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ARTICLE

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Association of cigarette smoking and tar and nicotine intake with development of type 2 diabetes mellitus in men and women from the general population: the MONICA/KORA Augsburg Cohort Study

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Abstract *Aims/hypothesis:* We examined sex-specific associations between cigarette smoking and incident type 2 diabetes mellitus in Germany. *Subjects, materials and methods:* The study was based on 5,470 men and 5,422 women (aged 25–74 years) without diabetes who participated in one of the three population-based MONICA Augsburg surveys between 1984 and 1995. Incident cases of type 2 diabetes were assessed using follow-up questionnaires. Hazard ratios (HRs) were estimated from Cox proportional hazard models. *Results:* Up to 31 December 2002 a total of 409 cases of incident type 2 diabetes among men and 263 among women were registered. The number of cigarettes and the nicotine and tar consumption per day were associated with a significantly increased risk of type 2 diabetes among men, but not among women; this could be due to the low power of the study in women. After multivariable adjustment, the HRs for type 2 diabetes compared with never-smokers were 1.48, 2.03 and 2.10 for men smoking 1 to 14, 15 to 19 and ≥20 cigarettes/day (p for trend <0.0001) and 1.25, 1.34 and 1.37 for women smoking 1 to 9, 10 to 19 and ≥20 cigarettes/day (p for trend 0.0985). Compared with never-smokers, the HRs for increasing tar intake in men (1–167, 168–259 and ≥260 mg/day) were 1.45, 2.32 and 2.07 (p for trend <0.0001); the respective HRs in women (1–89, 90–194 and ≥195 mg/day) were 1.18, 1.57 and 1.24 (p for trend 0.1159). *Conclusions/interpretation:* Cigarette smoking is an important modifiable risk factor of type 2 diabetes particularly in men from the general population.

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Abbreviations HR: hazard ratio

Introduction

Type 2 diabetes mellitus is a polygenetic disease and environmental factors such as physical inactivity, an unhealthy diet and obesity play a major role in disease development [1, 2]. A growing body of evidence now indicates that cigarette smoking is independently associated with the development of type 2 diabetes in adults. Most [3–9], but not all previous prospective epidemiological studies [10] have suggested that smoking is a risk factor for type 2 diabetes among middle-aged men. However, studies in women have been limited [9, 11–13]. A number of prior studies included smoking as only one of many possible risk factors that might be associated with type 2 diabetes [4, 10, 14, 15]. Hence, large cohort studies with a substantial follow-up incorporating the frequency and intensity of cigarette smoking are necessary to investigate the relationship between smoking and diabetes more precisely in both sexes [3, 9, 11]. Thus, we investigated sex-specific associations between cigarette smoking and the risk of type 2 diabetes in a large population-based cohort study. The specific aim of the present study was to examine the impact of tar and nicotine intake on disease development in 25- to 74-year-old men and women.

Subjects, materials and methods

MONICA studies and study protocol

The presented data were derived from the population-based MONICA (Monitoring Trends and Determinants on Cardiovascular Diseases) Augsburg (Southern Germany) studies conducted between 1984 and 1995. The MONICA

Augsburg project was part of the multinational WHO MONICA project and the design of both projects has been described in detail elsewhere [16, 17]. Briefly, three independent cross-sectional surveys were carried out in the city of Augsburg and the counties of Augsburg and Aichach-Friedberg in 1984/1985, 1989/1990 and 1994/1995 to estimate the prevalence and distribution of cardiovascular risk factors among men and women. Altogether 13,427 persons (6,725 men, 6,702 women, response 77%) aged 25 to 74 years participated in at least one of the three cross-sectional studies. All subjects were prospectively followed within the framework of the Cooperative Research in the Region of Augsburg (KORA).

Mortality was ascertained by regularly checking the vital status of all sampled persons of the three MONICA surveys through the population registries. In 1987/1988, 1997/1998 and 2002/2003 the health status of all living persons was assessed by follow-up questionnaires. Follow-up information was available for 12,075 persons. Up to 31 December 2002, a total of 1,551 participants (1,031 men, 520 women) had died. All subjects who had died between baseline and follow-ups were also included in the analyses if follow-up information could be ascertained (see section 'Ascertainment of diabetes').

For the present analyses, we excluded persons with prevalent type 2 diabetes at baseline (n=597), and subjects who developed other types of diabetes than type 2 diabetes during the follow-up period (n=18). We also excluded 79 subjects from whom no information about diabetes status at follow-up was available, and all subjects with incomplete data on any of the covariables (n=489). Finally, the prospective analyses comprised 10,892 non-diabetic MONICA participants (5,470 men and 5,422 women) aged 25 to 74 years at baseline. Written informed consent was obtained from each study participant and the study was approved by the local ethics committee.

Data collection

Baseline information on sociodemographic variables, physical activity level, medication use, parental history of diabetes and alcohol consumption was gathered by trained medical staff during a standardised interview. In addition, all participants underwent an extensive standardised medical examination including the collection of a non-fasting blood sample. All measurement procedures have been described elsewhere in detail [16, 18]. Actual hypertension was defined as blood pressure values ≥160/95 mmHg and/or use of antihypertensive medication, given that the subjects were aware of being hypertensive. Dyslipidaemia was defined as a ratio of total cholesterol to HDL-cholesterol of ≥5.0. Participants were classified as active during leisure time if they regularly participated in sports in summer and winter and if they were active for at least 2 h/week in both seasons. Study participants provided information about whether they had ever smoked cigarettes regularly (never, past only, occasional or regular). Regular smokers were asked about the number of cigarettes smoked per day and the age at which they began to smoke. On the basis of brand name reported by each regular smoker at baseline examination, nicotine and tar yield were assigned on the basis of lists published by cigarette manufacturers.

A non-fasting venous blood sample was obtained from all study participants while sitting. Total serum cholesterol analyses were carried out with an autoanalyser using an enzymatic method (CHOD-PAP; Boehringer Mannheim, Mannheim, Germany). HDL-cholesterol was also measured enzymatically after precipitation of the apoprotein B-containing lipoproteins with phosphotungstate/Mg^{2+} (Boehringer Mannheim).

Ascertainment of diabetes

In the 1987/1988, 1997/1998 and 2002/2003 follow-up questionnaires, we enquired about the diagnosis of diabetes. All incident cases of type 2 diabetes which had been diagnosed up to 31 December 2002 were included. Self-reported incident cases of diabetes mellitus and the date of diagnosis were validated by hospital records or by contacting the subject's treating physician. Furthermore, the hospital records of those deceased during the follow-up period without a diagnosis of type 2 diabetes at baseline were also examined and/or their last treating physicians were contacted. The records were searched for or the physicians were asked for a history of diabetes, and if a person had suffered from diabetes the type of diabetes and the date of diagnosis were ascertained.

Statistical analyses

The duration of the follow-up was calculated as the interval between the baseline examination and the diagnosis of type 2 diabetes, death or the date when the 1987, 1998 or 2002 follow-up questionnaire was completed. All analyses were performed separately for men and women. The χ^2-test was used to test the differences in prevalences. The general linear model was used to compare means (F-test).

Altogether, two sex-specific analyses to examine associations between smoking at baseline and the risk of type 2 diabetes were conducted. For the first analysis the regular smokers were categorised into sex-specific tertiles of cigarettes smoked per day. The used cut-points (33rd and 66th percentiles) in men were 15 and 20 cigarettes/day and in women 10 and 20 cigarettes/day. Thus, for the first analysis the study population was stratified into the following six categories: (1) never-smokers; (2) ex-smokers; (3) occasional smokers; (4) regular smokers of 1 to 14 cigarettes/day for men and 1 to 9 cigarettes/day for women; (5) regular smokers of 15 to 19 cigarettes/day for men and 10 to 19 cigarettes/day for women; or (6) regular smokers of ≥20 cigarettes/day for men and women. Relative risks of incident type 2 diabetes were computed for groups 2, 3, 4, 5 and 6 as compared with group 1. In the Cox proportional hazards models we adjusted either for age (continuous) and survey (model 1) or for age,

survey, education (</≥ 12 years), parental history of diabetes (yes/no and unknown), actual hypertension (yes/no), dyslipidaemia (yes/no), physical activity level (active/inactive), alcohol intake (non-drinkers [0 g/day], intake of 0.1–19.9 and ≥20 g/day for women and 0.1–39.9 and ≥40 g/day for men) and BMI (continuous) (model 2).

For the second analysis, the daily total consumption of tar and nicotine was calculated for each regular smoker by multiplying the number of cigarettes by the respective yield of the cigarettes. The regular smokers were stratified into three sex-specific groups of nicotine and tar consumption. The used cut-points (33rd and 66th percentiles) of nicotine consumption were 11 and 18 mg/day for men and 6 and 12 mg/day for women and of tar consumption 168 and 260 mg/day for men and 90 and 195 mg/day for women. Thus, for the second analysis, the male study participants were categorised into the categories: (1) never-smokers; (2) ex-smokers; (3) occasional smokers; (4) regular smokers of 1 to 167 mg tar/day (1–11 mg nicotine); (5) regular smokers of 168 to 259 mg tar/day (12–17 mg nicotine); or (6) regular smokers of ≥260 mg tar/day (≥18 mg nicotine). Accordingly, the female participants were stratified into: (1) never-smokers; (2) ex-smokers; (3) occasional smokers; (4) regular smokers of 1 to 89 mg tar/day (1–6 mg nicotine); (5) regular smokers of 90 to 194 mg tar/day (7–11 mg nicotine); or (6) regular smokers of ≥195 mg/day (≥12 mg nicotine). In this analysis, in the first model relative risks of incident type 2 diabetes were computed for groups 2, 3, 4, 5 and 6 as compared with group 1, adjusted for age and survey. The second model included all previous factors plus education, parental history of diabetes, actual hypertension, dyslipidaemia, physical activity level, alcohol intake and BMI. Linear trend was tested by fitting categories of smoking as an ordinal variable into the model.

Results are presented as hazard ratios (HRs) and 95% CIs. Significance tests were two-tailed and p values <0.05 are regarded as statistically significant. All analyses were performed using the Statistical Analysis System (Version 8.2; SAS Institute, Cary, NC, USA).

Results

During follow-up, there were 409 incident cases of type 2 diabetes among the 5,470 men and 263 cases among the 5,422 women (median follow-up period 12.5 years). Tables 1 and 2 show the sex-specific baseline characteristics of the study sample according to smoking status. Mean age, BMI, history of hypertension, dyslipidaemia, level of physical activity, alcohol intake and education years differed significantly by smoking status in men and women. In both sexes, current smokers were younger than never- and ex-smokers. Regular male and female smokers had the lowest BMI and consumed more alcohol than never-smokers. Male ex-smokers had most frequently a history of hypertension, whereas among women a history of hypertension was most frequent in never-smokers. Dyslipidaemia was most frequently observed in men and women who smoked ≥20 cigarettes/day.

Smoking was significantly associated with incident type 2 diabetes in men (Table 3). The multivariable-adjusted HRs for male regular smokers were 1.48 (95% CI 1.00–2.21) for consumption of 1 to 14 cigarettes/day, 2.03 (95% CI 1.15–3.59) for consumption of 15 to 19 cigarettes/day and 2.10 (95% CI 1.54–2.86) for consumption of ≥20 cigarettes/day. In women, the point estimates were somewhat less-elevated but power to detect an association was low and the wide CIs included zero. The HRs for female regular smokers were 1.25 (95% CI 0.66–2.38) for consumption of 1 to 9 cigarettes/day, 1.34 (95% CI 0.72–2.50)

Table 1 Baseline characteristics according to smoking status among men

Characteristics	Never-smokers	Ex-smokers	Occasional smokers	Regular smokers (cigarettes/day)			p
				1–14	15–19	≥20	
No. of participants	1,669	2,088	187	435	198	893	
Mean age (years)	46.3	51.8	44.1	47.1	42.9	42.9	<0.0001
Age at beginning of smoking (years)	–	–	19.0	18.6	18.3	17.6	0.0002
Obesity (%)[a]	15.0	21.4	15.0	14.5	11.6	15.6	<0.0001
Mean BMI (kg/m^2)	26.7	27.6	27.0	26.5	25.9	26.6	<0.0001
Actual hypertension (%)[b]	20.8	29.2	20.9	18.8	14.7	17.9	<0.0001
Dyslipidaemia (%)[c]	39.4	43.7	36.9	49.9	49.0	54.7	<0.0001
Mean total cholesterol (mmol/l)	5.9	6.2	5.9	6.2	6.1	6.2	<0.0001
Mean HDL-cholesterol (mmol/l)	1.3	1.3	1.3	1.3	1.3	1.2	<0.0001
Positive parental history of diabetes (%)	18.5	17.2	12.8	17.0	17.7	20.8	0.0798
Physically active (%)[d]	24.3	23.8	25.7	22.5	25.3	15.1	<0.0001
Mean alcohol intake (g/day)	24.3	30.5	32.4	32.1	28.7	41.9	<0.0001
Education (<12 years) (%)	57.2	65.7	59.9	69.2	66.7	75.3	<0.0001

[a]BMI ≥30 kg/m^2
[b]Blood pressure ≥160/95 mmHg and/or use of antihypertensive medication given that the subjects were aware of being hypertensive
[c]Ratio of total cholesterol to HDL-cholesterol ≥5.0
[d]Regularly participating in sports in summer and winter for at least 2 h/week in both seasons

Table 2 Baseline characteristics according to smoking status among women

Characteristics	Never-smokers	Ex-smokers	Occasional smokers	Regular smokers (cigarettes/day)			*p*
				1–9	10–19	≥20	
No. of participants	3,282	987	176	259	355	363	
Mean age (years)	49.6	44.8	40.2	42.3	41.7	40.7	<0.0001
Age at beginning of smoking (years)	–	–	22.0	20.8	19.7	18.3	<0.0001
Obesity (%)[a]	21.4	16.5	10.2	12.0	10.7	10.2	<0.0001
Mean BMI (kg/m^2)	26.5	25.7	24.9	25.3	24.5	24.5	<0.0001
Actual hypertension (%)[b]	21.5	13.2	16.5	11.6	11.8	12.1	<0.0001
Dyslipidaemia (%)[c]	17.6	12.9	12.5	16.2	17.8	23.7	<0.0001
Mean total cholesterol (mmol/l)	6.0	5.9	5.7	5.8	5.9	5.9	<0.0001
Mean HDL-cholesterol (mmol/l)	1.6	1.7	1.7	1.6	1.6	1.5	<0.0001
Positive parental history of diabetes (%)	11.6	16.3	16.5	12.7	11.0	13.8	0.0021
Physically active (%)[d]	37.4	46.5	48.9	41.7	37.8	35.5	<0.0001
Mean alcohol intake (g/day)	8.1	10.6	12.5	9.5	10.3	13.4	<0.0001
Education (<12 years) (%)	82.3	73.0	71.0	79.2	82.3	81.3	<0.0001

[a]BMI ≥30 kg/m^2
[b]Blood pressure ≥160/95 mmHg and/or use of antihypertensive medication given that the subjects were aware of being hypertensive
[c]Ratio of total cholesterol to HDL-cholesterol ≥5.0
[d]Regularly participating in sports in summer and winter for at least 2 h/week in both seasons

for consumption of 10 to 19 cigarettes/day and 1.37 (95% CI 0.77–2.46) for consumption of ≥20 cigarettes/day after multivariable adjustment. There was no significant excess risk of diabetes for ex- and occasional smokers in either sex.

Table 4 shows sex-specific HRs for diabetes according to total daily tar and nicotine intake. In this analysis, also a significant association between tar and nicotine consumption and risk of diabetes was observed among men. The multivariable-adjusted HRs in men were 1.45, 2.32 and 2.07 for consumption of 1 to 167, 168 to 259 and ≥260 mg tar/day, respectively, in comparison with never-smokers. The multivariable-adjusted HRs for nicotine intake were 1.70, 1.70 and 2.16 for consumption of 1 to 11, 12 to 17 and ≥18 mg/day, respectively, compared with never-smokers.

Again, incidence of type 2 diabetes was not significantly associated with smoking in women. However, the results do not exclude a modest association. Compared with never-smokers, the HRs in women were 1.18, 1.57 and 1.24 for consumption of 1 to 89, 90 to 194 and ≥195 mg tar/

Table 3 Sex-specific risk of incident type 2 diabetes (HRs and 95% CIs) by smoking habits

	n	Cases	Person-years	Age- and survey-adjusted	Multivariable-adjusted[a]
Men					
Never-smokers[b]	1,669	89	18,571	1.00	1.00
Ex-smokers	2,088	175	22,316	1.26 (0.98–1.63)	1.11 (0.86–1.44)
Occasional smokers	187	12	2,097	1.40 (0.76–2.55)	1.27 (0.69–2.32)
Regular smokers					
1–14 cigarettes/day	435	34	4,573	1.46 (0.98–2.16)	1.48 (1.00–2.21)
15–19 cigarettes/day	198	14	2,134	1.78 (1.01–3.12)	2.03 (1.15–3.59)
≥20 cigarettes/day	893	85	9,611	2.43 (1.79–3.28)	2.10 (1.54–2.86)
				p for trend <0.0001	*p* for trend <0.0001
Women					
Never-smokers[b]	3,282	179	37,537	1.00	1.00
Ex-smokers	987	42	11,070	1.08 (0.77–1.52)	1.20 (0.86–1.69)
Occasional smokers	176	8	2,168	1.42 (0.70–2.91)	1.65 (0.80–3.40)
Regular smokers					
1–9 cigarettes/day	259	10	3,005	1.17 (0.62–2.23)	1.25 (0.66–2.38)
10–19 cigarettes/day	355	11	4,080	1.03 (0.56–1.90)	1.34 (0.72–2.50)
≥20 cigarettes/day	363	13	3,985	1.37 (0.77–2.44)	1.37 (0.77–2.46)
				p for trend 0.2789	*p* for trend 0.0985

[a]Adjusted for BMI (continuous), dyslipidaemia, actual hypertension, parental history of diabetes, physical activity, alcohol intake, education (</≥12 years), age (continuous) and survey
[b]Reference group

Table 4 Sex-specific risk of incident type 2 diabetes (HRs and 95% CIs) by total tar and nicotine consumption (mg/day)

	Cigarettes/day, median (min–max)	*n*	Cases	Model 1[a]	Model 2[a]
Men					
Never-smokers[b]	–	1,669	89	1.00	1.00
Ex-smokers[c]	–	2,088	175	1.26 (0.97–1.63)	1.12 (0.86–1.44)
Occasional smokers[c]	–	187	12	1.40 (0.76–2.55)	1.27 (0.69–2.32)
Regular smokers					
Total tar consumption (mg/day)					
1–167	10 (1–60)	507	36	1.38 (0.94–2.04)	1.45 (0.98–2.14)
168–259	15 (6–40)	253	26	2.35 (1.51–3.64)	2.32 (1.49–3.61)
≥260	23 (12–80)	766	71	2.44 (1.78–3.36)	2.07 (1.50–2.87)
				p for trend <0.0001	*p* for trend <0.0001
Total nicotine consumption (mg/day)					
1–11	10 (1–30)	508	43	1.61 (1.12–2.32)	1.70 (1.18–2.45)
12–17	20 (10–60)	379	29	1.71 (1.12–2.61)	1.70 (1.11–2.61)
≥18	25 (12–80)	639	61	2.68 (1.93–3.73)	2.16 (1.54–3.03)
				p for trend <0.0001	*p* for trend <0.0001
Women					
Never-smokers[b]	–	3,282	179	1.00	1.00
Ex-smokers[c]	–	987	42	1.08 (0.77–1.52)	1.20 (0.86–1.69)
Occasional smokers[c]	–	176	8	1.42 (0.70–2.91)	1.65 (0.80–3.39)
Regular smokers					
Total tar consumption (mg/day)					
1–89	6 (1–30)	324	11	1.02 (0.55–1.88)	1.18 (0.64–2.18)
90–194	13 (7–40)	324	13	1.34 (0.76–2.36)	1.57 (0.88–2.81)
≥195	20 (12–65)	329	10	1.23 (0.64–2.36)	1.24 (0.64–2.40)
				p for trend 0.3751	*p* for trend 0.1159
Total nicotine consumption (mg/day)					
1–6	6 (1–30)	345	14	1.19 (0.69–2.07)	1.38 (0.79–2.39)
7–11	12 (5–30)	266	8	1.00 (0.49–2.03)	1.20 (0.58–2.46)
≥12	20 (12–65)	366	12	1.35 (0.74–2.46)	1.36 (0.74–2.49)
				p for trend 0.3551	*p* for trend 0.1060

[a]Model 1: adjusted for age (continuous) and survey; model 2: adjusted for BMI (continuous), dyslipidaemia, actual hypertension, parental history of diabetes, physical activity, alcohol intake, education (</≥12 years), age (continuous) and survey
[b]Reference group
[c]No data on nicotine and tar consumption available

day, respectively, in multivariable-adjusted analysis. The respective HRs were 1.38, 1.20 and 1.36 for a nicotine consumption of 1 to 6, 7 to 11 and ≥12 mg/day.

Discussion

The present population-based study showed that regular smoking was associated with a significantly increased risk of type 2 diabetes among men. In women, the point estimates were somewhat less elevated and associations were not significant, which could be due to the relatively low power of the study in women. The risk for type 2 diabetes in men increased in a dose–response manner as the number of cigarettes per day and the nicotine and tar consumption per day increased. The associations remained after adjustment for potential confounders for type 2 diabetes. However, no significant association between ex-smoking or occasional smoking and type 2 diabetes was found in either sex.

In agreement with the present study, the Physicians Health Study reported a 70% increase in the risk of diabetes in men who smoked >20 cigarettes/day after multivariable adjustment. In this study a dose–response gradient between the number of cigarettes smoked per day and the risk of diabetes was also observed [3]. During 25 years of follow-up in a Dutch study [4] the relative risk of diabetes was 3.3 (95% CI 1.4–7.9) among men who smoked >20 cigarettes/day compared with never-smokers, after adjustment for multiple confounders. Also the Health-Professionals' Study showed that the risk of diabetes among men smoking ≥25 cigarettes/day was 1.94 (95% CI 1.25–3.03) compared with non-smokers [5]. A higher risk of type 2 diabetes for smoking men was also reported from a British study [19], a Finnish study [12], three Japanese studies [6, 8, 13] and The Cancer Prevention Study [9]. Another British study reported that the risk of diabetes was 50% higher among smokers. However, this association was not independent of other risk factors [14]. Furthermore, contrary to the present study, three prior studies conducted

in the 1970s and 1980s failed to show a relationship between smoking and type 2 diabetes in men [10, 15, 20].

In women, not as many studies have been performed. Among 114,247 women participating in the Nurses' Health Study, those who smoked ≥25 cigarettes/day had a relative risk of type 2 diabetes of 1.4 (95% CI 1.2–1.7) compared with never-smokers in multivariable-adjusted analysis [11]. Data from The Cancer Prevention Study showed that the risk of diabetes was increased in women who smoked more than one and two packs per day (risk compared with non-smokers 1.21 and 1.74, respectively) [9]. A Japanese Study found a 50% excess risk of diabetes for current smoking among middle-aged women [13]. Moreover, very recently a Finnish study reported a multivariable-adjusted relative risk of type 2 diabetes of 1.46 (95% CI 1.21–1.76) among women smoking <20 cigarettes/day and 1.87 (95% CI 1.36–2.59) among women smoking ≥20 cigarettes/day [12]. In contrast, cigarette smoking was not an independent predictor of type 2 diabetes in a cohort study including also women with impaired glucose tolerance [20]. In addition, in the Framingham Study no significant association between smoking and type 2 diabetes was found among women during an 8-year follow-up [10].

In the present study, a higher proportion of men in comparison with women were regular smokers. Also, the number of cigarettes smoked per day was higher among men than women. Thus, the differences in smoking behaviour might explain why smoking as a risk factor had an impact on diabetes development in men but not in women in this study. Another possible explanation could be that the present study is smaller than other studies on this issue [9, 11] and might not have had the power to show a moderate association between cigarette consumption and type 2 diabetes in women.

The underlying mechanism of how cigarette consumption increases the risk of type 2 diabetes is not entirely clear. Previous studies showed that smoking may contribute to the development of insulin resistance because smoking increases blood glucose levels after an oral glucose challenge and may impair insulin sensitivity [21]. Facchini et al. have shown that the ability of insulin to stimulate glucose uptake is significantly lower in chronic cigarette smokers than in non-smokers [22]. Other investigators have suggested that cigarette smoking increases insulin resistance by altering the distribution of body fat, that is by increasing abdominal fat distribution and a greater waist-to-hip ratio, which may affect glucose tolerance [23]. Another study demonstrated that smoking acutely impairs insulin-stimulated glucose transport in skeletal muscle [24]. Furthermore, smoking increases free radical oxidative damage and oxidative stress [25], factors that may also contribute to the development of type 2 diabetes [26]. Finally, it was speculated that nicotine, carbon monoxide or other agents in tobacco smoke may have direct toxic effects on the pancreas and insulin receptor sensitivity [27, 28].

The findings of the present study are consistent with some of these previous studies [3, 7–9] showing a dose–response relationship between the number of cigarettes smoked per day and the risk of type 2 diabetes in men. In addition, this study, for the first time, reported that the risk of type 2 diabetes in men increased with increasing nicotine and tar consumption per day in a graded manner. Thus, the present findings support the assumption that the degree of insulin resistance is associated with the number of cigarettes smoked [29]. Furthermore, these data suggest that in addition to the number of cigarettes smoked daily, the question of low- or high-tar cigarettes are usually consumed may be relevant when estimating the risk of disease development. More research is needed to elucidate how tobacco and its ingredients induce type 2 diabetes. In particular, it remains to be investigated whether sex-specific mechanisms apply with regard to this issue.

The MONICA/KORA Augsburg Study has several limitations that need to be considered. The follow-up was not complete for all participants of the original study who were still alive in 1987, 1998 and 2002, which might have introduced a selection bias. Since diabetic patients have an increased risk of dying of a cardiovascular disease they could also be lost by selective mortality during follow-up. Furthermore, response bias cannot be excluded in our study. Although we adjusted for a variety of confounders, in the present study no data such as information on diet or fat distribution were available. Therefore, we cannot exclude the presence of residual confounding. Finally, in the present study only self-reported information on diabetes status of the subjects or use of antidiabetic medication was available. Although this information was validated with medical records, it is likely that the group of non-diabetic persons may include subjects with undetected diabetes. The strengths of the MONICA/KORA Augsburg Cohort Study are primarily its prospective design, the representativeness of the cohort, based on a random sample of the general population and the availability of data on lifestyle and multiple cardiovascular risk factors. Furthermore, in contrast to most other prospective studies of this kind in which diagnosis of diabetes was based upon self-report, diabetes diagnosis in the present study was based on physician-validated diagnosis of type 2 diabetes.

In summary, this study demonstrated a significant dose–response relationship between nicotine and tar intake and the development of type 2 diabetes in men. No significant association was found between smoking and type 2 diabetes in women; however, this could be due to the relatively low power of the study in women. Thus, the present findings from a large population-based cohort suggested that cigarette smoking in addition to other lifestyle-related risk factors can modify the incidence of type 2 diabetes, especially in men.

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Duality of interest None of the authors are aware of any duality of interest.

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