Title: Cohort Profile: The Mysuru stUdies of Determinants of Health in Rural Adults (MUDHRA), India.

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Running Title: MUDHRA Cohort profile.

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ABSTRACT

Between 2006 and 2010, from the 16 randomly selected villages from rural areas of Mysore district, in south India, 8457 subjects aged 30 and above were screened for symptoms of chronic respiratory disease. Of the 8457 subjects, 1692 were invited for further evaluation of lung function and COPD by spirometry, and 1085 of these subjects underwent lung function assessments for prevalent COPD and its risk factors. These 1085 subjects who were then aged between 35 and 80 years constituted the MUDHRA cohort. A threshold of biomass fuel smoke exposure for a diagnosis of chronic bronchitis was established and a minimum biomass exposure index of 60 was necessary to have significant risk for developing chronic bronchitis.

Five years later (between 2014-2016), 869 of the 1085 were followed up with repeat lung function assessments for incident COPD and all-cause mortality. A subset of these (n=200) had blood tests for vitamin D levels, antioxidant activity, an assessment for anxiety and depression and another subset (n=98) had bioplex assay for 40 serum cytokines.

Researchers needing access to this data can contact Dr. Mahesh PA, Professor, Department of Pulmonary Medicine, JSS Medical College, JSS Academy of Higher Research and Research, Mysuru, India (mahesh1971in@yahoo.com).

Keywords: Chronic lung disorders, COPD, Asthma, spirometry, biomass, smoking.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of global burden, morbidity and mortality and is projected to be third leading cause of death by 2030 (1–3).

Out of more than 170 million COPD patients worldwide, More than 3 million people died in 2015. COPD accounts for 2.6% of the global Disability-adjusted life years (DALY). The burden of COPD is particularly high in rural areas of low- and middle- income countries and it is the second leading cause of death in India (1,4,5) due to higher levels of smoking, ambient air pollution, exposure to biomass, ozone, occupational particulate matter and environmental tobacco smoke (4,6). More than 3 billion people in the world are exposed to biomass smoke compared to 1 billion smokers. We have shown previously that more than 90% of rural households use biomass fuels and more than 50% of rural men smoke. Despite this, there are limited data on the prevalence of COPD and its burden in rural India (5).

In India, more than 70% of the population lives in rural areas (7). Prevalence of COPD reported from the population based studies from rural India were not derived from standardised lung function assessments, but based on questionnaire criterion (5,8–23). Furthermore, in many studies the participants were not randomly selected from the general population, which limits the generalizability of the study findings. In these studies, the association of dose of biomass smoke exposure with chronic respiratory disorders, particularly among non-smokers was not examined. These studies were primarily cross-sectional in design and limited to reporting prevalent COPD, where participants were not followed-up to estimate the incidence of chronic respiratory disorders (5,8–23). Therefore, **M**ysuru st**U**dies of **D**eterminant of **H**ealth of **R**ural **A**dults (MUDHRA) cohort was set up to address some of these limitations and specifically examine the risk factors for prevalent and incident COPD cases among rural men and women in southern India.

COPD is characterized by local as well as systemic inflammation involving various chemokine and cytokines and the pulmonary inflammation extends into systemic circulation (24–28). The pulmonary and systemic inflammation in COPD is due to exposure to important risk factors in Indians such as tobacco smoking (usually in males) or biomass smoke exposure (usually females). These exposures lead to increase in pro-inflammatory cytokines and reduced anti-inflammatory and homeostatic cytokines.

There is paucity of understanding the interaction of various cytokines and chemokines especially in biomass smoke related COPD and preliminary data has shown that biomass smoke related COPD is different from tobacco smoke related COPD (29). Some of the cytokines are associated with increased inflammation in COPD (interleukin-6 (IL-6), tumour necrosis factor - α (TNF-α)), progression of disease (IL-2) or neutrophil recruitment (Granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-8), whereas anti-inflammatory cytokines help to mitigate the inflammation (IL-10). There was a need to understand cytokine signatures in COPD due to tobacco and biomass smoke. A sub-sample of the cohort was evaluated for the cytokine signatures in tobacco smoke and biomass smoke related COPD.

STUDY PARTICIPANTS

Of the seven *talukas* (sub-districts) in the district of Mysuru, two were randomly selected; rural Mysuru with 176 villages and Nanjangud with 131 villages. According to the 2001 Registrar General India census (7), each of these villages had 1800-2200 men and women above thirty years of age and potentially eligible for recruitment. Sample size estimation informed that we had to screen at least 8000 men and women aged above 30 years from these villages to obtain approximately 1000 symptomatic chronic chest disease cases. This estimation was based on an estimated prevalence of 5% COPD in this population, with 80% power and 10% Standard Error. Therefore, of the 307 villages, 8 villages from Mysuru and 8 villages from Nanjangud were randomly selected. Figure 1 is a map of India illustrating the site of sampling from which the MUDHRA cohort was set up.

Trained field workers conducted a door-to-door survey of all households (n= 3139) from these 16 villages to identify those above 30 years of age. The houses were visited at least on three separate occasions before declaring them as “non-responders” or “locked houses” (n=196). Potentially eligible members from each of the household underwent a standardised structured interview from “The Burden of Obstructive Lung Diseases” (BOLD) study (30). This questionnaire obtained information about socio-demographics,

respiratory symptoms, self-reported diagnosis of respiratory disease and other non-communicable diseases, medical history of consultation with doctor or hospitalisation, exposure to risk factors for chest disorders like biomass fuel smoke and tobacco smoke.

In the first phase, a total of 8457 subjects [3953 women (46.7%) and 4054 men (53.3%)] from 3943 households were screened for symptoms of chronic respiratory diseases and prevalence of chronic bronchitis. Data were also collected on socioeconomic status, education, occupation, tobacco and alcohol consumption, and biomass exposure. Twenty percent (n=1692) of these subjects were randomly invited for further evaluation of lung function and COPD by spirometry. Among 1692 subjects, 423 declined to participate (62 men and 361 women). More females than males refused to participate due to socio cultural issues. Of 1269 subjects who had spirometry, 1085 satisfied American Thoracic Society (ATS) Standards (31). Except for age and gender, other demographic characteristics were similar between the subjects with and without spirometry. These 1085 men and women constituted the MUDHRA Cohort. Figure 2 depicts the flowchart for subject sampling and participation in different phases of the study.

After the baseline assessment for chronic lung disorders and its risk factors during 2006-2010, the cohort was retraced and examined 5 years later between 2014-2016. The follow-up evaluation of the cohort was to establish the incidence rates of COPD, its predictors and other chronic lung disorders. The baseline assessments were repeated and 869 subjects had acceptable spirometry in the follow up.

During this follow up, a nested case-control design, a subset (n=200; 100 with COPD and 100 without) were evaluated further to examine the hypothesis if lower levels of vitamin D, oxidative stress markers and higher levels of depressive symptoms were associated with a greater decline in lung function [manuscript under preparation].

In a smaller subset of tobacco smokers with and without COPD (n=50), we examined the serum levels of 8 cytokines. Later, in another subset of the cohort (n=98), we

examined the levels and interactions of 40 serum cytokines and chemokines by multiplexed immune-assay system in subjects with COPD related to tobacco smoking (males) and biomass fuels (females) compared to subjects exposed to similar levels of risk factors (tobacco smoking in males and biomass exposure in females) but had not developed COPD to assess whether immune inflammatory signatures between tobacco smoking and biomass fuel exposure related to COPD were different (32) [manuscript submitted].

MEASUREMENTS

The demographic, socio economic, health related, respiratory symptoms, risk factors, spirometry and lab variables measured during the different phases have been listed in Table 1. Chronic bronchitis was defined as having cough with phlegm on most of the days for 3 months for at least 2 consecutive years (2). COPD was defined as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometry guidelines "post bronchodilator FEV1/FVC <0.7" (2) and asthma was defined as per the Global Initiative for Asthma (GINA) spirometry guidelines "increase of 12% and 200 mL in FEV1 in post bronchodilator spirometry test" (33).

(Table 1 here)

KEY FINDINGS

Of the 8457 men and women screened for establishing this cohort, the prevalence of cough and phlegm for one month duration was 14.3%, chronic cough and phlegm (for 3 months duration) was 8.4%, and 7.7% for chronic bronchitis. These were more common among the elderly, men and current smokers (41–43).

A threshold of biomass fuel exposure for diagnosis of chronic bronchitis was established for the first time in a rural population. Biomass exposure index was first described by Behera et al (44) that considered the average hours of exposure to biomass smoke in a day multiplied by the number of years of exposure. We identified that a minimum

biomass exposure index of 60 was necessary to have a significant risk for developing chronic bronchitis as compared to the general population. Increased exposure to biomass smoke increased the rates of chronic bronchitis in women (42). Additional respiratory risk factors such as dusty occupation was observed in 58.2% and passive smoking in 10.95% of study subjects.

Studies have shown that Biomass smoke exposure is a significant factor rivalling tobacco smoke both for the development of COPD as well as mortality associated with COPD (45,46). Increased biomass exposure was associated with increasing severity of airflow limitation and advanced COPD according to GOLD criteria (47). The importance of biomass in COPD is further confirmed by studies that have longitudinally evaluated the effect of switching over to cleaner fuel as compared to continuing biomass exposure and observed more than 50% decrease in risk of developing COPD (48).

Indoor levels of CO (carbon monoxide), SO_2 (Sulphur dioxide) and NO (nitric oxide) during cooking, and three hours thereafter were measured in fifty randomly chosen participant households. The levels for all of these were higher at unacceptable levels. [Peak CO 999 ppm (parts per million) and a time weighted average (TWA) 596 ppm; SO_2 levels reached a peak of 99.9 ppm and a TWA of 23.4 ppm; peak NO level of 38.3 ppm with TWA of 5.7 ppm]. At three hours the levels of CO, SO_2 and NO remained high and unacceptable at 37 ppm, 15 ppm and 4 ppm respectively [manuscript under preparation].

Of the 1085 constituent members of the cohort, nine of 915 men (1%) and one of 170 women (0.6%) were diagnosed with COPD. The most common abnormality on spirometry in both sexes was a restrictive defect (40%), and this was significantly more common among women as compared to men in those aged less than 40 years (28% of men vs 43% in women). Prevalence of asthma confirmed by spirometry was 6.9% (75 out of 1085) in our study. [manuscript under preparation].

At five years follow-up, 72 of the 573 (12.6%) with chronic bronchitis and 17 of 296 (5.7%) without chronic bronchitis were deceased indicating a much higher all-cause 5-year mortality in those with chronic bronchitis [manuscript under preparation].

The nested case-control study (n=98) identified Chemokine (C-C motif) ligand CCL20, CCL27 and CXCL13 as putative, plausibly homeostatic biomarkers for biomass smoke induced COPD. Ten cytokines and chemokines exhibited higher concentrations in TS-CONTROL (tobacco smoke exposed controls) compared to TS-COPD (tobacco smoke exposed COPD cases). Comparison of cytokine and chemokine concentrations among BM-COPD versus TS-COPD and BM-CONTROL versus TS-CONTROL subjects also revealed distinct molecular profiles (49) [manuscript submitted].

STRENGTHS AND WEAKNESSES

The main strength of the MUDHRA cohort is that it is population based and representative of the rural population in southern India. This is the single largest rural cohort in India where all participants had undergone standardized assessments for diagnosis of COPD according to ATS criteria, with a repeat assessment for lung function at five-year follow-up. Very few declined to participate at baseline (less than 5%) and in the follow-up (<7%) studies. We measured CO, SO_2 and NO in a subset but not in all households. Particulate matter (PM2.5, PM10) were not measured. Participants were not examined for cardio-metabolic disorders. Though all-cause mortality was reported for the cohort at five-year follow-up, the cause of death was not ascertained. We intend to overcome this by establishing probable cause of death by conducting a standardised verbal autopsy interview with a reliable informant of the deceased and recording the cause of death from medical records or death certificate.

DATA ACCESSIBILITY

The study data are not freely available, but the MUDHRA Cohort team would welcome collaborations with other researchers. For further information, contact Dr. Mahesh PA

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CONFLICT OF INTEREST

Competing Interests: The authors declare that they have no competing interests.

Abbreviations

ATS : American Thoracic Society

BM : Biomass smoke

BOLD Study : Burden of obstructive lung diseases study

CAT : COPD Assessment Test

CCL : Chemokine (C-C motif) ligand

CO : carbon monoxide

COPD : Chronic obstructive pulmonary disease

CXCL: Chemokine (C-X-C motif) ligand

FRAP : Ferric reducing antioxidant power

GINA : Global Initiative for Asthma

GM-CSF : Granulocyte-macrophage colony stimulating factor

GOLD : Global Initiative for Chronic Obstructive Lung Disease

HAM-A : Hamilton assessment scale for Anxiety

HAM-D : Hamilton assessment scale for Depression

IL- : Interleukin-

MUDHRA : Mysuru stUdies of Determinant of Health of Rural Adults

NO : Nitric oxide

ppm : Parts per million

SD : Standard deviation

SO_2 : Sulphur dioxide

TBARS : Thiobarbituric acid reactive substances

TNF : Tumour necrosis factor

TS : Tobacco smoke

TWA : time weighted average

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Table 1: The list of variables collected during the different phases of the study.

Dataset	Numbers	Available Data
Baseline	N=8457 Age 30-105 years Mean Age 48.5 (standard deviation 12.5) 2006-2009	Demographics: Age, Gender, Village, Taluk. Socio-economic indicators: Education, Occupation, Type of house, Number of people at home, Number of room at home, Land ownership, Vehicle ownership, Type of Latrine, Source of Drinking water, Presence of Indoor Animals. Health related: Respiratory symptoms: Cough, phlegm, breathlessness, wheeze. Self-reported diagnosis of Respiratory diseases: Emphysema, Asthma, Allergic bronchitis, chronic bronchitis, COPD, lung cancer, Tuberculosis. Self-reported diagnosis of Non-communicable diseases: Hypertension, diabetes mellitus, stroke, heart disease. Medical history of consultation with doctor or hospitalization: Consulted or Admitted for breathlessness, days of hospitalization, chest surgeries, hospitalization in childhood for respiratory illness. Risk factors for chest disorders: Tobacco smoking: type of smoking (beedi, cigarette, both), age of start, years of smoking, frequency, current smoking status, pack years, smoking index. Biomass fuel smoke exposure: years of exposure, hours exposed in a day, biomass index. Environmental exposure to dust at work, tobacco smoke. Type of fuel used for domestic work (kerosene, gas, biomass) presence of chimney and Early life events. Knowledge and attitudes of smokers towards tobacco smoking and Nicotine dependence:

		Fagerstorm questionnaire (subset N=900) (8,34).
MUDHRA Cohort	N=1085 Age 35-80 years Mean Age 49.9 (standard deviation 10.5) 2009-2010	Height, weight, Body Mass Index Lung function: Spirometry pre- and post-bronchodilator forced vital capacity, forced expiratory volume in the first second.
First Follow up	N=869 Age=43-90 years Mean Age 60.7 (standard deviation 12.9) 2014-2016	Respiratory symptom severity indicators: COPD Assessment Test (CAT) (35), St. Georg's Respiratory Questionnaire - COPD (SGRQ-C) (36), Modified Medical Research Council (mMRC) Dyspnoea scale (37). Assessment of Physical Activity/Exercise capacity: Six-minute walk distance (38). Lung function test: Spirometry: pre- and post-bronchodilator forced vital capacity, forced expiratory volume in the first second. Mental Health : Hamilton Anxiety and Depression HAM-A (39) and HAM-D (40) scales. Serum vitamin D levels (n=200) Serum Antioxidant reserves Thiobarbituric acid reactive substances (TBARS) and ferric reducing antioxidant power (FRAP) (n=200) Forty Serum Cytokines and Chemokines (n=98)

Age in years, mean age (standard deviation)**.**

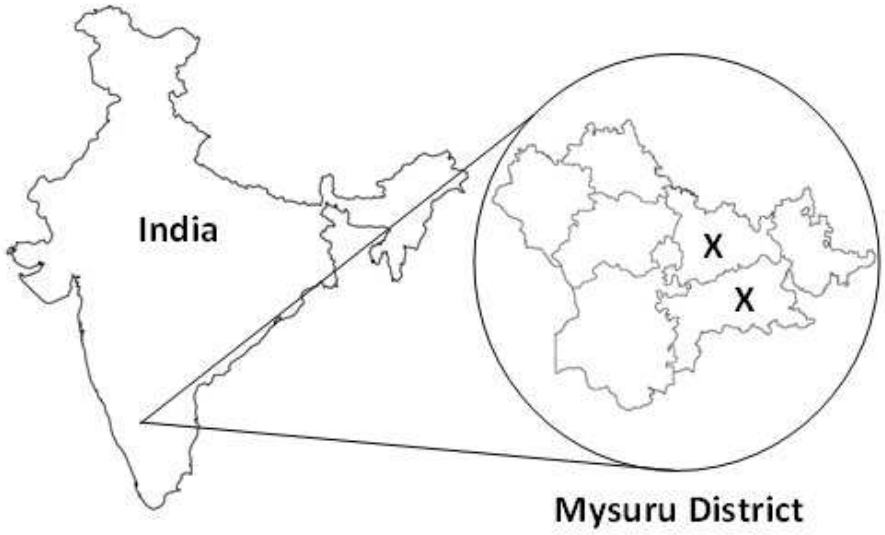

Figure 1: Map of India illustrating the site of sampling from which the MUDHRA cohort was set up (X).

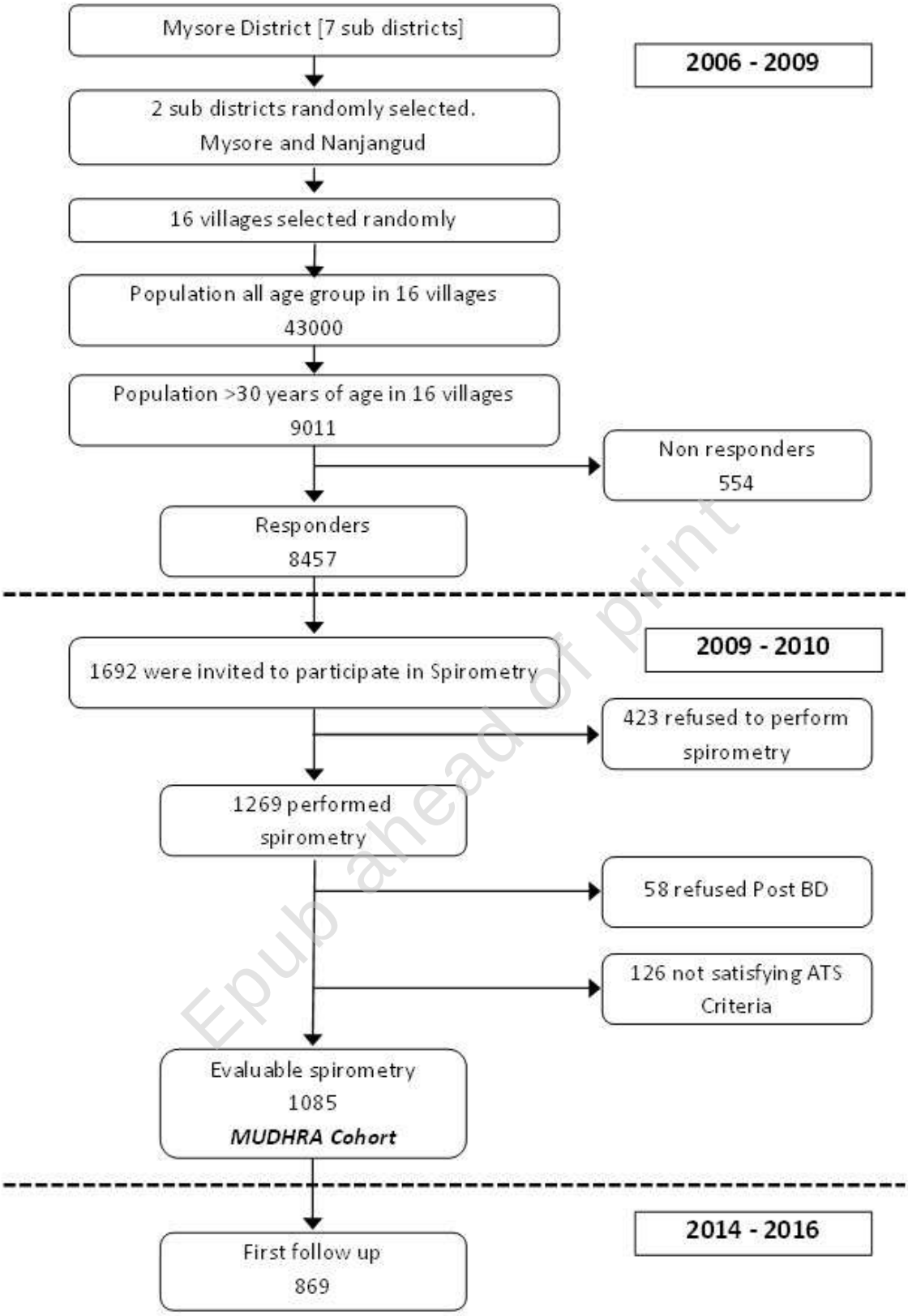

Figure 2: Flowchart for subject sampling and participation in different phases of the study.