Ther Adv Musculoskel Dis
2021, Vol. 13: 1–9
DOI: 10.1177/1759720X20973916

Epidemiology of cardiac or orthopedic procedures in gout *versus* rheumatoid arthritis: a national time-trends study

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Abstract

Aims: To examine the secular trends in the number and rates of in-hospital cardiac and orthopedic procedures in people with gout and rheumatoid arthritis (RA), and the United States (US) general population, from 1998 to 2014.

Methods: We examined the frequency of seven common cardiac and orthopedic procedures in hospitalized people with gout, RA, or the general population using the 1998–2014 US National Inpatient Sample (NIS). Poisson regression evaluated the differences in frequencies in 1998 *versus* 2014, between gout and RA, and within each cohort.

Results: Both in-hospital cardiac and orthopedic procedures increased in gout and RA with time, in contrast with declining cardiac procedures in the general US population. Cardiac procedures were significantly higher in gout *versus* RA in 1998 (59% higher) and 2014 (92% higher). The rate of cardiac procedures increased from 36.6 to 82.8 in gout and from 20.1 to 33.1 in RA per 100,000 NIS claims from 1998 to 2014. Orthopedic procedures became more common than cardiac procedures in gout and RA by 2014. In RA, the cardiac–orthopedic procedure volume difference was significant in 1998 and 2014. We noted no significant difference between cardiac *versus* orthopedic procedures in 1998 in gout, but the difference was significant in 2014. Orthopedic procedures in gout were significantly lower than RA in 1998 (33% lower), but were significantly higher than RA in 2014 (5% higher).

Conclusion: Increasing in-hospital cardiac procedures in gout and RA contrasting with declining general US population rates indicated that optimal management of systemic inflammation and an early diagnosis of gout and RA are needed. The rate of increase in orthopedic procedures exceeded that in cardiac procedures. A much greater volume and rate of increase in common in-hospital cardiac and orthopedic procedures in gout compared to RA indicates that an aggressive approach to treat-to-target in gout is needed to potentially reduce the associated healthcare burden and cost.

Keywords: arthroplasty, burden, cardiac procedure, gout, healthcare utilization, orthopedic procedure, outcomes, resource utilization, rheumatoid arthritis, time-trends study

Received: 29 June 2020; revised manuscript accepted: 26 October 2020.

Plain language summary

Cardiac and orthopedic procedures rising faster for gout compared to rheumatoid arthritis in the United States

We performed a national US study of the most common cardiac versus orthopedic procedures from 1998 to 2014. We found that over time, the number and the rate of cardiac procedures increased in people with gout (2.2-fold higher) or rheumatoid arthritis (1.6-fold higher). This

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was surprising, since during the same time, we noted a decrease in cardiac procedures in the general U.S. population. The rate of cardiac procedures in gout was 2.5-fold higher than that in rheumatoid arthritis, 82.8 vs. 33.1 per 100,000 NIS claims in 2014. Interestingly, orthopedic procedures were more common than cardiac procedures in both gout and RA in all periods. Also, the difference in the numbers of cardiac vs. orthopedic procedures increased over time in both gout and RA. Gout outpaced rheumatoid arthritis for both the total number and the rate of cardiac or orthopedic procedures over time. Therefore, our study provides an understanding of an increasing procedure burden in gout compared to rheumatoid arthritis, and to the general U.S. people with these conditions.

Introduction

Cardiac and orthopedic procedures are the commonest procedures performed in aging Americans, accounting for three of the top six procedures for any hospitalization in the United States (US) in 2014.[1] In 2014, 10.1 million inpatient hospital stays in the US involved 14.2 million procedures, with aggregate hospital costs of US $187.1 billion.[1] The orthopedic procedures are among the fastest growing procedures in the US.[1]

Gout and rheumatoid arthritis (RA) are the first and the second most common inflammatory arthritis in adults. Hospitalization rate for gout has been increasing in the recent years, with a reduction in people with RA, and, as a result, gout hospitalizations have surpassed RA hospitalizations.[2] Systemic inflammation in inflammatory arthritis is associated with accelerated atherosclerosis and high cardiovascular disease rates.[3,4] Elective orthopedic procedures, including total joint replacement, are common in RA and gout due to associated joint involvement. Optimal treatment and treat-to-target strategies implemented in RA treatment can reduce systemic inflammation and potentially improve its downstream effects[5]; a similar impact on gout outcomes is also possible with a treat-to-target strategy.[6] The excess cardiovascular disease risk in RA is similar to that in diabetes.[7] This led to the development of a European League Against Rheumatism (EULAR) guideline for cardiovascular risk mitigation in RA in 2009,[8] updated in 2015/2016.[9] Thus, cardiovascular morbidity with RA is well established and well studied. On the other hand, there is evidence both for and against the independent association of gout and hyperuricemia with cardiovascular disease risk.[10]

To our knowledge, there are no studies of time-trends in US national estimates of cardiac *versus* orthopedic procedures in people with gout compared with people with RA. Our study objective was to compare time-trends in cardiac and orthopedic procedures in people with gout *versus* RA, in reference to the general population. A better knowledge of time-trends of cardiac and orthopedic procedures in gout compared with RA can inform resource allocation. We hypothesized that (1) RA would be associated with higher in-hospital annual volume and rates of both procedures at the beginning and the end of our study period, but that the gout-RA gap will narrow over time; (2) the increase in annual volume of in-hospital orthopedic procedures will be higher than cardiac procedures in both gout and RA; and (3) the increase in annual volumes of in-hospital orthopedic and cardiac procedures in gout or RA will outpace that in the general US population.

Methods

The data for this analysis comes from the 1998 to 2014 US Nationwide Inpatient Sample (NIS). We chose 2014 as the last study year, since the coding system changed from International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) codes in 2014 to ICD-10-CM codes in 2015. The NIS represents a 20% stratified sample of all hospital discharges for the United States. The universe of US community hospitals is divided into strata using five hospital characteristics: ownership/control, bed size, teaching status, urban/rural location, and the nine US census divisions (the four census regions were used prior to the 2012 NIS).[11] Starting in 2012, a systematic sampling design was used to construct the NIS database with a stratified sample of discharges that was drawn from all hospitals in the hospital frame.[11] Prior to 2012, the NIS was a stratified probability sample of hospitals in the frame (included all hospitals in the state inpatient database), with sampling probabilities proportional to the number of US community hospitals in each stratum.[11] The NIS contains data from >7 million hospital stays each year (unweighted) and estimates >35 million

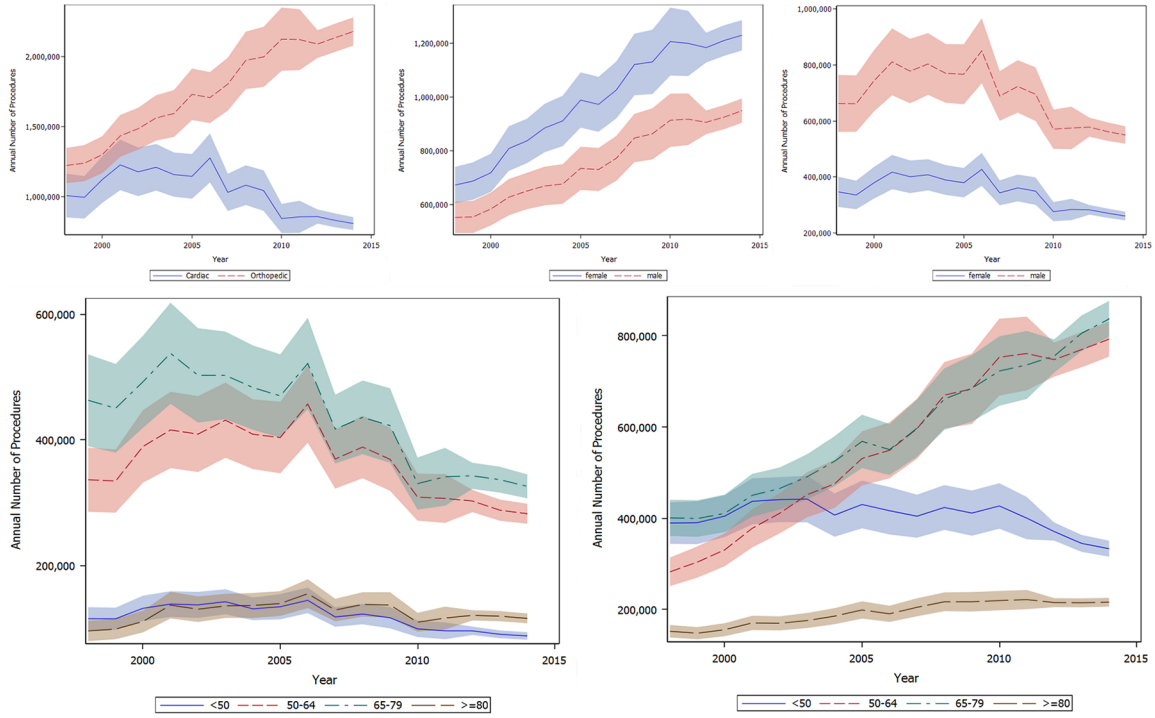

Figure 1. Time-trends in the number of in-hospital cardiac and orthopedic procedures annually in the US general population during the study period 1998–2014 showing the overall trend (A), orthopedic procedures by sex (B), cardiac procedures by sex (C), cardiac procedures by age groups (D), and orthopedic procedures by age groups (E). The *x*-axes represent the study year and *y*-axes show the number of annual procedures. Estimates over time are shown with the line, and the shaded area represents the upper and thw lower 95% CI. The *y*-axis scales differ between panels.
CI, confidence interval; US, United States.

hospitalizations nationally (weighted). The NIS is drawn from all States participating in Healthcare Cost and Utilization Project (HCUP), covering more than 97% of the US population.

Procedure codes (in any position) based upon Clinical Classification Software (CCS) designations as provided by the Agency for Healthcare Research and Quality (AHRQ) were assessed. We identified the most common 4 orthopedic procedures and 3 cardiac procedures among the top 15 procedures in 2012 in the US,[1] or the top 10 procedures with the greatest increase in rate in the US in 2003–2012.[1] All the included orthopedic and cardiac procedures are also expensive to the healthcare system. We used procedure codes to identify these procedures – a validated approach[12,13]: percutaneous coronary angioplasty (PTCA; procedure code 45), coronary artery bypass graft (CABG; procedure code 44), heart valve procedures (procedure code 43), knee joint replacement (procedure code 152), total and partial hip joint replacement (procedure code 153), spinal fusion (procedure code 158), and laminectomy/excision of intervertebral disc (procedure code 3). We identified gout by the presence of ICD-9-CM code, 274.xx and RA by ICD-9-CM code 714.xx,[14,15] in any diagnosis position [primary or non-primary (secondary)] – a validated approach. When multiple occurrences of a procedure occurred in the same discharge, such as two procedure codes for knee arthroplasty, only the first was counted. However, if a cardiac and orthopedic procedure happened to be in the same discharge, one of each were counted.

We compared the annual estimates for in-hospital cardiac and orthopedic procedures over the study period for the general population, overall and by sex and age. We compared them in people with gout and RA. We calculated the 95% confidence intervals (CI) for the annual in-hospital procedures for each year. Poisson regression was used to evaluate differences in frequencies of in-hospital cardiac or orthopedic procedures between gout and RA, and, within each cohort,[16] comparing the counts in 1998–2014. We also compared the respective procedure rates per 100,000 hospitalizations in various subgroups and over time.

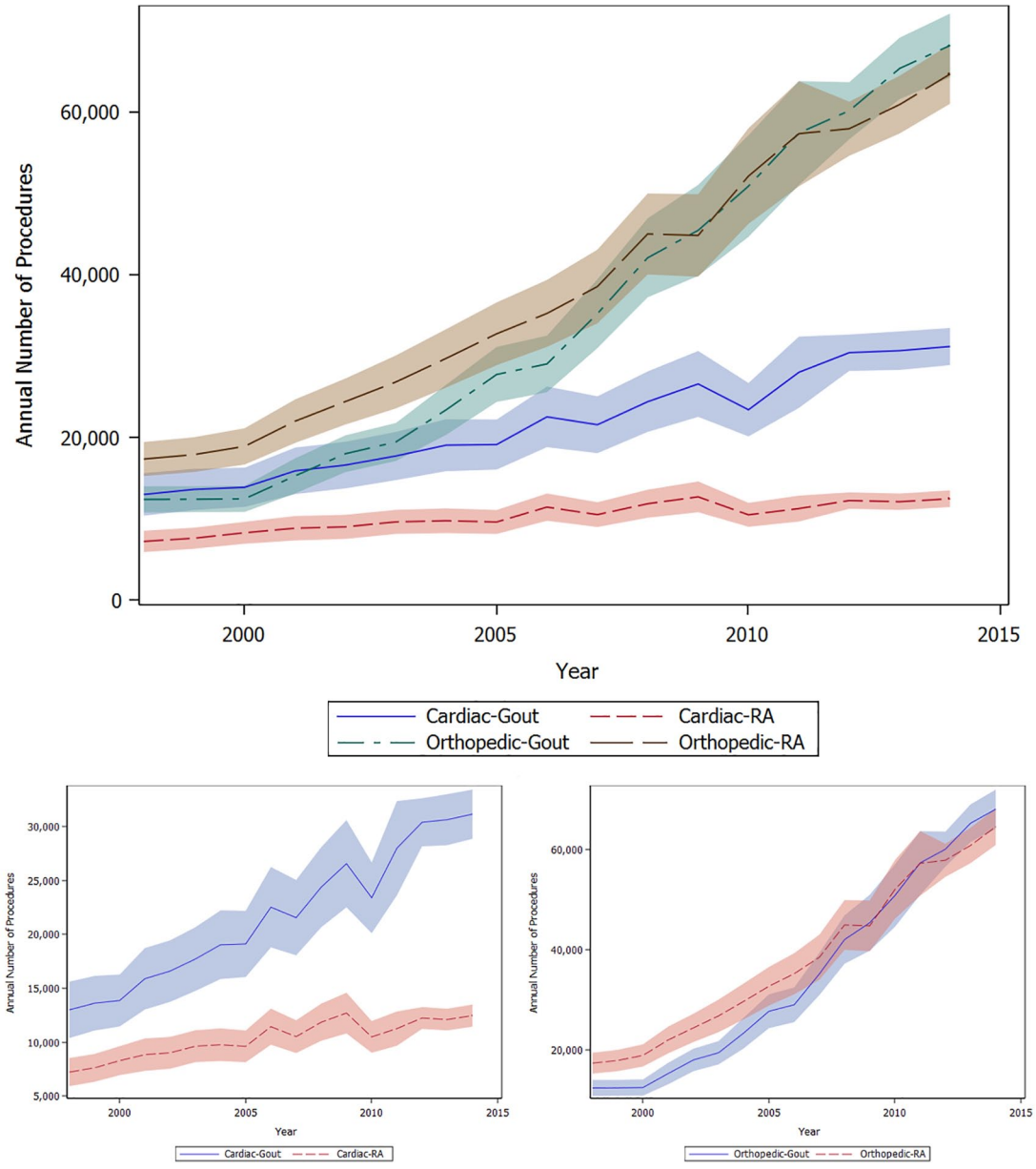

Figure 2. Time-trends in the number of in-hospital cardiac and orthopedic procedures annually from 1998 to 2014 in people with gout or RA during the study period showing the overall trends. The *x*-axes represent the study year and *y*-axes show the number of annual procedures. Estimates over time are shown with the line and the shaded area represents the upper and the lower 95% CI. The *y*-axes scales differ between panels b and c.
CI, confidence interval; RA, rheumatoid arthritis.

Results

Overall in-hospital cardiac versus *orthopedic procedure time-trends in the general US population*

The annual volume and rate per 100,000 NIS claims for in-hospital cardiac procedure decreased and orthopedic procedure increased from 1998 to 2014, with an accelerating divergence since 2003 (Figure 1a; Appendix 1). The total NIS claims were 33.9 million in 1998 and 35.3 million in 2014, that is, relatively stable over time (Appendix 1), which indicated that the time-trends in annual procedure volumes would be consistent with time-trends in rates per 100,000 NIS claims over time. Men accounted for the majority of in-hospital cardiac procedures, while women accounted for the majority of overall orthopedic procedures (Figure 1b–c). The majority of cardiac or orthopedic

procedures were performed in people 50–79 years old (Figure 1d–e; green and salmon colors). The rate of cardiac procedures per 100,000 NIS claims decreased from 2977 in 1998 to 2292 in 2014; the rate of orthopedic procedures increased from 3609 in 1998 to 6160 in 2014 (Appendix 1).

Gout versus *RA: time-trends in cardiac* versus *orthopedic procedures*

In-hospital cardiac versus orthopedic procedure volume over time. Both in-hospital cardiac and orthopedic procedures increased in gout and RA over time; orthopedic procedures were more common in both. In RA, the difference between the number of in-hospital cardiac and orthopedic procedures was significant in 1998 and 2014 (Figure 2). In people with gout, there was no significant difference in the numbers of in-hospital cardiac *versus* in-hospital orthopedic procedures in 1998, but there was a significant difference in 2014 (Figure 2).

In-hospital procedures in gout versus *RA.* The in-hospital cardiac procedures were significantly higher in gout *versus* RA for in both 1998 (59% higher) and 2014 (92% higher) (Figure 2), and the gout-RA gap increased significantly from 1998 to 2014. In-hospital orthopedic procedures in gout were slightly lower than RA in 1998 (33% lower), caught up with those of RA in 2005, and were higher than RA in 2014 (5% higher; Figure 2); none of the differences were statistically significant.

Total hospitalizations and increase in procedure rates in gout versus *RA.* The total number of all gout and RA hospitalizations (regardless of procedures) increased from 1998 to 2014 (Appendix 2). The rate of all gout and RA hospitalizations per 100,000 NIS claims increased 3.3-fold for gout and 2.0-fold for RA (Appendix 3; primary or secondary diagnosis). The corresponding increase in the in-hospital annual cardiac and orthopedic procedure rates per 100,000 NIS claims in two populations from 1998 to 2014 and the respective annual rates in 1998 and 2014 were as follows: (1) gout, 2.3-fold for cardiac (1998, 36.6 to 2014, 82.8) and 5.1-fold for orthopedic (34.2 to 174.6); and (2) RA, 1.6-fold for cardiac (20.1 to 33.1) and 2.4-fold for orthopedic (70.2 to 170.8), respectively (Appendix 3; primary or secondary diagnosis).

Proportion of total hospitalizations in gout versus *RA that were cardiac* versus *orthopedic procedures.* Of all hospitalizations with cardiac/orthopedic procedures, the proportion of people with each as primary or secondary diagnosis increased from 1998 to 2014: (1) in-hospital cardiac procedures: 1.2–3.6% with gout; 0.7–1.4% with RA; and (2) in-hospital orthopedic procedures: 0.9–2.8% with gout; 1.9–2.8% with RA (Appendix 4). The mean age increased minimally from 1998 to 2014: (1) in-hospital cardiac procedures: gout, 66.7–68.9 years; RA, 66.4–68.1 years; (2) in-hospital orthopedic procedures: gout, 68.8–67.8 years; RA, 64.5–65.1 years (Appendix 5).

Discussion

Our study is among the first to compare the national time-trends in these procedures for gout *versus* RA, and to compare time-trends in these diseases to that of the general US population, using a national representative database. Arthritis and musculoskeletal diseases are the most common reasons for disability in Americans,[17] making this an important study question.

In contrast to declining absolute numbers of in-hospital cardiac procedures nationally in the US from 1998 to 2014, we found increasing numbers of in-hospital cardiac procedures in both gout and RA. Chronic systemic inflammation, oxidative stress, and increased prevalence of traditional coronary artery disease (CAD) risk factors are shared by both gout and RA,[3,4] which likely contributed to worsening cardiac morbidity in these conditions, while it improved in the general population. This procedure increase in gout over the 17-year study period may be partially attributable to an increasing prevalence of gout in the US,[18] a high medical comorbidity load in people with gout,[19] and/or a 2- to 3-fold increase in the burden of several medical comorbidities (diabetes, renal disease, hyperlipidemia, morbid obesity) in people with gout over time.[20] A lower threshold for the diagnosis of cardiovascular disease in people with gout or RA due to increased awareness over time may have also contributed. Since 2009, more diagnoses codes were also allowed in the NIS, that is, up to 15 codes could be listed before 2009 and up to 25 afterwards. If surgeons were more likely to record gout or RA after 2009, this may be partially responsible for the increase noted after 2009; however, all trends we noted were already evident prior to 2009, so this is unlikely to account for a substantial variability in time-trends. This contrast in in-hospital cardiac procedures rates between general population *versus* gout and RA calls for the development and implementation of preventive and treatment programs for cardiovascular disease in

gout and RA. The US population increased from 276.1 million in 1998 to 320.1 million in 2014 according to the US census bureau,[21,22] that is, 16% over a 17-year period. This population increase does not explain an almost doubling of orthopedic procedures or 20% reduction in cardiac procedures.

While the reasons cited above might explain the increase in cardiac procedures in gout or RA *versus* the general population, they cannot explain the time-trend procedure volume differences between gout and RA. Gout was associated with a higher number of cardiac procedures than RA in 1998 and 2014. We also found a sustained significant separation between gout and RA during the entire study period, and a significant increase in the gout-RA cardiac procedure difference over time. We were surprised that the annual volume of cardiac procedures in gout exceeded those in RA, both in 1998 and 2014, despite a much greater recognition of increased cardiovascular disease risk in RA compared with gout.[7–9,23,24] This was contrary to our main hypothesis. Rates of cardiac procedures per 100,000 NIS claims increased 2.3-fold for gout (36.6–82.8) *versus* 1.6-fold for RA (20.1–33.1) from 1998 to 2014, supporting one of our hypotheses. A supportive finding was an observation of an increasing proportion of people within all in-hospital cardiac procedures over the study period that had a diagnosis of gout or RA, although this should be interpreted with caution due to the lack of concurrent population-based data on disease incidence/prevalence in the US in the same period. In a similar period of 1994–2007, the incidence of RA increased by 2.5% per year from 1995 to 2007 in women but not in men, and age- and sex-adjusted prevalence increased from 0.62% in 1995 to 0.72% in 2005[25]; the incidence of gout doubled from 66.6/100,000 in 1989–1992 to 136.7/100,000 general population in 2009–2010.[20]

A more rapid increase in the prevalence of gout *versus* RA in the general US population,[18,26] and a greater increase in all gout *versus* all RA hospitalizations in our study (3.3-fold for gout and 2.0-fold for RA from 1998 to 2014) may have contributed partially to these trends. Despite chronic systemic inflammation in both gout and RA, other specific mechanisms increasing CAD risk might differ between gout and RA.[3,4] Significant advances in discovery of new therapeutics for RA and the implementation of a treat-to-target approach in RA contrast with poor management of gout, might partially explain increasing differences in cardiac procedures between gout and RA over time.[5,6,27] These time-trends in cardiac and orthopedic procedures might partially explain the previously described differences in the overall hospitalization rates between gout and RA,[2] since hospitalizations with procedures accounted for almost half of all hospitalizations.[1]

Another interesting finding was that orthopedic procedures in people with gout were significantly lower than RA in 1998 by 33%, but surpassed those in RA in 2014 by 5%. Our study puts gout as the number one concomitant inflammatory arthritis condition ahead of RA in people undergoing orthopedic procedures – a novel finding. Most of these orthopedic procedures are mostly elective. Our findings have potential implications for future healthcare resources allocation by policy makers. Reasons may be similar to those postulated for gap in cardiac procedures. A contributor to higher rates of orthopedic procedure might be the overall increasing surgery volume for these procedures in the general US population,[28] as confirmed in our study as well. This would explain increasing rates in both gout and RA, but not the narrowing of the difference between gout and RA. The allowance for listing 25 diagnoses since 2009 compared with 15 prior to 2009 might also partially explain increasing rates of gout diagnosis.

The 3.3-fold increase in all gout hospitalizations in the US from 1998 to 2014 in our study extends the previous findings of an increase in all gout hospitalizations over time, including a 2-fold increase in the US from 1994 to 2011 and a 2-fold increase in Canada from 2000 to 2011.[2,29]

Study limitations were that NIS counts discharges, not people, therefore all analyses have hospitalization as the unit of measure. Longitudinal studies (readmission; longer-term outcomes) are not possible given the nature of the data. Simultaneous bilateral arthroplasties (<3% knee and <1% hip arthroplasties), though a very small proportion, are coded with a single procedure code, and therefore can not be distinguished from unilateral procedures. NIS does not include military or Veterans Affairs hospitals. We limited the data to 2014 to avoid secular trends in procedure coding due to the transition from ICD-9-CM/procedure coding system (PCS) to ICD-10-CM/PCS codes in October 2015; 1998 was chosen as the first study year due to addition of new/change of variables that were consistent after this year.[30] Study strengths include our use of a generalizable

sample, and a large sample size, which leads to robust estimates. NIS does not allow longitudinal data analyses. Therefore, the risk of revision hip or knee arthroplasty cannot be assessed, neither was this our study focus.

In conclusion, in contrast to a decreasing in-hospital cardiac procedure frequency in the general population, it continued to increase in people with gout and RA from 1998 to 2014. Rates of cardiac and orthopedic procedures per 100,000 NIS hospitalizations increased in both gout and RA, and the relative increase was more in gout compared with RA. Our study substantiates the comparative burden of the most common and expensive in-hospital cardiac and orthopedic procedures in the United States in people with gout compared with RA, two of the most common rheumatic diseases, with higher burden in gout for both procedures in 2014. The widening gap in cardiac procedures between gout and RA and crossing over for orthopedic procedures over time indicates that optimal treatment and treat-to-target implemented in RA treatment may need to be implemented in gout to improve disease outcomes and associated morbidity and resource burden.[5,6]

Author contributions

Jasvinder A. Singh designed the study, developed the study protocol, reviewed analyses and wrote the first draft of the paper. John D. Cleveland performed the data abstraction and data analyses. Both authors revised the manuscript, read, and approved the final manuscript.

Conflict of interest statement

There are no financial conflicts related directly to this study. JAS has received consultant fees from Crealta/Horizon, Medisys, Fidia, UBM LLC, Trio health, Medscape, WebMD, Clinical Care options, Clearview Healthcare Partners, Putnam Associates, Focus Forward, Navigant Consulting, Spherix, Practice Point Communications, the National Institutes of Health and the American College of Rheumatology. JAS owns stock options in Vaxart Pharmaceuticals and Charlotte's Web Holdings, Inc. JAS previously owned stock options in Amarin, Viking, and Moderna pharmaceuticals. JAS is on the speaker's bureau of Simply Speaking. JAS is a member of the executive of Outcomes Measures in Rheumatology (OMERACT), an organization that develops outcome measures in rheumatology and receives arms-length funding from 12 companies. JAS serves on the FDA Arthritis Advisory Committee. JAS is the chair of the Veterans Affairs Rheumatology Field Advisory Committee. JAS is the editor and the Director of the University of Alabama at Birmingham (UAB) Cochrane Musculoskeletal Group Satellite Center on Network Meta-analysis. JAS previously served as a member of the following committees: member, the American College of Rheumatology's (ACR) Annual Meeting Planning Committee (AMPC) and Quality of Care Committees, the Chair of the ACR Meet-the-Professor, Workshop and Study Group Subcommittee and the co-chair of the ACR Criteria and Response Criteria subcommittee. JDC has no conflicts. There are no non-financial competing interests for either author.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This material is the result of work supported by research funds from the Division of Rheumatology at the University of Alabama at Birmingham and the resources and use of facilities at the Birmingham VA Medical Center, Birmingham, Alabama, USA. The funding body did not play any role in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

Availability of data and materials

These data are easily available from the Agency for Healthcare Research and Quality (AHRQ's) "Healthcare Cost and Utilization Project (HCUP)" and can be obtained after completing an on-line Data Use Agreement training session and signing a Data Use Agreement. The contact information for requesting the data is as follows:
HCUP Central Distributor
Phone: (866) 556-4287 (toll-free)
Fax: (866) 792-5313
E-mail: HCUPDistributor@ahrq.gov

Ethics/IRB approval and consent to participate

The University of Alabama at Birmingham's Institutional Review Board (IRB) approved this study and all investigations were conducted in conformity with ethical principles of research (UAB X120207004). The IRB waived the need for an informed consent for this database study.

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Supplemental material

Supplemental material for this article is available online.

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