Author's response to reviews

Title: Tobacco smoking and all-cause mortality in a large Australian cohort study: findings from a mature epidemic with current low smoking prevalence

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Author's response to reviews: see over
Dear Lin,

Re: Tobacco smoking and all-cause mortality in a large Australian cohort study: findings from a mature epidemic with current low smoking prevalence

Please find attached our response to your reviewer and editorial comments and a revised paper for your consideration. The reviewers’ comments are in italics, with our point-by-point response under each of them. As requested in your email, we have conducted the additional analyses requested by Reviewer 2 and agree that these strengthen the paper.

We very much hope you will now find our paper suitable for publication in BMC Medicine. Please do not hesitate to contact me at emily.banks@anu.edu.au or +61 2 6125 0328 if you require anything further.

With best wishes,

Yours sincerely,

[Signature]

Professor Emily Banks, Professor Alan Lopez on behalf of the authors
RESPONSE TO REVIEWERS’ COMMENTS

REVIEWER ONE

MAJOR
1.1 My guess is that cardiovascular disease makes up a great part of the deaths. Total cholesterol and blood pressure are not accounted for. The authors refer to high blood pressure as the number one risk factor for global disease burden. This could be commented.

It is true that cardiovascular disease is a common cause of death: in 2012, 29.9% of registered deaths in Australia were caused by diseases of the circulatory system (ICD-10 codes 100-199) ([http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2012~Main%20Features~Diseases%20of%20the%20Circulatory%20System%20%200-199%20%200-199|http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2012~Main%20Features~Diseases%20of%20the%20Circulatory%20System%20%200-199%20%200-199]).

High blood pressure and dyslipidaemia are considered to be intermediate factors on the causal chain between cigarette smoking and death from cardiovascular disease. Adjusting for intermediate causal factors can lead to incorrectly attenuated risk estimates—hence these factors were not adjusted for in our analyses. We note these factors were appropriately not adjusted for in other major contemporary analyses of smoking and mortality.1-4

1.2 Age (age attained) was the time variable in the Cox regression models. The relative risks tend to diminish as the absolute risks get larger. The absolute risks increase with increasing age. Therefore it is likely that the proportionality assumption is violated for many of the variables. In this case the authors have used “a stratified or time-dependent form of the model”. Could you expand on these models?

That is correct. When a violation of proportionality assumption was detected in covariates other than the main exposure, a stratified Cox model was fitted. The stratifications used in the different analyses are summarised in the table below. We intended to use a time dependent form of the model in case of violations in the main exposure, but no such violations were detected.

Table 1. Analysis and stratification of Cox models

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Variables stratified due to proportionality violations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base models</td>
<td>None</td>
</tr>
<tr>
<td>Adjusted models</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>education</td>
</tr>
<tr>
<td>Birth decade</td>
<td>alcohol, education, income</td>
</tr>
<tr>
<td>Smoking intensity</td>
<td>income</td>
</tr>
<tr>
<td>Age since stopping</td>
<td>alcohol, education</td>
</tr>
</tbody>
</table>

To address the reviewers’ comments we have added the following to the methods section (p7):

“No violations of the proportionality assumption were detected for the main exposure. Minor violations were observed in covariates for the following models and a stratified Cox model fitted: overall analyses of current and past versus never smokers — model stratified by education; analyses relating to birth decade — model stratified by alcohol, education and income; analyses relating to number of cigarettes smoked per day — model stratified by income; analyses relating to age at smoking cessation — model stratified by alcohol and education.”

1.3 One item on the questionnaire read: “Have you ever been a regular smoker?”. What is meant by the term regular? Is it daily smoking? If a person smokes ten cigarettes every Saturday, and only on Saturdays, is he/she a regular smoker? Every Saturday seems regular to me.
This questionnaire item is based on that from the Million Women Study follow up questionnaire, to allow international comparability. Of those answering ‘yes’ to smoking regularly, data on cigarettes smoked per day is given in table 2 in the manuscript and further detail is given below.

Table 2. Smoking intensity among smokers

<table>
<thead>
<tr>
<th>Smoking intensity (cig/day)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 3</td>
<td>3,335</td>
<td>3.9</td>
</tr>
<tr>
<td>4-14</td>
<td>30,193</td>
<td>35.2</td>
</tr>
<tr>
<td>15-24</td>
<td>32,295</td>
<td>37.7</td>
</tr>
<tr>
<td>25+</td>
<td>18,489</td>
<td>21.6</td>
</tr>
<tr>
<td>Missing</td>
<td>1,356</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>85,668</strong></td>
<td></td>
</tr>
</tbody>
</table>

We agree with the reviewer that people who smoke weekly may consider themselves “regular smokers”. However, as shown above, a high proportion (>95%) of “regular” current/former smokers smoked an average of >3 cigs/day and 59% smoked on average at least 15 cigs/day.

1.4 How many of the smokers smoked a pipe or cigar or a combination?

Of the 84,312 participants with relevant data, 81,179 (96%) smoked only cigarettes, 1,572 (2%) smoked only pipes/cigars and 1,561 (2%) reported smoking both.

This has now been added to the first paragraph of the results section.

1.5 Have many past smokers switched to smokeless tobacco (snuff)?

We do not have direct data on smokeless tobacco use in past smokers, however use of smokeless tobacco is very uncommon in Australia, in contrast to certain Nordic countries and parts of the United States. Importation and supply have been illegal in Australia since 1991, under sections 65C(1)(b) and (c) of the Trade Practices Act (Cth), and use has been negligible since then, with the most recent estimates indicating that 0.57% (95%CI 0.40–0.74) of past smokers had used smokeless tobacco in the last 12 months. Furthermore, use was particularly uncommon in the age group included in our study, with 0.27% (0.17–0.37) of those aged 50 or older reporting use within the last 12 months.

We have added the following to the sixth paragraph of the discussion:

“Although we do not have direct data on use of smokeless tobacco products among participants, importation and supply of these products have been illegal in Australia since 1991, and use has been negligible since then."

1.6 What is the correlation between age at baseline and duration of smoking?

Age at baseline is very strongly and positively correlated with duration of smoking (r=0.8). With the majority of smokers starting to smoke during a narrow age period (13-15 years of age), duration among current smokers is virtually a function of current age. The scatter plot showing smoking duration and age at baseline among current smokers is given below.
We have added the following to the results section (p9) to address the reviewers’ comment:

“Because of the narrow age range of commencing smoking, duration of smoking among current smokers was strongly correlated with current age (r=0.8).”

1.7 As background (line 7 from bottom) the authors write:“..., Australia has relied on the findings from other studies conducted in the UK and US,....... to underpin estimation of the population impact of smoking”. How do the findings from this study fit in?

The findings from this study are consistent with international evidence and this is outlined in the second paragraph of the Discussion:

“These findings are virtually identical to those on the contemporary risks of smoking from the UK and US.”.

MINOR
1.8 In table 2 some figures are with and some are without the comma. For instance 3,814 and 3085.

Thank you for pointing this out. This has now been amended.

REVIEWER TWO
MAJOR
2.1 Page 5- comment if NSW smoking prevalence and mortality rates/risks by cause are typical of rest of Australia.

New South Wales is the most populous state in Australia, comprising 32% of Australian residents, according to most recent estimates. Mortality rates by age are similar for NSW and the whole of Australia. For example:

Ischaemic heart diseases standardised death rates (2012): 96/100,000 for males and 53.6 per 100,000 for females. Cerebrovascular disease standardised death rates (2012): 38/100,000 for males and 38.9/100,000 for females.

NSW: Ischaemic heart diseases standardised death rates (2012): 94.3/100,000 for males and 51.5 per 100,000 for females. Cerebrovascular disease standardised death rates (2012): 41.8 /100,000 for males and 40.2 per 100,000 for females
Reference:
http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2012~Main%20Features~Diseases%20of%20the%20Circulatory%20System%20%28I00-%20I99%29~10031

Smoking prevalence in NSW is similar to that for the whole of Australia, for the most recent state based data. Specifically, in Australia: 17.5% of adults were current smokers, 29.8% were past smokers and 52.7% were never smokers in 2011/12. In NSW: 15.7% of people were current smokers, 28.6% were past smokers and 55.6% were never smokers in 2011/12.6

We have now added the following to the discussion section (p13):
“NSW is the most populous state in Australia, comprising around one-third of the total population. Smoking prevalences6 and cause-specific death rates for major causes of death7 and are similar in NSW to those observed nationally.”

2.2 page 6- reverse causality is addressed, but the authors might still be overestimating hazards among recent quitters. Can they add an analyses where current smokers are defined as current smokers plus recent quitters (say within 2-3 years). This is particularly important as the follow up period is short, and it may not be so easy to exclude the first few years of follow up.

We agree that there are potential issues with overestimating hazards among recent quitters. Among the 66,378 former smokers with information on age at stopping, 4,701 (7.1%) had quit in the three year period prior to study entry.

Table 3. Main results and sensitivity analyses changing the definition of current and former smokers

<table>
<thead>
<tr>
<th></th>
<th>Male HR (95% CI)</th>
<th>Female HR (95% CI)</th>
<th>Sensitivity analysis combining recent quitters with current smokers Male HR (95% CI)</th>
<th>Female HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never Smoker</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Former Smoker</td>
<td>1.34 (1.24-1.45)</td>
<td>1.54 (1.40-1.70)</td>
<td>1.34 (1.24-1.44)</td>
<td>1.47 (1.33-1.62)</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>2.82 (2.49-3.19)</td>
<td>3.08 (2.63-3.60)</td>
<td>2.65 (2.36-2.96)</td>
<td>3.26 (2.84-3.75)</td>
</tr>
</tbody>
</table>

In response to the reviewers’ comments we have added the following to the methods section (p7):
“Sensitivity analyses were conducted: (i) adjusting additionally for physical activity; and (ii) categorizing current smokers as those who reported being current smokers at baseline and past smokers who had ceased smoking 3 or fewer years prior to baseline.”

And we have added this to the results section (p8):
“Nor did the RR for mortality in current and former versus never smokers change substantially when current smokers were defined as individuals reporting current smoking at baseline or within three years prior to baseline (for men RR (95%CI) using the new definitions of current/recent versus never smokers: 2.65 (2.36-2.96) and former versus never smokers: 1.34 (1.24-1.44) – corresponding figures for women were 3.26 (2.84-3.75) and 1.47 (1.33-1.62)).”

2.3 page 8- details on the re-survey smoking prevalence by age would be helpful, perhaps in the way of another table. Was there substantial quitting between baseline and re-survey, in a way that would suggest the estimated HRs might be conservative?

Supplementary table 1 gives data on quitting between baseline and resurvey, among those completing both baseline and resurvey questionnaires. It demonstrates a quit rate of around one
third among current smokers, between surveys. This is consistent with the rapid reduction in smoking in Australia demonstrated in Figure 1 in the manuscript. We agree with the reviewer that this is likely to lead to conservative estimates of relative risk. We have now added the following to the results section of the manuscript (p9):

“Data from the 3-year resurvey indicated consistency of reporting of never-smoker and ex-smoker status, with little misclassification and very few indicating that they had taken up smoking between surveys (Supplementary Table 1). Among current smokers at baseline who completed the 3-year resurvey, around one-third indicated that they were no longer smoking at resurvey, with those smoking fewer cigarettes per day more likely to quit (Supplementary Table 1).”

We have also added this to the discussion section (p12):

“In keeping with the continuing decline in smoking prevalence in Australia, the resurvey data indicate that a substantial minority of current smokers at baseline ceased smoking during the follow up period. This suggests that the estimated hazard ratios for mortality among current smokers at baseline are likely to be conservative.”

The table below shows the proportion of current smokers at baseline continuing to smoke at follow up, by age. Since no systematic pattern was observed, we do not consider this adds materially to the paper and could be confusing to the reader. We have therefore not created an additional table. We are happy to take editorial advice on this matter.

Table 4. Percentage of current smokers at baseline who were still smoking at follow-up by sex and age group

<table>
<thead>
<tr>
<th></th>
<th>45-64 years</th>
<th>65-79 years</th>
<th>80 years or older</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN</td>
<td>66.9%</td>
<td>61.1%</td>
<td>77.8%</td>
</tr>
<tr>
<td></td>
<td>(810/1,210)</td>
<td>(198/324)</td>
<td>(35/45)</td>
</tr>
<tr>
<td>WOMEN</td>
<td>71.3%</td>
<td>65.7%</td>
<td>72.7%</td>
</tr>
<tr>
<td></td>
<td>(1,105/1,550)</td>
<td>(163/248)</td>
<td>(16/22)</td>
</tr>
</tbody>
</table>

2.4 page 9 - smoking prevalence in the cohort was only 7.7% vs 13% in Australia. Can they comment on any overall differences between cohort and Australia’s population? This is particularly relevant for Figure 5 (page 11)- is the decade of life lost applicable to all of Australia or only to the cohort? This is unclear in the results. (The Pirie paper (MWS) and Jha paper (NHIS) took the relative risks and applied these to the absolute death rates for the UK/US; the NHIS population was representative but the MWS and this study are not, hence these differences in absolute risk might be important to comment).

Participants in cohort studies are generally healthier and more health conscious than non-participants and this is illustrated in the current study by a lower smoking prevalence among the 45 and Up Study cohort compared to the Australian population. However, while representativeness is important for prevalence surveys which seek to estimate the prevalence of a specific factor in the general population, representativeness is not required for reliable estimates of relative risk based on internal comparisons within study populations. 8,9 This, along with the consistency of our results with those of other studies internationally, indicates that there is no evidence to suggest that the lower smoking prevalence of the 45 and Up Study cohort has unduly affected the reliability of our relative risk estimates. This point has been addressed on Page 13, as follows:

“Around 12% of individuals aged 45 and over in New South Wales were estimated to be current smokers at the time when the 45 and Up Study commenced 8 and, following exclusions, current smokers made up around 8% of the cohort. It should be noted that
although the 45 and Up Study is, like the vast majority of cohort studies, not strictly representative of the general population, the results presented here are based on internal comparisons within the cohort and are likely to be reliable. Moreover, as the British Doctors Study illustrates, cohort studies do not need to be representative to produce effect estimates that are generalisable.”

While the reliability of our relative risk estimates do not require cohort smoking prevalences to be representative of the Australian population, the reviewer is correct to point out that the absolute risk estimates in Figure 5 do require representative estimates of smoking prevalences and death rates. We have now modified the text on Page 7 (modifications in red), to make it clear that Australian absolute death rates and smoking prevalences were used in the calculations of absolute risk:

“Separately for males and females, absolute mortality rates for Australian smokers and non-smokers for age group i (45-54, 55-64 and 65-74 years) were estimated by \( M_i/(1 + (RR - 1)P_i) \) for non-smokers and RR times this for smokers\(^{10}\) (where \( M_i \) and \( P_i \) represent 2010/11 Australian population mortality rates and smoking prevalences estimated from other sources respectively,\(^{7,6}\) and RR represents all-cause current smoker versus never-smoker relative risks estimated in the current study).”

In addition, we have modified the following text on Page 11 to indicate that the results in Figure 5 represent the absolute risks for the Australian population not the study cohort.

“In Australia, male and female smokers were estimated to have the same risks of death 9·6 and 10·1 years earlier than 75 year old non-smokers, respectively (Figure 5). Starting from age 45, 44·6\% of male smokers in Australia would be estimated to die by age 75, compared to 18·9\% of male non-smokers. Corresponding figures for females were 33·0\% for smokers and 12·2\% for non-smokers.”

2.5 comment on any change in the tar/other component of cigarettes smoked by various birth cohorts (as occurred in France).

Although the tar content of cigarettes in Australia is not routinely monitored, sales weighted mg/cigarette has fallen over time, e.g. from 19.6mg in 1969 and 9.3 mg in 1989 (http://www.tobaccoinaustralia.org.au/fandi/fandi/c05s3.htm). In 1994, the tar content of Australian cigarettes dropped to 5.6mg, (range 1-12.4mg) lower that that observed in the USA (10.8: Range 0.8-19mg) http://www.tobaccoinaustralia.org.au/12-5-comparison-of-australian-and-united-states-cl).

We have added the following on page 12 to address this comment:

“Consistent relative risks among successive birth cohorts were observed despite falling tar content in cigarettes observed over the last four decades.\(^{11}\)”

Minor comments
2.6 table 2- clearer labels please on smoking duration *(years).
This has now been amended.

2.7 the figure showing RRs by decade of birth shows no clear relationship of risk among former smokers by birth cohort? How does this square with the figure showing male/female combined risks for ex-smokers by age of cessation?

We agree this is an interesting question. However, it is difficult to comment on the mortality RR by birth cohort among former smokers. Detailed analyses by age at quitting and time since quitting within each cohort would be required to do so; power would be limited for such detailed analyses and we consider this beyond the scope of the paper.