 International Journal of Epidemiology 2001;**30**:540–546

Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study

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Objective	Only a few prospective studies have examined the relationship between the frequency of cigarette smoking and the incidence of diabetes mellitus. The purpose of this study was to determine whether greater frequency of cigarette smoking accelerated the development of diabetes mellitus, and whether quitting reversed the effect.
Methods	Data were collected in the Cancer Prevention Study I, a prospective cohort study conducted from 1959 through 1972 by the American Cancer Society where volunteers recruited more than one million acquaintances in 25 US states. From these over one million original participants, 275 190 men and 434 637 women aged ⩾30 years were selected for the primary analysis using predetermined criteria.
Results	As smoking increased, the rate of diabetes increased for both men and women. Among those who smoked ⩾2 packs per day at baseline, men had a 45% higher diabetes rate than men who had never smoked; the comparable increase for women was 74%. Quitting smoking reduced the rate of diabetes to that of non-smokers after 5 years in women and after 10 years in men.
Conclusions	A dose-response relationship seems likely between smoking and incidence of diabetes. Smokers who quit may derive substantial benefit from doing so. Confirmation of these observations is needed through additional epidemiological and biological research.

Keywords	Diabetes mellitus, smoking, prospective study
Accepted	5 September 2000

More than a dozen prospective epidemiological studies of diabetes incidence have included cigarette smoking as a possible risk factor[1–15] (Table 1), but most have included it as only one of many variables that might be associated with diabetes. Consequently, many of these studies may have inadequately assessed the frequency and intensity of cigarette smoking. Thus, additional studies that incorporate the frequency and intensity of cigarette smoking using large cohorts and substantial follow-up are needed to enhance our understanding of the relationship between diabetes and smoking. For the present study, we explored the effect of cigarette smoking on diabetes incidence in both men and women by examining data from the American Cancer Society's Cancer Prevention Study I, a large prospective cohort study with detailed information on cigarette smoking.

Methods

The Cancer Prevention Study I was designed to assess risk factors for cancer.[16] More than one million participants aged ⩾30 years were recruited by volunteers in 25 states between October 1959 and March 1960. They completed a baseline questionnaire on their personal habits and medical history, including their smoking history (intensity and frequency) and whether they had ever been told they had diabetes mellitus. American Cancer Society volunteers were instructed to report annually on the vital status of the people they enrolled and to make several attempts to trace a missing participant before filing a report of 'not traced'. In addition, the American Cancer Society volunteers distributed follow-up questionnaires in 1961, 1963, and 1965 with questions on hospitalizations, surgical operations, and diseases diagnosed in the preceding 2 years, current smoking habits, and changes in residence.

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Table 1 Previous prospective incidence studies in which the association between cigarette smoking and diabetes mellitus was examined

Author (Date)	Estimated effect[a]		No. of subjects followed		Description
	Men	Women	Men	Women	
Paffenbarger (1973)[1]	[b]	–	26 954	–	College men were followed for 16–50 years to determine diabetes status. Definition of cigarette smoking not reported.
Medalie (1975)[2]	[b]	–	8688	–	5-year cumulative incidence study of male Israeli government and municipal wokers aged ⩾40 years. Definition of cigarette smoking not reported.
Butler (1982)[3]	[b]	[b]	1303	1951	A large proportion of Tecumseh, Michigan residents aged ⩾20 years were followed for an average of 16 years. Definition of cigarette smoking not reported.
Balkau (1985)[4]	[b]	[b]	118	147	Adult residents of the Pacific Island of Nauru were followed for 6–7 years. Cigarette smoking was defined as ever smoked cigarettes.
Wilson (1986)[5]	[b]	[b]	1377	1881	8-year follow-up of participants in the Framingham Heart Study who were aged ⩾50 years at the 12th examination. Cigarette use at baseline was defined as per cent who smoked cigarettes at baseline.
Ohlson (1988)[6]	[b]	–	766	–	13.5-year follow-up of men living in Gothenburg, Sweden, who were born in 1913. A five-category tobacco use index was created: (1) non-smokers, (2) ex-smokers, (3) smokers of 1–14 g daily, (4) 15–25 g daily, and (5) ⩾25 g daily.
Feskens (1989)[7]	3.9	–	841	–	25-year follow-up study of men free of diabetes at baseline who had lived in Zutphen, the Netherlands for ⩾5 years. Men who smoked >20 cigarettes per day were compared with non-smokers.
McPhillips (1990)[8]	[b]		1847		Men and women aged 40–79 years were followed from baseline to determine cumulative incidence of diabetes 10–15 years later. Definition of smoking not given.
Cassano (1992)[9]	1.5	–	1955	–	Men aged 20–80 years who were enrolled in 1963 in the Department of Veterans Affairs Normative Aging Study were followed for an average of 18 years. Cigarette users at baseline were compared with non-users.
Rimm (1993)[10]	–	1.4[c]	–	114 247	12-year follow-up study of female registered nurses aged 30–55 years free of diabetes, cancer, and cardiovascular disease at baseline. Women who smoked ⩾25 cigarettes per day were compared with non-smokers.
Shaten (1993)[11]	[d]	–	6000	–	5-year cumulative incidence study of men from 22 clinical centres in the US enrolled in the 'usual care' group of the Multiple Risk Factor Intervention Trial. Smoking was defined as per cent of people who smoked cigarettes at baseline.
Hanson (1995)[12]	–	1.0	502	906	Pima Indians were followed for a median duration of 7 years. Among men, smoking was treated as an effect modifier and no estimate of effect was available for them.
Perry (1995)[13]	1.2	–	7097	–	Men aged 40–59 years were selected at random from the age-sex register of one general practice in each of 24 towns in England, Wales, and Scotland and followed for an average of 12.8 years. Current smoking was associated with diabetes incidence, but number of cigarettes was not associated with diabetes.
Rimm (1995)[14]	1.9[c]	–	41 810	–	6-year follow-up study of male health professionals aged 40–75 years free of diabetes, cancer, and cardiovascular disease at baseline. Men who smoked ⩾25 cigarettes per day were compared with non-smokers.
Kawakami (1997)[15]	3.2[c]	–	2312	–	8-year follow-up study of male Japanese employees aged 18–53 years free of diabetes at baseline. Men who smoked ⩾25 cigarettes per day were compared with never smokers.

[a] Fully adjusted risk or rate ratios unless otherwise noted.

[b] The estimate of effect was not available; the authors report that after multivariate modelling, cigarette use was not significantly related to diabetes incidence.

[c] Confidence interval does not overlap 1.0.

[d] The estimate of effect was not available; the authors report that after multivariate modelling, cigarette use protected against diabetes development.

In October 1972, American Cancer Society volunteers distributed a final follow-up questionnaire, this one including questions on personal habits, medical history of disease, and cancer diagnosis and treatment during the respondent's lifetime. Finally, the study attempted to obtain a death certificate for every participant who died before October 1972. The cause of death, which was determined for 92.2% of participants who died during the study period, was coded by a nosologist using

the International Classification of Diseases, Seventh Revision.[17] Additional details of the study have been published previously.[16,18]

An incident case of diabetes mellitus was determined by: (1) a report of diabetes on any of the follow-up questionnaires, or (2) a death certificate listing diabetes as an underlying or contributing cause of death and a review to determine that all previous questionnaires had been completed indicating no previously diagnosed diabetes. For cases, person-years of follow-up were calculated by subtracting the date of the baseline questionnaire from the date of first diagnosis or death. Because date of diagnosis of diabetes was not reported on the questionnaires, we estimated the date of diagnosis as the midpoint of the date of the questionnaire on which diabetes was first reported and the date of the questionnaire that preceded it. People who were alive at first follow-up and failed to complete the first follow-up questionnaire were classified as missing. All others participants were classified as non-cases in the analysis. For non-cases who were lost to follow-up between the first follow-up questionnaire and the 1972 interview, person-years of follow-up were calculated by subtracting the date of the baseline interview from the date of their most recently completed interview. For non-cases who died from causes other than diabetes mellitus, person-years of follow-up were calculated by subtracting the date of the baseline interview from the date of death. For non-cases who completed the 1972 interview, person-years of follow-up were calculated by subtracting the date of baseline interview from the date of the 1972 interview.

Of 453 872 men and 589 811 women aged ⩾30 years with complete baseline questionnaires, we first excluded people reporting a previous diagnosis of diabetes (men, n = 10 075; women, n = 10 753). We then excluded those who did not fill out their own baseline questionnaire (men, n = 71 660; women, n = 30 928). Finally, we excluded anyone we could not classify as a current, former, or never smoker and any person who smoked cigars, cigarillos, or pipes exclusively (men, n = 48 199; women, n = 8663).

We conducted three sex-specific analyses to examine associations between smoking at baseline and the incidence of diabetes mellitus. The first analysis estimated diabetes incidence by five categories of smoking frequency (never smoker, former smoker, current smoker of <1, 1–1.99, ⩾2 packs per day); a second analysis estimated rates by eight categories created by combined smoking frequency and duration into pack-years of smoking (never smoker, current smoker with 0.1–9.9, 10.0–19.9, 20.0–29.9, 30.0–39.9, 40.0–49.9, 50.0–59.9, ⩾60 pack-years). The third analysis examined diabetes incidence for never smokers and for those who at baseline reported quitting for 0.1–4.9 years, 5.0–9.9 years, and ⩾10 years. Packs per day was measured by answers to two questions: (1) Do you now smoke? and (2) If yes, how many cigarettes do you smoke per day? We converted cigarettes per day into packs per day by dividing the number of cigarettes by 20. Pack-years were calculated by multiplying the number of years a person had smoked by the number of packs smoked at baseline, on average, per day. In all three analyses, we adjusted for either age alone or for several baseline characteristics potentially related to diabetes: age (continuous), age^2 (continuous), dietary fat index (continuous), carbohydrate index (continuous), body mass index (BMI) (kg/m^2), BMI^2, race (white, black), educational background (less than high school graduate, high school graduate, some college), alcoholic drinks per day (none, 0.1–1.9, 2.0–3.9, ⩾4.0), and usual level of exercise at work or play (none or slight, moderate, heavy). The fat index was derived by summing weekly days of consumption of seven foods (eggs, cheeses, butter, fatty meats, fried foods, hot dogs, and whole milk) and then dividing the result by seven. The carbohydrate index was derived in identical fashion using the following food items: dessert, candy, pancakes, cereal, pasta, rice, potatoes, fruit, breads, vegetables, salad, and soda.

In all three analyses, we excluded anyone who was missing information on the covariates described above. For the first analysis, we also excluded current smokers with no information on cigarette smoking per day. After these exclusions, our cohort for the first analysis consisted of 275 190 men and 434 637 women, of whom 10 634 men and 14 763 women developed diabetes mellitus during the follow-up. In the second analysis, we also excluded those people who were missing information on duration of smoking—an essential component in calculating pack-years of smoking. This resulted in a cohort consisting of 208 506 men and 405 459 women. In the final analysis, we included only former smokers and those who reported at baseline that they had never smoked cigarettes. This cohort consisted of 117 550 men and 306 050 women.

For each analysis, we used proportional hazards analysis to estimate the incidence density ratio (IDR); a measure of the association between the exposure and diabetes incidence with adjustments as noted.[19,20] We also assessed the validity of the proportional hazard assumption for each of the various models by examining Schoenfeld residuals and their correlations with time.[21]

Results

Among men, heavy smokers (⩾1 pack/day) were younger, greater consumers of fat and alcohol, more likely to have completed some college, more likely to be white, and more sedentary than people who smoked less heavily or not at all (Table 2). Among women in the same type of comparison, heavy smokers were also younger, more likely to be white, heavier drinkers, and more sedentary, but they were not more likely to have gone to college and did not consume more fat (Table 3).

For men, the age-adjusted IDR among current smokers (using never smoker as the referent) increased as packs per day rose (Table 4). This was also true for the fully adjusted IDR: <1 pack per day, 1.05 (95% CI : 0.98–1.12); 1–1.99 packs, 1.19 (95% CI : 1.13–1.26); ⩾2 packs, 1.45 (95% CI : 1.34–1.57). Former smokers had a fully adjusted IDR of 1.07 (95% CI : 1.02–1.13). The association between smoking and diabetes was not modified by body weight. Among men who were of normal weight (BMI <25.0), those who smoked ⩾2 packs had an IDR of 1.43 compared to an IDR of 1.00 for those who had never smoked (referent category). Among overweight men (BMI 25.0–29.9), the comparable IDR were 2.56 and 1.83. Overweight increased the rate of diabetes. For example, among men who had never smoked, men who were obese (BMI ⩾30) or overweight (BMI 25.0–29.9) had substantially higher rates of diabetes than did men who were of normal weight (BMI <25) (i.e. for obese, never smoker, IDR = 3.56; for overweight, never smoker, IDR = 1.83;

Table 2 Means and percentages for selected baseline characteristics in relation to cigarette smoking among 275 190 men in the Cancer Prevention Study I, 1959–1972

	Baseline smoking status				
Characteristic	Never smoker	Former smoker	<1 pack[a] per day	1–1.9 packs per day	⩾2 packs per day
No. studied	64 192	63 162	44 027	86 228	17 581
Mean age (years)	54.2	54.7	52.9	50.2	49.3
Mean fat index[b]	4.3	4.2	4.5	4.6	4.7
Mean carbohydrate index[b]	5.8	5.7	5.6	5.5	5.3
Mean body mass index[b] (kg/m^2)	25.8	25.7	24.8	24.8	25.6
Race (%)					
White	98.6	99.4	97.1	99.1	99.7
Black	1.4	0.6	2.9	0.9	0.3
Education (%)					
Less than high school	36.8	38.0	42.6	38.8	30.8
High school graduate	18.4	17.2	18.6	22.5	21.9
Some college	44.8	44.8	38.8	38.7	47.3
Alcohol drinks per day (%)					
None	72.5	55.5	54.2	48.0	37.3
0.1–1.9	12.4	19.9	19.9	19.7	17.6
2.0–3.9	6.6	13.2	13.6	16.9	20.8
⩾4	8.5	11.4	12.3	15.4	24.3
Exercise at work or play (%)					
None or slight	20.4	25.4	20.4	22.9	33.4
Moderate	63.8	63.7	65.7	62.4	53.9
Heavy	15.8	11.9	13.9	14.7	12.7

[a] One pack equals 20 cigarettes.

[b] See text for definition.

Table 3 Means and percentages for selected baseline characteristics in relation to cigarette smoking among 434 637 women in the Cancer Prevention Study I, 1959–1972

	Baseline smoking status				
Characteristic	Never smoker	Former smoker	<1 pack[a] per day	1–1.9 packs per day	⩾2 packs per day
No. studied	281 868	26 047	71 322	51 230	4170
Mean age (years)	53.1	48.5	48.0	46.8	46.6
Mean fat index[b]	3.8	3.8	3.8	3.8	3.7
Mean carbohydrate index[b]	5.7	5.7	5.6	5.4	5.1
Mean body mass index[b] (kg/m^2)	24.8	24.0	23.2	23.0	23.4
Race (%)					
White	98.4	98.9	97.6	99.2	99.7
Black	1.6	1.3	2.4	0.8	0.3
Education (%)					
Less than high school	37.1	23.5	25.3	25.3	23.4
High school graduate	26.3	27.0	30.6	33.3	31.0
Some college	36.6	49.5	44.1	41.4	45.6
Alcohol drinks per day (%)					
None	80.8	60.3	58.2	50.1	39.4
0.1–1.9	8.8	20.6	21.4	21.9	19.6
2.0–3.9	2.8	9.3	10.3	15.5	20.9
⩾4	7.6	9.8	10.1	12.5	20.1
Exercise at work or play (%)					
None or slight	14.6	20.6	17.0	19.7	27.7
Moderate	76.1	71.5	74.7	71.1	62.3
Heavy	9.3	7.9	8.3	9.2	10.0

[a] One pack equals 20 cigarettes.

[b] See text for definition.

Table 4 Cigarette smoking and risk of diabetes mellitus among 275 190 men and 434 637 women in the Cancer Prevention Study I, 1959–1972

	Baseline smoking status				
Characteristic	Never smoker	Former smoker	<1 pack[a] per day	1–1.9 packs per day	⩾2 packs per day
Men					
Cases	2602	2621	1476	3083	852
Person-years	610 207	578 420	402 440	785 508	155 415
Incidence rate	0.0043	0.0045	0.0037	0.0039	0.0055
Age-adjusted IDR[b]	1.00	1.06	0.90	1.01	1.46
(95% CI)	(ref.)	(1.00–1.12)	(0.84–0.96)	(0.96–1.06)	(1.35–1.57)
Multivariate IDR	1.00	1.07	1.05	1.19	1.45
(95% CI[c])	(ref.)	(1.02–1.13)	(0.98–1.12)	(1.13–1.26)	(1.34–1.57)
Women					
Cases	10 710	803	1715	1368	167
Person-years	2 715 862	255 816	694 454	487 363	38 475
Incidence rate	0.0039	0.0031	0.0025	0.0028	0.0043
Age-adjusted IDR	1.00	0.90	0.72	0.87	1.37
(95% CI)	(ref.)	(0.84–0.97)	(0.69–0.76)	(0.82–0.92)	(1.18–1.60)
Multivariate IDR	1.00	1.07	0.98	1.21	1.74
(95% CI)[c]	(ref.)	(0.99–1.15)	(0.93–1.03)	(1.14–1.29)	(1.49–2.03)

[a] One pack equals 20 cigarettes.

[b] Incidence density ratio.

[c] Adjusted for age, body mass index, alcohol use, race, amount of exercise, educational level, and dietary intakes of fats and carbohydrates. Quadratic terms were also included for age and body mass index.

for normal weight, never smoker, IDR = 1.00). Among men who smoked ⩾2 packs per day, the rate of diabetes increased approximately 40% in all BMI categories (i.e. for obese, ⩾2 packs per day, IDR = 5.24; for overweight, ⩾2 packs per day, IDR = 2.56; for normal weight, ⩾2 packs per day, IDR = 1.43) (data not shown).

For women, compared to never smokers, the fully adjusted IDR for the association of amount of cigarettes smoked with diabetes mellitus were as follows: <1 pack per day, 0.98 (95% CI : 0.92–1.05); 1–1.99 packs per day, 1.20 (95% CI : 1.11–1.29); ⩾2 packs per day, 1.74 (95% CI : 1.49–2.03) (Table 4). As for men who had never smoked, women who were obese or overweight had substantially higher rates of diabetes than did women who were not overweight (i.e. for obese, never smoker, IDR = 4.86; for overweight, never smoker, IDR = 2.27; for normal weight, never smoker, IDR = 1.00)—but, yet again, diabetes increased at a similar rate for heavy smokers in all BMI categories (e.g. for obese, ⩾2 packs per day, IDR = 8.98; for overweight, ⩾2 packs per day, IDR = 3.92; for normal weight, ⩾2 packs per day, IDR = 1.54) (data not shown).

When we examined pack-years we obtained similar results—an incremental association in both men and women (data not shown). For men with 10.0–19.9 pack-years at baseline, the IDR was 1.03, but for men with ⩾60 pack-years it was 1.40. For women, the comparable IDR were 1.11 and 1.61.

Our third analysis tested whether the positive association between cigarette smoking and diabetes could be reversed by removing the exposure. Among men, those who had quit for <5 years had a 20% higher rate of diabetes than never smokers (IDR = 1.20, 95% CI : 1.09–1.32) (Table 5). For those quitting 5–9.9 years before baseline, the IDR was slightly elevated (IDR = 1.12, 95% CI : 1.03–1.21). When cessation was ⩾10 years previous, the IDR was virtually the same as the referent group (IDR = 0.99, 95% CI : 0.92–1.07). Somewhat similar results were obtained for women: <5 years since cessation, IDR = 1.19, 95% CI : 1.04–1.37; 5.0–9.9 years, IDR = 0.99, 95% CI : 0.86–1.13; ⩾10 years, IDR = 1.02, 95% CI : 0.91–1.15).

Discussion

In this study, we found a dose-response relationship between cigarettes smoked per day and the incidence of diabetes mellitus for both men and women. We also found that women who had quit for ⩾5 years and men who had quit for ⩾10 years had essentially the same incidence of diabetes as those who had never smoked cigarettes.

This positive relationship between cigarettes smoked and diabetes incidence has been noted in two other prospective studies.[10,14] Generally, if one can combine evidence from prospective studies of a dose-response relationship with evidence that removal of the exposure diminishes risk, the argument is quite plausible that the exposure has caused the outcome.[22] Even so, several other criteria should be met before seriously entertaining the notion that cigarette smoking is a cause of diabetes. Among these criteria are consistency of findings, having a plausible biological mechanism, and evidence that one has ruled out other possible explanations.[22]

Including our study, only a third of the studies that have looked for an association between cigarette smoking and diabetes incidence, have found a positive relationship.[7,9,10,14,15] We should note, however, that most of the previous studies have either not clearly reported how they measured cigarette smoking, or they reported use of a crude measure of cigarette smoking. In contrast, of the six previous studies that clearly defined smoking exposure as the amount of cigarettes or tobacco consumed per day,[6,7,10,13–15] four reported positive associations, with the strongest effect always occurring in people who smoked approximately ⩾1 pack per day.[7,10,14,15] For

Table 5 Time since smoking cessation and risk of diabetes mellitus among 117 550 men and 306 050 women in the Cancer Prevention Study I, 1959–1972

	Time since smoking cessation (years)			
Characteristic	Never smoker	0.1–4.9	5.0–9.9	⩾10.0
Men				
Cases	2602	521	839	845
Person-years	610 207	110 682	184 461	197 250
Incidence rate	0.0043	0.0047	0.0045	0.0043
Age-adjusted IDR[a]	1.00	1.16	1.08	0.97
(95% CI)	(ref.)	(1.06–1.28)	(1.00–1.17)	(0.90–1.05)
Multivariate IDR	1.00	1.20	1.12	0.99
(95% CI)	(ref.)	(1.09–1.32)	(1.03–1.21)	(0.92–1.07)
Women				
Cases	10 710	213	223	293
Person-years	2 715 862	63 404	79 894	94 469
Incidence rate	0.0039	0.0034	0.0028	0.0031
Age-adjusted IDR	1.00	0.98	0.82	0.89
(95% CI)	(ref.)	(0.86–1.12)	(0.72–0.93)	(0.79–1.00)
Multivariate IDR	1.00	1.19	0.99	1.02
(95% CI)	(ref.)	(1.04–1.37)	(0.86–1.13)	(0.91–1.15)

[a] Incidence density ratio.

example, in comparisons among men who smoked that much with non-smokers, the rate of diabetes was four times as high in the Zutphen study[7] and approximately twice as high in the Health Professional's Follow-up Study.[14] Among female nurses who smoked ⩾25 cigarettes per day, in a comparison with non-smokers[10] the effect was more modest (rate ratio 1.42, 95% CI : 1.18–1.72). Of the two studies that examined amount smoked and did not find a positive association, one included pipe and cigar smokers along with cigarette smokers,[6] a decision that might have influenced the association. Another factor that may explain some discrepancies between studies is that a pack of cigarettes smoked in the 1960s, for example, may provide a different level of exposure than a pack of cigarettes smoked in the 1990s. This might happen as a result of changes in cigarette manufacturing such as production of cigarettes with filters or lower tar and nicotine content.

Several plausible biological mechanisms have been advanced to explain an association between cigarette smoking and incidence of diabetes, but much more research is needed in this area. Some investigators have suggested that cigarette smoking generally increases insulin resistance by altering the distribution of body fat or by exerting a direct toxic on pancreatic tissue.[10,14] Another mechanism that may be advanced parallels that proposed to explain how physical inactivity and obesity increase risk for diabetes: the transport of glucose into fat and skeletal muscle cells is impaired. In the case of smoking, a chemical component of cigarettes may directly alter intracellular glucose transport, or may indirectly alter it through changes in serum chemistry or diminished vascular blood flow.[23] As cigarettes contain about 3500 different compounds in the particulate phase and 500 gaseous compounds in the volatile phase,[24] precisely elucidating such mechanisms may be a formidable task indeed. Finally, a study that used an open-muscle biopsy procedure found that insulin-stimulated glucose transport in skeletal muscle of habitual cigarette smokers was relatively impaired in a comparison with non-smokers.[25] Apparently, this was not due to a direct effect on the number of glucose tranporter proteins but more likely to increased serum concentrations of serum-free fatty acids and triglycerides.

Our study was limited in several ways that may have influenced our findings. First, we used self-reported diabetes along with death certificates to uncover cases of diabetes. During the time of our study, we suspect that less than half the people with diabetes knew that they had it.[26] Therefore, diabetes would be underreported in our study. This is not expected to bias our results, however, unless smokers and non-smokers are differentially aware of their true diabetes status. This could occur, for example, if smokers use health services more frequently than non-smokers resulting in an increased detection of diabetes among smokers. If smokers are diagnosed at higher rates than non-smokers, the resulting bias (away from the null value) would lead us to report a stronger positive association between smoking and diabetes than actually exists. Conversely, if smokers are diagnosed at lower rates than non-smokers, any bias would be toward the null value. In one report, smokers were marginally less likely than non-smokers to use health services.[14] In another report, smokers with diabetes were less likely to have been diagnosed with the disease than were non-smokers with diabetes.[27] Therefore, our results are most likely conservative estimates of the smoking and diabetes association. Second, a substantial number of smokers quit smoking after baseline. Indeed, during the 13 years included in our study, the prevalence of cigarette smoking declined from 54% to 28% in men and from 29% to 21% in women. We could only approximate the dates of quitting smoking and diabetes diagnosis; we did not account for quitters after baseline in our analysis. Our inability to correct for this misclassification probably resulted in our underestimating the true association between smoking and diabetes incidence. Finally, some covariates in our study were measured better than others.

Depending on the association of smoking and diabetes with the potential confounder, residual confounding could have biased our results either positively or negatively. In our study we found that the association of diabetes with well-established risk factors such as higher BMI (rate increased 20% for each BMI unit) and older age (rate increased 3% for each year of age) paralleled or was stronger than that found in a number of other studies;[12,28,29] thus, we were confident that for some of the variables in our study measurement error posed no greater problem than that found in other epidemiological studies.

In conclusion, given the relatively small number of epidemiological studies on diabetes that have assessed smoking frequency and intensity, other methodological limitations of these studies and of the current study, and our lack of understanding of how cigarette smoking might cause diabetes, we need additional evidence that cigarette smoking causes diabetes. To clarify a causal association, future research will need to address these important issues. Notwithstanding the need for such research, our study provides clear evidence of a dose-dependent association between cigarette smoking and diabetes as well as evidence that removal of the exposure diminishes the risk of developing diabetes.

Acknowledgement

We thank Frank Vinicor, MD for his helpful suggestions and expert advice on diabetes.

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