PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Real-life impact of uncontrolled severe asthma on mortality and healthcare use in adolescents and adults: findings from the retrospective, observational RESONANCE study in France
AUTHORS	Roche, Nicolas; Garcia, Gilles; de Larrard, Alexandre; Cancalon, Charlotte; Bénard, Stève; Perez, Vincent; Mahieu, Aymeric; Vieu, Laurine; Demoly, Pascal

VERSION 1 – REVIEW

REVIEWER	Licari, Amelia IRCCS Policlinico San Matteo
REVIEW RETURNED	20-Feb-2022

GENERAL COMMENTS	This is an excellent study reporting the burden of severe asthma in adolescents and adults in the real-life setting. Severe asthma represents a critical public health issue as it impacts on mortality, morbidity and health resource use. Among the merits of this work, the prevalence of severe asthma is defined as 4.5% of asthma patients and 0.15% of the general French population.

REVIEWER	Verhamme, Katia Erasmus Medical Center, Medical Informatics KV works for a research department who received/receives unconditional research grants from Yamanouchi, Pfizer/BI, Novartis, GSK, Chiesi, Astra Zeneca, Amgen, Janssen and the EMA, none of which are related to the content of this paper.
REVIEW RETURNED	18-Mar-2022

GENERAL COMMENTS	I would like to thank the editors allowing me to review this important paper on characteristics, health care use and mortality of severe uncontrolled asthma vs asthma vs the general population. The paper is well written with important findings, but I have some questions mainly related to the methodology and I will address these following the order of the paper. Some comments or minor and some are major. 1/ Historical information on comorbidities, healthcare use, and treatments received were collected in the 5 years preceding the index date to assess baseline characteristics.==> does this mean that all individuals had 5 years of medical history? 2/ The uncontrolled severe asthma cohort was matched to the general population based on age, sex and CMU-c status whereas the uncontrolled severe asthma cohort was PS matched to the

	asthma population. Is there a reason why differences in matching was applied? My main concern is on the matching on PS for the uncontrolled severe asthma cohort vs the asthma cohort. I'm wondering whether there was not a risk of over adjustment especially as matching was done on criteria which were also part of the definition of uncontrolled asthma like history of hospitalisations. I understand that the authors wanted to address risk of mortality in an unbiased way but I'm wondering whether this is needed here? Would matching on age, sex not have been good enough? Also matching is done on characteristics which are often also typical for severe asthma like comorbidity of diabetes mellitus, nasal polyposis, etc. With regard to the matching please also provide some details on how matching was done e.g. exact PS matching, caliper matching, nearest neighbour, ..Also the table the authors refer to showing that covariates were well balanced following PS matching was not provided? 3/ The paper mentions the following: "The primary objective of this study was to assess the number and proportion of uncontrolled severe asthmatic patients aged 12 and older". Wouldn't it be more interesting not only to provide numbers and proportions but also to provide characteristics of patients with asthma and those with uncontrolled severe asthma? For that reason, I would also have loved to have a table on baseline characteristics and not only on what happens to these patients during follow-up. 4/ In the method section clarify that categorical variables are not only described as frequencies but also as proportion? (with 95% CI where relevant) 5/ Cohorts were followed for 2 years after the index date to assess the outcomes of interest. But of course not all individual had 2 years of fup? What happened to these patients? Follow-up was censored I suppose? 6/ Mortality is one of the outcomes. Did you have information on cause of death? 7/ How is health care utilization and associated costs assessed? The manuscripts states that Costs were adjusted to 2018 Euros (€; date of data access) but what this means to me is unclear 8/ With regard to the construction of CCM: was only history of cardiovascular disease, diabetes, psychiatric disease, and cancer comorbidity addressed? But CCM is broader than this and for instance also includes info on kidney function, dementia, rheumatoid arthritis, etc ? 9/ You select 3 cohorts that you identify in 2014 and which you follow over time. What happens if a patient from the asthma cohort progresses into severe, uncontrolled asthma? Does this patient stay in the original cohort cohort? Similar for individuals not having asthma and later developing asthma? 10/ In the result section you state: "Figure 2 shows survival over time among the 3 cohorts. Compared with both control cohorts, the increased risk of mortality was observed early, and the difference increased during follow-up."

	Please be more specific: this is about increased risk of mortality for patients with uncontrolled severe asthma 11/ In the result section you state: “The Cox model for mortality risk showed a significant impact of a history of psychiatric diseases (Table S1, Supplementary File). In the category “without history of psychiatric diseases”, the mortality risk increased significantly by an average of 3.25 in the uncontrolled severe asthmatic cohort compared to the general population cohort (hazard ratio [HR]: 3.25; 95% CI: 2.14, 4.92). Likewise, other comorbidities increased mortality risk in the uncontrolled severe asthmatic cohort, especially for cancer (HR: 2.40; 95% CI: 1.64, 3.50; Table S1).” It's difficult for me to understand what this table S1 is about. For instance the first row, is this risk of mortality for patients with uncontrolled severe asthma vs the general population in a strata of patients with history of psychiatric diseases? Second row, in another stratum (without psychiatric diseases). And next you provide HR for the individual comorbidities (adjusted for fact whether they had uncontrolled severe asthma or not? And then you stratify in the control group and in the group of patients with uncontrolled severe asthma to investigate effect of mortality of psychiatric conditions and you notice that it is a risk factor in patients without asthma but not in patients with severe uncontrolled asthma. I don’t understand why you want to put that much emphasis on the effect of psychiatric conditions? This was not your main research question and you were probably not able to optimally control for confounding in this analysis? For which factors did you adjust? Is also difficult to interpret this table if you do not have details on the actual number of patients with these conditions. 12/ In the discussion section you mention: “This is the first study to specifically compare uncontrolled severe asthmatic patients with the overall asthmatic population.” Is this correct? Aren’t there other studies describing characteristics of uncontrolled severe asthmatic patients? Eg * Comparison of the Proportion and Healthcare Utilisation of Adult Patients with Uncontrolled Severe Asthma versus Non-Severe Asthma Seen in a Southeast Asian Hospital-Based Respiratory Specialist Clinic by Tay et al, *A systematic literature review of burden of illness in adults with uncontrolled moderate/severe asthma by Czira et al in Respiratory Medicine (2022) where some of the papers have “well-controlled asthma” as reference category? *Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population by Kerkhof et al published in Thorax (but this deals with eosinophilic asthma) 13/ in the discussion section you mention: “An important finding highlighted by this study is that the cost of uncontrolled severe asthma was partly explained by healthcare received by patients who ended up by dying during follow- up, emphasizing the importance of healthcare expenses during the last months or years of life in this population” This is true of course but costs in the last months of their year or

	probably also much higher for patients without (uncontrolled severe) asthma. It felt a little bit cynical to me and not clear what was meant by this statement unless you want to emphasize the importance of close management, optimal control as preventive measures in order to avoid these costs? 14/ Figure S1: Correct typo: R03R03 should be R03 Don't call it a "pump of B2 agonists" but better canister or an inhaler? 15/ With regard to the exclusion of COPD: Your list of respiratory conditions is broader than just COPD eg J96 Respiratory failure, not elsewhere classified E84 Mucoviscidosis J92.0 Pleural plaque with presence of asbestos J94.8 Other specified pleural conditions 16/ Related to this, what is not entirely clear to me is why you state the following in the discussion: "some COPD patients also suffering from asthma may have been included given the average age of the asthmatic cohorts." ==> this would only be the case if disease codes for COPD were not used and thus these patients could not be excluded? 17/ Is there a reason why mortality rates were not provided? You have number of events and follow-up time so you could have provided mortality rates?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Amelia Licari, IRCCS Policlinico San Matteo Comments to the Author:
This is an excellent study reporting the burden of severe asthma in adolescents and adults in the real-life setting.
Severe asthma represents a critical public health issue as it impacts on mortality, morbidity and health resource use. Among the merits of this work, the prevalence of severe asthma is defined as 4.5% of asthma patients and 0.15% of the general French population.

We thank you for this very positive feedback on our work.

Reviewer: 2
Dr. Katia Verhamme, Erasmus Medical Center Comments to the Author:
I would like to thank the editors allowing me to review this important paper on characteristics, health care use and mortality of severe uncontrolled asthma vs asthma vs the general population.
The paper is well written with important findings, but I have some questions mainly related to the methodology and I will address these following the order of the paper. Some comments or minor and some are major.

1/ Historical information on comorbidities, healthcare use, and treatments received were collected in the 5 years preceding the index date to assess baseline characteristics.==> does this mean that all individuals had 5 years of medical history?

All individuals had 5 years of data collected from the EGB database, *i.e.*, from their index date in 2014 and back to January 1st, 2009.

Comorbidities were derived from algorithms based on hospital diagnostic codes, dispensed treatments and chronic illness health insurance codes during the 5 years before index date.
Asthma-related healthcare use (medical devices of interest, medical procedures and biological procedures) and asthma-related treatments were collected during the year before index date, as well as history of other treatments of interest.

2/ The uncontrolled severe asthma cohort was matched to the general population based on age, sex and CMU-c status whereas the uncontrolled severe asthma cohort was PS matched to the asthma population. Is there a reason why differences in matching was applied? My main concern is on the matching on PS for the uncontrolled severe asthma cohort vs the asthma cohort. I'm wondering whether there was not a risk of over adjustment especially as matching was done on criteria which were also part of the definition of uncontrolled asthma like history of hospitalisations. I understand that the authors wanted to address risk of mortality in an unbiased way but I'm wondering whether this is needed here? Would matching on age, sex not have been good enough? Also matching is done on characteristics which are often also typical for severe asthma like comorbidity of diabetes mellitus, nasal polyposis, etc.

We thank you for this very relevant comment.
The matching processes were defined based on the questions that each process was designed to address:

- The first question was the global burden of uncontrolled severe asthma.

To address this point, the comparison was to be done with the general population, which required simple socio-demographic matching on age, sex and CMU-c status.
To limit the influence of possible confounders, an adjustment on age, history of cardiovascular disease, diabetes, psychiatric disease, and cancer was realised in a post-hoc analysis using a Cox regression model to compare mortality between the uncontrolled severe asthmatic cohort and general population.

- The second question was the specific impact of lack of control and severity in patients with asthma.

This required to compare patients with uncontrolled severe asthma with other patients with asthma. For this comparison the purpose of matching was to limit the contribution of factors that could be associated with uncontrolled severe asthma but also with asthma in general, even if some would be more frequent in patients with uncontrolled severe asthma. To achieve this, the propensity score approach was selected, and socio-demographic characteristics, comorbidities of interest and their treatments, as well as history of healthcare use were integrated in the propensity score.
Conversely, we did not match on treatments related to asthma and hospitalizations related to asthma that constitute proxies to define control or severity of asthma.
We acknowledge that this approach could lead to some degree of over adjustment, thereby minimizing the burden of lack of asthma control and severity. Therefore, our estimates of this burden may be considered as somehow conservative which we underline now in the revised version of the manuscript. However, it must be noted that, as shown in the added Figure S2 on the quality of propensity score matching, standardized differences are quite similar before and after matching for nasal polyposis and diabetes, which does not support the hypothesis of over adjustment with respect to these comorbidities.

With regard to the matching please also provide some details on how matching was done e.g. exact PS matching, caliper matching, nearest neighbour, ..Also the table the authors refer to showing that covariates were well balanced following PS matching was not provided?

We used a direct matching for matching uncontrolled severe asthma cohort to general population, and a nearest neighbour propensity score matching for matching uncontrolled severe asthma cohort to asthma cohort. The quality of both matchings was evaluated with standardized mean differences between variables measured before and after matching, with the objective of standardized mean differences < 0,1 and as close as possible to 0 after matching.
Detailed information on the methods used, and the standardized mean differences before and after matching for both matchings, are provided in the manuscript and in the Supplementary File (Table S1, Table S2, and Figure S2), respectively.

3/ The paper mentions the following: "The primary objective of this study was to assess the number and proportion of uncontrolled severe asthmatic patients aged 12 and older". Wouldn't it be more interesting not only to provide numbers and proportions but also to provide characteristics of patients with asthma and those with uncontrolled severe asthma? For that reason, I would also have loved to have a table on baseline characteristics and not only on what happens to these patients during follow-up.

Following this comment, we added in the Supplementary File the characteristics of patients before and after matching for both comparisons (*i.e.* between uncontrolled severe asthmatic cohort and general population and between uncontrolled severe asthmatic cohort and other asthmatic cohort).
As mentioned in the answer to comment #2, the mean standardized differences are also reported.

4/ In the method section clarify that categorical variables are not only described as frequencies but also as proportion? (with 95% CI where relevant)

We apologize for this error. All categorical variables were provided exclusively as frequencies. 95% confidence intervals were not provided. Qualitative variables were compared between cohorts using Mc Nemar tests.
We modified the manuscript accordingly.

5/ Cohorts were followed for 2 years after the index date to assess the outcomes of interest. But of course not all individual had 2 years of fup? What happened to these patients? Follow-up was censored I suppose?

Patient were followed from index date and up to two years of follow-up or death, whichever occurs first. Therefore, patients were censored at two years of follow-up, or death. We modified the manuscript accordingly.
Of note, there is limited number of patients lost to follow-up in EGB, since this database includes a random sample (1/97th) of the entire French population from birth until death.

6/ Mortality is one of the outcomes. Did you have information on cause of death?

Unfortunately, the cause of death is not available in EGB. Therefore, we assessed all-cause mortality.

7/ How is health care utilization and associated costs assessed? The manuscripts states that Costs were adjusted to 2018 Euros (€; date of data access) but what this means to me is unclear

We thank you for this comment that allows us to clarify the manuscript.
Healthcare use refer to both in-patient and out-patient healthcare consumption with identification of different categories such as hospitalizations, emergency department visits, medical or paramedical consultations, laboratory tests, and treatments dispensed in community pharmacies, all of which are available in EGB at the patient level.
We allocated to each category of healthcare use the corresponding cost from the collective perspective, *i.e.* the cost presented for reimbursement.
Costs evolve over the years. To ensure homogeneity, we used the 2018 consumer price index - health data index (4011-E) - published by national institute of statistics and economic studies (*Institut national de la statistique et des études économiques*, INSEE).
We modified the manuscript to bring this information.

8/ With regard to the construction of CCM: was only history of cardiovascular disease, diabetes, psychiatric disease, and cancer comorbidity addressed? But CCM is broader than this and for instance also includes info on kidney function, dementia, rheumatoid arthritis, etc ?

We have clarified this point.

We used the Charlson Comorbidity Index weighted on age, based on the algorithm developed and adapted for French healthcare claims databases (*Bannay et al*. The Best Use of the Charlson Comorbidity Index With Electronic Health Care Database to Predict Mortality. Med Care. 2016).

It includes myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connectivitis, ulcer disease, mild liver disease, uncomplicated diabetes, complicated diabetes, hemiplegia, moderate or severe kidney disease, cancer (including lymphomas and leukemias and excluding pathologies skin neoplastics), moderate or severe liver disease, metastatic pathology, and HIV/AIDS. This Index and other comorbidities were integrated for propensity score matching between uncontrolled severe asthma cohort and asthma cohort.

Some comorbidities, identified though dedicated algorithms, were selected using a backward variable selection from pre-listed clinically relevant variables, to be included in the final Cox regression model for comparison of mortality between the uncontrolled severe asthmatic cohort and general population: age, history of cardiovascular disease, diabetes, psychiatric disease, and cancer.

9/ You select 3 cohorts that you identify in 2014 and which you follow over time. What happens if a patient from the asthma cohort progresses into severe, uncontrolled asthma? Does this patient stay in the original cohort? Similar for individuals not having asthma and later developing asthma?

We thank you for this very relevant comment.
The patients were identified as suffering from uncontrolled severe asthma, other type of asthma, or belonging to the general population in year 2014.
All patients remained assigned to their original cohort during the whole follow-up even if makers of their medical conditions changed. We acknowledge that this approach is conservative and may therefore minimize differences between groups. However, we believe that attempting to re-assign patients would introduce excessive complexity and subsequent risks of mis-classification. In addition, since the follow-up is limited to two years, this impact of not re-assigning patients is probably limited since cohort studies found that most of patients with asthma tend to stay in their corridor of severity. We added a discussion section in the manuscript accordingly.

10/ In the result section you state: "Figure 2 shows survival over time among the 3 cohorts. Compared with both control cohorts, the increased risk of mortality was observed early, and the difference increased during follow-up."
Please be more specific: this is about increased risk of mortality for patients with uncontrolled severe asthma

We thank you for this comment. We modified the text in the manuscript accordingly: "Figure 2 shows survival over time among the 3 cohorts. Compared with both control cohorts, the increased risk of mortality in uncontrolled severe asthma cohort was observed early and became higher during follow-up."

11/ In the result section you state: "The Cox model for mortality risk showed a significant impact of a history of psychiatric diseases (Table S1, Supplementary File). In the category "without history of psychiatric diseases", the mortality risk increased significantly by an average of 3.25 in the uncontrolled severe asthmatic cohort compared to the general population cohort (hazard ratio [HR]: 3.25; 95% CI: 2.14, 4.92). Likewise, other comorbidities increased mortality risk in the uncontrolled severe asthmatic cohort, especially for cancer (HR: 2.40; 95% CI: 1.64, 3.50; Table S1)."

It's difficult for me to understand what this table S1 is about. For instance the first row, is this risk of mortality for patients with uncontrolled severe asthma vs the general population in a strata of patients with history of psychiatric diseases? Second row, in another stratum (without psychiatric diseases). And next you provide HR for the individual comorbidities (adjusted for fact whether they had uncontrolled severe asthma or not? And then you stratify in the control group and in the group of patients with uncontrolled severe asthma to investigate effect of mortality of psychiatric conditions and you notice that it is a risk factor in patients without asthma but not in patients with severe uncontrolled asthma. I don't understand why you want to put that much emphasis on the effect of psychiatric conditions? This was not your main research question and you were probably not able to optimally control for confounding in this analysis? For which factors did you adjust? Is also difficult to interpret this table if you do not have details on the actual number of patients with these conditions.

We agree with the reviewer that further analyses of the relations between uncontrolled severe asthma and psychiatric disorders on the one hand, and between psychiatric disorders and mortality on the other do not belong to the a priori defined scope of the study.
However, considering the significant interaction found in the Cox model, it appeared necessary to assess the impact of uncontrolled severe asthma according to history of psychiatric disease. Following the reviewer's comment, we modified the manuscript to highlight this interaction, and deleted the analysis of the impact of psychiatric disease on mortality according to the type of asthma, since it could be difficult to interpret.

12/ In the discussion section you mention: "This is the first study to specifically compare uncontrolled severe asthmatic patients with the overall asthmatic population."

Is this correct? Aren't there other studies describing characteristics of uncontrolled severe asthmatic patients?
*Eg * Comparison of the Proportion and Healthcare Utilisation of Adult Patients with Uncontrolled Severe Asthma versus Non-Severe Asthma Seen in a Southeast Asian Hospital-Based Respiratory Specialist Clinic by Tay et al,*

**A systematic literature review of burden of illness in adults with uncontrolled moderate/severe asthma by Czira et al in Respiratory Medicine (2022) where some of the papers have "well-controlled asthma" as reference category?*

**Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population by Kerkhof et al published in Thorax (but this deals with eosinophilic asthma)*

We agree with the reviewer. Actually, we were referring to studies in the French population, which we mistakenly did not mention. We have added this to the revised manuscript.

13/ in the discussion section you mention: "An important finding highlighted by this study is that the cost of uncontrolled severe asthma was partly explained by healthcare received by patients who ended up by dying during follow- up, emphasizing the importance of healthcare expenses during the last months or years of life in this population"

This is true of course but costs in the last months of their year or probably also much higher for patients without (uncontrolled severe) asthma. It felt a little bit cynical to me and not clear what was meant by this statement unless you want to emphasize the importance of close management, optimal control as preventive measures in order to avoid these costs?
Indeed, we agree that the increase in healthcare expenses during the last months of life is a general finding in all populations.
We changed the formulation of this sentence to make this point clearer: "This study highlighted the excess healthcare costs during the last months of life in uncontrolled severe asthma, accounting for part of the excess cost associated with this condition overall, given their excess mortality rate during the follow-up period".

14/ Figure S1: Correct typo: R03R03 should be R03 Don't call it a "pump of B2 agonists" but better canister or an inhaler?

We thank you for this comment.
We modified the ATC class in the Supplementary File.
Moreover, we modified the inclusion criteria originally mentioned as "≥1 filled prescription of a pump of β2-agonist/month". In fact, it referred to the research of "at least 10 filled prescriptions of SABA (short-acting β2-agonist) in year 2014".

15/ With regard to the exclusion of COPD: Your list of respiratory conditions is broader than just COPD eg
J96 Respiratory failure, not elsewhere classified
E84 Mucoviscidosis
J92.0 Pleural plaque with presence of asbestos
J94.8 Other specified pleural conditions

We thank you for this comment.
Indeed, this definition is broader than just COPD therefore we now mention “Other chronic pulmonary disease” in the revised manuscript and Supplementary File.

16/ Related to this, what is not entirely clear to me is why you state the following in the discussion: “some COPD patients also suffering from asthma may have been included given the average age of the asthmatic cohorts.” ==> this would only be the case if disease codes for COPD were not used and thus these patients could not be excluded?

In our study, asthma was defined based on the existence of asthma related hospitalizations, ALD code for asthma, and asthma treatments. Importantly, many of these treatments are also used for other chronic pulmonary diseases, such as COPD.
To limit the inclusion of patients with other chronic pulmonary diseases including COPD, we used exclusion criteria based on ICD-10 hospitalization codes or ALD codes.
However, there is a risk to still include COPD patients in the study population if ALD for COPD has not been declared, or if a patient has never been hospitalized during the last 5 years.
This has been made clearer in the manuscript.

17/ Is there a reason why mortality rates were not provided? You have number of events and follow-up time so you could have provided mortality rates?

We showed crude cumulative all-cause mortality rates at two years (Figure 2) and probability of survival at two years (Table 1), for the three cohorts.
It seemed to us more appropriate to show the data this way, using the same cut-off at two years for all outcomes, and mortality rates did not appear to provide additional information.

VERSION 2 – REVIEW

REVIEWER	Verhamme, Katia Erasmus Medical Center, Medical Informatics KV works for a research group who received/receives unconditional research grants from Pfizer/BI, Yamanouchi, GSK, Chiesi, Novartis, Amgen, J&J, Astra Zeneca.
REVIEW RETURNED	06-Jun-2022

GENERAL COMMENTS	First of all, I appreciate the efforts that the authors took to address my comments/questions. I only have some final comments/questions: 1/ With regard to the cost - in your answer you specify that you used the 2018 consumer price index. In the manuscript itself, "adjustment to 2018 Euros (€) " - this does not mean a cost of 2018 euro but the 2018 consumer price index. I would adjust in the text as it is still confusing the way it is written. Also cost of an ED visit seems to be cheap in France? Mean of 6 euro for an ED visit in the general population? 2/ I'm still struggling somewhat with mortality in uncontrolled asthma in patients with and without psychiatric conditions. This was based on checking for interaction so am I correct to assume that you created an interaction term between uncontrolled severe asthma or

	general population and psychiatric conditions and then checked whether this interaction was significant. And the results in table S3- these are the results of the multivariate analysis including age, cardiovascular conditions, diabetes, cancer, uncontrolled asthma &psychiatric conditions (with general population and psychiatric condition as reference), uncontrolled asthma without psychiatric conditions (with general population without psychiatric condition as reference)? But would the message then be that risk of mortality is only higher in patients with uncontrolled asthma but without psychiatric conditions. Also did you check for the effect of adjustment of psychotropic drugs (which you also have in your dataset) 3/ finally, although the paper is well written, would be good to have some final language checks eg "It would occurred if ALD for COPD" vs. "this would have occurred"; "This emphasized that close attention should" vs "this study emphasizes" or "Results of our study emphasize" But please be informed that I'm not native English either and the paper is well written! 4/ Strengths and limitations of the study: you have • "This is the first study to specifically compare patients with uncontrolled severe asthma with the overall asthmatic population. " But as you correctly pointed out in the answers to the reviewers comments, this holds for the situation in France which you re-phrased in in the discussion, "This is the first study to specifically compare patients with uncontrolled severe asthma with the overall asthmatic population, in the French population."==> better rephrase it in the strengths and limitations as well

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Dr. Katia Verhamme, Erasmus Medical Center Comments to the Author:
First of all, I appreciate the efforts that the authors took to address my comments/questions.
I only have some final comments/questions:

1/ With regard to the cost - in your answer you specify that you used the 2018 consumer price index. In the manuscript itself, "adjustment to 2018 Euros (€) " - this does not mean a cost of 2018 euro but the 2018 consumer price index. I would adjust in the text as it is still confusing the way it is written. Also cost of an ED visit seems to be cheap in France? Mean of 6 euro for an ED visit in the general population?

We apologize for the lack of clarity in the manuscript.
Indeed, we adjusted all costs evaluated between 2014 (index date) and 2016 to 2018 euros, using the 2018 consumer price index published by *Institut National de la Statistique et des Études Économiques, INSEE*. The goal was to provide costs corresponding to those applicable at the date of data access. The corresponding sentence in the manuscript was rephrased as follows (page 9):
"Costs were evaluated from the collective perspective, and all costs collected between 2014 and 2016 were reevaluated with adjustment to correspond to 2018 Euros (€) using the 2018 consumer price index (health data index 4011-E, published by national institute of statistics and economic studies, Institut National de la Statistique et des Études Économiques, INSEE), since 2018 was the date of data access."

The costs presented in Table 2 correspond to costs per patient. We found a mean cost per patient from the general population of 6 euros for emergency department (ED) visits without hospitalization. However, not all patients (2,217 patients in general population cohort) had an ED visit, which is responsible for this weak mean cost of ED visit per patient. Details were brought to the manuscript, and cost rounding was harmonized (pages 16-18).

2/ I'm still struggling somewhat with mortality in uncontrolled asthma in patients with and without psychiatric conditions. This was based on checking for interaction so am I correct to assume that you created an interaction term between uncontrolled severe asthma or general population and psychiatric conditions and then checked whether this interaction was significant. And the results in table S3- these are the results of the multivariate analysis including age, cardiovascular conditions, diabetes, cancer, uncontrolled asthma &psychiatric conditions (with general population and psychiatric condition as reference), uncontrolled asthma without psychiatric conditions (with general population without psychiatric condition as reference)?
But would the message then be that risk of mortality is only higher in patients with uncontrolled asthma but without psychiatric conditions. Also, did you check for the effect of adjustment of psychotropic drugs (which you also have in your dataset)

We indeed created interaction terms between uncontrolled severe asthma or general population and each of the other covariates (*i.e.* age, history of cardiovascular diseases, diabetes, psychiatric disease, and cancer) to check if these interactions were significant.
Only the interaction between uncontrolled severe asthma or general population and history of psychiatric disease was significant, so this interaction term was added to the final Cox model.
Then, the hazard-ratios were directly obtained from this model, as clarified in the new version of the corresponding paragraph of the results section (page 12), as follows:
"Due to a significant interaction between population (uncontrolled severe asthma or general population) and history of psychiatric disease in the Cox model assessing mortality risk, impact of population was assessed by history of psychiatric disease, and impact of history of psychiatric disease was assessed by population (Table S3, Supplementary File). Uncontrolled severe asthma increased mortality risk, only for patients without history of psychiatric disease (hazard ratio [HR]: 3.25; 95% CI: 2.14, 4.92). The difference in mortality risk between patients with uncontrolled severe asthma and general population was not significant in patients with history of psychiatric disease (HR: 1.22; 95% CI: 0.66, 2.26). Comorbidities (age, history of cardiovascular disease, diabetes, and cancer) increased mortality risk, especially cancer (HR: 2.40; 95% CI: 1.64, 3.50). Among subjects without history of psychiatric disease, overall survival was lower in the uncontrolled severe asthmatic cohort compared to the general population, with a difference of 10% at 24 months (Figure S4, Supplementary File)."

We do agree that the message is that increased risk of mortality is only higher in patients with uncontrolled severe asthma from the population without history of psychiatric disease. This increased risk was not found in patients with uncontrolled severe asthma from the population with history of psychiatric disease.
We did not adjust on the use of psychotropic treatments (anxiolytics, antidepressants, and neuroleptics) since we did not plan to explore mortality in population with history of psychiatric disease. Indeed, the results of hazard-ratios were all obtained from the same final Cox model, so the impact of uncontrolled severe asthma in the population with a history of psychiatric disease was only adjusted on age, history of cardiovascular diseases, diabetes and cancer. We did not conduct any other in-depth analysis assessing factors associated with mortality in subjects with a history of psychiatric disease since it was not the purpose of this study.

We modified the manuscript to highlight the key message (page 12, see above), and to raise the limit concerning the lack of adjustment on psychotropic drugs use, as follows (pages 20-21): *"uncontrolled severe asthma was associated with increased mortality, only for patients without history of psychiatric disease. This increased risk was not found in patients with history of psychiatric disease, however the statistical model was only adjusted for age, history of cardiovascular disease, diabetes, and cancer but not for other potential confounders such as psychotropic drugs use since we did not aim at assessing factors associated with mortality in subjects with a history of psychiatric disease."*

Results of hazard-ratios of history of psychiatric disease, in population with uncontrolled severe asthma, and in general population were also added in Supplementary Material Table S3 (page 9 in

Supplementary) in order to be more exhaustive, even if we don't interpret these hazard-ratios in the manuscript.

3/ Finally, although the paper is well written, would be good to have some final language checks eg "It would occurred if ALD for COPD" vs. "this would have occurred"; "This emphasized that close attention should" vs "this study emphasizes" or "Results of our study emphasize"
But please be informed that I'm not native English either and the paper is well written!

These modifications and overall language and formulation check were brought to the manuscript (all pages).

4/ Strengths and limitations of the study:
you have •"This is the first study to specifically compare patients with uncontrolled severe asthma with the overall asthmatic population. "
But as you correctly pointed out in the answers to the reviewers comments, this holds for the situation in France which you re-phrased in in the discussion, "This is the first study to specifically compare patients with uncontrolled severe asthma with the overall asthmatic population, in the French population."==> better rephrase it in the strengths and limitations as well

We thank you for this comment. We modified the "Strengths and Limitations" section of the manuscript accordingly (page 4).

VERSION 3 – REVIEW

REVIEWER	Verhamme, Katia Erasmus Medical Center, Medical Informatics Katia Verhamme conducts research within the field of respiratory pharmaco-epidemiology. Her research group receives/received unconditional research grants from Yamanouchi, Pfizer-Boehringer Ingelheim, Novartis, GSK, Chiesi none of which could be perceived as conflict of interest to the reviewed paper
REVIEW RETURNED	25-Jul-2022

GENERAL COMMENTS	Very nice paper and I do appreciate the efforts spend by the co-authors to address my questions (if relevant) and to amend the paper accordingly. It was a pleasure to review this paper and get feedback from the authors.