

BMJ Open Gout and hearing impairment in the elderly: a retrospective cohort study using the US Medicare claims data

Jasvinder A Singh,^{1,2,3} John D Cleveland²

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¹Medicine Service, VA Medical Center, Birmingham, Alabama, USA

²Department of Medicine, School of Medicine, University of Alabama, Birmingham, Alabama, USA

³Division of Epidemiology, School of Public Health, University of Alabama, Birmingham, Alabama, USA

Correspondence to
Dr Jasvinder A Singh;
javinder.md@gmail.com

ABSTRACT

Objectives To evaluate whether gout is associated with a higher risk of hearing loss in older adults.

Design Retrospective cohort study.

Setting USA.

Participants 5% random sample of US Medicare claims 2006–2012, representative of US adults aged 65 years or older.

Primary and secondary outcomes Incident (new) hearing loss identified by the presence of at least two claims at least 4 weeks apart with an International Classification of Diseases, Ninth Revision, 389.xx, with no respective claim in the baseline 1-year observation period.

Results Among the 1.71 million eligible people, 89 409 developed incident hearing impairment. The crude incidence rates of incident hearing impairment in people with versus without gout were 16.9 vs. 8.7 per 1000 person-years. Using Cox regression analyses adjusted for demographics, medical comorbidity and common cardiovascular and gout medications, we found that gout was associated with a significantly higher HR of incident hearing impairment, HR was 1.44 (95% CI 1.40 to 1.49, $p < 0.0001$). Findings were confirmed in sensitivity analyses that substituted continuous Charlson-Romano Index with categorical variable or all comorbidities and additionally cardiovascular risk factors, with minimal attenuation of HR.

Conclusions Gout is associated with a higher risk of development of hearing loss in older adults. Future studies need to assess the underlying mechanisms of this association.

INTRODUCTION

Hearing loss is a common problem in the ageing population. The 2005–5006 National Health and Nutritional Examination Survey (NHANES) data showed that more than two-thirds of US adults aged 70 years or older had hearing loss,¹ while another population-based study found a prevalence of 46% in US adults aged 48–92 years.² People with hearing loss continue to have further decline in hearing.³ Hearing loss is associated with self-reported communication difficulties, difficulty with activities of daily living (ADLs) and instrumental ADLs and a lower quality of life.^{4–6} Hearing loss is associated with a higher risk of incident

Strengths and limitations of this study

- Study findings are only generalisable to adults aged 65 years or older.
- We used the diagnostic codes for both the outcome and the exposure, which puts results at the risk of misclassification bias, which we estimate would bias our estimates towards null.
- Lack of laboratory measures, including serum urate, or markers of inflammation or oxidative stress limited us from assessing whether they are the underlying mechanisms of this association.
- Despite controlling for several potential confounders, residual confounding is possible, due to an observational study design.
- Our study strengths were that we included a representative large sample of US adults aged 65 years or older, an adequate number of events occurred and our study findings were robust in multiple sensitivity models.

dementia⁷; sudden hearing loss is associated with a higher risk of stroke.⁸ Thus, hearing loss, with its consequences and long-term individual and societal burden, is a significant public health problem.

A recent study using the NHANES data found that older age, male sex and white race were strongly associated with hearing loss after multivariate adjustment¹; cardiovascular disease, loud noise, diabetes and smoking were also associated.^{9–10} In mouse cochlea, increased oxidative stress and inflammation may trigger cell death pathways.¹¹ Other studies have also shown that oxidative stress, inflammation and autophagic stress can potentiate noise-induced or age-related hearing loss.^{11–14}

Another condition with risk factors similar to hearing loss (older age, male sex, cardiovascular disease) is gout, the most common inflammatory arthritis in adults. The hallmarks of gout are hyperuricaemia and urate crystal formation that are associated with inflammation^{15–16} and oxidative stress,^{17–21} pathological processes which are also

implicated in the pathogenesis of hearing loss.^{11–14} Based on this similarity in pathogenesis, we hypothesised that gout in the elderly will be independently associated with a higher risk of new-onset hearing loss after adjusting for known risk factors, and that this association will vary by important biological variables, such as age, sex and race. Our objective was to address these questions.

METHODS

Data sources and study sample

We used the 5% Medicare claims data from 2006 to 2012. People were eligible for this study if they were Medicare fee-for-service recipients with part A and/or B, but not Medicare Advantage plan (part C; claims incomplete) and a valid US mailing address.

Predictor of interest

The predictor of interest was existing gout, identified by the occurrence of two International Classification of Diseases, Ninth Revision (ICD-9-CM) codes for 274.xx, on two claims at least 4 weeks apart, an approach shown to be valid in observational studies with specificity and sensitivity of $\geq 90\%$.²²

Independent variable/outcome of interest

The outcome we were interested in was incident (new) hearing impairment, identified by the presence of at least two claims at least 4 weeks apart with an ICD-9-CM, 389.xx,²³ and its absence in the baseline 1-year period. We included patient demographics, age, sex and race, based on the data obtained from the Medicare denominator file and the beneficiary summary file. We assessed medical comorbidity using the Charlson-Romano Comorbidity Index which is a validated measure of comorbidity, developed for claims data.²⁴ It was obtained from inpatient and outpatient Medicare claims and treated as a continuous variable (main analysis). We used the Medicare part D prescription claims file to assess the use of common cardiovascular drugs (statins, beta-blockers, diuretics and ACE inhibitors) and drugs for gout (allopurinol, febuxostat), as surrogates for the severity (and the presence) of the underlying conditions which they were used to treat.

Patient and public involvement

The development of the research question was informed by several patients with gout seen at the University of Alabama at Birmingham (UAB) General Rheumatology Clinic and the UAB Gout Clinic who asked us about the possible link of gout and their chronic condition(s), including hearing loss. This prompted us to perform this study. Patients were not involved in study design or conduct. Administrative dataset does not contain identifiable information for patients, and therefore, patients can not be contacted for dissemination of study findings. The publication of this manuscript is our planned dissemination of the findings to the public.

Statistical analyses

We calculated crude incidence rates for the occurrence of incident hearing impairment in patients with versus without gout at baseline. Characteristics of people with versus without hearing impairment were compared using Student's t-test or χ^2 test, as appropriate. We used multi-variable-adjusted Cox proportional hazard model to assess whether gout diagnosis at baseline was associated with a new diagnosis of hearing impairment during the follow-up, while adjusting for demographics, comorbidity and common medications (model 1). Sensitivity analyses modelled Charlson-Romano Index in categories (model 2) or as individual comorbidities plus hyperlipidemia, hypertension and coronary artery disease, ie, cardiovascular risk factors (model 3). Subgroup analyses were done to assess if gout's association with hearing impairment varied by age, gender, race and tobacco use disorder.

RESULTS

Of the 1.71 million people in our cohort, 89 409 developed incident hearing impairment (table 1). Compared with the people without, people with hearing impairment were older, less likely to be black and had higher medical comorbidity (table 1). The crude incidence rates of incident hearing impairment in people with versus without gout were 16.9 vs 8.7 per 1000 person-years.

In multivariable-adjusted analyses, we found that gout was associated with a significantly increased HR of new-onset hearing impairment, HR was 1.44 (95% CI 1.40 to 1.49), confirmed with minimal attenuation of HR in sensitivity analyses (models 2 and 3; table 2).

In subgroup analyses, the HR of gout with hearing loss was similar across age, gender and race subgroups, although the interaction term was statistically significant for age, gender and race (p values < 0.0001 , 0.001 and 0.05, respectively; table 3). Gout was significantly associated with hearing impairment in people without tobacco use disorder and in those with tobacco use disorder, but the interaction term was statistically not significant (table 3).

DISCUSSION

In this study of adults aged 65 years or older, we found an independent association of gout with a 44% higher risk of new hearing impairment after adjusting for demographics, medical comorbidities and the commonly used medications for cardiovascular disease and gout. These findings were robust across multiple sensitivity analyses.

Our study has several limitations. Our study findings are only generalisable to adults aged 65 years or older. We used the diagnostic codes for outcome and exposure, which are subject to misclassification bias, which would bias our estimates towards null and indicates that our estimates were conservative. However, we used valid algorithms for identifying people with hearing loss and gout.^{22 23} We did not have access to laboratory measures, including serum urate, or markers of inflammation (eg,

Table 1 Demographic and clinical characteristics of people with hearing impairment

	Entire cohort	Hearing impairment during the follow-up		P values
		No	Yes	
Total, N	1 716 438*	1 627 029	89 409	
Age, mean (SD)	75.3 (7.6)	75.2 (7.6)	76.5 (7.3)	<0.0001
Gender, N (%)				<0.0001
Male	728 050 (42.4)	691 144 (42.5)	36 906 (41.3)	
Female	988 388 (57.6)	935 885 (57.5)	52 503 (58.7)	
Race/ethnicity, N (%)				<0.0001
White	1 477 659 (86.1)	1 397 909 (85.9)	79 750 (89.2)	
Black	141 798 (8.3)	137 200 (8.4)	4 598 (5.1)	
Other/unknown	96 981 (5.7)	91 920 (5.6)	5 061 (5.7)	
Charlson-Romano comorbidity score, mean (SD)	1.60 (2.39)	1.59 (2.40)	1.75 (2.23)	<0.0001
Charlson-Romano comorbidity score categories, N (%)				<0.0001
0	905 578 (52.8%)	866 797 (53.3%)	38 781 (43.4%)	
1	172 125 (10.0%)	160 939 (9.9%)	11 186 (12.5%)	
≥2	638 735 (37.2%)	599 293 (36.8%)	39 442 (44.1%)	
Charlson-Romano Comorbidities, N (%)				
Myocardial infarction	68 199 (4.0)	64 294 (4.0)	3 905 (4.4)	<0.0001
Heart failure	201 363 (11.7)	190 652 (11.7)	10 711 (12.0)	0.018
Peripheral vascular disease	166 866 (9.7)	156 169 (9.6)	10 697 (12.0)	<0.0001
Cerebrovascular disease	166 659 (9.7)	156 026 (9.6)	10 633 (11.9)	<0.0001
Dementia	77 454 (4.5)	74 434 (4.6)	3 020 (3.4)	<0.0001
Chronic pulmonary disease	267 689 (15.6)	251 447 (15.5)	16 242 (18.2)	<0.0001
Connective tissue disease	47 429 (2.8)	43 887 (2.7)	3 542 (4.0)	<0.0001
Peptic ulcer disease	32 397 (1.9)	30 202 (1.9)	2 195 (2.5)	<0.0001
Mild liver disease	8 440 (0.49)	7 957 (0.49)	483 (0.54)	0.033
Diabetes	317 322 (18.5)	299 093 (18.4)	18 229 (20.4)	<0.0001
Diabetes with end organ damage	93 630 (5.5)	87 895 (5.4)	5 735 (6.4)	<0.0001
Hemiplegia	14 238 (0.83)	13 515 (0.83)	723 (0.81)	0.48
Renal failure/disease	59 136 (3.4)	56 187 (3.5)	2 949 (3.3)	0.013
Any tumour, leukaemia or lymphoma	171 928 (10.0)	160 323 (9.9)	11 605 (13.0)	<0.0001
Moderate or severe liver disease	1 985 (0.12)	1 905 (0.12)	80 (0.09)	0.018
Metastatic cancer	17 831 (1.0)	17 109 (1.1)	722 (0.81)	<0.0001
AIDS	546 (0.03)	520 (0.03)	26 (0.03)	0.64
Hypertension	826 095 (48.1)	771 614 (47.4)	54 481 (60.9)	<0.0001
Hyperlipidaemia	594 495 (34.6)	552 056 (33.9)	42 439 (47.5)	<0.0001
Coronary artery disease	300 512 (17.5)	280 016 (17.2)	20 496 (22.9)	<0.0001
Obesity	35 772 (2.1)	33 622 (2.1)	2 150 (2.4)	<0.0001

Bold values represent statistically significant difference with a p-value of <0.05.

*Cohort selected for study of incident hearing loss that had a baseline period of 365 days without a diagnosis of hearing loss.

C reactive protein) or oxidative stress. Therefore, we could not assess whether these mechanisms underlie the noted association between gout and hearing loss. Due to an observational study design, residual confounding from unmeasured variables (prior noise exposure or the

use of ototoxic drugs) is possible, despite the fact that we controlled for several potential confounders. We examined additional outcomes in other related papers but did not make any adjustment for multiple testing in this analysis; however, even after correction for 15 hypothesis

Table 2 Association of gout and other risk factors with hearing impairment

	Multivariable-adjusted model 1*		Multivariable-adjusted model 2*		Multivariable-adjusted model 3*	
	HR (95% CI)	P values	HR (95% CI)	P values	HR (95% CI)	P values
Age (in years)						
65 to <75	Ref		Ref		Ref	
75 to <85	1.60 (1.58 to 1.63)	<0.0001	1.57 (1.55 to 1.60)	<0.0001	1.54 (1.52 to 1.56)	<0.0001
≥85	2.32 (2.28 to 2.37)	<0.0001	2.28 (2.23 to 2.33)	<0.0001	2.32 (2.27 to 2.36)	<0.0001
Gender						
Male	Ref		Ref		Ref	
Female	1.00 (0.98 to 1.01)	0.62	1.00 (0.98 to 1.01)	0.67	0.98 (0.97 to 0.99)	0.003
Race						
White	Ref		Ref		Ref	
Black	0.60 (0.58 to 0.62)	<0.0001	0.61 (0.59 to 0.62)	<0.0001	0.62 (0.60 to 0.64)	<0.0001
Other	0.93 (0.90 to 0.96)	<0.0001	0.94 (0.92 to 0.97)	<0.0001	0.97 (0.94 to 1.00)	0.033
Charlson-Romano Score, per unit change	1.10 (1.09 to 1.10)	<0.0001	NA		NA	
Charlson-Romano Score						
0	NA		Ref		NA	
1			1.54 (1.51 to 1.57)	<0.0001		
≥2			1.75 (1.73 to 1.78)	<0.0001		
Gout	1.44 (1.40 to 1.49)	<0.0001	1.42 (1.38 to 1.46)	<0.0001	1.32 (1.28 to 1.36)	<0.0001

NA, not applicable; Ref, referent category.

Bold represents statistical significance, with a p value <0.05.
 *Model 1 included Charlson-Romano Score as a continuous variable; model 2 replaced it with categorised Charlson-Romano Score and model 3 replaced it with each of the 17 Charlson-Romano comorbidities plus hyperlipidemia, hypertension and coronary artery disease, ie, cardiovascular risk factors. All models were also adjusted for medications for cardiovascular diseases (statins, beta-blockers, diuretics, ACE inhibitors) and for urate-lowering therapies for gout (allopurinol, febuxostat).

Table 3 Association of gout with hearing impairment, in predefined subgroups by race, gender, age and tobacco use disorder

	Multivariable-adjusted model 1		Multivariable-adjusted model 1		Multivariable-adjusted model 1	
	HR (95% CI)	P values	HR (95% CI)	P values	HR (95% CI)	P values
	65–75 years		75–85 years		>85 years	
Gout	1.50 (1.44 to 1.57)	<0.0001	1.39 (1.33 to 1.46)	<0.0001	1.42 (1.30 to 1.54)	<0.0001
	Female		Male			
Gout	1.37 (1.31 to 1.44)	<0.0001	1.50 (1.44 to 1.56)	<0.0001		
	Black		White		Other race	
Gout	1.56 (1.40 to 1.73)	<0.0001	1.43 (1.38 to 1.48)	<0.0001	1.53 (1.36 to 1.73)	<0.0001
	No tobacco use disorder		Tobacco use disorder			
Gout	1.44 (1.40 to 1.49)	<0.0001	1.48 (1.12 to 1.96)	0.006		

Age×gout p value<0.0001.

Sex×gout p value 0.001.

Race×Gout p value 0.05.

Smoking×gout p value 0.93.

HRs that are significant with p value <0.05 are in bold.

testing, the Bonferroni corrected p value would be 0.003 which was higher than the p value reported in our study. This means that even when corrected for multiple testings, the current study findings would still be significant. It is possible that a longer baseline period with no diagnosis would further increase the possibility of not missing the baseline diagnosis of hearing loss; however, this would lead to smaller cohort for observation of incident hearing loss cases and a shorter observation period. Weighing pros and cons, we chose to keep baseline period at 12 months which is standard for Medicare database studies (12–18 months).

Our study strengths were the inclusion of a representative sample of US adults aged 65 years or older, a large sample with an adequate number of events, and the robustness of our study findings.

To our knowledge, this study is among the first to describe an association of gout with hearing loss in older adults. However, other related studies of hyperuricaemia have shown similar findings. In a recent Korean study, a higher serum urate (sUA) was significantly associated with new age-related hearing loss in multivariable-adjusted analyses in adults 40 years or older.²⁵ The previous study examined the association of hyperuricaemia with hearing loss and recruited people during a regular health check-up at a medical centre, as opposed to our study which examined the association of gout with hearing loss, and assessed all Americans aged 65 years or older. While the use of audiometry and the assessment of serum urate is an advantage with the previous study, the inclusion of a large representative study sample and the adjustment for common medication use and medical comorbidities is a strength of our study. Our study results are not directly comparable with those from the previous study, since the risk factors, while somewhat related, are not the same.

A recent case report of conductive hearing loss due to urate deposits in the middle ear likely illustrates the pathogenic role of urate crystals in hearing loss in the

most severe forms of gout.²⁶ Our finding of the 32%–44% increased hazards of hearing loss associated with the diagnosis of gout must be interpreted in the proper clinical context. An early recognition of hearing loss related to the presence of gout may have a meaningful clinical implication. Although the increased risk is not twofold or threefold higher (which is not an uncommon finding in epidemiological studies for a polygenic disease), it seems clinically meaningful. Screening and diagnosis of hearing loss is relatively inexpensive, and the economic impact of hearing loss is large, estimated at US\$750 billion lost each year globally.²⁷ Hearing loss has a significant impact on quality of life, both physical and mental/emotional health, and a higher severity of hearing loss is associated with larger deficits in quality of life⁴; it is also associated with cognitive decline.²⁸ Hearing aids not only improve the hearing, but may also protect against cognitive impairment and disability, improving quality of life of aged people.⁶ With an increasing emphasis on prevention of hearing loss,²⁹ recognition of novel risk factors, such as gout, pave the way for an early diagnosis and potentially preventing more severe hearing loss in an ageing population, and decreasing the overall associated costs and disability.

Gout is a chronic inflammatory arthritis characterised by hyperuricaemia and urate crystal formation which subsequently lead to inflammation^{15 16} and oxidative stress.^{17–21} These processes could be one of the potential explanations of the association. Levels of serum malondialdehyde (MDA), a marker of lipid peroxidation, were significantly higher and antioxidant enzymes, erythrocyte superoxide dismutase (SOD) and erythrocyte catalase levels were lower in patients with gout.¹⁸ Treatment with allopurinol, a xanthine oxidase inhibitor that lowers serum urate, decreased serum MDA and increased erythrocyte SOD and catalase within 3 months of treatment.¹⁸ The use of febuxostat, another xanthine oxidase inhibitor urate-lowering drug, was associated with a reduction in the level

of derivatives of reactive oxygen metabolites.³⁰ Recurrent acute gout attacks are caused by urate-crystal-induced recruitment of leucocytes, activation of the complement system and the NALP3 inflammasome, leading to activation and extracellular release of interleukin (IL)-1 β and IL-18 and downstream effects of inflammation.^{15 31}

Both inflammation and increased oxidative stress are also implicated in the pathogenesis of hearing loss.^{11–14 32} In a mouse model of age-related hearing loss, the cochlear levels of MDA (a lipid peroxidation product) were significantly higher, proinflammatory cytokine (tumor necrosis factor (TNF)- α , IL-1 β) levels were higher¹¹ and mitochondrial DNA damage more frequent, compared with mice resistant to hearing loss.¹¹ In a mouse model of age-related hearing loss with an early decline of the endocochlear potential due to severe mitochondrial and vascular pathologies in the cochlear stria vascularis, pathological alterations in antioxidant and nutrient and energy-sensing pathways (mammalian target of rapamycin (mTOR) and phosphatase and tensin homolog deleted on chromosome 10 (PTEN)/Protein kinase B (AKT)) occurred in the cochleae of young mice before major hearing loss.¹² Treatment with antioxidant corrected pathological molecular changes and endocochlear potential.¹² In a mouse model of age-related decline of hearing, the loss of sensory hair cells, spiral ganglion neurons and/or stria vascularis degeneration in the cochlea were associated with low expression of antioxidants and dysregulated reactive species, and Wnt signaling and mitochondrial molecular transport-regulator gene expressions in the cochlear tissues.¹³ In an animal model of noise-induced hearing loss, systemic administration of the water-soluble coenzyme Q (Co-Q) analogue reduced oxidative-induced cochlear damage, hearing loss and cortical dendritic injury and increased the cochlear levels of Co-Q.¹⁴ Increased oxidative stress and inflammation may trigger cell death pathways in the cochlea.¹¹

In a large cohort study, statistically significant associations between long-term serum C-reactive protein levels and incident hearing impairment were observed in adults aged <60 years.³³ We hypothesise that hyperuricaemia-related inflammation and oxidative stress pathways potentially link gout to the risk of hearing loss in the older adults. These hypotheses need to be tested in future studies which should examine as to which factors contribute to this increased risk and to what extent. Randomised trials of urate-lowering drugs and/or those that reduce oxidative stress independent of urate-lowering are needed to assess their effect on reduction of the risk of hearing loss in older adults.

In conclusion, we found that gout was associated with a higher risk of hearing loss in the elderly, independent of demographic, comorbidities and use of common medications. Future studies should explore whether hyperuricaemia, or inflammation or oxidative stress play a role in this association, and whether treatments that target these pathways can reduce the role of hearing loss in elderly with gout.

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Contributors JAS designed the study, developed study protocol, reviewed analyses and wrote the first draft of the paper. JDC performed the data abstraction and data analyses. All authors made revisions to the manuscript, read and approved the final manuscript.

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Patient consent Not required.

Ethics approval The University of Alabama at Birmingham's Institutional Review Board approved this study, and all investigations were conducted in conformity with ethical principles of research.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement These data can be obtained from the Centers for Medicare and Medicaid Services (CMS) Chronic Condition Data Warehouse. Data requests can be made to the following email address: (datauseagreement@cms.hhs.gov). The DUA agreement with CMS does not allow us to share these data due to the inclusion of PHI and PII data and the rules of use of Medicare data. We are ready to share the data with colleagues, after obtaining appropriate permissions from CMS Chronic Condition Data Warehouse and the University of Alabama at Birmingham Ethics Committee, related to HIPAA and Privacy policies. Additional information about these data can be found at <https://www.resdac.org/resconnect/articles/148>

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