

# Smoking and Risk for Diabetes Incidence and Mortality in Korean Men and Women

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**OBJECTIVE** — Mounting evidence suggests that smoking is a cause of type 2 diabetes. We explored the association of cigarette smoking with diabetes incidence and mortality in a large cohort of Koreans.

**RESEARCH DESIGN AND METHODS** — A 14-year prospective cohort study was performed on 1,236,443 Korean men and women, aged 30–95 years at baseline, who underwent standardized biennial medical examinations provided by the National Health Insurance Corporation (NHIC). Incident diabetes was identified on the basis of outpatient visits, hospitalization, or prescription medication treatment for diabetes, as captured in the NHIC database. Diabetes mortality was obtained through the national statistical office. Cox proportional hazards models were used to investigate associations of smoking with indicators of diabetes and diabetes mortality.

**RESULTS** — Smoking was significantly associated with increased risk for diabetic outpatient treatment, hospitalization, and mortality among both men and women, and the risk among current smokers increased modestly with the number of cigarettes smoked daily ( $P_{\text{trend}} < 0.0001$  for all associations). Compared with never smokers, current male smokers who smoked  $\geq 20$  cigarettes/day had increased risk for incident diabetes defined by outpatient treatment (adjusted hazard ratio 1.55 [1.51–1.60]), incident diabetes defined by  $\geq 3$  prescription medications for diabetes (1.71 [1.63–1.80]), and death from diabetes (1.60 [1.25–2.06]). The risks for outpatient treatment among smokers were higher in men than in women with evidence for effect modification by sex and age ( $P_{\text{interaction}} < 0.0001$ ).

**CONCLUSIONS** — Our study provides longitudinal evidence that smoking increases the risk of incident diabetes and mortality.

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Tobacco smoking is well established as a causal risk factor for multiple diseases (1). Since the early 1990s, active smoking has been assessed as a risk factor for type 2 diabetes in multiple cohort studies (2,3). In a 2007 systematic review, Willi et al. (2) found that active smoking was associated with a higher incidence of type 2 diabetes based on evidence from 25 cohort studies. The pooled adjusted relative risk (RR) was 1.44 (95% CI 1.31–1.58), and there was an indication of a dose-response relationship with amount smoked. The hy-

pothesis that smoking increases risk for incident type 2 diabetes draws plausibility from the general inflammation caused by smoking and the increased insulin resistance and greater abdominal obesity in smokers (1,4). Given the immediate metabolic consequences of smoking, current smokers may be at greater risk than former smokers (4). With regard to mortality, it is well established that diabetic individuals who smoke are at greatly increased risk for dying because of the increased risk for cardiovascular disease caused by smoking (1,5).

Since the meta-analysis by Willi et al. (2), three more cohort studies on smoking and diabetes have been reported (6–8). Two were in Korea, the location of our study. Hur et al. (6) followed a cohort of 27,635 men through the Korean Medical Insurance Corporation and found that sustained active smoking was associated with a 60% increase in risk, whereas risk declined with increasing duration of cessation. In a cohort study of 4,041 men in urban and rural Korea, former and current smokers had significantly increased risk for type 2 diabetes, and the risk increased among current smokers with number of cigarettes smoked (7). The third study, conducted in New York, showed that current smokers had more than a twofold increased risk for onset of impaired fasting glucose after 6 years of follow-up among those who were normoglycemic at baseline (8).

Smoking has not yet been designated as a cause of diabetes in reports of the U.S. Surgeon General or other authoritative groups. To obtain additional evidence on smoking as a potential cause of type 2 diabetes, we explored the association of smoking with diabetes in a cohort study of 1.3 million Koreans, the Korean Cancer Prevention Study (KCPS) (9,10). Because of the richness of the clinical data available in the KCPS and the high prevalence of smoking among Korean men, we were able to assess smoking as a risk factor for incident diabetes ascertained using clinical indicators based on outpatient visit and hospitalization diagnoses and on medication prescriptions.

## RESEARCH DESIGN AND METHODS

The design and baseline characteristics of the KCPS have been described previously (9). It includes 1,329,525 Korean men and women aged 30–95 years who participated in a National Health Insurance Corporation (NHIC) medical evaluation between 1992 and 1995 with biennial follow-up evaluations through 2006. The numbers of baseline enrollees by year were 784,870 in 1992, 367,903 in 1993, 98,417 in 1994, and 78,335 in 1995. All enrollees in the NHIC underwent standardized examinations at local hospitals.

We excluded 904 participants who

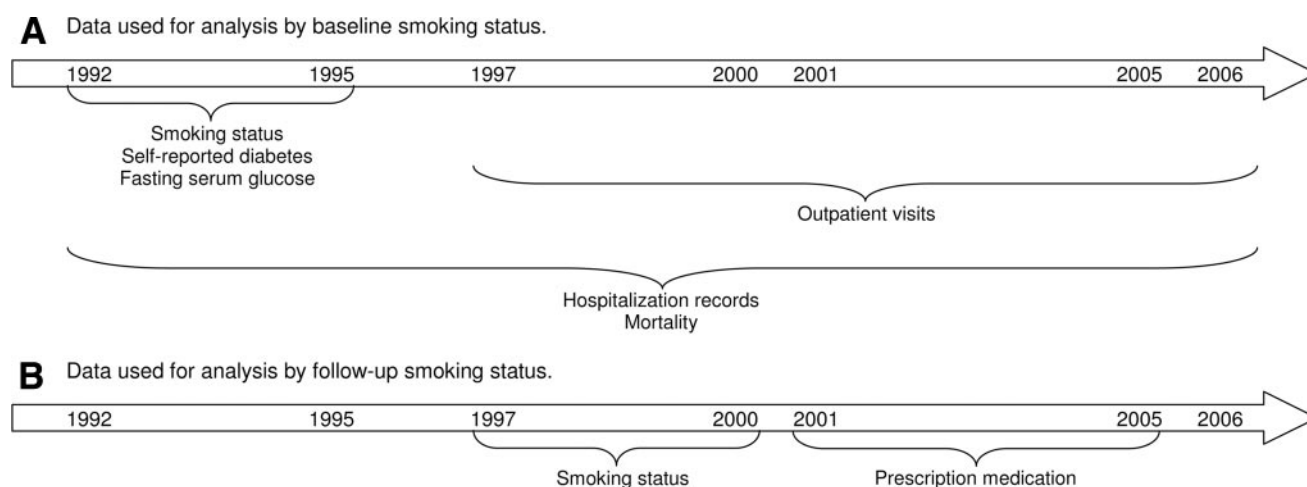
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**Figure 1**—Timeline for the Korean Cancer Prevention Study data collection, 1992–2006. A: Data used for analysis by baseline smoking status. B: Data used for analysis by follow-up smoking status.

died before 1993 along with 64,507 participants who reported having diabetes on enrollment. Also excluded were 27,671 participants with missing information on smoking, BMI, or alcohol consumption at enrollment. The final sample for this analysis included 1,236,443 participants. For the analyses of incident diabetes as assessed by prescriptions during the window 2001–2005, those with diabetes before 2000 ( $n = 53,639$ ), without a follow-up survey or missing data on BMI or alcohol consumption ( $n = 397,582$ ), or with inconsistent smoking data between baseline and follow-up ( $n = 76,961$ ) were excluded. Therefore, the final sample size for the analysis of incident diabetes based on prescription medication was 708,261 participants.

Informed consent was not specifically obtained because the study involved routinely collected data. The institutional review boards of Yonsei University and the Johns Hopkins Bloomberg School of Public Health approved the study.

## Data collection

**Standardized questionnaire.** During the biennial visits at both baseline and follow-up examinations, participants reported their smoking habits, including number of cigarettes smoked per day and duration of cigarette smoking in years for current smokers, along with other health information including alcohol consumption and exercise. History of past or prevalent diabetes was also included in the baseline questionnaire.

**Medical examination.** Fasting serum glucose measurements were obtained during medical evaluations for routine

clinical purposes. Each hospital had internal and external quality control procedures directed by the Korean Association of Laboratory Quality Control (9). Data for weight and height were also obtained.

**Outpatient visit and hospitalization.** All outpatient and hospitalization records from 1993 through 2006 were captured by the NHIC. Outpatient treatment and hospitalization due to diabetes were defined according to ICD-10 codes (E11–E11x and E14–E14x). Outpatient records were not complete for 1993 through 1996.

**History of prescription medication for diabetes.** Between 2001 and 2005, 16 diabetes-related medications and the insulin pump were listed in the medication database at the Health Insurance Review and Assessment Service; the medications included insulin, acarbose, glibenclamide, gliclazide, glimepiride, glipizide, gliquidone, repaglinide, nateglinide, metformin, voglibose, rosiglitazone, pioglitazone, combination sulfonyl and metformin, and combination thiazolidinedione and metformin.

**Mortality data.** Vital status of all participants was tracked from 1993 through 2006 and the underlying cause of death was obtained as reported to the national statistical office. Data for mortality from diabetes (ICD-10 codes E11–E11x and E14–E14x) were captured, and mortality ascertainment was complete for all Korean residents.

## Follow-up and outcome classification

The primary outcome variables were incident diabetes defined by outpatient treatment for diabetes (at least three visits for diabetes care per 365 days), hospitalization due to diabetes (at least one hospital-

ization for diabetes during the study period), use of prescription medication for diabetes management or treatment, and mortality due to diabetes. For analyses related to indicators of incident diabetes, we excluded individuals with prevalent diabetes at baseline, defined as self-reported history of diabetes or fasting serum glucose  $>125$  mg/dl.

Baseline smoking status (Fig. 1A) was used for analyses of hospitalization, mortality, and outpatient data. Hospitalization and mortality data were available for the entire study period, and complete outpatient data were available from 1997 to 2006.

Medication data were limited to 2001–2005. In the analysis of medication data, we used the follow-up smoking status reported between 1997 and 2000 (Fig. 1B), because the medication data were available only from 2001 through 2005.

## Statistical analysis

Smoking status was classified as never, current, and former, and current smokers were further classified as smoking 1–9, 10–19, or  $\geq 20$  cigarettes/day. Self-reported smokers at entry who reported never smoking at follow-up ( $n = 76,961$ , 17.1% of current and former smokers at baseline) were not reclassified and were excluded from the analysis. Alcohol consumption was categorized as 0, 1–24, 25–49, 50–99, and  $\geq 100$  g/day. BMI was categorized as  $<18.5$ , 18.5–19.9, 20.0–21.4, 21.5–22.9, 23.0–24.9, 25.0–26.4, 26.5–27.9, 28.0–29.9, 30–31.9, and  $\geq 32.0$  kg/m<sup>2</sup>. Indicator variables, corresponding to these categories, were used

Table 1—Baseline characteristics of participants without diabetes at enrollment in the Korean Cancer Prevention Study, 1992–2006

	Men			Women		
	Never smoker	Former smoker	Current smoker	Never smoker	Former smoker	Current smoker
n	163,838	162,548	461,378	421,847	9,079	17,753
Age (years)	45.2 ± 11.1	47.1 ± 11.6	44.0 ± 10.7	48.4 ± 11.6	63.2 ± 11.8	62.7 ± 10.1
Weight (kg)	66.3 ± 8.5	66.5 ± 8.5	65.8 ± 8.7	55.8 ± 7.8	53.8 ± 8.7	52.2 ± 9.0
BMI (kg/m <sup>2</sup> )	23.4 ± 2.6	23.4 ± 2.5	23.1 ± 2.6	23.2 ± 3.1	23.5 ± 3.3	22.7 ± 3.4
Alcohol drinking (g/day)	10.7 ± 24.4	13.0 ± 26.2	20.7 ± 35.4	0.2 ± 1.7	0.4 ± 2.8	0.6 ± 4.4
Fasting serum glucose (mg/dl)	89.2 ± 12.8	89.5 ± 12.8	88.6 ± 13.1	87.0 ± 12.3	89.0 ± 13.3	88.5 ± 13.3

Data are means ± SD.

for the analysis. Medication history was categorized by the number of prescriptions for diabetes given within any 365-day span during the follow-up period of 2001–2005 and stratified as  $\geq 1$  prescriptions/365 days or  $\geq 3$  prescriptions/365 days.

Analyses were stratified by sex and adjusted for age at enrollment (using age and the square of age [age<sup>2</sup>]), alcohol consumption, BMI, and exercise. Cox proportional hazards models were used to evaluate the association of smoking with risk for the various diabetes indicators. All Cox models were tested for and met the proportional hazards assumption. In a sensitivity analysis for mortality, we excluded the first 2 years of follow-up to assess the potential role of reverse causality, i.e., that smoking status changed because of a diabetes diagnosis. Modification of the effect of smoking was

assessed by inclusion of interaction terms of smoking category indicators with indicator variables for age, sex, BMI, and alcohol drinking. All analyses were conducted using SAS (version 9.1; SAS Institute, Cary, NC).

**RESULTS**— For diabetes hospitalization and mortality, the full study population of 1,236,443 individuals (787,764 men and 448,679 women) was largely middle-aged on enrollment (median age 45 years; interquartile range 37–55 years). Consistent with national data at that time, the majority of men were smokers (58.6% current smokers and 20.6% former smokers among those without diabetes). Among current male smokers without diabetes, 27.2% smoked 1–9 cigarettes daily, 42.0% smoked 10–19 cigarettes daily, and 30.8% smoked  $\geq 20$  cigarettes daily. In contrast, <6.0% of

women without diabetes reported smoking cigarettes (4.0% current smokers and 2.0% former smokers). Over the follow-up period, which was as long as 14 years, there were 1,185 deaths (748 men and 737 women) from diabetes, 11,398 individuals met the hospitalization criteria for incident diabetes, and 89,422 met the outpatient visit criteria. Among those meeting the hospitalization criteria, 79.2% also met the outpatient criteria. Table 1 summarizes the baseline characteristics of study participants without diabetes at enrollment.

We first assessed the relationship of baseline smoking status with indicators of incident diabetes and diabetes mortality (Table 2). In both men and women, smoking was associated with increased risk for  $\geq 3$  outpatient visits for diabetes, hospitalization due to diabetes, and death of diabetes. The risks were higher in cur-

Table 2—Adjusted hazard ratios (95% CI) for indicators of incident diabetes and for diabetes mortality by baseline smoking status, alcohol intake, and exercise in men and women in the Korean Cancer Prevention Study, 1992–2006

Baseline characteristics	Men			Women		
	Incident diabetes			Incident diabetes		
	Outpatient visits	Hospitalization records	Death of diabetes	Outpatient visits	Hospitalization records	Death of diabetes
Never smoker	1.0	1.0	1.0	1.0	1.0	1.0
Former smoker	1.10 (1.07–1.13)	1.12 (1.03–1.21)	0.96 (0.76–1.22)	1.19 (1.10–1.28)	1.31 (1.11–1.55)	1.33 (0.93–1.90)
Current smoker (cigarettes smoked daily)*						
1–9	1.30 (1.25–1.32)	1.50 (1.38–1.62)	1.63 (1.29–2.07)	1.34 (1.25–1.44)	1.43 (1.21–1.68)	1.86 (1.35–2.58)
10–19	1.37 (1.34–1.41)	1.58 (1.47–1.71)	1.44 (1.14–1.82)	1.26 (1.14–1.38)	1.65 (1.35–2.02)	1.91 (1.26–2.89)
$\geq 20$	1.55 (1.51–1.60)	1.79 (1.66–1.93)	1.60 (1.25–2.06)	1.33 (1.15–1.53)	1.57 (1.14–2.16)	3.38 (2.03–5.63)
Alcohol intake (g/day)						
0	1.0	1.0	1.0	1.0	1.0	1.0
1–24	0.95 (0.93–0.97)	0.86 (0.82–0.91)	0.85 (0.72–0.99)	0.90 (0.87–0.93)	0.83 (0.76–0.92)	0.94 (0.72–1.23)
25–49	0.99 (0.96–1.02)	0.94 (0.86–1.02)	1.01 (0.74–1.38)			
50–99	1.05 (1.01–1.08)	1.11 (1.01–1.23)	1.02 (0.66–1.56)	1.85 (0.77–4.43)	3.05 (0.43–21.7)	NE
$\geq 100$	1.04 (0.99–1.10)	1.28 (1.10–1.48)	1.12 (0.57–2.19)			
Exercise	0.94 (0.92–0.96)	0.98 (0.93–1.03)	0.89 (0.76–1.04)	1.03 (1.00–1.06)	1.02 (0.94–1.10)	0.95 (0.74–1.22)

Hazard ratios were adjusted for age, age<sup>2</sup>, alcohol drinking, BMI, and exercise. Data collection periods for outpatient visits, hospitalization, and death were 1997 through 2006, 1993 through 2006, and 1993 through 2006, respectively. NE, not estimated due to small of number of instances. \* $P_{\text{trend}} < 0.0001$  for all associations.

Table 3—Adjusted hazard ratios (95% CI) for diabetes medication prescription by follow-up smoking status, alcohol intake, and exercise in men and women of the Korean Cancer Prevention Study, 1992–2006

Follow-up characteristics	Men		Women	
	≥1 prescription/ 365 days	≥3 prescriptions/ 365 days	≥1 prescription/ 365 days	≥3 prescriptions/ 365 days
Never smoker	1.0	1.0	1.0	1.0
Former smoker	1.17 (1.14–1.21)	1.28 (1.22–1.35)	1.06 (0.94–1.19)	1.09 (0.89–1.33)
Current smoker (cigarettes smoked daily)*				
1–9	1.11 (1.07–1.15)	1.37 (1.29–1.45)	1.20 (1.09–1.31)	1.39 (1.20–1.62)
10–19	1.17 (1.14–1.20)	1.54 (1.48–1.61)	1.17 (1.04–1.32)	1.61 (1.35–1.93)
≥20	1.25 (1.21–1.29)	1.71 (1.63–1.80)	1.09 (0.85–1.39)	1.61 (1.12–2.30)
Alcohol intake (g/day)				
0	1.0	1.0	1.0	1.0
1–24	0.96 (0.94–0.98)	0.96 (0.93–1.00)	0.98 (0.95–1.02)	0.96 (0.90–1.03)
25–49	0.99 (0.96–1.03)	1.01 (0.96–1.07)		
50–99	1.02 (0.98–1.06)	1.09 (1.02–1.16)	2.21 (0.92–5.32)	5.61 (1.81–17.40)
≥100	0.95 (0.89–1.02)	1.00 (0.90–1.11)		
Exercise	0.93 (0.91–0.95)	0.86 (0.83–0.89)	0.98 (0.94–1.01)	0.93 (0.87–0.99)

Hazard ratios were adjusted for age, age<sup>2</sup>, alcohol drinking, BMI, and exercise. Data collection period for prescription medication was 2001 through 2005. \* $P_{\text{trend}} < 0.0001$  for any prescriptions in men and  $\geq 3$  prescriptions in women;  $P = 0.0062$  for  $\geq 1$  prescription in women.

rent smokers than in former smokers, and there was an indication of increasing risk with increasing number of cigarettes smoked daily among current smokers ( $P_{\text{trend}} < 0.0001$ ). For outpatient visits for diabetes, risks among smokers were higher in men than in women, with evidence for effect modification by sex and age ( $P_{\text{interaction}} < 0.0001$ ). There was some indication of increased risk for incident diabetes with alcohol drinking among men but without a dose response. Exercise, as reported at baseline, was marginally associated with decreased risk for incident outpatient visit for diabetes in men.

For the analysis of the association of smoking with prescription medications for diabetes, the sample included 708,261 individuals. Compared with the full cohort, this group tended to be younger, reflecting the start of the window with medication data ~7 years after enrollment. Over the follow-up period of 2001 through 2005, there were 6,815 cases of incident diabetes based on  $\geq 1$  prescriptions and 2,427 based on  $\geq 3$  prescriptions. Among men, smoking was associated with increased risk for incident diabetes defined by use of prescription medication for diabetes (Table 3). Risk increased with increasing number of cigarettes smoked daily. The association was stronger for those given  $\geq 3$  prescriptions annually than for those given  $\geq 1$  prescription annually. A similar association was observed among women who were cur-

rent smokers. There was evidence of effect modification by sex and age ( $P_{\text{interaction}} < 0.0001$ ). Alcohol drinking was not significantly associated with use of diabetes medication among men, but the risk was significantly higher among women who consumed  $>50$  g of alcohol/day. Exercise decreased the risk for incident diabetes.

Among current male smokers, the increasing risk of incident diabetes with increasing amount of cigarettes smoked daily, as reported at entry, persisted with control for duration of smoking. We did not find an indication that risk increased as duration increased, after controlling for amount smoked. Mortality was not associated with either amount smoked or duration of smoking in the fully adjusted model (supplementary Table 1, available in an online appendix at <http://care.diabetesjournals.org/cgi/content/full/dc10-0261/DC1>).

We also explored modification of the effect of smoking on risk for diabetes by alcohol consumption and BMI. For both, the data did not indicate that their presence modified the risks of smoking.

**CONCLUSIONS**— Using a large cohort and multiple indicators for the occurrence of type 2 diabetes, we have shown that cigarette smoking is associated with incident diabetes and with mortality from diabetes. The effect was greater among current smokers than among former smokers. Among current smokers, the risk for incident diabetes increased slightly with amount smoked, but not

with duration of smoking. The association of smoking with diabetes was robust to control for potential confounding factors including age, BMI, alcohol drinking, and exercise. The association was stronger in men and at younger ages and was not modified by alcohol consumption or BMI.

The association of smoking with type 2 diabetes has been examined previously in multiple studies. The 2007 meta-analysis by Willi et al. (2) included 25 cohort studies with 45,844 cases of incident diabetes. All but one of the individual studies demonstrated a positive association with smoking. As observed in the KCPS cohort, there was evidence of a dose-response relationship among current smokers with amount smoked. Our confirmatory findings from a single cohort of 1.3 million are based on a far larger number of cases of incident diabetes than in the meta-analysis and add greatly to the evidence from Asian populations.

Type 2 diabetes is rapidly increasing in Asia, driven in part by increasing obesity (11). Imaging studies suggest that Asians may have greater visceral adiposity at any particular BMI than Caucasians and hence a greater risk for type 2 diabetes (11). To date there have been eight cohort studies of smoking and diabetes in Asian populations, involving diverse populations and various outcome measures (12–17). Most show increased risk for type 2 diabetes in current smokers and the majority of the effect estimates indicate an

approximate doubling of risk, somewhat higher than that observed in our study. The lower hazard rates among former smokers suggest that the acute effects of smoking on insulin resistance may play a role in the contribution of smoking to the onset of diabetes (4).

We found that risk for incident diabetes increased with amount smoked; the magnitude of the increase was comparable to the estimate made by Willi et al. (2) (relative risk 1.61 for smokers of  $\geq 20$  cigarettes/day vs. never smokers). Risk did not increase with duration of smoking in our study. We did not identify other reports providing similar estimates. Several found that risk increased with pack-years of smoking, but this cumulative measure combines amount smoked with duration of smoking (14,18,19).

We found strong evidence for effect modification by age, with significantly lower risks at older ages, regardless of the outcome indicator. This pattern could reflect a depletion of susceptible individuals at older ages, lower amount smoked by older individuals, and possibly greater misclassification of exposures and outcomes in older participants. A similar pattern of effect modification has been observed for cigarette smoking and cardiovascular disease. For example, in the American Cancer Society's Cancer Prevention Study (CPS) I, risks for coronary heart disease and cerebrovascular disease declined progressively with increasing age, such that for individuals aged  $\geq 80$  years, risks were not increased among current smokers (20). Our findings are in contrast to those presented in the meta-analysis by Willi et al. (2). They found a higher pooled estimate in those aged  $\geq 50$  years compared with younger individuals. However, the comparison of relative risks by age was based on different sets of studies for the two age strata. With regard to BMI, Willi et al. (2) also found significantly greater risk for individuals with BMI of  $\geq 25$  kg/m<sup>2</sup>. In contrast, we found no evidence for greater risk in those with higher BMI. The lower risks in women are likely to reflect the lower number of cigarettes smoked per day by Korean women (10).

Potential limitations of this study primarily reflect the need to rely on self-report for tobacco and alcohol use and on medical database information for establishing the diagnosis of diabetes, leading to concern for potential misclassification of exposures and outcomes. Smoking status was updated during the follow-up

visit, however, and self-report of smoking in Korea has been shown to be valid when compared by use of cotinine (21). Because the follow-up data collection on smoking occurred at various points after enrollment, we could not update duration of smoking for analytical purposes. Consequently, our analyses could not explore risk in relation to lengthening duration of exposure or cessation during follow-up.

For establishing the occurrence of incident diabetes, we used three different indicators based on outcomes unlikely to be subject to substantial misclassification and found similar results with each. Our definitions were intended to exclude individuals being evaluated for diabetes who did not actually have the disease. Consequently, for incident disease we required at least three outpatient visits or prescription of a therapeutic agent once or three times, the latter being less subject to misclassification. For establishing the diagnosis of prevalent disease, we relied in part on self-report, which may be subject to misclassification. We do not anticipate that misclassification of either smoking or the outcome variables would systematically induce a positive association of smoking with diabetes.

There are limitations to the generalizability of the findings. The age range of the population did not extend to adolescents and young adults, who are now experiencing type 2 diabetes because of extreme obesity. The majority of the study population were middle-class, employed individuals, who may be healthier than the general population in Korea. Although incidence rates of disease probably differ by socioeconomic status, there is little reason to suspect that the risk factor–disease relationship should markedly differ.

The mounting evidence on smoking and diabetes, particularly in Asians, suggests that smoking should be considered as a potentially reversible cause of diabetes. Our findings greatly strengthen the available evidence on smoking and diabetes and should be considered as a further basis for controlling tobacco use in Korea and throughout Asia.

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S.H.J. analyzed data and wrote the manuscript. A.W.F. and J.M.S. contributed to discussion and reviewed/edited the manuscript.

N.W.H. provided input to data analysis and reviewed/edited the manuscript.

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