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Association between the fatty liver index and chronic kidney disease: the population-based KORA study

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ABSTRACT

Background. We aimed to evaluate the relationship of fatty liver, estimated by the fatty liver index (FLI), with kidney function and chronic kidney disease (CKD) in a German cohort study, given the lack of prospective evidence in Europeans.

Methods. We included 2920 participants (51.6% women, mean age 56.1 years) from the KORA study, of which 1991 were followed up for an average of 6.5 years (± 0.3). Kidney function was assessed using the glomerular filtration rate estimated by creatinine (eGFR-Cr) or cystatin C (eGFR-cC). We used multiple logistic or linear regressions to evaluate the associations between the FLI, kidney function and CKD (eGFR < 60 ml/min/1.73 m^2) and mediation analysis to explore the mediation effects of metabolic factors.

Results. The prevalence of FLI ≥60 and CKD was 40.4% and 5.6% at baseline, respectively, and 182 participants developed CKD during the follow-up. Cross-sectionally, FLI was significantly inversely associated with eGFR-cC {$\beta = -1.14$ [95% confidence interval (CI) −1.81 to −0.47]} and prevalent CKD based on eGFR-cC [OR 1.28 (95% CI 1.01–1.61)], but not with other markers. After adjusting for lifestyle factors, we found a positive association between FLI and incident CKD defined by eGFR-cC or/eGFR-Cr, which was attenuated after controlling for metabolic risk factors. Mediation analysis showed that the association was completely mediated by inflammation, diabetes and hypertension jointly.

Conclusion. The positive association between FLI and CKD incidence was fully mediated by the joint effect of metabolic risk factors. Future longitudinal studies need to explore the chronological interplay between fatty liver, cardiometabolic risk factors and kidney function with repeated measurements.

Keywords: cardiometabolic risk factors, chronic kidney disease, European cohort, fatty liver index, mediation analysis

INTRODUCTION

Chronic kidney disease (CKD) affects 8–16% of the population in developed countries and its prevalence continues to increase worldwide, accelerated by the increase in metabolic risk factors such as diabetes, hypertension and obesity [1, 2]. Nevertheless, the management of traditional cardiometabolic risk factors has shown limited efficacy in curtailing the incidence of CKD [1]. Kidney function at its late stage represents an independent risk factor for cardiovascular morbidity, mortality and decreased quality of life, with a high burden on healthcare systems [2].

Fatty liver, a condition characterized by ectopic fat accumulation in the hepatic cells [3], is closely related to a spectrum of cardiometabolic risk factors involved in the pathophysiology of CKD and represents a potential novel modifiable risk factor for CKD [4]. Indeed, cross-sectional studies have shown a 2- to 10-fold increased prevalence of CKD among people with fatty liver compared with those without [5]. However, longitudinal evidence relating fatty liver to incident CKD in the general population is controversial and largely limited to Asian populations [6–10]. Due to genetic predisposition and environmental factors, discrepancies have arisen between populations with different ethnic backgrounds

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KEY LEARNING POINTS

What is already known about this subject?

- People with fatty liver are at higher risk of developing chronic kidney disease (CKD), but it is still debatable if fatty liver constitutes an independent risk factor for CKD.
- Cardiometabolic conditions, such as diabetes and hypertension, are commonly involved in the pathogenesis of both fatty liver and CKD.
- The longitudinal evidence on the association between fatty liver and incident CKD has been contradictory and largely restricted to Asian populations.

What this study adds?

- In a large German cohort study, we found a positive association between fatty liver estimated by the fatty liver index (FLI) and CKD development after adjusting for lifestyle factors, but additional adjustment for cardiometabolic risk factors attenuated this association.
- The putative positive association between increased FLI and the risk of CKD was completely mediated by metabolic risk factors, i.e. diabetes, hypertension and inflammation, concomitant to fatty liver.

What impact this may have on practice or policy?

- Continuous clinical monitoring and management of accompanying comorbidities such as diabetes and hypertension in people with or at increased risk for fatty liver is recommended in order to prevent the development and progression of CKD.
- The use of easy and cost-effective indices (such as FLI) to estimate fatty liver risk in ambulatory or low-resource settings could help identify people who require close cardiometabolic monitoring as a measure for CKD prevention.

[11]. European population studies are limited by their low number of subjects and by their selective samples (e.g. hospitalized patients) [12–14]. Therefore, prospective studies investigating the association between fatty liver and CKD in general European populations are needed.

Unlike the gold standard diagnosis for fatty liver, i.e. liver biopsy, the fatty liver index (FLI) is a cost-effective and non-invasive tool to predict fatty liver in the general population [15, 16]. Based on body mass index (BMI), waist circumference, triglycerides (TGs) and gamma-glutamyl transferase (GGT), FLI has shown excellent performance in ruling in or ruling out fatty liver [15, 17–19].

In this prospective, population-based cohort study using FLI as a surrogate marker for fatty liver, we aimed to assess the association of FLI with kidney function and CKD development. Furthermore, we explored the potential joint-mediating role of the most important cardiometabolic risk factors, including diabetes, hypertension and inflammation, in this relationship.

MATERIALS AND METHODS

Population

The KORA (Cooperative Health Research in the Region of Augsburg) S4 survey was conducted between 1999 and 2001 and recruited 4261 participants ages 25–74 years from the general population. All participants underwent a standardized interview and a medical examination for the assessment of socio-economic and anthropometric measurements, lifestyle and physical health status [20–22]. The participants were followed up in a second visit between 2006 and 2008 (KORA F4, 3080 participants) and a third visit between 2013 and 2014 (KORA FF4, 2279 participants). The original aim of the S4/F4/FF4 study was to investigate the prevalence, trajectories and risk factors of cardiometabolic outcomes in the general population [20–22].

For the present analysis, KORA F4 was used as the baseline examination, since liver enzymes necessary for calculation of the FLI were lacking in S4. The study sample for the cross-sectional analyses included 2920 participants (1508 women, 1412 men) (see Fig. 1 for details). Of these, 2076 participated in the FF4 follow-up examination. After applying further exclusion criteria listed in Fig. 1, the final study population for the longitudinal analysis comprised 1991 participants (1018 women, 973 men) (Fig. 1).

All study participants provided written informed consent. The study was approved by the ethics committees of the Bavarian Chamber of Physicians (approval 06068), in adherence with the Declaration of Helsinki.

Laboratory and clinical measurements

After an overnight fast of at least 8 hours, a random spot urine sample and a blood sample without stasis were collected from each participant. Before blood sampling, participants were asked if they had a chronic infection with hepatitis B or C virus (HBV/HCV). Blood samples were kept at 4°C until centrifugation. Liver enzymes GGT, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were analysed using the Cobas system (Roche Diagnostics, Mannheim, Germany) according to the recommendations of the International Federation of Clinical Chemistry from 1983 (confirmed and extended in 2002) [23]. Serum total cholesterol (CHOL Flex), high-density lipoprotein cholesterol (HDL-C; AHDL Flex) and low-density lipoprotein cholesterol (LDL-C; ALDL Flex) concentrations were measured accord-

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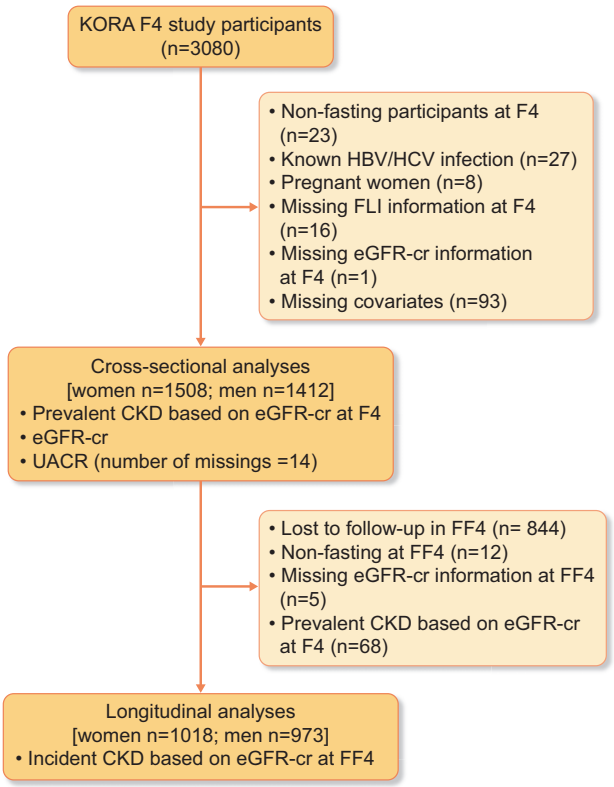

Figure 1: Flow chart of the study population. eGFR-Cr based on the equation established by the CKD-EPI (2009).

ing to the enzymatic methods (CHOD-PAP; Dade Behring, Marburg, Germany). TGs were measured by an enzymatic colour test (GPO-PAP method, TGL Flex; Dade Behring). Serum creatinine was assessed by a modified kinetic rate Jaffe method (Krea Flex; Dade Behring). High-sensitivity C-reactive protein (CRP) and serum cystatin C were determined by nephelometry on a BN II analyser (Siemens, Erlangen, Germany) from the frozen plasma and serum samples that were stored at −80°C until assaying. Urinary albumin and urinary creatinine concentrations were determined from the frozen urine samples that were stored at −80°C until assaying. Urinary creatinine was measured by a modified kinetic rate Jaffe method (CREATININ-JK, Greiner, Bahlingen, Germany) on a Cobas Mira analyser (Roche Diagnostics) [24] and urinary albumin was measured by nephelometry on a BN II analyser (Siemens).

Other clinical measurements, including oral glucose tolerance test, blood pressure and anthropometric measurements, and lifestyle ascertainment are described in the Supplementary Material [23, 25–28].

Definition of FLI

FLI was calculated based on BMI, waist circumference, TGs and GGT according to the algorithm developed by Bedogni *et al.* (15):

$$\text{FLI} = (e^{0.953*\log e(\text{TG}) + 0.139*\text{BMI} + 0.718*\log e(\text{GGT}) + 0.053*\text{waist circumference} - 15.745)}/(1 + e^{0.953*\log e(\text{TG}) + 0.139*\text{BMI} + 0.718*\log e(\text{GGT}) + 0.053*\text{waistcircumference} - 15.745)} * 100,$$

where TG is measured in milligrams per decilitre, GGT in units per litre and waist circumference in centimetres. The score ranges from 0 to 100, with an FLI <30 ruling out and an FLI ≥60 ruling in fatty liver.

Definition of estimated glomerular filtration rate (eGFR) and CKD

The eGFR was calculated from serum creatinine (eGFR-Cr), considering age, race and sex, in accordance with the equation established by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [29]. Serum cystatin C has been suggested to be an alternative glomerular filtration marker, which is less affected by ethnicity and muscle mass volume [30]. We also used serum cystatin C to calculate eGFR (eGFR-cC) based on the CKD-EPI 2012 cystatin C equation [31].

The level of eGFR-Cr was assessed both in the baseline F4 study and in the follow-up FF4 study for defining CKD-related outcomes. CKD was defined as an eGFR-Cr <60 ml/min/1.73 m^2. Incident CKD was defined as having an eGFR-Cr ≥60 ml/min/1.73 m^2 at the baseline and an eGFR-Cr <60 ml/min/1.73 m^2 at the follow-up visit. The same criteria were used when defining CKD based on eGFR-cC.

Urinary albumin:creatinine ratio (UACR)

The UACR reflects elevated urinary protein and is another marker of kidney function decline. The UACR was calculated by dividing the urinary albumin concentration (in milligrams) by the urinary creatinine concentration (in grams). Albuminuria was defined as a UACR ≥30 mg/g (32).

Statistical analysis

Baseline characteristics of the participants were compared among the categories of the FLI. Continuous variables are displayed as the arithmetic mean and standard deviation (SD) when normally distributed or the median and interquartile range (IQR) when non-normally distributed. For categorical variables, counts and percentages are shown. Differences in the baseline characteristics between the FLI categories were tested with analysis of variance (ANOVA) for continuous variables and chi-squared tests for categorical variables.

The FLI was *Z*-standardized prior to the subsequent analyses. We used linear regression to examine the association between the FLI and continuous outcomes (i.e. baseline eGFR and baseline UACR). Because the exact time of CKD diagnosis was not available, we could not calculate the time-to-event data of incident CKD, so we used logistic regression to examine the association between the FLI and binary outcomes (i.e. prevalent and incident CKD). Three models were constructed based on potential confounders and mediators from previous literature. Model 1 was adjusted for age and sex. Model 2 was further adjusted for lifestyle factors, including smoking status, physical activity and alcohol consumption. In order to investigate the effect of potential mediators in this relationship, we added individually one at a time metabolic risk factors

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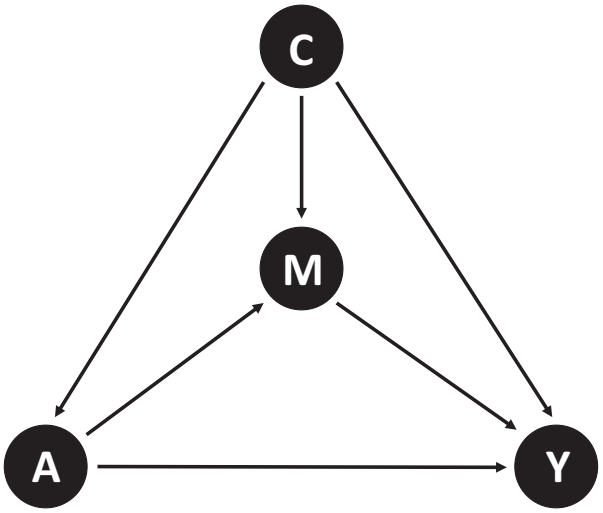

Figure 2: Directed acyclic graph of the variables used in the mediation analysis. **A** (exposure): FLI (continuous) or FLI ≥60 as a proxy for fatty liver; **M** (mediators): CRP (continuous), hypertension (yes/no), diabetes (yes/no); **Y** (outcome): incident CKD (yes/no); **C** (covariates not affected by the exposure): age, sex, smoking, physical activity, alcohol intake.

representing hyperlipidaemia (i.e. total cholesterol and HDL-C), hypertension (yes/no), inflammation (CRP) and diabetes (yes/no) to model 2. Model 3 was adjusted for all the above-mentioned metabolic risk factors simultaneously. For incident CKD, we calculated model 4, which was additionally adjusted for baseline eGFR.

Some investigations suggested that a more severe phenotype of fatty liver involving liver injury would be more detrimental to cardiometabolic health [33, 34]. Therefore we also examined incident CKD in relation to a more severe condition of fatty liver with liver injury, defined as an FLI ≥60 and elevated ALT levels (men: ≥500 nkat/l; women: ≥317 nkat/l) [35, 36].

Sensitivity analyses were done among participants without excessive alcohol intake (men <30 g/day, women <20 g/day) and intake of steatogenic drugs, including corticosteroid, tamoxifen and methotrexate. The interaction between the FLI and hypertension or diabetes was examined by entering a multiplication term (FLI × hypertension/diabetes) into the regression models. It has been implied that fatty liver could increase the risk of CKD, especially among diabetes patients, so we stratified our analysis according to the presence of diabetes at baseline. Since sex differences in fatty liver prevalence are observed in the general population, we also repeated the analysis within each sex stratum.

We performed causal mediation analysis to quantify the extent to which the association between the FLI and incident CKD was mediated by cardiometabolic risk factors (Fig. 2). Of note, because TGs, an important parameter of hyperlipidaemia, were included in the calculation of the FLI, we only considered hypertension, inflammation (measured through CRP) and diabetes to be potential mediators of the relationship between the FLI and incident CKD. Due to the high correlation between these factors, the mediation effects of the single factors were not exclusive of each other [37]. Therefore we assessed the effect mediated jointly by all three mediators together [37]. Covariates not affected by the exposure [38], including age, sex, smoking, physical activity and alcohol intake, were adjusted in the mediation analysis.

The mediation analysis was based on the counterfactual framework introduced by Robins and Greenland [39] and Pearl [40]. The total effect (TE) of the FLI on CKD can be decomposed into a direct effect (DE) and an indirect effect (IE), whereby the DE depicts the effect of the exposure on the outcome that is independent of the mediators. The IE depicts the effect of the exposure on the outcome that could be explained by the mediators. The proportion of the association explained by the mediators [IE/(DE + IE)] was estimated to quantify the magnitude of mediation. The TE, DE and IE were estimated using the regression-based approach proposed by Valeri *et al.* [41] and VanderWeele *et al.* [37], which allows for multiple correlated mediators to be considered jointly. The R package 'CMAverse' (R Foundation for Statistical Computing, Vienna, Austria) was used for the mediation analyses. Direct counterfactual imputation was used to obtain the mediation effects. Standard errors of the mediation effects were estimated by bootstrapping 200 times.

A P-value <.05 was set as the significance level. All analyses were performed with R version 4.1.0 (R Foundation for Statistical Computing).

RESULTS

Cross-sectional analyses

Among 2920 participants eligible for the cross-sectional analyses, 1181 (40.4%) had an FLI ≥60 and 163 (5.6%) had prevalent CKD (based on eGFR-Cr). The participants were on average 56 years old and there were slightly more women [1058 (51.6%)] than men [1412 (48.4%)]. Most of them were overweight, with an average BMI of ∼28 kg/m^2. Table 1 shows the baseline characteristics of the participants according to the FLI categories. Participants in higher FLI categories were older and more likely to be men. They had higher BMIs and larger waist circumferences. They had an unfavourable lifestyle as well as a worse metabolic profile, such as suffering more frequently from hyperlipidaemia, hypertension and diabetes. Meanwhile, higher CRP concentrations, lower baseline eGFR-Cr/eGFR-cC levels and higher CKD prevalence were observed among them. Participants in the highest FLI category had higher UACRs and suffered more frequently from albuminuria.

A 1 SD increase of the FLI was significantly associated with a lower eGFR-Cr at baseline only in models 1 and 2. Further adjustment for metabolic risk factors, especially the inclusion of hypertension and CRP, substantially attenuated the associations {$\beta = -0.43$ [95% confidence interval (CI) 1.09–0.23]}. Accordingly, a higher FLI was significantly associated with higher odds of prevalent CKD defined by eGFR-Cr in models 1 and 2. However, adjustment for metabolic risk factors substantially attenuated the associations [odds ratio (OR) 1.23 (95% CI 0.95–1.58)] (Table 2).

In contrast, the association between a higher FLI and lower baseline eGFR-cC and higher odds of prevalent CKD defined by eGFR-cC remained significant even after metabolic risk

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Table 1: Baseline characteristics of participants according to the cut-off points of the FLI.

Characteristics	FLI <30 ($n = 1006$)	FLI ≥30–<60 ($n = 733$)	FLI ≥60 ($n = 1181$)	Total ($N = 2920$)	*P*-value
Age (years)	50.6 (12.2)	57.5 (13.5)	59.8 (12.2)	56.1 (13.2)	**<.001**
Women, *n* (%)	751 (74.7)	335 (45.7)	422 (35.7)	1508 (51.6%)	**<.001**
BMI (kg/m^2)	23.5 (2.3)	27.0 (2.3)	31.6 (4.3)	27.6 (4.8)	**<.001**
Waist circumference (cm)	80.1 (7.2)	92.9 (5.5)	106.0 (10.3)	93.8 (14.0)	**<.001**
Smoking, *n* (%)					**<.001**
Never smoker	454 (45.1)	320 (43.7)	447 (37.8)	1221 (41.8%)	
Ex-smoker	353 (35.1)	265 (36.2)	564 (47.8)	1182 (40.5%)	
Smoker	199 (19.8)	148 (20.2)	170 (14.4)	517 (17.7)	
Physically active, *n* (%)	630 (62.6)	417 (56.9)	554 (46.9)	1601 (54.8%)	**<.001**
Alcohol consumption, *n* (%)					**<.001**
None	308 (30.6)	213 (29.1)	351 (29.7)	872 (29.9)	
Moderate	529 (52.6)	381 (52.0)	546 (46.2)	1456 (49.9%)	
Excessive	169 (16.8)	139 (19.0)	284 (24.0)	592 (20.3)	
Systolic blood pressure (mmHg)	113.8 (16.3)	123.2 (17.9)	128.7 (17.9)	122.2 (18.5)	**<.001**
Diastolic blood pressure (mmHg)	71.8 (8.7)	75.2 (9.5)	78.0 (10.5)	75.1 (10.0)	**<.001**
Hypertension, *n* (%)	154 (15.3)	285 (38.9)	674 (57.1)	1113 (38.1%)	**<.001**
Total cholesterol (mg/dl)	207.4 (36.8)	217.6 (38.0)	221.8 (41.1)	215.8 (39.4)	**<.001**
HDL-C (mg/dl)	64.2 (14.1)	55.1 (12.8)	49.5 (11.9)	56.0 (14.4)	**<.001**
LDL-C (mg/dl)	125.2 (32.7)	140.8 (33.0)	142.2 (35.5)	136.0 (34.8)	**<.001**
TGs (mg/dl), median (IQR)	68.0 (53.0–92.8)	104.0 (78.0–133.0)	149.0 (110.0–207.0)	104.0 (71.0–149.0)	**<.001**
ALT (µkat/l)	0.3 (0.2)	0.4 (0.2)	0.5 (0.3)	0.4 (0.3)	**<.001**
AST (µkat/l)	0.4 (0.1)	0.4 (0.2)	0.5 (0.3)	0.4 (0.2)	**<.001**
GGT (U/l), median (IQR)	21.0 (17.0–26.0)	28.0 (22.0–37.0)	40.0 (29.0–62.0)	28.0 (21.0–43.0)	**<.001**
CRP (mg/l), median (IQR)	0.7 (0.3–1.3)	1.2 (0.6–2.5)	1.9 (1.0–3.8)	1.2 (0.6–2.6)	**<.001**
Diabetes, *n* (%)	15 (1.5)	66 (9.0)	247 (20.9)	328 (11.2)	**<.001**
Antihypertensive medication, *n* (%)	120 (11.9)	221 (30.2)	548 (46.4)	889 (30.4)	**<.001**
eGFR-Cr (ml/min/1.73 m^2)	93.5 (14.8)	87.1 (16.9)	83.5 (16.8)	87.8 (16.7)	**<.001**
eGFR-cC (ml/min/1.73 m^2)	100.6 (16.4)	90.8 (20.3)	85.9 (20.7)	92.2 (20.2)	**<.001**
Prevalent CKD (eGFR-Cr <60), *n* (%)	17 (1.7)	45 (6.1)	101 (8.6)	163 (5.6)	**<.001**
Prevalent CKD (eGFR-cC <60), *n* (%)	21 (2.1)	63 (8.6)	142 (12.0)	226 (7.7)	**<.001**
Albuminuria, *n* (%)	54 (5.4)	50 (6.8)	158 (13.5)	262 (9.0)	**<.001**
UACR (mg/g), median (IQR)	5.5 (3.7–9.8)	5.2 (3.4–9.9)	6.8 (3.9–14.7)	5.9 (3.7–11.5)	**<.001**
FLI at baseline	14.3 (8.1)	44.6 (8.8)	81.2 (11.4)	49.0 (30.6)	**<.001**

Values are presented as mean (SD) unless stated otherwise.
P-values were generated by ANOVA for continuous variables and chi-squared test for categorical variables. *P*-values <.05 are shown in bold.
eGFR-Cr was based on the equation established by the CKD-EPI (2009). eGFR-cC was on the equation established by the CKD-EPI (2012).
Excessive alcohol consumption was defined as men with an alcohol intake ≥30 g/day and women ≥20 g/day.
Number of missing values for eGFR-cC was 1.
Number of missing values for albuminuria was 14.

Table 2: Association of the FLI with kidney function and prevalent CKD in the KORA F4 study.

Variable	*n*	Model 1	*P*-value	Model 2	*P*-value	Model 3	*P*-value
		β (95% CI)		β (95% CI)		β (95% CI)	
eGFR-Cr	2920	−1.73 (−2.25 to −1.21)	<.001	−1.81 (−2.33 to −1.28)	<.001	−0.43 (−1.09–0.23)	.201
eGFR-cC	2919	−3.31 (−3.85 to −2.76)	<.001	−3.20 (−3.74 to −2.65)	<.001	−1.14 (−1.81 to −0.47)	.001
UACR	2906	0.09 (0.05–0.13)	<.001	0.08 (0.04–0.12)	<.001	−0.02 (−0.08–0.03)	.351
		OR (95% CI)		OR (95% CI)		OR (95% CI)	
Prevalent CKD based on eGFR-Cr	2920	1.57 (1.27–1.94)	<.001	1.61 (1.30–2.00)	<.001	1.23 (0.95–1.58)	.117
Prevalent CKD based on eGFR-cC	2919	1.72 (1.41–2.08)	<.001	1.70 (1.40–2.07)	<.001	1.28 (1.01–1.61)	.039

Model 1 was adjusted for age and sex.
Model 2: model 1 + smoking, physical activity and alcohol consumption.
Model 3: model 2 + total cholesterol, HDL-C, CRP, diabetes and hypertension.
The FLI was standardized prior to the analysis. The coefficient estimates represent the change of the outcomes corresponding to a 1 SD increase of the FLI.
Prevalent CKD was defined as eGFR-Cr or eGFR-cC <60 ml/min/1.73 m^2 at the baseline F4 study.
eGFR-Cr was based on the equation established by the CKD-EPI (2009). eGFR-cC was based on the equation established by the CKD-EPI (2012).

factor adjustments in model 3 [eGFR-cC: $\beta = -1.14$ (95% CI −1.81 to −0.47); CKD: OR 1.28 (95% CI 1.01–1.61)]. A higher FLI was not associated with baseline UACR after adjustment for metabolic risk factors [$\beta = -0.02$ (95% CI −0.08–0.03)] (Table 2).

Longitudinal analyses

During a mean follow-up of 6.5 years (SD 0.3), 182 (9.1%) participants newly developed CKD (based on eGFR-Cr), with half of the incident cases among participants with a baseline FLI ≥60. In the regression analyses, a 1 SD increase in the

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Table 3: Association of the FLI or severe phenotype of fatty liver with liver injury and incident CKD (based on eGFR-Cr/cC) in the KORA F4-FF4 study.

	FLI		Fatty liver with liver injury	
Model	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Incident CKD based on eGFR-Cr ($n = 1991$)				
Model 1	1.26 (1.03–1.53)	.023	1.16 (0.77–1.74)	.476
Model 2	1.24 (1.02–1.51)	.035	1.12 (0.74–1.69)	.590
Model 2 + total cholesterol and HDL-C	1.13 (0.90–1.42)	.282	0.94 (0.61–1.45)	.784
Model 2 + CRP	1.16 (0.94–1.43)	.168	1.04 (0.68–1.57)	.866
Model 2 + diabetes	1.18 (0.96–1.45)	.121	1.01 (0.66–1.55)	.961
Model 2 + hypertension	1.10 (0.89–1.35)	.387	0.96 (0.63–1.46)	.842
Model 3	0.91 (0.70–1.17)	.446	0.77 (0.49–1.20)	.242
Model 4	0.85 (0.65–1.12)	.247	0.70 (0.43–1.14)	.151
Incident CKD based on eGFR-cC ($n = 1927$)				
Model 1	1.66 (1.35–2.04)	<.001	1.85 (1.24–2.75)	.003
Model 2	1.64 (1.33–2.02)	<.001	1.84 (1.23–2.76)	.003
Model 2 + total cholesterol and HDL-C	1.59 (1.26–2.01)	<.001	1.60 (1.05–2.44)	.030
Model 2 + CRP	1.38 (1.10–1.72)	.005	1.54 (1.02–2.32)	.040
Model 2 + diabetes	1.71 (1.38–2.12)	<.001	1.90 (1.26–2.87)	.003
Model 2 + hypertension	1.51 (1.22–1.87)	<.001	1.64 (1.09–2.46)	.018
Model 3	1.27 (0.98–1.65)	.076	1.35 (0.87–2.10)	.177
Model 4	1.11 (0.83–1.47)	.485	1.29 (0.78–2.12)	.319

Model 1 was adjusted for age and sex.
Model 2: model 1 + smoking, physical activity and alcohol consumption.
Model 3: model 2 + total cholesterol, HDL-C, CRP, diabetes and hypertension.
Model 4: model 3 + baseline eGFR-Cr/cC.
The FLI was standardized prior to the analysis. The coefficients represent the OR of incident CKD according to a 1 SD increase of the FLI.
Fatty liver with liver injury was defined as a FLI ≥60 and elevated ALT levels (men: ≥500 nkat/l; women: ≥317 nkat/l).
Incident CKD was defined as an eGFR-Cr/cC <60 ml/min/1.73 m^2 at the follow-up FF4 study and eGFR-Cr/cC ≥60 ml/min/1.73 m^2 at the baseline F4 study.
eGFR-Cr was based on the equation established by the CKD-EPI (2009). eGFR-cC was based on the equation established by the CKD-EPI (2012).

FLI was significantly associated with higher odds of developing CKD after age, sex and lifestyle adjustment [model 2: OR 1.24 (95% CI 1.02–1.51)]. However, further adjustment for metabolic risk factors evidently undermined the associations [model 3: OR 0.91 (95% CI 0.70–1.17)] (Table 3). Moreover, fatty liver with liver injury (FLI ≥60 with elevated ALT levels) was not associated with incident CKD in any of the models [model 3: OR 0.77 (95% CI 0.49–1.20)] (Table 3). Analyses with incident CKD defined by eGFR-cC showed that a 1 SD increase in the FLI was associated with higher odds of incident CKD in models 1 and 2 [model 2: OR 1.64 (95% CI 1.33–2.02)]. However, further adjustment for metabolic risk factors attenuated the association [model 3: 1.27 (95% CI 0.98–1.65)] (Table 3). Similarly, fatty liver with liver injury was only associated with incident CKD based on eGFR-cC in models 1 and 2 [model 2: 1.84 (95% CI 1.23–2.76)], but not after adjustment for all metabolic risk factors [model 3: 1.35 (95% CI 0.87–2.10)] (Table 3).

Sensitivity analyses

After excluding participants with excessive alcohol intake or steatogenic medication intake, the regression analyses yielded similar results for both cross-sectional and longitudinal analyses (Supplementary Tables 1 and 3). We found significant interaction between the FLI and diabetes for the association between the FLI and baseline eGFR-Cr (*P* for interaction = .002). In the subgroup analysis we found that among participants with diabetes their FLI was significantly associated with lower baseline eGFR-Cr [β −3.81 (95% CI −6.32 to −1.31)] as well as higher odds of prevalent CKD based on eGFR-Cr [OR = 1.95 (95% CI 1.09–3.49)] in the full model, whereas in the non-diabetic group, we did not find any significant association (Supplementary Table 2). Longitudinally, we found that the FLI was not associated with incident CKD in the full model in either subgroup (Supplementary Table 2). We did not observe any interaction for the FLI with hypertension in the association analyses. In the sex-stratified analysis, effect estimates were similar in men and women and they did not reach statistical significance (Supplementary Table 4).

Mediation analysis

When CRP, diabetes and hypertension were examined together for their joint mediation effects, a 1 SD increase in the FLI indirectly increased the odds of developing incident CKD through these three mediators [OR 1.21 (95% CI 1.08–1.32)]. When the regression was conditional on all three potential mediators, the FLI had a non-significant inverse direct effect on incident CKD [0.995 (95% CI 0.84–1.18)]. Consequently, the proportion mediated by all three potential mediators jointly exceeded 100% (101.9%; $P = .02$) (Table 4). Of note, the proportion mediated exceeding 100% represents a mathematical result accounting for the directional change of the association between the FLI and incident CKD after adjusting for all three mediators in the model. To help with the intuitive understanding, we ran the mediation analysis comparing the highest FLI category (FLI ≥60) to the lowest (FLI <30) and also found an indirect increase in incident CKD through the mediators [1.52 (95% CI 1.21–1.79)]. The proportion mediated through CRP, diabetes and hypertension was 92.9% (Table 4). These results suggest that the effect of the FLI on incident CKD was completely mediated by inflammation, diabetes and hypertension jointly. The sensitivity analysis with CKD

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Table 4: Mediation analysis for the association between the FLI and CKD (based on eGFR-Cr) development mediated through the joint effect of diabetes, inflammation and hypertension.

Variable	Multiple mediators					
	FLI (1 SD increase)		FLI ≥30–<60 (*ref* FLI<30)		FLI ≥60 (*ref* FLI<30)	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Direct effect	0.996 (0.84–1.18)	.95	1.18 (0.83–1.78)	.43	1.04 (0.67–1.57)	.77
Indirect effect	1.21 (1.08–1.32)	**<.001**	1.24 (1.09–1.33)	**<.001**	1.52 (1.21–1.79)	**<.001**
Total effect	1.20 (1.03–1.38)	**.02**	1.47 (1.04–2.16)	**.02**	1.59 (1.05–2.23)	**.04**
Proportion mediated (%)	101.9	**.02**	60.8	**.02**	92.9	**.04**

Incident CKD was defined as an eGFR-Cr <60 ml/min/1.73 m^2 at the follow-up FF4 study and eGFR-Cr ≥60 ml/min/1.73 m^2 at the baseline F4 study.
Total, direct and indirect effects were estimated with age, sex, smoking, physical activity and alcohol intake as covariates not affected by the exposure. Effect estimates with *P*-values <.05 were shown in bold.
Multiple mediators included CRP (continuous), diabetes (yes/no) and hypertension (yes/no). The causal effects were estimated by considering all three potential mediators jointly in the mediation analysis.
eGFR-Cr was based on the equation established by the CKD-EPI (2009).

based on eGFR-cC showed similar results (Supplementary Table 5).

DISCUSSION

In this population of middle-aged and older German participants, we found that a higher FLI was associated with lower eGFR and increased risk of CKD development during 6.5 years of follow-up, independent of lifestyle risk factors. However, further cardiometabolic adjustments substantially undermined the associations. Mediation analysis indicated that the putative association between the FLI/fatty liver and the risk of developing CKD was completely jointly mediated by diabetes, hypertension and inflammation.

Accumulating evidence has shown that individuals with fatty liver had a higher risk of developing CKD [4]. However, it is still highly debatable if fatty liver constitutes an independent risk factor for CKD. Although extensive research efforts have been focused on detangling the relation between fatty liver and CKD, the majority of these studies have taken place in Asian populations [42]. Contradictory results have been observed in the existing evidence found among Caucasian populations [10, 12–14, 43]. Two large longitudinal studies found that people with fatty liver were 50% more likely to develop CKD than those without, matched on age, sex and other cardiorenal risk factors [12, 43]. Nevertheless, their retrospective design and inclusion of only people with physician visits subject these studies to misclassification and selection bias. On the other hand, a prospective study in the general European population could not confirm that fatty liver diagnosed by computed tomography (CT) or the elevation of GGT independently increased the incidence of CKD [14]. Accordingly, a mendelian randomization study using genetic instrumental variables identified for CT-measured fatty liver in a population with European ancestry found no evidence that fatty liver causally impaired renal function [9]. Therefore it is likely that the observed positive associations in the literature could be explained by reverse causation or residual confounding [6, 12, 43, 44].

Most existing studies have diagnosed fatty liver by ultrasound [6,13,44], which shows only moderate diagnostic sensitivity when lipid content of the hepatocytes is <30% [45]. Consequently, only fatty liver with a higher fat content could have been diagnosed with ultrasound. The positive associations found in these studies suggest that fatty liver in a more advanced stage might be more relevant to the pathogenesis of CKD, possibly driven by the accompanying cardiometabolic risk factors [4, 46]. In line with our results, data from the population-based Framingham study comprised predominantly of individuals of European descent, suggested that neither increased liver fat quantified by CT nor fatty liver with liver injury, was independently associated with CKD risk [10].

Previous research has shown a close relationship between fatty liver and diabetes, and fatty liver seems to particularly increase the risk of developing CKD among diabetes patients [13, 47]. However, in our subgroup analysis, we found that the FLI was not associated with the risk of incident CKD in those with and without diabetes. On the other hand, people with fatty liver very often exhibit other components of metabolic syndrome, such as atherogenic dyslipidaemia and hypertension, suggesting that the association between fatty liver and CKD could be mediated by these cardiometabolic risk factors [4, 47]. In our mediation analysis, we found that the increased risk of developing CKD due to an increase in the FLI or being in the highest category of the FLI (FLI ≥60) was completely mediated by the joint effect of diabetes, inflammation and hypertension. These results show that cardiometabolic risk factors may be the main drivers for CKD development among people with increased liver fat content and fatty liver patients should be evaluated for components of metabolic syndrome in order to mitigate the development of cardiorenal complications [28].

Until now, most of the existing studies have used the Modification of Diet in Renal Disease creatinine model to estimate GFR, which tends to underestimate renal function, especially in Caucasian women [48]. We used the CKD-EPI equation for eGFR-Cr, which could better categorize renal function with regard to adverse clinical outcomes [48]. However, although serum creatinine is widely used in clinical practice to estimate GFR, evidence shows that it can be influenced by muscle mass, advanced liver disease and other factors such as age, diet and race [30, 49], as opposed to serum cystatin C [30]. In our analysis, the discrepancy between prevalent CKD defined by eGFR-Cr and eGFR-cC in relation to the FLI could be due to the high proportion (40.4%) of participants with high fatty liver risk (FLI ≥60) and overweight in our study population, among whom serum creatinine is likely to overestimate and misclassify renal function [49, 50].

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Our study has several strengths. It is one of the few studies that has prospectively examined the association between fatty liver and incident CKD in a population-based cohort with European participants. A diverse set of cardiometabolic risk factors allowed us to adjust the models and rigorously perform mediation analysis. However, some limitations also need to be mentioned. The literature has indicated that the temporal directionality between fatty liver and cardiometabolic comorbidities could be reversed [51]. Therefore the results of the mediation analysis are only valid with the assumption that the pathway suggested in our analysis holds true. Due to the inclusion of TGs and BMI in the FLI calculation, to avoid collinearity we did not further adjust for these covariates in the regression models. Non-invasive imaging methods such as CT show higher sensitivity in assessing fatty liver. In particular, magnetic resonance spectroscopy and/or magnetic resonance imaging-derived proton density fat fraction are deemed the state-of-the-art methods for non-invasive quantification of hepatic fat. However, CT exerts potential radiation hazards and magnetic resonance imaging is still not commonly available due to high costs. In comparison, the FLI as a cost-effective tool has consistently demonstrated good accuracy for predicting the presence of fatty liver in several validation studies with imaging data, making it an adequate marker for population studies [17–19, 36].

CONCLUSION

We found that an increased FLI, a measure for fatty liver, was associated with an increased risk of developing CKD, independent of lifestyle factors in a general German population. However, the relationship was completely mediated by the joint effect of diabetes, inflammation and hypertension. People with an elevated FLI/fatty liver are recommended to undertake regular medical visits to monitor and manage their cardiometabolic health, including diabetes and hypertension, to prevent the progression of CKD. Future prospective studies need to investigate the chronological interaction and causal relationship of fatty liver, metabolic risk factors and kidney function with frequent follow-up visits.

SUPPLEMENTARY DATA

Supplementary data is available at *ndt* online.

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AUTHORS' CONTRIBUTIONS

X.C. designed the analyses, interpreted the data and drafted the manuscript. J.N. and B.T. contributed to the conception, design and interpretation of the data and approval of the manuscript. S.H., A.P., W.R. and W.K. contributed substantially to the interpretation of the data and critically revised the manuscript for important intellectual content.

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due to data protection reasons. The data will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

W.K. has received Grants and provision of reagents to institution from Singulex, Dr. Beckmann Pharma, Abbott, Roche Diagnostics, consulting fees from AstraZeneca, Novartis, Amgen, Pfizer, the Medicines Company, DalCor Pharmaceuticals, Kowa, Corvidia Therapeutics, OMEICOS, Daiichi Sankyo, Novo Nordisk, Esperion, LIB Therapeutics, NewAmsterdam Pharma, Genentech, and lecture fees from BristolMyers Squibb, Novartis, Amgen, Berlin-Chemie, Sanofi, AstraZeneca. W.R has received consulting fees for attending educational sessions or advisory boards from AstraZeneca, Boehringer Ingelheim and NovoNordisk. The authors have no conflicts of interest to declare that are relevant to the content of this article. The results presented in this article have not been published previously in whole or part, except in abstract format.

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