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Association of passive and active smoking with incident type 2 diabetes mellitus in the elderly population: the KORA S4/F4 cohort study

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Abstract Active smoking is a risk factor for type 2 diabetes (T2DM), but it is unclear whether exposure to environmental tobacco smoke (ETS) is also associated with T2DM. The effect of passive and active smoking on the 7-year T2DM incidence was investigated in a population-based cohort in Southern Germany (KORA S4/F4; 1,223 subjects aged 55–74 years at baseline in 1999–2001, 887 subjects at follow-up). Incident diabetes was identified by oral glucose tolerance tests or by validated physician diagnoses. Among never smokers, subjects exposed to ETS had an increased diabetes risk in the total sample (odds ratio (OR) = 2.5; 95% confidence interval (CI): 1.1, 5.6) and in a subgroup of subjects having prediabetes at baseline (OR = 4.4; 95% CI: 1.5, 13.4) after adjusting for age, sex, parental diabetes, socioeconomic status, and lifestyle factors. Active smoking also had a statistically significant effect on diabetes incidence in the total sample (OR = 2.8; 95% CI: 1.3, 6.1) and in prediabetic subjects (OR = 7.8; 95% CI: 2.4, 25.7). Additional adjustment for components of the metabolic syndrome including waist circumference

did not attenuate any of these associations. This study provides evidence that both passive and active smoking is associated with T2DM.

Keywords Diabetes mellitus · Prediabetes · Prospective studies · Smoking · Environmental tobacco smoke

Abbreviations

BMI	Body mass index
CI	Confidence interval
ETS	Environmental tobacco smoke
HOMA-IR	Homeostatis model assessment of insulin resistance
HR	Hazard ratio
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
OGTT	Oral glucose tolerance test
OR	Odds ratio
RR	Relative risk
SES	Socioeconomic status
T2DM	Type 2 diabetes mellitus

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Introduction

The effect of environmental tobacco smoke (ETS) on the risk of type 2 diabetes (T2DM) has so far been investigated in two prospective studies, and the results were not unambiguous [1, 2]: In the CARDIA study, no significantly increased risk of T2DM was found for never smokers exposed to ETS, whereas a significantly higher incidence of diabetes was observed in a Japanese study in a cohort of

workers. Moreover, exposure to ETS was significantly associated with the incidence of glucose intolerance, a precursor of T2DM, in the CARDIA study [1].

Contrary to the sparse and unclear results concerning the association between ETS exposure and T2DM, active smoking has been shown to be an established risk factor for T2DM. Willi et al. recently pooled data of 25 cohort studies on the association of smoking and diabetes incidence, and found an adjusted relative risk (RR) of 1.44 (95% confidence interval (CI): 1.31, 1.58) [3]. In 24 of these studies, a relative risk larger than one was found, and in 19, a significantly increased risk of diabetes was reported. Moreover, a dose–response relationship was shown in this meta-analysis: subjects smoking more than 20 cigarettes per day had a larger diabetes risk than current smokers smoking less (pooled RR = 1.61 (95%-CI: 1.43, 1.80), and pooled RR = 1.29 (95%-CI: 1.13, 1.48), respectively, compared to non-smokers). Three further studies from the 1980s were not considered in the review [4–6]. In two of these studies with rather small numbers of diabetes cases, no association between active smoking and diabetes incidence was reported [4, 5]. Recently, results of four additional cohort studies with somewhat inconsistent findings were published [7–10]. Nevertheless, effects of active smoking on the development of diabetes are hardly in doubt. As Willi et al. stated in their review, further studies should focus on the careful measurement and adjustment for potential confounders in order to clarify the mechanism of the smoking–diabetes–relationship [3].

In this study, we examined the association of the risk of developing T2DM assessing active and passive smoking jointly in a population-based cohort of elderly subjects. We hypothesized that both passive and active smoking are predictors of diabetes incidence, and we investigated the relationship between smoke exposure and T2DM with adjustment for a large number of sociodemographic and lifestyle factors, as well as for the components of the metabolic syndrome.

Materials and methods

Study population

The KORA (Cooperative Health Research in the Region of Augsburg) S4 Survey is a population-based study conducted in Southern Germany using the same region and study methods as the previous WHO MONICA Augsburg project. 2,656 subjects in the age of 55–74 years were invited to participate in the baseline survey between 1999–2001, and 1,653 (62%) subjects were investigated. 131 subjects with known T2DM were excluded, and after exclusion of further drop-outs 1,353 non-diabetic subjects

underwent an oral glucose tolerance test (OGTT) at baseline [11].

The present study includes all subjects without known or newly diagnosed T2DM at baseline ($n = 1,223$). All subjects with completed OGTT at baseline were re-invited in 2006–2008 (F4 survey). Among these subjects, 98 had died before the time of the follow-up examination, and 887 (73%) subjects participated in the follow-up. Informed consent was obtained from the participants. The survey was approved by the ethics committee of the Bavarian Medical Association.

Ascertainment of diabetes and prediabetes in the follow-up

Subjects reporting a physician diagnosis of T2DM or use of anti-diabetic medications in the follow-up were classified as incident diabetes cases only, if their reports were validated by contacting the physicians who had treated them. For the remaining subjects, OGTTs with a 75 g oral load of anhydrous glucose were conducted to ascertain diabetes status. OGTTs were performed in the morning hours (7:00–11:00 h). Subjects were instructed to fast for 10 h overnight, to avoid heavy physical activity and not to smoke before or during the OGTT. Subjects with fever, infections or acute gastrointestinal diseases were excluded from the test. Impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and newly diagnosed T2DM were defined according to 1999 WHO criteria [12]. Prediabetes comprised isolated IFG, isolated IGT, and combined IFG and IGT. We used the original IFG criteria (6.1–6.9 mmol/l) for the present analysis, as recommended by the European Diabetes Epidemiology Group [13]. Newly diagnosed diabetes and validated physician diagnosis were considered as incident diabetes.

Assessment of smoking status

The category of current (or, synonymously, active) smokers comprised regular smokers (smoking daily) and occasional smokers (not smoking daily). The baseline questionnaire included the smoking status (regular/occasional/past/never smoker), the number of cigarettes smoked daily (for regular smokers only), the largest number of cigarettes ever smoked daily for a whole year (for current and past smokers), and the year of beginning and (in case of past smokers) of stopping smoking. ETS was characterized by questions whether, and if so, how much other persons smoked in the workplace or in the household of the participants at baseline (very much/much/hardly/not at all). At follow-up, the current smoking status was inquired again. Subjects were classified into five mutually exclusive categories at baseline: never smokers unexposed to ETS,

never smokers exposed to ETS, past smokers unexposed to ETS, past smokers exposed to ETS, and current smokers. Subjects were regarded as passive smokers if any ETS exposure was reported. Assuming 20 cigarettes per pack, pack-years were calculated using the formula “(cigarettes per day/20) \times number of years smoked”.

Anthropometric and laboratory measurements have been described elsewhere [11]. Information about sociodemographic variables, medical history, alcohol consumption and physical activity was gathered in a structured interview. Socioeconomic status (SES) was assessed as previously described, based on income, educational level and occupational status [14]. Dietary intake was assessed with a short 27 item qualitative food frequency list (FFL). The participants were asked to recall their “average intake” of each item in the following six frequency categories: almost daily, several times per week, about once a week, several times per month, once a month or less, never. Details on a very similar FFL have been described elsewhere [15].

Statistical analyses

Continuous variables were calculated as mean \pm standard deviation (SD) or geometric mean \times/\div standard deviation factor (SDF). Baseline characteristics of the five smoke exposure categories were compared using *F*-tests in case of normally distributed variables; and for log-normal variables, *F*-tests were performed on a log-scale. Logistic regression was used to compare binomial proportions. For the total of all subjects, for subjects having prediabetes at baseline, as well as for subjects with normoglycemia (baseline), cumulative incidences of diabetes cases were calculated for each smoking category.

Multivariate logistic regression models were fitted with smoking status as main independent variable and incident diabetes as dependent variable. Four different models were fitted: two models adjusting for potential confounders (age, sex, parental diabetes, SES, alcohol consumption, physical activity, intake of meat and sausage, intake of salad and vegetables, intake of whole-grain bread, coffee consumption), and two models additionally adjusting for potential mediators (waist circumference, blood pressure, triglycerides, HDL-cholesterol, fasting insulin, serum adiponectin).

Age, waist circumference, and the log values of serum adiponectin and fasting insulin were included as continuous variables. The following covariables were dichotomized: high alcohol intake: ≥ 40 g/day in men, ≥ 20 g/day in women; high physical activity level: ≥ 1 h sports per week during leisure time in either summer or winter; large waist circumference ≥ 102 and ≥ 88 cm for men and women, respectively; hypertension: blood pressure of 140/90 mmHg or higher, or antihypertensive medication, given that the subjects were aware of being hypertensive;

hypertriglyceridemia ≥ 175 mg/dl; low HDL-cholesterol: ≤ 40 mg/dl in males, ≤ 50 mg/dl in women; intake of meat and sausage (intake of meat, sausage or ham almost daily or several times a week); intake of salad and vegetables (intake of salad, cooked or uncooked vegetables almost daily or several times a week); intake of whole-grain bread (intake of whole-grain bread, brown bread or crispbread almost daily or several times a week); coffee consumption (more than three cups of coffee a day).

Each of the four models was fitted for the total cohort, for subjects with baseline prediabetes and for subjects with normoglycemia. Some additional analyses were done. The ETS-diabetes-association was investigated in analyses confined to diabetes cases identified by OGTTs, and it was studied in a subgroup without passive smokers in the workplace. Moreover, in a multivariate linear regression model, the influence of the smoking status on the log HOMA-IR value was assessed. The insulin resistance score HOMA-IR was calculated as fasting plasma glucose (mmol/l) \times fasting serum insulin (mU/l)/22.5.

Separately for regular and past smokers, the impact of lifetime pack-years until the baseline investigation on glucose values (fasting and 2 h glucose values at baseline and in the follow-up) as well as on incident diabetes was assessed in confounder-adjusted linear and logistic regression models, respectively.

To examine how duration of abstinence influenced the diabetes risk of ex-smokers, we fitted model 2 (Table 3) again, splitting the category of ex-smokers without ETS exposition into two categories, i. e., ex-smokers with abstinence times of less than 10 years, and ex-smokers with abstinence times of at least 10 years.

The level of significance was set at 5%. The analyses were carried out using SAS version 9.2 (SAS institute, Cary, NC, USA).

Results

Descriptive statistics

For two participants, information about smoking status was incomplete, so analyses were done with 885 subjects. 93 cases of T2DM were observed in the follow-up (cumulative incidence of diabetes: 10.5%) among whom 60 cases were identified by OGTTs and 33 by validated physician diagnoses.

Table 1 shows the baseline characteristics of the survey participants stratified by the five smoke exposure categories. Subjects who were neither current smokers nor exposed to ETS were more than 3 years older than subjects currently smoking or exposed to ETS. The proportion of men was lowest in unexposed never smokers (29%

Table 1 Baseline characteristics by smoke exposure status: the KORA S4/F4 cohort study (Augsburg, Southern Germany)

	Never smokers/no ETS	Never smokers/yes ETS	Past smokers/no ETS	Past smokers/yes ETS	Current smokers	<i>P</i>
<i>N</i>	350	88	264	73	110	
Age	64.1 (5.3)	60.5 (4.8)	64.7 (5.3)	60.5 (4.7)	60.5 (4.8)	0.001**, #
Sex (males) (%)	29.1	40.9	69.3	80.8	61.8	0.001**, ###
BMI (males) (kg/m ²)	27.6 (2.9)	27.6 (4.0)	28.3 (3.2)	29.1 (4.4)	27.2 (3.0)	0.01*, #
BMI (females) (kg/m ²)	28.2 (4.5)	29.5 (5.0)	28.1 (4.4)	25.3 (2.8)	27.4 (4.7)	0.03*, #
Waist circumference (males) (cm)	99.1 (7.8)	97.8 (10.0)	100.0 (8.5)	102.9 (10.7)	98.2 (9.3)	0.02*, #
Waist circumference (females) (cm)	89.4 (10.6)	91.2 (11.2)	88.3 (10.4)	82.9 (7.1)	88.5 (10.7)	0.12#
Systolic blood pressure (mmHg)	132.2 (19.4)	133.9 (19.5)	137.0 (17.4)	131.7 (19.7)	126.3 (17.2)	0.001**, #
Fasting glucose (mg/dl)	98.1 (9.3)	99.1 (8.8)	99.4 (9.0)	100.4 (9.5)	97.0 (9.7)	0.11#
2-h glucose (mg/dl)	113.9 (29.8)	114.6 (33.0)	115.5 (30.4)	112.3 (31.8)	103.9 (29.1)	0.06#
HOMA-IR	2.5 {1.9}	2.7 {2.2}	2.4 {1.8}	2.5 {1.9}	2.3 {2.1}	0.43###
Triglycerides (mg/dl)	110.0 {1.6}	117.9 {1.7}	111.6 {1.6}	113.8 {1.6}	128.1 {1.6}	0.07###
Fasting insulin (mU/l)	10.4 {1.8}	11.2 {2.2}	9.9 {1.7}	10.0 {1.8}	9.7 {2.0}	0.55###
Alcohol intake (% above critical value ^a)	14.9	14.8	25.8	27.4	25.5	0.09###
Physically active ^b (%)	48.6	42.1	52.7	31.5	42.6	0.01*, ###
Low SES (%)	25.4	19.3	10.2	12.3	10.9	0.01*, ###

BMI body mass index; *ETS* environmental tobacco smoke; *HOMA-IR* homeostatis model assessment of insulin resistance; *SES* socioeconomic status

Means (standard deviation) or geometric means {standard deviation factor}

* $P < 0.05$, ** $P < 0.01$

^a ≥ 40 g/day (males), ≥ 20 g/day (females)

^b ≥ 1 h sports/week

F-test; ## log *F*-test; ### logistic regression. All analyses adjusted for age and sex

compared to 41% in never smokers exposed to ETS). In men, the BMI was lowest in current smokers; in women, past smokers exposed to ETS had an even lower BMI than current smokers. In both sexes, current smokers had lower waist circumferences than never smokers unexposed to ETS. The lowest fasting and 2-h glucose levels, as well as the lowest fasting insulin levels, were found in current smokers. High amounts of alcohol were more often consumed in past and current smokers than in never smokers.

Among the 88 never smokers exposed to ETS, 6 (7%) reported that they were very much exposed, 28 (32%) reported that they were much exposed, and 54 (61%) reported little exposure. For the 73 former smokers with ETS exposure, the corresponding figures were 14 (19%), 25 (34%) and 34 (47%), respectively.

Association of smoking status with risk of diabetes

The cumulative incidence of T2DM in the follow-up was lowest in never smokers not exposed to ETS (7.1%) (Table 2). The cumulative incidence ranged from 11.4 to 13.7% in the other smoke exposure categories. When the

analysis was confined to prediabetic subjects, incident diabetes was observed in 16.5% of the never smokers unexposed to ETS. This incidence was about two times greater in never smokers exposed to ETS, and it was about three times greater in current smokers. In a subgroup analysis with normoglycemic subjects, there were little differences in the cumulative incidence of T2DM between the five smoke exposure categories.

Table 3 shows the results of multivariate logistic regression models, investigating the relationship of smoking status with diabetes risk (cumulative 7 year incidence) for the total sample and for the subgroups of prediabetic and normoglycemic subjects, respectively. In model 1 adjusting for sex, age, and parental diabetes, never smokers exposed to ETS displayed a significantly higher risk of T2DM compared to unexposed never smokers. Significantly increased diabetes risks were also found for past smokers with passive smoke exposure as well as for current smokers. Additional adjustment for SES and lifestyle factors including diet did not attenuate these odds ratios (model 2), and for current smokers, the association with diabetes incidence became even stronger. The smoking-diabetes relationships were slightly attenuated upon further

Table 2 Cumulative 7 year incidence of diabetes by smoke exposure status at baseline: the KORA S4/F4 cohort study (Augsburg, Southern Germany)

	Total sample (n = 885)		Subjects with prediabetes at baseline		Subjects with normoglycemia at baseline	
	N	Cases (%)	N	Cases (%)	N	Cases (%)
Never smokers/no ETS	350	25 (7.1%)	97	16 (16.5%)	253	9 (3.6%)
Never smokers/yes ETS	88	10 (11.4%)	24	8 (33.3%)	64	2 (3.1%)
Past smokers/no ETS	264	35 (13.3%)	75	27 (36.0%)	189	8 (4.2%)
Past smokers/yes ETS	73	10 (13.7%)	23	8 (34.8%)	50	2 (4.0%)
Current smokers	110	13 (11.8%)	19	9 (47.4%)	91	4 (4.4%)

ETS environmental tobacco smoke

Table 3 Association of smoke exposure status at baseline with T2DM risk in the total sample and in stratified analyses for prediabetic and normoglycemic participants, multivariate logistic regression models: the KORA S4/F4 cohort study (Augsburg, Southern Germany)

Smoke exposure category	Model 1		Model 2		Model 3		Model 4	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Total sample (prediabetes + normal glucose tolerance)								
n	885		882		884		862	
Never/no ETS	1.0		1.0		1.0		1.0	
Never/yes ETS	2.4	1.1, 5.5*	2.5	1.1, 5.6*	2.3	1.02, 5.3*	2.4	0.996, 5.9
Past/no ETS	1.5	0.8, 2.7	1.6	0.9, 3.0	1.5	0.8, 2.8	1.7	0.9, 3.3
Past/yes ETS	2.4	1.01, 5.7*	2.8	1.1, 6.8*	2.0	0.8, 4.8	2.6	0.99, 6.8
Current smokers	2.2	1.01, 4.7*	2.8	1.3, 6.1*	2.2	1.01, 4.8*	3.2	1.4, 7.5**
Prediabetes (baseline)								
n	238		238		238		233	
Never/no ETS	1.0		1.0		1.0		1.0	
Never/yes ETS	4.0	1.4, 11.8*	4.4	1.5, 13.4**	4.5	1.5, 13.5**	5.0	1.5, 17.1*
Past/no ETS	2.3	1.01, 5.1*	2.4	1.1, 5.6*	2.5	1.1, 5.8*	2.3	0.9, 5.9
Past/yes ETS	2.8	0.9, 8.7	3.1	0.9, 10.3	2.4	0.7, 7.9	3.0	0.8, 11.3
Current smokers	5.4	1.8, 16.5**	7.8	2.4, 25.7**	5.4	1.7, 17.0**	8.0	2.2, 28.6**
Normal glucose tolerance (baseline)								
n	647		644		646		604	
Never/no ETS	1.0		1.0		1.0		1.0	
Never/yes ETS	1.2	0.2, 6.1	1.3	0.3, 6.8	1.1	0.2, 5.3	1.1	0.2, 6.0
Past/no ETS	1.0	0.3, 2.9	1.0	0.3, 3.0	1.0	0.3, 2.8	1.0	0.3, 3.1
Past/yes ETS	1.6	0.3, 8.5	1.9	0.3, 10.3	1.3	0.2, 7.1	1.7	0.3, 10.2
Current smokers	1.7	0.5, 6.1	2.1	0.5, 7.9	1.6	0.4, 5.9	1.8	0.5, 7.4

OR odds ratio; CI confidence interval; ETS environmental tobacco smoke

* P < 0.05, ** P < 0.01

Model 1: adjusted for age, sex and parental diabetes

Model 2: adjusted for age, sex, parental diabetes, socioeconomic status, alcohol intake, physical activity, intake of meat and sausage, intake of salad and vegetables, intake of whole-grain bread, and coffee consumption

Model 3: adjusted for age, sex, parental diabetes and waist circumference

Model 4: adjusted for age, sex, parental diabetes, socioeconomic status, alcohol intake, physical activity, intake of meat and sausage, intake of salad and vegetables, intake of whole-grain bread, and coffee consumption, waist circumference, blood pressure, hypertriglyceridemia, HDL-cholesterol, log insulin, log adiponectin

adjustment for waist circumference (model 3). After additional adjustment for components of the metabolic syndrome including waist circumference, adiponectin, and fasting insulin, a threefold diabetes risk was found for

current smokers, and a borderline significant risk was observed for never smokers with ETS exposure (model 4). Similar results were obtained when adjusting for BMI instead of waist circumference (data not shown).

Separate analysis of prediabetic and normoglycemic subjects

Overall, a stronger relationship between smoking and diabetes risk was found in prediabetic subjects than in the total sample (Table 3). Significantly higher risks of T2DM were found in all smoke exposure categories except for past smokers with ETS exposure after adjusting for age, sex, parental diabetes, SES and lifestyle factors (model 2). In subgroup analyses for normoglycemic subjects, no significant effects of smoke exposure were observed. Interaction between prediabetes at baseline (yes/no) and smoking status was not statistically significant ($P = 0.44$ in model 1, $P = 0.39$ in model 2).

Association of pack-years with glucose values

In regular smokers, lifetime pack-years until the baseline investigation had a statistically significant effect on fasting glucose both at baseline and follow-up, as well as on baseline 2-h glucose (Table 4). In past smokers, a significant effect of pack-years on glucose levels was found for fasting glucose at baseline (Table 5). In regular smokers, pack-years had a statistically significant effect on incident diabetes after adjusting for sex, age, parental diabetes, SES, alcohol intake, physical activity and diet (OR = 1.05; 95%-CI: 1.01, 1.09). In past smokers, this association was not significant (OR = 1.00; 95%-CI: 0.99, 1.02).

Additional analyses

In additional analyses including only diabetes cases identified by OGTTs in the follow-up, a significantly increased risk of T2DM was again found for never smokers exposed to ETS in the total sample and in prediabetic subjects,

respectively (adjustment for age, sex, parental diabetes, SES and lifestyle factors, data not shown).

In an analysis where never and past smokers exposed to ETS at the workplace were excluded, the diabetes risk of never smokers exposed to ETS at home compared to never smokers without ETS exposure was larger than in the whole sample ($N = 804$; OR = 3.3; 95%-CI: 1.3, 8.7 with adjustment for age, sex, parental diabetes, SES, alcohol intake, physical activity and diet, according to model 2 in Table 3). A corresponding analysis confined to never smokers exposed to ETS at the workplace was not done because there were only three diabetes cases in this category.

In a confounder-adjusted model with baseline data, it could be seen that in never smokers exposed to ETS and in current smokers log HOMA-IR values as indicator of insulin resistance were not significantly different from the log HOMA-IR values of unexposed never smokers (data not shown).

Models according to model 2 (table 3) were fitted again, splitting the category of ex-smokers without ETS exposures into subjects with abstinence times of less than 10 years, and abstinence times of at least 10 years, respectively. When normoglycemic and prediabetic subjects were included, ex-smokers with at least 10 years of abstinence showed a decline in the OR for the risk of diabetes (OR = 1.3, 95%-CI: 0.7–2.5), whereas ex-smokers with less than 10 years of abstinence showed an increase in diabetes risk (OR = 3.5, 95%-CI: 1.3–9.4) compared to the effect observed in the total group (OR = 1.6, 95%-CI: 0.9–3.0). For prediabetes subjects alone, the odds ratio of ex-smokers with at least 10 years of abstinence was 1.9 (95%-CI: 0.8–4.8), and the odds ratio of ex-smokers with less than 10 years of abstinence was 6.1 (95%-CI: 1.6–22.8).

Table 4 Association of lifetime pack-years up to baseline investigation with glucose values (mg/dl, fasting and 2-h glucose, at baseline and in the follow-up) in regular smokers, multivariate linear regression models: the KORA S4/F4 cohort study (Augsburg, Southern Germany)

	Pack-years A ^a				Pack-years B ^b			
	<i>N</i>	β	95%-CI	<i>P</i>	<i>N</i>	β	95%-CI	<i>P</i>
Baseline fasting glucose	94	0.14	0.03, 0.25	0.01*	93	0.08	0.001, 0.16	0.03*
Baseline 2-h glucose	94	0.51	0.19, 0.83	0.002**	93	0.32	0.11, 0.55	0.003**
Fasting glucose (follow-up)	94	0.30	0.12, 0.47	0.001**	93	0.20	0.08, 0.32	0.001**
2-h glucose (follow-up)	89	0.15	-0.46, 0.75	0.63	88	0.10	-0.31, 0.52	0.61

Adjusted for: age, sex, parental diabetes, socioeconomic status, alcohol intake, physical activity, intake of meat and sausage, intake of salad and vegetables, intake of whole-grain bread, and coffee consumption

β regression coefficient; CI confidence interval

* $P < 0.05$, ** $P < 0.01$

^a Pack-years based on the average number of cigarettes per day

^b Pack-years based on the largest number of cigarettes per day ever smoked for a whole year

Table 5 Association of lifetime pack-years up to baseline investigation with glucose values (mg/dl, fasting and 2-h glucose, at baseline and in the follow-up) in past smokers, multivariate linear regression models: the KORA S4/F4 cohort study (Augsburg, Southern Germany)

	<i>n</i>	β	95%-CI	<i>P</i>
Baseline fasting glucose	317	0.05	0.01, 0.10	0.02*
Baseline 2-h glucose	317	0.09	-0.06, 0.23	0.25
Fasting glucose (follow-up)	317	0.06	-0.005, 0.12	0.07
2-h glucose (follow-up)	304	-0.01	-0.21, 0.18	0.92

Pack-years based on the largest number of cigarettes per day ever smoked for a whole year

Adjusted for: age, sex, parental diabetes, socioeconomic status, alcohol intake, physical activity, intake of meat and sausage, intake of salad and vegetables, intake of whole-grain bread, and coffee consumption

β regression coefficient; *CI* confidence interval

* $P < 0.05$

Discussion

This 7-year prospective study showed that both passive and active smoking increased the risk of T2DM. After adjusting for potential confounders including age, sex, parental diabetes, SES, alcohol consumption, physical activity and diet, a significantly increased diabetes risk was observed in current smokers and in never smokers exposed to ETS. Further adjustment for variables of the metabolic syndrome, for adiponectin, and insulin levels did not attenuate the smoking-diabetes relationships. In subgroup analyses among subjects with baseline prediabetes, higher diabetes risks among current smokers and passive smokers were found than in the total sample. However, there was no indication of an interaction between prediabetes and smoking with regard to T2DM development. In normoglycemic subjects, in none of the smoke exposure categories a significantly increased diabetes risk was found.

Comparison with other studies

In the CARDIA study, a significantly increased risk of diabetes had not been observed for never smokers with ETS exposure compared to never smokers without ETS exposure (HR = 1.40, 95%-CI: 0.84–2.33). Two reasons might explain the different findings of the CARDIA study and the present study:

First, in the CARDIA study, fasting blood glucose levels as well as self-reported history of diabetes but no OGTTs were used to define the outcome. In this study, however, OGTTs were used unless there was a self-reported history of T2DM validated by a physician diagnosis. In analyses confined to diabetes cases identified by OGTTs, never

smokers exposed to ETS were still shown to be at a significantly increased risk of T2DM. Second, the two study populations were quite different: In the CARDIA study, the mean age at baseline was 25 years, but it was 63 in the KORA study. Moreover, in the CARDIA study, 50% of the participants were Afro-Americans.

The association between current smoking and T2DM found in this study after multivariable adjustment (OR = 2.8, 95%-CI: 1.3, 6.1) was stronger than the corresponding association calculated in a recent meta-analysis including 25 studies (RR = 1.44, 95%-CI: 1.31, 1.58) [3]. For means of better comparison, our odds ratio was transformed into a relative risk (RR = 2.5, 95%-CI: 1.3, 4.5) using a method given by Zhang and Yu [16]. However, two differences have to be considered. First, the category of reference in other studies consisted of never smokers, irrespective of exposure to ETS whereas in our study the reference category consisted of never smokers without ETS exposure [3]. Second, contrary to most of the other studies included in the meta-analysis [3], we separated models adjusting for potential confounders (Table 3, models 1–2) from models which additionally included potential mediators like components of the metabolic syndrome (models 3–4). Even after adjusting for the metabolic syndrome, for the adipocytokine adiponectin, and for fasting insulin as indicator of insulin resistance, we found an almost three-fold elevated risk for current smoking. The lack of reduction of the smoking-diabetes association upon this additional adjustment suggests that the effect of active smoking on diabetes incidence can be explained neither by waist circumference nor by potential influences of smoking on factors of the metabolic syndrome.

Separate analysis for prediabetic and normoglycemic subjects

We did the multivariate analyses separately for prediabetic and normoglycemic subjects. For current smoking, a strongly significant effect was found for prediabetic subjects. For normoglycemic subjects, the risk of active smoking was even somewhat larger than the one found in the metaanalysis by Willi et al. [3] but it was not statistically significant due to the small sample size. Among never smokers with ETS exposure, an effect was only seen in prediabetic subjects. In spite of the different effects of smoking in prediabetic and normoglycemic subjects, an interaction term of prediabetes (yes/no) and smoking status which was added to model 2 in the logistic regression analysis, was not statistically significant. This interaction term had four degrees of freedom, and we suppose that the sample was too small to show a statistically significant interaction. We looked at changes in the risk factor profile during the follow-up (like BMI, waist circumference, blood

pressure), and we compared these changes between never smokers with ETS exposure and never smokers without ETS exposure in prediabetic subjects on the one side and normoglycemic subjects on the other side. However, changes in the risk factor profiles could not explain why in never smokers an effect of ETS exposure was only found in prediabetic subjects.

Subgroup analyses for prediabetic and normoglycemic subjects were rarely done in other studies. Contrary to our results, Foy et al. found that the diabetes risk of current smokers was lower in prediabetic subjects and higher in normoglycemic subjects compared to the total sample [17]. However, subjects were younger at baseline (40–69 years) than subjects in the KORA cohort.

Association of pack-years with glucose values in regular and past smokers

In this study, in regular smokers pack-years until the baseline investigation were significantly associated with fasting glucose at baseline and at follow-up, as well as with baseline 2-h glucose. In past smokers, a significant association was found between lifetime pack-years and fasting glucose at baseline. These findings demonstrate that there is a dose-relationship between the cumulative exposure to cigarette smoking and blood glucose. Dose-effect relationships between smoking and T2DM incidence have been found in other studies using either pack-years [18–20] or cigarettes per day [20–22] as measures of exposure. Other authors, however, did not find such a dose-effect relationship [23–25].

Causality of the association and possible pathways

For the relationship of active smoking and diabetes, it has been pointed out that several of the Bradford Hill criteria for causation are fulfilled [3]. For passive smoking, evidence for causation is less clear. First, in the present cohort study with a follow-up of 7 years, the exposure preceded the incidence of diabetes. Nevertheless, a temporal relationship cannot be taken for granted because most subjects with incident diabetes were prediabetic at baseline so that processes leading to later diabetes had possibly already started at baseline. Second, in never smokers, the association of exposure to ETS with incident diabetes could be considered as fairly strong because odds ratios were larger than two. However, this association was based on only ten new diabetes cases. Third, in never smokers, a dose-relationship could not be analyzed due to the small figure of incident cases. Fourth, there is still a lack of studies showing that the relationship of passive smoking and diabetes risk holds for different populations using different methods. Fifth, potential pathways leading from tobacco

smoking to T2DM have so far mainly been suggested for active smoking. Possible mechanisms of the effects of secondhand smoke have hardly been investigated. However, as the concentration of many smoke ingredients is higher in sidestream smoke than in mainstream smoke [26, 27], secondhand smoke leads to large health risks although passive smokers have a lower overall smoke exposure than active smokers. So, the association between passive smoking and diabetes risk is in line with the present knowledge of pathological processes and can be considered as plausible.

Possible pathways leading from smoking to type 2 diabetes

In smokers, it has been shown that the insulin-mediated glucose-uptake is lower than in non-smokers in some studies [28–30]. However, other studies did not find impaired insulin sensitivity in smokers [31–33]. Smoking leads to an adverse distribution of body fat with smaller body mass indices but larger waist-to-hip ratios in smokers [34–36]. Thus, abdominal obesity, which is a strong risk factor for T2DM [37], is more prevalent in smokers. Furthermore, tobacco ingredients are likely to have toxic effects on the pancreas [38], a finding which is consistent with a higher risk of pancreatic cancer in smokers [39]. Furthermore, elevated levels of C-reactive protein [40, 41] and plasma fibrinogen [30, 40, 41] have been found in smokers, suggesting that tobacco smoke might activate inflammation leading to T2DM. Smoking causes oxidative stress, which has been implicated to be responsible for the observed systematic inflammatory responses and might also contribute to endothelial dysfunction [42]. Finally, smoking contributes to dyslipidaemia because smokers have higher levels of free fatty acids, triglycerides, and LDL cholesterol, and lower levels of HDL-cholesterol [30, 43], factors usually associated with T2DM. Thus, the smoking-diabetes relationship is plausible from a pathophysiological point of view. However, our study failed to show an impairment of insulin sensitivity in smokers as measured by the HOMA-IR index. Moreover, in this study, effects of smoking on diabetes incidence could be explained neither by altered fat distribution nor by factors of the metabolic syndrome.

Strengths and limitations of the study

Our study had several strengths. It was a population-based study, and contrary to many other studies, incident diabetes was assessed by OGTT in addition to validated self-reports. Smoke exposure status was thoroughly assessed by several questions, some of which were asked more than once in slightly different formulations. Associations between

smoke exposure and T2DM were adjusted for a large number of factors, and potential confounders were separated from potential mediators.

There are also important limitations in our study. First, possible confounders like physical activity or alcohol consumption were only assessed once at baseline. However, insufficient adjustment for confounders could also lead to a downward bias, e.g. in case of moderate alcohol intake which is inversely related to diabetes incidence [19, 44]. Passive smoking often occurs in the workplace, so professional activity could be a confounder of the relationship between ETS exposure of never smokers and diabetes risk. However, this relationship was not attenuated when analyses were confined to passive smokers at home. Second, we considered only current passive smoking, and, if subjects stated that other persons smoked in their workplace or in the household, this might not in any case mean an exposure to ETS (e.g., partners smoking on the balcony). However, classifying subjects not exposed to ETS as passive smokers would be non-differential misclassification and lead to an underestimate of the relationship between passive smoking and diabetes incidence. Third, as the number of cases among current smokers was small, we did not distinguish current smokers who had stopped smoking in the follow-up from the ones who continued smoking. Depending on the effects of smoking cessation this could have led to an under- or overestimate of the diabetes risk of active smoking. Fourth, non-participants turned out to be sicker than participants (data not shown). An elevation of baseline glucose levels in non-participants compared to participants was found in current smokers and in the reference category (i.e. never smokers without ETS exposure), and this elevation turned out to be larger in current smokers. This suggests that the healthy-participant effect probably led to a downward bias of the smoking-diabetes relationship.

In conclusion, this study shows that both passive and active smoking are risk factors of T2DM in an elderly population. Thus, it gives support to efforts to ban smoking in public buildings, encourage the declaration of private homes as smoke-free, and encourage the delivery of smoking cessation interventions.

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