International Journal of Cardiology 167 (2013) 342–350

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Excess risk of mortality and cardiovascular events associated with smoking among patients with diabetes: Meta-analysis of observational prospective studies

Rui Qin [a,1], Tao Chen [b,1], Qingqing Lou [a,*], Dahai Yu [c]

[a] Jiangsu Province Hospital on Integration of Chinese and Western Medicine, Nanjing, China
[b] Cardiovascular Institute and Fuwai Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China
[c] Institute of Metabolic Science, Cambridge University Hospital NHS Foundation Trust, Cambridge CB2 0QQ, UK

ARTICLE INFO

Article history:
Received 29 August 2011
Received in revised form 7 December 2011
Accepted 24 December 2011
Available online 16 January 2012

Keywords:
Diabetes Mellitus
Cardiovascular disease
Mortality
Systematic review

ABSTRACT

Background: Numerous studies have demonstrated that both smoking and diabetes are risk factors for mortality and caused-specific cardiovascular events. However, few studies systematically investigated to what extent the excess risk could be attributed to smoking among diabetic patients.
Methods: Literature references were searched up to April 2011 in MEDLINE and EMBASE, supplemented by manual searches. Inclusion criteria were prospective cohort studies, assessment of the association between smoking and total mortality, cardiovascular death, incidence of coronary heart disease (CHD), stroke and myocardial infarction (MI) in diabetic patients.
Results: Of 3758 studies in the literature searched, 46 were eligible with approximately 130,000 diabetic patients. The relative risk (RR) comparing smokers with nonsmokers was 1.48[95% confidential interval (CI): 1.34–1.64] for total mortality (27 studies), 1.36(1.22–1.52) for cardiovascular mortality (9 studies), 1.54(1.31–1.82) for CHD (13 studies), 1.44(1.28–1.61) for stroke (9 studies) and 1.52(1.25–1.83) for MI (7 studies). Furthermore, the excess risk was observed among former and current smokers with a greater risk in current smokers. Subgroup analysis showed that the increased risk appeared to be consistent regardless of several study characteristics with the RRs ranging from 1.31 to 1.94 for all-cause mortality, 1.37 to 2.28 for CHD, 1.21 to 1.87 for stroke, 1.13 to 1.74 for cardiovascular mortality and 1.15 to 2.01 for MI.
Conclusion: Smoking amplified the risk of mortality as well as cardiovascular events and the effect size for CHD appeared to be higher than other events in diabetic patients. Moreover, a trend of decreasing risk was observed among smoking quitters.

1. Introduction

Although it is well known that smoking is strongly associated with the risk of diabetes [1], many patients persist smoking even after being diagnosed with diabetes. Furthermore, numerous studies have demonstrated that both smoking and diabetes are risk factors for mortality and caused-specific cardiovascular events [2–4]; however, some studies failed to find an association between smoking and adverse outcomes among diabetic patients [5–7], others successfully found a positive association [8–10]. In addition, studies which investigated the statistical interaction between diabetes and smoking on the risk of major cardiovascular outcomes aroused conflicting results [9,11]. Therefore, it remains uncertain whether the excess risk of cardiovascular disease (CVD) outcomes with smoking could be overwhelmed by diabetes.

With the current high prevalence of smoking and the increasing rates of diabetes [12–14], it is important to perform a systematic review and meta-analysis to determine a more precise estimate of different cardiac events or mortality associated with smoking among patient with diabetes.

2. Method

2.1. Search strategy

A systematic literature search was undertaken in the databases of MEDLINE (1948 to April 2011) and EMBASE (1980 to April 2011) using the following strategy recommended for systematic reviews of observational studies [15]. Exp *smoking* or exp *smoking cessation* was cross-referenced with exp *diabetes mellitus* and the following outcome terms: exp *mortality* or exp *stroke* or exp *cardiovascular disease* or exp *myocardial infarction* or exp *myocardial ischemia* or exp *coronary artery disease* or exp *myocardial revascularization* and the final study design term: exp *incidence* or exp *follow-up studies* or exp *cohort studies* or exp *prognosis*. In addition, searches were limited to published English language articles and studies in humans. To ensure a broad search, reference lists of identified studies and review articles were also searched.

2.2. Eligibility criteria

All eligible publications had to meet the pre-specified inclusion criteria: 1) prospective studies (observational cohort study, prospective nested case–control) in persons with diabetes; 2) studies reporting endpoints of all-cause mortality or CVD events (defined as coronary heart disease(CHD), stroke, myocardial infarction(MI) or

* Corresponding author at: Department of Health Education, Jiangsu Province Hospital on Integration of Chinese and Western Medicine, #100 Shizi Street Hongshan Road, Nanjing 210028, China. Tel.: +86 153 1201 9129.
E-mail address: lqq188@yahoo.com (Q. Lou).
[1] Equal contribution.

0167-5273/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2011.12.100

mortality from cardiovascular disease); 3) studies specifying the number of selected events above; 4) studies assessing the relative risk and its 95% CI between smoking and eligible outcomes.

2.3. Study selection

Two authors (R.Q. and T.C.) independently reviewed the article titles and abstracts for eligibility and obtained full-text articles where eligibility was definite or unclear. Discrepancies in articles selected for inclusion were resolved through discussion and consensus. Multiple publications from one study were eligible if they reported results with different outcomes.

2.4. Data abstraction and synthesis

Data extraction was done independently by the two reviewers (R.Q. and T.C.). Details were collected on study design, study sample, population characteristics (for example, sex and age range), the type of endpoints and the number of each event, estimates of the relative risk (RR), odds ratio (OR) or hazards ratio (HR) associated with smoking. If available, we extracted any reported risks of outcomes for former or current smokers compared with never smokers.

Attention was limited to the estimated RRs where the data were presented as only a dose–response (that is different amount of smoked relative to never smokers). In this case, random effects meta-analysis was used to combine RRs across different amount of smoked within the study. After then, the recalculated single, study-specific relative risk was pooled with those of other studies. The same analytical pattern was performed when the studies reported the estimated RRs of smoking separately by current or former.

Where two or more RRs were available with varying degrees of confounder adjustment, the most highly adjusted RRs were selected. Where separate effects were reported (e.g. reporting effect for men and women separately), these were taken as different study populations.

2.5. Statistical methods

For primary analyses, individuals were classified as smoker (which included former smokers) or never smokers. For those studies that recorded the relevant information, participants were further categorized as those who were never smokers, former smokers or current smokers for further analyses.

In order to obtain an overall estimate of the risk associated with smoking, we considered all of OR, RR and HR as estimates of the relative risk and weighted the log of the odds ratios, risk ratios, hazard ratios by the inverse of their variance. Heterogeneity of RRs across studies was assessed using Der Simonian and Laird Q and the I^2 statistics [16,17]. Sensitivity analysis and subgroup analysis was performed to explore the potential source of heterogeneity on the results from the selected study characteristics. We also performed a sensitivity analysis excluding the studies where the calculated relative risk was applied. Furthermore, the estimated risk for former or current smokers was calculated. Publication bias was assessed through Egger's tests.

3. Result

3.1. Identification of studies

The initial search strategy yielded 3758 citations: 1024 from MEDLINE and 2734 from EMBASE. Of these, 182 duplicated publications were excluded and a further 3423 were excluded after an evaluation of the title and abstract. This left 153 studies for full-text review. An additional four articles were obtained by hand searching bibliographies of eligible articles and prior reviews. However, after second round of screening, 111 articles were excluded for the reasons listed in Fig. 1, leaving 46 articles for final inclusion in this study. Agreement between the 2 reviewers for study eligibility was high (weighted Kappa coefficient = 0.87).

3.2. Study characteristics

The relevant features of the included 46 articles with 126,943 patients are reported in Table 1. Of these articles, 2 were nested case–control studies, and 6 were from the same cohorts but reported different outcomes. The majority of studies were conducted in Western countries, mostly from the U.S., however, there was only 1 study from Japan and 2 from China. Duration of follow-up ranged from 2.1 years to 20 years with a median follow-up of 7.58 years. Smoking rates in these studies ranged from 15% to 69%.

38 studies reported both male and female participants without stratifying by sex, whereas 2 studies reported only men, 2 reported only women and 4 reported only for women and men separately. 5

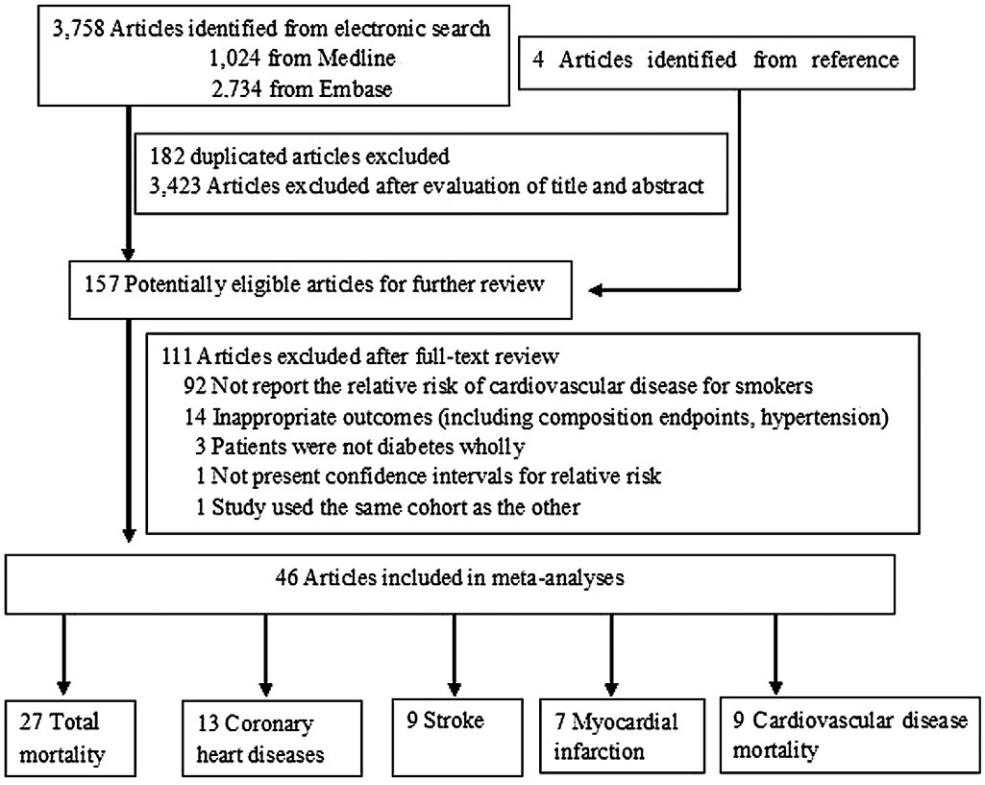

Fig. 1. Process of study selection.