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The Relationship Between Uric Acid Levels and The Progression of End-Stage Renal Disease : A Systematic Review

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ABSTRACT

Introduction: Elevated serum uric acid (SUA) is associated with chronic kidney disease (CKD) progression, but large trials of urate-lowering therapy (ULT) show conflicting results. This systematic review synthesizes evidence on the relationship between SUA levels and end-stage renal disease (ESRD) progression.

Methods: We screened longitudinal studies (RCTs, etc) examining SUA as a predictor or intervention for CKD progression to ESRD (eGFR <15 mL/min/1.73m², dialysis, or transplantation). Data extraction focused on SUA measurement, ESRD outcomes, confounders, and ULT effects.

Results: Among 80 included sources (total >3.4 million patients), observational studies consistently showed that hyperuricemia predicts ESRD (HR 1.53–2.84) and rapid eGFR decline (OR 1.38–3.77) with dose-response relationships (1,2,5,18). The association was nonlinear: hazard of kidney failure increased sharply above 11 mg/dL, while mortality showed a U-shaped relationship with nadir

at 5 mg/dL (6). Large RCTs (FEATHER, CKD-FIX, PERL) found no significant benefit of ULT on eGFR slope, but meta-analyses of smaller trials reported modest eGFR preservation (mean difference 1.81–4.10 mL/min/1.73m²) (1,8,9). Achieving SUA <6 mg/dL, not merely initiating ULT, was associated with 37–63% fewer renal events (11,12). Effect modification by baseline CKD stage, proteinuria, sex, and disease etiology was prominent.

Discussion: The observational-evidence and RCT-evidence discordance is explained by low progression rates in control arms, insufficient target SUA achievement, and population heterogeneity. ULT appears most beneficial in early CKD (stages 1–3), rapidly progressive disease, and when SUA target <6 mg/dL is reached. In advanced CKD, very low SUA may be harmful.

Conclusion: Elevated SUA is a robust independent risk factor for CKD progression, but ULT benefits are conditional on patient selection and target attainment. Future trials should enroll high-risk, hyperuricemic patients with progressive disease and titrate to SUA <6 mg/dL.

Keywords: Uric acid, chronic kidney disease, end-stage renal disease, hyperuricemia, urate-lowering therapy, disease progression

INTRODUCTION

Chronic kidney disease (CKD) affects approximately 10–15% of the global adult population and carries a high risk of progression to end-stage renal disease (ESRD), which requires dialysis or kidney transplantation and is associated with substantial morbidity, mortality, and healthcare costs (1). Identifying modifiable risk factors to slow CKD progression is therefore a major clinical priority.

Serum uric acid (SUA), the end product of purine metabolism, has long been recognized as a marker of kidney dysfunction because uric acid excretion is impaired as glomerular filtration rate (eGFR) declines. However, a growing body of evidence suggests that elevated SUA may itself accelerate kidney damage through multiple mechanisms, including activation of the renin-angiotensin system, induction of endothelial dysfunction, oxidative stress, and tubulointerstitial fibrosis (3,5,18,49). Observational studies have repeatedly found that hyperuricemia predicts faster eGFR decline and higher ESRD risk, even after adjusting for traditional confounders (1,2,17,78).

Despite this consistent association, the causal role of uric acid in CKD progression remains controversial. Several large, well-designed randomized controlled trials (RCTs) of urate-lowering therapy (ULT)—including allopurinol and febuxostat—have failed to demonstrate a significant slowing of eGFR decline compared to placebo (13,14,15). This has led to a clinical dilemma: should asymptomatic hyperuricemia in CKD patients be treated to prevent renal progression?

The **research problem** is that the evidence base is fragmented and contradictory, with observational studies suggesting benefit but high-quality RCTs showing null results. The **research gap** lies in understanding why this discordance exists and identifying which patient subgroups, if any, derive renal benefit from ULT. The **novelty** of this systematic review is its comprehensive synthesis of both observational and interventional studies, with detailed attention to effect modifiers, dose-response relationships, nonlinear associations, and the critical distinction between ULT exposure versus achieved SUA target.

Objectives: To systematically review the relationship between SUA levels and ESRD progression, evaluate the effects of ULT on renal outcomes, and identify factors that explain heterogeneity across studies.

Hypothesis: Elevated SUA is an independent risk factor for CKD progression, but the benefit of ULT is conditional on baseline progression rate, CKD stage, and achievement of target SUA <6 mg/dL.

Benefits: This review will inform clinical decision-making regarding ULT prescription in hyperuricemic CKD patients and guide future trial design.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate The Relationship Between Uric Acid Levels and The Progression of End-Stage Renal Disease.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population**: Does the study include patients with chronic kidney disease (any stage) or patients at risk for kidney disease?
- **Uric Acid Exposure**: Does the study measure serum uric acid levels as a primary exposure or predictor variable?
- **ESRD Outcome**: Does the study include progression to end-stage renal disease, initiation of renal replacement therapy (dialysis or transplantation), or reaching eGFR <15 mL/min/1.73m² as a primary or secondary outcome?

- **Study Design**: Is the study design longitudinal (cohort study, case-control study, randomized controlled trial, systematic review, or meta-analysis)?
- **Quantitative Data**: Does the study provide quantitative data on the association between uric acid levels and ESRD progression?
- **Follow-up Duration**: Does the study have a follow-up duration of at least 6 months?
- **Chronic vs Acute Disease**: Does the study focus on chronic kidney disease progression rather than solely on acute kidney injury without chronic progression?
- **Study Type Quality**: Is the study type appropriate for systematic review (i.e., NOT a case report, case series, editorial, or conference abstract)?
- **Uric Acid Timing**: Are uric acid levels measured before or during progression to ESRD (i.e., NOT only measured after initiation of renal replacement therapy)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

PICO Component	Keyword 1	Keyword 2	Keyword 3	Keyword 4
P (Population)	Chronic Kidney Disease (CKD)	End-Stage Renal Disease (ESRD)	CKD stages 3–5	Patients at risk of kidney failure
I (Intervention / Exposure)	Serum Uric Acid (SUA) levels	Hyperuricemia	Urate-lowering therapy (ULT)	Xanthine oxidase inhibitors

C (Comparison)	Normouricemia	Low uric acid trajectory	Placebo / no ULT	Standard care without target SUA control
O (Outcome)	Progression to ESRD	eGFR decline (e.g., ≥30% or ≥3 mL/min/1.73m²/year)	Initiation of renal replacement therapy (dialysis/transplantation)	Kidney failure / composite renal endpoint

The Boolean MeSH keywords inputted on databases for this research are: *("Chronic Kidney Disease" OR "End-Stage Renal Disease" OR "CKD stages 3-5" OR "Patients at risk of kidney failure") AND ("Serum Uric Acid levels" OR "Hyperuricemia" OR "Urate-lowering therapy" OR "Xanthine oxidase inhibitors") AND ("Normouricemia" OR "Low uric acid trajectory" OR "Placebo" OR "Standard care without target SUA control") AND ("Progression to ESRD" OR "eGFR decline" OR "Initiation of renal replacement therapy" OR "Kidney failure")*

Data extraction

- **Study Design & Population**:

  Extract study design and key population characteristics relevant to uric acid-ESRD relationship, including:

  - Study type (RCT, etc)
  - Sample size and follow-up duration
  - Baseline CKD stage or eGFR range
  - Key population demographics (age, gender, comorbidities)
  - Setting and geographic location

- Inclusion/exclusion criteria related to kidney disease or uric acid

- **Uric Acid Assessment**:

  Extract all details about how uric acid levels were measured and categorized for analysis of ESRD progression, including:

  - Method of uric acid measurement
  - Baseline uric acid levels (mean, median, ranges)
  - How hyperuricemia was defined (cut-off values)
  - Uric acid categories used in analysis
  - Whether baseline UA only or serial measurements
  - Any mention of urate crystal presence in kidneys

- **ESRD Progression Outcomes**:

  Extract how end-stage renal disease progression was defined and measured, including:

  - Primary endpoint definition (eGFR decline, doubling of creatinine, ESRD, dialysis initiation, kidney failure)
  - Specific eGFR thresholds used to define progression
  - Secondary renal outcomes assessed
  - Follow-up duration and measurement intervals
  - How eGFR was calculated (equation used)
  - Any mention of proteinuria progression

- **Uric Acid-ESRD Relationship**:

  Extract the main findings about the relationship between uric acid levels and ESRD progression, including:

  - Direction and strength of association (hazard ratios, odds ratios, beta coefficients with confidence intervals)
  - Dose-response relationships across uric acid categories
  - Statistical significance of associations
  - Whether relationship was independent after adjustment
  - Any differences between crude and adjusted analyses
  - Magnitude of eGFR decline per unit increase in uric acid

- **Confounders & Adjustments**:

  Extract information about potential confounding factors and statistical adjustments made when analyzing the uric acid-ESRD relationship, including:

  - List of confounders adjusted for in multivariate models
  - Baseline characteristics that differed by uric acid levels
  - Whether hypertension, diabetes, cardiovascular disease, medications were controlled for
  - How proteinuria was handled in analyses
  - Any propensity score matching or other adjustment methods
  - Sensitivity analyses performed

- **Uric Acid Interventions**:

  For intervention studies, extract details about uric acid-lowering therapy and its effects on ESRD progression, including:

  - Type of uric acid-lowering medication (allopurinol, febuxostat, etc.)
  - Dose and duration of treatment
  - Achieved uric acid reduction (baseline vs. post-treatment levels)
  - Primary renal outcomes in intervention vs. control groups
  - Effect sizes and statistical significance of renal benefits
  - Adverse events related to uric acid-lowering therapy
  - NOTE: Mark as N/A if study did not involve uric acid-lowering interventions

- **Effect Modification**:

  Extract any subgroup analyses or effect modification related to the uric acid-ESRD relationship, including:

  - Differences by baseline CKD stage or eGFR level
  - Modification by presence/absence of proteinuria
  - Differences by age, gender, diabetes status, or other patient characteristics
  - Stronger/weaker associations in specific populations
  - Dialysis modality differences (hemodialysis vs. peritoneal dialysis)
  - Any paradoxical relationships noted in advanced CKD/dialysis populations

- **Proposed Mechanisms**:

  Extract any discussion of biological mechanisms by which uric acid might affect ESRD progression, including:

  - Crystal-dependent vs. crystal-independent mechanisms
  - Effects on glomerular hypertension, arteriolosclerosis, interstitial fibrosis
  - Role of inflammation, oxidative stress, or endothelial dysfunction
  - Whether authors propose uric acid as causal factor vs. marker
  - Animal model findings mentioned
  - Antioxidant vs. pro-oxidant effects discussed

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Chronic Kidney Disease" OR "End-Stage Renal Disease" OR "CKD stages 3-5" OR "Patients at risk of kidney failure") AND ("Serum Uric Acid levels" OR "Hyperuricemia" OR "Urate-lowering therapy" OR "Xanthine oxidase inhibitors") AND ("Normouricemia" OR "Low uric acid trajectory" OR "Placebo" OR "Standard care without target SUA control") AND ("Progression to ESRD" OR "eGFR decline" OR "Initiation of renal replacement therapy" OR "Kidney failure")*	14
Semantic Scholar	*("Chronic Kidney Disease" OR "End-Stage Renal Disease" OR "CKD stages 3-5" OR "Patients at risk of kidney failure") AND ("Serum Uric Acid levels" OR "Hyperuricemia" OR "Urate-lowering therapy" OR "Xanthine oxidase inhibitors") AND ("Normouricemia" OR "Low uric acid trajectory" OR "Placebo" OR "Standard care without target SUA control") AND ("Progression to ESRD" OR "eGFR decline" OR "Initiation of renal replacement therapy" OR "Kidney failure")*	250
Springer	*("Chronic Kidney Disease" OR "End-Stage Renal Disease" OR "CKD stages 3-5" OR "Patients at risk of kidney failure") AND ("Serum Uric Acid levels" OR "Hyperuricemia" OR "Urate-lowering therapy" OR "Xanthine oxidase inhibitors") AND ("Normouricemia" OR "Low uric acid trajectory" OR "Placebo" OR "Standard care without target SUA control") AND ("Progression to ESRD" OR "eGFR decline" OR "Initiation of renal replacement therapy" OR "Kidney failure")*	422
Google Scholar	*("Chronic Kidney Disease" OR "End-Stage Renal Disease" OR "CKD stages 3-5" OR "Patients at risk of kidney failure") AND ("Serum Uric Acid levels" OR "Hyperuricemia" OR "Urate-lowering therapy" OR "Xanthine oxidase inhibitors") AND ("Normouricemia" OR "Low uric acid trajectory" OR "Placebo" OR "Standard care without target SUA control") AND ("Progression to ESRD" OR "eGFR decline" OR "Initiation of renal replacement therapy" OR "Kidney failure")*	923
Wiley Online Library	*("Chronic Kidney Disease" OR "End-Stage Renal Disease" OR "CKD stages 3-5" OR "Patients at risk of kidney failure") AND ("Serum Uric Acid levels" OR "Hyperuricemia" OR "Urate-lowering therapy" OR "Xanthine oxidase inhibitors") AND ("Normouricemia" OR "Low uric acid trajectory" OR "Placebo" OR "Standard care without target SUA control") AND ("Progression to ESRD" OR "eGFR decline" OR "Initiation of renal replacement therapy" OR "Kidney failure")*	2

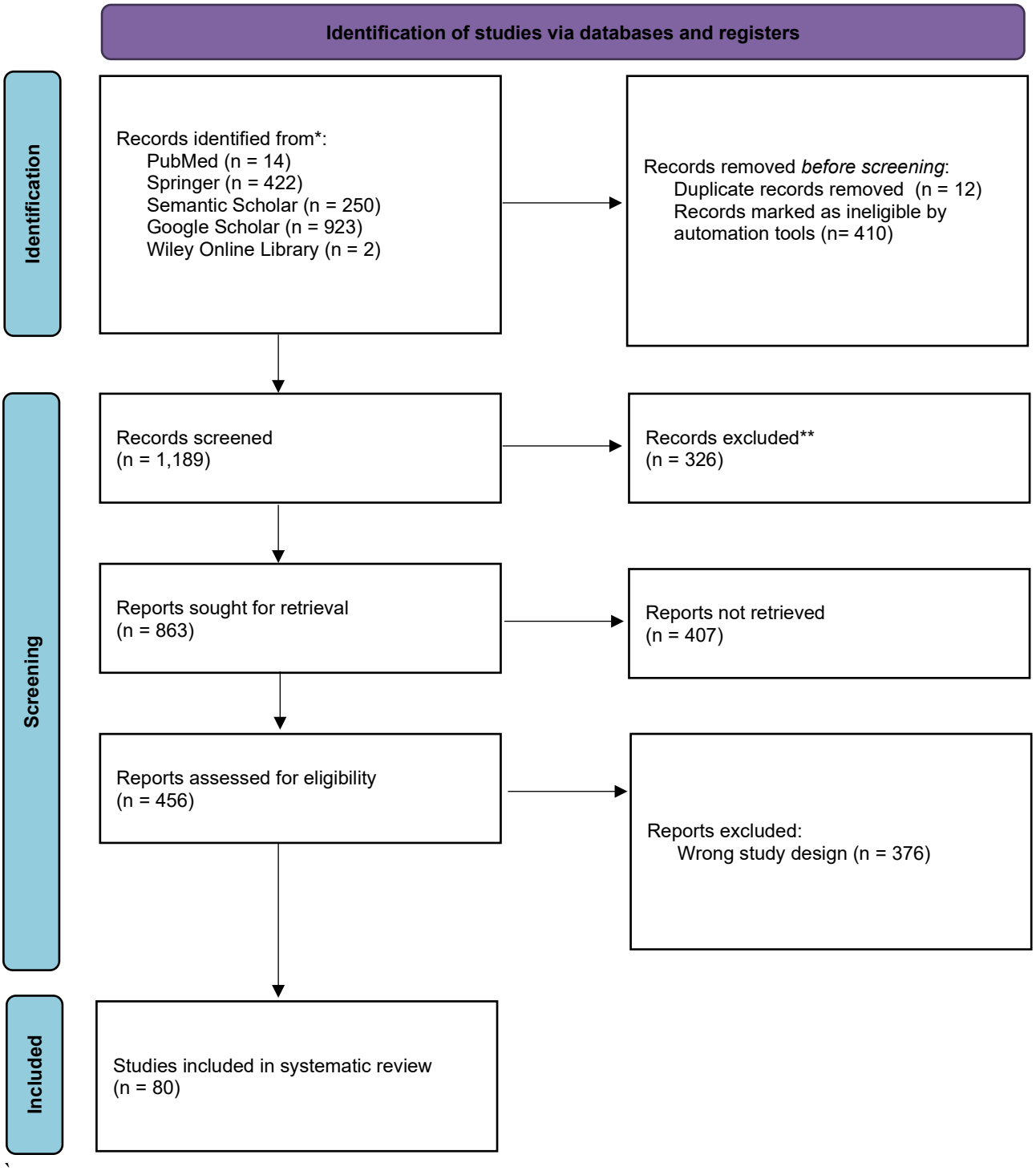

Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

The 80 sources included in this review span a wide range of study designs, populations, and geographic settings. The following table summarizes the key characteristics of each included source.

Study	Sample Size	Follow-up	Baseline CKD Stage / eGFR	Population
Ching-Wei Tsai et al., 2018 [2]	5,090 CKD patients [2]	13 years [2]	Not specified [2]	Age 20–90 years, pre-ESRD care registry [2]
M. Prezelin-Reydit et al., 2020 [17]	2,781 patients [17]	Median 3.2 years [17]	CKD stages 3–5, median eGFR 31.8 mL/min/1.73m² [17]	Median age 69 years, 65.5% men, 40 French nephrology clinics [17]
Ching-Wei Tsai et al., 2017 [18]	739 patients [18]	~4.25 years [18]	Divided across eGFR strata including <15 to ≥90 mL/min/1.73m² [18]	Patients with hyperuricemia or on ULT, Taiwan [18]

Study	Sample Size	Follow-up	Baseline CKD Stage / eGFR	Population
Kyle E. Rodenbach et al., 2015 [19]	678 cross-sectional; 627 longitudinal [19]	5 years [19]	Median GFR 47.8 mL/min/1.73m² [19]	Children/adolescents, median age 12.3 years, 62% male, 52 North American sites [19]
Gen-yang Cheng et al., 2013 [20]	348 cases [20]	8 years [20]	Not specified [20]	IgA nephropathy patients [20]
Szu-Chia Chen et al., 2013 [21]	540 patients [21]	33.4 months [21]	CKD stages 3–5 [21]	Not specified [21]
Xiaole Su et al., 2017 [8]	1,211 CKD patients (16 trials) [8]	Median 12 months (range 6–84 months) [8]	Not specified [8]	Adults with CKD on ULT [8]
Yoonjin Kim et al., 2015 [22]	158 patients [22]	Median 118.5 weeks [22]	Stage 3 CKD [22]	Hyperuricemic CKD patients, Korea [22]
Dong-Jin Park et al., 2020 [23]	137 patients [23]	85 months [23]	Mean eGFR 100.3±47.9 mL/min/1.73m² [23]	Lupus nephritis, mean age 32.2 years, predominantly female (89.9%), Korea [23]

Study	Sample Size	Follow-up	Baseline CKD Stage / eGFR	Population
Y. Miao et al., 2011 [24]	1,342 patients [24]	First 6 months [24]	Not specified [24]	Type 2 diabetes with nephropathy [24]
Gérald Lévy et al., 2014 [11]	16,186 patients [11]	Up to 3 years [11]	Excludes CKD stages 4–5 [11]	Hyperuricemic adults ≥18 years, Kaiser Permanente Southern California [11]
A. Hart et al., 2014 [25]	Not specified [25]	5 years [25]	Kidney transplant recipients [25]	Renal allograft recipients [25]
Yan Huang et al., 2012 [26]	12 cohort studies, 45–488 participants each [26]	1–10 years [26]	Not specified [26]	Renal transplant recipients, multiple countries [26]
A. Tiku et al., 2021 [15]	443 + 369 + 530 patients across three trials [15]	≥2 years each [15]	Stage 3 (mean eGFR 45) and stages 3–4 (mean eGFR 31.7) and type 1 DM (mean eGFR 74.7) [15]	Asymptomatic hyperuricemia, advanced CKD, diabetic kidney disease [15]

Study	Sample Size	Follow-up	Baseline CKD Stage / eGFR	Population
K. Lee et al., 2015 [27]	158 patients [27]	1,050±759 days [27]	Stage 3 CKD [27]	Hyperuricemic CKD patients, Korea [27]
Chunlei Yao et al., 2019 [28]	3,432 patients [28]	Median 30 months [28]	Not specified [28]	Type 2 diabetes mellitus, Chinese communities [28]
Suryeong Go et al., 2020 [29]	143,762 subjects [29]	>12 years [29]	Mean eGFR 94.3±15.2 mL/min/1.73m² [29]	General population health check-up, Korea [29]
Gaurav Sharma et al., 2021 [1]	131 studies, 3,414,226 patients [1]	6 months–31 years (observational); mean 11.6 months (ULT trials) [1]	Incident CKD stage 3 (eGFR <60) [1]	General and CKD populations, multiple countries [1]
M. Prezelin-Reydit et al., 2023 [6]	2,781 patients [6]	Median 3.2 years [6]	CKD stages 3–5 [6]	Median age 69 years, 66% men, France [6]

Study	Sample Size	Follow-up	Baseline CKD Stage / eGFR	Population
H. Katsuyama et al., 2019 [4]	Not explicitly stated [4]	6 months [4]	Not specified [4]	CKD patients on topiroxostat, Japan [4]
A. Tiku et al., 2018 [13]	443 patients [13]	108 weeks [13]	CKD stage 3, SUA 7.0–10.0 mg/dL [13]	Adult Japanese patients, asymptomatic hyperuricemia [13]
Kang Zhang et al., 2022 [30]	11,548 patients from 14 studies [30]	Not specified [30]	Not specified [30]	IgA nephropathy, Asia and Western countries [30]
S. Sezer et al., 2014 [31]	96 patients [31]	12 months [31]	CKD stages 3–4, mean eGFR 44.62±14.38 mL/min/1.73m² [31]	Mean age 65.3 years, 57% male [31]
M. Tai-Seale et al., 2013 [32]	33,745 patients [32]	2002–2010 [32]	CKD stages 1–3 [32]	Adults ≥18 years, Kaiser Permanente Southern California [32]

Study	Sample Size	Follow-up	Baseline CKD Stage / eGFR	Population
Jinting Pan et al., 2023 [33]	846 patients [33]	Median 4.8 years [33]	Baseline eGFR ≥60 mL/min/1.73m² [33]	Type 2 diabetes mellitus, China [33]
Yu Li et al., 2024 [34]	5,421 individuals [34]	~4 years (2011–2015) [34]	Mean eGFR 89.7 mL/min/1.73m² [34]	Middle-aged and elderly, China [34]
Katsunori Yanai et al., 2023 [35]	34 patients [35]	12 months [35]	CKD stages G3–5, mean eGFR 32.0±13.3 mL/min/1.73m² [35]	Hyperuricemic advanced CKD, mean age 68.6 years [35]
Chia-Lin Lee et al., 2022 [36]	808 patients [36]	6 months minimum [36]	CKD stage 3 [36]	Mixed comorbidities including diabetes and cardiovascular disease [36]

Study	Sample Size	Follow-up	Baseline CKD Stage / eGFR	Population
T. Hosoya et al., 2014 [37]	400 patients planned [37]	108 weeks [37]	CKD stage 3, eGFR 30–59 mL/min/1.73m² [37]	Japanese patients ≥20 years, asymptomatic hyperuricemia, no gout [37]
Hongtao Yang et al., 2022 [38]	100 patients [38]	12 months [38]	CKD stages 3–4 [38]	Asymptomatic hyperuricemia, seven medical centers, China [38]
Shuo-Chun Weng et al., 2016 [39]	2,460 adults [39]	Not specified [39]	Not specified [39]	Adults on ULT ≥3 months [39]
Carmine Zoccali & D. Bolignano, 2020 [14]	369 enrolled (185 allopurinol, 184 placebo) [14]	~104 weeks [14]	CKD stages 3–4, mean eGFR 31.7 mL/min/1.73m² [14]	Adults without gout, Australia and New Zealand [14]
S. Tsai et al., 2019 [40]	808 patients [40]	6 months minimum [40]	CKD stage 3 [40]	Diabetes mellitus subgroup noted [40]

Study	Sample Size	Follow-up	Baseline CKD Stage / eGFR	Population
Xuemei Liu et al., 2018 [9]	832 CKD participants (12 RCTs) [9]	4–24 months [9]	Not specified [9]	Adult CKD patients [9]
George J. Schwartz et al., 2022 [41]	153 glomerular + 540 non-glomerular [41]	Not specified [41]	Not specified [41]	Children/adolescents with CKD [41]
Y. Maruyama et al., 2021 [42]	4,277 CKD patients (11 studies) [42]	<1 year (6 studies), ≥1 year (5 studies) [42]	eGFR <60 mL/min/1.73m² [42]	Non-dialyzed adult CKD patients, Asia, North America, Europe [42]
Sima Golmohammadi et al., 2017 [43]	Not specified [43]	12 months [43]	CKD stages 3–4, stratified by mild and severe GFR impairment [43]	Not specified [43]

Study	Sample Size	Follow-up	Baseline CKD Stage / eGFR	Population
Yuka Sato et al., 2019 [16]	Not specified [16]	Typically 6 months–2 years [16]	Not specified [16]	CKD patients with hyperuricemia [16]
Yipeng Han et al., 2022 [44]	123 biopsy-proven LN patients (primary); meta-analysis [44]	Median 3.67 years [44]	Not specified [44]	Lupus nephritis, Southern Chinese population [44]
Aamir Nabi et al., 2025 [45]	152 patients [45]	24 months [45]	CKD stages 2–4 [45]	Mean age 58.4 years, 61% male, Peshawar [45]
Gerald D. Levy & T. Craig Cheetham, 2015 [46]	93 patients [46]	6 months [46]	CKD stages 3–4 [46]	Not specified [46]
M. Kuwabara et al., 2017 [5]	12,578 subjects [5]	5 years [5]	Excluded eGFR <60 mL/min/1.73m² [5]	Age 30–85 years, general population, Tokyo, Japan [5]

Study	Sample Size	Follow-up	Baseline CKD Stage / eGFR	Population
K. Iseki et al., 2013 [47]	16,630 participants [47]	10 years [47]	Not specified [47]	Community-based screening, Okinawa, Japan [47]
Yongjun Shi et al., 2011 [48]	353 (cohort); 40 (RCT) [48]	5 years (cohort); 6 months (RCT) [48]	Not specified [48]	IgA nephropathy patients [48]
S. Sedaghat et al., 2013 [49]	2,601 subjects [49]	~6.5 years [49]	Mean eGFR 77.15 mL/min/1.73m² [49]	Age ≥55 years, Rotterdam, Netherlands [49]
Tahir Kanji et al., 2015 [50]	992 participants (19 RCTs) [50]	2 days–24 months [50]	eGFR <60 mL/min/1.73m² [50]	CKD stages 3–5, 10 countries [50]
K. Hanai et al., 2018 [7]	7,033 type 2 diabetic patients [7]	Not specified [7]	Non-CKD (eGFR ≥60) and CKD (eGFR <60) [7]	Type 2 diabetes mellitus [7]

Study	Sample Size	Follow-up	Baseline CKD Stage / eGFR	Population
B. S. Pai et al., 2013 [51]	183 patients [51]	2 years [51]	eGFR <90 mL/min/1.73m² [51]	Mean age ~51 years, Hyderabad, India [51]
Liyi Liu et al., 2021 [52]	1,534 subjects [52]	4 years (2012–2016) [52]	Not specified [52]	Age 40–75 years, community-based, Guangzhou, China [52]
Xiuxiu Lai et al., 2022 [53]	425 subjects [53]	3 years [53]	eGFR <60 mL/min/1.73m² [53]	Elderly Chinese adults, age 71–100 years [53]
F. G. Sharbaf et al., 2024 [54]	698 participants (4 trials) [54]	Mean 22.5 months [54]	Not specified [54]	Children and adults with CKD and hyperuricemia [54]
C. Reátegui-Sokolova et al., 2016 [55]	186 SLE patients [55]	Mean 2.3 years [55]	Not specified [55]	Mean age at diagnosis 36.8 years, predominantly Mestizo, rheumatology clinic [55]

Study	Sample Size	Follow-up	Baseline CKD Stage / eGFR	Population
Fan Lin et al., 2016 [56]	837 patients [56]	3.5 years [56]	Mean eGFR 74.78±28.74 mL/min/1.73m² [56]	Elderly hypertensive patients, mean age 69.0 years, China [56]
A. Ozdemir & A. Inci, 2017 [57]	132 patients [57]	12 months [57]	CKD stage 3 [57]	41 females, 91 males; pre-dialysis polyclinic [57]
Y. Shibagaki et al., 2014 [58]	70 patients [58]	24 weeks [58]	CKD stages 3b, 4, and 5 [58]	Not specified [58]
Yuxin Luo et al., 2023 [10]	17 RCTs [10]	Not specified [10]	CKD stages 1–3 [10]	Asian countries focus; patients <60 years highlighted [10]
Xuemei Liu et al., 2018a [59]	208 patients [59]	6 months [59]	CKD stages 3–5, mean eGFR ~28–31 mL/min/1.73m² [59]	Chinese Han patients, hyperuricemia [59]
Yuki Tsuruta et al., 2014 [60]	73 patients [60]	1 year [60]	eGFR <45 mL/min/1.73m² [60]	Age mean ~68–73 years, renal clinic, Japan [60]

Study	Sample Size	Follow-up	Baseline CKD Stage / eGFR	Population
N. Ueno, 2018 [61]	34 patients [61]	52 weeks [61]	Not specified [61]	Type 2 diabetic patients with hyperuricemia [61]
Yukinao Sakai et al., 2014 [62]	60 patients [62]	6 months before and after [62]	67% with eGFR <30 mL/min/1.73m² [62]	CKD on allopurinol, switched to febuxostat, Japan [62]
N. Ueno, 2017 [63]	34 patients [63]	52 weeks [63]	Mean eGFR 66.0±3.1 mL/min/1.73m² [63]	Type 2 diabetic patients, Japan [63]
A. Whelton et al., 2013 [64]	551 subjects [64]	Up to 48 months [64]	Not specified [64]	Gout patients on febuxostat [64]
Xin Zhang et al., 2019 [65]	152 patients [65]	6 months [65]	CKD stages 2–3 [65]	Hyperuricemia, CKD [65]
Yueh-Lung Peng et al., 2020 [66]	1,050 CKD patients (525 per group) [66]	2.5 years [66]	Excluded eGFR ≤15 mL/min/1.73m² [66]	Adult CKD patients, Taiwan [66]

Study	Sample Size	Follow-up	Baseline CKD Stage / eGFR	Population
B. Ghang et al., 2024 [12]	5,002 gout patients [12]	Median 2.5 years [12]	Not specified [12]	Gout patients on ULT [12]
A. Anwar et al., 2017 [67]	120 patients [67]	8 months [67]	CKD stages 3–5 [67]	Mean age 45–49 years, predominantly male, Dhaka, Bangladesh [67]
Seokwoo Park et al., 2022 [68]	654 per group [68]	Median ~411–552 days [68]	Baseline eGFR ~39–40 mL/min/1.73m² [68]	~20% diabetic, ~60% on ACEi/ARB, Seoul, South Korea [68]
O. Kurihara et al., 2023 [69]	53 patients [69]	Mean 9.8 months [69]	Mean eGFR 38.7 mL/min/1.73m² [69]	Hyperuricemia with severe renal dysfunction [69]
Y. Waheed et al., 2025 [70]	316 patients [70]	12 months [70]	Non-dialysis CKD stages 3–4 [70]	Mean age ~54 years, ~55% male, China [70]

Study	Sample Size	Follow-up	Baseline CKD Stage / eGFR	Population
M. Kuwabara et al., 2017a [71]	13,070 subjects [71]	5 years [71]	Excluded eGFR <60 mL/min/1.73m² [71]	Age 30–85 years, general population, Tokyo, Japan [71]
B. Ghang et al., 2022 [72]	4,144 gout patients [72]	Median 3.1 years [72]	Not specified [72]	Gout patients on ULT [72]
L. Khimion et al., 2022 [73]	45 patients [73]	6 months [73]	CKD stages 3b–5 [73]	Age ~61 years, pre-dialysis and hemodialysis [73]
Y. Waheed et al., 2025a [74]	200 patients [74]	12 months [74]	CKD stages 3–4 [74]	Age 20–80 years, Xuzhou area, China [74]
Huifang Wang et al., 2017 [75]	98 patients [75]	6 months [75]	CKD stages 3–5 [75]	No significant demographic differences between groups [75]
T. Kumagai et al., 2017 [76]	Not applicable [76]	Not applicable [76]	Not specified [76]	Not specified [76]

Study	Sample Size	Follow-up	Baseline CKD Stage / eGFR	Population
M. Mauer & A. Doria, 2020 [77]	Not applicable [77]	Not applicable [77]	Not specified [77]	Diabetic kidney disease [77]
Yu-lin Li et al., 2011 [78]	276,801 (incidence); 3,004 (prognosis) [78]	Not specified [78]	Not specified [78]	Not specified [78]
A. Testa et al., 2014 [3]	755 CKD patients + 211 healthy volunteers [3]	Median 36 months [3]	Not specified [3]	CKD patients from same geographic area as healthy volunteers [3]
M. Goicoechea et al., 2010 [79]	113 patients [79]	Mean 23.4 months [79]	eGFR <60 mL/min/1.73m² [79]	Presence of diabetes and coronary heart disease noted [79]
Won Jin Kim et al., 2014 [80]	512 patients [80]	Not specified [80]	Preserved eGFR ≥60 mL/min/1.73m² [80]	Type 2 diabetes mellitus, normouricemia at baseline, South Korea [80]

The body of evidence is heterogeneous in design, ranging from large population-based cohorts enrolling over 100,000 individuals [29] and meta-analyses incorporating more than 3 million patients [1] to small single-center retrospective analyses with fewer than 40 participants [61, 63]. Geographically, the literature is heavily weighted toward East Asian populations, particularly Japanese, Korean, Taiwanese, and Chinese cohorts, with more limited representation from European [17, 49] and North American [11, 19, 32] populations. Baseline CKD severity varies widely: some studies enrolled patients with preserved kidney function or CKD stage 1–3 [5, 32] while others specifically targeted advanced CKD stages 3b–5 [58, 73]. Several studies focused on disease-specific subpopulations, including IgA nephropathy [20, 30, 48], lupus nephritis [23, 44, 55], renal transplant recipients [25, 26], type 2 diabetes [7, 28, 33, 80], and type 1 diabetes with diabetic kidney disease [15]. Studies of children and adolescents are represented by two CKiD cohort analyses [19, 41].

Effects of Uric Acid Levels on Kidney Disease Progression

Observational Evidence: Uric Acid as a Risk Factor

General and CKD populations

The observational literature overwhelmingly documents a positive association between elevated serum uric acid (SUA) and accelerated renal function decline or end-stage renal disease (ESRD). The largest meta-analysis, incorporating 131 studies with over 3.4 million patients [1], found hyperuricemia to be significantly associated with rapid eGFR decline ≥3 mL/min/1.73m²/year (OR 1.38, 95% CI 1.20–1.59), albuminuria (OR/HR 1.94, 95% CI 1.34–2.79), incident CKD (OR/HR 2.13, 95% CI 1.74–2.61), and kidney failure (HR 1.53, 95% CI 1.18–1.99) [1]. An earlier meta-analysis of 21 cohort studies involving 276,801 individuals for incidence and 3,004 for prognosis found that hyperuricemia increased the risk of incident kidney disease (RR 1.49, 95% CI 1.27–1.75), worsened renal function (RR 1.35, 95% CI 1.12–1.63), and increased mortality (RR 1.67, 95% CI 1.29–2.16) [78].

Within CKD-specific prospective cohorts, the trajectory-based analysis of 5,090 patients from a 13-year pre-ESRD registry demonstrated a clear dose-response relationship: compared to a low SUA trajectory, adjusted hazard ratios for incident ESRD were 1.89 (95% CI 1.37–2.60) for a

moderate trajectory, 2.49 (95% CI 1.75–3.55) for moderate-high, and 2.84 (95% CI 1.81–4.47) for a high trajectory [2]. For all-cause mortality, the corresponding hazard ratios were 1.38, 1.95, and 4.52 respectively [2], and the unfavorable effect of elevated trajectories was significantly stronger among patients not receiving urate-lowering therapy at baseline (P for interaction = 0.018) [2].

In the large CKD-REIN French cohort (n=2,781, CKD stages 3–5), each 100 µmol/L increment in current uric acid was associated with a 16% increased hazard of the composite outcome of renal replacement therapy (RRT) or death before RRT (aHR 1.16, 95% CI 1.07–1.26) [17]; the analogous hazard ratios for RRT alone and death before RRT were 1.18 (95% CI 1.04–1.34) and 1.16 (95% CI 1.05–1.28), respectively [17]. Critically, after further adjustment for individual eGFR trajectory, this association attenuated substantially (aHR 1.06, 95% CI 0.98–1.16) [17], raising important questions about whether SUA acts independently of kidney function decline or is partly a marker of it.

Among 739 hyperuricemic or ULT-treated patients in Taiwan followed for approximately 4 years, each 1 mg/dL increase in baseline SUA was associated with a 7% higher risk of progression to renal failure (HR 1.07, 95% CI 1.00–1.14) [18], and a 1 mg/dL increase in uric acid was associated with an additional eGFR decline of 1.6 mL/min/1.73m²/year (β = -1.6, 95% CI -2.2 to -1.0) [18]. This study further demonstrated a dose-response relationship across UA categories (<6, 6–8, 8–10, ≥10 mg/dL) [18].

A large general-population cohort from Japan (n=12,578, followed 5 years) found that each 1 mg/dL increase in baseline SUA was associated with 27% greater odds of rapid eGFR decline (OR 1.27, 95% CI 1.17–1.38), and each 1 mg/dL increase in SUA over 5 years conferred 3.77-fold greater odds of rapid eGFR decline (OR 3.77, 95% CI 3.35–4.26) [5]. These findings were replicated in a companion PowerPoint presentation of the same dataset [71]. A 10-year community-based study in Okinawa (n=16,630) found that each 1 mg/dL increase in uric acid was associated with eGFR declines of 1.91–4.19 mL/min/1.73m² depending on baseline uricemia status, with change in uric acid representing a stronger predictor of eGFR decline than baseline level or the presence of hypertension or diabetes [47].

In a Chinese longitudinal study of 5,421 middle-aged and elderly individuals, each 1 mg/dL increase in baseline SUA carried an OR of 1.68 (95% CI 1.48–1.90) for rapid eGFR decline, while each 1 mg/dL increase in the change in SUA carried an OR of 1.92 (95% CI 1.71–2.16) for rapid eGFR decline [34]. Among 1,534 community-based participants followed for 4 years, uric acid lowering (quartile 1 vs. quartile 4 of SUA change) was associated with substantially reduced risk of renal function decline (HR 0.64, 95% CI 0.49–0.85) and increased probability of renal function improvement (HR 2.27, 95% CI 1.45–3.57) [52].

In a cohort of 425 elderly Chinese individuals (age 71–100 years), there was a strong dose-response with each successive SUA quartile: ORs for development of CKD were 1.79, 3.40, and 6.79 for the second, third, and fourth quartiles relative to the first [53]; each 1 mg/dL increase in baseline SUA yielded an OR of 1.76 for renal failure [53], and each 1 mg/dL increase in SUA was associated with an additional 1.25 mL/min/1.73m² decrease in eGFR over 3 years [53]. A retrospective 3.5-year study of 837 elderly hypertensive patients found that each 100 μmol/L increase in baseline uric acid was associated with a 5.684 mL/min/1.73m² lower eGFR [56], and patients with increased uric acid over follow-up had 1.64-fold higher odds of renal function decline (95% CI 1.129–2.378) [56]. Among 2,601 Rotterdam Study participants followed for 6.5 years, each 1 mg/dL increase in SUA was associated with a 0.19 mL/min/1.73m²/year faster annual eGFR decline [49].

In a 152-patient cohort from Pakistan followed for 24 months, CKD progression occurred in 42.3% of hyperuricemic versus 24.7% of normouricemic patients (p=0.01), with a HR of 1.76 (95% CI 1.18–2.84) for CKD progression in the hyperuricemic group [45]; the eGFR drop rate was 12.8±6.3 versus 7.4±4.9 mL/min/1.73m² over 24 months (p=0.002) [45].

Non-linear relationships and the U-shaped association

Two studies from the CKD-REIN cohort have particularly illuminated the shape of the SUA-outcome relationship. The 2023 analysis by Prezelin-Reydit et al., using spline modeling of longitudinal SUA, found that the hazard of kidney failure increases with increasing current SUA, with a plateau between 6 and 10 mg/dL and a sharp increase above 11 mg/dL [6]. In contrast, the hazard of death exhibited a U-shaped relationship: the risk of dying was approximately twice as

high at both 3 mg/dL and 11 mg/dL compared to a reference of 5 mg/dL [6]. This indicates that very low SUA levels—below 5 mg/dL—are independently associated with pre-ESRD mortality [6], a finding with important implications for aggressive urate-lowering.

A complementary finding emerged from a Korean cohort of 143,762 general-population adults followed for over 12 years: in men, both the lowest (<4.1 mg/dL) and highest (≥7.8 mg/dL) SUA groups displayed elevated ESRD risk relative to the middle group (HR 2.41 and 1.74, respectively) [29], while in women, no significant association between SUA and incident ESRD was found [29]. The U-shape was thus present in men but absent in women [29].

Disease-specific populations

IgA nephropathy: A meta-analysis of 14 studies including 11,548 patients found that hyperuricemia was an independent prognostic factor for IgA nephropathy-related kidney failure, with an adjusted RR of 2.12 (95% CI 1.64–2.73); elevated SUA as a continuous variable was also associated with kidney failure (adjusted RR 1.25 per unit increase, 95% CI 1.19–1.31) [30]. In a single-center 348-patient longitudinal study, the prevalence of ESRD at follow-up was 64.71% among patients with high SUA versus 35.00% among those with normal levels ($p<0.05$) [20], and high SUA was correlated with greater glomerular sclerosis and tubulointerstitial injury scores [20]. A 353-patient retrospective cohort confirmed that hyperuricemia independently predicted renal survival at 1, 3, and 5 years after adjusting for baseline eGFR [48].

Lupus nephritis: In the KORNET lupus nephritis registry (n=137, followed 85 months), SUA >7 mg/dL was an independent predictor of CKD development (HR 2.437, p=0.020) [23]. Among 123 Southern Chinese biopsy-proven LN patients, each unit increase in SUA (continuous) was associated with an HR of 1.003 (95% CI 1.001–1.005) for LN progression, and hyperuricemia categorically conferred an HR of 1.780 (95% CI 1.201–2.639) [44], with the association significant in women but not reaching significance in men [44]. Among 186 SLE patients from a Latin American cohort, higher baseline uric acid was associated with new renal damage at univariable (HR 2.24, 95% CI 1.50–3.34) and multivariable (HR 3.21, 95% CI 1.39–7.42) levels [55].

Diabetic kidney disease: In 7,033 type 2 diabetic patients stratified by baseline eGFR, there was a significant interaction: each 1 mg/dL increase in SUA increased the risk of ≥30% eGFR

decline by 13% in non-CKD patients (HR 1.13, 95% CI 1.05–1.22), but was inversely associated with progression in established CKD patients (HR 0.93, 95% CI 0.88–0.99) [7] —suggesting the relationship may reverse or attenuate once significant nephropathy is established. Among 3,432 Chinese T2DM community patients, the SUA/creatinine ratio was an independent predictor of renal progression (HR 1.364, 95% CI 1.131–1.646) [28]. In 512 normouricemic T2DM patients with preserved function, the highest SUA quartile (within normal range) was associated with HR 2.97 (95% CI 1.15–7.71) for developing CKD stage 3 or greater [80]. Two studies from a single research group of 34 type 2 diabetic patients found a significant negative relationship between SUA changes and eGFR changes ($r=-0.40$, $p=0.03$) [63], with eGFR improving significantly when urate was lowered to <6.0 mg/dL [61]. A trajectory analysis of 846 T2DM patients (baseline eGFR ≥60) found that the high SUA trajectory group had substantially elevated risks for composite renal endpoints, including eGFR reduction ≥50% (HR 6.90, 95% CI 2.27–20.96) and serum creatinine doubling (HR 6.29, 95% CI 2.03–19.52) [33], with no significant interaction by sex, age, BMI, or HbA1c [33].

Renal transplant recipients: A meta-analysis of 12 cohort studies found that hyperuricemia in kidney transplant recipients was associated with lower eGFR, higher serum creatinine, and was an independent risk factor for chronic allograft nephropathy (adjusted HR 1.65, 95% CI 1.02–2.65) and graft loss (adjusted HR 2.01, 95% CI 1.39–2.94) [26]. In the ABCAN post hoc analysis, each 1 mg/dL higher time-varying uric acid was associated with a 2.39 mL/min lower final GFR ($p<0.001$), and baseline SUA was associated with doubling of interstitium or ESRD from IF/TA (OR 1.83, 95% CI 1.06–3.17, $p=0.03$) [25].

Children and adolescents: In the CKiD cohort (n=627 longitudinal), children with SUA >7.5 mg/dL had 38% shorter time to the composite endpoint of >30% GFR decline or RRT initiation (relative time 0.62, 95% CI 0.45–0.85), establishing hyperuricemia as an independent risk factor for faster CKD progression in pediatric patients [19]. A longitudinal analysis of 693 CKiD participants found that each 1 mg/dL increase in uric acid over follow-up was independently associated with concurrent eGFR decreases of -5.7% (95% CI -8.4% to -3.0%) in glomerular CKD

and -5.1% (95% CI -6.3% to -4.0%) in non-glomerular CKD [41], with stronger effects at lower baseline SUA levels.

General population and hypertension: In the Rotterdam Study, the SUA-incident CKD association was only significant in hypertensive subjects (P for interaction = 0.046) [49], with those in the highest SUA quartile having more than three times the risk of CKD compared to those in the lowest quartile [49]. SUA was not a significant predictor of incident CKD in the full population without stratification [49], suggesting hypertension as a key effect modifier.

The following table summarizes the key effect estimates from observational studies.

Study	Population	Uric Acid Metric	Outcome	Effect Estimate	Adjusted?
Ching-Wei Tsai et al., 2018 [2]	CKD patients (n=5,090) [2]	SUA trajectory (high vs. low) [2]	Incident ESRD [2]	HR 2.84 (95% CI 1.81–4.47) [2]	Yes [2]
Ching-Wei Tsai et al., 2018 [2]	CKD patients (n=5,090) [2]	SUA trajectory (high vs. low) [2]	All-cause mortality [2]	HR 4.52 (95% CI 2.48–8.26) [2]	Yes [2]
M. Prezelin-Reydit et al., 2020 [17]	CKD stages 3–5 (n=2,781) [17]	Per 100 µmol/L increase in current UA [17]	RRT or death before RRT [17]	aHR 1.16 (95% CI 1.07–1.26) [17]	Yes [17]
Ching-Wei Tsai et al., 2017 [18]	Hyperuricemic CKD, Taiwan (n=739) [18]	Per 1 mg/dL increase in baseline SUA [18]	Kidney failure [18]	HR 1.07 (95% CI 1.00–1.14) [18]	Yes [18]

Study	Population	Uric Acid Metric	Outcome	Effect Estimate	Adjusted?
Kyle E. Rodenbach et al., 2015 [19]	Children/adolescents with CKD (n=627) [19]	SUA >7.5 vs. <5.5 mg/dL [19]	>30% GFR decline or RRT [19]	Relative time 0.62 (95% CI 0.45–0.85) [19]	Yes [19]
Gen-yang Cheng et al., 2013 [20]	IgA nephropathy (n=348) [20]	High vs. normal SUA [20]	ESRD at follow-up [20]	64.71% vs. 35.00% ($p<0.05$) [20]	Not specified [20]
Szu-Chia Chen et al., 2013 [21]	CKD stages 3–5 (n=540) [21]	Higher UA + LVMI vs. others [21]	Progression to dialysis [21]	HR 1.830 (95% CI 1.007–3.326, p=0.048) [21]	Yes [21]
Dong-Jin Park et al., 2020 [23]	Lupus nephritis (n=137) [23]	SUA >7 vs. ≤7 mg/dL [23]	Progression to CKD [23]	HR 2.437 (p=0.020) [23]	Yes [23]
Y. Miao et al., 2011 [24]	T2DM with nephropathy (n=1,342) [24]	Per 0.5 mg/dL decrement in SUA [24]	Renal events (creatinine doubling or ESRD) [24]	6% risk reduction (independent of eGFR and albuminuria) [24]	Yes [24]

Study	Population	Uric Acid Metric	Outcome	Effect Estimate	Adjusted?
Gérald Lévy et al., 2014 [11]	Hyperuricemic adults (n=16,186) [11]	Per 1 mg/dL increase in baseline sUA [11]	Renal disease progression [11]	HR 1.11 (95% CI 1.04–1.19) [11]	Yes [11]
A. Hart et al., 2014 [25]	Renal transplant recipients [25]	Per 1 mg/dL increase in time-varying UA [25]	Final GFR [25]	-2.39 mL/min lower final GFR ($p<0.001$) [25]	Yes [25]
Yan Huang et al., 2012 [26]	Renal transplant recipients (12 cohorts) [26]	Hyperuricemia vs. normouricemia [26]	Graft loss [26]	Adjusted HR 2.01 (95% CI 1.39–2.94) [26]	Yes [26]
Chunlei Yao et al., 2019 [28]	T2DM community patients (n=3,432) [28]	UA/creatinine ratio [28]	Renal disease progression [28]	HR 1.364 (95% CI 1.131–1.646, p=0.001) [28]	Yes [28]
Suryeong Go et al., 2020 [29]	General population, males (n=76,784) [29]	SUA <4.1 mg/dL vs. 5.0–6.8 mg/dL [29]	Incident ESRD [29]	HR 2.409 (95% CI 1.312–4.423) [29]	Yes [29]

Study	Population	Uric Acid Metric	Outcome	Effect Estimate	Adjusted?
Gaurav Sharma et al., 2021 [1]	General/CKD populations (131 studies) [1]	Hyperuricemia (highest vs. lowest tertile) [1]	Kidney failure [1]	HR 1.53 (95% CI 1.18–1.99) [1]	Yes [1]
M. Prezelin-Reydit et al., 2023 [6]	CKD stages 3–5 (n=2,781) [6]	cUA >11 vs. 5 mg/dL [6]	Kidney failure (non-linear) [6]	HR 1.70 (95% CI 1.18–2.47) above plateau [6]	Yes [6]
Kang Zhang et al., 2022 [30]	IgA nephropathy (14 studies, n=11,548) [30]	Hyperuricemia vs. normouricemia [30]	Kidney failure [30]	Adjusted RR 2.12 (95% CI 1.64–2.73) [30]	Yes [30]
K. Hanai et al., 2018 [7]	T2DM non-CKD (n=4,994) [7]	Per 1 mg/dL increase in SUA [7]	≥30% eGFR decline or RRT [7]	HR 1.13 (95% CI 1.05–1.22) [7]	Yes [7]
K. Hanai et al., 2018 [7]	T2DM with CKD (n=2,039) [7]	Per 1 mg/dL increase in SUA [7]	≥30% eGFR decline or RRT [7]	HR 0.93 (95% CI 0.88–0.99) [7]	Yes [7]

Study	Population	Uric Acid Metric	Outcome	Effect Estimate	Adjusted?
S. Sedaghat et al., 2013 [49]	General population ≥55 years (n=2,601) [49]	Per 1 mg/dL increase in SUA [49]	Annual eGFR decline [49]	-0.19 mL/min/1.73 m²/year [49]	Yes [49]
M. Kuwabara et al., 2017 [5]	General population (n=12,578) [5]	Per 1 mg/dL increase over 5 years [5]	Rapid eGFR decline [5]	OR 3.77 (95% CI 3.35–4.26) [5]	Yes [5]
K. Iseki et al., 2013 [47]	Community-based (n=16,630) [47]	Per 1 mg/dL increase in UA [47]	eGFR decline over 10 years [47]	1.91–4.19 mL/min/1.73 m² per group [47]	Yes [47]
Yipeng Han et al., 2022 [44]	Lupus nephritis (n=123) [44]	SUA (continuous) [44]	LN progression [44]	HR 1.003 (95% CI 1.001–1.005) per µmol/L [44]	Not specified [44]
C. Reátegui-Sokolova et al., 2016 [55]	SLE patients (n=186) [55]	SUA (continuous, baseline) [55]	New renal damage [55]	HR 3.21 (95% CI 1.39–7.42, multivariable) [55]	Yes [55]

Study	Population	Uric Acid Metric	Outcome	Effect Estimate	Adjusted?
A. Testa et al., 2014 [3]	CKD patients (n=755) [3]	GLUT9 rs734553 risk allele (Mendelian randomization) [3]	>30% GFR decline, dialysis, or transplantation [3]	HR 2.35 (95% CI 1.25–4.42, p=0.008) [3]	Yes [3]
Won Jin Kim et al., 2014 [80]	T2DM with preserved eGFR (n=512) [80]	Highest vs. lower SUA quartiles [80]	CKD stage 3 or greater [80]	HR 2.97 (95% CI 1.15–7.71) [80]	Yes [80]
George J. Schwartz et al., 2022 [41]	Children with CKD (n=693) [41]	Per 1 mg/dL increase in SUA [41]	eGFR change (%) [41]	-5.7% to -3.3% per 1 mg/dL increase [41]	Yes [41]
Xiuxiu Lai et al., 2022 [53]	Elderly Chinese (n=425) [53]	Per 1 mg/dL increase in baseline SUA [53]	Renal failure (eGFR <60) [53]	OR 1.76 (95% CI 1.45–2.14) [53]	Yes [53]
Fan Lin et al., 2016 [56]	Hypertensive elderly (n=837) [56]	Per 100 µmol/L increase in baseline UA [56]	eGFR decline [56]	-5.684 mL/min/1.73 m² [56]	Yes [56]

Study	Population	Uric Acid Metric	Outcome	Effect Estimate	Adjusted?
B. Ghang et al., 2022 [72]	Gout patients on ULT (n=4,144) [72]	Average SUA ≥6 mg/dL [72]	CKD progression (eGFR slope <0) [72]	Adjusted OR 1.73 (95% CI 1.49–2.01, p<0.0001) [72]	Yes [72]
Jinting Pan et al., 2023 [33]	T2DM patients (n=846) [33]	High vs. low SUA trajectory [33]	Composite renal endpoint [33]	HR 8.04 (95% CI 2.68–24.18) [33]	Yes [33]
Yu Li et al., 2024 [34]	Middle-aged/elderly China (n=5,421) [34]	Per 1 mg/dL increase in SUA change [34]	Rapid eGFR decline [34]	OR 1.92 (95% CI 1.71–2.16) [34]	Yes [34]
Liyi Liu et al., 2021 [52]	Community-based China (n=1,534) [52]	Lowest vs. highest quartile of SUA change [52]	Renal function decline (>10% eGFR drop) [52]	HR 0.64 (95% CI 0.49–0.85) [52]	Yes [52]
Aamir Nabi et al., 2025 [45]	CKD stages 2–4 (n=152) [45]	Hyperuricemia vs. normouricemia [45]	CKD progression (25% eGFR drop) [45]	HR 1.76 (95% CI 1.18–2.84) [45]	Not specified [45]

Study	Population	Uric Acid Metric	Outcome	Effect Estimate	Adjusted?
Yu-lin Li et al., 2011 [78]	Meta-analysis (n=3,004 prognosis) [78]	Hyperuricemia [78]	Kidney function deterioration [78]	RR 1.35 (95% CI 1.12–1.63) [78]	Yes [78]

The observational data are highly consistent across study designs, populations, and geographic settings in demonstrating a positive association between elevated SUA and worse renal outcomes. The association persists after adjustment for common confounders including eGFR, proteinuria, hypertension, diabetes, and cardiovascular disease in most studies [1, 18, 49].

Effects of Urate-Lowering Therapy (ULT) on Renal Progression

The question of whether ULT causally retards CKD progression has been examined in multiple systematic reviews and meta-analyses, with results that differ meaningfully by the methodological quality and patient selection of the included trials.

The largest meta-analysis of RCTs (131 studies; Sharma et al., 2021 [1]) found that ULT use for ≥1 year was associated with significantly improved eGFR (MD 1.81 mL/min/1.73m², 95% CI 0.26–3.35), lower serum creatinine (MD -0.33 mg/dL, 95% CI -0.47 to -0.19), and reduced proteinuria (MD -5.44 mg/day, 95% CI -8.49 to -2.39), but no difference in kidney failure [1]. Su et al. (2017) [8], pooling 16 RCTs (1,211 patients), found a 55% relative risk reduction for kidney failure events (RR reduction 31–64%, $p<0.001$), a 60% relative risk reduction for cardiovascular events, and a 4.10 mL/min/1.73m²/year slower eGFR decline in ULT recipients (95% CI 1.86–6.35) [8]. Liu et al. (2018) [9] pooled 12 RCTs (832 patients) and found a mean difference in eGFR favoring ULT of 3.88 mL/min/1.73m² (95% CI 1.26–6.49, $p=0.004$), with a reduced risk of worsening kidney function, ESRD, or death (RR 0.39, 95% CI 0.28–0.52) [9]. Kanji et al. (2015) [50], pooling trials comparing allopurinol to inactive control, found a pooled mean difference in eGFR of 3.2 mL/min/1.73m² (95% CI 0.16–6.2, $p=0.039$) [50]. Sharbaf et al. (2024) [54], including

four trials of allopurinol in 698 patients (mean follow-up 22.5 months), found a significant increase in eGFR (SMD 2.04, 95% CI 0.60–3.49, p=0.005) and a significant decrease in SUA (SMD -5.16, 95% CI -8.31 to -2.01, p=0.001), with no significant difference in adverse effects [54]. Luo et al. (2023) [10], including 17 RCTs of asymptomatic hyperuricemia, found ULT was associated with higher eGFR (WMD 3.679 mL/min/1.73m², 95% CI 1.592–5.766, p=0.001), lower serum creatinine (WMD -46.131 μmol/L, p<0.0001), and lower incidence of serum creatinine doubling (RR 0.314, 95% CI 0.203–0.485) [10], with the benefit most pronounced in those with CKD stages 1–3, those <60 years, and those from Asian countries [10].

However, Maruyama et al. (2021) [42], pooling 11 studies with 4,277 CKD patients, found no statistically significant difference in eGFR between ULT and control groups (MD 2.52, 95% CI -0.15 to 5.18) [42], though the trend favored ULT. Allopurinol showed superior eGFR preservation compared to newer xanthine oxidase reductase (XOR) inhibitors in subgroup analyses of this review [42].

Large high-quality RCTs: null results

Three large, well-powered, placebo-controlled RCTs constitute the highest-quality evidence and each returned null results, as summarized by Tiku et al. (2021) [15]:

The FEATHER trial (443 Japanese patients with CKD stage 3 and asymptomatic hyperuricemia, mean eGFR 45 mL/min/1.73m², mean SUA 7.8 mg/dL) found no statistically significant difference in eGFR slope between febuxostat and placebo at 108 weeks (mean difference 0.70 mL/min/1.73m², 95% CI -0.21 to 1.62) [13]. Subgroup analyses suggested possible benefit in patients without proteinuria and those with lower creatinine, but these were exploratory and interpreted cautiously [13].

The CKD-FIX trial (369 patients with CKD stages 3–4, mean eGFR 31.7 mL/min/1.73m², mean SUA 8.2 mg/dL, high progression risk defined by elevated albuminuria or recent eGFR decline) found that allopurinol did not significantly slow eGFR decline compared to placebo at 104 weeks (mean difference -0.10 mL/min/1.73m²/year, 95% CI -1.18 to 0.97, p=0.85) [14]. Serious adverse events were similar between groups (46% allopurinol vs. 44% placebo) [14].

The PERL trial (530 patients with type 1 diabetes and diabetic kidney disease, mean eGFR 74.7 mL/min/1.73m², mean SUA 6.1 mg/dL) similarly showed no meaningful kidney benefit despite sustained urate reduction with allopurinol [15, 15].

Individual intervention studies

The following table summarizes the primary findings from individual intervention studies.

Study	Agent	Duration	SUA Change	Renal Outcome (Intervention)	Renal Outcome (Control)	p-value / Effect
M. Goicoechea et al., 2010 [79]	Allopurinol 100 mg/d [79]	~24 months [79]	Significantly decreased [79]	eGFR +1.3±1.3 mL/min/1.73m² [79]	eGFR -3.3±1.2 mL/min/1.73m² [79]	Significant, independently of age, sex, DM, CRP, albuminuria RAS blockers [79
S. Sezer et al., 2014 [31]	Allopurinol (dose not specified) [31]	12 months [31]	Significantly decreased (p=0.00) [31]	GFR +3.3±1.2 mL/min/1.73m²/ year [31]	GFR -1.3±0.6 mL/min/1.73m² [31]	p=0.04 [31]
B. S. Pai et al., 2013 [51]	Allopurinol 100 mg/d [51]	2 years [51]	Significant decrease [51]	No significant eGFR change [51]	Significant eGFR decline [51]	Significant between-group difference [51]

Study	Agent	Duration	SUA Change	Renal Outcome (Intervention)	Renal Outcome (Control)	p-value / Effect
Sima Golmohammadi et al., 2017 [43]	Allopurinol 100 mg/d [43]	12 months [43]	Significant decrease (p=.004) [43]	Stage 3 (mild): significant GFR increase (p<.001) [43]	Stage 4 (severe): no significant GFR change [43]	Stage-dependent benefit [43]
A. Ozdemir & A. Inci, 2017 [57]	Allopurinol 150 mg/d [57]	12 months [57]	Significant decrease (p<0.05) [57]	eGFR +1.02±8.89 mL/min/1.73m² (NS) [57]	eGFR -2.59±7.9 mL/min/1.73m² (p=0.012) [57]	Between-group NS for allopurino (p=0.352) [57]
A. Anwar et al., 2017 [67]	Allopurinol 100 mg/d [67]	8 months [67]	Significant decrease [67]	eGFR and Scr improvement (NS) [67]	eGFR decline, Scr increase (significant) [67]	Not statistically significant for main renal outcomes [67]
Carmine Zoccali & D. Bolignano, 2020 (CKD-FIX) [14]	Allopurinol 100–300 mg/d [14]	104 weeks [14]	Not specified [14]	eGFR -3.33 mL/min/1.73m²/ year [14]	eGFR -3.23 mL/min/1.73m² /year [14]	Mean difference -0.10 (95% CI -1.18 to 0.97), p=0.85 [14]

Study	Agent	Duration	SUA Change	Renal Outcome (Intervention)	Renal Outcome (Control)	p-value / Effect
Yongjun Shi et al., 2011 [48]	Allopurinol 100–300 mg/d [48]	6 months [48]	Not specified [48]	No significant change in renal progression or proteinuria [48]	Not applicable [48]	NS [48]
A. Tiku et al., 2018 (FEATHER) [13]	Febuxostat 10–40 mg/d (escalating) [13]	108 weeks [13]	Not specified [13]	eGFR slope 0.23±5.26 mL/min/1.73m²/ year [13]	eGFR slope -0.47±4.48 mL/min/1.73m² /year [13]	Mean difference 0.70 (95% CI -0.21 to 1.62), NS [13]
Gerald D. Levy & T. Craig Cheetham, 2015 (Sircar trial) [46]	Febuxostat 40 mg/d [46]	6 months [46]	-3.8 mg/dL (active) vs. -0.5 mg/dL (placebo) [46]	eGFR +3.2 mL/min/1.73m² [46]	eGFR -4.4 mL/min/1.73m² [46]	p<0.004 for proportion with ≥10% eGFR decline [46]
Hongtao Yang et al., 2022 [38]	Febuxostat (target SUA <6 mg/dL) [38]	12 months [38]	Target achieved [38]	14.9% reached ≥30% eGFR decline [38]	28.9% reached ≥30% eGFR decline [38]	Febuxostat significantly slowed eGFR decline [38]

Study	Agent	Duration	SUA Change	Renal Outcome (Intervention)	Renal Outcome (Control)	p-value / Effect
Y. Waheed et al., 2025 [70]	Febuxostat 40 mg/d [70]	12 months [70]	6.85 to 5.27 mg/dL [70]	eGFR +3.98 mL/min from 34.48 baseline [70]	eGFR declined [70]	$p<0.001$ for both SUA reduction and eGFR increase [70]
H. Katsuyama et al., 2019 (topiroxostat) [4]	Topiroxosta t [4]	6 months [4]	Significantl y decreased at 3 and 6 months [4]	eGFR trend toward increase at 6 months [4]	Not applicable [4]	Significant decrease in urinary protein positivity [4]
Katsunori Yanai et al., 2023 [35]	Dotinurad [35]	12 months [35]	7.1 to 5.9 mg/dL [35]	Annual eGFR change improved from -6.0 to -0.9 mL/min/1.73m²/ year ($p<0.05$) [35]	No change in control [35]	$p<0.05$ [35]

Study	Agent	Duration	SUA Change	Renal Outcome (Intervention)	Renal Outcome (Control)	p-value / Effect
O. Kurihara et al., 2023 [69]	Dotinurad [69]	Mean 9.8 months [69]	Significantly decreased [69]	Significant eGFR improvement in eGFR <30 group (p=0.032) [69]	No significant change in eGFR ≥30 groups [69]	Significant in eGFR <30 only [69]
Yuki Tsuruta et al., 2014 [60]	Febuxostat vs. allopurinol [60]	1 year [60]	Febuxostat: 6.1→5.7 mg/dL; Allopurinol: 6.2→6.6 mg/dL [60]	eGFR 27.3→25.7 mL/min (febuxostat) [60]	eGFR 26.1→19.9 mL/min (allopurinol) [60]	β=-0.22145, p<0.05 for switch to febuxostat [60]
Xuemei Liu et al., 2018a [59]	Febuxostat vs. allopurinol [59]	6 months [59]	96.4% vs. 37.5% achieved sUA <360 μmol/L [59]	eGFR 28.45→30.65 mL/min (febuxostat) [59]	Not specified separately [59]	Not specified [59]

Study	Agent	Duration	SUA Change	Renal Outcome (Intervention)	Renal Outcome (Control)	p-value / Effect
Huifang Wang et al., 2017 [75]	Febuxostat 40/20 mg/d vs. allopurinol 100 mg/d [75]	6 months [75]	Greater SUA reduction in febuxostat group [75]	eGFR +2.23 mL/min/1.73m² [75]	eGFR -4.36 mL/min/1.73m² [75]	p=0.037; per 60 µmol/L SUA decrease: eGFR +1.149 mL/min (p=0.003) [75]
Xin Zhang et al., 2019 [65]	Febuxostat vs. allopurinol [65]	6 months [65]	Greater in febuxostat group [65]	Lower proportion with ≥10% eGFR decline [65]	Higher proportion with ≥10% eGFR decline [65]	Febuxostat independent predictor of reduced eGFR decline [65]
Seokwoo Park et al., 2022 [68]	Allopurinol vs. febuxostat [68]	~411–552 days [68]	Allopurinol: -1.58 mg/dL; Febuxostat: -2.69 mg/dL [68]	Lower incidence of 30% eGFR decline and ESRD (allopurinol) [68]	Higher incidence (febuxostat) [68]	HR for ESRD 1.91 (95% CI 1.42–2.58) favoring allopurinol [68]

Study	Agent	Duration	SUA Change	Renal Outcome (Intervention)	Renal Outcome (Control)	p-value / Effect
Yueh-Lung Peng et al., 2020 [66]	Febuxostat vs. allopurinol [66]	2.5 years [66]	Febuxostat more effective [66]	No significant difference in eGFR decline ≥30% [66]	No significant difference [66]	NS [66]
Yoonjin Kim et al., 2015 [22]	Allopurinol or febuxostat vs. none [22]	Median 118.5 weeks [22]	SUA lower in ULT group [22]	eGFR change -1.19±12.07 mL/min/1.73m² [22]	eGFR change -7.37±11.17 mL/min/1.73m² [22]	p=0.001; renal progression 12.3% vs. 27.9% (p=0.01) [22]
Gérald Lévy et al., 2014 [11]	Allopurinol (all patients) [11]	Up to 3 years [11]	Largest in ≥80% adherence group (-3.1 mg/dL) [11]	SUA <6 mg/dL: 37% fewer events [11]	SUA ≥6 mg/dL (on treatment): higher event rate [11]	HR 0.63 (95% CI 0.5–0.78, p<0.0001) [11]
M. Tai-Seale et al., 2013 [32]	ULT (type not specified) >70% of time [32]	2002–2010 [32]	Not specified [32]	20% reduction in events [32]	Higher event rate [32]	HR 0.8 (95% CI 0.71–0.90) [32]

Study	Agent	Duration	SUA Change	Renal Outcome (Intervention)	Renal Outcome (Control)	p-value / Effect
N. Ueno, 2017 [63]	Allopurinol, benzbromarone, or febuxostat [63]	52 weeks [63]	7.8→5.5 mg/dL [63]	eGFR significantly increased; UACR decreased in no-microalbuminuria patients [63]	Not applicable [63]	Significant improvement in eGFR (p=0.03 for SUA-eGFR correlation) [63]
L. Khimion et al., 2022 [73]	Febuxostat vs. allopurinol [73]	6 months [73]	Target achieved more often with febuxostat (90% vs. 37.1%) [73]	Significant positive GFR changes in febuxostat group [73]	GFR deterioration in 31.8% of allopurinol group [73]	p<0.001 for target SUA achievement [73]
Y. Waheed et al., 2025a [74]	Febuxostat or allopurinol vs. no ULT [74]	12 months [74]	Significant reduction in ULT group [74]	eGFR improved; HR 0.4732 for eGFR decline (95% CI 0.335–0.666) [74]	Higher rate of eGFR decline [74]	p=0.0001 [74]

Study	Agent	Duration	SUA Change	Renal Outcome (Intervention)	Renal Outcome (Control)	p-value / Effect
Yukinao Sakai et al., 2014 [62]	Febuxostat (switched from allopurinol) [62]	6 months [62]	8.4→6.2 mg/dL [62]	eGFR increase +2.3±5.6 mL/min/1.73m²; eGFR slope became positive [62]	eGFR slope was negative on allopurinol [62]	p=0.0027 [62]
Y. Shibagaki et al., 2014 [58]	Febuxostat (escalating dose) [58]	24 weeks [58]	>40% reduction in CKD stage 3b; >50% in stages 4–5 [58]	eGFR increase tendency; urinary protein reduction tendency [58]	Not applicable [58]	Not formally assessed vs. control [58]
A. Whelton et al., 2013 [64]	Febuxostat 80 or 120 mg/d [64]	Up to 48 months [64]	Mean SUA 9.8 mg/dL at baseline [64]	Per 1 mg/dL SUA reduction: preservation of 1.15 mL/min eGFR [64]	Not applicable [64]	p<0.001 [64]

Study	Agent	Duration	SUA Change	Renal Outcome (Intervention)	Renal Outcome (Control)	p-value / Effect
B. Ghang et al., 2024 (CARES post hoc) [12]	Febuxostat or allopurinol [12]	Median 2.5 years [12]	Not specified [12]	65.3% did not experience eGFR decline [12]	SUA ≥6 mg/dL associated with decline [12]	aOR 0.66 (95% C 0.57–0.77) for SUA <6 mg/dL [12]
Y. Miao et al., 2011 [24]	Losartan (uricosuria as mechanism) [24]	6 months [24]	-0.16 mg/dL vs. placebo [24]	Renal events reduced with SUA reduction [24]	Higher event rate [24]	6% risk reduction per 0.5 mg/dL decrement (independent of eGFR and albuminuria) [24]

Allopurinol versus febuxostat: comparative effectiveness

Multiple studies have directly compared allopurinol and febuxostat. Febuxostat achieves greater absolute SUA reductions in most comparative studies [60, 66, 68] due to its efficacy at CKD-appropriate doses, whereas allopurinol doses are constrained by renal function. Paradoxically, a well-conducted propensity score-matched multicenter Korean cohort (n=654 per group) found that febuxostat was associated with significantly higher risk of 30% eGFR decline (HR 1.26, 95% CI 1.03–1.54) and ESRD (HR 1.91, 95% CI 1.42–2.58) compared to allopurinol, despite achieving greater SUA reduction (-2.69 vs. -1.58 mg/dL) [68], and the annual eGFR decline was faster with febuxostat by 2.14 mL/min/1.73m²/year [68]. In contrast, several smaller studies and series found superior eGFR outcomes with febuxostat compared to allopurinol [59, 60, 65, 75]. The meta-analysis by Maruyama et al. (2021) found that allopurinol was associated with superior eGFR

preservation in subgroup analysis, while the newer XOR inhibitors febuxostat and topiroxostat showed no significant effects on eGFR changes as a group [42]. The Peng et al. (2020) propensity score-matched Taiwan cohort found no significant difference in eGFR decline between the two agents [66].

Novel uricosuric agents have been assessed in small retrospective studies. Dotinurad, a selective urate reabsorption inhibitor, significantly reduced SUA from 7.1±0.8 to 5.9±1.0 mg/dL and significantly improved annual eGFR change from -6.0±12.9 to -0.9±4.6 mL/min/1.73m²/year ($p<0.05$) in 34 advanced CKD patients [35]. In a separate series of 53 patients, dotinurad showed significant eGFR improvement only in those with eGFR <30 mL/min/1.73m², not in those with higher baseline eGFR [69].

The importance of achieved uric acid target

Multiple studies converge on the finding that achieving an SUA target below 6 or 7 mg/dL, rather than simply initiating ULT, is the critical determinant of renal benefit. In the large Kaiser Permanente observational database (n=16,186), time on ULT was not independently associated with renal outcomes, but patients achieving SUA <6 mg/dL experienced a 37% reduction in outcome events (HR 0.63, 95% CI 0.50–0.78, $p<0.0001$) [11]. Kim et al. (2015) found that an actual (AUC-adjusted) SUA <7 mg/dL reduced the risk of renal disease progression by 69.4% [22], and goal-directed ULT showed better clinical outcomes than maintaining initial ULT dose [22]. The CARES post hoc analysis (n=5,002 gout patients) found that maintaining average SUA <6 mg/dL was associated with an adjusted odds ratio of 0.66 (95% CI 0.57–0.77) for eGFR decline [12], and average SUA ≥6 mg/dL was associated with 1.73-fold greater odds of CKD progression (95% CI 1.49–2.01, $p<0.0001$) [72]. Among gout patients on ULT in the CARES reanalysis, 65.3% did not experience eGFR decline over a median 2.5-year follow-up [12], supporting the view that ULT with adequate target attainment may be nephroprotective in patients with established CKD and gout.

Effect modification by CKD stage and rate of progression in control arms

A key observation by Sato et al. (2019) [16] is that among trials where the control arm experienced progressive kidney function deterioration (≥4 mL/min/1.73m² over 6 months to 2 years), ULT consistently conferred clinical benefit, whereas in trials without observable control-arm

progression, ULT appeared ineffective [16]. This pattern explains much of the heterogeneity: the FEATHER trial's control group experienced a negligible mean eGFR decline of only ~1.0% over 108 weeks [13], making it virtually impossible to detect a slowing effect. The CKD-FIX trial enrolled a high-progression-risk population and still found no effect, though recruitment was stopped early at 59% of the planned sample [14]. By contrast, smaller positive trials enrolled more rapidly progressive cohorts.

Golmohammadi et al. (2017) found that allopurinol benefit was significant in patients with mild GFR impairment (30–60 mL/min/1.73m²) but not in those with severe impairment (15–30 mL/min/1.73m²) [43], suggesting potential stage-dependent effects. Luo et al. (2023) meta-analytically confirmed benefit specifically in CKD stages 1–3 but not in more advanced stages [10].

Subgroup Effects and Effect Modification

Proteinuria

Two studies found that the effect of SUA on CKD progression was stronger in patients without proteinuria compared to those with proteinuria [18]. In the FEATHER trial, the only positive subgroup finding was in the no-proteinuria subgroup, though this was an exploratory analysis underpowered by the overall low progression rate [13]. Among type 2 diabetic patients with hyperuricemia treated with urate-lowering therapy, SUA reduction decreased urinary albumin-to-creatinine ratio in those without microalbuminuria but not in those with macroalbuminuria [61, 63], suggesting that ULT benefit on proteinuria may be limited to earlier stages of nephropathy.

Sex

Several studies identified sex as an important modifier. The large Korean population cohort found the U-shaped SUA-ESRD relationship only in men, not in women [29]. Among CKD-REIN patients, the association between current UA and the hazard of kidney failure appeared stronger in women for UA levels up to 7 mg/dL [6]. In lupus nephritis, the SUA-renal progression association was statistically significant in women but not men [44]. The correlation between SUA change and eGFR decline was more pronounced in females in two separate Chinese cohort studies [34, 53].

Baseline eGFR and CKD stage

The paradoxical finding in diabetic patients—where higher SUA was protective in established CKD but detrimental in preserved kidney function—is particularly important [7]. This U-shaped or reversal effect at lower eGFRs may reflect the dual role of uric acid as both an oxidant (at high concentrations when driving pathology) and an antioxidant (at lower concentrations in a state of high oxidative stress in advanced uremia). Dotinurad showed significant eGFR improvement only in the most impaired group (eGFR <30 mL/min/1.73m²) [69], and topiroxostat's effect on eGFR strengthened over time with greater SUA reduction [4].

Disease-specific populations

Among IgA nephropathy patients, the SUA-progression association was stronger in Asian countries than Western countries and less conspicuous in older patients or those with lower baseline eGFR [30]. In renal transplant recipients, the association was modified by race, study type, and definition of hyperuricemia [26]. The Mendelian randomization study by Testa et al. (2014), using the GLUT9 rs734553 SNP as an instrumental variable, found that the risk allele conferred a 2.35-fold higher risk of CKD progression (95% CI 1.25–4.42, p=0.008), independent of proteinuria, GFR, and other risk factors [3], providing genetic evidence for a causal relationship between SUA and renal progression.

Proposed Biological Mechanisms

Multiple biological pathways have been proposed to explain why uric acid may accelerate renal progression. The literature identifies both crystal-dependent and crystal-independent mechanisms [9, 18]. Crystal-independent mechanisms are considered to be of greater relevance in CKD progression and include: (1) stimulation of vascular smooth muscle cell proliferation in afferent arterioles, leading to glomerular hypertension [4, 5]; (2) activation of the renin-angiotensin-aldosterone system [5, 34, 51]; (3) induction of endothelial dysfunction through reduced nitric oxide bioavailability [49, 60]; (4) pro-inflammatory effects including induction of oxidative stress [70, 74]; and (5) tubulointerstitial inflammation and fibrosis [9, 25]. Animal model data support a causal mechanism: oxonic acid–induced hyperuricemia in rats leads to glomerular hypertension,

arteriolosclerosis, and tubulointerstitial fibrosis, all of which are reversed by allopurinol treatment [46, 76].

A complicating factor is that uric acid also possesses antioxidant properties, particularly in extracellular compartments, which may explain its potentially protective role in advanced uremia (where oxidative stress is extreme) [6]. Crystal-dependent mechanisms—monosodium urate deposits in renal tubules and interstitium—are also recognized but are generally considered less prominent in the CKD progression context compared to their role in acute urate nephropathy or gouty nephropathy [4, 18]. For IgA nephropathy specifically, SUA-induced proliferation of mesangial cells via the NADPH/ROS/ERK1/2 signaling pathway and induction of arteriolar hyalinosis have been proposed [30].

Synthesis

The apparent contradiction

The observational literature is virtually unanimous in finding a positive association between elevated SUA and accelerated renal progression, with consistent dose-response relationships and effect sizes (HR or OR 1.35–2.84 across diverse populations, designs, and endpoints). Yet the three largest and most rigorously designed placebo-controlled RCTs—FEATHER, CKD-FIX, and PERL—all failed to demonstrate that SUA-lowering therapy meaningfully slows CKD progression [13–15], while most smaller and shorter trials, as well as multiple meta-analyses, report benefit [8–10, 54].

Explaining the heterogeneity

Trial design and progression rate in control arms. The most parsimonious explanation for the discordance between smaller positive trials and the three large null trials is the systematic failure of large trials to enroll patients with measurably progressive disease. The FEATHER trial's control arm experienced <1% eGFR decline over 108 weeks [13] —an extraordinarily low progression rate that would preclude detecting any treatment benefit regardless of SUA manipulation. When positive trials are examined, the control arm uniformly demonstrates meaningful progression (≥4 mL/min/1.73m² decline over the study period) [16], consistent with the mechanism whereby ULT can only visibly benefit patients who are actually progressing. This

observation, formalized by Sato et al. (2019), is a dose-response argument applied at the trial level: the "dose" of CKD progression in the control arm determines the detectable effect window [16].

Statistical power and population selection. The CKD-FIX trial was stopped at 59% enrollment due to slow recruitment [14], and though it enrolled high-progression-risk patients (elevated albuminuria or recent eGFR decline), its sample size of 369 may have been insufficient to detect a clinically important but modest effect. The PERL trial enrolled patients with relatively well-preserved eGFR (mean 74.7 mL/min/1.73m²) and near-normal SUA levels (mean 6.1 mg/dL) [15], meaning the margin for SUA reduction was small and the eGFR trajectory over a short trial may be dominated by metabolic and glycemic factors rather than UA-mediated injury.

Target SUA attainment versus time on treatment. Multiple observational studies distinguish between duration of ULT exposure and actual target SUA achievement, consistently finding that treatment duration alone is not what drives renal benefit, but rather achieving SUA below the 6–7 mg/dL threshold [11, 12, 22, 72]. Large observational data from over 16,000 hyperuricemic patients showed no effect of time on ULT, but a 37% reduction in events in those achieving SUA <6 mg/dL [11]. This distinction is methodologically important: RCTs that demonstrate overall SUA lowering but do not stratify outcomes by achieved SUA target may mask benefit in a subset reaching target.

Population heterogeneity and effect modification. Benefit from ULT appears concentrated in earlier CKD stages (1–3) [10], younger patients (<60 years) [10], Asian populations [10], and patients without heavy proteinuria [13, 18]. The paradoxical inverse association in type 2 diabetic patients with established CKD (eGFR <60 mL/min/1.73m²) [7] and the U-shaped mortality risk for both very low and very high SUA levels in CKD patients [6] caution against uniform application of aggressive urate lowering across all CKD stages. In advanced CKD, uric acid's antioxidant properties may confer relative protection, and iatrogenic lowering of SUA could theoretically remove a protective mechanism [6]. The Mendelian randomization evidence from Testa et al. (2014) supports causality in general CKD [3] but does not resolve whether causality persists in all stages.

Febuxostat vs. allopurinol mechanisms. The discordant finding that febuxostat achieves greater SUA reduction yet may not confer superior (and possibly inferior) renal protection compared to allopurinol is poorly understood [42, 68]. Allopurinol has xanthine oxidase-independent antioxidant and anti-inflammatory effects that febuxostat may lack, including broader reductions in oxidative stress markers [68]. This could explain why allopurinol benefits CKD outcomes through mechanisms partially independent of SUA lowering per se, while febuxostat—more purely a urate-lowering agent—does not show equivalent benefits in CKD despite superior SUA control. The CARES secondary reanalysis, which pooled both agents and found consistent benefit with SUA <6 mg/dL [12], suggests that at sufficient target attainment, the class may not matter; but the single-arm comparative study by Park et al. raises the possibility of class-specific differences that warrant prospective investigation [68].

In summary, the available evidence supports the conclusion that elevated SUA is a robust, independent risk factor for CKD progression and ESRD across diverse populations, disease etiologies, and study designs. The failure of large RCTs to demonstrate clear ULT benefit is best explained by enrollment of low-progression-risk cohorts (particularly FEATHER), premature stopping and underpowering (CKD-FIX), and selection of populations where SUA may play a less dominant pathogenic role (PERL in type 1 diabetes with near-normal SUA). Urate-lowering therapy is most likely to retard CKD progression when applied to patients with: (1) measurably progressive disease (eGFR decline ≥3–4 mL/min/1.73m²/year), (2) substantial hyperuricemia, (3) earlier CKD stages (particularly stages 1–3), and (4) achievement of target SUA <6–7 mg/dL. The application of ULT in advanced CKD warrants caution given potential U-shaped relationships between SUA and mortality and the lack of benefit in the highest-quality trials targeting this population.

DISCUSSION

This systematic review synthesizes data from 80 studies, including meta-analyses covering over 3.4 million patients, to evaluate the relationship between SUA and ESRD progression. The findings reveal a striking discordance: observational evidence almost uniformly supports a positive, dose-dependent association between hyperuricemia and worse renal outcomes, yet the largest and

most rigorous placebo-controlled RCTs of ULT have failed to demonstrate significant nephroprotection. Understanding this paradox requires a detailed examination of study design, population selection, progression rates, achieved SUA targets, and effect modification.

Observational evidence: consistent and dose-dependent

Across diverse populations—including general cohorts, CKD stages 1–5, diabetic kidney disease, IgA nephropathy, lupus nephritis, renal transplant recipients, and children—elevated SUA consistently predicts ESRD and rapid eGFR decline. The largest meta-analysis (131 studies, 3.4 million patients) reported that hyperuricemia was associated with a 53% higher risk of kidney failure (HR 1.53, 95% CI 1.18–1.99) and a 38% higher risk of rapid eGFR decline (OR 1.38, 95% CI 1.20–1.59) (1). A trajectory analysis of 5,090 CKD patients over 13 years demonstrated a clear dose-response: compared to low SUA trajectory, adjusted HRs for ESRD were 1.89, 2.49, and 2.84 for moderate, moderate-high, and high trajectories, respectively (2). Each 1 mg/dL increase in SUA was associated with an additional eGFR decline of 1.6 mL/min/1.73m²/year (18).

The relationship is nonlinear. In the CKD-REIN cohort (n=2,781), the hazard of kidney failure increased with current SUA, plateaued between 6–10 mg/dL, and rose sharply above 11 mg/dL (aHR 1.70 vs. 5 mg/dL) (6). Conversely, mortality showed a U-shaped relationship: risk was approximately twice as high at both 3 mg/dL and 11 mg/dL compared to 5 mg/dL (6). Similarly, a Korean general-population study found that in men, both the lowest (<4.1 mg/dL) and highest (≥7.8 mg/dL) SUA groups had elevated ESRD risk (HR 2.41 and 1.74, respectively) relative to the middle group (29). These findings indicate that very low SUA—below 5 mg/dL—is independently associated with higher mortality in CKD, raising caution about aggressive urate lowering in advanced disease.

Disease-specific populations show consistent but sometimes modified associations. In IgA nephropathy, hyperuricemia was an independent predictor of kidney failure (adjusted RR 2.12, 95% CI 1.64–2.73) (30). In lupus nephritis, SUA >7 mg/dL predicted CKD development (HR 2.437) (23). In renal transplant recipients, hyperuricemia was associated with graft loss (adjusted HR 2.01) (26). In children with CKD, SUA >7.5 mg/dL was associated with 38% shorter time to eGFR decline or RRT (19).

A notable exception was found in type 2 diabetic patients with established CKD (eGFR <60 mL/min/1.73m²): each 1 mg/dL increase in SUA was inversely associated with progression (HR 0.93, 95% CI 0.88–0.99) (7). This paradoxical finding suggests that in advanced diabetic kidney disease, uric acid may lose its pathogenic role or even become protective, possibly due to its antioxidant properties in a state of extreme oxidative stress.

Interventional evidence: null large trials vs. positive meta-analyses

The three largest and most methodologically rigorous RCTs—FEATHER (febuxostat vs. placebo in CKD stage 3, mean eGFR 45, n=443), CKD-FIX (allopurinol vs. placebo in CKD stages 3–4, mean eGFR 31.7, n=369), and PERL (allopurinol vs. placebo in type 1 diabetes with DKD, mean eGFR 74.7, n=530)—all failed to show a significant benefit of ULT on eGFR slope (13,14,15). In CKD-FIX, the mean difference in eGFR decline was -0.10 mL/min/1.73m²/year (95% CI -1.18 to 0.97, p=0.85) (14). In FEATHER, the mean difference was 0.70 mL/min/1.73m²/year (95% CI -0.21 to 1.62) (13).

In contrast, multiple meta-analyses of smaller RCTs reported significant benefits. Sharma et al. (2021) found that ULT for ≥1 year improved eGFR (MD 1.81 mL/min/1.73m²) and reduced proteinuria (MD -5.44 mg/day) but did not reduce kidney failure (1). Su et al. (2017) reported a 55% relative risk reduction for kidney failure events and a 4.10 mL/min/1.73m²/year slower eGFR decline (8). Liu et al. (2018) found a mean eGFR difference of 3.88 mL/min/1.73m² favoring ULT (9). Luo et al. (2023) found that ULT was associated with higher eGFR (WMD 3.68 mL/min/1.73m²) and lower risk of serum creatinine doubling (RR 0.314) (10). Kanji et al. (2015) reported a pooled eGFR difference of 3.2 mL/min/1.73m² (50).

This discordance is best explained by four factors:

1. Progression rate in control arms. Sato et al. (2019) observed that in trials where the control arm experienced meaningful progression (≥4 mL/min/1.73m² decline over the study period), ULT consistently showed benefit; in trials without control-arm progression, ULT appeared ineffective (16). The FEATHER control group had a negligible eGFR decline of only ~1% over 108 weeks, making it impossible to detect a slowing effect (13). This is a fundamental issue of assay sensitivity: a treatment cannot be shown to slow progression if no progression occurs.

2. Achieved SUA target vs. treatment initiation. Observational data strongly indicate that achieving a target SUA below 6–7 mg/dL, not simply initiating ULT, is the critical determinant of renal benefit. In the Kaiser Permanente cohort (n=16,186), time on ULT was not associated with outcomes, but patients achieving SUA <6 mg/dL had a 37% reduction in events (HR 0.63, 95% CI 0.50–0.78) (11). In the CARES post-hoc analysis, average SUA ≥6 mg/dL was associated with 1.73-fold greater odds of CKD progression (12). Kim et al. (2015) found that an actual SUA <7 mg/dL reduced renal progression risk by 69.4% (22). Most large RCTs did not stratify outcomes by achieved SUA target, potentially masking benefit in the subset reaching target.

3. Population heterogeneity and effect modification. Benefit from ULT appears concentrated in specific subgroups: earlier CKD stages (1–3) (10), younger patients (<60 years) (10), Asian populations (10), patients without heavy proteinuria (13,18), and those with measurable progression at baseline (16). The FEATHER trial's only positive subgroup was the no-proteinuria group, though this was exploratory (13). In contrast, the PERL trial enrolled type 1 diabetics with near-normal SUA (mean 6.1 mg/dL) and well-preserved eGFR, leaving little room for benefit (15). The CKD-FIX trial enrolled high-risk patients but was stopped early at 59% of planned enrollment, reducing power (14).

4. Stage-dependent and U-shaped relationships. In advanced CKD, aggressive SUA lowering may be harmful. The U-shaped association between SUA and mortality (6) and the paradoxical inverse association in diabetic CKD (7) suggest that uric acid may have antioxidant properties that become protective when oxidative stress is extreme. This is supported by dotinurad studies showing eGFR improvement only in patients with eGFR <30 mL/min/1.73m² (69), and topiroxostat showing renoprotective effects that strengthened with greater SUA reduction (4).

Comparative effectiveness of ULT agents

Febuxostat achieves greater absolute SUA reduction than allopurinol in most studies (60,66,68). However, a large propensity score-matched Korean cohort (n=654 per group) paradoxically found that febuxostat was associated with higher risk of 30% eGFR decline (HR 1.26) and ESRD (HR 1.91) compared to allopurinol, despite greater SUA reduction (68). Allopurinol has xanthine oxidase-independent antioxidant and anti-inflammatory effects that

febuxostat may lack, which could explain this discrepancy (68). Other studies have found febuxostat superior (59,60,65,75) or equivalent (66) to allopurinol. Maruyama et al. (2021) found that allopurinol was associated with superior eGFR preservation in subgroup analysis, while newer XOR inhibitors showed no significant effect (42).

Novel uricosuric agents like dotinurad have shown promise in small studies: in 34 advanced CKD patients, dotinurad reduced SUA from 7.1 to 5.9 mg/dL and improved annual eGFR change from -6.0 to -0.9 mL/min/1.73m²/year ($p<0.05$) (35). However, these findings require confirmation in larger RCTs.

Proposed mechanisms

The literature identifies both crystal-dependent and crystal-independent mechanisms (9,18). Crystal-independent mechanisms are considered more relevant in CKD progression and include: (1) stimulation of afferent arteriolar smooth muscle proliferation causing glomerular hypertension (4,5); (2) activation of the renin-angiotensin-aldosterone system (5,34,51); (3) endothelial dysfunction via reduced nitric oxide bioavailability (49,60); (4) induction of oxidative stress and inflammation (70,74); and (5) tubulointerstitial fibrosis (9,25). Animal models support causality: oxonic acid-induced hyperuricemia in rats causes glomerular hypertension, arteriolosclerosis, and interstitial fibrosis, all reversed by allopurinol (46,76). Mendelian randomization using the GLUT9 rs734553 SNP found that the risk allele conferred a 2.35-fold higher risk of CKD progression (95% CI 1.25–4.42), providing genetic evidence for causality (3).

CONCLUSION AND RECOMMENDATIONS

Conclusion

Elevated serum uric acid is a robust, independent, dose-dependent risk factor for the progression of chronic kidney disease to end-stage renal disease across diverse populations, disease etiologies, and study designs. Observational evidence consistently demonstrates that hyperuricemia predicts faster eGFR decline, higher ESRD incidence, and worse outcomes in specific conditions such as IgA nephropathy, lupus nephritis, and renal transplantation.

However, the failure of large, high-quality randomized controlled trials to demonstrate clear renoprotection from urate-lowering therapy indicates that the relationship is more complex than simple causality. The discordance between observational and trial evidence is best explained by: (1) insufficient progression rates in control arms of major trials, which precluded detection of treatment effects; (2) failure to stratify outcomes by achieved SUA target, when target attainment (SUA <6 mg/dL) rather than treatment initiation appears to drive benefit; (3) significant population heterogeneity, with benefit concentrated in earlier CKD stages (1–3), patients with measurable progression, and those without heavy proteinuria; and (4) potential harm from aggressive urate lowering in advanced CKD due to U-shaped associations with mortality.

Clinical recommendations: Urate-lowering therapy is most likely to retard CKD progression when applied to patients with: (a) measurable progressive disease (eGFR decline ≥3–4 mL/min/1.73m²/year), (b) substantial hyperuricemia (SUA >8 mg/dL), (c) early-to-moderate CKD (stages 1–3), and (d) achievement of target SUA <6–7 mg/dL. In advanced CKD (stages 4–5) or diabetic kidney disease with established nephropathy, routine ULT for renal protection is not supported by current evidence and may be harmful.

Recommendations for future research: Future trials should: (1) enrich enrollment for patients with rapid prior eGFR decline; (2) titrate ULT to achieve SUA <6 mg/dL and analyze outcomes by target attainment; (3) stratify by baseline CKD stage, proteinuria status, and disease etiology; (4) include longer follow-up durations (>2 years); (5) compare allopurinol and febuxostat head-to-head with attention to xanthine oxidase-independent effects; and (6) explore novel uricosuric agents in well-powered RCTs.

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