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 Farmer1,2

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 seven articles reporting eight 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 (I²=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 multicomponent smoking cessation interventions carried out over a period of at least 1 year, and also assess impact on glycaemic control.

Strengths and limitations of this study

- It is the first systematic review of randomised trials of smoking cessation interventions in diabetes.
- The statistical power of our attempts to pool data is limited by the small number of trials published to date and a relatively small number of participants in the published trials.
- Interventions offered and groups studied are heterogeneous.
- Available evidence to inform treatment strategies for smoking cessation in type 2 diabetes is limited.

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 on 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 Patients with diabetes who smoke have higher glycated haemoglobin (HbA1c) levels4 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 programmes 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 (see online supplementary 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 with usual care, counselling or optional medication (less intensive interventions). We included trials reporting at least one of the following outcomes: (1) smoking cessation, (2) glycaemic control, (3) 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, characterise 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 Group13 for identifying randomised controlled trials of smoking cessation together with the Cochrane Metabolic and Endocrine Disorders Group14’s search strategy for interventions in type 1 or type 2 diabetes using the high sensitivity options (see online supplementary 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 3 September 2013. We also searched clinicaltrials.gov, isrctn.org, anzctr.org.au and International Clinical Trials Registry Platform for ongoing trials. References from bibliographies of included trial reports and results of a search on Web of Science Citation Index for those reports were also reviewed. 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 a consensus. Full-text articles were further assessed and data were entered into a prespecified table including 12 entry fields (see online supplementary appendix 3). The data extraction table included information on: (1) trial methodology, setting and duration of follow-up; (2) population characteristics; (3) type of intervention and (4) 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% CI was the primary outcome measure. We assumed a risk ratio (RR) of 1.0 for a non-significant result. We calculated pooled means and SDs and obtained SDs from SEs 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 citing or cited by 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 6-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 Australia17 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 publications17 21 did not include information on the type of diabetes. Two trials21 22 included only men.

Intervention
Five trials assessed either non-pharmacological interventions to support smoking cessation17 19 21 or referral to a smoking cessation clinic.22 Interventions reported in three other trials included optional nicotine replacement therapy (NRT) without bupropion18 20 or with bupropion.23

The intervention was delivered by nursing staff or allied health professionals in three trials18 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 focusing 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

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

Records identified through database searching \((n = 2914)\)

Additional records identified through other sources \((n = 15)\)

Records after duplicates removed \((n = 1783)\)

Records screened \((n = 1783)\)

Records excluded \((n = 1669)\)

Full-text articles assessed for eligibility \((n = 114)\)

Included in qualitative synthesis \((\text{Articles } n = 7)\)

\((\text{T}\text{rials } n = 8)\)

Trials included in quantitative synthesis \((\text{meta-analysis})\) \((n = 4)\)

Not a randomised controlled trial \((n = 43)\)

Not exclusively in diabetes \((n = 29)\)

Not exclusively in smokers \((n = 26)\)

Intervention not designed to support smoking cessation \((n = 5)\)

Abstract, full paper screened \((n = 3)\)

Abstract, author did not reply \((n = 1)\)
<table>
<thead>
<tr>
<th>Source</th>
<th>Setting</th>
<th>Duration, months</th>
<th>Sample size</th>
<th>Mean (SD) age, years</th>
<th>Men, n (%)</th>
<th>T1D, n (%)</th>
<th>T2D, n (%)</th>
<th>More intensive intervention</th>
<th>Less intensive intervention</th>
<th>Percentage followed up</th>
<th>Primary or efficacy outcome*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ardon et al</td>
<td>Diabetes clinic, UK</td>
<td>6</td>
<td>60</td>
<td>29 (7)</td>
<td>29 (48)</td>
<td>50 (83)</td>
<td>10 (17)</td>
<td>Doctor’s advice and information pack followed by a home visit by health visitor</td>
<td>Routine doctor’s advice</td>
<td>100</td>
<td>Breath CO and urinary cotinine</td>
</tr>
<tr>
<td>Canga et al</td>
<td>12 primary care practices and 2 hospitals, Spain</td>
<td>6</td>
<td>280</td>
<td>55 (15)</td>
<td>240 (86)</td>
<td>85 (30)</td>
<td>195 (70)</td>
<td>Research nurse interview with follow-up by telephone, post and visits; optional NRT</td>
<td>Usual care including advice to stop smoking</td>
<td>99</td>
<td>Smoking cessation assessed by urinary cotinine</td>
</tr>
<tr>
<td>Fowler et al</td>
<td>University hospital, Australia</td>
<td>6</td>
<td>18</td>
<td>47 (9)</td>
<td>Not reported</td>
<td>3† (17)</td>
<td>15† (83)</td>
<td>In newly diagnosed diabetes; counselling (smokescreen programme) at diagnosis</td>
<td>Counselling (smokescreen programme) 2 months after diagnosis</td>
<td>83</td>
<td>Plasma cotinine</td>
</tr>
<tr>
<td>Fowler et al</td>
<td>University hospital, Australia</td>
<td>6</td>
<td>16</td>
<td>53 (13)</td>
<td>Not reported</td>
<td>9† (56)</td>
<td>7† (44)</td>
<td>In pre-existing diabetes; counselling (smokescreen programme)</td>
<td>Diabetes-specific counselling</td>
<td>88</td>
<td>Plasma cotinine</td>
</tr>
<tr>
<td>Hokanson et al</td>
<td>Large diabetes centre, USA</td>
<td>6</td>
<td>114</td>
<td>54 (9)</td>
<td>65 (57)</td>
<td>–</td>
<td>114 (100)</td>
<td>Face-to-face counselling followed by repeated telephone counselling and optional NRT or bupropion</td>
<td>Standard care including referral to cessation programmes</td>
<td>63</td>
<td>Self-reported 7-day point prevalence of smoking cessation confirmed by saliva cotinine</td>
</tr>
<tr>
<td>Ng et al</td>
<td>2 diabetes clinics, Indonesia</td>
<td>6</td>
<td>71</td>
<td>56 (9)</td>
<td>71 (100)</td>
<td>–</td>
<td>71 (100)</td>
<td>Doctor’s advice and visual materials with referral to cessation clinic</td>
<td>Doctor’s advice and visual materials</td>
<td>79</td>
<td>Self-reported 7-day point prevalence abstinence</td>
</tr>
<tr>
<td>Sawicki et al</td>
<td>Diabetes clinic, Germany</td>
<td>6</td>
<td>89</td>
<td>38 (12)</td>
<td>54 (61)</td>
<td>72 (81)</td>
<td>17 (19)</td>
<td>10 weekly behavioural sessions by a therapist with optional NRT</td>
<td>A single unstructured session by a physician with optional NRT</td>
<td>100</td>
<td>Smoking cessation assessed by urine cotinine</td>
</tr>
<tr>
<td>Thankappan et al</td>
<td>2 diabetes clinics, India</td>
<td>6</td>
<td>224</td>
<td>53 (9)</td>
<td>224 (100)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Doctor’s advice, educational materials and three 30 min non-doctor counselling sessions</td>
<td>Doctor’s advice and educational materials</td>
<td>88</td>
<td>Self-reported 7-day smoking abstinence</td>
</tr>
</tbody>
</table>

* Primary outcome unless it was not specified in the article.
† Assumption on the type of diabetes was made on the basis of reported treatment with insulin.
CO, carbon monoxide; NRT, nicotine replacement therapy; T1D, type 1 diabetes; T2D, type 2 diabetes.
review, one European trial assesses the efficacy and safety of smoking cessation with varenicline tartrate in patients with diabetes. The two other ongoing trials carried out in North America and Asia assess the effectiveness of behavioural interventions.

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

Outcomes

Four 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), urinary cotinine or salivary cotinine. Two trials assessed only self-reported cessation, and two trials reported only a total number of people with biochemically verified cessation in the study population. 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, see online supplementary 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. Two trials 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 that 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

| 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 | 0 (0%)                | 1 (3%)               | Incidence ratio (95% CI) | 7.5 (2.3 to 24.4) |
|                                 | Canga et al     | 25 (17%)             | 3 (2%)               | χ² test for difference in abstinence rate | p=0.077 |
|                                 | Hokanson et al  | 4 (7%)                | 2 (4%)               | Difference in point prevalence of cessation | Reported as not significant |
|                                 | Sawicki et al   | 2 (5%)                | 7 (16%)              |               |        |
| Urinary cotinine–creatinine ratio, µg/mg | Ardron et al | 7.6 (4.4)             | 6.7 (4.4)            |               |        |
| Breath CO (µL/L) HbA1c <7% (53 mmol/mol) | Ardron et al | 18.2 (10.0)           | 19.4 (8.9)           | Difference in proportion of patients achieving HbA1c <7% | Reported as not significant |
|                                 | Hokanson et al  | 35 (61%)             | 43 (75%)             |               |        |
| Self-reported measures           |                 |                      |                      |               |        |
| 7-day abstinence                 | Ng et al        | 14 (37%)             | 10 (30%)             | Allocation effect in logistic regression model | Reported as not significant |
|                                 | Thankappan et al | 58 (52%)           | 14 (13%)             | Adjusted OR (95% CI) | 8.4 (4.1 to 17.1) |
| Number of cigarettes smoked daily | Canga et al     | 15.5†                 | 18.1†                | Difference in change in mean cigarettes per day from baseline (95% CI) | −3.0 (−1.1 to −4.9) |
| >50% reduction in number of cigarettes smoked daily | Thankappan et al | 20 (18%)             | 25 (22%)             | Adjusted OR (95% CI) | 1.9 (0.8 to 4.1) |
| Attempts to quit or reduce smoking | Ng et al       | 21 (55%)             | 16 (48%)             | Allocation effect in logistic regression model | Reported as not significant |
| Incidence of smoking relapse     | Canga et al     | 49 (33%)             | 14 (11%)             | Difference (95% CI) in incidence of relapse | 22.8 (13.6 to 32.0) |

Data presented as number of events (%) or mean (SD).
†Reported as a primary outcome.
††SDs not reported.
CO, carbon monoxide; HbA1c, glycated haemoglobin.
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). 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, jointly accounting for 44% 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, 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 (1) all eligible trials and (2) 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, but the results were not compared between allocated trial groups. In one trial, proportions of patients with HbA1c <7% (53 mmol/mol) in more intensive and less intensive intervention groups were reported at 6 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.

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**Figure 2** Summary of authors’ judgements on the risk of bias in reviewed trials.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>More intensive</th>
<th>Less intensive</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ardon 1988</td>
<td>0</td>
<td>30</td>
<td>0.33 [0.01, 7.87]</td>
</tr>
<tr>
<td>Canga 2000</td>
<td>25</td>
<td>147</td>
<td>7.54 [2.33, 24.40]</td>
</tr>
<tr>
<td>Fowler 1989</td>
<td>4</td>
<td>57</td>
<td>2.00 [0.38, 10.49]</td>
</tr>
<tr>
<td>Fowler 1989a</td>
<td>2</td>
<td>44</td>
<td>0.29 [0.06, 1.33]</td>
</tr>
<tr>
<td>Sokownik 1993</td>
<td>2</td>
<td>44</td>
<td>0.29 [0.06, 1.33]</td>
</tr>
<tr>
<td>Ng 2010</td>
<td>2</td>
<td>44</td>
<td>0.29 [0.06, 1.33]</td>
</tr>
<tr>
<td>Thankappan 2013</td>
<td>2</td>
<td>44</td>
<td>0.29 [0.06, 1.33]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>278</td>
<td>265</td>
<td>1.32 [0.23, 7.43]</td>
</tr>
<tr>
<td>Total events</td>
<td>31</td>
<td>13</td>
<td>[1, 100]</td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>$\tau^2=2.24$</td>
<td>$Ch^2=12.40$, df = 3 ($p=0.005$); $I^2=76%$</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td>$Z=0.31$ ($p=0.76$)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3** Forest plot showing pooled analysis of trials reporting biochemically verified point prevalence of smoking cessation.
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 randomisation, 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 in which smoking cessation was a part of a more extensive complex intervention and in which 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 and more likely to stop smoking after hospitalisation compared with patients without diabetes. 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 and cardiovascular disease, 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. The datasheets for most recommended first-line smoking cessation medications caution against their use in diabetes. Moreover, studies report that smoking cessation may worsen metabolic profile and glycaemic control and lead to weight gain. We have identified four trials not included in the narrative review, two predating the narrative review. Further data from randomised trials of interventions evaluating smoking outcomes, weight change and glycaemic control would inform treatment strategies in a population in which smoking cessation is likely to have high absolute benefits. The issue of safety of such treatments is partly addressed in an ongoing trial of varenicline for smoking cessation in diabetes, but the follow-up period of 6 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.

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 service 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 1 year.

Acknowledgements The authors would like to thank Mr Joey Yang for help in carrying out an assessment of the risk of bias in included trials.

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

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Competing interests AF is an NIHR Senior Investigator and also receives funding from Oxford NIHR Biomedical Research Centre.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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REFERENCES


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 levels4 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 medications9 caution against their use in diabetes.8,10 Moreover, the reports that smoking cessation may worsen metabolic profile and glycaemic control11,12 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?

<table>
<thead>
<tr>
<th>Question component</th>
<th>Question term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Adults (&gt;18 years) with type 1 or type 2 diabetes</td>
</tr>
</tbody>
</table>
| 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:

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study period</th>
<th>Study setting</th>
<th>Study population</th>
<th>Proportion depressed</th>
<th>Type of intervention (pharmacological/non-pharmacological)</th>
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</thead>
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<tr>
<td>Assessed interventions</td>
<td>Duration of follow-up</td>
<td>Method of analysis</td>
<td>Outcomes</td>
<td>Methodological quality</td>
<td>Summary of key results</td>
</tr>
</tbody>
</table>

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 reassessment 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

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:**

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<td>34</td>
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<tr>
<td>Scopus</td>
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<td></td>
</tr>
</tbody>
</table>

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**

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

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#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
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Embase (OvidSP)

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2 diabet*.ti,ab,ot. 542710
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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
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25 (singl* adj blind*).ti,ab. 14132
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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)

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2 diabet*.ti,ab,ot. 411846
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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/
8 diabet* insipidus.ti,ab,ot. 6799
9 7 or 8 8870
10 6 not 9 457756
11 Smoking Cessation/
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/
16 Nicotine/
17 "Tobacco Use Disorder"/ 8359
18 Tobacco Smoke Pollution/
19 exp Smoking/pc, th [Prevention & Control, Therapy] 16628
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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
32  10 and 20 and 31
33  (2012* or 2013*).ed,dp,yr.
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PsycINFO (OvidSP)

1 Diabetes/ or Diabetes Mellitus/  
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3 (IDDM or NIDDM or MODY or T1DM or T2DM or T1D or T2D).ti,ab,ot.  
4 (non insulin* depend* or non insulin* depend* or non insulin?depend* or non insulin?depend*).ti,ab,ot.  
5 (insulin* depend* or insulin?depend*).ti,ab,ot.  
6 1 or 2 or 3 or 4 or 5  
7 exp Diabetes Insipidus/  
8 diabet* insipidus.ti,ab,ot.  
9 7 or 8  
10 6 not 9  
11 ((smoking or tobacco) adj cessation).ti,ab.  
12 ((quit* or stop* or cease* or giv*) adj5 smoking).ti,ab.  
13 smoking cessation/  
14 tobacco smoking/  
15 smokeless tobacco/  
16 nicotine/  
17 11 or 12 or 13 or 14 or 15 or 16  
18 10 and 17  
19 limit 18 to "therapy (maximizes sensitivity)"  
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21 19 and 20
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Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC
Timespan=2012-01-01 - 2013-09-04 (Processing Date)

**SCOPUS**

\[
((\text{TITLE-ABS-KEY(diabet*)}) \text{ AND } ((\text{TITLE-ABS-KEY("smoking cessation")}) \text{ OR } ((\text{TITLE(smoking W/5 (quit* OR stop* OR ceas* OR giv*)) OR ABS(smoking W/5 (quit* OR stop* OR ceas* OR giv*))))) OR ((\text{TITLE(smoking W/5 (quit* OR stop* OR ceas* OR giv*))})) OR ABS(smoking W/5 (quit* OR stop* OR ceas* OR giv*))))) \text{ AND } ((\text{TITLE(random* OR blind* OR allocat* OR assign* OR tria* OR placebo* OR crossover* OR cross-over*)}) \text{ OR } \text{ABS(random* OR blind* OR allocat* OR assign* OR trial* OR placebo* OR crossover* OR cross-over*)})) \text{ AND } \text{LIMIT-TO(PUBYEAR, 2013) OR LIMIT-TO(PUBYEAR, 2012))}
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<td>Ovid Clinical Queries: Treatment (2 or more terms high sensitivity)</td>
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### Appendix 3. Data extraction table.

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<th>Duration of follow-up</th>
<th>Method of analysis</th>
<th>Outcomes</th>
<th>Methodological quality</th>
<th>Summary of key results</th>
</tr>
</thead>
</table>

Nagrebetsky et al 2013, University of Oxford