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Metabolic associated fatty liver disease is a risk factor for chronic kidney disease

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ABSTRACT

Background and Aims: To clarify the relationship between metabolic dysfunction-associated fatty liver disease (MAFLD) and chronic kidney disease (CKD).

Methods: The participants were divided into four groups by the presence or absence of fatty liver disease (FLD) and metabolic dysfunction (MD). MAFLD was defined as having both FLD and MD, whereas CKD was defined as having an estimated glomerular filtration rate of <60 mL/min/1.73 m^2 and/or proteinuria.

Results: In this cross-sectional study of 27,371 participants, the proportions of those in the non-FLD without MD, non-FLD with MD, FLD without MD, and MAFLD groups were 48.7, 28.2, 2.3, and 20.8%, respectively. Compared with non-FLD without MD, MAFLD was associated with the risk of CKD (adjusted odds ratio 1.83 [1.66–2.01], $P < 0.001$), whereas FLD without MD was not (1.02 [0.79–1.33], $P = 0.868$). Moreover, compared with FLD without MD, MAFLD was associated with the risk of CKD (1.19 [1.09–1.31], $P < 0.001$). In this retrospective cohort study, 16,938 of 27,371 participants underwent a median 4.6 (2.0–8.1) years follow-up, and incident data of non-FLD without MD, non-FLD with MD, FLD without MD, and MAFLD were 21.0, 31.1, 26.1, and 31.1 cases per 1,000 person-years, respectively. Compared with the non-FLD without MD, MAFLD was associated with the risk of incident CKD (adjusted hazard ratio 1.24 [1.14–1.36], $P < 0.001$), whereas FLD without MD was not (1.11 [0.85–1.41], $P = 0.433$).

Conclusions: MAFLD was associated with a risk of CKD, whereas FLD without MD was not a risk for CKD.

INTRODUCTION

Chronic kidney disease (CKD), a cause of end-stage renal failure, cardiovascular disease, and mortality[1–3], is a one of the important public health issues. The number of patients with CKD is increasing and one-eighth of people have CKD in Japan[4]. Thus, identifying people at risk of developing CKD is needed to prevent future cases of CKD.

Nonalcoholic fatty liver disease (NAFLD), which is reported to be a risk factor for type 2 diabetes mellitus[5,6] and cardiovascular disease[7,8], has a close relationship with insulin resistance[9]. There is a close association between NAFLD and CKD[10,11]. Since the current definition of NAFLD needs to exclude heavy drinking and other chronic liver disease, the term metabolic dysfunction-associated fatty liver disease (MAFLD) is suggested to express liver diseases associated with known metabolic dysfunction (MD)[12,13].

In recent years, MAFLD has been found to be a more practical and precise definition for a high risk of hepatic disease progression than is NAFLD[14]. However, the association between MAFLD and extra-hepatic disease remains unknown. Recent cross-sectional studies have shown that the association between MAFLD and the presence of CKD is inconsistent[15,16]. Therefore, this cross-sectional and retrospective large-scale cohort study researched the effect of MAFLD on the risk of the presence and newly developing CKD.

METHODS

Study population and setting

This historical cohort study, called **NAGALA** (**NA**fld in **G**ifu **A**rea, **L**ongitudinal **A**nalysis) study, comprised participants of a medical health checkup program at Asahi University Hospital

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(Gifu, Japan). The detailed aim and features of the participants and the medical health checkup program in Japan have been reported previously[17]. The Asahi University Hospital Ethics Committee approved the study (2018-05-03), and it was performed under the principles of the Declaration of Helsinki. Informed consent was obtained in the form of opt-out. Medical data of the participants were collected and stored in a database after excluding personal identifiable data. We selected the examiners of this medical health checkup program from January 2004 to December 2014. In the cross-sectional study, exclusion criteria were as follows: lack of covariates data, including lifestyle factors, abdominal ultrasonography, high-density lipoprotein (HDL) cholesterol, and creatinine; and in the retrospective cohort study, exclusion criteria were: CKD at baseline examination and not receiving follow-up examination.

Data collection

The data for the medical history and lifestyle factors were collected by self-completion questionnaire[17]. In summary, ethanol intake per week was calculated based on the type and amount of alcohol consumed in the past month. Smoking was categorized as not smoking, former smoking, and current smoking and exercise activity or performing any kind of sports once or more per week regularly was defined as an exerciser[18].

Sitting blood pressure was measured once in most participants; although for those with hypertensive or prehypertensive blood pressure levels, up to three measurements were taken at 1 to 2 min intervals and the lowest data were used. Body mass index (BMI) (kg/m^2) was calculated as body weight (kg)/height^2 (m^2).

The venous blood after overnight fasting was sampled. Fasting plasma glucose, hemoglobin A1c (HbA1c), creatinine, uric acid, triglyceride, and HDL cholesterol levels were measured. The estimated glomerular filtration rate (eGFR) was estimated by the formula for Japanese: $194 \times \mathrm{Cre}^{-1.094} \times \mathrm{age}^{-0.287}$ (mL/min/1.73 m^2) ($\times 0.739$ if women)[19]. In addition, urine specimens were sampled, asking participants not to collect at a certain time before the samples were collected. Proteinuria was defined as a positive dipstick test result (positive: 1+ or greater)[20,21].

Fatty liver disease (FLD) was diagnosed by the results of abdominal ultrasonography without checking any other personal data. FLD was defined as having both hepatorenal contrast and liver brightness[22].

Definition of metabolic associated fatty liver disease

MAFLD was defined by the presence of both fatty liver disease and one of the following three criteria of metabolic dysfunction[13]; (1) overweight or obesity, (2) type 2 diabetes mellitus, or (3) metabolic dysregulation among non-overweight individuals. Metabolic dysregulation was defined when having two or more of the following criteria: (1) prediabetes (fasting glucose levels 5.6–6.9 mmol/L or HbA1c 5.7–6.4%), (2) triglyceride ≥1.70 mmol/L or usage of medication for dyslipidemia, (3) low HDL-C of <1.3 mmol/L for women and <1.0 mmol/L for men, (4) high blood pressure of ≥130/85 mmHg or usage of medication for hypertension, and (5) high waist circumference ≥80 cm in women and ≥90 cm in men[13].

Definition of CKD

Chronic kidney disease was defined as having proteinuria and/or an eGFR of <60 mL/min/1.73 m^2[21].

Outcome of this study

The outcome of this study was the presence of incident CKD.

Statistical analysis

We used JMP version 13.2.1 (SAS Institute Inc., Cary, North Carolina) for statistical analyses. A value of P <0.05 was considered statistically significant. Data were expressed as median (first quartile–third quartile), mean (standard deviation), or number (percentage).

The participants were divided into four groups according to the presence of FLD and/or MD; non-FLD without MD; non-FLD with MD; FLD without MD; and MAFLD.

To evaluate the continuous variables, we used the *t*-test, the Mann–Whitney *U* test, one-way ANOVA with Tukey honestly significant difference or the Kruskal-Wallis test with Steel-Dwass, and to evaluate the categorical variables, we used Pearson's chi-squared test. Before performing further analyses, logarithmic transformation was performed because alcohol consumption was a skewed variable.

To calculate the odds ratio (OR) of MAFLD on the presence of CKD, logistic regression analyses were performed adjusting for sex, age, logarithm (alcohol consumption + 1), smoking, and exercise.

Then, to calculate the hazard ratio (HR) for incident CKD, we used the Cox proportional hazard model adjusting for sex, age, logarithm (alcohol consumption + 1), smoking, exercise, and creatinine.

Furthermore, we evaluated the HRs for incident CKD among the participants whose eGFR was ≥75 mL/min/1.73 m^2, adjusting for sex, age, logarithm (alcohol consumption + 1), smoking, exercise, and creatinine[23,24].

Moreover, we evaluated the HRs for incident eGFR of <60 mL/min/1.73 m^2 or proteinuria adjusting for sex, age, logarithm (alcohol consumption + 1), smoking, exercise, and creatinine.

Lastly, the analyses with a high waist circumference of ≥90 cm in women and ≥85 cm in men, which is Japanese criteria of metabolic syndrome[25], were also performed.

RESULTS

Study participants

In this study comprising 27,941 participants, 540 were excluded; thus, 27,371 participants were included in the cross-sectional study (Figure 1). After exclusion, 16,938 participants were included in the retrospective cohort study (Figure 1).

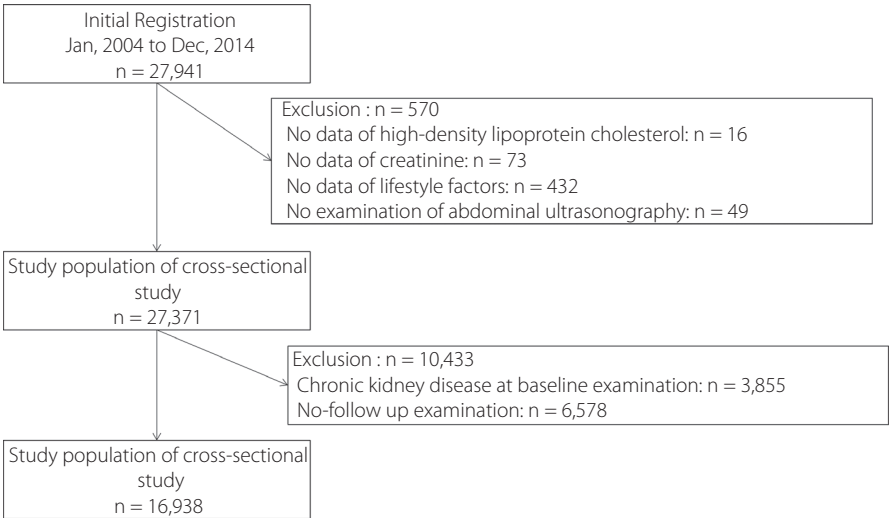

Figure 1 | Inclusion and exclusion flow.

Cross-sectional study

The baseline data of the cross-sectional study participants are shown in Table 1. The average age was 45.7 (10.1) years and 59.0% of the participants were men. The proportions of those with CKD, MD, and FLD were 14.1% (3,855 participants), 49.0% (13,412 participants), and 23.1% (6,312 participants), respectively. The proportions of participants with non-FLD without MD, non-FLD with MD, FLD without MD, and MAFLD were 48.7, 28.2, 2.3, and 20.8%, respectively. The participants with MAFLD had a higher BMI and worse metabolic dysregulation. In addition, the proportions of eGFR of <60 mL/min/1.73 m^2, proteinuria, and CKD were different among the groups.

Table 2 shows the odds ratio (OR) for the presence of CKD. The MAFLD group was at a risk of the presence of CKD, using the non-FLD group as a reference (adjusted OR 1.83 [95% CI 1.66–2.01], $P < 0.001$), whereas the FLD without MD group was not (adjusted OR 1.02 [95% CI 0.79–1.33], $P = 0.868$). In addition, using the FLD without MD as a reference (adjusted OR 1.19 [95% CI 1.09–1.31], $P < 0.001$) or non-FLD with MD group as a reference (adjusted OR 1.78 [95% CI 1.37–2.32], $P < 0.001$), the MAFLD group was at a risk of CKD.

Retrospective cohort study

The baseline characteristics of the participants who were excluded because of no follow-up and those of participants who received follow-up are shown in Table S1. The metabolic parameters of the participants who were excluded because of no follow-up were worse than those without.

The retrospective cohort participants' baseline data are shown in Table 3. The proportions of MD and FLD were 46.3% (7,837 participants) and 22.0% (3,727 participants), respectively. The proportions of non-FLD without MD, non-FLD with MD, FLD without MD, and MAFLD groups were 51.3, 26.7, 2.4, and 19.6%, respectively. The MAFLD group had a higher BMI and worse metabolic dysregulation than the other groups.

During the median 4.6 (2.0–8.1) years follow-up, 16.5% (n = 2,803/16,938) participants were newly diagnosed with CKD (2,491 participants had an eGFR of <60 mL/min/1.73 m^2, 298 participants had proteinuria, and 14 participants had both).

The incident CKD rate in the non-FLD without MD, non-FLD with MD, FLD without MD and MAFLD groups were 21.0 (cases/person-years = 1,129/53,856.5), 31.1 (914/29,359.6), 26.1 (66/2,527.3), and 31.1 (694/22,287.1) cases per 1,000 person-years, respectively.

Table 4 shows the HRs for the incident CKD. Using the non-FLD without MD group as the reference, the MAFLD group was at risk of incident CKD (adjusted HR 1.30 [95% CI 1.14–1.36], $P < 0.001$). On the contrary, the FLD without MD group was not at risk of CKD (adjusted HR 1.11 [95% CI 0.85–1.41], $P = 0.433$). Compared with the FLD without MD group (adjusted HR 1.17 [95% CI 0.91–1.51], $P = 0.223$) or the non-FLD with MD group (adjusted HR 1.04 [95% CI 0.94–1.15], $P = 0.436$), the MAFLD group was not associated as having a higher risk of incident CKD.

Sub-analyses among the participants with eGFR of ≥75 mL/min/1.73 m^2

Furthermore, Table 5 shows the hazard ratios for incident CKD among the participants who had an eGFR of ≥75 mL/min/1.73 m^2. Using the non-FLD without MD group as the reference, the MAFLD group was at risk of incident CKD (adjusted HR 1.57 [95% CI 1.22–2.02], $P < 0.001$). However, the FLD without MD group was not at risk of CKD (adjusted HR 0.73 [95% CI 0.31–1.44], $P = 0.387$). In addition, using the FLD without MD group as the reference, the MAFLD group

Table 1 | Characteristics cross-sectional study participants according to the presence of fatty liver disease and/or metabolic dysfunction

	All	Non-FLD without MD	Non-FLD with MD	FLD without MD	MAFLD	*P* value
N	27,371	13,335 (48.7)	7,724 (28.2)	624 (2.3)	5,688 (20.8)	-
Age (years)	45.7 (10.1)	43.3 (9.6)	48.3 (10.4)*	46.2 (9.6)	47.6 (9.4)	<0.001
Men§	16,158 (59.0)	5,538 (41.5)	5,388 (69.8)	486 (77.9)	4,746 (83.4)	<0.001
Body mass index (kg/m^2)	22.6 (3.3)	20.2 (1.7)	24.1 (2.3)*	21.6 (1.1)	26.3 (3.1)	<0.001
Waist circumstance (cm)	78.1 (9.6)	71.4 (6.2)	82.1 (6.6)*	77.9 (4.8)	88.3 (7.8)	<0.001
Systolic blood pressure (mmHg)	117.7 (16.4)	109.7 (13.1)	123.6 (15.5)*	115.6 (11.7)	128.5 (15.6)	<0.001
Diastolic blood pressure (mmHg)	73.6 (11.2)	68.3 (9.2)	77.5 (10.5)*	72.6 (8.1)	81.1 (10.4)	<0.001
Fasting plasma glucose (mmol/L)	5.4 (1.0)	5.0 (0.4)	5.6 (1.0)*	5.3 (0.4)	6.0 (1.4)	<0.001
HbA1c (%)	5.3 (0.6)	5.1 (0.3)	5.4 (0.6)*	5.3 (0.4)	5.7 (0.9)	<0.001
HbA1c (mmol/mol)	34.6 (6.8)	32.7 (3.4)	35.1 (6.9)*	34.0 (4.0)	38.3 (10.3)	<0.001
Triglycerides (mmol/L)	0.8 (0.5–1.2)	0.6 (0.4–0.8)	0.9 (0.6–1.4)*	1.0 (0.7–1.3)*	1.4 (0.9–1.9)	<0.001
HDL cholesterol (mmol/L)	1.4 (0.4)	1.6 (0.4)	1.3 (0.4)	1.4 (0.3)	1.2 (0.3)	<0.001
Overweight or obesity§	11,123 (40.6)	0 (0)	5,940 (76.9)	0 (0)	5,183 (40.6)	<0.001
Abdominal obesity§	4,664 (17.0)	198 (1.5)	1,867 (24.2)	13 (2.1)	2,586 (45.5)	<0.001
Hypertension§	7,105 (26.0)	1,019 (7.6)	3,107 (40.2)	72 (11.5)	2,907 (51.1)	<0.001
Low HDL cholesterol§	5,654 (20.7)	1,148 (8.6)	2,194 (28.4)	70 (11.2)	2,242 (39.4)	<0.001
Hypertriglyceridemia§	3,455 (12.6)	183 (1.3)	1,282 (16.6)	38 (6.1)	1,952 (34.3)	<0.001
Prediabetes/ diabetes§	6,914 (25.3)/ 1,415 (5.2)	1,416 (10.6)/ 0 (0)	2.814 (36.4)/ 585 (7.6)	158 (25.3)/ 0 (0)	2,526 (44.4)/ 830 (14.6)	<0.001
Creatinine (μmol/L)	73.1 (22.9)	67.7 (18.1)	77.2 (31.8)*	75.9 (14.2)*	79.8 (14.6)	<0.001
eGFR (mL/min/1.73m^2)	74.3 (13.8)	77.5 (13.9)	71.4 (13.0)*	74.2 (12.2)	70.9 (13.0)	<0.001
Uric acid (μmol/L)	295.2 (81.6)	262.8 (71.3)	310.5 (77.5)*	325.3 (69.4)	347.0 (76.9)	<0.001
Estimated glomerular filtration rate of <60 mL/min/1.73 m^2§	3,680 (13.4)	1,157 (8.7)	1,392 (18.0)	72 (11.5)	1,059 (18.6)	<0.001
Proteinuria§	270 (1.0)	77 (0.6)	90 (1.2)	3 (0.5)	100 (1.8)	<0.001
CKD§	3,855 (14.1)	1,218 (9.1)	1,439 (18.6)	73 (11.7)	1,125 (19.8)	<0.001
Ex-/current smoker§	6,081 (22.2)/ 6,828 (25.0)	2,125 (15.9)/ 2,707 (20.3)	2,036 (26.4)/ 2,236 (29.0)	167 (26.8)/166 (26.6)	1,753 (30.8)/ 1,719 (30.2)	<0.001
Alcohol consumption (g/week)	2.8 (0–87.5)	1 (0–60)	18 (1–126)*	1 (0–64.5)†	10.4 (0–110)	<0.001
Exerciser§	4,931 (18.0)	2,403 (18.0)	1,565 (20.3)	121 (19.4)	842 (14.8)	<0.001

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FLD, fatty liver disease; HDL, high-density lipoprotein; MD, metabolic dysfunction; MFLD, metabolic dysfunction-associated fatty liver disease. Data are number (percentage) or mean (standard deviation) or median (first quartile –third quartile). The analyses of continuous variables among groups were evaluated by one-way ANOVA and Tukey honestly significant difference test or Kruskal-Wallis test and Steel-Dwass test. *vs Non-FLD without MD. †vs Non-FLD with MD. ‡vs FLD without MD. The analyses of categorical variables among groups were performed by χ^2 test. §$P < 0.05$.

was at risk of incident CKD (adjusted HR 2.16 [95% CI 1.01–4.65], $P = 0.048$).

Sub-analyses of incident eGFR of <60 mL/min/1.73 m^2 or proteinuria

Using the non-FLD without MD group as the reference, the MAFLD group was at risk of incident eGFR of <60 mL/min/1.73 m^2 (adjusted HR 1.26 [95% CI 1.14–1.39], $P < 0.001$). However, the FLD without MD group was not at risk of incidence of eGFR of <60 mL/min/1.73 m^2 (adjusted HR 1.14 [95% CI 0.87–1.47], $P = 0.326$) (Table S2). Compared with the FLD without MD group (adjusted HR 1.08 [95% CI 0.83–1.41], $P = 0.568$) or the non-FLD with MD group (adjusted HR 0.98 [95% CI 0.88–1.09], $P = 0.727$), the MAFLD group was not associated with a higher risk of incident eGFR <60 ml/min/1.73 m^2.

Furthermore, the MAFLD group was at risk of proteinuria, using the non-FLD without MD group as the reference (adjusted HR 1.95 [95% CI 1.47–2.59], $P < 0.001$). On the other hand, the FLD without MD group was not at risk of incident proteinuria (adjusted HR 0.93 [95% CI 0.36–1.95], $P = 0.868$) (Table S2). Compared with the FLD without MD group (adjusted HR 2.09 [95% CI 0.92–4.77], $P = 0.079$) or the non-FLD with MD group (adjusted HR 1.81 [95% CI 1.33–2.47], $P < 0.001$), the MAFLD group was associated with a higher risk of the incident proteinuria.

Sub-analyses of high waist circumference with Japanese criteria of metabolic syndrome

The analyses of high waist circumference with the Japanese criteria of metabolic syndrome are shown in Table S3. The results

Table 2 | Odds ratio for the presence of chronic kidney disease according to the presence of fatty liver disease and/or metabolic dysfunction

	Unadjusted model	*P* value	Adjusted model	*P* value
Non-fatty liver disease without metabolic dysfunction	1 (Reference)	–	1 (Reference)	–
Non-fatty liver disease with metabolic dysfunction	2.28 (2.10–2.47)	<0.001	1.53 (1.40–1.68)	<0.001
Fatty liver disease without metabolic dysfunction	1.32 (1.03–1.69)	0.031	1.02 (0.79–1.33)	0.868
Metabolic dysfunction-associated fatty liver disease	2.45 (2.25–2.68)	<0.001	1.83 (1.66–2.01)	<0.001
Men	–	–	1.12 (1.02–1.24)	0.022
Age (per 1 year)	–	–	1.09 (1.09–1.10)	<0.001
Habit of exercise	–	–	1.16 (1.06–1.27)	<0.001
Ex-smoker	–	–	1.03 (0.93–1.14)	0.540
Current smoker	–	–	0.76 (0.68–0.84)	<0.001
Logarithm (alcohol consumption + 1) (Δ1 incremental)	–	–	0.99 (0.97–1.01)	0.260

Logistic regression analyses were performed to evaluate the effect of metabolic dysfunction-associated fatty liver disease on the presence of chronic kidney disease.

Table 3 | Characteristics of retrospective cohort study participants according to the presence of fatty liver disease and/or metabolic dysfunction

	Non-FLD without MD	Non-FLD with MD	FLD without MD	MAFLD	*P* value
N	8,692 (51.3)	4,519 (26.7)	409 (2.4)	3,318 (19.6)	–
Age (years)	42.6 (8.8)	46.4 (9.3)*	45.2 (8.6)	46.1 (8.7)*	<0.001
Men§	3,653 (42.0)	3,172 (70.2)	328 (80.2)	2,800 (84.4)	<0.001
Body mass index (kg/m^2)	20.2 (1.7)	24.1 (2.3)*	21.6 (1.1)	26.2 (3.1)	<0.001
Waist circumstance (cm)	71.3 (6.2)	82.0 (4.9)*	77.9 (4.9)	88.1 (7.7)	<0.001
Systolic blood pressure (mmHg)	109.3 (12.9)	122.6 (15.0)*	115.2 (11.8)	127.1 (14.8)	<0.001
Diastolic blood pressure (mmHg)	68.0 (9.1)	77.0 (10.4)*	72.1 (8.1)	80.3 (10.1)	<0.001
Fasting plasma glucose (mmol/L)	5.0 (0.4)	5.5 (0.9)*	5.3 (0.4)	6.0 (1.4)	<0.001
HbA1c (%)	5.1 (0.3)	5.3 (0.6)*	5.3 (0.4)*	5.6 (0.9)	<0.001
HbA1c (mmol/mol)	32.5 (3.4)	34.7 (6.6)*	33.9 (4.0)	37.8 (10.2)	<0.001
Triglycerides (mmol/L)	0.6 (0.4–0.8)	0.9 (0.6–1.4)*	1.0 (0.7–1.3)*	1.3 (0.9–1.9)	<0.001
HDL cholesterol (mmol/L)	1.6 (0.4)	1.3 (0.4)	1.4 (0.3)*	1.2 (0.3)	<0.001
Overweight or obesity§	0 (0)	3,503 (77.5)	0 (0)	3,028 (91.3)	<0.001
Abdominal obesity§	113 (1.3)	1,028 (22.8)	4 (1.0)	1,440 (43.4)	<0.001
Hypertension§	585 (6.7)	1,649 (36.5)	47 (11.5)	1,570 (47.3)	<0.001
Low HDL cholesterol§	785 (9.0)	1,306 (28.9)	40 (9.8)	1,303 (39.3)	<0.001
Hypertriglyceridemia§	105 (1.2)	727 (16.1)	25 (6.1)	1,098 (33.1)	<0.001
Prediabetes/diabetes§	899 (10.3)/0 (0)	1,579 (34.9)/300 (6.6)	105 (25.7)/0 (0)	1,453(43.8)/424 (12.8)	<0.001
Creatinine (μmol/L)	66.2 (12.8)	73.1 (12.6)*	74.2 (12.2)*	76.3 (11.4)	<0.001
eGFR (mL/min/1.73 m^2)	79.0 (12.4)	74.9 (10.3)*	76.4 (10.3)*	74.4 (11.4)	<0.001
Uric acid (μmol/L)	259.3 (70.4)	304.8 (75.9)*	323.5 (66.6)	341.7 (75.3)	<0.001
Ex-/current smoker§	1,349 (15.5)/1,759 (20.2)	1,137 (25.2)/1,363 (30.2)	114 (27.9)/103 (25.2)	973 (29.3)/1,024 (30.9)	<0.001
Alcohol consumption (g/week)	1 (0–60)	18 (1–126)*	1 (0–60)	10.3 (0–110)	<0.001
Exerciser§	1,537 (17.7)	848 (18.8)	73 (17.9)	472 (16.1)	<0.001

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FLD, fatty liver disease; HDL, high-density lipoprotein; MD, metabolic dysfunction; MFLD, metabolic dysfunction-associated fatty liver disease. Data are number (percentage) or mean (standard deviation) or median (first quartile–third quartile). The analyses of continuous variables among groups were evaluated by one-way ANOVA and Tukey honestly significant difference test or Kruskal-Wallis test and Steel-Dwass test. *vs Non-FLD without MD. †vs Non-FLD with MD. ‡vs FLD without MD. The analyses of categorical variables among groups were performed by χ^2 test. §$P < 0.05$.

[Correction added on 15 November 2021, after first online publication: Several errors in table 3 have been corrected accordingly.]

were almost the same as the high waist circumference with the international expert consensus statement.

DISCUSSION

This study investigated the association between MAFLD and the risk of CKD. It clarified that the MAFLD group was at risk of CKD compared with the non-FLD without MD group, whereas the FLD without MD group was not at risk of CKD. Furthermore, the MAFLD group was associated with a higher risk of CKD than the FLD without MD group.

MAFLD is a new concept and is more practical for identifying hepatic disease progression than NAFLD[14]. To focus on metabolic

Table 4 | Hazard ratio for incident chronic kidney disease according to the presence of fatty liver disease and/or metabolic dysfunction

	Unadjusted model	*P* value	Adjusted model	*P* value
Non-fatty liver disease without metabolic dysfunction	1 (Reference)	–	1 (Reference)	–
Non-fatty liver disease with metabolic dysfunction	1.37 (1.25–1.49)	<0.001	1.24 (1.14–1.36)	<0.001
Fatty liver disease without metabolic dysfunction	1.11 (0.86–1.41)	0.411	1.11 (0.86–1.42)	0.426
Metabolic dysfunction-associated fatty liver disease	1.46 (1.33–1.61)	<0.001	1.30 (1.17–1.43)	<0.001
Creatinine (μmol/L)			1.11 (1.11-1.12)	<0.001
Men	–	–	0.10 (0.09–0.12)	<0.001
Age (per 1 year)	–	–	1.08 (1.08–1.09)	<0.001
Habit of exercise	–	–	1.09 (1.00–1.20)	0.061
Ex-smoker	–	–	1.01 (0.91–1.13)	0.779
Current smoker	–	–	0.95 (0.86–1.06)	0.370
Logarithm (alcohol consumption + 1) (Δ1 incremental)	–	–	1.01 (0.99–1.03)	0.523

Cox proportional hazard model was performed to calculate the hazard ratio (HR) for incident chronic kidney disease.

dysfunction, it is expected that more efficient and effective treatments will be developed[26]. However, the relationship between MAFLD and extra-hepatic disease, including CKD, remains to be clarified. Recent cross-sectional studies showed that the relationship between MAFLD and the presence of CKD has been inconsistent[15,16]. However, this study clarified that the MAFLD group was at risk of both the presence and incidence of CKD, whereas the FLD without MD group was not at risk.

The possible link between MAFLD and CKD is insulin resistance[9]. Insulin resistance contributes to the progression of CKD through several mechanisms, such as downregulation of the natriuretic peptide system, sodium retention, and sympathetic nervous system activation[27]. In addition, insulin resistance contributes to the progression of CKD by intermediate mechanisms, such as left ventricular hypertrophy[28], vascular dysfunction[29], and atherosclerosis[30]. Previous studies have revealed that NAFLD is associated with a risk of CKD[10,11]. Metabolic dysfunction, including overweight or obesity, type 2 diabetes mellitus, or metabolic dysregulation among non-overweight individuals is associated with insulin resistnace[13]. It has been reported that there is a relationship between these criteria and insulin resistance[31–33]. In addition, there is an association among overweight or obesity[34,35], type 2 diabetes mellitus[35], or metabolic dysregulation among non-overweight individuals[34] and CKD. In summary, MAFLD is associated with CKD.

However, the FLD without MD group was not at risk of the presence and incident CKD. The risk of CKD in the FLD without MD group was not higher than that in the non-FLD without MD group in both cross-sectional and retrospective cohort studies. These results indicated that the concept of MAFLD is suitable for extracting a truly high-risk population from FLD individuals. Furthermore, MAFLD rather than FLD without MD or non-FLD with MD is at higher risk of incident proteinuria, although there was no difference between MAFLD and FLD without MD or non-FLD with MD on the risk of the incident CKD or eGFR <60 ml/min/1.73 m^2. Proteinuria is reported to be associated with a risk factor of end-stage kidney disease[36], rapid eGFR decline[37], cardiovascular diseases (CVD)[38], and mortality[36,38]. Therefore, it would be desirable to focus on the underlying MD associated with MAFLD for prevention or reduction of CKD.

Table 5 | Hazard ratio for incident chronic kidney disease according to the presence of fatty liver disease and/or metabolic dysfunction among the participants whose estimated glomerular filtration rate ≥75 mL/min/1.73 m^2

	Unadjusted model	*P* value	Adjusted model	*P* value
Non-fatty liver disease without metabolic dysfunction	1 (Reference)	–	1 (Reference)	–
Non-fatty liver disease with metabolic dysfunction	1.57 (1.26–1.94)	<0.001	1.34 (1.07–1.67)	0.012
Fatty liver disease without metabolic dysfunction	0.81 (0.35–1.59)	0.560	0.73 (0.31–1.44)	0.387
Metabolic dysfunction-associated fatty liver disease	1.73 (1.36–2.17)	<0.001	1.57 (1.22–2.02)	<0.001
Creatinine (μmol/L)			1.05 (1.03-1.08)	<0.001
Men	–	–	0.31 (0.19–0.50)	<0.001
Age (per 1 year)	–	–	1.06 (1.05–1.07)	<0.001
Habit of exercise	–	–	1.09 (0.85–1.39)	0.487
Ex-smoker	–	–	1.02 (0.77–1.35)	0.917
Current smoker	–	–	1.10 (0.85–1.42)	0.461
Logarithm (alcohol consumption + 1) (Δ1 incremental)	–	–	1.01 (0.96–1.06)	0.656

Cox proportional hazard model was performed to calculate the hazard ratio (HR) for incident chronic kidney disease.

Although there was no relationship between smoking or drinking and the incidence of CKD, previous studies showed that there is an association between smoking[39,40], BMI[41], drinking[40,42], educational status[43], and the incidence of CKD.

Our study has some limitations. First, although liver biopsy is the gold standard for the diagnosis of FLD, we did not perform liver biopsies in such a large number of apparently healthy individuals, and ultrasonography is reported to be useful in clinical practice and high sensitivity and specificity in the diagnosis of FLD[44]. Second, this study was conducted in Japan, and there is a possibility that the results might not be generalizable to other countries and populations. Moreover, this was a health examination-based cohort study in one region; and thus, there is also a possibility that the results might not be generalizable to other regions or with different background factors[45]. In addition, the prevalence of exercise in our study (18%) was lower than that in other previous studies (15–40%)[41,43] and the prevalence of current smokers (25%) in our study was higher than that in other previous studies (10–25%)[39,43]. Thus, there is a possibility that less frequent exercise and higher smoking rates mean a lower socioeconomic environment. Third, data on insulin, high sensitivity C-reactive protein, and standard oral glucose tolerance test were absent. Lastly, the definition of proteinuria was assessed using the dipstick test; thus, we could not quantitate proteinuria. However, the dipstick test was found to be a useful tool, and it was reported that most patients with a 1+ or more on dipstick test had microalbuminuria or more[20]. Moreover, the serum creatinine level and proteinuria were measured only once, although the diagnosis of CKD required at least two out of three measurements.

In conclusion, MAFLD was associated with a risk of CKD, whereas FLD without MD was not associated with a risk of CKD. Thus, MAFLD, a new concept in FLD, is an important treatment target for extra-hepatic disease.

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DISCLOSURE

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Approval of the research protocol: The Asahi University Hospital Ethics Committee approved the study (ID: 2018-05-03 and date: 03 May, 2018), and it was performed under the principles of the Declaration of Helsinki.

Informed consent: Informed consent was obtained in the form of opt-out.

Approval date of Registry and the Registration No. of the study/trial: N/A.

Data sharing statement: The data used in this study and the data sets analyzed are available from the corresponding author upon request.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Characteristics of participants with and without follow-up

Table S2 | Hazard ratio for incident chronic kidney disease according to the presence of fatty liver disease and/or metabolic dysfunction

Table S3 | Odds ratio for presence of chronic kidney disease and hazard ratio for incident chronic kidney disease according to the presence of fatty liver disease and/or metabolic dysfunction using the high waist circumference with Japanese criteria of metabolic syndrome