Supplementary materials

Methods (Continues)

Laboratory and clinical measurements

An oral glucose tolerance test (OGTT) was given to all participants without clinically validated diabetes. Fasting glucose was determined in preprandial serum after an overnight fast of at least 8 hours. Two-hour glucose (2h glucose) was determined in serum samples 2 hours after intake of a standard 75g of OGTT. Both fasting and 2h glucose were measured by a hexokinase method (GLU Flex, Dade Behring, Deerfield, USA). According to the criteria of the World Health Organization (1), diabetes was defined as fasting glucose > 6.9 mmol/L and/or 2h glucose > 11.0 mmol/L. Prediabetes was defined by OGTT as isolated impaired glucose tolerance (IGT: 2h glucose between 7.8 and 11.0 mmol/L) or isolated impaired fasting glucose (IFG: fasting glucose between 6.1 and 6.9 mmol/L) or both IGT and IFG. Normoglycaemia was defined if fasting glucose < 6.1mmol/L and 2h glucose < 7.8 mmol/L. Participants with prediabetes and normoglycaemia were deemed as not having diabetes.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times at the right arm after at least fifteen minutes of quiet sitting using an automatic device (OMRON HEM 705-CP). Participants with blood pressure $\geqslant$ 140/90 mmHg or use of antihypertensive medication given that participants were aware of having hypertension, were defined as having hypertension. Intake of antihypertensive medication in the last seven days prior to the interview was ascertained. According to the antihypertensive compounds of the medication, they were

classified as beta-blocker, calcium antagonist, angiotensin-converting-enzyme inhibitor (ACE inhibitor), diuretics, angiotensin II antagonist and other antihypertensive medications (2).

Anthropometric measurements and interviews

Waist circumference, height and weight were measured based on protocols described elsewhere (3). Baseline information on sociodemographic status, physical activity level, alcohol consumption as well as smoking habit were ascertained during an interview conducted by trained medical workers (4). Alcohol consumption (g/day) was calculated from beer, wine and spirits intake on the last weekday and weekend prior to the interview. Men with daily alcohol consumption ≥ 30 g/day and women ≥ 20 g/day were defined as excessive alcohol drinkers (5). The duration of leisure time sport activity in winter and summer was assessed separately with the following categories: >2h/week (scored 1), 1-2 h/week (scored 2), <1 h/week (scored 3), none (scored 4). Scores for summer and winter were summed up to generate a total score for physical activity. Participants were classified as 'physically inactive' if they had a total score ≥ 5, and 'physically active' otherwise. Smoking status was classified as never smoker, ex-smoker and smoker.

Reference

1. Organization WH. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1, Diagnosis and classification of diabetes mellitus. Geneva: World health organization; 1999.
2. Scholze J. Empfehlungen zur Hochdruckbehandlung in der Praxis. *Notfall & Hausarztmedizin*. 2005;31(04):152-9.
3. Rathmann W, Haastert B, Icks Aa, et al. High prevalence of undiagnosed diabetes mellitus in Southern Germany: target populations for efficient screening. The KORA survey 2000. *Diabetologia*. 2003;46(2):182-9.

4. Rückert I-M, Heier M, Rathmann W, et al. Association between markers of fatty liver disease and impaired glucose regulation in men and women from the general population: the KORA-F4-study. *PLoS One*. 2011;6(8):e22932.
5. EASL, EASD, EASO. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol*. 2016;9(2):65-90.

Supplementary table 1. Association of fatty liver index with kidney function and prevalent chronic kidney disease in the KORA F4 study among participants without excessive alcohol intake and steatogenic medication intake.

	N	Model 1	*p* value	Model 2	*p* value	Model 3	*p* value
		β, 95% CI		**β, 95% CI**		**β, 95% CI**	
eGFR-cr	2,292	**-1.77 (-2.35, -1.18)**	**< 0.001**	**-1.79 (-2.38, -1.19)**	**< 0.001**	-0.36 (-1.11, 0.39)	0.343
eGFR-cc	2,291	**-3.35 (-3.95, -2.75)**	**< 0.001**	**-3.20 (-3.80, -2.60)**	**< 0.001**	**-1.23 (-1.97, -0.49)**	**0.002**
UACR	2,279	**0.08 (0.04, 0.13)**	**< 0.001**	**0.07 (0.03, 0.11)**	**< 0.001**	-0.03 (-0.08, 0.03)	0.391
		OR, 95% CI		**OR, 95% CI**		**OR, 95% CI**	
Prevalent CKD based on eGFR-cr	2,292	**1.60 (1.27, 2.02)**	**< 0.001**	**1.61 (1.27, 2.03)**	**< 0.001**	1.21 (0.91, 1.60)	0.190
Prevalent CKD based on eGFR-cc	2,291	**1.72 (1.39, 2.13)**	**< 0.001**	**1.72 (1.38, 2.14)**	**< 0.001**	**1.32 (1.02, 1.71)**	**0.037**

Model 1 was adjusted for age, sex

Model 2: Model 1 + smoking, physical activity, alcohol consumption

Model 3: Model 2 + total cholesterol, HDL-C, CRP, diabetes, hypertension

Fatty liver index was standardized prior to the analysis. The coefficient estimates represent the change of the outcomes corresponding to 1-standard deviation increase of the fatty liver index.

Prevalent CKD was defined as eGFR-cr or eGFR-cc < 60 ml/min per 1.73 m^2 at the baseline F4 study.

Excessive alcohol intake was defined as men with alcohol intake ≥ 30 g/day and women with alcohol intake ≥ 20 g/day.

Steatogenic medication included corticosteroid, tamoxifen and methotrexate.

Abbreviations: CKD, chronic kidney disease; eGFR-cr, estimated glomerular filtration rate by serum creatinine, based on the equation established by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI 2009); eGFR-cc, estimated glomerular filtration rate by serum cystatin C, based on the equation established by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI 2012); UACR, urinary albumin to creatinine ratio; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; OR, odds ratio; β, β-estimate.

Supplementary table 2. Cross-sectional and longitudinal relations of fatty liver index to kidney function and chronic kidney disease according to the presence of diabetes at baseline.

	eGFR-cr at baseline	*p* value	UACR at baseline*	*p* value	Prevalent CKD based on eGFR-cr	*p* value	Incident CKD based on eGFR-cr‡	*p* value
	β, 95% CI		**β, 95% CI**		**OR, 95% CI**		**OR, 95% CI**	
Participants with diabetes (n= 328)	**-3.81 (-6.32, -1.31)**	**0.004**	-0.16 (-0.38, 0.06)	0.152	**1.95 (1.09, 3.49)**	**0.026**	1.02 (0.51, 2.06)	0.947
Participants without diabetes (n=2,592)	-0.15 (-0.83, 0.54)	0.678	0.02 (-0.04, 0.07)	0.535	1.11 (0.82, 1.49)	0.509	0.81 (0.60, 1.10)	0.178

Cross-sectional models were adjusted for age, sex, smoking, physical activity, alcohol consumption, total cholesterol, HDL-C, CRP and hypertension.

Longitudinal models were adjusted for age, sex, smoking, physical activity, alcohol consumption, total cholesterol, HDL-C, CRP, hypertension and baseline eGFR-cr.

Fatty liver index was standardized prior to the analysis. The coefficient estimates represent the change of the outcomes corresponding to 1-standard deviation increase of the fatty liver index.

Prevalent CKD was defined as eGFR-cr < 60 ml/min per 1.73 m^2 at the baseline F4 study.

Incident CKD was defined as eGFR-cr < 60 ml/min per 1.73 m^2 at the follow-up FF4 study and eGFR-cr ≥ 60 ml/min per 1.73 m^2 at the baseline F4 study.

*Cross-sectional models with baseline UACR included 326 participants with diabetes and 2,580 participants without diabetes due to missing values in baseline UACR.

‡Longitudinal models with incident CKD based on eGFR-cr included 155 participants with diabetes and 1,836 participants without diabetes.

Abbreviations: CKD, chronic kidney disease; eGFR-cr, estimated glomerular filtration rate by serum creatinine, based on the equation established by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI 2009); UACR, urinary albumin to creatinine ratio; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; OR, odds ratio; β, β-estimate.

Supplementary table 3. Association of fatty liver index or severe phenotype of fatty liver with liver injury and incident chronic kidney disease (based on eGFR-cr/cc) in the KORA F4-FF4 study among participants without excessive alcohol intake and steatogenic medication intake.

	Fatty liver index		**Fatty liver with liver injury**	
	OR, 95% CI	*p* value	**OR, 95% CI**	*p* value
Incident CKD based on eGFR-cr (n=1,560)				
Model 1	**1.26 (1.01, 1.57)**	**0.043**	1.30 (0.82, 2.06)	0.273
Model 2	1.23 (0.98, 1.53)	0.074	1.23 (0.77, 1.97)	0.392
Model 2 + total cholesterol and HDL-C	1.12 (0.86, 1.44)	0.400	1.05 (0.64, 1.71)	0.863
Model 2 + CRP	1.15 (0.91, 1.46)	0.244	1.14 (0.71, 1.84)	0.584
Model 2 + Diabetes	1.17 (0.93, 1.48)	0.187	1.12 (0.69, 1.82)	0.646
Model 2 + hypertension	1.12 (0.88, 1.40)	0.380	1.07 (0.67, 1.74)	0.770
Model 3	0.92 (0.69, 1.22)	0.547	0.87 (0.52, 1.45)	0.594
Model 4	0.85 (0.62, 1.15)	0.291	0.78 (0.45, 1.34)	0.365
Incident CKD based on eGFR-cc (n=1,511)				
Model 1	**1.73 (1.37, 2.19)**	**<0.001**	**1.93 (1.22, 3.05)**	**0.006**
Model 2	**1.69 (1.33, 2.13)**	**<0.001**	**1.92 (1.21, 3.07)**	**0.007**
Model 2 + total cholesterol and HDL-C	**1.65 (1.26, 2.16)**	**<0.001**	**1.66 (1.02, 2.72)**	**0.044**
Model 2 + CRP	**1.42 (1.10, 1.82)**	**0.007**	1.61 (1.00, 2.60)	0.050
Model 2 + diabetes	**1.74 (1.37, 2.22)**	**<0.001**	**1.96 (1.22, 3.16)**	**0.006**
Model 2 + hypertension	**1.57 (1.24, 2.00)**	**<0.001**	**1.74 (1.09, 2.80)**	**0.022**
Model 3	1.31 (0.97, 1.77)	0.078	1.41 (0.85, 2.35)	0.185
Model 4	1.12 (0.81, 1.56)	0.497	1.36 (0.76, 2.43)	0.294

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, hypertension
Model 4: Model 3 + baseline eGFR-cr/cc

Fatty liver index was standardized prior to the analysis. The coefficients represent the odds ratio of incident CKD according to 1-standard deviation increase of the fatty liver index.
Fatty liver with liver injury was defined as fatty liver index ≥ 60 and elevated ALT levels (men: ALT ≥ 500nkat/L; women: ALT ≥ 317 nkat/L).
Incident CKD was defined as eGFR-cr/cc< 60 ml/min per 1.73 m^2 at the follow-up FF4 study and eGFR-cr/cc ≥ 60 ml/min per 1.73 m^2 at the baseline F4 study.
Excessive alcohol intake was defined as men with alcohol intake ≥ 30 g/day and women with alcohol intake ≥ 20 g/day.
Steatogenic medication included corticosteroid, tamoxifen and methotrexate.

Abbreviations: CKD, chronic kidney disease; eGFR-cr, estimated glomerular filtration rate by serum creatinine, based on the equation established by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI 2009)); eGFR-cc, estimated glomerular filtration rate by serum cystatin C, based on the equation established by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI 2012); HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; ALT, alanine transaminase; OR, odds ratio; 95% CI, 95% confidence interval.

Supplementary table 4. Sex-stratified association between fatty liver index and incident chronic kidney disease (based on eGFR-cr) in the KORA F4-FF4 study.

	Men (n=973)		Women (n=1,018)	
Incident CKD	**OR, 95% CI**	*p* value	**OR, 95% CI**	*p* value
Model 1	1.24 (0.91, 1.67)	0.168	1.25 (0.96, 1.62)	0.097
Model 2	1.22 (0.89, 1.66)	0.215	1.27 (0.98, 1.66)	0.074
Model 3	0.88 (0.60, 1.28)	0.490	0.94 (0.66, 1.35)	0.745
Model 4	0.91 (0.61, 1.36)	0.639	0.82 (0.55, 1.22)	0.321

Model 1 was adjusted for age

Model 2: Model 1 + smoking, physical activity and alcohol consumption.

Model 3: Model 2 + total cholesterol, HDL-C, CRP, diabetes, hypertension

Model 4: Model 3 + baseline eGFR-cr.

Fatty liver index was standardized prior to the analysis. The coefficients represent the odds ratio of incident CKD according to 1-standard deviation increase of the fatty liver index.
Incident CKD was defined as eGFR-cr < 60 ml/min per 1.73 m^2 at the follow-up FF4 study and eGFR-cr ≥ 60 ml/min per 1.73 m^2 at the baseline F4 study.

Abbreviations: CKD, chronic kidney disease; eGFR-cr, estimated glomerular filtration rate by serum creatinine, based on the equation established by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI 2009); HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; OR, odds ratio; 95% CI, 95% confidence interval.

Supplementary table 5. Mediation analysis for the association between fatty liver index and CKD (based on eGFR-cc) development mediated through the joint effect of diabetes, inflammation and hypertension.

			Multiple mediators			
	Fatty liver index		30 ≤ FLI < 60		FLI ≥ 60	
	OR, 95% CI	*p* value	**OR, 95% CI**	*p* value	**OR, 95% CI**	*p* value
Direct effect	**1.21 (1.03, 1.42)**	**0.01**	**1.60 (1.09, 2.60)**	**0.03**	**1.65 (1.12, 2.58)**	**0.01**
Indirect effect	**1.21 (1.11, 1.32)**	**<0.001**	**1.31 (1.18, 1.50)**	**< 0.001**	**1.57 (1.31, 1.91)**	**< 0.001**
Total effect	**1.46 (1.28, 1.68)**	**<0.001**	**2.10 (1.46, 3.36)**	**< 0.001**	**2.59 (1.82, 4.03)**	**< 0.001**
Proportion mediated (%)	**55.2%**	**<0.001**	**45.4%**	**< 0.001**	**92.9%**	**< 0.001**

Incident CKD was defined as eGFR-cc < 60 ml/min per 1.73 m^2 at the follow-up FF4 study and eGFR-cc ≥ 60 ml/min per 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* value < 0.05 were shown in bold.

Multiple mediators included C-reactive protein (continuous), diabetes (yes/no) and hypertension (yes/no). The causal effects were estimated by considering all three potential mediators jointly in the mediation analysis.

Abbreviations: CKD, chronic kidney disease; eGFR-cc, estimated glomerular filtration rate by serum cystatin C, based on the equation established by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI 2012); SD, standard deviation; OR, odds ratio; 95% CI, 95% confidence interval.