Dear Dr. Mons

Manuscript ID BMJ.2014.023331 entitled "Smoking is a strong independent risk factor of cardiovascular outcomes even at older age – Meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium"

We are pleased to say that we would like to publish it in the BMJ as long you are willing and able to revise it as we suggest below. We are provisionally offering acceptance but will make the final decision when we see the revised version. The report from the manuscript meeting, the comments from the reviewers and general requirements for submission are available at the end of this letter.

Deadline: Because we are trying to facilitate timely publication of manuscripts submitted to BMJ, your revised manuscript should be submitted by one month from today's date. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

Yours sincerely,

Jose Merino
jmerino@bmj.com,

**Report from The BMJ’s manuscript committee meeting**

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder (chair), John Deeks (statistician), Emma Parish, Wim Weber, Georg Roggla, Wim Weber, Rebecca Burch, Tiago Villanueva, Kristina Fister.

Decision: provisional acceptance

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

- We felt that the study adds only incrementally but since it is such a large study, it may be more definitive than others, and the message that smoking cessation efforts should continue, even among those older than 60, is important (are those 60-69 elderly?)

- This study is well done. One limitation is the use of a single measure of smoking status, at baseline, rather than repeated measures. There do not seem to be repeated assessments of smoking status in the cohorts and baseline status is presumed to remain constant. Can the authors please comment on this issue?

- We would like more description of the calculation of the risk advancement period (RAP) – this is not standard output from these models, but seems a good way of summarizing the impact.

- The title should be modified since it should be descriptive but not announce the findings. The authors may want to look for advice in the BMJ instructions for authors.

- The “What this study adds” box needs to be in bullet points, it seems too narrative
at the moment.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

*****Reviewer(s)' Comments to Authors*****

Reviewer: 1

Recommendation:

Comments:
This is a very important article that investigates the impact of smoking & smoking cessation in terms of hazard ratios (HRs) and risk advancement periods (RAPs) on cardiovascular mortality and incidence in more than 500,000 subjects aged more than 60 years of 25 cohorts participating to the CHANCES consortium. In my opinion, the article is well written and concise. Tables and figures are all informative. The choice to present sub-analyses in the Appendix is good. The tables and figures presented in the main texts are the most important and in my opinion don't need to be moved in the Appendix. Thus, the article is already good for publication.

Additional Questions:
Please enter your name: Giuseppe Gorini

Job Title: MD, epidemiologist

Institution: Cancer Research & Prevention Institute (ISPO), Florence, Italy

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: None to declare

Reviewer: 2

Recommendation:

Comments:
Originality
1. This manuscript is aimed at analyzing the relative risk and the risk advancement periods of cardiovascular death, acute coronary and stroke events in people aged 60 or over by means of a meta-analyses of individual data from 25 cohorts. The topic is original given the scanty research done in aged people, especially taking into account that counseling and intervention programs addressing quitting smoking over 60 years old have almost been neglected.
2. The authors insist in the Background section about the paucity of previous studies in old people. Although this is important, the authors should strengthen that encouraging smoking cessation in old people has been usually neglected and hence smoking cessation in people over 60 is not frequent (perhaps some figures from the last available Eurobarometer on smoking could illustrate it).

Importance of work to general readers
3. This work is of importance not only to tobacco control researchers but to clinicians, policy makers and the general public. De-constructing the myth that quitting smoking over a certain age (let's say the sixties) is a very important public health topic.

Scientific reliability
4. The research question is clearly defined and the results presented offer a proper answer.

Overall design of study
The meta-analysis of individual data used in this study is adequate and allows the authors to conduct several analyses, including stratified and sensitivity analysis. There are some limitations that the authors have addressed in the Discussion section.

Participants studied
The authors offer a detailed description of the cohorts included in the meta-analysis. 5. The CHANCES Consortium is introduced in the Methods section (page 8, lines 10-22). The authors should include the CHANCES website address within the text.

6. From the description of the cohorts, it is clear that some other non-CHANCES cohorts were included. Thus, the inclusion in the title of the reference to the CHANCES consortium is misleading (“...of the CHANCES consortium”).

Methods
The Results section presents adequately the data sources, the variables used and the statistical methods.
7. The authors have chosen a Cox regression model for the analysis of the cohorts. This non- or semi-parametric model relies in the assumption of the proportionality of hazards. Have the authors checked (statistically or graphically) this assumption in their individual datasets and in the pooled dataset?

8. The authors perform a meta-analysis and hence some readers would immediately think or even expect a flow-diagram following the PRISMA Statement as in most systematic reviews. In this case the meta-analysis does not derive from a previous systematic review, and hence following most of the items from the PRISMA Statement is not appropriate.

9. The authors have presented some results to assess a dose-response relationship (HR according to smoking status categories, or according to number of cigarettes per day smoked or time since quitting). However, there are no statistics testing the dose-response associations observed. Chi-squared tests for trends could be included in tables and figures and hence strengthen the reliability of the associations observed.

Interpretation and conclusions
10. The authors should strengthen the utility of the results for prevention, especially the use of RAPs in the context of clinical or community programs.

Additional Questions:
Please enter your name: Esteve Fernández
Job Title: Associate Professor of Public Health
Institution: Catalan Institute of Oncology / University of Barcelona
Reimbursement for attending a symposium?: No
A fee for speaking?: No
A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

**Information on revision the format and content of the article and submitting the revision**

1. Deadline: Your revised manuscript should be returned within one month.

2. Online and print publication: All original research in The BMJ is published with open access. The full text online version of your article, if accepted after revision, will be the indexed citable version (full details are at http://resources.bmj.com/bmj/about-bmj/the-bmjs-publishing-model). The print and iPad BMJ will carry an abridged version of your article. This abridged version of the article is essentially an evidence abstract called BMJ pico, which we would like you to write using the template downloadable at http://resources.bmj.com/bmj/authors/bmj-pico. Publication of research on bmj.com is definitive and is not simply interim "epublication ahead of print", so if you do not wish to abridge your article using BMJ pico, you will be able to opt for online only publication. Please let us know if you would prefer this option. If your article is accepted we will invite you to submit a video abstract, lasting no longer than 4 minutes, and based on the information in your paper’s BMJ pico evidence abstract. The content and focus of the video must relate directly to the study that has been accepted for publication by The BMJ, and should not stray beyond the data.

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4. How to submit your revised article: Log into http://mc.manuscriptcentral.com/bmj and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) and Committee in the space provided. You can use this space to document any changes you make to the original manuscript and to explain your responses. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s). As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation ‘Revised Manuscript Marked copy’. Your original files are available to you when you upload your revised manuscript. Please
delete any redundant files before completing the submission.

When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision. Please include these items in the revised manuscript to comply with BMJ style (see: http://www.bmj.com/about-bmj/resources-authors/article-submission/article-requirements and http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists).

Please include these items in the revised manuscript to comply with BMJ style (see: http://www.bmj.com/about-bmj/resources-authors/article-submission/article-requirements and http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists).

1. What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

2. Name of the ethics committee or IRB, ID# of the approval, and a statement that participants gave informed consent before taking part. If ethics committee approval was not required, please state so clearly and explain the reasons why (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines.)

3. A statement that any identifiable patients have provided their signed consent to publication. Please submit, as a supplemental file, the signed BMJ patient consent form for publication in The BMJ of any information about identifiable individual patients. Publication of any personal information about a patient in The BMJ, for example in a case report or clinical photograph, will normally require the signed consent of the patient.

4. Signed patient consent form(s), if the article gives enough personal information about any patient(s). This sometimes occurs even in research papers - for example in a table giving demographic and clinical information about a small subgroup in a trial or observational study, or in quotes/tables in a qualitative study - (see http://resources.bmj.com/bmj/authors/editorial-policies/copy_of_patient-confidentiality)

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9. A data sharing statement declaring what further information and data you are willing to make available, over and above the results reported in the paper. Suggested wording: "Data sharing: technical appendix, statistical code, and dataset [state whether any patient level data have been anonymised] are available at this repository or website OR from the corresponding author at ". If there are no such further data available, please use this wording: "Data sharing: no additional data available". For papers reporting the main results of trials of drugs or devices we require that the authors state, at a minimum, that the relevant anonymised patient level data are available on reasonable request from the authors. The BMJ has partnered with the Dryad Digital Repository datadryad.org to make open deposition easy and to allow direct linkage by doi from the dataset to The BMJ article and back - we encourage authors to use this option
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12. Patient-centered research statement. For studies that are relevant to patients we expect authors to report in their articles the extent of their study’s patient-centeredness. In the Methods section, please state whether patients, service users, careers, or lay people were involved in the design of this study, development and selection of outcome measures, and participant recruitment and study conduct. In addition, describe any plans to disseminate the results to study participants. For clinical trials, describe whether you assessed the burden of the intervention on patients’ quality of life and health and what evaluation method was used; in the results section please describe what you found.

13. Please ensure the paper complies with The BMJ’s style, as detailed below:

a. Title: this should include the study design e.g. "systematic review and meta-analysis."

b. Abstract: Please include a structured abstract with key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research). For every clinical trial - and for any other registered study- the last line of the abstract must list the study registration number and the name of the register.

c. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.

d. Methods: For an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found.

e. Results: Please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/. Please include in the results section of your structured abstract (and, of course, in the article’s results section) the following terms, as appropriate:

i. For a clinical trial: Absolute event rates among experimental and control groups; RRR (relative risk reduction); NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000.)

ii. For a cohort study: Absolute event rates over time (e.g. 10 years) among exposed and non-exposed groups; RRR (relative risk reduction.)

iii. For a case control study: OR (odds ratio) for strength of association between exposure and outcome.

iv. For a study of a diagnostic test: Sensitivity and specificity; PPV and NPV (positive and negative predictive values.)

v. For a systematic review and/or meta-analysis: Point estimates and confidence
intervals for the main results; one or more references for the statistical package(s) used to analyse the data, e.g. RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers e.g. STATA, but please say in the text which version you used. For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

f. Discussion: To minimise the risk of careful explanation giving way to polemic, please write the discussion section of your paper in a structured way. Please follow this structure: i) statement of principal findings of the study; ii) strengths and weaknesses of the study; iii) strengths and weaknesses in relation to other studies, discussing important differences in results; iv) what your study adds (whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses); v) meaning of the study, including possible explanations and implications for clinicians and policymakers and other researchers; vi) how your study could promote better decisions; vi) unanswered questions and future research

g. Footnotes and statements

END