Reviewer's report

Title: 25-hydroxyvitamin D deficiency, exacerbation frequency and human rhinovirus exacerbations in chronic obstructive pulmonary disease

Version: 1 Date: 24 February 2012

Reviewer: Alice Wood

Reviewer's report:

I have structured my report according to the questions asked of reviewers for BMC Pulm Med, and then listed revisions requested in the 3 categories stated.

1. Is the question posed by the authors well defined?
There are a number of questions clearly stated by the authors in the background section, although it is not made clear whether all were equally important or one of them was the primary outcome measure; I have assumed that the first stated question was the outcome of most interest for the purpose of this review. These questions are as follows:
(a) Are COPD patients deficient in 25-hydroxyvitamin D more likely to be frequent exacerbators, relative to those with insufficient or normal levels?
(b) Do COPD patients deficient in 25-hydroxyvitamin D have reduced outdoor activity or altered susceptibility to HRV (including viral load) at exacerbation than those with insufficient or normal levels?
(c) Do VDR polymorphisms differ between frequent and infrequent exacerbators?

2. Are the methods appropriate and well described?
The processes of patient recruitment to the London COPD cohort are well described and widely accepted as robust. Ethical approval is stated, and definition of exacerbation frequency is both clearly stated and the categories widely accepted. The methods of vitamin D measurement, viral typing and genotyping are adequately described. It is not clear in the methods why these particular VDR polymorphisms were chosen – I presume it is because of known functionality, since association with infectious disease for VDR is mentioned in the discussion. Statistical analysis is described in an appropriate amount of detail, and power stated for the primary outcome measure. The genetic analyses are almost certainly underpowered; this is not stated or discussed.

3. Are the data sound?
Sufficient detail on the patient cohort is given in either text or tables in the results section. The data shows the expected change in vitamin D levels between seasons in patients who were not taking calcichew D3, and that this difference was not detectable in the patients on this supplement. There was no difference in vitamin D levels between frequent and infrequent exacerbators after taking season into account. The expected changes with vitamin D levels with time
outdoors were shown (i.e. vitamin D levels dropped with lower sunlight exposure – consistent with known vitamin D biology). There was no relationship between vitamin D, HRV or exacerbation severity, nor were there any significant genetic effects seen.

The data seems sound in that it agrees with known vitamin D biology, and the methods for obtaining and analysing it were satisfactory. This does not remove the question of power for secondary outcome measures.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
Yes, the authors discuss their primary outcome measure in context of the data. Concepts pertaining to time spent outdoors and vitamin D levels, and how this might influence management in future are also covered, whilst acknowledging limitations to the conclusions they can make. Similarly the interesting difference between Calcichew D3 supplemented and non-supplemented individuals is discussed in light of current thinking on the amount of D3 required to maintain levels, and small cohort size. Conclusions about the relationship of viral and genetic data to vitamin D are appropriately cautious, since power is uncertain here.

I would have welcomed a bit further discussion on the relative influence of bacterial exacerbations, if culture data is available. It is also important to note that a trial of vitamin D supplementation in COPD has now been published – it would be helpful if these could be added and discussed (Lehouck et al, Ann Intern Med (2012) 156: 105-14). Other data on relationship of vitamin D levels to exacerbations in COPD has been published which would also be useful to add and discuss briefly (Kunisaki et al, AJRCCM (2012) 185: 286-90).

6. Are limitations of the work clearly stated?
For the most part, yes. Power on secondary outcomes is not usually stated in any manuscript, but some acknowledgment of small cohort size for epidemiological and genetic work could be added to the discussion.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Yes – there are many publications on the London cohort, which are mentioned here.

8. Do the title and abstract accurately convey what has been found?
Yes

9. Is the writing acceptable?
Yes.
Discretionary Revisions
Discussion of power issues for secondary analyses.

Minor Essential Revisions
Confirmation of primary outcome measure in background section.
Addition of any data available on bacterial influences on exacerbations in the cohort, and relationship to vitamin D (as done for HRV) – if not available then lack of data could be acknowledged in discussion.
Addition of reference to vitamin D trial published in COPD, and their findings in context of those reported by the authors here. Addition of Kunisaki et al, AJRCCM 2012.

Major Compulsory Revisions
Nil

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare I have no competing interests