Smoking as a Modifiable Risk Factor for Type 2 Diabetes in Middle-Aged Men

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OBJECTIVE — To examine the effects of cigarette smoking, giving up smoking, and primary or secondary pipe or cigar smoking on the risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS — A prospective study followed 7,735 men aged 40–59 years from general practices in 24 British towns for an average of 16.8 years. Incident cases of physician-diagnosed diabetes were ascertained by repeated postal questionnaires and systematic reviews of primary care records.

RESULTS — A total of 290 incident cases of diabetes were found in 7,124 men with no history of diabetes, coronary heart disease, or stroke. Cigarette smoking was associated with a significant increase in risk of diabetes, even after adjustment for age, BMI, and other potential confounders. The benefit of giving up smoking was only apparent after 5 years of smoking cessation, and risk reverted to that of never-smokers only after 20 years. The risk of diabetes in those who switched from smoking cigarettes to pipe or cigars remained equal to the risk in continuing cigarette smokers. Men who gave up smoking during the first 5 years of follow-up showed significant weight gain and subsequently higher risk of diabetes than continuing smokers.

CONCLUSIONS — Cigarette smoking is an independent and modifiable risk factor for type 2 diabetes. Smoking cessation is associated with weight gain and a subsequent increase in risk of diabetes, but in the long term, the benefits of giving up smoking outweigh the adverse effects of early weight gain.

Cigarette smoking is well established as a causal factor in coronary heart disease (CHD) and stroke. It is not a well-documented risk factor for type 2 diabetes, although diabetes and CHD have many common causal factors (1,2). A recent review of smoking and diabetes concluded that evidence that smoking is associated with the development of diabetes was still preliminary (3). However, three large prospective studies suggest that smoking is associated with the development of type 2 diabetes in men and women (4–6), consistent with evidence linking smoking and insulin resistance (7–9). Smoking cessation is often accompanied by substantial weight gain (10), and obesity is an important risk factor for development of diabetes (11–13). It is not clear whether the benefits of giving up smoking outweigh the adverse effect of weight gain. The effect of pipe or cigar smoking (primary or secondary) on the development of diabetes is also not known. An earlier report from the British Regional Heart Study based on 11.8 years of follow-up observed a significant positive relationship between current cigarette smoking and diabetes after adjustment for age and BMI (2). This association was attenuated in the multivariate analyses, which included possible mediating factors, but no attempt was made to separate potential confounders from mediating factors. The effects of smoking cessation and of primary and secondary pipe or cigar smoking were not examined. This study of the risk of developing type 2 diabetes is based on longer follow-up (16.8 years), and we examine the relationship with cigarette smoking, the influence of smoking cessation, and the effect of primary or secondary pipe or cigar smoking.

RESEARCH DESIGN AND METHODS

— The British Regional Heart Study is a prospective study of cardiovascular disease comprising 7,735 men, aged 40–59 years, selected from age-sex registers of one general practice in each of 24 towns in England, Wales, and Scotland. The criteria for selecting the town, the general practice, and the subjects, as well as the methods of data collection, have been reported previously (14). The study was approved by the Ethical Committee of the Medical Research Council (U.K.). Research nurses administered a standard questionnaire to each participant, including questions on smoking habits, alcohol intake, physical activity, and medical history. Details of classification methods for smoking status, physical activity, and BMI have been reported (14,15). Several physical measurements were recorded, and nonfasting blood samples were collected for measurement of biochemical and hematologic variables. Glucose concentration was measured in serum with an automated analyzer (Technicon SMA 12/60; Technicon, Tarrytown, NY). Diurnal variation in glucose concentration was modest; the peak-trough difference was 0.4 mmol/l (16).

BMI. Weight and height were measured at screening, and BMI was calculated as weight/height-squared (2). Five years later (Q5), the men were asked to state their weight in pounds or kilograms, and BMI was calculated for each man based on

reported weight and on measured height at screening. Obesity is defined as BMI ≥28 kg/m², representing the highest quintile of the BMI distribution in all men at screening.

Physical activity. The men were asked to indicate their usual pattern of physical activity, and a physical activity (exercise) score was derived for each man based on the frequency and type (intensity) of physical activity (15). The men were grouped into six broad categories based on their total score: inactive, occasional, light, moderate, moderately vigorous, and vigorous.

Pre-existing ischemic heart disease and stroke. The men were asked whether a doctor had ever told them that they had angina or myocardial infarction (heart attack or coronary thrombosis), stroke, and a number of other disorders. The World Health Organization (WHO) (Rose) chest pain questionnaire was administered at the initial examination, and electrocardiography (three orthogonal leads) was performed at rest. Men with evidence of CHD were defined as those with a diagnosis of angina or heart attack made by a doctor, a response on WHO (Rose) chest pain questionnaire indicating angina or possible myocardial infarction (17), or electrocardiographic evidence of definite or possible myocardial ischemia or myocardial infarction (18). Men with evidence of CHD but no recollection of a physician's diagnosis of CHD are referred to as "CHD (undiagnosed)."

Smoking
Participants were classified into eight groups, based on their smoking status at screening: *1*) *never-smokers*, those who had never smoked cigarettes and did not currently smoke a pipe or cigars; *2*) *primary pipe/cigar smokers*, those who had never smoked cigarettes and currently smoked a pipe or cigars; *3*) *ex–cigarette smokers*, those who previously smoked cigarettes and did not currently smoke pipe or cigars; *4*) *secondary pipe/cigar smokers*, former cigarette smokers who currently smoked pipe or cigars; and *5–8*) *current cigarette smokers* at four levels: 1–19, 20, 21–39, and 40 cigarettes or more per day, irrespective of whether they have ever smoked pipe or cigars. Information on total duration of smoking was available for both former and current cigarette smokers and was referred to as "smoking years," irrespective of the quantity of cigarettes smoked. Pack-years of smoking were determined on the basis of 20 cigarettes per pack. For ex-smokers, data were available on the number of years since the participant had last regularly smoked cigarettes before screening, referred to as "years since quitting," as well as the number of cigarettes smoked previously (19). In some analyses, all current smokers were combined and ex-smokers were divided into subgroups according to "years since quitting." Smoking status was not available in 16 men; therefore, they have been excluded from the analysis. For ex-smokers, data on years since quitting were not available in 31 men. Blood cadmium concentrations were measured in this cohort and are strongly associated with smoking status (20). Mean blood cadmium concentration has been shown to decline markedly within 1–2 years of quitting and then to converge more slowly to the levels of never-smokers after 10 years of smoking cessation (20).

5th-Year questionnaire
Five years after screening (1983–1985), a postal questionnaire (Q5) similar to that administered at screening was sent to all surviving participants and detailed information obtained on changes in smoking behavior and other risk factors. A total of 98% of the survivors responded (7,275 men), and 7,234 of those survivors provided valid information on their smoking habits at both periods.

Measures of weight change
The percentage change in body weight between screening and the 5th-year questionnaire was determined for each participant (21). Weight loss was defined as a loss of ≥4% of body weight; weight gain was defined as a gain of ≥4% of body weight. Participants who had gained or lost <4% of body weight were classified as stable. The men were grouped into four weight-change categories: *1*) weight loss, *2*) stable, *3*) gain of 4–10%, and *4*) gain of >10%.

Follow-up
All men were followed for all causes of mortality, cardiovascular morbidity, and development of diabetes from screening until December 1995, a mean period of 16.8 years (range 15.5–18.0 years) (22). Information on death was collected through the established "tagging" procedures provided by the National Health Service registers. New cases of diabetes were ascertained by postal questionnaires completed by surviving subjects at the 5th and 12th year after screening, by systematic biennial reviews of primary care records, and by review of all death certificates for any mention of diabetes. A diagnosis of diabetes was not accepted on the basis of questionnaire data unless confirmed in the primary care records, based on the 1985 WHO criteria (23). All men with a history of diabetes, or diabetes diagnosed after screening but in the calendar year of screening, and men with serum glucose level ≥11.1 mmol/l at screening were excluded from analyses ($n = 158$). In addition, all men with recollection of a physician's diagnosis of CHD or stroke ($n = 438$) and men with missing data on smoking ($n = 15$) were excluded; a total of 7,124 men remained. Data on follow-up since the 5th-year questionnaire are presented for an average follow-up of 11.8 years (range 10.5–13.0 years) and overall follow-up has been achieved for 99% of the cohort.

Statistical methods
The Cox proportional hazards model (24) was used to obtain the relative risks for the smoking groups adjusted for age and potential confounders. Smoking was fitted as a categorical variable. In some analyses, all ex-smokers were combined and all current smokers were combined. In the adjustment, physical activity, social class, alcohol intake, pre-existing CHD (undiagnosed), and antihypertensive treatment were fitted as categorical variables. Age and BMI were fitted as continuous variables. The validity of the proportional hazards assumption in Cox's model was checked by fitting a time-dependent interaction variable $X = X(t)$ with the smoking groups, where $X(t) = \log(t)$ (25). Direct standardization was used to obtain age-adjusted diabetes rates/1,000 person-years by smoking categories.

RESULTS — After exclusion of known diabetic patients at screening and men with recall of a doctor diagnosis of CHD and stroke, there were 290 incident cases of diabetes over the mean follow-up period of 16.8 years in the 7,124 men with available information on smoking status, a rate of 2.7/1,000 person-years.

Table 1—*Type 2 diabetes incidence rate per 1,000 person-years and adjusted relative risk in 7,124 middle-aged British men during 16.8 years mean follow-up by smoking status at screening and in relation to years since cessation of smoking cigarettes recorded at screening*

Smoking group	Men (*n*)	Mean BMI	Cases (*n*)	Rate/1,000 person-years	Adjusted relative risk (95% CI)		
					A*	B†	C‡
Never-smokers	1,541	25.60	47	1.9	1.00	1.00	1.00
Primary pipe/cigar smokers	185	25.30	6	2.1	1.04 (0.45, 2.44)	1.18 (0.50, 2.77)	1.24
All current smokers	2,942	24.94	127	2.9	1.52 (1.10,2.10)	1.74 (1.24,2.43)	1.70
Light smokers (1–19/day)	1,065	25.00	49	3.1	1.59 (1.06, 2.37)	1.79 (1.20, 2.68)	1.80
Moderate/heavy smokers (≥20/day)	1,877	24.91	78	2.8	1.50 (1.04, 2.16)	1.71 (1.19, 2.45)	1.64
Secondary pipe/cigar smokers	542	25.49	28	3.4	1.72 (1.07, 2.74)	1.79 (1.20, 2.68)	1.89
Ex-smokers	1,914	26.04	82	2.8	1.40 (0.97, 2.00)	1.33 (0.92, 1.90)	1.32
Time since quitting (years at screening)							
<5	421	26.17	25	3.8	1.98 (1.23, 3.18)	1.89 (1.16, 3.06)	1.78
5–10	392	26.30	15	2.5	1.29 (0.73, 2.29)	1.20 (0.67, 2.15)	1.26
11–19	534	26.05	25	3.0	1.50 (0.93, 2.41)	1.42 (0.87, 2.31)	1.42
≥20	536	25.74	17	2.1	0.99 (0.57, 1.71)	0.95 (0.54, 1.67)	0.98

*A, adjusted for age; †B, adjusted for age and BMI; ‡C, adjusted for age, BMI, physical activity, alcohol intake, social class, indication of pre-existing CHD (undiagnosed), and antihypertensive treatment.

Smoking status and risk of diabetes

All current smokers combined had a significantly higher age-adjusted relative risk of diabetes than never-smokers (reference group) (Table 1). When current smokers were separated by quantity of cigarettes smoked, there was little difference in risk between light (1–19/day) and heavier smokers (≥20/day). Smokers were also divided into three groups based on their smoking years: 1–20, 21–30, and ≥31 years, and risk was increased in all three groups without any clear trend (data not shown). No relationship was seen between pack-years of smoking and the incidence of diabetes among smokers. Ex–cigarette smokers who were not currently smoking pipe or cigars showed lower risk than all current smokers but a higher (nonsignificant) risk than never-smokers. Primary pipe/cigar smokers showed similar risk to never-smokers but secondary pipe/cigar smokers showed significantly higher risk than never-smokers.

Smoking status is strongly associated with BMI: weight was higher in ex–cigarette smokers and lowest in cigarette smokers (Table 1). Adjustment for age and BMI increased the risk seen in current smokers but had little effect on risk estimates in other smoking categories. Further adjustment for other potential confounders, i.e., physical activity, social class, alcohol intake, pre-existing CHD (undiagnosed), and antihypertensive treatment, made small differences to the relative risks seen. Cadmium concentrations were strongly and positively related to risk of diabetes. However, when analysis was restricted to current cigarette smokers, no trend in risk of diabetes was observed.

Exclusion of men with incident CHD and stroke

The increased risk of diabetes associated with cigarette smoking and secondary pipe or cigar smoking was seen even after exclusion of 1,116 men who had developed a major CHD or stroke event during the 16.8-year average follow-up, although the relative risk associated with cigarette smoking, adjusted for all variables as shown in Table 1 (column C), was slightly attenuated (relative risk 1.52, 95% CI 1.03–2.24; current versus never-smokers). The adjusted relative risk of secondary pipe or cigar smoking was 1.76 (95% CI 1.04–2.98). Further exclusion of 420 men who reported calf pain on walking on the level (possible peripheral vascular disease) in the 1992 questionnaire resulted in no change in the findings.

Smoking cessation and risk of diabetes

Ex-smokers were separated according to the number of years since quitting measured at baseline (Table 1). Risk of diabetes decreased with increasing years since quitting. After adjustment for age and BMI, the benefit of giving up smoking was apparent in those who had quit >5 years before screening: risk reverted to that of never-smokers in those who had given up at least 20 years before screening. Men who had given up in the 5 years before screening showed slightly higher risk than current smokers, even after adjustment for BMI. Further adjustment for other confounders slightly reduced the risk in this group. Because those who quit smoking in the 5 years before screening are more likely to have smoked for a longer period, we examined the effects of time since quitting on the risk of diabetes, stratified by the number of years smoked (<30 vs. ≥30 years). Among men who had quit smoking for >5 years before screening, the number of years smoked made no significant difference to risk. However, in recent quitters, the increased risk was seen only in those who had smoked ≥30 years (data not shown).

Smoking, BMI, and high serum glucose level

Obesity and high serum glucose level are strong risk factors for type 2 diabetes (2). The relationship between smoking and diabetes was examined by presence or absence of obesity or high serum glucose level (≥6.2 mmol/l). Age-adjusted rates of diabetes were three to four times higher in obese men than in nonobese men and in those with higher concentrations of serum glucose. After adjustment for a wide range of possible confounding variables, current cigarette smoking and secondary pipe/cigar smoking were associated with increased risk of diabetes in both nonobese and obese men as well as in both serum glucose groups. The benefit of giving up smoking was seen in obese sub-

Table 2—*Quitting smoking recorded at Q5 (5 years after screening), BMI and weight change at Q5, and adjusted relative risk of type 2 diabetes over the subsequent 11.8-year follow-up*

| Smoking group | n | Percentage of weight gain | | Mean weight gain† | BMI | | Adjusted relative risk of diabetes (95% CI) | |
		Any	>10%		Q1	Q5	A‡	B§
Never-smokers*	1,576	25.9	3.9	7.1	25.49	25.75	1.00	1.00
Continuing smokers	1,980	32.2	7.2	8.3	24.90	25.26	1.59 (1.04, 2.43)	1.61 (1.05, 2.46)
Secondary pipe/cigar smokers	430	31.6	6.7	7.9	25.46	25.82	2.16 (1.26, 3.71)	2.15 (1.24, 3.70)
Ex-smokers at Q1 and Q5	1,643	25.6	3.2	7.1	25.92	26.12	1.43 (0.93, 2.18)	1.45 (0.95, 2.21)
Recent ex-smokers (smokers at Q1, ex-smokers at Q5)	567	54.3	19.2	9.4	25.07	26.24	2.34 (1.41, 3.88)	2.03 (1.22, 3.37)

*Includes primary pipe and cigar smokers; †only in men who gained >4% body weight; ‡A, adjusted for age, physical activity, social class, alcohol intake at screening, quitting drinking alcohol, preexisting CHD, antihypertensive treatment at Q5, and initial BMI; §B, as A, but adjusted for BMI at Q5 rather than initial BMI.

jects and those with higher serum glucose levels (data not shown).

Giving up smoking during 5 years of initial follow-up and risk of diabetes

In men who were current smokers at screening, we examined the effect of giving up smoking during the first 5 years of follow-up on weight gain from Q1 to Q5 and on risk of diabetes in the subsequent 11.8-year follow-up (Table 2). The analysis was confined to the subgroup of men who completed the 5th-year questionnaire (Q5). Further exclusion was made of men in whom CHD, stroke, or diabetes had been diagnosed between screening and the 5th-year questionnaire, leaving 6,196 men and 208 incident cases over the follow-up period of 11.8 years (10.5–13.0) from Q5.

Continuing smokers and secondary pipe/cigar smokers showed significantly higher risk than never-smokers. Long-term ex-smokers showed intermediate risk. A total of 23% of current smokers at screening (n = 567) claimed to have quit smoking at Q5 (recent ex-smokers). These men were far more likely to gain weight than any other smoking group. At screening, these recent ex-smokers had similar, though slightly higher, BMI levels than continuing smokers, but at Q5, weight was highest in the recent ex-smokers. Recent ex-smokers showed the highest relative risk of diabetes after adjustment for initial BMI and potential confounders (Table 2, column A). Adjustment for attained BMI at Q5 rather than initial BMI reduced the risk in recent ex-smokers (Table 2, column B), but they still showed higher risk than continuing smokers and similar risk to secondary pipe/cigar smokers. The increased risk in

recent ex-smokers was seen in both men who had not gained weight (relative risk 2.72) and men who had gained weight (relative risk 2.31). The pattern of risk of diabetes in relation to smoking cessation was broadly similar to that seen at screening (Table 1).

CONCLUSIONS — In this study of middle-aged British men, risk of type 2 diabetes was significantly increased in cigarette smokers compared with never-smokers, despite their lower body weight. The relationship was stronger after adjustment for BMI and persisted after additional adjustment for other potential confounders. This is consistent with recent prospective studies of men in the U.S. and Japan (4,5) and of women in the U.S. (6). However, in contrast to these three studies, which suggested a dose-response or threshold relationship with the amount of cigarettes smoked, we observed a similar significant increase in risk in both light smokers (1–19 cigarettes per day) and heavy smokers (≥20 cigarettes per day). The U.S. Health Professional Study (6-year follow-up) reported a dose-response relationship with increasing amount of cigarettes from 1.37 in light smokers (1–14 cigarettes per day) to 1.94 in heavier smokers (≥25 cigarettes per day) (4). The U.S. Nurses Health Study of women (8-year follow-up) observed a relative risk of 1.42 in women who smoked ≥25 cigarettes per day compared with those who had never smoked (6). No increase was seen in light smokers (1–14 or 15–24 cigarettes per day). The Japanese Study (8-year follow-up) also reported a threshold effect with increased risk in those smoking ≥16 cigarettes per day) (5). The study also suggested that starting

smoking at a younger age was associated with an increased risk. However, among current smokers in our study, risk was increased irrespective of smoking years or age at starting smoking (data not shown). This discrepancy may relate to the longer follow-up in our study (average 16.8 years) compared with 6–8 years in the other three studies. Our earlier report based on 11.8-year follow-up showed a positive but weaker association between cigarette smoking and risk of diabetes than that observed in the present study (2). Therefore, it may take longer for the effects of light smoking to become apparent. It is unlikely that the lack of dose-response seen in this study is due to under-reporting of cigarette smoking in the light-smoking group, because blood cadmium level, which is a strong biological marker of smoking, showed a strong dose-response relationship with number of cigarettes reported. When analysis of the risk of diabetes in relation to cadmium concentration was restricted to current smokers, no trend in risk was seen, supporting the absence of a dose-response relationship with quantity of cigarettes smoked or pack-years.

Earlier studies

Of the three earlier studies based on different follow-up periods—the Zutphen study (25 years) (26), the Framingham Study (8 years) (27), and the Israeli Study (5 years) (28)—only the longer-duration study (Zutphen) showed cigarette smoking to be an important risk factor. The Zutphen study reported a significant threefold increase in risk of diabetes among men smoking ≥20 cigarettes per day compared with nonsmokers, but no information was given about light smok-

ers (26). The inconsistency between our data and some of the earlier studies may reflect our longer duration of follow-up and the inclusion of ex-smokers in their baseline group.

Pipe/cigar smokers

Primary pipe/cigar smokers showed similar risk to never-smokers, but men who switched from smoking cigarettes to pipe/cigar showed increased risk similar to current cigarette smokers. The high risk of diabetes retained in secondary pipe/cigar smokers may reflect inhalation habits and tobacco consumption levels as well as the chronic effects of previous cigarette smoking (29).

Smoking cessation and risk of diabetes

Men who quit smoking within 5 years before screening were substantially heavier than current smokers, and significant weight gain was seen in subjects who quit smoking during the first 5 years of follow-up. Men who quit during the 5 years before screening showed no reduction in risk compared with current smokers and the increased risk in this group was most marked in obese subjects. In addition, the increased risk was confined to those who had smoked for ≥30 years (data not shown). The residual effects of smoking seem to be of considerable importance to risk of diabetes. Men who quit smoking during the first 5 years of follow-up (recent ex-smokers) showed increased risk compared with continuing smokers, suggesting that there is an increase in risk of diabetes after smoking cessation, possibly due to the combined chronic effects of smoking and the substantial weight gain. However, in the long term, quitting smoking was associated with a reduction in risk compared with current smokers. As the increased risk is seen in both men who gained weight and in men who did not, it suggests that the residual effects of smoking are possibly of greater importance than the weight gain.

Biological mechanisms

Smoking may contribute to the development of diabetes through alterations in fat distribution (6), which is associated with insulin resistance (8,30), and through a direct toxic effect on pancreatic tissue (6). It has been shown that smoking cessation increases insulin sensitivity and improves the lipoprotein profile, despite a modest increase in weight (31). This suggests that the smoking-related risk of diabetes is reversible in individuals who quit smoking. In the long run, based on this study, the beneficial effects of smoking cessation outweigh the effects of weight gain; ex-smokers of ≥20 years' duration are no longer at increased risk of diabetes.

Sources of bias

Reliance on documented physician-diagnosed cases of diabetes represents an important limitation of this study, considering the prevalence of undiagnosed diabetes. However, the key methodological issue in this study is the possibility of ascertainment bias. It may be argued that smokers may be more likely to have had contact with their general practitioner and, thus, are more likely to have undergone diagnostic testing for diabetes. However, the positive relationship was still present after exclusion of all men who had developed CHD or stroke during follow-up, who would certainly have been seen by their physicians. Furthermore, until recently, there was no systematic screening for diabetes in the U.K. among people at high risk of diabetes but without clinical symptoms. Therefore, the increased risk seen in both light and heavy smokers is unlikely to be due to bias in ascertainment.

Unmeasured and residual confounding

Studies of this nature will always carry uncertainty arising from unmeasured and residual confounding. For example, we have no measurements of dietary intake or any measure of central obesity, which are both areas of possible confounding. Although it could be argued that as the effects of smoking on central obesity may mediate (in part) the effect of smoking on risk of diabetes, adjustment for central obesity may not be appropriate. There is also the possibility of residual confounding arising from imprecise measurement of those variables that have been entered into the adjustment processes, especially with regard to physical activity.

There now seems to be sufficient evidence to indicate that cigarette smoking is an independent and modifiable risk factor for type 2 diabetes. Individuals who switch from smoking cigarettes to pipe/cigars retain the risk level of continuing cigarette smokers. Although smoking cessation is often accompanied by weight gain, the long-term benefit of quitting smoking outweighs the adverse effects of weight gain. Regular moderate physical activity and dietary modification should be actively encouraged upon cessation of smoking (32,33).

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