Smoking increases the risk of diabetic foot amputation: A meta-analysis

MIN LIU[1*], WEI ZHANG[2*], ZHAOLI YAN[1] and XIANGZHEN YUAN[3]

[1]Department of Endocrinology, Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia Autonomous Region 010050; [2]Department of Ophthalmology, Affiliated People's Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia Autonomous Region 010020; [3]Health Care Center, Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia Autonomous Region 010050, P.R. China

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Abstract. Accumulating evidence suggests that smoking is associated with diabetic foot amputation. However, the currently available results are inconsistent and controversial. Therefore, the present study performed a meta-analysis to systematically review the association between smoking and diabetic foot amputation and to investigate the risk factors of diabetic foot amputation. Public databases, including PubMed and Embase, were searched prior to 29th February 2016. The heterogeneity was assessed using the Cochran's Q statistic and the I^2 statistic, and odds ratio (OR) and 95% confidence interval (CI) were calculated and pooled appropriately. Sensitivity analysis was performed to evaluate the stability of the results. In addition, Egger's test was applied to assess any potential publication bias. Based on the research, a total of eight studies, including five cohort studies and three case control studies were included. The data indicated that smoking significantly increased the risk of diabetic foot amputation (OR=1.65; 95% CI, 1.09-2.50; P<0.0001) compared with non-smoking. Sensitivity analysis demonstrated that the pooled analysis did not vary substantially following the exclusion of any one study. Additionally, there was no evidence of publication bias (Egger's test, t=0.1378; P=0.8958). Furthermore, no significant difference was observed between the minor and major amputation groups in patients who smoked (OR=0.79; 95% CI, 0.24-2.58). The results of the present meta-analysis suggested that smoking is a notable risk factor for diabetic foot amputation. Smoking cessation appears to reduce the risk of diabetic foot amputation.

Correspondence to: Professor Xiangzhen Yuan, Health Care Center, Affiliated Hospital of Inner Mongolia Medical University, 1 Channel North Street, Hohhot, Inner Mongolia Autonomous Region 010050, P.R. China
E-mail: xiangzhenyuan621@126.com

*Contributed equally

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Introduction

Diabetic foot is the most common, long-term and feared complication of diabetes and it is the principal cause of hospitalization among patients with diabetes (1). Diabetic foot is characterized by sensory, motor and autonomic neuropathy and peripheral vascular disease, which may lead to the development of ulceration, infection and gangrene (2). The ultimate outcome of diabetic foot is amputation, which is associated with relatively high morbidity and mortality (3). It has been estimated that ~15% of patients with diabetes develop foot ulcers and 15-20% of these foot ulcers require a lower extremity amputation (LEA) (4). LEA markedly increases financial burden on healthcare resources and individuals (5). Therefore, it is necessary to identify potential underlying risk factors as early as possible to prevent its progression into LEA.

The adverse effect of consumption of tobacco on health has been extensively studied and confirmed. Smoking is a potentially avoidable cause of mortality and smoking cessation is one of the most cost effective ways to prevent diseases. An increasing number of studies have been performed that demonstrated that smoking is one of the most important and modifiable risk factors involved in a number of human diseases, including cardiovascular and cerebrovascular disease (6-8). The morbidity and mortality rates of coronary heart disease, hypertension, cerebrovascular disease and peripheral vascular disease are significantly increased by cigarette smoking (9). A combination of carbon monoxide and hemoglobin produces carboxyhemoglobin, which causes a decline in the oxygen transport capacity of blood. The decrease of oxygen transport capacity results in tissue hypoxia in different organs and subsequently leads to arteriospasm (10). Chronic hypoxia is responsible for compensatory erythrocytosis, resulting in increasing blood viscosity and decreasing tissue perfusion (11). These factors are detrimental for the healing of diabetic foot ulcers, which may increase the risk of diabetic foot amputation. Previously, a number of studies have addressed the association between cigarette smoking and diabetic foot amputation; however, the conclusions were controversial. A number of

epidemiological studies have suggested that smoking is a risk factor for amputation (12,13). However, other studies indicated that there was no association between smoking and diabetic foot amputation (14,15).

Therefore, the present study systematically reviewed the literature and performed a meta-analysis to improve the evaluation and assessment of the association between cigarette smoking and diabetic foot amputation. The present study may provide evidence for the identification of risk factors for diabetic foot amputation, thereby preventing the development of amputation and providing a theoretical basis for clinical treatment.

Materials and methods

Data sources. Electronic databases, including PubMed (ncbi.nlm.nih.gov/pubmed) and Embase (embase.com), were systematically searched. Additionally, a manual search of the literature was performed to screen more relevant studies. The key words used during the search were: ('Diabetic foot' OR 'diabetes foot' OR 'diabetes feet') AND ('amputation' OR 'amputated') AND ('smoking' OR 'smoke'). The deadline for the search was 29th February 2016.

Study selection. The inclusion criteria were as follows: i) The study was relevant to the association between smoking and diabetic foot amputation; ii) and the study provided the information that the distribution of smoking in the diabetic foot amputation group and non-amputation group or the information should include odds ratio (OR) and 95% confidence interval (CI), or they may be calculated according to the original data. The exclusion criteria were as follows: i) Non-original article, including reviews, reports, letters or comments; and ii) studies with unavailable data for analysis.

Data extraction and quality assessment. The data were extracted independently by two reviewers according to a standardized protocol using a data-collection form (16). The information was abstracted using a form including the first author's name, publication year, study year, research type, number of patients in diabetic foot amputation group and non-amputation group, age and gender, number of patients with hypertension and demographic characteristics. To further reveal the relationship between smoking and diabetic foot amputation, patients were divided into minor amputation group and major amputation group. Minor amputation refers an amputation distal to the tarsometatarsal joint, and while major amputation refers to one through or proximal to the tarsometatarsal joint. The Newcastle-Ottawa Scale (NOS) was used in the present study to assess the quality of the literature (17). NOS has strict scoring criteria for epidemiological study and was calculated based on three primary components, including the selection of study groups (0-4 points), the quality of adjustment for confounding (0-2 points) and the ascertainment of outcome of interest in the cohorts (0-3 points). The total score of NOS was 9 points. Scores ≥7 points were considered as high-quality research, 4-6 points were indicative of medium quality and <3 points were recorded as low quality. Duplication was avoided by consensus.

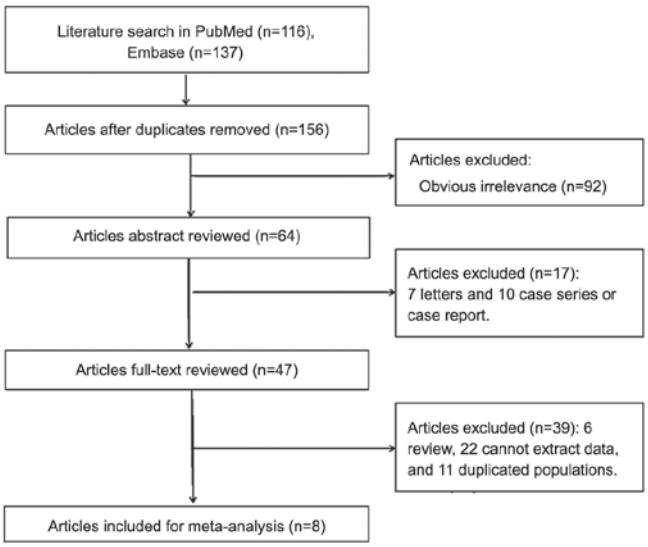

Figure 1. Literature search and study selection flow diagram.

Statistical analyses. All data in the present study were analyzed using software R 3.12 (www.r-project.org), and the effect sizes were OR and 95% CI (18). The heterogeneity test was based on the Cochran's Q statistic and the I^2 statistic (19). The random effects model was selected for heterogeneous outcomes ($P<0.05$ or $I^2 \geq 50\%$), and otherwise, the fixed effects model was performed for homogeneous outcomes ($P \geq 0.05$ and $I^2 < 50\%$) (20). $P<0.05$ was considered to represent statistically significant differences. A sensitivity analysis was performed by removing studies one at a time to confirm the robustness of the results (21). Publication bias was assessed by performing the Egger's test (22).

Results

Characteristics of the eligible studies. The process of selecting studies in the present study is presented in Fig. 1. A total of 253 articles were potentially relevant to the search terms based on the search criteria, with 116 articles from the PubMed and 137 articles from the Embase database. Following the elimination of duplicated documents (97 articles), 156 studies remained. The present study then excluded 92 studies that were irrelevant. The remaining 64 articles were screened by assessing the titles and abstracts and 17 documents were excluded (seven letters and 10 case series or case reports). Following the reading of the full text of the remaining 47 articles, 39 articles were excluded, including six reviews, 22 articles in which the data could not be extracted and 11 articles with duplicated populations. Finally, eight documents were included in this meta-analysis (23-30).

Characteristics of the enrolled studies. Table I indicates the basic information of the studies involved in the meta-analysis. The enrolled eight studies included five cohort studies (22-24,26,27) and three case control studies (20,21,25). The publication year ranged from 1992-2015. The region of these studies included Turkey, USA, China, UK and Costa Rica. The ages for the subjects ranged from 33.2-64.4 years. The NOS scores of the included studies were all ≥4, demonstrating that the studies were medium and high quality.

Table I. Characteristics of studies included in the meta-analysis.

Author, year	Study location	Study year	Study style	Group	n	Age, years	Males (n)	Hypertension (n)	Diabetes duration, years	Neuropathy (n)	Retinopathy (n)	Nephropathy (n)	Nos	(Refs.)
Yesil, *et al* 2009	Turkey	1999-2008	Cohort	A	213	64.60±9.69	154	126	17.42±9.89	165	137	113	5	(30)
				Non	361	61.89±10.59	237	184	15.793±8.72	318	226	189		
Gürlek, *et al* 1998	Turkey	NA	Case-control study	A	54	59.3±9.3	38	15	13.1±8.5	38	34	22	4	(24)
				Non	93	59.2±10.5	59	27	12.9±8.2	70	67	41		
Reiber, *et al* 1992	USA	1984-1987	Case-control study	A	80	63.4±11.9	NA	NA	13.3±10.5	NA	NA	NA	5	(28)
				Non	236	61.1±10.0	NA	NA	10.9±9.7	NA	NA	NA		
Jiang, *et al* 2015	China	2000-2009	Cohort	Mi	118	61.0 (range, 57.0-78.0)	83	82	NA	21	49	48	7	(25)
				Ma	15	63.5 (range, 56.0-72.0)	12	9	NA	0	5	8		
				Non	536	64.0 (range, 55.0-72.0)	340	296	NA	89	216	211		
Chaturvedi, *et al* 2002	UK	1992-1997	Case-control study	A	172	69±0.8	68	145±1.8[a]	11±0.6	89	56	43	6	(23)
				Non	376	68±0.5	51	149±1.3[a]	8±0.4	51	16	4		
Resnick, *et al* 1999	USA	1971-1992	Cohort	A	108	61.1±10.1	55	64	NA	NA	NA	NA	5	(29)
				Non	14,299	48.8±15.6	5,756	3,900	NA	NA	NA	NA		
Laclé and Valero-Juan 2012	Costa Rica	2001-2007	Cohort	A	21	60.6±12.0	11	11	12.9±6.6	15	13	15	6	(26)
				Non	528	58.3±12.8	188	309	6.9±6.9	75	46	82		
Nerone, *et al* 2013	USA	2000-2011	Cohort	Mi	111	53.117±11.107	65	NA	NA	NA	NA	NA	6	(27)
				Ma	52	56.231±10.764	34	NA	NA	NA	NA	NA		

[a]Systolic blood pressure, mmHg. NOS, Newcastle-Ottawa Scale; NA, no answer; A, amputation; non, non-amputation; Mi, minor amputation; Ma, major amputation.

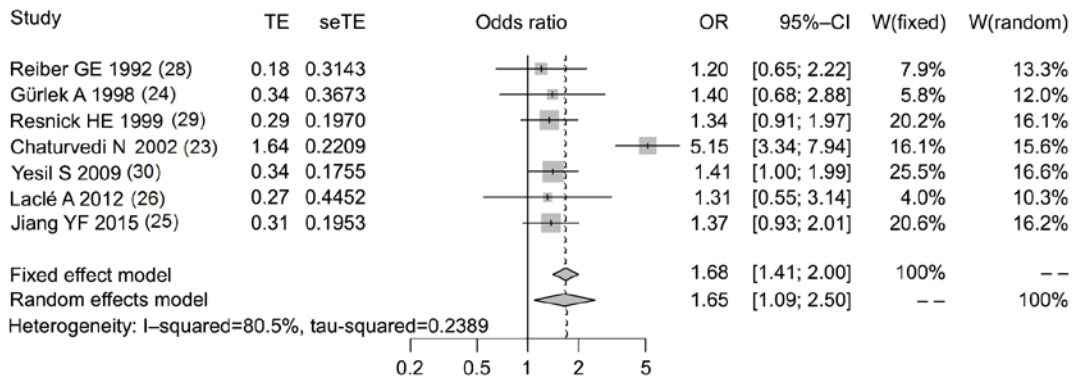

Figure 2. Forest plot of the risk of smoking on diabetic foot amputation. OR, odds ratio; CI, confidence interval; TE, estimated effect; seTE, standard error estimated effect; W, weighted.

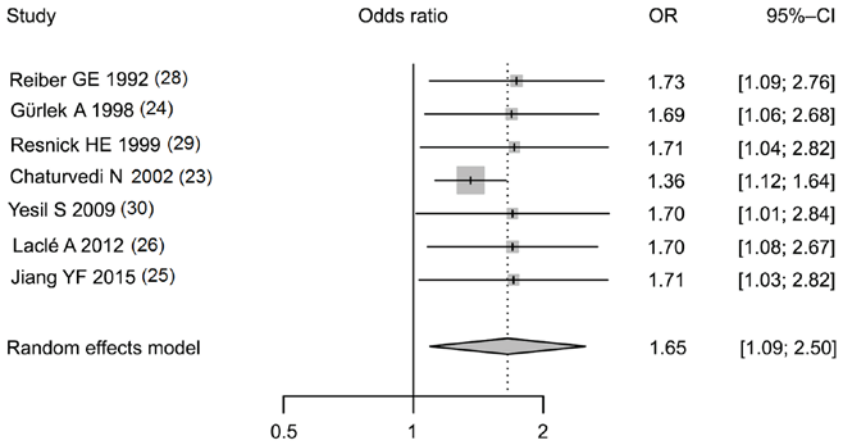

Figure 3. Forest plot of sensitivity analysis. OR, odds ratio; CI, confidence interval.

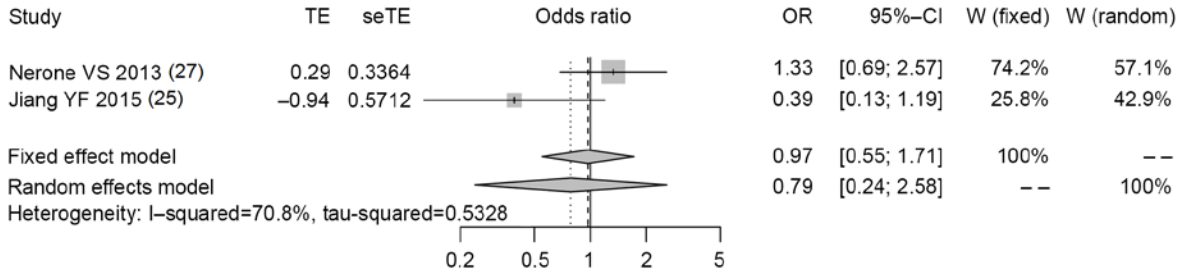

Figure 4. Forest plot of the risk of smoking on minor amputation group and major amputation group. OR, odds ratio; CI, confidence interval; TE, estimated effect; seTE, standard error estimated effect; W, weighted.

Meta-analysis of quality assessment and pooled analysis. The present study initially performed a heterogeneity test to assess the heterogeneity of the studies analyzed using the Cochran's Q statistic and the I^2 statistic. The result of the heterogeneity test was I^2=80.5 (P<0.001), indicating a heterogeneity among studies. Therefore, a random-effects model was used in this meta-analysis. As presented in Fig. 2, the results of a forest plot demonstrated that smoking significantly promoted the risk of diabetic foot amputation (OR=1.65; 95% CI, 1.09-2.50; P<0.0001) compared with non-smoking individuals. A sensitivity analysis was applied to evaluate the stability of the results. The results of sensitivity analysis indicated that the pooled analysis did not vary substantially following the exclusion of any one study from the analysis; ORs ranged from a low 1.36 (95% CI, 1.12-1.64) to a high 1.73 (95% CI, 1.09-2.76; Fig. 3), confirming the stability of the results. Additionally, Egger's test was performed to confirm whether there was a publication bias. The results demonstrated that there was no evidence of publication bias (t=0.1378; P=0.8958). Furthermore, it was observed that no significant difference was identified between the minor amputation group and major amputation group in patients who smoked (OR=0.79; 95% CI, 0.24-2.58), demonstrating that smoking had no effect on either minor or major amputation (Fig. 4).

Discussion

In the present study, the association between cigarette smoking and diabetic foot amputation was investigated by a meta-analysis. The results from the present meta-analysis indicated a clear association between smoking and the increased risk of diabetic foot amputation. Based on the data from eight studies (five cohort studies and three case control studies), smokers had an increased risk of diabetic foot amputation compared with nonsmoking individuals. However, there is no marked difference for the risk of minor or major amputation in the amputation group.

Identification of risk factors for diabetic foot amputation may be useful in the primary prevention, earlier diagnosis, treatment and increase of survival of patients with diabetes. A notable amount of literature exists on risk factors for amputation among patients with diabetes. A number of risk factors have been reported, including age (31,32), gender (33,34), ischemic heart disease (31), hypertension (31), peripheral artery disease (35), nephropathy (36), duration of diabetes (37) and hemoglobin A1C (38,39). However, there are inconsistencies among studies regarding smoking as a risk factor for diabetic foot amputation. A study by Selby and Zhang (40) suggested that cigarette smoking was unrelated to amputation risk and a study by Stewart (41) indicated that cigarette smoking had no influence on diabetes mellitus-related amputation levels. By contrast, a number of studies have demonstrated that smoking is a significant covariate factor in diabetic foot amputation (25,30,42). The evidence supporting smoking as a risk factor is that heavy smokers are more prone to develop peripheral vascular disease that may result in a marked degree of arterial compromise, requiring amputation (41).

To systematically assess the relationship between smoking and the increased risk of diabetic foot amputation, the present study performed a meta-analysis. A total of eight studies were selected based on the research. The pooled effect indicated that smoking increased the risk of diabetic foot amputation. The results also demonstrated that there was no significant difference for the risk of minor amputation and major amputation in the amputation group. The results were similar to a study conducted by Nerone *et al* (27), in which smoking made no difference to the amputation outcome (minor or major amputation). The combined results of the primary analysis of the present study indicated no significant publication bias. However, heterogeneity was substantial in the present study. The reasons and sources may be diverse. In the present study, the regions involved included Turkey, USA, China, UK and Costa Rica. The differences among countries, ethnicity, life style, living environment, cultural exchange, the level of economic development may contribute to the results, in addition to the gender, age and sample size of each study. Furthermore, the definition of smoking habits, the duration of smoking and patients with different concomitant diseases may have influenced the results.

There are a number of strengths in the present meta-analysis. The present study investigated the association between cigarette smoking and diabetic foot amputation using meta-analysis for the first time, to the best of our knowledge, and identified that smoking is a risk factor of diabetic foot amputation. The results of the present study may provide evidence of risk factors of diabetic foot amputation. However, the present results should be cautiously interpreted due to certain limitations. Firstly, a correction for covariates was not performed and further subgroup analyses were not possible due to incomplete data from the included studies. These factors may be potential confounders, which may affect the results of meta-analyses. Secondly, the possibility of confounding variables cannot be excluded because the included studies were all observational studies. Thirdly, the limited quantity of the included studies may have influenced the authenticity of the results.

In conclusion, the results of the present systematic review and meta-analysis suggested that smoking increases the development of diabetic foot amputation. Smoking cessation may be a good way to reduce the risk of diabetic foot amputation. Due to the deficiency of studies included in the analysis, which cannot be ignored, an increased quality and quantity of studies should be included in future studies to verify the present results.

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