Elevated gamma-glutamyl transferase has a non-linear association with incident non-alcoholic fatty liver disease in the non-obese Chinese population: a secondary retrospective study

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Research Article

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Abstract

Background

Effective and applicable predictors of non-alcoholic fatty liver disease (NAFLD) are needed for the non-obese Chinese population. We investigated whether serum gamma-glutamyl transferase (GGT) was associated with incident NAFLD in the non-obese Chinese population.

Methods

This was a retrospective cohort study that enrolled a total of 33153 initially NAFLD-free individuals who underwent a health examination in Wenzhou Medical Center of Wenzhou People's Hospital from January 2010 to December 2014. We determined the relationship between GGT at enrollment and incident NAFLD during follow-up in 11906 persons. The relationship between GGT levels and incident NAFLD was analyzed using Cox regression and generalized additive models after adjustment for demographic and clinical variables. In addition, we also performed a subgroup analysis, which was explored by Cox proportional hazard models. It was stated that the data had been downloaded from the DATADRYAD website.

Result

Multivariable Cox regression models were used to estimate the hazard ratio (HR) for GGT with incident NAFLD after adjusted demographic and clinical variables. (HR, 1.010; 95% CI, 1.007–1.012; $P < 0.001$). The incident NAFLD in the highest quartile of GGT levels was 3.653 times as high (95% confidence interval, 2.915 to 4.579) as that in the lowest quartile. A non-linear relationship was firstly detected between GGT and incidence of NAFLD, which had an inflection point of GGT was 26U/L. The effect sizes and the confidence intervals on the left and right sides of the inflection point were 1.104(1.089–1.120)and 1.001（0.999–1.004）, respectively. In subgroup analyses, the hazard ratio for incident NAFLD remained consistent across subgroups.

Conclusion

In conclusion, the GGT level in the non-obese Chinese population was statistically significantly associated with incident NAFLD. The relationship between GGT level and incident NAFLD is non-linear. When GGT level is less than 26 U/L, GGT was strong positively with incident NAFLD.

Background

Non-alcoholic fatty liver disease (NAFLD) is characterized by the excessive fat deposition in the liver that is not caused by alcohol, which leads to a progression of non-alcohol steatohepatitis[1, 2]. It is a growing

public health burden affecting approximately one-quarter of adults worldwide[3, 4] and is recognized as a major cause of liver-related morbidity and mortality[2, 5, 6]. Several insulin resistance-related diseases further contribute to the progression of NAFLD, including metabolic syndrome,type2 diabetes metabolic syndrome[7].

Gamma-glutamyltransferase (GGT), which is secreted mainly by the liver, has been regarded as a biomarker of liver disease[8]. Decreased serum GGT levels are associated with the improvement of liver histology[9]. Weight loss reduces the GGT level in patients with NAFLD[10]. In Chinese, recent studies explore the decreased GGT levels associated with the improvement of metabolic disturbances after the routine treatment of NAFLD[3]. Previous research reported that the GGT level is as a marker of NAFLD in patients with metabolic syndrome[11]. Up to 80% of NAFLD patients were caused by obese[12]. However, the percentage of NAFLD in the non-obese or lean patients is increasing. In the non-obese Chinese population, a better biomarker to predict the development of NAFLD is needed to be explored. The relationship between the baseline GGT and incident NAFLD in the non-obese Chinese population should be elucidated.

In the present study, we postulate that GGT may serve as an early predictor for the incident NAFLD in the non-obese Chinese population. To test this hypothesis, we used the previously published data for secondary data analysis; we explored the relationship between GGT level and the risk of incident NAFLD in the non-obese Chinese population. In addition, we used the generalized additive models to achieve the optimal cutoff point for GGT.

Methods

Study Design and participants

The raw data was obtained from the 'DATADRYAD' database freely. The authors of the original study have waived all copyright and related ownership of these data. Therefore, we could use these data for secondary analysis without infringing on the authors' rights. The rationale and study design have been described in detail previously[13]. Briefly, This was a longitudinal study conducted from January 2010 to December 2014 which enrolled a total of 33153 initially NAFLD-free individuals who underwent a health examination in Wenzhou Medical Center of Wenzhou People's Hospital. Of these participants, 16980 were excluded according to the exclusion criteria. A total of 16173 initially NAFLD-free non-obese individuals were included in this study. Individuals were excluded if they reported excess alcohol consumption (>140 g/week for men and >70 g/ week for women), or had a history of viral hepatitis, autoimmune hepatitis, or other known causes of chronic liver disease; a body mass index (BMI) of ≥25 kg/m^2; a low-density liptein cholesterol (LDL-c) of >3.12 mmol/L; were taking antihypertensive agents, anti-diabetic agents or lipid-lowing agents; and were lost to follow-up or their data were missing.

According to our study of these 16173 participants, 4267 were excluded according to the exclusion criteria. Individuals were excluded if the GGT value was missing or it was extreme value. A total of 11906

initially NAFLD-free non-obese individuals were included in this study. About 2044 participants developed NAFLD during follow-up.

Diagnosis of NAFLD by ultrasonography

The ultrasound diagnostic criteria for NAFLD are based on the criteria recommended by the Chinese Liver Disease Association[14], which has been described in detail previously.

Data collection

Baseline clinical examinations were performed as described previously[13]. BMI (kg/m^2) was calculated as weight in kilograms divided by height in m^2. Blood pressure was measured using an automated sphygmomanometer with the participant in a quiet environment and a sitting position. The biochemical measurements included albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin(TB), Direct Bilirubin (DBIL), Globulin (GLB), fasting plasma glucose (FPG), blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), total cholesterol (TC), Triglyceride (TG), high-density liptein cholesterol (HDL-c), and LDL-c. All values were measured by an automated analyzer (Abbott AxSYM) using standard methods.

Follow-up and outcome definitions

The follow-up evaluations were performed annually during the observation period. The outcome was the incident NAFLD, diagnose by ultrasonic examination.

Statistical analysis

The purpose of multiple imputations is to generate possible values for missing values, which had been used in multivariate data sets. The participants were stratified by quartiles of GGT. Continuous variables were expressed as the means ± standard deviations or as medians and interquartile ranges, and categorical variables were expressed as proportions. We used chi-square tests to compare categorical variables and one-way ANOVA or Kruskal-Wallis test to compare continuous variables.

The hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of NAFLD associated with GGT levels were estimated using Cox proportional hazards models without and with controlled the effect of clinically important confounding variables, including age, gender, BMI, SBP, DBP, TC, TG, HDL-C, LDL-C, ALT, AST, ALP, ALB, GLB, TB, DBIL, BUN, Cr, UA, FBG. To ensure the robustness of data analysis, we did a sensitivity analysis by converted the GGT into a categorical variable and calculated the *P* for trend. We used a smooth curve fitting (penalty curve method) and a generalized additive model (GAM) to address the non-linear relationship of GGT with the incident NAFLD. As the non-linearity relationship was observed, a two-piecewise linear regression model was performed to calculate the threshold effect of the GGT on the incident NAFLD in terms of the smoothing plot. The best-fitting model was determined based on the *p*-value of the log of the likelihood ratio. We also conducted a subgroup analysis (age, gender, BMI, SBP, DBP, HDL-C, ALT, Cr, UA, FBG), which was explored by Cox proportional hazard models with adjusted

for all the factors except for the stratification factor itself. NAFLD-free survival curves were used by the Kaplan-Meier method. The log-rank test was used to compare the Kaplan–Meier hazard ratios for adverse events and their corresponding 95% CIs. All of the analyses were performed using statistical software package R (http://www.R-project.org, The R Foundation) and Empower-Stats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA). Two-tailed *P* values of less than 0.05 were considered to indicate statistical significance.

Result

Study Participants and the Baseline Characteristics

We identified 11906 participates (54.69% male and 45.31% female) who met our inclusion criteria (Fig.1). The age of the participants ranged from 14 to 95 years, with a mean of 43.26 years. A total of 2044 participants developed NAFLD during the median follow-up of 2.05 years. The baseline characteristics of the participants were stratified by the quartiles of the GGT(≤16 U/L, 16-21 U/L, 21-31 U/L, > 31 U/L)which were shown in Table1. Participants with the highest GGT had higher BMI, blood pressure levels (including both SBP and DBP), FPG, UA, TC, LDL-c, Cr, ALT, AST.

Univariate analyses

Univariate Cox proportional hazards analyses were undertaken in order to compare GGT to other variables which are known to be of value in predicting NAFLD (Table 2). In univariate analysis, the results showed that age, BMI, SBP, DBP, TC, TG, LDL, AST, ALT, ALP, BUN, Cr, UA and FBG were positively correlated with the probability of NAFLD.

Relationship between GGT levels and incident NAFLD during Follow-up

Among 11906 participants of the study cohort who had a median follow-up period of 24.97 (21.88-38.10) months, we determined whether baseline GGT level was associated with progression to NAFLD. NAFLD developed in 2044 participants (17.17%) during follow-up. A higher GGT level at baseline was associated with a significantly greater incidence of NAFLD ($P<0.001$) (Fig.2). The rate of NAFLD was 35.22% at 2 years among participants with a GGT level of at least 21U/L (third and fourth quartiles), as compared with 8.82% among participants with a GGT level of less than 21U/L (first and second quartiles)

Participants with a GGT level in the third quartile had a risk of incident NAFLD that was 4 times that of participants in the first (lowest) quartile, and participants in the fourth quartile had a risk that was 7 times that of participants in the first quartile (Table 3). This association of GGT and NAFLD persisted despite adjustment for age, gender, BMI, SBP and DBP (model I) or inclusion of the baseline mentioned above characteristics and TC, TG, HDL-C, LDL-C, ALT, AST, ALP, ALB, GLB, TB, DBIL, BUN, Cr, UA and FBG (model II) (Table 3). Then we used a GAM to insert the continuity covariate into the equation as a curve, this generally remained consistent with model II (OR 1.004; 95% CI 1.004，1.007), this demonstrated the robustness of the results (Table 3).

The analyses of the non-liner relationship

We used a GGM model and smooth curve fitting (penalty curve method) to explore the potential relationship between GGT level and the incident NAFLD. Therefore, a non-linear relationship of GGT level with incidence NAFLD was detected, which has not been explored in previous studies. We found that the relationship between GGT level and incidence NAFLD was also non-linear (after adjusting age, gender, BMI, SBP, DBP, FPG, TC, LDL, Scr, smoking, drinking status and family history of diabetes) (Fig.3). Using a two-piecewise linear regression model and recursive algorithm, we calculated that the inflection point of GGT was 26U/L (Log-likelihood ratio test P < 0.001). When GGT levels were≤26U/L, a 1-unit increase in the GGT level was associated with a 10.4% greater adjusted odds ratio of incident NAFLD (OR 1.104; 95% CI 1.089, 1.120) and when GGT levels were 26U/L, no relationship was observed with incident NAFLD (OR 1.001; 95% CI 0.999, 1.004, P: 0.364) (Table 4). There was a threshold effect between GGT and incident NAFLD.

The results of subgroup analyses

We performed sensitivity analyses to determine whether age, gender, BMI, SBP, DBP, TC, TG, HDL-C, LDL-C, ALT, AST, ALP, ALB, GLB, TB, DBIL, BUN, Cr, UA, FBG influenced the relationship between the GGT level and the incidence of NAFLD. In subgroup analyses, the hazard ratio for incident NAFLD remained consistent across subgroups (Table 5). These findings suggest that GGT is independently associated with the incidence of NAFLD.

Discussion

This study in the non-obese Chinese population provided evidence that GGT level at baseline was associated with incident NAFLD during follow-up. Concurrently, a saturation effect was detected between the GGT level and incident NAFLD, with an inflection point at 26U/L. Moreover, in multivariate analysis of the subgroup, GGT was also as an independent biomarker to predict the incidence of NAFLD.

NAFLD is a world public health problem[15], which is accompanied by liver dysfunction. The abnormal of liver enzymes are the markers of NAFLD in the general population[16]. As reports, the abnormal GGT is associated with the future development of the fatty liver[17]. Our study showed that the baseline GGT predicted the incident NAFLD during follow in the non-obese Chinese population,which supports the previous similar studies. From a traditional perspective, central obesity and metabolic syndrome increase the risk of NAFLD[18, 19]. However, the percentage of non-obese patients with NAFLD is increasing now[20]. In our research, we firstly investigated the relationship between GGT and NAFLD in the non-obese Chinese population with a larger sample. Previous studies used propensity scores to divide GGT into two categorical variables, which would greatly damage the variable's information[11]. Moreover, previous studies did not further explore the possible curvilinear relationship between GGT and NAFLD. On the contrary, in our study, GGT was as a continuous variable. We observed a significant association between GGT (1 U/L increase) and incident NAFLD after adjusting the confounding variables (HR = 1.010, 95% CI 1.007, 1.012). The highest quartile of GGT was associated with increased risk for NAFLD by 2-fold

compared with the lowest quartile. Although our conclusion is consistent with previous research, our research is more ideal from the perspective of information preservation. At the same time, the large sample of the non-obese Chinese population we studied helps the research to be successfully promoted among the Chinese population who are under physical examination. Elevated GGT reminds the population of the high risk of NAFLD during follow up, which will be an alarm for people to adjust their living habits in advance to reduce the incidence of NAFLD[21].

A GGM model and smooth curve fitting were applied to explore the nonlinear relationship between GGT level and incident NAFLD. We also used two piecewise linear regression to determine the relationship in detail. In the present study, the inflection point was 26U/L after adjusting the confounding variables (including age, gender, BMI, SBP, DBP, TC, TG, HDL-C, LDL-C, ALT, AST, ALP, ALB, GLB, TB, DBIL, BUN, Cr, UA, FBG). When GGT levels were ≤ 26U/L, a 1-unit increase in the GGT level was associated with a 10.4% greater adjusted odds ratio of incident NAFLD (OR 1.104; 95% CI 1.12, 5.87) and when GGT levels were 26U/L, no relationship was observed with incident NAFLD.

The present study has some strengths. (1) We demonstrated results in the non-obese Chinese cohort with a wider range of sample sizes compared with previous similar studies, allowing for subgroup analyses and adjustment for clinically confounding variables. (2) We use GGT as both categorical variable and continuous variable for statistical analysis, which greatly protects the integrity of the data and enhances the robustness of the results. (3) When we adjusted the confounding factors, we considered the possibility of the curve relationship and made a curve adjustment. (4) We explored the non-linear relationship by used a GAM model and a smooth curve fitting and further explore this; we gave the inflection point for the first time in the non-obese Chinese population; therefore, our analysis has greater clinical value.

Our study had several limitations. Firstly, our study was limited by the inclusion of only Chinese in prospective cohorts, necessitating validation studies from multiethnic subjects. Secondly, the diagnosis of NAFLD was dependent on ultrasonography but not liver biopsy. Thirdly, the relationship between the GGT level and the different stages of NAFLD could not be done. Lastly, although we adjusted for the confounding factors, but some unmeasured factors such as physical activity and dietary factors cannot be adjusted in our study. Further investigations in a longer follow up with more meticulous method are needed.

Conclusions

We found a positive and non-linear relationship between GGT and incident NAFLD in the non-obese Chinese population. Elevated GGT level at baseline was associated with an increased risk of NAFLD. When GGT is less than 26, it is positively related to incident NAFLD. Thus, abnormal GGT supports identifying the no-obese Chinese population at risk of NAFLD in advance, enabling early and optimized therapy to improve patient outcomes. We hope that this study can provide a reference for clinicians.

Abbreviations

ALB: albumin; ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; BMI: body mass index; BUN: blood urea nitrogen; Cis: confidence intervals; Cr: creatinine; DBP: diastolic blood pressure; DBIL: direct bilirubin; FPG: fasting plasma glucose; GAM: generalized additive model; GLB: globulin; GGT: gamma-glutamyltransferas; HDL-c: high density liptein cholesterol; LDL-c: low density liptein cholesterol; NAFLD: non-alcoholic fatty liver disease; SBP: systolic blood pressure; TB: total bilirubin; TC: total cholesterol; TG: triglyceride; UA: uric acid.

Declarations

Acknowledgements

Not application

Authors' contributors

LLW contributed to the conception and design of the study. MZ was responsible for data analysis, LLW and MZ were responsible for data interpretation. HFH wrote the original draft and QJW verified the data. All authors were involved in the reviewing and editing of the manuscript and approved the final version.

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Availability of data and materials

Data can be downloaded from 'DATADRYAD' database (www.Datadryad.org).

Ethics approval and consent to participate

In the previously published article[13], Dan-Qin Sun, et al. has clearly stated that: the study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all Participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Tables

Table 1. The baseline characteristics of participants

GGT (U/L)	Q1 (≤16)	Q2 (16 to≤21)	Q3 (21 to≤31)	Q4 (≥31)	*P*-value
Participants	2401	3077	3448	2980	
Age, years	42.63 ± 14.96	43.06 ± 15.01	43.39 ± 15.12	43.81 ± 14.63	0.028
Gender -n (%)					<0.001
Female	1231 (51.27%)	1416 (46.02%)	1524 (44.20%)	1224 (41.07%)	
Male	1170 (48.73%)	1661 (53.98%)	1924 (55.80%)	1756 (58.93%)	
BMI (kg/m2)	20.76 ± 1.93	21.17 ± 2.01	21.84 ± 2.01	22.42 ± 1.81	<0.001
SBP (mmHg)	115.36 ± 15.70	119.93 ± 16.52	124.32 ± 16.26	127.66 ± 16.55	<0.001
DBP (mmHg)	69.48 ± 9.39	72.20 ± 9.75	74.92 ± 10.14	77.11 ± 10.38	<0.001
TC (mmol/L)	4.42 ± 0.70	4.54 ± 0.72	4.62 ± 0.72	4.79 ± 0.77	<0.001
TG (mmol/L)	0.89 (0.70-1.14)	1.01 (0.79-1.33)	1.22 (0.92-1.65)	1.52 (1.11-2.16)	<0.001
HDL-c (mmol/L)	1.55 ± 0.35	1.49 ± 0.35	1.41 ± 0.35	1.36 ± 0.35	<0.001
LDL-c (mmol/L)	2.13 ± 0.45	2.24 ± 0.47	2.32 ± 0.47	2.36 ± 0.46	<0.001
ALT (U/L)	12.00 (10.00-16.00)	14.00 (11.00-18.00)	17.00 (14.00-23.00)	23.00 (17.00-32.00)	<0.001
AST (U/L)	19.00 (17.00-22.00)	20.00 (18.00-23.00)	21.50 (19.00-25.00)	24.00 (21.00-29.00)	<0.001
ALP (mmol/L)	62.52 ± 17.67	68.98 ± 19.42	74.28 ± 21.08	79.31 ± 25.74	<0.001
ALB (U/L)	44.15 ± 2.75	44.49 ± 2.73	44.70 ± 2.78	44.71 ± 2.79	<0.001
GLB (g/L)	29.01 ± 3.99	29.35 ± 3.97	29.39 ± 3.82	29.45 ± 4.07	<0.001
TB (umol/L)	10.90 (8.30-14.10)	11.02 (8.40-14.30)	11.70 (8.91-14.90)	11.80 (9.20-15.20)	<0.001
DBIL (umol/L)	2.00 (1.40-2.75)	2.02 (1.44-2.78)	2.10 (1.50-2.80)	2.08 (1.44-2.83)	0.211
BUN (mmol/L)	4.34 ± 1.39	4.51 ± 1.33	4.67 ± 1.33	4.77 ± 1.55	<0.001
Cr (umol/L)	74.30 ± 18.51	80.15 ± 19.96	86.74 ± 20.85	90.12 ± 34.70	<0.001
UA (umol//L)	240.63 ± 78.66	273.12 ± 83.65	303.91 ± 79.35	339.09 ± 84.52	<0.001
FBG (mmol/L)	5.02 ± 0.54	5.13 ± 0.68	5.24 ± 0.83	5.39 ± 1.06	<0.001

Continuous data are expressed as mean ± SD or median (interquartile range). Categorical data are expressed as n (%).

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; DBIL, Direct Bilirubin; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, γ-glutamyl transpeptidase; GLB, globulin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TB, total bilirubin; TC, total cholesterol; TG, triglyceride; UA, uric acid.

Table 2. The results of univariate COX regression

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; DBIL, Direct Bilirubin; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, γ-glutamyl transpeptidase; GLB, globulin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TB, total bilirubin; TC, total cholesterol; TG, triglyceride; UA, uric acid.

Table 3 Relationship between GGT and the incident NAFLD in different models

Crude model: we did not adjust other covariants.

Model I: we adjust age, gender, BMI, SBP, DBP

Model II: we adjust age, gender, BMI, SBP, DBP, TC, TG, HDL-C, LDL-C, ALT, AST, ALP, ALB, GLB, TB, DBIL, BUN, Cr, UA, FBG.

GAM: All covariates listed in Model II were adjusted. However, continuous covariates were adjusted as non-linearity.

CI, confidence; GGT, γ-glutamyl transpeptidase; HR, hazard ratio; Ref, reference.

Table 4 The result of two-piecewise linear regression model

	Statistics	HR（95%CI）	*P*-value
Age, years	43.26 ± 14.94	1.01 (1.00, 1.01)	<0.001
Gender -n (%)		0.2083	
Female	5395 (45.31%)	Ref	
Male	6511 (54.69%)	1.06 (0.97, 1.15)	
BMI (kg/m2)	21.60 ± 2.04	1.68 (1.63, 1.73)	<0.001
SBP (mmHg)	122.22 ± 16.88	1.01 (1.01, 1.02)	<0.001
DBP (mmHg)	73.67 ± 10.33	1.03 (1.03, 1.04)	<0.001
TC (mmol/L)	4.60 ± 0.74	1.28 (1.22, 1.35)	<0.001
TG (mmol/L)	1.36 ± 0.92	1.19 (1.17, 1.20)	<0.001
HDL-c (mmol/L)	1.45 ± 0.36	0.27 (0.23, 0.31)	<0.001
LDL-c (mmol/L)	2.27 ± 0.47	1.78 (1.61, 1.97)	<0.001
ALT (U/L)	19.59 ± 15.49	1.01 (1.01, 1.01)	<0.001
AST (U/L)	22.72 ± 8.78	1.01 (1.01, 1.01)	<0.001
ALP(mmol/L)	71.80 ± 22.14	1.01 (1.01, 1.01)	<0.001
ALB (U/L)	44.54 ± 2.77	0.99 (0.98, 1.01)	0.4209
GLB (g/L)	29.32 ± 3.96	1.02 (1.01, 1.03)	<0.001
TB (umol/L)	12.04 ± 5.07	0.99 (0.99, 1.00)	0.1830
DBIL (umol/L)	2.22 ± 1.17	0.68 (0.65, 0.71)	0.437
BUN(mmol/L)	4.58 ± 1.41	0.88 (0.85, 0.91)	<0.001
Cr (umol/L)	83.37 ± 25.16	1.00 (1.00, 1.00)	<0.001
UA (umol//L)	292.00 ± 88.80	1.00 (1.00, 1.00)	<0.001
FBG (mmol/L)	5.21 ± 0.82	1.22 (1.19, 1.25)	<0.001

We adjusted age, gender, BMI, SBP, DBP, TC, TG, HDL-C, LDL-C, ALT, AST, ALP, ALB, GLB, TB, DBIL, BUN, Cr, UA, FBG.

CI, Confidence interval; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; GGT, γ-glutamyl transpeptidase;

Table 5 Effect size of GGT on NAFLD in prespecified and exploratory subgroups

Variable	Crude model (HR, 95%CI, *P*)	Model I (HR, 95% CI, *P*)	Model II (HR, 95% CI, *P*)	GAM (HR, 95% CI, *P*)
GGT	1.020(1.018-1.022)□ 0.001	1.013 (1.011, 1.015) □0.001	1.010 (1.007, 1.012)□0.001	1.004 (1.002, 1.007) □0.001
GGT (quartile)				
Q1	Ref	Ref	Ref	Ref
Q2	2.176 (1.717, 2.757)□0.001	1.809 (1.427, 2.293)	1.661 (1.308, 2.108)□0.001	1.402 (1.100, 1.785) □0.001
Q3	5.066 (4.075, 6.298)□0.001	3.335 (2.678, 4.154)	2.888 (2.310, 3.609)□0.001	2.103 (1.671, 2.648) □0.001
Q4	8.202 (6.625, 10.156)□0.001	4.548 (3.661, 5.650)	3.653 (2.915, 4.579)□0.001	2.347 (1.853, 2.973)□0.001
P for trend	<0.001	<0.001	<0.001	<0.001

Incident NAFLD	HR (95% CI)	*P*
Fitting model by standard linear regression	1.010□1.007-1.012□	□0.001
Fitting model by two-piecewise linear regression		
Inflection point of GGT		
≤26U/L	1.104□1.089-1.120□	□0.001
>26U/L	1.001□0.999-1.004□	0.3640
P for log likelihood ratio test	□0.001	

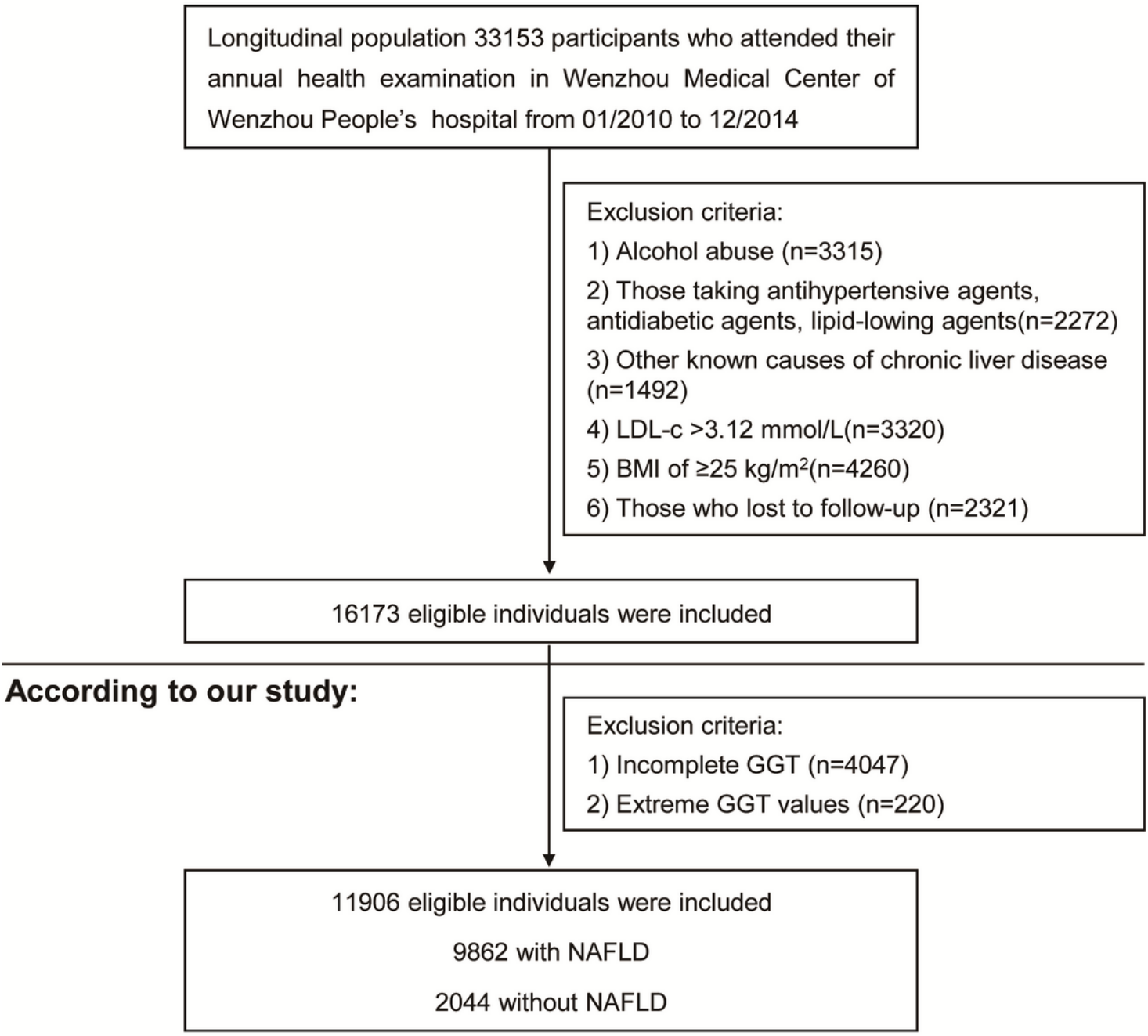
Characteristic	No of participants	HR (95%CI)	*P* value	*P* for interacion
Age, years			0.5082	
< 30	2251	1.005 (0.999, 1.010)	0.1221	
30 to < 40	3549	1.010 (1.006, 1.014)	<0.001	
40 to < 50	2700	1.011 (1.006, 1.016)	<0.001	
50 to < 60	1570	1.009 (1.003, 1.015)	0.003	
60 to < 70	826	1.005 (0.996, 1.014)	0.272	
≥70	1010	1.010 (1.003, 1.018)	0.009	
Gender			0.2162	
Female	5395	1.008(1.005-1.011)	<0.001	
Male	6511	1.011(1.008-1.013)	<0.001	
BMI (kg/m2)			0.1886	
< 18.5	942	1.038 (0.932, 1.155)	0.499	
≥ 18.5, < 24	9377	1.013 (1.010, 1.015)	<0.001	
≥ 24	1587	1.009 (1.005, 1.012)	<0.001	
SBP (mmHg)			0.9399	
< 140	10188	1.009(1.007-1.012)	<0.001	
≥ 140	1718	1.010(1.005-1.014)	<0.001	
DBP (mmHg)			0.7567	
< 90	10941	1.010(1.007-1.012)	<0.001	
≥ 90	965	1.010(1.005-1.016)	<0.001	
HDL-c (mmol/L)				0.6828
1	1014	1.007 (1.001, 1.013)	0.0179	
≥1	10892	1.009 (1.006, 1.011)	<0.001	
ALT (U/L)				0.0011
≤40	11314	1.012 (1.010, 1.015)	<0.001	
40	592	1.003 (0.998, 1.008)	0.1828	
Cr (mmol/L)				0.0769
< 82	5919	1.007 (1.003, 1.010)	<0.001	

Note 1: Above model adjusted for age, gender, BMI, SBP, DBP, , TC,

≥ 82	5987	1.011 (1.008, 1.014)	<0.001	
UA (umol//L)				0.3937
420	10962	1.010 (1.008, 1.012)	<0.001	
≥420	944	1.007 (1.002, 1.013)	0.007	
FBG (mmol/L)				0.2557
6.1	11074	1.010 (1.008, 1.013)	<0.001	
≥6.1	832	1.007 (1.002, 1.012)	0.009	

TG, HDL-C, LDL-C, ALT, AST, ALP, ALB, GLB, TB, DBIL, BUN, Cr, UA, FBG. Note 2: In each case, the model is not adjusted for the stratification variable.

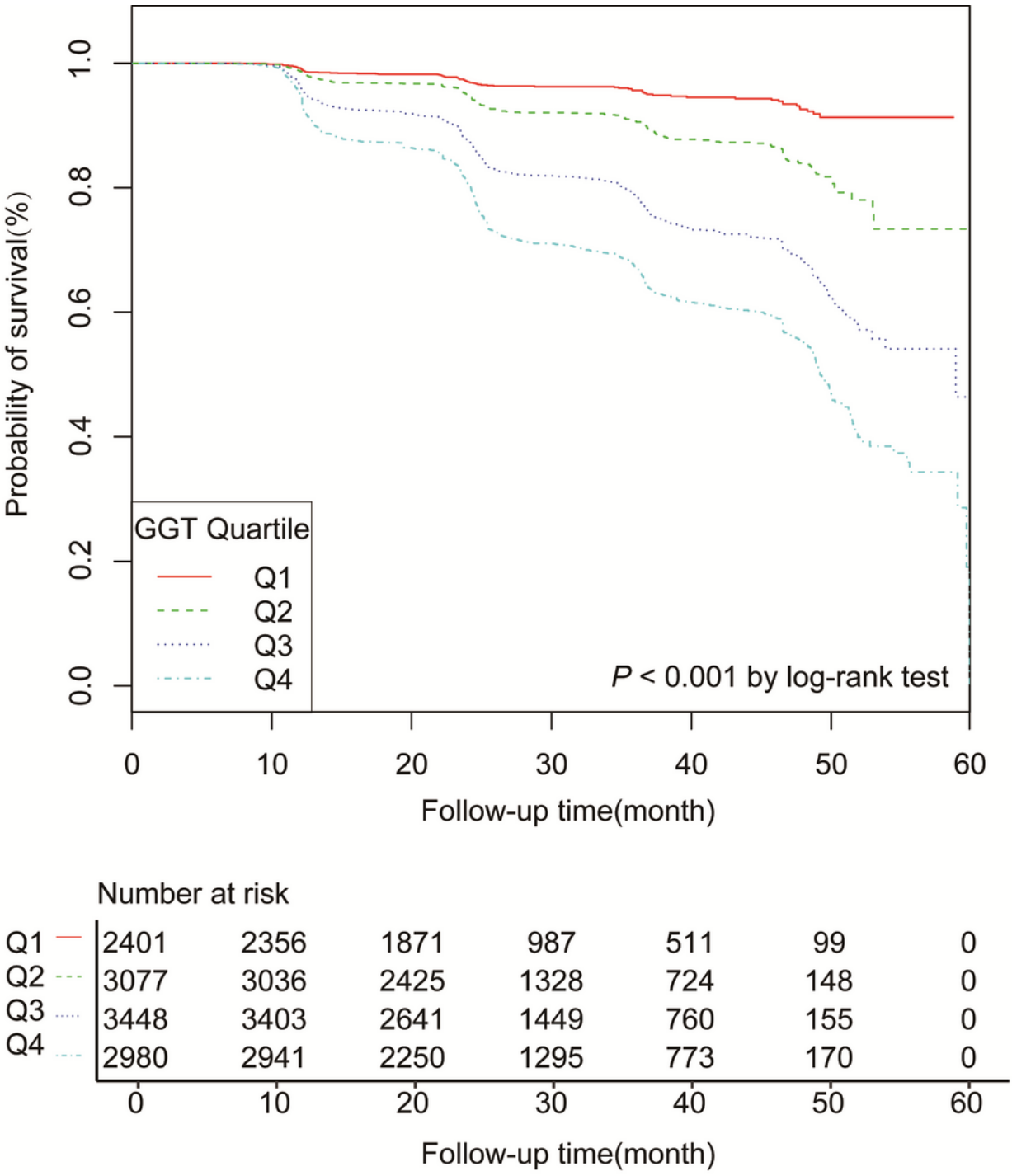
Figures



Study design and participant flow

Figure 1

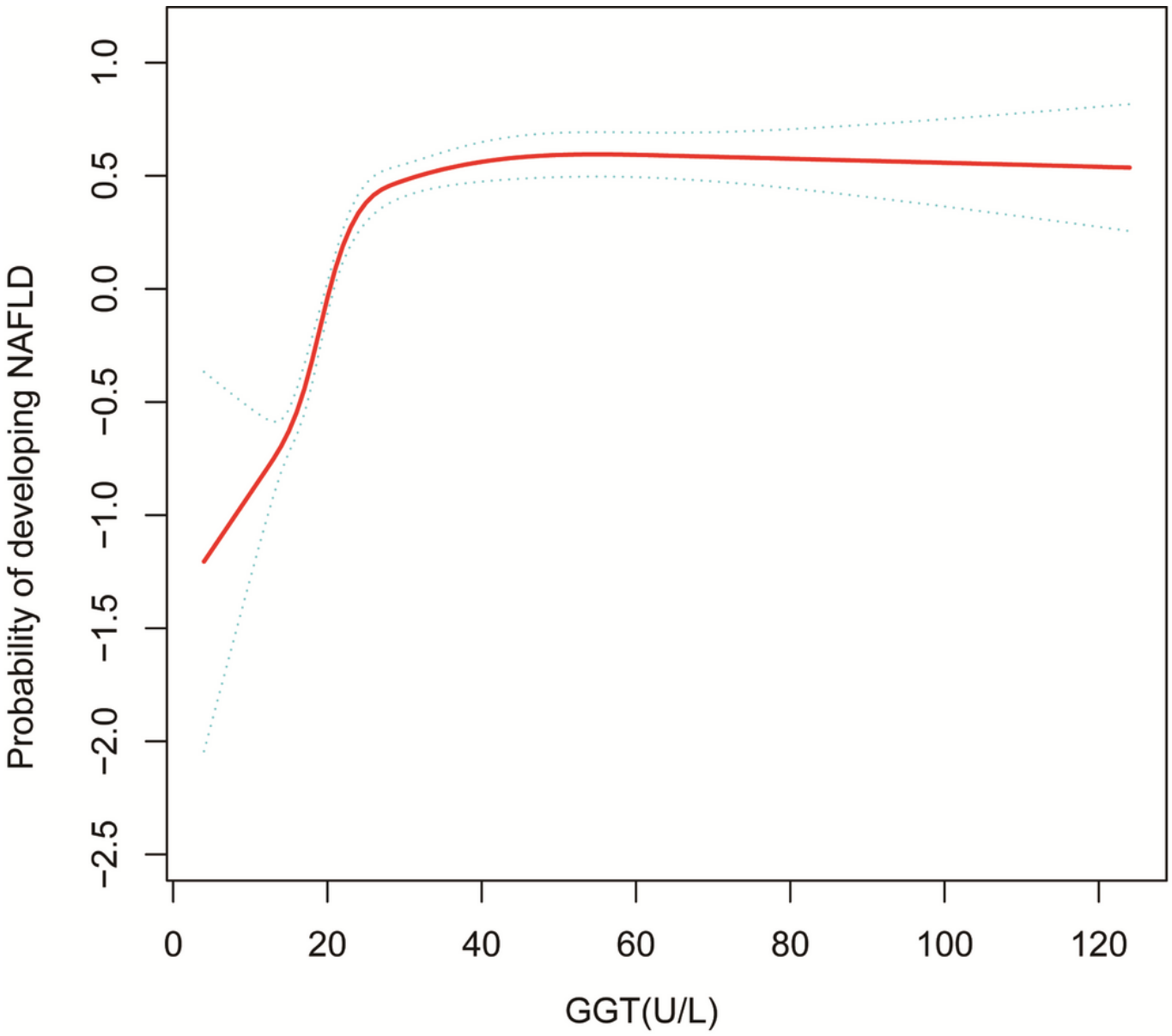
See image above for figure legend.



Kaplan–Meier event-free survival curve. Kaplan–Meier analysis of incident NAFLD based on GGT quartiles

Figure 2

See image above for figure legend.



Association of GGT with the risk of NAFLD

The non-linear relationship between GGT and incident of NAFLD. A non-linear relationship between them was detected after adjusting for age, gender, BMI, SBP, DBP, TC, TG, HDL-C, LDL-C, ALT, AST, ALP, ALB, GLB, TB, DBIL, BUN, Cr, UA, FBG.

Figure 3

See image above for figure legend.