

Higher fatty liver index is associated with increased risk of new onset heart failure in healthy adults: A nationwide population-based study in Korea

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Abstract

Background Heart failure (HF) is relatively common cardiovascular disease with high mortality and morbidity. Although it is associated with many cardiovascular risk factors, the association between nonalcoholic fatty liver disease (NAFLD), the most common chronic liver disease, and HF has not been evaluated in a large-scale cohort study. Thus, we evaluated the ability of the fatty liver Index (FLI), a surrogate marker of NAFLD, to predict the development of HF in healthy individuals.

Methods We evaluated 308,578 healthy persons without comorbidities who underwent the National Health check-ups in the republic of Korea from 2009 to 2014. The association between the FLI and HF was analyzed using multivariate Cox proportional-hazards models.

Results During a median of 5.4 years' follow-up, 2,532 subjects (0.8%) were newly diagnosed with HF. Subjects were categorized into quartile groups according to FLI (Q1, 0-4.9; Q2, 5.0-12.5; Q3, 12.6-31.0; and Q4, >31.0). The cumulative incidence of HF was significantly higher in subjects with the highest FLI than in those with the lowest FLI (Q1, 307 [0.4%] and Q4, 890 [1.2%]; $P < 0.001$). Adjusted hazard ratios (HRs) indicated that the highest FLI was independently associated with an increased risk for HF (HR between Q4 and Q1, 2.709; 95% confidence interval=2.380-3.085; $P < 0.001$). FLI was significantly associated with increased risk of new-onset HF regardless of their baseline characteristics.

Conclusions Higher FLI was independently associated with increased risk of HF in healthy Korean population.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease. Its estimated prevalence is 15-30% in general population [1]. The prevalence of NAFLD has been increasing along with an increased incidence of obesity, insulin resistance, and non-insulin dependent diabetes, and metabolic syndrome [2]. NAFLD can be found in 60-70% among obese or diabetic patients [1]. Many previous studies reported a positive association between NAFLD and established cardiovascular risk factors, including abdominal obesity, dyslipidemia, insulin resistance, and hypertension [3]. These cardiovascular risk factors are also components of metabolic syndrome. NAFLD is regarded as the hepatic manifestation of metabolic syndrome. In patients with NAFLD, cardiovascular disease is the third most common cause of death after extrahepatic malignancies and liver-related complications [4, 5].

Heart failure (HF) is one of the major cardiovascular diseases with high morbidity, mortality, which exerts a high cost on healthcare systems globally [6, 7]. The prevalence of HF is approximately 1–2% in the adult population in developed countries, and its increasing prevalence is more than 10% among people over 70 years of age [6, 8]. HF and NAFLD often coexist due to their common risk factors and similar pathophysiological processes [9, 10]. HF alone may cause liver disease and vice versa in the absence of other cardiovascular risk factors [10].

Several previous studies with a small sample size on co-existing NAFLD and HF [11, 12] reported a simple association in cross-sectional analysis. In this study, a large cohort of healthy Korean adults without known cardiovascular risk factors and co-morbidities was analyzed to evaluate the association between NAFLD and new-onset HF.

Methods

Data sources

The National Health Insurance Service-National Sample Cohort 2.0 (NHIS-NSC 2.0) data set, which comprises more than 97% of Korean citizens affiliated with the obligatory public health insurance program of the National Insurance Health Service (NIHS) was analyzed for this study. The total population ($n=48,222,537$) was classified into 2,142 groups according to their age, sex, residing cities, eligible status, and income levels. From each stratum, randomly selected 2.1% individuals ($n=1,021,208$) in the year of 2006 were included in NHIS-NSC 2.0 data. In addition, retrospective and prospective follow-up data collected from 2002 to 2015 were included in the data set [13]. The individuals included in NHIS-NSC 2.0 are representative of the entire Korean population.

The cohort data was composed of four data sets: (1) sociodemographics; (2) medical claims including information on diagnosis based on the 10th revision of the International Classification of Disease (ICD-10) codes, admission, and treatment; (3) the results of the National Health Screening; (4) information on the medical institutions. The Korean national health check-ups comprise of the questionnaires on medical history and health-related behaviors such as smoking and alcohol consumption, chest X-rays, physical examinations, and blood tests. About 72.1% of the eligible population had completed the National Health screening programs, according to the 2013 NHIS statistics [13]. The cohort data also included mortality statistics from the death registration database of Statistics Korea.

The study protocol was approved by the NHIS review committee for accessing NHIS-NSC 2.0 data and also approved by the Institutional Review Board of the Chungnam National University Hospital in Daejeon, Korea (IRB No. 2019-10-053). The board waived the requirement for informed consent, for NHIS-NSC 2.0 data was public.

Study population

Study subjects were any Korean citizens who had completed the National Health check-up at least once from 2009 to 2014. Data from the first check-up was defined as the index data, and the year when the index check-up was done was the index year. Subjects with age \geq 20 years old were included, whereas subjects meeting the pre-specified exclusion criteria were excluded. All subjects previously diagnosed with HF were excluded for the purpose of the study. Other exclusion criteria were comorbid conditions that could affect the onset of HF, including hypertension, diabetes, atrial fibrillation, cerebrovascular disease, ischemic heart disease, peripheral vascular disease, valvular heart disease, chronic kidney disease, and chronic pulmonary disease. Subjects on prescribed medications such as oral hypoglycemic agents, antihypertensives, or lipid-lowering drugs within one year before the index check-up, subjects with hypertension (systolic blood pressure \geq 140mmHg or diastolic blood pressure \geq 90mmHg), and subjects with elevated fasting blood glucose \geq 126mg/dL at the index check-up were excluded. Subjects with risk factors that could affect the FLI, such as liver disease and autoimmune disease diagnosed before the index year, were excluded. Finally, those with any missing data in the index check-up were also excluded.

Definition of HF

The primary outcome of this study was HF incidence in relation to the FLI. The incidence of HF was defined as the first HF occurrence documented on the medical record at least two separate days of outpatient visits and admission, or one-time record of death due to heart failure. The diagnosis of HF was screened in data from questionnaires and the 1-year medical claim data before the index year. The presence of HF was defined using the following ICD-10 codes in the medical claim dataset: "Hypertensive heart disease with HF" (I10.0), "Hypertensive heart disease with hypertensive kidney disease with HF" (I13.0), "Hypertensive heart disease with hypertensive kidney disease with HF and kidney failure" (I13.2), "Ischemic cardiomyopathy" (I25.5), "Dilated cardiomyopathy" (I42.0), "Cardiomyopathy, unspecified" (I42.9), "Cardiomyopathy in diseases classified elsewhere" (I43), "HF" (I50) including "Congestive HF" (I50.0), "Left ventricular failure" (I50.1), and "HF, unspecified" (I50.9).

Definition/Ascertainment of covariates

Body mass index (BMI) was weight (kg) over height (m)-squared. The population with a BMI of \geq 25 kg/m² was regarded as obese according to the World Health Organization guideline for the Asian population [14]. Smoking status was classified into three categories: non-smoker, ex-smoker, and current smoker. Alcohol consumption and physical activity were reported using standard self-reporting questionnaires. The total amount of alcohol consumption was calculated by multiplying the number of days per week of drinking and the amount of alcohol consumed per day. Levels of physical activity were estimated by summing up the intensity levels of workout in METs multiplied by the number of days per week of each intensity level : (1) 30-min of light exercise (2 METs); (2) 30-min of moderate exercise (3 METs); (3) 20-min of vigorous exercise (6 METs).

Blood samples were analyzed in a number of qualified institutions, which were annually audited by the Korean Association of External Quality Assessment Service. Data were reviewed at the time of HF occurrence, disqualification of the NHIS (death or immigration), or the end of the study (December 31th, 2015).

Calculation of the fatty liver index

The FLI is a well-validated surrogate marker for identifying patients with NAFLD [13]. The FLI was calculated with triglycerides (TG), BMI, gamma-glutamyl transferase (GGT), and waist circumference (WC) with the following equation:

$$FLI = (e^{0.953 \cdot \log_e (TG) + 0.139 \cdot BMI + 0.718 \cdot \log_e (GGT) + 0.053 \cdot WC - 15.745}) / (1 + e^{0.953 \cdot \log_e (TG) + 0.139 \cdot BMI + 0.718 \cdot \log_e (GGT) + 0.053 \cdot WC - 15.745}) \cdot 100$$

The original study on the FLI used 60 as the cutoff value, and the FLIs higher than 60 indicated fatty liver with a positive likelihood ratio of 4.3 in the general population [15]. Although the FLI is simple to calculate and easy to screen fatty liver disease, there has been insufficient

evidence to use the same value in Asians because of lower BMI and WC than other ethnic populations [16]. In this study, instead of using the absolute value of the calculated FLI, subjects were grouped into quartiles according to their FLI range, and each quartile group was used in the statistical analysis to determine the relationship between FLI and new-onset HF.

Statistical analysis

Continuous variables were used as mean \pm standard deviation and categorical parameters as the numbers with a percentage. All statistical analyses were performed using R software version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). Statistical differences between the FLI quartiles were estimated using the Chi-square test and one-way analysis of variance tests. Cumulative event rates of the FLI quartiles were calculated with the Kaplan-Meier method and compared with each other using a log-rank test. Adjusted hazard ratios (HR) and 95% confidence interval (CI) for HF incidence were estimated using Cox proportional hazard regression analysis. In the multivariate analysis, age and sex were adjusted in Model 1. In Model 2, clinical characteristics associated with new-onset HF of borderline statistical significance ($P < 0.100$) were adjusted in addition to age and sex. Confounding factors, such as hypertension and diabetes, were excluded because of their strong association with NAFLD. Using NAFLD with other risk factors in a multivariate model raises the possibility of introducing multicollinearity into the model. The variance inflation factor (VIF) in all models (Supplementary Table 1) was examined, and VIF levels were less than 10, which resolved the multicollinearity. P-values of < 0.05 were considered statistically significant.

Results

Baseline characteristics of the participants

A total of 308,578 subjects were analyzed after excluding 248,306 subjects who met the exclusion criteria. The number of subjects matching each exclusion criteria was presented in Figure 1. Study population was divided into four groups according to their FLI quartile values; first quartile (Q1) of the FLI = 0 - 4.9; second quartile (Q2) of the FLI = 5.0 - 12.5; third quartile (Q3) of the FLI = 12.6 - 31.0; and fourth quartile (Q4) of the FLI > 31.0 . The comparisons of baseline clinical characteristics and laboratory findings according to the FLI quartiles were summarized in Table 1. The subjects with higher FLIs had a trend toward older ages and a higher proportion of males.

Numbers of subjects with high BMI, high waist circumference, hypertension, and a heavier amount of alcohol consumption, and a proportion of current smokers tended to increase from Q1 to Q4. Serum levels of fasting glucose, total cholesterol, triglyceride, and LDL cholesterol were increasing from Q1 to Q4.

Association between FLI and the incidence of HF

The median follow-up duration was 5.4 years (interquartile range: 4.1 - 6.3 years), and 2,532 subjects (0.8%) had new-onset HF. Table 2 shows the result of the univariate analysis of new-onset HF. Male gender, older age, higher BMI, higher total cholesterol, higher TG, and lower HDL cholesterol levels were significantly associated with new-onset HF. Cumulative incidences of new-onset HF, by the FLI quartiles, were presented in Figure 2. The incidence of new-onset HF was significantly higher in subjects with higher FLIs, compared to those with lower FLIs (Q1, 307 [0.4%]; Q2, 543 [0.7%]; Q3, 792 [1.0%]; and Q4, 890 [1.2%], $P < 0.001$ by the Log-rank test). In the multivariate models, the model 1 was adjusted for age, and the model 2 was for clinical characteristics with borderline statistical significance in addition to age and sex; the association between the FLI quartile and HF incidence remained statistically significant in each model in the time-dependent Cox proportional hazard analysis (Table 3). Drawn from the previous studies, specific ranges of the FLI cutoff values were used to categorize the study population ($0 \leq \text{FLI} < 30$, $30 \leq \text{FLI} < 60$, and $\text{FLI} \geq 60$, by Bedogni et al. [13]; $0 \leq \text{FLI} < 25$, $25 \leq \text{FLI} < 35$, and $\text{FLI} \geq 35$ for male, $0 \leq \text{FLI} < 10$, $10 \leq \text{FLI} < 20$, and $\text{FLI} \geq 20$ for female, by Yang et al. [15]). Regardless of the FLI ranges, a group with the highest FLI had the highest risk for new-onset HF (Supplementary Table 1).

Subgroup analysis

The adjusted HRs of subgroups were summarized in Figure 3. The FLI was a significant determinant of new-onset HF in all subgroups evaluated (Figure 3).

Discussion

This study showed that a higher FLI was associated with an increased risk of new-onset HF in the healthy Korean adult population. Multivariate models were adopted to control several confounding factors such as hypertension and diabetes, which are well-known risk factors for HF. A more direct association between NAFLD and HF was evaluated by excluding hypertension and diabetes from the multivariate models, and the association was found in most subgroups.

The association between fatty liver and HF has been observed in several studies [11, 12]. Mildly elevated serum GGT level in the absence of excessive alcohol consumption was found to be a long-term, independent predictor of incident HF in large population-based observational studies [18-20]. Zhang et al. reported that 37 patients had NAFLD among 102 patients with HF with reduced ejection fraction (HFrEF) (36.3%) screened with ultrasonography [12]. In the Framingham study, a high borderline level of GGT, even within the normal range, was associated with an increased risk of HF by 1.71 times (95% CI=1.21-2.41), compared to less than median levels of GGT [18]. The use of GGT levels improved risk re-classification modestly (net reclassification index, 5.7%; P=0.01) in the HF prediction [18]. In a prospective cohort study in Finland, including 18,353 men and 19,726 women of 25-74 years of age, moderate to high levels of serum GGT (from the 50th to the 90th percentiles) were significantly associated with the incidence of HF. The predictive power of serum GGT in association with HF was stronger in participants aged less than 60 years [20].

The presence of NAFLD was associated with higher BMI, higher left ventricular (LV) mass index, and more severe LV fibrosis [12]. Other studies showed that patients with NAFLD had increased LV wall thickness and varying degrees of subclinical LV systolic or diastolic dysfunction [21, 22]. Increased LV wall thickness and fibrosis are markers of LV diastolic dysfunction regardless of symptoms. Jung et al. showed that groups with mild and moderate to severe NAFLD had a higher risk of abnormal LV relaxation compared to normal controls [21]. In cohort study of 20,821 healthy Korean adults, odds ratios for abnormal LV relaxation (mild group: 1.29 [95% CI of 1.15 - 1.46]; moderate to severe group: 1.95 [95% CI of 1.61 - 2.35]) and odds ratios for relative wall thickness greater than 0.42cm (mild group: 1.26 [95% CI of 1.05 - 1.52]; moderate to severe group: 1.46 [95% CI of 1.08 - 1.95]) both increased.

The proposed mechanisms of increased LV wall thickness include insulin resistance [23], increased activity of the renin-angiotensin-aldosterone system (RAAS) [24], and endothelial dysfunction and inflammation [11]. Insulin resistance may contribute to the development of LV hypertrophy and HF through increased renal sodium retention and activation of the sympathetic nervous system [25, 26]. Increased activity of the sympathetic nervous system can also accelerate the process of hepatic fibrosis [27]. Mediators of the RAAS, especially angiotensin II and aldosterone, play important roles in the development of hypertension and HF. Angiotensin II can also be expressed by activated human hepatic stellate cells [24]. Activated RAAS causes hepatic injury and induces fibrosis through angiotensin II-mediated stimulation of fibroblast proliferation and release of inflammatory cytokines [28]. Endothelial dysfunction, in part of the inflammatory process, can increase arterial stiffness and LV afterload through increased vascular tone, sympathetic overactivity, and sodium retention [29]. Inflammation can promote coronary atherosclerosis and increase the risk for cardiomyopathy and conduction abnormalities [11]. Inflammatory mediators also affect the progression of fatty liver disease via impaired fatty acid oxidation, increased oxidative stress, and local inflammation [30].

NAFLD was associated with poor prognosis in chronic and acute HF patients [31, 32]. Although the exact mechanism of this remains unclear, there are several proposed explanations; increased coronary atherosclerosis, LV hypertrophy and dysfunction, and aortic valve calcification [33-35]. Because the liver plays an important role in regulating antioxidant and anti-inflammatory processes [36], hepatic dysfunction can aggravate chronic inflammation and oxidative tissue injury in HF patients [37]. These impaired immunological processes through the hepatic injury may further deteriorate the prognosis of HF patients [38].

Limitations

This study has several limitations. First, the accuracy of HF diagnosis was not validated in this study. The records of medical claims and the National Health Screening data were used for identifying HF patients, and the incidence of new-onset HF was estimated only using the NHIS-NSC 2.0 data based on the ICD-10 code. If the information on echocardiographic imaging and serum biomarkers, including B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide, were available, the diagnosis of HF would have been more accurate. Further studies are needed to identify HF patients more accurately when using national health insurance data. Second, this study is observational and could not identify other contributable factors in the development of HF in relation to fatty liver. Third, 45% of the participants in the cohort were excluded due to their comorbidities, and this could affect the representativeness and generalizability of the findings. Finally, this study included only Koreans, and caution should be taken in extrapolating the study's conclusion to other ethnic populations.

Conclusions

In the healthy Korean population, higher FLI was independently associated with increased risk for new-onset HF.

Clinical perspectives

Identification of increased HF risk may have important public health implications because the management of metabolic syndrome and prevention of HF are important in reducing cardiovascular morbidity and mortality. Further studies are needed to document the effect of management of NAFLD, not only on the risk of new-onset HF but also on the risk reduction of cardiovascular morbidity and mortality.

Declarations

Ethics approval and consent to participate

Institutional Review Board of Chungnam National University Hospital approved this study protocol (IRB No. 2019-10-053). Our IRB waived the requirement for informed consent.

Consent for publication

Not applicable

Availability of data and material

The datasets used and analyzed during the present study are available from the National Health Insurance Service. It can be used after the acquisition of the right to use this data.

Competing interests

None. The authors have nothing to declare.

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AUTHOR CONTRIBUTIONS

RJH and PJH: study conception and design, acquisition of data, interpretation of data, drafting of the manuscript, and critical revision; LHB: acquisition of data, analysis and interpretation of data; and YYH, KMS, KYG, PGM, LJH, and SIW: interpretation of data, and critical revision.

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Tables

Table 1. Baseline characteristics and laboratory findings.

	FLI quartile				P-value	P for trend
	Q1	Q2	Q3	Q4		
Baseline characteristics						
Age, years	36.7±11.4	41.9±12.4	44.0±12.4	43.1±11.3	<0.001	<0.001
Male sex (%)	12,102(15.7)	30,737(39.8)	46,692(60.5)	62,507(81.0)	<0.001	<0.001
Height, cm	161.4±7.2	163.4±8.9	165.6±9.3	168.8±8.4	<0.001	<0.001
Weight, Kg	52.2±6.1	59.1±7.3	65.4±8.3	75.0±10.4	<0.001	<0.001
BMI, Kg/m ²	20.0±1.7	22.1±1.8	23.8±2.1	26.3±2.8	<0.001	<0.001
Waist circumference, cm	67.9±4.9	74.9±4.8	80.5±5.1	87.6±6.5	<0.001	<0.001
WHR, %	0.3±0.0	0.4±0.0	0.4±0.0	0.4±0.1	<0.001	<0.001
SBP, mmHg	111.0±11.1	115.4±11.1	118.6±10.6	121.8±10.0	<0.001	<0.001
DBP, mmHg	69.4±8.0	72.0±7.9	74.0±7.6	76.3±7.1	<0.001	<0.001
Smoking					<0.001	<0.001
Non-smoker	65,184(84.5)	53,779(69.7)	42,729(55.4)	28,355(36.8)		
Ex-smoker	3,609(4.7)	6,720(8.7)	10,711(13.9)	14,058(18.2)		
Current-smoker	8,350(10.8)	16,638(21.6)	23,713(30.7)	34,732(45.0)		
Alcohol consumption						
Amount, g/week	31.6±77.4	49.5±102.2	73.9±129.6	122.5±174.0	<0.001	<0.001
Activity, MET-min/week	346.7±350.8	379.7±382.7	388.8±388.1	374.6±373.4	<0.001	<0.001
Laboratory findings						
AST, IU/L	19.8±8.0	21.7±12.4	23.7±16.7	29.4±33.0	<0.001	<0.001
ALT, IU/L	14.5±8.9	17.9±12.2	22.9±22.2	36.3±50.5	<0.001	<0.001
GGT, IU/L	14.2±5.6	19.1±9.9	28.1±20.3	60.3±62.4	<0.001	<0.001
Hemoglobin, g/dL	13.0±1.4	13.6±1.6	14.2±1.6	14.9±1.4	<0.001	<0.001
Fasting glucose, mg/dL	87.9±9.5	90.3±10.2	92.2±10.7	94.8±11.4	<0.001	<0.001
Total cholesterol, mg/dL	176.9±33.6	187.1±35.9	196.2±39.3	207.0±40.7	<0.001	<0.001
Triglyceride, mg/dL	62.6±22.5	88.0±34.0	119.9±53.6	197.6±132.6	<0.001	<0.001
HDL cholesterol, mg/dL	64.1±24.8	59.3±19.9	55.5±25.8	51.7±32.0	<0.001	<0.001
LDL cholesterol, mg/dL	109.4±257.2	113.6±143.5	121.2±134.2	122.6±129.0	<0.001	<0.001
Creatinine, mg/dL	0.9±1.0	1.0±1.1	1.0±1.1	1.1±1.2	<0.001	<0.001
GFR, mL/min/1.73m ²	90.2±27.9	90.3±28.0	92.6±29.4	99.7±30.2	<0.001	<0.001

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, DBP: diastolic blood pressure, GFR: glomerular filtration rate, GGT: gamma-glutamyl transferase, HDL: high-density lipoprotein, LDL: low-density lipoprotein, SBP: systolic blood pressure, WHR: waist-hip ratio

Table 2. The Univariate analysis of new-onset heart failure.

Characteristics	Value	N	HF (%)	HR	95% CI		P-value
					Lower	Upper	
Total	Total	308,578	2,532(0.8)				
Sex	Female	156,540	1,263(0.8)		Reference		
	Male	152,038	1,269(0.8)	1.113	1.030	1.204	0.007
Age, year	20-34	99,774	119(0.1)		Reference		
	35-49	130,099	637(0.5)	3.908	3.213	4.753	<0.001
	50-64	65,907	1,067(1.6)	12.536	10.371	15.153	<0.001
	65-74	10,374	497(4.8)	35.791	29.298	43.722	<0.001
	≥75	2,424	212(8.7)	75.652	60.429	94.711	<0.001
	Continuous			1.087	1.084	1.090	<0.001
	BMI, Kg/m ²	<18.5	16,662	101(0.6)	1.075	0.870	1.328
18.5-19.9		33,181	177(0.5)	0.929	0.786	1.098	0.390
20-22.4		89,515	625(0.7)		Reference		
22.5-24.9		90,961	814(0.9)	1.115	1.005	1.238	0.041
≥25		78,259	815(1.0)	1.417	1.276	1.573	<0.001
Continuous				1.058	1.045	1.072	<0.001
Smoking		Non-smoker	190,047	1,599(0.8)		Reference	
	Ex-smoker	35,098	320(0.9)	0.934	0.812	1.074	0.340
	Current-smoker	83,433	613(0.7)	1.120	0.997	1.259	0.057
Alcohol consumption, g/week	0	149,779	1,557(1.0)		Reference		
	≤140	110,537	626(0.6)	0.882	0.798	0.975	0.014
	>140	48,262	349(0.7)	0.991	0.871	1.126	0.890
	Continuous			1.000	1.000	1.000	0.960
SBP, mmHg	<120	165,193	1,019(0.6)		Reference		
	120-139	143,385	1,513(1.1)	1.295	1.195	1.404	<0.001
	Continuous			1.013	1.010	1.017	<0.001
DBP, mmHg	<80	210,638	1,513(0.7)		Reference		
	80-89	97,940	1,019(1.0)	1.220	1.126	1.322	<0.001
	Continuous			1.016	1.011	1.022	<0.001
FBS, mg/dL	< 100	246,415	1,876(0.8)		Reference		
	100 - 125	62,163	656(1.1)	1.042	0.953	1.140	0.370
	Continuous			1.003	1.000	1.007	0.058
Activity, MET-min/week	<500	221107	1871(0.8)				
	500-999	65361	453(0.7)	0.877	0.791	0.972	0.013
	≥1000	22110	208(0.9)	0.890	0.770	1.027	0.110
	Continuous			1.000	0.999	1.000	0.210
Waist circumference, cm	Continuous			1.027	1.022	1.032	<0.001
Total cholesterol, mg/dL	Continuous			1.001	1.000	1.002	<0.001
Triglyceride, mg/dL	Continuous			1.001	1.000	1.001	<0.001
HDL-cholesterol, mg/dL	Continuous			0.997	0.995	0.999	0.014
LDL-cholesterol, mg/dL	Continuous			1.000	1.000	1.000	0.290

BMI: body mass index, CI: confidential interval, DBP: diastolic blood pressure, FBS: fasting blood glucose, HDL: high-density lipoprotein, HF: heart failure, HR: hazard ration, LDL: low-density lipoprotein, MET: the metabolic equivalent of task, SBP: systolic blood pressure

Table 3. Association between the fatty liver index and new-onset heart failure.

FLI	N.	New-onset HF	Univariate			Model 1*			Model 2†		
			HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
FLI quartile				Reference			Reference			Reference	
Q1 (0 - 4.9)	77,143	307(0.4)									
Q2 (5.0 - 12.5)	77,137	543(0.7)	1.691	1.470-1.945	<0.001	1.104	0.958-1.271	0.171	1.071	0.930-1.234	0.339
Q3 (12.6 - 31.0)	77,153	792(1.0)	2.409	2.112-2.748	<0.001	1.386	1.212-1.586	<0.001	1.314	1.147-1.504	<0.001
Q4 (> 31.0)	77,145	890(1.2)	2.709	2.380-3.085	<0.001	1.857	1.620-2.127	<0.001	1.710	1.489-1.964	<0.001

*Cox proportional hazard models including age, and sex as covariates

†Cox proportional hazard models including age, sex, smoking, amount of alcohol drinking, activity, systolic blood pressure, diastolic blood pressure, fasting blood glucose, cholesterol, and fatty liver index as covariates.

CI: confidential interval, FLI: fatty liver index, HR: hazard ratio

Supplementary Table

Supplementary Table 1. Association between the fatty liver index and new-onset heart failure.

FLI	N.	New-onset HF	Univariate			Model 1*			Model 2†		
			HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
FLI criteria 1											
0 ≤ FLI < 30	228,136	1,608(0.7)	Reference			Reference			Reference		
30 ≤ FLI < 60	54,563	614(1.1)	1.538	1.402-1.688	<0.001	1.376	1.250-1.514	<0.001	1.320	1.198-1.453	<0.001
FLI ≥ 60	25,879	310(1.2)	1.669	1.478-1.885	<0.001	1.961	1.727-2.227	<0.001	1.849	1.622-2.106	<0.001
FLI criteria 2‡											
Low probability	178,464	10,20(0.6)	Reference			Reference			Reference		
Intermediate probability	46,892	480(1.0)	1.735	1.556-1.933	<0.001	1.233	1.105-1.376	<0.001	1.196	1.072-1.334	0.001
High probability	83,222	1,032(1.2)	2.104	1.930-2.294	<0.001	1.631	1.496-1.779	<0.001	1.557	1.423-1.704	<0.001

*Cox proportional hazard models including age, and sex as covariates

†Cox proportional hazard models including age, sex, smoking, amount of alcohol consumption, physical activity, systolic blood pressure, diastolic blood pressure, fasting blood glucose, cholesterol, and the fatty liver index as covariates.

‡Low probability: 0 ≤ FLI < 25 for male, 0 ≤ FLI < 10 for female; intermediate probability: 25 ≤ FLI < 35 for male, 10 ≤ FLI < 20 for female; high probability: FLI ≥ 35 for male, FLI ≥ 20 for female

CI: confidential interval, FLI: fatty liver index, HR: hazard ratio

Figures

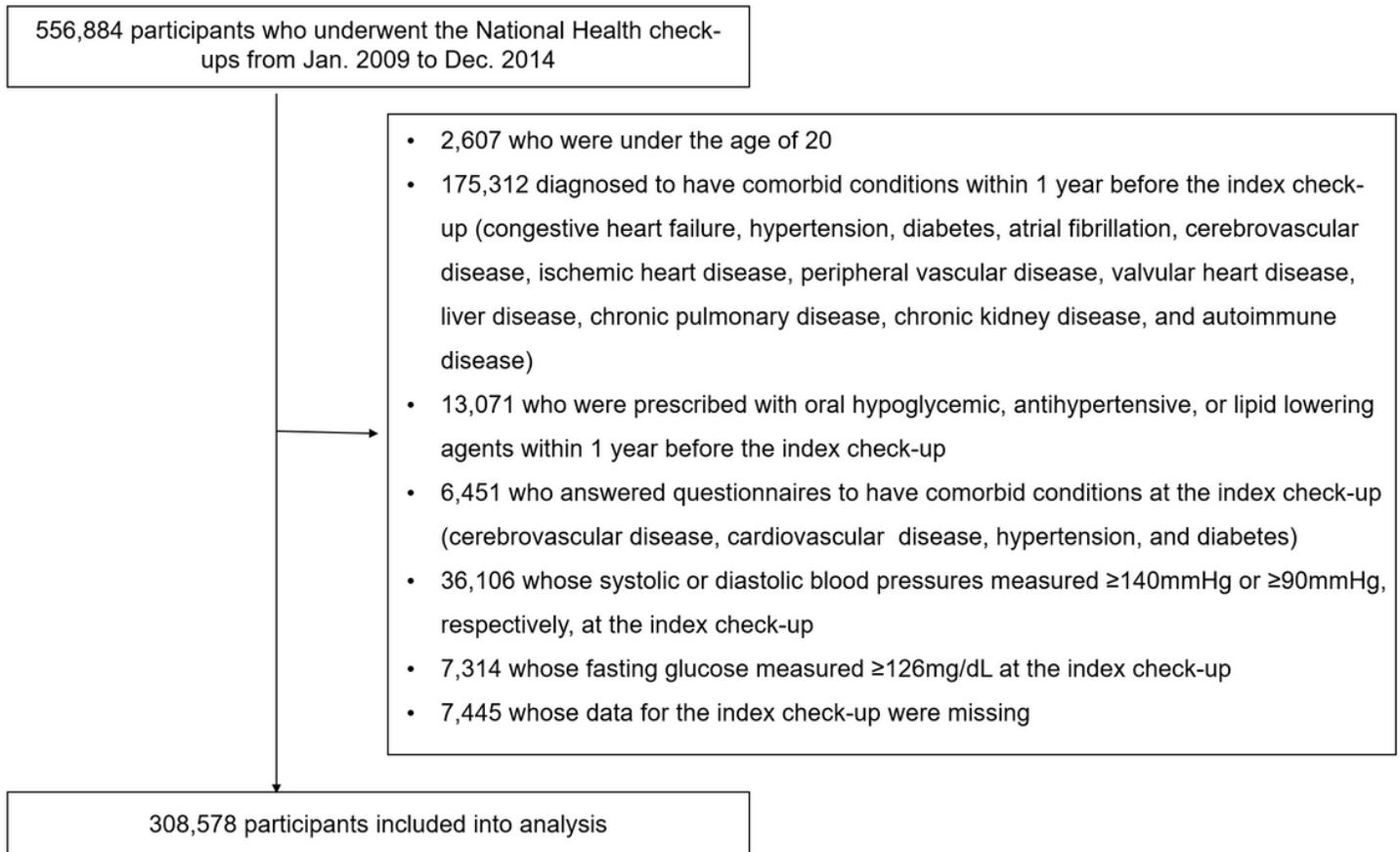
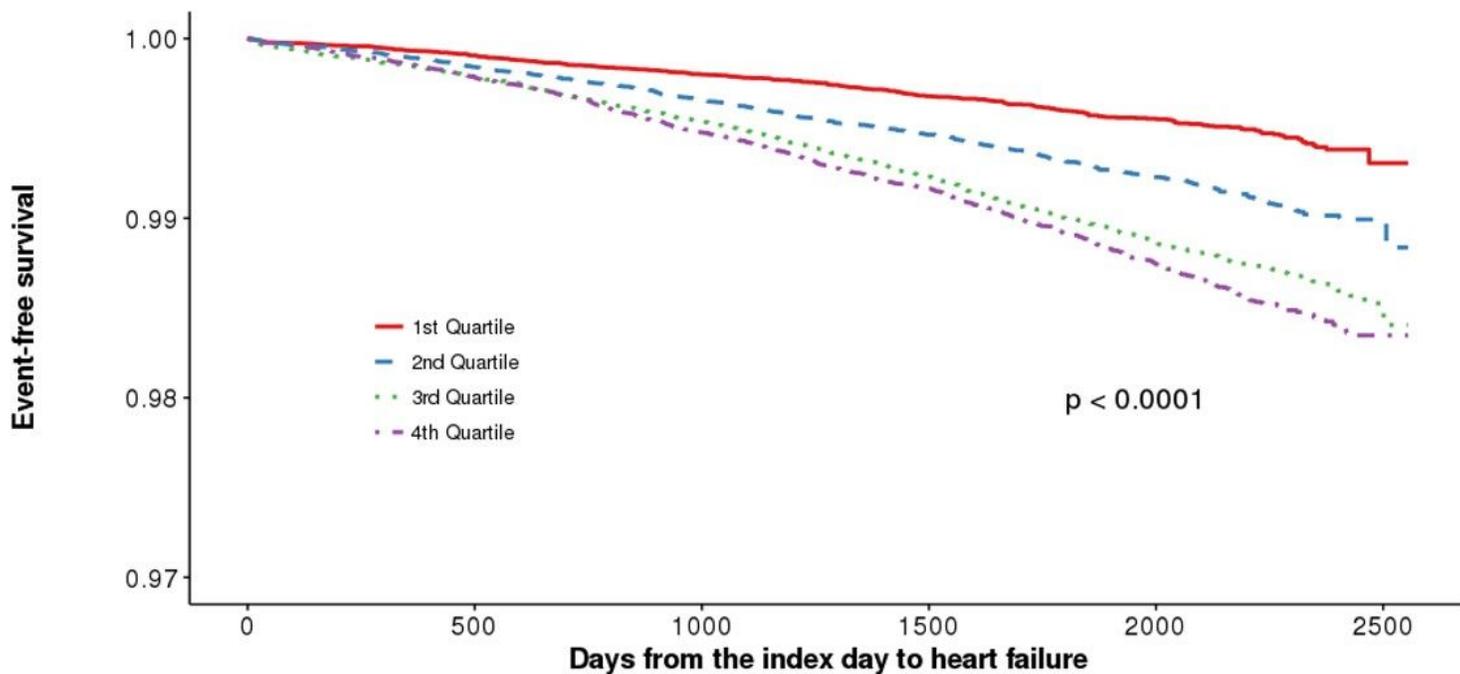


Figure 1

The overview of the study population.



Number at risk

1st Quartile -	77143	73291	64459	52624	33140	331
2nd Quartile -	77137	74041	66734	55826	36734	636
3rd Quartile -	77153	74404	67701	57300	38947	820
4th Quartile -	77145	74148	67523	57230	38927	701

Figure 2

Cumulative incidence of new-onset heart failure according to the quartiles. Statistical significance using the log-rank test.

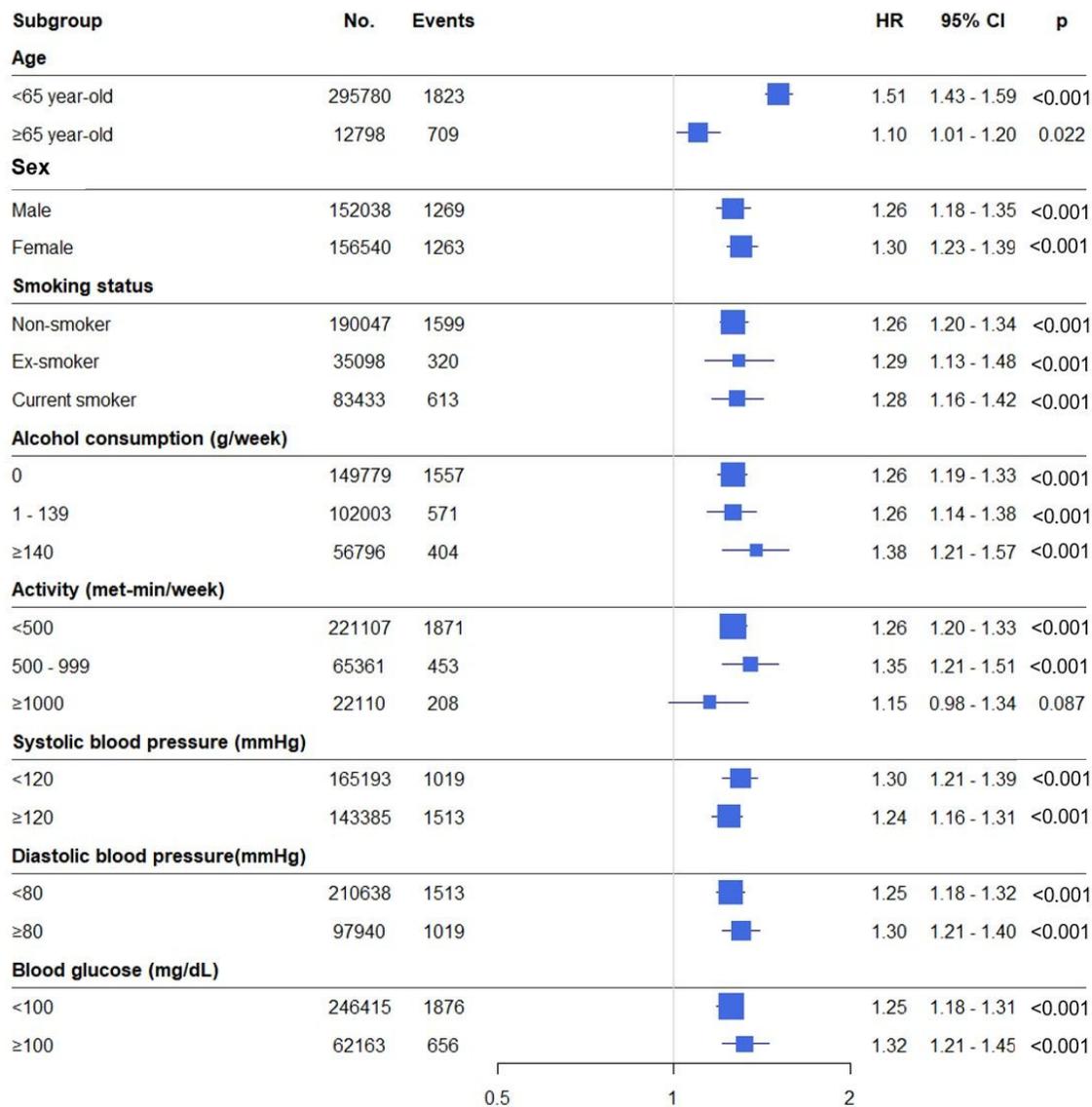


Figure 3

The Forest plots of hazard ratios for new-onset heart failure stratified by various clinical characteristics. CI = confidence interval; HR = hazard ratio.