Sex, Smoking, and Risk for Subarachnoid Hemorrhage

Joni Valdemar Lindbohm, MD; Jaakko Kaprio, MD, PhD; Pekka Jousilahti, MD, PhD; Veikko Salomaa, MD, PhD; Miikka Korja, MD, PhD

Background and Purpose—Women are at higher risk for subarachnoid hemorrhage (SAH) than men for unknown reasons. Also cumulative effects of smoking have been neglected among prospective studies. We studied associations between smoking habits and SAH and interactions between known SAH risk factors in a prospective population-based study.

Methods—The population-based FINRISK study cohort of 65 521 individuals was followed up for 1.38 million person-years. We used the Cox proportional hazards model to calculate hazard ratios and evaluated additive and multiplicative interactions between study variables, with all analyses adjusted for known SAH risk factors.

Results—During follow-up, we identified 492 SAHs (266 women). Smoking had a linear dose-dependent and cumulative association with risk for SAH in both sexes. Women smoking >20 cigarettes per day had a hazard ratio of 8.35 (95% confidence interval, 3.86–18.06) compared with a hazard ratio of 2.76 (95% confidence interval, 1.68–4.52) in men in the same cigarettes per day group. Hazard ratios differed by sex in all cigarettes per day and pack-year categories; this association was stronger in women in all categories (P=0.01). When an adjusted model included interaction terms between sex and cigarettes per day or pack-years, female sex was no longer an independent SAH risk factor. Former smokers had a markedly decreased risk for SAH in both sexes when compared with current smokers.

Conclusions—Smoking has a dose-dependent and cumulative association with SAH risk, and this risk is highest in female heavy smokers. Vulnerability to smoking seems to explain in part the increased SAH risk in women.

(*Stroke*. 2016;47:1975-1981. DOI: 10.1161/STROKEAHA.116.012957.)

Key Words: cohort studies ■ risk factors ■ sex characteristics ■ smoking ■ subarachnoid hemorrhage

According to prospective cohort studies, smoking is the most important lifestyle risk factor for subarachnoid hemorrhage (SAH)[1–3] and accounts for at least one third of all cases.[4,5] In addition, earlier studies report that women are at higher risk for SAH with adjusted hazard ratios (HRs) from 1.4 to 1.9 compared with men,[1–3] but the reason for this sex difference has remained unresolved. Retrospective case–control studies have suggested that an increasing number of cigarettes smoked per day (CPD) elevates the risk gradually.[4,6,7]

Our aim was to examine associations between smoking habits and SAH in a large, population-based, prospective cohort. We also focused on interaction or effect modification between smoking habits and sex because this approach remains unstudied. In addition, we evaluated whether smoking elevates the risk of sudden deaths from SAH outside hospitals or in emergency rooms more than hospitalizations. Finally, we evaluated the effect of smoking cessation on risk for future SAH.

Methods

Data Collection

The research protocol has been described in detail.[2,8,9] In brief, the National FINRISK Surveys have been conducted every 5 years since 1972, with independent, population-based, random samples from various geographical areas of Finland. Alcohol consumption, history of hypertension, medication for hypertension, smoking status, and socioeconomic status were assessed by a standardized self-administered questionnaire. Individuals with a history of hypertension or medication for hypertension received the classification hypertensive. Experienced nurses performed clinical measurements including systolic blood pressure, height, and weight and acquired semifasting blood samples for cholesterol measurement after at least 4-hour fasting.

Follow-Up

Follow-up started at enrollment and ended at first-ever SAH, death, or on December 31, 2011, whichever came first. The nationwide Hospital Discharge Register and Causes of Death Register identifies fatal (including outside of hospital and emergency-room SAH deaths) and nonfatal SAHs with high accuracy.[10] Sudden deaths from SAH were defined as deaths away from hospitals and those occurring

Received January 27, 2016; final revision received June 4, 2016; accepted June 15, 2016.

From the Department of Public Health, University of Helsinki, Helsinki, Finland (J.V.L., J.K.); Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland (J.V.L., M.K.); National Institute for Health and Welfare, Helsinki, Finland (J.K.); and Institute for Molecular Medicine Finland, Helsinki, Finland (P.J., V.S.).

Presented in part at the European Society of Cardiology Congress, London, United Kingdom, August 29–September 2, 2015, and at the European Association of Neurosurgical Societies Annual Meeting, Madrid, Spain, October 18–21, 2015.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.116.012957/-/DC1.

Correspondence to Joni Valdemar Lindbohm, MD, Department of Public Health, P.O. Box 20 (Tukholmankatu 8B), FI-00014 University of Helsinki, Finland. E-mail joni.lindbohm@helsinki.fi

in emergency rooms. Sudden deaths from SAH were confirmed in autopsy, and a nosologist checked and corrected the underlying cause of death when necessary. The follow-up was complete for deaths and hospitalizations, when hospitalized patients continued to live in Finland.[9] Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement[11] guided the reporting.

Smoking

Those participants who reported no smoking at all or <100 cigarettes in their lifetime were considered never-smokers. Occasional smokers had smoked on a nondaily basis during the past 6 months before enrollment. Recent quitters were participants who had quit smoking within 6 months before enrollment; former smokers had quit >6 months before enrollment. Current smokers reported how many cigarettes they smoked per day on average, separately for manufactured and self-rolled cigarettes, and the sum of these 2 comprised their CPD.

On the basis of previous studies, we estimated that 1 cigar increased risk for SAH as much as 1 cigarette and 1 pipeful of tobacco as much as 3 cigarettes.[12–16] For analyses, we divided smoking status into 8 categories: never-smokers, occasional smokers, former smokers, recent quitters, and further to 4 groups of current smokers. Current smokers were categorized on the basis of CPD into 1 to 10, 11 to 20, 21 to 30, and ≥31 CPD. Analyses using pack-years (PYs) included only current smokers. PYs were calculated by multiplying the number of CPD by the number of years the person had smoked before enrollment; this number was then divided by 20 (one pack=20 cigarettes). PYs were categorized as none (for all but current smokers), <5 PYs, 5 to 10 PYs, and then in 10-PY intervals until >50 PYs. Smoking status was available for 99.4% of the participants, CPDs for 99.2%, and PYs for 98.8% of the current smokers.

Statistical Analyses

Because of <2% of missing data per variable, we used complete case analyses. We used the Cox proportional hazard model to calculate HRs and 95% confidence intervals (CIs) in adjusted models. On the basis of previous prospective and population-based studies,[1–3] our final model included age, smoking, systolic blood pressure, body mass index, cholesterol, sex, and study area and year. The preliminary models examined also the role of alcohol consumption and socioeconomic status. According to Schoenfeld residuals and log–log inspection, our models met the proportional assumption criteria. The likelihood ratio test (LRT) served to evaluate the evidence of multiplicative interactions and departure from linearity in adjusted models; a LRT *P* value of <0.10 was considered evidence of possible interaction. A method described by Andersson et al[17] served in assessing additive interactions by calculating a relative excess risk because of interaction, attributable proportion, and synergy index (SI) in adjusted models. We defined the evidence for additive interaction as strong when at least 2 of relative excess risk because of interaction, attributable proportion, or SI had *P* values <0.05. Competing risk incidence estimates were calculated by the method described by Fine and Gray.[18] Population attributable risk was estimated by the following formula: population attributable risk=p_f (HR-1)/[p_f (HR-1)+1], where p_f is population fraction of smokers. All statistical analyses used Stata Corp version 12.1 (Stata Corp, College Station, TX).

Ethics Statement

Ethical approval came from the corresponding ethics committee according to the commonly required research procedures and Finnish legislation for each survey, and the study was conducted according to the World Medical Association's Declaration of Helsinki on ethical principles for medical research. From 2002 onward, written informed consent has been provided by each participant.[8]

Results

Cohort

The study cohort comprised 65 521 participants (33 805 women) who participated in the baseline surveys between 1972 and 2007. A total of 492 first-ever SAHs (266 women) were recorded during the 1.38 million person-years of follow-up. The mean and median ages of the participants were 45.3 (SD, 12.1) and 45.0 years. Median follow-up time for SAH cases was 14.8 years and for the whole cohort 21.1 years.

Smoking

At baseline, 19% of women and 38% of men were current smokers. Men had smoked longer, smoked more daily, and their total exposure (as PYs) was greater than in women (Table 1). Because only 3 occasional smokers had SAH, calculation of HRs for this group was omitted. Current smokers had an HR of 2.77 (95% CI, 2.22–3.46) in comparison with never-smokers. In analysis by sex, HR was 2.20 (95% CI, 1.56–3.10) for male smokers and 3.43 (95% CI, 2.58–4.55) for female smokers. This translates to a population attributable risk estimate of 31% in both men and women. Recent quitters were at higher risk (HR, 1.93 [95% CI, 0.98–3.79]) for SAH than were former smokers (HR, 1.34 (95% CI, 0.98–1.82]). Light smokers (1–10 CPD) were at elevated risk, and this risk increased gradually, reaching an HR of 3.91 (95% CI, 1.97–7.75) among very heavy smokers with >30 CPD (Table 2). A linear dose-dependent relationship also existed between CPD and risk for SAH in all models (Table 2). The association of smoking status with SAH risk was stronger in women in all groups (LRT *P*=0.01), indicating multiplicative interaction between sex and CPD (Table 2). In the CPD group, 21 to 30 women had an HR of 8.35 (95% CI, 3.86–18.06) compared with an HR of 2.76 (95% CI, 1.68–4.52) in men (Table 2). The cumulative incidence by smoking status and CPD category with a competing risk model in Figure 1 shows the higher lifetime risk in women than in men.

Pack-Years

When compared with never-smokers, current smokers with <5 PYs had an elevated risk, with an HR of 2.13 (95% CI, 1.44–3.16); this risk gradually increased, reaching an HR of 5.62 (95% CI, 2.88–10.97) among those with >50 PYs. PYs had a linear dose-dependent relationship with SAH risk and a stronger association with the risk in women than in men (LRT *P*=0.08; Table 3). When we compared PY categories of current smokers with nonsmokers (by combining both quitter groups with never-smokers), we found even stronger evidence supporting the sex difference (LRT *P*=0.02).

Interactions

Because our analysis revealed multiplicative interactions between CPD and sex, and between PYs and sex, we included these interaction terms in a fully adjusted models. In these models, female sex was no longer an independent risk factor for SAH (CPD-model: HR, 1.18 [95% CI, 0.86–1.62] and PY-model: HR, 1.05 [95% CI, 0.82–1.34]). Moreover, an adjusted model (with all categorical variables) including only never-smokers (effects of smoking excluded) showed that female sex was not an independent risk factor (HR, 1.19 [95% CI, 0.85–1.67]). In addition, we found some evidence of an additive interaction between sex and smoking; in the 11 to 20 and 21 to 30 CPD categories, the relative excess risk because of interactions were 2.11 and 6.90 (Figure 2). To conduct analyses similar to those in

Table 1. Baseline Characteristics of SAH Risk Factors Among Nonsmokers and Current Smokers for the Entire Cohort and SAH Cases, for All Individuals and by Sex

	Cohort	Men	Women	SAH	SAH Men	SAH Women
Nonsmokers						
Participants	46 823	19 107	27 716	278	100	178
Age, y	46.3 (12.2)	46.5 (12.5)	46.1 (12.1)	47.6 (10.8)	45.2 (10.6)	48.3 (10.7)
Alcohol, g/wk	41.5 (75.8)	66.7 (99.0)	22.4 (42.6)	43.9 (92.9)	73.1 (123.2)	21.1 (49.6)
BMI, kg/m^2	26.6 (4.5)	26.8 (3.8)	26.4 (4.9)	26.7 (4.3)	26.5 (3.3)	26.7 (4.7)
Cholesterol, mmol/L	6.0 (1.3)	5.9 (1.2)	6.0 (1.3)	6.4 (1.5)	6.3 (1.5)	6.4 (1.5)
SBP, mm Hg	141.5 (21.8)	143.1 (19.6)	140.4 (23.1)	150.9 (24.9)	148.1 (20.3)	152.4 (27.0)
Smokers						
Participants	18 277	11 958	6319	213	121	92
Age, y	42.3 (11.3)	42.9 (11.4)	41.0 (11.1)	42.6 (10.8)	43.7 (9.9)	41.1 (11.8)
Alcohol, g/wk	87.4 (133.4)	113.6 (157.0)	48.7 (71.4)	103.2 (139.5)	127.4 (153.8)	73.9 (115.2)
CPD	15.5 (9.0)	17.8 (9.1)	11.3 (7.2)	16.6 (8.7)	19.4 (8.6)	12.7 (7.0)
PYs	17.2 (15.0)	20.4 (15.8)	10.8 (10.8)	18.6 (15.5)	23.7 (16.9)	11.5 (9.7)
BMI, kg/m^2	25.7 (4.2)	25.9 (3.8)	25.2 (4.7)	25.2 (3.6)	25.6 (3.3)	24.7 (3.9)
Cholesterol, mmol/L	6.0 (1.3)	6.2 (1.3)	5.7 (1.2)	6.4 (1.4)	6.6 (1.2)	6.1 (1.5)
SBP, mm Hg	139.1 (20.1)	142.8 (19.3)	132.3 (19.9)	143.0 (22.3)	146.5 (21.4)	138.4 (22.7)

Values are given as Mean (SD). BMI indicates body mass index; CPD, cigarettes per day; PY, pack-year; SAH, subarachnoid hemorrhage; and SBP, systolic blood pressure.

previous prospective studies,[1–3] which found female sex to be an independent risk factor for SAH, we combined all CPD groups into a current smokers group and compared this group to never-smokers. In this fully adjusted model, we found only weak evidence of multiplicative interaction (P=0.16) and small additive interaction (relative excess risk because of interaction=0.94), as expected. Moreover, female sex emerged again as an independent risk factor with an HR of 1.44 (95% CI, 1.18–1.75), and multiplicative interaction was no longer evident. Similarly, when we divided the categorical systolic blood pressure variable into 2 groups: normotensives and hypertensives, the adjusted model found no interactions between sex and smoking, and female sex emerged again as a risk factor, with an HR of 1.33 (95% CI, 1.07–1.65). We found no other strong multiplicative or additive effect modifications or interactions between any risk factors mentioned in this study.

Smoking rates by sex may differ between older and more recent cohorts, which may in part explain the effect modification. We thus performed an analysis of only the more recent cohorts between 1982 and 2007, but the results remained the same. Moreover, the results remained the same in all age groups with a reasonable number of participants.

Table 2. Risk for SAH by Smoking Status and CPD Category Among Current Smokers Relative to Never-Smokers for All Cases, and Separately by Sex

	Overall, HR (95% CI)	No. of SAHs	Men, HR (95% CI)	No. of SAHs	Women, HR (95% CI)	No. of SAHs
Never-smokers (reference category)	1	…	1	…	1	…
Former smokers (quit >6 mo earlier)	1.34 (0.98–1.82)	60	1.26 (0.84–1.88)	47	1.14 (0.64–2.04)	13
Recent quitters (<6 mo earlier)	1.93 (0.98–3.79)	10	1.47 (0.59–3.67)	6	2.57 (0.94–6.97)	4
1–10 CPD	2.54 (1.90–3.40)	63	1.93 (1.17–3.18)	22	2.95 (2.07–4.22)	41
11–20 CPD	2.82 (2.14–3.70)	96	2.13 (1.46–3.11)	61	3.89 (2.63–5.74)	35
21–30 CPD	3.79 (2.51–5.71)	30	2.76 (1.68–4.52)	23	8.35 (3.86–18.10)	7
≥31 CPD	3.91 (1.97–7.75)	9	3.64 (1.79–7.40)	9	…	0
Linearity departure P	0.62	…	0.51	…	0.30	…
Increase per CPD	1.04 (1.03–1.05)	…	1.03 (1.02–1.04)	…	1.07 (1.05–1.08)	…

Model is adjusted for age, sex, SBP, BMI, cholesterol, study year, and area. Values are given as HRs and 95% CI, likelihood ratio test P=0.01 for difference between sexes. BMI indicates body mass index; CPD, cigarettes per day; CI, confidence interval; HR, hazard ratio; SAH, subarachnoid hemorrhage; and SBP, systolic blood pressure.

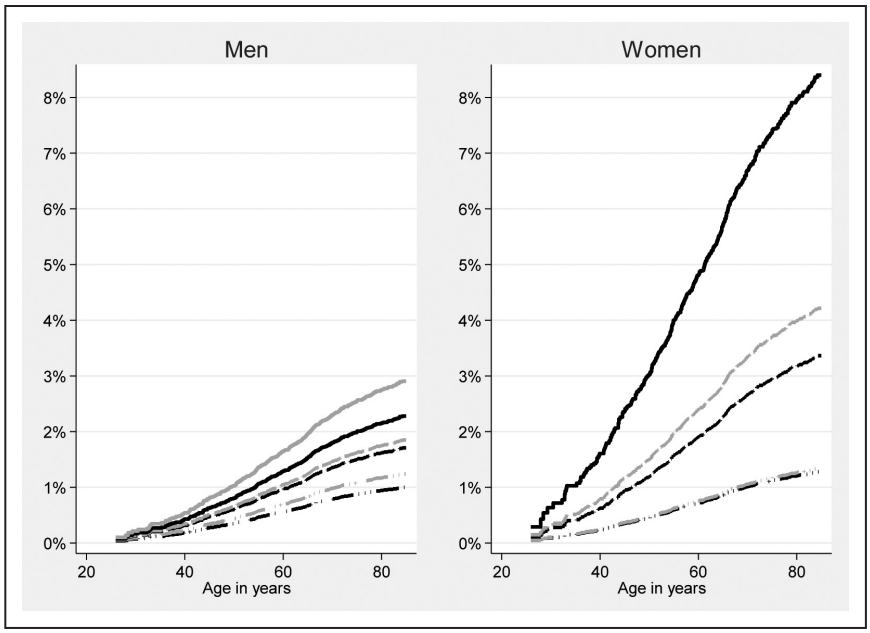

Figure 1. Incidence rates of subarachnoid hemorrhage (SAH) shown by a competing risks model; the y axis describes competing risk rate, and the x axis, age in years. Competing risk rate described by sex and by smoking status; never-smokers (dash-dot black), former smokers (dash-dot gray), 1–10 CPD (dash black), 11–20 CPD (dash gray), 21–30 CPD (solid black), and 30< CPD (solid gray). No SAH cases was observed in women smoking >30 CPD. The model is adjusted for age, body mass index, CPD, cholesterol, systolic blood pressure, sex, study year, and study area.

Sudden Deaths From SAH

An adjusted model including only sudden deaths from SAH showed an increased risk in each CPD category when compared with those for hospitalized SAH patients (Table I in the online-only Data Supplement). This model suggested that all CPD categories elevated the risk of sudden death from SAH more in women than in men (Table II in the online-only Data Supplement).

Discussion

Our results suggest that female sex may not be an independent risk factor for SAH, challenging the current understanding of SAH epidemiology. We found that multiplicative and additive effect modification[19] between sex and CPD may explain why previous prospective studies[2,3,20,21] find female sex to be an independent risk factor for SAH. In other words, if cumulative doses of smoking are not taken into account by sex, categorical analyses may suggest that female sex is a strong risk factor for SAH. We found no other strong multiplicative or additive effect modifications or interactions between any risk factor mentioned in this study. Furthermore, our results confirm retrospective case–control study findings[4,6,7] that suggest that smoking is a dose-dependent risk factor for SAH. Even though smoking seems to affect the risk particularly in women, it is important to recognize that the dose-dependent association exists in both sexes and in former and current smokers. Even light smoking (1–10 CPD) elevated the risk for SAH, and this risk increased rapidly after only 0.05 to 5 PYs in both men and women. The risk was lower among former smokers in both sexes, suggesting that smoking cessation reduces risk. Because of difference in smoking prevalence by sex, however, population attributable risk estimate was the same for both sexes. The results were same in all age groups with reasonable number of participants.

Table 3. Risk for SAH by PY Exposure Among Current Smokers Relative to Never-Smokers for All Cases, and Separately by Sex

PY category	Overall, HRs and 95% CI	No. of SAHs	Men, HRs and 95% CI	No. of SAHs	Women, HRs and 95% CI	No. of SAHs
Never-smokers (reference category)	1	214	1	47	1	161
0.05–5	2.11 (1.42–3.12)	31	1.88 (0.97–3.66)	11	2.16 (1.32–3.53)	20
5–10	2.54 (1.71–3.76)	32	1.59 (0.84–3.03)	12	3.40 (2.09–5.54)	20
10–20	2.99 (2.17–4.13)	55	2.01 (1.27–3.18)	30	4.37 (2.81–6.78)	25
20–30	2.94 (1.95–4.43)	33	1.97 (1.17–3.32)	23	4.99 (2.59–9.60)	10
30–40	3.64 (2.27–5.84)	22	2.60 (1.50–4.50)	18	5.12 (1.86–14.10)	4
40–50	4.67 (2.47–8.81)	11	3.30 (1.60–6.79)	9	7.39 (1.78–30.70)	2
>50	5.62 (2.88–11.00)	10	4.75 (2.36–9.56)	10	…	0
Linearity departure *P*	0.10	…	0.80	…	0.07	…
Increase per PY	1.02 (1.01–1.03)	…	1.02 (1.01–1.03)	…	1.03 (1.02–1.05)	…

The HR for never-smokers is the reference category (HR=1). Model is adjusted for age, sex, SBP, BMI, cholesterol, study year, and area. BMI indicates body mass index; CI, confidence interval; HR, hazard ratio; PY, pack-year; SAH, subarachnoid hemorrhage; and SBP, systolic blood pressure.

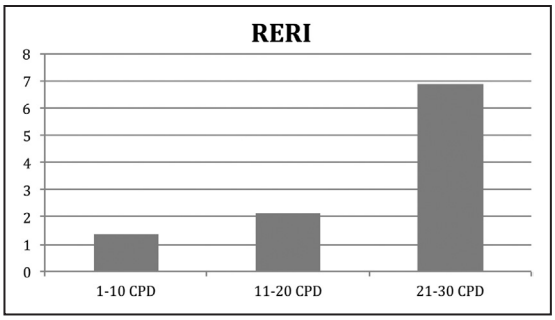

Figure 2. Increase in relative excess risk because of interaction (RERI) by cigarettes per day (CPD) group in women when compared with men in the same CPD group. Increase in RERI shown on the y axis by CPD group in women when compared with men (*P* values 0.06, 0.02, and 0.08). The model is adjusted for age, body mass index, cholesterol, CPD, systolic blood pressure, sex, study year, and area. Corresponding attributable proportion values are 0.39 (*P*=0.02), 0.47 (*P*<0.0001), and 0.69 (*P*<0.0001) and synergy index values are 2.18 (*P*=0.10), 2.58 (*P*=0.01), and 4.36 (0.006).

Given that retrospective[6,22–29] and many prospective[21,30–34] risk factor studies do not include in their analyses sudden deaths from SAH, we also looked into whether such a selection bias could confound the results of risk factor studies. According to our data, smokers have an increased risk of sudden death from SAH, and this risk may be particularly high in female smokers. Because ≈20% of SAH patients die before hospitalization,[9] and these patients may have the worst risk factor profiles, risk factor studies excluding sudden deaths may be somewhat unreliable. Finally, we found no interactions between other SAH risk factors, suggesting that, in risk factor studies, these are independent and important to take into account.

Our observation of decreasing risk for SAH among former smokers is in line with findings of retrospective studies,[4,6] which suggest that risk decreases rapidly among those who have quit recently (within 1 year) and continues to decrease, reaching the risk level of never-smokers within 5 years. The same studies[4,6] have reported that even light smoking leads to an increased risk for SAH. Our results are in accordance with this. Moreover, our findings agree with other cardiovascular disease study findings, suggesting that smoking has a dose-dependent association with risk for acute myocardial infarction[35] and stroke[36] and that risk decreases considerably after smoking cessation.[35,37] Our findings are also in line with findings on myocardial infarction showing an effect modification between smoking and sex.[38,39]

Biological mechanisms for the deleterious effects of smoking on women are unknown, but it is possible that smoking reduces estrogen levels, which further leads to collagen depletion, inflammation, and dysfunction of mural cells in vessel walls.[40] This cascade is the main event in a tendency for vessel walls to degrade.[41,42] Early menopause with an early additional decrease in estrogen levels is more common among smokers,[43,44] and this may further associate in middle-aged female smokers with the formation and rupture of intracranial aneurysms. In line with this reasoning, large prospective studies have reported that the risk for SAH in women surpasses the risk in men after 55 years of age.[2,21]

The strengths of our study include, to our knowledge, the following: the longest follow-up—40 years—among cardiovascular risk factor studies,[8] the highest number of first-ever SAHs among prospective SAH risk factor studies, a prospective set-up reducing risk for information bias and reverse causality, a population-based cohort including sudden deaths from SAH, detailed data on smoking that allow reliable subgroup analyses, and accurate SAH diagnosis.[45] These factors enabled us to calculate the additive interactions preferred in describing biological interactions,[17,46] and thereafter, our results indicated that smoking is more hazardous to women.

However, our study also has limitations. First, because of the study design, we do not know how the participants' smoking patterns evolved during the period after the baseline survey. Although smoking habits are quite stable, during a long follow-up, about half of all smokers will quit, as based on a birth-cohort analysis.[47] This, however, only should weaken the associations between SAH and CPD and between SAH and PYs. The same applies to associations between sex and CPD and between sex and PYs. Second, we could not include alcohol consumption in our final adjusted model because of the small number of never-smokers with high alcohol consumption, as we have reported earlier.[2] Nevertheless, the associations of CPD and PYs with SAH remained essentially the same whether or not alcohol consumption was included in the adjusted model. Moreover, because socioeconomic status relates to smoking habits, alcohol consumption, and other cardiovascular disease risk factors,[48,49] as well as SAHs,[50] we also included in our analysis socioeconomic status as years of education. This adjustment, however, did not change the associations or effect modifications significantly, so we excluded it from the final model. Third, we could not take into account medication for hypertension and hypercholesterolemia. This could theoretically affect interactions between other risk factors but would be unlikely to change the effect modification observed between sex and smoking. Finally, the external validity of Finnish studies is sometimes questioned, as the incidence of SAH is believed to be exceptionally high in Finland.[51–54] For example, the latest pooled risk analysis, the PHASES risk prediction model,[52] does not predict 5-year risk of aneurysm rupture reliably, as discussed recently.[55] After pooling previous studies, the authors concluded that incidence of SAH is higher in Finland than in other western countries.[52] Thus, these authors excluded Finnish cohorts from the final risk prediction model, which was based on only 2 studies, namely, the highly selected International Study of Unruptured Intracranial Aneurysms (ISUIA)[56] with 59 SAH patients and a Dutch study[57] with only 1 patient with SAH. However, a recent opinion article in *Nature Reviews Neurology*[55] suggested that the incidence of SAH in Finland is similar to that in other countries, which, as in Finland, also include sudden deaths in their incidence estimates. In fact, the first study on the nationwide (not only population-based) incidence of SAH in Finland, which identified 6885 incident SAHs during 79 083 579 cumulative person-years, confirmed recently that the Finnish incidence rate of SAH is not exceptional, when compared with incidences that include sudden SAH deaths outside hospitals.[58] This indicates that our results are perhaps generalizable.

Conclusions

Our results suggest that smoking is an important dose-dependent risk factor for SAH and has a stronger association with this risk in women. This effect modification seems to explain why previous studies report female sex as an independent risk factor for SAH. The results emphasize the importance of worldwide smoking cessation agendas and active treatment of nicotine dependence.

Acknowledgments

We thank Carolyn Brimley Norris for language revision.

Sources of Funding

This work was supported by the Department of Public Health in University of Helsinki.

Disclosures

J. Kaprio has consulted for Pfizer on nicotine dependence from 2012 to 2014. The other authors report no conflicts.

References

1. Knekt P, Reunanen A, Aho K, Heliövaara M, Rissanen A, Aromaa A, et al. Risk factors for subarachnoid hemorrhage in a longitudinal population study. *J Clin Epidemiol*. 1991;44:933–939.
2. Korja M, Silventoinen K, Laatikainen T, Jousilahti P, Salomaa V, Hernesniemi J, et al. Risk factors and their combined effects on the incidence rate of subarachnoid hemorrhage–a population-based cohort study. *PLoS One*. 2013;8:e73760. doi: 10.1371/journal.pone.0073760.
3. Sandvei MS, Lindekleiv H, Romundstad PR, Müller TB, Vatten LJ, Ingebrigtsen T, et al. Risk factors for aneurysmal subarachnoid hemorrhage - BMI and serum lipids: 11-year follow-up of the HUNT and the Tromsø Study in Norway. *Acta Neurol Scand*. 2012;125:382–388. doi: 10.1111/j.1600-0404.2011.01578.x.
4. Anderson CS, Feigin V, Bennett D, Lin RB, Hankey G, Jamrozik K; Australasian Cooperative Research on Subarachnoid Hemorrhage Study (ACROSS) Group. Active and passive smoking and the risk of subarachnoid hemorrhage: an international population-based case-control study. *Stroke*. 2004;35:633–637. doi: 10.1161/01.STR.0000115751.45473.48.
5. Bonita R. Cigarette smoking, hypertension and the risk of subarachnoid hemorrhage: a population-based case-control study. *Stroke*. 1986;17:831–835.
6. Kim CK, Kim BJ, Ryu WS, Lee SH, Yoon BW. Impact of smoking cessation on the risk of subarachnoid haemorrhage: a nationwide multicentre case control study. *J Neurol Neurosurg Psychiatry*. 2012;83:1100–1103. doi: 10.1136/jnnp-2012-302538.
7. Longstreth WT Jr, Nelson LM, Koepsell TD, van Belle G. Cigarette smoking, alcohol use, and subarachnoid hemorrhage. *Stroke*. 1992;23:1242–1249.
8. Borodulin K, Vartiainen E, Peltonen M, Jousilahti P, Juolevi A, Laatikainen T, et al. Forty-year trends in cardiovascular risk factors in Finland. *Eur J Public Health*. 2015;25:539–546. doi: 10.1093/eurpub/cku174.
9. Korja M, Silventoinen K, Laatikainen T, Jousilahti P, Salomaa V, Kaprio J. Cause-specific mortality of 1-year survivors of subarachnoid hemorrhage. *Neurology*. 2013;80:481–486. doi: 10.1212/WNL.0b013e31827f0fb5.
10. Tolonen H, Salomaa V, Torppa J, Sivenius J, Immonen-Räihä P, Lehtonen A; FINSTROKE register. The validation of the Finnish Hospital Discharge Register and Causes of Death Register data on stroke diagnoses. *Eur J Cardiovasc Prev Rehabil*. 2007;14:380–385. doi: 10.1097/01.hjr.0000239466.26132.f2.
11. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Int J Surg*. 2014;12:1500–1524. doi: 10.1016/j.ijsu.2014.07.014.
12. Baker F, Ainsworth SR, Dye JT, Crammer C, Thun MJ, Hoffmann D, et al. Health risks associated with cigar smoking. *JAMA*. 2000;284:735–740.
13. Iribarren C, Tekawa IS, Sidney S, Friedman GD. Effect of cigar smoking on the risk of cardiovascular disease, chronic obstructive pulmonary disease, and cancer in men. *N Engl J Med*. 1999;340:1773–1780. doi: 10.1056/NEJM199906103402301.
14. Shaper AG, Wannamethee SG, Walker M. Pipe and cigar smoking and major cardiovascular events, cancer incidence and all-cause mortality in middle-aged British men. *Int J Epidemiol*. 2003;32:802–808.
15. Tverdal A, Bjartveit K. Health consequences of pipe versus cigarette smoking. *Tob Control*. 2011;20:123–130. doi: 10.1136/tc.2010.036780.
16. Wannamethee SG, Lowe GD, Shaper AG, Rumley A, Lennon L, Whincup PH. Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. *Eur Heart J*. 2005;26:1765–1773. doi: 10.1093/eurheartj/ehi183.
17. Andersson T, Alfredsson L, Källberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. *Eur J Epidemiol*. 2005;20:575–579.
18. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999:94:496–509.
19. VanderWeele TJ. On the distinction between interaction and effect modification. *Epidemiology*. 2009;20:863–871. doi: 10.1097/EDE.0b013e3181ba333c.
20. Juvela S, Poussa K, Porras M. Factors affecting formation and growth of intracranial aneurysms: a long-term follow-up study. *Stroke*. 2001;32:485–491.
21. Suzuki K, Izumi M, Sakamoto T, Hayashi M. Blood pressure and total cholesterol level are critical risks especially for hemorrhagic stroke in Akita, Japan. *Cerebrovasc Dis*. 2011;31:100–106. doi: 10.1159/000321506.
22. Adamson J, Humphries SE, Ostergaard JR, Voldby B, Richards P, Powell JT. Are cerebral aneurysms atherosclerotic? *Stroke*. 1994;25:963–966.
23. Broderick JP, Viscoli CM, Brott T, Kernan WN, Brass LM, Feldmann E, et al; Hemorrhagic Stroke Project Investigators. Major risk factors for aneurysmal subarachnoid hemorrhage in the young are modifiable. *Stroke*. 2003;34:1375–1381. doi: 10.1161/01.STR.0000074572.91827.F4.
24. Canhão P, Pinto AN, Ferro H, Ferro JM. Smoking and aneurysmal subarachnoid haemorrhage: a case-control study. *J Cardiovasc Risk*. 1994;1:155–158.
25. Inagawa T. Risk factors for the formation and rupture of intracranial saccular aneurysms in Shimane, Japan. *World Neurosurg*. 2010;73:155–164, discussion e23. doi: 10.1016/j.surneu.2009.03.007.
26. Ohkuma H, Tabata H, Suzuki S, Islam MS. Risk factors for aneurysmal subarachnoid hemorrhage in Aomori, Japan. *Stroke*. 2003;34:96–100.
27. Park JK, Kim HJ, Chang SJ, Koh SB, Koh SY. Risk factors for hemorrhagic stroke in Wonju, Korea. *Yonsei Med J*. 1998;39:229–235. doi: 10.3349/ymj.1998.39.3.229.
28. Tokuda Y, Stein GH. Serum lipids as protective factors for subarachnoid hemorrhage. *J Clin Neurosci*. 2005;12:538–541. doi: 10.1016/j.jocn.2004.07.021.
29. Vlak MH, Rinkel GJ, Greebe P, Greving JP, Algra A. Lifetime risks for aneurysmal subarachnoid haemorrhage: multivariable risk stratification. *J Neurol Neurosurg Psychiatry*. 2013;84:619–623. doi: 10.1136/jnnp-2012-303783.
30. Cui R, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, et al; JACC Study Group. Serum total cholesterol levels and risk of mortality from stroke and coronary heart disease in Japanese: the JACC study. *Atherosclerosis*. 2007;194:415–420. doi: 10.1016/j.atherosclerosis.2006.08.022.
31. Gatchev O, Råstam L, Lindberg G, Gullberg B, Eklund GA, Isacsson SO. Subarachnoid hemorrhage, cerebral hemorrhage, and serum cholesterol concentration in men and women. *Ann Epidemiol*. 1993;3:403–409.
32. Neaton JD, Wentworth DN, Cutler J, Stamler J, Kuller L. Risk factors for death from different types of stroke. Multiple Risk Factor Intervention Trial Research Group. *Ann Epidemiol*. 1993;3:493–499.
33. Suh I, Jee SH, Kim HC, Nam CM, Kim IS, Appel LJ. Low serum cholesterol and haemorrhagic stroke in men: Korea Medical Insurance Corporation Study. *Lancet*. 2001;357:922–925. doi: 10.1016/S0140-6736(00)04213-6.
34. Tirschwell DL, Smith NL, Heckbert SR, Lemaitre RN, Longstreth WT Jr, Psaty BM. Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups. *Neurology*. 2004;63:1868–1875.
35. Teo KK, Ounpuu S, Hawken S, Pandey MR, Valentin V, Hunt D, et al; INTERHEART Study Investigators. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet*. 2006;368:647–658. doi: 10.1016/S0140-6736(06)69249-0.

36. Wolf PA, D'Agostino RB, Kannel WB, Bonita R, Belanger AJ. Cigarette smoking as a risk factor for stroke. The Framingham Study. *JAMA*. 1988;259:1025–1029.
37. Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Rosner B, et al. Smoking cessation and decreased risk of stroke in women. *JAMA*. 1993;269:232–236.
38. Björck L, Rosengren A, Wallentin L, Stenestrand U. Smoking in relation to ST-segment elevation acute myocardial infarction: findings from the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions. *Heart*. 2009;95:1006–1011. doi: 10.1136/hrt.2008.153064.
39. Oliveira A, Barros H, Lopes C. Gender heterogeneity in the association between lifestyles and non-fatal acute myocardial infarction. *Public Health Nutr*. 2009;12:1799–1806. doi: 10.1017/S1368980008004588.
40. Jayaraman T, Paget A, Shin YS, Li X, Mayer J, Chaudhry H, et al. TNF-alpha-mediated inflammation in cerebral aneurysms: a potential link to growth and rupture. *Vasc Health Risk Manag*. 2008;4:805–817.
41. Chalouhi N, Ali MS, Starke RM, Jabbour PM, Tjoumakaris SI, Gonzalez LF, et al. Cigarette smoke and inflammation: role in cerebral aneurysm formation and rupture. *Mediators Inflamm*. 2012;2012:271582. doi: 10.1155/2012/271582.
42. Frösen J, Tulamo R, Paetau A, Laaksamo E, Korja M, Laakso A, et al. Saccular intracranial aneurysm: pathology and mechanisms. *Acta Neuropathol*. 2012;123:773–786. doi: 10.1007/s00401-011-0939-3.
43. Gold EB, Bromberger J, Crawford S, Samuels S, Greendale GA, Harlow SD, et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. *Am J Epidemiol*. 2001;153:865–874.
44. Sun L, Tan L, Yang F, Luo Y, Li X, Deng HW, et al. Meta-analysis suggests that smoking is associated with an increased risk of early natural menopause. *Menopause*. 2012;19:126–132. doi: 10.1097/gme.0b013e318224f9ac.
45. Leppälä JM, Virtamo J, Heinonen OP. Validation of stroke diagnosis in the National Hospital Discharge Register and the Register of Causes of Death in Finland. *Eur J Epidemiol*. 1999;15:155–160.
46. VanderWeele TJ, Robins JM. The identification of synergism in the sufficient-component-cause framework. *Epidemiology*. 2007;18:329–339. doi: 10.1097/01.ede.0000260218.66432.88.
47. Jousilahti P, Vartiainen E, Korhonen HJ, Puska P, Tuomilehto J. Is the effect of smoking on the risk for coronary heart disease even stronger than was previously thought? *J Cardiovasc Risk*. 1999;6:293–298.
48. Laaksonen M, Uutela A, Vartiainen E, Jousilahti P, Helakorpi S, Puska P. Development of smoking by birth cohort in the adult population in eastern Finland 1972-97. *Tob Control*. 1999;8:161–168.
49. Luoto R, Pekkanen J, Uutela A, Tuomilehto J. Cardiovascular risks and socioeconomic status: differences between men and women in Finland. *J Epidemiol Community Health*. 1994;48:348–354.
50. Jakovljević D, Sivenius J, Sarti C, Torppa J, Mähönen M, Immonen-Räihä P, et al. Socioeconomic inequalities in the incidence, mortality and prognosis of subarachnoid hemorrhage: the FINMONICA Stroke Register. *Cerebrovasc Dis*. 2001;12:7–13. doi: 47674.
51. de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. *J Neurol Neurosurg Psychiatry*. 2007;78:1365–1372. doi: 10.1136/jnnp.2007.117655.
52. Greving JP, Wermer MJ, Brown RD Jr, Morita A, Juvela S, Yonekura M, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol*. 2014;13:59–66. doi: 10.1016/S1474-4422(13)70263-1.
53. Linn FH, Rinkel GJ, Algra A, van Gijn J. Incidence of subarachnoid hemorrhage: role of region, year, and rate of computed tomography: a meta-analysis. *Stroke*. 1996;27:625–629.
54. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. *Lancet*. 2007;369:306–318. doi: 10.1016/S0140-6736(07)60153-6.
55. Korja M, Kaprio J. Controversies in epidemiology of intracranial aneurysms and SAH. *Nat Rev Neurol*. 2016;12:50–55. doi: 10.1038/nrneurol.2015.228.
56. Wiebers DO, Whisnant JP, Huston J 3rd, Meissner I, Brown RD Jr, Piepgras DG, et al; International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet*. 2003;362:103–110.
57. Wermer MJ, van der Schaaf IC, Velthuis BK, Majoie CB, Albrecht KW, Rinkel GJ. Yield of short-term follow-up CT/MR angiography for small aneurysms detected at screening. *Stroke*. 2006;37:414–418. doi: 10.1161/01.STR.0000199077.06390.35.
58. Korja M, Lehto H, Juvela S, Kaprio J. Incidence of subarachnoid hemorrhage is decreasing together with decreasing smoking rates. *Neurology*. In press.