PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Gouty arthritis, systolic dysfunction and heart Failure: results from a 30-year prospective cohort Study
AUTHORS	Krishnan Eswar

VERSION 1 - REVIEW

REVIEWER	Mara McAdams DeMarco Johns Hopkins No conflict of interest
REVIEW RETURNED	17/08/2011

THE STUDY	Overall, this is an important and interesting research question. However, I have concerns about the analysis and presentation of the research findings. This paper could benefit from the inclusion of a statistician or epidemiologist. 1) The paper could be written more clearly. For example, the structure of the introduction, methods, results and conclusions make it difficult to follow. Additionally, it would help to present the findings with consistent number of significant digits and report what the ranges are in the results (I assume they are 95% CI, but it is unclear). Finally, the methods are partially described in the results and the results in the methods. 2) The authors should comment on the representativeness of the public access FOS cohort. Additionally, they should comment on the representativeness of the participants who attended the sixth visit. Specifically, how did they differ from the baseline cohort? 3) The methods section would be strengthened by explaining the timing of the data collection. Specifically, how was heart failure identified from the medical chart review. Importantly, it is unclear when and how often heart failure was collected. This is important for the determination of incident heart failure. 4) Similarly, how often was gout measured in the cohort and prescription drug use collected? It is important to describe the data collection and provide more information on the timing of gout onset with respect to baseline and heart failure. What % of those classified as having gout were identified by the clinical determination, the prescription drug use and by both. Justification of this gout classification should be provided as it is not consistent with the definition used in previous studies of gout in the Framingham cohort (Bhole, 2009). Additionally, if allopurinol is associated with a decreased risk of heart failure, why combine treated and untreated gout? 5) The number of gout cases should be specifically mentioned in the

	Results section. Furthermore, the study population with gout in Table 1 (n=228) is not the same as Table 5 (n=229). 6) It is unclear why certain covariates were entered into the models. Were they confounders? If so, how was this determined? Additionally, it is unclear how the covariates were entered into the Cox model: time-varying or time-fixed? What was the justification of this decision? 7) The statistical analysis section of the methods lists that the author used “a cohort analysis.” This is not standard epidemiology terminology and should read survival analysis. Additionally, the author did not perform longitudinal analysis and this phrase should not be included in the methods. 8) The Cox model should include gout as a time-varying absorbent state. Starting follow-up at the time of gout onset may lead to bias as those with gout are older and thus more likely to develop heart failure. It is unclear whether the increased HR is an artifact or this bias or a true result. Finally, the time scale should be age to better control for confounding by age. 9) For the cross sectional analysis, it is unclear whether gout was defined prior to visit 6. For this analysis, why was a generalized linear model used for continuous outcomes rather than a linear model? 10) The subgroup analyses in Table 2 was not described in the methods. This subgroup analysis would be strengthened by showing whether there is effect modification of these chronic conditions by gout. 11) In Table 4, why list the statistical method and Beta coefficients in the table? These should be interpreted for the reader. Additionally, the models should be limited to a standard population with all the available echocardiographic measures. This will allow for comparison of associations across measures. 12) Was atherosclerosis considered as a potential link (confounder) of gout and heart failure? The introduction makes a compelling argument of atherosclerosis as a shared risk factor but there is no mention of this in the methods or results. 13) What is the role of diuretics in the association of gout and heart failure? Was the role of diuretics evaluated? 14) Why focus on all cause mortality and not CVD specific mortality? 15) This paper could be strengthened by including serum urate level in the analysis. I am not convinced that the observed association of gout and heart failure is not due to serum urate as a shared risk factor. This is the argument that is made in the discussion yet not tested in the paper. If serum urate level was not available, this should be listed in the limitations. Minor points: 1) Table 1 describes the cohort characteristics by gout status and not the full cohort.

	2) What is the time scale for the N-A plot? 3) In Table 1, the prevalence of ever and current % smokers is similar. This seems surprising.
RESULTS & CONCLUSIONS	The author was unclear about CONSORT items: 7,8,9,12B,12C,16 and 21. These issues are discussed in detail above

REVIEWER	Dr Karen Douglas Consultant Rheumatologist Dudley Group NHS FT Dudley West Midlands UK
REVIEW RETURNED	20/09/2011

THE STUDY	This is an important research question that requires further clarification. A long term large prospective population study, such as the FOS is warranted to answer this question. The definition of Gout I suspect will have underestimated the number of cases of gout, which the authors acknowlegde may introduce a type 2 error. The echocardiographic data from visit 6 would have been around 1995 and hence at least a decade prior to the final follow-up. It would ahve strenghtened the study greatly if echo data were available for end of folllow-up. It would also be interesting to compare the echo findings of those particpants who later developed gout, ie did echo abnormalities precede the diagnosis? In the measurements of covariates there are some contradictions that require clarification, such as it is intially stated the information on renal dysfunction, and medication were collected but then prpodeds to state that renal laboratory measurements and medication details were not available. Please clarify and define renal dysfunction
RESULTS & CONCLUSIONS	Though the results are by and large clear and credible I am concerned by the small numbers of participants who developed both heart failure and gout and would question if this compromises the statistical validity on this aspect which is such an important outcome. I would welcome independant advise from a stastician on this. One point of view that has been raised previously in the literature that has not been addressed here is that though gout appears to associate with CVD this does not necessarily imply its causality which may purely be a confounder for other mechanisms.

REVIEWER	Dietrich Rothenbacher Director Institut of Epidemiology and Medical Biometry Ulm University Ulm
REVIEW RETURNED	11/10/2011

REPORTING & ETHICS	Eswar Krishnan reports the association of gout with left ventricular function and heart failure in part of the Framingham Offspring Study (FOS). In addition he also analyzed the association of gout with all-cause mortality. During a median follow-up time of 15.9 years 201 incident cases of heart failure were recorded in the n=4989 subjects with a mean age of 36 years at baseline. N=228 subjects had a

	study-physician diagnosis of gout at baseline. The investigator found an independent increase of the risk of gout for heart failure with an overall HR of 1.76 (95% CI 1.04-2.95). In addition, in the cross-sectional part of the study all measures associated with heart failure were related to the absence or presence of gout. Specific comments: 1) The statistical section should describe by which criteria the models were constructed and how the variables included in the models were coded (it is unclear whether they had been included in categories, continuously, etc.) 2) At the beginning of the results section a flow diagram should be used to demonstrate the number and flow of the patients and indicate when the measurements had been taken included in this report. 3) For figure 1 a p-value should be provided that quantifies the difference among the curves 4) The characteristics in table one should be better characterized, e.g. it is unclear what “diuretic users” means, is this self-report at baseline, within 30 days at baseline etc.). Please specify. 5) Also the characteristics “renal dysfunction”, “diabetes” etc. should be labeled clearer. Is it self-reported history? 6) The added value of table 2 is not obvious to me - numbers of the various subgroups are not included and it is difficult to compare the HR of gout for incident heart failure directly as the numbers are unknown. Another way to address the question would be the formal investigation of effect modification of the various disease entities, but limited power may be a factor. 7) Table 3: is there any measure adjusted for age (and evtl. gender)? I would recommend a minimum adjustment as age is clearly different in the groups as can be seen in table 1. The table 3 is also wrongly referenced in the results section (see page 13 line 17). 8) Table 4: numbers should be added to table. A minimum adjustment for age for GLM results should be done.

VERSION 1 – AUTHOR RESPONSE

Dear Editors and Reviewers,

Thank you for carefully reading and providing excellent critique. The manuscript has been revised thoroughly. The following provides point by point response to comments. Additionally we are uploading a tracked version for your review.

There were a couple of suggestions that we had to (most respectfully) disagree. However we are receptive to edification of the reviewers think we are wrong. In such cases please provide methodological citations.

REVIEWER 1

1) The paper could be written more clearly. For example, the structure of the introduction, methods, results and conclusions make it difficult to follow. Additionally, it would help to present the findings with consistent number of significant digits and report what the ranges are in the results (I assume they are 95% CI, but it is unclear). Finally, the methods are partially described in the results and the results in the methods.

• Thank you for these comments- We have revised accordingly

2) The authors should comment on the representativeness of the public access FOS cohort.

Additionally, they should comment on the representativeness of the participants who attended the sixth visit. Specifically, how did they differ from the baseline cohort?

• Small number (n=135, ~2%) were excluded because of identifiablility/ data sharing consent unavailability. We cannot compare them with the rest as such data were not provided to us. The data comparing participants at baseline and at visit 6 have been provided (Table 2)

3) The methods section would be strengthened by explaining the timing of the data collection. Specifically, how was heart failure identified from the medical chart review. Importantly, it is unclear when and how often heart failure was collected. This is important for the determination of incident heart failure.

• Done. Please also see Table 1 for heart failure definitions.

4) Similarly, how often was gout measured in the cohort and prescription drug use collected? It is important to describe the data collection and provide more information on the timing of gout onset with respect to baseline and heart failure. What % of those classified as having gout were identified by the clinical determination, the prescription drug use and by both. Justification of this gout classification should be provided as it is not consistent with the definition used in previous studies of gout in the Framingham cohort (Bhole, 2009). Additionally, if allopurinol is associated with a decreased risk of heart failure, why combine treated and untreated gout?

• Gout was assessed at all except visit 1. Gout medication information was available from Visit 3 onwards. The definition that you are describing is for the Framingham Heart study not Framingham Offspring study (presented here). The methods are likely to identical as the research staff and protocols were based on the same group but we cannot say as such in the manuscript as the data documentation available to us does not explicitly say so.

5) The number of gout cases should be specifically mentioned in the Results section. Furthermore, the study population with gout in Table 1 (n=228) is not the same as Table 5 (n=229).

• Done

6) It is unclear why certain covariates were entered into the models. Were they confounders? If so, how was this determined? Additionally, it is unclear how the covariates were entered into the Cox model: time-varying or time-fixed? What was the justification of this decision?

• Covariate were chosen based on our prior knowledge of risk factors (AHA position statement). Bivariate analysis results are provided in response to reviewer #3. These covariates were retained in the mode regardless of the strength of independent contributions to the model fit or individual statistical significance.

7) The statistical analysis section of the methods lists that the author used “a cohort analysis.” This is not standard epidemiology terminology and should read survival analysis. Additionally, the author did not perform longitudinal analysis and this phrase should not be included in the methods.

• The reviewer is confused/misinformed on both the counts. The term cohort analyses is well established in the literature- I welcome her to search Pubmed for this term and to discover the thousands of manuscripts including those from the BMJ and the PLoS journals.

• Our study has longitudinal analysis of incidence of heart failure.

8) The Cox model should include gout as a time-varying absorbent state. Starting follow-up at the time of gout onset may lead to bias as those with gout are older and thus more likely to develop heart failure. It is unclear whether the increased HR is an artifact or this bias or a true result. Finally, the time scale should be age to better control for confounding by age.

• I am uncertain what the reviewer means by " time-varying absorbent state", but to clarify, we used only time varying covariates in our Cox models (for time variable measures). If this is not what was intended please provide us a citation so that we can evaluate and if appropriate use such methods.
• We disagree with the suggestion to use age as a time variable in the regressions but have used age as a covariate. The cross-sectional correlation between age and time to event was 0.31 for those who met our study definition of heart failure. If the reviewer disagrees, please provide us methodological citation that justifies her position.
9) For the cross sectional analysis, it is unclear whether gout was defined prior to visit 6.

• Yes

For this analysis, why was a generalized linear model used for continuous outcomes rather than a linear model?
• We have removed the said analyses and have presented adjusted means and proportions
10) The subgroup analyses in Table 2 was not described in the methods. This subgroup analysis would be strengthened by showing whether there is effect modification of these chronic conditions by gout.
• Table 2 was presented to emphasize consistency. There were no statistically intereactions and we have removed the Table -per methodological reviewer's suggestions

11) In Table 4, why list the statistical method and Beta coefficients in the table? These should be interpreted for the reader. Additionally, the models should be limited to a standard population with all the available echocardiographic measures. This will allow for comparison of associations across measures.

• This Table has been removed
12) Was atherosclerosis considered as a potential link (confounder) of gout and heart failure? The introduction makes a compelling argument of atherosclerosis as a shared risk factor but there is no mention of this in the methods or results.
• The reviewer may be right or perhaps wrong in her speculation. Please provide literature that establishes atherosclerosis as a risk factor for gout. We are not aware of any such recent data. Regardless, our data does not permit assessment of causal pathways.
13) What is the role of diuretics in the association of gout and heart failure? Was the role of diuretics evaluated?

• We cannot assess this as the use of diuretics is intertwined with presence of hypertension, hyperuricemia and to a lesser extent renal dysfunction. Our models lose power once you start using nesting or two stage regressions. However the idea is great and we hope to test that possibility
•
14) Why focus on all cause mortality and not CVD specific mortality?
All participants had heart failure- the n's were too small to make meaningful conclusions about individual causes of death

15) This paper could be strengthened by including serum urate level in the analysis. I am not convinced that the observed association of gout and heart failure is not due to serum urate as a shared risk factor. This is the argument that is made in the discussion yet not tested in the paper. If serum urate level was not available, this should be listed in the limitations.
• Serum urate was available only in the first 2 visits. This has been addressed in the limitations section

Minor points:

1) Table 1 describes the cohort characteristics by gout status and not the full cohort.

• This has been provided in the new Table 1

2) What is the time scale for the N-A plot?
• Years

3) In Table 1, the prevalence of ever and current % smokers is similar. This seems surprising.
• Ever smoker was an error and has been removed

Reviewer: Dr Karen Douglas, Consultant Rheumatologist, Dudley Group NHS FT, Dudley, West Midlands

This is an important research question that requires further clarification. A long term large prospective population study, such as the FOS is warranted to answer this question. The definition of Gout I suspect will have underestimated the number of cases of gout, which the authors acknowlegde may introduce a type 2 error. The echocardiographic data from visit 6 would have been around 1995 and hence at least a decade prior to the final follow-up. It would ahve strenghtened the study greatly if echo data were available for end of folllow-up. It would also be interesting to compare the echo findings of those particpants who later developed gout, ie did echo abnormalities precede the diagnosis?
• Unfortunately Follow up echo data were not available
• We were interested in the hypothesis that gut preceded the onset of heart failure and not vice versa. HF before gout might mean that heart failure increase creatinine or include medications that can increase uric acid and cause gout- reverse causation. Hence the analyses that the reviewer suggest is not within the scope of this manuscript.

In the measurements of covariates there are some contradictions that require clarification, such as it is intially stated the information on renal dysfunction, and medication were collected but then prpodeds to state that renal laboratory measurements and medication details were not available. Please clarify and define renal dysfunction

• The nature of the user data agreement precluded sharing of the actual serum creatinine measurements; we have access to the created variable renal dysfunction yes/no, based on the study investigators. This has been clarified in themethods section.
Though the results are by and large clear and credible I am concerned by the small numbers of participants who developed both heart failure and gout and would question if this compromises the statistical validity on this aspect which is such an important outcome. I would welcome independant advise from a stastician on this.
One point of view that has been raised previously in the literature that has not been addressed here is that though gout appears to associate with CVD this does not necessarily imply its causality which may purely be a confounder for other mechanisms.
• The statistical reviewer's comments and responses are provided below. Basically, the relatively small number of events can reduce the statistical power to detect small differences (type-2 error); In this study the differences in incidence between gout and non-gout groups were so large (~3 fold) as to confer power for our analyses.
Reviewer: Dietrich Rothenbacher, Director, Institut of Epidemiology and Medical Biometry, Ulm University

Eswar Krishnan reports the association of gout with left ventricular function and heart failure in part of the Framingham Offspring Study (FOS). In addition he also analyzed the association of gout with all-

cause mortality. During a median follow-up time of 15.9 years 201 incident cases of heart failure were recorded in the n=4989 subjects with a mean age of 36 years at baseline. N=228 subjects had a study-physician diagnosis of gout at baseline. The investigator found an independent increase of the risk of gout for heart failure with an overall HR of 1.76 (95% CI 1.04-2.95). In addition, in the cross-sectional part of the study all measures associated with heart failure were related to the absence or presence of gout.

• Specific comments:

• 1) The statistical section should describe by which criteria the models were constructed and how the variables included in the models were coded (it is unclear whether they had been included in categories, continuously, etc.)
• Done- Please also see response to reviewer 1 question 6. The bivariate regression analyses results are shown below.
Hazard ratio 95% confidence interval
Age (continuous) 1.835 1.538 2.19
Female gender (categorical) 0.348 0.257 0.472
Alcohol
(categorical) 0.787 0.592 1.047
BMI
(Continuous) 1.043 1.015 1.072

SBP
(Continuous) 1.032 1.026 1.038
Anti-hypertensive
(categorical) 2.505 1.884 3.33
Renal dysfunction
(categorical) 3.53 2.283 5.459
Valvular Heart disease
(categorical)
1.542 0.981 2.423
•
2) At the beginning of the results section a flow diagram should be used to demonstrate the number and flow of the patients and indicate when the measurements had been taken included in this report.
• Done- Figure 1

3) For figure 1 a p-value should be provided that quantifies the difference among the curves
• Done- Figure 2
4) The characteristics in table one should be better characterized, e.g. it is unclear what “diuretic users” means, is this self-report at baseline, within 30 days at baseline etc.). Please specify.
• Done

5) Also the characteristics “renal dysfunction”, “diabetes” etc. should be labeled clearer. Is it self-reported history?
• Renal dysfunction was a calculated variable provided by the FOS team. We did not have access to serum creatinine levels; other comorbidities were defined using standard criteria cited where appropriate. Please see the text

6) The added value of table 2 is not obvious to me - numbers of the various subgroups are not included and it is difficult to compare the HR of gout for incident heart failure directly as the numbers are unknown. Another way to address the question would be the formal investigation of effect modification of the various disease entities, but limited power may be a factor.

• Agree-This Table has been removed; the purpose was to show consistency. There were no significant two way interactions

7) Table 3: is there any measure adjusted for age (and evtl. gender)? I would recommend a minimum adjustment as age is clearly different in the groups as can be seen in table 1. The table 3 is also wrongly referenced in the results section (see page 13 line 17).

• Entirely new Table that provides measures adjusted for age and BMI (two largest risk factors) as well as measures adjusted for other risk factors.

8) Table 4: numbers should be added to table. A minimum adjustment for age for GLM results should be done.

• Table 4 has been removed