Non-alcoholic Fatty Liver Disease and the Risk of Incident Atrial Fibrillation in Young Adults: A Nationwide Population-Based Cohort Study

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Background: Non-alcoholic fatty liver disease (NAFLD) is a multisystem disease including cardiovascular. However, the association between NAFLD and the risk of incident atrial fibrillation (AF), especially in young adults, remains unclear. We aimed to evaluate the association between NAFLD as assessed by the fatty liver index (FLI) and the risk of AF in young adults.

Methods: We identified individuals aged 20–39 years who underwent health examinations conducted by the Korean National Health Insurance Corporation between January 2009 and December 2012. Individuals with significant liver disease, heavy alcohol consumption, or prevalent AF were excluded. We categorized based on FLI: <30, 30 to <60, and ≥60. Incident AF was evaluated as the primary outcome.

Results: We included 5,333,907 subjects (mean age, 31 ± 5 years; men, 57%). During a mean follow-up of 7.4 ± 1.1 years, 12,096 patients had newly diagnosed AF (incidence rate 0.31 per 1,000 person-years). After adjustment, subjects with FLI 30 to <60 and FLI ≥60 showed a higher risk of AF compared to those with FLI <30 (hazard ratio [HR] 1.21, 95% confidence interval [CI, 1.15–1.27] and HR 1.47, 95% CI [1.39–1.55], $p < 0.001$, respectively). In women, the increased AF risk was accentuated in the higher FLI group than in the individuals with FLI<30, compared with men (p-for-interaction = 0.023). A higher incident AF risk in the higher FLI groups was consistently observed in various subgroups.

Conclusion: Among young adults, NAFLD assessed using FLI was positively correlated with the AF risk. These findings support the evidence of AF screening in young adults with high FLI scores.

Keywords: non-alcoholic fatty liver disease, fatty liver index, atrial fibrillation, young, adult

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia, with a healthcare burden that is expected to continuously increase worldwide (1, 2). AF increases the risk of all-cause mortality and morbidity than in the general population, especially in young patients (3, 4). It is a significant risk factor for acute ischemic stroke, although it is relatively uncommon in young adults (5).

Even though some risk factors differentiate among different age groups, Non-genetic risk factors such as obesity, smoking, and hypertension are consistently associated with the risk of incident AF irrespective of age group (6). Consequently, recent studies have focused on evaluating risk factors of AF as a cluster of metabolic disease (7–10). Non-alcoholic fatty liver disease (NAFLD) is one of the factors being evaluated as a possible surrogate marker for such metabolic unhealthiness.

NAFLD is a disease of epidemic proportions in high-income countries being responsible for approximately one-quarter of the global population, up to 30% in Korea (11). The prevalence and burden of NAFLD are expected to rise, especially in young adults (12). The associations between ultrasonography diagnosed NAFLD and an increased risk of AF have been reported (13–15). However, the association between NAFLD as assessed by the fatty liver index (FLI) with risk of AF in young adults in a large population remains unknown. FLI is a surrogate marker with validated accuracy of 0.84 (95% confidence interval [CI] 0.81–0.87) in detecting fatty liver, (16) and is used for screening NAFLD in epidemiological studies of the general population (17–19).

Therefore, this study aimed to evaluate the association between NAFLD assessed by the FLI and the risk of AF in young adults aged 20–39 years in a large nationwide population-based cohort study.

METHODS

This study used all the data from claims database, the Korean National Health Insurance Service (NHIS). The NHIS in South Korea covers over 50 million people residing in South Korea. Among the total population, the biannually employed, household and 20-year-old or older dependent family members (biannually), and medical aid beneficiary householders aged 19–64 years (biannually) are the candidates of the general National Health Screening Program of Korea. The National Health Screening Program of Korea consists of seven categories, including physical examination and other laboratory examinations (blood tests, urine examination, and chest radiography), and ~74.1% of the candidates participated in 2019 (20). The database by the National Health Information Database contains information on not only demographic variables and date of death, but also information on health behaviors (21, 22). Our study used data collected between January 1, 2009, and December 31, 2012.

This study was exempted from institutional review board (IRB) review (IRB no. E-2105-116-1219) as the study used anonymized data. The informed consent could not be acquired as the database was de-identified when provided from the NHIS. The approval for the use of the released database from 2009 to 2012 by the NHIS was received in 2021.
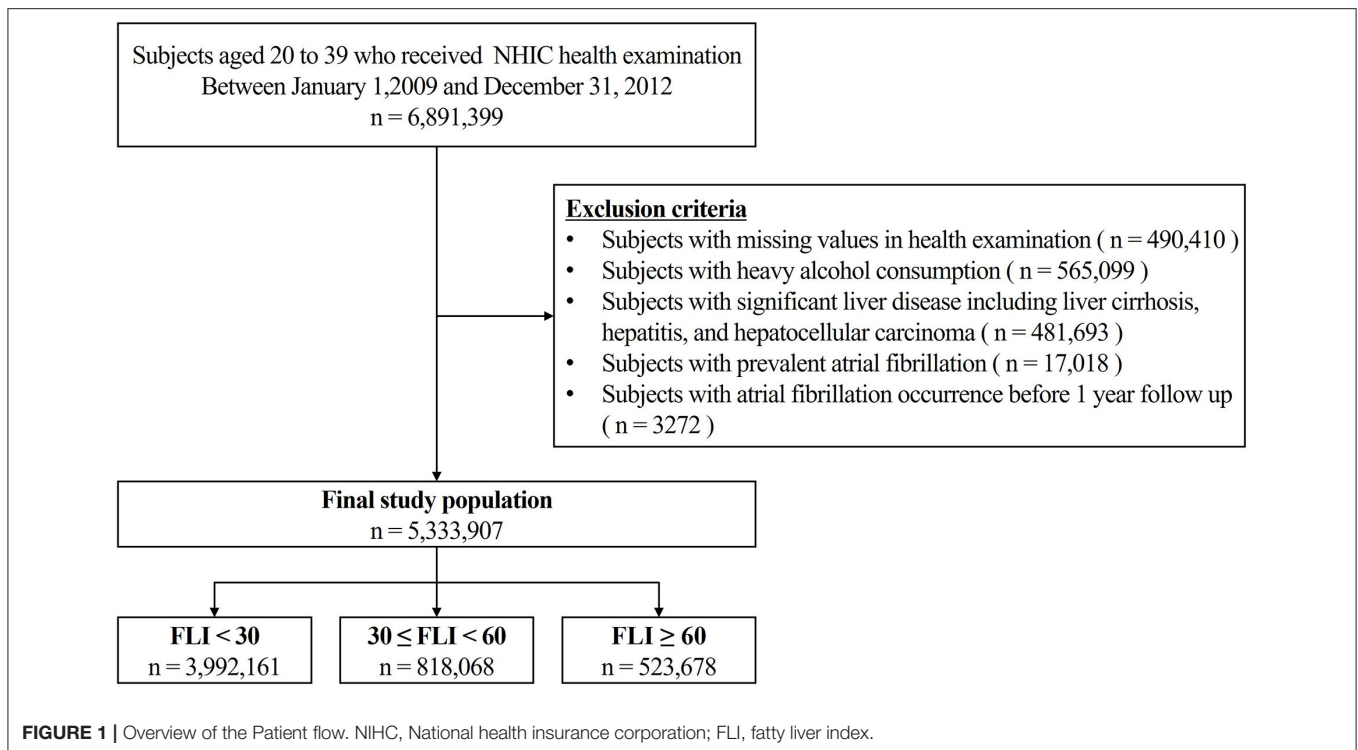
Study Population

Subjects aged 20–39 years who underwent health examinations conducted by the Korean National Health Insurance Corporation between January 1, 2009, and December 31, 2012, were identified ($n = 6,891,399$). We excluded patients with heavy alcohol consumption (>30 g/day, $n = 565,099$; 8.2%) based on the self-reported questionnaire in a health examination, significant liver disease (liver cirrhosis, hepatitis, and hepatocellular carcinoma) and those with prevalent AF before enrollment (**Figure 1**).

Definition of Non-alcoholic Fatty Liver Disease

In this study, FLI was used to define NAFLD. The standard diagnosis of NAFLD requires hepatic steatosis confirmation by histologic or radiographic examination in the absence of excessive alcohol consumption and other liver diseases (23, 24). The gold standard for diagnosing NAFLD is liver biopsy, but ultrasonography is also reported to have reliability and accuracy in diagnosing NAFLD with area under the summary receiving operating characteristics curve of 0.93 (25). However, liver biopsy and ultrasonography have limited usability in screening for NAFLD, especially in a large population study.

In this context, the FLI proposed by Bedogni et al. is an alternative option for diagnosing NAFLD as the formula contains body mass index (BMI), waist circumference, triglyceride (TG), and gamma glutamyl transpeptidase (GGT), which are easy to obtain (16).

$$FLI = \frac{e0.953 \times \log e(TG) + 0.139 \times BMI + 0.718 \times \log e(GGT) + 0.053 \times \text{waist circumference} - 15.745}{1 + e0.953 \times \log e(TG) + 0.139 \times BMI + 0.718 \times \log e(GGT) + 0.053 \times \text{waist circumference} - 15.745}$$

In a previous study which validated FLI values using fatty liver diagnosed by ultrasonography, a an FLI <30 (negative likelihood ratio = 0.2) rules out and a an FLI ≥60 (positive likelihood ratio = 4.3) rules in fatty liver (16). This cut-off value has been used widely in other populations (18, 19, 26). Following these cut-offs, in our study, we set the group with FLI <30 who were less likely to have a clinical fatty liver as a reference group, and those with FLI ≥60 were defined as patients with NAFLD. Considering that FLI reflects hepatic steatosis and insulin resistance, we assumed that FLI has a meaning of the metabolic healthiness of individuals as a continuous variable, even though FLI value of 30 to <60 is under the NAFLD cutoff. In previous studies, not only the patients with NAFLD (FLI ≥60), but those with FLI 30 to <60 also had a higher risk of diabetes mellitus or cardiovascular diseases compared to those with FLI <30 (27, 28). Therefore, we analyzed patients with FLI 30 to <60 as an independent group. In consideration of FLI being a continuous variable, we also used the decile groups of the study population for a supplementary analysis: FLI < 1.94, FLI < 3.04, FLI < 4.53, FLI < 6.74, FLI < 10.16, FLI < 15.56, FLI < 24.16, FLI < 37.82, FLI < 59.51, 59.51 ≤ FLI.

FIGURE 1 | Overview of the Patient flow. NIHC, National health insurance corporation; FLI, fatty liver index.

Covariates

Comorbidities were defined using the International Classification of Disease, Tenth, Clinical Modification (ICD-10-CM) codes. Hypertension and diabetes mellitus were defined with an additive requirement of a minimum of one prescription of anti-hypertensive or anti-diabetic drugs, respectively [22]. Detailed information on the definition of each covariate is summarized in **Supplementary Table 1**. The general health examination included systolic and diastolic blood pressure, weight, height, BMI, and waist circumference. The laboratory results consisted of fasting glucose, estimated glomerular filtration rate (eGFR), total cholesterol, TG, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) [22, 29, 30]. The self-reported questionnaire consisted of information on smoking behavior (never, ex-, or current), alcohol consumption behavior (none, mild to moderate, or heavy), and regular exercise [22, 31, 32]. The low income was defined as the lowest 20% among the entire Korean population and those supported by medical aid.

Study Outcomes

Incident AF was defined as the first occurrence of AF during at least two different days of hospital visits (outpatient) or the first admission or death with ICD-10-CM codes (I48; AF and atrial flutter). The use of I48 as a definition of AF have been validated with a positive predictive value of 94.1% [33]. The index year was defined as the first NHIS health examination, and those who developed AF before 1 year from the index year were considered irrelevant to NAFLD and were excluded. Data were censored at the time of the event, whichever came first: incidence of AF, disqualification from the NHIS (immigration or death), or end of the study (December 31, 2018).

Statistical Analysis

The descriptive values of the baseline characteristics were described as percentages for categorical data and mean ± standard deviation for continuous variables. The serum TG level was presented as a geometric mean (95% CI). One-way analysis of variance and chi-square tests were performed to evaluate the differences between the FLI groups. *Post hoc* tests for pairwise comparisons were performed.

The incidence rate (IR) of AF was measured as the number of incident AF events per 1,000 person-years. Kaplan-Meier analyses were used to plot the cumulative incidences of AF in the FLI groups, with a log-rank *p*-value for the comparison of statistical significance between the groups. Cox proportional hazards regression analysis was used to estimate hazard ratios (HRs) and 95% CIs of AF incidence. A total of three models with different combinations of covariates were used for the evaluation: unadjusted model (model 1), model adjusted for age and sex (model 2), model adjusted for age, sex, smoking, alcohol consumption, regular exercise, diabetes mellitus, hypertension, dyslipidemia, heart failure, prior ischemic stroke, prior myocardial infarction, chronic obstructive pulmonary disease, chronic kidney disease, sleep apnea, hyperthyroidism, and low income (Model 3).

Subgroup analyses were performed according to age (<30 and ≥30 years), sex, obesity (BMI <25 and BMI ≥25), central obesity (waist circumference: men <90 cm, women <85 cm, and men ≥90 cm or women ≥85 cm), alcohol consumption (none and mild), and income (low and others).

We performed sensitivity analyses to provide complementary results for the healthy population who did not have significant cardiovascular comorbidities, such as hypertension, diabetes

TABLE 1 | Baseline characteristics of the study population.

	Total (n = 5,333,907)	FLI			P-value
		<30 (n = 3,992,161)	30 to <60 (n = 818,068)	≥60 (n = 523,678)	
Age, years					
Mean ± SD	30.7 ± 5.0	30.1 ± 5.1	32.5 ± 4.4	32.8 ± 4.3	<0.001
<30	43.1	48.8	27.8	23.9	<0.001
≥30	56.9	51.2	72.2	76.1	
Sex (men)	56.5	45.2	88.7	92.3	<0.001
Comorbidities					
Hypertension	6.6	3.2	11.6	24.0	<0.001
Diabetes mellitus	1.7	0.9	2.7	6.9	<0.001
Dyslipidaemia	6.4	3.2	11.8	22.8	<0.001
Heart failure	0.1	0.0	0.1	0.1	<0.001
Prior ischemic stroke	0.1	0.0	0.1	0.1	<0.001
Prior MI	0.1	0.1	0.1	0.1	<0.001
CKD	2.7	2.7	2.8	2.6	<0.001
COPD	2.5	2.6	2.4	2.5	<0.001
Sleep apnea	0.07	0.05	0.13	0.21	<0.001
Thyroid disease	1.6	1.8	1.1	0.9	<0.001
Social history					
Smoking					<0.001
Non-smoker	58.5	66.9	36.2	28.8	
Ex-smoker	9.7	8.2	14.7	13.8	
Current smoker	31.8	24.9	49.1	57.4	
Alcohol consumption					<0.001
Non-drinker	41.2	45.1	30.7	27.4	
Mild (0–30 g/day)	58.8	54.9	69.3	72.6	
Regular exercise	12.5	12.2	13.8	13.0	<0.001
Low income	16.4	17.8	12.5	12.0	<0.001
Health examination					
SBP (mmHg)	117.1 ± 13.0	114.5 ± 12.0	123.1 ± 12.0	128.2 ± 13.4	<0.001
DBP (mmHg)	73.4 ± 9.3	71.6 ± 8.6	77.2 ± 8.8	81.0 ± 9.9	<0.001
BMI (kg/m^2)					
Mean ± SD	22.8 ± 3.6	21.5 ± 2.5	25.7 ± 2.3	28.9 ± 3.4	<0.001
≥25	24.8	8.6	61	91.3	<0.001
WC (cm)					
Mean ± SD	76.9 ± 10.2	73.1 ± 7.4	85.5 ± 5.4	93.1 ± 9.9	<0.001
Men ≥ 90, Women ≥ 85	12.0	2	25.2	67.7	<0.001
Laboratory results					
eGFR (mL/min/1.73 m2)	96.1 ± 49.8	96.9 ± 48.3	93.8 ± 53.6	93.7 ± 54.5	<0.001
Fasting Glucose (mg/dL)	90.5 ± 16.0	88.7 ± 12.6	93.7 ±18.6	99.4 ± 27.3	<0.001
Total cholesterol (mg/dL)	183.9 ± 35.9	177.3 ± 32.4	198.5 ± 36.5	211.6 ± 39.8	<0.001
HDL-C (mg/dL)	57.7 ± 25.6	60.0 ± 22.3	51.9 ± 32.2	49.2 ± 33.2	<0.001
LDL-C (mg/dL)	104.8 ± 34.5	101.0 ± 31.2	115.9 ± 38.7	115.9 ± 43.4	<0.001
*TG (mg/dL)	93.9 (93.9–94.0)	76.2 (76.1–76.2)	150.8 (150.6–150.9)	221.8 (221.5–222.1)	<0.001

Categorical variables were presented as a percentage and continuous variables were presented as mean and standard deviation. For pairwise comparisons, Tukey's post hoc test revealed a significant difference (P < 0.001) between each pair of groups in all variables.
*TG was presented as geometric mean (95% confidence interval).
BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; MI, myocardial infarction; SBP, systolic blood pressure; TG, triglyceride; WC, waist circumference.

mellitus, dyslipidemia, heart failure, and prior ischemic stroke and myocardial infarction at baseline.

Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

A total of 5,333,907 patients were finally included in this study and categorized into three groups: FLI < 30 ($n = 3,992,161$, 75%), FLI 30 to < 60 ($n = 818,068$, 15%), and FLI ≥ 60 ($n = 523,678$, 10%). The subjects in the higher FLI group were men and showed a higher prevalence of comorbidities, including hypertension, diabetes mellitus, dyslipidemia, heart failure, prior ischemic stroke, previous myocardial infarction, and sleep apnea. The higher FLI groups had a higher proportion of current smokers and subjects with mild alcohol consumption and higher mean BMI and waist circumference levels than the lower FLI groups. In addition, patients with higher FLI values showed higher fasting glucose, total cholesterol, LDL-C, TG, and lower HDL-C than those with lower FLI values. Low income was more common in the lower FLI group (**Table 1**). For pairwise comparisons, Tukey's *post hoc* test revealed a significant difference ($P < 0.001$) between each pair of groups in all variables.

Risk of Incident AF According to FLI Values
During a mean follow-up duration of 7.4 ± 1.1 years, 12,096 subjects were newly diagnosed with AF (IR 0.31 per 1,000 person-years). The crude IR of AF increased in subjects with a higher FLI: 0.25 for the FLI < 30 group, 0.42 for FLI 30 to < 60, and 0.58 for FLI ≥ 60 groups, respectively (*P* for trends < 0.001, **Figure 2**).

The cumulative incidence curves for AF according to different FLI ranges are shown in **Figure 3**.

After multivariable adjustment by model 3, compared to subjects with FLI <30, those with higher FLI were associated with a higher risk of incident AF (FLI 30 to <60 group: HR 1.21, 95% CI 1.15 to 1.27, and FLI≥60 group: HR 1.47, 95% CI 1.39 to 1.55) (**Figure 2** and **Supplementary Table 2**). The increased risk of AF in subjects with higher FLI was slightly accentuated in women than in men (*P*-for-interaction = 0.023, **Figure 2**).

FLI in a Decile Group
The adjusted HR of FLI in decile groups are described in **Figure 4**. The adjusted HR showed consistently increasing trend in the total population (*P* < 0.001) and in subgroup of women (*P* < 0.001). In subgroup of men, the adjusted HR decreased to 0.67 (95% CI 0.49 to 0.92) at decile group 2. More detailed adjusted HRs are presented at **Supplementary Table 3**.
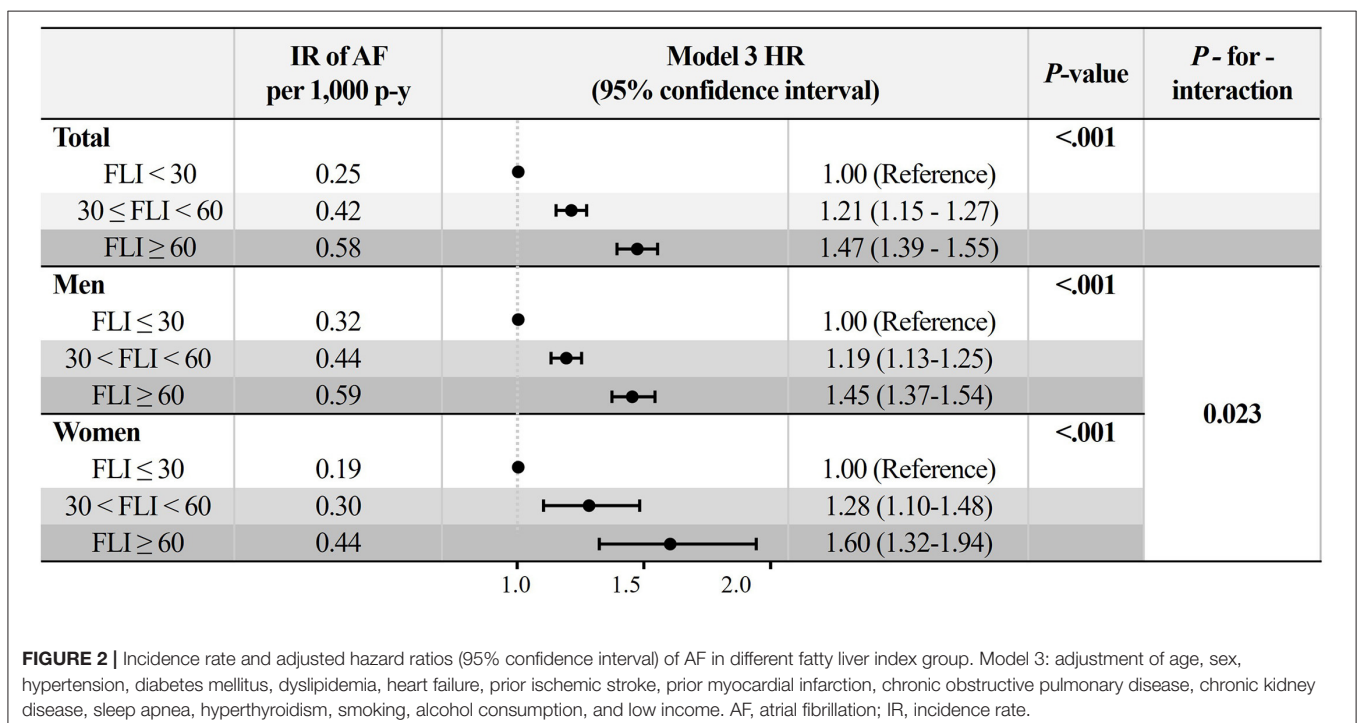
Subgroup Analyses
All subgroups showed a consistent trend of increased risk of AF in the higher FLI group after adjustment for Model 3 (**Figure 5**). *P*-for-interaction was insignificant in all subgroups, except for sex.

Sensitivity Analysis
In those without significant cardiovascular comorbidities, the sensitivity analysis for an apparently healthy population showed findings consistent with the main results.

In an apparently healthy population, subjects with higher FLI were associated with an increased risk of incident AF compared to those with FLI <30 (FLI 30 to <60 group: HR 1.23, 95%
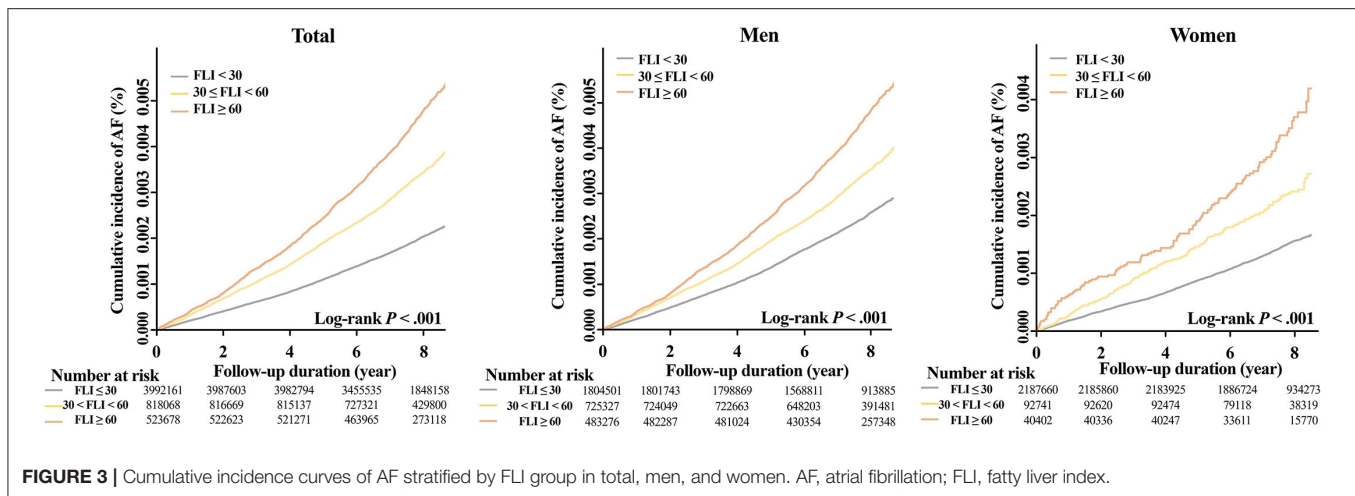
	IR of AF per 1,000 p-y	Model 3 HR (95% confidence interval)		*P*-value	*P* - for - interaction
Total				**<.001**	
FLI < 30	0.25		1.00 (Reference)		
30 ≤ FLI < 60	0.42		1.21 (1.15 - 1.27)		
FLI ≥ 60	0.58		1.47 (1.39 - 1.55)		
Men				**<.001**	
FLI ≤ 30	0.32		1.00 (Reference)		
30 < FLI < 60	0.44		1.19 (1.13-1.25)		
FLI ≥ 60	0.59		1.45 (1.37-1.54)		**0.023**
Women				**<.001**	
FLI ≤ 30	0.19		1.00 (Reference)		
30 < FLI < 60	0.30		1.28 (1.10-1.48)		
FLI ≥ 60	0.44		1.60 (1.32-1.94)		

FIGURE 2 | Incidence rate and adjusted hazard ratios (95% confidence interval) of AF in different fatty liver index group. Model 3: adjustment of age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, prior ischemic stroke, prior myocardial infarction, chronic obstructive pulmonary disease, chronic kidney disease, sleep apnea, hyperthyroidism, smoking, alcohol consumption, and low income. AF, atrial fibrillation; IR, incidence rate.

FIGURE 3 | Cumulative incidence curves of AF stratified by FLI group in total, men, and women. AF, atrial fibrillation; FLI, fatty liver index.
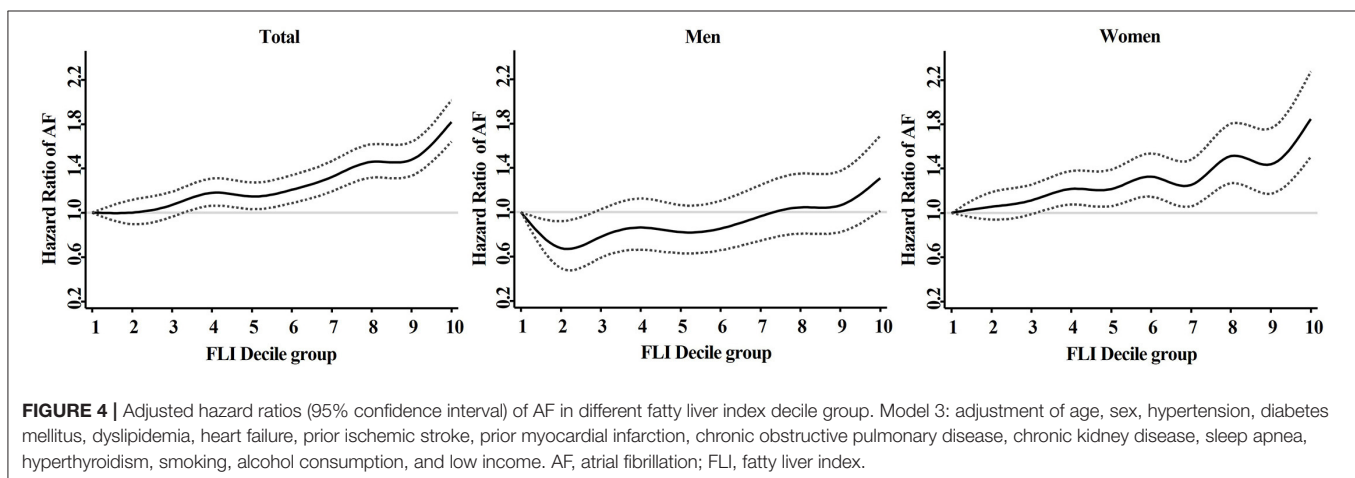

FIGURE 4 | Adjusted hazard ratios (95% confidence interval) of AF in different fatty liver index decile group. Model 3: adjustment of age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, prior ischemic stroke, prior myocardial infarction, chronic obstructive pulmonary disease, chronic kidney disease, sleep apnea, hyperthyroidism, smoking, alcohol consumption, and low income. AF, atrial fibrillation; FLI, fatty liver index.

CI 1.16 to 1.30, FLI ≥60 group: HR 1.56, 95% CI 1.45 1.66) (**Table 2**).

DISCUSSION

In this large-scale nationwide population-based cohort study, our main findings were as follows: (1) young adults with higher FLI had a higher risk of incident AF; (2) a positive correlation between FLI and the risk of AF was consistently observed in various subgroups without significant interaction except for sex; (3) increased risk of AF in subjects with higher FLI was more accentuated in women than in men; and (4) the association between higher FLI and increased risk of AF was consistently observed in apparently healthy subjects without significant cardiovascular comorbidities.

To the best of our knowledge, this is the first study to assess the risk of incident AF in young adults using FLI in a large population-based study.

In previous studies, the association between NAFLD and the risk of AF has been reported in selected patients with comorbidities or age of middle to elderly or those with definite ICD-10 code diagnosis of NAFLD (13, 15, 34). For example,

Targher et al. have shown ultrasonography diagnosed NAFLD to be associated with an increased odds ratio of AF over 5 folds in patients with type 2 diabetes (13, 14). The Oulu Project Elucidating Risk of Atherosclerosis (OPERA) study showed that the risk of AF increased up to ∼2-fold with ultrasonography diagnosed NAFLD in middle-aged hypertensive subjects (15). Furthermore, Labenz et al. reported that NAFLD, as defined by ICD-10 code, was significantly associated with the incidence of AF in both patients with age 18–40 years and 41–60 years in the German population with HR of 2.98 (95% CI 1.22 to 7.93) and 1.48 (95% CI 1.21 to 1.81), respectively (34). Regarding Korean population, Roh et al. previously reported an increased risk of AF up to 1.55 (95% CI 1.19 to 2.04) in a higher FLI quartile group in the Korean population (17). However, these studies did not precisely compare the association between FLI and the risk of AF in the young age group.

Although the prevalence of NAFLD is increasing by aging, NAFLD is common even in young adults (22.4% in the 30s vs. 34.0% in the 70s) (35). In AF, aging is the most potent risk factor with relatively low prevalence in young adults (1). The clinical impact of AF could be greater in young adults. AF is not
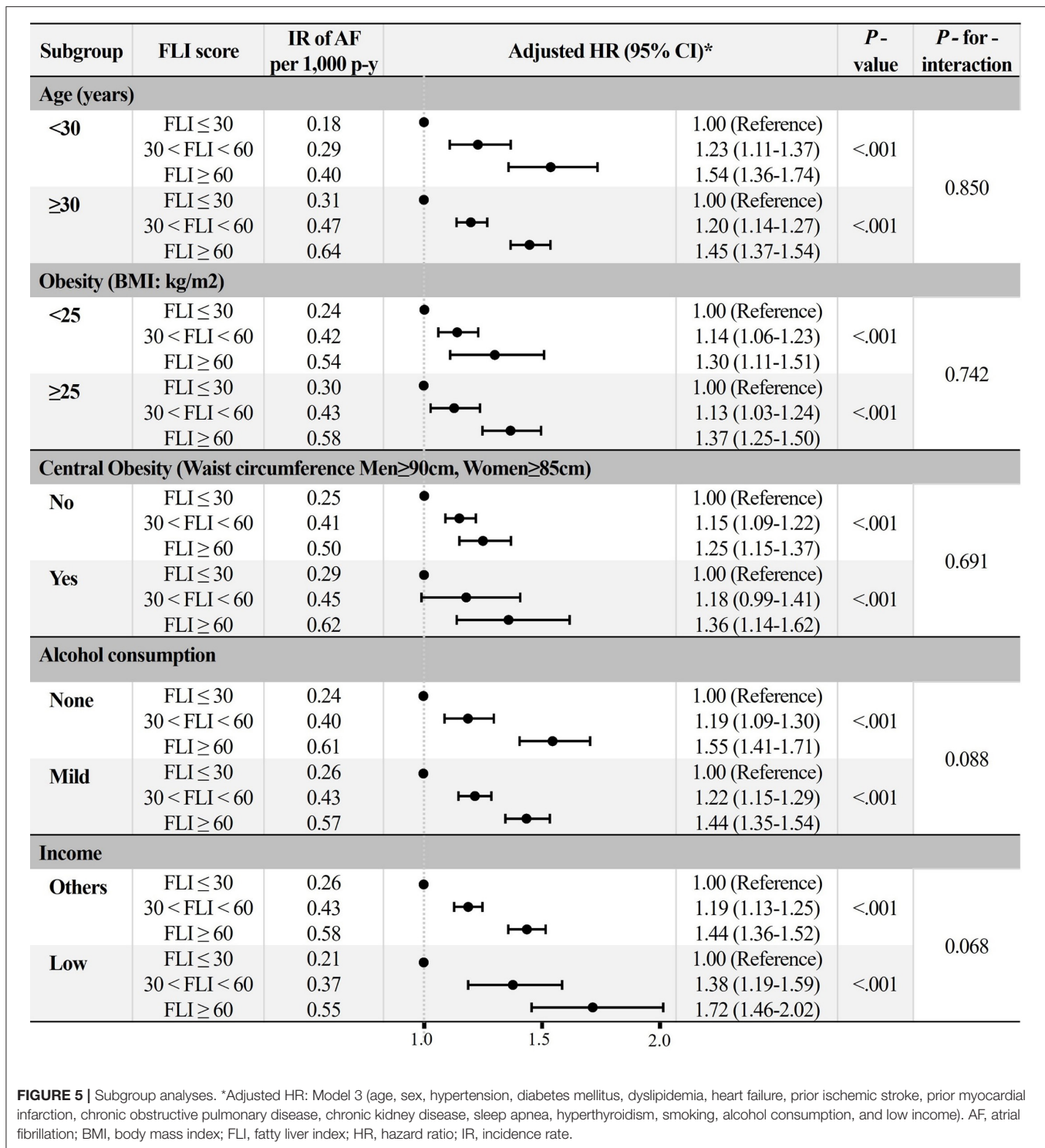
Subgroup	FLI score	IR of AF per 1,000 p-y	Adjusted HR (95% CI)*		P-value	P-for-interaction
Age (years)						
<30	FLI ≤ 30	0.18		1.00 (Reference)		
	30 < FLI < 60	0.29		1.23 (1.11-1.37)	<.001	
	FLI ≥ 60	0.40		1.54 (1.36-1.74)		
≥30	FLI ≤ 30	0.31		1.00 (Reference)		0.850
	30 < FLI < 60	0.47		1.20 (1.14-1.27)	<.001	
	FLI ≥ 60	0.64		1.45 (1.37-1.54)		
Obesity (BMI: kg/m2)						
<25	FLI ≤ 30	0.24		1.00 (Reference)		
	30 < FLI < 60	0.42		1.14 (1.06-1.23)	<.001	
	FLI ≥ 60	0.54		1.30 (1.11-1.51)		0.742
≥25	FLI ≤ 30	0.30		1.00 (Reference)		
	30 < FLI < 60	0.43		1.13 (1.03-1.24)	<.001	
	FLI ≥ 60	0.58		1.37 (1.25-1.50)		
Central Obesity (Waist circumference Men≥90cm, Women≥85cm)						
No	FLI ≤ 30	0.25		1.00 (Reference)		
	30 < FLI < 60	0.41		1.15 (1.09-1.22)	<.001	
	FLI ≥ 60	0.50		1.25 (1.15-1.37)		0.691
Yes	FLI ≤ 30	0.29		1.00 (Reference)		
	30 < FLI < 60	0.45		1.18 (0.99-1.41)	<.001	
	FLI ≥ 60	0.62		1.36 (1.14-1.62)		
Alcohol consumption						
None	FLI ≤ 30	0.24		1.00 (Reference)		
	30 < FLI < 60	0.40		1.19 (1.09-1.30)	<.001	
	FLI ≥ 60	0.61		1.55 (1.41-1.71)		0.088
Mild	FLI ≤ 30	0.26		1.00 (Reference)		
	30 < FLI < 60	0.43		1.22 (1.15-1.29)	<.001	
	FLI ≥ 60	0.57		1.44 (1.35-1.54)		
Income						
Others	FLI ≤ 30	0.26		1.00 (Reference)		
	30 < FLI < 60	0.43		1.19 (1.13-1.25)	<.001	
	FLI ≥ 60	0.58		1.44 (1.36-1.52)		0.068
Low	FLI ≤ 30	0.21		1.00 (Reference)		
	30 < FLI < 60	0.37		1.38 (1.19-1.59)	<.001	
	FLI ≥ 60	0.55		1.72 (1.46-2.02)		

1.0   1.5   2.0

FIGURE 5 | Subgroup analyses. *Adjusted HR: Model 3 (age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, prior ischemic stroke, prior myocardial infarction, chronic obstructive pulmonary disease, chronic kidney disease, sleep apnea, hyperthyroidism, smoking, alcohol consumption, and low income). AF, atrial fibrillation; BMI, body mass index; FLI, fatty liver index; HR, hazard ratio; IR, incidence rate.

easily curable, significantly affects patients' quality of life, and is associated with increased risks of cognitive dysfunction, stroke, heart failure, and all-cause death. The relative risks of AF-related complications are generally more prominent in young patients. However, the risk factors and substrate abnormalities for AF in young adults were not well-defined (36). Looking into the risk factor for AF by different age groups, the impact of metabolic factors such as diabetes mellitus or abdominal obesity on the risk of AF was more prominent in young adults aged 20 to <40 years (6). Identifying risk factors for AF in young adults and managing these properly might be needed to reduce the risk of AF.

TABLE 2 | Sensitivity analyses: analyses on subjects without significant cardiovascular comorbidities including hypertension, diabetes mellitus, dyslipidaemia, heart failure, prior ischemic stroke, and prior myocardial infarction.

	FLI score	Number	Event	IR	Model 3 HR (95% CI)	P-value
Total	FLI < 30	3,714,063	6,356	0.23	1.00 (reference)	<0.001
	30 ≤ FLI < 60	627,307	1,785	0.38	1.23 (1.16–1.30)	
	FLI ≥ 60	297,746	1,093	0.49	1.56 (1.45–1.66)	
Men	FLI < 30	1,636,994	3,600	0.30	1.00 (reference)	<0.001
	30 ≤ FLI < 60	556,890	1,655	0.40	1.21 (1.14–1.29)	
	FLI ≥ 60	273,866	1,030	0.50	1.53 (1.42–1.64)	
Women	FLI < 30	2,077,069	2,756	0.18	1.00 (reference)	<0.001
	30 ≤ FLI < 60	70,417	130	0.26	1.27 (1.06–1.51)	
	FLI ≥ 60	23,880	63	0.37	1.88 (1.46–2.41)	

IR, per 1,000 person-years.
Model 3: age, sex, smoking, alcohol consumption, regular exercise, diabetes mellitus, hypertension, dyslipidaemia, heart failure, prior ischemic stroke, prior myocardial infarction, chronic obstructive pulmonary disease, chronic kidney disease, sleep apnea, hyperthyroidism, and low income.
CI, confidence interval; DM, diabetes mellitus; DL, dyslipidaemia; FLI, fatty liver index; HF, heart failure; HR, hazard ratio; HTN, hypertension; IR, incidence rate; MI, myocardial infarction.

It is still uncertain whether NAFLD is a risk factor for AF alone or simply reflects associated cardiovascular disease. However, the association between FLI and increased risk of AF might be due to FLI being a surrogate marker of metabolic unhealthiness. Previous studies have shown an increased risk of AF in metabolically unhealthy subjects with increased central obesity and BMI (7–10). As such components are also used in FLI, the correlation shown might simply be due to the reflection of the metabolic unhealthiness of the individual. This metabolic unhealthiness represented as FLI was associated with AF incident regardless of the amount of alcohol consumption (none or mild) in this study. With a recent update in the nomenclature NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD) (37), the metabolic unhealthiness has gained more emphasis. The diagnostic criteria of MAFLD includes BMI, TG, and waist circumference which are main components of FLI. FLI might help identifying those at higher risk of incident AF among the heterogeneous population of MAFLD.

Because increased FLI served as a surrogate marker for insulin resistance, insulin resistance occurred both atrial structural remodeling and abnormal intracellular calcium homeostasis, contributing to increased AF susceptibility (38–41). In a recent study (40, 41), insulin resistance-induced animals had a more susceptible atrium than the controls, with abnormal diastolic calcium leak and repetitive ectopic focal discharge in isolated atrial myocytes and whole atria, implying that calcium-related triggered activity as the mechanism of AF. Additionally, rats with insulin resistance demonstrated increased oxidative stress, NADPH oxidase activity, and CaMKII oxidation, as well as calcium handling- and structural remodeling processes.

Systemic inflammation may be an important mediator of pathophysiological links between NAFLD and AF. Those with NAFLD have increased accumulation of TG in the liver, increased free fatty acid, and increased production of reactive oxidative species, resulting in activation of the inflammatory response (42, 43). Previous studies have shown that increased low-grade, long-standing systemic inflammation in the liver leads to extrahepatic disease (44). For example, tumor necrosis factor α is one of the pro-inflammatory cytokines increased in the NAFLD model

of mouse (45) and is associated with AF (46, 47). Thus, FLI, a surrogate marker of NAFLD, might reflect the systemic pro-inflammation state in NAFLD, leading to incident AF.

In this study, the FLI group showed an increased risk of AF along with an increase in the FLI group even at 30 to <60, which is not considered to be NAFLD in the "usual" cut-off value of 60. This trend was consistent in subgroup analyses of age, sex, obesity, central obesity, alcohol consumption, and income, which showed a consistent increase in the risk of AF along with higher FLI. This consistency may be evidence for lifestyle modification targeted at controlling factors even in subjects who are considered to be at risk of NAFLD and those who are diagnosed with NAFLD. Indeed, lifestyle modification is part of the integrated approach to AF characterization and treatment (48, 49). Such an integrated approach to AF management has been associated with improved clinical outcomes (50, 51).

Generally, NAFLD is more prevalent and severe in men than in women throughout reproductive age (52–54). Consistent with this, male predominancy was observed in subgroups with FLI ≥60 in the present analysis. The sex difference in the prevalence of NAFLD might be caused by the difference of tissue vulnerability on the proinflammatory/profibrotic cytokines, the effect of sex hormone, or the differences in the comorbid condition such as obesity, insulin resistance, and dyslipidemia. Although there was an uneven distribution of sexes within each FLI group, there was a statistically significant association between higher FLI and increased risk of AF in both men and women subgroups. In the present study, the risk of incident AF according to higher FLI values was slightly accentuated in women (P-for-interaction = 0.023).

Although the mechanism cannot be fully explained, there are possible hypothesis for the accentuation in women. The increased NAFLD is associated with increased epicardial adipose tissue and pericardial adipose tissue (PAT), (55–57) but the effect of PAT differs according to sex (58). PAT was more strongly associated with TG, impaired fasting glucose, and metabolic syndrome in women, (58) thus affecting the difference in the risks of incident AF between men and women.

Limitations

This study had some limitations. First, the validation of NAFLD diagnosis could not be performed due to the absence of information on ultrasonography or histologic data. However, the external validation of FLI has already shown an area under receiver operating characteristics (AUROC) curve of 0.807 (59). In the Korean population, the AUROC of FLI was found to be 0.785 (60). Second, those with undetected asymptomatic AF could be underdiagnosed leading to underestimation of this arrhythmia (4, 61, 62). Third, unmeasured confounders including echocardiographic data and values which reflect inflammatory status, such as C-reactive protein (63), tumor necrosis factor (46), and interleukin-6 (64), could not be adjusted for, as they are not regularly checked in a health examination. In addition, although the prevalence and incidence of significant heart valve disease might be relatively low in this young population, the presence of valvular heart diseases might affect the risk of AF. We could not evaluate the genetic predisposition for AF in this population due to the inherent limitation of the data source. Fifth, we included variables for the multivariable Cox analysis that showed significant differences among groups in baseline characteristics. These selected comorbidities and lifestyle factors were well-known independent risk factors for AF or recently validated from the Korean nationwide population dataset (6, 65). There is a possibility of the presence of interactions among different variables. Sixth, we applied the same FLI cut-off for men and women in this analysis. In a previous report, different FLI cut-offs for men and women would be suggested to predict NAFLD (66). Instead of applying different cut-off in different sexes, we complementarily provided the results of FLI decile (in total population: FLI < 1.94, FLI < 3.04, FLI < 4.53, FLI < 6.74, FLI < 10.16, FLI < 15.56, FLI < 24.16, FLI < 37.82, FLI < 59.51, 59.51 ≤ FLI) and the risk of AF in both men and women. Similarly, although the cut-off value for alcohol consumption differs between different sexes, we used a single cut-off of 30 for both sexes. This might have affected the increased risk of AF in women. Lastly, our study was analyzed in a homogenous Korean population and cannot be directly generalized to other ethnicities.

CONCLUSIONS

Among young adults, NAFLD assessed using FLI was positively correlated with the risk of AF. These findings support the evidence of AF screening in young adults with high FLI scores.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://nhiss.nhis.or.kr/bd/ab/bdaba021eng.do, Korean National Health Insurance Service.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Seoul National University Hospital Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

This study was coordinated by E-KC as the principal investigator. S-WL and K-DH went over the statistics. JCho and S-RL contributed to writing and original draft preparation with support from H-JA, SK, S-HP, HL, JChu, and MH. SO and GL supervised the findings of this work. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.832023/full#supplementary-material

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