PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Demographic, lifestyle, and comorbid risk factors for all-cause mortality in a Danish cohort of middle-aged adults with incident asthma
AUTHORS	Tupper, Oliver Djurhuus; Andersen, ZJ; Ulrik, Charlotte

VERSION 1 – REVIEW

REVIEWER	Toppila-Salmi, Sanna Helsingin ja Uudenmaan sairaanhoitopiiri, Skin and Allergy Hospital
REVIEW RETURNED	16-Mar-2021

GENERAL COMMENTS	The study question is important and may have clinical relevance in prevention of excess mortality due to asthma and co-morbidities. There are some concerns. 1. How was asthma diagnosed? Was it based on lung function test results? Or only on data of hospital visit due to asthma-like symptoms? 2. The N of asthmatics and N of deaths among asthmatics was low 3. The population was from two big cities of Denmark. It would have been better if the study population had covered also people living in countryside. 4. Did socioeconomic status, allergic diseases, or ASA-intolerance affect the results? 5. A limitation is that early-life background factors were not available. They could affect the results. 6. Was data of asthma severity available? if yes please consider to evaluate it also?

REVIEWER	Rovina, Nicoletta University of Athens
REVIEW RETURNED	11-May-2021

GENERAL COMMENTS	In this study Dr Tupper et al aimed to identify factors associated with all-cause mortality in adults with incident asthma. The interesting fact in this study is that a relatively high number of persons with incident asthma were followed-up for 20 years, with no loss to follow-up. However there are some issues to be addressed 1. The diagnosis of asthma was based on registered information and not on an objective assessment-this may include diagnosis biases that are difficult to by identified and or clarified in a further

	analysis. Perhaps, taking also in account the medication used for the management of each occasion would be more helpful in the characterization.
	2. Since included patients were these with first-ever admission to a hospital, emergency department, or outpatient clinic with a primary diagnosis of asthma moderate and severe asthma may be the main asthma population of this study. Therefore, the findings of the study do not reflect all asthma severity spectrum
	3.The diagnosis of asthma was based on the records of ICD-10 codes so there may be a proportion of misdiagnosis.
	4. The prevalence of asthma in this cohort is way too low (about 1%) in comparison to general population data. Is this indicative of limitations deriving from the records in the registry?
	5. In page 288 authors state "reported physical activity for some was reported multiple years before the first contact for incident asthma. We can, therefore, not be sure that the level of physical activity still applies at follow-up". As physical activity is one of the main outcomes of this study, this statement compromises its strength
	6. In pages 232-233 "Additionally, is there an upper limit of activity were the risks of adverse outcomes outweigh the benefits". This phrase does not make sense, please clarify
	7. In page 294 this phrase also needs clarification "As the number of events in this cohort study was not substantial and therefore not meeting the traditional, events per variable of 10 rule. There is, therefore, a risk of both type 1 and 2 errors".
	8. Language editing should be performed

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Sanna Toppila-Salmi, Helsingin ja Uudenmaan sairaanhoitopiiri

Comments to the Author:
The study question is important and may have clinical relevance in prevention of excess mortality due to asthma and co-morbidities. There are some concerns.
1. How was asthma diagnosed? Was it based on lung function test results? Or only on data of hospital visit due to asthma-like symptoms?

Author response: The diagnosis of asthma was based on data from hospital visits, where the attending physician has assigned the ICD code for asthma as the primary reason for the visit. We have adjusted the methods section to clarify this and it is discussed in the limitations section.

2. The N of asthmatics and N of deaths among asthmatics was low

Author response: We absolutely agree, and it is one of the primary limitations of the study. However, due to the novelty of the findings (physical activity and comorbidities in relation to mortality among patients with asthma) the study adds important information to our current knowledge.

3. The population was from two big cities of Denmark. It would have been better if the study population had covered also people living in countryside.

Author response: This was, based on the selection of the original sample (years ago) not an option,

and, on the other hand, based on the possible differences in level and type of physical activity between persons living in big cities compared with those living in the countryside might have hampered the interpretation of the findings.

4. Did socioeconomic status, allergic diseases, or ASA-intolerance affect the results?

Author response: Apart from marriage status, unfortunately, we do not have access to this data in the present cohort, and based on our knowledge of free healthcare etc. in Denmark, we do not believe that taken these factors into account would have substantially affected the findings.

5. A limitation is that early-life background factors were not available. They could affect the results.

Author response: Yes, absolutely, there is a plethora of variables that would have been ideal to have included in the model. Due to the setup of the cohort, as mentioned above, we only have access to lifestyle and comorbidity

6. Was data of asthma severity available? if yes please consider to evaluate it also?

Author response: Data on asthma severity is not available, this has been added to the limitations.

Reviewer: 2
Dr. Nicoletta Rovina, University of Athens

Comments to the Author:
In this study Dr Tupper et al aimed to identify factors associated with all-cause mortality in adults with incident asthma.

The interesting fact in this study is that a relatively high number of persons with incident asthma were followed-up for 20 years, with no loss to follow-up.

However there are some issues to be addressed

1. The diagnosis of asthma was based on registered information and not on an objective assessment- this may include diagnosis biases that are difficult to by identified and or clarified in a further analysis. Perhaps, taking also in account the medication used for the management of each occasion would be more helpful in the characterization.

Author response: Data on asthma medication is not available to us in this cohort, but we agree this would certainly strengthen the study. Diagnosis of asthma based on register information, while not ideal, has merit in identifying potential risk factors previously not studied as shown in a previously published paper, referenced in the article.

2. Since included patients were these with first-ever admission to a hospital, emergency department, or outpatient clinic with a primary diagnosis of asthma moderate and severe asthma may be the main asthma population of this study. Therefore, the findings of the study do not reflect all asthma severity spectrum.

Author response: Indeed, this may potentially limit generalisability, though a paper from 2014 showed that 25% of asthma patients admitted in Denmark had mild or moderate asthma. This possible limitation has been added to the limitations sub-section.

3.The diagnosis of asthma was based on the records of ICD-10 codes so there may be a proportion

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of misdiagnosis.

Author response: Yes, while not ideal, in terms of identifying risk factors associated with specific outcomes registry based diagnosis have previously been shown to be robust.

4. The prevalence of asthma in this cohort is way too low (about 1%) in comparison to general population data. Is this indicative of limitations deriving from the records in the registry?

Author response: The low prevalence is due to excluding participants with a known asthma diagnosis at baseline and only identifying patients with a first-time hospital contact for asthma.

5. In page 288 authors state "reported physical activity for some was reported multiple years before the first contact for incident asthma. We can, therefore, not be sure that the level of physical activity still applies at follow-up". As physical activity is one of the main outcomes of this study, this statement compromises its strength

Author response: Clarifying the studies limitations is important to allow the reader to determining the applicability of the findings. Our study has numerous limitations. However, due to the novelty of the findings, we feel it is an important contribution. Further studies identifying how varying types and intensities of physical activity affect mortality in individuals with asthma, would be an important next step. However, there is some evidence that, to a certain extent, activity levels persist throughout life.

6. In pages 232-233 "Additionally, is there an upper limit of activity were the risks of adverse outcomes outweigh the benefits". This phrase does not make sense, please clarify

Author response: Thank you, the sentence has been rephrased for clarity. The question raised was, whether at a very high level of physical activity, persons with asthma may not experience a benefit of decreased mortality risk.

7. In page 294 this phrase also needs clarification "As the number of events in this cohort study was not substantial and therefore not meeting the traditional, events per variable of 10 rule. There is, therefore, a risk of both type 1 and 2 errors".

Author response: The sentence has been edited for clarification.

8. Language editing should be performed

Author response: The article has been reviewed for grammar, phrasing and clarity.

VERSION 2 – REVIEW

REVIEWER	Toppila-Salmi, Sanna Helsingin ja Uudenmaan sairaanhoitopiiri, Skin and Allergy Hospital
REVIEW RETURNED	01-Jul-2021

GENERAL COMMENTS	The author seems to have responded to the questions adequately and revised the manuscript well. Thank you.

REVIEWER	Rovina, Nicoletta University of Athens
REVIEW RETURNED	26-Jun-2021

GENERAL COMMENTS	All the concerns raised are covered by authors clarifications

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Dr. Sanna Toppila-Salmi, Helsingin ja Uudenmaan sairaanhoitopiiri
Comments to the Author:
The author seems to have responded to the questions adequately and revised the manuscript well. Thank you.

Reviewer2
Dr. Nicoletta Rovina, University of Athens
Comments to the Author:
All the concerns raised are covered by authors clarifications