mild, moderate, and severe NAFLD, respectively, compared with no NAFLD. There was no significant interaction between NAFLD severity and diabetes in the model. The results were similar when analyzed by Hodges' criteria, although the odds ratio for mild NAFLD did not reached statistical significance (Table 3). We performed sensitivity analyses using different criteria for QTc prolongation: (1) QTc ≥440 ms in men or ≥450 ms in women; (2) QTc ≥440 ms in men or ≥460 ms in women; (3) QTc ≥470 ms and alcohol consumption, with estimated alcohol consumption of either <10 g per week or none (nondrinker). In these sensitivity analyses, the severity of NAFLD remained significantly associated with a higher risk of QTc prolongation after changing the criteria for QTc prolongation and the criteria for alcoholic consumption in the majority of the subgroups (Tables 4 through 6). Moderate and severe NAFLD were consistently associated with higher risk of QTc prolongation using the criteria for QTc interval ≥440 ms in men and ≥450 ms in women or ≥440 ms in men and ≥460 ms in women. The association between NAFLD and QTc prolongation using the criteria for QTc intervals ≥470 ms was attenuated, especially among those participants who never drank (Tables 4 through 6).

Discussion

The main finding of this study was that NAFLD was associated with a prolonged QTc interval and a higher risk of prolonged QTc interval in the general population that was independent of

Table 1. Baseline Characteristics Stratified by the Severity of NAFLD

Baseline Characteristics N=31 116	No NAFLD n=18 225	NAFLD			*P* Value for Heterogeneity	*P* Value for Trend
		Mild n=9152	Moderate n=2976	Severe n=796		
Age, y	48.8 (12.8)	52.2 (11.0)	51.4 (11.0)	48.9 (11.0)	<0.001	<0.001
Sex, male, n (%)	7843 (42.6)	5660 (61.5)	2139 (71.5)	568 (73.9)	<0.001	<0.001
Comorbidities						
Diabetes, n (%)	1133 (6.2)	1210 (13.2)	697 (23.4)	221 (29.0)	<0.001	<0.001
Hypertension, n (%)	2970 (16.3)	2800 (30.6)	1237 (41.6)	424 (55.6)	<0.001	<0.001
Metabolic syndrome, n (%)	1096 (6.0)	1931 (21.1)	1170 (39.3)	440 (57.7)	<0.001	<0.001
Coronary artery disease, n (%)	170 (1.0)	106 (1.2)	55 (1.9)	20 (2.7)	<0.001	<0.001
Stroke, n (%)	69 (0.4)	60 (0.7)	13 (0.5)	1 (0.1)	0.008	0.325
Chronic obstructive pulmonary disease, n (%)	570 (3.3)	307 (3.5)	105 (3.7)	35 (4.8)	0.123	0.037
Smoking, n (%)	1976 (10.9)	1396 (15.3)	557 (18.7)	146 (19.2)	<0.001	<0.001
Anthropometric measures						
Body mass index, kg/m^2	22.4 (2.8)	25.2 (2.8)	27.2 (3.2)	29.6 (4.2)	<0.001	<0.001
Waist circumference, cm	81.3 (8.1)	88.7 (7.4)	93.5 (8.2)	99.1 (10.2)	<0.001	<0.001
Systolic blood pressure, mm Hg	119.5 (15.4)	127.6 (15.2)	132.8 (14.8)	137.2 (16.5)	<0.001	<0.001
Diastolic blood pressure, mm Hg	71.6 (10.1)	76.7 (10.4)	80.2 (10.3)	82.9 (11.2)	<0.001	<0.001
Biochemistry						
Cholesterol, mg/dL	199.1 (35.8)	208.9 (36.6)	211.9 (38.0)	215.7 (39.9)	<0.001	<0.001
HDL cholesterol, mg/dL	51 (12.1)	44.3 (9.6)	41.2 (8.2)	40.1 (7.3)	<0.001	<0.001
LDL cholesterol, mg/dL	112.1 (31.5)	125.9 (32.7)	130.3 (34.2)	133.5 (35.7)	<0.001	<0.001
Triglycerides, mg/dL	94.1 (52.4)	146.3 (85.6)	180.9 (113)	204.1 (141.4)	<0.001	<0.001
Aspartate aminotransferase, U/L	22.3 (9.6)	24.4 (11.0)	30.9 (18.1)	35.8 (18.1)	<0.001	<0.001
Alanine transaminase, U/L	21.1 (16.6)	29.4 (19.6)	45.6 (29.4)	57.7 (33.1)	<0.001	<0.001
Glucose, fasting, mg/dL	90.6 (15.4)	98.3 (22.5)	104.9 (28)	109.4 (33.6)	<0.001	<0.001
Glucose, postprandial, mg/dL	115.2 (43.5)	129.5 (52.6)	142.9 (62.5)	149.1 (62.9)	<0.001	<0.001
Hemoglobin A1c, %	5.5 (0.6)	5.8 (0.8)	6 (1.0)	6.2 (1.1)	<0.001	<0.001
Estimated glomerular filtration rate, mL/min per 1.73 m^2	77.9 (14.3)	76.1 (13.2)	76 (13.2)	77.3 (14.2)	<0.001	<0.001
Creatinine, mg/dL	0.9 (0.3)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	<0.001	<0.001
Sodium, mmol/L	141.1 (2.3)	141.4 (2.3)	141.3 (2.3)	141.0 (2.5)	<0.001	<0.001
Potassium, mmol/L	4.05 (0.34)	4.07 (0.33)	4.09 (0.33)	4.07 (0.33)	<0.001	<0.001
Hypokalemia	690 (3.8%)	358 (3.9%)	104 (3.5%)	43 (5.6%)	0.051	0.275
High sensitivity C-reactive protein, mg/dL	0.13 (0.31)	0.19 (0.41)	0.26 (0.48)	0.34 (0.61)	<0.001	<0.001
Medications						
Antiplatelet medications, n (%)	394 (2.6)	284 (3.6)	129 (5.1)	27 (4.0)	<0.001	<0.001
Anticoagulant medications, n (%)	177 (1.15)	167 (2.12)	63 (2.47)	23 (3.41)	<0.001	<0.001
Steroids, n (%)	186 (1.2)	88 (1.1)	29 (1.1)	6 (0.9)	0.814	0.392
Metabolic syndrome, n (%)	1096 (6.0)	1931 (21.1)	1170 (39.3)	440 (57.7)	<0.001	<0.001
ECG findings						
Heart rate, beats/min	65.2 (45.4)	66.4 (9.8)	68.5 (16.1)	70.3 (10.7)	<0.001	<0.001
QT interval, ms	403.2 (34.8)	402.3 (22.8)	404 (23.8)	407 (23.3)	<0.001	<0.001

Continued

Table 1. Continued

Baseline Characteristics N=31 116	No NAFLD n=18 225	NAFLD			*P* Value for Heterogeneity	*P* Value for Trend
		Mild n=9152	Moderate n=2976	Severe n=796		
QTc interval, ms (by Bazett's formula)	418.9 (60.4)	422.5 (44.8)	430.9 (49.2)	439.9 (48.2)	<0.001	<0.001
QTc interval, ms (by Hodges' formula)	411.6 (32.9)	413.4 (32.6)	418.6 (33.3)	424.6 (34.4)	<0.001	<0.001
QTc >440 ms, n (%) (by Bazett's formula)	5302 (29.1)	2923 (31.9)	1190 (40.0)	366 (48.0)	<0.001	<0.001
QTc >440 ms, n (%) (by Hodges' formula)	3412 (18.7)	1823 (19.9)	755 (25.4)	239 (31.3)	<0.001	<0.001
Left ventricular hypertrophy, n (%)	703 (3.8)	527 (5.7)	186 (6.2)	46 (6.0)	<0.001	<0.001

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, non-alcoholic fatty liver disease; QTc, corrected QT.

traditional risk factors for prolonged QTc intervals. Our findings extend previous understanding of the association of QTc prolongation and NAFLD in patients with diabetes to a broader population.

The mechanism underlying the association between NAFLD and QTc prolongation is not totally clear. Traditional cardiometabolic risk factors have been associated with the QTc interval. The prevalence of diabetes, hypertension, and smoking has been found to increase progressively as the QT interval increases in a large population-based cohort study.[10] Lower levels of high-density lipoprotein cholesterol were also shown to be positively associated with QT prolongation.[23] In a pilot study, reconstituted high-density lipoprotein was shown to shorten the QT interval in cardiomyocytes and in dyslipidemic patients and healthy volunteers.[24] In our study, we observed a significant association of blood pressure, hemoglobin A1c, and high-density lipoprotein concentration with QTc interval. The association between the severity of NAFLD and QTc interval remained significant after rigorous adjustment for these factors.

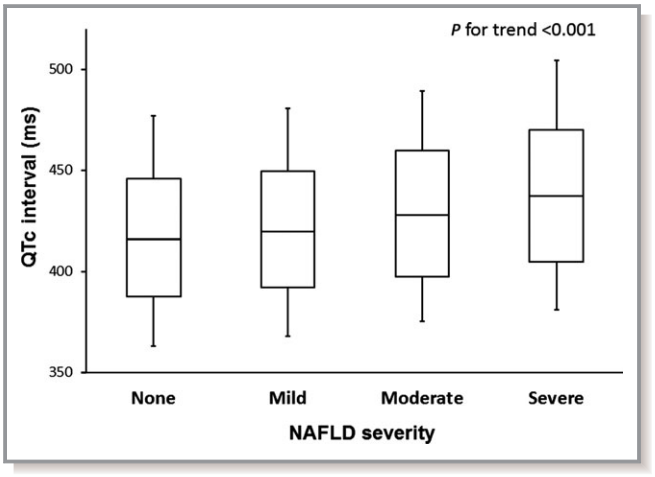

Figure. The box plot of QTc intervals (in milliseconds) according to different severities of NAFLD (none, mild, moderate, and severe). The QTc interval increased with increasing severity of NAFLD (*P* for trend <0.001). The box represents the 25th and 75th percentiles, whereas the whiskers represent the 10th and 90th percentiles. NAFLD indicates nonalcoholic fatty liver disease; QTc, corrected QT.

Another potential mechanism that contributes to the association between NAFLD and the QTc interval is inflammation. The inflammatory marker C-reactive protein has been associated with the QTc interval in prior studies.[25,26] In a recent study among 1716 elderly participants, high-sensitivity C-reactive protein was associated with QTc prolongation in men, whereas soluble tumor necrosis factor receptor 1 was associated with QTc prolongation in women.[27] In vitro studies have shown that TNF-α induces calcium leakage from the sarcoplasmic reticulum, causing action potential prolongation and arrhythmias.[28,29] In our study, we also observed an association between high-sensitivity C-reactive protein and the QTc interval. The association between the presence and the severity of NAFLD and QT interval remained significant after adjustment for high-sensitivity C-reactive protein.

A third potential mechanism that contributes to the association between NAFLD and the QT interval is reflected by the overactivated sympathetic nervous system that occurs in NAFLD. The sympathetic nervous system has long been associated with QTc prolongation.[30] In our prior study among 497 participants with and without NAFLD, the presence of NAFLD was associated with higher sympathetic activity, as assessed by heart rate variability analysis. This association was independent of leptin or subclinical inflammation.[31] We did not measure the sympathetic activity in this current study. Further investigation is warranted to determine whether sympathetic overactivity contributes to QTc prolongation among patients with NAFLD.

Clinical Implications

In the general population, QTc prolongation has been associated with adverse outcomes in many but not all epidemiology studies. The early Framingham Heart Study did

DOI: 10.1161/JAHA.115.001820

Table 2. Association Between QTc Interval and Clinical Variables: Multivariable Linear Regression Model

	QTc Interval by Bazett's Criteria				QTc Interval by Hodges' Criteria			
	Women (n=15 107)		Men (n=16 026)		Women (n=15 107)		Men (n=16 026)	
	β Coefficient (95% CI)	*P* Value	β Coefficient (95% CI)	*P* Value	β Coefficient (95% CI)	*P* Value	β Coefficient (95% CI)	*P* Value
NAFLD severity								
Mild	1.46 (−0.52 to 3.44)	0.148	3.29 (1.5 to 5.08)	<0.001	1.16 (−0.24 to 2.56)	0.104	1.79 (0.50 to 3.08)	0.007
Moderate	7.6 (3.97 to 11.22)	<0.001	6.4 (3.74 to 9.05)	<0.001	4.89 (2.32 to 7.46)	<0.001	4.19 (2.27 to 6.10)	<0.001
Severe	11.84 (5.12 to 18.55)	0.001	13.71 (9.16 to 18.25)	<0.001	8.5 (3.74 to 13.27)	<0.001	9.42 (6.14 to 12.7)	<0.001
Age, y	−0.18 (−0.27 to −0.10)	<0.001	0.23 (0.16 to 0.31)	<0.001	−0.03 (−0.09 to 0.03)	0.318	0.27 (0.22 to 0.32)	<0.001
Coronary artery disease	2.65 (−7.23 to 12.53)	0.602	7.54 (1.74 to 13.34)	0.011	1.9 (−5.11 to 8.9)	0.596	6.31 (2.13 to 10.49)	0.003
Stroke	−15.54 (−30.24 to −0.84)	0.038	3.4 (−5.47 to 12.26)	0.453	−10.66 (−21.09 to −0.23)	0.045	1.53 (−4.86 to 7.92)	0.639
Metabolic syndrome	3.54 (1.15 to 5.92)	0.004	6.94 (4.86 to 9.01)	<0.001	2.74 (1.05 to 4.43)	0.002	5.3 (3.8 to 6.8)	<0.001
Smoking	−5.53 (−9.52 to −1.54)	0.007	−1.83 (−3.65 to −0.02)	0.048	−3.07 (−5.90 to −0.24)	0.033	−0.71 (−2.02 to 0.60)	0.287
Systolic blood pressure, mm Hg	0.57 (0.52 to 0.63)	<0.001	0.62 (0.56 to 0.68)	<0.001	0.38 (0.33 to 0.42)	<0.001	0.43 (0.39 to 0.47)	<0.001
Body mass index, kg/m^2	−0.50 (−0.78 to −0.22)	<0.001	−1.11 (−1.4 to −0.82)	<0.001	−0.27 (−0.47 to −0.07)	0.008	−0.69 (−0.9 to −0.48)	<0.001
HbA1c, %	4.3 (3.14 to 5.46)	<0.001	3.57 (2.65 to 4.50)	<0.001	2.68 (1.86 to 3.51)	<0.001	2.23 (1.56 to 2.89)	<0.001
Cholesterol, mg/dL	0.00 (−0.02 to 0.03)	0.821	0.03 (0.01 to 0.06)	0.007	0.00 (−0.02 to 0.02)	0.954	0.02 (0.00 to 0.03)	0.056
HDL cholesterol, mg/dL	−0.01 (−0.09 to 0.07)	0.788	−0.12 (−0.22 to −0.03)	0.014	0.01 (−0.04 to 0.06)	0.744	−0.04 (−0.11 to 0.03)	0.275
Triglycerides, mg/dL	0.04 (0.03 to 0.06)	<0.001	0.01 (0 to 0.02)	0.02	0.03 (0.02 to 0.04)	<0.001	0.01 (0 to 0.01)	0.120
Aspartate aminotransferase, U/L	0.01 (−0.06 to 0.09)	0.711	0.11 (0.05 to 0.18)	<0.001	0.03 (−0.02 to 0.08)	0.265	0.10 (0.05 to 0.14)	<0.001
Estimated glomerular filtration rate, mL/min per 1.73 m^2	0.3 (0.24 to 0.36)	<0.001	0.16 (0.1 to 0.23)	<0.001	0.2 (0.16 to 0.24)	<0.001	0.11 (0.06 to 0.15)	<0.001
Sodium, mmol/L	0.11 (−0.2 to 0.43)	0.485	0.43 (0.1 to 0.76)	0.010	0.05 (−0.17 to 0.28)	0.640	0.33 (0.1 to 0.57)	0.006
Potassium, mmol/L	−6.89 (−9.07 to −4.71)	<0.001	−11.44 (−13.67 to −9.21)	<0.001	−5.95 (−7.5 to −4.40)	<0.001	−9.09 (−10.7 to −7.48)	<0.001
C-reactive protein, mg/dL	13.52 (11.31 to 15.74)	<0.001	12.05 (10.31 to 13.78)	<0.001	8.51 (6.94 to 10.08)	<0.001	8.10 (6.85 to 9.35)	<0.001
Antiplatelet agent	−1.86 (−7.59 to 3.87)	0.525	−0.56 (−4.42 to 3.31)	0.777	−1.88 (−5.95 to 2.19)	0.365	−0.21 (−3.00 to 2.58)	0.881
Anticoagulant	4.97 (−2.68 to 12.61)	0.203	−6.22 (−11.44 to −1.00)	0.02	2.92 (−2.51 to 8.34)	0.292	−3.75 (−7.51 to 0.02)	0.051
Left ventricular hypertrophy	−4.35 (−8.19 to −0.51)	0.027	−4.42 (−7.54 to −1.30)	0.006	−0.50 (−3.23 to 2.22)	0.717	−0.49 (−2.74 t o 1.76)	0.671

HbA1c indicates hemoglobin A1c; HDL, high-density lipoprotein; NAFLD, non-alcoholic fatty liver disease; QTc, corrected QT.

Table 3. Multivariable Logistic Regression: Severity of NAFLD to Predict QTc Prolongation (QTc ≥440 ms) Among All Participants

		Mild		Moderate		Severe	
		Women	Men	Women	Men	Women	Men
NAFLD Severity	n (Women/Men)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Unadjusted	15 107/16 026	1.42 (1.32 to 1.53)§	1.23 (1.14 to 1.34)§	2.61 (2.26 to 3.00)§	1.83 (1.65 to 2.03)§	3.45 (2.57 to 4.62)§	2.73 (2.28 to 3.26)§
Model 1	15 107/16 026	1.33 (1.22 to 1.44)§	1.16 (1.06 to 1.26)§	2.22 (1.92 to 2.57)§	1.62 (1.45 to 1.80)§	2.72 (2.02 to 3.67)§	2.28 (1.892.74)§
Model 2							
All participants, by Bazett's criteria	15 107/16 026	1.11 (1.01 to 1.21)†	1.11 (1.01 to 1.21)†	1.61 (1.36 to 1.90)§	1.39 (1.22 to 1.59)§	1.31 (1.16 to 2.24)‡	1.87 (1.51 to 2.31)§
All participants, by Hodges' criteria	15 107/16 026	1.04 (0.93 to 1.15)	0.97 (0.86 to 1.09)	1.36 (1.14 to 1.62)‡	1.20 (1.02 to 1.41)†	1.37 (0.99 to 1.89)‡	1.56 (1.21 to 1.99)§
Subgroup analyses*							
Age group							
1st tertile	5193/5218	1.31 (1.06 to 1.62)†	1.22 (1.01 to 1.48)†	1.76 (1.09 to 2.86)†	1.44 (1.11 to 1.87)‡	2.29 (0.81 to 6.50)	1.93 (1.33 to 2.79)§
2nd tertile	5108/5244	1.02 (0.87 to 1.20)	1.09 (0.92 to 1.30)	1.23 (0.9 to 1.68)	1.29 (1.02 to 1.63)†	1.22 (0.68 to 2.17)	1.82 (1.25 to 2.64)‡
3rd tertile	4806/5564	1.11 (0.95 to 1.29)	0.97 (0.84 to 1.14)	1.86 (1.45 to 2.39)§	1.29 (1.03 to 1.61)†	1.85 (1.16 to 2.95) ‡	1.77 (1.18 to 2.66)‡
Diabetes status							
Without	13 767/14 102	1.09 (0.98 to 1.21)	1.13 (1.02 to 1.26)†	1.49 (1.21 to 1.82)§	1.34 (1.15 to 1.56)§	1.49 (0.99 to 2.24)	1.96 (1.53 to 2.52)§
With	1340/1924	1.08 (0.8 to 1.45)	0.81 (0.63 to 1.06)	1.77 (1.18 to 2.64)‡	1.19 (0.87 to 1.62)	1.75 (0.94 to 3.26)	1.51 (0.97 to 2.36)
Hypertension status							
Without	12 522/11 173	1.12 (1.00 to 1.25)	1.23 (1.08 to 1.39) ‡	1.43 (1.14 to 1.79)‡	1.5 (1.25 to 1.80)§	1.72 (1.06 to 2.82)†	1.89 (1.35 to 2.64)§
With	2585/4853	1.01 (0.83 to 1.23)	0.88 (0.76 to 1.03)	1.72 (1.28 to 2.3)§	1.1 (0.9 to 1.34)	1.36 (0.85 to 2.18)	1.61 (1.2 to 2.15) ‡
Metabolic syndrome							
Without	9706/9585	1.13 (1.00 to 1.28)†	1.27 (1.12 to 1.43)§	1.76 (1.29 to 2.40)§	1.67 (1.36 to 2.05)§	2.57 (1.19 to 5.57)†	2.67 (1.71 to 4.16)§
With	3424/4875	0.96 (0.81 to 1.13)	0.83 (0.71 to 0.98)†	1.38 (1.1 to 1.74)‡	1 (0.82 to 1.20)	1.31 (0.89 to 1.93)	1.33 (1.02 to 1.73)†
HDL cholesterol status							
Normal	8498/9824	1.08 (0.94 to 1.25)	1.21 (1.07 to 1.38) ‡	2.06 (1.51 to 2.83)§	1.7 (1.4 to 2.05)§	1.36 (0.66 to 2.79)	2.73 (1.98 to 3.77)§
Abnormal	6522/6088	1.08 (0.94 to 1.23)	0.9 (0.78 to 1.05)	1.35 (1.08 to 1.69)‡	1 (0.82 to 1.21)	1.56 (1.06 to 2.30)†	1.27 (0.94 to 1.71)
Body mass index status							
1st tertile	7500/3045	1 (0.83 to 1.21)	1.18 (0.91 to 1.54)	1.91 (1.03 to 3.54)†	1.02 (0.56 to 1.86)	1.01 (0.24 to 4.30)	0.24 (0.03 to 2.09)
2nd tertile	4340/5861	1.18 (1.01 to 1.37)†	1.23 (1.06 to 1.43)‡	1.34 (0.95 to 1.88)	1.66 (1.29 to 2.14)§	1.32 (0.55 to 3.15)	2.23 (1.16 to 4.27)†
3rd tertile	3246/7081	1.12 (0.93 to 1.34)	1.05 (0.9 to 1.22)	1.69 (1.32 to 2.15)§	1.23 (1.03 to 1.47)*	1.65 (1.1 to 2.47)*	1.57 (1.22 to 2.02)§

Continued

DOI: 10.1161/JAHA.115.001820

Table 3. Continued

NAFLD Severity	n (Women/Men)	Mild		Moderate		Severe	
		Women	Men	Women	Men	Women	Men
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Left ventricular hypertrophy							
Without	14 559/15 122	1.1 (0.99 to 1.22)	1.08 (0.98 to 1.20)	1.6 (1.33 to 1.92)§	1.31 (1.14 to 1.50)§	1.48 (1.04 to 2.10)*	1.85 (1.48 to 2.32)§
With	548/904	0.88 (0.56 to 1.37)	0.97 (0.67 to 1.39)	1.18 (0.62 to 2.22)	1.56 (0.91 to 2.66)	1.62 (0.51 to 5.11)	1.86 (0.74 to 4.64)

Model 1: adjusted for age, sex. Model 2: adjusted for age, sex, diabetes, hypertension, cholesterol, HDL, triglycerides, aspartate aminotransferase, body mass index, left ventricular hypertrophy, a history of coronary artery disease, hypokalemia, estimated glomerular filtration rate, high-sensitivity C-reactive protein, smoking, and metabolic syndrome (the fully adjusted model). HDL indicates high-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; OR, odds ratios; QTc, corrected QT.

*In the subgroup analyses, all variables in model 2 other than the variable for stratification were included; all of the subgroup analyses were analyzed by Bazett's criteria, †$P<0.05$, ‡$P<0.01$, §$P<0.001$.

not reveal an association between QTc interval with all-cause mortality or sudden death.[32] The later studies, including the Cardiovascular Health Study, the Strong Heart study, the Rotterdam study, the NHAMES study, and a recent meta-analysis, have all supported the association between QT prolongation and increased cardiovascular mortality and sudden cardiac death in the general population.[9–12] QT prolongation among patients with diabetes has also been associated with all-cause and cardiovascular mortality.[33,34] QT prolongation among those with hepatic disease has mostly been investigated among patients with liver cirrhosis. QT prolongation is common in patients with liver cirrhosis and is associated with a lower survival rate.[35] The QTc interval is normalized after liver transplantation among half of the patients with liver cirrhosis and QT prolongation.[36] The association between the QTc interval and NAFLD has been found in patients with diabetes,[14] but it has not yet been demonstrated in the general population. The independent value of this association to predict cardiovascular outcomes among patients with NAFLD has not yet been validated. Given the fact that NAFLD has an increased risk for cardiovascular morbidity and mortality,[6] a search for every possible link between NAFLD and cardiovascular disease is key to improving outcomes among these patients. Our findings suggest that NAFLD-associated QT prolongation might be a link to adverse cardiovascular outcomes among these patients. Further confirmation using a large cohort study to assess whether QTc prolongation among patients with NAFLD independently contributes to future cardiovascular events or all-cause mortality is warranted.

The strengths of this study include the large sample size and a standardized protocol from a health management program to collect blood samples and perform ECG recordings. Moreover, sensitivity analyses using different formulas for QTc interval and different criteria for QTc prolongation and alcohol consumption minimized bias from misclassification. Finally, the independent association after adjustment of various cardiometabolic risk factors, including metabolic syndrome, clearly demonstrated the contribution of NAFLD to QTc prolongation.

Limitations

Our study has several limitations. First, the design of this study was cross-sectional and thus could not validate the causal relationship between NAFLD and QT intervals. Future interventional studies with exercise or weight loss to downgrade the severity of NAFLD may help elucidate the temporal relationship between NAFLD and QTc. Second, the diagnosis of NAFLD was assessed by abdominal ultrasound, which has sensitivity of 85% to 90% and specificity of 70% to 80% to detect liver fat >10%. The sensitivity and specificity are lower

Table 4. Multivariable Logistic Regression: Severity of NAFLD to Predict QTc Prolongation by 3 Different QTc Criteria in All Participants

		QTc ≥440 ms (Men) or ≥450 ms (Women)			QTc ≥440 ms (Men) or ≥460 ms (Women)			QTc ≥470 ms		
		Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
	n	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
All participants*	31 116	1.08 (1.01 to 1.15)†	1.37 (1.24 to 1.52)†	1.73 (1.45 to 2.05)†	1.06 (0.99 to 1.14)	1.36 (1.22 to 0.51)†	1.65 (1.38 to 1.96)†	0.97 (0.89 to 1.06)	1.22 (1.07 to 1.39)†	1.45 (1.18 to 1.78)†
Subgroup analyses*										
Age group										
1st tertile	10 405	1.3 (1.14 to 1.49)§	1.41 (1.14 to 1.74)‡	1.85 (1.35 to 2.55)§	1.25 (1.09 to 1.44)‡	1.37 (1.11 to 1.70)‡	1.75 (1.27 to 2.41)§	1.1 (0.92 to 1.32)	1.34 (1.02 to 1.75)†	1.4 (0.94 to 2.07)
2nd tertile	10 347	1.04 (0.92 to 1.17)	1.32 (1.11 to 1.58)‡	1.5 (1.11 to 2.03)‡	1.04 (0.92 to 1.18)	1.34 (1.12 to 1.61)‡	1.48 (1.09 to 2.01)†	0.96 (0.82 to 1.12)	1.07 (0.84 to 1.34)	1.12 (0.77 to 1.62)
3rd tertile	10 364	1.05 (0.94 to 1.17)	1.47 (1.25 to 1.73)§	1.79 (1.33 to 2.42)§	1.03 (0.92 to 1.15)	1.43 (1.21 to 1.68)§	1.74 (1.28 to 2.35)§	0.98 (0.86 to 1.13)	1.4 (1.15 to 1.70)§	1.79 (1.27 to 2.51)§
Sex										
Female	15 102	1.06 (0.96 to 1.17)	1.41 (1.19 to 1.68)§	1.57 (1.14 to 2.17)‡	1.02 (0.91 to 1.13)	1.38 (1.15 to 1.65)§	1.41 (1.01 to 1.95)†	0.96 (0.85 to 1.08)	1.29 (1.06 to 1.57)†	1.34 (0.95 to 1.88)
Male	16 014	1.11 (1.01 to 1.22)†	1.39 (1.22 to 1.59)§	1.87 (1.51 to 2.31)§	1.11 (1.01 to 1.22)†	1.39 (1.22 to 1.59)§	1.87 (1.51 to 2.31)§	0.99 (0.87 to 1.13)	1.22 (1.02 to 1.46)†	1.58 (1.2 to 2.07)§
Diabetes										
Without	27 855	1.1 (1.03 to 1.19)‡	1.36 (1.21 to 1.53)§	1.66 (1.36 to 2.04)§	1.09 (1.01 to 1.18)†	1.35 (1.2 to 1.52)§	1.63 (1.32 to 2.01)§	0.99 (0.9 to 1.09)	1.23 (1.06 to 1.43)‡	1.35 (1.05 to 1.75)†
With	3261	0.95 (0.79 to 1.15)	1.33 (1.05 to 1.68)†	1.67 (1.17 to 2.37)‡	0.92 (0.76 to 1.11)	1.31 (1.04 to 1.67)†	1.58 (1.11 to 2.24)†	0.89 (0.71 to 1.11)	1.19 (0.9 to 1.56)	1.45 (0.98 to 2.13)
Hypertension										
Without	23 685	1.14 (1.05 to 1.23)‡	1.45 (1.27 to 1.66)§	1.72 (1.33 to 2.22)§	1.12 (1.03 to 1.22)‡	1.45 (1.26 to 1.66)§	1.64 (1.26 to 2.13)§	1.02 (0.91 to 1.14)	1.31 (1.1 to 1.56)‡	1.19 (0.85 to 1.67)
With	7431	0.94 (0.84 to 1.07)	1.19 (1.01 to 1.40)†	1.51 (1.18 to 1.94)§	0.94 (0.83 to 1.06)	1.18 (1 to 1.39)†	1.49 (1.17 to 1.91)‡	0.89 (0.77 to 1.03)	1.1 (0.91 to 1.34)	1.47 (1.11 to 1.94)‡
Metabolic syndrome										
Without	26 479	1.1 (1.02 to 1.19)†	1.46 (1.29 to 1.65)§	2.05 (1.6 to 2.64)§	1.09 (1.01 to 1.18)†	1.45 (1.28 to 1.65)§	2 (1.55 to 2.58)§	0.99 (0.9 to 1.10)	1.35 (1.15 to 1.58)§	1.46 (1.05 to 2.01)†
With	4637	0.9 (0.77 to 1.07)	1.07 (0.88 to 1.29)	1.23 (0.94 to 1.60)	0.88 (0.74 to 1.03)	1.04 (0.86 to 1.27)	1.18 (0.91 to 1.54)	0.84 (0.7 to 1.02)	0.97 (0.78 to 1.22)	1.2 (0.89 to 1.62)

Continued

DOI: 10.1161/JAHA.115.001820

DOI: 10.1161/JAHA.115.001820

Table 4. Continued

		QTc ≥440 ms (Men) or ≥450 ms (Women)			QTc ≥440 ms (Men) or ≥460 ms (Women)			QTc ≥470 ms		
		Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
	n	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
HDL cholesterol status										
Without	24 830	1.1 (1.02 to 1.19)†	1.53 (1.35 to 1.73)§	1.95 (1.56 to 2.43)§	1.08 (1.00 to 1.17)	1.52 (1.34 to 1.72)§	1.87 (1.49 to 2.34)§	1 (0.91 to 1.11)	1.38 (1.18 to 1.61)§	1.62 (1.25 to 2.10)§
With	6085	0.96 (0.83 to 1.12)	1.05 (0.87 to 1.27)	1.3 (0.97 to 1.74)	0.96 (0.83 to 1.11)	1.05 (0.87 to 1.27)	1.3 (0.97 to 1.74)	0.8 (0.66 to 0.98)†	0.87 (0.68 to 1.11)	1.06 (0.73 to 1.54)
Body mass index status										
1st tertile	10 541	1.04 (0.89 to 1.21)	1.46 (0.98 to 2.16)	0.57 (0.18 to 1.83)	1.02 (0.87 to 1.19)	1.44 (0.96 to 2.15)	0.45 (0.13 to 1.64)	0.87 (0.71 to 1.06)	1.41 (0.9 to 2.22)	0.49 (0.11 to 2.26)
2nd tertile	10 198	1.16 (1.04 to 1.29)‡	1.42 (1.17 to 1.73)§	1.91 (1.15 to 3.16)†	1.13 (1.02 to 1.26)†	1.47 (1.2 to 1.79)§	1.81 (1.08 to 3.02)†	1.06 (0.92 to 1.22)	1.25 (0.97 to 1.60)	1.13 (0.58 to 2.19)
3rd tertile	10 319	1.07 (0.96 to 1.20)	1.35 (1.17 to 1.55)§	1.6 (1.3 to 1.97)§	1.08 (0.96 to 1.21)	1.33 (1.15 to 1.53)§	1.56 (1.26 to 1.92)§	1.01 (0.86 to 1.17)	1.25 (1.04 to 1.49)†	1.44 (1.12 to 1.84)‡
Left ventricular hypertrophy										
Without	29 665	1.09 (1.01 to 1.17)†	1.37 (1.23 to 1.53)§	1.68 (1.4 to 2.02)§	1.07 (1 to 1.15)	1.36 (1.22 to 1.51)§	1.62 (1.35 to 1.94)§	0.99 (0.9 to 1.09)	1.24 (1.08 to 1.42)‡	1.4 (1.13 to 1.74)‡
With	1451	0.98 (0.74 to 1.29)	1.33 (0.89 to 1.99)	1.64 (0.81 to 3.29)	0.93 (0.7 to 1.24)	1.32 (0.88 to 1.97)	1.85 (0.92 to 3.74)	0.76 (0.53 to 1.08)	1.01 (0.62 to 1.64)	1.41 (0.65 to 3.06)

HDL indicates high-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; OR, odds ratios; QTc, corrected QT.

*Adjusted for age, diabetes, hypertension, cholesterol, HDL, triglycerides, aspartate aminotransferase, body mass index, left ventricular hypertrophy, a history of coronary artery disease, hypokalemia, estimated glomerular filtration rate, high-sensitivity C-reactive protein, smoking, and metabolic syndrome. In the subgroup analyses, all variables other than the variable for stratification were included. Analyzed by Bazett's criteria, †$P<0.05$, ‡$P<0.01$, §$P<0.001$.

Table 5. Multivariable Logistic Regression: Severity of NAFLD to Predict QTc Prolongation by Different QTc Criteria Among Participants With Alcohol Consumption <10 g Per Week

	n	QTc ≥440 ms			QTc ≥440 ms (men) or ≥450 ms (Women)			QTc ≥440 ms (Men) or ≥460 ms (Women)			QTc ≥470 ms		
		Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Participants with alcohol consumption <10 g/week*	24 648	1.12 (1.05 to 1.21)†	1.42 (1.27 to 1.58)†	1.71 (1.42 to 2.07)†	1.09 (1.01 to 1.17)†	1.35 (1.21 to 1.51)†	1.74 (1.44 to 2.10)†	1.07 (1 to 1.16)	1.33 (1.19 to 1.49)†	1.65 (1.36 to 2.00)†	0.98 (0.89 to 1.07)	1.19 (1.04 to 1.37)†	1.45 (1.16 to 1.81)†
Subgroup analyses*													
Age group													
1st tertile	8656	1.32 (1.14 to 1.52)§	1.55 (1.24 to 1.93)§	1.88 (1.33 to 2.64)§	1.31 (1.13 to 1.51)§	1.44 (1.15 to 1.8)‡	1.95 (1.39 to 2.74)§	1.26 (1.08 to 1.46)‡	1.4 (1.11 to 1.76)‡	1.82 (1.29 to 2.57)§	1.14 (0.94 to 1.38)	1.41 (1.06 to 1.87)†	1.5 (0.99 to 2.29)
2nd tertile	8078	1.16 (1.03 to 1.31)†	1.38 (1.14 to 1.67)§	1.5 (1.08 to 2.09)†	1.08 (0.95 to 1.22)	1.34 (1.11 to 1.63)‡	1.49 (1.07 to 2.07)†	1.07 (0.94 to 1.22)	1.34 (1.10 to 1.64)‡	1.4 (1.00 to 1.96)†	0.99 (0.84 to 1.17)	1.08 (0.84 to 1.4)	1.09 (0.72 to 1.63)
3rd tertile	7914	1.05 (0.94 to 1.18)	1.46 (1.22 to 1.74)§	1.93 (1.40 to 2.65)§	1.05 (0.94 to 1.18)	1.39 (1.17 to 1.66)§	1.85 (1.35 to 2.55)§	1.03 (0.91 to 1.16)	1.35 (1.13 to 1.62)‡	1.82 (1.32 to 2.52)§	0.96 (0.83 to 1.12)	1.28 (1.03 to 1.59)†	1.85 (1.3 to 2.64)§
Sex													
Female	12 660	1.16 (1.05 to 1.28)‡	1.63 (1.37 to 1.95)§	1.71 (1.22 to 2.41)‡	1.1 (0.99 to 1.22)	1.45 (1.21 to 1.74)§	1.72 (1.23 to 2.40)‡	1.05 (0.94 to 1.18)	1.4 (1.16 to 1.69)§	1.51 (1.08 to 2.12)†	0.97 (0.86 to 1.11)	1.28 (1.05 to 1.58)†	1.36 (0.95 to 1.95)
Male	11 988	1.1 (0.99 to 1.22)	1.34 (1.16 to 1.55)§	1.83 (1.45 to 2.31)§	1.1 (0.99 to 1.22)	1.34 (1.16 to 1.55)§	1.83 (1.45 to 2.31)§	1.1 (0.99 to 1.22)	1.34 (1.16 to 1.55)§	1.83 (1.45 to 2.31)§	1.00 (0.86 to 1.15)	1.17 (0.96 to 1.43)	1.6 (1.19 to 2.15)‡
Diabetes													
Without	22 212	1.16 (1.07 to 1.25)§	1.39 (1.23 to 1.58)§	1.7 (1.36 to 2.11)§	1.11 (1.03 to 1.20)‡	1.33 (1.17 to 1.51)§	1.67 (1.34 to 2.07)§	1.1 (1.01 to 1.19)†	1.31 (1.15 to 1.49)§	1.61 (1.28 – 2.00)§	0.99 (0.89 to 1.10)	1.19 (1.01 to 1.39)†	1.35 (1.03 to 1.76)†
With	2436	0.93 (0.76 to 1.14)	1.38 (1.06 to 1.8)†	1.65 (1.12 to 2.43)†	0.98 (0.8 to 1.21)	1.37 (1.05 to 1.78)†	1.79 (1.22 to 2.63)‡	0.94 (0.77 to 1.17)	1.35 (1.03 to 1.75)†	1.68 (1.15 to 2.47)‡	0.94 (0.74 to 1.19)	1.23 (0.91 to 1.66)	1.57 (1.04 to 2.39)†
Hypertension													
Without	19 036	1.2 (1.11 to 1.31)§	1.57 (1.36 to 1.8)§	1.77 (1.34 to 2.34)§	1.15 (1.06 to 1.26)‡	1.5 (1.30 to 1.73)§	1.79 (1.36 to 2.37)§	1.13 (1.03 to 1.24)‡	1.48 (1.28 to 1.71)§	1.66 (1.25 to 2.20)§	1.01 (0.90 to 1.14)	1.28 (1.06 to 1.55)‡	1.27 (0.89 to 1.82)
With	5612	0.94 (0.82 to 1.07)	1.14 (0.95 to 1.37)	1.48 (1.13 to 1.93)‡	0.95 (0.83 to 1.09)	1.11 (0.93 to 1.33)	1.49 (1.14 to 1.94)‡	0.94 (0.83 to 1.08)	1.10 (0.91 to 1.32)	1.48 (1.14 to 1.93)‡	0.92 (0.78 to 1.08)	1.08 (0.88 to 1.34)	1.47 (1.09 to 1.98)†
Metabolic syndrome													
Without	21 168	1.16 (1.07 to 1.25)§	1.52 (1.33 to 1.74)§	2.16 (1.65 to 2.82)§	1.12 (1.03 to 1.21)‡	1.44 (1.26 to 1.65)§	2.13 (1.63 to 2.79)§	1.10 (1.01 to 1.19)†	1.43 (1.25 to 1.65)§	2.01 (1.53 to 2.64)§	0.99 (0.89 to 1.10)	1.29 (1.09 to 1.54)‡	1.5 (1.07 to 2.11)†
With	3480	0.93 (0.77 to 1.11)	1.06 (0.86 to 1.32)	1.18 (0.88 to 1.59)	0.93 (0.78 to 1.12)	1.06 (0.85 to 1.31)	1.23 (0.92 to 1.64)	0.92 (0.76 to 1.10)	1.03 (0.83 to 1.28)	1.20 (0.90 to 1.60)	0.91 (0.74 to 1.13)	1 (0.78 to 1.28)	1.26 (0.91 to 1.75)

Continued

DOI: 10.1161/JAHA.115.001820

Table 5. Continued

		QTc ≥440 ms			QTc ≥440 ms (men) or ≥450 ms (Women)			QTc ≥440 ms (Men) or ≥460 ms (Women)			QTc ≥470 ms		
		Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
	n	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
HDL cholesterol status													
Without	19 758	1.16 (1.07 to 1.26)§	1.58 (1.39 to 1.81)§	2 (1.57 to 2.55)§	1.12 (1.03 to 1.22)‡	1.49 (1.30 to 1.70)§	2 (1.57 to 2.54)§	1.10 (1.00 to 1.20)†	1.46 (1.27 to 1.68)§	1.88 (1.48 to 2.4)§	1 (0.9 to 1.11)	1.3 (1.1 to 1.54)‡	1.58 (1.2 to 2.09)‡
With	4769	0.98 (0.83 to 1.14)	1.08 (0.88 to 1.32)	1.32 (0.96 to 1.8)	0.98 (0.83 to 1.14)	1.08 (0.88 to 1.32)	1.32 (0.96 to 1.8)	0.98 (0.83 to 1.14)	1.08 (0.88 to 1.32)	1.32 (0.96 to 1.80)	0.85 (0.69 to 1.06)	0.94 (0.72 to 1.23)	1.21 (0.81 to 1.8)
Body mass index status													
1st tertile	8741	1.07 (0.92 to 1.24)	1.35 (0.89 to 2.06)	0.58 (0.17 to 1.94)	1.02 (0.87 to 1.20)	1.34 (0.87 to 2.04)	0.47 (0.13 to 1.73)	1.01 (0.85 to 1.20)	1.42 (0.92 to 2.18)	0.32 (0.07 to 1.50)	0.85 (0.69 to 1.05)	1.45 (0.9 to 2.35)	0.26 (0.03 to 2.06)
2nd tertile	8012	1.21 (1.09 to 1.35)§	1.58 (1.28 to 1.95)§	2.28 (1.31 to 3.96)‡	1.17 (1.05 to 1.31)‡	1.46 (1.18 to 1.81)§	2.29 (1.32 to 3.96)‡	1.13 (1.00 to 1.27)†	1.48 (1.19 to 1.84)§	2.25 (1.29 to 3.90)‡	1.07 (0.92 to 1.25)	1.28 (0.98 to 1.68)	1.47 (0.75 to 2.89)
3rd tertile	7855	1.13 (1 to 1.28)	1.39 (1.2 to 1.62)§	1.65 (1.32 to 2.06)§	1.11 (0.98 to 1.26)	1.34 (1.15 to 1.56)§	1.64 (1.31 to 2.05)§	1.11 (0.98 to 1.27)	1.31 (1.12 to 1.53)§	1.57 (1.25 to 1.97)§	1.02 (0.87 to 1.21)	1.19 (0.98 to 1.45)	1.44 (1.1 to 1.88)‡
Left ventricular hypertrophy													
Without	23 607	1.14 (1.06 to 1.23)§	1.43 (1.27 to 1.60)§	1.68 (1.38 to 2.04)§	1.11 (1.03 to 1.19)‡	1.36 (1.21 to 1.53)§	1.70 (1.40 to 2.06)§	1.08 (1 to 1.17)†	1.33 (1.18 to 1.50)§	1.61 (1.32 to 1.96)§	1 (0.9 to 1.1)	1.21 (1.05 to 1.40)‡	1.41 (1.12 to 1.78)‡
With	1041	0.95 (0.7 to 1.29)	1.3 (0.82 to 2.06)	2.13 (0.98 to 4.65)	0.97 (0.71 to 1.33)	1.26 (0.8 to 2.00)	1.84 (0.85 to 3.96)	0.93 (0.67 to 1.28)	1.3 (0.82 to 2.07)	2.14 (0.99 to 4.62)	0.77 (0.51 to 1.14)	0.97 (0.55 to 1.69)	1.61 (0.7 to 3.73)

HDL indicates high-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; OR, odds ratios; QTc, corrected QT.

*Adjusted for age, diabetes, hypertension, cholesterol, HDL, triglycerides, aspartate aminotransferase, body mass index, left ventricular hypertrophy, a history of coronary artery disease, hypokalemia, estimated glomerular filtration rate, high-sensitivity C-reactive protein, smoking, and metabolic syndrome. In the subgroup analyses, all variables other than the variable for stratification were included. Analyzed by Bazett's criteria, †$P<0.05$, ‡$P<0.01$, §$P<0.001$.

DOI: 10.1161/JAHA.115.001820

Table 6. Multivariable Logistic Regression: Severity of NAFLD to Predict QTc Prolongation by Different Criteria Among Participants Without Any Alcohol Consumption

		QTc ≥440 ms			QTc ≥440 ms (Men) or ≥450 ms (Women)			QTc ≥440 ms (Men) or ≥460 ms (Women)			QTc ≥470 ms		
		Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
	n	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Participants without alcohol consumption*	10 127	1.07 (0.97 to 1.19)	1.37 (1.16 to 1.61)†	1.85 (1.39 to 2.46)†	1.05 (0.95 to 1.17)	1.28 (1.09 to 1.51)†	1.78 (1.34 to 2.35)†	1.01 (0.9 to 1.12)	1.23 (1.0 to 1.46)†	1.67 (1.26 to 2.22)†	0.88 (0.77 to 1.00)	1.08 (0.89 to 1.31)	1.34 (0.90 to 1.84)
Subgroup analyses*													
Age group													
1st tertile	3216	1.23 (0.99 to 1.53)	1.32 (0.92 to 1.88)	2.11 (1.21 to 3.68)‡	1.22 (0.98 to 1.53)	1.16 (0.81 to 1.67)	2.21 (1.27 to 3.83)‡	1.16 (0.91 to 1.46)	1.18 (0.81 to 1.7)	2.15 (1.24 to 3.74)‡	1.04 (0.78 to 1.39)	1.25 (0.8 to 1.95)	1.6 (0.83 to 3.06)
2nd tertile	3213	1.18 (0.99 to 1.42)	1.5 (1.11 to 2.01)‡	1.72 (1.03 to 2.88)†	1.11 (0.92 to 1.34)	1.46 (1.08 to 1.96)†	1.63 (0.98 to 2.72)	1.09 (0.89 to 1.33)	1.44 (1.06 to 1.96)†	1.56 (0.93 to 2.64)	1.04 (0.82 to 1.32)	1.08 (0.74 to 1.57)	1.23 (0.67 to 2.25)
3rd tertile	3698	0.99 (0.85 to 1.16)	1.44 (1.12 to 1.84)‡	1.97 (1.27 to 3.07)‡	1 (0.85 to 1.17)	1.35 (1.05 to 1.73)†	1.76 (1.14 to 2.73)†	0.95 (0.81 to 1.12)	1.25 (0.97 to 1.62)	1.61 (1.04 to 2.51)†	0.77 (0.64 to 0.94)†	1.12 (0.84 to 1.49)	1.44 (0.9 to 2.32)
Sex													
Female	6768	1.12 (0.99 to 1.27)	1.57 (1.25 to 1.96)§	1.91 (1.25 to 2.94)‡	1.09 (0.95 to 1.24)	1.36 (1.09 to 1.71)‡	1.71 (1.13 to 2.58)†	1.02 (0.88 to 1.18)	1.29 (1.02 to 1.64)†	1.57 (1.03 to 2.38)†	0.93 (0.79 to 1.09)	1.18 (0.91 to 1.53)	1.23 (0.79 to 1.91)
Male	3359	0.98 (0.82 to 1.17)	1.2 (0.93 to 1.54)	1.86 (1.25 to 2.78)‡	0.98 (0.82 to 1.17)	1.2 (0.93 to 1.54)	1.86 (1.25 to 2.78)‡	0.98 (0.82 to 1.17)	1.2 (0.93 to 1.54)	1.86 (1.25 to 2.78)‡	0.73 (0.57 to 0.93)†	0.92 (0.66 to 1.27)	1.45 (0.9 to 2.34)
Diabetes													
Without	8911	1.12 (1 to 1.25)	1.39 (1.15 to 1.68)§	1.78 (1.27 to 2.48)§	1.07 (0.95 to 1.20)	1.26 (1.04 to 1.53)†	1.64 (1.17 to 2.29)‡	1.03 (0.91 to 1.16)	1.2 (0.99 to 1.46)	1.5 (1.07 to 2.11)†	0.88 (0.76 to 1.02)	1.06 (0.84 to 1.34)	1.17 (0.79 to 1.75)
With	1216	0.89 (0.68 to 1.16)	1.21 (0.85 to 1.72)	1.81 (1.04 to 3.17)†	0.97 (0.74 to 1.28)	1.26 (0.88 to 1.79)	1.95 (1.13 to 3.38)†	0.95 (0.72 to 1.25)	1.3 (0.91 to 1.86)	2.06 (1.19 to 3.56)‡	0.87 (0.64 to 1.18)	1.14 (0.77 to 1.67)	1.64 (0.93 to 2.87)
Hypertension													
Without	7748	1.16 (1.02 to 1.31)†	1.48 (1.2 to 1.83)§	1.7 (1.12 to 2.58)†	1.11 (0.97 to 1.26)	1.38 (1.12 to 1.71)‡	1.64 (1.08 to 2.48)†	1.07 (0.94 to 1.23)	1.33 (1.06 to 1.65)†	1.56 (1.02 to 2.37)†	0.93 (0.79 to 1.09)	1.11 (0.85 to 1.46)	1.06 (0.63 to 1.79)
With	2379	0.88 (0.73 to 1.06)	1.15 (0.88 to 1.50)	1.74 (1.16 to 2.61)‡	0.91 (0.75 to 1.10)	1.09 (0.83 to 1.42)	1.68 (1.13 to 2.51)†	0.87 (0.71 to 1.06)	1.07 (0.82 to 1.41)	1.6 (1.07 to 2.39)†	0.78 (0.62 to 0.97)†	1.01 (0.75 to 1.36)	1.37 (0.89 to 2.10)
Metabolic syndrome													
Without	8683	1.13 (1 to 1.26)†	1.46 (1.2 to 1.79)§	2.13 (1.43 to 3.16)§	1.09 (0.97 to 1.23)	1.33 (1.09 to 1.64)‡	1.97 (1.33 to 2.91)§	1.04 (0.92 to 1.18)	1.28 (1.04 to 1.58)†	1.82 (1.23 to 2.71)‡	0.92 (0.79 to 1.07)	1.17 (0.91 to 1.50)	1.36 (0.85 to 2.16)
With	1444	0.82 (0.63 to 1.06)	1.03 (0.76 to 1.41)	1.29 (0.82 to 2.01)	0.86 (0.67 to 1.12)	1.06 (0.78 to 1.44)	1.34 (0.86 to 2.08)	0.85 (0.65 to 1.10)	1.04 (0.76 to 1.43)	1.33 (0.86 to 2.07)	0.72 (0.54 to 0.96)†	0.87 (0.61 to 1.23)	1.06 (0.66 to 1.71)

Continued

Table 6. Continued

		QTc ≥440 ms			QTc ≥440 ms (Men) or ≥450 ms (Women)			QTc ≥440 ms (Men) or ≥460 ms (Women)			QTc ≥470 ms		
		Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
	n	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
HDL cholesterol status													
Without	8670	1.1 (0.99 to 1.24)	1.49 (1.23 to 1.81)[§]	2.28 (1.60 to 3.25)[§]	1.08 (0.96 to 1.21)	1.35 (1.12 to 1.64)[‡]	2.09 (1.48 to 2.95)[§]	1.03 (0.91 to 1.16)	1.30 (1.07 to 1.59)[‡]	1.96 (1.39 to 2.78)[§]	0.9 (0.78 to 1.04)	1.12 (0.89 to 1.41)	1.44 (0.99 to 2.1)
With	1425	0.88 (0.67 to 1.14)	1 (0.71 to 1.41)	1.17 (0.7 to 1.96)	0.88 (0.67 to 1.14)	1.00 (0.71 to 1.41)	1.17 (0.7 to 1.96)	0.88 (0.67 to 1.14)	1 (0.71 to 1.41)	1.17 (0.7 to 1.96)	0.67 (0.47 to 0.95)[†]	0.84 (0.54 to 1.29)	0.97 (0.51 to 1.84)
Body mass index status													
1st tertile	4090	1.01 (0.82 to 1.25)	1.28 (0.68 to 2.40)	0.39 (0.08 to 1.96)	0.93 (0.75 to 1.17)	1.12 (0.59 to 2.12)	0.19 (0.02 to 1.59)	0.96 (0.75 to 1.21)	1.35 (0.71 to 2.58)	0.21 (0.02 to 1.76)	0.83 (0.63 to 1.10)	1.44 (0.72 to 2.87)	1 (1 to 1)[§]
2nd tertile	3077	1.24 (1.06 to 1.46)[‡]	1.44 (1.06 to 1.98)[†]	1.93 (0.83 to 4.50)	1.26 (1.06 to 1.49)[‡]	1.36 (0.99 to 1.87)	1.74 (0.75 to 4.07)	1.18 (0.99 to 1.40)	1.4 (1.01 to 1.93)[†]	1.44 (0.6 to 3.5)	1.03 (0.83 to 1.27)	1.26 (0.85 to 1.87)	1.25 (0.44 to 3.52)
3rd tertile	2941	1.02 (0.85 to 1.22)	1.36 (1.08 to 1.7)[‡]	1.84 (1.31 to 2.59)[§]	0.99 (0.83 to 1.19)	1.25 (1 to 1.57)	1.75 (1.25 to 2.45)[‡]	0.94 (0.77 to 1.13)	1.14 (0.9 to 1.44)	1.61 (1.15 to 2.25)[‡]	0.82 (0.65 to 1.02)	0.96 (0.73 to 1.26)	1.2 (0.82 to 1.76)
Left ventricular hypertrophy													
Without	9646	1.09 (0.98 to 1.22)	1.37 (1.16 to 1.63)[§]	1.82 (1.36 to 2.44)[§]	1.07 (0.96 to 1.19)	1.28 (1.08 to 1.52)[‡]	1.77 (1.32 to 2.37)[§]	1.02 (0.91 to 1.14)	1.23 (1.03 to 1.47)[†]	1.65 (1.23 to 2.21)[§]	0.88 (0.77 to 1.01)	1.11 (0.9 to 1.37)	1.35 (0.97 to 1.88)
With	481	0.81 (0.52 to 1.25)	1.48 (0.79 to 2.80)	2.32 (0.73 to 7.38)	0.84 (0.54 to 1.31)	1.35 (0.72 to 2.54)	1.71 (0.56 to 5.23)	0.82 (0.52 to 1.30)	1.38 (0.73 to 2.62)	2.17 (0.7 to 6.73)	0.71 (0.42 to 1.19)	0.80 (0.38 to 1.69)	1.25 (0.37 to 4.23)

HDL indicates high-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; OR, odds ratios; QTc, corrected QT.

*Adjusted for age, diabetes, hypertension, cholesterol, HDL, triglycerides, aspartate aminotransferase, body mass index, left ventricular hypertrophy, a history of coronary artery disease, hypokalemia, estimated glomerular filtration rate, high sensitivity C-reactive protein, smoking, and metabolic syndrome. In the subgroup analyses, all variables other than the variable for stratification were included. Analyzed by Bazett's criteria, [†]$P<0.05$, [‡]$P<0.01$, [§]$P<0.001$.

DOI: 10.1161/JAHA.115.001820

for detecting liver fat <10%.[37] Consequently, our study might have underestimated the prevalence of NAFLD. Third, some factors including adipocytokines, fasting insulin, homeostatic model assessment–insulin resistance, sympathetic activity, unreported medication use, and genetic factors were not measured in this study. The possible confounding effects of these factors cannot be excluded. Finally, our results could not explain the underlying mechanism of the association between NAFLD and QT prolongation. Further studies are needed to clarify the mechanism.

Conclusion

The severity of NAFLD was associated with prolonged QTc intervals and higher risk for QTc prolongation in the general population with or without diabetes.

Acknowledgments

The authors thank the Health Management Center at the National Taiwan University Hospital for assistance. Author contributions: Hung, Tseng, and M.-F. Chen designed and performed the study, analyzed data, and wrote and edited the manuscript. C.-C. Chen, Liao, M.-F. Chen, Ho, Lin, Yang and Wu conceived and participated in the study design, evaluated the results, and edited the manuscript. Tseng, Tu, C.-C. Chen, Liao, Lee and Chiu performed ultrasonography and collected data. Hung, Tseng, Tu, Yang, Wu and M.-F. Chen contributed to the discussion and edited the manuscript. All authors read and approved the final manuscript.

Disclosures

None.

References

1. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol*. 2003;98:960–967.
2. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology*. 2012;55:2005–2023.
3. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology*. 2004;40:1387–1395.
4. Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterology*. 2011;141:1249–1253.
5. Mahady SE, George J. Management of nonalcoholic steatohepatitis: an evidence-based approach. *Clin Liver Dis*. 2012;16:631–645.
6. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med*. 2010;363:1341–1350.
7. Ballestri S, Lonardo A, Bonapace S, Byrne CD, Loria P, Targher G. Risk of cardiovascular, cardiac and arrhythmic complications in patients with non-alcoholic fatty liver disease. *World J Gastroenterol*. 2014;20:1724–1745.
8. Sauer AJ, Moss AJ, McNitt S, Peterson DR, Zareba W, Robinson JL, Qi M, Goldenberg I, Hobbs JB, Ackerman MJ, Benhorin J, Hall WJ, Kaufman ES, Locati EH, Napolitano C, Priori SG, Schwartz PJ, Towbin JA, Vincent GM, Zhang L. Long QT syndrome in adults. *J Am Coll Cardiol*. 2007;49:329–337.
9. Robbins J, Nelson JC, Rautaharju PM, Gottdiener JS. The association between the length of the QT interval and mortality in the Cardiovascular Health Study. *Am J Med*. 2003;115:689–694.
10. Straus SM, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, Deckers JW, Kingma JH, Sturkenboom MC, Stricker BH, Witteman JC. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol*. 2006;47:362–367.
11. Zhang Y, Post WS, Blasco-Colmenares E, Dalal D, Tomaselli GF, Guallar E. Electrocardiographic QT interval and mortality: a meta-analysis. *Epidemiology*. 2011;22:660–670.
12. Zhang Y, Post WS, Dalal D, Blasco-Colmenares E, Tomaselli GF, Guallar E. QT-interval duration and mortality rate: results from the Third National Health and Nutrition Examination Survey. *Arch Intern Med*. 2011;171:1727–1733.
13. Dekker JM, Feskens EJ, Schouten EG, Klootwijk P, Pool J, Kromhout D. QTc duration is associated with levels of insulin and glucose intolerance. The Zutphen Elderly Study. *Diabetes*. 1996;45:376–380.
14. Targher G, Valbusa F, Bonapace S, Bertolini L, Zenari L, Pichiri I, Mantovani A, Zoppini G, Bonora E, Barbieri E, Byrne CD. Association of nonalcoholic fatty liver disease with QTc interval in patients with type 2 diabetes. *Nutr Metab Cardiovasc Dis*. 2014;24:663–669.
15. Tseng PH, Lee YC, Chiu HM, Chen CC, Liao WC, Tu CH, Yang WS, Wu MS. Association of diabetes and HbA1c levels with gastrointestinal manifestations. *Diabetes Care*. 2012;35:1053–1060.
16. Ma WY, Yang CY, Shih SR, Hsieh HJ, Hung CS, Chiu FC, Lin MS, Liu PH, Hua CH, Hsein YC, Chuang LM, Lin JW, Wei JN, Li HY. Measurement of waist circumference: midabdominal or iliac crest? *Diabetes Care*. 2013;36:1660–1666.
17. Little RR, Rohlfing CL, Wiedmeyer HM, Myers GL, Sacks DB, Goldstein DE, Committee NS. The national glycohemoglobin standardization program: a five-year progress report. *Clin Chem*. 2001;47:1985–1992.
18. American Diabetes A. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2014;37(suppl 1):S81–S90.
19. Tan CE, Ma S, Wai D, Chew SK, Tai ES. Can we apply the National Cholesterol Education Program Adult Treatment panel definition of the metabolic syndrome to Asians? *Diabetes Care*. 2004;27:1182–1186.
20. Rautaharju PM, Surawicz B, Gettes LS, Bailey JJ, Childers R, Deal BJ, Gorgels A, Hancock EW, Josephson M, Kligfield P, Kors JA, Macfarlane P, Mason JW, Mirvis DM, Okin P, Pahlm O, van Herpen G, Wagner GS, Wellens H; American Heart Association E, Arrhythmias Committee CoCC, American College of Cardiology F, Heart Rhythm S. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol*. 2009;53:982–991.
21. Hodges M, Salerno D, Erlinen D. Bazett's QT correction reviewed: evidence that a linear QT correction for heart rate is better. *J Am Coll Cardiol*. 1983;1:694.
22. Needleman L, Kurtz AB, Rifkin MD, Cooper HS, Pasto ME, Goldberg BB. Sonography of diffuse benign liver disease: accuracy of pattern recognition and grading. *AJR Am J Roentgenol*. 1986;146:1011–1015.
23. Grandinetti A, Chow DC, Miyasaki M, Low P. Association of increased QTc interval with the cardiometabolic syndrome. *J Clin Hypertens*. 2010;12:315–320.
24. Den Ruijter HM, Franssen R, Verkerk AO, van Wijk DF, Vaessen SF, Holleboom AG, Levels JH, Opthof T, Sungnoon R, Stroes ES, Kuivenhoven JA, Coronel R. Reconstituted high-density lipoprotein shortens cardiac repolarization. *J Am Coll Cardiol*. 2011;58:40–44.
25. Kazumi T, Kawaguchi A, Hirano T, Yoshino G. C-reactive protein in young, apparently healthy men: associations with serum leptin, QTc interval, and high-density lipoprotein-cholesterol. *Metabolism*. 2003;52:1113–1116.
26. Kim E, Joo S, Kim J, Ahn J, Kim J, Kimm K, Shin C. Association between C-reactive protein and QTc interval in middle-aged men and women. *Eur J Epidemiol*. 2006;21:653–659.
27. Medenwald D, Kors JA, Loppnow H, Thiery J, Kluttig A, Nuding S, Tiller D, Greiser KH, Werdan K, Haerting J. Inflammation and prolonged QT time: results from the Cardiovascular Disease, Living and Ageing in Halle (CARLA) study. *PLoS One*. 2014;9:e95994.
28. Duncan DJ, Yang Z, Hopkins PM, Steele DS, Harrison SM. TNF-alpha and IL-1beta increase Ca^{2+} leak from the sarcoplasmic reticulum and susceptibility to arrhythmia in rat ventricular myocytes. *Cell Calcium*. 2010;47:378–386.

29. Abramochkin DV, Kuzmin VS, Mitrochin VM, Kalugin L, Dvorzhak A, Makarenko EY, Schubert R, Kamkin A. TNF-alpha provokes electrical abnormalities in rat atrial myocardium via a NO-dependent mechanism. *Pflugers Arch*. 2013;465:1741–1752.
30. Magnano AR, Holleran S, Ramakrishnan R, Reiffel JA, Bloomfield DM. Autonomic nervous system influences on QT interval in normal subjects. *J Am Coll Cardiol*. 2002;39:1820–1826.
31. Liu YC, Hung CS, Wu YW, Lee YC, Lin YH, Lin C, Lo MT, Chan CC, Ma HP, Ho YL, Chen CH. Influence of non-alcoholic fatty liver disease on autonomic changes evaluated by the time domain, frequency domain, and symbolic dynamics of heart rate variability. *PLoS One*. 2013;8:e61803.
32. Goldberg RJ, Bengtson J, Chen ZY, Anderson KM, Locati E, Levy D. Duration of the QT interval and total and cardiovascular mortality in healthy persons (the Framingham Heart Study experience). *Am J Cardiol*. 1991;67:55–58.
33. Veglio M, Sivieri R, Chinaglia A, Scaglione L, Cavallo-Perin P. QT interval prolongation and mortality in type 1 diabetic patients: a 5-year cohort prospective study. Neuropathy Study Group of the Italian Society of the Study of Diabetes, Piemonte Affiliate. *Diabetes Care*. 2000;23:1381–1383.
34. Cox AJ, Azeem A, Yeboah J, Soliman EZ, Aggarwal SR, Bertoni AG, Carr JJ, Freedman BI, Herrington DM, Bowden DW. Heart rate-corrected QT interval is an independent predictor of all-cause and cardiovascular mortality in individuals with type 2 diabetes: the Diabetes Heart Study. *Diabetes Care*. 2014;37:1454–1461.
35. Bernardi M, Calandra S, Colantoni A, Trevisani F, Raimondo ML, Sica G, Schepis F, Mandini M, Simoni P, Contin M, Raimondo G. Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. *Hepatology*. 1998;27:28–34.
36. Bal JS, Thuluvath PJ. Prolongation of QTc interval: relationship with etiology and severity of liver disease, mortality and liver transplantation. *Liver Int*. 2003;23:243–248.
37. Bohte AE, van Werven JR, Bipat S, Stoker J. The diagnostic accuracy of US, CT, MRI and 1H-MRS for the evaluation of hepatic steatosis compared with liver biopsy: a meta-analysis. *Eur Radiol*. 2011;21:87–97.