PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	EARLY WEIGHT GAIN AFTER STOPPING SMOKING: A PREDICTOR OF OVERALL LARGE WEIGHT GAIN? A SINGLE-SITE RETROSPECTIVE COHORT STUDY.
AUTHORS	Pankova, Alexandra; Kralikova, Eva; Zvolska, Kamila; Stepankova, Lenka; Blaha, Milan; Ovesná, Petra; Aveyard, Paul

VERSION 1 – REVIEW

REVIEWER	Francesco Pistelli, MD, PhD Pulmonary Unit, Cardiothoracic and Vascular Department, University Hospital of Pisa, Italy
REVIEW RETURNED	28-May-2018

GENERAL COMMENTS	General comments This study aims to assess whether the weight gain within 3 months after quitting smoking predicts the total weight gain after 12 months since the quit date, among smokers treated in a centre for tobacco dependence in Prague, Czech Republic, as part of a clinical routine in the real-life. A large (n=1050) study sample is analysed by using adequate study design and statistical analyses. The research topic has clinical and practical interest for the assisted smoking cessation. This reviewer has a few concerns. Specific comments Major - Using NRT was associated with lower weight gain. It would be interesting to evaluate the effect of specific types of NRT (i.e., patches, gums, lozenges, inhalers, or the combination of patch plus an ad libitum type of NRT). For example, it is known that the use of nicotine gums is associated with lower weight gain after smoking cesstion. Such observation should be also considered when discussing the result that using NRT was associated with lower weight gain. - According to baseline characteristics reported in table 1, each patient could have more than one pharmacotherapy. It should be clarified if the results from the multiple linear model (table 5) refer to the use of single pharmacotherapies or combinations of pharmacotherapies. - Information on duration of the use of the various phamacotherapies (including descriptive statistics on mean or median) should be provied. Such information should be also discussed (see Discussion section, page 20, lines 13-18). - All participants signed a written informed consent prior to study participation (see page 8, line 9). However ethics approval of the study is not reported.

	- English language may be improved in some parts of the manuscript (for example, page 14, lines 30-32; page 19, lines 9-11; page 19, lines 26-29; etc.) Minor - Abstract, Results section. "use of NRT ... associated with greater weight gain". Indeed, "not using nicotine replacement therapy" was a significant factor for prediction of higher post cessation weight gain according to multivariate linear regression analysis (see page 16, linee 32-36). - Data analysis section, lines 31-36 "... from other centres for the treatment of tobacco dependence". Clarify if the analysed dataset included data collected in more than one centre. - Table 5. Data regarding using no medications should be provided. This is important to support the assertion "... and using either no medication or ..." at page 18, lines 8-11. - Table 5. Provide the legend for BMI, BDI, FTCD. - Table 5. Add "score" to "FTCD".

REVIEWER	Riccardo Polosa University of Catania, Italy
REVIEW RETURNED	31-May-2018

GENERAL COMMENTS	GENERAL COMMENTS The authors examined in a large retrospective cohort whether early significant post-cessation weight gain would predict large weight gain at later time points. The paper has value in itself, but - as currently stands - adds confusion to an already complex topic. Most importantly, there are methodological flaws that require correction. This paper may be published if authors are willing to repeat their analysis in accordance to my recommendations (see below). MAJOR POINTS Although the reason and the scope for conducting the analysis is clear, I am unconvinced that gathering information about early significant post-cessation weight gain has any practical value. Any effort to prevent post-cessation weight gain should be put in place before any significant weight gain becomes apparent. This is the key to success in any weight management program. In the context of smoking cessation, it is a well known fact that those who experience a large gain in body weight often prefer to relapse back to smoking in order to quickly regain control of their weight. Moreover, the offer of escalation in weight management (as proposed by the Authors), is hardly viewed by smokers as a viable option. The study is set to allow a precise measure of weight gain trajectories in a large population of quitters. Unfortunately, the population assessed at 1 month is not the same at subsequent follow ups; the number of continuous abstainers at 1-yr follow up is even higher than those at earlier time points (!). In trying to illustrate trajectories in body weight changes, only abstainers who have been recorded at all and each time points should be included in the analysis. This methodological caveat might also explain why some study findings are at disagreement with those of other studies.

	The authors must restrict their analysis only to the data collected from continuous abstainers throughout the whole observation period (i.e. at each and all of the follow ups). To this end a definition of consistent continuous abstinence from tobacco smoking throughout the study must be provided. Hopefully, there will be more clarity in the results. Minor Points You stated “All participants signed a written informed consent prior to study participation” I do not think this is accurate. The data has been retrospectively collected from 2005 to 2013 and participation to a smoking cessation program was on a voluntary basis.

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1
Reviewer Name: Francesco Pistelli, MD, PhD
Institution and Country: Pulmonary Unit, Cardiothoracic and Vascular Department, University Hospital of Pisa, Italy
Competing Interests: None declared

General comments
This study aims to assess whether the weight gain within 3 months after quitting smoking predicts the total weight gain after 12 months since the quit date, among smokers treated in a centre for tobacco dependence in Prague, Czech Republic, as part of a clinical routine in the real-life.
A large (n=1050) study sample is analysed by using adequate study design and statistical analyses.
The research topic has clinical and practical interest for the assisted smoking cessation. This reviewer has a few concerns.

Specific comments
Major
- Using NRT was associated with lower weight gain. It would be interesting to evaluate the effect of specific types of NRT (i.e., patches, gums, lozenges, inhalers, or the combination of patch plus an ad libitum type of NRT). For example, it is known that the use of nicotine gums is associated with lower weight gain after smoking cessation. Such observation should be also considered when discussing the result that using NRT was associated with lower weight gain.
Response: The Cochrane review of interventions to prevent weight gain on smoking cessation showed no evidence that the effect of NRT on preventing weight gain differed by type of NRT (http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD006219.pub3/full). This is an analysis of trials, and we are not convinced that adding observational data on this really adds useful information to the manuscript. The effect of NRT depends upon the nicotine concentration, not the delivery mode, and we know that different forms of NRT are roughly equally effective for smoking cessation and deliver similar amounts of nicotine.
We have performed further analyses in order to assess the possible effect of the use of different types of medications to the post-cessation weight gain, including different types of NRT (see tables below).

Overall (1-year) weight change according to used pharmacotherapy:
Valid N Mean Median

Bupropion no 961 4.05 3.49
yes 89 4.42 3.62
Varenicline no 378 4.05 3.24
yes 672 4.10 3.60
NRT patches no 855 3.93 3.34
yes 195 4.78 4.50
NRT oral no 748 4.03 3.50
yes 302 4.22 3.45
- NRT inhaler no 920 4.07 3.50
yes 130 4.17 3.61
- NRT lozenges no 959 4.12 3.52
yes 91 3.76 3.30
- NRT gums no 911 4.01 3.49
yes 139 4.60 3.77
NRT patches AND oral no 901 3.98 3.39
yes 149 4.73 4.47

The model for weight gain with multivariable adjustment (as in Table 5) showed the following results (see table below).
Beta P-value
NRT patches 0.634 0.294
NRT inhaler -1.150 0.067
NRT lozenges -0.857 0.236
NRT gums -0.414 0.496

- According to baseline characteristics reported in table 1, each patient could have more than one pharmacotherapy. It should be clarified if the results from the multiple linear model (table 5) refer to the use of single pharmacotherapies or combinations of pharmacotherapies.
Response: This information has been clarified in the heading of Table 5 in the article.

- Information on duration of the use of the various pharmacotherapies (including descriptive statistics on mean or median) should be provided. Such information should be also discussed (see Discussion section, page 20, lines 13-18).
Response: The length of pharmacotherapy did not significantly differ between different types of medications (see table below). The information about the similarity in duration of use has been added to the article.

Length of pharmacotherapy (months):
Valid N Mean Median
Bupropion 89 5.25 3.65
Varenicline 672 4.82 3.96
NRT patches 195 2.72 2.20
NRT oral 302 4.43 2.88
- NRT inhalator 130 3.74 2.57
- NRT lozenges 91 4.11 2.73
- NRT gums 139 4.28 2.04

NRT was used by 598 patients (and this is mentioned in Table 1 in the article). The mean duration of the use of oral forms of NRT was 4.43 months (median 2.88 months) and the mean use of nicotine patches was 2.72 months (median 2.2 months) – see table above. Also this information has been added to the article.

- All participants signed a written informed consent prior to study participation (see page 8, line 9). However ethics approval of the study is not reported.
Response: This study was approved by the Ethics Committee of the General University in Prague, Czech Republic. This information is now included in the manuscript.
- English language may be improved in some parts of the manuscript (for example, page 14, lines 30-32; page 19, lines 9-11; page 19, lines 26-29; etc.)
Response: We have improved the English language throughout including the sentences described above.

Minor
- Abstract, Results section. "use of NRT ... associated with greater weight gain". Indeed, "not using nicotine replacement therapy" was a significant factor for prediction of higher post cessation weight gain according to multivariate linear regression analysis (see page 16, linee 32-36).
Response: We have simplified the presentation of this so it is now showing the use of NRT was associated with less weight gain and this is consistent throughout.

- Data analysis section, lines 31-36 "... from other centres for the treatment of tobacco dependence". Clarify if the analysed dataset included data collected in more than one centre.
Response: Data were from one centre only and this information was corrected in the manuscript and added to the manuscript title as well.
- Table 5. Data regarding using no medications should be provided. This is important to support the assertion "... and using either no medication or ..." at page 18, lines 8-11.
Response: No medication is correlated with included variables (using bupropion, varenicline, NRT). If we built another model, using any medication was not statistically significant.

- Table 5. Provide the legend for BMI, BDI, FTCD.
Response: The legend for BMI, BDI and FTCD has been provided in Table 5.
** added
- Table 5. Add "score" to "FTCD".
Response: This information has been added to Table 5.

Reviewer: 2
Reviewer Name: Riccardo Polosa
Institution and Country: University of Catania, Italy
Competing Interests: None Declared

GENERAL COMMENTS
The authors examined in a large retrospective cohort whether early significant post-cessation weight gain would predict large weight gain at later time points. The paper has value in itself, but - as currently stands - adds confusion to an already complex topic. Most importantly, there are methodological flaws that require correction. This paper may be published if authors are willing to repeat their analysis in accordance to my recommendations (see below).

MAJOR POINTS

Although the reason and the scope for conducting the analysis is clear, I am unconvinced that gathering information about early significant post-cessation weight gain has any practical value. Any effort to prevent post-cessation weight gain should be put in place before any significant weight gain becomes apparent. This is the key to success in any weight management program. In the context of smoking cessation, it is a well known fact that those who experience a large gain in body weight often prefer to relapse back to smoking in order to quickly regain control of their weight.

Moreover, the offer of escalation in weight management (as proposed by the Authors), is hardly viewed by smokers as a viable option.

Response: We understand that this is the referee's opinion but according to our knowledge, it is not backed sufficiently by the evidence. One of the authors of this manuscript and his colleagues have run two trials that aimed to recruit people who were trying to stop smoking and where the weight management support was offered alongside stopping smoking. These are: https://trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-14-182 and https://trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-11-94.
Both these trials failed to recruit because people who were trying to stop smoking were not generally interested in weight gain control, or at least insufficiently interested in weight control to join a prevention programme. In this manuscript, therefore, we are aiming to assess a different strategy to see whether it may be an alternative to this approach. It is plausible that the experience of unwanted and rapid weight gain could motivate engagement with a programme to prevent this, especially so if we know that such weight gain predicts large future gains. However, by intervening early, the person would have gained only a small amount of weight and therefore there is a chance to reverse this with effective support.

- The study is set to allow a precise measure of weight gain trajectories in a large population of quitters. Unfortunately, the population assessed at 1 month is not the same at subsequent follow ups; the number of continuous abstainers at 1-yr follow up is even higher than those at earlier time points (!). In trying to illustrate trajectories in body weight changes, only abstainers who have been recorded at all and each time points should be included in the analysis. This methodological caveat might also explain why some study findings are at disagreement with those of other studies.
The authors must restrict their analysis only to the data collected from continuous abstainers throughout the whole observation period (i.e. at each and all of the follow ups). To this end a definition of consistent continuous abstinence from tobacco smoking throughout the study must be provided. Hopefully, there will be more clarity in the results.
Response: The nature of all cohort studies is that all participants are not present on every occasion despite investigators' best efforts. There are at least two ways to approach to this. The first is to exclude everyone who did not complete every visit and the second is to analyse the whole data set. This referee prefers one approach. The advantage is that we can see truly longitudinal changes. The disadvantage is that it's plausible that selection of only those who adhere perfectly to the follow-up schedule is missing people whose weight trajectories differ from those who do not adhere and results suffer from selection bias. In response to this request, we have repeated the main analysis where we examine the predictive ability of early weight regain on later weight regain but only with those present at both time points and we find the results are the same (see table below). We have not included the full analysis to keep the article more concise but have mentioned this in the methods (sensitivity analysis) and the results.
The model including everyone present is reported for the editors below, but the results are very similar to the one including everyone.

Multiple model (N=566)
Personal characteristics Beta P-value
Weight change in third month (%) 0.052 0.262
Female 0.684 0.033
Age at baseline visit (years) 0.002 0.841
BMI (kg/m2) -0.020 0.127
FTCD score 0.049 0.583
Cigarettes per day -0.002 0.908
Age at regular smoking initiation (years) -0.009 0.823
Bupropion 0.338 0.529

Varenicline -0.068 0.857
Nicotine replacement therapy -0.739 0.033
Physical activity 0.215
Intercept 2.878 0.015

Minor Points

You stated, “All participants signed a written informed consent prior to study participation” I do not think this is accurate. The data has been retrospectively collected from 2005 to 2013 and participation to a smoking cessation program was on a voluntary basis.
Response: This is accurate. Because the aim was to use data from this routine clinic population for studies such as this, all participants signed a consent form to allow this. We have clarified the statement to ‘All participants signed a consent form to allow their data to be used in future studies such as this.’

VERSION 2 – REVIEW

REVIEWER	Francesco Pistelli, MD, PhD Pulmonary Unit, Cardiothoracic and Vascular Department, University Hospital of Pisa, Italy
REVIEW RETURNED	14-Aug-2018

GENERAL COMMENTS	In the opinion of this reviewer, the authors have adequately addressed the concerns raised by the reviewers, the paper has improved and it is now suitable for publication.

REVIEWER	Riccardo Polosa University of Catania - Italy
REVIEW RETURNED	23-Aug-2018

GENERAL COMMENTS	Minor Comment 1. The possibility that offering of escalation in weight management is not often viewed by many smokers as a viable option should be discussed. 2. It is good that the authors have analysed data from abstainers throughout the whole observation period (i.e. at each and all of the follow ups). Please use this dataset in your revision To keep your article more concise, I suggest you remove the whole sample analysis instead.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Riccardo Polosa

Institution and Country: University of Catania - Italy

Please state any competing interests or state ‘None declared’: None declared

Minor Comment

1. The possibility that offering of escalation in weight management is not often viewed by many smokers as a viable option should be discussed.

We devote a paragraph to this issue in the previous version and have altered this in response to this request. The paragraph now reads:

These data have important implications for the treatment of tobacco dependence. We have conducted trials of interventions to limit weight gain where the interventions to do so have started concurrently with the attempt to achieve abstinence [37, 38]. These interventions have proved unpopular with people trying to stop smoking and the trials have failed to recruit. A promising avenue that may increase participants' desire to address weight gain may have been to wait until excess weight gain had been manifest and then intervene with a weight control programme. However, this study shows that, while early excessive weight gain does predict subsequent higher weight gain, it does so only weakly; many people who will not gain excessively would need to be treated and some people who will gain excessive weight will not be offered treatment. It may therefore be necessary to find ways to reframe the offer of weight control so that it is more attractive to people attempting to stop smoking, which may be helped if we can identify those at the greatest risk of health-damaging weight gain.

2. It is good that the authors have analysed data from abstainers throughout the whole observation period (i.e. at each and all of the follow ups). Please use this dataset in your revision To keep your article more concise, I suggest you remove the whole sample analysis instead.

In our previous response to this point, we argued that all cohort studies suffer loss to follow-up and that investigators vary somewhat in their response to this. However, in our experience, it is unusual to do what the referee suggests because in most studies, only a minority are present on every single follow-up occasion. What is more typical is to take our approach and use all the data available, but to do sensitivity analysis to assess the possible impact of this.

The referee suggests that following his approach would make the article shorter but it would not. We would simply replace one set of analyses by another set and we feel that the analysis on all those present would be more informative to readers. The sensitivity analysis methods are briefly described and the results summarised as similar to the full analysis, so this adds minimally to the manuscript length but provides important reassurance.