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Metabolic dysfunction-associated fatty liver disease can significantly increase the risk of chronic kidney disease in adults with type 2 diabetes

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ABSTRACT

Aims: This study is to explore the relationship between metabolic dysfunction-associated fatty liver disease (MAFLD) and chronic kidney disease (CKD) among populations with type 2 diabetes through longitudinal cohort study.

Methods: 3,627 subjects who had received at least three health examinations between 2008 and 2015 were included. CKD was stated as subjects with an eGFR < 60 mL/min per 1·73 m2 or the occurrence of 2 or more proteinuria during their follow-up.

Results: After median of 10·0 years follow up, 837 (23·1%) developed CKD (244·7 per 10,000 person-years; 95 % CI, 228.4 − 261·8). MAFLD ([HR] 1·46; 95 % CI 1·26-1·70, P < 0.001) acts as an important risk factor of developing CKD. After adjusting for confounding factors, this association was consistent (HR 1·30; 95 % CI 1·11-1·53, P < 0.001). In stratified analysis, subjects aged < 60 years were likely to have greater risk of MAFLD-related CKD (HR 1·58 and 1·03; 95 % CI 1·28-1·95 and 0·79-1·33, P < 0.001 in both cases, respectively).

Conclusions: The risk of developing CKD in type 2 diabetes adults with MAFLD was higher, especially if they are below 60 years old. This study underscores the importance of early prevention strategies for MAFLD to reduce the occurrence of CKD in type 2 diabetes adults.

1. Introduction

Type 2 diabetes is an important public health problem threatening the global adult health that as a non-communicable disease and its prevalence has increased year by year. Type 2 diabetes can progress to a variety of macrovascular and microvascular complications that can lead to death in patients [1]. A mathematical model study showed that the prevalence of type 2 diabetes in 20–79 year olds is anticipated to increase from 10·5% in 2021 to 12·2% in 2045, with approximately 783 million people being affected [2].

Chronic kidney disease (CKD) is another public health problem of global concern which affecting 10 % of adults [3]. CKD is a preventable and treatable disease and global health policies should be developed in order to reduce its incidence [3]. In addition, CKD eventually progresses towards end-stage kidney disease (ESKD) that eventually requires renal transplant, and inevitably reduces the life expectancy of patients. As present, approximately 2·5 million people receive kidney transplants, and that number will more than double by 2030 [4]. The prevalence of CKD is about 10.8 % among the huge Chinese adult population [5]. CKD progressively leads to an irreversible decline in the functions of the kidneys. It is estimated that about 40 % of the type 2 diabetes population will progress to CKD [6]. Therefore, there is a urgent need to keep the CKD from adults with type 2 diabetes through appropriate interventions.

According to previous guidelines, non-alcoholic fatty liver disease (NAFLD) is diagnosed when the liver fat exceeds 5 % of the liver weight after excluding for other competing factors such as the consumption of alcohol excessively and the presence of hepatitis [7]. Approximately 25 % of adults worldwide currently have NAFLD [8]. In China, NAFLD

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occurs in approximately 30 % of adults probably, and the prevalence is more pronounced in those living in urban when compared to rural areas. This condition is known to be more common in the male population [9]. There are many metabolic risk factors that are shared between NAFLD and CKD and these include type 2 diabetes, overweight, dyslipidemia and hypertension [10]. In subjects with NAFLD, 20 to 55 % will progress to CKD, whereas in the general population this is reduced to 5 to 35 %. Studies have shown that NAFLD may also be one of the independent risk factors for developing CKD [11–15].

Due to the limitations of its definition in its practical clinical application, NAFLD is recognized only as a metabolic liver disease. In 2020, several experts from various countries around the world suggested a new definition of MAFLD [16]. According to the latest MAFLD definition criteria, a patient with MAFLD can be defined as having a confirmed fatty liver and being either overweight or obese as well as having type 2 diabetes or a metabolic disorder [17]. The definition of MAFLD reflects on liver disease being theresult of a complex set of metabolic disorders and it can coexist with either excessive drinking or with other chronic liver complications [18,19]. Notably, there is growing evidence that MAFLD patients are more likely to have multiple metabolic diseases, more severe liver fibrosis and greater risk of CKD when compared to subjects with NAFLD [20,21].

Since MAFLD has a more convenient definition and clinical application, exploring the relationship between MAFLD and CKD will lead to better prevention of CKD. However, the long-term impact of MAFLD on the occurrence and development of CKD in patients with type 2 diabetes remains unclear. This is of great significance for formulating intervention measures to manage type 2 diabetes patients with MAFLD and reduce complications of diabetes. However, there is few study on explore whether MAFLD will contribute to the development of CKD in adults with type 2 diabetes. Clinical practice and public health could both benefit from resolving this problem. The conclusions of such studies would help to formulate intervention measures for type 2 diabetes to reduce the occurrence of complications. Therefore, this retrospective large-scale, 14-year longitudinal follow-up cohort study was to observe the effect of MAFLD on the development of CKD in adults with type 2 diabetes.

2. Methods

2.1. Study design and subjects

We used an Active Health Management Platform to construct a retrospective cohort study (https://www.chictr.org.cn/index.aspx; registration number: ChiCTR2200058543). Briefly, the Active Health Management Platform uses an advanced medical data management system to monitor subjects and to link and index all their consultation records held by the hospital. It contains outpatient, inpatient and physical examination data, covering consultation records, test reports, examination reports, electronic medical records and other medical data for all the outpatient, inpatient and physical examination subjects. When a patient comes to the clinic, the medical information generated is automatically integrated into this platform. Subjects who had at least three health examinations at the People's Hospital of Guangxi Zhuang Autonomous Region, China, between 2008 and 2015 were selected for this cohort (n = 49719). We set the date of the first health examination as the index date. Adult subjects with the following characteristics will be excluded: 1) lack of data on demographic characteristics, 2) baseline estimated glomerular filtration rate (eGFR) < 60 mL/min per 1·73 m2 or a higher level of proteinuria, 3) failure to meet type 2 diabetes diagnostic criteria, 4) lack of laboratory test data for the diagnosis of MAFLD and 5) follow-up time < 1 year. 3,627 subjects were used in this project for data analysis (Fig. 1).

This study was conducted in accordance with the guidelines of the approved Helsinki Declaration and was approved by the Ethics Committee of t the People's Hospital of Guangxi Zhuang Autonomous Region, China. Informed consent was not needed because this study involved the use of retrospectively collected data which were anonymized.

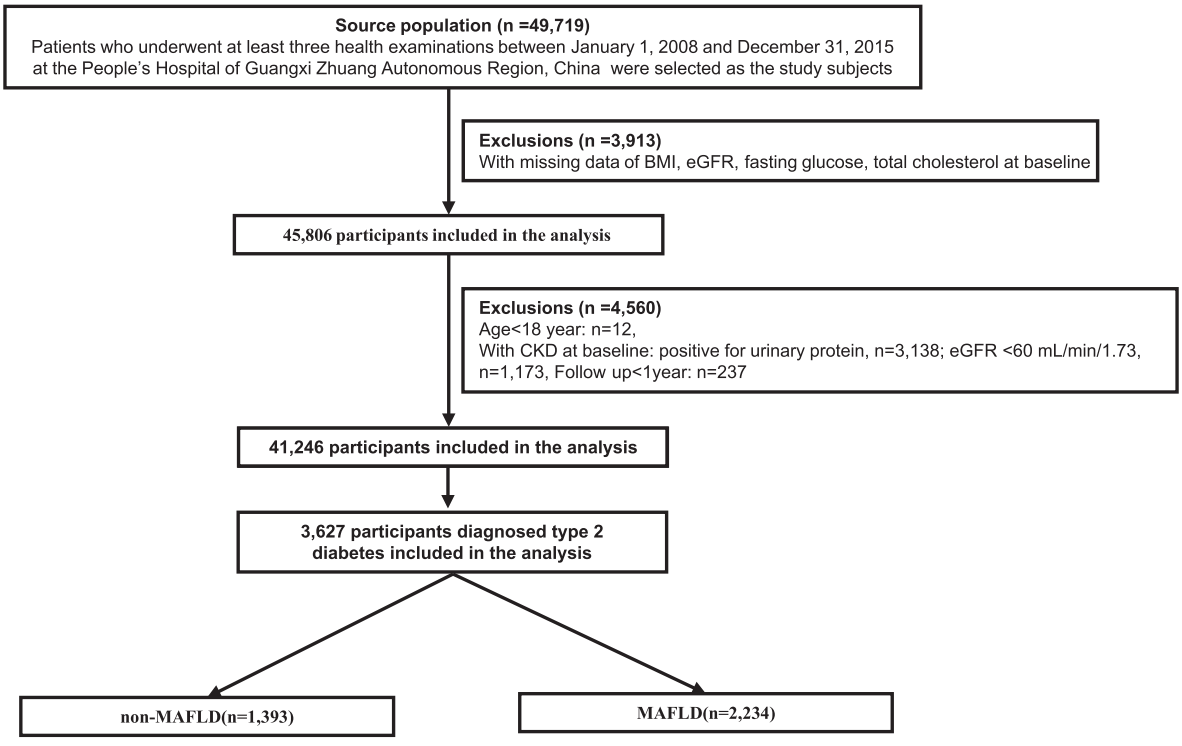

Fig. 1. Flow chart for the selection of participants from the Active Health Management Platform.

2.2. Ascertainment of MAFLD

We use ultrasound images to diagnose fatty liver according to the Asia-Pacific Guidelines [22]. Subjects both have fatty liver and type 2 diabetes were diagnosed MAFLD [17].

2.3. Data collection and measurements

Baseline demographic characteristics, imaging characteristics and laboratory test data were retrieved from the Active Health Management Platform. If data were missing at the index date, the data closest to the index date were entered. The Chronic Kidney Disease Epidemiology Collaboration equation for eGFR served as a measure kidney function [23]. The covariates assessed in the study included BMI at baseline, hypertension, type 2 diabetes and dyslipidemia. BMI was categorized as normal weight (<23) and overweight and obese (≥23). Systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg were judged as having hypertension. In addition. fasting blood glucose ≥ 7·0 mmol/L or HbA1c ≥ 6·5 were judged as type 2 diabetes. LDL cholesterol ≥ 2·6 mmol/L or triglycerides ≥ 1·7 mmol/L were judged as dyslipidemia. All laboratory tests and examinations were carried out in the laboratory of the health examination hospital.

2.4. Outcome of study

Participants with the onset of CKD or proteinuria were followed from enrollment until their last health examinations or medical visit. A censored event is a failure to follow up or the termination of the study. The primary outcomes included the occurrence of CKD, which was defined as subjects who either had an eGFR < 60 mL/min/1·73 m^2 or the occurrence of 2 or more incidents of proteinuria by the dipstick method during the follow-up period.

2.5. Statistical analysis

Medians and interquartile ranges (IQRs) are used to represent continuous variables, while numbers and percentages are used to represent categorical variables. In order to compare continuous variable baseline data between MAFLD and non-MAFLD groups, the Mann-Whitney *U* test was used, and to compare categorical baseline data between MAFLD and non-MAFLD groups, the chi-square test was used.

The incidence rates of CKD were computed by dividing the number of new CKD cases by the number of person-years contributed by people at risk during the follow-up time. CKD incidence between MAFLD and non-MAFLD was estimated using Kaplan-Meier analysis, and using log-rank tests to compared the differences between the two groups. A Cox hazard model was used to calculate the hazard ratios (HRs) and 95 % confidence intervals (CIs) for the risk between MAFLD and CKD. In this study, Schoenfeld residuals were used as a means of confirming the proportional hazards assumption. Covariate selection and other potential confounders were identified using a backward selection procedure and literature data, respectively [21]. The covariates in Model 1 were not adjusted, age and gender are adjusted in Model 2 and additional adjustments were made for comorbidities such as hypertension, dyslipidemia, and overweight/obesity in model 3. A further adjustment was made for basal eGFR levels, aspartate aminotransferase (AST), LDL and alanine aminotransferase (ALT) in Model 4.

Finally, several subgroup analyses were performed using pre-specified subgroups of age (<60 versus ≥ 60 year-olds), gender (males versus females), overweight/obesity (BMI < 23 versus BMI ≥ 23 kg/m2) and LDL (<2·6 versus ≥ 2·6 mmol/L), presence of hypertension (no versus yes) and dyslipidemia (no versus yes). SPSS 18 and R software (version 3.3.2) packages were used for statistical analysis. The *P* values were double-tailed, and a significance level of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Subject characteristics of baseline

Among the 3, 627 type 2 diabetes subjects (median [IQR] age 50·0 [43·0-57·0] years, 68·5% male), the prevalence of MAFLD among type 2 diabetes subjects was 61·6%. 837 (23·1%) developed CKD during follow-up. Subjects with new cases of CKD were more likely to be elderly, either overweight or obese, hypertensive, MAFLD and have a higher BMI, waist circumference, fasting glucose, creatinine and have a lower eGFR than subjects who did not have evidences in CKD in the follow-up (Table 1).

3.2. CKD outcome event rates and associations with MAFLD

During the median follow-up time of 10·0 years (IQR: 7·4-12·0 years), there were 34,206·9 person-years and CKD occurred in 837 (23·1%) subjects (244·7/10,000 person-years; 95 % CI, 228·4-261·8). In MAFLD patients, the incidence of CKD was 192·2/10,000 person-years (169·4-217·1) compared with 278·6/1000 person-years (256·4-302·3)

Table 1
Baseline clinical and biochemical characteristics of the cohort stratified by presence of incident CKD at follow-up.

Characteristic	Whole cohort (n = 3,627)	No incident CKD (n = 2,790)	Incident CKD (n = 837)	P-value
Age years	50·0 (43·0-57·0)	48·0 (42·0-56·0)	55·0 (47·0-64·0)	<0.001
Gender, men (%)	2483 (68·5%)	1888 (67·7%)	595 (71·1%)	0.062
BMI kg/m^2	25·5 (23·6-27·6)	25·3 (23·5-27·4)	25·9 (23·9-28·1)	<0.001
Waist circumference cm	90·0 (85·0-96·0)	90·0 (85·0-95·0)	92·0 (87·0-98·0)	<0.001
Systolic blood pressure mmHg	132·0 (121·0-145·0)	131·0 (120·0-143·0)	137·0 (126·0-153·0)	<0.001
Diastolic blood pressure mmHg	80·0 (73·0-88·0)	80·0 (72·0-88·0)	82·0 (74·0-90·0)	<0.001
Fasting glucose, mmol/L	6·5 (6·1-7·2)	6·5 (6·0-7·1)	6·7 (6·3-7·9)	<0.001
ALT U/L	24·0 (18·0-35·0)	24·0 (18·0-35·0)	24·0 (18·0-35·0)	0.439
AST U/L	23·0 (19·0-28·0)	23·0 (19·0-28·0)	23·0 (19·0-28·0)	0.975
GGT U/L	32·0 (21·0-53·0)	31·0 (21·0-52·0)	34·0 (21·0-56·0)	0.188
TC mmol/L	5·3 (4·7-6·0)	5·3 (4·7-6·0)	5·3 (4·7-6·0)	0.875
HDL cholesterol mmol/L	1·2 (1·0-1·4)	1·2 (1·0-1·4)	1·2 (1·0-1·4)	0.073
TG mmol/L	1·7 (1·1-2·7)	1·7 (1·1-2·7)	1·8 (1·1-2·8)	0.115
LDL cholesterol mmol/L	3·5 (2·9-4·0)	3·5 (2·9-4·0)	3·5 (3·0-4·0)	0.681
Creatinine μmol/L	76·0 (64·0-86·0)	76·0 (64·0-85·0)	78·0 (67·0-89·0)	<0.001
eGFR mL/min/1·73 m2	96·2 (85·4-105·3)	97·6 (87·5-106·1)	89·7 (78·3-102·1)	<0.001
Hypertension	1410 (38·9%)	988 (35·4%)	422 (50·4%)	<0.001
Dyslipidemia	2647 (73·0%)	2051 (73·5%)	596 (71·2%)	0.188
Overweight/obesity	2969 (81·9%)	2259 (81·0%)	710 (84·8%)	0.011
MAFLD	2234 (61·6%)	1655 (59·3%)	579 (69·2%)	<0.001

Values are expressed as medians and interquartile ranges (IQRs) or number (%). Abbreviations: BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; MAFLD, metabolic dysfunction-associated fatty liver disease.

in subjects without MAFLD. Patients with MAFLD had higher HRs for CKD than the ones without MAFLD, with HRs for CKD of 1·46 (95 % CI 1·26, 1·70), 1·41 (95 % CI 1·22-1·64), 1·28 (95 % CI 1·09-1·50) and 1·30 (95 % CI 1·11-1·53) for Models 1 to 4, respectively (Table 2). According to the Kaplan-Meier analysis that the patients with MAFLD showed a significantly greater cumulative incidence of CKD than in those with no MAFLD ($P < 0.001$) (Fig. 2).

3.3. Subgroup analysis

Subgroup analysis revealed that the MAFLD-related CKD risk was stronger among subjects who were aged below 60 years old than those equaled to or greater than 60 years (P values for interactions = 0.013). However, no significant heterogeneity was found in the other subgroups (all P values for interactions greater than 0.05) (Fig. 3).

4. Discussion

In this 14-year retrospective cohort study of Chinese subjects with type 2 diabetes, we found that the risk of a new episode of CKD in subjects with MAFLD during follow-up were higher when compared with subjects without MAFLD. The results were consistent after adjusting for confounding factors such as demographic characteristics, comorbidities and laboratory tests. In addition, we found subjects aged < 60 years old were at greater risk of MAFLD -related CKD than subjects aged ≥ 60 years.

The present study provides further evidence for long-term outcomes between MAFLD and CKD [21,24–26]. A study from a cohort with a median of 5·1 years follow-up showed that participants with MAFLD had a 39 % greater risk in the development of CKD than those without MAFLD (HR 1·39; 95 % CI 1·33-1·46) [21]. Another cohort study with a 6·3 years median follow-up using a health examinations database also revealed that subjects with MAFLD showed a 1·12-fold higher risk of developing CKD when compared with those without MAFLD (HR 1·12; 95 % CI 1·02-1·26) [24]. In addition, a cohort study from China showed that subjects with MAFLD were at greater risk in the development of CKD (RR 1·64; 95 % CI 1·39-1·94). The mean follow-up of that study was 4·6 years [26]. A Japanese retrospective cohort study also showed that MAFLD was related to a 24 % higher risk of developing CKD (HR 1·24; 95 % CI 1·14-1·36) [25]. Our findings are similar to the studies described above, in which type 2 diabetes subjects with MAFLD account for an approximately 30 % greater occurrence of CKD when compared to subjects without MAFLD when other factors are adjusted. The results of subgroup analyses reached the same conclusion eadjusted for other factors, suggesting that MAFLD plays a significant role in the development of CKD in adults with type 2 diabetes without regards to their metabolic status.

Notably, our study extends the previous findings to type 2 diabetes subjects. This has important public health implications for interventions to prevent associated complications in type 2 diabetes patients. The occurrence of both MAFLD and type 2 diabetes is increasing and these are conditions are becoming a major public health crisis leading to increased mortality [2]. CKD leads to an irreversible decline of the normal functions of the kidneys and it progresses slowly, and eventually progresses to ESKD, when it may require dialysis treatment. There is also a high risk of mortality and morbidity associated with it [3]. Approximately 40 % of type 2 diabetes patients will develop CKD [27]. Our findings provide new evidence regarding the longitudinal association of MAFLD and CKD in adults with type 2 diabetes, suggesting that type 2 diabetes subjects with MAFLD have a higher risk of developing CKD and should optimize their renal function prevention strategies. These findings emphasize that early prevention of MAFLD in type 2 diabetes subjects is very important. They provide a reliable and convincing basis for the developing preventive measures against both type 2 diabetes and MAFLD. Studies have shown that population-specific systematic intervention strategies, such as strict implementation of treatment guidelines for hypertension and diabetes, provision of better nutrition, physical activity and health education services, regular testing for albuminuria and the regular medications, including ACE inhibitors and ARBs, can help to reduce diabetes-related renal failure by 54 %[28].

Studies that explore the mechanisms underlying the relationship of MAFLD and CKD are rare. According to the latest definition, a fatty liver in type 2 diabetes subjects is judged as MAFLD. Therefore, the possible mechanism of how MAFLD contributes to the incident of CKD among adults with type 2 diabetes can be explained by NAFLD studies. Firstly, studies have shown that polymorphisms in genes including *PNPLA3*, *HSD17B13*, *TM6SF2*, *MBOAT7* and *GCKR* might play important roles during the development from NAFLD to CKD [20]. Secondly, it has been shown that there is a correlation between high levels of circulating fatty acid binding protein 4 (FABP4) and MAFLD [29]. FABP4, secreted by adipocytes, plays a vital role in insulin resistance, atherosclerosis and vascular remodeling by acting as an adipokine [30]. There is also evidence that FABP4 is linked with glomerular damage, tubule-interstitial injury [31] and reduced eGFR [32]. MAFLD patients have been reported to show dysregulated adipokines, including decreased adiponectin and increased FABP4 [29], and reduced eGFR [33]. Thirdly, it was shown that the gut–liver–kidney signaling axis, which affects microbiota of the gut and intestinal barrier integrity, can be used to explain how NAFLD progresses to CKD [34,35]. The gut microbiota acts as a greatly versatile ecosystem that influences physiological processes in different hosts. Symbiotic and probiotic organisms as well as some food components can produce metabolites such as uremic toxins by altering the diversity of the intestinal microbiota. These metabolites require aggressive renal clearance and they can also affect kidney and liver functions. Finally, hyperglycemia itself can lead to structural changes in the kidney, such as thickened glomerular basement membranes, loss of endothelial cell fenestration, expansion of the thylakoid matrix, podocyte detachment and pedicle detachment [36]. Therefore, adults type 2 diabetes with MAFLD are in a greater risk of developing CKD if they have poor glycemic control.

This study is the first study to exploration the role of MAFLD in the development of CKD in adults with type 2 diabetes by constructing a longitudinal cohort study. However, there are several limitations in this research. Firstly, there is a possibility of selection bias in this study

Table 2
Risk of incident chronic kidney disease in participants with and without MAFLD.

Group	Events	Person-Years	Incidence Rate (per 10,000 person-years)	Hazard Ratio (95 % confidence interval)							
				Model 1	P-value	Model 2	P-value	Model 3	P-value	Model4	P-value
non-MAFLD	258	13427·3	192·2(169·4-217·1)	Reference		Reference		Reference		Reference	
MAFLD	579	20779·6	278·6(256·4-302·3)	1·46 (1·26-1·70)	<0.001	1·41(1·22-1·64)	<0.001	1·28(1·09-1·50)	<0.001	1·30(1·11-1·53)	<0.001

Model 1 was unadjusted.
Model 2: Total group adjusted for age and sex.
Model 3: model 2, with additional adjustments for hypertension, dyslipidemia and overweight/obesity.
Model 4: model 3, with additional adjustments for LDL, AST, ALT and basal eGFR.

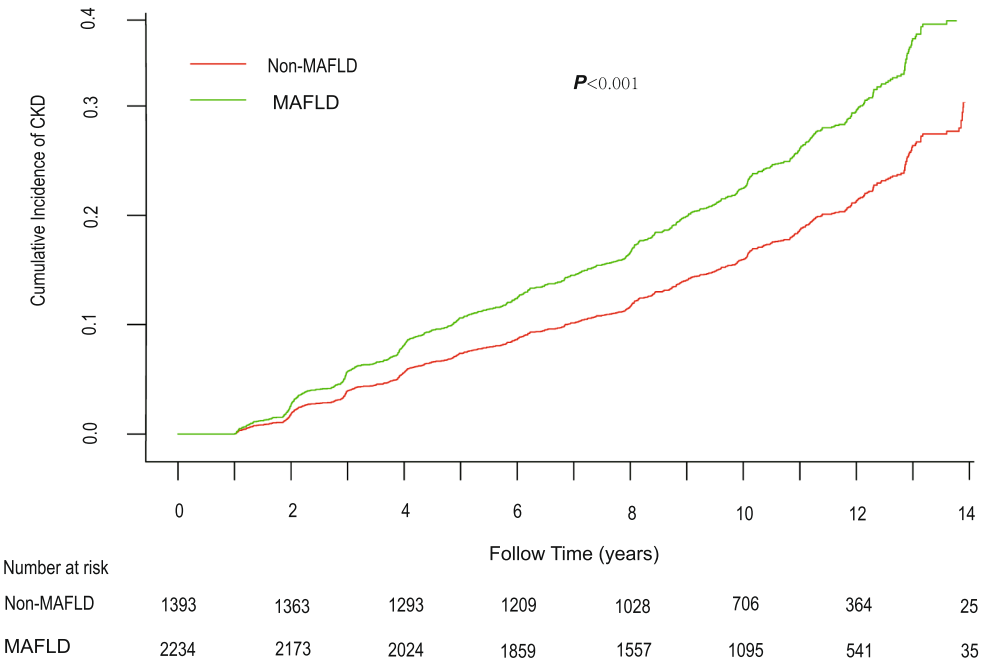

Fig. 2. The cumulative incidence of chronic kidney disease. Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease.

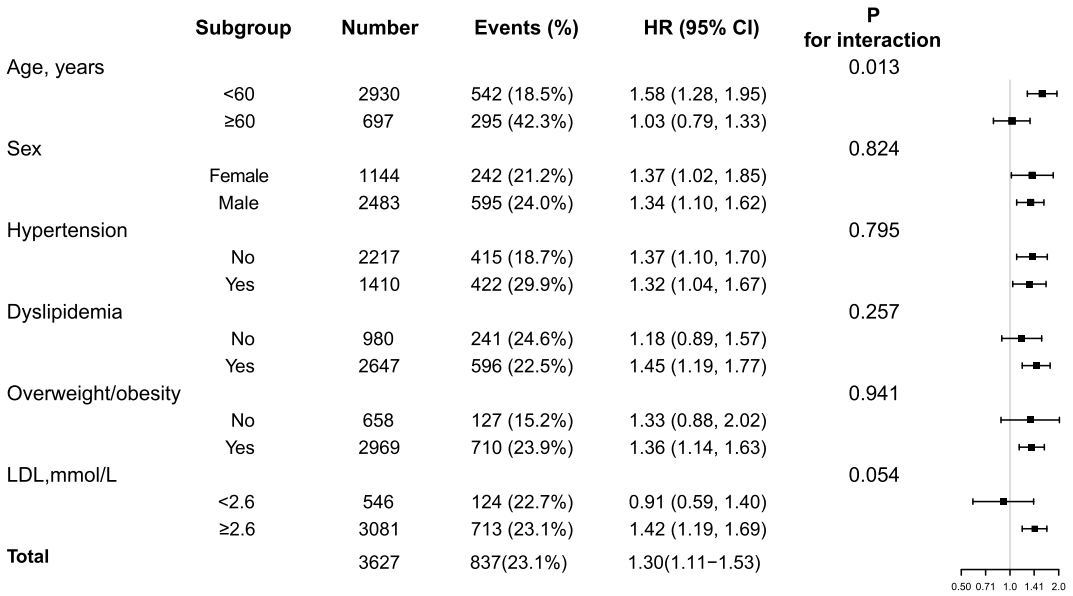

Fig. 3. Forest plots showing the effect of metabolic-dysfunction associated fatty liver disease on the incidence of chronic kidney disease. Abbreviations: HR, hazard ratio; CI, confidence interval. Each stratification was adjusted for all the factors (age, sex, hypertension, dyslipidemia, overweight/obesity, diabetes mellitus, LDL, AST, ALT and creatinine) except the stratification factor itself.

because the subjects were residents of urban areas who received consecutive annual health examinations at a hospital, and we excluded 1927 individuals due to lack of MAFLD diagnostic data. Secondly, a liver biopsy is the preferred approach to identify a fatty liver, but this procedure was not performed in individuals undergoing health examinations because of its invasive nature. However, in large-scale epidemiological studies, the use of ultrasound which has both high sensitivities and specificities, has been used to diagnose fatty livers successfully [37] and it is therefore the preferred modality for detecting hepatic steatosis due to low cost, ease of use and non-invasive nature [38]. Thirdly, subjects were not tested for proteinuria quantitatively in this study, so only qualitative methods were used to assess this parameter. In addition, some subjects with acute renal injury may be classified as CKD due to the examination of renal function according to the annual health examination. Fourthly, in this study, we did not collect some data to diagnose metabolic abnormalities, such as insulin, standard oral glucose tolerance test and high-sensitivity C-reactive protein level. Hence, some MAFLD subjects were likely to have been used for the analysis. Fifth, the severity of hepatic steatosis was not considered. Sixth, because metabolic abnormalities vary with the subject's lifestyle and are a dynamic process, judging these parameters based on the baseline metabolic status does not always reflect its true level. Seventh, this study was not able to adequately collect subjects' concomitant therapy, such as use of ACE-inhibitors/sartans, diuretics, statins and

anti-diabetic drugs, therefore the impact of concomitant therapy on outcomes could not be assessed. In addition, changes in the follow-up time of baseline characteristics of the subjects were not included in the statistical analysis; therefore, the impact of changes in baseline characteristics over time on outcomes could not be assessed either. Eighth, the results presented here were obtained from a Chinese adult population undergoing physical health examinations, and the results cannot be extrapolated to others around the world. Similar studies based on different metabolic risk factors in other regions worldwide are needed to validate the results of this study. Finally, because this study was observational and retrospective, residual confounding factors are a potential limitation. The causal relationship remains to be further explored.

5. Conclusion

This study suggested that type 2 diabetes patients with MAFLD had greatly risk of developing CKD, especially for patients who are younger. These findings confirm the importance of interventions for early prevention of MAFLD. This may significantly reduce the incidence of type 2 diabetes complications, thereby reducing the burden of the disease.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region, China. It was conducted according to the approved guidelines and the Declaration of Helsinki. Informed consent was not needed because this study invoved the use of retrospectively collected data which were anonymized.

Consent for publication

All authors have read and approved the manuscript for publication.

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CRediT authorship contribution statement

Suosu Wei: Conceptualization, Methodology, Investigation, Supervision, Writing – original draft, Writing – review & editing. **Jian Song:** Methodology, Investigation, Visualization, Supervision, Writing – original draft, Writing – review & editing. **Yujie Xie:** Methodology, Investigation, Visualization, Writing – review & editing. **Junzhang Huang:** Methodology, Investigation, Visualization, Writing – review & editing. **Jianrong Yang:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2023.110563.

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