Original article

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Smoking and cardiovascular disease in patients with type 2 diabetes: a prospective observational study

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Background Cigarette smoking is a major risk factor for cardiovascular disease. In type 2 diabetes mellitus (T2D), medications such as antihypertensives and statins can reduce the increased cardiovascular risk. The aim of this study was to evaluate the impact of cigarette smoking on major adverse cardiovascular event (MACE) and all-cause mortality in patients with T2D in a relatively well treated Swedish cohort.

Methods Seven hundred and sixty-one patients with T2D aged 55–66 years were followed in the prospective observational CArdiovascular Risk factors in patients with DIabetes – a Prospective study in Primary care (CARDIPP) study. Baseline data included blood samples of markers of dysglycemia and inflammation, blood pressure as well as questionnaire responses regarding cigarette smoking. Participants were followed for incidence of MACE and all-cause mortality.

Results Of the included 663 participants, the mean age was 60.6 (SD 3.1) years and 423 (63.8%) were men. Levels of C-reactive protein and vitamin D, as well as the proportion of participants treated with antihypertensives, acetylic salicylic acid, statins, and diabetes medications, were similar between smokers and nonsmokers. Median follow-up time was 11.9 (Q1–Q3 10.8–12.7) years. Cigarette smoking was associated with all-cause mortality [hazard ratio 2.24 (95% confidence interval, 95% CI 1.40–3.56), $P < 0.001$], but not MACE [hazard ratio 1.30 (95% CI 0.77–2.18), $P = 0.328$].

Conclusion In patients with T2D, cigarette smoking was not associated with an increased risk of MACE. This raises the question of whether cardioprotective drugs in individuals with T2D to some degree mitigate the cardiovascular harm of smoking, even though they do not affect other dire consequences of smoking.

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Introduction

Cigarette smoking is a major risk factor for cardiovascular disease.[1,2] However, it is unclear if this is caused by the tobacco, the nicotine, or the smoke. Nicotine increases heart rate and blood pressure (BP), but whether this is a link between cigarette smoking and cardiovascular disease is debated.[1]

Both cigarette smoking and cardiovascular disease are associated with low-grade inflammation, thus providing a potential link.[1,3–5] Furthermore, several biomarkers of inflammation are elevated in cigarette smokers, including C-reactive protein (CRP).[6] One hypothesis is that cigarette smoking, by way of oxidative stress, reduces nitric oxide production, causing endothelial dysfunction and decreased flow-mediated dilation in arteries. Reduced flow-mediated dilation is an early marker of vascular injury and seen in users of both smoking and nonsmoking tobacco.[1,2] The inflammatory markers CRP and vitamin D are interrelated, and both are associated with cardiovascular disease. CRP is associated with atherosclerosis and cardiovascular events, as well as insulin resistance and obesity.[7] Vitamin D deficiency is also associated with cardiovascular disease, as well as hypertension and T2D.[8–10]

Both cigarette smoking and nicotine use are also associated with the development of insulin resistance and T2D, and improved insulin resistance is seen in cigarette smokers who quit smoking.[11,12] The cause of this effect on glycemic control is unknown, but one theory is that cigarette smoking causes increased catecholamines, which increases hepatic gluconeogenesis and glycogenolysis.[11] Cigarette smoking is also associated with abdominal obesity, which is a known risk factor for T2D. Furthermore, nicotine use is associated with increased cortisol, thus providing a possible link between cigarette smoking, abdominal obesity and the development of T2D.[13] To further complicate matters, nicotine enhances satiety, and replacement with nicotine after quitting cigarette

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smoking reduces the increase in body weight that usually follows cessation of cigarette smoking.[14,15] Also, the increase in BP induced by nicotine is rather modest, similar in magnitude to that induced by caffeine.[16]

Several medications used in the treatment of T2D, hypertension, and hyperlipidemia have anti-inflammatory effects. Statins reduce inflammation in several ways, and are associated with reduced levels of CRP and TNF-α.[5,17] Combination therapy of statins and ezetimibe reduces CRP more than statins alone.[5] Renin-angiotensin system blockers have previously been shown to reduce CRP in the context of T2D and cardiovascular disease, and have recently been investigated for their potential anti-inflammatory effects in the context of COVID-19 infections.[5,18] At least some calcium channel antagonists also reduce CRP.[5] Acetylic salicylic acid (ASA) reduces the risk of cardiovascular events, and the risk reduction is greater in those with higher CRP.[5] However, results conflict as to whether ASA reduces CRP.[5] The combination of these multifactorial interventions in patients with T2D decreases cardiovascular mortality.[19]

We aimed to study the association between cigarette smoking and major adverse cardiovascular event (MACE) in patients with T2D, hypothesizing that the negative cardiovascular effects of cigarette smoking could be offset by the intensive treatment of cardiovascular risk factors in these individuals.

Materials and methods

The prospective, observational CArdiovascular Risk factors in patients with DIabetes – a Prospective study in Primary care (CARDIPP) study followed 761 patients with T2D, aged 55–66 years, recruited between 2005 and 2008.[20] In brief, patients were evaluated with office BP, sagittal abdominal diameter (SAD), BMI, blood samples [glycated hemoglobin (HbA1c), CRP, vitamin D, triglycerides, and Apolipoprotein B/Apolipoprotein A1 ratio (ApoB/ApoA1)], and extensive electronic questionnaires regarding known comorbidities, medications (antihypertensives, acetylsalicylic acid, statins, insulin, and oral antidiabetics), alcohol intake, and cigarette smoking habits (past and current) on dedicated computers at the trial offices. Patients were followed for incidence of MACE and all-cause mortality until the end of 2018 using the national Swedish Cause of Death and Hospitalization Registries. All participants with recorded smoking status, and no previous myocardial infarction or ischemic stroke, were included in the current study.

Ex-smokers were classified as nonsmokers. MACE was defined as first fatal or nonfatal hospitalization for acute myocardial infarction (ICD-10 code I21) or stroke (ICD-10 codes I60, I61, I63.0-I63.5, I63.8-I63.9, I64), or cardiovascular mortality (ICD-10 codes I00-99). CRP values below 5 were included to represent low-grade inflammation. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, loop diuretics, and beta blockers were categorized as antihypertensives. Metformin, dipeptidyl peptidase-4 inhibitors, sulfonylureas, acarbose, thiazolidinediones, meglitinides, and glucagon-like peptide-1 receptor agonist were categorized as 'antidiabetics others', to separate them from insulin.

Baseline characteristics were presented for all participants. Continuous variables were shown as the mean and standard deviation, and differences between smokers and nonsmokers were tested using a two-sided Mann–Whitney *U* test. Categorical variables were presented as the frequency and percentage, and differences between smokers and nonsmokers were tested using a chi-squared test. Values for BMI, SAD, and SBP were also presented separately for men and women to account for sex differences.

A Cox proportional hazard model analysis was used to investigate the risk of MACE and all-cause mortality respectively for smokers compared with nonsmokers. This analysis was repeated for men and women respectively. The Cox proportional hazard model analyses were controlled for age, sex, BMI, SAD, SBP, ApoB/ApoA1 ratio, triglycerides, HbA1c, smoking status, CRP, and serum vitamin D. The analysis of all-cause mortality was also presented as a Kaplan–Meier curve.

Posthoc analyses of baseline variables for smokers were made in relation to the number of cigarettes consumed per day: fewer than 10, 10 up to fewer than 20, and 20 or more. *P* for trend was tested using a Jonckheere-Terpstra test for continuous variables and a Cochran Armitage test for categorical variables.

Statistical tests were two-tailed and *P*-values of less than 0.05 were considered statistically significant. R version 4.3.0 and RStudio version 2023.03.1+446 were used for data analyses.

Results

Out of 761 participants in the cohort, 13 were excluded due to missing cigarette smoking status, 67 participants were excluded due to a history of myocardial infarction and 16 participants were excluded due to a history of stroke. Thus, 663 participants were included in the study.

Median follow-up time was 11.9 (Q1–Q3 10.8–12.7) years. The mean age was 60.6 (SD 3.1) years and 423 (63.8%) of the participants were men (Table 1). Compared with nonsmokers, smokers had lower mean BMI [28.6 (SD 4.9) vs. 30.4 (SD 4.7) kg/m^2, $P < 0.001$] and lower mean SBP [135.4 (SD 17.2) vs. 138.3 (SD 15.6) mmHg, $P = 0.016$] (Table 1).

Table 1 Baseline characteristics of nonsmokers, smokers, and all participants respectively

	Nonsmokers $n=541$	Smokers $n=122$	All participants $N=663$	P
Sex, men, *n* (%)	355 (65.6)	68 (55.7)	423 (63.8)	0.052
Age, years, mean (SD)	60.7 (3.0)	60.2 (3.1)	60.6 (3.1)	0.094
Diabetes duration, years, mean (SD)	7.1 (6.3)	7.5 (5.7)	7.2 (6.2)	0.268
BMI, kg/m^2, mean (SD)	30.4 (4.7)	28.6 (4.9)	30.1 (4.8)	<0.001
Men	29.9 (4.2)	28.1 (4.7)	29.6 (4.3)	0.005
Women	31.4 (5.5)	29.2 (5.1)	30.9 (5.5)	0.015
SAD, cm, mean (SD)	25.6 (3.7)	24.9 (4.0)	25.5 (3.8)	0.050
Men	25.7 (3.6)	25.0 (4.0)	25.6 (3.7)	0.172
Women	25.5 (3.8)	24.7 (4.0)	25.3 (3.9)	0.205
SBP, mmHg, mean (SD)	138.3 (15.6)	135.4 (17.2)	137.8 (15.9)	0.016
Men	138.2 (14.8)	134.4 (17.5)	137.6 (15.3)	0.010
Women	138.5 (17.1)	136.7 (16.9)	138.1 (17.0)	0.459
ApoB/ApoA1 ratio, mean (SD)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.938
Triglycerides, mmol/l, mean (SD)	1.7 (1.0)	2.0 (1.1)	1.8 (1.0)	0.005
HbA1c, mmol/mol, mean (SD)	52.5 (11.3)	55.1 (14.0)	53.0 (11.9)	0.141
CRP, mg/l, mean (SD)	1.5 (1.3)	1.5 (1.2)	1.5 (1.3)	0.588
Vitamin D, nmol/l, mean (SD)	51.5 (21.6)	48.6 (23.3)	50.9 (22.0)	0.109
Antihypertensives, *n* (%)	333 (61.6)	78 (63.9)	411 (62.0)	0.699
ASA, *n* (%)	133 (24.6)	24 (19.7)	157 (23.7)	0.292
Statins, *n* (%)	286 (52.9)	57 (46.7)	343 (51.7)	0.244
Antidiabetics insulin, *n* (%)	169 (31.2)	32 (26.2)	201 (30.3)	0.328
Antidiabetics others, *n* (%)	324 (59.9)	71 (58.2)	395 (59.6)	0.809
Alcohol intake, *n* (%)	446 (82.4)	112 (91.8)	558 (84.2)	0.022

Differences between smoking statuses were tested using a two-sided Mann–Whitney *U* test for continuous variables and a χ^2 test for categorical variables. Antihypertensives included angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, loop diuretics and beta blockers. Antidiabetics others included metformin, dipeptidyl peptidase-4 inhibitors, sulfonylureas, acarbose, thiazolidinediones, meglitinides, and glucagon-like peptide-1 receptor agonist. ApoB/ApoA1, Apolipoprotein B/apolipoprotein A1; ASA, acetylsalicylic acid; BP, blood pressure; CRP, C-reactive protein; SAD, sagittal abdominal diameter.

Levels of CRP and serum vitamin D, as well as the proportion of participants treated with antihypertensives, ASA, statins, and diabetes medications, were similar between smokers and nonsmokers (Table 1). Smokers more often consumed alcohol than nonsmokers [$n=112$ (91.8%) vs. $n=446$ (82.4%), $P=0.022$] (Table 1).

Of all participants, 85 (12.8%) developed MACE and 82 (12.4%) died during follow-up. Cigarette smoking was associated with all-cause mortality (hazard ratio 2.24, 95% CI 1.40–3.56, $P<0.001$), but not MACE (hazard ratio 1.30, 95% CI 0.77–2.18, $P=0.328$) (Table 2 and Fig. 1). The association between smoking and all-cause mortality remained when analyzing men and women separately, except for in the multivariate analysis of women, where smoking was no longer significantly associated with all-cause mortality, although there was a trend (hazard ratio 2.32, 95% CI 0.56–9.68, $P=0.248$) (Supplementary Tables 1 and 2, http://links.lww.com/JCM/A568). In an ad-hoc univariate cox proportional hazard model, comparing participants who had previously smoked to those who had never smoked, no difference was seen in all-cause mortality [hazard ratio 1.63 (95% CI 0.92–2.89), $P=0.092$, not shown].

Levels of serum vitamin D were associated with decreased risk of MACE (hazard ratio 0.99, 95% CI 0.97–1.00, $P=0.013$) but did not affect the risk of all-cause mortality (hazard ratio 0.99, 95% CI 0.98–1.00, $P=0.098$) (Table 2). CRP was associated with an increased risk of MACE in the univariate but not multivariate analysis (hazard ratio 1.21, 95% CI 1.02–1.44, $P=0.032$, and hazard ratio 1.03, 95% CI 0.84–1.27, $P=0.768$, respectively), and was not associated with the risk of all-cause mortality (hazard ratio 1.14, 95% CI 0.94–1.38, $P=0.192$) (Table 2).

Explorative posthoc analyses were performed to study the dose response and cumulative effects of cigarette smoking. The number of cigarettes consumed per day, categorized as fewer than 10, 10 or more up to fewer than 20 and 20 or more, was not associated with any baseline variable except for sex, whereby men were more common in the higher consumption groups [from $n=13$ (41.9%) among those smoking fewer than 10 cigarettes per day, up to $n=23$ (79.3%) for those smoking 20 or more cigarettes per day, P for trend $=0.004$] (Supplementary Table 3, http://links.lww.com/JCM/A568).

Discussion

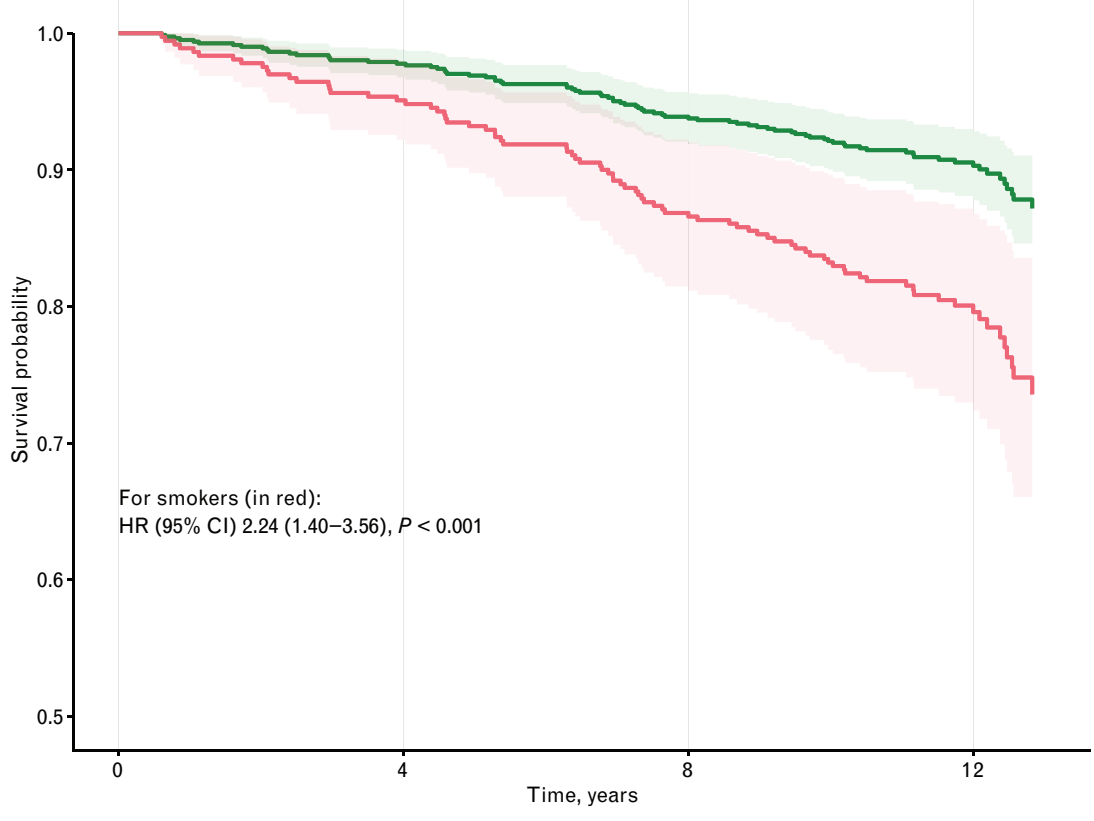
It is well known that cigarette smoking is associated with an increased risk of cardiovascular disease, including for patients with T2D.[1,2,21,22] However, in the current study, cigarette smoking was not associated with an increased

Table 2 A Cox proportional hazard model of all participants showing the hazard ratio, 95% confidence interval, and *P*-value for smoking in relation to all-cause mortality and major adverse cardiovascular event (MACE), respectively

	All-cause mortality, $n=82$				MACE, $n=85$			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	1.03 (0.96–1.11)	0.364	1.07 (0.97–1.17)	0.190	1.01 (0.94–1.08)	0.817	0.98 (0.89–1.08)	0.696
Sex, men	1.27 (0.80–2.02)	0.312	1.51 (0.75–3.02)	0.244	1.58 (0.98–2.55)	0.060	3.11 (1.37–7.07)	0.007
Diabetes duration	1.02 (0.99–1.05)	0.176	1.01 (0.96–1.05)	0.747	1.05 (1.02–1.07)	<0.001	1.03 (1.00–1.07)	0.040
BMI	1.03 (0.99–1.08)	0.118	1.01 (0.90–1.13)	0.907	1.06 (1.02–1.10)	0.005	1.00 (0.90–1.10)	0.963
SAD	1.07 (1.02–1.13)	0.012	1.05 (0.93–1.19)	0.444	1.11 (1.06–1.17)	<0.001	1.11 (0.99–1.24)	0.064
SBP	1.00 (0.98–1.01)	0.788	1.00 (0.99–1.02)	0.609	1.01 (1.00–1.03)	0.034	0.99 (0.98–1.01)	0.474
ApoB/ApoA1 ratio	0.80 (0.20–3.12)	0.743	0.83 (0.13–5.39)	0.844	4.18 (1.23–14.23)	0.022	1.41 (0.25–8.06)	0.698
Triglycerides	1.24 (1.04–1.47)	0.015	1.39 (1.09–1.76)	0.007	1.21 (1.01–1.43)	0.034	1.02 (0.76–1.36)	0.909
HbA1c	1.01 (0.99–1.02)	0.457	1.01 (0.99–1.03)	0.507	1.03 (1.02–1.05)	<0.001	1.03 (1.01–1.05)	0.003
Smoking	2.24 (1.40–3.56)	<0.001	2.42 (1.26–4.64)	0.008	1.30 (0.77–2.18)	0.328	1.10 (0.52–2.30)	0.802
CRP	1.14 (0.94–1.38)	0.192	1.08 (0.86–1.35)	0.530	1.21 (1.02–1.44)	0.032	1.03 (0.84–1.27)	0.768
Serum vitamin D	0.99 (0.98–1.00)	0.098	1.00 (0.98–1.01)	0.612	0.99 (0.97–1.00)	0.013	0.98 (0.97–1.00)	0.026

Smoking was associated with an increased risk of all-cause mortality, but not MACE, in both the univariate and multivariate analyses. ApoB/ApoA1, Apolipoprotein B/apolipoprotein A1; BP, blood pressure; CRP, C-reactive protein; MACE, major adverse cardiovascular event; SAD, sagittal abdominal diameter.

Fig. 1



Cumulative survival probability of all-cause mortality in smokers (red) and nonsmokers (green) during follow-up.

risk of MACE, even after adjusting for the lower BMI, SAD, and SBP of smokers. An explanatory factor could be the relatively low incidence of MACE in this cohort. However, cigarette smoking was associated with increased all-cause mortality, related to other severe morbidities such as lung cancer and chronic obstructive pulmonary disease. Furthermore, smokers and nonsmokers in this cohort had similar levels of inflammatory markers, as well as a similar proportion of participants with medications for cardiovascular comorbidities, including hypertension, hyperlipidemia, and T2D. All of these medications have anti-inflammatory effects.[5,17,18] Thus, one hypothesis is that the anti-inflammatory effects of these medications counteract the negative pro-inflammatory effects, and thus cardiovascular risk, of cigarette smoking in individuals with T2D. However, other cardiovascular protective mechanisms of these medications could also partly or fully explain the lack of increased cardiovascular risk of cigarette smoking seen in this cohort. Smokers also had better BP control, which is in line with previous studies, and which may partly be explained by the lower body weight of smokers which was also seen in our cohort.[23]

BMI and sagittal abdominal diameter were lower for smokers compared with nonsmokers. This could potentially be explained by the increased metabolic rate, and increased energy expenditure, as well as decreased food intake, associated with nicotine.[14,24,25] This could be explained by the inclusion of ex-smokers in the nonsmokers groups, and the weight gain associated with cessation of cigarette smoking.[26] T2D duration, male sex, and HbA1c were all associated with increased risk of MACE, and serum vitamin D was associated with decreased risk of MACE.

Our study has some limitations. Not only cigarette smoking status, in particular, but also past medical history, including myocardial infarction and stroke, as well as current medications, were self-reported and thus could be influenced by conformity bias. Ex-smokers and never-smokers were analyzed together as nonsmokers, which is a potential source of inaccuracy as ex-smokers may have ceased cigarette smoking only shortly before the study began. Self-reported smoking status was collected at the time of inclusion, but not at follow-up, so the total cigarette smoking exposure cannot be assessed. Medications were likewise reported at baseline but not available at follow-up. The current cohort had relatively short T2D duration, and the cohort was relatively young and healthy, which may have mitigated the results. Finally, as this was an observational study, the data cannot be used to firmly determine cause and effect. The main limitation is the relatively few cases of MACE and the limited number of smokers.

In conclusion, this study suggests that smoking does not increase the risk of MACE in a Swedish cohort of patients with T2D, who had good risk factor control and in fact lower BP than nonsmokers, even though the risk of all-cause mortality was increased. This raises the question of whether cardioprotective drugs in individuals with T2D to some degree mitigate the cardiovascular harm of smoking, even though they do not affect other dire consequences of smoking. Larger observational studies of these new findings, including individuals with T2D of longer duration, would be of interest.

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Conflicts of interest

There are no conflicts of interest.

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