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Metabolic dysfunction-associated fatty liver disease increases risk of chronic kidney disease: a systematic review and meta-analysis

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ABSTRACT

Background and aim Metabolic dysfunction-associated fatty liver disease (MAFLD) is an alternative description and classification of non-alcoholic fatty liver disease (NAFLD) that may have better utility than NAFLD in clinical practice. We performed a meta-analysis to quantify the magnitude of the association between MAFLD and risk of both prevalent and incident chronic kidney disease (CKD).

Methods We systematically searched PubMed, Medline (OVID), Embase (OVID), Web of Science and Cochrane Library from database inception until 29 May 2022. We included observational studies examining the association between MAFLD and risk of CKD, defined by estimated glomerular filtration rate ≤60 mL/min/1.73 m^2 or presence of abnormal albuminuria. Meta-analysis was performed using random-effects models to obtain summary HRs or ORs with 95% CIs.

Results Seventeen observational studies with aggregate data on 845 753 participants were included in meta-analysis. In the 7 cohort studies, the pooled random-effects HR for incident CKD in patients with MAFLD was 1.29 (95% CI 1.17 to 1.41, I^2=87.0%). In the 10 cross-sectional studies, the pooled random-effects OR for prevalent CKD in patients with MAFLD was 1.35 (95% CI 1.11 to 1.64, I^2=92.6%).

Conclusion MAFLD is significantly associated with an increased prevalence and incidence of CKD.

PROSPERO registration number CRD42022352366.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Studies have shown that Metabolic Associated Fatty Liver Disease (MAFLD) may progress to cirrhosis and contribute to the development of several important extrahepatic diseases, such as cardiovascular disease and chronic kidney disease.

⇒ Chronic kidney disease (CKD) is a progressive and permanent loss of kidney function that leads to significantly increased morbidity and mortality. According to global burden of disease data, CKD is projected to be the fifth leading cause of death worldwide by 2040.

WHAT THIS STUDY ADDS

⇒ In the 7 cohort studies, the pooled random-effects HR for incident CKD in MAFLD patients was 1.29 (95% CI 1.17 to 1.41, I^2=87.0%).

⇒ In the 10 cross-sectional studies, the pooled random-effects OR for prevalent CKD in MAFLD patients was 1.35 (95% CI 1.11 to 1.64, I^2=92.6%).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Healthcare professionals should be aware that risk of incident CKD is moderately increased in patients with MAFLD.

⇒ Earlier intervention for MAFLD could be a novel target for the prevention and treatment of CKD.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver diseases worldwide, affecting up to ~30% of adults in the general population, up to ~55% of patients with type 2 diabetes mellitus (T2DM) and >50% patients with moderate or severe obesity.[1 2] The histological spectrum of NAFLD can be categorised into simple steatosis and non-alcoholic steatohepatitis (NASH) that may progress to cirrhosis and hepatocellular carcinoma.[3] The new definition of metabolic dysfunction-associated fatty liver disease (MAFLD) has been proposed by a consensus of international experts in 2020; notably, this newly proposed MAFLD definition does not require the exclusion of other aetiologies of hepatic steatosis, such as excessive alcohol intake, viral infections or use of hepatotoxic medications.[4] As such, it has been suggested that MAFLD could replace the 'old' term NAFLD both in clinical practice and in research studies. The diagnosis of MAFLD requires the presence of hepatic steatosis *plus* at least one of the following

three metabolic risk abnormalities: overweight/obesity, T2DM or evidence of metabolic dysregulation (defined as the presence of at least two of seven metabolic risk factors featuring the metabolic syndrome in lean individuals, including also increased homeostatic model assessment for insulin resistance score and elevated plasma C reactive protein levels).[5] A recent meta-analysis of about 10 million individuals reported a global prevalence of MAFLD of 38.8% in adults.[6] In addition, it has been reported that MAFLD may progress to cirrhosis and promote the development of some important extrahepatic diseases, such as cardiovascular disease and chronic kidney disease (CKD).[7 8]

CKD is a progressive disease with permanent loss of the kidney function, which causes a significant increase in morbidity and mortality. In 2017, the global prevalence of CKD is estimated to be around 9%,[9] resulting in about 1.2 million deaths and 35.8 million disability-adjusted life-years.[9] Furthermore, based on global burden of disease data, CKD is predicted to become the fifth leading global cause of death by 2040.[10 11] Consequently, the search for novel risk factors for CKD should improve strategies for identification of high-risk patient subgroups and potentially reduce the clinical adverse impact of CKD.[12] In this setting, identification of MAFLD as a novel risk factor of CKD is attracting considerable scientific attention.[7]

A nationwide cohort study of 268 946 middle-aged individuals who underwent National Health Insurance Service health examinations in Korea found that compared with non-MAFLD participants, those with MAFLD had a nearly 40% increase in risk of incident CKD.[13] While these results have been consistent with other published studies,[14–16] a retrospective cohort analysis of 143 210 patients with obesity from the Truven Health MarketScan Database reported that MAFLD was not significantly associated with an increased risk of incident CKD.[17] In addition, in a cross-sectional analysis of the US Third National Health and Nutrition Examination Survey, the authors showed that patients with MAFLD had a significantly higher prevalence of CKD than those with NAFLD.[18] In such study, MAFLD was associated with a higher risk of CKD stage ≥1 and abnormal albuminuria, but not CKD stage ≥3.[18] That said, given the conflicting results on the association between MAFLD and CKD risk reported in previously published studies, there is a need to undertake review and pool the existing evidence to assess the association between MAFLD and risk of CKD.

Therefore, our aim was to undertake a comprehensive meta-analysis of observational studies to quantify the magnitude of the association between MAFLD and the risk of both prevalent and incident CKD, according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[19 20]

METHODS

Registration of review protocol

The protocol for this systematic review was registered in advance with PROSPERO (International Prospective Register of Systematic Reviews, no. CRD42022352366).

Search strategy and selection criteria

We systematically searched potential publications in five large electronic databases (PubMed, Medline (OVID), Embase (OVID), Web of Science and Cochrane Library), from database inception until 29 May 2022. According to our search and selection procedures, all articles retrieved were first assessed by screening the titles and abstracts, and then the relevant full texts were evaluated. Study selection was conducted independently by two authors (JZ and D-QS).

The inclusion criteria of the meta-analysis were as follows: (1) longitudinal cohort studies or cross-sectional studies, (2) studies investigating the association between MAFLD and risk for CKD, (3) adult (aged >18 years) individuals of any sex or ethnicity and (4) studies with a diagnosis of MAFLD and CKD. Hepatic steatosis had to be diagnosed by one of the following approaches: (1) liver histology, (2) imaging methods (ultrasonography, CT or magnetic resonance-based techniques) and (3) biomarker panels. The exclusion criteria of the meta-analysis were as follows: (1) animal studies, (2) reviews, conference proceedings, letters, case reports or comments, (3) studies in children/adolescents or pregnant women, (4) studies in patients with type 1 diabetes and (5) non-English language studies. In cases of disagreement on the inclusion or exclusion of a given study, the third author (M-HZ) was brought in to discuss the issue until a consensus was reached.

Data extraction and bias assessment

Data were extracted independently by two authors (JZ and D-QS). The detail of the data extraction is described in online supplemental methods. In cases of disagreement on data extraction from each included study, the issues were discussed with a third author (M-HZ) and a consensus was reached. An assessment of study quality was performed independently by the two aforementioned authors on the basis of either the Newcastle Ottawa Scale (NOS) for cohort studies or the Agency for Healthcare Research and Quality (AHRQ) Scale for cross-sectional studies, respectively[21] (online supplemental tables S1 and S2).

Data analysis

Data analyses were performed by statistical software (STATA, V.14.0, StataCorp, College Station, Texas, USA). For dichotomous data, the random-effects ORs for cross-sectional studies, and the random-effects HRs for cohort studies and 95% CIs were calculated. Heterogeneity was assessed using the χ^2 test for Cochran's Q statistic and calculating I^2 statistics. The random-effects model was conducted when there was a significant heterogeneity with I^2 statistic >50% or p value <0.10. We further

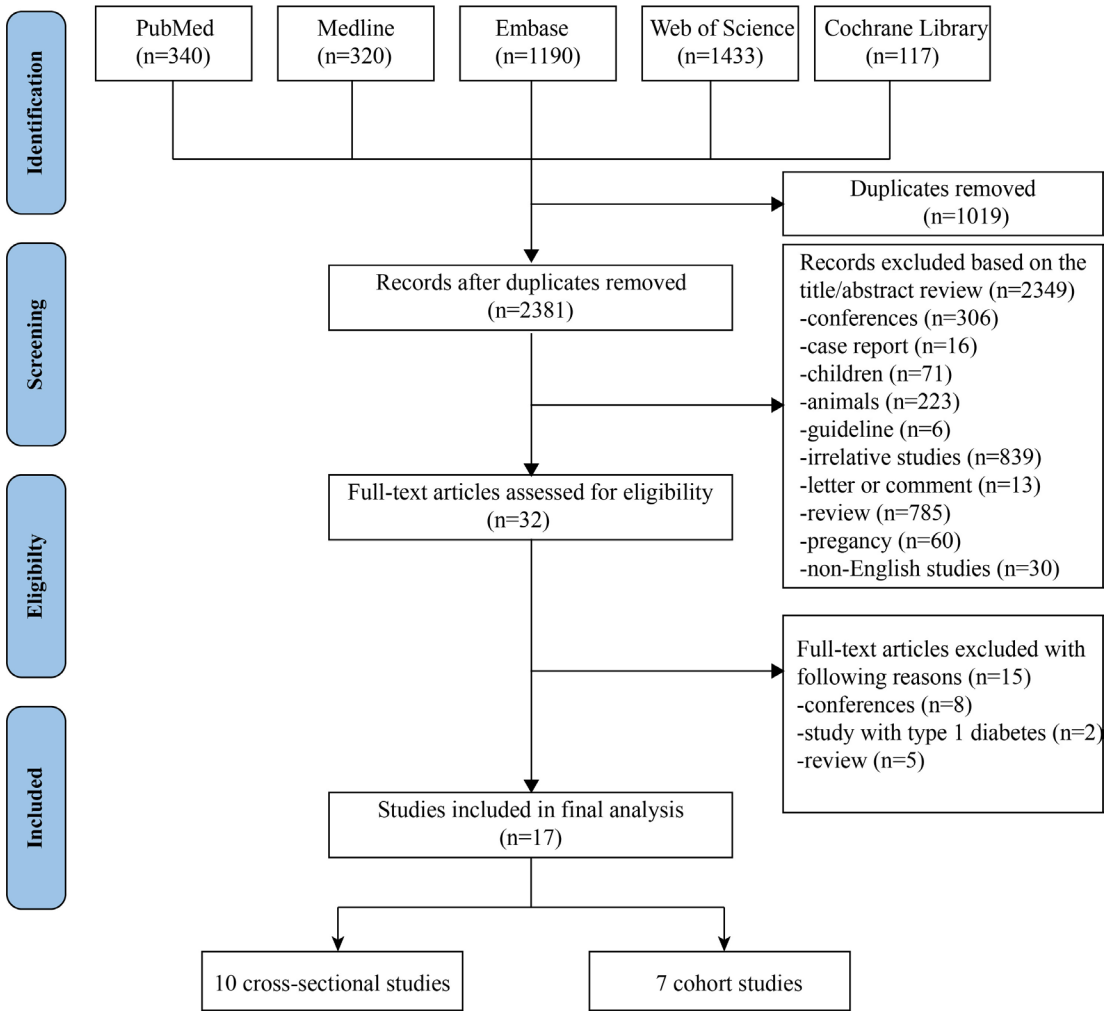

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of the meta-analysis.

conducted subgroup analyses. We also conducted sensitivity analysis to assess the stability of the pooled results. The effect on the combined effect size was explored by excluding some low quality studies or using different efficacy evaluation criteria and statistical methods. The effect on the combined effect size was explored by excluding some low quality studies or using different efficacy evaluation criteria and statistical methods.

RESULTS

The results of study selection

Overall, 3400 published articles were initially retrieved by our search strategy. After removing duplicate studies, 2381 publications were screened. Excluding records based on the title/abstracts, 32 articles remained for further investigation. Of these articles, 12 further publications were removed, including conference studies, a review and studies involving patients with type 1 diabetes. A total of 17 observational studies were then included in final analysis. Figure 1 summarises the PRISMA flow diagram for search and selection processes of the meta-analysis.

Characteristics of included studies

Table 1 shows the main characteristics of the included observational studies with a total of 845 753 participants, including 10 cross-sectional studies[18 22–31] and 7 retrospective cohort studies.[13–17 32 33] Hepatic steatosis was diagnosed by ultrasonography (eight studies),[8 14–16 18 31–33] FibroScan (four studies)[23 25 30 34] biomarker panels (fatty liver index, hepatic steatosis index, NAFLD liver fat score or ultrasound fatty liver index) (four studies),[13 26 28] liver histology (one study)[29] or International Classification of Diseases, Ninth Revision, Clinical Modification (one study).[17] In seven studies, MAFLD was defined by the presence of hepatic steatosis *plus* at least one of the three metabolic risk abnormalities, including T2DM, overweight/obesity or metabolic dysregulation.[13–16 18 28 30] In 10 studies, MAFLD was defined exclusively by the coexistence of hepatic steatosis and T2DM,[17 22 23 25 26 29 31–33 35] whereas in one study MAFLD was diagnosed by the coexistence of hepatic steatosis and obesity.[17] In all studies, CKD was defined as estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2 and/or abnormal albuminuria (ie, urinary albumin-to-creatinine ratio

Table 1 Main characteristics of included studies

Study	Age	Male (%)	Country	Participant	MAFLD diagnosis	CKD definition	Covariate adjustments
Cohort study				**Description**			
Jung *et al*[13]	57.54±8.1	54.03	Korea	268946 participants underwent National Health Insurance Service health examination	Fatty liver index	eGFR ≤60 mL/min/1.73 m^2 or presence of albuminuria	Age, sex, income level, hypertension, diabetes mellitus, congestive heart failure, cerebrovascular disease, ischaemic heart disease, exercise frequency, alcohol intake, smoking, lipid-lowering agents, antiplatelet agents, LDL-cholesterol, serum AST, ALT and creatinine levels
Hashimoto *et al*[14]	45.7±10.1	59	Japan	16938 participants of a medical health check-up programme at Asahi University Hospital	Ultrasonography	eGFR ≤60 mL/min/1.73 m^2 or presence of albuminuria	Age, sex, exercise, smoking, alcohol consumption
Tanaka *et al*[15]	48±8	65.2	Japan	13159 Japanese subjects who received annual health examinations	Ultrasonography	eGFR ≤60 mL/min/1.73 m^2 or presence of albuminuria	Age, sex, eGFR, smoking, ischaemic heart disease, diabetes mellitus, overweight/obesity, hypertension and dyslipidaemia
Liang *et al*[16]	61.85±4.82	42.4	China	6176 subjects from a community-based cohort study	Ultrasonography	eGFR ≤60 mL/min/1.73 m^2 or presence of albuminuria	Sex, age, educational background, smoking status and leisure-time exercise
Park *et al*[17]	51	53	USA	262619 newly diagnosed patients with NAFLD and 769 878 patients without NAFLD from the Truven Health Analytic MarketScan Commercial and Medicare Supplemental databases	ICD-9-CM	eGFR ≤60 mL/min/1.73 m^2	Age, sex, diabetes, hypertension, obesity, hyperlipidemia, coronary artery disease, peripheral vascular disease, cerebrovascular disease, heart failure, chronic obstructive pulmonary disease, cirrhosis, decompensated cirrhosis or hepatocellular carcinoma, use of ACE-inhibitors or angiotensin receptor blockers, mean number of outpatient visits and mean number of inpatient visits
Saito *et al*[32]	55.4±10.5	61.6	Japan	584 patients with T2DM	Ultrasonography	eGFR ≤60 mL/min/1.73 m^2 or presence of albuminuria	Age, sex, BMI, HbA1c, baseline eGFR, smoking and drinking status (current or past), comorbidities (hypertension, dyslipidaemia) and use of glucose-lowering and antihypertensive medications
Targher *et al*[33]	57.9±3.6	60.93	Italy	1760 patients with T2DM and normal or near-normal kidney function and without overt proteinuria	Ultrasonography	eGFR ≤60 mL/min/1.73 m^2 or presence of proteinuria	Sex, age, BMI, waist circumference, blood pressure, smoking, diabetes duration, HbA1c, lipids, baseline eGFR, microalbuminuria and hypoglycaemic, lipid-lowering, antihypertensive or antiplatelet drugs
Cross-sectional studies				**Description**			
Sun *et al*[18]	43.20±16.10	45.94	China	12571 individuals from the Third National Health and Nutrition Examination Survey	Ultrasonography	eGFR ≤60 mL/min/1.73 m^2 or presence of albuminuria	Sex, age, ethnicity, diabetes and alcohol intake
Lee *et al*[22]	66.13±10.77	34.24	Taiwan	1992 patients with T2DM	Ultrasonography	eGFR ≤60 mL/min/1.73 m^2	Age, sex, smoking, diabetes duration, obesity, BMI, systolic blood pressure, LDL-cholesterol, triglycerides, HbA1c, uric acid, transaminases, insulin treatment, antihypertensive or lipid-lowering drugs

Continued

Table 1 Continued

Study	Age	Male (%)	Country	Participant	MAFLD diagnosis	CKD definition	Covariate adjustments
Lombardi *et al*[23]	68±10	52	Italy	394 patients with T2DM	FibroScan	eGFR ≤60 mL/min/1.73 m^2 or presence of albuminuria	Centre, age, sex, smoking, diabetes duration, HbA1c, waist circumference, hypertension, use of ACE-inhibitors or angiotensin receptor blockers, statin use, uric acid, LDL-cholesterol, HDL-cholesterol, insulin therapy or ultrasonographic steatosis grade 3
Mantovani *et al*[24]	69.9±7	48.2	Italy	137 patients with non-insulin-treated T2DM	FibroScan	eGFR ≤60 mL/min/1.73 m^2 or presence of albuminuria	Age, sex, diabetes duration, HbA1c, smoking, hypertension, use of antihypertensive drugs, BMI, HOMA-IR, plasma high-sensitivity C reactive protein
Mikolasevic *et al*[25]	60.95±11.15	47.3	Croatia	442 patients with T2DM (for at least 5 years)	FibroScan	eGFR ≤60 mL/min/1.73 m^2 or the presence of albuminuria	None
Morieri *et al*[26]	68.8±11.1	57.4	Italy	78 895 patients with T2DM from 46 diabetes clinics	Hepatic steatosis index	eGFR ≤60 mL/min/1.73 m^2 or presence of albuminuria	Age, sex
Zhang *et al*[28]	None	None	USA	US National Health and Nutrition Examination Surveys, 1999–2002, 2003–2006, 2007–2010 and 2011–2016	Ultrasound-fatty liver index	eGFR ≤60 mL/min/1.73 m^2 or presence of albuminuria	None
Heidari and Gharebaghi[29]	50.79±10.49	32.16	Iran	225 patients with T2DM	Imaging or histology	eGFR ≤60 mL/min/1.73 m^2 or the presence of albuminuria	None
Deng *et al*[30]	51.71±17.62	48.57	China	4869 patients from National Health and Nutrition Examination Survey 2017–2018	FibroScan	eGFR ≤60 mL/min/1.73 m^2 or presence of albuminuria	None
Sirota *et al*[31]	41.78±6.52	45.25	USA	11 469 adults who participated in the National Health and Nutrition Examination Survey 1988–1994	Ultrasonography	eGFR ≤60 mL/min/1.73 m^2 or the presence of albuminuria	Age, race, sex, hypertension, diabetes, systolic blood pressure, waist circumference, triglycerides, HDL-cholesterol, HOMA-IR

MAFLD definition: (1) hepatic steatosis and one of three conditions: (i) overweight or obese; (ii) T2DM; (iii) metabolic abnormalities. (2) Diagnosis of hepatic steatosis was made on the basis of characteristic sonographic features: evidence of diffuse hyperechogenicity of liver relative to kidneys, ultrasound beam attenuation and poor visualisation of intrahepatic structures. (3) Evidence of diffuse hyperechogenicity in the liver relative to the kidneys, poor visualisation of intrahepatic structures and ultrasound beam attenuation. (4) Controlled attenuation parameter and liver stiffness measurement. (5) (i) Hepatic steatosis based on imaging or histology; (ii) lack of high consumption of alcohol; (iii) lack of another reason for hepatic steatosis and (iv) lack of another synchronic reason for the chronic liver disease. (6) Hepatorenal echo contrast, liver parenchymal brightness, deep beam attenuation and vessel blurring.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; LDL, low-density lipoprotein; MAFLD, metabolic dysfunction-associated fatty liver disease; T2DM, type 2 diabetes mellitus.

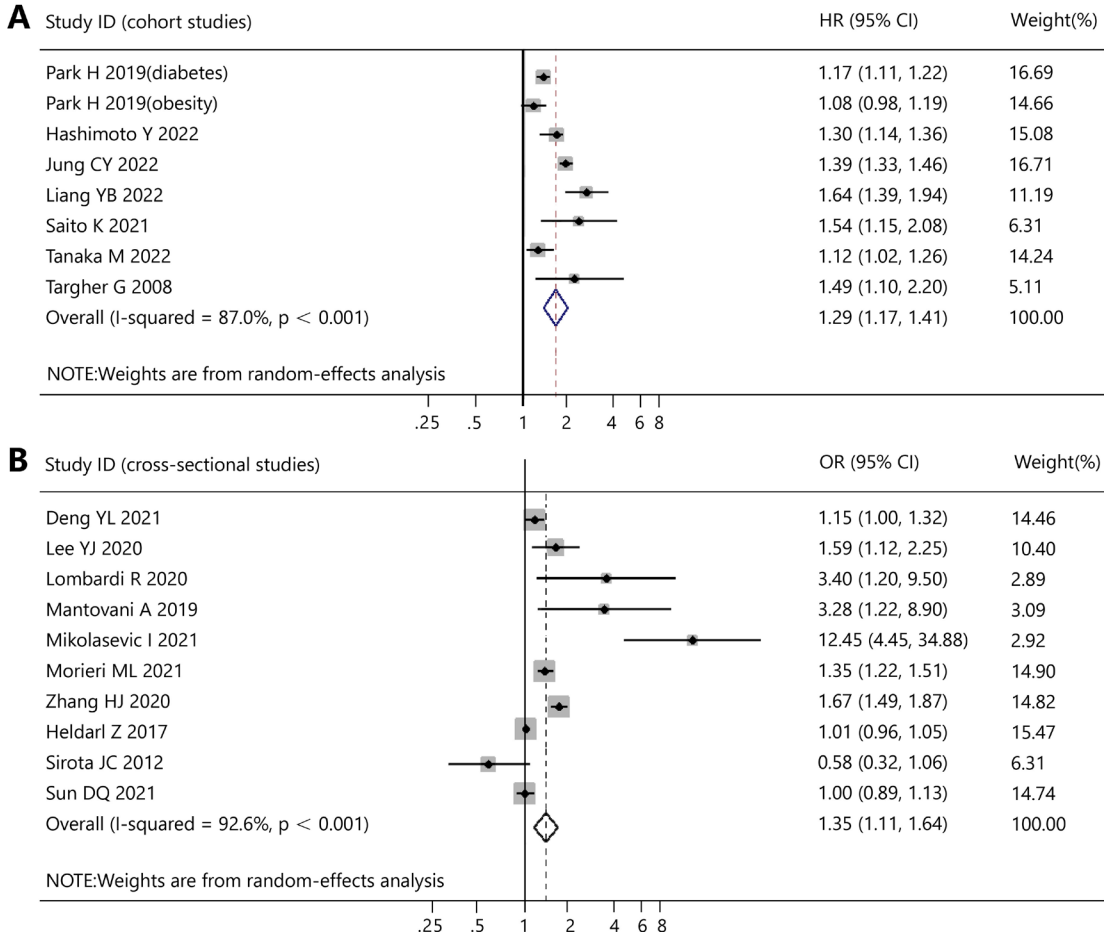

Figure 2 Association between MAFLD and risk of incident CKD. (A) Association between MAFLD and risk of incident CKD in cohort studies. (B) Association between MAFLD and risk of prevalent CKD in cross-sectional studies. CKD, chronic kidney disease; MAFLD, metabolic dysfunction-associated fatty liver disease.

≥30 mg/g). The NOS and AHRQ scores were used for assessing the quality of cohort studies and cross-sectional studies, respectively (online supplemental tables S1 and S2).

Association of MAFLD with risk of incident CKD

In the seven cohort studies included, the presence of MAFLD was significantly associated with a higher risk of incident CKD (pooled random-effects HR 1.29, 95% CI 1.17 to 1.41, I^2=87.0%, p<0.001), over a median follow-up of 6 years (IQR 4.6–10 years) (figure 2A). In the 10 cross-sectional studies included, the presence of MAFLD was significantly associated with a higher likelihood of prevalent CKD (pooled random-effects OR 1.35, 95% CI 1.1 to 1.64, I^2=92.6%, p<0.001) (figure 2B).

Subgroup analyses and meta-regressions

To explore possible sources of heterogeneity across the eligible studies, we carried out some subgroup analyses. In cohort studies, the association between MAFLD and risk of incident CKD remained significant in patient subgroups, stratified by study country, modality of MAFLD diagnosis, CKD definition, study quality or severity of MAFLD-related fibrosis (figures 3–4, online supplemental figures S2 and S4 and table 2). MAFLD was also associated with an increased risk of CKD after stratification by participants' characteristics (table 2).

The same subgroup analyses were also conducted in cross-sectional studies. We found that MAFLD was significantly associated with a higher likelihood of prevalent CKD in patient subgroups, stratified by CKD definition, MAFLD severity, study quality and degree of covariate adjustment (figures 3–4, online supplemental figures S3 and S5 and table 2). While MAFLD was not associated with risk of prevalent CKD in studies conducted in participants from America and Asia, in studies with hepatic steatosis defined by ultrasonography or histology and in studies with MAFLD diagnosed by the coexistence of hepatic steatosis with at least one of the following three metabolic risk abnormalities (namely overweight/obesity, T2DM or evidence of metabolic dysregulation).

Meta-regression was also used to explore possible sources of heterogeneity, while no variables were found affecting the association of MAFLD with and increased CKD riskonline supplemental (online supplemental table S3).

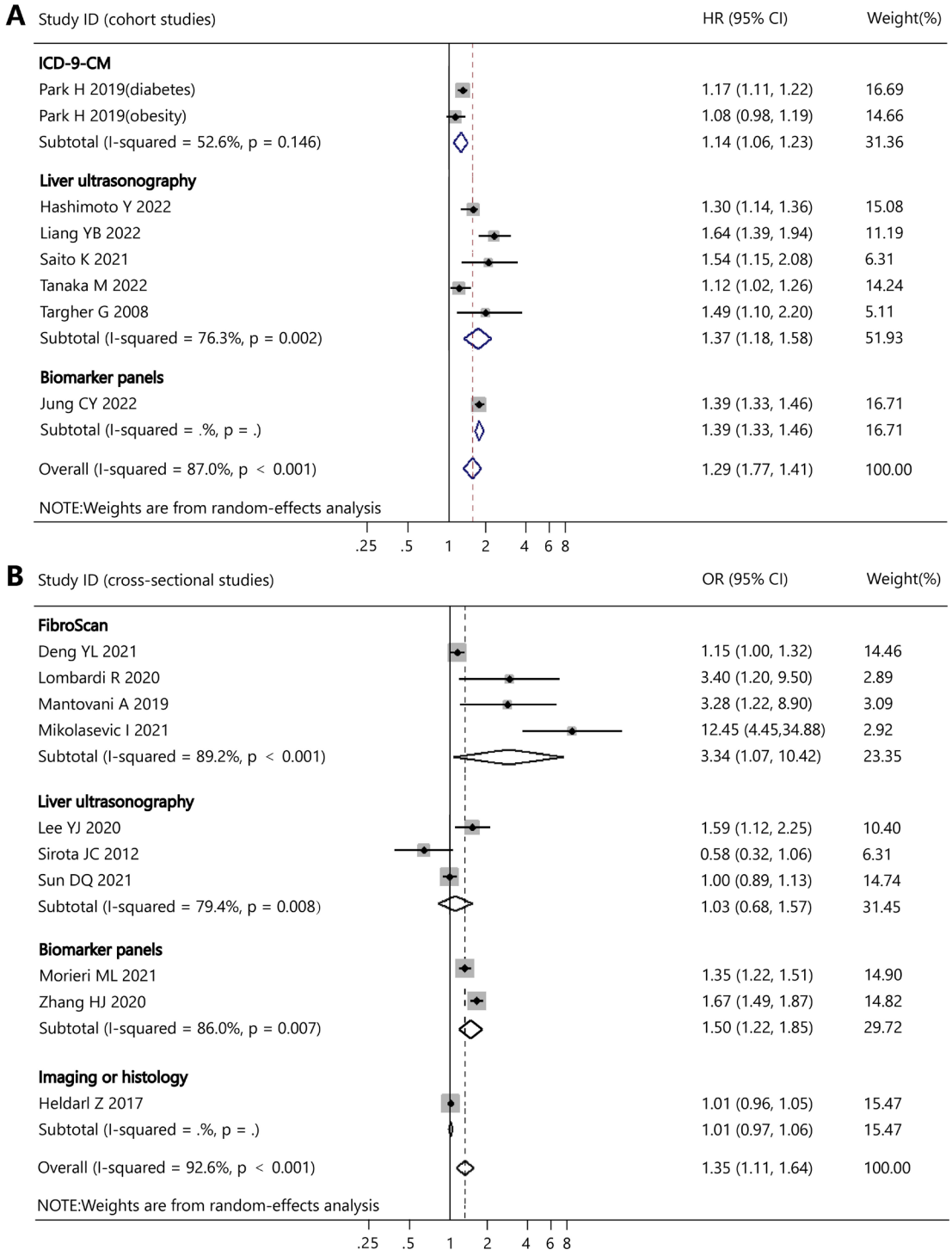

Figure 3 Subgroup analysis for MAFLD-related risk of incident CKD by modality of MAFLD diagnosis. (A) Subgroup analysis for MAFLD-related risk of incident CKD by modality of MAFLD diagnosis in cohort studies. (B) Subgroup analysis for MAFLD-related risk of prevalent CKD by modality of MAFLD diagnosis in cross-sectional studies. CKD, chronic kidney disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; MAFLD, metabolic dysfunction-associated fatty liver disease.

Association between severity of MAFLD and risk of CKD

The severity of MAFLD was assessed non-invasively as hepatic steatosis alone or presence of both hepatic steatosis and advanced fibrosis (by using non-invasive fibrosis biomarkers). There were only two studies that have assessed the association between MAFLD-related fibrosis and risk of CKD, with a pooled random-effects HR of 1.54 (95% CI 1.15 to 2.07, p=0.004) for the risk of incident CKD in patients with MAFLD from one cohort study, and a random-effects OR of 3.28 (95% CI 1.21 to 8.86, p=0.019) for the risk of prevalent CKD in patients with MAFLD from one

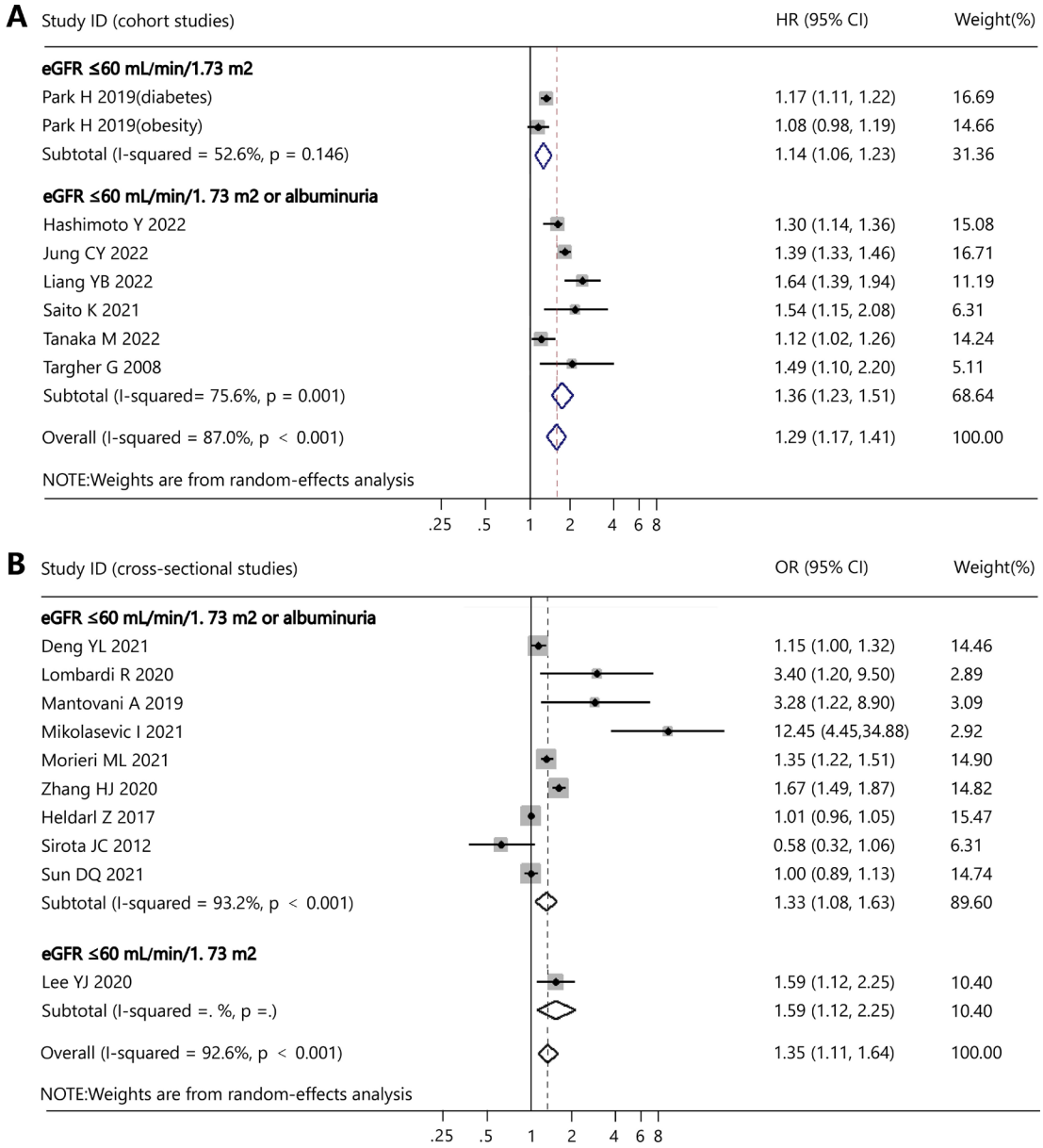

Figure 4 Subgroup analysis for MAFLD-related risk of incident CKD by CKD definition. (A) Subgroup analysis for MAFLD-related risk of incident CKD by CKD definition in cohort studies. (B) Subgroup analysis for MAFLD-related risk of prevalent CKD by CKD definition in cross-sectional studies. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MAFLD, metabolic dysfunction-associated fatty liver disease.

cross-sectional study (online supplemental figure S1).

Sensitivity analyses

To assess the impact of each study on the final outcome, we performed a sensitivity analysis. We use an impact test approach, which excludes each included study individually, to test whether excessive impact from individual studies would have a significant impact on the final results. Interestingly, we found that after excluding each eligibility study, the overall effect on MAFLD-associated CKD risk was not significant, as shown in figure 5. This indicates that our results have a certain robustness.

Publication bias assessment

The visual inspection and formal statistical tests (p values of 0.743 and 0.711 for the Egger's test and Begg's test in cohort studies; and p values of 0.092 and 0.474 for the Egger's test and Begg's test in cross-sectional studies, respectively) did not show any statistically significant asymmetry of the funnel plots, thus suggesting that publication bias was unlikely.

DISCUSSION

To the best of our knowledge, the present meta-analysis assessing the association between MAFLD and the risk of prevalent and incident CKD is the largest and most

Table 2 Subgroup analyses examining the associations between MAFLD and the risk of incident (by cohort studies) or prevalent (by cross-sectional studies) CKD

	Cohort studies		Cross-sectional studies	
	HR (95% CI), I^2 statistics, n-comparisons, participants (n)	P value	OR (95% CI), I^2 statistics, n-comparisons, participants (n)	P value
Total	1.29 (1.17 to 1.41), I^2=87.0%, n=7, 726 270 participants	0.001	1.35 (1.11 to 1.64), I^2=92.6%, n=10, 119 483 participants	<0.001
Age				
< 60 years	1.24 (1.13 to 1.37), I^2=86.3%, n=717 673 participants	0.001	1.03 (0.93 to 1.13), I^2=54.2%, n=29 164 participants	0.590
≥60 years	1.64 (1.39 to 1.94), I^2=nd, n=6873 participants	0.001	2.53 (1.47 to 4.35), I^2=83.2%, n=284 415 participants	0.001
Male (%)				
<0.50	1.64 (1.39 to 1.94), I^2=nd, n=71 767 participants	0.001	1.20 (0.98 to 1.46), I^2=85.2%, n=31 804 participants	0.073
≥0.50	1.24 (1.13 to 1.37), I^2=86.3%, n=6873 participants	0.001	1.85 (0.78 to 4.35), I^2=67%, n=281 775 participants	0.161
Country/Continent				
America	1.14 (1.06 to 1.23), I^2=52.6%, n=1, 407 577 participants	0.001	1.03 (0.37 to 2.89), I^2=91.4%, n=2, 18 600 participants	0.960
Asia	1.35 (1.21 to 1.51), I^2=80.2%, n=5, 316 933 participants	0.001	1.08 (0.97 to 1.20), I^2=67.8%, n=4, 19 687 participants	0.175
Europe	1.49 (1.05 to 2.11), I^2=nd, n=1, 1760 participants	0.024	3.46 (1.22 to 9.79), I^2=87.2%, n=4, 282 423 participants	0.020
MAFLD diagnosis				
ICD-9-CM	1.14 (1.06 to 1.23), I^2=52.6%, n=2, 407 577 participants	0.001	None	
FibroScan	None		3.34 (1.07 to 10.42), I^2=89.2%, n=4, 5911 participants	0.038
Biomarker panels	1.39 (1.33 to 1.46), I^2=nd, n=1, 268 946 participants	<0.001	1.50 (1.22 to 1.85), I^2=86.0%, n=2, 288 512 participants	<0.001
Ultrasonography	1.37 (1.18 to 1.58), I^2 =76.3%, n=5, 49 747 participants	<0.001	1.03 (0.68 to 1.57), I^2=79.4%, n=3, 26 032 participants	0.886
Imaging or histology	None		1.01 (0.97 to 1.06), I^2=nd, n=1, 255 participants	0.663
CKD definition				
eGFR ≤60 mL/min/1.73 m^2 alone	1.14 (1.06 to 1.26), I^2=52.6%, n=2, 407 577 participants	0.001	1.59 (1.12 to 2.25), I^2=nd, n=1, 1992 participants	0.009
eGFR ≤60 mL/min/1.73 m^2 or presence of albuminuria	1.36 (1.23 to 1.51), I^2=75.6%, n=6, 318 693 participants	<0.001	1.33 (1.08 to 1.63), I^2=93.2%, n=9, 318 718 participants	0.007
Participants' characteristics				
Patients with T2DM only	1.32 (1.08 to 1.62), I^2=59.6%, n=3, 266 711 participants	0.008	1.50 (1.12 to 2.01), I^2=90.8%, n=7, 296 139 participants	0.007
Patients with obesity only	1.08 (0.98 to 1.19), I^2=nd, n=1, 143 210 participants	0.12	None	
General population	1.34 (1.19 to 1.50), I^2=89.6%, n=4, 316 349 participants	<0.001	1.24 (0.91 to 1.71), I^2=95.0%, n=3, 24 571 participants	0.178
Adjusted or unadjusted models				
Adjusted	1.29 (1.17 to 1.41), I^2=87.0%, n=7, 726 270 participants	0.001	1.36 (1.07 to 1.74), I^2=88.5%, n=7, 315 075 participants	0.014
Unadjusted	None		1.34 (0.95 to 1.89), I^2=92.2%, n=3, 5635 participants	0.094
MAFLD alone or MAFLD-related fibrosis				
MAFLD alone	1.27 (1.15 to 1.40), I^2=88.4%, n=7, 725 686 participants	<0.001	1.31 (1.08 to 1.60), I^2=93.2%, n=9, 320 573 participants	0.006
MAFLD-related fibrosis	1.54 (1.15 to 2.07), I^2=nd, n=1, 584 participants	0.004	3.28 (1.21 to 8.86), I^2=nd, n=1, 137 participants	0.019
High study quality				
Yes	1.36 (1.23 to 1.51), I^2=75.6%, n=6, 318 693 participants	<0.001	1.32 (1.05 to 1.66), I^2=93.2%, n=8, 39 192 participants	0.017
No	1.14 (1.06 to 1.23), I^2=52.6%, n=2, 407 577 participants	0.001	1.82 (0.80 to 4.16), I^2=67.0%, n=2, 281 518 participants	0.153

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; MAFLD, metabolic dysfunction-associated fatty liver disease; T2DM, type 2 diabetes mellitus.

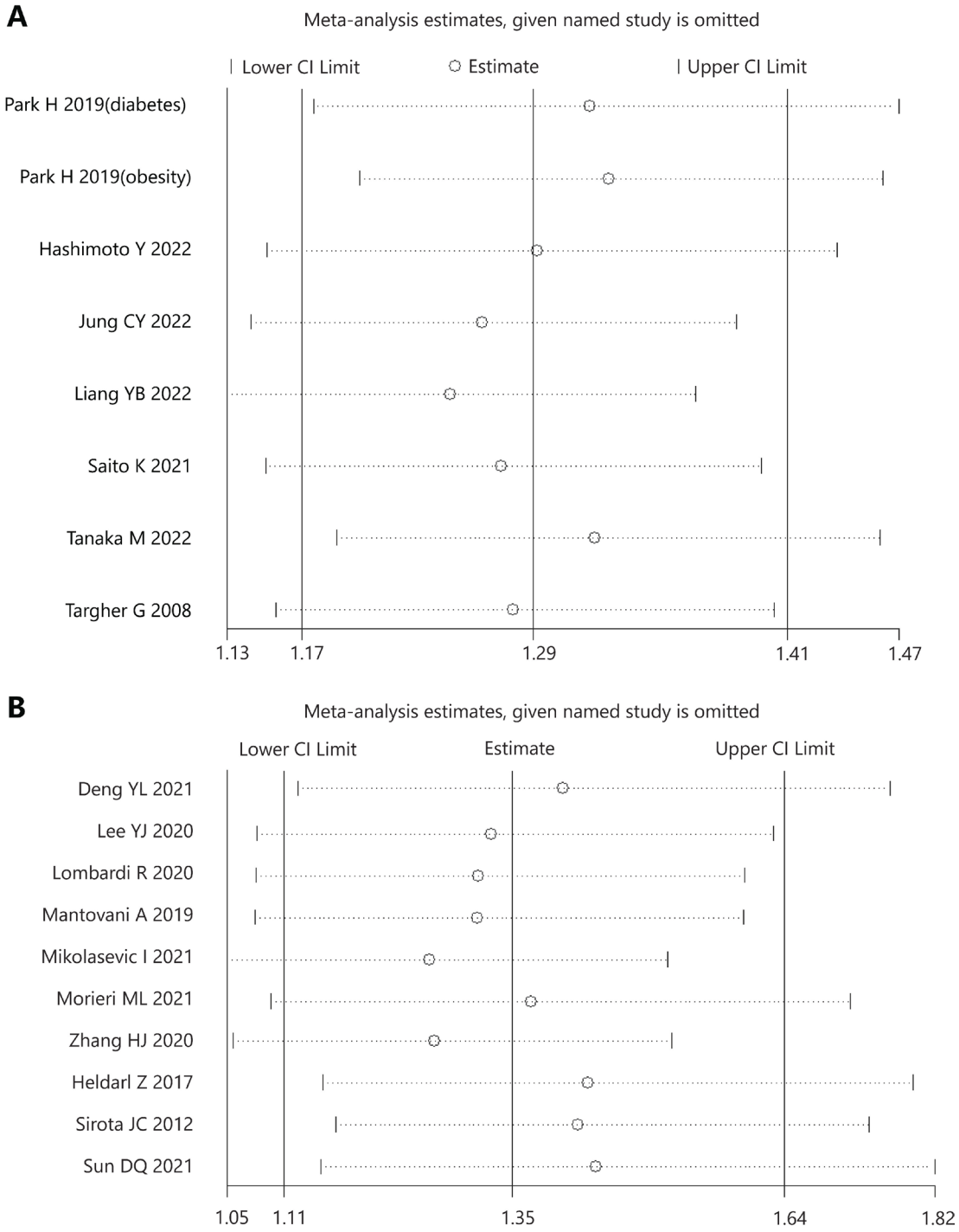

Figure 5 Risk of incident CKD in MAFLD: sensitivity analysis. (A) Risk of incident CKD in MAFLD: sensitivity analysis in cohort studies. (B) Risk of prevalent CKD in MAFLD: sensitivity analysis in cross-sectional studies. CKD, chronic kidney disease; MAFLD, metabolic dysfunction-associated fatty liver disease.

comprehensive assessment of this association to date. In this meta-analysis of 20 observational studies with aggregate data on about 1 million middle-aged individuals from different countries, we found that MAFLD was significantly associated with an approximately 30% increased risk of both prevalent and incident CKD. In particular, the magnitude of the MAFLD-related risk of incident CKD remained essentially unchanged even after stratification by study country, modality of MAFLD diagnosis, CKD definition or study quality. The risk of incident CKD stage ≥3 remained significant also in those cohort studies where analyses were adjusted for common renal risk factors. Furthermore, the risk of CKD seemed to be higher among patients with MAFLD with greater severity of liver fibrosis (assessed by fibrosis biomarkers). However, additional larger studies are needed to better examine this issue. Thus, the results of our meta-analysis indirectly support the concept that interventions against

MAFLD might be an effective target for the prevention and treatment of CKD.

In this meta-analysis, we found that the newly proposed MAFLD definition was able to identify individuals at risk of developing CKD as effectively as the NAFLD definition, a finding which has been reported in some previous meta-analyses.[34 36] A nationwide cohort study of 268 946 middle-aged individuals also suggested that MAFLD identified patients who developed CKD better than NAFLD, over a median follow-up of 5.1 years.[13] That said, however, it is important to underline that the results of the present meta-analysis do not allow us to determine whether MAFLD predicts the risk of incident CKD better than NAFLD, because there are very few cohort studies that simultaneously examined the comparative effects of MAFLD and NAFLD definitions on the risk of developing CKD.

The association between diabetes and CKD is well-known. Although MAFLD is an emerging definition, many studies have found a correlation between MAFLD and CKD, which is independent of diabetes. Park *et al* found that the incidence of CKD in patients with diabetes combined with NAFLD was 16.4 per 1000 person-years, and the incidence of CKD in patients with diabetes without NAFLD was 13.6 per 1000 person-years.[17] The incidence of CKD in patients with NAFLD without diabetes was 5.3 per 1000 person-years. This indicated that the incidence of CKD is higher in patients with diabetes and NAFLD compared with patients with diabetes or NAFLD. Another study by Targher *et al* found that patients with diabetes with NAFLD had a 49% increased risk of CKD compared with patients with diabetes alone (adjusted HR 1.49, 95% CI 1.10 to 2.20).[33] This work also further suggests that NAFLD can independently increase the risk of developing CKD. Meanwhile, the study by Lee *et al* also found that MAFLD was independently associated with CKD (adjusted OR 1.59, 95% CI 1.12 to 2.25), and that patients with diabetes with MAFLD had a higher risk of CKD than patients with diabetes without MAFLD.[34] These findings also support the association between MAFLD and CKD from another side.

To date, the possible mechanisms underpinning the observed association between MAFLD and increased risk of CKD are currently understood, but they can be explained by several factors. First, MAFLD and CKD share common pathophysiological pathways, for example, insulin resistance.[37 38] The coexistence of hepatic lipid accumulation and metabolic dysfunction leads to the development of hepatic and systemic insulin resistance,[3] which may further exacerbate the risk of CKD development and progression, possibly via activation of sympathetic nervous system, down-regulation of natriuretic peptide system and exacerbation of sodium retention.[39–41] Second, hepatic lipid accumulation can promote vascular dysfunction and atherosclerosis, which may induce intrarenal low-grade inflammation, increased oxidative stress and secretion of multiple profibrogenic cytokines, thereby resulting in atherosclerotic-nephropathy and CKD.[39 42] Hepatic lipid accumulation is also typically accompanied by ectopic fat accumulation in other sites, such as increased perirenal fat thickness.[43] In turn, increased perirenal fat is associated with higher risk of CKD among individuals with metabolic disorders, such as T2DM and hypertension.[44 45] Moreover, hepatic lipid accumulation may contribute to hepatic fibrogenesis, possibly through some genetic variants (eg, the rs738409 C>G variant of the patatin-like phospholipase domain containing three genes) that may trigger specific fibrogenic pathways or promote hepatic steatosis and inflammation by creating an unfavourable microenvironment.[46 47] In turn, hepatic fibrosis may contribute to CKD development, mainly through the production of a variety of pro-inflammatory and profibrogenic cytokines, such as interleukin-6, fibroblast growth factor-21 and transforming growth factor-beta.[48 49]

We found that the presence of MAFLD (as detected by biomarker panels or ultrasonography) conferred a nearly 40% increased risk of incident CKD in cohort studies. In addition, we found that the risk of incident CKD appeared to increase further with greater severity of MAFLD. In fact, the presence of MAFLD-related fibrosis, as assessed by the fibrosis-4 score, was found to be associated with a nearly 55% increase in risk of incident CKD, even after adjusting for age, sex, body mass index, drinking status, smoking, baseline eGFR, haemoglobin A1c, comorbidities and use of glucose-lowering medications.[32] This latter result is also consistent with the findings of a previous meta-analysis of 33 observational studies showing that patients with NAFLD and advanced fibrosis had a higher risk of incident CKD compared with their counterparts without advanced fibrosis.[48] To date, however, there are few longitudinal cohort studies that have diagnosed MAFLD by liver biopsy to evaluate the association between the histological severity of MAFLD and risk of CKD.

Evidence from the US Preventive Services Task Force and the American College of Physicians is currently insufficient to recommending a routine screening for CKD in asymptomatic adults without classical risk factors for CKD.[50 51] However, the findings of our meta-analysis suggest that case finding for MAFLD may be worthwhile, especially in patients with CKD stage 3 or more (with or without coexisting abnormal albuminuria), even in the absence of classical risk factors for CKD, particularly in those individuals with MAFLD and suspected advanced fibrosis. It is important to note that early identification of decreased kidney function in individuals with MAFLD might provide support for adjusting drug dosages to avoid further renal injury induced by drug accumulation. In addition, the occurrence of CKD in individuals with MAFLD may further promote both the progression of MAFLD and the development of cardiovascular disease, which is the predominant cause of mortality in people with MAFLD.[8 52]

Pharmacotherapies have become a major focus in the management of MAFLD and CKD. Evidence from randomised controlled trials shows that inhibitors of the renin-angiotensin system, statins and certain glucose-lowering agents (such as glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter-2 inhibitors) may exert beneficial effects by improving hepatic steatosis and decreasing urinary protein excretion in patients with MAFLD and CKD.[7 53–56] In addition, pentoxifylline and omega-3 polyunsaturated fatty acids may improve plasma lipid profile and inflammatory biomarkers in patients with MAFLD and CKD.[57–61] However, there are still no definitive curative treatments for patients with MAFLD and CKD. Lifestyle interventions (eg, hypocaloric diet, smoking cessation and increased physical activity) should also be advocated in most patients with MAFLD and CKD.[7 62 63]

Our meta-analysis has some important limitations, which are strictly inherent to the design of the eligible studies. First, our meta-analysis cannot prove causality between MAFLD and risk of CKD, due to the observational study design of the included studies. Second, the heterogeneity is high in final analyses due to pooling crude estimates and adjusted estimates, which may affect the reliability of our results. Our subgroup analyses suggested that the high heterogeneity of the pooled analysis of cohort studies is partly explained by interstudy differences in study country, modalities of MAFLD diagnosis and degree of covariate adjustments. Conversely, the high heterogeneity of the pooled analysis of cross-sectional studies is partly explained by interstudy differences in study country, diagnostic methods for identifying MAFLD, CKD definition and study quality. Third, there is only one cohort study that used liver biopsy for diagnosing and staging MAFLD and the definition of MAFLD are heterogeneous in the included studies, which may have weakened the reliability and applicability of our results. Therefore, further well-designed cohort studies are required to prove whether the severity of liver disease in MAFLD further amplifies the increased risk of developing CKD. Fourth, the eGFR values in most of the included studies were estimated by either the CKD Epidemiology Collaboration or the Modification of Diet in Renal Disease study equations, while the accuracy of these two creatinine-based GFR estimating equations is lower, especially in individuals with MAFLD and obesity.

Despite these limitations, the present meta-analysis has important strengths. To our knowledge, our study is the first meta-analysis to examine the association between MAFLD and risk of both prevalent and incident CKD using data from large cross-sectional and cohort studies from different countries, and the included subjects are likely to be an accurate reflection of individuals with MAFLD, who are seen in routine clinical practice. In addition, the overall quality of both cohort and cross-sectional studies included in the meta-analysis was acceptable, according to the NOS and AHRQ scores. Finally, visual inspection of the funnel plots and formal statistical tests did not show any significant publication bias.

In conclusion, the results of this updated meta-analysis provide evidence that the presence of MAFLD is significantly associated with an increased prevalence and incidence of CKD. Our findings suggest that MAFLD might become a target for the prevention and treatment of CKD. However, future well-designed studies are needed to evaluate strategies and interventions to prevent or slow the development and progression of CKD in individuals with MAFLD.

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