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ACTIVE SMOKING AND THE RISK OF TYPE 2 DIABETES : A SYSTEMATIC REVIEW AND META-ANALYSIS

THESE

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Active Smoking and the Risk of Type 2 Diabetes: A Systematic Review and Meta-analysis

Tabagisme actif et risque de diabète de type 2 : revue systématique et méta-analyse

Introduction : plusieurs études observationnelles suggèrent qu'il existe une association entre le tabagisme actif et l'incidence du diabète de type 2. Toutefois de telles études n'ont jamais été synthétisées de façon systématique.

Objectif : conduire une revue systématique avec meta-analyse des études évaluant l'association entre le tabagisme actif et l'incidence du diabète de type 2.

Méthode : nous avons effectué une recherche dans les bases de donnée électroniques MEDLINE et EMBASE de 1966 à mai 2007, et l'avons complétée par une recherche manuelle des bibliographies des articles clés retenus ainsi que par la recherche d'abstracts de congrès scientifiques et le contact d'experts. Pour être inclues dans notre revue, les études devaient avoir un design de type cohorte, reporter un risque de glycémie à jeun élevée, d'intolérance au glucose ou de diabète de type 2 en relation avec le statut tabagique des participants lors du recrutement et devaient exclure les sujets avec un diabète au début de l'étude. Deux auteurs ont sélectionné de façon indépendante les études et ont extrait les données. Les risques relatifs de diabète étaient ensuite compilés, utilisant un modèle de type « random effect ».

Résultats : la recherche a aboutit à 25 études de cohorte prospectives (N=1'165'374 participants) et a reporté en tout 45'844 cas de diabète de type 2 pendant une durée de suivi s'étendant sur 5 à 30 années. Sur les 25 études, 24 reportaient un risque augmenté de diabète chez les fumeurs par comparaison aux non fumeurs. Le risque relatif (RR) commun de toutes les études était de 1.44 (intervalle de confiance (IC) à 95% : 1.31-1.58). Le risque de diabète était plus élevé chez les fumeurs de plus de 20 cigarettes par jour (RR : 1.61, IC 95% : 1.43-1.80) en comparaison aux fumeurs ayant une consommation inférieure (RR : 1.29, IC 95% : 1.13-1.48) et le risque était moindre pour les anciens fumeurs (RR : 1.23; IC 95% : 1.14-1.33) comparé aux fumeurs actifs. Ces éléments parlent en faveur d'un effet dose-réponse et donc d'une relation de causalité, sans pour autant la prouver.

Conclusion : notre étude révèle que le tabagisme actif est associé avec un risque augmenté de 44% de diabète de type 2. Des recherches futures sont nécessaires pour évaluer si cette association est causale et pour clarifier les mécanismes d'action. Dans l'intervalle, les professionnels de santé devraient mentionner l'éviction du diabète comme une raison supplémentaire d'arrêter de fumer ou de ne pas commencer à fumer.

Active Smoking and the Risk of Type 2 Diabetes

A Systematic Review and Meta-analysis

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Context Observational studies have suggested an association between active smoking and the incidence of type 2 diabetes.

Objective To conduct a systematic review with meta-analysis of studies assessing the association between active smoking and incidence of type 2 diabetes.

Data Sources A search of MEDLINE (1966 to May 2007) and EMBASE (1980 to May 2007) databases was supplemented by manual searches of bibliographies of key retrieved articles, reviews of abstracts from scientific meetings, and contact with experts.

Study Selection Studies were included if they reported risk of impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes in relationship to smoking status at baseline; had a cohort design; and excluded persons with diabetes at baseline.

Data Extraction and Data Synthesis Two authors independently extracted the data, including the presence or absence of active smoking at baseline, the risk of diabetes, methods used to detect diabetes, and key criteria of study quality. Relative risks (RRs) were pooled using a random-effects model. Associations were tested in subgroups representing different patient characteristics and study quality criteria.

Results The search yielded 25 prospective cohort studies (N=1.2 million participants) that reported 45 844 incident cases of diabetes during a study follow-up period ranging from 5 to 30 years. Of the 25 studies, 24 reported adjusted RRs greater than 1 (range for all studies, 0.82-3.74). The pooled adjusted RR was 1.44 (95% confidence interval [CI], 1.31-1.58). Results were consistent and statistically significant in all subgroups. The risk of diabetes was greater for heavy smokers (≥20 cigarettes/day; RR, 1.61; 95% CI, 1.43-1.80) than for lighter smokers (RR,1.29; 95% CI, 1.13-1.48) and lower for former smokers (RR, 1.23; 95% CI, 1.14-1.33) compared with active smokers, consistent with a dose-response phenomenon.

Conclusion Active smoking is associated with an increased risk of type 2 diabetes. Future research should attempt to establish whether this association is causal and to clarify its mechanisms.

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SMOKING IS THE LEADING CAUSE of avoidable death globally.[1] Every year about 4 million people die because of smoking and it is estimated that tobacco causes about 8.8% of deaths worldwide.[2] The magnitude of this public health challenge is growing, and estimates suggest that as many as 10 million people may die from smoking-related causes in 2025.[3] The prevalence of diabetes is also expected to have a major increase by the year 2025,[4] a concerning trend given that diabetes imposes a significant public health burden and large demands on health care systems.[5]

A number of primary studies have assessed the association between smoking and incidence of glucose abnormalities, suggesting that active smoking could be independently associated with glucose intolerance, impaired fasting glucose, and type 2 diabetes; smoking may therefore be a modifiable risk factor for type 2 diabetes. Some of these studies have been summarized in qualitative reviews.[6-8] However, to our knowledge, the quality of existing studies has not been systematically assessed and the clinical features of these studies have not been fully assessed to further characterize this potential association and its determinants.

We therefore conducted a systematic review and meta-analysis of pro-

See also p 2675 and Patient Page.

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spective cohort studies describing the association between active smoking and the incidence of diabetes or other glucose metabolism irregularities.

METHODS

Search Strategy

We conducted a systematic literature search of MEDLINE (1966 to May 2007) and EMBASE (1980 to May 2007) for studies describing the association between active smoking (in contrast to passive or secondhand smoking) and impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes. In addition, we searched the reference lists of all identified relevant publications, reviewed abstracts of selected scientific meetings (the Society for Research on Nicotine and Tobacco and the American Diabetes Association meetings) and contacted experts in smoking cessation and diabetes. We considered articles published in any language. We used a literature searching approach described by Egger et al[9] for identifying observational studies and studies of prognosis.

Three search themes were combined using the Boolean operator "and." The first theme, glucose metabolism irregularity, combined exploded versions of Medical Subject Headings (MeSH) *diabetes mellitus, type 2* or *diabetes mellitus* or *prediabetic state* or *metabolic syndrome X* or *glucose intolerance* or *hyperglycemia* or *glucose metabolism disorders* or *insulin resistance* or *glucose tolerance test* or text words *insulin sensitivity* or *impaired fasting glucose* or *impaired glucose tolerance* or *IGT* or *IFG*. The second theme, smoking, combined exploded versions of MeSH terms *smoking* or *smoking cessation* or *smoke inhalation injury* or *tobacco, smokeless* or *tobacco use cessation* or *tobacco use disorder* or *tobacco* or *nicotine* or text words *nicotine dependence* or *tobacco dependence* or *smoking dependence* or *cigarette**. The third theme, studies with a prospective design, combined exploded versions of MeSH terms *incidence* or *cohort studies* or *follow-up studies* or *prognosis* or *early diagnosis* or *survival analysis* or text words *course* or *predict** or *prognos**. Because we focused on original studies and observational cohort studies, we excluded other design types using the Boolean operator "not": *meta-analysis* (MeSH term) or *review* (publication type) or *case-control studies* (MeSH term). No previous meta-analyses were identified.

Selection Criteria

Two reviewers (C.W. and P.B.) identified articles eligible for further review by performing an initial screen of identified abstracts or titles. Articles were considered for inclusion in the systematic review if they reported data from an original study (ie, no review articles) and reported the incidence of impaired fasting glucose, glucose intolerance, or type 2 diabetes in active cigarette smokers. We used broad inclusion criteria for studies, including all spectra of glucose abnormality (from impaired fasting glucose to diabetes type 2) and smoking status. The observed agreement between reviewers for eligibility of articles on this first screening was 94.6%, corresponding to modest agreement (κ=0.40). Articles were retained when either of the 2 reviewers believed that it should be retained.

The second screening was based on full-text review. To be included, studies had to be cohort studies (prospective cohort or historical cohort) with an adult population (≥16 years) exposed to active cigarette smoking and a comparison group of nonsmokers. One of the outcomes had to be the incidence of impaired glucose tolerance, impaired fasting glucose, or type 2 diabetes. Exclusion criteria were studies that included participants with diabetes at the beginning of the study or that used an inappropriate comparison group (a comparison group that was not nonsmokers or former smokers). The agreement between reviewers for eligibility of articles was 96.0%, with a κ of 0.86. Any disagreement was resolved by consensus.

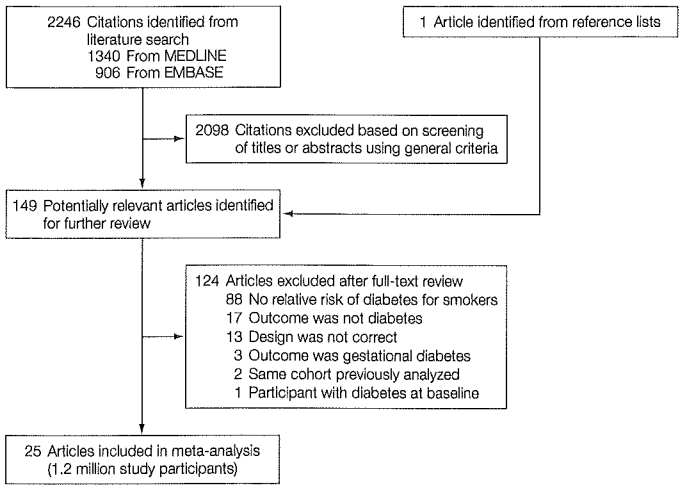
Data Extraction

The key exposure variable was the presence or absence of active smoking at baseline, and the preferred reference group was "never smokers." The majority of studies (n=18) defined a group of former smokers but 7 studies dichotomized the exposure variable (smokers vs nonsmokers) without mentioning whether the nonsmoking group included former smokers. We considered this heterogeneous group as nonsmokers in the pooled analysis and performed a sensitivity analysis that only included studies with a reference group defined as strictly never smokers.

The outcome variable of interest was defined as the presence or absence of type 2 diabetes, impaired fasting glucose, glucose intolerance, or a combination of these. The definitions and diagnostic procedures used to define this outcome varied somewhat across studies because of the different countries and periods in which the studies were performed. The American Diabetes Association and the World Health Organization now share identical diagnostic criteria for type 2 diabetes[10] but definitions have changed over time. Moreover, the prevalence of diabetes can change as a function of diagnostic criteria used.[11] The criteria used in the studies retrieved included the World Health Organization 1985 criteria[12] (fasting glucose threshold ≥140 mg/dL; to convert glucose to mmol/L, multiply by 0.0555), the World Health Organization 1999 criteria[13] or the American Diabetes Association 1997[14] criteria (fasting glucose threshold ≥126 mg/dL), or other criteria (fasting glucose threshold ≥110 mg/dL or ≥120 mg/dL).

In all analyzed studies, participants were screened for diabetes at baseline and excluded if found to have diabetes. However, baseline diabetes screening methods also varied across studies and could be a biological screening (blood tests or urine analysis), patient report, or physician report. The methods used to screen for glucose metabolism irregularities in the follow-up periods varied across studies and included

Figure 1. Flowchart of Meta-analysis



a biological screening, participant's report with or without confirmation (by physician, registry, or subsequent biological testing), or physician's report with or without confirmation (by registry or biological testing).

We then extracted any reported relative risks (RRs), hazard ratios, odds ratios (ORs), or incidence density ratios for the risk of developing diabetes or other glucose metabolism irregularities for active smokers compared with nonsmokers. Both unadjusted and adjusted values were extracted for these measures of risk. If available, we extracted any reported risks of diabetes for former smokers compared with never smokers and for heavy smokers and lighter smokers compared with never smokers.

We also extracted information on key indicators of study quality, using the Meta-analysis of Observational Studies in Epidemiology (MOOSE) standards[15] for reporting of meta-analyses of observational studies. We considered inclusion of consecutive participants in a cohort (all participants presenting with study inclusion criteria during a specific period should be included in a cohort), follow-up duration (the duration should be long enough to allow for a latent period), blinding study personnel evaluating key outcomes to exposure status, and statistical adjustment for the main confounding factors of interest (sex, socioeconomic level, physical activity, age, obesity, diet, ethnicity, increased waist circumference, alcohol consumption, heredity, hypercholesterolemia, blood pressure, fasting blood glucose, comorbidities, and use of antihypertensive drugs).

Statistical Analysis

The RRs were used as the common measure of association across studies. To do this, the hazard ratios and incidence density ratios were directly considered as RRs. The ORs were transformed into RRs using the formula $RR = OR/[(1-P_0)+(P_0 \times OR)]$, in which P_0 is the incidence of the outcome of interest in the nonexposed group.[16] This method of transformation has some limitations and can underestimate the variance of the RRs derived from the ORs.[17,18] We therefore performed a sensitivity analysis that excluded the 5 studies in which this transformation was performed. We also compared the results applying the Miettinen test-based approach[19] for calculating the variance of the lnRR (variance lnRR = variance lnOR × [lnRR/lnOR]).

Meta-analysis was performed using Stata version 9.1 (StataCorp, College Station, Texas). We used the "metan" command in Stata to pool the lnRR across studies using the DerSimonian and Laird random-effects model.[20] Forest plots were used to visually assess the RR estimates and corresponding 95% confidence intervals (CIs) across studies. Analyses were stratified by study quality criteria and by participant characteristics.

To assess for heterogeneity of RRs across studies, the Cochrane Q statistic (significance level of $P \leq .10$) and the I^2 statistic were calculated.[21,22] Meta-regression and sensitivity analysis were performed to assess the effects of selected study quality and clinical factors on diabetes risk.

The possibility of publication bias was assessed using the Begg test and visual inspection of a funnel plot.[23,24] We also performed the Duval and Tweedie nonparametric "trim and fill" procedure to further assess the possible effect of publication bias in our meta-analysis.[21] This method considers the possibility of hypothetical "missing" studies that might exist, imputes their RRs, and recalculates a pooled RR that incorporates the hypothetical missing studies as though they actually existed.

RESULTS

Literature Search

The search strategy retrieved 2246 unique citations: 1340 from MEDLINE and 906 from EMBASE. Of these, 2098 citations were excluded after the first screening based on abstracts or titles, leaving 148 articles for full-text review (FIGURE 1). Hand searching of the bibliographic references of these articles identified 1 additional article, for a total of 149 articles for full-text review. On this review, 124 articles were excluded for the reasons listed in Figure 1, leaving 25 studies for final inclusion in the systematic review and meta-analysis.

Two supplementary studies were identified that had been published only as abstracts from conference proceedings of scientific meetings.[25,26] They were not included in the pooled

Table 1. Characteristics of Studies Included in the Meta-analysis

Source	Cohort Designation	Total No. of Patients	Diabetes Incidence (Cases/ 1000 Person-Years), %	Diabetes Incidence by Smoking Status, No./Total			Diabetes Measure	FGT Used for Diabetes Detection, mg/dL	Baseline Diabetes Screening Method	Maximum Follow-up, y
				Current	Non	Former				
Cassano et al,[31] 1992	Normative Aging Study Cohort of Veterans	1972[a]	NA	76/ 708	51/ 569	98/ 690	Biologically screened	≥140	Biological screening	26
Perry et al,[32] 1995	British Regional Heart Study	7577[a]	2.2	[b]/ 3125	[b]/ 1787	[b]/ 2649	Patient reported	NA	Biological screening	13
Rimm et al,[33] 1995	Health Professional's Follow-up Study	39 745	2.2	65[b]/ 3585	188[b]/ 19 386	239[b]/ 16 774	Patient reported	≥140	Patient questionnaire	6
Kawakami et al,[34] 1997	Japanese cohort of male employees	2312	2.2	[b]/ 1420	[b]/ 583	[b]/ 309	Biologically screened	≥140	Patient questionnaire	8
Njolstad et al,[35] 1998	Cardiovascular Disease Study	11 654	1.2	67/ 5921	95/ 5733	NA	Registry consultation or patient reported	NA	Biological screening	12
Sugimori et al,[36] 1998	Database accumulated from MHTS	2573	NA	[b]	[b]	[b]	Biologically screened	≥110	Biological screening	16
Uchimoto et al,[37] 1999	Osaka Health Survey	6250	7.4	302/ 3880	79/ 1302	69/ 1068	Biologically screened	≥126	Biological screening	16
Strandberg et al,[38] 2000	Helsinki Business Study	1802	2.4	[b]/ 550	[b]/ 608	[b]/ 644	Mixed methods	≥120	Biological screening	20
Nakanishi et al,[39] 2000	Japanese male office workers	1266	9.1	42/ 646	7/ 407	5/ 213	Biologically screened	≥126	Biological screening	5
Manson et al,[40] 2000	Physician's Health Study	21 068	3.0	127/ 2229	323/ 10 511	320/ 8258	Patient reported	NA	Patient questionnaire	12
Will et al,[41] 2001	Cancer Prevention Study I	709 827	3.8	8661/ 274 558	13 312/ 346 060	3424/ 89 209	Physician reported	NA	Patient questionnaire	13
Wannamethee et al,[42] 2001	British Regional Heart Study	6397	2.7	127[b]/ 2942	47[b]/ 1541	82[b]/ 1914	Patient reported	≥140	Biological screening	18
Hu et al,[27] 2001	Nurse's Health Study	84 941	2.5	620[b]/ NA	1446[b]/ NA	1217[b]/ NA	Patient reported	≥140	Patient questionnaire	16
Montgomery and Ekbom,[43] 2002	British National Child Development Study	4917	NA	15/ 1666	13/ 3251	NA	Patient reported	NA	Medical examination and record reviews	17
Sawada et al,[44] 2003	Male Employees Cohort	4745	4.3	[b]/ 3190	[b]/ 1555	[b]	Biologically screened	≥126	Biological screening	14
Sairenchi et al,[45] 2004	Japanese who underwent health checkups	128 141	13.0	[b]	[b]	[b]	Biologically screened	≥126	Biological screening	9
Carlsson et al,[46] 2004	Nord-Trondelag Health Survey	38 805	NA	170/ NA	365/ NA	203/ NA	Patient reported	≥110	Patient questionnaire	11
Eliasson et al,[47] 2004	Northern Sweden MONICA Study	1275	2.4	8/ 235	7/ 761	12/ 279	Patient reported	≥126	Patient questionnaire	13
Lyssenko et al,[48] 2005	Botnia study	2115[a]	NA	[b]/ 799	[b]/ 1277	[b]	Biologically screened	≥126	Biological screening	12
Patja et al,[49] 2005	4 surveys in Finland	41 372	3.3	799/ 12 498	1567/ 22 957	404/ 5917	Registry consultation	NA	Patient questionnaire	30
Waki et al,[50] 2005	JPHC Study	28 893	NA	391/ 7363	586/ 18 338	206/ 3192	Patient reported	NA	Patient questionnaire	10
Tenenbaum et al,[51] 2005	Benzafibrate Infarction Prevention Study	630	NA	18/ 78	32/ 195	48/ 357	Biologically screened	≥126	Biological screening	9
Foy et al,[52] 2005	Insulin Resistance Atherosclerosis Study	906	NA	32/ 128	60/ 424	56/ 354	Biologically screened	≥140	Biological screening	5
Meisinger et al,[29] 2006	MONICA/KORA Augsburg Cohort Study	10 892	5.5	187/ 2866	268/ 4951	217/ 3075	Patient reported	NA	Patient questionnaire	18
Houston et al,[53] 2006	CARDIA Study	4572	3.1[c]	NA/ 1386	NA/ 2565	NA/ 621	Biologically screened	≥126	Biological screening	15

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; FGT, fasting glucose threshold; JPHC, Japan Public Health Center; KORA, Cooperative Research in the Region of Augsburg; MONICA, Monitoring Trends and Determinants of Cardiovascular Disease; MHTS, Multiphasic Health Testing and Services; NA, not recorded or available.
SI conversion factor: To convert glucose to mmol/L, multiply by 0.0555.
[a] Does not equal total for diabetes incidence by smoking status due to missing data.
[b] Missing data by category. There were a total of 194 new cases of diabetes for Perry et al; 509 for Rimm et al; 41 for Kawakami et al; 296 for Sugimori et al; 94 for Strandberg et al; 3300 for Hu et al; 280 for Sawada et al; 7990 for Sairenchi et al; and 127 for Lyssenko et al.
[c] Incidence at 15 years derived from Kaplan-Meier analysis.

analyses because of lack of details on key study variables and because of study quality. Risks were given for subgroups of smokers (heavy and lighter smokers) and were higher for smokers vs nonsmokers. However, there were not sufficient data to calculate a mean risk for smokers and therefore they could not be included with other studies in sensitivity analyses.

The review identified 2 articles that were based on overlapping data from the Nurses' Health study[27,28] and 2 articles that were based on overlapping data from the Monitoring Trends and Determinants of Cardiovascular Disease (MONICA) Augsburg cohort study.[29,30] We avoided duplicate inclusion of data by selecting only the more complete article from each cohort.

Study Characteristics

Characteristics of the 25 selected studies are shown in TABLE 1.[27,29,31-53] All were prospective cohort studies. All studies reported the incidence of diabetes as an outcome of interest except 1 study[53] that reported the incidence of a composite outcome (diabetes and/or impaired fasting glucose). The association between smoking and diabetes was the primary outcome of interest for 16 studies, whereas it was a secondary question in 9 studies.

Diabetes was screened with biological measures in 11 studies, was reported by patients or physicians in 11 studies, and was determined by other methods (hospital medical registries, insurance registries) in 3 studies. Regarding cut-point definitions for diabetes, 6 studies used a fasting glucose threshold of 140 mg/dL or higher, 8 studies used a threshold of 126 mg/dL or higher, 1 study used a threshold of 120 mg/dL or higher, 2 studies used a threshold of 110 mg/dL or higher, and 8 studies did not explicitly mention the criteria that they used. Screening for diabetic participants at baseline was performed using a biological screening for 14 studies and by asking patients or physicians for the other 11.

The selected studies were published between 1992 and 2006, and the number of participants per study ranged from 630 to 709 827, for a total of 1.2 million participants across studies (45 844 incident cases of diabetes). Seven studies were conducted in the United States, 7 in Japan, 6 in Scandinavian countries, 3 in the United Kingdom, 1 in Germany, and 1 in Israel. Eleven studies involved men only, 1 study involved only women, and the other 13 studies included both men and women. Mean body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of participants ranged from 22.3 to 28.4 and mean age at baseline varied from 16 to 60.7 years. The percentage of smokers ranged from 9% to 67% and the pooled percentage of smokers was 35%.

The cohort study quality criteria of blinding to ascertain outcome and recruiting consecutive patients were not explicitly specified in any of the studies that we selected. Follow-up ranged from 5 to 30 years; average (mean or median) follow-up duration was given for only 9 studies. The frequency of follow-up was at least once per year for 9 studies, once every 2 years for 4 studies, and at baseline and the end of the study for the remaining 12 studies. The proportion of patients with complete follow-up to the end of the study was given for 17 studies and ranged from 69.2% to 99.7%.

Adjusted RRs could be determined for all studies, either as reported or by conversion from ORs (TABLE 2). Most risk measures were adjusted for age (22 studies) and BMI (22 studies); fewer were adjusted for physical activity (13 studies), alcohol consumption (14 studies), heredity (10 studies), education (6 studies), diet (2 studies), or waist circumference (3 studies).

Risk of Diabetes for Smokers Compared With Nonsmokers

Among the 25 selected studies, all but one[35] found an association between active smoking and an increased risk of diabetes, although not all were statistically significant. Three studies reported unadjusted RRs[43,52,53]; the pooled crude RR estimate from these studies was 1.89 (95% CI, 1.58-2.27). All 25 studies provided adjusted risks expressed as RRs, hazard ratios, incidence density ratios, or ORs, and the derived fully adjusted RRs ranged from 0.82 to 3.74. Active smokers had an increased risk of developing type 2 diabetes compared with nonsmokers, with a pooled RR of 1.44 (95% CI, 1.31-1.58) (FIGURE 2).

A sensitivity analysis that excluded all studies for which the OR to RR conversion was used had a similar result, with a pooled RR of 1.44 (95% CI, 1.30-1.59). Using the test-based approach by Miettinen[19] to calculate the variance resulted in essentially identical results (RR, 1.44 [95% CI, 1.31-1.58]). In a sensitivity analysis that included only the 18 studies in which the comparison was defined as strictly nonsmokers (without former smokers), the pooled RR was 1.45 (95% CI, 1.31-1.62).

There was evidence of statistical heterogeneity of RRs across studies (Q statistic, 98.08; $P<.001$; I^2, 75.5%). These measurements of heterogeneity were likely driven by the extremely large overall number of participants in our analysis (>1 million). The point estimates of the RRs were consistently greater than 1 in all but 1 study, and study subgroups were more homogeneous.

Stratified Analyses

To explore the study heterogeneity, we performed stratified analyses across a number of key study characteristics and clinical factors (TABLE 3). The finding of increased diabetes risk in smokers was consistently found in all of the stratified analyses. Study quality characteristics did not seem to markedly influence the results, although studies that met more quality criteria tended to report a slightly stronger association of smoking with diabetes incidence. For example, stronger associations between smoking and diabetes incidence were found in studies that were

adjusted to 8 or more confounding factors, if smoking and incidence of diabetes was the primary outcome, and if a biological screening for diabetes was performed at baseline (Table 3).

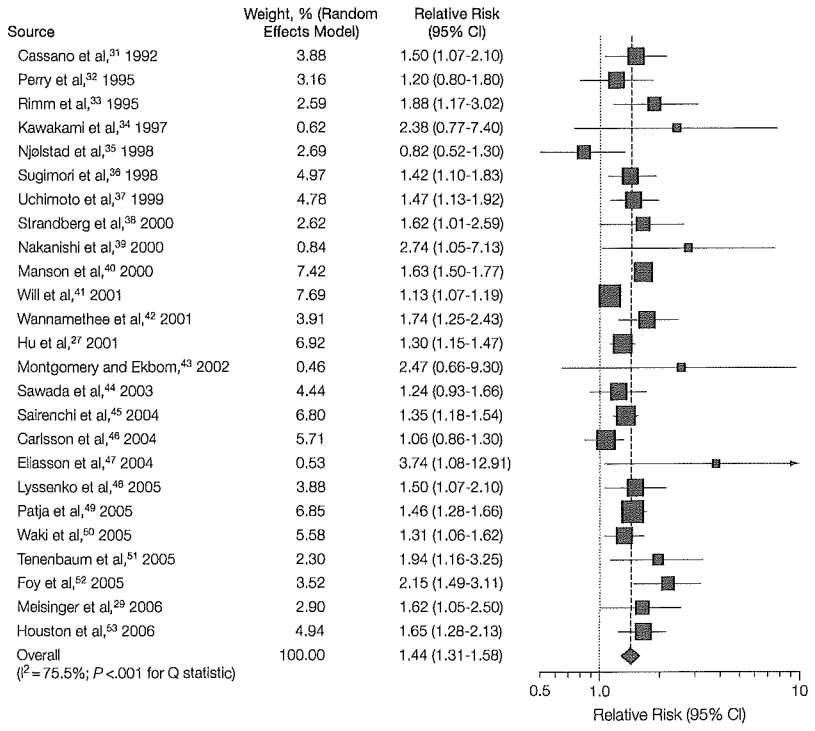
The characteristics of participants included in the primary studies also seemed to be associated with the results. For example, studies reported a stronger association between smoking and diabetes incidence if they included older participants (mean age of participants, ≥50 years) or when the participants tended to be overweight or obese (mean BMI of participants, ≥25) (Table 3). In studies that included both men and women, the pooled risk was similar in both sexes (pooled RR of 1.28 [95% CI, 1.12-1.45] for men and 1.25 [95% CI, 1.06-1.65] for women).

Table 2. Confounding Factors and Methods for Adjustment

Source	Method for Adjustment	Risk Expression	Confounding Factors
Cassano et al,[31] 1992	Proportional hazards regression	HR	Age, BMI, waist circumference
Perry et al,[32] 1995	Proportional hazards regression	RR	Age, BMI, blood pressure, triglycerides, HDL cholesterol, heart rate, uric acid
Rimm et al,[33] 1995	Multiple logistic regression	RR	Age, heredity, BMI, physical activity, alcohol consumption
Kawakami et al,[34] 1997	Proportional hazards regression	HR	Age, heredity, education, BMI, physical activity, alcohol consumption, occupation, type of work shift
Njolstad et al,[35] 1998	Proportional hazards regression	RR	Age, ethnicity, blood pressure, physical activity, total cholesterol, triglycerides, HDL cholesterol, antihypertensive treatment, height, glucose
Sugimori et al,[36] 1998	Proportional hazards regression	HR	Age, heredity, BMI, blood pressure, alcohol consumption, total cholesterol, fasting glucose, eating breakfast, uric acid, dairy intake
Uchimoto et al,[37] 1999	Proportional hazards regression	RR	Age, heredity, BMI, physical activity, alcohol consumption, total cholesterol, triglycerides, HDL cholesterol, fasting plasma glucose, hematocrit
Strandberg et al,[38] 2000	Multiple logistic regression	RR	BMI, blood pressure, triglycerides
Nakanishi et al,[39] 2000	Proportional hazards regression	RR	Age, heredity, BMI, blood pressure, physical activity, alcohol consumption, total cholesterol, triglycerides, HDL cholesterol, levels of fasting plasma glucose, uric acid, hematocrit
Manson et al,[40] 2000	Proportional hazards regression	RR	Age, BMI, blood pressure, physical activity, alcohol consumption, total cholesterol, parental history of myocardial infarction before age 60 years, treatment assignment
Will et al,[41] 2001	Proportional hazards regression	IDR	Age, ethnicity, education, BMI, physical activity, diet, alcohol consumption
Wannamethee et al,[42] 2001	Proportional hazards regression	RR	Age, education, BMI, physical activity, alcohol consumption, antihypertensive treatment, preexisting coronary heart disease
Hu et al,[27] 2001	Multiple logistic regression	RR	Age, heredity, study period, menopausal status, use of postmenopausal hormone therapy
Montgomery and Ekbom,[43] 2002	Multiple logistic regression	OR	Sex, BMI, maternal smoking during pregnancy, age mother left school, birth weight, mother's age at birth, family social class at birth
Sawada et al,[44] 2003	Proportional hazards regression	RR	Age, heredity, BMI, blood pressure, alcohol consumption
Sairenchi et al,[45] 2004	Proportional hazards regression	RR	Age, heredity, BMI, blood pressure, total cholesterol, triglycerides, HDL cholesterol, antihypertensive treatment, fasting glucose status
Carlsson et al,[46] 2004	Multiple logistic regression	OR	Sex, age, BMI[a]
Eliasson et al,[47] 2004	Multiple logistic regression	OR	Age, BMI, follow-up duration
Lyssenko et al,[48] 2005	Proportional hazards regression	HR	BMI
Patja et al,[49] 2005	Proportional hazards regression	HR	Sex, age, education, BMI, blood pressure, physical activity, alcohol consumption, coffee consumption, study year
Waki et al,[50] 2005	Multiple logistic regression	OR	Age, heredity, BMI, blood pressure, physical activity, alcohol consumption
Tenenbaum et al,[51] 2005	Proportional hazards regression	HR	Sex, age, BMI, blood pressure, total cholesterol, triglycerides, presence of NYHA III functional class, glucose, previous myocardial infarction, peripheral vascular disease, anginal syndrome, bezafibrate treatment
Foy et al,[52] 2005	Multiple logistic regression	OR	Sex, age, ethnicity, BMI, waist circumference, blood pressure, physical activity, alcohol consumption, triglycerides, HDL cholesterol, clinic, glucose tolerance status
Meisinger et al,[29] 2006	Proportional hazards regression	HR	Age, heredity, education, BMI, blood pressure, physical activity, alcohol consumption, total cholesterol, triglycerides, HDL cholesterol, survey
Houston et al,[53] 2006	Proportional hazards regression	HR	Sex, age, ethnicity, education, waist circumference, blood pressure, physical activity, diet, alcohol consumption, triglycerides, C-reactive protein, insulin concentration, health insurance

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HR, hazard ratio; IDR, incidence density ratio; NYHA, New York Heart Association; OR, odds ratio; RR, relative risk.
[a] Results persisted after adjustment for age, BMI, physical activity, alcohol consumption, and education.

Figure 2. Adjusted Relative Risks of Diabetes for Current Smokers Compared With Nonsmokers



CI indicates confidence interval. Size of data markers indicates the weight of the study.

The stratified analyses shown in Table 3 suggest a dose-response relationship between smoking and diabetes. The association between smoking and diabetes was stronger for heavy smokers (≥20 cigarettes/day; RR, 1.61 [95% CI, 1.43-1.80]) compared with lighter smokers (RR, 1.29 [95% CI, 1.13-1.48]). The association also was weaker for former smokers (RR, 1.23 [95% CI, 1.14-1.33]) than it was for active smokers.

The association between smoking and diabetes was slightly stronger if there was a biological screening for diabetes during follow-up (RR, 1.49 [95% CI, 1.35-1.63]) compared with cases reported by patient or physician (RR, 1.39 [95% CI, 1.20-1.62]). The association between smoking and diabetes was also stronger for the 6 studies in which a glucose threshold of 140 mg/dL or higher was used (RR, 1.63 [95% CI, 1.33-1.99]) compared with 8 studies in which a glucose threshold of 126 mg/dL or higher was used (RR, 1.47 [95% CI, 1.30-1.65]). In a sensitivity analysis of the 24 studies that reported only on the incidence of diabetes (excluding the 1 study that evaluated the risk of impaired glucose tolerance[53]), the overall pooled result did not change (RR, 1.43 [95% CI, 1.30-1.57]).

Publication Bias

Visual inspection of the Begg funnel plot revealed asymmetry ($P < .001$) (FIGURE 3A). This raises the possibility of publication bias, although the Begg test was not statisitically significant ($z = 1.45$; $P = .15$). Because of this, we undertook a sensitivity analysis using the trim and fill method,[54] which conservatively imputes hypothetical negative unpublished studies to mirror the positive studies that cause funnel plot asymmetry. The imputed studies produce a symmetrical funnel plot (Figure 3B). The pooled analysis incorporating the hypothetical studies continued to show a statistically significant association between smoking and diabetes (RR, 1.32 [95% CI, 1.21-1.44]; $P < .001$).

COMMENT

There is an extensive body of literature reporting on the association between active cigarette smoking and the incidence of diabetes. The 25 studies that we identified report RRs that, while somewhat variable in magnitude, indicate a positive association in all but 1 study. Furthermore, the association persists and remains statistically significant across a number of stratified analyses exploring clinical and study quality factors, and also persists in sensitivity analyses performed to assess the potential effect of varying diabetes outcome definitions and hypothetical unpublished studies. Given this consistency, we conclude that the relevant question should no longer be whether this association exists, but rather whether this established association is causal.

Observational primary studies cannot prove causality. However, the studies in this review do meet several of the Hill criteria[55] for causation. First, there is an appropriate temporal relationship: the cigarette smoking preceded diabetes incidence in all studies. Second, the findings are consistent with a dose-response relationship, with stronger associations for heavy smokers relative to lighter smokers and for active smokers relative to former smokers. However, an observed dose-response relationship can arise from the intensity of clustering with other diabetes risk factors such as lack of physical activity and unhealthy diet. Third, there is theoretical biological plausibility for causality in that smoking may lead to insulin resistance or inadequate compensatory insulin secretion responses according to several[56-61] but not all[62] studies. Smoking also has a clinically significant effect on both oral and intravenous glucose tolerance tests that could influence diabetes detec-

tion.[60,63-65] This could be due to a direct effect of nicotine or other components of cigarette smoke on beta cells of the pancreas, as suggested by the association of cigarette smoking with chronic pancreatitis and pancreatic cancer.[66] Fourth, there is consistency of this association across 24 studies, as shown by the forest plot (Figure 2). Fifth, the strength of the association with diabetes is not negligible in the context of tobacco research.

Conversely, there are also possible noncausal explanations for this association. Smoking is often associated with other unhealthy behaviors that favor weight gain and/or diabetes, such as lack of physical activity, poor fruit and vegetable intake, and high alcohol intake.[67,68] Furthermore, this clustering of behaviors is more prevalent in individuals of lower socioeconomic status.[69,70] Some of these factors were considered and adjusted for

Table 3. Stratified Analyses of Pooled Relative Risks of Diabetes for Smokers

Stratified Analysis[a]	Total No.		Pooled RR (95% CI)	*P* Value	
	Trials	Patients		Heterogeneity	Meta-regression[b]
Study Quality Characteristics					
Adjustment for confounding factors					
Minimal (≤7 factors)	13	933 738	1.32 (1.19-1.46)	.01	<.001
Substantial (≥8 factors)	12	231 636	1.52 (1.38-1.68)	.04	
Incidence of diabetes as the primary outcome					
Yes	16	1.1 million	1.50 (1.33-1.69)	<.001	.001
No	9	66 248	1.34 (1.20-1.49)	.49	
Type of outcome measure[c]					
Biologically measured	11	865 309	1.49 (1.35-1.63)	.30	<.001
Patient or physician reported	11	955 064	1.39 (1.20-1.62)	<.001	
Other	3	54 828	1.29 (0.91-1.82)	.05	
Type of screening for diabetes at baseline[c]					
Biological screening	14	181 327	1.47 (1.33-1.63)	.13	<.001
Patient questionnaire	10	984 047	1.39 (1.20-1.61)	<.001	
Other	1	4917	2.47 (0.65-9.30)	NA	
Fasting glucose threshold, mg/dL					
≥140	6	137 000	1.63 (1.33-1.99)	.06	.13
≥126	8	148 994	1.47 (1.30-1.65)	.30	.27
≥120	1	1802	1.62 (1.01-2.59)	NA	.53
≥110	2	41 378	1.22 (0.91-1.62)	.08	.62
Nonspecified (reference)	8	836 200	1.33 (1.11-1.59)	.002	[d]
Mean follow-up, y					
≤10	9	216 175	1.70 (1.42-2.03)	.14	<.001
>10	15	942 949	1.35 (1.21-1.51)	<.001	
Patient Characteristics					
Mean body mass index[e]					
<25	8	813 427	1.34 (1.13-1.58)	<.001	<.001
≥25	10	112 363	1.57 (1.35-1.82)	.11	
Mean age, y					
<50	15	163 103	1.39 (1.26-1.54)	.09	<.001
≥50	5	772 176	1.62 (1.24-2.13)	<.001	
Smoker type					
Heavy (≥20 cigarettes/d)	6	154 165	1.61 (1.43-1.80)	.36	[f]
Light (<20 cigarettes/d)	6	154 165	1.29 (1.13-1.48)	.21	
Former vs never smokers	17	1.1 million	1.23 (1.14-1.33)	<.01	
Active smokers vs nonsmokers	25	1.2 million	1.44 (1.31-1.58)	<.001	
Sex[g]					
Men	7	932 894	1.28 (1.12-1.45)	.02	[f]
Women	7	932 894	1.25 (1.06-1.46)	.02	

Abbreviations: CI, confidence interval; NA, not applicable because only 1 study; RR, relative risk.
SI conversion factor: To convert glucose to mmol/L, multiply by 0.0555.
[a] Relative risks adjusted for the most variables are taken for each study.
[b] Represents the test for the significance of the effect modification across strata.
[c] Metaregression was performed for the first 2 categories.
[d] No *P* values were given for this group.
[e] Calculated as weight in kilograms divided by height in meters squared.
[f] Meta-regression was not possible.
[g] Included only studies with a population of both men and women.

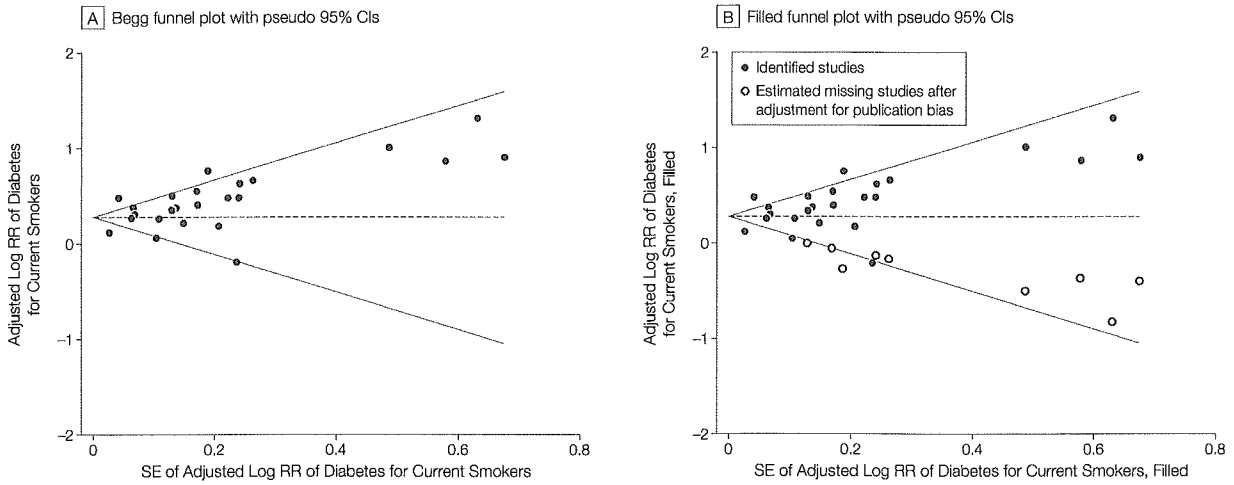
in the studies included in our review, but the extent to which these potential intervening factors were controlled for in the individual studies was generally limited. The lack of adjustment for socioeconomic status (only 6 studies adjusted for socioeconomic status or education), diet (only 2 studies), physical activity (only 13 studies), and alcohol consumption (only 14 studies) could contribute to a noncausal association between smoking and diabetes.

Smokers tend to be thinner than nonsmokers or former smokers, and several studies have shown that smokers' BMI is lower.[71-73] However, there is evidence that smokers (especially heavy smokers) tend to have higher BMIs than lighter smokers and even some nonsmokers.[74] In addition to a clustering of risky behaviors, this finding could be due to the weight cycling phenomenon. Smokers tend to gain weight when they quit smoking; the stronger the dependence, the greater the risk of relapse.[75,76] Therefore, heavy smokers may need several attempts before they definitively quit smoking, and they gain weight during these attempts that they never completely manage to lose when they relapse. Furthermore, with a normal BMI, smokers tend to have a greater risk of abdominal fat accumulation compared with nonsmokers.[62,77-79] The mechanism is not well elucidated but because smoking has an antiestrogenic effect,[80,81] it could be related to a hormonal imbalance that could lead to central obesity. Obesity and weight gain are strong risk factors for developing type 2 diabetes[82,83] and several studies also show that abdominal obesity is associated with the development of type 2 diabetes.[84,85]

Limitations of this meta-analysis must be considered. First, the quality of individual studies was not always optimal, as shown by the general lack of information on blinding and recruiting of consecutive patients for all studies. Second, conversion of ORs to RRs[15] could have underestimated the variance of the RRs derived from ORs. However, a sensitivity analysis that excluded the affected studies and use of the Miettinen test-based approach to calculate variance of the lnRR had only an extremely small effect on the results. Third, there is heterogeneity of RRs across studies, corresponding in part to heterogeneity in study definitions. However, stratified analyses showed pooled RRs consistently greater than 1 across a number of clinical factors. Fourth, the funnel plot analysis showed some asymmetry suggesting the possibility of publication bias. The trim and fill sensitivity analysis did not change the general result (although the strength of the association was slightly attenuated), suggesting that the association is not an artifact of unpublished negative studies. Nevertheless, that possibility is not fully excluded by this method.

Considering the consistent finding of increased diabetes incidence associated with active cigarette smoking across a large number of studies, we believe that there is no need for further cohort studies to test this hypothesis. However, there is a need for studies that include detailed measurement and adjustment for potential confounding factors such as socioeconomic status, education, and exercise with a goal of establishing whether the association with smoking is causal. We recommend that future studies focus on plausible causal mechanisms or mediating factors such as obesity, lack of physical activity, dietary habits, and stress levels.

Figure 3. Funnel Plots Without and With Trim and Fill



The pseudo 95% confidence interval (CI) is computed as part of the analysis that produces the funnel plot, and corresponds to the expected 95% CI for a given standard error (SE). RR indicates relative risk.

Author Contributions: Dr Willi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Willi, Ghali, Cornuz.
Acquisition of data: Willi, Bodenmann.
Analysis and interpretation of data: Willi, Ghali, Faris, Cornuz.
Drafting of the manuscript: Willi, Bodenmann.
Critical revision of the manuscript for important intellectual content: Ghali, Faris, Cornuz.
Statistical analysis: Willi, Ghali, Faris.
Obtained funding: Cornuz.
Administrative, technical, or material support: Bodenmann, Ghali.
Study supervision: Ghali, Cornuz.
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