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Smoking, Smoking Cessation, and the Risk for Type 2 Diabetes Mellitus: A Cohort Study

Hsin-Chieh Yeh, PhD^{1,2}, Bruce B. Duncan, MD, PhD^{3,4}, Maria Ines Schmidt, PhD^{3,4}, Nae-Yuh Wang, PhD¹, and Frederick L. Brancati, MD, MHS^{1,2}

¹Department of Medicine, Johns Hopkins University, Baltimore, Maryland, USA

²Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland, USA

³Graduate Studies Program in Epidemiology, Federal University of Rio Grande do Sul, Porto Alegre, RS Brazil

⁴Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA

Abstract

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 due to cessation-related weight gain.

Design—Prospective cohort study.

Setting—The Atherosclerosis Risk in Communities (ARIC) study.

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

Measurements—We assessed smoking by interview at baseline and at subsequent follow-ups. 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, 1,254 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, lipids, blood pressure, and ARIC center, compared with adults who never smoked the hazard ratio 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 the most 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.

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 therefore 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.

METHODS

The ARIC Study

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 the following 4 U.S. communities: 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 have been 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 Visits 2 to 4, 1990 to 1998), and annual telephone contacts thereafter up to 2004. Institutional review boards of all participating institutions approved the study protocols.

Composition of the Study Cohort

For the primary analyses during 9 years of follow-up through visit 4, we excluded persons on the basis of 1 of the following criteria (persons can be excluded for multiple reasons): ethnicity other than black or white ($n = 48$), preexisting diabetes at baseline ($n = 1,870$), missing data on smoking or diabetes status at baseline ($n = 394$), no follow-up or incomplete incident diabetes information ($n = 1,147$), missing data on relevant baseline covariates ($n = 85$), self-reported asthma or chronic lung disease ($n = 1,704$), or prevalent heart disease ($n = 807$). The study sample consisted of 10,892 adults without diabetes at baseline (Figure 1). To further study the change of smoking status from baseline to 3-year follow-up and the risk for diabetes at later follow-up clinic visits, we excluded persons who had incident diabetes at the 3-year follow-up ($n = 769$) in whom smoking data were missing at the time ($n = 232$),

who were new or relapsed smokers ($n = 378$), in whom reporting on smoking status was inconsistent ($n = 151$), or in whom data on weight were missing ($n = 224$). Therefore, we included 9,398 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 (that is, 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 smokers, former smokers, or persons who never smoked) by interview at baseline and at subsequent follow-up clinic visits. We asked smokers (current or former) 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 regarding 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 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.

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 triglyceride level (12) by enzymatic methods and high-density lipoprotein (HDL) cholesterol

level after dextran-magnesium precipitation (13). We measured leukocyte count locally by 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 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 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 to 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 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 as well as risk for diabetes at the 6- and 9-year follow-up visits in 9,398 participants 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 center. We further adjusted for baseline values of the variable of interest and exact time 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 smoking categories and the never-smokers group, as well as corresponding p values and CIs.

To investigate possible mediators of cessation-related diabetes risk, we performed additional multivariable analyses by using the Cox model to investigate 2 possible mediators: 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 into 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 (as 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 through 17 years of follow-up, we conducted supplementary 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 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, 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 were 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, stratified 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, 1,254 adults developed type 2 diabetes. A graded relationship existed between pack-years of smoking and incidence rates of type 2 diabetes. Diabetes incidence rose from 13.3 per 1,000 person-years in persons who never smoked to 18.5 per 1,000 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 ratio 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).

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, the adjusted hazard ratios of incident diabetes during 9 years of follow-up were 1.16 (CI, 0.99 to 1.36), 1.21 (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 6 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 2,018 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 center (Appendix Table), adults who quit smoking between baseline and visit 2, compared with their counterparts who never smoked, had significantly lower body weight, smaller waist circumference, lower HDL cholesterol level, higher triglyceride level, lower blood pressure, and higher leukocyte count at baseline. Prospectively, these new quitters, compared with persons who never smoked, had more significant increases in weight, waist circumference, and fasting glucose. They also had a small but statistically significant decrease in leukocyte count ($p = 0.001$). On the other hand, persons who continued to smoke, compared with those who never smoked, displayed 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 the Cox proportional hazards models, compared with persons who had 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 continuing smokers but essentially unchanged in former smokers (Table 2, Model 4).

Identification of High-Risk Subgroup 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]). Male quitters who, regardless of age, smoked 20 or more cigarettes per day before quitting but did not gain more than 4 kg between baseline and visit 2 also had 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 were associated with 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 in part may be due to the modest sample size of the new-quitters group.

Supplementary Analysis on Long-Term Risk After Quitting

In this set of analyses, 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).

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, peaking within 3 years of quitting, but 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/day; 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 continued 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 keywords “diabetes” and “cessation,” we found few studies that investigated smoking cessation and changes in metabolic profiles. Balkau and colleagues (4) analyzed data from 1,958 men and 2,028 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 (7%), glucose (0.11 mmol/L [1.98 mg/dL]), triglyceride level (8%), waist circumference (0.97 cm), and BMI (0.31 kg/m²) 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/m²) 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 7,124 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 weight gain (mean weight gain, 9.4 kg vs. 7.1 kg in persons who never smoked) and subsequently higher risk for diabetes than persons who never smoked (adjusted relative risk, 2.03 [CI, 1.22 to 3.37]). 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 $\alpha 7$ 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. Second, smokers might be underrepresented in later years of follow-up due to higher mortality or lower response rates. Third, 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. Fourth, an observational study cannot prove causality. Quitters may have been at inherently higher

risk for diabetes before quitting, although we have 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 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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APPENDIX

Figure 1.

Nine-year adjusted hazard ratio (1990–1998) for incident diabetes in 10,892 middle-aged adults by tertile of pack-years of smoking at baseline (1987–1989). Estimates are simultaneously adjusted for race, sex, ARIC study center, level of education, baseline age, body mass index, waist circumference, physical activity, triglycerides, HDL cholesterol, and systolic blood pressure. Bars indicate 95% confidence intervals. Never-smokers comprise the reference group. Summary relative hazards [95% CI] were estimated in a model in which pack-years were handled as a continuous variable.

Figure 1.
Study flow diagram
Individuals may have met more than 1 exclusion criteria.

Figure 2.

Nine-year adjusted hazard ratio (1990–1998) for incident diabetes in 10,892 middle-aged adults by years of quitting before baseline (1987–1989). Estimates are simultaneously adjusted for race, sex, ARIC Study center, level of education, baseline age, body mass index, waist circumference, physical activity, triglycerides, HDL cholesterol, and systolic blood pressure. Bars indicate 95% confidence intervals. Never-smokers comprise the reference group.

Figure 3. Adjusted hazard ratios for incident self-reported diabetes over 12 years by smoking status in 10,406 middle-aged adults without diabetes at baseline and 3-year follow-up

The diamonds connected by the solid line represents hazard ratios of adults who quit smoking between baseline (Visits 1, 1987–89) and Visit 2 (1990–1992), and continued cessation up to the interval prior to the clinic follow-up visits or telephone interviews where hazard ratios were estimated. The circles connected by the dotted line represents hazard ratios of smokers who continued smoking up to the prior interval. Non-smokers comprise the reference group (not depicted on the graph). Estimates are simultaneously adjusted for race, sex, ARIC study center, level of education, baseline age, body mass index, waist circumference, physical activity, triglycerides, HDL cholesterol, and systolic blood pressure. The bars indicate upper and lower confidence intervals; (for the sake of clarity, only one interval is shown for each estimate).

Table 1

Baseline characteristics according to cumulative exposure to smoking in 10,892 middle aged adults without diabetes at baseline.

	Never smoked	Cumulative Pack-years by Tertile			p value [†]
	0 (N = 4,900)	1 – 13 (n = 2,022)	14 – 30 (N = 2,007)	30+ (N = 1,963)	
Male, %	30	44	52	67	<0.001
White Race, %	74	73	79	85	<0.001
Mean age at baseline (SD), years	54 (5.7)	53 (5.6)	53 (5.8)	55 (5.3)	<0.001
Education <12 years, %	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

[†]P-values correspond to significance tests using Pearson's chi-square test for categorical variables or Analysis of Variance F-test for continuous variables at baseline.

Table 2

Incidence diabetes (ARIC Visit 3 and Visit 4) by smoking status in 9,846 middle aged adults without diabetes at baseline and at 3-year follow-up. Data presented are incidence rates (95% CI) by smoking status and hazard ratios (95% CI) if a given smoker group vs never-smokers.

	Never smoked (N = 4,090)	Ex-smokers (N=2,910)	New quitters (N=380)	Continuing smokers (N=2,018)
Unadjusted incident rate, per 1,000 person-year	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]

Model 1: Adjusted for race, sex, ARIC study center, level of education, baseline age, body mass index, waist circumference, physical activity, triglycerides, HDL cholesterol, and systolic blood pressure.

Model 2: adjusted for all factors in Model 1 + weight change

Model 3: adjusted for all factors in Model 1 + baseline leukocyte count

Model 4: adjusted for all factors in Model 1 + weight change and baseline leukocyte count

Adjusted baseline mean[§] [95% confidence interval] and mean change[‡] [95% confidence interval] from baseline to 3-year follow-up in selected traits by smoking status in 9,398 middle aged adults without diabetes at baseline and 3-year follow-up

Appendix Table 1

	Never Smoked (N = 4,090)	Ex-smokers (N=2,910)	New quitters (n=380)	Continuing smokers (N=2,018)	p, F-test
Baseline Weight (Kg)	77.3 [76.8 – 77.7]	78.1 [77.6 – 78.6]	73.9 [72.5 – 75.3]	72.6 [72.0 – 73.3]	<0.001
Weight (Kg)	1.1 [1.0 – 1.3]	1.2 [1.1 – 1.4]	3.8 [3.3 – 4.2]	0.6 [0.4 – 0.8]	<0.001
Baseline Waist circumference (cm)	95.4 [95.0 – 95.8]	96.0 [95.5 – 96.5]	93.1 [92.0 – 94.4]	92.4 [92.0 – 93.0]	<0.001
Waist circumference (cm)	1.1 [0.9 – 1.3]	1.2 [1.0 – 1.4]	3.2 [2.6 – 3.9]	0.6 [0.4 – 0.9]	<0.001
Baseline Fasting glucose, mmol/L	5.41 [5.39 – 5.42]	5.46 [5.43 – 5.47]	5.40 [5.36 – 5.45]	5.40 [5.38 – 5.43]	<0.001
mg/L	97.5 [97.2 – 97.7]	98.3 [98.0 – 98.6]	97.3 [96.5 – 98.2]	97.4 [97.0 – 97.7]	
Fasting glucose, mmol/L	0.20 [0.19 – 0.22]	0.21 [0.19 – 0.23]	0.29 [0.24 – 0.34]	0.20 [0.18 – 0.22]	0.004
mg/dL	3.6 [3.4 – 3.9]	3.9 [3.6 – 4.2]	5.1 [4.3 – 5.9]	3.7 [3.2 – 4.0]	
Baseline HDL cholesterol, mmol/L	1.40 [1.38 – 1.41]	1.41 [1.39 – 1.42]	1.30 [1.26 – 1.34]	1.32 [1.30 – 1.34]	<0.001
mg/dL	54.0 [53.5 – 54.4]	54.3 [53.8 – 54.9]	50.7 [49.1 – 52.2]	50.8 [50.1 – 51.5]	
HDL cholesterol, mmol/L	–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
mg/dL	–2.2 [–2.5 to –2.0]	–2.0 [–2.3 to –1.6]	–0.9 [–1.9 to 0.1]	–2.9 [–3.3 to –2.4]	
Baseline Triglycerides, mmol/L	1.32 [1.30 – 1.36]	1.41 [1.38 – 1.44]	1.50 [1.43 – 1.60]	1.41 [1.38 – 1.46]	<0.001
mg/dL	116 [114 – 118]	123 [121 – 126]	132 [125 – 139]	125 [122 – 128]	
Triglycerides, mmol/L	0.06 [0.04 – 0.08]	0.06 [0.04 – 0.09]	0.13 [0.06 – 0.20]	0.09 [0.06 – 0.12]	0.21
mg/dL	5.6 [3.8 – 7.5]	5.6 [3.5 – 7.9]	11.3 [5.4 – 17.2]	7.6 [5.0 – 10.2]	
Baseline Systolic Blood Pressure, mm/Hg	120 [119 – 121]	119 [119 – 120]	117 [116 – 117]	117 [115 – 118]	<0.001
Systolic blood pressure, mm/Hg	1.0 [0.6 – 1.4]	1.0 [0.6 – 1.5]	2.5 [1.2 – 3.7]	0.7 [0.1 – 1.2]	<0.001
Baseline Diastolic blood pressure, mm/Hg	74 [73.7 – 74.4]	73 [73.0 – 73.7]	71 [70.2 – 71.1]	70 [70.0 – 71.1]	<0.001
Diastolic blood pressure, mm/Hg	–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
Baseline leukocyte count, × 10 ⁹ cells/L	5.4 [5.39 – 5.49]	5.6 [5.5 – 5.7]	6.9 [6.8 – 7.1]	7.3 [7.2 – 7.3]	<0.001
Leukocyte count, × 10 ⁹ cells/L	–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

[§] Adjusted for gender, race, baseline age, physical activity, educational level, and ARIC study center.

[‡] Adjusted for gender, race, baseline age, physical activity, educational level, baseline values, time interval between baseline and 3-year follow-up, and ARIC Study center.