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Original Article

Economic Burden of Asthma in Northwest Iran

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Abstract

Background: The economic burden of asthma is a major public health concern. This study estimates the economic burden of asthma in Northwest of Iran.

Methods: A longitudinal study was conducted between 2017 and 2018 in Tabriz (Iran) using the Persian version of the Work Productivity and Activity Impairment (WPAI) questionnaire. Direct and indirect costs associated with asthma were estimated based on the societal perspective, prevalence-based approach, and bottom-up method. Annual indirect costs were estimated using the human capital (HC) method. The structural equation model was used to evaluate the relationship between costs, sex, and asthma severity.

Results: A total of 621 patients with asthma were enrolled in the study. Significant differences were found between female and male patients for the mean cost of radiology (P=0.006), laboratory (P=0.028), and diagnostic (P=0.017) tests at baseline, and for laboratory (P=0.012), and diagnostic (P=0.027) tests at one-year follow-up. The more severe asthma, the more significant the costs for annual physician office visits (P=0.040) and medications (P=0.013). As asthma severity increased, significantly higher expenditures were observed in women for days lost from work at baseline (P=0.009) and one-year follow-up (P=0.001), and in men for productivity loss at work due to impairment at baseline (P=0.045). A significant association between indirect costs and the cost of impairment-related lost productivity at work (β=3.29, P<0.001), and between severe asthma and indirect costs (β=32.36, P<0.001) was observed.

Conclusion: High costs are incurred by Iranian asthma patients, especially because of impairment-related productivity loss at work associated with asthma exacerbation.

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Keywords ● Asthma ● Economic burden ● Cost of illness ● Socioeconomic factors ● Work performance

What's Known

- Worldwide, the economic burden of asthma is immense.
- Due to gender bias in healthcare, it is recommended to develop gender-specific evidence-based guidelines.

What's New

- Laboratory and diagnostic tests pose substantial costs to male asthma patients.
- Regression coefficients of the structural equation modeling (SEM) predicted a significant association between severe asthma and indirect costs in the three distinct explanatory models (total, female, and male participants).

Introduction

Bronchial asthma is the most prevalent non-communicable disease worldwide with long-term social impact and immense economic burden. The higher the prevalence and years lived with disability (YLD) due to bronchial asthma, the lower the rate of healthy life expectancy (HALE). Such a negative correlation imposes a huge economic burden on society due to days lost from work/school, impairment-related productivity loss, and increased cost of medical care.[1-3] According to data published by the European Respiratory Society (ERS), the total economic burden of asthma in Europe in 2011 was approximately €33.9 billion,

of which €14.4 billion was related to indirect costs (productivity loss due to absenteeism and presenteeism, and early retirement on health grounds). The remaining expenditure was related to medication costs and the cost of primary care.[4] Based on a pooled sample, in 2013, 7.3% of the population in the United States had asthma at a total cost of $81.9 billion.[5]

The prerequisite for good public health policy decision-making in patients with asthma is a good understanding of the disease and access to accurate data. From the societal perspective, the latter portrays the scale, severity, and consequences of the disease. It also facilitates the development of a country-specific strategy to manage and control asthma.[5, 6] In Iran, the prevalence of asthma in 2015-2016 was reported at 8.9% of the total population.[7] However, only a few studies provided an estimate of the social impact and economic burden of the disease; all based on self-administered questionnaires.[6, 8, 9]

Cost of illness (COI) studies, based on the incidence or prevalence of a disease, are an evaluation technique to identify and measure the direct, indirect, and intangible costs of the disease to society. It provides an approximation of the opportunity cost of lost resources due to illness. The method includes three phases (identification, measurement, and valuation of resources) to estimate the average cost imposed by an illness in a given period of time.[10, 11]

Gender bias is reported in healthcare across the board, from health status to prescribing drugs, disease type, and even in medical research.[12] For the sake of good practice, it is therefore important to develop gender-specific evidence-based guidelines. In this context, the present study aimed to evaluate direct medical and non-medical costs as well as indirect expenditures in patients with asthma. In addition, based on a method proposed in a previous study,[13] the effect of sex and asthma severity on direct and indirect costs was assessed.

Materials and Methods

Prevalence-based COI and longitudinal observational studies were conducted between 2017 and 2018 at various respiratory clinics in Tabriz (Iran). Patients diagnosed with asthma by a pulmonologist were recruited regardless of sex and age. The only inclusion criterion was the diagnosis of asthma according to the European Thoracic Society/American Thoracic Society (ERS/ATS) criteria.[14] Patients with any other respiratory disease or unwillingness to participate in the study were excluded. The sample size was calculated based on a minimum effect size of r=0.18 with α=0.05 for a targeted 90% power using G*Power software, version 3.1.2.[15] A sample size of 320 participants was estimated. However, considering 20% attrition probability and a design effect of 1.5, 621 patients were recruited. The recruited patients were grouped based on the severity of asthma, namely intermittent, mild persistent, moderate persistent, and severe persistent.[16] They were followed over one year period after which the total COI was estimated.

The study was approved by the Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran (code: IR.TBZMED.REC.1397.801). Written informed consent was obtained from adult patients or parents of the participating children.

Data Collection

Costs were estimated using the bottom-up and human capital approaches. The three phases of identification, measurement, and valuation of resources were used to estimate the average cost imposed by the illness.[10] To this end, the Persian version of the work productivity and activity impairment in patients with asthma (WPAI-AQ) questionnaire was used. The reliability and validity of the Persian version of the questionnaire were already confirmed in a previous study.[17] The questionnaire includes 34 items divided into three sections. The first section includes items related to demographic and anthropometric variables, such as socioeconomic, smoking, and insurance status. The second section covers asthma severity such as grade and symptoms. Finally, the third section includes items related to direct medical and non-medical costs as well as indirect expenditures. Direct medical costs include the actual costs to patients and those covered by insurance companies, e.g., physician office visits, radiology, laboratory, and diagnostic tests (spirometry, oximetry), prescription medication, emergency visits, and hospitalization. Depending on the type of health care insurance, 30%-70% of the costs are covered by insurance companies. Non-medical costs include payments by patients for travel, lodging, and transportation. In addition, indirect costs were also addressed in the WPAI-AQ questionnaire and covered the costs related to the effect of the disease on the quality of life due to impairment, productivity loss due to activity impairment, and days lost from work/school.

The participants were instructed by an expert on how to complete the self-report WPAI-AQ questionnaire. They were requested to complete the questionnaire quarterly for one year, either in one of the clinics or through a telephone interview.

Cost Calculation

Based on the data published by the International Monetary Fund (IMF), gross domestic product (local currency unit) (GDP-LCU) was divided by active population to calculate indirect costs, which is a key parameter for policymakers in developing health strategies.[18-20]

Mathematical Model and Variables

Structural equation modeling (SEM) was used to determine the predictive relationships between latent and observed variables. SEM encompasses a measurement model and a structural model. It can be used for confirmatory models, as it provides model-fit information on the consistency of the hypothesized conceptual model data to find a causal relationship between variables and theoretical structures.[21-23] Accordingly, we examined the relationship of direct and indirect costs (latent variables) with the corresponding indicators (observed variables). Indicators included medical and non-medical costs (direct costs), days lost from work/school, impairment-related productivity loss (indirect costs), the stage of asthma, and the sex of the participants.

Statistical Analysis

Quantitative data were expressed as mean with 95% confidence interval (CI). The unpaired *t* test was used to examine the difference between male and female patients in terms of asthma severity. The analysis of variance (ANOVA) was used to compare asthma severity between the patients.

To develop the model, normal distribution of univariate and multivariate variables was initially examined using Kolmogorov-Smirnov and Mardia's tests with skewness and kurtosis indices, respectively. Then, bivariate correlation and confirmatory factor analysis (CFA) were performed. SEM was used as the theoretical structure. The missing data ranged from 1.81% to 13.21%, for which the maximum likelihood method was used.[24] To assess the relationship between variables, 5% significance level, the goodness of fit, comparative fit index (CFI) (cutoff≥0.95), root mean square error of approximation (RMSEA) (cutoff≤0.06), and standardized root mean square residual (SRMR) (cutoff≤0.08) were used. The data from SEM were presented using the regression coefficient β with 95% CI. Data were analyzed using Stata software, version 15.0 (StataCorp LLC, College Station, TX, USA). $P<0.05$ was considered statistically significant.

Table 1: General characteristics of the asthma patients (n=621)

Variable		Results
Age (years, mean±SD)		50.65±17.95
Sex (n, %)	Women	372 (59.9)
	Men	249 (40.1)
Education (n, %)	Illiterate	196 (31.7)
	Lower secondary education	213 (34.3)
	Post-secondary non-tertiary education	106 (17.0)
	Bachelors of science	39 (6.2)
	≥Master of science	67 (10.8)
Weight (kg, mean±SD)		74.7±36.34
BMI (kg/m^2, mean±SD)		28.72±15.16
Smoking status (n, %)	Non-smoker	381 (61.4)
	Passive	66 (10.6)
	Ex-smoker	148 (23.8)
	Active	26 (4.2)
Asthma duration (years, mean±SD)		8.09±10.5
Asthma stage (n, %)	Intermittent	60 (9.7)
	Mild persistent	290 (46.6)
	Moderate persistent	180 (29.0)
	Severe persistent	91 (14.7)
Family history of asthma (n, %)	Yes	230 (37.0)
Insurance contract (n, %)	Yes	568 (91.5)
Type of insurance (n, %)	Health insurance	399 (64.2)
	Rural insurance	87 (14.0)
	Others	135 (21.7)
Private insurance (n, %)	Yes	102 (16.4)
Asthma symptoms under control (n, %)	Diurnal	521 (84.3)
	Nighttime	454 (73.6)
Use of quick-relief or rescue inhaler (n, %)		464 (74.8)
Activity level (n, %)		187 (30.2)

Results

Baseline characteristics of the patients are presented in table 1. More than 70% of the patients were in the category of mild (47.5%) and moderate persistent (28.9%) asthma. Furthermore, 60% of the patients were non-smokers, and more than 80% exhibited diurnal variation in asthma. While 84.3% of patients had public health insurance, only 16.4% had private insurance contracts.

The estimated direct costs at baseline between male and female patients showed a significant difference in costs for radiology (P=0.006), laboratory (P=0.028), and diagnostic (P=0.017) tests. Based on the one-year follow-up data, there was a significant difference between the costs covered by the patients and insurance companies for laboratory (P=0.012) and diagnostic (P=0.027) tests. However, except for the laboratory costs, there was no significant difference in the costs covered by insurance companies between male and female patients (table 2).

The results showed that asthma exacerbation was directly related to a significantly higher mean expenditure per patient (e.g., medical visits, radiology, diagnostic tests, and medications). The one-year follow-up data showed a significant variation in the number of physician office visits and medication costs (table 3). However, no significant difference was found in expenditure by the insurance companies for housewives.

Indirect cost analysis was performed for both sexes. As shown in table 4, the cost of lost productivity at work at both one week and one-year follow-up was higher in male than female patients. For both sexes, the highest indirect costs were impairment-related productivity followed by the lost productive time.

The results showed significantly higher costs due to days lost from work/school. We also found a direct relationship between the cost of impairment-related productivity loss and asthma

Table 2: Estimation of direct medical and non-medical costs† covered by patient and insurance companies in terms of sex

Costs		Women (n=372)		Men (n=249)		P value*
		Mean±SD‡	95% CI‡	Mean±SD‡	95% CI‡	
Physician office visits	Patient	13.9±11.2	12.1-15.8	14.6±11.5	12.2-15.8	0.663
	Insurance	4.8±3.8	4.2-5.3	6.2±4.9	4.2-8.2	0.087
Annual physician office visits	Patient	25.0±18.7	20.3-29.6	28.5±20.1	21.9-35.1	0.373
	Insurance	9.3±7.5	8.2-10.4	13.9±9.3	7.4-20.5	0.072
Radiological tests	Patient	29.6±22.9	24.1-35.0	17.9±13.6	13.3-24.5	0.006
	Insurance	9.4±7.8	6.1-12.7	7.60±4.9	5.9-9.3	0.461
Annual radiological tests	Patient	36.6±29.9	29.5-43.6	26.9±22.8	16.8-37	0.116
	Insurance	10.9±9.1	7.4-14.4	8.6±5.8	6.6-10.5	0.358
Laboratory tests	Patient	20.5±17.3	17.0-24.0	39.2±25.33	17.3-61.1	0.028
	Insurance	10.0±7.9	8.4-11.7	12.5±7.4	10.2-14.7	0.091
Annual laboratory tests	Patient	25.1±21.4	20.3-29.9	44.1±31.33	24.8-63.4	0.012
	Insurance	10.5±8.0	9.0-11.9	14.1±10.7	11.2-17.0	0.015
Diagnostic tests	Patient	13.9±11.5	12.6-15.2	16.4±11.8	14.8-18.0	0.017
	Insurance	3.1±2.6	2.7-3.5	2.7±0.22	2.6-2.7	0.226
Annual diagnostic tests	Patient	21.1±19.6	19.0-23.2	25.1±21.4	22.2-27.9	0.027
	Insurance	3.3±2.7	2.9-3.8	3.0±1.4	2.7-3.3	0.375
Medications	Patient	60.2±38.7	56.2-64.1	65.92±42.2	60.6-71.2	0.082
	Insurance	58.9±48.5	53.7-64.0	60.8±48.5	54.5-67.1	0.639
Annual medications	Patient	155.7±133.9	138.4-172.9	160.3±140.7	140.0-180.7	0.736
	Insurance	134.3±88.5	119.5-149.0	130.7±95.5	106.5-154.6	0.789
Emergency medical services	Patient	17.4±11.6	8.5-26.3	23.5±13.1	15.2-31.8	0.284
	Insurance	25.6±20.9	14.0-37.2	58.1±54.5	23.8-92.3	0.056
Annual emergency medical services	Patient	-	-	-	-	-
	Insurance	-	-	-	-	-
Hospitalization	Patient	44.7±33.9	28.4-61.0	39.7±25.2	28.2-51.1	0.594
	Insurance	723.6±512.2	468.9-978.3	683.0±381.7	509.2-856.7	0.778
Annual hospitalization	Patient	93.6±54.7	9.1-178.1	87.7±61.1	28.9-146.4	0.906
	Insurance	907.9±888.6	532.7-1,283.2	1,192.1±1,027.3	785.7-1,598.5	0.299
Transportation	Patient	15.3±12.3	13.0-17.0	16.1±13.3	13.4-18.8	0.674
Annual transportation	Patient	25.0±20.1	21.3-28.8	26.3±22.5	22.2-30.3	0.671
Lodgings	Patient	-	-	-	-	-
Annual lodgings	Patient	54.5±20.7	3.2-105.7	28.7±10.5	12.0-45.4	0.080

†Based on the local currency unit (GDP-LCU)/active Iranian population, ‡Obtained from baseline and each quarter within one year, *Independent sample *t* test, P<0.05 was considered statistically significant.

Table 3: Estimation of direct medical and non-medical costs† covered by patients and insurance companies in terms of asthma severity

Costs		Intermittent		Mild persistent		Moderate persistent		Severe persistent		P value*
		Mean±SD‡	95% CI‡	Mean±SD‡	95% CI‡	Mean±SD‡	95% CI‡	Mean±SD‡	95% CI‡	
Physician office visits	Patient	11.29±10.97	6.5-16.1	10.68±8.68	9.0-12.3	13.88±10.80	10.5-17.3	18.90±15.57	13.7-24.1	0.003
	Insurance	5.08±2.88	3.4-6.7	4.70±4.20	4.0-5.4	4.39±2.09	3.9-4.9	5.01±4.64	3.4-6.6	0.825
Annual physician office visits	Patient	21.56±16.59	15.1-28.0	19.92±17.21	17.1-22.7	24.83±17.78	16.7-33.0	32.84±22.69	20.5-45.1	0.040
	Insurance	9.16±7.50	5.0-13.3	10.25±8.56	7.9-12.6	8.38±5.79	7.0-9.7	11.02±10.61	7.5-14.5	0.494
Radiological tests	Patient	63.57±59.63	0-158.4	22.57±16.49	16.6-28.5	23.88±14.03	18.2-29.5	25.5±20.11	16.6-34.4	0.003
	Insurance	6.12±5.77	0-58.0	9.35±5.58	7.3-11.4	10.56±5.72	7.9-13.2	9.35±5.44	6.6-12.1	0.693
Annual radiological tests	Patient	52.08±45.10	14.4-89.8	29.12±21.50	23.3-35.0	35.94±29.75	21.7-50.2	29.09±24.8	20.3-37.9	0.214
	Insurance	13.95±8.29	0-40.3	12.00±8.05	9.7-14.3	11.21±7.50	8.5-14.0	9.38±5.93	6.9-11.9	0.518
Laboratory tests	Patient	23.36±16.41	0-49.5	22.50±17.74	18.2-26.8	35.76±20.31	3.6-67.9	33.25±23.54	9.9-56.6	0.644
	Insurance	11.68±8.20	0-24.7	10.64±6.84	8.9-12.4	11.51±8.22	8.5-14.5	10.52±9.23	6.2-14.8	0.949
Annual laboratory tests	Patient	25.53±22.22	2.2-48.9	29.67±25.67	23.0-36.4	37.44±25.78	14.6-60.3	37.04±26.42	11.9-62.1	0.816
	Insurance	13.91±12.02	0-28.8	11.32±8.80	9.4-13.3	12.57±9.48	9.6-15.5	11.80±9.04	7.9-15.7	0.852
Diagnostic tests	Patient	12.59±8.63	9.0-16.2	11.35±10.14	9.9-12.8	13.16±11.82	11.1-15.3	17.81±13.72	14.5-21.1	0.001
	Insurance	2.56±0.01	2.5-2.6	2.87±2.23	2.4-3.3	3.19±2.53	2.6-3.8	2.74±0.55	2.5-3.0	0.714
Annual diagnostic tests	Patient	21.76±16.65	15.0-28.5	19.30±17.38	16.6-22.0	19.80±18.83	16.5-23.1	25.61±24.63	19.7-31.5	0.142
	Insurance	2.88±0.90	2.1-3.6	3.23±2.52	2.7-3.7	3.43±2.65	2.8-4.1	2.73±0.54	2.5-3.0	0.644
Medications	Patient	46.94±32.88	34.4-59.4	54.47±38.06	49.5-59.4	60.38±39.80	53.7-67.1	75.02±48.51	64.5-85.6	0.001
	Insurance	46.73±37.52	30.9-62.7	65.32±45.21	59.3-71.3	61.42±48.64	53.0-70.0	60.73±50.48	49.3-72.1	0.295
Annual medications	Patient	112.46±91.46	77.7-147.3	140.04±121.02	120.1-160.0	145.2±124.73	119.6-170.8	203.48±169.63	152.7-254.3	0.013
	Insurance	116.21±98.97	60.8-117.6	130.17±109.83	115.7-144.6	112.27±99.80	93.0-131.5	109.01±97.59	85.4-132.6	0.348
Emergency medical services	Patient	-	-	27.02±15.07	11.2-42.8	14.81±11.22	1.0-28.7	21.16±13.84	4.0-38.4	0.362
	Insurance	-	-	41.61±36.37	2.0-81.4	49.10±38.61	13.4-84.8	35.25±31.25	2.45-68.1	0.846
Annual emergency medical services	Patient	-	-	-	-	-	-	-	-	-
	Insurance	-	-	-	-	-	-	-	-	-
Hospitalization	Patient	-	-	43.03±28.49	28.9-57.2	33.95±30.47	0-67.8	44.13±18.69	26.8-61.4	0.746
	Insurance	-	-	772.63±515.14	516.5-1,028.8	479.03±393.08	150.4-807.7	838.47±355.03	510.1-1,166.8	0.252
Annual hospitalization	Patient	-	-	65.57±51.48	30.7-100.4	35.64±32.34	12.1-59.2	132.23±106.11	0-280.0	0.274
	Insurance	-	-	1,117.66±950.51	716.3-1519.0	553.00±357.11	297.5-808.5	1,686.19±1,352.57	718.6-2,653.8	0.088
Transportation	Patient	13.19±10.33	4.8-21.6	13.13±11.02	10.9-15.3	16.15±12.63	11.9-20.4	15.77±12.97	11.29-20.3	0.504
Annual transportation	Patient	24.00±20.12	10.6-37.4	25.08±20.60	20.6-29.6	24.00±18.84	17.7-30.3	23.57±20.34	17.5-29.6	0.983
Lodgings	Patient		-	-	-	-	-	-	-	-
Annual lodgings	Patient		-	38.29±18.05	0-200.5	28.92±11.78	0-58.17	-	-	0.207

†Based on local currency unit (GDP-LCU)/active Iranian population (analysis of variance for variables), ‡Obtained from baseline and each quarter within one year, *Analysis of variance, P<0.05 was considered statistically significant.

Table 4: Estimation of indirect costs† at one week and one-year follow-up in terms of sex

Duration	Costs	Women		Men		P value*	Total	
		Mean±SD	95% CI	Mean±SD	95% CI		Mean±SD	95% CI
Seven days	Days lost from work	32.11±19.70	6.68-57.54	60.24±38.74	38.21-82.27	0.238	54.87±34.36	36.42-73.33
	Productivity loss at work due to impairment	120.40±115.71	79.37-161.43	120.32±111.60	101.68-138.97	0.997	120.34±112.05	103.53-137.15
	Days lost from school	-	-	1.92±1.35	0.0-4.60	-	1.55±1.10	0.0-1.72
	Activity loss at school due to impairment	-	-	7.27±3.92	0.0-15.03	-	5.88±3.18	0.0-12.17
One year	Days lost from work	66.04±33.02	0.0-133.31	106.03±60.59	63.21-148.85	0.400	98.40±53.51	61.64-135.16
	Productivity loss at work due to impairment	189.06±168.06	114.05-264.07	231.27±199.37	188.62-273.91	0.380	223.22±193.26	186.08-260.35
	Days lost from school	-	-	2.24±1.46	0.0-5.12	-	1.81±1.18	0.0-4.14
	Activity loss at school due to impairment	-	-	7.27±3.93	0.0-15.03	-	5.88±3.18	0.0-12.17

†Based on the local currency unit (GDP-LCU)/active Iranian population, *Independent sample *t* test

severity in both male and female patients. However, at one-year follow-up, costs due to days lost from work/school were significantly higher in male patients (table 5).

A multivariate causal analysis was performed on three distinct explanatory models, namely male participants, female participants, and total participants. These were analyzed in terms of direct and indirect costs (latent variables), the corresponding indicators, asthma severity, and the sex of the participants (observed variables). SEM was then performed separately for each of the three models. The final fit indices for the total explanatory model based on pre-defined cutoffs were CFI=0.98, RMSEA=0.03, and SRMR=0.06.[25] Unstandardized regression weights were used in the confirmatory model (measurement) between two latent variables and the corresponding observed indicators. The results showed a significant and good discriminant predictive relationship between direct costs and medical costs for the three models; total participants (P=0.032), female participants (P=0.023), and male participants (P<0.001). Similarly, between indirect costs and the cost of impairment-related productivity loss, these values were P<0.001, P=0.023, and P<0.001, respectively (table 6). In terms of the confirmatory model (structural), a significant predictive relationship was found between severe asthma and indirect costs in the model for total participants (P<0.001), female participants (P=0.011), and male participants (P<0.006) (table 6).

The results also showed a positive correlation between two latent variables (direct and indirect costs) in the model for total participants (r=0.243, P<0.001), female participants (r=0.176, P=0.001), and male participants (r=0.303, P<0.001). As depicted in figure 1, the links for standardized coefficients had similar associations as the unstandardized coefficients.

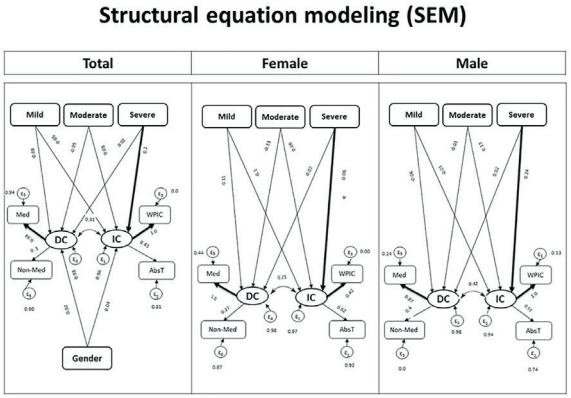

Figure 1: The results of structural equation modeling showing standardized regression weights for the predicated costs. DC: Direct costs; IC: Indirect costs; Med: Medical costs; Non-Med: Non-medical costs; WPIC: Work productivity impairment costs; AbsT: Absent time; Mild: Mild persistent asthma; Moderate: Moderate persistent asthma; Severe: Severe persistent asthma. Thick lines represent P≤0.05 and thin lines represent weak relationships. Total model fit indices CFI (0.98), RMSEA (0.03), and SRMR (0.06).

Discussion

The findings of the present study indicated that direct costs related to laboratory and diagnostic tests, both at baseline and one-year follow-up, were significantly higher in males than female

Table 5: Estimation of indirect costs† at one week and one-year follow-up in terms of asthma severity

Variable	Duration	Costs	Intermittent		Mild persistent		Moderate persistent		Severe persistent		P value*
			Mean±SD	95% CI	Mean±SD	95% CI	Mean±SD	95% CI	Mean±SD	95% CI	
Women	Seven days	Days lost from work	-	-	18.32± 15.08	4.74-31.89	35.82± 29.85	0.0-135.28	186.58± 172.16	0.0-2,367.58	0.009
		Productivity loss at work due to impairment	65.67± 65.60	0.0-900.15	101.50± 94.70	50.48-152.51	157.62± 114.70	15.21-300.03	197.02± 185.76	0.0-1,865.97	0.528
		Days lost from school	-	-	-	-	-	-	-	-	-
		Activity loss at school due to impairment	-	-	-	-	-	-	-	-	-
	One-year	Days lost from work	-	-	31.21± 26.54	11.23-51.18	35.82± 29.85	0.0-135.28	552.26± 552.0	0.0-710.11	0.001
		Productivity loss at work due to impairment	-	-	167.17± 149.43	80.17-254.17	157.62± 114.70	15.21-300.03	476.14± 344.79	0.0-4,857.12	0.193
		Days lost from school	-	-	-	-	-	-	-	-	-
		Activity loss at school due to impairment	-	-	-	-	-	-	-	-	-
Men	Seven days	Days lost from work	19.07± 17.05	0.0-41.50	55.29± 31.10	18.24-92.34	44.12± 29.02	12.36-75.88	113.98± 99.30	27.06-200.90	0.166
		Productivity loss at work due to impairment	58.38± 55.74	3.70-113.07	105.21± 98.66	73.52-136.91	111.07± 104.47	74.61-147.52	170.16± 128.84	113.03-227.28	0.045
		Days lost from school	-	-	0.92± 0.91	0.91-2.75	6.59±5.39	0.0-17.55	-	-	0.426
		Activity loss at school due to impairment	-	-	6.70± 6.70	0.0-20.18	20.28± 12.86	0.0-46.44	-	-	0.447
	One-year	Days lost from work	35.66± 29.67	0.0-82.59	123.82± 59.67	28.09-219.56	79.46± 55.12	24.60-134.32	171.99± 132.30	33.36-310.62	0.509
		Productivity loss at work due to impairment	142.29± 125.27	0.0-306.85	224.50± 193.23	144.0-305.0	221.17± 192.09	134.86-307.48	329.86± 306.81	191.71-468.02	0.284
		Days lost from school	-	-	1.83±1.82	0.0-5.50	6.59±5.39	0.0-17.55	-	-	0.552
		Activity loss at school due to impairment	-	-	6.70±6.00	0.0-20.18	20.28± 12.86	0.0-46.44	-	-	0.447

†Based on local currency unit (GDP-LCU)/active Iranian population (analysis of variance for variables), *Analysis of variance, P<0.05 was considered statistically significant.

patients with asthma. Similarly, the costs of medication and physician office visits increased significantly with asthma exacerbation. These findings were in line with other studies in Iran and the United States.[5, 6, 8, 26] In contrast, a systematic review reported that direct costs were higher in female patients as a result of inadequate medication, improper use of the inhaler device, or the presence of comorbidity.[27] The difference in the results could be attributed to various parameters. For example, the prevalence of severe asthma is slightly higher in men (58.3%) than in women. Besides, it seems that female patients can cope better with the treatment than male patients. Consequently, they have less severe asthma exacerbations resulting in improved clinical management and reduced health-related costs.[28, 29] Nonetheless, the evidence does not support the role of sex on variables affecting direct costs.[28]

Table 6: The results of multivariate causal analysis between direct and indirect costs in terms of sex and asthma severity (unstandardized regression weight)

Variable	SEM	Indicator	Costs	β	95% CI	P value
Total	Structural model	Women	Direct	Reference		
		Men	Direct	0.48	-1.87, -2.84	0.688
		Intermittent	Direct	Reference		
		Mild persistent	Direct	-1.71	-4.08, -0.66	0.157
		Moderate Persistent	Direct	-1.25	-3.89, -1.39	0.354
		Severe Persistent	Direct	2.52	-1.27, -6.30	0.193
		Women	Indirect	Reference		
		Men	Indirect	5.00	-5.48, -15.47	0.350
		Intermittent	Indirect	Reference		
		Mild persistent	Indirect	-6.06	-19.11, -6.98	0.362
		Moderate Persistent	Indirect	3.71	-10.58, -17.99	0.611
		Severe Persistent	Indirect	32.36	14.46, 50.27	<0.001
	Measurement model	Direct Costs	Non-medical	Reference		
		Direct Costs	Medical	20.57	1.74, 39.40	0.032
		Indirect Costs	Days lost	Reference		
		Indirect Costs	Productivity loss	3.29	2.36, 4.21	<0.001
Women	Structural model	Intermittent	Direct	Reference		
		Mild persistent	Direct	-46.90	107.17, 13.37	0.127
		Moderate Persistent	Direct	-42.84	109.07, 23.38	0.205
		Severe Persistent	Direct	34.41	-52.73, -121.54	0.439
		Intermittent	Indirect	Reference		
		Mild persistent	Indirect	2.83	-16.11, -21.76	0.770
		Moderate Persistent	Indirect	3.85	-14.05, -21.75	0.674
		Severe Persistent	Indirect	33.39	7.52, 59.26	0.011
	Measurement model	Direct Costs	Non-medical	Reference		
		Direct Costs	Medical	13.58	1.85,25.31	0.023
		Indirect Costs	Days lost	Reference		
		Indirect Costs	Productivity loss	1.78	0.25, 3.23	0.023
Men	Structural model	Intermittent	Direct	Reference		
		Mild persistent	Direct	-28.63	110.64, 53.37	0.494
		Moderate Persistent	Direct	-7.99	-94.98, -79.01	0.857
		Severe Persistent	Direct	67.16	-30.22, -164.55	0.176
		Intermittent	Indirect	Reference		
		Mild persistent	Indirect	-1.21	-48.50, -38.07	0.952
		Moderate Persistent	Indirect	-9.31	-53.85, -35.22	0.682
		Severe Persistent	Indirect	68.94	18.42, 109.41	0.006
	Measurement model	Direct Costs	Non-medical	Reference		
		Direct Costs	Medical	16.44	10.39, 22.49	<0.001
		Indirect Costs	Days lost	Reference		
		Indirect Costs	Productivity loss	2.05	0.96, 3.15	<0.001

SEM: Structural equation modeling, P<0.05 was considered statistically significant.

A previous study projected the economic burden of asthma in the United States and estimated an additional direct cost of $1,056 by 2038, compared to 2019, in patients with uncontrolled versus controlled asthma.[30] Based on our results, the total annual direct costs for each patient with asthma were estimated at $432, of which 90% was related to medical and 10% to non-medical costs. The increase in direct costs could be attributed to severe cases requiring more emergency drugs, systematic use of corticosteroids, visits to emergency departments, and hospitalization.[5, 30]

Our results on indirect costs showed that the cost of productivity loss at work was higher in male than female patients with asthma. Over 60% of the indirect costs were related to productivity loss due to impairment. Our findings may seem to be an overestimate, however, inaccuracies in other studies resulted in an underestimation of direct costs of asthma.[31] We address this potential inaccuracy by using the Persian version of the WPAI-AQ questionnaire, which allowed a detailed assessment of presenteeism and absenteeism on weekly basis.[17] As a result, our estimation of the indirect costs appears to be more realistic than other studies conducted in Iran.[5, 6] However, in line with previous studies, we found that the cost due

to days lost from work in men with severe asthma was significantly high.[6, 32]

A few recent economic surveys of Iranian patients with asthma reported that medical costs remained constant and that the highest indirect costs were related to days lost from work/school.[6, 27] It is noteworthy that in these surveys, absenteeism from work/school was the only question about indirect costs. In our study, we found that indirect costs were about 70%-80% of the direct costs irrespective of asthma severity. In addition, the cost of impairment-related productivity loss at work, which is about 70%-90% of the indirect cost related to asthma severity and sex, could be explained by the limitations of the health system in Iran. For example, the lack of a well-developed primary healthcare system for asthma, high costs associated with asthma (e.g., medications), and low-income individuals. These are indicative of suboptimal asthma control and poor health-related quality of life. On the other hand, because of the need for a monthly salary, patients with asthma must attend work (presenteeism) despite the intangible costs of the disease, which in turn negatively affect their productivity.[5, 27, 30] We observed the same situation for asthma severity, although the associated direct and indirect costs were roughly the same. The cost of days lost due to severe asthma was reported to be a significant proportion of indirect costs.[4, 26]

The prevalence of asthma in Iran is about 8.9%. Considering the 83 million population, this amounts to 7,400,000 patients and is equivalent to $3.2 billion in direct costs and $2.5 billion in indirect costs due to days lost from work or impairment-related productivity loss. A previous study on the economic burden of asthma in Greece estimated the cost of treatment per patient at €895 ($1,054), of which 90% were medical, 6% non-medical, and 4% indirect costs. Medical and non-medical costs represented 90% and 10% of the total annual direct costs, respectively.[4] In the United States, the annual cost for all patients with asthma due to loss of income and productivity during 2008-2013 were estimated at $120 (days lost from work) and $89 (days lost from school), respectively.[3, 5] In comparison, our results showed different percentages for the direct and indirect costs. The difference could be explained by the lack of a comprehensive medical referral system for such patients in Iran, which can result in poor prevention, diagnosis, treatment, and health care utilization; leading to increased morbidity. In addition, increased asthma exacerbation resulted in days lost from work/school and impairment-related productivity/activity loss at work/school. Another explanation may be the clarity of the questions in the WPAI-AQ, which allowed patients to fully understand the questions and provide clear answers. Last but not least, the cost estimation method could also be the source of the differences. We used GDP-LCU and active population to estimate indirect costs, which allows extrapolation of the estimates to the whole country.

The results of our study on patients with private health insurance showed that insurance companies almost fully covered the cost of hospitalization and almost 80% of medications. Furthermore, the results of SEM for the three groups (male, female, and all participants) indicated significant relationships between indirect costs and productivity loss due to impairment and asthma severity. Our results are in line with a previous study reporting that severe persistent asthma is associated with a greater percentage (28%) of impairment than mild-to-moderate persistent asthma.[15]

The main limitation of the study is related to the estimation of costs covered by insurance companies. Since these companies offer various insurance contracts for the payment of incurred claims, we used annual insurance premiums to estimate the costs. Therefore, we could not accurately estimate the indirect costs covered by the insurance companies. Since no figures were available, we estimated medication costs based on insurance claims by the patients, which may contain certain inaccuracies. In addition, the sample size included a limited number of children. Another limitation is related to national currency fluctuations due to economic conditions.

Conclusion

The cost of asthma, particularly severe asthma, is significant for Iranian patients and society as a whole. The cost of laboratory and diagnostic testing was the highest in male patients. The highest cost was related to physician office visits and medication and was correlated with asthma severity. Overall, the cost of medication (by the patients) and hospitalization (by insurance companies) accounted for the largest portion of the total medical costs. Indirect costs due to days lost from work were predominantly high in male patients, whereas the cost of productivity loss due to impairment increased in line with asthma severity. Our findings provide a set of indicators to develop strategies for improving systemic health assessments (in particular for asthma phenotypes), preventing acute asthma exacerbations, and reducing the effect of environmental factors to effectively manage the economic burden on Iranian asthma patients.

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Authors' Contribution

All authors contributed to the study conception, design, and preparation of the manuscript. A. Sharifi, K. Ansarin, and AH. Jafari Rouhi participated in patient selection. E. Seyedrezazadeh was involved in data acquisition. E. Seyedrezazadeh, N. Gilani, M. Yousefi, and I. Dastan performed the statistical analysis and data interpretation.

Conflict of Interest: None declared.

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