Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies

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Summary

Background Prevalence of smoking is increasing in women in some populations and is a risk factor for coronary heart disease. Whether smoking confers the same excess risk of coronary heart disease for women as it does for men is unknown. Therefore, we aimed to estimate the effect of smoking on coronary heart disease in women compared with men after accounting for sex differences in other major risk factors.

Methods We undertook a systematic review and meta-analysis of prospective cohort studies published between Jan 1, 1966, and Dec 31, 2010, from four online databases. We selected cohort studies that were stratified by sex with measures of relative risk (RR), and associated variability, for coronary heart disease and current smoking compared with not smoking. We pooled data with a random-effects model with inverse variance weighting, and estimated RR ratios (RRRs) between men and women.

Findings We reviewed 8005 abstracts and included 26 articles with data for 3·91 million individuals and 67·075 coronary heart disease events from 86 prospective trials. In 75 cohorts (2·4 million participants) that adjusted for cardiovascular risk factors other than coronary heart disease, the pooled adjusted female-to-male RRR of smoking compared with not smoking for coronary heart disease was 1·25 (95% CI 1·12–1·39, p=0·0001). This outcome was unchanged after adjustment for publication bias and there was no evidence of important between-study heterogeneity (p=0·21). The RRR increased by 2% for every additional year of study follow-up (p=0·03). In pooled data from 53 studies, there was no evidence of a sex difference in the RR between participants who had previously smoked compared with those who never had (RRR 0·96, 95% CI 0·86–1·08, p=0·53).

Interpretation Whether mechanisms underlying the sex difference in risk of coronary heart disease are biological or related to differences in smoking behaviour between men and women is unclear. Tobacco-control programmes should consider women, particularly in those countries where smoking among young women is increasing in prevalence.

Introduction Worldwide, there are 1·1 billion smokers, of whom a fifth are women. Every year, more than 5 million deaths occur that are directly attributed to tobacco, with 1·5 million of these deaths occurring in women. These figures are projected to increase to 8 million female deaths by 2030 if patterns of smoking persist. However, these estimates are based on two assumptions: first, that the male-to-female smoking ratio persists, which is an unlikely scenario because of the reported increased uptake of smoking in young women compared with young men in some countries; and second, that smoking affects men and women equally, which might not be true for all diseases. For example, women who smoke have a significantly greater relative risk (RR) of lung cancer than do male smokers; and there is some debate about whether this sex difference is also true for smoking and coronary heart disease.

In 1998, Prescott and colleagues reported that women who smoked had a 50% greater coronary risk than did their male counterparts, leading them to conclude that "women may be more sensitive than men to some of the harmful effects of smoking". Estimates of the sex-specific associations between smoking and subsequent coronary heart disease from large prospective studies such as the Nurses Health Studies (all women), and the British Doctors Study (separate studies for men and women) vary, possibly because of differences in study design, classification of smoking status, and amount of adjustment for confounders. Therefore, whether any reported sex difference between these studies is real or an artifact of methodological differences cannot be established. Direct comparisons of the relation between smoking and coronary heart disease in men and women can be made through internal, within-study comparisons in studies with male and female participants, thereby reducing the role of extraneous, between-study factors. The largest meta-analysis to date to do this comparison is the Asia Pacific Cohort Studies Collaboration (APCSC), which reported evidence of a sex difference in the effect of smoking on risk of coronary heart disease (smoking was more hazardous in women than it was in men) but only for the heaviest smokers. However, this
study was restricted in geographical scope, and thus did not take account of all the available data, and did not directly estimate the relative effects of smoking between the sexes.

To establish whether women who smoke are at greater risk of coronary heart disease than are men who smoke, irrespective of smoking intensity and independent of other risk factors, we undertook a meta-analysis of prospective cohort studies (including APCSC) that reported sex-specific effects of smoking on subsequent risk of coronary heart disease.

**Methods**

**Search strategy and selection criteria**

We undertook a systematic review of the published work without language restrictions according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. We selected relevant studies published between Jan 1, 1966, and Dec 31, 2010, from CINAHL, Embase, PubMed, and Cochrane Library databases with the following combined text and MeSH heading search strategy: “smoking” OR “cigarettes” OR “tobacco” AND “coronary heart disease” OR “ischaemic heart disease” AND “cohort” AND “men” AND “women”.

We scrutinised references from these studies to identify other relevant studies.

We included studies in this review if they had published quantitative estimates (including variability) of the association between cigarette smoking and coronary heart disease in men and women, and had been adjusted at least for age. Studies were excluded if they had not reported a means of estimation of the variance around the point estimate or if they were undertaken for single-sex populations or in populations that predominantly had individuals with an underlying pathological disorder (eg, type 1 or type 2 diabetes, previous cardiovascular disease, kidney dysfunction, or cancer). When possible, data for the strength of association in former smokers was also extracted, as was information according to the amount of adjustment within a study. If possible, we also extracted baseline prevalence of smoking and average follow-up of the cohort. For two of the studies included (the Scottish Heart Health Extended Cohort Study [SHHEC] and the APCSC) we included additional unpublished results in our meta-analysis. For the first American Cancer Society Cancer Prevention Study (CPS-I), in which relevant summary statistics (for former versus never smokers) were not available from the basic source, Poisson regression was used to estimate RRs from tabulated data.

**Statistical analysis**

The primary analysis was a comparison of the sex-specific RR of coronary heart disease (fatal or non-fatal) in current smokers versus non-smokers. For every study, sex-specific RRs and 95% CIs were used to estimate the female-to-male ratio of RRs (RRR) and 95% CIs. Pooled estimates across studies were obtained by means of random-effects models, after log transformation. Studies were weighted according to an estimate of statistical size, defined as the inverse of the variance of the log RR. These RRR were computed for the comparison of current smokers with non-smokers (defined either as not current or never smokers), separately for studies with only age-adjusted estimates and then for those studies with multiple-adjusted (taking the maximum adjustment set) estimates. We did not combine the age and multiple-adjusted estimates from all 26 articles due to the heterogeneity between studies. Instead, the pooled age-adjusted estimate and the pooled multiple-adjusted estimate were reported separately.

We undertook four sensitivity analyses. First, we repeated the primary analysis with fatal coronary heart disease as the outcome. Second, we separately estimated the RRR for studies that compared current smokers with never-smokers and for studies that compared current smokers with those who were currently not smoking (but could have previously smoked). Third, we did the primary analysis within common age strata with data from those studies that had either reported age-specific sex estimates or when individual participant data were available to permit an analysis by age. Fourth, we compared the RRR for studies derived from Asia versus those from the rest of the world.

In a secondary analysis, we calculated RRR and 95% CI comparing former with never-smokers.

We estimated percentage of variability between studies attributable to between-study heterogeneity with the $I^2$ statistic and used random effects meta-regression to assess the contribution to heterogeneity of mean duration of study follow-up, the prevalence of female smoking, and the ratio of female-to-male prevalence of smoking. We
used funnel plots of the natural log of the RRR against its standard error to assess publication bias and trim and fill analyses to adjust the RRRs for the presence of publication bias.6 We did all analyses with Stata version 11.0.

**Role of the funding source**

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

We identified 8005 articles, of which 56 (1%) included data for the association between smoking and coronary heart disease. 30 (54%) of these 56 studies were excluded, mainly because they did not provide sex-stratified estimates of RR (figure 1). 26 articles with information from 86 cohort studies were eligible for inclusion.13,15,16,22–44 Two of these articles contained information about 60 cohort studies; 21 cohorts contributed to one publication from the Diverse Populations Collaboration25 (webappendix p 1) and 39 cohorts contributed to one publication from the Asia Pacific Cohort Studies Collaboration (webappendix p 2).13 One article included data from three cohorts.29 Additional data from the CPS-I study26 were sourced from tabulated data that were available online,17 whereas age-adjusted28 and multiple-adjusted44 RRs from CPS-II were sourced from

### Table 2: Data on studies contributing to RRs from the Asia Pacific Cohort Studies Collaboration and the Diverse Populations Collaboration

<table>
<thead>
<tr>
<th>Study/Author</th>
<th>Year</th>
<th>Country cohort</th>
<th>Number of participants</th>
<th>Mean age (SD) or age range, years</th>
<th>Smoking status, %</th>
<th>Maximum adjustment available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia Pacific Cohort Studies Collaboration* (2005)7</td>
<td>1961–99</td>
<td>Pool of 39 cohorts</td>
<td>560 246 (35%)</td>
<td>46–5</td>
<td>Fatal or non-fatal</td>
<td>6 8</td>
</tr>
<tr>
<td>Carnethon (2006)27</td>
<td>1967–73</td>
<td>USA (Chicago Heart Association)</td>
<td>36 987 (43 6%)</td>
<td>Male 39 7; female 39 6</td>
<td>Fatal</td>
<td>32</td>
</tr>
<tr>
<td>Collins (1996)29</td>
<td>1980</td>
<td>Fiji</td>
<td>1196 (54.7%)</td>
<td>&gt;20</td>
<td>Fatal</td>
<td>11</td>
</tr>
<tr>
<td>CPS-I (1995)13</td>
<td>1959–65</td>
<td>USA</td>
<td>1 051 018 (24 9%)</td>
<td>≥30</td>
<td>Fatal</td>
<td>6</td>
</tr>
<tr>
<td>CPS-II (2005)14</td>
<td>1982–86</td>
<td>USA</td>
<td>1 185 106 (27 6%)</td>
<td>≥30</td>
<td>Fatal</td>
<td>6</td>
</tr>
<tr>
<td>Ferrie (2009)14</td>
<td>1966–67</td>
<td>UK</td>
<td>1 916 (33 6%)</td>
<td>Male 48 (8); female 47 (7)</td>
<td>Fatal</td>
<td>40</td>
</tr>
<tr>
<td>Foderaus (1988)27</td>
<td>1967</td>
<td>Sweden (twin registry)</td>
<td>10 945 (54.8%)</td>
<td>36–81</td>
<td>Fatal</td>
<td>21</td>
</tr>
<tr>
<td>Fraser (1992)41</td>
<td>1976</td>
<td>USA (Adventist health)</td>
<td>27 658 (62 6%)</td>
<td>Male 51 6; female 53 5 (16)</td>
<td>Fatal</td>
<td>6</td>
</tr>
<tr>
<td>Honjo (2010)33</td>
<td>1980–90</td>
<td>Japan (JPHC, TPCS, JACC)</td>
<td>296 836</td>
<td>Male 54 1 (9 7); female 54 5 (9 8)</td>
<td>Fatal</td>
<td>8–10</td>
</tr>
<tr>
<td>Houterman (2003)27</td>
<td>1974–80</td>
<td>Netherlands</td>
<td>49 153 (55 5%)</td>
<td>30–54</td>
<td>Fatal</td>
<td>20</td>
</tr>
<tr>
<td>Howaza (2007)29</td>
<td>1980</td>
<td>Japan (NIPPON DATABASE)</td>
<td>891 287 (55 5%)</td>
<td>50 1 (13)</td>
<td>Fatal</td>
<td>19</td>
</tr>
<tr>
<td>Jensen (2008)27</td>
<td>1993–97</td>
<td>Denmark (Danish Diet Cancer and Health)</td>
<td>54 873 (56 6%)</td>
<td>56</td>
<td>Fatal or non-fatal</td>
<td>Median 7 7</td>
</tr>
<tr>
<td>Jousilahti (1999)30</td>
<td>1982, 1987</td>
<td>Finland</td>
<td>14 786 (52.0%)</td>
<td>25–64</td>
<td>Fatal or non-fatal</td>
<td>7–12</td>
</tr>
<tr>
<td>Joutilainen (2004)35</td>
<td>1982–84</td>
<td>Finland</td>
<td>129 635 (55.0%)</td>
<td>Male 55 5; female 56 2</td>
<td>Fatal</td>
<td>13</td>
</tr>
<tr>
<td>LaCroix (1991)27</td>
<td>1981–83</td>
<td>USA</td>
<td>71 728 (62.3%)</td>
<td>&gt;65</td>
<td>Fatal</td>
<td>5</td>
</tr>
<tr>
<td>Lam (2007)27</td>
<td>1998–2000</td>
<td>Hong Kong</td>
<td>55 165 (66.6%)</td>
<td>&gt;65</td>
<td>Fatal</td>
<td>41</td>
</tr>
</tbody>
</table>

See Online for webappendix (Continues on next page)

www.thelancet.com Published online August 11, 2011 DOI:10.1016/S0140-6736(11)60781-2 3
## Articles

<table>
<thead>
<tr>
<th>Baseline study dates</th>
<th>Country cohort details</th>
<th>Participants (% female)</th>
<th>Mean age (SD) or age range, years</th>
<th>CHD outcome</th>
<th>Mean duration, years</th>
<th>Number of CHD events (% female)</th>
<th>Current smoker, %</th>
<th>Former smoker, %</th>
<th>Maximum adjustment available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee (2006)</td>
<td>USA (Strong Heart Study)</td>
<td>4372</td>
<td>Male 55%; female 56.6</td>
<td>Fatal or non-fatal</td>
<td>12</td>
<td>724</td>
<td>Female 29.7%; male 41.4%</td>
<td>NA</td>
<td>Age</td>
</tr>
<tr>
<td>Liu (2004)</td>
<td>China</td>
<td>30,121 (46.7%)</td>
<td>Male 47.4; female 46.3</td>
<td>Fatal or non-fatal</td>
<td>10</td>
<td>816</td>
<td>Female 4%; male 59%</td>
<td>NA</td>
<td>Age</td>
</tr>
<tr>
<td>Marin (2006)</td>
<td>Spain</td>
<td>4,124</td>
<td>Male 50.4; female 52.8 (16)</td>
<td>Fatal or non-fatal</td>
<td>5</td>
<td>155</td>
<td>Female 13%; male 34%</td>
<td>NA</td>
<td>Age</td>
</tr>
<tr>
<td>Nilsson (2006)</td>
<td>Sweden (Malmo Preventive Project)</td>
<td>32,715 (31.4%)</td>
<td>Male 43.7; female 49.7</td>
<td>Fatal or non-fatal</td>
<td>20</td>
<td>3,072 (12.9%)</td>
<td>Female 37%; male 49%</td>
<td>NA</td>
<td>Age, diabetes, BMI, hypercholesterolemia, alcohol, PA, hypertension, history of MI</td>
</tr>
<tr>
<td>Njølstad (1996)</td>
<td>Norway (Finnmark Study)</td>
<td>11,843 (48.1%)</td>
<td>43.4 (5.3)</td>
<td>Fatal or non-fatal</td>
<td>12</td>
<td>598</td>
<td>Female 43.9%; male 56.9</td>
<td>Female 16.7%; male 7.3%</td>
<td>Age</td>
</tr>
<tr>
<td>Qvist (1996)</td>
<td>Turkey</td>
<td>3,082 (51.2%)</td>
<td>Male 56.6; female 49.7</td>
<td>Fatal or non-fatal</td>
<td>5</td>
<td>304</td>
<td>Female 17.9%; male 52.2</td>
<td>Female 3.7%; male 21.0%</td>
<td>Age, BP, diabetes, TC, PA</td>
</tr>
<tr>
<td>Qvist (1996)</td>
<td>Sweden (Swedish Level of Living)</td>
<td>5,006 (52.0%)</td>
<td>Male 35–64; female 56.2</td>
<td>Fatal or non-fatal</td>
<td>10</td>
<td>264 (28.9%)</td>
<td>NA</td>
<td>NA</td>
<td>Age, obesity, hypertension, PA</td>
</tr>
<tr>
<td>Paganini-Hill (1994)</td>
<td>USA</td>
<td>12,868 (64.0%)</td>
<td>73</td>
<td>Fatal or non-fatal</td>
<td>10</td>
<td>2,180 (28.9%)</td>
<td>Female 58%; male 71%</td>
<td>NA</td>
<td>Age</td>
</tr>
<tr>
<td>Schohr (2002)</td>
<td>Denmark (Copenhagen City Heart)</td>
<td>12,077 (53.6%)</td>
<td>Male 54 (11); female 54 (10)</td>
<td>Fatal or non-fatal</td>
<td>21</td>
<td>2,180 (28.9%)</td>
<td>Female 58%; male 71%</td>
<td>NA</td>
<td>Age, TC, PA, alcohol, education, income, BMI, diabetes, hypertension</td>
</tr>
<tr>
<td>Shankar (2008)</td>
<td>Singapore</td>
<td>61,320 (26.3%)</td>
<td>Male 56.6; female 56.2</td>
<td>Fatal or non-fatal</td>
<td>16</td>
<td>2,008 (37.1%)</td>
<td>Female 38%; male 38%</td>
<td>Female 21%; male 33%</td>
<td>Age, TC, HDL cholesterol, SBP, diabetes</td>
</tr>
<tr>
<td>Wen (2004)</td>
<td>Taiwan</td>
<td>86,580 (38.7%)</td>
<td>Male 35–44; female 45</td>
<td>Fatal or non-fatal</td>
<td>16</td>
<td>2,008 (37.1%)</td>
<td>Female 38%; male 38%</td>
<td>Female 21%; male 33%</td>
<td>Age, TC, HDL cholesterol, SBP, diabetes</td>
</tr>
<tr>
<td>Woodward (2007)</td>
<td>Scotland (SHHEC)</td>
<td>13,297 (50.8%)</td>
<td>Male 30–74</td>
<td>Fatal or non-fatal</td>
<td>16</td>
<td>2,008 (37.1%)</td>
<td>Female 38%; male 38%</td>
<td>Female 21%; male 33%</td>
<td>Age, TC, HDL cholesterol, SBP, diabetes</td>
</tr>
</tbody>
</table>

For some studies with more than one adjustment, age-adjusted results were also available (see webappendix p 5). Three studies contributed data only to the secondary analysis that examined the relation between former smokers compared with non-smokers. CHD=coronary heart disease. TC=total cholesterol. SBP=systolic blood pressure. BMI=body-mass index. NA=information not available from published reports. CPS-I=American Cancer Society Prevention Study-I. CPS-II=American Cancer Society Prevention Study-II. PA=physical activity. JPHC=Japan Public Health Center-Based Prospective. TPCS=Three-Prefecture Cohort Study. JACC=Japan Collaborative Cohort Collaboration. TG=triglycerides. MI=myocardial infarction. SHHEC=Scottish Heart Health Extended Cohort study. For more details see webappendix p 2. For more details see webappendix p 1.

### Table: Characteristics of included studies

Separate articles. Three other articles with information for the secondary analysis were identified from our searching of citations. 64,65,66 Overall, data for 3,912,809 individuals were available for the primary analysis, in whom there were at least 67,075 fatal and non-fatal coronary heart disease events (three of the included studies of 28,106 individuals did not report the number of coronary heart disease events and therefore the actual number of events was unable to be precisely determined (table and webappendix p 1). Mean duration of follow-up varied from 5 years to 40 years. 39 cohorts were from Asia (24% of individuals), 22 from the USA (65%), 16 from Europe (8%), and nine from Australia, New Zealand, and the Pacific islands (3%). The two American Cancer Society studies had 57% of all individuals and 42% of all coronary heart disease events.

21 papers reported the sex-specific prevalence of smoking, which varied substantially by study and sex. The prevalence of smoking was 2–71% in men and 1–44% in women. In all but two studies, the prevalence of smoking was higher in men than it was in women, particularly in Asia, where typically less than 10% of women were smokers compared with more than 50% of men. Smoking cessation was also higher in men (10–40%) than it was in women (2–21%; table).

13 articles with data for 54 cohort studies for 3,349,001 (86%) individuals and at least 43,606 (63%) events (three studies did not report the number of coronary heart disease events) reported age-adjusted RR estimates for fatal and non-fatal coronary heart disease associated with smoking (webappendix p 5). The age-adjusted pooled RR (female to male) was 1.11 (95% CI 0.99–1.26, p=0.06; webappendix p 6). There was significant heterogeneity between the studies (I²=68–0%, p<0.0001). Visual inspection of the funnel plot (webappendix p 7) suggests that there was some publication bias, adjustment for which had marginal effect on the age-adjusted estimate (RRR 1.10, 95% CI 0.99–1.24, p=0.08).

17 reports with information from 75 cohort studies with data for 240,9955 (62%) individuals and 43,995 (66%) coronary heart disease events reported estimates of the
The pooled RRR (female to male) increased by 2% for every extra year of study follow-up (RRR 1.02, 95% CI 1.002–1.03, p=0.03; webappendix p 10). There was no evidence of any difference in the RRR according to the percentage of female smokers (p=0.49) or the ratio of female-to-male smokers in the cohorts (p=0.42). Neither was there evidence that the association differed by region (p=0.63); the multiple adjusted RRR (female to male) for studies undertaken in the Asia-Pacific region was 1.41 (95% CI 0.89–2.23) compared with 1.25 (1.12–1.39) for those undertaken in Europe and North America.

We examined the association between smoking and coronary heart disease in current smokers versus non-smokers across consecutive age-groups from 30 years to 80 years or older with data from CPS-II,24 and new analyses from APCSC13 and the SHHEC15 cohorts. We obtained data for 16 327 coronary heart disease events (24.3% of the total number of events). In all age groups with the exception of the youngest (30–44 years), the effect of smoking on risk of coronary heart disease was greater in women than it was in men.
men although the difference was only significant for the group aged 60–69 years. There was no clear evidence that the sex differential was either attenuated or strengthened with increasing age (webappendix p 11).

13 articles with data from 53 cohort studies reported the risk of coronary heart disease in former smokers compared with never smokers (webappendix pp 3 and 12). In eight studies, the RRR were below unity (suggesting an increased beneficial effect of smoking cessation in men compared with women), whereas in the remaining seven studies the reverse pattern was reported. There was no statistical evidence that the beneficial effects of quitting smoking on subsequent risk of coronary heart disease differed between men and women (RRR 0·96, 95% CI 0·86–1·08, p=0·53 [I²=28·1%, p=0·15]; figure 3).

Adjustment for publication bias did not change outcomes (0·95, 0·84–1·07, p=0·41; webappendix p 13).

Figure 3: Female-to-male relative risk ratios for coronary heart disease, ex-smoking compared with never-smoking
*Age adjusted. All other studies are multiple-adjusted (see table 1). For this analysis, 15 multiple-adjusted or age-adjusted estimates from 13 articles were pooled; APCSC provided separate estimates for cohorts from Asia and ANZ and Carnethon reported results for blacks and white. Box sizes are in proportion to study weights. APCSC=Asia Pacific Cohort Studies Collaboration. CPS=Cancer Prevention Study.

Discussion
Cigarette smoking is one of the main causes of coronary heart disease worldwide and will remain so as populations that have so far been relatively unscathed by the smoking epidemic begin to smoke to a degree previously noted only in high-income countries. This expectation is especially true for young women in whom the popularity of smoking, particularly in some low-income and middle-income countries, might be on the rise.4 The effects of this rise are particularly concerning as evidence from our review of data from more than 2·4 million people and more than 44000 coronary heart disease events suggests that, compared with nonsmokers, women who smoke have a 25% greater RR of coronary heart disease than do male smokers, independent of other cardiovascular risk factors. Furthermore, our primary analysis might have underestimated the true RR difference between the sexes for several reasons. First, compared with men, smoking is relatively infrequent in women in some regions of the world, especially in regions of Asia where the prevalence of smoking in women is typically less than 10%.48 As the health effects of smoking in a population only become fully apparent about 50 years after a substantial proportion of young adults have adopted the habit, it will be some years before the full effect of smoking on coronary heart disease risk is known in women. Nonetheless, most of the studies we identified reported higher, not lower, RRs of coronary heart disease in female smokers than in male smokers.

Second, the number of cigarettes smoked per day and the percentage of heavy smokers is generally higher in...
men than it is in women. For example, data from the US 2004 National Health Interview Survey\(^a\) reported that the mean consumption of cigarettes per day was 18.1 for men and 15.3 for women. In APCSC, women in Asia and Australia and New Zealand smoked fewer cigarettes than did their male equivalents (10 vs 15 cigarettes per day in Asia and 16 vs 18 cigarettes per day in Australia and New Zealand).\(^{13}\) Consequently, if the risks were equivalent then male smokers should have a greater RR of coronary heart disease than should female smokers, which is contrary to the findings of our analysis.

Finally, previous studies have reported striking discrepancies, especially in women from some ethnic groups, between self-reported smoking habits and serum cotinine concentrations—a specific biomarker of nicotine absorption—suggesting that more women than men underreport their smoking habit.\(^{16}\) Underreporting of smoking status would have resulted in misclassification of some current smokers as non-smokers (more so in women than in men), resulting in an attenuation of the magnitude of the relationship between smoking and coronary heart disease, particularly in women, and further underestimating the RR difference between male and female smokers.

Duration of smoking is an important determinant of smoking-related coronary heart disease risk, and might thus have an effect on the sex ratio of RRs. Although direct examination of the effect of duration of smoking was not possible in this meta-analysis, the length of study follow-up was used as a proxy measure. The finding that, among smokers, the excess risk of coronary heart disease in women compared with men increases by 2% for every extra year of study follow-up lends support to the idea of a pathophysiological basis for the sex difference. For example, women might extract a greater quantity of carcinogens and other toxic agents from the same number of cigarettes than men.\(^{11}\) This occurrence could explain why women who smoke have double the risk of lung cancer compared with their male counterparts.\(^7\) Excess risk of coronary heart disease in female smokers might be an artifact of the data due to competing risks: men who smoke might die from some other smoking-related disease such as lung cancer before they have the chance to develop coronary heart disease. This effect could be especially relevant to Asian cohorts, in which men have been smoking for much longer and at a higher intensity than have women. However, in several cohorts from the USA and high-income countries in Europe where the maturity of the smoking epidemic is comparable in men and women, the sex-risk differential was still apparent. Therefore, the underlying mechanisms by which smoking might be more hazardous in female smokers are unclear.

Previous studies suggested that disease associations with risk factors are strongest in the youngest age groups. For example, the International Studies of Infarct Survival reported that at 30–49 years of age the rates of myocardial infarction in smokers were about five times those in non-smokers whereas at ages 50–59 years they were only three times those in non-smokers.\(^{17}\) To examine whether this finding would extend to age-specific differences in sex RRR we examined this issue among the three cohorts with age-specific data available across common age ranges. However, our analysis did not provide clear evidence of either systematic strengthening or attenuation of the sex ratio with age.

The main strengths of this meta-analysis were its size and diversity of study populations. The consistency in study findings, combined with no evidence of important publication bias, supports the robustness of the study findings. There are, however, some limitations of this meta-analysis, in addition to the lack of standardisation for dose and duration of smoking. We were unable to adjust for the use of oral contraceptives, which are associated with substantially increased risk of coronary heart disease in women who smoke. Rates of use of oral contraceptives vary considerably by country, and tend to be much higher in high-income countries than they are in low-income and middle-income countries in Asia.\(^{11}\) Hence, given the low use of oral contraceptives in Asian women, their use is unlikely to explain the higher coronary heart disease risks noted in female smokers than in male smokers from the Asian cohorts we analysed. Furthermore, use of oral contraceptives in women who smoke has also been reported to be significantly lower than it is in non-smoking women (26.9% vs 34.6%).\(^{14}\) suggesting that their use is unlikely to have been a major source of confounding.

A further limitation of our findings was the inconsistency between studies in how non-smokers were defined. Some studies defined non-smokers as people who had never smoked whereas others defined them as not-current smokers (implying that at some point they had smoked but had quit). However, the results from our sensitivity analysis suggested that the results did not differ significantly depending on how non-smokers were classified. Furthermore, any error in interpretation of our primary analysis will be to underestimate the true excess risk incurred by smoking in women (because the RRR was reduced in those studies with non-smoking as the reference). Another limitation was the lack of individual participant data, which precluded the undertaking of more in-depth sensitivity analyses than were reported here. Instead, we used between-study meta-regressions, when possible.

Thus, after allowing for classic cardiovascular risk factors, women had a significant 23% increased risk for coronary heart disease conferred by cigarette smoking compared with men. However, the precise mechanisms for this difference is unclear. Clinically, physicians and health professionals should be encouraged to increase their efforts at promotion of smoking cessation in all individuals. Present trends in female smoking, and this report, suggest that inclusion of a female perspective in tobacco-control policies is crucial.
Contributors
RRH and MW contributed equally to the design, research, analysis, and presentation of this report.

Conflicts of interest
We declare that we have no conflicts of interest.

References


