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ORIGINAL ARTICLE

Metabolic dysfunction–associated fatty liver disease predicts new onset of chronic kidney disease better than fatty liver or nonalcoholic fatty liver disease

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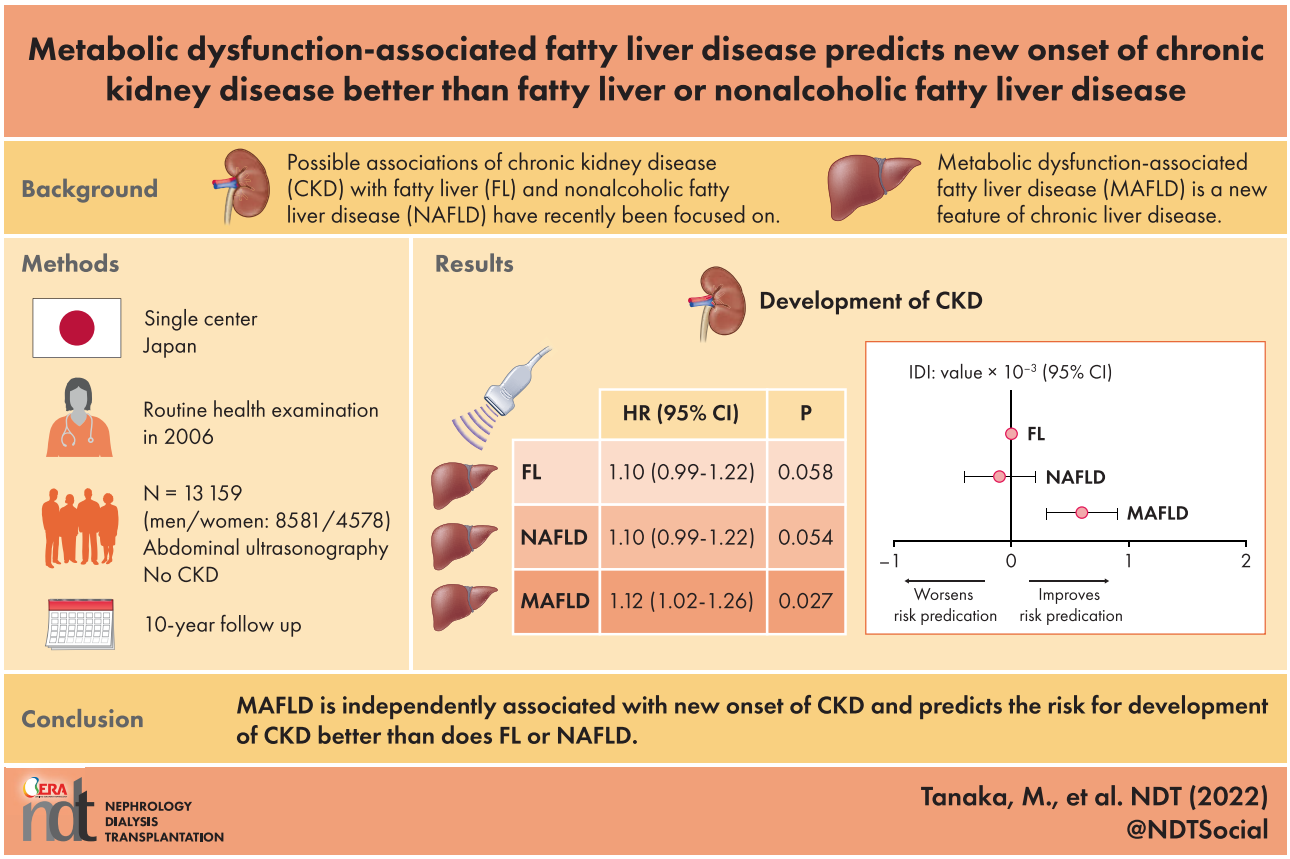
GRAPHICAL ABSTRACT



ABSTRACT

Background. Possible associations of chronic kidney disease (CKD) with fatty liver (FL) and nonalcoholic fatty liver disease (NAFLD) have recently been focused on. Metabolic dysfunction–associated fatty liver disease (MAFLD), defined as FL with overweight/obesity, type 2 diabetes mellitus

or metabolic abnormalities, has been proposed as a new feature of chronic liver disease. However, the relationship between MAFLD and new onset of CKD has not been fully addressed.

Methods. We investigated the associations of FL, NAFLD and MAFLD with the development of CKD, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or positive for urinary protein, over a 10-year period in 28 890 Japanese subjects who received annual health examinations. After exclusion of subjects with no data for abdominal ultrasonography and subjects with CKD at baseline, a total of 13 159 subjects (men 8581, women 4578; mean age 48 years) were recruited.

Results. The prevalence of FL, NAFLD and MAFLD was 34.6% (men 45.1%, women 15.1%), 32.8% (men 42.7%, women 14.5%) and 32.3% (men 42.4%, women 13.4%), respectively. During the 10-year follow-up period, 2163 subjects (men 1475, women 688) had new onset of CKD. Multivariable Cox proportional hazards model analyses showed that MAFLD [hazard ratio 1.12 (95% confidence interval 1.02–1.26); $P = .027$] but not FL or NAFLD was an independent risk factor for new onset of CKD after adjustment of age, sex, eGFR, current smoking habit, ischemic heart disease, diabetes mellitus, overweight/obesity, hypertension and dyslipidemia. The addition of MAFLD [continuous net reclassification improvement (NRI) 0.154, integrated discrimination improvement (IDI) 0.0024] to traditional risk factors without metabolic abnormalities significantly improved the discriminatory capacity better than did the addition of FL (NRI 0.138, IDI 0.0018) or NAFLD (NRI 0.132, IDI 0.0017).

Conclusions. MAFLD is modestly and independently associated with new onset of CKD and predicts the risk for development of CKD better than FL or NAFLD.

Keywords: CKD, metabolic syndrome, obesity, type 2 diabetes, ultrasonography

INTRODUCTION

Chronic kidney disease (CKD) and nonalcoholic fatty liver disease (NAFLD) have been recognized as global public health problems and a possible association between CKD and NAFLD has recently been focused on [1]. CKD not only precedes end-stage renal failure, but also increases the risk for cardiovascular events even in the early stages of CKD [2, 3]. On the other hand, NAFLD is associated with lifestyle-related diseases such as obesity and metabolic syndrome [4] and the prevalence of NAFLD has been reported to be ∼10–30% in adults in health checkup examinations [5]. Attention has also been paid to NAFLD as a cause of liver cirrhosis and hepatocellular carcinoma [6, 7] as well as hypertension and diabetes mellitus [4, 8]. It has recently been shown that NAFLD diagnosed by liver biopsy or abdominal ultrasonography is associated with the prevalence and incidence of CKD [9, 10]. We and others previously showed that a high level of fatty liver index (FLI), a noninvasive and simple biomarker for diagnosis of NAFLD [11, 12], predicts new onset of CKD [13] as well as hypertension [14], diabetes mellitus [15] and ischemic heart disease [16].

A new concept of metabolic dysfunction–associated fatty liver disease (MAFLD) with no relevance to alcohol consumption has recently been proposed [17]. The criteria for diagnosis of MAFLD are evidence of fatty liver (FL) and one of the following three criteria: overweight/obesity, presence of type 2 diabetes mellitus and evidence of metabolic dysregulation. The prevalence of MAFLD has been reported to be 26.1% (men 35.4%, women 14.1%) in China ($n = 139\,170$, mean age: 47 years) [18] and 34.8% (men 38.5%, women 31.1%) in National Health and Nutrition Examination Survey (NHANES) data from the USA [19]. It has also been reported that MAFLD is associated with the development of cardiovascular events [20–23] and that MAFLD predicts the progression of atherosclerotic cardiovascular risk better than NAFLD [20].

To date, there have been four studies, including two cross-sectional studies [24, 25] and two longitudinal studies [26, 27], showing an association between MAFLD and CKD (Supplementary data, Table S1). One of the two cross-sectional studies, which was a study conducted in the USA using 4868 subjects, showed that MAFLD was not independently associated with CKD [24]. Conversely, the other cross-sectional study, which was conducted in China using 12 571 subjects, showed that MAFLD identified patients with CKD better than did NAFLD [25]. The results of the two longitudinal studies were also contradictory. A cohort study in China using 6873 subjects showed that switching of NAFLD to MAFLD did not greatly affect the associations with the development of CKD during a 4.6-year period [26]. The other longitudinal cohort study in Japan using 16 938 subjects showed that MAFLD, but not the presence of FL without metabolic dysfunction, led to a higher risk for the development of CKD than the absence of FL [27]. It should be noted that diabetes mellitus was adjusted in the two cross-sectional studies [24, 25] but not in the two longitudinal studies [26, 27] (Supplementary data, Table S1). However, diabetes mellitus as an adjustment has a concern about multicollinearity since diabetes mellitus is a parameter for the diagnosis of MAFLD [17].

To determine the reason for the inconsistent findings, we compared the risk of FL, NAFLD and MAFLD for the development of CKD and we investigated the discriminatory capacity for predicting CKD using a large number of Japanese subjects ($n = 13\,159$) in the present study.

MATERIALS AND METHODS

Study subjects and outcomes

All individuals who received annual health examinations at Keijinkai Maruyama Clinic, Sapporo, Japan in 2006 were initially enrolled in this registry ($n = 28\,990$). A flow chart of the selection of study participants is presented in Fig. 1. Prespecified exclusion criteria were the absence of data for abdominal ultrasonography at baseline and the presence of CKD at baseline. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or positive for urinary protein by the dipstick method. After exclusion, a total of 13 159 subjects (men 8581, women 4578) who received health examinations at least once in the period from 2007 to

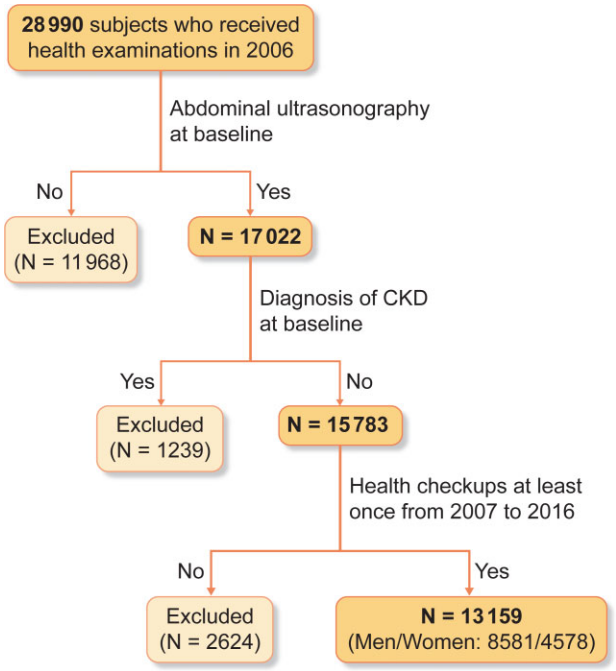


FIGURE 1: Flow chart of the selection of study participants. Among 28 990 subjects enrolled in 2006, a total of 13 159 subjects (men 8581, women 4578) were recruited for analyses in the present study. CKD was defined as an eGFR <60 mL/min/1.73 m^2 or positive for proteinuria.

2016 were recruited in the present study. The clinical endpoint was the development of CKD during the 10-year follow-up period.

The study conformed to the principles outlined in the Declaration of Helsinki and was performed with the approval of the institutional ethics committee of Sapporo Medical University (29-2-64, 30-2-32). Written informed consent was obtained from all of the subjects.

Measurements

After fasting overnight, medical examinations including blood pressure measurement and collection of urine and blood were performed. Height and weight were measured in light clothing without shoes and body mass index (BMI) was calculated as kilograms of weight divided by the square of height in meters. As an indicator of renal function, eGFR was calculated by the following equation: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine$^{(-1.094)}$ × age$^{(-0.287)}$ × 0.739 (if female) [28].

A self-administered questionnaire was performed to obtain information on current smoking habit, alcohol drinking habit (≥3 times/week), past histories of ischemic heart disease and viral hepatitis and use of drugs for diabetes mellitus, hypertension and dyslipidemia. Diabetes mellitus was diagnosed in accordance with the guidelines of the American Diabetes Association [29]: fasting plasma glucose ≥126 mg/dL, hemoglobin A1c ≥6.5% or self-reported use of antidiabetic drugs. Hypertension was diagnosed as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or self-reported use of antihypertensive drugs. Dyslipidemia was diagnosed as low-density lipoprotein (LDL) cholesterol ≥140 mg/dL, high-density lipoprotein (HDL) cholesterol <40 mg/dL, triglycerides ≥150 mg/dL or self-reported use of antidyslipidemic drugs.

Definition of MAFLD and NAFLD

MAFLD was diagnosed by evidence of hepatosteatosis determined by abdominal ultrasonography with one of the following three criteria: type 2 diabetes mellitus, overweight/obesity (BMI ≥23 in Asians) and evidence of metabolic abnormalities as previously reported [17, 30]. FL was determined by using abdominal ultrasonography. Evidence of metabolic abnormalities was defined as the presence of at least two metabolic risk abnormalities, including waist circumference ≥90/80 cm in Asian men and women; blood pressure ≥130/85 mmHg or specific drug treatment; plasma triglycerides ≥150 mg/dL or specific drug treatment; plasma HDL cholesterol <40 mg/dL for men and <50 mg/dL for women or specific drug treatment; prediabetes (fasting glucose levels of ∼100–125 mg/dL, 2-hour postload glucose levels of 140–199 mg/dL or hemoglobin A1c of 5.7–6.4%); homeostasis model assessment of insulin resistance (HOMA-R) ≥2.5 (no measurement in the present study); and plasma high-sensitivity C-reactive protein level >2 mg/L (no measurement in the present study).

NAFLD was diagnosed by the presence of FL determined by abdominal ultrasonography in the recruited subjects who had no findings of viral hepatitis and no excess alcohol consumption (alcohol equivalent ≥30 g/day for men, ≥20 g/day for women).

Abdominal ultrasonography

Abdominal ultrasonography was performed as an option that had been offered to all participants using SSA-250A or SSA-340A (Toshiba Medical, Otawara, Japan) by 10 well-experienced echographers with at least 5 years of experience who were trained by gastroenterologists with >5 years of experience in 2006. FL was determined by any findings of high-intensity bright liver, hepatorenal contrast, vascular obscuration and deep attenuation in the liver [31, 32]. The images and the presence of hepatic steatosis were independently reviewed by certified gastroenterologists who were blinded to clinical data.

Statistical analysis

Numeric variables are expressed as mean ± standard deviation (SD) for parameters with normal distributions and as median [interquartile range (IQR)] for parameters with skewed distributions. The distribution of each parameter was tested for its normality using the Shapiro–Wilk W test. Clinical parameters were divided into two subgroups according to the absence and presence of FL or MAFLD. Comparisons between two groups for parametric and nonparametric parameters were performed by using Student's *t*-test and the Mann–Whitney U test, respectively. McNemar's test was used to compare groups

Table 1. Characteristics of the recruited subjects

Characteristics	Total ($n = 13\,159$)	Men ($n = 8581$)	Women ($n = 4578$)	*P*-value
Age (years), mean ± SD	48 ± 8	48 ± 9	47 ± 9	<.001
BMI, mean ± SD	23 ± 3	24 ± 3	21 ± 3	<.001
Waist circumference (cm), mean ± SD	83 ± 9	86 ± 9	79 ± 9	<.001
Systolic blood pressure (mmHg), mean ± SD	116 ± 16	119 ± 15	110 ± 16	<.001
Diastolic blood pressure (mmHg), mean ± SD	74 ± 11	77 ± 10	69 ± 10	<.001
Current smoking habit, *n* (%)	4491 (35.3)	3691 (44.6)	800 (18.0)	<.001
Alcohol drinking habit, *n* (%)	4509 (34.3)	3757 (43.8)	752 (16.4)	.378
Comorbidity, *n* (%)				
Hypertension	2175 (16.5)	1708 (19.9)	467 (10.2)	<.001
Diabetes mellitus	706 (5.4)	612 (7.1)	94 (2.1)	<.001
Dyslipidemia	3126 (24.1)	2031 (23.7)	1136 (24.8)	.146
Ischemic heart disease	139 (1.1)	119 (1.4)	20 (0.4)	<.001
FL	4558 (34.6)	3869 (45.1)	689 (15.1)	<.001
NAFLD	4326 (32.8)	3661 (42.7)	665 (14.5)	<.001
MAFLD	4253 (32.3)	3681 (42.4)	612 (13.4)	<.001
Biochemical data				
Hemoglobin (g/dL), mean ± SD	14.3 ± 1.5	15.1 ± 1.0	12.9 ± 1.2	<.001
Albumin (g/dL), mean ± SD	4.4 ± 0.2	4.4 ± 0.2	4.3 ± 0.2	<.001
Blood urea nitrogen (mg/dL), mean ± SD	14.1 ± 3.3	14.6 ± 3.2	13.2 ± 3.1	<.001
Creatinine (mg/dL), mean ± SD	0.72 ± 0.14	0.79 ± 0.10	0.59 ± 0.08	<.001
eGFR (mL/min/1.73 m^2), mean ± SD	85.4 ± 13.7	84.3 ± 13.1	87.6 ± 14.4	<.001
Uric acid (mg/dL), mean ± SD	5.5 ± 1.4	6.0 ± 1.2	4.3 ± 0.9	<.001
AST (U/L), median (IQR)	21 (18–26)	22 (19–28)	19 (16–22)	<.001
ALT (U/L), median (IQR)	21 (15–31)	25 (18–36)	15 (12–20)	<.001
γ-GTP (U/L), median (IQR)	31 (19–57)	42 (27–73)	18 (14–27)	<.001
FPG (mg/dL), mean ± SD	92 ± 18	95 ± 19	88 ± 13	<.001
Hemoglobin A1c (%), mean ± SD	5.3 ± 0.6	5.3 ± 0.7	5.2 ± 0.5	<.001
LDL cholesterol (mg/dL), mean ± SD	122 ± 30	123 ± 30	119 ± 30	<.001
HDL cholesterol (mg/dL), mean ± SD	60 ± 15	55 ± 15	69 ± 15	<.001
Triglycerides (mg/dL), median (IQR)	93 (64–137)	110 (78–160)	67 (50–93)	<.001

AST, aspartate aminotransferase; ALT, alanine aminotransferase; FPG, fasting plasma glucose; γ-GTP, γ-glutamyl transferase.

for categorical data. Hazard ratios (HRs), 95% confidence intervals (CIs) and Akaike's information criterion (AIC) for the development of CKD in subjects with FL, in those with NAFLD and in those with MAFLD were calculated by adjustment of confounders indicated by a meta-analysis [33] including age, sex, eGFR, current smoking habit and ischemic heart disease in multivariable Cox proportional hazard model analyses after consideration of multicollinearity. In some models, diabetes mellitus, overweight/obesity or metabolic abnormalities including hypertension and dyslipidemia were also incorporated into multivariable analyses, although there was a concern about multicollinearity since those parameters were used for diagnosis of MAFLD. Parameters with a lower AIC score constitute a better-fit model. Since MAFLD is defined as evidence of hepatosteatosis with type 2 diabetes mellitus, overweight/obesity or evidence of at least two metabolic abnormalities [17, 30], diabetes mellitus, overweight/obesity, hypertension and dyslipidemia were excluded from the traditional risk factors in discriminatory analyses for comparisons of FL, NAFLD and MAFLD. To compare the discrimination for the development of CKD between the models adjusted for confounders as traditional risk factors without metabolic abnormalities including age, sex, eGFR, current smoking habit and ischemic heart disease for CKD with and without FL, between those with and without NAFLD or between those with and without MAFLD, C-statistics analogous to the area under the receiver operating characteristics curve (AUC) were estimated using the method of DeLong *et al.* [34]. Moreover, the increased discriminatory value of FL or MAFLD was examined by continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) [35, 36]. *P*-values < .05 was considered statistically significant. All data were analyzed using EZR [37] and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of the study subjects

Basal characteristics of the enrolled and excluded subjects are shown in Supplementary data, Table S2. The excluded subjects were significantly younger than the enrolled subjects and had a lower eGFR than that of the enrolled subjects. The basal characteristics of the recruited subjects are shown in Table 1. The prevalence of FL, NAFLD and MAFLD was 34.6% (men 45.1%, women 15.1%), 32.8% (men 42.7%, women 14.5%) and 32.3% (men 42.4%, women 13.4%), respectively, being significantly higher in men than in women. The basal characteristics of the subjects divided by the presence of FL, those divided by the presence of NAFLD and those divided by

Table 2. Characteristics of subjects divided by the presence of MAFLD

Characteristics	MAFLD positive ($n = 4253$)	MAFLD negative ($n = 8906$)	P-value
Age (years), mean ± SD	49 ± 8	47 ± 9	<.001
Male, *n* (%)	3641 (85.6)	4940 (55.5)	<.001
BMI, mean ± SD	26 ± 3	21 ± 2	<.001
Waist circumference (cm), mean ± SD	91 ± 7	79 ± 7	<.001
Systolic blood pressure (mmHg), mean ± SD	122 ± 15	113 ± 15	<.001
Diastolic blood pressure (mmHg), mean ± SD	79 ± 10	72 ± 10	<.001
Current smoking habit, *n* (%)	1565 (38.1)	2926 (34.0)	<.001
Alcohol drinking habit, *n* (%)	1482 (34.8)	3071 (34.0)	.336
Comorbidity, *n* (%)			
Hypertension	1158 (27.2)	1017 (11.4)	<.001
Diabetes mellitus	493 (11.6)	213 (2.4)	<.001
Dyslipidemia	1277 (30.0)	1890 (21.2)	.008
Ischemic heart disease	83 (2.0)	56 (0.6)	<.001
FL	4253 (100)	305 (3.4)	<.001
Biochemical data			
Hemoglobin (g/dL), mean ± SD	15.0 ± 1.2	14.0 ± 1.5	<.001
Albumin (g/dL), mean ± SD	4.4 ± 0.2	4.3 ± 0.2	<.001
Blood urea nitrogen (mg/dL), mean ± SD	14.5 ± 3.1	13.9 ± 3.3	<.001
Creatinine (mg/dL), mean ± SD	0.76 ± 0.13	0.70 ± 0.14	<.001
eGFR (mL/min/1.73 m^2), mean ± SD	83.9 ± 13.6	86.1 ± 13.7	<.001
Uric acid (mg/dL), mean ± SD	6.1 ± 1.3	5.1 ± 1.3	<.001
AST (U/L), median (IQR)	24 (20–31)	20 (17–23)	<.001
ALT (U/L), median (IQR)	32 (23–47)	18 (14–24)	<.001
γ-GTP (U/L), median (IQR)	50 (31–83)	25 (17–43)	<.001
FPG (mg/dL), mean ± SD	99 ± 23	88 ± 14	<.001
Hemoglobin A1c (%), mean ± SD	5.6 ± 0.8	5.2 ± 0.5	<.001
LDL cholesterol (mg/dL), mean ± SD	130 ± 30	118 ± 29	<.001
HDL cholesterol (mg/dL), mean ± SD	52 ± 12	64 ± 15	<.001
Triglycerides (mg/dL), median (IQR)	132 (95–188)	78 (56–111)	<.001

AST, aspartate aminotransferase; ALT, alanine aminotransferase; FPG, fasting plasma glucose; γ-GTP, γ-glutamyl transferase.

the presence of MAFLD are shown in Table 2 and Supplementary data, Tables S3 and S4, respectively. Subjects with FL, those with NAFLD and those with MAFLD were older, included a significantly higher percentage of men and had significantly greater BMI and waist circumference; higher systolic and diastolic blood pressures; higher frequencies of hypertension, diabetes mellitus and dyslipidemia and higher levels of hemoglobin, albumin, uric acid and parameters of liver enzymes and glucose and lipid metabolism except for HDL cholesterol than subjects without FL, those without NAFLD and those without MAFLD, respectively. Subjects with FL, those with NAFLD and those with MAFLD had a significantly lower eGFR than subjects without FL, those without NAFLD and those without MAFLD, respectively. The prevalence of FL was 2.6% in subjects without NAFLD (Supplementary data, Table S4) and 3.4% in subjects without MAFLD (Table 2).

Incidence of new onset of CKD during a 10-year follow-up period

The mean follow-up period was 6.3 years (range 1–10) and follow-up summation was 84 151 person-years (men 55 001, women 30 150). Among the 13 159 recruited subjects, 2163 (men 1475, women 688) had new onset of CKD during the 10-year period. The incidence rate of CKD was 25.7 (men 26.8, women 22.8) per 1000 person-years in all of the subjects.

Impact of FL on new onset of CKD during the follow-up period

As shown in Supplementary data, Table S5, multivariable Cox proportional hazards analysis showed that the presence of FL was associated with a 1.25-fold increase in the HR for new onset of CKD after adjustment for age, sex and eGFR (Model 1). When current smoking habit and ischemic heart disease were additionally incorporated, FL was an independent determinant of the development of CKD [HR 1.26 (95% CI 1.14–1.38); $P < .001$] (Model 2). When diabetes mellitus was additionally incorporated, FL remained an independent determinant of the development of CKD (Model 3). With further additional adjustment of overweight/obesity, hypertension and dyslipidemia in Model 3, the presence of FL was not an independent determinant of the development of CKD (Model 4) (Fig. 2A). Since there were no significant interactions between sex and FL for new onset of CKD in those models (Supplementary data, Table S5), analyses were performed in total subjects but not in subjects divided by sex.

Impact of NAFLD on new onset of CKD during the follow-up period

As shown in Supplementary data, Table S6, multivariable Cox proportional hazards analysis showed that the presence of NAFLD was associated with a 1.24-fold increase in the

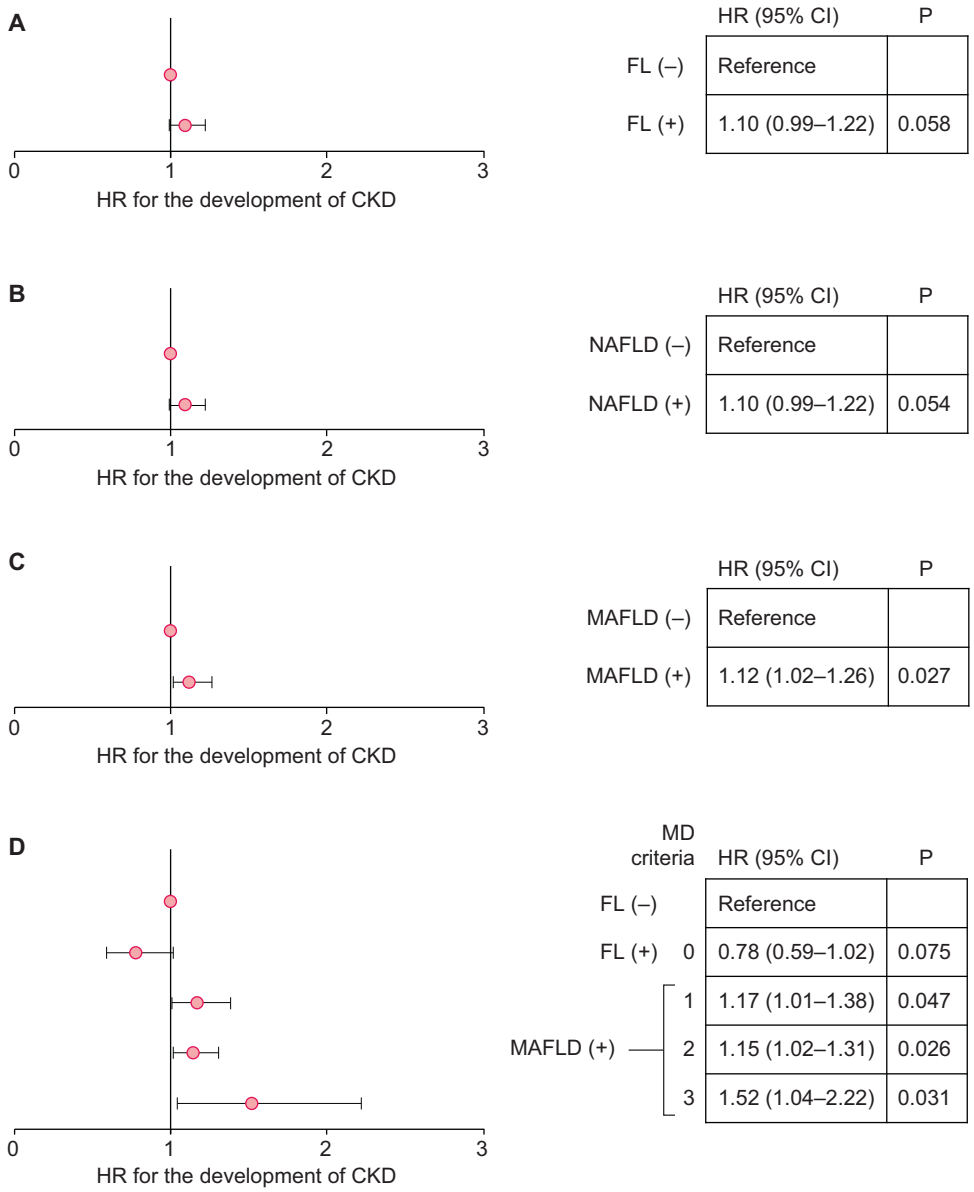


FIGURE 2: HRs for new onset of CKD by FL, NAFLD and MAFLD. (**A–D**) HRs and 95% CIs for the development of CKD by the presence of (**A**) FL (**B**) NAFLD, (**C**) MAFLD and (**D**) FL with the number of metabolic dysfunction (MD) criteria for diagnosis of MAFLD including type 2 diabetes mellitus, overweight/obesity and metabolic abnormalities analyzed by multivariable Cox proportional hazards models after adjustment for age, sex, eGFR, current smoking, ischemic heart disease, diabetes mellitus, overweight/obesity, hypertension and dyslipidemia.

HR for new onset of CKD after adjustment for age, sex and eGFR (Model 1). When current smoking habit and ischemic heart disease were additionally incorporated, NAFLD was an independent determinant of the development of CKD [HR 1.25 (95% CI 1.14–1.37); $P < .001$] (Model 2). When diabetes mellitus was additionally incorporated, NAFLD remained an independent determinant of the development of CKD (Model 3). With further additional adjustment of overweight/obesity, hypertension and dyslipidemia in Model 3, the presence of NAFLD was not an independent determinant of the development of CKD (Model 4) (Fig. 2B). Since there were no significant interactions between sex and NAFLD for new onset of CKD in those models (Supplementary data, Table S6), analyses were performed in total subjects but not in subjects divided by sex.

Impact of MAFLD on new onset of CKD during the follow-up period

As shown in Supplementary data, Table S7, multivariable Cox proportional hazards analysis showed that the presence of MAFLD was associated with a 1.29-fold increase in the HR for new onset of CKD after adjustment for age, sex and eGFR (Model 1). When current smoking habit and ischemic heart disease were additionally incorporated, MAFLD was an independent determinant of the development of CKD

[HR 1.30 (95% CI 1.19–1.43); $P < .001$] (Model 2). Since MAFLD was defined as hepatosteatosis with diabetes mellitus, overweight/obesity or metabolic abnormalities including hypertension and dyslipidemia, there was a concern about multicollinearity for those parameters. However, when diabetes mellitus was additionally incorporated, MAFLD remained an independent determinant of the development of CKD (Model 3). With further additional adjustment for overweight/obesity, hypertension and dyslipidemia into Model 3, the presence of MAFLD remained an independent determinant of the development of CKD [HR 1.12 (95% CI 1.02–1.26); $P = .027$], with the minimum AIC among the models (Model 4 AIC: 37 534; Fig. 2C). Since there were no significant interactions between sex and MAFLD for new onset of CKD in those models (Supplementary data, Table S7), analyses were performed in total subjects but not in subjects divided by sex.

Multivariable Cox proportional hazards model analyses were also performed in subjects divided by the presence of FL as well as the number of metabolic dysfunction criteria for diagnosis of MAFLD, including type 2 diabetes mellitus, overweight/obesity and metabolic abnormalities (Models 1–4; Supplementary data, Table S8). Subjects with MAFLD diagnosed by FL and the number of metabolic dysfunction criteria $\geq$1, but not subjects with FL who had no metabolic dysfunction, had significantly higher HRs for new onset of CKD than did subjects without FL after adjustment for age, sex and eGFR (Model 1), after the addition of current smoking habit and ischemic heart disease into Model 1 (Model 2), after the addition of diabetes mellitus into Model 2 (Model 3) and after the addition of overweight/obesity, hypertension and dyslipidemia into Model 3 (Model 4; Fig. 2D).

Discriminatory capacity of the addition of FL, NAFLD or MAFLD for predicting CKD

As shown in Supplementary data, Table S9, the addition of FL into traditional risk factors without metabolic abnormalities for the development of CKD, including age, sex, eGFR, current smoking habit and ischemic heart disease, significantly improved the discriminatory capacity assessed by using continuous NRI (0.138, $P < .001$) and IDI (0.0018, $P < .001$; Fig. 3A). There was no significant difference in the AUC between traditional risk factors with and without FL. On the other hand, the addition of NAFLD into the risk factors for CKD also significantly improved the discriminatory capacity assessed by using continuous NRI (0.132, $P < .001$) and IDI (0.0017, $P < .001$; Fig. 3A; Supplementary data, Table S9). There was no significant difference in the AUC between traditional risk factors with and without NAFLD. Furthermore, the addition of MAFLD into the risk factors for CKD also significantly improved the discriminatory capacity assessed by using continuous NRI (0.154, $P < .001$) and IDI (0.0024, $P < .001$; Fig. 3A; Supplementary data, Table S9). There was no significant difference in the AUC between traditional risk factors with and without MAFLD.

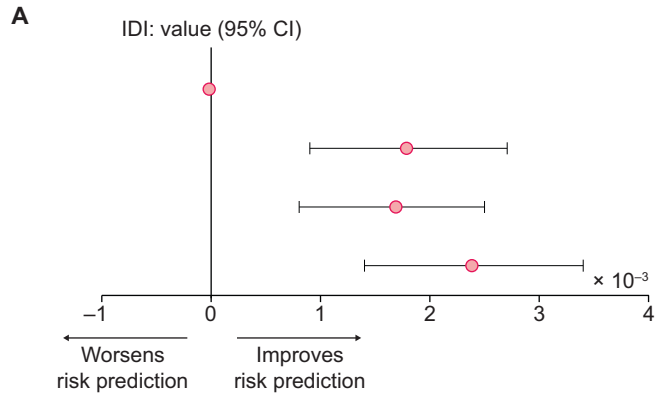
For comparisons of FL, NAFLD and MAFLD, metabolic abnormalities including diabetes mellitus, overweight/obesity, hypertension and dyslipidemia were excluded from the traditional risk factors in discriminatory analyses. However, when diabetes mellitus, overweight/obesity, hypertension and dyslipidemia were added to traditional risk factors without metabolic abnormalities, the addition of FL (0.0010, $P = .004$), NAFLD (0.0009, $P < .001$) or MAFLD (0.0013, $P < .001$) also significantly improved the discriminatory capacity assessed by using IDI (Supplementary data, Table S10).

When the traditional model including age, sex, eGFR, current smoking habit and ischemic heart disease with FL was used as a reference, the traditional model with NAFLD did not have a significant improvement in discriminatory capacity for predicting development of CKD in IDI (Fig. 3B) and continuous NRI (Supplementary data, Table S9). On the other hand, when the traditional model with FL was used as a reference, the traditional model with MAFLD had a significant improvement in discriminatory capacity for predicting development of CKD in IDI (0.0006, $P < .001$; Fig. 3B) and continuous NRI (0.098, $P < .001$; Supplementary data, Table S9). Furthermore, when the traditional model with NAFLD was used as a reference, the traditional model with MAFLD had a significant improvement in discriminatory capacity for predicting development of CKD in IDI (0.0007, $P < .001$; Fig. 3C) and continuous NRI (0.137, $P < .001$; Supplementary data, Table S9).

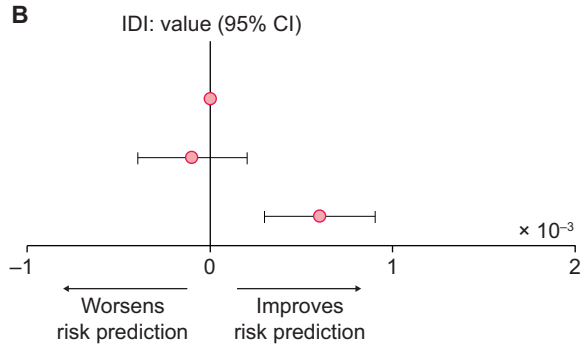
A summary of reclassification for the addition of FL, NAFLD or MAFLD to traditional risk factors without metabolic abnormalities is shown in Table 3. Among the subjects who had developed CKD, the number of subjects with appropriate reclassification into a higher risk category in the traditional models with FL and MAFLD was 28 and 33, respectively. Among subjects who had not developed CKD, the number of subjects with appropriate reclassification into a lower risk category in the traditional models with FL and MAFLD was 195 and 298, respectively. On the other hand, among the subjects who had developed CKD, the number of subjects with appropriate reclassification into a higher risk category in the traditional models with NAFLD and MAFLD was 35 and 47, respectively. Among subjects who had not developed CKD, the number of subjects with appropriate reclassification into a lower risk category in the traditional models with FL and MAFLD was 270 and 399, respectively.

DISCUSSION

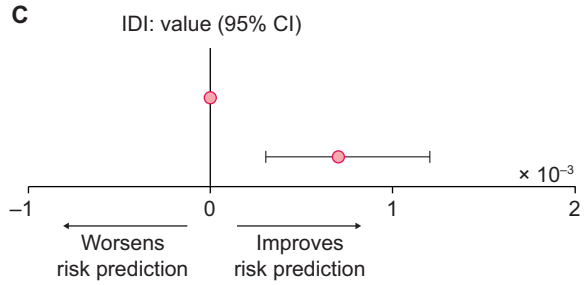
The present study showed that FL, NAFLD and MAFLD were independently associated with the risk for development of CKD after adjustment for traditional risk factors including age, sex, eGFR, current smoking and ischemic heart disease during a 10-year period in a Japanese general population. After additional adjustment for diabetes mellitus, overweight/obesity, hypertension and dyslipidemia, MAFLD [HR 1.12 (95% CI 1.02–1.26); $P = .027$], but not FL or NAFLD, was a modest and independent risk factor for new onset of CKD (Fig. 2). In addition, HRs for new onset of CKD in the presence of FL significantly increased with an increase in the number of metabolic dysfunction criteria for diagnosis of MAFLD



	Value (95% CI) [× 10^{-3}]	*P*-value
Traditional model	Reference	
+ FL	1.8 (0.9–2.7)	< 0.001
+ NAFLD	1.7 (0.8–2.5)	< 0.001
+ MAFLD	2.4 (1.4–3.4)	< 0.001



Traditional model	Value (95% CI) [× 10^{-3}]	*P*-value
+ FL	Reference	
+ NAFLD	–0.1 ([–0.4]–0.2)	0.436
+ MAFLD	0.6 (0.3–0.9)	< 0.001



Traditional model	Value (95% CI) [× 10^{-3}]	*P*-value
+ NAFLD	Reference	
+ MAFLD	0.7 (0.3–1.2)	< 0.001

FIGURE 3: Improvement of discrimination of CKD risk by FL, NAFLD and MAFLD. (**A**–**C**) Discriminatory values of the addition of FL, NAFLD, MAFLD to traditional risk factors without metabolic abnormalities for new onset of CKD including age, sex, eGFR, current smoking habit and ischemic heart disease analyzed by IDI using the (**A**) traditional model, (**B**) traditional model with FL and (**C**) traditional model with NAFLD as references.

including type 2 diabetes mellitus, overweight/obesity and metabolic abnormalities compared with the HR in the absence of FL as the reference (Fig. 2D; Supplementary data, Table S8). Furthermore, the discriminatory capacity assessed by using continuous NRI and IDI was significantly improved in the traditional model with MAFLD compared with that in the traditional model with FL or that in the traditional model with NAFLD (Fig. 3; Supplementary data, Table S9). The number of appropriate reclassifications was larger in the traditional model with MAFLD than in the traditional model with FL or in the traditional model with NAFLD in both subjects who had developed CKD and subjects who had not developed CKD (Table 3). Taken together, the results of the present study support the notion that MAFLD predicts the risk for development of CKD better than FL or NAFLD.

Analyses using continuous NRI and IDI, but not the AUC, showed that the addition of FL, NAFLD or MALFD to the traditional risk factors improved the discriminatory capacity (Supplementary data, Tables S9 and S10). Risk models evaluated using the AUC have been criticized as being an insensitive measure and as having little direct clinical relevance [38]. Therefore the value of biomarkers evaluated by using AUC alone may be overlooked [39, 40]. Considering the results of Cox proportional hazards models as well as the significant improvement in continuous NRI and IDI with the incorporation of FL, NAFLD or MAFLD into a traditional model with or without metabolic abnormalities, hepatosteatosis was an independent risk factor for the development of CKD. However, the effect sizes of NRI in the addition of MAFLD, FL and NAFLD into traditional risk factors without metabolic abnormalities

Table 3. Reclassification for the absolute risk for development of CKD

Number of subjects who developed CKD

Traditional model* + FL	Traditional model* + MAFLD: Quartiles	<1.15%	1.15–1.61%	1.61–2.14%	>2.14%
	<1.15%	375	3	0	0
	1.15–1.61%	4	341	11	0
	1.61–2.14%	0	10	420	19
	>2.14%	0	0	14	966

Number of subjects who developed CKD

Traditional model* + NAFLD	Traditional model* + MAFLD: Quartiles	<1.14%	1.14–1.59%	1.59–2.09%	>2.09%
	<1.14%	373	7	0	0
	1.14–1.59%	8	337	14	0
	1.59–2.09%	0	9	405	26
	>2.09%	0	0	18	966

Number of subjects who did not develop CKD

Traditional model* + FL	Traditional model* + MAFLD: Quartiles	<1.15%	1.15–1.61%	1.61–2.14%	>2.14%
	<1.15%	2869	43	0	0
	1.15–1.61%	77	2774	82	0
	1.61–2.14%	0	124	2648	70
	>2.14%	0	0	97	2212

Number of subjects who did not develop CKD

Traditional model* + NAFLD	Traditional model* + MAFLD: Quartiles	<1.14%	1.14–1.59%	1.59–2.09%	>2.09%
	<1.14%	2851	58	0	0
	1.14–1.59%	116	2716	99	0
	1.59–2.09%	0	160	2585	113
	>2.09%	0	0	123	2175

*Traditional model includes age, sex, eGFR, current smoking habit and ischemic heart disease.

were 0.154, 0.138 and 0.132, respectively (Supplementary data, Table S9). Those levels were <below 0.20, which is considered weak [36]. Therefore MAFLD modestly predicted the risk for development of CKD better than FL or NAFLD.

Since MAFLD was defined as hepatosteatosis with type 2 diabetes mellitus, overweight/obesity or metabolic abnormalities including hypertension and dyslipidemia, only age, sex, eGFR, current smoking habit and ischemic heart disease were used as confounding factors for the development of CKD [33] after consideration of multicollinearity in analyses of multivariable Cox proportional hazards models (Models 1 and 2 in Supplementary data, Tables S5–S8) and discriminatory capacity (Fig. 3, Table 3). However, we also performed analyses using multivariable Cox proportional hazards models including diabetes mellitus, overweight/obesity, hypertension and dyslipidemia (Models 3 and 4 in Supplementary data, Tables S5–S8). In the fully-adjusted model (Fig. 2, Model 4 in Supplementary data, Tables S5–S8), MAFLD, but not FL or NAFLD, was an independent predictor of the development of CKD with the minimum AIC.

To the best of our knowledge, there have been two studies showing an association between MAFLD and new onset of CKD (Supplementary data, Table S1). A cohort study using 6873 Chinese individuals (men 2915, women 3958) for a mean follow-up period of 4.6 years showed that subjects with MAFLD had a higher risk for the development of CKD than subjects with the absence of FL as the reference [26]. However, the change from NAFLD [risk rate 1.70 (95% CI 1.43–2.01)] to MAFLD [risk rate 1.64 (95% CI 1.39–1.94)] did not greatly affect the risk for development of CKD [26]. The other cohort study using 16 938 Japanese subjects (men 9848, women 7090) for a median follow-up period of 4.6 years showed that MAFLD [HR 1.24 (95% CI 1.14–1.36)], but not FL without metabolic dysregulation [HR 1.11 (95% CI 0.85–1.41)], was independently associated with the risk for development of CKD when the absence of FL was used as the reference [27], which was similar to the results of the present study showing that MAFLD, but not FL without metabolic dysfunction, was an independent risk factor for new onset of CKD when the absence of FL was used as the reference (Fig. 2D; Supplementary data, Table S8). The reasons for the contradictory results are unclear, but there were several different points in the previous two studies. In the former and latter studies, the references for indirect comparison with MALFD were NAFLD [26] and FL [27], respectively. Furthermore, renal function at baseline, which strongly affects renal outcome, was considered a covariate in the latter study [27] but not in the former study [26]. In the present study, we compared MFLAD with FL and NAFLD and used renal function at baseline as a covariate.

Biomarkers as well as abdominal ultrasonography and liver biopsy have been recommended for detection of FL in the definition of MAFLD [17]. A noninvasive method is useful for daily medical care and epidemiological studies using a large number of subjects. In the original report about MAFLD, the use of FLI, which is calculated using BMI, waist circumference and levels of triglycerides and γ-glutamyl transferase [11], was recommended for detection of hepatic steatosis as a

reliable biomarker [17], although optimal cutoff values of FLI should be required according to sex and races [11, 12, 41]. There have been several studies showing that a high level of FLI is independently associated with the development of CKD [13] as well as hypertension [14], diabetes mellitus [15], ischemic heart disease [16] and heart failure [42]. These results, including the results of the present study, suggest that both hepatosteatosis itself and the body's internal environment with hepatosteatosis cause deterioration of renal function.

Several underlying mechanisms of the link between hepatosteatosis and the development of CKD have been considered. Both FL and CKD share important cardiometabolic risk factors and common pathogenetic mechanisms including obesity, hypertension, insulin resistance and dyslipidemia [43, 44]. Since MAFLD is defined as obesity, type 2 diabetes mellitus or metabolic dysregulation in addition to FL, it is reasonable that MAFLD predicts the development of CKD more accurately than does FL. A recent review about the association between MAFLD and CKD enumerated genotypes of several genes, including *PNPLA3*, *HSD17B13*, *TM6SF2*, *MBOAT7* and *GCKR*, and the gut–liver–kidney axis as potential mechanisms [45]. Furthermore, a steatotic and inflamed liver has been reported to be a relevant source of proinflammatory, profibrogenic and antifibrinolytic molecules, including fetuin-A, fibroblast growth factor 2, tumor necrosis factor-α, transforming growth factor-β and plasminogen activator inhibitor-1, which theoretically can promote kidney injury [46]. MAFLD has also been reported to be associated with a high level of circulating fatty acid–binding protein 4 (FABP4) [47], which is secreted from adipocytes and acts as an adipokine for the development of insulin resistance, atherosclerosis and vascular remodeling [48–51]. It has been shown that FABP4 is associated with glomerular injury [52, 53], tubulointerstitial injury [54–56] and a decline in eGFR [57]. Furthermore, it has been reported that plasma activity of xanthine oxidoreductase, a potential enhancer of reactive oxidative stress [58], was strongly associated with liver dysfunction [59] and was independently associated with levels of adiponectin and FABP4 [60]. Dysregulation of adipokines, including decreased adiponectin and increased FABP4, has been reported to be observed in individuals with MAFLD [47], and it may cause renal dysfunction as well as atherosclerosis and cardiovascular events in connection with metabolic inflammation [50, 51, 61]. Several bioactive molecules may act as interorgan communication between the liver and kidney.

The present study has some limitations. First, the possibility of selection bias in the samples cannot be excluded since the study subjects were urban residents who received annual health checkups in a single clinic. Second, proteinuria was assessed only by the qualitative method since quantitative data for proteinuria were not available. In addition, since the renal function was assessed by annual health checkups, some patients with acute kidney injury but not CKD as the clinical endpoint might have been included in the present study. Third, for the determination of metabolic abnormalities, measurements of insulin and high-sensitivity C-reactive protein and an oral glucose tolerance test were not performed in the present study. Therefore some patients with MAFLD may be overlooked. Fourth, the pathological severity of hepatic steatosis determined by using abdominal ultrasonography was not taken into consideration. Fifth, hepatitis B surface antigen and hepatitis C antibody were not investigated in the present study. Therefore some patients with viral hepatitis might have been included in the present study, although the prevalence of hepatitis B (0.63%) and that of hepatitis C (0.49%) were reported to be relatively low in the Japanese population [62, 63]. Finally, it has been reported that measures of NRI are prone to produce false-positive results in the absence of prespecified risk thresholds [64, 65]. Therefore IDI was also investigated for discriminatory capacity in the present study.

In conclusion, MAFLD is modestly and independently associated with new onset of CKD during a 10-year period in a Japanese general population and predicts the risk for development of CKD better than FL or NAFLD. A further understanding of the mechanisms for the link between MAFLD and CKD may enable the development of new therapeutic strategies for the prevention of end-stage renal failure.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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AUTHORS' CONTRIBUTIONS

M.T. and M.F. designed the study, performed data analyses and wrote the article. S.T., K.M. and Y.H. performed data analyses. N.H. performed data collection. H.O. supervised the analyses. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

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