

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Effectiveness of Smoking Cessation Interventions in Smokers with Cerebrovascular Disease: A systematic review.
AUTHORS	Edjoc, Rojjiemiahd ; Reid, Robert; Sharma, Mukul

VERSION 1 - REVIEW

REVIEWER	Tim Pickles, Statistician, South East Wales Trials Unit, Cardiff University
REVIEW RETURNED	22-Sep-2012

GENERAL COMMENTS	<p>Reviewer: Tim Pickles, Statistician, South East Wales Trials Unit, Cardiff University</p> <p>Quick summary:</p> <p>This systematic review and meta analysis provides an interesting look into smoking cessation in those with cerebrovascular disease. I believe however that the data extraction is flawed (by errors, and by inconsistencies in how to deal with smokers lost to follow-up), which leads to an unusable result. The bulk of the paper is well written, though there are a few sloppy mistakes surrounding grammar, syntax and numbers. Table 1 also needs to be tidied.</p> <p>I have a number of comments, corrections and questions I would like to highlight here. Some of them may be personal preference but I hope none are trivial. I am going to refer to decimal places (dps) in the following as they are a particular bugbear of mine ...</p> <p>Abstract:</p> <ul style="list-style-type: none"> • Eligibility criteria do not match those in Methods. If the 31st December 2011 cut off is true then Frandsen et al. 2012 (!!) can't be included • Alter cessation rates and result given following comments • Give the p-value 3dps <p>Article Summary:</p> <ul style="list-style-type: none"> • Spelling of 'assess' <p>Introduction:</p> <ul style="list-style-type: none"> • Comma following 'as of 2009' • 'smoked', not 'smoke', in 'in the United States smoke cigarettes' • Change '< 10 cigarettes a day' to 'between 1 and 10 cigarettes a day', else light smoker definition includes non smokers • Remove apostrophe in '(SCI's)' <p>Methods:</p> <ul style="list-style-type: none"> • Replace '4) Finally' with 'Finally,', as this is not the 4th point reasons to include
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	<ul style="list-style-type: none"> • We don't know who 'NB' is. Noone with these initials in the three authors • What is 'type stroke diagnosis'? Do you mean 'type of stroke diagnosis'? <p>Results:</p> <ul style="list-style-type: none"> • Is 12.5 a standard deviation? If so then write SD and not +/- . Also give the SD 2dps. Not quite sure how you know the mean age if you suggest it is not reported for Ellis et al. 2005/McManus et al. 2009 in Table 1 • Alter cessation rates and result given following comments • Give the p-value 3dps • Gaps between '=' signs. Do you want any or not? (See 'n=78' and 'n= 76') • Replace all '/' with 'out of'. You are not dividing anything here • Give all percentages 1dp. It currently ranges between 0 and 2dps • Comma after 'There were 205 patients recruited' • The statements regarding smokers at follow-up in the second study should be after the first mention of reference 10 • The percentage of 0.07 is out by 100, i.e. $100/13 = 7.7$ • Can you justify the reasoning behind assuming that a 'minimal smoking cessation intervention group' is equivalent to a 'control group'? It clearly isn't the same thing • The cessation rates for the fourth study are the wrong way round • Two mentions of Jadad score (page 6 and 9). Only need one • 'Limited' is a strong word in describing 94 participants. It was only a pilot study after all • Comma after 'lie in a double-blind randomization design' <p>Data Extraction Problems in Results of individual studies and risk of bias across studies</p> <ul style="list-style-type: none"> • There may be a problem with the results you extract for the first study (reference 8). I find the cessation rates to be 22 out of 60 (36.7%) for the control arm and 21 out of 48 (43.8%) for the intervention arm. The denominators you provide for these rates are those smoking at baseline. However, given loss to follow-up, I don't know that you can assume to know what these baseline smokers are doing at 1 year. I am aware that it is sometimes accepted that 'lost to follow-up' is equivalent to 'current smoker' but you have not done this for the second study • There is a problem with the results you extract for the second study (references 9 and 10). For the intervention group, 13 of the 36 smokers at baseline are followed up and are still smoking. The information at the bottom of Table 1 in ref 10 suggests 1 has stopped smoking, hence 14 of the 36 intervention smokers were followed up, 1 of which quit. This means that the cessation rate is 1 out of 14 (7.1%). For the control group, I think your result is correct, assuming that by 'restarted', the authors mean that a patient stopped and then started again in the 1 year period. So of the 14 followed up smokers, 0 quit. • The results you pull from the fourth study (reference 12) may also be problematic in the same way as the first study, in assuming that 'lost to follow-up' is equivalent to 'current
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	<p>smoker'. This again doesn't fit in with the second study</p> <ul style="list-style-type: none"> You need either these results (remove those lost to follow-up) <table border="1" style="width: 100%; text-align: center;"> <thead> <tr> <th>Study</th> <th>Intervention Cessation Rate</th> <th>Control Cessation Rate</th> </tr> </thead> <tbody> <tr> <td>1 (reference 8)</td> <td>21 out of 48 (43.8%)</td> <td>22 out of 60 (36.7%)</td> </tr> <tr> <td>2 (references 9 and 10)</td> <td>1 out of 14 (7.1%)</td> <td>0 out of 14 (0%)</td> </tr> <tr> <td>3 (reference 11)</td> <td>4 out of 15 (26.6%)</td> <td>2 out of 13 (15.4%)</td> </tr> <tr> <td>4 (reference 12)</td> <td>16 out of 43 (37.2%)</td> <td>13 out of 41 (31.7%)</td> </tr> </tbody> </table> <ul style="list-style-type: none"> Or these results (retain those lost to follow-up as smokers) <table border="1" style="width: 100%; text-align: center;"> <thead> <tr> <th>Study</th> <th>Intervention Cessation Rate</th> <th>Control Cessation Rate</th> </tr> </thead> <tbody> <tr> <td>1 (reference 8)</td> <td>21 out of 76 (27.6%)</td> <td>22 out of 78 (28.2%)</td> </tr> <tr> <td>2 (references 9 and 10)</td> <td>1 out of 36 (2.7%)</td> <td>0 out of 42 (0%)</td> </tr> <tr> <td>3 (reference 11)</td> <td>4 out of 15 (26.6%)</td> <td>2 out of 13 (15.4%)</td> </tr> <tr> <td>4 (reference 12)</td> <td>16 out of 49 (32.7%)</td> <td>13 out of 45 (28.9%)</td> </tr> </tbody> </table> <p>Discussion:</p> <ul style="list-style-type: none"> Comma after 'There are several limitation in the present study' Comma after 'that explore this area of stroke prevention' 'There was a high degree of heterogeneity' is not true, as $I^2=0.00$, which is full homogeneity. There maybe a large amount of variability but this is not explained by heterogeneity <p>Conclusion:</p> <ul style="list-style-type: none"> Remove apostrophe in 'SCI's' both times <p>References:</p> <ul style="list-style-type: none"> Nothing <p>Tables and Figures:</p> <ul style="list-style-type: none"> Figure 2: alter cessation rates (and hence result) as suggested above Description of Control missing for Frandsen et al. 2012. Need to show the difference between the intensive and minimal interventions here Alter cessation rates as advised in Results Patient Characteristics poorly described. Remove Nsmokers from all and just copy baseline characteristics for each study, separating by group ... <ul style="list-style-type: none"> For instance, for Wolfe et al. 2010: <ul style="list-style-type: none"> Intervention: 61 (22.3%) over 80 years, 126 (46.2%) female, 76 (27.9%) smokers. Control: 50 (20.2%) over 80 years, 118 (47.8%) female, 78 (32.2%) smokers. For Ellis et al. 2005/McManus et al. 2009, mean age (along with a 95% CI) and gender are given at baseline in Ellis et al. 2005. Also report numbers of smokers from Ellis et al. 2005, not McManus et al. 2009 Where do you get a mean age for Frandsen et al. 2012? Table 1 in this paper gives categories of ages 	Study	Intervention Cessation Rate	Control Cessation Rate	1 (reference 8)	21 out of 48 (43.8%)	22 out of 60 (36.7%)	2 (references 9 and 10)	1 out of 14 (7.1%)	0 out of 14 (0%)	3 (reference 11)	4 out of 15 (26.6%)	2 out of 13 (15.4%)	4 (reference 12)	16 out of 43 (37.2%)	13 out of 41 (31.7%)	Study	Intervention Cessation Rate	Control Cessation Rate	1 (reference 8)	21 out of 76 (27.6%)	22 out of 78 (28.2%)	2 (references 9 and 10)	1 out of 36 (2.7%)	0 out of 42 (0%)	3 (reference 11)	4 out of 15 (26.6%)	2 out of 13 (15.4%)	4 (reference 12)	16 out of 49 (32.7%)	13 out of 45 (28.9%)
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REVIEWER	Kate Cahill Senior Research Fellow Oxford University UK No competing interests
REVIEW RETURNED	24-Sep-2012

THE STUDY	<p>The research question is appropriate, although some might question the ethics of minimising or withholding interventions from stroke victims, when the generic efficacy of such interventions is already well-established, and the recommendation to conduct more studies of this type.</p> <p>The four studies are well summarised, but critical differences between them are not fully explored.</p> <p>The types of intervention were extremely variable, i.e. pharma + advice components versus usual care (not defined, Wolfe); standard outpatient advice + post-discharge extra care from a stroke nurse specialist versus the standard care only (Ellis); free NRT + counselling versus prescription NRT + counselling (Papadakis); inpatient counselling + NRT + post-discharge counselling versus the same regimen without the post-discharge counselling (Frandsen). The “control” condition in Frandsen is arguably more intensive than the intervention in Wolfe. The fact that studies were set in different countries (UK, Canada, Denmark) has implications for level and type of intervention available/affordable. The studies are too different to be combined meaningfully, even though the I2 estimate is 0%. In fairness, the authors recognise this limitation but nonetheless perform the meta-analysis.</p> <p>Outcomes are also extremely heterogeneous: Papadakis was testing whether free NRT led to higher quit rates than prescription NRT; the smoking outcome in Ellis was reduction rather than cessation. Final estimates ranged from six months to 3½ years. Cessation was by self-report, by biochemical verification, and by self-report occasionally contradicted by biochemical testing. Some outcomes were based on intention-to-treat analysis, and others not. The numbers allocated to intervention and control groups for Ellis (p. 7 47-54) are in a muddle, because the two study reports (Ellis and McManus) do not agree on numbers allocated. Ellis gives totals randomized, and McManus starts from totals at last follow-up. These discrepancies tend to undermine the findings across the board.</p> <p>Minor points:</p> <p>The abstract describes the inclusion criteria as “trials published prior to the 31st December 2011”. This should read “conducted prior to ...” (Frandsen was conducted in 2005/6, but published in April 2012).</p> <p>In the methodological appraisal, Ellis is unfavourably compared with Wolfe and Papadakis, for being a single blind randomization design,</p>
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	<p>while the latter two are cluster-randomized. This confuses blinding with randomization procedures; and furthermore only Wolfe cluster-randomized, deploying multiple GP practises across two London boroughs, while the other three were single-site trials.</p> <p>In the article summary, one of the key messages is that “the review is underpowered to achieve statistically significant results”. Both the systematic review and the studies are underpowered, but the implication that bigger and more studies would achieve statistical significance is questionable. More power would produce more precision and smaller confidence intervals, but is unlikely to push the results into significance.</p> <p>In the description of methods section consider adding the type of effect estimate used, and perhaps expand a little on the meaning of the I2, including potential cut-off points.</p>
RESULTS & CONCLUSIONS	<p>The main limitations of the meta-analysis are two-fold: firstly, the validity of combining four such small and disparate studies, and secondly two numeric errors in the meta-analysis itself.</p> <p>The meta-analysis includes numeric errors in two of the four studies. The text reports the denominators in Papadakis as 15 (I) and 13 (C) while the MA has them respectively as 19 and 15; Frandsen is correctly given in the text as 49 (I) and 45 (C) while the MA gives them as 49 and 58. If you recalculate the RR on the correct figures you get an RR of 1.09 (CI 0.75 to 1.59), not 1.19 (0.81 to 1.73). Oddly, the summary figures on p6 (I150-52) are correctly given, though the intervention quit rate seems a little out.</p>

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1

Thank you for your recommendation in paragraph 2. We recognize that the differences in intervention between studies might limit the information provided by the meta-analysis. As requested, the meta-analysis and any information in the manuscript pertaining to it has been removed. Also as requested by Reviewer 1, critical differences between studies in particular the intervention used by each study has been added in the discussion.

“ A meta-analysis was not performed due to the variability in the intervention used by each study. Wolfe and colleagues employed pharmacotherapy and advice on the use of these pharmacotherapies (8). Ellis/McManus and associates (9, 10) used standard outpatient advice with post-discharge care from a nurse specialist. Papadakis and colleagues used cost-free pharmacotherapy with counseling support and follow-up. Finally, Frandsen et al. (11) used intensive counseling support with cost-free pharmacotherapy. Given these differences in interventions and that each study was set in different countries (United Kingdom, Canada and Denmark) would not have provided meaningful results from a meta-analysis.”

Thank you for this recommendation in paragraph 3. We recognize that not having a consistent way of extracting the data from each study may undermine the findings. To consistently extract the data from each study, we have decided to use follow-up numbers from each study instead of baseline and include patients who were lost to follow-up in the denominator. Hence the cessation rates for each study in the intervention and control is as follows:

Study	Intervention	Cessation Rate	Control	Cessation Rate
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- 1 (reference 8) 21/76 (27.6%) 22 /78 (28.2%)
- 2 (references 9/10) 1/ 36 (2.8%) 0/ 42 (0%)
- 3 (reference 11) 4/15 (26.6%) 2/13 (15.4%)
- 4 (reference 12) 16/49 (32.7%) 13/45 (28.9%)

Thank you for this recommendation in paragraph 4 under the minor points heading. This has been change to reflect this recommendation.

Thank you for the recommendation in paragraph 5 regarding the methodological appraisal. This discussion has been removed from the manuscript.

Thank you for the recommendation in paragraph 7. Since we are eliminating the meta-analysis portion of the paper, we will no longer require a description of the I2 index.

Thank you for the recommendation in paragraph 9. As previously discussed, these inconsistencies regarding data extraction has been rectified by using follow-up data and included lost to follow-up in the denominators (see table above).

Response to Reviewer 2

Thank you for your recommendations. All syntax, grammar and decimal place suggested changes have been applied to the current manuscript.

As per your question regarding the use of the control group for the minimal smoking cessation intervention we justify this in the following manner. For the purpose of this review, the intensive smoking cessation intervention was regarded as the intervention group as this would be above and beyond what would be available in a 'real world' setting. To simplify the comparison group and due to the accessibility of smoking cessation counseling through a primary care physician or even a smoker's helpline, the minimal smoking cessation intervention group was considered the 'control' group.

Also in regards to extracted data, all cessation rates have been extracted from follow-up data and all lost to follow-up patients have been included in the denominator as per the provided table.

Table 1 has been tidied as per the reviewer's suggestion: description of the control group for Frandsen's study have been added; patient characteristics have been updated as requested; mean age have been updated for Frandsen's study; cessation rates have been updated.

VERSION 2 – REVIEW

REVIEWER	Tim Pickles, Statistician, South East Wales Trials Unit, Cardiff University
REVIEW RETURNED	20-Nov-2012

GENERAL COMMENTS	<p>The authors have duly responded to the previous set of comments and have made the sensible decision to drop the meta-analysis. I have a few small comments to add having looked at the revised version.</p> <p>Abstract:</p> <ul style="list-style-type: none"> • Put '(SCIs)' after 'smoking cessation interventions' in the Objective
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	<ul style="list-style-type: none"> • The number of patients is 354 <p>Article Summary:</p> <ul style="list-style-type: none"> • Definition of TIA <p>Introduction:</p> <ul style="list-style-type: none"> • Space in 'to1.6' <p>Methods:</p> <ul style="list-style-type: none"> • In study selection, 'We' after 2) and 3) should be 'we' • In study selection, space in '.Finally' <p>Results:</p> <ul style="list-style-type: none"> • Space in '(28.9%)respectively' • Remove space in '(n =28)' <p>Tables and Figures:</p> <ul style="list-style-type: none"> • Table 1: For Ellis et al. 2005/McManus et al. 2009, you present a mean and a 95% CI for age. So remove 'SD' and write '95% CI'. Number of control smokers is 42. Percentage of control males is 49.5% (i.e., don't assume you can just put .0 on the end of an integer percentage and assume it still correct!)
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VERSION 2 – AUTHOR RESPONSE

Thank you for your thorough review of our paper. We have applied all of your suggested changes to the current submitted manuscript.