REVIEWS

The Effect of Cigarette Smoking on Diabetic Peripheral Neuropathy: A Systematic Review and Meta-Analysis

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OBJECTIVE: Studies suggest that smoking may be a risk factor for the development of microvascular complications such as diabetic peripheral neuropathy (DPN). The objective of this study was to assess the relationship between smoking and DPN in persons with type 1 or type 2 diabetes.

RESEARCH DESIGN AND METHODS: A systematic review of the PubMed, Embase, and Cochrane clinical trials databases was conducted for the period from January 1966 to November 2014 for cohort, cross-sectional and case–control studies that assessed the relationship between smoking and DPN. Separate meta-analyses for prospective cohort studies and case–control or cross-sectional studies were performed using random effects models.

RESULTS: Thirty-eight studies (10 prospective cohort and 28 cross-sectional) were included. The prospective cohort studies included 5558 participants without DPN at baseline. During follow-up ranging from 2 to 10 years, 1550 cases of DPN occurred. The pooled unadjusted odds ratio (OR) of developing DPN associated with smoking was 1.26 (95 % CI 0.86–1.85; I^2=74 %; evidence grade: low strength). Stratified analyses of the prospective studies revealed that studies of higher quality and with better levels of adjustment and longer follow-up showed a significant positive association between smoking and DPN, with less heterogeneity. The cross-sectional studies included 27,594 participants. The pooled OR of DPN associated with smoking was 1.42 (95 % CI 1.21–1.65; I^2=65 %; evidence grade: low strength). There was no evidence of publication bias.

CONCLUSIONS: Smoking may be associated with an increased risk of DPN in persons with diabetes. Further studies are needed to test whether this association is causal and whether smoking cessation reduces the risk of DPN in adults with diabetes.

KEYWORDS: Diabetes; Smoking cessation; Comorbidity.

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Diabetic peripheral neuropathy (DPN), also known as distal symmetrical polyneuropathy or sensorimotor neuropathy, is part of a wider spectrum of microvascular complications of diabetes that includes ulcer/amputation, erectile dysfunction, and autonomic dysfunction. DPN is the most common of these, affecting approximately 30 % of persons with diabetes [1–3]. Symptoms include numbness, tingling, or a burning sensation in the legs and hands, typically in a "stocking and glove" distribution [1]. Ultimately, muscle weakness, loss of reflexes, and foot deformities can result, leading to end clinical sequelae of ulcers, potential infection, and amputation for some patients with poorly controlled disease.

The pathogenesis of DPN involves a complex interaction between metabolic and vascular factors [1 4]. Hyperglycemia, the most commonly described factor, leads to nerve cell damage through several mechanisms, including oxidative stress and polyol accumulation [3]. Reduced nerve perfusion, endoneurial hypoxia, and endothelial dysfunction also contribute to neuropathy development [1].

Previous studies have investigated potential risk factors for DPN, including hypertension, microalbuminuria, dyslipidemia, and, of particular interest, cigarette smoking [5–7]. There appears to be an increased likelihood of neuropathy in people with diabetes who smoke, although prior studies investigating this relationship included only a small number of participants [7].

In order to better assess the relationship between smoking and diabetic neuropathy, we conducted a systematic review and meta-analysis of cross-sectional, case–control, prospective, and retrospective cohort studies.

RESEARCH DESIGN AND METHODS

Search Strategy and Selection Criteria

We conducted a search of the PubMed (January 1966 to November 2014), Embase (January 1980 to November 2014), and Cochrane clinical trials (to November 2014) databases, and we also searched the references of the relevant retrieved articles. Studies that assessed the effect of cigarette smoking on the risk of peripheral neuropathy among patients with type 1 or type 2 diabetes were included (population of interest). Only participants with diabetes at baseline were included, as we were interested primarily in the effect of smoking on diabetic complications. The exposure of interest was cigarette smoking. In order to be considered for inclusion in the systematic review, studies had to include a control or comparison group of participants with diabetes who did not smoke. The outcome of interest was DPN.

Cohort studies as well as cross-sectional and case–control studies were included based on our search results. For cohort studies, we included studies with at least 1 year of follow-up, as we assumed a latency period of at least 1 year for smoking to influence the development of diabetic neuropathy. We considered studies published in all languages and did not restrict our search to published studies.

We used a combination of three search themes: 1) diabetes, 2) smoking, and 3) neuropathy. The full electronic search is available in the online Appendix 1.

Study Selection

An initial screening of retrieved citations was performed based on titles and abstracts; each citation was screened by two coauthors (CC, MJC, FE or KJS). The inclusion criteria for this first screening were as follows: population with diabetes (type 1 or type 2), neuropathy as one recorded outcome (not necessarily the primary outcome), and identification as prospective, cohort, or cross-sectional study. We included studies even if they did not mention smoking exposure in the title or abstract. Exclusion criteria included gestational diabetes, animal studies, and non-original study design (such as reviews, editorials, or case reports/case series). A second screening was then performed based on full-text review of retained citations. The exclusion criteria were the same as those for the first screen, with the addition of the following: 1) smoking–neuropathy relationship was not assessed and/or data did not allow calculating it manually, 2) peripheral neuropathy was not one of the outcomes, or 3) persons without diabetes were included. Two reviewers (CC, MJC, FE, or KJS) independently reviewed the articles, and any disagreement was resolved by consensus.

Data Extraction and Quality Assessment

Two authors independently extracted the data from selected studies. To evaluate the risk of bias in individual studies and to assess overall quality, we considered several criteria based on the Newcastle-Ottawa scale [8]. For cohort studies, the Newcastle-Ottawa scale has three categories: 1) selection (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration that outcome of interest was not present at start of study) (0–4 points); 2) comparability (comparability of cohorts on the basis of design or analyses) (0–2 points); and 3) outcome (assessment of outcome, was follow-up long enough for outcomes to occur, adequacy of follow-up of cohorts) (0–3 points). We used a modified version of the Newcastle-Ottawa scale for case–control studies in order to evaluate the quality of cross-sectional studies. In the modified version, we deleted the question on selection of controls (in the "selection" category, yielding a maximum of 3 points) and the questions on methods of ascertainment for cases and controls and non-response rate (in the "exposure" section, yielding a maximum of 2 points). We reported the score for each subcategory in the extraction form. We defined the quality of studies as good if they had the maximum scores for selection and exposure and at least one point for comparability. Other studies were considered suboptimal, and were classified as moderate quality if they had at least one point for each Newcastle-Ottawa scale category, and low quality if one or more categories had no points. Two authors also independently evaluated the strength of the body of evidence separately for each meta-analysis, using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group criteria [9]. The following domains were evaluated: consistency, directness, precision, dose–response association, and residual confounding. The strength of evidence was considered as "high" if there was high confidence that the evidence reflected the true effect; "moderate" if there was moderate confidence that the evidence reflected the true effect, and it was possible that further research would change the estimate; "low" if there was low confidence that the evidence reflected the true effect, and further research was likely to change the estimate; and "insufficient" if evidence was unavailable. Studies reported risk ratios (RRs), odds ratios (ORs), or absolute numbers in describing the relationship between smoking and DPN. As most prospective and cross-sectional studies reported ORs, and not all studies provided information to convert OR into RR, we used ORs in our meta-analyses. For studies that provided neither OR nor RR, we calculated unadjusted ORs and confidence intervals (CIs) manually.

Data Synthesis and Analysis

We pooled our results using the DerSimonian and Laird random effects model [10], since we expected to observe heterogeneity among studies. Anticipated sources of heterogeneity included study population (persons with type 1 versus type 2 diabetes), definition of smoking, and definition of neuropathy, and were defined a priori. We explored other sources of heterogeneity for three variables that were added post hoc: level of adjustment, mean duration of follow-up (for prospective studies only), and level of quality assessed with the Newcastle-Ottawa scale [8]. We then performed stratified

analyses to assess/explore potential sources of heterogeneity linked to a priori and post hoc variables. In parallel, we performed univariate meta-regression analyses to quantify potential source of heterogeneity. We performed separate meta-analyses stratified by type of design. To assess heterogeneity, the Q-statistic and I^2 statistic were calculated [11 12]. The possibility of publication bias was assessed using the Begg test and visual inspection of the funnel plot [13 14]. Stata software (Version13; StataCorp LP, College Station, TX, USA) was used for statistical analysis.

RESULTS

Study Selection

In terms of study selection, the initial search included 2006 citations from the PubMed, Embase and Cochrane clinical trials databases. After excluding duplicates, 1554 unique citations were available (see Fig. 1). After the first screening, 126 citations were considered for further review. In a second screening, 88 studies were excluded based on full-text review. Agreement between reviewers at this stage was good, with a Kappa of 0.78. Reasons for exclusion in this phase included the lack of an estimate (or numbers to allow manual calculation) of the smoking–neuropathy relationship (n=54), an outcome other than peripheral neuropathy (n=30), and inclusion of participants without diabetes (n=4). Ultimately, 38 studies were selected for inclusion in the systematic review, and we performed separate meta-analyses for the ten prospective studies [5 15–23] and 28 cross-sectional studies [6 7 24–49].

Smoking and incidence of diabetic peripheral neuropathy in prospective cohort studies

The main individual characteristics of the prospective studies are shown in Table 1. Together, they comprised 5558 participants: three studies in individuals with type 2 diabetes, six studies with type 1 diabetes, and one study that included both participants with type 1 and type 2 diabetes. Participants were from different settings including inpatient, outpatient and the community; mean age of participants ranged from 25 to 66 years old and mean diabetes duration ranged from 0 to 17 years. All studies excluded participants with neuropathy at baseline and participants were followed for 2 to 10 years. Peripheral neuropathy screening was done by neurological

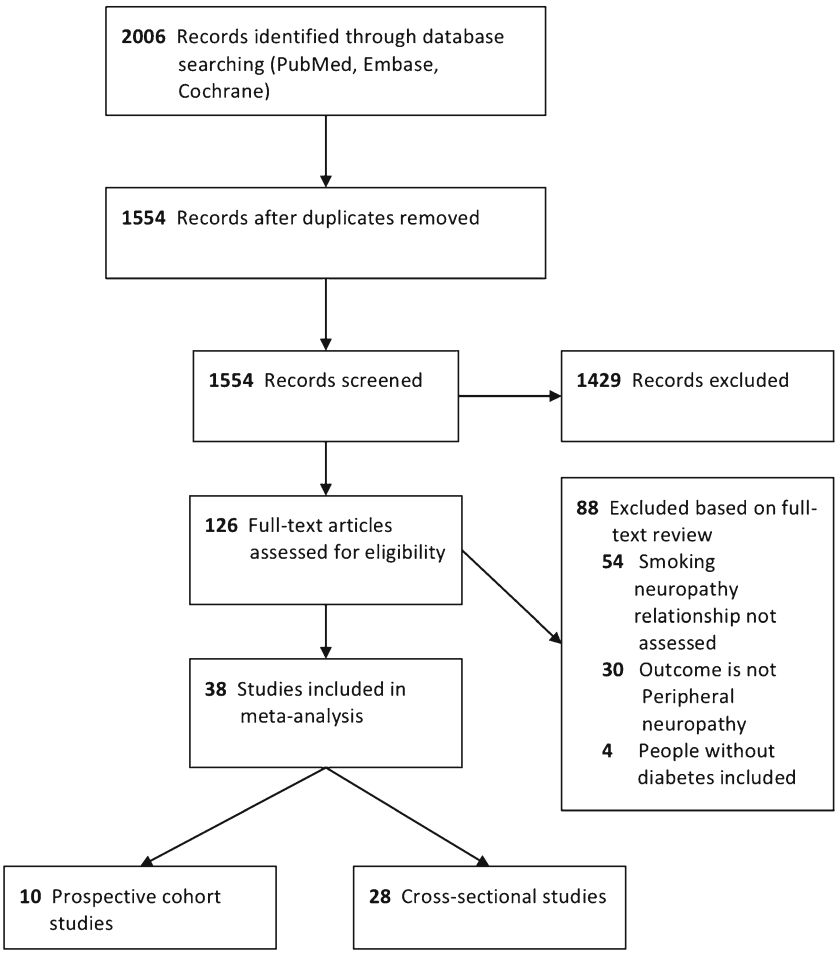

Fig. 1 Study flow diagram

history and examination in most studies [5 17–20 23], by electromyography to measure nerve conduction velocities in one study [15], by measure of vibration perception using biothesiometry in one study [22], and by monofilament examinations in two studies [16 21]. The definition of smoking exposure varied among studies; six studies compared ever smokers (i.e. current and former smokers) to never smokers, one study compared current to nonsmokers (i.e. former and never smokers), and three studies did not clearly specify the smoking comparison groups. Most studies provided ORs; two provided RRs, and one provided numbers of smokers and nonsmokers and of participants in each category who developed peripheral neuropathy. All but one study performed multivariable-adjusted analyses; five controlled for at least A1C and diabetes duration, and four adjusted for either A1C or diabetes duration and several other confounders (see Online Appendix 2). The quality of studies varied. Most were considered to be of good quality, with maximum points for selection and exposure criteria on the Newcastle-Ottawa scale [5 17–20 22]; however, three were classified as moderate quality [16 21 23], and one as low quality [15], largely due to the risk of selection bias and poorly defined outcomes [15 16 21 23].

Table 1 Characteristics of prospective studies included in the meta-analysis

Author, year	Country/ region	Sample size	Population	Type of DM	% men	Mean age	Mean DM duration	Neuropathy screening	Smoking comparison	FUP (years)	Estimate
Lehtinen et al., 1993	Finland	113	Subjects with newly diagnosed DM from the community	2	51	56.4	0	Nerve conduction velocities	NS	5	N
Adler et al., 1997	USA	387	US veterans followed in an outpatient clinic	Both	96	61.7	9.8	Monofilament examination	Current vs. former+ never smokers	2.6	OR
Forrest et al., 1997	USA	453	Subjects with childhood-onset DM	1	49	25.1	16.9	Neurological examination	Current+ former vs. never smokers	5.3	RR
Sands et al., 1997	USA	231	Bi-ethnic population in Colorado	2	NS	NS	NS	Neurological examination and history	Current+ former vs. never smokers	4.7	OR
Christen et al., 1999	USA	407	Participants in a multi-center drug (sorbinil) trial	1	75	31.4	6.5	Neurological examination and history	Current+ former vs. never smokers*	2	RR
Tesfaye et al., 2005	Europe	1172	Subjects randomly selected from 31 diabetes clinics	1	51	30.7	12.4	Neurological examination	Current+ former vs. never smokers	7.3	OR
Sibal et al., 2006	UK	334	Outpatients who received diabetes services	1	54	39	20	Neurological examination and history	NS	9	OR
Gerrits et al., 2008	Netherlands	973	Subjects from primary care	2	46	66	4	Monofilament examination	NS	3.1	OR
Elliott et al., 2009	Europe	1407	Subjects randomly selected from 31 diabetes clinics	1	48	31.5	13.1	Vibration perception threshold as measured by biothesiometry	Current+ former vs. never smokers	7.3	OR
Uruska et al., 2014	Poland	81	Patients treated with intensive insulin from onset of disease	1	63	34	10	Neurological examination (monofilament, vibration, temperature and ankle reflex)	Current+ former vs. never smokers	10	OR

DMdiabetes mellitus, NSnon-specified, FUPfollow-up, OR odds ratio, RRrelative risk, Nnumber or proportion
** In the age-adjusted analyses, current smokers compared to never smokers; in the multivariable-adjusted model, ever compared to never smokers*

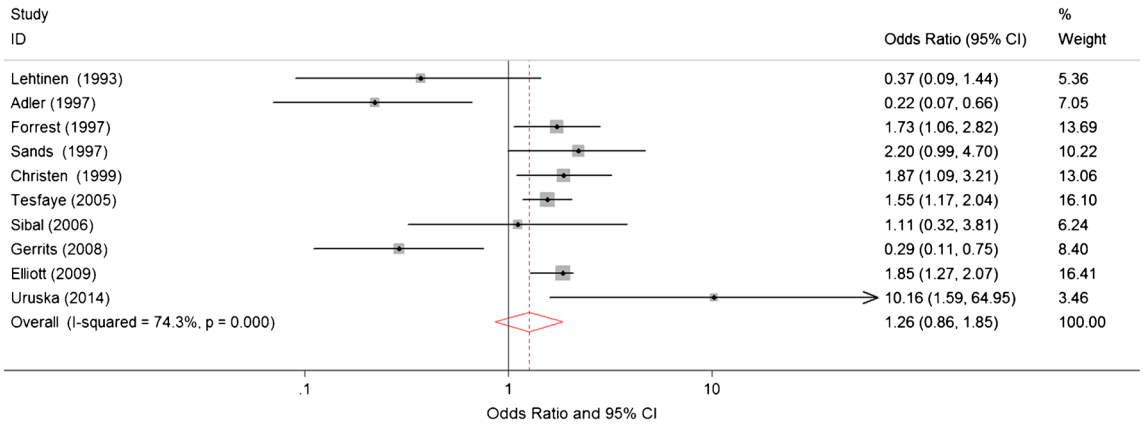

Fig. 2 Forest plot for prospective studies: adjusted odds ratios of neuropathy for smokers versus nonsmokers. Dashed vertical line represents the estimated pooled effect size; points in grey squares with lines represent odds ratios and 95 % CIs of individual studies; the open diamond represents a visual summary of the overall 95 % CI of the effect estimate of smoking on the incidence of DPN. Studies to the right of the solid vertical line indicate a positive association between smoking and DPN; studies to the left indicate a negative association.

With regard to the incidence of DPN, seven studies showed a positive association with smoking and three showed a negative association; the OR ranged from 0.22 to 10.16. When we pooled the data using a random effects model, the pooled OR was 1.26 (95 % CI 0.86–1.85; Fig. 2). The strength of evidence was considered low according to GRADE criteria (see Online Appendix 3). There was evidence of high heterogeneity across studies, as suggested by the *I-squared* statistic (I^2=74 %). Visual inspection of the funnel plot (Online Appendix 4) and Begg's test (p value=0.72) did not suggest publication bias (i.e. no evidence of small negative unpublished studies), but showed a cluster of medium to large negative studies. Attempting to correct for eventual small unpublished negative studies using the "trim and fill" method in Stata [50] did not significantly change the results (OR 1.26, 95 % CI 0.86–1.83). In stratified analyses, studies of higher quality and with better levels of adjustment and longer follow-up showed a stronger positive association between smoking and DPN (Table 2). Studies including persons with type 1 diabetes showed increased risk of DPN for smokers than non-smokers, whereas studies in individuals with type 2 diabetes showed no statistically significant association.

Smoking and prevalence of diabetic peripheral neuropathy in cross-sectional studies

The primary individual characteristics of the cross-sectional studies are shown in Table 3. They included a total of 27,594 participants; 21 studies included persons with type 2 diabetes, three studies with type 1 diabetes, and four studies with both type 1 and type 2 diabetes. The mean age of the participants ranged from 19 to 68 years, and the mean duration of diabetes encompassed 0 to 20 years. There was high heterogeneity in the definition of exposure: seven studies compared current smokers to nonsmokers (i.e. former and never smokers), four studies compared ever smokers (i.e. current and former smokers) to never smokers, six studies compared current vs. never smokers, two studies compared smokers of 30 or more pack-years to smokers of less than 30 pack-years, one study compared smokers of<20 pack-years to never smokers, and eight studies did not specify the comparison groups. The majority of studies expressed the estimate in OR; two used RR and nine used numbers or proportions, allowing us to manually calculate unadjusted OR and 95 % CI. Seven studies controlled for at least A1C and diabetes duration, one adjusted for either A1C or diabetes duration, four adjusted for some confounders but not A1C and diabetes duration, and 16 did not adjust for potential confounders (see Online Appendix). Based on the Newcastle-Ottawa scale, ten studies were rated as moderate quality [6 7 24 31 33 34 36 37 49] and 18 as low quality [25–30 35 38–48], largely because of selection bias, lack of adjustment for confounders, or poorly defined exposure and/or outcome. The majority of studies showed increased odds of neuropathy for smokers compared with non-smokers, and ORs ranged from 0.68 to 8.20. The pooled OR using a random effects model was 1.42 (95 % CI 1.21–1.65; see Fig. 3). The strength of evidence was considered low according to GRADE criteria (see Online Appendix 3). There was evidence of some heterogeneity among studies (I^2=65 %, and there was no evidence of publication bias, as suggested by both visual inspection of the funnel plots (Online Appendix 6) and Begg's test (p value=0.17). In stratified analyses, studies with higher levels of adjustment, those that included participants with type 1diabetes, and those comparing ever vs. never smokers showed a higher and stronger association between smoking and DPN. (Table 2)

Table 2 Stratified analyses for prospective and cross-sectional studies

Stratified analysis	Total number of studies	OR	(95 % CI)	*I-squared*	P value from metareg*
Adjustment for confounding factors					
Prospective studies					0.71
Adjusted for at least HbA1c and DM duration	5	1.47	(1.01–2.13)	71.8 %	
Not adjusted for HbA1c and DM duration	5	1.03	(0.34–3.09)	79.2 %	
Cross-sectional studies					0.31
Adjusted for at least HbA1c and DM duration	7	1.59	(1.23–2.06)	43.6 %	
Not adjusted for HbA1c and DM duration	21	1.36	(1.11–1.66)	69.2 %	
Type of diabetes					
Prospective studies					0.02
Type 1	6	1.74	(1.48–2.04)	0 %	
Type 2	3	0.65	(0.16–2.71)	83.2 %	
Both	1	0.22	(0.07–0.66)	–	
Cross-sectional studies					0.19
Type 1	3	3.02	(2.03–4.47)	11.7 %	
Type 2	21	1.24	(1.08–1.44)	50.5 %	
Both	4	1.55	(0.94–2.57)	63.2 %	
Smoking exposure					
Prospective studies					0.007
Ever (current+former) vs. never smoker	6	1.77	(1.51–2.08)	0 %	
Current vs. never smoker	1	0.22	(0.07–0.66)	–	
Non-specified	3	0.47	(0.21–1.06)	31.6 %	
Cross-sectional studies					0.79
Ever (current+former) vs. never smoker	4	1.78	(1.39–2.29)	10.6 %	
Current vs. nonsmokers (former+never)	7	1.38	(0.87–2.20)	70.0 %	
Current vs. never smoker	6	1.58	(1.00–2.48)	74.2 %	
Non-specified or other definition	11	1.28	(1.03–1.60)	57.2 %	
	Mean follow-up				
Prospective studies					0.322
<5 years	4	0.77	(0.25–2.31)	86.4 %	
≥5 years	6	1.63	(1.21–2.21)	47.7 %	
Level of quality (NOS scale)					
Prospective studies					0.02
Good	6	1.73	(1.48–2.03)	0 %	
Moderate	3	0.73	(0.11–4.69)	84.8 %	
Low	1	0.37	(0.09–1.48)	–	
Cross-sectional studies					0.39
Moderate	10	1.53	(1.26–1.84)	34.3 %	
Low	18	1.35	(1.08–1.70)	71.8 %	

* *P value for meta-regression using the "metareg" Stata command, NOSNewcastle-Ottawa scale*

CONCLUSIONS

In summary, we found a positive association between smoking and the prevalence and incidence of DPN. The ten prospective studies (5558 participants) showed no significant association between smoking and diabetic neuropathy, with low evidence strength. However, the studies were heterogeneous, and stratified analyses did show a significant trend toward less heterogeneity when stratified by quality and longer follow-up. Prospective studies comparing ever-smokers (current and former smokers) with never smokers as well as those including participants with type 1 diabetes showed a stronger positive association between smoking and DPN. These studies were also of higher quality, however, and may not have necessarily reflected a real effect modification. In addition, the 28 cross-sectional studies with a total of 27,594 participants showed a moderate association between smoking and DPN, with low evidence strength. There was substantial heterogeneity among the cross-sectional meta-analyses. However, in stratified analyses, studies with higher levels of adjustment and of higher quality showed a stronger positive association between smoking and DPN, with less heterogeneity.

In persons without diabetes, cigarette smoking has been positively associated with increased levels of A1C, a surrogate for metabolic control, which reflects average glycemia over the previous 2 or 3 months [51]. A previous meta-analysis showed a 44 % increased risk of developing type 2 diabetes for smokers compared with nonsmokers [52]. Among persons with diabetes, prior studies have suggested that smoking is also associated with insulin resistance [53] and higher insulin needs [54 55], and thus poor metabolic control [56–61]. As microvascular complications in individuals with type 1 or type 2 diabetes are highly linked to metabolic control [62 63], A1C probably acts as a mediator in the relationship between smoking and DPN. However, the fact that the association remains positive after adjusting for A1C suggests that hyperglycemia may not entirely mediate this relationship. Furthermore, smoking is associated with oxidative stress, systemic inflammation, and endothelial dysfunction independent of diabetes [64–66], and it may increase the risk of nerve damage through these pathways in parallel with metabolic factors. Smoking may also have direct toxic effects, and may induce DPN via hypoxemia and microvascular insufficiency. Similar

Table 3 Characteristics of cross-sectional studies included in the meta-analysis

Author	Country	Sample size	Population	Type of DM	% Men	Mean age	Mean DM duration	Neuropathy screening	Smoking measure	Estimate
Maser et al., 1989	USA	363	Cohort of patients with recent diagnosis	1	50	28.4	19.9	Neurological examination and history	Current+ former vs. never smokers	OR
Mitchell et al., 1990	USA	214	Patients admitted to the inpatient diabetic clinic of a university hospital	1	37	46	14.7	Neurological examination and history	Smoking≥ 30 vs. < 30 pack-years	OR
Franklin et al., 1994	USA	277	Biethnic population in Colorado	2	43	59.5	9.7	Neurological examination and history	< 20 pack-years vs. never smokers	OR
Gregory et al., 1994	UK	136	Newly diagnosed patients admitted to a hospital	2	50	68	0	Neurological examination and history	Smoking≥ 30 vs. < 30 pack-years	N
Matsumoto et al., 1994	Japan	742	Outpatients who visited the diabetic unit of a department of internal medicine	2	54	49	1.3	Information from patient charts and neurological examination	NS	OR
Zafra Mezcua et al., 2000	Spain	504	Patients visiting a medical outpatient clinic	2	42	63.9	8.6	Medical chart review	NS	RR
Barbosa et al., 2001	Portugal	93	Patients in primary health care	2	40	65.4	10.1	Neurological examination	Current vs. never smokers	N
Gomez-Viera et al., 2001	Cuba	200	Patients diagnosed in clinic	Both	37	.	.	Clinical diagnosis with neural induction exam corroboration	NS	RR
Tapp et al., 2003	Australia	821	Population-based survey	2	51	63.1	0.2	Neurological examination and history	Current vs. former+ never smokers	OR
Boru et al., 2004	Turkey	866	Patients who attended a diabetic clinic	2	40	57.2	8.5	Neurological examination and history	NS	OR
Tamer et al., 2006	Turkey	191	Patients with type 2 DM recruited	2	43	58.7	.	Neurological examination and electromyography	Current+ former vs. never smokers	OR
Al-Mahroos et al., 2007	Bahrain	1477	Patients from specialized clinics	2	43	57.3	9.5	Neurological examination and history	NS	OR
Cho et al., 2010	Korea	90	Patients who underwent workup for peripheral polyneuropathy	2	51	59	8.7	Neurological examination and history	NS	OR
Jianbo et al., 2011	China	227	Inpatients and outpatients	2	.	64.5	9.3	Neurological exam and electromyography	Current vs. never smokers	N
Spallone et al., 2011	Italy	191	Diabetic patients with suspected neuropathic pain referred to a center	Both	56.5	58.6	16.7	History+ electrodiagnostic studies in selected cases	NS	OR
Wang et al., 2011	USA	816	Patients referred to a diabetes education program	2	45.2	57	.	Questionnaires and review of medical records	Current+ former vs. never smokers	OR

(*continued on next page*)

Table 3. (continued)

Author	Country	Sample size	Population	Type of DM	% Men	Mean age	Mean DM duration	Neuropathy screening	Smoking measure	Estimate
Abougalambou et al., 2012	Malaysia	1077	Patients followed in an outpatient diabetic clinic	2	45.2	.	.	Neurological exam	Current vs. former+ never smokers	OR
Ji et al., 2012	China	565	Mostly inpatients	2	47.8	66.6	16.2	Medical history and/or symptoms and/or neurological exam	Current vs. never smokers	N
Katulanda et al., 2012	Sri Lanka	337	Non-institutionalized adults from the community	2	37.1	56.8	6.3	Symptoms and neurological exam	Current vs. former+ never smokers	OR
Rasul et al., 2012	Austria	120	Patients from an outpatient clinic	2	59.2	62.9	12.7	Neurological exam and nerve conduction velocity	Current vs. never smokers	N
Eleftheradiou et al., 2013 (Abstract)	Greece	71	Patients from an outpatient clinic	2	63.4	67.7	15	Neuropathy symptoms and neuropathy disability scores, vibration perception threshold	Current vs. former+ never smokers	OR
Molina et al., 2013	Spain	405	Patients from a diabetes clinic and primary care clinic	2	58.3	66	12.7	Semmes-Weinstein monofilament test	Current vs. former+ never smokers	N
Aubert et al., 2014	France	198		2	79.8	65	13	Neuropathy disability score or inability to perceive monofilament	Current vs. former+ never smokers	N
Bener et al., 2014	Qatar	1633		Both	51.6	45.3	7.3	Not specified	Current vs. former+ never smokers	OR
Brownrigg et al., 2014	UK	13,043		2	51.8	63.8	.	Semmes-Weinstein monofilament test	Current vs. never smokers	N
Hu et al., 2014	China	937	Diabetic inpatients at a clinical diabetes medical center	2	57.7	59.6	9.8	Neurological examination and nerve conduction tests	NS	N
Jaiswal et al., 2014 (Abstract)	USA	1448	Participants in the SEARCH for Diabetes in Youth Study	1	50	19	8	Symptoms and neurological exam	Current vs. never smokers	OR
Wang et al., 2014	Saudi Arabia	552	Persons with diabetes from the community	Both	62.7	53.4			Current+ former vs. never smokers	OR

DMdiabetes mellitus, NSnon-specified, FUPfollow-up, OR odds ratio, RR relative risk, N number or proportion

to what occurs with larger vessels (coronary arteries), smaller arteries, including the vasa nervorum, can be damaged by smoking, which in turn leads to the development and progression of DPN. Smoking has been found to be a causal variable in other microvascular complications such as retinopathy and nephropathy, and similar mechanisms might occur for DPN to damage those target organs [67]. Finally, confounding factors could also contribute to the association between smoking and DPN. Smokers may have poorer adherence to recommended self-care compared with nonsmokers [68]. Smokers also tend to accumulate unhealthy behaviors, including alcohol abuse, lack of physical activity, and diets rich in fat and poor in fruits and vegetables [69]. However, while these factors may contribute to diabetes complications through poorer diabetes control, they do not entirely explain the association that remains after adjusting for diabetes control.

Our study has several strengths. We retrieved and pooled a substantial number of studies assessing the association between smoking and DPN. Contrary to other microvascular complications such as

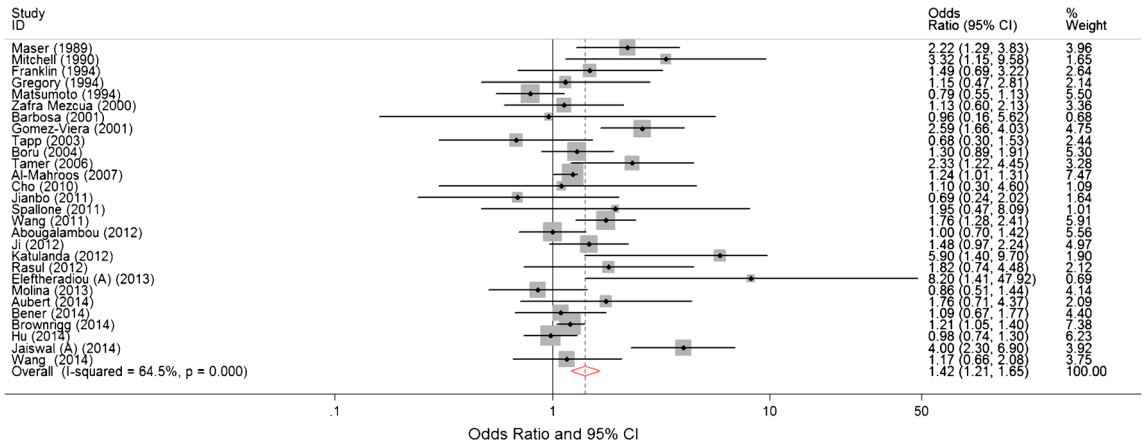

Fig. 3 Forest plot for cross-sectional studies: adjusted odds ratios of neuropathy for smokers versus nonsmokers. Dashed vertical line represents the estimated pooled effect size; points in grey squares with lines represent odds ratios and 95 % CIs of individual studies; the open diamond represents a visual summary of the overall 95 % CI of the effect estimate of smoking on the prevalence of DPN. Studies to the right of the solid vertical line indicate a positive association between smoking and DPN; studies on the left indicate a negative association.

nephropathy or retinopathy, few studies to date had shown a clear positive association between smoking and DPN. Indeed, few studies have been directly designed to measure the impact of smoking on DPN. The complex multifactorial pathogenesis of DPN makes it difficult to measure the effect of smoking on this unique outcome. Many prospective studies and some cross-sectional studies included in our meta-analysis provided adjusted estimates that permitted controlling for some potential confounders and exploring mediating factors.

Our study has several limitations, including the relatively small number of prospective studies and the heterogeneity among studies. Stratified analyses allowed us to address the source of heterogeneity, but given the limited number of prospective studies and the post hoc nature of some of these analyses, we cannot draw firm conclusions regarding the stratified analyses. For example, studies including participants with type 1 diabetes were of higher quality, rendering it difficult to conclude that the association between smoking and DPN was significant only among persons with type 1 but not type 2 diabetes. Another limitation is that the cross-sectional studies were of medium to poor quality. Some did not adjust for the main confounders, some did not assess the outcome clinically, and the smoking exposure was highly variable among studies. Finally, we cannot prove that the association we observed is causal, since all of the studies identified were observational in nature.

Few studies have prospectively assessed the impact of smoking cessation on the control of diabetes and diabetes complications. We identified only one study that prospectively assessed the impact of smoking cessation on DPN [70]. Among 193 participants newly diagnosed with type 2 diabetes and microalbuminuria, 62 % had quit smoking at 12 months. In this population, the prevalence of DPN decreased significantly more in participants who quit smoking than those who continued ($p<0.04$), but no absolute numbers were given. This was also the case for microalbuminuria, peripheral vascular disease, blood pressure, and dyslipidemia. This unique study of suboptimal quality suggests that the effect of smoking on DPN might be reversible, but more research is needed to assess the effect of smoking cessation on diabetes control and microvascular complications.

In conclusion, smoking may be associated with an increased risk of developing DPN. This is an important finding, as this exposure is a modifiable behavior to be targeted in clinical practice based on diabetes guideline recommendations [71]. Future research should be focused on evaluating the impact of smoking cessation on improvement of diabetic neuropathy, and on helping to establish a causal link between exposure and outcome.

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