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The association between steatotic liver disease and chronic kidney disease: a meta-analysis and Mendelian randomization study highlighting metabolic comorbidities

Xiang Ji[1,2,6], Jinguo Jiang[1,2,6], Yunyun Liu[3], Liuxin Li[2], Honghao Yang[2], Zheng Ma[2], Chenying Wang[1,2], Tingjing Zhang[4], Yuhong Zhao[1,2], Yashu Liu[5]✉ and Yang Xia[1,2]✉

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Steatotic liver disease (SLD)—a term encompassing nonalcoholic fatty liver disease (NAFLD), metabolic-associated fatty liver disease (MAFLD), and metabolic dysfunction-associated steatotic liver disease (MASLD)—and chronic kidney disease (CKD) are major global health concerns. Metabolic factors, including obesity, type 2 diabetes, hypertension, and dyslipidemia, are integral to the definitions of MAFLD and MASLD and may confound their association with CKD. This study aimed to update a meta-analysis on the association between SLD and CKD risk and to conduct a two-sample Mendelian randomization (MR) analysis to explore the causal roles of SLD and metabolic factors in CKD. We systematically searched PubMed, Embase, and Web of Science up to November 5, 2024, for eligible studies. Random-effects models were used to pool odds ratios (ORs) with 95% confidence intervals (CIs). Two-sample MR was performed using the inverse-variance weighted (IVW) method as the primary model, with additional methods applied for sensitivity analyses. A total of 34 studies involving 3,783,136 participants were included in the meta-analysis. The results demonstrated significant positive associations between MAFLD, NAFLD, and MASLD with CKD (MAFLD: OR 1.41 [1.07–1.84], RR 1.64 [1.39–1.94], HR 1.64 [1.39–1.94]; NAFLD: OR 1.19 [1.08–1.31], RR 1.66 [1.45–1.91], HR 1.43 [1.31–1.55]; MASLD: HR 1.34 [1.08–1.67]). These findings support a significant association between SLD (MAFLD, NAFLD, and MASLD) and an increased risk of CKD. However, Mendelian randomization (MR) analysis found no causal effect of SLD on CKD risk. In contrast, genetically predicted metabolic factors—including body mass index (BMI), waist circumference, type 2 diabetes, systolic and diastolic blood pressure, triglycerides, and high-density lipoprotein cholesterol—were significantly associated with an increased CKD risk. These findings suggest that metabolic dysfunction, rather than SLD itself, may be the main driver of CKD risk. This underscores the clinical importance of early screening and intervention for metabolic health in patients with SLD to reduce the burden of CKD.

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INTRODUCTION

Chronic kidney disease (CKD) is a critical global health concern, primarily due to its potential to cause irreversible renal function loss [1]. Recent studies highlighted its close association with cardiovascular diseases, anemia, sarcopenia, altered mineral metabolism, and metabolic acidosis [2, 3]. Globally, CKD affects approximately 9.1% of the population [4], with projections indicating that, in a worst-case scenario, it could contribute to nearly 4 million deaths annually by 2040 [5]. Consequently, identifying and addressing modifiable risk factors to prevent CKD is an urgent public health priority.

Over the past four decades, nonalcoholic fatty liver disease (NAFLD) has become the most prevalent chronic liver disease worldwide and can be intervened through lifestyle and medical treatment at the early stage [6, 7]. In response to its increasing prevalence and the global rise in metabolic disorders, an international panel of hepatologists introduced the new term metabolic-associated fatty liver disease (MAFLD) [8]. The introduction of this new concept has sparked intense debate, prompting a recent multi-society Delphi consensus to recommend replacing NAFLD with metabolic dysfunction-associated steatotic liver disease (MASLD) [9].

The incidence of CKD is closely linked to steatotic liver disease (SLD) status. While the biological mechanisms linking SLD to CKD remain unclear, the shared physiological pathologies between the liver and kidneys are well-established [10, 11]. Considering the potential social, communicational, and cultural implications of this new nomenclature, many studies have explored the association between SLD and CKD. However, the findings from these studies have been inconsistent, with some reporting a significant positive association between SLD and CKD, while others found no significant association [12–16]. These inconsistencies may be attributable to differences in study design, study populations, diagnostic criteria, and sample size across studies, which could

[1]Department of Clinical Epidemiology, Shengjing Hospital of China Medical University, Shenyang, China. [2]Liaoning Key Laboratory of Precision Medical Research on Major Chronic Disease, Shenyang, China. [3]School of Public Health, Zhejiang University School of Medicine, Hangzhou, China. [4]School of Public Health, Wannan Medical College, Wuhu, China. [5]Department of General Surgery, Shengjing Hospital of China Medical University, Shenyang, China. [6]These authors contributed equally: Xiang Ji, Jinguo Jiang.
✉email: yashu_liu@126.com; xytmu507@126.com; yxia@cmu.edu.cn

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lead to variation in effect estimates. Although previous meta-analyses and reviews have explored the association between SLD and CKD, the limitations of traditional observational research and bias from various confounding factors have hindered the elucidation of the causal association [17–24]. The genetic link between SLD and CKD remains unexplored. Mendelian randomization (MR) provides an analytical framework that utilizes genetic variants as instrumental variables (IVs) to mitigate bias stemming from confounding and reverse causation [25]. As genetic variants are randomly allocated at conception, the MR framework, under specific conditions, bears similarities to randomized controlled trials, thereby providing more dependable causal inferences compared to conventional observational designs [26]. Moreover, SLD is closely associated with various metabolic abnormalities, and the definition transition from NAFLD to MASLD further emphasizes the pathophysiological role of metabolic dysfunction factors in the progression of fatty liver disease. However, it remains unclear whether the association between SLD and CKD stems from the liver itself or the metabolic abnormalities associated with SLD.

Thus, we aimed to update a meta-analysis to assess the prognostic impact of SLD on CKD risk by synthesizing longitudinal evidence from the general population. Additionally, we conducted two-sample MR analyses to determine the causal relationships between SLD, metabolic factors (selected according to the definitions of MAFLD and MASLD), and CKD.

METHODS

Meta-analysis

Search strategy. We followed the criteria for systematic review and meta-analysis during the literature selection process. The protocol for this meta-analysis has been registered with PROSPERO (CRD42022367063).

This meta-analysis was conducted in accordance with the Meta-analyses Of Observational Studies in Epidemiology guidelines [27]. We systematically searched PubMed, Web of Science, and Embase databases for relevant publications released from our project's inception until November 5, 2024. The search strategy detailed are shown in Table S1. To ensure comprehensiveness, we manually searched the reference lists of pertinent reviews and related studies, capturing additional articles that may not have appeared in the initial database search. This thorough approach enhances the authority and representativeness of our meta-analysis.

Study selection. Two independent authors conducted the study selection and exclusion procedures. The studies included in our analysis met the following criteria: (1) the study design was observational; (2) SLD was investigated as the exposure, encompassing NAFLD, MAFLD, and MASLD. NAFLD was defined as hepatic steatosis in individuals who consumed little or no alcohol and had no other specific causes of liver disease [7]; MAFLD was defined as hepatic steatosis accompanied by overweight or obesity, type 2 diabetes (T2D) or evidence of metabolic dysregulation [8]; and MASLD was defined as hepatic steatosis in the presence of at least one cardiometabolic risk factor [9]; (3) the diagnosis of SLD was based on ultrasonography, blood biomarkers, indices, such as the fatty liver index (FLI), controlled attenuation parameter by transient elastography, liver biopsy, or international classification of diseases (ICD) codes, as described in the original studies; (4) CKD was reported as the outcome, diagnosed according to estimated glomerular filtration rate (eGFR), proteinuria, or albumin-to-creatinine ratio (ACR), or ICD codes; (5) sufficient data were provided to calculate risk estimates with corresponding 95% confidence intervals (CIs); (6) articles were published in English. Notably, there were no restrictions on the participants in these studies regarding gender, age, race, or ethnicity, and specific disease.

Studies were excluded based on the following criteria: (1) they focused on populations with specific diseases, such as T2D; (2) they lacked original data, including commentaries, letters, or unpublished findings; (3) they reported risk estimates that were not amenable to summarization; (4) in cases where multiple studies were conducted in the same population, only the study with the highest level of evidence was included, while the others were excluded.

We assessed the methodological quality of the included studies using both the Newcastle-Ottawa Scale (NOS) and the National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies [28, 29]. The NOS evaluates the risk of bias in cohort studies across three domains: selection of participants, comparability of study groups, and ascertainment of outcomes, with total scores ranging from 0 to 9. Scores of 7–9 were considered good quality, 4–6 as fair quality, and <4 as poor quality [30]. For cross-sectional studies, we applied the NIH 14-item checklist, where scores of 13–14 were rated as good, 9–12 as fair, and <9 as poor [31]. Based on these criteria, all studies were categorized into three quality levels: good, fair, and poor [28].

Data synthesis and analysis for meta-analysis. In the meta-analysis, odds ratios (ORs), relative risks (RRs), and hazard ratios (HRs) were treated as distinct effect measures and therefore analyzed separately to avoid potential bias due to their non-equivalence. Each effect measure was pooled using a random-effects model to account for between-study heterogeneity. Statistical heterogeneity was assessed using the I^2 statistic, with thresholds of approximately <50%, 50–75%, and >75% indicating low, moderate, and high heterogeneity, respectively [32]. Publication bias was evaluated through funnel plots as well as Egger's and Begg's tests [33]. All effect estimates were expressed with 95% confidence intervals (CIs).

To understand the sources of heterogeneity in the included articles, we performed meta-regression and subgroup analyses according to study design, quality assessment, sample size, diagnostic methods for exposure factors, age and ethnicity of the included population for each article. Additionally, for the sensitivity analysis, we employed an exclusion-by-exclusion approach. This step evaluated whether the inclusion or exclusion of certain studies significantly altered the original meta-analysis results.

All analyses were performed using STATA version 17.0. All *P*-values were two-tailed, and difference with $P < 0.05$ were considered statistically significant.

Mendelian randomization

Data source. Two-sample MR analysis was conducted to assess the relationships between SLD and CKD. Besides, we used a two-sample MR method to test relationships between metabolic factors and CKD. IVs for the MR of genetic associations with NAFLD and metabolic factors were obtained from publicly available databases (IEU Open GWAS). The phenotypic code used of NAFLD and metabolic factors were showed in Table S2. Summary-level data on CKD were obtained from the IEU Open GWAS, and the phenotypic code used was "ieu-a-1102" (CKDGen). The original studies adhered to the principles of informed consent and ethical guidelines. Inverse variance weighting (IVW) was applied to analyze the association between NAFLD and metabolic factors with CKD. The detailed information was provided in https://gwas.mrcieu.ac.uk.

Statistical analysis for MR. The genome-wide significance level for IVs was set at $P < 5 \times 10^{-8}$. Moreover, the identified single-nucleotide polymorphisms (SNPs) were clumped for linkage disequilibrium (LD) using a stringent clumping threshold of $R^2 < 0.001$ within a 10,000 kb window, with LD estimated using the European samples from the 1000 Genome Project as the

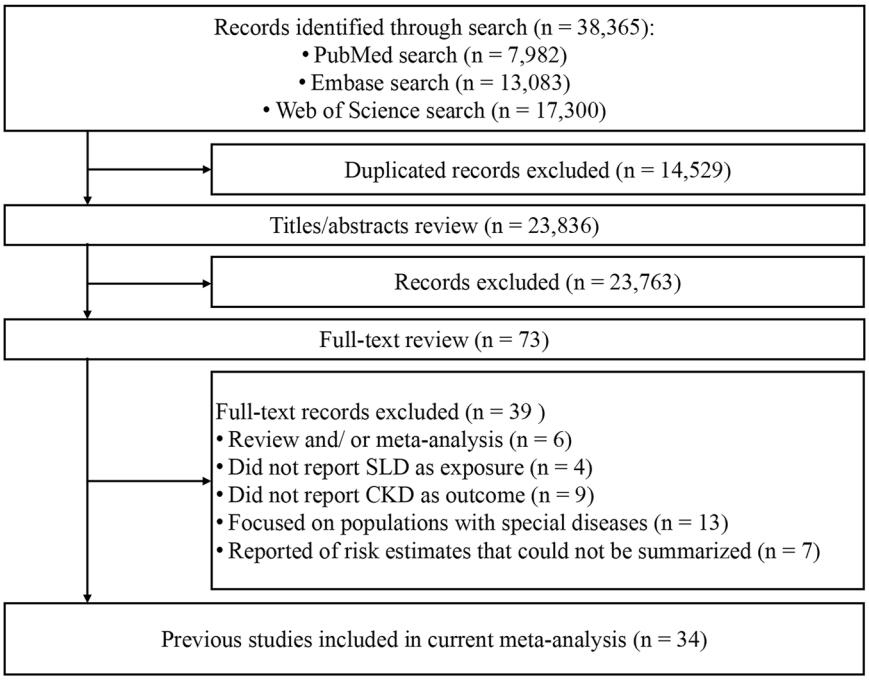

Fig. 1 The flowchart of the study inclusion process. MASLD metabolic dysfunction-associated steatotic liver disease, MAFLD metabolic-associated fatty liver disease, NAFLD non-alcoholic fatty liver disease, CKD chronic kidney disease.

reference [34]. The F-statistic was used to eliminate bias in the results caused by weak IVs. The F-statistic is calculated as $F = (N-K-1)/K \times R^2/(1-R^2)$, $K = n$ SNP merged, $N =$ sample size in the discovery GWAS, and R^2 reflects the degree to which the instrumental variable explains the exposure.

Only one SNP (Table S2) were identified as robustly associated with NAFLD, 324 SNPs associated with body mass index (BMI), 270 SNPs associated with waist circumference, 112 SNPs associated with T2D, 295 SNPs associated with systolic blood pressure (SBP), 296 SNPs associated with diastolic blood pressure (DBP), 155 SNPs associated with triglyceride (TG) and 171 SNPs associated with high-density lipoprotein cholesterol (HDL-C).

We sought to utilize genetic variations that are associated with NAFLD and metabolic factors (such as BMI, waist circumference, T2D, SBP, DBP, TG, and HDL-C) to investigate their potential causal relationship with CKD. In this study, we applied the inverse-variance weighted (IVW) method with multiplicative random effects as the primary MR model to estimate the causal effects [35]. The IVW estimates were used as the main results. To assess the robustness of these findings, we performed sensitivity analyses using the weighted median [36], MR-Egger [37], and MR-PRESSO [38], which make different assumptions about the validity of IVs and the presence of pleiotropy. Heterogeneity among SNP estimates was evaluated using Cochran's Q statistic, and horizontal pleiotropy was assessed using the MR-Egger intercept. Throughout our study, we employed two-sided *P*-values.

All statistical analyses were conducted utilizing the "MRPRESSO" and "TwoSampleMR" packages within the R software environment.

RESULTS

Literature search

A comprehensive search across three databases (PubMed, Web of Science, and Embase) yielded a total of 38,365 publications. Figure 1 illustrated the detailed literature screening processes. After the exclusion of duplications and papers that did not meet the inclusion criteria, we obtained 73 full-text articles of potentially relevant studies. Upon a thorough examination of these texts, 39 articles were excluded. Consequently, a total of 34 studies were ultimately included in the present meta-analysis [12–16, 39–67].

Characteristics of the included studies

The main baseline characteristics of the included studies were summarized in Table S3. In addition, we have added Table S4, which lists all studies excluded after the full-text screening stage, together with the reasons for exclusion. Among the 34 studies, 29 examined the association between NAFLD and CKD, 13 focused on MAFLD, and two investigated MASLD. Seven studies analyzed both NAFLD and MAFLD in relation to CKD, while one examined both MAFLD and MASLD. All studies adopted either a cross-sectional or cohort design.

Geographically, 25 studies were conducted in Asian countries and 10 in non-Asian countries. Regarding diagnostic approaches, 22 studies used ultrasonography, 10 employed the FLI, and 3 used the ICD codes to diagnose SLD. Notably, one study included two cohorts from different ethnic groups, using ultrasonography for the Asian cohort and ICD codes for the non-Asian cohort [63]. In total, the meta-analysis encompassed 3,783,136 participants and 172,255 CKD cases. Participants were drawn from the general population, defined as individuals without major pre-existing conditions, such as T2D. The mean age of participants was 52.3 years. All studies adjusted for age and sex, except one, which reported a higher kidney disease burden among men with MAFLD [14].

The quality assessment results were shown in Tables S5 and S6. In conclusion, nine cross-sectional studies and 12 cohort studies were of high quality, while six cross-sectional studies and seven cohort studies were of fair quality.

SLD with CKD

The association between MAFLD and CKD is presented in Fig. 2. A total of 13 studies were included. The pooled results indicated that MAFLD was also positively associated with CKD. Cross-sectional studies showed a higher prevalence of CKD (OR = 1.41, 95%

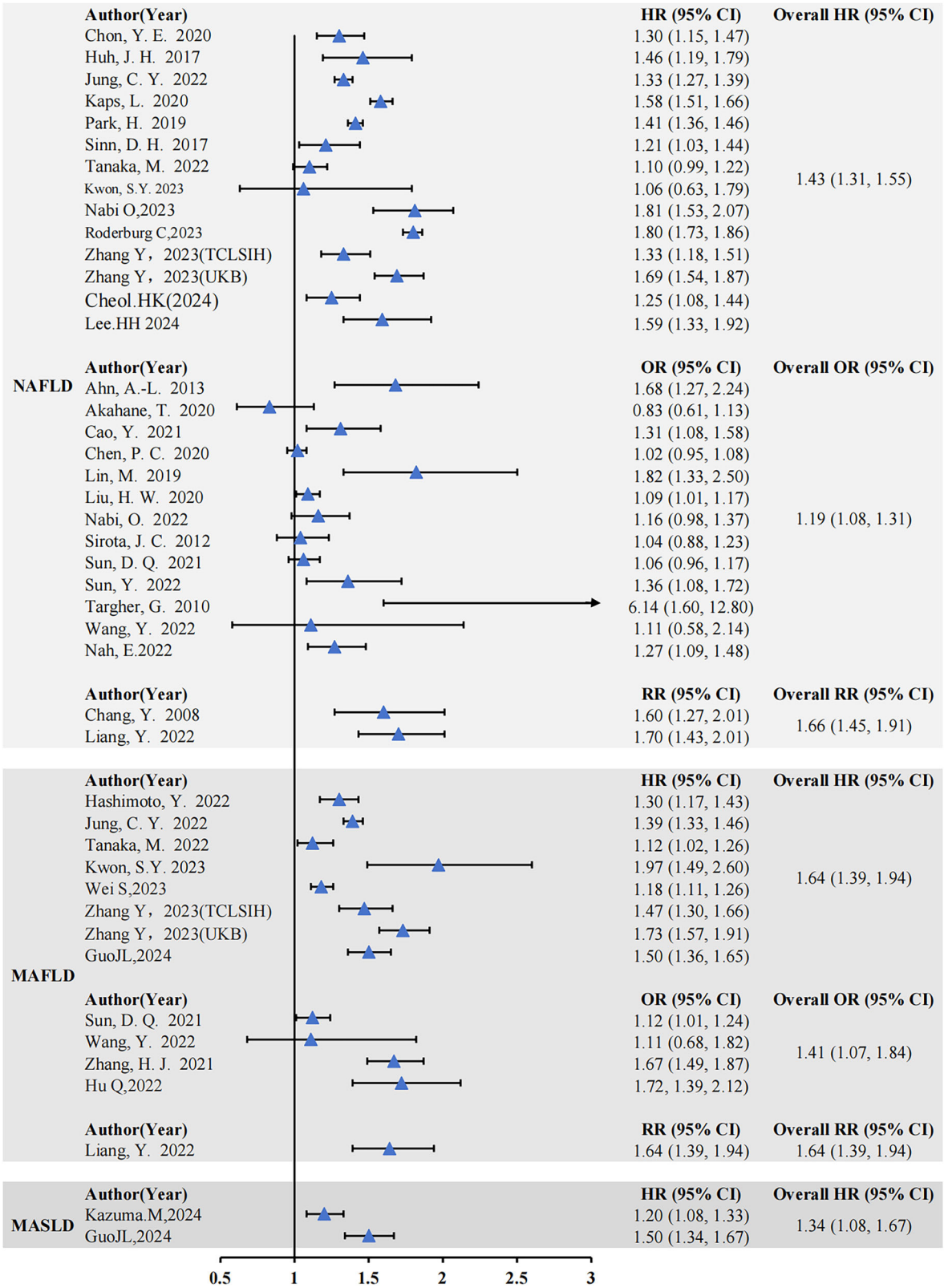

Fig. 2 Overall pooled analysis of the associations between MASLD, MAFLD, NAFLD, and CKD. CKD chronic kidney disease, MASLD metabolic dysfunction-associated steatotic liver disease, MAFLD metabolic-associated fatty liver disease, NAFLD non-alcoholic fatty liver disease, CI confidence interval, HR hazard ratio, RR relative risk, OR odds ratio, I^2 inconsistency index.

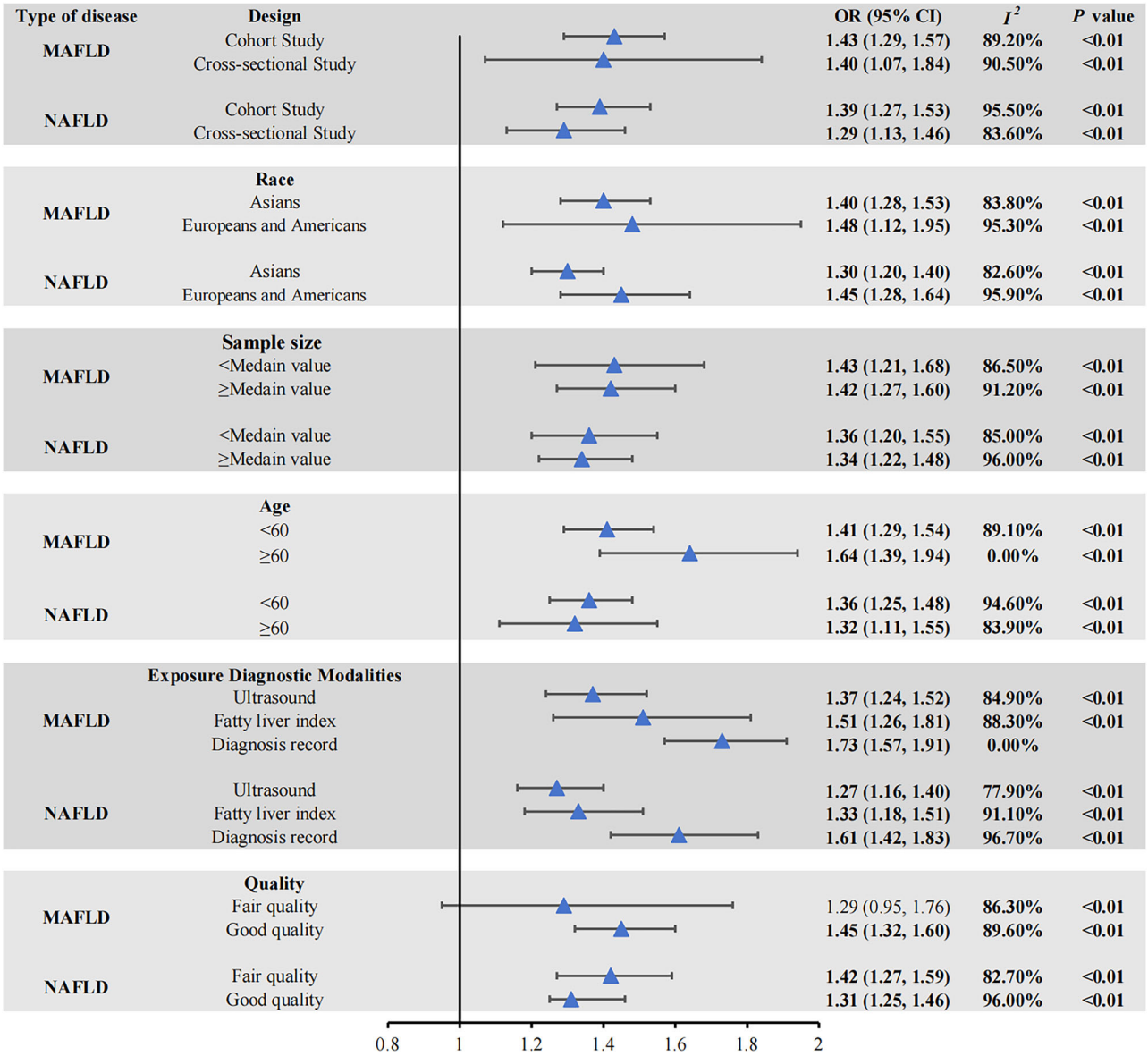

Fig. 3 Subgroup analysis of the associations between MASLD, MAFLD, NAFLD, and CKD. CKD chronic kidney disease, MASLD metabolic dysfunction-associated steatotic liver disease, MAFLD metabolic-associated fatty liver disease, NAFLD non-alcoholic fatty liver disease, OR odds ratio, CI confidence interval.

CI = [1.07–1.84]), and cohort studies revealed a higher incidence of CKD (RR = 1.64, 95% CI = [1.39–1.94]; HR = 1.64, 95% CI = [1.39–1.94]). Sensitivity analysis, which involved the successive exclusion of articles, confirmed the stability of these results (Fig. S1). Egger's test revealed no publication bias. (Begg's test $P = 0.360$, Egger's test $P = 0.345$, Fig. S2).

The association between NAFLD and CKD is presented in Fig. 2. A total of 29 studies were included. The pooled analyses demonstrated that NAFLD was significantly associated with CKD. Specifically, cross-sectional studies indicated a higher prevalence of CKD among individuals with NAFLD (OR = 1.19, 95% CI = [1.08–1.31]), while cohort studies showed an increased incidence of CKD (RR = 1.66, 95% CI = [1.45–1.91]; HR = 1.43, 95% CI = [1.31–1.55]). Sensitivity analysis, which involved the successive exclusion of articles, confirmed the stability of these results (Fig. S3). Egger's test revealed no publication bias. (Begg's test $P = 0.237$, Egger's test $P = 0.237$, Fig. S4).

The association between MASLD and CKD is presented in Fig. 2. Two cohort studies were included, both consistently indicating that MASLD was positively associated with incident CKD (HR = 1.34, 95% CI = [1.08–1.67]).

Taken together, these results demonstrate that individuals with SLD have an elevated risk of both prevalent and incident CKD, and the consistent direction of associations across different study designs and effect measures supports the robustness of our findings.

Subgroup analyses and meta-regressions

To comprehensively understand the sources of heterogeneity in all the included studies, we performed subgroup analyses based on the variables extracted, as detailed in Fig. 3. The results of almost all subgroup analyses indicated that both NAFLD and MAFLD were positively associated with CKD compared to their respective controls (all $P < 0.01$).

We classified the participants into two subgroups for MAFLD according to each study's design (cross-sectional and cohort). Cross-sectional (OR = 1.40, 95% CI = 1.07–1.84) and cohort studies (OR = 1.43, 95% CI = 1.29–1.57) demonstrated a significant

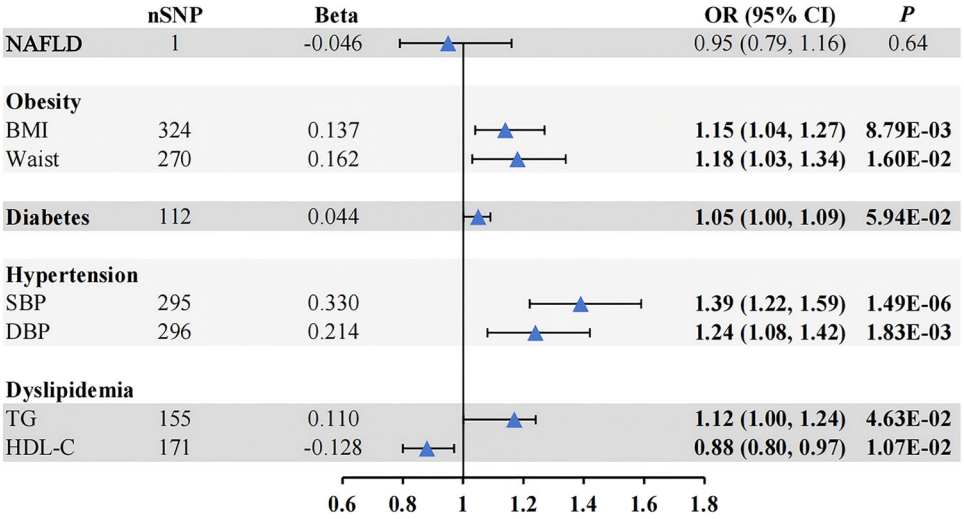

Fig. 4 Associations of NAFLD and metabolic factors with CKD by two-sample MR analysis. MR Mendelian randomization, CKD chronic kidney disease, NAFLD non-alcoholic fatty liver disease, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, TG triglycerides, HDL-C high-density lipoprotein cholesterol, OR odds ratio, CI confidence interval.

positive association between MAFLD and CKD. When stratified by race, MAFLD showed a positive association with CKD in Asians (OR = 1.40, 95% CI = 1.28–1.53) and Europeans/Americans (OR = 1.48, 95% CI = 1.12–1.95). Similarly, the association was positive in studies with both larger (≥median size, OR = 1.42, 95% CI = 1.27–1.60) and smaller (<median size, OR = 1.43, 95% CI = 1.21–1.68) sample sizes. Age-based subgroup analysis revealed a positive association in participants aged ≥ 60 years (OR = 1.64, 95% CI = 1.39–1.94) and <60 years (OR = 1.41, 95% CI = 1.29–1.54). Studies of good quality (OR = 1.45, 95% CI = 1.32–1.60) and fair quality (OR = 1.29, 95% CI = 0.95–1.76) did not find a significant association. Based on diagnostic modalities (ultrasound, FLI, or ICD), all three methods (ultrasound: OR = 1.37, 95% CI = 1.24–1.52; FLI: OR = 1.51, 95% CI = 1.26–1.81; ICD: OR = 1.73, 95% CI = 1.57–1.91) showed a positive association with CKD.

For NAFLD, the analysis followed a similar pattern. Both cross-sectional (OR = 1.29, 95% CI = 1.13–1.46) and cohort studies (OR = 1.39, 95% CI = 1.27–1.53) showed a significant positive association with CKD. Race-based subgroup analysis indicated a positive association in both Asians (OR = 1.30, 95% CI = 1.20–1.40) and Europeans/Americans (OR = 1.45, 95% CI = 1.28–1.64). Studies with larger (≥median size, OR = 1.34, 95% CI = 1.22–1.48) and smaller (<median size, OR = 1.36, 95% CI = 1.20–1.55) sample sizes both showed a positive association. Age-based subgroup analysis indicated a positive association in participants aged ≥ 60 years (OR = 1.32, 95% CI = 1.11–1.55) and <60 years (OR = 1.36, 95% CI = 1.25–1.48). Good quality studies (OR = 1.31, 95% CI = 1.25–1.46) showed a significant positive association, while those assessed as fair quality (OR = 1.42, 95% CI = 1.27–1.59) reported a positive association. The diagnostic methods (ultrasound, FLI, or ICD) all indicated a positive association with CKD (ultrasound: OR = 1.27, 95% CI = 1.16–1.40; FLI: OR = 1.33, 95% CI = 1.18–1.51; ICD: OR = 1.61, 95% CI = 1.42–1.83).

Additionally, meta-regression analysis indicated that factors, such as study design, race, sample size, age, diagnostic modalities of exposure, and study quality, were not significant contributors to the heterogeneity in the associations between MAFLD, NAFLD, and CKD, as reported in Tables S7 and S8.

Mendelian randomization results

The causal relationship between SLD and CKD was analyzed by two-sample MR. As depicted in Fig. 4, our findings indicate that NAFLD was not causally associated with the risk of CKD (OR = 0.95, 95% CI = 0.79–1.16, $P_{\text{Wald ratio}} = 0.64$). In contrast, metabolic factors were significantly causally associated with an increased risk of CKD (BMI: OR = 1.15, 95% CI = 1.04–1.27, $P_{\text{IVW}} = 8.79\text{e-}03$; waist circumference: OR = 1.18, 95% CI = 1.03–1.34, $P_{\text{IVW}} = 1.60\text{e-}02$; T2D: OR = 1.05, 95% CI = 1.00–1.09, $P_{\text{IVW}} = 5.94\text{e-}02$; SBP: OR = 1.39, 95% CI = 1.22–1.59, $P_{\text{IVW}} = 1.49\text{e-}06$; DBP: OR = 1.24, 95% CI = 1.08–1.42, $P_{\text{IVW}} = 1.83\text{e-}03$; TG: OR = 1.12, 95% CI = 1.00–1.24, $P_{\text{IVW}} = 4.63\text{e-}02$; HDL-C: OR = 0.88, 95% CI = 0.80–0.97, $P_{\text{IVW}} = 1.07\text{e-}02$).

DISCUSSION

Our meta-analysis revealed a positive association between SLD and CKD using observational data. However, two-sample MR analysis found no evidence of a causal relationship between SLD and CKD. In contrast, MR analyses of metabolic factors showed that genetically predicted metabolic factors are associated with a higher risk of CKD. These findings suggest that the positive association observed in epidemiological studies may be driven by comorbidities arising from metabolic abnormalities, rather than a direct relationship between fatty liver disease and CKD.

SLD and CKD are significant global public health burdens. Over the past four decades, SLD has emerged as the most prevalent chronic liver disease globally, affecting about 25% of the population, with its prevalence continuing to rise [6]. In the next 20 years, the impact of CKD on health will rise from 16th to 5th in the world [68]. Previous observational studies have investigated the association between SLD and CKD. For instance, one meta-analysis concluded that NAFLD was associated with a 1.45-fold increased long-term risk of developing CKD stage ≥3 [18]. Additionally, another meta-analysis found that elevated liver stiffness was associated with higher odds of kidney outcomes in NAFLD patients [17]. Moreover, a meta-analysis examining the link between MAFLD and CKD risk confirmed a positive association between the two [24]. These findings are consistent with the results of our meta-analysis. However, previous studies have primarily been observational, which are inherently limited in their ability to infer causality. Furthermore, the definition of NAFLD has recently been updated to MAFLD and MASLD, placing greater emphasis on the comorbid state of metabolic abnormalities and fatty liver disease. It remains unclear whether the associations observed in previous studies represent a causal relationship or are

merely a result of the shared metabolic abnormalities common to both SLD and CKD.

To validate the causal relationship between SLD and CKD, we further employed a MR analysis. The results indicated that there is no causal relationship between SLD and CKD. However, it's evident that the liver and kidneys share several physiological pathologies and metabolic factors, and these metabolic factors are closely associated with both liver and kidney diseases [10, 11]. Thus, to interpret the findings from observational studies and clarify the role of these metabolic factors in the pathogenesis of CKD, we employed MR to investigate the causal relationship between the metabolic factors, as defined within the criteria for MAFLD and MASLD, and the incidence of CKD. The results revealed that, except for T2D, metabolic factors, such as BMI, waist circumference, SBP, DBP, TG and HDL-C, were causally associated with CKD. These MR findings suggest that the underlying cause of CKD in patients with SLD is primarily attributable to abnormal glucose and lipid metabolism, rather than being a direct consequence of fatty liver disease itself. SLD and CKD are essentially comorbid conditions arising from metabolic dysfunction, rather than representing a temporal or causal relationship between the two.

Abnormal glucose and lipid metabolism represents the shared pathological basis of SLD and CKD [69]. Excessive nutrient intake and fat accumulation can induce metabolic dysfunction, including disturbances in bioenergetic balance and insulin resistance in peripheral tissues, such as the liver [70]. These conditions can also trigger a chronic systemic inflammatory state marked by elevated cytokine levels [71]. Moreover, these metabolic abnormalities and inflammatory factors can compromise kidney function, particularly by impairing glomerular filtration [72, 73]. These physiological and pathological mechanisms are consistent with our MR findings, indicating that the pathways underlying the associations of abnormal glucose and lipid metabolism with liver and kidney functions could be different, without a direct pathological connection between fatty liver disease and CKD. The discrepancy between the null MR finding for NAFLD and the positive associations reported in observational studies may be explained by several biological and methodological considerations. First, NAFLD is a heterogeneous condition ranging from simple steatosis to steatohepatitis and fibrosis, and genetic instruments capturing NAFLD susceptibility may not fully reflect the metabolic dysfunction and advanced disease stages that drive kidney injury [74, 75]. Second, many observational studies may be confounded by coexisting metabolic risk factors, such as obesity, hypertension, and diabetes, which are strongly associated with both NAFLD and CKD and could account for the observed associations [76, 77]. Third, systemic inflammation, oxidative stress, and insulin resistance are key mechanisms implicated in both NAFLD and CKD, but these processes may be more directly mediated by metabolic traits than by hepatic fat accumulation itself [78, 79]. Taken together, these considerations suggest that NAFLD may act more as a marker of underlying metabolic dysfunction rather than as a direct causal driver of CKD, which is consistent with the null MR finding.

It is important to note that the definition of fatty liver disease has recently evolved from NAFLD to MASLD, shifting from liver fat deposition that excludes other known causes of liver injury (such as hepatitis and alcohol consumption) to a definition explicitly characterized by liver fat deposition accompanied by metabolic abnormalities [80]. This transition emphasizes the critical role of metabolic dysfunction in the progression of fatty liver disease. When considering MASLD (encompassing both liver fat deposition and metabolic abnormalities) as a whole, it is evident that MASLD is a risk factor for CKD. Our findings also support the updated definition of SLD. Specifically, the MR results for NAFLD do not explain the positive association observed between SLD and CKD in the population. However, due to the absence of GWAS studies specific to MASLD, we are currently unable to investigate the causal relationship between MASLD and CKD using MR methods. Future research should focus on conducting MR studies exploring MASLD and CKD, along with further basic research to elucidate the distinct mechanisms through which metabolic dysfunction contributes to the pathogenesis of SLD and CKD.

This study is the first to the causal relationship between SLD and CKD using bidirectional MR approach. The findings suggest that the observed association in epidemiological studies may be driven by metabolic dysfunction comorbidities rather than a direct causal relationship between SLD and CKD. From a clinical perspective, these findings imply that risk stratification in patients with SLD should prioritize the evaluation of metabolic abnormalities and that closer surveillance of kidney function is particularly warranted in those with metabolic dysfunction. From a public health standpoint, the results also support the broader implementation of the MASLD diagnostic framework, which integrates metabolic risk into clinical practice and may facilitate earlier identification of high-risk individuals.

Our study has several limitations. First, meta-analyses that include observational studies raise concerns about selection and recall biases. Second, despite adjusting for traditional CKD risk factors like age, sex, obesity, hypertension, and T2D, the potential for unmeasured confounders introducing confounding bias cannot be discounted. Third, in the meta-analysis, the *P*-value from the meta-regression was nonsignificant and failed to provide further insights into the sources of heterogeneity. This limitation implies that unmeasured factors may underlie the observed heterogeneity, necessitating further investigation. Fourth, although our main analyses distinguished effect measures according to study design, and the findings from subgroup analyses were directionally consistent with the primary results, caution is still warranted when interpreting the findings due to potential differences in study populations and sample sizes across included studies. Fifth, in the MR study, the number of SNPs associated with SLD was relatively small, resulting in a lower proportion of explained genetic variation. Finally, despite the employment of the MR method to mitigate the potential impact of pleiotropy-induced confounding, we are unable to entirely eliminate residual bias, a recognized constraint of MR studies. Moreover, because genome-wide association studies (GWAS) specifically focused on MASLD are not yet available, we were unable to directly assess the causal relationship between MASLD and CKD in the MR framework. Future large-scale GWAS of MASLD are warranted to enable such analyses and provide more comprehensive insights into the causal pathways linking MASLD and CKD.

CONCLUSION

In conclusion, the association between SLD and CKD likely arises primarily from their shared metabolic risk factors, rather than from a causal relationship between the two conditions.

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AUTHOR CONTRIBUTIONS

Xiang Ji: conceptualization; writing-original draft. Jinguo Jiang: conceptualization; writing-original draft. Yunyun Liu: writing–review and editing. Liuxin Li: writing–review and editing. Honghao Yang: writing–review and editing. Zheng Ma: supervision. Tingjing Zhang: supervision. Chenying Wang: writing–review and editing. Yuhong Zhao: writing–review and editing. Yashu Liu: supervision; formal analysis; writing–review and editing. Yang Xia: conceptualization; formal analysis; writing–review and editing; supervision; project administration; funding acquisition.

COMPETING INTERESTS

The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to Yashu Liu or Yang Xia.

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