Review

Is There any Gender Difference for Smoking Persistence or Relapse Following Diagnosis or Hospitalization for Coronary Heart Disease? Evidence From a Systematic Review and Meta-Analysis

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Abstract

Introduction: Persistent smoking in patients diagnosed with coronary heart disease (CHD) has a significant effect on morbidity and mortality. Although there has been considerable debate around gender differences in smoking cessation, conclusive evidence on how gender impacts rates of smoking cessation and/or relapse following CHD diagnosis is lacking.

Aims and Methods: Our aim was to test the hypothesis that female smokers with CHD were more likely to persist in smoking or relapse post-diagnosis or hospitalization than male smokers. We searched PubMed and Web of Science databases for studies published in the last 10 years. Meta-analyses were conducted using a random effects model.

Results: Sixteen studies met the inclusion criteria. The aggregated sample size was 36,591, 20,617 (56%) were smokers of which 2,564 (12%) were female. Meta-analyses of eight studies where smoking prevalence could be measured, showed that females were less likely to be smokers at baseline than males (OR = 0.30, 95% CI = 0.13 to 0.70). Overall, one in two (47%) smokers persisted in smoking/relapsed following a diagnosis or hospitalization for CHD; but there was no gender difference in the rate of persistent smoking/relapse (OR = 1.07, 95% CI = 0.95 to 1.21).

Conclusions: Female smokers with CHD were relatively uncommon in the included study populations. However, the rate of persistent smoking/relapse was high in both female and male smokers following a diagnosis or hospitalization for CHD. Therefore similar, sustained smoking cessation efforts are warranted for both genders.
Implications: There was no gender difference for persistent smoking/relapse following a diagnosis or hospitalization for CHD, but the rate was high in both female and male smokers. Therefore, similar, sustained smoking cessation efforts are warranted for both genders.

Introduction

Coronary heart disease (CHD) is the leading cause of death worldwide and smoking is one of the main modifiable risk factors. CHD includes acute coronary syndrome, which incorporates myocardial infarction (MI) and unstable angina, as well as chronic conditions such as stable angina and chronic ischemic heart disease. Within 5 years of first MI more than one in three people die, more than one in five have a recurrent event, and more than one in 10 develop heart failure. In 2013, CHD accounted for over 8 million deaths worldwide, and was the largest cause of death.

The association between smoking and CHD—as well as cancer and other diseases—is well established; it is estimated that globally 12% of CHD deaths are attributable to tobacco, and in the US tobacco smoking and exposure to secondhand smoke are responsible for almost one-third of CHD deaths. Smoking has been identified as one of the most important modifiable risk factors for cardiovascular morbidity and mortality and is consistently used in the assessment of cardiovascular risk. There is a concern that the disease risk associated with smoking may be even greater for females than for males. Data from the United Kingdom showed that the relative risk of death from CHD in females who smoked was more than four times that of females who had never smoked. Furthermore, a recent systematic review and meta-analysis found that females who smoked had a 25% greater relative risk of CHD than male smokers. Although smoking cessation is a well-established public health priority, and rates of smoking are in decline in developed countries, smoking amongst females worldwide has been predicted to double in developing countries and tobacco use continues to be the leading cause of preventable death.

Whilst life-saving secondary prevention interventions exist for people diagnosed with CHD, the benefits achieved from these treatments is lower in patients who smoke. Smoking cessation in patients diagnosed with CHD significantly reduces further cardiac morbidity and mortality. Conversely, continued smoking has been associated with progression of CHD and re-stenosis following coronary interventions. In spite of this, many CHD patients persist in smoking or relapse post-discharge from hospital. Smoking cessation and relapse are recognized in the literature as a complex set of behaviors, influenced by socioeconomic factors, depression and anxiety, physical and psychological dependence, weight gain concerns and home/work environment as well as physiological attributes.

Literature on tobacco use and smoking cessation interventions suggests that differences exist between females and males who smoke. For example, research has considered the role of sex hormones and the menstrual cycle in relation to gender differences in smoking behavior. Consequently, there has been some speculation and debate regarding whether females have more difficulty in quitting smoking than males or are more vulnerable to relapse. Gender differences in the experience of smoking cessation and relapse in patients with CHD have implications for the design and implementation of smoking cessation interventions. To date there has been no published systematic review focusing on gender differences in relapse in the CHD population. Therefore, this study aims to test the hypothesis that female smokers are more likely to persist in smoking or relapse than males following a diagnosis or hospitalization for CHD.

Methods

Literature Search Strategy

We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline for systematic reviews and meta-analysis. Predetermined search criteria were used to extract relevant studies published in peer reviewed, scientific literature. PubMed and Web of Science databases were searched for studies published in the last 10 years, and the final search was conducted on February 16, 2015, with no further limitations. We restricted our search to 10-year limit, because smoking prevalence and policies have changed in recent years due to progressive global implementation of the World Health Organization Framework Convention on Tobacco Control (WHO FCTC). Our intention to conduct this systematic review was to test the hypothesis within a recent period, to get an indication whether further research would be required or not on this issue. We used the following search terms: (Ischemic heart disease* OR Ischaemic heart disease* OR Cardiovascular disease* OR Cardiovascular risk* OR Myocardial ischaemia* OR Myocardial ischemia* OR Myocardial ischaemia* OR Myocardial ischaemia* OR Myocardial ischaemia* OR Acute Coronary Syndrome* OR Angina pectoris OR Unstable angina* OR Microvascular angina* OR Coronary disease* OR Coronary heart disease* OR Coronary aneurysm* OR Coronary artery disease* OR Coronary occlusion* OR Coronary stenosis* OR Coronary thrombosis* OR Coronary vasoospasm* OR Myocardial infarct* OR Myocardial stunning* OR Cardiogenic shock* OR Myocardial reperfusion injury OR Heart disease*) AND (Woman OR Women OR Female*) AND (smoking cessation OR Quit smoking OR Quit tobacco OR Smoking intervention* OR Smoking cessation relapse*)

Inclusion Criteria

The aim was to identify studies reporting smoking cessation and/or persistent smoking or relapse amongst CHD patients by gender. The initial search revealed 3599 articles from which 274 were removed as duplicates. Firstly, articles were screened for relevance by two reviewers based on titles and abstracts, and articles not relevant to the hypothesis were excluded. Remaining studies were reviewed in detail by two separate researchers to determine whether they related to CHD populations and included results (raw data or odds ratios [ORs] and confidence intervals [CIs]) of smoking cessation and/or persistence/relapse by gender. Areas of uncertainty or disagreement between the two researchers were resolved by discussion. Detailed search results are presented in Figure 1.

In total, 16 studies were selected which informed the current understanding of persistent smoking or relapse amongst females compared to males following a diagnosis or hospitalization for...
A data extraction spreadsheet was used to extract the following information: study description: author, study year, study design and population description, and (by gender) the total sample size, number of smokers at baseline, number of ceased smokers, number of persistent/relapsed smokers, OR and 95% CI for persistence/relapse by gender if available, definition of relapse and length of follow-up period.

Statistical Analyses

Statistical analyses were performed using MedCalc for Windows Version 13.3.3 (MedCalc software, Ostend, Belgium). ORs and 95% CIs for female to male smoking prevalence and female to male smoking persistence/relapse were calculated or extracted from the article. Meta-analyses were carried out using the Comprehensive Meta-Analysis package, version 2 (Biostat, Englewood, NJ) and the results for smoking persistence/relapse are summarized in chronological order of publication in a forest plot. The more conservative random effects model was utilized rather than the fixed effects approach, as differences between the included studies precluded the assumption of a common effect size. Sensitivity analyses were performed by recalculating the overall OR with each study removed from the overall sample to determine the impact of studies with large numbers and by subgroup (upper age limit of the study population, baseline diagnosis type of the study population, baseline coronary interventions of the study population, baseline smoking prevalence, definition of persistent smoking/relapse, and length of follow-up).

Critical Appraisal

Quality of the selected studies was assessed using the Cochrane Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.38

Results

Characteristics of the 16 included studies have been summarized in Supplementary Table 1. On aggregate, the sample size was 36,591, 20,617 (56%) were smokers of which 2,564 (12%) were female. The average age range of the study population of the selected studies was 51–64 years. The profile of each study population in terms of gender and smoking status at baseline is presented in Figure 2, demonstrating that the majority of CHD patients were male and that female smokers were a minority. Half of the included studies only recruited patients who were smokers at baseline,22,25,26,28,31,33,36,37 therefore, the prevalence of smoking at baseline in the aggregated sample is likely to be larger than in the general CHD population. Study populations were homogenous as they had all been diagnosed or hospitalized with CHD. Four studies were limited to MI26,28,29,34; three studies included only patients who had received a coronary intervention (Percutaneous Coronary Interventions [PCI] and/or coronary artery bypass grafting [CABG] and/or valve surgery),23,24,32 whereas others included CHD patients with or without intervention. Four studies had an upper age limit, meaning that elderly patients were excluded from the sample.32,34,35,37 Two studies were based on data from the multi-country European Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE) survey, but there was no overlap in the study populations since these articles were from separate waves of the survey.35,37 In most cases, study populations were recruited from hospitals or patient databases, with one exception which included a population sample.10

Smoking Prevalence at Baseline

Amongst the eight studies which recruited both smokers and non-smokers with CHD,21,24,27,29,30,32,34,35 the average smoking prevalence at baseline was 51% (SD ±15). Prevalence of smoking at baseline by gender is shown.
Females with CHD were significantly less likely to be smokers than males in six of the eight studies. The average rate of smoking at baseline in females was 31% (SD ±14) compared to 57% (SD ±18) in males ($P < .0001$). Subsequently, meta-analyses of all eight studies revealed that females had a 70% lower odds of being smokers at baseline than males ($OR = 0.30$, 95% CI $= 0.13$ to 0.70). The direction of effect did not differ when sensitivity analyses were conducted excluding each study in turn or by subgroup analyses (data analyses not shown).

### Persistent Smoking/Relapse

Rates of persistent smoking/relapse by gender are presented (Table 1) and ranged from 7% to 63%, with smoking relapse being lowest in the study limited to patients interviewed 90 days following CABG.29 On average, across 14 studies which provided the number of persistent/relapsed smokers as opposed to ORs and CIs, almost one in two (47% SD ±16) smokers was still smoking at follow-up. Persistent smoking/relapse was significantly higher in females in two studies,23,25 but was similar between genders in all other studies. There was no gender difference in the rate of persistent smoking/relapse in the meta-analyses of all 16 included studies ($OR = 1.07$, 95% CI $= 0.95$ to 1.21) and this result was consistent when sensitivity analyses were conducted excluding each study in turn and also when we considered the overall OR in the fixed effects model (Figure 3).

Smoking status at follow-up was invariably based on patients’ self-reporting, but follow-up periods within which persistent smoking behavior or relapse was assessed varied considerably between studies (Supplementary Table 1). Length of follow-up was summarized into five categories which showed that: three studies followed patients up to 3 months23,31,32; two up to 6 months22,32; four up to 12 months23,27,31,36; six followed patients for 1–3 years23,24,30,34,35,37; and, one study followed patients for up to 13 years.28 Relapse rates were lower in the studies which followed-up only until 3 months and higher in studies which followed-up until 12 months, but length of follow-up did not affect the direction of effect when sensitivity analyses were conducted. The rate of relapse was similar in males and females even when the results were analyzed by subgroup classified on length of follow-up category.

### Quality Level of the Selected Studies

Grading was undertaken independently by two authors. The GRADE approach was designed to be used in evaluating clinical trials/interventions being systematically reviewed and, therefore, observational studies have a default rating of “low.”38 Although upgrading and downgrading of studies can occur in some circumstances, all of the observational studies in this current review remained in the low-quality category.39 The two randomized controlled trials included in the review were also rated “low,” because they did not provide the number of persistent/relapsed smokers by gender; they provided ORs which we were able to include in the meta-analyses.

### Discussion

The key finding of this systematic review and meta-analyses was that, although female smokers formed only a small minority of the
CHD population, those still smoking at the time of diagnosis or hospitalization were just as likely as male smokers to persist in smoking or relapse following hospital discharge.

The finding that just over half of the aggregated study population were smokers, whilst considerably higher than smoking prevalence in the general population where each of the studies originated, is comparable to other studies of patients with CHD. Although the number of smokers worldwide continues to increase due to population growth, the prevalence of smoking has declined over the last 25 years so that 6% of females and 31% of males worldwide are currently estimated to smoke. However, population smoking prevalence varies considerably around the world from less than 5% to more than 40% in some countries. Smoking prevalence also varies by age group, tending to be higher amongst young people and decline with age; for example, in Australia 8% of females and 12% of males in the 65–74 age group smoke, compared with national averages of 14% and 18% respectively.

In our study we found a gender difference in the prevalence of smoking, whereby females with CHD were significantly less likely to be smokers at baseline compared to males. However, the prevalence of persistent or relapsed smoking was similar between genders.

### Table 1. Prevalence of Smoking at Baseline and Smoking Relapse by Gender

<table>
<thead>
<tr>
<th>Source</th>
<th>Smokers at baseline</th>
<th>Persistent/relapsed smokers at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males, n (%&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>Females, n (%&lt;sup&gt;b&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Kinjo et al.</td>
<td>1276 (63.1)</td>
<td>148 (26.6)</td>
</tr>
<tr>
<td>Rallidis et al.</td>
<td>607 (72.2)</td>
<td>60 (35.3)</td>
</tr>
<tr>
<td>Scholte op Reimer et al.</td>
<td>1829 (43.2)</td>
<td>415 (31.5)</td>
</tr>
<tr>
<td>Dawood et al.</td>
<td>429 (100)</td>
<td>210 (100)</td>
</tr>
<tr>
<td>Ota et al.</td>
<td>81 (100)</td>
<td>9 (100)</td>
</tr>
<tr>
<td>Pietrobon et al.</td>
<td>107 (79.9)</td>
<td>39 (56.5)</td>
</tr>
<tr>
<td>Vogiatzis et al.</td>
<td>320 (100)</td>
<td>100 (100)</td>
</tr>
<tr>
<td>Colivicchi et al.</td>
<td>1018 (100)</td>
<td>276 (100)</td>
</tr>
<tr>
<td>Gerber et al.</td>
<td>667 (100)</td>
<td>101 (100)</td>
</tr>
<tr>
<td>Planer et al.</td>
<td>119 (100)</td>
<td>30 (100)</td>
</tr>
<tr>
<td>Chen et al.</td>
<td>8185 (59.1)</td>
<td>304 (8.1)</td>
</tr>
<tr>
<td>Newsom et al.</td>
<td>286 (25.6)</td>
<td>204 (23.2)</td>
</tr>
<tr>
<td>Blum et al.</td>
<td>78 (47.3)</td>
<td>69 (33.0)</td>
</tr>
<tr>
<td>de Boer et al.</td>
<td>428 (66.2)</td>
<td>12 (3.3)</td>
</tr>
<tr>
<td>Berndt et al.</td>
<td>457 (100)</td>
<td>168 (100)</td>
</tr>
<tr>
<td>Prugger et al.</td>
<td>2166 (100)</td>
<td>419 (100)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Percentage of males in sample who were smokers at baseline; 100% where all study participants were smokers, therefore P value not applicable.

<sup>b</sup>Percentage of females in sample who were smokers at baseline; 100% where all study participants were smokers, therefore P value not applicable.

<sup>c</sup>Percentage of smokers at baseline who were persistent/relapsed smokers at follow-up.

<sup>d</sup>P value for these two studies extracted from results of multivariate analysis presented in article.

Figure 3. Forest plot showing gender differences for persistent smoking or relapse post coronary heart disease (CHD) diagnosis or hospitalization.

Abbreviations: OR = odds ratio; CI = confidence interval.
than males to be smokers at the time of diagnosis or hospitalization, which is consistent with patterns of smoking prevalence by gender in the global population as well as those found in many other CHD studies.40,41,46–48 There is a possibility that, because female smokers form such a minority of the CHD population, delivery of smoking cessation advice and intervention for females could be overlooked. This is a concern because, as foreshadowed, the risks from smoking are even greater for females than males and the dangers of relapse post-diagnosis or hospitalization for CHD are significant in terms of subsequent mortality and morbidity in both genders.8,19,23,16,42

In this meta-analysis, the rate of persistent smoking or relapse post-diagnosis or hospitalization was similar amongst females and males. This is contrary to our hypothesis which suggested that females might find it more difficult to quit smoking than males and, therefore, be more vulnerable to relapse. However, a nonsignificant relationship between relapse and gender has been noted in several other CHD studies.14,47–51 Recent population cohort studies and meta-analyses of non-CHD populations have also found that females were neither less likely to quit smoking nor less successful in their quit attempts than males.20,22 Whilst gender does not, therefore, appear to be a predictor for relapse, factors which have been found to be associated with failed quit attempts or resumption postdischarge include: low-confidence in quitting; fewer prior attempts to quit; low household income; having other smokers in the household; high nicotine dependence; low self-efficacy; severity of withdrawal symptoms; lower education level; ethnicity; behavioral and psychosocial factors.14,16,19,51–55 People who are depressed or suffer from anxiety or psychiatric disorders are known to be particularly vulnerable to relapse.14,56 Women have been shown to find smoking cessation more difficult at certain stages of the menstrual cycle; but in light of the older age of onset of CHD in women,2 it is unlikely to be a factor in smoking relapse amongst this generally post-menopausal cohort.

The relationships between clinical factors such as type of CHD diagnosis, disease severity, extent of coronary intervention and rate of relapse are interesting, though not fully understood. Whilst those relationships were outside the specific aims of this systematic review, we found that the study in which all patients underwent CABG had the highest cessation rate.25 A recent randomized controlled trial with 5-year follow-up reported that coronary revascularization reduced the number of smokers by half, which led the investigators to think about the effectiveness of smoking cessation advice at the time of revascularization.66 Whilst others have also found high rates of abstinence for CABG patients compared to those admitted for MI,43 one study noted that previous CABG appeared to be a paradoxically positive predictor of relapse.66 Perez et al.66 hypothesized that undergoing CABG might lead patients to mistakenly think their diseases were cured and be more complacent about smoking cessation. Another study found that higher cessation rates in CABG patients 1 month post-procedure were no longer apparent at 12 months, which caused the investigators to wonder whether longer hospitalization due to CABG was an influencing factor for short-term abstinence.67 It is interesting to note that the two studies included in our review in which the rate of relapse was significantly higher in females than males were those which only included patients who had received PCI with stent or underwent cardiac surgery,23,24 although rates of relapse did not differ significantly by gender in the study limited to CABG patients.26 Blum et al.24 interpreted the lower rate of cessation in females as a weakness of the intervention, suggesting that in future it should be better targeted towards females.

Hospitalization with acute coronary syndrome has been identified as a teachable moment for smoking cessation, but nevertheless—as confirmed in this review—rates of relapse are often high.57 Patients may feel greater motivation to quit following a health scare and use the period of enforced abstinence in hospital to kick-start their cessation attempt.48,68 However, the duration of hospitalization for MI can be quite short and lack of time may impede the delivery of smoking cessation support. A longer stay in hospital or longer recovery period (eg, related to more severe, multi-vessel or major artery disease, coronary interventions or CABG) has been shown to positively influence smoking cessation, possibly because it gives clinicians more time to try to motivate patients and their relatives to quit smoking.28,32,49,57

Half of the patients in our study were able to quit smoking spontaneously but the other half (47%) continued to smoke post-diagnosis or hospitalization. This is consistent with other studies which have noted 30%–60% smoking relapse rates in CHD populations.14,49,50 In our review, although rates of persistent smoking/relapse were lower in studies which had relatively short (3 months) follow-up periods, length of follow-up did not affect the direction of the effect in meta-analysis of relapse by gender, which was consistently similar in females and males. The weeks immediately following hospital discharge are often when patients are most susceptible to relapse, as they settle back into their normal routine and lifestyle.24 The follow-up periods in the included studies varied from 3 months to 13 years, and we note that both studies which found a higher rate of relapse amongst females than males had relatively long follow-up periods (>1 year).23,24 In relation to the length of follow-up, in their systematic review and meta-analysis of relapse after 1 year of abstinence, Hughes et al.59 concluded that a nonsignificant amount of relapse occurs after a year but did not report on that by gender.

High rates of persistent smoking/relapse post-diagnosis or hospitalization for CHD highlight the importance of interventions which support patients and improve smoking cessation. Although, as we have shown, the rate of persistent smoking/relapse is similar in females and males, gender differences in the experience of smoking and relapse remain important issues for an effective intervention design. For example, it has been demonstrated that females attempting to quit experience a higher impact of depression, more severe withdrawal symptoms, more fear of weight gain and have a greater reliance on social supports than males, prompting the World Health Organization Framework Convention on Tobacco Control to recommend a gendered perspective in prevention programs.17 However, evidence to date indicates that, although female specific programs do help women to stop smoking, such programs produce similar abstinence rates to nongender-specific programs.33 Attendance at cardiac rehabilitation has been shown to be effective in improving smoking cessation, nevertheless substantial proportion of attendees are known to relapse within a few weeks.23,33 Evidence also suggests that intensive, sustained interventions, involving behavioral modification counseling along with pharmacotherapy, nursing interventions and interventions addressing tempting situations, are the most effective.60–63 Multifactorial lifestyle interventions to improve modifiable risk factors, including smoking cessation, diet and physical activity, have also been shown to reduce mortality and morbidity in CHD patients.44 Few studies in our review involved a specific smoking intervention, but amongst those that did, three noted improved smoking cessation in the intervention group,22,23,28 whilst
the fourth found no additional benefit of bupropion over and above intensive nurse counseling.62 Many tools to assist in smoking cessation support have been validated for use by health care professionals, including motivational interviewing and use of the 5 As (Ask, Advise, Assess, Assist, Arrange) when addressing patient’s tobacco use.67 Motivational interviewing has been shown to improve rates of smoking cessation and nurse-led motivational interviewing has been used successfully in patients.68 The delivery of smoking cessation advice for patients post acute coronary syndrome is also recognized as being the responsibility of physicians in general practices.69 In light of the fact that smoking cessation is so important, and because admission to hospital provides patients with an impetus to quit smoking, more consistent and sustained interventions are required in order to capitalize on this opportunity to provide cessation support to both female and male smokers.62,63,67

Limitations
There was heterogeneity between studies in terms of sample populations, follow-up and interventions. However, we addressed that by using the random effects model and conducting sensitivity analyses to ensure that variances in study design did not change our overall findings. Since smoking prevalence was not the main objective of the review, we included a number of studies where all participants were smokers in the baseline. This means that our prevalence of 7% female smokers in the aggregated sample is likely to be an overestimate. We addressed that issue by analyzing prevalence in females versus males in the eight studies which also included nonsmokers.

Conclusion
Female smokers with CHD were relatively uncommon in the included study populations. The rate of persistent smoking/relapse was high in both female and male smokers following a diagnosis or hospitalization for CHD, however, there was no gender difference. Therefore, similar, sustained smoking cessation efforts are warranted for both genders.

Supplementary Material
Supplementary Table 1 can be found online at http://www.ntr.oxfordjournals.org

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Declaration of Interests
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References


