Tobacco use and risk of acute stroke in 32 countries in the INTERSTROKE study: a case–control study

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Summary

Background Smoking is a major risk factor for the global burden of stroke. We have previously reported a global population attributable risk (PAR) of stroke of 12.4% associated with current smoking. In this study we aimed to explore the association of current tobacco use with different types of tobacco exposure and environmental tobacco smoke (ETS) exposure on the risk of stroke and stroke subtypes, and by regions and country income levels.

Methods The INTERSTROKE study is a case–control study of acute first stroke and was undertaken with 13,462 stroke cases and 13,488 controls recruited between January 11, 2007 and August 8, 2015 in 32 countries worldwide. Association of risk of tobacco use and ETS exposure were analysed with overall stroke, ischemic and

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intracerebral hemorrhage (ICH), and with TOAST etiological stroke subtypes (large vessel, small vessel, cardioembolism, and undetermined).

Findings Current smoking was associated with an increased risk of all stroke (odds ratio [OR] 1.64, 95% CI 1.46–1.84), and had a stronger association with ischemic stroke (OR 1.85, 95% CI 1.61–2.11) than ICH (OR 1.19 95% CI 1.00–1.41). The OR and PAR of stroke among current smokers varied significantly between regions and income levels with high income countries (HIC) having the highest odds (OR 3.02 95% CI 2.24–4.10) and PAR (18.6%, 15.1–22.8%). Among etiological subtypes of ischemic stroke, the strongest association of current smoking was seen for large vessel stroke (OR 2.16, 95% CI 1.63–2.87) and undetermined cause (OR 1.97, 95% CI 1.55–2.50). Both filtered (OR 1.73, 95% CI 1.50–1.99) and non-filtered (OR 2.59, 95% CI 1.79–3.77) cigarettes were associated with stroke risk. ETS exposure increased the risk of stroke in a dose-dependent manner, exposure for more than 10 h per week increased risk for all stroke (OR 1.95, 95% CI 1.69–2.27), ischemic stroke (OR 1.89, 95% CI 1.59–2.24) and ICH (OR 2.00, 95% CI 1.60–2.50).

Interpretation There are significant variations in the magnitude of risk and PAR of stroke according to the types of tobacco used, active and ETS exposure, and countries with different income levels. Specific strategies to discourage tobacco use by any form and to build a smoke free environment should be implemented to ease the global burden of stroke.

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Keywords: Stroke subtypes; Tobacco; Environmental smoking; Risk factor; International

Research in context

Evidence before this study

We searched PubMed with the search terms "stroke", "stroke subtypes", "smoking", "tobacco", "cigarette" "second hand smoking", "environmental tobacco smoking", "ischemic stroke", "intracerebral hemorrhage", "risk factors", "population attributable risk", "global", "international", and "global disease burden" for articles published in English before December 10, 2023. We found epidemiological studies, national surveys, meta-analysis, major subtypes of strokes for all types of tobacco exposure and Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019 and Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. We did not observe an international study of active and passive tobacco exposure for all stroke and major pathological and etiological subtypes of stroke in standardized design and methods and in all major regions globally.

Added value of this study

This study extended our previous finding of tobacco exposure heightened the risk for ischemic stroke and intracerebral hemorrhage globally, by categorizing stroke into ischemic and hemorrhagic pathological subtypes and further to classify ischemic stroke into large vessel, small vessel, cardioembolism and undetermined stoke. With the sample size to 26,950 participants from 32 countries, we reported the association of stroke subtypes with active and environmental tobacco smoking in men and women, young and old, with regions of world and by level of income in countries. The stroke risk and population attributable risk among current smokers in different regions and income levels of countries vary significantly. Environmental smoke is harmful and dose dependent, especially for intracerebral hemorrhage. There is no residual risk for stroke detected after smoke cessation over 12 months.

Implications of all the available evidence

Available evidence suggests that different strategy and effort to stop smoking should be in place to combat globally and regional burden of stroke, and tobacco control may have different impact according to regions and countries. Environmental smoking increases stroke risk in dose dependent manner, this should encourage all government to build smoke free environment worldwide to combat stroke.

Introduction

Tobacco use is the second leading cause of early death and disability worldwide and an avoidable cause of cardiovascular diseases.[1] It is estimated that 29.6% of male and 5.3% of female are daily smokers worldwide.[2] In 2016, there were 5.5 million deaths and 116.4 million disability adjusted life years lost (DALYs) due to stroke, accounting for 11.5% of global deaths.[1] Despite a recent decline in the global prevalence of smoking overall, some countries are experiencing an increase among both male and female.[3]

Smoking is an established risk factor for stroke.[4,5] Smoking is also a major risk factor for the global burden of stroke, ranking 5th overall amongst all stroke risk factors for males and females combined.[5] However, the ranking of smoking risk varies between 4th and 10th among different regions and countries.[1] In the INTERSTROKE study, we have previously reported a global population attributable risk (PAR) of stroke of 12.4% associated with current smoking, with a higher risk for ischemic stroke than intracerebral hemorrhage (ICH).[6] Environmental tobacco smoke (ETS) exposure, also refer as secondhand tobacco smoke, is a debated risk factor for stroke, although prospective and cross-sectional studies have shown that overall exposure and high exposure to ETS increased the risk for stroke.[7–10] Some reports suggested that the risk of stroke due to tobacco use begins to decrease soon after quitting.[11]

INTERSTROKE is the largest international study to report on the association of tobacco exposure with stroke incidence. In the current analyses, we extended our report to the association of stroke with different types of tobacco exposure, including non-smoked tobacco (e.g., chewed and pipes) and ETS (weekly hours of exposure) in different regions of the world and by country income levels, and within different pathological subtypes of stroke and etiological subtypes of ischemic stroke by TOAST classification,[12] and may provide key insights into new opportunities for more effective smoking cessation interventions nationally and internationally.

Methods

Procedures

INTERSTROKE is a large, international case–control study. Participants were recruited between January 11, 2007 and August 8, 2015, from 142 centers in 32 countries worldwide.[6] According to in geographical and ethnical characteristics, seven regions include: Western Europe/North America (Australia, Canada, Denmark, Germany, Sweden, UK, and Ireland), Eastern/central Europe/Middle East (Croatia, Poland, Russia, Turkey, Iran, Saudi Arabia, Kuwait, and United Arab Emirates), Africa (Mozambique, Nigeria, Sudan, and Uganda), South Asia (India and Pakistan), China, South East Asia (Philippines, Thailand, and Malaysia), and South America (Argentina, Brazil, Chile, Colombia, Ecuador, and Peru). We also divided participants into four groups according to average income of countries, including high income countries (HIC), upper middle income countries-1 (UMIC-1), upper middle income countries-2 (UMIC-2), low middle income countries and low income countries (LMIC/LIC).

Cases were patients with acute first ever stroke (within 5 days of symptoms onset and 72 h of hospital admission), whose neuroimaging by CT or MRI was completed within 1 week of presentation. Stroke was defined with the WHO clinical criteria. For patients unable to communicate, proxy respondents were used. Detailed eligible proxy criteria were described elsewhere.[6] In this article, we included cases with acute ischemic stroke and ICH, and etiological subtypes of ischemic stroke by the TOAST classification, which includes cardioembolism, large vessel, small vessel, and other/undetermined stroke subtypes.[12] Controls were either community-based or hospital based and detailed inclusion criteria were described previously.[6] The study was approved by the ethics committees in all participating centers. All participants, and/or their proxy, provided written informed consent before taking part in the study.

Trained staff administered a structured questionnaire and did physical examinations for cases and controls in the same procedure. Participants were asked whether they regularly used any of the following tobacco products: cigarettes, smoked non-cigarette tobacco (beedies, pipes or cigars), smokeless non-cigarette tobacco (chewing tobacco, paan, snuff, sheesha or water pipe), and other tobacco.[13] For cigarettes (and beedies), the number smoked per day, the type of cigarettes (filter, nonfilter, or both), and the brands of cigarettes commonly smoked were recorded. Categories of tobacco use were defined as follows: current smokers were individuals who consumed any tobacco (including beedies, pipes, and any other forms) in the previous 12 months, and included those who had quit within the past year. Former smokers had quit more than a year previously. Never smokers were those who responded that they had never used tobacco products regularly. Regular users were individuals who used at least one tobacco product daily. Exposure to ETS was recorded by asking about the smoking habits of family members, friends, or co-workers, whether these individuals smoked regularly in the participants' presence, the number of times per day that ETS exposure exceeded 5 consecutive minutes, the average number of hours per week of exposure over the past 12 months, and smoking habits of the spouse. Information of participants on physiological measurement (height, weight, blood pressure, etc.), laboratory measures (cholesterols, apolipoproteins B and A1, etc.) and questionnaires (education, income, psychosocial factors, personal and family history of cardiovascular disease, etc.) were recorded.[6] Participants were divided into young and older age

groups, which defined that young age: female ≤65 years, male ≤55 years, and older age: female >65 years, male >55 years.

Statistical methods

Univariate associations were used for frequency tables. For comparisons of prevalence of tobacco use across regions and country income levels, the potential differences in age structure of the populations were accounted for by direct standardization of the frequencies to the overall INTERSTROKE age distribution with a four-level age strata (≤49, 50–59, 60–69, ≥70 years). Continuous variables were presented with standard deviations for mean, and interquartile range for median. Sex-specific quintile values in controls were used to categorize continuous variables. In multivariable unconditional logistic regression models, adjustment for age, sex, geographical region, apolipoprotein B/apolipoprotein A1 ratio, obesity, history of hypertension, history of diabetes, diet, activity, and alcohol use was used to control for confounding factors. All statistical tests of hypotheses are two-sided.

PAR and their 95% CI were calculated by a method based on unconditional logistic regression and with the Interactive Risk Attributable Program by the US National Cancer Institute, 2002.[14] The PAR presented are adjusted for confounders in a similar fashion to the corresponding logistic regression models for odds ratio (OR) estimates and stratified by subgroups of interest. The PAR calculation uses the prevalence rates of risk factors in the control group and the estimate of relative risk. In the analysis of PAR in subgroups (e.g., male and females or by regions and country income levels) the actual prevalence and relative risks observed in the specific subgroups were used and are presented here.

Statistical analyses and graphics were produced with SAS (version 9.2), R statistical program (version 3.2.4), and TIBCO Spotfire S-Plus (version 8.2) for Windows.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The baseline characteristics of controls and cases according to pathological subtypes of stroke and etiological subtypes of ischemic stroke are presented in Table 1. These characteristics include the various types of tobacco used, age, body mass index (BMI), waist to hip ratio (WHR), total cholesterol, LDL, HDL, ApoB, ApoA1, and ApoB/ApoA1 ratio. For the entire cohort (cases and controls), data were missing in 299 (1.1%) participants for psychosocial factors, five (0.02%) participants for self-reported history of diabetes mellitus, 719 (2.67%) participants for waist-to- hip ratio, and 34 (0.13%) participants for alcohol. Data on lipids were available in 23,907 (88.8%) of participants and data for HbA 1c were available in 21,894 (81.3%) of participants.

The prevalence of smoking was listed in Table 2 for control subjects categorized by region, sex, age, the number of tobacco products used from 1 to 9, 10 to 19, and over 20 per day. Smoking habits varied markedly by regions. Among female, the prevalence of current smoking for young female in eastern Europe/North America and Eastern/central Europe/Middle East were 16.0% and 16.4% respectively. In other regions, the prevalence was less than 10% for both young and older females. Among male, the highest rate of current smoking among young participants was in China (56.7%). Overall, more than one third of young male were current smokers in South East Asia and Eastern/central Europe/Middle East (45.9% and 34.8%, respectively) (Table 2).

Table 3 shows that, compared with never smokers, current smoking was associated with all stroke (OR 1.64; 95% CI 1.46–1.84), ischemic stroke (1.85; 1.61–2.11) and ICH (1.19; 1.00–1.41). Within etiological subtypes of ischemic stroke, current smokers had OR of 1.56 (95% CI 0.99–2.46) for cardioembolic stroke, 2.16 (1.63–287) for large vessel stroke, 1.66 (1.37–2.01) for small vessel stroke, and 1.97 (1.55–2.50) for undetermined/other stroke.

All forms of tobacco, used alone or in combination, increased risk for all stroke. Among different types of tobacco, filtered cigarettes had OR of 1.73 (1.50–1.99), non-filtered cigarettes 2.59 (1.79–3.77), combined use of filtered and non-filtered cigarettes 2.81 (1.87–4.22), and beedies alone 2.39 (1.58–3.61). For ischemic stroke, risk varied with different tobacco use, ORs for non-filter cigarettes was 3.37 (2.16–5.24), for both filter/non-filter 2.87 (1.84–4.48), for beedies alone 3.39 (2.06–5.57). The use of pipes, or chewing tobacco alone did not reach statistical significance. Among etiological subtypes of ischemic stroke, similar risk profiles were recorded. For ICH stroke, ORs were statistically significant for non-filtered cigarettes 2.04 (1.15–3.63), both filter/non-filter cigarettes 2.23 (1.16–4.30), and chew alone 1.53 (1.03–2.27) (Table 3).

Increasing number of cigarettes smoked per day was associated with a graded increase in odds of ischemic stroke in both male and female (Fig. 1A and Supplementary Table 1), and in all etiological subtypes of ischemic stroke (Fig. 1B), particularly in large vessel stroke (Supplementary Table 1). And former smoking was not associated with increased risk for acute stroke (Supplementary Table 1). The risk of all stroke for current smoking was higher in young than in older participants among heavy smokers (≥20 cigarettes per day), that ORs were 2.49 (1.78–3.47) for people under 50 years of age and 1.74 (1.21–2.50) for those older than 70 years (Supplementary Table 2 and Supplementary Fig. 1). Association of current smoking with ischemic stroke

	Controls	Ischemic stroke					ICH
		Cardioembolism	Large vessel	Small vessel	Other/Undetermined TOAST	Total	
Total, N	13,488	1198	2119	4007	3078	10,402	3060
Male, N (%)	8035 (59.6)	621 (51.8)	1279 (60.4)	2447 (61.1)	1837 (59.7)	6184 (59.5)	1837 (60.0)
Young Age[a], N (%)	5940 (44.0)	355 (29.6)	785 (37.0)	1619 (40.4)	1299 (42.2)	4058 (39.0)	1576 (51.5)
Former Smoker, N (%)	2150 (15.9)	329 (27.5)	317 (15.0)	475 (11.9)	467 (15.2)	1588 (15.3)	287 (9.4)
Current Smoker, N (%)	3017 (22.4)	217 (18.1)	720 (34.0)	1371 (34.2)	873 (28.4)	3181 (30.6)	897 (29.3)
Never Smoker, N (%)	8321 (61.7)	652 (54.4)	1082 (51.1)	2161 (53.9)	1738 (56.5)	5633 (54.2)	1876 (61.3)
Tobacco Products Used							
Cigarettes, N (%)	4059 (30.1)	507 (42.3)	859 (40.5)	1482 (37.0)	1043 (33.9)	3891 (37.4)	850 (27.8)
Beedies, N (%)	498 (3.7)	10 (0.8)	114 (5.4)	232 (5.8)	207 (6.7)	563 (5.4)	160 (5.2)
Pipes/Cigars, N (%)	265 (2.0)	59 (4.9)	33 (1.6)	67 (1.7)	65 (2.1)	224 (2.2)	18 (0.6)
Chewing Tobacco, N (%)	657 (4.9)	13 (1.1)	99 (4.7)	216 (5.4)	109 (3.5)	437 (4.2)	246 (8.0)
Paan, N (%)	197 (1.5)	6 (0.5)	23 (1.1)	32 (0.8)	33 (1.1)	94 (0.9)	36 (1.2)
Snuff, N (%)	101 (0.7)	4 (0.3)	9 (0.4)	9 (0.2)	18 (0.6)	40 (0.4)	13 (0.4)
Sheesha/water pipe, N (%)	25 (0.2)	3 (0.3)		13 (0.3)	21 (0.7)	37 (0.4)	6 (0.2)
Other Tobacco product, N (%)	30 (0.2)	5 (0.4)	9 (0.4)	9 (0.2)	23 (0.7)	46 (0.4)	6 (0.2)
ETS exposure, N (%)	5687 (42.2)	454 (37.9)	959 (45.6)	2120 (52.9)	1429 (38.9)	4280 (46.4)	1511 (49.4)
Cigarettes/Beedies per Day, (IQR)	12.0 (7.0–20.0)	10.0 (7.0–20.0)	12.0 (6.5–20.0)	15.0 (10.0–20.0)	10.0 (6.0–20.0)	15.0 (8.0–20.0)	10.0 (6.0–20.0)
Age (yrs), (SD)	61.3 (13.3)	66.7 (15.0)	63.4 (13.1)	62.7 (12.9)	61.7 (14.0)	63.0 (13.6)	59.3 (13.1)
BMI (kg/m2), (IQR)	25.1 (22.5–28.1)	26.2 (23.6–29.7)	25.5 (22.7–28.7)	25.1 (22.7–28.0)	25.4 (23.0–28.6)	25.4 (22.8–28.5)	24.5 (22.0–27.5)
Waist-to-Hip, (IQR)	0.9 (0.9–1.0)	0.9 (0.9–1.0)	0.9 (0.9–1.0)	0.9 (0.9–1.0)	0.9 (0.9–1.0)	0.9 (0.9–1.0)	0.9 (0.9–1.0)
Cholesterol (mmol/L), (IQR)	4.8 (4.0–5.5)	4.4 (3.7–5.2)	4.6 (3.8–5.5)	4.7 (3.9–5.5)	4.7 (3.9–5.5)	4.6 (3.9–5.5)	4.6 (3.9–5.3)
LDL (mmol/L), (IQR)	2.8 (2.2–3.5)	2.7 (2.0–3.3)	2.9 (2.2–3.5)	2.8 (2.2–3.5)	2.9 (2.2–3.6)	2.8 (2.2–3.5)	2.8 (2.2–3.5)
HDL (mmol/L), (IQR)	1.1 (0.9–1.4)	1.1 (0.9–1.3)	1.0 (0.8–1.2)	1.0 (0.8–1.3)	1.1 (0.9–1.3)	1.0 (0.9–1.3)	1.2 (0.9–1.4)
non-HDL (mmol/L), (IQR)	3.6 (2.9–4.3)	3.3 (2.6–4.0)	3.5 (2.8–4.4)	3.6 (2.8–4.3)	3.6 (2.8–4.4)	3.5 (2.8–4.3)	3.3 (2.7–4.1)
ApoA 1 (g/L), (IQR)	1.4 (1.2–1.6)	1.2 (1.0–1.4)	1.2 (1.0–1.4)	1.3 (1.1–1.5)	1.2 (1.1–1.5)	1.2 (1.1–1.5)	1.3 (1.1–1.5)
ApoB (g/L), (IQR)	1.0 (0.8–1.1)	1.0 (0.8–1.2)	1.0 (0.8–1.2)	1.0 (0.8–1.2)	1.0 (0.8–1.2)	1.0 (0.8–1.2)	0.9 (0.7–1.1)
ApoB/ApoA1, (IQR)	0.7 (0.6–0.9)	0.8 (0.6–1.0)	0.8 (0.7–1.0)	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.7 (0.6–0.9)

Continuous variables are reported by mean (SD) or median (IQR). Note: % does not include missing values for the variable presented. ETS = Environmental tobacco smoke. [a]Young age: female ≤65 years, male ≤55 years.

Table 1: **Prevalence of risk factors in stroke cases and controls.**

TOAST subtypes in different age groups is shown in Supplementary Fig. 1. Compared with never smokers, there was no significant association of former smoking with stroke (OR 0.97, 95% CI 0.86–1.09).

The magnitude of odds ratio and PAR of stroke associated with current smoking varied by regions (P-interaction = 0.0005) (Fig. 2A–C and Supplementary Table 3). The Western Europe/North America region had the highest relative risk of all stroke (OR 3.22 (2.31–4.50) and ischemic stroke (OR 3.51; 2.48–4.97) among current smokers, and the largest PAR of for all stroke (18.6%) and ischemic stroke (19.8%), especially for young smokers with respective PARs of 36.2% for all stroke and 38.2% for ischemic stroke. Across income levels, we observed differences (P-interaction <0.0001) with a decrease in odds ratio from 3.03 in high income countries to 1.32 in LMIC/LICs (Supplementary Table 3 and Fig. 2A). Across all income levels, PARs were higher in young smokers (Supplementary Table 3 and Fig. 2B) than that of older smokers. A clear dose–response relation existed between number of cigarettes smoked per day and risk of stroke in income regions, especially in HIC (OR 5.52; 3.51–8.67) (Fig. 2C). There were significant interactions of age, region, and income levels with ORs and PARs for all stroke and ischemic stroke.

Overall, 42.2% of controls reported exposure to ETS (Table 1). Among never smokers, longer exposure hours to ETS increased the odds of ischemic stroke, ICH and TOAST subtypes, and over 10 h exposure weekly increased the risk of all stroke (OR 1.95; 1.69–2.27), ischemic stroke (OR 1.89; 1.59–2.24) and ICH (OR 2.00; 1.60–2.50) (Supplementary Table 4). The association of current smoking and ETS was consistent in the presence or absence of the other risk factors (Supplementary Tables 5 and 6).

Discussion

The current study extends our previous finding that tobacco use increases the risk for all stroke, and pathological, and etiological stroke subtypes. Our findings have relevance to global efforts to reduce exposure to

	Never smoker		Former smoker		Current smoker							
					Any		1–9 cig/day		10–19 cig/day		≥20 cig/day	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Overall												
Young	2569 (88.1)	1340 (50.0)	179 (6.1)	364 (13.6)	168 (5.7)	976 (36.4)	74 (2.5)	263 (9.8)	59 (2.0)	268 (10.0)	35 (1.2)	445 (16.6)
Older	1960 (83.3)	2409 (50.0)	293 (12.4)	1311 (27.2)	100 (4.2)	1098 (22.8)	43 (1.8)	241 (5.0)	33 (1.4)	347 (7.2)	24 (1.0)	510 (10.6)
Western Europe/North America												
Young	154 (53.5)	143 (54.6)	88 (30.6)	71 (27.1)	46 (16.0)	48 (18.3)	16 (5.6)	14 (5.3)	19 (6.6)	13 (5.0)	11 (3.8)	21 (8.0)
Older	312 (63.7)	346 (40.6)	150 (30.6)	447 (52.5)	28 (5.7)	59 (6.9)	15 (3.1)	13 (1.5)	7 (1.4)	30 (3.5)	6 (1.2)	16 (1.9)
Eastern/central Europe/Middle East												
Young	163 (70.3)	130 (43.9)	31 (13.4)	63 (21.3)	38 (16.4)	103 (34.8)	10 (4.3)	27 (9.1)	16 (6.9)	28 (9.5)	12 (5.2)	48 (16.2)
Older	263 (80.9)	243 (45.4)	50 (15.4)	188 (35.1)	12 (3.7)	104 (19.4)	5 (1.5)	24 (4.5)	4 (1.2)	26 (4.9)	3 (0.9)	54 (10.1)
Africa												
Young	278 (93.3)	124 (59.0)	6 (2.0)	49 (23.3)	14 (4.7)	37 (17.6)	7 (2.3)	24 (11.4)	5 (1.7)	8 (3.8)	2 (0.7)	5 (2.4)
Older	158 (94.6)	187 (68.5)	7 (4.2)	60 (22.0)	2 (1.2)	26 (9.5)	1 (0.6)	11 (4.0)	1 (0.6)	12 (4.4)		3 (1.1)
South Asia												
Young	663 (99.4)	413 (72.2)	2 (0.3)	30 (5.2)	2 (0.3)	129 (22.6)	1 (0.2)	86 (15.0)	1 (0.2)	28 (4.9)		15 (2.6)
Older	246 (99.6)	585 (72.6)	1 (0.4)	78 (9.7)		143 (17.7)		63 (7.8)		42 (5.2)		38 (4.7)
China												
Young	958 (97.6)	327 (37.0)	2 (0.2)	56 (6.3)	21 (2.2)	500 (56.7)	11 (1.2)	55 (6.2)	6 (0.6)	138 (15.6)	4 (0.4)	307 (34.8)
Older	614 (93.6)	654 (44.0)	8 (1.2)	195 (13.1)	34 (5.2)	638 (42.9)	12 (1.8)	82 (5.5)	13 (2.0)	199 (13.4)	9 (1.4)	357 (24.0)
South East Asia												
Young	207 (85.9)	102 (38.1)	11 (4.6)	43 (16.0)	23 (9.5)	123 (45.9)	17 (7.1)	36 (13.4)	4 (1.7)	48 (17.9)	2 (0.8)	39 (14.6)
Older	95 (86.4)	77 (32.9)	9 (8.2)	91 (38.9)	6 (5.5)	66 (28.2)		15 (6.4)	5 (4.5)	22 (9.4)	1 (0.9)	29 (12.4)
South America												
Young	218 (87.6)	103 (53.9)	39 (13.9)	52 (27.2)	24 (8.5)	36 (18.8)	12 (4.3)	21 (11.0)	8 (2.8)	5 (2.6)	4 (1.4)	10 (5.2)
Older	282 (76.6)	311 (49.8)	68 (18.5)	252 (40.3)	18 (4.9)	62 (9.9)	10 (2.7)	33 (5.3)	3 (0.8)	16 (2.6)	5 (1.4)	13 (2.1)

Data are number (%). The denominator of the percentage is the number of the age + gender group corresponding in overall or regions. Young: female ≤65 years, male ≤55 years. Older: female >65 years, male >55 years. cig/day = cigarettes or beedie per day.

Table 2: **Numbers and percentages of never, former, and current smokers in controls by region, sex, and age.**

tobacco. First, tobacco control measures should not only focus on preventing youth from starting, but also promote quitting smoking for current smokers. Our results suggested that smoking cessation is not associated with increased residual risk for acute stroke (Supplementary Table 1), regardless the cessation period from 12 months and longer (Supplementary Table 7). This observation is consistent with estimates of stroke reduction following cessation reported in the Korean National study,[15] but in contrast with report that the residual risk for Acute Myocardial Infarction (AMI) lasts more than 20 years after cessation.[13] We also found no residual risk of large vessel stroke. These observations suggests that there may be differing causal pathways between smoking and stroke risk versus AMI risk, which may involve inflammation,[16,17] blood pressure surge,[18,19] arterial wall damage,[20] and abnormal blood coagulations.[21]

Second, reductions in smoking rates will have different effects on stroke risk among male and female, young and old, and related mostly to difference in prevalence of smoking among male and female and age groups of different regions of the world. Regional differences in smoking pattern are most marked by sex, with tobacco use in developing countries are high for male, but low in female (Table 2). In the current study, smoking prevalence is high in China and East Asia, East/Central Europe, especially in the young with heavy smoking, consistent with global pattern of lifetime risk for stroke.[22] The association of stroke risk with tobacco exposure differs by age, making it critical to target younger age groups. We observed an 8-fold risk increase of large vessel stroke for age group of 50–59 who smoked more than 20 cig/day (Supplementary Table 2). Even though age is an important intrinsic factor that modulates the stroke risk and young smokers had higher ORs, we should not neglect the tobacco control among the middle aged and older smokers. Smoke cessation will have broader health benefits far beyond the stroke, such as reducing various form of cancers, ischemic heart diseases, and respiratory diseases.[5] In addition to differing prevalence by regions and income-levels, we also observed differences in the magnitude of risk, with highest OR for high-income countries in Western Europe and North America. This finding has also been observed in INTERHEART study,[23] and may relate to differences in type of tobacco smoked (e.g., tar content), or presence of competing risk factors, or in

Tobacco type	All stroke	Ischemic stroke					ICH
		Cardioembolism	Large vessel	Small vessel	Other/Undetermined TOAST	Total	
All type of tobacco	1.64 (1.46–1.84)	1.56 (0.99–2.46)	2.16 (1.63–2.87)	1.66 (1.37–2.01)	1.97 (1.55–2.50)	1.85 (1.61–2.11)	1.19 (1.00–1.41)
Cigarettes							
Filter	1.73 (1.50–1.99)	1.62 (0.97–2.71)	2.59 (1.83–3.67)	1.94 (1.53–2.45)	1.85 (1.39–2.46)	2.01 (1.70–2.36)	1.10 (0.89–1.37)
Non-filter	2.59 (1.79–3.77)	2.02 (0.35–11.61)	5.73 (2.29–14.33)	2.26 (1.18–4.32)	3.31 (1.55–7.11)	3.37 (2.16–5.24)	2.04 (1.15–3.63)
Both	2.81 (1.87–4.22)	1.67 (0.30–9.22)	4.12 (1.63–10.44)	3.02 (1.57–5.83)	3.09 (1.42–6.71)	2.87 (1.84–4.48)	2.23 (1.16–4.30)
Beedie	2.39 (1.58–3.61)	1.54 (0.04–64.83)	3.69 (1.28–10.65)	3.45 (1.66–7.17)	3.27 (1.46–7.33)	3.39 (2.06–5.57)	1.00 (0.56–1.79)
Pipes/Cigars	1.96 (0.58–6.61)	1.19 (0.13–11.21)	0.28 (0.01–9.46)	4.49 (0.25–82.14)	3.65 (0.19–69.27)	1.81 (0.50–6.60)	2.72 (0.18–40.34)
Chewing Tobacco	1.27 (0.93–1.71)	5.13 (0.27–97.97)	1.04 (0.44–2.47)	0.97 (0.61–1.56)	1.57 (0.77–3.23)	1.15 (0.79–1.68)	1.53 (1.03–2.27)

Data are OR (95% CI) of all stroke or stroke subtype with control, in different tobacco type with never smoke as reference. ORs were adjusted for age, self-reported hypertension or blood pressure≥140/90 mm Hg, physical activity, diet and alcohol intake. Filter: filter cigarettes among current smokers; Non-filter: non-filter cigarettes among current smokers; both: both filter and non-filter cigarettes among current smokers; Beedie: use beedie alone among current smokers; Pipes/Cigars: use pipes/cigars alone among current smokers; Chewing Tobacco: use chewing tobacco alone among current smokers.

Table 3: **Risk of stroke associated with type of tobacco used in current smoker.**

unmeasured confounders, we could not further explore such as income levels within each region due to the sample size limitation. We also cannot rule out the presence of Neyman's fallacy, albeit stroke risk by regions and country income levels has been adjusted for age, sex, regions and other covariates.

Third, reduction in smoking rates is anticipated to have proportionally different reductions in rates of stroke subtypes. We observed the highest risk with large vessel stroke, which is consistent with the indirect comparison of higher risk associated with AMI than large vessel stroke which have shared pathogenesis (atherosclerosis),

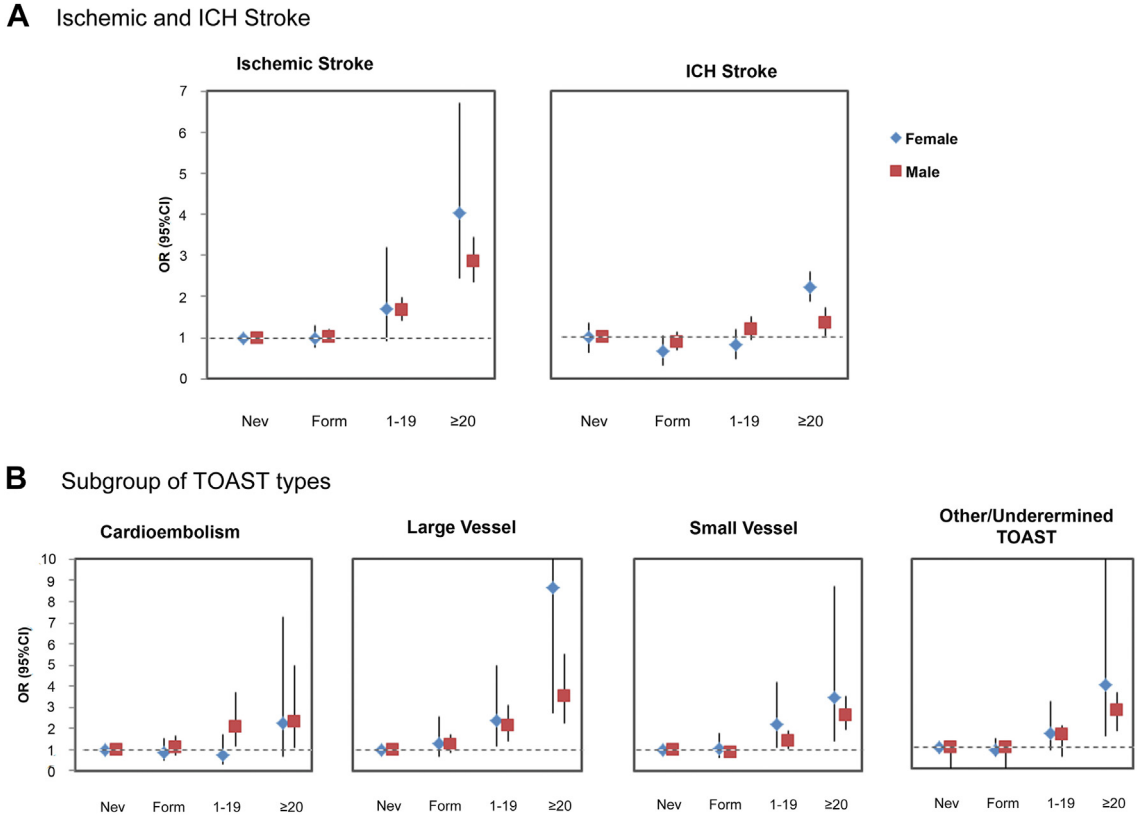

Fig. 1: **Risk of stroke associated with numbers smoked by sex.** Increasing number of cigarettes smoked per day was associated with a graded increase in odds of ischemic stroke in both male and female (A), and in all subtypes of ischemic stroke (B). Nev = never smokers. Form = former smokers. 1–19 = currently smoking 1–19 cigarettes per day. ≥20 = currently smoking 20 or more cigarettes per day.

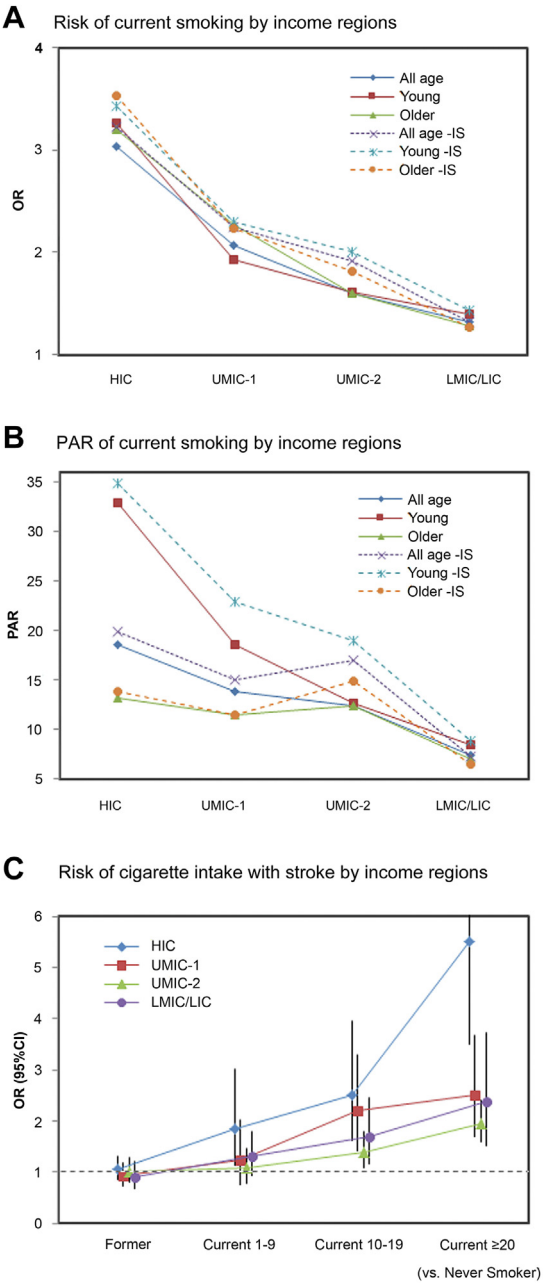

Fig. 2: **Risk of stroke associated with smoke in income regions.** The magnitude of odds ratio (A) and PAR (B) of all stroke and Ischemic stroke associated with current smoking varied by income countries (C) Odds ratios of all stroke with increasing number of cigarettes smoked per day in different income countries. HIC = High income country; UMIC = Upper middle income country; LMIC = Low middle income country; LIC = Low income country. Young = female ≤65 years, male ≤55 years; Older = female >65 years, male >55 years. IS = Ischemic stroke; All age-IS, Young-IS and Older-IS mean corresponding age groups in IS subtype. Form = former smokers. Current 1–9 = currently smoking 1–9 cigarettes per day. Current 10–19 = currently smoking 10–19 cigarettes per day. Current ≥20 = currently smoking 20 or more cigarettes per day.

although the PAR for AMI reported in INTERHEART of 35.7%[23] is higher than that reported for large vessel ischemic stroke in INTERSTROKE (PAR 18.9, 95% CI 11.4–24.4), however, the rates of all stroke subtypes are anticipated to be reduced by lowering rates of smoking.

Fourth, findings from our study add to the literature on the association of stroke with differing types of tobacco exposure. Any forms of tobacco use is harmful, whether smoked or chewed, filtered or non-filtered, beedie, chew alone or combined. Non-filtered/filtered combined users appear to have highest risk for all stroke. The dose-dependent association of increasing odds of all stroke and its etiological subtypes with increasing number of cigarettes smoked per day (Supplementary Table 8) is an important message to individuals who cannot stop smoking but can reduce their daily consumption. Every cigarette counts in modulating the stroke risk, therefore every cigarette that one can avoid each day would reduce the risk of stroke.

The current study reports ETS exposure is harmful to all stroke and its subtypes. Over 10 h/wk exposure to ETS double the risk for all stroke (OR 1.95, 1.69–2.27). ETS showed a graded increase in risk for large vessel, small vessel and cardioembolic stroke. Interestingly, the risk with most exposed group doubled for ICH, compare to active smoking of 1.19 for the same patient group. A prospective study showed never smoking Japanese female exposed to household ETS increased stroke mortality for subarachnoid hemorrhage and ICH subtypes, but not for cerebral infarction.[24] Previous meta-analysis showed a relative risk of 1.44 on exposure to ETS for stroke, which included 28 studies which differ significantly on study design, exposure index, and disease classification.[7,10] US national health and nutrition examination estimated ETS with odds ratio of 1.46 for stroke, and 2 folds increase in mortality after stroke.[25] In current study, we employed standardized structured questionnaires and protocols, and adjusted for behavioral and modifiable covariables in 32 countries.

The study demonstrated that smoke free tobacco such as chewing increased the risk predominantly for ICH, but not for ischemic stroke (Table 3). Whether there is specific effect of smoke free tobacco remains to be investigated. It is known that smoke free tobacco may have different chemical composition with the smoking tobacco, and the mixture of compounds from inhaled tobacco depends on the temperature of how tobacco products were heated or burned.[16]

Our study has limitations, including those inherent in a case–control study design. Information on smoking status relied on questionnaire, which may be vulnerable to recall and social desirability bias.[26] However, the prevalence of smoking among controls is consistent with the GBD[1] and PURE[27] cohort studies. The current studies rely on self-reported tobacco use and exposure which may underestimate the exposure to ETS.[28,29] There are reports that cohort studies on ETS tend to yield smaller odds than

case control studies.[9,10] Another limitation is that we recruited stroke survivors, which excluded those who died before reaching the hospitals. Even so, compared with the large proportion of out-of-hospital deaths in AMI, this is a comparatively minor issue. A key potential limitation in a case control study is whether the control group is representative. Relative to the current study, we note that the prevalence of smoking in the INTERSTROKE study are in accordance with prevalence of the regions reported previously.[30,31] There were multiple analyses carried out in the study, might increase the chance of false positive findings.

In conclusion, our data showed that active smoking or exposure to ETS is associated with increased risk for all stroke and major pathological and etiological subtypes. There are sex and regional variations between high, middle, and low income countries in prevalence of tobacco use and ETS exposure. Stroke subtypes may be related to tobacco exposure heterogeneously. Tobacco control should be tightened to encourage young people to refrain from starting smoking as well as promote quitting smoking, and further legislation should be developed to build and support a smoke free environment.

Contributors

All authors contributed to the discussions and interpretation of the data, and to the writing of the report. Salim Yusuf, Martin J. O'Donnell, Lisheng Liu, Xingyu Wang: conceptualisation; Hongye Zhang, Xin Liu, Matthew McQueen, Guillaume Pare, Graeme J. Hankey: data curation; Guillaume Pare: formal analysis, funding acquisition, investigation, methodology; Sumathy Rangarajan, Siu Lim: project administration, resources, software, supervision, validation, visualisation,; Purnima Rao-Melacini and John Ferguson: statistical analyses; Xingyu Wang, Xin Liu, Martin J. O'Donnell: writing – original draft, and writing; Allan Sniderman: review & editing; Denis Xavier, Prem Pais, Patricio Lopez-Jaramillo, Albertino Damasceno, Peter Langhorne, Annika Rosengren, Antonio L. Dans, Ahmed Elsayed, Alvaro Avezum, Charles Mondo, Conor Judge, Hans-Christoph Diener, Danuta Ryglewicz, Anna Czlonkowska, Nana Pogosova, Christian Weimar, Romana Iqbal, Rafael Diaz, Khalid Yusoff, Afzalhussein Yusufali, Aytekin Oguz, Ernesto Penaherrera, Fernando Lanas, Okechukwu S. Ogah, A. Ogunniyi, Helle K. Iversenaa, German Malaga, Zvonko Rumboldt, Shahram Oveisgharan, Fawaz Al Hussainae, Yongchai Nilanont, all authors had full access to data and reviewed and approved the drafts of the manuscript. No medical writer or other people were involved in the design, analysis or writing of this manuscript.

Data sharing statement

Qualifying researchers who wish to access our data should submit a proposal with a valuable research question to Dr. Martin O'Donnell. Proposals will be assessed by a committee formed from the trial management group. Available data include de-identified individual participant data and a data dictionary.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102515.

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