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ORIGINAL ARTICLE

Association of MAFLD with end-stage kidney disease: a prospective study of 337,783 UK Biobank participants

Shen Chen[1] · Juan Pang[2] · Rong Huang[3] · Hongliang Xue[4] · Xu Chen[2,5]

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Abstract

Introduction Metabolic dysfunction-associated fatty liver (MAFLD) has been found to be associated with the prevalence of chronic kidney disease (CKD). However, it is unknown whether MAFLD is associated with CKD development and the incidence of end-stage kidney disease (ESKD). We aimed to clarify the association between MAFLD and incident ESKD in the prospective UK Biobank cohort.

Methods We analyzed the data of 337,783 UK Biobank participants and relative risks for the ESKD were calculated by using the Cox regression analysis.

Results Among 337,783 participants over a median duration of 12.8 years follow-up, a total of 618 ESKD cases were diagnosed. Participants with MAFLD were twice likely to develop ESKD (hazard ratio [HR] 2.03, 95% confidence interval [CI] 1.68–2.46, $p < 0.001$). The association of MAFLD with ESKD risk remained significant in both non-CKD and CKD participants. Our results also showed that there were graded associations between liver fibrosis scores and the risk of ESKD in MAFLD cases. Compared to non-MAFLD individuals, the adjusted HRs for incident ESKD in MAFLD patients with increasing levels of NAFLD fibrosis score were 1.23 (95% CI 0.96–1.58), 2.45 (1.98–3.03) and 7.67 (5.48–10.73), respectively. Furthermore, the risking alleles of *PNPLA3* rs738409, *TM6SF2* rs58542926, *GCKR* rs1260326 and *MBOAT7* rs641738 amplified the MAFLD effect on ESKD risk. In conclusion, MAFLD is associated with incident ESKD.

Conclusion MAFLD may help identify the subjects at high risk of ESKD development and MAFLD interventions should be encouraged to slow down CKD progression.

Keywords MAFLD · End-stage kidney disease · UK Biobank · Liver fibrosis scores · Polygenic risk score

Abbreviations

AKI	Acute kidney injury
ALP	Alkaline phosphatase
ALT	Alanine transaminase

Shen Chen and Juan Pang contributed equally to this article.

✉ Hongliang Xue
rossxue666@gmail.com

✉ Xu Chen
cxu1024@gmail.com

Shen Chen
chensh325@mail.sysu.edu.cn

Juan Pang
pangj7@mail2.sysu.edu.cn

Rong Huang
huangrong9277@163.com

[1] Department of Toxicology, School of Public Health, Sun Yat-Sen University, Guangzhou, People's Republic of China

[2] Department of Nutrition, School of Public Health, Sun Yat-Sen University (Northern Campus), No.74, 2nd Zhongshan Road, Guangzhou 510080, People's Republic of China

[3] Medical Science and Technology Innovation Center, Jinan Central Hospital, Shandong First Medical University, Taian, Jinan, China

[4] Department of Nutrition, School of Public Health, Guangzhou Medical University, 195 Dongfeng W Rd., Guangzhou 510080, People's Republic of China

[5] Department of Molecular, Cellular, and Developmental Biology, University of Colorado, Boulder, USA

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AST	Aspartate transaminase
CI	Confidence interval
CKD	Chronic kidney disease
CRP	C-reactive protein
eGFR	Estimated glomerular filtration rate
ESKD	End-stage kidney disease
FIB-4	Fibrosis 4 score
GBD	Global burden of disease
GGT	Gamma-glutamyl transferase
HDL-c	High-density lipoprotein (HDL) cholesterol
ICD-10	International classification of disease version 10
HR	Hazard ratio
LDL-c	Low-density lipoprotein- cholesterol
MAFLD	Metabolic dysfunction-associated fatty liver disease
NAFLD	Non-alcoholic fatty liver disease
PRS	Polygenic risk score
RRT	Renal replacement therapy
SD	Standard deviation
T2D	Type 2 diabetes

Introduction

Chronic kidney disease (CKD) has become a global public health issue. It is estimated that 15% general population is affected by CKD [1]. Regardless of the underlying etiology, most CKD cases are irreversible and can further progress to end-stage kidney disease (ESKD) [2, 3]. ESKD is a life-threatening condition in which a person's kidney function has decreased to the level that kidneys are unable to work on their own. Patients with ESKD must receive a kidney transplant or long-term dialysis to survive. According to the Global Burden of Disease (GBD) research, age-standardized incidence of ESKD treated by kidney transplantation or dialysis significantly increased by 34.4% and 43.1%, respectively, from 1990 to 2017 [4]. However, current treatment for CKD has limited effectiveness [3]. Thus, identifying risk factors of CKD and ESKD progression to stop or reverse the disease progression may shed light on alleviating CKD and ESKD burden.

Non-alcoholic fatty liver disease (NAFLD) is characterized by the accumulation of fat in the liver in the absence of other etiologies for fatty live such as excessive alcohol intake, virus hepatitis and drugs [5]. It is estimated that 25% of the global adult population is affected by NAFLD [6–8]. Increased evidence indicates that NAFLD is a purely metabolic dysfunction liver disease which is a part of complex metabolic disorders. And a panel of hepatologists proposed using metabolic dysfunction-associated fatty liver disease (MAFLD) to replace NAFLD [9–11]. The diagnosis criteria of MAFLD are different from NAFLD, which are based on evidence of hepatic steatosis with T2DM, overweight/obesity, or metabolic dysfunction [12]. MAFLD has a widespread adverse health effect due to the combination of hepatic steatosis and metabolism dysfunction. Kim et al. found that MAFLD was associated with increased all-cause mortality rather than NAFLD [13]. Another study found that MAFLD was more accurate for identifying patients with a higher risk of liver disease progression compared to NAFLD [14]. Moreover, the association between NAFLD and CKD has been reported by many epidemiological studies [15]. Recently, Sun et al. suggest that MAFLD identifies CKD patients better than NAFLD [16]. However, to date, no large prospective studies are available that have investigated the association between MAFLD and CKD progression to ESKD. In this study, we used UK Biobank data to prospectively explore the association between MAFLD and ESKD in 337,783 participants over a median duration of 12.8 years.

Methods

Study population

The UK Biobank is a large-scale prospective cohort study that recruited over 500,000 participants aged 40–69 years in 2006–2010 from 22 assessment centers across the United Kingdom. The details of UK Biobank design and methods have been described in previous literature [17]. This study was conducted under application number 76670. At baseline, participants completed a touch-screen questionnaire and a computer-assisted interview. Anthropometric measurements are assessed by trained staff at baseline. Blood, urine, and saliva samples were collected for biochemical analyses and genome-wide genotyping. Detailed information about the study methods is available on the UK Biobank website (https://www.ukBiobank.ac.uk/). This study only included participants with a Caucasian ethnic background, and we excluded participants with missing data in alcohol use, genetic variants, and variables for the calculation of eGFR and clinical scores. We also removed the participants with withdrawn consent or diagnosed as ESKD at baseline. Finally, a total of 337,783 participants were included in this study.

MAFLD and NAFLD diagnosis

The diagnosis of MAFLD was based on international panel of hepatologists consensus. Due to the scarcity of histological and imaging data for the liver, the diagnosis of hepatic steatosis was according to the fatty liver index (FLI) with validated cut-off values of ≥ 60 [18]. The FLI was calculated by the following formula: $100 \times e^{[0.953 \times \ln(\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \ln(\text{GGT}) + 0.053 \times \text{waist circumfere}}$

nce-15.745]/1 + e^[0.953 × ln(triglycerides) + 0.139 × BMI + 0.718 × ln(GGT) + 0.053 × waist circumference-15.745]. MAFLD was diagnosed in subjects when they had both FLI-diagnosed hepatic steatosis and one of the following conditions: (1) overweight/obesity (BMI ≥ 25 kg/m^2); (2) presence of type 2 diabetes (T2D); (3) at least two metabolic abnormalities, including hypertension, prediabetes, insulin resistance, increased serum triglycerides level, increased waist circumference, and low HDL cholesterol level. Due to the missing serum insulin data in the UK Biobank, we did not assess insulin resistance. Participants were defined as having T2D if they met one of the following conditions (1) had International Classification of Disease version 10 (ICD-10) codes of E11 before the baseline assessment visit; (2) had a self-reported diagnosis of T2D; (3) received treatment with hypoglycemic; (4) had HbA1c level > 47 mmol/mol. Hypertension was diagnosed if participants received treatment with antihypertensive medication or had mean blood pressure greater than 130/85 mm Hg. NAFLD was diagnosed in subjects when they had FLI-diagnosed hepatic steatosis but without (1) hospital diagnosis of other causes of liver diseases; (2) hospital diagnosis of liver cancer; (3) excessive alcohol consumption (≥ 30 g for male or ≥ 20 g for female). Participants met only NAFLD, MAFLD or both NAFLD and MAFLD diagnosis criteria were categorized into non-MAFLD NAFLD, non-NAFLD MAFLD or NAFLD-MAFLD groups, respectively [19].

Liver fibrosis score calculation

The severity of MAFLD was assessed by the liver fibrosis scores including NAFLD fibrosis score (NFS), fibrosis 4(FIB-4) score, and Forns score. The liver fibrosis scores were calculated as follows:

1) NFS: − 1.675 + [0.037 × age(years)] + [0.094 × BMI(kg/m^2)] + [1.13 × T2D (yes = 1, no = 0)] + [0.99 × AST/ALT ratio] − [0.013 × platelet count(10^9/L)] − [0.66 × albumin(g/dL)]. The lower cutoff and upper cutoff for advanced fibrosis were − 1.455 and 0.676, respectively [20].
2) FIB-4: (Age × AST)/(Platelets × ALT$^{0.5}$). The lower cutoff and upper cutoff for advanced fibrosis 1.30 and 2.67, respectively [21].
3) Forns score: 7.811 − 3.13 × ln(platelet count) + 0.781 × ln(GGT) + 3.467 × ln(age) − 0.014 × cholesterol. The lower cutoff and upper cutoff for advanced fibrosis 4.2 and 6.9, respectively [22].

CKD assessment

We calculated the estimate glomerular filtration rate (eGFR) by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (23). The eGFR was calculated as follows: eGFR = 141 × [minimum (serum creatinine/κ, 1)$^{\alpha}$] × [maximum (serum creatinine/κ, 1)$^{-1.209}$] × (0.993^{age}) × 1.018 [if female], where α is − 0.329 for females and − 0.411 for males and κ is 0.7 for females and 0.9 for males. CKD is defined as the presence of an abnormality in renal function for more than 3 months. In this study, CKD was diagnosed when the individuals had eGFR < 60 ml/min/1.73 m^2

Genotyping

The genotyping information was derived from two similar arrays (UK BiLEVE and UK Biobank Axiom arrays). Information about arrays and genotyping process was provided in detail elsewhere. *PNPLA3* rs738409 C > G (p.I148M), *TM6SF2* rs58542926 C > T (p.E167K), *MBOAT7* rs641738 C > T and *GCKR rs1260326* C > T (p.P446L) were coded 0, 1 and 2 for non-carriers, heterozygous carriers, and homozygous carriers of the minor allele, respectively. A polygenic risk score (PRS) has been developed to summarize the impact of genetic predisposition to fatty liver. The PRS was calculated as the sum of these risk-increasing alleles.

Outcome

ESKD cases were ascertained by the algorithm devised by UK Biobank, which were generated based on the hospital admission HER records, self-report verified by nurse interview, or death certificate records. ESKD patients are treated with renal replacement therapy (RRT). However, acute kidney injury (AKI) patients have also received RRT treatment. To exclude the AKI cases, this algorithm devised by the UK Biobank team identifies participants who received RRT and had indicators of CKD stage 5 (GFR < 15 ml/min/1.73 m^2) as ESKD cases. Detailed information about the algorithm can be found on the website (https://Biobank.ndph.ox.ac.uk/showcase/ukb/docs/alg_outcome_ESKD.pdf).

Covariates

We calculated the daily alcohol intake by adding the average daily alcohol intake of each type of alcoholic drink. Smoking status were categorized as current smokers, ex-smokers and never smokers. Townsend deprivation index is an index to measure the social deprivation in which the subject lives [24]. The index was calculated immediately prior to subjects participating in the UK Biobank.

Statistical analysis

Continuous variables were expressed as mean with standard deviation (SD) or median with interquartile range. Student's *t* test was used for the normal continuous variables to

compare the differences between MAFLD and non-MAFLD subjects, while Kruskal–Wallis's test was used for the non-normal continuous variables. Categorial variables were presented as frequencies with percentages and Fisher's exact test was used to compare the differences between MAFLD and non-MAFLD subjects.

To investigate the association between NAFLD/MAFLD and ESKD incident, Cox proportional hazards model was used. Each participant's person-years were calculated from the date of recruitment to the date of death, reported ESKD diagnosis, or 30th November 2021, whichever occurred first. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. We conducted a univariable Cox regression analysis and two sets of multivariable-adjusted models. In the basic model, age and sex were adjusted. And in the expanded model, age, sex, assessment center, deprivation index, smoking status, alcohol intake, fasting glucose, serum triglycerides (TG), serum ALT, and systolic blood pressure (SBP) were adjusted. We also stratified participants by sex and CKD status and performed the subgroups Cox regression using the same models. The assumption that hazards are proportional at each point in time throughout follow-up was verified.

We also assessed the association of the severity of MAFLD with ERSD in MAFLD subjects. Briefly, non-MAFLD cases were regarded as the reference group and the liver fibrosis scores were categorized according to the cutoff values for advanced fibrosis in MAFLD subjects. Cox regression models were used to estimate the ESKD risk. To explore the potential interaction effects on ESKD between MAFLD and genetic variants including *PNPLA3* rs738409, *TM6SF2* rs58542926, *GCKR* rs1260326 and *MBOAT7* rs641738, we set non-MAFLD cases with noncarriers of risk-increasing allele as the reference group and then estimated the association between MAFLD subjects with different genotypes and ESKD risks. PRS was calculated and PRS was categorized according to low (PRS < 1), intermediate (1 ≤ PRS < 5), and high levels (PRS ≥ 5) in MAFLD subjects. Cox regression models were used to estimate the ESKD risk. The p value for all statistical analyses was two-tailed and p value < 0.05 was regarded as statistically significant. We performed all the analysis using R (4.0.2).

Results

Participant characteristics

A total of 337,783 participants were included in this study. Among them, 130,725 subjects had MAFLD. The baseline characteristics of the participants were presented in Table 1. Compared to non-MAFLD individuals, subjects with MAFLD tended to be male, older, and had higher levels of socioeconomic deprivation. MAFLD subjects were more likely to be frequent smokers and drinkers. They also had lower HDL and higher values of TC, LDL, CRP, Hb1Ac, serum glucose and serum liver enzyme compared to non-MAFLD individuals. Moreover, we found that MAFLD subjects showed significantly lower eGFR levels and had a higher prevalence of CKD compared to non-MAFLD individuals.

Association between MAFLD and risk of ESKD

Cox regression analyses were first done to explore the associations between NAFLD/MAFLD and ESKD. Compared to non-NAFLD/MAFLD controls, the associations of non-NAFLD MAFLD or NAFLD-MAFLD with ESKD risk were significant while non-MAFLD NAFLD was not associated with ESKD risk (Supplemental Table 1). These results suggest that the diagnostic criteria of MAFLD may be more sensitive to predict the risk of ESKD. Thus, we mainly explored the association between MAFLD and ESKD risk in the following analyses.

During the median 12.8 (interquartile 12.1–13.5) years of follow-up, 235 (0.11%) ESKD occurred in individuals without MAFLD and 383 (0.29%) participants with MAFLD developed ESKD. To investigate the association between MAFLD and ESKD, Cox regression analyses were performed. As shown in Table 2, after adjustment for sex and age, MAFLD was notably associated with a higher risk of ESKD (HR 2.15, 95% CI 1.82–2.54, $p < 0.001$). Moreover, our results showed that MAFLD participants had a 103% higher relative hazard of ESKD incidence (HR 2.03, 95% CI 1.68–2.46, $p < 0.001$) after adjustment for age, sex, assessment center, deprivation index, smoking status, alcohol intake, fasting glucose, serum TG, serum ALT, and SBP. The association of MAFLD with ESKD risk remained significant in both male and female participants.

To further explore whether the association between MAFLD and ESKD incidence was altered in different kidney function states, we divided the participants into non-CKD and CKD groups according to the baseline eGFR levels. In non-CKD group, after adjustment MAFLD cases exhibited a significantly increased risk of ESKD (HR 1.47, 95% CI 1.12–1.93, $p = 0.006$). Similar results were found in CKD individuals. Participants with CKD and MAFLD showed a 34% higher relative hazard of ESKD incidence compared to CKD patients without MAFLD in adjusted model 3 (HR 1.56, 95% CI 1.20–2.04, $p < 0.001$).

MAFLD severity and risk of ESKD

Liver fibrosis which is the indicator of MAFLD severity can be assessed by several clinical scoring systems [25]. To explore the association between MAFLD severity and ESKD

Table 1 Baseline characteristics in subject with or without MAFLD

Characteristics	Non-MAFLD	MAFLD	*p* value
Sample size	207,058	130,725	
Male	72,861 (35.2%)	83,868 (64.2%)	< 0.001
Age (years)	56.40 (8.13)	57.58 (7.72)	< 0.001
Deprivation index	− 1.72 (2.84)	− 1.28 (3.07)	< 0.001
Alcohol intake (g/day)	10.39 [1.66, 20.79]	12.54 [0.55, 28.39]	< 0.001
Smoking status			< 0.001
Never	121,276 (58.6%)	62,222 (47.6%)	
Former	65,859 (31.8%)	53,906 (41.2%)	
Current	19,923 (9.6%)	14,597 (11.2%)	
Waist circumstance (cm)	82.71 (8.92)	102.60 (9.95)	< 0.001
BMI	24.90 (2.81)	31.46 (4.42)	< 0.001
CKD	3118 (1.5%)	3834 (2.9%)	< 0.001
Type 2 diabetes	3307 (1.6%)	11,391 (8.7%)	< 0.001
Hypertension	76,348 (36.9%)	87,039 (66.6%)	< 0.001
Albumin (g/L)	45.30 (2.58)	45.15 (2.63)	< 0.001
Serum triglycerides (mmol/L)	1.35 (0.62)	2.40 (1.17)	
Serum cholesterol (mmol/L)	5.71 (1.09)	5.73 (1.22)	< 0.001
CRP (mg/L)	0.98 [0.51, 1.95]	2.14 [1.15,4.11]	< 0.001
HDL-c (mmol/L)	1.58 (0.38)	1.26 (0.29)	< 0.001
LDL-c (mmol/L)	3.53 (0.83)	3.65 (0.92)	< 0.001
Glucose (mmol/L)	4.97 (0.89)	5.34 (1.54)	< 0.001
Glycated hemoglobin (mmol/mol)	34.82 (4.67)	37.73 (8.10)	< 0.001
ALP (U/L)	80.45 (23.40)	88.48 (28.31)	< 0.001
ALT (U/L)	19.45 (9.62)	30.09 (16.97)	< 0.001
AST (U/L)	24.56 (8.07)	28.71 (11.79)	< 0.001
GGT (U/L)	21.20 [16.30, 29.30]	39.80 [28.10, 61.00]	< 0.001
eGFR (ml/min/1.73 m^2)	92.17 (12.70)	90.42 (14.01)	< 0.001

BMI body mass index, *CKD* chronic kidney disease, *CRP* C-reactive protein, *HDL-c* high-density lipoprotein (HDL) cholesterol, *LDL-c* low-density lipoprotein (HDL) cholesterol, *ALP* alkaline phosphatase, *ALT* alanine transaminase, *AST* aspartate transaminase, *GGT* gamma-glutamyl transferase, *eGFR* estimated glomerular filtration rate

incidence, we stratified the MAFLD subjects into separate groups according to the non-invasive fibrosis scores. The baseline characteristics of the MAFLD subjects with different levels of NAFLD fibrosis score were presented in Supplemental Table 2. Compared to non-MAFLD individuals, the adjusted HRs for ESKD incidence in MAFLD patients with increasing levels of NFS were 1.23 (95% CI 0.96–1.58), 2.45 (1.98–3.03) and 7.67 (5.48–10.73), respectively (Table 3). Similarly, MAFLD subjects with the highest risk class of FIB-4 also showed significant increased HR for ESKD incidence (HR 4.29, 95% CI 2.72–6.78, $p < 0.001$) compared with non-MAFLD participants. Moreover, there was a graded association between Fones score and the risk of ESKD. Significant association was observed in MAFLD participants with intermediate Fones score (HR 2.43, 95% CI 1.97–3.00, $p < 0.001$) or high Fones score (HR 6.22, 95% CI 4.38–8.83, $p < 0.001$). Overall, these data indicate that MAFLD patients with higher liver fibrosis scores had a greater risk of ESKD occurrence.

Association between MAFLD and risk of ESKD by genetic risk

PNPLA3 rs738409, *TM6SF2* rs58542926, *GCKR* rs1260326 and *MBOAT7* rs641738 have been shown to associate with the outcomes of fatty liver disease [26]. We next assessed the effects on ESKD risk of these genetic variants in non-MAFLD and MAFLD subjects. As shown in Supplemental Table 3, all these four genetic variants were not associated with increased ESKD risk in non-MAFLD participants. However, in MAFLD subjects after adjustment for confounding variables, risking alleles of *PNPLA3* rs738409, *TM6SF2* rs58542926, *GCKR* rs1260326 and *MBOAT7* rs641738 were all found to be significantly associated with the occurrence of ESKD (Fig. 1). Compared with non-MAFLD subjects with the CC genotype of *TM6SF2* rs58542926, the HR for ESKD increased from 1.95 (95% CI 1.59–2.39) in MAFLD subjects with CC genotype to 6.19 (95% CI 2.53–15.14) in those subjects with TT genotype (Fig. 1a). Similarly, risking

Table 2 Association of MAFLD with incident ESRD in the overall population and in the subgroups of different sex or baseline CKD states

	Incidence of ESRD (*n*, %)	Model 1 (HR and 95% CI)	*p*	Model 2 (HR and 95% CI)	*p*	Model 3 (HR and 95% CI)	*p*
Overall							
Non-MAFLD	235/207058 (0.11%)	Reference		Reference		Reference	
MAFLD	383/130725 (0.29%)	2.63 (2.23, 3.09)	< 0.001	2.15 (1.82, 2.54)	< 0.001	2.03 (1.68, 2.46)	< 0.001
Male							
Non-MAFLD	110/72861 (0.15%)	Reference		Reference		Reference	
MAFLD	289/83868 (0.34%)	2.31 (1.85, 2.88)	< 0.001	2.25 (1.81, 2.81)	< 0.001	2.16 (1.68, 2.76)	< 0.001
Female							
Non-MAFLD	125/134197 (0.093%)	Reference		Reference		Reference	
MAFLD	94/46857 (0.20%)	2.18 (1.67, 2.85)	< 0.001	2.02 (1.55, 2.65)	< 0.001	1.85 (1.34, 2.54)	< 0.001
Non-CKD							
Non-MAFLD	126/203940 (0.062%)	Reference		Reference		Reference	
MAFLD	174/126891 (0.14%)	2.26 (1.80, 2.84)	< 0.001	1.81 (1.43, 2.30)	< 0.001	1.47 (1.12, 1.93)	0.006
CKD							
Non-MAFLD	109/3118 (3.50%)	Reference		Reference		Reference	
MAFLD	209/3834 (5.45%)	1.64 (1.30, 2.07)	< 0.001	1.43 (1.13, 1.82)	0.003	1.56 (1.20, 2.04)	< 0.001

Model 1 is univariable Cox regression analysis

Model 2 is adjusted by age and sex

Model 3 is adjusted by age, sex, assessment center, deprivation index, smoking status, alcohol intake, fasting glucose, serum ALT, serum TG, and SBP

Table 3 Association of the severity of MAFLD with incident ESRD

	Incidence of ESRD (*n*, %)	Model 1 (HR and 95% CI)	*P*	Model 2 (HR and 95% CI)	*P*	Model 3 (HR and 95% CI)	*P*
NFS							
Non-MAFLD	235/207058 (0.11%)	Reference		Reference		Reference	
MAFLD with NFS < − 1.455	121/78761 (0.15%)	1.35 (1.09, 1.68)	0.007	1.24 (0.99, 1.55)	0.064	1.23 (0.96, 1.58)	0.095
MAFLD with − 1.455 ≤ NFS < 0.676	212/49015 (0.43%)	3.97 (3.30, 4.79)	< 0.001	2.86 (2.35, 3.47)	< 0.001	2.45 (1.98, 3.03)	< 0.001
MAFLD with NFS ≥ 0.676	50/2949 (1.70%)	17.29 (12.74, 23.46)	< 0.001	11.87 (8.68, 16.23)	< 0.001	7.67 (5.48, 10.73)	< 0.001
FIB-4							
Non-MAFLD	235/207058 (0.11%)	Reference		Reference		Reference	
MAFLD with FIB-4 < 1.30	170/75690 (0.22%)	1.98 (1.62, 2.41)	< 0.001	1.99 (1.62, 2.43)	< 0.001	1.80 (1.44, 2.25)	< 0.001
MAFLD with 1.30 ≤ FIB-4 < 2.67	191/51791 (0.37%)	3.37 (2.79, 4.08)	< 0.001	2.22 (1.81, 2.72)	< 0.001	2.18 (1.75, 2.72)	< 0.001
MAFLD with FIB-4 ≥ 2.67	22/3244 (0.68%)	6.82 (4.40, 10.55)	< 0.001	4.00 (2.57, 6.25)	< 0.001	4.29 (2.72, 6.78)	< 0.001
Forns score							
Non-MAFLD	235/207058 (0.11%)	Reference		Reference		Reference	
MAFLD with score < 4.2	79/57047 (0.14%)	1.21 (0.94, 1.56)	0.139	1.31 (1.01, 1.69)	0.041	1.18 (0.90, 1.56)	0.232
MAFLD with 4.2 ≤ score < 6.9	256/68932 (0.37%)	3.37 (2.83, 4.03)	< 0.001	2.49 (2.06, 3.01)	< 0.001	2.43 (1.97, 3.00)	< 0.001
MAFLD with score ≥ 6.9	48/4746 (1.01%)	10.10 (7.41, 13.78)	< 0.001	6.12 (4.41, 8.49)	< 0.001	6.22 (4.38, 8.83)	< 0.001

Model 1 is univariable Cox regression analysis

Model 2 is adjusted by age and sex

Model 3 is adjusted by age, sex, assessment center, deprivation index, smoking status, alcohol intake, fasting glucose, serum ALT, serum TG, and SBP

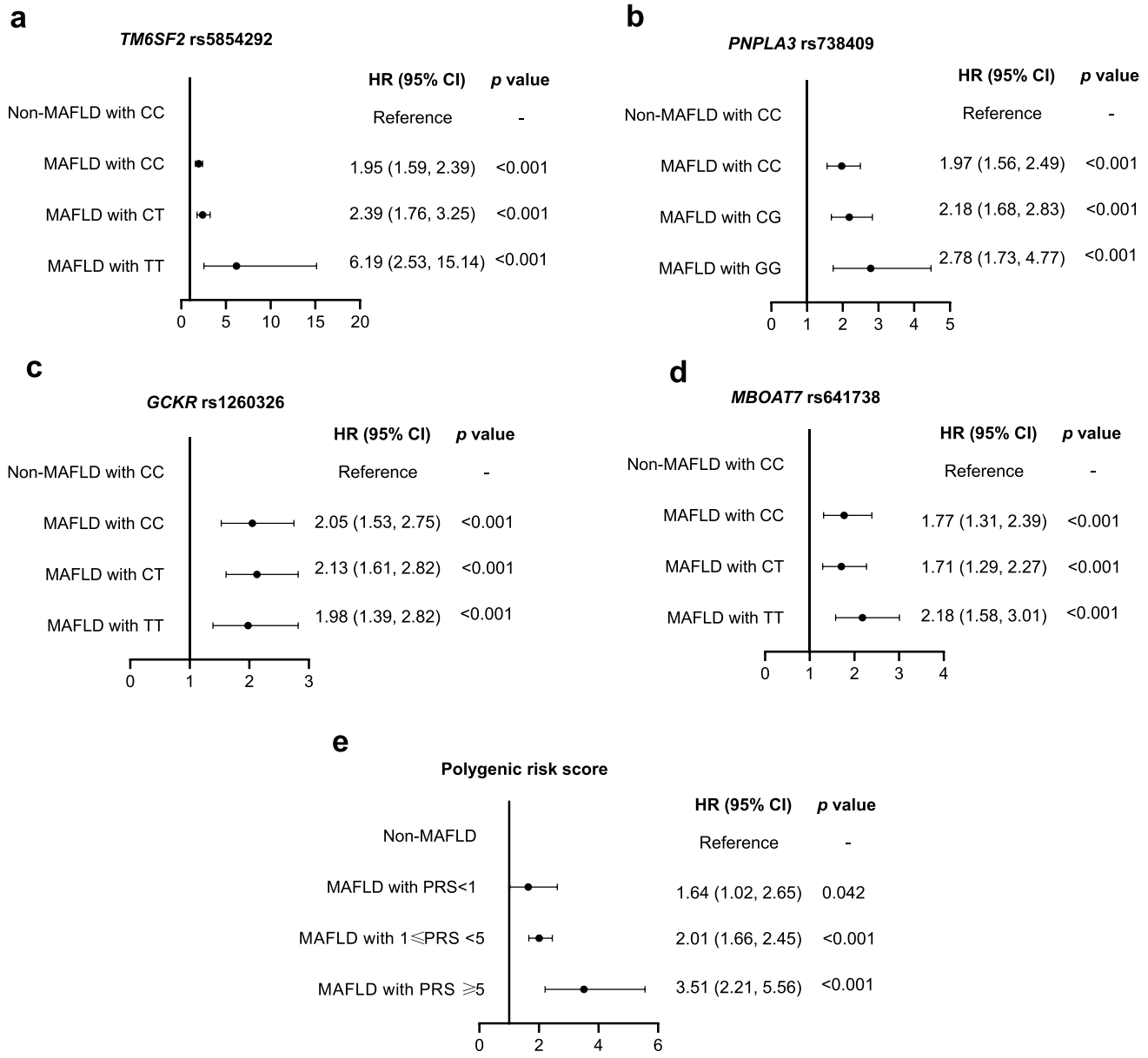

Fig. 1 Association of fatty liver-related genetic variants with incident ESRD in MAFLD cases according to genotype of TM6SF2 rs5854292 (**a**), PNPLA3 rs738409 (**b**), GCKR rs1260326 (**c**), MBOAT7 rs641738 (**d**), and polygenic risk score (**e**). HR, hazard ratio; CI, confidence interval. The HRs and its CIs were calculated from the Cox regression model. The model was adjusted by age, sex, assessment center, deprivation index, smoking status, alcohol intake, fasting glucose, serum ALT, serum TG, and SBP

allele of *PNPLA3* rs738409, *GCKR* rs1260326 and *MBOAT7* rs641738 also enhanced the MAFLD effects on the risk of ESKD (Fig. 1b–d). Finally, we combined all these four genetic variants to calculate PRS. Although PRS was not associated with ESKD risk in non-MAFLD cases (Supplemental Table 3), the increasing PRS score was notably associated with a higher risk of ESKD in MAFLD individuals. Compared to non-MAFLD individuals, the effect estimate increased from 1.64 (95% CI 1.02–2.65) in MAFLD subjects with low levels of PRS to 3.51 (95% CI 2.21–5.56) in those with high levels of PRS (Fig. 1e). Collectively, these results clearly suggest that genetic traits were able to predict ESKD risk in MAFLD individuals.

Discussion

The novel findings of this large-scale prospective cohort study from the UK Biobank database suggest that MAFLD is significantly associated with the incidence of ESKD in both

non-CKD and CKD participants. Moreover, increased liver fibrosis scores which are the indicators of MAFLD severity are strongly associated with a higher risk of ESKD and risking alleles of *PNPLA3* rs738409, *TM6SF2* rs58542926, *GCKR* rs1260326 and *MBOAT7* rs641738 amplify the MAFLD effect on ESKD. To our knowledge, this is the first prospective community-based cohort study to examine the association between MAFLD and the risk of ESKD, and to investigate the associations between the severity of MAFLD, risking genetic traits of MAFLD and ESKD.

The relationship between NAFLD and CKD has been verified by several studies [27–30]. The cross-sectional studies found that the prevalence of CKD ranged from 5 to 30% in non-NAFLD subjects, while this number increased to 20–55% among patients with NAFLD [31]. However, whether NAFLD plays a causal role in the progression of CKD remains debatable. The Valpolicella Heart Diabetes Study found that the presence of NAFLD in T2D patients increased the risk of incident CKD (HR 1.49, 95% CI 1.1–2.2) [32]. Similarly, Park et al. also found that after adjusting for confounding variables, NAFLD was statistically associated with incident CKD (HR 1.58, 95% CI 1.5–1.7) [33]. To date, no other prospective studies have been conducted to examine the association between NAFLD and the advanced stage of CKD-ESKD in both non-CKD and CKD subjects. Recently, renaming NAFLD to MAFLD has been proposed by an international panel of hepatologists. The diagnosis criteria of MAFLD are different from NAFLD and MAFLD was characterized by the coexistence of metabolic dysfunctions [34]. To identify fatty liver patients by NAFLD or MAFLD definitions are highly consistent [16]. However, the MAFLD definition encourages holistic therapy for patients with fatty liver disease linked with metabolic dysfunction. MAFLD definition also guides clinicians to incorporate fatty liver disease in novel clinical trial designs for patients with metabolic diseases [35]. Interestingly, one cross-sectional study suggested that MAFLD identified CKD patients better than NAFLD [16]. In this study, we also found that MAFLD patients showed decreased levels of eGFR compared to non-MAFLD cases. More importantly, for the first time, over median of 12.8 follow-up years, we found that MAFLD was significantly associated with the incident ESKD both in non-CKD and CKD individuals, which suggested that MAFLD was a risk factor to drive the development of CKD and CKD progression to ESKD.

Severity of NAFLD has been reported to be associated with CKD in some small sample size case–control studies [36–38]. Studies found that the histological severity of NAFLD (mainly the fibrosis stage) was significantly associated with lower eGFR and abnormal albuminuria [36–38]. However, it is impractical to conduct a liver biopsy in a large community-based cohort study and non-invasive clinical fibrosis are easy and convenient to calculate to assess the liver fibrosis risk in patients with liver disease [25]. Previous studies have demonstrated that intermediate and high liver fibrosis scores were positively associated with a higher risk of severe liver disease in general or NAFLD population [39]. Moreover, MAFLD subjects with higher liver fibrosis scores were more likely to have CKD and abnormal albuminuria [16]. Importantly, in this study our results also showed that compared to non-MAFLD cases, MAFLD individuals with increased liver fibrosis scores were strongly associated with the incident ESKD, which suggested that severe MAFLD might accelerate CKD development and progression to ESKD.

Both genetic and environmental factors interact to influence fatty liver disease development, progression, and outcomes [40]. Hepatic steatosis is a complex and heritable trait [41]. Genetic variations in genes involved in lipid metabolism predispose to the progression and outcome of fatty liver disease. Previous genome-wide association studies (GWAS) have found a series of a genetic risk factor for fatty liver, including *PNPLA3* rs738409 [42], *TM6SF2* rs58542926 [43], *GCKR* rs1260326 [44] and *MBOAT7* rs641738 [45]. And these variants were found to be associated with outcomes of MAFLD including the incidence of cancer and severe liver disease [46, 47]. In this study, our results also suggested that risking alleles of all these four variants were notably associated with the risk of ESKD in MAFLD patients. Polygenic risk score is to combine and gather numerous variants to maximize the contribution of genetics. PRS score may help identify HCC, and severe liver disease risks [39, 47, 48]. Although PRS was not associated with the incident ESKD in non-MAFLD participants, we found that increased PRS score was significantly associated with a greater risk of ESKD in MAFLD individuals.

The mechanisms linking MAFLD to ESKD may be explained by the following points. First, MAFLD is a part of complex metabolic dysfunction. MAFLD may causally or at least in part promote the CKD progression to ESKD via a series of cardiometabolic risk factors including visceral adiposity, dyslipidemia, insulin resistance and other metabolic syndrome features [15, 49]. Secondly, dysbiosis and disturbed intestinal function may be linked to MAFLD and CKD via gut-liver-kidney axis. For example, dietary choline and carnitine are transformed to trimethylamine (TMA) by gut microbiota, which are further converted into trimethylamine N-oxide (TMAO) in the liver by flavin-containing monooxygenase [50]. TMAO requires active elimination by the kidney and is found to promote CKD progression [51]. Last but not the least, oxidative stress may be a mediator of the link between MAFLD and ESKD. Dyslipidemia and increasing oxidative stress are key features of fatty liver disease, which can lead to a reduction of an antioxidant factor produced by kidneys

such as the Klotho and promote CKD progression [15, 52, 53]. It is worth noting that the precise mechanisms underlying the association between MAFLD and ESKD are still unclear and further studies are needed to better understand the underlying mechanisms.

There were some limitations in this study. First, FLI rather than liver biopsy which is the gold standard was used to diagnose hepatic steatosis. However, it is not feasible to conduct a liver biopsy in large-scale cohort studies. The accuracy of FLI has been verified and FLI is proposed to be used to diagnose MAFLD in the guideline [9, 54, 55]. Second, ERSD cases were identified using data from death records and hospital admission. Thus, we cannot further explore the associations between MAFLD and the trajectory of kidney function over the follow-up years. Third, UK Biobank is not the perfect representative of the UK population given self-referral and selection bias. Fourth, the population were divided into non-CKD and CKD groups according to the baseline GFR levels. Whether the low GFR states in CKD subjects last for more than 3 months were unclear. Lastly, given the inherent limitations of prospective cohort studies, residual and unmeasured confounding variables may exist to influence the association between MAFLD and ESKD.

In conclusion, using large-scale prospective data from UK Biobank, we found that MAFLD is associated with ESKD in both non-CKD and CKD participants. Moreover, increased liver fibrosis scores and genetic risk scores are significantly associated with a greater risk of ESKD in MAFLD subjects. These results suggest that improving MAFLD might be a promising preventive and therapeutic approach to stop or slow down CKD progression.

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Data availability Data may be obtained from a third party and are not publicly available. The UK Biobank will make the source data available to all bonafide researchers for all types of health-related research that is in the public interest, without preferential or exclusive access for any persons. All researchers will be subject to the same application process and approval criteria as specified by UK Biobank. For more details on the access procedure, see the UK Biobank website: http://www.ukbiobank.ac.uk/register-apply.

Declarations

Conflict of interest Shen Chen, Juan Pang, Rong Huang, Hongliang Xue and Xu Chen: Nothing to report.

Ethical approval The UK Biobank research was approved by the North West Multi-Centre Research Ethics Committee (Ref: 11/NW/0382) and all participants provided written informed consent.

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