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A cross-sectional study on prevalence of chronic obstructive pulmonary disease (COPD) in India- Rationale and methods

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Abstract:

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is one of the major preventable chronic respiratory diseases (CRD) and estimated that 210 million people are affected with COPD in India. It is projected to become 3rd leading cause of death in 2030. Characteristically COPD management guidelines vary across regions indicating genotypical and phenotypical variations. Co-existence of other important CRD and COPD can adversely influence the prognosis.

India is a large country with large burden and varied risk factors for COPD. Valid prevalence estimates employing spirometry as the diagnostic tool and accounting for other important co-morbid conditions are not available in India. To address the knowledge gap and build a base to undertake cohort studies as well as to explore the genotypical and phenotypical variations among COPD patients in India, this study protocol was designed. The primary objective is to estimate the prevalence COPD among adults aged 25 year and above in India. The secondary objectives are identifying the risk factors for COPD and important comorbid conditions like asthma and TB. The currently available definitions for COPD diagnosis in India will be validated.

Methods and analysis: This will be a cross-sectional analytical study among populations of sub-urban areas of Chennai and Shillong, which represent South and Northeastern regions of India. We will collect data on socio-demographic, economic characteristics, risk factors of COPD and co-morbidities. Case definition of COPD and asthma adopted from Global Alliance against Obstructive Lung Diseases (GOLD) and Global Initiative for Asthma (GINA). Data will be analyzed for estimation of prevalence of COPD and co-morbidities and identification of associated factors.

Ethics and dissemination: This study was approved by the ethics committees (NIE/IHEC/201401-01" and "NEIGR/IEC/2013/80"). The results will be disseminated thorough publications in peer-reviewed scientific journals as well as submission of report to the public health system for developing appropriate management policies.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The current study will generate reliable prevalence estimates of COPD in two geographic regions of India and identify risk factors using internationally accepted standard methods, procedures and appropriate sampling method.
- The study will provide prevalence estimates of COPD among adults as well as younger adults, which are particularly important in Indian context and has not been adequately explored so far.
- We anticipate that doing spirometry testing in the field conditions will be challenging.
- Also, due to non-availability of reliable reference values for spirometry, we will have to apply correction factors while adapting reference equations developed for population in the Western countries.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is one of the major preventable chronic respiratory diseases (CRD). Global Initiative for Obstructive Lung Disease (GOLD) describes COPD as a common preventable and treatable disease, which is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.[1]

COPD is reported to have an estimated burden of 210 million people worldwide.[2] COPD was the 4th leading cause of death (5.1%) in 2004 and is projected to be the 3rd (8.6%) in 2030.[3] Also COPD is a major cause of chronic morbidity, ranked 11th in 2002 and projected to be 7th in 2030.[4] Globally, prevalence of COPD in adults ranges between 0.2% in Japan and 37% in USA.[5] The Burden of Obstructive Lung Disease (BOLD) group reported an average COPD prevalence of 10.1% globally with wide variations across the participating countries.[6]

Additionally, COPD also contributes to the economic burden on the patient as well as the health care infrastructure in the country, with 2-4 fold higher costs than asthma and ischaemic heart disease (IHD).[7,8]

Various prevalence studies conducted in Europe and Americas reported wide variation in COPD prevalence rates across countries. They used a uniform BOLD standardized methodology.[6,9] The prevalence studies from Southeast Asia are scarce and many of the available estimates have been derived using non-standardized methodology. Even these studies have reported wide variation in the COPD prevalence.[10,11] It is widely accepted that ethnicity is an important factor responsible for the observed variability in COPD prevalence. A study conducted in UK reported the effect of ethnicity in prevalence and severity COPD.[12]

WHO estimates suggest that 90% COPD related deaths occur in low and middle income countries. India and China with 33% of the total human population account for 66% of the global COPD mortality.[13] Further, it has been estimated that COPD mortality is likely to grow 160% in Southeast Asian region in the coming decades.[14] Globally the increase in the burden of COPD has been attributed to cigarette smoking amongst men and women, longer survival of populations and high level of air pollution, particularly in developing countries.[2,7]

India is a large country with varied socio-demographic profile, cultural practices and ethnicity. Hence the risk factors for COPD are also likely to be different across regions. Together COPD, asthma and other respiratory diseases are the second (10.2%) leading cause of death in population aged 25-69 years in India as reported in 2001-2003[15] and account for 3% of disability adjusted years (DALYs) lost.[16] COPD accounts for about 500,000 deaths in India, which is more than 4 times the number of people who die due to COPD in USA and Europe.[17] A recently completed nationwide questionnaire based study estimated the COPD prevalence of 3.49% in India (ranging from 1.1% in Mumbai to 10% in Thiruvananthapuram).[18] Spirometry test was not employed for diagnosis of COPD in this study, and it is therefore possible that the reported COPD burden could have underestimated. Recently, Burden of Obstructive Lung Disease (BOLD) study in Pune, Mumbai and Srinagar reported overall COPD prevalence estimates 6.25%, 6.8% and 16.05% respectively.[19] Though the study adopted standardized procedures, the study did not have adequate power to generate dependable prevalence estimates.

Recent literature shows co-existence of other important CRDs such as asthma and post TB sequelae with COPD. These conditions are considered as important predisposing

conditions for development of COPD and can seriously influence the course of the disease.[20] No COPD study has estimated the burden of these important co-morbid conditions of COPD.

With out having valid baseline prevalence estimate from various regions in India, uniform national guidelines have not been developed. As of now valid and large-scale spirometry based community oriented nationwide prevalence estimates are not available.[5]

We propose the present study to estimate the prevalence of COPD in the population in Chennai in South India and Shillong in North Eastern India. The current prevalence study has been suitably designed and adequately powered to generate robust COPD prevalence estimates and will use internationally accepted standardized methodology to estimate the prevalence of COPD and other co-morbidities (asthma and post-TB sequelae) and for identification of associated risk factors in the study area. Upon successful completion of this study, it has been planned to undertake identical studies to estimate prevalence of COPD and identify associated risk factors at several other sites in India, representing different geographical areas and socio-cultural-ethnic backgrounds.

METHODS AND ANALYSIS

Objectives

Primary objective

•To estimate the prevalence of asymptomatic and symptomatic COPD among adults in the study area

Secondary objectives

•To identify the risk factors for COPD in the study area

•To estimate the prevalence of asthma and post-TB sequelae in the study population

•To validate the lower limit of normal (LLN) prediction formula for diagnosis of COPD

Study design:

The proposed study is cross-sectional analytical study will be conducted in adult populations living in sub-urban areas of Chennai and Shillong cities, located in South and Northeast regions of India respectively.

Study sites:

Chennai

National Institute of Epidemiology (NIE) will carry out the study in Chennai. NIE has a sub-urban cohort setting in Ayapakkam area of Chennai, which is located adjacent to the Institute. Approximately 10,600 households have been mapped and enumerated covering an approximate population of 45,000. The sample for the study will be drawn from this cohort setting.

Shillong

North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS) will carry out the study in sub-urban area of Shillong City. The area has been used to conduct community based research projects by NEIGRIHMS.

Study population:

All residents of the study areas in Chennai and Shillong who have aged 25 years or more and are able to provide written informed consent will be eligible to participate in this study. The study will have adequate intake of males and females in the age groups

of 25-40 years and 41 + years to estimate the prevalence in these categories independently.

Rationale for including individuals in 25-40 years age

Generally, age above 40 years is considered as COPD target age group. This is primarily based on assumption that tobacco smoking, which is the primary risk factor for COPD, begins in adolescence, and it would take 20-25 years of exposure to tobacco smoke to induce COPD characteristic pathophysiologic changes in human lungs. However, in India domestic exposure to indoor-air pollution emitted by burning biomass and other health-adverse fuels, has emerged as another important risk factor for COPD. As the exposure to indoor air pollution may begin from infancy or childhood in homes where biomass fuel is a traditional fuel for cooking, it is likely that young adults in Indian subcontinent may also develop COPD at an early age. In humans, until the age of 25 years the lung function keeps on increasing and after 25 years lung function undergoes a natural physiological decline. Therefore, we wish to evaluate the population at 25-40 years of age also for prevalence of COPD and associated risk factors.

The following criteria that could affect the safety of the study participants during spirometry testing or that could influence the of spirometry outcome were considered exclusion criteria:

1. Any surgery in abdomen, chest or eye in the last three months
2. Women in last trimester of pregnancy
3. Myocardial infarction with in the last three months
4. Hospitalization due to any heart problem with in the past month
5. Currently on treatment for TB
6. Resting pulse more than 120 per minute
7. Respiratory infection including common cold in the last three weeks
8. Use of bronchodilators in the last 6 hours

The following definitions were adopted for the study:

Chronic Obstructive Pulmonary Disease (COPD): Using one of the two standard spirometry definitions:

1. Post bronchodilator FEV1/FVC <70%[1]
2. Post-bronchodilator FEV1/FVC <Lower Limit of Normal (LLN#)[21,22]

Presence of airflow obstruction is the key in diagnosing COPD as documented by reduction of FEV_1/FVC ratio. Another important sign of COPD is decline in FEV_1, which is a measure of severity of airflow obstruction.

The Global Initiative for Obstructive Lung Disease (GOLD) Committee published a consensus statement in 2001 for use of a fixed FEV_1/FVC <0.70 value and fixed FEV_1 values to classify severity of COPD. However more recently it has been accepted that the prevalence of spirometry-based COPD is greater while using fixed value of FEV_1/FVC in comparison to using the lower limit of normal (LLN). A longitudinal study reported that the in-between group (twilight zone) appeared to have a higher risk of hospitalization and mortality attributable to some lung pathology. Therefore it is believed that using the LLN of FEV_1/FVC underestimates COPD.

In the absence of clear evidence in India in favor of either of the two above-mentioned definitions, we decided to diagnose COPD based on both definitions. This will enable us to determine which criterion is better and more clinically relevant in our setting.

Asthma: The diagnosis of asthma will be done using Global Initiative for Asthma (GINA)[23] guidelines mentioned as under:

Positive bronchodilator (BD) reversibility test (more likely to be positive if BD medication is withheld before test: Short Acting Beta Agonist [SABA] ≥4 hours, Long Acting Beta Agonist [LABA] ≥15 hours):

Increase in FEV_1 of >12% and 200 mL from baseline, 10-15 minutes after 400 mcg of salbutamol or equivalent

Post TB sequelae: Information on past history of pulmonary TB will be collected using a validated questionnaire. The chest X-ray will be done for diagnosing the radiological sequelae of pulmonary TB. The lung function effects of pulmonary TB on COPD will be measured using spirometry.

Data collection

Before beginning the study an extensive round of training of the field workers to conduct this community-based study will be organized. This will be followed by some practice sessions in the community, and once the investigators are confident of the field workers' field-level competence, they will be instructed to initiate the study. The data will be collected using a tablet-based computer systems.

The study will include the following study tools and domains of inquiry:

- Questionnaires
  - Core questionnaire
  - Occupational questionnaire
  - Stages of change questionnaire
  - Biomass questionnaire
  - Miscellaneous questionnaire
  - Spirometry questionnaire
  - Minimal data / refusal questionnaire
- Anthropometry: standing height and weight
- Pre and Post bronchodilator spirometry testing

The study questionnaires had been adapted from the Burden of Obstructive Disease (BOLD) study. The permission to utilize the adapted questionnaires in India has already been taken from the BOLD committee. Every subject will answer an interviewer administered questionnaire. The anthropometry measurements and spiormetry testing will be done at the household level. The procedure will be regularly evaluated by the NIE team for quality assurance.

Spirometry:

Spirometry will be performed both pre and post 400 mcg inhaled salbutamol. Post – bronchodilator FEV1/FVC <70% or < lower limit of normal will be the diagnostic criteria for COPD. Spirometry results will be checked for quality according to the American Thoracic Society / European Respiratory Society (ATS/ERS) guidelines for spriometry.

Sample size and sampling plan

For COPD prevalence estimation, we will consider the following strata of populations:
Stratum 1: 25-40 year old males
Stratum 2: 25-40 year old females
Stratum 3: 41+ year old males
Stratum 4: 41+ year old females

Sample size calculation for each site[#]

Sample size required for 41+ year age group is 3600 individuals (1800 each in male and female strata) which was calculated based on the assumptions that reported prevalence of COPD in this age group is 5%[19] with an absolute precision of 1% with 95% confidence interval and design effect as 1.15.

Sample size required for 25-40 years age group is 6300 individuals (3150 each in male and female strata), which was calculated based on the assumptions that assumed prevalence of COPD in this age group is 2.5% with an absolute precision of 0.5% with 95% confidence interval and design effect as 1.15.

Sample size formula[41] $n = [DEFF*N*p*q]/ [(d^2/Z^2_{1-\alpha/2}*(N-1)+p*q]$

[#] Sample size has been calculated taking into consideration of the minimal estimate of prevalence of COPD and not based on prevalence of TB and asthma.

Sampling strategy

The entire study area will be divided into 60 equal clusters based on total number of households. Single stage cluster sampling method will be adopted for recruiting the required number of participants. Sampling will be done from all the geographical clusters. From each cluster 83 males (for 41+ years = 30 and for 25-40 years = 53) and 83 females (for 41+ years = 30 and for 25-40 years = 53) will be assessed for COPD. Random selection of a HH in a cluster will be the starting point of the survey. Next nearest neighbor concept will be adopted for subsequent sampling until required numbers in all strata per cluster are achieved. All the eligible members in the selected households will be included in the study.

Data management and analysis

The data from the tablet computers will be transferred to the NIE data management server on a daily basis from both Chennai and Shillong sites. Necessary steps will be taken while designing the data collection platform for minimizing the missing data. Descriptive statistics including means, standard deviations, medians, and frequencies will be computed accordingly. Prevalence of COPD and asthma will be estimated according to the definition. Odds ratio (adjusted and unadjusted) will be estimated for the factors associated with COPD, asthma and co-morbidities. Odds ratio of COPD among the participants with history of asthma and vice versa will be estimated. Odds ratio will be estimated for COPD and asthma in participants with past history of TB. Burden of COPD will be estimated in terms of impact on quality of life, activity limitation, respiratory symptoms and use of healthcare services. The distribution of various known community level risk factors will be described. The sensitivity and specificity of selected clinical symptoms for COPD will be assessed using spirometry as the gold standard.

Discussion

Epidemiology of COPD in India has a lot of unanswered questions and there is a paucity of systematically collected prevalence data using well-standardized protocols from India. Most of the available prevalence estimates are not based on spirometry testing or adopted non-standard method[18, 24-40], However spirometry has been internationally accepted gold standard for diagnosis of COPD.[1] Hence the available data cannot be interpreted in the global context. A recent study on COPD prevalence from three cities in India using standardized methodology did not have adequate sample size to reflect the true burden of the disease.[19] Further the same study did not represent South and Eastern parts of India.

Also, no study in India has concurrently estimated the other CRDs like asthma and post-TB sequelae, which are important co-morbidities of COPD and are reported to have significant impact on clinical presentation and prognosis of the disease. The current study will generate reliable prevalence estimates and describe risk factors in the community using standardized methods. The same study will also estimate COPD prevalence and describe risk factor among younger adults among whom information on COPD burden is not available readily. Upon successful completion of the project, additional studies will be carried out in different representative geographical regions and socio-cultural-ethnic backgrounds in India using identical study protocols. Knowledge of prevalence of COPD from multiple sites would also help in modeling studies to estimate the COPD disease burden at the national and sub-national levels.

Limitations

Spirometry testing in the field will be challenging in this study, however we will train our technicians appropriately in the technique of spirometry. Non-availability of valid spirometric reference equations for Indian population will be another limitation for which we will have to make some assumptions during the data analysis.

Outcome

This study will be the first of its kind in India and will specifically contribute to developing a long-term cohort study to describe the clinical progression of COPD in various populations in India and also contribute in evaluation of interventions. Further we will integrate genotyping data for study of genotypes of asthma and COPD, which could provide a replicable model to study and control life style diseases in developing countries.

ETHICS AND DISSEMINATION

The final study protocol, including the final version of the other essential documents, had been reviewed and approved in writing by the Institutional Human Ethics Committees of NIE (ID # NIE/IHEC/201401-01) and NEIGRIHMS (ID #NEIGR/IEC/2013/80). Written informed consent will be obtained from all participants before enrollment in the study. All the study procedures will be done free of cost at the doorstep of the households of the participants. The participant will be referred to the nearest public health facility for appropriate treatment, if COPD or any other ailment / abnormality is detected during the examination.

This study will provide population based COPD prevalence estimates, based on internationally accepted standardized methods. We will disseminate the study findings by developing manuscripts with high impact for publication in the peer-reviewed scientific journals. Due to the interdisciplinary applicability nature of the study findings, we will also present the study findings in national and international conferences, which will attract the researchers in the field for collaboration. The study findings will be submitted to the public health system for developing appropriate

management policies.

Contributorship statement

RP drafted the article. RP, PK, VS, AB, BB, PKB and SMM contributed to the development of study design and participant recruitment plan. PK and VS provided expertise on calculation of sample size and development of data analysis plan. All authors provided feedback and approved the final protocol

Competing interest

There are no competing interests

Funding

Funding has been approved for the study for Shillong site from Science and Engineering Research Board, Department of Science and Technology, Government of India through grant # EMR/2015/000737. The data collection for the study will be initiated in January 2017 and currently in the process pre-initiation arrangements.

Data sharing statement

The study has not yet initiated and currently there are no data available from the study.

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Research Checklist

Item No	Description	Yes/No/Not applicable
1.	**Title and abstract**	Yes
2.	Introduction Background/rationale Objectives	Yes
3.	Methods Study design Setting Participants Variables Data sources/ measurement Bias Study size Quantitative variables Statistical methods (data analysis plan)	Yes
4.	Results	Not applicable
5.	Discussion Limitation Interpretation Generalizability	Yes
6.	Other information Funding	Yes

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A cross-sectional study on prevalence of chronic obstructive pulmonary disease (COPD) in India- Rationale and methods

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Abstract:

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is one of the major preventable chronic respiratory diseases (CRD) and estimated that globally 210 million people are affected with COPD. Global and National guidelines exist for the management of Asthma and COPD and albeit evidence based, they are inadequate to address the phenotypical and genotypical heterogeneity in India. Co-existence of COPD and other CRDs can adversely influence the prognosis of COPD.

India is a large country with varied risk factors and huge burden of COPD, but valid prevalence estimates employing spirometry as the diagnostic tool and accounting for important co-morbid conditions are not available. To address this knowledge gap and to build a data-base to undertake long-term cohort studies to explore the phenotypical and genotypical heterogeneity among COPD patients in India, this study protocol was designed. The primary objective is to estimate the prevalence of COPD among adults aged ≥25 years for each gender separately in India. The secondary objectives are identifying the risk factors for COPD and important comorbid conditions like asthma and Post-TB sequelae. The currently available definitions for COPD diagnosis in India will also be validated.

Methods and analysis: This will be a cross-sectional study among populations of sub-urban areas of Chennai and Shillong, which represent South and Northeastern regions of India. We will collect data on socio-demographic, economic characteristics, risk factors of COPD and co-morbidities. GOLD and GINA definitions will be used for diagnosis of COPD and asthma. Data will be analyzed for estimation of prevalence of COPD and asthma and identification of associated factors.

Ethics and dissemination: This study was approved by the respective institutional ethics committees. The results will be disseminated through publications in the peer-reviewed journals as well as submission of report to the public health system of India for developing appropriate research and management policies.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The current study will generate reliable prevalence estimates of COPD in two geographic regions of India and identify risk factors using internationally accepted standard methods, procedures and appropriate sampling methods.
- The study will provide prevalence estimates of COPD among adults as well as younger adults for each gender separately, which are particularly important in Indian context considering the higher use of biomass fuels and higher prevalence of tuberculosis and its sequelae, which has not been adequately explored so far.
- We anticipate that doing spirometry testing in the field conditions will be challenging.
- Due to non-availability of reliable reference values for spirometry in India, we will use multi-ethnic reference equations by Global Lung Initiative (GLI) 2012 for making diagnosis of COPD and asthma.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is one of the major preventable chronic respiratory diseases (CRD). Global Initiative for Obstructive Lung Disease (GOLD) describes COPD as a common preventable and treatable disease, which is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.[1]

COPD is reported to have an estimated burden of 210 million people worldwide.[2] COPD was the 4th leading cause of death (5.1%) in 2004 and is projected to be the 3rd (8.6%) in 2030.[3] Also COPD is a major cause of chronic morbidity, ranked 11th in 2002 and projected to be 7th in 2030.[4] Globally, prevalence of COPD in adults ranges between 0.2% in Japan and 37% in USA.[5] In a recent study the Burden of Obstructive Lung Disease (BOLD) group reported an average COPD prevalence of 10.1% globally with wide variations across the participating countries.[6]

Additionally, COPD also contributes to the economic burden on the patient as well as the health care infrastructure in the country, with 2-4 fold higher costs than asthma and ischaemic heart disease (IHD).[7,8]

Various prevalence studies conducted in Europe and Americas reported wide variation in COPD prevalence rates across countries. They used a uniform BOLD standardized methodology.[6,9] The prevalence studies from Southeast Asia are scarce and many of the available estimates have been derived using non-standardized methodology. Even these studies have reported wide variation in the COPD prevalence.[10,11] It is widely accepted that ethnicity is an important factor responsible for the observed variability in COPD prevalence. A study conducted in UK reported the effect of ethnicity in prevalence and severity of COPD.[12]

WHO estimates suggest that 90% of the COPD related deaths occur in low and middle income countries. India and China with 33% of the total human population account for 66% of the global COPD mortality.[13] Further, it has been estimated that COPD mortality is likely to grow 160% in Southeast Asian region in the coming decades.[14] Globally the increase in the burden of COPD has been attributed to cigarette smoking amongst men and women, longer survival of populations and high level of air pollution, particularly in developing countries.[2,7]

India is a large country with varied socio-demographic profile, cultural practices and ethnicity. Hence the risk factors for COPD are also likely to be different across regions. Together COPD, asthma and other respiratory diseases are the second (10.2%) leading cause of death in population aged 25-69 years in India as reported in 2001-2003[15] and account for 3% of disability adjusted life years (DALYs) lost.[16] COPD accounts for about 500,000 deaths in India, which is more than 4 times the number of people who die due to COPD in USA and Europe.[17] A recently completed nationwide questionnaire based study estimated the COPD prevalence of 3.49% in India (ranging from 1.1% in Mumbai to 10% in Thiruvananthapuram).[18] Spirometry test was not employed for diagnosis of COPD in this study, and it is therefore possible that the reported COPD burden could have been underestimated. Recently, BOLD study conducted in Pune, Mumbai and Srinagar reported overall COPD prevalence estimates of 6.25%, 6.8% and 16.05% respectively.[19] Though the study adopted standardized procedures, the study did not have adequate power to generate dependable prevalence estimates apart from the wide variations of prevalence.

Recent literature shows co-existence of other important CRDs such as asthma and post TB sequelae with COPD. These conditions are considered as important predisposing

conditions for development of COPD and can seriously influence the course of the disease.[20] No COPD study has estimated the burden of these important co-morbid conditions of COPD in India.

Without having valid baseline prevalence estimate for COPD from various regions in India, uniform national guidelines can not be developed. As of now valid, large-scale spirometry and community-based prevalence estimates are not available for India as a whole.[5]

Since prevalence estimates were available from the BOLD study conducted in two urban centers from Western India and one center from Northern India, we propose the present study to estimate the prevalence of COPD in the population in Chennai in South India and Shillong in North Eastern India. The current study has been suitably designed and adequately powered to generate robust prevalence estimates of COPD and other co-morbidities (asthma and post-TB sequelae) using internationally accepted standardized methodology. This study will also identify associated risk factors for COPD.

METHODS AND ANALYSIS

Objectives

Primary objective

- To estimate the prevalence of COPD among adults aged ≥ 25 years for each gender separately

Secondary objectives

- To identify the risk factors for COPD
- To estimate the prevalence of asthma and post-TB sequelae
- To validate the lower limit of normal (LLN) prediction formula for diagnosis of COPD

Study design:

The proposed study is a cross-sectional study and will be conducted in adult populations living in sub-urban areas of Chennai and Shillong cities, located in South and Northeast regions of India respectively.

Study sites:

Chennai

National Institute of Epidemiology (NIE) will carry out the study in Chennai. NIE has a sub-urban cohort setting in Ayapakkam area of Chennai, which is located adjacent to the Institute. Approximately 10,600 households have been mapped and enumerated covering an approximate population of 45,000. The sample for the study will be drawn from this cohort setting.

Shillong

North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS) will carry out the study in sub-urban area of Shillong City. The area has been used to conduct community based research projects by NEIGRIHMS.

Study population:

All residents of the study areas in Chennai and Shillong who are aged ≥ 25 years and are able to provide written informed consent will be eligible to participate in this study.

Rationale for including individuals in 25-40 years age

Generally, age above 40 years is considered as COPD target age group. This is primarily based on the assumption that tobacco smoking, which is the primary risk factor for COPD, begins in adolescence, and it would take 20-25 years of exposure to tobacco smoke to induce characteristic pathophysiologic changes of COPD in human lungs. However, in India domestic exposure to indoor-air pollution emitted by burning solid biomass, other health-adverse fuels and mosquito coil use has emerged as another important risk factor for COPD. As the exposure to indoor air pollution may begin from infancy or childhood in homes where biomass fuel is a traditional fuel for cooking, it is likely that young adults in Indian subcontinent may also develop COPD at an early age. In humans, the lung function keeps on increasing till early adulthood and after that undergoes a natural physiological decline.[21] Therefore, we wish to evaluate the population at 25-40 years of age also for prevalence of COPD and associated risk factors.

The following conditions that could affect the safety of the study participants during spirometry testing or influence the outcome of spirometry are considered as the exclusion criteria:

1. Any surgery in abdomen, chest or eye in the last three months
2. Women in last trimester of pregnancy
3. Myocardial infarction in the last three months
4. Hospitalization due to any heart problem within the past month
5. Currently on treatment for TB
6. Resting pulse more than 120 per minute
7. Respiratory infection including common cold in the last three weeks
8. Use of bronchodilators in the last 6 hours

The following definitions are adopted for the study:

a. Chronic Obstructive Pulmonary Disease (COPD): Using one of the two standard spirometry definitions:

1. Post bronchodilator $FEV_1/FVC < 70\%$[1]
2. Post-bronchodilator $FEV_1/FVC <$ Lower Limit of Normal (LLN#)[22,23]

Presence of airflow obstruction is the key in diagnosing COPD as documented by reduction of FEV_1/FVC ratio. Another important sign of COPD is decline in FEV_1, which is a measure of severity of airflow obstruction.

The Global Initiative for Obstructive Lung Disease (GOLD) Committee published a consensus statement in 2001 for use of a fixed $FEV_1/FVC < 70\%$ value and fixed FEV_1 values to classify severity of COPD. However more recently it has been accepted that the prevalence of spirometry-based COPD is greater while using fixed value of FEV_1/FVC in comparison to using the lower limit of normal (LLN). A longitudinal study reported that the in-between group (twilight zone) appeared to have a higher risk of hospitalization and mortality attributable to some lung pathology. Therefore it is believed that using the LLN of FEV_1/FVC underestimates COPD.

In the absence of clear evidence in India in favor of either of the two above-mentioned definitions, we decided to diagnose COPD based on both definitions. This will enable us to determine which criterion is better and more clinically relevant in our setting.

b. Asthma: The diagnosis of asthma will be done using Global Initiative for Asthma (GINA)[24] guidelines, 2015 mentioned as under:

1. History of variable respiratory symptoms
2. Confirmed variable expiratory airflow limitation with pre and post bronchodilator spirometry.

Positive bronchodilator (BD) reversibility test (more likely to be positive if BD medication is withheld before test: Short Acting Beta Agonist [SABA] withheld for ≥4 hours, Long Acting Beta Agonist [LABA] withheld for ≥15 hours): Increase in FEV_1 of >12% and 200 mL from baseline, 10-15 minutes after 400 mcg of salbutamol or equivalent

c. Post TB sequelae: Information on past history of pulmonary TB will be collected using a validated questionnaire. The chest X-ray will be done for diagnosing the radiological sequelae of pulmonary TB. The lung function effects of pulmonary TB on COPD will be measured using spirometry.

Data collection

The data will be collected using tablet-based computers. All the study procedures will be done at the convenient access points for the participants. The procedures will be regularly evaluated by the NIE team for quality assurance. The study will include the following study tools and domains of inquiry:

- Questionnaires
  - Core questionnaire
  - Occupational questionnaire
  - Stages of change questionnaire
  - Biomass questionnaire
  - Miscellaneous questionnaire
  - Spirometry questionnaire
  - Minimal data / refusal questionnaire

The study questionnaires have been adapted from the BOLD study. The permission to utilize the adapted questionnaires in India has already been taken from the BOLD committee. Every participant will answer an interviewer-administered questionnaire. The questionnaires are in English language and will be forward translated into Tamil and Khasi for Chennai and Shillong respectively, since the primary spoken language is not English in both the sites. The translations will be pretested in a smaller group for validation and back-translated by a different group.

- Anthropometry: standing height and weight will be measured using National Health and Nutrition Examination Survey (NHANES) III Anthropometry Procedures Manual. [25]
- Spirometry testing

We will use the ndd Easyone™ spirometer for carrying out spirometry testing in this study. Pre and post short acting bronchodilator inhaled spirometry testing will be done according to ATS/ERS Taskforce standardization guidelines for spirometry 2005.[25] The FEV_1, FVC and FEV_1/FVC are three spirometry measurements that will be collected as part of the study.

The central team will provide training to the master trainers from each site. The spirometry technicians will be provided one week training in all components of the spirometry procedure by the master trainers, which will include hands on field training also. They will be certified if they satisfactorily complete the training. During the actual fieldwork, their performance will be monitored by the site investigators using standard checklist as a quality assurance measure. Further their performance will be assessed by the central spirometry quality control team and a report on individual technicians will be sent to the study sites on monthly basis. If necessary the QC team will suggest repeated

training of the technician/s and subsequent recertification. Spirometry results will be checked for quality according to the American Thoracic Society / European Respiratory Society (ATS/ERS) guidelines for spriometry.[26]

The ndd Easyone™ spirometer meets ATS standards for spirometry, which has been designed to require no calibration. However a calibration check will be done on daily basis for ensuring that the spirometer is reading accurately and the same will be documented.

Sample size and sampling plan

For COPD prevalence estimation, we will consider the following strata of populations:

Stratum 1: 25-40 year old males

Stratum 2: 25-40 year old females

Stratum 3: 41+ year old males

Stratum 4: 41+ year old females

Sample size calculation for each site[#]

Sample size required for 41+ year age group is 3600 individuals (1800 each in male and female strata) which was calculated based on the assumptions that reported prevalence of COPD in this age group is 5%[19] with an absolute precision of 1% with 95% confidence interval and design effect as 1.15.

Sample size required for 25-40 years age group is 6300 individuals (3150 each in male and female strata), which was calculated based on the assumptions that assumed prevalence of COPD in this age group is 2.5% with an absolute precision of 0.5% with 95% confidence interval and design effect as 1.15.

Sample size formula[27] $n = [DEFF*N*p*q]/ [(d^2/Z^2_{1-\alpha/2}*(N-1)+p*q]$

[#] Sample size has been calculated taking into consideration of the minimal estimate of prevalence of COPD and not based on prevalence of TB and asthma.

Sampling strategy

The entire study area will be divided into 60 equal portions consisting of 175 adjacent households, which will form a cluster. Single stage cluster sampling method will be adopted for recruiting the required number of participants in each of 60 clusters From each cluster 83 males (for 41+ years = 30 and for 25-40 years = 53) and 83 females (for 41+ years = 30 and for 25-40 years = 53) will be assessed for COPD. Random selection of a household in a cluster will be the starting point of the survey. All the eligible members in that selected household will be included in the study. Next nearest neighbourhood concept will be adopted until the required sample size in each stratum is achieved.

Data management and analysis

The questionnaire and anthropometry measurement data from the tablet computers will be transferred to the data management server at NIE on a daily basis from both Chennai and Shillong sites. Necessary steps will be taken while designing the data collection platform for minimizing the missing data.

The spirometry data will be transferred to the designated computers in the study sites on daily basis by the technicians. In the next step, the collated spirometry data will be sent to the central server at NIE on weekly basis in an Access database through secured and encrypted Internet platform. Spirometry reading team (SRT) at NIE will grade and assign score to each test. The SRT will also review the quality of tests by each spirometry technician and recommend corrective measures, if necessary. Duplicate data will be

remaining at the study site. The FEV_1, FVC and FEV_1/FVC are three spirometric measurements, which will be considered for analysis. We will use Global Lung Initiative (GLI) 2012 prediction equations for interpreting the observed lung volumes.[28]

Descriptive statistics including proportions, mean and standard deviation, median and interquartile range will be computed based on cluster sampling. Prevalence of COPD and asthma for each age group and gender will be estimated based on cluster sampling. Odds ratio (adjusted and unadjusted) will be estimated for the factors associated with COPD and asthma through logistic regression analysis. Odds ratio (adjusted and unadjusted) will also be estimated for the co-morbidities including TB with COPD and asthma through logistic regression analysis. Burden of COPD will be estimated in terms of impact on quality of life, activity limitation, respiratory symptoms and use of healthcare services. The distribution of various known community level risk factors will be described. The sensitivity and specificity of selected clinical symptoms for COPD will be assessed using spirometry as the gold standard.

Quality Control

The manual of procedures is in place for all components of the study. The site investigators will serve as master trainers and be trained and certified by the central team. Study staff will be trained and certified in their respective activity by the master trainers before initiation of the study. The training and certification activity will be supervised by the central team for assuring the quality of the process.

All questions in the questionnaires are coded for ease of data analysis and comparability between study sites. The study sites will submit the forward-translated version of the questionnaires to the QC team at NIE. The translated versions will be back-translated to English and checked for assuring the questionnaires are comparable with the original after accounting the cultural norms of the respective areas.

The study tools will be pilot tested for operational feasibility and finalized before initiation of the survey.

Discussion

Epidemiology of COPD in India has a lot of unanswered questions and there is a paucity of systematically collected prevalence data using well-standardized protocols from India. Most of the available prevalence estimates are not based on spirometry testing or adopted non-standard method.[18, 29-45] However spirometry has been internationally accepted gold standard for diagnosis of COPD.[1] Hence the available data cannot be interpreted in the global context. A recent study on COPD prevalence from three cities in India using standardized methodology did not have adequate sample size to reflect the true burden of the disease.[19] Further the same study did not represent Southern and Eastern parts of India.

Also, no study in India has concurrently estimated the other CRDs like asthma and post-TB sequelae, which are important co-morbidities of COPD and are reported to have significant impact on clinical presentation and prognosis of the disease. The current study will generate reliable prevalence estimates and describe risk factors in the community using standardized methods. The same study will also estimate COPD prevalence and describe risk factor among younger adults among whom information on COPD burden is not available readily. Upon successful completion of the project, we shall be able to decide whether more centers need to be included in future studies of similar nature to have a clearer holistic picture of prevalence of COPD across country. Knowledge of prevalence of COPD from multiple sites would also help in modeling studies to estimate the COPD disease burden at the national and sub-national levels. Further the prevalence study sites

will act as future focal points for subsequent long-term cohort studies to define phenotypes and genotypes of obstructive lung diseases in India.

Limitations

Non-availability of valid spirometric reference equations for Indian population will be a limitation, for which we propose to use GLI 2012 equations for data analysis.

Outcome

This study will be the first of its kind in India and will specifically contribute to developing a long-term cohort study to characterize the heterogeneity of COPD in various parts of India and amongst various ethnic groups and also contribute in defining the phenotypes and gnotypes of COPD by subsequent studies. This may provide a replicable model to study the prevalence and heterogeneity of COPD in India and other developing countries.

ETHICS AND DISSEMINATION

The final study protocol, including the final version of the other essential documents, had been reviewed and approved in writing by the Institutional Human Ethics Committees of NIE (ID # NIE/IHEC/201401-01) and NEIGRIHMS (ID #NEIGR/IEC/2013/80). Written informed consent will be obtained from all participants before enrollment in the study. All the study procedures will be done free of cost at the convenient access points for the participants. The participant will be referred to the nearest public health facility for appropriate treatment, if COPD or any other ailment / abnormality is detected during the examination.

This study will provide population based COPD prevalence estimates, based on internationally accepted standardized methods. We will disseminate the study findings by developing manuscripts with high impact for publication in the peer-reviewed scientific journals. Due to the interdisciplinary applicability nature of the study findings, we will also present the study findings in national and international conferences, which will attract the researchers in the field for collaboration. The study findings will be submitted to the public health system of India for developing appropriate research and management policies.

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Contributorship statement

RP drafted the article. RP, PK, VS, AB, BB, PKB and SMM contributed to the development of study design and participant recruitment plan. PK and VS provided expertise on calculation of sample size and development of data analysis plan. All authors provided feedback and approved the final protocol.

Competing interest

There are no competing interests.

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Data sharing statement

The study has not yet initiated and currently there are no data available from the study.

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A cross-sectional study on prevalence of chronic obstructive pulmonary disease (COPD) in India- Rationale and methods

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A cross-sectional study on prevalence of chronic obstructive pulmonary disease (COPD) in India- Rationale and methods

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Abstract:

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is a common preventable and treatable chronic respiratory disease (CRD), which affects 210 million people globally. Global and National guidelines exist for the management of COPD. Although evidence based, they are inadequate to address the phenotypic and genotypic heterogeneity in India. Co-existence of other CRD can adversely influence the prognosis of COPD.

India has a huge burden of COPD with various risk factors and co-morbid conditions. However, valid prevalence estimates employing spirometry as the diagnostic tool and data on important co-morbid conditions are not available. To address this knowledge gap and eventually to build a database to undertake long-term cohort studies to describe the phenotypic and genotypic heterogeneity among COPD patients in India, this study protocol is designed.

The primary objective is to estimate the prevalence of COPD among adults aged ≥25 years for each gender in India. The secondary objective is to identify the risk factors for COPD and important comorbid conditions like asthma and Post-TB sequelae. It is also proposed to validate the currently available definitions for COPD diagnosis in India.

Methods and analysis: A cross-sectional study will be undertaken among the populations of sub-urban areas of Chennai and Shillong cities, which represent Southern and Northeastern regions of India. We will collect data on socio-demographic variables, economic characteristics, risk factors of COPD and co-morbidities. GOLD and GINA definitions will be used for diagnosis of COPD and asthma. Data will be analyzed for estimation of prevalence of COPD, asthma and associated factors.

Ethics and dissemination: This study proposal was approved by the respective institutional ethics committees of participating institutions. The results will be disseminated through publications in the peer-reviewed journals and a report will be submitted to the concerned public health authorities in India for developing appropriate research and management policies.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The current study will generate reliable prevalence estimates of COPD in two geographic regions of India by employing internationally accepted standard methods, procedures and appropriate sampling methods.
- The study will provide prevalence estimates of COPD among adults as well as younger adults for each gender separately, which are particularly important in Indian context on the backdrop of higher use of biomass fuels as well as higher prevalence of asthma, tuberculosis and its sequelae, which has not been adequately explored so far.
- We anticipate that performing spirometry testing in the field conditions will be challenging.
- Due to non-availability of reliable reference values for spirometry in India, we will use multi-ethnic reference equations by Global Lung Initiative (GLI) 2012 for making the diagnosis of COPD and asthma.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is one of the major preventable chronic respiratory diseases (CRD). Global Initiative for Obstructive Lung Disease (GOLD) describes COPD as a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.[1]

COPD is reported to have an estimated burden of 210 million people worldwide.[2] Globally COPD was the 4th leading cause of death (5.1%) in 2004 and is projected to be at the 3rd position (8.6%) in 2030.[3] Also COPD is a major cause of chronic morbidity, ranked 11th in 2002 and projected to be rise to 7th place in 2030.[4] Prevalence of COPD in adults ranges between 0.2% in Japan and 37% in USA.[5] The Burden of Obstructive Lung Disease (BOLD) group recently reported an average global COPD prevalence of 10.1% with wide variations across the participating countries.[6]

Additionally, COPD contributes to the economic burden faced by the patient as well as the health care infrastructure in the country, incurring 2-4 fold higher costs compared to asthma and ischaemic heart disease (IHD).[7,8]

Various prevalence studies conducted in Europe and Americas reported wide variation in COPD prevalence rates across countries. They had employed a uniform BOLD standardized methodology.[6,9] The prevalence studies from Southeast Asia are scarce and many of the available estimates have been derived using non-standardized methodology. However, even these studies have reported a wide variation in the COPD prevalence.[10,11]

It is widely accepted that ethnicity is responsible for the observed variability in COPD prevalence. A study conducted in UK reported the effect of ethnicity in prevalence and severity of COPD.[12]

WHO estimates suggest that 90% of the COPD related deaths occur in low and middle income countries. India and China constituting 33% of the total human population account for 66% of the global COPD mortality.[13] Further, it has been estimated that COPD associated mortality is likely to grow 160% in Southeast Asian region in the coming decades.[14] Globally the increase in the burden of COPD has been attributed to cigarette smoking among men and women, longer survival of populations and high level of air pollution, particularly in developing countries.[2,7]

India is a large country of people having varied socio-demographic profile, cultural practices and ethnicities. Hence the risk factors for COPD are also likely to be different across various Indian states and regions. Together COPD, asthma and other respiratory diseases are the second (10.2%) leading cause of death in the population aged 25-69 years in India as reported in 2001-2003[15] and they account for 3% of disability adjusted life years (DALYs) lost.[16] Of the CRD, COPD accounts for about 500,000 deaths in India, which is more than 4 times the number of people who die due to COPD in USA and Europe.[17] A recently completed nationwide questionnaire based study estimated the COPD prevalence of 3.49% in India (ranging from 1.1% in Mumbai to 10% in Thiruvananthapuram).[18] Spirometry test was not employed for diagnosis of COPD in this study, and it is therefore possible that the reported COPD burden could be underestimated. Recently, BOLD study conducted in Pune, Mumbai and Srinagar reported overall COPD prevalence estimates of 6.25%, 6.8% and 16.05% respectively.[19] Though the study adopted standardized procedures, the study did not have adequate power to generate dependable prevalence estimates apart from the wide variations of prevalence.

Recent literature shows co-existence of other important CRD such as asthma and post TB sequelae with COPD. These conditions are considered as important predisposing conditions for development of COPD and can seriously influence the course of the disease.[20] No COPD study has estimated the burden of these important co-morbid conditions in India.

Without having valid baseline prevalence estimate for COPD from various regions in India, uniform national guidelines can not be developed. As of now, valid, large-scale spirometry based and community-level prevalence estimates are not available from India as a whole.[5]

Since prevalence estimates were available from the BOLD study conducted in two urban centers from Western India and one center from Northern India, we propose the present study to estimate the prevalence of COPD in Chennai in South India and Shillong in North Eastern India. The current study has been suitably designed and adequately powered to generate robust prevalence estimates of COPD and other co-morbidities (asthma and post-TB sequelae) using internationally accepted standardized methodology. This study will also identify associated risk factors for COPD.

METHODS AND ANALYSIS

Objectives

Primary objective

- To estimate the prevalence of COPD among adults aged ≥ 25 years for each gender separately

Secondary objectives

- To identify the risk factors for COPD
- To estimate the prevalence of asthma and post-TB sequelae among adults aged ≥ 25 years for each gender separately
- To validate the lower limit of normal (LLN) prediction formula for diagnosis of COPD

Study design:

The proposed cross-sectional study will be conducted in adult populations living in sub-urban areas of Chennai and Shillong cities, located in South and Northeast regions of India respectively.

Study sites:

Chennai

National Institute of Epidemiology (NIE) will carry out the study in Chennai. Adjacent to the Insttitue, NIE has a sub-urban cohort setting in Ayapakkam area of Chennai. Approximately 10,600 households have been mapped and enumerated covering an approximate population of 45,000. The sample for the study will be drawn from this cohort setting.

Shillong

North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS) will carry out the study in sub-urban area of Shillong City in Meghalaya

state of India. The area has been used to conduct community based research projects by NEIGRIHMS.

Study population:

All residents of the study areas in Chennai and Shillong cities aged ≥ 25 years and who are able to provide written informed consent will be eligible to participate in this study.

Rationale for including individuals in 25-40 years age

Generally, age above 40 years is considered as COPD target age group. This is primarily based on the assumption that tobacco smoking, which is the primary risk factor for COPD, begins in adolescence, and it would take 20-25 years of exposure to tobacco smoke to induce characteristic pathophysiologic changes of COPD in human lungs. However, in India domestic exposure to indoor-air pollution resulting from burning solid biomass, other health-adverse fuels and mosquito coil use has emerged as another important risk factor for COPD. As the exposure to indoor air pollution may begin from infancy or childhood in homes where biomass fuel is a traditional fuel for cooking, young adults in Indian subcontinent are likely to develop COPD at an early age. In humans, the lung function keeps improving till early adulthood and subsequently undergoes a natural physiological decline.[21] Therefore, we wish to estimate the prevalence of COPD in the population between 25 and 40 years of age and identify associated risk factors.

The following conditions that could either affect the safety of the study participants during spirometry testing or influence the outcome of spirometry are considered as the exclusion criteria:

1. Any surgery in abdomen, chest or eye in the last three months
2. Women in last trimester of pregnancy
3. Myocardial infarction in the last three months
4. Hospitalization due to any heart problem within the past month
5. Currently on treatment for TB
6. Resting pulse more than 120 per minute
7. Respiratory infection including common cold in the last three weeks
8. Use of bronchodilators in the last 6 hours

The following definitions are adopted for the study:

a. Chronic Obstructive Pulmonary Disease (COPD): Any one of the following two standard spirometry definitions:

1. Post bronchodilator $FEV_1/FVC < 70\%$[1]
2. Post-bronchodilator $FEV_1/FVC <$ Lower Limit of Normal (LLN#)[22,23]

Presence of airflow obstruction is the key in diagnosing COPD as documented by reduction of FEV_1/FVC ratio. Another important sign of COPD is decline in FEV_1, which is a measure of severity of airflow obstruction.

The GOLD Committee published a consensus statement in 2001 for the use of a fixed $FEV_1/FVC < 70\%$ value and fixed FEV_1 values to classify severity of COPD.[24] Lately, it has been realized that the prevalence of spirometry-based COPD is higher while using fixed value of FEV_1/FVC in comparison to using the LLN.[25] A longitudinal study reported that the in-between group appeared to have a higher risk of hospitalization and mortality attributable to some lung pathology. Therefore it is believed that using the LLN of FEV_1/FVC underestimates COPD.[26]

In the absence of clear evidence in India in favor of either of the two above-mentioned definitions, we decided to diagnose COPD based on both definitions. This will enable us to determine which criterion is better and more clinically relevant for COPD diagnosis in the Indian setting.

b. Asthma: The diagnosis of asthma will be done using Global Initiative for Asthma (GINA)[27] guidelines:

1. History of variable respiratory symptoms
2. Confirmed variable expiratory airflow limitation with pre and post bronchodilator spirometry.

Positive bronchodilator (BD) reversibility test (more likely to be positive if BD medication is withheld before test: Short Acting Beta Agonist [SABA] withheld for ≥4 hours, Long Acting Beta Agonist [LABA] withheld for ≥15 hours): Increase in FEV_1 of >12% and 200 mL from baseline, 10-15 minutes after 400 mcg of salbutamol or equivalent

c. Post TB sequelae: Information on past history of pulmonary TB will be collected using a validated questionnaire. The chest X-ray will be done for diagnosing the radiological sequelae of pulmonary TB. The lung function effects of pulmonary TB on COPD will be measured using spirometry.

Data collection

The data will be collected using tablet-based computers. All the study procedures will be done at convenient access points for the participants. The procedures will be regularly evaluated by the NIE team for quality assurance. The study will include the following study tools and domains of inquiry:

Questionnaires

- Core questionnaire
- Occupational questionnaire
- Stages of change questionnaire
- Biomass questionnaire
- Miscellaneous questionnaire
- Spirometry questionnaire
- Minimal data / refusal questionnaire

The study questionnaires will be adapted from the BOLD study. The permission to utilize the adapted questionnaires in India has already been taken from the BOLD committee. Every participant will answer an interviewer-administered questionnaire. The original questionnaires are in English language and will be appropriately translated into Tamil and Khasi languages for Chennai and Shillong sites respectively, since the primary spoken language is not English at both these sites. The translations will be pretested in a smaller group for validation and back-translated by a different group.

- Anthropometry: Standing height and weight will be measured as directed by National Health and Nutrition Examination Survey (NHANES) III Anthropometry Procedures Manual. [28]
- Spirometry testing

We will use the ndd Easyone™ spirometer for carrying out spirometry testing in this study. Pre and post short acting bronchodilator inhaled spirometry testing will be done according to American Thoracic Society/European Respiratory Society (ATS/ERS) Taskforce standardization guidelines for spirometry 2005.[29] As part of the study, three spirometry measurements namely FEV_1, FVC and FEV_1/FVC will be estimated.

The central team will provide training to the master trainers from each site. The spirometry technicians will be provided one week training in all components of the spirometry procedure by the master trainers, which will include hands on field training also. They will be certified if they satisfactorily complete the training. During the actual fieldwork, their performance will be monitored by the site investigators using standard checklist as a quality assurance measure. Further, their performance will be assessed by the central spirometry quality control team and a report on individual technicians will be sent to the study sites on monthly basis. If necessary the QC team will suggest additional training of the technician/s and subsequent recertification. Spirometry results will be checked for quality according to the ATS/ERS guidelines for spriometry.[29]

The ndd Easyone™ spirometer meets ATS standards for spirometry, which has been designed to require no calibration. However a calibration check will be done on a daily basis for ensuring that the spirometer is reading accurately and the same will be documented.

Sample size and sampling plan

For COPD prevalence estimation, we will consider the following strata of populations:

Stratum 1: 25-40 year old males
Stratum 2: 25-40 year old females
Stratum 3: 41+ year old males
Stratum 4: 41+ year old females

Sample size calculation for each site[#]

Sample size required for 41+ year age group is 3600 individuals (1800 each in male and female strata) which was calculated based on the assumptions of lowest reported prevalence of COPD in this age group in India is about 5%[19] with an absolute precision of 1%, 95% confidence interval and design effect as 1.15.

Sample size required for 25-40 years age group is 6300 individuals (3150 each in male and female strata), which was calculated based on the assumptions of assumed prevalence of COPD in this age group is 2.5% (50% of the prevalence of COPD in 41+ age group) with an absolute precision of 0.5%, 95% confidence interval and design effect as 1.15.

Sample size formula[30] $n = [DEFF*N*p*q]/ [(d^2/Z^2_{1-\alpha/2}*(N-1)+p*q]$

[#]Sample size has been calculated based on the reported prevalence of COPD[19] and not based on prevalence of TB and asthma.

Sampling strategy

The entire study area will be divided into 60 equal portions consisting of 175 adjacent households, which will form a cluster. Single stage cluster sampling method will be adopted for recruiting the required number of participants in each of 60 clusters. From each cluster 83 males (for 41+ years = 30 and for 25-40 years = 53) and 83 females (for 41+ years = 30 and for 25-40 years = 53) will be assessed for COPD. Random selection of a household in a cluster will be the starting point of the survey. All the eligible members in that selected household will be included in the study. Next nearest neighbourhood concept will be adopted until the required sample size in each stratum is achieved.

Data management and analysis

The questionnaire and anthropometry measurement data from the tablet computers will be transferred to the data management server at NIE on a daily basis from both Chennai and Shillong sites. Necessary steps will be taken while designing the data collection tools and actually collecting the data to minimize missing data.

The spirometry data will be transferred to the designated computers in the study sites on daily basis by the technicians. In the next step, the collated spirometry data will be sent to the central server at NIE on weekly basis in an Access database using a secured and encrypted Internet platform. Spirometry reading team (SRT) at NIE will grade and assign score to each test. The SRT will also review the quality of tests by each spirometry technician and recommend corrective measures, if necessary. Duplicate data will be retained at the study site. The three spirometric measurements, namely FEV_1, FVC and FEV_1/FVC will be considered for analysis. We will use Global Lung Initiative (GLI) 2012 prediction equations for interpreting the observed lung volumes.[31]

Descriptive statistics including proportions, mean and standard deviation, median and interquartile range will be computed as applicable to cluster sampling. Prevalence of COPD and asthma for each age group and gender will be estimated based on cluster sampling. Odds ratio (adjusted and unadjusted) will be estimated for the factors associated with COPD and asthma through logistic regression analysis. Odds ratios (adjusted and unadjusted) will also be estimated for the co-morbidities including TB with COPD and asthma through logistic regression analysis. Burden of COPD on life will be estimated in terms of impact on quality of life, activity limitation, respiratory symptoms and use of healthcare services. The distribution of various known community level risk factors will be described. The sensitivity and specificity of selected clinical symptoms for COPD will be assessed using spirometry as the gold standard.

Quality Control

The manual of procedures is in place for all components of the study. The site investigators will serve as master trainers and be trained and certified by the central team. Study staff will be trained and certified in their respective activities and functions by the master trainers before initiation of the study. The training and certification activity will be supervised by the central team for assuring the quality of the process.

All questions in the questionnaires are coded for ease of data analysis and to ensure comparability between study sites. The study sites will submit the forward-translated version of the questionnaires to the QC team at NIE. The translated versions will be back-translated to English and checked for assuring the questionnaires are comparable with the original after accounting the cultural norms of the respective areas.

The study tools will be pilot tested for operational feasibility and finalized before initiation of the survey.

Discussion

Epidemiology of COPD in India has a lot of unanswered questions and there is a paucity of systematically collected prevalence data using well-standardized protocols from India. Most of the available prevalence estimates are not based on spirometry testing or adopted non-standard method.[18, 32-48] However spirometry is the internationally accepted gold standard for diagnosis of COPD.[1] Hence the available data cannot be interpreted in the global context. A recent study on COPD prevalence from three cities in India using standardized methodology did not have adequate sample size to reflect the true burden of the disease.[19] Further the same study did not represent Southern and Eastern parts of India.

Also, no study in India has concurrently estimated the other CRD like asthma and post-TB sequelae, which are important co-morbidities of COPD and are reported to have

significant impact on clinical presentation and prognosis of the disease. The current study will generate reliable prevalence estimates and describe risk factors in the community using standardized methods. The same study will also estimate COPD prevalence and describe risk factors among younger adults. In this age group the information on COPD burden is not readily available. Upon successful completion of the project, we will be able to decide whether more centers will be required to obtain more dependable, uniform and geographically more representative data that could provide a clear and holistic picture of prevalence of COPD across country. Knowledge of prevalence of COPD from multiple sites would also help in "modeling studies" for COPD disease burden estimation at the national and sub-national levels. Further the prevalence study sites will act as future focal points for initiating long-term cohort studies to define phenotypes and genotypes of obstructive lung diseases in India.

Limitations

Non-availability of valid spirometric reference equations for Indian population will be a limitation, for which we propose to use GLI 2012 equations for data analysis.

Outcome

This study will be the first of its kind in India and will specifically contribute to developing a long-term cohort study to characterize the heterogeneity of COPD in various parts of India and in various ethnic groups. It will also contribute to clearly define the phenotypes and genotypes of COPD in subsequent studies. This may provide a replicable model to study the prevalence and heterogeneity of COPD in India and other developing countries.

ETHICS AND DISSEMINATION

The final study protocol, including the final version of the other essential documents, have been reviewed and approved in writing by the Institutional Human Ethics Committees of NIE (ID # NIE/IHEC/201401-01) and NEIGRIHMS (ID #NEIGR/IEC/2013/80). Written informed consents will be obtained from all the participants before enrollment in the study. All the study procedures will be done free of cost at the convenient access points for the participants. The participant will be referred to the nearest public health facility for appropriate treatment, if COPD or any other ailment / abnormality gets detected during the examination.

This study will provide population based COPD prevalence estimates, based on internationally accepted standardized methods. We will disseminate the study findings by publishing manuscripts of high impact for publication in the peer-reviewed scientific journals. Due to the interdisciplinary nature of the study findings, we will also present the study findings in national and international conferences, which will attract the researchers in the field for collaboration. The study findings will be submitted to the concerned public health authorities in India for developing appropriate research and management policies.

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Contributorship statement

RP drafted the article. RP, PK, VS, AB, BB, PKB and SMM contributed to the development of study design and participant recruitment plan. PK and VS contributed in calculation of sample size, sampling design and development of data analysis plan. All authors provided feedback and approved the final protocol.

Competing interest

There are no declared competing interests.

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Funding has been approved for the study for Shillong site from Science and Engineering Research Board, Department of Science and Technology, Government of India through grant # EMR/2015/000737. The data collection for the study will be initiated in March 2017 and the site is currently in the process of finalizing pre-initiation arrangements. We have approached other agencies to seek funding support for the Chennai site.

Data sharing statement

The study has not yet initiated and currently there are no data available from the study.

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