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Tobacco smoke adverse effects comparison based on gender: Meta-analysis

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ABSTRACT

Background: Several studies have suggested varying degrees of vulnerability to the detrimental effects of tobacco smoking between females and males. However, conflicting findings on sex-specific differences in the negative impact of tobacco smoking have emerged. This study conducts a comprehensive review of the available evidence to assess the adverse effects of smoking with respect to gender.

Materials and Methods: From an initial pool of 99 primary studies conducted before 2010, 26 studies were selected for inclusion in this meta-analysis. Among these, 15 were cohort studies, 4 were cross-sectional studies, 4 were case-control studies, and 2 were systematic reviews. Fixed-effect models and meta-regression were employed to derive pooled risk ratios (RR), and P-value functions were utilized to assess the consistency of the results.

Results: The pooled risk ratio for men who were current smokers, concerning all-cause mortality, was 0.954 (95% CI 0.866-1.05). For women who were current smokers, the pooled risk ratio for cardiovascular disorders was 1.2 (95% CI 1.18-1.22). Notably, female current smokers exhibited a significantly more rapid annual decline in FEV% predicted with increasing age compared to their male counterparts (as indicated by linear regression analysis: $R^2 = 0.56$; $p = 0.008$). However, the relative risk for bone-related disorders was found to be higher in male current smokers than in their female counterparts.

Conclusion: The findings of this study underscore that both males and females face an elevated risk of experiencing the adverse effects of smoking. Nonetheless, the magnitude of these effects differs based on gender. Further research is warranted to validate the outcomes of this study.

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1. Introduction

1.1. Historical perspective on tobacco smoking

The history of tobacco smoking is intricately interwoven with the evolution of global exploration. Indigenous populations in the American subcontinent and Australia had been growing, chewing, and smoking tobacco long before European explorers set foot on these lands. The act of smoking gradually spread to Europe during the 16th century, with Sir Walter Raleigh's introduction of tobacco to England

during the reign of Queen Elizabeth I. However, King James I, in the early 17th century, launched the first anti-smoking campaign, in direct opposition to Raleigh and tobacco's popularity. Parliament further acknowledged the appeal of tobacco by imposing substantial duties on it, leading to the paradoxical situation where the state both encouraged smoking for economic reasons and issued stern warnings about its associated hazards.¹

1.2. An overview of smoking prevalence

In developed countries, tobacco is responsible for 24% of male and 7% of female mortality, with some former

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socialist economies and parts of the USA seeing this rate surge to over 40%. Cigarette smoking began to rise among females after the rapid proliferation of smoking among males in the United States and Northern European countries before the 1950s.² Smoking represents a substantial and avoidable contributor to morbidity and mortality in the United Kingdom, playing a pivotal role in various diseases, including cardiovascular diseases, chronic obstructive pulmonary disease (COPD), lung cancer, and numerous other cancers, as well as peptic ulcers and other health conditions. In 2005, self-reported cigarette smoking among British adults stood at 25% for men and 23% for women. Despite recent reductions in smoking prevalence, it remains a significant public health challenge in the UK.³

Over the past 25 years, there has been a significant surge in smoking in developing countries. By 2030, it is projected that tobacco will cause ten million deaths annually, with 70% of these deaths occurring in developing countries if current smoking trends persist. This will have significant economic and public health repercussions in countries that can least afford it.⁴ Notably, a study conducted in Addis Ababa found an overall smoking prevalence of 2.9%, with 4.5% in men and 0.4% in women. While men typically exhibit higher smoking prevalence than women, this trend has been noted in other studies as well. For instance, a study in Arua, Uganda, reported an overall smoking prevalence of 21.9%, with 12.2% in women and 25.5% in men. However, smoking prevalence in Kampala, the capital city, was substantially lower at 5.3%. A study in Kenya also revealed that the rate of ever-smoking among students was 38.6% for men and 17.9% for women. It appears that Ethiopia has maintained a low smoking prevalence among its youth, consistent with reports from the 1980s and 1990s.^{5,6}

For most developing countries, evaluating tobacco-attributable mortality is challenging. Cigarette sales have surged in recent years, with male smoking prevalence exceeding 50% in many parts of the developing world, and chronic disease mortality rates already high in parts of Asia and Latin America. During the 1990s, it was estimated that there would be approximately one million deaths annually due to tobacco in the developing world. Worldwide, tobacco was believed to be responsible for an average of about three million deaths annually during the 1990s, with a range of uncertainty between two to four million.^{7,8}

1.3. Pharmacology of nicotine

Nicotine has both stimulant and depressant effects on the human body. Smokers often report increased alertness coupled with some muscle relaxation. Nicotine activates the reward system in the brain's nucleus accumbens, resulting in elevated levels of extracellular dopamine, a phenomenon observed in rats following nicotine injections. Additionally, nicotine influences other physiological systems, including

the release of endogenous opioids and glucocorticoids. Nicotine dependence has been associated with depressed mood (dysthymic disorder and affective disorder), though it remains unclear whether depression serves as a precursor to smoking or develops as a consequence of nicotine dependence. Smoking withdrawal is linked to increased depression, a factor contributing to relapse.⁹

1.4. Adverse effects of tobacco smoking

1.4.1. Total mortality

Compared to never-smokers, primary smokers demonstrated a slightly elevated risk of total mortality ($p = 0.06$). After full adjustments, a significant increase in total mortality risk was observed for primary smokers compared to never-smokers (RR = 1.44, 95% CI: 1.19, 1.74). This heightened risk applied to both cardiovascular and non-cardiovascular causes (RR = 1.49, 95% CI: 1.13, 1.96 and RR = 1.40, 95% CI: 1.08, 1.78, respectively). Notably, the risk was highest for current smokers and exhibited a dose-response relationship with the number of cigarettes smoked.¹⁰

1.4.2. Cancer

Current cigarette smokers were found to have the highest risk of total cancer, displaying a strong dose-response effect. Primary smokers also displayed a higher adjusted risk of total cancer compared to never-smokers, albeit non-significantly. Both groups demonstrated a significantly higher risk of smoking-related cancers, with risk levels approaching those seen in light cigarette smokers. The increased risk predominantly stemmed from a markedly elevated risk of lung cancer. The relative risk for smoking-related cancers was calculated at 2.67 (95% CI: 1.70, 4.26).¹⁰

1.4.3. Major cardiovascular events

Primary pipe and cigar smokers, when used as the baseline, exhibited an age-adjusted risk that was initially non-significant for major coronary heart disease (CHD) and stroke events. However, full adjustments increased their relative risk, rendering the results significant for major CHD events and marginally significant for stroke events.¹⁰

1.4.4. Effect on lung function

Cigarette smoking stands as the single most important modifiable risk factor for reduced lung function in adults. It is associated with an accelerated decline in lung function. This relationship is evident in both male and female subjects across all racial groups studied. The Beijing Respiratory Health Study, a community-based cross-sectional study in adults, offers an opportunity to delve further into gender differences regarding smoking's effects on pulmonary function. The available data from this study, alongside previously published data, were used to assess whether there

was an association between gender differences in smoking prevalence and gender differences in smoking's effects.^{11,12} Although gender differences have been explored in some studies, few have commented on variations between men and women in pulmonary function changes concerning smoking history.^{13,14} This meta-analysis aims to bridge that knowledge gap.

Studies that were included in this meta-analysis are the following

2. Materials and Methods

2.1. Search for relevant studies

The identification of primary studies concerning the adverse effects of smoking in relation to gender was conducted through a computerized literature search of PubMed/Medline and HINARI up to August 2010. Appropriate keywords, such as "adverse effects of smoking" and "gender," were employed to yield relevant results. All publications in the public domain examining the relationship between the adverse effects of smoking and gender differences were included in this review. Studies were categorized based on their design, encompassing cohort, case-control, cross-sectional, and other study types. In cases where a study yielded multiple results, each result was extracted accordingly. Adjusted risk estimates, including relative risks (RR) or odds ratios (OR), were extracted from each study. If a study did not provide adjusted results, unadjusted estimates, such as percentages, were collected.

2.2. Study selection and data abstraction

The principal objective of this study was to assess the impact of gender among current smokers concerning various diseases. To minimize methodological biases, a refined selection process was applied. Out of the ninety-nine papers published between 1994 and 2009, those that did not differentiate relative risk between males and females and studies that exclusively involved either female or male subjects (but not both) were excluded. Articles that reported combined results for both genders were also excluded.

2.3. Statistical analysis

The Risk Ratio (RR) was employed to evaluate the influence of smoking on gender in the context of specific diseases. This was calculated by dividing the relative risk for females by that for males. For studies that did not present results in the form of relative risk or odds ratio (e.g., FEV decrease), a separate analysis was conducted. The annual decline of FEV1% pred, adjusted by age, was assessed using linear regression techniques in MS Excel. Moreover, the results were aggregated based on the type of disease using statistical software, CMA version 2. In each result, the

mean age was utilized. The RR concerning the gender effect attributable to the adverse effects of smoking was presented in the form of a forest plot. Cumulative meta-analysis was conducted, calculating and graphing cumulative results at the time each study was published. Meta-regression was employed to explore the association between RR among men and women in relation to age.

3. Results

A total of 99 studies, 17 cohort, 8 cross sectional, 6 case-control, and other studies were searched and 26 of them included in the meta-analysis.

The total risk ratio was 0.8 (table 4). The pooled risk ratio with 95% confidence interval is 0.954 (0.866-1.05) (table 5). Even though the studies are done in different countries the majority of them have similar results. Five out of six studies found statistically significant positive summary RRs, while one study showed RR that was elevated, but not significant¹⁹.

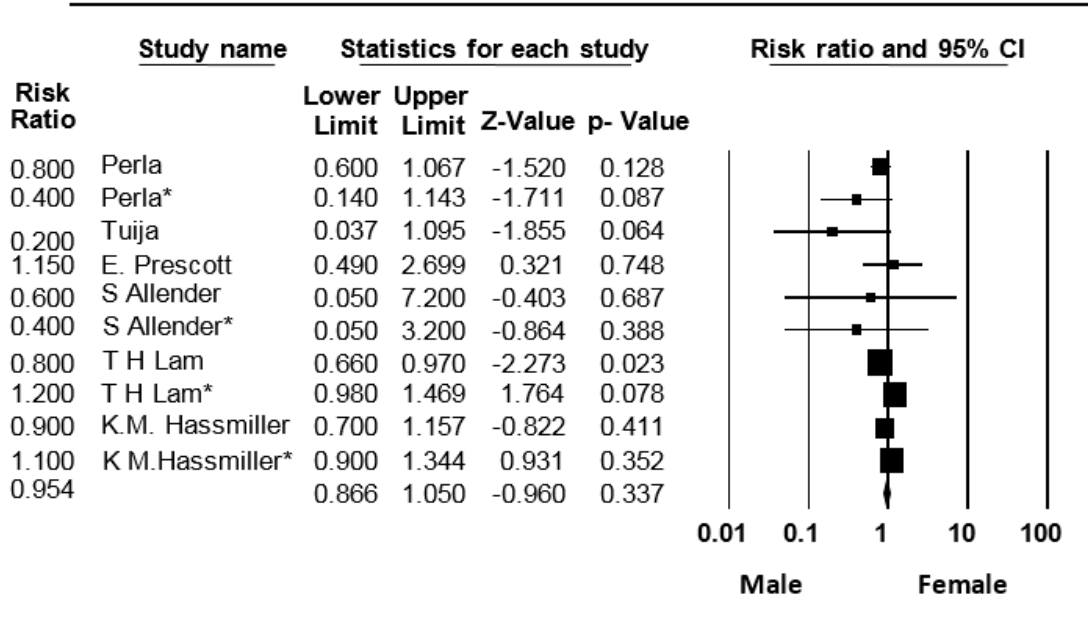
The total Risk ratio was 1.4 (table 6) and the pooled risk ratio was 1.2 (95% CI 1.18-1.22) (table 7). One study was presented with three results while two studies were found to compare men and women with two results, the rest were presented with single results. In a sensitivity analysis eliminating each study from the overall analysis, the summary RR ranged from 0.5 to 4.6 and the lower limit as well as the upper limit of the 95% CI never crossed (1.18-1.22).

ummarizes the annual decline in FEV1% pred in both men and women according to smoking status. In general, older cohorts experienced a faster decline in FEV1% pred/yr compared with younger cohorts and current smokers had a faster decline in FEV1% pred/yr compared with never smokers. In current smokers, with increasing age, women had a significantly faster decline in FEV1% pred /yr compared with men ($R^2 = 0.56$; $p = 0.008$),

The two studies indicate the effect of cigarette smoking average was 0.6 Risk Ratio.

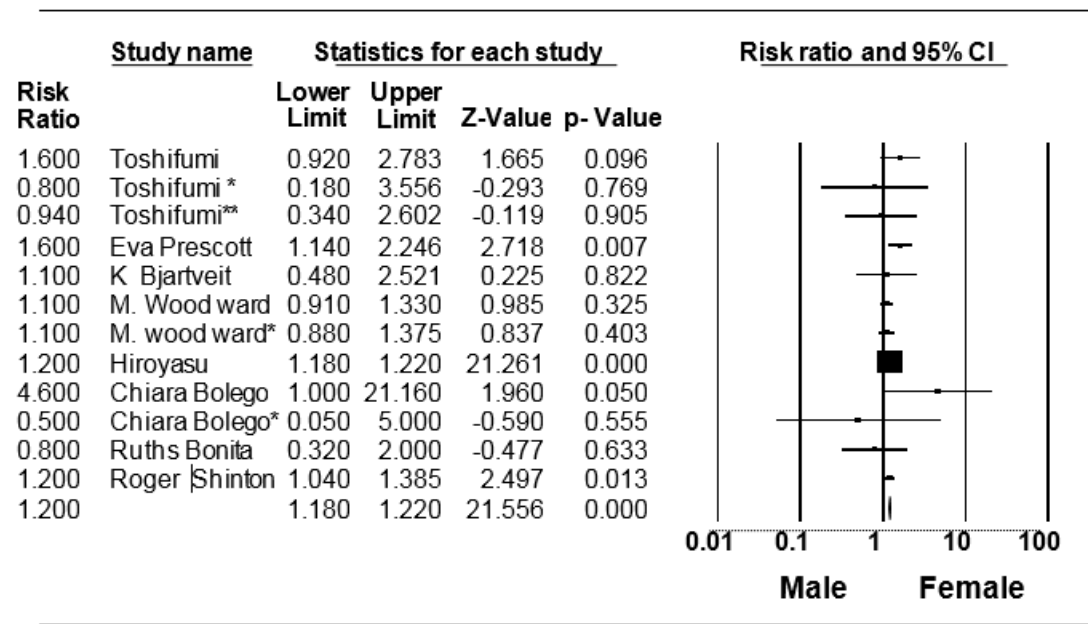
4. Discussion

In this systematic review, we observed gender-related differences in the adverse effects of smoking. Notably, the mortality rate ratio tended to be higher in male smokers than in female smokers. These findings align with studies conducted by Perla and colleagues, who suggested that the difference in smoking duration between men and women could explain the greater rate difference in smoking-related causes of death among men. This is in contrast to the findings by Prescott et al., who found higher relative risks for women in mortality due to respiratory and vascular diseases but no gender difference in mortality for smoking-related cancers, except in the case of vascular disease, especially cerebrovascular disease.^{15,19,36}



Meta-Analysis

Figure 1: The Risk Ratio of mortality and disability among current smoking men and women



Meta-Analysis

Figure 2: The risk ratio of cardiovascular disease among males and females

Table 1: Cohort studies

First name of the Author	Country	Age
Perla et al, 2001 ¹⁵	Scotland	>45
tuija martelin,2004 ¹⁶	Finland	>15
Susanne, 2000 ¹⁷	Copenhagen	-
Toshifumi Mannami,2010 ¹⁸	Japan	40-59
E.Prescott, 1997 ¹⁹	Copenhagen	44-64
K Bjartveit, 2005 ²⁰	Norway	35-49
M.Woodward, 2005 ²¹	Asia/Australia	-
Chinn et al ,2005 ²²	London	20-44 years
Rijcken et al, 1995 ²³	Netherlands.	39
Tashkin et al, 1984 ²⁴	Los Angeles	25 to 64
Sherrill et al,1996 ²⁵	Arizona	48
K. PATJA,2005 ²⁶	Finland	30-50
Hiroyasu Iso, 2004 ²⁷	Japan	40–79
John E. Connett,2002. ¹⁴	United states	35–60
James et al,2005. ²⁸		

Table 2: Cross sectional studies

First name of the Author	Country	Age
William M, 2000. ²⁹	Asians	30 -85
P Egger, 1996. ³⁰	USA	61-73
Viegi et al,2001. ³¹	Italy	20-40
X. Xu, 1994. ¹⁹	China	40–69
Langhammer, ¹⁵	Norway	≥20

Table 3: Other Studies included in the Meta analysis

First name of the Author	Type of the study	Country	Age
S Allender, 2009 ³	Systematic review	UK	
Chiara Bolego,2001 ²	Systematic review	Italy	35–52
T H Lam, 2001 ³²	Case control	Hong Kong,	3569 >70
Ruths Bonita,1999 ³³	Case control	New Zealand	35-74
Wen Qi Gan,2006 ³⁴	Systematic review		45-50
K.M. Hassmiller. ³⁵	Case control	South Africa China	≥25 35-69

Additional research by S. Allender and colleagues indicated relatively higher mortality rates and disability in males compared to females. Moreover, a study conducted in Africa by K.M. Hassmiller and colleagues revealed a relationship between smoking and 135 deaths from tuberculosis. Adjusting for age and education, it was determined that individuals of all ages who ever smoked were more likely to die from respiratory tuberculosis, with a stronger risk increase among those aged 35–69 compared to those over 70. This study also established a significant dose-response relationship in men of both age groups, where a higher number of cigarettes smoked per day correlated with a higher risk of death from respiratory tuberculosis.^{3,35}

The systematic review further illustrated that male smokers, in comparison to female smokers, experienced a higher incidence of cardiovascular complications. Research conducted by Toshifumi and colleagues supported a positive relationship between smoking and the risk of total stroke and subarachnoid hemorrhage in both men and women

after adjusting for known cardiovascular risk factors and lifestyle. The association between smoking and the risk of subarachnoid hemorrhage was particularly strong, leading to a 3.6-fold excess risk in men and a 2.7-fold excess risk in women. Additionally, men exhibited a 1.6-fold excess risk of ischemic stroke among current smokers compared to never-smokers, while women displayed a similar but statistically insignificant excess risk.¹⁸

Studies by M. Woodward and colleagues indicated that younger individuals and women had higher relative risks of cardiovascular disease (CVD) from smoking. Importantly, it was observed that Asians, predominantly Caucasian Australians, and New Zealanders exhibited a similar increase in proportional cardiovascular risk from smoking cigarettes and a comparable reduction in relative risk after quitting. Our findings, which revealed greater relative risks for coronary heart disease (CHD) from smoking among women compared to men, aligned with recent literature.²¹ However, one study from the west of Scotland showed no

Table 4: Studies that compare RR of mortality and disability among current smoking men and women

First name of the Author	Country	Study population	Study period	Age	Female RR	Male RR	Risk ratio	Adverse effect of smoking (inclusion criteria)
Perla 2001	Scotland	7045 men and 8348 women	1972-1976	53	1.41 4.73	1.83 11.1	0.8 0.4	Age- standard mortality due to other cause other than cancer Ratio RR lung cancer mortality
TuijaMartelin	Finland	5854 Number of Deaths of men and 1197 of women	1991–1993	40	5%(0.05)	28%(0.28)	0.2	proportion of deaths attributable to smoking.
E.Prescott S Allender	Copenhagen UK	6505 women and 5644 men 4338 papers were searched and only 135 paper included	1976-1998 studies, published between 1997 and 2007	54 -	2.14 8.5%(0.05) 11%(0.11)	1.86 15.4%(0.15) 27%(0.27)	1.15 0.6 0.4	Relative Risk of all cause of mortality in smoker population smoking attributable mortality
T H Lam, K.M. Hassmiller	Hong Kong South Africa China	27 507 dead cases included 3 374 urban males, 4 542 rural males, 1 598 urban females, and 2 652 rural females	(mid)December 1997 to mid/January 1999	52 70 25 52	1.62 1.68 1.5 1.6	1.92 1.41 1.7 1.4	0.8 1.2 0.9 1.1	risk ratios comparing smokers with nonsmokers for all deaths, Risk ratios of death from TB for smokers compared to non-smokers

Table 5: Studies that compare RR of Cardiovascular disease among males and females

First name of the Author	Country	Study population	Study period	Age	Female RR	Male RR	Risk ratio	Adverse effect of smoking (inclusion criteria)
Toshifumi et al	Japan	19 782 men and 21 500 women prior diagnosis of stroke	Prospective Study 1990 to 1992	50	1.98 2.70	1.27 3.60	1.6 0.8	RR of Stroke RR of subarachnoid
Eva Prescott et al 2002	Copenhagen	13,897 subjects, born after 1920	followed for 7–16 yrs	54	2.24	1.43	1.6	Hemorrhage RR of stroke RR of Myocardial infarction I
K Bjartveit et al	Norway	23 521 men and 19 201 women,	1972 to 1978	42	2.94	2.74	1.1	Adjusted RR ischemic heart disease
M. Woodward et al	Asia/Australia	analysis of 40 cohort studies			1.42	1.29	1.1	RR for stroke
M. Woodward et al	Asia/Australia				1.73	1.56	1.1	RR for CHD
Hiroyasu et al	Japan Italy New Zealand	41,782 men and 52,901 women	between 1989–1990	60 44 55 75	23.3% 3 1.66 1.56	18.7% 6 2.10 1.32	1.2 4.6 0.5 0.8 1.2	relative risks for total cardiovascular disease CHD RR of MI risk of acute stroke RR of stroke
Chiara Bolego Ruths Bonita Roger Shinton		242 women						

Table 6: Studies that compare the FEV decrease among current smoking males and females

First name of the Author	Age	Female smoker/non	Males moker/non	Defference in decrease in FEV
Viegi et al,2001	32	0.12	0.13	-0.01
Chinn et al ,2005	34	0.88	0.84	0.04
Rijcken et al, 1995	39	0.97	1.1	-0.14
Jedrychow ski et al, 1986	40	1.41	1.46	-0.05
James et al,2005	42	1.05	1.22	-0.17
Tashkin et al, 1984	46	1.97	2.15	-0.18
Sherrill et al,1996	48	0.66	0.49	0.17
Connett et al, 2003	48	1.20	1.05	0.15
X. Xu,1992	49	1.51	1.44	0.05

Table 7: Cigarette smoking and bone mineral density

First name of the Author	Country	Age	Female	Male	Female /male risk ratio	Disease
P Egger	USA	67	0.004	0.011	0.36	Decrease in BMD
Susanne	Copenhagen	53	1.36	1.59	0.85	RR of Hip fracture

difference between the sexes, which contradicted a national Scottish study of similar size³⁷. For both CHD and stroke, the greater relative risks for women compared to men at all ages may be attributed to the anti-estrogenic effect experienced by women from smoking, whereas both men and women share the thrombogenic effect.¹⁹ Ruth Bonita and colleagues confirmed a substantially increased risk of stroke in both men and women who were active cigarette smokers.³³

Tobacco smoking exerts a detrimental impact on the airways. Multiple studies have identified a strong association between tobacco smoking and reduced forced expiratory volume in one second (FEV1) in both sexes. While it is suggested that adverse smoking effects on pulmonary function are more pronounced in women than in men, one study conducted in the USA found significant gender differences in the effects of cigarette smoking only for black individuals, particularly showing that black men who smoked experienced greater smoking-related declines in FEV1 compared to black women. This discrepancy may be attributed to the cross-sectional nature of the analysis and the reliance on between-subject sources of variability, representing a potential limitation.^{11,29}

Furthermore, the present meta-analysis unveiled that female smokers, in comparison to male smokers, experienced a more rapid decline in lung function beyond the age of 45 to 50 years. This trend was evident even in female smokers who consumed a modest number of cigarettes (<15 g/day). In non-smokers or ex-smokers, there were no significant gender-related changes in FEV1% pred over time, although considerable heterogeneity existed across the studies.³⁴ These findings emphasize the importance of considering gender-related differences when assessing the impact of smoking on health outcomes.

The graph in Figure 3 illustrates the analysis of the relationship between age and gender-related differences in the annual decline in FEV1% pred. Above the origin of the graph, there is a more rapid increase in females, while below the origin, there are faster increases in males.

These data suggest that female smokers exhibit increased susceptibility to chronic obstructive pulmonary disease (COPD), particularly after the age of 45 to 50 years. Similar findings were reported by Prescott and colleagues in two independent population samples: the Copenhagen City Heart Study (CCHS) and Glostrup Population Studies. In both samples, female smokers experienced a swifter decline in lung function compared to male smokers. In the CCHS, it was estimated that female current smokers lost 7.4 ml of FEV1 per pack-year, while male current smokers lost 6.3 ml per pack-year. Notably, between 1971 and 2000 in the United States, there was a fivefold increase in the mortality rate of COPD in women, and in 2000, for the first time, more women died from COPD than men.^{19,38}

The mechanisms responsible for the heightened susceptibility of women to the adverse effects of cigarette smoke were not fully understood. However, there was a growing consensus that inflammation plays a central role in the pathobiology of COPD. This inflammatory process affects both the lung (airways and parenchyma) and the systemic circulation. The intensity of this inflammation in the airways and systemic circulation was associated with the severity of FEV1 impairment, with women more likely to demonstrate airway inflammation compared to men.³⁴

In terms of bone health, at the femoral neck, there was a reduction in bone mineral density (BMD) due to smoking. Among men, each decade of smoking was associated with a 1.1% deficit in hip bone density. In contrast, among women, the reduction was 0.4%, nearly three times lower than that found in men over the same time frame, indicating that men are at a higher risk of hip fractures than women.³⁰ Smoking exerts adverse effects on bone strength through the direct toxicity of nicotine and non-nicotine components of cigarette smoke. It also indirectly affects bone strength through decreased intestinal calcium absorption and alterations in estrogen metabolism or production.¹⁷

5. Conclusion

Based on the analysis, it is evident that all mortality cases related to smoking were consistently higher in men than in women. Moreover, males demonstrated a higher susceptibility to hip fractures and bone-related disorders than females. Female smokers exhibited a higher relative risk of cardiovascular disorders than male smokers, even after adjusting for major cardiovascular risk factors. This raises questions about whether tobacco smoke may be more detrimental to women, particularly in terms of ischemic heart disease. Furthermore, beyond the age of 45 to 50 years, female smokers appeared to experience an accelerated decline in FEV1% pred/yr compared to male smokers.

Considering the increasing incidence of smoking-related diseases in both female and male populations, there is an urgent need to promote smoking abstinence and cessation among both genders. While both males and females face a high risk of adverse effects from smoking, the magnitude of these effects varies by gender. It should be noted that this study has limitations, including the exclusion of ex-smokers and former smokers, which may affect the results of the meta-analysis. Therefore, future research with a specific focus on gender-related adverse effects of smoking is essential to validate these initial findings.

6. Source of Funding

None.

7. Conflict of Interest

None.

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