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)	Direct and indirect economic and health consequences of COPD in Denmark - A national register based study - 1998-2010.
AUTHORS	Løkke, Anders; Hilberg, Ole; Tønnesen, Philip; Ibsen, Rikke; Kjellberg, Jakob; Jennum, Poul

VERSION 1 - REVIEW

REVIEWER	Thomas Ringbaek Hvidovre Hospital; Copenhagen, Denmark
REVIEW RETURNED	10-Oct-2013

GENERAL COMMENTS	This study evaluates the health burden of COPD – both before and after initial diagnosis. Especially the period before the initial diagnose is interesting. Furthermore, it's the first study to evaluate the socioeconomic impact of COPD of an entire nation over a time of 12 years. Data are extracted from a couple of national databases in Denmark in the period 1998 to 2010. 131,811 patients with COPD were compared with 131,811 randomly selected controls matched for relevant factors. They found that COPD patients had significantly higher risk of dying compared to controls, and the annual extra costs (direct and indirect costs) were 8,572 EURO for COPD patients. Surprisingly, the extra costs were considerable already 11 years before initial diagnosis. It is for one to think of under-diagnosis of COPD or inadequate adjustment for socioeconomic factors. Undiagnosed COPD is well known, however, is that the entire explanation? Controls were matched for education level, however, is this adequate adjustment for socioeconomic factors? We know that socioeconomic factors pay a role in developing COPD. This should be discussed in the paper. COPD patients diagnosed by the GP´s and not seen in the secondary health sector (hospitals) are not included – a may be included as controls. This allows for bias in both directions. The authors write that a number of controls has undiagnosed COPD (approx. 10%). Where does the 10% come from? The ref. 25 describes about 80% with undiagnosed COPD.

REVIEWER	E.F.M. Wouters Department of Respiratory Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands
REVIEW RETURNED	12-Nov-2013

GENERAL COMMENTS	The manuscript describes the economic consequences of COPD of an entire nation before and after diagnosis. The study provides highly relevant data regarding health direct and indirect costs of COPD over a time period of 12 years. Despite the unique data set, following remarks can be addressed by the authors:
	1. The authors formulate that data are presented as means because some patients had a very high resource consumption. According the opinion of the reviewer, this data set can offer additional unique data by splitting out this hugh number of COPD patients based on medical consumption into high, mean and low consumers. It would be very interesting to analyze direct and indirect costs for these subgroups and to compare survival rates. Although the data set does not permit real characterisation of the COPD patients, this approach will fit with current concepts about phenotyping of COPD patients.
	2. The authors formulate that included patients were registered in the National Patient registry: patients in the primary care sector were not included. The authors focus attention on possible underestimation of the number of COPD patients. Considering the health economical perspective of the manuscript, the authors must also mention the possible overestimation of direct and indirect costs based on the applied entry definition.
	3. Although the authors focus attention on the difficulties in interpreting figure 3, combination of the data in table 3 and figure 3 can become confusing for the reader of the journal.

VERSION 1 – AUTHOR RESPONSE

Reviewer Thomas Ringbæk:
Q1: As allready discussed underdiagnosis accounts for some of the observed difference - it takes years to develop clinical significant COPD - however it is not unrealistic that the economic sideeffects of developing COPD can be measured along the way and that it becomes more pronounced with disease progression.
The study only includes COPD-patients known in the secondary sector (A and B diagnosis and ambulatory visits). This tends to bias the results as well. Finally matching - including for education - tends to level out some of the differences in the patient and the control group. Especially matching for education seems to be well validated. Having said this there might still be some difference based on social factors. The economic factors are actually the ones we want to evaluate in this study and therefore it is not possible to adjust for this. Ideally the study should have been matched for smoking as this obviously accounts for a substantial part of the observed difference but smoking data were not avaliable.
All the above mentioned arguments are now mentioned in the paper.

Q2: Ref. 25 actually say 13 percent of whom 80% had no symptoms (80 percent of 13 is approx. 10%). In ref. 26 approx. 20 percent is found by case finding in symptomatic smokers - so this also fits well with the mentioned 10%.

Reviewer EFM Wouters:
Q1: Interesting thought. The data is register based and high costs are primarily caused by hospital admissions. In Denmark approx. 10 % dies during hospitals admissions and 1/3 is dead within a year of admission. High costs are - at least to some extend - obligated to be caused by hospital admissons

and thus also dead. It can be done. We can make an abitrary cut of and Thus divide the patients into 3 Groups. It is a bit difficult from the question to understand exatly which econony data that you wish to use - all costs, direct, inderect, medicine use others?! It has to be considered carefully - if you divide by economy you will also end up with pre-dified Groups if economy is also the observed outcome?!

Q2: This is correct. The article actually adresses this point allready in the discussion - saying that their is a risk of underestimationand that this will tend to bias the results as these people are less sick. Now further details have been added to adress this.

Q3: This is true. We have tried to explain it in details - hopefully it is possible to understand now?!