

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.

Diabetes Care 28:2501–2507, 2005

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 deter-

mine 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

From the Department of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina.

Address correspondence and reprint requests to Capri G. Foy, PhD, MS, Piedmont Plaza II, 2000 W. First St., Office 250, Winston-Salem, NC 27104. E-mail: cfoy@wfubmc.edu.

Received for publication 21 March 2005 and accepted in revised form 20 June 2005.

Abbreviations: FSGIT, frequently sampled intravenous glucose tolerance test; IGT, impaired glucose tolerance; IRAS, Insulin Resistance Atherosclerosis Study; NGT, normal glucose tolerance; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

© 2005 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

~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 \geq 140 mg/dl and <200 mg/dl. Diabetes was defined as fasting glucose concentration \geq 140 mg/dl or 2-h glucose concentration \geq 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) \times years smoked], and participants were grouped according to the following categories: never, former smokers with <20 pack-years, former smokers with \geq 20 pack-years, current smokers with <20 pack-years, and current smokers with \geq 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 \geq 140 mmHg; diastolic blood pressure \geq 90 mmHg; or current pharmaceutical treatment for hypertension.

Insulin sensitivity. The baseline insulin sensitivity index (S_I) 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_I 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_I value of 0, the natural log of ($S_I + 1$) 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 χ^2 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 \times clinic interaction). Adjusted model 2 represented adjusted model 1 plus anthropo-

Table 1—Descriptive characteristics of participants at baseline

| Characteristic | Never smoker | Former smoker | Current smoker | P |
|--|----------------------|----------------------|----------------------|--------|
| n | 424 | 354 | 128 | |
| Demographic/behavioral | | | | |
| Sex | | | | |
| Female | 293 (69.1) | 151 (42.7) | 70 (54.7) | <0.001 |
| Male | 131 (30.9) | 203 (57.3) | 58 (45.3) | |
| Ethnicity | | | | |
| Non-Hispanic African American | 103 (24.3) | 96 (27.1) | 41 (32.0) | 0.004 |
| White | 178 (42.0) | 152 (42.9) | 32 (25.0) | |
| Hispanic American | 143 (33.7) | 106 (29.9) | 55 (43.0) | |
| Age (years) | 54.11 ± 8.55 | 56.06 ± 7.95 | 52.52 ± 8.74 | <0.001 |
| Physical activity (kcal · kg ⁻¹ · year ⁻¹) | 14,826.52 ± 2,565.94 | 14,962.77 ± 2,766.80 | 15,436.21 ± 3,092.37 | 0.19 |
| Alcohol consumption (g/day) | 3.36 ± 7.55 | 8.32 ± 14.96 | 12.47 ± 17.36 | <0.001 |
| Anthropometric measures | | | | |
| BMI (kg/m ²) | 28.85 ± 5.97 | 28.21 ± 5.00 | 27.59 ± 5.88 | 0.06 |
| Waist circumference (cm) | 89.35 ± 13.25 | 91.53 ± 11.46 | 89.87 ± 14.01 | 0.06 |
| Metabolic syndrome risk factors | | | | |
| S ₁ (10 ⁻⁴ · min ⁻¹ · μU ⁻¹ · ml ⁻¹) | 2.10 ± 1.91 | 2.23 ± 2.09 | 2.41 ± 2.22 | 0.32 |
| Acute insulin response (pmol · ml ⁻¹ · min ⁻¹) | 471.86 ± 529.84 | 492.71 ± 445.63 | 532.23 ± 460.44 | 0.47 |
| Glucose tolerance | | | | |
| NGT | 279 (65.8) | 236 (66.7) | 88 (68.8) | 0.82 |
| IGT | 145 (34.2) | 118 (33.3) | 40 (31.3) | |
| HDL (mg/dl) | 47.22 ± 14.54 | 47.00 ± 15.76 | 44.93 ± 15.00 | 0.31 |
| Triglycerides (mg/dl) | 129.31 ± 83.25 | 136.31 ± 85.34 | 138.49 ± 96.61 | 0.41 |
| Hypertension | | | | |
| No | 295 (69.6) | 243 (68.6) | 101 (78.9) | 0.07 |
| Yes | 129 (30.4) | 111 (31.4) | 27 (21.1) | |
| Diabetes at 5 years | | | | |
| No | 364 (85.8) | 298 (84.2) | 96 (75.0) | 0.01 |
| Yes | 60 (14.2) | 56 (15.8) | 32 (25.0) | |

Data are n (%) or means ± SD.

metric 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 α 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%) 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 ± 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 \times clinic interaction term. Current smokers displayed a significantly higher incidence of diabetes at 5 years than never smokers (odds ratio [OR] 2.06, $P = 0.006$). 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

Table 2—Five-year diabetes incidence for cigarette smoking among total sample and glucose tolerance categories

| Smoking categories | n | Unadjusted | n | Adjusted model 1* | n | Adjusted model 2† | n | Adjusted model 3‡ |
|--------------------|-----|-------------------|-----|-------------------|-----|-------------------|-----|-------------------|
| Total sample | | | | | | | | |
| n | | 906 | | 895 | | 892 | | 888 |
| Never | 424 | 1.0 | 419 | 1.0 | 418 | 1.0 | 416 | 1.0 |
| Former | 354 | 1.14 (0.78–1.69) | 349 | 1.13 (0.74–1.72) | 347 | 1.20 (0.77–1.85) | 345 | 1.31 (0.82–2.09) |
| Current | 128 | 2.02 (1.25–3.28)§ | 127 | 2.06 (1.23–3.46)§ | 127 | 2.36 (1.37–4.05)§ | 127 | 2.66 (1.49–4.77)§ |
| NGT | | | | | | | | |
| n | | 603 | | 596 | | 594 | | 593 |
| Never | 279 | 1.0 | 275 | 1.0 | 274 | 1.0 | 274 | 1.0 |
| Former | 236 | 1.28 (0.62–2.65) | 234 | 1.12 (0.52–2.42) | 233 | 1.21 (0.54–2.69) | 232 | 1.32 (0.58–3.03) |
| Current | 88 | 3.91 (1.85–8.29) | 87 | 3.30 (1.44–7.56)§ | 87 | 4.03 (1.69–9.62)§ | 87 | 5.27 (2.11–13.16) |
| IGT | | | | | | | | |
| n | | 303 | | 299 | | 298 | | 295 |
| Never | 145 | 1.0 | 144 | 1.0 | 144 | 1.0 | 142 | 1.0 |
| Former | 118 | 1.14 (0.68–1.91) | 115 | 1.30 (0.74–2.30) | 114 | 1.33 (0.75–2.37) | 113 | 1.44 (0.79–2.62) |
| Current | 40 | 1.48 (0.72–3.05) | 40 | 1.63 (0.74–3.56) | 40 | 1.76 (0.79–3.92) | 40 | 1.58 (0.69–3.64) |

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 1.05, $P = 0.02$, and OR 1.06, $P = 0.006$, respectively), and displayed a trend toward significance in adjusted models 3 and 4 (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 (4.06, $P < 0.001$, and 3.44, $P = 0.001$, respectively). In adjusted models 3 and 4, participants with hypertension exhibited increased incidence of diabetes compared with those with normal blood pressure (4.27, $P < 0.001$, and 3.58, $P = 0.001$). Finally, in adjusted model 4, increased insulin sensitivity was associated with lower incidence of diabetes (0.43, $P = 0.05$).

Pack-years

Among the pooled sample in adjusted models 1 and 2, current smokers with <20 pack-years exhibited increased incidence of diabetes compared with never smokers (OR 2.56, $P = 0.004$, and OR

2.88, $P = 0.002$, respectively). Age was associated with increased incidence of diabetes in adjusted models 1 and 2 (1.03, $P = 0.01$, and 1.04, $P = 0.003$, 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_1 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

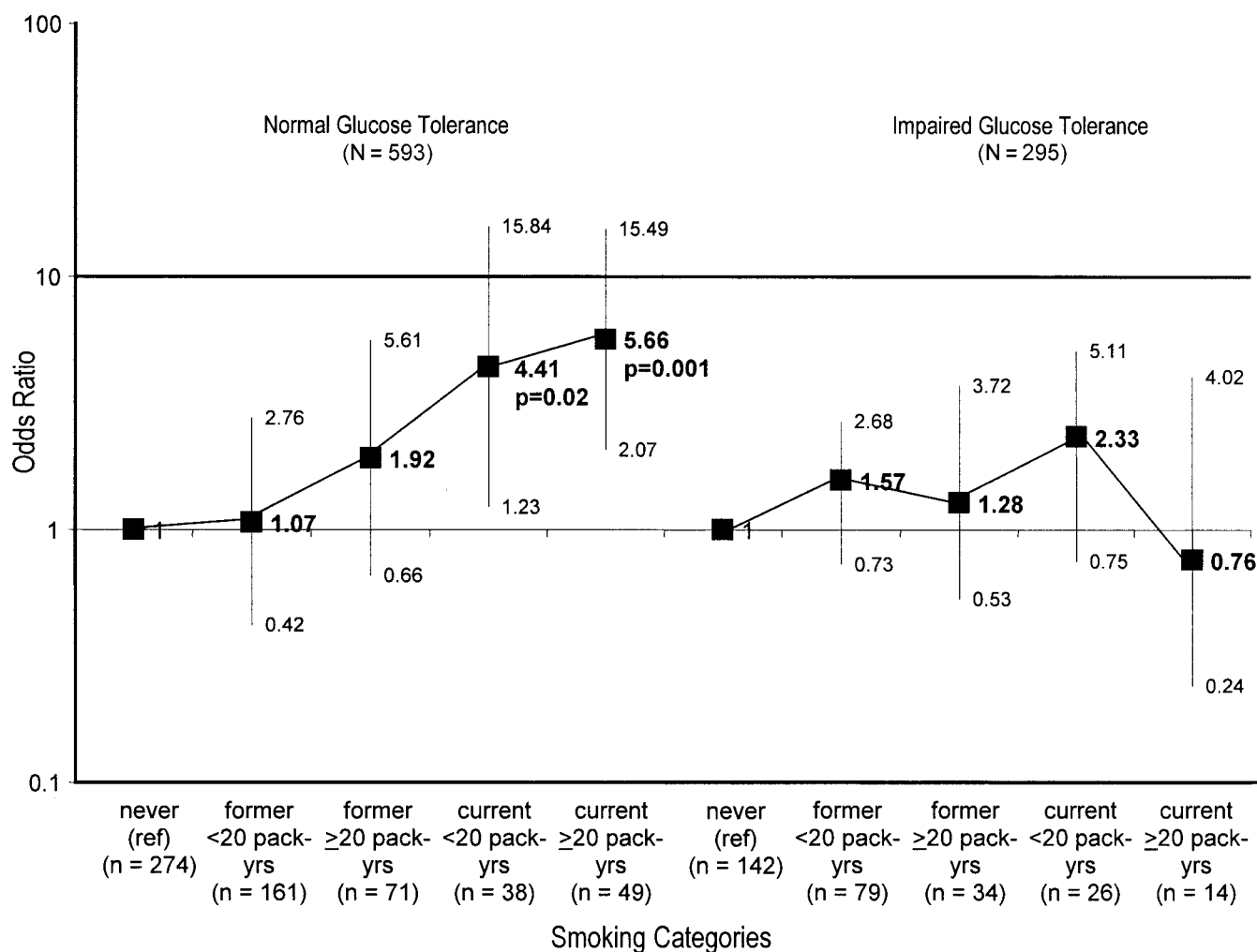


Figure 1—Odds ratios and corresponding 95% CIs for incident diabetes by pack-year category and glucose tolerance status in adjusted model 3 (smoking categories adjusted for age, sex, ethnicity, clinic, BMI, waist circumference, glucose tolerance status, HDL cholesterol level, triglyceride level, hypertension, and ethnicity \times clinic).

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 <20 cigarettes/day or \geq 20 cigarettes/day demonstrated significantly increased risk of self-reported diabetes, with a dose-response relationship being observed between increases in smoking and risk of diabetes. Wannamethee et al.

(6), studying 7,735 men in the British Regional Heart Study, found that cigarette smoking was associated with 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_1 . 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-

pants 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 HbA_{1c} 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 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.

Acknowledgments—This work was supported by the National Heart, Lung and Blood Institute of the National Institutes of Health (Grants HL47887, HL47889, HL47890, HL47892, and HL47902) and by the General Clinical Research Centers Program of the National Center for Research Resources (M01 RR431 and M01 RR01346). C.G.F. was supported through grants from the Robert Wood Johnson Foundation's Program of Research Integrating Substance Use in Mainstream Healthcare (PRISM), the National Institute on Drug Abuse, and the National Institute on Alcohol Abuse and Alcoholism administered by the Treatment Research Institute (A.T. McLellan, PhD, and B.J. Turner, MD, Co-Directors).

References

1. Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, Marks JS: The continuing increase of diabetes in the U.S. *Diabetes Care* 24:412, 2001
2. King H, Aubert RE, Herman WH, Aarnio P: Global burden of diabetes, 1995–2005: prevalence, numerical estimates, and projections. *Diabetes Care* 21:1414–1431, 1998
3. Perry IJ, Wannamethee SG, Walker MK, Thompson AG, Whincup PH, Shaper AG: Prospective study of risk factors for development of non-insulin dependent diabetes in middle-aged British men. *BMJ* 310: 560–564, 1995
4. Uchimoto S, Tsumura K, Hayashi T, Sue-matsu C, Endo G, Fujii S, Okada K: Impact of cigarette smoking on the incidence of type 2 diabetes mellitus in middle-aged Japanese men: the Osaka Health Survey. *Diabet Med* 16:951–955, 1999
5. Manson JE, Ajani UA, Liu S, Nathan DM, Hennekens CH: A prospective study of cigarette smoking and the incidence of diabetes mellitus among US male physicians. *Am J Med* 109:538–542, 2000
6. Wannamethee SG, Shaper AG, Perry IJ: Smoking as a modifiable risk factor for type 2 diabetes in middle-aged men. *Diabetes Care* 24:1590–1595, 2001
7. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC: Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. *BMJ* 310:555–559, 1995
8. Keen H, Jarrett RJ, McCartney P: The ten-year follow-up of the Bedford survey (1962–1972): glucose tolerance and diabetes. *Diabetologica* 22:73–78, 1982
9. Wilson PW, Anderson KM, Kannel WB: Epidemiology of diabetes mellitus in the elderly: the Framingham Study. *Am J Med* 80:3–9, 1986
10. Eliasson B: Cigarette smoking and diabetes. *Prog Cardiovasc Dis* 45:405–413, 2003
11. Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP: The continu-

- ing epidemics of obesity and diabetes in the United States. *JAMA* 286:1195–1200, 2001
12. Wagenknecht LE, Mayer EJ, Rewers M, Haffner S, Selby J, Borok GM, Henkin L, Howard G, Savage PJ, Saad MF, et al: The Insulin Resistance Atherosclerosis Study (IRAS) objectives, design, and recruitment results. *Ann Epidemiol* 5:464–472, 1995
 13. Stern MP, Rosenthal M, Haffner SM, Hazuda HP, Franco LJ: Sex difference in the effects of sociocultural status on diabetes and cardiovascular risk factors in Mexican Americans: the San Antonio Heart Study. *Am J Epidemiol* 120:834–851, 1984
 14. Hamman RF, Marshall JA, Baxter J, Kahn LB, Mayer EJ, Orleans M, Murphy JR, Lezotte DC: Methods and prevalence of non-insulin dependent diabetes mellitus in a biethnic Colorado population: the San Luis Valley Diabetes Study. *Am J Epidemiol* 129:296–311, 1989
 15. Haffner SM, D'Agostino RB Jr, Saad MF, Rewers M, Mykkanen L, Selby J, Howard G, Savage PJ, Hamman RF, Wagenknecht LE, et al: Increased insulin resistance and insulin secretion in nondiabetic African-Americans and Hispanics compared to non-Hispanic whites: the insulin resistance atherosclerosis study. *Diabetes* 45:742–748, 1996
 16. World Health Organization. *Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
 17. Mayer-Davis EJ, D'Agostino R Jr, Karter AJ, Haffner SM, Rewers MJ, Saad M, Bergman RN: Intensity and amount of physical activity in relation to insulin sensitivity: the Insulin Resistance Atherosclerosis Study. *JAMA* 279:669–674, 1998
 18. Bell RA, Mayer-Davis EJ, Martin MA, D'Agostino RB, Haffner SM: Associations between alcohol consumption and insulin sensitivity and cardiovascular disease risk factors. *Diabetes Care* 23:1630–1636, 2000
 19. Bergman RN, Finegood DT, Ader M: Assessment of insulin sensitivity in vivo. *Endocrinol Rev* 6:45–86, 1985
 20. Rimm EB, Manson JE, Stampfer MJ, Colditz GA, Willet WC, Rosner B, Hennekens CH, Speizer FE: Cigarette smoking and the risk of diabetes in women. *Am J Public Health* 83:211–214, 1993
 21. Henkin L, Zaccaro D, Haffner S, Karter A, Rewers M, Sholinsky P, Wagenknecht L: Cigarette smoking, environmental tobacco smoke exposure and insulin sensitivity: the Insulin Resistance Atherosclerosis Study. *Ann Epidemiol* 9:290–296, 1999
 22. Wareham NJ, Ness EM, Byrne CD, Cox BD, Day NE, Hales CN: Cigarette smoking is not associated with hyperinsulinemia: evidence against a causal relationship between smoking and insulin resistance. *Metabolism* 45:1551–1556, 1996
 23. Matthews CE, Freedson PS, Hebert JR, Stanek EJ III, Merriam PA, Rosal MC et al: Seasonal variation in household, occupational, and leisure time physical activity: longitudinal analyses from the seasonal variation of blood cholesterol study. *Am J Epidemiol* 153:172–183, 2001
 24. Greenfield TK, Kerr WC: Tracking alcohol consumption over time. *Alcohol Res Health* 27:30–38, 2003
 25. Shimokata H, Muller DC, Andres R: Studies in the distribution of body fat. III. Effects of cigarette smoking. *JAMA* 261:1169–1173, 1989
 26. Frati AC, Iniesta F, Ariza CR: Acute effect of cigarette smoking on glucose tolerance and other cardiovascular risk factors. *Diabetes Care* 19:112–118, 1996
 27. Celermajer DS, Sorensen KE, Georgakopoulos D, Bull C, Thomas O, Robinson J, Deanfield JE: Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation* 88:2149–2155, 1993
 28. Hoffman D, Hoffman I, El-Bayoumy K: The less harmful cigarette: a controversial issue: a tribute to Ernst L. Wynder. *Chem Res Toxicol* 14:767–790, 2001
 29. Schwartz GG, Il'yasova D, Ivanova A: Urinary cadmium, impaired fasting glucose, and diabetes in the NHANES III. *Diabetes Care* 26:468–470, 2003
 30. Solberg LI, Desai JR, O'Connor PJ, Bishop DB, Devlin HM: Diabetic patients who smoke: are they different? *Ann Fam Med* 2:26–32, 2004
 31. Nakanishi N, Nakamura K, Matsuo Y, Suzuki K, Tatara K: Cigarette smoking and risk for impaired fasting glucose and type 2 diabetes in middle-aged Japanese men. *Ann Intern Med* 133:183–191, 2000
 32. Zhang Y, Yu KF: What's the relative risk? *JAMA* 280:1690–1691, 1998