ARTICLE | Annals of Internal Medicine

Smoking, Smoking Cessation, and Risk for Type 2 Diabetes Mellitus

A Cohort Study

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Background: Cigarette smoking is an established predictor of incident type 2 diabetes mellitus, but the effects of smoking cessation on diabetes risk are unknown.

Objective: To test the hypothesis that smoking cessation increases diabetes risk in the short term, possibly owing to cessation-related weight gain.

Design: Prospective cohort study.

Setting: The ARIC (Atherosclerosis Risk in Communities) Study.

Patients: 10 892 middle-aged adults who initially did not have diabetes in 1987 to 1989.

Measurements: Smoking was assessed by interview at baseline and at subsequent follow-up. Incident diabetes was ascertained by fasting glucose assays through 1998 and self-report of physician diagnosis or use of diabetes medications through 2004.

Results: During 9 years of follow-up, 1254 adults developed type 2 diabetes. Compared with adults who never smoked, the adjusted hazard ratio of incident diabetes in the highest tertile of pack-years was 1.42 (95% CI, 1.20 to 1.67). In the first 3 years of follow-up, 380 adults quit smoking. After adjustment for age, race, sex, education, adiposity, physical activity, lipid levels, blood pressure, and ARIC Study center, compared with adults who never smoked, the hazard ratios of diabetes among former smokers, new quitters, and continuing smokers were 1.22 (CI, 0.99 to 1.50), 1.73 (CI, 1.19 to 2.53), and 1.31 (CI, 1.04 to 1.65), respectively. Further adjustment for weight change and leukocyte count attenuated these risks substantially. In an analysis of long-term risk after quitting, the highest risk occurred in the first 3 years (hazard ratio, 1.91 [CI, 1.19 to 3.05]), then gradually decreased to 0 at 12 years.

Limitation: Residual confounding is possible even with meticulous adjustment for established diabetes risk factors.

Conclusion: Cigarette smoking predicts incident type 2 diabetes, but smoking cessation leads to higher short-term risk. For smokers at risk for diabetes, smoking cessation should be coupled with strategies for diabetes prevention and early detection.

Primary Funding Source: National Heart, Lung, and Blood Institute and National Institute of Diabetes and Digestive and Kidney Diseases.

Ann Intern Med. 2010;152:10-17. www.annals.org

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An extensive body of literature (1) consistently identifies cigarette smoking as a risk factor for incident diabetes. Therefore, smoking cessation should decrease diabetes risk among current smokers, perhaps by reducing systemic inflammation, which is a well-established risk factor for incident diabetes (2). However, smoking cessation is also associated with substantial weight gain (3), which could tip the balance toward increased risk. Few studies (4–7) have investigated metabolic changes or diabetes risk after smoking cessation. We analyzed longitudinal data from the ARIC (Atherosclerosis Risk in Communities) Study, a biracial, community-based study of 15 792 middle-aged adults, to test the hypothesis that although smoking is an independent predictor of incident type 2 diabetes, smoking cessation increases diabetes risk in the short term, possibly because of cessation-related weight gain.

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Methods

The ARIC Study is an ongoing prospective cohort study designed to assess subclinical and clinical atherosclerosis in a cohort of adults aged 45 to 64 years who were selected by using probability sampling from Forsyth County, North Carolina; Jackson, Mississippi; the northwestern suburbs of Minneapolis, Minnesota; and Washington County, Maryland. By design, the Jackson site exclusively recruited African Americans, thereby accounting for about 90% of African Americans in the study. Most of the remaining African Americans came from the Forsyth County cohort. The sampling procedure and methods used in the ARIC Study are described elsewhere (8). Our study was based on 17-year follow-up data, including a baseline visit from 1987 through 1989, 3 follow-up clinic visits scheduled approximately 3 years apart (ARIC Study visits 2 to 4, 1990 to 1998), and annual telephone contact thereafter up to 2004. Institutional review boards of all participating institutions approved the study protocols.

Study Cohort

For the primary analyses during 9 years of follow-up through visit 4, we excluded persons who met at least 1 of the following criteria (persons can be excluded for multiple reasons): ethnicity other than black or white ($n = 48$), diabetes at baseline ($n = 1870$), missing data on smoking or diabetes status at baseline ($n = 394$), no follow-up or incomplete incident diabetes information ($n = 1147$),

Context

Smokers are at higher risk for diabetes than nonsmokers, but we do not know whether smoking cessation reduces diabetes risk. Smoking cessation reduces systemic inflammation and might reduce diabetes risk via this mechanism. However, quitters often gain weight, which could increase diabetes risk.

Contribution

In a 9-year follow-up of 10 892 adults with no diabetes at baseline, those who smoked had a higher risk for diabetes than those who never smoked (hazard ratio, 1.42 [95% CI, 1.20 to 1.67]). Among smokers who quit, diabetes risk was highest within 3 years of quitting, was mediated by weight gain, and decreased to no excess risk by 12 years.

Implication

Smokers who quit should receive advice about avoiding weight gain and about diabetes prevention and early detection.

—The Editors

missing data on relevant baseline covariates (n = 85), self-reported asthma or chronic lung disease (n = 1704), or prevalent heart disease (n = 807). Our sample consisted of 10 892 adults without diabetes at baseline (**Figure 1**). To further study change in smoking status from baseline to 3-year follow-up and risk for diabetes at later follow-up clinic visits, we excluded 769 persons who had incident diabetes at the 3-year follow-up, 232 in whom smoking data were missing at that time, 378 who were new or relapsed smokers, 151 in whom reporting on smoking status was inconsistent, and 224 in whom data on weight were missing. Therefore, we included 9398 adults without diabetes at baseline or 3-year follow-up for this part of the analysis.

In the supplementary analysis of long-term risk up to 2004, we used only self-reported information from clinic visits (1987 to 1998) and telephone interviews (1999 to 2004) to define incident cases (physician diagnosis or use of diabetes medications), resulting in 10 406 at-risk adults without diabetes at baseline and 3-year follow-up.

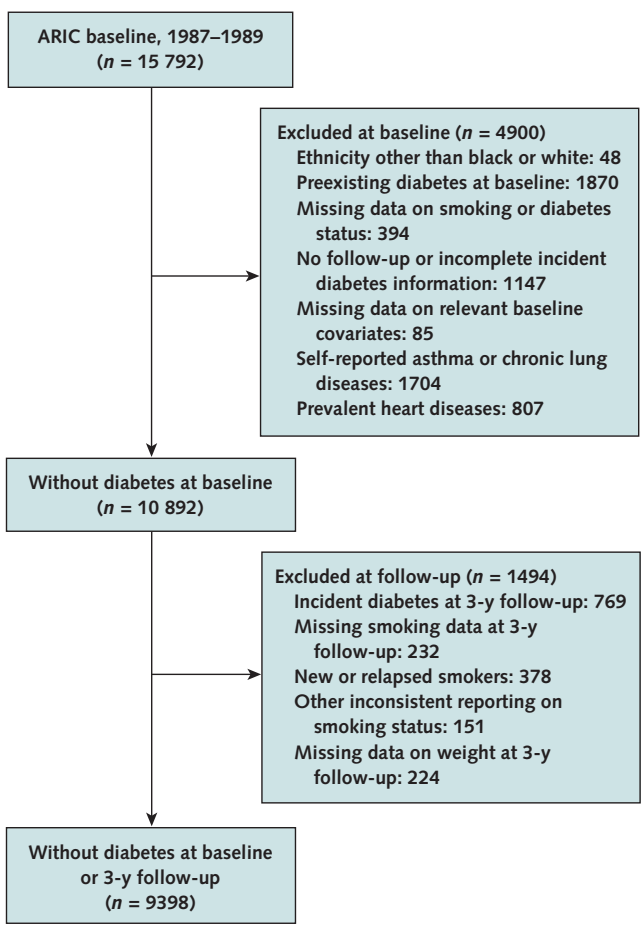
Smoking Assessment

We assessed smoking status (current, former, or never) by interview at baseline and at subsequent follow-up clinic visits. We asked current or former smokers the average number of cigarettes smoked daily during the time they smoked. We calculated pack-years of smoking as the average number of cigarettes per day times the years of smoking, divided by 20. We calculated years since quitting before baseline as baseline age minus the recalled age of quitting. In analyses of change of smoking status from baseline to 3-year follow-up, we characterized smoking status as never-smoker, former smoker at baseline, new quitter (smoker at baseline but former smoker at follow-up), and continuing smoker (smoker at both baseline and follow-up).

Incident Type 2 Diabetes Mellitus

We classified persons as having diabetes if they met any of the following criteria, adapted from the 1997 American Diabetes Association criteria: fasting glucose level of at least 7.0 mmol/L (126 mg/dL); nonfasting glucose level of at least 11.1 mmol/L (200 mg/L); current use of diabetes medication; or a positive response to the question, "Has a doctor ever told you that you had diabetes (sugar in the blood)?" In the primary analysis based on fasting glucose level and self-report, fasting glucose level was available for more than 95% of participants at each of the 4 clinic visits (1987 to 1998), regardless of smoking status. According to customary practice, persons who met criteria for diabetes on a single occasion were considered to have diabetes for the remainder of follow-up, regardless of subsequent changes in interview responses or glucose level.

Figure 1. **Study flow diagram.**



Individuals may have met more than 1 exclusion criterion. ARIC = Atherosclerosis Risk in Communities.

Other Baseline Variables

Information on age, sex, race, education level, and family history of diabetes was based on self-report. We assessed physical activity by using a modified version of the questionnaire developed by Baecke and colleagues (9), from which we derived a sport index, ranging from 1 (lowest) to 5 (highest). We measured weight, height, waist circumference, and blood pressure by standardized procedures (10). We determined systolic and diastolic blood pressure as the mean of the second and third of 3 standardized measurements by using a random-zero sphygmomanometer after 5 minutes of rest (11). We asked participants to fast for at least 8 hours before morning blood collection. We assessed serum glucose level by a modified hexokinase–glucose-6-phosphate dehydrogenase procedure. We measured total triglycerides (12) by enzymatic methods and high-density lipoprotein (HDL) cholesterol after dextran-magnesium precipitation (13). We measured leukocyte count locally by using automated cell counters (14).

Statistical Analysis

We first grouped participants by cumulative pack-years assessed at baseline. Distribution of pack-years among smokers was approximately normal and was categorized into tertiles. Adults who never smoked comprised the reference group. We determined means and frequencies of potential confounders assessed at baseline for each smoking category. We used an analysis of variance F test and Pearson chi-square test to assess the statistical significance of the differences across the 4 smoking categories. We used linear regression and a chi-square test for trend to assess the significance level for linear trend.

We calculated incidence rates of diabetes for each smoking category by using a person-years approach. For participants without diabetes, we calculated person-years from baseline to the last clinic visit date. For participants with incident diabetes, we assigned the date of occurrence according the method described by Duncan and colleagues (15) as the date when fasting glucose level reached the diagnostic threshold of 7 mmol/L (26 mg/dL), estimated with linear interpolation. We used Cox proportional hazards models for multivariable analysis to derive adjusted hazards for incident diabetes by categories of smoking status compared with persons who never smoked. We adjusted all multivariable Cox models for race, sex, ARIC Study center, education, baseline age, body mass index (BMI), waist circumference, physical activity index, triglyceride level, HDL cholesterol level, and systolic blood pressure. We confirmed the proportionality assumption by examining Schoenfeld residuals (16). We used the Efron method (17) to handle ties.

To assess effects of smoking cessation on diabetes risk, we calculated years since quitting in former smokers (baseline age minus recalled age at the time of quitting), then stratified the study population into 6 smoking categories: never-smokers, former smokers (4 categories), and current smokers. Next, we prospectively investigated changes in metabolic features and risk for diabetes at the 6- and 9-year follow-up visits in 9398 participants, as associated with change of smoking status from baseline to 3-year follow-up (visit 2). We classified smoking status into 4 categories: persons who never smoked, persons who did not resume smoking through visit 2, persons who smoked at baseline but quit smoking by visit 2 (new quitters), and persons who continued smoking through visit 2. We estimated the associations between smoking categories and incidence diabetes in both sets of analyses by using Cox models.

We assessed the relation between change of smoking status and selected metabolic variables—including baseline values, as well as changes in weight, waist circumference, fasting glucose level, total triglyceride level, HDL cholesterol level, systolic and diastolic blood pressure, and leukocyte count—by using a series of linear regression models that adjusted for sex, race, age, physical activity index (scale of 1 [lowest] to 5 [highest]), educational level, and ARIC Study center. We further adjusted for baseline values of the variable of interest and exact interval between baseline and 3-year follow-up when studying changes in metabolic variables. We used multivariable linear regression models to obtain adjusted means and mean differences between the smoking groups and never-smokers, as well as corresponding *P* values and CIs.

We performed additional multivariable analyses by using the Cox model to investigate 2 possible mediators of cessation-related diabetes risk: weight gain (baseline to visit 2) and leukocyte count at baseline—an indicator of smoking-induced systemic inflammation. First, we separately adjusted for weight gain and leukocyte count; we then simultaneously adjusted for both in a model that already included race, sex, ARIC Study center, level of education, baseline age, BMI, waist circumference, physical activity, triglyceride level, HDL cholesterol level, and systolic blood pressure.

To explore the potential of using readily available characteristics to identify high-risk subgroups among new quitters in primary care settings, we conducted post hoc analyses of diabetes risk (compared with persons who never smoked) associated with various demographic (age, race, and sex), anthropometric (weight change), and behavioral (cigarettes per day) factors. We dichotomized continuous variables on the basis of distributional or conventional cutoffs. Older age, heavier smoking before quitting, and greater weight gain after quitting were believed to impose higher risk among new quitters. We first stratified analyses by sex and race. We subsequently combined categories with similar risks to allow fewer subgroups and more stable hazard estimates through multivariable Cox regression modeling after adjustment for other potential covariates.

To extend estimation of long-term trends in diabetes risk associated with smoking and smoking cessation throughout 17 years of follow-up, we conducted supple-

mentary analyses, including self-reported data from follow-up telephone interviews from 1999 through 2004. To maintain consistency in outcome assessment, this supplementary analysis incorporated self-reported data only from the clinic visits (1987 through 1998) and ignored available data on fasting glucose level. To be consistent with the approximate 3-year interval between follow-up clinic visits, we abstracted smoking status and incident diabetes cases every 3 years from the annual telephone interviews and calculated the risks for up to 12 years after the participant quit. We assumed that incident cases occurred at the midpoint between the last visit or phone call at which diabetes was reported to be absent and the first visit or phone call at which diabetes was found. This approach has been used in other ARIC publications (18, 19).

Like most reports based on observational studies, ours did not apply multiplicity adjustments for the number of statistical tests conducted. However, the primary analyses were based on a priori hypotheses, and most statistical tests were done to identify potential confounders and mediators for the observed associations of incident diabetes risk with smoking and smoking cessation.

Tests of significance were 2-tailed, with an α level of 0.05. We performed analyses by using SAS, version 9.1 (Cary, North Carolina), and Stata/SE, version 10.0 (College Station, Texas).

Role of the Funding Source

The ARIC Study is supported by contracts from the National Heart, Lung, and Blood Institute (NHLBI) and by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The NHLBI was involved in the design and management of the ARIC study and remains involved in its ongoing conduct, but neither NHLBI nor NIDDK was involved in the conception or execution of this paper. The writing group had full access to all study data and had final responsibility for the decision to submit the manuscript for publication.

RESULTS

Baseline Characteristics

Table 1 shows baseline characteristics of 10 892 adults who initially did not have diabetes, by pack-years of smoking. Persons with higher cumulative smoking exposure were significantly more likely to be male, white, and less educated and to have a higher leukocyte count and waist-to-hip ratio but lower BMI (all P for linear trend $<$ 0.001).

Incident Type 2 Diabetes

During 9 years of follow-up, 1254 adults developed type 2 diabetes. A graded relationship existed between pack-years of smoking and incidence rates of type 2 diabetes. Diabetes incidence increased from 13.3 per 1000 person-years in persons who never smoked to 18.5 per 1000 person-years in the highest tertile of pack-years, corresponding to an age- and race-adjusted relative risk for 1.40 (95% CI, 1.20 to 1.64). In multivariable analyses using Cox proportional hazards models, the significant, graded association between pack-years and incidence of diabetes persisted after adjustment for race, sex, ARIC Study center, level of education, baseline age, BMI, waist circumference, physical activity, triglyceride level, HDL cholesterol level, and systolic blood pressure. Compared with persons who never smoked, the adjusted hazard ratios of diabetes among persons who smoked no more than 13 pack-years, 14 to 30 pack-years, and more than 30 pack-years were 1.09 (CI, 0.92 to 1.28), 1.38 (CI, 1.18 to 1.61), and 1.42 (CI, 1.20 to 1.67), respectively (**Appendix Figure**, available at www.annals.org).

Smoking Cessation and Diabetes Risk

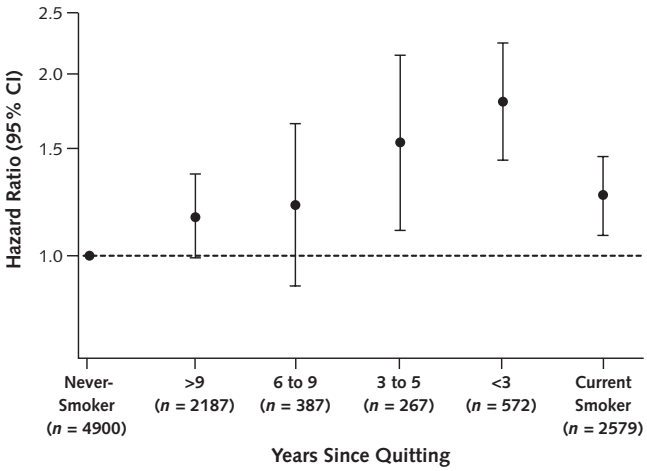
After adjustment for race, sex, ARIC Study center, level of education, baseline age, BMI, waist circumference, physical activity, triglyceride level, HDL cholesterol level, and systolic blood pressure, compared with participants who never smoked, hazard ratios of incident diabetes during 9 years of follow-up were 1.16 (CI, 0.99 to 1.36), 1.21

Table 1. **Characteristics of 10 892 Middle-Aged Adults Without Diabetes at Baseline**

Characteristic	Never-Smokers (n = 4900)	Smokers			*P* Value*
		≤13 Pack-Years (n = 2022)	14–30 Pack-Years (n = 2007)	>30 Pack-Years (n = 1963)	
Men, %	30	44	52	67	<0.001
White race, %	74	73	79	85	<0.001
Mean age at baseline (SD), *y*	53.7 (5.7)	53.0 (5.6)	53.5 (5.8)	55.0 (5.3)	<0.001
Education <12 y, %	17	18	20	25	<0.001
Parental history of diabetes, %	13	12	12	11	0.48
Mean physical activity index score (SD)	2.4 (0.8)	2.5 (0.8)	2.5 (0.8)	2.4 (0.8)	<0.001
Mean body mass index (SD), kg/m^2	27.6 (5.3)	27.2 (5.1)	26.8 (4.6)	26.6 (4.5)	<0.001
Mean waist-to-hip ratio (SD)	0.91 (0.08)	0.91 (0.08)	0.92 (0.07)	0.94 (0.07)	<0.001
Hypertension, %	39	37	34	37	<0.001
Mean leukocyte count (SD), $\times 10^9$ *cells/L*	5.4 (1.5)	5.7 (1.6)	6.4 (1.9)	7.0 (2.1)	<0.001

* Calculated by using the Pearson chi-square test for categorical variables or analysis of variance F test for continuous variables at baseline.

Figure 2. **Nine-year adjusted hazard ratio (1990–1998) for incident diabetes in 10 892 middle-aged adults, by years since quitting before baseline (1987–1989).**



Estimates are simultaneously adjusted for race, sex, Atherosclerosis Risk in Communities Study center, level of education, baseline age, body mass index, waist circumference, physical activity, triglyceride level, high-density lipoprotein cholesterol level, and systolic blood pressure. Bars indicate 95% CIs. Never-smokers are the reference group.

(CI, 0.89 to 1.65), 1.54 (CI, 1.10 to 2.14), 1.80 (CI, 1.44 to 2.25), and 1.26 (CI, 1.08 to 1.46) in former smokers who quit more than 9 years before the baseline visit, 6 to 9 years before, 3 to 5 years before, and within 3 years before and in current smokers, respectively (**Figure 2**).

From baseline to the 3-year clinic visit, 380 participants quit smoking and 2018 participants continued to smoke. Compared with their counterparts who continued to smoke, those who quit had significantly fewer pack-years of smoking (28 vs. 31; $P < 0.001$) and lower leukocyte counts (7.0×10^9 cells/L vs. 7.2×10^9 cells/L; $P = 0.017$) at baseline, but no significant differences existed in sex ($P = 0.48$), race ($P = 0.159$), age ($P = 0.156$), level of education ($P = 0.106$), parental history of diabetes ($P = 0.146$), physical activity ($P = 0.92$), BMI ($P = 0.26$), waist-to-hip ratio ($P = 0.86$), or percentage of hypertension ($P = 0.68$) for baseline comparisons.

In multivariable linear regression models adjusting for sex, race, baseline age, physical activity, educational level, and ARIC Study center (**Appendix Table**, available at www.annals.org), adults who quit smoking between baseline and visit 2 had significantly lower body weight, smaller waist circumference, lower HDL cholesterol level, higher triglyceride level, lower blood pressure, and higher leukocyte count at baseline than their counterparts who never smoked. Prospectively, these new quitters, compared with persons who never smoked, had more significant increases in weight, waist circumference, and fasting glucose level. They also had a small but statistically significant decrease in leukocyte count ($P < 0.001$). Compared with persons who never smoked, those who continued to smoke had less gain in weight and waist circumference, greater decreases in diastolic blood pressure and HDL cholesterol level, and a greater increase in leukocyte count.

In multivariable analyses using Cox proportional hazards models, compared with persons who never smoked, the adjusted hazard ratios of diabetes among former smokers at baseline, new quitters, and continuing smokers were 1.22 (CI, 0.99 to 1.51), 1.73 (CI, 1.19 to 2.53), and 1.31 (CI, 1.04 to 1.65), respectively, after adjustment for race, sex, ARIC Study center, level of education, baseline age, BMI, waist circumference, physical activity, triglyceride level, HDL cholesterol level, and systolic blood pressure (**Table 2**, model 1).

Possible Mediators of Diabetes Risk

Adjustment for weight gain partially explained excess risk in new quitters but did not account for excess risk in continuing smokers (**Table 2**, model 2). Adjustment for leukocyte count attenuated the risk relationships in both new quitters and continuing smokers (**Table 2**, model 3). When simultaneously adjusted for both possible mediators, diabetes risk was markedly attenuated in new quitters and

Table 2. **Incident Diabetes (ARIC Visits 3 and 4) by Smoking Status in 9398 Middle-Aged Adults Without Diabetes at Baseline and at 3-Year Follow-up***

Incident Rate	Never-Smokers (*n* = 4090)	Former Smokers (*n* = 2910)	New Quitters (*n* = 380)	Continuing Smokers (*n* = 2018)
Unadjusted, per 1000 person-years	10.1 (8.9–11.6)	13.2 (11.6–15.3)	17.8 (12.2–25.2)	13.3 (10.9–15.7)
Model 1†	1.0	1.22 (0.99–1.51)	1.73 (1.19–2.53)	1.31 (1.04–1.65)
Model 2‡	1.0	1.22 (0.99–1.49)	1.53 (1.04–2.24)	1.34 (1.06–1.70)
Model 3§	1.0	1.20 (0.98–1.48)	1.40 (0.94–2.07)	1.04 (0.81–1.35)
Model 4‖	1.0	1.21 (0.98–1.48)	1.24 (0.83–1.84)	1.08 (0.84–1.39)

ARIC = Atherosclerosis Risk in Communities.
* Data are incidence rates (95% CI) by smoking status and hazard ratios (95% CI) of a given smoker group versus never-smokers.
† Adjusted for race, sex, ARIC Study center, level of education, baseline age, body mass index, waist circumference, physical activity, triglyceride level, high-density lipoprotein cholesterol level, and systolic blood pressure.
‡ Adjusted for all factors in model 1 plus weight change.
§ Adjusted for all factors in model 1 plus baseline leukocyte count.
‖ Adjusted for all factors in model 1 plus weight change and baseline leukocyte count.

continuing smokers but essentially unchanged in former smokers (**Table 2**, model 4).

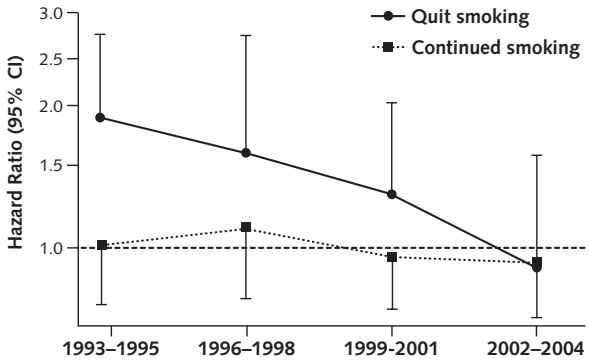
Identification of High-Risk Subgroups Among New Quitters

We conducted a series of post hoc analyses to identify high-risk subgroups of new quitters by using various categories of sex, race, age, weight change, and cigarettes per day. Compared with persons who never smoked, male new quitters with the highest diabetes risk seemed to be those who were aged 60 years or older at visit 2, smoked 20 or more cigarettes per day before quitting, and gained more than 4 kg between baseline and visit 2 (hazard ratio, 3.44 [CI, 1.07 to 11.04]), followed by men younger than 60 years who had the same smoking and weight-gain experiences (hazard ratio, 2.28 [CI, 1.05 to 4.93]). Regardless of age, male quitters who smoked 20 or more cigarettes per day before quitting but did not gain more than 4 kg between baseline and visit 2 also had an increased, although not statistically significant, risk (hazard ratio, 1.96 [CI, 0.79 to 4.82]). Among female new quitters, those who smoked fewer than 20 cigarettes per day before quitting but gained more than 4 kg between baseline and visit 2 had the highest diabetes risk (hazard ratio, 2.69 [CI, 1.25 to 5.79]). We did not find statistically significantly increased risk in other subgroups, which may be due in part to the modest size of the new-quitters group.

Supplementary Analysis of Long-Term Risk After Quitting

We calculated hazard ratios (**Figure 3**) based on self-reported diabetes through 2004. The highest diabetes risk in quitters occurred during the first 3 years after quitting (hazard ratio, 1.89 [CI, 1.26 to 2.82]), then gradually decreased until no excess risk was seen at 12 years. In contrast, risk for diabetes in continuing smokers remained flat during extended follow-up, with hazard ratios ranging from 0.93 (CI, 0.71 to 1.22) to 1.10 (CI, 0.78 to 1.56).

Figure 3. **Adjusted hazard ratios for incident self-reported diabetes during 12 years in 10 406 middle-aged adults without diabetes at baseline and 3-year follow-up.**



Patients, *n*	1993–1995	1996–1998	1999-2001	2002–2004
	Clinic	Clinic	Telephone	Telephone
At risk	10 406	10 004	9744	9256
Quit	423	395	381	359
Continued	2210	2133	2079	1987

The circles connected by the solid line represent adults who quit smoking between baseline (1987–1989) and visit 2 (1990–1992). The squares connected by the dotted line represent smokers who continued to smoke. Nonsmokers are the reference group (not shown). Estimates are simultaneously adjusted for race, sex, Atherosclerosis Risk in Communities Study center, level of education, baseline age, body mass index, waist circumference, physical activity, triglyceride level, high-density lipoprotein cholesterol level, and systolic blood pressure. Bars indicate upper and lower CIs (for clarity, only one interval is shown for each estimate).

DISCUSSION

In this prospective study of middle-aged men and women, greater cumulative exposure to cigarette smoking predicted development of type 2 diabetes. As expected, the association was graded and was independent of many potentially confounding factors. However, smoking cessation did not seem to reduce this risk; on the contrary, adults who quit smoking experienced relatively more adverse changes in their metabolic profile and an increased risk for incident diabetes that peaked within 3 years of quitting but was still observable 6 years after quitting. The increased risk seemed to be partially mediated by weight gain and systemic inflammation.

Our finding of a 40% increase in hazard ratio for smokers is similar to that of a recent meta-analysis (1) of 25 prospective cohort studies with follow-up ranging from 5 to 30 years, which reported pooled adjusted relative risk for diabetes of 1.44 (CI, 1.31 to 1.58) for current smokers compared with nonsmokers. The gradient across the intensity of smoking exposure is similar. In the meta-analysis, the risk for diabetes was greater for heavy smokers (>20 cigarettes/d; relative risk, 1.61 [CI, 1.43 to 1.80]) than for lighter smokers (relative risk, 1.29 [CI, 1.13 to 1.48]) or former smokers (relative risk, 1.23 [CI, 1.14 to 1.33]) compared with continuing smokers. However, the meta-analysis did not address the effects of smoking cessation.

After searching MEDLINE for all pertinent literature published in English until January 2009 using the keywords "diabetes" and "cessation," we found few studies that investigated smoking cessation and changes in metabolic profiles. Balkau and colleagues (4) analyzed data from 1958 men and 2028 women aged 30 to 65 years who were in the DESIR (Data from an Epidemiological Study on the Insulin Resistance Syndrome) cohort. The authors observed that a reduction of 10 cigarettes per day over 3 years was associated with significant increases in insulin level (7%), glucose level (0.11 mmol/L [1.98 mg/dL]), triglyceride level (8%), waist circumference (0.97 cm), and BMI (0.31 kg/m^2) in men and significant increases in HDL cholesterol level (0.06 mmol/L [2.32 mg/dL]), waist circumference (1.1 cm), and BMI (0.59 kg/m^2) in women. Although our results are presented in a different format, we

found a similar spectrum of adverse metabolic changes in adults who quit smoking entirely.

Only 2 studies (6, 7) have investigated smoking cessation in relation to diabetes risk. In 7124 men in the British Regional Heart Study who initially did not have diabetes, Wannamethee and colleagues (6) found that men who quit smoking in the first 5 years of follow-up had significant mean weight gain (9.4 kg vs. 7.1 kg) and subsequently higher risk for diabetes (adjusted relative risk, 2.03 [CI, 1.22 to 3.37]) than persons who never smoked. More recently, Hur and colleagues (7) reported on 27 635 Korean men aged 35 to 44 years who initially did not have diabetes and who were members of the Korean Medical Insurance Corporation Study cohort. In this cohort, compared with nonsmokers, men who quit smoking in the past 2 to 6 years had a 2-fold increased risk for diabetes (relative risk, 2.13 [CI, 1.51 to 3.00]). However, our study expanded on the short-term deleterious changes in diabetes risk factors found with quitting: In addition to large weight gain, we observed large gains in waist circumference and sustained elevation of inflammation, as indicated by leukocyte count.

Our study suggests that heavy smokers with evidence of systemic inflammation who gain substantial weight after quitting are at the highest risk for diabetes. Past studies have found a link between inflammation and rapid fatty tissue deposition (20), obesity (especially in quitters) (21), insulin resistance (22), lipoprotein metabolism (23), and glucose homeostasis (24). Heavy smoking is also a marker of nicotine exposure. Withdrawal of nicotine may lead to increased appetite and excess caloric intake (25).

We were surprised that continuing smokers experienced only a small excess risk for diabetes during extended follow-up, despite the inflammatory burden imposed by smoking. A possible explanation is that nicotine and its metabolites, through α-7 nicotinic acetylcholine receptors, may exert anti-inflammatory effects. These effects have been documented elsewhere in leukocyte cells and adipocytes, both in vitro (26, 27) and in vivo (28, 29).

Strengths of our study include a community-based sampling method; a biracial cohort; availability of blood measurements; extensive data on potential confounders; a large sample size, which increased precision and permitted simultaneous statistical adjustment for multiple variables; and up to 17 years of follow-up, which offered the opportunity to study long-term effects, including changes in smoking exposure. Nevertheless, several limitations deserve mention. First, like most epidemiologic studies of type 2 diabetes, we did not require consistent glucose elevation or repeated confirmations of diabetes self-report to classify persons as having diabetes: Once criteria were met on a single occasion, persons were considered to have diabetes for the remainder of follow-up. To the extent that this convention reduced the specificity of diabetes classification, it may have led us to underestimate the strength of the associations we observed. Second, in the supplementary analysis, we based ascertainment of diabetes and smoking status on telephone interviews. Data obtained from telephone interviews may not have been equivalent to those obtained in face-to-face interviews at clinic visits. Third, smokers might be underrepresented in later years of follow-up owing to higher mortality or lower response rates. Fourth, given the strong relation between type 2 diabetes and central adiposity, even the most meticulous adjustment for BMI and waist circumference leaves some possibility of residual confounding. Finally, an observational study cannot prove causality. Quitters may have been at inherently higher risk for diabetes before quitting, although we accounted for a wide range of established diabetes risk factors, including age, BMI, physical activity, and lipids.

Our study has 2 main implications. First, despite the well-established association of cumulative smoking with long-term diabetes risk, smoking cessation does not seem to reduce the short-term risk for diabetes but rather increases it. Of course, smoking cessation has many beneficial health effects that outweigh this short-term risk. Nonetheless, physicians should be aware of this elevated risk and should consider countermeasures, especially for heavy smokers. Such countermeasures might include lifestyle counseling and aggressive weight management, use of nicotine replacement therapy—which seems to blunt weight gain related to quitting (30)—and more frequent checking of blood glucose as a means of early detection. Second, our results imply that smoking prevention should be superior to smoking cessation as a means of reducing smoking-related risk for diabetes in the general population.

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Acknowledgment: The authors thank the staff and participants in the ARIC Study for their important contributions.

Grant Support: The ARIC Study is supported by contracts from the NHLBI (N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022) and a grant from the NIDDK (5R01-DK56918-03).

Potential Conflicts of Interest: *Grants received:* H.C. Yeh (NIDDK), B.B. Duncan (Brazilian National Research Council), N.Y. Wang (NIDDK, National Center for Research Resources), F.L. Brancati (NIDDK).

Reproducible Research Statement: *Study protocol:* ARIC protocols are available in the public domain through the ARIC Web site (www.cscc.unc.edu/aric/). *Statistical code:* Not available. *Data set:* ARIC data are available through request from the NHLBI data repository.

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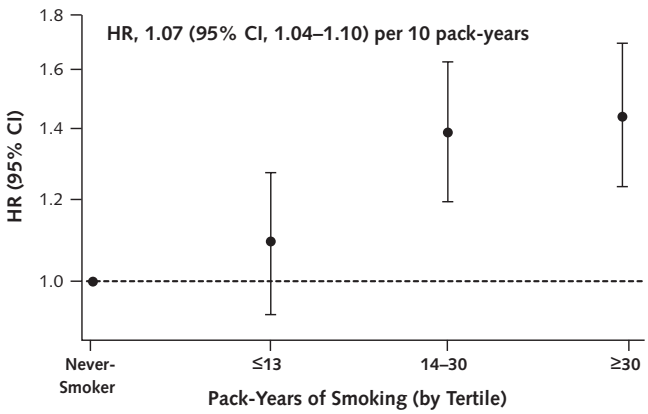
Appendix Figure. **Nine-year adjusted hazard ratio for incident diabetes in 10 892 middle-aged adults, by tertile of pack-years of smoking at baseline.**



Estimates are simultaneously adjusted for race, sex, Atherosclerosis Risk in Communities Study center, level of education, baseline age, body mass index, waist circumference, physical activity, triglyceride level, high-density lipoprotein cholesterol level, and systolic blood pressure. Bars indicate 95% CIs. Never-smokers are the reference group. Summary HRs were estimated in a model in which pack-years were handled as a continuous variable. HR = hazard ratio.

Appendix Table. **Selected Traits From Baseline to 3-Year Follow-up in 9398 Middle-Aged Adults Without Diabetes at Baseline and 3-Year Follow-up***

Characteristic	Never-Smokers (n = 4090)	Former Smokers (n = 2910)	New Quitters (n = 380)	Continuing Smokers (n = 2018)	F Test P Value
Weight, *kg*					
Baseline	77.3 (76.8 to 77.7)	78.1 (77.6 to 78.6)	73.9 (72.5 to 75.3)	72.6 (72.0 to 73.3)	<0.001
Change	1.1 (1.0 to 1.3)	1.2 (1.1 to 1.4)	3.8 (3.3 to 4.2)	0.6 (0.4 to 0.8)	<0.001
Waist circumference, *cm*					
Baseline	95.4 (95.0 to 95.8)	96.0 (95.5 to 96.5)	93.1 (91.98 to 94.4)	92.4 (91.98 to 93.0)	<0.001
Change	1.1 (0.9 to 1.3)	1.2 (1.0 to 1.4)	3.2 (2.6 to 3.9)	0.6 (0.4 to 0.9)	<0.001
Fasting glucose level, *mmol/L*					
Baseline	5.41 (5.39 to 5.42)	5.46 (5.43 to 5.47)	5.40 (5.36 to 5.45)	5.40 (5.38 to 5.43)	<0.001
Change	0.20 (0.19 to 0.22)	0.21 (0.91 to 0.23)	0.29 (0.24 to 0.34)	0.20 (0.18 to 0.22)	0.004
Fasting glucose level, *mg/dL*					
Baseline	97.5 (97.2 to 97.7)	98.3 (98.0 to 98.6)	97.3 (96.5 to 98.2)	97.4 (97.0 to 97.7)	<0.001
Change	3.6 (3.4 to 3.9)	3.9 (3.6 to 4.2)	5.1 (4.3 to 5.9)	3.7 (3.2 to 4.0)	0.004
HDL cholesterol level, *mmol/L*					
Baseline	1.40 (1.38 to 1.41)	1.41 (1.39 to 1.42)	1.30 (1.26 to 1.34)	1.32 (1.30 to 1.34)	<0.001
Change	−0.06 (−0.07 to −0.05)	−0.05 (−0.06 to −0.04)	−0.02 (−0.05 to 0.03)	−0.07 (−0.08 to −0.06)	<0.001
HDL cholesterol level, *mg/dL*					
Baseline	54.0 (53.5 to 54.4)	54.3 (53.8 to 54.9)	50.7 (49.1 to 52.2)	50.8 (50.1 to 51.5)	<0.001
Change	−2.2 (−2.5 to −2.0)	−2.0 (−2.3 to −1.6)	−0.9 (−1.8 to 0.1)	−2.9 (−3.3 to −2.4)	<0.001
Triglyceride level, *mmol/L*					
Baseline	1.32 (1.30 to 1.36)	1.41 (1.38 to 1.44)	1.50 (1.43 to 1.60)	1.41 (1.38 to 1.46)	<0.001
Change	0.06 (0.04 to 0.08)	0.06 (0.04 to 0.09)	0.13 (0.06 to 0.20)	0.09 (0.06 to 0.12)	0.21
Triglyceride level, *mg/dL*					
Baseline	116 (114 to 118)	123 (121 to 126)	132 (125 to 139)	125 (122 to 128)	<0.001
Change	5.6 (3.8 to 7.5)	5.6 (3.5 to 7.9)	11.3 (5.4 to 17.2)	7.6 (5.0 to 10.2)	0.21
Systolic blood pressure, *mm Hg*					
Baseline	120 (119 to 121)	119 (119 to 120)	117 (116 to 117)	117 (115 to 118)	<0.001
Change	1.0 (0.6 to 1.4)	1.0 (0.6 to 1.5)	2.5 (1.2 to 3.7)	0.7 (0.1 to 1.2)	<0.001
Diastolic blood pressure, *mm Hg*					
Baseline	74 (73.7 to 74.4)	73 (73.0 to 73.7)	71 (70.2 to 71.1)	70 (70.0 to 71.1)	<0.001
Change	−0.6 (−0.9 to −0.4)	−0.9 (−1.2 to −0.7)	−0.5 (−1.3 to −0.3)	−2.0 (−2.4 to −1.7)	<0.001
Leukocyte count, × 10^9 *cells/L*					
Baseline	5.4 (5.39 to 5.49)	5.6 (5.5 to 5.7)	6.9 (6.8 to 7.1)	7.3 (7.2 to 7.3)	<0.001
Change	−0.2 (−0.23 to −0.15)	−0.1 (−0.2 to −0.1)	−0.5 (−0.6 to −0.3)	0.3 (0.2 to 0.4)	<0.001

ARIC = Atherosclerosis Risk in Communities; HDL = high-density lipoprotein.
* All values are adjusted means (95% CI). Baseline mean is adjusted for race, sex, ARIC Study center, level of education, baseline age, and physical activity. Mean change is adjusted for race, sex, ARIC Study center, level of education, baseline age, physical activity, baseline values, and time between baseline and 3-year follow-up.