Author's response to reviews

Title: Tobacco smoking as a prospective risk factor for depression and poorer quality of life in heart disease

Authors:

Lesley Stafford (lesley.stafford@thewomens.org.au)
Michael Berk (mikebe@barwonhealth.org.au)
Henry J Jackson (henryjj@unimelb.edu.au)

Version: 4 Date: 13 October 2012

Author's response to reviews: see over
Dear Ursula

RE: MS: 1541120338788701 - Tobacco smoking as a prospective risk factor for depression and poorer quality of life in heart disease

Thank you very much for the opportunity to resubmit a revised version of the above manuscript to BMC Medicine. We have attached an amended manuscript with tracked changes and have addressed the reviewers’ comments in the section below. Our comments are provided in red font.

We hope that these changes meet with your approval and look forward to hearing from you.

Yours sincerely

Lesley Stafford
Michael Berk
Henry Jackson

Reviewer 1

In their article entitled “Tobacco smoking as a prospective risk factor for depression and poorer quality of life in heart disease”, Stafford, et al., describe the relationship between smoking at the time of an index cardiac event (PTCA, myocardial infarction, or coronary bypass graft surgery) and subsequent measures of depression at 3 months, 6 months, and 9 months. Smoking increased the likelihood of a diagnosis of major depressive disorder, or a diagnosis of minor depression, dysthymia, or major depressive disorder, at 3 months, but not at 6 months or 9 months. The authors conclude that smoking is an independent risk factor for the subsequent development of depression in patients with coronary disease, especially in the first three months following a cardiac event.

The question posed by the investigators is important in understanding the relationships between smoking, depression, and coronary heart disease. The methods are appropriate and well-described. The findings are interesting, the data are presented clearly, and the manuscript is well-written.

Major compulsory revisions:
1. It is this reviewer’s opinion that the authors’ conclusions are not fully justified by the data, and should probably be modified. Although an association between smoking and subsequent depression is demonstrated, the interpretation that depression results from tobacco use is not well founded in the absence of data on depression status before or at the time of the index event. An equally plausible explanation of the findings is that depression led to tobacco use, and that smokers had more depressive symptoms even before their cardiac events.
It is acknowledged in the manuscript that depression status at the exact time of index event is unknown. As stated in Procedures (p4), baseline data were not collected from participants while in hospital, both to reduce the burden on the patients and to avoid confounding of depression with the stress of acute illness. However, we do include data on past history of depression in all multivariate analyses and this variable is well known as the most important risk factor for subsequent depression. This information and the reviewer’s comment has been added to the limitations of the manuscript reflecting that depression may have led to tobacco use (p11 lines 24-28).

2. The participants should be more fully characterized. It is unclear, for example, how many of the study cohort presented with myocardial infarction, or with revascularization via a percutaneous procedure or surgery. Similarly, there is no data regarding treatment of the subjects. In particular, it would be instructive to know how many were treated with anti-depressant drugs, and how many were started on anti-depressants following their index cardiac events.

All of this information i.e., CAD presentation types (p8, lines 8-11), treatment with anti-depressants at index event and subsequent to index event has been added to the manuscript. This information has been added to Table 1 (description of sample at T1, see p20).

3. It is not clear that patients who had coronary bypass graft surgery should be grouped with those who experienced a myocardial infarction or underwent percutaneous revascularization, in light of the potential for bypass surgery to alter cognitive function. The authors should examine whether their findings are consistent amongst subjects with different presentations.

Patients who underwent bypass surgery have now been separated from those who had MI or stenting. A new dichotomous variable, CABG vs MI/PTCA, has been created. All univariate and multivariate analyses have been redone with this new variable now included. This new variable has been added to analyses in Tables 1, 2, 3, 4, and 5. Relevant changes have then been made in the Results section of the manuscript.

Discretionary revisions
1. There is no description of exercise patterns or participation in cardiac rehabilitation programs in the study cohort. Exercise may be as effective as anti-depressant medications in improving mood in coronary disease patients. If available, this data should be presented.

The number of patients known to have attended cardiac rehabilitation has been added to the manuscript in Table 1 (see p20) with univariate analysis results reported on p9 line2. These data were not added to multivariate analysis because of missing data for six patients and resultant loss of power and because of variability in the amount of time after the index event that participants attended rehabilitation. This means that a variable representing attendance at rehabilitation could not reliably be used as a predictor in all analyses because it may not yet have occurred at T1 or T2.

Reviewer 2
I do see the relevance of this paper, which addresses the potential effects of tabacco use on risk of depression and reduced quality of life. However, I do see some serious limitations that I feel need to be discussed before this manuscript could be considered for publication.

major compulsory revisions:
The design that has been used is somewhat awkward: is there any reason why you have chosen not to repeat the MINI assessment after 3 months? Why the switch to HADS?

The MINI is used to establish a diagnosis while the HADS is used to track changes in symptoms. A sentence to this effect has been added on p5 lines 13-14.

Why was HRQOL only evaluated at T3 and not at T1? This seems to me a bit arbitrary.

HRQOL was evaluated at T1, T2 and T3 in the original study. Since HRQOL is a secondary outcome in the current paper, we have chosen to report the prospective association between T1 smoking and T3 HRQOL only. If considered appropriate by the editors, we can include the additional four sets of analyses (mental and physical HRQOL) to show the multivariate analyses of smoking and T1 HRQOL and T2 HRQOL.

Most importantly, however, I am not quite convinced that what the authors report as a potential effect of tobacco use is really an effect. Table 1 clearly shows that smokers differ from non-smokers in many ways that may have affected their results. To solve this, the authors have chosen in their analyses to statistically control for confounders in a single model. Unfortunately, since this is the only model they present, it is unclear how much of the observed associations can be explained by these confounders. I would prefer to see an analysis in which adjusted and unadjusted results are shown.

The unadjusted results for the six logistic regression analyses of depression have now been included. These are shown in Table 2 (MDD, ADD and T2 depression) and Table 3 (T3 depression, ‘persistently depressed’, and ‘ever depressed’). Previously, summary information for all six analyses had been contained in Table 2, but with the addition of the unadjusted results, it is necessary to split the information over two tables. For HRQOL, both adjusted and unadjusted results were shown in the first version of the manuscript.

More importantly however this still does not solve the problem that many of the smokers were already depressed before the cardiac event. There are quite some indications that about half of the post-MI depressions were already existing before the MI. Given that depression increases the risk of smoking or failing to quit smoking, this is probably the most important confounder to take care of. Or perhaps even, first select patients who were not depressed and evaluate whether smoking affects the risk of incident depression.

As noted above in response to a comment from Reviewer 1, it is acknowledged in the manuscript that depression status at the exact time of index event is unknown. As stated in Procedures (p4), baseline data were not collected from participants while in hospital, both to reduce the burden on the patients and to avoid confounding of depression with the stress of acute illness. However, we do include data on past history of depression in all multivariate analyses and this variable is well known as the most important risk factor for subsequent depression.