PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence of lifestyle characteristics in glucocorticoid users and nonusers: A Danish population-based cross-sectional study
AUTHORS	Laugesen, Kristina; Petersen, Irene; Pedersen, Lars; Breinholt Larsen, Finn; Jørgensen, Jens Otto; Sørensen, Henrik T.

VERSION 1 – REVIEW

REVIEWER	Adel Mansur University Hospitals Birmingham, Birmingham, UK
REVIEW RETURNED	10-May-2019

GENERAL COMMENTS	This is a large survey based study that explored life style (BMI, alcohol, smoking, daily activities, etc) differences between people exposed to systemic corticosteroids (ever, recent, current) and those never exposed. The study showed no real difference between the groups except for marginal increase in obesity in the OCS exposed group and female OCS users had lower risk of alcohol consumption than the non users. The authors argued that their findings of life style can be used in future OCS observational studies where life style effects not available. The study seemed overall well written and presented. I still however wish to have further clarification on the strength of the message being conveyed here. The cross sectional nature of the study limits significantly this study ability to establish any temporal relationship between OCS use and life style effects. this is being acknowledge by the authors but they need to dilute the overall conclusion of the study in the abstract and manuscript. The observed increase in prevalence of obesity in the OCS group was statistically significant but is small and the difference alcohol consumption is only seen between females with probable overall conclusion of only small marginal difference between the groups!! this require further discussion and clarification. Specific Q1.title: consider some adjustment to reflect outcome or message! Q2. the relation between obesity and OCS is well known (does this study add any thing new?) Authors needs to clarify that further in the discussion. Q3. Tables 1 and 2: please add p-values

REVIEWER	Jenny Hong St Paul's Hospital, Canada
REVIEW RETURNED	02-Jul-2019

GENERAL COMMENTS	Overall: The authors should have labelled corticosteroid use based on dose/duration rather than ever/never use… long term steroids use are what is likely going to cause the adverse effect effects in patients. Because of potential misclassification of corticosteroid use from short establishment of the prescription database.. the study did not provide much more information than what is already known in literature. This study has cofounders likely affected their results . Introduction - Line 11- 16: Authors should note how long of duration and at what doses of corticosteroid does these adverse effects occur- it is very general and incorrect to say that any use of corticosteroids cause these effects. Short term, low dose corticosteroid are not associated with the adverse effects as mentioned by the authors Study Population/ Life style data - What was the original intent of the survey, was it also used for other studies? - How was the survey conducted? If via telephone how are the data collectors trained? - Were incentives given for completing the survey? Data on medication use - The term 'corticosteroid use' is very general.. the study would have provided more information by looking at steroid doses/duration instead of ever use/never use Statistical analyses - Line 30-39: Why is COPD the only medical condition that the authors had interest in? Corticosteroid short term can also be used in patients with asthma, gout, rash, oncology use - The definition of COPD used in this study would have missed out a lot of patients with actual COPD, would suggest the authors to use a definition that is cited by medical literature. Results: - Line 12: would be interesting to know socioeconomics status of the respondents as that may play a role in their lifestyle – if that is not captured, should be mentioned as a limitation Discussion - Line 3-5: There are studies that looked at obesity among corticosteroid use: Savas M, Wester VL, Staufenbiel SM, et al. Systematic evaluation of corticosteroid use in obese and non-obese individuals: a multi-cohort study. Int J Med Sci. 2017;14(7):615-621. https://doi.org/10.7150/ ijms.19213.

REVIEWER	Christoph R. Meier Department of Pharmaceutical Sciences University of Basel Switzerland
REVIEW RETURNED	03-Jul-2019

GENERAL COMMENTS	The authors of this Danish study linked data from a questionnaire survey to medication use, in particular oral glucocorticoids (GC), which was retrieved from the Danish National Health Service Prescription database (DNHSPD). They explored whether users of oral glucocorticoids differ with regard to lifestyle characteristics from non-users and reported as main findings that GC users had a higher prevalence of obesity and that female users were more likely high-ris alcohol consumers than on-users of GC. The study is solid, and the linkage of survey data to electronic records an interesting method that is only possible in countries with unique personal identifiers, such as Denmark. The paper is nicely written and concise. The results are per se not breathtaking, but can be of interest in the context of interpreting drug safety studies of GC, when data on lifestyle factors as potential confounders are lacking; they could help estimating the impact of unmeasured potential confounders, given that the population under study is similar to the Danish population. The survey was conducted in 2010. Even though there is no reason to expect major changes in the findings over time, it may be good to explain to the reader why the authors analyzed the data some nine years later. The authors state in the limitations that a third of all randomly selected did not participate in the survey, and that this may have caused a biased estimate. On the other hand, a participation rate of two thirds is remarkable, compared to many other survey studies. How do the authors explain such a high response rate? Why did the authors only stratify their analyses by sex, but not by age? They included people above the age of 24 years, but there may be substantial differences between a 25-year old and an 80-year old GC user. Did the authors ‘a priori’ not consider age differences relevant enough for stratified analyses?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Adel Mansur
Institution and Country: University Hospitals Birmingham, Birmingham, UK
Please state any competing interests or state ‘None declared’: none

Please leave your comments for the authors below

1. This is a large survey based study that explored life style (BMI, alcohol, smoking, daily activities, etc.) differences between people exposed to systemic corticosteroids (ever, recent, current) and those never exposed. The study showed no real difference between the groups except for marginal increase in obesity in the OCS exposed group and female OCS users had lower risk of alcohol consumption than the non users. The authors argued that their findings of life style can be

used in future OCS observational studies where life style effects not available. The study seemed overall well written and presented. I still however wish to have further clarification on the strength of the message being conveyed here. The cross sectional nature of the study limits significantly this study ability to establish any temporal relationship between OCS use and life style effects. This is being acknowledge by the authors but they need to dilute the overall conclusion of the study in the abstract and manuscript. The observed increase in prevalence of obesity in the OCS group was statistically significant but is small and the difference alcohol consumption is only seen between females with probable overall conclusion of only small marginal difference between the groups!! This require further discussion and clarification.

Reply to comment #1:

Thank you very much for your valuable comments.
We have diluted the conclusion in the abstract and in the manuscript.

The conclusion in the abstract now reads:
"Our study provides a framework for quantifying potential uncontrolled confounding by lifestyle factors in studies of systemic glucocorticoids." Page 3, lines 6-7.

The conclusion in the manuscript now reads:
"In conclusion, glucocorticoid users had a slightly higher prevalence of obesity and female glucocorticoid users had a slightly lower prevalence of high-risk alcohol consumption compared to never users. Smoking habits, diet and physical activity did not differ substantially according to use of glucocorticoids. Our study provides a framework for quantifying potential uncontrolled confounding by lifestyle factors in studies of systemic glucocorticoids." Page 14, lines 20-24.

2. Title: consider some adjustment to reflect outcome or message!

Reply to #2:

In order to reflect the aim and message of our study we have reconsidered and altered the title and it now reads:
"Prevalence of lifestyle characteristics in glucocorticoid users and nonusers: A Danish population-based cross-sectional study"

3. The relation between obesity and OCS is well known (does this study add anything new?) Authors needs to clarify that further in the discussion.

Reply to #3

We agree to this comment.
We have extended the discussion:
"Data on lifestyle among glucocorticoid users is sparse, although truncal obesity is a well-known feature of glucocorticoid excess.[3, 28] In addition, one study reported higher prevalence of glucocorticoid use in obese vs. non-obese people [29] and one study found that overweight and obesity were risk factors of self-reported arthritis.[19] In contrast, the prevalence of overweight and obesity was lower in people with inflammatory bowel disease than healthy controls.[20] While arthritis and inflammatory bowel disease are potential indications for glucocorticoid treatment, these populations do not compare directly to our study population. Due to the cross-sectional design of our study, we were not able to investigate if glucocorticoid use predicted obesity or vice versa and the study did not aim to investigate adverse effects of glucocorticoids. Nevertheless, we found higher prevalence of obesity in current continuing users of glucocorticoids compared to current new users

and increasing prevalence of obesity with increasing cumulative glucocorticoid dose. These results may indicate that glucocorticoid use precedes obesity." Page 12, lines 21-24 and page 13, lines 1-9.

In addition, we have elaborated on the fact that our study was cross-sectional and did not aim or was designed to evaluate adverse effects of glucocorticoids:
"Last, as this study had a cross-sectional design, it was unable to evaluate whether lifestyle predicts glucocorticoid use or vice versa. Still, the study did not aim or was designated to evaluate adverse effects of glucocorticoids." Page 14, lines 9-11.

4. Tables 1 and 2: please add p-values

Reply to #4:

We kindly suggest not to add P-values to Table 1a and Table 1b to avoid relying on significance testing (expressed by p-values) for the interpretation of data. For references please see the Editorials in the American Statistical Association (R. L. Wasserstein et al. Moving to a World Beyond "p < 0.05" Am. Stat. https://doi.org/10.1080/00031305.2019.1583913; 2019), in Nature (It's time to talk about ditching statistical significance. Nature. 2019 Mar;567(7748):283. doi: 10.1038/d41586-019-00874-8) and in NEJM (Harrington D et al., New Guidelines for Statistical Reporting in the Journal. N Engl J Med. 2019 Jul 18;381(3):285-286. doi: 10.1056/NEJMe1906559.). Or Rothman. Six persistent research misconceptions. J Gen Intern Med. 2014 Jul;29(7):1060-4. doi: 10.1007/s11606-013-2755-z.

Reviewer: 2
Reviewer Name: Jenny Hong
Institution and Country: St Paul's Hospital, Canada
Please state any competing interests or state 'None declared': None declared
Please leave your comments for the authors below

5. Overall: The authors should have labelled corticosteroid use based on dose/duration rather than ever/never use… long term steroids use are what is likely going to cause the adverse effect effects in patients. Because of potential misclassification of corticosteroid use from short establishment of the prescription database.. the study did not provide much more information than what is already known in literature. This study has cofounders likely affected their results.

Reply to #5:

Thank you for your comments.
It is important for us to clarify that the aim of this study is not to investigate a casual association between glucocorticoid use and lifestyle or to investigate adverse effects of glucocorticoids. The aim of this study is simply to describe lifestyle according to glucocorticoid use and to inform readers on the prevalence of lifestyle characteristics according to glucocorticoid use vs. non-use. As confounding is anchored to causal associations, confounding cannot (by definition) be an issue in this study.
Our study aim is to contribute to quantifying the amount of potential uncontrolled confounding by lifestyle factors in other observational studies of glucocorticoids. Many data sources used for observational safety studies lack data on lifestyle. As result, uncontrolled confounding due to unmeasured lifestyle factors may bias observational studies on glucocorticoid use and adverse events. This limitation is for example pointed out in "Johannesdottir S, et al. Use of glucocorticoids and risk of venous thromboembolism: a nationwide population-based case-control study. JAMA Intern Med. 2013 May 13;173(9):743-52. doi: 10.1001/jamainternmed.2013.122."

One important practical implication of our study is to serve as an external source for bias analyses in other observational studies. The goal of a bias analysis is to correct the estimate of the association between the exposure and the outcome to equal what it would have been, had the unmeasured confounder been controlled for in the analysis. To perform a bias analysis you need to assign values to following bias parameters: i) The association between the confounder and the outcome. ii) The prevalence of the confounder among those with exposure of interest. Iii) The prevalence of the confounder among those without exposure of interest (Lash TL et al. Good practices for quantitative bias analysis.Int J Epidemiol. 2014 Dec;43(6):1969-85. doi: 10.1093/ije/dyu149.). Our study informs readers on the latter two parameters.

We recognize that the aim of this study may not been written clearly. Therefore, we have rewritten parts of the Introduction, Discussion and Conclusions.

The last part of the Introduction now reads:
"To quantify the amount of potential uncontrolled confounding by lifestyle factors in observational studies of systemic glucocorticoids we used data from a population based health survey and conducted a cross-sectional study to examine prevalence of lifestyle factors according to glucocorticoid use." Page 4, lines 17-20.

A section in the discussion now reads:
"Our study has important implications for quantifying the amount of potential uncontrolled confounding by lifestyle factors in observational studies of systemic glucocorticoids. Results from this study may guide assessment of the association between lifestyle and glucocorticoid use and can for example be used in a bias analysis when data on lifestyle factors is not available. Yet, it must be acknowledged that any assessment should not be based solely on associations found in this study. Directed acyclic graphs (DAGs) could be applied to ensure that recorded lifestyle factors are not mediators or colliders." Page 14, lines 12-18.

A section in the Discussion now reads:
"Last, as this study had a cross-sectional design, it was unable to evaluate whether lifestyle predicts glucocorticoid use or vice versa. Still, the study did not aim or was designed to evaluate adverse effects of glucocorticoids." Page 14, lines 9-11.

The conclusion has been rewritten and now reads:
"In conclusion, glucocorticoid users had a slightly higher prevalence of obesity and female glucocorticoid users had a slightly lower prevalence of high-risk alcohol consumption compared to never users. Smoking habits, diet and physical activity did not differ substantially according to use of glucocorticoids. Our study provides a framework for quantifying potential uncontrolled confounding by lifestyle factors in studies of systemic glucocorticoids." Page 14, lines 20-24.

We agree that dose and duration of glucocorticoid use is important.
We have conducted analyses on cumulative glucocorticoid dose expressed in prednisolone equivalents (<100 mg, 100-499 mg, 500-999 mg, 1000-1,999 mg, 2,000-4,999 mg, ≥5,000 mg), please see Figure 3 and Figure 4. In the first version of this study, we investigated total number of prescription as a marker of dose. Nevertheless, we believe that cumulative dose is a better choice. Therefore, we have omitted results on total number of prescription from the Supplementary.
Unfortunately, the Danish prescription databases do not contain information on prescription duration or prescribed daily dose. However, current new use and current continuing use may approximate short-term and long-term use.
Due to our aim of informing future observational studies on the amount of potential uncontrolled confounding by lifestyle factors in studies of systemic glucocorticoids, we have decided to keep our results on ever, current, recent, former and never users of systemic glucocorticoids.

Introduction

6. Line 11- 16: Authors should note how long of duration and at what doses of corticosteroid does these adverse effects occur- it is very general and incorrect to say that any use of corticosteroids cause these effects. Short term, low dose corticosteroid are not associated with the adverse effects as mentioned by the authors

Reply to #6:

Please see our answer provided to your overall comment. Importantly, this study does not aim to investigate adverse effects of glucocorticoids and we do not claim that glucocorticoids cause any lifestyle effects. We apologize that this has not been stated clearly enough in the original version of the manuscript and as described above we have altered the Introduction, Discussion and diluted the conclusion and interpretation of our results. In addition, we have conducted analyses on cumulative glucocorticoid.

Study Population/ Life style data

7. What was the original intent of the survey, was it also used for other studies?

Reply to #7:

The “How are you?” survey is a public funded survey based on validated questions on e.g. health behaviors, self-rated health and well-being. The main incentive of the survey is to map health and health behaviors among citizens in order to promote better health through targeted prevention and intervention by Danish health authorities.

We have added this information to the Method section:
“The main incentive of the survey was to map health and health behaviours among citizens in order to promote better health through targeted prevention and intervention by Danish health authorities. Yet, data are available for research also.” Page 5, lines 12-15.

The survey has been used for Danish public health reports as well as for other research. Please visit https://www.defactum.dk/om-DEFACTUM/projektsite/hvordan-har-du-det/rapporter-og-analyser/artikler-fra-hvordan-har-du-det/ for an overview of published studies.

8. How was the survey conducted? If via telephone how are the data collectors trained?

Reply to #8:

The questionnaire was sent by post and had to be returned by mail in reply enveloped (postage was prepaid). If people did not answer up to three reminders were sent by post.

We have extended the description of the survey in the Method section:
“The questionnaire was sent by post and had to be returned by mail in reply enveloped (postage was prepaid). Up to three reminders were sent if people did not answer. The first 1,000 people answering the questionnaire were promised two tickets for the cinema. In addition, participants were able to win lottery gifts.” Page 5, lines 19-22.

9. Were incentives given for completing the survey?

Reply to #9:

Yes. The first 1,000 people answering the questionnaire were promised two tickets for the cinema. In addition, participants were able to win lottery gifts.
We have extended the description of the survey, please see above.

Data on medication use

10. The term 'corticosteroid use' is very general. The study would have provided more information by looking at steroid doses/duration instead of ever use/never use

Reply to #10:

Please see our answer provided to your overall comment. As mentioned, we agree that dose and duration of glucocorticoid use is important. Therefore, we have conducted analyses on cumulative glucocorticoid dose (please see Figure 3 and Figure 4). Unfortunately, the Danish prescription databases do not contain information on prescription duration or prescribed daily dose.
Due to our aim of informing future observational studies on the amount of potential uncontrolled confounding by lifestyle factors in studies of systemic glucocorticoids, we have decided to keep our analyses on ever, current, recent, former and never users of systemic glucocorticoids.

Statistical analyses
11. Line 30-39: Why is COPD the only medical condition that the authors had interest in? Corticosteroid short term can also be used in patients with asthma, gout, rash, oncology use

Reply to #11:

We agree that glucocorticoids are used for a wide range of medical conditions. Unfortunately, treatment indication is not captured in the Danish registries. We have added this as a limitation to the study:
"Fourth, we did not stratify on socio economic status and were not able to identify treatment indication." Page 14, lines 2-3.

12. The definition of COPD used in this study would have missed out a lot of patients with actual COPD, would suggest the authors to use a definition that is cited by medical literature.

Reply to #12:

We argue that only very mild COPD (MRC=1 and GOLD A) is not captured by this algorithm as Danish treatment guidelines for COPD recommends either LABA, LAMA or combinations of LABA, LAMA or ICS for patient with COPD severity besides very mild COPD.
For references, please see:
https://vejledninger.dsam.dk/kol/?mode=visKapitel&cid=977&gotoChapter=984
Based on this comment as well as your comment above we have deleted the COPD stratified results from the main manuscript and moved them to the Supplementary Table 5. In addition, we have changed the wording to "potential COPD" rather than COPD throughout the manuscript.

Results:

13. Line 12: would be interesting to know socioeconomics status of the respondents as that may play a role in their lifestyle – if that is not captured, should be mentioned as a limitation

Reply to #13:

We agree. Following sentence has been added to the limitations:
“Fourth, we did not stratify on socio economic status and were not able to identify treatment indication.” Page 14, lines 4-5.

Discussion

14. Line 3-5: There are studies that looked at obesity among corticosteroid use: Savas M, Wester VL, Staufenbiel SM, et al. Systematic evaluation of corticosteroid use in obese and non-obese individuals: a multi-cohort study. Int J Med Sci. 2017;14(7):615-621. https://doi.org/10.7150/ijms.19213.

Reply to #14:

Thank you for providing use this reference. We have incorporated the reference into the manuscript (reference #29) and modified the Discussion:
“Data on lifestyle among glucocorticoid users is sparse, although truncal obesity is a well-known feature of glucocorticoid excess.[3, 28] In addition, one study reported higher prevalence of glucocorticoid use in obese vs. non-obese people [29] and one study found that overweight and obesity were risk factors of self-reported arthritis.[19] In contrast, the prevalence of overweight and obesity was lower in people with inflammatory bowel disease than healthy controls.[20] While arthritis and inflammatory bowel disease are potential indications for glucocorticoid treatment, these populations do not compare directly to our study population. Due to the cross-sectional design of our study, we were not able to investigate if glucocorticoid use predicted obesity or vice versa and the study did not aim to investigate adverse effects of glucocorticoids. Nevertheless, we found higher prevalence of obesity in current continuing users of glucocorticoids compared to current new users and increasing prevalence of obesity with increasing cumulative glucocorticoid dose. These results may indicate that glucocorticoid use precedes obesity.” Page 12, lines 21-24 and page 13, lines 1-9.

Reviewer: 3
Reviewer Name: Christoph R. Meier
Institution and Country: Department of Pharmaceutical Sciences
University of Basel
Switzerland
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
The authors of this Danish study linked data from a questionnaire survey to medication use, in particular oral glucocorticoids (GC), which was retrieved from the Danish National Health Service Prescription database (DNHSPD). They explored whether users of oral glucocorticoids differ with regard to lifestyle characteristics from non-users and reported as main findings that GC users had a higher prevalence of obesity and that female users were more likely high-ris alcohol consumers than on-users of GC. The study is solid, and the linkage of survey data to electronic records an interesting method that is only possible in countries with unique personal identifiers, such as Denmark. The paper is nicely written and concise. The results are per se not breathtaking, but can be of interest in the context of interpreting drug safety studies of GC, when data on lifestyle factors as potential confounders are lacking; they could help estimating the impact of unmeasured potential confounders, given that the population under study is similar to the Danish population.

15. The survey was conducted in 2010. Even though there is no reason to expect major changes in the findings over time, it may be good to explain to the reader why the authors analyzed the data some nine years later.

Reply to comment #15:

Thank you very much for your constructive feedback.
The “How are you?” survey is a public funded survey with the main incentive to map health and health behaviors among citizens in order to promote better health through targeted prevention and intervention by Danish health authorities. Hence, the survey was not conducted with the aim of this particular research project, which explain the time lag. Nevertheless, we agree that data are still valid and can be used for research. We have added following explanation to the manuscript:
“The main incentive of the survey was to map health and health behaviours among citizens in order to promote better health through targeted prevention and intervention by Danish health authorities. Yet, data are available for research also.” Page 5, lines 12-15.

16. The authors state in the limitations that a third of all randomly selected did not participate in the survey, and that this may have caused a biased estimate. On the other hand, a participation rate of two thirds is remarkable, compared to many other survey studies. How do the authors explain such a high response rate?

Reply to #16:

The questionnaire was sent by post and had to be returned by mail in reply enveloped (postage was prepaid). Up to three reminders were sent if people did not answer. The first 1,000 people answering the questionnaire were promised two tickets for the cinema. In addition, participants were able to win lottery gifts.

We have extended the description of the survey in the Method section:
“The questionnaire was sent by post and had to be returned by mail in reply enveloped (postage was prepaid). Up to three reminders were sent if people did not answer. The first 1,000 people answering the questionnaire were promised two tickets for the cinema. In addition, participants were able to win lottery gifts.” Page 5, lines 19-22.

17. Why did the authors only stratify their analyses by sex, but not by age? They included people above the age of 24 years, but there may be substantial differences between a 25-year old and an 80-year old GC user. Did the authors ‘a priori’ not consider age differences relevant enough for stratified analyses?

Reply to #17:

Thank you for this very relevant comment. We have performed stratified analyses by age group (25-44 years of age, 45-64 years of age and ≥ 65 years of age) and we found no substantial differences by age group. The stratified analyses are now presented in Supplementary Table 6 and Supplementary Table 7.

VERSION 2 – REVIEW

REVIEWER	Jenny Hong St. Paul's Hospital, Vancouver, BC, Canada
REVIEW RETURNED	29-Sep-2019

GENERAL COMMENTS	The comments from before has been addressed. On page 12, line 20, best to write out the aPR ratios instead of having the reader to flip back and forth to figure 3 and 4. The limitations of this paper has been addressed by the authors

REVIEWER	Christoph R. Meier Basel Pharmacoepidemiology Unit Department of Pharmaceutucal Sciences University of Basel, Switzerland
REVIEW RETURNED	18-Sep-2019

GENERAL COMMENTS	The authors adequately revised the manuscript and is now ready for publication in my view.