Uncontrolled Gout and Metabolic Disorders

NP-38435 (v5.0) July 2025

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Contents

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CV, cardiovascular; sUA, serum uric acid.

What is Gout?

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Gout is the Most Common Form of Inflammatory Arthritis[1,2]

Gout is a systemic autoinflammatory disease caused by chronic MSU crystal deposition[3–5]

Characteristics[4]

- Redness
- Joint swelling
- Severe pain
- Tophi
- Joint damage

Gout is associated with:[1,2,6–8]

- ↑ **Increased healthcare utilization**
- ↓ **Impaired physical functioning**
- ↓ **Reduced health-related QoL**

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MSU, monosodium urate; QoL, quality of life.

1. Francis-Sedlak M, et al. *Rheumatol Ther* 2021;8:183–197; 2 Dalbeth N, et al. *Nat Rev Dis Primers* 2019;5:69; 3. An J, et al. *J Rheumatol* 2024;51:848–861; 4. Dalbeth N, et al. *Lancet* 2021;397:1843–1855; 5. Khanna P, et al. *J Clin Med* 2020;9:3204; 6. Brook RA, et al. *Curr Med Res Opin* 2010;26:2813–2821; 7. Becker MA, et al. *J Rheumatol* 2009;36:1041–1048; 8. Strand V, et al. *Rheumatol Ther* 2024;11:1271–1290.

Disease Progression in Gout

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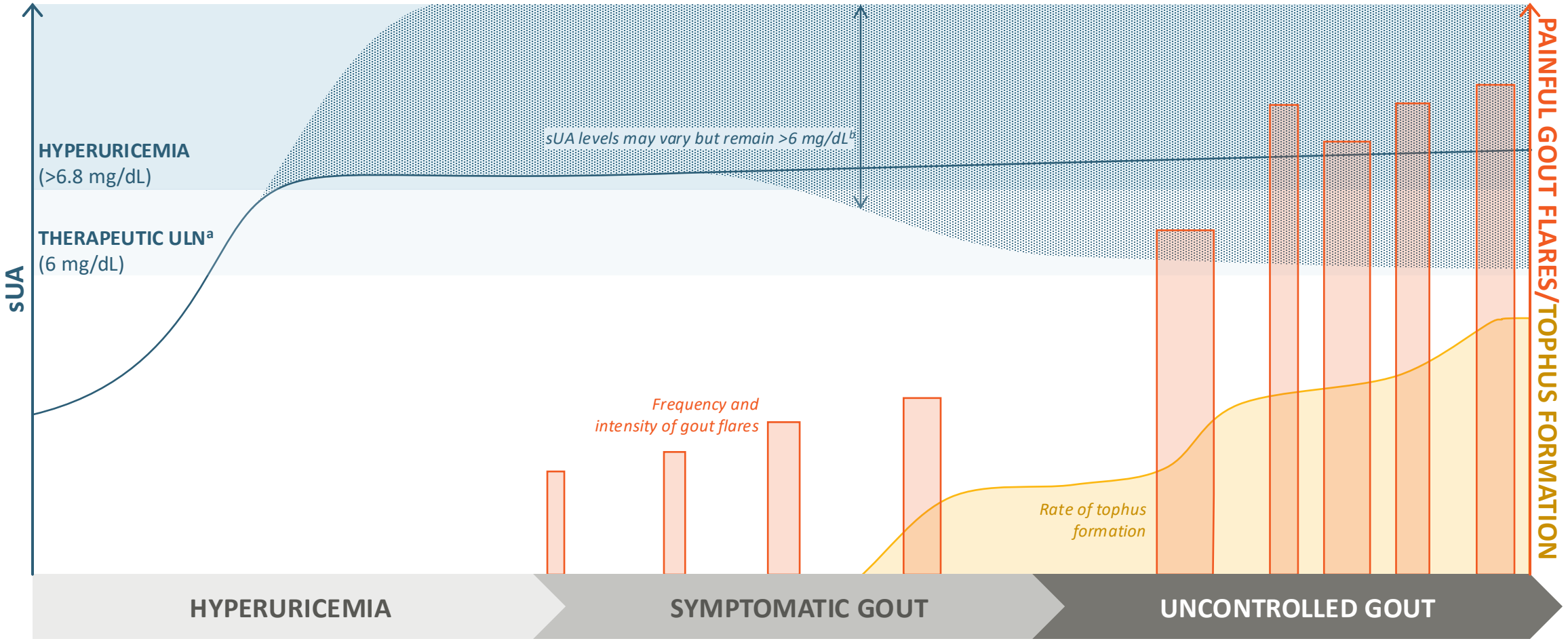
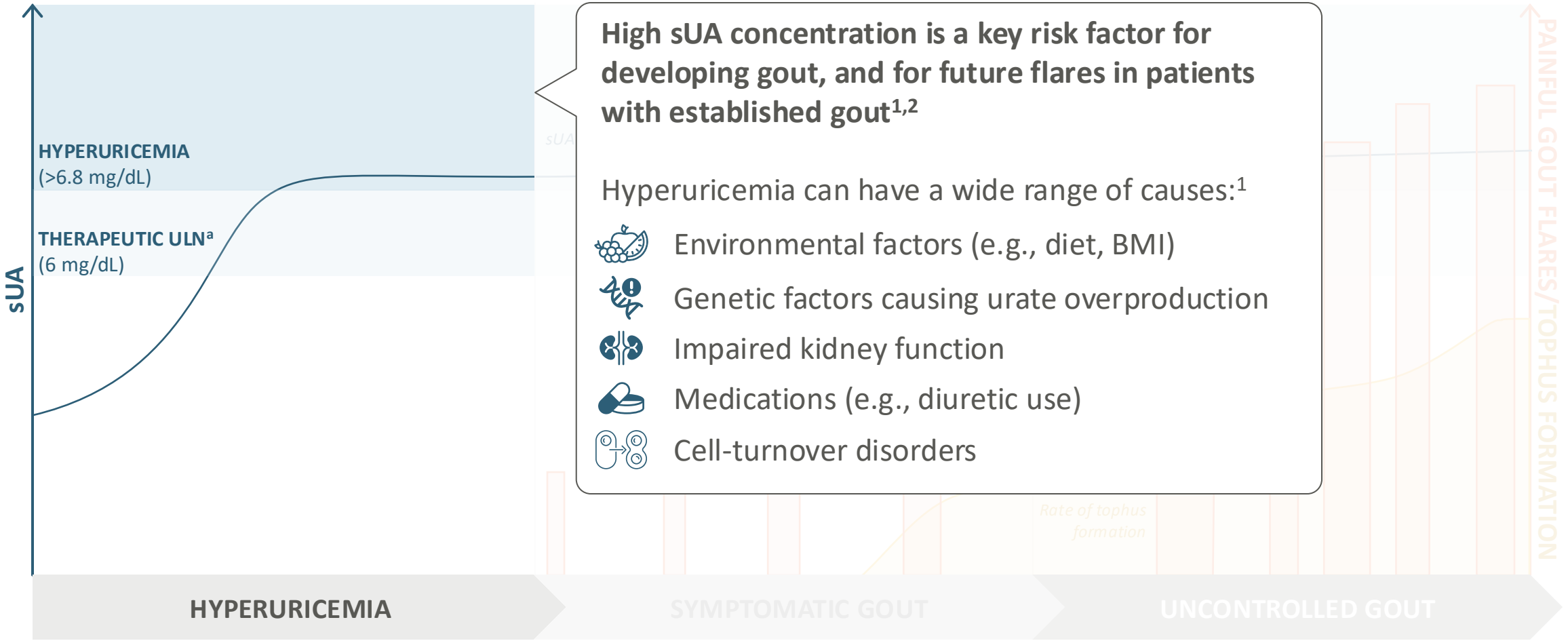
The Progression of Gout[1,2]



Schematic representation of sUA, gout flare frequency and intensity, and MSU crystal deposition with tophus formation over the course of disease progression to uncontrolled gout.
[a]Therapeutic ULN defined as the recommended sUA target for urate-lowering therapies.[3] [b]Transient normalization of sUA may occur during a gout flare.[1]
MSU, monosodium urate; sUA, serum uric acid; ULN, upper limit of normal.
1. Dalbeth N, et al. *Nat Rev Dis Primers* 2019;5:69; 2. Edwards, N.L. (2008). Gout. In: Klippel et al. (eds) Primer on the Rheumatic Diseases. Springer, New York, NY; 3. FitzGerald JD, et al. *Arthritis Care Res (Hoboken)* 2020;72:744–760.

Hyperuricemia[1]

Asymptomatic Elevation of sUA



High sUA concentration is a key risk factor for developing gout, and for future flares in patients with established gout[1,2]

Hyperuricemia can have a wide range of causes:[1]

- Environmental factors (e.g., diet, BMI)
- Genetic factors causing urate overproduction
- Impaired kidney function
- Medications (e.g., diuretic use)
- Cell-turnover disorders

Schematic representation of sUA, gout flare frequency and intensity, and MSU crystal deposition with tophus formation over the course of disease progression to uncontrolled gout.
[a]Therapeutic ULN defined as the recommended sUA target for urate-lowering therapies.[3]
BMI, body mass index; MSU, monosodium urate; sUA, serum uric acid; ULN, upper limit of normal.
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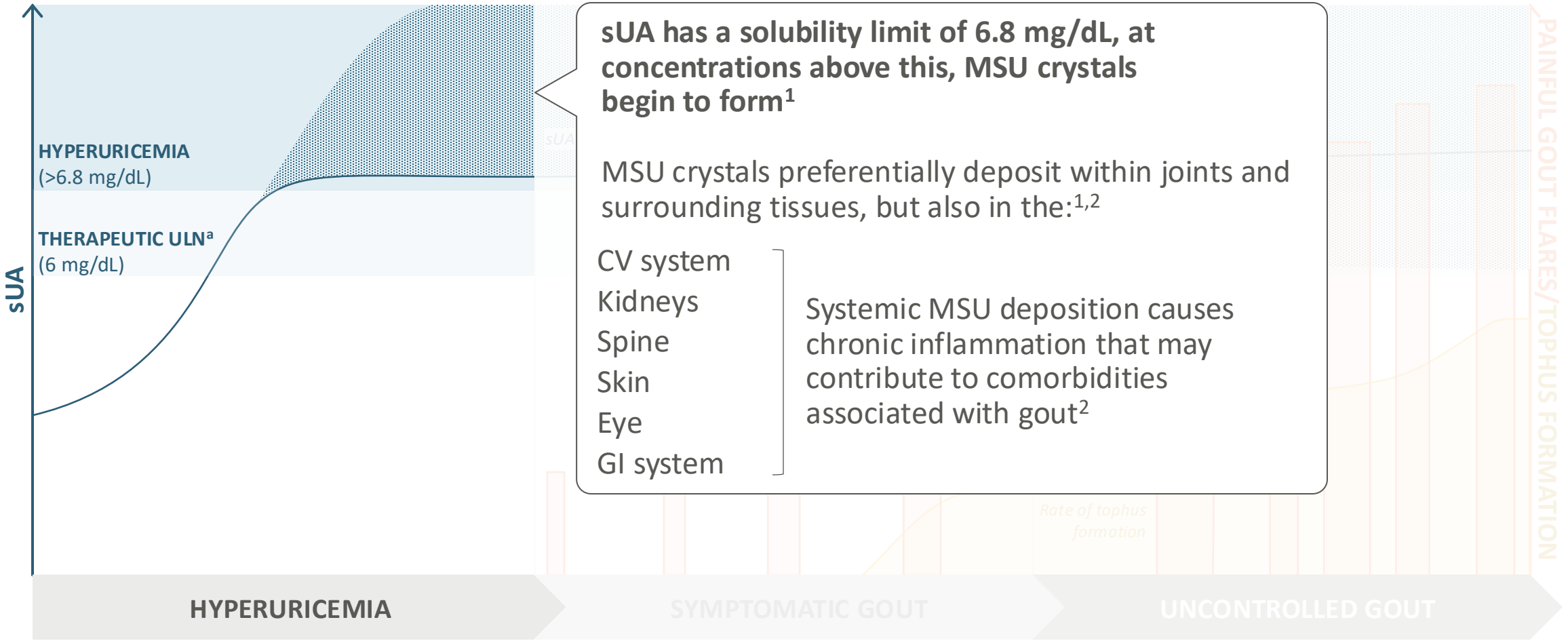
Hyperuricemia[1]

Asymptomatic MSU Crystal Deposition



sUA has a solubility limit of 6.8 mg/dL, at concentrations above this, MSU crystals begin to form[1]

MSU crystals preferentially deposit within joints and surrounding tissues, but also in the:[1,2]

- CV system
- Kidneys
- Spine
- Skin
- Eye
- GI system

Systemic MSU deposition causes chronic inflammation that may contribute to comorbidities associated with gout[2]

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[a]Therapeutic ULN defined as the recommended sUA target for urate-lowering therapies.[3]
CV, cardiovascular; GI, gastrointestinal; MSU, monosodium urate; sUA, serum uric acid; ULN, upper limit of normal.

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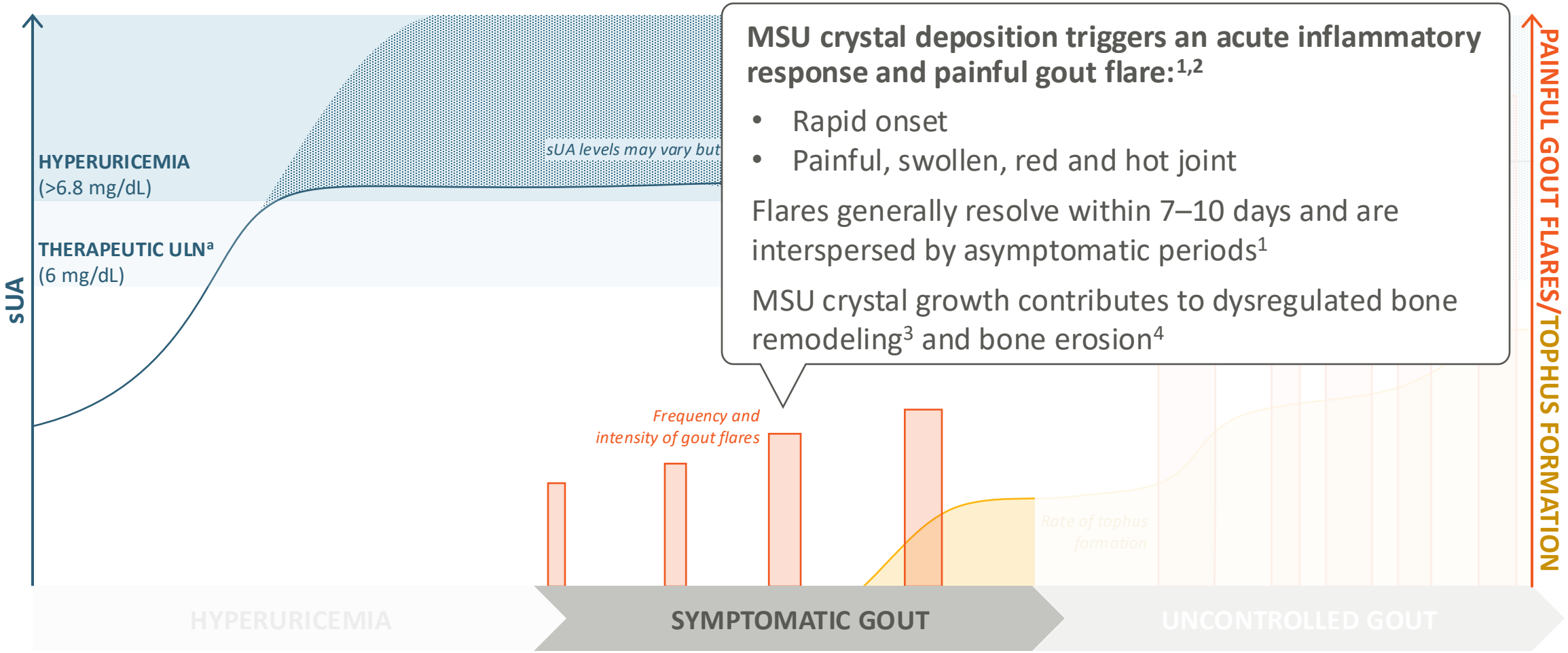
Symptomatic Gout[1]

Painful Gout Flares with Increasing Duration, Frequency and Intensity



MSU crystal deposition triggers an acute inflammatory response and painful gout flare:[1,2]

- Rapid onset
- Painful, swollen, red and hot joint

Flares generally resolve within 7–10 days and are interspersed by asymptomatic periods[1]

MSU crystal growth contributes to dysregulated bone remodeling[3] and bone erosion[4]

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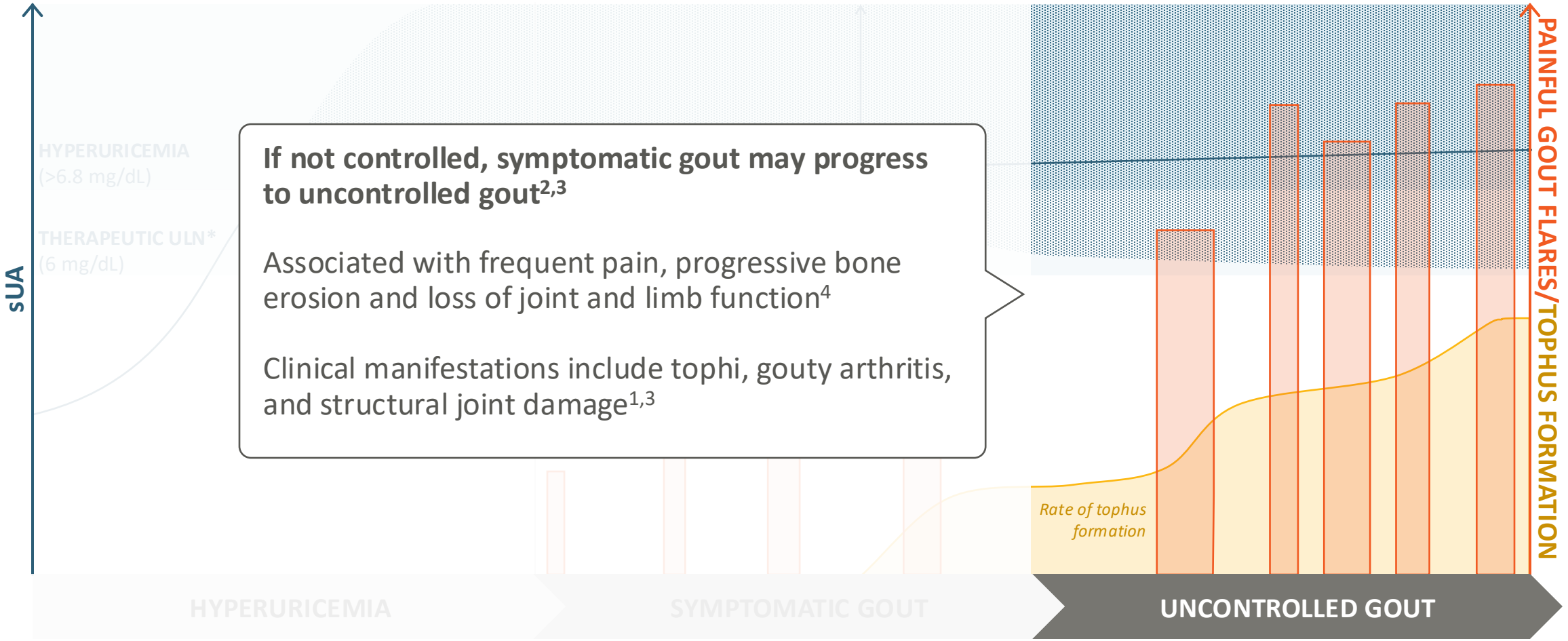
1. Dalbeth N, et al. *Nat Rev Dis Primers* 2019;5:69; 2. Dalbeth N, et al. *Lancet* 2021;397:1843–1855; 3. Chhana A, et al. *Arthritis Res Ther* 2018;20:208; 4. Schlesinger N, et al. *Nat Rev Rheumatol* 2023;19:640–649; 5. FitzGerald JD, et al. *Arthritis Care Res (Hoboken)* 2020;72:744–760.

Uncontrolled Gout[1]

Tophus Formation and Progressive Joint Damage and Disability



Schematic representation of sUA, gout flare frequency and intensity, and MSU crystal deposition with tophus formation over the course of disease progression to uncontrolled gout.
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Uncontrolled Gout

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Uncontrolled Gout is Characterized by Tophus Formation and Progressive Joint Damage and Disability

2–6% patients with symptomatic gout have sUA levels ≥6 mg/dL despite higher doses of ULT,[a] or ULT intolerance or contraindication[1,2]

Characteristics[1–6]

- Persistent hyperuricemia with recurrent flares
- Tophi
- Joint deformities
- Bone erosions
- Chronic pain
- Loss of function and disability

Contributing factors[3,6–8]

- Delayed prescribing, inadequate titration, ineffective therapy
- Gout severity
- Poor adherence
- Failure to modify lifestyle/diet

[a]Allopurinol, febuxostat, or probenecid.
sUA, serum uric acid; ULT, urate-lowering therapy.

1. Francis-Sedlak M, et al. *Rheumatol Ther* 2021;8:183–197; 2. Schlesinger N, Lisky P. *Semin Arthritis Rheum* 2020;50:S31–S38; 3. Fels E, Sundy JS. *Curr Opin Rheumatol* 2008;20:198–202;
4. Botson JK, et al. *Curr Rheumatol Rep* 2022;24:12–19; 5. Stamp LK, Gaffo A. *Expert Opin Biol Ther* 2023;23:1151–1154; 6. Dalbeth N, et al. *Lancet* 2021;397:1843–1855;
7. FitzGerald JD, et al. *Arthritis Care Res (Hoboken)* 2020;72:744–760; 8. Edwards NL, Sundy JS. *Arth Rheum* 2008;58:2587–90.

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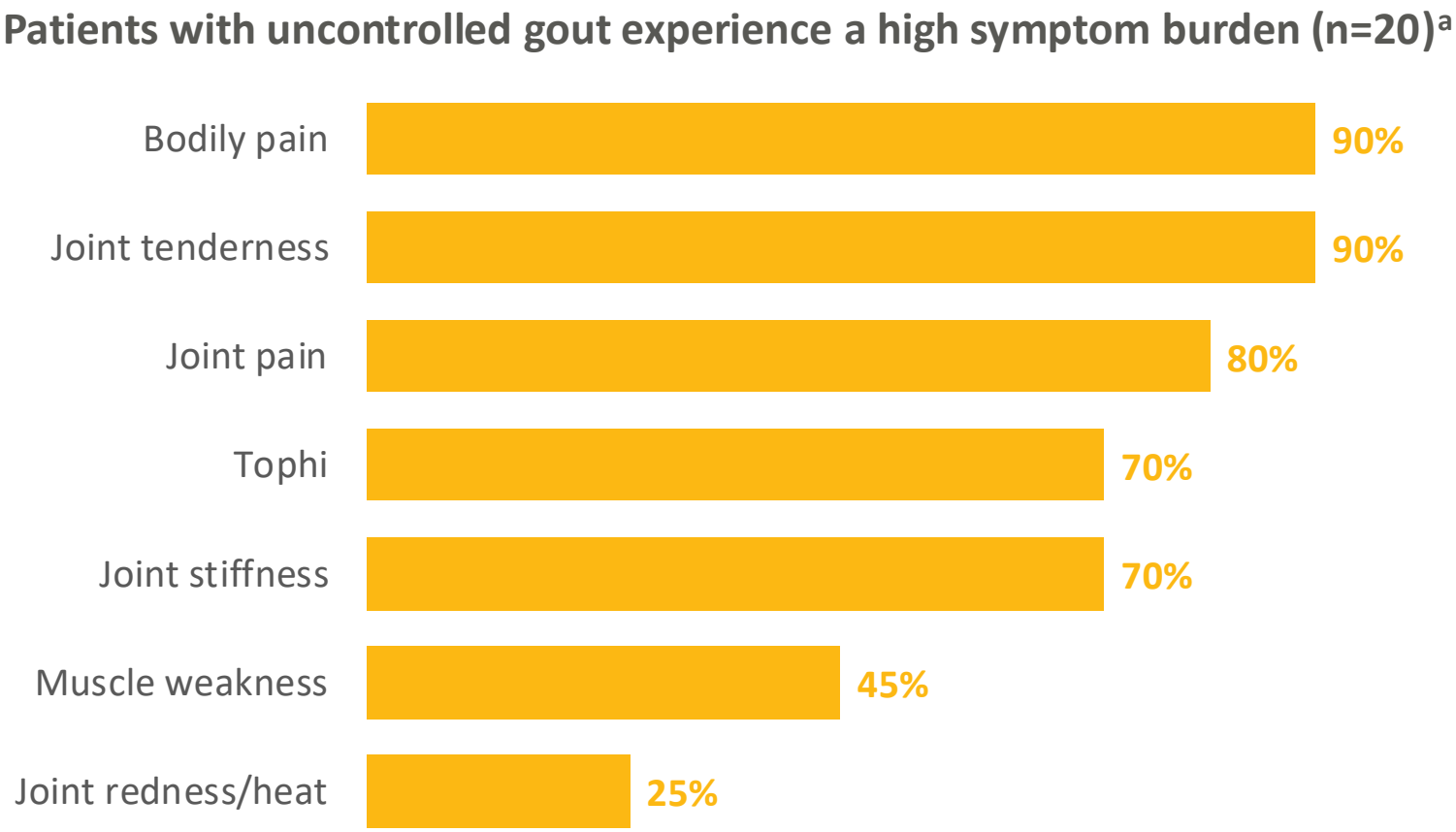
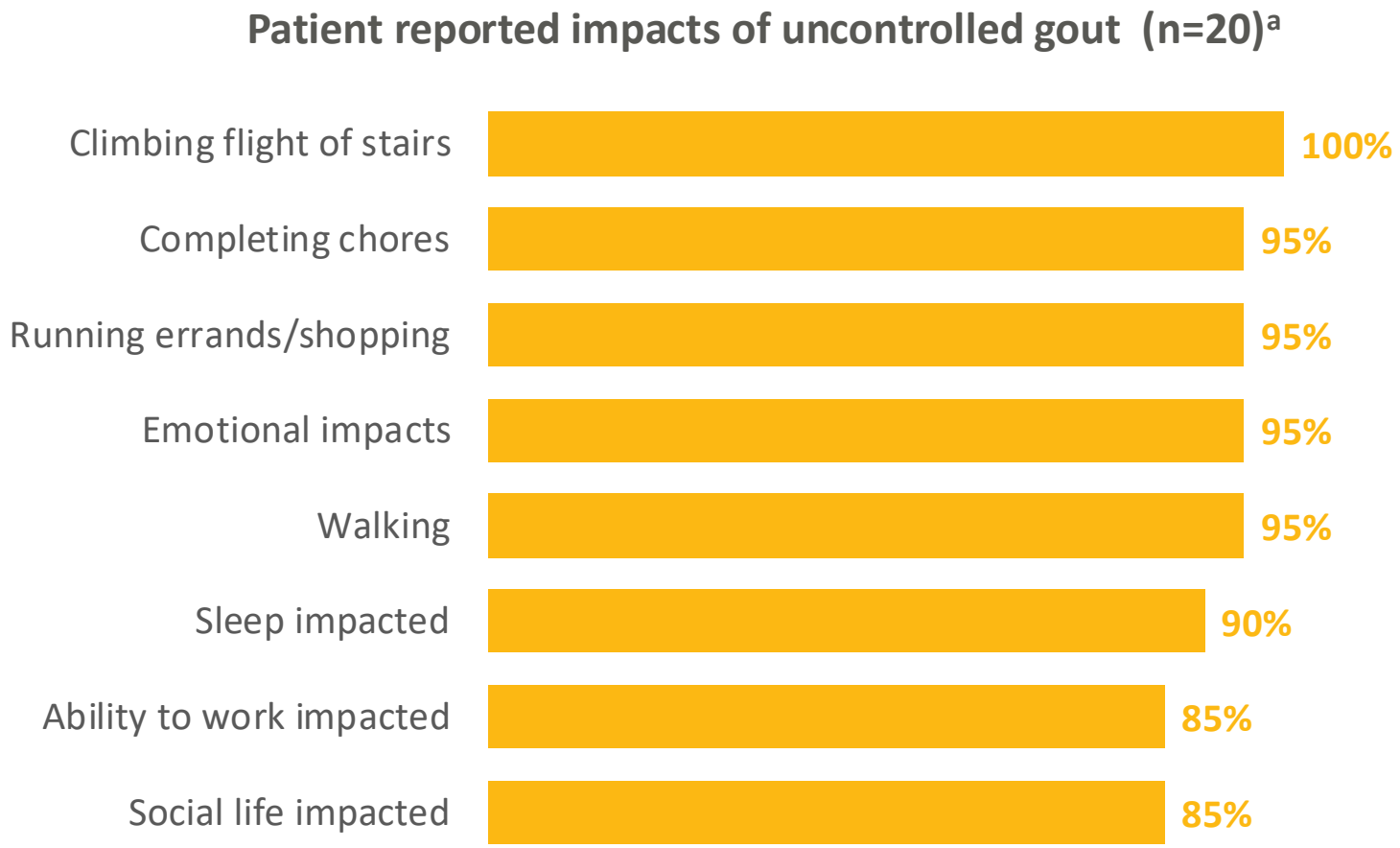
Uncontrolled Gout is a Debilitating Disease with High Symptom Burden



[a]A targeted literature review and qualitative participant concept elicitation interviews (~90 minutes duration) were conductedand used to develop a conceptual model for symptoms and impacts of uncontrolled gout. Participants were US-based, and aged ≥18 years with a history of symptomatic gout and uncontrolled gout (n=20).
SD, standard deviation.
Strand V, et al. *Rheumatol Ther* 2024;11:1271–1290.

Uncontrolled Gout Often Has Physical, Emotional, and Social Impacts on the Everyday Lives of Patients



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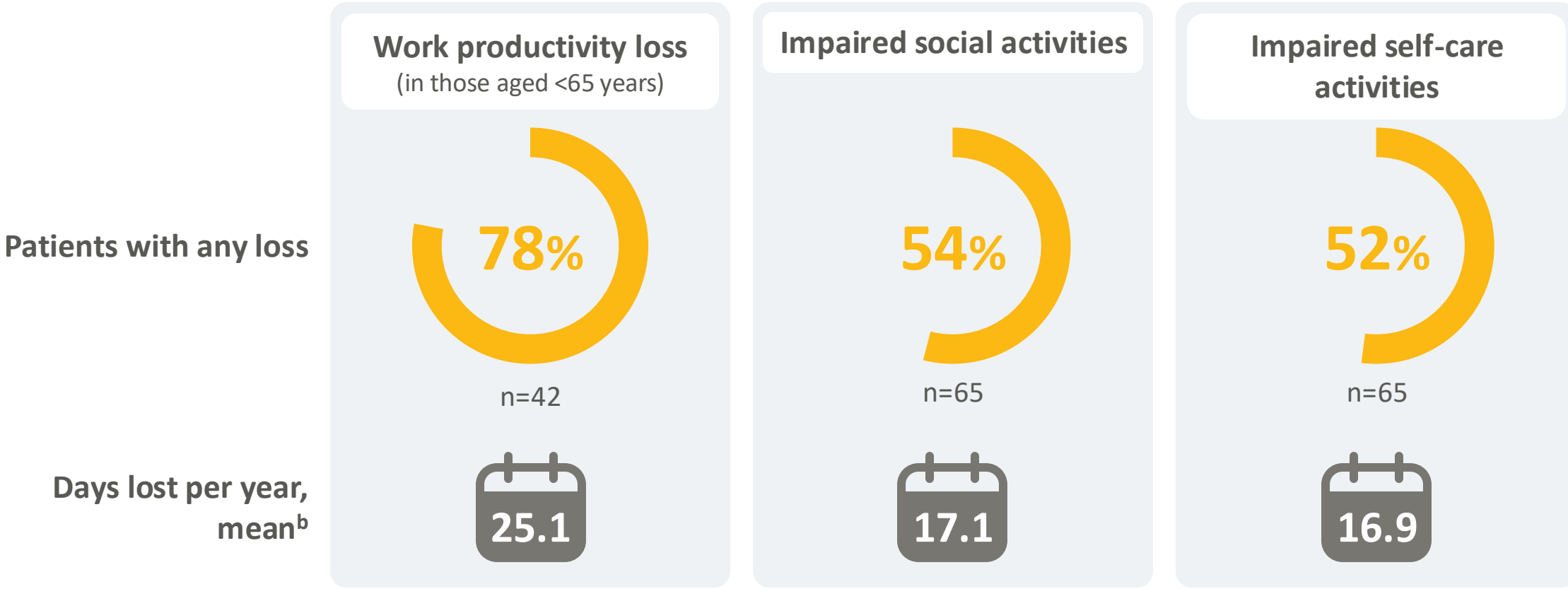
Strand V, et al. *Rheumatol Ther* 2024;11:1271–1290.

Flares in Patients with Uncontrolled Gout Impact Work Productivity and Social Activities

Among patients with uncontrolled gout reporting ≥1 flare per year:[a]



[a]A 1-year prospective observational study was conducted among patients with symptomatic disease at 24 sites in the US in 2001 (N=110). Inclusion criteria required patients (1) aged ≥18 years, (2) to have documented, crystal-proven gout, (3) to have symptomatic gout, and (4) to be intolerant or unresponsive to conventional therapy (sUA ≥6.0 mg/dL) [b]Data represents mean overall, including patients with no days lost.[1]
sUA, serum uric acid.

Edwards NL, et al. *J Med Econ* 2011;14:10–15.

Genetics

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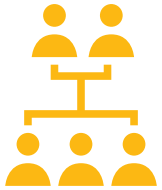
Genetics Play a Role in sUA Variability and Gout



The risk of developing gout is ~2× higher in people with a family history[a,1]

25–60% of sUA variability is explained by genetic factors[2]

⅔ of sUA comes from endogenous sources,[3] and genetic variants can influence these endogenous processes, resulting in uric acid over-production and/or underexcretion[4]

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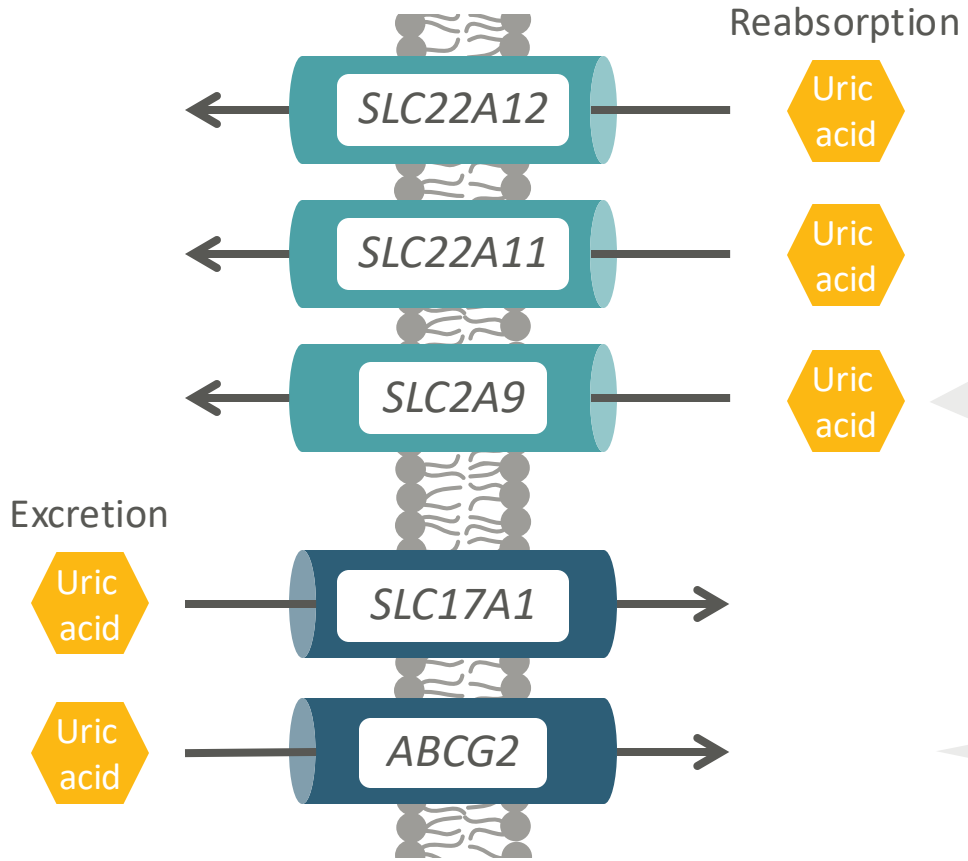
[a]Risk of gout in individuals with affected first-degree relatives versus the general population: men, RR 1.91 (95% CI 1.90–1.93); women, RR 1.97 (95% CI 1.94–1.99). Nationwide, population-based study using the Taiwan national health insurance database.[1]

CI, confidence interval; RR, risk ratio; sUA, serum uric acid.

1. Kuo C-F, et al. *Ann Rheum Dis* 2015;74:369–374; 2. Major TJ, et al. *BMJ* 2018;363:k3951; 3. Zhang Y, et al. *Nutrients* 2022;14:3525; 4. Reginato AM, et al. *Nat Rev Rheumatol* 2012;8:610–621.

Variants in Genes Encoding Uric Acid Transporters are Associated with sUA Levels[1]

UA transporters are located in the kidneys and gut[1]



The variant *rs12498742* in *SLC2A9* has a stronger sUA-elevating effect in women[1,2]

SLC2A9 variants are important for uric acid control across ancestral groups, including European, African-American, Indian, Japanese, and East Asian[1]

The variant *rs2231142* in *ABCG2* has a stronger sUA-elevating effect in men[1,2]

Figure adapted from Dalbeth N, et al. *BMC Med* 2017:15:108 (CC BY 4.0; http://creativecommons.org/licenses/by/4.0/).
sUA, serum uric acid.
1. Dalbeth N, et al. *BMC Med* 2017:15:108; 2. Köttgen A, et al. *Nat Genet* 2013;45:145–154. Supplementary Information.

Variants in Apolipoprotein-Encoding and Inflammatory Genes are Associated with Gout[1,2]

The T-allele of the variant *rs670* in *APOA1* was associated with a 47% increased risk of gout[a,1]
OR 1.47 (95% CI 1.14–1.90)

The G-allele of the variant *rs5128* in *APOC3* was associated with a 14% decreased risk of gout[a,1]
OR 0.86 (95% CI 0.74–0.99)

APOA1 and *APOC3* may be involved in regulating inflammatory processes in gout[1]

The NLRP3 inflammasome is involved in flare triggering, and variants in genes related to its activation have been associated with gout[2]

[a]Case-control, candidate gene study in people of European and Polynesian descent to replicate the prior observed association of *APOA1* variant *rs670* and *APOC3* variant *rs5128* with gout (cases, n=2690; controls, n=10,803).[1,3]
CI, confidence interval; NLRP3, NOD-like receptor family pyrin domain-containing protein 3; OR, odds ratio.

1. Rasheed H, et al. *Rheumatol* 2016;55:1421–1430; 2. Terkeltaub R. *BMC Med* 2017;15:158; 3. Rasheed H, et al. *Rheumatol* 2016;55:1421–1430. Supplementary Appendix.

Genetic Factors May Form the Link Between Gout and Comorbidities[1]

Two separate gene clusters have been associated with sUA and different comorbid traits[1]

CKD cluster[1]
sUA + serum creatinine

Metabolic cluster[1]
sUA + BMI, systolic blood pressure, and blood glucose

These genetic clusters agree with previously observed phenotypic gout patterns[1,2]
Gout only | Gout + CKD | Gout + metabolic disease

The association between gout and comorbidities may not be causative;[3] instead there may be simultaneous genetic effects on the phenotype of both traits[1]

BMI, body mass index; CKD, chronic kidney disease; sUA, serum uric acid.

1. Reynolds RJ, et al. *Eur J Hum Genet* 2021;29:1438–1445; 2. Bevis M, et al. *Rheumatol* 2018;57:1358–1363; 3. Sumpter NA, et al. *Curr Opin Rheumatol* 2020;32:126–133.

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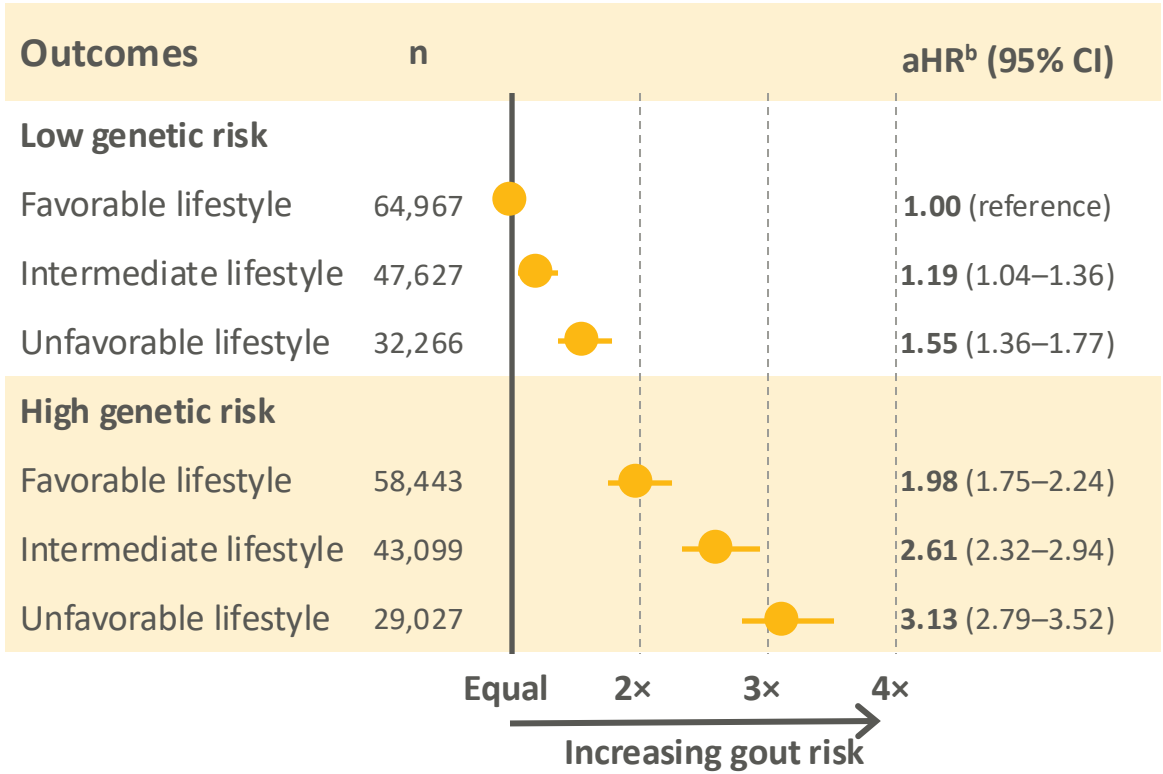
Genetics and Dietary Factors can Interact to Modulate Gout Risk and Progression[1–3]

Genetics and lifestyle modify the risk of gout[a,1]



51% Attributable proportion of gene–diet interaction to incident gout risk[c,2]

50.7× ODDS

A high genetic risk score combined with alcohol use increased risk of tophi beyond genetics or alcohol use alone[d,3]

Low-risk + alcohol | OR 1.29 (95% CI 0.54–3.10)

High-risk | OR 3.81 (95% CI 1.31–11.11)

High-risk + alcohol | OR 50.65 (95% CI 12.30–208.64)

[a]Population-based cohort study (UK Biobank) of adults aged 40–79 years (white British descent; n=416,481). Healthy lifestyle factors included no/moderate alcohol consumption, not smoking, regular physical activity, and a healthy diet. Unfavorable, intermediate, and favorable lifestyles were defined as having 0–1, 2, or 3–4 healthy lifestyle factors, respectively. Weighted polygenic risk scores were calculated using 33 SNPs independently associated with gout.[1] [b]Adjusted for sex, age, socioeconomic status, education level, CRP, serum creatinine, cholesterol, triglycerides, CVD, diabetes, hypertension, and BMI.[1] [c]Prospective cohort of female nurses (Nurses' Health Study; discovery cohort; n=18,244) aged 30–55 years, primarily of European descent. The replication cohort included a further 136,786 women from the Nurses' Health Study II, Women's Genome Health Study, and the UK Biobank. Genetic risk score was constructed using 114 SNPs associated with serum urate. A dietary score was given based on adherence to the Dietary Approaches to Stop Hypertension diet.[2] [d]Case-control study of Taiwanese Han men (n=558). Genetic risk score was generated according to the presence of risk alleles associated with gout in 3 SNPs.[3]

aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; CRP, c-reactive protein; CVD, cardiovascular disease; OR, odds ratio; SNP, single nucleotide polymorphism.

1. Zhang Y, et al. *BMC Med* 2022;20:138; 2. Lin K, et al. *Arthritis Rheumatol* 2023;75:1028–1038; 3. Tu H-P, et al. *J Hum Genet* 2016;61:803–810.

Diet

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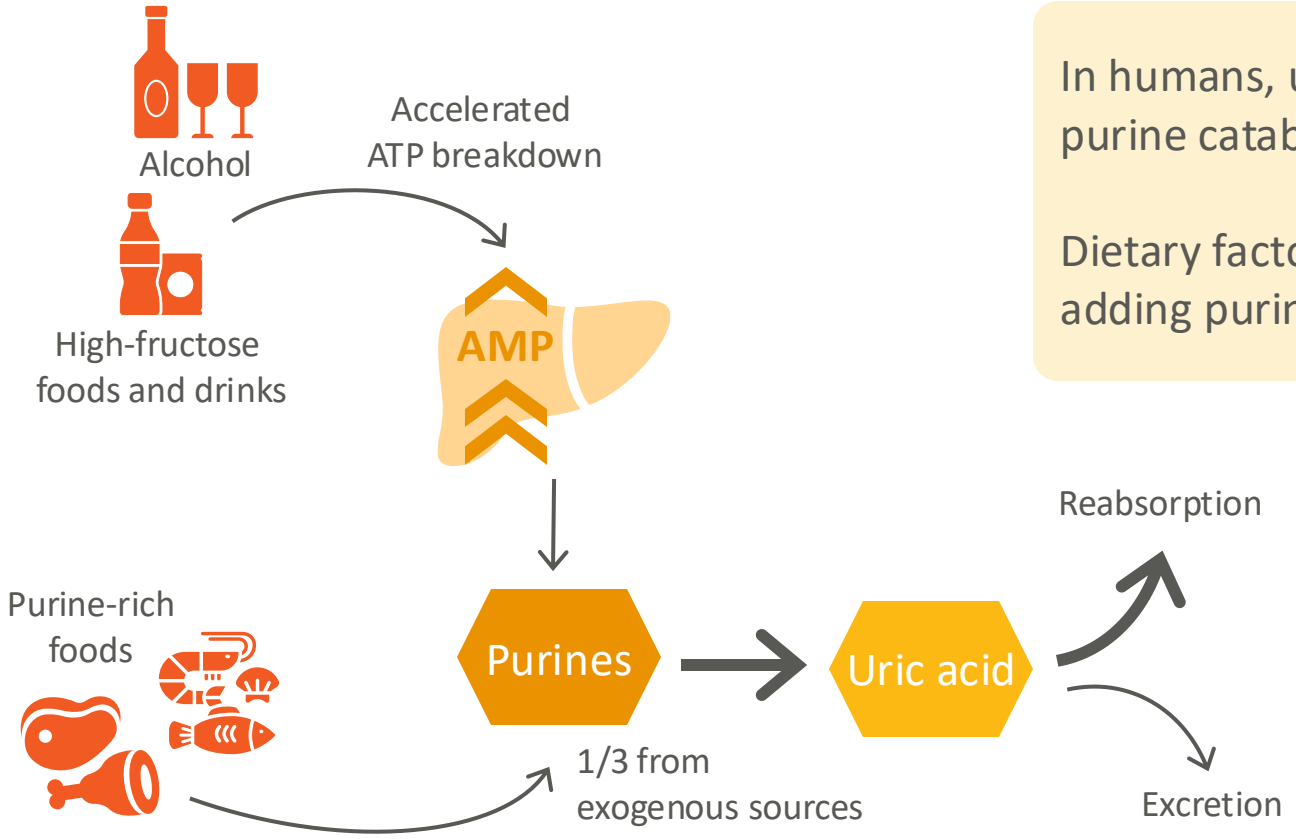
Purine Overload Contributes to Hyperuricemia[1]



In humans, uric acid is the final breakdown product in purine catabolism[1]

Dietary factors can lead to elevations in sUA by directly adding purines, or by altering metabolic processes[1]

Associated with higher sUA levels[2,3]	Associated with lower sUA levels[2,3]
Beer	Eggs
Liquor	Peanuts
Wine	Cold cereal
Potatoes	Skim milk
Poultry	Cheese
Soft drinks	Brown bread
Beef, pork, or lamb	Margarine
Seafood	Non-citrus fruit

Figure developed from information in Zhang Y, et al. *Nutrients* 2022;14:3525.
AMP, adenosine monophosphate; ATP, adenosine triphosphate; sUA, serum uric acid.
1. Zhang Y, et al. *Nutrients* 2022;14:3525; 2. Major TJ, et al. *BMJ* 2018;363:k3951; 3. Choi HK, et al. *Arthritis Rheum* 2005;52:283–289.

Cardiometabolic Diets can Lower sUA in Patients with Hyperuricemia and Cardiometabolic Comorbidities[1–5]

Mediterranean Diet[1]

73% higher odds of reversing hyperuricemia[a]

aOR[b] 1.73 (95% CI 1.04–2.89)

Elderly participants (men, 55–80 years; women, 60–80 years) with high CV risk

DASH Diet[2]

0.53 mg/dL greater reduction in sUA[c]

β –0.53 (95% CI –0.96, –0.09)

Adults with elevated blood pressure or hypertension[6]

Weight Loss Diet[3,4]

1.9–2.4 mg/dL reduction in sUA[d]

Adults aged 40–65 years with BMI ≥27 kg/m^2 or T2D or CHD

Traditional low-purine diets for gout and cardiometabolic diets recommend minimizing red meat and sugar intake[3]

High BMI is an important modifiable risk factor for hyperuricemia[5]

Population attributable risk 44% (95% CI 41–48)

[a]In the highest category of baseline adherence to the diet versus the lowest. Cross-sectional and prospective analysis from the PREDIMED trial, with median 5 years of follow-up. A validated 14-item questionnaire was used to assess diet adherence. n=964 patients with hyperuricemia (>7 mg/dL in men; >6 mg/dL in women). Mediterranean diet is characterized by high consumption of fruits, vegetables, legumes, olive oil, legumes, olive oil, nuts, and whole grains; moderate consumption of wine, dairy, and poultry; and a low consumption of red meat, sweet beverages, creams, and pastries.[1] [b]Adjusted for intervention group, age, BMI, recruitment center, current smoking status, former smoking status, physical activity, educational level, blood pressure, total energy intake, caffeine intake, antihypertensive agent use, oral hypoglycemic agent use, allopurinol use, presence of diabetes, and weight changes.[1] [c]In patients with baseline sUA ≥7 mg/dL consuming the DASH diet versus control diet for 8 weeks (N=44; prespecified subgroup analysis by categories of baseline sUA). sUA levels were measured in stored serum samples from the parallel-arm, 8-week DASH trial. DASH diet emphasizes fruits, vegetables, whole grains, lean proteins, and low-fat dairy while limiting foods high in saturated fat, sugar, and sodium.[2,6]
[d]At 6 months. Secondary analysis of stored blood samples (n=235) from the DIRECT trial, which compared three weight-loss diets. The low-carbohydrate, non–restricted calorie diet was adapted from the Atkins diet; participants started with an induction phase aimed to provide 20 g of carbohydrates per day for the first 2 months, which was gradually increased to a maximum of 120 g/day.[3,4]
β, between-group difference; aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; CHD, coronary heart disease; CV, cardiovascular; sUA, serum uric acid; T2D, type 2 diabetes.

. 1. Guasch-Ferré M, et al. *J Gerontol A Biol Sci Med Sci* 2013;68:1263–1270; 2. Juraschek SP, et al. *Arthritis Rheumatol* 2021;73:1014–1020. Supplementary Material; 3. Yokose C, et al. *Curr Opin Rheumatol* 2021;33:135–144; 4. Yokose C, et al. *Diabetes Care* 2020;43:2812–2820; 5. Choi HK, et al. *Arthritis Rheumatol* 2020;72:157–165; 6. Juraschek SP, et al. *Arthritis Rheumatol* 2021;73:1014–1020.

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Gut Microbiome

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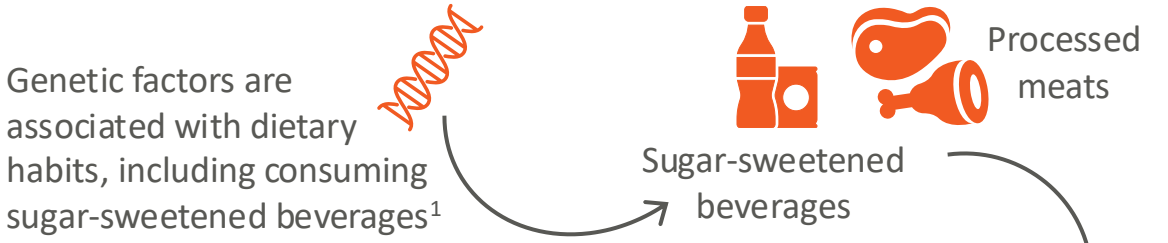
Diet Can Alter the Composition of the Gut Microbiome (Dysbiosis), Contributing to Cardiometabolic Disease[1–3]



A Mediterranean-style diet is associated with microbial species that can reduce inflammation and increase SCFA levels[3]

Dysbiosis

- Decreased microbial diversity[2]
- Microbial species that may increase inflammation[3]

Dysbiosis may contribute to the **comorbidities** associated with gout, including cardiometabolic disease (CVD, diabetes, metabolic syndrome)[2,3]

Three microbial genes[a] are suggested to be significantly enriched in gout patients and are linked to dysbiosis that is associated with increased sUA[4]

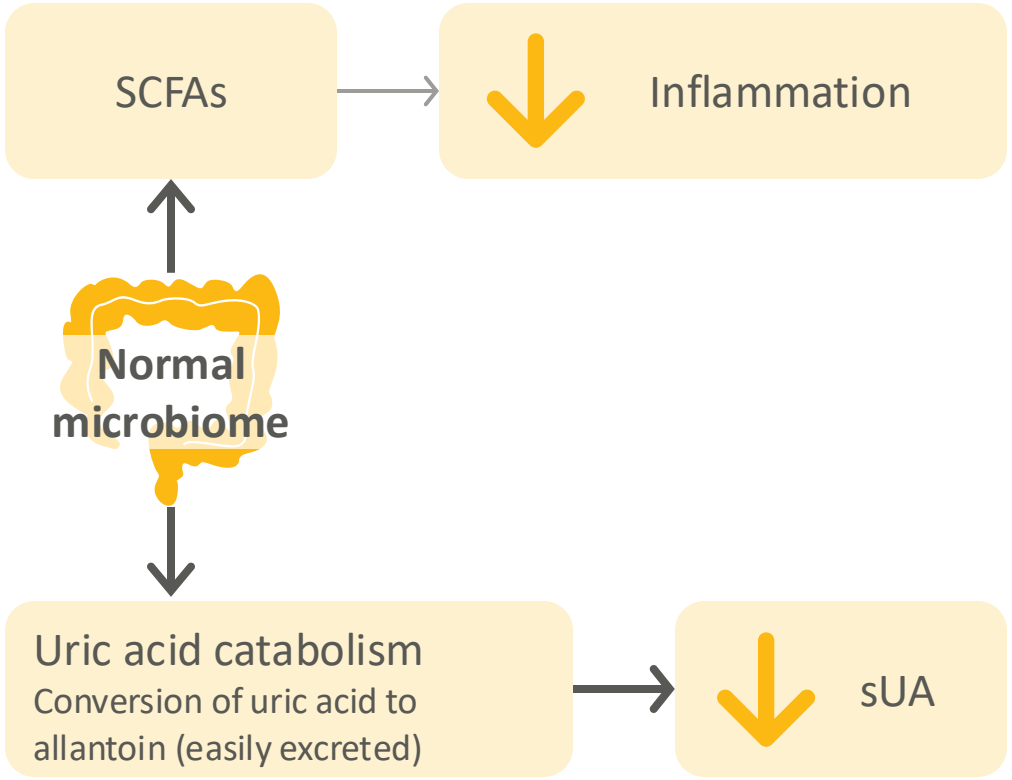
[a]15049 (exo-alpha-sialidase), 415936 (N-6 DNA methylase), and 1697136 (relaxase/mobilization nuclease domain-containing protein).[4]

CVD, cardiovascular disease; DNA, deoxyribonucleic acid; SCFA, short-chain fatty acid; sUA, serum uric acid.

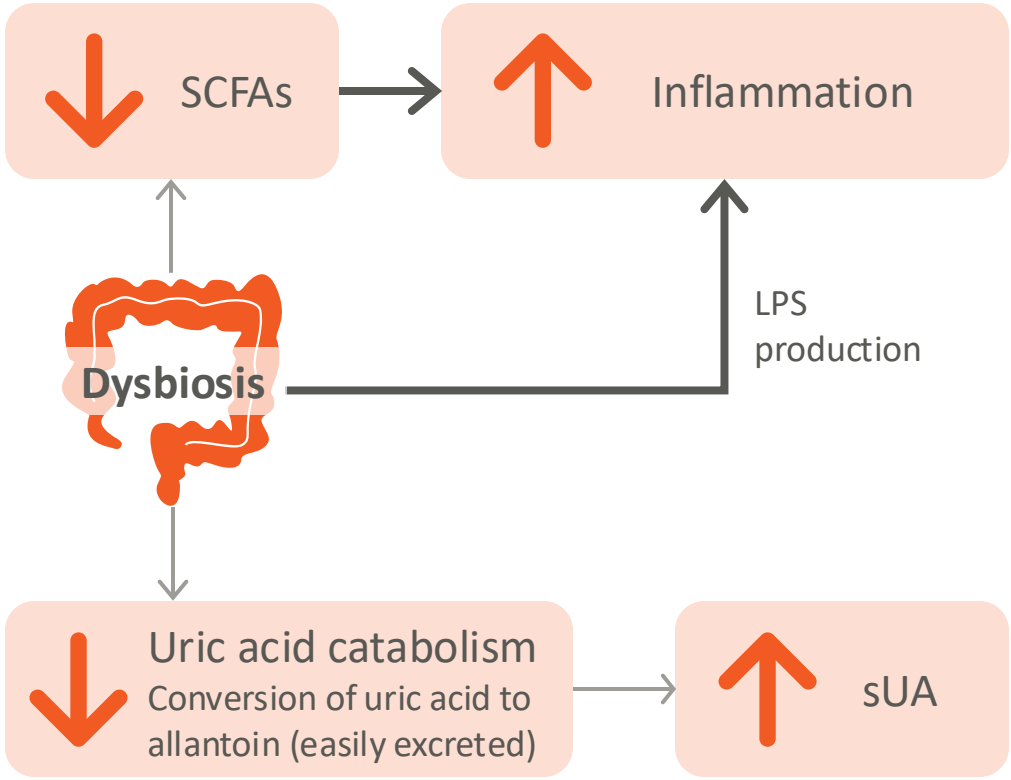
1. Major TJ, et al. *BMJ* 2018;363:k3951; 2. Walker RL, et al. *Genome Med* 2021;13:188; 3. Bolte LA, et al. *Gut* 2021;70:1287–1298; 4. Chu Y, et al. *NPJ Biofilms Microbiomes* 2021;7:66.

Altered Composition of the Gut Microbiome (Dysbiosis) May Contribute to Hyperuricemia and Gout[1,2]

The normal gut microbiome regulates inflammation and sUA by producing SCFAs and catabolising uric acid[1,2]



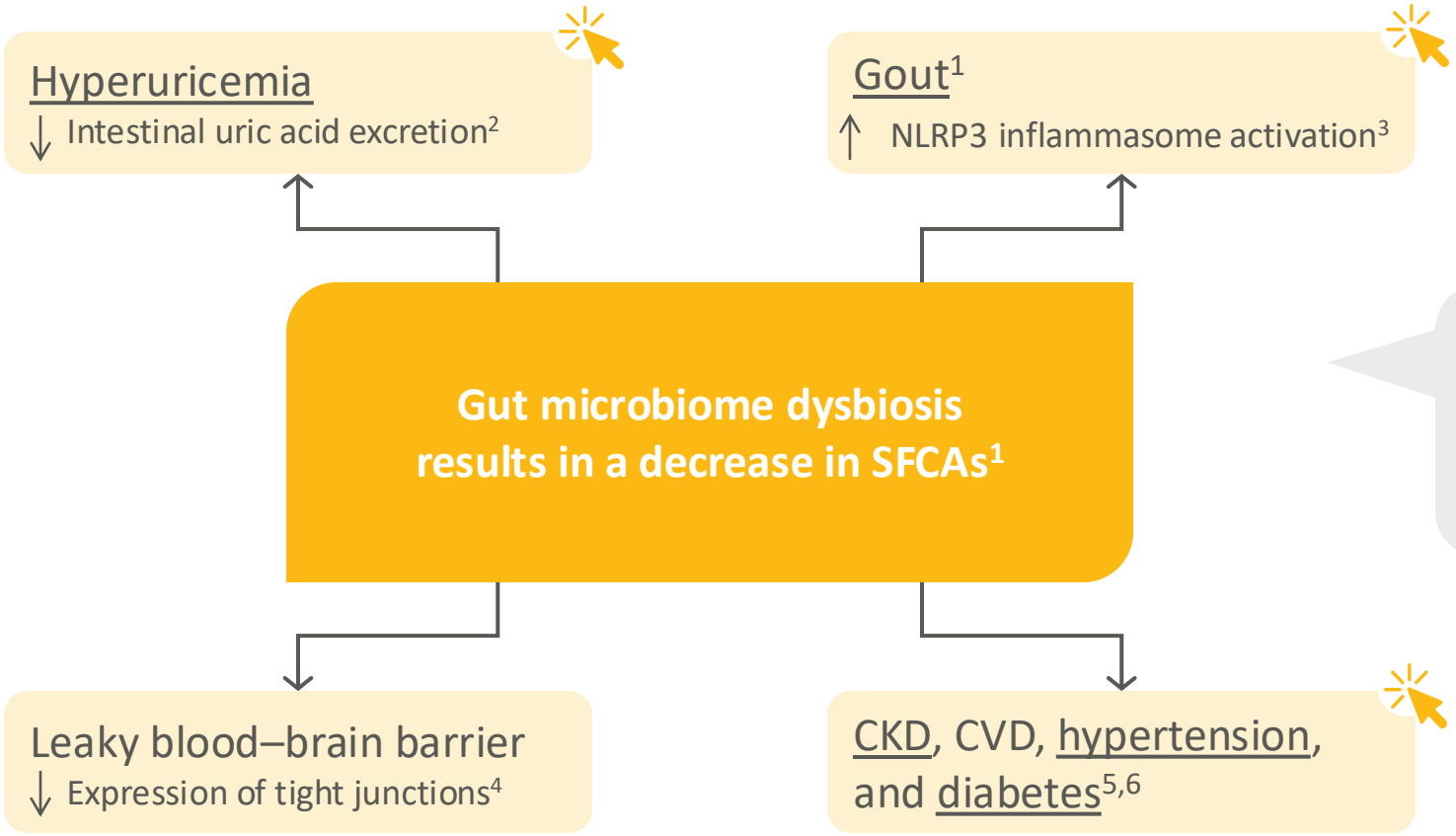
In dysbiosis, the gut microbiome promotes inflammation and catabolises less uric acid[1,2]



LPS, lipopolysaccharide; SCFA, short-chain fatty acid; sUA, serum uric acid.

1. Tong S, et al. *Front Cell Infect Microbiol* 2022;12:1051682; 2. Shirvani-Rad S, et al. *Front Med* 2023;10:1163778.

Gut Microbiome Dysbiosis May Lead to Gout and Associated Cardiometabolic Disease via Decreased SCFAs[1–6]



The impact of treatment on gut microbiome, metabolic disorders, and the blood–brain barrier should be considered

NP-38435

CKD, chronic kidney disease; CVD, cardiovascular disease; NLRP3, NOD-like receptor family pyrin domain-containing protein 3; SFCA, short-chain fatty acid.

1. Shirvani-Rad S, et al. *Front Med* 2023;10:1163778; 2. Singh AK, et al. *World J Gastroenterol* 2024;30:4404–4410; 3. Yuan X, et al. *Redox Biol* 2018;16:21–31; 4. Silva YP, et al. *Front Endocrinol* 2020;11:25; 5. Magliocca G, et al. *Int J Mol Sci* 2022;23:5354; 6. Zhang D, et al. *Cell Commun Signal* 2023;21:212.

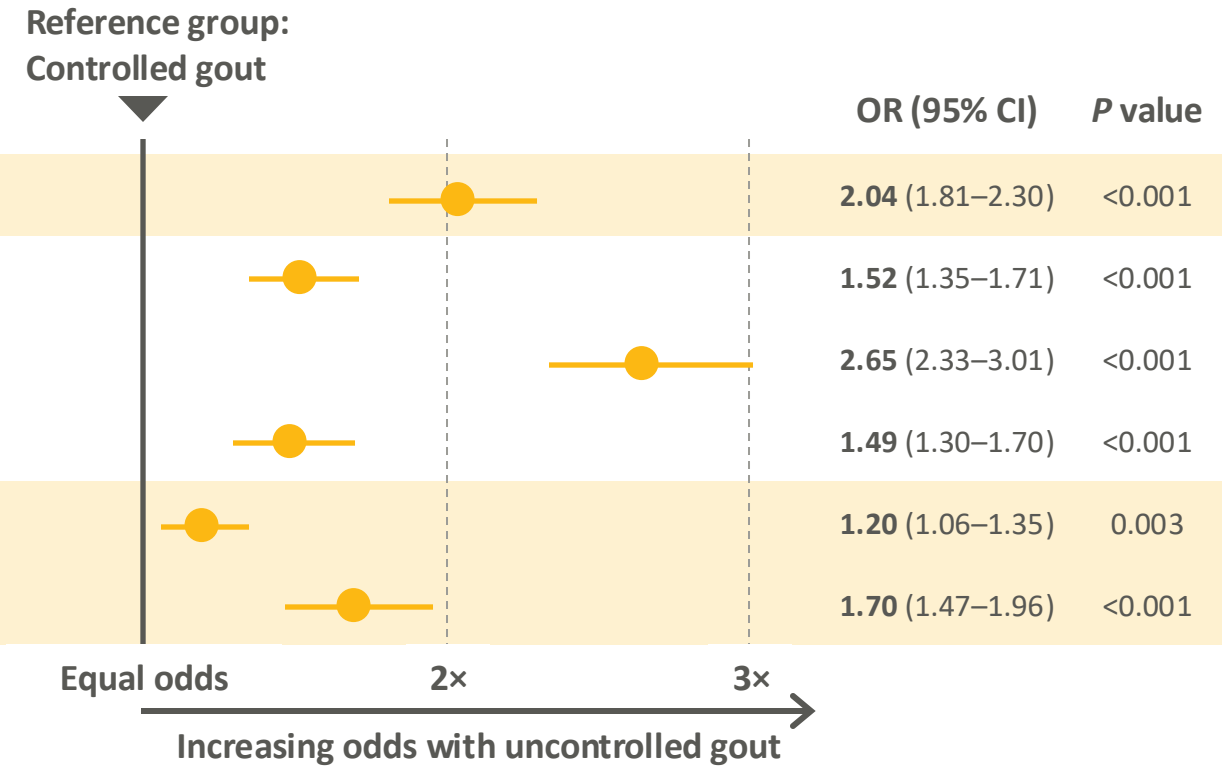
sUA, Gout, and Comorbidities

NP-38435

sUA, serum uric acid.

Patients with Uncontrolled Gout have a Higher Prevalence of Metabolic Disorders Compared with Patients with Controlled Gout[a,1]

Comorbidity type, n (%)[1]	Controlled gout (n=5473)	Uncontrolled gout[a] (n=1358)	OR (95% CI)	*P* value
CKD	1772 (32.4)	671 (49.4)	**2.04** (1.81–2.30)	<0.001
CV disease	2500 (45.7)	761 (56.0)	**1.52** (1.35–1.71)	<0.001
Heart failure	1039 (19.0)	520 (38.3)	**2.65** (2.33–3.01)	<0.001
Atrial fibrillation	1098 (20.1)	369 (27.2)	**1.49** (1.30–1.70)	<0.001
Diabetes	2730 (49.9)	738 (54.3)	**1.20** (1.06–1.35)	0.003
With renal manifestations	842 (15.4)	320 (23.6)	**1.70** (1.47–1.96)	<0.001



Comorbidities may reflect local, chronic inflammation from systemic uric acid deposition[2]

Uric acid deposition has been observed in:[2]

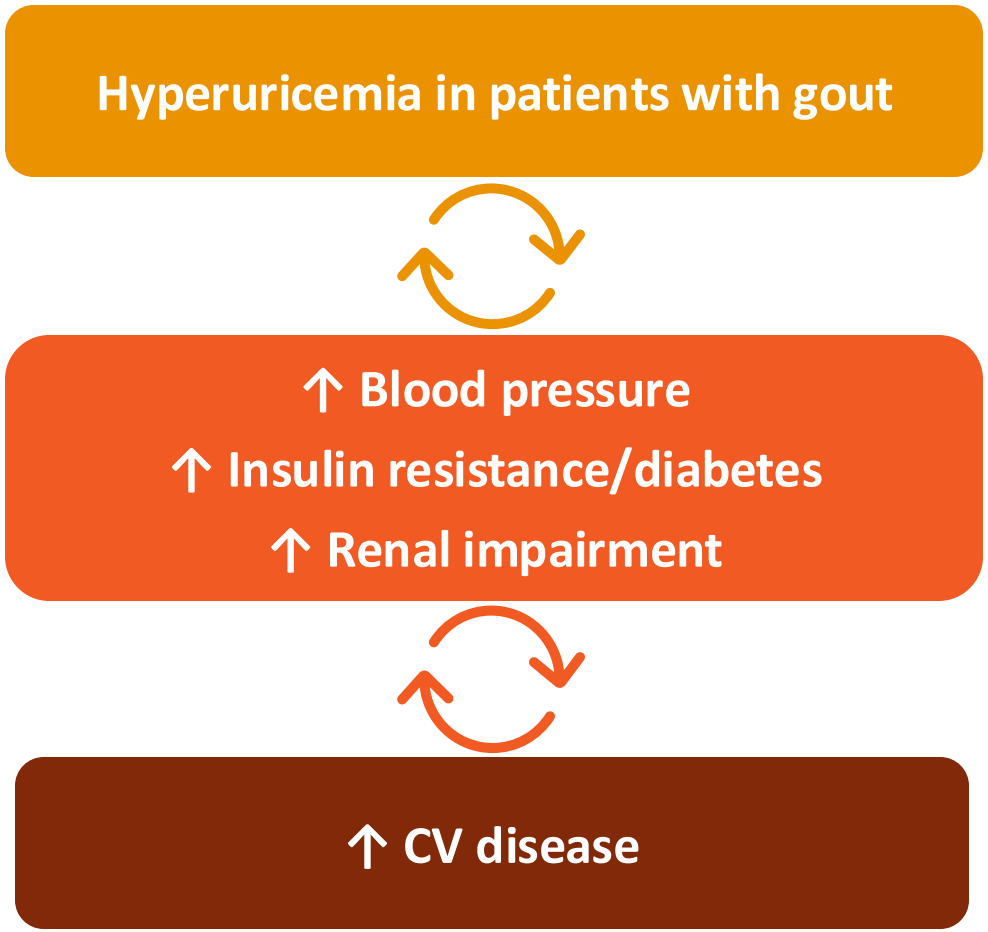
- Blood vessels
- Heart
- Kidney
- Spine
- Eye
- Skin
- GI system

[a]Data from adult patients with gout and who had at least 90 days of continuous ULT was collected from the Humana Research Database from 2007–2016. A total of 6831 patients were identified that met the inclusion criteria (5473 patients had controlled gout and 1358 patients had uncontrolled gout). Uncontrolled gout was defined as sUA ≥8.0 mg/dL.[1]

CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; GI, gastrointestinal; OR, odds ratio; sUA, serum uric acid; ULT, urate-lowering therapy.

1. Francis-Sedlak M, et al. *Rheumatol Ther* 2021;8:183–197; 2. Khanna P, et al. *J Clin Med* 2020;9:3204.

Hyperuricemia in Patients with Gout Contributes to Metabolic Dysfunction, which Drives Metabolic and CV Disease[1,2]



Drivers of metabolic dysfunction

- Inflammatory pathways[2]
- Endothelial dysfunction[2]
- Oxidative stress[2]

Adapted from Kanbay M, et al. *Eur J Intern Med* 2016;29:3–8.
CV, cardiovascular disease.
1. Kanbay M, et al. *Eur J Intern Med* 2016;29:3–8; 2. Xiong Q, et al. *Int J Endocrinol* 2019;2019:9691345.

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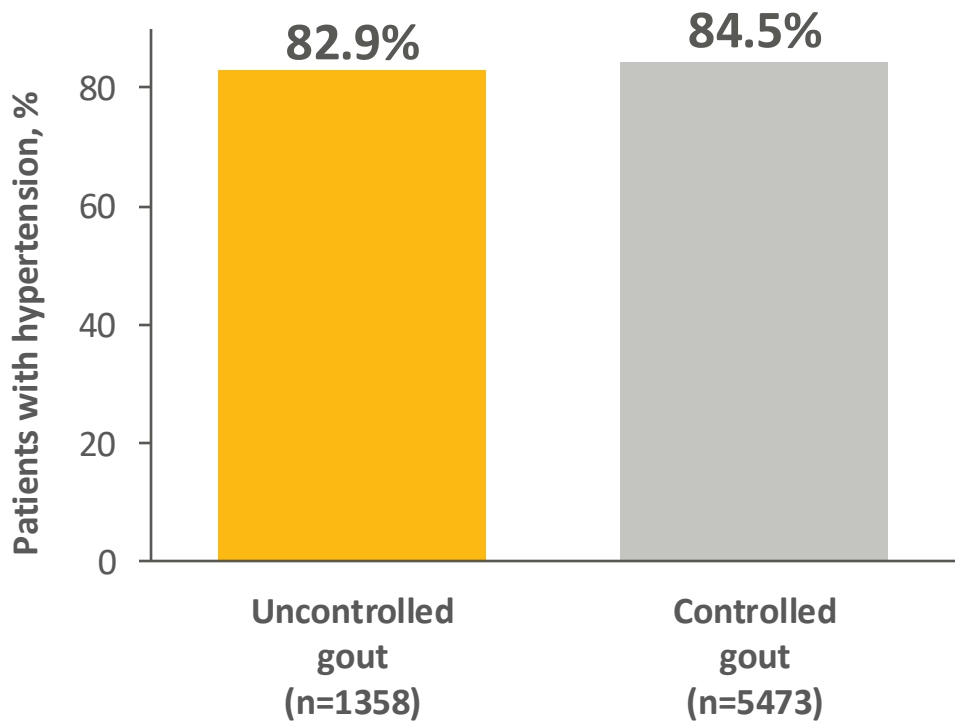
Hypertension

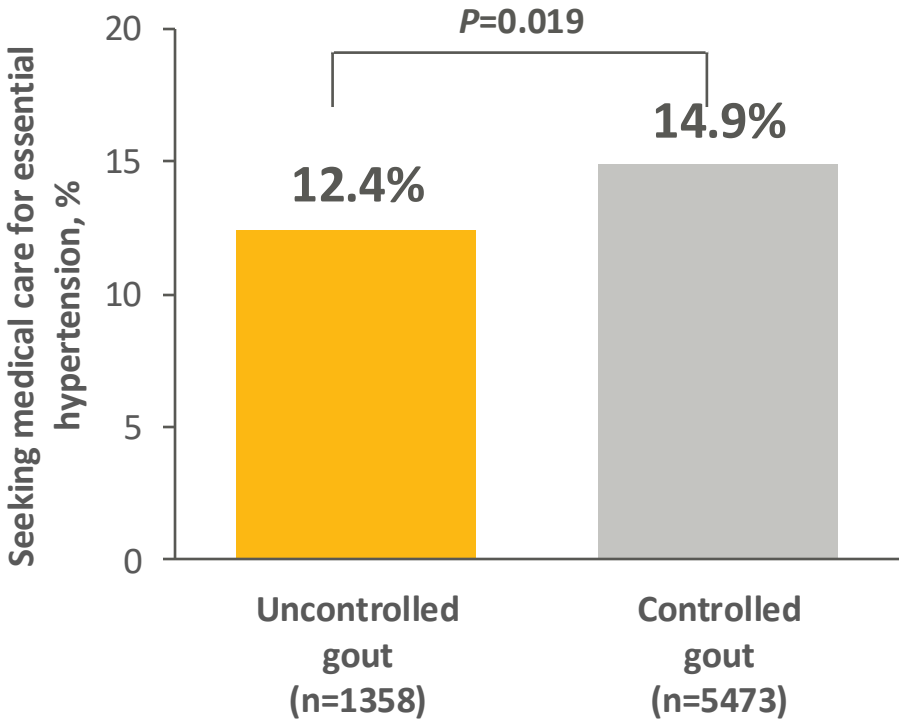
NP-38435

Most Patients with Gout also have Hypertension[1,2]

Hypertension is equally prevalent among patients with uncontrolled gout and controlled gout[a,2]



Patients with uncontrolled gout are less likely to seek medical care for unspecified essential hypertension than patients with controlled gout[a,2]



[a]Data from adult patients with gout and who had at least 90 days of continuous ULT was collected from the Humana Research Database from 2007–2016. A total of 6831 patients were identified that met the inclusion criteria (5473 patients had controlled gout and 1358 patients had uncontrolled gout). Uncontrolled gout was defined as sUA ≥8.0 mg/dL.[2]

sUA, serum uric acid; ULT, urate-lowering therapy..

1. Zhu Y, et al. *Am J Med* 2012;125:679–687; 2. Francis-Sedlak M, et al. *Rheumatol Ther* 2021;8:183–197.

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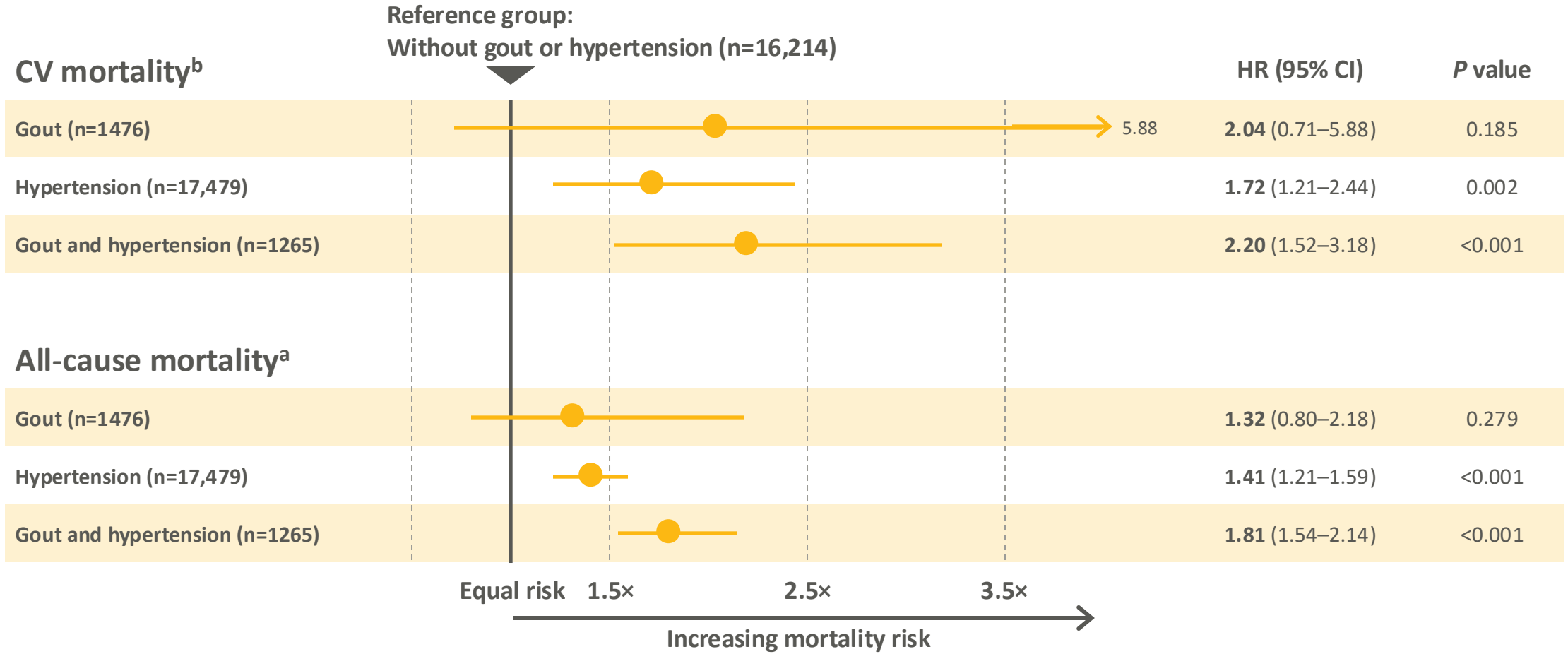
Gout is an Additive Risk Factor for All-Cause and CV Mortality in People with Hypertension[a]



[a]A retrospective cohort study was conducted, enrolling individuals with hyperuricemia (sUA >7 mg/dL for males and >6 mg/dL forfemales; n=5841) and gout (self-reported, physician-diagnosed; n=1476) from the US NHANES between 2007–2018. Participants were categorized as having hypertension if ≥1 of: having been told by a HCP they had hypertension; were taking antihypertensive medication; their average systolic blood pressure was ≥130 mmHg and diastolic blood pressure ≥80 mmHg in three times. Participants were followed until death or 21 December 2019 (median follow-up 7.25 years; N=30,819). [b]Adjusted for age, gender, and ethnicity.
CI, confidence interval; CV, cardiovascular; HCP, healthcare provider; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey; sUA, serum uric acid.
Che J, et al. *J Hypertens* 2024;42:1390–1398.

Hyperuricemia Associated with Gout May Contribute to Hypertension Through Multiple Mechanisms[1,2]

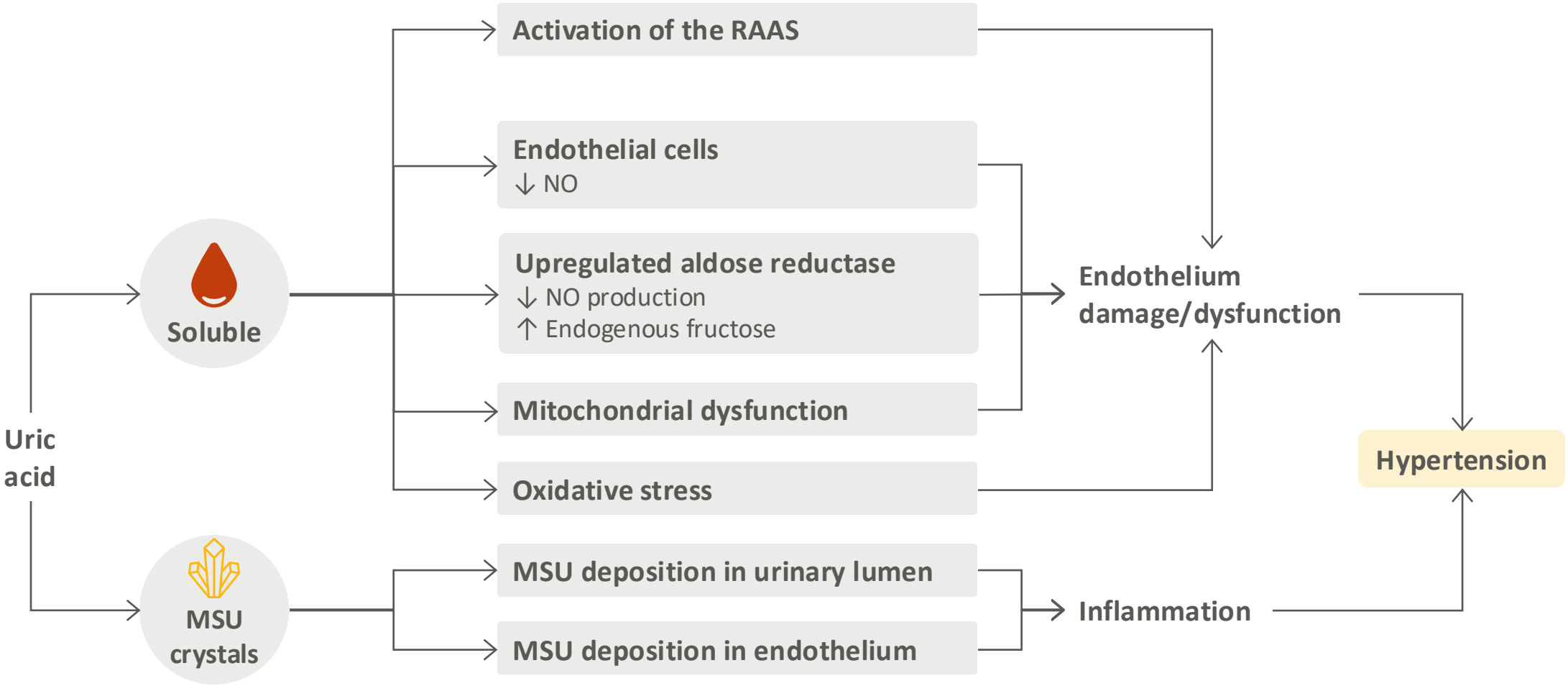
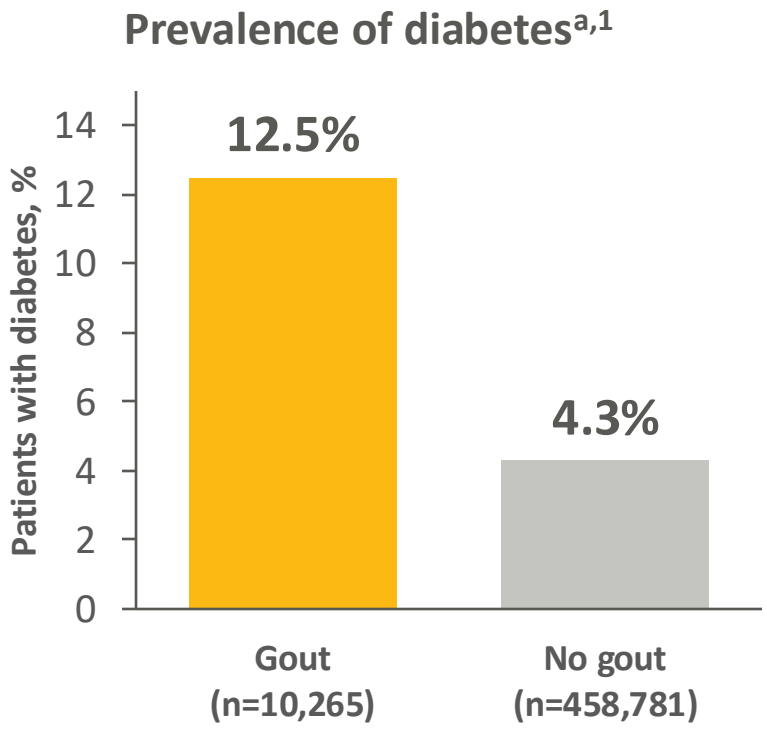


Figure adapted from Lanaspa MA, et al. *Hypertens Res* 2020;43:832–834.
MSU, monosodium urate; NO, nitric oxide; RAAS, renin-angiotensin-aldosterone system.
1. Sanchez-Lozada LG, et al. *Am J Hypertens* 2020;33:583–594; 2. Lanaspa MA, et al. *Hypertens Res* 2020;43:832–834.

Type 2 Diabetes

NP-38435

Gout is an Independent Risk Factor for Diabetes[1,2]



1.2× ODDS

Gout increases the odds of type 2 diabetes by 21%, independent of sUA level[b,1]
OR 1.21 (95% CI 1.13–1.30)

Women with gout have a higher risk for developing type 2 diabetes than men[c,2]

↑ 97% RISK
aHR 1.97 (95% CI 1.81–2.14)[d]

↑ 62% RISK
aHR 1.62 (95% CI 1.54–1.70)[d]

[a]A case-control study (N=458,781) was conducted, using UK Biobank participants aged 40–69 years without gout, recruited between 2006–2010, to examine the association between comorbidities and serum urate. A separate analysis was conducted to examine the association between comorbidities and gout (N=10,265).[1] [b]Adjusted for age, sex, BMI, hypertension, diabetes mellitus, ischemic heart disease, heart failure, CKD, smoking, alcohol, Townsend deprivation index, and sUA.[1] [c]Data from the Longitudinal Health Insurance Database 2010 of Taiwan's NHIRD (1998–2010) were included in this retrospective study to investigate the association between gout and diabetes (n=29,765 with gout and n=59,530 without gout).[2] [d]Adjusted for comorbidities.[2]
aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; NHIRD, National Health Institute Research Database; OR, odds ratio; sUA, serum uric acid.
1. Sandoval-Plata G, et al. *Rheumatology (Oxford)* 2021;60:3243–3251; 2. Tung YC, et al. *Am J Med* 2016;129:1219.e17–1219.e25.

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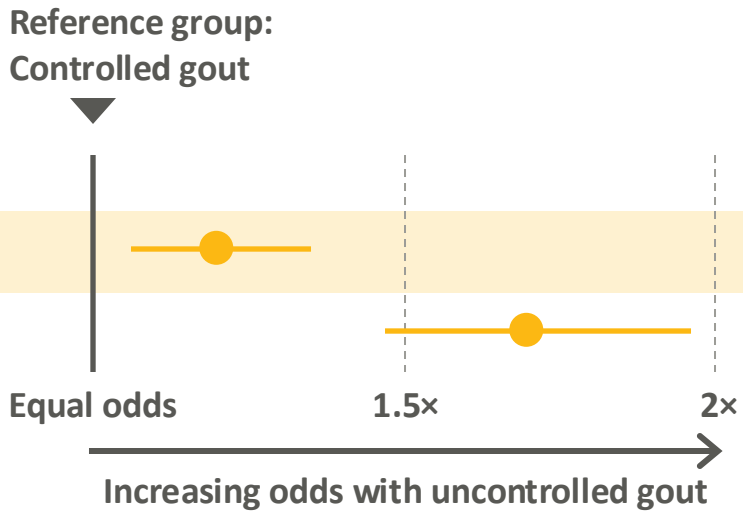
Diabetes is More Prevalent in Patients with Uncontrolled than Controlled Gout[a,1]

	Controlled gout (n=5473)	Uncontrolled gout[b] (n=1358)	OR (95% CI)	*P* value
Diabetes, n (%)[1]	2730 (49.9%)	738 (54.3%)	**1.20** (1.06–1.35)	0.003
With renal manifestations	842 (15.4%)	320 (23.6%)	**1.70** (1.47–1.96)	<0.001



Hyperuricemia increases the risk of type 2 diabetes[c,2]

Every 1 mg/mL increase in sUA = **6% increased risk of type 2 diabetes[2]**

RR 1.06 (95% CI 1.04–1.07)

High sUA has been associated with tubular damage and kidney inflammation in patients with type 2 diabetes[3]

[a]Data from adult patients with gout and who had at least 90 days of continuous ULT was collected from the Humana Research Database from 2007–2016. A total of 6831 patients were identified that met the inclusion criteria (5473 patients had controlled gout and 1358 patients had uncontrolled gout). [b]Uncontrolled gout was defined as sUA ≥8.0 mg/dL. [c] Seven articles, derived from 8 prospective cohort studies, were identified in this meta-analysis investigating the association between sUA and type 2 diabetes (N=32,016; n=2930 incident type 2 diabetes). Duration of follow-up in the studies ranged from 3.5–28 years (median 11 years).[2]

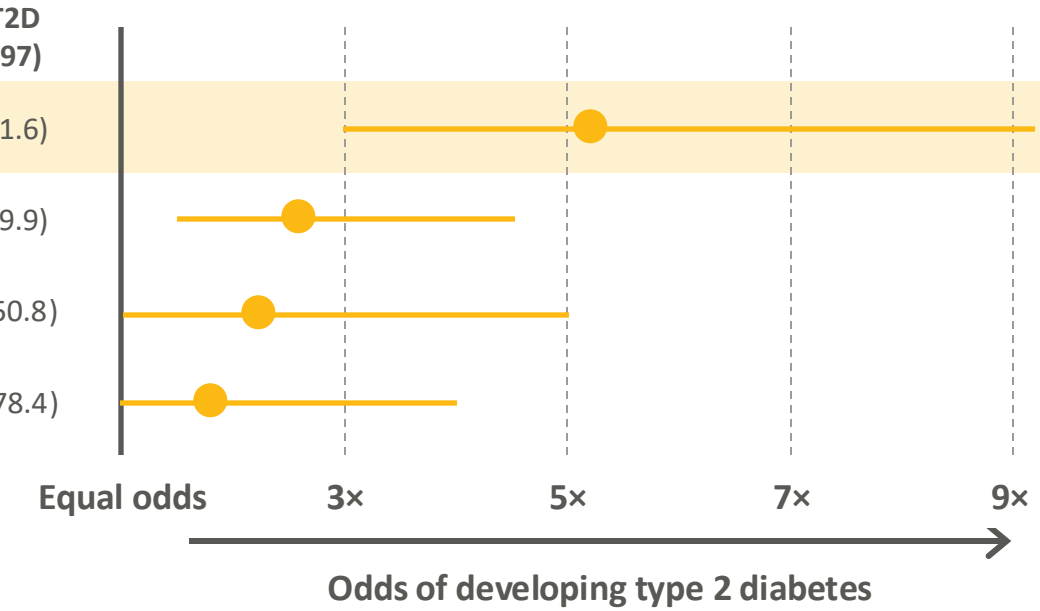
CI, confidence interval; OR, odds ratio; RR, relative risk; sUA, serum uric acid; ULT, urate-lowering therapy.

1. Francis-Sedlak M, et al. *Rheumatol Ther* 2021;8:183–197; 2. Lv Q, et al. *PLoS One* 2013;8:e5684; 3. Guarda NS, et al. *Dis Biomarkers* 2019;6025804.

Development of Diabetes May be Linked to Gout Severity[1]

Flares, tophi, and elevated sUA increase the odds of developing type 2 diabetes in patients with gout (N=444)[a,1]

Parameter, n (%)	T2D (n=108)	No T2D (n=297)	OR (95% CI)	*P* value
≥4 arthritis attacks/year	73 (67.6)	94 (31.6)	**5.23** (2.98–9.19)	0.0001
Presence of tophi	64 (59.38)	89 (29.9)	**2.61** (1.50–4.54)	0.001
sUA ≥8.07 mg/dL	77 (71.3)	151 (50.8)	**2.26** (1.02–5.01)	0.044
Hypertension	94 (87)	233 (78.4)	**1.82** (0.83–4.02)	0.137



Women with diabetes have a 48% increased risk of gout flares[2]

[a]A prospective, single-center study was conducted in Russia to assess the impact of various risk factors for T2D in patients with gout (N=444). The inclusion criteria were age ≥18 years and diagnosed gout, without T2D. Duration of follow-up was 5.66 (2.69–7.64 years).[1]

CI, confidence interval; OR, odds ratio; sUA, serum uric acid; T2D, type 2 diabetes.

1. Zheliabina OV, et al. *Dokl Biochem Biophys* 2023;511:195–202; 2. Primatesta P, et al. *BMC Musculoskelet Disord* 2011;12:103.

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Hyperuricemia Associated with Gout Contributes to the Risk of Diabetes via Multiple Pathways[1–3]

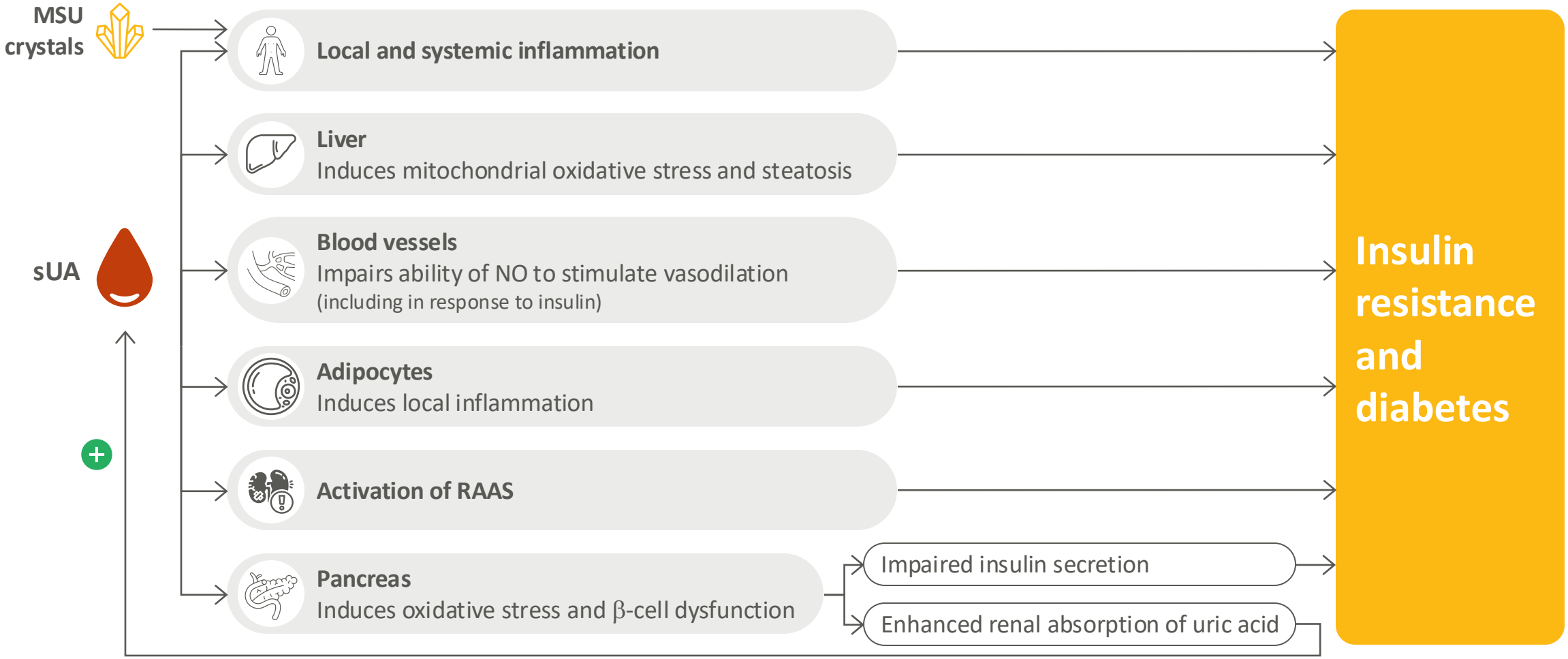

Figure adapted from Du L, et al. *Signal Transduct Target Ther* 2024;9:212 and Johnson RJ, et al. *Diabetes* 2013;62:3307–3315.
NO, nitric oxide; RAAS, renin-angiotensin-aldosterone system; sUA, serum uric acid.
1. Xiong Q, et al. *Int J Endocrinol* 2019;2019:9691345; 2. Du L, et al. *Signal Transduct Target Ther* 2024;9:212; 3. Johnson RJ, et al. *Diabetes* 2013;62:3307–3315.

Renal Impairment

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The Relationship Between Gout and CKD is Complex[1]

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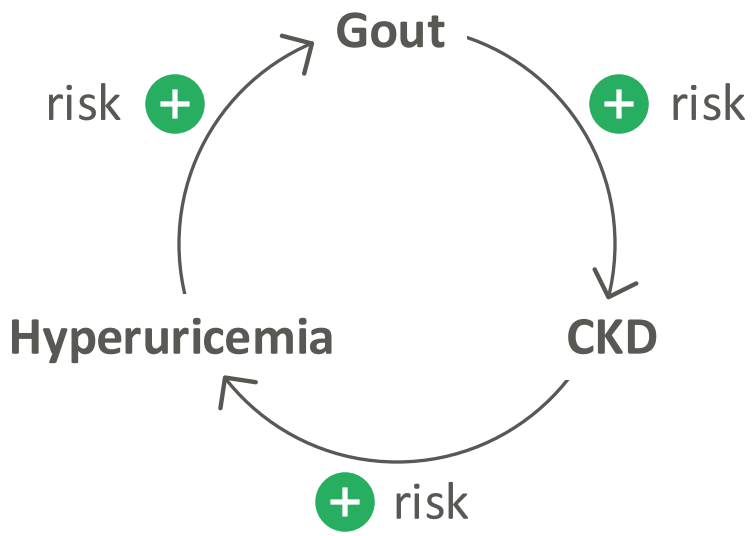
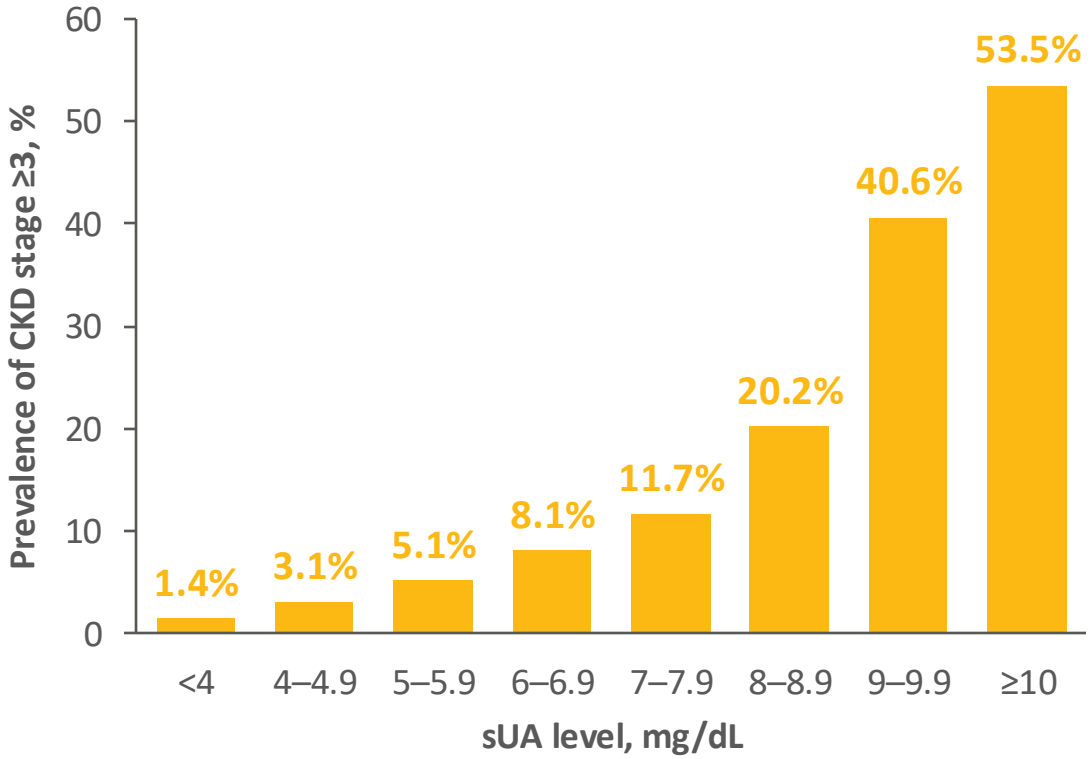
Gout is associated with the development of CKD,[2,3] and people with CKD are also at risk for hyperuricemia, a risk factor for gout[1]



Hyperuricemia is associated with an increased prevalence of stage ≥3 CKD[a,3]



[a]Data from 5707 participants (≥20 years) from the US NHANES 2007–2008 were analyzed. Prevalence and population estimates of comorbidities in patients with gout and various levels of hyperuricemia were calculated and compared with those without these conditions.

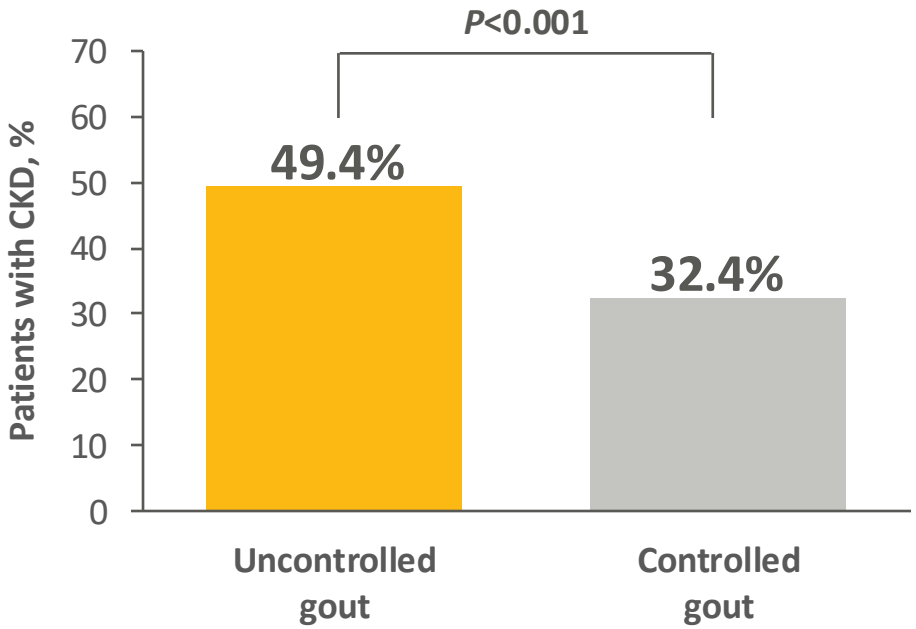
CKD, chronic kidney disease; NHANES, National Health and Nutrition Examination Survey; sUA, serum uric acid.

1. Jaffe DH, et al. *BMC Rheumatol* 2019;3:11; 2. Sandoval-Plata G, et al. *Rheumatology (Oxford)* 2021;60:3243–3251; 3. Zhu Y, et al. *Am J Med* 2012;125:679–687.

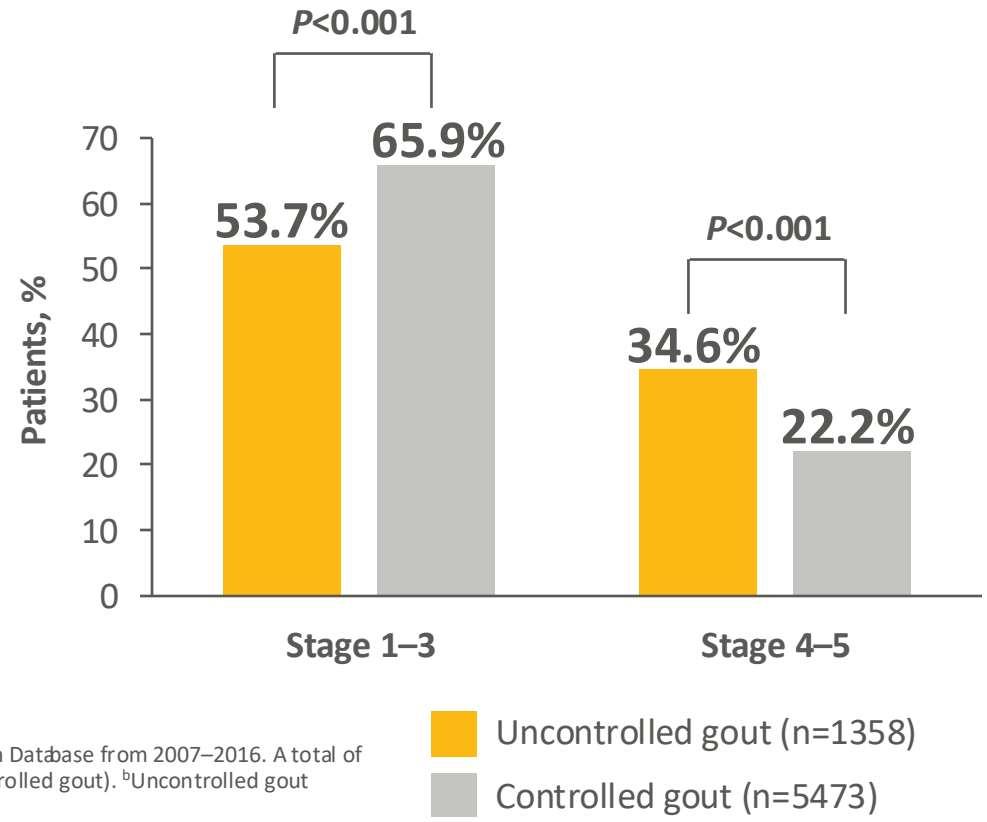
Renal Impairment is More Prevalent in Patients with Uncontrolled Gout than those with Controlled Gout[a]

2× ODDS

Patients with uncontrolled gout are twice as likely to develop CKD than those with controlled gout[b]
OR 2.04 (95% CI 1.81–2.30)



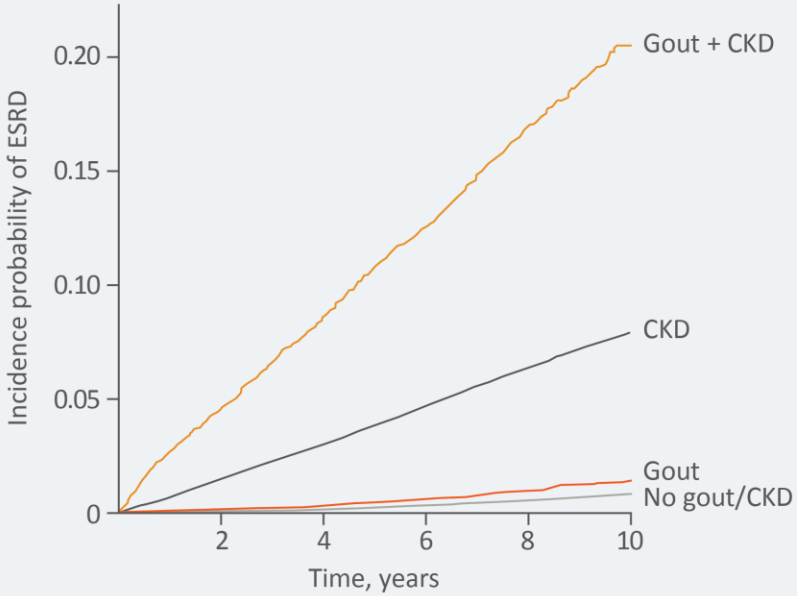
CKD is often more advanced in patients with uncontrolled gout than patients with controlled gout[a]



[a]Data from adult patients with gout and who had at least 90 days of continuous ULT was collected from the Humana Research Database from 2007–2016. A total of 6831 patients were identified that met the inclusion criteria (5473 patients had controlled gout and 1358 patients had uncontrolled gout). [b]Uncontrolled gout was defined as sUA ≥8.0 mg/dL.
CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio; sUA,serum uric acid; ULT, urate-lowering therapy.
Francis-Sedlak M, et al. *Rheumatol Ther* 2021;8:183–197.

Gout Increases the Risk of ESRD in Patients with T2D and CKD[a]

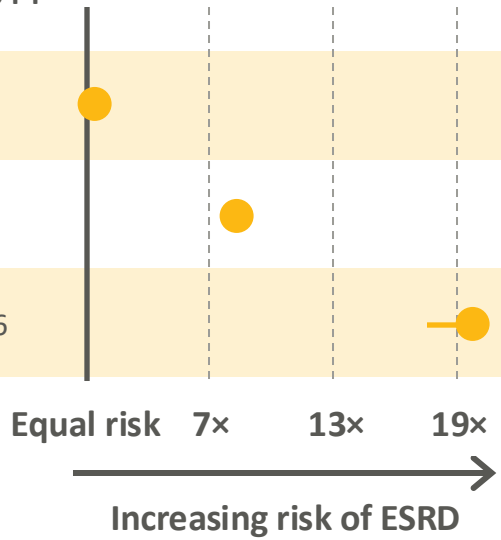
The incidence of ESRD is significantly higher in T2D patients with CKD who also have gout (*P*<0.001)



Gout increases the risk of ESRD in patients with T2D, particularly in patients with concurrent CKD

Reference group:
No CKD and no gout (n=759,374)

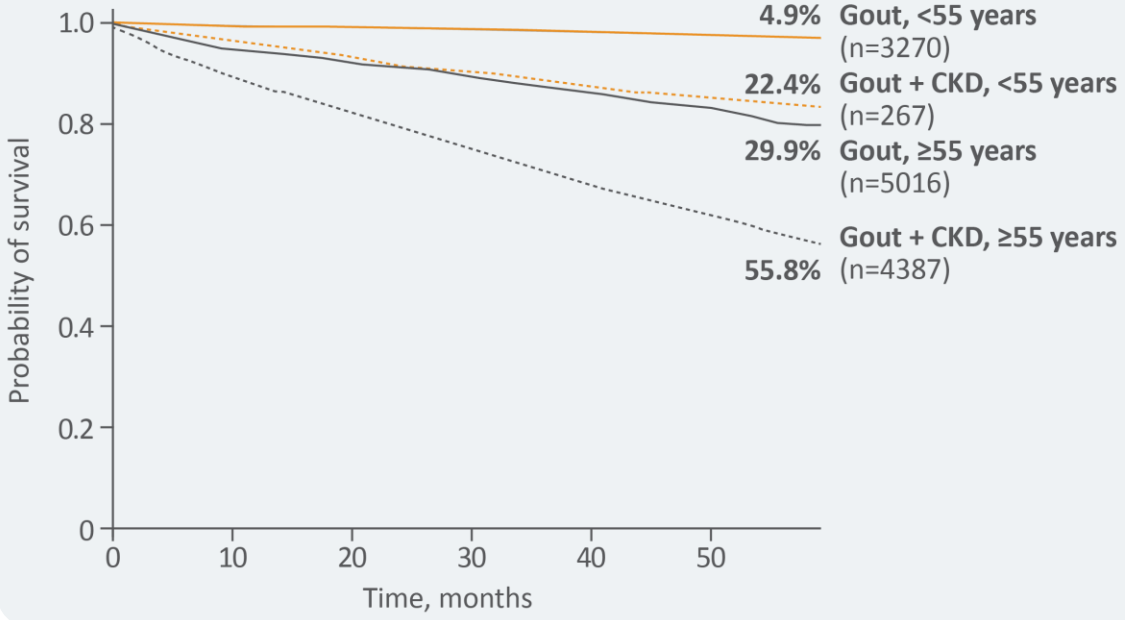
	n	ESRD events, n	IR/1000 PY	aHR[b] (95% CI)
Gout	21,685	257	1.34	**1.49** (1.32–1.69)
CKD	81,225	5395	8.20	**8.45** (8.11–8.80)
Gout + CKD	5498	932	23.06	**19.90** (17.58–20.32)



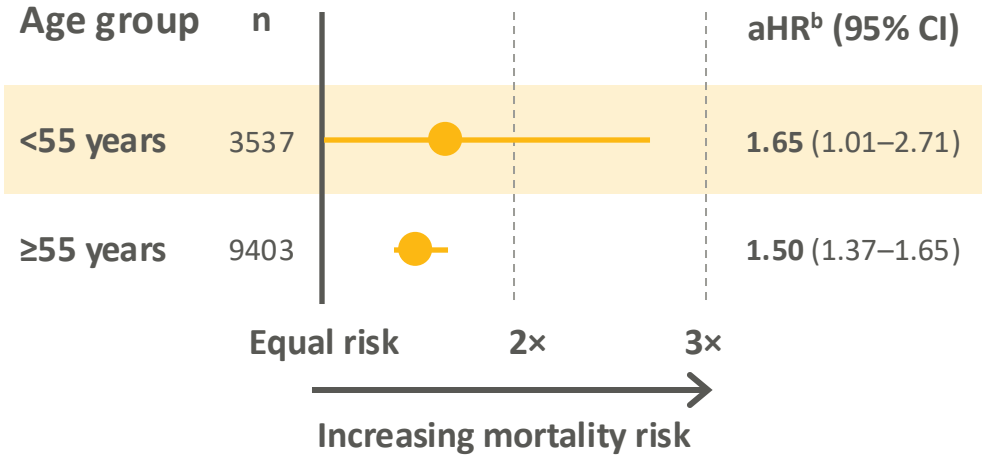
[a]Patients with T2D from the Korean National Health Insurance Service who had health checkups in 2009, were included in this retrospective cohort study (N=847,884). This study aimed to investigate the combined effect of CKD and gout on the development of ESRD among patients with T2D. Patients were followed up until the date of ESRD diagnosis or December 2018, whichever occurred first. [b]Adjusted for age, sex, BMI, alcohol consumption status, smoking status, regular exercise, low 25% income, presence of hypertension and dyslipidemia, fasting blood glucose, duration of diabetes, prescription number of oral hypoglycemic agents, and insulin users.
aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; ESRD, end-stage renal disease; IR, incidence rate; PY, person years; T2D, type 2 diabetes.
Jung I, et al. *Endocrinol Metab (Seoul)* 2024;39:748–757.

Gout is Associated with Increased Mortality and Decreased Survival Time in Patients with CKD[a]

5-year survival is lowest among patients aged ≥55 years with gout and CKD



Gout increases the risk of mortality up to 65% in patients with CKD



[a]In this retrospective cohort study, data from 12,940 adult patients (n=8286 with CKD; n=4654 without CKD) with newly diagnosed gout were obtained from the Clalit Health Services database (January 2006–December 2009) and followed for 5 years. The study aimed to determine if healthcare utilization and survival differed between patients with incident gout in the presence or absence of CKD. Patients were stratified by CKD status and age group (<55 years and ≥55 years). [b]Adjusted for age, sex, SES, CCI, smoking status, BMI, sUA control (< or ≥6 mg/dL), and gout medication.

aHR, adjusted hazard ratio; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; CKD, chronic kidney disease; SES, socioeconomic status; sUA, serum uric acid.

Jaffe DH, et al. *BMC Rheumatol* 2019;3:11.

Hyperuricemia Associated with Gout May Contribute to CKD Through Multiple Mechanisms[1–3]

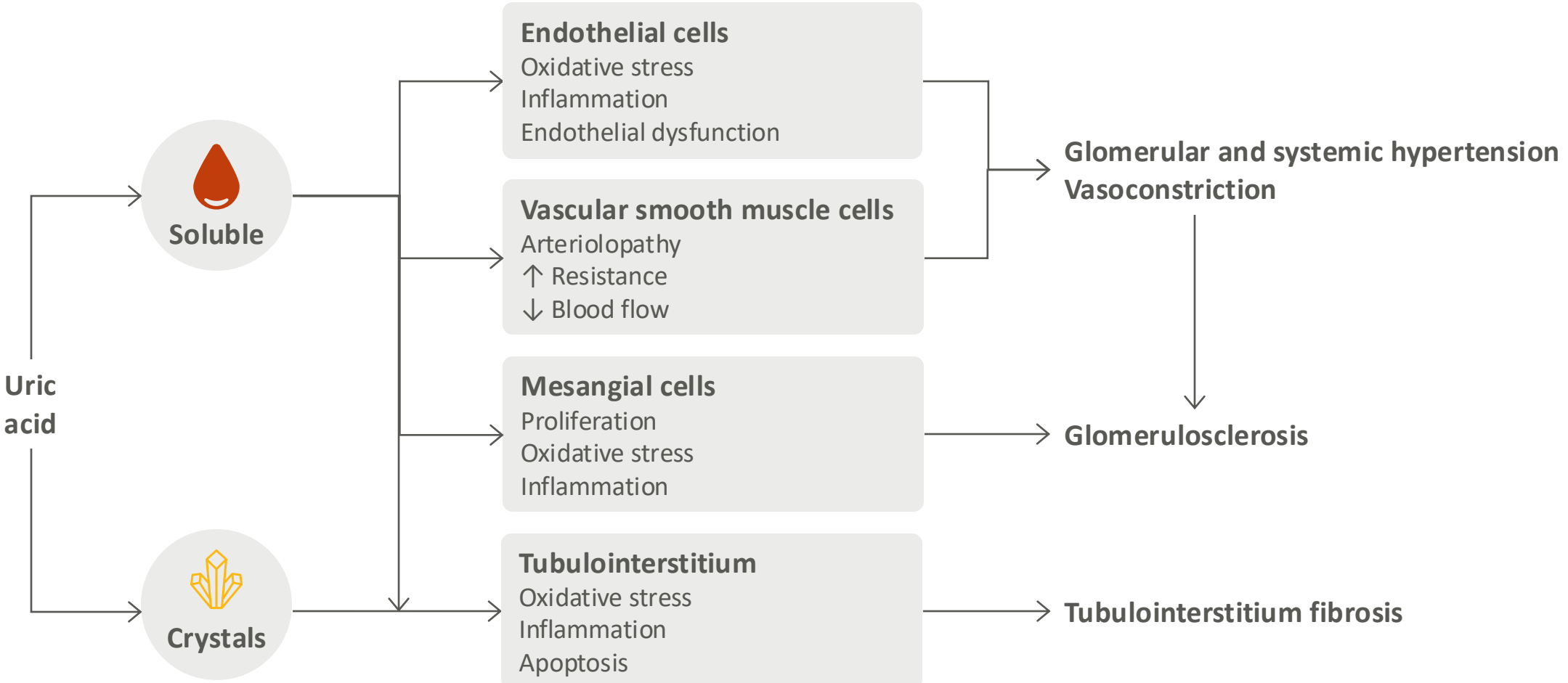


Figure adapted from Johnson RJ, et al. *Am J Kidney Dis* 2018;71:851–865.
CKD, chronic kidney disease.
1. Johnson RJ, et al. *Nephrol Dial Transplant* 2013;28:2221–2228; 2. Johnson RJ, et al. *Am J Kidney Dis* 2018;71:851–865; 3. Johnson RJ, et al. *Kidney Int Rep* 2023;8:229–239.

CV Disease

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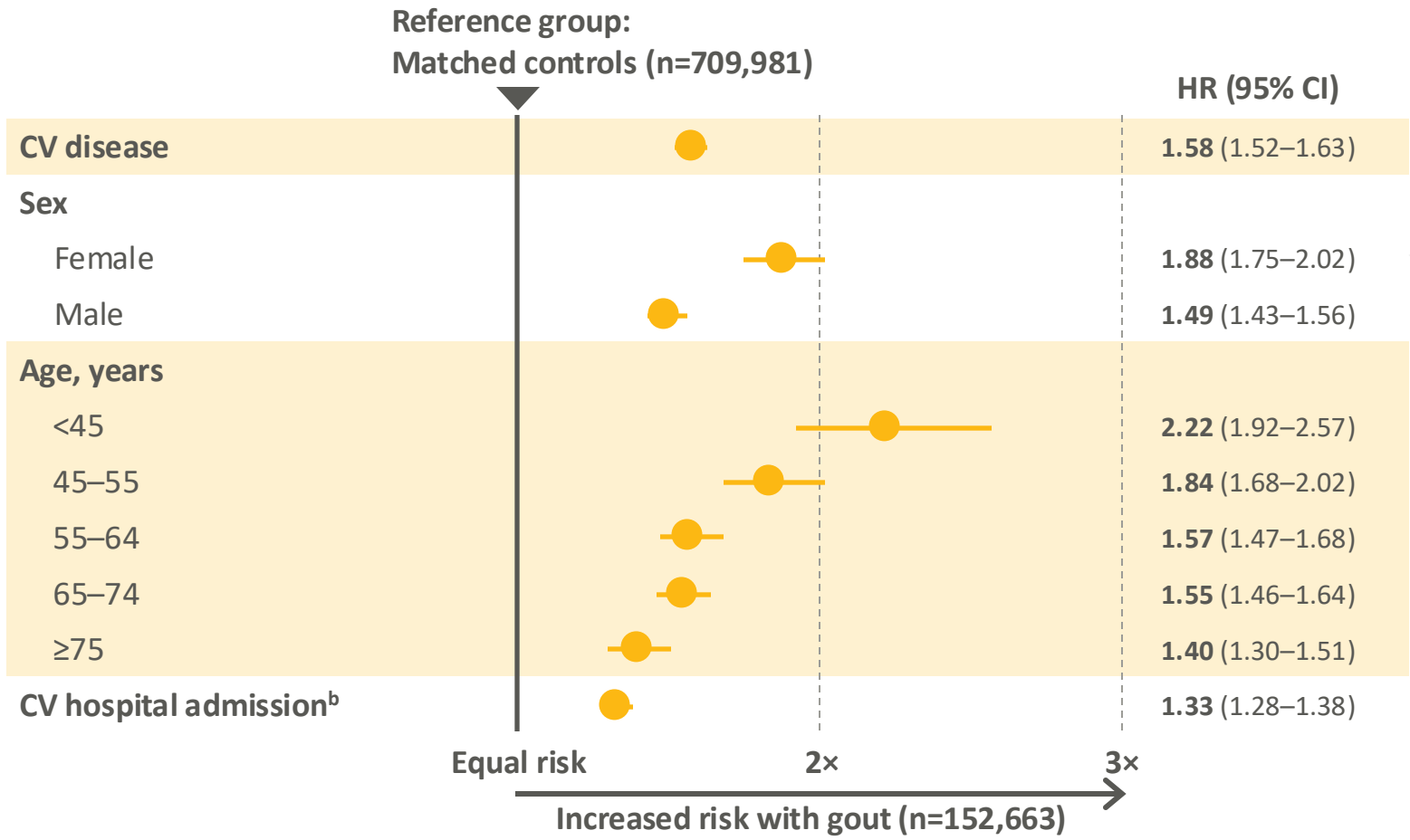
CV, cardiovascular.

Gout is Associated with CV Disease[1–4]

Gout increases the risk of CV disease[a,1]



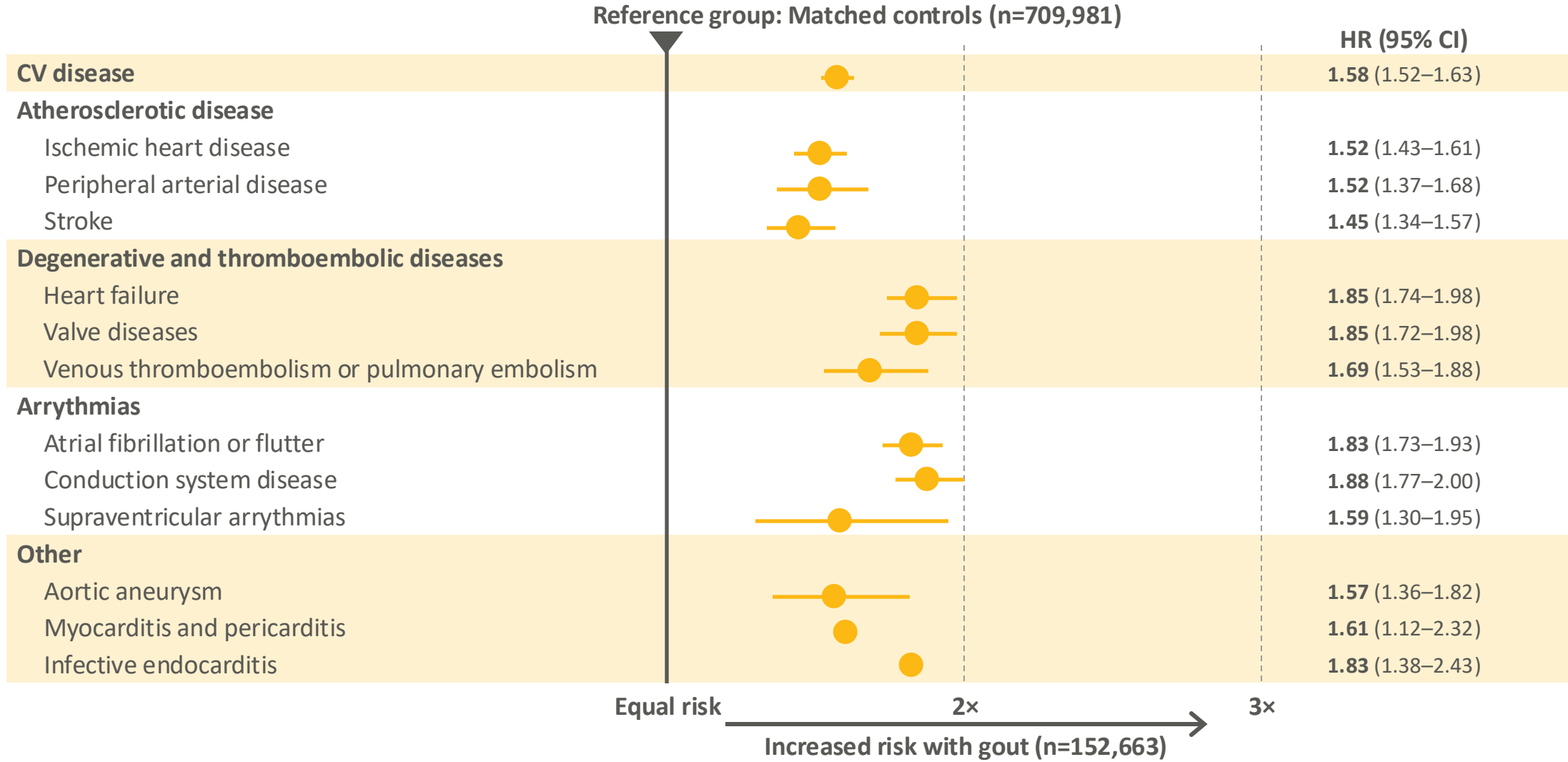
The risk of CV disease is higher in women with gout[1]

Gout appears to amplify the risk of CV disease in younger individuals[1]

[a]In this case-control study, 152,663 patients with gout and 709,981 matched controls were identified from the UK Clinical Practice Research Datalink between January 2000 and December 2017. The study assessed the association of gout with the development of CV disease. Patients were ≤80 years at diagnosis of gout, and free of CV disease until 12 months after incident gout. Median follow-up was 6.5 years (IQR 3.1–10.5).[1] [b]Sensitivity analysis.[1]
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IQR, interquartile range.

1. Ferguson LD, et al. *Lancet Rheumatol* 2024;6:e156–e167; 2. Krishnan E, et al. *Arch Intern Med* 2008;168:1104–1110; 3. Sandoval-Plata G, et al. *Rheumatology (Oxford)* 2021;60:3243–3251; 4. Han Y, et al. *J Transl Med* 2023;21:463

Gout Increases the Risk of a Range of CV Diseases



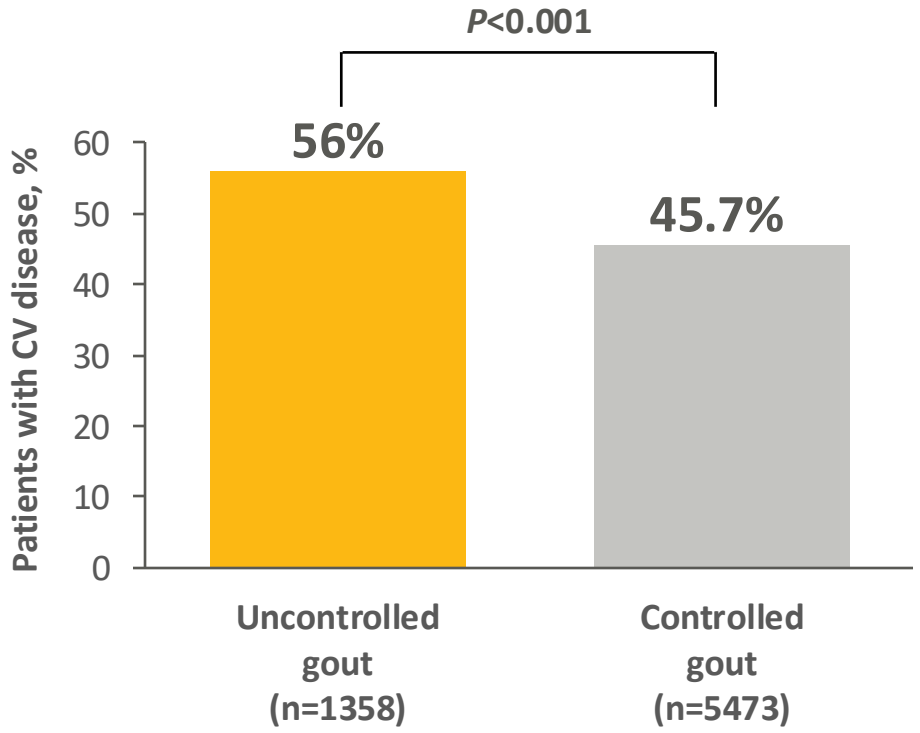
[a]In this case-control study, 152,663 patients with gout and 709,981 matched controls were identified from the UK Clinical Practice Research Datalink between January 2000 and December 2017. The study assessed the association of gout with the development of CV disease. Patients were ≤80 years at diagnosis of gout, and free of CV disease until 12 months after incident gout. Median follow-up was 6.5 years (IQR 3.1–10.5).

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IQR, interquartile range.

Ferguson LD, et al. *Lancet Rheumatol* 2024;6:e156–e167.

CV Disease is More Prevalent in Patients with Uncontrolled Gout[1,2]

CV disease is more prevalent among patients with uncontrolled gout than controlled gout[2]



1.5× ODDS

Patients with uncontrolled gout are 52% more likely to develop CV disease than those with controlled gout[b,2]
OR 1.52 (95% CI 1.35–1.71)

[a]Data from adult patients with gout and who had at least 90 days of continuous ULT was collected from the Humana Research Database from 2007–2016. A total of 6831 patients were identified that met the inclusion criteria (5473 patients had controlled gout and 1358 patients had uncontrolled gout).[2] [b]Uncontrolled gout was defined as sUA ≥8.0 mg/dL.[2]
CI, confidence interval; CV, cardiovascular; OR, odds ratio; sUA, serum uric acid; ULT, urate-lowering therapy.
1. Zhu Y, et al. *Am J Med* 2012;125:679–687; 2. Francis-Sedlak M, et al. *Rheumatol Ther* 2021;8:183–197.

Elevated sUA Levels are Associated with an Increased Risk of CV Mortality[1–5]

Increasing sUA levels are associated with increased risk of CV and all-cause mortality[1,2]

Every 1 mg/mL increase in sUA

2× increased risk of CV mortality[a,1]

53% increased risk of all-cause mortality[a,1]

CV mortality | HR 2.08 (95% CI 1.46–2.97)[b]
All-cause mortality | HR 1.53 (95% CI 1.21–1.93)[b]

sUA levels that are associated with an increased risk of CV mortality are lower than the levels used to define clinical hyperuricemia[c,1]

[a]This study was a multicenter, retrospective, observational cohort study analyzing 22,714 patients with hypertension.The study aimed to define the level of uricemia above which the independent risk of CV disease may increase. Patients were followed for ≥20 years.[1] [b]Adjusted for sex, smoking, diabetes mellitus, hypertension, total cholesterol, alcohol use, creatinine and CKD, hematocrit, and diuretic use.[1] [c]sUA of 5.6 mg/dL associated with increased risk of CV disease mortality.[1]
CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; HR, hazard ratio; sUA, serum uric acid.
1. Virdis A, et al. *Hypertension* 2020;72:302–308; 2. Zhu J, et al. *Front Med (Lausanne)* 2022;8:817150; 3. Yin Y, et al. *Front Cardiovasc Med* 2024;11:1306026; 4. Han Y, et al. *J Transl Med* 2023;21:463;
5. Zuo T, et al. *BMC Cardiovasc Disord* 2016;16:207.

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Hyperuricemia and Gout May Contribute to Development of CV Disease via Multiple Pathways[1,2]

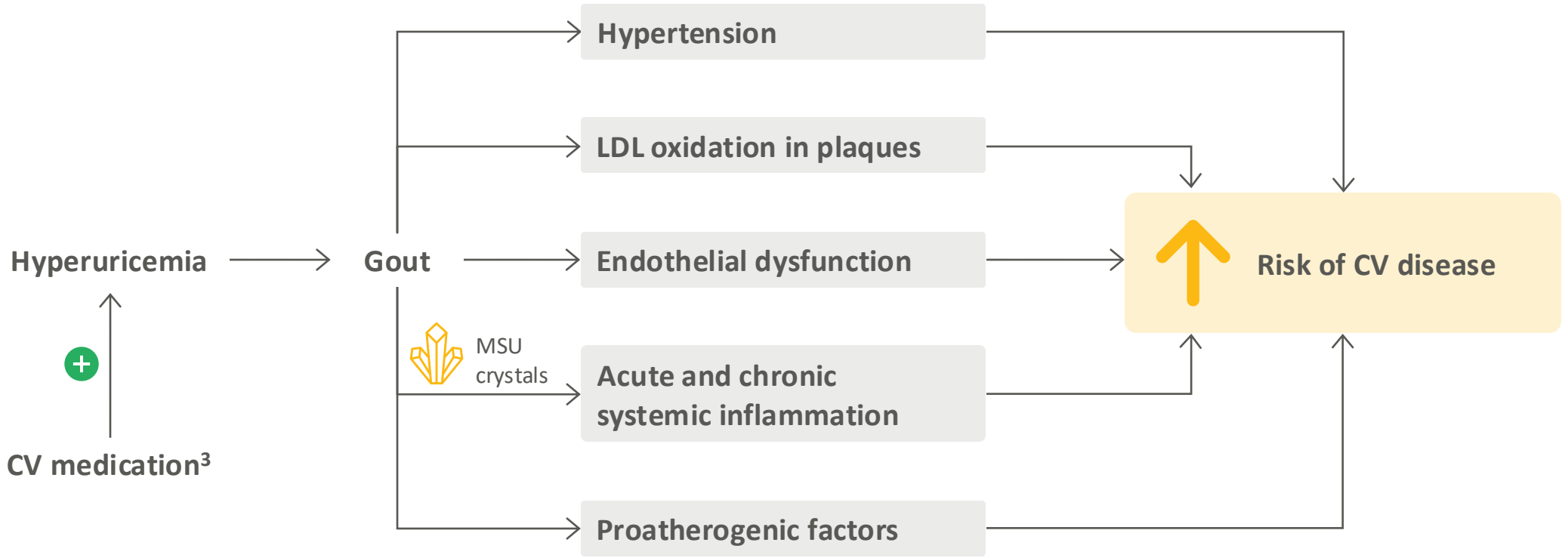

Figure adapted from Singh JA. *Ann Rheumatol Dis* 2015;74:631–634.
CV, cardiovascular; LDL, low density lipoprotein; MSU, monosodium urate.
1. Kimura Y, et al. *Int J Mol Sci* 2021;22:12394; 2. Singh JA. *Ann Rheumatol Dis* 2015;74:631–634; 3. Stamp LK, Chapman PT. *Rheumatology (Oxford)* 2013;52:34–44.

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Summary

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Summary

Elevated sUA and gout are associated with a range of metabolic disorders[1]

Hyperuricemia and gout are implicated in metabolic disorders through numerous mechanisms and pathways[2–7]

Patients with uncontrolled gout have a higher prevalence of metabolic comorbidities compared with patients with controlled gout[8]

Diet alters the gut microbiome, and interacts with genetics to contribute to hyperuricemia, gout, and comorbidities[9–12]

sUA, serum uric acid.

1. Kanbay M, et al. *Eur J Intern Med* 2016;29:3–8; 2. Sanchez-Lozada LG, et al. *Am J Hypertens* 2020;33:583–594; 3. Lanaspa MA, et al. *Hypertens Res* 2020;43:832–834; 4. Du L, et al. *Signal Transduct Target Ther* 2024;9:212; 5. Johnson RJ, et al. *Diabetes* 2013;62:3307–3315; 6. Johnson RJ, et al. *Kidney Int Rep* 2023;8:229–239; 7. Singh JA. *Ann Rheumatol Dis* 2015;74:631–634; 8. Francis-Sedlak M, et al. *Rheumatol Ther* 2021;8:183–197; 9. Guasch-Ferré M, et al. *J Gerontol A Biol Sci Med Sci* 2013;68:1263–1270; 10. Zhang Y, et al. *BMC Med* 2022;20:138. Supplementary Material; 11. Bolte LA, et al. *Gut* 2021;70:1287–1298; 12. Tong S, et al. *Front Cell Infect Microbiol* 2022;12:1051682.

Appendix

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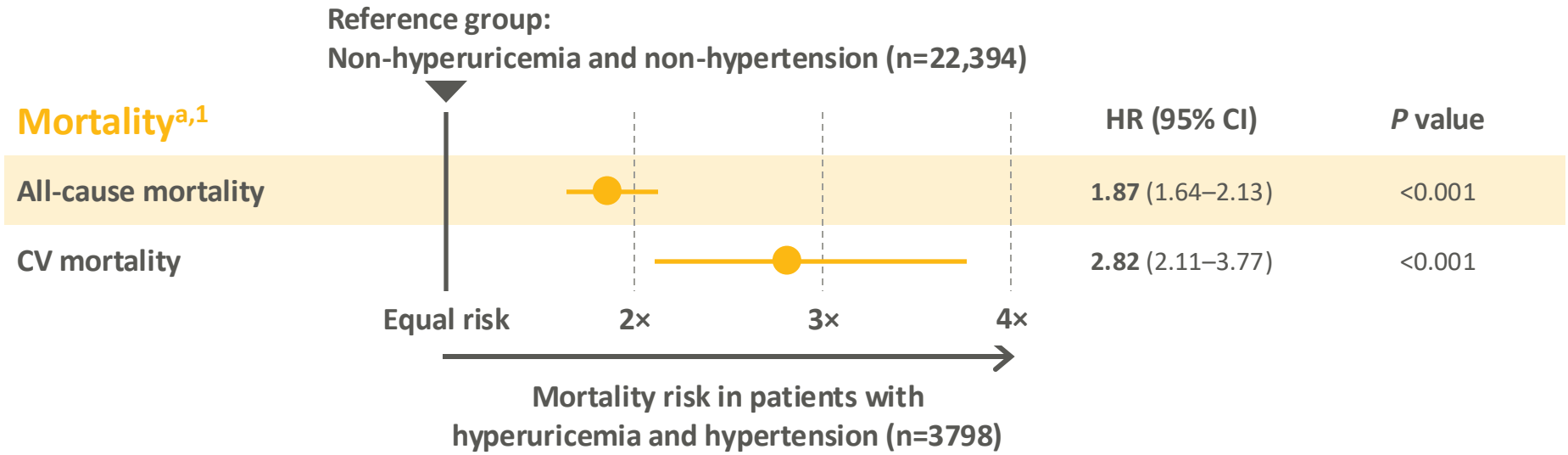
Hyperuricemia is Associated with an Increased Risk of Fatal CV Events in Patients with Hypertension[1–3]



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[a]This study included participants aged >20 years from the NHANES 2001–2018 (N=38,644; n=6956 with hyperuricemia; n=31,688 without hyperuricemia). The study was performed to prospectively investigate the association of serum urate levels with all-cause mortality in a nationally representative sample of American adult patients with hypertension. Median follow-up was 78 months for all patients with hyperuricemia.[1]

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey.

1. Yin Y, et al. *Front Cardiovasc Med* 2024;11:1306026; 2. Verdecchia P, et al. *Hypertension* 2000;36:1072–1078; 3. Che J, et al. *J Hypertens* 2024;42:1390–1398.

Hyperuricemia Increases the Risk of Hypertension in Patients with Gout[1]

Patients with gout and hyperuricemia have hypertension[2]

Hyperuricemia is strongly associated with developing hypertension[1,3–6]

Hyperuricemia increases the risk of hypertension by 73%[a,b,1]
RR 1.73 (95% CI 1.46–2.06)

Every 1 mg/mL increase in sUA = **15% increase in incident hypertension[1]**

RR 1.15 (95% CI 1.06–1.26)

[a]This systematic review included cohort studies and nested case-control studies with ≥100 aged 18–89 years participants (N=97,824 from 25 studies). The study was conducted to assess the association between uric acid and hypertension to clarify whether uric acid is an independent risk factor for hypertension. Follow-up duration varied from 2–21.5 years.[1] [b]Categorical data; continuous data: RR 1.22 (95% CI, 1.03–1.45).[1]
CI, confidence interval; RR, relative risk; sUA, serum uric acid.

1. Wang J, et al. *PLoS One* 2014;9:e114259; 2. Zhu Y, et al. *Am J Med* 2012;125:679–687; 3. Yin Y, et al. *Front Cardiovasc Med* 2024;11:1306026; 4. Che J, et al. *J Hypertens* 2024;42:1390–1398;
5. Tatsumi Y, et al. *Hypertens Res* 2020;43:442–449; 6. Kuwabara M, et al. *Hypertens Res* 2014;37:785–789.

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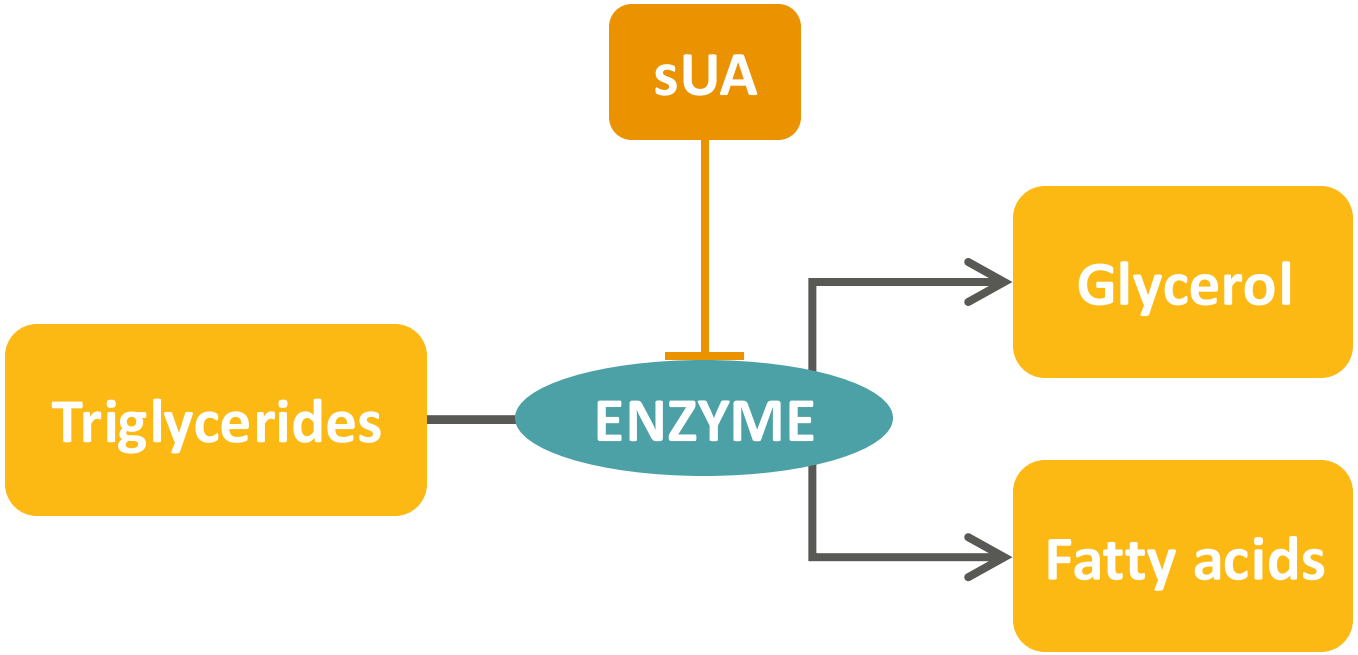
sUA May Contribute to Hypertriglyceridemia

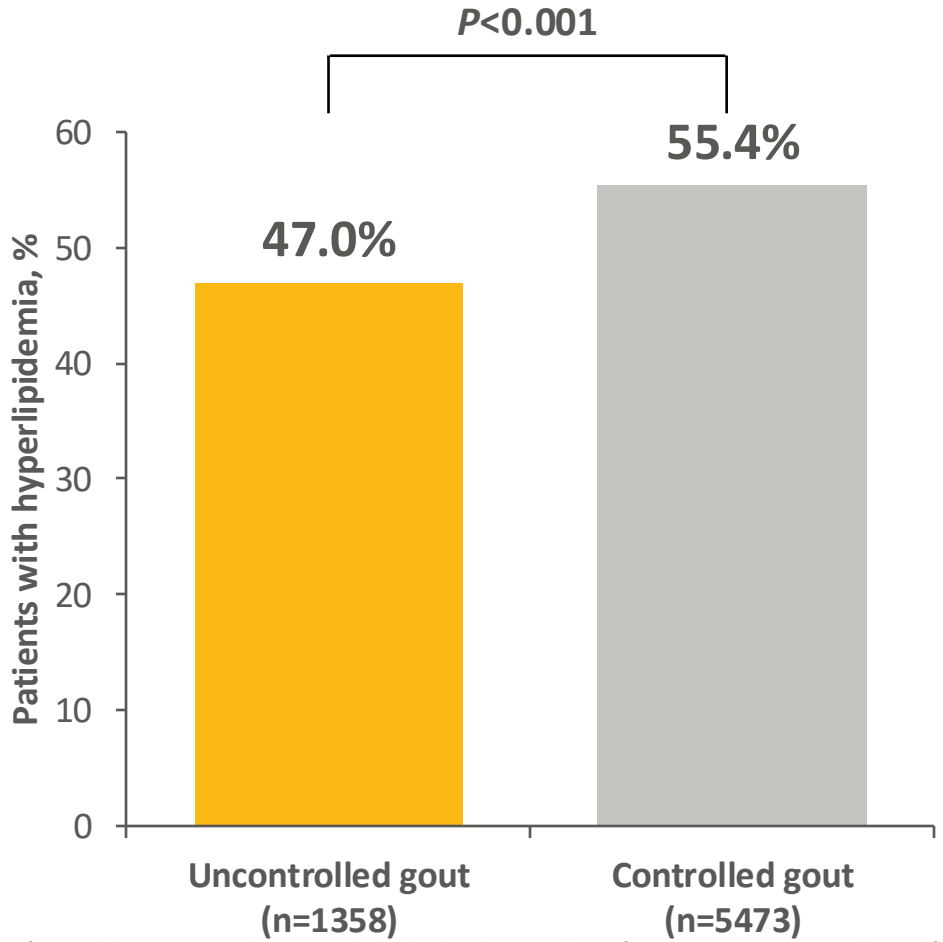
High sUA may inhibit the enzyme that catalyzes the decomposition of triglycerides, leading to increased risk of hypertriglyceridemia[1,2]



sUA, serum uric acid.

1. Tan MY, et al. *Front Endocrinol (Lausanne)* 2023;14:1215521; 2. Zheng R, et al. *Ann Clin Lab Sci* 2017;47:586–591.

Hyperlipidemia is Less Prevalent in Patients with Uncontrolled Gout[a,1]



Patients with hyperlipidemia are 18% less likely to have uncontrolled gout than patients without hyperlipidemia[b,2]

OR 0.82 (95% CI 0.68–0.98), *P*=0.031

- This could be due to the lipid-lowering effects of antihypertensive medications,[3] as their use in patients with uncontrolled gout was associated with lower odds of poorly-controlled gout[2]

[a]Data from adult patients with gout and who had at least 90 days of continuous ULT was collected from the Humana Research Database from 2007–2016 (N=6831; n=5473 with controlled gout; n=1358 with uncontrolled gout).[1]

[b]Retrospective cohort study using data extracted from electronic health records from 8 public primary care clinics in Singapore (N=7970). Eligible patients had a diagnosis of gout and made ≥2 visits to a public primary care clinic between 1 January 2018 and 31 December 2019. This study aimed to determine the demographic and clinical risk factors associated with poor gout control among Asian adults who are managed in primary healthcare clinics.[2]

CI, confidence interval; OR, odds ratio; ULT, urate-lowering therapy.

1. Francis-Sedlak M, et al. *Rheumatol Ther* 2021;8:183–197; 2. Oka P, et al. *Front Med (Lausanne)* 2023;10:1253839; 3. Stamp LK, Chapman PT. *Rheumatology (Oxford)* 2013;52:34–44.

Treatment of Metabolic Comorbidities Alters sUA Levels in Patients with Gout

Increase sUA

- Beta blockers[1]
- Diuretics[1]

Decrease sUA

- ACE inhibitors[1]
- Calcium channel blockers[1]
- SGLT2 inhibitors[2,3]

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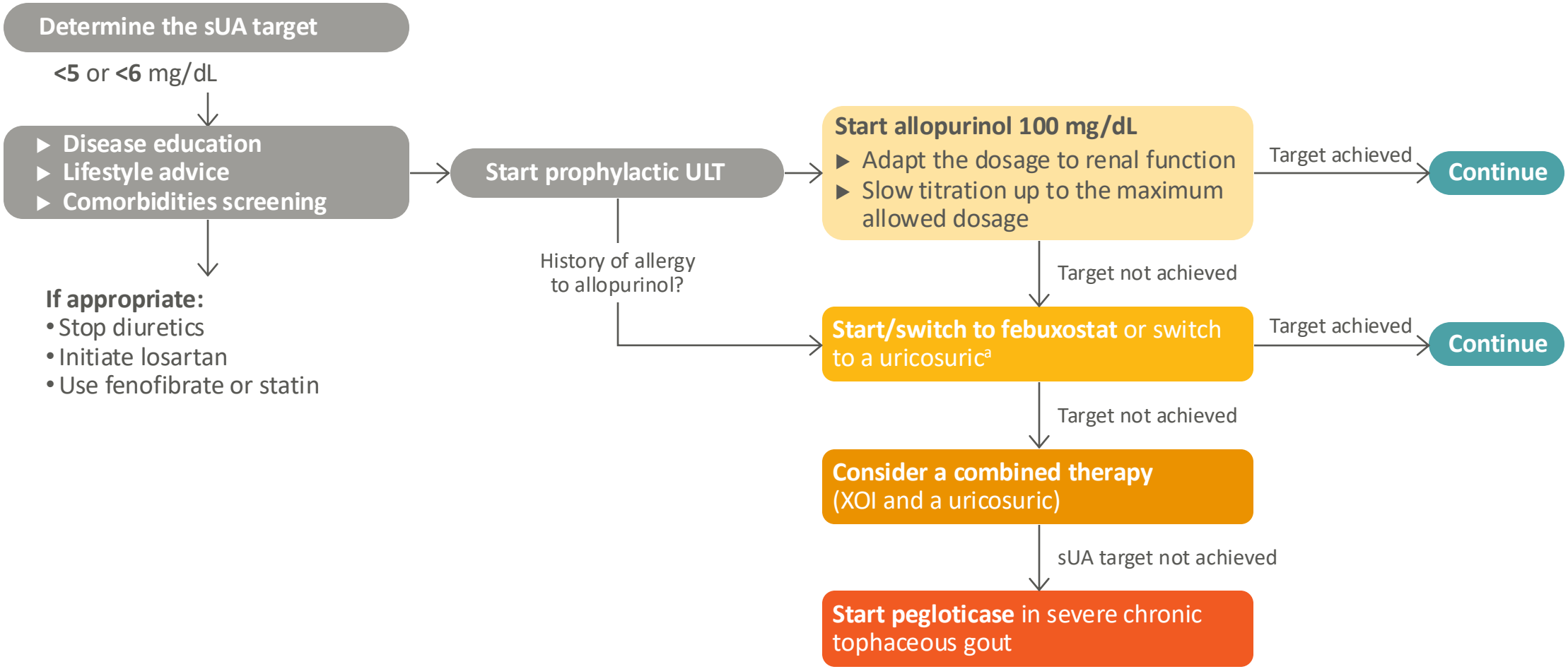
ACE, angiotensin converting enzyme; SGLT2, sodium–glucose co-transporter-2; sUA, serum uric acid.

1. Stamp LK, Chapman PT. *Rheumatology (Oxford)* 2013;52:34–44; 2. Bailey C, et al. *Ther Adv Endocrinol* 2024;15:20420188241269178; 3. Wei J, et al. *JAMA Netw Open* 2023;6:e2330885.

EULAR 2016 Recommendation for the Management of Hyperuricemia in Patients with Gout



[a]At this stage, combined allopurinol and a uricosuric is also recommended.
EULAR, European Alliance of Associations for Rheumatology; sUA, serum uric acid; ULT, urate-lowering therapy; XOI, xanthine oxidase inhibitor.
Richette P, et al. *Ann Rheum Dis* 2017;76:29–42.

ACR 2020 Guidelines for Management of Gout

ULT initiation →	Strongly recommended	Conditionally recommended
Indication for pharmacologic ULT	≥1 subcutaneous tophi **OR** Evidence of radiographic damage **OR** Frequent gout flares (≥2 annually)	Previously experienced >1 flare but have infrequent flares (<2/year) **OR** Experienced first flare **and** CKD stage ≥3, **OR** SU >9 mg/dl, **OR** urolithiasis
Recommendations for choice of initial ULT	• Allopurinol is the preferred first-line treatment for all patients (including those with CKD stage ≥3) • An XOI inhibitor is recommended over probenecid for those with CKD stage ≥3 • Initiate concomitant anti-inflammatory prophylaxis therapy[a] for 3–6 months	
When to consider switching ULT treatment	Switch to pegloticase when XOI treatment, uricosurics, and other ULT have failed to achieve the sUA target **and** there are frequent gout flares (≥2 flares/year) **OR** non-resolving subcutaneous tophi	Switch to 2nd XOI preferred to adding a uricosuric agent in those with persistently high sUA concentrations[b] despite maximum-tolerated/FDA-indicated XOI dose **and** who have continued frequent gout flares (>2 flares/year), **OR** if non-resolving SC tophi

[a]For example, colchicine, NSAIDs, prednisone/prednisolone. [b]>6 mg/dL.
ACR, American College of Rheumatology; CKD, chronic kidney disease; FDA, US Food and Drug Administration; NSAID, non-steroidal anti-inflammatory drug; SC, subcutaneous; sUA, serum uric acid; ULT, urate-lowering therapy; XOI, xanthine oxidase inhibitor.
FitzGerald JD, et al. *Arthritis Care Res* 2020;72:744–760.

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Thank you

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