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:

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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

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