Smoking cessation in adults with diabetes: a systematic review and meta-analysis of data from randomised controlled trials

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Complete List of Authors:	Nagrebetsky, Alexander; University of Oxford, Department of Primary Care Health Sciences Brettell, Rachel; University of Oxford, Department of Primary Care Health Sciences Roberts, Nia; University of Oxford, Bodleian Health Care Libraries Farmer, Andrew; University of Oxford, Department of Primary Care Health Sciences; School for Primary Care Research, National Institute for Health Research,
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SMOKING CESSATION IN ADULTS WITH DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS OF DATA FROM RANDOMISED CONTROLLED TRIALS.

Alexander Nagrebetsky [1, 2], Rachel Brettell [1], Nia Roberts [3], Andrew Farmer [1, 2]

1 Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
2 School for Primary Care Research, National Institute for Health Research, UK
3 Bodleian Health Care Libraries, University of Oxford, Oxford, UK

Highest earned degrees: AN, MSc; RB, BMBCh; NR, MSc; AF, DM.

Address for correspondence: Andrew Farmer, Department of Primary Care Health Sciences, Radcliffe Observatory Quarter, Woodstock Road, Oxford OX2 6GG, United Kingdom; andrew.farmer@phc.ox.ac.uk; +441865289280

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ABSTRACT

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

Design: A systematic review and meta-analysis of randomised trials of smoking cessation interventions was conducted. Electronic searches were carried out on the following databases: Medline, Embase, CINAHL, and PsycINFO to September 2013. Searches were supplemented by review of trial registries and references from identified trials. Citations and full-text articles were screened by two reviewers. A random-effect Mantel-Haenszel model was used to pool data.

Setting: Primary, secondary and tertiary care.

Participants: Adults with type 1 or type 2 diabetes.

Interventions: Smoking cessation interventions or medication (more intensive interventions) compared to usual care, counselling or optional medication (less intensive interventions).

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

Results: We screened 1783 citations and reviewed 7 articles reporting 8 trials in 872 participants. All trials were of 6 months duration. Three trials included pharmacotherapy for smoking cessation. The risk ratio of biochemically verified smoking cessation was 1.32 (95% CI 0.23 to 7.43) for the more intensive interventions compared to less intensive interventions with significant heterogeneity ($I^2 = 76\%$). Only one trial reported measures of glycaemic control.

Conclusions: There is an absence of evidence of efficacy for more intensive smoking cessation interventions in people with diabetes. The more intensive strategies tested in trials to date include

interventions used in the general population, adding in diabetes specific education about increased risk. Future research should focus on multi-component smoking cessation interventions carried out over a period of at least one year, and also assess impact on glycaemic control.

ARTICLE SUMMARY

Article focus

- This article focuses on the efficacy of interventions to support smoking cessation in adult patients with diabetes.

Key messages

- Despite an excess cardiovascular risk in people with diabetes, the number of trials evaluating the effects of smoking cessation interventions in this group is very limited.
- The interventions were not specifically tailored for people with diabetes apart from the inclusion of educational components.
- Pooled results did not provide evidence of efficacy for smoking cessation interventions in people with diabetes.

Strengths and limitations of this study

- The major strength of this article is that it is the first systematic review of randomised trials of smoking cessation interventions in diabetes.
- The main limitations of this study are the small number of trials published to date and heterogeneity in interventions offered and groups studied.

INTRODUCTION

For adults with diabetes, as in the wider population, smoking is associated with an increased risk of cardiovascular events and death. A recent systematic review and meta-analysis of prospective studies in diabetes reported that smoking increased the risk of death by 48%, coronary heart disease by 54%, stroke by 44% and myocardial infarction by 52%.[1] The risk for coronary heart disease, stroke and proteinuria is directly related to the number of cigarettes smoked per day.[2, 3] Diabetes patients who smoke have higher HbA1c levels [4] and are more likely to experience severe hypoglycaemia.[5]

People with diabetes who stop smoking are likely to have a lower risk of death and cardiovascular events compared with those who continue to smoke.[1] Smoking cessation is also associated with a reduction in levels of albuminuria, improvement of glycaemic control and lipid profile.[6] Smoking cessation has been recommended as a routine component of the treatment of diabetes by the American Diabetes Association,[7] although evidence to guide best practice is limited.[8]

People with diabetes are faced with the challenge of extensive changes in their lifestyle, a burden that may be increased by attempts to stop smoking.[9, 10] Tailoring smoking cessation programs to the needs of people with diabetes may lead to improved outcomes compared with usual care, but may also further increase the burden of self-management. Concerns have also been expressed regarding weight gain associated with smoking cessation. [11]

We therefore carried out a systematic review of randomised controlled trials reporting the effects of smoking cessation interventions in diabetes to inform clinical practice and identify potential for further research to improve patient outcomes.

METHODS

Eligibility criteria

We carried out this systematic review in accordance with the study protocol (Web Appendix 1).[12] Peer-reviewed journal articles and conference abstracts that reported the results of a randomised controlled trial and met the following eligibility criteria were eligible for inclusion: trials recruiting non-pregnant adults with type 1 or type 2 diabetes who smoked at baseline, evaluating pharmacological or non-pharmacological interventions intended to support smoking cessation (more intensive interventions) compared to usual care, counselling or optional medication (less intensive interventions). We included trials reporting at least one of the following outcomes: i) smoking cessation, ii) glycaemic control, iii) weight. There were no restrictions on length of follow up or language of publication.

Search strategy

We based our search strategy on that used by the Cochrane Tobacco Addiction Group [13] for identifying randomised controlled trials of smoking cessation together with the Cochrane Metabolic and Endocrine Disorders Group [14] search strategy for interventions in type 1 or type 2 diabetes using the high sensitivity options (Web Appendix 2).

We searched the following online-databases: Cochrane Central Register of Controlled Trials [The Cochrane Library, Wiley] (Issue 9, 2013), Medline [OvidSP] (1946 – present), Embase [OvidSP] (1974 – present), CINAHL [EbscoHOST] (1980 – present), PsycINFO [OvidSP] (1967 – present) and Science Citation Index, Social Sciences Citation Index, Conference Proceedings Citation Index- Science & Conference Proceedings Citation Index – Social Science & Humanities [Web of Knowledge] (1945 – present). The most recent search date was September 3, 2013. We also searched clinicaltrials.gov, isrctn.org, anzctr.org.au and International Clinical Trials Registry

Platform for ongoing trials. We also reviewed references from bibliographies of included trial reports and results of a search on Web of Science Citation Index for those reports. We contacted authors of potentially eligible conference abstracts.

Study selection and data extraction

Two reviewers (AN and RB) independently screened the titles and abstracts of identified citations to select those requiring full-text assessment. Where there was disagreement, a third reviewer (AF) assessed the records to reach consensus. Full-text articles were further assessed and data were entered into a pre-specified table including 12 entry fields (Web Appendix 3). Data extraction table included information on: i) trial methodology, setting and duration of follow-up; ii) population characteristics; iii) type of intervention; iv) analyses and outcomes.

Data reported for intention-to-treat analyses were selected at the longest follow-up point. We assumed a diagnosis of type 1 diabetes in insulin-treated participants if the type of diabetes was not otherwise specified.

Data analysis

We used the Cochrane Collaboration's tool to assess risk of bias at the outcome level.[15] Bias was assessed in duplicate with disagreements resolved by a third reviewer. The assessed domains were random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment and completeness of outcome data. Trials deemed to have a high risk of detection bias due to assessing only self-reported smoking cessation were not included in the primary analysis of objectively measured cessation data.

The risk ratio (RR) for biochemically verified smoking cessation with 95% confidence interval (CI) was the primary outcome measure in this analysis. We made an a priori decision to use the

random effect model to take into account the variability of studied populations and intervention types. 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. The main meta-analysis included all measures of biochemically verified smoking cessation outcomes. We also pooled data on self-reported smoking cessation: i) in all eligible trials and ii) in trials with biochemically verified smoking cessation. We calculated pooled means and standard deviations (SD) and obtained SDs from standard errors of the mean using formulas recommended by the Cochrane Collaboration.[16]

RESULTS

A total of 2914 citations were identified (Figure 1) from electronic searches. A further 15 relevant publications were identified as cited by or citing included trial reports. After removing duplicates we screened 1783 citations. Based on the title and abstract, 1669 were assessed as ineligible. The full text of the remaining 114 articles was assessed for eligibility. Most were excluded as not reporting a randomised controlled trial (n = 43), or included patients who did not have diabetes (n = 29) or did not smoke (n = 26). One potentially eligible conference abstract could not be retrieved. We contacted the first author, but received no reply. We selected seven articles reporting eight trials for inclusion.

Duration and settings

All eight trials were reported in English and had a six-month maximum duration of follow-up. Two were reported in a single article.[17] Three trials were carried out in Europe,[18-20] two in Asia,[21, 22] two in Australia [17] and one in North America.[23]

Population

In total, 872 smokers with type 1 or type 2 diabetes participated in the reviewed trials (Table 1). Three trials reported in two publications [17, 21] did not include information on the type of diabetes. Two trials [21, 22] included only men.

Table 1. Characteristics of trials included in the analysis.

Source	Setting	Duration, months	Sample size	Mean (SD) age, years	Men, n (%)	T1D, n (%)	T2D, n (%)	More intensive intervention	Less intensive intervention	Percentage followed up	Primary or efficacy outcome**
Ardron et al 1988 [19]	Diabetes clinic, UK	6	60	29 (7)	29 (48)	50 (83)	10 (17)	Doctor's advice and information pack followed by a home visit by health visitor	Routine doctor's advice	100%	Breath CO and urinary cotinine
Canga et al 2000 [20]	12 primary care practices and 2 hospitals, Spain	6	280	55 (15)	240 (86)	85 (30)	195 (70)	Research nurse interview with follow-up by telephone, post and visits; optional NRT	Usual care including advice to stop smoking	99%	Smoking cessation assessed by urinary cotinine
Fowler et al 1989 [17]	University hospital, Australia	6	18	47 (9)	Not reported	3* (17)	15* (83)	In newly diagnosed diabetes; counselling (Smokescreen program) at diagnosis	Counselling (Smokescreen program) 2 months after diagnosis	83%	Plasma cotinine
Fowler et al 1989 [17]	University hospital, Australia	6	16	53 (13)	Not reported	9* (56)	7* (44)	In pre-existing diabetes; counselling (Smokescreen Program)	Diabetes-specific counselling	88%	Plasma cotinine
Hokanson et al 2006 [23]	Large diabetes centre, USA	6	114	54 (9)	65 (57)	-	114 (100)	Face-to-face counselling followed by repeated telephone counselling and optional NRT or bupropion	Standard care including referral to cessation programs	63%	Self-reported 7-day point prevalence of smoking cessation confirmed by saliva cotinine
Ng et al 2010 [22]	2 diabetes clinics, Indonesia	6	71	56 (9)	71 (100)	-	71 (100)	Doctor's advice and visual materials with referral to cessation clinic	Doctor's advice and visual materials	79%	Self-reported 7-day point prevalence abstinence
Sawicki et al 1993 [18]	Diabetes clinic, Germany	6	89	38 (12)	54 (61)	72 (81)	17 (19)	10 weekly behavioural sessions by a therapist with optional NRT	A single unstructured session by a physician with optional NRT	100%	Smoking cessation assessed by urine cotinine
Thankappan et al 2013 [21]	2 diabetes clinics, India	6	224	53 (9)	224 (100)	Not reported	Not reported	Doctor's advice, educational materials and three 30-min non-doctor counselling sessions	Doctor's advice and educational materials	88%	Self-reported 7-day smoking abstinence

*Assumption on the type of diabetes was made on the basis of reported treatment with insulin.
** Primary outcome unless it was not specified in the article.
SD – standard deviation; T1D – type 1 diabetes; T2D – type 2 diabetes; NRT – nicotine replacement therapy.

Intervention

Five trials assessed either non-pharmacological interventions to support smoking cessation [17, 19, 21] or referral to a smoking cessation clinic.[22] Interventions reported in three other trials included optional nicotine replacement therapy (NRT) without bupropion [18, 20] or with bupropion.[23]

The intervention was delivered by nursing staff or allied health professionals in three trials [18, 20, 23] and by both doctors and nursing staff or allied health professionals in two trials.[19, 21] In one trial, the intervention included advice from a doctor and referral to cessation clinic.[22] In two other trials intervention delivery was not specified.[17] The interventions were not specifically tailored for people with diabetes apart from the inclusion of educational components focussing on the effects of smoking on the complications of diabetes and glycaemic control.

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]

The less intensive intervention comparator groups received usual care involving advice to stop smoking in three trials,[20, 22, 23] counselling about general health risks of smoking in another three trials [17, 21, 22] and diabetes-specific counselling in one trial.[17] In one trial optional NRT was reported as used in addition to counselling in the comparator group.[18]

Outcomes

Four out of eight trials included a definition of the primary outcome (Table 2). In four trials smoking cessation was biochemically verified using concentration of breath carbon monoxide (CO),[19] urinary cotinine,[19, 20] or salivary cotinine.[23] Two trials assessed only self-reported

cessation,[21, 22] and two trials reported only a total number of people with biochemically verified cessation in the study population.[17] All trials measured smoking cessation as point-prevalence abstinence.

Risk of bias

All trials were deemed to have low risk of attrition bias and most trials were assessed as having low risk of detection bias (Figure 2, Web Appendix 4). Most trials provided incomplete information on random sequence generation, allocation concealment and blinding of participants and personnel.

Primary outcome

Trial findings are summarised in Table 2. One article reporting two trials included only the overall number of patients who stopped smoking in both trials.[17] Two trials [21, 22] were excluded from pooled analysis due to high risk of detection bias as a consequence of self-reported cessation outcomes.

Pooled data from the four trials [18-20, 23] which reported point-prevalence of biochemically verified smoking cessation in both trial arms are summarised in Figure 3. For 543 participants, 44 smoking cessation events are reported. The likelihood of biochemically verified smoking cessation was 32% higher in patients who received more intensive intervention compared with less intensive intervention, although this effect was not significant (RR 1.32, 95% CI 0.23 to 7.43).

Table 2. Outcomes and effect sizes of interventions to support smoking cessation.

Type of outcome	Study	More intensive intervention	Less intensive intervention	Comparison	Effect
Objective measures					
Biochemically verified smoking cessation	Ardron et al 1988 [19]	0	1 (3%)	-	-
	Canga et al 2000* [20]	25 (17%)	3 (2%)	Incidence ratio (95% CI)	7.5 (2.3 – 34.4)
	Hokanson et al 2006*[23]	4 (7%)	2 (4%)	Chi-squared test for difference in abstinence rate	p = 0.077
	Sawicki et al 1993 [18]	2 (5%)	7 (16%)	Difference in point-prevalence of cessation	Reported as not significant
Urinary cotinine-creatinine ratio, µg/mg	Ardron et al 1988 [19]	7.6 (4.5)	6.7 (4.4)	-	-
Breath CO (µL/L)	Ardron et al 1988 [19]	18.2 (10.0)	19.4 (8.9)	-	-
HbA1c <7% (53 mmol/mol)	Hokanson et al 2006 [23]	35 (61%)	43 (75%)	Difference in proportion of patients achieving HbA1c <7%	Reported as not significant
Self-reported measures					
7-day abstinence	Ng et al 2010* [22]	14 (37%)	10 (30%)	Allocation effect in logistic regression model	Reported as not significant
	Thankappan et al 2013* [21]	58 (52%)	14 (13%)	Adjusted odds ratio (95% CI)	8.4 (4.1 – 17.1)
Number of cigarettes smoked daily	Canga et al 2000 [20]	15.5**	18.1**	Difference in change in mean cigarettes per day from baseline (95% CI)	-3.0 (-1.1 – -4.9)
>50% reduction in number of cigarettes smoked daily	Thankappan et al 2013 [21]	20 (18%)	25 (22%)	Adjusted odds ratio (95% CI)	1.9 (0.8 – 4.1)
Attempts to quit or reduce smoking	Ng et al 2010 [22]	21 (55%)	16 (48%)	Allocation effect in logistic regression model	Reported as not significant
Incidence of smoking relapse	Canga et al 2000 [20]	49 (33%)	14 (11%)	Difference (95% CI) in incidence of relapse	22.8% (13.6 – 32.0)

Data presented as number of events (%) or mean (SD).
* Reported as a primary outcome. ** Standard deviations not reported.
CO – carbon monoxide, SD – standard deviation, CI – confidence interval

There was substantial heterogeneity between the results of trials included in the pooled analysis of the primary outcome ($\chi 2$ test for heterogeneity, P = 0.006; I^2 = 76%). Two trials,[18, 19] jointly accounting for 45% of the weight of these results, reported point estimates of effects that suggested a greater likelihood of smoking cessation in the less intensive intervention group compared with the more intensive intervention group. In one trial,[19] the only biochemically-verified incident of smoking cessation was recorded in a less intensive intervention group patient who stopped smoking after sustaining a myocardial infarction.

In the pooled analyses of self-reported smoking cessation outcomes in (i) all eligible trials and (ii) in trials also reporting biochemically verified smoking cessation, participants allocated to more intensive intervention had respectively 1.85 times (RR 1.85, 95% CI 0.81 to 4.22) or 1.39 times (RR 1.39, 95% CI 0.28 to 6.92) greater likelihood of cessation compared with patients allocated to the less intensive intervention.

Secondary outcomes

Other outcomes reported related to smoking outcomes and metabolic outcomes (Table 2). Continuous measures of urinary cotinine-creatinine ratio and breath CO were reported for one trial, [19] but the results were not compared between allocated trial groups. In one trial [23] proportions of patients with HbA1c <7% (53 mmol/mol) in more intensive and less intensive intervention groups were reported at six months (61% vs. 75%), but were not significantly different (p=0.16). No trials reported other objectively measured short-term or long-term cardiovascular risk or safety data.

DISCUSSION

Despite an excess cardiovascular risk in people with diabetes, we have identified only a small number of trials evaluating the effect of smoking cessation interventions in this group. Interventions tested in the trials were similar to those used in the general population and included counselling, referral and advice, with, for some, the addition of diabetes specific education. Interventions and comparator groups were heterogenous and the pooled results did not provide evidence of efficacy for smoking cessation interventions in people with diabetes. Only one trial reported data on glycaemic outcomes, which were not significantly different between intervention groups.

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.

Some studies suggest that smokers with diabetes may be more motivated to stop smoking, than the general smoker population [25] and more likely to stop smoking after hospitalisation compared with patients without diabetes.[26] There is no evidence from our review that, if such motivation is present, it translates into improved outcomes. In other high risk patient groups, for example, chronic obstructive pulmonary disease [27] and cardiovascular disease,[28] higher point estimates of the effect of intervention on smoking cessation are reported with most trials extending to 12-month follow-up.

An earlier, narrative review has examined the issues associated with smoking cessation in diabetes and identified some of the reasons why evaluation of smoking cessation interventions in this group may have been dealt with cautiously.[8] The datasheets for most recommended first-line smoking cessation medications [29] caution against their use in diabetes.[8, 30] Moreover, studies report that smoking cessation may worsen metabolic profile and glycaemic control [31, 32] and lead to weight gain.[33] We have identified four trials not included in the narrative review, two predating the narrative review.[17, 19]

Further data from randomised trials of interventions evaluating smoking outcomes, weight change and glycaemic control would inform treatment strategies in a population where smoking cessation is likely to have high absolute benefits.[1] The issue of safety of such treatments is partly addressed in an ongoing trial of varenicline for smoking cessation in diabetes,[24] but the follow up period of six months is likely to be too short to identify sustained effects. Trials assessing combinations of NRT with varenicline or bupropion in addition to non-pharmacological interventions may, in any case, better reflect clinical practice.[29]

Despite the potential health benefits of smoking cessation in diabetes, there has been limited work on developing and evaluating tailored interventions to support smoking cessation in these patients. From a health-services perspective, it would be important to know whether a tailored intervention is more effective in this patient group than providing the same management as for the general population. Given the high burden of self-management required of people with diabetes, it is possible that integrating an intervention with routine care may be more effective than managing the problem separately. Further work is needed to explore the role of this approach in clinical care using trial designs with follow up extending to at least one year.

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COMPETING INTERESTS

None declared.

AUTHORS' CONTRIBUTIONS

AF and AN designed the protocol and the methods. All authors contributed to data extraction. AN carried out the statistical analysis. All authors contributed to drafting of the article and approved the final manuscript.

DATA SHARING

No additional unpublished data from the review are available.

REFERENCES

1. Qin R, Chen T, Lou Q, Yu D. Excess risk of mortality and cardiovascular events associated with smoking among patients with diabetes: meta-analysis of observational prospective studies. International journal of cardiology 2013;167(2):342-50.

2. Hsu CC, Hwang SJ, Tai TY, Chen MC, Huang SJ, Shin CP, et al. Cigarette smoking and proteinuria in Taiwanese men with Type 2 diabetes mellitus. Diabetic medicine 2010;27:295-302.

3. Fagard RH. Smoking amplifies cardiovascular risk in patients with hypertension and diabetes. Diabetes care 2009;32 Suppl 2:S429-31.

4. Nilsson PM, Gudbjornsdottir S, Eliasson B, Cederholm J, Register SC. Smoking is associated with increased HbA1c values and microalbuminuria in patients with diabetes - data from the National Diabetes Register in Sweden. Diabetes & metabolism 2004;30:261-268.

5. Hirai FE, Moss SE, Klein BE, Klein R. Severe hypoglycemia and smoking in a long-term type 1 diabetic population: Wisconsin Epidemiologic Study of Diabetic Retinopathy. Diabetes care 2007;30:1437-1441.

6. Voulgari C, Katsilambros N, Tentolouris N. Smoking cessation predicts amelioration of microalbuminuria in newly diagnosed type 2 diabetes mellitus: a 1-year prospective study. Metabolism: clinical and experimental 2011;60:1456-1464.

7. American Diabetes Association. Standards of Medical Care in Diabetes - 2013. Diabetes care 2012;36:S11-S66.

8. Tonstad S. Cigarette smoking, smoking cessation, and diabetes. Diabetes research and clinical practice 2009;85:4-13.

9. Bohlen K, Scoville E, Shippee ND, May CR, Montori MV. Overwhelmed Patients: A videographic analysis of how patients with type 2 diabetes and clinicians articulate and address treatment burden during clinical encounters. Diabetes care 2011;35(1):47-49.

10. Vijan S, Hayward RA, Ronis DL, Hofer TP. Brief report: The burden of diabetes therapy. Journal of General Internal Medicine 2005;20(5):479-482.

11. Farley AC, Hajek P, Lycett D, Aveyard P. Interventions for preventing weight gain after smoking cessation. Cochrane Database of Systematic Reviews 2012;1:CD006219.

12. A systematic literature review and meta-analysis to assess the effects of interventions to support smoking cessation in adult patients with diabetes: study protocol. http://www.phc.ox.ac.uk/

13. Lancaster T, Stead L, Cahill K, Hartmann-Boyce J, Mehta M, West R, et al. Cochrane Tobacco Addiction Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)) 2012. Available from: http://onlinelibrary.wiley.com/o/cochrane/clabout/articles/TOBACCO/sect0.html

14. Richter B, Bergerhoff K, Paletta G, Bandeira-Echtler E. Cochrane Metabolic and Endocrine Disorders Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)) 2007. Available from: http://onlinelibrary.wiley.com/o/cochrane/clabout/articles/ENDOC/frame.html

15. Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

16. Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

17. Fowler PM, Hoskins PL, McGill M, Dutton SP, Yue DK, Turtle JR. Anti-smoking programme for diabetic patients: the agony and the ecstasy. Diabetic medicine 1989;6:698-702.

18. Sawicki PT, Didjurgeit U, Muhlhauser I, Berger M. Behaviour therapy versus doctor's anti-smoking advice in diabetic patients. Journal of internal medicine 1993;234:407-409.

19. Ardron M, MacFarlane I, Robinson C, Heyningen C, Calverley P. Anti-smoking advice for young diabetic smokers: is it a waste of breath? Diabetic medicine 1988;5:667-670.

20. Canga N, Irala J, Vara E, Duaso MJ, Ferrer A, Martinez-Gonzalez MA. Intervention study for smoking cessation in diabetic patients: a randomized controlled trial in both clinical and primary care settings. Diabetes care 2000;23:1455-1460.

21. Thankappan K, Mini G, Daivadanam M, Vijayakumar G, Sarma P, Nichter M. Smoking cessation among diabetes patients: results of a pilot randomized controlled trial in Kerala, India. BMC public health 2013;13:47.

22. Ng N, Nichter M, Padmawati RS, Prabandari YS, Muramoto M. Bringing smoking cessation to diabetes clinics in Indonesia. Chronic illness 2010;6:125-135.

23. Hokanson JM, Anderson RL, Hennrikus DJ, Lando HA, Kendall DM. Integrated tobacco cessation counseling in a diabetes self-management training program: a randomized trial of diabetes and reduction of tobacco. Diabetes Educator 2006;32:562-570.

24. Efficacy And Safety Of Smoking Cessation With Varenicline Tartrate In Diabetic Smokers: (DIASMOKE). Available from: http://clinicaltrials.gov/show/NCT01387425

25. Wilkes S, Evans A. A cross-sectional study comparing the motivation for smoking cessation in apparently healthy patients who smoke to those who smoke and have ischaemic heart disease, hypertension or diabetes. Family Practice 1999;16(6):608-10.

26. Duffy SA, Munger A, Karvonen-Gutierrez CA, Piette JD, Kao TA. Post-discharge tobacco cessation rates among hospitalized US veterans with and without diabetes. Diabetic Medicine 2012;29(7):e96-e101.

27. Piresyfantouda R, Absalom G, Clemens F. Smoking Cessation Interventions for Chronic Obstructive Pulmonary Disease - A Review of the literature. Respiratory care 2013. doi:10.4187/respcare.01923.

28. Eisenberg MJ, Blum LM, Filion KB, Rinfret S, Pilote L, Paradis G, et al. The efficacy of smoking cessation therapies in cardiac patients: a meta-analysis of randomized controlled trials. The Canadian journal of cardiology 2010;26(2):73-9.

29. 2008 PHS Guideline Update Panel, Liaisons, and Staff. Treating tobacco use and dependence: 2008 update U.S. Public Health Service Clinical Practice Guideline executive summary. Respiratory care 2008;53:1217-1222.

30. British Medical Association and the Royal Pharmaceutical Society of Great Britain. British National Formulary. 64th ed. London: BMJ Group and Pharmaceutical Press. 2012.

31. Balkau B, Vierron E, Vernay M, Born C, Arondel D, Petrella A, et al. The impact of 3-year changes in lifestyle habits on metabolic syndrome parameters: the D.E.S.I.R study. European journal of cardiovascular prevention and rehabilitation 2006;13:334-340.

32. Iino K, Iwase M, Tsutsu N, Iida M. Smoking cessation and glycaemic control in type 2 diabetic patients. Diabetes, obesity & metabolism 2004;6:181-186.

33. Aubin HJ, Farley A, Lycett D, Lahmek P, Aveyard P. Weight gain in smokers after quitting cigarettes: meta-analysis. BMJ (Clinical research ed.) 2012;345:e4439.

Figure 1. A flow diagram of literature search, screening and selection.

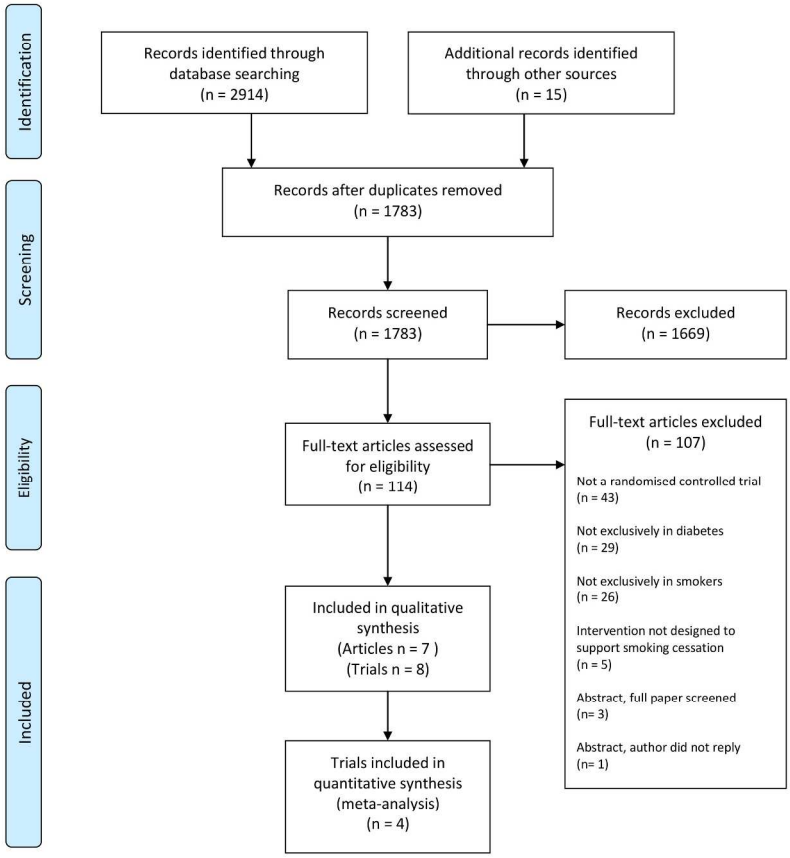

Figure 1. Flow diagram of literature search, screening and selection for analysis.
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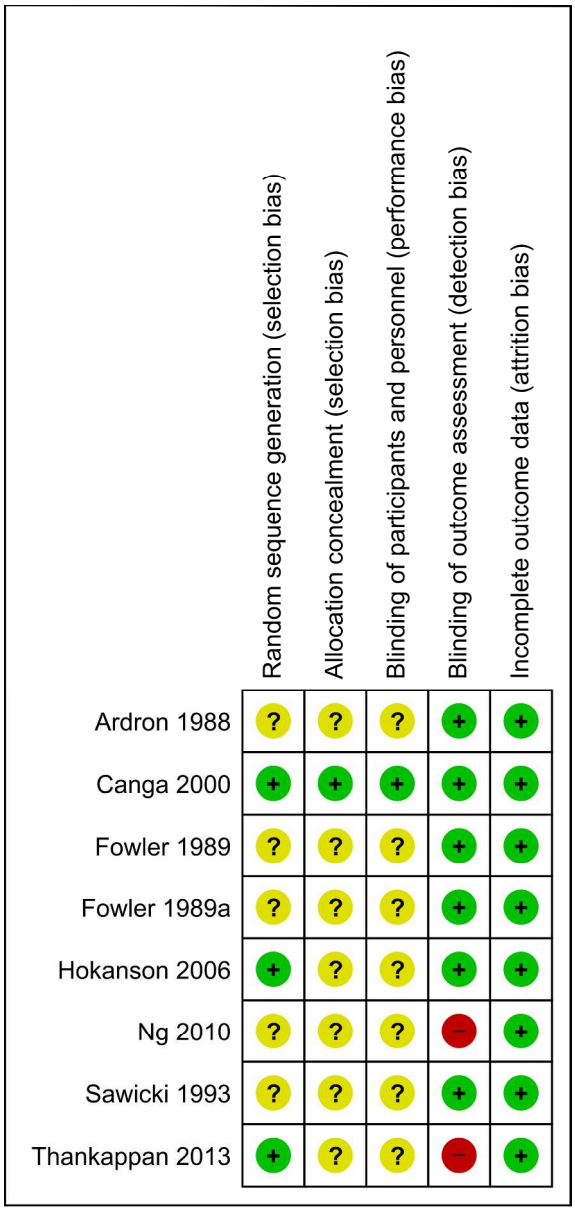


Figure 2. Summary of authors' judgements on the risk of bias in reviewed trials.
190x401mm (300 x 300 DPI)

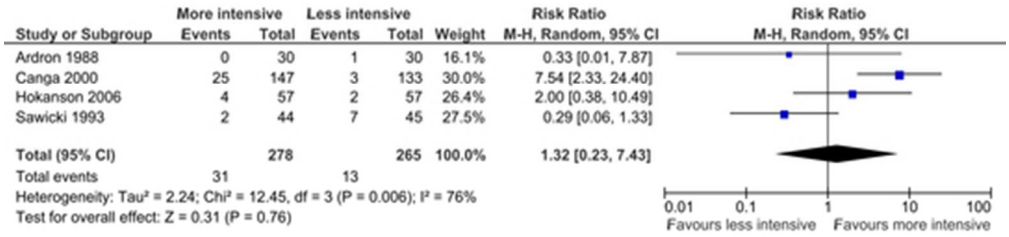


Figure 3. Forest plot showing pooled analysis of trials reporting biochemically verified point-prevalence of smoking cessation.
45x11mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2,3,4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5,6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6,7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7, Appendix 3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7,8

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7,8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8, Appendix 1
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Figure 2, Appendix 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Protocol

Title:

A systematic literature review and meta-analysis to assess the effects of interventions to support smoking cessation in adult patients with diabetes.

Collaborators:

Andrew Farmer

Alexander Nagrebetsky

Rachel Brettell

Nia Roberts

Background

In patients with diabetes smoking is associated with increased morbidity and mortality. A recent systematic review and meta-analysis of prospective studies in diabetes demonstrated that smoking significantly increased the risk of death by 48%, coronary heart disease by 54%, stroke by 44% and myocardial infarction by 52%.[1] The risk for coronary heart disease, stroke and proteinuria is directly related to the number of cigarettes smoked per day.[2,3] Diabetes patients who smoke have higher HbA1c levels[4] and are more likely to experience severe hypoglycaemia.[5]

Patients with diabetes who stopped smoking are likely to have lower risk of death and cardiovascular events compared to those who continue to smoke.[1] Smoking cessation is also associated with decreased rates of microalbuminuria, improvement of glycaemic control and lipid profile.[6] Smoking cessation has been recommended as a routine component of the treatment of diabetes by the American Diabetes Association.[7] However, the evidence base for selecting appropriate interventions is limited.[8]

A very small number of randomised controlled trials of non-pharmacological interventions have been non-systematically reviewed.[8] However, there appear to be no systematic reviews of trials of pharmacological or behavioural interventions to support smoking cessation in diabetes. The lack of reliable safety and efficacy data on pharmacological interventions may prevent physicians from supporting smoking cessation in diabetes using pharmacotherapy.[8] The datasheets for most of the recommended first-line medications[9] caution against their use in diabetes.[8,10] Moreover, the reports that smoking cessation may worsen metabolic profile and glycaemic control[11,12] further contribute to the uncertainty about the benefits and harms of smoking cessation in diabetes. A systematic review of reports on the effects of interventions to support smoking cessation in diabetes will consolidate the existing evidence and identify important areas for further research.

Aim

To assess and summarise the effects of interventions to support smoking cessation in adult patients with diabetes.

Literature search

Previous reviews

Prior to the main review we will attempt to identify previous similar reviews by searching for "smoking AND diabetes AND review" in the following databases: Cochrane Library, Database of Abstracts and Reviews (DARE), PubMed, CINAHL, Web of Science and PsycInfo. We will also attempt to identify ongoing clinical trials by searching clinicaltrials.gov and WHO International Clinical Trials Registry Platform.

Search question

The literature search will be based on the question: What are the effects of interventions to support smoking cessation in adult patients with diabetes?

Question component	Question term
Population	Adults (>18 years) with type 1 or type 2 diabetes
Intervention	Non-pharmacologic
	Pharmacologic
Main outcome	Smoking cessation rate
Secondary outcomes, assessed in responders to the intervention	Glycaemic control
	Blood pressure
	Weight including BMI
	Adverse event rate
	Microalbuminuria
	Lipid profile- at least one of: LDL, HDL, TG, Total cholesterol
	Change in treatment
	Cardiovascular events

Databases

The following databases will be searched:

1) Cochrane Central Register of Controlled Trials (CCTR); 2) PubMed; 3) Scopus; 4) Embase.

Study inclusion criteria

We will carry out a two-stage review of randomised controlled trials (RCTs) of interventions to support smoking cessation in patients >18 years old with type 1 or type 2 diabetes. All eligible studies will report at least one of the following outcomes: 1) smoking cessation rate; 2) glycaemic control assessed as HbA1c; 3) weight including body mass index. No language restrictions will be imposed. The first stage of the analysis will include studies where: 1) all participants at baseline are smokers and 2) all participants at baseline have diabetes. The second stage of the analysis will also

include studies where smokers with diabetes represent a subgroup of the study population and the proportion of smokers with diabetes at baseline and at follow-up is either reported in the publication or is provided by the authors upon request.

Search strategy

We will use the search strategy employed by the Cochrane Tobacco Addiction Group for identifying RCTs in smoking combined with the Cochrane Metabolic and Endocrine Disorders Group search strategy for type 1 or type 2 diabetes. High sensitivity options will be chosen.

The obtained results will be supplemented with 1) references from bibliographies of the identified literature and 2) citation search using Science Citation Index.

Selection and data extraction

Two non-blinded reviewers will carry out independent selection of articles based on the inclusion criteria listed above. Details of selected studies will be entered into a predefined table:

Reference	Study period	Study setting	Study population	Proportion depressed	Type of intervention (pharmacological/non-pharmacological)

Assessed interventions	Duration of follow-up	Method of analysis	Outcomes	Methodological quality	Summary of key results

We will report measures of possible bias and the measures assessing the potential for not reporting data. Conflicting selections and quality assessments will be resolved by joint re-assessment and discussion.

Analysis

Data presentation

We will present the included studies in a tabular summary and point estimates of reported effects in a graphical summary. A separate summary of point estimates of secondary outcomes will be presented if sufficient data is available.

Statistical methods

We made an a priori decision to use the random effect analysis since the identified studies are likely to include different studied populations and intervention types. Thus, observing a fixed effect of an intervention is improbable. Heterogeneity will be assessed using the Cochrane Q divided by the degrees of freedom. If deemed feasible by reviewers, a funnel plot will be used to assess the publication bias.

Subgroup analyses

If sufficient data is available we will carry out the following analyses:

1) By secondary outcomes in responders vs non-responders
2) By intervention type
3) By type of diabetes

Dissemination of findings

Obtained results will be presented within the Department of Primary Care Health Sciences at the University of Oxford and, if feasible, submitted for publication in a peer-reviewed journal.

References

1. Qin R, Chen T, Lou Q, Yu D. Excess risk of mortality and cardiovascular events associated with smoking among patients with diabetes: Meta-analysis of observational prospective studies. International journal of cardiology 2013; 167(2):342-50

2. Fagard RH. Smoking amplifies cardiovascular risk in patients with hypertension and diabetes. Diabetes care. 2009;32 Suppl 2:S429-31.

3. Hsu CC, Hwang SJ, Tai TY, et al. Cigarette smoking and proteinuria in Taiwanese men with Type 2 diabetes mellitus. Diabetic medicine. 2010; 27:295-302.

4. Nilsson PM, Gudbjornsdottir S, Eliasson B, Cederholm J, Register SC. Smoking is associated with increased HbA1c values and microalbuminuria in patients with diabetes--data from the National Diabetes Register in Sweden. Diabetes & metabolism. 2004;30:261-268.

5. Hirai FE, Moss SE, Klein BE, Klein R. Severe hypoglycemia and smoking in a long-term type 1 diabetic population: Wisconsin Epidemiologic Study of Diabetic Retinopathy. Diabetes care. 2007;30:1437-1441.

6. Voulgari C, Katsilambros N, Tentolouris N. Smoking cessation predicts amelioration of microalbuminuria in newly diagnosed type 2 diabetes mellitus: a 1-year prospective study. Metabolism: clinical and experimental. 2011;60:1456-1464.

7. American Diabetes Association. Standards of Medical Care in Diabetes - 2013. Diabetes care 2012; 36:S11-S66.

8. Tonstad S. Cigarette smoking, smoking cessation, and diabetes. Diabetes research and clinical practice. 2009;85:4-13.

9. 2008 PHS Guideline Update Panel, Liaisons, and Staff. Treating tobacco use and dependence: 2008 update U.S. Public Health Service Clinical Practice Guideline executive summary. Respiratory care. 2008;53:1217-1222.

10. British Medical Association and the Royal Pharmaceutical Society of Great Britain. British National Formulary. 64th ed. London: BMJ Group and Pharmaceutical Press. 2012

11. Iino K, Iwase M, Tsutsu N, Iida M. Smoking cessation and glycaemic control in type 2 diabetic patients. Diabetes, obesity & metabolism. 2004;6:181-186.

12. Balkau B, Vierron E, Vernay M, et al. The impact of 3-year changes in lifestyle habits on metabolic syndrome parameters: the D.E.S.I.R study. European journal of cardiovascular prevention and rehabilitation. 2006;13:334-340.

Search strategy

Title: A systematic literature review and meta-analysis to assess the effects of interventions to support smoking cessation in adult patients with diabetes.

Search summary:

We searched the Cochrane Central Register of Controlled Trials [The Cochrane Library, Wiley] (Issue 4, 2012), Medline [OvidSP] (1946 – present), Embase [OvidSP] (1974 – present), CINAHL [EbscoHOST] (1980 – present), PsycINFO [OvidSP] (1967 – present) & Science Citation Index, Social Sciences Citation Index, Conference Proceedings Citation Index- Science & Conference Proceedings Citation Index- Social Science & Humanities [Web of Knowledge] (1945 – present). The original search was run 14th May 2012, an update search was run 1st October 2012. The final update search was run 4th September 2013.

We searched trial registries for ongoing trials. We scanned reference lists of relevant articles and contacted researchers in the field.

Search methods:

Database name:	Interface:	Year range:	Date searched:	Hits:
CINAHL	EbscoHOST	1980 –	04/09/13	34
Cochrane Central Register of Controlled Trials	Cochrane Library, Wiley	Iss 9. 2013		6
Embase	OvidSP			
Medline	OvidSP	1974 –		126
PsycINFO	OvidSP	1946 –		83
Science Citation Index, Social Sciences Citation Index, Conference Proceedings Citation Index- Science & Conference Proceedings Citation Index- Social Science & Humanities	Web of Knowledge	1967 – 1945 -		19 93
Scopus	Elsevier			100
Unique references from May 2012 search = 1480 Unique references from Oct 2012 update = 115 References retrieved in this update = 461 Duplicates removed = 290 Final total = 1766 Unique references for Sep 2013 update = 171				
Limits: Human: animal studies excluded Publication type: RCTs				

Other resources searched:

Trial registers:

- ClinicalTrials.gov http://clinicaltrials.gov – Added from 01/01/2012-04/09/2013= 10 results
- WHO http://apps.who.int/trialsearch/ - Added from 01/01/2012-04/09/2013= 8 results

16 new results once deduplicated

Search terms used:

"smoking cessation" AND diabetes
Condition=Diabetes AND Intervention=smoking

Other search methods used:

- Review of reference lists
- Contacted the following authors: Thomas, Janet L.

Search strategies:

CINAHL

S21	S20 Limiters - Published Date: 20120101-20130931	34
S20	S10 and S18 Limiters - Clinical Queries: Therapy - High Sensitivity	151
S19	S10 and S18	558
S18	S11 or S12 or S13 or S14 or S15 or S16 or S17	16395
S17	TI (((quit* or stop* or cease* or giv*) n5 smoking)) OR AB (((quit* or stop* or cease* or giv*) n5 smoking))	2984
S16	TI (smoking cessation OR tobacco cessation) OR AB (smoking cessation OR tobacco cessation)	5442
S15	(MH "Nicotine Patch")	293
S14	(MH "Nicotine Replacement Therapy")	874
S13	(MH "Smoking/PC/TH")	4127
S12	(MH "Tobacco") OR (MH "Tobacco, Smokeless")	3491
S11	(MH "Smoking Cessation") OR (MH "Smoking Cessation Programs")	9416
S10	S6 NOT S9	70595
S9	S7 or S8	240
S8	TI diabet* insipidus OR AB diabet* insipidus	148
S7	(MH "Diabetes Insipidus")	192
S6	S1 or S2 or S3 or S4 or S5	70760
S5	TI (insulin* depend* or insulin?depend*) OR AB (insulin* depend* or insulin?depend*)	1513
S4	TI (non insulin* depend* or non insulin* depend* or non insulin?depend* or non insulin?depend*) OR AB (non insulin* depend* or non insulin* depend* or non insulin?depend* or non insulin?depend*)	569
S3	TI (IDDM or NIDDM or MODY or T1DM or T2DM or T1D or T2D) OR AB (IDDM or NIDDM or MODY or T1DM or T2DM or T1D or T2D)	1909
S2	TI diabet* OR AB diabet*	55873
S1	(MH "Diabetes Mellitus+")	56134

Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley)

ID Search
#1 MeSH descriptor: [Diabetes Mellitus] explode all trees
#2 diabet*:ti,ab,kw
#3 IDDM or NIDDM or MODY or T1DM or T2DM or T1D or T2D:ti,ab,kw
#4 non insulin* depend* or non insulin depend* or non insulin?depend* or non insulin?depend:ti,ab,kw
#5 insulin* depend* or insulin?depend*:ti,ab,kw
#6 #1 or #2 or #3 or #4 or #5
#7 MeSH descriptor: [Diabetes Insipidus] explode all trees
#8 diabet* insipidus:ti,ab,kw
#9 #7 or #8
#10 #6 not #9
#11 MeSH descriptor: [Tobacco Use Cessation] explode all trees
#12 MeSH descriptor: [Tobacco] explode all trees
#13 MeSH descriptor: [Nicotine] explode all trees
#14 MeSH descriptor: [Tobacco Use Disorder] explode all trees
#15 MeSH descriptor: [Tobacco Smoke Pollution] explode all trees
#16 MeSH descriptor: [Smoking] explode all trees and with qualifiers: [Prevention & control - PC, Therapy - TH]
#17 ((smoking or tobacco) next cessation):ti,ab,kw
#18 ((quit* or stop* or cease* or giv*) near smoking):ti,ab,kw
#19 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20 #10 and #19

Embase (OvidSP)

1	exp Diabetes Mellitus/	572211
2	diabet*.ti,ab,ot.	542710
3	(IDDM or NIDDM or MODY or T1DM or T2DM or T1D or T2D).ti,ab,ot.	35227
4	(non insulin* depend* or non insulin* depend* or non insulin?depend* or non insulin?depend*).ti,ab,ot.	12485
5	(insulin* depend* or insulin?depend*).ti,ab,ot.	33290
6	1 or 2 or 3 or 4 or 5	672891
7	exp Diabetes Insipidus/	11125
8	diabet* insipidus.ti,ab,ot.	8319
9	7 or 8	12401
10	6 not 9	663690
11	smoking cessation/ or smoking cessation program/	36479
12	tobacco dependence/	12329
13	tobacco/ or smokeless tobacco/	33838
14	nicotine replacement therapy/	2903
15	nicotine gum/ or nicotine lozenge/ or nicotine patch/ or nicotine vaccine/	2923
16	smoking/pc, th [Prevention, Therapy]	8268
17	((smoking or tobacco) adj cessation).ti,ab.	19294
18	((quit* or stop* or cease* or giv*) adj5 smoking).ti,ab.	12708
19	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	85348
20	random*.ti,ab.	853850
21	factorial*.ti,ab.	22168
22	(crossover* or cross over*).ti,ab.	70017
23	placebo*.ti,ab.	199972
24	(doubl* adj blind*).ti,ab.	146490
25	(singl* adj blind*).ti,ab.	14132
26	assign*.ti,ab.	234619
27	allocat*.ti,ab.	80752
28	volunteer*.ti,ab.	178753
29	crossover-procedure/	38291
30	double-blind procedure/	119862
31	single-blind procedure/	18184

32	randomized controlled trial/	357716
33	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	1395000
34	10 and 19 and 33	534
35	(2012* or 2013*).em,dp,yr.	2434440
36	34 and 35	126

Medline (OvidSP)

1	exp Diabetes Mellitus/	315240
2	diabet*.ti,ab,ot.	411846
3	(IDDM or NIDDM or MODY or T1DM or T2DM or T1D or T2D).ti,ab,ot.	25647
4	(non insulin* depend* or non insulin* depend* or non insulin?depend* or non insulin?depend*).ti,ab,ot.	10679
5	(insulin* depend* or insulin?depend*).ti,ab,ot.	28202
6	1 or 2 or 3 or 4 or 5	465021
7	exp Diabetes Insipidus/	6897
8	diabet* insipidus.ti,ab,ot.	6799
9	7 or 8	8870
10	6 not 9	457756
11	Smoking Cessation/	20837
12	"Tobacco Use Cessation"/	755
13	((smoking or tobacco) adj cessation).ti,ab.	17133
14	((quit* or stop* or cease* or giv*) adj5 smoking).ti,ab.	11236
15	tobacco/ or tobacco, smokeless/	26600
16	Nicotine/	21738
17	"Tobacco Use Disorder"/	8359
18	Tobacco Smoke Pollution/	10633
19	exp Smoking/pc, th [Prevention & Control, Therapy]	16628
20	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	92023
21	randomized controlled trial.pt.	383307
22	controlled clinical trial.pt.	88946
23	randomized.ab.	298936
24	placebo.ab.	160755
25	drug therapy.fs.	1741540
26	randomly.ab.	211895
27	trial.ab.	314995
28	groups.ab.	1349081
29	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	3371868
30	exp animals/ not humans.sh.	4021928

31	29 not 30	2889885
32	10 and 20 and 31	602
33	(2012* or 2013*).ed,dp,yr.	2269358
34	32 and 33	83

PsycINFO (OvidSP)

1	Diabetes/ or Diabetes Mellitus/	10050
2	diabet*.ti,ab,ot.	17407
3	(IDDM or NIDDM or MODY or T1DM or T2DM or T1D or T2D).ti,ab,ot.	822
4	(non insulin* depend* or non insulin* depend* or non insulin?depend* or non insulin?depend*).ti,ab,ot.	188
5	(insulin* depend* or insulin?depend*).ti,ab,ot.	928
6	1 or 2 or 3 or 4 or 5	17632
7	exp Diabetes Insipidus/	143
8	diabet* insipidus.ti,ab,ot.	209
9	7 or 8	242
10	6 not 9	17401
11	((smoking or tobacco) adj cessation).ti,ab.	7083
12	((quit* or stop* or cease* or giv*) adj5 smoking).ti,ab.	4471
13	smoking cessation/	8438
14	tobacco smoking/	21293
15	smokeless tobacco/	507
16	nicotine/	7566
17	11 or 12 or 13 or 14 or 15 or 16	28732
18	10 and 17	239
19	limit 18 to "therapy (maximizes sensitivity)"	109
20	(2012* or 2013*).up,dp,yr.	319784
21	19 and 20	19

Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI) , Conference Proceedings Citation Index- Science (CPCI-S) & Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) (Web of Knowledge)

Set	Results	
# 6	93	#3 AND #4 AND #5 Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=2012-01-01 - 2013-09-04 (Processing Date)
# 5	272,437	TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)
# 4	3,998	TS=("smoking cessation") OR TS=(((quit* or stop* or cease* or giv*) SAME smoking))
# 3	49,778	#1 NOT #2
# 2	363	TS=("diabetes insipidus")
# 1	50,141	TS=(diabet*) OR TS=(IDDM OR NIDDM OR MODY OR T1DM OR T2DM OR T1D OR T2D) OR TS=("non insulin* depend*" OPR "non insulin* depend*" OR "non insulin?depend*" OR "non insulin?depend*") OR TS=("insulin* depend*" or "insulin?depend*")

SCOPUS

((TITLE-ABS-KEY(diabet*)) AND ((TITLE-ABS-KEY("smoking cessation")) OR ((TITLE(smoking W/5 (quit* OR stop* OR ceas* OR giv*)) OR ABS(smoking W/5 (quit* OR stop* OR ceas* OR giv*)))) OR ((TITLE(smoking W/5 (quit* OR stop* OR ceas* OR giv*)) OR ABS(smoking W/5 (quit* OR stop* OR ceas* OR giv*)))) OR (TITLE(smoking* OR smoker* OR tobacco OR nicotine)))) AND ((TITLE(random* OR blind* OR allocat* OR assign* OR trial* OR placebo* OR crossover* OR cross-over*) OR ABS(random* OR blind* OR allocat* OR assign* OR trial* OR placebo* OR crossover* OR cross-over*))) AND (LIMIT-TO(PUBYEAR, 2013) OR LIMIT-TO(PUBYEAR, 2012))

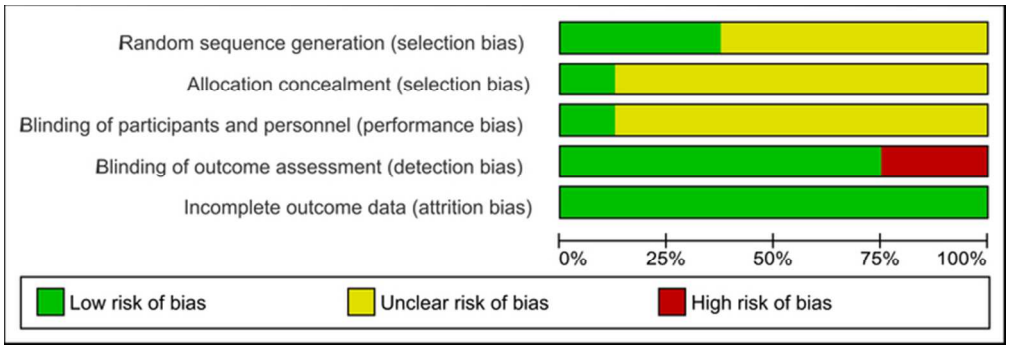
Methodological search filters:

CINAHL	**RCTS:** EbscoHOST Clinical Queries: Therapy – High Sensitivity Reference: Wong SS, Wilczynski NL, Haynes RB.Optimal CINAHL search strategies for identifying therapy studies and review articles. J Nurs Scholarsh. 2006;38(2):194-9. http://www3.interscience.wiley.com/journal/118600195/abstract?CRETRY=1&SRETRY=0 (See table 3)
Embase	**RCTs** Ovid Clinical Queries: Treatment (2 or more terms high sensitivity) Reference: Wong SS, Wilczynski NL, Haynes RB.Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. J Med Libr Assoc. 2006 Jan;94(1):41-7. http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=16404468 (See table 3)
Medline	**RCTs** Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format http://www.cochrane-handbook.org (Section 6.4.11)
PsycINFO	**RCTs:** Ovid Clinical Queries: Treatment (high sensitivity) Reference: Eady AM, Wilczynski NL, Haynes RB. PsycINFO search strategies identified methodologically sound therapy studies and review articles for use by clinicians and researchers. J Clin Epidemiol. 2008 Jan;61(1):34-40. http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=18083460 (see table 2)

Appendix 3. Data extraction table.

Reference	Study period	Study setting	Study population	Proportion depressed	Type of intervention (pharmacological/non-pharmacological)	Assessed interventions	Duration of follow-up	Method of analysis	Outcomes	Methodological quality	Summary of key results

Nagrebetsky et al 2013, University of Oxford



Appendix 4. Risk of bias presented as percentages across all included trials.
64x21mm (300 x 300 DPI)

Smoking cessation in adults with diabetes: a systematic review and meta-analysis of data from randomised controlled trials

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004107.R1
Article Type:	Research
Date Submitted by the Author:	24-Jan-2014
Complete List of Authors:	Nagrebetsky, Alexander; University of Oxford, Department of Primary Care Health Sciences Brettell, Rachel; University of Oxford, Department of Primary Care Health Sciences Roberts, Nia; University of Oxford, Bodleian Health Care Libraries Farmer, Andrew; University of Oxford, Department of Primary Care Health Sciences; School for Primary Care Research, National Institute for Health Research,
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Smoking and tobacco, Diabetes and endocrinology
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, PREVENTIVE MEDICINE, GENERAL MEDICINE (see Internal Medicine)

TITLE PAGE

For submission to BMJ Open

Study type: research article

SMOKING CESSATION IN ADULTS WITH DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS OF DATA FROM RANDOMISED CONTROLLED TRIALS.

Alexander Nagrebetsky [1, 2], Rachel Brettell [1], Nia Roberts [3], Andrew Farmer [1, 2]

1 Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
2 School for Primary Care Research, National Institute for Health Research, UK
3 Bodleian Health Care Libraries, University of Oxford, Oxford, UK

Highest earned degrees: AN, MSc; RB, BMBCh; NR, MSc; AF, DM.

Address for correspondence: Andrew Farmer, Department of Primary Care Health Sciences, Radcliffe Observatory Quarter, Woodstock Road, Oxford OX2 6GG, United Kingdom; andrew.farmer@phc.ox.ac.uk; +441865289280

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ABSTRACT

Objectives: 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.

Design: A systematic review and meta-analysis of randomised trials of smoking cessation interventions was conducted. Electronic searches were carried out on the following databases: Medline, Embase, CINAHL, and PsycINFO to September 2013. Searches were supplemented by review of trial registries and references from identified trials. Citations and full-text articles were screened by two reviewers. A random-effect Mantel-Haenszel model was used to pool data.

Setting: Primary, secondary and tertiary care.

Participants: Adults with type 1 or type 2 diabetes.

Interventions: Smoking cessation interventions or medication (more intensive interventions) compared to usual care, counselling or optional medication (less intensive interventions).

Outcome measures: 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.

Results: We screened 1783 citations and reviewed 7 articles reporting 8 trials in 872 participants. All trials were of 6 months duration. Three trials included pharmacotherapy for smoking cessation. The risk ratio of biochemically verified smoking cessation was 1.32 (95% CI 0.23 to 7.43) for the more intensive interventions compared to less intensive interventions with significant heterogeneity ($I^2 = 76\%$). Only one trial reported measures of glycaemic control.

Conclusions: There is an absence of evidence of efficacy for more intensive smoking cessation interventions in people with diabetes. The more intensive strategies tested in trials to date include interventions used in the general population, adding in diabetes specific education about increased risk. Future research should focus on multi-component smoking cessation interventions carried out over a period of at least one year, and also assess impact on glycaemic control.

ARTICLE SUMMARY

Article focus

- This article focuses on the efficacy of interventions to support smoking cessation in adult patients with diabetes.

Key messages

- Despite an excess cardiovascular risk in people with diabetes, the number of trials evaluating the effects of smoking cessation interventions in this group is very limited.
- The interventions were not specifically tailored for people with diabetes apart from the inclusion of educational components.
- Pooled results did not provide evidence of efficacy for smoking cessation interventions in people with diabetes.

Strengths and limitations of this study

- The major strength of this article is that it is the first systematic review of randomised trials of smoking cessation interventions in diabetes.
- The main limitations of this study are the small number of trials published to date and heterogeneity in interventions offered and groups studied.

INTRODUCTION

For adults with diabetes, as in the wider population, smoking is associated with an increased risk of cardiovascular events and death. A recent systematic review and meta-analysis of prospective studies in diabetes reported that smoking increased the risk of death by 48%, coronary heart disease by 54%, stroke by 44% and myocardial infarction by 52%.[1] The risk for coronary heart disease, stroke and proteinuria is directly related to the number of cigarettes smoked per day.[2, 3] Diabetes patients who smoke have higher HbA1c levels [4] and are more likely to experience severe hypoglycaemia.[5]

People with diabetes who stop smoking are likely to have a lower risk of death and cardiovascular events compared with those who continue to smoke.[1] Smoking cessation is also associated with a reduction in levels of albuminuria, improvement of glycaemic control and lipid profile.[6] Smoking cessation has been recommended as a routine component of the treatment of diabetes by the American Diabetes Association,[7] although evidence to guide best practice is limited.[8]

People with diabetes are faced with the challenge of extensive changes in their lifestyle, a burden that may be increased by attempts to stop smoking.[9, 10] Tailoring smoking cessation programs to the needs of people with diabetes may lead to improved outcomes compared with usual care, but may also further increase the burden of self-management. Concerns have also been expressed regarding weight gain associated with smoking cessation. [11]

We therefore carried out a systematic review of randomised controlled trials reporting the effects of smoking cessation interventions in diabetes to inform clinical practice and identify potential for further research to improve patient outcomes.

METHODS

Eligibility criteria

We carried out this systematic review in accordance with the study protocol (Web Appendix 1).[12] Peer-reviewed journal articles and conference abstracts that reported the results of a randomised controlled trial and met the following eligibility criteria were eligible for inclusion: trials recruiting non-pregnant adults with type 1 or type 2 diabetes who smoked at baseline, evaluating pharmacological or non-pharmacological interventions intended to support smoking cessation (more intensive interventions) compared to usual care, counselling or optional medication (less intensive interventions). We included trials reporting at least one of the following outcomes: i) smoking cessation, ii) glycaemic control, iii) weight. There were no restrictions on length of follow up or language of publication. We included trials that did not report biochemically verified smoking cessation to fully capture the available evidence, characterize smoking status as reported in these trials and to add to the available data from which we could analyse effects of interventions on glycaemic control and weight where such additional data were available.

Search strategy

We based our search strategy on that used by the Cochrane Tobacco Addiction Group [13] for identifying randomised controlled trials of smoking cessation together with the Cochrane Metabolic and Endocrine Disorders Group [14] search strategy for interventions in type 1 or type 2 diabetes using the high sensitivity options (Web Appendix 2).

We searched the following online-databases: Cochrane Central Register of Controlled Trials [The Cochrane Library, Wiley] (Issue 9, 2013), Medline [OvidSP] (1946 – present), Embase [OvidSP] (1974 – present), CINAHL [EbscoHOST] (1980 – present), PsycINFO [OvidSP] (1967 – present) and Science Citation Index, Social Sciences Citation Index, Conference Proceedings

Citation Index- Science & Conference Proceedings Citation Index – Social Science & Humanities [Web of Knowledge] (1945 – present). The most recent search date was September 3, 2013. We also searched clinicaltrials.gov, isrctn.org, anzctr.org.au and International Clinical Trials Registry Platform for ongoing trials. We also reviewed references from bibliographies of included trial reports and results of a search on Web of Science Citation Index for those reports. We contacted authors of potentially eligible conference abstracts.

Study selection and data extraction

Two reviewers (AN and RB) independently screened the titles and abstracts of identified citations to select those requiring full-text assessment. Where there was disagreement, a third reviewer (AF) assessed the records to reach consensus. Full-text articles were further assessed and data were entered into a pre-specified table including 12 entry fields (Web Appendix 3). Data extraction table included information on: i) trial methodology, setting and duration of follow-up; ii) population characteristics; iii) type of intervention; iv) analyses and outcomes.

Data reported for intention-to-treat analyses were selected at the longest follow-up point. We assumed a diagnosis of type 1 diabetes in insulin-treated participants if the type of diabetes was not otherwise specified.

Data analysis

We used the Cochrane Collaboration's tool to assess risk of bias at the outcome level.[15] Bias was assessed in duplicate with disagreements resolved by a third reviewer. The assessed domains were random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment and completeness of outcome data. Trials deemed to have a high risk of detection bias due to assessing only self-reported smoking cessation were not included in the primary analysis of objectively measured cessation data.

The risk ratio (RR) for biochemically verified smoking cessation with 95% confidence interval (CI) was the primary outcome measure in this analysis. We made an a priori decision to use the random effect model to take into account the variability of studied populations and intervention types. 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 $\chi 2$ test and the I^2 statistic to assess heterogeneity. The main meta-analysis included all measures of biochemically verified smoking cessation outcomes. We also pooled data on self-reported smoking cessation: i) in all eligible trials and ii) in trials with biochemically verified smoking cessation. We calculated pooled means and standard deviations (SD) and obtained SDs from standard errors of the mean using formulas recommended by the Cochrane Collaboration.[16]

RESULTS

A total of 2914 citations were identified (Figure 1) from electronic searches. A further 15 relevant publications were identified as cited by or citing included trial reports. After removing duplicates we screened 1783 citations. Based on the title and abstract, 1669 were assessed as ineligible. The full text of the remaining 114 articles was assessed for eligibility. Most were excluded as not reporting a randomised controlled trial (n = 43), or included patients who did not have diabetes (n = 29) or did not smoke (n = 26). One potentially eligible conference abstract could not be retrieved. We contacted the first author, but received no reply. We selected seven articles reporting eight trials for inclusion.

Duration and settings

All eight trials were reported in English and had a six-month maximum duration of follow-up. Two were reported in a single article.[17] Three trials were carried out in Europe,[18-20] two in Asia,[21, 22] two in Australia [17] and one in North America.[23]

Population

In total, 872 smokers with type 1 or type 2 diabetes participated in the reviewed trials (Table 1). Three trials reported in two publications [17, 21] did not include information on the type of diabetes. Two trials [21, 22] included only men.

Table 1. Characteristics of trials included in the analysis.

Source	Setting	Duration, months	Sample size	Mean (SD) age, years	Men, n (%)	T1D, n (%)	T2D, n (%)	More intensive intervention	Less intensive intervention	Percentage followed up	Primary or efficacy outcome**
Ardron et al 1988 [19]	Diabetes clinic, UK	6	60	29 (7)	29 (48)	50 (83)	10 (17)	Doctor's advice and information pack followed by a home visit by health visitor	Routine doctor's advice	100%	Breath CO and urinary cotinine
Canga et al 2000 [20]	12 primary care practices and 2 hospitals, Spain	6	280	55 (15)	240 (86)	85 (30)	195 (70)	Research nurse interview with follow-up by telephone, post and visits; optional NRT	Usual care including advice to stop smoking	99%	Smoking cessation assessed by urinary cotinine
Fowler et al 1989 [17]	University hospital, Australia	6	18	47 (9)	Not reported	3* (17)	15* (83)	In newly diagnosed diabetes; counselling (Smokescreen program) at diagnosis	Counselling (Smokescreen program) 2 months after diagnosis	83%	Plasma cotinine
Fowler et al 1989 [17]	University hospital, Australia	6	16	53 (13)	Not reported	9* (56)	7* (44)	In pre-existing diabetes; counselling (Smokescreen Program)	Diabetes-specific counselling	88%	Plasma cotinine
Hokanson et al 2006 [23]	Large diabetes centre, USA	6	114	54 (9)	65 (57)	-	114 (100)	Face-to-face counselling followed by repeated telephone counselling and optional NRT or bupropion	Standard care including referral to cessation programs	63%	Self-reported 7-day point prevalence of smoking cessation confirmed by saliva cotinine
Ng et al 2010 [22]	2 diabetes clinics, Indonesia	6	71	56 (9)	71 (100)	-	71 (100)	Doctor's advice and visual materials with referral to cessation clinic	Doctor's advice and visual materials	79%	Self-reported 7-day point prevalence abstinence
Sawicki et al 1993 [18]	Diabetes clinic, Germany	6	89	38 (12)	54 (61)	72 (81)	17 (19)	10 weekly behavioural sessions by a therapist with optional NRT	A single unstructured session by a physician with optional NRT	100%	Smoking cessation assessed by urine cotinine
Thankappan et al 2013 [21]	2 diabetes clinics, India	6	224	53 (9)	224 (100)	Not reported	Not reported	Doctor's advice, educational materials and three 30-min non-doctor counselling sessions	Doctor's advice and educational materials	88%	Self-reported 7-day smoking abstinence

*Assumption on the type of diabetes was made on the basis of reported treatment with insulin.
** Primary outcome unless it was not specified in the article.
SD – standard deviation; T1D – type 1 diabetes; T2D – type 2 diabetes; NRT – nicotine replacement therapy.

Intervention

Five trials assessed either non-pharmacological interventions to support smoking cessation [17, 19, 21] or referral to a smoking cessation clinic.[22] Interventions reported in three other trials included optional nicotine replacement therapy (NRT) without bupropion [18, 20] or with bupropion.[23]

The intervention was delivered by nursing staff or allied health professionals in three trials [18, 20, 23] and by both doctors and nursing staff or allied health professionals in two trials.[19, 21] In one trial, the intervention included advice from a doctor and referral to cessation clinic.[22] In two other trials intervention delivery was not specified.[17] The interventions were not specifically tailored for people with diabetes apart from the inclusion of educational components focussing on the effects of smoking on the complications of diabetes and glycaemic control.

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.

The less intensive intervention comparator groups received usual care involving advice to stop smoking in three trials,[20, 22, 23] counselling about general health risks of smoking in another three trials [17, 21, 22] and diabetes-specific counselling in one trial.[17] In one trial optional NRT was reported as used in addition to counselling in the comparator group.[18]

Outcomes

Four out of eight trials included a definition of the primary outcome (Table 2). In four trials smoking cessation was biochemically verified using concentration of breath carbon monoxide (CO),[19] urinary cotinine,[19, 20] or salivary cotinine.[23] Two trials assessed only self-reported cessation,[21, 22] and two trials reported only a total number of people with biochemically verified cessation in the study population.[17] All trials measured smoking cessation as point-prevalence abstinence.

Risk of bias

All trials were deemed to have low risk of attrition bias and most trials were assessed as having low risk of detection bias (Figure 2, Web Appendix 4). Most trials provided incomplete information on random sequence generation, allocation concealment and blinding of participants and personnel.

Primary outcome

Trial findings are summarised in Table 2. One article reporting two trials included only the overall number of patients who stopped smoking in both trials.[17] Two trials [21, 22] were excluded from pooled analysis due to high risk of detection bias as a consequence of self-reported cessation outcomes.

Pooled data from the four trials [18-20, 23] which reported point-prevalence of biochemically verified smoking cessation in both trial arms are summarised in Figure 3. For 543 participants, 44 smoking cessation events are reported. The likelihood of biochemically verified smoking cessation was 32% higher in patients who received more intensive intervention compared with less intensive intervention, although this effect was not significant (RR 1.32, 95% CI 0.23 to 7.43).

Table 2. Outcomes and effect sizes of interventions to support smoking cessation.

Type of outcome	Study	More intensive intervention	Less intensive intervention	Comparison	Effect
Objective measures					
Biochemically verified smoking cessation	Ardron et al 1988 [19]	0	1 (3%)	-	-
	Canga et al 2000* [20]	25 (17%)	3 (2%)	Incidence ratio (95% CI)	7.5 (2.3 – 24.4)
	Hokanson et al 2006*[23]	4 (7%)	2 (4%)	Chi-squared test for difference in abstinence rate	p = 0.077
	Sawicki et al 1993 [18]	2 (5%)	7 (16%)	Difference in point-prevalence of cessation	Reported as not significant
Urinary cotinine-creatinine ratio, µg/mg	Ardron et al 1988 [19]	7.6 (4.5)	6.7 (4.4)	-	-
Breath CO (µL/L)	Ardron et al 1988 [19]	18.2 (10.0)	19.4 (8.9)	-	-
HbA1c <7% (53 mmol/mol)	Hokanson et al 2006 [23]	35 (61%)	43 (75%)	Difference in proportion of patients achieving HbA1c <7%	Reported as not significant
Self-reported measures					
7-day abstinence	Ng et al 2010* [22]	14 (37%)	10 (30%)	Allocation effect in logistic regression model	Reported as not significant
	Thankappan et al 2013* [21]	58 (52%)	14 (13%)	Adjusted odds ratio (95% CI)	8.4 (4.1 – 17.1)
Number of cigarettes smoked daily	Canga et al 2000 [20]	15.5**	18.1**	Difference in change in mean cigarettes per day from baseline (95% CI)	-3.0 (-1.1 – -4.9)
>50% reduction in number of cigarettes smoked daily	Thankappan et al 2013 [21]	20 (18%)	25 (22%)	Adjusted odds ratio (95% CI)	1.9 (0.8 – 4.1)
Attempts to quit or reduce smoking	Ng et al 2010 [22]	21 (55%)	16 (48%)	Allocation effect in logistic regression model	Reported as not significant
Incidence of smoking relapse	Canga et al 2000 [20]	49 (33%)	14 (11%)	Difference (95% CI) in incidence of relapse	22.8% (13.6 – 32.0)

Data presented as number of events (%) or mean (SD).
* Reported as a primary outcome. ** Standard deviations not reported.
CO – carbon monoxide, SD – standard deviation, CI – confidence interval

There was substantial heterogeneity between the results of trials included in the pooled analysis of the primary outcome ($\chi 2$ test for heterogeneity, P = 0.006; I^2 = 76%). Two trials,[18, 19] jointly accounting for 45% of the weight of these results, reported point estimates of effects that suggested a greater likelihood of smoking cessation in the less intensive intervention group compared with the more intensive intervention group. In one trial,[19] the only biochemically-verified incident of smoking cessation was recorded in a less intensive intervention group patient who stopped smoking after sustaining a myocardial infarction.

In the pooled analyses of self-reported smoking cessation outcomes in (i) all eligible trials and (ii) in trials also reporting biochemically verified smoking cessation, participants allocated to more intensive intervention had respectively 1.85 times (RR 1.85, 95% CI 0.81 to 4.22) or 1.39 times (RR 1.39, 95% CI 0.28 to 6.92) greater likelihood of cessation compared with patients allocated to the less intensive intervention.

Secondary outcomes

Other outcomes reported related to smoking outcomes and metabolic outcomes (Table 2). Continuous measures of urinary cotinine-creatinine ratio and breath CO were reported for one trial, [19] but the results were not compared between allocated trial groups. In one trial [23] proportions of patients with HbA1c <7% (53 mmol/mol) in more intensive and less intensive intervention groups were reported at six months (61% vs. 75%), but were not significantly different (p=0.16). No trials reported other objectively measured short-term or long-term cardiovascular risk or safety data.

DISCUSSION

Despite an excess cardiovascular risk in people with diabetes, we have identified only a small number of trials evaluating the effect of smoking cessation interventions in this group. Interventions tested in the trials were similar to those used in the general population and included counselling, referral and advice, with, for some, the addition of diabetes specific education. Interventions and comparator groups were heterogeneous and the pooled results did not provide evidence of efficacy for smoking cessation interventions in people with diabetes. Only one trial reported data on glycaemic outcomes, which were not significantly different between intervention groups.

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 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.

Some studies suggest that smokers with diabetes may be more motivated to stop smoking, than the general smoker population [27] and more likely to stop smoking after hospitalisation compared with patients without diabetes.[28] There is no evidence from our review that, if such motivation is present, it translates into improved outcomes. In other high risk patient groups, for example, chronic obstructive pulmonary disease [29] and cardiovascular disease,[30] higher point estimates of the effect of intervention on smoking cessation are reported with most trials extending to 12-month follow-up.

An earlier, narrative review has examined the issues associated with smoking cessation in diabetes and identified some of the reasons why evaluation of smoking cessation interventions in this group may have been dealt with cautiously.[8] The datasheets for most recommended first-line smoking cessation medications [31] caution against their use in diabetes.[8, 32] Moreover, studies report that smoking cessation may worsen metabolic profile and glycaemic control [33, 34] and lead to weight gain.[35] We have identified four trials not included in the narrative review, two predating the narrative review.[17, 19]

Further data from randomised trials of interventions evaluating smoking outcomes, weight change and glycaemic control would inform treatment strategies in a population where smoking cessation is likely to have high absolute benefits.[1] The issue of safety of such treatments is partly addressed in an ongoing trial of varenicline for smoking cessation in diabetes,[24] but the follow up period of six months is likely to be too short to identify sustained effects. Trials assessing combinations of NRT with varenicline or bupropion in addition to non-pharmacological interventions may, in any case, better reflect clinical practice.[31]

Despite the potential health benefits of smoking cessation in diabetes, there has been limited work on developing and evaluating tailored interventions to support smoking cessation in these patients. From a health-services perspective, it would be important to know whether a tailored

intervention is more effective in this patient group than providing the same management as for the general population. Given the high burden of self-management required of people with diabetes, it is possible that integrating an intervention with routine care may be more effective than managing the problem separately. Further work is needed to explore the role of this approach in clinical care using trial designs with follow up extending to at least one year.

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AUTHORS' CONTRIBUTIONS

AF and AN designed the protocol and the methods. All authors contributed to data extraction. AN carried out the statistical analysis. All authors contributed to drafting of the article and approved the final manuscript.

COMPETING INTERESTS

None declared.

DATA SHARING STATEMENT

No additional data

REFERENCES

1. Qin R, Chen T, Lou Q, et al. Excess risk of mortality and cardiovascular events associated with smoking among patients with diabetes: meta-analysis of observational prospective studies. International journal of cardiology 2013;167(2):342-50.

2. Hsu CC, Hwang SJ, Tai TY, et al. Cigarette smoking and proteinuria in Taiwanese men with Type 2 diabetes mellitus. Diabetic medicine 2010;27:295-302.

3. Fagard RH. Smoking amplifies cardiovascular risk in patients with hypertension and diabetes. Diabetes care 2009;32 Suppl 2:S429-31.

4. Nilsson PM, Gudbjornsdottir S, Eliasson B, et al. Smoking is associated with increased HbA1c values and microalbuminuria in patients with diabetes - data from the National Diabetes Register in Sweden. Diabetes & metabolism 2004;30:261-268.

5. Hirai FE, Moss SE, Klein BE, et al. Severe hypoglycemia and smoking in a long-term type 1 diabetic population: Wisconsin Epidemiologic Study of Diabetic Retinopathy. Diabetes care 2007;30:1437-1441.

6. Voulgari C, Katsilambros N, Tentolouris N. Smoking cessation predicts amelioration of microalbuminuria in newly diagnosed type 2 diabetes mellitus: a 1-year prospective study. Metabolism: clinical and experimental 2011;60:1456-1464.

7. American Diabetes Association. Standards of Medical Care in Diabetes - 2013. Diabetes care 2012;36:S11-S66.

8. Tonstad S. Cigarette smoking, smoking cessation, and diabetes. Diabetes research and clinical practice 2009;85:4-13.

9. Bohlen K, Scoville E, Shippee ND, et al. Overwhelmed Patients: A videographic analysis of how patients with type 2 diabetes and clinicians articulate and address treatment burden during clinical encounters. Diabetes care 2011;35(1):47-49.

10. Vijan S, Hayward RA, Ronis DL, et al. Brief report: The burden of diabetes therapy. Journal of General Internal Medicine 2005;20(5):479-482.

11. Farley AC, Hajek P, Lycett D, et al. Interventions for preventing weight gain after smoking cessation. Cochrane Database of Systematic Reviews 2012;1:CD006219.

12. A systematic literature review and meta-analysis to assess the effects of interventions to support smoking cessation in adult patients with diabetes: study protocol. http://www.phc.ox.ac.uk/

13. Lancaster T, Stead L, Cahill K, et al. Cochrane Tobacco Addiction Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)) 2012. Available from: http://onlinelibrary.wiley.com/o/cochrane/clabout/articles/TOBACCO/sect0.html

14. Richter B, Bergerhoff K, Paletta G, et al. Cochrane Metabolic and Endocrine Disorders Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)) 2007. Available from: http://onlinelibrary.wiley.com/o/cochrane/clabout/articles/ENDOC/frame.html

15. Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

16. Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

17. Fowler PM, Hoskins PL, McGill M et al. Anti-smoking programme for diabetic patients: the agony and the ecstasy. Diabetic medicine 1989;6:698-702.

18. Sawicki PT, Didjurgeit U, Muhlhauser I, et al. Behaviour therapy versus doctor's anti-smoking advice in diabetic patients. Journal of internal medicine 1993;234:407-409.

19. Ardron M, MacFarlane I, Robinson C, et al. Anti-smoking advice for young diabetic smokers: is it a waste of breath? Diabetic medicine 1988;5:667-670.

20. Canga N, Irala J, Vara E, et al. Intervention study for smoking cessation in diabetic patients: a randomized controlled trial in both clinical and primary care settings. Diabetes care 2000;23:1455-1460.

21. Thankappan K, Mini G, Daivadanam M, et al. Smoking cessation among diabetes patients: results of a pilot randomized controlled trial in Kerala, India. BMC public health 2013;13:47.

22. Ng N, Nichter M, Padmawati RS, et al. Bringing smoking cessation to diabetes clinics in Indonesia. Chronic illness 2010;6:125-135.

23. Hokanson JM, Anderson RL, Hennrikus DJ, et al. Integrated tobacco cessation counseling in a diabetes self-management training program: a randomized trial of diabetes and reduction of tobacco. Diabetes Educator 2006;32:562-570.

24. Efficacy And Safety Of Smoking Cessation With Varenicline Tartrate In Diabetic Smokers: (DIASMOKE). Available from: http://clinicaltrials.gov/show/NCT01387425.

25. Smoking Cessation Intervention for Diabetic Patients: (SSTOP). Available from: http://clinicaltrials.gov/show/NCT01501877.

26. A randomized controlled trial of a tailored intervention compared to usual care on smoking type 2 diabetic patients to promote smoking cessation and improved glycaemic control. Available from: http://www.controlled-trials.com/ISRCTN34551140.

27. Wilkes S, Evans A. A cross-sectional study comparing the motivation for smoking cessation in apparently healthy patients who smoke to those who smoke and have ischaemic heart disease, hypertension or diabetes. Family Practice 1999;16(6):608-10.

28. Duffy SA, Munger A, Karvonen-Gutierrez CA, et al. Post-discharge tobacco cessation rates among hospitalized US veterans with and without diabetes. Diabetic Medicine 2012;29(7):e96-e101.

29. Piresyfantouda R, Absalom G, Clemens F. Smoking Cessation Interventions for Chronic Obstructive Pulmonary Disease - A Review of the literature. Respiratory care 2013. doi:10.4187/respcare.01923.

30. Eisenberg MJ, Blum LM, Filion KB, et al. The efficacy of smoking cessation therapies in cardiac patients: a meta-analysis of randomized controlled trials. The Canadian journal of cardiology 2010;26(2):73-9.

31. 2008 PHS Guideline Update Panel, Liaisons, and Staff. Treating tobacco use and dependence: 2008 update U.S. Public Health Service Clinical Practice Guideline executive summary. Respiratory care 2008;53:1217-1222.

32. British Medical Association and the Royal Pharmaceutical Society of Great Britain. British National Formulary. 64th ed. London: BMJ Group and Pharmaceutical Press. 2012.

33. Balkau B, Vierron E, Vernay M, et al. The impact of 3-year changes in lifestyle habits on metabolic syndrome parameters: the D.E.S.I.R study. European journal of cardiovascular prevention and rehabilitation 2006;13:334-340.

34. Iino K, Iwase M, Tsutsu N, et al. Smoking cessation and glycaemic control in type 2 diabetic patients. Diabetes, obesity & metabolism 2004;6:181-186.

35. Aubin HJ, Farley A, Lycett D et al. Weight gain in smokers after quitting cigarettes: meta-analysis. BMJ (Clinical research ed.) 2012;345:e4439.

FIGURE 1. FLOW DIAGRAM OF LITERATURE SEARCH, SCREENING AND SELECTION FOR ANALYSIS.

FIGURE 2. SUMMARY OF AUTHORS' JUDGEMENTS ON THE RISK OF BIAS IN REVIEWED TRIALS.

FIGURE 3. FOREST PLOT SHOWING POOLED ANALYSIS OF TRIALS REPORTING BIOCHEMICALLY VERIFIED POINT-PREVALENCE OF SMOKING CESSATION.

TITLE PAGE ***** VERSION WITH TRACKED CHANGES *****

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SMOKING CESSATION IN ADULTS WITH DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS OF DATA FROM RANDOMISED CONTROLLED TRIALS.

Alexander Nagrebetsky [1, 2], Rachel Brettell [1], Nia Roberts [3], Andrew Farmer [1, 2]

1 Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
2 School for Primary Care Research, National Institute for Health Research, UK
3 Bodleian Health Care Libraries, University of Oxford, Oxford, UK

Highest earned degrees: AN, MSc; RB, BMBCh; NR, MSc; AF, DM.

Address for correspondence: Andrew Farmer, Department of Primary Care Health Sciences, Radcliffe Observatory Quarter, Woodstock Road, Oxford OX2 6GG, United Kingdom; andrew.farmer@phc.ox.ac.uk; +441865289280

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ABSTRACT

Objectives: To evaluate the effects of more intensive smoking cessation interventions compared to less intensive interventions on smoking cessation~~, glycaemic control and weight~~ in people with type 1 or type 2 diabetes.

Design: A systematic review and meta-analysis of randomised trials of smoking cessation interventions was conducted. Electronic searches were carried out on the following databases: Medline, Embase, CINAHL, and PsycINFO to September 2013. Searches were supplemented by review of trial registries and references from identified trials. Citations and full-text articles were screened by two reviewers. A random-effect Mantel-Haenszel model was used to pool data.

Setting: Primary, secondary and tertiary care.

Participants: Adults with type 1 or type 2 diabetes.

Interventions: Smoking cessation interventions or medication (more intensive interventions) compared to usual care, counselling or optional medication (less intensive interventions).

Outcome measures: 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.

Results: We screened 1783 citations and reviewed 7 articles reporting 8 trials in 872 participants. All trials were of 6 months duration. Three trials included pharmacotherapy for smoking cessation. The risk ratio of biochemically verified smoking cessation was 1.32 (95% CI 0.23 to 7.43) for the more intensive interventions compared to less intensive interventions with significant heterogeneity ($I^2 = 76\%$). Only one trial reported measures of glycaemic control.

Conclusions: There is an absence of evidence of efficacy for more intensive smoking cessation interventions in people with diabetes. The more intensive strategies tested in trials to date include interventions used in the general population, adding in diabetes specific education about increased risk. Future research should focus on multi-component smoking cessation interventions carried out over a period of at least one year, and also assess impact on glycaemic control.

ARTICLE SUMMARY

Article focus

- This article focuses on the efficacy of interventions to support smoking cessation in adult patients with diabetes.

Key messages

- Despite an excess cardiovascular risk in people with diabetes, the number of trials evaluating the effects of smoking cessation interventions in this group is very limited.
- The interventions were not specifically tailored for people with diabetes apart from the inclusion of educational components.
- Pooled results did not provide evidence of efficacy for smoking cessation interventions in people with diabetes.

Strengths and limitations of this study

- The major strength of this article is that it is the first systematic review of randomised trials of smoking cessation interventions in diabetes.
- The main limitations of this study are the small number of trials published to date and heterogeneity in interventions offered and groups studied.

INTRODUCTION

For adults with diabetes, as in the wider population, smoking is associated with an increased risk of cardiovascular events and death. A recent systematic review and meta-analysis of prospective studies in diabetes reported that smoking increased the risk of death by 48%, coronary heart disease by 54%, stroke by 44% and myocardial infarction by 52%.[1] The risk for coronary heart disease, stroke and proteinuria is directly related to the number of cigarettes smoked per day.[2, 3] Diabetes patients who smoke have higher HbA1c levels [4] and are more likely to experience severe hypoglycaemia.[5]

People with diabetes who stop smoking are likely to have a lower risk of death and cardiovascular events compared with those who continue to smoke.[1] Smoking cessation is also associated with a reduction in levels of albuminuria, improvement of glycaemic control and lipid profile.[6] Smoking cessation has been recommended as a routine component of the treatment of diabetes by the American Diabetes Association,[7] although evidence to guide best practice is limited.[8]

People with diabetes are faced with the challenge of extensive changes in their lifestyle, a burden that may be increased by attempts to stop smoking.[9, 10] Tailoring smoking cessation programs to the needs of people with diabetes may lead to improved outcomes compared with usual care, but may also further increase the burden of self-management. Concerns have also been expressed regarding weight gain associated with smoking cessation. [11]

We therefore carried out a systematic review of randomised controlled trials reporting the effects of smoking cessation interventions in diabetes to inform clinical practice and identify potential for further research to improve patient outcomes.

METHODS

Eligibility criteria

We carried out this systematic review in accordance with the study protocol (Web Appendix 1).[12] Peer-reviewed journal articles and conference abstracts that reported the results of a randomised controlled trial and met the following eligibility criteria were eligible for inclusion: trials recruiting non-pregnant adults with type 1 or type 2 diabetes who smoked at baseline, evaluating pharmacological or non-pharmacological interventions intended to support smoking cessation (more intensive interventions) compared to usual care, counselling or optional medication (less intensive interventions). We included trials reporting at least one of the following outcomes: i) smoking cessation, ii) glycaemic control, iii) weight. There were no restrictions on length of follow up or language of publication. We included trials that did not report biochemically verified smoking cessation to fully capture the available evidence, characterize smoking status as reported in these trials and to add to the available data from which we could analyse effects of interventions on glycaemic control and weight where such additional data were available.

Search strategy

We based our search strategy on that used by the Cochrane Tobacco Addiction Group [13] for identifying randomised controlled trials of smoking cessation together with the Cochrane Metabolic and Endocrine Disorders Group [14] search strategy for interventions in type 1 or type 2 diabetes using the high sensitivity options (Web Appendix 2).

We searched the following online-databases: Cochrane Central Register of Controlled Trials [The Cochrane Library, Wiley] (Issue 9, 2013), Medline [OvidSP] (1946 – present), Embase [OvidSP] (1974 – present), CINAHL [EbscoHOST] (1980 – present), PsycINFO [OvidSP] (1967 – present) and Science Citation Index, Social Sciences Citation Index, Conference Proceedings

Citation Index- Science & Conference Proceedings Citation Index – Social Science & Humanities [Web of Knowledge] (1945 – present). The most recent search date was September 3, 2013. We also searched clinicaltrials.gov, isrctn.org, anzctr.org.au and International Clinical Trials Registry Platform for ongoing trials. We also reviewed references from bibliographies of included trial reports and results of a search on Web of Science Citation Index for those reports. We contacted authors of potentially eligible conference abstracts.

Study selection and data extraction

Two reviewers (AN and RB) independently screened the titles and abstracts of identified citations to select those requiring full-text assessment. Where there was disagreement, a third reviewer (AF) assessed the records to reach consensus. Full-text articles were further assessed and data were entered into a pre-specified table including 12 entry fields (Web Appendix 3). Data extraction table included information on: i) trial methodology, setting and duration of follow-up; ii) population characteristics; iii) type of intervention; iv) analyses and outcomes.

Data reported for intention-to-treat analyses were selected at the longest follow-up point. We assumed a diagnosis of type 1 diabetes in insulin-treated participants if the type of diabetes was not otherwise specified.

Data analysis

We used the Cochrane Collaboration's tool to assess risk of bias at the outcome level.[15] Bias was assessed in duplicate with disagreements resolved by a third reviewer. The assessed domains were random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment and completeness of outcome data. Trials deemed to have a high risk of detection bias due to assessing only self-reported smoking cessation were not included in the primary analysis of objectively measured cessation data.

The risk ratio (RR) for biochemically verified smoking cessation with 95% confidence interval (CI) was the primary outcome measure in this analysis. We made an a priori decision to use the random effect model to take into account the variability of studied populations and intervention types. 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 $\chi 2$ test and the I^2 statistic to ~~test for~~assess heterogeneity. The main meta-analysis included all measures of biochemically verified smoking cessation outcomes. We also pooled data on self-reported smoking cessation: i) in all eligible trials and ii) in trials with biochemically verified smoking cessation. We calculated pooled means and standard deviations (SD) and obtained SDs from standard errors of the mean using formulas recommended by the Cochrane Collaboration.[16]

RESULTS

A total of 2914 citations were identified (Figure 1) from electronic searches. A further 15 relevant publications were identified as cited by or citing included trial reports. After removing duplicates we screened 1783 citations. Based on the title and abstract, 1669 were assessed as ineligible. The full text of the remaining 114 articles was assessed for eligibility. Most were excluded as not reporting a randomised controlled trial (n = 43), or included patients who did not have diabetes (n = 29) or did not smoke (n = 26). One potentially eligible conference abstract could not be retrieved. We contacted the first author, but received no reply. We selected seven articles reporting eight trials for inclusion.

Duration and settings

All eight trials were reported in English and had a six-month maximum duration of follow-up. Two were reported in a single article.[17] Three trials were carried out in Europe,[18-20] two in Asia,[21, 22] two in Australia [17] and one in North America.[23]

Population

In total, 872 smokers with type 1 or type 2 diabetes participated in the reviewed trials (Table 1). Three trials reported in two publications [17, 21] did not include information on the type of diabetes. Two trials [21, 22] included only men.

Table 1. Characteristics of trials included in the analysis.

Source	Setting	Duration, months	Sample size	Mean (SD) age, years	Men, n (%)	T1D, n (%)	T2D, n (%)	More intensive intervention	Less intensive intervention	Percentage followed up	Primary or efficacy outcome**
Ardron et al 1988 [19]	Diabetes clinic, UK	6	60	29 (7)	29 (48)	50 (83)	10 (17)	Doctor's advice and information pack followed by a home visit by health visitor	Routine doctor's advice	100%	Breath CO and urinary cotinine
Canga et al 2000 [20]	12 primary care practices and 2 hospitals, Spain	6	280	55 (15)	240 (86)	85 (30)	195 (70)	Research nurse interview with follow-up by telephone, post and visits; optional NRT	Usual care including advice to stop smoking	99%	Smoking cessation assessed by urinary cotinine
Fowler et al 1989 [17]	University hospital, Australia	6	18	47 (9)	Not reported	3* (17)	15* (83)	In newly diagnosed diabetes; counselling (Smokescreen program) at diagnosis	Counselling (Smokescreen program) 2 months after diagnosis	83%	Plasma cotinine
Fowler et al 1989 [17]	University hospital, Australia	6	16	53 (13)	Not reported	9* (56)	7* (44)	In pre-existing diabetes; counselling (Smokescreen Program)	Diabetes-specific counselling	88%	Plasma cotinine
Hokanson et al 2006 [23]	Large diabetes centre, USA	6	114	54 (9)	65 (57)	-	114 (100)	Face-to-face counselling followed by repeated telephone counselling and optional NRT or bupropion	Standard care including referral to cessation programs	63%	Self-reported 7-day point prevalence of smoking cessation confirmed by saliva cotinine
Ng et al 2010 [22]	2 diabetes clinics, Indonesia	6	71	56 (9)	71 (100)	-	71 (100)	Doctor's advice and visual materials with referral to cessation clinic	Doctor's advice and visual materials	79%	Self-reported 7-day point prevalence abstinence
Sawicki et al 1993 [18]	Diabetes clinic, Germany	6	89	38 (12)	54 (61)	72 (81)	17 (19)	10 weekly behavioural sessions by a therapist with optional NRT	A single unstructured session by a physician with optional NRT	100%	Smoking cessation assessed by urine cotinine
Thankappan et al 2013 [21]	2 diabetes clinics, India	6	224	53 (9)	224 (100)	Not reported	Not reported	Doctor's advice, educational materials and three 30-min non-doctor counselling sessions	Doctor's advice and educational materials	88%	Self-reported 7-day smoking abstinence

*Assumption on the type of diabetes was made on the basis of reported treatment with insulin.
** Primary outcome unless it was not specified in the article.
SD – standard deviation; T1D – type 1 diabetes; T2D – type 2 diabetes; NRT – nicotine replacement therapy.

Intervention

Five trials assessed either non-pharmacological interventions to support smoking cessation [17, 19, 21] or referral to a smoking cessation clinic.[22] Interventions reported in three other trials included optional nicotine replacement therapy (NRT) without bupropion [18, 20] or with bupropion.[23]

The intervention was delivered by nursing staff or allied health professionals in three trials [18, 20, 23] and by both doctors and nursing staff or allied health professionals in two trials.[19, 21] In one trial, the intervention included advice from a doctor and referral to cessation clinic.[22] In two other trials intervention delivery was not specified.[17] The interventions were not specifically tailored for people with diabetes apart from the inclusion of educational components focussing on the effects of smoking on the complications of diabetes and glycaemic control.

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.~~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]~~

The less intensive intervention comparator groups received usual care involving advice to stop smoking in three trials,[20, 22, 23] counselling about general health risks of smoking in another three trials [17, 21, 22] and diabetes-specific counselling in one trial.[17] In one trial optional NRT was reported as used in addition to counselling in the comparator group.[18]

Outcomes

Four out of eight trials included a definition of the primary outcome (Table 2). In four trials smoking cessation was biochemically verified using concentration of breath carbon monoxide (CO),[19] urinary cotinine,[19, 20] or salivary cotinine.[23] Two trials assessed only self-reported cessation,[21, 22] and two trials reported only a total number of people with biochemically verified cessation in the study population.[17] All trials measured smoking cessation as point-prevalence abstinence.

Risk of bias

All trials were deemed to have low risk of attrition bias and most trials were assessed as having low risk of detection bias (Figure 2, Web Appendix 4). Most trials provided incomplete information on random sequence generation, allocation concealment and blinding of participants and personnel.

Primary outcome

Trial findings are summarised in Table 2. One article reporting two trials included only the overall number of patients who stopped smoking in both trials.[17] Two trials [21, 22] were excluded from pooled analysis due to high risk of detection bias as a consequence of self-reported cessation outcomes.

Pooled data from the four trials [18-20, 23] which reported point-prevalence of biochemically verified smoking cessation in both trial arms are summarised in Figure 3. For 543 participants, 44 smoking cessation events are reported. The likelihood of biochemically verified smoking cessation was 32% higher in patients who received more intensive intervention compared with less intensive intervention, although this effect was not significant (RR 1.32, 95% CI 0.23 to 7.43).

Table 2. Outcomes and effect sizes of interventions to support smoking cessation.

Type of outcome	Study	More intensive intervention	Less intensive intervention	Comparison	Effect
Objective measures					
Biochemically verified smoking cessation	Ardron et al 1988 [19]	0	1 (3%)	-	-
	Canga et al 2000* [20]	25 (17%)	3 (2%)	Incidence ratio (95% CI)	7.5 (2.3 – 24.4)
	Hokanson et al 2006*[23]	4 (7%)	2 (4%)	Chi-squared test for difference in abstinence rate	p = 0.077
	Sawicki et al 1993 [18]	2 (5%)	7 (16%)	Difference in point-prevalence of cessation	Reported as not significant
Urinary cotinine-creatinine ratio, µg/mg	Ardron et al 1988 [19]	7.6 (4.5)	6.7 (4.4)	-	-
Breath CO (µL/L)	Ardron et al 1988 [19]	18.2 (10.0)	19.4 (8.9)	-	-
HbA1c <7% (53 mmol/mol)	Hokanson et al 2006 [23]	35 (61%)	43 (75%)	Difference in proportion of patients achieving HbA1c <7%	Reported as not significant
Self-reported measures					
7-day abstinence	Ng et al 2010* [22]	14 (37%)	10 (30%)	Allocation effect in logistic regression model	Reported as not significant
	Thankappan et al 2013* [21]	58 (52%)	14 (13%)	Adjusted odds ratio (95% CI)	8.4 (4.1 – 17.1)
Number of cigarettes smoked daily	Canga et al 2000 [20]	15.5**	18.1**	Difference in change in mean cigarettes per day from baseline (95% CI)	-3.0 (-1.1 – -4.9)
>50% reduction in number of cigarettes smoked daily	Thankappan et al 2013 [21]	20 (18%)	25 (22%)	Adjusted odds ratio (95% CI)	1.9 (0.8 – 4.1)
Attempts to quit or reduce smoking	Ng et al 2010 [22]	21 (55%)	16 (48%)	Allocation effect in logistic regression model	Reported as not significant
Incidence of smoking relapse	Canga et al 2000 [20]	49 (33%)	14 (11%)	Difference (95% CI) in incidence of relapse	22.8% (13.6 – 32.0)

Data presented as number of events (%) or mean (SD).
* Reported as a primary outcome. ** Standard deviations not reported.
CO – carbon monoxide, SD – standard deviation, CI – confidence interval

There was substantial heterogeneity between the results of trials included in the pooled analysis of the primary outcome ($\chi 2$ test for heterogeneity, P = 0.006; I^2 = 76%). Two trials,[18, 19] jointly accounting for 45% of the weight of these results, reported point estimates of effects that suggested a greater likelihood of smoking cessation in the less intensive intervention group compared with the more intensive intervention group. In one trial,[19] the only biochemically-verified incident of smoking cessation was recorded in a less intensive intervention group patient who stopped smoking after sustaining a myocardial infarction.

In the pooled analyses of self-reported smoking cessation outcomes in (i) all eligible trials and (ii) in trials also reporting biochemically verified smoking cessation, participants allocated to more intensive intervention had respectively 1.85 times (RR 1.85, 95% CI 0.81 to 4.22) or 1.39 times (RR 1.39, 95% CI 0.28 to 6.92) greater likelihood of cessation compared with patients allocated to the less intensive intervention.

Secondary outcomes

Other outcomes reported related to smoking outcomes and metabolic outcomes (Table 2). Continuous measures of urinary cotinine-creatinine ratio and breath CO were reported for one trial, [19] but the results were not compared between allocated trial groups. In one trial [23] proportions of patients with HbA1c <7% (53 mmol/mol) in more intensive and less intensive intervention groups were reported at six months (61% vs. 75%), but were not significantly different (p=0.16). No trials reported other objectively measured short-term or long-term cardiovascular risk or safety data.

DISCUSSION

Despite an excess cardiovascular risk in people with diabetes, we have identified only a small number of trials evaluating the effect of smoking cessation interventions in this group. Interventions tested in the trials were similar to those used in the general population and included counselling, referral and advice, with, for some, the addition of diabetes specific education. Interventions and comparator groups were heterogeneous and the pooled results did not provide evidence of efficacy for smoking cessation interventions in people with diabetes. Only one trial reported data on glycaemic outcomes, which were not significantly different between intervention groups.

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 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.

Some studies suggest that smokers with diabetes may be more motivated to stop smoking, than the general smoker population [27] and more likely to stop smoking after hospitalisation compared with patients without diabetes.[28] There is no evidence from our review that, if such motivation is present, it translates into improved outcomes. In other high risk patient groups, for example, chronic obstructive pulmonary disease [29] and cardiovascular disease,[30] higher point estimates of the effect of intervention on smoking cessation are reported with most trials extending to 12-month follow-up.

An earlier, narrative review has examined the issues associated with smoking cessation in diabetes and identified some of the reasons why evaluation of smoking cessation interventions in this group may have been dealt with cautiously.[8] The datasheets for most recommended first-line smoking cessation medications [31] caution against their use in diabetes.[8, 32] Moreover, studies report that smoking cessation may worsen metabolic profile and glycaemic control [33, 34] and lead to weight gain.[35] We have identified four trials not included in the narrative review, two predating the narrative review.[17, 19]

Further data from randomised trials of interventions evaluating smoking outcomes, weight change and glycaemic control would inform treatment strategies in a population where smoking cessation is likely to have high absolute benefits.[1] The issue of safety of such treatments is partly addressed in an ongoing trial of varenicline for smoking cessation in diabetes,[24] but the follow up period of six months is likely to be too short to identify sustained effects. Trials assessing combinations of NRT with varenicline or bupropion in addition to non-pharmacological interventions may, in any case, better reflect clinical practice.[31]

Despite the potential health benefits of smoking cessation in diabetes, there has been limited work on developing and evaluating tailored interventions to support smoking cessation in these patients. From a health-services perspective, it would be important to know whether a tailored

intervention is more effective in this patient group than providing the same management as for the general population. Given the high burden of self-management required of people with diabetes, it is possible that integrating an intervention with routine care may be more effective than managing the problem separately. Further work is needed to explore the role of this approach in clinical care using trial designs with follow up extending to at least one year.

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COMPETING INTERESTS

None declared.

AUTHORS' CONTRIBUTIONS

AF and AN designed the protocol and the methods. All authors contributed to data extraction. AN carried out the statistical analysis. All authors contributed to drafting of the article and approved the final manuscript.

REFERENCES

1. Qin R, Chen T, Lou Q, Yu D. Excess risk of mortality and cardiovascular events associated with smoking among patients with diabetes: meta-analysis of observational prospective studies. International journal of cardiology 2013;167(2):342-50.

2. Hsu CC, Hwang SJ, Tai TY, Chen MC, Huang SJ, Shin CP, et al. Cigarette smoking and proteinuria in Taiwanese men with Type 2 diabetes mellitus. Diabetic medicine 2010;27:295-302.

3. Fagard RH. Smoking amplifies cardiovascular risk in patients with hypertension and diabetes. Diabetes care 2009;32 Suppl 2:S429-31.

4. Nilsson PM, Gudbjornsdottir S, Eliasson B, Cederholm J, Register SC. Smoking is associated with increased HbA1c values and microalbuminuria in patients with diabetes - data from the National Diabetes Register in Sweden. Diabetes & metabolism 2004;30:261-268.

5. Hirai FE, Moss SE, Klein BE, Klein R. Severe hypoglycemia and smoking in a long-term type 1 diabetic population: Wisconsin Epidemiologic Study of Diabetic Retinopathy. Diabetes care 2007;30:1437-1441.

6. Voulgari C, Katsilambros N, Tentolouris N. Smoking cessation predicts amelioration of microalbuminuria in newly diagnosed type 2 diabetes mellitus: a 1-year prospective study. Metabolism: clinical and experimental 2011;60:1456-1464.

7. American Diabetes Association. Standards of Medical Care in Diabetes - 2013. Diabetes care 2012;36:S11-S66.

8. Tonstad S. Cigarette smoking, smoking cessation, and diabetes. Diabetes research and clinical practice 2009;85:4-13.

9. Bohlen K, Scoville E, Shippee ND, May CR, Montori MV. Overwhelmed Patients: A videographic analysis of how patients with type 2 diabetes and clinicians articulate and address treatment burden during clinical encounters. Diabetes care 2011;35(1):47-49.

10. Vijan S, Hayward RA, Ronis DL, Hofer TP. Brief report: The burden of diabetes therapy. Journal of General Internal Medicine 2005;20(5):479-482.

11. Farley AC, Hajek P, Lycett D, Aveyard P. Interventions for preventing weight gain after smoking cessation. Cochrane Database of Systematic Reviews 2012;1:CD006219.

12. A systematic literature review and meta-analysis to assess the effects of interventions to support smoking cessation in adult patients with diabetes: study protocol. http://www.phc.ox.ac.uk/

13. Lancaster T, Stead L, Cahill K, Hartmann-Boyce J, Mehta M, West R, et al. Cochrane Tobacco Addiction Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)) 2012. Available from: http://onlinelibrary.wiley.com/o/cochrane/clabout/articles/TOBACCO/sect0.html

14. Richter B, Bergerhoff K, Paletta G, Bandeira-Echtler E. Cochrane Metabolic and Endocrine Disorders Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)) 2007. Available from: http://onlinelibrary.wiley.com/o/cochrane/clabout/articles/ENDOC/frame.html

15. Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

16. Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

17. Fowler PM, Hoskins PL, McGill M, Dutton SP, Yue DK, Turtle JR. Anti-smoking programme for diabetic patients: the agony and the ecstasy. Diabetic medicine 1989;6:698-702.

18. Sawicki PT, Didjurgeit U, Muhlhauser I, Berger M. Behaviour therapy versus doctor's anti-smoking advice in diabetic patients. Journal of internal medicine 1993;234:407-409.

19. Ardron M, MacFarlane I, Robinson C, Heyningen C, Calverley P. Anti-smoking advice for young diabetic smokers: is it a waste of breath? Diabetic medicine 1988;5:667-670.

20. Canga N, Irala J, Vara E, Duaso MJ, Ferrer A, Martinez-Gonzalez MA. Intervention study for smoking cessation in diabetic patients: a randomized controlled trial in both clinical and primary care settings. Diabetes care 2000;23:1455-1460.

21. Thankappan K, Mini G, Daivadanam M, Vijayakumar G, Sarma P, Nichter M. Smoking cessation among diabetes patients: results of a pilot randomized controlled trial in Kerala, India. BMC public health 2013;13:47.

22. Ng N, Nichter M, Padmawati RS, Prabandari YS, Muramoto M. Bringing smoking cessation to diabetes clinics in Indonesia. Chronic illness 2010;6:125-135.

23. Hokanson JM, Anderson RL, Hennrikus DJ, Lando HA, Kendall DM. Integrated tobacco cessation counseling in a diabetes self-management training program: a randomized trial of diabetes and reduction of tobacco. Diabetes Educator 2006;32:562-570.

24. Efficacy And Safety Of Smoking Cessation With Varenicline Tartrate In Diabetic Smokers: (DIASMOKE). Available from: http://clinicaltrials.gov/show/NCT01387425.

25. Smoking Cessation Intervention for Diabetic Patients: (SSTOP). Available from: http://clinicaltrials.gov/show/NCT01501877.

26. A randomized controlled trial of a tailored intervention compared to usual care on smoking type 2 diabetic patients to promote smoking cessation and improved glycaemic control. Available from: http://www.controlled-trials.com/ISRCTN34551140.

27. Wilkes S, Evans A. A cross-sectional study comparing the motivation for smoking cessation in apparently healthy patients who smoke to those who smoke and have ischaemic heart disease, hypertension or diabetes. Family Practice 1999;16(6):608-10.

28. Duffy SA, Munger A, Karvonen-Gutierrez CA, Piette JD, Kao TA. Post-discharge tobacco cessation rates among hospitalized US veterans with and without diabetes. Diabetic Medicine 2012;29(7):e96-e101.

29. Piresyfantouda R, Absalom G, Clemens F. Smoking Cessation Interventions for Chronic Obstructive Pulmonary Disease - A Review of the literature. Respiratory care 2013. doi:10.4187/respcare.01923.

30. Eisenberg MJ, Blum LM, Filion KB, Rinfret S, Pilote L, Paradis G, et al. The efficacy of smoking cessation therapies in cardiac patients: a meta-analysis of randomized controlled trials. The Canadian journal of cardiology 2010;26(2):73-9.

31. 2008 PHS Guideline Update Panel, Liaisons, and Staff. Treating tobacco use and dependence: 2008 update U.S. Public Health Service Clinical Practice Guideline executive summary. Respiratory care 2008;53:1217-1222.

32. British Medical Association and the Royal Pharmaceutical Society of Great Britain. British National Formulary. 64th ed. London: BMJ Group and Pharmaceutical Press. 2012.

33. Balkau B, Vierron E, Vernay M, Born C, Arondel D, Petrella A, et al. The impact of 3-year changes in lifestyle habits on metabolic syndrome parameters: the D.E.S.I.R study. European journal of cardiovascular prevention and rehabilitation 2006;13:334-340.

34. Iino K, Iwase M, Tsutsu N, Iida M. Smoking cessation and glycaemic control in type 2 diabetic patients. Diabetes, obesity & metabolism 2004;6:181-186.

35. Aubin HJ, Farley A, Lycett D, Lahmek P, Aveyard P. Weight gain in smokers after quitting cigarettes: meta-analysis. BMJ (Clinical research ed.) 2012;345:e4439.

Figure 1. A flow diagram of literature search, screening and selection.

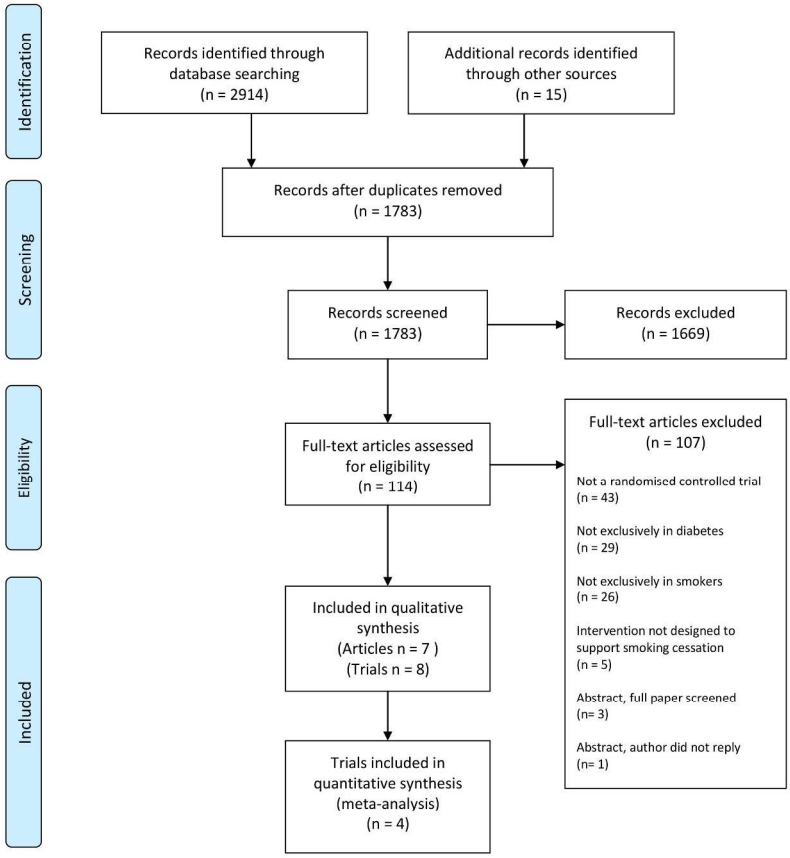


Figure 1. Flow diagram of literature search, screening and selection for analysis.
215x279mm (300 x 300 DPI)

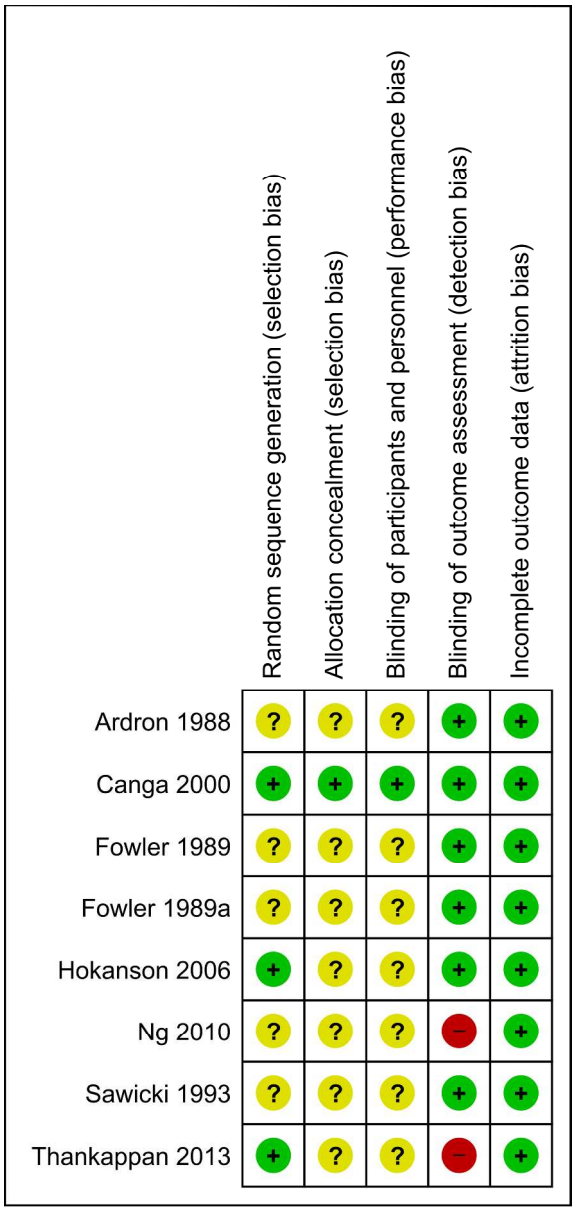


Figure 2. Summary of authors' judgements on the risk of bias in reviewed trials.
190x401mm (300 x 300 DPI)

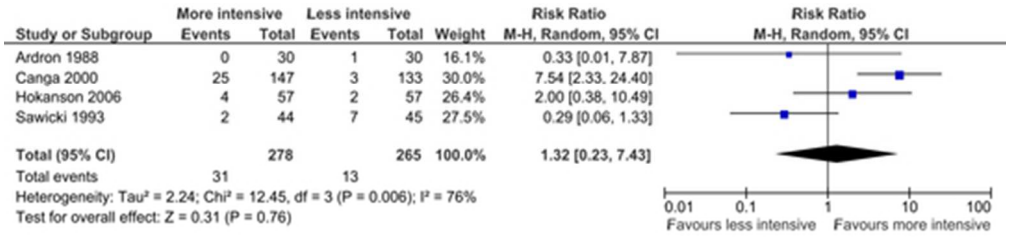


Figure 3. Forest plot showing pooled analysis of trials reporting biochemically verified point-prevalence of smoking cessation.
45x11mm (300 x 300 DPI)

Appendix 1. Protocol

Title:

A systematic literature review and meta-analysis to assess the effects of interventions to support smoking cessation in adult patients with diabetes.

Collaborators:

Andrew Farmer

Alexander Nagrebetsky

Rachel Brettell

Nia Roberts

Background

In patients with diabetes smoking is associated with increased morbidity and mortality. A recent systematic review and meta-analysis of prospective studies in diabetes demonstrated that smoking significantly increased the risk of death by 48%, coronary heart disease by 54%, stroke by 44% and myocardial infarction by 52%.[1] The risk for coronary heart disease, stroke and proteinuria is directly related to the number of cigarettes smoked per day.[2,3] Diabetes patients who smoke have higher HbA1c levels[4] and are more likely to experience severe hypoglycaemia.[5]

Patients with diabetes who stopped smoking are likely to have lower risk of death and cardiovascular events compared to those who continue to smoke.[1] Smoking cessation is also associated with decreased rates of microalbuminuria, improvement of glycaemic control and lipid profile.[6] Smoking cessation has been recommended as a routine component of the treatment of diabetes by the American Diabetes Association.[7] However, the evidence base for selecting appropriate interventions is limited.[8]

A very small number of randomised controlled trials of non-pharmacological interventions have been non-systematically reviewed.[8] However, there appear to be no systematic reviews of trials of pharmacological or behavioural interventions to support smoking cessation in diabetes. The lack of reliable safety and efficacy data on pharmacological interventions may prevent physicians from supporting smoking cessation in diabetes using pharmacotherapy.[8] The datasheets for most of the recommended first-line medications[9] caution against their use in diabetes.[8,10] Moreover, the reports that smoking cessation may worsen metabolic profile and glycaemic control[11,12] further contribute to the uncertainty about the benefits and harms of smoking cessation in diabetes. A systematic review of reports on the effects of interventions to support smoking cessation in diabetes will consolidate the existing evidence and identify important areas for further research.

Aim

To assess and summarise the effects of interventions to support smoking cessation in adult patients with diabetes.

Literature search

Previous reviews

Prior to the main review we will attempt to identify previous similar reviews by searching for "smoking AND diabetes AND review" in the following databases: Cochrane Library, Database of Abstracts and Reviews (DARE), PubMed, CINAHL, Web of Science and PsycInfo. We will also attempt to identify ongoing clinical trials by searching clinicaltrials.gov and WHO International Clinical Trials Registry Platform.

Search question

The literature search will be based on the question: What are the effects of interventions to support smoking cessation in adult patients with diabetes?

Question component	Question term
Population	Adults (>18 years) with type 1 or type 2 diabetes
Intervention	Non-pharmacologic
	Pharmacologic
Main outcome	Smoking cessation rate
Secondary outcomes, assessed in responders to the intervention	Glycaemic control
	Blood pressure
	Weight including BMI
	Adverse event rate
	Microalbuminuria
	Lipid profile- at least one of: LDL, HDL, TG, Total cholesterol
	Change in treatment
	Cardiovascular events

Databases

The following databases will be searched:

1) Cochrane Central Register of Controlled Trials (CCTR); 2) PubMed; 3) Scopus; 4) Embase.

Study inclusion criteria

We will carry out a two-stage review of randomised controlled trials (RCTs) of interventions to support smoking cessation in patients >18 years old with type 1 or type 2 diabetes. All eligible studies will report at least one of the following outcomes: 1) smoking cessation rate; 2) glycaemic control assessed as HbA1c; 3) weight including body mass index. No language restrictions will be imposed. The first stage of the analysis will include studies where: 1) all participants at baseline are smokers and 2) all participants at baseline have diabetes. The second stage of the analysis will also

include studies where smokers with diabetes represent a subgroup of the study population and the proportion of smokers with diabetes at baseline and at follow-up is either reported in the publication or is provided by the authors upon request.

Search strategy

We will use the search strategy employed by the Cochrane Tobacco Addiction Group for identifying RCTs in smoking combined with the Cochrane Metabolic and Endocrine Disorders Group search strategy for type 1 or type 2 diabetes. High sensitivity options will be chosen.

The obtained results will be supplemented with 1) references from bibliographies of the identified literature and 2) citation search using Science Citation Index.

Selection and data extraction

Two non-blinded reviewers will carry out independent selection of articles based on the inclusion criteria listed above. Details of selected studies will be entered into a predefined table:

Reference	Study period	Study setting	Study population	Proportion depressed	Type of intervention (pharmacological/non-pharmacological)

Assessed interventions	Duration of follow-up	Method of analysis	Outcomes	Methodological quality	Summary of key results

We will report measures of possible bias and the measures assessing the potential for not reporting data. Conflicting selections and quality assessments will be resolved by joint re-assessment and discussion.

Analysis

Data presentation

We will present the included studies in a tabular summary and point estimates of reported effects in a graphical summary. A separate summary of point estimates of secondary outcomes will be presented if sufficient data is available.

Statistical methods

We made an a priori decision to use the random effect analysis since the identified studies are likely to include different studied populations and intervention types. Thus, observing a fixed effect of an intervention is improbable. Heterogeneity will be assessed using the Cochran's Q divided by the degrees of freedom. If deemed feasible by reviewers, a funnel plot will be used to assess the publication bias.

Subgroup analyses

If sufficient data is available we will carry out the following analyses:

1) By secondary outcomes in responders vs non-responders
2) By intervention type
3) By type of diabetes

Dissemination of findings

Obtained results will be presented within the Department of Primary Care Health Sciences at the University of Oxford and, if feasible, submitted for publication in a peer-reviewed journal.

References

1. Qin R, Chen T, Lou Q, Yu D. Excess risk of mortality and cardiovascular events associated with smoking among patients with diabetes: Meta-analysis of observational prospective studies. International journal of cardiology 2013; 167(2):342-50

2. Fagard RH. Smoking amplifies cardiovascular risk in patients with hypertension and diabetes. Diabetes care. 2009;32 Suppl 2:S429-31.

3. Hsu CC, Hwang SJ, Tai TY, et al. Cigarette smoking and proteinuria in Taiwanese men with Type 2 diabetes mellitus. Diabetic medicine. 2010; 27:295-302.

4. Nilsson PM, Gudbjornsdottir S, Eliasson B, Cederholm J, Register SC. Smoking is associated with increased HbA1c values and microalbuminuria in patients with diabetes--data from the National Diabetes Register in Sweden. Diabetes & metabolism. 2004;30:261-268.

5. Hirai FE, Moss SE, Klein BE, Klein R. Severe hypoglycemia and smoking in a long-term type 1 diabetic population: Wisconsin Epidemiologic Study of Diabetic Retinopathy. Diabetes care. 2007;30:1437-1441.

6. Voulgari C, Katsilambros N, Tentolouris N. Smoking cessation predicts amelioration of microalbuminuria in newly diagnosed type 2 diabetes mellitus: a 1-year prospective study. Metabolism: clinical and experimental. 2011;60:1456-1464.

7. American Diabetes Association. Standards of Medical Care in Diabetes - 2013. Diabetes care 2012; 36:S11-S66.

8. Tonstad S. Cigarette smoking, smoking cessation, and diabetes. Diabetes research and clinical practice. 2009;85:4-13.

9. 2008 PHS Guideline Update Panel, Liaisons, and Staff. Treating tobacco use and dependence: 2008 update U.S. Public Health Service Clinical Practice Guideline executive summary. Respiratory care. 2008;53:1217-1222.

10. British Medical Association and the Royal Pharmaceutical Society of Great Britain. British National Formulary. 64th ed. London: BMJ Group and Pharmaceutical Press. 2012

11. Iino K, Iwase M, Tsutsu N, Iida M. Smoking cessation and glycaemic control in type 2 diabetic patients. Diabetes, obesity & metabolism. 2004;6:181-186.

12. Balkau B, Vierron E, Vernay M, et al. The impact of 3-year changes in lifestyle habits on metabolic syndrome parameters: the D.E.S.I.R study. European journal of cardiovascular prevention and rehabilitation. 2006;13:334-340.

Appendix 2. Search strategy

Title: A systematic literature review and meta-analysis to assess the effects of interventions to support smoking cessation in adult patients with diabetes.

Search summary:

We searched the Cochrane Central Register of Controlled Trials [The Cochrane Library, Wiley] (Issue 4, 2012), Medline [OvidSP] (1946 – present), Embase [OvidSP] (1974 – present), CINAHL [EbscoHOST] (1980 – present), PsycINFO [OvidSP] (1967 – present) & Science Citation Index, Social Sciences Citation Index, Conference Proceedings Citation Index- Science & Conference Proceedings Citation Index- Social Science & Humanities [Web of Knowledge] (1945 – present). The original search was run 14th May 2012, an update search was run 1st October 2012. The final update search was run 4th September 2013.

We searched trial registries for ongoing trials. We scanned reference lists of relevant articles and contacted researchers in the field.

Search methods:

Database name:	Interface:	Year range:	Date searched:	Hits:
CINAHL	EbscoHOST	1980 –	04/09/13	34
Cochrane Central Register of Controlled Trials	Cochrane Library, Wiley	Iss 9. 2013		6
Embase	OvidSP			
Medline	OvidSP	1974 –		126
PsycINFO	OvidSP	1946 –		83
Science Citation Index, Social Sciences Citation Index, Conference Proceedings Citation Index- Science & Conference Proceedings Citation Index- Social Science & Humanities	Web of Knowledge	1967 – 1945 -		19 93
Scopus	Elsevier			100
Unique references from May 2012 search = 1480 Unique references from Oct 2012 update = 115 References retrieved in this update = 461 Duplicates removed = 290 Final total = 1766 Unique references for Sep 2013 update = 171				
Limits: Human: animal studies excluded Publication type: RCTs				

Other resources searched:

Trial registers:

- ClinicalTrials.gov http://clinicaltrials.gov – Added from 01/01/2012-04/09/2013= 10 results
- WHO http://apps.who.int/trialsearch/ - Added from 01/01/2012-04/09/2013= 8 results

16 new results once deduplicated

Search terms used:

"smoking cessation" AND diabetes
Condition=Diabetes AND Intervention=smoking

Other search methods used:

- Review of reference lists
- Contacted the following authors: Thomas, Janet L.

Search strategies:

CINAHL

S21	S20 Limiters - Published Date: 20120101-20130931	34
S20	S10 and S18 Limiters - Clinical Queries: Therapy - High Sensitivity	151
S19	S10 and S18	558
S18	S11 or S12 or S13 or S14 or S15 or S16 or S17	16395
S17	TI (((quit* or stop* or cease* or giv*) n5 smoking)) OR AB (((quit* or stop* or cease* or giv*) n5 smoking))	2984
S16	TI (smoking cessation OR tobacco cessation) OR AB (smoking cessation OR tobacco cessation)	5442
S15	(MH "Nicotine Patch")	293
S14	(MH "Nicotine Replacement Therapy")	874
S13	(MH "Smoking/PC/TH")	4127
S12	(MH "Tobacco") OR (MH "Tobacco, Smokeless")	3491
S11	(MH "Smoking Cessation") OR (MH "Smoking Cessation Programs")	9416
S10	S6 NOT S9	70595
S9	S7 or S8	240
S8	TI diabet* insipidus OR AB diabet* insipidus	148
S7	(MH "Diabetes Insipidus")	192
S6	S1 or S2 or S3 or S4 or S5	70760
S5	TI (insulin* depend* or insulin?depend*) OR AB (insulin* depend* or insulin?depend*)	1513
S4	TI (non insulin* depend* or non insulin* depend* or non insulin?depend* or non insulin?depend*) OR AB (non insulin* depend* or non insulin* depend* or non insulin?depend* or non insulin?depend*)	569
S3	TI (IDDM or NIDDM or MODY or T1DM or T2DM or T1D or T2D) OR AB (IDDM or NIDDM or MODY or T1DM or T2DM or T1D or T2D)	1909
S2	TI diabet* OR AB diabet*	55873
S1	(MH "Diabetes Mellitus+")	56134

Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley)

ID Search
#1 MeSH descriptor: [Diabetes Mellitus] explode all trees
#2 diabet*:ti,ab,kw
#3 IDDM or NIDDM or MODY or T1DM or T2DM or T1D or T2D:ti,ab,kw
#4 non insulin* depend* or non insulin depend* or non insulin?depend* or non insulin?depend:ti,ab,kw
#5 insulin* depend* or insulin?depend*:ti,ab,kw
#6 #1 or #2 or #3 or #4 or #5
#7 MeSH descriptor: [Diabetes Insipidus] explode all trees
#8 diabet* insipidus:ti,ab,kw
#9 #7 or #8
#10 #6 not #9
#11 MeSH descriptor: [Tobacco Use Cessation] explode all trees
#12 MeSH descriptor: [Tobacco] explode all trees
#13 MeSH descriptor: [Nicotine] explode all trees
#14 MeSH descriptor: [Tobacco Use Disorder] explode all trees
#15 MeSH descriptor: [Tobacco Smoke Pollution] explode all trees
#16 MeSH descriptor: [Smoking] explode all trees and with qualifiers: [Prevention & control - PC, Therapy - TH]
#17 ((smoking or tobacco) next cessation):ti,ab,kw
#18 ((quit* or stop* or cease* or giv*) near smoking):ti,ab,kw
#19 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20 #10 and #19

Embase (OvidSP)

1	exp Diabetes Mellitus/	572211
2	diabet*.ti,ab,ot.	542710
3	(IDDM or NIDDM or MODY or T1DM or T2DM or T1D or T2D).ti,ab,ot.	35227
4	(non insulin* depend* or non insulin* depend* or non insulin?depend* or non insulin?depend*).ti,ab,ot.	12485
5	(insulin* depend* or insulin?depend*).ti,ab,ot.	33290
6	1 or 2 or 3 or 4 or 5	672891
7	exp Diabetes Insipidus/	11125
8	diabet* insipidus.ti,ab,ot.	8319
9	7 or 8	12401
10	6 not 9	663690
11	smoking cessation/ or smoking cessation program/	36479
12	tobacco dependence/	12329
13	tobacco/ or smokeless tobacco/	33838
14	nicotine replacement therapy/	2903
15	nicotine gum/ or nicotine lozenge/ or nicotine patch/ or nicotine vaccine/	2923
16	smoking/pc, th [Prevention, Therapy]	8268
17	((smoking or tobacco) adj cessation).ti,ab.	19294
18	((quit* or stop* or cease* or giv*) adj5 smoking).ti,ab.	12708
19	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	85348
20	random*.ti,ab.	853850
21	factorial*.ti,ab.	22168
22	(crossover* or cross over*).ti,ab.	70017
23	placebo*.ti,ab.	199972
24	(doubl* adj blind*).ti,ab.	146490
25	(singl* adj blind*).ti,ab.	14132
26	assign*.ti,ab.	234619
27	allocat*.ti,ab.	80752
28	volunteer*.ti,ab.	178753
29	crossover-procedure/	38291
30	double-blind procedure/	119862
31	single-blind procedure/	18184

32	randomized controlled trial/	357716
33	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	1395000
34	10 and 19 and 33	534
35	(2012* or 2013*).em,dp,yr.	2434440
36	34 and 35	126

Medline (OvidSP)

1	exp Diabetes Mellitus/	315240
2	diabet*.ti,ab,ot.	411846
3	(IDDM or NIDDM or MODY or T1DM or T2DM or T1D or T2D).ti,ab,ot.	25647
4	(non insulin* depend* or non insulin* depend* or non insulin?depend* or non insulin?depend*).ti,ab,ot.	10679
5	(insulin* depend* or insulin?depend*).ti,ab,ot.	28202
6	1 or 2 or 3 or 4 or 5	465021
7	exp Diabetes Insipidus/	6897
8	diabet* insipidus.ti,ab,ot.	6799
9	7 or 8	8870
10	6 not 9	457756
11	Smoking Cessation/	20837
12	"Tobacco Use Cessation"/	755
13	((smoking or tobacco) adj cessation).ti,ab.	17133
14	((quit* or stop* or cease* or giv*) adj5 smoking).ti,ab.	11236
15	tobacco/ or tobacco, smokeless/	26600
16	Nicotine/	21738
17	"Tobacco Use Disorder"/	8359
18	Tobacco Smoke Pollution/	10633
19	exp Smoking/pc, th [Prevention & Control, Therapy]	16628
20	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	92023
21	randomized controlled trial.pt.	383307
22	controlled clinical trial.pt.	88946
23	randomized.ab.	298936
24	placebo.ab.	160755
25	drug therapy.fs.	1741540
26	randomly.ab.	211895
27	trial.ab.	314995
28	groups.ab.	1349081
29	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	3371868
30	exp animals/ not humans.sh.	4021928

31	29 not 30	2889885
32	10 and 20 and 31	602
33	(2012* or 2013*).ed,dp,yr.	2269358
34	32 and 33	83

PsycINFO (OvidSP)

1	Diabetes/ or Diabetes Mellitus/	10050
2	diabet*.ti,ab,ot.	17407
3	(IDDM or NIDDM or MODY or T1DM or T2DM or T1D or T2D).ti,ab,ot.	822
4	(non insulin* depend* or non insulin* depend* or non insulin?depend* or non insulin?depend*).ti,ab,ot.	188
5	(insulin* depend* or insulin?depend*).ti,ab,ot.	928
6	1 or 2 or 3 or 4 or 5	17632
7	exp Diabetes Insipidus/	143
8	diabet* insipidus.ti,ab,ot.	209
9	7 or 8	242
10	6 not 9	17401
11	((smoking or tobacco) adj cessation).ti,ab.	7083
12	((quit* or stop* or cease* or giv*) adj5 smoking).ti,ab.	4471
13	smoking cessation/	8438
14	tobacco smoking/	21293
15	smokeless tobacco/	507
16	nicotine/	7566
17	11 or 12 or 13 or 14 or 15 or 16	28732
18	10 and 17	239
19	limit 18 to "therapy (maximizes sensitivity)"	109
20	(2012* or 2013*).up,dp,yr.	319784
21	19 and 20	19

Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI) , Conference Proceedings Citation Index- Science (CPCI-S) & Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) (Web of Knowledge)

Set	Results	
# 6	93	#3 AND #4 AND #5 Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=2012-01-01 - 2013-09-04 (Processing Date)
# 5	272,437	TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)
# 4	3,998	TS=("smoking cessation") OR TS=(((quit* or stop* or cease* or giv*) SAME smoking))
# 3	49,778	#1 NOT #2
# 2	363	TS=("diabetes insipidus")
# 1	50,141	TS=(diabet*) OR TS=(IDDM OR NIDDM OR MODY OR T1DM OR T2DM OR T1D OR T2D) OR TS=("non insulin* depend*" OPR "non insulin* depend*" OR "non insulin?depend*" OR "non insulin?depend*") OR TS=("insulin* depend*" or "insulin?depend*")

SCOPUS

((TITLE-ABS-KEY(diabet*)) AND ((TITLE-ABS-KEY("smoking cessation")) OR ((TITLE(smoking W/5 (quit* OR stop* OR ceas* OR giv*)) OR ABS(smoking W/5 (quit* OR stop* OR ceas* OR giv*)))) OR ((TITLE(smoking W/5 (quit* OR stop* OR ceas* OR giv*)) OR ABS(smoking W/5 (quit* OR stop* OR ceas* OR giv*)))) OR (TITLE(smoking* OR smoker* OR tobacco OR nicotine)))) AND ((TITLE(random* OR blind* OR allocat* OR assign* OR trial* OR placebo* OR crossover* OR cross-over*) OR ABS(random* OR blind* OR allocat* OR assign* OR trial* OR placebo* OR crossover* OR cross-over*))) AND (LIMIT-TO(PUBYEAR, 2013) OR LIMIT-TO(PUBYEAR, 2012))

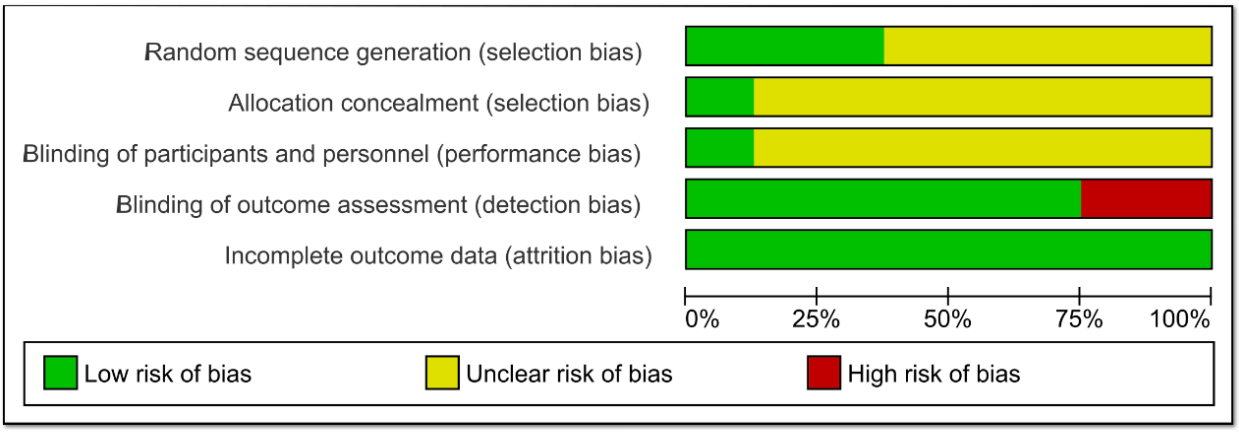
Methodological search filters:

CINAHL	**RCTS:** EbscoHOST Clinical Queries: Therapy – High Sensitivity Reference: Wong SS, Wilczynski NL, Haynes RB.Optimal CINAHL search strategies for identifying therapy studies and review articles. J Nurs Scholarsh. 2006;38(2):194-9. http://www3.interscience.wiley.com/journal/118600195/abstract?CRETRY=1&SRETRY=0 (See table 3)
Embase	**RCTs** Ovid Clinical Queries: Treatment (2 or more terms high sensitivity) Reference: Wong SS, Wilczynski NL, Haynes RB.Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. J Med Libr Assoc. 2006 Jan;94(1):41-7. http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=16404468 (See table 3)
Medline	**RCTs** Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format http://www.cochrane-handbook.org (Section 6.4.11)
PsycINFO	**RCTs:** Ovid Clinical Queries: Treatment (high sensitivity) Reference: Eady AM, Wilczynski NL, Haynes RB. PsycINFO search strategies identified methodologically sound therapy studies and review articles for use by clinicians and researchers. J Clin Epidemiol. 2008 Jan;61(1):34-40. http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=18083460 (see table 2)

Appendix 3. Data extraction table.

Reference	Study period	Study setting	Study population	Proportion depressed	Type of intervention (pharmacological/non-pharmacological)	Assessed interventions	Duration of follow-up	Method of analysis	Outcomes	Methodological quality	Summary of key results

Nagrebetsky et al 2013, University of Oxford



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2,3,4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5,6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6,7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7, Appendix 3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7,8

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7,8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8, Appendix 1
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Figure 2, Appendix 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Manuscript: bmjopen-2013-004107.R1 Nagrebetsky et al.

Smoking cessation in adults with diabetes: a systematic review and meta-analysis of data from randomised controlled trials.

Reviewer's Comments	Response
Editor	
Appears well conducted and nicely written up. It's a good RQ and it seems original.	
1. Please justify in the paper why you included 2 trials without biochemical confirmation (eg salivary cotinine).	Thank you for this helpful suggestion. We have added the rationale for including two trials without biochemical confirmation of smoking status in the *Methods*/*Eligibility* criteria. "We included trials that did not report biochemically verified smoking cessation to fully capture the available evidence, characterize smoking status as reported in these trials and to add to the available data from which we could analyse effects of interventions on glycaemic control and weight where such additional data were available."
Reviewer Boris Mankovsky	
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.	

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.	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."
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.	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.
3. I believe that the article is of some interest to the readers provided that all limitations of the study are carefully mentioned.	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.	
1. 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?	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."
2. 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.	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.	
1. Did the authors test for publication bias?	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*. "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:	
1. The authors need to clarify in the Objectives of the Abstract that they have only considered diabetic populations	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."
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.	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 $\chi 2$ 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 $\chi 2$ test and the I^2 statistic to assess heterogeneity."

	Previous 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 the I^2 statistic to test for heterogeneity."
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.	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.
4. The I2 statistic quantifies heterogeneity, rather than 'tests' for it.	Thank you. We have corrected the sentence as described in item 2.
5. The data analysis section only focuses on smoking cessation as an outcome, when other diabetic related outcomes were also considered	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.
6. Also, the details reported in the 'outcomes' section of the Results only focus on smoking cessation	Please refer to the response above.
7. More details about the three ongoing trials would have been useful to include in the results section	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: "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]"
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.	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)
9. The discussion would benefit from including a full section of the limitations and strengths of the review	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."