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

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Abstract

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

Research Design and Methods: A systematic review of PubMed, EMBASE, and Cochrane Clinical Trials databases was conducted from 1966 to November 2014 for cohort, cross-sectional and case-controlled 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 5,558 participants without DPN at baseline. During a follow up ranging from 2 to 10 years, 1,550 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=74.3%; Evidence grade: moderate strength). Overall prospective studies were of moderate to high quality according to the Newcastle-Ottawa scale. Including only the six studies of moderate quality, we found a higher and significant association, with an adjusted OR of 1.73 (95% CI 1.48-2.03, I^2=0%, Evidence grade: moderate strength). 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=64.5%; Evidence grade: moderate strength). Overall cross-sectional studies were of low to moderate quality, and after exclusion of studies of low quality (n=4), the OR was 1.29 (95% CI 1.13-1.48; I^2=50.5%). There was no evidence of publication bias.

Conclusions: Smoking may be associated with an increased risk of DPN in people with diabetes. Future studies are needed to test whether smoking cessation reduces the risk of DPN

in adult with diabetes.

Diabetic peripheral neuropathy, also known as distal symmetrical polyneuropathy or sensorimotor neuropathy, is part of a wider spectrum of microvascular complications of diabetes; other microvascular complications include ulcer/amputations, erectile dysfunction and autonomic dysfunction. Diabetic peripheral neuropathy is the most common microvascular complication of diabetes, affecting approximately 30% of people with diabetes[1-3]. Symptoms include numbness, tingling or 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.

There is a complex interaction between metabolic and vascular factors in the pathogenesis of diabetic peripheral neuropathy[1,4]. Hyperglycemia has been the primary factor described and leads to nerve-cell damage through several mechanisms, including oxidative stress or 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 diabetic peripheral neuropathy, 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; however, prior studies investigating this relationship only included 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, analyzing cross-sectional, case control, prospective and retrospective cohort studies.

Research Design and Methods

Search Strategy and Selection Criteria

We searched PubMed (1966 to November 2014), Embase (1980 to November 2014) and Cochrane Clinical Trials (until November 2014). 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, all studies had to include a control or comparison group of participants with diabetes who did not smoke. The outcome of interest was diabetic peripheral neuropathy.

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

For our search, we combined 3 search themes: 1) diabetes, 2) smoking and 3) neuropathy. The full electronic search is available in the **online appendix 1**.

Study Selection

A first screen of retrieved citations was performed based on titles and abstracts; each citation was screened by 2 different co-authors (CC, MJC, FE or KJS). The inclusion criteria for this first screen were the following: population with diabetes (type 1 or type 2) at baseline, neuropathy as one recorded outcome (not necessarily the primary outcome), and identification as prospective, cohort or cross-sectional studies. We included studies even if they did not mention smoking exposure in the title or abstract (although it was preferable).

Exclusion criteria included gestational diabetes, animal studies, or non-original study design (such as reviews, editorials, and case reports/case series). A second screen was then performed based on full-text review of retained citations. Exclusion criteria were the same as for the first screen, with the addition of the following criteria: 1) Smoking-neuropathy relationship was not assessed and/or data did not allow calculating it by hand; 2) Peripheral neuropathy was not one of the outcomes; or 3) People 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 assess overall quality, we considered several criteria based on the Newcastle-Ottawa scale[8]. The Newcastle-Ottawa scale for cohort studies has 3 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). The Newcastle-Ottawa scale exists for case control studies and we used a modified version 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 to 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 to a maximum of 2 points). We reported the score for each subcategory in the extraction form. We defined Additionally, we evaluated the strength of evidence of the studies using the Cochrane GRADE criteria[9]. By definition, observational studies are considered "Low quality" with the GRADE approach. We upgraded studies to "Moderate

quality" if they met at least one of the following factors: 1. "Large magnitude of effect"; 2. "All plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results show no effect"; or 3. "Dose-response gradient". Studies were downgraded to "Very low quality" if at least one of the following factors was present: 1. "Limitations in the design and implementation of available studies suggesting high likelihood of bias"; 2. "Indirectness of evidence"; 3. "Unexplained heterogeneity or inconsistency of results"; 4. "Imprecision of results"; or 5. "High probability of publication bias".

Studies reported risk ratios (RR), odds ratios (OR) or absolute numbers when describing the relationship between smoking and diabetic peripheral neuropathy. As most prospective and cross-sectional studies reported ORs and not all studies provided information to convert OR into RR, we used OR in our meta-analyses. For studies that did not provide OR or RR, we calculated unadjusted ORs and Confidence intervals (CI) manually.

Data Synthesis and Analysis

We pooled our results using the DerSimonian and Laird random effect model[10] because we expected to have heterogeneity between studies. Anticipated sources of heterogeneity included study population (people 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 3 variables that were added post-hoc: level of adjustment, mean duration of follow-up (for prospective study 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 metaregression 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 squared statistic were calculated[11,12].

125 The possibility of publication bias was assessed using the Begg test and visual inspection of
126 the funnel plot[13,14]. STATA 13 (StataCorp, College Station, Texas) was used for statistical
127 analyses.

Results

Study Selection

In terms of study selection, the initial search included 2006 citations from PubMed, Embase and Cochrane Clinical Trials databases. After excluding duplicates, 1554 unique citations were available (see **Figure 1**). After the first screen, 126 citations were considered for further review. After a second screen, 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 at this point included no estimate (or numbers to allow manual calculation) of the smoking-neuropathy relationship (n=54), outcome other than peripheral neuropathy (n = 30), or inclusion of participants without diabetes (n = 4). Finally, 38 studies were selected for final inclusion in the systematic review and we performed separate meta-analyses for the 10 prospective studies[5,15-23] and the 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**. They include 5,558 participants in total; 3 studies include participants with type 2 diabetes, 6 studies included participants with type 1 diabetes and 1 study 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 history and examination in most studies[5,17-20,23], by electromyography to measure nerve conduction velocities in one study[15], through measure of vibration perception with biothesiometers in one study[22], and by monofilament examinations in two studies[16,21]. The definition of smoking exposure varied between studies; six studies compared ever smokers (i.e. current and former smokers) to never smokers, one

study compared current to non smokers (i.e. former and never smokers) and 3 studies did not clearly specify the smoking comparison groups. Most studies provided OR, two RR and one gave numbers of smokers and non smokers and of participants who developed peripheral neuropathy in each category. All studies except one performed multivariable-adjusted analyses; five controlled for at least A1C and diabetes duration and 4 adjusted for either A1C or diabetes duration and several other confounders - see **Online appendix 2**. The quality of studies varied. Most were considered good quality with maximum points for selection and exposure criteria on the Newcastle-Ottawa scale; however, two were classified as suboptimal for quality with lower scores [15,16] . Using the GRADE criteria, two studies were rated as "Low quality"[21,23], two were downgraded as "Very low"[15,16] because of a poorly defined outcome and risk of selection bias, and six were upgraded to "Moderate quality"[5,17-20,22] mainly due to adjustment for confounding factors and a dose-response gradient. In terms of the incidence of diabetic peripheral neuropathy, 7 studies showed a positive association with smoking and 3 showed a negative association, 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 of 0.86 – 1.85) - see **Figure 2**. There was evidence of high heterogeneity across studies as suggested by the *I-squared* statistic (I^2= 74.3%). Visual inspection of the funnel plot (**Online appendix 3**) and the Begg 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. Trying 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). However, when restricting the analysis to studies of highest quality (i.e with "Moderate quality" using the GRADE criteria for prospective studies) the pooled OR was 1.73 (95% CI 1.48-2.03) with no evidence of heterogeneity (I^2= 0%) (**Figure 3**). In stratified analyses, studies with higher quality, better level of adjustment and longer follow-up showed a stronger

positive association between smoking and diabetic peripheral neuropathy (**Table 2**). Studies including people with type 1 diabetes showed increased risks of diabetic peripheral neuropathy for smokers compared with non-smokers whereas studies with people with type 2 diabetes did not show a statistically significant association between diabetic peripheral neuropathy and smoking.

Smoking and prevalence of diabetic peripheral neuropathy in cross sectional studies

The main individual characteristics of the cross-sectional studies are shown in **Table 3**. They include 27,594 participants in total; 21 studies include people with type 2 diabetes, 3 with type 1 diabetes and 4 with both type 1 and type 2 diabetes. Mean age of participants ranged from 19 to 68 years old and mean diabetes duration ranged from 0 to 20 years. There was a high heterogeneity in the definition of exposure: 7 studies compared current smokers to non smokers (i.e. former and never smokers), 4 studies compared ever smokers (i.e. current and former smokers) to never smokers, 6 studies compared current vs. never smokers, 2 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 8 studies did not specify the comparison groups. The majority of studies expressed the estimate in OR, two used RR and 9 used number or proportions, allowing us to calculate unadjusted OR and 95% CI manually. Seven studies controlled for at least A1C and diabetes duration, one adjusted for either A1C or diabetes duration, 4 adjusted for some confounders but not A1C and diabetes duration and 16 did not adjust for potential confounders.- see **Online appendix 4**. Using the GRADE criteria, most studies were rated as "Low quality" and 4 studies were downgraded as "Very low"[25,28-30] mainly because of selection bias, lack of adjustment for confounders and 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 of 1.21 – 1.65) - see **Figure 4**. There was evidence of some heterogeneity between studies (I^2 = 64.5%). There was no evidence of publication bias as suggested by both visual inspection of the funnel plots (**Online appendix 5**) and the Begg test (p-value = 0.17). In stratified analyses, studies with higher level of adjustment, studies which included participants with type 1diabetes and those comparing ever vs. never smokers showed a higher and stronger association between smoking and diabetic peripheral neuropathy. (**Table 2**) When analyses were restricted to studies with the highest available level of evidence (i.e. "Low quality" using the GRADE criteria) the pooled OR was 1.29 (95% CI 1.13-1.48; I^2=50.5%). When analyzing only studies which provided adjusted estimates OR was 1.59 (95% CI 1.28-1.97, I^2=43.4%).

Conclusions

In summary, we found a positive association between smoking and diabetic peripheral neuropathy prevalence and incidence. Although we performed two different meta-analyses, both had similar findings and suggest that smoking is associated with an increased risk of peripheral neuropathy among people with diabetes. There was substantial heterogeneity for both prospective and cross-sectional meta-analyses. However, in stratified analyses, studies with higher level of adjustment, longer follow-up (prospective studies only) and good level of quality showed a stronger positive association between smoking and diabetic peripheral neuropathy with less heterogeneity. Prospective studies comparing ever smokers (current and former smokers) vs. never smokers as well as those including participants with type 1 diabetes showed a stronger positive association between smoking and diabetic peripheral neuropathy. However these studies were of higher quality and might not necessarily reflect a real effect modification.

In people without diabetes, cigarette smoking has been shown to be positively associated with A1C, a surrogate for metabolic control which reflects average glycemia over the past months[51]. A previous meta-analysis has shown that smokers have a 44% increased risk of developing type 2 diabetes compared with non smokers[52]. Among people with diabetes prior studies suggest that smoking is also associated with insulin resistance[53], higher insulin needs[54,55] and thus poor metabolic control[56-61]. As microvascular complications in people 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 diabetic peripheral neuropathy. However, the fact that the association remains positive after adjustment 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]. It might increase the risk of nerve damage through these pathways in parallel to metabolic factors. Smoking may also have direct toxic effects and induce diabetic peripheral neuropathy via hypoxemia and microvascular insufficiency. Similar to what occurs with larger vessels (coronary arteries), smaller arteries, including vasa nervorum, might be damaged by smoking which, in turn, leads to development and progression of diabetic peripheral neuropathy. Smoking has been found to be a causal variable in other microvascular complications such as retinopathy or nephropathy, and similar mechanisms might occur for diabetic peripheral neuropathy to damage those target organs[67]. Finally, confounding factors might also contribute to the association between smoking and diabetic peripheral neuropathy. Smokers might have poorer adherence to recommended self-care compared with non-smokers[68]. Smokers also tend to accumulate unhealthy behaviors such as alcohol abuse, lack of physical activity or a diet rich in fat and poor in fruits and vegetables[69]. Though these

252 factors might contribute to diabetes complications through poorer diabetes control, they do
253 not entirely explain the association, which remains after adjustment for diabetes control.
254
255 Our study has several strengths. We retrieved and pooled a substantial number of studies,
256 assessing the association between smoking and diabetic peripheral neuropathy. Contrary to
257 other microvascular complications such as nephropathy or retinopathy, few studies had to
258 date shown a clear positive association between smoking and diabetic peripheral neuropathy.
259 Indeed, few studies have been directly designed to measure the impact of smoking on
260 diabetic peripheral neuropathy and the complex, multifactorial pathogenesis of diabetic
261 peripheral neuropathy makes it difficult to measure the effect of smoking on a unique
262 outcome. Many prospective studies and some cross-sectional studies, included in our meta-
263 analysis, provided adjusted estimates which permitted control for some potential confounders
264 and exploration of mediating factors.
265
266 Our study has several limitations including the relatively small number of prospective studies
267 and the heterogeneity between studies. Stratified analyses allowed us to address the source of
268 heterogeneity but due to limited number of prospective studies, some conclusions cannot be
269 drawn. For example, studies including participants with type 1 diabetes were of higher
270 quality, and it is thus difficult to conclude that the association between smoking and diabetic
271 peripheral neuropathy is significant only among people with type 1 diabetes and not in those
272 with type 2 diabetes. Another limitation is that the cross-sectional studies were of medium to
273 poor quality. Some did not adjust for the main confounders, some did not assess the outcome
274 clinically, and the smoking exposure was very variable between studies. Finally, we cannot
275 prove that the association we observed is causal because of the design and limitations of our
276 selected studies.

Few studies have prospectively assessed the impact of smoking cessation on diabetes control and complications. We identified only one study which prospectively assessed the impact of smoking cessation on diabetic peripheral neuropathy [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 diabetic peripheral neuropathy decreased significantly more in participants who quit smoking compared to those who continued ($p < 0.04$), but no absolute numbers were given. This was also the case for microalbuninuria, peripheral vascular disease, blood pressure and dyslipidemia. This unique study of suboptimal quality suggests that the effect of smoking on diabetic peripheral neuropathy might be reversible, but more research is needed to assess the effect of smoking cessation on diabetes control and micro-vascular complications.

In conclusion, smoking might be associated with an increased risk of developing diabetic peripheral neuropathy. This is an important finding as this exposure is a modifiable behavior to be targeted in clinical practice, as recommended in diabetes guidelines[71]. Even though we cannot exclude the possibility of confounding, it seems reasonable based on the consistency of results and plausibility of biological hypothesis that the association might be causal or at least of concern for clinicians. Future research should be focused on evaluating the impact of smoking cessation on improvement of diabetic neuropathy, helping to establish a causal link between exposure and outcome.

Author's contributions:

CC contributed to the study conception and design, the data research, extraction, led the analyses, and drafted the manuscript, MJC and FE contributed to the study conception and design, the data research, extraction, the interpretation of data and the drafting of the manuscript as well as its review, KJS contributed to the data research, extraction, the interpretation of data and reviewed and edited the manuscript. NAR contributed to the study conception, interpretation of data and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Conflict of interest:

NR has been an unpaid consultant to Pfizer and Alere Wellbeing and receives royalties from UpToDate for chapters on smoking cessation. All other authors declare that they do not have a conflict of interest

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Figure 4: Forest plot for cross-sectional studies: Adjusted Odds Ratios of Neuropathy for Smokers Compared with Nonsmokers

Online appendix files

Online appendix 1: Electronic search strategy

Online appendix 1: Level of adjustment and quality of prospective studies

Online appendix 2: Funnel plot for prospective studies

Online appendix 3: Level of adjustment and quality of cross-sectional studies

Online appendix 4: Funnel plot for cross-sectional studies

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 y	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	Biethnic 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 of a drug (Sorbinil) multi-center 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 attended diabetes services	1	54	39	20	Neurological examination and history	NS	9	OR
Gerrits et al.,	Netherlands	973	Subjects from	2	46	66	4	Monofilament	NS	3.1	OR

2008			primary care					examination			
Elliott et al., 2009	Europe	1407	Subjects randomly selected from 31 diabetes clinics	1	48	31.5	13.1	Vibration perception threshold measured by biothesiometers	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

DM = diabetes mellitus, NS = non specified, FUP = follow-up, OR=Odds ratio, RR=Relative risk, N=number or proportion

* In the age-adjusted analyses, compared current smokers to never smokers, in the multivariable-adjusted model compares ever to never smokers

Table 2: Stratified analyses for prospective and cross-sectional studies

Stratified analysis	Total number of trials	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. non smokers (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 (GRADE criteria)					
Prospective studies					0.007
Moderate	6	1.73	(1.48-2.03)	0%	
Low	2	1.57	(0.05-50.83)	91%	
Very low	2	0.27	(0.11-0.65)	0%	
Cross sectional studies					0.75
Low	22	1.29	(1.13-1.48)	50.5%	
Very low	4	1.30	(0.61-2.75)	68.3%	

+ P-value for metaregression using the “metareg” Stata command

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[6666666666666666666]	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 attending 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's charts and neurological examination t	NS	OR
Zafra Mezcua et al., 2000	Spain	504	Patients attending a medical outpatient clinic	2	42	63.9	8.6	Medical chart review	NS	RR
Barbosa et al., 2001	Portugal	93	Patients from primary health cares	2	40	65.4	10.1	Neurological examination	Current vs. never smokers	N
Gomez-Viera et al.,	Cuba	200	Patients diagnosed in clinic	Both	37	.	.	Clinical diagnosis with	NS	RR

2001								neuroinduction exam corroboration		
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 work-ups 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	Neurologic exam and electromyography	Current vs. never smoker	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	OR

									smokers	
Abougalambou et al., 2012	Malaysia	1077	Patient followed in an outpatient diabetic clinic	2	45.2	.	.	Neurologic 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 neurologic 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 symptom 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	Current vs. former + never smokers	N

								monofilament		
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	13043		2	51.8	63.8	.	Semmes-Weinstein monofilament test	Current vs. never smokers	N
Hu et al., 2014	China	937	Diabetic inpatients ate a clinical medical center of diabetes	2	57.7	59.6	9.8	Neurological examination and nerve conduction tests	NS	N
Jaiswal et al., 2014 (Abstract)	USA	1448	Participants to the SEARCH for diabetes in youth study	1	50	19	8	Symptoms and neurologic exam	Current vs. never smokers	OR
Wang et al., 2014	Saudi Arabia	552	People with diabetes from the community	Both	62.7	53.4	.		Current + former vs. never smokers	OR

DM = diabetes mellitus, NS = non specified, FUP = follow-up, OR=Odds ratio, RR=Relative risk, N=number or proportion

Figure 1:

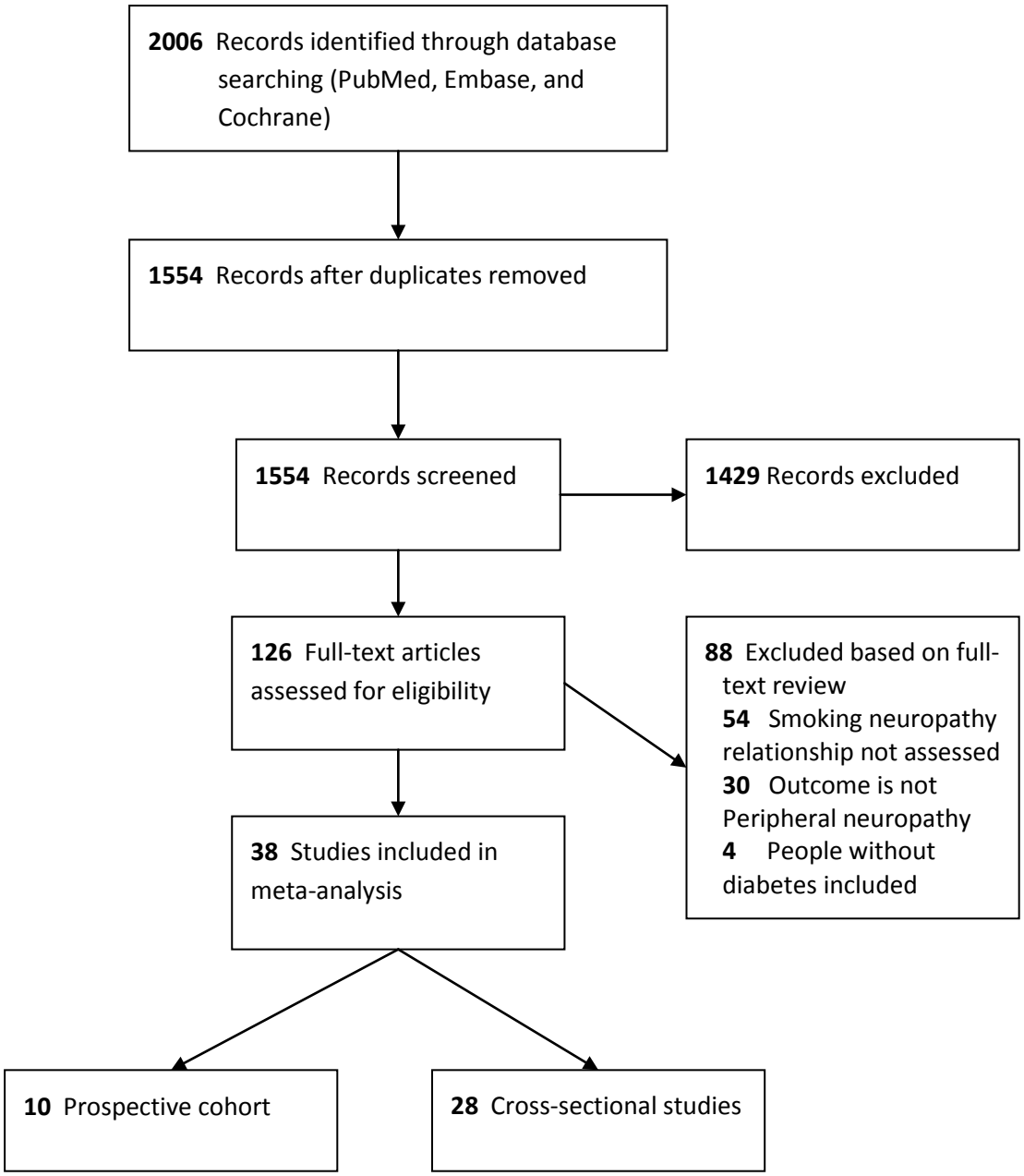
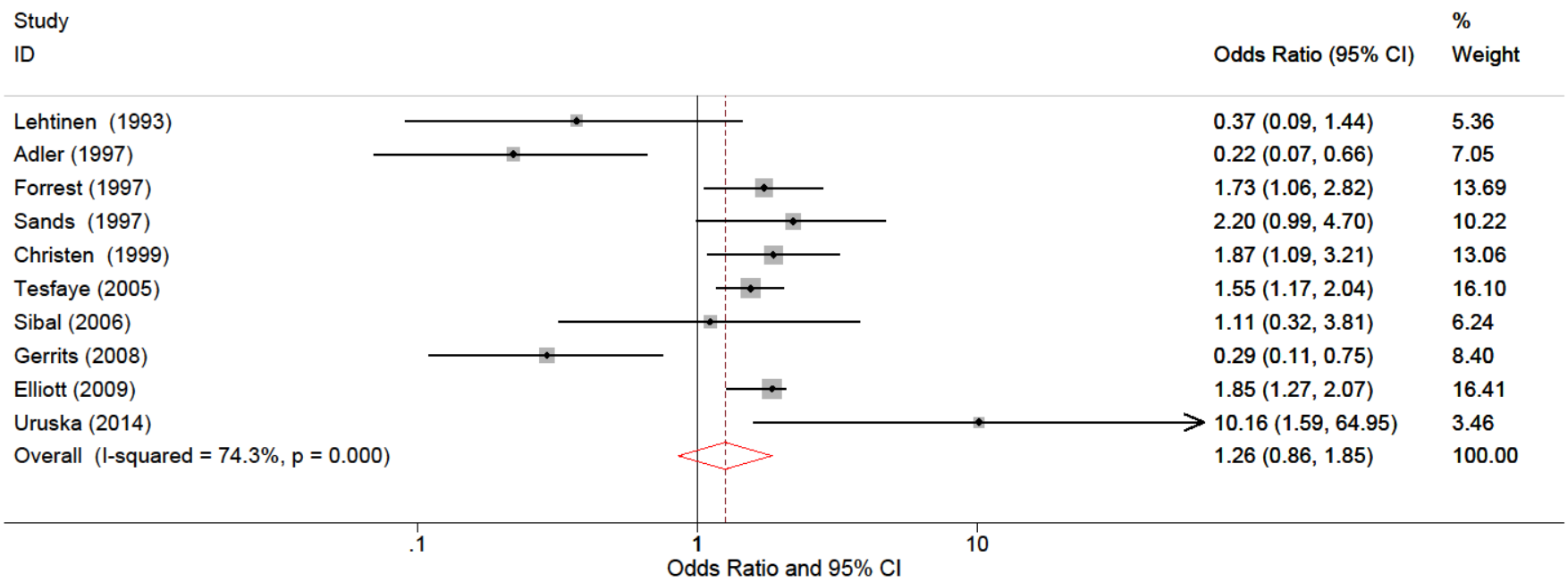
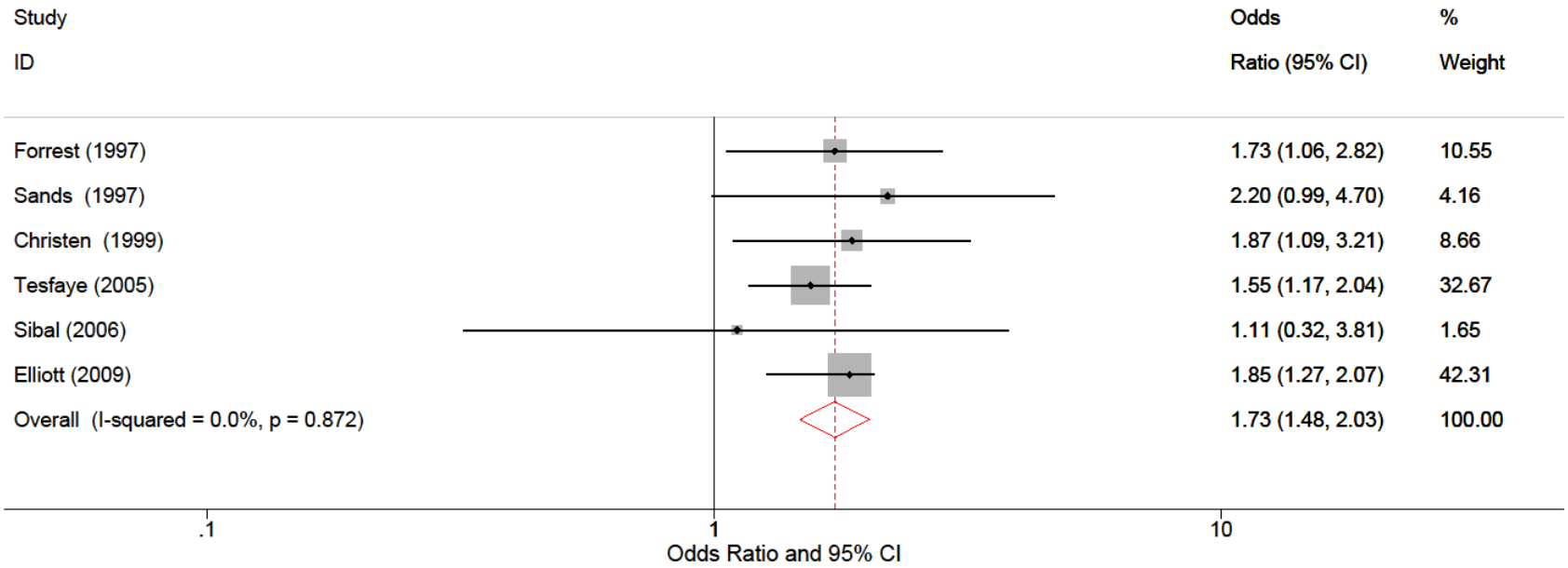

2006 Records identified through database searching (PubMed, Embase, and Cochrane)
1554 Records after duplicates removed
1554 Records screened
1429 Records excluded
126 Full-text articles assessed for eligibility
88 Excluded based on full-text review
54 Smoking neuropathy relationship not assessed
30 Outcome is not Peripheral neuropathy
4 People without diabetes included
38 Studies included in meta-analysis
10 Prospective cohort
28 Cross-sectional studies

Figure 2



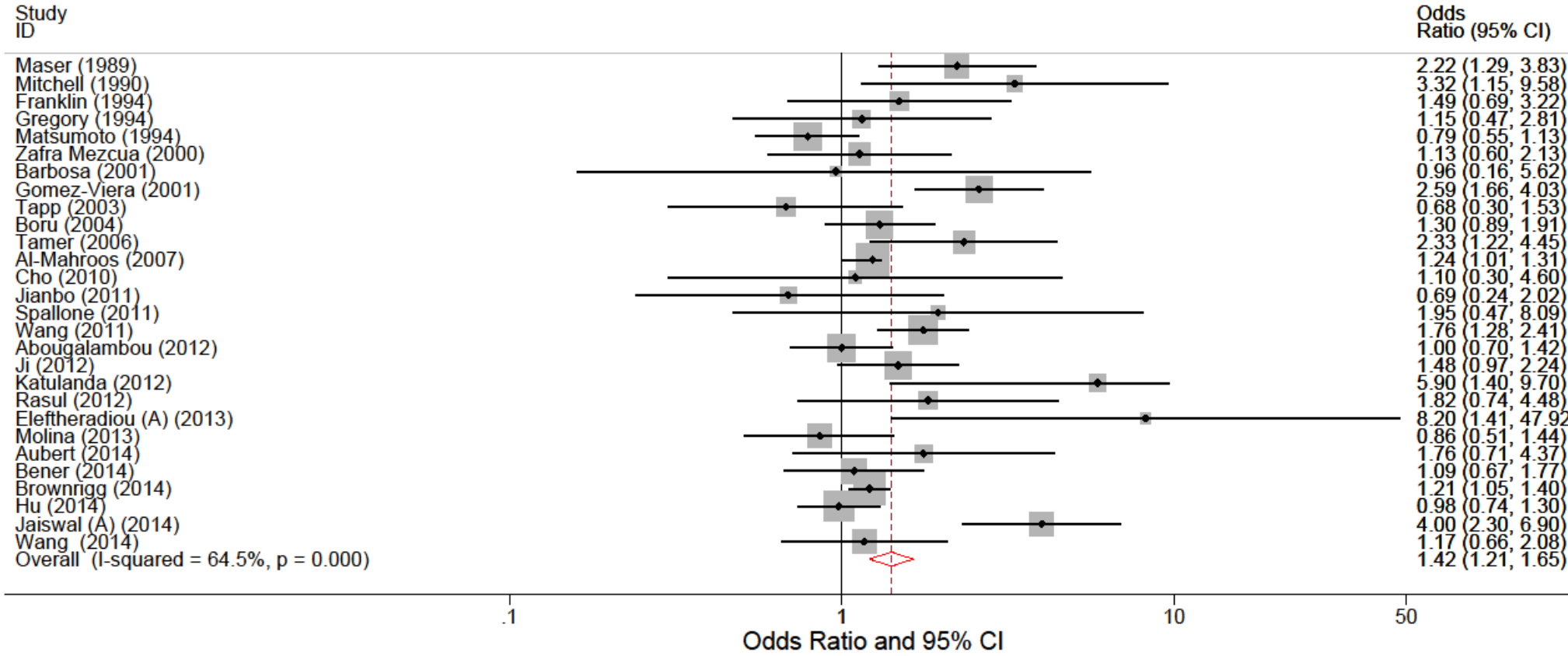
Dashed vertical line represents the estimated pooled effect size estimate; points in grey squares with lines represent odds ratios and 95% CIs of individual studies; the open diamond represent a visual summary of the overall 95% CI of the effect estimate of smoking on the incidence of DPN. Studies on the right of the 1 vertical line indicate a positive association between smoking and DPN, studies on the left a negative association.

Figure 3



Dashed vertical line represents the estimated pooled effect size estimate; points in grey squares with lines represent odds ratios and 95% CIs of individual studies; the open diamond represent a visual summary of the overall 95% CI of the effect estimate of smoking on the incidence of DPN. Studies on the right of the 1 vertical line indicate a positive association between smoking and DPN, studies on the left a negative association.

Figure 4



Dashed vertical line represents the estimated pooled effect size estimate; points in grey squares with lines represent odds ratios and 95% CIs of individual studies; the open diamond represent a visual summary of the overall 95% CI of the effect estimate of smoking on the prevalence of DPN. Studies on the right of the 1 vertical line indicate a positive association between smoking and DPN, studies on the left a negative association.

Online appendix 1

A) Electronic search strategy for PubMed (performed on November 17, 2014):

((polyneuropath*[tiab] OR neuropath*[tiab]) OR ("Peripheral Nervous System Diseases"[Mesh]) OR ((("Diabetic Neuropathies"[Mesh]) OR "Polyneuropathies"[Mesh]) OR "Diabetic Foot"[Mesh])) AND (("Diabetes Mellitus, Type 2"[Mesh] OR "Diabetes Mellitus, Type 1"[Mesh]) OR (diabetes[tiab] OR diabetic*[tiab])) AND ((("Smoking"[Mesh] OR "Smoking Cessation"[Mesh]) OR ("Tobacco Use Cessation"[Mesh] OR "Tobacco Use Disorder"[Mesh] OR "Tobacco, Smokeless"[Mesh] OR "Tobacco"[Mesh])) OR "Nicotine"[Mesh]) OR (smoking[tiab] OR smoker*[tiab] OR cigarett*[tiab] OR tobacco[tiab] OR nicotine[tiab])).

B) Electronic search strategy for Embase (performed on November 17, 2014):

'diabetic neuropathy'/exp OR 'peripheral neuropathy'/exp OR 'polyneuropathy'/exp AND [embase]/lim

'diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus'/exp OR 'insulin dependent diabetes mellitus'/exp AND [embase]/lim

'smoking'/exp OR 'smoking cessation'/exp OR 'smokeless tobacco'/exp OR 'tobacco dependence'/exp OR 'tobacco'/exp OR 'nicotine'/exp AND [embase]/lim

Online appendix 2: Level of adjustment and quality of prospective studies

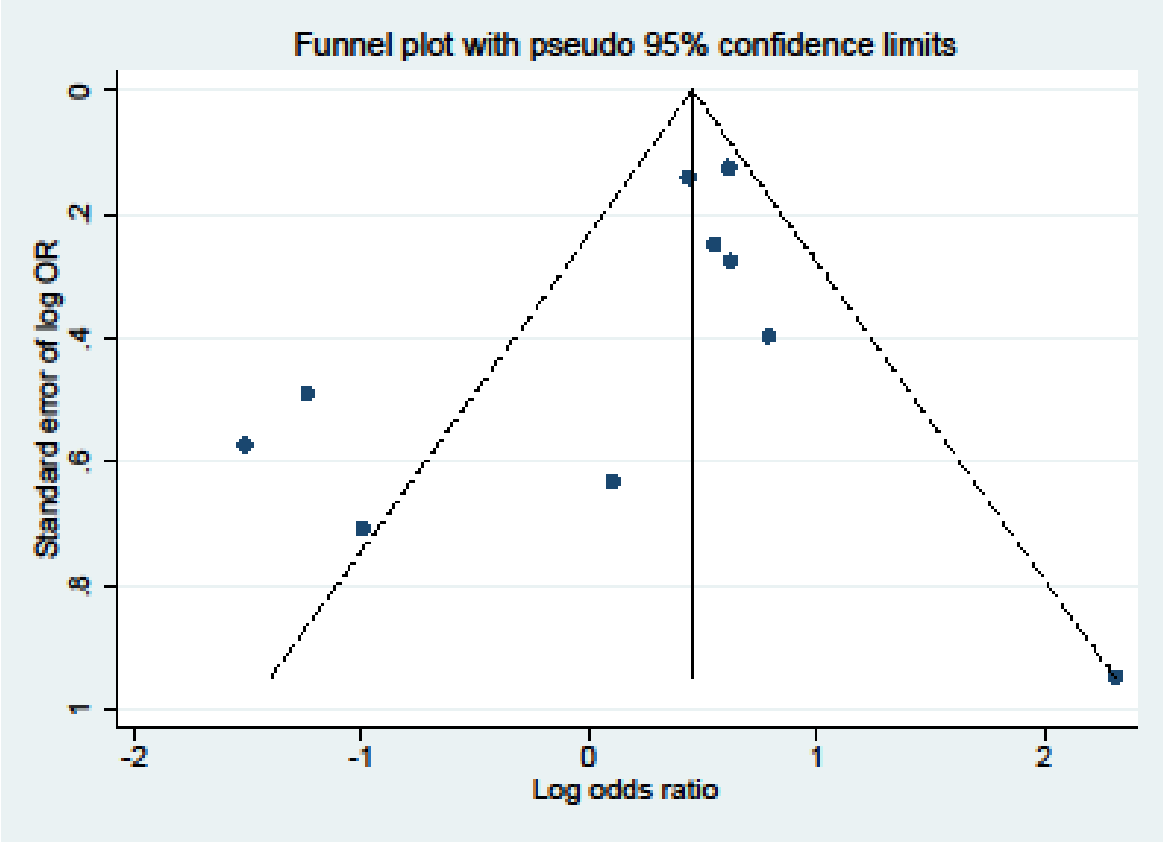
Author, year	Adjustment	Quality score (NOS scale)		
		Selection[1]	Comparability[2]	Exposure[3]
Lehtinen et al., 1993	-	***	-	**
Adler et al., 1997	HbA1c, height, history of ulcer, age, alcohol, albumin, creatinin	*	*	*
Forrest et al., 1997	HbA1c, DM duration, height, hypertension	****	**	***
Sands et al., 1997	HbA1c, DM duration, age, insulin treatment, ethnicity, gender, history of myocardial infarct, angina	****	**	***
Christen et al., 1999	HbA1c, age, drug (Sorbinil vs plabebo), height, gender	****	*	***
Tesfaye et al., 2005	HbA1c, DM duration	****	*	***
Sibal et al., 2006	DM duration, systolic blood pressure, diastolic blood pressure, total cholesterol, glomerular filtration rate, triglycerides, microalbuminuria, retinopathy, foot complications	****	*	***
Gerrits et al., 2008	HbA1c, DM duration, sex, systolic blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, body-mass index, skin autofluorescence	****	**	***
Elliott et al., 2009	HbA1C, DM duration, hypertension, body-mass index, retinopathy, cardiovascular disease history, cholesterol, triglycerides, albumin	****	*	***
Uruska et al., 2014	HbA1c, age, sexe, hypertension	***	*	*

HbA1c= glycated heamoglobin, DM=diabetes mellitus

NOS scale = Newcastle Ottawa scale

[1] Selection : minimum = -, maximum =****, [2] Comparability: minimum = -, maximum = **, [3] Exposure: minimum = -, maximum = ***

Online appendix 3



Online appendix 4: Level of adjustment and quality of cross-sectional studies

Author, year	Adjustment	Quality score (NOS scale)		
		Selection[1]	Comparability[2]	Exposure[3]
Maser et al., 1989[666666666666666666666]	HbA1c,DM duration, HDL-cholesterol, macrovascular disease	*	**	*
Mitchell et al., 1990	HbA1c, DM duration	*	*	*
Franklin et al., 1994	HbA1c, DM duration, age, ethnicity, systolic blood pressure, height, insulin use, alcohol, serum lipids, peripheral vascular disease, fasting C-peptide	*	**	*
Gregory et al., 1994	-	*	-	*
Matsumoto et al., 1994	-	**	-	**
Zafra Mezcua et al., 2000	-	***	-	*
Barbosa et al., 2001	-	*	-	*
Gomez-Viera et al., 2001	-	*	-	*
Tapp et al., 2003	-	*	-	*
Boru et al., 2004	HbA1c, DM duration, retinopathy, hypertension, hyperlipidemia, alcohol	*	**	*
Tamer et al., 2006	HbA1c, DM duration, gender, age, hypertension, cholesterol, triglycerides, drug usage, neuropathic complaints	*	**	*
Al-Mahroos et al., 2007	HbA1c, DM duration, gender, age, hypertension, cholesterol, triglycerides, body-mass index, waist circumference	*	**	*

Cho et al., 2010	Retinopathy, systolic blood pressure, diastolic blood pressure, gamma-glutamyl transferase, Aspartate amino transferase, urine albunine/creatinie, C-reactive protein	*	*	*
Jianbo et al., 2011	-	***	-	*
Spallone et al., 2011	HbA1c, DM duration, gender, age, systolic blood pressure, triglycerides, peripheral arterial disease, Valsalva ratio, type of DM, body-mass index, waist circumference , Michigan Diabetic Neuropathy Score	*	**	*
Wang et al., 2011	DM duration, sex, race, education, self foot exam, foot exam by medical doctor	*	*	*
Abougalambou et al., 2012	-	***	-	*
Ji et al., 2012	-	***	-	*
Katulanda et al., 2012	-	***	-	*
Rasul et al., 2012	-	***	-	*
Eleftheradiou et al., 2013 (abstract)	Sex, age, body-mass index			
Molina et al., 2013	-	**	-	**
Aubert et al., 2014	-	***	-	**
Bener et al., 2014	-	**	-	*
Brownrigg et al., 2014	-	****	-	**
Jaiswal et al., 2014 (abstract)	-			
Hu et al., 2014	-	**	-	**

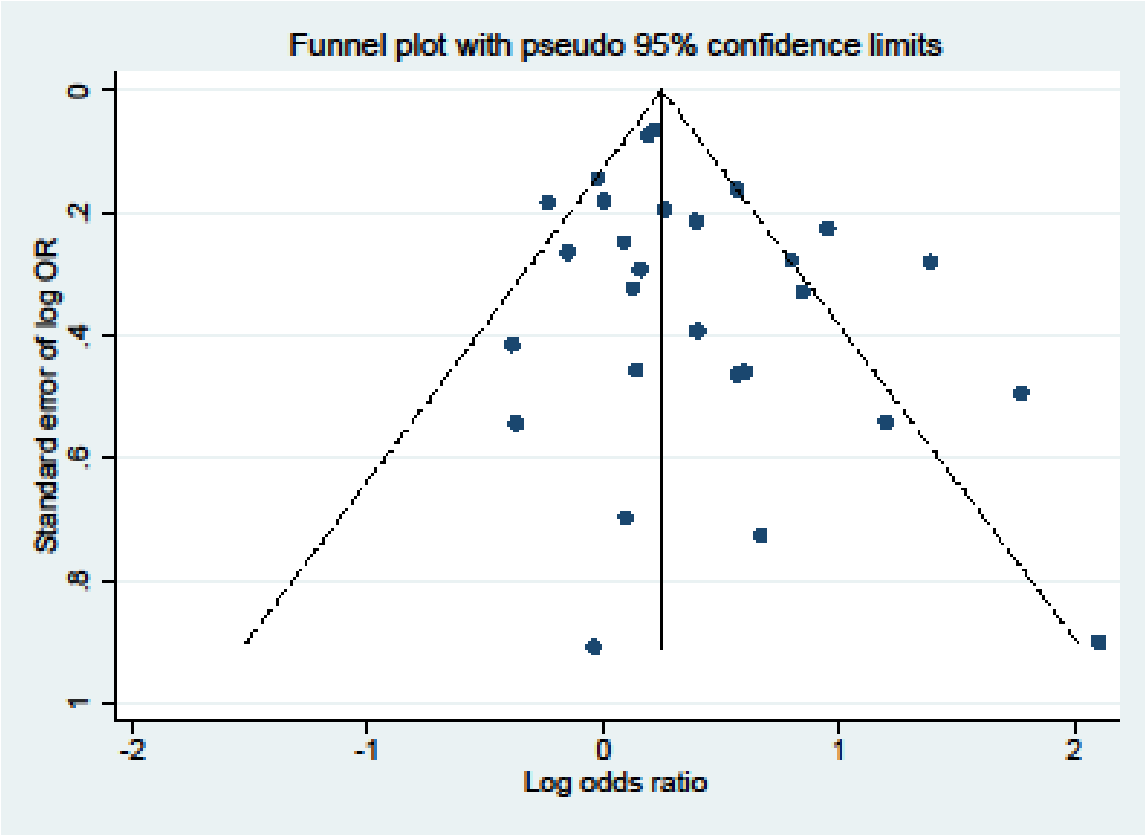
Wang et al., 2014	Sex, age, nationality	***	*	*

HbA1c= glycated heamoglobin, DM=diabetes mellitus, NA= not applicable

NOS scale = Newcastle Ottawa scale

[1] Selection : minimum = -, maximum =***, [2] Comparability: minimum = -, maximum = **, [3] Exposure: minimum = -, maximum = **

Online appendix 5


Funnel plot with pseudo 95% confidence limits
Standard error of log OR
0
.2
.4
.6
.8
1
-2
-1
0
1
2
Log odds ratio