Smoking and Incidence of Diabetes Among U.S. Adults

Findings from the Insulin Resistance Atherosclerosis Study

CAPRI GABRIELLE FOY, PHD, MS  
RONNY A. BELL, PHD  
DEBORAH F. FARMER, PHD  
DAVID C. GOFF, JR., MD, PHD  
LYNNE E. WAGENKNECHT, DRPH

OBJECTIVE — The objective of this study was to determine the association between smoking and incident diabetes among U.S. adults.

RESEARCH DESIGN AND METHODS — The Insulin Resistance Atherosclerosis Study (IRAS) was a prospective study of the associations of insulin sensitivity and cardiovascular risk factors. We examined the relationship between smoking status categories (never, former, and current) and incident 5-year type 2 diabetes among 906 participants free of diabetes at baseline. We also considered the effect of pack-year categories (never, former <20 pack-years, former ≥20 pack-years, current <20 pack-years, and current ≥20 pack-years) upon diabetes incidence.

RESULTS — Of current smokers, 96 (25%) developed diabetes at 5 years, compared with 60 (14%) never smokers. After multivariable adjustment, current smokers exhibited increased incidence of diabetes compared with never smokers (odds ratio [OR] 2.66, P = 0.001). Similar results were found among current smokers with ≥20 pack-years with normal glucose tolerance (5.66, P = 0.001).

CONCLUSIONS — Smoking shares a robust association with incident diabetes, supporting the current Surgeon General’s warnings against cigarette smoking.

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Cigarette smoking exacts an indisputable and devastating toll on public health. Diabetes also presents a formidable public health burden (1), and its prevalence is expected to increase dramatically by the year 2025 (2). Although cigarette smoking has been established as a risk factor for cardiovascular disease, its association with type 2 diabetes is less clear. Exploring this relationship is prudent because diabetes and cardiovascular disease share many risk factors, including older age, upper body fat distribution, and physical inactivity (3,4).

Several (5–7) but not all (8,9) prospective, population-based studies have demonstrated that cigarette smoking is associated with an increased risk of diabetes. However, as Eliasson notes in his review (10), many studies have relied upon self-report of glucose tolerance status and anthropometric measures. Also, although the prevalence of diabetes is higher among women, African Americans, and Hispanic Americans (11), most studies have been conducted largely among white men. Finally, the degree to which the relationship between cigarette smoking and incident diabetes is dose-dependent is not conclusive.

In consideration of these issues, the purpose of this investigation was to determine the association between smoking and incidence of diabetes among participants in the Insulin Resistance Atherosclerosis Study (IRAS). The IRAS sample provides an excellent opportunity to examine this relationship in a cohort with equal representation according to sex and three ethnic groups, while using repeated direct and standardized measures of glucose tolerance, blood pressure, and anthropometric measures.

RESEARCH DESIGN AND METHODS — Briefly, the major purpose of IRAS was to assess the cross-sectional and prospective relationships between insulin resistance and clinical and subclinical atherosclerosis among U.S. adults between 40 and 69 years of age (12). The IRAS protocol was approved by the institutional review boards of all clinical centers and the coordinating center (Wake Forest University School of Medicine), and informed consent was obtained for all participants. IRAS participants were recruited from four sites: Los Angeles and Oakland, California; San Antonio, Texas; and the San Luis Valley, Colorado. Recruitment of non-Hispanic white and non-Hispanic African-American participants in California occurred through Kaiser Permanente, a nonprofit HMO. Recruitment of non-Hispanic whites and Hispanic enrollees occurred in the San Antonio and San Luis Valley clinics primarily as part of the San Antonio Heart Study (13) and the San Luis Valley Diabetes Study (14). The sampling strategy was to obtain equal numbers of participants according to sex, ethnicity, and glucose tolerance status (normal glucose tolerance [NGT], impaired glucose tolerance [IGT], or type 2 diabetes). Individuals taking insulin were excluded. From the 3,416 potential participants contacted, 1,625 agreed to participate (48% recruitment rate).

Baseline and 5-year clinical examinations

The IRAS baseline clinical examination was conducted between 1992 and 1993, and consisted of two 4-h visits scheduled...
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~1 week apart (15). Participants were asked to refrain from alcohol consumption and heavy exercise for 24 h, from food for 12 h, and from smoking on the day of the examination. The first visit included a 75-g oral glucose tolerance test during which blood was collected for fasting and 2-h glucose samples.

Participants were recruited to return for a follow-up examination after ~5 years from the date of the baseline clinical examination. Although many of the measures obtained during the baseline examination were repeated during the 5-year visit, we considered only the effect of baseline smoking status and covariates upon 5-year incident diabetes among participants who were free of diabetes at baseline.

**Outcome variable**

Glucose tolerance status was determined during the first visit of the clinical examination using a 75-g oral glucose tolerance test (Orangedex; Custom Laboratories, Baltimore, MD) and was classified as NGT, IGT, or diabetes using 1985 World Health Organization (WHO) criteria (16). NGT was defined as fasting and 2-h glucose concentration <140 mg/dl. IGT was defined as fasting glucose concentration <140 mg/dl and 2-h glucose concentration ≥140 mg/dl and <200 mg/dl. Diabetes was defined as fasting glucose concentration ≥140 mg/dl or 2-h glucose concentration ≥200 mg/dl, or current use of hypoglycemic agents. This investigation involved participants with NGT or IGT at baseline who completed the 5-year assessment. Participants who met WHO glucose tolerance criteria at the 5-year assessment were considered to have developed incident diabetes.

**Smoking status**

Cigarette smoking habits at baseline were assessed by a structured interview during one of the two IRAS visits, from which participants were grouped according to three mutually exclusive categories. Participants who had smoked <100 cigarettes in their lifetime were classified as never smokers. Participants who had smoked >100 cigarettes in their lifetime but who were not active smokers at the assessment were labeled as past smokers. Finally, individuals who were currently smoking were connoted as current smokers.

Participants were also queried about number of cigarettes smoked daily and years of smoking. Assuming 20 cigarettes per pack, pack-years were estimated using the following formula [(cigarettes per day/20) × years smoked]), and participants were grouped according to the following categories: never, former smokers with <20 pack-years, former smokers with ≥20 pack-years, current smokers with <20 pack-years, and current smokers with ≥20 pack-years.

**Covariates**

**Demographic/behavioral.** Age, sex, and ethnicity were assessed through self-report. Total energy expenditure was assessed via a structured interview using a modification of a standardized instrument (17). Usual intake of alcohol during the previous month was estimated using a 10-item questionnaire, from which alcohol intake was calculated as grams per day from beer, wine, or liquor (18).

**Anthropometric.** Height, weight, and waist circumference were measured using standardized protocols across clinics. Weight and height were measured in duplicate, and BMI was defined as body weight in kilograms divided by the square of height in meters. Waist circumference was measured in duplicate on bare skin during midrespiration using a steel tape at the natural indentation between the 10th rib and the iliac crest to the nearest 0.5 cm.

**Metabolic syndrome components.** Glucose tolerance status was categorized as either normal (NGT) or impaired (IGT). HDL cholesterol and triglyceride concentrations were determined from fasting plasma samples at the central IRAS laboratory (Medlantic Research Institute, Washington, DC) using the Lipid Research Clinics methodology and were expressed in milligrams per deciliter. Blood pressure was measured three times using a mercury manometer after a 5-min rest. The average of the last two measurements was used to characterize the blood pressure. Hypertension was defined as the presence of one of the following: systolic blood pressure ≥140 mmHg; diastolic blood pressure ≥90 mmHg; or current pharmaceutical treatment for hypertension.

**Insulin sensitivity.** The baseline insulin sensitivity index (S) was assessed by the frequently sampled intravenous glucose tolerance test (FSIGT) with minimal model analyses (12). FSIGTs were performed with insulin (0.03 units/kg) and glucose (0.3 g/kg body wt) injections at 0 and 20 min, respectively. Insulin was used instead of tolbutamide to ensure accurate computation of the S index across ranges of glucose tolerance. Blood samples were collected at 12 time points for determination of glucose and insulin measures. Blood levels of insulin and glucose were assessed in a central laboratory (University of Southern California, Los Angeles, CA); plasma glucose was measured using the glucose oxidase technique on an automated autoanalyzer (YSI, Yellow Springs, OH), and insulin was assessed by radioimmunoassay. These values were used to estimate the parameters of the minimal model using the MINIMOD mathematical modeling method (19), which correlates well with the euglycemic clamp method. Because 10.2% of the sample had an S index of 0, the natural log of (S index + 1) was calculated for each participant (17).

**Statistical analyses**

Preliminary descriptive statistics were generated for the sample to determine whether there were differences among smoking categories upon covariates. With smoking category as the factor, one-way ANOVAs were conducted for the continuous variables, and Pearson χ² tests were conducted to ascertain whether there were differences between the groupings of smoking on categorical covariates.

The relationship between smoking categories and incident diabetes was examined through performance of four separate logistic regression models. We tested a priori hypotheses regarding the effect of sex and glucose tolerance interactions with smoking status interactions in predicting incident diabetes. However, these interactions were not significant, driving the decision to conduct analyses among the pooled sample without these interactions. We also initially included environmental exposure to cigarette smoke at home or work and cardiovascular disease (defined as either electrocardiographic evidence of a myocardial infarction, or self-report of stroke or coronary artery bypass graft surgery) as covariates; however, these variables did not contribute significantly to the model and were excluded from our final models.

We first performed an unadjusted model of the effect of smoking upon incident diabetes. Adjusted model 1 tested the effect of smoking category upon incident diabetes, adjusted for demographic and behavioral covariates (age, sex, ethnicity, total energy expenditure, alcohol consumption, clinic, and ethnicity × clinic interaction). Adjusted model 2 represented adjusted model 1 plus anthropo-
metabolic measures (BMI and waist circumference). Adjusted model 3 portrayed adjusted model 2 with other metabolic syndrome components (glucose tolerance, triglyceride levels, HDL cholesterol levels, and hypertension). Finally, adjusted model 4 denoted adjusted model 3 plus insulin sensitivity. We also included C-reactive protein, fibrinogen, and plasminogen activator inhibitor 1 as covariates in an adjusted model 5 to examine the role of inflammatory factors on incidence of diabetes, but these variables did not contribute to the model and are thus not presented here. Identical analyses were conducted to assess the effect of pack-year categories in the pooled sample. Significant pack-year by glucose tolerance interactions in adjusted models 3 and 4 drove the decision to conduct subgroup analyses among participants with NGT and IGT.

The alpha level for testing the significance of effects in each model was set a priori at $P < 0.05$, and the significance level for interaction terms was set at $P < 0.10$. All analyses were conducted using SPSS version 10.1.

**RESULTS** — Demographic, behavioral, anthropometric, and metabolic risk factor characteristics of the entire sample are shown in Table 1. Among the 1,087 participants who were free of diabetes at baseline, 906 (83.3%) completed the follow-up assessment at 5 years. Among never smokers, 293 (69.6%) were women, whereas 203 former smokers (57.3%) were men. Of never smokers 42% were non-Hispanic whites, whereas Hispanics represented 43% of current smokers. The youngest mean age was observed among current smokers, and current smokers had the highest amounts of daily alcohol consumption. Smokers also displayed a trend toward lower BMI and trends toward higher levels of total energy expenditure, lower HDL cholesterol and higher triglyceride concentrations, and lower prevalence of hypertension. Finally, among former smokers, the mean length of time since quitting was $17.8 \pm 11.6$ years.

**Total sample**

The results of all models among the pooled sample are shown in Table 2. From the original sample size of 906 participants, missing values for physical activity ($n = 11$) reduced the sample size to 895 for adjusted model 1, which tested the effect of smoking status upon diabetes incidence adjusted for demographic factors (age, sex, ethnicity, and clinic), behavioral factors (total energy expenditure and alcohol consumption), and an ethnicity × clinic interaction term. Current smokers displayed a significantly higher incidence of diabetes at 5 years than never smokers (odds ratio [OR] $2.06$, $P = 0.005$). With the exception of age being associated with higher incidence of diabetes ($1.03$, $P = 0.01$), there were no other significant effects for any of the covariates.

Table 2 also displays the results of adjusted model 2, which represented adjusted model 1 plus BMI and waist circumference.
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Table 2—Five-year diabetes incidence for cigarette smoking among total sample and glucose tolerance categories

<table>
<thead>
<tr>
<th>Smoking categories</th>
<th>n</th>
<th>Unadjusted</th>
<th>n</th>
<th>Adjusted model 1‡</th>
<th>n</th>
<th>Adjusted model 2†</th>
<th>n</th>
<th>Adjusted model 3‡</th>
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<tr>
<td>Total sample</td>
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<td></td>
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<td></td>
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<tr>
<td>Never</td>
<td>424</td>
<td>906</td>
<td>419</td>
<td>1.0</td>
<td>418</td>
<td>1.0</td>
<td>416</td>
<td>1.0</td>
</tr>
<tr>
<td>Former</td>
<td>354</td>
<td>1.14 (0.78–1.69)</td>
<td>349</td>
<td>1.13 (0.74–1.72)</td>
<td>347</td>
<td>1.20 (0.77–1.85)</td>
<td>345</td>
<td>1.31 (0.82–2.09)</td>
</tr>
<tr>
<td>Current</td>
<td>128</td>
<td>2.02 (1.25–3.28)</td>
<td>127</td>
<td>2.06 (1.23–3.46)</td>
<td>127</td>
<td>2.36 (1.37–4.05)</td>
<td>127</td>
<td>2.66 (1.49–4.77)</td>
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<tr>
<td>NGT</td>
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<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Never</td>
<td>279</td>
<td>1.0</td>
<td>275</td>
<td>1.0</td>
<td>274</td>
<td>1.0</td>
<td>274</td>
<td>1.0</td>
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<tr>
<td>Former</td>
<td>236</td>
<td>1.28 (0.62–2.65)</td>
<td>234</td>
<td>1.12 (0.52–2.42)</td>
<td>233</td>
<td>1.21 (0.54–2.69)</td>
<td>232</td>
<td>1.32 (0.58–3.03)</td>
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<tr>
<td>Current</td>
<td>88</td>
<td>3.91 (1.85–8.29)</td>
<td>87</td>
<td>3.30 (1.44–7.56)</td>
<td>87</td>
<td>4.03 (1.69–9.62)</td>
<td>87</td>
<td>5.27 (2.11–13.16)</td>
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<tr>
<td>IGT</td>
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<td></td>
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<tr>
<td>Never</td>
<td>145</td>
<td>1.0</td>
<td>144</td>
<td>1.0</td>
<td>144</td>
<td>1.0</td>
<td>142</td>
<td>1.0</td>
</tr>
<tr>
<td>Former</td>
<td>118</td>
<td>1.14 (0.68–1.91)</td>
<td>115</td>
<td>1.30 (0.74–2.30)</td>
<td>114</td>
<td>1.33 (0.75–2.37)</td>
<td>113</td>
<td>1.44 (0.79–2.62)</td>
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<tr>
<td>Current</td>
<td>40</td>
<td>1.48 (0.72–2.05)</td>
<td>40</td>
<td>1.63 (0.74–3.56)</td>
<td>40</td>
<td>1.76 (0.79–3.92)</td>
<td>40</td>
<td>1.58 (0.69–3.64)</td>
</tr>
</tbody>
</table>

Data are OR (95% CI) unless otherwise indicated. *Adjusted for age, sex, ethnicity, total energy expenditure, alcohol consumption, clinic, and ethnicity × clinic. †Adjusted for age, sex, ethnicity, clinic, BMI, waist circumference, and ethnicity × clinic. §Adjusted for age, sex, ethnicity, clinic, BMI, waist-to-hip ratio, glucose tolerance status, HDL cholesterol level, triglyceride level, hypertension, and ethnicity × clinic. ‡Significant at the <0.01 level; |significant at the <0.001 level.

circumference. Current smokers displayed greater incidence of diabetes than never smokers (OR 2.36, \( P = 0.002 \)). Age was significantly associated with higher incidence of diabetes (1.04, \( P = 0.003 \)) as was BMI (1.09, \( P = 0.01 \)).

The results of adjusted model 3, which represented adjusted model 2 with glucose tolerance status, HDL cholesterol, triglycerides, and hypertension status are reported in Table 2. Current smokers displayed a higher incidence of diabetes than never smokers (OR 2.66, \( P = 0.001 \)). BMI was associated with higher incidence of diabetes (1.09, \( P = 0.01 \)). Participants with IGT displayed a higher incidence of diabetes than those with NGT (5.04, \( P < 0.001 \)). Higher levels of HDL cholesterol were associated with lower incidence of diabetes (0.97, \( P = 0.002 \)). Participants with hypertension displayed increased incidence of diabetes compared with those without hypertension (2.02, \( P = 0.002 \)).

Finally, in adjusted model 4, which consisted of adjusted model 3 plus insulin sensitivity, current smokers displayed a higher incidence of diabetes than never smokers (OR 2.69, \( P = 0.002 \)). BMI was associated with increased incidence of diabetes (1.08, \( P = 0.05 \)). Participants with IGT displayed significantly higher incidence of diabetes than those with NGT (3.70, \( P < 0.001 \)), and participants with hypertension exhibited higher incident diabetes than those without hypertension (1.75, \( P = 0.02 \)). Finally, increased insulin sensitivity was associated with lower incidence of diabetes (0.38, \( P = 0.001 \)).

Glucose tolerance status subgroup analyses
Among participants with normal glucose tolerance, current smokers exhibited a higher risk of diabetes than never smokers in all adjusted models (Table 2). Among covariates, age was significantly associated with a higher incidence of diabetes in adjusted models 1 and 2 (OR 1.03, \( P = 0.01 \), and 1.04, \( P = 0.003 \), respectively), and displayed a trend toward significance in adjusted models 3 and 4 (OR 1.04, \( P = 0.07 \), and 1.04, \( P = 0.07 \), respectively). In adjusted models 2 and 3 and adjusted model 4 increases in BMI were accompanied with a trend toward a higher incidence of diabetes (1.10, \( P = 0.08 \), and 1.11, \( P = 0.06 \), respectively). In adjusted models 3 and 4, participants with hypertension displayed a higher risk of diabetes than those without hypertension (1.09, \( P = 0.004 \), and 1.09, \( P = 0.02 \), respectively). BMI was associated with increased incidence of diabetes in adjusted models 2 and 3 (1.09, \( P = 0.01 \), and 1.09, \( P = 0.02 \), respectively). Participants with hypertension displayed increased odds of diabetes in adjusted models 3 and 4 (1.99, \( P = 0.002 \), and 1.77, \( P = 0.01 \), respectively). In adjusted models 3 and 4, a significant pack-year × glucose tolerance interaction was observed, with current smokers having ÷20 pack-years and IGT displaying lower incidence of diabetes than never smokers with normal glucose tolerance (0.22, \( P = 0.07 \), and 0.17, \( P = 0.07 \), respectively). Finally, \( S_5 \) was associated with a lower incidence of diabetes (0.35, \( P < 0.001 \)) in adjusted model 4. The ORs for the pack-year categories in the subgroup analyses according to glucose tolerance status are displayed in Fig. 1.

CONCLUSIONS — This study was designed to determine the effect of smoking upon incidence of diabetes among adults. Collectively, current smokers had greater incidence of diabetes than never smokers after adjustment for several demographic, behavioral, anthropometric, and metabolic syndrome risk factors. Similar results were found in subgroup analyses among participants with NGT. Among participants with NGT, current smokers with ÷20 pack-years or ÷20 pack-years demonstrated increased risk
of diabetes compared with never smokers, suggesting that all levels of cigarette smoking carry increased risk of development of diabetes. Interestingly, these associations were not observed among participants with IGT. We also found that former smokers did not have a significantly increased risk of diabetes compared with never smokers, suggesting that this risk factor is modifiable.

Other prospective studies have shown similar results. Manson et al. (5), studying 21,068 U.S. male physicians for an average of 12 years in the Physicians’ Health Study, found that compared with never-smokers, past smokers and current smokers of \( \geq 20 \) cigarettes/day or \( \geq 20 \) cigarettes/day demonstrated significantly increased risk of diabetes after adjustment for confounders. However, a dose-response relationship was not observed in this cohort. In a comparatively rare study among women, Rimm et al. (20) investigated the relationship between baseline smoking and incidence of diabetes among 114,247 female nurses in the Nurses’ Health Study who were free of diabetes, cardiovascular disease, and cancer. Results indicated that current smokers exhibited an increased risk of diabetes, with a significant dose-response relationship for higher levels of smoking.

However, several cross-sectional studies have failed to illustrate a relationship between smoking and aspects of glucose regulation. Henkin et al. (21), in an analysis of 1,481 IRAS participants, found that after adjustment for potential confounders, active smoking was not associated with \( S_g \). Wareham et al. (22), studying 1,122 participants in the Isle of Ely Study, found that after adjustment for BMI, waist-to-hip ratio, physical activity, and alcohol consumption, current smokers exhibited lower fasting and 120-min levels of insulin after a 75-g oral glucose tolerance test.

We found that among participants with IGT, former or current smoking was not associated with significantly higher incidence of diabetes compared with never smoking. This finding may be partly explained by further inspection of the frequencies of glucose tolerance in adjusted model 3, which demonstrated that although 101 (33.3%) participants with IGT developed diabetes between the baseline and 5-year assessments, IGT was reversed to NGT in 81 (26.7%) partici-
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pacts by the 5-year assessment, illustrating the transient nature of the IGT state. We also performed subgroup analyses in which we compared never smokers (reference) to a combined category of former/current smokers. In adjusted model 3 among the pooled sample, former/current smokers exhibited significantly higher incidence of diabetes than never smokers (OR 1.61, P = 0.03). Among participants with NGT, former/current smokers displayed significantly higher incidence of diabetes than never smokers (2.10, P = 0.05). However, among participants with IGT, former/current smokers did not display significantly higher odds for incident diabetes (1.47, P = 0.18).

We also found that total energy expenditure and alcohol consumption were not associated with increased incidence of diabetes. We conducted additional analyses that substituted baseline vigorous energy expenditure and alcohol consumption categories based on a standard of 12 g/drink including: never (reference), former (>1 year since last drink), moderate (<1 drink/day for women and <2 drinks/day for men), and heavy (≥1 drink/day for women and ≥2 drinks/day for men) as covariates. These analyses also failed to yield significant results. These findings may partly be explained by the fact that physical activity and alcohol consumption patterns may fluctuate considerably over time (23,24); thus, participants may have changed their physical activity habits and alcohol consumption patterns between the baseline and 5-year assessments.

Our findings prompt reflection upon the biologic plausibility and possible mechanisms of the relationship between smoking and diabetes. Consistent with other reports, we found that smokers displayed lower BMI, yet higher waist-to-hip ratio compared with never smokers, suggesting increased abdominal adiposity (25). Acute bouts of smoking have been shown to provoke hyperglycemia, hyperinsulinemia, and elevated blood pressure (26). Smoking may also lead to impaired endothelial function (27), which may result in reduced insulin sensitivity. Cigarettes contain multiple noxious substances besides nicotine, such as cadmium (28), which is also linked to increased risk of diabetes (29).

This investigation possessed several strengths. In particular, this study extended current knowledge by including direct assessments of glucose tolerance, BMI, cholesterol levels, and hypertension, in contrast to earlier studies using self-report solely (10). In addition, our logistic regression models contemplated the influence of several pertinent demographic, behavioral, anthropometric, and metabolic syndrome variables, which collectively strengthen the external validity of our findings. However, we did rely on self-report measures of smoking, as is common in observational epidemiological studies in which smoking is not a primary end point. Although we adjusted for several potential confounders such as physical activity, alcohol intake, and metabolic syndrome components, smokers may also demonstrate other behaviors that we did not assess, including lower compliance than nonsmokers in checking glucose levels and receiving HbA1c assessments (30). We also did not include dietary patterns or smoking status at the 5-year follow-up assessment. In addition, we found that 37 of the 128 (29%) current smokers at baseline reported being former smokers at the 5-year follow-up assessment, possibly indicating that the actual strength of association between smoking and diabetes may be underestimated (31). Paradoxically, however, our analyses also may have overestimated the magnitude of association. Zhang and Yu (32) offer admonitions against implicit reliance on logistic regression ORs when the incidence of an outcome is more than 10% and the OR is more than 2.5. Within our pooled sample, we found an incidence rate of diabetes of 14.2% among never smokers (Table 1), with a logistic regression OR in adjusted model 3 of 2.66 never smokers (Table 1), with a logistic regression OR in adjusted model 3 of 2.66 for current smokers (Table 2). The corrected relative risk for current smokers in adjusted model 3 was found to be 2.15 (95% CI 1.20–3.87). Within our subgroup analyses, the low incidence rates of diabetes of never smokers with NGT (5.4%) and the low OR for current smokers with IGT (1.58 in adjusted model 3) did not meet the conditions deemed necessary for the Zhang and Yu correction.

These results suggest that along with its other numerous threats to public health, smoking may be an independent risk factor for diabetes. This temporal relationship is biologically plausible, is consistent with the extant literature, and gives further credence to current recommendations against the adoption and maintenance of smoking, particularly for individuals who are at high risk of developing diabetes.

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