Research Square

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Lower creatinine to cystatin C ratio is associated with an increased risk of MAFLD: A cross-sectional and prospective study of 368,634 UK Biobank participants

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Abstract

Background & Aims: Metabolic associated fatty liver disease (MAFLD) affects about a quarter of the world's adults, and screening out the high-risk population with at an early stage is a challenge. As a sarcopenia index, the relationship between creatinine to cystatin C ratio (CCR) and MAFLD remains unclear. This cross-sectional, prospective study aimed to explore the relationship between CCR and MAFLD.

Methods: This study included 368,634 participants from the UK Biobank for cross-sectional and prospective analyses. MAFLD was diagnosed according to international expert consensus, and mild and severe liver fibrosis were defined by FIB-4. Univariate and multivariate logistic regression analyses were used to calculate odds ratios (ORs) to evaluate the association between CCR levels and MAFLD. Cox regression models were used to determine the association between CCR and MAFLD-related severe liver disease (SLD).

Results: We grouped the study participants according to CCR tertiles. In cross-sectional and prospective analyses, participants in CCR tertile 1 had the highest MAFLD risk (OR 1.075, 95%CI 1.058-1.093, *P*<0.001, and OR 1.340, 95%CI 1.077-1.669, *P*=0.009). In males, CCR was significantly associated with severe liver fibrosis (OR 1.657, 95%CI 1.476-1.859, *P*<0.001). Cox analyses showed that participants in CCR tertile 1 had the highest risk of MAFLD-related SLD (HR 4.23, 95%CI 3.54-4.05, *P*<0.001), and the SLD cumulative incidence during follow-up was obviously higher than others.

Conclusion: Our results indicated that lower CCR was significantly associated with higher risk of MAFLD. Moreover, CCR can predict the risk of MAFLD-related SLD and severe liver fibrosis, which can potentially be used as a large-scale non-invasive tool to dynamically monitor the occurrence and development of MAFLD.

Introduction

An international consensus panel proposed replacing non-alcoholic fatty liver disease(NAFLD) with metabolic associated fatty liver disease(MAFLD) in 2020.[1] MAFLD affects approximately one quarter of the world's adult population, with a prevalence rate of 50.7% among overweight and obese individuals.[2, 3] The number of patients with hepatocellular carcinoma (HCC) associated with MAFLD has significantly increased.[4] MAFLD poses a major health and economic burden to all societies and has no approved pharmacotherapy.[2, 5] Therefore, it is of crucial to identify the risk factors for MAFLD and screen the population at high risk in the early stages.

Studies have indicated that the loss of skeletal muscle mass may contribute to insulin resistance and accumulation of triglycerides in the liver.[6, 7] Sarcopenia was associated with severe liver fibrosis and was an independent risk factor for non-alcoholic steatohepatitis and severe fibrosis.[8, 9] However, the association between sarcopenia and MAFLD remains unclear. According to the existing international consensus, the diagnosis of sarcopenia requires the assessment of muscle mass, muscle strength, and physical performance. Dual-energy x-ray absorptiometry (DXA), computed tomography (CT), bioelectrical impedance analysis (BIA), and magnetic resonance imaging (MRI) scan were commonly used to measure muscle mass.[10, 11] However, these methods are not widely used due to their high cost, radioactivity and non-feasibility.[12]

Kashani et al. proposed the use of the creatinine-to-cystatin C ratio (CCR) as sarcopenia index to evaluate muscle mass. When CCR is low, it indicates a reduction in the skeletal muscle. [13] Compared to conventional diagnostic methods, CCR is more convenient and less expensive. The efficacy of CCR as a biomarker of muscle mass has been verified in multiple populations,[12, 14] and it is better than BIA for determining sarcopenia.[15]

This cross-sectional and prospective study, we aimed to explore the relationship between CCR and MAFLD.

Method

Study participants

This study obtained participants' information from the UK Biobank. The UK Biobank is a nationwide prospective cohort study that enrolled more than 500,000 participants from 22 medical centers between 2006 and 2010. The UK Biobank study was approved by the Research Tissue Bank approval from the Northwest Multi-Centre Research Ethics Committee. And written informed consent to participate in the UK Biobank study was obtained from all participants. The present study was undertaken under application number 92668. The exclusion criteria were as follows: (1) insufficient information for evaluating MAFLD status; (2) missing information on age, sex, and race; (3) missing or abnormal values of laboratory test indicators; and (4) an eGFR < 60 mL/min/1.73 m^2.

Diagnosis of MAFLD

According to an International Expert Consensus, the diagnosis of MAFLD is based on fat accumulation in the liver (hepatic steatosis) in addition to one of the following three criteria: overweight or obesity (body mass index [BMI] ≥ 25 kg/m^2 in Caucasians or BMI ≥ 23 kg/m^2 in Asians), presence of type 2 diabetes mellitus (T2DM), or evidence of metabolic dysregulation.[2] Hepatic steatosis is determined based on histological (biopsy), imaging, or blood biomarker evidence. Because the imaging and histological data for the liver in the UK Biobank cohort were unavailable, we calculated the fatty liver index (FLI) for each participant and defined hepatic steatosis as FLI ≥ 60.[16] T2DM was diagnosed when participants met one of the following conditions: (1) hemoglobin A1c (HbA1c) > 47 mmol/mol, (2) with 10th international disease classification (ICD) codes of E11.0-E11.9 or ICD-9 code of 250, and (3) regular use of anti-diabetic medications. Metabolic abnormalities included increased waist circumference (WC) (WC ≥ 102 cm in Caucasian men and ≥ 88 cm Caucasian women or ≥ 90 cm in Asian men and ≥ 80 cm in Asian women), arterial hypertension (blood pressure ≥ 130/85 mmHg or specific drug treatment), hypertriglyceridemia (plasma triglycerides ≥ 150 mg/dl [≥ 1.70 mmol/L] or specific drug treatment), low high-density lipoprotein (HDL) cholesterol (plasma HDL cholesterol < 40 mg/dl [< 1.0 mmol/L] for men and < 50 mg/dl [< 1.3 mmol/L] for women or specific drug treatment), prediabetes (fasting glucose levels 100–125 mg/dl [5.6–

6.9 mmol/L], 2-hour post-load glucose levels 140–199 mg/dl [7.8–11.0 mmol], or HbA1c 5.7–6.4% [39 to 47 mmol/mol]), insulin resistance (homeostasis model assessment of insulin resistance score ≥ 2.5), and C-reactive protein (CRP) > 2mg/L [2].

Prospective analysis

Participants without MAFLD at baseline and the follow-up data available for the diagnosis of MAFLD were screened to form a prospective cohort. The relationship between baseline CCR and the risk of developing MAFLD was analyzed in this prospective cohort.

MAFLD-related clinical outcomes

The outcomes of interest were incident MAFLD-related liver fibrosis and severe liver disease (SLD). FIB-4 was used to diagnosis liver fibrosis, 1.3 < FIB-4 < 2.67 was defined as mild liver fibrosis and FIB-4 > 2.67 was defined as severe liver fibrosis.[17] Follow-up data from patients with MAFLD at baseline were used to determine whether these patients subsequently developed SLD. SLD was defined as a composite diagnosis of cirrhosis, decompensated liver disease (i.e., esophageal varices with or without bleeding, portal hypertension, hepatorenal syndrome, liver failure), hepatocellular carcinoma, and/or liver transplantation (ICD-10 C22.0, I85.0, I85.9, K70.3, K70.4, K72.1, K72.9, K74.1, K74.2, K74.6, K76.6, K76.7, Z94.4).[18]

Statistical analysis

Continuous variables were presented as median (quartiles 1, and quartiles 3), and categorical variables were presented as n (%). We used Student's t-test, the Mann–Whitney U test and χ^2 test to compare the differences between different CCR group. Logistic regression analysis was used to calculate odds ratio (OR) and 95% confidence interval (CI) to evaluate the association among CCR levels, MAFLD, and severe liver fibrosis. Because MAFLD was diagnosed using laboratory indicators, the follow-up time could not be determined. The prospective analysis of the association between CCR and the incidence of MAFLD was performed using logistic regression. The follow-up time for SLD was available, using COX proportional hazard regression models to investigate the impact of CCR on the occurrence of SLD. The strength of associations was expressed by means of hazard ratio (HR) and 95% CI. Several multivariable models were constructed with confounders: Model 1 was adjusted for age, sex and race; Model 2 was further adjusted for T2DM and HbA1c; Model 3 additionally adjusted for HDL, low-density lipoprotein (LDL), triacylglycerol (TG) and cholesterol; and Model 4 was additionally adjusted for BMI and WC. Subgroup analyses involving stratification by sex were performed to identify the interactive factors. All analyses were performed using the R program (version 4.2.2). Statistical significance was defined as a two-tailed *P*-value < 0.05.

Results

Baseline characteristics of study participants

After the exclusion of 133,747 individuals according to the exclusion criteria, 368,634 patients were included in the analysis (Fig. 1). We grouped the study participants according to CCR tertiles. The baseline characteristics of the study participants were shown in Table 1. Participants were also grouped according to whether they had MAFLD or not, and 139,002 participants had a diagnosis of MAFLD at baseline (Supplementary Table 1). The median patient age was 58 years, and the level of CCR gradually decreased with growth. Most participants were females. There were noticeable differences in clinical and anthropometric characteristics according to the grouping of CCR: participants with low CCR had higher levels of BMI, HbA1c, HDL, LDL, triglyceride, and cholesterol whereas the WC, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and albumin (ALB) levels were lower. Patients with a lower CCR had a worse metabolic status.

Table 1
Characteristics of study participants according to the CCR tertiles

//	Total	CCR tertile 1	CCR tertile 2	CCR tertile 3	*P*
	n = 368634	n = 121649	n = 121652	n = 125333	
Age	58 (50, 63)	60 (54, 65)	58 (50, 63)	54 (47, 61)	< 0.001
Sex					< 0.001
Female	198310 (54)	100323 (82)	66023 (54)	31964 (26)	
Male	170324 (46)	21326 (18)	55629 (46)	93369 (74)	
Race					< 0.001
White	350986 (95)	115955 (95)	116696 (96)	118335 (94)	
Asian-British	7857 (2)	3386 (3)	2369 (2)	2102 (2)	
Black-British	4680 (1)	632 (1)	1040 (1)	3008 (2)	
Mixed	2051 (1)	569 (0)	645 (1)	837 (1)	
Other	3060 (1)	1107 (1)	902 (1)	1051 (1)	
BMI (Kg/m^2)	26.74 (24.19, 29.8)	27.33 (24.34, 31.15)	26.54 (23.99, 29.58)	26.49 (24.25, 29)	< 0.001
WC (cm)	90 (81, 99)	88 (79, 98)	89 (79, 99)	91 (83, 99)	< 0.001
Creatinine (umol/L)	70.4 (61.5, 80.5)	60.8 (55.1, 67.4)	69.9 (63.2, 77.3)	81.3 (73.6, 89.3)	< 0.001
Cystatin C (mg/L)	0.88 (0.8, 0.98)	0.93 (0.85, 1.03)	0.88 (0.8, 0.97)	0.85 (0.78, 0.93)	< 0.001
CCR	79.45 (70.37, 89.32)	66.67 (61.88, 70.27)	79.27 (76.35, 82.26)	93.6 (89.08, 100.24)	< 0.001
AST (U/L)	24.3 (21, 28.7)	23.8 (20.6, 28)	24.1 (20.9, 28.4)	25.1 (21.6, 29.5)	< 0.001
ALT (U/L)	20.11 (15.44, 27.19)	19.2 (14.95, 25.78)	19.7 (15.13, 26.76)	21.44 (16.36, 28.82)	< 0.001
GGT (U/L)	26.3 (18.6, 40.5)	25.1 (18.1, 39.2)	25.6 (18.1, 39.7)	28.1 (19.9, 42.3)	< 0.001
ALB (g/L)	45.23 (43.54, 46.94)	44.79 (43.12, 46.48)	45.24 (43.58, 46.92)	45.64 (43.97, 47.33)	< 0.001
T2DM					< 0.001
0	360043 (98)	117935 (97)	118998 (98)	123110 (98)	
1	8591 (2)	3714 (3)	2654 (2)	2223 (2)	
HbA1C (mmol/mol)	35.2 (32.8, 37.8)	35.9 (33.4, 38.5)	35.1 (32.7, 37.6)	34.6 (32.3, 37.1)	< 0.001
HDL (mmol/L)	1.4 (1.18, 1.67)	1.44 (1.21, 1.71)	1.41 (1.18, 1.69)	1.35 (1.15, 1.61)	< 0.001
LDL (mmol/L)	3.55 (2.99, 4.13)	3.64 (3.06, 4.24)	3.52 (2.97, 4.1)	3.48 (2.94, 4.05)	< 0.001
TG (mg/dL)	131.49 (93.5, 188.69)	137.69 (99.26, 193.47)	127.59 (90.94, 184.09)	129.01 (90.67, 188.16)	< 0.001
CHOL (mmol/L)	5.68 (4.95, 6.43)	5.84 (5.09, 6.61)	5.66 (4.94, 6.39)	5.54 (4.86, 6.27)	< 0.001

Continuous variables were presented as median (Q1, Q3). Categorical variables were presented as n (%). BMI, body mass index; WC, waist circumference; CCR, creatinine-to-cystatin C ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; ALB, albumin; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triacylglycerol; CHOL, cholesterol.

Association between CCR and MAFLD

In the univariate logistic regression analysis, older age; male sex; Black; T2DM; and higher BMI, WC, HbA1c, LDL, TG and cholesterol were significantly associated with MAFLD. Asian population and higher HDL levels were protective factors against MAFLD (Supplementary Table 2). The risks of CCR tertile 2 and CCR tertile1 were 0.925 (95%CI 0.91–0.94, *P*< 0.001) and 1.075 (95%CI 1.058–1.093, *P*< 0.001) compared with CCR-tertile 3. After adjusting with covariates, the risk of MAFLD in CCR tertile 1 (OR 1.333, 95%CI 1.273–1.396, *P*< 0.001) was significantly higher than that in people with higher CCR (OR 1.075, 95%CI 1.035–1.117, *P*< 0.001) (Table 2). Subgroup analysis stratified by sex, showed that people in CCR tertile1 still had the highest risk of MAFLD, and that the risk in females was higher than that in males (OR 1.395, 95% CI 1.290–1.510, *P*< 0.001 vs OR 1.355, 95% CI 1.265–1.452, *P*< 0.001) (Table 2).

Table 2
Logistic regression analysis for the association between CCR and MAFLD

	Unadjusted			Model 1			Model 2			Model 3			Mo
	OR	95%CI	*P*	OR	95%CI	*P*	OR	95%CI	*P*	OR	95%CI	*P*	OR
Total [1]													
CCR tertile 3	Reference			Reference			Reference			Reference			Ref
CCR tertile 2	0.925	0.91–0.94	< 0.001	1.459	1.432–1.485	< 0.001	1.420	1.394–1.447	< 0.001	1.309	1.281–1.337	< 0.001	1.0
CCR tertile 1	1.075	1.058–1.093	< 0.001	2.878	2.817–2.94	< 0.001	2.650	2.593–2.709	< 0.001	2.001	1.952–2.052	< 0.001	1.3
Male													
CCR tertile 3		Reference			Reference			Reference			Reference		
CCR tertile 2	1.489	1.458–1.521	< 0.001	1.481	1.449–1.513	< 0.001	1.438	1.407–1.470	< 0.001	1.284	1.252–1.317	< 0.001	1.0
CCR tertile 1	2.039	1.977–2.102	< 0.001	2.030	1.967–2.095	< 0.001	1.868	1.809–1.928	< 0.001	1.530	1.474–1.589	< 0.001	1.3
Female													
CCR tertile 3		Reference			Reference			Reference			Reference		
CCR tertile 2	1.710	1.644–1.778	< 0.001	1.735	1.667–1.806	< 0.001	1.716	1.647–1.787	< 0.001	1.562	1.493–1.633	< 0.001	1.1
CCR tertile 1	3.907	3.767–4.052	< 0.001	3.903	3.758–4.055	< 0.001	3.645	3.506–3.789	< 0.001	2.702	2.588–2.820	< 0.001	1.3

Model 1 adjusted for age, sex[1] and race.

Model 2 adjusted for age, sex[1], race, DMT2 and HbA1C.

Model 3 adjusted for age, sex[1], race, DMT2, HbA1C, HDL, LDL, TG and cholesterol.

Model 4 adjusted for age, sex[1], race, DMT2, HbA1C, HDL, LDL, TG, cholesterol, BMI and WC.

Association between CCR and the incidence of MAFLD in the prospective cohort

This prospective cohort included 8724 participants. The cohort was followed for a median 4.5 years (interquartile range, 3.7 to 5.0 years), and 1,077 participants (12.3%) developed MAFLD during this period. The risk of subsequent MAFLD was significantly higher in participants with a lower CCR than in those with a higher CCR (OR 1.212, 95%CI 1.015–1.447, $P = 0.034$; OR 1.340, 95%CI 1.077–1.669, $P = 0.009$). The association was more significant in males (OR 1.308, 95%CI 1.060–1.615, $P = 0.012$); vs (OR 1.642, 95%CI 1.158–2.329, $P = 0.005$) (Fig. 2A, Supplementary Table 3).

Association between CCR and MAFLD-related outcomes

To explore the effect of CCR on MAFLD severity, we analyzed the association between CCR and severe liver fibrosis. CCR was significantly associated with the risk of severe liver fibrosis in males, but not in females. Compared to males with low CCR levels, the risks of severe liver fibrosis in males with high CCR level were 1.139 (95%CI 1.030–1.260, P = 0.011) and 1.657 (95%CI 1.476–1.859, P < 0.001), respectively (Fig. 2B, Supplementary Table 4).

1083 of 139,002 MAFLD patients developed SLD during follow-up, with a median follow-up time of 9.19 years, interquartile range of 6.29 years and 10.83 years. Cox analysis showed that participants in CCR tertile 1 had the highest risk of MAFLD-related SLD (HR 4.23, 95%CI 3.54–4.05, $P < 0.001$) (Table 3), and the SLD cumulative incidence during follow-up was obviously higher than others (Fig. 3).

Table 3
Prospective Cox regression analysis of the relationship between CCR and SLD

	Unadjusted			Model 1			Model 2			Model 3			Model 4		
	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*
Total [1]															
CCR tertile 3	Reference			Reference			Reference			Reference			Reference		
CCR tertile 2	1.91	1.61–2.26	< 0.001	1.92	1.62–2.28	< 0.001	1.86	1.57–2.21	< 0.001	1.90	1.60–2.25	< 0.001	1.75	1.47–2.09	< 0.001
CCR tertile 1	4.08	3.49–4.76	< 0.001	5.41	4.55–6.43	< 0.001	4.84	4.07–5.76	< 0.001	4.90	4.11–5.83	< 0.001	4.23	3.54–5.05	< 0.001
Male															
CCR tertile 3	Reference			Reference			Reference			Reference			Reference		
CCR tertile 2	2.20	1.84–2.63	< 0.001	1.97	1.65–2.36	< 0.001	1.93	1.61–2.30	< 0.001	1.99	1.66–2.39	< 0.001	1.85	1.54–2.22	< 0.001
CCR tertile 1	6.78	5.67–8.10	< 0.001	5.73	4.78–6.87	< 0.001	5.18	4.31–6.22	< 0.001	5.31	4.42–6.38	< 0.001	4.56	3.77–5.50	< 0.001
Female															
CCR tertile 3	Reference			Reference			Reference			Reference			Reference		
CCR tertile 2	1.26	0.64–2.45	0.504	1.10	0.56–2.14	0.789	1.08	0.55–2.11	0.818	1.12	0.57–2.19	0.741	1.11	0.57–2.17	0.766
CCR tertile 1	3.83	2.10-7.00	< 0.001	2.83	1.54–5.20	0.001	2.56	1.39–4.70	0.002	2.69	1.46–4.95	0.001	2.53	1.37–4.66	0.003
Model 1 adjusted for age, sex [1] and race.															
Model 2 adjusted for age, sex [1], race, DMT2 and HbA1C.															
Model 3 adjusted for age, sex [1], race, DMT2, HbA1C, HDL, LDL, TG and cholesterol.															
Model 4 adjusted for age, sex [1], race, DMT2, HbA1C, HDL, LDL, TG, cholesterol, BMI and WC.															

Discussion

In this study, we explored the relationship between CCR and the risk of MAFLD in a large cross-sectional prospective population. We found that a low CCR was significantly associated with a high risk of MAFLD. This association remained significant, even after adjusting for potential confounding factors. Additionally, CCR was significantly associated with severe liver fibrosis. The risk of MAFLD and severe liver fibrosis in the lowest CCR tertile increased by 33.3% and 61.7%, respectively, compared to the highest CCR tertile. Similar to other studies on chronic obstructive pulmonary disease,[19] cancer,[12, 14] and fatty liver,[20–22] our results show that people with lower CCR have worse clinical outcomes. However, these studies had only a few hundred or thousand participants, while 368,634 participants were included in our analysis. Our results were further verified in a prospective cohort analysis. In the prospective analysis, people in CCR tertile 1 had higher incidences of MAFLD and SLD. Some studies have proved that males bore the greatest burden of all metabolic diseases,[23] and males had a higher risk of fatty liver disease, steatohepatitis[24] and liver fibrosis.[25] It was also observed in our study that the association of CCR with the risk of developing MAFLD, liver fibrosis, and SLD was more significant in males, who had a higher risk of developing these diseases. Therefore, people with sarcopenia or reduced CCR, especially males, should be alert to the development of MAFLD.

Serum creatinine and cystatin C are widely used as laboratory values to determine kidney function. Normally, if renal function was impaired, the amount of creatinine and cystatin C cleared through the kidney decreases, increasing their serum levels.[26, 27] In our study, patients with eGFR < 60 mL/min/1.73 m^2 were excluded, reducing the impact of renal function impairment. In a study that explored the relationship between CCR and mortality in patients with cancer, the association between CCR and mortality was significant even after adjusting for underlying AKI, suggesting that the relationship with prognosis was independent of kidney injury status.[26]

Epidemiological studies have shown that low skeletal muscle mass is associated with MAFLD.[21, 28] CCR represents muscle mass,[13] and the skeletal muscle is the primary tissue responsible for insulin-mediated glucose disposal, and the prominent role of skeletal muscle in insulin resistance has been confirmed.[8, 29, 30] Thus, sarcopenia may lead to MAFLD via insulin resistance. However, sarcopenia has also been linked to MAFLD independent of insulin resistance or obesity.[31] The skeletal muscle is an endocrine organ that secretes myokines that mediate crosstalk among metabolic tissues such as the liver.[32] Interleukin-6 (IL-6) is a myokine that has a protective effect against the development of MAFLD in a mouse model.[33] Meanwhile, a study by Naoki Mizuno et.al suggested that an increase in the ratio of skeletal muscle mass to body fat mass was correlated with a reduction in liver fat accumulation and liver damage[34]

Sufficient muscle mass can alleviate hepatic lipid accumulation by reducing free fatty acid levels in the blood.[35] Therefore, individuals with high muscle mass or CCR are at a low risk of developing MAFLD.

There are no approved pharmacotherapies for MAFLD, and the current treatment of choice is lifestyle modification including diet and exercise.[2] Increased skeletal muscle mass may be a promising treatment option for MAFLD.[36–38] Both creatinine and cystatin C can be measured quickly by blood sampling. CCR can be used to evaluate muscle mass more easily than MRI, CT, or other methods, which is a significant advantage for risk monitoring in large populations.

However, this study has some limitations. Due to the unavailability of hepatic imaging or biopsy data, we used the FLI to diagnose MAFLD. Although FLI is a simple and commonly accepted indicator of human fatty liver disease in the absence of imaging and histological data,[39, 40] liver biopsy is the gold standard for diagnosing liver steatosis. Second, we adjusted for several confounding factors in the multivariate analyses; however, other unknown factors might also have influenced the results. Last, most participants in this study were European, and the conclusions may not be generalizable to other ethnic populations. We hope to validate our results in other populations in the future.

Conclusion

Our results indicated that lower CCR was significantly associated with higher risk of MAFLD. Moreover, CCR can predict the risk of MAFLD-related SLD and severe liver fibrosis, which can potentially be used as a large-scale non-invasive tool to dynamically monitor the occurrence and development of MAFLD.

Declarations

Ethics approval and consent to participate The study was conducted in accordance with the Declaration of Helsinki. UK Biobank was approved by the North West Multi-Centre Research Ethics Committee (Ref: 11/NW/0382), and all participants provided written informed consent to participate in the UK Biobank study. The study protocol is available online (http://www.ukbiobank.ac.uk/). This work was conducted using the UK Biobank resource under project number 92668.

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

Competing interests The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author's contributions: Jiaren Wang, Lin Zeng, Chang Hong, Hao Cui and Hongbo Zhu participated in the design of the study, interpreted the data, and drafted the manuscript. Qimei Li, Yan Li, Ruining Li and Jingzhe He critically revised the manuscript for important intellectual content. Hong Zhu, Li Liu and Lushan Xiao participated in the design of study, data download, statistical analyses, and supervised the study. All authors have made a significant contribution to this study and have approved the final manuscript.

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Figures

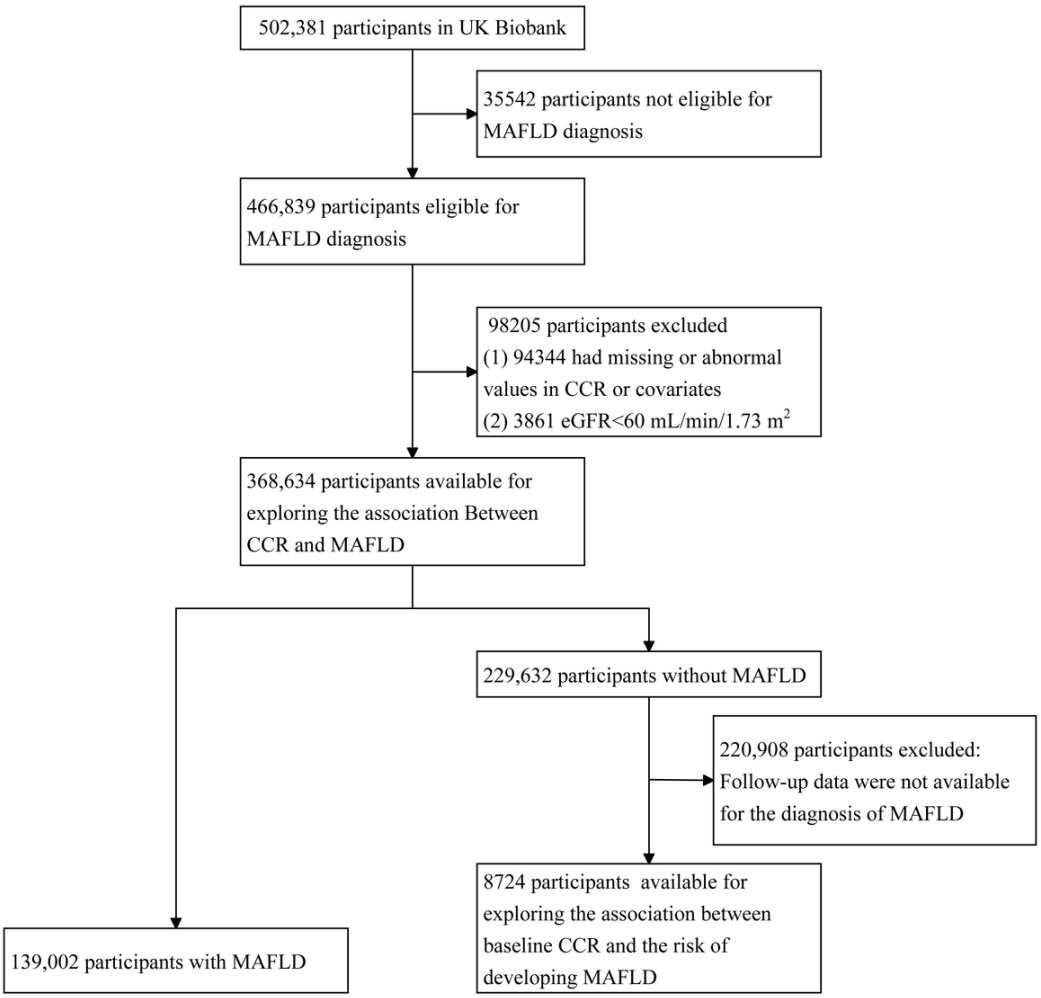


Figure 1

Flowchart of the participants selection process in the study

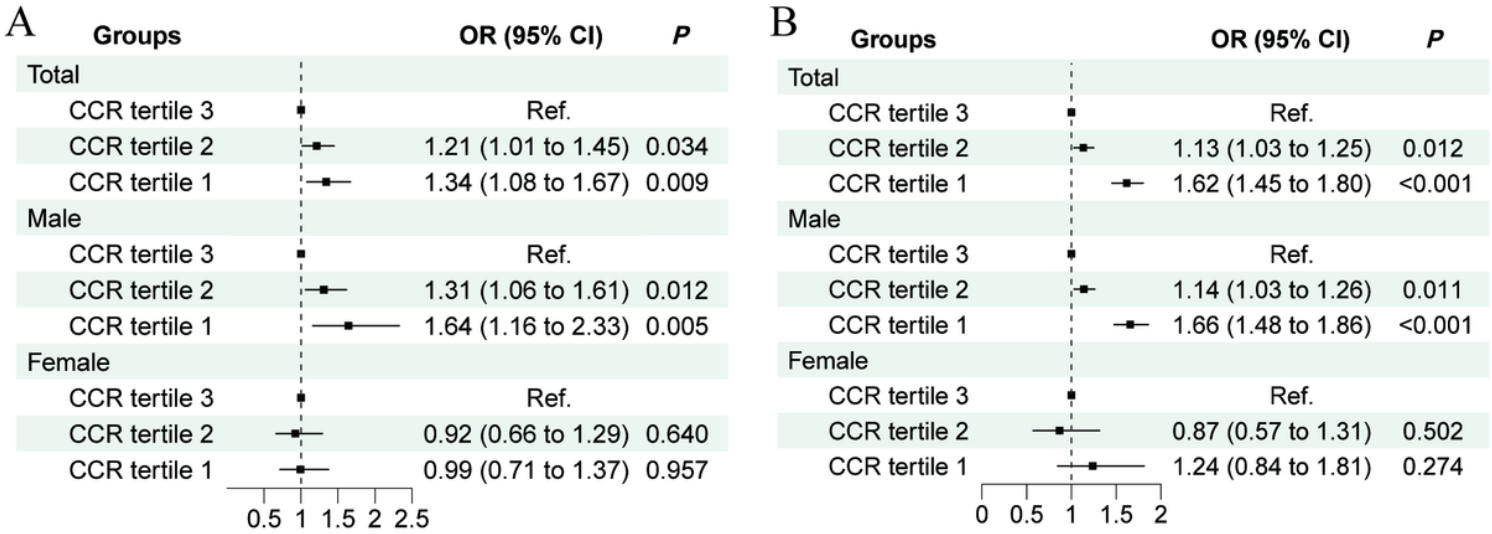


Figure 2

(A) Association of CCR with MAFLD in prospective cohort adjusted for the Model 4; (B) Association of CCR with severe liver fibrosis adjusted for the Model 4

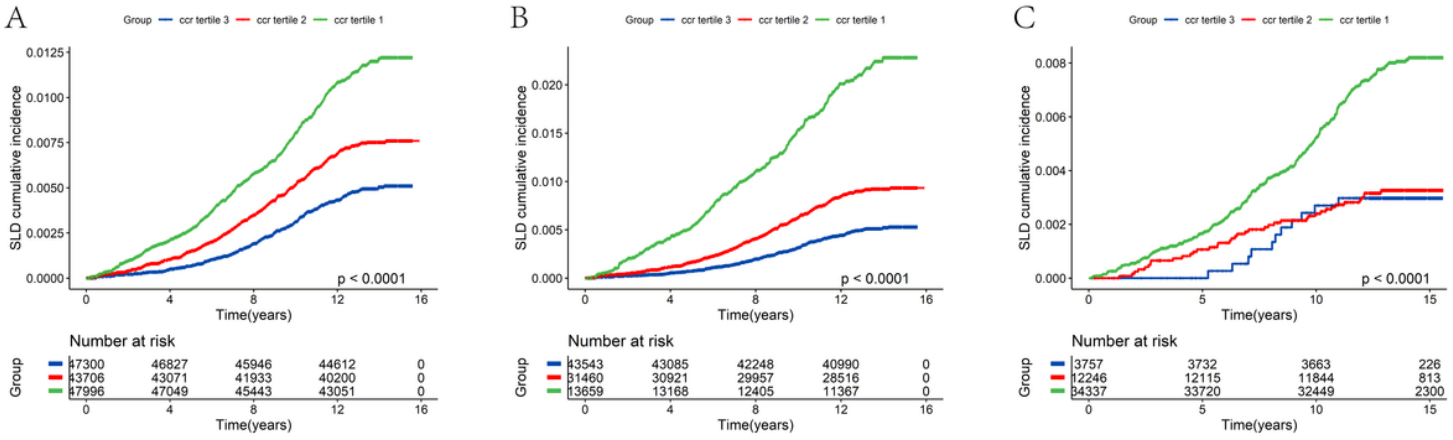


Figure 3

Association of CCR with the SLD cumulative incidence. (A) Total; (B) Males; (C) Females

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