Nonalcoholic Fatty Liver Disease and Risk of Myocardial Infarction and Stroke in Young Adults: A Nationwide Population-Based Study

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Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is associated with increased risk of cardiovascular diseases (CVDs). Because studies of young adults are limited, we investigated the relationship between NAFLD and cardiovascular events among a nationally representative sample of young adults in Korea.

Methods: This population-based cohort study from the Korean National Health Insurance Service included adults who were 20–39 years old when they underwent a health examination from 2009–2012. NAFLD was defined as fatty liver index (FLI) ≥ 60 , and participants were divided into three groups according to FLI (<30 , 30–59, and ≥ 60) to investigate the effect of steatosis by grade.

Results: Among 5,324,410 participants, 9.8% had an FLI ≥ 60 . There were 13,051 myocardial infarctions (MI, 0.39%) and 8,573 strokes (0.26%) during a median follow-up of 8.4 years. In multivariable analysis, NAFLD was associated with a higher risk of MI and stroke (hazard ratio [HR]=1.69; 95% confidence interval [CI]: 1.61–1.77 and HR=1.73; 95% CI: 1.63–1.84, respectively). MI and stroke had dose-dependent relationships with FLI (HR=1.28 in FLI 30–59 and 1.73 in FLI ≥ 60 for MI and HR=1.18 in FLI 30–59 and 1.41 in FLI ≥ 60 for stroke, respectively).

Conclusions: NAFLD was an independent predictor of MI and stroke in young adults. These results suggest that primary prevention of CVD should be emphasized in young adults with NAFLD.

Introduction

The proportions of myocardial infarction (MI) and stroke that affect young individuals have been increasing.[1 2] The proportion of acute MI hospitalizations among adults 35–54 years old, particularly among women, increased significantly from 1995 to 2014 [1], and the prevalence of ischemic stroke among adults 20–64 years old almost doubled from 1990 to 2013.[3] Because young adults are at important productive and reproductive stages of their lives, often including an active family life, the burden of cardiovascular disease (CVD) in young adults may affect all areas of life including physical, social, mental, and financial aspects.[4] These people remain high risk for recurrent events.[5] However, the definition of young age in previous studies varies from < 30 years old⁶ to < 60 years old,[1, 7, 8] and studies focusing on individuals younger than 40 are rare. Additionally, current risk calculators, such as the atherosclerotic cardiovascular disease (ASCVD) risk algorithm that determines 10-year risk for an ASCVD event are based on older populations and are less applicable to patients < 40 years old who are not generally considered candidates for preventive treatment with a statin.[9]

Nonalcoholic fatty liver disease (NAFLD) has been increasing in young adults and has become a significant public health burden.[10] NAFLD prevalence in young patients has risen to 20% with a mean onset age of 24 years.[11] Because NAFLD is an important risk factor for CVD, increasing CVD risk by 1.64 times,[12] it could have broad implications in the context of a CVD epidemic. However, the association between NAFLD and CVD has mostly been evaluated in middle-aged and elderly adults (mean age ranges: 43–63 years [12, 13, 14]).

Therefore, our aim was to investigate the association between NAFLD and CVD risk, including MI and stroke, among young adults less than 40 years using nationally representative Korean population data.

Methods

Data source

In this study, we obtained data from the Korean National Health Insurance System (NHIS), which is a national insurer managed by the Korean government and to which approximately 97% of the Korean population subscribes.[15] The NHIS conducts biennial health examinations for local householders or employees 40 years old and younger. The NHIS database contains health records, including sociodemographic data (age, sex, and income level), anthropometric measurements, laboratory tests (e.g., lipid profiles, blood glucose.), lifestyle behaviors (smoking, alcohol consumption, and physical activity), medical diagnoses (based on International Classification of Diseases, 10th revision [ICD-10]), and treatment data for the Korean population. This database has been widely used for various epidemiologic studies.[16, 17]

Study sample

A total of 6,891,399 adults aged 20–39 years who underwent health screening examinations from 2009–2012 (index year considered the baseline) were included. Patients who met the following criteria were excluded from the study: heavy alcohol consumption (≥ 30 g of alcohol/day, $n = 596,061$), previous diagnosis of hepatocellular carcinoma (C22.0, $n = 29,816$), previous diagnosis of liver cirrhosis [K703 (alcoholic cirrhosis), K746 (other and unspecified cirrhosis)] or any hepatitis [B15 (acute hepatitis A), B16 (acute hepatitis B), B17 (other acute viral hepatitis), B18 (chronic viral hepatitis), B19 (unspecified viral hepatitis)] ($n = 485,882$), history of MI (I21, I22, $n = 19,541$) or stroke (I63, I64) before the index year ($n = 12,124$), or had missing information ($n = 423,565$). The final study population included 5,324,410 subjects who were analyzed.

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (E-2012-106-1183) and conformed to the ethical guidelines of the Declaration of Helsinki. The requirement for patient informed consent was waived because de-identified secondary data were used.

NAFLD measurement

Although ultrasonography is a first-line screening technique in clinical practice [18], ultrasonography is not included in the NHIS mass screening program. Therefore, the fatty liver index (FLI), a proxy marker of hepatic steatosis, was used to assess NAFLD presence and grade. FLI scores range from 0–100, with < 30 representing low risk for fatty liver and ≥ 60 representing high risk.[19] Thus, we defined the NAFLD and control groups as $FLI \geq 60$ and < 60 , respectively.[20] It was previously validated to detect ultrasound-diagnosed fatty liver with an area under the receiver operating characteristics curves ranging from 0.79–0.87 in the Korean population.[21, 22] To further investigate the effect of steatosis grade, we categorized the participants into three FLI groups (< 30 , $30 - 59$, and ≥ 60).

$$FLI = [(e^{0.953 \times \ln \text{triglyceride} + 0.139 \times \text{BMI} + 0.718 \times \ln \text{GGT} + 0.053 \times \text{WC} - 15.745}) / (1 + e^{0.953 \times \ln \text{triglyceride} + 0.139 \times \text{BMI} + 0.718 \times \ln \text{GGT} + 0.053 \times \text{WC} - 15.745})] \times 100$$

Study outcomes

The primary endpoints of this study were newly diagnosed MI or stroke. MI was defined as record of ICD-10 codes I21 or I22 during hospitalization or these codes having been recorded at least two times. Stroke was defined as record of ICD-10 codes I63 or I64 during hospitalization with claims for brain computerized tomography or magnetic resonance imaging.[23] Although it was difficult to clearly define stroke subtype, we attempted to exclude hemorrhagic stroke, as described in a previous study.[24] The study population was followed from baseline to the date of study outcomes, censoring data (e.g., outmigration), or until December 31, 2018, whichever occurred first.

Covariates

As described previously [25], standardized self-reported questionnaires were used to collect data at the time of enrollment. Briefly, age, sex, smoking status (non-smokers, ex-smokers, and current smokers), and alcohol consumption (none and mild (< 30 g/day)) data were used in these analyses. Regular physical exercise was defined as engaging in exercise on a routine basis with moderate to high-intensity activity $\geq$ 3 times/week. Regular exercise was defined as performing > 20 minutes of strenuous physical activity at least three times per week or > 30 minutes of moderate physical activity at least five times per week. Income level was dichotomized at the lowest 20%. Comorbidities were defined using ICD-10 diagnosis codes, prescription information in the year prior to health screening, and health screening results. Physical examination was performed by measuring height, weight, systolic blood pressure, and diastolic blood pressure according to standardized methods. Blood pressure was measured after the participant had been seated for 5 min in the appropriate position by a trained clinician.

Criteria for hypertension were I10–I13 or I15 claim codes plus $\geq$ 1 prescription for an antihypertensive agent, or systolic/diastolic blood pressure $\geq$ 140/90 mmHg. Criteria for diabetes were E11–E14 claim codes plus $\geq$ 1 prescription for an antidiabetic medication per year, or a fasting glucose level $\geq$ 126 mg/dL. Criteria for dyslipidemia were E78 claim code plus $\geq$ 1 prescription for a lipid-lowering agent, or total cholesterol $\geq$ 240 mg/dL. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate < 60 mL/min/1.73 m² by the Modification of Diet in Renal Disease equation. Body mass index (BMI) was calculated as weight (kg) divided by the square of the person's height (m). After an overnight fast of $\geq$ 8 h, blood specimens were obtained from each participant.

Statistical analyses

Data are presented as means $\pm$ standard deviations for normally distributed continuous variables and as proportions for categorical variables, unless otherwise indicated. Log transformations were performed for non-normally distributed variables. Comparisons of baseline characteristics were conducted using independent t-tests and analysis of variance for continuous variables and chi-square tests for categorical variables.

The incidence rate of the primary outcome was calculated by dividing the number of incident cases by the total follow-up period and presented as per 1000 person-years. Cox-proportional hazard regression was performed to estimate the risk of cardiovascular events. Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for lifestyle factors such as smoking status, alcohol consumption, physical activity, hypertension, dyslipidemia, and CKD. Model 3 was additionally adjusted for BMI. Stratified analyses were performed according to age, sex, hypertension, dyslipidemia, obesity (BMI ≥ 25), alcohol consumption, regular physical exercise, and smoking status. To test for potential effect modification, forest plots for the risk of outcome according to risk factor subgroups were constructed.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria, <http://www.Rproject.org>). A two-sided P -value < 0.05 was considered statistically significant.

Results

Baseline characteristics of the study population

The median follow-up duration was 8.4 years and fatty liver prevalence, based on an FLI ≥ 60 , was 9.8%. The baseline characteristics of each group are shown in Table 1. Compared with the control group (FLI < 60), people in the NAFLD group (FLI ≥ 60) were older, more likely to be male and current smokers, and had higher alcohol consumption, physical exercise, and income level ($P < 0.001$ for all). Additionally, subjects with NAFLD were more likely to have diabetes, hypertension, dyslipidemia, and CKD than those without NAFLD ($P < 0.001$). Most anthropometric and laboratory variables (including BMI, systolic/diastolic blood pressure, fasting glucose, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol) were less metabolically favorable in the NAFLD group compared with the non-NAFLD (all $P < 0.001$).

Table 1
Baseline participant characteristics according to fatty liver index

	Fatty liver index < 60	Fatty liver index ≥ 60	P-value
<i>n</i>	4,802,589	521,821	
Age, years	30.5 ± 5.0	32.8 ± 4.3	< 0.0001
Male (%)	2,524, 413 (52.6)	481, 541 (92.3)	< 0.0001
Smoking (%)			< 0.0001
Non-smoker	2,963,942 (61.7)	150,164 (28.8)	
Ex-smoker	446,112 (9.3)	71,918 (13.8)	
Current smoker	1,392,535 (29.0)	299,739 (57.4)	
Alcohol consumption (%)			< 0.0001
None	2,049,364 (42.7)	142,769 (27.4)	
Mild	2,753,225 (57.3)	379,052 (72.6)	
Regular exercise, yes (%)	597,740 (12.5)	67,619 (13.0)	< 0.0001
Income (lowest 20%)	810,224 (16.9)	62,556 (12.0)	< 0.0001
Body mass index (kg/m ²)			< 0.0001
< 18.5	429,702 (9.0)	60 (0.0)	
< 23	2,566,709 (53.4)	6,751 (1.3)	
< 25	964, 204 (20.1)	38,708 (7.4)	
< 30	801,638 (16.7)	309,485 (59.3)	
≥ 30	40,336 (0.8)	166, 817 (32.0)	
Systolic blood pressure (mmHg)	115.9 ± 12.4	128.2 ± 13.4	< 0.0001
Diastolic blood pressure (mmHg)	72.6 ± 8.9	81.0 ± 9.9	< 0.0001
Comorbidity			
Diabetes (%)	55, 866 (1.2)	35,924 (6.9)	< 0.0001
Hypertension (%)	222,703 (4.6)	124,771 (23.9)	< 0.0001
NOTE: Data are presented as means ± standard deviations for continuous variables and n (%) for categorical variables.			
Abbreviations: CKD, chronic kidney disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein			
*Geometric means			

	Fatty liver index < 60	Fatty liver index ≥ 60	P-value
Dyslipidemia (%)	221,505 (4.6)	118,511 (22.7)	
CKD (%)	131,562 (2.7)	13,417 (2.6)	
Laboratory findings			
Serum glucose (mg/dL)	89.5 ± 13.9	99.3 ± 27.2	< 0.0001
LDL cholesterol (mg/dL)	114.8 ± 275.4	121.5 ± 155.7	< 0.0001
HDL cholesterol (mg/dL)	58.6 ± 26.3	49.2 ± 36.1	< 0.0001
Triglyceride (mg/dL)*	85.5 (85.5–85.6)	221.9 (221.5–222.2)	< 0.0001
NOTE: Data are presented as means ± standard deviations for continuous variables and n (%) for categorical variables.			
Abbreviations: CKD, chronic kidney disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein			
*Geometric means			

Risk of myocardial infarction and stroke with NAFLD

The incidence rates of MI and stroke were higher in the NAFLD (FLI ≥ 60) group compared with the control (FLI < 60) group. After adjusting for age, sex, smoking, alcohol consumption, regular exercise, diabetes, hypertension, dyslipidemia, CKD, and BMI, the risk of MI and stroke were significantly higher in the NAFLD group, compared with the control group (hazard ratio [HR] = 1.69; 95% confidence interval [CI]: 1.61–1.77 and HR = 1.73; 95% CI: 1.63–1.84, respectively; Table 2). The relationships between risk of MI or stroke and FLI were dose-dependent (HR = 1.28 in FLI 30–59 and 1.73 in FLI ≥ 60 for MI and HR = 1.18 in FLI 30–59 and 1.41 in FLI ≥ 60 for stroke, respectively).

Table 2
Risk of cardiovascular event according to fatty liver index

Fatty liver index	Events (n)	Follow-up duration (person-years)	Incidence rate (per 1,000 p-y)	Adjusted HR (95% CI)		
				Model 1	Model 2	Model 3
Myocardial infarction						
< 60	9785	40,176,291.19	0.244	1 (Ref.)	1 (Ref.)	1 (Ref.)
≥ 60	3266	4,391,182.59	0.744	3.30 (2.92–3.16)	2.27 (2.18–2.37)	1.69 (1.61–1.77)
< 30	6902	33,278,802.01	0.207	1 (Ref.)	1 (Ref.)	1 (Ref.)
30–59	2883	6,897,489.18	0.418	1.52 (1.45–1.59)	1.35 (1.29–1.42)	1.28 (1.22–1.34)
≥ 60	3266	4,391,182.59	0.744	2.64 (2.52–2.76)	1.92 (1.82–2.02)	1.73 (1.63–1.84)
Stroke						
< 60	6007	40,184,075.51	0.164	1 (Ref.)	1 (Ref.)	1 (Ref.)
≥ 60	1996	4,394,802.68	0.447	2.71 (2.58–2.85)	2.06 (1.96–2.18)	1.47 (1.39–1.56)
< 30	4749	33,283,912.13	0.143	1 (Ref.)	1 (Ref.)	1 (Ref.)
30–59	1858	6,900,163.38	0.269	1.46 (1.38–1.55)	1.28 (1.21–1.36)	1.18 (1.11–1.26)
≥ 60	1966	4,394,802.68	0.447	2.36 (2.23–2.50)	1.64 (1.54–1.74)	1.41 (1.32–1.51)
Abbreviations: p-y, person-year; HR, hazard ratio; CI, confidence interval						
Model 1: Adjusted for age and sex						
Model 2: Adjusted for age, sex, smoking, alcohol consumption, regular exercise, diabetes, hypertension, dyslipidemia, and chronic kidney disease						
Model 3: Model 2 plus adjusted for body mass index						

Stratified analyses according to subgroups

We performed stratified analyses by various factors including age, sex, diabetes, hypertension, dyslipidemia, and obesity, which showed that the associations between high FLI and increased MI risk were consistent across all strata regardless of baseline characteristics (Fig. 1). With regard to stroke, this relationship was generally consistent except for subjects with diabetes who showed low prevalence (n =

91,790, 1.72%) in the study population and a limited number of outcome events (555 cases, **Supplementary Table 1**).

Discussion

This is the first study to our knowledge that shows a relationship between NAFLD (defined using FLI) and cardiovascular events, particularly MI and stroke, among young adults 20–39 years old. Risk for MI and stroke increased significantly in young adults with NAFLD compared with a control group, independent of conventional cardiovascular risk factors. Also, there was a dose-dependent increase in MI and stroke risk according to steatosis grade.

Youth-onset NAFLD is thought to be a more progressive disease, leading to advanced fibrosis, compared with adult-onset NAFLD,[26] and it has a stronger association with CVD.[27] However, evaluations of the association between NAFLD and cardiovascular events in adults under 40 years are limited. In this study, high HRs for MI and stroke were observed in subjects younger than 30 years as well as in subjects 30 years and older (HR 1.43 and 1.80 for MI and HR 1.63 and 1.35 for stroke, respectively), suggesting an adverse relationship between NAFLD and CVD risk even at a relatively young age. When we categorized FLI values into three groups (< 30 , $30-59$, and ≥ 60), there was a dose-dependent increase MI and stroke risk. These results suggest FLI is an independent predictor of CV events and, thus, FLI may be of clinical value for identifying young-adult patients who require intense lifestyle modification. Additionally, there was an increased risk of MI and stroke, even at lower FLI levels ($30-59$) that generally do not meet the criteria for NAFLD, implying a need for early detection of high-risk subjects via FLI score.

The mechanisms linking NAFLD with CV events in young adults are not yet fully elucidated, but several hypotheses exist. First, obesity is a strong risk factor for NAFLD in young people and is considered an initial stage of chronic and metabolic inflammatory disease. In adipose tissue, leukocytes generate sustained pro-inflammatory processes that have negative effects on adipocyte insulin sensitivity and contribute to insulin resistance,[28] which contributes to myocardial damage.[29] Indeed, younger MI patients are reported to have more central obesity and higher BMI compared with control subjects.[30] Second, the rising prevalence of conventional cardiovascular risk profiles such as dyslipidemia [31], high blood pressure [32], and increased carotid intimal medial thickness [33] are strongly associated with NAFLD in children and adolescents, implying a close link between early atherosclerosis and NAFLD in young adults. When we adjusted for traditional cardiovascular risk factors, including obesity, the independent association between NAFLD and CVD remained. Third, CVD risk may be determined by genetic or metabolic factors in young adults with NAFLD.[34] Stroke onset younger than 35 years is likely to have other underlying mechanisms including non-atherosclerotic arteriopathy, changes in hemostatic balance, vasospasm and coagulation disorder,[35] or advanced liver disease, which are associated with imbalances in pro- and anti-coagulation.[36] However, further prospective studies are needed to confirm the independent role of NAFLD in CVD pathogenesis in young adults.

In this study, analyses stratified by baseline variables showed no strong effect modifiers between FLI and outcome variables, indicating that the results are generally consistent, regardless of baseline characteristics such as hypertension, dyslipidemia, obesity, or regular exercise. Although not statistically significant, the association between NAFLD and incident MI or stroke was slightly higher among people without regular exercise, suggesting the potential for regular exercise to reduce CVD risk.

This study provides new insights for understanding the relationship between CVD and NAFLD in young adults and presents a strategy for early identification of individual risk factors for appropriate CVD prevention. For asymptomatic young people, especially those under 40 years, it is difficult to evaluate CVD risk. For example, the ASCVD risk algorithm only applies to individuals 40–75 years old. Because the parameters included in the FLI are easily accessible in clinical practice, our results can be used to establish a strategy to identify NAFLD in young-adult patients at higher risk of early onset CVD and to reduce their future risk of CVD.

This study has some limitations. First, because of its population-based observational design, our study cannot establish a causal relationship. Second, using FLI as a surrogate marker of fatty liver cannot accurately quantify steatosis presence and severity.[37] It was impossible to differentiate simple steatosis from steatohepatitis, and various severities of NAFLD may affect CVD events differently. However, the association with multiple-site atherosclerosis and cardiovascular mortality was well defined in a large cohort study,[38] and the use of FLI is practical for screening the general population in epidemiologic studies.[39] Third, because MI and stroke diagnoses were based on claims data using the ICD-10 code, it is possible that these conditions were under- or overestimated. However, the definition we used in this study has been validated in several previous studies.[34, 24, 40] Also, we excluded patients who had only one diagnosis in an outpatient clinic to avoid overestimation. Lastly, because the NHIS health exam is provided to young adult workers and householders, only half of young adults were eligible. Further replicative research using more accurate measures to diagnose cardiovascular events is needed to validate our results.

Conclusion

NAFLD is associated with an increased risk of MI and stroke in young adults under 40 years and our results suggest that FLI can be an effective surrogate to identify younger subjects with NAFLD who have a higher risk of early-onset cardiovascular events. These results suggest that specialized clinical and research attention is needed to prevent CVD in young adults with NAFLD.

Declarations

Ethics approval and consent to participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised

in 2008. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (2012-106-1183) and confirmed to the ethical guidelines of the World Medical Association Declaration of Helsinki. The requirement for informed consent from individuals was waived because de-identified secondary data was used.

Consent for publication

Not applicable

Availability of data and material

Publicly available datasets were analyzed in this study. This data can be found here:

[<https://nhiss.nhis.or.kr/REQ000047265-004>].

Conflict of Interest (Col) statements

GE Chung, EJ Cho, J-J Yoo, Y Chang, Y Cho, S-H Park, K Han, S-M Jeong, KW Yoon, DW Shin, SJ Yu, YJ Kim, J-H Yoon declare that they have no conflict of interest. The manuscript must also be accompanied with the Copyright/Authorship/Disclosure form that contains the Col statements signed by each author.

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Authors Contributions:

GE Chung and EJ Cho reviewed the data, drafted and revised the manuscript. J-J Yoo, Y Chang, Y Cho, S-M Jeong, KW Yoon, YJ Kim and JH Yoon collected and reviewed the data and revised the manuscript. S-H Park and K Han performed statistical analyses and revised the manuscript. DW Shin and SJ Yu conceived and designed the study, collected the data, and revised the manuscript. All authors reviewed the manuscript.

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Figures

Figure 1

Forest plot showing the HRs of the association between FLI (<30, 30–60, and ≥60) and incident myocardial infarction (A) and stroke (B) in different subgroups: age <30 vs. ≥30 years; male vs. female; no diabetes vs. diabetes; no hypertension vs. hypertension; no dyslipidemia vs. dyslipidemia; non-obese (BMI <25) vs. obese (BMI ≥25); non-smoking, ex-smoking, or current smoking; non-alcohol consumption vs. mild alcohol consumption; and no regular exercise vs. regular exercise. Adjusted for age, sex, body mass index, alcohol consumption, smoking, regular exercise, income, diabetes mellitus, hypertension, dyslipidemia, and chronic kidney disease. HRs are represented by black squares; 95% CIs are denoted by

horizontal whiskers. Abbreviations: BMI, body mass index; CI, confidence interval; FLI, fatty liver index; HR, hazard ratio.

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