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ORIGINAL RESEARCH

Elevated Fatty Liver Index Is Independently Associated With New Onset of Hypertension During a 10-Year Period in Both Male and Female Subjects

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BACKGROUND: Fatty liver index (FLI), a predictor of nonalcoholic fatty liver disease, has been reported to be associated with several metabolic disorders. Because of a sex difference in FLI level, we hypothesized that FLI is associated with development of hypertension to a greater extent in men or women.

METHODS AND RESULTS: We investigated the relationship between FLI and development of hypertension during a 10-year period in a general population of subjects who received annual health examinations (n=28 990). After exclusion (44.9%) of subjects with missing data and those with hypertension at baseline, a total of 15 965 subjects (men/women: 9466/6499) were included. FLI level was significantly higher in men than in women. During the 10-year period, 2304 men (24.3%) and 745 women (11.5%) had new onset of hypertension. Multivariable Cox proportional hazard models with a restricted cubic spline showed that the hazard ratios (HRs) for development of hypertension after adjustment of age, systolic blood pressure, estimated glomerular filtration rate, habits of smoking and alcohol drinking, family history of hypertension, and diagnosis of diabetes mellitus and dyslipidemia increased gradually with increase in FLI in men and increased rapidly and then slowly with increase in FLI in women. There was a significant interaction between FLI and sex for the risk of hypertension in all of the subjects (P=0.049). The addition of FLI to traditional risk factors significantly improved the discriminatory capability.

CONCLUSIONS: A high level of FLI predicts the development of hypertension in both men and women, although distribution patterns of HRs were different between sexes.

Key Words: hypertension ■ lipids ■ liver ■ obesity

Hypertension has been reported to be linked to several diseases, including diabetes mellitus, chronic kidney disease, and cerebral and cardiovascular diseases, which are a major cause of death worldwide.[1,2] Traditional risk factors for hypertension include renal dysfunction, expressed as a low estimated glomerular filtration rate (eGFR), smoking habit, family history of hypertension, and comorbidities of diabetes mellitus and dyslipidemia.[3] The prevalence of hypertension has increased and remains high, and about 35% of individuals in East Asia are hypertensive despite substantial regional and global efforts.[4] Therefore, it is important to identify individuals who are at high risk for the development of hypertension.

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CLINICAL PERSPECTIVE

What Is New?

- The relationships of fatty liver index, a noninvasive and simple biomarker for diagnosis of nonalcoholic fatty liver disease, as a continuous variable and categorized tertile subgroups with the development of hypertension during a 10-year follow-up period were investigated in a large number of subjects divided by sex.
- A high level of fatty liver index, originally developed as an indicator of nonalcoholic fatty liver disease, predicts the development of hypertension during a 10-year period in both men and women, although distribution patterns of the adjusted hazard ratios are different between sexes.
- The addition of fatty liver index to traditional risk factors significantly improves the discriminatory capability for prediction of the development of hypertension.

What Are the Clinical Implications?

- A further understanding of the mechanism of the link between fatty liver index and hypertension may enable the development of new therapeutic strategies for prevention of hypertension.

Nonstandard Abbreviations and Acronyms

FLI	fatty liver index
GGT	γ-glutamyl transferase
NAFLD	nonalcoholic fatty liver disease
T1	first tertile
T3	third tertile
WC	waist circumference

Nonalcoholic fatty liver disease (NAFLD) has been attracting attention as a cause of liver cirrhosis and hepatocellular carcinoma.[5,6] NAFLD is diagnosed in ≈10% to 30% of adults by health examinations,[7] and the number of patients with NAFLD has recently been increasing.[8] NAFLD has also been highlighted as a lifestyle-related disease that is associated with obesity, metabolic syndrome, type 2 diabetes mellitus, insulin resistance, dyslipidemia, and cardiovascular disease.[9,10] It has recently been proposed that liver disease associated with metabolic dysfunction should be newly defined as metabolic dysfunction–associated fatty liver disease.[11] It has been reported that prevalence of NAFLD is higher in men, but sex difference in the association between NAFLD and its related diseases remains unclear.[7,8]

Diagnosis of NAFLD has required liver biopsy,[12] but several noninvasive procedures have recently been established using liver ultrasonography, computed tomography, magnetic resonance spectroscopy, and several biochemical indexes, including fatty liver index (FLI).[13] FLI, which is calculated by using body mass index (BMI), waist circumference (WC), and levels of γ-glutamyl transferase (GGT) and triglycerides, is a noninvasive and simple biomarker for diagnosis of NAFLD[14] and has a high concordance with the histological criteria for NAFLD.[15–17] This noninvasive index enables analysis of the roles of NAFLD in various diseases using a large group of study subjects.

Approximately 50% of hypertensive subjects have been shown to have NAFLD in cross-sectional studies.[18–20] However, there have been few studies on the possible association of NAFLD itself with the development of hypertension in a general population independent of conventional and other metabolic risk factors. To the best of our knowledge, there have been only 3 studies on the association between FLI level and development of hypertension.[21–23] Logistic regression analyses using 1521 subjects (men/women: 484/1037) in an average follow-up period of 2.6 years in Korea[21] and 2565 subjects (men/women: 1138/1427) in a follow-up period of 9 years in France[22] showed that odds ratios for the development of hypertension were higher in the high FLI group than in the low FLI group, although the cumulative incidence of hypertension was not analyzed in those studies. A longitudinal study using 334 280 Korean subjects (men/women: 161 338/172 942) also showed that there was an association between FLI level and the risk of cumulative incidence of hypertension during a median follow-up period of 5.2 years.[23] However, despite the fact that there is a sex difference in the level of FLI,[16] there has been no study in which the relationship between FLI level and development of hypertension was investigated separately in men and women.[21–23]

Therefore, the association between FLI and development of hypertension in subjects divided by sex has not been fully characterized. We hypothesized that FLI is associated with new onset of hypertension to a greater extent in men or women. In the present study, we investigated the relationships of FLI as a continuous variable and categorized tertile subgroups with the development of hypertension during a 10-year follow-up period in a large number of subjects divided by sex.

METHODS

This study was a cohort study in Japan that was conducted as a project of the Broad-Range Organization for Renal, Arterial, and Cardiac Studies by Sapporo Medical University Affiliates (BOREAS) investigators and was designed as the BOREAS-HT1 study.

The study conformed to the principles outlined in the Declaration of Helsinki and was performed with the approval of the institutional ethical committee of Sapporo Medical University (number: 30-2-32). Written informed consent was obtained from all of the subjects. The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Subjects

All of the subjects who received annual health examinations at Keijinkai Maruyama Clinic, Sapporo, Japan, in 2006 were enrolled in this registry (n=28 990).[24,25] A flowchart of the study participants is shown in Figure 1. Prespecified exclusion criteria were the absence of data for blood pressure, BMI, WC, triglycerides, and GGT and diagnosis of hypertension at baseline. After exclusion, a total of 15 965 subjects (men/women: 9466/6499) who received health examinations at least once in the period from 2007 to 2016 were included in the present study. Because fatty liver was not evaluated by liver ultrasonography, computed tomography, and other procedures, subjects with fatty liver at baseline were not excluded in the present study. A self-administered questionnaire survey was performed to obtain information on smoking habit, alcohol drinking habit, and use of drugs for diabetes mellitus, hypertension, and dyslipidemia.

Measurements

Medical examinations and samplings of urine and blood were performed after an overnight fast. Blood pressure was measured twice consecutively on the upper arm using a sphygmomanometer (number 601; Kenzmedico, Saitama, Japan), and average blood pressure was used for analysis. Body height and weight were measured in light clothing without shoes, and BMI was calculated as body weight in kilograms divided by height in meters squared. eGFR was calculated by the following equation for Japanese people: eGFR (mL/min/1.73 m^2)=194×serum creatinine(

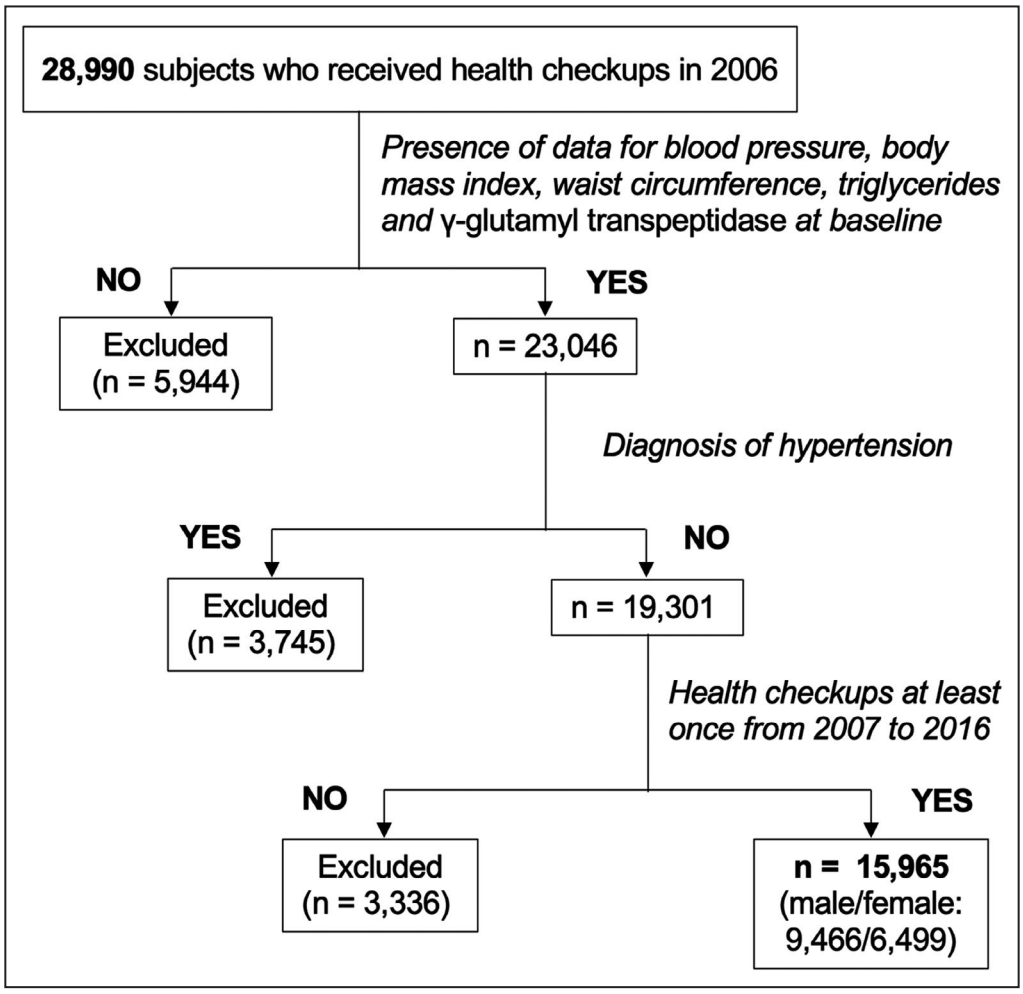

Figure 1. Flowchart of the selected study participants.
Among 28 990 subjects enrolled in 2006, a total of 15 965 (men/women: 9466/6499) were finally included for analyses in the present study.

$^{-1.094)}$×age$^{(-0.287)}$×0.739 (if woman).[26] FLI was calculated using the algorithm reported by Bedogni et al[14]: FLI=[e$^{(0.953\times\ln\ (\text{triglycerides})+0.139\times\text{BMI}+0.718\times\ln\ (\text{GGT})+0.053\times\text{WC}-15.745)}$]/[1+e$^{(0.953\times\ln\ (\text{triglycerides})+0.139\times\text{BMI}+0.718\times\ln\ (\text{GGT})+0.053\times\text{WC}-15.745)}$]×100.

Hypertension was diagnosed in accordance with the guideline of the Japanese Society of Hypertension[27]: systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or self-reported use of antihypertensive drugs. Diabetes mellitus was diagnosed in accordance with the guideline of the American Diabetes Association[28]: fasting plasma glucose ≥126 mg/dL, hemoglobin A1c ≥6.5%, or self-reported use of antidiabetic drugs. Dyslipidemia was diagnosed as low-density lipoprotein cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, triglycerides ≥150 mg/dL, or self-reported use of antidyslipidemic drugs.

Statistical Analysis

Numeric variables are expressed as mean±SD for parameters with normal distributions and as medians (interquartile ranges) for parameters with skewed distributions. The distribution of each parameter was tested for its normality using the Shapiro-Wilk W test. Comparison between 2 groups was done with Mann-Whitney *U* test. Clinical parameters were divided into 3 subgroups according to tertiles of FLI at baseline (first tertile [T1]–third tertile [T3]) in both male and female subjects. Intergroup differences in percentages of demographic parameters were examined by the χ^2 test. One-way ANOVA was used for detecting significant differences between data in multiple groups. The association between FLI levels at baseline and the development of hypertension was investigated by multivariable Cox proportional hazard models with a restricted cubic spline after adjustment of confounders, including age, systolic blood pressure, eGFR, smoking habit, alcohol drinking habit, family history of hypertension, and diagnosis of diabetes mellitus and dyslipidemia at baseline. The hazard ratios (HRs) and 95% CIs for the development of hypertension in FLI level at baseline in both male and female subjects were calculated by adjustment of the confounders. The association between FLI at baseline and systolic blood pressure during a 10-year follow-up period after adjustment of confounders was analyzed by using a linear mixed effects model. To compare the discrimination for development of hypertension between the models adjusted for confounders as traditional risk factors for hypertension with and without FLI level, C-statistics analogous to the area under the receiver operating characteristic curve were estimated.[29,30] A *P* value of <0.05 was considered statistically significant. All data were analyzed by using EZR[31] and R version 3.6.1.

RESULTS

Characteristics of the Study Subjects

Basal characteristics of the included subjects are shown in Table 1. Components of FLI calculation, including BMI, WC, GGT, and triglycerides, were significantly higher in male subjects than in female subjects. FLI level was significantly higher in male subjects (median [interquartile range], 28.8 [12.8–53.4]) than in female subjects (median [interquartile range], 5.8 [2.9–13.9]). The frequencies of habits of smoking and alcohol drinking were lower in female subjects than in male subjects.

Basal characteristics of male and female subjects divided by subgroups according to tertiles of FLI at baseline are shown in Tables 2 and 3, respectively. Higher tertiles of FLI were accompanied by larger BMI and WC, higher frequencies of habits of alcohol drinking and smoking, diabetes mellitus and dyslipidemia, higher levels of systolic and diastolic blood pressures, hemoglobin, platelets, uric acid, aspartate aminotransferase, alanine aminotransferase, GGT, fasting plasma glucose, hemoglobin A1c, low-density lipoprotein cholesterol, and triglycerides, and lower level of high-density lipoprotein cholesterol in both sexes. In addition, higher tertiles of FLI were accompanied by higher blood urea nitrogen and lower eGFR in female subjects.

Cumulative Incidence for New Onset of Hypertension During a Follow-Up Period

The mean follow-up period was 6.0 years (range, 1–10 years), and follow-up summation was 95 822 (men/women: 55 848/39 974) person-years. Among the 15 965 included subjects (men/women: 9466/6499), 2304 male subjects (24.3%) and 745 female subjects (11.5%) developed new onset of hypertension during a 10-year period (Table 4). The cumulative incidence rate of hypertension was 272 (95% CI, 264–281) (men/women: 336 [324–348]/175 [163–187]) per 1000 person-years in all of the subjects, and the rates in tertiles of FLI (T1–T3) in both male and female subjects are shown in Table 4. The prevalences of fatty liver determined by the FLI criteria for diagnosis of NAFLD in Asian subjects (men/women: FLI ≥35/FLI ≥25)[16] and in the original study (FLI ≥60)[14] are also shown in Table 4.

Impact of FLI Level at Baseline on New Onset of Hypertension During a Follow-Up Period

Multivariable Cox proportional hazard models with a restricted cubic spline showed that the HR for development of hypertension increased with a higher FLI level at baseline after adjustment of age, systolic blood pressure, eGFR, habits of smoking and alcohol

Table 1. Characteristics of the Included Subjects at Baseline (n=15 965)

Characteristic	Men (n=9466)	Women (n=6499)	*P* Value
Age, y	45±11	44±11	<0.001
Body mass index	23.6±3.1	21.3±3.2	<0.001
Waist circumference, cm	84.5±8.5	77.4±8.9	<0.001
Systolic blood pressure, mm Hg	115±12	107±13	<0.001
Diastolic blood pressure, mm Hg	74±9	67±9	<0.001
Smoking habit	4498 (49.8)	1347 (21.6)	<0.001
Alcohol drinking habit	4867 (51.4)	1607 (24.7)	<0.001
Family history			
Hypertension	1670 (17.6)	1866 (28.7)	<0.001
Comorbidity			
Diabetes mellitus	430 (4.5)	71 (1.1)	<0.001
Dyslipidemia	3457 (36.5)	1196 (18.4)	<0.001
Biochemical data			
Hemoglobin, g/dL	15.2±1.0	12.9±1.2	<0.001
Platelet, $10^4/\mu L$	23.4±4.9	24.6±5.5	<0.001
Albumin, g/dL	4.4±0.2	4.3±0.2	<0.001
Blood urea nitrogen, mg/dL	14.6±3.3	13.1±3.2	<0.001
Creatinine, mg/dL	0.80±0.23	0.59±0.09	<0.001
eGFR, mL/min/1.73 m^2	84.8±13.9	88.0±15.4	<0.001
Uric acid, mg/dL	6.0±1.2	4.3±0.9	<0.001
AST, U/L	22 (19–27)	18 (16–22)	<0.001
ALT, U/L	24 (17–35)	14 (12–19)	<0.001
GGT, U/L	37 (24–64)	17 (14–24)	<0.001
FPG, mg/dL	94±20	86±12	<0.001
Hemoglobin A1c, %	5.4±0.7	5.2±0.5	<0.001
Total cholesterol, mg/dL	203±34	200±34	<0.001
LDL cholesterol, mg/dL	122±31	114±31	<0.001
HDL cholesterol, mg/dL	56±14	70±15	<0.001
Triglycerides, mg/dL	105 (73–152)	63 (47–87)	<0.001
FLI	28.8 (12.8–53.4)	5.8 (2.9–13.9)	<0.001

Variables are expressed as number (percentage), mean±SD, or median (interquartile range). ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; FPG, fasting plasma glucose; GGT, γ-glutamyl transpeptidase; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

drinking, family history of hypertension, and diagnosis of diabetes mellitus and dyslipidemia at baseline in both men (Figure 2A) and women (Figure 2B), although distribution patterns of HRs were different by sex. The HR gradually increased with a higher FLI in male subjects (Figure 2A). On the other hand, in female subjects, the HR quickly increased with a higher FLI until the FLI level of 20 and then slowly increased with a higher FLI to the FLI level of 100 (Figure 2B). There was a significant interaction between FLI and sex for the adjusted HR of development of hypertension in all subjects (P=0.049).

When the T1 group of FLI was used as the reference, multivariable Cox proportional hazard model analysis after adjustment of age, systolic blood pressure, eGFR, habits of smoking and alcohol drinking, family history of hypertension, and diagnosis of diabetes mellitus and dyslipidemia at baseline showed that HRs for development of hypertension in the second tertile group (HR, 1.29; 95% CI, 1.13–1.47) and T3 group (HR, 1.55; 95% CI, 1.35–1.77) were significantly higher than HR in the T1 group of FLI in male subjects (Table 5). In female subjects, the adjusted HR in the T3 group of FLI (HR, 1.52; 95% CI, 1.20–1.93) was significantly higher than that in the T1 group of FLI in female subjects (Table 5).

Association Between FLI at Baseline and Systolic Blood Pressure During the Follow-Up Period

Linear mixed effects model analyses after adjustment of age, eGFR, habits of smoking and alcohol drinking, family history of hypertension, and diagnosis of diabetes mellitus and dyslipidemia at baseline showed

Table 2. Characteristics of Male Subjects With Tertiles of FLI at Baseline (n=9466)

Characteristic	T1 (0.8–17.4) (n=3168)	T2 (17.5–43.9) (n=3150)	T3 (44.0–99.7) (n=3148)	*P* Value
Age, y	42±12	47±10	46±9	<0.001
Body mass index	21.0±1.8	23.4±1.8	26.3±2.9	<0.001
Waist circumference, cm	76.7±5.4	84.6±4.8	92.1±6.9	<0.001
Systolic blood pressure, mm Hg	111±12	115±12	118±11	<0.001
Diastolic blood pressure, mm Hg	71±9	74±8	76±8	<0.001
Smoking habit	1473 (48.8)	1464 (48.8)	1561 (51.9)	0.019
Alcohol drinking habit	1398 (44.1)	1713 (54.4)	1756 (55.8)	<0.001
Family history				
Hypertension	486 (15.3)	601 (19.1)	583 (18.5)	<0.001
Comorbidity				
Diabetes mellitus	75 (2.4)	134 (4.3)	221 (7.0)	<0.001
Dyslipidemia	453 (14.3)	1122 (35.6)	1882 (59.8)	<0.001
Biochemical data				
Hemoglobin, g/dL	14.8±1.0	15.1±1.0	15.5±1.1	<0.001
Platelet, 10^4/μL	22.9±4.7	23.6±5.1	23.5±5.1	<0.001
Albumin, g/dL	4.4±0.2	4.4±0.2	4.5±0.2	<0.001
Blood urea nitrogen, mg/dL	14.7±3.5	14.7±3.5	14.5±3.2	0.174
Creatinine, mg/dL	0.80±0.21	0.82±0.39	0.81±0.13	0.012
eGFR, mL/min/1.73 m^2	85.1±14.0	82.3±13.9	82.6±14.1	<0.001
Uric acid, mg/dL	5.7±1.1	6.1±1.2	6.6±1.2	<0.001
AST, U/L	21 (17–23)	24 (19–26)	31 (22–34)	<0.001
ALT, U/L	20 (15–24)	28 (19–33)	45 (27–53)	<0.001
GGT, U/L	30 (20–34)	53 (30–61)	108 (51–125)	<0.001
FPG, mg/dL	89±9	92±9	95±12	<0.001
Hemoglobin A1c, %	5.1±0.4	5.3±0.4	5.4±0.4	<0.001
Total cholesterol, mg/dL	194±30	206±32	216±35	<0.001
LDL cholesterol, mg/dL	116±28	126±30	126±33	<0.001
HDL cholesterol, mg/dL	62±15	56±14	51±12	<0.001
Triglycerides, mg/dL	78 (58–94)	120 (87–144)	197 (125–230)	<0.001

Variables are expressed as number (percentage), mean±SD, or median (interquartile range). ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; FPG, fasting plasma glucose; GGT, γ-glutamyl transpeptidase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; T1, first tertile; T2, second tertile; and T3, third tertile.

a significant association between FLI at baseline and systolic blood pressure during the 10-year follow-up in female subjects (interaction of FLI with follow-up year, estimate, 0.003; $P<0.001$) and a positive tendency of the interaction in male subjects (estimate, 0.001; $P=0.109$) (Table 6).

Discriminatory Capacity of the Addition of FLI for Predicting Development of Hypertension

The addition of FLI level to traditional risk factors for development of hypertension, including age, systolic blood pressure, eGFR, habits of smoking and alcohol drinking, family history of hypertension, and presence of diabetes mellitus and dyslipidemia, modestly but significantly increased the area under the receiver operating characteristic curve in both men (0.777 versus 0.782; $P<0.001$) and women (0.824 versus 0.829; $P<0.001$) (Table 7).

DISCUSSION

The present study showed that FLI as an indicator of NAFLD was independently associated with the risk for development of hypertension during a 10-year period in both male and female subjects. Multivariable Cox proportional hazard models with a restricted cubic spline showed that HRs for development of hypertension after adjustment of traditional risk factors increased with a higher FLI level at baseline in both men

Table 3. Characteristics of Female Subjects With Tertiles of FLI at Baseline (n=6499)

Characteristic	T1 (0.4–3.6) (n=2168)	T2 (3.7–9.9) (n=2177)	T3 (10.0–97.8) (n=2154)	*P* Value
Age, y	38±10	44±10	49±10	<0.001
Body mass index	18.9±1.5	20.8±1.7	24.3±3.2	<0.001
Waist circumference, cm	69.8±4.5	76.5±4.7	86.1±7.7	<0.001
Systolic blood pressure, mm Hg	102±2	106±13	112±13	<0.001
Diastolic blood pressure, mm Hg	64±8	67±9	71±9	<0.001
Smoking habit	447 (21.6)	434 (20.8)	466 (22.5)	0.415
Alcohol drinking habit	462 (21.3)	566 (26.0)	579 (26.9)	<0.001
Family history				
Hypertension	523 (24.1)	636 (29.2)	707 (32.8)	<0.001
Comorbidity				
Diabetes mellitus	2 (0.1)	15 (0.7)	54 (2.5)	<0.001
Dyslipidemia	181 (8.3)	288 (13.2)	727 (33.8)	<0.001
Biochemical data				
Hemoglobin, g/dL	12.7±1.2	12.8±1.2	13.2±1.1	<0.001
Platelet, $10^4/\mu L$	23.6±5.0	24.5±5.5	25.6±5.6	<0.001
Albumin, g/dL	4.3±0.2	4.3±0.2	4.3±0.2	0.001
Blood urea nitrogen, mg/dL	13.0±3.3	13.1±3.2	13.3±3.3	0.009
Creatinine, mg/dL	0.59±0.10	0.59±0.08	0.59±0.10	0.988
eGFR, mL/min/1.73 m^2	90.6±15.3	87.7±15.0	86.0±15.6	<0.001
Uric acid, mg/dL	4.0±0.8	4.2±0.8	4.7±1.0	<0.001
AST, U/L	18 (16–20)	19 (16–21)	22 (17–24)	<0.001
ALT, U/L	14 (10–16)	15 (11–17)	22 (14–25)	<0.001
GGT, U/L	16 (12–17)	20 (14–22)	36 (18–39)	<0.001
FPG, mg/dL	83±7	86±12	90±14	<0.001
Hemoglobin A1c, %	5.1±0.3	5.2±0.5	5.3±0.6	<0.001
Total cholesterol, mg/dL	186±31	198±32	213±34	<0.001
LDL cholesterol, mg/dL	102±26	113±28	128±32	<0.001
HDL cholesterol, mg/dL	75±14	72±14	64±14	<0.001
Triglycerides, mg/dL	49 (37–57)	67 (51–79)	106 (71–126)	<0.001

Variables are expressed as number (percentage), mean±SD, or median (interquartile range). ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; FPG, fasting plasma glucose; GGT, γ-glutamyl transpeptidase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; T1, first tertile; T2, second tertile; and T3, third tertile.

and women, although distribution patterns of HRs were different between sexes. In addition, HRs in the T3 group of FLI were significantly higher than those in the T1 group as the reference in both sexes. Linear mixed effects model analyses showed a significant positive interaction between FLI at baseline and systolic blood pressure during the follow-up in women and a positive tendency of the interaction in men. Furthermore, the addition of FLI to traditional risk factors significantly improved the discriminatory capability of regression models for predicting development of hypertension in both sexes. These findings suggest that measurement of FLI calculated by noninvasive circulating factors and indexes of obesity instead of performing ultrasound and/or biopsy in the liver can predict not only NAFLD but also the risk of hypertension during follow-up.

Two previous studies using 1521 Korean subjects (men/women: 484/1037) for an average follow-up period of 2.6 years[21] and 2565 French subjects (men/women: 1138/1427) in a follow-up period of 9 years[22] showed that odds ratios for the development of hypertension determined by logistic regression analyses were significantly higher in the high FLI group (FLI ≥60), a group diagnosed as NAFLD, and in the middle FLI group (FLI 30–59) than in the low FLI group (FLI <30), a group diagnosed as non-NAFLD. However, in those studies,[21,22] the HR of cumulative incidence of hypertension was not analyzed by using Cox proportional hazard models, and the sex difference in FLI level was not taken into consideration despite the fact that there is a sex difference in the level of FLI.[16] Furthermore, it is not clear whether categorization of FLI using FLI

Table 4. Development of Hypertension During the Follow-Up Period in Subjects With Tertiles of FLI at Baseline

Variable	All	T1	T2	T3
Number				
Men	9466	3168	3150	3148
Women	6499	2168	2177	2154
FLI, range				
Men	0.8–99.7	0.8–17.4	17.5–43.9	44.0–99.7
Women	0.4–97.8	0.4–3.6	3.7–9.9	10.0–97.8
Possible fatty liver (men/women: FLI ≥35/FLI ≥25), n (%)				
Men	3991 (42.2)	0 (0)	843 (26.8)	3148 (100)
Women	878 (13.5)	0 (0)	0 (0)	878 (40.8)
FLI ≥60, n (%)				
Men	1839 (19.4)	0 (0)	0 (0)	1839 (58.4)
Women	190 (2.9)	0 (0)	0 (0)	190 (8.8)
New onset of hypertension, n (%)				
Men	2304 (24.3)	412 (17.9)	804 (34.9)	1088 (47.2)
Women	745 (11.5)	115 (15.4)	181 (24.3)	449 (60.3)
Cumulative incidence rate, value per 1000 person-years (95% CI)				
Men	336 (324–348)	185 (168–201)	354 (333–375)	463 (441–484)
Women	175 (163–187)	85 (69–100)	131 (112–150)	312 (285–337)

FLI indicates fatty liver index; T1, first tertile; T2, second tertile; and T3, third tertile.

≥60 or FLI <30 is optimal because of the possibility of racial difference in cutoff levels of FLI for diagnosis of NAFLD.[14–17] It has been reported that the cutoff level of FLI for diagnosis of NAFLD seems to be lower in Asians than in Europeans: FLI ≥30 in China[17] and FLI ≥60 in Italy.[14] In addition, the subjects were not divided by sex in both of those studies, suggesting that there might be racial and sex differences in cutoff levels of FLI for diagnosis of NAFLD. To the best of our knowledge, the sex difference in the FLI value for diagnosis of NAFLD was considered in only one study performed in Taiwan, and the cutoff levels in male and female subjects in that study were FLI ≥35 and FLI ≥25, respectively.[16] In the present study, most of the men (100%) and women (40.8%) in the T3 group of FLI met the FLI criteria for diagnosis of NAFLD (men/women: FLI ≥35/FLI ≥25).[16] In female subjects, FLI level might be a risk factor for development of hypertension regardless of the presence of NAFLD.

Another longitudinal study using 334 280 Korean subjects (men/women: 161 338/172 942) showed that the risk of cumulative incidence of hypertension during a median follow-up period of 5.2 years was higher in the high FLI groups than in the lowest FLI group in quartiles.[23] However, FLI level was not divided by sex in that study.[23] In the present study, distribution patterns of adjusted HRs and FLI levels were different between men and women (Figure 2), and there was a significant interaction between FLI level and sex for the adjusted risk of development of hypertension. Therefore, we investigated the HRs of cumulative incidence of hypertension analyzed by using Cox proportional hazard models in 15 965 Japanese subjects (men/women: 9466/6499) divided by sex for a 10-year follow-up period. When FLI level is analyzed by both sexes together, the risk for development of hypertension might be underestimated in female subjects. Analysis divided by sex or at least categorization of FLI, such as tertiles and quartiles divided by sex, would be essential for investigation.

There are several possible mechanisms of the link between NAFLD and development of hypertension. It has been reported that angiotensin II–mediated signaling at multiple levels is involved in the development and progression of NAFLD, including increased steatosis, inflammation, insulin resistance, and fibrosis.[32] Dysregulation of the renin-angiotensin system may play a substantial role in the development of hypertension in NAFLD. Pre–diabetes mellitus and newly diagnosed type 2 diabetes mellitus have also been reported to be risk factors for hypertension.[33] It has been reported that FLI is associated with new onset of diabetes mellitus in subjects with pre–diabetes mellitus[34,35] and in a general population.[36] Pre–diabetes mellitus may contribute to the development of hypertension, although subjects with diabetes mellitus at baseline were excluded in the present study. As other possible mechanisms, the 2 diseases also share risk factors for metabolic syndrome, including obesity, insulin resistance, dyslipidemia, and chronic inflammation.[37,38] It has been reported that insulin resistance with visceral obesity causes compensatory hyperinsulinemia, leading to the development of hypertension and NAFLD.[39] Compensatory hyperinsulinemia

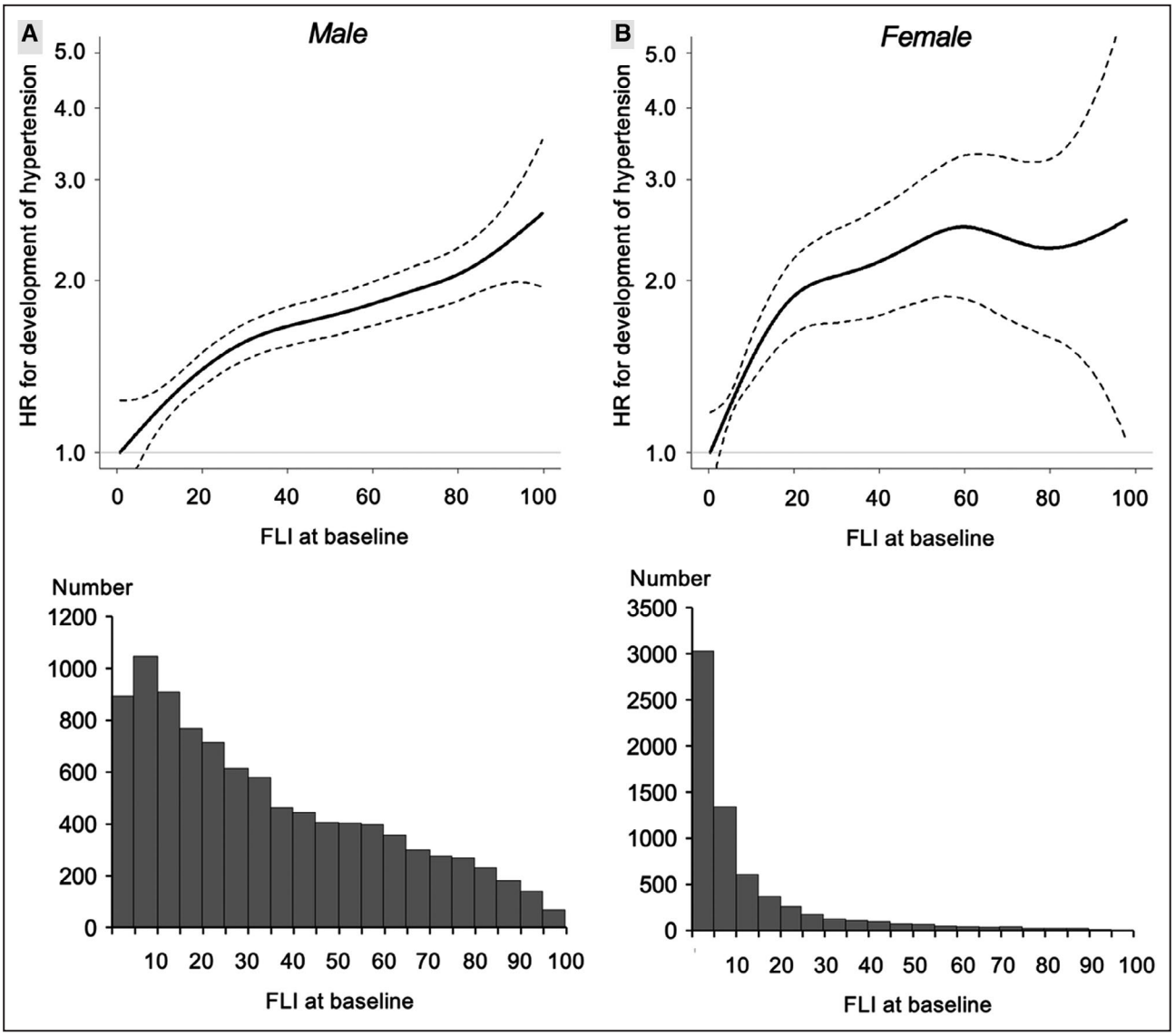

Figure 2. Hazard ratios (HRs) for the development of hypertension by fatty liver index (FLI) at baseline.
A and **B**, HRs for the development of hypertension by FLI at baseline in male subjects (**A**) and female subjects (**B**) analyzed by multivariable Cox proportional hazard models with a restricted cubic spline after adjustment of age, systolic blood pressure, estimated glomerular filtration rate, habits of smoking and alcohol drinking, family history of hypertension, and diagnosis of diabetes mellitus and dyslipidemia at baseline. Solid line: HR; dashed line: 95% CI. The reference values of FLI in male and female subjects were 0.8 and 0.4 as minimum values, respectively. Histograms of FLI levels in men and women are also shown.

attributable to insulin resistance with visceral obesity has been reported to cause activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, hyperleptinemia, and stimulation of the brain melanocortin system, which play a critical role in initiating hypertension.[40] Furthermore, the metabolic effects of insulin resistance, including hypertriglyceridemia, appear to interact synergistically with increased blood pressure to cause vascular and kidney injury that can exacerbate the hypertension.[40] A steatotic and inflamed liver has been reported to be a relevant source of proinflammatory, profibrogenic, and antifibrinolytic molecules called hepatokines, which theoretically can promote dysfunction of the vasculature, leading to hypertension.[41] In addition, xanthine oxidoreductase, a rate-limiting enzyme of uric acid production in the purine metabolism, is abundantly expressed in the liver and can increase reactive oxygen species by generating superoxide and hydrogen peroxide.[42] It has been reported that plasma xanthine oxidoreductase activity is a novel biomarker of metabolic disorder[43] and is independently associated with adipokines and hepatokines.[44] A change in xanthine oxidoreductase activity was shown to be significantly associated with changes in liver enzymes and body weight.[45] Inadequate activation of xanthine

Table 5. Multivariable Cox Proportional Hazard Analyses for Development of Hypertension in Tertiles of FLI

Variable	Men (n=9466)		Women (n=6499)	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
FLI				
T1	Reference	…	Reference	…
T2	1.29 (1.13–1.47)	<0.001	0.95 (0.73–1.23)	0.695
T3	1.55 (1.35–1.77)	<0.001	1.52 (1.20–1.93)	<0.001
Age (per 1 y)	1.03 (1.02–1.03)	<0.001	1.03 (1.02–1.04)	<0.001
SBP (per 1 mm Hg)	1.08 (1.07–1.08)	<0.001	1.09 (1.08–1.09)	<0.001
eGFR (per mL/min/1.73 m^2)	1.00 (0.99–1.00)	0.215	1.00 (0.99–1.00)	0.641
Smoking habit	1.15 (1.05–1.26)	0.002	1.31 (1.07–1.60)	0.010
Alcohol drinking habit	1.20 (1.09–1.32)	<0.001	1.26 (1.06–1.50)	0.010
Family history of hypertension	1.32 (1.19–1.46)	<0.001	1.24 (1.05–1.46)	0.010
Diabetes mellitus	1.17 (0.98–1.39)	0.080	1.30 (0.82–2.05)	0.264
Dyslipidemia	1.14 (1.04–1.26)	0.008	1.29 (1.07–1.54)	0.006
	AIC=33 206		AIC=9690	

AIC indicates Akaike information criterion; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; HR, hazard ratio; SBP, systolic blood pressure; T1, first tertile; T2, second tertile; and T3, third tertile.

oxidoreductase in NAFLD may promote oxidative stress–related tissue injury, including injury of endothelial cells and the kidney,[42] possibly leading to elevated blood pressure.

The present study has some limitations. First, because the study subjects had a yearly health checkup at a single urban clinic, the possibility of sample selection bias cannot be ruled out. Most of the subjects in this study were employees of companies and their family members in Sapporo. Employees in Japan often move from one city to another because of a change in the office or company, and most of the companies allow employees to select a clinic for annual health checkups from several health checkup centers. Thus, we speculate that moving from Sapporo and changing the clinic for health checkups are the main reasons for unavailability of data during the follow-up. According to the national death registry in Japan (http://www.ipss.go.jp/), mortality rates of male and female subjects aged 45 to 49 years in 2019 were 1.8% and 1.1%, respectively. Therefore, the reason for most of the missing subjects is unlikely to be mortality or poor health status. Second, because diagnosis of hepatic steatosis was performed by FLI but not by liver biopsy and imaging techniques, the severity of hepatic steatosis was not taken into consideration. Third, accurate information on alcohol consumption was not obtained in the present study. Fourth, the presence of hepatitis B and hepatitis C was unknown at baseline, although prevalence of hepatitis B (0.63%) and hepatitis C (0.49%) was reported to be relatively low in the Japanese population.[46,47] Fifth, although risk factors for hypertension at baseline were adjusted in multivariable Cox proportional hazard models, those risk factors during the follow-up period were not used for adjustment of the models. Furthermore, the association between change in FLI and development of hypertension needs to be investigated in the future. Sixth, information on the status of menopause, which may affect results in women, was not available in the present study. Finally, although the definition of hypertension was used as blood pressure of ≥140/90 mm Hg, according to the guideline of the Japanese Hypertension Society[27] in the present study, the results were almost the same when the definition of hypertension was used as blood pressure of ≥130/80 mm Hg, according to 2017 American College of Cardiology/American Heart Association hypertension guidelines[48] (Figure S1 and Table S1).

Table 6. Mixed Effects Model Analyses for Systolic Blood Pressure During the 10-Year Follow-Up

Variable	Men (n=9466)			Women (n=6499)		
	Estimate	SE	*P* Value	Estimate	SE	*P* Value
FLI (per 1)	0.106	0.005	<0.001	0.178	0.011	<0.001
Follow-up year (per 1 y)	0.678	0.022	<0.001	0.671	0.020	<0.001
Interaction (FLI—follow-up year)	0.001	0.001	0.109	0.003	0.001	<0.001

The model was adjusted by age, estimated glomerular filtration rate, smoking habit, alcohol drinking habit, family history of hypertension, and diagnosis of diabetes mellitus and dyslipidemia at baseline. FLI indicates fatty liver index.

Table 7. Discrimination of the Addition of FLI Into Traditional Risk Factors for Hypertension

Variable	AUC	
	Value (95% CI)	*P* Value
Men		
Traditional model*	0.777 (0.765–0.788)	…
Traditional model*+FLI	0.782 (0.771–0.794)	<0.001
Women		
Traditional model*	0.824 (0.807–0.840)	…
Traditional model*+FLI	0.829 (0.813–0.845)	<0.001

AUC indicates area under the curve; and FLI, fatty liver index.

*Traditional model includes age, systolic blood pressure, estimated glomerular filtration rate, smoking habit, alcohol drinking habit, family history of hypertension, and diagnosis of diabetes mellitus and dyslipidemia.

In conclusion, a high level of FLI, originally developed as an indicator of NAFLD, predicts the development of hypertension during a 10-year period in both men and women, although distribution patterns of the adjusted risk of hypertension are different between sexes. The addition of FLI to traditional risk factors significantly improves the discriminatory capability for prediction of the development of hypertension. A further understanding of the mechanism of the link between FLI and hypertension may enable the development of new therapeutic strategies for prevention of hypertension.

ARTICLE INFORMATION

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None.

Supplementary Material

Table S1
Figure S1

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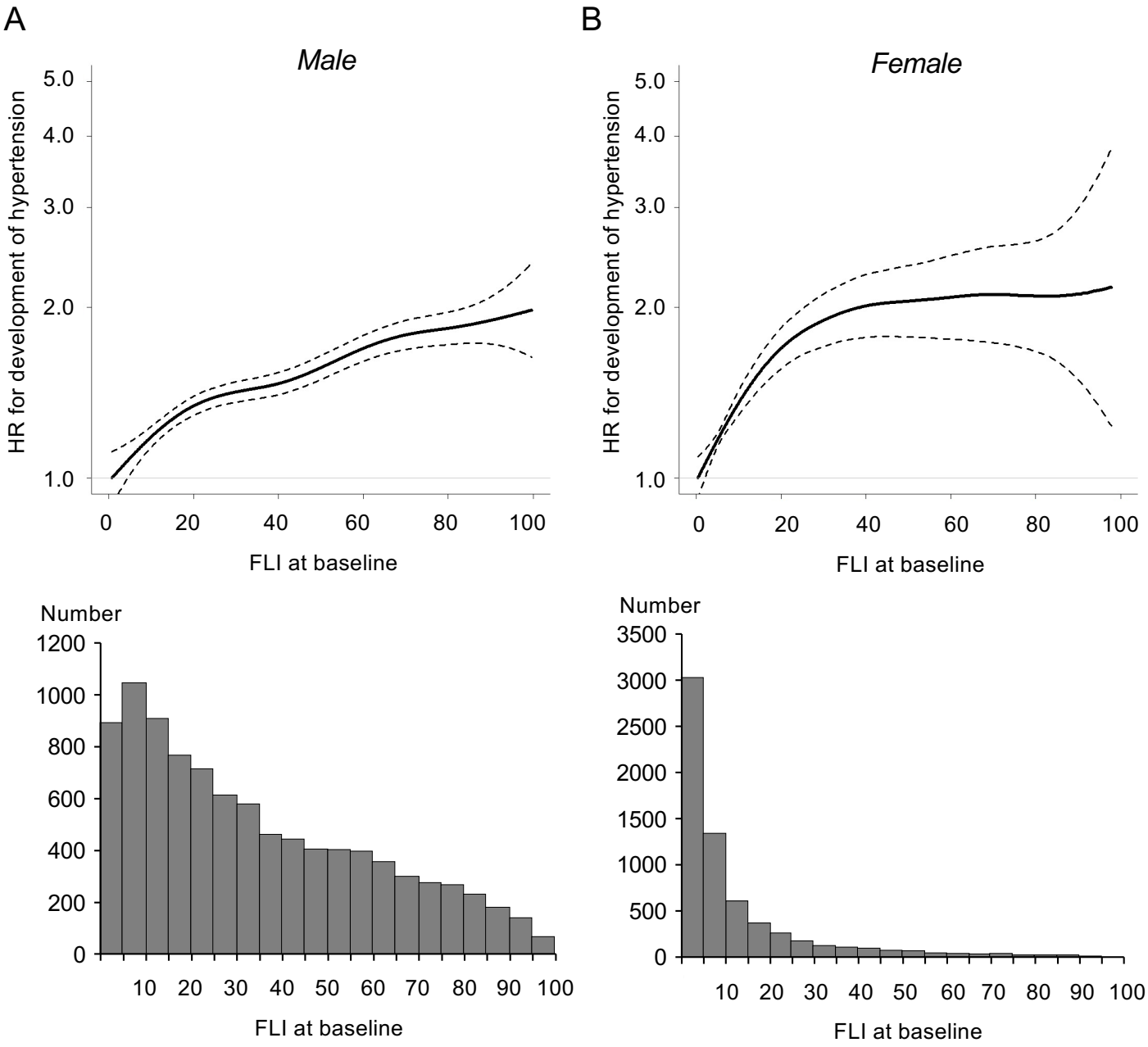
SUPPLEMENTAL MATERIAL

Table S1. Multivariable Cox proportional hazard analyses for development of hypertension (≥ 130/80) in tertiles of FLI.

	Male (n = 6,040)		Female (n = 5,485)	
	HR (95% CI)	P	HR (95% CI)	P
FLI				
T1	Reference	-	Reference	-
T2	1.25 (1.13-1.38)	< 0.001	1.20 (1.02-1.40)	0.029
T3	1.46 (1.31-1.61)	< 0.001	1.78 (1.52-2.07)	< 0.001
Age (per 1 year)	1.02 (1.01-1.02)	< 0.001	1.03 (1.02-1.04)	< 0.001
SBP (per 1 mmHg)	1.05 (1.04-1.05)	< 0.001	1.06 (1.05-1.07)	< 0.001
eGFR (per mL/min/1.73m^2)	1.00 (0.99-1.00)	0.681	1.00 (0.99-1.00)	0.856
Smoking habit	0.93 (0.86-0.99)	0.042	1.02 (0.89-1.17)	0.795
Alcohol drinking habit	1.14 (1.05-1.22)	< 0.001	1.15 (1.02-1.30)	0.023
Family history of hypertension	1.14 (1.04-1.25)	0.005	1.10 (0.98-1.23)	0.102
Diabetes Mellitus	0.97 (0.82-1.17)	0.778	1.44 (0.98-2.11)	0.061
Dyslipidemia	1.07 (0.99-1.16)	0.098	1.17 (1.02-1.33)	0.021
	AIC = 44,988		AIC = 20,779	

AIC, Akaike's information criterion; CI, confidence interval; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; SBP, systolic blood pressure; HR, hazard ratio.

Figure S1. Hazard ratios for the development of hypertension by FLI at baseline.



A, B. Hazard ratios (HRs) for the development of hypertension (≥ 130/80) by fatty liver index (FLI) at baseline in male subjects (A) and female subjects (B) analyzed by multivariable Cox proportional hazard models with a restricted cubic spline after adjustment of age, systolic blood pressure, estimated glomerular filtration rate, habits of smoking and alcohol drinking, family history of hypertension, and diagnosis of diabetes mellitus and dyslipidemia at baseline. Solid line: HR; dashed line: 95% confidence interval. The reference values of FLI in male and female subjects were 0.8 and 0.4 as minimum values, respectively. Histograms of FLI levels in males and females are also shown.