Smoking and Long-Term Risk of Type 2 Diabetes: The EPIC-InterAct Study in European Populations

Diabetes Care 2014;37:3164–3171 | DOI: 10.2337/dc14-1020

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OBJECTIVE

The aims of this study were to investigate the association between smoking and incident type 2 diabetes, accounting for a large number of potential confounding factors, and to explore potential effect modifiers and intermediate factors.

RESEARCH DESIGN AND METHODS

The European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct is a prospective case-cohort study within eight European countries, including 12,403 cases of incident type 2 diabetes and a random subcohort of 16,835 individuals. After exclusion of individuals with missing data, the analyses included 10,327 cases and 13,863 subcohort individuals. Smoking status was used (never, former, current), with never smokers as the reference. Country-specific Prentice-weighted Cox regression models and random-effects meta-analysis were used to estimate hazard ratios (HRs) for type 2 diabetes.

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Received 23 April 2014 and accepted 19 September 2014.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-1020/-/DC1.

RESULTS

In men, the HRs (95% CI) of type 2 diabetes were 1.40 (1.26, 1.55) for former smokers and 1.43 (1.27, 1.61) for current smokers, independent of age, education, center, physical activity, and alcohol, coffee, and meat consumption. In women, associations were weaker, with HRs (95% CI) of 1.18 (1.07, 1.30) and 1.13 (1.03, 1.25) for former and current smokers, respectively. There was some evidence of effect modification by BMI. The association tended to be slightly stronger in normal weight men compared with those with overall adiposity.

CONCLUSIONS

Former and current smoking was associated with a higher risk of incident type 2 diabetes compared with never smoking in men and women, independent of educational level, physical activity, alcohol consumption, and diet. Smoking may be regarded as a modifiable risk factor for type 2 diabetes, and smoking cessation should be encouraged for diabetes prevention.

Evidence is accumulating that smoking is associated with a higher risk of type 2 diabetes. In the 2007 meta-analysis of Willi et al. (1), including 25 prospective cohort studies, current smokers had a significantly higher risk of developing type 2 diabetes compared with never smokers (relative risk [RR] 1.44 [95% CI 1.31, 1.58]). In a 2014 updated meta-analysis, including 46 studies, current smoking was associated with a pooled RR of 1.37 (95% CI 1.31, 1.44) (2). The association between smoking and incident diabetes differed between men and women in the updated meta-analysis, with a slightly higher risk for men (2). Although a definitive causal association has not been established, a relationship between cigarette smoking and type 2 diabetes is biologically plausible. Smoking increases blood glucose concentration after an oral glucose tolerance challenge (3) and may impair insulin sensitivity (4). Smoking is associated with higher energy expenditure and lower appetite, which could explain lower body weight in smokers and weight gain after smoking cessation (5). Furthermore, although smokers tend to have a lower BMI than nonsmokers, smokers are more likely to have abdominal fat accumulation (6). Because abdominal obesity is related to insulin resistance and the development of type 2 diabetes, it is possible that smokers have a higher risk of type 2 diabetes because of the presence of abdominal obesity. However, whether an association between smoking and type 2 diabetes is mediated by overall and/or regional adiposity is not fully clear.

Conversely, noncausal explanations are also possible for the association between smoking and type 2 diabetes. Smoking is associated with other unhealthy behaviors that may have an impact on type 2 diabetes, such as insufficient physical activity, higher alcohol consumption, and diets low in fruits and vegetables (7). This clustering of unhealthy behaviors is more common among people of lower socioeconomic status (SES). SES is a complex indicator of lifestyle, behavior, knowledge of health promotion, and access to health services. Type 2 diabetes is more prevalent among lower SES groups (8).

Many previous studies did not take these factors fully into account. For example, only 11 of the 46 studies included in the updated meta-analysis adjusted the analyses for dietary factors, and another 13 adjusted for educational level (2). Therefore, any reported association between smoking and diabetes could be a result of residual confounding (1). In addition, the relationship between smoking and type 2 diabetes in different countries needs to be investigated for country-specific variations in smoking behavior and patterns of confounding.

To elucidate these unresolved issues in the relationship between smoking and type 2 diabetes, we investigated the association between smoking and incidence of type 2 diabetes while accounting for a large number of potential confounding factors, including age, dietary factors, physical activity, and educational level. Furthermore, potential heterogeneity between men and women was studied. Finally, we explored whether the relationship between smoking and type 2 diabetes is modified by overall or regional adiposity. These issues were addressed in the European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct study, a case-cohort study of participants from eight European countries.

RESEARCH DESIGN AND METHODS

Population

The InterAct project investigates how genes and lifestyle factors interact in their influence on the risk of type 2 diabetes development. The design and methods of the EPIC-InterAct study have been previously described (9). In brief, InterAct consortium partners ascertained and verified incident cases of type 2 diabetes occurring in EPIC cohorts between 1991 and 2007 from 8 of the 10 EPIC countries (26 centers). Multiple sources of evidence were used for ascertainment and verification of incident type 2 diabetes in the entire EPIC data set: self-report, linkage to primary care registers, secondary care registers, medication use, hospital admission data, and mortality data. EPIC participants without stored blood (n = 109,625) or without reported diabetes status (n = 5,821) were not eligible for the EPIC-InterAct study. In a total of 340,234 EPIC participants with a mean duration of follow-up of 11.7 (0–17.5) years, 12,403 verified incident cases of type 2 diabetes were identified. A center-stratified, random subcohort of 16,835 individuals was selected; after exclusion of 548 individuals with prevalent diabetes and 133 with unknown diabetes status, the subcohort included 16,154 individuals. Because of random selection, this subcohort also included a random set of 778 individuals who had developed type 2 diabetes during follow-up. From a total of 27,779 participants, we excluded people with unknown smoking status (n = 339) and people who exclusively smoked cigars or pipes (n = 558). In addition, we excluded participants with missing information on number of cigarettes per day, on time since quitting, and on potential confounding/intermediate factors (n = 1,539). Finally, people with missing waist circumference measurements were excluded (n = 1,829), leaving for the current analyses a total of 10,327 incident type 2 diabetes cases and 13,863 subcohort individuals, of whom 676 developed incident type 2 diabetes.

Assessment of Smoking

Information about smoking status at baseline (never, former, current), age at starting and quitting smoking, type of tobacco (cigarettes, cigars, pipes), current number of cigarettes smoked

(current smoking intensity), lifetime number of cigarettes (lifetime smoking intensity), and duration of cigarette smoking at baseline was collected by lifestyle questionnaires in all centers. Pack-years of cigarette smoking was calculated as (lifetime smoking intensity / 20) × duration of smoking. On average, a pack contains 20 cigarettes.

Other Covariates

Occupational and leisure time physical activity were assessed with a questionnaire and categorized according to the Cambridge Physical Activity Index (10). Diet was assessed using a self- or interviewer-administered dietary questionnaire developed and validated within each country to estimate usual individual food intake (11). Educational level was self-reported and categorized as follows: no formal education (reference), primary school, technical school, secondary school, and university degree. History of previous illness included cardiovascular disease (angina, stroke, myocardial infarction), previous cancers, hypertension and hyperlipidemia, and/or use of medication. Additionally, information on family history of type 2 diabetes in a first-degree relative was recorded for all participants except for those in Italy; Spain; Heidelberg, Germany; and Oxford, U.K. BMI and waist circumference were measured according to standardized operating procedures. Waist circumference was not measured in the Umeå center in Sweden. Overweight and obesity (i.e., overall adiposity) were defined as a BMI ≥25 and ≥30 kg/m^2, respectively. Abdominal obesity (i.e., regional adiposity) was defined as a waist circumference ≥88 cm for women and ≥102 cm for men.

Statistical Analyses

All analyses were carried out for men and women separately. A modified Cox proportional hazards regression [modified for case-cohort designs (12) with Prentice weighting (13)] was used to estimate hazard ratios (HRs). Age was used as the primary time axis, with age at recruitment as the starting age and age at diagnosis of type 2 diabetes, death, or censoring (31 December 2007), whichever came first, as the exit age. HRs were first calculated for the entire case-cohort. Next, country-specific HRs were estimated with adjustment for study center. These were included in random-effects meta-analysis, and forest plots are shown (Supplementary Data), with heterogeneity between countries explored by I^2.

First, smoking status was modeled in three categories, and former and current smokers were compared with never smokers (reference). Second, for dose-response analyses for time since quitting and smoking intensity, smoking status was modeled with four dummy variables comparing two groups of former smokers (having stopped <10 years and ≥10 years before recruitment) and two groups of current smokers (smoking at recruitment <20 cigarettes/day or ≥20 cigarettes/day) to never smokers.

Model 1 was adjusted for age only. Educational level and the lifestyle factors of physical activity and consumption of alcohol, coffee, tea, vegetables, fruits, meat (total), and fish (total) were considered as potential confounding variables. Those variables were added one at a time to the age-adjusted model. Variables that changed the β coefficients for smoking status by ≥10% were included in the multivariable models. In model 2, educational level was included as well as center, physical activity, and consumption of alcohol, coffee, and meat. In a sensitivity analysis, model 2 was used to assess whether hypertension and family history of diabetes were potential confounding factors. Models 3 and 4 were constructed to study whether BMI and waist circumference were potential intermediate factors in the association between smoking and incident diabetes already adjusted for confounding factors.

Effect modification was tested using the interaction terms of smoking status categories with BMI (continuous), waist circumference (continuous), hypertension (yes/no), and family history of diabetes (yes/no) and in a model with adjustment for BMI or waist circumference. *P* values for the interaction terms were obtained by the Wald test per country and pooled using random-effects meta-analysis. A two-sided $P < 0.05$ ($P < 0.10$ for interaction terms) was considered statistically significant. All analyses were performed with SAS version 9.3 software (SAS Institute, Cary, NC) except for the meta-analysis, which was conducted with Stata 13 software (StataCorp, College Station, TX).

RESULTS

Compared with the participants included in the analyses (10,327 incident type 2 diabetes cases; 13,863 subcohort individuals, including 676 incident type 2 diabetes cases), the excluded participants were younger (mean [SD] 51.9 [10.0] vs. 54.1 [8.4] years), had a lower BMI (27.3 [5.0] vs. 27.6 [4.8] kg/m^2) and a larger waist circumference (93.3 [14.4] vs. 90.8 [13.7] cm), were more frequently men (53.8 vs. 40.8%), were more physically inactive (30.3 vs. 25.9%), and were less frequently never smokers (35.3 vs. 45.4%). In addition, the excluded participants had a lower consumption of alcohol, fruits and vegetables, meat, and fish but a higher consumption of coffee and tea (data not shown).

Baseline characteristics of the subcohort stratified by sex and smoking status are shown in Table 1 (men) and Table 2 (women). Never smoking men less frequently had abdominal obesity, were the most physically active, and had the highest educational level. Current smoking men had the lowest educational and physical activity levels and reported the lowest consumption of fruits and vegetables and highest consumption of alcohol, fish, and meat. The incidence of type 2 diabetes was similar in former and current smokers.

In contrast, women who never smoked were the oldest and had the highest BMI and largest waist circumference and the lowest educational and physical activity level. The current smoking women reported the lowest consumption of fruits and vegetables and the highest consumption of meat and coffee and were more likely to be normal weight. Incidence of type 2 diabetes was the lowest in former smoking women.

Information about the distribution of smoking characteristics by country can be found in Supplementary Table 1. Overall, the number of cigarettes per day and pack-years of smoking was higher among men than among women.

Table 3 shows that former and current smoking men had a higher hazard of type 2 diabetes than never smoking men (Table 3, model 1). Adjustment for educational level, center, physical activity, and consumption of alcohol, coffee, and meat resulted in an attenuation of the hazard, particularly in current smoking men (model 2, HR [95% CI]: 1.40 [1.26, 1.55]

Table 1—Baseline characteristics of the EPIC-InterAct subcohort,* men, stratified by smoking status

Men (n = 4,979)	Never smokers (n = 1,582)	Former smokers (n = 1,993)	Current smokers (n = 1,404)
Age (years)	53.0 (8.6)	54.8 (8.2)	51.9 (8.2)
Number of cigarettes/day	—	—	16 (10–20)
Pack-years of smoking	—	15.0 (7.0–25.0)	24.8 (15.8–34.5)
Time since quitting smoking (years)	—	14.5 (7.0–23.0)	—
Low education	917 (58.0)	1,237 (62.1)	982 (69.9)
Lifestyle factors			
Physically inactive	232 (14.7)	344 (17.3)	296 (21.1)
Alcohol intake (g/day)	12.4 (3.5–27.1)	16.7 (6.5–35.0)	20.0 (6.8–40.9)
Vegetables (g/day)	157.6 (104.7–244.8)	156.0 (102.8–240.2)	136.7 (85.9–215.2)
Fruits (g/day)	181.3 (100.1–312.9)	172.1 (92.2–296.8)	123.0 (51.8–250.0)
Meat (g/day)	96.7 (62.3–136.4)	98.1 (65.5–136.6)	110.6 (28.2–149.7)
Fish (g/day)	36.3 (19.3–62.1)	36.2 (18.7–62.5)	37.5 (18.8–65.5)
Coffee (g/day)	205.2 (60.3–500.0)	290.1 (90.0–582.4)	280.5 (100.7–900.0)
Tea (g/day)	0 (0–150)	2.5 (0–150.0)	0 (0–17.0)
Risk factors			
BMI (kg/m^2)	26.5 (3.5)	27.1 (3.4)	26.5 (3.6)
Normal/overweight/obesity (%)	34.1/51.0/14.9	28.8/52.5/18.8	34.7/49.9/15.5
Waist (cm)	94.1 (9.7)	95.9 (9.9)	94.9 (10.1)
Abdominal obesity	321 (20.3)	513 (25.7)	322 (22.9)
Systolic blood pressure (mmHg)	136 (18)	139 (19)	136 (18)
Diastolic blood pressure (mmHg)	84 (11)	86 (11)	84 (10)
Hypertension	19.3	23.3	16.2
Hyperlipidemia	22.9	27.3	24.7
Self-reported heart disease/stroke (%)	1.4/0.9	4.5/1.7	1.7/1.1
Family history of T2D† [n/N (%)]	123/732 (16.8)	147/943 (15.6)	79/523 (15.1)
Incident T2D	4.7	7.4	7.3

Data are mean (SD), median (interquartile range), or n (%) unless otherwise indicated. Low education was defined as no formal education, primary school, or technical school. Physically inactive was defined as inactive according to the Cambridge Physical Activity Index. Hypertension was considered present if there was a self-report of hypertension, use of blood pressure–lowering medication, or physician diagnosis of hypertension. Hyperlipidemia was considered present if there was a self-report of hyperlipidemia, use of lipid-lowering medication, or a physician diagnosis of hyperlipidemia. Family history of T2D was present if a first-degree relative was recorded to have T2D. T2D, type 2 diabetes. *Complete case sample. †Family history not recorded in Italy; Spain; Heidelberg, Germany; and Oxford, U.K.

for former smokers, 1.43 [1.27, 1.61] for current smokers).

In women, a slightly different pattern was observed. Former and current smokers had a significantly higher hazard of type 2 diabetes compared with never smokers after adjustment for educational level, center, physical activity, and consumption of alcohol, coffee, and meat (model 2, HR [95% CI]: 1.18 [1.07, 1.30] for former smokers, 1.13 [1.03, 1.25] for current smokers) (Table 3). Country-specific HRs for men and women are shown in Supplementary Figs. 1–4. Evidence for heterogeneity was only present for former smoking women (I^2 = 60.1, P = 0.01) (Supplementary Fig. 3, model 2), but this was largely accounted for by BMI (I^2 = 29.9, P = 0.20) (Supplementary Fig. 4, model 4 [including BMI]).

Additional adjustment for hypertension did not materially change the HRs for either sex (data not shown). Additional adjustment for family history of diabetes in the subset of the population with information on family history (a total of 6,404 incident type 2 diabetes cases and 6,409 subcohort individuals, of whom 281 developed type 2 diabetes) resulted in a slightly stronger association only for current smoking men compared with never smokers (data not shown).

The introduction of the potential intermediate factor waist circumference attenuated the HRs for former smoking men but did not affect the HRs for current smoking men (Table 3, model 3). In contrast, adjustment for BMI resulted in a small attenuation of the association in former smoking men but a higher HR for current smoking men (1.57 [1.38, 1.79]) (Table 3, model 4). In women, adjustment for waist circumference or BMI (Table 3, models 3 and 4) did not affect the HRs for former smokers. The hazard of diabetes for current smoking women compared with never smokers was higher after adjustment for waist circumference (model 3) and BMI (model 4) (1.39 [1.25, 1.56] and 1.47 [1.32, 1.65], respectively).

Dose-Response Analyses

Long-term quitters (≥10 years since quitting) had a higher hazard of type 2 diabetes than never smokers but a lower hazard than former smokers who quit more recently in both men and women. Current smoking men and women with the highest smoking intensity had the highest hazard of type 2 diabetes compared with never smokers (Supplementary Table 2).

Effect Modification

There was some evidence of effect modification by waist circumference and BMI in current smokers in men and in women for both former and current smokers. Analyses in strata of waist circumference and BMI, however, only showed slightly higher HRs for former and current smoking normal weight (BMI <25 kg/m^2) men (Table 4). Results

Table 2—Baseline characteristics of the EPIC-InterAct subcohort,* women, stratified by smoking status

Women (n = 8,884)	Never smokers (n = 5,027)	Former smokers (n = 1,889)	Current smokers (n = 1,968)
Age (years)	53.2 (8.9)	52.3 (9.2)	50.6 (8.9)
Number of cigarettes/day	—	—	12 (6–20)
Pack-years of smoking	—	7.0 (2.8–22.5)	15.0 (8.1–24.0)
Time since quitting (years)	—	14.0 (6.5–22.0)	—
Low education	3,486 (69.4)	1,067 (56.5)	1,323 (67.2)
Lifestyle factors			
Physically inactive	1,516 (30.1)	351 (18.6)	532 (27.0)
Alcohol intake (g/day)	2.2 (0.0–9.1)	6.0 (1.3–14.3)	5.1 (0.6–14.2)
Vegetables (g/day)	174.2 (114.6–256.0)	166.5 (115.1–249.5)	145.2 (100.4–220.0)
Fruits (g/day)	243.0 (141.7–362.9)	217.3 (124.4–328.4)	170.3 (90.8–281.3)
Meat (g/day)	62.8 (40.1–90.8)	65.5 (41.6–92.3)	70.4 (47.4–99.3)
Fish (g/day)	29.0 (15.5–49.8)	24.6 (11.6–44.6)	28.9 (14.3–49.8)
Coffee (g/day)	184.4 (60.0–450.7)	300.0 (114.3–581.4)	396.2 (139.4–750.0)
Tea (g/day)	0 (0–185.7)	24.6 (0–318.2)	0 (0–85.2)
Risk factors			
BMI (kg/m^2)	26.3 (4.7)	25.4 (4.2)	24.8 (4.1)
Normal/overweight/obesity	44.4/36.2/19.4	53.8/33.4/12.8	59.7/29.9/10.4
Waist (cm)	82.4 (11.5)	80.3 (10.8)	79.5 (10.5)
Abdominal obesity	1,489 (29.6)	430 (22.8)	380 (19.3)
Systolic blood pressure (mmHg)	132 (20)	131 (19)	128 (20)
Diastolic blood pressure (mmHg)	81 (11)	81 (10)	79 (11)
Hypertension	21.3	16.0	14.0
Hyperlipidemia	17.3	12.9	12.1
Self-reported heart disease/stroke (%)	0.5/0.5	0.9/0.7	0.6/0.9
Family history of T2D† [n/N (%)]	497/2,199 (22.6)	216/1,093 (19.8)	206/919 (22.4)
Incident T2D	4.1	3.5	4.1

Data are mean (SD), median (interquartile range), or n (%) unless otherwise indicated. Low education was defined as no formal education, primary school, or technical school. Physically inactive was defined as inactive according to the Cambridge Physical Activity Index. Hypertension was considered present if there was a self-report of hypertension, use of blood pressure–lowering medication, or physician diagnosis of hypertension. Hyperlipidemia was considered present if there was a self-report of hyperlipidemia, use of lipid-lowering medication, or a physician diagnosis of hyperlipidemia. Family history of T2D was present if a first-degree relative was recorded to have T2D. T2D, type 2 diabetes. *Complete case sample. †Family history not recorded in Italy; Spain; Heidelberg, Germany; and Oxford, U.K.

of the dose-response analyses in strata of BMI showed a similar pattern (i.e., slightly higher HRs in lean former and current smokers) (Supplementary Table 3). There was some evidence of effect modification by hypertension in both sexes, but stratified analyses showed an inconsistent pattern (Table 4). There was no evidence for effect modification by family history (data not shown).

CONCLUSIONS

The main finding of this study is that former smokers and current smokers both have a higher risk of incident type 2 diabetes, with a somewhat stronger association in men than in women. The association was independent of educational level and lifestyle influences such as physical activity, alcohol consumption, and consumption of coffee and meat. Diabetes risk diminished for former smokers with a longer time since quitting and was higher for current smokers with a

Table 3—HRs for incident type 2 diabetes, comparing former and current smokers with never smokers in the EPIC-InterAct study

		Former		Current	
	Never	HR	95% CI	HR	95% CI
Men					
Model 1 = age	1	1.45	1.31, 1.60	1.57	1.41, 1.75
Model 2 = 1 + education, center, PA, alcohol, coffee, meat	1	1.40	1.26, 1.55	1.43	1.27, 1.61
Model 3 = 2 + waist circumference	1	1.25	1.12, 1.40	1.45	1.28, 1.65
Model 4 = 2 + BMI	1	1.29	1.15, 1.45	1.57	1.38, 1.79
Women					
Model 1 = age	1	1.06	0.96, 1.16	1.05	0.96, 1.16
Model 2 = 1 + education, center, PA, alcohol, coffee, meat	1	1.18	1.07, 1.30	1.13	1.03, 1.25
Model 3 = 2 + waist circumference	1	1.19	1.06, 1.33	1.39	1.25, 1.56
Model 4 = 2 + BMI	1	1.23	1.10, 1.37	1.47	1.32, 1.65

HRs (95% CIs) were derived from modified Cox proportional hazards regression and are pooled estimates from country-specific analyses using a random-effects meta-analysis. PA, physical activity.

Table 4—HRs for incident type 2 diabetes according to smoking status across strata of waist circumference, BMI, and hypertension in the EPIC-InterAct study

		Former		Current		
	Never	HR	95% CI	HR	95% CI	*P* value for interaction former/current
Men						
Waist <102 cm	1	1.32	1.16, 1.51	1.66	1.42, 1.93	
Waist ≥102 cm	1	1.20	1.00, 1.43	1.51	1.24, 1.84	0.18/0.05* 0.48/0.41†
BMI <25 kg/m^2‡	1	1.59	1.21, 2.09	1.76	1.32, 2.34	
BMI ≥25 kg/m^2	1	1.23	1.09, 1.39	1.47	1.28, 1.69	0.21/0.06* 0.15/0.07†
No hypertension	1	1.37	1.20, 1.56	1.63	1.41, 1.89	
Hypertension	1	1.15	0.94, 1.40	1.67	1.32, 2.11	0.02/0.85
Women						
Waist <88 cm	1	1.18	1.03, 1.37	1.49	1.29, 1.73	
Waist ≥88 cm	1	1.19	1.02, 1.39	1.41	1.20, 1.65	0.09/0.01* 0.54/0.45†
BMI <25 kg/m^2‡	1	1.07	0.87, 1.32	1.43	1.17, 1.74	
BMI ≥25 kg/m^2	1	1.20	1.05, 1.36	1.36	1.19, 1.55	0.11/0.08* 0.22/0.46†
No hypertension	1	1.10	0.97, 1.25	1.52	1.34, 1.73	
Hypertension	1	1.54	1.28, 1.86	1.35	1.08, 1.65	<0.001/<0.001

HRs (95% CIs) from modified Cox proportional hazards regression models. HRs adjusted for age, alcohol consumption, physical activity, coffee and meat consumption, educational level, and BMI. **P* value for interaction for former and current smokers with waist circumference and BMI as continuous variables. †*P* value for interaction for former and current smokers with waist circumference and BMI as binary variables. ‡HR for BMI adjusted for waist circumference.

higher smoking intensity in both sexes. The association between smoking status and incident diabetes tended to be slightly stronger in men and women without overall and regional adiposity.

Strengths

The major strengths of this study are the prospective cohort design with a large sample size and the high number of incident diabetes cases with confirmed diagnosis identified during long-term follow-up. The measurements in the EPIC cohort included detailed assessment of smoking, diet, physical activity, and measured waist circumference and BMI. These cohort features allowed us to control for a large number of potential confounders and to explore effect modifiers and intermediate factors. The Europe-wide scale of the investigation increases the generalizability of the findings.

Limitations

The people who were excluded from the data analyses were younger, had a lower BMI and larger waist circumference, and had a lower consumption of alcohol, fruits and vegetables, meat, and fish but a higher consumption of coffee and tea. In addition, the excluded people were less frequently never smokers and more frequently men and physically inactive. Whether and in what direction this has affected the association under study is difficult to predict. Some of these differences may have led to an overestimation of the association (e.g., the difference in age and BMI), whereas others may have introduced an underestimation of the association (the difference in percentage of men). We cannot exclude the possibility that the differences in lifestyle factors between included and excluded participants may have given rise to a biased assessment of the impact of the lifestyle factors on the association between smoking status and incident type 2 diabetes.

Current Results in the Context of Previous Findings

The current findings are consistent with the results of the meta-analysis by Willi et al. (1) that showed a positive association of former smoking (RR [95% CI] 1.23 [1.14, 1.33]) with incident type 2 diabetes and with the results of the meta-analysis in the Surgeon General's report, which demonstrated a positive association of current smoking with incident type 2 diabetes (1.37 [1.31, 1.44]) (2). The merit of the current study is the ability to adjust for adverse lifestyle factors associated with both smoking and type 2 diabetes. Previous studies mostly took such factors into account as physical activity and alcohol consumption (14,15), but only 11 of the 46 studies included in the updated meta-analysis also adjusted for dietary factors (2).

Differences Between Men and Women

In the current study, the risk of type 2 diabetes associated with smoking was lower for women than for men, particularly for current smokers (HR 1.43 [1.27, 1.61]) in men vs. 1.13 [1.03, 1.25] in women). Additionally, the effect of adjustment differed between men and women wherein adjustment for confounding factors attenuated the risk in men, but in women, the risk was higher after adjustment. This might be partly due to the different distribution of diabetes risk factors among women across categories of smoking status compared with men. Women who were never smokers were the oldest and the most obese with the lowest education level, whereas men who were never smokers less frequently had abdominal obesity, were the most physically active, and had the highest educational level. In the updated meta-analysis, the association between smoking and incident type 2 diabetes was slightly stronger for men (2). Two other studies, which were published after the cutoff date of the updated meta-analysis, also showed a slightly higher risk for men (16,17).

Former Smokers and Time Since Quitting

The current finding of a lower risk for diabetes with a longer time since quitting is in line with the few previous studies with data on time since quitting (15,18–21). In the present study, long-term quitters still had a slightly elevated risk compared with never smokers,

including after adjustment for BMI or waist circumference. Taken together, these results provide some evidence that the effect of smoking on diabetes is reversible. Although smoking cessation is documented to be associated with an initial gain in weight (5), the current and previous studies show that in the long term, quitting smoking is beneficial for diabetes risk.

Dose Response in Current Smokers

Consistent with most other studies on the relationship between smoking and diabetes showing that diabetes risk rises with smoking intensity (2,14,18,19,22–29), we observed a dose-response relationship with a higher risk among men and women who smoked more cigarettes per day. The finding that diabetes risk diminishes with time since quitting and that smoking intensity is positively associated with type 2 diabetes may be an indication of a causal relationship between smoking and diabetes. The association between passive smoking and glucose intolerance and type 2 diabetes (30,31) may be an additional indication. Plausible mechanisms include impaired insulin sensitivity by smoking (4) either by direct toxic effects of smoke on the endothelial lining of blood vessels (32) or through increased abdominal fat accumulation in smokers (6). Direct toxic effects of nicotine or other components of cigarette smoke on pancreatic β-cells is also a possibility because smoking is associated with chronic pancreatitis and pancreatic cancer (33). Another indication for these direct effects is the cross-sectional observation in a recent meta-analysis that the mean HbA_{1c} concentrations in various nondiabetic populations were lowest in never smokers, intermediate in former smokers, and highest in current smokers (34). Another mechanism may be that smoking is associated with chronic low-grade inflammation (32), which in turn is associated with the occurrence of type 2 diabetes (35). On the other hand, we cannot exclude the possibility that the dose-response relationship between time since quitting and smoking intensity and incident diabetes may be the result of clustering of smoking with other (unmeasured or poorly measured) diabetes risk factors, even after adjustment for a large number of potential confounding factors.

Role of Confounding and Intermediate Factors

This study is one of the first with data on a large array of potential confounding factors, ranging from detailed information on diet, family history, and physical activity to measured waist circumference and BMI. Although adjustment for educational level, physical activity, and consumption of alcohol, coffee, and meat had some impact on the risk estimates for type 2 diabetes, the association between smoking status and type 2 diabetes was independent of these factors.

The association between current smoking and type 2 diabetes was stronger after adjustment for waist circumference or BMI in this study, particularly in women. This may be explained by the smaller waist circumference and lower BMI observed in current smoking compared with never smoking women (negative confounding). Previous studies addressing the individual impact of BMI on the association between current smoking and type 2 diabetes also found stronger associations after adjustment in both men and women (14,15,28). Most previous studies took BMI into account in multivariable models, but fewer also included waist circumference (2,14,23,24,30,31,36,37). The results from the current study illustrate the importance of considering waist circumference as an intermediate factor in the association between smoking and incident type 2 diabetes, particularly in current smoking women.

The association between smoking status and incident diabetes in this study tended to be slightly stronger in men without overall adiposity. Previous studies show inconsistent results, ranging from no evidence of effect modification by BMI (24,37) to slightly stronger associations in people with overall obesity (1). Taken together, further studies are needed to resolve this issue of effect modification by overall and regional adiposity in the association between smoking and type 2 diabetes.

In conclusion, in men and women, both former and current smoking were associated with a higher risk of type 2 diabetes compared with never smoking. These associations were independent of educational level, physical activity, and dietary factors. Diabetes risk diminished with a longer time since quitting for former smokers and was higher for current smokers with higher smoking intensity. Smoking may be regarded as one of the modifiable risk factors for type 2 diabetes, and smoking cessation should be encouraged for diabetes prevention.

Acknowledgments. The authors thank all EPIC participants and staff for contributing to this study. They also thank Nicola Kerrison (MRC Epidemiology Unit, Cambridge, U.K.) for managing the data for the EPIC-InterAct project. L.A. thanks the participants of the Spanish EPIC cohort for contributing to the study as well as the team of trained nurses who participated in the recruitment.

Funding. Funding for the InterAct project was provided by the European Union FP6 program (grant number LSHM_CT_2006_037197). In addition, InterAct investigators acknowledge funding from the following agencies: A.M.W.S. and D.L.v.d.A, Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), and Statistics Netherlands; P.M.N., Swedish Research Council; E.A., Health Research Fund (FIS) of the Spanish Ministry of Health, Navarre Regional Government, and CIBERESP; J.W.B. and Y.T.v.d.S., verification of diabetes cases in EPIC-NL funded by NL Agency grant IGE05012 and an Incentive Grant from the Board of the UMC Utrecht; P.W.F., Swedish Research Council, Swedish Diabetes Association, and Swedish Heart-Lung Foundation; J.M.H., Health Research Fund of the Spanish Ministry of Health, Murcia Regional Government (no. 6236); R.K., German Cancer Aid, German Ministry of Research (BMBF); T.J.K., Cancer Research UK; K.O., Danish Cancer Society; S.P., Compagnia di San Paolo; M.L.R., Regional Government of Asturias; O.R., The Västerboten County Council; B.T., German Cancer Aid; A.T., Danish Cancer Society; R.T., AIRE-ONLUS - Ragusa, AVIS-Ragusa, and Sicilian Regional Government; and E.R., Imperial College Biomedical Research Centre.

Duality of Interest. P.W.F. acknowledges funding by Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. A.M.W.S., D.L.v.d.A, and P.M.N. contributed to the study concept and design, data acquisition, data analysis and interpretation, drafting and critical review of the manuscript for important intellectual content, and final approval of the manuscript. E.A. and D.G. contributed to the study concept and design, data acquisition, drafting and critical review of the manuscript for important intellectual content, and final approval of the manuscript. A.A., L.A., B.B., J.W.B., H.B., B.d.L.-G., G.F., E.J.M.F., P.W.F., S.G., J.M.H., R.K., T.J.K., K.O., D.P., S.P., M.L.R., O.R., N.R., C.S., M.-J.S., M.B.S., N.S., B.T., A.T., R.T., Y.T.v.d.S., and E.R. contributed to the data acquisition, critical review of the manuscript for important intellectual content, and final approval of the manuscript. C.L., S.J.S., and N.G.F. contributed to the data acquisition, data analysis and interpretation, critical revision of the

manuscript for important intellectual content, and final approval of the manuscript. N.J.W. contributed to the study concept and design, data analysis and interpretation, data acquisition, critical review of the manuscript for important intellectual content, and final approval of the manuscript. N.J.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Part of this study was presented as a poster at the 49th Annual Meeting of the European Association for the Study of Diabetes (EASD), Barcelona, Spain, 23–27 September 2013.

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