PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence and determinants of cigarette smoking relapse among US adult smokers - a longitudinal study
AUTHORS	Alboksmaty, Ahmed; Agaku, Israel Terungwa; Odani, Satomi; Filippidis, Filippos

VERSION 1 – REVIEW

REVIEWER	Ramces Falfán-Valencia Instituto Nacional de Enfermedades Respiratorias Ismael Cosio Villegas. México
REVIEW RETURNED	13-Jun-2019

GENERAL COMMENTS	Reviewer opinion This study provides an insight into predictors of cigarette smoking relapse in a sample of the adult US population. In a longitudinal study, authors explore smoking relapse over the course one year. In general, the manuscript is well written, study design, statistical analysis, and results description are consistent with the research problem. Previously, genetic factors have been described associated with quitting smoking and relapse, a brief paragraph about it would be useful in the introduction section. Minor comments: Results over Hispanics subjects should be addressed in caution since only almost 130 subjects are included. Please avoid referrer to “Whites” (abstract and discussion), instead use Caucasian ancestry.

REVIEWER	Lukman Thalib Qatar University Qatat
REVIEW RETURNED	27-Jul-2019

GENERAL COMMENTS	The manuscript may benefit from reconsidering the following: 1. Table 2 may be better presented as a forrest plot for ease of reading. 2. Limitations on how important potential confounders could not be adjusted for and other issues pertaining to limitations of this research should be broadened. Identifying the factors that were well established to be related to relapse in the literature and why they could not be adjusted for and if adjusted for would the current findings be different could be included. In other words, what were identified a priori to be adjusted for and what were not available (not even proxies) need to be clarified. Note that this is an observational studies that are hugely influenced by the confounders.

	3. Over reliance on p-values while the sample size are restricted need to be carefully addressed. For example, authors suggest no gender differences in relapse despite 10% reduction but as they appear to have relied on p values to come to judgement? 4. Do they need chi-square tests and univariate logistic regressions? 5. Language could be revised. May be contractions could be avoided. For example, 'nor' is indicated as "or". Flow could be improved. if the focus is determinants or overall and subgroup prevalence of relapse need to be clear. 6. In one place the paper appear to say it is only focusing on cigarette smoking, while later the paper reports on four types of NCTP? Clarity helps. 7. Conclusions in the abstract and the main conclusion could be significant improved to reflect what was found and what the real clinical implications of the findings. Conclusion should also reflect the limitations of the study.

REVIEWER	János Sándor Department of Preventive Medicine, Faculty of Public Health, University of Debrecen, Hungary
REVIEW RETURNED	29-Jul-2019

GENERAL COMMENTS	The paper deals with the occurrence of relapse after smoking cessation, and it tries to identify factors influencing that. The main advantage of the study is that it is focused on the population level importance of smoking relapse. (Our knowledge is much more restricted in this aspect than our knowledge on smoking relapse epidemiology in clinical samples of treated patients.) The secondary analysis utilizes a well-constructed database built-up by a cohort investigation. A rare outcome is investigated in sample derived from a nationally representative cohort. The paper is basically well structured. Problems are mentioned below: Introduction The research need is presented convincingly, and the problems caused by the lack of knowledge are introduced properly. The section that summarizes the known risk factors of smoking relapse needs some completion. It is known that the relapse is basically determined by the exposure to any kind of support in the abstinence period, the quality of this support. Also, it is well described that the pregnancy, the diagnosis of a new chronic disease or a new complication of an existing chronic disease have remarkable influence on smoking behavior. Furthermore, the knowledge related to the smoking and smoking relapse is of importance in the respect of relapse frequency, as well. These factors should not be omitted in the summary. Objectives The aim is properly specified apart from the negligent use of "smoking" term. My understanding is that the paper is about the cigarette smoking relapse. It needs correction. Methods Data source Data source is properly described. The basic cohort of TUS-CPS is introduced. I think that to use of peer-reviewed references (there is 40 papers by Pubmed “TUS-CPS”search) for this cohort investigation would be much better solution than to use a link for the project’s website.

	It needs some explanation why to publish these results (originated from 2010 and 2011) in 2019. The process of sample generation is clearly described. I miss the evaluation of the difference between 80% self-respondents and the other 20% of participants. It is not explained how this restriction influenced the representativity of the sample. The same is the problem with the 796 participants who changed their “ever smoker” status. I miss explicit evaluation of the influence of this change for the observed results. (Maybe, the required sentences can be inserted into the discussion section.) Measures It is not self-evidence that the regular smokers and the occasional smokers are justified to be categorized into a common category. It needs some explanation. Statistical analysis There is no argumentation for use of forward stepwise regression approach to define the indicator set for multiple logistic modelling. I think that the use of chi-squared test and univariate logistic regression modelling is redundant. I cannot find the AIC and BIC values in the manuscript. Weights were applied but the process of weighting is not declared. Results I think that the 3258 subjects met the inclusion and avoid the exclusion criteria. “Weighted %” in column head of Table 1 needs explanation. Regarding Table 2: "Weighted" mentioned in the title is not specified. (see above) “95% CI” in column head should be replaced with lower and upper limits of 95% CI. There is no results presented which could support the omission of family income, education level, NCTP use, and smoke-free workplace from the multiple logistic regression modelling. (Each of these items apart from NCTP use has significant influence on relapse.) P-values from chi-squared tests are not presented. The promised AIC and BIC values are not showed for model presented in Table 3 (and the related tables of supplementary materials). A kind of r-squared is also missing. Discussion The use of "smoking" should be replaced by "cigarette smoking" throughout the section. I found the comparison of the authors’ observation with other published results needs extension to make it possible to formulate opinion on the consistency of authors’ achievements. The misclassification of abstinence period is acknowledged but the consequence of this validity issue on the conclusion is not evaluated. The potential biases related to the sampling process (exclusion of not self-responding, high frequency of misclassified ever smokers) is not discussed. It is not clear why did not present the extrapolation of the results for the US adult population (the basic cohort is representative for US states and for the US). The statement of “Our analysis contributes to the limited literature on smoking relapse.” should be specified more considering that the relapse epidemiology is poorly described by the literature for

	populations. Knowledge on determinants for patient groups providing with cessation support is much better known. I think that the design appropriateness should be discussed. The cohort investigation is not our primary choice in studying relatively rare outcome. Conclusion Conclusions do not correspond to the objectives: the observed prevalence of relapse is not included in the conclusion. Determinants of relapse mentioned in the conclusion will be convincing if the validity problems will be discussed and the missed statistical results will be presented – and if the results of these missing discussions and presentations will not undermine the validity.

REVIEWER	Rahim Moineddin University of Toronto
REVIEW RETURNED	26-Aug-2019

GENERAL COMMENTS	The data is old, 2010-2011. Why authors couldn't use more recent data?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Ramces Falfán-Valencia
Institution and Country: Instituto Nacional de Enfermedades Respiratorias Ismael Cosio Villegas. México
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Reviewer opinion
This study provides an insight into predictors of cigarette smoking relapse in a sample of the adult US population. In a longitudinal study, authors explore smoking relapse over the course one year.
In general, the manuscript is well written, study design, statistical analysis, and results description are consistent with the research problem.

Response: We thank the reviewer for the positive review of our work.

Previously, genetic factors have been described associated with quitting smoking and relapse, a brief paragraph about it would be useful in the introduction section.

Response: We thank the reviewer for mentioning the potential role of genetic factors. We have now added some text in the introduction to highlight the previous studies have reported a link between genetic factors and smoking behaviour. We did not explore genetic factors in our study, hence we did not expand on this topic further, but we now mention it in the section about study limitations.

Minor comments:
Results over Hispanics subjects should be addressed in caution since only almost 130 subjects are included.

Response: The reviewer is correct in pointing this out. As a response, we have mentioned the limited sample size of the Hispanic population in the Results. We also mentioned in the Discussion (strengths and limitations section) that findings in certain smaller subgroups, such as the Hispanics, should be

interpreted with caution.

Please avoid referrer to “Whites” (abstract and discussion), instead use Caucasian ancestry.

Response: We appreciate this comment by the reviewer and understand why the term “Caucasian” may be preferable to “Whites”. However, within this particular context, we do not think that the term “Whites” may lead to inappropriate racial interpretations. This is the standard term used for Caucasian in the vast majority of US surveys and relevant publications; therefore preserving the original terminology of the survey is useful to allow comparisons with other studies and to avoid confusion among people who are familiar with the survey analysed.

Reviewer: 2

Reviewer Name: Lukman Thalib
Institution and Country:
Qatar University
Qatat
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
The manuscript may benefit from reconsidering the following:
1. Table 2 may be better presented as a forrest plot for ease of reading.

Response: We have replaced Table 2 with a Forrest plot (Figure 2) which better illustrates the differences in the prevalence of relapse among different subgroups.

2. Limitations on how important potential confounders could not be adjusted for and other issues pertaining to limitations of this research should be broadened. Identifying the factors that were well established to be related to relapse in the literature and why they could not be adjusted for and if adjusted for would the current findings be different could be included. In other words, what were identified a priori to be adjusted for and what were not available (not even proxies) need to be clarified. Note that this is an observational studies that are hugely influenced by the confounders.

Response: In response to this comment, we have edited the limitations section of the manuscript. This now includes that the study was not originally designed to explore the main research question of our analysis, which resulted in certain factors missing from our study altogether. Such factors include genetic factors and health literacy regarding smoking hazards. It is unclear how these may have influenced the results, but we d explicitly mention that some of the findings should be interpreted with caution and avoid any causal language to describe the associations found.

3. Over reliance on p-values while the sample size are restricted need to be carefully addressed. For example, authors suggest no gender differences in relapse despite 10% reduction but as they appear to have relied on p values to come to judgement?

Response: We appreciate this comment. We fully agree that p-values should not be the sole criterion to evaluate associations. Actually, we don’t even report p-values in this manuscript. However, we do report 95% CI, which provide an indication of the uncertainty of the estimates. In the majority of cases in this analysis, whenever there is clear suggestion of an association the 95% CI do not cross 1 as well. In the case of sex, there is some suggestion that males were less likely to relapse, but the CI were very wide (0.61-1.37). Therefore, we have now added in the results that there is a suggestion of an association with sex.

4. Do they need chi-square tests and univariate logistic regressions?

Response: We have removed Chi-square test results from the manuscript as recommended by the reviewer, however, we have kept the results of the univariate models (in a table) to show how adjusting for potential confounders may have affected the associations. Only the fully adjusted estimates are discussed in the text.

5. Language could be revised. May be contractions could be avoided. For example, 'nor' is indicated as "or". Flow could be improved. if the focus is determinants or overall and subgroup prevalence of relapse need to be clear.

Response: We reviewed and edited the text to improve the flow. Regarding the main focus of the study, we wanted to explore both the prevalence and determinants of smoking relapse among the study population. We were of course restricted to investigate only the factors that were included in the TUS-CPS survey, but the aim of the study to investigate both is highlighted clearly both in the title and the last paragraph of the introduction.

6. In one place the paper appear to say it is only focusing on cigarette smoking, while later the paper reports on four types of NCTP? Clarity helps.

Response: Our analysis focused only on cigarette smoking relapse. We do refer to the use of NCTP as one of the possible determinants of relapse. NCTP was included in a regression model as one of the independent variables. We have slightly edited the Methods section of the paper to clarify that the outcome is cigarette smoking relapse and NCTP use is explored as an independent variable in the regression model.

7. Conclusions in the abstract and the main conclusion could be significant improved to reflect what was found and what the real clinical implications of the findings. Conclusion should also reflect the limitations of the study.

Response: We have now edited the conclusions in both the abstract and the main text to focus more clearly on the findings of this study and to highlight the limitations and the need for further research designed explicitly to explore this research question.

Reviewer: 3

Reviewer Name: János Sándor
Institution and Country: Department of Preventive Medicine, Faculty of Public Health, University of Debrecen, Hungary
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
The paper deals with the occurrence of relapse after smoking cessation, and it tries to identify factors influencing that. The main advantage of the study is that it is focused on the population level importance of smoking relapse. (Our knowledge is much more restricted in this aspect than our knowledge on smoking relapse epidemiology in clinical samples of treated patients.) The secondary analysis utilizes a well-constructed database built-up by a cohort investigation. A rare outcome is investigated in sample derived from a nationally representative cohort. The paper is basically well structured. Problems are mentioned below:

Response: We thank the reviewer for the overall positive assessment of our work.

Introduction
The research need is presented convincingly, and the problems caused by the lack of knowledge are introduced properly.
The section that summarizes the known risk factors of smoking relapse needs some completion. It is known that the relapse is basically determined by the exposure to any kind of support in the abstinence period, the quality of this support. Also, it is well described that the pregnancy, the diagnosis of a new chronic disease or a new complication of an existing chronic disease have remarkable influence on smoking behavior. Furthermore, the knowledge related to the smoking and smoking relapse is of importance in the respect of relapse frequency, as well. These factors should not be omitted in the summary.

Response: We thank the reviewer for this comment. As a response, we have heavily edited the introduction to include several additional factors that have been shown to be associated with relapse. Most of them are only briefly mentioned, due to word limitations, but appropriate references have been added to make the section more complete.

Objectives
The aim is properly specified apart from the negligent use of "smoking" term. My understanding is that the paper is about the cigarette smoking relapse. It needs correction.

Response: The word ‘cigarette’ has been added to provide clarity regarding our aim.

Methods

Data source
Data source is properly described. The basic cohort of TUS-CPS is introduced. I think that to use of peer-reviewed references (there is 40 papers by Pubmed “TUS-CPS”search) for this cohort investigation would be much better solution than to use a link for the project’s website.

Response: We have included a reference for a peer-reviewed published study while keeping the reference for the original webpage of the survey as well. This would allow researchers to easily access the original data.

It needs some explanation why to publish these results (originated from 2010 and 2011) in 2019.

Response: This is a fair point. This cohort of the survey 2010-11 is the most recent longitudinal cohort of the national survey that assessed the subject of interest, smoking relapse behaviour. We have referred to that in the methods section as well as highlighting that in the limitations of the study, indicating that the tobacco products environment has changed considerably since 2011; therefore, our findings may not fully reflect the current conditions in the US.

The process of sample generation is clearly described. I miss the evaluation of the difference between 80% self-respondents and the other 20% of participants. It is not explained how this restriction influenced the representativity of the sample. The same is the problem with the 796 participants who changed their “ever smoker” status. I miss explicit evaluation of the influence of this change for the observed results. (Maybe, the required sentences can be inserted into the discussion section.)

Response: Indeed, these elements of the study may have introduced selection bias, which would have an impact on the representativeness of the study sample. There is no indication to suggest that this bias would have a specific direction, so we can’t comment further on the issue. However, this is a key limitation of the study and hence, we have explicitly included this in the limitations section.

Measures
It is not self-evidence that the regular smokers and the occasional smokers are justified to be categorized into a common category. It needs some explanation.

Response: Thanks for highlighting that point. We have merged these two answers into one driven by the fact that even very low cigarette consumption is associated with significant health risks. We now mention this explicitly in the Methods/Measures section.

Statistical analysis
There is no argumentation for use of forward stepwise regression approach to define the indicator set for multiple logistic modelling.

Response: We apologise for the confusion. We didn't follow a forward stepwise approach. Factors identified as potentially relevant in existing literature were considered for inclusion in the model. The final specification of the model was decided based on an iterative approach using AIC/BIC criteria. We have removed the mention of the forward stepwise approach and clarify the process in the Statistical analysis section.

I think that the use of chi-squared test and univariate logistic regression modelling is redundant.

Response: We agree with the reviewer and have removed chi-squares from our manuscript.

I cannot find the AIC and BIC values in the manuscript.

Response: AIC/BIC values were used to compare different specifications of our model and decide which one better fits our data. We now mention the AIC/BIC values of the final model in a footnote in table 2.

Weights were applied but the process of weighting is not declared.

Response: We have used the official weights provided in the original datasets of the survey, which we now mention explicitly in the Methods section.

Results
I think that the 3258 subjects met the inclusion and avoid the exclusion criteria.

Response: Indeed. We have reworded this sentence.

"Weighted %" in column head of Table 1 needs explanation.

Response: We have added a footnote.

Regarding Table 2:
"Weighted" mentioned in the title is not specified. (see above)
"95% CI" in column head should be replaced with lower and upper limits of 95% CI.

Response: We have now replaced table 2 with figure 2 and have added a footnote to clarify these points.

There is no results presented which could support the omission of family income, education level, NCTP use, and smoke-free workplace from the multiple logistic regression modelling. (Each of these

items apart from NCTP use has significant influence on relapse.)

Response: As mentioned in earlier comments, we built the model exploring different specifications and looking for the most parsimonious model that could adequately fit with our data. Based on this process, which we described in the methods, the addition of these variables did not improve the model. Hence, although in theory they might influence the outcome, they did not provide more explanatory power in addition to the variables already included in our final model presented.

P-values from chi-squared tests are not presented.

Responses: Chi-squares have been removed from the manuscript.

The promised AIC and BIC values are not showed for model presented in Table 3 (and the related tables of supplementary materials). A kind of r-squared is also missing.

Response: We have added a footnote, as mentioned above.

Discussion
The use of "smoking" should be replaced by "cigarette smoking" throughout the section.

Response: As mentioned in an earlier comment, we have now clarified in the Methods section that smoking refers to cigarette smoking specifically.

I found the comparison of the authors' observation with other published results needs extension to make it possible to formulate opinion on the consistency of authors' achievements.

Response: We now refer to more previous studies and compare our findings with past results. Overall, based on this and other reviewers' comments, we have edited and expanded the discussion, within the limits of the available word count.

The misclassification of abstinence period is acknowledged but the consequence of this validity issue on the conclusion is not evaluated.

Response: We thank the reviewer for this comment. Although this is a limitation of the study, we have no reason to believe it may have introduced systematic error in our analysis. We have added this in the Discussion section.

The potential biases related to the sampling process (exclusion of not self-responding, high frequency of misclassified ever smokers) is not discussed.

Response: We have added this in the limitations section of the Discussion, as mentioned in an earlier response.

It is not clear why did not present the extrapolation of the results for the US adult population (the basic cohort is representative for US states and for the US).

Response: The reviewer raises an important point. This was indeed possible, but we felt that, considering that the data is 8 years old and both the population and the prevalence of smoking in the US have changed, such a number would have limited importance. In our study we focus on the proportion of quitters who relapse.

The statement of "Our analysis contributes to the limited literature on smoking relapse." should be

specified more considering that the relapse epidemiology is poorly described by the literature for populations. Knowledge on determinants for patient groups providing with cessation support is much better known.

Response: We have now specified that we refer to smoking relapse epidemiology at the population level.

I think that the design appropriateness should be discussed. The cohort investigation is not our primary choice in studying relatively rare outcome.

Response: We appreciate this important comment. We have considered other study designs, but the outcome is not particularly rare in the cohort (6.8% in the overall sample) hence we believe that a cohort study is appropriate to explore for the outcome of interest.

Conclusion
Conclusions do not correspond to the objectives: the observed prevalence of relapse is not included in the conclusion. Determinants of relapse mentioned in the conclusion will be convincing if the validity problems will be discussed and the missed statistical results will be presented – and if the results of these missing discussions and presentations will not undermine the validity.

Response: We have included the observed prevalence and have edited the conclusions, also based on comments by other reviewers.

Reviewer: 4

Reviewer Name: Rahim Moineddin
Institution and Country: University of Toronto
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
The data is old, 2010-2011. Why authors couldn't use more recent data?

Response: As mentioned in an earlier response this was the last longitudinal wave of this national study that assessed relapse.

VERSION 2 – REVIEW

REVIEWER	Ramcés Falfán-Valencia Instituto Nacional de Enfermedades Respiratorias Ismael Cosio Villegas
REVIEW RETURNED	27-Oct-2019

GENERAL COMMENTS	The authors have attended all of my concerns.

REVIEWER	Lukman Thalib Qatar University Qatar
REVIEW RETURNED	17-Oct-2019

GENERAL COMMENTS	Revision is satisfactory.

REVIEWER	János Sándor Department of Preventive Medicine

	University of Debrecen Hungary
REVIEW RETURNED	30-Oct-2019

GENERAL COMMENTS	All of my comments were properly addressed. I have no further comments/suggestions.

REVIEWER	Rahim Moineddin University of Toronto Canada
REVIEW RETURNED	29-Oct-2019

GENERAL COMMENTS	I have no further comments.