

Metabolic Dysfunction-Associated Fatty Liver Disease and Long-term Kidney Function Decline: A 16-Year Population-Based Cohort Study

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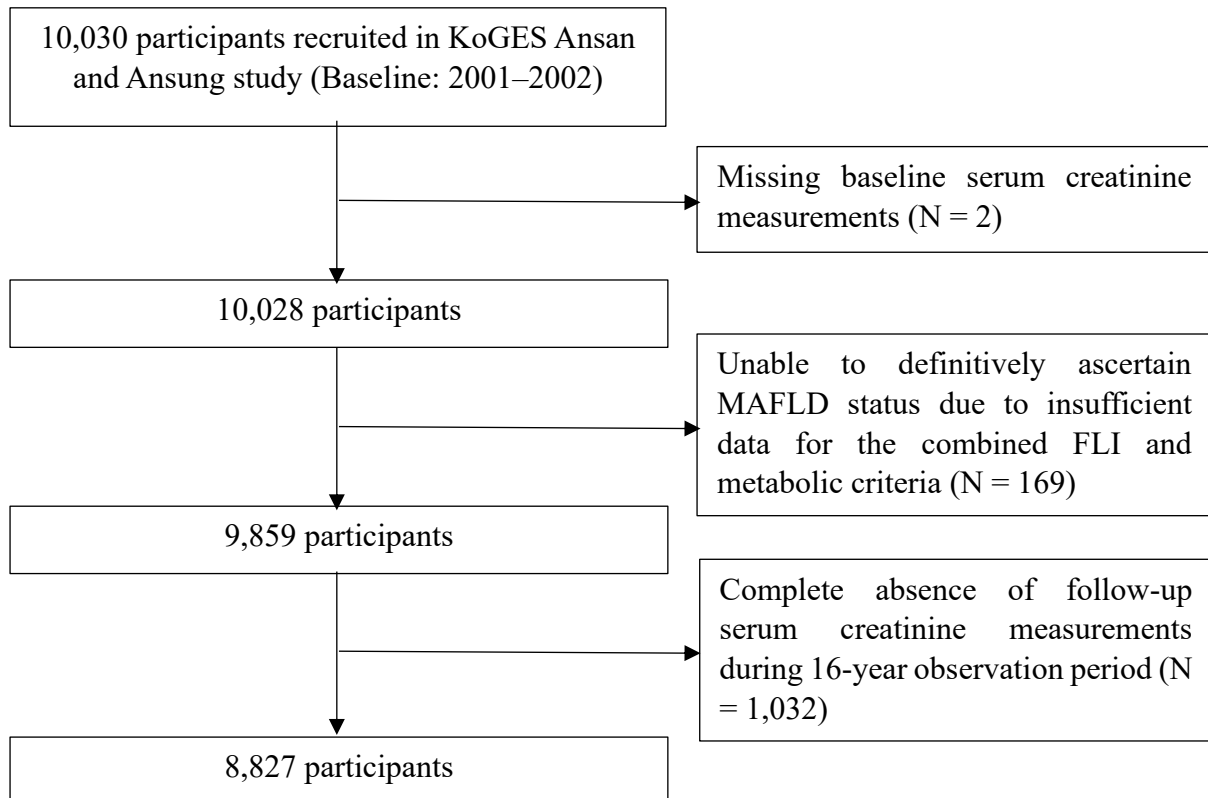
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Supplementary Figure S1. Flowchart of cohort construction and participant selection.



Supplementary Table S1. Distribution of the number of eGFR measurements per participant (N = 8,827).

No. of measurements	N	%
2	738	8.4%
3	650	7.4%
4	593	6.7%
5	566	6.4%
6	604	6.8%
7	790	9.0%
8	1,934	21.9%
9	2,952	33.4%

Values are n (%). The mean total number of eGFR measurements per participant, including the baseline assessment, was 6.78 (SD 2.39; median 8, IQR 5–9). Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation.

Supplementary Table S2. Distribution of last observed follow-up wave, by MAFLD status.

Last observed wave	No MAFLD (N = 4,849)	MAFLD (N = 3,978)	Total (N = 8827)
Wave 2 (~2 yr)	260 (5.4%)	200 (5.0%)	460 (5.2%)
Wave 3 (~ 4 yr)	211 (4.4%)	210 (5.3%)	421 (4.8%)
Wave 4 (~ 6 yr)	150 (3.1%)	152 (3.8%)	302 (3.4%)
Wave 5 (~8 yr)	167 (3.4%)	175 (4.4%)	342 (3.9%)
Wave 6 (~10 yr)	192 (4.0%)	163 (4.1%)	355 (4.0%)
Wave 7 (~12 yr)	143 (3.0%)	150 (3.8%)	293 (3.3%)
Wave 8 (~14 yr)	302 (6.2%)	287 (7.2%)	589 (6.7%)
Wave 9 (~16 yr, full follow-up)	3,424 (71.0%)	2,641 (66.4%)	6,065 (68.7%)

Values are n (%). Percentages are calculated within each MAFLD status column (No MAFLD, MAFLD) and for the Total column, within the overall cohort. “Last observed wave” indicates the final follow-up wave at which a participant had a non-missing eGFR measurement and was used to characterize the distribution of observed follow-up rather than to determine the specific reason for attrition. Abbreviations: eGFR, estimated glomerular filtration rate; MAFLD, metabolic dysfunction-associated fatty liver disease.

Supplementary Table S3. Kidney function at the 16-year (eighth follow-up wave) visit, by MAFLD status (N = 6,065).

	No MAFLD (N = 3,424)	MAFLD (N = 2,641)	<i>P</i> value
Serum creatinine, mg/dL, mean $\pm$ SD	0.76 $\pm$ 0.35	0.86 $\pm$ 0.43	
Serum creatinine, mg/dL, median (IQR)	0.72 (0.63–0.84)	0.81 (0.69–0.94)	<0.001
eGFR, mL/min/1.73 m ² , mean $\pm$ SD	88.2 $\pm$ 13.4	83.9 $\pm$ 16.0	
eGFR, mL/min/1.73 m ² , median (IQR)	91.1 (82.7– 97.4)	87.9 (76.3– 94.8)	<0.001

Values reflect each participant's measurement at the eighth follow-up wave (~16 years after baseline); this is a subset of the full analytic cohort (N = 8,827) restricted to participants who reached this final wave. P-values were derived from the Wilcoxon rank-sum test. Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range; MAFLD, metabolic dysfunction-associated fatty liver disease; SD, standard deviation.

Supplementary Table S4. Association between MAFLD and absolute eGFR change for 16 years among 6,065 participants.

		Cases, N		Beta coefficient (95% confidence interval)						
		Model 1		<i>P</i>	Model 2		<i>P</i>	Model 3		<i>P</i>
No MAFLD	3,424	Reference			Reference			Reference		
MAFLD	2,641	-0.64 (-1.41, 0.14)		0.106	-1.21 (-2.17, -0.27)		0.012	-2.02 (-2.76, -1.28)		<0.001

Model 1 is unadjusted. Model 2 is a case-mix adjusted model including age, sex, diabetes mellitus, hypertension, dyslipidemia, cerebrovascular disease, coronary artery disease, smoking status, binge drinking, physical activity, AFR, SBP and DBP. Model 3 is a fully adjusted model including hemoglobin, albumin, total cholesterol, AST, ALT, baseline eGFR, albuminuria, and all variables included in model 2. Abbreviations: eGFR, estimated glomerular filtration rate; MAFLD, metabolic dysfunction-associated fatty liver disease

Supplementary Table S5. Sensitivity analysis: Association between MAFLD (FLI ≥ 60 as an alternative threshold) and eGFR slope and incident CKD.

	eGFR slope		Incident CKD	
	Beta coefficient*	<i>P</i> value	Hazard ratio*	<i>P</i> value
	(95% CIs)		(95% CIs)	
No MAFLD	Reference		Reference	
MAFLD	−0.14 (−0.27, −0.02)	0.027	1.25 (1.09, 1.44)	0.002

*Models are adjusted for including age, sex, diabetes mellitus, hypertension, dyslipidemia, cerebrovascular disease, coronary artery disease, smoking status, binge drinking, physical activity, abdominal fat ratio, systolic blood pressure, diastolic blood pressure, hemoglobin, albumin, total cholesterol, aspartate aminotransferase, alanine aminotransferase, baseline eGFR, and albuminuria.

Abbreviation: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; MAFLD, metabolic dysfunction-associated fatty liver disease

Supplementary Table S6. Association between MAFLD and a composite incident CKD outcome incorporating new-onset dipstick proteinuria.

Panel A. Composite outcome incidence

Definition	Cases, n (%)	N at risk
Primary: new-onset eGFR <60 mL/min/1.73 m ²	1,662 (19.5%)	8,517
Composite: eGFR <60 or new-onset dipstick proteinuria ≥1+	1,906 (22.4%)	8,517

Panel B. Fully adjusted Cox proportional hazards model (composite outcome)

Variable	Hazard ratio	95% CI	P value
MAFLD	1.27	1.13 to 1.43	<0.001
Age, yr	1.07	1.06 to 1.08	<0.001
Male	0.64	0.55 to 0.74	<0.001
Diabetes mellitus	1.78	1.55 to 2.05	<0.001
Hypertension	1.26	1.12 to 1.41	<0.001
Hyperlipidemia	1.00	0.75 to 1.34	0.983
Coronary artery disease	1.12	0.84 to 1.48	0.448
Cerebrovascular disease	1.39	1.02 to 1.91	0.039
Current smoking	1.22	1.06 to 1.39	0.004
Binge drinking	0.96	0.84 to 1.10	0.563
Physical activity	0.86	0.76 to 0.98	0.026
Abdominal fat ratio	1.78	0.53 to 5.99	0.350
SBP, mmHg	1.006	1.002 to 1.010	0.002
DBP, mmHg	1.000	0.993 to 1.006	0.924
Hemoglobin	1.03	0.99 to 1.08	0.158
Albumin	0.65	0.54 to 0.79	<0.001
Total cholesterol	1.002	1.000 to 1.003	0.017
AST	0.999	0.993 to 1.005	0.558
ALT	1.002	0.998 to 1.005	0.182
Baseline eGFR	0.96	0.96 to 0.97	<0.001

Composite outcome defined as new-onset eGFR <60 mL/min/1.73 m² or new-onset dipstick urine protein ≥1+ (among participants without proteinuria at baseline). A single fully adjusted model was fit for this sensitivity analysis (covariates as in the primary Model 3, Table 3). Abbreviations: ALT, alanine aminotransferase; AST,

aspartate aminotransferase; CI, confidence interval; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MAFLD, metabolic dysfunction-associated fatty liver disease; SBP, systolic blood pressure.

Supplementary Table S7. Association between MAFLD and kidney outcomes among participants free of both diabetes and hypertension at baseline (N = 7,068).

Panel A. eGFR slope (fully adjusted linear mixed-effects model)

Variable	Coefficient	95% CI	<i>P</i> value
MAFLD	−0.30	−0.41 to −0.19	<0.001
Age, yr	−0.10	−0.10 to −0.09	<0.001
Male	0.71	0.57 to 0.85	<0.001
Hyperlipidemia	−0.23	−0.54 to 0.08	0.148
Coronary artery disease	−0.08	−0.49 to 0.33	0.696
Cerebrovascular disease	−0.60	−1.11 to −0.10	0.020
Current smoking	−0.06	−0.18 to 0.06	0.312
Binge drinking	0.18	0.07 to 0.29	0.002
Physical activity	0.28	0.16 to 0.40	<0.001
Abdominal fat ratio	1.13	−0.05 to 2.31	0.059
SBP, mmHg	−0.006	−0.010 to −0.002	0.006
DBP, mmHg	0.003	−0.004 to 0.009	0.402
Hemoglobin	0.03	−0.01 to 0.07	0.122
Albumin	0.29	0.11 to 0.47	0.001
Total cholesterol	−0.001	−0.002 to 0.001	0.337
AST	0.004	−0.001 to 0.008	0.089
ALT	−0.001	−0.004 to 0.002	0.507
Albuminuria	−0.86	−1.26 to −0.46	<0.001
Baseline eGFR	−0.059	−0.062 to −0.055	<0.001

Panel B. Incident CKD (fully adjusted Cox proportional hazards model)

Variable	Hazard ratio	95% CI	<i>P</i> value
MAFLD	1.35	1.16 to 1.57	<0.001
Age, yr	1.09	1.08 to 1.10	<0.001
Male	0.54	0.44 to 0.65	<0.001
Hyperlipidemia	0.98	0.64 to 1.54	0.942
Coronary artery disease	0.99	0.62 to 1.59	0.977

Cerebrovascular disease	1.48	0.88 to 2.50	0.138
Current smoking	1.15	0.96 to 1.38	0.137
Binge drinking	0.98	0.81 to 1.18	0.801
Physical activity	0.88	0.74 to 1.05	0.149
Abdominal fat ratio	0.88	0.17 to 4.53	0.877
SBP, mmHg	1.008	1.002 to 1.013	0.006
DBP, mmHg	0.997	0.989 to 1.005	0.477
Hemoglobin	1.04	0.98 to 1.11	0.204
Albumin	0.59	0.46 to 0.77	<0.001
Total cholesterol	1.001	0.999 to 1.003	0.172
AST	0.999	0.992 to 1.005	0.641
ALT	1.001	0.997 to 1.005	0.654
Baseline eGFR	0.95	0.95 to 0.96	<0.001

Analysis restricted to participants free of both diabetes mellitus and hypertension at baseline (N = 7,068), in response to the concern that the higher prevalence of these comorbidities in the MAFLD group could account for the observed primary association. Diabetes mellitus and hypertension are excluded from the covariate list because they define the subgroup itself. The eGFR slope model additionally included a participant-level random intercept and random slope with an unstructured covariance structure. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MAFLD, metabolic dysfunction-associated fatty liver disease; SBP, systolic blood pressure.

Supplementary Table S8. Sensitivity analysis modeling diabetes, hypertension, and blood pressure as time-varying covariates.

Panel A. eGFR slope (one-stage mixed-effects model with time-varying diabetes, hypertension, SBP, and DBP)

	Model 1 (unadjusted)	Model 2 (case-mix)	Model 3 (fully adjusted)
MAFLD × follow-up time ¹ (Δslope)	−0.031 (−0.070 to 0.008) P = 0.124	0.0005 (−0.039 to 0.040) P = 0.980	−0.011 (−0.053 to 0.032) P = 0.617
MAFLD (baseline- level eGFR difference)	−2.51 (−2.99 to −2.02) P <0.001	−2.02 (−2.58 to −1.47) P <0.001	−1.25 (−1.61 to −0.89) P <0.001
N (person-visit observation)	59,822	57,958	57,817
N (participants)	8,827	8,567	8,541

Panel B. Incident CKD (extended Cox model with time-varying diabetes, hypertension, SBP, and DBP)

	Model 1 (unadjusted)	Model 2 (case-mix)	Model 3 (fully adjusted)
MAFLD, HR (95% CI)	1.60 (1.44 to 1.77) P <0.001	1.32 (1.16 to 1.50) P <0.001	1.36 (1.19 to 1.55) P <0.001
No. of subjects	8,282	—	—
No. of failures	1,510	—	—

Complete-case sensitivity analysis (not multiple-imputation based), performed separately from the primary analysis. The primary eGFR-slope analysis (Table 2) used a two-stage approach (individual slopes estimated from a mixed-effects model, followed by regression of the estimated slopes on MAFLD status). Because a scalar per-participant slope cannot accommodate covariates that change at every follow-up wave, Panel A instead uses a one-stage mixed-effects model in which MAFLD, follow-up time, and their interaction are modeled jointly. The two frameworks are not numerically equivalent; therefore, the MAFLD × time interaction coefficients in Panel A should not be directly compared in magnitude with the primary β coefficients in Table 2. The relevant comparison is the direction and statistical significance of the MAFLD × time interaction across Models 1–3. Diabetes, hypertension, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were entered as time-varying covariates using each participant’s value at the start of each follow-up interval (Panel

B) or at each observed wave (Panel A); all other covariates were entered using baseline values. Model 1 is unadjusted. Model 2 is case-mix adjusted (age, sex, hyperlipidemia, coronary artery disease, cerebrovascular disease, smoking, binge drinking, physical activity, abdominal fat ratio, plus time-varying diabetes, hypertension, SBP, and DBP). Model 3 additionally adjusts for hemoglobin, albumin, total cholesterol, AST, ALT, albuminuria, and baseline eGFR — the same fully adjusted covariate set as the primary Model 3 (Table 2 and 3), except that diabetes, hypertension, SBP, and DBP are time-varying in the present analysis rather than represented by baseline value. ¹The MAFLD × time interaction term represents the difference in annual eGFR change associated with MAFLD in the one-stage model; it is not directly comparable in magnitude with the primary two-stage β coefficient (β , -0.29; 95% CI, -0.39 to -0.18; $P < 0.001$).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MAFLD, metabolic dysfunction-associated fatty liver disease; SBP, systolic blood pressure.

Supplementary Table S9. Association between MAFLD and incident eGFR <45 mL/min/1.73 m², a stricter alternative outcome definition.

Panel A. Outcome incidence

Definition	N at risk	Events, n (%)
Primary: new-onset eGFR <60 mL/min/1.73 m ²	8,517	1,662 (19.5%)
Stricter: new-onset eGFR <45 mL/min/1.73 m ²	8,670	310 (3.6%)

Panel B. MAFLD and incident eGFR <45 mL/min/1.73 m², by adjustment level (multiple imputation, Rubin's rules combined)

	Model 1 (unadjusted)	Model 2 (case-mix)	Model 3 (fully adjusted)
Hazard ratio (95% CI)	1.91 (1.52–2.40)	1.22 (0.92–1.61)	1.21 (0.90–1.62)
<i>P</i> value	<0.001	0.160	0.208

Multiple imputation (10 datasets, multivariate normal imputation of baseline covariates with missingness) combined via Rubin's rules, consistent with the primary analysis. N at risk for the eGFR <45 definition (8,670) excludes participants with baseline eGFR <45 mL/min/1.73 m² or baseline albuminuria, mirroring the exclusion criteria used for the primary eGFR <60 definition. Model 1 is unadjusted. Model 2 is case-mix adjusted (age, sex, diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, cerebrovascular disease, smoking, binge drinking, physical activity, abdominal fat ratio, SBP, and DBP). Model 3 additionally adjusts for hemoglobin, albumin, total cholesterol, AST, ALT, albuminuria, and baseline eGFR. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DBP, diastolic blood pressure, eGFR, estimated glomerular filtration rate; MAFLD, metabolic dysfunction-associated fatty liver disease; SBP, systolic blood pressure.

Supplementary Table S10. Association between MAFLD and a $\geq 40\%$ decline in eGFR from baseline, a well-studied surrogate endpoint for clinically important kidney outcomes.

	Model 1	Model 2 (case-mix)	Model 3 (fully
	(unadjusted)		adjusted)
Hazard ratio (95% CI)	1.43 (1.26–1.61)	1.29 (1.106–1.51)	1.29 (1.106–1.52)
<i>P</i> value	<0.001	0.002	0.002

Among 8,827 participants at risk, 1,000 (11.3%) experienced a $\geq 40\%$ decline in eGFR from baseline. Multiple imputation (10 datasets, multivariate normal imputation of baseline covariates with missingness) combined via Rubin's rules, consistent with the primary analysis. Model 1 is unadjusted. Model 2 is case-mix adjusted (age, sex, diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, cerebrovascular disease, smoking, binge drinking, physical activity, abdominal fat ratio, SBP, and DBP). Model 3 additionally adjusts for hemoglobin, albumin, total cholesterol, AST, ALT, albuminuria, and baseline eGFR. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DBP, diastolic blood pressure, eGFR, estimated glomerular filtration rate; MAFLD, metabolic dysfunction-associated fatty liver disease; SBP, systolic blood pressure.