**Author's response to reviews**

**Title:** The association of gout with sleep disorders: a cross-sectional study in primary care

**Authors:**

Edward Roddy (e.roddy@keele.ac.uk)
Sara Muller (s.muller@keele.ac.uk)
Richard Hayward (r.hayward@keele.ac.uk)
Christian D Mallen (c.d.mallen@keele.ac.uk)

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**Author's response to reviews:** see over
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Dear Dr Cooper,

Re: MS 9351435797356347 The association of gout with sleep disorders: a cross-sectional study in primary care

Thank you for forwarding the reviewers’ comments on this manuscript which we read with great interest. In conjunction with my co-authors, the following changes have been made to the manuscript in light of these comments:

Reviewer 1 (Ning-hung Chen)

The authors using a database in primary care group to analysis the relationship of sleep apnea, sleep disorders and gout.
This is an interesting topic that few researchers had been addressed on. However, there are some concerns on this manuscript

1. The diagnosis of gout, sleep apnea, and sleep disorders:
Is there a standardized diagnosis criteria set for the Read code of gout?
In page 7: cases: authors described: “received a Read code for gout and found features of inflammation and distribution of affected joints consistent with a diagnosis of gout”, Could authors clarified the criteria of the diagnosis of Gout in Read code.
Also the same as the diagnosis of sleep apnea, is there any objective diagnosis criteria of sleep apnea in Read code?

RESPONSE: Read codes for gout and obstructive sleep apnoea syndrome do not include standardized objective diagnostic criteria but provide a means of standardising recording of diagnoses by general practitioners. The Read-coded diagnosis records the diagnosis made by the general practitioner. As described on page 6, the Read code classification is a hierarchy of morbidity, symptom and process codes, which is widely used in primary care in the UK. The general practices which contribute data to the CiPCA database regularly undergo cycles of training, assessment and feedback to ensure that at least one Read code is entered for each patient consultation providing high-quality computerised morbidity coding. The text on page 7, which the reviewer highlights above, describes the findings of our previous study which demonstrated the validity of the diagnosis of gout amongst those people who had a Read code for gout in the CiPCA database but was not repeated in the current study.

2. Control: match for age and gender only? obesity is also a risk factor for both gout and obstructive sleep apnea

RESPONSE: We agree that obesity is an important risk factor for both gout and obstructive sleep apnoea syndrome. Unfortunately, obesity and body mass index are poorly recorded in primary care consultation databases and hence could not be either matched or adjusted for. This limitation of the study is acknowledged in the Discussion section of both the original and revised manuscripts (page 13).

3. In this study, authors report a diagnosis of sleep apnea only 0.7% which is much lower than general population report all over the world, please try to explain.

RESPONSE: We agree that obesity is an important risk factor for both gout and obstructive sleep apnoea syndrome. Unfortunately, obesity and body mass index are poorly recorded in primary care consultation databases and hence could not be either matched or adjusted for. This limitation of the study is acknowledged in the Discussion section of both the original and revised manuscripts (page 13).
RESPONSE: The occurrence of obstructive sleep apnoea syndrome was defined in our study by the entry of a sleep apnoea Read-code by a general practitioner in the CIPCA database. The most likely explanation for the lower prevalence of sleep apnoea in our study compared to other general population studies which employed more definitive diagnostic methods is that obstructive sleep apnoea is under-diagnosed by general practitioners. Under-diagnosis is mentioned in the Background section of our manuscript (page 4, paragraph 2) and also acknowledged as a potential limitation of our study in the discussion section (page 14). The following sentence has been added to the Discussion section (page 14):

“Indeed, the prevalence of obstructive sleep apnoea syndrome is lower in our study than in previous general population studies which have employed more definitive diagnostic methods [11,12].”

4. From the results of this study, any sleep problem or Non-apnea sleep problem is the independent risk factor of gout, whereas the sleep apnea is not an independent factor. In Discussion, authors try to explain the correlation of sleep apnea as the risk factor to gout rather than Non-apnea sleep problem. Authors should focus more to explain their positive results about the Non-apnea sleep problem.

RESPONSE: We acknowledge that our discussion focussed too heavily on the hypothesised association between gout and obstructive sleep apnoea syndrome that was not confirmed. We have therefore significantly reduced the discussion of this hypothesised association on pages 13/14 emphasising merely that the study was under-powered and therefore that in the presence of a credible underlying mechanism further adequately-powered epidemiological studies are required.

An additional paragraph has been inserted commenting on the association between gout and non-sleep apnoea sleep disorders (page 14):

“We found a significant association between gout and non-sleep apnoea sleep disorders. These disorders consisted of a heterogeneous group of conditions, most commonly insomnia and non-specific sleep disorders (data not shown). To our knowledge, associations between these conditions and either gout or hyperuricaemia have not been studied previously and we are not aware of biological mechanisms to link them with either hyperuricaemia or crystal formation. More detailed study of this association, which specific sleep disorders are associated with gout, and the mechanisms underlying this association is warranted.”

5. In page 13, authors discuss: “some patients with obstructive sleep apnoea syndrome will have either been misdiagnosed as having another sleep problem, in which case they would have been classified firstly as “any sleep problem” and then as a “non-sleep apnoea sleep problem” in this study, or gone unrecognised altogether.” Is there any evidence support this discussion? If it is, how can we trust the Reed code is correct for all sleep disorders or gout? Then the entire database for statistic is unreliable.

RESPONSE: We realise that there is no evidence to support the statement that obstructive sleep apnoea might be misdiagnosed as another sleep disorder and agree that we have over-emphasised this possibility. However, there is evidence that obstructive sleep apnoea is under-recognised in primary care. We have therefore re-
ordered this sentence to place non-diagnosis of a sleep disorder first as the most likely explanation and then misdiagnosis as another sleep diagnosis as a possible alternative as follows (page 13):

“It seems likely therefore that some patients with obstructive sleep apnoea syndrome will have gone unrecognised altogether [13,14,43] although it is also possible that some may have been misdiagnosed as having another sleep problem, in which case they would have been classified firstly as “any sleep problem” and then as a “non-sleep apnoea sleep problem” in this study.”

There is some evidence, however, that when a general practitioner makes a diagnosis of obstructive sleep apnoea, that diagnosis is usually correct supporting the validity of a Read code-based diagnosis. Furthermore, as explained in our response to point 1 above, all general practitioners in participating practices receive specific training to ensure high-quality morbidity coding. The following sentence has been added to the Discussion section (page 13):

“However, previous studies indicate that a diagnosis of obstructive sleep apnoea made by a general practitioner is usually correct [14,44].”

6. In the discussion, authors described this is the first research about sleep with gout. Actually, Abrams B et al. in his study published at Sleep. 28(2):275, 2005 Feb. reported gout with sleep apnea already

RESPONSE: We thank the reviewer for highlighting the omission of this published case report. We have added the reference at the end of the sentence in the Background section which states that little consideration appears to have been given to the possibility of an association between obstructive sleep apnoea syndrome and gout (page 5). We have also revised the first sentence of the Discussion section (page 12) to include this reference as follows:

“To our knowledge, apart from one previous case report [27], this is the first empirical epidemiological study to explore an association between gout and obstructive sleep apnoea syndrome.”

7. The authors mentioned in Discussion section “a potential mechanism by which hypercapnia-induced acidosis might predispose to gout” is not appropriate. Episodes of hypercapnia after apneas and hypopneas results in hypocapnia. This situation rarely causes respiratory acidosis.

RESPONSE: We thank the reviewer for pointing out this factual error and have deleted this point from both the discussion (page14, first paragraph) and background (page 5, first paragraph, final sentence) sections.

Reviewer 2 (Martin Underwood)
Thank you for asking me to review this paper that is a first exploration of a hypothesised link between sleep apnoea and gout that is independent of their common association with metabolic syndrome. The potential importance of the hypothesised link is that if it exists then identifying those with gout who also have sleep apnoea could provide a specific treatment that may reduce uric acid. I have no major concerns about the conduct of the study. It is, inevitably, limited by the nature and size of the underlying data sources. Overall the paper contributes to our understanding of the epidemiology of gout.
Major Revisions
1. The discussion does not adequately recognise that this is a negative study. The original hypothesis has not been proven. That sleep problems other than sleep apnoea are associated with gout cannot be used as supportive evidence. These other sleep problems cover a wide range of different disorders and there is no ‘a priori’ reason to consider that a substantial proportion of these represent undiagnosed sleep apnoea. Clearly the point estimate for the OR is sufficiently large that an association cannot be excluded; larger studies would be needed to address this. To put this into a clinical context, however, only 11/1,689 of those with gout were recorded as having sleep apnoea. This leads me to doubt whether any such association, if it exists, is of great clinical importance; unless of course there is substantial under-recognition of sleep apnoea in this population. I think the discussion needs to more accurately reflect that this is a negative study and not to speculate on what one might have suggested if the study had been positive. Negative studies are really important and we should not try to make them sound positive.

RESPONSE: We thank the reviewer for the several suggestions made here. We have reduced the discussion of the hypothesised association between gout and obstructive sleep apnoea syndrome and added an additional paragraph discussing the association between gout and non-sleep apnoea sleep disorders. Please see response to reviewer 1 point 4 above.

We agree that there is no a priori evidence to support our suggestion that a substantial proportion of those with non-sleep apnoea sleep disorders represent undiagnosed obstructive sleep apnoea syndrome and have downplayed this possibility whilst emphasising the more likely situation that some cases of obstructive sleep apnoea syndrome are simply not diagnosed at all – please see response to reviewer 1 point 5 above.

As discussed above (please see response to reviewer 1 point 3 above), obstructive sleep apnoea syndrome is under-recognised in primary care. It seems likely therefore that more than 11 of the 1,689 gout cases had obstructive sleep apnoea syndrome. We believe that, even in the absence of an independent association, the findings of our univariate analysis suggest that clinicians should be aware that gout and sleep apnoea can co-exist particularly as the diagnosis of sleep apnoea has important implications for driving. This is acknowledged in the Discussion section of both the original and revised manuscripts (page 14).

2. Can the authors provide reassurance that they have taken clustering by practice into account in their analyses; this might have increased variance and hence widened the confidence intervals. It would be really useful if they could present the intra-cluster correlation coefficients for main analyses to help inform others who wish to do work in this area

RESPONSE: We thank the reviewer for pointing out the potential for clustering by practice. We have checked for this by testing the intra-practice correlation in a multi-level model with no independent variables. This was negligible (after rounding, this was estimated by Stata to be 0). We have not therefore provided an estimate of the ICC coefficients. We have however, explained that we carried out this procedure and described the findings. Based on this result, we have retained our original single-level logistic regression models.
The following text has been added to the statistical analysis section of the Methods (page 9):

“In order to assess the extent of clustering of patients within general practices, a multi-level model with no independent variables was fitted. Based on the findings of this model, multi- or single-level logistic regression models were fitted as appropriate to assess the association between gout and the presence of sleep disorders.”

Accordingly, the following text has been added to the Results (page 10):

“There was no effect of clustering by general practice. Hence, single level logistic regression models, adjusted for practice, were used for all analyses.”

Minor revisions

3. Would ‘non-sleep apnoea sleep problems’ be better written as ‘non sleep-apnoea sleep problems’? Also need consistency between text and tables.

RESPONSE: We respectfully thank the reviewer for this suggestion but feel that “non-sleep apnoea sleep problems” is better than “non sleep-apnoea sleep problems” as this is consistent with the wide use of the term “sleep apnoea” in the published literature rather than “sleep-apnoea”. The labelling of table 2 has been amended to ensure consistency with the text.

4. I think there is too much detail in Table 1. I do not think that practice specific data contribute to the understanding of the work. The section on year of first gout consultation is confusing – since controls did not have a gout consultation. The number of controls is inevitably driven by number of cases and so these could be omitted.

RESPONSE: Practice-specific data and data concerning year of first gout consultation have been removed from table 1 (page 24).

On behalf of my co-authors, I would be grateful if the manuscript could be reconsidered for publication in *BMC Musculoskeletal Disorders*.

Yours sincerely,

Dr Edward Roddy