

Serum Uric Acid Identifies a Kidney Filtration–Risk Phenotype in Diabetes-Enriched Non-Obese Metabolic Dysfunction-Associated Steatotic Liver Disease: A Multicentre Cohort Study

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Abstract

Background and hypothesis: Kidney risk varies in non-obese metabolic dysfunction-associated steatotic liver disease (MASLD). We tested whether baseline serum uric acid (SUA) identifies a phenotype prone to later loss of filtration.

Methods: We included 2,047 adults with clinician-adjudicated MASLD and body mass index below 25 kg/m². SUA was standardised within sex. The core outcome was the first single-visit estimated glomerular filtration rate (eGFR) decrease of at least 30% after a 180-day landmark and within five years. Centre-stratified Cox models adjusted for prespecified clinical factors.

Results: Type 2 diabetes was present in 1,910 participants (93.3%). Model B included 1,102 participants and 85 events. Each 1-SD higher SUA was associated with a later eGFR decrease of at least 30% (hazard ratio [HR] 1.46, 95% confidence interval [CI] 1.19–1.79; $P < 0.001$). Model-standardised risks at the mean and + 1 SD were 6.06% and 8.47% at three years, and 12.82% and 17.53% at five years. Results were concordant for later eGFR below 60 mL/min/1.73 m² (HR 1.37, 95% CI 1.07–1.74) and a 40% eGFR decrease (HR 1.48, 95% CI 1.11–1.98), and remained evident after multiple imputation and repeat-testing weighting. Albuminuria was not clearly associated (HR 1.19, 95% CI 0.98–1.44). The 730-day landmark estimate was attenuated (HR 1.22, 95% CI 0.89–1.67).

Conclusions: Higher baseline SUA identified a kidney filtration–risk phenotype in diabetes-enriched non-obese MASLD. It should prompt closer renal surveillance, but does not establish causal injury, confirmed chronic kidney disease progression, or an indication for urate-lowering treatment.

KEY LEARNING POINTS

What was known

- Non-obese MASLD is metabolically heterogeneous; a body mass index below the obesity threshold does not ensure low kidney risk.
- Higher SUA has been linked to filtration decline in non-obese adults and in type 2 diabetes, but longitudinal evidence within established non-obese MASLD has been limited.

This study adds

- Each 1-SD higher sex-standardised SUA was associated with a 46% higher rate of a later single-visit eGFR decrease of at least 30%; findings were concordant for a 40% decrease and later eGFR below 60 mL/min/1.73 m².
- Model-standardised five-year risk rose from 12.82% at the sex-specific mean of SUA to 17.53% at +1 SD. Albuminuria did not show the same clear association, and the 730-day landmark estimate was attenuated.

Potential impact

- SUA can sharpen kidney risk review in diabetes-enriched non-obese MASLD when interpreted with baseline and repeat eGFR, albuminuria, blood pressure, glycaemic control, and kidney-protective treatment.
- The findings support surveillance, not causal attribution or urate-lowering treatment solely to preserve kidney filtration.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) places hepatic steatosis in an explicit cardiometabolic setting [1, 2], but body size remains an imperfect guide. In Asian adults, body mass index (BMI) below 23 kg/m² defines a strict lean phenotype; BMI below 25 kg/m² captures the broader non-obese group used here [3]. Both are heterogeneous [4, 5]. People below the obesity threshold may still carry substantial glycaemic, vascular, hepatic and kidney burden.

Serum uric acid (SUA) is a plausible marker of this hidden heterogeneity. Higher SUA has been associated with incident fatty liver in non-obese young adults, prevalent fatty liver in non-obese adults with type 2 diabetes, and nearly twice the odds of non-alcoholic fatty liver disease when the highest and lowest concentrations were compared in meta-analysis [6–8]. Yet the direction of the relationship is unsettled. Mendelian-randomisation and genetic-score studies did not support genetically higher SUA as a cause of fatty liver [9, 10]. Long-term outcome studies add another layer: lean MASLD may carry higher all-cause and cardiovascular mortality despite fewer non-fatal cardiovascular events than non-lean disease [11, 12], and SUA itself has been associated with cardiovascular mortality in fatty liver populations [13]. These findings make SUA clinically interesting, but they do not define what the marker means for kidney health within established non-obese MASLD.

Kidney involvement matters. Meta-analyses associate fatty liver phenotypes with incident chronic kidney disease (CKD), with pooled hazard ratios of 1.35–1.37 [14, 15], and cohort data link metabolic fatty liver definitions with new CKD [16]. SUA is closely related to filtration and albumin excretion [17–19], making renal handling and reverse association central to interpretation. Creatinine-based eGFR equations and CKD chronicity criteria also require precise outcome labelling [20, 21]. In adjacent populations, lower time-averaged SUA was associated with better renal survival in type 2 diabetes and CKD [22], while a recent MASLD meta-analysis estimated CKD incidence at 22.17 per 1,000 person-years [23]. Higher SUA was also linked to subsequent eGFR decline in a non-obese health-check cohort and a type 2 diabetes cohort [24, 25]. A population study using updated MASLD definitions found greater longitudinal kidney risk, although liver fat rather than SUA was the exposure [26].

Whether a single baseline SUA measurement resolves kidney-risk heterogeneity after restriction to non-obese MASLD remains unclear. We examined sex-standardised SUA in a pooled multicentre cohort with repeated kidney measurements. The core analysis assessed the first single later eGFR decrease of at

least 30% after a 180-day landmark. Later eGFR below 60 mL/min/1.73 m², a 40% decrease, model-standardised absolute risk, repeated eGFR trajectories and albuminuria tested how far the filtration signal extended.

MATERIALS AND METHODS

Study design and data source

We conducted a retrospective multicentre cohort study in a pooled, de-identified, clinician-reviewed routine-care database. Index visits ranged from 15 June 2017 to the data cutoff on 19 May 2026. Source-level analyses examined coverage, precision, and internal consistency, never institutional performance. The longitudinal extension followed an initial feasibility analysis of repeated kidney measurements. Its outcome hierarchy, 180-day landmark, exposure, covariates, diagnostics, and sensitivity analyses were recorded before the final frozen rerun; the Supplement documents this sequence and uses anonymous source codes where required.

Participants

Eligible participants were aged at least 18 years and had clinician-adjudicated steatotic liver disease, at least one cardiometabolic risk factor, BMI below 25 kg/m², recorded sex, and baseline SUA between 50 and 1,200 µmol/L. Viral hepatitis, an unavailable unique de-identified participant key, and an ambiguous index sequence were exclusion criteria. Diagnoses and medication fields were used as the clinically adjudicated values supplied in the pooled database.

Cardiometabolic risk was operationalised by at least one of the following: BMI at least 23 kg/m²; waist circumference at least 90 cm in men or 85 cm in women; blood pressure at least 130/85 mm Hg or recorded hypertension; glycated haemoglobin (HbA1c) at least 5.7%, glucose at least 5.6 mmol/L, or recorded diabetes; triglycerides at least 1.7 mmol/L or recorded hyperlipidaemia; or high-density lipoprotein cholesterol at most 1.0 mmol/L in men or 1.3 mmol/L in women. The earliest visit meeting all criteria defined the index date. This choice did not depend on a subsequent outcome or on record completeness. BMI below 23 kg/m² defined the strict-lean subgroup [3].

Serum uric acid exposure

The primary exposure was baseline SUA standardised separately in women and men; the estimate represents a 1-SD higher concentration within sex. Supplementary specifications used SUA per 100 µmol/L, sex-specific quartiles, clinical hyperuricaemia, and restriction to 100–700 µmol/L. Clinical hyperuricaemia was SUA above 420 µmol/L in men or 360 µmol/L in women.

Kidney outcomes

Serum creatinine was harmonised to $\mu\text{mol/L}$. eGFR was calculated with the 2021 CKD-EPI creatinine equation without a race coefficient [20]. Urine albumin-to-creatinine ratio (UACR) was harmonised to mg/g; values reported in mg/mmol were converted according to the prespecified mapping.

The core outcome was the first eGFR value at or below 70% of baseline after a 180-day landmark and within five years. Eligible participants had baseline eGFR of at least 30 mL/min/1.73 m², no qualifying decrease on days 0–179, and post-landmark eGFR testing. We call this a later single-visit detection, not confirmed CKD progression; trial-surrogate use of a 30% decrease ordinarily requires a defined interval and confirmation [27].

The key secondary outcome was a first later eGFR below 60 mL/min/1.73 m² among participants with baseline eGFR at least 60, no early value below 60, and post-landmark testing. A single-visit eGFR decrease of at least 40% was a prespecified robustness outcome. The albuminuria analysis required baseline UACR below 30 mg/g, no UACR at or above 30 mg/g during days 0–179, and at least one later measurement; the outcome was the first later UACR at or above 30 mg/g. In keeping with KDIGO chronicity principles, no single eGFR or UACR abnormality was labelled confirmed CKD [21].

Persistent decline required a second qualifying value 90–365 days after the first. Only 29 participants met this definition, and the proportional-hazards diagnostic failed; we therefore report fixed-time Kaplan–Meier risks without a Cox effect estimate.

Repeated eGFR and fixed-window outcomes

The eGFR-level trajectory analysis combined the index value and all eGFR measurements through five years. Participants needed at least three measurements spanning at least 180 days. Linear mixed-effects models included source fixed effects, participant-specific random intercepts and time slopes, and an SUA-by-time interaction. A baseline-anchored analysis modelled follow-up eGFR with baseline eGFR entered as a main effect; change-from-baseline parameterisations tested sensitivity. Fixed-window analyses used the measurement closest to 365 days within days 270–455 and the measurement closest to 730 days within days 547–913.

Covariates and model hierarchy

Covariates were chosen from clinical knowledge and the analysis plan, not from statistical significance. In centre-stratified Cox models, Model A included age, sex, baseline eGFR, and centred index year. Model B added BMI, waist circumference, systolic blood pressure, HbA1c, and type 2 diabetes. Model C further included log baseline UACR, log triglycerides, high-density lipoprotein cholesterol, smoking, and current alcohol use. Model D added recorded use of renin–angiotensin system inhibitors, sodium–glucose cotransporter 2 inhibitors, diuretics, urate-lowering treatment, glucagon-like peptide-1 receptor agonists, and statins. Model B was the main clinical model. Models C and D were expanded sensitivity analyses because event information was limited relative to their covariate count.

Statistical analysis

Continuous variables are median [interquartile range] and categorical variables n/N (%). Standardised mean differences describe baseline imbalance; baseline hypothesis-test P values were not used. Landmark follow-up ran from day 180 to the first outcome, last outcome-specific measurement, five years, or data cutoff. Cox models used Efron tie handling and source-stratified baseline hazards. We report hazard ratios (HRs) with 95% confidence intervals (CIs); Schoenfeld residuals assessed the exposure proportional-hazards assumption.

Models C and D used 20 chained-equation imputations with predictive mean matching; outcomes were not imputed and estimates were pooled with Rubin's rules. Ridge-penalised Cox models left SUA unpenalised while shrinking Model B covariates.

Restricted cubic splines used knots at the 10th, 50th, and 90th SUA percentiles. Model A standardised three- and five-year risks at -1 , 0 , and $+1$ SD; 199 of 200 stratified bootstrap replicates completed. Stabilised inverse-probability weighting addressed observed differences in post-landmark eGFR testing, with balance, overlap, weight range, and effective sample size examined.

Bias-directed analyses used 365- and 730-day landmarks; kidney-function, albuminuria, diabetes, hyperfiltration, treatment, and SUA restrictions; inverse-probability weighting; and leave-one-source-out analyses. A source-by-SUA interaction assessed internal heterogeneity. One source, with six core-risk-set participants and no trajectory cohort, remained in the baseline description but was excluded from longitudinal models. No pre-index eGFR measurements were available, precluding a pre-index slope or time-averaged baseline filtration measure.

Core and key secondary outcomes retain two-sided raw P values. No data-driven model selection was used. Analyses followed STROBE and the RECORD extension for routinely collected health data [28].

Ethics

The study was conducted in accordance with the Declaration of Helsinki. The current de-identified retrospective multicentre analysis was approved by the Medical Ethics Committee of The Affiliated Hospital of Qingdao University (QYFY WZLL 50602; 5 August 2026), which waived the requirement for additional individual informed consent because the study used previously collected routine-care data and involved no additional participant contact. Local data collection and research use were covered by approvals from the Ethics Committee of Karamay People's Hospital (ZXYJHKYEC-2019-001-01), the Medical Ethics Committee of Sheyang County Diabetes Specialist Hospital (Approval No. 096), the Ethics Committee of Yuhuan Second People's Hospital Health Community Group (Approval No. 2264), and the Research Ethics Committee of Zhengzhou People's Hospital (KY-2023-004-02). All data were de-identified before pooled analysis.

RESULTS

Cohort assembly and baseline profile

The database contained 229,765 visits from 67,495 people. Sequential eligibility criteria produced 2,047 index participants (Fig. 1): median age 56.0 [49.0, 63.0] years, 926 (45.2%) women, median BMI 23.7 [22.7, 24.3] kg/m², and 1,910 (93.3%) with type 2 diabetes. The strict-lean subgroup comprised 623 (30.4%); 341 (16.7%) had clinical hyperuricaemia.

Compared with normal SUA, hyperuricaemia was accompanied by lower baseline eGFR (98.6 vs 106.2 mL/min/1.73 m²; SMD – 0.557), higher triglycerides, more hypertension, and higher UACR. Baseline eGFR and UACR were available in 1,814 (88.6%) and 1,809 (88.4%) participants (Table 1).

Table 1
Baseline characteristics according to clinical hyperuricaemia status

Characteristic	Evaluable, n	Overall	Normal serum uric acid	Clinical hyperuricaemia	Standardised mean difference
Demographics and anthropometrics					
Age, years	2047	56.0 [49.0, 63.0]	56.0 [49.0, 63.0]	56.0 [48.0, 65.0]	-0.02
Women	2047	926/2047 (45.2%)	776/1706 (45.5%)	150/341 (44.0%)	-0.03
Body mass index, kg/m ²	2047	23.7 [22.7, 24.3]	23.6 [22.7, 24.3]	23.7 [22.8, 24.3]	0.027
Waist circumference, cm	2031	87.0 [83.0, 90.1]	87.0 [83.0, 90.0]	87.2 [84.0, 92.0]	0.157
Laboratory and hemodynamic measures					
Serum uric acid, µmol/L	2047	302.0 [250.0, 365.0]	284.0 [241.0, 331.0]	447.0 [404.0, 490.0]	2.709
Systolic blood pressure, mm Hg	2047	128.0 [119.0, 140.0]	128.0 [119.0, 140.0]	128.0 [119.0, 140.0]	0.069
Diastolic blood pressure, mm Hg	2047	77.0 [70.0, 84.0]	77.0 [70.0, 84.0]	78.0 [71.0, 85.0]	0.061
HbA1c, %	2004	8.8 [7.2, 10.5]	8.9 [7.3, 10.5]	8.4 [6.8, 10.2]	-0.204
Triglycerides, mmol/L	2039	1.7 [1.2, 2.6]	1.6 [1.1, 2.4]	2.2 [1.4, 3.5]	0.395
HDL cholesterol, mmol/L	2029	1.1 [1.0, 1.3]	1.1 [1.0, 1.4]	1.1 [0.9, 1.2]	-0.19
LDL cholesterol, mmol/L	1806	2.9 [2.3, 3.6]	2.9 [2.3, 3.6]	2.9 [2.3, 3.7]	-0.011
Alanine aminotransferase, U/L	2040	21.0 [15.0, 32.0]	21.0 [15.0, 31.0]	22.0 [15.0, 40.0]	0.173
Aspartate aminotransferase, U/L	2040	19.0 [15.0, 24.8]	18.0 [15.0, 24.0]	20.6 [16.0, 27.0]	0.14

Note: Continuous data are median [interquartile range]; categorical data are n/N (%). Clinical hyperuricaemia was SUA > 360 µmol/L in women or > 420 µmol/L in men. The normal-SUA group comprised all other participants. No hypothesis-test P values are shown; SMD denotes standardised mean difference.

Characteristic	Evaluable, n	Overall	Normal serum uric acid	Clinical hyperuricaemia	Standardised mean difference
Demographics and anthropometrics					
FIB-4 index	1786	1.1 [0.8, 1.6]	1.1 [0.8, 1.5]	1.1 [0.8, 1.6]	-0.007
Kidney measures					
eGFR, mL/min/1.73 m ²	1814	105.4 [97.1, 113.0]	106.2 [99.1, 113.4]	98.6 [80.5, 109.6]	-0.557
Urine albumin-to-creatinine ratio, mg/g	1809	8.3 [3.7, 22.7]	8.0 [3.5, 21.3]	10.4 [4.5, 31.9]	0.254
UACR ≥ 30 mg/g	1809	361/1809 (20.0%)	279/1509 (18.5%)	82/300 (27.3%)	0.212
eGFR < 60 mL/min/1.73 m ²	1814	60/1814 (3.3%)	29/1514 (1.9%)	31/300 (10.3%)	0.357
Clinical history and subclinical vascular phenotype					
Type 2 diabetes	2047	1910/2047 (93.3%)	1603/1706 (94.0%)	307/341 (90.0%)	-0.145
Hypertension	2047	916/2047 (44.7%)	728/1706 (42.7%)	188/341 (55.1%)	0.251
Coronary heart disease	2047	162/2047 (7.9%)	135/1706 (7.9%)	27/341 (7.9%)	0.0
Stroke	2047	114/2047 (5.6%)	91/1706 (5.3%)	23/341 (6.7%)	0.059
Carotid plaque	1663	676/1663 (40.6%)	569/1387 (41.0%)	107/276 (38.8%)	-0.046
baPWV ≥ 1800 cm/s	1954	687/1954 (35.2%)	556/1630 (34.1%)	131/324 (40.4%)	0.131
Treatment recorded at the index visit					
Urate-lowering treatment	2047	30/2047 (1.5%)	7/1706 (0.4%)	23/341 (6.7%)	0.346
Diuretic	2047	72/2047 (3.5%)	48/1706 (2.8%)	24/341 (7.0%)	0.196
<i>Note: Continuous data are median [interquartile range]; categorical data are n/N (%). Clinical hyperuricaemia was SUA > 360 µmol/L in women or > 420 µmol/L in men. The normal-SUA group comprised all other participants. No hypothesis-test P values are shown; SMD denotes standardised mean difference.</i>					

Characteristic	Evaluable, n	Overall	Normal serum uric acid	Clinical hyperuricaemia	Standardised mean difference
Demographics and anthropometrics					
Renin–angiotensin system inhibitor	2047	525/2047 (25.6%)	419/1706 (24.6%)	106/341 (31.1%)	0.146
SGLT2 inhibitor	2047	464/2047 (22.7%)	378/1706 (22.2%)	86/341 (25.2%)	0.072
GLP-1 receptor agonist	2047	52/2047 (2.5%)	38/1706 (2.2%)	14/341 (4.1%)	0.107
Statin	2047	775/2047 (37.9%)	645/1706 (37.8%)	130/341 (38.1%)	0.006
<i>Note: Continuous data are median [interquartile range]; categorical data are n/N (%). Clinical hyperuricaemia was SUA > 360 µmol/L in women or > 420 µmol/L in men. The normal-SUA group comprised all other participants. No hypothesis-test P values are shown; SMD denotes standardised mean difference.</i>					

Core and secondary kidney outcomes

After excluding the source with structural absence of longitudinal follow-up, 1,110 participants entered the core risk set and 86 had a first single-visit eGFR decrease of at least 30%. Model B included 1,102 participants and 85 events over 2,672 person-years (31.8 per 1,000 person-years). Each 1-SD higher sex-standardised SUA was associated with a 46% higher event rate (HR 1.46, 95% CI 1.19–1.79; $P < 0.001$; proportional-hazards $P = 0.313$) (Table 2; Fig. 2). Model A gave an HR of 1.43 (95% CI 1.16–1.77; $P < 0.001$).

Table 2
Associations between serum uric acid and later single-visit kidney outcome detections

Outcome	Analysis	Model	Risk set, n	Model, n	Events, n	Hazard ratio (95% CI)	P value	PH diagnostic P value
Later single-visit eGFR decline $\geq$ 30%	Complete case	Model A	1110	1110	86	1.43 (1.16–1.77)	< 0.001	0.176
Later single-visit eGFR decline $\geq$ 30%	Complete case	Model B	1110	1102	85	1.46 (1.19–1.79)	< 0.001	0.313
Later single-visit eGFR decline $\geq$ 30%	Multiple imputation	Model C	1110	1110	86	1.34 (1.08–1.67)	0.009	—
Later single-visit eGFR decline $\geq$ 30%	Multiple imputation	Model D	1110	1110	86	1.39 (1.11–1.74)	0.003	—
Later single-visit eGFR < 60 mL/min/1.73 m ²	Complete case	Model A	1085	1085	62	1.34 (1.05–1.71)	0.021	0.060
Later single-visit eGFR < 60 mL/min/1.73 m ²	Complete case	Model B	1085	1077	61	1.37 (1.07–1.74)	0.012	0.119
Later single-visit UACR $\geq$ 30 mg/g	Complete case	Model A	676	676	119	1.14 (0.95–1.37)	0.160	0.603
Later single-visit UACR $\geq$ 30 mg/g	Complete case	Model B	676	673	117	1.19 (0.98–1.44)	0.080	0.502
Later single-visit eGFR decline $\geq$ 40%	Complete case	Model B	1115	1107	43	1.48 (1.11–1.98)	0.008	0.448

Note: Hazard ratios are per 1-SD higher SUA standardised within sex. Follow-up began at the 180-day landmark and ended at five years. Model A adjusted for age, sex, baseline eGFR and index year with centre-stratified baseline hazards. Model B additionally adjusted for body mass index, waist circumference, systolic blood pressure, HbA1c and type 2 diabetes. Models C and D are Rubin-pooled expanded sensitivity models. A single later abnormality is not confirmed CKD progression.

Model A standardisation placed the three-year risk at 4.31% (95% CI 2.60–6.03) at – 1 SD of SUA, 6.06% (4.15–7.49) at the mean, and 8.47% (5.74–10.59) at + 1 SD. Corresponding five-year risks were 9.27% (5.78–13.28), 12.82% (8.41–16.27), and 17.53% (11.51–22.17). Relative to the mean, + 1 SD corresponded to absolute risk differences of 2.41 percentage points (0.64–3.83) at three years and 4.71 points (1.17–7.65) at five years.

For later single-visit eGFR below 60 mL/min/1.73 m², Model B included 1,077 participants and 61 events (23.0 per 1,000 person-years). The HR per 1-SD higher SUA was 1.37 (95% CI 1.07–1.74; P = 0.012; proportional-hazards P = 0.119). A later eGFR decrease of at least 40% occurred in 43 of 1,107 Model B participants and showed a concordant association (HR 1.48, 95% CI 1.11–1.98; P = 0.008). The albuminuria analysis included 673 participants and 117 events; its estimate did not exclude the null (HR 1.19, 95% CI 0.98–1.44; P = 0.080) (Table 2).

Expanded adjustment and bias-directed analyses

Multiple imputation retained 1,110 participants and 86 events. Rubin-pooled HRs were 1.34 (95% CI 1.08–1.67) for Model C and 1.39 (1.11–1.74) for Model D. Ridge penalisation reproduced the Model B estimate. Weighting for post-landmark testing gave an HR of 1.40 (1.12–1.74), an effective sample size of 1,101.6, and a maximum absolute weighted SMD of 0.006.

The 365-day landmark remained close to the core result (HR 1.43, 95% CI 1.13–1.80); at 730 days it weakened and crossed 1 (HR 1.22, 0.89–1.67). Diabetes and preserved-function restrictions, and exclusions for urate-lowering treatment, possible hyperfiltration, or extreme SUA, retained the primary direction (Table 3; Figure S1).

Table 3
Key sensitivity analyses for later single-visit eGFR decline of at least 30%

Analysis	Model, n	Events, n	Hazard ratio (95% CI)	P value
365-day landmark	972	71	1.43 (1.13–1.80)	0.003
730-day landmark	732	44	1.22 (0.89–1.67)	0.225
Participants with type 2 diabetes	1033	82	1.48 (1.21–1.83)	< 0.001
Baseline eGFR $\geq$ 60 mL/min/1.73 m ²	1076	78	1.44 (1.17–1.79)	< 0.001
Baseline eGFR $\geq$ 90 mL/min/1.73 m ² and UACR < 30 mg/g	679	36	1.73 (1.29–2.32)	< 0.001
Exclude the event-rich centre	626	35	1.31 (0.94–1.83)	0.113
Stabilised IPW for post-landmark testing	1110	86	1.40 (1.12–1.74)	0.003
Ridge-penalised Cox model ($\theta = 1$)	1102	85	1.46 (1.19–1.79)	< 0.001
<i>Note: Estimates are per 1-SD higher sex-standardised SUA. Unless stated otherwise, analyses use Model B. IPW denotes inverse-probability weighting. The leave-one-centre-out result is an influence analysis; it does not establish centre effect modification.</i>				

Source-specific estimates showed no statistical evidence of heterogeneity (P for interaction = 0.794), although precision varied. Removing the source contributing more than half of core events left 626 participants and 35 events; the estimate remained positive but imprecise (HR 1.31, 95% CI 0.94–1.83). The spline supported an overall association (P = 0.001) without clear non-linearity (P = 0.242).

Repeated eGFR and persistent decline

The eGFR-level mixed model included 872 participants and 4,899 measurements. Each 1-SD higher SUA corresponded to an additional annual eGFR difference of -0.325 mL/min/1.73 m² (95% CI -0.593 to -0.056 ; P = 0.018). The baseline-anchored model used 4,027 follow-up measurements and gave a smaller, less precise coefficient of -0.246 mL/min/1.73 m² per year (95% CI -0.537 to 0.046 ; P = 0.099) (Fig. 3; Table S8).

Fixed-window findings were not uniform. At approximately 12 months, the adjusted eGFR difference per 1-SD higher SUA was -0.868 mL/min/1.73 m² (95% CI -2.329 to 0.592 ; P = 0.244; n = 620). At approximately 24 months, it was -1.707 mL/min/1.73 m² (95% CI -2.791 to -0.623 ; P = 0.002; n = 676). Twenty-nine participants met the persistence definition. Overall descriptive Kaplan–Meier risks were 2.06% (95% CI 1.26–3.36) at three years and 6.01% (3.81–9.43) at five years; no inferential Cox estimate was promoted.

DISCUSSION

The central finding is clinically clear, but its limits matter. Higher baseline SUA identified a filtration-risk phenotype within diabetes-enriched non-obese MASLD. The association appeared across the primary 30% eGFR-decline endpoint and two filtration-based secondary endpoints, and its absolute size was clinically visible: model-standardised five-year risk rose from 12.82% at the sex-specific mean to 17.53% at + 1 SD. Albuminuria did not show the same clear pattern, and longer landmarks reduced precision. The result is therefore specific to later loss of filtration, not a general claim of progressive kidney disease.

This distinction matters because lower BMI is often read as reassurance. A global meta-analysis estimated lean fatty liver prevalence at 4.1% overall and 4.8% in Asian populations [5]. Compared with non-lean MASLD, lean MASLD has been associated with higher all-cause mortality (HR 1.26) and cardiovascular mortality (HR 1.22), despite lower incident non-fatal cardiovascular disease (HR 0.89) [11]. An updated meta-analysis found the same tension between event and mortality outcomes [12]. Our question was narrower. Every participant was below BMI 25 kg/m², yet SUA separated groups with different subsequent filtration risk. It adds information within a non-obese category; it neither makes BMI irrelevant nor replaces direct kidney measurements.

The magnitude sits between useful external comparators. In 13,133 normotensive, normoglycaemic, non-obese adults, the highest versus lowest SUA quartile carried a 3.70-fold risk of a 30% eGFR decline and a 2.2-fold risk of incident CKD [24]. That selected health-check population differs sharply from ours. In 3,123 adults with type 2 diabetes, the corresponding eGFR-decline relative risk was 1.55 (95% CI 1.07–2.26); the accompanying meta-analysis gave a pooled relative risk of 2.33 [25]. A 2026 T2D-CKD cohort found better renal survival when time-averaged SUA remained below 360 µmol/L (HR 0.63, 95% CI 0.41–0.98) [22]. Our per-SD HR of 1.46 is closer to the T2D cohort estimate, fitting a population in which diabetes was almost ubiquitous. The contribution is to localise that filtration signal to clinician-adjudicated non-obese MASLD and define its absolute scale and limits.

MASLD creates a relevant kidney backdrop. Meta-analyses associated fatty liver phenotypes with incident CKD at HRs of 1.37 and 1.35 [14, 15]. The latest pooled estimate places CKD prevalence in MASLD at 15.22% and incidence at 22.17 per 1,000 person-years, with diabetes nearly doubling CKD odds [23]. Our rate of 31.8 per 1,000 person-years is not directly comparable: the endpoint was a single 30% eGFR decrease, not incident CKD, and the cohort came from diabetes-focused care.

Reverse association through kidney handling remains the strongest alternative explanation. In URRAH, hyperuricaemia was roughly ten times more frequent at eGFR below 60 than above 90 mL/min/1.73 m² [17]. Here, median baseline eGFR was 98.6 mL/min/1.73 m² in clinical hyperuricaemia and 106.2 with normal SUA (SMD – 0.557). Sex standardisation, baseline-eGFR adjustment, landmarking, preserved-function restrictions, and hyperfiltration exclusion reduced this concern without resolving it. The 730-day attenuation (HR 1.22, 95% CI 0.89–1.67) shows that the association was not temporally invariant and argues against treating the 180-day estimate as proof that SUA preceded injury.

The weaker albuminuria result does not cancel the filtration finding. eGFR decline and albuminuria are overlapping, non-equivalent diabetic kidney phenotypes. Filtration can deteriorate before or without

albuminuria [32]; in NEFRON, 55% of adults with T2D and eGFR below 60 had persistently normal albumin excretion [34]. CRIC and related cohorts show wide risk gradients across albuminuria strata [33, 35]. When both domains worsen, risk compounds: in 1,417 adults with T2D, a > 30% UACR rise, rapid eGFR decline, and their combination were associated with kidney failure at HRs of 2.31, 4.19, and 5.60, respectively [36]. Our smaller, unscheduled albuminuria analysis yielded HR 1.19 (95% CI 0.98–1.44). SUA therefore aligned more clearly with filtration in this dataset; the result does not prove absence of glomerular injury.

Repeated measures put the threshold result on a clinical scale. +1 SD of SUA corresponded to an additional -0.325 mL/min/1.73 m² per year, or about -1.6 over five years if the contrast remained linear. eGFR slope is prognostically relevant; ADVANCE-ON associated substantial decline with a 30% higher rate of later major outcomes [37]. Our parameterisations were not interchangeable, however. The baseline-anchored coefficient was -0.246 per year and crossed the null, the 12-month fixed-window result was null, and the 24-month contrast was -1.707 mL/min/1.73 m². The five-year figure is therefore scale, not an observed causal loss.

Randomised evidence defines the treatment boundary. PERL found no measured-GFR benefit from allopurinol in type 1 diabetes (slope difference -0.6 mL/min/1.73 m² per year, 95% CI -1.5 to 0.4) [29]. CKD-FIX likewise found no benefit in progressive stage 3–4 CKD (difference -0.10 , 95% CI -1.18 to 0.97) [30]. FEATHER did not show a significant febuxostat benefit in stage 3 CKD with asymptomatic hyperuricaemia (difference 0.70 , 95% CI -0.21 to 1.62) [31]. These trials differ from our cohort and do not address gout treatment. They nevertheless prevent conversion of an observational association into urate lowering solely to preserve eGFR.

The earliest eligible index visit, sex-aware exposure, delayed landmark, source-stratified hazards, baseline-eGFR control, absolute risks, multiple imputation, ridge penalisation, and repeat-testing weighting strengthen the risk-marker conclusion. Routine-care follow-up remains a limitation. One source had almost no longitudinal coverage; another supplied more than half the events. Interaction testing was null ($P = 0.794$), but omission of the event-rich source left only 35 events and a positive, non-significant estimate. That is an influence and precision issue, not proof of effect heterogeneity. Creatinine-based eGFR may shift with acute illness or muscle mass; acute kidney injury, hospitalisation, and death were incompletely captured. No pre-index slope was available, and only 29 events were confirmed. The diabetes-focused setting limits extrapolation to community MASLD.

The clinical implication is direct. In diabetes-enriched non-obese MASLD, higher SUA identifies people more likely to show later loss of kidney filtration. Because SUA is inexpensive and routinely available, a high value should trigger review of baseline and repeat eGFR, UACR, blood pressure, glycaemic control, intercurrent illness, and kidney-protective treatment. It should not trigger urate-lowering therapy by itself. Prospective cohorts with scheduled kidney measurements and confirmed chronic endpoints are needed. Until then, SUA is a pragmatic filtration-risk flag—clear enough to strengthen surveillance, but not a causal biomarker or treatment indication.

Declarations

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

W.L. and J.Z. contributed equally. W.L., J.Z. and Y.W. conceived the study. W.L. performed the formal analysis, prepared the figures and drafted the manuscript. J.Z., W.Lv., L.X., K.S., Y.L., S.H., S.W., Y.D., Q.D. and Q.Z. contributed to data curation, clinical review and interpretation. Q.Z. coordinated site data and contributed to supervision. Y.W. supervised the study and coordinated project administration. All authors critically reviewed and approved the final manuscript. Y.W. is the guarantor and accepts responsibility for the integrity of the work and the decision to publish.

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DATA AVAILABILITY STATEMENT

De-identified participant-level data cannot be released publicly because they remain subject to institutional permissions, privacy safeguards and data-use restrictions. Aggregate model outputs, variable definitions and non-disclosive reproducibility materials accompany the submission. Additional aggregate results or a limited analytic dataset may be considered on reasonable request to the corresponding authors, subject to approval by the participating institutions and an appropriate data-use agreement.

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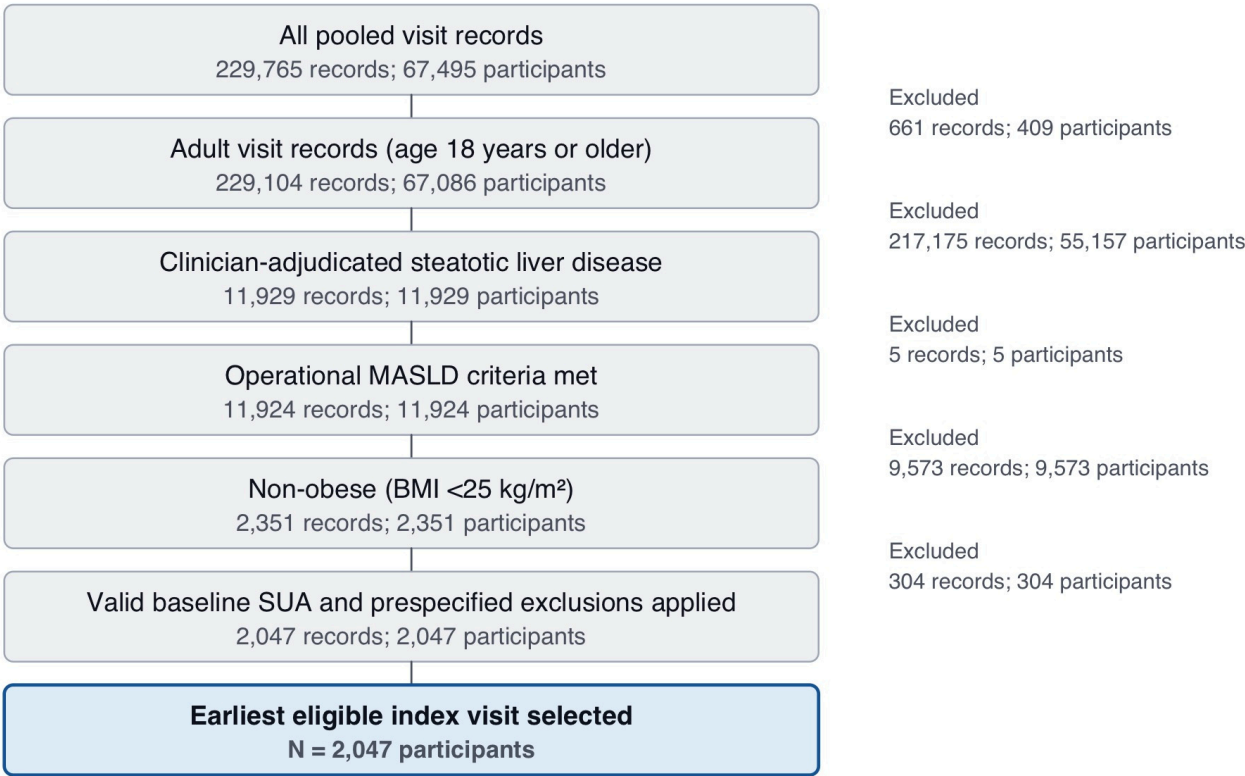
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Figures

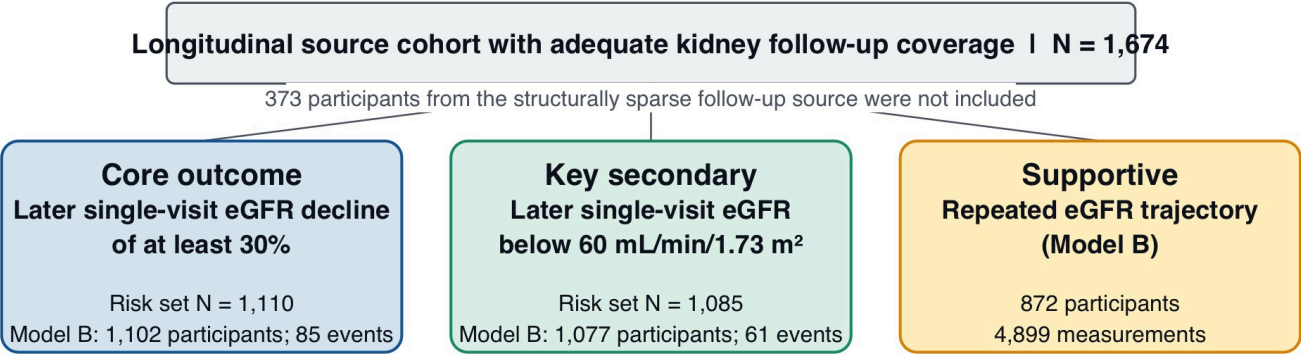
Cohort construction and longitudinal analytic sets

Multicentre real-world cohort; counts refer to records or participants as labelled

A Sequential cohort construction



B Longitudinal analytic branches



Single later abnormal values were analysed as detections, not as confirmed chronic kidney disease progression.

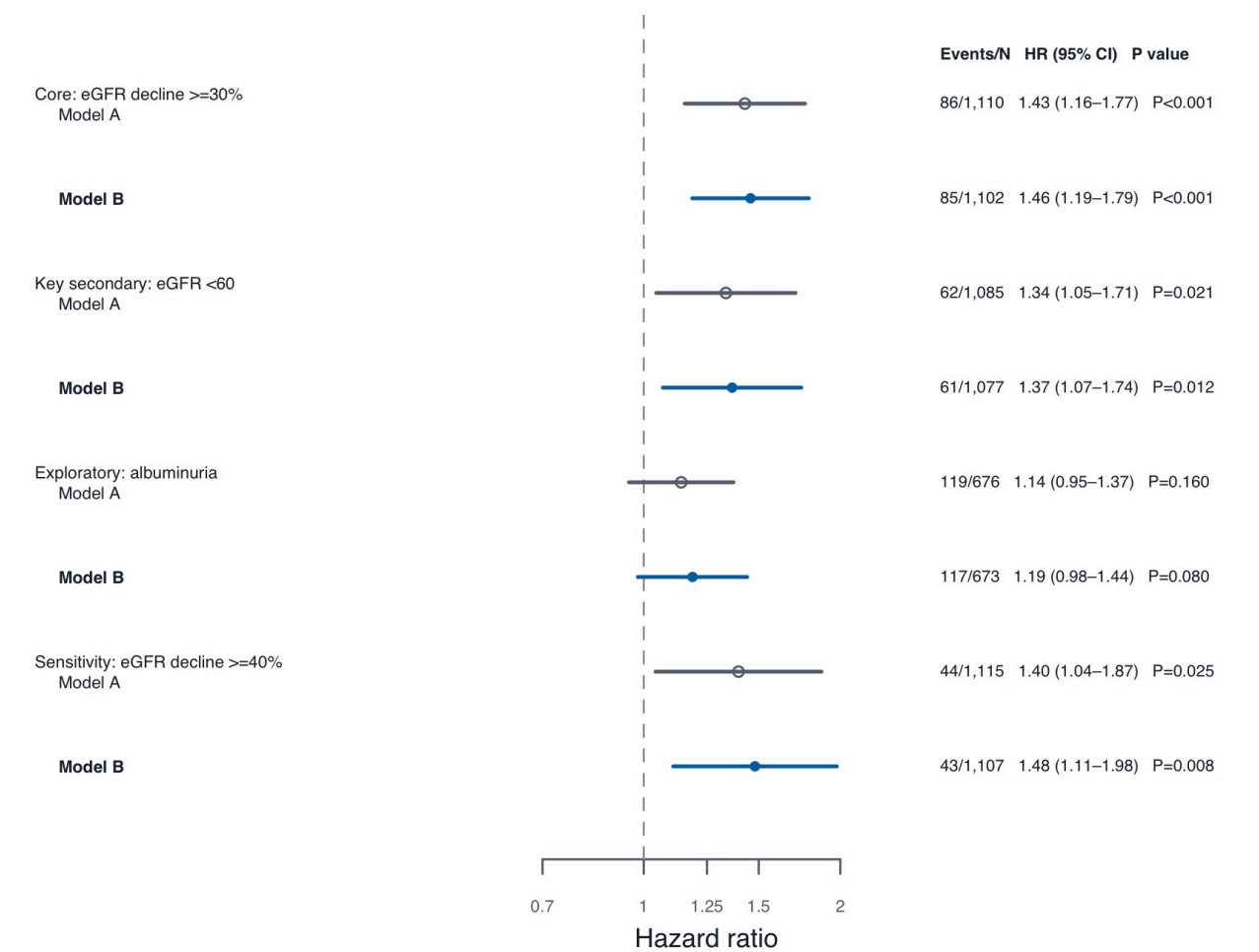
Figure 1

Cohort construction and longitudinal kidney analysis populations. Panel A shows sequential selection from the pooled visit-record database to the index cohort. Panel B shows the populations used for the core eGFR-decrease outcome, later eGFR below 60 mL/min/1.73 m², and supportive repeated-eGFR

modelling. The source with structural absence of follow-up kidney coverage was retained in the baseline cohort and excluded from longitudinal models.

Serum uric acid and later kidney outcome detections

Hazard ratios per 1-SD higher sex-standardized SUA; 180-day landmark; up to 5 years



Open circles: Model A. Filled circles: Model B. Single detections are not confirmed progression.

Figure 2

Main longitudinal kidney outcome estimates. Forest plot of source-stratified HRs and 95% CIs per 1-SD higher sex-standardised SUA for the core 30% eGFR-decrease outcome, later eGFR below 60 mL/min/1.73 m², later albuminuria, and a 40% eGFR decrease. Denominators differ by outcome eligibility. A single later abnormal value denotes an outcome detection, not confirmed CKD progression.

Supportive eGFR trajectories

Model B; 872 participants; 4,899 total measurements and 4,027 follow-up measurements

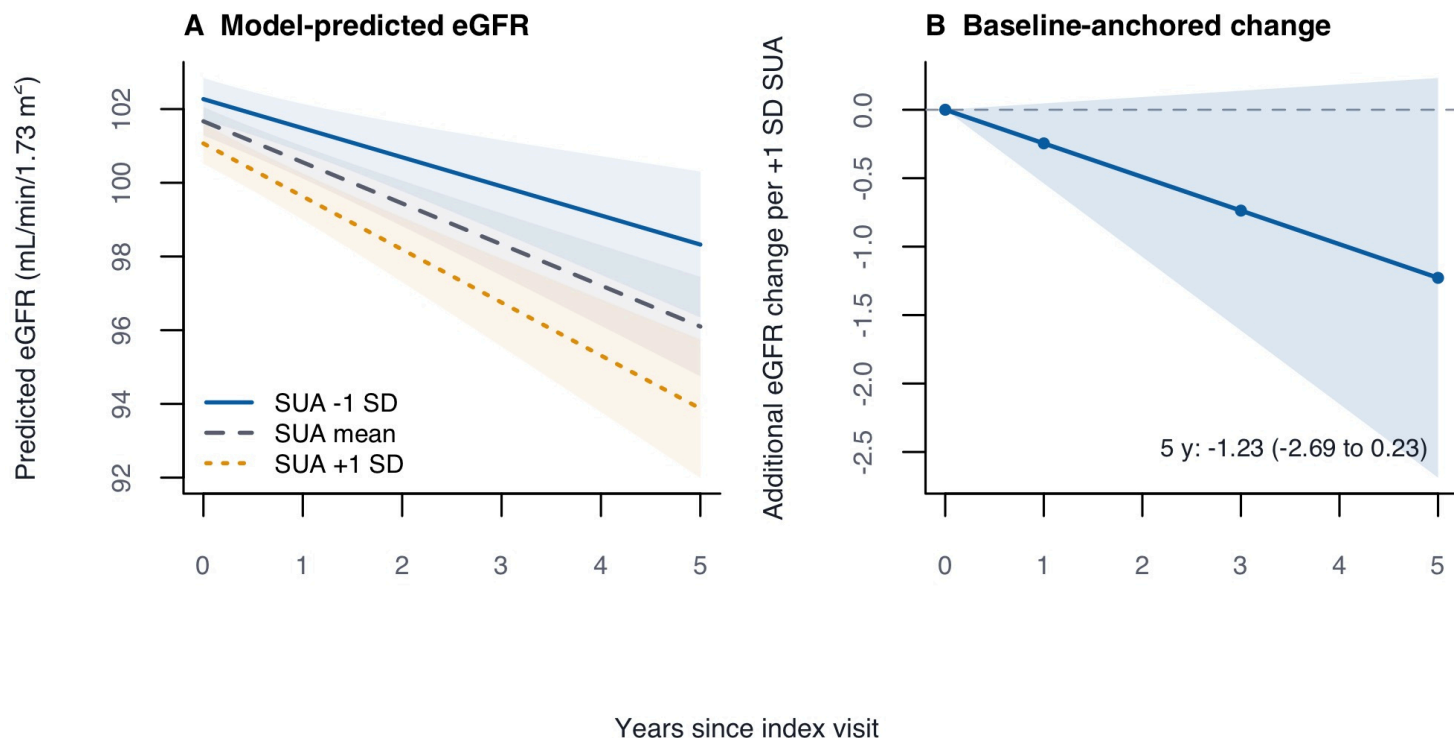


Figure 3

Supportive eGFR trajectories by baseline serum uric acid. Panel A shows model-estimated eGFR levels at -1, 0, and +1 sex-specific SD of SUA. Panel B shows the baseline-anchored SUA-by-time estimate. Models include source fixed effects and participant-specific random intercepts and time slopes. Shaded bands denote 95% CIs.

Supplementary Files

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