Smoking is Associated with Increased Risk of Major Bleeding: A Prospective Cohort Study

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Abstract

Background Tobacco smoking represents the most preventable cause of several fatal and disabling diseases worldwide. Several ingredients in tobacco have been suspected to cause changes in the arterial wall leading to instability of blood vessels. The association of smoking with major bleeding is largely unexplored. We tested the hypothesis that smoking and high tobacco consumption are associated with increased risk of bleeding.

Materials and Methods This is a prospective cohort study with a mean follow-up of 5.9 years including 99,359 individuals from the Copenhagen General Population Study, with a questionnaire including self-reported smoking status and information on smoking intensity in cigarettes per day and pack-years. In this study, 17,555 were current smokers, 40,182 former smokers and 41,622 were never smokers.

Results Multivariable adjusted hazard ratios for current smokers versus never smokers were 1.49 (95% confidence interval [CI]: 1.38–1.61) for any major bleeding, 1.71 (1.37–2.13) for intracranial bleeding, 1.35 (1.14–1.60) for airway bleeding, 2.20 (1.84–2.62) for gastrointestinal bleeding and 1.39 (1.26–1.55) for urinary bleeding. Increased smoking intensity was also associated with increased risk of any major bleeding, where $>$ 40 pack-years in current and former smokers compared with never smokers had a multivariable adjusted hazard ratio of 1.59 (95% CI: 1.45–1.73) (p for trend across four groups: $<$ 0.001). Also, current smokers smoking $>$ 20 cigarettes per day compared with former and never smokers had a corresponding hazard ratio of 1.67 (1.51–1.85) (p for trend across four groups: $<$ 0.001).

Conclusion Current smokers have an increased risk of any major bleeding as well as of intracranial, airway, gastrointestinal and urinary bleeding. Also, increased smoking intensity was associated with increased risk of major bleeding.

Keywords
- tobacco
- pack-years
- haemorrhage
- epidemiology

Introduction

Tobacco smoking represents the most preventable cause of several fatal and disabling diseases worldwide.[1–4] Smoking causes lung cancer, other cancers, cardiovascular disease, chronic obstructive pulmonary disease and peripheral arterial disease, among others. In 1964 to 2012, an estimated 17.7 million deaths were related to smoking in the United States alone.[4] If current trends continue, tobacco will kill 1,000

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million people prematurely during this century and tobacco will kill at least one-third of smokers.[2]

The nicotine in tobacco is proposed to have a damaging effect on the arterial wall, causing endothelial dysfunction and harmful haemodynamic effects making the arterial wall fragile.[5,6] Major bleeding can be caused by local factors such as trauma or invasive procedures, or by systemic factors such as the use of anti-thrombotic medication, for example, anticoagulants.[7] Some studies have suggested hypertension as a risk factor and obesity as a possible protective factor for bleeding; however, there is no consensus on this.[8] The IMPROVE bleeding risk score is used to assess the risk of bleeding for patients admitted to hospitals when considering giving prophylactic treatment for deep venous thromboses.[9,10] The score is calculated by adding factors that was found to be associated with increased risk of fatal or major bleeding, including renal failure, cancer, rheumatic disease, hepatic failure, low platelet count and active gastroduodenal ulcer. It is currently unknown if smoking is associated with increased risk of any major bleeding, and therefore whether smoking should be included in bleeding risk scores to better predict patient prognosis.

We tested the hypotheses that smoking and high tobacco consumption are associated with increased risk of bleeding.[6,7] This was tested for any major bleeding, and separately for intracranial bleeding, airway bleeding, gastrointestinal bleeding and urinary bleeding using 99,359 individuals from the Copenhagen General Population Study.

Materials and Methods

The Copenhagen General Population Study

This study of the Danish general population was initiated in 2003 and ended recruitment for the first examination in 2014. Individuals were selected based on the National Danish Civil Registration System, a system that registers all individuals living in Denmark, from municipalities around Herlev and Gentofte Hospital covering both high-, middle- and low-income areas, and city as well as countryside. We invited all adults of Danish descent aged 20 to 100 years and 42% of those invited, participated. Data were obtained from a self-administered questionnaire and, on the day of the examination, a physical examination was performed, blood samples were taken and the questionnaire was checked by an examiner. The study was approved by a Danish ethical committee and by Herlev and Gentofte Hospital, and written informed consent was obtained from all participants. See ►**Supplementary Fig. S1** (available in the online version) for flowchart on individuals included in the analyses.

Endpoints

Participants were followed using their unique Central Person Registration number and the National Danish Patient Registry, a public registry to which all hospital contacts in Denmark have been reported since 1977, and the National Danish Causes of Death Registry, to which all death certificates have been reported since 1977. Registers are 100% complete, that is, no individuals are lost to follow-up. The endpoint of any major bleeding was defined as intracranial bleeding (International Classification of Diseases, 10th edition [ICD-10], codes I60-I62, I69.0 and I69.2), airway bleeding (ICD-10 codes J94.2 and R04), gastrointestinal bleeding (ICD-10 codes K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K92.0, K92.1 and K92.2) or urinary bleeding (ICD-10 codes N02 and R31.9) up until November 2014, emigration ($n = 393$) or death ($n = 5717$) (►**Supplementary Table S1**, available in the online version). Diagnoses were collected from inpatient or outpatient hospital records as either main cause of admission or as a complication during hospitalization. Information from general practitioners was not included.

Conditions Used for Stratification

Information on diagnoses of invasive cancers was obtained from the Danish Cancer Registry, and includes all cancers except non-melanoma skin cancer. Ischaemic heart disease was defined with ICD 8th edition (ICD-8)codes 410–414 and ICD-10 codes I20-I25 and ischaemic cerebrovascular disease with ICD-8 codes 433–435 and ICD-10 codes I63-I64 and G45. Chronic obstructive pulmonary disease was defined as a forced expiratory volume in one second/forced vital capacity ratio under the lower limit of normal, the fifth percentile of a frequency distribution, excluding participants with self-reported asthma. Low-grade inflammation was defined as individuals with a high-sensitive C-reactive protein $\geq$3 mg/L.

Smoking Status and Intensity

The participants of the Copenhagen General Population Study answered questions on smoking habits in the self-administered questionnaire. They were asked if they were current smokers and, if not, whether they formerly had been smokers. Questions also included how many years they had been smoking, when they started/stopped and the number of cigarettes, cigars, cheroots and/or pipe-tobacco they smoked/had smoked per day. Based on these answers, the participants were divided into never smokers, former smokers or current smokers. Current smokers were individuals smoking one or more cigarettes per day and/or individuals stating they were current smokers on the questionnaire. Former smokers were individuals who previously smoked one or more cigarettes per day and/or individuals stating they were former smokers on the questionnaire. Also, for both former and current smokers, cumulative tobacco consumption was calculated as pack-years, where one pack-year is 20 cigarettes (or equivalent) smoked every day for 1 year. Finally, we calculated the number of cigarettes (or equivalent) smoked per day, if the participant was currently smoking at the time of examination.

Other Covariates

The covariates used for adjustment in our analysis were chosen because they were associated with smoking and/or risk of bleeding. All covariates were based on information obtained on the day of examination by the questionnaire, the physical examination and/or the blood samples. Hypertension was a measured systolic blood pressure $\geq$140 mm Hg ($\geq$135 mm Hg for diabetics), a measured diastolic blood pressure $\geq$90 mm Hg

(≥85 mm Hg for diabetics) and/or use of antihypertensive medication as stated on the questionnaire. The participants reported their weekly alcohol intake in units per week (one unit is equivalent to 12 g of alcohol). Kidney function was evaluated by estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration formula including creatinine, age and sex. Body mass index (BMI) was calculated as measured weight in kilograms divided by measured height in metres squared (kg/m^2). Level of education was divided into no education (after secondary school), lower education (≤3 years vocational or academic), higher education (> 3 years) or university education. Civil status was divided into married/co-habiting, not married, separated/divorced or widow/widower. International normalized ratio (INR) for coagulation factor II, VII and X was measured in all individuals on fresh samples using a standard hospital assay. Information on fat intake was retrieved from the questionnaire and individuals were divided into high and low fat intake. Physical activity was divided into physical inactivity defined as doing no or light physical activity in leisure time for less than 4 hours per week and moderate/vigorous physical activity defined as doing more than 4 hours of light physical activity or at least 2 hours of vigorous physical activity in leisure time per week. Co-morbidities were scored using the Charlson comorbidity index, a severity weighted index of co-morbid conditions including acquired immunodeficiency syndrome/human immunodeficiency virus, any malignancy (except malignant neoplasms of the skin), cerebrovascular disease, chronic pulmonary disease, congestive heart failure, dementia, diabetes without chronic complications, diabetes with chronic complications, haemiplegia/paraplegia, metastatic solid tumours, mild liver disease, moderate/severe liver disease, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease and rheumatic disease.

Statistical Analyses

All statistical analyses were done using Stata 13.1. Cuzick non-parametric test for trend or Mann–Whitney test were used to test for differences in continuous and categorical variables between different smoking statuses.

We analysed age-at-event using left truncation (delayed entry) and age as time scale. Hazard ratios with 95% confidence intervals (CIs) were calculated by Cox proportional hazards regression for incident bleeding events occurring after the assessment of smoking history, adjusted multivariable for covariates associated with smoking and/or risk of bleeding. Multivariable adjustment was for sex, age (as time scale), BMI, anticoagulant therapy (by INR activated partial thromboplastin time and coagulation factors II, VII and X), acetylsalicylic acid use, educational level and civil status.

Information on covariates other than age and sex were 98.5% complete, and if values were missing, these were imputed based on age and sex using the Stata command 'mi impute'; if only individuals with complete data were analysed, results were similar to those reported.

The proportional hazard assumption was judged by visual inspection of cumulative hazard logarithm plots against age; no major violations were observed. Individuals with major bleeding events before study entry were excluded. Multiplicative interaction of smoking status with other risk factors was evaluated by including two-factor interaction terms between smoking status and other examined risk factors continuously or categorized in the multivariable Cox regression model. Additive interactions were examined by the synergy index.

Cumulative incidences of smoking status and pack-years were plotted using a non-parametric cumulative incidence estimation including competing risk of death, using the user-written Stata command 'stcompet', and differences between groups were examined using log-rank trend tests.

Incidence rate ratios (IRRs) with 95% CI were calculated using a negative binomial regression model assessing the risk of bleeding according to smoking status. IRR is the ratio of two incidence rates. The incidence rate is defined as the number of events divided by the person-time at risk. We used negative binomial regression using the Stata command: nbreg *y x covariates*, exposure (*follow-up time*) irr.

Results

Baseline characteristics of all individuals are shown in ►**Table 1**. Individuals in the never smoking group were drinking less alcohol, were better educated and a higher per cent were married/co-habitant. Note that 17,555 were current smokers, 40,182 former smokers and 41,622 were never smokers. During follow-up, 11,339 individuals had an incident of major bleeding, and of these, 1,119 had intracranial bleeding, 2,788 had airway bleeding, 1,903 had gastrointestinal bleeding and 6,322 had urinary bleeding (some individuals had more than one of these types of bleeding endpoints). Mean follow-up time was 5.9 years ranging from 0.1 to 11 years.

Risk of Major Bleeding by Smoking Status

Multivariable adjusted hazard ratios for current smokers versus never smokers were 1.71 (95% CI: 1.39–2.13) for intracranial bleeding, 1.35 (1.14–1.60) for airway bleeding, 2.20 (1.84–2.62) for gastrointestinal bleeding and 1.39 (1.26–1.55) for urinary bleeding (►**Fig. 1**). When combining all four types of bleeding endpoints, the corresponding hazard ratio was 1.49 (1.38–1.61) for any major bleeding. Corresponding hazard ratios of former smokers versus never smokers were above 1.0; however, these hazard ratios were only significant for any major bleeding and for gastrointestinal bleeding. Multivariable adjustment was for age, sex, units of alcohol per week, BMI, INR, educational level and civil status. When using repeated events, results were similar (►**Supplementary Fig. S2**, available in the online version). When results were further adjusted for fat intake, physical activity and co-morbidities at baseline, results were similar; however, results for former smokers were attenuated (►**Supplementary Fig. S3**, available in the online version).

For former smokers, the hazard ratio of any major bleeding compared with never smokers was 1.4 (1.2–1.7) for individuals who quit smoking 0 to 1 year ago, and 1.0 (0.9–1.1) for those who quit smoking > 20 years ago (►**Supplementary Fig. S4**, available in the online version).

Table 1 Baseline characteristics of individuals in the Copenhagen General Population Study

	Smoking		
	Current	Former	Never
Number	17,555	40,182	41,622
Women, %	53	52	59
Age, y	57 (48–65)	60 (51–69)	56 (46–66)
Alcohol, units/d[a]	9 (3–18)	9 (4–16)	7 (3–12)
Hypertension, %	64	70	65
BMI, kg/m^2	25 (23–28)	26 (24–29)	25 (23–28)
eGFR, mL/min/1.73 m^2	82 (70–91)	79 (68–89)	80 (70–91)
INR > 1.1, %	18	22	25
aPTT, s	28 (26–31)	28 (26–30)	28 (26–30)
Factor II, VII and X, %	100 (87–114)	95 (82–109)	93 (81–107)
Platelet count, 10^9/L	282 (239–330)	271 (232–316)	270 (232–314)
ALAT, U/L	19 (15–26)	21 (16–28)	20 (15–27)
ASA, %	13	15	9
> 3 years education, %	31	47	49
Married/co-habitant, %	66	64	77
Pack-years	26 (14–40)	12 (5–25)	–

Abbreviations: ALAT, alanine aminotransferase; aPTT, activated partial thromboplastin time; ASA, acetylsalicylic acid; BMI, body mass index; eGFR, estimated glomerular filtration rate; INR, international normalized ratio for coagulation factor II, VII and X.
Note: Continuous variables are median (interquartile range).
[a]One unit = 12 g of alcohol.

Risk of Major Bleeding by Smoking Status in Different Sub-Groups of Pre-Existing Disease and Possible Confounders

For analyses in sub-groups of individuals with or without cancer, ischaemic heart disease or ischaemic cerebrovascular disease, chronic obstructive pulmonary disease or low-grade inflammation at baseline, the multivariable adjusted hazard ratios for any major bleeding for current smokes versus never smokers were statistical significant except for in individuals with cancer (►**Fig. 2**). For former versus never smokers, the corresponding hazard ratios were all nominally above 1.0; however, the risk estimates were not significant except for in individuals without low-grade inflammation at baseline. The tests for interaction were significant for with or without ischaemic heart disease or ischaemic cerebrovascular disease at baseline; however, the risk estimates were similar.

For all analyses in sub-groups, the multivariable adjusted hazard ratio for any major bleeding for current smokers versus never smokers remained highly statistically significant (►**Supplementary Fig. S5**, available in the online version). Corresponding hazard ratios for any major bleeding in former smokers versus never smokers were all (except for platelet counts < 200) above 1.0; however, most risk estimates were not statistically significant. Importantly, however, as none of the tests of interaction for sub-groups in current or former smokers versus never smokers were statistically significant (►**Supplementary Fig. S5**, available in the online version), the association observed overall will also be true in the different sub-groups.

Risk of Major Bleeding by Higher Smoking Intensity

Smoking intensity among current and former smokers as measured in pack-years versus never smokers was associated with a dose-dependent increased risk of any major bleeding and of all bleeding endpoints separately (p for trend across four groups: 0.01 to < 0.001) (►**Fig. 3**). Individuals with > 40 pack-years compared with never smokers had a hazard ratio of 1.59 (95% CI: 1.45–1.73) (p for trend across four groups: < 0.001) for risk of any major bleeding in multivariable adjusted analysis. The corresponding hazard ratios were 1.59 (1.25–2.06) ($p < 0.001$) for intracranial bleeding, 1.56 (1.30–1.87) ($p < 0.001$) for airway bleeding, 2.23 (1.86–2.70) ($p < 0.001$) for gastrointestinal bleeding and 1.40 (1.24–1.58) ($p < 0.001$) for urinary bleeding.

Similarly, number of cigarettes smoked per day among current smokers versus former and never smokers were associated with a dose-dependent increased risk of any major bleeding and of all bleeding endpoints separately (p for trend across four groups: 0.002 to < 0.001). Current smokers who smoked > 20 cigarettes per day compared with former and never smokers had a hazard ratio of 1.67 (1.51–1.85) ($p < 0.001$) for risk of any major bleeding in multivariable adjusted analysis. The corresponding hazard ratios were 2.11 (1.59–2.79) ($p < 0.001$) for intracranial bleeding, 1.36 (1.10–1.70) ($p < 0.001$) for airway bleeding, 2.67 (2.18–3.27) ($p < 0.001$) for gastrointestinal bleeding and 1.50 (1.30–1.71) ($p < 0.001$) for urinary bleeding.

Cumulative Incidences of Major Bleeding for Smokers versus Never Smokers

The cumulative incidences of any major bleeding as a function of age were increased in current smokers and in former smokers compared with never smokers (p for trend: < 0.001 by the log-rank test) (►**Fig. 4**). The cumulative incidences of any major bleeding as a function of age were also increased in individuals with > 40 pack-years, 21 to 40 pack-years and 1 to 20 pack-years compared with never smokers (p for trend: < 0.001).

Discussion

We found that current smokers compared with never smokers in the general population had an increased risk of any major bleeding, and increased risk of intracranial, airway, gastrointestinal and urinary bleeding. Furthermore, we found that there was an increased risk of any major bleeding and risk of all four sub-types of bleeding with increased number of pack-years and increased number of cigarettes smoked per day.

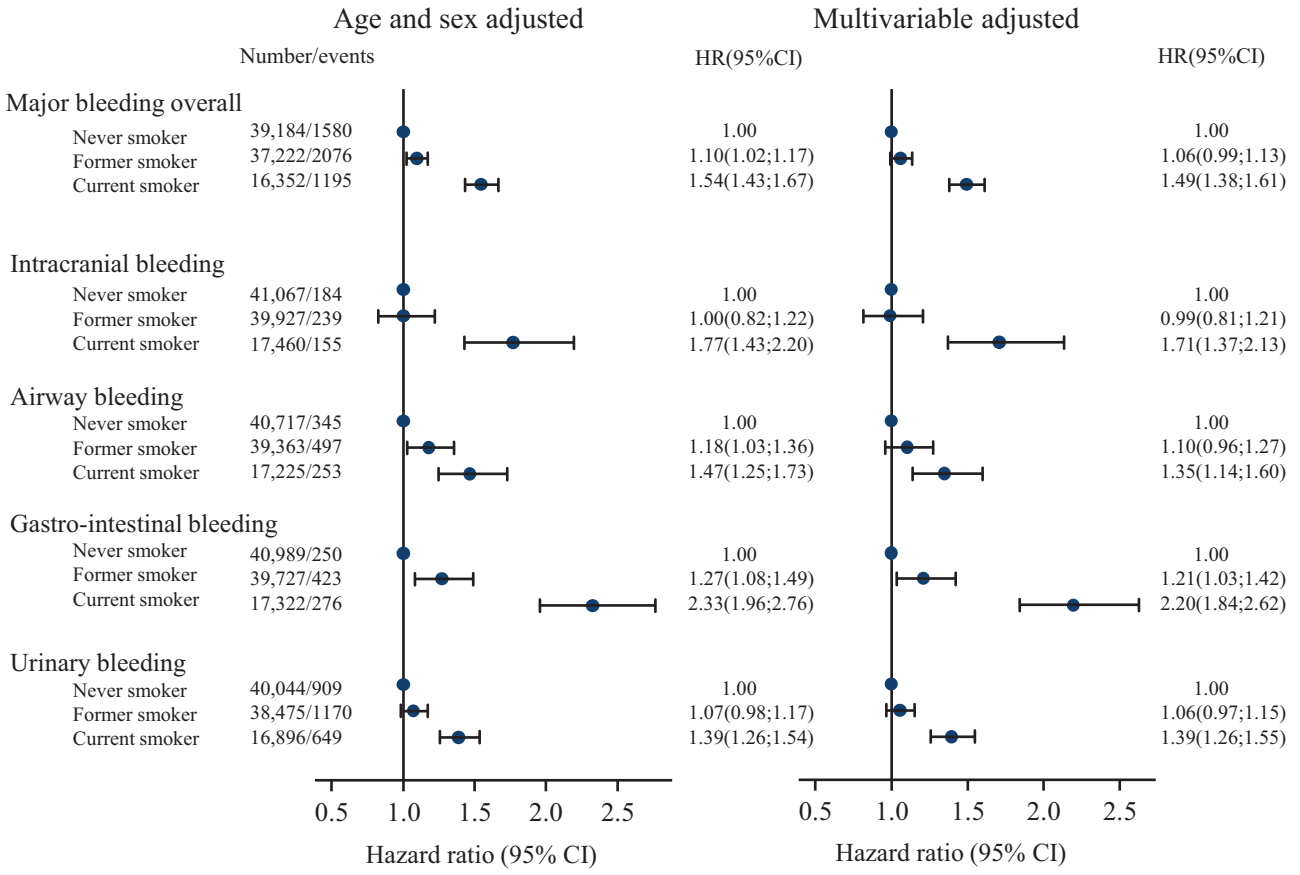

Fig. 1 Hazard ratios and 95% confidence intervals for any major bleeding, for intracranial, airway, gastrointestinal and urinary bleeding in current and former smokers versus never smokers. Multivariable adjustment was for sex, age (as time scale), body mass index, alcohol consumption, international normalized ratio, activated partial thromboplastin time, acetylsalicylic acid use, educational level and civil status. Based on 99,359 individuals from the Copenhagen General Population Study. CI, confidence interval.

Mechanistically, it is plausible that tobacco smoking can lead to fragile vessels prone to rupture and consequently to bleeding episodes, as tobacco in cigarettes, cigars, cheroots and pipe-tobacco contains several thousand chemicals including a vast amount of toxins.[11,12] These toxins can cause structural damage to the vessel wall by the development of free radicals, which may be acute as well as long term. Further, smoking has been shown to impair the production of nitric oxide in the endothelium,[5] and nitric oxide, produced in response to increased blood flow and other physiological stimuli, is an important regulator of the smooth muscle tone in the vessel wall. Smoking can therefore result in an impairment of dilation in the endothelium and consequently in more rigid arteries and vessels. This leads to increased shear stress at the endothelial surface likely leading to a leaky endothelium allowing different cells and proteins to pass. Such alterations may in some cases lead to damage of the endothelium, causing the vessel to rupture and bleeding to occur. In this study, we found that both current and former smokers had increased risk of bleeding; however, it was mainly former smokers who had quit recently who were at increased risk, indicating that it might mainly be high doses of toxins present in the bloodstream that can lead to bleeding events and that the vessels perhaps regenerate after several years following quitting of smoking.

To the best of our knowledge, the risk of any major bleeding among smokers versus non-smokers is largely unexplored as is the association of daily smoking intensity and number of pack-years with risk of major bleeding and organ-specific bleeding; however, the risk of a few organ-specific types of bleeding in relation to smoking status has been investigated.[13–15] Cigarette smoking has been shown to be an independent risk factor for both ischaemic and haemorrhagic stroke in both men and women.[16] Two large prospective cohort studies, one in 22,022 men and one in 39,783 women found an increased risk of haemorrhagic stroke, intra-cerebral haemorrhage and sub-arachnoid haemorrhage among smokers and an increase in the risk with increased amount smoked.[17,18] One large Finnish prospective study of 36,686 individuals also found an increased risk of haemorrhagic stroke among smokers versus non-smokers.[19] Another study of 66,820 elderly Chinese found that smoking was associated with a two- to threefold higher risk of haemorrhagic stroke, intra-cerebral haemorrhage and sub-arachnoid haemorrhage.[20] Also, in 475,734 Korean men, it was found that among smokers quitting smoking

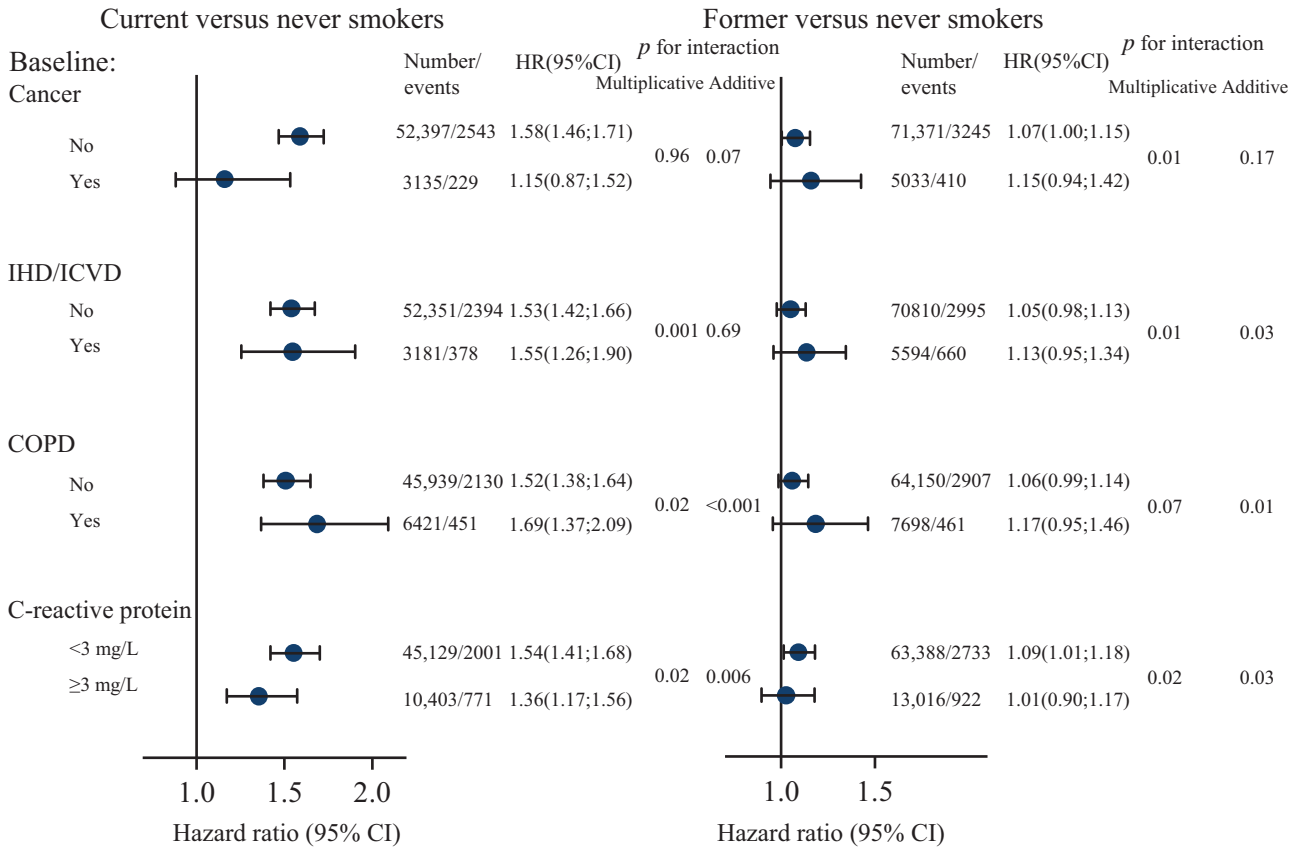

Fig. 2 Multivariable adjusted hazard ratios and 95% confidence interval for risk of any major bleeding in current smokers versus never smokers (left panel), and in former smokers versus never smokers (right panel). Analyses were stratified according to disease or marker of disease (C-reactive protein) at baseline possibly associated with the outcome. Multivariable adjustment was for sex, age (as time scale), body mass index, alcohol consumption, international normalized ratio, activated partial thromboplastin time, acetylsalicylic acid use, educational level and civil status. Based on 99,359 individuals from the Copenhagen General Population Study. CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; IHD, ischaemic heart disease; ICVD, ischaemic cerebrovascular disease.

significantly reduced the risk of sub-arachnoid haemorrhage.[21] Furthermore, a review from 2005 found that smoking is one of the most important risk factors for sub-arachnoid haemorrhage.[13,22] Taken together, these findings support our results that current smoking increases the risk of intracranial bleeding.

Previously, mainly smaller studies have examined the association of smoking with gastrointestinal bleeding, with conflicting results, and most studies were case–control studies and had limited data on smoking status.[14,15] Most studies are made in a sub-group of gastrointestinal bleeding such as peptic ulcer bleeding. One case–control study of 203 patients with ulcer bleeding and 203 controls found an odds ratio of 2.2 (95% CI: 1.04–4.7) for risk of ulcer bleeding among current smokers compared with non-smokers.[14] Others have also found an increased risk of peptic ulcer bleeding among smokers,[15,23,24] whereas some have not.[14,25] A meta-analysis found a dose-dependent increase in risk of upper gastrointestinal bleeding with smoking intensity.[26] One prospective study including 48,000 men did not find an increased risk of major gastrointestinal bleeding among current or past smokers or in relation to pack-years of smoking.[27] However, another prospective including 5,888 elderly men and women found that current smokers had a higher risk of hospitalization for gastrointestinal bleeding than non-smokers.[28]

To the best of our knowledge, no studies have examined the association between smoking and airway bleeding. However, the possible association of increased risk of cryptogenic haemoptysis and smoking has been proposed but not investigated.[29] For urinary bleeding, one prospective study of 56,632 individuals found that among asymptomatic healthy adults, current smoking was associated with an increased odds of having microscopic haematuria.[30]

One limitation of our study is that the diagnoses of bleeding were based on hospital discharge records and death certificates, and therefore only include either major bleedings severe enough to result in a hospital visit or bleedings in relation to a hospital visit or death. Conversely, it could be argued that this is a strength as we only examine the risk associated with major bleedings. Further, haematuria could be microscopic or gross with different aetiologies for each, some of them are not major bleedings (some patients with glomerulonephropathies, cystitis and nephrolithiasis) and some of them are associated with smoking (malignancies); however, the association between smoking and major bleeding was also observed from intracranial bleeding where most events represents major bleeding and only a minority will be

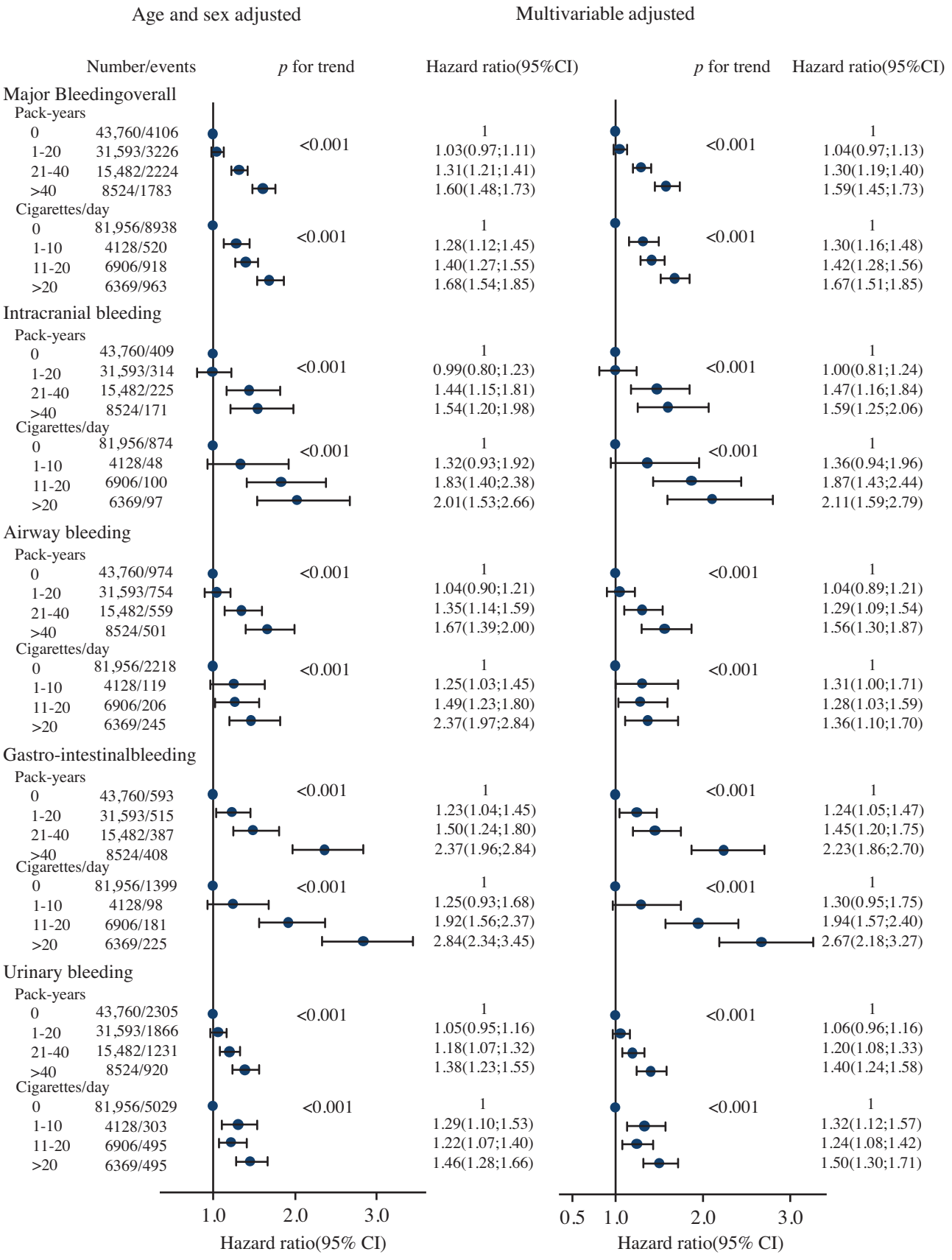

Fig. 3 Multivariable adjusted hazard ratios and 95% confidence intervals for any major bleeding, for intracranial, airway, gastrointestinal and urinary bleeding for increasing pack-years in current and former smokers and for increasing cigarettes smoked per day in current smokers. Multivariable adjustment is for sex, age (as time scale), body mass index, alcohol consumption, international normalized ratio, activated partial thromboplastin time, acetylsalicylic acid use, educational level and civil status. Based on 99,359 individuals from the Copenhagen General Population Study. CI, confidence interval.

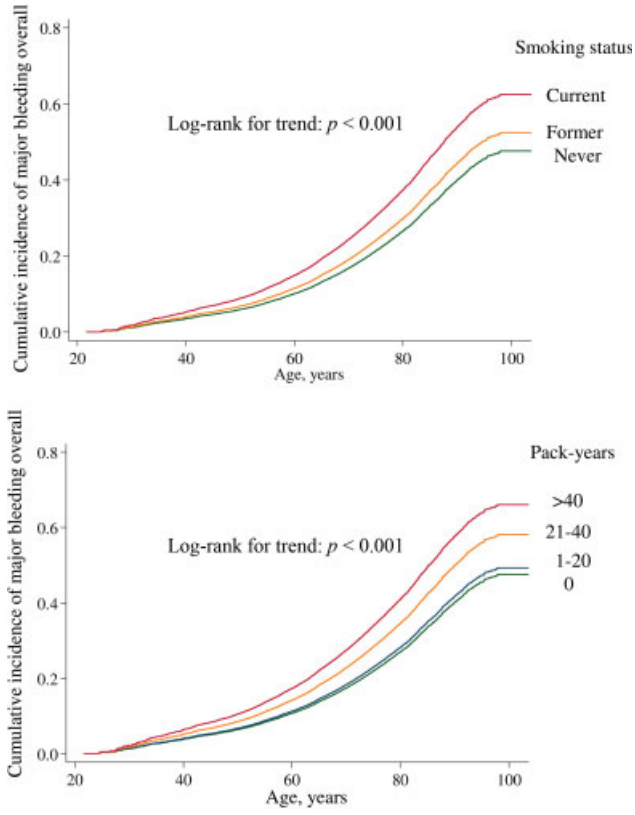

Fig. 4 Cumulative incidences of any major bleeding by age and as a function of current, former and never smokers (top panel) and as a function of pack-years smoked (bottom panel). Based on 99,359 individuals from the Copenhagen General Population Study.

related to cancer. Another limitation is that we only included individuals of white Danish descent and the result may therefore not necessarily apply to other ethnicities; however, we are not aware of any data suggesting that the present results should not be applicable to most races. Yet, another limitation is that we may not have adjusted for all potential confounders such as the use of anti-platelet therapy other than aspirin, such as clopidogrel, ticagrelor, prasugrel and cilostazol, and also non-steroid anti-inflammatory drugs and the presence of *Helicobacter pylori*, liver cirrhosis, varices, haemorrhoids, inflammatory bowel disease, trauma, falls or the use of COX-2 inhibitors could be potential confounders. Finally, smoking status and number of cigarettes smoked is based on questionnaire data, and this could result in reporter bias. However, as such a bias most likely will be non-differential to major bleeding episodes occurring later in life; such potential bias would only bias the results towards the null hypothesis and therefore cannot explain the present results.

For practical purposes, the finding in this study that smoking was associated with increased risk of major bleeding suggests that smoking could be included in the IMPROVE bleeding risk score to better identify patients in need of prophylactic treatment for deep venous thromboses.[9,10]

In conclusion, in this study current smokers have an increased risk of any major bleeding as well as of intracranial, airway, gastrointestinal and urinary bleeding. Also, in this study, increased intensity of smoking as measured by pack-years as well as cigarettes smoked per day were associated with increased risk of all four sub-types of bleedings.

What is known about this topic?

- A systematic review from 2005 found that smoking is one of the most important risk factors for sub-arachnoid haemorrhage.
- Further previous smaller studies have published conflicting results as for the association between smoking and peptic ulcer bleeding. One case–control study including 406 individuals found an increased odds ratio of 2.2 for risk of peptic ulcer for smokers versus non-smokers.
- No studies have to the best of our knowledge analysed the association between smoking and major bleeding overall. Also, the association of smoking intensity and number of pack-years with risk of major bleeding has not been investigated.

What does this paper add?

- Our study suggests that current smokers have an increased risk of major bleeding overall as well as of intracranial, airway, gastrointestinal and urinary bleeding.
- Also, increased intensity of smoking as measured by pack-years among current and former smokers as well as cigarettes smoked per day among current smokers were associated with increased risk of all types of bleeding.

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Conflict of Interest
None declared.

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References

1 Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. JAMA 2004;291(10):1238–1245
2 Frieden TR, Bloomberg MR. How to prevent 100 million deaths from tobacco. Lancet 2007;369(9574):1758–1761
3 Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med 2013;368(04):341–350
4 Holford TR, Meza R, Warner KE, et al. Tobacco control and the reduction in smoking-related premature deaths in the United States, 1964-2012. JAMA 2014;311(02):164–171

5 Powell JT. Vascular damage from smoking: disease mechanisms at the arterial wall. Vasc Med 1998;3(01):21–28
6 Yalcin E, de la Monte S. Tobacco nitrosamines as culprits in disease: mechanisms reviewed. J Physiol Biochem 2016;72(01): 107–120
7 Khan F, Datta YH. Risk of bleeding during long-term anticoagulation with warfarin: a tertiary care center experience. Blood Coagul Fibrinolysis 2015;26(01):110–112
8 Braekkan SK, van der Graaf Y, Visseren FL, Algra A. Obesity and risk of bleeding: the SMART study. J Thromb Haemost 2016;14(01): 65–72
9 Decousus H, Tapson VF, Bergmann JF, et al; IMPROVE Investigators. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. Chest 2011; 139(01):69–79
10 Hostler DC, Marx ES, Moores LK, et al. Validation of the International Medical Prevention Registry on Venous Thromboembolism Bleeding Risk Score. Chest 2016;149(02):372–379
11 Bluhm AL, Weinstein J, Sousa JA. Free radicals in tobacco smoke. Nature 1971;229(5285):500
12 Ding YS, Zhang L, Jain RB, et al. Levels of tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons in mainstream smoke from different tobacco varieties. Cancer Epidemiol Biomarkers Prev 2008;17(12):3366–3371
13 Feigin VL, Rinkel GJ, Lawes CM, et al. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. Stroke 2005;36(12):2773–2780
14 Stack WA, Atherton JC, Hawkey GM, Logan RF, Hawkey CJ. Interactions between Helicobacter pylori and other risk factors for peptic ulcer bleeding. Aliment Pharmacol Ther 2002;16(03):497–506
15 Weil J, Langman MJ, Wainwright P, et al. Peptic ulcer bleeding: accessory risk factors and interactions with non-steroidal anti-inflammatory drugs. Gut 2000;46(01):27–31
16 Peters SA, Huxley RR, Woodward M. Smoking as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 81 cohorts, including 3,980,359 individuals and 42,401 strokes. Stroke 2013;44(10):2821–2828
17 Kurth T, Kase CS, Berger K, Schaeffner ES, Buring JE, Gaziano JM. Smoking and the risk of hemorrhagic stroke in men. Stroke 2003; 34(05):1151–1155
18 Kurth T, Kase CS, Berger K, Gaziano JM, Cook NR, Buring JE. Smoking and risk of hemorrhagic stroke in women. Stroke 2003;34(12):2792–2795
19 Zhang Y, Tuomilehto J, Jousilahti P, Wang Y, Antikainen R, Hu G. Lifestyle factors on the risks of ischemic and hemorrhagic stroke. Arch Intern Med 2011;171(20):1811–1818
20 Xu L, Schooling CM, Chan WM, Lee SY, Leung GM, Lam TH. Smoking and hemorrhagic stroke mortality in a prospective cohort study of older Chinese. Stroke 2013;44(08):2144–2149
21 Song YM, Cho HJ. Risk of stroke and myocardial infarction after reduction or cessation of cigarette smoking: a cohort study in Korean men. Stroke 2008;39(09):2432–2438
22 Feigin V, Parag V, Lawes CM, et al; Asia Pacific Cohort Studies Collaboration. Smoking and elevated blood pressure are the most important risk factors for subarachnoid hemorrhage in the Asia-Pacific region: an overview of 26 cohorts involving 306,620 participants. Stroke 2005;36(07):1360–1365
23 Savage RL, Moller PW, Ballantyne CL, Wells JE. Variation in the risk of peptic ulcer complications with nonsteroidal antiinflammatory drug therapy. Arthritis Rheum 1993;36(01):84–90
24 Tzourmakliotis D, Economou M, Manolakopoulos S, et al. Clinical significance of cytotoxin-associated gene A status of Helicobacter pylori among non-steroidal anti-inflammatory drug users with peptic ulcer bleeding: a multicenter case-control study. Scand J Gastroenterol 2004;39(12):1180–1185
25 Ng TM, Fock KM, Khor JL, et al. Non-steroidal anti-inflammatory drugs, Helicobacter pylori and bleeding gastric ulcer. Aliment Pharmacol Ther 2000;14(02):203–209
26 Lewis SC, Langman MJ, Laporte JR, Matthews JN, Rawlins MD, Wiholm BE. Dose-response relationships between individual non-aspirin nonsteroidal anti-inflammatory drugs (NANSAIDs) and serious upper gastrointestinal bleeding: a meta-analysis based on individual patient data. Br J Clin Pharmacol 2002;54(03):320–326
27 Strate LL, Singh P, Boylan MR, Piawah S, Cao Y, Chan AT. A prospective study of alcohol consumption and smoking and the risk of major gastrointestinal bleeding in men. PLoS One 2016;11 (11):e0165278
28 Kaplan RC, Heckbert SR, Koepsell TD, et al; Cardiovascular Health Study Investigators. Risk factors for hospitalized gastrointestinal bleeding among older persons. J Am Geriatr Soc 2001;49(02): 126–133
29 Hiyama J, Horita N, Shiota Y, Ono T, Yamakido M. Cryptogenic hemoptysis and smoking. Chest 2002;121(04):1375–1376
30 Jeong CW, Lee S, Byun SS, Lee DH, Lee SE. No increase in risk of microscopic hematuria with aspirin use by asymptomatic healthy people. JAMA Intern Med 2013;173(12):1145–1146