Author's response to reviews

**Title:** Impact Of Occupational Exposure On the clinical characteristics of COPD

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Author's response to reviews: see over
As requested, we submit a new version of our manuscript.
We provide a point-by-point response to the reviewers, as follows.
We join a revised version of our paper, with the modifications in color, and the sentences suppressed (CODP revision).
A definitive version is also joined (COPD-BMC-PH).

**Reviewer 1**

**General Comments:**
This well written manuscript describes the results of a multi centre cross-sectional study of 591 smokers in order to assess the impact occupational exposures have on COPD.
This subject matter addresses a potentially important public health problem and the work should be of interest to both clinicians and researchers. The conclusion that the researchers make from the data is that self reported exposures to vapors, dust, gases and fumes were associated with being male, older and having more asthma-like symptoms and atopy, suggesting that even in smokers or ex smokers with COPD, occupational exposures are associated with distinct patient characteristics which might be the consequence of gene-environment interactions. The authors justifiably remark that their work needs to be confirmed and expanded to other cohorts and that we should try and identify which pollutants are involved.
The methodology involved respiratory physicians prospectively recruiting patients with COPD and using validated questionnaires. Occupational exposures were assessed using the ECRHS derived occupational questions and the job exposure matrix was used to analyse the individuals who reported VDGF exposures.
The discussion appropriately highlights the study's strengths and weaknesses and draws appropriate conclusions.

**Specific comments for review:**

**Abstract** - I wonder whether the statement regarding gene-environment interactions would maybe be better placed in the discussion rather than the abstract as I am not sure that the data supports this statement strongly enough for it to appear in the abstract.

*We agree with the reviewer that this statement refers only to a general hypothesis, which presented data do not allow to test formally. Therefore it was deleted from the abstract.*

**Background** – well written and appropriately succinct.

**Methods** – What does BPCO stand for??

*"Initiatives BPCO" is the registered name of the French group involved in the cohort follow-up. BPCO stands for “bronchopneumopathie chronique obstructive”, the French term for COPD. To avoid confusion, the name of the group was removed from the methods section, and is now mentioned only in the authors list.*
Results –
2nd para page 8 – gas not gaz?
  Gas is the English term for gaz, as used, e.g., in the ECRHS studies.

figure 1 should have a label for the y axis.
  The y axis label (%) has been added.

Discussion – page 11… 3rd para. “Since the late 1960s, it HAS BEEN known that....”
  Has been” was added.

In summary I believe that this is well written study on an important topic that provides good evidence and justification for more work in this area.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests

Reviewer 2

Major comments

I think it is valuable to establish cohorts of patients (subjects) with COPD, and future follow-ups of such cohorts giving longitudinal data will be valuable. The main problem when establishing hospital-based cohorts of COPD is the selection bias, which may hamper the external validity of the results.

This study comprises 615 patients collected during 3½ year from 17 university departments. That means a recruitment rate of 10.3 patients/year/hospital. That seems to be quite few.

How were the criterias for inclusion?

This low inclusion is of interest as probably both age, severity and occupational exposures may be factors associated with both referral and inclusion?

Centers were asked to include all patients with spirometry-confirmed COPD during their participation to the cohort recruitment. Obviously, including all consecutive COPD patients visiting each center during all the recruitment period would have been the ideal way of recruiting such a cohort population. However, in the present study as in many others, competitive tasks prevented recruitment from being exhaustive. Therefore, the number of patients per center was indeed variable, depending on the local resources affected to the study and the duration of active participation to the cohort constitution. This issue has been acknowledged in the revised discussion, which also mentions that it is unlikely to bias significantly the results of the present analyses since there was no specific guidance regarding recruitment of patients with risk factors other than smoking.
Were the patients part of a drug trial, which also may have affected the inclusion? *Patients could not be included if they participated to another study, which indeed partly explains differences in numbers of included patients between centers.*

Please, comment this in greater detail. *Selection of patients presenting to specialist respiratory clinics in tertiary care hospitals obviously introduces a selection bias that prevents our results from being generalized to the broader population of COPD patients. The proportion of patients with occupational exposures in our study is similar to what has been reported in other cohorts. Therefore, the selection bias mentioned above appears quite unlikely to influence the results of the present analyses, in which we mainly compared patients with and without occupational exposures. However, we have no way of formally testing this issue, as now mentioned in the revised discussion.*

The statistical analysis is not sufficient. The authors present only univariate analyses, but to be properly analyzed multivariate analysis should have been performed. One multiple logistic regression model could be “COPD severity=age smoking VGDF atopy”. This was just a suggestion.

We indeed performed a multivariate logistic regression analysis to determine whether and how recorded risk factors (i.e., gender, age, smoking status, history of respiratory infections during infancy, atopy, coexistent asthma and occupational exposures) explain the severity of airflow obstruction. This analysis was performed with the 4 GOLD stages as dependent variable, then repeated with 3 severity stages after grouping GOLD stages I and II (due to the low number of GOLD stage I patients). The cumulative r-squared of the models reached only 0.01, meaning that risk factors are not significantly related to the severity of airflow obstruction in patients followed-up for COPD (which is consistent with results of several cohort studies), and suggesting the lack of relevance of the models. This was also confirmed by the lack of concordance between the results of the two models (with 4 and with 3 severity stages). Therefore, we propose not mentioning these analyses. However, if the reviewer or the editor wishes, we could add a comment on this point in the discussion section.

The description of smoking habits is confusing. In the part “Risk factors” are stated in the last paragraph that patients were categorized as current smokers, past smokers or never smokers. However, in the results all patients seem to be current or former smokers. Please, explain. *To limit the risk of including “pure” or predominantly asthmatic subjects with fixed airflow obstruction and thereby to “secure” the diagnosis of COPD, it happened that all centers included only smokers or ex-smokers.*

If only smokers were included, where are the never smokers? Five to ten percent of the COPD occurs among never-smokers. This has to be discussed. *This point has been added to the discussion.*
It is also tricky to analyze interaction with smoking, if there are no never smokers in the material. Please, comment on this.

Indeed, we can only compare the cumulative tobacco consumption and the proportions of current and former smokers between patients with and without occupational exposures. For the same reason, cumulative smoking and past or current smoking are the only variables that can be introduced in the multivariate models aiming at explaining the severity of airflow obstruction (see below). In the revised discussion, we now acknowledge that the lack of never-smokers in these analyses is a limitation.

I suggest the title would be “Occupational exposure and severity of COPD”. Actually, we believe that, in our cohort, occupational exposures influence not only the disease’s severity, but also some clinical features of importance that do not directly relate to severity, such as wheezing or hay fever. Therefore, we suggest to change the title for: IMPACT OF OCCUPATIONAL EXPOSURE ON THE CLINICAL CHARACTERISTICS OF COPD.

Minor comments

Background, second para. I suggest that the term “occupational COPD” is not used. It is impossible at the individual level to know if the COPD is occupational. The term “occupational COPD” has been replaced by “COPD associated with occupational exposure”.

I do find any results regarding the HAD scale mentioned in the last para under data collection. Actually, HAD questionnaires were missing in 49.5% of subjects (n=193/591). Therefore, although we performed the analyzes (see below), we believe that it is highly hazardous to draw any conclusion. Thus, we propose not mentioning them and removed all mentions of HAD scores. However, if the reviewer or editor wishes, we could add them to the manuscript.

<table>
<thead>
<tr>
<th>HAD³</th>
<th>All</th>
<th>VDGF +</th>
<th>VDGF –</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety %</td>
<td>30</td>
<td>22</td>
<td>34</td>
<td>0.043</td>
</tr>
<tr>
<td>Depression %</td>
<td>20</td>
<td>19</td>
<td>20</td>
<td>NS</td>
</tr>
</tbody>
</table>

Forth para – discussion. I do not agree that it is an important strength that the study only included smokers, see comments above. We agree with the reviewer that the lack of never-smokers makes the study population unrepresentative of the whole COPD population, and limits some of the analyses, which has been added in the revised discussion. However, we believe that it also strengthens the diagnosis of COPD in that it limits the risk
of including pure or predominantly asthmatic subjects, which is also mentioned in the discussion.

Are the p-values in the Tables for the difference between VGDF+ and VGDF-?
Explain that, please.

Yes, p-values in the Tables are for differences between VGDF+ and VGDF- (This has been added to the Tables)

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need

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**Reviewer 3**
The objective of the present study was to characterize the clinical pattern of COPD, according to reported occupational exposure experience to vapors, dust, gases and fumes (VDGF).
The authors analyzed data from a cross-sectional study of COPD cases, all smokers. COPD patients with stable GOLD-based diagnosis (FEV1/FVC<0.70) were recruited from Jan 2005 to August 2008 to a cross-sectional study across France. Patients with asthma or other significant disease were excluded. Occupational exposure to VDGF was ascertained by a single question: “Have you ever worked in a job which exposed you to vapors, dust, gas, or fumes?”
The clinical pattern characterization was based on a questionnaire ascertained: hay fever, life-time atopic dermatitis, life-time asthma, respiratory symptoms of chronic bronchitis, shortness of breath, life-time wheeze, exacerbations, current sputum, current wheeze, SGRQ total score, and GOLD Stage I-IV categorization of the subjects.
The results show that those reported to be exposed to VDGF had higher prevalence of reported hay fever, life-time asthma and wheeze and were more likely to interrupt their work because of their respiratory problems. The result suggests that atopic background predisposes individuals with occupational exposure to the development of COPD.

Comments:
1. The authors report that spirometry was obtained according to international standards (Quanjer PH et al, 1993), yet pre-bronchodilator (pre-BD) spirometry data are not available. Were only post-BD tests obtained?
   
   *Post-bronchodilator FEV1 was recorded. Reversibility testing was not available for all patients, due to the real-life nature of the study. Therefore, we could not analyze the relationship between the degree of reversibility and occupational exposures, which is indeed a limitation, as now acknowledged in the revised discussion.*

Generally, post-bronchodilator spirometry is done to exclude patients with asthma. In Table 2, FEV1% is provided. Is this FEV1% predicted or the FEV1/FVC ratio this is not clear, also is this pre- or post- BD test?
Spirometry variables are provided as postbronchodilator

2. The weakness of the study is lack of actual lung function data and comparison with predicted values, especially since the authors set up to characterize clinical characteristics of the patients.

   FEV1 is indeed provided as % predicted. Due to the real-life nature of the diagnostic work-up, other lung function variables (such as lung volumes or diffusion capacity) and 6MWT were lacking in many patients, which prevented us from analyzing them reliably. This is now acknowledged in the revised version of the discussion.

The GOLD Stage criteria, especially GOLD Stage I often includes individuals whose lung function is within the normal limits based on the 5th percent (i.e., LLN criteria) for healthy nonsmokers.

   In a previously published analysis of this cohort aiming at identifying COPD phenotypes, all analyses were performed using both the fixed FEV1/FVC threshold (0.70) and the LLN to define airflow obstruction, which did not change the results (Burgel et al., Eur Respir J 2010). In addition, the proportion of GOLD stage 1 is very low in our cohort (6%), as well as the proportion of subjects aged less than 50 years (8.6%). Therefore, we propose to keep the GOLD definition of airflow obstruction in order to ensure the comparability of our cohort with others recruited using the fixed threshold.

3. The authors should discuss that the results show that the patients exposed to VDGF had higher frequency of GOLD Stage I and lower Frequency of GOLD Stage IV category. Was this trend statistically significant?

   As mentioned in table 2, the severity distribution did not differ significantly between groups (p=0.15).

4. The interpretation of the study is focused primarily on the increased prevalence of hay fever, asthma and wheezing in the exposed subjects. The authors should also point out and discuss the result showing that the unexposed cases had higher consumption of tobacco smoking (significantly higher pack-years) and much higher frequency of GOLD Stage IV (20.4 vs. 14.4%), suggesting higher prevalence of more serious impairment that may be driven by higher tobacco smoking consumption induced impairment (likely higher severity of emphysema, since very few occupational exposures cause emphysema on their own). Does the smoking consumption (pack-years) differ by the severity of impairment (i.e., GOLD Stage I-IV) between the two groups?

   Cumulative smoking and FEV1 (% predicted) were not correlated (r=0.08), which has been added to the results section.

5. The authors report that they used JEM to identify the likely type of occupational exposure (mineral dust, biological pollutants, and gas, vapors, fumes). Yet, they never used the data to relate this exposure types to the presence of atopy, hay fever, asthma, and wheezing. Generally mineral dust does not increase the prevalence of asthma like disease, but those with asthma may be more affected by this exposure.
Indeed, these analyses were performed. However, the relatively low number of patients in each individual category of occupational exposure makes it difficult to draw any firm conclusion. As suggested by the reviewer, exposure to mineral dust was not related to asthma, atopy or wheezing, while there was a marginal association with hay fever (p=0.07). Exposure to biological pollutants was associated with atopy only (p=0.03). Exposure to vapors, gas and fumes did not relate to any of these factors. Differences mentioned in the initial version of the manuscript were significant only when all kinds of exposures were considered together, which is likely related to the higher numbers of patients per group, making the global analysis more robust. Therefore, we propose to avoid providing results of separate analyzes for each type of exposure since they would be difficult to interpret due to small patients numbers. However, if the reviewer or the editor wishes, we could add a comment on this point in the discussion section.

6. The discussion is often confusing and not focused on their own results. For example, when discussing the role of atopy in the development of COPD related to occupational exposure, the authors never attempted to interpret their own data with respect to the type of exposure established by the JEM versus atopic status, etc.

The limitation mentioned above regarding individual analyzes for each type of occupational exposure has been added to the revised discussion.

7. The authors set out to assess interactions between exposure, smoking and atopy, yet they have not done any analysis regarding this objective. It looks like this objective was added as an afterthought. For example, the authors could have analyzed in more detail tobacco consumption, and type of occupational exposure by the severity of disease.

Multivariate analyzes were performed to determine the respective contributions of cumulative smoking, occupational exposures and other recorded risk factors (i.e., gender, age, history of respiratory infections during childhood, atopy and coexistent asthma) to the severity of airflow obstruction. However, as mentioned in answers to reviewer #2, the cumulative r-squared of the best-fitting model reached only 0.01, meaning that risk factors are not significantly related to the severity of airflow obstruction in patients followed-up for COPD (which is consistent with results of several cohort studies), and suggesting the lack of relevance of these models. This was also confirmed by the lack of concordance between the results of the two studied models (one with 4 and one with 3 severity stages, the latter combining GOLD stages I and II). Therefore, we propose not mentioning these analyzes. However, if the reviewer or the editor wishes, we could add a comment on this point in the discussion section.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Reviewer 4

Major Compulsory Revisions
I would rather prefer the title to be more specific on the particular aspect of COPD (e.g. Mortality, clinical presentation e.tc.) and be changed from the impact of occupation exposure on COPD to either of these mentioned below.
1. Impact of occupational exposures on clinical pattern of COPD.
Or possibly use a catchy phrase like
2. Occupational related COPD : An emerging phenotype in COPD

The title has been changed in “Impact of occupational exposures on the clinical characteristics of COPD”. We suggest not to use the term “phenotype” which implies a prospective assessment of differences in outcomes between the identified clinical patterns, which is not available yet for our patients population.

Minor Essential Revisions
3. The abbreviations’ BPCO and other ones used in the manuscript should be defined when it is first used.

“BPCO” has been removed from the text (see answer to reviewer #1). Other abbreviations are defined when they appear first in the manuscript.

4. The objectives of the study in the last paragraph on page 4 can be rephrased into a single sentence.

A single sentence is now used to summarize the study goals, as follows: “The present analysis was designed to explore the influence of occupational exposures on disease characteristics in a patients series of 591 smokers or ex-smokers with well-defined COPD”.

5. The author need to state the source(s) of the hospital anxiety and depression (HAD) scale was used to identify mood disorders in study on first paragraph on page 6.

As mentioned in answers to reviewer #2, HAD questionnaires were actually missing in 49.5% of subjects (n=193/591). Therefore, although we performed some exploratory analyzes on HAD scores (see answer to reviewer #2), we believe that it is highly hazardous to draw any conclusion. Thus, we propose not mentioning them and removed all mentions of HAD questionnaires and scores. However, if the reviewer or editor wishes, we could add them to the manuscript.

6. The statistical analysis on page 7 is not detailed. The authors need to state why median was preferred for some variables and percentages for other, as not every reader understand basic statistics. Please specify the test used for these variables analysis.

These details were added to the “statistics” paragraph of the methods section, as suggested by the reviewer :

“Data are reported as median [Q1-Q3] for quantitative variables or % for categorical variables, as appropriate. Univariate comparisons between patients exposed or not to VDGF were performed using Chi-square test test
for qualitative variables and the two-sided non-parametric Wilcoxon test for quantative variables.”

7. In view of the fact the data were secondary data from previous study I think the statistic is okay.

8. There few typographical error and spelling mistakes that need to corrected

   The manuscript has been thoroughly reviewed by a native English-speaking medical writer.

9. The strength and the limitation of the study can moved from page 9 to just before the conclusion section

   As suggested by the reviewer, this paragraph was moved just before the conclusion.

10. In figure 1 The first column in figure 1 should be labeled as characteristics /variables

    The label has been added as suggested.

   Percentages in bracket (%) should be inserted in front of hay fever, life time asthma and Atopic dermatitis and (yrs) after age in column 1.

    This change has been made as suggested.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

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

**Declaration of**

**Reviewer 5**

Essentially speaking, this is a retrospective study which included assessment of symptoms, work-disability and pulmonary function tests in COPD patients with and without the history of exposure to vapors, dusts, gas or fumes (VDGF) ever in the past. Such a classification based on self-reported recall exposure to a wide variety of vapors, dusts, gas or fumes is somewhat arbitrary considering the huge variations in the types, degree and duration of exposures. Moreover, the VDGF exposed patients were older, male subjects with more asthma-like symptoms and atopy. This is an obvious sample/selection bias. These differences themselves can explain the differences in work-related morbidity in the exposed patients than the exposure to the occupational VDGF.

We agree with the reviewer that we cannot exclude that some sample/selection biases may have influenced the relationships between occupational exposures, clinical features and working difficulties. However, such biases are almost inherent to the nature of such a study, aiming at assessing the contribution of occupational exposures to the clinical presentation of COPD patients in a real-life setting. Although we acknowledge that a history of occupational exposure was identified using relatively “crude”
questions, these have been previously used in well-recognized cohort studies such as the ECRHS. In addition, the reality of occupational exposure was confirmed using job-exposure matrix, both in our studies and in others. Finally, previous studies confirmed that the crude questions on self-reported exposures are accurate to identify associations between occupation and disease. This point is indeed developed in the discussion section with reference to the following papers: