HHS Public Access

Author manuscript

J Am Geriatr Soc. Author manuscript; available in PMC 2024 September 01.

Published in final edited form as:

J Am Geriatr Soc. 2023 September ; 71(9): 2798–2809. doi:10.1111/jgs.18395.

The association of allopurinol with persistent physical disability and frailty in a large community based older cohort

Zhen Zhou, PhD[a,b], **Joanne Ryan, PhD**[b], **Mark R. Nelson, MBBS, PhD**[a], **Robyn L. Woods, PhD**[b], **Suzanne G. Orchard, PhD**[b], **Chao Zhu, PhD**[c], **Julia F-M Gilmartin-Thomas, PhD**[b,d,e], **Michelle A. Fravel, PharmD**[f], **Alice J. Owen, PhD**[b], **Anne M. Murray, MD MSc**[g], **Sara E. Espinoza, MD**[h], **Michael E. Ernst, PharmD**[f,i]

[a]Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia

[b]School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia

[c]Department of Neuroscience, Central Clinical School, Monash University, Melbourne, VIC, Australia

[d]Institute for Health & Sport, Victoria University, VIC, Australia

[e]Australian Institute for Musculoskeletal Science, VIC, Australia

[f]Department of Pharmacy Practice and Science, College of Pharmacy, The University of Iowa, Iowa, IA, USA

[g]Berman Center for Outcomes & Clinical Research, Hennepin HealthCare Research Institute, and Department of Medicine, Geriatrics Division, Hennepin Healthcare, Minneapolis, MN, USA

[h]University of Texas Health Science Center and Geriatric Research, Education & Clinical Center, San Antonio and South Texas Veterans Health Care System, San Antonio, TX, USA

[i]Department of Family Medicine, Carver College of Medicine, The University of Iowa, Iowa, IA, USA.

Abstract

Background: The protective effects of allopurinol on physical function in older adults are not well understood, despite its potential to improve functional gains and reduce sarcopenia. This study aims to determine the association between allopurinol, persistent physical disability and frailty in older gout patients.

Correspondence to: 1. Zhen Zhou PhD, zhen.zhou@utas.edu.au; Telephone: +61 0448160512; Fax: +61 03 62267704; Menzies Institute for Medical Research, University of Tasmania, 17 Liverpool Street, Hobart, TAS 7000, Australia. Twitter handle: @zhenzhou11, 2. Michael E. Ernst, PharmD, michael-ernst@uiowa.edu; Department of Family Medicine, 01291-A PFP, The University of Iowa, 200 Hawkins Dr, Iowa City, IA 52242.

Author Contributions: Study concept and design: all authors. Acquisition, analysis, or interpretation of data: ZZ, JR, MRN, RLW, ME; Statistical analysis: ZZ; Drafting of the manuscript: ZZ; Critical revision of the manuscript for important intellectual content: all authors; Guarantor: ME.

Conflict of interest: MN reported receiving honoraria from Sanofi and Amgen as well as Bayer for materials in ASPREE and NHMRC grant support for STAREE. Others declare that they have no conflict of interests.

Online Supplementary Materials

Supplement to: Zhou Z, Ryan J, Nelson M, et al. The association of allopurinol with persistent physical disability and frailty in a large community based older cohort.

Methods: This analysis used data from a randomized trial in an older cohort, ASPirin in Reducing Events in the Elderly (ASPREE). ASPREE recruited 19,114 participants aged ≥65 years without prior cardiovascular events, dementia, or independence-limiting physical disability at trial enrolment. This analysis examined the association of baseline and time-varying allopurinol use with persistent physical disability and new-onset frailty in participants with gout at baseline (self-report or use of any anti-gout medications). Frailty was measured using the Fried frailty phenotype (score≥3/5) and a deficit accumulation frailty index (FI) (score>0.21/1.0). Multivariable Cox proportional-hazards models were used for main analyses.

Results: This analysis included 1,155 gout participants, with 630 taking allopurinol at baseline and 525 not. During a median follow-up of 5.7 years, 113 new allopurinol users were identified. Compared with non-users, baseline allopurinol use was associated with a significant risk reduction of persistent physical disability (Adjusted HR 0.46, 95%CI 0.23–0.92, *P*=0.03). The strength of the association was modestly attenuated in the time-varying analysis (Adjusted HR 0.56, 0.29–1.08, *P*=0.08). No significant associations with frailty measures were observed for either baseline allopurinol use (Fried frailty: Adjusted HR 0.83, 0.62–1.12; FI: Adjusted HR 0.96, 0.74–1.24) or time-varying allopurinol use (Fried frailty: Adjusted HR 0.92, 0.69–1.24; FI: Adjusted HR 1.02, 0.78–1.33).

Conclusions: Allopurinol use in older adults with gout is associated with a reduced risk of persistent physical disability but not associated with risk of frailty.

Keywords

Allopurinol; gout; physical disability; frailty; older population

INTRODUCTION

Gout, caused by hyperuricemia, is a common type of inflammatory arthritis that predominantly affects older adults.(1) The prevalence of gout and hyperuricemia in the U.S. population over 65 years of age is estimated to be 10% and 21%, respectively.(2) The main clinical manifestations of gout in older adults include acute gout attacks, frequent symmetric or asymmetric polyarticular involvement, and tophi formation that can lead to excruciating joint pain and severe swelling and irreversible joint damage.(3) Gout and hyperuricemia in older adults have also been linked to cardiometabolic syndromes, cardiovascular disease, impaired renal function, and possibly dementia.(4,5) These complications and associated comorbidities, if left untreated, may result in new onset or progressive physical disability and frailty, severely compromised quality of life, and ultimately the loss of independence and death.

Allopurinol, a xanthine oxidase inhibitor, is the most widely used urate-lowering therapy over long-term for managing hyperuricemia, preventing gout flares and sequelae.(6) Allopurinol was found to have pleiotropic effects other than urate-lowering in previous studies such as alleviating inflammation and oxidative stress, improving endothelial function, and pain relief by modulating adenosine activities.(7) It was also shown that allopurinol can improve muscle weakness, prevent muscle mass loss and atrophy, improve functional gains and reduce sarcopenia in older adults.(8–11) Further, allopurinol was

also documented to reduce inflammation and improve endothelial function in common age-related morbidities such as metabolic syndromes,(12) cardiovascular diseases,(13) chronic obstructive pulmonary disease,(14) kidney and liver diseases.(15,16) As gout symptoms, sarcopenia and other co-existing health conditions can contribute together to persistent physical disability and frailty in older adults, there is a potential that allopurinol may play a role in preventing physical disability and frailty in older patients with gout and ultimately improve their quality of life and life expectancy.(17) However, there is lack of direct evidence in this regard and previous studies focusing on effect of allopurinol on physical function were limited by the small sample sizes and short follow-up periods.

The ASPirin in Reducing Events in the Elderly (ASPREE, NCT01038583) was a contemporary, randomized, placebo-controlled, clinical trial determining the effect of daily low-dose aspirin in community-dwelling, initially healthy older adults.(18–21) To further explore the mechanism by which previous, limited studies, have shown an association between allopurinol and functional gains, we have leveraged the prospective data collected on participants from the ASPREE trial and its post-trial observational follow-up, to evaluate whether allopurinol use is associated with reduced risks of persistent physical disability and onset frailty in older adults with gout.

METHODS

Study population.

Between March 2010 and December 2014, ASPREE recruited 19,114 community-dwelling participants in Australia (87% of the entire cohort) and the U.S. (13%), who were aged 70 years or above (65 years or above for U.S. African-American or Hispanic participants). At trial enrolment, participants were free of diagnosed dementia, independence-limiting physical disability (defined as severe difficulty or an inability to perform, or requiring assistance in performing, any one of 6 basic Activities of Daily Living (ADL) assessment (22)), and a history of cardiovascular events. Other key exclusion criteria include a systolic blood pressure (SBP) ≥180 mmHg and/or a diastolic blood pressure ≥105 mmHg, any serious intercurrent illness likely to cause death within the next 5 years, a current or recurrent condition with a high risk of major bleeding, and anaemia (defined as haemoglobin levels in males: <12 g/dL, females: <11 g/dL). The ASPREE intervention phase ended in June 2017 after which participants were continued to be followed in the ongoing observational phase, ASPREE-eXTension (XT) cohort study. The present analysis followed participants from trial enrolment through to the second ASPREE-XT annual study visit (last visit completed in August 2019). The study rationale, methods, and findings of the ASPREE trial are published elsewhere.(18–21)

The main analysis of this study included participants who had gout at baseline, defined as a self-reported gout history in the medical history questionnaire administrated at trial enrolment or use of any anti-gout medications (ATC code: M04A) at baseline. The time-varying analysis additionally included new users of any anti-gout medications during the follow-up. Data regarding medication use were collected from primary care physician records or self-report via in-person interviews at ASPREE trial enrolment and at annual ASPREE follow-up visits.

Study exposure.

Allopurinol use in ASPREE participants was captured at baseline and at the time of the annual follow-up visit. The main analysis focused on baseline allopurinol use and additional analyses considered allopurinol and other gout medication use as time-varying, given that allopurinol use after baseline was only captured at every annual follow-up visit, and thus the exact timing cannot be identified. Participants not using allopurinol medication (non-users) were used as the reference group.

Study outcomes.

Persistent physical disability endpoint was defined as a self-reported response of 'a lot of difficulty', 'unable to do' the activity or the requirement for assistance for the same basic Activity of Daily Living (ADL)(22) at consecutive administrations of the ADL questions approximately 6 month apart. The time of reaching this endpoint was the first reported date when physical disability was detected and subsequently confirmed as persistent approximately 6 months later. If the ADL questions could not be administered, the date of assessment for requiring admission to care for assistance with daily living activities was deemed a persistent physical disability endpoint.(20) Admissions to care were adjudicated by expert panels. The most common ADLs responsible for persistent physical disability were bathing and dressing followed by transferring and walking as previously reported.(23)

Two frailty classifications as per previous ASPREE post-hoc analyses were used in this study.(24,25)

a. **Adapted Fried frailty.** Participants were classified into non-frail, pre-frail, and frail groups according to five domains of frailty characteristics. These included:

- Body mass index (BMI) <20kg/m^2;
- Hand grip strength in lowest 20% of participants by sex and Fried-defined sex-specific BMI categories;
- Exhaustion (taken from the self-reported Center of Epidemiologic Studies Depression Scale, 10-item version [CES-D-10](26) responses for depression measurement, indicating at least one of the following conditions was present for 3 days or more during the last week, "I felt that everything I did was an effort" or "I could not get going");
- Three metre gait speed in lowest 20% of participants by sex and Fried-defined sex-specific height categories, and;
- Limited physical activity (taken from the self-reported Life questionnaire, indicating yes to "In the last 2 weeks, no walking outside the home, or walked outside home but longest amount of time walked without sitting down to rest was less than 10 minutes").

'*Pre-frail*' included anyone meeting 1 or 2 criteria and '*Frail*' included anyone meeting 3 or more criteria of the adapted Fried frailty criteria.(27)

b. **Deficit-accumulation frailty index (FI)**.(28) A Frailty index composed of 67 deficits was constructed and validated using participants' follow-up data collected at annual visits. The included items covered cognitive function, physical activity, functionally engaging activities, mental health, comorbidities, laboratory tests, and self-rated health status. The FI was calculated by summing all items of deficit divided by the total number of items for which data were available. We excluded participants at any follow-up visit who had fewer than 50 deficit items. Participants were categorized as non-frail (≤0.10/1.0), prefrail (<0.10 and ≤0.21/1.0), or frail (>0.21/1.0).(24,29) The details of FI construction and validation in the ASPREE population has been published elsewhere.(25)

Statistical analyses.

Baseline allopurinol use.—Cox proportional hazards regression model was used to analyse the association between baseline allopurinol use and the first event of each study outcome. Participants were censored if they developed events, died, or reached the end of follow up, whichever occurred first. Covariates adjusted in the regression models were selected on the basis of a known association, from prior literature and clinical judgement, with study exposure and/or outcomes. These include age, sex, race (white/non-white), country (Australia/U.S.), polypharmacy (used 5 prescription medications or more), other anti-gout medication use (123 colchicine, 7 probenecid, 2 febuxostat), and precision variables including smoking (never/former/current), alcohol consumption (never/former/current), chronic kidney disease (CKD; defined as an estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73m^2 or urinary albumin to creatinine ratio ≥3mg/mmol), diabetes (self-report or fasting glucose ≥126mg/dL or on glucose-lowering medications), BMI categories (≤25, 25 to <30, ≥30 kg/m^2), mean SBP, mean total cholesterol (TC), mean gait speed (sec/ 3 metre walking), mean grip strength of strongest hand, and randomized study assignment (aspirin/placebo). Crude cumulative incidence of individual outcomes in allopurinol users and non-users were plotted. In frailty analyses, 141 and 186 participants who were frail at baseline or had no relevant information during the follow-up were further excluded from the Fried Frailty and FI analysis, respectively. Outcome analysis for persistent physical disability was repeated by excluding baseline frail participants and analyses for frailty were repeated in non-frail and pre-frail participants, separately. Proportional hazards assumptions were tested with Schoenfeld residuals, and no violation was observed. Subgroup analyses was conducted for all outcomes by sex and ASPREE randomised assignment (low-dose aspirin/placebo).

Time-varying allopurinol use.—Marginal structural models (MSM) with inverse probability weights (IPW) were used to estimate the causal effects of time-varying allopurinol.(30) To eliminate the effect of simultaneous change of other anti-gout treatments over time, other anti-gout medication use was also treated as a time-varying variable when generating IPW. Other covariates were adjusted for in the regression model at baseline levels.

We also analysed the associations of baseline and time-varying allopurinol use with changes in scores of the Fried frailty (scores 0–5) and FI on a continuous scale using linear

mixed models with adjustment made for all baseline covariates. Similar to the time-varying analysis of allopurinol in MSM, other anti-gout medication use was treated as a time-varying variable in the linear mixed-effect regression model.

Ancillary analysis.—More analyses were performed to examine the association of baseline allopurinol use with other patient-centred outcomes including myocardial infarction, stroke, and mortality outcomes. Unrevealing these associations may help explain the underlying mechanisms if there is any potential impact of allopurinol on physical disability and frailty.

Most analyses were performed using Stata 17.0 (StataCorp, College Station, Texas), except for the analyses using MSM, which was performed with R (R Foundation for Statistical Computing), version 1.1.456. All statistical tests were 2 sided, and p values <0.05 were considered to indicate statistical significance.

RESULTS

Baseline Characteristics.

In the ASPREE, 1,189 out of 19,114 participants reported gout history and/or used any anti-gout medications at baseline. After excluding 34 participants who missed baseline data on covariates, 1,155 participants were included in the main analysis, with 1050 (90.9%) self-reporting a history of gout and 105 (9.1%) reported use of anti-gout medications but not a gout history. Of those taking allopurinol (n=630), 85.2% also self-reported gout; of 525 allopurinol non-users including 91 participants using other anti-gout medications, 97.7% (n=153) self-reported gout. During a median (interquartile range [IQR]) follow-up of 5.7 (4.9–7.0) years, 113 new allopurinol users and 54 new users of other anti-gout medications were identified; 144 out of 630 (23%) baseline allopurinol user discontinued medication temporarily or permanently during the entire follow-up. Participants' baseline characteristics are shown in Table 1. Compared with non-users, allopurinol users were more likely to be male and a current smoker. They also had greater gait speed and grip strength of strongest hand and a higher prevalence of CKD, diabetes, obesity, and polypharmacy, but were less likely to take other anti-gout medications.

Allopurinol Use and Persistent Physical Disability.

The cumulative incidence rate of persistent physical disability was 4.5 and 5.5 cases per 1000 person-years in allopurinol users and non-users, respectively. Compared with non-users, allopurinol use at baseline was associated with a significantly lowered risk of persistent physical disability (adjusted HR 0.46, 95% CI 0.23–0.92, P =0.03). The strength of the association between allopurinol use and persistent physical disability was modestly attenuated in the time-varying analysis, with the adjusted HR of 0.56 (95% CI 0.29–1.08, P =0.08) (Figure 1, Table 2). When repeating the analysis after excluding frail participants at baseline, the adjusted HR was 0.44 (95% CI 0.21–0.92, P=0.03).

Allopurinol Use and Frailty.

The cumulative incidence rates in the allopurinol users and non-users were 47.8 and 40.3 per 1000 person-years, respectively, for the Fried frailty, were and 60.7 and 54.9 per 1000 person-years, respectively, for the deficit accumulation FI. There was no significant association between baseline allopurinol use and Fried frailty (adjusted HR 0.83, 95% CI 0.62–1.12, P=0.23), nor between allopurinol use and FI (adjusted HR 0.96, 95% CI 0.74–1.24, P=0.75), or when treating allopurinol as a time-varying variable (P>0.50). (Figure 1, Table 2) Subgroup analyses found that baseline allopurinol use appears to be associated with a reduced risk of incident Fried frailty among non-frail participants at baseline (adjusted HR 0.54, 95% CI 0.30–0.98, P=0.04) but not in those who were pre-frail at baseline (adjusted HR 0.95, 95% CI 0.67–1.35, P=0.77) (Table 3). In additional analyses using multivariable linear mixed models, baseline allopurinol use was neither associated with change in Fried frailty scores (adjusted β 0.007, SE 0.009, P=0.42) nor with change in FI scores (adjusted β 0.0002, SE 0.005, P=0.77) over time. These results were essentially unchanged when treating allopurinol and other gout medications as time-varying variables. (Table 4)

Subgroup analyses found no interaction between allopurinol and sex and between allopurinol and ASPREE randomised assignment (low-dose aspirin/placebo) for all outcomes (Supplementary Table S1).

Ancillary analysis.

Baseline allopurinol use was associated with 44% reduced risk of myocardial infarction though this result was not statistically significant (HR: 0.56, 95%CI 0.31–1.05). No evidence was found for the association of allopurinol with incident stroke, all-cause mortality, CVD mortality and cancer mortality (Supplementary Table S2).

DISCUSSION

This post-hoc analysis investigated the relationship between allopurinol use and risk of incident persistent physical disability and frailty in a large community-based older cohort of individuals with gout. We found that, compared to non-users, baseline allopurinol use was associated with a 54% reduced risk of persistent physical disability. The similar association for trend was seen in the model that included allopurinol as time-varying, although the strength of the association was modestly attenuated (44% reduced risk). This nuance might be explained by the small event numbers leading to less stable risk estimates, discontinuations of allopurinol use during the follow-up, or a delay in the time needed for allopurinol to take an effect and its potential benefit to emerge. No associated benefits were found for frailty modalities with either baseline or time-varying allopurinol use.

The strong protective association between allopurinol use and physical disability may be explained by allopurinol conferring benefits on improving gout symptoms and multiple gout-associated complications, on physical functioning, including gout-associated arthritic pain and stiffness, and cardiometabolic outcomes. In supporting our findings, a small-scale randomized trial found that allopurinol improved 6-min walk distance in 214 patients with impaired physical function (6-min walk distance <400m), though it did not

improve muscle efficiency as measured by post-exercise skeletal muscle phosphocreatine recovery rate.(31) A more recent cross-sectional study including 296 patients who had undergone hemodialysis found that use of a xanthine oxidoreductase inhibitor (allopurinol, febuxostat, or topiroxostat) was associated with reduced risks of sarcopenia and severe sarcopenia, greater muscle mass and strength, and a better physical performance.(32) Our sensitivity analysis has shown a similar positive result of the association between allopurinol and physical disability in the overall ASPREE population. Consistent with previous studies(33,34) showing a cardioprotective effect of allopurinol, our study found allopurinol users had a 44% lower risk of myocardial infarction. Although this was not statistically significant, myocardial infarction is a major contributor to the loss of independence and physical function.(35) This may serve as another explanation for the possible benefits of allopurinol against physical disability in older people.

In this study, we found no overall association of allopurinol use and increased risk of frailty. Although frailty and disability are closely related, frailty is a geriatric syndrome conceptualized as a consequence to reduced physiological reserve due to aging. Physical disability commonly arises from dysfunction of one system or multiple systems, which allopurinol may target (e.g., musculoskeletal system).(36)

Notwithstanding the potential for reduced risk of physical disability, clinicians must be vigilant of allopurinol's related adverse drug reactions and drug-drug interactions before prescribing. Allopurinol is known to be linked to a severe and potentially life-threatening drug reaction commonly characterized by fever, rash, and multiorgan failure, including drug reactions with eosinophilia and systemic symptoms, toxic epidermal necrolysis, Stevens-Johnson syndrome, and drug-induced hypersensitivity syndrome.(37) Likewise, allopurinol can interact with other medications resulting in toxicity (e.g. mercaptopurine or azathioprine).(38)

Study strengths.

To the best of our knowledge, this is the first prospective non-random observational study investigating whether allopurinol use was associated with persistent physical disability and frailty in older people with gout. The study quality is reassured by using a well-characterised, large, community-based study cohort with long-term systematic follow-up and rigorous outcome adjudication from a large-scale contemporary randomized clinical trial. The study findings are intriguing and of clinical importance and more rigorous studies are warranted to provide robust data and clarify the underlying pharmacological mechanisms of actions.

Study limitations.

First of all, ours was an observational analysis which means no causal relationship can be determined, and bias from unmeasured/unobserved confounders cannot be ruled out. In particular, as the frequency and severity of gout symptoms were not recorded and the fact that allopurinol users would likely have had more frequent and/or severe prior gout symptoms than non-users, lack of consideration of these factors may introduce indication bias and influence the analysis results towards null. In addition, serum uric acid levels

were also not collected, so the level of management of gout in each participant and the lack of adjustment for this variable in our analyses might impact the study results. Thirdly, medication dose information and duration of allopurinol use were not collected as part of the ASPREE study. Hence, we were incapable of exploring any dose-response relationship. Older people are usually put on a low treatment dose or under-treated, particularly those with impaired renal function, due to its associated adverse effects which is potentially life-threatening.(37) Fourthly, the ASPREE trial excluded older individuals who had any prior cardiovascular event. Our sample was healthier overall; thus, these results may not be generalizable to the general older population, which has a higher prevalence of cardiovascular disease and risk factors for disability. Lastly, 14.8% of baseline allopurinol users did not self-report gout history. The history of gout was collected at baseline visit when comorbidities were recorded. As these were self-reported, participants taking allopurinol may have under-reported gout history. Also, it cannot be ruled out that a small group of participants used allopurinol for hyperuricaemia.

In conclusion, allopurinol use in older adults with gout is associated with a reduced risk of persistent physical disability but not associated with risk of frailty. Future randomized trials and high-quality population-based observational studies are needed to determine whether allopurinol can prevent physical disability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENT:

Funding:

The ASPREE and ASPREE-XT studies are supported by grants (U01AG029824 and U19AG062682) from the National Institute on Aging and the National Cancer Institute at the National Institutes of Health in the United States, by grants (334047 and 1127060) from the National Health and Medical Research Council of Australia, and by Monash University and the Victorian Cancer Agency.

Sponsor's Role:

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

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Key points

- Gout can lead to severe and excruciating joint pain and swelling and irreversible joint damage in older adults and it has been linked to cardiometabolic syndromes, cardiovascular disease, impaired renal function, and possibly dementia.
- There is lack of direct epidemiological evidence for the effect of allopurinol on persistent physical disability and frailty in older populations, which are two important overarching outcomes that reflect the accumulative burden of gout and its associated complications and sequalae.
- This study found that allopurinol use in older individuals with gout is associated with a reduced risk of persistent physical disability but not associated with risk of frailty.

Why does this matter?

With the aging population and increased life expectancy, preventing persistent physical disability and frailty to further fend off permanent residential care and premature death in older people, has been increasingly recognised as a major public health priority. Gout in older adults can significantly compromise older people's physical function and quality of life mainly through leading to several joint pain, swelling and damage. Our study reveals a significant beneficial effect of allopurinol on preventing persistent physical disability in older adults with gout, with implications for promoting healthy aging in this specific patient group.

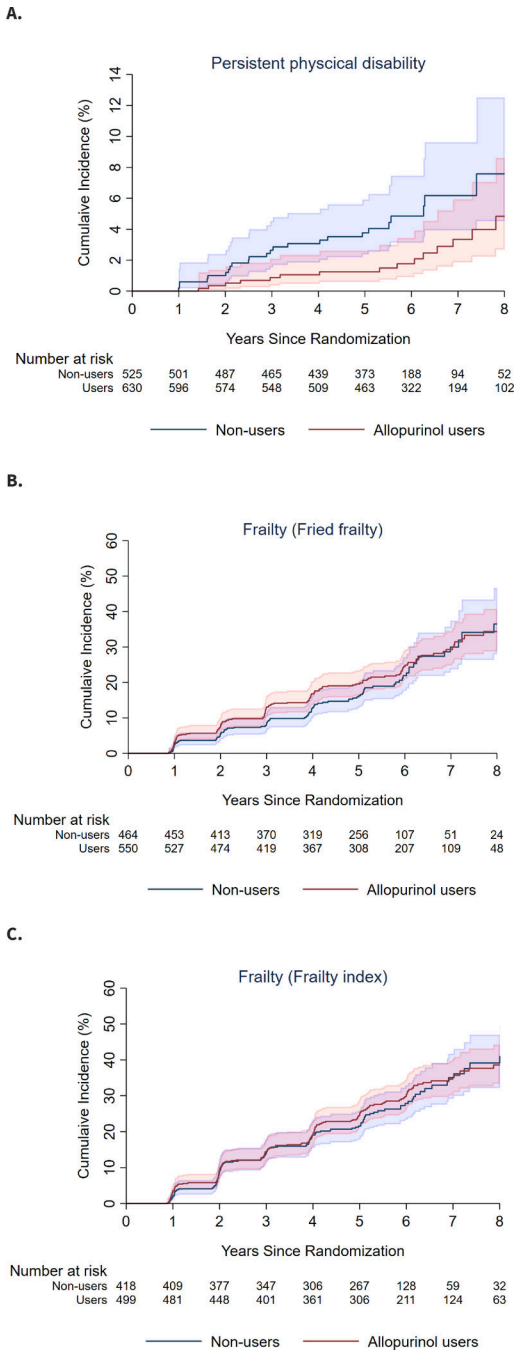

Figure 1.

Cumulative incidence of persistent physical disability and frailty according to Fried frailty phenotype and frailty index in baseline allopurinol users and non-users.

The blue line and its shading represent the cumulative incidence of events and 95% confidence interval (CI) of allopurinol non-users, and the red line and its shading represent the cumulative incidence of events and 95% CI of allopurinol users.

Table 1.

Baseline characteristics of the study population (those with gout) and by baseline allopurinol use.

Characteristic	Overall (n=1,155)	Non-users* (n = 525)	Allopurinol users (n = 630)
Age, median (IQR), year	74.2 (71.9–77.6)	74.1 (71.7–77.0)	74.5 (72.0–78.0)
Female, n (%)	253 (21.9)	136 (25.9)	117 (18.6)
Country, n (%)			
Australia	1077 (93.3)	487 (92.8)	590 (93.7)
United States	78 (6.8)	38 (7.2)	40 (6.4)
Race, n (%)			
White	1087 (94.1)	495 (94.3)	592 (94.0)
Non-white	68 (5.9)	30 (5.7)	38 (6.0)
Smoking, n (%)			
Never	487 (42.2)	220 (41.9)	267 (42.4)
Former	619 (53.6)	285 (54.3)	334 (53.0)
Current	49 (4.2)	20 (3.8)	29 (4.6)
Alcohol consumption, n (%)			
Never	120 (10.4)	58 (11.1)	62 (9.8)
Former	82 (7.1)	41 (7.8)	41 (6.5)
Current	953 (82.5)	426 (81.1)	527 (83.7)
Chronic kidney disease, n (%)			
No	635 (55.0)	308 (58.7)	327 (51.9)
Yes	427 (37.0)	166 (31.6)	261 (41.4)
Uncertain (missing)	93 (8.1)	51 (9.7)	42 (6.7)
Diabetes, n (%)			
No	936 (81.0)	430 (81.9)	506 (80.3)
Yes	219 (19.0)	95 (18.1)	124 (19.7)
BMI categories, kg/m^2, n (%)			
Under/normal weight (<25)	144 (12.5)	73 (13.9)	71 (11.3)
Over-weight (25 to <30)	486 (42.1)	230 (43.8)	256 (40.6)
Obese (≥30)	525 (45.5)	222 (42.3)	303 (48.1)
Total cholesterol, mean ± SD, mmol/L	4.9 ± 1.0	5.0 ± 1.0	4.8 ± 0.9
SBP, mean ± SD, mm Hg	141.3 ± 16.3	141.7 ± 16.3	141.0 ± 16.3
Polypharmacy, n (%)	511 (44.3)	191 (36.4)	320 (50.8)
Other anti-gout agent, n (%)	132 (11.4)	91 (17.3)	41 (6.5)
Randomized aspirin, n (%)	612 (53.0)	286 (54.5)	326 (51.8)
Mean gait speed, mean ± SD, sec/3m	3.2 ± 0.9	3.1 ± 0.8	3.2 ± 0.9
Grip strength of strongest hand, kg, mean ± SD	31.1 ± 10.1	30.8 ± 10.1	31.3 ± 10.1
Self-report gout history, n (%)	1050 (90.9%)	513 (97.7%)	537 (85.2%)
Frailty status (Fried)			
Non-frail	625 (54.1)	290 (55.2)	335 (53.2)
Pre-frail	495 (42.9)	219 (41.7)	276 (43.8)

Characteristic	Overall (n=1,155)	Non-users* (n = 525)	Allopurinol users (n = 630)
Frail	35 (3.0)	16 (3.1)	19 (3.0)
Frailty status (FDAI)			
Non-frail	472 (40.9)	211 (40.2)	261 (41.4)
Pre-frail	544 (47.1)	248 (47.2)	296 (47.0)
Frail	139 (12.0)	66 (12.6)	73 (11.6)

Abbreviations: BMI, body mass index, IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation.

*Non-users include those who self-reported a history of gout and did not take allopurinol at baseline, and those who did not report a history of gout but reported use of anti-gout medications other than allopurinol.

Diabetes is defined from self-report or fasting glucose ≥ 126mg/dL or on glucose-lower medications. Chronic kidney disease is defined as an estimated glomerular filtration rate < 60 ml/min/1.73m^2 or urinary albumin to creatinine ratio ≥3mg/mmol. Polypharmacy was defined as the use of five or more prescription drugs.

Table 2.

Hazard of incident persistent physical disability and frailty (Fried frailty and deficit accumulation frailty index) between allopurinol users and non-users with gout.

	Main analysis for baseline allopurinol use					Time-varying analysis	
	Cases/Total (rate per 1000 person-years)	Crude HR (95% CI)	P value	Fully adjusted HR (95% CI)	P value	MSM HR (95% CI)	P value
Persistent physical disability							
Non-users	24/525 (8.5)	1.00 (Ref)	0.03	1.00 (Ref)	0.03	1.00 (Ref)	0.08
Users	16/630 (4.5)	0.48 (0.26–0.91)		0.46 (0.23–0.92)		0.56 (0.29–1.08)	
Fried Frailty							
Non-users	89/464 (40.3)	1.00 (Ref.)	0.36	1.00 (Ref.)	0.23	1.00 (Ref)	0.59
Users	131/550 (47.8)	1.13 (0.87–1.49)		0.83 (0.62–1.12)		0.92 (0.69–1.24)	
Frailty index							
Non-users	119/440 (54.9)	1.00 (Ref)	0.48	1.00 (Ref)	0.75	1.00 (Ref)	0.90
Users	164/529 (60.7)	1.09 (0.86–1.40)		0.96 (0.74–1.24)		1.02 (0.78–1.33)	

Abbreviations: CI, confidence interval; HR, hazard ratio; MSM, marginal structural model.

'Users' and 'non-users' refer to the prescription of allopurinol. For all outcomes, only the first event was counted. A respective 141 and 186 participants who were frail at baseline or had no relevant information during the follow-up were further excluded from the Fried Frailty and frailty index analysis. In the fully adjusted model, adjustment was made for age, sex, race/ethnicity, country, smoking, alcohol consumption, chronic kidney disease, diabetes, systolic blood pressure, total cholesterol, polypharmacy, other anti-gout medication use, gait speed, grip strength of strongest hand, and ASPREE study assignment (aspirin/placebo). Baseline frailty status (non-frail/pre-frail) was additionally adjusted for frailty analysis.

Table 3.

Subgroup analysis for risk of incident frailty by baseline frailty status and use of allopurinol

	Cases/Total (events per 1000 person-years)	Crude HR (95% CI)	P value	Fully adjusted HR (95% CI)	P value
Frailty (Fried criteria)					
Not frail at baseline					
Non-users	26/268 (19.2)	1.00 (Ref)		1.00 (Ref)	
Users	33/304 (20.0)	0.92 (0.55–1.54)	0.75	0.54 (0.30–0.98)	0.04
Pre-frail at baseline					
Non-users	62/194 (73.1)	1.00 (Ref)		1.00 (Ref)	
Users	98/245 (90.2)	1.22 (0.88–1.67)	0.23	0.95 (0.67–1.35)	0.77
Frailty index					
Not frail at baseline					
Non-users	22/198 (19.8)	1.00 (Ref)		1.00 (Ref)	
Users	32/240 (22.5)	1.11 (0.64–1.92)	0.70	1.00 (0.54–1.84)	1.00
Pre-frail at baseline					
Non-users	95/220 (94.9)	1.00 (Ref)		1.00 (Ref)	
Users	125/259 (103.1)	1.06 (0.81–1.39)	0.65	0.92 (0.69–1.23)	0.57

‘Users’ and ‘non-users’ refer to the prescription of allopurinol at baseline. In the fully adjusted model, adjustment was made for age, sex, race/ethnicity, country, smoking, alcohol consumption, chronic kidney disease, diabetes, systolic blood pressure, total cholesterol, polypharmacy, other anti-gout medication use, gait speed, grip strength of strongest hand, and ASPREE study assignment (aspirin/placebo). Baseline frailty status (non-frail/pre-frail) was additionally adjusted for frailty analyses. Abbreviations: CI, confidence interval; HR, Hazard ratio.

Table 4.

The association between allopurinol use and frailty in participants with gout.

	Crude model			Fully adjusted model		
	β	SE	*P*	β	SE	*P*
Baseline allopurinol use versus non-use						
Frailty (Fried Criteria)	0.008	0.009	0.39	0.007	0.009	0.42
Frailty (Frailty index)	0.0002	0.0005	0.60	0.0002	0.0005	0.77
Time-varying allopurinol use versus non-use						
Frailty (Fried Criteria)	−0.001	0.009	0.90	0.0004	0.009	0.97
Frailty (Frailty index)	0.0002	0.0005	0.66	0.0003	0.0005	0.61

Abbreviations: SE, standard error.

Frailty data were taken from the annual visit at baseline (annual visit 0), 1–9 years. The data were fitted using linear mixed models to calculate the change in frailty scores over time between allopurinol users and nonusers. Annual frailty index determination was treated as a continuous variable representing time. The models were constructed by entering baseline allopurinol use, annual visit, baseline allopurinol × annual visit interaction, baseline covariates, and random intercept, on time. The presented β was the coefficient of the baseline (or time-varying) allopurinol × annual visit interaction, which was interpreted as the mean difference in the annual rate of change in frailty score between allopurinol users and non-users. In the fully adjusted model, adjustment was made for age, sex, race/ethnicity, country, smoking, alcohol consumption, chronic kidney disease, diabetes, systolic blood pressure, total cholesterol, polypharmacy, other anti-gout medication use at baseline (or time-varying), gait speed, grip strength of strongest hand, and ASPREE study assignment (aspirin/placebo). Baseline frailty status (non-frail/pre-frail) was additionally adjusted for frailty analyses.