

Estimating the Direct Medical Costs of Smoking-Attributable Non-communicable Diseases in Northeastern Iran From 2015 to 2023

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Azam Abbasi^{1,2}, Amirmohammad Tajik^{3,4} , Farshad Sharifi⁵, Javad Moghri^{1,2}, Mitra Momken⁶, Zeinab Khalse⁷ and Mehdi Varmaghani^{1,2}

Abstract

Introduction: Smoking remains a significant public health issue, leading to severe non-communicable diseases (NCDs) and a considerable economic burden, particularly in low- and middle-income countries. In Iran, smoking-attributable diseases account for substantial healthcare costs. This study aims to estimate the direct medical costs of smoking-attributable NCDs in hospitals affiliated with Mashhad University of Medical Sciences from 2015 to 2023.

Methods: A descriptive-analytical study was conducted using a cross-sectional design, analyzing hospital records from 2015 to 2023. The study population included all patients aged 35 and older with smoking-attributable NCDs hospitalized during this period. The smoking-attributable fraction (SAF) was calculated using prevalence data for current and former smokers and relative risk estimates for various NCDs. Direct medical costs were extracted from the hospital information system and analyzed using Microsoft Excel 2019 and STATA 14 software.

Results: The total direct medical costs of smoking-related NCDs averaged \$10.5 million annually, with male patients accounting for 93.4% of these costs. Cardiovascular diseases were the largest cost driver, comprising 74.1% of the total expenses, followed by respiratory diseases (15.2%) and cancers (10.7%). The attributable risk for smoking-related diseases was consistently higher in men, particularly for lung cancer (76.9%) and chronic obstructive pulmonary disease (68.3%).

Conclusion: Smoking imposes a significant financial burden on the healthcare system, particularly for male patients. Targeted tobacco control interventions, such as increased taxation and public awareness campaigns, are urgently needed to reduce smoking prevalence and mitigate its economic impact on healthcare systems. Comprehensive policies could alleviate the strain on Iran's healthcare system and improve public health outcomes.

Keywords

smoking, noncommunicable diseases, cost of illness, cost analysis, Iran

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¹Social Determinants of Health Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

²Department of Management Sciences and Health Economics, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran

³Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Iran

⁴School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

⁵Elderly Health Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

⁶Department of Clinical Pharmacy, Faculty of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

⁷School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

Corresponding author:

Mehdi Varmaghani, Social Determinants of Health Research Center, Mashhad University of Medical Sciences, Mashhad, Iran; Department of Health Economics and Management Sciences, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran.

Email: mehdivarmaghani@gmail.com



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Introduction

Humans have been using tobacco for centuries, but it didn't emerge until the 19th century that cigarettes were mass-produced.¹ Since then, cigarette smoking has become a global epidemic.² Today, nearly one in three adults worldwide, or approximately 1.1 billion people, are smokers.³⁻⁵ Shockingly, around 80% of these smokers reside in low- and middle-income countries.^{6,7} The total number of smokers is projected to reach approximately 1.6 billion by 2025.⁴ As per the World Health Organization's 2024 report, these statistics reveal a pressing need for immediate action. The prevalence of current cigarette smoking was 17.5% in the United States, 13% in Canada, 11.8% in Australia, and 23% in China.⁸ In the same report, the smoking prevalence in Iran was 8.9%, in Saudi Arabia 9.7%, in Egypt 17.9%, in Turkey 27.5%, and in Thailand 19.3%.⁸

The health consequences of smoking, in addition to nicotine addiction, include the development of fatal and debilitating diseases and the risk of premature death.^{9,10} Half of the individuals who smoke long-term will eventually be killed by tobacco, with half of these deaths occurring during their productive middle age, leading to the loss of 20 to 25 years of life.¹¹ The diseases associated with smoking are well-documented and include lung cancer, cancers of other organs, ischemic heart disease, and other cardiovascular diseases, as well as respiratory diseases such as emphysema and tuberculosis.¹²⁻¹⁷ Currently, the annual death toll from tobacco use worldwide exceeds 5 million and is expected to rise to over 8 to 10 million by 2030.^{18,19} More than 80% of these deaths occur in low- and middle-income countries.²⁰ In Iran, 14% of deaths and 16.3% of all cancer deaths are attributed to cigarette smoking.²¹⁻²³ What's more alarming is that these deaths are largely preventable.

In high-income countries, healthcare costs attributable to smoking account for between 6% and 15% of total annual healthcare expenditures.²⁴⁻²⁶ In low- and middle-income countries, these percentages may not be similar due to the earlier stages of the tobacco-related disease epidemic and other qualitative differences.²⁷⁻²⁹ However, since cigarette smoking has been increasing in these countries since around 1970, these costs are of significant concern to these governments. The economic burden of smoking is not just a statistic but a call for cost-effective interventions to curb this epidemic.

Non-communicable diseases (NCDs) currently disproportionately affect low- and middle-income countries, where nearly three-quarters of deaths from NCDs (28 million deaths) occur.^{30,31} According to the World Health Organization, in Iran, 82% of deaths (304 400 people) in 2016 were due to NCDs.³² The mortality rate was 43% for cardiovascular diseases, 16% for cancers, 4% for chronic respiratory diseases, 4% for diabetes, and 15% for other NCDs.⁸ These diseases account for more than 76% of the total burden of disease. Smoking is one of the most significant risk factors associated with the development of NCDs.^{30,31}

According to a comprehensive report by the National Institute of Health Research and the Non-Communicable

Diseases Research Center, based on data from the STEP-wise survey conducted in 2021, the prevalence of current smokers in Khorasan Razavi was 7.8%, the prevalence of former smokers was 3.7%, and the average number of cigarettes smoked per day was 7.7.³³⁻³⁵ In Iran, approximately 50 billion cigarettes are consumed annually, with nearly 10 trillion rials spent on purchasing this product and two to three times this amount spent on treating related diseases.³⁶

Taking into account the detrimental and destructive effects of smoking on the country's economy and noting that prior studies have focused on only a limited range of non-communicable diseases (NCDs), this study seeks to estimate the direct medical costs related to smoking-attributable NCDs in hospitals associated with Mashhad University of Medical Sciences from 2015 to 2023.

Methods

This descriptive-analytical research was conducted as a cross-sectional analysis. It was carried out as a census, examining the records of all patients with NCDs hospitalized in the affiliated hospitals within the specified timeframe, provided their data were available in the hospital information system. The study population includes all patients with smoking-attributable NCDs who were hospitalized in the hospitals affiliated with Mashhad University of Medical Sciences from 2015 to 2023. The hospitals included in the study are Akbar, Ibn Sina, Omolbanin, Omid, Khatam Al-Anbia, Dr Sheikh, Dr Shariati, Kamiab, Hasheminejad, Montaseriyeh, Imam Reza, Ghaem, and Taleghani. All hospitals that were included in the study were affiliated with Mashhad University of Medical Sciences. These hospitals are tertiary referral centers, covering a population of 5 335 433 people. Direct medical costs are funded through basic insurance, supplementary insurance, government contributions, and out-of-pocket payments. The focus on adults aged 35 and above is justified by the fact that the onset of smoking-attributable diseases may take several decades, and the health effects of smoking are cumulative over years of exposure. Consequently, most studies on smoking-related costs concentrate on this age group.³⁷ This study, therefore, provides a comprehensive understanding of the direct medical costs of smoking-attributable NCDs and their impact on the healthcare system among this age group.

The inclusion criteria for this study were meticulously designed to be comprehensive and representative. Patients must be 35 years or older and hospitalized in one of the hospitals affiliated with Mashhad University of Medical Sciences in Mashhad city. This inclusivity, which specifically included a range of hospitals in Mashhad City, ensures the validity of our study and respects the diverse population affected by smoking-attributable NCDs. On the other hand, patients younger than 35 years old or those admitted to the hospitals of Mashhad University of Medical Sciences outside the city of Mashhad are excluded from the study.

A series of meticulous steps were undertaken to estimate the direct medical costs of smoking-attributable NCDs in hospitals affiliated with Mashhad University of Medical Sciences from 2015 to 2023. This rigorous approach, which

included determining the relative risk of mortality from smoking-related NCDs (RR_i) based on data from a reference study³⁸ and extracting the prevalence of current and former smokers in Khorasan Razavi from the Risk Factors Survey in Iran.^{28,39} The 2021 data was utilized due to the lack of significant difference between the data from 2016 and 2021. The smoking-attributable fraction (SAF_{ij}) for NCD mortality was then calculated, representing the proportion of NCD deaths that can be attributed to smoking, and it was categorized by disease and population subgroup. Subsequently, the total direct medical costs of the NCDs under study (THE_{ij}) were extracted from the hospital information system, accessed through the Vice-Chancellor for Treatment, covering the period from 2015 to 2023 for the hospitals affiliated with Mashhad University of Medical Sciences. Finally, the direct medical costs attributable to smoking-related NCDs were estimated, ensuring a thorough and reliable research process.

The attributable risk is calculated with the following formula^{37,40}:

$$\text{SAFi} = (\text{Pc} * (\text{RRic} - 1) + \text{Pf} * (\text{RRif} - 1)) / (\text{Pc} * (\text{RRic} - 1) + \text{Pf} * (\text{RRif} - 1) + 1) * 100\%$$

Where Pc is the prevalence of current smokers, Pf is the prevalence of former smokers, RR_{ic} is the relative risk of smoking-related disease i for current smokers compared to non-smokers, RR_{if} is the relative risk of smoking-related disease i for former smokers compared to non-smokers.

The direct medical costs of smoking are the costs of smoking-related diseases, which are obtained by multiplying the attributable risk by the total medical costs of smoking is calculated with the following formula³⁷:

$$\text{SAEikj} = \text{SAFij} * \text{THEikj}$$

Where SAF_{ij} is the smoking-attributable risk for disease i in population subgroup j and THE_{ikj} is the total cost of disease i with health services of type k in population subgroup j.

The tools used for data collection in this study included hospitalization bills of patients admitted to hospitals affiliated with Mashhad University of Medical Sciences, as recorded in the Hospital Information System (HIS), along with relevant articles and reports.^{8,21-23} The HIS, a comprehensive and reliable database of patient records and billing information, played a crucial role in this study, providing accurate and detailed data for our analysis. Data collection methods involved accessing the HIS to extract patient demographic details and billing information, reviewing articles to obtain the relative mortality risk for the NCDs under study, and examining related reports to gather prevalence statistics for current and former smokers. For data analysis, the extracted information was input into STATA, categorized by the diseases under study (using ICD-10 codes), prevalence data for current and former smokers by population subgroups, and the relative risk of mortality for the NCDs. The data was coded, categorized, and used to develop formulas to calculate the smoking-attributable fraction and the direct medical costs associated

with these diseases, followed by the generation of final reports for each. The software used for analysis included Microsoft Excel 2019 and STATA version 14.

Results

Demographic Characteristics

The demographic characteristics of the patients are presented in Table 1. According to these results, about 56% of all patients (221 402) are men. The average age of patients is 62.4 years, with a standard deviation of 13.1 years. The minimum age is 35, and the maximum age is 117 years. About 57% of the patients have Iranian Health insurance, about 31% have Social Security insurance, about 4% have Medical Service of the Armed Forces insurance, about 3% have other insurance, and about 5% of patients have no insurance.

Attributable Risk

The amount of attributable risk by disease, gender, and age category is calculated and listed in Table 2. Overall, males exhibited substantially higher attributable risks across all disease categories than females. For lung cancer, the risk in males averaged 76.9%, with the highest in the 65-74 age group at 82.8%. In contrast, females had a much lower average risk of 14.9%, peaking at 17.6% in the same age group. Other cancers showed a similar pattern, with males facing an average risk of 16.1% and females a notably lower risk of 0.8%. Coronary heart disease also demonstrated a stark gender disparity, with males averaging a 24.9% risk, particularly high at 34.0% in the 35-54 age group, while females had an average risk of just 2.2%. For other heart diseases, the risk in males was 17.0%, again with a peak in the 55-64 age group (21.6%), whereas females showed minimal risk across all age groups, averaging 1.0%. The trend continued with cerebrovascular diseases, where males had a 16.1% average risk, highest in the 55-64 age group (21.6%), while females had a consistently low risk, averaging 1.0%. In other vascular diseases, males averaged a 33.0% risk, with the highest being 51.7% in the 65-74 age group, while females showed a lower but still concerning

Table 1. The Demographic Characteristics of the Patients.

Demographic information		
Sex	Female	97 543 (44.1%)
	Male	123 859 (55.9%)
Insurance	Iranian health insurance	125 308 (56.6%)
	Social security insurance	68 865 (31.1%)
	Medical services of the armed forces insurance	9554 (4.3%)
	Others	6066 (2.7%)
	No insurance	11 609 (5.3%)
Supplementary insurance	YES	4753 (2.2%)
	NO	216 649 (97.8%)
Age	Minimum	35
	Maximum	117
	Average	62.4
	Standard deviation	13.1

Table 2. The Amount of Attributable Risk by Disease, Gender, and Age Group.

Diseases	Female					Male				
	35-54	55-64	65-74	≥75	Average	35-54	55-64	65-74	≥75	Average
Lung cancer	10.2%	14.4%	17.6%	17.2%	14.9%	70.2%	75.6%	82.8%	79.1%	76.9%
Other cancers ^a	0.3%	1.0%	1.0%	0.9%	0.8%	12.6%	13.7%	20.0%	18.1%	16.1%
Coronary heart disease	3.6%	2.0%	2.1%	1.2%	2.2%	34.0%	26.0%	24.3%	15.1%	24.9%
Other heart disease ^b	1.3%	1.0%	0.8%	0.7%	1.0%	18.4%	21.6%	17.8%	10.3%	17.0%
Cerebrovascular diseases	1.3%	0.9%	1.2%	0.7%	1.0%	18.4%	21.6%	16.7%	7.8%	16.1%
Other vascular diseases ^c	1.3%	0.9%	5.2%	4.3%	2.9%	18.4%	21.6%	51.7%	40.2%	33.0%
Chronic obstructive pulmonary diseases	4.8%	7.2%	26.7%	15.9%	13.7%	39.0%	71.0%	83.5%	79.5%	68.3%

^aOther heart diseases include rheumatic heart disease, pulmonary heart disease, and other forms of heart disease.

^bOther vascular diseases include atherosclerosis, aortic aneurysm, and other arterial diseases.

^cOther cardiovascular diseases are comprised of other heart disease, cerebrovascular disease, and other vascular diseases.

risk of 2.9%, peaking in those aged 75 and older at 4.3%. Chronic obstructive pulmonary disease (COPD) presented one of the highest risks for males, averaging 68.3%, with the peak at 83.5% in the 65-74 age group. Although at a lower risk, females still had a significant average of 13.7%, with the highest risk of 26.7% in the 65-74 age group.

Overall, the data indicates that the attributable risk for smoking-related chronic diseases is consistently higher in males than in females across all age groups. The highest risks were generally observed in the older age groups (65-74 and ≥75), particularly for lung cancer, other vascular diseases, coronary heart disease, and COPD (Figure 1)

Direct Medical Cost of Non-communicable Diseases Attributed to Smoking

The direct medical costs of non-communicable diseases attributed to smoking by disease and gender in the years 2015 to 2023 have been calculated and presented in Table 3 and Figure 2.

The direct medical costs attributable to smoking-related non-communicable diseases from 2015 to 2023 reveal a stark disparity between male and female patients, with males bearing the overwhelming majority of these costs. Across all disease categories, the total costs for males

consistently exceeded those for females, accounting for an average of 93.4% of the total costs, while females contributed just 6.6%. (Figure 3)

In absolute terms, the total direct medical costs for males averaged \$9.8 million annually, peaking at \$12.5 million in 2015. While considerably lower, the costs for females averaged \$0.7 million annually, peaking at \$0.9 million in 2017.

Cardiovascular diseases were the costliest category for both genders, but particularly for males, where it accounted for an average of 70.4% of their total smoking-attributable medical costs. In comparison, females spent an average of 3.7% on cardiovascular diseases. Within this category, ischemic heart disease alone constituted 50.5% of the costs for males and 2.6% for females. Respiratory diseases were the second most significant cost driver, particularly COPD, which represented 12.8% of the total costs for males and 2.4% for females. The costs for cancers also demonstrated a substantial gender gap, with males averaging 10.1% of their total costs in this category while females averaged only 0.6%.

Based on the data provided by Table 4, the cost distribution analysis for direct medical costs attributable to smoking in public hospitals from 2015 to 2023 highlights

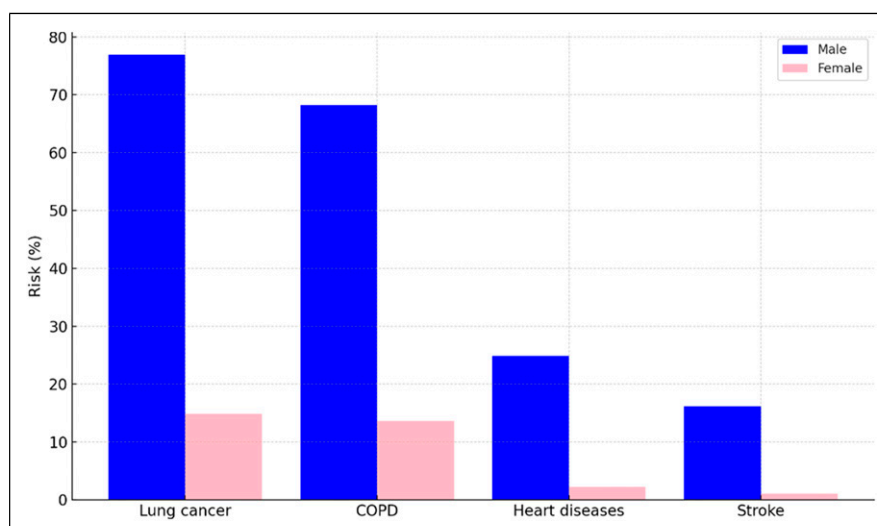
**Figure 1.** Attributable Risk by Disease and Gender.

Table 3. The Direct Medical Costs of Non-communicable Diseases Attributed to Smoking by Disease and Gender in the Years 2014 to 2023 (in Thousands of US Dollars).

Diseases names	Gender	2015	2016	2017	2018	2019	2020	2021	2022	2023	Average	Percentage
Cancers	Female	48.4	77.3	66.7	91.8	53.1	31.7	36.3	69.0	93.7	63.1	0.6%
	Male	983.9	1380.8	1312.7	1237.1	893.8	470.2	741.6	1109.4	1434.3	1062.6	10.1%
Tracheal, bronchus, and lung	Female	33.6	58.2	50.1	73.7	42.0	25.4	25.5	55.3	78.9	49.2	0.5%
	Male	442.9	667.6	694.7	579.4	449.5	171.6	310.0	518.4	852.2	520.7	5.0%
Lip, pharynx, and oral cavity	Female	1.0	1.3	1.0	1.4	0.7	0.4	0.7	1.3	1.0	1.0	0.0%
	Male	39.9	35.0	34.1	28.1	21.3	11.7	15.9	28.3	32.7	27.4	0.3%
Esophageal	Female	4.5	5.6	5.0	5.0	2.4	1.2	2.7	3.4	3.1	3.6	0.0%
	Male	79.6	126.3	113.7	94.0	66.1	41.6	67.1	80.7	70.9	82.2	0.8%
Stomach	Female	3.7	5.2	4.9	4.6	2.5	1.7	2.4	3.5	4.2	3.6	0.0%
	Male	205.4	270.5	201.1	240.0	170.5	104.2	139.6	161.8	204.9	188.7	1.8%
Pancreas	Female	1.9	2.3	1.7	2.3	1.6	0.7	1.1	1.7	2.0	1.7	0.0%
	Male	58.1	78.5	76.5	57.4	33.8	24.5	32.5	66.2	56.6	53.8	0.5%
Larynx	Female	0.3	0.2	0.5	0.4	0.8	0.1	0.3	0.3	0.4	0.4	0.0%
	Male	43.5	41.1	48.7	58.6	31.3	29.3	38.0	63.7	32.6	43.0	0.4%
Cervical	Female	0.6	0.8	0.6	0.9	0.2	0.3	0.4	0.4	0.5	0.5	0.0%
	Male	-	-	-	-	-	-	-	-	-	-	0.0%
Kidney and renal pelvis	Female	0.2	0.4	0.2	0.5	0.2	0.1	0.5	0.5	0.5	0.3	0.0%
	Male	14.6	17.7	20.4	25.9	7.1	9.1	17.8	21.6	21.4	17.3	0.2%
Bladder	Female	0.6	0.5	0.4	0.9	0.4	0.3	0.7	0.8	1.0	0.6	0.0%
	Male	50.4	46.4	56.4	62.5	51.7	35.1	73.9	99.0	84.8	62.2	0.6%
Leukemia	Female	2.0	2.8	2.2	2.2	2.4	1.5	2.0	1.8	2.2	2.1	0.0%
	Male	49.4	97.6	67.1	91.3	62.5	43.0	46.8	69.7	78.2	67.3	0.6%
Cardiovascular diseases	Female	562.5	540.3	461.3	460.8	334.7	167.5	246.9	330.1	384.0	387.6	3.7%
	Male	10 618.7	9836.5	8600.9	8811.6	6350.2	3373.9	4960.0	6396.2	7670.0	7402.0	70.4%
Ischemic heart disease	Female	400.6	361.6	314.9	334.0	236.5	116.6	169.5	218.5	262.8	268.3	2.6%
	Male	7650.9	7069.5	6090.5	6662.5	4705.4	2395.3	3480.0	4402.9	5323.8	5309.0	50.5%
Other heart diseases	Female	87.5	94.7	72.8	61.2	47.6	19.4	27.7	43.7	48.9	56.0	0.5%
	Male	1568.3	1471.3	1192.3	984.1	743.4	367.6	553.0	712.9	872.5	940.6	9.0%
Stroke	Female	39.4	62.4	66.7	59.1	43.5	27.8	33.7	48.2	52.6	48.1	0.5%
	Male	609.1	957.7	1199.1	1038.4	761.1	574.7	609.5	837.1	1038.2	847.2	8.1%
Atherosclerosis	Female	5.7	2.3	0.8	-	1.2	1.3	1.7	0.2	0.2	1.5	0.0%
	Male	89.3	27.9	1.8	2.1	11.2	2.9	7.3	7.4	1.4	16.8	0.2%
Aortic aneurysm	Female	7.1	3.5	3.4	3.0	2.9	1.5	1.7	0.2	0.2	2.6	0.0%
	Male	206.3	101.6	52.6	77.3	76.1	21.3	7.3	7.4	1.4	61.3	0.6%
Other vascular diseases	Female	22.2	15.8	2.7	3.5	3.1	0.9	12.0	16.3	15.7	10.2	0.1%
	Male	494.7	208.4	64.5	47.1	53.0	12.1	219.3	305.7	312.4	190.8	1.8%
Respiratory diseases	Female	143.7	259.3	415.7	298.9	280.2	53.3	122.0	338.1	315.8	247.5	2.4%
	Male	931.9	990.9	1807.8	1524.0	1979.4	344.3	682.8	1807.9	2038.6	1345.3	12.8%
Bronchitis, emphysema	Female	5.0	1.1	15.6	3.0	2.6	3.0	1.9	4.8	2.4	4.4	0.0%
	Male	26.3	66.5	61.9	32.4	14.1	4.0	12.2	48.6	51.0	35.2	0.3%
Chronic obstructive pulmonary diseases	Female	138.6	258.2	400.1	295.9	277.6	50.3	120.2	333.4	313.4	243.1	2.3%
	Male	905.6	924.4	1745.9	1491.6	1965.2	340.3	670.6	1759.3	1987.7	1310.1	12.5%
Total	Female	754.5	876.8	943.7	851.5	668.0	252.5	405.2	737.3	793.5	698.1	6.6%
	Male	12 534.5	12 208.2	11 721.4	11 572.8	9223.3	4188.3	6384.4	9313.5	11 142.9	9809.9	93.4%
Total	All patients	13 289.0	13 085.2	12 665.2	12 424.3	9891.4	4440.8	6789.7	10 050.7	11 936.4	10 508.1	100.0%

the significant financial burden placed on various payers, including primary insurance, out-of-pocket expenses, the government, and supplemental insurance. Primary insurance consistently covered the majority of these costs, accounting for an average of 80.1% of the total expenditure. This amounted to an average annual cost of \$8.4 million, culminating in \$11.1 million in 2016. Out-of-pocket expenses represented the second largest share, averaging

13.2% of the total cost. Patients directly contributed an average of \$1.4 million annually, reaching \$1.9 million in 2023. The government's share of the expenses was relatively smaller, averaging 5.8% annually. This amounted to an average of \$0.6 million annually, with the highest expenditure recorded in 2023 at \$0.9 million. Supplemental insurance covered the most minor portion, contributing just 1% on average. This equated to an average annual cost of

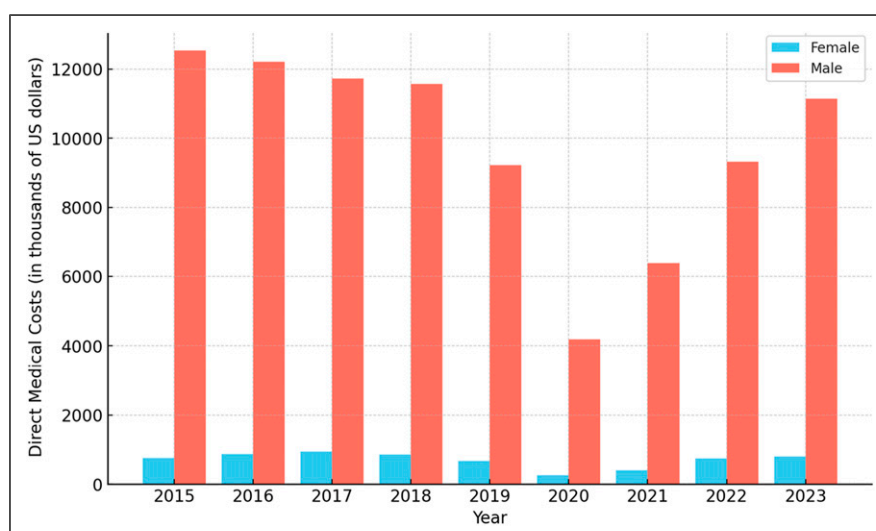


Figure 2. The Proportion of Direct Medical Costs Attributed to Smoking by Disease and Gender (2015-2023).

\$0.1 million, peaking at \$0.2 million in 2015. The total direct medical costs associated with smoking amount to an average of \$10.5 million annually.

Discussion

Our study aimed to estimate the direct medical costs of smoking-attributable non-communicable diseases (NCDs) in Mashhad University of Medical Sciences Hospitals from 2015 to 2023. Data from the Non-Communicable Diseases Risk Factors Survey Atlas for 2021 and other studies indicates that the prevalence of current smokers in Khorasan Razavi Province is approximately 10.3%.^{39,41} Additionally, according to the 2016 National Population and Housing Census data, the population of Mashhad is 3 012 090.⁴² Consequently, the number of smokers in Mashhad is estimated to be approximately 240 000 individuals. Given that the average lifetime medical cost for a smoker is approximately \$6000 higher than that for a non-smoker, and the life expectancy at birth for smokers is 69.7 years for men

and 75.6 years for women, the total annual medical cost per smoker is estimated to be 82.6 dollars.⁴³⁻⁴⁵ Thus, the total direct medical costs for smokers in Mashhad amount to approximately 19.3 million dollars.

The findings of other studies on the estimation of smoking-attributable risk in Iran and the associated costs are also aligned with our study.^{46,47} Still, they may vary in a few sections due to differences in the sources used for relative risk extraction. Moreover, the present study examined 18 diseases or groups of diseases attributable to smoking. The attributable risk for trachea, bronchus, and lung cancer in men in our study is 76.9%. This result is similar to the findings of a study by Varmaghani et al at 75.8% but differs from the results of the study of Rezaei et al at 43.5%.^{46,47} In women, the attributable risk in the present study is 14.9%, which aligns with the findings of Rezaei et al (11.5%) but differs from those of Varmaghani et al (62.3%). The lower attributable risk in women is due to the lower prevalence of current female smokers compared to male smokers. The attributable risk for ischemic heart

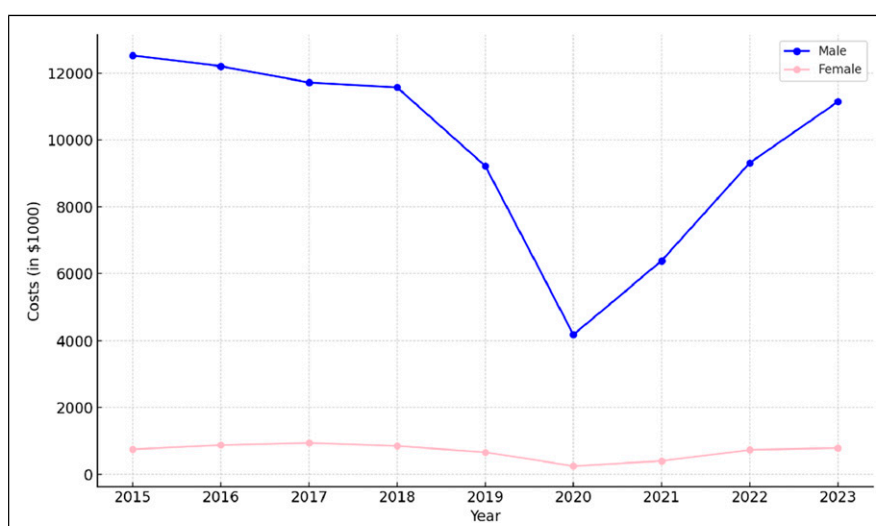


Figure 3. Trends in Costs Over Time (2015-2023).

Table 4. The Cost Distribution Analysis for Direct Medical Costs Attributable to Smoking in Public Hospitals From 2015 to 2023.

Diseases	2015	2016	2017	2018	2019	2020	2021	2022	2023	Average	Percentage
Primary insurance	10 806.0	11 050.9	10 542.5	10 103.8	7849.9	3501.6	5231.5	7660.8	8963.4	8412.3	80.1%
Out of pocket	1414.1	1230.9	1400.6	1536.3	1479.4	627.0	1103.2	1717.1	1929.0	1382.0	13.2%
Government	833.8	779.8	665.5	659.2	441.7	270.0	374.3	543.7	877.9	605.1	5.8%
Supplemental insurance	235.0	23.6	56.7	125.0	120.4	42.2	80.7	129.1	166.1	108.7	1.0%
Total	13 289.0	13 085.2	12 665.2	12 424.3	9891.4	4440.8	6789.7	10 050.7	11 936.4	10 508.1	100.0%

disease in men in our study is 24.9%. This is somewhat similar to the findings of Rezaei et al (13.8%) but differs from those of Varmaghani et al (7.4%). In women, the attributable risk in the present study is 2.2%, which is consistent with the estimate by Varmaghani et al (2.4%) but differs from that of Rezaei et al (6.1%). The attributable risk for stroke in men in our study is 16.1%, which is somewhat similar to the findings of Varmaghani et al (11.3%). In women, the risk is 1.0%, which aligns with the results of Varmaghani et al (1.6%). The attributable risk for COPD in men in our study is 68.2%, which is consistent with the findings of Varmaghani et al (67%) but differs from those of Rezaei et al (21.4%). The attributable risk in women in our study is 13.7%, which is relatively similar to the findings of Rezaei et al (9.9%) and somewhat consistent with Varmaghani et al (17.8%).

In the present study, the direct medical costs attributable to smoking for lung cancer, ischemic heart disease, stroke, and COPD in Mashhad in 2016 are estimated to be \$10.4 million. In the study by Varmaghani et al. (2016), these costs were estimated at \$2 million, which is different from the cost estimates in the present study.⁴⁶ However, some costs in our study align with the costs reported by Varmaghani et al in 2016 such as lung cancer and COPD. These results are consistent with those of Rezaei et al in 2014, who estimated the total direct medical costs for lung cancer, ischemic heart disease, and COPD in Iran at \$75.7 million (including 4% for lung cancer, 82% for ischemic heart disease, and 14% for COPD). Our estimations for these diseases in 2015 were \$254 million (including 5% for lung cancer, 84% for ischemic heart disease, and 11% for COPD).⁴⁷

Our study found that the total direct medical costs attributable to smoking for both genders in Mashhad hospitals averaged \$10.5 million annually. Significant variations are noted when comparing these costs with similar studies in other regions. For instance, a systematic review of studies in China estimated the direct medical costs of smoking-attributable diseases to range from 9.3 million to 60.0 million dollars, with the most significant proportion allocated to outpatient visits, which accounted for 49.2-68.9% of direct costs.⁴⁸ Our study similarly found that the highest costs were for cardiovascular diseases, especially ischemic heart disease, which accounted for 70.4% of the total costs for males. However, unlike the Chinese studies where outpatient costs dominated, our study observed that inpatient costs for chronic conditions like COPD and other heart diseases significantly contributed to the total cost, indicating a difference in healthcare cost structures between these regions. Further, the study by Goodchild et al. in 2018 estimated that globally, healthcare expenditures due to

smoking-attributable diseases totaled Purchasing Power Parity (PPP) \$467 billion in 2012, which constituted about 5.7% of the global health expenditure.⁴⁹ This proportion is comparable to the statistics reported in high-income countries like the United States. (6-8%) but is lower than that in India (4.7%). According to Goodchild et al, in 2018, the cost of diseases attributed to smoking in Iran in 2012 was estimated at \$873.2 million (our results were \$352.6 million for the country). Our study shows that smoking-attributable healthcare costs in Iran, as represented by data from Mashhad hospitals, might constitute a more substantial portion when considering both inpatient and outpatient costs together. The results of the study conducted by Koronayou and colleagues indicated that the direct medical costs of all smoking-related diseases, including both communicable respiratory diseases and non-communicable diseases (such as cancers, cardiovascular diseases, respiratory diseases, neurological disorders, gastrointestinal diseases, diabetes, musculoskeletal disorders, and physical injuries), amounted to \$159 million in Bahrain, \$527 million in Kuwait, \$222 million in Oman, \$246 million in Qatar, \$2119 million in Saudi Arabia, and \$1150 million in the United Arab Emirates.⁵⁰ In the present study, conducted in 2023, the direct medical costs in the country were estimated at approximately \$316.7 million. However, it should be noted that this estimate does not include all smoking-attributable diseases, direct non-medical costs, or indirect costs related to smoking.

Our findings revealed a substantial gender disparity in direct medical costs, with males accounting for higher costs compared with females. This is consistent with other studies, such as those conducted in Hong Kong and Taiwan, which also reported higher costs for males.^{51,52} For example, in Hong Kong, a study by McGhee et al in 2006 found that the direct and indirect costs due to smoking-related diseases were significantly higher among men than women, especially in diseases like lung cancer and COPD.⁵² The gender differences are largely due to higher smoking prevalence among men and the associated risk factors that lead to more severe health outcomes.⁵³⁻⁵⁵

Our study found that the direct medical costs of smoking-related diseases have been on a declining trend from 2015 to 2020 in Iran. The impact of inflation in the years 2021, 2022, and 2023 has not been uniform across the Iranian economy, with inflation in the healthcare sector, particularly the growth of personnel costs, being lower than in other economic sectors. Despite the significant depreciation of Iran's official currency during this period, some healthcare costs, such as physician visits, certain nursing expenses, and the procurement of medications for patients, have not increased in line with inflation. This discrepancy

has led to a decline in the quality of services provided to patients.^{6,56} The sharp decline in direct medical costs observed in 2020 can be attributed to the extraordinary economic challenges faced by Iran during this period, particularly the unprecedented devaluation of the Iranian Rial.⁵⁷ In 2020, the exchange rate of the Rial to the US dollar experienced a dramatic increase, reflecting heightened economic instability and inflationary pressures.⁵⁸ When the healthcare costs, originally incurred in Iranian Rials, are converted to US dollars for analysis, the substantial devaluation of the Rial results in a seemingly significant reduction in the dollar-denominated costs. However, this decline is not representative of the actual healthcare expenditure within the local context. In fact, when assessed in the local currency, healthcare costs for smoking-attributable non-communicable diseases (NCDs) did not decrease; rather, they likely increased due to inflation affecting medical supplies, personnel wages, and healthcare services.

This discrepancy underscores the importance of considering local economic conditions, especially in studies that involve currency conversion for international comparisons. Without accounting for the devaluation of the Rial, the interpretation of trends in direct medical costs could be misleading. Future research on healthcare expenditures in similar economic contexts should account for exchange rate volatility and provide dual analyses in both local currency and standardized international currencies to offer a more accurate depiction of the economic burden.

Our study has several strengths and limitations. One of the key strengths is its comprehensive approach to estimating the direct medical costs of smoking-attributable non-communicable diseases (NCDs) over an extended period of eight years, from 2015 to 2023. This long-term analysis provides a robust overview of the economic burden of smoking on the healthcare system, specifically within the context of hospitals affiliated with Mashhad University of Medical Sciences. The use of extensive hospital information systems and rigorous data collection methods ensured the accuracy and reliability of the findings. The study also utilized a detailed methodology to calculate smoking-attributable fractions (SAFs) and relative risks, allowing for precise cost estimation across different disease categories and demographic groups. Furthermore, by focusing on adults aged 35 and older, the study effectively captured the most impacted population group, where the cumulative effects of smoking over decades are most evident.

However, several limitations should be noted. Firstly, the study is based on data from a single medical university's affiliated hospitals, which may not fully represent the broader national or regional healthcare landscape. This focus could lead to potential biases in cost estimates, as healthcare practices, costs, and patient demographics can vary significantly across different regions. Secondly, the study primarily relies on direct medical costs. It does not comprehensively address indirect costs such as lost productivity, caregiving, or long-term disability, which are significant components of the overall economic burden of smoking. Additionally, the study did not differentiate between different types of smoking (e.g., active vs passive

smoking) or the varying intensity and duration of smoking, which could influence the accuracy of the SAFs and cost estimations. The reliance on secondary data sources for relative risk and prevalence rates may also introduce some uncertainties due to potential variations in study designs and populations in the referenced studies. Another limitation of this study is not conducting a power analysis to determine the minimum sample size, as it aimed to include all eligible hospitalized patients from 2015 to 2023. While this method improves the accuracy of estimating direct medical costs, it could restrict specific statistical analyses for some patient groups. There are also limitations regarding the HIS system. The limitations of the HIS include issues with data accuracy and completeness, which can affect research and clinical decisions. Compatibility problems between different HIS platforms can hinder data sharing. Technological limitations, such as outdated software or hardware, may cause delays or errors. Insufficient user training can lead to data entry mistakes, compromising system effectiveness. Also, Since the HIS only records cost data related to individuals, hospitals, and insurers, and our study was based on utilizing these hospital data without direct access to patients, we were unable to calculate indirect costs. Lastly, the study did not account for possible confounding factors such as comorbidities or socioeconomic status, which could impact both smoking prevalence and healthcare costs. Despite these limitations, our study provides valuable insights into the economic impact of smoking on the healthcare system in Mashhad, the second most populated city in Iran. It highlights the urgent need for effective tobacco control policies and cost-effective interventions.

Conclusion

This research highlights the significant financial burden of cigarette smoking on insurance companies, individuals, and governments, underscoring the need for comprehensive tobacco control policies and targeted interventions, especially among men. One effective strategy to reduce smoking rates is the implementation of higher cigarette taxes, which not only make smoking less affordable but also generate government revenue that can be reinvested in healthcare. Additionally, targeted public health campaigns aimed at high-risk groups can raise awareness of smoking's dangers and its contribution to non-communicable diseases. Combining these measures with accessible smoking cessation programs can lower smoking rates, reduce healthcare costs, and improve workforce productivity, ultimately easing the financial strain on healthcare systems and improving public health, particularly in lower-middle-income countries like Iran.

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ORCID iDs

Amirmohammad Tajik  <https://orcid.org/0000-0002-3767-9921>
Mehdi Varmaghani  <https://orcid.org/0000-0001-6249-821X>

Ethics Approval

Ethical considerations: The study has been approved by the Ethics Committee of Mashhad University of Medical Sciences, with the code IR.MUMS.FHMPM.REC.1400.084. All participants provided written informed consent forms for the various aspects of data collection. The study was also implemented following the principles and regulations of confidentiality and privacy. All research methods were carried out following relevant guidelines and rules.

Authors' Contributions

AMT, AA, and MV contributed to the designing and running the model. AMT and AA gathered the required data for the model, including literature review, cost, and efficacy data. AA and MV contributed to the study's statistical and epidemiological parts and double-checked all analyses. AMT, ZK, MM, and AA wrote the manuscript. JM, FSH, and MV reviewed the manuscript and double-checked all the analyses. All authors participated in reviewing the manuscript and its revision, and they were involved in research, interpretation, and finalizing the manuscript.

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Data Availability Statement

The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Transparency Statement

The lead author, Dr Mehdi Varmaghani, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and if relevant, registered) have been explained. All authors have read and approved the final version of the manuscript. Dr Mehdi Varmaghani, the corresponding author, had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

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