Original Contribution

Smoking and Diabetes: Does the Increased Risk Ever Go Away?

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Recent studies reported that smoking cessation leads to higher short-term risk of type 2 diabetes than continuing to smoke. However, the duration of increased diabetes risk following smoking cessation needs further investigation. We followed 135,906 postmenopausal women aged 50–79 years enrolled in the Women's Health Initiative between September 1, 1993, and December 31, 1998, over an average of 11 years to examine the association between smoking cessation and risk of diabetes using Cox proportional hazard multivariable-adjusted regression models. Compared with that for never smokers, the risk for diabetes was significantly elevated in current smokers (hazard ratio = 1.28, 95% confidence interval: 1.20, 1.36) but was even higher in women who quit smoking during the first 3 years of follow-up (hazard ratio = 1.43, 95% confidence interval: 1.26, 1.63). Among former smokers, the risk of diabetes decreased significantly as the time since quitting increased and was equal to that of never smokers following a cessation period of 10 years. In new quitters with low cumulative exposure (<20 pack-years), diabetes risk was not elevated following smoking cessation. In conclusion, the risk of diabetes in former smokers returns to that in never smokers 10 years after quitting, and even more quickly in lighter smokers.

risk factors; smoking; smoking cessation; type 2 diabetes

A body of literature shows that cigarette smoking is associated with an increased risk of type 2 diabetes (1). Therefore, smoking cessation should reduce the risk of diabetes among current smokers. However, smoking cessation can also be accompanied by substantial weight gain (2, 3), which may subsequently increase the risk of diabetes (4).

Three epidemiologic studies have prospectively investigated smoking cessation in relation to diabetes risk (5–7). All of them observed that, within the first 5 years, individuals who stopped smoking had a higher short-term risk of type 2 diabetes than those who continued to smoke (5–7). However, 2 of these studies were conducted only among middle-aged men (5, 6). Another recent study (7) that included both men and women did not perform separate analyses by gender. Thus, it is uncertain whether a similar pattern between smoking cessation and risk of diabetes is present among women. Women tend to gain more weight than men after quitting smoking (8). Hence, the increased short-term diabetes risk

associated with smoking cessation might be more pronounced in women.

Two previous studies have looked at the impact of weight gain after quitting smoking on the relationship between smoking cessation and diabetes risk, with mixed findings (6, 7). Yeh et al. (7) found that adjustment for weight gain partially explained the excess diabetes risk in new quitters. Wannamethee et al. (6) reported that a significant increased risk of diabetes associated with smoking cessation was seen both in men who gained weight and in men who did not. Therefore, it is unclear whether the increased risk of diabetes associated with smoking cessation is due to the residual cumulative effects of smoking, substantial weight gain, or a combination of both.

In this study, we assessed the relationship between smoking cessation and risk of developing type 2 diabetes in the Women's Health Initiative (WHI)—a large prospective study, with detailed information on smoking status, cumulative exposure, weight changes, and potential confounders. Our brief report

on this subject (9) found that there was an increased risk of diabetes in new quitters and that weight gain was 1 factor contributing to the elevated risk. In this paper, we conducted additional analyses examining whether the risk of diabetes differs by the cumulative amount of smoking and whether the duration of increased risk following smoking cessation differs by cumulative exposure.

MATERIALS AND METHODS

Women's Health Initiative

Designed to address the major causes of morbidity and mortality in postmenopausal women (10), the WHI included both clinical trials and an observational study. Details of the scientific rationale, eligibility requirements, and baseline characteristics of the participants in the WHI have been published elsewhere (11–15). Briefly, a total of 161,808 women aged 50–79 years were recruited at 40 clinical centers throughout the United States between September 1, 1993, and December 31, 1998. The WHI clinical trial includes 4 overlapping components: 2 hormone therapy trials (27,347 women), a dietary modification trial (48,835 women), and a calcium/vitamin D supplementation trial (36,282 women). Participants in the observational study were 93,676 women who were screened for the clinical trial but proved to be ineligible or unwilling to participate or were recruited through a direct invitation for the observational study. The study was overseen by ethics committees at all 40 clinical centers and at the coordinating center, as well as by a data and safety monitoring board. All participants in the WHI gave informed consent and were followed prospectively.

Study population

We included participants in both the WHI clinical trial and WHI observational study. The associations between smoking cessation and the risk of incident diabetes were assessed at 2 different time points. First, at baseline we compared never smokers, former smokers and current smokers. Second, starting at the year 3 follow-up, we also looked at the group of new quitters (women who smoked at baseline but had quit smoking at the year 3 follow-up). The following participants were excluded from the original cohort of 161,808: 14,849 women who had a history of cancer (except nonmelanoma skin cancer) at baseline; 783 women who had no follow-up time; 8,441 women who had diabetes at baseline; and 1,829 women who had missing values for smoking and diabetes at baseline. This left 135,906 women for our first set of analyses on the risk of diabetes among former and current smokers at baseline. In the second set of analyses assessing the association between smoking cessation and the risk of diabetes in subsequent years, we further excluded 752 never or former smokers who reported newly initiating smoking at the year 3 follow-up; 15,836 women who had no follow-up information at year 3; 1,414 women who had no follow-up observation time close to the year 3 scheduled visit (defined as follow-up time shorter than 2 years or longer than 4 years since baseline); 690 women who had missing values for smoking at the year 3 follow-up; and 2,122 women who developed diabetes

between baseline and the year 3 follow-up. Thus, 115,092 women remained for this analysis and were followed for an average of about 8.5 years after year 3.

Measurement of exposures, confounders, and outcomes

Smoking information at baseline. We considered all available information on smoking at enrollment, including smoking status (never, former, and current), the age of smoking initiation, the number of cigarettes smoked per day, the duration of smoking in years, and age at the time of quitting among former smokers. Duration of smoking for former smokers at baseline was calculated in years by using baseline age minus age at the time of quitting.

New quitters between baseline and the year 3 follow-up. Study participants changing smoking habits between baseline and the year 3 follow-up were classified as never smokers, former smokers, continuing smokers, and new quitters. The *never smokers* were those women who were never smokers at both baseline and the year 3 follow-up. The *former smokers* were defined as women who classified themselves as former smokers both at baseline and the year 3 follow-up. The *continuing smokers* were defined as women who smoked at baseline and the year 3 follow-up. The *new quitters* were defined as women who smoked at baseline but were abstinent at the year 3 follow-up. A small proportion of women (0.6%) who changed smoking status from never or former smokers at baseline to current smokers in year 3 were excluded.

Confounders. The potential confounders considered in multivariable analyses included age at enrollment (<55, 55–59, 60–64, 65–69, 70–74, ≥75 years), ethnicity (American Indian or Alaska Native, Asian or Pacific Islander, black or African American, Hispanic/Latino, non-Hispanic white, and other), education (high school or less, some college/technical training, college or some postcollege, and master's degree or higher), body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, ≥40), waist circumference (continuous), physical activity as metabolic equivalent tasks per week: <5, 5–<10, 10–<20, 20–<30, ≥30), alcohol intake (nondrinker, past drinker, <1 drink/month, from 1 drink/month to <1 drink/week, 1–<7 drinks/week, ≥7 drinks/week), hypertension (yes, no), and high cholesterol requiring pills (yes, no). All these potential confounders measured at baseline were used. In addition, we also calculated weight gain from baseline to year 3 of follow-up and used 4 categories selected a priori on the basis of conventional cutpoints (weight gain stayed within 2.5 kg, weight gain was 2.5–<5 kg, weight gain was ≥5 kg, weight loss was 2.5–<5 kg, and weight loss was ≥5 kg).

Ascertainment of incident diabetes and follow-up. The definition of incident diabetes was a positive answer to the questions regarding "newly prescribed treatment for diabetics with pills or insulin shots" or a positive answer to the question using "diet and/or exercise for diabetes" on any of the semiannual or annual follow-up questionnaires. The date of diabetes onset was assigned as the midpoint between the dates between the survey when diabetes was self-reported and the previous survey. As indicated above, when we assessed the association between smoking status at baseline and the risk of diabetes, all women with prevalent diabetes at baseline were excluded. When we assessed the association between

the changes of smoking status between baseline and year 3 follow-up and the risk of diabetes, all incident diabetes cases before the year 3 follow-up were excluded. Self-reported diabetes in the WHI has been found to be a reliable indicator of diagnosed diabetes based on medication inventories, fasting glucose levels, and medical record review (16, 17).

In the analyses of baseline smoking status and risk of diabetes, all participants were followed from baseline to diabetes diagnosis, date of death, loss to follow-up, or September 30, 2010, whichever occurred first. As of September 30, 2010, with an average 11 years of follow-up from baseline, 15,076 women developed type 2 diabetes. This first set of analyses included information available only at baseline. In the second set of analyses of changes in smoking status from baseline to year 3 follow-up, participants were followed from year 3 follow-up to diabetes diagnosis, date of death, loss to follow-up, or September 30, 2010, whichever occurred first. From baseline to the year 3 visit, 5,335 women continued to smoke, and 2,054 women newly quit smoking. Over an average 8.5 years of follow-up since year 3, 535 women developed

diabetes among women who continued to smoke and 254 women developed diabetes among women who newly quit smoking.

Statistical analysis

We described the distribution of demographic characteristics and factors related to diabetes and tobacco behavior by changes of smoking status between baseline and the year 3 follow-up in Table 1. A χ^2 test was used to evaluate differences for categorical covariates, and analysis of variance was used for continuous variables.

Cox proportional hazards regression models were used to estimate hazard ratios and 95% confidence intervals of 1) risk of diabetes among former smokers and current smokers, relative to never smokers at baseline; 2) risk of diabetes among former smokers and current smokers, relative to never smokers at baseline, stratified by different years since quitting in former smokers (<5, 5–<10, 10–<20, 20–30, and ≥30 years) and cumulative amount of smoking in former and

Table 1.   Baseline Characteristics of Participants and Weight Changes by Changes of Smoking Status Between Baseline and Year 3 Follow-up, the Women's Health Initiative, United States, 1993–1998

Variable	Never Smokers (n = 59,904)		Former Smokers (n = 47,799)		Continuing Smokers (n = 5,335)		New Quitters (n = 2,054)		P Value[a]
	%	Mean	%	Mean	%	Mean	%	Mean	
Age at baseline, years		63.4		63.0		61.0		61.2	0.3
White, non-Hispanic ethnicity	83.2		87.9		80.2		81.8		0.3
College graduate or above education	41.1		42.7		30.7		35.3		0.0002
Body mass index[b]		27.5		27.7		26.5		27.0	0.002
Waist circumference, cm		84.6		85.9		84.8		85.2	0.2
Physical activity, METs/week		12.4		13.9		9.0		10.5	<0.0001
Alcohol intake, ≥7 drinks/week	66.6		79.5		78.3		79.4		0.5
Hypertension, yes	30.9		30.8		26.4		27.1		0.8
High cholesterol requiring pills, yes	12.1		12.7		12.5		11.7		0.005
Smoking metrics									
Age at smoking initiation, years				20.4		20.9		21.8	<0.0001
Average no. of cigarettes/day				15.3		16.2		12.2	<0.0001
No. of smoking years				19.9		37.8		33.5	<0.0001
No. of smoking pack-years				18.5		31.8		23.0	<0.0001
Type of weight change between baseline and year 3 visit									<0.0001
Weight stable (within 2.5 kg)	49.7		47.4		42.4		30.6		
Weight gain									
2.5–<5 kg	15.0		14.9		14.6		18.2		
≥5 kg	10.2		11.6		12.3		30.5		
Weight loss									
2.5–<5 kg	10.0		9.9		11.0		5.1		
≥5 kg	9.1		9.2		11.5		5.9		

Abbreviation: MET, metabolic equivalent task.

[a] There is a significant difference across the 4 groups for all listed variables; all P values were less than 0.01. The P value is testing the difference between continuing smokers and new quitters.

[b] Body mass index: weight (kg)/height (m)^2.

current smokers (<10, 10–<20, 20–<30, 30–<40, 40–<50, and ≥50 years); 3) risk of diabetes among former smokers, continuing smokers, and new quitters, relative to never smokers at year 3; and 4) risk of diabetes among continuing smokers and new quitters at year 3 stratified by different cumulative amount of smoking. For the combined effect of smoking category and cumulative amount of smoking, we created a new variable coded as never smokers, former smokers at baseline, continuing smokers, <20 pack-years; new quitters, <20 pack-years; continuing smokers, 20–<40 pack-years; new quitters, 20–<40 pack-years; continuing smokers, ≥40 pack-years; and new quitters, ≥40 pack-years. In the multivariable models, we adjusted for potential baseline confounders including age, ethnicity, education, body mass index, waist circumference, alcohol consumption, physical activity, hypertension, and high cholesterol requiring pills. Four dietary variables, including total energy intake, dietary total fat, daily fruit consumption, and daily vegetable consumption, were further added into models but did not change results substantially; thus, they were not included in our final model. Because we combined cases from both the WHI observational study and the clinical trial, different study cohorts (participation in the observational study or clinical trials and different treatment assignments for all 4 clinical trials) were treated as strata in the model in order to take account of possible different baseline hazards in different subgroups.

Tests for trend were performed by treating ordinal variables as continuous variables in the proportional hazard models without the reference group included. The proportionality assumption was satisfied for all exposure variables of interest, and potential confounding variables were based on graphs of scaled Schoenfeld residuals (18).

Finally, we performed a cubic spine function to investigate the nonlinear relationship between years since quitting through the year 3 follow-up (including both new quitters and former smokers) and the risk of diabetes (19) after adjustment for the same potential confounders as mentioned above. All tests were 2 sided, and a significance level of 0.05 was used. All statistical analyses were conducted by using SAS, version 9.2, software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Baseline characteristics

Baseline characteristics by changes of smoking status between baseline and the year 3 follow-up are shown in Table 1. Compared with continuing smokers, new quitters were significantly more likely to have a college level or above education, have higher body mass index, be more physically active, have a lower prevalence of high cholesterol requiring pills, have initiated smoking at a later age, smoke fewer cigarettes per day, have shorter duration of smoking, and have fewer smoking pack-years. However, new quitters were more likely to gain substantial weight (all $P < 0.05$). There were no significant differences in the other baseline characteristics between continuing smokers and new quitters, including age, race, waist circumference, alcohol intake, hypertension history, and total energy intake (Table 1).

Smoking status at baseline and risk of diabetes

Compared with the risk among never smokers, the overall risk of diabetes in former smokers was not elevated (hazard ratio (HR) = 1.00, 95% confidence interval (CI): 0.97, 1.04), after adjustment for potential confounders (Table 2). However, within the group of former smokers at baseline, the risk of diabetes decreased significantly as the time since quitting increased, and it was equal to that of never smokers following a cessation period of 10 years. In addition, the risk of

Table 2. Hazard Ratios and 95% Confidence Intervals for Incident Diabetes Since Baseline in Relation to Smoking Status and Cumulative Exposure at Baseline, Women's Health Initiative, United States, 1993–2010[a]

Exposure	No. of Cases	Multivariable Adjusted	
		HR	95% CI
Smoking status			
Never smokers	7,727	1	
Former smokers	6,188	1.00	0.97, 1.04
Years since quit smoking			
<5	620	1.15	1.06, 1.25
5–<10	850	1.14	1.06, 1.22
10–<20	1,608	1.01	0.96, 1.07
20–<30	1,384	0.94	0.89, 1.00
≥30	1,344	0.94	0.88, 0.99
P_{trend}[b]		<0.0001	
No. of smoking pack-years among former smokers			
<10	2,538	0.97	0.93, 1.02
10–<20	1,068	0.97	0.91, 1.03
20–<30	655	0.97	0.89, 1.05
30–<40	683	1.09	1.00, 1.18
40–<50	172	1.25	1.08, 1.46
≥50	725	1.10	1.02, 1.19
P_{trend}[b]		<0.0001	
Current smokers	1,161	1.28	1.20, 1.36
No. of smoking pack-years among current smokers			
<10	268	1.20	1.06, 1.36
10–<20	230	1.35	1.18, 1.55
20–<30	183	1.20	1.03, 1.39
30–<40	119	1.12	0.93, 1.35
40–<50	134	1.28	1.07, 1.52
≥50	215	1.48	1.29, 1.70
P_{trend}[b]		0.17	

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] In the multivariable models, we adjusted for potential confounders including age, ethnicity, education, body mass index, waist circumference, alcohol consumption, physical activity, hypertension, and high cholesterol requiring pills.
[b] The trend test did not include the reference group.

Table 3. Effect of Duration Since Quitting (Years) on Diabetes Risk Stratified by Number of Smoking Pack-Years in Former Smokers at Baseline, Women's Health Initiative, United States, 1993–2010

	<20 Smoking Pack-Years			20–<40 Smoking Pack-Years			≥40 Smoking Pack-Years		
	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI
Never smokers	7,727	1		7,727	1		7,727	1	
Years since quit smoking									
<5	160	0.92	0.79, 1.08	201	1.19	1.04, 1.38	233	1.30	1.14, 1.48
5–<10	285	1.08	0.96, 1.22	272	1.15	1.02, 1.30	265	1.19	1.05, 1.35
10–<20	790	1.04	0.97, 1.12	457	0.96	0.87, 1.05	280	1.00	0.88, 1.13
20–<30	989	0.94	0.88, 1.003	254	0.94	0.83, 1.06	63	0.86	0.67, 1.10
≥30	1,150	0.94	0.88, 1.00	81	0.92	0.73, 1.14	23	1.51	0.99, 2.30
P_{trend}[a]		0.08			0.005			0.02	

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] The P_{trend} was tested among former smokers.

diabetes was significantly greater with higher pack-years of cigarette smoking. Although the overall risk of diabetes was significantly elevated in current smokers (HR = 1.28, 95% CI: 1.20, 1.36), we did not observe that the risk of diabetes was significantly associated with pack-years of cigarette smoking.

After stratifying by pack-years of smoking among former smokers, we found that the risk of diabetes among women with low (<20 pack-years) previous cumulative smoking exposure who were abstinent less than 10 years was similar to that in never smokers, while the increased risk of diabetes did not return to that in never smokers until after 10 years of smoking cessation in former smokers with medium and high previous cumulative exposures (Table 3).

New quitters and risk of diabetes

Compared with the hazard ratio for women who never smoked, the hazard ratios of diabetes were 1.20 (95% CI: 1.09, 1.31) among continuing smokers and 1.43 (95% CI: 1.26, 1.63) among new quitters, after adjustment for age, ethnicity, education, body mass index, waist circumference, alcohol consumption, physical activity, hypertension, and high cholesterol requiring pills (Table 4). After further adjustment for weight gain, the hazard ratio for diabetes remained similar among continuing smokers (HR = 1.20, 95% CI: 1.10, 1.32) but attenuated slightly among new quitters (HR = 1.36, 95% CI: 1.19, 1.54) (Table 4). However, the hazard ratio reduction among new quitters was not statistically significant comparing before and after adjustment for weight gain. Analysis stratified by the number of smoking pack-years at baseline revealed that there was a significant graded association between smoking pack-years and incidence of diabetes in new quitters before adjustment for weight gain in the model (P = 0.03), but the dose-response trend became statistically nonsignificant after adjustment for weight gain (P = 0.13). In addition, we performed a sensitivity analysis by removing the first 2 years of follow-up to check the possibility of reverse causality. After further adjustment for weight gain, the hazard ratios for diabetes were 1.17 (95% CI: 1.06, 1.29) among continuing smokers and 1.28

(95 CI: 1.11, 1.47) among new quitters, which results were similar to those of the main analysis.

Cubic spline analysis showed a nonlinear relationship between years since quitting and the risk of diabetes, confirming the categorical analysis of years since quitting. The risk of diabetes was highest among new quitters, and then the risk reduced to that in never smokers after 10 years of smoking cessation (Figure 1).

DISCUSSION

In this large, prospective study in postmenopausal women, we observed that the risk of diabetes was significantly elevated in current smokers. Among former smokers, years since quitting and low cumulative smoking exposure were both significantly inversely associated with diabetes risk, and the risk of diabetes decreased to that in never smokers after 10 years of smoking cessation. In former smokers with low cumulative previous exposure, the increased risk of diabetes dissipated soon after quitting. In addition, we observed that new quitters had the highest risk of diabetes, especially among heavy smokers. After adjustment for weight gain, the increased risk of diabetes remained higher than that of nonsmokers, although it did not differ significantly from that of continuing smokers. These results suggest that weight gain may not be the only factor contributing to the elevated risk of diabetes in new quitters and that the residual effects of smoking may be important as well.

There is an extensive body of literature reporting on the association between cigarette smoking and the incidence of diabetes (1, 7, 20, 21). Our findings of an elevated risk of diabetes in postmenopausal women who are current smokers is consistent with the results from a recent meta-analysis of 25 prospective cohort studies on active smoking and diabetes (1) and results from recent cohort studies published after the review (7, 20, 21). The magnitude of the hazard ratio we observed for current smoking (HR = 1.28, 95% CI: 1.20, 1.36) was lower than the recent pooled adjusted relative risk (HR = 1.44, 95% CI: 1.31, 1.58) but was similar to that of the pooled adjusted relative risk of 1.25 (95% CI: 1.06, 1.46)

Table 4.   Hazard Ratios and 95% Confidence Intervals for Incident Diabetes Since Year 3 Follow-up in Relation to Changes in Smoking Status Between Baseline and Year 3 Follow-up, Women's Health Initiative, United States, 1993–2010

Exposure	No. of Cases	Model 1[a]		Model 2[a]		Model 3[a]		Model 4[a]	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Never smokers	5,735	1		1		1		1	
Former smokers at baseline	4,532	1.00	0.96, 1.04	0.99	0.95, 1.03	1.00	0.96, 1.04	0.99	0.95, 1.03
Continuing smokers	535	1.20	1.09, 1.31	1.20	1.10, 1.32				
No. of smoking pack-years at baseline									
<20	202					1.20	1.04, 1.38	1.20	1.04, 1.39
20–<40	158					1.14	0.97, 1.34	1.14	0.98, 1.34
≥40	169					1.23	1.06, 1.44	1.24	1.06, 1.45
P_{trend}[b]						0.76		0.87	
New quitters	254	1.43	1.26, 1.63	1.36	1.19, 1.54				
No. of smoking pack-years at baseline									
<20	131					1.29	1.09, 1.54	1.25	1.05, 1.49
20–<40	64					1.57	1.22, 2.01	1.46	1.14, 1.87
≥40	58					1.75	1.35, 2.27	1.59	1.23, 2.07
P_{trend}[b]						0.03		0.13	

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] In model 1 and model 2, the main exposure was coded as never smokers, former smokers at baseline, continuing smokers, and new quitters. In model 3 and model 4, the main exposure was coded as never smokers, former smokers at baseline, continuing smokers, <20 pack-years; new quitters, <20 pack-years; continuing smokers, 20–<40 pack-years; new quitters, 20–<40 pack years; continuing smokers, ≥40 pack-years; new quitters, ≥40 pack-years. For model 1 and model 3, we adjusted for potential confounders, including age, ethnicity, education, body mass index, waist, alcohol consumption, physical activity, hypertension, and high cholesterol requiring pills. For model 2 and model 4, we further adjusted for weight gain between baseline and the year 3 visit.

[b] The trend test did not include the reference group.

among women from stratified analyses of studies that included both men and women (1). Although the exact mechanism has not been fully established, it is proposed that the potential biological mechanisms by which smoking increases risk of diabetes may be through the general inflammation caused by smoking (22, 23), increased insulin resistance or inadequate compensatory insulin secretion responses, and greater abdominal obesity in smokers (23–28) or through a direct toxic effect on pancreatic tissue (29, 30).

Several longitudinal studies investigated the association of smoking cessation on the risk of diabetes. Most studies (5–7, 20, 31), but not all (32), observed that the risk of diabetes decreased gradually as the time since quitting increased, although the years since quitting required for the risk to return to that in never smokers were inconsistent. The study by Will et al. (31) reported that smoking cessation–reduced risk of diabetes was equivalent to that of nonsmokers after 5 years for women and 10 years for men. The study by Wannamethee et al. (6) reported that the risk of diabetes following a cessation period of 20 years was equal to that of never smokers, and the Nurses' Health Study (20) reported that the risk of diabetes went back to that of never smokers following a cessation period of 30 years. To our knowledge, no previous study has examined the association between cumulative exposure and the duration of increased diabetes risk.

Taken together, these data suggest that, despite undesirable weight gain that often follows smoking cessation, stopping smoking could decrease the risk of developing diabetes

and other metabolic perturbations in the long run. Studies have demonstrated that stopping smoking can improve blood lipid levels by increasing high density lipoprotein cholesterol and reducing low density lipoprotein cholesterol, regardless of any weight gain (33). Over time, smoking cessation increases insulin sensitivity and improves the lipoprotein profile (34, 35), although these improvements are not reported consistently (23, 36, 37).

Our results among former smokers are consistent with a reduction in risk for former smokers who quit 20 or more years ago, although there was an elevated diabetes risk among new quitters. It suggests that perhaps there is no overall increase in lifetime risk of diabetes associated with former smoking but just an acceleration in the onset of diabetes in this group of susceptible individuals. However, any increase in the average duration of diabetes and the higher risk of associated complications among former smokers appear to be greatly offset by the other health benefits of quitting. Recent research highlights the loss of a decade of life among smokers and confirms that quitting smoking at any age dramatically lowers mortality (38, 39).

Strengths of our study include the prospective design, the large size and broad geographical distribution of the cohort, the large number of diabetes cases, and detailed information on smoking, weight change, and potential confounders. The large number of cases enabled us to thoroughly assess how the excess risk of diabetes among new quitters was affected by cumulative smoking before quitting or weight gain after
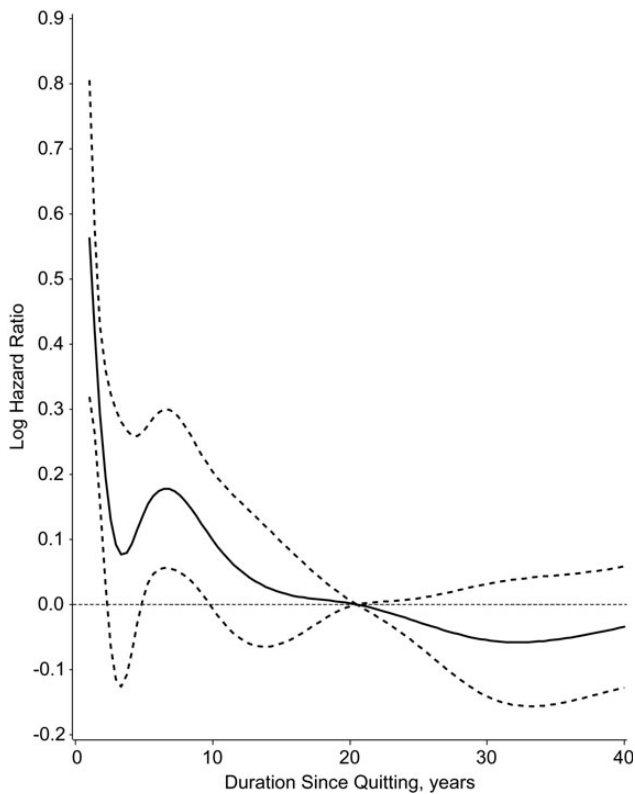
Figure 1. Effects of duration since quitting by year 3 follow-up on diabetes risk among 115,092 women, the Women's Health Initiative, United States, 1993–1998. The log hazard ratio is the natural logarithm of the hazard ratio of former smokers by duration since quitting, compared with never smokers. Solid curve, point estimator; dashed curves, 95% confidence interval.

quitting. However, several limitations deserve mention. First, we used self-reported diabetes status. This may reduce the specificity of diabetes classification and lead to some degree of case misclassification. However, the misclassification bias is likely to be nondifferential, which may have led us to underestimate the strength of the association we observed. In addition, a validation study in the WHI has shown a high concordance of self-report with a "gold standard" based on medical record review and with medication inventories (16, 17). Second, given the strong relationship between type 2 diabetes and adiposity, even the most careful adjustment for body mass index and waist circumference may leave some possibility of residual confounding. Third, we lacked information on treatments, such as nicotine replacement, that women used for quitting. It is possible that nicotine may have direct toxic effects on the pancreas and insulin receptor sensitivity (40, 41). Fourth, it is possible that some of the observed association may be due to detection bias. For example, in some women, smoking cessation may have been triggered by a diagnosis of another disease, such as cardiovascular disease, pulmonary embolism, or cancer. These women may have more contact with the medical system that, in turn, led to detection of undiagnosed diabetes. However, the proportion of women

who quit smoking in proximity to the incidence of these types of conditions was low, suggesting that the observed association is unlikely to have been substantially affected by detection bias. In addition, the WHI has a low rate of smoking relative to this age group in the general population, and thus, it is possible that results could differ in populations that include more smokers.

In conclusion, our prospective analysis suggests that the increased risk of diabetes associated with quitting is confined to heavy smokers. Despite the risk that smoking cessation can result in weight gain and subsequently a short-term increased risk of diabetes among heavy smokers, the risk of diabetes diminishes over the long term and returns to that in never smokers 10 years after quitting.

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