

# Burden of Obstructive Lung Disease Study in Tehran: Research Design and Lung Spirometry Protocol

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**Date of Submission:** Jan 16, 2014

**Date of Acceptance:** Aug 13, 2014

**How to cite this article:** Sharifi H, Masjedi MR, Emami H, Ghanei M, Buist S. Burden of Obstructive Lung Disease Study in Tehran: Research Design and Lung Spirometry Protocol. *Int J Prev Med* 2014;5:1439-45.

## ABSTRACT

**Background:** Chronic obstructive pulmonary diseases (COPD) are planned to rank fifth in burden of disease and third with respect to mortality by 2020. Carrying out research regarding different aspects of COPD is mentioned as important health priorities by academic institutions and governments. The burden of 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. The goal of the present project is to describe the prevalence and determining the causes and risk factors of COPD in the population of Tehran city.

**Methods:** This cross-sectional study follows a stratified cluster sampling strategy with proportional allocation within strata. The target population is all noninstitutionalized inhabitants, aged 18-40 in one group and over 40 in another, who inhabit in Tehran city. The stratification of the sample according to the 22 municipal districts of Tehran is incorporated in the sampling process. Proportional to the number of households in the 22 districts, the appropriate number of clusters is weighted according to each district. For each cluster, a team of three members approaches the index household, which is specified through the aforementioned random selection of clusters, and continues the enumeration in 10 neighbor households in a systematic manner.

**Results:** As a study protocol, there are no specific results to present; our purpose is to share our design with the scientific body.

**Conclusions:** We expect that findings from the BOLD study in Tehran will show the status of COPD and its causes in the community.

**Keywords:** Chronic bronchitis, chronic obstructive pulmonary disease, Iran, prevalence

## INTRODUCTION

Chronic obstructive pulmonary diseases (COPD) are planned to rank fifth in burden of disease and third (postheart attack and stroke) with respect to mortality by 2020 worldly wide.<sup>[1,2]</sup> Besides, COPD fails to receive sufficient care from the health

care community and governments and is rather unfamiliar 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 spirometric ratio of 0.7 or lower limit of normal method.<sup>[3]</sup>

Carrying out research regarding different aspects of COPD is mentioned as important health priorities by academic institutions and governments, both for its high prevalence in different regions<sup>[4]</sup> and because this disease proved to be potentially preventable<sup>[5]</sup> by smoking cessation, and air pollution control. There are a few published studies regarding this issue amongst Iranian population. It seems that insufficient distribution of spirometers in general clinics is a considerable reason that leads to underestimation of COPD in developing countries like Iran.<sup>[6]</sup> To the best of our knowledge, this is the first Interval study performed in Tehran regarding the prevalence of COPD. The burden of 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.<sup>[7]</sup>

In this paper, we report a tailored BOLD design to provide a standardized framework for estimating COPD prevalence, risk factors, and economic burden in Iran.

### Specific objectives

- To measure the prevalence of COPD and its risk factors in Tehran
- To estimate the burden of COPD in terms of its impact on quality-of-life, activity limitation, respiratory symptoms, and use of health care services
- To determine the extent to which variations in risk factors contribute to variations in the prevalence of COPD
- To describe the distribution of COPD according to age, sex, and smoking history
- To describe the main clinical symptoms reported by subjects diagnosed with COPD
- To assess the sensitivity and specificity of selected clinical symptoms for COPD using lung function testing as the gold standard.

## METHODS

The Tehran BOLD Study has been designed as a cross-sectional survey among population of Tehran.

### Population and sampling strategy

Since 1976, Tehran province includes seven cities and amongst them Tehran is the biggest one. The 2011 census recorded Tehran region's population as 12 million, 8.1 million of which belonged to Tehran city. The sampling frame in this study is the population of Tehran city. Table 1 shows the distribution of families and population in 22 municipal districts according to the 2011 census. It is considered that the present population in this area is nearly 8.1 million, but there is no evidence suggesting any change in the distribution. Accordingly, we will distribute our sample on the basis of the population size of each district in 2011.

### Number of households in Tehran city

Census 2011 statistics demonstrated that there are 1,660,219 households and 8,154,051 inhabitants

**Table 1:** Distribution of Tehran population in 22 municipal districts

Province	District	Family	Male	Female	Total
Tehran	1	141,426	216,011	223,456	439,467
Tehran	2	205,883	312,830	320,087	632,917
Tehran	3	106,046	148,621	165,491	314,112
Tehran	4	270,948	429,903	431,377	861,280
Tehran	5	255,333	391,297	402,453	793,750
Tehran	6	73,212	110,751	119,229	229,980
Tehran	7	108,728	150,025	159,720	309,745
Tehran	8	125,757	185,515	192,603	378,118
Tehran	9	50,591	80,744	77,772	158,516
Tehran	10	104,720	150,050	152,802	302,852
Tehran	11	98,556	142,877	146,007	288,884
Tehran	12	76,628	122,141	118,579	240,720
Tehran	13	89,582	136,706	139,321	276,027
Tehran	14	153,649	244,122	240,211	484,333
Tehran	15	192,610	325,313	313,427	638,740
Tehran	16	89,928	144,578	143,225	287,803
Tehran	17	75,872	125,364	123,225	248,589
Tehran	18	115,151	199,623	191,745	391,368
Tehran	19	70,349	124,481	119,869	244,350
Tehran	20	104,275	170,859	170,002	340,861
Tehran	21	50,381	82,014	80,667	162,681
Tehran	22	38,106	65,476	63,482	128,958
Total		2,597,731	4,059,301	4,094,750	8,154,051

in Tehran city. The number of households within each district of Tehran city are presented in Table 1.

### Sample size

In order to calculate sample size, the aim we have considered is to estimate the prevalence of variables with proportions as little as 0.02 ( $P$ ). On this assumption, for a 95% confidence interval ( $Z_{1-\alpha/2} = 1.96$ ) and precision of 0.05 ( $d$ ), the sample size, considering previous studies, is calculated as follows:

$$N = \frac{(0.89)0.11*(1.96)^2}{(0.05)^2}$$

Considering a design effect of 1.5, prevalence rate of 11% (considering similar article published in Iran),<sup>[8]</sup> and a response rate of 60%,<sup>[8]</sup> total sample size is calculated by 375 which becomes in two different sexes by 750.

Burden of lung disease study is designed primarily as a COPD prevalence survey amongst noninstitutionalized adults aged 40 years and over.

This age range was chosen for efficiency, as the prevalence of COPD climbs steeply over age 40. In order to develop valid estimates of future burden of disease, researchers are encouraged to survey an additional cohort on the prevalence of smoking and other key risk factors. The additional cohort, made up of at least the same number of participating men and women aged 18-39 years, will not be asked to provide lung function measurements.

### Sampling plan

This study follows a stratified cluster sampling strategy with proportional allocation within strata. The target population is all noninstitutionalized inhabitants, aged 18-40 in one group and over 40 in another, who inhabit in Tehran city in the year 2013.

The stratification of the sample according to the 22 municipal districts of Tehran city is incorporated in the sampling process. Proportional to the number of households in the 22 districts [Table 1], the appropriate number of clusters is weighted according to each district. The decision about the number of clusters is 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 dressed in white medical overall and a driver) approaches the index household, which is specified through the aforementioned random selection of clusters, and continues the enumeration in 10 neighbor households in a systematic manner by proceeding round in a clock-wise direction. In indexed household, if there is more than one eligible person, interviewers are advised to use Kish method to choose the right participant(s). They introduce themselves by presenting their identification cards. Then they describe the project to the main person of the households. The household members are informed that they will be visited by the project staff. The team members approach clusters on Sundays and Mondays, and participants are examined on Fridays (formal weekend in Iran). At the end, all eligible household members are invited to complete questionnaires and if required pass spirometry test.

### Nonresponse

Eligible subjects who do not attend the examination process following the initial meeting will be contacted twice in subsequent weeks. Those who fail to appear even after the third invitation will be substituted by new subjects.

Although we try to keep nonresponse to a minimum number, any nonresponders should be characterized as much as possible using a short questionnaire. These data are used to determine ways in which they differ from responders and to gauge the likely impact of their nonresponse on the results of the study.

### Examination protocol

The examination protocol includes 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. They also perform pre- and post-bronchodilator spirometry tests. Spirometry records provide the 1-s and 6-s forced expiratory volumes (FEV1 and FEV6) and the forced vital capacity (FVC).

### Questionnaires

The Core questionnaire was developed from preexisting validated questionnaires that had already been used in multi-national studies. The questionnaire obtains information about

respiratory symptoms (cough, sputum, wheezing, shortness of breath); exposure to potential risk factors, including smoking; occupation; respiratory diagnoses (e.g. asthma, emphysema, COPD, chronic bronchitis); co-morbidities; health care utilization; medication use; activity limitation; and health status. It includes sections taken from the 1978 ATS/DLD Respiratory Symptom Questionnaire,<sup>[9]</sup> Respiratory Health Study,<sup>[10]</sup> the CNR study,<sup>[11]</sup> and the OLIN study.<sup>[12]</sup> It also includes the Short Form-12 to assess overall health status.<sup>[13]</sup>

Participants also are expected to complete an occupational questionnaire and (for current cigarette smokers) a “stages of change” questionnaire<sup>[2]</sup> that assesses readiness to quit smoking. There is also a questionnaire to assess exposure to biomass fuels used in the home for either heating or cooking. All questionnaires were translated to Persian first and then back translated to English by a different translator. The questionnaires are administered by trained and certified staff; self-administration of questionnaires is not allowed.

#### **Spirometry**

The single most important outcome measure obtained as part of this protocol is spirometry before and after administration of 200 mg (2 puffs) of salbutamol. The use of a bronchodilator is important because present diagnostic criteria for COPD recommend the use of postbronchodilator values for the diagnosis and classification of severity.<sup>[2]</sup> The methods developed for BOLD meet or exceed the ATS standards<sup>[13]</sup> for acceptable equipment and technique. The primary spirometry measurements to be used for analysis include the FEV<sub>1</sub>, the FVC, and the FEV<sub>6</sub>, allowing comparison of FEV<sub>1</sub>/FVC and FEV<sub>1</sub>/FEV<sub>6</sub> as measures of airflow limitation. The FEV<sub>6</sub> has been demonstrated as a viable surrogate for the FVC and has important advantages – it requires only 6 s of exhalation time and has about 25% less variability than the FVC.<sup>[14]</sup> In epidemiologic studies, there are significant advantages to requiring only 6 s of maximal exhalation, such as less coaching time, less chance of dizziness, and less physical discomfort to participants than a complete exhalation. To optimize quality control in this study, all teams are required to use the 2120 In2itive Vitalograph Spirometer, which was chosen because it provides an acceptable

degree of accuracy, robustness, portability, and ease of storage. It can be used easily in the field and where there is no electric power available. The 2012 In2itive Hand held Spirometry and Spirotrac V Part. No.79000 has been approved by National Research Institute of Tuberculosis and Lung Diseases as meeting predetermined performance criteria relating to reliability of measurement, suitability for field use, and ease of access to data.

#### **Other clinical measurements**

Participant’s height and weight are measured by trained field staff. Use of a wall-mounted stadiometer is recommended for height measurement to provide maximum quality control. Height and weight are measured with participants wearing indoor clothing without shoes. All teams are equipped with the same trade mark of stadiometers and weight scales.

#### **Definitions**

Chronic obstructive pulmonary disease is defined as a disease state characterized by airflow limitation that is not fully reversible.<sup>[15]</sup> The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Removal from the exposure usually slows the progression of disease.<sup>[15]</sup> COPD, once present, may have a lengthy and costly course.

A diagnosis of COPD should be considered in anyone, particularly smokers, with symptoms of cough, sputum production, or dyspnea, and/or a history of exposure to risk factors for the disease. Cigarette smoking is by far the most important risk factor in most countries, but other factors, such as heavy occupational exposures to particulates and indoor and outdoor air pollution, can be causally related to COPD when the exposures are sufficient.<sup>[15]</sup> Genetic risk factors may modify the risk, but these are poorly understood at present.

In line with GOLD criteria, a simple spirometric classification of disease severity into four stages is recommended [Table 2]. Spirometry is essential for diagnosis and provides a useful description of the severity of pathologic changes in COPD.

Specific spirometric cut points (e.g., postbronchodilator FEV<sub>1</sub>/FVC ratio, 0.70 or FEV<sub>1</sub>, 80, 50, or 30% predicted) are used for purposes of simplicity; these cut points have not been clinically validated.<sup>[13,16]</sup>



**Table 2:** Spirometric classification of chronic obstructive pulmonary disease severity based on postbronchodilator FEV1

Stage I: Mild
FEV1/FVC <0.70
FEV1 ≥80% predicted
Stage II: Moderate
FEV1/FVC <0.70
50% ≤ FEV1 <80% predicted
Stage III: Severe
FEV1/FVC, 0.70
30% ≤ FEV1 <50% predicted
Stage IV
Very severe FEV1/FVC, 0.70
FEV1 <30% predicted or FEV1 <50%

\*Predicted plus chronic respiratory failure; \*Respiratory failure: Arterial partial pressure of oxygen (PaO<sub>2</sub>) <8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO<sub>2</sub> (PaCO<sub>2</sub>) >6.7 kPa (50 mm Hg) while breathing air at sea level. FEV1=Forced expiratory volumes in 1 s, FVC=Forced vital capacity

### Observers training and quality assurance

Special attention should be paid to the quality of all measurements in this survey.<sup>[17]</sup>

All interviewers take part in a comprehensive training course run by National Research Institute of Tuberculosis and Lung Disease, which has been developed for conducting the protocol. Prior to undertaking the protocol, staff must be trained and certified in study procedures. Two members of our site attend a central training session to be trained as “master trainers” and be certified to help additional staff at the site. The course includes a full range of education and practice to ensure that all interviewers have a sufficient-based knowledge of the study process, study purposes, data forms, and technical skills needed to conduct the protocol in a scientifically sound manner. All staffs have to complete the training course prior to getting involved in the study. The program director and manager directly supervise the staff training process.

All interviewers receive regular quality control visits from the project manager who checks their performance. In addition, the data are reviewed periodically, and feedback is given to the observers weekly.

### Humanity and ethics

The study is approved by the Research and Ethics Committee of Shahid Beheshti University

of Medical Sciences and Ethics Committee of National Research Institute of Tuberculosis and Lung Disease. Participants must provide informed consent for all aspects of the study. The exact wording of the consent documents is approved by Ethics Committee. Participants who are unwilling to provide informed consent are ineligible to participate in the study. All subjects included in this study will be informed about the project and the procedures in their native language before being enrolled. They will be informed that their participation is entirely voluntary and they may decide to withdraw from the study at any time.

The participants’ agreement for examination will be obtained in written form. The confidentiality of all study participants will be protected in accordance with a good epidemiological practice.

### Data handling and statistical analysis

#### Data entry

During the enumeration process, as data on each household are completed, a supervisor will do a check to see that all data is collected properly. Once data collection is completed for any given district, a copy of the data is also retained at the center for data safety purpose.

#### Data editing

During data entry, the forms will be checked for completeness and consistency by the data entry software. If the forms are not filled in completely, the concerned person will be consulted to fill in the missing data or clarify an inconsistent data. All changes and coding will be made in ink by crossing out the original data and recording the new data beside it.

### Statistical analysis

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

In addition to performing edit checks on data as part of its ongoing quality control activities, statistical team will generate a basic statistical report for each district’s data and separate this report, along with the district’s cleaned dataset,

at the conclusion of each district's data collection activities. This report will include response rates, characteristics of responders and nonresponders, univariate statistics on all study variables, and tables showing (properly weighted) COPD prevalence estimates, both overall and for selected subsets of the population.

The report will also summarize the derivation of weights used for computing the prevalence estimates and their standard deviations (SDs). This basic statistical report may form the basis of a site-specific paper or may be used in conjunction with other locally conducted analyses to develop site-specific manuscripts. Primary responsibility for developing site-specific manuscripts rests with the local principal investigator.

## DISCUSSION

This study protocol describes the study design and respiratory examination of a cross-sectional population-based study in Tehran population. We expect that findings from this study will show the status of respiratory problems and their risk factors in the community; estimating the burden of COPD in terms of its impact on quality-of-life, activity limitation, respiratory symptoms, and use of health care services; and making available worldwide a model to project future burden of disease for COPD in Iran and similar countries. This study will highlight the people who should be targeted by intervention programs for prevention of COPD.

Besides, in order to develop valid estimates of future burden of disease, we are also encouraged to survey an additional cohort of noninstitutionalized individuals aged 18-39 years on the prevalence of smoking and other key risk factors in these groups. These individuals will not be asked to provide lung function measurements. Completion of this portion of the study is strongly encouraged.

In addition, estimates of incidence rates for COPD, mortality rates, and smoking prevalence in younger population will be used to determine future costs associated with the disease.

As the population in different areas of Tehran is not uniform, a weighting procedure is used to make the sample as representative of the general population in Tehran as possible.

This protocol also summarizes the derivation of weights used for computing the prevalence

estimates and their SDs. Data from each district will be used as a basis for further investigation or for presentations and publications.

Descriptive statistics is applied using weighting adjustment to allow for the survey design, including clustering and stratification of the sample, and also for nonparticipation. Due to these weighting adjustments, standard error of the mean, instead of the conventional SD, will be calculated to indicate variability around the mean values of continuous variables.

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**Source of Support:** Nil, **Conflict of Interest:** None declared.