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Does metabolic dysfunction-associated fatty liver disease increase the risk of chronic kidney disease? A meta-analysis of cohort studies

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Abstract

Objective Metabolic dysfunction-associated fatty liver disease (MAFLD) has been used to characterize patients with fatty liver and metabolic dysfunction. The association between MAFLD and chronic kidney disease (CKD) remains undefined. We present high-quality evidence obtained from cohort studies examining if MAFLD leads to an increased risk of CKD.

Methods PubMed, CENTRAL, Embase, Scopus, and Web of Science were searched from the earliest possible date to 17th May 2024 for cohort studies examining the link between MAFLD and CKD.

Results Eight studies with nine cohorts were included. Pooled analysis of all nine cohorts showed that MAFLD was an independent predictor of CKD (HR: 1.38 95% CI: 1.24, 1.53 $I^2 = 95\%$). No change in results was noted on sensitivity analysis. We also noted no change in the significance of effect size on subgroup analysis based on study design (prospective or retrospective), country of origin (China, Korea, Japan, or UK), the incidence of CKD in the cohort (> 10% or ≤ 10%) and if the study adjusted for cardiovascular disease, diabetes, hypertension, and smoking status. Further, meta-analysis showed that MAFLD was still a risk factor for CKD in men (HR: 1.38 95% CI: 1.22, 1.56 $I^2 = 86\%$), women (HR: 1.51 95% CI: 1.25, 1.82 $I^2 = 87\%$), overweight (HR: 1.41 95% CI: 1.20, 1.66 $I^2 = 89\%$) and non-overweight cohorts (HR: 1.35 95% CI: 1.20, 1.53 $I^2 = 9\%$).

Conclusion MAFLD is an independent predictor of CKD. The association seems persistent irrespective of sex, body mass index, and other CKD risk factors.

Keywords Fatty liver, Hepatic steatosis, Renal disease, Metabolic dysfunction, Risk

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Introduction

Chronic kidney disease (CKD) is a major public health issue affecting a large population globally. About 700 million individuals were diagnosed with CKD in 2017 resulting in about 1.2 million deaths worldwide [1]. A number of patients with CKD can progress to end-stage renal disease (ESRD) [2]. ESRD is a life-threatening condition wherein the kidneys have completely failed to function and patients require renal replacement therapy or kidney transplant for survival [3]. Not only do patients with ESRD have poor overall survival, but it also significantly adds to the patient morbidity and psychological and economic burden on the individual and caregivers [4, 5]. Given the limitations of current treatments for CKD [6], risk factors for CKD must be identified so that interventions can be designed to reduce the burden of the disease.

Non-alcoholic fatty liver disease (NAFLD) is a condition defined by excessive fat accumulation in the liver that cannot be attributed to excessive alcohol, viral hepatitis, and drugs [7]. About 25–30% of the general population is affected with NAFLD and a large proportion of patients have metabolic comorbidities [8]. To encompass the metabolic dysfunction associated with NAFLD, a panel of hepatologists proposed a change of nomenclature to metabolic dysfunction-associated fatty liver disease (MAFLD) [9]. While a diagnosis of NAFLD requires hepatic steatosis of ≥5% without concurrent liver disease and alcohol consumption, MAFLD uses the same criteria for hepatic steatosis but also includes metabolic dysregulation factors as a prerequisite for diagnosis. Further, the term Metabolic dysfunction-associated steatotic liver disease (MASLD) has also been suggested which encompasses hepatic steatosis, along with one or more of the specified five cardiometabolic risk factors [10]. In the past few years, MAFLD has been found to be more practical and precise for assessing the risk of hepatic disease progression as compared to NAFLD [10, 11]. However, the association between MAFLD and extra-hepatic diseases remains unclear. Previously, NAFLD has been shown to increase the risk of CKD [12], nevertheless, such evidence for MAFLD is still elusive. In 2023, Agustani et al. [13] in their systematic review demonstrated a positive association between MAFLD and CKD but their evidence was generated predominantly from cross-sectional studies. Cross-sectional studies do not determine causality and hence provide poor-quality evidence. In the hierarchy of evidence, a meta-analysis of cohort studies ranks higher than a meta-analysis of cross-sectional studies [14]. We hereby present an updated meta-analysis of only cohort studies examining the risk of CKD in MAFLD patients.

Materials and methods

Electronic search

The present review conforms to the PRISMA [15] reporting guidelines. The study protocol was archived in the National Institute for Health Research Prospero International Prospective Register of Systematic Reviews (CRD42024533242).

Articles were identified by two reviewers independently on five online repositories. PubMed, CENTRAL, Embase, Scopus, and Web of Science from the earliest possible date to 17th May 2024. Medical Subject Heading terms and keywords were combined to develop with following search query: ((((Metabolic dysfunction-associated fatty liver disease) OR (MAFLD)) OR (liver steatosis)) OR (Fatty liver)) AND ((chronic kidney disease) OR (renal disease)). It was replicated in all the mentioned databases. No limits were placed on language and date of publication. Search limits were from the earliest possible date to 17th May 2024. To supplement the primary search, the authors manually scanned references of included publications and gray literature by means of Google Scholar.

Search results were pooled from all databases following which duplicates were removed. The two authors first checked the studies by reading the titles and abstracts. Relevant articles were identified and their full-texts retrieved. These underwent further review wherein the authors read the complete texts and took a call on the inclusion of the study based on predefined criteria. The authors discussed and resolved all disagreements.

Eligibility criteria

We included all full-text original publications of retrospective or prospective cohort studies. Studies were to be conducted on the adult population with exposure to MAFLD and outcomes as CKD on follow-up. Studies were to provide clear definitions of MAFLD and CKD. All definitions reported by studies were acceptable. Studies were to report an adjusted association between MAFLD and CKD as odds, risk, or hazard ratio (HR) with corresponding 95% confidence intervals.

Studies not included in the review were those only on NAFLD and not reporting separate data on MAFLD. Cross-sectional studies, duplicate studies, abstracts, editorials, and reviews were also not included. For articles in which the study population was repeated, the article with the largest sample size or reporting the most appropriate outcome was included.

Data management

The authors collected the following information from all studies: author name, year of publication, database, location, study design, population included, sample size, age and gender, diagnosis of MAFLD & CKD, incidence of

CKD, CKD risk factors, covariates adjusted, follow-up and outcome. The reviewers cross-checked the outcome data for correctness. Additionally, data on any subgroups reported by the studies were also extracted and such data was used to conduct separate meta-analyses based on gender, body mass index, etc.

Risk of bias

The Newcastle-Ottawa Scale (NOS) was utilized [16]. The scale has three blocks with a total of eight items examining selection, comparability, and outcome evaluation and articles are given points from zero to nine. A higher score indicates better quality. Both authors were involved in assessing the study quality. The authors resolved differences after discussion.

Statistical analysis

Random-effects meta-analysis was conducted on "Review Manager" (RevMan, version 5.3; Denmark; 2014). Due to the low incidence of CKD, risk ratios and HR were combined as a single entity. Multivariable adjusted data was combined to calculate pooled HRs. The I^2 allowed the investigation of the heterogeneity among studies. The higher the I^2 is, the more significant the heterogeneity in the meta-analysis. Egger's test determined the possibility of publication bias. Sensitivity analysis was conducted to deal with high heterogeneity by removing one study and pooling the effects of the remaining studies. Subgroup analysis was performed based on study design, country of origin, incidence of CKD (>10% or ≤10%), and if the study adjusted for cardiovascular disease (CVD), diabetes mellitus (DM), hypertension (HT), baseline estimated glomerular filtration rate (eGFR), and smoking status. We also conducted a random-effects meta-regression using Meta-essentials (https://www.erim.eur.nl/research-support/meta-essentials/) using the moderators: sample size, age, male gender, DM, HT, smoking, and follow-up.

Results

Characteristics of retrieved studies

From the five databases, we identified 15,077 studies using the search query (Figure-1). A large number of studies duplicate entries (n=9533) and hence removed electronically. The reviewers screened 5544 records and sought 30 articles for full-text review. Inter-reviewer agreement was found to be high for this part (kappa=0.84). These 30 studies were matched against the inclusion criteria and eight studies incorporating nine cohorts were found eligible [17–24]. There was no disagreement between authors for the final included studies.

As demonstrated in Table-1, most studies were on Asian populations from the countries of Japan, China, and Korea. One study [24] included a cohort from the UK Biobank. All studies were recently published (2022–2024). Baseline CKD patients were excluded from all studies. The combined sample size of all cohorts was 598,531. MAFLD was defined using the standard definition [9] by all included studies which were fatty liver on hepatic ultrasonography and at least one of the following three conditions: (1) overweight; (2) Type 2 DM; (3) at least two of the following seven metabolic conditions: increased waist circumference, blood pressure, triglycerides, high-sensitivity C-reactive protein level, and insulin resistance, decreased high-density lipoprotein-cholesterol, and prediabetes. CKD was defined as the presence of one of the following: eGFR<60mL/min/1.73 m^2, proteinuria, or urine albumin/creatinine ratio≥30 mg/g. One study [24] also ascertained CKD as a "clinical diagnosis of CKD". The median follow-up ranged from 4.6 to 12.9 years. All studies found MAFLD to be a significant risk factor for CKD. The NOS score of the studies was either 7 or 8 indicating good quality.

Meta-analysis

Pooled analysis of all nine cohorts showed that MAFLD was an independent predictor of CKD (HR: 1.38 95% CI: 1.24, 1.53 I^2=95%) (Figure-2). No publication bias was noted on Egger's test (p=0.72). The relationship between MAFLD and CKD persisted in sensitivity analysis and exclusion of any study did not change the results (Table-2).

Details of subgroup analysis are shown in Table-3. We noted no change in the significance of effect size on subgroup analysis based on study design (prospective or retrospective), country of origin (China, Korea, Japan, or UK), incidence of CKD in the cohort (>10% or ≤10%) and if the study adjusted for CVD, DM, HT, eGFR and smoking status. Meta-regression results are shown in Table 4. None of the moderators were found to significantly impact the results.

Subgroup analyses conducted by the individual studies are shown in Table-5. Zhang et al. [24] examined the risk of CKD based on sex, MAFLD definition including at least one metabolic abnormality, eGFR calculated using the CKP-EPI equation, in 40-70-year-old participants, and with healthy lifestyle factors. The authors noted an increased risk of CKD in all subgroups. However, when the cohort was distributed based on the number of healthy lifestyle factors, a lower number of factors was found to increase the risk of CKD. Wei et al. [23] classified their cohort based on sex, age, HT, dyslipidemia, overweight, and DM and noted an increased risk of CKD in all subgroups. Tanaka et al. [18] demonstrated that the risk of CKD was related to the severity of metabolic dysfunction with a higher number of metabolic abnormalities increasing the risk of CKD. Kwon et al. [22] divided their cohort based on overweight and DM status and noted an increased risk of CKD in all subgroups. Liang

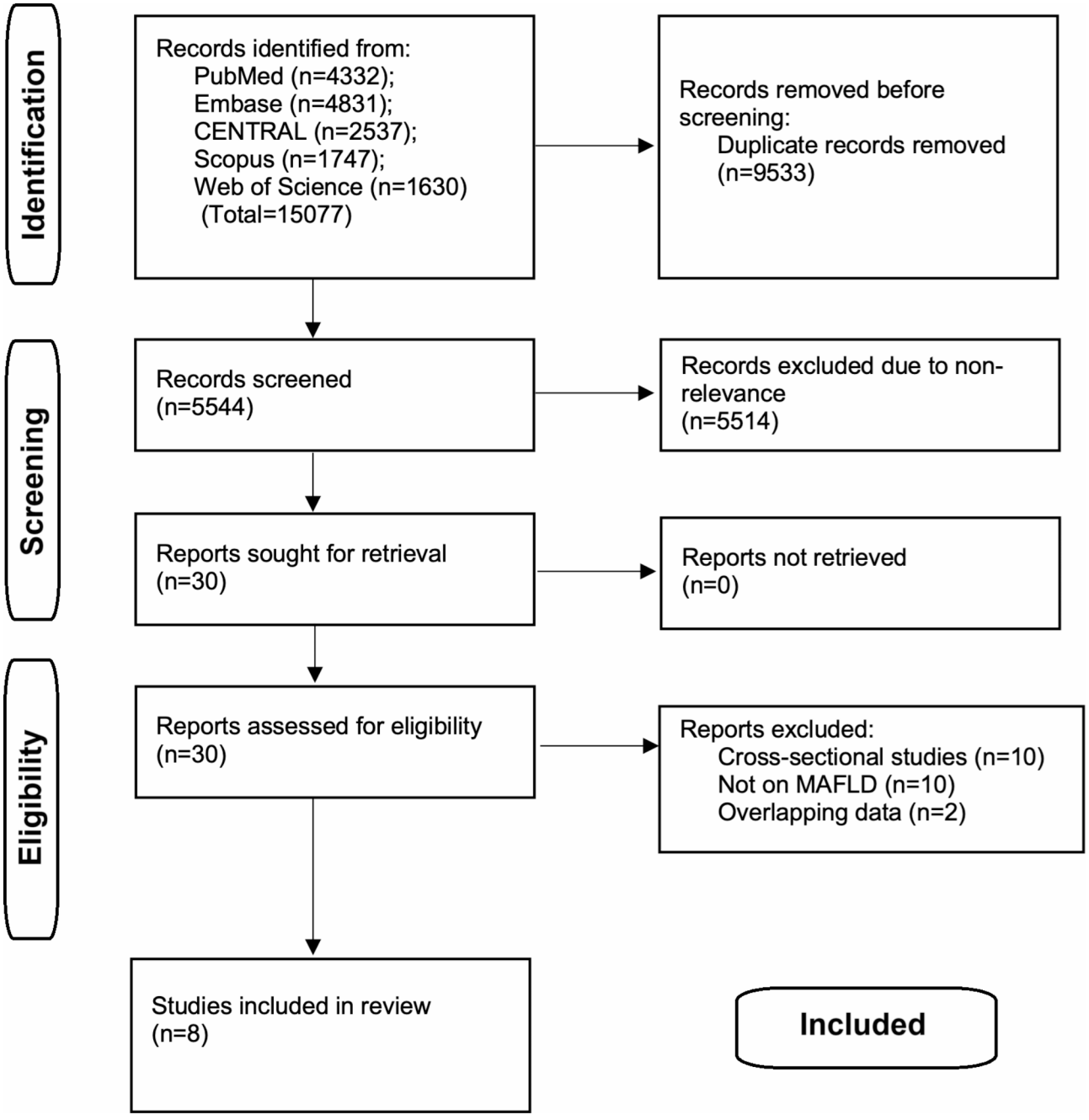

Fig. 1 PRISMA flowchart

et al. [21] noted that the risk of CKD was not increased in MAFLD patients with excessive alcohol consumption and hepatitis B virus infection. Jung et al. [20] conducted subgroup analyses based on age, sex, overweight, low-density lipoprotein levels, DM, and alcohol use and found an increased risk of CKD in all subgroups. Hashimoto et al. [19] conducted separate analyses for populations with baseline eGFR≥75mL/min/1.73 m^2 and still found an increased risk of CKD with MAFLD. They also segregated CKD patients defined based on eGFR and proteinuria only to find persistent positive associations. However, when using high waist circumference based on Japanese criteria for defining metabolic syndrome, the authors noted no significant relationship between MAFLD and CKD.

Based on the data available from different subgroups, we were able to conduct separate analyses for men, women, and overweight category (yes or no). Meta-analysis showed that MAFLD was a risk factor for CKD in men (HR: 1.38 95% CI: 1.22, 1.56 I^2=86%), women (HR:

Table 1 Study summary

First author, year, reference number	Design	Database	Excluded patients	Demographic details	Diagnosis of MAFLD	Diagnosis of CKD & percentage of cases	CKD Risk factors (%)	Covariates adjusted	Mean/ Median follow-up	Outcome	NOS score
Gao 2024 [17]	R	Kailuan cohort, China	CKD at baseline, loss to follow-up, missing data	*N* = 79,450 Age = 50.7 yrs Men (%) = 80.4	Standard definition*	eGFR < 60 mL/min/1.73 m^2 or proteinuria; 25.7%	Excessive drinking = 18.1 Smoking = 34.9 DM = 8.3 HT = 41.2 DL = 45.3	Age, sex, smoking habits, drinking consumption, exercise, education, income, baseline eGFR, uric acid, alanine aminotransferase, metabolic dysfunction, use of antihyperglycemic agents, use of antihypertensive agents, use of antilipidemic agents	12.9 yrs	MAFLD was associated with increased risk of CKD [HR: 1.12 (1.09, 1.16)].	8
Zhang 2023 [24]	P	Tianjin Chronic Low-grade Systemic Inflammation and Health Cohort Study, China	Cancer, CVD, CKD at baseline, loss to follow-up, missing data	*N* = 25,974 Age = 41.3 yrs Men (%) = 54.2	Standard definition*	eGFR < 60 mL/min/1.73 m^2 or proteinuria or a clinical diagnosis of CKD; 4.4%	DM = 4.7 Smoking = 20.1 Heavy drinker = 13	Age, sex, education levels, employment status, household income, total energy intake, other kidney diseases, family history of diseases (hypertension, cardiovascular disease, and diabetes), and baseline eGFR	NR	MAFLD was associated with increased risk of CKD [HR: 1.47 (1.30, 1.66)].	8
	P	UK Biobank Study	Cancer, CVD, CKD at baseline, loss to follow-up, missing data	*N* = 113,954 Age = 55.4 yrs Men (%) = 49.9	Standard definition*	eGFR < 60 mL/min/1.73 m^2, or a clinical diagnosis of CKD; 1.6%	DM = 4.9 Smoking = 44.4 Heavy drinker = 40.2	Age, sex, education levels, Townsend deprivation index, total energy intake, other kidney diseases, family history of diseases (hypertension, cardiovascular disease, and diabetes), and baseline eGFR	NR	MAFLD was associated with increased risk of CKD [HR: 1.73 (1.57, 1.91)].	8
Wei 2023 [23]	R	People's Hospital of Guangxi Zhuang Autonomous Region, China	CKD at baseline, loss to follow-up, missing data	*N* = 41,246 Age = NR Men (%) = 54.3	Standard definition*	eGFR < 60 mL/min per 1.73 m^2 or 2 incidents of proteinuria; 13%	DM = 8.8 HT = 16.1 DL = 54.3 High BMI = 68	Age, sex, HT, DL, high BMI, DM, low-density lipoprotein, aspartate aminotransferase, alanine aminotransferase, and creatinine	10 yrs	MAFLD was a risk factor for incident CKD [HR:1.18 (1.11, 1.26)]	8
Tanaka 2023 [18]	P	Keijinkai Maruyama Clinic, Japan	CKD at baseline, loss to follow-up, missing data	*N* = 13,159 Age = 48 yrs Men (%) = 65.2	Standard definition*	eGFR < 60 mL/min per 1.73 m^2 or proteinuria by the dipstick method; 16.4%	HT = 16.5 DM = 5.4 DL = 24 CVD = 1	Age, sex, eGFR, current smoking, CVD, DM, high BMI, HT, DL	6.3 yrs	MAFLD was a risk factor for incident CKD [HR:1.12 (1.02, 1.26)]	8
Kwon 2023 [22]	R	Health Promotion Center at Samsung Medical Center, Korea	Cancer, liver cirrhosis, baseline CKD, loss to follow-up, missing data	*N* = 21,713 Age = 44 yrs Men (%) = 68	Standard definition*	eGFR < 60 mL/min per 1.73 m^2 or urine albumin/creatinine ratio ≥ 30 mg/g; 4.2%	DM = 5.3 HT = 32.9	Age, sex, eGFR, smoking, physical activity, prediabetes, DM, HT, CVD, Non-alcoholic fatty liver disease fibrosis score, BMI	5.3 yrs	MAFLD was a risk factor for incident CKD [HR:1.97 (1.49, 1.60)]	8

Table 1 (continued)

First author, year, reference number	Design	Database	Excluded patients	Demographic details	Diagnosis of MAFLD	Diagnosis of CKD & percentage of cases	CKD Risk factors (%)	Covariates adjusted	Mean/ Median follow-up	Outcome	NOS score
Liang 2022 [21]	P	Shanghai Nicheng Cohort Study, China	CKD at baseline, loss to follow-up, missing data	*N* = 6148 Age = NR Men (%) = NR	Standard definition*	eGFR < 60 mL/min per 1.73 m^2 or urine albumin/creatinine ratio ≥ 30 mg/g; 10.4%	NR	Age, sex, educational background, smoking status, and leisure-time exercise at baseline	4.6 yrs	MAFLD was a risk factor for incident CKD [RR:1.64 (1.39, 1.94)]	7
Jung 2022 [20]	R	Korean National Health Insurance Service database	CKD at baseline, loss to follow-up, missing data	*N* = 268,946 Age = 57 Men (%) = 54	Standard definition*	eGFR < 60 mL/min per 1.73 m^2 or proteinuria; 3%	Smoking = 35.6 DM = 20 HT = 36.9 CVD = 11.6	Age, sex, income level, comorbidities of HT, DM, congestive heart failure, cerebrovascular disease, ischemic heart disease, exercise frequency, alcohol intake, smoking status, use of anti-dyslipidemic agents, non-steroidal anti- inflammatory drugs or anti-platelet agents, low density lipoprotein-cholesterol, serum aspartate aminotransferase; alanine aminotransferase, and creatinine	5.1 yrs	MAFLD was a risk factor for incident CKD [HR:1.35 (1.33, 1.46)]	8
Hashimoto 2022 [19]	R	NAfld in Gifu Area, Longitudinal Analysis, Japan	CKD at baseline, loss to follow-up, missing data	*N* = 27,941 Age = NR Men (%) = 54	Standard definition*	eGFR < 60 mL/min per 1.73 m^2 or proteinuria; 16.5%	High BMI = 30.1 HT = 25.9 DM = 12.8 DL = 12.6 Smoker = 25	Sex, age, alcohol consumption, smoking, exercise, and creatinine	4.6 yrs	MAFLD was a risk factor for incident CKD [HR:1.30 (1.17, 1.43)]	7

P, prospective; R, retrospective; CVD, cardiovascular disease; CKD, chronic kidney disease; N, number of participants; yrs, years; NOS, Newcastle Ottawa scale; DM, diabetes mellitus; DL, dyslipidemia; HT, hypertension; MAFLD, metabolic dysfunction-associated alcoholic fatty liver disease; eGFR, estimated glomerular filtration rate; USG, ultrasonography; HR, hazard ratio; RR, risk ratio

*Hepatic USG and at least one of the following three conditions: (1) overweight; (2) Type 2 DM; (3) at least two of the following seven metabolic conditions: increased waist circumference, blood pressure, triglycerides, high-sensitivity C-reactive protein level, and insulin resistance, decreased high density lipoprotein-cholesterol, and prediabetes

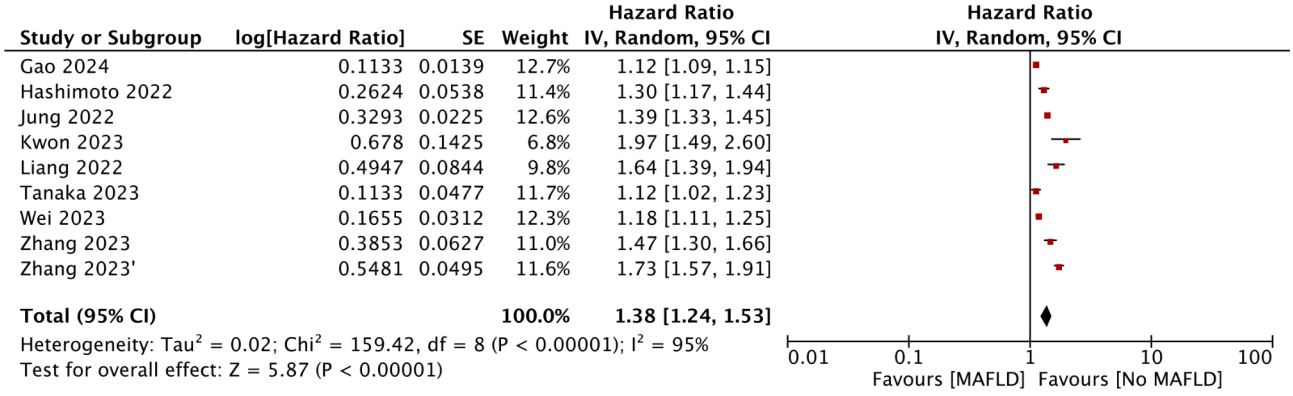

Fig. 2 Meta-analysis of the association between MAFLD and CKD

Table 2 Outcomes of sensitivity analysis

Study excluded	Resultant hazard ratio [95% confidence intervals]
Gao 2024 [17]	1.42 [1.27, 1.58]
Hashimoto 2022 [19]	1.39 [1.24, 1.56]
Jung 2022 [20]	1.38 [1.22, 1.56]
Kwon 2023 [22]	1.34 [1.20, 1.49]
Liang 2022 [21]	1.35 [1.21, 1.51]
Tanaka 2023 [18]	1.42 [1.26, 1.59]
Wei 2023 [23]	1.41 [1.25, 1.60]
Zhang 2023 [24]	1.37 [1.22, 1.53]
Zhang 2023'[24]	1.33 [1.20, 1.47]

1.51 95% CI: 1.25, 1.82 I^2=87%), overweight (HR: 1.41 95% CI: 1.20, 1.66 I^2=89%) and non-overweight cohorts (HR: 1.35 95% CI: 1.20, 1.53 I^2=9%) (Figure-3).

Discussion

Our study presents the first meta-analysis of only cohort studies examining the risk of CKD in patients with MAFLD. Aggregating data from nine large cohorts with a pooled sample size of 598,531 participants, we found that MAFLD is a significant and independent predictor of incident CKD. We also showed that the risk was irrespective of the sex and overweight status of the individual. The results were robust on multiple subgroup analyses indicating a strong association between MAFLD and CKD.

Ever since the term NAFLD was introduced in the medical texts, there has been a debate around a change of nomenclature to better indicate the pathophysiology, and disease process, and also include other superficial

Table 3 Subgroup analysis of the meta-analysis

Variable	Group	Cohorts	Hazard ratio [95% confidence intervals]	I^2
Design	Prospective	4	1.47 [1.18, 1.83]	93
	Retrospective	5	1.29 [1.15, 1.45]	97
Country	China	4	1.31 [1.15, 1.48]	92
	Japan	2	1.20 [1.04, 1.39]	77
	Korea	2	1.59 [1.10, 2.29]	86
	UK	1	1.73 [1.57, 1.91]	-
Incidence of CKD	> 10%	5	1.23 [1.12, 1.34]	85
	≤ 10%	4	1.57 [1.34, 1.84]	91
Adjusted for CVD	Yes	3	1.36 [1.13, 1.64]	91
	No	6	1.38 [1.20, 1.59]	95
Adjusted for DM	Yes	4	1.29 [1.14, 1.46]	92
	No	5	1.43 [1.17, 1.75]	96
Adjusted for HT	Yes	4	1.29 [1.14, 1.46]	92
	No	5	1.43 [1.17, 1.75]	96
Adjusted for smoking status	Yes	6	1.33 [1.19, 1.49]	97
	No	3	1.44 [1.12, 1.85]	96
Adjusted for baseline eGFR	Yes	5	1.42 [1.16, 1.73]	96
	No	4	1.35 [1.20, 1.51]	88

CKD, chronic kidney disease; HT, hypertension; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate

Table 4 Details of meta-regression analysis

Moderator	Beta	SE	-95% CI	+95% CI	*P* value
Sample size	0.0000000	0.0000008	-0.0000018	0.0000019	0.97
Age	0.0011520	0.0005103	-0.0001596	0.0024637	0.24
Male	-0.0062314	0.0063446	-0.0212340	0.0087713	0.326
Diabetes mellitus	-0.0117687	0.0136838	-0.0441258	0.0205884	0.39
Hypertension	0.0090391	0.0075505	-0.0103700	0.0284482	0.23
Smoking	0.0091273	0.0104861	-0.0199868	0.0382414	0.38
Follow-up	-0.0412013	0.0232988	-0.0982113	0.0158087	0.07

SE, standard error; CI, confidence intervals

Table-5. Subgroup analysis reported by the included studies

histopathological similarities to alcohol-related liver disease [8, 25]. Finally, in 2020, a consensus panel of experts utilized a 2-stage Delphi consensus model and proposed the term MAFLD to better define the spectrum of fatty liver disease [9]. It succeeded in NAFLD which was diagnosed based on the exclusion of subjects with alcohol intake and provided a more comprehensive definition that incorporated metabolic dysregulation associated with NAFLD. The change of definition has brought along changes in disease characteristics as well when compared to NAFLD. Lin et al. [26] in one of the first studies examined a large database of 13,083 cases and noted that 31.4% of the population was diagnosed with MAFLD while 33.23% had NAFLD. Importantly, they showed that individuals with MAFLD were aged, had higher body mass index, an increased proportion of DM and HT, higher insulin resistance, and lipid and liver enzyme levels. Since MAFLD has increased focus on metabolic dysfunction and is associated with worse disease characteristics, it is necessary to examine if the risk of extrahepatic complications has also correspondingly worsened with such a change of definition [27]. Guerreiro et al. [28] recently compared cardiovascular risk and CVD between NAFLD and MAFLD and showed that cardiovascular risk was intermediate/high in both diseases while CVD occurred in 12.8% and 20.1% of individuals with NAFLD and MAFLD respectively, though the difference was not statistically significant. Another meta-analysis [11] of 11 studies has compared cardiovascular events and all-cause mortality between NAFLD and MAFLD patients. The authors found that the risk of all-cause mortality in MAFLD was 2.8 times as compared to NAFLD. The study also showed a statistically significant 1.48 times higher risk of cardiovascular mortality and 18% increase in the risk of cardiovascular events in patients with MAFLD [11]. In this context, it is important to explore if MAFLD has an association with CKD, another relevant extrahepatic complication that has shown a positive relationship with NAFLD.

Previously, Mantovani et al. [12] in a meta-analysis of 13 cohort studies including 1,222,032 individuals showed that NAFLD was associated with a significant increase in the risk of CKD (defined as eGFR < 60mL/min/1.73 m^2 or proteinuria) over a median follow-up of 9.7 years (HR: 1.45 95% CI: 1.33, 1.54). In the context of MAFLD, Agustani et al. [13] recently published their review of 11 studies (seven cross-sectional and four cohort studies) and showed that MAFLD increased the prevalence (Odds ratio 1.50 95% CI: 1.02, 2.23) and incidence of CKD (HR: 1.35 95% CI: 1.18, 1.52). Building upon their review, we conducted an updated literature search and included five more cohorts to present the best quality evidence on the risk of CKD in MAFLD patients to date. Our results showed that MAFLD patients have a 38% increased risk of CKD compared to non-MAFLD controls. Adding credibility to the results was the consistent positive association reported by all included studies and the robustness of the effect size on sensitivity analysis. On the sequential exclusion of individual cohorts, we noted that the risk of CKD did not vary much and ranged from 33 to 42%. Nevertheless, high heterogeneity was noted in the meta-analysis which demands caution in the interpretation of results.

Exploring the potential causes of heterogeneity we divided the studies into multiple subgroups. However, we noted that the positive association persisted irrespective of the study design (prospective and retrospective studies), country of origin (China, Korea, Japan, or the UK), and incidence of CKD in the cohort (>10% or ≤10%). Further, there were minimal differences amongst studies on the method of assessment of MAFLD and CKD. All studies used the standard definition of MAFLD and utilized ultrasonography to determine fatty liver. Minor variations were noted in the definition of CKD with studies using proteinuria, urine albumin/creatinine ratio, and also "clinical diagnosis of CKD" to identify the outcome group. Since, separate data was not available from all studies based on the specific criteria of identification of CKD, a subgroup analysis was not possible. While this could be one cause of high inter-study heterogeneity, another possible cause may be the differences in the adjusted confounders. All studies reported adjusted associations between MAFLD and CKD but did not necessarily include all important covariates. DM, HT, CVD, and

Table 5 Subgroup analysis reported by the included studies

Study	Variable	Outcome
Zhang 2023 (Tianjin Chronic Low-grade Systemic Inflammation and Health Cohort Study)	Sex	Men HR: 1.51 (1.31, 1.73) Women HR: 1.40 (1.04, 1.88)
	MAFLD definition included only one metabolic abnormality	HR: 1.44 (1.27, 1.63)
	eGFR was calculated using the CKD-EPI equation	HR: 1.46 (1.28, 1.65)
	40–70 year old participants	HR: 1.73 (1.46, 2.05)
	Healthy lifestyle factors	0–1 healthy lifestyle factors HR: 2.08 (1.51, 2.88) 2 healthy lifestyle factors HR: 1.65 (1.34, 2.04) 3–4 healthy lifestyle factors HR: 1.21 (1.01, 1.45)
Zhang 2023 (UK Biobank Study)	Sex	Men HR: 1.54 (1.37, 1.74) Women HR: 2.04 (1.75, 2.39)
	MAFLD definition included only one metabolic abnormality	HR: 1.71 (1.55, 1.89)
	eGFR was calculated using the CKD-EPI equation	HR: 1.67 (1.52, 1.83)
	CKD genetic risk score	Low HR: 2.17 (1.80, 2.62) Intermediate HR: 1.71 (1.44, 2.03) High HR: 1.87 (1.61, 2.18)
	Healthy lifestyle factors	0–1 healthy lifestyle factors HR: 1.89 (1.46, 2.46) 2 healthy lifestyle factors HR: 1.75 (1.47, 2.08) 3–4 healthy lifestyle factors HR: 1.63 (1.43, 1.87)
Wei 2023	Sex	Men HR: 1.16 (1.07–1.26) Women HR: 1.32 (1.18–1.48)
	Age	< 60 years HR: 1.32 (1.22–1.42) ≥ 60 years HR: 1.04 (0.91–1.19)
	Hypertension	Yes HR: 1.27 (1.13–1.42) No HR: 1.22 (1.13–1.33)
	Dyslipidemia	Yes HR: 1.31 (1.20–1.42) No HR: 1.11 (0.99–1.24)
	Overweight	Yes HR: 1.23 (1.15–1.32) No HR: 1.32 (1.06–1.65)
	Diabetes	Yes HR: 1.35 (1.15–1.59) No HR: 1.22 (1.13–1.33)
Tanaka 2023	Severity of MAFLD	Metabolic dysfunction 0 h: 0.78 (0.59–1.02) Metabolic dysfunction 1 h: 1.17 (1.01–1.38) Metabolic dysfunction 2 h: 1.15 (1.02–1.31) Metabolic dysfunction 3 h: 1.52 (1.04–2.22)
Kwon 2023	Overweight	High HR: 2.94 (1.91–4.55) Low HR: 2.14 (1.15–3.97)
	Diabetes	Yes HR: 2.20 (1.67–2.90) No HR: 1.39 (1.18–1.65)
Liang 2022	Excessive alcohol consumption	RR: 1.09 (0.69–1.73)
	With Hepatitis B virus infection	RR: 1.35 (0.78–2.35)

Table 5 (continued)

Study	Variable	Outcome
Jung 2022	Age	< 60 years HR: 1.41 (1.31–1.52)
		≥ 60 years HR: 1.38 (1.30–1.47)
	Sex	Men HR: 1.38 (1.30–1.46)
		Women HR: 1.37 (1.27–1.48)
	Overweight	Yes HR: 1.34 (1.27–1.41)
		No HR: 1.33 (1.17–1.51)
	Diabetes	Yes HR: 1.41 (1.30–1.52)
		No HR: 1.37 (1.30–1.46)
	Low-density lipoprotein mg/dl	< 100 h: 1.39 (1.28–1.50)
		> 100 h: 1.38 (1.30–1.46)
	Alcohol use	Yes HR: 1.35 (1.20–1.52)
		No HR: 1.40 (1.33–1.47)
Hashimoto 2022	With eGFR of ≥ 75 mL/ min/1.73 m^2	HR 1.57 (1.22–2.02)
	With eGFR < 60 mL/ min/1.73 m^2	HR 1.24 (1.11–1.38)
	With proteinuria	HR 1.95 (1.47–2.59)
	Using the high waist circumference with Japanese criteria of metabolic syndrome	HR 1.24 (0.96–1.61)

HR, hazard ratio; RR, risk ratio; eGFR, estimated glomerular filtration rate; MAFLD, metabolic dysfunction-associated alcoholic fatty liver disease

smoking are known risk factors for CKD [29]. Hence, we segregated studies based on the adjustment of these risk factors only to note a firm positive relationship between MAFLD and CKD. None of the subgroup analyses were able to bring down the inter-study heterogeneity indicating other factors at play like baseline patient characteristics, severity of disease, duration of follow-up, etc. Further, a meta-regression based on sample size, age, male gender, DM, HT, smoking, and follow-up also did not show any significant relationship with the effect size. It is pertinent to note that liver disease can be complicated by glomerular diseases such as membranous nephropathy and IgA nephropathy which in turn could increase the risk of CKD [31]. Since the included studies did not present information on these glomerular disease, we were unable to assess their implication on the study outcomes. However, we did conduct a subgroup analysis for studies which adjusted for baseline eGFR only to note no change in the association between MAFLD and CKD.

To further investigate the association between the two entities, we also examined all subgroups reported by individual studies and were able to collate separate data based on sex and overweight status. In literature, obese MAFLD has been shown to have worse outcomes as compared to non-obese MAFLD [30]. However, we did not note a major change in the risk of CKD between overweight and non-overweight groups (41% vs. 35% increased risk respectively). Similarly, the association was significant in both men and women. Likewise, the risk of CKD has been shown to be persistent in NAFLD patients irrespective of sex, obesity, HT, DM, and other conventional CKD risk factors [12].

While there is no single explanation for the strong positive association between MAFLD and CKD, many potential links exist. First, a genetic association has been found with several genes identified in the etiology of MAFLD (PNPLA3, TMS6SF2, MBOAT7, and GCKR). Heightened activity of these genes has been found in hepatic stellate cells leading to fat accumulation and increased lipogenesis. The gene PNPLA3 also has a role in the development of CKD by enhancing ectopic lipid deposition in the kidneys [32]. Secondly, MAFLD patients have increased levels of fatty acid-binding protein-4 which is secreted by fat cells and can cause increased insulin resistance, vascular remodeling, and atherosclerosis [33, 34]. Fatty acid-binding protein-4 is also implicated in glomerular injury, tubulointerstitial fibrosis, and reduced eGFR [35, 36]. Thirdly, the gut-liver-kidney axis could be another potential mechanism. The gut microbiota secretes several metabolites that not only regulate gut function but also extra-intestinal organs like the kidney, liver, and brain [37]. The uraemic toxin of tri-methylamine N-oxide produced by the gut microbes can worsen both fatty liver and CKD [38]. On one hand, it increases liver de

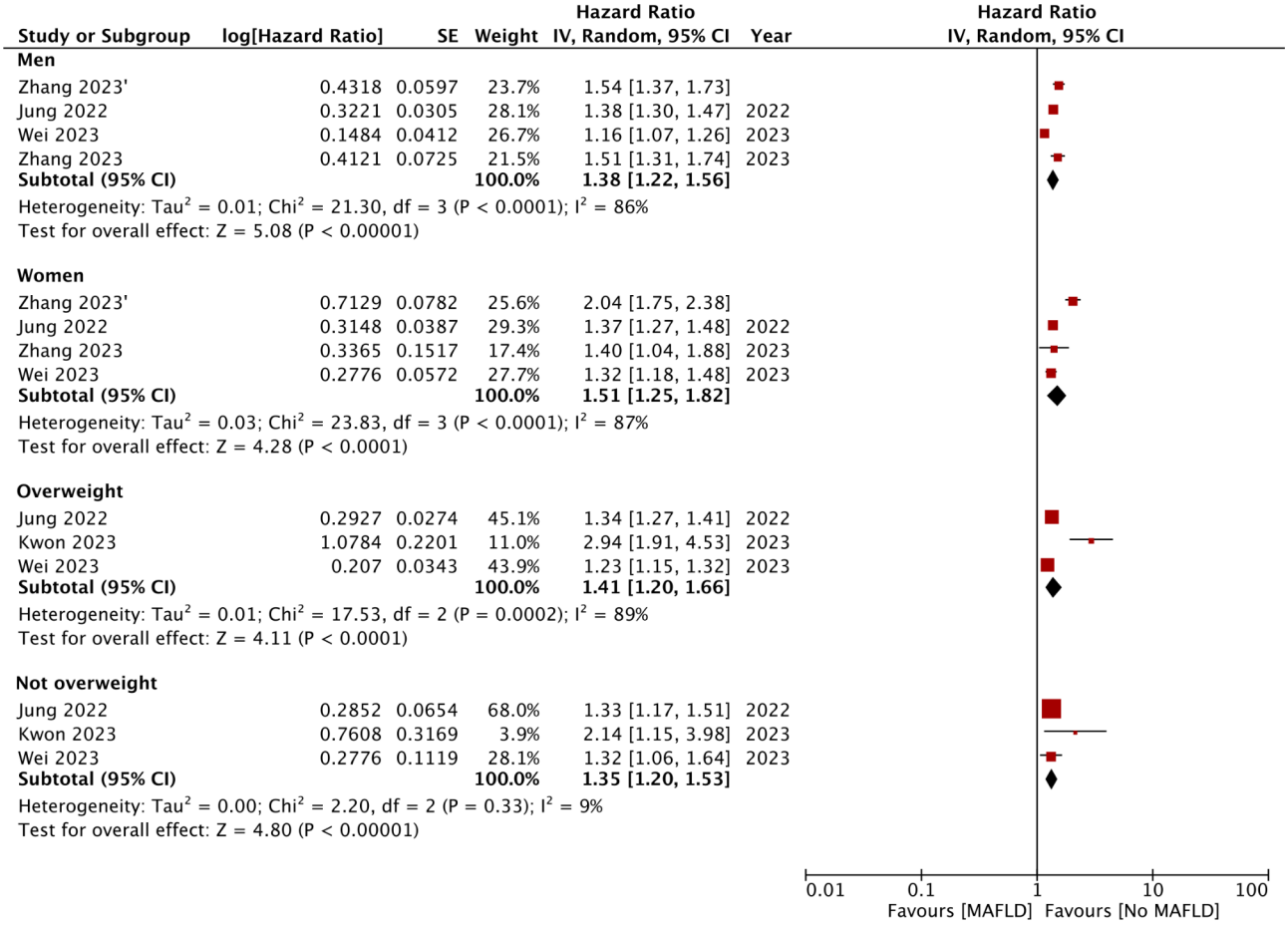

Fig. 3 Meta-analysis of the association between MAFLD and CKD for men, women, overweight and non-overweight participants

novo lipogenesis by obstructing the farnesoid X receptor thereby aggravating fatty liver [39]. On the other hand, it has an important role in tubulointerstitial fibrosis and injury-worsening CKD in patients with fatty liver [40].

Our study has important clinical implications. Given the large prevalence of MAFLD [8], it is necessary for clinicians to know the risk of important extra-hepatic manifestations of the disease, especially like CKD which can lead to significant disability, mortality and reduction in quality of life [4, 5]. In view of the presented evidence, we believe that MAFLD patients should be regularly screened for CKD for early identification of the disease so that timely measures which can reduce the progression of the disease can be initiated. It is known that no specific curative treatment is available for MAFLD and CKD. But lifestyle modifications, hypocaloric diet and exercise can lead to weight loss which promotes the regression of liver disease and thereby may reduce the risk of CKD [41]. Moreover, research indicates that glucose-lowering agents (like pioglitazone, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransporter-2 inhibitors) can have beneficial effects in NAFLD/MAFLD by reducing hepatic fat content and steatohepatitis along with improvement of cardiorenal outcomes irrespective of the presence of DM [42].

There are some limitations to our study. Despite an updated literature search, we had only nine cohorts for the meta-analysis. Some studies were retrospective and could be prone to bias owing to the study design. Secondly, variations in the CKD definition and follow-up period between studies are important limitations. CKD is a slowly developing disease and it is unclear how long a follow-up is necessary to truly demonstrate the risk of CKD in MAFLD. Thirdly, despite including only adjusted data, several unknown confounders could have been missed by the included studies thereby skewing the current results. Fourthly, much of the data was from the Asian population with only one study from Europe. More data is needed from Western countries to generalize the results. Lastly, we were unable to explore the relationship between baseline MAFLD severity and disease duration and risk of CKD due to lack of sufficient data in the included studies. A detailed subgroup analysis or meta-regression based on these variables would have provided important clinical information for stratification of the risk of CKD in patients with MAFLD.

We believe that despite these limitations, a number of strengths make this meta-analysis an important addition to the literature. This is the first meta-analysis of cohort studies providing the best available evidence on the risk of CKD in MAFLD. The large sample size, uniformity in the definition of MAFLD, similar non-exposure group, and use of adjusted data impart credibility to the review. We presented a detailed sensitivity analysis, subgroup analysis, and narrative review of subgroups of the included studies to ensure a comprehensive review of the relationship between the two entities.

Conclusions

Evidence for good-quality cohort studies shows that MAFLD is a risk factor for CKD. The association seems persistent irrespective of sex, body mass index, and other CKD risk factors. Further investigations are needed to explore if the risk of CKD varies with the severity of MAFLD. Also, MAFLD patients need to be counseled and closely monitored for the development of CKD.

Author contributions

Conception and design: WL. Data collection and Analysis and interpretation of data: WL, XS. Writing, review, and/or revision of the manuscript: WL.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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