Original Article

Burden of obstructive lung disease study in Tehran: Prevalence and risk factors of chronic obstructive pulmonary disease

Hooman Sharifi, Mohammad Reza Masjedi[1], Habib Emami, Mostafa Ghanei[2], Alireza Eslaminejad[1], Golnar Radmand[1], Sonia Buist[3]

Tobacco Prevention and Control Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, [1]Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, [2]Baqiyatallah Research Center of Gastroentrology and Liver diseases, Baqiyatallah University of Medical Sciences, Tehran, Iran, [3]Oregon Health and Science University, Portland, Oregon, USA

ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) was ranked the sixth-most common cause of death worldwide in 1990, but now it is the third-most common cause. The goal of the present study was to assess the prevalence and determine the causes and risk factors of COPD in Tehran. **Materials and Methods:** This study followed a stratified cluster sampling strategy with proportional allocation within strata. The target population was all non-institutionalized inhabitants, aged 18 to 40 in one group and over 40 in another who resided in Tehran in 2013. The core questionnaire was developed from pre-existing validated questionnaires that had already been used in multi-national studies. The single most important outcome measure obtained as part of this protocol was spirometry before and after the administration of 200 mg (two puffs) of salbutamol. **Results:** The most commonly reported respiratory symptoms were: sputum production in 291 patients (16.2%) [95% confidence interval (CI): 14.5-17.9%], chronic cough in 171 (9.5%) (95% CI: 8.2-10.9%), wheezing in 377 (21.0%) (95%CI: 19.1-22.9%) and dyspnea in 388 patients (21.6%) (95% CI: 19.7-23.5%). The overall COPD prevalence defined by the post-bronchodilator spirometric functional criteria was 9.2%. This value in men (10.1%) was higher than in women (8.5%); the prevalence was significantly higher in subjects aged over 55 years ($P \leq 0.002$). The prevalence of COPD was strongly dependent on smoking status, especially in ex-smokers, and increased considerably with age. 69% of patients with COPD were non-smoker. **Conclusion:** The high prevalence of verified COPD, a great deal of which was undiagnosed before by a physician, highlights the necessity of raising awareness of this disease among health professionals, and use of spirometry in the primary care setting. A future cross-sectional and prospective cohort study should be performed to explore all risk factors and their impact on decline in lung function and worsening of respiratory symptoms especially in non-smokers.

KEY WORDS: Chronic obstructive pulmonary disease, Iran, prevalence

Address for correspondence: Prof. Mohammad Reza Masjedi, Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran. E-mail: drhooman2000@yahoo.com

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) was ranked as the sixth-most common cause of death worldwide in 1990, but is now the third-most common cause;[1] it has been ranked fourth in developed countries, with approximately 2.75 million deaths per year, or 4.8% of all deaths in these countries.[2]

It has been estimated that the global burden of chronic respiratory diseases (CRDs) will increase notably in the future, even though a lot of preventable CRDs can be controlled with adequate management in both developed and developing countries.[3] COPD is characterized by chronic inflammation and non-fully reversible airflow

obstruction, involving structural changes in the lungs that can be demonstrated by a postbronchodilator FEV1/FVC ratio of 70% ("fixed ratio").[4]

Tobacco smoking has proven to be the most important risk factor for development of COPD;[5] however, not all patients with COPD have a history of smoking. It seems that about 50% of cases worldwide are related to smoking,[6] and an estimated 10%-12% of individuals with COPD have never smoked.[7] In other words, non-fully reversible airflow obstruction also occurs in nonsmokers. Iran is a developing country where the smoking rate (14.8%) is lower than that observed in many developed countries.[8]

National estimates of COPD prevalence are usually based on self-reported questionnaires without objective measurement of lung function by spirometry testing.

One survey of COPD in Isfahan estimated the prevalence of 5.7%.[9] Several investigations, using spirometry, conducted in different countries have demonstrated the under-diagnosis of COPD. The most extreme example was observed in Japan, where the results of the 2004 population-based prevalence of COPD survey contrasts with the estimates of the Japanese Ministry of Health (10.9% *vs.* 0.3%, respectively).[10] Similar rates of under diagnosis have been frequently reported.[11]

Considering the impact of COPD, it seems that this chronic disease fails to receive sufficient attention from the healthcare community and governments and is rather unknown among the public. A great problem seems to be the lack of information about the prevalence and risk factors of COPD, especially in developing countries.

The estimation of COPD prevalence undoubtedly depends on the characteristics of screened population and criteria used to diagnose COPD, with continuing debate over the fixed spirometry ratio of 0.7 or lower limit of normal.[12]

Research on different aspects of COPD is an important health priority of academic institutions and governments, both for its high prevalence in different regions[13] and because this disease has proven to be potentially preventable[14] by cessation of smoking and air pollution control.

Although COPD is one of the leading causes of mortality and morbidity, epidemiological data on COPD are very limited in the Eastern Mediterranean Region, including Iran. The international, population-based Burden of Obstructive Lung Disease (BOLD) initiative was designed a decade ago to develop robust models that can be used to estimate the prevalence and current and future economic burden of COPD.[15]

The goal of our study was to describe the prevalence and determine the causes and risk factors of COPD in Tehran.

MATERIALS AND METHODS

Population and sampling strategy
The sample in this study was the population of Tehran. It was considered to be 8.1 million.

Sample size
Considering a design effect of 1.5, prevalence rate of 11% in previous studies, and a response rate of 60%, total sample size was calculated to be 750.

Sampling plan
This study followed a stratified cluster sampling strategy with proportional allocation within strata. The target population was all non-institutionalized inhabitants, aged 18-40 in one group and over 40 in another, who resided in Tehran in 2013.

The stratification of the sample was based upon the 22 municipal districts of Tehran. Proportional to the number of households in the 22 districts, the appropriate number of clusters was weighted according to each district. The number of clusters was based on total sample size, mean household members, and logistical facilities for subject enumeration, transport, and examination.

For each cluster, a team of three members (one male and one female aged less than 28 as interviewers) approached the index household, specified through the aforementioned random selection of clusters, and continued the enumeration in 10 neighboring households in a systematic manner. In the indexed household if there was more than one person, interviewers were advised to use the Kish method to choose the right participant(s). This method is a table of numbers, and is named according to the statistician who invented it (the number of people in the household is discovered, and a random number is chosen to select a particular person).

Examination protocol
The examination protocol included a questionnaire covering respiratory symptoms, health status, activity limitation, and exposure to potential risk factors, such as tobacco smoke, occupational risk factors, and biomass exposure. Subjects also underwent pre- and post-bronchodilator spirometry tests. Spirometry records provide the 1-second and 6-second forced expiratory volumes (FEV1 and FEV6) and the forced vital capacity (FVC).

Questionnaires
The core questionnaire was developed from pre-existing validated questionnaires that had already been used in multi-national studies.[5] The questionnaire contained information about respiratory symptoms, exposure to potential risk factors such as smoking, occupation, respiratory diseases, co-morbidities, healthcare provisions, medication use, activity limitation, and health status.

Participants also completed an occupational questionnaire and a "stages of change" questionnaire assessed readiness

of current cigarette smokers to quit smoking. There was also a questionnaire to assess exposure to biomass fuels used at home for either heating or cooking. All questionnaires were translated to Persian first and then back translated to English by a different translator. Trained certified staffs administered the questionnaires; self administration of questionnaires was not allowed.

Spirometry

The single most important outcome measure obtained as part of this protocol was spirometry results before and after the administration of 200 mg (2 puffs) of salbutamol. Our diagnosis of COPD was based on documentation of FEV1/FVC below the fixed ratio of 0.7. To optimize quality control in this study, all teams were required to use the 2120 In2itive Vitalograph Spirometer. This particular device was chosen because of its accuracy, robustness, portability, and ease of storage. Also, it can be used easily in the field and where there is no electric power. The 2120 In2itive Vitalograph Spirometer has been approved by the National Research Institute of Tuberculosis and Lung Disease to meet the predetermined performance criteria in terms of the reliability of measurement, suitability for field use, and easy access to data.

COPD was defined using the Global Initiative for Obstructive Lung Disease definition of post-bronchodilator FEV1/FVC of 0.7. Identification of symptomatic patients was based on clinical diagnosis of dyspnea, chronic cough or sputum production.[5]

Statistical analysis

In calculating standard errors and the 95% confidence interval for categorical and continuous variables, the cluster sampling design was taken into account and adjusted. In addition to descriptive analyses, odds ratios were calculated with multivariate logistic regression in order to control potential confounding variables, and account for cluster design effects.

RESULTS

Participants

A total of 1,798 individuals were visited in 22 districts of Tehran; 811 (45.1%) men and 987 (54.9%) women participated in the structured interviews. These districts were located in the north, south, west, east, and center of Tehran. Table 1 shows the demographic characteristics of subjects.

Smoking habits

A history of current or past smoking was more frequent in men than women. Of all participants, 190 (10.6%) were smokers; out of which, 168 (88.4%) were men and 22 (11.6%) were women; 151 (8.4%) were ex-smokers [Table 1].

Amongst subjects with COPD according to the spirometry tests, 9 (12.6%) were smokers, 13 (18.3%) were ex-smokers, and 49 (69%) were non-smokers.

Table 1: Demographic characteristics

Characteristics	Subjects number	%
Gender		
Male	811	45.1
Female	987	54.9
Age year		
<40	891	49.6
+40	900	50.1
Unknown	7	0.4
Mean±SD	42.96±15.85	
Smoking status		
Non-smoker	1457	81.0
Ex-smoker	151	8.4
Current smoker	190	10.6
Male	168	88.4
Female	22	11.6

SD: Standard deviation

Respiratory symptoms in subjects

The most commonly reported respiratory symptoms were: Sputum production in 291 patients (16.2%) (95% CI: 14.5-17.9%), chronic cough in 171 (9.5%) (95% CI: 8.2-10.9%), wheezing in 377 (21.0%) (95% CI: 19.1-22.9%) and dyspnea in 388 patients (21.6%) (95% CI: 19.7-23.5%). Of patients over 40 years, 337 men and 438 women underwent spirometry measurement and 125 participants did not meet spirometry criteria [Table 2]. The overall COPD prevalence defined by the post-bronchodilator spirometric functional criteria was 9.2%, higher in men (10.1%) than in women (8.5%); the prevalence was significantly higher in subjects aged over 55 years [$P \leq 0.002$, Tables 2 and 3, Figure 1].

The prevalence of self-reported chronic bronchitis, emphysema or COPD in all participants over 40- years was 333 (37%). This value is four times more than the estimated prevalence of GOLD stage I or higher COPD in our study. The prevalence of prior medical diagnosis among all participants over 40-years was 37 (4.1%). In both cases, women were higher compared to men [Table 2].

Multivariate relationships

We performed univariate and multivariate logistic regression to assess the association of COPD and risk factors. In univariate logistic regression, the odds ratio (OR) for gender was 1.195 (95% CI: 0.733-1.949), and after including age, gender, smoking habits, family history of obstructive airway disease, and socio-economic group in the model, and after mutual adjustment for all these potential factors in the model, we found that age and smoking were the two major risk factors in our understudy population. The prevalence of COPD was strongly dependent on smoking status, especially in ex-smokers, and increased considerably with age [Table 4].

DISCUSSION

In this study, we estimated the prevalence of COPD using questionnaires and spirometry of people aged 18 years and older living in Tehran. The sample in this

Table 2: COPD prevalence according to age, gender, and COPD definition criteria*

Age, year	Female 438	Male 337	Total 775	Female 508	Male 392	Total 900	Female 508	Male 392	Total 900
40-54	15 (3.4)	8 (2.4)	23 (3.0)	15 (3.0)	2 (0.6)	17 (1.9)	123 (24.2)	57 (14.5)	180 (20.0)
≥55	22 (5.0)	26 (7.7)	48 (6.2)	11 (1.8)	11 (2.8)	20 (2.2)	87 (17.1)	66 (16.8)	153 (17.0)
Total	37 (8.5)	34 (10.1)	71 (9.2)	24 (4.7)	13 (3.3)	37 (4.1)	210 (41.3)	123 (31.4)	333 (37.0)
95% CI	5.9-11.1	6.9-13.3	7.2-11.2	2.9-6.6	1.5-5.1	2.8-5.4	37.1-45.6	26.8-36.0	33.8-41.2

*Data are presented as No. (%) unless otherwise indicated. COPD definition criteria, Spirometry: Postbronchodilator, Medical: Prior medical diagnosis, Clinical: Chronic bronchitis, FEV1/FVC <70%. CI: Confidence interval, COPD: Chronic obstructive pulmonary disease

Table 3: COPD distribution according to socio-demographic and disease characteristics

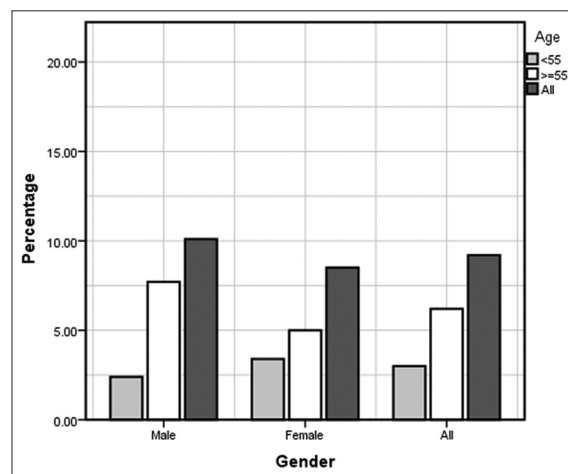| Characteristics	No COPD (n=711)	COPD (n=71) (%)	95% CI (%)	Total (n=782)
Gender				
Male	80.1%	9.9	6.7-13.1	343
Female	91.6%	8.4	5.8-11.0	439
Age				
<55 years	94.1%	5.9	3.6-8.3	387
≥55 years	87.6%	12.4	9.1-15.7	388
Education				
Illiterate	100%	0	-	2
<5 years of school	87.0%	13.0	9.1-16.8	312
5-12 years of school	91.3%	8.7	5.6-11.7	335
University education	97.0%	3.0	0.0-6.0	133
Body mass index				
Normal weight	83.2%	16.8	0-36.7	178
Overweight and obese	93.3%	6.7	4.7-8.7	595
Smoking				
Current smoker	86.6%	13.4	5.1-21.8	67
Ex-smoker	85.4%	14.6	7.1-22.1	89
Non-smoker	Non-smoker	7.8	5.7-9.9	626

CI: Confidence interval, COPD: Chronic obstructive pulmonary disease

Table 4: The odds ratio for having COPD (according to spirometry results)

Characteristic	categories	OR	95% CI
Age	≥55	2.17	1.27-3.71
	<55	1	
Smoking status	Current smoker	1.83	0.78-4.31
	Ex-Smoker	2.29	1.05-4.98
	Non-Smoker	1	
Gender	Male	0.71	0.38-1.30
	Female	1	
BMI	>25	0.38	0.22-0.64
	≤25	1	

Odds ratios adjusted for age, smoking status, sex and BMI with 95% confidence interval. OR: Odds ratio, BMI: Body mass index, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease

Figure 1: Chronic obstructive pulmonary disease (COPD) prevalence by gender

Town), Australia (Sydney), and Turkey (Adana).[16] These differences could be attributed to different rates of smoking habits in these regions, or possibly other risk factors, which have not been assessed yet and need further investigations (e.g., air pollution, district, biomass fuel, etc.). Moreover, similar findings were obtained in many other previous epidemiological studies.[17,18]

According to a study done in Isfahan, another mega city in Iran, the prevalence of airway limitation in the general population 40 years and older was 5.7%.[9] However, the above-mentioned studies had a different methodology and there seems to be a lack of relative longitudinal studies, conducted locally in Iran; whereas in other countries, researchers like Vasankari *et al.* compared the prevalence of COPD throughout a decade and found no increase in the prevalence trend in Finland.[19] Soriano *et al.* found an unexpected decrease in COPD prevalence in Spain.[20] The data from our present study will serve as a baseline for future studies on COPD.

study was representative of Tehran's adult population and the participation rates were exceptionally high for a comprehensive survey like this one. The key finding of this prevalence survey was that 9.2% of the residents of the capital of Iran, aged 40 years or older, had at least Stage I COPD, and this was more common in men than in women. This finding is similar to the results of studies in many other countries using the same BOLD methodology. COPD prevalence in Tehran is within the range found in other Asian countries like China (Guangzhou), and Philippines (Manila), but is lower than the observed prevalence in South Africa (Cape

The higher percentage of women in the study (54.9%) cannot be explained by the composition of the population in Iran, which is nearly equal between genders[21] but, mainly, by the cultural trait that women spend more time at home than men. In this study, the COPD prevalence in women was lower than that in men. This could be due to the fact that Iranian women are less likely to smoke. This situation proved to be contrary to some developed countries, where the prevalence of smoking in women

is higher than men and the same for COPD.[17] There has been considerable controversy as to whether women are at equal or perhaps at greater risk than men given an equal exposure. This controversy has not been resolved, although there is increasing evidence that women may be more vulnerable.[22] In developing countries, the increase in smoking among women, that is likely to occur, will probably lead to a tidal wave of COPD as women have more exposure and live longer. Women are also more likely than men to be exposed to high indoor air pollution levels in developing countries. Fossil fuel pollution has been found to have a greater effect on women compared to men.[23]

It had been difficult for a long time to estimate the COPD prevalence,[5] and there has been an ongoing discussion about how to improve early detection of COPD. In this report, we found a low prevalence (4.1%) of previously diagnosed COPD, and a high prevalence of self-reporting. The stepwise and slow progressive nature of COPD means that most sufferers tend not to complain of respiratory symptoms and consequently the disease usually remains undetected by health providers for many years. Moreover, an insufficient distribution of spirometers in the clinics may influence the prevalence of undiagnosed COPD cases. Another reason for the high rate of undiagnosed patients seems to be physicians' and patients' attitudes. Studies have shown that under-diagnosis of COPD has been raised partly due to "physicians' delay", i.e., doctors who do not suspect underlying COPD[24] and partly because of "patients' delay", i.e., patients who self-report good health.[25] However, the early stages of COPD are difficult to diagnose without spirometry. Actually, spirometry is not widely used among Iranian general physicians. This study suggests that general clinics must be equipped with spirometers in order to reduce the number of undiagnosed COPD cases. This is particularly relevant when evaluating the respiratory function of individuals with clinical signs of airflow obstruction.

It seems that primary screening for airflow obstruction with a handheld spirometer prior to full spirometry testing, which is easy to carry-out in all settings, could be considered as an efficient way to screen or find new COPD cases.[26]

In this study, we found that the prevalence of airflow limitation was higher in individuals who had ever smoked, which is similar to previous reports.[27] The odds of COPD were higher for ex-smokers. These figures suggest that approximately 25% of never-in-life smokers may develop COPD; although this figure has been reported from 15% to 50% in the literature.[17,28] Early detection of COPD seems to be important for early smoking cessation intervention and the administration of beta-agonists and inhaled corticosteroids.

Since this was a cross-sectional study, we were not able to assess the outcomes of COPD. However, the prevalence of COPD in non-smokers was 7.8%, which is similar to other countries in similar studies[28,29] and suggests that factors other than smoking exposure might also be involved in COPD.

However, it is surprising that in this study, a majority of patients with COPD were never smoker. The first reason could be that the subjects in our study were from general population, and were likely to have better lung function and fewer symptoms than a hospitalized COPD population. The second reason could be explained by available epidemiologic data which demonstrate that domestic biomass, fuel smoke, indoor air pollution, poor economic and social status, and existence of asthma might be important causes of COPD in never smokers.[30,31]

A future cross-sectional and prospective cohort study should be performed to explore these risk factors and their impact on decline in lung function and worsening of respiratory symptoms especially in non-smokers.

The present study may be subject to several biases: Although a weighting procedure was performed to make the sample as representative as possible, there was still a possibility of a selection bias because there was no means to evaluate the reasons of rejection, which could have led to an overestimation or underestimation of COPD prevalence. The authors of this study guess that refusals were linked to cultural traits, lack of motivation, illiteracy, or maybe chronic conditions that individuals did not want to disclose (cancer or other diseases). There is also a possibility of information bias in this study; as in all studies requiring questionnaires, relying on individuals reporting for different variables may include a recall bias (previous exposure data for example) or subjectivity bias (report of weight, height and symptoms for example). The main strength of this survey was the use of BOLD protocol, with a precise methodology to attain the upmost accuracy of the survey and a high-quality post-bronchodilator spirometry. This methodology ensured that data were as easy to compare as possible with other BOLD studies.[15] However, the methods used in the study are the ones that are currently being used in a large number of countries all over the world for this kind of study. As far as we realize, PREPOCOL study is the first population-based study done in South America and PLATINO is the second in Latin America, which used a spirometric definition (post-bronchodilator FEV1/FVC ratio of 70%) as the primary standard for determining the COPD prevalence. Although the use of a fixed ratio may underestimate the prevalence of airway obstruction in young and overestimate it in older individuals, we decided on BOLD method to facilitate the comparison of the prevalence with that determined by other studies.[5,29]

CONCLUSIONS

The 9.2% prevalence of COPD indicates that this disease is common in Tehran. The high prevalence of verified COPD, a great deal of which was undiagnosed before by a

physician, provokes the necessity of raising awareness of this disease among health professionals, and the necessity to use spirometry in the primary care setting.

Prevention programs including smoking cessation interventions must be implemented to reduce prevalence, morbidity, and mortality of COPD. Thus, it is crucial for physicians to identify the high-risk group and offer them spirometry testing for early detection of COPD, which may motivate them to quit smoking.

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