Original Article

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TANAFFOS

Persons at High-Risk and Low-Risk for Chronic Obstructive Pulmonary Disease: Results from the BOLD Study in Iran

Hooman Sharifi [1], Makan Sadr [2], Maryam Akhtari [1], Maryam Tavanarezaei [3], Zahra Hesami [1], Alireza Eslaminejad [3], Mostafa Ghanei [4]

[1] Tobacco Prevention and Control Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [2] Virology Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [3] Chronic Respiratory Diseases Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [4] Chemical Injuries Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran

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Correspondence to: Sadr M

Address: Virology Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Email address: sadr.makan@gmail.com

Background: Chronic obstructive pulmonary disease (COPD) is a common, heterogeneous, and largely preventable respiratory condition that is frequently undiagnosed until advanced stages. We estimated the prevalence of COPD risk categories in Iran and examined factors associated with high-risk status.

Materials and Methods: A population-based survey using stratified cluster sampling was conducted in five major Iranian provinces, representing approximately 36% of the national population. Non-institutionalized adults aged ≥18 years completed standardized questionnaires, SF-12 health-related quality-of-life assessments, and pre- and post-bronchodilator spirometry under the tailored Burden of Lung Disease protocol. Participants were classified as diagnosed COPD (DN), high risk (HR; ≥10 years of tobacco use plus ≥1 respiratory symptom), or low risk (LR).

Results: Among 533 participants (mean age, 53.2 ± 1.83 years; 43.9% men), 5.0% (95% CI: 3.17–6.83) had diagnosed COPD, 13.2% (95% CI: 12.92–13.48) were high risk, and 81.8% (95% CI: 78.55–85.05) were low risk. Dyspnea on exertion (43.6%), productive cough (27.1%), and frequent shortness of breath (32.1%) were common and occurred more frequently in DN and HR groups. High-risk status was more prevalent among men, current smokers, and adults aged >45 years. Tobacco use for ≥10 years was strongly associated with HR classification. Smoking patterns and symptom burden varied substantially across provinces. DN and HR participants had significantly poorer SF-12 physical and mental health scores than LR participants (P<0.001).

Conclusion: A substantial proportion of Iranian adults are at high risk for COPD, indicating an important burden of potentially undiagnosed disease. Targeted screening, smoking-cessation initiatives, and earlier primary-care intervention may improve COPD detection and prevention.

Keywords: COPD; Prevalence; Risk categories; Smoking; Respiratory symptoms; Iran

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is considered a heterogeneous, common, and largely preventable chronic respiratory disease, defined by persistent respiratory symptoms and airflow limitation (1). Until recently, this concept led to the expectation that COPD would mainly be identified in older individuals, when pathophysiological changes are already well established, thereby limiting opportunities to modify the disease trajectory (2). This assumption has essentially prevented early detection of patients with initial or mild diseases who may derive greater benefit from timely intervention (3). Therefore, broader efforts are needed not only for secondary prevention but also for primary

prevention by increasing recognition of those most likely to benefit from early intervention. Several published studies have shown that many individuals at risk for COPD or with undiagnosed disease remain unidentified (4,5). It should also be noted that despite the high morbidity and mortality associated with COPD, awareness in low- and middle-income countries (LMICs) is often low, and robust data on the true burden of disease in these settings remain limited (6,7).

Recent updates from the Global Burden of Disease (GBD) 2019 and 2021 studies confirm that COPD remains among the leading causes of death and disability worldwide, with a disproportionate burden in low- and middle-income countries, where exposure to biomass fuels, occupational hazards, and environmental pollutants contributes substantially to disease risk (8,9).

Prevalence studies are essential for evaluating the burden and risk factors of chronic diseases such as COPD. To our knowledge, only a few studies have investigated this issue in Iran (10,11). In our previous work, consistent with other studies, we found that the prevalence of airflow limitation was higher among individuals who had ever smoked tobacco (1,12,13). However, a considerable proportion of individuals with COPD had never used tobacco (4,14-16). Furthermore, although active smoking remains the principal risk factor, the independent association between second-hand smoke exposure and COPD has not been consistently demonstrated in epidemiologic studies (17). More recent analyses also indicate that COPD remains substantially underdiagnosed worldwide, particularly in primary care settings, where limited access to spirometry is a major barrier to early detection (18).

In the Middle East and South Asia, including Iran, evidence on COPD underdiagnosis remains limited, underscoring the need for improved diagnostic awareness and wider implementation of spirometry in routine clinical practice (18). These observations suggest that although tobacco smoking is an important risk factor, it does not fully account for the substantial burden of COPD at the population level.

In 2014, a COPD prevalence study using stratified cluster sampling was introduced in Iran (19). The tailored Burden of Lung Disease (BOLD) design was subsequently implemented in five provinces in 2019 (11). Findings from the BOLD study provide valuable information on the status of pulmonary diseases and their associated risk factors in the community, offering a model for predicting the future burden of COPD. This study highlights individuals who should be more carefully targeted by health programs aimed at preventing COPD.

We hypothesized that, given the high prevalence and progressive nature of the disease, this survey could serve as a valuable tool for describing respiratory symptoms and health-related characteristics in the general adult population, particularly among individuals who are undiagnosed or at significant risk of developing COPD.

MATERIALS AND METHODS

The BOLD study protocol in Iran has been previously published (19,20), and was applied consistently throughout the project (20**).** The sampling frame included all non-institutionalized inhabitants of five major sites/ provinces in Iran: Tehran, Khorasan Razavi, Mazandaran, Kerman, and Khuzestan. Together, these sites represent nearly 36.2% of the total population of Iran. The study was approved by the Ethics Committee of the National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences (IR.SBMU.NRITLD.REC.1395.225).

Sample Size

The sample size was calculated based on an assumed disease prevalence of 50%, a 2% accuracy, a 95% confidence interval (CI), a cluster impact of 2, and an expected response rate of 90%. Sample size calculations were performed separately by sex and age group, including participants aged 18–25, 25–45, and >45 years.

Sampling Plan

This study used a stratified cluster sampling design. Samples were selected proportionally from the defined strata. The target population included all non-institutionalized inhabitants, categorized into the predefined age groups used in the study. Clusters were allocated to each province in proportion to the number of households. The number of clusters was determined based on the total required sample size and the mean number of household members.

From the selected clusters, all eligible adults in chosen households were invited to participate. Individuals were excluded only if they declined participation, were unavailable after repeated visits, or were unable to complete the questionnaire or spirometry. Participants whose spirometry did not meet BOLD quality-control criteria were not included in the final analytic sample. The final number of participants, therefore, reflects all individuals who completed the questionnaire and produced acceptable spirometric data.

Examination Protocol

In 2019, the principal investigator and faculty members from the five study sites held a workshop to standardize the survey procedures. The examination protocol included an interviewer-administered self-reported questionnaire that collected data on respiratory symptoms and demographic and clinical characteristics, including age, sex, educational attainment, smoking status, history of tuberculosis, history of working in dusty jobs, and biomass exposure.

The questionnaire set also included the validated 12-Item Short Form Health Survey (SF-12), which evaluates health-related quality of life across two components: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). Standard scoring procedures were applied to derive these composite indices (21).

Height and weight were measured using calibrated stadiometers and adult weighing scales, and pre- and post-bronchodilator spirometry were performed. Spirometry data included forced expiratory volume in 1 second (FEV1), forced expiratory volume in 6 seconds (FEV6), and forced vital capacity (FVC).

Spirometry

The primary outcome measure was spirometry before and after administration of 200 mg (2 puffs) of salbutamol (20). For quality control, all teams were instructed to use the 2120 In2itive Vitalograph Spirometer, which was selected because of its acceptable precision, validity, adjustability, and serviceability. Each test required a minimum of three acceptable maneuvers, defined as curves without hesitation, with complete exhalation, and free of artifacts affecting FEV1 or FVC. The 2120 In2itive Vitalograph Spirometer had been approved by the National Research Institute of Tuberculosis and Lung Diseases for meeting predefined performance criteria relating to measurement reliability, suitability for field use, and data accessibility.

COPD prevalence and risk categories

Three COPD risk categories were defined based on diagnosed COPD status, respiratory symptoms, and tobacco use duration:

1) **Diagnosed COPD (DN):** participants with a provider diagnosis of COPD.

2) **High-risk (HR):** participants without a COPD diagnosis, who had a history of ≥10 years of tobacco-product use, and ≥1 respiratory symptom, defined as frequent productive cough, frequent shortness of breath (SOB), or decreased physical activity due to breathing problems.

3) **Low-risk (LR):** participants who were neither diagnosed with COPD nor classified as high risk.

Statistical analysis

All statistical analyses were performed using SPSS version 21. A p-value <0.05 was considered statistically significant. The analysis primarily focused on estimating COPD prevalence across the defined risk categories. For each prevalence estimate, percentages and 95 % confidence intervals were calculated using the binomial distribution. Descriptive statistics were used to summarize participant characteristics. Categorical variables were presented as frequencies and percentages and compared between

groups using the chi-square test. Continuous variables were expressed as mean ± standard error (SE), and differences between groups were assessed using the independent samples t-test.

RESULTS

Among the 533 participants, 43.9 % were men and 56.1% women, and the mean age was 53.20±1.83 years. There was no significant difference in age between men and women (P-value=0.9). Of all participants, 84 (15.8%) were current or former smokers, and 391(73.4%) had a smoking history of 10 years or more. Most participants were from Tehran province (215, 40.3%).

The prevalence of respiratory symptoms was 43.6% for dyspnea on exertion, 27.1% for frequent productive cough, and 32.1% for frequent shortness of breath. These symptoms were not mutually exclusive; therefore, some participants reported more than one symptom simultaneously.

Comparison across age groups showed that respiratory symptoms were more common in participants older than 45 years than in younger groups, with an age-related increase in COPD-related complaints (Figure 1).

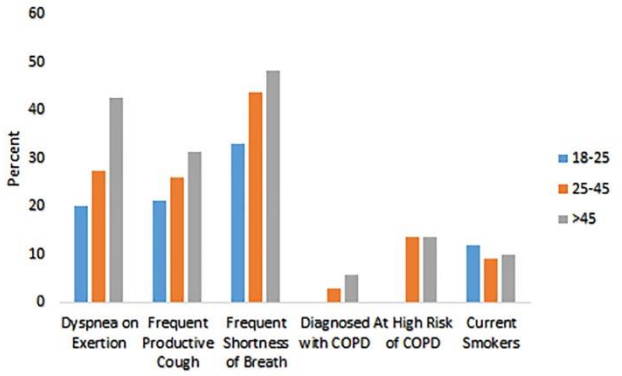

Figure 1. Prevalence of respiratory symptoms, current smoking, and COPD risk among adults aged 18 years and older across age categories

According to the defined criteria, three risk categories for COPD were identified. The prevalence of DN, HR, and LR was 5.0% (95% CI: 3.17-6.83), 13.2% (95% CI: 12.92-13.48), and 81.8% (95% CI: 78.55-85.05), respectively. The mean age was 55.69±2.67 years in the DN group, 53.57±2.05 years in the HR group, and 50.35±0.76 years in the LR group.

As shown in Figure 2, current smoking patterns varied across provinces and age groups. Younger adults (18–25 years) had the highest smoking prevalence in Khouzestan, while participants aged 25–45 years showed the greatest rates in Kerman. In older adults (>45 years), smoking was most common in Mazandaran, with lower prevalence in Tehran and Khorasan.

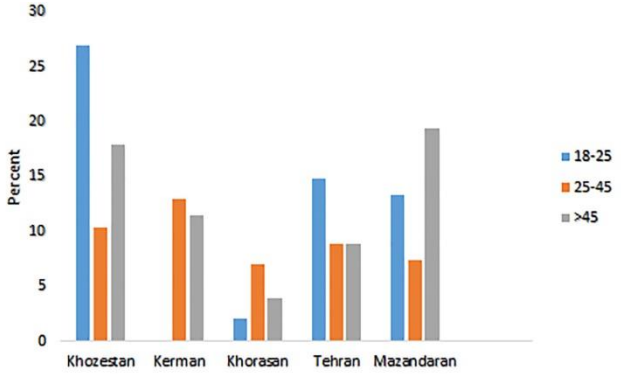

Figure 2. Current smoking rate among adults aged 18 years and older in selected provinces

The distribution of COPD risk categories by participant characteristics is presented in Table 1. Overall, the frequency of DN differed significantly from LR, and HR also differed significantly from LR (P <0.001), and men showed a higher prevalence of both DN and HR compared with women. DN and HR were more common in participants older than 45 years, whereas younger individuals were predominantly LR. Provincial variation was evident, with the highest DN prevalence observed in Kerman (13.9%) and the highest HR prevalence in Mazandaran (40%). Current and long-term smokers exhibited substantially higher HR prevalence, while LR was most common among never smokers.

The prevalence of comorbidities, health impairment as measured by the SF-12 questionnaire, and respiratory symptoms across COPD categories is shown in Table 2. Hypertension had the highest prevalence among the comorbidities, with 40.7% in the DN group, 33.3% in the HR group, and 30.5% in the LR group. Coronary heart disease and diabetes were also relatively common. Poor general health was more frequent in the DN group than in

the LR group (P<0.001), and it was also more frequent in the HR group than in the LR group (P<0.001). Low PCS and MCS scores were less frequent in the LR group than in the other risk categories (P<0.001). Difficulty walking was more common in the DN and HR groups than in the LR group (P<0.001). Dyspnea on exertion was more frequent in the DN group, while frequent productive cough and frequent shortness of breath were more frequent in the HR group than in the LR group (P<0.001).

Provincial differences in symptom patterns are shown in Figure 3. Dyspnea on exertion was most common in Kerman, productive cough was highest in Khouzestan and Kerman, and frequent shortness of breath predominated in Khouzestan and Khorasan, with lower levels in Tehran and Mazandaran.

Table 3 shows strong provincial differences in symptom prevalence across COPD risk groups. HR participants had the highest symptom burden, with frequent shortness of breath reaching 83% in Mazandaran, 100% in Khorasan, and 100% in Kerman. DN cases in Khorasan and Khouzestan also showed uniformly high symptoms (100% across several measures). In contrast, LR groups consistently reported far fewer symptoms, such as 12.5% productive cough in Mazandaran and 12-57% dyspnea on exertion in most provinces. Tehran displayed the lowest rates among DN individuals (e.g., 28.6% shortness of breath), with only modest increases in HR participants (e.g., 10% dyspnea on exertion).

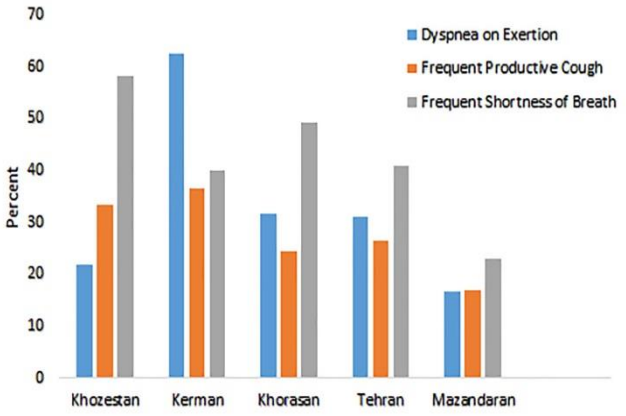

Figure 3. Prevalence of respiratory symptoms in selected provinces

Table 1. Prevalence of COPD risk categories in adults over 18 years according to demographic characteristics

Variable		DN [a] (n=27) (%, 95% CI)		HR [b] (n=33) (%, 95% CI)		LR [c] (n=203) (%, 95% CI)		P- value DN vs. HR	P- value DN vs. LR	P- value HR vs. LR
Overall		5	(3.17-6.83)	13.2	(12.92-13.48)	81.8	(78.55-85.05)	0.23	<0.001	<0.001
Sex	Men	6.4	(3.27-9.53)	36	(35.39-36.61)	57.6	(51.28-63.92)	0.02	0.001	<0.001
	Women	3.9	(1.73-6.97)	1.2	(1.08-1.32)	94.9	(92.44-97.39)	1.00	<0.001	0.002
Age, year	18-25	0	-	0	-	100	-	-	0.2	<0.001
	25-45	3	(0.63-5.38)	13.5	(13.02-13.98)	83.5	(78.33-88.67)	1.00	0.004	<0.001
	>45	5.7	(3.21-8.19)	13.5	(13.13-13.87)	80.8	(76.58-85.02)	0.36	<0.001	<0.001
Province	Mazandaran	3.7	(0-7.86)	40	(38.92-41.08)	56.3	(45.36-67.24)	0.04	0.4	0.001
	Khorasan	2.8	(0.8-6.61)	8.4	(7.76-9.04)	88.8	(81.52-96.08)	1.00	0.001	<0.001
	Ahvaz	3.8	(0.68-6.92)	14.6	(14.02-15.18)	81.6	(75.27-87.93)	1.00	0.007	<0.001
	Kerman	13.9	(9.02-18.78)	10.3	(9.87-10.73)	75.8	(69.76-81.84)	1.00	<0.001	0.01
	Tehran	4.1	(0-9.39)	13.3	(12.39-14.21)	82.6	(72.49-92.71)	1.00	0.02	<0.001
Education	Uneducated or basic	6.1	(3.29-8.91)	13.1	(12.70-13.5)	80.8	(76.17-85.43)	0.6	<0.001	<0.001
	High school	4	(0.78-7.13)	17.5	(16.89-18.11)	78.5	(71.95-85.05)	1.00	0.009	<0.001
	University	3.7	(0.12-7.28)	7.7	(7.19-8.21)	88.6	(82.58-94.62)	1.00	0.01	0.001
Smoking	Never smoker	4.2	(2.35-6.05)	-	-	95.8	(93.95-97.65)	-	<0.001	-
	Current smoker	9.1	(0.6-17.60)	72.7	(71-38-74.02)	18.2	(6.8-29.60)	0.01	1.00	0.01
	Ex- smoker	7.1	(0-14.87)	81	(79.81-82.19)	11.9	(2.11-21.69)	0.003	1.00	0.19
Smoking duration, year	<10	4.2	(2.36-6.04)	-		95.8	(93.96-97.64)	-	<0.001	-
	>=10	9	(2.65-15.35)	84.6	(83.80-85.40)	6.4	(0.97-11.83)	<0.001	-	-

Table 2. Prevalence of health characteristics and respiratory symptoms in adults over 18 years old according to COPD risk

	DN [a] (n=27) (%, 95% CI)		HR [b] (n=33) (%, 95% CI)		LR [c] (n=203) (%, 95% CI)		P- value		
							DN vs. HR	DN vs. LR	HR vs. LR
Chronic conditions									
Coronary heart disease	11.1	(0-22.95)	24.2	(9.59-38.81)	24.8	(18.86-30.74)	1.00	0.02	<0.001
Blood pressure	40.7	(22-59.23)	33.3	(17.22-49.38)	30.5	(24.17-36.83)	0.58	<0.001	<0.001
Diabetis	23.1	(7.2-39)	9.1	(0-18.91)	23.8	(17.94-29.66)	1.00	<0.001	0.001
Lung cancer	0	-	-	-	-	-	-	-	-
CVA	0	-	0	-	1.5	(0-3.17)	0.2	<0.001	<0.001
TB	0	-	-	-	-	-	-	-	-
Health impairment									
General health, fair or poor	66.7	(49.23-84.37)	60.6	(52.2-69)	55.1	(48.26-61.94)	0.21	<0.001	<0.001
MCS[+], low	40	(21.52-58.48)	33.3	(17.22-49.38)	29	(22.76-35.24)	0.59	<0.001	<0.001
PCS[++], low	30.3	(6.52-37.88)	22.4	(14.62-45.98)	22.2	(16.66-28.14)	0.57	<0.001	<0.001
Difficulty walking or climbing stairs	25.6	(0-22.95)	18.2	(5.04-31.36)	11.1	(19.60-31.60)	1.00	0.01	<0.001
Respiratory symptoms									
Frequent shortness of breath	47	(28.17-66.83)	33	(16.96-49.04)	15	(10.09-19.91)	0.2	<0.001	<0.001
Frequent productive cough	40.7	(22.17-59.23)	42.4	(25.54-59.26)	38.9	(32.19-45.61)	0.3	<0.001	<0.001
Dyspnea on exertion	53.3	(34.48-72.12)	36.4	(19.98-52.82)	39.9	(33.16-46.64)	0.59	<0.001	<0.001

[+]Mental cumponent summary, [++]Physical cumponent summary

Table 3. Prevalence of respiratory symptoms in adults over 18 years old, at risk for COPD, according to selected provinces

Province	Frequent shortness of breath						Frequent productive cough						Dyspnea on exertion					
	DN [a] (n=27) (%, 95% CI)		HR [b] (n=33) (%, 95% CI)		LR [c] (n=203) (%, 95% CI)		DN [a] (n=27) (%, 95% CI)		HR [b] (n=33) (%, 95% CI)		LR [c] (n=203) (%, 95% CI)		DN [a] (n=27) (%, 95% CI)		HR [b] (n=33) (%, 95% CI)		LR [c] (n=203) (%, 95% CI)	
Mazandaran	50	(29-71)	83.3	(72.3-94.3)	100	(100-100)	50	(35.6-70.0)	83.3	(77.3-89.3)	12.5	(5.5-20)	100	(100-100)	16.7	(6.7-26.8)	12.5	(6.5-18.5)
Khorasan	100	(100-100)	100	(100-100)	87.3	(80.1-94)	75	(64.5-85.5)	14.3	(11.3-17.3)	33.8	(18.8-52.6)	50	(41-59)	57.1	(37.2-77)	33.8	(15-48.8)
Khouzestan	100	(100-100)	100	(100-100)	100	(100-100)	33.7	(28.7-38.7)	28.6	(18.6-50.6)	48.6	(36.6-56.6)	0	(0-0)	42.9	(32-54)	28.6	(11-46.2)
Kerman	50	(31.5-68.5)	100	(100-100)	90.5	(79.7-100)	37.5	(28.5-46.5)	100	(100-100)	81	(74-88)	100	(100-100)	100	(100-100)	57.1	(40-74.1)
Tehran	28.6	(15.9-41.3)	100	(100-100)	100	(100-100)	25	(15-35)	30	(23.5-36.5)	30.2	(26.7-33.5)	0	(0-0)	10	(3-27)	49.2	(35-63.4)

DISCUSSION

We evaluated demographic characteristics, smoking status, and respiratory symptoms among adults from five provinces in Iran according to three defined COPD risk categories, including diagnosed, high-risk, and low-risk groups. In this study, a considerable proportion of participants (13.2%) fell into the high-risk group across provinces from different regions of Iran, indicating a substantial population at risk of developing COPD. COPD was confirmed by spirometry in 5% of all subjects. Similar results have been reported elsewhere; for example, COPD prevalence of 6-7% has been documented among adults in the United States (22,23).

It has been demonstrated by Martinez *et al.* that for two decades, approximately 70% of participants aged 20 to 79 years with spirometry-based obstruction were not diagnosed as having COPD (24). Other national sample studies have reported even higher rates of undiagnosed COPD, exceeding 80% (14,15).

In the present study, many characteristics were similar between the diagnosed and high-risk groups. However, the frequency of men in the high-risk group was higher than in the diagnosed group. Women were more frequently classified as low risk, and this difference was significant. Pleasants et al. similarly reported that the percentage of females was greater among those with

diagnosed COPD, whereas males were more likely to be at high risk (25).

Regarding age groups, all individuals aged 18-25 years were categorized as low risk. Smoking status was the most important factor examined across groups. The frequency of current smokers was significantly higher in the high-risk group compared with both the diagnosed and low-risk groups. Among non-smokers, the frequency of low-risk status was significantly higher than that of diagnosed COPD. Cigarette smoking is consistently identified as an important risk factor for COPD. It has even been proposed as a main cause in younger adults, with a clear dose–response pattern in which the risk of COPD increases progressively with higher cumulative smoking exposure, including rising incidence across <10, 10–20, and ≥20 pack-year categories (26,27). The estimated proportion of COPD attributable to smoking has been widely cited (17,20). As previously reported (11), a significant association exists between current and ex-smokers and COPD in Iran. Other studies have similarly shown a higher prevalence of diagnosed and high-risk COPD among smokers (5,28). Multiple studies demonstrate that more than 15% of smokers will develop chronic airway obstruction according to COPD criteria, with estimates ranging from 25%-50 % (29-31).

These findings suggest that evaluating smoking status in primary care settings as an indicator of high-risk status may contribute to earlier diagnosis and potentially to preventive interventions. Another noteworthy finding is that smoking for more than ten years was significantly more common in the high-risk group than in the diagnosed group, further highlighting the importance of smoking duration as a risk factor in the development of COPD.

The most common respiratory symptom overall was shortness of breath, followed by cough with phlegm and dyspnea. Importantly, all these symptoms were significantly more common in the diagnosed COPD and high-risk groups compared with the low-risk group.

Strengths and Limitations

A key strength of this study is the inclusion of participants from both rural and urban areas across major provinces, providing a diverse and regionally representative sample of adults. The assessment of respiratory symptoms, smoking exposure, and health impairment in the general population allowed for the identification of groups at high risk for having or developing COPD. The multicenter design enhances the generalizability of the findings.

However, the study also has limitations. The cross-sectional design does not allow for assessment of temporal or causal relationships between risk factors and COPD development. Reliance on self-reported smoking history and symptoms may introduce recall bias. Additionally, although the sample was drawn from multiple provinces, it may not fully capture all socioeconomic and environmental variations across the entire country. Finally, the classification of high-risk individuals was based on defined criteria rather than longitudinal clinical outcomes, which may affect risk categorization.

CONCLUSION

This study provides a comprehensive overview of respiratory symptoms, smoking behavior, and COPD risk categories among adults from five provinces in Iran. We identified a substantial proportion of individuals at high risk for COPD, as well as a notable burden of undiagnosed disease. Smoking status and duration were strongly associated with both diagnosed and high-risk COPD, underscoring the need for targeted screening and early intervention strategies in primary care.

By characterizing symptom patterns and identifying individuals who may benefit from further evaluation, these findings can support national efforts in advocacy, policy making, and clinical practice aimed at earlier detection and prevention of COPD.

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