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)	Smoking cessation in adults with diabetes: a systematic review and meta-analysis of data from randomised controlled trials
AUTHORS	Nagrebetsky, Alexander; Brettell, Rachel; Roberts, Nia; Farmer, Andrew

VERSION 1 - REVIEW

REVIEWER	Boris Mankovsky Department of Diabetology, National Medical Academy for Postgraduate Education, Kiev, Ukraine
REVIEW RETURNED	20-Oct-2013

GENERAL COMMENTS	In the article the results of the meta-analysis of the studies comparing more and less intensive smoking cessation interventions in special population of patients with diabetes mellitus are presented. No evidence of the efficacy of more intensive approach was found. The data presented are of some interest as it is well known that patients with diabetes mellitus represent the high and very high risk group for cardiovascular morbidity and mortality and the effect of so called "classic" risk factors such as smoking is amplified in subjects with diabetes. Therefore, smoking cessation is very important task in the clinical practice of diabetes care. The results obtained are based on the small number of the studies which are quite heterogeneous which is correctly admitted by the authors. My concern is the secondary outcome of the study which is the influence of intensive smoking cessation strategy on the glycemic control. However, authors were able to identify only 1 study which provided such information. I do not think that it is worth to mention this outcome as the secondary objective of the study. Also, there is no data available regarding the influence of intensive smoking cessation on the weight of patients. The changes of weight should be probably omitted from the study objectives. I believe that the article is of some interest to the readers provided that all limitations of the study are carefully mentioned.

REVIEWER	Peter M Nilsson Lund University Department of Clinical Sciences Sweden
REVIEW RETURNED	27-Oct-2013

GENERAL COMMENTS	This is a timely review on one important topic and updated to

	present time covering the area.
	It is a bit strange that the Abstract indicates that only studies were selected if biochemical methods were used to assess smoking cessation rates, but two of the studies included did not use such methodology (21,22). Why these exceptions?
	A total of only 872 smokers were included in the intervention studies. This may imply that the non-significant findings where substantially influenced by low statistical power. The authors should comment on this aspect I think.

REVIEWER	Serena Tonstad Ulleval University Hospital, Department of Preventative Cardiology
REVIEW RETURNED	28-Oct-2013

GENERAL COMMENTS	This is an interesting systematic review and meta-analysis of randomized clinical trials of intensive versus non-intensive smoking cessation interventions in persons with diabetes. Out of a total of 2914 citations the authors identified 8 eligible trials which could be included in the analysis. The search strategy is comprehensive, the statistical methods are appropriate and the authors assessed the study quality, and there was low risk of bias in the studies. Patients who received more intensive interventions compared to less intensive interventions had a 32% higher likelihood of biochemically verified smoking cessation, but this was far from statistically significant (RR=1.32, 95% CI: 0.23-7.45, n=4).
	The main limitation of the meta-analysis is the low number of studies included in the analysis and therefore lack of statistical power to detect a significant association. Although the number of studies is small and no firm conclusions can be drawn it could inform additional studies on the topic.
	Did the authors test for publication bias?

REVIEWER	Gopalakrishnan Netuveli University of East London, UK
REVIEW RETURNED	25-Nov-2013

GENERAL COMMENTS	This is a well written and clear paper.

REVIEWER	Jo Leonardi-Bee University of Nottingham UK
REVIEW RETURNED	21-Dec-2013

GENERAL COMMENTS	The authors have conducted a systematic review and meta-analysis to assess the effectiveness of more intensive interventions on smoking cessation and diabetic related outcomes. The authors have

	conducted the review to a high quality. The searching for literature is up to date and used a comprehensive search strategy. The most appropriate meta-analysis model was used in the analyses. Specific comments are:
	1. The authors need to clarify in the Objectives of the Abstract that they have only considered diabetic populations
	2. The methods are generally described very clearly; however, some of the methods do not completely follow what is presented in the protocol, for example the Cochrane Q test is mentioned in the protocol, but the I2 test is mentioned in the methods of the manuscript; however, both are presented in the results section.
	3. The longest follow-up was used in the analyses; however, this has the potential to introduce bias in the pooled estimates due to the likely difference in effectiveness over time, where intervention are likely to be less effective at longer follow-up times. Also, it would be interesting for the authors to have conducted meta-analysis of earlier time points to assess if there was any beneficial effect between the treatment groups.
	4. The I2 statistic quantifies heterogeneity, rather than 'tests' for it.
	5. The data analysis section only focuses on smoking cessation as an outcome, when other diabetic related outcomes were also considered
	6. Also, the details reported in the 'outcomes' section of the Results only focus on smoking cessation
	7. More details about the three ongoing trials would have been useful to include in the results section
	8. The figures and tables are presented clearly; however, the upper confidence interval for the Canga 2002 study in Table 2 does not equate to that presented in Figure 3.
	9. The discussion would benefit from including a full section of the limitations and strengths of the review

VERSION 1 – AUTHOR RESPONSE

<u>Reviewer Boris Mankovsky</u>

In the article the results of the meta-analysis of the studies comparing more and less intensive smoking cessation interventions in special population of patients with diabetes mellitus are presented. No evidence of the efficacy of more intensive approach was found.

The data presented are of some interest as it is well known that patients with diabetes mellitus represent the high and very high risk group for cardiovascular morbidity and mortality and the effect of so called "classic" risk factors such as smoking is amplified in subjects with diabetes. Therefore, smoking cessation is very important task in the clinical practice of diabetes care.

The results obtained are based on the small number of the studies which are quite heterogeneous which is correctly admitted by the authors.

Reviewer's Comments

1.My concern is the secondary outcome of the study which is the influence of intensive smoking cessation strategy on the glycemic control. However, authors were able to identify only 1 study which provided such information. I do not think that it is worth to mention this outcome as the secondary objective of the study.

Response Thank you. We agree with your suggestion to remove the objective from the *Abstract* since it was not achieved due to lack of data in the identified literature.   We have therefore modified the *Objectives* section of the *Abstract.*

Modified version:

"To evaluate the effects of more intensive smoking cessation interventions compared to less intensive interventions on smoking cessation in people with type 1 or type 2 diabetes."

Previous version:

"To evaluate the effects of more intensive smoking cessation interventions compared to less intensive interventions on smoking cessation, glycaemic control and weight."

Reviewer's Comments

2.Also, there is no data available regarding the influence of intensive smoking cessation on the weight of patients. The changes of weight should be probably omitted from the study objectives.

Response

Indeed, none of the identified trials reported the effects of interventions to support smoking cessation on body weight. We have omitted this outcome from the *Objectives* section of the *Abstract* as shown above.

Reviewer's Comments

I believe that the article is of some interest to the readers provided that all limitations of the study are carefully mentioned.

Response

We agree that the limitations of our work need to be described in greater detail. We have expanded the discussion of strengths and limitations in the *Discussion* by adding the following comments*.*

"Most of the included trials provided incomplete information on randomization, allocation concealment and blinding of participants and personnel which may potentially introduce bias at the level of individual trials.

This review does not include trials where smoking cessation was a part of a more extensive complex intervention and where only a proportion of patients had diabetes and smoked at baseline. This limited the number of trials to be reviewed and the size of reviewed population, but allowed us to measure specifically the effect of smoking cessation by reducing the extent of performance bias and detection bias arising from multiple interventions and multiple measurements."

Reviewer Peter M Nilsson

This is a timely review on one important topic and updated to present time covering the area.

Reviewer's Comments

It is a bit strange that the Abstract indicates that only studies were selected if biochemical methods were used to assess smoking cessation rates, but two of the studies included did not use such methodology (21,22). Why these exceptions?

Response

Thank you for pointing out the lack of clarity in the *Abstract.* We have included trials reporting both self-reported and biochemically verified smoking cessation. The main meta-analysis reported in this review included trials with biochemically verified smoking cessation and thus minimized the potential

impact of detection bias on the pooled estimates of effect. We summarized lower quality data in a separate pooled analysis of self-reported smoking cessation outcomes.

We have clarified the inclusion of trials with self-reported smoking cessation in the *Abstract/Outcome measures*.

Modified version:

"Biochemically verified smoking cessation was the primary outcome. Secondary outcomes were adverse events and effects on glycaemic control. We also carried out a pooled analysis of self-reported smoking cessation outcomes."

Previous version:

"Biochemically verified smoking cessation was the primary outcome. Secondary outcomes were adverse events and effects on glycaemic control."

Reviewer's Comments

A total of only 872 smokers were included in the intervention studies. This may imply that the non-significant findings where substantially influenced by low statistical power. The authors should comment on this aspect I think.

Response

Thank you for this helpful comment. We have reflected this possibility in the *Discussion*.

Modified version:

"…The statistical power of the meta-analysis is limited by the small number of trials published to date and a relatively small number of participants in the published trials. Limited statistical power may partially explain the lack of significant findings in the pooled analysis…"

Previous version:

"…The statistical power of the meta-analysis is limited by the small number of trials published to date and a relatively small number of participants in the published trials…"

Reviewer Serena Tonstad

This is an interesting systematic review and meta-analysis of randomized clinical trials of intensive versus non-intensive smoking cessation interventions in persons with diabetes. Out of a total of 2914 citations the authors identified 8 eligible trials which could be included in the analysis.

The search strategy is comprehensive, the statistical methods are appropriate and the authors assessed the study quality, and there was low risk of bias in the studies. Patients who received more intensive interventions compared to less intensive interventions had a 32% higher likelihood of biochemically verified smoking cessation, but this was far from statistically significant (RR=1.32, 95% CI: 0.23-7.45, n=4).

The main limitation of the meta-analysis is the low number of studies included in the analysis and therefore lack of statistical power to detect a significant association. Although the number of studies is small and no firm conclusions can be drawn it could inform additional studies on the topic.

Thank you for requesting clarification on this important methodological aspect of our work. We tested for publication bias using funnel plots in Cochrane Review Manager v5.2. There was no evidence of publication bias: two out of four trials reporting biochemically verified smoking cessation were plotted to the left of the summary estimate. We did not include the funnel plot in the manuscript since this technique requires a large number of studies to produce an informative image. However, we included a comment on publication bias in the *Discussion*.

Reviewer's Comments

Did the authors test for publication bias?

Response

"Our analysis includes equal numbers of studies reporting positive and negative effect estimates, which reduces the likelihood of publication bias."

Reviewer Gopalakrishnan Netuveli

This is a well written and clear paper.

Reviewer Jo Leonardi-Bee

The authors have conducted a systematic review and meta-analysis to assess the effectiveness of more intensive interventions on smoking cessation and diabetic related outcomes. The authors have conducted the review to a high quality. The searching for literature is up to date and used a comprehensive search strategy. The most appropriate meta-analysis model was used in the analyses. Specific comments are:

Reviewer's Comments

The authors need to clarify in the Objectives of the Abstract that they have only considered diabetic populations

Response

Thank you for raising this important detail. We have clarified the study population in the Abstract/Objectives. This section has also been modified based on comment 1 from reviewer Boris Mankovsky.

Modified version:

"To evaluate the effects of more intensive smoking cessation interventions compared to less intensive interventions on smoking cessation in people with type 1 or type 2 diabetes."

Previous version:

"To evaluate the effects of more intensive smoking cessation interventions compared to less intensive interventions on smoking cessation, glycaemic control and weight."

Reviewer's Comments

The methods are generally described very clearly; however, some of the methods do not completely follow what is presented in the protocol, for example the Cochrane Q test is mentioned in the protocol,

Thank you. We agree that we need to clarify these methodological details. Both Cochran's Q test and I^2 test were carried out simultaneously when we created Forest plots in Cochrane Review Manager v5.2. Both tests give similar statistical information since I^2 is obtained from Cochran's Q statistic. However, we wanted to quantify heterogeneity by including the value of I^2. We have now listed the Cochran's Q test (also known as Cochran's χ2 test) in the *Methods* section of the manuscript.

Modified version:

"The meta-analysis was carried out in Review Manager version 5.2.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) using Mantel-Haenszel method and Cochran's χ2 test and the I^2 statistic to assess heterogeneity."

Previous version:

but the I2 test is mentioned in the methods of the manuscript; however, both are presented in the results section.

Response

"The meta-analysis was carried out in Review Manager version 5.2.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) using Mantel-Haenszel method and the I^2 statistic to test for heterogeneity."

Reviewer's Comments

The longest follow-up was used in the analyses; however, this has the potential to introduce bias in the pooled estimates due to the likely difference in effectiveness over time, where intervention are likely to be less effective at longer follow-up times. Also, it would be interesting for the authors to have conducted meta-analysis of earlier time points to assess if there was any beneficial effect between the treatment groups.

Response

Thank you for this interesting suggestion. We agree that longer follow-up may result in lower success rates when trials with different duration of follow-up are compared. However, all trials identified in this review had a 6-month duration of follow-up. We did not analyse earlier time points based on recommendations that duration of follow-up in smoking cessation trials should be at least 6 to 12 months:

West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction. 2005; 100(3):299-303.

Reviewer's Comments

The I2 statistic quantifies heterogeneity, rather than 'tests' for it.

Response

We accept that our review focuses only on smoking cessation as an outcome. Although we intended to explore a much broader area of effects of smoking cessation interventions in people with diabetes, there is very little data to analyse. The outcomes of interest pre-specified in our protocol included glycaemic control, blood pressure, weight, microalbuminuria, adverse event rate, change in treatment and cardiovascular events. However, among the identified trials, only one included proportions of patients with HbA1c <7%. Other outcomes of interest were not reported.

Reviewer's Comments

Also, the details reported in the 'outcomes' section of the Results only focus on smoking cessation

We are grateful for this practical suggestion. The *Results* section has been modified to include more information on the ongoing trials.

Modified version:

"We did not identify any trials that specifically assessed pharmacological interventions, although among the three identified ongoing trials not included in this review, one European trial assesses the efficacy and safety of smoking cessation with varenicline tartrate in diabetes patients. [24] Two other ongoing trials carried out in North America [25] and Asia [26] assess the effectiveness of behavioural interventions."

Previous version:

Reviewer's Comments

More details about the three ongoing trials would have been useful to include in the results section

Response

"We did not identify any trials that specifically assessed pharmacological interventions, although among three identified trials in progress, one is designed to assess the efficacy and safety of smoking cessation with varenicline tartrate in diabetes patients.[24]"

Reviewer's Comments

The figures and tables are presented clearly; however, the upper confidence interval for the Canga 2002 study in Table 2 does not equate to that presented in Figure 3.

Response

Thank you for this helpful comment. The upper limit of the 95% confidence interval for the incidence ratio of biochemically verified smoking cessation in a trial by Canga et al was listed incorrectly in Table 2. We have corrected the confidence interval.

Modified version:

7.5 (2.3 – 24.4)

Previous version:

7.5 (2.3 – 34.4)

Reviewer's Comments

The discussion would benefit from including a full section of the limitations and strengths of the review

Response

We have incorporated the reviewers' suggestions and expanded the discussion of strengths and limitations of our work.

Modified version:

"This is, to our knowledge, the first systematic review of randomised trials of smoking cessation interventions in diabetes. Our analysis includes equal numbers of studies reporting positive and negative effect estimates, which reduces the likelihood of publication bias. The statistical power of the meta-analysis is limited by the small number of trials published to date and a relatively small number of participants in the published trials. Limited statistical power may partially explain the lack of significant findings in the pooled analysis. There are too few trials to draw conclusions about the types of intervention, and differences between type 1 and type 2 diabetes. The extent of heterogeneity in

interventions, and intervention and comparator groups, also limited our ability to draw conclusions based on our findings. Most of the included trials provided incomplete information on randomization, allocation concealment and blinding of participants and personnel which may potentially introduce bias at the level of individual trials.

This review does not include trials where smoking cessation was part of complex interventions and where only a proportion of patients had diabetes and smoked at baseline. This limited the number of reviewed trials and the size of reviewed population, but allowed us to measure specifically the effect of smoking cessation by reducing statistical noise from performance bias and detection bias due to multiple interventions and multiple measurements."

Previous version:

"This is, to our knowledge, the first systematic review of randomised trials of smoking cessation interventions in diabetes. Our analysis includes equal numbers of studies reporting positive and negative effect estimates, which reduces the likelihood of publication bias. The statistical power of the meta-analysis is limited by the small number of trials published to date and a relatively small number of participants in the published trials. There are too few trials to draw conclusions about the types of intervention, and differences between type 1 and type 2 diabetes. The extent of heterogeneity in interventions, and intervention and comparator groups, also limited our ability to draw conclusions based on our findings."

VERSION 1 - REVIEW

REVIEWER	Dr. Boris Mankovsky National Medical Academy for Postgraduate Education, Kiev, Ukraine
REVIEW RETURNED	03-Feb-2014

GENERAL COMMENTS	Authors have addressed all my previous comments convincingly. I do not have any other concerns regarding this submission.