

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

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Background and Purpose—It is currently unknown whether the excess risk of stroke by smoking is the same for women and men. We performed a systematic review and meta-analysis to estimate the effect of smoking on stroke in women compared with men.

Methods—PubMed MEDLINE was systematically searched for prospective population-based cohort studies published between January 1, 1966, and January 26, 2013. Studies that presented sex-specific estimates of the relative risk of stroke comparing current smoking with nonsmoking and its associated variability were selected. The sex-specific relative risks and their ratio (RRR), comparing women with men, were pooled using random-effects meta-analysis with inverse variance weighting. Similarly, the RRR for former versus never smoking was pooled.

Results—Data from 81 prospective cohort studies that included 3 980 359 individuals and 42 401 strokes were available. Smoking was an independent risk factor for stroke in both sexes. Overall, the pooled multiple-adjusted RRR indicated a similar risk of stroke associated with smoking in women compared with men (RRR, 1.06 [95% confidence interval, 0.99–1.13]). In a regional analysis, there was evidence of a more harmful effect of smoking in women than in men in Western (RRR, 1.10 [1.02–1.18]) but not in Asian (RRR, 0.97 [0.87–1.09]) populations. Compared with never-smokers, the beneficial effects of quitting smoking among former smokers on stroke risk were similar between the sexes (RRR, 1.10 [0.99–1.22]).

Conclusions—Compared with nonsmokers, the excess risk of stroke is at least as great among women who smoke compared with men who smoke. (*Stroke*. 2013;44:2821–2828.)

Key Words: meta-analysis ■ risk factors ■ sex differences ■ smoking ■ stroke

Worldwide, >5 million people die from smoking or other forms of tobacco use each year, accounting for 6% of all deaths among women and 12% of all deaths among men.^{1,2} These figures are projected to increase to an annual 8 million smoking-related deaths in 2030 if the trends remain unchanged.³ In the West, the epidemic of tobacco use in men has had its peak and is in slow decline, but the epidemic among men and women (particularly among young women) in some low- and middle-income countries will not reach its peak until well into the 21st century.^{1,4–6} The projected burden of smoking is, therefore, likely to become even greater than has been currently forecasted and is likely to be disproportionately distributed between women and men. Furthermore, the sex differential in the burden of smoking may further widen because the detrimental effects of smoking are stronger for women than for men in some diseases, including lung cancer and coronary heart disease (CHD).^{7–10} Indeed, in a recent overview

the excess risk of smoking-related CHD was observed to be 25% higher in women than in men.¹¹

Stroke is the world's second leading cause of death and disability, accounting for 10% of the global disease burden.¹² Cigarette smoking has been shown to be an independent risk factor for both ischemic and hemorrhagic stroke in both men and women.¹³ Overall, smokers have an approximate doubling in the risk of incurring a stroke during their lifetime compared with never-smokers.^{5,6} Recent estimates indicate that ≈19% of the burden of stroke is because of current smoking.¹⁴ Yet, this estimate assumes that the effect of smoking is the same in women and men who smoke, which may not necessarily be a valid assumption. Some, but not all,^{15,16} large-scale studies have suggested that, as with CHD, smoking has a greater relative effect on stroke risk in women compared with their male equivalents, especially among the heaviest smokers.^{13,17} Thus, given the unequivocal link between smoking and stroke,

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quantifying any sex difference in the relative effect of smoking on stroke risk is of major importance both clinically and from a public health perspective.

In the present meta-analysis, we systematically reviewed the available literature for prospective studies that reported sex-specific effects of smoking on the risk of stroke. This enabled the most reliable examination that has hitherto been possible for any sex difference in stroke risk associated with cigarette smoking.

Methods

Search Strategy and Selection Criteria

A systematic search was performed at PubMed MEDLINE (www.ncbi.nlm.nih.gov) on January 26, 2013, using the following MeSH search terms: cerebrovascular disorders, and smoking or tobacco, and female or women, and male or men, or sex, and cohort studies. We scanned references to identify other potentially relevant studies that were missed in our search.

Studies were included if they provided relative risks (RR; or equivalents) of the association between current cigarette smoking and stroke in men and women. Studies were excluded if they had not adjusted for at least age, did not provide information on the variance associated with the point estimate, and were performed in populations that predominantly included individuals with a history of cardiovascular disease or other underlying pathological disorders (eg, diabetes mellitus, renal disease, or cancer). In case of duplicate reports from the same study, we included the most recent publication or the publication with the longest follow-up period. If available, we also extracted data on the strength of association in former smokers, on the baseline prevalence of smoking, and on the average follow-up of the cohort. In addition, the authors had access to individual participant data from 4 studies: the Scottish Heart Health Extended Cohort Study (SHHEC), the Asia Pacific Cohort Studies Collaboration (APCSC) that comprised 44 cohorts, the National Health and Nutrition Examination Survey III (NHANES), and the Atherosclerosis Risk in Communities Study (ARIC).^{18–21}

Statistical Analysis

Our primary end point was combined fatal or nonfatal stroke (*International Classification of Diseases, Ninth Revision*, codes 430–438), and our primary metrics were the pooled multiple-adjusted RR and RR ratio (RRR) for current smokers versus nonsmokers (either not current or never-smokers). The multiple adjustments made were allowed to vary by study, but had to include ≥ 1 other risk factor for stroke in addition to age. For each study, we extracted the sex-specific RRs for current smokers versus nonsmokers and 95% confidence intervals (CIs), from which we estimated the women-to-men ratio of RRs (RRR) and 95% CIs.¹¹ After log-transformation of study-specific estimates, pooled estimates across studies were obtained using random-effects meta-analysis. The inverse of the variance of the log RR was used to weight studies.²² An identical approach was used for RRRs.

We predefined many sensitivity analyses. First, we repeated our analyses using estimates that were adjusted for age only. Second, we performed our primary analysis using fatal stroke only as the outcome. Third, we selected those studies that compared the multiple-adjusted RR of current smokers with never-smokers (as opposed to using the nonsmoker category that would also have included former smokers). Fourth, we compared the multiple-adjusted RRR for studies from Asia (Asian cohorts) with those from the West (Western cohorts). Fifth, we repeated the primary analysis by age group (<65 versus ≥ 65 years) using all data available (either age- or multiple-adjusted RRR). Sixth, the effect of the dose–response relationship was evaluated by calculating the age- or multiple-adjusted RRR and 95% CI in 3 groups of increasing smoking intensity (ie, <10, 10–20, and >20 cigarettes per day). Finally, we separately estimated the age- or multiple-adjusted RRR of hemorrhagic and ischemic stroke from studies that provided estimates of both.

In addition, we evaluated whether the effects of smoking cessation differed by sex by estimating the RRR and 95% CI comparing former with never-smokers. Given the limited number of studies reporting RRs on smoking cessation, we did not stratify on age- or multiple-adjusted results but rather used the maximal adjustment set available from each study.

The I^2 statistic was used to estimate the percentage of variability between studies because of between-study heterogeneity.^{23,24} Random-effects meta-regression analyses were used to assess whether differences in the mean duration of study follow-up, the prevalence of women smoking, the women-to-men ratio of prevalence of smoking, and the baseline year of the study contributed to heterogeneity between studies. The possibility of publication bias was examined graphically using funnel plots. All analyses were performed using Stata version 11.0.

Results

The systematic search identified 663 articles that were subsequently examined on title and abstract. Of these, 136 articles were selected because they reported the association between smoking and the risk of stroke (Figure 1). After full-text evaluation, 16 articles were selected that provided information from 34 cohorts on sex differences in the association between smoking and stroke in the general population (Table).^{5,6,15,16,25–35} These data were extended with data from ARIC,¹⁸ NHANES III,¹⁹ APCSC,²⁰ and SHHEC,²¹ adding a further 47 cohorts.

Baseline characteristics of all 81 cohorts included in this study are described in the Table. Overall, data on 3980359 individuals were available, in whom ≥ 2401 fatal and nonfatal strokes were documented (1 study, including 56167 individuals, did not report the number of stroke events).²⁷ Fifty-four cohorts came from Asia (31% of the individuals), 12 from the United States (62%), 6 from Europe (4%), and 9 from Australia or New Zealand (3%). Eighteen studies reported sex-specific prevalence rates of current smoking, and 17 studies reported the sex-specific prevalence rates of former smoking. As anticipated, the prevalence of current smoking varied widely among sexes, regions, and studies and ranged from 8% to 59% in men and from 1% to 51% in women. The prevalence of current smoking was higher in men than in women in all but 4 studies. This sex difference was most pronounced in Asian populations, where typically <10% of women smoked compared with >50% of men. Smoking cessation was also more prevalent in men than in women in all studies, but the disparity was especially noticeable in Asian cohorts.

Multiple-Adjusted Estimates for Stroke Associated With Current Smoking Versus Nonsmoking

Data from 76 cohorts that included 3817289 individuals (96% of the total population) and 39042 stroke events were available for the primary analysis of multiple-adjusted association between combined fatal and nonfatal stroke and current smoking. Compared with nonsmoking, current smoking was associated with 83% (95% CI, 1.58–2.12) increased risk in women and 67% (95% CI, 1.49–1.88) increased risk in men (Figure 2 and Figure I in the online-only Data Supplement). The pooled RRR (women to men) of risk of stroke associated with current smoking was 1.06 (95% CI, 0.99–1.13; $P=0.10$; Figure 3). There was no evidence for between-study heterogeneity ($I^2=3.1\%$; $P=0.42$) or of publication bias (Figure II in the online-only Data Supplement).

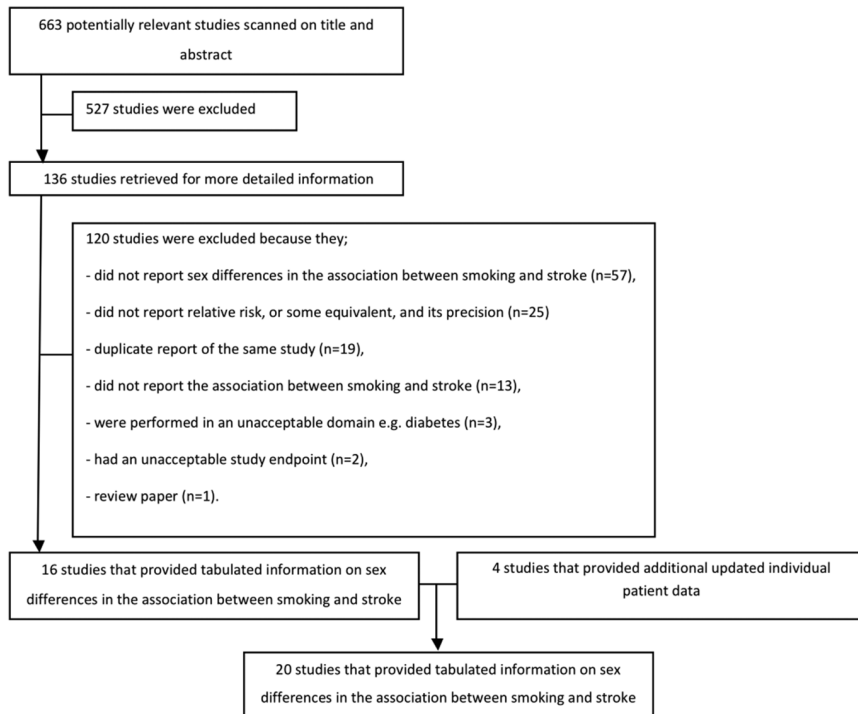


Figure 1. Flowchart of the systematic review for the primary analysis.

Sensitivity Analyses

There was no evidence to suggest that the pooled RRR was different according to the duration of follow-up ($P=0.53$), the percentage of women who smoked ($P=0.82$), the ratio of women to men who smoked in the studies ($P=0.73$), or the median year of study baseline ($P=0.66$). Twelve studies, with data from 63 cohorts that included 3 438 747 (86%) individuals and 35 267 stroke events, reported on the age-adjusted relationship between combined fatal and nonfatal stroke and smoking. In this analysis, the smoking-related excess risk of stroke was 62% (95% CI, 1.39–1.89) in women and 49% (95% CI, 1.32–1.69) in men (Figure III in the online-only Data Supplement). The age-adjusted pooled RRR was 1.04 (95% CI, 0.98–1.11; Figure IV in the online-only Data Supplement). There was moderate heterogeneity between studies ($P=17.0\%$; $P=0.27$). The multiple-adjusted RRR in 69 cohorts with 3 393 786 individuals and ≥ 31 241 events was 1.04 (95% CI, 0.91–1.18) when only fatal strokes were considered (Figure V in the online-only Data Supplement). The multiple-adjusted RRR for fatal and nonfatal stroke events (58 cohorts, 3 303 875 individuals, and 29 554 events) was 1.04 (95% CI, 0.98–1.12) when never-smokers instead of non-smokers were used as the reference group (Figure V in the online-only Data Supplement).

There was some evidence that the multiple-adjusted association differed slightly between Asian and Western cohorts; the RRR for the 51 Asian cohorts (1 090 285 individuals, 12 656 strokes) was 0.97 (95% CI, 0.87–1.09) versus 1.10 (95% CI, 1.02–1.18) in the 25 Western cohorts (2 727 004 individuals, 26 356 events; Figure V in the online-only Data Supplement). Finally, there was no significant difference in the risk of stroke between younger (≤ 65 years) and older (> 65 years) men and women. The RRR was 1.16 (95% CI, 0.92–1.46) for the younger age group and was 0.84 (95% CI,

0.67–1.06) for the older age group (Figure V in the online-only Data Supplement).

Dose–Response Association

Data on the association between stroke and dose of daily smoked cigarettes across subgroups of < 10 , 10 to 20, and > 20 cigarettes per day versus nonsmoking were available from 2 published studies and were combined with new analyses of data from APCSC, SHHEC, ARIC, and NHANES III (52 cohorts, 1 001 070 individuals, and 9 296 strokes). The RRRs in these subgroups were 0.94 (95% CI, 0.72–1.21), 0.91 (95% CI, 0.67–1.22), and 1.31 (95% CI, 1.00–1.72), respectively (Figure V in the online-only Data Supplement). Further examination of these data suggested that the excess RR of stroke in women smoking heavily was dependent on data from 1 small study.²⁷ Restriction to analyses of individual participant data alone resulted in an attenuation of the effect size so that the risks of smoking-related stroke were comparable in both sexes, irrespective of the number of cigarettes smoked per day. The RRRs were 0.93 (95% CI, 0.69–1.26), 0.79 (95% CI, 0.61–1.03), and 1.13 (95% CI, 0.91–1.40) across subgroups of < 10 , 10 to 20, and > 20 cigarettes per day, respectively.

Stroke Subtypes

The association between smoking and stroke subtypes was examined using data from 60 cohorts (992 859 individuals [25% of all individuals], 4894 ischemic strokes, and 1990 hemorrhagic strokes; Figure V in the online-only Data Supplement). Compared with nonsmoking, current smoking was associated with an increased risk of ischemic stroke of 54% (95% CI, 1.21–1.96) in women and 53% (95% CI, 1.28–1.82) in men. The pooled RRR for ischemic stroke was 0.97 (95% CI, 0.79–1.18; $P=0.73$). For hemorrhagic stroke, the increased risk associated with current smoking compared

Table. Characteristics of Included Studies

Study Name/First Author	Baseline Study, Years	Country	Study Size (% Women)	Age Range, Years	Strokes, n (% Women)	F or NF	Study Duration, Years	Current Smoker (%)		Former Smoker, %		Maximum Adjustment Available
								M	W	M	W	
APCSC ANZ ²⁰	1961–1999	Pool of 9 cohorts	99 624 (45)	20–104	1671 (41)	F/NF	7	20	14	42	20	Age, SBP, DM, HDL, TC
APCSC Asia ²⁰	1961–1999	Pool of 35 cohorts	500 819 (34)	20–107	4653 (31)	F/NF	7	59	5	9	1	Age, SBP, DM, HDL, TC
ARIC ¹⁸	1987–1989	United States	15 732 (55)	45–64	1073 (50)	F/NF	18	28	25	44	22	Age, SBP, DM, HDL, TC
CNHS ¹⁵	1991–2000	China	1 698 71	40+	3979 (42)	F/NF	8	59	13	3	1	Age, educ, smoking, alc, PA, BMI, SBP, region, urbanization, CVD, DM
CPS I ⁵	1959–1965	United States	518 982 (65)	55–85	6233 (59)	F	6	40	15	17	4	Age, race, educ
CPS II ⁵	1982–1988	United States	746 485 (61)	55–85	4037 (57)	F	6	24	18	43	21	Age, race, educ
Contemporary cohorts ⁵	2000–2010	United States	956 756 (56)	55–85	7536 (55)	F	10	9	10	55	41	Age, race, educ
EPIC-Norfolk ³¹	1993–2007	United Kingdom	20 040 (55)	40–79	599 (52)	F/NF	11	12	11	53	32	Age, BMI, SBP, TC, aspirin use, DM, SES
EPOCH-JAPAN ³⁵	1977–1997	Japan	66 592 (59)	40–89	893 (48)	F	10	54	5	22	1	Age, SBP, TC, BMI, cohort
GPO study ²⁵	1966–1967	United Kingdom	1916 (34)	35–70	120 (38)	F	40	58	51	19	13	Age
JACC, JPHC 1 and 2, TPCS ²⁶	1980–1990	Japan	296 836 (53)	40–79	3131 (43)	F	10	54	8	25	2	Age, cohort
Lam ²⁷	1998–2000	China	56 167 (67)	65+	NA	F	4	19	4	40	8	Age, educ, alc, PA, BMI, medical history, self-reported health status, monthly expenditure
LWC study ³²	1981–1998	United States	13 254 (64)	44–101	1984 (61)	F/NF	17	8	12	57	32	Age
MORGAM ³⁰	1982–1997	Europe	93 695	19–77	3142 (41)	F/NF	13	NA	NA	NA	NA	Age, SBP, DBP, HDL, BMI
NHANES I ¹⁶	1971–1992	United States	12 932 (59)	25–75	929	F/NF	18	15	24	NA	NA	Age, race, educ, blood pressure, TC, DM, overweight
NHANES III ¹⁹	1988–1994	United States	18 603 (46)	18–90	329 (42)	F	13	31	21	30	16	Age, SBP, DM, HDL, TC
NHIS ⁶	1997–2004	United States	202 248 (56)	25–79	378 (37)	F	7	26	21	29	20	Age, educ, alc, BMI
North Karelia and Kuopio ³³	1972–1992	Finland	28 618 (51)	30–59	361 (45)	F	20	NA	NA	NA	NA	Age, DBP, TC
SCH study ²⁸	1993–1998	Singapore	61 320 (56)	45–74	832 (48)	F	12	36	6	21	3	Age, dialect, recruitment year, educ, alcohol, PA
SHHEC ²¹	1984–1987	Scotland	13 287 (51)	30–74	1083 (43)	F/NF	16	38	38	33	21	Age, SBP, DM, HDL, TC
Wen ²⁹	1982–1992	Taiwan	86 580 (39)	35+	423 (2)	Fatal	20	41	1	11	0	Age

alc indicates alcohol; AHT, antihypertensive; ANZ, Australia and New-Zealand; APCSC, Asia Pacific Cohort Studies Collaboration; ARIC, Atherosclerosis Risk in Communities study; BMI, body mass index; CNHS, China National Hypertension survey; CPS, Cancer Prevention Study; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; educ, educational level; EPIC-Norfolk, European Prospective Investigation into Cancer-Norfolk; EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; F, fatal; GPO study, General Post Office study; HDL, high-density lipoprotein cholesterol; JACC study, Japan Collaborative Cohort study; JPHC study, Japan Public Health Center-based prospective study; LWC study, Leisure World Cohort study; MONICA, Monica risk, genetics, archiving and monograph; MORGAM, MONica (Monitoring of Trends and Determinants in Cardiovascular Disease) Risk, Genetics, Archiving and Monograph; NA, not available; NF, not fatal; NHANES, National Health and Nutrition Examination Survey; NHIS, National Health Interview Survey; PA, physical activity; recruit year, recruitment year; SBP, systolic blood pressure; SES, socioeconomic status; SCH study, Singapore Chinese Health study; SHHEC, Scottish Heart Health Extended Cohort study; TC, total cholesterol; and TPCS, Three-Prefecture Cohort Study.

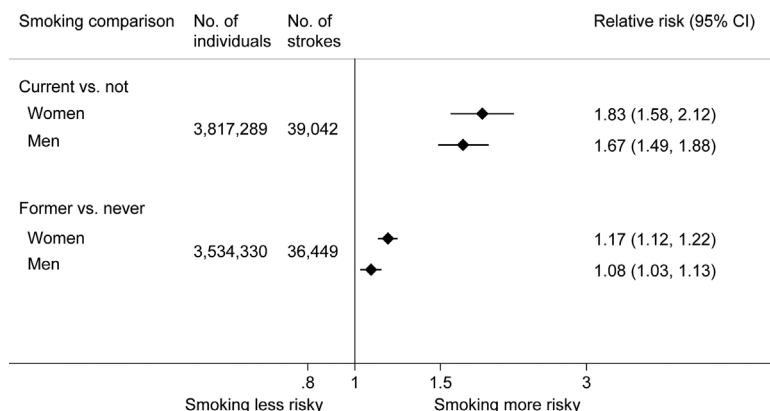


Figure 2. Pooled relative risk of stroke associated with current smoking vs nonsmoking and former smoking vs never smoking in men and women. Lines, and width of the summary diamond, show 95% confidence intervals (CI).

with nonsmoking was 63% (95% CI, 1.21–2.19) in women and 22% (95% CI, 0.98–1.51) in men. The pooled RRR for hemorrhagic stroke suggested a significant increased RR of 17% in women who smoked compared with men: RRR 1.17 (95% CI, 1.02–1.34; $P=0.02$).

Risk of Stroke in Former Smokers Versus Never-Smokers

Thirteen studies, with data from 72 cohorts that included 3 534 330 individuals (89% of all individuals) and 36 449 strokes, reported on the risk of stroke in former smokers compared with never-smokers. The excess risk of former smoking versus never smoking was 17% (95% CI, 1.12–1.22) in women and 8% (95% CI, 1.03–1.13) in men (Figure 2). There was no evidence that the beneficial effects of quitting smoking on risk of stroke differed between the sexes (RRR, 1.10 [95% CI, 0.99–1.22]; Figure 4).

Discussion

Cigarette smoking is one of the leading causes of death and disability in the world and accounts for 6.3% of the global burden of disease.³⁶ Its importance as a major cause of

ill-health is likely to continue for decades to come because smoking rates in low- and middle-income countries (where the majority of the population lives) continue to rise unimpeded.^{1–3,34} Previously, it has been shown that—all else being equal—smoking has a much more hazardous effect on the RR of CHD among women than men; we, therefore, questioned whether this may also be true for stroke, which, in the case of ischemic stroke at least, shares similar risk factors and pathophysiology to that of CHD.^{11,37} In the current pooled analysis of prospective data from more than ≈4 million individuals and >42 000 strokes from 81 cohorts worldwide, we confirmed the importance of cigarette smoking as a major and independent risk factor for stroke and its major subtypes in all individuals. Overall, the risk of stroke in men and women who smoked was 67% and 83% greater compared with nonsmoking individuals. However, unlike CHD where there was clear evidence of a significant sex difference between men and women, for stroke the evidence indicates that smoking confers a similar risk in women and men alike, independent of differences in other risk factors. Importantly, we demonstrated that, compared with never-smokers, former

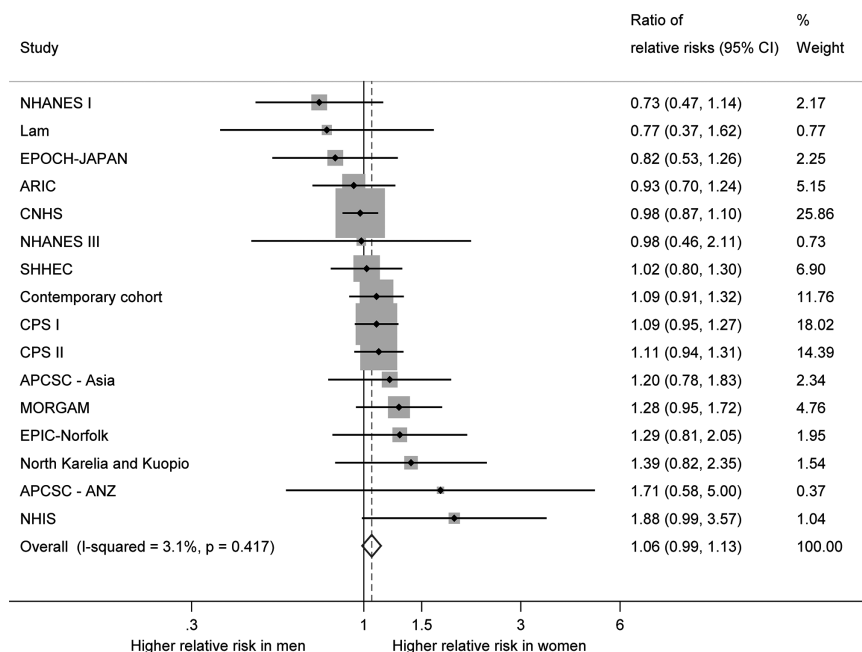


Figure 3. Multiple-adjusted women-to-men ratio of relative risks of stroke associated with smoking vs nonsmoking by study. Lines, and width of the summary diamond, show 95% confidence intervals (CIs). Boxes are drawn in proportion to study weights. APCSC indicates Asia Pacific Cohort Studies Collaboration; ANZ, Australia and New-Zealand; ARIC, Atherosclerosis Risk in Communities study; CNHS, China National Hypertension survey; CPS, Cancer Prevention Study; EPIC, European Prospective Investigation into Cancer; EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; NHANES, National Health and Nutrition Examination Survey; NHIS, National Health Interview Survey; and SHHEC, Scottish Heart Health Extended Cohort study.

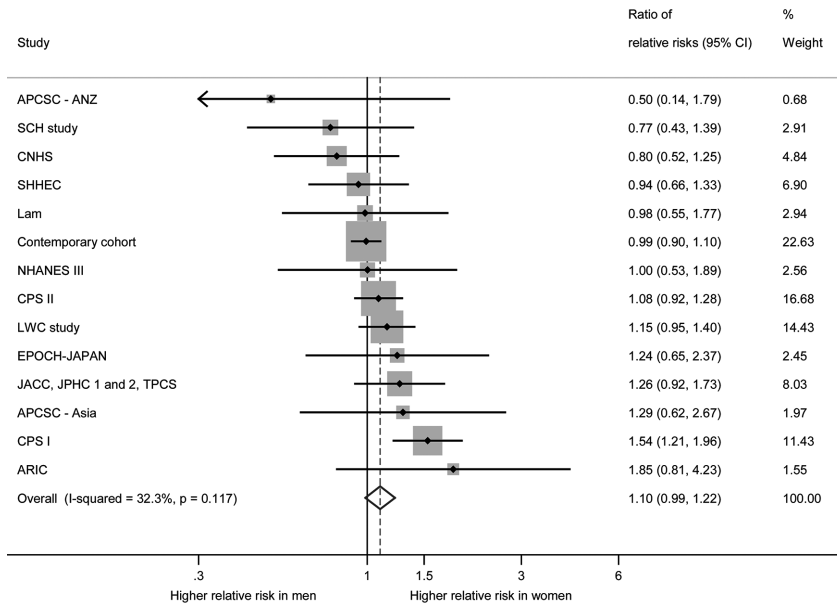


Figure 4. Women-to-men ratio of relative risks of stroke associated with former smoking vs never smoking by study. Lines, and width of the summary diamond, show 95% confidence intervals (CIs). Boxes are drawn in proportion to study weights. ANZ indicates Australia and New-Zealand; APCSC, Asia Pacific Cohort Studies Collaboration; ARIC, Atherosclerosis Risk in Communities study; CNHS, China National Hypertension Survey; CPS, Cancer Prevention Study; EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; JACC, Japan Collaborative Cohort; JPHC study, Japan Public Health Center-based prospective study; LWC, Leisure World Cohort; NHANES, National Health and Nutrition Examination Survey; SCH, Singapore Chinese Health; SHHEC, Scottish Heart Health Extended Cohort study; and TPCS, Three-Prefecture Cohort Study.

smokers of both sexes have a much lower risk of stroke than do current smokers, with no evidence to indicate that the benefits of smoking cessation differ by sex. The consistency in the similarity of the strength of the association between smoking and stroke risk in women and men was apparent in the majority of the sensitivity analyses that were performed. For hemorrhagic stroke, however, smoking conferred a greater relative hazard in women than in men. It is possible that these findings are an artifact of the data because of the large number of comparisons performed, but we are unable to preclude the possibility of a sex difference for this major stroke subtype entirely.

It is, however, possible that the small sex difference in smoking-related risk of stroke—10% excess risk to the detriment of women—that was observed in Western but not Asian populations is real and potentially an underestimate of the true difference for several reasons. First, compared with men, the smoking epidemic among women is relatively immature in several regions of the world. This is especially true in parts of Asia where the prevalence of smoking in women is typically <10%.³⁸ As the health effects of smoking in a population only become fully apparent about a half-century after a significant proportion of younger adults have adopted the habit, it will be some years before the full impact of smoking on stroke risk becomes apparent in women. Despite this, most of the Western studies reported higher, not lower, RRs of stroke among women who smoked compared with male smokers.^{39,40} Second, the number of cigarettes smoked per day and the percentage of heavy smokers are generally higher in men compared with women. For example, data from the US 2004 National Health Interview Survey reported that the mean consumption of cigarettes per day was 18.1 in men and 15.3 in women.⁴¹ Similarly, in APCSC, women in both Asia and Australia and New Zealand smoked fewer cigarettes than their male equivalents: 10 versus 15 cigarettes per day in Asia and 16 versus 18 cigarettes per day in Australia and New-Zealand.¹³ Hence, if smoking confers the same hazard

in women as it does in men, one would expect male smokers to have a greater RR of stroke compared with female smokers because of their greater cumulative exposure to smoking. This hypothesis is not supported by the findings of this meta-analysis. Instead, this analysis suggests that the effects of heavy smoking, defined as smoking >20 cigarettes per day, may be substantially greater in women than in men. Finally, previous studies have reported significant under-reporting of smoking habit, particularly in women from some ethnic groups,^{42,43} when smoking status was assessed by measuring serum cotinine levels, a specific biomarker of nicotine absorption.⁴⁴ Under-reporting of smoking status would have resulted in misclassification of some current smokers as nonsmokers (more so in women than in men), resulting in a diminution of the relationship between smoking and stroke risk, particularly in women, further underestimating the RR difference between male and female smokers.

The lack of any clear evidence of a sex difference in smoking-related risk of stroke in the main analysis is an intriguing finding, given the strong evidence that smoking confers a greater excess risk of CHD in women compared with men. These data would suggest that the sex difference in smoking-related risk of CHD is unlikely to be mediated by differences in smoking-related behavior (such as greater degree of smoke inhalation by women) because the sex effect would also be shown for stroke. Instead, it is plausible that some of the pathways mediating the relationship between smoking and coronary risk are more susceptible to the antioestrogenic effect of smoking than those governing the relationship between smoking and stroke risk. For example, reduced estrogen levels in smokers are considered to impact negatively on components of the lipid profile (a major risk factor for CHD and, to a lesser extent, for stroke) causing elevations in total cholesterol and triglycerides while lowering levels of high-density lipoprotein cholesterol.⁴⁵

This meta-analysis provides the largest and most diverse prospective evaluation of the sex differential effects of

smoking on risk of stroke. We obtained data from the published literature that was extended with individual participant data from 4 established population-based databases to which we had direct access. Our findings were robust for an extensive series of sensitivity analyses, and there was neither visual nor statistical evidence of publication bias present. Limitations of our study include the lack of standardization in study design and duration, end point definition (all strokes or fatal only), study populations, classification of the reference group of smoking, and amount of adjustment for confounders within studies from which we included published results. Some studies defined nonsmokers as those who had never smoked, whereas other studies defined them as those who were currently not smoking, without taking into consideration their smoking history. All these sources of between-study heterogeneity are likely to have resulted in random misclassification and thus in conservative estimates of the RRR. We performed stratified analyses based on level adjustment for confounders, smoking classification, and end point definition and found no effect of any of these study characteristics on our primary results. In addition, the meta-regression analyses did not provide any evidence of a substantial effect of differences in study duration, amount of women who smoke, or women-to-men smoke ratio on our results. Another limitation was the paucity of studies that reported on the duration of smoking, which did not allow us to perform more in-depth analyses on the potential sex differential effect of duration of smoking on stroke risk. Finally, because information on menopausal status and use of hormone replacement therapy were not available, we were unable to evaluate whether they had any modifying effect on the relationship between smoking and risk of stroke in women.

Conclusions

Cigarette smoking is a major and modifiable risk factor for stroke, where it confers a similar hazard in women as in men. Similarly, the benefits of smoking cessation on future risk of stroke are the same in both sexes. Tobacco control policies that target both smoking initiation and cessation should be a mainstay of stroke primary prevention programs, particularly in low- and middle-income countries, which shoulder the greatest dual burden of tobacco exposure and stroke.

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Disclosures

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that Drs Peters, Huxley, and Woodward have no nonfinancial interests that may be relevant to the submitted work. Dr Peters collected the data, performed the analysis, and drafted the article; Dr Huxley interpreted the data and drafted the article; Dr Woodward supervised the statistical analysis, interpreted the data, and drafted the article. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of data analysis. Ethics approval was not required for this review.

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