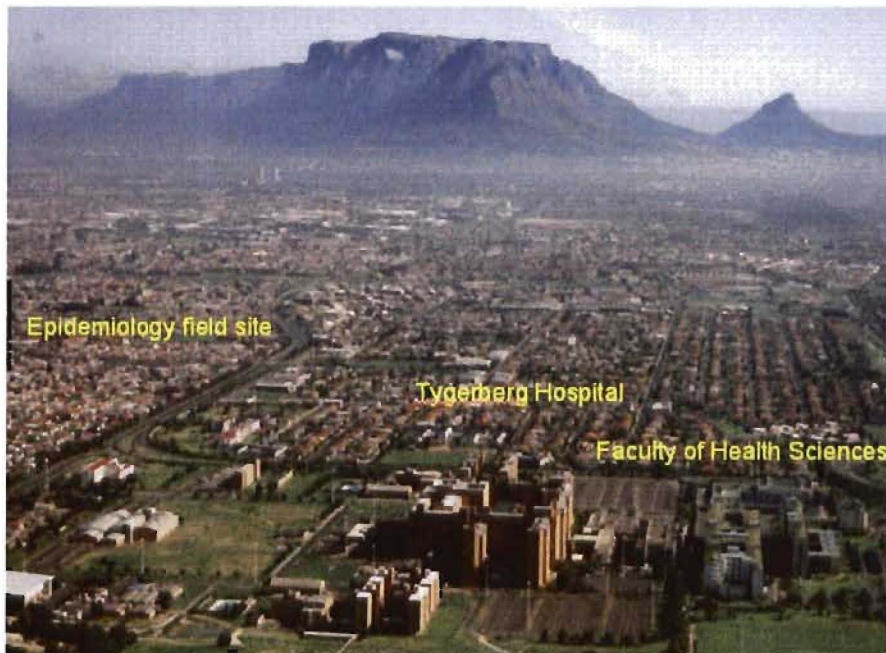


**RESPIRATORY SYMPTOMS AND CHRONIC
OBSTRUCTIVE PULMONARY DISEASE:
Prevalence and risk factors in a
predominantly low-income urban area of
Cape Town, South Africa**



Anamika Jithoo

**Thesis presented for the Degree of
DOCTOR OF PHILOSOPHY
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UNIVERSITY OF CAPE TOWN
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I dedicate this thesis to Sri Gurudev, Swami Sivananda.

DECLARATION

This thesis is presented in fulfilment of the requirements of the degree of Doctor of Philosophy (PhD) in the Department of Medicine, Faculty of Health Sciences, University of Cape Town, October 2006. The work on which this thesis is based is the author's original research, except as stated in the acknowledgements, and has not, in whole or in part, been submitted towards another degree, at this university or elsewhere. The university is empowered to reproduce either the whole or any portion of the contents for purposes of research.

NOTE FROM THE AUTHOR

Through the process of this doctoral work, I have learned many things; one of which is to persevere and believe in myself against all odds. I have been very fortunate to have concurrently studied coursework for a Master in Public Health Degree which has equipped me with the tools that have allowed the marriage of Respiratory Medicine with Epidemiology. Along the way, I acquired the skill of analysis of population data both through formal teaching of medical statistics, and trial and error. I am much the richer for this very interesting, if painful process. I have truly enjoyed discovering the results of these studies, and I hope that you will likewise enjoy reading this thesis.

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This thesis is the result of a synthesis of two population-based studies, involving over five and a half years of work. The author was fully involved in the conception of the studies, development of the research questions and protocol including the sampling strategy, development of the questionnaires, employment and training of fieldworkers, day-to-day management of fieldwork, quality control and supervision of pulmonary function testing, questionnaire administration and data capture. The literature review, hypotheses generation, data cleaning and analytic strategy, all statistical analysis and data interpretation was performed by the author, with guidance, insightful advice and constructive criticism from Professor Eric Bateman, Department of Medicine, University of Cape Town, as internal supervisor, and co-supervisor the late Professor Neil White, prior to his passing in 2004. My sincere thanks to both, especially to Professor Bateman upon whose truly exceptional knowledge I drew greatly throughout the entire period, and particularly in the last months of writing.

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The BOLD study was funded by grants from Research for International Tobacco Control (RITC), which is a subsidiary of the International Development Research Centre (IDRC), the South African Medical Research Council, the South African Thoracic Society GlaxoSmithKline Pulmonology Research Fellowship and the University of Cape Town Lung Institute.

ABSTRACT

The continuing worldwide increase in the incidence of chronic obstructive pulmonary disease (COPD) has led to international initiatives to improve surveillance and identify preventable risk factors for this and related chronic lung diseases. The studies reported here aimed to examine the prevalence and risk factors for respiratory symptoms and COPD; to introduce and test surveillance methodologies; and to inform treatment and control measures for this disease. The Lung Health Survey 2002 sampled 3512 individuals aged ≥ 15 years from an urban population of 36,334 in the predominantly low-income area of Ravensmead and Uitsig, Cape Town, South Africa. Information on respiratory symptoms, risk factors and healthcare utilisation was collected using a respiratory questionnaire which included questions that had been validated elsewhere. In 2005, a subsample of 960 persons aged ≥ 40 years participated in the Burden of Obstructive Lung Disease (BOLD) study comprised of a questionnaire and pre and postbronchodilator spirometry, in order to assess the prevalence of COPD.

A high prevalence of respiratory symptoms of 38.3% was reported. Tobacco smoking showed a consistent positive association with chronic bronchitis, wheeze, dyspnoea and cough. Strong associations with cannabis smoking, pulmonary tuberculosis, occupational exposures and low socioeconomic status were found. The association of cannabis smoking with respiratory symptoms suggest that it may be a risk factor for COPD.

The BOLD study revealed an exceptionally high prevalence of COPD in both men and women aged 40 years and older (29% and 20%, respectively) reflecting the very high prevalence of smoking in both sexes in the test area. The majority of those affected had moderate to severe disease, that is, symptoms with spirometric impairment (GOLD Stage II and higher). Even non-smoking women had a comparatively high prevalence of COPD (12.6%), attributable to other risk factors such as tuberculosis and occupational exposures. Previous pulmonary tuberculosis was shown to be a strong predictor of COPD, which warrants further study. Review of healthcare utilisation confirmed significant under-recognition and undertreatment within local health services.

These results confirm the need to prioritise preventative and treatment strategies for obstructive lung disease in South Africa.

GLOSSARY

AHR:	Airway Hyperresponsiveness
ATS:	American Thoracic Society
BHR:	Bronchial Hyperresponsiveness
BOLD:	Burden of Obstructive Lung Disease
BMRC:	British Medical Research Council
BTS:	British Thoracic Society
CI:	Confidence Interval
CMA:	Cape Metropolitan Area
COPD:	Chronic Obstructive Pulmonary Disease
DALY:	Disability-Adjusted Life Year
DOPS:	Diffuse Obstructive Pulmonary Syndrome
ECCS:	European Community for Coal and Steel
ECRHS:	European Community Respiratory Health Survey
ERS:	European Thoracic Society
EUROSCOP:	European Respiratory Society study on chronic obstructive pulmonary diseases
ETS:	Environmental Tobacco Smoke
FEV ₁ :	Forced Expiratory Volume in one second
FVC:	Forced Vital Capacity
GOLD:	Global Initiative for Chronic Obstructive Lung Disease
GINA:	Global Initiative for Asthma
HIV:	Human Immunodeficiency Virus
ISAAC:	International Study of Asthma and Allergy in Children
IUATLD:	International Union Against Tuberculosis and Lung Diseases
IBERPOC:	<i>Estudio Epidemiológico de la EPOC en España</i>
IDRC:	International Development Research Centre
LHS2002:	Lung Health Survey 2002
NHANES:	National Health and Nutrition Examination Survey
NHLBI:	National Heart, Lung and Blood Institute
NICE:	National Institute of Clinical Excellence
OLIN:	Obstructive Lung Disease in Northern Sweden
OR:	Odds Ratio
PAF:	Population Attributable Fraction
PALSA:	Practical Approach to Lung Disease in South Africa
PLATINO:	<i>Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar</i>
RITC:	Research for International Tobacco Control
SADHS:	South African Demographic and Health Survey
TB:	Tuberculosis
UK:	United Kingdom
US:	United States
VC:	Vital Capacity
WHO:	World Health Organisation

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CHAPTER 1: INTRODUCTION

1.1. Background

Chronic Obstructive Pulmonary Disease (COPD) has in recent years become an emerging public health crisis with new smoking in developing countries and aging populations worldwide.¹ Both rich and poor are affected, but it remains mainly a disease of the poor which has long been marginalised by government health departments and even scientists to a certain extent.¹ Other diseases of abuse associated with the affluent are the subject of lots of research, government guidelines etc. COPD remains shrouded by nihilism and has not completely lost its ignominious historic label of a self-inflicted disease. Although not yet displaying the full pattern of a world epidemic, prevalence appears to be rising worldwide, despite decreases seen in developed countries.

Reasons for the growing importance of COPD and the urgency to study it include the following. Firstly, in the developed world, life expectancy continues to increase, resulting in an aging population. Although smokers die younger than their peers, improved survival from infectious diseases and other degenerative diseases such as cardiovascular disease creates scope for more to develop this form of degenerative lung disease. Secondly, a consequence of globalisation is the opening up of new markets in developing countries for multinational tobacco companies.¹ Finally, it is becoming evident that other factors contribute aetiologically to the development of this disease, and a significant proportion of those affected are not smokers. In addition, smoking is not a sufficient explanation for COPD. There is therefore a need to study the causes and nature of the COPD that forms part of this 'new epidemic' in the developing world and in countries undergoing epidemiologic transition.²

In a World Health Organisation (WHO) commissioned study, Murray and Lopez estimated that COPD was the sixth most common cause of mortality in 1990 and predicted that it would move into 3rd position by 2020.³ Unlike asthma, premature death is common in COPD and the resulting years of life lost and those spent with a decreased quality of life are considerable. Morbidity and disability from symptomatic disease results in decreased productivity, high costs from health service use and treatment, work absenteeism and psychosocial effects on the individual and the family. Termed the "hidden epidemic"⁴, the affected people are elderly and become increasingly incapacitated, and so their retreat from society can go undetected. At a

country level, South Africa can ill-afford this added burden of chronic disease, faced as it is with the burden of trauma, infectious disease, and HIV, resulting in a quadruple burden of disease.⁵ Although COPD is ranked 16th in the top twenty individual causes of premature mortality (years of life lost), and seventh as a cause of morbidity, its true impact might be underestimated by under registration of deaths and underrecognition of disease.⁶ Despite this, COPD is ranked 8th as a cause of death in the Western Cape Province.⁷

Over the last few decades, there has been an increase in the burden of obstructive lung disease worldwide accompanied by a greater awareness of and changes in the profile of risk factors for the disease. COPD is currently one of the most common chronic diseases in adults and is likely to be responsible for considerable morbidity and mortality in South Africa. However, to date there are no population-based studies to assess the prevalence of COPD in South Africa, and thereby stimulate awareness of the disease. This awareness is necessary for both healthcare practitioners and society, as it will facilitate prevention, early and correct diagnosis, and appropriate information and treatment for patients.⁸ This will also allow for better advocacy to reduce smoking and other risk factors for the disease. The diagnostic shift that has occurred in developed countries appears to be slower in South Africa. But in order for early diagnosis to occur, there needs to be a higher suspicion, in order to assist with prevention of disease progression.

Also of importance is the identification and control of risk factors for COPD as the first step in the primary prevention of this disease, and the most appropriate and cost-effective way of tackling health problems. In the case of tobacco use and COPD, this approach has been recommended by the WHO to be feasible and effective.⁹ The most practical and effective of measures are anti-smoking initiation and smoking cessation initiatives.

The first comprehensive study of health was the South Africa Demographic and Health Survey of 1998 (SADHS). According to this survey, the prevalence of self-reported doctor-diagnosed chronic bronchitis in men from the Western Cape Province was higher than in other provinces, affecting 9.4% of men of all ages, compared to 0.7% in the Free State Province and 5.7% in Gauteng.¹⁰ Even though the differences may represent inequitable health services, the high prevalence amongst women in the Western Cape women (11.4%) was of concern.¹⁰ While surveys of this nature lack diagnostic precision, they may indicate sentinel symptom

complexes that represent disease trends, and point to the likelihood of high COPD prevalence in both sexes in this province. This is in contrast to a global trend of higher reported prevalence of COPD in men compared to women.

The use of standardised questionnaires for collecting data on symptoms is considered the method of choice in “first phase” population surveys. These have been used successfully in asthma studies to make comparisons of prevalence between regions and countries.²⁹ Until recently, this has been difficult in COPD studies. In the absence of established longitudinal study cohorts, sentinel surveillance is useful to examine whether obstructive lung disease is becoming more common. In addition, the current objective gold standard for COPD diagnosis requires the use of spirometry in order to accurately stage disease and it is essential to have a baseline prevalence of disease in order to inform and plan healthcare strategies, policy and legislation.

Results of studies of the prevalence and risk factors for respiratory symptoms and COPD have to be interpreted in the context of the past few centuries’ political, social and economic circumstances in South Africa.¹¹ These forces have shaped the distribution and determinants of both obstructive and infective lung diseases. They are reflected in the lung health of this community and other similar communities affected by poverty. Poverty is associated with noxious agents such as occupational exposures, tobacco and a high burden of infectious disease such as tuberculosis.

The increasing worldwide burden of COPD has made the measurement of prevalence a global research priority. Assessing the size of the problem is a first step in attracting public interest, driving political will, legislation and allocation of the resources necessary to address COPD. This thesis reports one of the first community studies in South Africa to assess the prevalence and risk factors for respiratory symptoms in a defined population. It comprises two linked studies, the first involving a respiratory questionnaire supported by investigations in a carefully sampled population, and the second, performed in a subsample, providing spirometric assessment using the internationally standardised Burden of Obstructive Lung Disease (BOLD) methodology.

1.2. Historical perspective

The segregation of South African society along ethnic lines that was national government policy until 1994, resulted in exaggerated social, geographical and economic differentiation that have had a profound effect upon all spheres of life, including education and health. In spite of the reforms of the past ten years of democracy, this differentiation persists today. The population in the Western Cape Province comprises several groups of varying size, which reflect the process of colonisation, migration patterns and the laws enforced by the apartheid government. Until recently the largest group was of mixed ancestry, the so-called 'Cape Coloured'ⁱ group.

The diversity of the population of the Western Cape presented a challenge for the design of the studies reported in this thesis. Since socioeconomic status is a powerful determinant of health in general and lung health in particular, one is faced with a situation of sampling a city with such extremes of socioeconomic status. Different options were considered. The first was to select a sample representative of the demographics of the population. Although ideal in terms of representation, this approach has the potential to dilute local risk factors that might operate in sections of the community, and a far larger sample size would be needed to analyse associations with risk factors. However, other objectives of the study influenced the selection of the study population. Established residential areas in the Western Cape have relatively stable, non-mobile communities. Secondly, these communities being largely a working class group, many persons are low to intermediate with respect to income and education, but at high risk of lung disease because of their pattern of smoking and occupational exposures. Thirdly, the opportunity was presented to study two suburbs of Cape Town that had been well characterised by researchers from the University of Stellenbosch who have been investigating tuberculosis in the community. The suburbs are two adjacent predominantly low-income suburbs known as Ravensmead and Uitsig. Further details of the study population and area are presented in Chapter 4.

ⁱ This term had been introduced by the apartheid government to refer to persons of mixed ancestry who form a large proportion of the Western Cape Province. The term continues to be used by the democratically elected government and in current published health literature and appears quoted as such from the source literature, in this thesis.

1.3. The Lung Health Survey 2002 (LHS2002) and the Burden of Obstructive Lung Disease (BOLD) Study

The community of Ravensmead and Uitsig, and the Western Cape region it belongs to, is firstly distinguished by a high prevalence of smoking - reported in the SADHS as being 57% in men and 40% in women. These are one of the highest smoking prevalences amongst the nine provinces of South Africa, and among the highest in the world. However, the number of cigarettes consumed per capita, is in a low range of 1-14 cigarettes per day.¹⁰

The second distinguishing factor of this community is that it has a very high prevalence of pulmonary tuberculosis (TB) estimated at 10 per 1000 population.ⁱⁱ This 'epidemic' of tuberculosis has occurred over decades, and in spite of considerable research into possible reasons, the causes of the epidemic are elusive.ⁱⁱⁱ There are some clues, such as the very well-recognised association of tuberculosis with urban poverty, harking back to the time of the industrial revolution in England; and the association of TB with tobacco smoking. It is suspected that this high burden of tuberculosis might have an impact on chronic lung disease.

An increase in tuberculosis has occurred in spite of what has been judged by the WHO Stop TB Programme as a Tuberculosis Control Programme of "moderate" quality.¹² It also preceded the appearance of the Human Immunodeficiency Virus (HIV) infection as a risk factor for acquiring tuberculosis, the Western Cape currently being the least affected province of South Africa.

Thirdly, it is possible that Cape Town has a higher prevalence of asthma and allergic diseases than other parts of the country; however there are few data on the prevalence of COPD. Most asthma prevalence data from South Africa is from the Western Cape Province with a prevalence of 10.8% reported among children.¹³ The SADHS reported a national self-reported asthma prevalence of 7% in men and 9% in women, and a prevalence of chronic bronchitis of 2.8% in women and 2.3% in men.¹⁰ While statistics for most of South Africa and the rest of the continent of Africa are sparse, these diseases are thought to be less common in other regions than they are in the Western Cape. Using the globally validated epidemiologic methods of the

ⁱⁱ Den Boon S, van Lill SWP, Borgdorff MW, Enarson DA, Verver S, Bateman ED, Irusen E, Lombard CJ, White NW, de Villiers C, Beyers N. High prevalence of previously treated tuberculosis in Cape Town, South Africa (unpublished manuscript)

International Study of Asthma and Allergy in Children methodology (ISAAC) for children aged 13-14 years, 13.3% reported that they had ever had asthma, while 16.0% had experienced wheeze in the last 12 months, which is above the global average.¹⁴ South Africa (Western Cape) is ranked 25th amongst almost 100 countries of the world recently surveyed in the Global Burden of Asthma Survey, published by the Global Initiative for Asthma (GINA) in 2004. This estimate is based on symptom data of children in a single area of South Africa and has limited generalisability to the country, as wide variations in the prevalence of current asthma symptoms are thought to apply.

The burden of respiratory disease in Cape Town is suspected to be high. In 1999, a survey of patients presenting to a primary care centre in Cape Town confirmed that 28% of patients presented for treatment of respiratory symptoms.¹⁵ It is suspected that much of this is chronic respiratory disease such as asthma, COPD and tuberculosis (TB).

Over the past fifteen years the TB Research Unit of Stellenbosch University has been involved in multidisciplinary research focussing on reasons for the high incidence of TB in the Western Cape. These studies have been performed in Ravensmead and Uitsig. In addition to TB, it was suspected that other forms of lung disease were also highly prevalent, which lead to an interest in further research in these areas.

During 2001, the University of Stellenbosch TB Research Unit in collaboration with the UCT Lung Institute began a project that developed into a multi-component survey of the two suburbs of interest. This study, the Lung Health Survey 2002 (LHS2002) aimed to establish the prevalence of lung diseases and their possible contributory causes. This was a comprehensive survey, unique in studying respiratory disease in all age groups.

The LHS2002 provided an opportunity to study not only diseases that present the greatest burden upon health resources, but also their relation to one another and with co-morbidities, and the ability to investigate the influence of environmental factors upon the prevalence of disease. An added benefit of undertaking this research in Ravensmead and Uitsig was the low prevalence of HIV infection in these suburbs, a prevalence that is expected to rise over the next decade. It is anticipated that the prevalence and profile of lung disease is going to change, and that the HIV epidemic may have different effects upon the prevalence of certain respiratory diseases. It will

increase the prevalence of active TB, but untreated, it could be associated with a fall in the prevalence of COPD through its effect upon life expectancy.

Improvements in economic status which occur without measures to reduce the prevalence of smoking might lead to increased cigarette consumption. This could result in increasing morbidity from chronic bronchitis and COPD, and in due course of lung cancer and other smoking related pathology.

The initial survey was followed by three separate Part Two studies, performed independently by different investigators. The first was a detailed study of asthma and allergy in children aged 0 -14 years who participated in the Lung Health Survey 2002. This study by Dr Charles Obihara et al was designed to assess the prevalence of symptoms of asthma and allergic disorders, the associations between these disorders and tuberculosis, and the influence of co-morbidities like helminth infection and environmental factors upon the development of allergic disease - the “hygiene hypothesis”.^{16 iii}

The second study by Dr Emmerentia Van Schalkwyk et al examined the prevalence of asthma in young adults between the ages 15 and 44 years using the European Community Respiratory Health Survey (ECRHS) methods to assess airway hyperresponsiveness (AHR) and asthma.¹⁷

The third ‘follow-up’ study is the Burden of Obstructive Lung Disease (BOLD) study, performed by the author in collaboration with researchers from the Oregon Health Sciences University and Kaiser Permanente Centre for Health Research in Portland, Oregon in the United States. The BOLD study is a worldwide initiative aimed at developing a standardised protocol to obtain information about the prevalence and burden of Chronic Obstructive Pulmonary Disease (COPD) and of factors responsible for, or associated with this disease. The BOLD protocol has been developed with the intention that it be used in many countries and regions in the world to generate reliable, comparable data on COPD and smoking. One of the foci is an economic evaluation of the burden of tobacco-related disease, to inform health interventions and the development of tobacco control policies.

ⁱⁱⁱ Jithoo A, Bateman ED, van Lill S, Irusen E, Van Schalkwyk E, Beyers N. The Lung Health Survey 2002. Protocol for the UCT Research Ethics Committee. 2002. (unpublished).

Although ideally the BOLD study could have been performed at the same time as the LHS2002, and a spirometric assessment as an immediate second phase of the LHS2002 was originally envisaged and planned, the latter was amended because it became obvious that using the BOLD methodologies would have several advantages over the locally developed protocol. Since the BOLD methodology was under development, this involved a delay of almost two years before the second phase could be performed, and the Cape Town site became only the fourth international site to use this methodology. Obvious advantages of this decision were the following:

- (a) Using an internationally standardised protocol allowed for accurate comparisons of results with other sites and countries.
- (b) The quality control process provided by the BOLD operations centre added value to the test results.
- (c) The prescribed spirometric equipment, having been internationally accepted, ensured acceptability of the results to an international audience.

The methodology has been developed and tested by the BOLD researchers under the auspices of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).¹⁸ Initial validation/pilot studies were performed in Turkey and China. In the next phase, it was used in Austria, Iceland, Sweden and in this study site in Cape Town, South Africa. This was the first population-based study of COPD in South Africa^{iv}, and to our knowledge, one of the first in Africa. The skills and expertise gained may be used to assist with the performance of the BOLD methodology in other parts of South and southern Africa. The information gained will also be used to highlight the impact of smoking upon lung health, and the importance of COPD.

Besides providing data on the prevalence and severity of COPD in the Ravensmead/Uitsig area, and the burden that this places upon health and social services, it was hoped that the study would provide information on the ways in which smoking and other risk factors contribute to diseases of the lungs in low-income communities. It was also intended to provide baseline data that might be used to track the effectiveness of anti-smoking legislation and other health measures.

^{iv} There are currently no other published population-based studies of COPD in South Africa.

1.4. Thesis Objectives

This thesis investigates the prevalence of respiratory symptoms and COPD, and associated risk factors in a predominantly low-income urban community of Cape Town, South Africa. Since distinguishing asthma from COPD on the basis of symptoms alone is not possible, some data relating to asthma will also be presented but is not the focus of the work.

The two hypotheses that will be investigated are that in this community in Cape Town:

1. The prevalence of respiratory symptoms is high, and may be higher than that estimated in the SADHS.
2. Factors other than tobacco smoking e.g. occupational exposures, cannabis smoking, poverty and previous TB are causatively linked to respiratory symptoms and COPD.

Five Questions are addressed:

1. What is the prevalence of respiratory symptoms (cough and sputum production, wheeze and dyspnoea) in adults ≥ 5 years of age in Ravensmead and Uitsig, Cape Town?
2. What are the risk factors for respiratory symptoms (determinants of obstructive lung disease) in this community?
3. What is the prevalence of COPD as defined by the Global Obstructive Lung Disease Initiative (GOLD)?
4. What are the associated risk factors for COPD?
5. What proportion of respiratory symptoms and obstructive lung disease is being recognised and treated and what are the implications of the prevalence of respiratory symptoms and COPD for healthcare services?

1.5. Thesis structure

This introductory chapter provides some general background on obstructive lung disease in South Africa and study objectives. It also presents definitions and nomenclature. Chapter Two is a literature review on the prevalence and risk factors for COPD such as tobacco smoking, occupational exposures and socio-demographic factors. Chapter Three reviews adult obstructive lung disease in South Africa, with particular emphasis on population-based literature from the last decade.

Chapter Four describes the methods of the two studies - the LHS2002 and the BOLD study, and Chapters Five and Six contain the results of the LHS2002. Chapter Five presents the prevalence of respiratory symptoms, prevalence of exposures and data on healthcare utilisation. Chapter Six reports an analysis of obstructive lung disease symptom-outcomes with various risk factors.

Chapter Seven reports results from the BOLD study in terms of prevalence of COPD and results of multiple logistic regression analysis of associations with risk factors. The results are discussed in Chapter Eight.

1.6. Nomenclature and Definitions

The use of different definitions and defining criteria for each of the diseases COPD and asthma have made it difficult to compare estimates from different studies in the past.¹⁹ During the last decade, efforts have been made to standardise not only the definition of COPD, but also the diagnosis and treatment of COPD, notably by the Global Initiative for Chronic Obstructive Lung Disease (GOLD)¹⁸ and the Global Initiative for Asthma (GINA).²⁰ A recent consensus document by the European Respiratory Society and American Thoracic Society served to unify global definitions and solidified the departure from older definitions of COPD.^{19 21}

1.6.1. Chronic bronchitis

For the purposes of this thesis the original British Medical Research Council (MRC) definition of chronic bronchitis is used: "cough with phlegm for three successive months for at least two successive years".²² This definition has been used in studies worldwide for over forty years and is advantageous in that it allows for comparison of prevalence across different studies.¹⁹

Chronic bronchitis is distinct from but often associated with COPD. Chronic bronchitis is a symptom complex and it must be noted that it occurs probably just as frequently as a symptom of asthma, as was first described by the great physician Osler who named it "chronic eosinophilic bronchitis" in the late 19th century.²³ In each individual, a different degree of inflammation and/or airways hyperresponsiveness (AHR) may occur with chronic bronchitis which may or may not result in airway obstruction. In the absence of spirometry, the prevalence of COPD cannot be directly inferred from the prevalence of chronic bronchitis²⁴, but its presence serves as an index of respiratory

symptoms, reflecting the respiratory health of a population. Other measures of reporting such as “doctor-diagnosed chronic bronchitis” or >3 episodes of bronchitis²⁵ in the past 12 months have also been used in population based studies, making some comparisons difficult because of a lack of standardisation of the definition across studies.

1.6.2. Emphysema

Emphysema is not a clinical but an anatomical definition referring to the “destruction of alveolar walls and the permanent enlargement of the airspaces distal to the terminal bronchioles”.^{30 31} It results in loss of elastic recoil, collapse of the terminal bronchioles and loss of intraluminal pressure³⁰, which results in airflow obstruction. The predominant symptom is progressively worsening dyspnoea, and clinically, CT imaging evidence can be used to make the diagnosis.

1.6.3. COPD

GOLD defines COPD as “a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases”.¹⁸ The GOLD guidelines and staging of disease are reviewed in Chapter 2. It refers to both symptoms and a history of exposure to risk factors as a basis for suspecting COPD, but spirometry is required to confirm the diagnosis.¹⁹ The GOLD definition refers to chronic bronchitis without airflow limitation as Stage 0 (at risk). This acknowledges that some persons may either have mildly reduced lung function that has not yet reached the threshold for diagnosis of COPD, or may simply have cough and phlegm that is unrelated to decline in lung function. The initial concept that Stage 0 represented persons at risk of developing COPD has however recently been questioned, as it has not been shown in prospective studies to be predictive.²⁶ For this reason Stage 0 has been omitted from the 2006, as yet unpublished update of the GOLD Severity Classification. However, the presence of symptoms provides a useful opportunity to review and prevent exposures to potential causative factors such as tobacco smoking, occupational or biomass fuel exposure. Stage I or higher COPD requires evidence of airflow limitation in terms of a post-bronchodilator ratio of Forced Expiratory Volume in one second (FEV₁) to Forced Vital Capacity (FVC) of less than 70%, with or without symptoms. Post-bronchodilator FEV₁ as a percentage of predicted value is used to determine the staging of severity of COPD from Stage I (mild) to Stage IV (very severe).¹⁹

1.6.4. Asthma

GINA defines asthma as “a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment”.²⁰ A postbronchodilator FEV₁/FVC \geq 70% and reversibility \geq 200ml and \geq 2% of baseline FEV₁ is required for the diagnosis of asthma but asthmatics on treatment or between attacks may have normal lung function.

1.6.5. Respiratory Symptoms

Questionnaire reporting of respiratory symptoms such as wheeze, cough and dyspnoea as well as symptom complexes are accepted methods of assessing disease at a population level. A symptom is defined as “any sensation or change in bodily function that is experienced by a patient and is associated with a particular disease”²⁷ and refers to the “subjective experience of disease, or a phenomenon that is experienced by an individual”.²⁸ Owing to its subjective nature, the reporting of symptoms may be biased, but for diseases such as asthma and COPD, questionnaire-based symptom definitions can be a useful alternative (in prevalence studies) to objective tests such as non-specific airway hyperresponsiveness (AHR).¹⁹

²⁹ Symptoms are defined as per questionnaire responses in this thesis.

As in the clinical setting, it is not easy to distinguish clearly between asthma and COPD in population studies on the basis of symptoms alone, particularly in smokers and the elderly. Many studies rely on symptom questionnaires such as the British MRC questionnaire that have been standardised and validated among adults in developed countries, but their validity in South Africa has not been established. Spirometry-based studies are lacking. The contribution of asthma, chronic bronchitis, emphysema and COPD to obstructive lung disease is not entirely clear. This interrelationship has been the source of controversy in the past, and continues to be so today.

Figure 1 shows the nonproportional Venn diagram published by the ATS in 1995 describing the relationships between the components of a spectrum of obstructive disease possible in persons with respiratory symptoms, a large proportion of which is asthma and COPD.³¹ Although asthma is by definition associated with reversible

airflow obstruction, the evidence of obstruction may have to be sought by methods such as the methacholine challenge testing or exercise. Those with completely reversible obstruction or “pure asthma” are represented by subset 9. It is sometimes clinically difficult to differentiate between partially reversible asthma and chronic bronchitis/emphysema patients with AHR, resulting in the former group being classified as having COPD (subset 6, 7 and 8) Subset eight refers to persons with all three diagnoses - asthma, chronic bronchitis and emphysema.^{31 32}

Emphysema and chronic bronchitis with airflow obstruction can occur together (subset 5). Asymptomatic or symptomatic emphysema is represented by subset 2 and 11 and chronic bronchitis without airflow obstruction by subset 1. Other lung diseases causing airflow obstruction such as cystic fibrosis are outside of the circles but within the box (subset 10).^{31 32} The GOLD definition of COPD would further include those with irreversible or partially reversible airflow limitation that would be a further subset of subset 10, and also those persons with reversible airflow limitation who have emphysema and/or chronic bronchitis (part of subsets 1, 2 and 11).³⁰

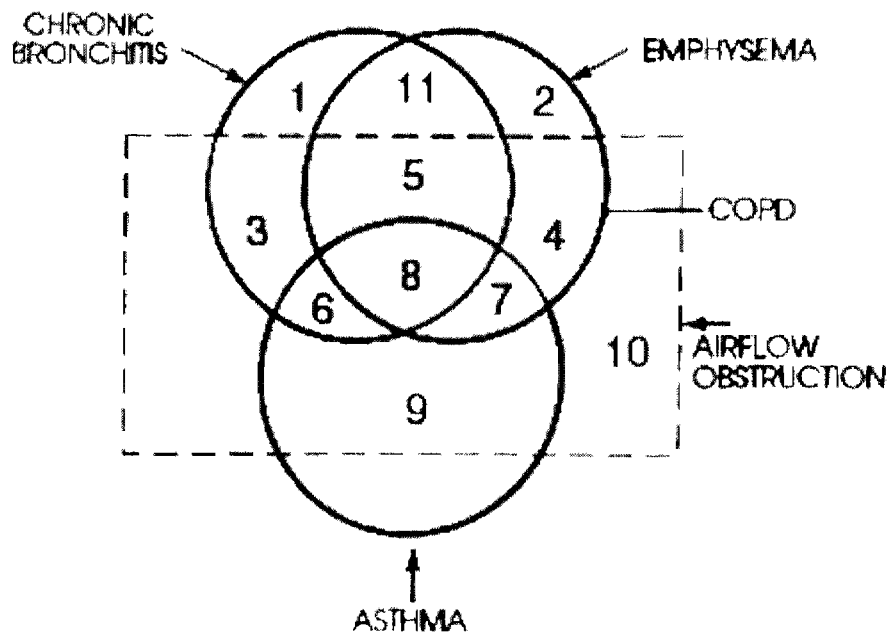


Figure 1: Nonproportional Venn diagram of COPD showing subsets of patients with chronic bronchitis, emphysema, and asthma (subsets with COPD shaded) from the American Thoracic Society: Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease.^{31 32}

The proportions in each category may vary according to the diagnostic criteria used and whether based on symptoms alone, spirometry, or symptoms and spirometry, and whether additional investigations like bronchial challenge are used. Proportionality has been ascribed to this diagram for some populations in developed countries such as the U.S. and the U.K.³²

The studies reported in this thesis permit comparison of respiratory disease detected with the first two of these diagnostic approaches (questionnaires and spirometry), and allow a comprehensive epidemiological perspective of the relationship between symptoms and the presence of obstructive lung disease in adults.

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CHAPTER 2: LITERATURE REVIEW: PREVALENCE AND RISK FACTORS FOR COPD

2.1. Introduction

The aim of this chapter is to provide a brief historical perspective and a broad overview of the world literature on population-based studies of obstructive lung disease with respect to COPD prevalence and risk factors.

As outlined in Chapter 1, the obstructive lung diseases include asthma, COPD and a number of other less common forms of lung disease that affect the airways. Owing to the wide aetiology of COPD, this chapter is not intended to be an exhaustive review of the literature on prevalence and each risk factor, but rather gives an overview with the focus on some important themes and an emphasis on more recent studies. With some exceptions, the studies for review were chosen on the basis of merit; the result of considerations of sample size, strength of associations and robustness of study design.

2.2. Historical Perspective

2.2.1. Recognition and terminology of Chronic Obstructive Pulmonary Disease

Chronic bronchitis and COPD are not new diseases. The ancients referred to many respiratory diseases under an umbrella term of 'catarrh'.¹ The invention of the stethoscope by the Frenchman Laennec in 1819 stimulated interest into lung disease and it was Laennec himself who made the classical description of emphysema as an anatomical construct in 1827.^{1 2} Badham is thought to have coined the term chronic bronchitis in 1808.³ A further development in understanding lung diseases was the invention of the spirometer by Hutchinson in 1842.¹

However, three prominent events in the 20th century stimulated interest in obstructive lung disease - the Meuse Valley poisonous smog in Belgium, the Donora catastrophe in Pennsylvania in 1948, and the great London Fog of 1952. All were associated with many deaths from respiratory disease. The Meuse Valley was the first recorded severe air pollution episode that resulted from industrial processes. A temperature inversion in the valley trapped poisonous smog thought to be fluorine from local factories, killing sixty inhabitants and affecting scores more.^{4 5} In Donora, twenty people died and over 7000 were hospitalised with respiratory symptoms after having been exposed to poisonous smog from a local industry where most of the residents worked.⁶ The subsequent London Fog disaster caused approximately 4000 deaths of

persons with chronic respiratory and cardiac disease.⁷ Later research has suggested that the figure may have been even as high as 12000.⁸ The London Fog resulted in increased awareness and provided the focus and motivation for the British MRC to research chronic bronchitis in ensuing years.

A milestone in our understanding of obstructive lung diseases was the CIBA symposium of 1958 which for the first time recommended that asthma and chronic bronchitis and emphysema be viewed as different diseases for classification, clinical and coding purposes.⁹ Prior to this, these terms were used interchangeably. A distinction was made between irreversible obstructive lung disease and emphysema, as it was recognised that some patients with irreversible obstructive lung disease showed no evidence of emphysema on post mortem examination. It was proposed that the term emphysema be reserved for those with clear radiological, clinical and physiologic evidence of emphysema.⁹

In the early 1960's, the American Thoracic Society and the British Medical Research Council concurred with this viewpoint at their respective meetings.^{10 11} In 1966, Briscoe¹² suggested that the term chronic obstructive pulmonary disease be used to cover chronic bronchitis and emphysema while Burrows et al¹³ preferred to distinguish between chronic airways obstruction (emphysema) and chronic bronchitis. In 1977, Fletcher and Peto described the natural history of the disease and described the two conditions, chronic bronchitis and emphysema, as different manifestations caused by cigarette smoking.¹⁴ However, the uncertainty of how to diagnose and describe the disease has continued well into the current era, and even within the last year, new recommendations for defining and staging COPD have been proposed (GOLD 2006 update – in press).

The role of measurements of lung function in the diagnosis and staging of obstructive lung disease had now become more important. Early attempts to measure lung function included the maximum breathing capacity as a measure of impairment. Tiffeneau was most famous for the Tiffeneau Index (FEV_1/FVC) which is used in the current definition criterion for COPD according to GOLD. Tiffeneau and Pinelli proposed the use of the forced expiratory volume in 1 second (FEV_1) as the basis for diagnosis and staging in 1947.¹⁵ This proposal was supported by Gaensler¹⁶ in 1951, and subsequently adopted by the British Thoracic Society in 1957.¹ Over half a century later, this measurement remains the most important for assessing airflow obstruction.

Along with this research came the recognition of the need to standardise questionnaires and methodology as major tools for use in respiratory epidemiologic studies. The British MRC questionnaire, published in 1960 was the first.¹⁷ It attempted to limit observer bias and some questions focused on the identification of chronic bronchitis. It also included questions on breathlessness as an indicator of respiratory disability.¹⁸ In 1962, the European Community for Coal and Steel (ECCS) built on the MRC questionnaire by adding questions on medical and occupational history.¹⁹ Subsequently, the American Thoracic Society (ATS) in collaboration with the Division of Lung Diseases (DLD) produced a questionnaire in 1978 (ATS-DLD-78).²⁰ Comstock et al compared the MRC questionnaire to this new instrument and viewed their performance as similar.²¹

The evolution of knowledge on COPD has resulted in changes in later versions of the MRC and ECCS questionnaires over the last three decades. Other questionnaires have also been developed – the International Union Against Tuberculosis and Lung Diseases (IUATLD) questionnaire (1984)²² provided more focus on asthma, as did the European Community Respiratory Health Survey (ECRHS) questionnaire.²³ However questions relating to chronic cough and phlegm continued to be borrowed from the revised MRC questionnaire. Despite major advances in technology and the development of lung function tests such as spirometry, diffusing capacity and CT lung density, questionnaires remain a major tool for population-based studies for their ease of use, low cost and the option of self-administration by participants.

Concepts and understanding of the pathogenesis and natural history of obstructive lung diseases evolved over the past fifty years, and at times have been polarised by contributions made by prominent researchers in different countries.

2.2.2. The British Hypothesis

The work of British clinicians and researchers, notably Fletcher, Peto, Reid, Holland and colleagues, resulted in the formulation of the so-called British hypothesis which stated that recurrent bronchial infections were the cause of progressive decline in lung function in smokers.

Chief amongst this evidence was the work by Fletcher and Peto who espoused the hypothesis and performed a study that was meant to demonstrate it, comparing the rate of decline of lung function in non smokers, former smokers and smokers.¹⁴

Two phenotypes were described – chronic bronchitis with progressive lung function impairment and parenchymal damage/emphysema and chronic bronchitis without emphysema. Both were related to smoking and could co-exist in the same person. Additionally they concluded that neither mucous hypersecretion nor bronchial infection cause COPD to progress more rapidly, and that chronic bronchitis and COPD were largely unrelated disease processes but both were caused predominantly by smoking.¹⁴ A subsequent 20 -25 year follow-up study of the Fletcher and Peto cohort found that the risk of death from COPD was strongly associated with the initial degree of airflow limitation, but not with mucous hypersecretion, further supporting the independence of the two processes.²⁴ This has been challenged by Annesi and Kauffmann (1986) who found that chronic mucous hypersecretion was significantly associated with mortality (OR 1.35 $p < 0.01$) in a cohort of working men after correcting for age, smoking and occupational exposures, suggesting that it is not an “innocent condition”.²⁵ Vestbo et al also found it to be associated with an increased risk of hospitalisation for COPD which could be related to an increased risk of bronchial infection.²⁹

Fletcher and Peto found that tobacco smoke exposure accelerated the decline in lung function in susceptible smokers and that those who stop smoking return to the rate of decline of never-smokers but do not regain their lung function.¹⁴ This view was later supported by the North American Lung Health Study which confirmed that in subjects who stop smoking the rate of FEV₁ decline was half that in intermittent quitters or continuing smokers, and comparable to that of never smokers.²⁶

The role of cigarette smoking as the sole cause of COPD was challenged by Holland and Reid who described an urban-rural difference in respiratory symptoms and lung function of postal service workers in London and three rural areas in the early 1960's.²⁷ They ascribed this difference to air pollution after correcting for smoking, occupation and socioeconomic status.²⁸

The relationship between respiratory infection and airflow limitation continues to be controversial. The British hypothesis was shelved for a while largely because of Fletcher's work which showed that the number of infections did not alter the slope of the decline in lung function but only caused temporary depressions in lung function. It is now being revived slightly for advanced COPD, the argument being that Fletcher's subjects were still relatively mild. The following studies have taken another look at the hypothesis in a new light.

The Copenhagen City Heart Study, a cohort study supported the original British hypothesis (but not Fletcher's subsequent opinion) by showing an increase in FEV₁ decline of 22.8ml/yr in men and 12.6ml/yr in women associated with chronic mucous hypersecretion.²⁹ The early identification of persons likely to have more rapid decline in lung function is still elusive as we are still unable to predict which chronic bronchitis patients will have accelerated decline or predict the rate of decline. Studies have been performed to examine levels of inflammatory markers (e.g. Von Willebrand Factor, a product of the respiratory and systemic endothelium³⁰), but none have yielded clinically useful results as yet.

Wilkinson et al and Hill et al have found that the rate of decline of lung function is related to bacterial load and species changes, independent of whether organisms were pathogenic or not.^{31 32} The role of inflammatory indicators in patients with and without pathogenic bacteria was examined by Banerjee et al, indicating that pathogenic bacteria cause more inflammation than their non-pathogenic counterparts.³³ Exacerbations of COPD seem to accelerate lung function decline³⁴ and it seems that chronic bronchitis is not entirely irrelevant to the progress of obstructive lung disease³⁵, but the contribution of chronic infection is still unclear.

2.2.3. The Dutch Hypothesis

In contrast to the British hypothesis, the Dutch hypothesis, developed in the 1960's by Orie et al³⁶(1961) and van der Lende (1969)³⁷, considered asthma, chronic bronchitis and emphysema to be different subgroups of the same disease process, with the possibility of overlap between them, meaning that more than one form may be present in the same person. According to this view pre-existing or hereditary hyper-responsiveness and atopy predispose to COPD as well as to asthma. Host characteristics such as atopy and airways hyperresponsiveness (AHR) influence and might determine an individual's responses to environmental exposures such as smoking and air pollution. Interaction of host and environmental factors determine whether an individual is healthy, develops asthma or irreversible lung function impairment.³⁸ The focus is on endogenous host characteristics as the principal determinant for the development of COPD, as opposed to exogenous factors as in the British hypothesis.

There appears to be more than circumstantial evidence for the Dutch hypothesis. Xu et al (1997) analysed a 24 year follow-up on the Vlagtwedde and Vlaardingen cohort studies and showed that increased airway responsiveness is positively associated

with the development of chronic respiratory symptoms and negatively associated with the remission of these symptoms, in support of the hypothesis.³⁹ However, the question of whether the AHR is a cause or a result of the pathological process remains. It is already known that narrowed airways are more hyperreactive than normal airways, as an increased resting bronchomotor tone may potentiate a subsequent constrictor stimulus.^{40 41} The argument that the AHR is measured prior to obvious obstruction³⁹ depends on how sensitive FEV₁ is for the abnormality and there is reasonable evidence that it is not very sensitive (see Chapter 8).⁴² In addition, accelerated annual decline in FEV₁ in smokers is associated with an increase in AHR as the FEV₁ falls.⁴¹

2.2.4. The American Perspective and mortality studies

Examination of the differences in the patterns and rates of mortality between the US and the UK in the 1960's and 70's have been of benefit in drawing attention to problems of disease definitions, classification and reporting. These mortality studies benefited their respective populations and the medical community by resulting in critical appraisal of the validity of mortality data and also resulted in an improvement in the definition of respiratory disease.^{43 44 45} They have highlighted problems with the classification of obstructive lung disease, particularly in relation to death certification, upon which the mortality statistics were based. Misclassification and incorrect attribution of cause of death data was shown to have resulted in much underestimation of disease, even as it does today in South Africa.^{45 46}

Subsequently, comparisons of the accuracy of death certification of respiratory disease have been made within the European Economic Community which showed differences between countries and within each country. These have highlighted the need for standardisation of respiratory disease classifications in order to achieve more accurate mortality statistics.⁴⁷

Reporting systems for mortality data in South Africa are lagging behind in making this transition to more accurate mortality reporting and in defining and communicating about respiratory disease.⁴⁸ These limitations occur particularly at the primary health care level⁴⁹, where asthma and bronchitis are terms often used interchangeably, and also to describe COPD. Diagnostic tools such as spirometry are not widely available or often used correctly.⁵⁰ This diagnostic misclassification probably makes South African mortality and morbidity data less reliable than data from established market economies but there is also little evidence to support the fact that developed

countries have better access to good quality spirometry, particularly at the primary care level. Regarding morbidity, questionnaire-based surveys play an important role in identifying those with respiratory symptoms, but are not good tools for identifying or classifying obstruction. Good local research is thus essential to provide data for estimating the burden of disease.

2.3. The Global Burden of COPD

COPD is a common cause of mortality and morbidity worldwide, and although the prevalence of disease varies widely within and between countries and regions, it presents a heavy direct and indirect economic and social burden in all countries of the world.⁵¹ However, recognition of this fact has been slow, and only in recent years has its true prevalence been established in some countries. In others, and in particular for the continent of Africa, very little data is available. This process has been slowed because of poor definitions of disease, methodological issues and resource constraints. In 1990, the World Health Organisation (WHO) commissioned a Global Burden of Disease study which estimated the current all-cause burden of disease in terms of morbidity (prevalence and quality of life), mortality and costs. In 2001, COPD was the fifth most common cause of death worldwide⁵², responsible for 4.7% of deaths and 2.0% of disability adjusted life years (DALYs).⁵³ A 30-year projection from 1990 predicted a steady rise in the number of COPD deaths to the third most common cause worldwide by 2020.⁵⁴ Most of the projected DALY burden will fall on developing countries.⁵⁴ In 1990, COPD was ranked as the twelfth most common cause of DALYs but this is set to rise to fifth by the year 2020.^{54 55}

Estimates for the developed world approximate that 400 000 deaths occur yearly in first world countries.⁶⁰ Data from the United States National Health and Nutrition Examination Surveys (NHANES) indicate that the burden of COPD has been increasing in the United States for the last few decades, where it is currently the fourth leading cause of death.⁵⁶ Death rates for men have showed signs of stabilising recently, but death rates for women appear to be increasing.⁵⁷

The lack of data for middle and low income countries is the result of poor routine data systems and a paucity of surveys.^{58 59} A reasonable prediction is that the prevalence of COPD will rise as tobacco use increases and populations age, particularly amongst women and older people.⁵⁹ Although the accuracy of estimates is questioned, evidence from East Asia suggests that the burden of disease is higher

than that estimated in the WHO report.⁵⁹ About 2.7 million deaths from COPD occurred in 2000, an increase of half a million from 1990. Half of the deaths were from the Western Pacific region, the majority of these in China.⁶⁰

In 2002, the estimates for Sub-Saharan Africa regional prevalence of mortality and morbidity were 65,000 deaths and 668,000 DALYs. This was estimated to be 0.3% of the regional total DALYs.⁶⁰ These estimates seem low, and the methods of collection of this ecologic data has been criticised by Halbert et al⁷² (see Section 2.4) as well as by the authors of the Global Burden of Disease Report themselves, emphasising that the quality and coverage of these statistics vary greatly. Table 1 presents the WHO COPD estimates of COPD while Tables 3 - 5 show the results of population-based studies.⁷² It is thought that the former has underestimated the prevalence of disease in Sub-Saharan Africa at 0.34% (see Table 1.). However, one of the reasons for this low estimate is that it samples all ages. Firstly, COPD in children and adults under the age of 40 is very rare and secondly, the population distribution in Sub-Saharan Africa is comprised disproportionately of these very groups. The WHO has used expert opinion for these prevalence estimates, which has been shown to differ in comparison with evidence based studies, most likely in favour of underestimation in this region.⁷²

One of the other major problems with the WHO estimates is that they are based on vital registration systems. In many countries, failure to capture all deaths, record the correct cause of death and specify underlying cause of death, and other coding problems can be substantial and even more so in developing countries.^{47 60}

Additionally, predicting future trends in disease is difficult. The two methods used (risk factor models and extrapolation of past trends) are complex, and based on assumptions e.g. that the dose response relationship with a risk factor will remain constant into the future.⁶⁰ In reality, these relationships are dynamic and vary over time in different populations.

Table 1: COPD prevalence estimates based on Expert opinion (WHO) ^{72*}

Country	Study, year	Diagnostic criteria	Sample, age	Prevalence (%)
China	WHO	Symptomatic COPD	All ages	2.50 (all) 2.66 (M) 2.37 (F)
Established market economies	WHO	Symptomatic COPD	All ages	0.54 (all) 0.69 (M) 0.38 (F)
Formerly socialist economies	WHO	Symptomatic COPD	All ages	0.53 (all) 0.74 (M) 0.35 (F)
India	WHO	Symptomatic COPD	All ages	0.39 (all) 0.44 (M) 0.34 (F)
Latin America & Caribbean	WHO	Symptomatic COPD	All ages	0.32 (all) 0.37 (M) 0.27 (F)
Middle Eastern Crescent	WHO	Symptomatic COPD	All ages	0.28 (all) 0.27 (M) 0.28 (F)
Other Asia and islands	WHO	Symptomatic COPD	All ages	0.23 (all) 0.29 (M) 0.18 (F)
Sub-Saharan Africa	WHO	Symptomatic COPD	All ages	0.34 (all) 0.44 (M) 0.25 (F)
World**	WHO (Murray & Lopez), 1996	Symptomatic COPD	All ages	0.83 (all) 0.93 (M) 0.73 (F)

* Halbert et al, 2003

**Global Burden of Disease Study

It is estimated that approximately 1% of the entire global population, and >10% of persons over 40 years suffer from COPD¹²⁶, but this estimate may be misleading because of the markedly heterogeneous nature of the world's communities, each with a different set of competing risk factors. There appear to be two reasons for the increasing prevalence – firstly, a true increase in cases of COPD and secondly, as a consequence of the successful reduction of premature deaths from infectious and cardiovascular disease in developed countries.^{126 141} The latter increases the potential for other degenerative diseases in the survivor population, and constitutes a shift in the burden of disease. As a consequence of these two factors, COPD is projected to move still higher in the rankings of morbidity and mortality in developed countries. However, in developing countries other factors may influence increases in prevalence such as increased tobacco smoking, poverty and infectious diseases such as tuberculosis. Where deaths from infectious diseases are in decline, and cigarette smoking and environmental air pollution increases, more COPD can be expected.¹⁴¹ On the other hand, reduction in life expectancy resulting from infection with HIV is likely to have the opposite effect.

2.4. Definitions of COPD

Despite many advances having been made in the terminology and staging of COPD, we have yet to derive a meaningful and unifying definition. The various definitions of COPD, including the current GOLD definition do not meet the criteria for a definition completely. Scadding (1963) asserted that a definition should provide a means by which an individual can be said to have a specific disease.⁶¹ A point of departure of the modern definitions is the fact that they are descriptive and contain features shared by other respiratory conditions and that are not exclusive to COPD, and they have many exceptions.

The definition and classification severity of COPD have an impact upon estimates of prevalence and are important in prevalence surveys. These have undergone some change over the last decade, and a variety of versions are currently in use. Each has its own advantages and limitations, and is used for different purposes, be they epidemiological, clinical or pathological. The British Thoracic Society (BTS), the National Institute of Clinical Excellence (NICE), the European Respiratory Society (ERS) and the American Thoracic Society (ATS) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) have all produced classification and staging systems that differ from one another, sometimes markedly.

The most widely used definitions are those from the ATS/ERS in 2004 and GOLD guidelines (2005).^{62 63} For the purposes of this thesis, the GOLD definition and staging criteria have been used, as required by the BOLD protocol (see Chapter 4). The definitions and staging of severity in the South African Thoracic Society COPD guidelines are based upon and are very similar to the GOLD guidelines.

COPD is defined by GOLD as “a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.”⁶³ According to Scadding’s essay on definitions, this can be criticised as not being an exact definition, though the criteria do approach one.

Table 2: Classification of severity and Staging of COPD according to the GOLD guidelines⁶³

Stage	Characteristics
0: At Risk	<ul style="list-style-type: none">• normal Spirometry• chronic symptoms (cough, sputum production)
I: Mild COPD	<ul style="list-style-type: none">• FEV₁/FVC < 70%• FEV₁ ≥80% predicted• with or without chronic symptoms (cough, sputum production)
II: Moderate COPD	<ul style="list-style-type: none">• FEV₁/FVC < 70%• 50% ≤FEV₁ < 80% predicted• with or without chronic symptoms (cough, sputum production)
III: Severe COPD	<ul style="list-style-type: none">• FEV₁/FVC < 70%• 30% ≤FEV₁ < 50% predicted• with or without chronic symptoms (cough, sputum production)
IV: Very Severe COPD	<ul style="list-style-type: none">• FEV₁/FVC < 70%• FEV₁ < 30% predicted or FEV₁ < 50% predicted plus chronic respiratory failure

Classification based on postbronchodilator FEV₁
FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; respiratory failure: arterial partial pressure of oxygen (PaO₂) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO₂ (PaCO₂) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level.

The GOLD classification of severity and staging is shown in Table 2. The cut-points between stages are pragmatic and have not having been clinically validated.⁶³ Its authors also acknowledge that there is an imperfect relationship between symptoms and airflow limitation, and that the severity of symptoms (quality of life limitation) and its complications are the most significant aspects of the disease. Using the GOLD classification system for staging in epidemiological studies is a robust way of diagnosing COPD, particularly because it uses postbronchodilator FEV₁.⁶⁴ The choice of a fixed criterion of FEV₁/FVC instead of using 70% of the age-predicted ratio has been criticised for overdiagnosing GOLD Stage I COPD and for overdiagnosing COPD in the elderly.^{65 71} In addition, GOLD stage 0 was found to be poorly predictive of progression of disease. The Copenhagen Heart Study found that 21% of those with GOLD Stage 0 had progressed to Stage I after 15 years and a further 19% without respiratory symptoms now met criteria for GOLD Stage I.⁶⁶ This emphasised the unreliability of symptoms i.e. the poor correlation between chronic bronchitis and COPD.

A comparison of the prevalence of GOLD Stage II and higher was made using the fixed ratio and the % predicted ratio (from the NHANES study), and this was found to be very similar. A paper by Celli et al⁶⁷ (2003) compared the following five criteria for definition of COPD and reported that estimates differed by more than 200%, depending on the definition used.

- 1) Self-reported chronic bronchitis or emphysema
- 2) $FEV_1 / FVC < 70\%$ and $FEV_1 < 80\%$ predicted (GOLD Stage II)
- 3) FEV_1 / FVC below the lower limit of normal
- 4) $FEV_1 / FVC < 88\%$ predicted in males and $< 89\%$ predicted in females (ERS criteria)
- 5) $FEV_1 / FVC < 70\%$ (fixed ratio)

The fixed ratio gave the highest estimates for older subgroups (>50 years), whereas the GOLD Stage II criteria produced the lowest estimates of all definitions that included spirometry. A case was made for considering the GOLD staging as superior to other definitions on the basis of simplicity and accuracy.⁶⁷ However, Hardie et al criticised this level of accuracy by providing results of 71 asymptomatic older non-smoking persons. Fifty percent of those over 80 years and 35% of those over 70 years had a prebronchodilator ratio of $< 70\%$, and a third of those over 80 years met the criteria for GOLD Stage II despite having had no smoking history or reported symptoms.⁶⁸ However, the GOLD classification can only be applied to postbronchodilator measurements⁶⁹, and therefore conclusions based on prebronchodilator measurements may be inaccurate. Bronchodilators may not make a significant difference to GOLD Stage I COPD as both FEV_1 and FVC are equally affected. GOLD uses a rather arbitrarily defined dose of 400 micrograms of salbutamol for bronchodilation, but one might equally argue that two weeks of a trial of steroids would be even more convincing at excluding asthma. This is often done in a clinical setting to classify cases, but in population studies it is not an option (for pragmatic and ethical reasons) and bronchodilators provide some practical attempt at addressing reversibility. Using a postbronchodilator ratio will reduce, but not eliminate, misclassification of asthma as COPD. For the purposes of epidemiological studies, this is an advantage. However, tests such as methacholine or histamine challenge are better indicators of AHR.

Self-reporting of both symptoms and doctor diagnoses have the problem of being non-specific and may result in overestimation of disease, and doctor-diagnosed disease may lack sensitivity as mild disease is frequently undiagnosed.¹¹³ Language also plays a significant role in the interpretation of questions that predict COPD. One language may use different words to describe breathlessness or wheeze and yet another may describe both symptoms using one word. In addition, questionnaires may not predict the persistence or severity of symptoms.⁷⁰

GOLD uses FEV₁ to classify severity and this measure is known to correlate poorly with quality of life, symptoms, exacerbation frequency and exercise tolerance.⁷¹ In addition, these FEV₁ cut-points were based on expert opinion and not evidence, for want of a better solution, and provide an attempt at classifying COPD without taking into account other components such as gas exchange derangements, hyperinflation, systemic effects⁷¹, which can only be gathered by clinical examination and investigations. Thus the GOLD classification, for the purpose of population surveys is easy to apply, but its limitations should be noted.

2.5. Prevalence of Obstructive Lung Disease from Population studies

Many population studies of COPD prevalence have been performed with the majority in Europe and North America. In 2003, Halbert et al have published a comprehensive review of population-based studies.⁷² A modified and updated version of information in tables from this review is presented in Tables 3 to 5. These list studies of chronic bronchitis and COPD worldwide according to survey methods used - spirometry-based, symptom-based (questionnaire-based) and patient-reported (either physician-diagnosed or self-reported). Recent studies published since 2003 are shown in italics.

Table 3: COPD prevalence estimates from spirometry-based studies⁷²

Country	Study, year	Participants	Diagnostic criteria	Sample, age(yrs)	Prevalence (%)
Brazil	Menezes ¹²⁰ , 2004	234	FEV ₁ /FVC<70%,	Random, Pelotas ≥40	15.2(all)
Denmark	Lange et al ⁷³ , 1989*	12698	FEV ₁ /FVC<70%, FEV ₁ <60% predicted	Random, Copenhagen, 20-90	3.7 (all)
England	Dickinson et al ⁷⁴ , 1999	353	FEV ₁ < fifth centile plus reversibility test	General practice group, 60–75	9.9 (all)
Finland	Isoaho et al ⁷⁵ , 1994	1196	Clinical examination plus spirometry	Random, Lieto, ≥65	12.5 (M) 3.0 (F)
	von Hertzen et al ⁷⁶ , 2000	7217	Clinical examination plus spirometry	Random, Finland ≥30	22.1 (M) 7.2 (F)
Greece	Tzanakis et al ¹⁰⁴ , 2004	888	FEV ₁ /FVC<70%,	Multiregional random,>35 current/ex smokers	11 (M)
					8.4 (all) 11.6 (M) 4.8 (F)
Italy	Viegi et al ²³² , 2000***	1828	ERS spirometric criteria	Random rural, low-pollution area ≥25	11.0 (all) 12.5 (M) 11.8 (F)
					10.9 (all) 16.4 (M) 5 (F)
Japan	Fukuchi et al ⁷⁹ , 2004 †	2343	FEV ₁ /FVC < 70%,	random ≥40	7.8 – 19.7 (all)
Latin America	Menezes et al ⁷⁷ , 2005‡	5315	FEV ₁ /FVC < 70%,	Stratified sample households, ≥40	4.1 (all)
Norway	Gulsvik ⁷⁸ , 1979	1209	Clinical examination plus spirometry	Random, Oslo 16–69	3.7 (M) 4.6 (F)
					1275
Spain	Marco Jordán et al ⁸⁰ , 1998	600	FEV ₁ /FVC < 70%, FEV ₁ < 80% predicted	Random, Guizpúzcoa, 40–60	4.5 (all) 4.8 (M) 4.2 (F)
					4035
United States	Mueller et al ¹⁰⁸ , 1971	609	FEV ₁ /FVC < 60%	Random, Glenwood Springs, 20–69	9.1 (all) 14.3 (M) 3.9 (F)
					16084

*Copenhagen City Heart Study

**Po Delta Valley

***IBERPOC

**** National Health and Nutrition Examination Survey III (NHANES III)

† NICE study

‡ PLATINO study

Table 4: COPD prevalence estimates from symptom-based studies (chronic bronchitis)

72

Country	Study, year	Participants	Diagnostic criteria	Sample, age	Prevalence (%)
Australia	Cullen et al ⁸¹ , 1968	3331	MRC criteria	Busselton ≥21	9 (M) 3 (F)
Brazil	Menezes ¹²⁰ , 2004	1046	MRC criteria	Pelotas ≥40	7.8 (all)
Brazil	Menezes et al ⁸² , 1994	1053	MRC criteria	Pelotas ≥40	12.7 (all) 17.9 (M) 9.1 (F)
Denmark	Lange et al ⁷³ , 1989*	12698	Daily phlegm ≥3 mo for ≥1 yr	Random, Copenhagen 20-90	10.1 (all) 12.5 (M) 8.2 (F)
England	Littlejohns et al ^{83 84} , 1989	1444	MRC criteria	General practice group, 40-74	16.7 (M) 7.1 (F)
Iceland	Magnússon, Gíslason ⁸⁵ , 1999	1175	ATS criteria	Icelandic males born in 1913 and 1943 (50, 80)	7.1, 16.7 (M)
India	Qureshi ⁸⁶ , 1994	560	MRC criteria	Residents of two Kashmir villages ≥15	7.7 (all) 7.6 (M) 7.8 (F)
India	Jindal et al ¹³⁹ , 2006	35295	MRC criteria	Random, Urban rural, 4 centres	4.1 (all)
Nepal	Pandey ²⁰⁸ , 1984	2826	MRC criteria	Residents of two rural communities ≥20	18.3 (all) 17.6 (M) 18.9 (F)
Former Rhodesia	Cookson, Mataka ¹²¹ , 1978	9287	MRC criteria	Gatooma ≥15	1.12 (all) 1.2 (M) 2.8 (F)
South Africa	Ehrlich et al ⁸⁷ , 2004	13826	MRC criteria	Nationally representative	2.3 (M) 2.8 (F)
Spain	Marco Jordán et al ⁸⁰ , 1998	600	ECSC***** criteria	Random, Guizpúzcoa 40-60	9.2 (M)
Sweden	Irnell and Kiviloog ⁸⁸ , 1968	41679	Cough ≥3 mo for ≥1 yr	Uppsala and environs 30-64	2.1 (all) 2.7 (M) 1.5 (F)
United States	Mueller et al ¹⁰⁸ , 1971	609	MRC criteria	Glenwood Springs, 20-69	17 (M) 10 (F)
	Higgins et al ⁸⁹ , 1977**	4699	Cough and phlegm ≥3 mo	Tecumseh, MI 20-74	17 (M) 6 (F)
Multiple	Menotti et al ⁹⁰ , 1997***	8122	Three criteria based on history and symptoms	15 cohorts of men, 7 countries 50-69	1.2-12.9 (M)
Europe, 16 countries (ECRHS)	Cerveri et al ⁹¹ , 2001****	17966	MRC criteria	35 selected centres 20-44	3.2 (all) 3.7 (M) 2.8 (F)

*Copenhagen City Heart Study

** Tecumseh

***Seven Countries Study

****ECRHS = European Community Respiratory Health Survey

*****ECSC = European Community for Coal and Steel

Table 5: COPD prevalence estimates from studies of patient-reported diagnosis⁷²

Country	Study, year	Participants	Diagnostic criteria	Sample, age	Prevalence (%)
Canada	Chen et al ²³⁰ , 2000*	7210	Physician diagnosed	Representative	1.8 (M)
				Canadians, 35–44	3.5 (F)
				Representative	1.5 (M)
				Canadians, 45–54	3.6 (F)
	Lacasse et al ⁹² , 1999*	17626	Physician diagnosed	Representative	5.0 (M)
				Canadians, 55–64	4.5 (F)
				Canadians	5.7 (all)
England	Littlejohns et al ^{83, 84} , 1989	1444	Patient report (chronic bronchitis)	Single general practice group	3.9 (M) 2.1 (F)
Estonia	Meren et al ⁹³ , 2001**	17525	Physician diagnosed (chronic bronchitis)	Random, 3 urban areas	10.7 (all) 9.3 (M) 11.5 (F)
Finland	Pallasaho et al ⁹⁴ , 1999***	6062	Physician diagnosed	Random, Helsinki, 20–69	3.7 (all)
Hong Kong	Lai et al ⁹⁵ , 1995	2032	Patient report of disease	Random, Hong Kong	8.0 (all) 10.7 (M) 5.5 (F)
South Africa	Ehrlich et al ⁸⁷ , 2004	13826	Physician diagnosed (chronic bronchitis /emphysema)	Nationally representative	4.2 (M) 4.8(F)
Sweden	Lundbäck et al ⁹⁶ , 1991	5698	Physician diagnosed	Non-random	4.1 (all)
				Norrbottnen	4.7 (M)
United States	Lebowitz et al ⁹⁶ , 1975****	3805	Patient report (chronic bronchitis)	Random, Malmöhus, 20–59	4.0 (F)
				Random, Anglo-white households in Tucson, AZ	3.7 (all)
				All ages	6.6 (all)
	Adams et al ⁹⁶ , 1999*****	63402	Patient report (chronic bronchitis)	Population-based, non-institutionalized	5.4 (all)

*National Population Health Survey

** FinEsS-Estonia

*** FinEsS-Helsinki

****Tucson

***** National Health Interview Survey

Prevalence studies in Europe

From a European perspective, two large population-based studies stand out from the rest. The first, the European Community Respiratory Health Survey (ECRHS) illustrates the wide variance in population prevalence of chronic bronchitis across countries.⁹¹ Performed in 35 centres across 16 countries, 18000 individuals aged 20–44 years were surveyed. The median prevalence of chronic bronchitis was 3.2%, but ranged from 0.7 to 9.7% (see Table 4). A second major observation was that the presence of symptoms of chronic bronchitis was found to be unrelated to airflow obstruction ($FEV_1 / FVC < 70\%$ and decreased FEV_1), challenging the concept that

chronic bronchitis is a marker for COPD.¹⁰⁰ Diagnosed asthma, followed by symptoms of wheeze and shortness of breath were found to be better predictors of airflow obstruction in the ECRHS study, suggesting rather that a variety of lung diseases associated with wheezing may be associated with decreased pulmonary function.¹⁰⁰ However, in terms of its relevance to COPD, it must be noted that this was a relatively young cohort.

The second major study was the IBERPOC Project (Estudio Epidemiológico de la EPOC en España), a Spanish epidemiologic study of 4035 persons aged 40 to 69 years which reported a prevalence of COPD of 14.3% in men and 3.9% in women.¹⁰¹ Half of the cases occurred in persons aged 60- 69 years and a quarter in each of age groups 40 – 49 and 50 – 59 years. There was a considerable degree of intra-country variability between the different sites. One of the limitations of this study was the upper age cut-off, which makes comparisons with other studies problematic as most do not set an upper age limit. The reported prevalence of symptoms is usually high in persons over the age of 70, but diagnostic confusion occurs because of cardiac and other co-morbidity. The IBERPOC study reported the prevalence of wheeze as 40%, cough as 13.8%, sputum production in 10.7% and exertional dyspnoea in 10.4%, with 48% of the population over 40 years reporting any respiratory symptom.

Similarly another European study also reported high symptom prevalences in mild to moderate COPD cases.¹⁰² The EUROSCOP study, though not a population prevalence study, highlighted a considerable degree of underdiagnosis across many European countries.¹⁰³

In 2004, Tzanakis et al reported a prevalence of 8.4% in persons aged >35 years in Greece.¹⁰⁴ This study was restricted to smokers over >100 lifetime cigarettes who had no other current/past other pulmonary disease or comorbid conditions that prevented either spirometry from being performed or the use of a bronchodilator, and accordingly cannot be viewed as a prevalence estimate. Only smokers were sampled, on the assumption that COPD is rare in never-smoking Greek adults, just as it is in other European countries.¹⁰¹ However, recent data from the BOLD study in Austria suggest that COPD in never smoking European adults may not be as rare as previously supposed, having identified agricultural exposure as a risk factor.¹⁰⁵

Prevalence studies in the United States

As in Europe, the prevalence of symptoms of COPD varies widely in different states and between men and women. Three early studies^{106 107 108} summarised below, used different definitions for COPD, and in these studies, attempts were made to separate persons with COPD from those with asthma.

A 1962 study of Berlin, New Hampshire by Ferris et al used the term chronic non-specific respiratory diseases and reported prevalence of 15.4 to 39.1% in men and 15.2 to 20.9% in women.^{109 106} A second outcome, irreversible obstructive disease (FEV₁ <60%) was present in 3.1 to 21.7% in men and 6.2 to 13.9% in women.¹⁰⁶ Among men, occupational exposures were considered to have been an important risk factor in this study setting.¹⁰⁹

In 1967, a study in Glenwood Springs, Colorado that employed a definition that included FEV₁/FVC ratio of <60% with respiratory symptoms of cough, sputum expectoration, wheeze or dyspnoea as indicating the presence of COPD, and reported a prevalence of COPD of 13% and of chronic bronchitis of 17% in men, and 4% and 10% respectively in women.¹¹⁰ A follow-up study seven years later by Petty et al found that those with spirometric abnormalities had showed worsening of these abnormalities, whereas those with symptoms alone had not developed spirometric abnormalities in the intervening years.¹¹¹ This result is consistent with results from the paper by Peto et al that related airflow limitation but not mucous hypersecretion to mortality from chronic lung disease.¹¹² These were also some of the first findings to provide evidence for the hypothesis that chronic bronchitis alone without airflow limitation is not related to the development of COPD. Of note, there were no identifiable sources of industrial or ambient air pollution in the study area.

In 1984, a third study from Tecumseh, Michigan was published which reported a prevalence of chronic bronchitis and/or obstructive airways disease of 14% in men and 8% in women, using a definition of FEV₁/FVC ratio of <80% and FEV₁ <65% predicted.¹¹³ There were also no other identifiable risk factors in Tecumseh at the time, apart from tobacco smoking.

Subsequently, two large cohort studies have tracked COPD prevalence in the United States – the National Health and Nutrition Examination Survey (NHANES III) and the Lung Health Study.^{51 114} The NHANES III study reported prevalences ranging from 7.3% in the 45-54 year age group to 22.9% in the 75 year age group with an overall

prevalence of 13.9% in adults, most with mild to moderate disease. The prevalence of mild or moderate COPD in the <55 year age group was lower, which may be attributed to the decline in smoking rates in the US. Reversibility testing or tests of AHR were not performed in this study. However, the overall prevalence of COPD appeared to be increasing.

Stang et al (2000) have used smoking rates in a model to estimate COPD prevalence in countries where population-based spirometric studies have not been performed, and have suggested that the proportion of cases of COPD diagnosed in the U.S. is between 14 and 46% of the actual number of COPD cases in the population, suggesting that even in developed economies, underdiagnosis is common.¹¹⁵ This proportion is assumed to be even lower in developing countries, where under recognition and misdiagnosis is a considerable problem.

Another first world example: Japan

The prevalence of COPD also varies amongst first world countries. Early reports from Japan suggested a very low population prevalence rate of 0.17%¹¹⁶ and in 1999 national prevalence was reported as 0.3%.¹¹⁷ These figures gave rise to postulations that the low prevalence was due to a long delay in the uptake of tobacco smoking after World War 2, for socioeconomic and cultural reasons. The increase in smoking accompanied economic growth from 1955 to 1973.^{116 118} The findings of the Nippon COPD Epidemiology (NICE) study in which the prevalence of COPD was found to be 10.9% in persons over the age of 40 using the GOLD criteria.¹¹⁹ This casts doubt upon the earlier figures, suggesting that there could have been methodological issues in the earlier studies, and has gone some way to countering the suggestion that the Japanese are genetically or constitutionally resistant to the effects of smoking.¹¹⁶

Studies from developing countries

There are few studies from developing countries. In contrast to developed countries, developing country smoking rates remain high and in some cases are even rising, particularly amongst women. This suggests that prevalence in these countries will increase. The effect of cigarette smoking in these countries is compounded by exposures to smoke from biomass fuels and outdoor air pollution.

Non-standardised study methods and definitions of COPD make comparisons of prevalence difficult and inaccurate. The recent PLATINO Study (Proyecto

Latinoamericano de Investigacion en Obstruccion Pulmonar) was unique in that it is the only published population-based cross sectional study of COPD examining five major Latin American cities (see Table 3).⁷⁷ PLATINO, being a precursor to the BOLD study, used standardised methods and quality control measures to ensure comparability across sites. Prevalence of COPD, defined as a postbronchodilator FEV₁/FVC ratio of <70%, ranged from 7.8% in Mexico City to 19.7% in Montevideo.⁷⁷ Only one other prevalence estimate from Pelotas, Brazil reported a prevalence of 15.8% in 2004.¹²⁰

Prior to the work reported in this thesis, the only population-based study from Africa was performed in Zimbabwe (former Rhodesia). In this study, the symptom-based prevalence of chronic bronchitis was 1.12%, using the MRC definition.¹²¹ Chaulet (1989) reviewed prevalence surveys of chronic bronchitis in occupational groups and hospital inpatient groups from some African countries, and estimated that “10 to 20% of the adult population had symptoms of chronic bronchitis”.¹²²

2.6. Risk Factors for Adult Obstructive Lung Disease

2.6.1. Introduction

Tobacco smoking and age are the two risk factors for COPD for which most evidence exists.^{123 124 101 125} However, evidence that has emerged over the last two decades has shifted the focus of COPD research toward examining other factors that may play a role. There is epidemiological evidence that a significant proportion of COPD worldwide is attributable to risk factors other than tobacco.¹²⁶

Both host and environmental exposures play a role in the aetiology of COPD. The NHLBI/WHO/GOLD definition of COPD makes reference to exposure to “noxious particles or gases”.⁶³ Non-smoking exposures are increasingly well recognised, especially host factors such as airway hyperresponsiveness (AHR), occupational exposures, outdoor and indoor air pollution, infections and low socioeconomic status. Genetic predisposition is also likely to play a role, but research to date is still in progress¹²⁷ Table 6 summarises the current state of knowledge of risk factors for COPD, initially tabulated by Siafakas et al¹²³ and subsequently by Viegi¹³⁸, which has been modified here to include cannabis and pulmonary tuberculosis.

Table 6: Known risk factors for COPD^{123 138}

Degree of certainty	Environmental factors	Host factors
Established/certain	Tobacco smoking	α_1 -antitrypsin deficiency
	Certain occupational exposures	
Good evidence	Outdoor air Pollution	Low birth weight
	Indoor air pollution (Biomass fuel)	Childhood respiratory infection
	Low socioeconomic status	
	ETS in childhood	Bronchial/ Airway
	Other occupational exposures	Hyperresponsiveness
	Alcohol intake	
Some evidence	<i>Cannabis smoking</i>	Family history
	<i>Pulmonary Tuberculosis</i>	Atopy (high IgE*)
Putative	Adenovirus infection	Genetic predisposition
	Dietary deficiency of vitamin C	Blood group A
	Poor glycaemic control	IgA** nonsecretor

*Immunoglobulin E ; **Immunoglobulin A

2.6.2. Brief reviews of individual risk factors

2.6.2.1. Tobacco smoking

Early studies

Tobacco smoking is the most well known risk factor for COPD, particularly in developed countries. After Fletcher's sentinel work described above¹⁴, evidence for smoking as a risk factor for COPD has been described in many studies.^{128 101 113 129}

¹³⁰ Most have been cross sectional in design, but a few provide longitudinal data.

One of the most important studies is that of Peto describing the consequences of tobacco smoking in a 40 year follow-up of British doctors.¹³¹ Smokers were found to have a seven fold higher mortality from COPD than non-smokers. A clear 'dose response' relationship was described with increasing number of cigarettes smoked per day and increasing mortality, with heavy smokers of >25 cigarettes per day having a 21 fold increased risk. Earlier results from this study (and other studies) had underestimated the risk associated with tobacco smoking, presumably owing to the short duration of follow-up. To quote Doll et al - referring to mortality from all tobacco-related disease:

"It now seems that about half of all regular cigarette smokers will eventually be killed by their habit".¹³¹

A further analysis of this study showed that tobacco smoking increased the risk of dying from COPD almost 13 fold.¹³²

Italian studies with diffusing capacity

Studies from the Po Delta and Northern and central Italy showed a higher prevalence of chronic cough and sputum in men and women who smoked, compared to their non-smoking counterparts.^{133 134} A notable difference in one of these studies was the use of diffusing capacity in a population-based survey. Those who smoked 10 cigarettes per day were almost twice as likely to have an abnormal diffusing capacity and a decrease in diffusing capacity was noted with cumulative cigarette use even in healthy smokers.^{134 135} Another population study to use this measurement was a recent Australian work by Matheson et al (2005) examining occupational exposures.¹⁶¹ (See section 2.7.2.2.)

Tobacco in developing countries: China and India.

The focus of tobacco use has shifted to developing countries, where it competes with other risk factors such as biomass fuel exposure and infectious diseases like tuberculosis. Tobacco companies have rapidly expanded their business in low and middle income developing countries which have among the highest rates of smoking in the world. Knowledge and understanding of the effects of tobacco smoking amongst laypersons in developing countries has been patchy and slow to develop. This is due to the power of political and economic entanglements that tobacco companies have with some governments and the strength of their advertising campaigns and sponsorship of sporting events and popular culture.

There are three recent large population-based prevalence surveys from developing countries. In the first, a prospective cohort study from China, a country with one of the highest smoking prevalences in the world, a strong relationship between all cause mortality and tobacco smoking was demonstrated, particularly among men (56 - 61%).^{136 137} Another longitudinal cohort study from Shanghai reported a 2.5 fold increased risk of death in male smokers after adjustment, and this study confirmed the strong positive dose response.^{137 138}

Finally, a recent Indian study reported ever-smoking rates of 28.5 % in men and 2.1% in women, most smoking bidi.¹³⁹ This highlights the socio-cultural differences between countries (developing vs. developed) that result in low smoking rates among women, a trend that is rapidly changing as more women take up the habit. Increasing

age, low socioeconomic status and rural residence were associated with higher smoking rates.¹³⁹ Compared to a developed country like Sweden, where smoking rates in men and women are almost equal¹⁴⁰, this gender disparity is striking. The population attributable fraction (PAF) for smoking-related COPD is a moving target owing to rising smoking rates and heterogeneous exposure patterns in South Africa and in many developing countries.

Establishing the Proportion of smokers who will develop COPD.

A widely quoted figure for the proportion of regular smokers that develop COPD is 15%.^{141 142} However the basis for this estimate is uncertain and has been questioned.¹⁴³ It can be argued that providing a single number is misleading, as prevalence is determined by definition of COPD, age-group, smoking history (pack years) and a number of other factors described in this chapter. The proportion that develop symptomatic disease (Stage II and higher) is probably the most important estimate to establish, although in view of the fact that early smoking cessation is the most effective intervention, the diagnosis of even Stage I disease is important. There are few studies that provide this information on the risk of developing COPD. Longitudinal studies are necessary for this purpose. In one study of longitudinal design, accelerated decline in lung function of two to five times that of the normal rate of 15 – 30ml/year has been reported in 15% of whites and 5% of Asians who smoke.¹⁴¹

In the cross sectional NHANES III study of persons aged 18 and older, 12.5% of current smokers, 9.4% of ex smokers, 3.1% of cigar smokers and 5.8% of never smokers were found to have COPD. Lundback et al (2003) challenged these estimates and suggested that “not 15 but 50% of smokers” will develop COPD.¹⁴⁴ Reporting results from the OLIN (Obstructive Lung Disease in Northern Sweden) cohort study, the prevalence of COPD according to the GOLD criteria was fifty percent in smokers aged 76-77 years, illustrating the point that prevalence in a cohort of smokers is highly dependent on age, and that if they lived long enough and had smoked sufficiently, a majority would develop symptomatic COPD. However, an important confounding factor in Lundbäck’s calculations is the unreliability of the GOLD diagnostic criteria in the elderly, and the FEV₁/FVC ratio of <70% that defines the presence of airflow obstruction. This is considered again in Chapter Eight.

Environmental tobacco smoke (ETS)

A paper by Svanes et al from the ECRHS assessed parental smoking in childhood and the risk of subsequent adult lung disease.¹⁴⁵ Despite the comparatively young age of the cohort of 20-44 years, there was a statistically significant association with both doctor-diagnosed chronic bronchitis (OR 1.3; CI: 1.1 – 1.6). A reduced FEV₁/FVC ratio was demonstrated if both parents smoked, and an association of borderline significance if one parent smoked. Another paper from the same study by Radon et al, examined workplace and home passive smoke exposure in German adults, reporting an adjusted risk of 1.9 for chronic bronchitis, which increased to a 3 fold risk with daily exposure on >8 hours a day. Likewise the risk of both asthma and wheezing doubled with increased exposure.¹⁴⁶ A third paper by Janssen et al found ETS (particularly in the workplace) to be associated with an increased risk of all respiratory symptoms (OR=1.3) and increased bronchial hyperresponsiveness.¹⁴⁷

A large sample size is necessary to show associations with ETS. A recent Indian study by Jindal et al, of over 35000 participants aged ≥35 years reported an odds ratio of 1.4 for chronic bronchitis among non-smokers with ETS exposure. In addition, a combination of ETS and exposure to solid fuel combustion revealed a stronger association.¹⁴⁸

Evidence from a meta-analysis by Strachan and Cook (1998) has confirmed that the maternal smoking is associated with a higher prevalence of reported wheeze in children.¹⁴⁹ Young children tend to spend more time with their mother and this is thought to be an important risk factor. Whether childhood ETS exposure is a risk factor for COPD later in life is not known. This is of particular relevance in the thesis study area (Ravensmead and Uitsig) as historically there is a high prevalence of women smokers in these areas.

2.6.2.2. Occupational Exposures

One in five cases of COPD (20%) is attributable to occupational exposures.¹⁵⁰ Many different occupational exposures have been implicated in the aetiology of both chronic bronchitis and COPD, such as mineral dusts, metals, smoke from biomass sources, organic dusts etc.

Overall, the effects of occupational exposures are thought to be less strong than that of smoking. However, recent evidence has shown that this may not be true of all occupational exposures and that similar patterns of decline in lung function to that of

Fletcher's associations with smoking may be possible, with a subgroup of persons having a large decline.¹⁵¹ Many studies have been performed in miners and pneumoconioses have been recognised as causing not only interstitial disease, but to have a major obstructive component.

Early studies

Early publications related specific industry exposures to respiratory symptoms and some to measures of lung function. The fact that only small effects were found by these studies could be attributed to the healthy worker bias, which should not be underestimated. Becklake published a review in 1985 suggesting that there was a causal association between occupational dust exposure and loss of lung function evidenced by longitudinal studies of industrial populations.¹⁵² A particularly important longitudinal study in support of this conclusion was by Kauffmann et al who showed an accelerated rate of decline in FEV₁ in dust exposed Parisian factory workers.¹⁵³ This study also found that exposure to dust, heat or certain gases alone or in combination caused an accelerated decline in FEV₁ in a dose related way. Greater effects were found in those with low occupational status (considered an indicator of low socioeconomic status) which was a risk factor independent of occupational exposure.¹⁵³

The Cracow study was a longitudinal thirteen year follow-up that showed a significantly increased rate of decline in FEV₁ with exposure to occupational dusts in men and with occupational exposure to variable temperatures in women.¹⁵⁴ Similarly, the Zutphen study followed up 878 men for 25 years and found an increased incidence density ratio of chronic respiratory symptoms or diagnoses in blue collar workers. Using a job exposure matrix, heavy metals, mineral dust and adhesives were associated with increased incidence of chronic non-specific lung disease.¹⁵⁵

Another population-based study of occupational exposures and respiratory symptoms by Korn et al (1987) showed a positive association of occupational dust or gas/fume exposure with chronic cough, chronic phlegm, persistent wheeze and breathlessness with odds ratios ranging from 1.3 to 1.6.¹⁵⁶ Occupational dust was also associated with a 1.5 times increased risk of COPD, defined as an FEV₁/FVC ratio of less than 0.6. This was a large population-based survey (8515 persons), as opposed to an industrial population, and it used a definition of COPD that would exclude those with mild disease, thus the findings are very relevant for their context.

ATS review

In 2003, The American Thoracic Society published a comprehensive review of studies of occupational exposures and COPD calculating a population attributable risk of 14 – 19%.¹⁵⁷ The main epidemiologic findings from this review were:

1. Most studies showed an annual decline in FEV₁ of 7-8 ml per year, after adjusting for smoking and age.
2. The effects of dust alone may be greater than that of tobacco smoking alone, in those workers who are heavily exposed.
3. In coal and hard rock miners, a relationship between dust exposure and the degree of emphysema was found, independent of tobacco smoking.

ECRHS- population sample

The European Community Respiratory Health Survey (ECRHS) group reported that occupational exposure to vapours, dust, gases or fumes was associated with chronic bronchitis among current smokers only (prevalence ratio of 1.2 - 1.7). Agricultural work, textile, paper, wood, chemical and food processing were associated with chronic bronchitis¹⁵⁸, but there was no clear association of self-reported occupational exposure with lung function¹⁵⁸, in contrast to other studies. The lack of association with lung function, most probably due to a healthy worker bias, is likely to be very important in this young population. A strength of this study is that it combined results from 14 European industrialised countries and thus had a large sample size of 13243 with some level of heterogeneity. Additionally it studied asthmatics and non asthmatics, smokers, ex and non smokers separately, which could be viewed as either a strength or a weakness of the study analysis. This was done on the basis of controlling for 'residual confounding' from smoking in unstratified analyses.

NHANES population sample

Two papers by Hnizdo et al^{159 160} (2004, 2002) from the United States NHANES III, involving a cohort of approximately 9500 persons aged 30-75 years, examined the risk of COPD associated with employment. The first paper reported that the estimated population attributable fraction (PAF) for COPD attributable to occupational exposures was 19.2% overall and 31.1% among never smokers; and implicated various jobs in armed forces, rubber, plastics and leather manufacturing, utilities, textile mill manufacturing, repair services and gas stations, transportation and trucking, healthcare, food, sales, construction and agriculture.¹⁵⁹

The second paper analysed the difference in the fraction of airflow obstruction cases associated with work, for three ethnic groups. The PAF was 22.2% for Caucasians, 23.4% for African Americans and 49% for Mexican Americans.¹⁶⁰ Mexican Americans are overrepresented in construction and agriculture which are two broad occupations that are associated with heavy dust exposure - different job predilections accounting for the difference in ethnic group prevalence.¹⁵¹ Other confounders such as socioeconomic differences, smoking and age were adjusted for in the analyses. It should be noted that these two papers used different definitions for COPD - the former classified COPD as FEV₁/FVC <70% and FEV₁ <80%, while the latter paper used a FEV₁/FVC ratio of <75% and FEV₁ of <80%. Using different definitions of COPD make comparisons between these two studies and with other COPD studies slightly inaccurate. However, the public health message is the demonstration of consistently high PAFs for work-associated COPD.

Australian population sample

A well-designed population based study among 1232 adults aged 25-70 years in Melbourne, Australia used a job exposure matrix (rather than a question on exposure), and detailed information on exposures was collected on work-history calendars. Symptoms and lung function were analysed and diffusing capacity was used to define COPD. For biological dusts, there was a 3 fold increased risk for chronic bronchitis and emphysema and 2.7 for COPD; the risks being higher in women than men.¹⁶¹ One major drawback of this study was the poor response rate of 42%, which may limit the generalisation of its conclusions.

Spanish community with duration of exposure

A Catalonian study of predominantly textile industry exposures showed a relationship with symptoms of chronic cough, sputum and wheeze.¹⁶² Those exposed to more than 15 years of dusts, gases or fumes had lower lung function than non exposed persons (decrease in FEV₁ of 80ml; decrease in FEV₁/FVC ratio of 1.7%). The measurement of duration of exposure was an important feature of this study distinguishing it from previous studies that reported only whether participants were ever exposed or not.

Developing country example: China – and interaction with tobacco smoking

A recent study from Southern China confirms the risk for COPD in coke oven workers.¹⁶³ A dose-dependent relationship was found between lung function and coke oven emissions. Benzene soluble fraction was used as a surrogate marker for

emissions. The odds ratio for COPD was 5.8 (95% CI: 3.13 – 10.76) for high cumulative exposure. The corresponding odds ratio for chronic cough and phlegm in this high exposure group was 3.1 (CI: 1.91 – 5.03). Even in the non smokers, a dose-response with odds ratios ranging from 3 to 6 was found. The highest exposure groups for both cigarette smoking and emissions had a 58 times increased risk of COPD compared to non exposed non-smokers. There is thus a significant interaction between smoking and coke oven emission exposure. This study is in keeping with another study on soft coal/anthracite exposure in the home, which was also associated with a high risk of COPD (OR 4.4).¹⁶³ Apart from the expected exposure-response gradient, an important finding was that cigarette smoking was shown to significantly interact with coke oven emission exposure.

Gene-environment interactions of occupational exposures and alpha 1 antitrypsin deficiency have also been described by Mayer et al (2000).¹⁶⁴ The major risk factor for COPD apart from the gene is tobacco smoking and this study identified occupational exposures as a significant independent risk factor in individuals with the deficiency.

Many of the studies on the relationship between occupational exposure and obstructive lung disease rely on self-reporting of ever being exposed to “vapours dusts, gases or fumes”. As this is a crude measurement of occupational exposure, one would expect that studies would be biased to the null, particularly when studying a heterogeneous, complex disease like COPD.

Occupational asthma, as it is a separate entity, is discussed briefly in Chapter 3.

2.6.2.3. Cannabis

Cannabis is classified as an illegal drug in most countries. In developed countries such as the UK, a recent media focus has made cannabis the focus of a political and public debate surrounding its reclassification. The adverse effects of cannabis smoking are numerous and probably underestimated – such as cardiovascular vasospastic effects, potential carcinogenic effects and the well-known neurologic effects¹⁶⁵ but comment here will be limited to the association with obstructive lung disease only.

An early study of the effects of cannabis on the lung performed on post mortem specimens of the lungs of cannabis smokers' revealed evidence of histopathologic changes. Morris (1985) found dose-related light to heavy alveolar infiltrations of

pigmented monocytes, and monocytic and lymphocytic interstitial infiltrations, pointing to an association with respiratory disease.¹⁶⁶

In 2002, the British Lung Foundation published a review of the impact of cannabis smoking on respiratory health, and cited that 3-4 cannabis cigarettes a day were associated with the same evidence of acute and chronic bronchitis and the same degree of damage to the bronchial mucosa as 20 or more cigarettes per day.¹⁶⁷ Another finding was that longitudinal studies carried out in the 1960's and '70's may not be indicative of the effects of cannabis smoked currently, because a modern "joint" may contain as much as 300mg of tetrahydrocannabinol (THC) compared to 10mg in the 1960's.^{168 169}

As with any material that is smoked, chronic cannabis smoking produces bronchitis.¹⁷⁰ There is evidence from many studies that smoking cannabis is associated with an increased prevalence of respiratory symptoms such as chronic cough and sputum production, wheeze, acute bronchitis and chronic bronchitis.

Population studies

To date, only four published studies have assessed the respiratory effects of cannabis at a population level – the Los Angeles, Tucson, Dunedin and NHANES cohorts.^{171 172 173 174}

In 1991, Sherrill et al analysed data on "non-tobacco cigarettes" from four consecutive surveys of the Tucson longitudinal study in Arizona, which spanned a six year period with 1802 participants aged 15 – 60 years.¹⁷¹ They found significant associations with wheeze (OR = 2.0), chronic cough (OR = 1.7) and chronic sputum (OR = 1.5), after adjusting for tobacco smoking. The participants showed no immediate decrease in symptoms after stopping smoking. Additionally, a reduction in FEV₁, Vmax50 and FEV₁ /FVC occurred a year or more after reporting non- tobacco smoking. Despite a low level of average consumption of less than one non- tobacco cigarette per day, it is notable that both respiratory symptoms and pulmonary function were affected. This cohort had been studied in 1987 by Bloom et al, and the important finding then was that non tobacco smoking alone had a larger effect on respiratory function than tobacco smoking alone in adults aged less than 40 years of age.¹⁷⁵ The study showed a small significant decrement in FEV₁ that was twice that associated with tobacco smoking.¹⁷¹

Taylor et al (2000) studied 943 young adults in Dunedin New Zealand (aged 21 years) and found that cannabis smokers reported more wheezing, exertional dyspnoea, night waking, chest tightness and early morning sputum production when compared to non smokers, after controlling for tobacco use.¹⁷³ The prevalence of these symptoms was found to be similar to persons smoking 1 – 10 tobacco cigarettes per day. Despite this being a young cohort, the proportion of cannabis smokers with an FEV₁/FVC ratio of <80% was significantly greater than that of non smokers (36% vs. 20%, p=0.04). Arguably, the effects of cannabis on respiratory function would only be expected to be evident after longer exposure, and at a later age, but these findings suggest that even with a relatively short duration of cannabis exposure, decline in lung function and presence of symptoms are significant.

However, Tashkin et al (1997) published data from a Los Angeles study of heavy cannabis-only smokers (>3 joints per day) and found that there was no evidence of an accelerated decline in FEV₁ with age in comparison with tobacco smoking. In addition, this study contradicted the other studies by noting that tobacco and cannabis did not appear to have additive effects on the lung.¹⁷² In support of the argument that cannabis is not associated with COPD, diffusing capacity for carbon monoxide (DLCO - which is usually a sensitive indicator for emphysema) was not reduced in the regular cannabis smokers.¹⁸¹ Limitations of this study include that it had a small number of participants who were also were relatively young (mean age of 33 years).

In this study, airways hyper-responsiveness (AHR) to methacholine was present in 23.3% of cannabis only smokers, 29.4% of tobacco smokers and 37.3% of mixed cannabis/tobacco smokers in comparison with 17.2% of non smokers.¹⁷⁶ Although the first two groups appear to have a higher prevalence AHR than non smokers, this difference was not significant, but mixed smoking was significant with AHR being more than twice that in non smokers (p<0.01)

The NHANES III was the first study providing evidence of the respiratory effects of cannabis in a large nationally representative sample.¹⁷⁴ Cannabis was found to be associated with chronic bronchitis, coughing on most days, sputum production, wheezing and chest sounds without a cold. A limitation of this study is that no information was collected regarding the frequency and amount used per day, the number of years of use or the modality of use (smoking vs. ingestion). Therefore analyses of cumulative usage (such as joint years) were not possible. Also, this

sample was restricted to persons aged 20 – 59 years of age, not allowing for analysis of the longer-term effects of cannabis in persons over 60 years, the age group at which COPD is most prevalent. Interestingly, there have been no studies assessing the effect of cannabis in persons over the age of 60. If we liken cannabis to tobacco smoking, a latent period between the onset of smoking and the development of lung damage is to be expected.¹⁷⁷

Some studies have implicated cannabis in the aetiology of COPD, and other studies are contradictory, suggesting that further research is necessary to provide more conclusive evidence. Another paper by Taylor et al (2002) from the Dunedin birth cohort found a marginally significant dose response relationship of cumulative cannabis use on FEV₁/FVC ($p < 0.09$), after adjusting for tobacco use, age and weight. A limitation, which is also a strength of this study, is that it again focussed on a young population, where one would not expect to find effects, but actually found that the effect of smoking cannabis in youth is not negligible and young cannabis smokers (particularly heavy smokers) were at a greater risk than previously supposed.¹⁷⁸ A more sceptical interpretation might be that such an “unlikely” result was more probably the result of residual confounding and that a smaller effect would be more plausible. Another notable point was that cannabis and tobacco smoking acted additively to influence FEV₁/FVC. There was no evidence of an interaction between the two exposures. Cannabis was both an independent and an additive risk factor for obstructive lung disease.

The percentage of cannabis smokers that develop COPD is not known.^{172 179} As mentioned previously, the presence of chronic bronchitis does not predict the development of airflow obstruction. A significant challenge in answering this question is the difficulty in quantifying exposures, which in turn makes it difficult to perform dose-response analyses. Quantification is hampered by the relatively greater number of tobacco cigarettes that most cannabis users smoke, and the varied methods of smoking cannabis. Issues include different sizes of cigarettes or pipe volumes, the tendency for joints to be shared, unreliable self reporting, varying puff volumes, differing retention times, filtering etc.¹⁷²

In summary, although there is strong evidence to suggest that cannabis smoking is associated with chronic bronchitis and upper airway pathology, its association with COPD remains uncertain.

Bullous lung disease

Cannabis has also been linked to the development of bullous lung disease, but evidence for this association appears to be lacking, and has recently been challenged. It is largely based on a report of only four cases.^{177 180 181 182} Cannabis use has not been definitively linked to mortality from lung disease.¹⁸³

Underreporting and concomitant tobacco use

An important issue in the quantification of cannabis use is underreporting. This may cause a significant bias in countries where cannabis is illegal, and reduce the strength of the signal in studies, suggesting that study results may be a conservative estimate of the true effects of cannabis on respiratory health.¹⁷⁴

It has also been reported that most users of cannabis also smoke tobacco, making it difficult to assess individual risks.¹⁷⁷ However, multivariable analysis should at least in part account for this, leaving misclassification as the main concern rather than residual confounding.

Infections and TB

Cannabis has been shown to reduce the generation of proinflammatory cytokines including TNF-alpha and granulocyte macrophage-colony stimulating factor (GM-CSF) as well as to impair the production of nitric oxide by alveolar macrophages. In theory this might impair host defences against lung pathogens, reduce immune function and predispose to the carcinogenesis and opportunistic infections.¹⁸⁴

These mechanisms could theoretically result in increased susceptibility to infections such as tuberculosis. Apart from one case report of chronic cannabis smoking leading to necrotising pulmonary granulomata as a result of possible fungal contamination of cannabis, no associations between cannabis and respiratory infections including tuberculosis have been confirmed.¹⁸⁵ However, the practice of sharing joints and other smoking appliances (e.g. pipes) might put smokers at some risk of cross-infection if shared with persons with TB.¹⁸⁶ This point may be of importance in this thesis study area, because social activities such as drinking in informal taverns (known as shebeens) have been shown to be associated with the spread of *Mycobacterium tuberculosis*, which itself is a risk factor for obstructive lung disease.¹⁸⁷

2.6.2.4. Tuberculosis

Previous pulmonary tuberculosis (TB) has been recognised as a risk factor for the development of obstructive lung disease, but whether lung function impairment caused by this disease should be included in the definition of COPD is uncertain. As mentioned above, the GOLD definition of COPD refers to inhaling of “noxious particles or gases”.⁶³

The exact mechanisms leading to airflow obstruction in patients with tuberculosis are not known, but are likely to include bronchial and peribronchial granulomas and fibrosis in the early recovery stages, with bronchiectasis and cystic changes in its more advanced cases. Clearly the latter can be distinguished, both radiologically and pathophysiologically, from COPD, but to exclude tuberculosis per se, is inconsistent since other infections are not excluded and they are likely to play a role. For example, a latent viral aetiology for the development of COPD has been proposed by Hogg (2001)¹⁸⁸ and recurrent infections are thought to be involved in its progression. In high TB prevalence areas, a significant proportion of the general population provide a history of TB infection. Are all to be excluded from the diagnosis of COPD? This and related questions need to be addressed.

Evidence of airflow obstruction in patients with TB.

Several studies have shown an association of pulmonary tuberculosis with obstructive lung disease at the time of diagnosis, during and after treatment.^{189 190 191 192 193} Ahn et al (1976) found that 57.5% of patients with mycobacterium tuberculosis infection had an FEV₁/FVC ratio of <70% and that worse lung function was associated with a greater extent of disease.¹⁹⁴ A South African study by Plit et al (1998) reported that after treatment 54% had improvement in pulmonary function, 28% had obstruction and 24% restriction post treatment.¹⁹⁵ The extent of pulmonary parenchymal involvement on pre-treatment chest radiography measured by a radiographic score was significantly associated with impairment of FEV₁ (% predicted).

It is interesting that other studies (including Plit et al) could not show a significant association between smoking and obstruction in TB patients.¹⁹⁵ Plit et al suggested that it was probable that the effect of inflammation from TB predominates over the slowly evolving effects of smoking.¹⁹⁵ It seems that tuberculous inflammation most likely occurs relatively rapidly and has greater potential for airway damage in a shorter space of time. Airflow limitation could be due to endobronchial and or

pulmonary tuberculosis. However, one should note that most studies have been performed in hospital patients, who are expected to be a more severe or complicated group. This could bias the characterisation of airflow obstruction. Most patients with pulmonary TB are treated as outpatients and population level data would include the full range of severity, from mild to severe. It would be useful to examine the association of obstruction (and restriction) with pulmonary TB at this level.

However classified, a large proportion of persons with a history of pulmonary tuberculosis have impaired lung function – obstruction or restriction.¹⁹³ Longitudinal studies have shown a decrease in lung function follow up. Vargha (1983)¹⁹⁶ found one group (60% of cases) to have obstruction and another group (40% of cases) to have no obstruction at discharge after treatment for pulmonary tuberculosis. At fifteen year follow-up, a decrease in FVC of 54ml per year occurred in those who had obstruction at discharge and a decrease of 28ml per year in those who were not obstructed at discharge, and suggesting that some patients had an ongoing obstructive process and some did not. There was no significant difference in loss of FEV₁ in the two groups (35ml and 29ml in obstructed and non obstructed groups respectively). One can draw a parallel with tobacco exposure, where some smokers have rapidly deteriorating lung function with smoking over time and some do not, following different courses. The course of disease can be postulated to be dependent on host factors such as pre-existing/precipitated AHR and/or environmental factors such as the strain of TB.

Of relevance to the study site of this thesis, a study from Cape Town, South Africa by Willcox and Ferguson (1989) found evidence of obstructive lung disease in 68% of patients treated for TB sixteen years before.¹⁹⁷ In keeping with the findings by other authors, an inverse relationship was found between FEV₁ and extent of disease on the original chest radiograph.

Only one longitudinal study in an occupational cohort of South African gold miners has compared pre TB and post TB lung functions. This study adjusted for both silicosis and smoking and found that 18.4% of miners had an FEV₁ <80% predicted after one episode of pulmonary tuberculosis.¹⁹³ This percentage rose to 27% after two episodes, and 35.2% after three or more episodes of TB.¹⁹⁸ The corresponding decrease in FEV₁ was 153ml, 326ml and 410ml respectively with proportional reductions in FVC. Miners who had an episode of TB had a 40ml per year greater loss of FVC and FEV₁ and more than double the risk of having respiratory symptoms

at follow up, compared to miners who did not have TB. Of note, the overall assessment was that the defect caused by TB was restrictive in nature. The risk of having restrictive impairment was ten fold greater than in those without TB, but there was no increased risk of obstructive lung disease, a finding that is at odds with other studies.¹⁹³ These results could possibly be biased by quality control of spirometry as poor quality spirometry can result in a false “restrictive” pattern.

A hospital-based study from Indonesia showed that even patients with mild tuberculosis may develop significant airway obstruction.^{59 199} Other smaller studies suggest that active tuberculosis is associated with bronchial hyperreactivity²⁰⁰, but whether this phenomenon persists is not known. In addition, tobacco smoking may play an important role as a confounder; because it has been identified as a risk factor for both tuberculosis infection and COPD (see Chapter 3).⁵⁹ Immune function can be compromised by many factors, including tobacco smoking, alcohol abuse, poor nutrition²⁰¹ and potentially even cannabis smoking, which may play a role in increasing the risk of infection and activation of TB. Overall, age, cumulative tobacco exposure and the extent of initial tuberculous disease are factors that contribute to the severity of airflow obstruction in patients who have been treated for pulmonary tuberculosis.^{59 190 192} To date, there appear to be no published studies that examine tuberculosis as a risk factor for COPD at the population level.

2.6.2.5. Air pollution

2.6.2.5.1. Indoor Air Pollution

In many countries, most people spend over three quarters of their time indoors²⁰² and this exposure to indoor air pollutants is of concern regarding the development of lung disease. Indoor pollutants of note are nitrogen dioxide, sulphur dioxide, particulates, tobacco smoke, asbestos and volatile organic compounds²⁰² among others, of which particulates pose the greatest risk, especially in developing countries.

The most important predictor of indoor air quality is outdoor air²⁰⁴ and levels of indoor air pollutants depend on other factors such as ventilation, dispersal and absorption. Particulate matter, CO, CH₄, NO₂ and various other pollutants which are similar to those found in tobacco smoke and coal, result from the burning of biomass fuels. Indoor open fires are inefficient and result in copious amounts of large particulate smoke (1-2mg particles). The exposure is also not consistent, so measurement by means of averages may be misleading as transient peaks of 20 – 30mg/m³ contribute

considerably to exposures and 60% of exposure occurs when a fire is either started or put out.²⁰³

A common scenario in many developing countries is the indoor use of a single source of biomass fuel for cooking and/or heating in poorly ventilated dwellings. Use of biomass fuels is closely linked to poverty and the majority of exposure occurs in developing countries and in women. Approximately 50% of the world population is thought to be exposed to biomass fuels. This constitutes more than 3 billion people and 90 percent of rural households, and the exposure contributes to 2 million deaths per year.²⁰⁴

Biomass fuel exposure features prominently in global exposure to toxins and the number of biomass stoves is expected to rise due to poverty and underdevelopment.²⁰⁴ In never smokers and non smokers it is one of the largest risk factors for obstructive lung disease, and is estimated to be the 10th largest cause of death in the world.²⁰⁵ Dossing et al (1994) showed that two thirds of Saudi Arabian non-smoking women with COPD had >20 years of biomass fuel exposure.²⁰⁶

There are relatively few population studies that investigate biomass fuels as a risk factor for obstructive lung disease. About thirty studies have shown a clear association with chronic bronchitis, but there are few studies with lung function and these show a mild association with the exposure. The collection of data in these studies could be a factor – few studies have actually measured the exposure and many rely on self-reporting. Exposure is often expressed in a similar fashion to pack years, known as hour years which is the number of hours per day multiplied by the number of years of exposure. A threshold value of >100 hour years has been used in some studies.

A 'first world' example

A Spanish study of 60 cases and 60 controls, with 50% being never smokers, reported an odds ratio of 1.8 for wood, 1.5 for charcoal and 4.5 for a combined exposure.²⁰⁷ One cannot ignore the fact that even populations in developed countries have a rural component and many older persons, irrespective of their current domicile, may have had significant past exposure.

Studies from developing countries

One of the first studies was by Pandey et al in 1984 who reported increased risk of chronic bronchitis in smokers and nonsmokers with biomass exposure in Nepal.²⁰⁸

In 1995 Zhou and colleagues reported a difference in comparative risk for COPD – using soft coal or anthracite was associated with a higher risk of 4.4 compared to firewood which had a risk of 1.5.²⁰⁹ A Turkish study showed a 2.5 times increased risk of COPD or chronic bronchitis with exposure to biomass fuel when compared to liquid petroleum gas exposure.²¹⁰ A study from Bogota, Columbia compared women with and without obstructive airways disease and found that the use of wood for indoor cooking was associated with a 3.4 times increased risk for obstructive lung disease.²¹¹ Passive (and active) smoking was also identified as significant risk factors in this setting.

A very recent study by Regalado et al (2006, in press), looked at 871 rural Mexican never smoking females aged over 38 years with no occupational exposures – a good group in which to study biomass fuel exposures, but nonetheless not a population sample. This is probably one of the first community studies to measure biomass in domestic smoke exposure. Overall, an association with cough and phlegm was confirmed, but no significant increased prevalence of COPD was found in exposed women. A decrease in FEV₁ of 81ml was noted in houses that had exposure of >2.6 mg/m³ and that the FEV₁/FVC ratio was also reduced with GOLD Stage II COPD more prevalent in the houses with higher exposures.²⁰³

Ramirez – Venegas et al (2006) recently published the first longitudinal study on the survival of biomass exposed women. They found that biomass exposed women had clinical COPD characteristics, quality of life and use of health resources that were similar to that of tobacco smokers.²¹² Mortality was also similar to tobacco smokers after taking into account that smokers developed more severe obstructive lung disease, confirming that biomass exposure contributes to premature mortality, despite overall severity of airflow obstruction being less than that of tobacco smokers.

2.6.2.5.2. Outdoor Air pollution

Outdoor air pollution from traffic, industry and other sources is the only exposure that affects almost the entire global human population. As mentioned earlier, the two major catastrophes this century should have intensified world efforts for clean air. However, certain areas of the world have worse air quality now, than England had

around the time of the industrial revolution. Holland published the earliest work in the 1960's comparing urban and rural post office employees, and found a greater prevalence of symptoms and lower lung function in the urban group, after taking into account smoking patterns, suggesting that local levels of air pollution could be implicated.^{27 28} The fact that they were all mail van drivers could have also suggested a link with transport as an occupation, implicated much later by Hnidzo et al from the NHANES III data.¹⁵⁹

Hodgkin et al (1984) found that persons living in a high photochemical pollution area had a 15 percent higher risk of COPD than those in a low photochemical pollution area, after adjusting for other important risk factors in a multivariate analysis.²¹³ This study is of note as the findings may be of relevance to this thesis' study site in Cape Town, which is often covered by a blanket of photochemical smog, known as the 'brown haze effect' (see Chapter 3).

Does air pollution merely exacerbate existing obstructive lung disease or is it an independent risk factor for the development of COPD? In order to answer this question one would need data from longitudinal studies, of which there is little, apart from the UCLA population studies of COPD. These which showed relatively large annual declines in FEV₁ which could be attributed to chemical pollutants, photochemical oxidants and particulates found in three urban areas that were studied. The comparison of two never smoking cohorts in Southern California found that SO_x, NO_x, hydrocarbons and particulates were associated with greater deterioration of spirometric measurements and delta N₂, suggesting that both the large and small airways were affected.²¹⁴ In addition, some recent cross sectional population studies give insight into the effects.

The effect of long term air pollution exposure on risk of respiratory symptoms was examined in a Swiss Study of Air Pollution and Lung Disease in Adults (SAPALDIA). This cross sectional study (which is now prospective) assessing 10 000 adults 18 – 60 years found that both annual mean NO₂ and total suspended particles of PM₁₀ were significantly associated with four symptoms: chronic cough, chronic phlegm, breathlessness and dyspnoea on exertion. The odds ranged from 1.3 to 1.5 for every 10 microgram increase in the PM₁₀ level²¹⁵ (particulate matter size of 10 micrograms).

The effects of traffic have also been implicated in the aetiology of obstructive lung disease. In many urban areas worldwide, houses are very close to streets which are

heavily populated with cars and trucks and many people spend outdoor time along the traffic routes.²¹⁶ A recent series of cross sectional studies of 55 year old German women examined the effects of living less than 100m from a major road. Physician diagnosis of chronic bronchitis was associated with a higher level of annual NO₂. Frequent cough was associated with NO₂ and living 100m from a major road; and FEV₁ /FVC ratio with NO₂, annual PM₁₀ and living 100 m from main road.²¹⁷ The obvious limitation of this study was that it sampled only women, and is therefore not generalisable to the whole population, but points to the respiratory hazards of urban air pollution.

Levels of air pollution in most developed countries appear to be declining. Unfortunately, developing countries have an added burden owing to unregulated industry or poor enforcement of legislature as well as use of biomass fuels. However, there are few data from some of the most polluted areas of the world.

2.6.2.6. Socio-economic factors

Lower socioeconomic status is consistently associated with poorer health, high morbidity and high mortality.²¹⁸ Many cross sectional studies have examined the relationship of COPD with socioeconomic status, measured as level of education, income or occupation.^{219 220 221 222 223 224} Some have used place of residence²²⁵ and/or housing conditions²²⁶ among other indicators.

In their review of socioeconomic status and COPD, Prescott and Vestbo suggested that the impact of socioeconomic status on COPD is the next most important factor after smoking.²²⁷ Socioeconomic status is also associated with other risk factors associated with lung function such as tuberculosis, childhood respiratory infections, smoking and occupation. It is difficult to disentangle the many factors that cluster with socioeconomic status, and might affect health - for example, housing, nutrition and life choices such as smoking.

Low socioeconomic status was associated with increased mortality from chronic bronchitis and emphysema in a large retrospective analysis from the UK.²²⁸ In addition a British cohort study revealed an association of respiratory symptoms and airflow limitation with both current low socioeconomic level and poor home environment at the age of two years.²²⁹ In Canada, a study that used income showed that men from low-income families had a 3.7 times increased risk of COPD compared to their high income counterparts, after adjusting for other relevant risk factors.²³⁰

From a developing country perspective, Menezes et al found the prevalence of chronic bronchitis to be higher in persons with a low socioeconomic status in a study from Pelotas, Brazil.⁸²

Eagan et al (2004) was the only cohort study that examined the cumulative incidence of respiratory symptoms by educational level found that the incidences decreased with increasing educational level, for all symptoms.²¹⁸ After adjusting for smoking, age, sex, hay fever, pack years and occupational exposures, those with a primary school education had an odds ratio of 1.4 for incidence of chronic cough and 2.5 for incidence of grade two dyspnoea, when compared to those with a university education. Similarly, another Nordic study found that those with primary school education were five times more likely to have airflow limitation than their university graduate counterparts, independent of smoking (OR 5.2; CI: 2.0 - 13.4).²²⁰ The corresponding risk for secondary school education was an odds ratio of 1.8 (1.2-2.7).

2.6.2.7. Gender

Apart from being considered as a risk factor for COPD, gender differences have also been considered in COPD severity, prevalence and mortality as well as airway hyperresponsiveness.²³¹ In 2000, studies by Sobradillo-Pena et al¹⁰¹, Viegi et al²³² and Mannino et al²³³ have all reported the prevalence of chronic bronchitis and COPD to be higher in men than in women. This is to be expected since historically, men have smoked more, and may be exposed more in the workplace.

Smoking rates in women are rising worldwide.⁵¹ As smoking rates in women have increased, so too has the prevalence of COPD in women in developed countries such as the UK.²³⁴ Gender differences in tobacco exposure are discussed in Section 2.6.1. Becklake and Kauffmann (1999) have published a comprehensive review on gender differences in airway behaviour examining biological and sociocultural determinants and suggest that the influence of sex and gender on airways diseases requires special study owing to inherent physiological differences between the sexes.²³⁵ It is possible that differences in airway behaviour could result in a different dose response or pattern of response to noxious agents.

It is thought by some that women are more predisposed to develop COPD from tobacco smoking at an earlier age, and with more severe effects on lung function

than men.²³¹ Three studies support the hypothesis that women are more susceptible to the noxious effects of tobacco smoke than men and therefore at a greater risk of developing COPD than men.^{236 237 238} However, findings from longitudinal studies such as the Lung Health Study, an Australian and a US study failed to demonstrate this effect^{239 240 241} as did a large metaregression analysis of eight studies.²⁴² In the EUROSCOP study, decreased baseline FEV₁ was associated with respiratory symptoms in male but not in female smokers, suggesting that FEV₁ in male and female smokers have a different pattern of response.^{231 248} Women are also thought to benefit more from smoking cessation than men and are more likely to reduce or quit.^{231 243}

In the developing country context, the contributions of other risk factors such as domestic biomass fuel exposure affect women disproportionately in addition to gender specific occupational exposures and certain infections.²⁴⁴ The effects of various risk factors other than smoking and biomass fuels in men and women have not been investigated to a great extent from a gender perspective.

COPD in nonsmokers with no clearly identifiable cause points to possible causes such as air pollution. Birring et al (2002) found that COPD in nonsmokers predominantly affects older females.¹⁴² By examining induced sputum, two pathologic subgroups were identified - a group with neutrophilic inflammation associated with organ specific autoimmune disease, commonly thyroid disease, and an eosinophilic group. The eosinophilic group was not associated with longstanding asthma and fixed airflow limitation from airway remodelling, nor was it associated with eosinophilic bronchitis/bronchiolitis. For the neutrophilic group, causes such as air pollution, occupational exposures and idiopathic constrictive bronchiolitis were considered. However, the frequency of autoimmune disease was much higher in this group, and the authors suggested an unrecognised autoimmune bronchitis or a postulated inflammatory component of the autoimmune disease arising from the shared embryologic origins of cells.

2.6.2.8. Body Mass Index

Body mass index (BMI) has in recent years been identified as a prognostic indicator in COPD, and is not a “risk factor” as such. The BODE Index is a grading system that is used to predict risk of death in persons with COPD. BODE is an acronym for Body Mass Index, airflow obstruction, dyspnoea and exercise capacity.²⁴⁵ Low body mass

index of ≤ 21 is associated with increased mortality and it is thought that the negative effects of low body weight may be at least partially reversed by nutrition.

Many studies that have examined the relationship between BMI with asthma, but few have examined the relationship with chronic bronchitis or COPD. Chinn et al showed that weight change had an independent effect on decline in FEV₁.²⁴⁶ Weight gain diminished the effect of quitting smoking by 38% in men and 17% in women. Guerra et al (2002) examined data from the Tucson study and showed that persons with asthma were more likely to be overweight or obese, those with chronic bronchitis to be obese and those with emphysema to be underweight.²⁴⁷ The EUROSCOP study suggested that obesity is a risk factor for dyspnoea and greater severity of COPD.²⁴⁸

The relationship between the onset of COPD and being underweight is not clear. The supposed direction of effect is that COPD is a “cause” for being underweight. Whether being underweight makes one more likely to develop COPD is not certain. A paper from the Baltimore Longitudinal Study on Aging, by Harik-Khan et al (2003) suggested that low BMI could be a risk factor for COPD rather than just an effect of the disease. Body Mass Index was measured before the diagnosis of COPD and an increased risk of developing COPD was found for men with a low BMI even after adjusting for many other known risk factors.²⁴⁹

However a Canadian study found that overweight women had a 2.4 times increased risk of COPD which was defined as self-reported doctor-diagnosed chronic bronchitis or emphysema.

2.6.2.9. Asthma, Airway Hyper responsiveness (AHR) and allergy

The role of AHR and allergy as risk factors for COPD is still uncertain.^{250 251} Early studies by Fletcher et al found that the rate of decline of FEV₁ was significantly higher for asthmatics compared to non-asthmatics, after adjusting for smoking.²⁵² Studies in children have shown that AHR contributes to lower lung growth. Juan et al compared the FEV₁/FVC curves for children aged 8-20 years over time and concluded that those with AHR progressed less favourably than their counterparts in terms of expected lung development.²⁵³

O’ Connor et al reported that AHR (to methacholine) predicted accelerated lung function decline after adjusting for confounders in a cohort of 912 men followed up for 3 years.²⁵⁴ The Lung Health Study provided more evidence that increased AHR to

methacholine was associated with accelerated decline in lung function over 5 years, and suggested that AHR is an important predictor of “progression of obstructive lung disease in continuing smokers with early COPD”.²⁵⁵ In addition Tashkin (1996) also found an interaction between smoking and AHR in this study.

A longitudinal study of 3099 participants at 20 year follow-up produced results in support of asthma as a risk factor for COPD. The Tucson Epidemiologic study of Airway Obstructive Diseases reported that active asthmatics (those that had ongoing asthma at the time of the first measurements) had a hazard ratio of 12.5 for developing COPD.²⁵⁶ The definition of COPD involved having a diffusing capacity or an FEV₁ of less than 80% predicted, accompanied by either physician-diagnosed emphysema or symptomatic chronic bronchitis. In addition, active asthmatics had a 10 fold greater risk for acquiring chronic bronchitis and a 17 times higher risk of being diagnosed with emphysema.²⁵⁶ Initial misclassification could have played some part in increasing the strength of associations, but is unlikely to be wholly responsible for these associations. Asthma and COPD diagnoses were also not fully validated, as there was no measurement of airway hyper-responsiveness or reversibility, but again misclassification from this source is likely to be limited in view of the fact that an objective measurement of diffusing capacity was included in the definitions.

An earlier paper from the Tucson study argued the reverse and classified asthma-related chronic airflow obstruction as “chronic asthmatic bronchitis”²⁵⁷ (not COPD). Similarly, a review of longitudinal changes in FEV₁ in asthma (from the Copenhagen City Heart Study) suggested that a subset of asthmatics may have nonreversible decline in lung function, but that this could not be called COPD.²⁵⁸ However, a subsequent revision removed the longitudinal part of the analysis and reached a different conclusion showing that the rate of decline in FEV₁ was increased in persons with new onset asthma (in a 5 year period). Those with chronic asthma had the same decline in FEV₁ as nonasthmatics.²⁵⁹ Another American study also found an effect of accelerated loss of lung function associated with asthma.²⁶⁰

The Busselton study suggested a real decline associated with asthma, finding reduced lung function at the beginning of adult life as well as an increased rate of decline thereafter. The authors suggested abnormalities in airway structure and function before the age of 19 (probably starting in early life) contribute to decreased lung function in adulthood.²⁶¹ In children, the effect of asthma on lung growth is also doubtful.²⁶²

It has been suggested that atopy and high serum IgE are risk factors for COPD,^{118 123} but this does not appear to be a widely accepted view. A study by Hospers et al (1999) reported that the presence of eosinophilia was associated with increased mortality from COPD, but only in association with a past history of asthma attacks.²⁶³ The Tucson study after adjusting for other important risk factors, failed to show associations between IgE and positive skin prick tests, and COPD. In contrast, Tracey et al found that positive skin prick tests, elevated IgE and AHR were associated with accelerated decline in FEV₁ in 324 elderly participants. This was evident especially in former and current smokers, and AHR preceded the onset of chronic lung symptoms.^{256 264 265} This may not be considered a convincing argument in the light of findings by Lim et al (1988) who studied changes in AHR to inhaled histamine over four years and found that ex-smokers had comparable levels of AHR at baseline and a normal age related decline thereafter.⁴¹

The mechanisms whereby the presence of asthma may contribute to the development of COPD are still uncertain, and require further research. The Dutch hypothesis, described above, considers AHR and atopy as host factors that can lead to airway remodelling and in due course to irreversible obstruction. However, cough and phlegm are symptoms of both asthma and COPD independently, and this is not necessarily related to chronic bronchitis.

2.6.2.10. Childhood chest disease

Some population studies have shown an association between childhood respiratory illness and resultant respiratory symptoms and decreased pulmonary function later in life. Cohort studies by Shaheen et al (1994, 1998) examined the effect of lower respiratory tract infections in childhood and found that pneumonia before the age of two years was associated with a decrease in mean FEV₁ in men, independent of smoking.^{266 267} Bronchitis, pneumonia and whooping cough in infancy were associated with a significant decrease in FEV₁, wheezing and persistent sputum production in later life.²⁷⁵ Pneumonia before the age of seven years was also associated with a significant decrease in FEV₁ and FVC in a cohort examined at age 35.²⁶⁸

There is also some suggestion that even earlier lung insults play a role in adult COPD. Prematurity with bronchopulmonary dysplasia (BPD), ventilator dependency have been implicated in later-life COPD that has a less typical origin. The title of one

such article was curious: “Some COPD will originate in neonatal Intensive Care Units”.²⁶⁹ Prematurity has been shown to result in frequent respiratory illnesses/infections in the first year of life, and persistent respiratory symptoms during childhood. Based on CT studies, the authors postulated that these individuals are likely to suffer from COPD in later life.

A paper by Northway et al (1990) assessed survivors of BPD and compared them to survivors of prematurity without BPD and to normal individuals.²⁷⁰ The survivors of BPD had lower FEV₁, FVC, air trapping (measured by a higher residual volume/TLC ratio) and a substantial number had a minimal response to bronchodilators, suggesting some evidence that early life exposures could be more closely related to adult COPD than was previously supposed.

“Wheezy bronchitis” is a term not used much now, but in the 1960’s, it was common nomenclature. A 1964 cohort containing asthmatics, normals and those with a history of “wheezy bronchitis”, now 45 – 50 years old were followed up by Edwards in 1989 and 2001.²⁷¹ The 1989 follow up of these patients showed no evidence of a difference in early adulthood, but a decade later (in 2001) revealed an average annual decline of 0.59L for those with no symptoms. Those with wheezy bronchitis had a greater average annual decline of 0.75L, suggesting that this accelerated decline could progress to COPD.²⁷¹ This highlights that fact that these effects may take decades to emerge or become apparent.

2.6.2.11. Other risk factors

Genetic host factors include the well-known alpha-1-antitrypsin deficiency, and the lesser-mentioned Ehlers-Danlos Syndrome, cutis laxa and Marfan syndrome.²⁴⁴ There appears to be a female preponderance of these genetic factors in the 5-12% of persons with COPD who have never smoked.^{181 244} Sandford and Silverman (2002) examined particular 3 genotypes of alpha-1-antitrypsin and the least favoured (PiZ) showed evidence of a gene-environment interaction – as pack years increased there was less favourable response to tobacco exposure.²⁷² Other genetic factors associated include alpha 1 antichymotrypsin, alpha-2-macroglobulin, vitamin D binding protein and blood group antigens.²⁷³

Low birth weight has also been implicated in the aetiology of COPD suggesting that it is probably related to poor lung development from poor nutrition in utero. This results in the decline in lung function that occurs naturally with age, actually starting at a

lower peak value than normal. The main evidence for this is from studies in England and Wales which found that low birth weight and childhood respiratory infection were associated with decreased adult lung function. In addition, death from COPD was associated with low birth weight and weight at one year. They found that infection in early childhood had a greater influence than cigarette smoking in determining the geographical distribution of chronic bronchitis.^{274 275} Similarly a South Indian study found both low birth weight and small head circumference at birth to be associated with a decreased FEV₁/FVC in men. This finding was independent of smoking.²⁷⁶

Results from the Copenhagen City Heart Study found alcohol consumption of more than 3 drinks a day to be associated with an almost 2 fold increase in risk for chronic bronchitis in the elderly.²⁷⁷ However, a Canadian study found no relationship of regular drinking with self-reported doctor-diagnosed chronic bronchitis or emphysema.

Apart from alcohol, other novel associations include an inverse association of glycaemic control with FEV₁ from the Framingham Heart Study²⁷⁸ and the Fremantle Diabetes study²⁷⁹; findings that could be relevant in diabetics, and deserve further attention as the obesity epidemic increases worldwide.

A review by Romieu and Trenga (2001) suggested that by decreasing the insults of oxidants, antioxidants in fresh fruit and vegetables (particularly vitamin C and E) could temper the development of chronic lung disease and decrease in lung function, encouraging higher intake and further longitudinal studies to investigate the hypothesis.²⁸⁰

HIV infection has recently been implicated in accelerating the onset of smoking-related emphysema. Diaz et al (2000) found that the incidence of emphysema in HIV positive patients was significantly higher than in HIV negative patients (15 vs. 2%).²⁸¹ HIV positive patients developed emphysema at a younger age than their negative counterparts. It was suggested that larger numbers of cytotoxic lymphocytes found in the bronchoalveolar lavage fluid may have a role in the pathogenesis of emphysema.

2.7. Conclusion

There are many methodological issues that have arisen in this review, such as confounding, bias and misclassification of disease status (as asthma). Definitions of

COPD are difficult to apply in practice, as studies are not usually able to routinely check or prove that there is an “abnormal inflammatory response”. Problems with comparisons of self-reported chronic bronchitis, different/changing spirometric criteria, and limitations of these criteria such as the reliability of a fixed ratio in older adults, all contribute to a non-standard approach to disease. Definitions are not applied uniformly across studies, and in addition, the epidemiological definition is not the same as the clinical or pathological definition of COPD.

The potential for publication bias also needs to be considered as a suspected factor even though there may be no clear evidence for it. An example is a review by Bero et al found that 80% of original journal articles on the effects of ETS reported a positive association, compared to 51% of symposium articles, suggesting that cigarette-industry sponsored symposia publish more negative findings than journals.^{282 283}

Different studies rely on different indicators of disease e.g. spirometry, diffusing capacity; others have reported only symptoms, and others have even performed CT scans. In a clinical situation, one is able to integrate symptoms, pulmonary function, CT etc. and make a diagnosis based on these, like the pieces of a puzzle.¹²⁶ However, in population studies, one often has only one or two pieces of the puzzle, sometimes based on crude measures of risk factors such as general occupational exposure questions, and therefore one would expect relationships to be biased towards the null, for a heterogeneous disease like COPD. A balance between the use of simple indicators that are useful and convenient and the more complex indicators needs to be decided upon, depending on the specific hypothesis of a study.

Overall, there has been an advance in the methodologies for studying the prevalence of COPD by means of standardised questionnaires and ways of measuring pulmonary function and there is some measure of agreement on the definition and classification of COPD. Epidemiological data on the prevalence and risk factors for COPD is an essential requirement for tracking trends, planning preventive strategies, improving healthcare and motivating governmental intervention. This review has highlighted some encouraging trends in the developed world including reductions in smoking amongst men. However, in some cases this gain has been diminished by an increase in smoking amongst women.

For the developing world, and countries in epidemiological transition such as South Africa, there is a particular need for population-based surveys. The review of risk

factors highlights the need for surveys in Africa to consider factors other than cigarette smoking, and in particular the role of domestic and industrial pollution, infections, including tuberculosis, and cannabis use. In the light of this, the South African perspective on obstructive lung disease is presented in the following chapter.

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CHAPTER 3: LITERATURE REVIEW: ADULT OBSTRUCTIVE LUNG DISEASE IN SOUTH AFRICA

3.1. Introduction and aim

The purpose of this chapter is to review obstructive lung disease in South Africa with respect to prevalence data, potential risk factors and management in the public health sector. In general, the pattern of obstructive lung disease in South Africa is similar to that in other developing countries and countries in epidemiologic transition, but the unique history of South Africa has played an important role in shaping the profile of risk factors. Interest in population research on obstructive lung disease has grown over the last decade with the recognition of the burden that these diseases place upon the health of the population.¹ The major risk factors that will be reviewed are tobacco smoking, cannabis smoking, TB, occupational exposures and air pollution. These risk factors may not necessarily be independent from one another.

Added to these is the impact of the rapid increase in the prevalence of tuberculosis and HIV-related lung disease over the past 10 years, which has changed the face of respiratory health in South Africa. The work reported in this thesis was performed in a setting of low HIV infection, but it is important to consider that as the prevalence of HIV increases in a community, the pattern of disease changes rapidly to one of more infections, both usual and opportunistic, and shortened life expectancy with reduced opportunity for the development of chronic degenerative diseases like COPD. This shift will not be considered in detail for two reasons. Firstly, because it is not relevant at the time of the studies reported here, and secondly, because it is difficult to predict the impact of the recent introduction of anti-retroviral drugs in South Africa upon this shift. Separate studies are required to examine these trends.

Some portions of this chapter have been adapted from a recent review of respiratory diseases in South Africa which was co-written by the author.¹

3.2. Methods used in the literature review.

Effort has been made to obtain South African publications on obstructive lung disease and the focus of this review is on literature published in the last decade. Important citations prior to 1994 are included. An internet search using the Pubmed search engine was performed using various keywords, e.g. COPD, chronic bronchitis

etc. The first South African Demographic and Health Survey as well as the South African Medical Research Council's technical reports have also been referenced. References from "grey" literature from the South African Medical Research Council's research database were also obtained. In addition, relevant theses and published books were consulted.

3.3. Burden of mortality and morbidity of COPD

Over the last decade, South Africa has been undergoing an epidemiological transition with increases in the burden of both poverty-related pre-transitional diseases such as tuberculosis, as well as post-transitional chronic diseases such as COPD.³ The coexistence of these diseases is responsible for much premature mortality and morbidity. South Africa suffers from a quadruple burden of disease of HIV/AIDS, diseases of poverty, emerging chronic diseases and injuries.²

Respiratory diseases excluding tuberculosis were ranked as the seventh highest cause of Disease Adjusted Life Years (DALYs) lost of 4.7%, according to the South African National Burden of Disease Study of 2000.³ COPD was responsible for 2.3% of all deaths, although only 1.1% of years of life lost (YLL), in keeping with the fact that most morbidity is experienced by older persons.⁴

The true proportion of deaths attributable to COPD is almost certainly higher, because of the inaccuracy of cause of death data. COPD is likely to be under-certified as an underlying cause where the immediate cause is stated as respiratory infection.¹ Inconsistent use of nomenclature by doctors, misdiagnosis and the lack of standard guidelines regarding the reporting of cause of death are factors that significantly obscure this estimate. Despite significant limitations (mainly underreporting) associated with cause of death reporting, COPD is ranked eighth amongst the leading causes of death in the Western Cape Province, being responsible for 3.8% of provincial deaths.⁴

The absence of accurate prevalence data on COPD in South Africa further hampers estimates of morbidity. To date there have been very few studies involving spirometry, which is necessary to make the diagnosis. The best available study is the South African Demographic and Health Survey performed in 1998, in which both symptoms of airflow limitation (e.g. wheeze and cough), self-reported respiratory diagnoses (e.g. asthma and emphysema), and peak expiratory flow rates were

obtained. Although the latter is not considered an adequate test for confirming the presence of COPD, it provided at least some indication of airflow limitation.⁸ These results will be considered below.

Unlike COPD, which is in 6th position as a cause of death globally, asthma is not ranked among the top 15 causes of death as it is largely an adequately controlled disease in developed countries. The prevalence of asthma in South Africa is estimated at 8.1% over all ages. South Africa ranked fourth in asthma mortality rate in the 5-34-year age group at approximately 1.5 per 100 000, falling between Turkmenistan and Uzbekistan in the ranking.⁵ Similarly, the asthma case fatality rate in South Africa was reported to be the fifth highest in the world at 18.5 per 100 000 asthmatics.⁵ If these statistics are viewed as health indicators, they suggest that the treatment of asthma in South Africa is suboptimal. Whether this is because of the relative unavailability of inhaled corticosteroids in many parts of the country, their use being associated with much of the decline in hospitalisations and deaths from asthma in other countries, or because of other deficiencies in care is not clear. This requires further research.

Since globally the burden of COPD is considered to be higher than that of asthma, one can expect that the situation for COPD in South Africa will be worse than that described for asthma. Although there is some evidence that overall tobacco use has decreased slightly over the last few years, the burden of smoking-related disease is likely to continue for many years and estimates of current and potential future burden is important for health planning.¹⁰ Current smokers are growing older and will soon place a further burden on an already strained South African public health service.

In developed countries, COPD is primarily caused by tobacco smoking, and prevention activities are appropriately directed at tobacco control. Though this has been the focus, studies have also shown substantial effects of occupational exposures. The contributions of these and other risk factors in a transitional country like South Africa are likely to be significant, but need to be assessed.

In South Africa, the patterns of asthma and COPD reflect the structure of society with industrialisation, high rates of smoking among some sections of the population, extensive urban and rural poverty, and the persistence of epidemic infectious diseases. In addition to tobacco smoking, post-tuberculous lung damage, occupational exposures, indoor and outdoor domestic air pollution and cannabis

smoking have been identified as potential risk factors for adult obstructive lung disease, particularly COPD.

3.4. Review of COPD Prevalence Studies

Studies of self-reported chronic bronchitis and respiratory symptoms in South Africa are presented in Table 7. Only one study, performed almost 30 years ago, involved lung function measurements.

Table 7: Prevalence of COPD and chronic bronchitis, respiratory symptoms and COPD in population surveys in South Africa¹

Study (yr published)	Population, (N, age range)	Outcome measure	Age (yr)	Prevalence (%)	
				Male	Female
Wicht ⁷ (1977)	Northern Suburbs, Cape Town (507, 20-80 yr)	FEV ₁ /VC < 70%	< 40	9	14
			> 40	37	21
		Chronic bronchitis***	< 40	4.3	1.8
			> 40	12.2	4.7
Ehrlich ⁵⁶ (2004)	National sample** (13 468, > 14 yr)	Chronic bronchitis***	15-43	1.5	1.9
			≥44	4.2	4.3
Nriagu ⁶ (1999)	South-central Durban* (693, > 17 yr)	-Chronic phlegm > 3 months in past year	> 17	31	
		-Doctor-diagnosed bronchitis		25	

FEV₁: Forced expiratory volume in one second. VC: Vital capacity

* Area in vicinity of petrochemical refineries and other industry; ** SADHS; *** Self-reported British MRC definition

Diffuse Obstructive Pulmonary Syndrome” (DOPS)⁷

A study by Wicht *et al.*⁷ examined the “Diffuse Obstructive Pulmonary Syndrome” which was published in 1977. This study was performed in Bellville, a suburb of Cape Town adjacent to Ravensmead and Uitsig (see Figure 4), with a population of 48000. Only 20 000 were included in the sampling frame. This study was performed during the height of the apartheid regime of the Nationalist government and had a sampling limitation in that the sample was drawn exclusively from the white Voters’ Roll:

“A sequential sampling technique enjoys a specific advantage inasmuch as the inclusion of persons in the survey in the order in which their names appear on the roll ensures unbiased sampling which is truly representative of the population”⁷

The first limitation was that over eighteen thousand blacks had been excluded from the sample which was claimed to be truly representative of the areas of Tygerberg. In addition, only two thirds of the adult white population were on the Voters' Roll. The second issue was a low response rate of 40 and 45% for women and men respectively, possibly attributable to the fact that participants were required to visit a hospital for investigations to be performed. Although unavoidable, this introduced further potential sampling bias as persons who considered themselves healthy or those who were already on treatment may have been underrepresented.

The clinical assessment of 272 men and 237 women participants included a respiratory questionnaire, detailed clinical examination, electrocardiography, chest radiography and pulmonary function testing. Approximately half the population was under the age of forty and therefore more likely to have asthma. The questionnaire was based on the 1966 British MRC questionnaire and included questions on respiratory symptoms and risk factors such as smoking and occupational exposure. The design of the study suggests that authors were examining the Dutch hypothesis. This is evident in their choice of terminology to describe obstructive lung disease. Diffuse obstructive pulmonary syndrome (DOPS) was a definition that included asthma, emphysema and chronic bronchitis. DOPS was categorised into three groups: those with respiratory symptoms or diagnosis of asthma/emphysema, those with $FEV_1/FVC < 70\%$, or both.

The prevalence of DOPS defined as respiratory symptoms/diagnosis of bronchial asthma or emphysema and/or $FEV_1/VC < 70\%$ was 45% and 43% in men and women respectively. It was also found that there was no statistically significant difference in prevalence of “DOPS” in smokers and non smokers. The symptoms of dyspnoea were excluded as a determinant of the diagnosis as the authors thought that there would be a problematic overlap with other conditions such as obesity or other non-respiratory conditions, implying that those with dyspnoea but no objective obstruction on spirometry were excluded. As dyspnoea is the predominant symptom of airflow obstruction, this was a curious exclusion. However, it was reasoned that as dyspnoea usually only occurs when there is significant obstruction, and this group

would have been identified by spirometry. An exception might be in asthma where airflow obstruction is intermittent and dyspnoea can occur without cough or wheeze.

In this study, the prevalence of chronic bronchitis was reported to be 8.1% in men and 3.4% in women (British MRC definition) overall, and 10.6% in persons over 40 years (12.2% in men and 4.7% in women). There was a high overall prevalence of ever wheezing of 19.2 and 12.5% in men and women respectively and 7.7 and 11.9% of men and women reported “bronchial asthma”. Increasing age was associated with increasing prevalence of all respiratory symptoms, particularly chronic bronchitis and wheeze, in keeping with the added burden of COPD. The prevalence of smoking in the study cohort was 71% in men and 38% in women. Evidence of airflow obstruction ($FEV_1/VC < 70\%$) was found in 22.4% in men and 25.7% in women. This definition differs from that of the current GOLD definition of COPD, in that it applied to prebronchodilator rather than postbronchodilator values.

The authors found that the use of the term emphysema was of no value in the questionnaire, presumably due to the unfamiliarity of the term in the study population. The thesis study population is likely to have a similar lack of familiarity with the term today, and even less familiarity with the medical acronym ‘COPD’. The terms ‘bronchitis’ or ‘asthma’ are often used by both practitioners and participants to describe either asthma or COPD.

Chronic bronchitis in the SADHS

The South African Demographic and Health Survey of 1998 (SADHS) was the first study to provide national prevalence figures for chronic bronchitis, viz. 2.3% in men and 2.8% in women > 14 years of age. Chronic bronchitis was defined as usual cough with phlegm every day for at least 3 months a year for at least 2 successive years.⁸ This prevalence is lower than that reported from other African countries. However, most of the latter have been performed in workforces exposed to dust and other respiratory hazards, and might not have reflected the general population of those countries.⁹ The slight female excess observed in the SADHS is surprising given that national figures for current smoking were 42% in men and only 11% among women. This raises the possibility of other significant exposures in women.⁸ Self-reported doctor-diagnosed “chronic bronchitis/emphysema” was reported by 4.2% of men and 4.8% of women with 2-3% in younger persons and 7-9% in the older age groups (over 44 years).

The South African population is heterogeneous in nature and South Africa still remains a country largely divided geographically along ethnic and socioeconomic lines as a legacy of the apartheid regime. In view of the diversity of the South African population, national prevalence figures have limited value, and more is gained from examining different communities and regions for locally applicable risk factors and associations. Important community-specific factors, especially those related to low socioeconomic status may apply even within cities like Cape Town or Johannesburg.

In the SADHS, men with the least and most education had higher prevalence than those with intermediate education. However, chronic bronchitis (defined by the MRC question) was highest in rural women, but urban prevalence of reported "chronic bronchitis/emphysema" was higher than non urban rates. Women with highest levels of education had the highest prevalence of airflow limitation defined by wheeze and shortness of breath, which could reflect a higher prevalence and/or greater awareness of symptoms. Although this was the case in women, the rate of airflow limitation generally increased with decreasing education.

In order to get an idea of the burden of chronic bronchitis and COPD, estimations of the prevalence of chronic bronchitis over the age of 40 are more useful. In reports from Asia and Africa the prevalence of chronic bronchitis in women over 45 ranges from 6.0 to 7.4 percent and in their male counterparts from 6.7 to 8.7 per cent.⁹ However, in the SADHS, the prevalence of self-reported doctor-diagnosed chronic bronchitis also varied markedly in different provinces. In the Western Cape chronic bronchitis was reported in 11.4% of women and 9.4% of men, with most other provinces reporting much lower rates.⁸ Similarly the incidence of self-reported (doctor-diagnosed) chronic bronchitis was 2767 and 2031 per 100 000 for Western Cape women and men respectively.

Prevalences in the age group 15-43 years in the SADHS were low compared to those from the European Community Respiratory Health Survey (age group 20-44 years) which reported a median prevalence of 2.6% with wide variations across countries (0.7% - 9.7%).¹⁰ Even in young persons, the authors suggested that only 30% of the geographical variability in prevalence could be accounted for by differences in smoking prevalence, indicating that the role of other environmental or genetic factors may be more significant than previously supposed.¹⁰ Similarly wide variability also occurs in South Africa.

In a recent French study the prevalence of chronic bronchitis (British MRC definition) was 4.1%, and that of chronic cough and expectoration 11.7%¹¹ showing that chronic cough and chronic expectoration are more prevalent than the classic British MRC definition of chronic bronchitis, and one should also consider persons with these symptoms to be at risk for COPD, as the GOLD Stage 0 suggests.

Tobacco smoking and a past history of tuberculosis emerged as important risk factors for chronic bronchitis in both men and women in the SADHS.⁵⁶ Occupational exposure to smoke, dust, fumes, strong smells, or working underground in a mine for more than a year was associated with chronic bronchitis in men. Domestic exposure to smoky fuels (coal, wood or other biomass) was associated with chronic bronchitis in women.

Further analysis of the SADHS (unpublished data, R Ehrlich) has confirmed that the highest prevalence of chronic bronchitis adjusted for age and smoking occurred in rural African women (3.2%).¹ As the prevalence of daily or occasional smoking in this group was only 7.5%, it was proposed that this excess might be the result of domestic pollution caused by fuel used in the home, especially that of biomass origin (wood, coal and dung).

Industrial air pollution in South Central Durban: respiratory symptoms⁶

The importance of environmental conditions in the aetiology of chronic bronchitis in South Africa is suggested by a study by Nriagu *et al* (1999).⁶ This study focused on the prevalence of asthma in a south-central Durban community, an area that had been identified as being severely polluted by heavy local industry such as refineries, petrochemical plants, pulp and paper mills lead, chromium and other metal processing plants. What is unique about the history of this area is its geographical location - a low-lying area adjacent to heavy industry, chosen as a black residential area by the apartheid government.

The authors found high prevalences of respiratory symptoms. The awareness of local industry as a potential health hazard could have created a source of reporting bias even though the authors cited that they had no reason to suspect such overreporting. The study was focused on persons with the highest risk of exposure to atmospheric pollution in the hope of highlighting environmental health risks associated with apartheid. Participants may have been more likely to report respiratory symptoms as they perceived that air pollution was implicated. However, it is unlikely that

overreporting could have been wholly responsible for the increased prevalence of symptoms in this area, and the results are plausible.

These local data report prevalences that are much higher than the national prevalence and may reflect the susceptibility of the lung to insults from the noxious effects of local air pollution. Although the study collected data on respiratory symptoms in adults, no mention is made of COPD. However, smoking was associated with both wheeze (OR 2.9; 95% CI 1.5 – 4.9) and shortness of breath with wheeze (OR 2.6; 95% CI: 1.4 – 4.8). The authors suggested that these results were consistent with other studies showing that ETS exposure is associated with asthma and wheeze. It is possible that some symptoms in older adults were related to active smoking, either alone or in association with air pollution. As a cross sectional study it had limitations in ascribing causality to the local air pollution, but certainly emphasised the role of industrial air pollution as a potent risk factor for the increased prevalence of respiratory symptoms.

Attributable fractions

Population studies may be used to estimate population attributable fractions, i.e. the proportion of the disease occurring in the population that is attributable to specified risk factors, on the assumption that the association is causal and that all causes have been identified and measured. This measure provides a broad perspective of the relative contributions of different putative factors. For example, in the analysis by Ehrlich (2004) of the contributions of past tuberculosis and occupational exposures on the prevalence of chronic bronchitis in South Africa⁵⁶ (see Table 8), the combined burden of past tuberculosis and occupational exposure in men was found to equal that of smoking. In women the combined burden of past tuberculosis and domestic fuel exposure appeared to exceed that of smoking.⁵⁶

Table 8: Population attributable fractions for modifiable risk factors for chronic bronchitis in South Africa⁵⁶

	Men (N=5 671)			Women (N=7 929)		
	P	POR	PAF	P	POR	PAF
Past tuberculosis	2.9	4.9	10	2.0	6.6	10
Occupational exposure	26.8	1.6	14	-	-	-
Smoky domestic fuel	-	-	-	33.8	1.5	14
Current smoking, 1-14/day	30.6	1.5	13	8.7	2.3	10
Current smoking, 15+/day	8.7	2.5	12	1.9	1.8	1

P: Population prevalence of exposure; POR: prevalence odds ratio; PAF: population attributable fraction (rounded)

3.5. Review of Asthma Prevalence Studies

Adult asthma has not received the same level of attention as childhood asthma in South Africa, and very few studies have been performed. The three surveys described above also reported on asthma (Tables 7 and 9). The SADHS reported a prevalence of wheeze of 11.7% in men and 14.5% in women aged 20 - 44 years compared to 2.7 and 3.1% for asthma diagnosis.⁵⁷ These figures are slightly lower than those reported for Europe in the ECRHS study, but underdiagnosis is likely. In the SADHS, a lower attained educational level was identified as a risk factor for wheeze.

Overall, in adults, wheeze was associated with age older than 44 years, indicating the non-specific nature and poor performance of wheeze in distinguishing between asthma and COPD. Three outcomes - wheeze, self-reported asthma diagnosis and chronic bronchitis - resulted in a similar risk factor profile comprising tuberculosis, tobacco smoking and occupational exposures, supporting the concept that these outcomes are non-specific. At a population level, unfamiliarity with terms like COPD, and lack of awareness of the disease, contribute to poor recognition of COPD in questionnaire-based studies in South Africa. A similar problem has been observed in other countries where community studies have shown that tobacco smoking was a stronger predictor than atopy for non-specific AHR in persons over 40 years highlighting the difficulty in adult surveys.¹²

Table 9: Prevalence of self-reported asthma and wheezing in adult populations in South Africa¹

Study (yr published)	Population, (N, age range)	Outcome measure	Prevalence %	
			Male	Female
Wicht ⁷ (1977)	Northern Suburbs, Cape Town (507, 20-80 yr)	- Self-reported asthma	7.7	11.9
		- Ever wheeze with shortness of breath	9.6	8.9
Nriagu ⁶ (1999)	South-Central Durban* (693, ≥17 yrs)	- Shortness of breath with wheeze past 12 months		28
		- Chest tightness		42
		- Wheezy chest ever		40
		- Asthma ever		12
Ehrlich ⁵⁷ (2005)	National sample (13 826, > 14 yr)	- Wheeze past 12 months	14.4	17.6
		- Asthma ever	3.7	3.8

* Residential areas in close proximity to petrochemical refineries and other industry

Asthma in children was addressed in the ISAAC (International Study of Asthma and Allergy in Children) which reported a questionnaire based prevalence of 16% for wheeze in the past 12 months and 13.3% for “asthma ever” in Cape Town (13-14 year olds).¹³ A higher prevalence of symptoms of asthma was associated with higher socioeconomic status, but poorer children had greater severity and frequency of symptoms.¹⁴ Low socioeconomic status was also strongly associated with asthma mortality and intensive care admission.^{1 13} This socioeconomic difference is probably an indicator of inadequate access to healthcare services and environmental exposures that aggravate asthma such as fungi in homes, ETS exposure etc.

Although there has been a decline in childhood asthma mortality overall in South Africa, the incidence of ventilation and ICU admissions remains unchanged.¹⁵ A socioeconomic divide is evident however, in that, in Cape Town, while asthma mortality in whites has halved over two decades, mortality in coloureds is unchanged.¹⁶

De Klerk et al have examined risk factors for near fatal asthma in adults presenting to a tertiary hospital in Cape Town and found no difference in access to care or medication when compared to controls with acute asthma from the same facility.¹⁷ However, the choice of controls in this study may have influenced the result. In a

population where there is little variation in access to care and medication, one would expect to find the full spectrum of asthma severity. The controls may simply have had milder disease. In this study, the asthma cases had a lower mean beta agonist use in the 24 hours preceding admission possibly suggesting inadequate patient education or impaired perception of the severity of symptoms. An association between near fatal asthma and previous tuberculosis was also found suggesting a previously undocumented role for tuberculosis in severe asthma. Tuberculosis was also shown to be an independent risk factor for both doctor-diagnosed asthma and wheezing at the national level.⁵⁷

Efforts to improve the quality of care offered to patients with asthma and other common respiratory disease at a primary care level has been addressed by the PALSA (Practical Approach to Lung Health in South Africa) initiative. This programme was first developed and tested in the Free State province and involved the development of a syndromic, integrated guideline for the diagnosis and care of patients with priority respiratory diseases including asthma and COPD. It comprised an educational outreach programme to enable nurse practitioners to use the guideline to manage these diseases, and an evaluative component that examined its utility in the field.¹⁸ The guideline was validated by comparing the nurse diagnosis and treatment to specialist diagnosis and treatment, confirming its performance.¹⁸ A second study, a pragmatic randomised controlled trial in 40 rural primary care clinics in the Free State province, examined its impact in changing clinical practice and certain process outcomes. Favourable outcomes included increased prescription of inhaled corticosteroids in the intervention group (OR 1.9; 95%CI 1.14 – 3.18) and more appropriate referrals of patients with lung disease to the next level of care.¹⁹

3.6. Management of COPD in South Africa

3.6.1. Guidelines for COPD management

The most recent South African consensus guidelines for the management of COPD were published in 2004.²⁰ These are similar to the GOLD guidelines but modifications relate chiefly to cost compromises required to make them relevant for the public health sector in South Africa. In addition, the South African guidelines acknowledge the impact of domestic and occupational exposures and previous lung infections, such as tuberculosis, in addition to tobacco consumption as risk factors for COPD. Major themes are smoking cessation strategies, the need to prevent exacerbations and improve quality of life of patients with COPD, the place of long-acting beta₂

agonists and long-acting anticholinergic drugs in achieving sustained bronchodilatation, and emerging evidence for a limited role for inhaled corticosteroids in the treatment of COPD.

3.6.2. Health Services and Essential Drug List Provision

The South African state-run health system is responsible for healthcare of the majority of the population. Twenty eight percent of all persons attending emergency care facilities at a local community health centre in Cape Town presented with cough and difficulty breathing.²¹ We can suggest from this estimate that respiratory disease accounts for significant use of public sector health resources in this setting.

The Standard Treatment guidelines and Essential Drug Lists (EDL) for South Africa firstly advise smoking cessation, “chest physiotherapy during infective episodes” and pulmonary rehabilitation.²² Inhaled ipratropium bromide and oral prednisone are suggested for management of chronic bronchitis/COPD, with addition of oral theophylline if the former two have “failed in exacerbations”, (a rather odd reversal of prednisone and theophylline).²² Inhaled steroids are suggested if reversibility of 15% and more than 200ml improvement in FEV₁ is present on lung function testing.

However, the delivery of these measures may be limited owing to a lack of trained staff and facilities, accompanied by a lack of awareness of guidelines or inability to deliver appropriate care. The National Primary Health Care Facilities Survey of 2003 found that there were both shortages and an inequitable distribution of healthcare personnel across provinces; community based service providers were few; equipment was seldom found in sufficient quantity and there was a lack of infrastructure and problems with crime at many facilities.²³ Less than 10% of the facilities had the full complement of the 25 drugs on the essential drug list in stock.²³ Steyn et al reported that 24.3% of all men who use prescription drugs in South Africa were taking them for asthma or chronic bronchitis and that blacks used drugs less frequently than any other ethnic group, suggesting inequitable use.²⁴

Recommendations from the SADHS suggested that there is a need to increase awareness of the South African guidelines for the management of COPD, by active professional development approaches aimed at smoking cessation advice, and training of primary care practitioners in the clinical evaluation of COPD, as well as the provision of equipment such as peak flow meters.⁸ Spirometry is not available at

primary care level, making confirmation of the diagnosis of COPD impossible without referral to a tertiary level hospital.

Early diagnosis and treatment of COPD is essential for effective management of patients and in order to reduce healthcare utilisation and thereby costs to the healthcare system. Smith et al (2001) performed a systematic review and found that patients with moderate COPD may gain from a nursing outreach programme in terms of decreased mortality and increased quality of life, but not those with severe disease, who have no reduction in hospital admissions.²⁵ In the South African context, it is suspected that most mild to moderate COPD is underrecognised and undertreated. Symptoms only occur when approximately 40% of lung function has been lost and people are likely to present late owing to this fact, and also as result of widespread lack of awareness and access to healthcare.

Smoking cessation is the most effective way of halting the progression of COPD in smokers. However, many smokers are unaware of effective cessation methods or underestimate the benefit thereof. The perception of smokers regarding their belief in the effectiveness of cessation methods is critical to their success. A Canadian study by Hammond et al (2004) found that participants who perceived cessation methods to be effective at baseline, were almost twice as likely to intend to quit, make a quit attempt at follow-up, and just under 4 times as more likely to use cessation assistance, e.g. nicotine patches, bupropion etc.²⁶ This has a bearing on the South African situation in that there are no formal group counselling or quit programmes and counselling by health professionals is limited. Faced with heavy patient loads, little time and limited support from other categories of health personnel in public sector clinics and hospitals, the importance of smoking cessation counselling is forgotten. Nicotine replacement therapy and bupropion are not available on the EDL, and healthcare practitioners receive little training on smoking cessation counselling. The PALSA initiative addresses advice and counselling for smoking cessation in its integrated guideline.¹⁹

3.6.3. Diagnosing COPD and the status of spirometry in South Africa

Spirometry is essential in the diagnosis and management of respiratory disease. An investigation into the quality of spirometry in South Africa performed in 1991 found very poor quality spirometry practice among 45 medical practitioners, including 26 physicians.²⁷ Knowledge of international spirometry standards, methods of measurement in different spirometers and methods of calibration ranged from poor to

completely unsatisfactory in most practices, as was the standard of test quality assessment and interpretation of results. Quality control is a key issue in spirometry since it is influenced not only by the properties of the instrument, but by patient and operator issues and a good understanding between them. There are no recent published data on the proportion of routine spirometry performed outside of specialist or research centres that meet these quality criteria.

Attempts to improve the standard of spirometry in South Africa is a long-standing issue and a number of guidelines on the subject have been published, applicable either to the occupational health arena, where routine spirometry is common, or for primary care.^{28 29 30} Spirometry is almost unheard of in the public primary health care system and is very rare in the private practices.

Recent improvements in technology may have come some way to improving the prospect of quality spirometry in primary care. The development of small accurate hand-held spirometers such as the ndd easyone® may make them suitable for the office/clinic setting in selected circumstances. With proper training, such devices could be useful in the diagnosis and management of COPD (and asthma) in South Africa as they are easy to use, do not require temperature and pressure controlled circumstances, have a reduced risk of cross infection and are easy to maintain (no closed systems with tubing etc). However, use of spirometry in primary care settings elsewhere has provided good evidence that it may not be practical or useful in resource-limited settings, owing to the cost of equipment, lack of access, and the time required to perform pre and postbronchodilator testing, as well as lack of familiarity with the tests.^{31 32} Moreover, the need for well-trained technologists and physicians³¹ is imperative if spirometry is to be helpful, without which it can even be a hindrance to syndromic management if not properly performed or interpreted. Identification of high risk persons by means of a questionnaire, in order to facilitate appropriate referral, may be more feasible in the primary care setting.³³

Application of appropriate predicted values for spirometry is essential to the identification of abnormal values and, in the context of COPD, for detecting those patients with early disease, so that secondary prevention can be offered. These need to be applicable to, and preferably derived from surveys performed in the community under study, because predicted values may differ for different groups. The obvious approach, recommended in most guidelines, of basing predicted values upon ethnicity, has been questioned, since ethnicity in many societies may simply be a

surrogate for socioeconomic status and reveal other exposures that influence lung capacity at the population level.³⁴ This will be considered further in this thesis. Considering its history, this is particularly true in South Africa. Louw and Goldin (1996) studied healthy South African men and published normal values for spirometry.³⁵ They supported the hypothesis that the ethnic differences in lung function measurements were not the result of genetic differences but, in common with other anthropometric parameters, these resulted from socio-economic deprivation.³⁶ Ethnicity/"race" were hypothesised not to be a direct predictor of lung size. The effects of the latter could be mediated by intrauterine conditions, poor nutrition and recurrent infections, all associated with low socioeconomic status. They found that "sitting height was a better anthropometric predictor of spirometry than standing height" and suggested that sitting height and socioeconomic status indicators should be included in regression equations.

There are few community-based surveys of lung function from which population-wide prediction equations can be derived. Most, like those by Hznido (2000) and Mokoetle (1994), have been performed in industry.^{37 38} Such surveys have significant limitations: they are usually confined to males in the working adult age-groups, and a healthy worker effect applies in many, especially in occupations like mining that involve manual labour. In 1994, White et al reviewed spirometric values reported in 29 studies of healthy African adults and pointed out that most variation is attributable to differences in population selection, altitude (elevation above sea level) of the test site, the date of the study (older studies may not represent current anthropomorphic features of modern populations), and other biological sources of variation, like subject height. These factors are important when evaluating inter- and intra-population comparisons of spirometric measurements.³⁹

The use of correction factors for different ethnic groups in South Africa is debatable, and may have more relevance in the individual clinical situations when trying to decide on the presence of lung pathology for treatment purposes. However, in the epidemiological context of population studies, their use is difficult to justify. The main objection to their use is that they may mask the effects of poverty, which in South Africa is strongly associated with ethnicity. Eliminating the contributions of socioeconomic status from studies assessing ethnic differences is almost impossible in this context.³⁴

3.7. Important risk factors in the South African and the local setting

3.7.1. Tobacco smoking

The prevalence of tobacco smoking in South Africa is high. Tobacco smoking was introduced by settlers in the 17th century and is a popular and socially acceptable habit, particularly in the Western Cape. It was not initially common amongst the indigenous peoples of Africa, and until recently, surveys of miners have confirmed low to moderate tobacco use, and little cigarette smoking.ⁱⁱ Little expendable income, and long shifts underground, where smoking is not permitted, may have served to limit opportunities for acquiring the habit. However, in the industry as a whole, the range of cigarette use varies over a wide range of 10 -75 packyears.⁴⁰ Cowie et al reported an average of 13.7 pack years in a cohort of gold miners who had been mining for an average of 29 years.⁴¹

The population of the Western Cape has had centuries to acquire the habit, which was introduced in the 17th century.ⁱ Until recently, smoking might have been constrained by their relatively low incomes.ⁱⁱ Until 20 years ago, part payment for workers was in the form of a ration of wine known as the “dop” system, a legacy of slave labour on the Cape wine farms. This system was limited in 1928 and outlawed in 1961, but it continued on some farms into the 1990s.⁴² Tobacco often formed part of this “privilege”. Wine, bread and tobacco were the “payment” that created entrenched social behaviour patterns and addiction to alcohol and tobacco.⁴³ Much has been written about the resultant alcoholism, but very little on the origins of the tobacco addiction that is still so prevalent in the Western and Northern Cape regions. Tobacco smoking in these areas is likely to have a large social component to addiction apart from the physiological addiction. Although practiced by both men and women, heavy smoking is not common. However, the improving economic status since democratisation in 1994 carries with it the risk that “light to moderate” smoking habits may be transformed into heavier smoking.

In studies conducted in 1995 and 1996 the South African adult smoking prevalence was 34% and 25% in 1998.^{44 45} The Global Youth Tobacco Survey of 1999 reported

ⁱ "To animate their lessons and to make them really hear the Christian prayers, each slave should be given a small glass of brandy and two inches of tobacco." An excerpt on "educating slave children" from the diary of Jan Van Riebeeck, a Dutch explorer who established the Cape Dutch settlement and introduced winemaking to the Cape. Motta M. South Africa's Children Are Victims of Nation's Alcoholism Culture. Stellenbosch, South Africa 29 December 2005. URL: <http://www.voanews.com/english/archive/2005-12/2005-12-29>

ⁱⁱ Jithoo A, Bateman ED, White NW. Grant proposal to Research for International Tobacco Control (IDRC) June 2004 (unpublished).

that 23% of South African adolescents aged between the ages of 13 and 15 years were current smokers with 28.8% of boys and 17.5% of girls smoking daily.⁴⁶ A repeat of this study in 2002 showed a drop in prevalence to 18.5% overall.⁴⁷ Colouredⁱⁱⁱ boys were more likely to smoke than their African counterparts, and 18% of adolescents smoked their first cigarette before the age of ten.

Smoking prevalence and patterns from the SADHS⁸

Prevalence varies greatly according to gender, ethnic group, education and geographical location and urban or non-urban residence. The SADHS recorded the first ever national prevalence of 24% overall, comprising 42% for men and 11% for women in 1998. Later national estimates from a different source reported a prevalence of 27.1% overall (44% in men and 11.7% in women) in 2000.⁴⁸

With increasing employment and expendable income, coupled with urbanisation and aggressive marketing by cigarette companies, more teenagers and young adults from previously disadvantaged backgrounds have started smoking. The SADHS reported that 75% of persons aged 15-24 years had attempted to stop smoking with a success rate of 14% of males and 39% in females, suggesting that it is difficult to quit (a worldwide phenomenon), and that men have greater difficulty doing so.³

Coloured (57%) and Asian men (54%) were more likely to smoke than African men (40%) or white men (39%), with men from the Western and Northern Cape having the highest rates.ⁱ The Northern and Western Cape had the highest prevalence, and the Northern Province the lowest. Those with the least formal education had the highest smoking rates, and more urban residents had ever used tobacco. Smoking starts early in life (24% of men in the 15-24 age group smoke) with a mean start age of 20 years and most persons smoke manufactured cigarettes. The practice of pipe smoking by middle-aged or older women was more common in some rural areas of South Africa. Older rural African men and women were more likely to smoke pipes than other groups.

ⁱⁱⁱ Ethnic group terminology is reported as used in the original data source.

Table 10: Prevalence of tobacco smoking in South Africa by Province in 1998⁸

	Men (%)	Women (%)
Eastern Cape	46	11
Free State	44	11
Gauteng	42	12
Kwa Zulu Natal	38	5
Limpopo	29	2
Mpumalanga	40	6
Northern Cape	58	31
North West	45	8
Western Cape	49	29
South Africa (Total)	42	11

There has also been an increase in the prevalence of smoking in women over the last few decades. These trends are evident in the wide range of prevalence or reported smoking amongst women in the different provinces. Women in the Western and Northern Cape provinces have a significantly higher prevalence of smoking than in any of the other provinces (see Table 10), and 40% of Coloured women are smokers, four times higher than their Asian counterparts (see Figure 2). Very few African and Asian women smoke, but there is a higher use of smokeless tobacco (snuff) in non-urban African women.⁸

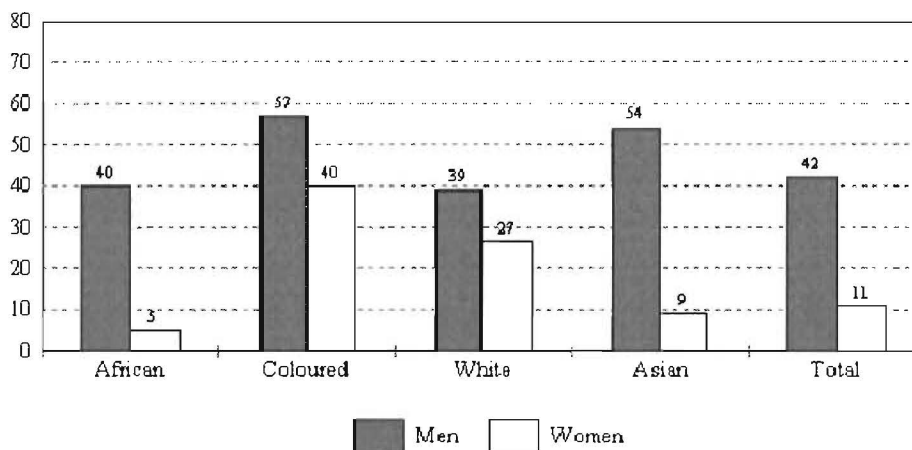


Figure 2: The South African national prevalence of smoking by population group and sex, South Africa, 1998⁸

A gender disparity is also evident in certain provinces such as Kwa Zulu Natal and Mpumalanga. Socio-cultural differences in composition of the population could account for the large gender differences in smoking prevalences (see Figure 2.). The

highest rates of smoking during pregnancy were noted among coloured women.^{8 49} A recent cross sectional study of pregnant coloured women in the Western Cape has found that 46% are smokers.⁴⁹ While the majority of women were aware of some of the dangers of smoking during pregnancy, 56% and 45% were unaware of the risk of premature labour and miscarriage respectively. Many (28%) had no intention of quitting and 20% of those who expressed a desire to quit had never made an attempt to do so.⁴⁹

3.7.2. Cannabis smoking

Cannabis has a long history of use in Cape Town, having been smoked since the 17th century^{iv} and is probably the most widely consumed recreational drug in the world. Cannabis use in South Africa, although illegal, is widespread and its potential harmful effects upon the respiratory system have been little researched or publicised.

Cannabis is the most commonly used illicit drug in South African adolescents, with particularly high rates of usage in Cape Town. A significant proportion of adult patients attending a public hospital trauma unit tested positive for cannabis, suggesting a link between its use and trauma, criminal activity and lawlessness.⁵⁰ Thirty two percent of male and 13% of female adolescents in Cape Town reported lifetime use, with 21.5% of males and 8.6% of females reporting use in the past year, reflecting that it appears to be a predominantly male phenomenon. Seven percent of adolescents reported use in the last year.⁵¹

Between 1990 and 2003, cannabis use doubled. Flischer et al have postulated that this may be due to more vigorous law enforcement in developed economies resulting in the exploitation of the South African market, and increased import across open borders after 1994.⁵² The cost of cannabis in South Africa is very low; only two Rands per 'bank bag'. An association with duration of urban residence has been reported. Rapid urbanisation and its accompanying problems of poverty, crime and housing predisposes to cannabis and other substance abuse.

^{iv} "As the story goes Jan van Hunks, a pirate in the early 18th century, retired from his eventful life at sea to live on the slopes of Devil's Peak. He spent his days sitting on the mountain smoking weed on his pipe. One day a stranger approached and asked to borrow some 'spliff'. After a bit of bragging, a smoking contest ensued which lasted for days. Van Hunks finally defeated the stoned stranger - who unfortunately turned out to be the devil - and they both vanished in a puff of cannabis smoke. Legend has it that the cloud of "tobacco" smoke they left became the "tablecloth" - the famous white cloud that spills over Table Mountain when the south-easter blows in summer." Anonymous. URL:<http://cybercapetown.com/CapeTown/myth.php>.

Cannabis smoked with methaqualone (a non-barbiturate sedative hypnotic) is the second most commonly abused drug in Cape Town and is known as a “white –pipe”, a form of drug abuse that appears to be unique to South Africa. Cannabis alone, or mixed with tobacco and/or methaqualone, is smoked in a makeshift pipe fashioned from a broken bottle neck (see Figure 3.).⁵³ As self-reported usage is likely to be understated owing to the sensitive nature of such questions, it is suspected that true prevalence of cannabis, and particularly methaqualone usage is considerably higher than that reported. There are no South African data on the effect of cannabis smoking on respiratory health in terms of risk of chronic bronchitis or COPD.



Figure 3: “White pipe” method of smoking cannabis in a makeshift “pipe” fashioned from a broken bottle neck⁵³

(With kind permission from H. Donson)

3.7.3. Tuberculosis

Studies of airflow obstruction as a result of past tuberculosis are few and have been reviewed in Chapter 2. Churchyard et al (2001) have shown that symptoms of cough and phlegm are associated with a past TB in South African gold miners, and its prevalence increased with severity of tuberculosis and lung function loss with the number of previous episodes of TB⁵⁴, suggesting greater damage to the airways. The proportion with chronic airflow limitation rose with each further episode.⁵⁵

A history of pulmonary tuberculosis has been shown to be the strongest predictor of both chronic bronchitis and wheeze in the general population in the SADHS.^{56,57} In the first paper on chronic bronchitis, past tuberculosis was associated with a significant odds ratio of 4.9 (95% CI 2.6 – 9.2) in men and 6.6 (95%CI 3.7 – 11.9) in women.⁵⁶ Past TB contributed a substantial population attributable fraction of 10%, even considering the relatively low population prevalence of past TB nationally (2-

3%) in comparison with other factors such as tobacco smoking.⁵⁶ The strength of association of past tuberculosis with chronic bronchitis exceeded that of smoking. This study confirmed the impact of the tuberculosis epidemic on chronic bronchitis at a national population level in South Africa.

The second paper from the SADHS found that a history of tuberculosis was also independently associated with both recent wheeze (OR 3.4; 95% CI 2.5 – 4.7) and asthma diagnosis (OR 2.2; 95% CI 1.5 – 3.2).⁵⁷ Past TB was also strongly associated with wheeze with breathlessness, wheeze without a cold and night waking due to wheeze. The authors suggested that misdiagnosis of post TB airflow limitation as asthma was possible. One does not know whether these persons had reversible airflow limitation or not. Secondly, the prescription of medications that are used to treat asthma could have led to participants reporting a diagnosis of asthma, and thirdly, both the wheeze and asthma question lack specificity to differentiate between asthma and COPD.⁵⁷ Further research into the pathophysiology of post TB airflow obstruction is required.

Some interesting research questions arise from this study regarding the characterisation of post tuberculous lung disease: What percentage has AHR and how should post TB lung disease, with and without AHR, be classified? Does TB cause asthma-like symptoms that are responsive to bronchodilators and steroids? What proportion have COPD and how should they be treated? Additionally, what is the nature or range of pathological lesions in the lungs in these patients? However classified, tuberculosis appears to be an important cause of chronic lung disease in South Africa.

An important observation in the LHS2002, reported by den Boon et al, is that tobacco smoking increased the risk of tuberculous infection as judged by a positive tuberculin reaction. Smokers had almost twice the risk of TB infection compared to never smokers, and those with a history of >15 pack years had the highest risk (OR 1.9, 95% CI 1.28 – 2.81).⁵⁸ The mechanism proposed was the reduction of host defences “favouring the persistence and/or replication of ingested mycobacteria by impairing the macrophage or dendritic cell function”. These results have implications for public health in South Africa. Although TB control is a national priority, prevalence and incidence continues to rise in the Western Cape, and also in other parts of the country where it is associated with a higher prevalence of HIV

3.7.4. Environmental air pollution

3.7.4.1. Indoor air

Combustion of biomass fuel in poorly ventilated dwellings is a recognised cause of chronic bronchitis in rural homes in several countries such as Columbia, Bolivia, Turkey Mexico and Iran.⁵⁹⁻⁶¹ The SADHS reported that in South Africa 32.6% of men and 38.2% of women were exposed to smoky domestic fuel (wood, coal or dung).^{8 62} A very strong association between exposure to smoky domestic fuel and markers of poverty and rural residence was observed. The same survey found an association between chronic bronchitis and smoky domestic fuel, but only amongst women.⁸ In South Africa, exposures in rural African women, the group most exposed to this form of indoor air pollution, are thus a major contributor to the higher prevalence of chronic bronchitis overall in women compared to men, despite lower smoking prevalences.⁶³

In addition to smoking, environmental and occupational exposure to asbestos, dusty occupations (in men) and indoor air pollution (biomass fuels) are also thought to contribute to the prevalence of lung cancer in the Northern Province of South Africa.⁶⁴

However, the situation in this and other parts of South Africa is also changing owing to an ambitious government programme to provide electricity to the majority of households. This programme has resulted in an increase in the proportion of households electrified from 36% in 1994 to about 68% (of 10 million households) at the end of 1999.⁶⁵ The percentage of urban households that had received this service was much higher than those in rural communities (80% versus 46%).

A significant proportion of the population is thus still dependent on highly polluting biomass fuel (wood, grass or dung) and fossil fuels (coal) for their indoor cooking and heating requirements. Rural homes in South Africa have been shown to have a higher level of respirable particulate matter and carbon monoxide than their electrified counterparts.⁶⁶ Even those with currently electrified dwellings may have had significant past exposure. In a survey performed in Cape Town, the use of paraffin was associated with higher levels of carbon monoxide in the home.⁶⁷

3.7.4.2. Outdoor air

In Cape Town, early 18th century legislation included strict fire safety measures, including rules against smoking outdoors, but this was obviously unrelated to air pollution concerns.^v However, air quality monitoring in South Africa is a relatively new phenomenon, unlike in the United Kingdom where it attracted a great deal of public health interest after the London Fog incident in 1952. The location of air sampling sites in the greater Cape Town Metropolitan area is shown in Figure 4.⁶⁹ High PM₁₀ levels have been recorded at informal settlements where biomass fuels are used. Both industry and vehicular emissions contribute to SO₂ (sulphur dioxide) and PM₁₀ (particulate matter size of 10 micrograms) emissions, nitrogen oxides (NO_x) carbon monoxide (CO) and volatile organic compounds. The most evidence exists for the role of SO₂ and PM₁₀ in exacerbating asthma and other chronic respiratory conditions in adults and children.^{vi}

There have been relatively few studies of air pollution in South Africa. The largest was the Vaal Triangle study undertaken in the early 1990s.⁶⁸ In this longitudinal study of children aged 8-12 years living in the northern regions of South Africa, lower respiratory tract illness (“bronchitis, chronic cough and chronic chest illnesses”) were reported in 28.9% of children.

In the City of Cape Town atmospheric concentrations of PM₁₀ particles have risen steadily over the last five years.⁶⁹ For example, levels in July 2005 exceeded the air quality guideline levels on 24 days.⁶⁹ A phenomenon known as the Brown Haze occurs over Cape Town during the less windy months of March to August. As a result of low level temperature inversion (when a layer of cold descending air traps air at the ground level) pollutants, and in particular PM_{2.5} particles from diesel- and petrol-powered vehicles, wood burning and industrial boilers, in addition to a significant organic carbon from an unknown source result in heavy pollution across the Cape flats.⁷⁰

^v Simon “Van der Stel proclaimed building safety regulations for houses, barns and kraals. Other regulations later followed regarding storage of wood, while inhabitants building new homes were encouraged to use tiles instead of thatch, and smoking in the streets were declared punishable by public lashings.” Anonymous. Available at URL: <http://www.capetownfire.com/html/history.html>

The study areas of Ravensmead and Uitsig lie within a zone containing both light and heavy industries (see Goodwood and Belville South in Figure 4) and within the areas subjected to the brown haze described above.⁷⁰

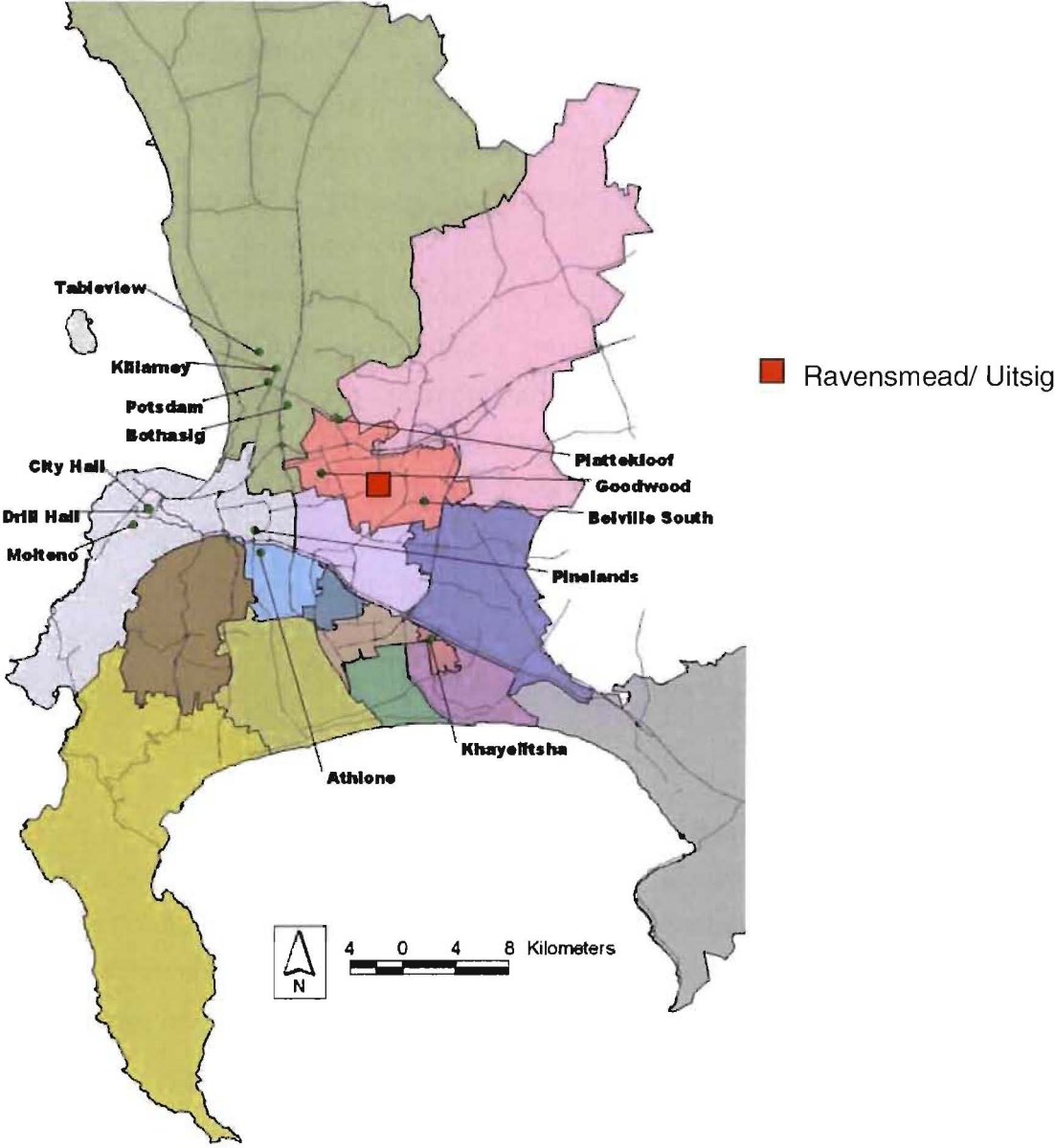


Figure 4: Map of Cape Town showing air pollution monitoring sites⁶⁹

The health effects of local air pollution in residential suburbs close to industrial areas have been investigated in both Durban and Cape Town. In the study by Nriagu et al. (discussed above) very high prevalences of respiratory symptoms were observed in South Central Durban.⁶ However, 12% of adults reported doctor-diagnosed asthma, in keeping with the prevalence in the rest of country, suggesting either under-diagnosis of these conditions or over-reporting of symptoms. Although the focus of

this study was asthma, the results point to the potential of air pollution contributing to the development of COPD. This potential also applies to Ravensmead and Uitsig.

In a second study, White et al also found a high prevalence of respiratory symptoms in children in the northwest suburbs of Cape Town in the vicinity of a petrochemical refinery. Twenty-four percent of children reported current and/or previous asthma, (see Figure 4, Tableview area)^{vi} considerably higher than the 13.3% reported for Cape Town as a whole in the 1995 ISAAC ($p < 0.01$).⁷¹ The prevalence of wheeze in the last 12 months was also double that of the whole city (31.6% vs. 16.0%), and 64.6% reported hayfever. Asthma and wheeze were associated with an estimated petrochemical emission exposure, incorporating wind direction and speed and distance from the refinery, using a meteorological instrument known as a wind-rose. A specific agent could not be identified. Monitored levels of sulphur dioxide in the area were relatively low. However, the study concluded that the petrochemical refinery emissions were a significant risk factor for asthma and asthma exacerbations among children in this area. The effect of these emissions on adults was not assessed and it is plausible that these exposures could be of importance in triggering asthma and COPD exacerbations in adults and may even be of importance in terms of lung function decline. This is a subject for future investigation.

3.7.5. Occupational Exposures

Occupational exposures contribute significantly to the prevalence of respiratory symptoms at the general population level, as described in Chapter 2 and above. The occupational lung diseases that have received the most attention over the past decade have been pneumoconiosis, particularly silicosis in gold miners, and occupational asthma.^{74 92 94 95 97}

Inhalation of silica dust is associated with silicosis, an increased lifetime risk of tuberculosis, COPD and even lung cancer.⁷² Black mineworkers have had the most significant exposure to mineral dusts, but prior to 1994, very few studies have been published^{73 74} and the intermediate and long term effects of occupational exposures in black miners are only now being highlighted. Prior studies were inhibited by large multinational mining companies, and attempts at improving work conditions and providing adequate compensation were suppressed by the apartheid government.⁷⁴

^{vi} White NW, Ehrlich RI, teWaterNaude J, Schutte A, Essack N, Roberts W. A study of allergic diseases and the urban environment in the northern communities of Cape Town South Africa. First Report. November 2003 (unpublished).

Very high prevalences of radiological silicosis of between 22 and 36% (depending on the reader) have been reported in migrant labourers from the Eastern Cape⁷⁵ and Botswana.⁷⁶ In addition both pneumoconiosis and tuberculosis were associated with airflow limitation. Past tuberculosis is a common cause of lung function loss in miners exposed to silica dust, irrespective of the presence of silicosis.⁷⁷ Having been exposed to significant quantity and duration of dust exposure, large fluctuations in temperature, overcrowded and unsatisfactory living conditions in compounds, and poor nutrition are all thought to contribute to the very high risk of contracting tuberculosis among black miners.⁷⁴ The life-long consequences of silica dust exposure are experienced in the progressive nature of silicosis long after ceasing dust exposure.^{75 76}

Churchyard et al (2004) have shown that this risk is present at a mean quartz exposure below the occupational exposure limit of 0.1mg/m³.⁷⁸ Long average duration of work, heavy dust exposure for shorter periods of time and failure to recognise mineral dust as a health hazard have contributed to a rising prevalence of silicosis especially in black mineworkers.^{73, 79} However, Marks (2001) noted that white mineworkers benefited from adequate compensation, paid leave and medical benefits, indicating recognition of the cause by the mining industry.⁷⁴

Dust exposure has been shown to be associated with the development of COPD. In 1990, Hnizdo showed that smoking and silica exposure acted synergistically in increasing the risk of death from COPD in white miners⁸⁰ and subsequently found that the average loss of FEV₁ attributable to the effects of 25 years of gold mining was 236 ml. This compares with a loss of 552ml associated with smoking one packet of cigarettes per day for 30 years.⁸¹ As smoking becomes more common among black mineworkers, the prevalence and severity of COPD can be expected to rise. A recent autopsy study of coal miners found length of service to be associated not only with silicosis and coal workers' pneumoconiosis defined pathologically, but also with emphysema after controlling for smoking.⁸²

The relationship between cor pulmonale and factors such as emphysema and silicosis was investigated in a necropsy based case control study which revealed marked emphysema as the highest risk factor for airflow obstruction (OR 21.32, CI 5.02 – 90.7), followed by extensive silicosis (OR 4.95, CI 2.92 -8.38), which was also responsible for restrictive impairment.⁸³ These results emphasise the high burden

borne by those with occupational exposures in South Africa.⁸³ Smoking was related to all outcomes of bronchitis and emphysema, but assumptions of high smoking rates as the major confounder of the effects of occupational exposure are too simplistic and need to be interrogated further.⁸⁴ Recent studies have supported that smoking and occupational exposures are associated with COPD both additively and independently.⁸⁵

Prior to the HIV pandemic, the incidence of tuberculosis, though high, was showing a decreasing trend. However, over the last decade, the impact of HIV has been very significant, causing a rise in the prevalence of tuberculosis in South Africa. HIV co-infection has led to a fourfold increase in the incidence rate among gold miners, reaching approximately 2000 per 100 000 miners in one group of mines in 2000.⁸⁶

Corbett et al (2000) have examined the effect of HIV infection and silicosis on the incidence of tuberculosis and found that HIV infection increased the incidence of tuberculosis fivefold and that silicosis increased the incidence of tuberculosis threefold.⁷⁸ The combined effect was multiplicative, increasing the incidence of tuberculosis 15 times. In light of this, control of silica exposure must be an urgent priority in all at risk settings. Unfortunately, the large pool of ex-miners with past silica exposure remain at lifelong risk of TB which will serve to perpetuate the epidemic.⁷⁸

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3.7.5.1. Occupational asthma

A Cape Town study of acute asthma cases showed that 12.9% of cases fulfilled the criteria for a diagnosis of occupational asthma (mainly spray painters and domestic workers) and 25.7% reported aggravation of asthma by occupational exposures.⁸⁸ As most cases of occupational asthma are not likely to be reported, the national incidence of 17.5 per million employed persons (based on 324 recorded cases over 2 years from a voluntary register) is understood to be a marked underestimation.⁸⁹

South African studies of occupational asthma report a prevalence of 12% and 9.2% respectively.^{90 91} In four studies by Jeebhay et al performed in the Western Cape Province, asthma attributed to spider mites, fish products and fish parasites, flour, grain and storage pests were reported with prevalences ranging from 3 to 13% of exposed workers.^{92 93 94 95} In addition to the agents mentioned above, isocyanates from products such as spray paints are also implicated. A follow-up study of occupational asthma reported that 16.2% of cases were no longer working and only 55% of workers had submitted claims for compensation.⁹⁶ It is possible that some of

the respiratory symptomatology recorded in the LHS2002 survey might have been due to occupational asthma or COPD caused by occupational exposures.

The last few years have seen an increased focus on the management of occupational lung disease, and guidelines for diagnosis, management and compensation have been published.^{97 98} The South African Department of Labour has recently published compensation guidelines that cover a wide range of conditions warranting compensation, most notably for tuberculosis in silica exposed workers and lung cancer.⁹⁹

3.8. Conclusion

Obstructive lung disease in South Africa is a source of both considerable mortality and decreased quality of life to the individual, and a drain on medical resources of the public sector. Very few studies have attempted to quantify the prevalence of disease and the burden that it imposes in South Africa.

However, the diversity in ethnicity, socioeconomic status and exposures in South African people makes it imperative that studies focus on different contexts and areas, particularly when aetiological relationships are being investigated. Such research is of more than academic interest as a large proportion of these diseases is preventable and measures to curtail exposures to such factors as tobacco smoke, occupational dusts and air pollution can be expected to result in improvements in the health of society.

The study of obstructive lung disease in a community like Ravensmead and Uitsig is useful owing to the fact that this community is exposed to a range of risk factors for lung disease common to large sections of the South African population, and provides the opportunity to examine the effects of these factors in a community setting. The study population, study area and methods used are described in the next chapter.

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CHAPTER 4: METHODS OF THE LUNG HEALTH SURVEY 2002 AND THE BOLD STUDY

4.1. Hypothesis and aim of studies

The LHS 2002 and the BOLD studies were designed to investigate the prevalence of respiratory symptoms of obstructive lung disease and their associated risk factors, and the prevalence and risk factors for COPD respectively. The hypothesis being examined was that the presence of chronic respiratory symptoms (other than those resulting from asthma) and of COPD, is significantly associated with factors other than tobacco smoking e.g. occupational exposures, cannabis smoking, tuberculosis and socioeconomic status.

4.2. Protocol overview

The LHS 2002 was a cross-sectional study involving a 15% random sample of addresses recruiting persons aged ≥ 15 years living at the sampled addresses. Study procedures included the administration of a respiratory questionnaire and height and weight measurements in the participant's homes. Tuberculin skin testing, chest radiography and sputum sampling were also performed for the concurrent tuberculosis prevalence study.

In 2005, the BOLD study sampled the same addresses and recruited persons aged ≥ 40 years to participate in an international multicomponent COPD study. This included the administration of a respiratory questionnaire and performance of pre- and postbronchodilator spirometry, and height and weight measurements in the participant's homes.

4.3. Study area and study population

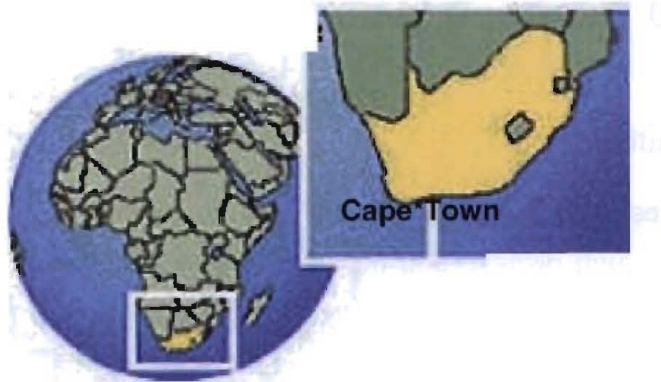


Figure 5: Map of Africa and South Africa showing Cape Town¹

Cape Town is situated at the south western tip of Africa, along the Atlantic coast (see Figure 5). The original indigenous inhabitants of the area were the San and Khoi peoples, and subsequently the Xhosa-speaking Nguni people from the Eastern Cape. It was established by the Dutch East India Company as a halfway-house for sailors on the way to the East in the mid 17th century in order to provide fresh water, food and shore leave. Settlers arrived in the 18th century, and were predominantly from England, Holland, France and Germany. People from Malaysia and Madagascar were also brought to the Cape in the 18th century to serve as slaves in the homesteads of the growing Cape colony.

Climatic factors are thought to influence the epidemiology of respiratory disease. For example, the Cape Peninsula alone constitutes the smallest of the seven floral kingdoms of the earth, yet boasts the greatest botanical diversity. A negative aspect of this fact is the corresponding plethora of pollens with potential for causing allergic sensitisation. The Mediterranean climate is characterised by winter rainfall, which may impact in several ways on the frequency, severity and patterns of transmission of respiratory infections, particularly tuberculosis. Winter rainfall is also favourable for growth of moulds and fungi, both in homes and out of doors, and aspergillus-related sensitisation is common amongst persons presenting with asthma and other allergic diseases.²

Cape Town is known for its natural beauty, making it a popular tourist destination. However, juxtaposed against paradise-like beaches and holiday homes for the wealthy, are a number of low-income areas and informal settlements, carrying a

significant burden of disease, notably lung disease, amongst the other problems associated with urban poverty, such as crime, alcoholism and gang-warfare.

It is in one of these areas that this research was conducted - two adjacent predominantly low-income suburbs of Cape Town, known as Ravensmead and Uitsig, both located in the City of Tygerberg area. These areas are characteristic of other areas in the Western Cape Province.

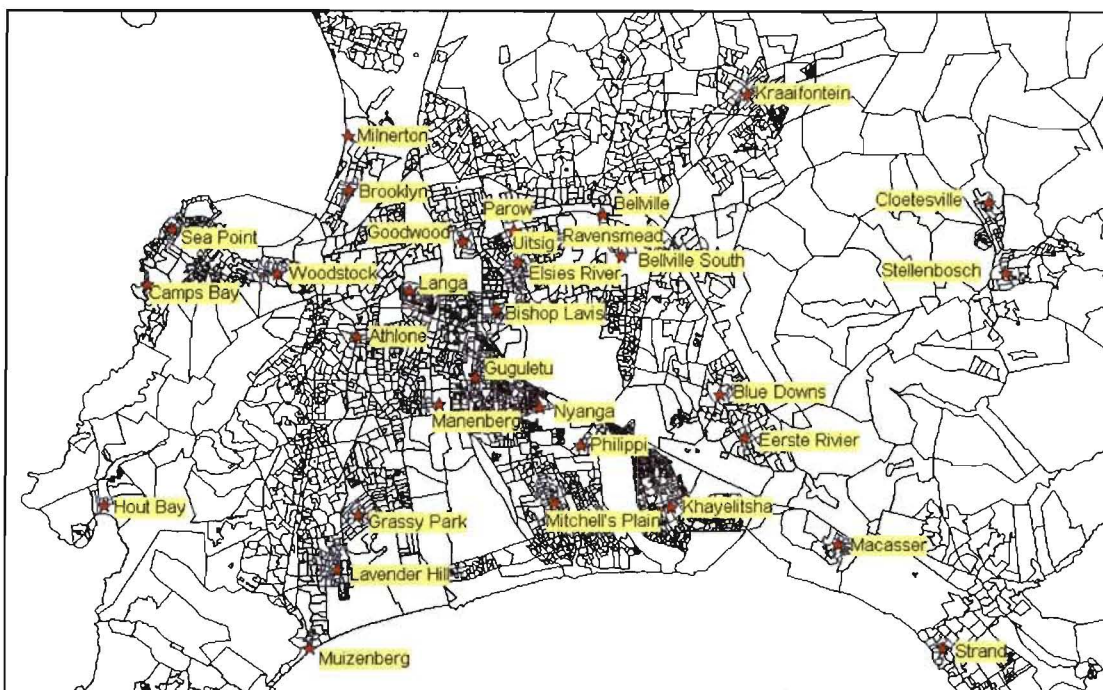


Figure 6: Map of Cape Metropolitan Area (CMA) showing Ravensmead and Uitsig

Being part of an area of Cape Town known as the Cape Flats, a giant sandbar linking the mountain chain of the Cape peninsula to the folded mountains of the Western Cape, these suburbs are sandy with sparse scrub vegetation.³ The Cape Flats was not populated in earlier times because of its cold and windy weather conditions and susceptibility to flooding during the winter. Summers are hot, dry and dusty, and the sandy soil is poorly suited to agriculture.⁴ During the early 1960's the apartheid/segregation policy of the Nationalist government known as the Group Areas Act resulted in forced relocation of persons classified as 'coloured' to newly established suburbs in demarcated areas of the Cape Flats. These were often at the outskirts of the towns that subsequently became part of the CMA. Ravensmead and Uitsig, which lie on the outskirts of Bellville, are two such suburbs covering 3.4 km² (see Figure 6). They form part of 5 densely populated areas of 163,000 persons in eleven square kilometers.⁴

These areas were poorly planned in terms of housing, schools, drainage, roads and facilities such as electricity and water. Most of the property is owned by the council/municipality, and rented to residents, some of whom can often ill-afford the cost. The pressure of poverty and housing shortages has led to significant overcrowding, with an average household size of 7-10 people.⁴ Housing ranges from small informal backyard shacks to modest single storey free standing homes with gardens, and poorer 'flats' or apartment blocks with access to facilities. Often the primary home owners or lessors charge rent for backyard shacks/buildings which are overcrowded with an average of 4.1 rooms.⁴ Thirty six percent of the population lives in these dwellings which are often not connected to water, electricity or sewage facilities, and therefore unsuitable for habitation.^{5 4}

Lower middle-income earners with better homes inhabit parts of Ravensmead. It has some local facilities such as a swimming pool, a community hall and a Community Health Centre (local state clinic).

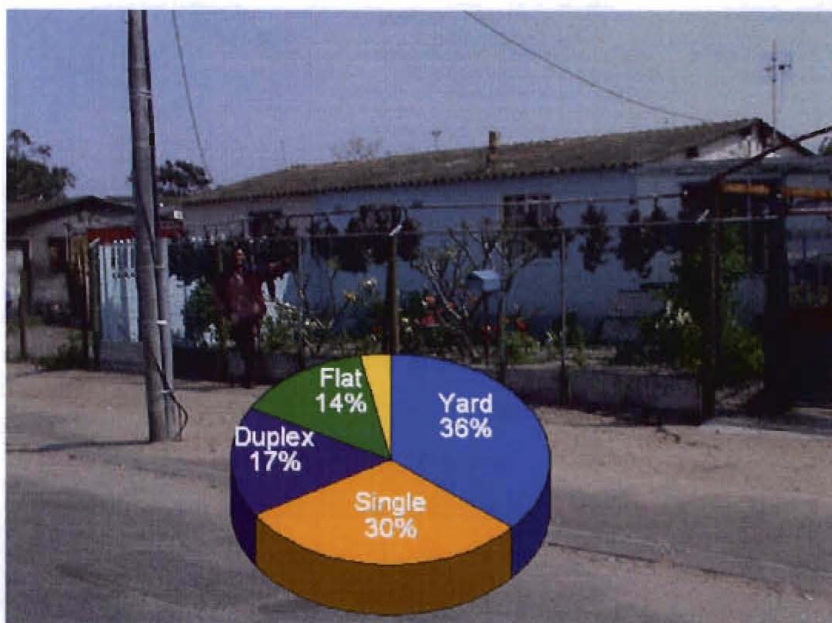


Figure 7 Housing distribution and type in Ravensmead and Uitsig⁵



Figure 8: An example of housing in Uitsig⁵

Uitsig is a predominantly low income area with poor housing. Paradoxically, its name in Afrikaans means panoramic view.



Figure 9: An example of housing in Ravensmead⁵



Figure 10: Local Community Health Centre (State Primary Health Care Clinic) in Ravensmead⁵

In 1996 the total population of South Africa was over forty million, of which an estimated four million people lived within the Western Cape Province.⁶ Of these, 3.5 million lived in urban locations, making the Western Cape Province the second highest urbanised population (89%) in South Africa.⁶ At the time of the study the population of the CMA was 3.1 million. The population distribution in the different local metropolitan council areas in the CMC is shown in Table 11. Approximately 69% of the population are in the cities of Cape Town and Tygerberg. The City of Tygerberg covers 423 square kilometres (19.7% of the CMA) and houses 32.3% of the population of the Cape Metropolitan Council (CMC).⁶

Table 11: Population distribution for the CMA by municipal area 1996⁶

(source: Cape Metropolitan Council: 1997)

Local Authority	% Population	% Total Area
Blaauwberg Municipality	4.6%	25.6% (551 km ²)
City of Cape Town	36.6%	13% (280 km ²)
City of Tygerberg	32.3%	19.7% (423 km ²)
Helderberg Municipality	4.8%	15.2% (328 km ²)
Oostenberg Municipality	9.3%	7.5% (162 km ²)
South Peninsula Municipality	12.3%	18.9% (407 km ²)
Cape Metropolitan Council (total)	100%	100% (2 151 km ²)

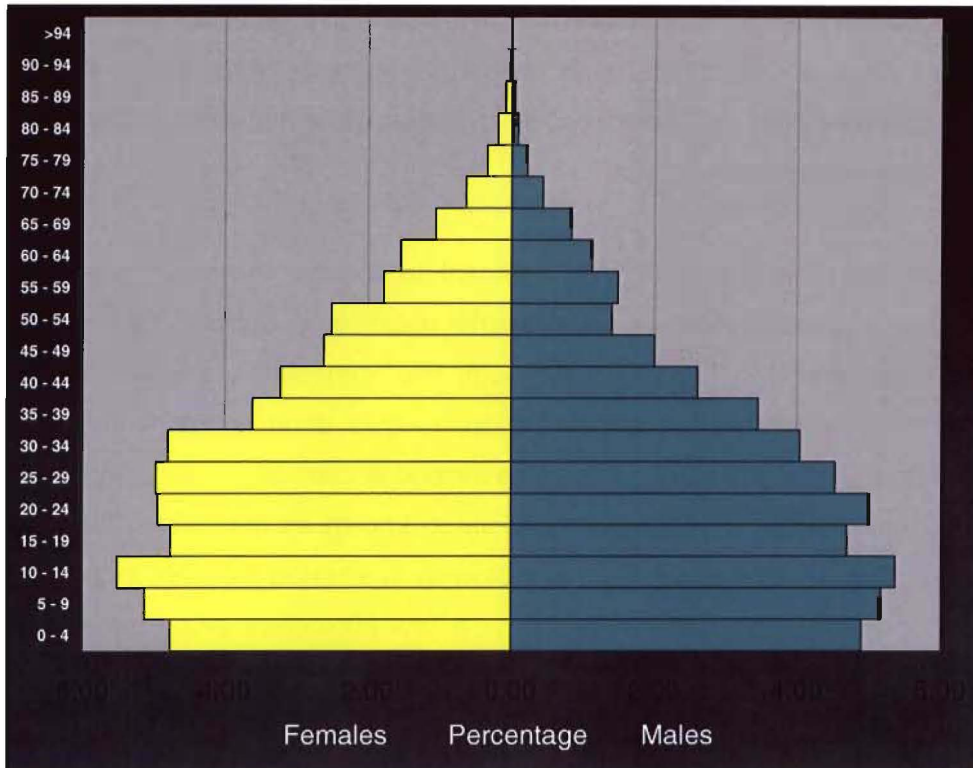


Figure 11: Population pyramid for Ravensmead and Uitsig (1996)

(With kind permission from Professor N Beyers)

The population of the City of Tygerberg is predominantly Afrikaans speaking. Ravensmead and Uitsig are considered to be relatively stable communities with low levels of influx and efflux. Because of the wide ethnic, cultural and geographic diversity in South Africa, no suburb or city in South Africa can be considered to represent the whole country. However, these suburbs represent a section of the population, at least in respect of their health needs and reliance on the state and city health sector for their medical needs.

Similar to other developing countries, the population is relatively young, with forty percent of the residents aged twenty years or younger (see Figure 13). The shape of the population pyramid tapers at the higher age groups, which is typical of a developing country, and unlike Northern American and European countries which have larger numbers in the older age groups.

Local factors with potential effects upon respiratory health

There are multiple local risk factors that are potentially hazardous to respiratory health, and could be associated with obstructive lung disease. These include air pollution, overcrowding, low socioeconomic status, poor nutrition and inadequate access to appropriate medical care.

Ravensmead and Uitsig are situated adjacent to a small industrial area and are within a short distance of two larger industrial areas (see Bellville, Parow, Bellville South and Goodwood in Figure 6). Although two immediately adjacent areas are monitored for ambient air pollution, no monitoring is done in the study area. Air pollution data from the adjacent areas often exceed acceptable levels⁷, and the study areas are also affected by photochemical smog known as the “brown haze effect” described in Chapter 3. A large national motorway is situated adjacent to the suburbs and the Cape Town international airport is a few kilometers away, presumably a source of air pollution, and clearly a source of noise pollution, with ascending and descending airplanes frequently seen flying low over this residential area. In addition, smoking in the home is probably more common as opposed to out of doors.

Environmental factors play an important role in lung health as the lungs are susceptible to atmospheric pollution (both indoor and outdoor), inhaled allergens and microbes of which mycobacterium tuberculosis has the most lasting effect. Indoor air pollution is of less importance in Ravensmead and Uitsig as all homes are electrified, and biomass fuels are only used as a supplementary source for heating and cooking. However, exposures could have occurred previously or in childhood.

Wet winters and overcrowding, caused by a housing shortage due to the Group Areas Act and forced removals, have resulted in the transmission and high prevalence of tuberculosis. Ravensmead and Uitsig are known to have one of the highest incidences of tuberculosis in the world, of 776/100 000.^{xi}

The HIV prevalence in the study areas was 7.9% in 2001, measured by Department of Health and Population Development Seventh National HIV survey of women attending antenatal clinics in South Africa.⁸ As pregnant women are considered a high risk group, the prevalence in the general population and particularly those over the age of 40 years is likely to have been much lower. Only 6% of newly diagnosed

^{xi} Van Lill S. 2003. Sampling document for the Lung Health Survey team (unpublished).

TB cases in the study area were HIV positive.^{xii} The prevalence of HIV infection in the Western Cape was, and remains, the lowest in the country.

Poverty is a strong independent risk factor for COPD (see Chapter 2). The median household income was R2732 (US\$ 546) per month in 1996 with most households falling in the lower end of the range. Although the average family size is five^{xi}, the number of persons living in a single dwelling is greater and sometimes people living in close proximity to one another are unrelated. Unemployment is high with only 36% of the population (≥ 15 years of age) employed in the formal sector. Forty seven percent of the population have an education of less than Grade seven.^{xi}

Medical services are provided by two health clinics. One, in Ravensmead, is a Community Health Centre, which provides primary health care, emergency services and chronic disease services (see Figure 12). The second clinic, in Uitsig, is a small nurse-run clinic with limited facilities catering for TB treatment and childcare services such as immunisation.

Alcohol abuse is a problem in the study areas. The density of informal taverns in the area is seventeen per square kilometre.⁴ Although no figures are available for these two suburbs, the SADHS reported that 33% of men and 30% of women in the Western Cape Province who report current alcohol use are risky drinkers (defined as ≥ 5 drinks per day in men and ≥ 3 drinks per day in women).¹⁰ Additional evidence for alcohol abuse is the high prevalence of Foetal Alcohol Syndrome in the Western Cape. Similarly, a very high proportion of women continue smoking during pregnancy (see Chapter 3).

4.4. The Part 1 Study: The Lung Health Survey 2002

The Lung Health Survey was a cross sectional study of 15% of addresses in Ravensmead and Uitsig. It was performed from July to November 2002. The portion of the survey reported in this thesis involved all non-institutionalised persons aged ≥ 15 years. Only persons not residing at the address at during the study period were excluded.

^{xii} Jithoo A, Bateman ED, van Lill S, Irusen E, Van Schalkwyk E, Beyers N. The Lung Health Survey 2002. Protocol for the UCT Research Ethics Committee. 2002. (unpublished).

4.4.1. Sampling frame and sample size

In 2001, Ravensmead and Uitsig had a population of 36,334 living in 5,592 households. The 1996 South African Population Census districts with enumerator sub-district (ESD) boundaries were used as a sampling frame. A geographical information specialist researched the study areas, and created and refined the sampling frame using a Geographical Information System (GIS). This is a form of mapping which uses aerial photography, computer graphics and databases to combine previously unrelated information in order to create a comprehensive map of the area, assigning each location a specific land-use.⁹ The resultant map detailed flats (apartments), houses and non-residential areas. The non-residential areas included open spaces, sports fields, churches, town halls, community centres, clinics, schools, shops, businesses and parking areas (see Figure 14).

The sampling design was a cross-sectional random cluster survey. The primary sampling unit or cluster was an address. An address was defined as a *Residential Geographical Location*. This could be either a physical street address (name and number) or the name and number of a flat. The reason for choosing an address as a cluster was firstly, administrative ease, and secondly, to fit in with the sampling design required for the aims of other sub-studies in the LHS2002, and particularly the tuberculosis prevalence study, in which household contacts were to be studied. A list of addresses was obtained from the local municipality

The average number of persons per address was calculated by dividing the number of people in an ESD by the number of addresses in that ESD. Of the total number of addresses, 656 (11.73%) were flats (apartments) and the remaining 4,936 (88.27%) were houses (single storey dwellings, some semi-detached). The number of persons per address in flats and houses were very similar, and ranged from 6.63 to 13.83 in flats and 5.5 - 12.9 in houses. The sample comprised 839 addresses which was a 15% simple random sample of all addresses (see Figure 15).

Trained community workers enumerated the occupants in each selected residential address, i.e. a new household census was performed prior to the data collection in order to accurately update the 1996 census information, which had been performed six years prior to the study. A 'dwelling questionnaire', completed for each dwelling at each residential address, collected demographic details of all residents, e.g. age and sex. A dwelling was defined as a place that provided shelter, cooking, washing and sleeping facilities. A household was defined as a house and any associated informal

dwelling or dwellings at the same address or on the same plot of land¹⁰, i.e. all residents at each address.

During the re-enumeration census, consent was sought from persons residing at each address. If the head of the household did not give consent for the household to be included, the address was replaced by a neighbouring address according to a fixed rule. The sampled house was replaced by a house to the right of it, and if that household refused, by the house to the left of the sampled household. This process was continued until a household willing to participate was located. Written informed consent was requested from all participants. The total number of potential participants was 3971 persons.

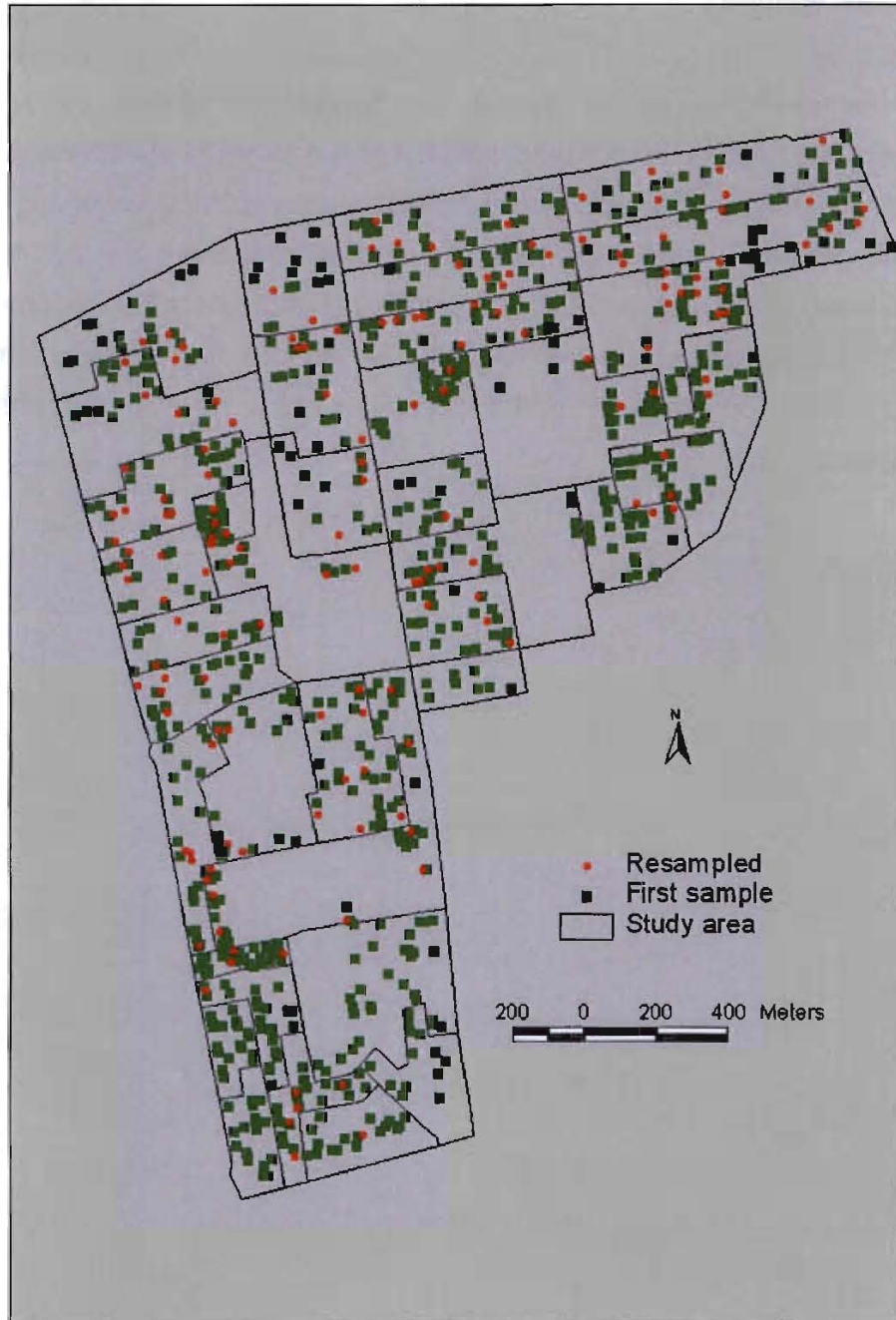


Figure 12: A map of Ravensmead and Uitsig identifying the addresses sampled (squares), and those selected to replace addresses where occupants did not consent to take part in the survey (circles)^{xi}

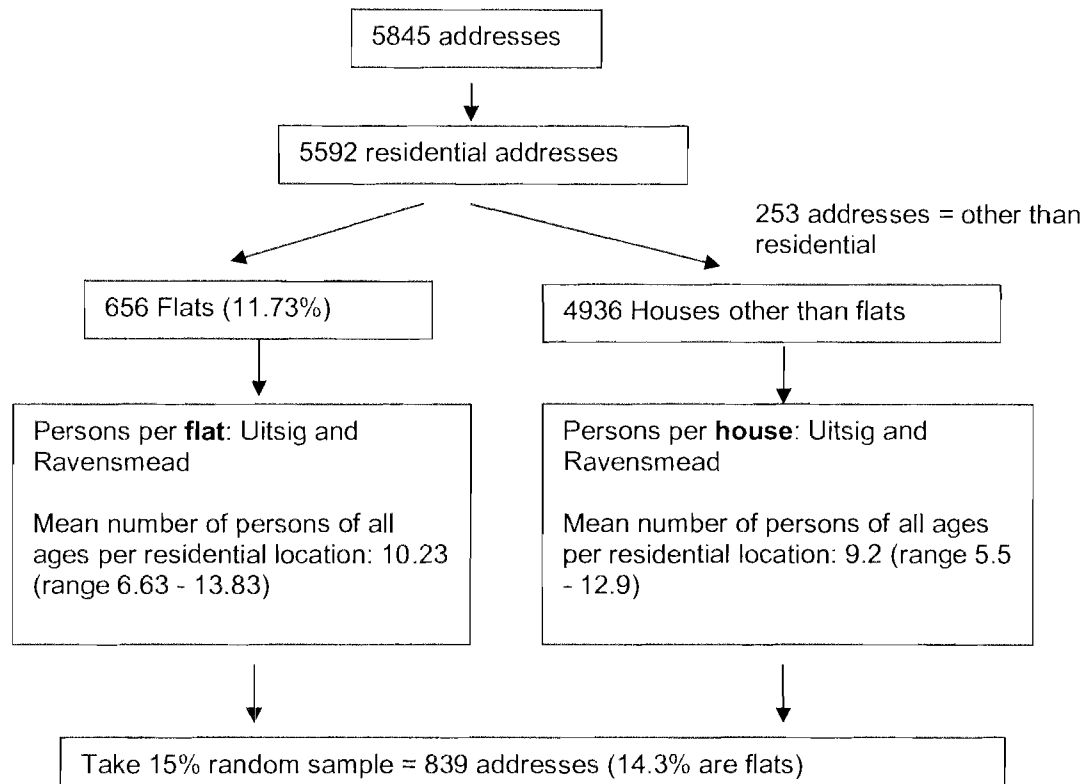


Figure 13: Flow diagram of steps followed to establish the population sample^{xi}

The sample size was based on the requirements for the concurrent tuberculosis prevalence survey. Owing to the relatively low prevalence of tuberculosis (in comparison with the expected prevalence of obstructive lung disease) a larger sample size was required than was necessary for studying respiratory symptoms such as chronic bronchitis. However, for studying the latter, it was assumed that the prevalence of chronic bronchitis would be 10.4% (based on the 1998 SADHS provincial average¹¹) Therefore, a sample size of 3500 would give a 95% confidence interval of 9.4 to 11.4 percent.

4.4.2. Study procedures

Individuals 15 years and older were assessed as follows:

1. Informed consent
2. Adult questionnaire
3. Measurement of height and weight
4. Tuberculin skin test
5. Examination for the presence of a Bacille Calmette-Guérin (BCG) scar
6. Chest radiograph
7. Sputum sample for smear examination for acid-fast bacilli. All smear positive sputum samples were set up for culture on Lowenstein Jensen slants.

4.4.2.1. Ethical considerations and informed consent

Permission to conduct the study was sought and obtained from the Head of the Local Department of Health (Cape Metropolitan Council) and the Provincial Department of Health. The Study was approved by both the Research Ethics Committee of the Health Sciences Faculty at the University of Cape Town and the University of Stellenbosch.

An information sheet accompanied the informed consent document. This described the study, clearly indicated that participation was voluntary and assured confidentiality (see Appendix 1). The interviewers explained this information to potential participants, who were given the opportunity to ask questions. No study procedures were undertaken unless the participants indicated that their questions had been answered to their satisfaction. Written signed informed consent was requested. Minors under the age of 18 years provided verbal assent and were required to obtain written informed consent from a parent or legal guardian, without which participation was not possible. All home interviews were conducted by trained interviewers and height, weight and tuberculin skin testing was conducted by registered nursing staff. Chest radiographs and collection of sputum samples were performed by qualified radiographers and a physiotherapist respectively.

The study results were presented to the community in a meeting convened in August 2003.

4.4.2.2. Lung Health Survey Questionnaire

Development of the questionnaire

A respiratory questionnaire was developed by the author in conjunction with the project team. This was an iterative process, involving multiple revisions, and took approximately ten months during the planning stage of the survey. The final questionnaire included questions from the European Community Respiratory Health Survey (ECRHS) (e.g. wheeze and phlegm questions) and other disease-specific international questionnaires, such as the American Thoracic Society Division of Lung Diseases-78 (ATS-DLD-78) (e.g. dyspnoea questions). Additional questions that had not been validated in other countries, for example, on exposures and symptoms of tuberculosis, were incorporated. Questions relating to demographic information, respiratory symptoms and diagnoses, potential risk factors of interest (including confounders) and healthcare utilisation were compiled into a single questionnaire (see Appendix 2).

The vast majority of inhabitants spoke Afrikaans, a pidgin language with Dutch as its predominant root, with words borrowed from German, Xhosa, Malaysian, French and English. Most persons were bilingual, speaking English as their second language with variable proficiency. The local dialect of Afrikaans differs from other parts of the country in terms of word-use and accent. The questionnaire was thus adapted, piloted and translated into Afrikaans by translators familiar with the local terminology.

Training of interviewers

Training of the fieldworkers was carried out in a three day workshop which covered questionnaire administration as its main component. The study background and objectives were presented and the interviewers were trained in basic questionnaire administration technique. The training involved the discussion of each question and role play of the study visit. This was performed individually and in small group sessions. The author and other team members critically appraised the role play and identified and discussed areas of concern. The need for standardisation without individual interpretation or explanation of questions was emphasized. All interviewers were bilingual and spoke both Afrikaans and English.



Figure 14: Some of the interviewers at the study site

Administration of questionnaires

Trained interviewers administered the questionnaire in a door-to-door household survey, both during and after working hours, to ensure inclusion of the working population. Quality control involved observation of interviewers by the project leaders, and scrutiny of all completed questionnaires for completeness, accuracy and consistency. Approximately 70% of the questionnaires were completed in July and August 2002, which are the winter months in South Africa.

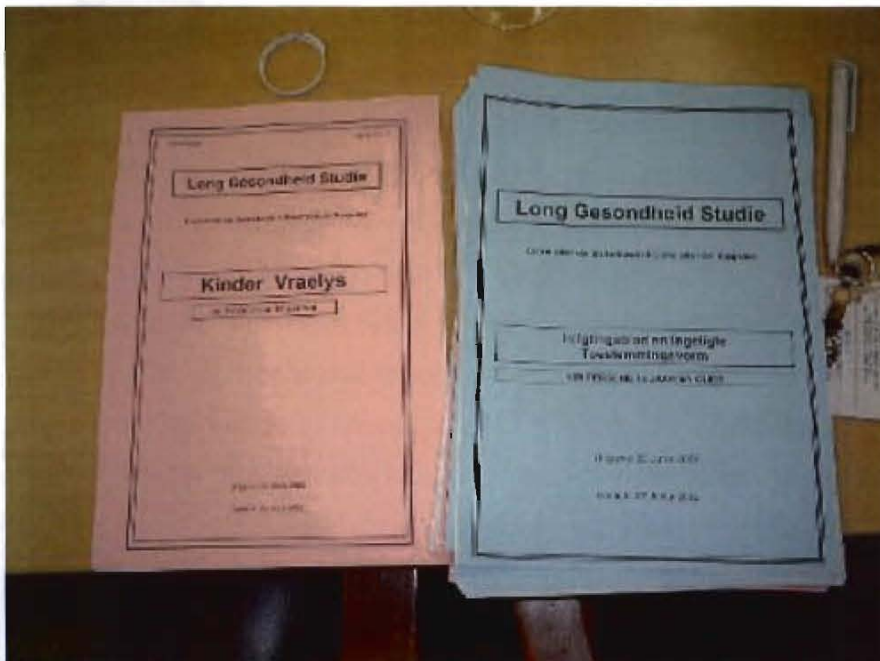


Figure 15: The Adult Lung Health Survey 2002 Questionnaire (right) and the corresponding Children's Questionnaire (left)

4.4.2.3. Height

Height was measured by asking the participant to remove their shoes and stand tall on a level surface, with their head, shoulders, buttocks and heels (together) firmly against a wall. Ensuring that the head was straightened, a headboard was placed firmly on top of the head at right angles to the wall, and a pencil line drawn where the headboard met the wall. The distance from the floor to the line was measured using a tape measure and recorded to the nearest 0.1cm. Nurses were trained to avoid the error of parallax by ensuring that they read the height measurement in the same horizontal plane as the pencil mark.

4.4.2.4. Weight

Participants were asked to remove their shoes and heavy outer clothing and stand on the digital scale which was placed in a firm flat surface. Weight was recorded to the nearest 0.1kg. Calibration of the scales was checked against an object of known weight.

4.4.2.5. Tuberculin Skin Testing and presence of BCG scar

The WHO standard tuberculin test (Mantoux method) employed a single batch of PPD (purified protein derivative) RT 23 (Statens Seruminstitut, Copenhagen). Two TU (0.1 ml RT 23) was injected intradermally in the ventral aspect of the left forearm, by an experienced nurse, and read after a period of 72 hours by the same person. The diameter of the induration in millimetres was measured in the transverse aspect of the left forearm with a set of callipers calibrated to the nearest 0.5mm. The presence or absence of a BCG scar was recorded by an experienced nursing sister.

4.4.2.6. Sputum collection and processing

Adults were asked to expectorate into the sputum jar, close it tightly and place it in a plastic bag provided. This was performed in a room with laminar airflow and ultraviolet light in order to prevent potential spread of organisms. This process was facilitated by a physiotherapist who explained the process of expectoration. Sputum specimens were processed using standardised methods. The macroscopic appearance of the sputum was recorded and sputum smears were stained with the Ziehl Neelsen technique. Each slide was examined for at least 20 minutes. Smear results were reported as +, ++, +++. Specimens were cultured on Lowenstein Jensen slants. At the end of each day, all cool boxes were thoroughly cleaned with hycolin.

4.4.2.7. Chest radiograph

The participants were requested to present for a chest radiograph at a nearby clinic. Transport was provided. In privacy, all females were asked whether they are pregnant, and if so, the chest radiograph was performed with a lead abdominal shield. Anteroposterior chest radiographs were performed by a trained radiographer, using 200 MA radiograph apparatus producing 35cm by 43cm films. The author or an experienced pulmonologist screened the films for serious abnormalities requiring urgent attention and these were referred (by means of a home-delivered referral letter and radiograph) to the Respiratory Clinic at the Tygerberg Hospital or Groote Schuur Hospital (or to their private doctor if the participant wished). There were a total of 40 patients identified for urgent referral and they had a wide range of conditions such as tuberculous pleural effusions, cardiac failure and lung cancer. The radiographs were read by an experienced pulmonologist using a modified version of the International Labour Organisation (ILO) Classification Reading Form. A subsample was reread by another physician in order to assess agreement and evaluate the form as an epidemiological tool.

Sputum sampling, Tuberculin Skin Testing and chest radiographs were performed as part of the component tuberculosis prevalence survey, and detailed results will not be reported in this thesis.

4.4.3. Data capture and statistical analysis

Double data-entry by a data capturer as well as a fax recognition system was used to capture and store the data in order to reduce the element of human error. The fax recognition system was an original prototype internet based-instrument called Prospect, developed by Dr David Carman. This was security controlled by a password system. Prospect involved an interface between the fax and computer, which allowed for the automatic 'reading' of questionnaire responses. The author checked the discordant data entries of the fax recognition system and the hand capture and corrected discrepancies against the original paper documents, which had been scanned into the Prospect system. A Microsoft Access database of the adult questionnaire responses was created. The author then extracted the data from the database by compiling queries in Access and importing the results of these queries into a STATA database. Analysis was performed using the survey estimation commands in the STATA 9.1® statistical package, taking into account both clustering and weighting (see Appendix 8 for the method used for developing analysis weights). The finite population correction factor was set at zero, in keeping with sampling with

replacement, and different sampling weights were applied to the replaced addresses. More details on the statistical analyses are included in the chapters of results that follow.

4.4.4. Safety and Medical Issues: Procedure for referral of subjects

The adult questionnaire contained an “action alert” against the questions referring to recent haemoptysis, untreated respiratory symptoms (such as dyspnoea) and systemic symptoms suggestive of tuberculosis, such as fever and loss of weight. After completion of the questionnaire, the interviewer referred the relevant questionnaire to the co-ordinating doctor (the author), who decided on one of the following courses of action.

Urgent referral was offered to participants who reported recent haemoptysis or who presented with any other obvious medical emergency. They were provided with a referral letter to either, the Respiratory Clinic at Tygerberg Hospital, or to the Respiratory Clinic at Groote Schuur Hospital for further assessment and management. Relevant details of the reason for referral were entered onto the standard referral letter and the patients were contacted and encouraged to attend the clinic on the same day, or within days. Participants could elect (at their own expense) to attend a private doctor, if they preferred. Where necessary, these participants (or other acute medical emergencies) were transported in the study vehicles to the Medical Emergency/ Casualty Department of Tygerberg Hospital for urgent assessment and care. The author also made a few home visits when interviewers were concerned about the illness of a participant. There were no adverse events associated with the conduct of study procedures.

Non urgent referral was offered to participants who reported untreated respiratory or systemic symptoms. The participants were given a referral letter, written by one of the coordinating doctors, usually within a week. Their radiographs were viewed by one of the doctors on the team. The patients were contacted and referred to the Respiratory Clinic at Tygerberg Hospital and further action was advised according to medical indications.

4.5. The Part 2 Study: The Burden of Obstructive Lung Disease Study (BOLD)

4.5.1. Sampling Design

The sampling plan was developed in collaboration with the BOLD sampling consultant. A population-based single-stage cluster sample was originally drawn in 2002 for the Lung Health Survey as described above. The main differences in sampling procedure between the two studies was that the second study sampled only adults aged 40 years or older, and a replacement procedure for households unwilling to participate was not employed. Instead, the original simple random sample of 833 addresses which had been selected for the Lung Health Survey 2002 was employed. The initial intention was to randomly select a subset of 520 of the 833 originally selected addresses and sample all age eligible individuals living at those addresses. However, owing to a lower than expected response rate, during the conduct of the study, the plan had to be adapted such that all 833 addresses were sampled.

For the purposes of BOLD, the original LHS 2002 enumeration lists compiled in 2002 were used as a guide, but these were updated to ensure that all age-eligible persons currently living at the selected addresses were listed and, if possible, recruited. The re-enumeration of the original planned 520 addresses was performed prior to commencing the study and the remaining addresses were enumerated during the study.

The majority (approximately two thirds) of the adults aged 40 years and above, who resided at the sampled addresses, participated in both the LHS 2002 and the BOLD Study. The additional one third of participants in the BOLD study comprised either LHS 2002 nonresponders or new persons residing at the sampled addresses.

The original sampling frame of 5592 addresses, assumed that none of the old addresses had been demolished and that no new addresses had been added in the intervening time between the two studies. As these had been stable residential areas for about 40 years, with very little undeveloped land that could be used to build more houses, this assumption seemed reasonable. Information from local housing services provided a small number of new addresses that had been added since the original survey (34 addresses), and all these houses were added to the sampling list, i.e. the

whole population of this new stratum were sampled. These addresses yielded a total of four eligible individuals, as most of the new houses were inhabited by persons aged below 40 years of age.

Although these new addresses effectively define a second stratum, the small size of this group suggested that formally accounting for them in the analysis would be unlikely to affect the prevalence estimates in any meaningful way. Accordingly, data on the four eligible individuals have been included in analyses, and the sample was treated as a single-stage cluster sample, with sampling weights calculated using the original 833 households as the sampling frame. For the LHS 2002, the addresses from both suburbs were pooled prior to drawing the sample. Thus, in the absence of the added households, this is viewed as a simple one-stage cluster sample from the combined sample of 5,592 addresses with no stratification by suburb (viz. Ravensmead versus Uitsig). See Appendix 9 for details on analysis weights.

4.5.2. Recruitment

Staff visited the initial sample of 520 addresses in order to invite them to participate and to enumerate the household in terms of the persons aged ≥ 40 years. This was done in November 2004 and information in the form of a “study flyer”, a single page introduction to the study, was given to the potential participants. Interviewers answered questions about the study. Where the participants had access to a telephone, their number was requested and recorded, and they were subsequently called in order to make an appointment for the study visit. This was the minority of cases, as many people did not have telephones. The remainder of persons at the 833 addresses were approached by interviewers during the study period, and the same procedure was followed, with provision of information and a study flyer. In many cases appointments were made for the study visit.

During the enumeration, when no-one was home, staff placed a “study flyer” in the post box or under the door if there was no post box. During the fieldwork period of January to June 2005, field staff visited the houses up to a maximum of 5 times on different days, and at different times (e.g. after hours, Saturdays) in order to attempt contact. Staff received varying responses from the potential participants. Those that declined outright and indicated that they would under no circumstances take part in the study were not approached again. Others, for whom the time or circumstances were not favourable at the time of the approach, were visited repeatedly until they either declined or participated.

For most of the study period (January to April 2005), four field teams worked in shifts. Towards the end of the study period two to three field teams were sufficient as participant numbers had reduced and recruitment became more difficult (May to June 2005), and more evening and weekend shifts were required in order to recruit working participants. One field team continued into July 2005 in order to hand-deliver copies of the spirometry results, referral letters and invitations to a study feedback meeting.

4.5.3. Study procedures

Individuals ≥ 40 years of age were assessed as follows:

1. Informed consent
2. Pre and postbronchodilator spirometry
3. BOLD questionnaires
4. Height
5. Weight

4.5.3.1. Ethical considerations

Permission to conduct the BOLD study was obtained from the Provincial Department of Health. Ethical approval was obtained from the UCT Research Ethics Committee of the Faculty of Health Sciences. Pulmonary function testing was performed by trained registered clinical technologists under supervision of a medical practitioner.

Written informed consent in accordance with the guidelines for Good Clinical Practice was taken prior to all study procedures for both studies. Participation was voluntary. Patient information sheets, informed consent forms and procedures as well as all methodologies have been reviewed and approved by the University of Cape Town Research Ethics Committee (see Appendix 3). In order to ensure confidentiality, no names or participant information was shared with anyone outside the project team. Participants were identified by means of a study number and there was no entry of names onto the web-based data transfer system for either questionnaire or spirometry data. Care was taken to explain study procedures during the informed consent process, and interviewers and technologists ensured that queries were answered to the participant's satisfaction. Interviewers were appropriately instructed regarding the sensitive nature of some of the questions.

All participants had their spirometry read by the author, and brief written practical advice regarding smoking cessation, or referral to their local health facility or private doctor, was provided for participants with untreated symptomatic disease. A copy of each participant's lung function with a referral letter, if necessary, was hand delivered to the participant's home (see Appendix 7) and participants were also invited to attend a community meeting to discuss the study results (see Appendix 6).

4.5.3.2. Training and preparation for the field work

Prior to undertaking the protocol, staff were trained and certified in study procedures at a 5-day training workshop in London, England. Two members of the research team, (the author and a clinical technologist) attended a central training session to be trained as "master trainers" and were certified to train additional staff at their sites. The coordinating centre monitored training and ensured that all staff who participated in the study were properly certified.

Initial staff training was performed over a one week period. The author facilitated and performed the questionnaire training and training on all study procedures. Initial spirometry training was performed jointly with a clinical technologist, and continued thereafter by the author. Three days of intensive training were followed by spirometry certification. This training followed the structure of the international standardised training to a large extent, but site-specific details were included. A short workshop was held with an anthropological researcher who has had considerable previous experience in the study area in order to brief the team regarding the sociocultural details of the community. These and other logistical issues were debated and discussed.

Prior to the formal training, BOLD team members were given the questionnaire and the detailed instructions, in order to practice administering it on colleagues and friends to familiarise themselves with the instrument. This allowed for raising awareness of difficulties and questions that would need discussion.

Compared to the central BOLD training, local training included more detailed question and answer sessions. Each question was reviewed and the interviewer instructions were discussed in detail. A pilot study was performed at the end of the training week, and a feedback day including review of training was held thereafter. Further review and training in the form of several mock sessions of different scenarios, followed by constructive criticism by the team and master trainer was

continued intermittently over the next two weeks, while completing the preparations for the study. Team members were made aware of the standards required for questionnaire administration and spirometry. They were encouraged to ask questions/clarifications and discuss their opinions, as well as introduce any new issues at the end of the session.

A strict standardised approach was adopted according to the BOLD protocol regarding questionnaire administration. In particular, the team members were trained never to try to interpret what the respondent meant by a given answer. Unless specific instructions were provided for interpreting responses to a given question, the interviewers were instructed to offer to read the question again, and if applicable, list the response options. Participants were encouraged to make their best guess. The burden of supplying a response was always placed on the participant. In the event of a participant not understanding the question or requesting an explanation, the interviewers were instructed not to try to provide their own explanation of the question, as this could introduce added variability, due to different interpretation of the questions from one interviewer to another. The BOLD central operations centre developed detailed instructions for administering and coding each study questionnaire to standardise how the questionnaire was administered and responses were scored. Attempts were made to conduct the questionnaire in a comfortable, private setting.

4.5.3.3. BOLD Questionnaires (see Appendix 4)

There were a total of seven sub-questionnaires, which focused on different aspects of the study. These were translated and incorporated into one document for ease of administration.

The following questionnaires were administered:

1. BOLD Spirometry /Safety questionnaire: This questionnaire was used to ascertain whether it was safe to attempt spirometry in the participant.
2. BOLD Core Questionnaire: Data on demographics, respiratory symptoms, risk factors and respiratory diagnoses
3. BOLD Occupational Questionnaire: A history of occupational exposure to specific agents
4. BOLD Biomass Fuel Questionnaire: Information on exposure to biomass fuels used for cooking or heating
5. BOLD Stages of Change Questionnaire (for smokers only): attitudes to smoking.

6. BOLD minimal data questionnaire (for non responders only): basic demographic data and smoking status and comorbidity
7. Participant tracking questionnaire (for all eligible persons notwithstanding participation): demographic data and reason for nonresponse, if applicable/available.

The BOLD Core questionnaire was developed by the BOLD international team, using where possible, existing validated questions or parts of questionnaires that have been used in international studies. The scope of the BOLD questionnaires was to gather information about respiratory symptoms (cough, sputum, wheezing, shortness of breath), exposure to potential risk factors, occupation and respiratory diagnoses (asthma, emphysema, COPD, chronic bronchitis, etc.).¹² Additionally, information on co-morbidities, health care utilisation, medication use, activity limitation, and health status was sought.¹²

The questionnaires included sections taken from the 1978 ATS/DLD Respiratory Symptom Questionnaire and the questionnaires used in the European Community Respiratory Health Survey and the US Lung Health Study. It also included the Short Form 12 (SF-12) to assess overall health status.¹² The BOLD questionnaires were translated from English to colloquial Afrikaans by the Stellenbosch University Language Centre following the recommended process of translation, back-translation, review and forward translation in order to ensure high quality and understandability.

All participants were required to complete the BOLD Core questionnaire, Stages of Change, Occupational and Biomass questionnaires. There was also a Minimal Data/Refusal questionnaire for participants who are not willing to participate in the full protocol, which collected basic demographic data and brief information on smoking status and comorbidities. All questionnaires were administered by trained staff. All eligible participants, irrespective of their participation, had a participant tracking form filled out, which collected demographic data and the reason for nonresponse, if available.



Figure 16: Questionnaire administration in a participant's home

In addition to the BOLD questionnaires, respiratory questionnaire items that formed part of the South African Demographic and Health Survey questionnaire of 1998 were included. These were used to assess consistency of questionnaire responses, and evaluate the performance of the questions in relation to the gold standard of pre- and post-bronchodilator spirometry. This component of the study was requested by the South African Medical Research Council under project direction by Dr Krisela Steyn, the Head of the Chronic Diseases of Lifestyle Group. These additional questions were included in a separate short questionnaire and administered after all of the BOLD questionnaires, but utilised the same ID as used on the BOLD questionnaires so that the data from the various questionnaires could be merged for analysis at a later stage. The findings of this validation study will not be reported in this thesis.

4.5.3.4. Measurement of height

The height of each participant was measured using a portable rigid extendable stadiometer which was placed against a wall (see Figure 17). The participant was asked to remove his/her shoes and hat, and height was measured with the subject standing on a firm level surface that was perpendicular to the stadiometer. He/she was instructed to stand erect with the feet flat on the floor, heels together, touching the base of the stadiometer. The back, shoulder blades and buttocks were to be in contact with the wall. The clinical technologist ensured that the participant's weight was evenly distributed on both feet, and arms relaxed at the sides with palms facing

inward. The participant was asked to face straight ahead and the technologist ensured that his/her head was in the horizontal (Frankfort) plane. At the time of the measurement, the participant was asked to inhale deeply and maintain a fully erect position without altering the load on the heels. The head board was brought down snugly, but not tightly, on the top of the participant's head and height was recorded to the nearest 0.1centimeter. Care was taken to avoid the error of parallax by ensuring that the eye of the technologist was at the same level of the head board. Small step stools were used extensively for this purpose, and great care was exercised in measuring height in order to achieve maximal accuracy (as height is a predictor of lung function).



Figure 17: Measurement of standing height

4.5.3.5. Measurement of Body mass

Body mass was measured using a digital scale. The scale was placed in a firm level surface. The participant was asked to remove heavy outer clothing, hats, heavy items in the pockets (such as wallets and keys) and shoes. The technologist ensured that the scale read zero before the measurement. The participant was then asked to stand on the centre of the scale platform, with arms relaxed at the sides and head erect, looking straight ahead. When the digital readout stabilised, the technologist recorded the measurement to the nearest 0.1 kilogram.

4.5.3.6. Spirometry

The methods developed for BOLD are suitable for field studies where temperature and humidity cannot be controlled, as it would be in ideal climate-controlled pulmonary function laboratories. The BOLD methodology requires the use of the ndd EasyOne™ spirometer. This spirometer fulfils requirements with respect to performance criteria relating to reliability of measurement, suitability for field use, and ease of access to data. This spirometer employs new ultrasound technology to assess flow rates and volumes and is not a closed system, which could potentially have created a source of cross-infection. Although the ndd Easyone® does not require calibration, calibration was checked and recorded on a daily basis using a three litre calibration syringe that had been stored next to the spirometer.

A safety questionnaire preceded all study procedures and was administered immediately following the informed consent (see Appendix 4). This questionnaire gathered information regarding the following:

1. Whether the manoeuvre would endanger the health of the participant
2. Whether the administration of a bronchodilator would pose a potential health risk, e.g. myocardial infarction in the last three months
3. Whether there was a temporary condition that would endanger the health of the participant, e.g. recent cataract surgery or major surgical procedure

The participant's resting pulse was also recorded and if >120 beats/min, the test was not performed, the field physician (author) was informed and the patient was referred to the nearest health facility. If there was any contraindication to spirometry, the participant was excluded from participating, and a minimal data and participant tracking form was completed.

A new spirette and spacer was used for each participant. The spirette was discarded and the spacers were sterilised at the end of each day. A cleaning procedure using a bactericidal solution that kills *Mycobacterium tuberculosis* and other microbes was used to sterilise spacers at the end of each day.

During the informed consent procedure, the purpose of the test was explained to the participant. The participant was assured that the procedure does not cause injury or pain. They were informed that in order to get valid results, they would have to blow out as hard and fast as possible, and that they would need to repeat the procedure a few times. The participant was asked if they wished to use the bathroom prior to the test to prevent urinary incontinence during the manoeuvre.

Technologists used a no-rinse hand sterilant to wash their hands and the participant's hands prior to the test. A paper towel was used to remove the mouthpiece (the Spirette™) from its packaging and insert it into the spirometer. The test was performed with the participant sitting in a chair without wheels. Dentures were left in place, unless they were loose, in which case the participant was asked to remove them. All manoeuvres were performed with a noseclip in place. The expiratory manoeuvre was then both explained and vigorously demonstrated to the participant, emphasising the amount of effort needed and correct placement of the mouthpiece. The participant then attempted the first manoeuvre and if this was satisfactory, two subsequent tests were performed.

The ndd easyone provided a useful feedback system in order to ensure good quality of expiratory manoeuvre. The feedback comprised specific messages after each attempt and scoring the quality of the test (A to E), indicating whether the quality of the loop was satisfactory. Feedback messages were easy to communicate to the patient such as “do not hesitate”, “blow harder”, “attempt <6 seconds” etc. In addition, the technologist was able to view the manoeuvre on the spirometer screen. A maximum of eight tests in total were attempted, and the standards required met or exceeded the ATS standards for acceptable equipment technique.



Figure 18: Spirometry being performed in a participant's home

The following measures are recorded from each attempt, and the best of three were saved:

1. Forced Vital Capacity (FVC)
2. Forced Expiratory Volume in one second (FEV_1)
3. The ratio of FEV_1 to FVC (FEV_1/FVC)
4. Forced Expiratory Volume in six seconds (FEV_6)
5. The ratio of FEV_1 to FEV_6 (FEV_1/FEV_6)

Three acceptable manoeuvres were needed to determine reproducibility and a minimum of two reproducible manoeuvres were required. The two highest values for FVC and FEV_1 were taken from acceptable forced expiratory manoeuvres that displayed minimal variability of within 200 millilitres of the second highest FVC and FEV_1 . The volume-time curves were inspected to determine if the size and shapes of the curves were reproducible. The ATS standards for spirometry were followed, which requires FEV_1 and FVC to be the best acceptable and reproducible manoeuvres. It was not necessary that they be taken from the same manoeuvre. The FEV_1/FVC and FEV_1/FEV_6 ratios were calculated as the ratio of the individual measurements.

Spirometry was measured before and after the administration of an inhaled, short-acting bronchodilator. Two puffs (200 micrograms) of Ventolin® (Salbutamol) were administered to participants using a spacer, and a stopwatch was used to ensure that a minimum of fifteen minutes had passed before the postbronchodilator measurements were taken.

4.5.4. Data entry and management

An experienced data capturer based at the South African Medical Research Council entered questionnaire data into a secure web-based data entry system. On a daily basis, questionnaire data were transferred directly to the Operations Centre, using a web-based data entry system. They were sent to a coordinating centre in Portland, Oregon, USA, where the questionnaires were scrutinised for completeness and quality. The data entry system used real-time edit checking, along with double entry of selected fields, to ensure that errors in data entry were minimized.

Spirometry data were downloaded daily and then uploaded onto a secure web-site. The transmission of spirometry records was done through secure, encrypted Internet transfer. Data was transmitted to the server at the coordinating centre using a

standard format (in an Access database), initially daily and later weekly. The use of the same spirometers and software made this both practical and easy. Duplicate data was stored at the University of Cape Town Lung Institute. The centre's data management system generated and provided the field team with periodic reports on the quality and completeness of the dataset. The centre was also provided with aggregate demographic data on the target population such as socio-economic status and air quality data for the geographic area in which the target population resides.

Once data collection was completed and queries resolved, the coordinating centre provided an electronic copy of the data for analyses. A copy of the data was also retained at the coordinating centre for pooled, international cross-site analyses.

The spirometry measurements used for analysis include FVC, FEV₁, FEV₆, peak flow, and total expiratory time. This allows for comparisons of FEV₁/FVC and FEV₁/FEV₆ as measures of airflow limitation.¹² All spirometry data was sent electronically to the BOLD Operations Centre in Portland, Oregon and they forwarded the data to the Pulmonary Function Reading Centre (PFRC), where each manoeuvre was graded and an overall quality score assigned to each participant's spirometry data. The PFRC also reviewed the quality of manoeuvres from each pulmonary function technician in order to monitor the quality of their work, so that corrective action could be taken if this was less than optimal.¹²

4.5.5. Quality Control

The BOLD project employed several measures to ensure a high level of quality control in all aspects of the study. Formal written procedures were available for all aspects of the study, from the selection of the study sample to the questionnaire, lung function testing, and the use of the data management system.

During fieldwork, the author performed periodic quality control visits reviewing each member of the team in the field, and gave them detailed feedback after the visit. Comment was made on interpersonal skills, accuracy of questionnaire administration, spirometry, time management etc. Queries and logistic or other problems were dealt with on an ad hoc basis.

Weekly staff meetings were held to discuss the week's progress, problems and solutions, and to evolve new strategies for recruitment and improved study procedures. Further training was carried out during these meetings, focussing on

identified problem areas and selected parts of the initial training were sometimes repeated in conjunction with discussions.

The ndd EasyOne™ Spirometer met high standards of quality control while still being affordable and suitable for field use. Staff from the PFRC directed the training of master trainers in lung function testing and supervised ongoing quality control monitoring of pulmonary function technicians. Several possible problems preventing acceptable manoeuvres were identified during training such as involuntary epiglottic closure, an early termination of the manoeuvre, variable effort, coughing, and leakage due to the participant's inability to keep a tight seal. More common problems included not taking a deep enough breath, or not exhaling as forcefully as possible at the start of the manoeuvre.

The BOLD operations centre also kept a strict quality control scoring system of each technologist and fed back regularly in order to inform the team of their performance. If a technologist was performing poorly, they were required to be retrained before continuing any further measurements. This mechanism was not necessary during the study, as team members were experienced in performing good spirometry and were able to provide good quality spirometry in the vast majority of cases. Even though this was a population survey with a proportion of elderly and infirm participants, 89% of the spirometry performed was classified as acceptable by the BOLD PFRC.

4.5.6. Data analysis

Data was analysed using the STATA statistical programme, which has commands and analysis techniques specifically designed for survey data, in order to calculate estimated population prevalence from the sample data, accounting for both clustering and weighting (see Appendix 8 and 9). All analyses were performed by the author at times in consultation with a statistician. Descriptive statistics, prevalence and age and sex stratified data are presented with 5% significance values using the chi squared test.

4.5.6.1. Quality control of spirometry

The quality scores for the FEV₁, FVC, and flow measurements were also recorded. According to ATS criteria, measurements that had a quality score of less than 2 (i.e., 0 or 1) were considered inappropriate for analysis, and these measurements were

excluded.^{xiii} The quality of the individual manoeuvres (e.g. effort, proper start, length of expiration, cough and other artefacts, etc.) and the reproducibility of the tracings are combined in the quality scores.

Individual tracings were reviewed for adequacy and unacceptable efforts were excluded. From among the remaining acceptable manoeuvres, the quality scores reflect the level of agreement for FEV₁ and FVC, as described in table 12. The quality control procedures used by the Pulmonary Function Reading Centre were more comprehensive than those recommended by the manufacturers of the ndd spirometer. In a few cases, acceptable ndd quality control scores were considered unacceptable by this stricter review process.

Table 12: Definition of spirometry quality scores for FEV₁ and FVC*

Quality Score	Interpretation
4	3 acceptable tests and variability** less than 76 ml
3	3 acceptable tests and variability** between 76-150 ml
2	3 acceptable tests and variability** between 151-200 ml
1	2 acceptable tests or variability** between 201-250 ml
0	<2 acceptable tests or variability** greater than 250 ml

* Separate QC scores for FEV₁ and FVC

** Difference between two highest FEV₁ or FVC readings

4.5.6.2. Classification of derived spirometry variables

The ndd spirometer retained a maximum of three tests. For each of these three manoeuvres the FEV₁, FEV₃ to FEV₇, FVC, peak expiratory flow (PEF), and FEF₂₅₇₅ was collected. The results from the “best” manoeuvre (i.e. the test resulting in the highest sum of FEV₁ and FVC) were used to define COPD as a postbronchodilator FEV₁/FVC ratio of <70%.

Pre- and post-bronchodilator FEV₁ and FVC are defined as the maximum of the corresponding FEV₁ and FVC values from the acceptable manoeuvres. Thus the FEV₁ and FVC do not necessarily come from the same manoeuvre. Additionally, there is no guarantee that either comes from the “best” manoeuvre (defined as that manoeuvre with the highest sum of FEV₁ and FVC). This is in keeping with the

^{xiii} Gillespie S, Kimes T, Cheek P, Allison M, Vollmer W. South Africa Cover Memorandum for BOLD spirometry data. 4 May 2006 (unpublished).

American Thoracic Society (ATS) guidelines. The following variables were used to classify the population according to GOLD COPD Stages 0-4, and to calculate the reference equations:

1. Pre FEV₁ = Maximum pre FEV₁ if quality score >1
2. Post FEV₁ = Maximum post FEV₁ if quality score >1
3. Pre FVC = Maximum pre FVC if quality score >1
4. Post FVC = Maximum post FVC if quality score >1,
5. Pre FEV₁/FVC = Maximum pre FEV₁/FVC if both pre FEV₁ quality score >1 and pre FVC quality score >1
6. Post FEV₁/FVC = Maximum FEV₁/FVC if both post FEV₁ quality score >1 and post FVC quality score >1

Any quality control score <1 was considered a missing value.

It is important to note that the definitive COPD variable (FEV₁/FVC<70%) is calculated as the ratio of the maximal values, rather than the maximum of the individual ratios.

4.5.6.3. Risk factor analysis

Risk factor variables were coded mainly as binary or categorical or less often, as continuous variables, where appropriate. Results of univariable analysis of risk factors are presented. Multiple logistic regression models were created for binary respiratory symptom outcomes providing odds ratios and 95% confidence intervals. Population attributable fractions are reported for each outcome. For the BOLD study, prevalence statistics are presented by age, sex and pack year categories. Multiple logistic regressions were performed with GOLD Stage I and Stage II as outcomes. Furthermore, a multinomial regression, with three mutually exclusive categories of COPD, was used to compare the risk factor profiles for moderate and severe disease. Further details of statistical analysis are presented in the relevant chapters.

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CHAPTER 5: RESULTS OF THE LUNG HEALTH SURVEY 2002: PREVALENCE OF RESPIRATORY SYMPTOMS, DIAGNOSES, RISK FACTORS AND HEALTHCARE UTILISATION

5.1 Introduction

This chapter presents the results from the Lung Health Survey Questionnaire on prevalence of self-reported respiratory symptoms and symptom-complexes and self-reported doctor diagnoses. Prevalence of risk factors and healthcare utilisation is also reported here. These results describe the study population in terms of symptoms of obstructive lung disease and potential determinants of this disease.

5.2. Statistical methods

Demographic details, symptom prevalence and self-reported disease prevalence of the interviewer administered questionnaire were analysed by age and sex. The initial few tables below describe the demographics of the population and represent the unweighted sample data. Thereafter, both clustering and weighting were taken into account when calculating prevalences. The estimated population prevalences are reported with accompanying standard errors. These were obtained from the 'Survey Analysis' commands in the STATA® statistical package. The primary sampling unit was set as the address identifier (cluster) and the population weight was set as the individual weights calculated by taking both replacement and the response rate into account. This allows for accurate estimation of population statistics (See Appendix 8).

Data are presented for the whole population aged ≥ 15 years, and stratified by sex where relevant. Where tables are stratified by sex, Pearson's chi-squared test is reported to assess whether there is a significant difference in prevalence between men and women. This test is reported in a column to the right of the gender-stratified prevalences, and the overall p value or the p for trend is reported. Where appropriate, analyses in persons ≥ 40 years of age have been performed e.g. prevalence of dyspnoea.

Tobacco smoking is categorised into 'light to moderate' smoking of 1-14 cigarettes per day, and heavy smoking of >15 cigarettes per day. Current cannabis smoking has been categorised into current 1-2 joints per day (moderate) and ≥ 3 joints per

day(heavy) based on the fact that 3-4 joints per day constitutes heavy smoking and is equivalent to 20 or more cigarettes per day.¹ Earlier literature has considered ≥ 2 joints per day as heavy use.²

5.3. Results

At the enumeration visit, 625 out of the 839 addresses (74%) consented to participation via the head of the household/s. Of the 214 non consenting addresses, 212 were replaced and two could not be replaced (see Chapter 4). Four addresses were found not to exist. Demographic characteristics (age and sex) of the occupants of 81 of the non-participating and all the participating addresses were collected. A comparison of the age and sex characteristics of the replaced addresses and the non-consenting addresses showed no significant difference with respect to age (t test = 0.33; p = 0.74) or sex (OR = 1.0; CI: 0.82 – 1.23) of the occupants.^{xiv} The final sample consisted of 833 addresses with 3971 eligible persons aged ≥ 15 years, of which 3512 gave consent and participated in the questionnaire. Age and/or sex data was missing or incorrect for 29 individuals (therefore not analysable on this basis) leaving 3483 (88%) with sufficient data for analysis. Of these 75% (2608) had a chest radiograph and attempted to provide a sputum sample and 45% (1170) produced a sputum sample for the TB prevalence survey.^{xiv}

5.3.1. Population demographics

5.3.1.1. Age and sex distribution

Table 13: Age and sex distribution of study sample ≥ 15 years of age (n = 3483)

		All		Men		Women		p value
		N	%	n	%	n	%	
Age	15-24	969	27.8%	429	28.7%	540	27.1%	<0.002*
	25-34	742	21.3%	321	21.5%	421	21.2%	
	35-44	732	21.0%	346	23.2%	386	19.4%	
	45-54	471	13.5%	191	12.8%	280	14.1%	
	55-64	331	9.5%	126	8.4%	205	10.3%	
	>65	237	6.8%	79	5.3%	158	7.9%	

* Pearson's chi-squared test reporting the significance of the difference between men and women.

The age and gender distribution of the sample is shown in table 13. The sample proportions mirror the population proportions quite closely. There were a higher proportion of female respondents which is in keeping with the population distribution

for the study areas (see Chapter 4, Figure 13). Approximately 70% of the sample was aged between 15 and 44 years, and 27.8% were teenagers and young adults aged 15 to 24 years. This needs to be borne in mind when interpreting population prevalence and symptoms of chronic bronchitis and COPD, which are primarily diseases of older persons.

In addition, small numbers of men in the >65 year age group could be indicative of early male mortality and/or relative longevity of women. The total number of men in the sample was 1493 (42.9%) and of women was 1990 (57.1%) and this distribution was significantly different ($p = 0.002$). The sample was made up almost exclusively of persons of mixed ethnic origins (see Chapter 4). Data on ethnicity were not collected.

5.3.1.2. Socioeconomic factors

Table 14: Sociodemographic characteristics of the study population (n = 3483)

Characteristics	All n (%)	Men % (SE)	Women % (SE)	p*
Income per person per month**				<0.001
>R2000/month	631 (18.4)	26.0 (1.3)	12.8 (0.9)	
R1000-R2000/month	623 (18.2)	19.4 (1.1)	17.3 (0.9)	
<R1000/month	2168 (63.4)	54.6 (1.4)	69.9 (1.1)	
Education				<0.001
>12 years	701 (20.1)	22.8 (1.2)	18.2 (1.0)	
8-12 years	1842 (52.9)	53.4 (1.4)	52.6 (1.2)	
1-7 years	832 (23.9)	21.1 (1.1)	26.0 (1.1)	
None	106 (3.0)	2.8 (0.4)	3.3 (0.4)	
Employment				
Employed	1480 (42.7)	52.5 (1.4)	35.4 (1.1)	<0.001
Unemployed	1983 (57.3)	47.5 (1.4)	64.6 (.1.1)	

* Pearson's chi-squared test reporting the significance of the difference between men and women.

**R1000month~US\$ 98.77 at the time of the study

The majority of the population had attended some level of secondary school, representing between 8 and 12 years of education. Many reported having had tertiary education, but in some cases this was curtailed prior to completing a course, diploma or degree. Unemployment levels were high with 57.3% of persons not earning at the time of the study. Of the unemployed persons, 664 were seeking work (20.1% of men and 18.3 % of women, not shown). The rest were not seeking work for various

reasons including being homemakers, disability, etc. The majority of the community were longstanding residents of the areas and the median number of years resident was 23.7 years.

5.3.2. Symptom prevalences

5.3.2.1. Cough and sputum

Table 15: Prevalence of symptoms of cough, sputum production, haemoptysis and related quality of life (n=3483)

Symptom	All n	All % (SE)	Men % (SE)	Women % (SE)	p*
Recent cough	681	19.5 (0.8)	21.1 (1.2)	18.4 (1.0)	0.041
Haemoptysis in last month	38	1.1 (0.2)	1.6 (0.3)	0.7 (0.2)	0.007
Haemoptysis in last 12 months	55	1.5 (0.2)	2.2 (0.4)	1.1 (0.2)	0.004
Usual winter morning phlegm	880	25.3 (0.9)	29.2 (1.4)	22.3 (1.1)	<0.001
Usual day/night winter phlegm	581	16.7 (0.8)	18.1 (1.1)	15.6 (0.9)	0.056
Phlegm for at least 3 months each year	333	9.6 (0.6)	11.1 (0.9)	8.4 (0.7)	0.007
Phlegm for at least 3 months a year for at least 2 successive years**	252	7.2 (0.5)	8.7 (0.9)	6.1 (0.6)	0.004
Chest problems that affected daily activities in the last 12 months	230	6.6 (0.5)	5.9 (0.7)	7.1 (0.6)	0.148
Chest illnesses with phlegm production	197	5.7 (0.5)	5.1 (0.7)	6.0 (0.6)	0.279
Number of phlegm producing illnesses that lasted a week or more					
1	111	3.1 (0.3)	2.8 (0.4)	3.5 (0.4)	0.5
≥2	76	2.2 (0.3)	2.2 (0.4)	2.2 (0.3)	

* Pearson's chi-squared test reporting the significance of the difference between men and women.

** British Medical Research Council definition of chronic bronchitis

A high proportion of the study population (25.3%) complained of usual winter morning phlegm and recent cough (19.5%). In general, men had more phlegm-producing symptoms than women (all phlegm questions) and 2.2% of men reported haemoptysis in the last 12 months, which was also more prevalent in men than women (p =0.004).

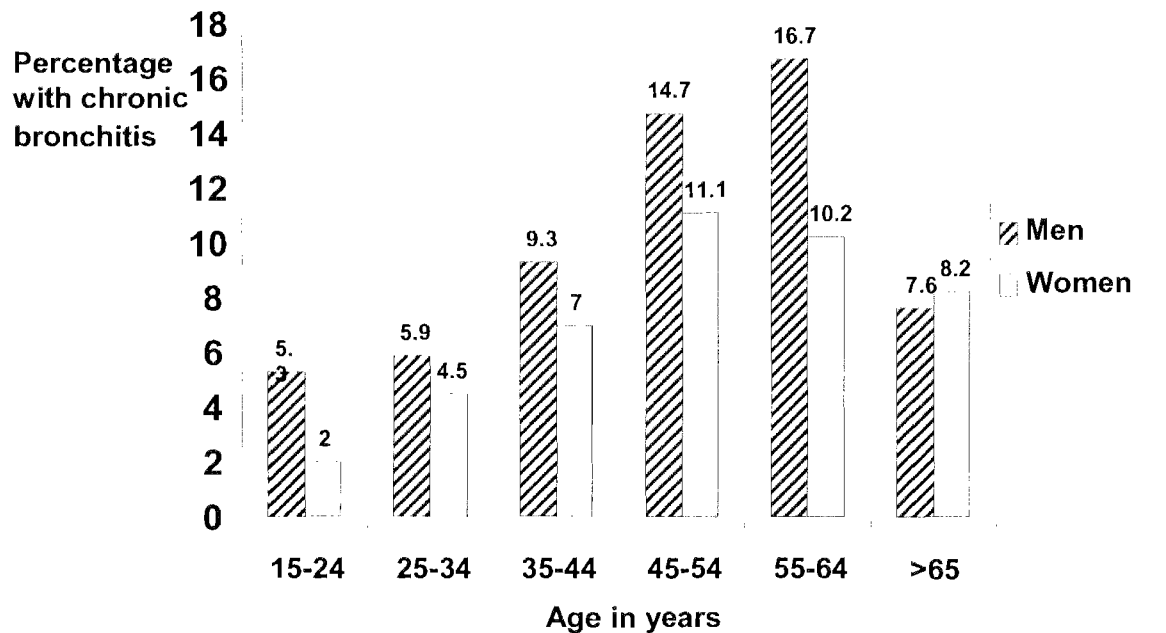


Figure 19: Prevalence of chronic bronchitis (British MRC definition) by age and sex (n=3483)

The British MRC definition of chronic bronchitis was met in 7.4% (6.1% of women and 8.7% of men aged 15 and over). This is defined as cough and phlegm for at least 3 months each year for at least two successive years. The prevalence of chronic bronchitis in persons aged 40 years and older was 12.6% in men and 9.2% in women (not shown). Figure 19 depicts the age and gender related prevalence of chronic bronchitis, Prevalence rose sharply with age up to the age group 55-64, but was consistently higher in men. The subsequent decrease in prevalence in the over 65 age group is most likely a survivor effect or a cohort effect.

Quality of life was affected in 6.6% of the population who reported that they had chest illness that had affected their daily activities in the last 12 months. Phlegm-producing chest illness lasting a week or more was reported by 5.7%, with no gender preponderance. Greater severity, suggested by the presence of two or more such illnesses in the last 12 months that lasted a week or more was reported in 2.2% of persons.

5.3.2.2. Wheeze, breathlessness with wheeze, night waking

Table 16: Prevalence of wheeze and rhinitis (n=3483)

Symptom	All (n)	All % (SE)	Men % (SE)	Women % (SE)	p*
Wheeze in last 12 months	449	12.9 (0.7)	12.4 (1.0)	13.3 (0.8)	0.5
Shortness of breath with wheeze	344	9.9 (0.6)	8.9 (0.8)	10.7 (0.8)	0.087
Wheezing without a 'cold'	282	8.1 (0.5)	8.3 (0.8)	7.9 (0.7)	0.7
Night waking from shortness of breath or tight chest in last 12 months	258	7.4 (0.5)	7.4 (0.8)	7.4 (0.6)	0.9
Ever had problems with sneezing, runny or blocked nose when not having a 'cold'	636	18.3 (0.7)	19.5 (1.1)	17.4 (0.9)	0.1
In last 12 months, ever had problems with sneezing, runny or blocked nose when not having a 'cold'	545	15.7 (0.7)	17.1 (1.1)	14.6 (0.8)	0.042

* Pearson's chi-squared test reporting the significance of the difference between men and women.

The population prevalence of wheeze in the last 12 months was 12.9%, with 9.9% experiencing shortness of breath with wheeze. Wheezing without a cold was noted by 8.1% and night waking with shortness of breath or a tight chest in the last 12 months reported by 7.4%. There were no significant gender differences in the prevalence of any questions concerning the symptom of wheeze.

Ever having symptoms associated with allergic rhinitis were reported by 18.3% of the population and 15.7% had these symptoms in the last 12 months. These symptoms were more prevalent in men ($p=0.042$).

5.3.2.3.Dyspnoea

Table 17: Prevalence of symptoms of breathlessness by age (n=3483)

Symptom	All (≥ 15 yr)		All (≥ 40 yr)	
	n	%	n	%
Any problem with breathing	427	12.3	224	15.9
Breathing problems				
1. Continuously (breathing never normal)	65	1.9	40	2.8
2. Repeatedly (but breathing returns to being completely normal)	227	6.5	118	8.4
3. Occasionally	131	3.8	63	4.5
Shortness of breath on walking fast on the level or light incline (Grade 0)	705	20.2	425	30.2
On the level, walks slower than peers of the same age as a result of shortness of breath (Grade 1)	442	12.7	302	21.5
Stops for breath when walking at own pace on the level (Grade 2)	357	10.3	251	17.9
Stops for breath after 100m on the level (Grade 3)	338	9.7	236	16.8
Too short of breath to leave the house, or on dressing/undressing (Grade 4)	224	6.4	171	12.2
Problem walking as a result of a condition other than heart or lung disease	311	8.9	244	17.4

High prevalences of dyspnoea were reported by persons aged 15 and older. Persons who had problems walking as a result of a condition other than heart or lung disease (such as joint disorders) were excluded from answering questions relating to walking. The prevalence of dyspnoea was higher in the persons aged 40 and older.

Grade two and higher dyspnoea was present in 10.3% of the population aged 15 and above and in 17.9% in persons aged 40 and older. Grade 2 was defined as stopping for breath while walking at one's own pace on level ground. As this level of dyspnoea is associated with a greater likelihood of heart or lung disease, it is used as a threshold symptom level in the analyses in Chapter Six in the assessment of risk factors.

Table 18: Prevalence of dyspnoea by sex in persons aged between 15 and 40 (n=2077)

Symptom	All n	All % (SE)	Men % (SE)	Women % (SE)	p*
Any problem with breathing	203	9.8 (0.7)	10.7 (1.0)	9.1 (0.9)	0.2
Breathing problems					
1. Continuously (breathing never normal)	25	1.2 (0.2)	1.1 (0.3)	1.3 (0.3)	
2. Repeatedly (but breathing returns to being completely normal)	109	5.3 (0.5)	6.1 (0.8)	4.6 (0.6)	0.4
3. Occasionally	68	3.3 (0.4)	3.5 (0.6)	3.1 (0.5)	
Shortness of breath on walking fast on the level or light incline (Grade 0)	280	13.5 (0.8)	11.2 (1.1)	15.3 (1.1)	0.011
On the level, walks slower than peers of the same age as a result of shortness of breath (Grade 1)	140	6.8 (0.6)	5.9 (0.8)	7.4 (0.8)	0.181
Stops for breath when walking at own pace on the level (Grade 2)	106	5.1 (0.6)	4.9 (0.8)	5.3 (0.7)	0.7
Stops for breath after 100m on the level (Grade 3)	102	4.9 (0.6)	4.7 (0.8)	5.1 (0.7)	0.7
Too short of breath to leave the house, or on dressing/undressing (Grade 4)	53	2.6 (0.4)	2.1 (0.5)	2.9 (0.5)	0.2
Problem walking as a result of a condition other than heart or lung disease	67	3.2 (0.4)	3.6 (0.6)	2.9 (0.5)	0.4

* Pearson's chi-squared test reporting the significance of the difference between men and women.

A relatively low prevalence of dyspnoea of any grade was noted in persons aged between 15 and 40 years (see Table 18.) and there appear to be no significant differences in prevalence between men and women. However, the women will be older so this may be irrelevant, but it still relevant in considering the burden on health services.

Table 19: Prevalence of dyspnoea by sex in persons aged ≥ 40 (n=1406)

Symptom	All n	All % (SE)	Men % (SE)	Women % (SE)	p*
Any problem with breathing	224	15.9 (1.0)	15.0 (1.5)	16.5 (1.3)	0.4
Breathing problems					
1. Continuously (breathing never normal)	40	2.8 (0.5)	3.8 (0.9)	2.2 (0.5)	
2. Repeatedly (but breathing returns to being completely normal)	118	8.4 (0.8)	8.2 (1.1)	8.5 (1.0)	0.016
3. Occasionally	63	4.5 (0.6)	2.8 (0.7)	5.7 (0.8)	
Shortness of breath on walking fast on the level or light incline (Grade 0)	425	30.2 (1.3)	26.2 (1.9)	33.0 (1.7)	0.006
On the level, walks slower than peers of the same age as a result of shortness of breath (Grade 1)	302	21.5 (1.2)	19.1 (1.7)	23.2 (1.5)	0.064
Stops for breath when walking at own pace on the level (Grade 2)	251	17.9 (1.1)	17.1 (1.6)	18.4 (1.4)	0.5
Stops for breath after 100m on the level (Grade 3)	236	16.8 (1.1)	15.9 (1.6)	17.4 (1.4)	0.5
Too short of breath to leave the house, or on dressing/undressing (Grade 4)	171	12.1 (0.9)	10.1 (1.3)	13.5 (1.2)	0.054
Problem walking as a result of a condition other than heart or lung disease	244	17.4 (1.1)	17.1 (1.6)	17.6 (1.3)	0.8

* Pearson's chi-squared test reporting the significance of the difference between men and women.

A high prevalence of dyspnoea symptoms (all grades) was noted in persons aged ≥ 40 years. Dyspnoea of grade two and higher occurred in 17.9% of this age group. Dyspnoea was more prevalent in women, but this was not statistically significant at the 5% level and could possibly reflect a reporting bias. Overall, 38.3% of the population reported the presence of at least one respiratory symptom (wheeze, cough/phlegm, or dyspnoea).

5.3.2.4. Symptoms of TB or systemic disease

Many participants reported the presence of a cough of recent onset (19.5%). Haemoptysis, a symptom more likely to be suggestive of tuberculosis in this context, was reported by 1.1% of the community and by 1.5% in the last 12 months. Details of the prevalence of symptoms of cough are presented in Tables 15 and 20.

Table 20: Prevalence of systemic symptoms suggestive of tuberculosis (n=3483)

Symptom	All n	All % (SE)	Men % (SE)	Women % (SE)	p*
Night sweats	319	9.2 (0.6)	12.3 (1.0)	6.8 (0.6)	<0.001
Fever	95	2.7 (0.3)	3.1 (0.5)	2.4 (0.4)	0.18
Weight loss	422	12.1 (0.7)	13.1 (1.0)	11.4 (0.8)	0.13
Recent cough	681	19.5 (0.8)	21.1 (1.2)	18.4 (1.0)	0.04
Haemoptysis in last month	38	1.1 (0.2)	1.6 (0.3)	0.7 (0.2)	0.007
Haemoptysis in last 12 months	55	1.5 (0.2)	2.2 (0.4)	1.1 (0.2)	0.004

* Pearson's chi-squared test reporting the significance of the difference between men and women.

Other non-specific systemic symptoms such as weight loss (12.1%) and night sweats (9.2%) were more common. The prevalence of night sweats was 12% in men and 8% in women (see Table 20.). Fever (current) was less common (2.7%). All symptoms suggestive of tuberculosis were more prevalent in men than women ($p < 0.05$), but the differences in prevalence were not significant for the non-specific symptoms of fever and weight loss ($p = 0.18$ and 0.13 respectively).

5.3.3. Self-reported doctor diagnoses

Table 21 presents participants' responses to the question on whether a doctor or healthcare worker had ever told them that they had any of the following diseases - tuberculosis, asthma, nasal symptoms, chronic bronchitis/emphysema, heart disease, other chest disease or pneumonia.

Table 21: Self-reported doctor-diagnosed chest diseases (n = 3483)

Doctor-diagnosed chest disease	All n	All % (SE)	Men % (SE)	Women % (SE)	p**
Tuberculosis	337	9.7 (0.6)	12.0 (0.9)	8.0 (0.7)	<0.001
Asthma	245	7.0 (0.4)	4.6 (0.5)	8.8 (0.6)	<0.001
'Hayfever'	235	6.7 (0.5)	5.5 (0.6)	7.6 (0.6)	0.011
Chronic bronchitis/emphysema	193	5.5 (0.4)	4.8 (0.6)	6.1 (0.6)	0.1
Heart disease	170	4.9 (0.4)	4.0 (0.5)	5.5 (0.5)	0.04
Other chest disease***	29	0.8 (0.2)	0.7 (0.2)	1.0 (0.2)	0.4
Pneumonia	9	*	*	*	*

* Asterisks indicate that a figure is based on fewer than 25 weighted cases and has been suppressed.

** Pearson's chi-squared test reporting the significance of the difference between men and women.

*** These participants reported a number of non specific answers like "one lung weaker" and other diagnoses - such as pulmonary embolus.

The most commonly self-reported doctor-diagnosed chest disease was tuberculosis (9.7%) which was more common in men than women (12.0% vs. 8.0%), followed by asthma (7.0%), which had a female predominance (8.8% vs. 4.6%). 'Hayfever' was next with a prevalence of 6.7%, women again more affected than men. Despite high levels of symptoms of cough and sputum production, chronic bronchitis was reported by 5.5%, with no gender difference in prevalence. The prevalence of heart disease was 4.9%, with women more likely to have reported the condition than men (4.0% vs. 5.5%). Other chest diseases and pneumonia were uncommon reported diagnoses.

5.3.4. Distribution of risk factors

5.3.4.1. Tobacco smoking

Table 22: Population estimate of tobacco exposure by sex (n=3483)

	All n (n=3483)	All % (SE) (n=3483)	Men % (SE) (n=1493)	Women % (SE) (n=1990)	p*
Never smokers	1475	42.4 (1.0)	32.8 (1.3)	49.6% (1.3)	
Ex smokers	266	7.6 (0.5)	8.0 (0.7)	7.3% (0.6)	
Current smokers (any amount)	1734	49.9 (1.1)	59.1 (1.4)	43.0 (1.3)	
Current 1 – 14 cigarettes per day	1339	38.5 (1.0)	42.9 (1.4)	35.3 (1.2)	
Current ≥15 cigarettes per day	354	10.2 (0.6)	14.1 (1.0)	7.3 (0.7)	<0.001
Pipe smoking only	41	1.2 (0.2)	2.2 (0.4)	0.4 (0.1)	

* Pearson's chi-squared test reporting the significance of the difference between men and women.

More women than men had never smoked (49.6% vs. 32.8%). Half the population (1734 or 49.9%) were current smokers at the time of the study, comprising 59.1% of men and 43.0% of women. Two thirds of men and half of women (67.1 vs. 50.4%) have smoked at least one cigarette a day for at least one year, constituting for this community, amongst the highest recorded prevalences of smoking in the world (far exceeding national and even provincial averages), particularly amongst women. This high prevalence of ever smoking was accompanied by low rates of quitting, reflected in the relatively small percentage (7.6%) of ex- smokers (see Table 22).

The distribution of tobacco exposure in men and women was significantly different ($p < 0.001$). The majority of smokers were light to moderate smokers (1 to 14 cigarettes per day), with slightly higher proportions of women falling into this group (42.9% vs. 35.3%). More men than women smoked more than 14 cigarettes per day (14.1% vs. 7.3%) and men were more likely to have smoked ≥ 20 cigarettes per day than women (see Table 24). It is important to note that even though men and women smokers had similar absolute values as totals, the proportion of men who smoked was much higher as they formed 43% of the population and women 57%. Pipe smoking only was practiced by the minority (41 persons; 1.3%) and very few persons smoked both pipes and cigarettes (5 persons). Pipe smoking was practiced predominantly by men (1.0%) and was very uncommon amongst women in this community.

Table 23: Prevalence of ever smoking tobacco by age and sex (n = 2000)

		All n (n=2000)	All % (SE) (n=2000)	Men % (SE) (n=1001)	Women % (SE) (n=999)	p*
Age	15-24	456	47.1 (1.7)	54.5 (2.6)	41.2 (2.2)	<0.001
	25-34	440	59.4 (2.0)	65.5 (2.8)	54.8 (2.5)	
	35-44	483	66.1 (1.9)	72.9 (2.4)	60.1 (2.6)	
	45-54	317	67.8 (2.3)	81.7 (2.8)	58.2 (3.0)	
	55-64	196	59.3 (2.8)	76.0 (3.9)	49.2 (3.5)	
	>65	107	45.2 (3.4)	68.2 (5.4)	33.7 (3.8)	
	Total	2000	57.6 (1.0)	67.1 (1.3)	50.4 (1.3)	

* Pearson's chi-squared test reporting the significance of the difference between men and women.

The prevalence of ever smoking tobacco was high at all ages in both men and women, with the lowest prevalence found in women aged over 65. The difference in prevalence of ever smoking in men and women was significant ($p < 0.001$). Table 23 shows that 47.1% of persons aged between 15 and 24 years had ever smoked, indicating that many individuals start smoking at an early age.

Percentage of persons

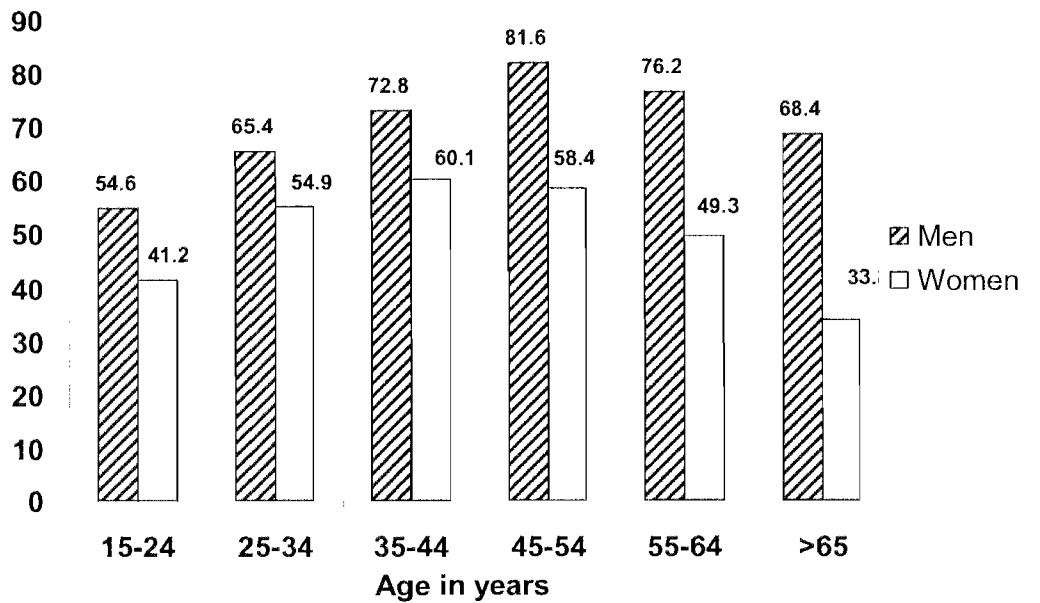


Figure 20: Prevalence of ever smoking tobacco by age and sex (n = 3483)

Table 24: Quantity of tobacco ever by sex (n= 1962)

Cigarettes per day*	All n (n=1962)	All % (SE) (n=1962)	Men % (SE) (n=985)	Women % (SE) (n=977)	p*
1 to 5	794	40.5 (1.3)	33.9 (1.7)	47.1 (1.7)	
6 to 10	678	34.5 (1.2)	35.6 (1.6)	33.5 (1.5)	
11 to 15	153	7.8 (0.6)	9.6 (1.0)	5.9 (0.8)	<0.001
16 to 20	267	13.6 (0.8)	16.6 (1.2)	10.6 (1.1)	
> 20	70	3.4 (0.5)	4.3 (0.7)	2.9 (0.5)	

* Pearson's chi-squared test reporting the significance of the difference between men and women.

Although 2000 persons had ever smoked tobacco at the time of the study, only 1962 persons gave complete data on the number of cigarettes per day. Three quarters of smokers (see Table 24 - 40.5% plus 34.5%) smoked between 1 and 10 cigarettes per day, making light to moderate usage the norm. Men were heavier users than women, with approximately 30% of men smoking more than 10 cigarettes per day. Almost half of women smokers (47.1%) smoked between 1 and 5 cigarettes per day and 80.6% of women smoked ten or less cigarettes per day.

Table 25: Patterns of tobacco smoking (n=2000)

	All: median (25th – 75th centile)	Men: median (25th - 75th centile)	Women: median (25th - 75th centile)
Age started smoking (range = 6-60 years of age)	16 (15 – 19)	16 (15 – 18)	17 (15 – 20)
Age stopped smoking (in ex smokers*)	35 (25 – 46)	35 (27 – 46)	34 (25 – 46)
Number of years smoked	16.3 (7.0 - 27.6)	16.7 (7.3 – 27.8)	15.7 (6.6 – 27.5)
Pack years	5.3 (1.9 – 11.9)	6.3 (2.2 – 13.8)	4.5 (1.7 – 9.9)

* An ex smoker is defined as a person who stopped smoking more than one month ago before the survey date.

A quarter of smokers had already started smoking by age 15 and half of smokers were smoking by age 16, while a further quarter had started by age 19, indicating a young age of onset of tobacco use. The median number of pack years is low at 5.3 and 75% of the population had a smoking history of less than 11.9 pack years. Men had a higher exposure than women (median 6.3 vs. 4.5 pack years). Half of those that did stop smoking did so by age 35. Both men and women had smoked for a similar number of years (median of 16.7 vs. 15.7 years). In the light of the fact that 70 percent of the population is under the age of 45 years, a median of 16.3 years of smoking is high.

5.3.4.2. Cannabis smoking

Table 26: Population estimate of cannabis exposure by sex (n=3483)

	All n (n=3483)	All % (SE) (n=3483)	Men % (SE) (n=1493)	Women % (SE) (n=1990)	p*
Never smokers	3088	88.7 (0.6)	77.0 (1.2)	97.5 (0.4)	
Ex smokers	173	5.0 (0.4)	9.8 (0.8)	1.4 (0.3)	
Current smokers (any amount)	222	6.4 (0.5)	13.2 (1.0)	1.2 (0.3)	<0.001
Current 1 – 2 joints per day	89	2.6 (0.3)	5.2 (0.6)	0.6 (0.2)	
Current ≥3 joints per day	57	1.6 (0.2)	3.4 (0.5)	0.3 (0.1)	
“Pipe” smoking only	76	2.2 (0.3)	4.7 (0.6)	0.3 (0.1)	

* Pearson's chi-squared test reporting the significance of the difference between men and women.

Regarding smoking, 411 persons (12%) admitted to smoking substances other than tobacco. Most (11.3% of the population) admitted to smoking cannabis when asked

directly “Have you ever smoked cannabis” (395 participants). Twenty three percent of men and 2.6 percent of women admitted to ever smoking cannabis. The majority of cannabis smokers were male and just under half of male smokers (9.8% of the male population) had already quit at the time of the survey. A significant proportion of men were current cannabis smokers (222 participants - 13.2%).

As very few females admitted to regularly smoking cannabis, female estimates are based on 51 female ever smokers and should thus be interpreted with caution. “Pipe” smoking (a pipe usually being a makeshift ‘pipe’ – see Figure 3) was practised by 118 persons and 76 of these (2.2% of the total population or 34.2% of cannabis users) smoked cannabis pipes exclusively. The remainder (42 persons) smoked both joints and pipes.

Of all persons who had ever smoked cannabis, 92.1 percent also smoked tobacco and only 7.9% had never smoked tobacco. There were thus very few exclusive cannabis smokers. Of all those who had ever smoked tobacco, 18.1% had ever smoked cannabis. Of all current tobacco smokers, 11.5% currently use cannabis (not shown).

Table 27: Prevalence of ever smoking cannabis by age and sex (n=3483)

		All n (n=394)	All % (SE) (n=394)	Men % (SE) (n=345)	Women % (SE) (n=51)	p**
Age	15-24	113	11.7 (1.2)	21.9 (2.2)	3.5 (0.8)	0.02
	25-34	88	11.9 (1.2)	23.3 (2.4)	3.1 (0.8)	
	35-44	99	13.6 (1.3)	24.7 (2.4)	3.6 (0.9)	
	45-54	55	11.7 (1.5)	26.6 (3.3)	1.4 (0.7)	
	55-64	33	9.9 (1.6)	25.3 (3.9)	0.5 (0.5)*	
	>65	6	*	*	*	
Total		394	11.3 (0.6)	23.0 (1.2)	2.6 (0.4)	

* Asterisks indicate that a figure is based on fewer than 12 weighted cases and has been suppressed.

** Pearson’s chi-squared test reporting the significance of the difference between men and women.

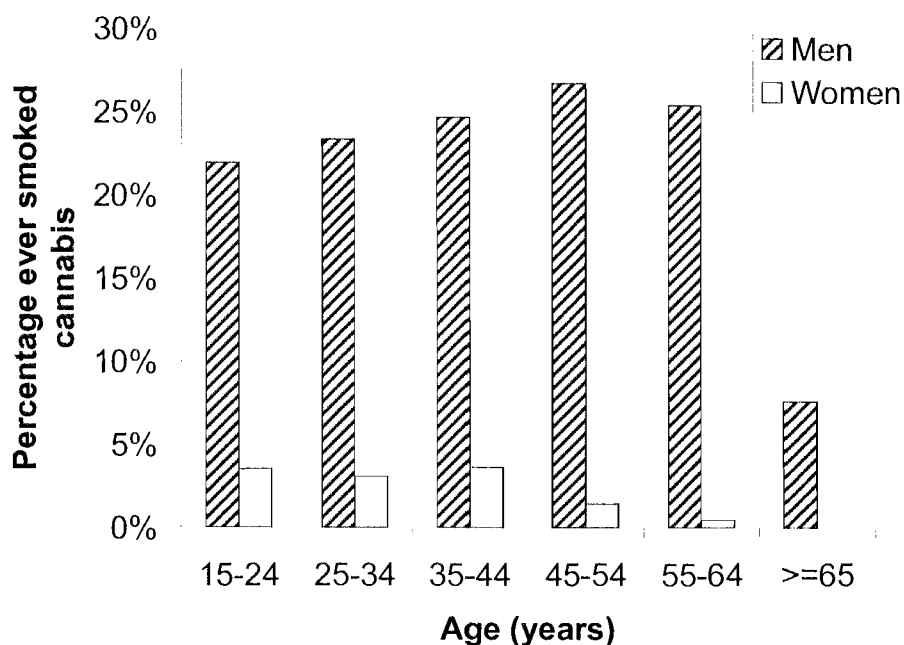


Figure 21: Prevalence of ever smoking cannabis by age and sex (n=3483)

Cannabis smoking has been practiced by a significant proportion of men in this population (23.0%), compared to 2.6% of women with relatively few commencing during each decade after the third decade (Figure 21 and Table 28).

Table 28: Prevalence of current smoking of cannabis by age and sex (n=3483)

	All n	All % (SE)	Men % (SE)	Women % (SE)	P**
Age					
15-24	70	7.2 (1.0)	13.7 (1.9)	2.0 (0.6)	
25-34	49	6.6 (0.9)	13.0 (1.9)	1.6 (0.6)	
35-44	63	8.6 (1.1)	16.7 (2.1)	1.3 (0.6)	
45-54	28	5.9 (1.1)	14.1 (2.6)	0.4 (0.4)	<0.001
55-64	12	3.6 (1.0)	9.5 (2.6)	*	
>65	*	*	*	*	
Total	222	6.4 (0.5)	13.2 (1.0)	1.2 (0.3)	

* Asterisks indicate that a figure is based on fewer than 12 weighted cases and has been suppressed.

** Pearson's chi-squared test reporting the significance of the difference between men and women.

Table 28 shows that a higher proportion of men are current cannabis smokers than women (13.2% vs. 2.6%; $p < 0.001$). The highest prevalence of current cannabis smoking was in men aged 35 - 44 (16.7%), and amongst women it was in the 15 - 24 age group (2.0%). This prevalence drops off by almost a half by the sixth decade and few persons older than 55 years smoke cannabis.

Table 29: Patterns of cannabis smoking (n=395)

	All: median (25th - 75th centile) (n=395)	Men: median (25th - 75th centile) (n=345)	Women: median (25th - 75th centile) (n=51)
Age started smoking (range = 6-60 years of age)	18 (16 – 20)	17 (16 – 20)	18 (16 – 23)
Age stopped smoking (in ex smokers*; n=173)	25 (19 – 33)	25 (19 – 35)	24 (19 – 29)
Number of years smoked	9 (3.2 – 20.9)	10 (3.8 – 21.9)	4.3 (1.8 – 11.1)
Joint years**	27.6 (9 – 68.4)	30.2 (10.7 – 76)	11.7 (4 – 25.4)

* An ex smoker is defined as a person who stopped smoking more than one month before the date of interview.

** 1 joint year = average of 1 joint per year for 1 year²

Most cannabis smokers had started smoking cannabis in their late teens and stopped in their late 20's or early 30's. A quarter of smokers had already started smoking by age 16, half by age 18 and three quarters by age 20, indicating a young age of onset of cannabis use. Half of those that quit smoking cannabis did so by 25 years of age.

Men smoked for a greater number of years than women (median of 10 vs. 4.3 years). In the light of the fact that 70 percent of the population is under the age of 45 years, a median of nine years of smoking is significant. The median number of joint years is high at 27.6 and 75% of the population had a smoking history of less than 68.4 joint years. Men had a much higher exposure than women (median 30.2 vs. 11.7 joint years).

5.3.4.3. Childhood chest illness

Table 30: Prevalence of childhood chest illness by sex (n=3483)

	All n	All % (SE)	Men % (SE)	Women % (SE)	p**
History of childhood chest illness with cough and shortness of breath (<12 yrs of age)	341	9.8 (0.5)	9.9 (0.8)	9.7 (0.7)	0.9
History of repeated/chronic childhood chest illness	231	6.6 (0.4)	6.4 (0.6)	6.8 (0.6)	0.6
Hospitalised for at least one night	114	3.3 (0.3)	3.5 (0.5)	3.1 (0.4)	0.5
Recall of diagnosis assigned to childhood illness***					
Total	253	7.3 (0.5)	6.7 (0.6)	7.7 (0.6)	0.3
• Asthma	124	3.6	See text	See text	
• Bronchitis	63	1.8	See text	See text	
• TB	27	0.8	*	*	*
• Pneumonia	19	0.5	*	*	*
• Other	18	0.5	*	*	*

* Asterisks indicate that a figure is based on fewer than 12 weighted cases and has been suppressed.

** Pearson's chi-squared test reporting the significance of the difference between men and women.

*** Not specified whether by doctor or other person (e.g. parent, friend etc.)

A history of childhood chest illness with cough and shortness of breath (<12 yrs of age) was recalled by 9.8% of the population. Approximately two thirds of the latter gave a history of repeated or chronic childhood chest illness (6.6%) and one third (3.3%) recalled being hospitalised for at least one night. There were no significant gender differences.

Asthma was the most commonly reported childhood chest illness (3.6% of the population). Of these, two thirds were women (62.8%) and approximately one third were men (37.2%), in keeping with the known female predominance of asthma. Similarly, of the 1.8% of the population who reported bronchitis as a childhood illness, 61% were women and 39% were men (not shown).

5.3.4.4. Occupational Exposures

Table 31: Prevalence of lifetime occupational exposure by sex (n=3483)

	All (n)	All % (SE)	Men % (SE)	Women % (SE)	p*
Silica exposure e.g. sand blasting, grinding, pottery, mining, gravestone/stone mason (1)	298	8.6 (0.5)	16.1 (1.0)	2.9 (0.4)	<0.001
Dust, gas, strong smells, chemicals, damp exposure (2)	821	23.6 (0.8)	32.9 (1.3)	16.7 (0.9)	<0.001
Occupational exposure (1 and/or 2)	914	26.3 (0.8)	37.1 (1.4)	18.1 (1.0)	<0.001
Had to leave work because occupational dust affected breathing	155	4.5 (0.4)	6.9 (0.7)	2.6 (0.4)	<0.001

* Pearson's chi-squared test reporting the significance of the difference between men and women.

Exposure to silica was more commonly reported by men than women (16.1% vs. 2.9%) as was general dust exposure (32.9 vs. 16.7). Occupational exposure was classified as a combination of silica and/or general dust exposure and has been used in the univariable and multivariable logistic regression in chapter six, as the variable for occupational exposure. Some persons (4.5%) reported having had to leave work because occupational dust exposure affected their breathing.

5.3.4.5. Caged birds

Table 32: Prevalence of exposure to caged birds (n=3483)

	All n	All % (SE)	Men % (SE)	Women % (SE)	p*
Exposure to caged pigeons/birds (not chickens)	430	12.4 (1.1)	12.2 (1.2)	12.5 (1.2)	0.7

* Pearson's chi-squared test reporting the significance of the difference between men and women.

Many participants (12.4%) reported keeping caged birds which is a common hobby in Cape Town. This exposure is a potential risk factor for lung disease through its association with Pigeon Fancier's disease, a form of extrinsic allergic alveolitis).

5.3.4.6. Alcohol use

Table 33: Prevalence of alcohol use in the population sample (n=3483)

Exposure	n	% of total
Drinks alcohol (current)	1222	35.1
Number of weekend days drinks alcohol (Friday to Sunday)		
1	330	9.5
2	502	14.4
3	353	10.1
Number of weekdays drinks alcohol (Mon to Thurs)		
1	90	2.6
2	61	1.8
3	28	0.8
4	78	2.2

Table 34: Population estimate of number of days of alcohol use per week (n = 3483)

Number of days of alcohol use per week	All n	All % (SE)	Men % (SE)	Women % (SE)	p*
0	2284	65.6% (1.0)	50.8% (1.4)	76.6% (1.2)	<0.001
1 – 2	762	21.9% (0.8)	29.0% (1.3)	16.6% (1.0)	
3 – 4	307	8.8% (0.6)	13.7% (1.0)	5.1% (0.6)	
≥5	129	3.7% (0.4)	6.4% (0.7)	1.7% (0.3)	

* Pearson's chi-squared test reporting the significance of the difference between men and women.

Alcohol use was reported by 35.1% of persons. Of these, most used alcohol on the weekend, with 9.5% consuming on one weekend day, 14.4% on two weekend days and 10.1% on 3 weekend days. Most persons (21.9%) drank alcohol on 1-2 days per week. The patterns of alcohol use in men and women were significantly different with 76.6 % of women reporting no alcohol use, compared to only 50.8% of men who claimed to be teetotalers (p<0.001).

For the purposes of defining regular alcohol use as a risk factor, this was defined as use on 3 weekend days and ≥2 week days. 208 persons (6%) fell into this group, while 3275 (94%) were either non, light or moderate users. Quantification of alcohol use was difficult and inaccurate, owing to the fact that the most common pattern of use involved sharing bottles of alcohol amongst a group of persons, so these data have not been used in analyses.

5.3.4.7. Domestic fuels

Table 35: Prevalence of domestic fuel use (n=3483)

Fuel Type	Cooking		Heating	
	n	% (SE)	n	% (SE)
Wood and coal	8	0.2 (0.1)	63	1.8 (0.4)
Gas	98	2.8 (0.6)	38	1.1 (0.4)
Electricity	3319	95.3 (0.7)	1519	43.7 (1.6)
Paraffin	9	0.3 (0.1)	48	1.4 (0.3)
Spirits	-	-	2	0.1 (0.0)
Unknown	49	1.3 (0.3)	1813	51.9 (1.6)

Current use of fuel other than electricity for cooking or heating was minimal, with 95.3% of persons using electricity. There are no data from the LHS on previous use of biomass fuels. Data on previous use have been collected in the part two study (BOLD) and also shows limited duration of exposure as this is an urban community. Data in Table 35 are not presented stratified by sex owing to the small numbers in groups using fuels other than electricity.

5.3.4.8. Body Mass Index

Table 36: Distribution of Body Mass Index categories by sex (n= 2758)

Body mass Index	All	All	Men	Women	p*
	n	% (SE)	% (SE)	% (SE)	
Underweight (BMI<18.5)	309	11.0 (0.7)	15.3 (1.1)	8.0 (0.7)	<0.001
Normal weight (BMI 18.5 - 24.9)	1233	43.9 (1.0)	53.3 (1.6)	37.3 (1.2)	
Overweight (BMI 25 – 30)	653	23.2 (0.8)	20.6 (1.3)	25.0 (1.1)	
Obese (BMI ≥30)	617	22.0 (0.9)	10.8 (1.0)	29.7 (1.2)	

* Pearson's chi-squared test reporting the significance of the difference between men and women.

Body Mass Index (BMI) is defined as weight in kilograms divided by the square of height in metres. A normal BMI was present in 53.3% of men and 37.3% of women aged ≥15 years. The prevalence of overweight and obesity in women was 25.0% and 29.7% respectively. A large gender difference is seen in the comparative figures for men - 20.6% and 10.8% respectively. Underweight was more prevalent in men (15.3% vs. 8.0%).

5.3.4.9. Tuberculosis

The prevalence of a history of tuberculosis is presented above in Table 21. It was the most commonly diagnosed respiratory illness in this population (9.7% of persons had a history of pulmonary tuberculosis), and was more common in men (12% in men vs. 8% in women, $p < 0.001$).

From the concurrent tuberculosis prevalence survey (a component study of the LHS2002), the prevalence of active tuberculosis was 10 per 1,000 (95% CI: 6.2 to 13.8 per 1,000), an estimate which was based on 26 bacteriologically confirmed TB cases (smear or culture positive) from a total of 2608 persons who provided a sputum sample.^{xiv} Ten out of the 18 smear positive cases had been previously treated (3.8 per 1,000; 95% CI: 1.5 to 6.2 per 1,000), and eight were new cases (3.1 per 1,000; 95% CI: 0.9 to 5.1 per 1,000). Thus more than half of the prevalent smear positive cases were previously treated.^{xiv}

5.3.5. Healthcare utilisation

5.3.5.1. Treatment

Table 37: Treatment for lung disease, including nasal allergy (n=3483)

Disease	n	%
Takes medication for chest disease, including nasal allergy*	324	9.3
Asthma	126	3.6
Hay fever	98	2.8
Other chest diseases	54	1.6
Tuberculosis	22	0.6
Chronic bronchitis/emphysema	35	1.0
Pleural disease	2	0.1
Pneumonia	5	0.1

*includes tablets, inhalers, nebulised medication

The majority of persons who are on medication were receiving medication for asthma (3.6%) and allergic rhinitis (2.8%), despite the high prevalence of symptoms of lung disease. One percent of the population reported receiving treatment for chronic

^{xiv} Den Boon S, van Lill SWP, Borgdorff MW, Enarson DA, Verver S, Bateman ED, Irusen E, Lombard CJ, White NW, de Villiers C, Beyers N. High prevalence of previously treated tuberculosis in Cape Town, South Africa. (unpublished manuscript).

bronchitis/emphysema. Of all persons with doctor-diagnosed asthma, 48.2% were on current treatment for asthma at the time of the study. Of all persons with doctor-diagnosed chronic bronchitis/emphysema, 12.1% were on current treatment for the same at the time of the study.

5.3.5.2. Use of services

Table 38: Source of medication, medical care and emergency medical care for lung disease (n=3483)

Health Care Provider	Source of Medication		Healthcare provider for medical care		Healthcare provider for emergency medical care	
	Usually n (%)	Sometimes n (%)	Usually n (%)	Sometimes n (%)	Usually n (%)	Sometimes n (%)
Clinic/day hospital	157 (4.5%)	66 (1.9%)	370 (10.6%)	210 (6.0%)	324 (9.3%)	144 (4.1%)
Private Hospital	5 (0.1%)	7 (0.2%)	160 (4.6%)	111 (3.2%)	100 (2.9%)	82 (2.4%)
Provincial Hospital	24 (0.7%)	14 (0.4%)	49 (1.4%)	33 (1.0%)	59 (1.7%)	46 (1.3%)
Chemist/Pharmacy	57 (1.6%)	26 (0.8%)	22 (0.6%)	19 (0.6%)	21 (0.6%)	17 (0.5%)
Private doctor	41 (1.2%)	33 (1.0%)	26 (0.8%)	34 (1.0%)	10 (0.3%)	13 (0.4%)
Traditional Healer	0 (0.0%)	0 (0.0%)	3 (0.1%)	4 (0.1%)	0 (0.0%)	0 (0.0%)
A friend	2 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	8 (0.2%)

The majority of persons (4.5%) usually received medication from the local district health clinic or day hospital (a state-run health service), and some visited a pharmacy (1.6%) or a private doctor (1.2%).

At least 8.4 percent of the population had a chest illness severe enough to cause them to attend a healthcare provider within the last 12 months, and the most commonly attended facility was a community health clinic (day hospital), followed by a private doctor or provincial hospital (usually by referral only).

The majority of individuals in Ravensmead and Uitsig attend the local district health clinic/day hospital for emergency care for chest illnesses (9.3%), but a minority always consulted a private doctor (2.9%). A small proportion used two or more providers interchangeably. The nearest provincial hospital (Tyberberg Hospital) is geographically very closely situated to the suburbs, and operates via a referral system.

Table 39: Hospitalisation and quality of life limitation due to chest illness (n=3483)

	n	%
Attended a hospital emergency department in the last 12 months		
1 occasion	116	3.3
Twice	53	1.5
≥3	59	1.7
Total	240	6.9
Admitted for at least one night for chest illness in last 12 months		
1-2 times	17	0.5
3-4	17	0.5
≥5	34	1.0
Total	76	2.2
Lost days of work as a result of chest illness in last 12 months		
1-7 days	49	1.4
≥8 days	21	0.6
Total	75	2.2
Lost activities of daily living from chest illness in last 12 months		
1-7days	59	1.7
≥8 days	30	0.9
Total	95	2.7

Almost seven percent of the population had attended a hospital emergency department in the last year for chest illness, about half of whom had attended only once. Slightly more men than women had attended (8% of men vs. 6% of women, not shown). Hospital admission for at least one night (owing to chest illness) was reported by 2.2% of persons, indicating that there is a significant proportion of uncontrolled or severe chest illness in this community. Of those with any respiratory symptoms, 11.3% had attended an emergency department in the last year, and 4.7% were hospitalised in the last year. Between 2.2 and 2.7 percent of persons had reported loss of productivity and/or activities of daily living as a result of chest illnesses in the last 12 months.

Table 40: Underdiagnosis and undertreatment of respiratory symptoms

Symptom	Doctor Diagnosis of asthma (%)	Doctor diagnosis of chronic bronchitis/ emphysema (%)	Any respiratory treatment (%)	Treatment for asthma (%)	Treatment for chronic bronchitis/ emphysema (%)
MRC chronic bronchitis	23.1	3.3	29.4	15.9	6.0
Wheeze in last 12 months	28.5	2.1	32.1	19.9	4.7
Wheeze with breathlessness	33.4	2.4	37.5	23.3	6.1
Dyspnoea grade 2+	21.6	3.0	27.3	15.2	4.9
Recent cough	11.3	2.4	19.1	8.1	2.9
Usual winter morning cough with phlegm	13.8	2.3	19.0	9.3	3.0
Any respiratory symptom (any of the above)	13.1	1.7	18.3	8.6	2.3

Table 40 represents subgroup analyses for persons with respiratory symptoms. The minority of persons with respiratory symptoms have reported a doctor-diagnosis of asthma, and even fewer have reported a diagnosis of chronic bronchitis/emphysema. Only 18.3% of persons with any respiratory symptom are on treatment. Many are diagnosed and treated as asthma.

5.3.6. Chest radiography

A total of 2608 participants had a chest radiograph performed, which represented three quarters (74.9%) of those who answered questionnaires. No abnormalities were found in 73.1% of radiographs (1908 films) and 26.9% had some abnormality reported. Parenchymal abnormalities occurred in 11.3%, pleural abnormalities in 5.2% and central structure abnormalities in 6.4% of films. Abnormalities inconsistent with tuberculosis were found in 12.9% of all films (337 films).

5.4. References

¹ British Lung Foundation. Cannabis: A Smoking Gun? The impact of cannabis smoking on respiratory health. London: BLF, 2002. URL: http://www.lunguk.org/downloads/A_Smoking_Gun.pdf. Accessed February 2006.

² Tashkin DP, Coulson AH, Clark VA, Simmons M, Bourque L, Duann S, Spivey GH, Gong H. Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. *Am Rev Respir Dis.* 1987 Jan;135(1):209–216.

CHAPTER 6: RISK FACTORS FOR SYMPTOMS OF CHRONIC LOWER RESPIRATORY DISEASE

6.1. Introduction and structure of the chapter

This chapter addresses the second question in this thesis: “What are the risk factors for symptoms of obstructive lung disease in this community (the determinants of obstructive lung disease)?” As there are several forms of obstructive lung disease and several symptoms and symptom complexes whereby they may present, none of which necessarily correlate with one another, this analysis of risk factors examines each of these symptoms/complexes separately. Perhaps the most distinctive is the diagnosis of chronic bronchitis because it is defined by symptoms, without the need for physiological assessment. The five symptoms/symptom complexes that will be analysed as clinical outcomes are:

1. Chronic bronchitis (British MRC definition) – chronic cough and phlegm for at least 3 months per year for at least two successive years.
2. Recent coughⁱ
3. Wheeze in the last 12 months
4. Wheeze with breathlessness in the last 12 months
5. Dyspnoea (Grade 2 and above) in the last 12 months

These are the common symptoms of obstructive lung disease in adults. In the context of the study population, reported symptoms are likely to be a better marker of obstructive lung disease than doctor-diagnosed illness. Reasons for this are underdiagnosis due to limited access to clinical services, and misclassification due to absence of lung function testing in most of the clinical facilities that serve this area. As demonstrated in Chapter 5, prevalence of these symptoms of obstructive lung disease in adults is very high.

In the assessment of association between these symptoms (as outcomes) and their known and suspected risk factors, the following factors were analysed: age, gender,

ⁱ Recent cough was the only other question on cough without reference to phlegm in the LHS2002 questionnaire. The choice of this symptom as one of the outcomes could be criticised as arbitrary. It was included in the questionnaire as a marker for untreated recent onset tuberculosis, owing to the high prevalence of TB in this community. Nonetheless, its analysis proves to be interesting.

income, education, tobacco smoking, cannabis smoking, occupational exposure, childhood chest illness, previous tuberculosis, domestic fuels, alcohol and body mass index.

Among the identifiable environmental causes of obstructive lung disease in adults, modifiable causes are of particular importance, as targeting them in the public health arena would allow for a significant improvement in the burden of obstructive lung disease. In particular, tobacco use, cannabis use, occupational exposures, obesity and tuberculosis merit attention.

6.2. Statistical Analysis

The entire dataset from the Lung Health Survey was used for this analysis. Data were analysed using the survey estimation commands in the STATA® statistical package. Appropriate adjustment for clustering, replacement and response rate was made by setting the primary sampling unit as an address identifier, and specifying individual weighting based on the replacement status and response rate for the age group (see Appendix 8). The number and percentage of persons reporting each outcome according to risk factor groups are shown in the first column of each outcome table.

Most variables have been coded as categorical variables and one of the levels of the variable that is considered to be “normative” was chosen as the reference group, allowing for comparison between this group and the other listed categories. For the few instances where continuous variables are used, odds ratios refer to the measure of effect of a one unit increment of that variable.

Univariable logistic regression was first employed in order to assess the relationship of the chosen outcomes and risk factors without correcting for the effect of other known risk factors and confounders. Estimated unadjusted odds ratios, 95% confidence intervals and their corresponding p values are reported in the middle two columns of each outcome table.

Multivariable analysis was the main statistical tool used to elucidate the relationships between the above-mentioned outcomes and various risk factors. All variables of *a priori* interest were included, and depending on whether the univariable associations were significant or not, risk factors were either included or excluded from the multivariable logistic regression model. In most cases, variables were included unless

there was a good reason to exclude them. Confounders that have been included in the analyses are doctor-diagnosed asthma, doctor-diagnosed heart disease and allergic rhinitis.

A priori suspected interactions between variables were tested by including interaction terms in the final models, and they are reported if significant. Since tobacco smoking is the major risk factor for obstructive lung disease in adults, but not all smokers develop obstructive lung disease, interactions between tobacco smoking and other risk factors were examined for significance.

The last two columns of each table show the fully adjusted odds ratios, 95% confidence intervals and corresponding p values. The model-building process was carried out with an inclusive slant, and stepwise logistic regression was not employed in the final modelling process because the reasons for including most of the putative risk factors was based on strong clinical evidence from published literature, as discussed in Chapter 2. The results of the adjusted multivariable logistic regressions represent the most important part of this chapter and are discussed in detail in Chapter 8.

For each multivariable logistic regression, a Goodness of Fit Test was applied in order to assess how well the chosen combination of variables in the fitted models explained the outcome in question.^{1 2} A good fit occurs when the differences between the observed and expected (fitted) values are small, and there is no systematic contribution of the differences to the error structure of the model.³ As it is essential to take the survey design into account, the Hosmer-Lemeshow Goodness-of-Fit test statistic was appropriately adjusted for clustering and weighting by using the STATA survey estimation package. A p value closer to 1 indicates a good result for this test because it means that the observed and fitted values are not significantly different. Models with p values greater than 0.05 can be considered to be satisfactory for the outcome in question.

Population attributable fractions have been calculated for those risk factors that are significant and modifiable, and they are reported and interpreted on the assumption of causality. The equation below has been used:

*Population Attributable fraction = $p (POR - 1) / [p (POR - 1) + 1]$ where POR = prevalence odds ratio as an estimate of relative risk, and p = prevalence of the risk factor in the population.

6.3. Results

6.3.1. Descriptive characteristics of the sample

Figure 22 lists the questions that were analysed in this chapter. Table 41 summarises the descriptive characteristics of the population in terms of the distribution of risk factors in the sample. Some of this information is included in Chapter 5. It is presented here to describe the categories, and the distribution of the categorical variables entered into the univariable and multiple logistic regression analyses.

Figure 22: Questions included in this analysis (see Appendix 2 for details)

- 1) Do you cough and produce phlegm on most days, for at least 3 months per year for at least 2 successive years?
- 2) Do you have a cough that began recently?
- 3) Have you had wheezing or whistling in your chest at any time in the last 12 months?
- 4) Have you been at all breathless when the whistling noise was present?
- 5) Do you ever have to stop for breath when walking at your own pace on the level?
Do you ever have to stop for breath after walking about 100 yards?
Are you too breathless to leave the house or breathless on dressing or undressing?
- 6) Do you usually bring up any phlegm from your chest first thing in the morning in the winter?
- 7) What is your usual monthly income (from all sources)?
- 8) What level of education did you reach?
- 9) Has a doctor/health worker ever told you that you have heart trouble?
- 10) Has a doctor/health worker ever told you that you have asthma?
- 11) Has a doctor/health worker ever told you that you have TB?
- 12) a) Have you smoked cigarettes for a year or longer?
b) How old were you when you started smoking?
c) Do you smoke now (within the last month)?
d) If no, how old were you when you stopped smoking?
e) On average, how much do you smoke or did you smoke? Number of cigarettes per day/number of pipe bowls per day.
- 13) a) Have you ever smoked cannabis?
b) How old were you when you started smoking cannabis?
c) Have you smoked cannabis in the last month?
d) If no, how old were you when you stopped smoking?
e) On average, how much do you smoke or did you smoke? Number of cigarettes per day/number of pipe bowls per day.
- 14) Have you ever worked in a job that exposed you to silica dust, or involve sand blasting? grinding, pottery, work in a quarry/mine or grave stone manufacturing?
- 15) Have you ever been exposed to other dusts, gases, strong smells, chemicals, fumes, at work?
- 16) Do you recall having any chest illnesses with cough and shortness of breath when you were a child? (<12 years)
- 17) What fuels are mostly used in the dwelling you spend most of your evenings?
- 18) Do you drink alcohol? (See Appendix for details)
- 19) Have you ever had a problem with sneezing, or a runny, or blocked nose when you DID NOT have a cold or the flu?

*British Medical Research Council definition of chronic bronchitis

Table 41: Distribution of characteristics of the population by gender (n=3483)

Characteristics	All n (%)	Men n (%)	Women n (%)	p*
Income**: >R2000/month	631 (18.4)	388 (26.0)	255 (12.8)	<0.001
R1000-R2000/month	623 (18.2)	290 (19.4)	344 (17.3)	
<R1000/month	2168 (63.4)	815 (54.6)	1391 (69.9)	
Education (years): >12 years	701 (20.1)	340 (22.8)	362 (18.2)	<0.001
8-12 years	1842 (52.9)	797 (53.4)	1046 (52.6)	
1-7 years	832 (23.9)	315 (21.1)	517 (26.0)	
None	106 (3.1)	41 (2.8)	65 (3.3)	
Age (years): 15-24	969 (27.8)	429 (28.7)	540 (27.1)	<0.001
25-34	742 (21.3)	321 (21.5)	421 (21.2)	
35-44	732 (21.0)	346 (23.2)	386 (19.4)	
45-54	471 (13.5)	191 (12.8)	280 (14.1)	
55-64	331 (9.5)	126 (8.4)	205 (10.3)	
>65	237 (6.8)	79 (5.3)	158 (7.9)	
Employment: Employed	1480 (42.7)	784 (52.5)	704 (35.4)	
Unemployed	1983 (57.3)	709 (47.5)	1286 (64.6)	
Tobacco: Never smoked	1475 (42.4)	490 (32.8)	987 (49.6)	<0.001
Ex smoker	266 (7.7)	119 (8.0)	146 (7.3)	
Current 1-14 cigarettes /day	1339 (38.5)	640 (42.9)	703 (35.3)	
Current >15 cigarettes/day	354 (10.2)	211 (14.1)	146 (7.3)	
Non cigarette only (pipe)***	41 (1.2)	33 (2.2)	8 (0.4)	
BMI: normal weight 18.5-25	1233 (43.8)	796 (53.3)	742 (37.3)	<0.001
Overweight BMI >25 & <30	653 (23.2)	308 (20.6)	498 (25.0)	
Obese BMI ≥30	617 (21.9)	161 (10.8)	591 (29.7)	
Underweight BMI <18.5	309 (11.0)	228 (15.3)	159 (8.0)	
Cannabis: Never	3088 (88.7)	1149 (77.0)	1940 (97.5)	<0.001
Ex Cannabis smoker	173 (5.0)	146 (9.8)	27 (1.4)	
Current 1-2 joints/day	89 (2.6)	77 (5.2)	11 (0.6)	
Current ≥3 joints/day	57 (1.6)	51 (3.4)	6 (0.3)	
Cannabis pipe only	76 (2.2)	70 (4.7)	6 (0.3)	
Occupational exposure: Never	2569 (73.8)	939 (62.9)	1630 (81.9)	<0.001
Ever	914 (26.2)	554 (37.1)	360 (18.1)	
Childhood chest illness: Never	3141 (90.2)	1345 (90.1)	1797 (90.3)	0.8906
Ever	341 (9.8)	148 (9.9)	193 (9.7)	
Previous tuberculosis: Never	3146 (90.3)	1314 (88.0)	1831 (92.1)	<0.001
Ever	337 (9.7)	179 (12.0)	159(8.0)	
Domestic fuels: Non- smoky	3415 (98.1)	1468 (98.4)	1947 (97.8)	0.1705
Smoky	67 (1.9)	24 (1.6)	43 (2.2)	
Asthma: Never diagnosed	3238 (93.0)	1424 (95.4)	1815 (91.2)	<0.001
Ever diagnosed	245 (7.0)	69 (4.6)	175 (8.8)	
Alcohol use: Non, light, moderate	3275 (94.0)	1341 (89.8)	1934 (97.2)	<0.001
Heavy	208 (6.0)	152 (10.2)	56 (2.8)	

* Chi squared test for the difference between men and women; **R1000month~US\$ 98.77; ***small numbers in this group

6.3.2. Analysis of risk factors for chronic bronchitis (Table 42)

Although present in a minority, the strongest risk factor for symptoms of chronic bronchitis in this population was heavy cannabis smoking of ≥ 8 joints per day (OR 5.3; 95 % CI: 2.5 – 11.4). Smoking 1-2 joints per day and a history of cannabis smoking were associated with a 3.5 and a 2.5 times increased risk respectively, exceeding even tobacco smoking in strength of association. Exclusive cannabis pipe smoking was also a significant risk factor (OR 3.6; 95% CI 1.7- 7.6)

Tobacco smoking of 1-14 cigarettes per day was associated with a 2.1 fold increase in risk, and >15 cigarettes per day with a 2.7 times increase in risk. Although there were small numbers of exclusive pipe smokers, this activity resulted in a 4.6 times increased risk. Being an ex tobacco smoker was not a risk factor for chronic bronchitis after adjusting for the other listed variables.

Occupational exposure was significantly associated with a 2 fold increased risk and both heavy alcohol use and tuberculosis showed borderline associations with chronic bronchitis. (OR 1.6; CI: 1.0 – 2.5 and OR 1.5; CI: 1.0 – 2.2 respectively)

Table 42: Analysis of risk factors for chronic bronchitis using survey estimation logistic regression (n = 3483)

	n (%) with CB**	Unadjusted OR (95% CI)	p*	Adjusted OR (95%CI)	p*
Income**: >R2000/month	25 (3.9)	1.0	<0.001	1.0	0.001
R1000-R2000/month	27 (4.4)	1.1 (0.6 – 1.9)		0.9 (0.5 – 1.8)	
<R1000/month	195 (9.0)	2.4 (1.5 – 3.8)		1.9 (1.1 – 3.2)	
Education: >12 years	25 (3.6)	1.0	<0.001	1.0	0.0434
8-12 years	99 (5.4)	1.6 (1.0 – 2.5)		1.3 (0.8 – 2.1)	
1-7 years	113 (13.6)	4.3 (2.7 – 6.7)		1.9 (1.1 – 3.3)	
None	13 (12.3)	3.8 (1.9 – 7.6)		1.8 (0.8 – 4.3)	
Age (years): 15-24	34 (3.5)	1.0	<0.001	1.0	<0.001
25-34	38 (5.1)	1.5 (0.9 – 2.3)		1.2 (0.7 – 2.0)	
35-44	59 (8.1)	2.4 (1.6 – 3.6)		1.7 (1.1 – 2.7)	
45-54	59 (12.5)	3.9 (2.6 – 5.9)		2.9 (1.8 – 4.7)	
55-64	42 (12.6)	4.0 (2.5 – 6.4)		2.9 (1.7 – 4.9)	
>65	19 (8.0)	2.4 (1.3 – 4.3)		2.5 (1.3 – 4.9)	
Tobacco: Never	47 (3.2)	1.0	<0.001	1.0	<0.001
Ex smoker	20 (7.5)	2.5 (1.4 – 4.2)		1.1 (0.6 – 1.9)	
Current 1-14 cigarettes/day	121 (9.0)	3.0 (2.1 – 4.2)		2.1 (1.4 – 3.1)	
Current >15 cigarettes/day	48 (13.6)	4.8 (3.1 – 7.4)		2.7 (1.6 – 4.5)	
Non cigarette only (pipe)	13 (31.7)	14 (6.6 – 29.7)		4.6 (1.9 – 10.7)	
BMI: Underweight	43 (13.9)	1.8 (1.2 – 2.7)	0.488	-	
18-24.9 normal weight	102 (8.3)	1.0		-	
Overweight BMI >25 & <30	34 (5.2)	0.6 (0.4 – 0.9)		-	
Obese BMI ≥30	30 (4.9)	0.6 (0.4 – 0.9)		-	
Cannabis: Never	167 (5.4)	1.0	<0.001	1.0	<0.001
Ex Cannabis smoker	29 (16.8)	3.5 (2.3 – 5.4)		2.5 (1.5 – 4.2)	
Current 1-2 joints/day	20 (22.4)	5.0 (3.0 – 8.3)		3.5 (1.8 – 6.7)	
Current ≥3 joints/day	17 (29.9)	7.4 (4.0 – 13.6)		5.3 (2.5 – 11.4)	
Cannabis pipe only	18 (23.8)	5.4 (3.1 – 9.6)		3.6 (1.7 – 7.6)	
Occupational exposure:					
Never	141 (5.5)	1.0	<0.001	1.0	<0.001
Ever	111 (12.1)	2.4 (1.8 – 3.1)		2.0 (1.4 – 2.8)	
Childhood chest illness:					
Never	201 (6.4)	1.0	<0.001	1.0	0.08
Ever	51 (15.0)	2.6 (1.8 – 3.6)		1.5 (1.0 – 2.3)	
Gender: Female	121 (6.1)	1.0	<0.001	1.0	0.72
Male	130 (8.7)	1.5 (1.1 – 1.9)		0.9 (0.7 – 1.3)	
Previous tuberculosis:					
Never	198 (6.3)	1.0	<0.001	1.0	0.05
Ever	54 (16.0)	2.8 (2.0 – 3.9)		1.5 (1.0 – 2.2)	
Domestic fuels: Non-smoky	246 (7.2)	1.0	0.55	-	
Smoky	6*** (9.0)	1.3 (0.6 – 2.8)		-	
Asthma: Never diagnosed	194 (6.0)	1.0	<0.001	1.0	<0.001
Ever diagnosed	58 (23.7)	4.9 (3.5 – 6.9)		4.9 (3.2 – 7.6)	
Alcohol use: Non, light, moderate	213 (6.5)	1.0	<0.001	1.0	0.05
Heavy	39 (18.8)	3.3 (2.3 – 4.7)		1.6 (1.0 – 2.5)	

* overall p value is reported for categorical variables; **Chronic bronchitis; ***R1000month~US\$ 98.77; *** small numbers in this group; Goodness of fit test: p= 0.098

Income and education are considered a proxy for socioeconomic status. Unlike in the South African national survey (SADHS)⁴, there was no evidence of correlation between these two variables (Pearson's correlation coefficient = 0.305; $p < 0.001$) and both were retained in the final model. Earning less than R1000 per month was significantly associated with chronic bronchitis (OR 1.9; 95% CI: 1.1 – 3.2) after adjusting for all the other risk factors and confounders. Despite the small range in income groupings, twice as many persons in this group had chronic bronchitis (9.0% vs. 3.9% and 4.4% in the slightly higher income groups).

Although individual categories were significant in the univariable but not in the multivariable model, lower levels of education were associated with an increased prevalence of chronic bronchitis, seen in the increasing odds ratios with decreasing levels of education. P for trend was 0.009 (OR 1.3; 95% CI: 1.1 – 1.7) indicating an upward trend (not shown).

Increasing age was clearly associated with chronic bronchitis. It is notable that significantly increased risk starts from the 35 – 44 year age group which has an OR of 1.7 (95% CI: 1.1 – 2.7). There is almost a three fold risk in the 45-64 year age group (OR 2.9), and the slight decrease in risk in the >65 group. Diagnosed asthma was included in this model as a confounder and adjusting for asthma strengthens the validity of the other associations. A history of childhood chest illness did not show significant association at the 5% level after adjustment for asthma.

Interactions between gender and BMI ($p = 0.34$) and gender and occupational exposure ($p = 0.08$) were not significant, as was an interaction between smoking and TB ($p = 0.5$).

The Hosmer-Lemeshow Goodness of Fit Test (for survey analysis) indicated that this combination of variables explains symptoms of chronic bronchitis adequately ($p = 0.098$)

Table 43: Analysis of risk factors for recent cough using survey estimation logistic regression (n=2758)

	n (%) with recent cough	Unadjusted OR (95% CI)	p*	Adjusted OR (95%CI)	p*
Income**: >R2000/month	81 (12.8)	1.0	<0.001	1.0	0.008
R1000-R2000/month	90 (14.5)	1.1 (0.8 – 1.6)		0.9 (0.6 – 1.4)	
<R1000/month	499 (23.0)	2.0 (1.6 – 2.6)		1.4 (1.0 – 2.0)	
Education: >12 years	87 (12.4)	1.0	<0.001	1.0	<0.001
8-12 years	308 (16.7)	1.4 (1.1 – 1.9)		1.3 (0.9 – 1.8)	
1-7 years	253 (30.4)	3.1 (2.3 – 4.1)		1.8 (1.3 – 2.7)	
None	33 (31.1)	3.2 (2.0 – 5.1)		3.0 (1.6 – 5.6)	
Age (years): 15-24	150 (15.5)	1.0	<0.001	1.0	0.5
25-34	121 (16.3)	1.1 (0.8 – 1.4)		1.1 (0.8 – 1.6)	
35-44	165 (22.5)	1.6 (1.2 – 2.1)		1.3 (0.9 – 1.9)	
45-54	108 (22.9)	1.6 (1.2 – 2.1)		1.2 (0.8 – 1.7)	
55-64	86 (26.0)	1.9 (1.4 – 2.6)		1.5 (0.96- 2.2)	
>65	50 (21.1)	1.5 (1.0 – 2.1)		1.2 (0.7 – 2.0)	
Tobacco: Never	175 (11.9)	1.0	<0.001	1.0	<0.001
Ex smoker	55 (20.7)	1.9 (1.4 – 2.8)		1.2 (0.8 – 1.7)	
Current 1-14 cigarettes/day	298 (22.3)	2.1 (1.7 – 2.6)		1.5 (1.2 – 1.9)	
Current >15 cigarettes/day	132 (37.3)	4.4 (3.3 – 5.9)		3.1 (2.2 – 4.4)	
Non cigarette only (pipe)	18 (43.9)	5.8 (3.1 – 11.0)		1.4 (0.6 – 3.1)	
BMI: Underweight	94 (30.4)	1.7 (1.2 – 2.2)	0.073	1.6 (1.1 – 2.1)	0.052
18-24.9 normal weight	256 (20.8)	1.0		1.0	
Overweight BMI >25 & <30	109 (16.7)	0.8 (0.6 – 1.0)		1.0 (0.7 – 1.3)	
Obese BM _≥ 30	112 (18.2)	0.8 (0.7 – 1.1)		1.0 (0.8 – 1.4)	
Cannabis: Never	521 (16.9)	1.0	<0.001	1.0	<0.001
Ex Cannabis smoker	55 (31.8)	2.3 (1.7 – 3.2)		1.6 (1.1 – 2.4)	
Current 1-2 joints/day	41 (46.1)	4.2 (2.7 – 6.5)		2.9 (1.6 – 5.1)	
Current ≥3 joints/day	27 (47.4)	4.4 (2.6 – 7.6)		2.2 (1.1 – 4.3)	
Cannabis pipe only	37 (48.7)	4.7 (2.9 – 7.6)		2.7 (1.4 – 5.1)	
Occupational exposure:					
Never	443 (17.2)	1.0	<0.001	1.0	0.010
Ever	238 (26.0)	1.7 (1.4 – 2.0)		1.3 (1.1 – 1.7)	
Childhood chest illness:					
Never	583 (18.6)	1.0	<0.001	1.0	0.101
Ever	98 (28.7)	1.8 (1.4 – 2.3)		1.3 (0.9 – 1.8)	
Gender: Female	366 (18.4)	1.0	0.041	1.0	0.074
Male	315 (21.1)	1.2 (1.0 – 1.4)		0.8 (0.6 – 1.0)	
Previous tuberculosis:					
Never	551 (17.5)	1.0	<0.001	1.0	<0.001
Ever	130 (38.6)	3.0 (2.3 – 3.8)		2.0 (1.5 – 2.7)	
Domestic fuels: Non-smoky	660 (19.3)	1.0	0.039	1.0	
Smoky	21 (31.3)	1.9 (1.0 – 3.5)			
Asthma: Never diagnosed	604 (18.7)	1.0	<0.001	1.0	0.043
Ever diagnosed	77 (31.4)	2.0 (1.5 – 2.7)		1.5 (1.0 – 2.2)	

* overall p value is reported for categorical variables; **R1000month~US\$ 98.77; Goodness of fit: p = 0.951

Table 43 continued:

	n (%) with recent cough	Unadjusted OR (95% CI)	P*	Adjusted OR (95%CI)	p*
Heart disease: Never diagnosed	624 (18.8)	1.0	<0.001	1.0	<0.001
Ever diagnosed	57 (35.5)	2.2 (1.5 – 3.1)		2.1 (1.4 – 3.3)	
Allergic rhinitis: Never diagnosed	491 (16.7)	1.0	<0.001	1.0	<0.001
Ever diagnosed	190 (34.9)	2.7 (2.1 – 3.3)		2.3 (1.8 – 3.0)	
Alcohol use: Non, light, moderate	596 (18.2)	1.0	<0.001	1.0	0.002
Heavy	85 (40.9)	3.1 (2.3 – 4.2)		2.0 (1.3 – 3.1)	

* overall p value is reported for categorical variables; **R1000month~US\$ 98.77

6.3.3. Analysis of risk factors for recent cough (Table 43)

As is the case with dyspnoea, low levels of education and income were strong predictors of recent cough. Cigarette smoking, any level of cannabis smoking, occupational exposure and being underweight were significant risk factors. Persons with previous tuberculosis were also twice as likely to have reported recent cough.

Hosmer and Lemeshow Goodness of fit: $p = 0.951$.

6.3.4. Analysis of risk factors for wheeze (Table 44)

Tobacco pipe smoking (OR 3.9; 95% CI: 1.5-10) and smoking ≥ 15 cigarettes per day (OR 3.6; 95% CI: 2.3 – 5.6) were the strongest predictors for wheeze in the last 12 months. Smoking 1-14 cigarettes per day resulted in a 2.2 times increased risk, and previous smoking showed borderline association after adjusting for the tabled risk factors.

As was the case with chronic bronchitis, current and previous cannabis smoking and cannabis pipe smoking were strongly associated with wheeze in the last 12 months, resulting in a >2 fold increase in risk, as was past tuberculosis (OR 2.1; 95% CI: 1.5 – 2.9). Obesity (BMI>30) resulted in an almost two fold increased risk (OR 1.9; 95% CI: 1.3 – 2.7). There was a doubling in the risk of wheeze over the age of 35 years, in comparison to the 15 – 25 year age group. Occupational exposure and female gender were positively associated with wheeze and heavy alcohol use and heart disease were marginally associated in the adjusted analyses. Neither income nor education level showed association with wheeze after adjustment. The Goodness-of-fit for this model was appropriate ($p = 0.731$).

Table 44: Analysis of risk factors for wheeze in the last 12 months using survey estimation logistic regression (n=2758)

	n (%) with wheeze	Unadjusted OR (95% CI)*	p*	Adjusted OR (95%CI)*	p*
Income**: >R2000/month	62 (9.8)	1.0	<0.001	1.0	0.054
R1000-R2000/month	56 (9.0)	0.9 (0.6 – 1.3)		0.7 (0.5 – 1.2)	
<R1000/month	326 (15.0)	1.6 (1.2 – 2.2)		1.2 (0.8 – 1.8)	
Education: >12 years	61 (8.7)	1.0	<0.001	1.0	0.036
8-12 years	200 (10.9)	1.3 (0.9 – 1.7)		1.3 (0.9 – 1.9)	
1-7 years	167 (20.1)	2.6 (1.9 – 3.6)		1.5 (1.0 – 2.3)	
None	21 (19.8)	2.6 (1.5 – 4.5)		1.6 (0.7 – 3.9)	
Age: 15-24	73 (7.5)	1.0	<0.001	1.0	0.001
25-34	65 (8.8)	1.2 (0.8 – 1.7)		1.0 (0.6 – 1.6)	
35-44	112 (15.3)	2.2 (1.6 – 3.0)		1.8 (1.2 – 2.8)	
45-54	90 (19.1)	2.9 (2.1 – 4.0)		2.1 (1.4 – 3.2)	
55-64	68 (20.5)	3.2 (2.2 – 4.5)		2.0 (1.2 – 3.3)	
>65	40 (16.9)	2.5 (1.7 – 3.7)		2.2 (1.2 – 4.0)	
Tobacco: Never smoked	109 (7.4)	1.0	<0.001	1.0	<0.001
Ex smoker	55 (20.7)	3.3 (2.3 – 4.6)		1.6 (1.0 – 2.6)	
Current 1-14 cigarettes /day	190 (14.2)	2.1 (1.6 – 2.7)		2.2 (1.6 – 3.1)	
Current >15 cigarettes/day	80 (22.6)	3.7 (2.7 – 5.0)		3.6 (2.3 – 5.6)	
Non cigarette only (pipe)	11 (26.8)	4.7 (2.2 – 10.3)		3.9 (1.5 -10.0)	
BMI: Underweight	47 (15.2)	1.3 (0.9 – 1.9)	0.013	1.2 (0.8 – 1.9)	0.006
18-24.9 normal weight	153 (12.4)	1.0		1.0	
Overweight BMI >25 and <30	79 (12.1)	1.0 (0.7 – 1.3)		1.2 (0.8 – 1.7)	
Obese BMI ≥30	111 (18.0)	1.5 (1.2 – 2.0)		1.9 (1.3 – 2.7)	
Cannabis: Never	346 (11.2)	1.0	<0.001	1.0	0.002
Ex Cannabis smoker	45 (26.0)	2.8 (1.9 – 4.0)		2.0 (1.2 – 3.3)	
Current 1-2 joints/day	23 (25.8)	2.8 (1.7 – 4.5)		2.4 (1.2 – 4.8)	
Current ≥3 joints/day	17 (29.8)	3.4 (1.9 – 5.8)		2.7 (1.3 – 5.7)	
Cannabis pipe only	18 (23.7)	2.4 (1.4 – 4.4)		1.8 (0.8 – 4.2)	
Occupational exposure:					
Never	269 (10.5)	1.0	<0.001	1.0	0.002
Ever	180 (19.7)	2.1 (1.7 – 2.6)		1.6 (1.2 – 2.1)	
Childhood chest illness:					
Never	332 (10.6)	1.0	<0.001	1.0	<0.001
Ever	117 (34.3)	4.4 (3.4 – 5.7)		2.4 (1.7 – 3.5)	
Gender: Female	264 (13.3)	1.0	0.468	1.0	0.018
Male	185 (12.4)	0.9 (0.8 – 1.1)		0.7 (0.5 – 0.9)	
Previous tuberculosis:					
Never	358 (11.4)	1.0	<0.001	1.0	<0.001
Ever	91 (27.0)	2.9 (2.2 – 3.7)		2.1 (1.5 – 2.9)	
Domestic fuels: Non-smoky	432 (12.7)	1.0	0.015	1.0	
Smoky	17 (25.4)	2.4 (1.1 – 4.7)			
Asthma: Never diagnosed	321 (9.9)	1.0	<0.001	1.0	<0.001
Ever diagnosed	128 (52.3)	9.9 (7.5 – 13.2)		7.2 (4.9 – 10.6)	
Heart disease: Never diagnosed	408 (12.3)	1.0	<0.001	1.0	0.047
Ever diagnosed	41 (24.1)	2.3 (1.6 – 3.2)		1.6 (1.0 – 2.5)	

Table 44 continued:

	n (%) with wheeze	Unadjusted OR (95% CI)*	p*	Adjusted OR (95%CI)*	p*
Allergic rhinitis: Never diagnosed	272 (9.3)	1.0	<0.001	1.0	<0.001
Ever diagnosed	177 (32.5)	4.7 (3.8 – 5.9)		3.9 (2.9 – 5.1)	
Alcohol use: Non, light, moderate	402 (12.3)	1.0	<0.001	1.0	0.050
Heavy	47 (22.6)	2.1 (1.5 – 2.9)		1.5 (1.0 – 2.3)	

*overall p value is reported for categorical variables; **R1000month~US\$ 98.77

6.3.5. Analysis of risk factors for wheeze with breathlessness (Table 45.)

Wheeze with breathlessness showed similar associations to wheeze in the last 12 months with the notable exceptions that cannabis smoking displayed an even more robust association, associated with a risk of up to 3.5 times more than those that had never smoked cannabis. Heavy alcohol use was also associated with a slightly higher risk (OR 1.7; CI: 1.1 – 2.8).

This was a good model with the observed and expected values not differing significantly (Goodness of fit: $p = 0.8$)

Table 45: Analysis of risk factors for wheeze with breathlessness in the last 12 months using survey estimation logistic regression (n=2758)

	n (%) wheeze with breathless- ness	Unadjusted OR (95% CI)*	p*	Adjusted OR (95%CI)*	p*
Income**: >R2000/month	39 (6.2)	1.0	<0.001	1.0	0.034
R1000-R2000/month	43 (6.9)	1.1 (0.7 – 1.8)		1.0 (0.6 – 1.7)	
<R1000/month	257 (11.9)	2.0 (1.4 – 2.9)		1.6 (1.0 – 2.5)	
Education: >12 years	43 (6.1)	1.0	<0.001	1.0	0.5
8-12 years	148 (8.0)	1.3 (0.9 – 1.9)		1.2 (0.8 – 1.8)	
1-7 years	137 (16.5)	3.0 (2.1 – 4.3)		1.5 (0.9 – 2.4)	
None	16 (15.1)	2.7 (1.5 – 4.9)		1.4 (0.5 – 3.5)	
Age: 15-24	46 (4.8)	1.0	<0.001	1.0	<0.001
25-34	57 (7.7)	1.7 (1.1 – 2.5)		1.7 (1.0 – 2.9)	
35-44	87 (11.9)	2.7 (1.9 – 3.9)		2.7 (1.6 – 4.4)	
45-54	68 (14.4)	3.4 (2.3 – 5.0)		2.8 (1.7 – 4.7)	
55-64	54 (16.3)	3.9 (2.6 – 5.8)		2.9 (1.6 – 5.0)	
>65	31 (13.1)	3.0 (1.9 – 4.7)		2.8 (1.5 – 5.5)	
Tobacco: Never smoked	86 (5.8)	1.0	<0.001	1.0	<0.001
Ex smoker	44 (16.5)	3.2 (2.2 – 4.7)		1.5 (0.9 – 2.6)	
Current 1-14 cigarettes /day	150 (11.2)	2.0 (1.5 – 2.7)		2.1 (1.4 – 3.0)	
Current >15 cigarettes/day	56 (15.8)	3.0 (2.1 – 4.3)		2.5 (1.5 – 4.0)	
Non cigarette only (pipe)	***5 (12.2)	2.3 (0.7 – 7.0)		1.5 (0.5 – 4.6)	
BMI: Underweight	37 (12.0)	1.3 (0.8 – 2.0)	0.027	1.3 (0.8 – 2.1)	0.035
18-24.9 normal weight	118 (9.6)	1.0		1.0	
Overweight BMI >25 & <30	61 (9.3)	1.0 (0.7 – 1.3)		1.1 (0.7 – 1.7)	
Obese BMI ≥30	86 (13.9)	1.5 (1.1 – 2.1)		1.8 (1.2 – 2.7)	
Cannabis: Never	266 (8.6)	1.0	<0.001	1.0	<0.001
Ex Cannabis smoker	34 (19.7)	2.6 (1.7 – 3.9)		2.1 (1.2 – 3.6)	
Current 1-2 joints/day	18 (20.2)	2.7 (1.5 – 4.7)		3.3 (1.5 – 7.2)	
Current ≥3 joints/day	15 (26.3)	3.8 (2.1 – 6.7)		3.5 (1.6 – 7.6)	
Cannabis pipe only	11 (14.5)	1.8 (0.9 – 3.6)		1.7 (0.6 – 4.8)	
Occupational exposure:					
Never	206 (8.0)	1.0	<0.001	1.0	0.015
Ever	138 (15.1)	2.0 (1.6 – 2.6)		1.5 (1.1 – 2.1)	
Childhood chest illness:					
Never	248 (7.9)	1.0	<0.001	1.0	<0.001
Ever	96 (28.2)	4.6 (3.5 – 6.0)		2.3 (1.5 – 3.4)	
Gender: Female	212 (10.7)	1.0	0.087	1.0	0.008
Male	132 (8.8)	0.8 (0.6 – 1.0)		0.6 (0.4 – 0.9)	
Previous tuberculosis:					
Never	270 (8.6)	1.0	<0.001	1.0	0.001
Ever	74 (22.0)	3.0 (2.2 – 4.0)		1.9 (1.3 – 2.7)	
Domestic fuels: Non- smoky	331 (9.7)	1.0	0.046	1.0	
Smoky	13 (19.4)	2.2 (1.0 – 5.0)			
Asthma: Never diagnosed	229 (7.1)	1.0	<0.001	1.0	<0.001
Ever diagnosed	115 (46.9)	11.6 (8.7 – 15.5)		8.2 (5.5 -12.3)	

Table 45 continued:

	n (%) wheeze with breathless- ness	Unadjusted OR (95% CI)*	p*	Adjusted OR (95%CI)*	p *
Heart disease: Never diagnosed	312 (9.4)	1.0	<0.001	1.0	0.137
Ever diagnosed	32 (18.8)	2.2 (1.5 – 3.3)		1.5 (0.9 – 2.5)	
Allergic rhinitis: Never diagnosed	195 (6.6)	1.0	<0.001	1.0	<0.001
Ever diagnosed	149 (27.3)	5.3 (4.2 – 6.7)		4.2 (3.1 – 5.8)	
Alcohol use: Non, light, moderate	305 (9.3)	1.0	<0.001	1.0	0.025
Heavy	39 (18.8)	2.2 (1.6 – 3.2)		1.7 (1.1 – 2.8)	

*overall p value is reported for categorical variables; **R1000month~US\$ 98.77; *** small numbers in these groups

6.3.6. Analysis of risk factors for dyspnoea (Table 46)

Low socioeconomic status was strongly associated with dyspnoea viz. earning less than R1000 per month and less than a high school education. Having no education increased the likelihood of dyspnoea threefold. After the age of 35 risk steadily increased and over 65s had the highest odds of dyspnoea (OR 5.7; 95% CI: 3.1 – 10.7).

Any level of current cigarette smoking, past cannabis smoking, and being either obese or underweight were all significant risk factors. Occupational exposure showed an association of borderline significance after adjustment. Persons with a previous history of tuberculosis were twice as likely to have reported dyspnoea of grade two or higher. Confounding by diagnosed asthma and heart disease were taken into account, both imparting a high risk for dyspnoea.

Table 46: Analysis of risk factors for dyspnoea (grade 2 or higher) in the last 12 months using survey estimation logistic regression (n=2758)

	n (%) with dyspnoea	Unadjusted OR (95% CI)	p*	Adjusted OR (95%CI)	p*
Income**: >R2000/month	35 (5.6)	1.0	<0.001	1.0	<0.001
R1000-R2000/month	44 (7.1)	1.3 (0.8 – 2.1)		1.1 (0.6 – 2.0)	
<R1000/month	326 (15.0)	3.0 (2.1 – 4.3)		2.4 (1.5 – 3.8)	
Education: >12 years	39 (5.6)	1.0	<0.001	1.0	0.017
8-12 years	155 (8.4)	1.6 (1.1 – 2.3)		1.4 (0.9 – 2.2)	
1-7 years	181 (21.8)	4.7 (3.3 – 6.8)		1.9 (1.2 – 3.0)	
None	32 (30.2)	7.4 (4.4 – 12.3)		3.1 (1.5 – 6.4)	
Age: 15-24	45 (4.6)	1.0	<0.001	1.0	<0.001
25-34	46 (6.2)	1.4 (0.9 – 2.1)		1.3 (0.8 – 2.2)	
35-44	86 (11.8)	2.7 (1.9 – 4.0)		2.7 (1.7 – 4.4)	
45-54	88 (18.7)	4.7 (3.2 – 6.9)		3.1 (1.8 – 5.1)	
55-64	74 (22.4)	5.9 (3.9 – 9.1)		3.7 (2.1 – 6.4)	
>65	67 (28.3)	8.1 (5.2 – 12.6)		5.7 (3.1 – 10.7)	
Tobacco: Never smoked	113 (7.7)	1.0	<0.001	1.0	0.007
Ex smoker	54 (20.3)	3.1 (2.1 – 4.4)		1.4 (0.9 – 2.2)	
Current 1-14 cigarettes /day	160 (12.0)	1.6 (1.3 – 2.1)		1.7 (1.2 – 2.4)	
Current >15 cigarettes/day	68 (19.2)	2.9 (2.0 – 4.1)		2.6 (1.7 – 4.2)	
Non cigarette only(pipe)	9 (22.0)	3.4 (1.6 – 7.3)		2.0 (0.7 – 5.5)	
BMI: Underweight	48 (15.5)	1.7 (1.2 – 2.5)	<0.001	1.7 (1.1 – 2.8)	<0.001
18-24.9 normal weight	119 (9.7)	1.0		1.0	
Overweight BMI >25 and <30	74 (11.3)	1.2 (0.9 – 1.6)		1.4 (0.9 – 2.0)	
Obese BMI ≥30	103 (16.7)	1.9 (1.4 – 2.5)		2.0 (1.4 – 2.8)	
Cannabis: Never	334 (10.8)	1.0	0.007	1.0	0.2
Ex Cannabis smoker	34 (19.7)	2.0 (1.3 – 3.0)		1.8 (1.0 – 3.1)	
Current 1-2 joints/day	15 (16.9)	1.7 (1.0 – 3.0)		1.5 (0.7 – 3.3)	
Current ≥3 joints/day	14 (24.6)	2.7 (1.5 – 4.8)		1.4 (0.6 – 3.3)	
Cannabis pipe only	10 (13.2)	1.2 (0.6 – 2.6)		1.1 (0.5 – 2.6)	
Occupational exposure:					
Never exposed	263 (10.2)	1.0	<0.001	1.0	0.041
Ever exposed	144 (15.8)	1.6 (1.3 – 2.1)		1.4 (1.0 – 1.9)	
Childhood chest illness:					
Never	333 (10.6)	1.0	<0.001	1.0	0.144
Ever	74 (21.7)	2.3 (1.7 – 3.1)		1.3 (0.9 – 2.0)	
Gender: Female	249 (12.5)	1.0	0.092	1.0	0.314
Male	158 (10.6)	0.8 (0.7 – 1.0)		0.8 (0.6 – 1.2)	
Previous tuberculosis:					
Never	327 (10.4)	1.0	<0.001	1.0	<0.001
Ever	80 (23.7)	2.7 (2.1 – 3.5)		2.1 (1.5 – 2.9)	
Domestic fuels: Non-smoky	397 (11.6)	1.0	0.5	1.0	-
Smoky	10 (14.9)	1.3 (0.6 – 2.8)		-	
Asthma: Never diagnosed	319 (9.9)	1.0	<0.001	1.0	<0.001
Ever diagnosed	88 (35.9)	5.1 (3.9 – 6.8)		3.8 (2.5 – 5.7)	

Table 46 continued:

	n (%) with dyspnoea	Unadjusted OR (95% CI)	p*	Adjusted OR (95%CI)	p*
Heart disease: Never diagnosed	342 (10.3)	1.0	<0.001	1.0	<0.001
Ever diagnosed	65 (38.2)	5.4 (3.9 – 7.4)		3.3 (2.1 – 5.2)	
Allergic rhinitis: Never diagnosed	274 (9.3)	1.0	<0.001	1.0	<0.001
Ever diagnosed	133 (24.4)	3.1 (2.5 – 3.9)		2.9 (2.2 – 3.9)	
Alcohol use: Non, light, moderate	369 (11.3)	1.0	0.004	1.0	0.074
Heavy	38 (18.3)	1.8 (1.2 – 2.6)		1.6 (1.0 – 2.5)	

**R1000month~US\$ 98.77; Goodness of fit: p= 0.509

6.3.7. Population Attributable Fractions (PAF)

In order to estimate the percentage of a given outcome in a population that can be attributed to or caused by a given risk factor, population attributable fractions have been calculated e.g. just under a third of chronic bronchitis cases in the population could have been avoided if no persons smoked 1-14 cigarettes per day.

Table 47: Population attributable fractions for chronic bronchitis

Risk Factor	Percentage exposed to risk factor	Prevalence Odds Ratio (multivariate model)	Population Attributable Fraction (%)
Income <R1000/month(poverty)	63.4	1.9	36.3
Light/moderate tobacco smoking	38.5	2.1	29.8
Heavy tobacco smoking	10.2	2.7	14.8
Occupational exposure	26.3	2.0	20.8
Past cannabis smoking	5.0	2.5	7.0
Moderate cannabis smoking	2.6	3.5	6.1
Heavy cannabis smoking	1.6	5.3	6.4
Past TB	9.7	1.5	4.6

Poverty (earning <R1000 per month) was responsible for 36.3% of all chronic bronchitis in this population. Tobacco smoking was collectively the cause of 45.5%, cannabis smoking 19.5%, and occupational exposure also significantly implicated with a PAF of 20.8%. One of the assumptions made in calculating population attributable fractions is that they are completely adjusted for confounders, which is often not the case, and this results in the total adding up to more than 100%. This inaccuracy of PAF's does not however detract from the broad public health messages that they deliver.

Table 48: Population attributable fractions for wheeze

Risk Factor	Percentage exposed to risk factor	Prevalence Odds Ratio (multivariate model)	Population Attributable Fraction (%)
Light/moderate tobacco smoking	38.5	2.2	31.6
Heavy tobacco smoking	10.2	3.6	21.0
Occupational exposure	26.3	1.6	13.6
Past cannabis smoking	5.0	2.0	4.8
Moderate cannabis smoking	2.6	2.4	3.5
Heavy cannabis smoking	1.6	2.7	2.6
Past TB	9.7	2.1	9.6
Obesity	21.9	1.9	16.5

Socioeconomic factors were not significantly implicated in the causation of wheeze. Tobacco smoking was the major risk factor (PAF = 52.5%) and cannabis smoking was responsible for 11%. The PAF associated with obesity was 16.5% and that with tuberculosis was 9.6%.

Table 49: Population attributable fractions for wheeze with breathlessness

Risk Factor	Percentage exposed to risk factor	Prevalence Odds Ratio (multivariate model)	Population Attributable Fraction (%)
Light/moderate tobacco smoking	38.5	2.1	29.8
Heavy tobacco smoking	10.2	2.5	13.3
Occupational exposure	26.3	1.5	11.6
Past cannabis smoking	5.0	2.1	5.2
Moderate cannabis smoking	2.6	3.3	5.6
Heavy cannabis smoking	1.6	3.5	3.8
Past TB	9.7	1.9	8.0
Obesity	21.9	1.8	14.9

The PAF's for wheeze with breathlessness were similar to those of wheeze in the last 12 months.

Table 50: Population attributable fractions for dyspnoea of grade 2 or higher

Risk Factor	Percentage exposed to risk factor	Prevalence Odds Ratio (multivariate model)	Population Attributable Fraction (%)
Income <R1000/month(poverty)	63.4	2.4	47.0
No education	3.1	3.1	6.1
Less than high school education	23.9	1.9	17.7
Light/moderate tobacco smoking	38.5	1.7	21.2
Heavy tobacco smoking	10.2	2.6	14.0
Occupational exposure	26.3	1.4	9.5
Past cannabis smoking	5.0	1.8	3.8
Obesity	21.9	2.0	18.0
Past TB	9.7	2.1	9.6

Socioeconomic factors feature prominently on the causation of dyspnoea. Poverty was a risk factor to which 47% of dyspnoea was attributable. Low levels of education/no education were responsible for 23.8%, tobacco for 35.2% and obesity for 18%.

Table 51: Population attributable fractions for recent cough

	Percentage exposed to risk factor	Prevalence Odds Ratio (multivariate model)	Population Attributable Fraction (%)
Light/moderate tobacco smoking	38.5	1.5	16.1
Heavy tobacco smoking	10.2	3.1	17.6
No education	3.1	3.0	5.8
Less than high school education	23.9	1.8	16.1
Occupational exposure	26.3	1.3	7.3
Past cannabis smoking	5.0	1.6	2.9
Moderate cannabis smoking	2.6	2.9	4.7
Heavy cannabis smoking	1.6	2.2	1.9
Past TB	9.7	2.0	8.8

Tobacco and cannabis smoking, socioeconomic factors and past TB featured in the causation of recent cough.

6.4. References

¹ Hosmer DW Jr. and Lemeshow S. 1980 Goodness-of-fit tests for the multiple logistic regression model. *Communications in Statistics: Theory and Methods, Part A* 9:1043-1069.

² Hosmer DW Jr. and Lemeshow S. 2000. *Applied Logistic Regression*. 2nd Ed. New York: Wiley

³ Archer KJ and Lemeshow S. Goodness-of-fit test for a logistic regression model fitted using survey sample data. 2006. *The Stata Journal*; 6(1):97-105.

⁴ Ehrlich R, White N, Norman R, Laubscher R, Steyn K, Lombard C, Bradshaw D. Predictors of chronic bronchitis in South African adults. *Int J Tuberc Lung Dis* 2004;8:369-376.

CHAPTER 7: RESULTS OF THE BURDEN OF OBSTRUCTIVE LUNG DISEASE STUDY (BOLD): SPIROMETRY

7.1. Aims of this chapter

This chapter addresses two questions posed in this thesis: “What is the prevalence of COPD as defined by the Global Obstructive Lung Disease (GOLD) Initiative?”, and “What are the associated risk factors for COPD?” The definition and severity classification of COPD used in the BOLD methodology is that of the GOLD guidelines. This, in contrast to the questionnaire-based approach described in the chapters above, is based predominantly on the results of spirometry performed before and after use of a bronchodilator.

7.2. Statistical analysis

The data reported were analysed using the survey estimation commands in the STATA® statistical package. Weighting and clustering were appropriately adjusted for by means of setting the primary sampling unit as an address identifier, and the individual weights according to the number of responders as a fraction of the total number of eligible participants at each address (see Appendix 9 for details on weighting). The first few tables describe the study population and tables thereafter report population estimates, corrected for both clustering and weighting.

7.2.1. BOLD Prediction Equations

Local prediction equations were derived from the study data on healthy never smokers, who had not reported asthma, emphysema, chronic bronchitis, COPD or TB. Regression models for each of prebronchodilator FEV₁, FVC, and FEV₁/FVC were fitted separately for men and women, using age and height as predictors (Table 52.). Age-squared and age-height interaction terms were also initially included in the model, but were removed due to non-significance. The height term for the FEV₁/FVC model was also not significant, so these models included only age. It must be noted that the local equations are not reliable owing to the very small number of healthy never smokers in this population, particularly in men.

The second set of equations used were the NHANES III equations for Caucasian subjects.¹ A summary of the best fitting NHANES regression equations are presented in Table 53. High values for R² confirm that a large amount of the variability is

explained by the model, suggesting that the equations based on this model are very accurate predictions for the population on which it is based (white Caucasians). These equations were considered suitable for use in the BOLD study for the following reasons:

1. During clinical evaluation of patients in Cape Town, reference equations for Caucasians are used for the study population. However there is no evidence for the accuracy of this practice.
2. Using local equations could mask the effect of other site-specific exposures (anything from the intrauterine environment to air pollution etc.), and there is one viewpoint that suggests that there is little evidence to suggest that ethnicity is a significant factor causing differences in lung function. Ethnicity may, and often does, act as a proxy for socioeconomic status, particularly in low-income local areas in South Africa. An alternative viewpoint is that there may be ethnic differences in lung function. For example, differences in height measurements based on the longer legs of African Americans due to a smaller trunk-leg ratio than their Caucasian counterparts may be important. This results in comparatively lower FEV₁ and FVC and higher FEV₁/FVC ratios in African-Americans in the NHANES III study.¹
3. Using standardised equations permits direct comparison with other sites.

Table 52: Summary of best-fitting regression models for healthy never-smoking men and women from study sample (local equations)

Gender	Outcome	N [#]	Constant	Age	Height	S _{y,x} [*]	R ²
Men	FEV ₁	47	-0.37855	-0.01970	0.02614	0.47491	0.3166
	FVC	44	-0.88594	-.02276	0.03487	0.57160	0.3400
	FEV ₁ /FVC	44	83.04251	-.08279		4.92228	0.0348
Women	FEV ₁	195	-0.01088	-0.02421	0.02181	0.35198	0.5492
	FVC	182	-1.24134	-0.02460	0.03330	0.40957	0.5260
	FEV ₁ /FVC	180	89.62623	-0.19073		6.11079	0.1201

[#] number of subjects used to fit the model. Data excluded from analysis if quality score = 0 or 1.

^{*}residual standard deviation about the regression line

Table 53: Summary of best fitting regression models for healthy never-smoking white men and women from the US NHANES III survey¹

Gender	Outcome	constant	Age	Height ²	Age ²	R ²
Men	FEV ₁	0.5536	-0.01303	0.00014098	-0.000172	0.8510
	FVC	-0.1933	0.00064	0.00018642	-0.000269	0.8668
	FEV ₁ /FVC	88.066	-0.207			0.3448
Women	FEV ₁	0.4333	0.00361	0.00011496	-0.000194	0.7494
	FVC	-0.3560	0.01870	0.00014815	-0.000382	0.7344
	FEV ₁ /FVC	90.809	-0.213			0.3955

Two sets of predicted values were calculated for FEV₁, FVC and FEV₁/FVC for each participant and thereafter % predicted values for each measure were calculated. For the purposes of risk factor analyses, predicted and %predicted values for postbronchodilator tests using the NHANES equations are used to classify COPD.

7.2.2. Risk Factor Analysis

Univariate analysis of each potential risk factor is presented, first for GOLD Stage I and higher, and second, for GOLD stage II and higher. Multivariable logistic regression for these two binary outcomes is also presented. Current literature suggests that stage II and higher COPD is the most conservative threshold to define persons with symptomatic disease.² Moderate or severe disease is of public health significance and may require treatment, affect quality of life and productivity.

In addition, another adjusted risk factor analysis of COPD using multinomial logistic regression is presented, classifying the outcome into a reference category of normal/GOLD stage 0; and two reported categories – GOLD Stage I/II (mild/moderate disease) and GOLD stage III/IV (severe disease).

This categorisation was chosen for two reasons. Firstly, the numbers in this sample are too small to classify COPD into 4 mutually exclusive categories for the purpose of logistic regression, because there are only 34 persons with GOLD Stage I disease. Secondly, the risk factors for mild/moderate disease might be different to those for severe disease. These results are presented in Table 79, and add an important opportunity for examining separate risk profiles for mild, moderate and severe disease.

The following equation was used to calculate pack years:

Number of cigarettes per day/20 X total number of years smoked

i.e. twenty cigarettes a day for one year or one cigarette a day for 20 years equals one pack year.

7.3. Results

Ten of the 833 eligible addresses proved to not exist and non-residential land uses such as a dam and a parking lot were found at the sites. This was thought to have occurred owing to severe flooding in the area many years ago. Of the remaining 823 addresses, 800 were fully enumerated and tracking forms were completed for all age-eligible people living in these 800 households, irrespective of participation.

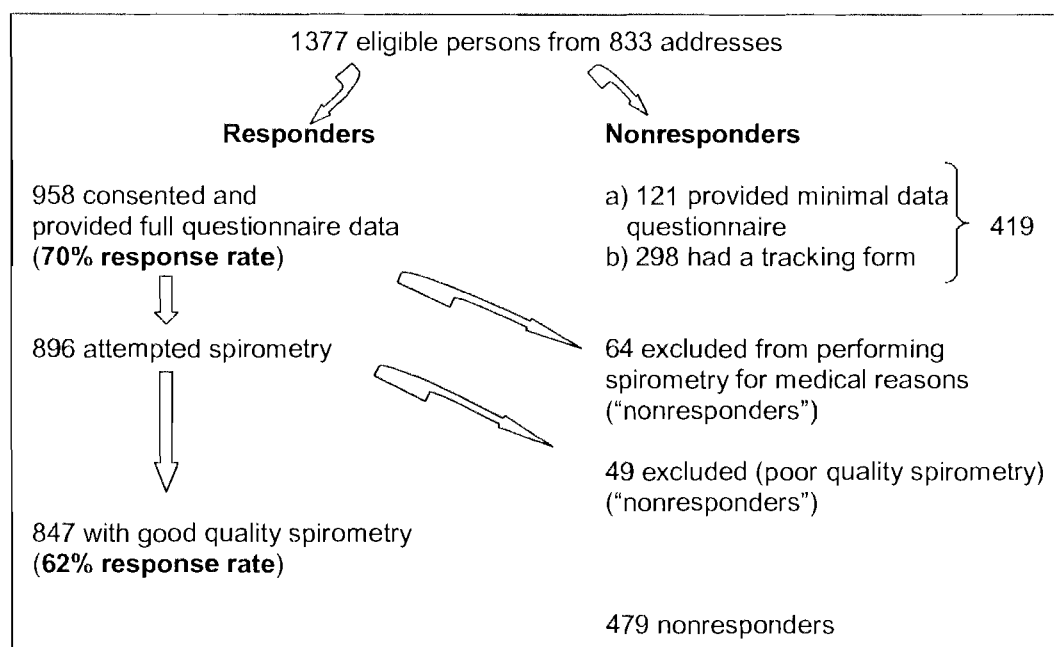


Figure 23: Response rates and disposition of participants in the BOLD study

Of 1377 potential participants, 115 answered the minimal data questionnaire (5 questions on smoking, age etc.) but did not consent to further participation. The core questionnaire was completed by 958 consenting individuals, 64 of whom were excluded from performing spirometry for medical reasons, e.g. severe illness. Of the 896 that attempted spirometry, 49 were excluded for not meeting quality control standards, leaving 847 individuals with analysable spirometric data.

7.3.1. Sample statistics

Table 54: Comparison of responders and nonresponders for the BOLD study

	Responders* n (%)	Nonresponders** n (%)	p***
Age	(n = 896)	(n = 479)	
40 – 49	356 (40%)	196 (41%)	0.006
50 – 59	276 (31%)	139 (29%)	
60 – 69	178 (20%)	72 (15%)	
70 +	86 (10%)	72 (15%)	
Gender	(n = 896)	(n = 479)	0.003
Male	335 (37%)	218 (46%)	
Female	561 (63%)	261 (54%)	
Smoking status	(n = 895)	(n = 180)[#]	0.03
Current	411 (46%)	66 (37%)	
Ex	193 (22%)	38 (21%)	
Never	291 (33%)	76 (42%)	
Doctor-diagnosed asthma, emphysema, CB or COPD[†]	(n = 896)	(n = 180)	0.02
Yes	170 (19%)	21 (12%)	
No	726 (81%)	159 (88%)	
Other co-morbid conditions[‡]	(n = 896)	(n = 180)	0.94
Yes	495 (55%)	100 (56%)	
No	401 (45%)	80 (44%)	

*Responders are those who have core questionnaire data and any post BD Spirometry;

** Nonresponders are eligible individuals at contacted households for whom at least one of these data elements is not available (including those with only pre BD spirometry).

***Two-sided p-value based on Pearson chi-square test.

[†] Per Question 3 on minimal data questionnaire for non responders, Question 12,13,14,15 on core questionnaire for responders

[‡] Per Question 4 on minimal data questionnaire for non responders, Question 16 on core questionnaire for responders

[#] Data on age and gender was available for more individuals than the other measures.

Table 55: Age and sex distribution of all persons who attempted spirometry* and those with good quality spirometry**

Age	Attempted spirometry*			Good quality spirometry**		
	All n	Men n (%)	Women n (%)	All n	Men n (%)	Women n (%)
40 – 49	356	139 (41.0%)	217 (39.0%)	335	132 (42.0%)	203 (38.0%)
50 – 59	276	101 (30.0%)	175 (31.0%)	263	92 (29.0%)	171 (32.0%)
60 – 69	178	67 (20.0%)	111 (20.0%)	167	63 (20.0%)	104 (20.0%)
70+	86	28 (8.0%)	58 (10.0%)	82	28 (9.0%)	54 (10.0%)
All	896	335 (37.4%)	561 (62.6%)	847	315 (37.2%)	532 (62.8%)

*Any persons who have core questionnaire data and any postbronchodilator spirometry.

**Core questionnaire and post BD spirometry with quality scores >1 for each of FEV₁ and FVC.

Table 55 shows that men and women constituted 37% and 63% of the sample respectively, both before and after the participants with poor spirometry were excluded. These proportions are similar to the population estimates for Ravensmead and Uitsig (43.8% and 56.2% for men and women respectively) in Table 56.

7.3.2. Population estimates of COPD

Table 56: Population age and sex distribution based on sample* and from the national census data (weighted) **

Age	Estimated			Census data		
	Men %	Women %	All %	Men %	Women %	All %
40 – 49	20.2%	23.5%	43.7%	20.2%	23.5%	43.7%
50 – 59	12.9%	16.5%	29.4%	12.9%	16.5%	29.4%
60 – 69	7.3%	10.6%	17.9%	7.3%	10.6%	17.9%
70+	3.4%	5.6%	9.0%	3.4%	5.6%	9.0%
All	43.8%	56.2%	100.0%	43.7%	56.3%	100.0%

*Weighted estimate based on responders.

** Statistics SA South Africa.

Table 57: Prevalence* of current smoking by age and sex

Age	All % (SE)	Men % (SE)	Women % (SE)
40 – 49	55.8% (2.9)	63.3% (4.3)	49.3% (3.7)
50 – 59	49.1% (3.4)	54.6% (5.3)	44.8% (4.1)
60 – 69	38.5% (4.0)	50.8% (6.6)	30.1% (4.6)
70+	23.2% (5.3)	41.1% (9.9)	12.1% (4.2)
All	47.8% (1.9)	56.9% (2.9)	40.6% (2.3)

*Weighted population estimate, with SE shown in parenthesis.

The current smoking rates in the population (Table 57) are 56.9% and 40.6% among men and women respectively, indicating that there has been no reduction in smoking rates between 2002 and 2005 in Ravensmead and Uitsig (see Chapter 5).

Table 58: Prevalence* of ever smoking by age and sex

Age	All % (SE)	Men % (SE)	Women % (SE)
40 – 49	71.0% (2.7)	80.7% (3.5)	62.6% (3.5)
50 – 59	73.1% (2.9)	84.7% (4.0)	63.9% (3.9)
60 – 69	68.2% (4.0)	83.7% (5.2)	57.6% (4.9)
70+	53.1% (6.1)	88.1% (5.1)	31.5% (6.4)
All	69.5% (1.8)	83.0% (2.2)	59.0% (2.3)

*Weighted population estimate, with SE shown in parenthesis.

The prevalence of ever smoking in Table 58 shows a consistently high prevalence in men (between 81% and 88%). Women aged more than 70 years have the lowest exposure of 31.5%, considerably different from their younger counterparts.

Table 59: Distribution* of pack years of smoking

Pack years	All %	Men %	Women %
Never smoker	30.5%	16.8%	41.0%
0 – 10	29.7%	31.5%	28.3%
10 – 20	19.8%	24.8%	16.0%
20+	20.0%	26.9%	14.7%
All	100.0%	100.0%	100.0%

*population estimates: weighted frequencies based on responders.

Men have had a considerably higher cumulative exposure to tobacco smoking than women as shown in Table 59. The majority of women smokers have a 0 - 10 pack year history, and 41% of women have never smoked cigarettes. Over 50% of the men in this population have a pack year history of >10 pack years and a quarter have a pack year history of more than 20 pack years.

Table 60: Mean (SD) of Post BD Spirometry by sex and smoking status*

	Men			Women		
	Current	Ex	Never	Current	Ex	Never
N	181	85	49	211	96	224
FEV ₁ (l)	2.55 (0.77)	2.60 (0.72)	3.06 (0.60)	1.94 (0.54)	1.85 (0.56)	2.09 (0.57)
FVC (l)	3.55 (0.78)	3.53 (0.75)	3.80 (0.69)	2.59 (0.57)	2.42 (0.59)	2.60 (0.65)
FEV ₁ /FVC (%)	71.2 (12.8)	73.0 (12.3)	80.6 (5.5)	74.3 (11.2)	76.0 (10.1)	80.3 (7.8)

*Core questionnaire and postbronchodilator spirometry with quality scores >1 for FEV₁ and FVC. Results are for observed sample only and are not population estimates.

Mean FEV₁, FVC and FEV₁/FVC values are consistently lower for current and ex smokers than never smokers in both men and women.

There was a significant difference in mean FEV₁ for current vs. never smoking women and men (p = 0.003 and p < 0.001 respectively). Mean FVC was significantly different in current vs. never smokers for men only. Mean FEV₁/FVC for current vs. never smokers is also significantly different in both men and women (p < 0.001 for men and women)

The differences between mean FEV₁, FVC and FEV₁/FVC in ex- vs. never smokers were not significant in men and women.

Table 61: Estimated population prevalence (SE) of GOLD Stage I or higher COPD* by age and sex

Age	All % (SE)	Men % (SE)	Women % (SE)
40 – 49	15.0 (2.2)	19.6 (3.7)	10.9 (2.4)
50 – 59	24.7 (3.1)	29.4 (5.0)	21.3 (3.5)
60 – 69	33.5 (4.0)	44.4 (6.8)	26.0 (4.4)
70+	44.8 (6.0)	45.5 (9.6)	44.4 (7.8)
All	23.8 (1.6)	28.7 (2.7)	20.0 (1.9)

*Post BD FEV₁/FVC < 70%

The prevalence of GOLD Stage I or higher COPD was 23.8% overall, 28.7% in men and 20.0% in women. Prevalence in the over 60 age group for men and the over 70 age group for both sexes is very high at approximately 45%.

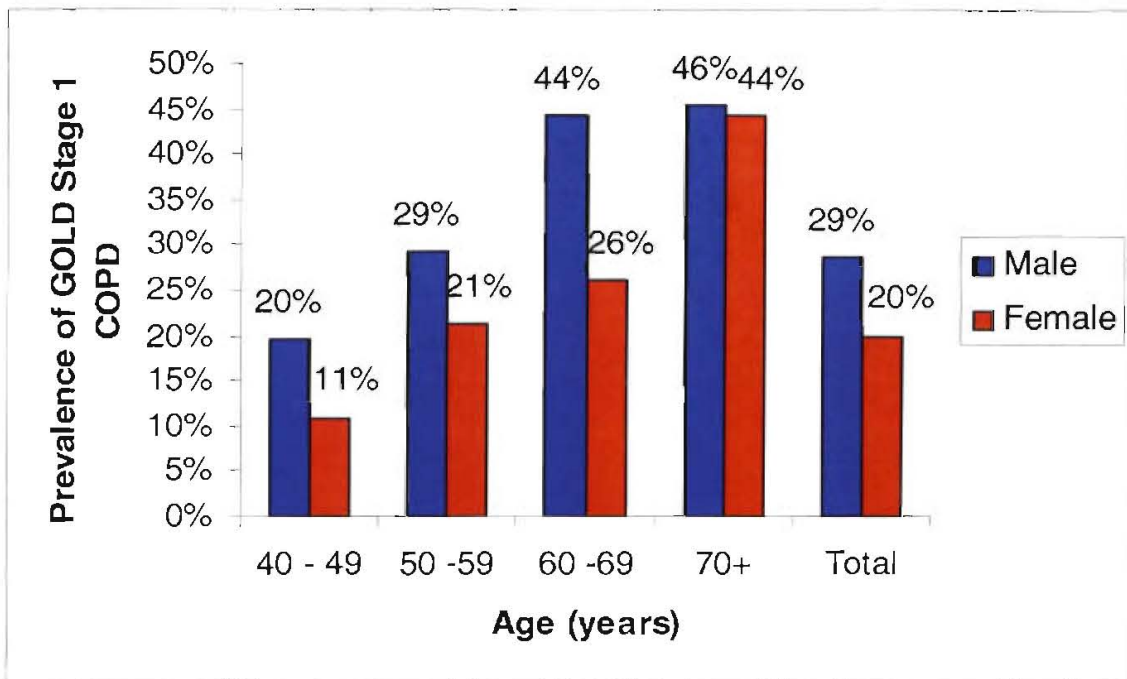


Figure 24: Estimated Population Prevalence of GOLD Stage I or higher COPD by age and sex

Table 62 Estimated population prevalence (SE) of GOLD Stage I or higher COPD* by pack years and sex

		Men % (SE)	Women % (SE)	All % (SE)
Pack years	Never smoker	4.6 (3.4)	12.6 (2.7)	10.7 (2.2)
	0 – 10	23.4 (4.8)	24.1 (3.7)	23.8 (3.0)
	10 – 20	38.4 (5.7)	25.1 (5.2)	32.3 (4.0)
	20+	41.9 (5.3)	27.2 (5.2)	35.8 (3.8)

*Post BD FEV₁/FVC<70%

A dose-response relationship is suggested by the increasing prevalence of COPD with increasing cumulative pack year exposure in men (range: 23.4% to 41.9%). This trend is not clear in women (24.1% to 27.2%). Additionally, never smoking women have a higher prevalence of GOLD Stage I or higher COPD than their male counterparts (12.6 vs. 4.6%).

The prevalence of GOLD Stage I and higher COPD was 10.7% in never smokers, 24.9% in former smokers and 31.4% in current smokers. The corresponding prevalence for GOLD Stage II and higher COPD was 6.8%, 21.0% and 25.7% respectively.

Table 63: Estimated population prevalence (SE) of GOLD Stage II or higher COPD* by age and sex (Local equations)

Age	All % (SE)	Men % (SE)	Women % (SE)
40 – 49	9.1 (1.9)	13.5 (3.3)	6.4 (1.9)
50 – 59	17.3 (2.6)	18.8 (4.1)	16.2 (3.2)
60 – 69	19.8 (3.3)	22.8 (5.6)	17.8 (3.7)
70+	21.3 (4.6)	28.2 (8.6)	16.5 (5.0)
All	14.8 (1.3)	17.8 (2.3)	12.4 (1.5)

*Post BD FEV₁/FVC<70% and post BD FEV₁<80% expected

The prevalence of GOLD Stage II and higher COPD using local equations confirms a prevalence of 17.8% in men and 12.4% in women, with men having a consistently higher prevalence than women in all age categories.

Table 64: Estimated population prevalence (SE) of GOLD Stage II or higher COPD* by age and sex (NHANES equations)

Age	All % (SE)	Men % (SE)	Women % (SE)
40 – 49	12.3 (2.0)	17.5 (3.6)	7.8 (2.1)
50 – 59	20.2 (2.7)	20.8 (4.3)	19.8 (3.4)
60 – 69	28.1 (3.7)	34.8 (6.6)	23.4 (4.3)
70+	30.8 (5.2)	28.2 (8.6)	32.7 (6.9)
All	19.1 (1.5)	22.2 (2.4)	16.7 (1.7)

*Post BD FEV₁/FVC<70% and post BD FEV₁<80% expected

Using the NHANES III equations resulted in a higher prevalence of GOLD Stage II and higher COPD (22.2% in men and 16.7% in women) than local equations (see Table 63 and 64). The age distribution of Stage II and higher is graphically represented in Figure 25 below, notably showing high prevalence of moderate to severe disease in the youngest age group (40 – 49 years), indicating that lung function impairment starts at a comparatively younger age in this community.

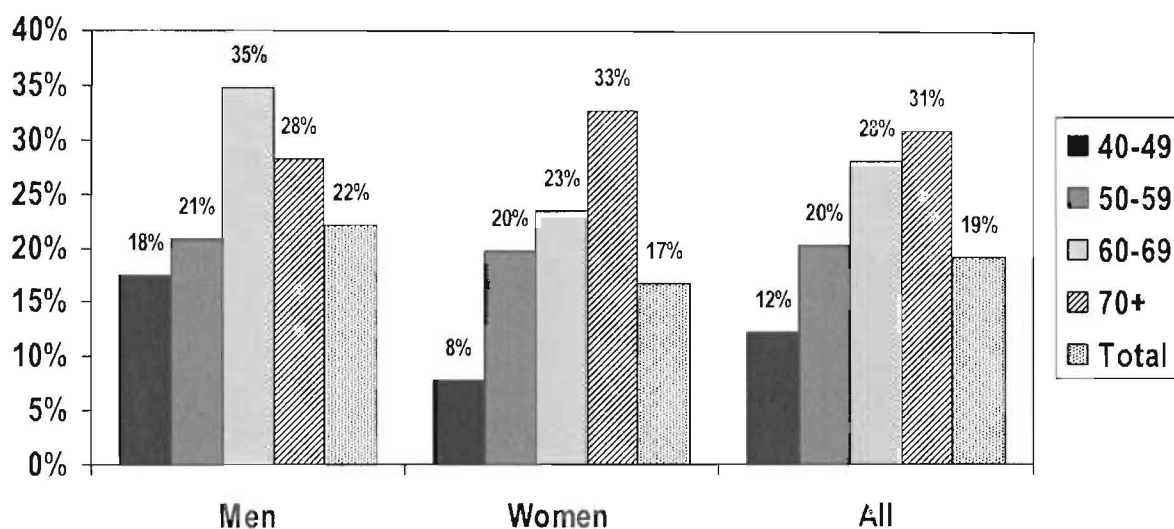


Figure 25: Estimated population prevalence of GOLD Stage II or higher COPD* by age and sex (using NHANESIII Equations)

* Post BD FEV₁/FVC <70% and post BD FEV₁ <80%

Table 65: Estimated population prevalence (SE) of GOLD Stage II or higher COPD* by pack years and sex (Local equations)

Pack years	All % (SE)	Men % (SE)	Women % (SE)
Never smoker	4.4 (1.3)	3.1 (3.0)	4.9 (1.4)
0 – 10	16.0 (2.5)	14.3 (3.8)	17.5 (3.4)
10 – 20	20.7 (3.5)	25.3 (5.1)	15.3 (4.2)
20+	23.1 (3.3)	24.7 (4.5)	20.7 (4.8)

*Post BD FEV₁/FVC<70% and post BD FEV₁<80% expected

Table 66: Estimated population prevalence (SE) of GOLD Stage II or higher COPD* by pack years and sex (NHANES equations)

Pack years	All % (SE)	Men % (SE)	Women % (SE)
Never smoker	7.0 (1.5)	3.1 (3.0)	8.2 (1.8)
0 – 10	19.6 (2.7)	16.2 (3.9)	22.5 (3.6)
10 – 20	25.6 (3.6)	30.8 (5.3)	19.4 (4.6)
20+	30.7 (3.7)	33.9 (5.1)	26.1 (5.1)

*Post BD FEV₁/FVC<70% and post BD FEV₁<80% expected

There is a higher prevalence of GOLD Stage II or higher COPD in women never smokers than their male counterparts (8.2% vs. 3.1%). Again, the dose-response effect in women is less steep (Figure 26). The reason could be the categorisation of pack years - most women have a cumulative exposure that is nearer the lower end of the category, e.g. 11 pack years, whereas more men are at the higher end of the category, e.g. 19 pack years.

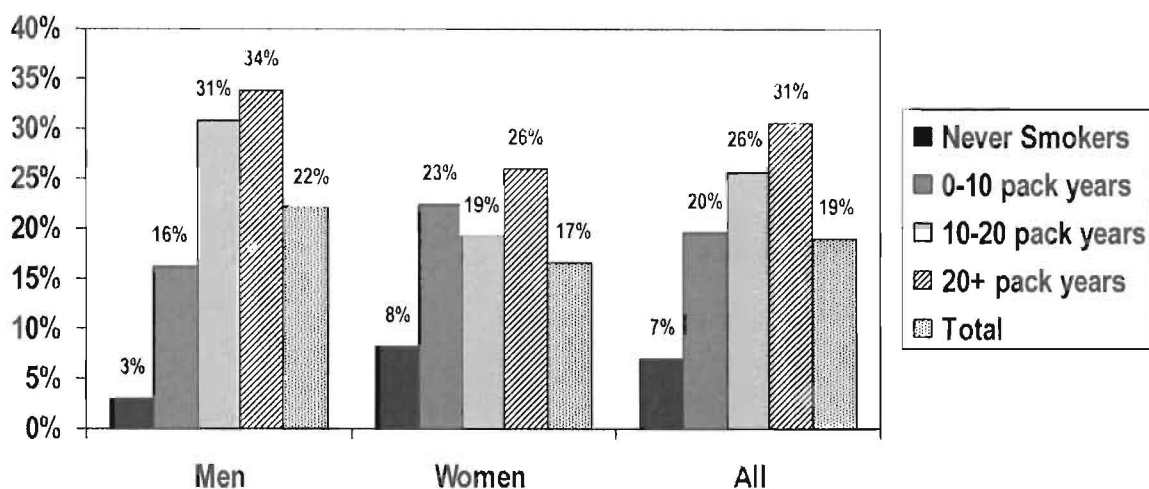


Figure 26: Estimated prevalence of GOLD Stage II or higher COPD* by pack years and sex (using NHANES III equations)

* Post BD FEV₁/FVC <70% and post BD FEV₁ <80%

Table 67: Sample statistics and population prevalence of GOLD COPD in mutually exclusive stages by sex

GOLD Stage	All n (%) for sample	All % (SE)	Men % (SE)	Women % (SE)
0	651 (76.9)	76.2 (1.6)	71.3 (2.7)	80.0 (1.9)
1	34 (4.0)	4.7 (0.9)	6.5 (1.6)	3.3 (1.0)
2	109 (12.9)	12.4 (1.2)	14.2 (2.1)	11.0 (1.4)
3	48 (5.7)	6.2 (0.9)	7.3 (1.6)	5.4 (1.1)
4	5 (0.6)	0.5 (0.2)	0.7 (0.4)	0.3 (0.2)

The prevalence of GOLD Stage II COPD was higher than other GOLD stages (12.9%) and most persons with COPD were in GOLD stages II and III. Overall, 19% of the population, and the majority of persons with COPD had moderate to severe disease (Table 64). The difference in prevalence of COPD between men and women was not significant at the 5% level ($p = 0.075$, not shown).

7.3.3. Symptoms in the BOLD sample

Table 68: Estimated population prevalence (SE) of Chronic Cough* by age and sex

Age	All % (SE)	Men % (SE)	Women % (SE)
40 – 49	13.5 (2.0)	11.6 (3.4)	15.1 (2.5)
50 – 59	12.3 (2.1)	15.3 (3.8)	9.9 (2.4)
60 – 69	10.5 (2.5)	15.7 (4.4)	7.0 (2.7)
70+	6.3 (2.6)	8.9 (5.0)	4.7 (2.7)
All	11.9 (1.2)	13.2 (2.1)	11.0 (1.4)

*Reported cough for three months or more per year.

Chronic cough was more commonly reported by younger women than older women, potentially indicative of an overlap with asthma in 40 - 50 year old women (bimodal distribution). There was a high prevalence of chronic cough in men in all the age categories (13.2% overall).

Table 69: Estimated population prevalence (SE) of Chronic Cough* by pack years and sex

Pack years	All % (SE)	Men % (SE)	Women % (SE)
Never smoker	3.9 (1.3)	5.1 (3.5)	3.5 (1.2)
0 – 10	14.3 (2.3)	12.7 (3.5)	15.8 (3.1)
10 – 20	15.4 (2.9)	14.4 (4.1)	16.5 (4.1)
20+	17.8 (3.1)	18.3 (4.3)	17.0 (4.5)

*Reported cough for three months or more per year.

The prevalence of chronic cough increases in both men and women as packyears increase, with similar prevalence in both sexes.

Table 70: Estimated population prevalence (SE) of Chronic Phlegm* by age and sex

Age	All % (SE)	Men % (SE)	Women % (SE)
40 – 49	17.1 (2.3)	17.9 (3.8)	16.4 (2.8)
50 – 59	13.3 (2.3)	14.6 (3.8)	12.3 (2.6)
60 – 69	12.1 (2.4)	15.7 (4.4)	9.7 (2.7)
70+	8.4 (3.0)	8.9 (5.0)	8.1 (3.7)
All	14.3 (1.3)	15.9 (2.2)	13.1 (1.6)

*Reported Phlegm for three months or more per year.

Chronic phlegm production was reported by 15.9% of men and 13.1% of women. Again similar prevalence in both sexes was noted.

Table 71: Estimated population prevalence (SE) of Chronic Phlegm* by pack years and sex

Pack years	All % (SE)	Men % (SE)	Women % (SE)
Never smoker	5.8 (1.5)	8.3 (4.6)	5.0 (1.4)
0 – 10	15.0 (2.5)	12.6 (3.6)	16.9 (3.4)
10 – 20	18.2 (3.2)	16.9 (4.3)	19.7 (4.5)
20+	21.9 (3.4)	22.1 (4.6)	21.6 (5.0)

*Reported Phlegm for three months or more per year.

A dose-response relationship with increasing pack years is evident.

Table 72: Estimated population prevalence (SE) of Self-reported Chronic Bronchitis* by age and sex

Age	All % (SE)	Men % (SE)	Women % (SE)
40 – 49	6.1 (1.4)	5.2 (2.3)	6.8 (1.8)
50 – 59	5.1 (1.4)	5.5 (2.5)	4.8 (1.6)
60 – 69	4.0 (1.5)	6.5 (3.2)	2.4 (1.4)
70+	1.1 (1.1)	3.0 (2.9)	0.0 (0.0)
All	5.0 (0.8)	5.3 (1.4)	4.7 (1.0)

*Chronic bronchitis is defined as both chronic cough and chronic phlegm for two or more years.

The prevalence of self-reported chronic bronchitis of 5.0% is lower than expected considering the 7.2% reported in the Lung Health Survey 2002 in participants aged 15 years and older. This will be discussed in Chapter 8.

Table 73: Estimated population prevalence (SE) of Self-reported Chronic Bronchitis* by pack years and sex

Pack years	All % (SE)	Men % (SE)	Women % (SE)
Never smoker	1.0 (0.6)	0.0 (0.0)	1.4 (0.8)
0 – 10	5.9 (1.5)	5.2 (2.4)	6.5 (2.0)
10 – 20	5.8 (1.9)	2.6 (1.8)	9.7 (3.2)
20+	9.1 (2.4)	11.8 (3.6)	5.1 (2.6)

* Chronic bronchitis is defined as both chronic cough and chronic phlegm for two or more years.

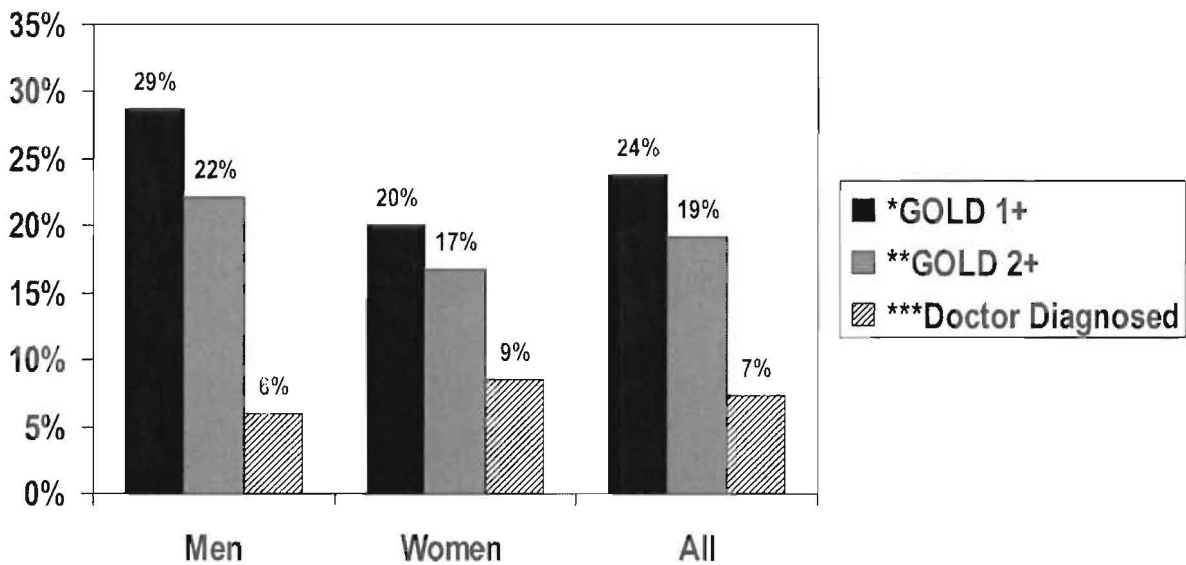
The low prevalence of self-reported chronic bronchitis in women with a >20 pack year history is curious (5.1% vs. 11.8% in men) and is discussed in chapter 8.

Table 74: Estimated population prevalence (SE) of Doctor-Diagnosed COPD*by age and sex

Age	Men % (SE)	Women % (SE)	All % (SE)
40 – 49	5.9 (2.1)	9.0 (2.1)	7.5 (1.5)
50 – 59	8.2 (2.9)	5.9 (1.8)	6.9 (1.6)
60 – 69	2.5 (1.8)	11.7 (3.1)	8.0 (2.0)
70+	5.9 (4.1)	8.1 (3.7)	7.3 (2.7)
All	6.0 (1.4)	8.5 (1.2)	7.4 (0.9)

*Includes chronic bronchitis, emphysema or COPD.

Doctor-diagnosed COPD is considered to be a less reliable indicator of obstructive lung disease in the survey area. The prevalence in women is higher than that in men (8.5% vs. 6.0%). Figure 27 summarises the prevalence of GOLD Stage I and higher, Stage II and higher and doctor-diagnosed COPD, highlighting the difference in prevalence according to definitions used.



*Post BD FEV₁/FVC<70%

** Post BD FEV₁/FVC <70% and post BD FEV₁ <80%

***Includes chronic bronchitis, emphysema or COPD

Figure 27: Population prevalence of GOLD Stage I or higher, Stage II or higher (NHANES III equations) and doctor-diagnosed COPD by sex

Table 75: Estimated population prevalence (SE) of Doctor-Diagnosed COPD* by pack years and sex

Pack years	All % (SE)	Men % (SE)	Women % (SE)
Never smoker	6.0 (1.6)	7.5 (4.3)	5.5 (1.6)
0 – 10	7.3 (1.6)	5.5 (2.3)	8.8 (2.2)
10 – 20	8.1 (2.1)	4.7 (2.4)	12.2 (3.7)
20+	9.3 (2.4)	6.9 (2.9)	12.6 (4.1)

*Includes chronic bronchitis, emphysema or COPD.

Women have approximately twice the prevalence of doctor-diagnosed COPD in comparison to men in all three pack year groupings. This could be due to comparatively higher health service utilisation in women, or more symptomatic disease.

7.3.3. Analysis of risk factors for COPD

Table 76 describes the population aged 40 and over in terms of the distribution of risk factors for COPD. The variables analysed from the BOLD dataset were age, sex, tobacco (including passive smoking), past TB, education level, occupational exposures, smoky domestic fuels, BMI, childhood hospitalisation for chest illness and family history of COPD/emphysema/chronic bronchitis. Confounders included in the analyses were doctor-diagnosed asthma and heart disease.

Information on cannabis smoking, income and alcohol use were collected in the Lung Health Survey and the effective sample size for these variables was smaller than all the other variables (approximately two-thirds of participants had this data - 580 of 847), and thus only univariate analysis is presented in the tables as they were not included in the final multivariate model. Logistic regression adjusting for these risk factors was performed in a separate model and results are presented in the text. Because of the interval between the surveys, this data might not represent the variable status at the time of the BOLD survey.

Univariable analyses of two alternate classifications for cannabis are presented.

Table 76: Distribution of characteristics of the BOLD sample by sex* (n = 847)

Characteristics	All (n = 847) n (%)	Men (n = 315) n (%)	Women (n = 532) n (%)	p*
Income † (n = 574):				
>R2000/month	104 (18.1)	61 (29.5)	43 (11.7)	<0.001
R1000-R2000/month	89 (15.5)	35 (16.9)	54 (14.7)	
<R1000/month	381 (66.4)	111 (53.6)	270 (73.6)	
Education (n = 847): >12 years	43 (5.1)	20 (6.4)	23 (4.3)	0.137
8-12 years	420 (49.6)	166 (52.7)	254 (27.7)	
1-7 years	344 (40.6)	116 (36.8)	228 (42.9)	
None	40 (4.7)	13 (4.1)	27 (5.1)	
Age (n = 847): 40 – 49	335 (39.6)	132 (41.9)	203 (38.2)	0.5
50 – 59	263 (31.1)	92 (29.2)	171 (32.1)	
60 – 69	167 (19.7)	63 (20.0)	104 (19.6)	
≥70	82 (9.7)	28 (8.9)	54 (10.2)	
Any specific occupational exposures (n = 847):				
Unexposed	547 (64.6)	162 (51.4)	385 (72.4)	<0.001
Exposed	300 (35.4)	153 (48.6)	147 (27.6)	
Tobacco (n = 846): Never smoked	195 (23.0)	42 (13.3)	153 (27.8)	<0.001
Passive smoker	75 (9.3)	7 (2.2)	72 (13.5)	
Ex smoker	181 (21.4)	85 (27.0)	96(18.1)	
Current smoker	392 (46.3)	181 (57.5)	211 (39.7)	
Tobacco pack year categories (n = 845): 0	276 (32.7)	51 (16.3)	225 (42.3)	<0.001
0 – 10	242 (28.6)	94 (30.0)	148 (27.8)	
10 – 20	161 (19.1)	77 (24.6)	84 (15.8)	
≥20	166 (19.6)	91 (29.1)	75 (14.1)	
BMI (n = 847): <18.5 (underweight)	65 (7.7)	36(11.4)	29 (5.5)	<0.001
18.5-25 (normal weight)	250(29.5)	134 (42.5)	116 (21.8)	
>25 and <30 (overweight)	228(26.9)	90(28.6)	138 (25.9)	
≥30 (obese)	304 (35.9)	55 (17.5)	249 (46.8)	
Cannabis † (n = 580):				
Never	516 (89.0)	148 (71.2)	368 (98.9)	<0.001
Ex-smoker	31 (5.3)	30 (14.4)	1 (0.3)	
Current smoker	33 (5.7)	30 (14.4)	3 (0.8)	
Cannabis † (n = 580):				
Never	516 (89.0)	148 (71.2)	368 (98.9)	<0.001
Ex-smoker	31 (5.3)	30 (14.4)	1 (0.3)	
Current 1-2 joints/day	13 (2.2)	11 (5.3)	2 (0.6)	
Current ≥3 joints/day	8 (1.4)	7 (3.4)	1 (0.3)	
Cannabis pipe only	12 (2.1)	12 (5.8)	0 (0.0)	

*Persons with acceptable quality spirometry results; ** Chi² test for difference between men and women

***small numbers in this group; **R1000month~US\$ 98.77; †From LHS2002 questionnaire responses

Table 76 continued:

Characteristics	All (n = 847) n (%)	Men (n = 315) n (%)	Women (n = 532) n (%)	p*
Occupational exposure (dusty job) (n = 847): Never	452 (53.4)	124 (39.4)	328 (61.6)	<0.001
Ever	395 (46.6)	191 (60.6)	204 (38.4)	
Childhood hospitalisation (n = 847): Never	815 (96.2)	302 (95.9)	513 (96.4)	0.731
Ever	32 (3.8)	13 (4.1)	19 (3.6)	
Previous tuberculosis (n = 847): Never	719 (84.9)	253 (80.3)	466 (87.6)	0.006
Ever	128 (15.1)	62 (19.7)	66 (12.4)	
Domestic fuels (n = 847): Non- smoky	457 (53.4)	160 (50.8)	297 (55.8)	0.042
Smoky	390 (46.0)	155 (49.2)	235 (44.2)	
Asthma (n = 847): Never diagnosed	724 (85.5)	279 (88.6)	445 (83.6)	0.192
Ever diagnosed	123 (14.5)	36 (11.4)	87 (16.4)	
Alcohol use† (n = 580): Non, light, moderate	548 (94.5)	183 (88.0)	365 (98.1)	<0.001
Heavy	32 (5.5)	25 (12.0)	7 (1.9)	
Heart disease (n = 847): Never diagnosed	769 (90.8)	297 (94.3)	472 (88.7)	<0.001
Ever diagnosed	78 (9.2)	18 (5.7)	60 (11.3)	
Family history of COPD (n = 847): No	715 (84.3)	277 (87.9)	438 (82.3)	0.122
Yes	132 (15.7)	38 (12.1)	94 (17.7)	

*Persons with acceptable quality spirometry results; ** Chi² test for difference between men and women

***small numbers in this group; **R1000month~US\$ 98.77; †From LHS2002 questionnaire responses.

Two thirds of the population earned less than R1000 per month, 15% R1000 – R2000 per month and 18.1% >R2000 per month. More than half the population had >8 years of education, but 5.1% of women and 4.1% overall reported no education at all. There were no significant differences between men and women regarding age (p = 0.5) and >70% of this sample was aged <60 years.

More men had a history of specified occupational exposures than women (48.6 vs. 27.6) and 35.4% overall. These occupations included any of the following: hard-rock mining, coal mining, sandblasting, working with asbestos, chemical or plastics manufacturing, flour, feed or grain milling, cotton or jute processing, foundry or steel milling, welding, fire fighting, or farming. Additionally, to the question “Have you ever worked in a dusty job”, 46.6% reported exposure (see Occupational Exposure- dusty job).

Table 76 shows the distribution of tobacco exposure. A total of 9.3% were passive smokers. Active smokers who had additional passive smoke exposure were excluded from this category and included in current or ex-smoking categories. Division of cumulative tobacco exposure into pack year categories showed that just under a third of this population had a 0 - 10 pack year history, but 19.1% and 19.6% respectively had a 10 - 20 pack year history and a >20 pack year history respectively.

A large proportion of women - 25.9% and 46.8% - were overweight and obese respectively.

There were small numbers in the cannabis exposure categories, both when cannabis was coded quantitatively and categorically, as never, ex and current* (see Table 76). A history of tuberculosis was reported by 15.1% of the sample. Domestic fuel exposure for more than 6 months was reported in 46% - most of this was past/childhood exposure as electrification had been introduced in the area many years before the study. Diagnosed asthma was an important confounder to consider and was reported in 14.5% of the sample. A family history of chronic bronchitis, COPD or emphysema was reported by 15.7%.

Table 77: Analysis of risk factors for GOLD Stage I or higher COPD using survey estimation logistic regression (n = 847)

	n (%) with Stage I COPD	Unadjusted OR (95% CI)	p	Adjusted OR (95%CI)	p
Income*: >R2000/month	16* (15.4)	1.0	0.03	1.0	
R1000-R2000/month	22* (24.7)	2.2 (1.0 – 4.7)			
<R1000/month	97 (25.5)	2.1 (1.1 – 3.8)			
Education: >12 years	5 *(11.6)	1.0	<0.001	1.0	0.9
8-12 years	79 (18.8)	2.0 (0.7 – 5.4)		1.0 (0.3 – 2.7)	
1-7 years	98 (28.5)	3.4 (1.3 – 9.1)		1.0 (0.4 – 2.9)	
None	14*(35.0)	6.1(1.8 – 20.1)		1.6 (0.4 – 6.5)	
Age: 40 – 49	46 (13.7)	1.0	<0.001	1.0	<0.001
50 – 59	60 (22.8)	1.9 (1.2 – 3.0)		2.4 (1.4 – 4.3)	
60 – 69	56 (33.5)	2.9 (1.8 – 4.2)		4.5 (2.5 – 8.3)	
≥70	34 (41.5)	4.6 (2.6 – 8.4)		8.7 (4.1 – 18.8)	
Any specific occupational exposures					
n = 847: Unexposed	128 (23.4)	1.0	0.743	1.0	
Exposed	68 (22.7)	0.9 (0.7 – 1.3)			
Tobacco: Never smoked	19 (9.7)	1.0	<0.001	1.0	
Passive smoker	9 (11.4)	1.0 (0.4 – 2.5)			
Ex smoker	46 (25.4)	2.7 (1.4 – 5.4)			
Current smoker	122 (31.1)	3.8 (2.1 - 7.0)			
Pack year categories: 0	28 (10.1)	1.0	<0.001	1.0	0.022
0 – 10	56 (23.1)	2.6 (1.5 – 4.6)		1.6 (0.9 – 3.0)	
10 – 20	50 (31.1)	4.0 (2.2 – 7.2)		3.1 (1.6 – 6.0)	
≥20	62 (37.4)	4.7 (2.7 – 8.1)		2.5 (1.4 – 4.5)	
BMI: Underweight	47 (72.3)	6.3 (3.3 – 12.0)	0.059	7.2 (3.4 – 15.1)	<0.001
18-24.9 normal weight	73 (28.0)	1.0		1.0	
Overweight BMI >25 and <30	37 (16.2)	0.5 (0.3 – 0.8)		0.6 (0.4 – 1.1)	
Obese BMI≥30	39 (12.8)	0.4 (0.3 – 0.6)		0.5 (0.3 – 0.9)	
Cannabis: Never	110 (21.3)	1.0	0.048	1.0	
Ex Cannabis smoker	12* (38.7)	2.1 (1.0 – 4.7)			
Current 1-2 joints/day	3*(23.1)	1.2 (0.3 – 4.5)			
Current ≥3 joints/day	6* (75.0)	10.3 (1.9 – 56.9)			
Cannabis pipe only	4* (33.3)	1.4 (0.4 – 5.6)			
Cannabis 2**: Never	110 (21.3)	1.0	0.06	1.0	
Ex Cannabis smoker	12* (38.7)	2.1 (1.0 – 4.7)			
Current Cannabis smoker	13* (39.4)	2.1 (1.0 – 4.5)			
Occupational exposure***: Never exposed					
	85 (18.8)	1.0	0.004	1.0	
Ever exposed	111 (28.1)	1.7 (1.2 – 2.3)		1.3 (0.9 – 2.0)	0.188
Childhood hospitalisation: Never					
	188 (23.1)	1.0	0.867	1.0	
Ever	8* (25.8)	1.1 (0.5 – 2.5)			

*R1000month~US\$ 98.7; **Alternative classification of cannabis smoking for univariate analysis; ***dusty job

Table 77 continued:

	n (%) with Stage I COPD	Unadjusted OR (95% CI)	p	Adjusted OR (95%CI)	P
Gender: Female	101 (19.0)	1.0	0.006	1.0	0.882
Male	95 (30.2)	1.6 (1.1 – 2.3)		1.0 (0.7 – 1.6)	
Previous TB: Never	133 (18.5)	1.0	<0.001	1.0	<0.001
Ever	63 (49.2)	4.2 (2.8 – 6.3)		3.4 (2.1 – 5.6)	
Domestic fuels: Non-smoky	90 (19.7)	1.0	0.039	1.0	0.09
Smoky	106 (27.2)	1.4 (1.0 – 2.0)		1.4 (0.9 – 2.2)	
Asthma: Never diagnosed	146 (20.2)	1.0	<0.001	1.0	<0.001
Ever diagnosed	50 (40.7)	2.5 (1.7 – 3.9)		3.0 (1.8 – 5.1)	
Heart disease: Never diagnosed	182 (23.7)	1.0	0.509	1.0	
Ever diagnosed	14 (18.0)	0.8 (0.4 – 1.6)			
Family history: No	158 (22.1)	1.0	0.21	1.0	
Yes	38 (28.8)	1.3 (0.8 – 2.1)			
Alcohol use: Non, light, moderate	124 (22.6)	1.0	0.138	1.0	
Heavy	11 (34.4)	1.8 (0.8 – 3.9)			
Allergic Rhinitis: Never diagnosed	113 (22.5)	1.0	0.216	1.0	
Ever diagnosed	22 (28.2)	1.4 (0.8 – 2.5)			

A history of 10 - 20 pack years resulted in a three fold increased risk and >20 pack years in a 2.5 fold increase for GOLD Stage I and higher COPD. Analysis of age revealed a linear association with a sharp gradient. Persons over the age of 70 had 8.7 times the risk of the 40 - 50 year age group. Previous TB was significantly associated with COPD (see later).

There was a strong association with being underweight, but the direction of effect cannot be established here, as many persons with COPD have muscle wasting and weight loss in the later stages of disease, and loss of weight is also associated with current (and perhaps past) tuberculosis infection, itself a risk factor. Only 7.7% of the population was underweight but 72.3% of this underweight group had COPD (Table 77). Overall, 24.0% of all persons with GOLD Stage I and higher COPD were underweight. Obesity seemed to be associated with a small protective effect ($p = 0.022$). Approximately 41% of persons defined as GOLD Stage I COPD by spirometry had a history of self-reported asthma. Misclassification could be a significant concern here as COPD/emphysema is commonly referred to as “asthma”. There was no association with education level.

Table 78: Analysis of risk factors for GOLD Stage II or higher COPD (NHANES equations) using survey estimation logistic regression (n=847)

	n (%) with Stage II COPD	Unadjusted OR (95% CI)	p	Adjusted OR (95%CI)	P
Income*: >R2000/month	10 (9.6)	1.0	0.015	1.0	
R1000-R2000/month	16 (18.0)	2.2 (0.9 – 5.7)			
<R1000/month	84 (22.1)	2.9 (1.4 – 6.3)			
Education: >12 years	2 (4.7)	1.0	0.011	1.0	0.6
8-12 years	69 (16.4)	4.7 (1.0 – 21.1)		3.0 (0.4 – 22.0)	
1-7 years	79 (23.0)	6.8(1.5 – 30.3)		2.5 (0.3 – 18.0)	
None	12 (30.0)	10.3(2.0 – 52.5)		2.8 (0.3 – 22.7)	
Age: 40 – 49	37 (11.0)	1.0	<0.001	1.0	<0.001
50 – 59	51 (19.4)	1.8 (1.1 – 3.0)		2.3 (1.3 – 4.3)	
60 – 69	48 (28.7)	2.8 (1.7 – 4.7)		4.2 (2.3 – 7.9)	
≥70	26 (31.7)	3.2 (1.7 – 5.8)		5.3 (2.5 – 11.4)	
Any specific occupational exposures n = 847:					
Unexposed	113 (20.7)	1.0	0.092	1.0	
Exposed	49 (16.3)	0.7 (0.5 – 1.0)			
Tobacco: Never smoked	13 (6.7)	1.0	<0.001	1.0	
Passive smoker	8 (10.1)	1.5 (0.6 – 3.9)			
Ex smoker	40 (22.1)	3.7 (2.0 – 6.7)			
Current smoker	101 (25.8)	4.8 (2.8 – 8.0)			
Pack year categories: 0	21 (7.6)	1.0	<0.001	1.0	<0.001
0 – 10	47 (19.4)	3.2 (1.8 – 5.8)		2.0 (1.0 – 3.9)	
10 – 20	40 (24.8)	4.6 (2.5 – 8.3)		3.6 (1.8 – 7.1)	
≥20	54 (32.5)	5.9 (3.4 – 10.3)		3.3 (1.7 – 6.4)	
BMI: <18 (underweight)	44 (67.7)	7.1 (3.7 – 13.7)	<0.001	8.5 (4.0 -17.8)	<0.001
18-24.9 (normal weight)	58 (23.2)	1.0		1.0	
>25 and <30 (overweight)	27 (11.8)	0.5 (0.3 – 0.8)		0.6 (0.3 – 1.0)	
≥30 (obese)	33 (10.9)	0.4 (0.3 – 0.7)		0.6 (0.3 – 1.0)	
a) Cannabis†: Never	91 (17.6)	1.0	0.057	1.0	
Ex-smoker	9 (29.0)	1.8 (0.8 – 4.3)			
Current 1-2 joints/day	1 (7.7)	0.4 (0.1 – 3.1)			
Current ≥3 joints/day	5 (62.5)	6.7 (1.5 – 30.2)			
Cannabis pipe only	4 (33.3)	1.8 (0.5 – 7.2)			
b) Cannabis†: Never	91 (17.6)	1.0	0.18	1.0	
Ex-smoker	9 (29.0)	1.8 (0.8 – 4.3)			
Current smoker	10 (30.3)	1.7 (0.8 – 3.7)			
Occupational exposure**:					
Never	75 (16.6)	1.0	0.058	1.0	0.9
Ever	87 (22.0)	1.4 (1.0 – 2.1)		1.0 (0.6 – 1.5)	
Childhood hospitalisation:					
Never	156 (19.1)	1.0	0.98	1.0	
Ever	6 (19.4)	1.0 (0.4 – 2.6)			

*R1000month~US\$ 98.7; † Data obtained from LHS2002; **dusty job

Table 78 continued:

	n (%) with Stage II COPD	Unadjusted OR (95% CI)	p	Adjusted OR (95%CI)	p
Gender : Female	87 (16.4)	1.0	0.054	1.0	0.596
Male	75 (23.8)	1.4 (1.0 – 2.0)		0.9 (0.5 – 1.4)	
Previous TB: Never	109 (15.2)	1.0	<0.001	1.0	<0.001
Ever	53 (41.4)	4.2 (2.7 – 6.5)		3.2 (1.9 – 5.4)	
Domestic fuels: Non-smoky	76 (16.6)	1.0	0.151	1.0	0.173
Smoky	86 (22.1)	1.3 (0.9 – 1.8)		1.4 (0.9 – 2.1)	
Asthma: Never diagnosed	118 (16.3)	1.0	<0.001	1.0	<0.001
Ever diagnosed	44 (35.8)	3.0 (1.9 – 4.6)		3.7 (2.2 – 6.4)	
Heart disease: Never diagnosed	152 (19.8)	1.0	0.114	1.0	
Ever diagnosed	10 (12.8)	0.6 (0.3 – 1.2)			
Family history of COPD: No	131 (18.4)	1.0	0.267	1.0	
Yes	31 (23.5)	1.3 (0.8 – 2.2)			
Alcohol use[†]: Non, light, moderate	102 (18.6)	1.0	0.281	1.0	
Heavy	8 (25.0)	1.6 (0.7 – 3.7)			
Allergic Rhinitis: Never diagnosed	90 (17.9)	1.0	0.074	1.0	
Ever diagnosed	20 (25.6)	1.7 (0.9 – 3.1)			

**R1000month~US\$ 98.7 † Data obtained from LHS2002.

Table 78 shows the analysis of GOLD Stage II and higher COPD to be similar to that of GOLD stage I and higher COPD, with significant associations with tuberculosis (OR 3.2; 95% CI: 1.9 – 5.4), underweight (OR = 8.5; 95% CI: 4.0 -17.8) and tobacco packyears.

A multivariate model (n= 571) including cannabis (ever vs. never) and income failed to show significant associations (p-values of 0.9 and 0.6 respectively (model not shown).

Table 79: Analysis of risk factors for COPD by GOLD staging using survey estimation multinomial logistic regression (n = 847)

	Stage I and II COPD			Stage III and IV COPD		
	n (%) Stage I/II COPD	Adjusted OR (95% CI)	p	n (%) Stage III/IV COPD	Adjusted OR (95%CI)	p
Education: ≥8 years	66 (46.2)	1.0	0.9	18 (34.0)	1.0	
<8 years	77 (53.9)	1.0 (0.7 – 1.6)		35 (66.0)	1.5 (0.7 – 3.3)	0.35
Age (continuous variable):	143 (16.9)	1.08 (1.054 - 1.104)	<0.001	53 (6.3)	1.07 (1.036 - 1.105)	<0.001
Pack year categories: 0	24 (16.8)	1.0		4 (7.6)	1.0	
0 – 10	45 (31.5)	1.9 (0.9 – 3.7)	0.07	11 (20.8)	2.4 (0.6 – 9.2)	0.2
10 – 20	34 (23.8)	2.7 (1.3 – 5.6)	0.006	16 (30.2)	13.8 (3.8 – 50.3)	<0.001
≥20	40 (28.0)	2.3 (1.2 – 4.2)	0.01	22 (41.5)	7.7 (2.2 – 27.0)	0.001
BMI: <18.5 (underweight)	27 (18.9)	5.7 (2.6 – 12.3)	<0.001	20 (37.4)	16.1(5.8 – 44.8)	<0.001
18.5 -24.9 (normal weight)	54 (37.8)	1.0		19 (35.9)	1.0	
>25 and <30 (overweight)	31 (21.7)	0.7 (0.4 – 1.2)	0.172	6 (11.3)	0.4 (0.1 – 1.4)	0.16
≥30 (obese)	31 (21.7)	0.5 (0.3 – 0.9)	0.03	8 (15.1)	0.6 (0.2 – 1.6)	0.27
Occupational exposure*:						
Never	64 (44.8)	1.0		21(39.6)	1.0	
Ever	79 (55.3)	1.4 (0.9 – 2.1)	0.177	32(60.4)	1.2 (0.6 – 2.4)	0.6
Gender: Female	74 (51.8)	1.0		27 (50.9)	1.0	
Male	69 (48.3)	1.2 (0.7 – 1.9)	0.5	26 (49.1)	0.7 (0.3 – 1.5)	0.35
Previous TB: Never	108 (75.6)	1.0		25 (47.2)	1.0	
Ever	35 (24.5)	2.6 (1.5 – 4.6)	0.001	28 (52.8)	8.9 (4.2 – 18.9)	<0.001
Domestic fuels: Non-smoky	65 (45.8)	1.0		24 (45.3)	1.0	
Smoky	77 (54.3)	2.3 (1.3 – 4.1)	0.2	29 (54.7)	1.8 (0.8 – 3.7)	0.14
Asthma: Never diagnosed	115 (80.4)	1.0		31 (58.5)	1.0	
Ever diagnosed	28 (19.6)	1.3 (0.5 – 3.3)	0.006	22 (41.5)	8.7 (3.7 – 20.2)	<0.001

* dusty job

The multinomial model (Table 79) showed a significant association of previous TB as a risk factor for COPD. The risk increased from 2.6 times increased risk for mild/moderate COPD (Stage I/II) to 8.9 in severe COPD (Stage III/IV).

Asthma was associated with a 2.3 times increased risk for mild/moderate COPD and this risk almost quadrupled to 8.6 for severe disease.

Cumulative smoking exposure of 0 - 10 pack years was not associated with a significantly increased odds of mild/moderate COPD ($p=0.07$) or severe COPD ($p=0.2$). A smoking history of 10 - 20 pack years carried a risk of 2.7 for mild/moderate disease and a risk of 13.8 for severe disease, (19.1% of the population smoked 10 - 20 pack years). A history of >20 pack years (19.6% of the population) was associated with a 2.3 times increased risk of mild/moderate disease and a 7.7 times increase for severe disease. The size and plausibility of effect is considered below by means of calculated population attributable fractions.

Being underweight was associated with a 5.7 fold and 16 fold increased odds of mild/moderate and severe disease respectively. There appeared to be some small protective effect for mild/moderate disease associated with obesity (OR 0.5; 95% CI: 0.3 - 0.9, $p=0.03$).

Interactions between BMI and gender, BMI and asthma, and TB and smoking were tested in the final model and none of them were found to be significant ($p=0.6$; $p=0.8$ and $p=0.8$ respectively).

Summary of association with tuberculosis

The prevalence of GOLD Stage I and higher COPD in those with and without a history of TB was 49.7% vs. 19.1% respectively ($p<0.001$). One third (32.1%) of persons with GOLD Stage I and higher COPD had a past history of TB.

The prevalence of GOLD Stage II and higher COPD in those with and without a history of TB was 42.2% vs. 14.9% respectively ($p<0.001$). One third (34.1%) of persons with GOLD Stage II and higher COPD had a past history of TB.

Table 77 shows that a strong association of GOLD Stage I and higher COPD with a past history of tuberculosis emerged (OR = 3.4; 95% CI: 2.1 – 5.6). This association is

maintained with GOLD Stage II and higher COPD (OR 3.2; 95%CI 1.9 - 5.4) (Table 77). Multinomial modelling has shown that the risk associated with past tuberculosis is highest in those with severe COPD (OR 8.9; 95%CI 4.2 - 18.9).

Of all persons with COPD, 13.3% were never smokers. In never smokers with past tuberculosis, 18.3% had GOLD Stage I or higher COPD, but this estimate was based on small numbers (4/20 persons - estimate corrected for weighting and clustering).

In never smokers with no past tuberculosis, 9.7% had GOLD Stage I or higher COPD (23/226 persons). The difference between the above two groups was not statistically significant ($p=0.2$), but no inferences can be made from estimates with such small numbers. Consequently the relationship of TB as a risk factor for COPD in never smoking men and women could not be examined separately to see if past tuberculosis was associated with COPD in never smokers.

Radiology to detect current and previous tuberculosis was performed in 75% of persons in the LHS2002, but not on those in the BOLD cohort. However, in the latter, two thirds had taken part in the LHS2002, and 58% (493/846) of the BOLD sample had a chest radiograph from the LHS2002. Radiographic evidence of tuberculosis was present in 17.4% of the BOLD sample.

The prevalence of GOLD Stage I and higher COPD in those with and without evidence of TB on chest radiograph was 60.3% vs. 16.2% respectively ($p<0.001$). In those with GOLD Stage I and higher COPD, 44% had evidence of tuberculosis on chest radiograph.

Overall 10.1% of the population (aged ≥ 40 years) had evidence of bronchodilator reversibility, defined as a ≥ 200 ml and $\geq 12\%$ change in FEV₁. Reversibility was present in 19.4% of participants with GOLD Stage I or higher COPD and 7.3% of those with no COPD ($p<0.001$). Reversibility was present in 13.9% of those persons with a past history of tuberculosis and in 9.5% of those with no history of tuberculosis ($p= 0.2$).

Table 80: Population attributable fractions for GOLD stage II (NHANES) or higher COPD

Risk Factor	Percentage exposed to risk factor	Prevalence Odds Ratio (Stage II or higher regression model)	Population Attributable Fraction (%)
0-10 pack years	28.6	2.0	22.2
10 – 20 pack years	19.1	3.6	33.2
>20 pack years	19.6	3.3	31.1
Underweight	7.7	8.5	36.6
Past TB	15.1	3.2	24.9

GOLD Stage II or higher was chosen as the outcome with which population attributable fractions were calculated as this is a threshold of practical and public health importance.², i.e. the prevalence odds ratios are from this model. Collectively, 86.5% of GOLD Stage II and higher COPD was attributable to cigarette smoking. Tuberculosis was responsible for 25%, and 36.6% was attributable to being underweight. Again, one of the assumptions made in calculating population attributable fractions is that they are completely adjusted for confounders, which is often not the case, and this results in the total adding up to more than 100%

No calculation was made of a PAF for cannabis and income (socioeconomic status) as they had been excluded from the final model (see above).

7.4. References

¹ Hankinson et al. Spirometric reference values from a sample of the general U.S. population. *Amer J Respir Crit Care Med*, 1999;159:179-187.

² Celli BR, Halbert RJ, Isonaka S, Schau B. Population impact of different definitions of airway obstruction. *Eur Respir J*. 2003 Aug;22(2):268-73.

CHAPTER 8: DISCUSSION

8.1. SUMMARY OF THE MAIN STUDY FINDINGS

1. The prevalence of respiratory symptoms in this community is high at 38.3%, reflecting the high rates of smoking and exposure to other harmful exposures in adults.
2. Other significant modifiable factors found to be associated with respiratory symptoms were cannabis smoking, pulmonary tuberculosis, occupational exposures, childhood chest illness and low socioeconomic status.
3. This is the first African study to examine the effects of cannabis smoking on respiratory health at a population level. A strongly positive association between cannabis smoking and respiratory symptoms was observed, but the small numbers and the resulting difficulty of quantitation of cannabis exposure prevented an assessment of a relationship with COPD and dose-dependency.
4. The prevalence of COPD in persons aged ≥ 40 years from Ravensmead and Uitsig in Cape Town (GOLD Stage I or higher of 24%) is amongst the highest yet reported from any part of the world.
5. The prevalence of COPD is high in both men and women reflecting the high prevalence of smoking among women in this community.
6. The majority of COPD is classified as GOLD Stage II and higher (19.1% of the population ≥ 40 years), confirming that the COPD is established and clinically significant and likely to be associated with significant morbidity, mortality and use of health resources.
7. The prevalence of COPD in never-smoking women is high, reflecting the aetiological role of risk factors such as tuberculosis, and/or early life lung insults. This raises the question of whether all those with symptoms and airflow limitation have COPD or other forms of lung disease associated with these features - for example, post-tuberculous lung disease and bronchiectasis.
8. The demonstration that a history of previous pulmonary tuberculosis is the strongest predictor of COPD (in terms of odds ratio, rather than the proportion affected) raises several questions: the first of which is whether COPD associated with previous tuberculosis should be considered as COPD or as a special sub-group of COPD that requires further study. This would be to characterise the pathophysiology (e.g. prevalence of AHR in this group), elucidate the mechanisms causing airflow obstruction, and examine its responsiveness to treatments developed for smoking-related COPD.
9. These studies confirm that obstructive lung disease (asthma and COPD) is underrecognised and undertreated, and that greater provision needs to be made for the needs of patients with these conditions, and for preventing them.

8.2. DISCUSSION OF METHODOLOGY:

The Lung Health Survey 2002 and The BOLD study

8.2.1. Study area and sample

Details of the study population and reasons for their selection for these studies have been provided in Chapters 3 and 4. The results of the study vindicate this choice, in that there was a sufficiently high response rate, mix of respiratory symptoms and COPD, and other respiratory diseases, and of risk factors to permit analysis of associations and interactions. The next relevant question is the generalisability of the prevalence findings to other parts of South Africa. This is difficult to estimate but is likely to be limited, owing to the heterogeneity of the South African population with respect to income, socio-economic status, occupational exposures, background prevalence of infections, and infectious diseases like tuberculosis, smoking and environmental atmospheric pollution. In recent years, the prevalence of HIV infection, with its attendant effects on the prevalence of lung disease and on survival, has added to the complexity of exposure to risk factors.

However, the prevalence results give an indication of the likely considerable burden of COPD in low-to-middle income urban South Africans, which represents a large proportion of the population. In fact, the growing number of persons living in urban poverty worldwide is likely to share many exposures with this group, making the evaluation of associations relevant to these contexts. From the SA Census figures of 2001, 56% of the population live in urban areas¹, and 38.6% of the population fall below the poverty line of R3000 per capita per annum.² In addition, in terms of smoking, although smoking rates in adults are high in this province, it is similar in others, particularly amongst males. However, amongst females the Western and Northern Cape are highest. Thus, to varying and proportionate extents, similar findings are likely in other regions and communities with similar risk exposure. The analysis of risk factors provides a means of profiling different areas and communities in South Africa for the likelihood of a high burden of COPD and symptoms of lung disease.

8.2.2. Survey design

A limitation of cross-sectional studies, like those reported here, are that, while they permit assessment of associations between risk factors and disease, they cannot confirm causality. Exposures and disease are assessed at the same time. Consequently, the temporal relationship between the exposure and the disease cannot

be assessed, unless the exposure remains constant over time e.g. sex, gene sequences. The associations may be chance phenomena (possible with small sample sizes), consequential or causal.³

8.2.3. Bias

Selection bias

As in most population-based studies, sampling was limited to the non-institutionalised population indicating that those from the area who were in prison or hospitalised were underrepresented, making selection not truly random. However, it is known that the characteristics of institutionalised persons are different to the rest of the population.

Secondly, only persons who were relatively “well” participated in the studies, and in the case of the BOLD study, only those who were able to perform satisfactory lung function tests were included in the study. Both of these represented further sources of selection bias. Reasons for not performing lung function testing included illness such as recent surgery, being bedridden, or inability to comply with the requirements of the test. Causes of the former and latter are many, and result in exclusion of a significant proportion of potential participants. In this study the total number excluded was 111 amounting to 11.6% of the random sample. Causes include inability to tolerate or adequately seal the lips around the mouthpiece or inability to perform reproducible forced expiratory manoeuvres. These reasons for excluding participants are more common in community studies where participants are untrained and unaccustomed to lung function testing, in the elderly, the frail, and patients with severe airflow obstruction. This presents a special challenge in COPD studies like the BOLD study, since these are performed in persons 40 years and older, many of them in older decades and with high prevalence of COPD and co-morbid diseases, particularly in this population. A selection bias thus operates against the disease in question, and the results are likely to under- rather than over-estimate the true prevalence.

Non-response bias is a form of non-systematic bias that is unavoidable because of the ethical need to ensure voluntary participation. In the LHS2002, replacement of non-responding households was undertaken, attempting to retain the geographic location of the original address, and in the hope of retaining characteristics such as socioeconomic status. However, some degree of bias would still have been introduced by this procedure, but the power maintained. In some cases, sampled persons did not

want to participate because of concerns about stigmatisation - perception that their household might be regarded as unhealthy, harbouring tuberculosis and other lung disease - or simply that they were not interested or did not want to divulge medical histories and other personal details of their household. Analysis of the responding vs. non-responding addresses confirmed that the age and sex of occupants of these categories were not significantly different. In addition, appropriate adjustment for replacements was made in the analyses. Since crude (unadjusted) prevalence estimates were very similar to prevalence estimates adjusted for clustering and non-response in both studies, it can be concluded that the effect of non-response is likely to have been minimal.

In the BOLD study, replacement procedures were not employed, resulting in a lower response rate. However, this response rate was still more than adequate for a population-based survey. In addition, demographic data were collected on the non-responders and this was compared to that of responders. Responders were found to be significantly different from non-responders with respect to age, sex, smoking status and whether or not they had doctor-diagnosed asthma, COPD, chronic bronchitis or emphysema, but were similar regarding the presence of comorbidity. Comparisons were also made of responders with and without quality spirometry and no significant differences were found for all the parameters mentioned above (results not presented).

An unusual additional form of “non-response” bias may have operated in the studies. Owing to funding and logistical difficulties the two studies could not be performed contemporaneously, but were performed two years apart. The delay in performing the BOLD study had several consequences. Firstly, a proportion of potential participants were lost to ‘follow up’ owing to death and relocation. This resulted in the BOLD study having to recruit additional participants. Secondly, it prevented direct comparison of results of the LHS2002 with the results of BOLD in all patients. Finally, the validity of responses to the LHS2002 questionnaire to health (and lung disease) status measured two years later has to be questioned. However, the latter provided the opportunity for comparing the reproducibility and consistency of responses over time – an analysis that has not been presented in this report. It should be noted that the BOLD study was designed to be an independent cross-sectional study, and sampled all individuals aged ≥ 40 years residing at the sampled addresses at the time of the study, and consequently does not coincide entirely on the LHS2002 sample. Approximately two thirds (68%) of the study population was common to both the studies (652/958).

In both studies, considerable effort was made to avoid the “sick population effect”, which is the converse of a healthy worker bias, where old and sick persons who are at home during the day, are overrepresented. To avoid this effect, participants were recruited at various times of the day, especially in the evenings and at weekends, in order to ensure that working persons were adequately represented. This strategy also resulted in higher response rates.

A final limitation which might have influenced the results of the studies is that the standardised BOLD questionnaire did not include questions on cannabis use and income. Consequently, we were unable to include one third of the BOLD sample in the analysis of the effects of cannabis on the prevalence of COPD (information was available from LHS2002 on only 580 of the 847 persons in the BOLD cohort). Since both cannabis and income were strongly associated with symptoms of obstructive lung disease in the LHS2002 analysis, their association with COPD was of particular interest. In the final multivariable analysis a separate model was run with the sample size of 580 persons, but this limited the power of the study and only limited conclusions could be drawn (as a consequence of the numbers with categorised cannabis exposure being low).

Information bias

On order to minimise interviewer bias, interviewers were trained appropriately using standard training (detailed in the manual of procedures of both studies), so that there was no interpretation of responses, or differences in effort to elicit responses. This point was stressed throughout the studies and quality control involved observation of interviewing, feedback and retraining (if necessary). Quality control in the BOLD study was more stringent than that employed in the Lung Health Survey, particularly with regard to interviewer technique and coaching to avoid pitfalls. In addition, the use of spirometry, an objective test for the presence of the target disease added more certainty than is possible with self-reported symptoms or self-reported doctor-diagnoses.

Some level of recall bias is inevitable in any questionnaire-based study. Participants may either exaggerate exposures such as to occupational agents (overreporting), or minimise exposures such as cannabis or cigarette smoking (underreporting). The impact of these sources of potential bias cannot be estimated, but their direction is

usually toward underreporting. For cannabis smoking, the magnitude of the bias is suspected to be higher in women, in whom it is less socially acceptable in this community. Women may be more embarrassed to declare use. However, since cannabis smoking is illegal, a disclosure bias is likely to operate in both sexes, but despite this, the prevalence of cannabis smoking in men is high. The difficulties in estimating this bias in population based-studies is acknowledged and it renders calculation of cumulative exposure of cannabis (joint-years) and even tobacco smoking (pack-years) somewhat inaccurate. This may account for the reported lack of evidence of a dose-related effect of cannabis smoking on COPD.

8.2.4. Misclassification

Asthma vs. COPD

Diagnosing asthma and COPD in adults in epidemiological studies can be difficult without the clinical perspective of a physician, especially in smokers and older persons. Respiratory questionnaires are good screening tools for identifying symptoms of obstructive lung disease, but most guidelines agree that spirometry should be the basis for diagnostic confirmation of COPD⁴ and an important tool for asthma diagnosis.⁵ However, as discussed below, even spirometry has limitations, and cannot on its own distinguish asthma and COPD. Instead, the most reliable diagnosis of both conditions requires both history and spirometry. Physical examination plays only a small part in this assessment, making it possible to perform population-based studies with symptom questionnaires, for the purpose of estimating prevalence. Other methods employed in surveys are questions on 'doctor-diagnosed' disease (asthma or COPD). However, this is an imprecise method and is highly dependent on health resources and access to physicians (and specialists) and confirmatory investigations like spirometry. For example, in a setting like Ravensmead/Uitsig, where most care is received in public primary care facilities that do not have spirometry, and where access to specialist clinics is limited, only the most severe cases of COPD and possibly even of asthma are likely to be diagnosed, and many of the diagnoses might be wrong. Thus, underdetection and underestimation of prevalence and severity are to be expected.

The condition most reliably reported in surveys is chronic bronchitis, since this relies entirely upon symptoms that can be elicited in a questionnaire. In the current studies, the diagnostic imprecision of distinguishing asthma from COPD was acknowledged. Both chronic bronchitis and COPD prevalence were reported recognising that in both

instances it would not be possible to exclude some contamination from asthma, either as pure cases, or in the form of patients with mixed disease (both asthma and COPD). In epidemiological terms, a method of reducing misclassification is to focus on the older age-groups, where COPD is more common than asthma (the reverse being true for those under 40 or 45 years). This was the only filter that was applied in the BOLD study.

In other settings, questionnaire responses perform well in differentiating persons with COPD from those with asthma. Besides age, increasing pack years, slow progressive worsening of cough or dyspnoea, breathing-related disability or hospitalisation, sputum quantity >15ml per day, “cold going to the chest”, and receipt of treatment for COPD have all been helpful in identifying subjects with COPD.⁵

The use and interpretation of spirometry in diagnosing COPD also requires some discussion. According to the GINA guidelines, asthma is defined as “a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.⁶ The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible, either spontaneously or with treatment”.⁶ By contrast, COPD is defined as “a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases”.⁴ Thus, the nature of airflow limitation differs in these conditions, but some important spirometric differences cannot be assessed in a cross-sectional survey – namely, its episodic nature, diurnal variation, variability over short periods of time, tendency to return to normal in asthma, and partial or total irreversibility, and progressive nature for COPD.

What can be assessed is reversibility following use of a bronchodilator, and whether the latter results in values that can be viewed to exclude persistent airflow obstruction (and FEV₁/FVC ratio of >70%). In COPD, the airflow limitation is only partially reversible (or poorly reversible). Thus, when testing for the presence of COPD, a post-bronchodilator test is recommended and most informative, whereas for asthma, FEV₁ measured before and after bronchodilator and/or tests of AHR are the standard approaches to diagnosis.

Another feature that is of some value is the magnitude of response to a bronchodilator. Although improvement of greater than 200ml (and $\geq 12\%$ of prebronchodilator value) is considered in guidelines to represent a significant improvement suggesting the presence of asthma, it has a poor discriminant value between these two conditions, but improvement of 400ml is recommended as a more robust indicator of asthma.⁷ Thus, for the purpose of surveys like the BOLD study that involve spirometry, certain rules apply. The presence of a $FEV_1/FVC \geq 70\%$ and reversibility ≥ 200 ml and $\geq 12\%$ of baseline FEV_1 suggests asthma or is compatible with COPD with a reversible component. In addition, in asthma, the FEV_1 between attacks can be normal or near normal. In COPD, in all but Stage I, a reduced FEV_1 is required. A value of $\leq 70\%$ is specified in the GOLD definition, but as discussed later, it can be argued that other figures, or even a figure that diminishes with increasing age, might be more reliable in confirming airflow obstruction. To ensure that it is 'fixed' rather than temporary bronchospasm, in COPD it is specified that the FEV_1 (and FEV_1/FVC) should be postbronchodilator. By contrast, a pre-bronchodilator value is more useful in asthma, since diagnostic evidence of obstruction may disappear following bronchodilator use.

In surveys, only a single spirometric measure is possible, or at most, as in the BOLD methodology, a pre- and post-bronchodilator value. Clinical studies have demonstrated that such single assessments are likely to underestimate asthma, since only a little over half of asthmatic patients demonstrate reversible airflow obstruction at any single assessment.⁸ This may be because their airflow limitation is mild and intermittent, or because they are receiving effective controller therapy (like inhaled corticosteroids), or because they have recently taken a bronchodilator.

Respiratory symptoms caused by non obstructive lung disease and other organ systems

Although in epidemiological studies, all chronic cough, sputum, wheeze and dyspnoea is assumed to be caused by obstructive lung disease, there are many other causes that need to be considered, particularly in communities with high levels of pulmonary co-morbidity like tuberculosis and pneumonia. For example, although bronchiectasis is a rare cause of cough in developed countries, it is a common consequence of pulmonary tuberculosis, measles and other forms of viral and post-viral infections in poor communities, and bears a strong relationship with socio-economic status. Furthermore, its course depends upon adequacy of treatment (treating infective episodes), which in

turn reflects access to care, more likely to be deficient in poor communities. Thus, while this cause of cough can be largely disregarded in developed countries, it should at least be considered in low-income communities.

Other pulmonary causes of respiratory symptoms include rare diseases like sarcoidosis and other interstitial lung diseases, bronchiolitis obliterans, allergic bronchopulmonary aspergillosis, endobronchial tumours or cysts, Churg-Strauss syndrome and chronic eosinophilic pneumonia among many others.⁹ The prevalence of these disease entities is very low in comparison to that of obstructive lung disease, and likely to be constant across survey areas (when comparing one community with another). Misclassification of these diseases, which is almost inevitable with the limited screening involved in prevalence surveys, has little practical significance, and a trivial effect on the assessment of risk factors for pulmonary disease.

Upper airway causes of respiratory symptoms include post nasal drip, congenital anomalies, infections, post traumatic injury, foreign bodies, vocal cord paralysis and extrinsic compression by tumours or inflammatory masses.⁹ Furthermore, left ventricular failure caused by valvular heart disease, cardiomyopathy, congenital heart disease and other cardiac disease may result in intermittent or persistent cough and even wheeze. Because Ravensmead and Uitsig appear to have a high prevalence of ischaemic heart disease, this cause may be significant in the over 40 year age group. For this reason, adjustment for diagnosed heart disease was made in multivariate analysis of risk factors for all associated symptom outcomes, i.e. cough, wheeze and dyspnoea. Known common gastrointestinal causes of respiratory symptoms include gastro-oesophageal reflux, oesophageal spasm and chronic gastric aspiration. These were not considered in the current surveys.

8.2.5. Questionnaires

The LHS2002 and the BOLD study questionnaires included questions that have been validated in other studies elsewhere in the world. The translation into Afrikaans, the language of the community studied, might have introduced a bias resulting from differences in language usage or interpretation. The BOLD study questionnaire went through a stringent forward and back translation process by language specialists in order to minimise this bias. During analysis, differences were noted in the reporting of “cough” and “phlegm”, in keeping with prior knowledge of language usage by physicians in the project team. Studies have shown that small differences in the

phrasing or local word use in a questionnaire can have a significant effect on prevalence estimates.¹⁰ Many persons who denied cough reported phlegm production, not necessarily linking the two processes to each other. The original MRC questions using the term “bring up phlegm” was used instead of “cough up phlegm”, which was appropriate in this setting because of local Afrikaans word usage. Importantly, the term used in Afrikaans is different to that used for vomiting because “bring up” in South African English usage can be used to describe vomiting in certain local contexts.

Ethnic differences in word descriptors used during bronchoconstriction have been described elsewhere¹¹, and similarly, differences in terminology for respiratory symptoms exist within different South African ethnic groups. Several other questions in the LHS2002 questionnaire were new, and developed for the study. These included questions relating to cannabis smoking and tuberculosis risk factors. The validity of some of the questions will be considered with the results of spirometry in a separate study, and are not presented here. Both the LHS2002 questionnaire and the BOLD questionnaire have the potential to be translated into the other national languages and be used in other parts of South Africa to assess lung health.

8.2.6. Spirometry as an outcome measure

Using measurements such as FEV₁ and FVC as a surrogate marker for severity of parenchymal damage and lung function, has been criticised owing to the fact that they are difficult manoeuvres that are highly effort dependent.¹² In addition they require very well trained technologists/healthcare workers for performance and quality control in order to be valid (of which there are very few in South Africa). The BOLD study employed a limited number of well-trained technologists and nurses in order to minimise inter-observer bias, and followed ATS recommendations for the performance of tests. The ndd Easyone® spirometer was well suited for a field study owing to its light robust design, accurate measurements and ability to be used in non- temperature and pressure controlled circumstances. In addition, its feedback system allowed for immediate identification of performance errors, accompanied by simple advice to correct the manoeuvre e.g. “don’t hesitate”, “blow <six seconds” etc.

It has been suggested that a more moderated manoeuvre such as the slow vital capacity may be a better indicator than a maximal effort manoeuvre.¹² However, even though the reproducibility of a slow vital capacity manoeuvre is better than that of the FEV₁, it is more difficult to perform both for the operator and the subject. Dirksen et al,

(2003) described FEV₁ as problematic because the standard deviation of repeated measurements of FEV₁ is larger than the annual decline in FEV₁, even in heavy smokers.¹³ However, Enright et al (2004) emphasize that in large-scale studies, 90% of persons perform FEV₁ with a limit of variation of 120ml.¹⁴

Other tests can be used to improve the precision of the diagnosis of COPD. These include more challenging lung function tests like the single breath CO diffusion capacity test, studies of lung compliance, and high resolution CT scans.¹² However, such methods are expensive, and not practical for community surveys, presenting problems in that they cannot be performed in the field. In addition, some procedures, like CT scanning, involve exposures that may not be acceptable for community-wide screening. Response rates for off-site tests in surveys are also significantly lower. For example, in the LHS2002, all participants were invited to present for a chest radiograph. In spite of provision of transport and the favourable location of the Radiograph site less than 1-2km from their homes, the response rate was only 75%.

The GOLD staging of severity of COPD using FEV₁ has been criticised as empiric and non-informative. However, it has recently been shown to perform well in a large study performed in the USA, the Atherosclerosis Risk in Communities (ARIC) study.¹⁵ In this eleven year cohort of persons aged 43- 66 at baseline, there was a clear increase in risk of increasing mortality from GOLD stages 0 to 4 (Hazard ratio 1.4 to 5.7). The presence and severity of respiratory symptoms were shown to also predict mortality.

The GOLD classification uses postbronchodilator FEV₁, raising concerns that the use of prebronchodilator measurements by some studies could lead to over estimation of the prevalence and severity of disease.¹⁶ Postbronchodilator measurements reduce (but do not eliminate) misclassification of asthma and there is some evidence to suggest that postbronchodilator FEV₁/FVC ratio is a better indicator of COPD than other measurements. Currently, reference values for prebronchodilator measurements are used for postbronchodilator results, a practice that may result in underestimation of disease severity. A first attempt at deriving postbronchodilator reference values has recently been published by Johannessen et al.¹⁷ There has also been recent interest in FEV₆ and FEV₁/ FEV₆ as a surrogate for FVC and FEV₁/FVC respectively, in order to detect obstruction.^{18 19}

8.3. DISCUSSION OF MAIN RESULTS

8.3.1. The Lung Health Survey 2002: Prevalence of Respiratory Symptoms (≥ 5 years)

Overall, 38.3% of the population reported the presence of at least one respiratory symptom, which is in keeping with high symptom prevalences found in other parts of the world such as Italy, Estonia, Sweden and Finland.^{20 21} Usual winter morning phlegm was the most commonly reported symptom (25.3%), followed by recent cough (19.5%), wheeze (12.9%) and dyspnoea grade 1 or higher (12.7%). Over seven percent of the population experienced night waking from dyspnoea or a tight chest in the last year, which suggested moderate to severe disease.

A significant proportion (18.2%) of persons aged ≥ 40 had grade 2 (or higher) dyspnoea. For the whole adult population ≥ 5 years or above this figure was 10.3%. This is a very high prevalence of breathlessness for the whole population, and, if correct, is likely to impact significantly upon productivity and activities of daily living. Its correlation with other symptoms and with spirometry in the BOLD study suggests that this is a valid observation.

A high prevalence (18.3%) of rhinitis symptoms was recorded, with men reporting significantly higher symptom prevalence in the last 12 months than women, possibly pointing to high levels of atopy in this community and/or greater exposure to occupational irritants (general dusts) or non-specific causes of rhinitis. Wheeze, chronic bronchitis and general dusts were significantly associated in the adjusted analysis of rhinitis (not presented).

Of the doctor-diagnosed respiratory conditions, asthma was the most commonly diagnosed obstructive lung disease (7%) followed by chronic bronchitis/emphysema (5.5%). However the problems associated with these diagnoses have been noted above.

8.3.2. Chronic bronchitis vs. COPD

The prevalence of chronic bronchitis in this population was higher than the national average prevalence and increased with age. Prevalence was higher in men than in women, in contrast to the SADHS and other studies, and was broadly consistent with

reported rates of smoking in these groups. However, a surprise finding was that, despite a higher prevalence of smoking in men, the prevalence of physician-diagnosed chronic bronchitis in women was higher. This requires further consideration. Gender differences in prevalence of chronic bronchitis and emphysema have been reported previously.²² Firstly, both chronic bronchitis and COPD are caused by cigarette smoke, and they may occur together or one without the other. Alternatively, cough and phlegm may, and often does, precede the development of airflow obstruction. Secondly, symptoms of chronic bronchitis, although well defined, are not specific, and similar symptoms may result from asthma (which is more common in adult women than men), heart failure, or simply reflect the greater tendency of women to report symptoms.

This variable association between chronic bronchitis and COPD is evident in the results of the BOLD study. In persons with chronic bronchitis aged ≥ 40 years (British MRC question from BOLD study), half (49.8%) had COPD. Conversely, just under a quarter (22.1%) with COPD reported symptoms of chronic bronchitis. Although this figure appears low, as reflected in Table 81, almost 60% of patients had chronic sputum production ('usual phlegm')

Usual phlegm was a more common symptom in those with COPD than the MRC definition of chronic bronchitis, which could signify less symptomatic disease or underestimation of symptoms. Of all persons with COPD ≥ 40 years, half reported usual phlegm in the absence of a cold (51.9%) and this prevalence was even higher for those with Stage II and higher disease (58.2%). Both these figures are similar to that recorded from other countries. For example results from Brazil show that 7.8% of persons reported chronic bronchitis and 15.2% had COPD.²³

A subgroup analysis of the prevalence of symptoms in persons with no COPD, GOLD Stage I and Stage II COPD is presented in Table 81 suggesting the unreliability of symptoms in indicating the presence of clinically significant COPD (Stage II).

Table 82 indicates the frequency of COPD in subgroups of symptomatic individuals, and notably 40% of persons with diagnosed asthma have GOLD Stage I or higher COPD.

Table 81 The frequency of respiratory symptoms, doctor-diagnosed disease and treatment in participants with COPD vs. those with no COPD *

	Subgroup with no COPD n=651	Subgroup with GOLD Stage I or higher COPD n= 196	Subgroup with GOLD Stage II or higher COPD n=162
% with usual phlegm	26.1	51.9	58.2
% with chronic cough**	8.0	23.7	28.6
% with chronic phlegm	10.8	27.0	31.3
% with chronic bronchitis***	9.5	22.1	25.0
% with wheeze	23.1	43.9	48.4
% with wheeze +dyspnoea	12.0	34.2	40.2
% with dyspnoea grade 2+	12.7	24.6	27.0
% with diagnosed CB /emphysema/COPD	9.5	15.9	17.4
% with diagnosed asthma	11.6	25.0	28.2
% on any treatment in last 12 months	5.8	20.4	22.5

* questionnaire responses from the BOLD study; ** most days, 3 months per year***British MRC definition of chronic bronchitis

Table 82: The frequency of COPD in persons with respiratory symptoms, doctor-diagnosed disease and those on treatment in persons aged ≥ 40 years *

	% with no COPD	% with GOLD Stage I or higher COPD	% with GOLD Stage II or higher COPD
Usual phlegm n=261	61.6	38.4	34.5
Chronic cough n= 98	51.9	48.1	46.6
Chronic phlegm **n=117	56.3	43.7	40.7
Chronic bronchitis*** n=100	50.3	49.8	48.0
Wheeze n=235	62.8	37.2	32.9
Wheeze +dyspnoea n=145	53.0	47.0	44.2
Dyspnoea grade 2+ n=138	62.4	37.6	33.2
Diagnosed CB /emphysema/COPD n=63	49	51.0	44.7
Diagnosed asthma n=123	59.7	40.3	36.4
Any treatment in last 12 months n=82	47.7	52.3	46.3

* questionnaire responses from the BOLD study; ** most days, 3 months per year***British MRC definition of chronic bronchitis

8.3.3. Healthcare utilisation

Under recognition

The results of the LHS2002 confirm the suspicion that symptomatic obstructive lung disease is underrecognised in the community. Of all persons reporting one or more current respiratory symptoms, only 13.1% had ever been diagnosed by a healthcare practitioner to have asthma, and 1.7% chronic bronchitis/emphysema. The remainder had either not presented for diagnosis or had not been offered a diagnosis. This result is consistent with that of Bheekie et al (1998) in a study of asthma in a low-to middle income area of Cape Town.²⁴

Failure to present for care is a significant reason for undiagnosed respiratory disease, as, particularly for chronic symptoms, patients accept the presence of respiratory symptoms, particularly if they are smokers, and view a smoker's cough as normal.²⁵ In clinical practice, patients often deny respiratory symptoms and upon further probing refer to a "normal cough", some feeling that their symptoms warrant neither reporting nor treatment.

Not surprisingly, many persons (57%) with documented airflow limitation (GOLD Stage I and higher) had no reported diagnosis of any obstructive lung disease, similar to findings from the NHANES III study.²⁶

This pattern of underdiagnosis of respiratory disease is documented in a study of children in Cape Town which showed that the parents of 53% of children with current asthma symptoms acknowledged that their children had ever had asthma and 37% acknowledged that they had current asthma.²⁷ Only 23% of the recognised group were on daily treatment compared with 3% in the unrecognised group. Current treatment was associated with having private medical insurance and higher socioeconomic status. Although current guidelines suggest inhaled long acting beta agonists in certain cases, they are of little practical use to the public sector where these drugs are not available²⁸, and even in the private sector where middle income earners would not be able to afford them easily.³³

Van Schalkwyk et al studied asthma in the LHS2002 sample of 2422 people, aged 20-44 years.²⁹ Twelve percent of those persons with doctor-diagnosed asthma displayed non-reversible obstruction, as did 13% of those with asthma-like symptoms, compared to 2% in the asymptomatic control group. This suggests asthma with fixed obstruction

due to airway remodelling, or probable COPD, which was suspected to manifest at an earlier age in this population, owing to high cumulative exposures, particularly smoking. There was also a high prevalence of AHR, with 23% of asymptomatic persons with no previous diagnoses testing positive to a methacholine challenge test. The reasons for this could be related to the high prevalence of smoking and tuberculosis, the former being known to be associated with AHR.

Undertreatment

Of all persons with doctor-diagnosed asthma, less than a half (48.2%) reported having received current treatment for asthma, suggesting undertreatment in many. However, since the indication for treatment is different for asthma and COPD, this must be considered according to diagnosis. In persons who reported doctor-diagnosed chronic bronchitis/emphysema, only 12.1% were on current treatment at the time of the study. Curiously, only 33% of persons who were on current treatment for chronic bronchitis/emphysema reported a doctor diagnosis. It is not possible to determine whether in the 67%, the patients were thought to have this diagnosis and simply not informed of this fact. Alternatively, since the treatment of asthma is similar to that for COPD, some of these might have been misdiagnosed or undiagnosed asthmatics. In either event, it points to the apparently imprecise diagnosis of respiratory symptoms in the health facilities and/or by private practitioners who serve these study areas, and/or unreliability of these questions in this setting.

This difference in treated proportions of asthma and COPD probably reflects not only the diagnostic difficulties of diagnosing the latter in primary care and without spirometry, but also uncertainty about appropriate treatment for this condition and when to commence it. However, a proportion of those not treated, would have had chronic bronchitis for which no specific therapy is indicated, and where the emphasis in primary care is simply to stop smoking. Not surprisingly, only 22.5% of those participants with GOLD Stage II or higher COPD were receiving any form of treatment.

Seven percent of the population reported requiring emergency care in a hospital emergency department in the last 12 months due to lung disease. This is a significant proportion of the general population, indicating uncontrolled and or severe lung disease in this community, and may indicate problems of access to care, misdiagnosis, unavailability of medication and poor adherence to therapy or comorbidity. Studies of asthma in local low-income communities have identified many barriers to care for these

diseases, including problems relating to health services and others that are associated with poverty. Health services-related problems include poor access (e.g. lack of transport especially in older adults), a preference for oral treatment,³⁰ unwillingness of the doctor and patient to label disease and inadequate follow-up.³³ Even in low income areas a combination of private practitioners and the teaching hospital (tertiary referral centre) was chosen in preference to local day hospitals.³¹ Ehrlich et al (1998) found that only 23% of the recognised asthmatic children were on daily treatment compared with 3% of their unrecognised counterparts.²⁷ Current treatment was associated with having private medical insurance and higher socioeconomic status. These observations are probably relevant to COPD as well.

Moosa et al (1996) have documented a local perception that inhalers are “addictive or weaken the heart”^{30 33}, which could account for decreased compliance which was reported in another local study by Jones et al.³² The latter study also documented that parents reported poor levels of service by doctors and public sector clinics, concluding that there was an urgent need to improve public sector asthma care and patient education, a sentiment that can be echoed for adult COPD. In addition, prescribers may have a preference for “broad spectrum” symptomatic treatment in addition to syrups being cheaper per unit purchase.³³ Evidence for this practice was also found in the SADHS where only 15% of patients used inhaled corticosteroids and 15% used inhaled beta agonists, with larger proportions using oral xanthines and adrenergics (39 and 28% respectively), while the rest did not report any regular treatment. This group included patients with “asthma and chronic bronchitis”.³⁹

8.3.4. The BOLD study (≥40years): Prevalence of COPD

The prevalence of COPD (GOLD Stage I or greater of 24% overall, 29% in men and 20% in women) in persons aged ≥40 years in Ravensmead and Uitsig is amongst the highest reported in a community study to date (see Chapter 2, Table 3). Amongst men, the next highest figures from surveys employing the similar methods are from Finland (22%) and Japan (16.4%).^{34 35} Even more striking was the very high prevalence in women (20%) for which there were no comparable estimates in the published literature. Approximately 1 in 5 women and 1 in 3 men aged ≥40 years have at least GOLD Stage I COPD.

The prevalence of GOLD Stage II or higher COPD is also very high – 19% overall using the NHANES III equations and 15% using locally derived prediction equations, indicating that most affected participants have moderate to severe disease. These high rates may reflect the high prevalence of smoking in the study population; current smoking, 56.9% in men and 40.6% in women, and ever smoking, 83% in men and 59% in women.

Prevalence of COPD in women over 70 appears to be relatively higher than in men using the NHANES equations. Prediction equations do not perform well in persons over the age of 70 years because using a fixed ratio (FEV₁/FVC) to define airway obstruction overestimates COPD in this age-group.¹¹ It might also be a healthy survivor effect as fewer males were represented in this age group, which may mean that males with COPD and other health effects of their smoking had resulted in their premature death, whereas in women, less and lighter smoking had allowed better survival with the burden of COPD occurring in a later decade of life. In addition these local equations are unreliable due to a number of factors.

8.3.4.1. Local equations vs. NHANES equations

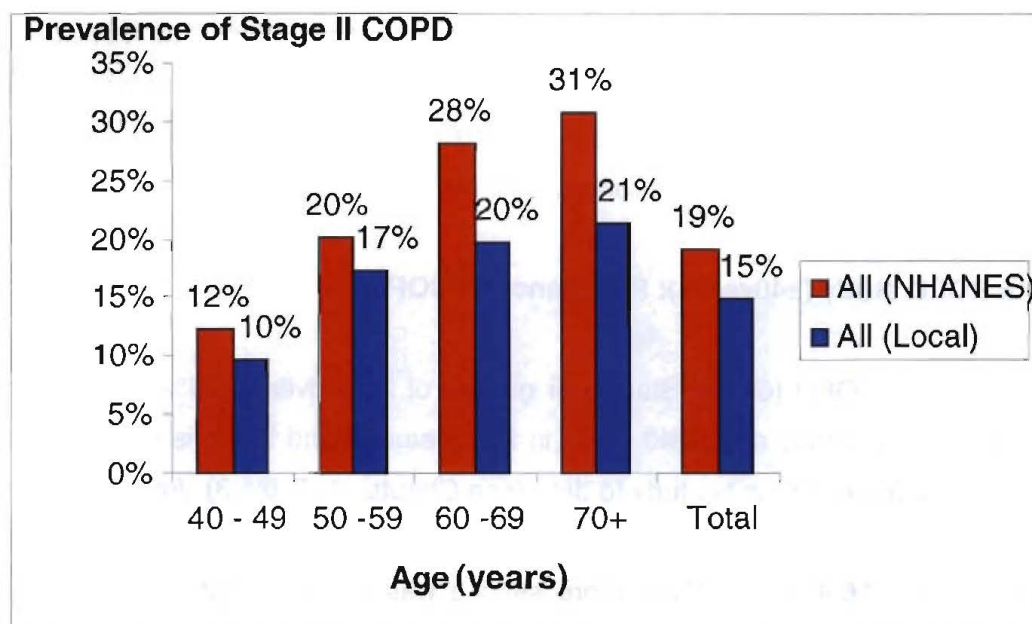


Figure 28: Estimated Population Prevalence of GOLD Stage II or higher COPD by age - NHANES equations vs. local equations

Estimates of the prevalence of COPD are influenced by the prediction equations that are applied to the results. As can be seen from Figure 8.1, the prevalence is higher when the NHANES prediction equations are used. Although it can be argued that local prediction equations, that is, equations derived from the study sample and then applied to the whole population to detect those with disease, might appear more appropriate, there are problems with this approach.³⁶ Firstly, since the majority of both men and women have smoked, and have a high prevalence of respiratory symptoms and co-morbid respiratory disease, equations are based on small numbers of non smokers with no history of respiratory disease.

An alternative approach is to use predicted equations from 'healthier' or less affected communities in South Africa of the same ethnic group. However, ethnically-determined predicted values for lung function are thought to be flawed by the close association of ethnicity with socioeconomic status. Studies by Goldin et al have considered ethnicity in South Africa to be a surrogate for socio-economic status, and suggest that the same prediction equations should be applied to all South Africans; supporting the hypothesis that "race" is not a direct genetic predictor of lung size.³⁷ This is the approach used in the SADHS survey.³⁹ Differences in poor communities related to influences dating back to intrauterine conditions (e.g. poor nutrition, and maternal smoking affecting lung growth and development) and those associated with poverty that extend into old age (e.g. continuing smoking, repeated respiratory infections, air pollution) need to be considered. An additional consideration is that residents of the study area are almost entirely of mixed ethnicity, and Caucasian predicted values are applied in clinical practice, presumably because other South African local equations are based on groups with Nguni or Sotho lineage, (but there is no evidence for this assumption). In a study of this nature, where the interest is in studying risk factors, it is more appropriate that equations be used that correctly identify the affected individuals, so that the effect of exposures can be quantified. In this circumstance, it can be argued that the NHANES III equations, even though they were derived from a white U.S. population, are adequate. This is the approach adopted in the analysis of the BOLD results.

8.4. Evaluation of Risk factors in the LHS2002 and BOLD studies

8.4.1. Tobacco Smoking

Prevalence and pattern of exposure

Prevalence of current smoking was very high among both men and women (59.1 vs. 43%) with the majority smoking between 1-14 cigarettes per day (light to moderate). Lifetime prevalence of ever smoking in both sexes is extremely high, compared with other countries, particularly amongst women (67.1 vs. 50.4%) and even higher in the \geq 40 year age group (83 vs. 59%). Most women smokers smoked between 1-10 cigarettes per day, the largest number fewer than 5 per day.

These results contrast with the smoking patterns in most developing countries, where women generally smoke less than men. However smoking in urban areas is fast growing worldwide, for example in China (78 in men vs. 35% in women).³⁸ Data from South Africa also shows that this difference usually less pronounced in urban than in rural areas.³⁹ However, the causes of the pattern of smoking amongst women in this study can be interpreted to some extent by the nature and history of the community. Firstly, it is a population in economic transition which, although poor, has some disposable income. Secondly, it has adopted urban habits, with restricted options for recreation. Thirdly, alcohol abuse is prevalent, dating back to the 'dop' system amongst farm workers, who received a daily ration of cheap wine, and often also cigarettes, as part payment for their labour. Smoking thus became entrenched as a social norm in both men and women. Finally, amongst women the pattern of smoking is light, suggesting that smoking is a social release. Most employed women work in factories where smoking is the norm during tea and lunch breaks. They may smoke to relieve the boredom, or because all their peers and friends do, and they smoke less in their homes. The majority of participants continue to smoke, as evidenced by the relatively small number of ex-smokers (7.6%), confirming both the addictive qualities of nicotine and the entrenched social acceptability of smoking. Smoking is still widely considered to be a socially acceptable practice, especially in the Western and Northern Cape Provinces, and equally amongst men and women.

The ratio of current to never smokers was lowest in the >65 age group. The lower prevalence of smoking in the older age groups could signify a healthy non-smoker survivor effect (most likely). Alternatively, higher quit rates with increasing age, or perhaps a cohort effect, if the norms of teenage years at which these persons would

have started smoking (the 1940's) did not encourage smoking. However, the latter is not likely (at least not for men) when one considers the prevalence of ever smoking. The trend for the proportion of smokers to decrease after the age of 40 is present in the study sample, but is not as marked as in other developed countries like Sweden.⁴⁰ Men tended to be heavier smokers than women, with more men reporting a history of more than 20 pack years, similar to other countries such as Estonia.⁴¹ Also contributing to cumulative exposure is an early median age of onset of smoking of 16 years of age which is concerning considering that lung growth is still in progress at this age. Although tobacco usage has decreased overall in South Africa, it is clear that in the two years between the two studies, current smoking prevalence did not change in this population.

Relationship between tobacco smoking and respiratory symptoms

As expected, cigarette smoking is strongly associated with all measured respiratory symptoms (chronic bronchitis, cough, wheeze and dyspnoea) in a dose-dependent manner with odds ratios between two and three. Of concern is the high prevalence of smoking in the young with early onset, especially in women. It is acknowledged that some of these symptoms may be due to a diagnosis of asthma which is adjusted for in the multiple logistic regression analysis.

Cigarette smoking resulted in a two to three fold increased risk for chronic bronchitis after adjustment for other factors. Former smoking was not associated with the presence of chronic bronchitis, in keeping with a median quit age of 35 years, suggesting lower cumulative exposure in ex-smokers as a result of fewer years of smoking and perhaps also fewer cigarettes per day in this group, or a reversible effect.

Although exclusive use of a pipe rather than cigarettes was relatively rare, it was associated with the greatest risk of chronic bronchitis (OR 4.6, 95% CI: 1.9 – 10.7). This could possibly be the result of an absence of filtration, greater puff volume, different retention times, particle size or tar yield, but these have not been quantified or studied before, in relation to risk for chronic bronchitis or COPD. However, such factors have been postulated to be of relevance in cannabis smoking.⁴²

In keeping with other studies^{43 44}, the analysis of smoking as a potential confounder of other associations, particularly that of cannabis use, odds ratios from 5 different multivariable models was compared. These models included the age of

commencement of smoking, current quantity and time since cessation in order to correct for 'residual confounding'. The odds ratios for all other risk factors did not vary significantly from the final model, confirming that the effect of smoking as a confounder was not significant, and that the associations of chronic bronchitis with other risk factors are robust.

Pipe smoking was only significantly associated with wheeze in the last 12 months. Past smoking was not significantly associated with any respiratory symptoms, which is in keeping with a median quit age of 35 years, indicating that stopping smoking decreases risk to close to that of never smokers.

Relationship between tobacco smoking and COPD in the ≥ 40 age group (as defined by GOLD)

In contrast to estimates suggesting that 15% of smokers develop COPD⁴⁵, 31% of current smokers, and 29.3% of ever smokers in this population aged ≥ 40 years have developed GOLD Stage I or higher COPD – twice the prevalence suggested by Barnes et al (2000). The BOLD study showed a COPD prevalence of 51.6% in ever smokers aged ≥ 70 years, which compares favourably with the results of the study reported by Lundback et al in which COPD was found in 50% of 76 - 77 year old ever smokers.⁴⁶ This finding suggests that, either half of ever smokers will develop COPD by age 70, or that the prediction equations for FEV₁/FVC ratio and FEV₁ for persons ≥ 70 years are not appropriate, as suggested by Hardie et al.¹¹ As pack years increased, COPD prevalence increased to 41.9% in men smoking >20 pack years. A high prevalence of COPD was also noted in persons aged 40 – 49 years, suggesting that COPD may begin at an earlier age in this population. In addition, not all individuals with COPD follow the classic linear course suggested by Fletcher and Peto (1977). The high prevalence of COPD in this community suggests that a higher proportion of individuals may follow the course that describes a faster decline in lung function, or that they started off with a lower baseline lung function that could be related to socioeconomic deprivation.

Environmental Tobacco Smoke (ETS)

In Ravensmead and Uitsig, the exposure to environmental tobacco smoke in the home is high. Although only 9.3% of persons aged ≥ 40 years reported ETS exposure, the prevalence and pattern of exposure needs to be interpreted in the context of high rates of active smoking. In order to appropriately analyse the effects of home ETS exposure,

mutually exclusive categories of smoke exposure had to be created, and thus former and current smokers were not included in the ETS group, even though they may have been exposed to ETS in addition to their current or past active exposure. In addition, there was no information available on those who were exposed in the workplace, which is a significant area of exposure shown to be associated with an increased risk of COPD,^{47 48 49} nor was an assessment made of environmental tobacco smoke exposure in places of recreation. The results of a study performed in Germany suggest that the risk of chronic bronchitis is increased three times by a daily exposure of more than eight hours.⁵⁰

Amongst men, a common past-time is alcohol (beer/low-quality wine) consumption in informal taverns (shebeens), which are often shacks/houses with little or no ventilation, and where smoke exposure is intense. In separate studies performed in the Ravensmead/Uitsig area, these social exposures in this setting have been associated with increased transmission of tuberculosis, presumably due to tuberculosis contacts in this setting.⁵¹ The effect on the development of respiratory symptoms and disease from tobacco and cannabis exposure may be an additional factor and requires further study.

In the LHS2002, more non-smoking women than men reported passive exposure to cigarette smoke (13.5 vs. 2.2%), but these figures need to be viewed against the higher smoking prevalence in men. Becklake and Kauffmann (1994) have suggested that women may be more susceptible to the effects of tobacco smoke.⁵² Exposure to ETS contributes to the greater prevalence of respiratory symptoms in non-smokers, especially amongst non-smoking women.⁵³ In Ravensmead and Uitsig, overcrowding in small volume houses or flats is common, suggesting that if even one of the family members smoked, the rest of the inhabitants are exposed to a considerable amount of ETS. No conclusions can be drawn from the BOLD data on ETS exposure in persons ≥ 40 years as there were only 9 persons with Stage I or higher COPD who had exclusive ETS exposure (owing to the high prevalence of current and ex smokers, which have been considered to be mutually exclusive from passive smokers).

8.4.2. Smoking of cannabis

Prevalence and pattern of exposure

Twenty three percent of men in the LHS2002 reported ever smoking cannabis and 13.2% were current smokers. A similar proportion of men of all age groups (10 – 17

percent) reported current use, confirming the status of regular cannabis use in this community, as an acceptable lifelong habit rather than an experimental phenomenon amongst adolescents and young adults. This pattern indicates that cannabis smoking in this community is not the domain of younger adults, as it is in many first world countries. Secondly, a link between tobacco and cannabis use is evident. The median age of onset of cannabis smoking is only one year later than that of cigarette smoking. This has implications for public health interventions – both need to be addressed simultaneously in the young. Thirdly, unlike tobacco smoking, it is uncommon amongst women. However, the illegal status of the drug poses a problem for the collection of accurate data, and can give rise to distorted prevalence figures (see Information Bias).

Relationship between cannabis smoking and respiratory symptoms

Cannabis emerged as one of the strongest predictors for chronic bronchitis, surpassing even tobacco smoking in strength of association with odds ratios ranging from 3.5 (95% CI 2.3 - 5.4) for ex smokers to 7.4 (95% CI 4.0 – 13.6) for heavy smokers. To our knowledge, this is the first study in Africa to evaluate cannabis use at a population level in the context of respiratory disease. A study from Tucson, Arizona reported more coughing, phlegm production and wheeze in cannabis smokers aged less than 40 years, irrespective of whether they also smoked tobacco.⁵⁴ Non- tobacco smoking had a larger effect on respiratory function than tobacco smoking alone, and the effect of both types of smoking was additive. Sherrill (1991) and Tashkin (1997) both showed that long-term cannabis smoking increased bronchitic symptoms.^{55 42 54}

Even in young adults, it has been shown that cannabis use is associated in a dose dependent manner with decline in FEV₁/FVC ratio, and that it is additive with tobacco in its effect on lung function.⁵⁶ Our findings suggest that the respiratory risks of long term cannabis smoking are independent of tobacco smoking. This has important public health implications as there currently appears to be little awareness of the prevalence of use and respiratory effects of cannabis. In fact, a common perception of users and the lay public is that it is safe, and instead, its marginal bronchodilator effects in asthma are cited as evidence that it is “good for the lungs”.⁵⁷ This view has been promoted in lay publications.⁵⁸ Clearly this situation requires the attention of those involved in smoking cessation initiatives.

Cannabis smoking was also significantly associated with an increased risk for wheeze in the last 12 months, wheeze with breathlessness, grade two or higher dyspnoea and

recent cough, in a dose dependent manner. However, cannabis pipe smoking was only significantly associated with recent cough. Unlike cigarette smoking, past cannabis smoking was significantly associated with all of the above symptoms, suggesting that stopping smoking does not decrease risk, despite the median age of quitting being only 25 years (compared to 35 years for tobacco smokers). The strength of these relationships with respiratory symptoms may be influenced by underreporting of cannabis use due to its illegal status. In spite of this, almost 20% (PAF) of chronic bronchitis in this community is attributable to cannabis smoking.

Relationship between cannabis smoking and COPD (as defined by GOLD)

More than one third (39.1%) of all ever cannabis smokers were shown to have Stage I COPD. However, like Tashkin et al (1997)⁴², owing to the small sample size of cannabis smokers and possible confounding with tobacco smoke, an association between cannabis smoking with COPD could not be confirmed. However, univariable analysis showed a positive association with ever smoking cannabis and GOLD Stage I and higher COPD (OR 2.1; 95% CI: 1.2 - 3.7), for which there were significant sample numbers (64 persons with the exposure and 25 of these with the outcome of COPD). Multivariable analysis showed no association of ever smoking cannabis and either GOLD Stage I and higher or GOLD Stage II and higher (NHANES). This does not exclude the possibility of a positive relationship, as there was a trend toward heavier cannabis smokers being at a significantly higher risk than former or current “light” smokers, but the numbers in these categories were too small to confirm these associations. Studies that include sufficient numbers of heavy cannabis smokers are needed to examine this relationship appropriately, as these findings could have public health significance in terms of smoking cessation. However, the current evidence is sufficient to consider cannabis as a likely contributory, if not sufficient cause, both of chronic respiratory symptoms and COPD. In view of its common use in South Africa, this should be the topic of further focussed research.

8.4.3. Previous TB

Prevalence and pattern of exposure

South Africa was ranked 8th in the world for the total number of TB cases per country and tenth in the world for incidence rates per population in 2003.^{59 xiv} The incidence of TB in the Western Cape Province is the highest in the country⁶⁰ and in Cape Town in 2002, the notification rate was 266 per 100,000.⁶¹ In Ravensmead and Uitsig, the notification rates have been steadily rising over the past few years from 228 per

100,000 in 1994 to 299 per 100,000 in 1998 and 341 per 100,000 in 2002.^{62 63 xvi} The LHS2002 reported the prevalence of tuberculosis in the study area to be very high at 10 per 1,000 (95% CI: 6.2 - 13.8 per 1000).^{xiv} A history of previous doctor-diagnosed TB was reported by 9.7% of adults aged ≥ 15 years and with significantly more men reporting past TB than women (12 vs. 8%; $p < 0.001$). Persons aged ≥ 40 years had a higher prevalence of past TB of 15.1% (19.7 in men vs. 12.4% in women; $p = 0.006$). Moreover, 12.9% of the population had chest radiograph evidence that was consistent with tuberculosis, possibly suggesting some proportion of undiagnosed disease.

The most concerning issue in Ravensmead and Uitsig is that previously treated smear-positive TB cases form more than half of the prevalent smear-positive cases, which is considered to be reinfection rather than reactivation.^{64 65} A discussion of this work and the reasons for high rates of transmission in the community are beyond the scope of this report. However, the impact of TB upon lung health and its association with obstructive/other forms of respiratory disease in adults is a particular focus of interest.

Relationship between previous pulmonary tuberculosis and respiratory symptoms

A history of tuberculosis was shown in the LHS2002 to be associated with twice the adjusted risk of wheeze, breathlessness with wheeze, dyspnoea of grade two or greater and recent cough. This strong and consistent adjusted association indicates that tuberculosis is an important cause of symptoms of airflow limitation. In the adjusted model for chronic bronchitis using the British MRC definition, the relationship was less strong (OR 1.5; 95% CI: 1.0 – 2.2). However, past TB was strongly associated with usual winter morning cough with phlegm. It is also possible that some individuals with airflow limitation have bronchiectasis related to childhood tuberculosis, but fulfil the definition for chronic bronchitis. Between 9 - 10 percent of current respiratory symptoms in this population can be attributed to past tuberculosis.

Relationship between previous pulmonary tuberculosis and COPD in the ≥ 40 age group (as defined by GOLD)

The major findings of the analysis were that almost half (49.2%) of all persons with past tuberculosis had GOLD Stage I and higher COPD, i.e. one in two past TB sufferers ends up with airflow limitation, and the vast majority of them have Stage II and higher

^{xvi} Den Boon S, van Lill SWP, Borgdorff MW, Enarson DA, Verver S, Bateman ED, Irusen E, Lombard CJ, White NW, de Villiers C, Beyers N. High prevalence of previously treated tuberculosis in Cape Town, South Africa (unpublished manuscript)

COPD (42% of all past TB patients). One third (32.1%) of all the persons with GOLD Stage I and higher COPD had a history of past TB.

The association of GOLD Stage I and higher COPD and previous pulmonary TB was strong (OR 3.4; 95% CI: 2.1 – 5.6) and the association with GOLD Stage II and higher COPD much the same. Multinomial modelling showed that the combination of GOLD Stage I and II COPD (exclusively) resulted in an OR of 2.6 (95% CI: 1.5 – 4.6), confirming the significant risk of mild to moderate COPD. However, a nine fold increase in association of past TB was apparent with GOLD Stage III and IV exclusively (OR 8.9; 95% CI: 4.2 – 18.9). These estimates, though based on relatively small numbers, are considered to be robust, owing to the large number of persons with the exposure within this group. Twenty eight out of the 53 persons (53%) with GOLD Stage III or IV COPD had a history of past TB, i.e. over half of the group. This can be compared to a parallel estimate for GOLD Stage I or II COPD of one quarter of the group (25%) having a history of TB. After heavy smoking, past TB was found to have the strongest association with COPD. There was no significant interaction between TB and smoking but the effect of TB and smoking is additive in the “causation” of COPD.

A quarter of all moderate to severe COPD in this population is attributable to past tuberculosis (PAF = 24.9%). This is possibly the first time that a population-based estimate of TB-attributable COPD has been calculated. This finding raises the question as to whether COPD associated with TB should be considered to be COPD or requires separate consideration as a special sub-group included in COPD classification systems.

Firstly, the association of tuberculosis with COPD is not new, but has been studied by others who have described both obstructive and restrictive lung disease in hospital-based and occupational cohorts. If this should not be called COPD, but post-tuberculous obstructive lung disease, should all persons with a history of TB, even distant (such as in childhood) and uncomplicated, be ineligible for a diagnosis of COPD? While this would be reasonable as a means of excluding patients with obvious radiologically evident fibrosis and bronchiectasis, it would have two negative consequences: to exclude the many patients with trivial evidence of structural lung damage following tuberculosis, which is a majority of such patients; and to underestimate the effects of their concurrent smoking. In view of the high prevalence of smoking in patients with TB, and the evidence that smoking increases the likelihood of

developing TB, and/or of having more severe disease with worse outcomes, excluding TB as a co-morbidity of COPD (and vice versa), will diminish the impact and relevance of this association. In addition, the importance of smoking cessation for both the prevalence of COPD and tuberculosis could be inappropriately minimised.

However, it might be argued that it is important to exclude patients with known TB, as the mechanism of airflow limitation is different in such patients and not likely to respond to the treatments available for smoking-related COPD. This pronouncement is premature since; firstly, the mechanisms of airflow limitation in tuberculosis are not known and have not been fully studied. Furthermore, they are likely to vary in different forms of pulmonary disease, and at different times in the course of disease. Thus during the active phase of bronchogenic spread, prebronchial and peribronchiolar inflammation and lymphoid tissue enlargement with various degrees of bronchial wall necrosis and ulceration are the likely causes.

During healing, endobronchial and peribronchial fibrosis become likely mechanisms. In those in which there is extensive lobar destruction, cavitation and post-tuberculous bronchiectasis, airflow in affected areas is likely to be affected in an unpredictable manner, with obstruction, or even restriction being the consequences. However, when confined to one lobe or limited parts of upper lobes, damage to some bronchi or one or two segments is likely to have a limited effect on overall spirometric values, and the weight of evidence points to a more generalized distribution of pathology accounting for the airflow limitation. Such abnormality can best be localised on a high resolution CT scan where the relationship between airway damage and areas of emphysema and gas trapping can be examined. At least anecdotal evidence in South African clinical practice suggests that the majority of patients with significant airflow limitation have evidence of emphysema in areas not affected by tuberculosis, and secondly, it is thought that airflow obstruction is rare in patients with tuberculosis who have never smoked. No conclusions regarding this could be made from the BOLD study owing to small numbers of non smokers with past TB. There was, however, no significant interaction between past tuberculosis and smoking.

Instead, the hypothesis to examine is whether the combined effects of smoking and tuberculosis promote more rapid progression of COPD in all regions of the lung including those not affected by TB. Regarding responsiveness to treatment of COPD associated with tuberculosis, there is as yet no evidence that this is different from that

of 'pure' smoking-related disease. This needs to be carried out in prospective trials. However, again, anecdotal experience of clinicians practicing in this region, is that these patients while not demonstrating reversibility on spirometry, benefit from conventional guideline-based management of their airflow limitation, comprising sustained use of bronchodilators (especially long-acting bronchodilators), and in some, inhaled and even oral glucocorticosteroids. This requires further study.

A high proportion of persons with GOLD Stage I or higher COPD (44%) had evidence of tuberculosis on chest radiograph supporting the aetiological role of tuberculosis by means other than self-reporting of disease. Sixty percent of persons with evidence of TB on the radiograph had GOLD Stage I or higher COPD, pointing to the high prevalence of COPD/airflow obstruction in those with previous TB.

Even if participants with TB are excluded from the analysis, the proportion with COPD remains high (19.1%). However, it is clear that past tuberculosis plays a significant role in the aetiology of COPD in the study population.

Another possible confounder in this study is the possibility of HIV infection. HIV infection status was not tested in this study, but its influence is likely to have been small for several reasons. Firstly, HIV infection per se is not known to be associated with COPD, and secondly the HIV infection rates in the study area are assumed to be lower than the overall suburb rate of 7.9% the year before the study (2001).⁶⁶ Prevalence estimates for Cape Town cover a wide range with very high prevalence in some areas and much lower rates in others. Statistics are obtained from antenatal sampling and the rates are highest in this young sexually active group, rather than the ≥ 40 year age group surveyed here.⁶⁷

8.4.4. Occupational exposures

Relationship between occupational exposures and respiratory symptoms

General occupational exposure to dust gases, chemicals or fumes and or silica dust was common with 26% of the LHS2002 population reporting exposure. Men had a significantly greater prevalence of exposure (37 vs.18%; $p < 0.001$). Independent of cigarette smoking, occupational exposures were associated with a two fold increased risk of chronic bronchitis. Weaker, but significant associations with wheeze and cough were observed. This could be due to the crude nature of the question, which can have the effect of diluting the exposure and biasing results towards the null. There was no

information on length of exposure indicating that some persons with limited or questionable exposures were included in the exposed group. Other studies have shown the effects of occupational exposure and cigarette smoking to be additive.⁶⁸

Relationship between occupational exposures and COPD in the ≥ 40 age group (as defined by GOLD)

The BOLD study collected data on specific occupational exposures (35.4%) as well as general exposures (46.6%). Although general exposures were associated in a univariable analysis of GOLD Stage I and higher COPD, this association was not present after adjusting for other risk factors. Specific occupational exposures were grouped together such that a variable named “any specific occupational exposure” was created in order to have sufficient number of exposed persons with COPD, which probably diluted the effects. This limitation could mean that it is possible that one or more specific occupational exposures had a relationship with COPD, but there were not enough persons with the exposure with quality spirometry, or with COPD, in order to analyse further. No significant association could be detected between specific and general occupational exposures and COPD. However, apart from the small numbers in both studies, the questions on occupations and exposures were limited and so were prone to subjective assessments of an unpleasant or potentially harmful work exposure. Although such questions have been shown to be useful in large studies, especially within relatively homogeneous exposure environments (that is, when they are used to quantify exposure) rather than in mixed exposure environments where the relative hazard of different exposures is difficult to differentiate.⁶⁹

8.4.5. Air Pollution

Indoor air pollution

Relationship between air pollution and respiratory symptoms

In the SADHS, indoor cooking in poorly ventilated homes was found to be associated with an increased prevalence of chronic bronchitis. This is attributable to the combustion products from biomass fuels used for cooking and heating.⁷⁰ African women in rural areas have been shown to have a higher prevalence of symptoms of airflow limitation than their urban counterparts, despite having lower rates of all forms of smoking. However, fewer than 2% of the LHS2002 population reported use of biomass fuels and over 95% of the homes have electricity. A limitation of the study was that only data on current exposure was collected and there were too few persons with

this exposure to analyse. In univariate analysis of the LHS2002 data, an association with wheeze was observed but this could not be interrogated further.

Relationship between indoor air pollution and COPD in the ≥ 40 age group (as defined by GOLD)

In the BOLD study, domestic fuel exposure was not shown to be associated with COPD. However, bias owing to misclassification was likely. Fuel exposure in the “exposed” group was unlikely to have been of both significant duration and intensity, again diluting a possible effect. The definition of fuel exposure was insufficiently specific and therefore, as with questions on occupational dust exposure, results were likely to be biased towards the null. When a stricter definition was applied, there was insufficient power owing to small numbers. Most exposures were likely to have occurred in childhood in the older age groups. Thus, no conclusions regarding biomass fuel exposure are possible from this study.

Outdoor Air pollution

The questionnaire did not include a question on air pollution, as other standardised questions have demonstrated poor validity in population studies owing to their subjective nature. Air pollution levels for two neighbourhoods bordering the study have confirmed low to moderate median levels of PM₁₀ particles and other pollutants, but experience a pattern of frequent peaks of pollution exceeding the recommended levels.⁷¹ Cape Town is known to be susceptible to “brown haze”, a form of photochemical smog when conditions are still (see Chapter 3). This is generated from a number of sources including large busy motorways and the international airport nearby, and is dissipated at times by the strong winds that blow out to sea in either a south-easterly or north-westerly direction.

Although no comment can be made about the health effects of urban air pollution in the study site, chronic bronchitis and symptoms of emphysema have been associated in studies performed in other countries (NHANES, SAPALDIA etc).^{72 73} Lower lung function and a more rapid decline in lung function suggest that air pollution may be involved in the pathogenesis of COPD⁷⁴, but evidence is less good for chronic effects than for acute. In addition, air pollution has also been suggested to be associated with increased morbidity and mortality from respiratory conditions and higher rates of hospitalisation or admission to emergency departments due to COPD on days with elevated pollution.⁷⁴ However, most recommendations are based on the incidence of cardiac death, as mortality from COPD has not been shown to be higher in polluted areas in the American Cancer Society study.⁷⁵ There is little information from other studies, as very few actually measure the air pollution.

8.4.6. Childhood chest illness

Ten percent of the population (>15 years) reported a history of childhood chest illness with cough and breathlessness. Wheeze and wheeze with breathlessness were strongly associated with a history of childhood chest illness suggesting that symptoms begin in childhood, suggesting both asthma and in keeping with the hypothesis that childhood chest illness is associated with symptoms of airflow limitation in later life. A history of childhood chest disease was weakly associated with chronic bronchitis. The analysis was adjusted for doctor-diagnosed asthma.

There were too few persons with a history of childhood chest illness in the BOLD sample to examine this relationship, the only question being on hospitalisation during childhood for respiratory disease.

8.4.7. Socioeconomic status

Income

Eighty two percent of the population, more of them resident in Uitsig, were below the poverty line, earning less than R2000 per month. The unemployment rate was very high (57%) and only 19% of the total population reported that they were actively seeking work. The rest were not seeking work for a variety of reasons such as being homemakers, retired or disabled. Income is considered a proxy for socioeconomic status and despite problems with accuracy of reporting owing to the sensitive nature of the question, it is nonetheless a good indicator of socioeconomic status that has been used in other studies worldwide. However, the lack of variability in this predominantly low income area reduces the possibility of analysing the effects of income upon lung symptoms and disease.

Despite the small range in income groups, the lowest income group of <R1000/month was strongly positively associated with the presence of chronic bronchitis and dyspnoea, but only marginally with wheeze. Independent of smoking, over one third of chronic bronchitis (36%) and just under half of dyspnoea (47%) in this population were attributable to low income. Income was associated with COPD in univariable analysis only. However, because of the time interval between the two studies, the data on income, which was obtained during the first study, may not represent household income status at the time of the BOLD study.

Education

In keeping with findings from a national survey⁷⁰, there was a trend to increasing prevalence of respiratory symptoms with decreasing education levels. Lower levels of education were associated with dyspnoea and recent cough, but not with wheeze or chronic bronchitis. There was no association of low education levels with COPD in the BOLD study. Unlike other studies, there was also no statistical correlation between income and education in this population. Previous studies have shown that the incidences for all respiratory symptoms (including cough and phlegm) decreased with increasing educational level after adjusting for all other known exposures,⁷⁶ and other studies have shown that higher educational levels are also associated with a decreased prevalence of smoking.⁷⁷ However, this is not true for the study population, where a high prevalence of smoking occurs among persons of all educational levels.

8.4.8. Age

Effects of age on prevalence and pattern of respiratory symptoms

The prevalence of COPD was clearly age dependent, both the result of cumulative exposures (particularly cigarette smoking), and related to the use of a fixed ratio in the GOLD definition. In this population, the prevalence of Stage I and higher COPD ranged from 15% in the 40 – 49 year age group to 44.8% in the over 70 year age group. This contrasts with the nationwide NHANES III study from the United States that reported prevalences ranging from 7.3% in the 45 – 54 year age group to 22.9% in the 75 year age group.⁷⁸

In both the LHS2002 and BOLD studies, after the age of 35, increasing age was consistently associated with increasing prevalence of chronic bronchitis, wheeze in the last 12 months, wheeze with breathlessness, dyspnoea of grade 2 and higher. This increase represents a transition from symptoms attributable mainly to asthma in the earlier age groups to an increasing proportion of symptoms attributable to chronic bronchitis and COPD.

In the LHS2002, women over 25 and men over 35 began to demonstrate an increased risk of symptoms of chronic bronchitis. This was followed by a steady increase in subsequent decades, suggesting that chronic bronchitis in these communities is developing at a younger age as reported in other studies^{79 39}, and that women may be at greater risk at an earlier age.⁸⁰ Apart from tobacco smoking, this could also be due to biomass fuel and occupational exposures in particular.

8.4.9. Sex

Prevalence and pattern of exposure

The study sample included many more women than men (a ratio of 5:3), and men were particularly under-represented in the older decades. This might represent the relative longevity of women and a survivor effect, in that there was a tailing off of subjects exposed to the most noxious influences in the highest age group, suggesting premature death of persons with these exposures.

Relationship with respiratory symptoms

The separate analysis of men and women was not pursued for two reasons. Firstly, it would have resulted in halving of the sample size, and secondly, it could not be clearly justified on the basis of non-significance of gender in the presented models. Views differ on this question. On the one hand performing gender specific analyses, may ascribe false associations by separating the sexes. On the other hand, a case can be made for presenting separate analyses for men and women based on the inherent physiological differences⁸² between the two sexes (host factor), which may affect the way in which environmental influences express their effects. Such differences in expression are thought to be obscured in analyses of the whole population.

In these studies, no association of sex with chronic bronchitis was found. This is not surprising considering the high levels of exposure to tobacco smoking in both men and women. Wheeze in the last 12 months and wheeze with breathlessness were significantly associated with female sex and could be accounted for by the predominance of asthma in this group, particularly in younger women. Dyspnoea and recent cough were not significantly associated with sex.

Relationship with COPD in the ≥ 40 age group (as defined by GOLD)

Susceptibility of women to tobacco smoke resulting in a decreased FEV₁ has been shown to be higher in other studies.^{81 82} No association was observed between sex and the presence of COPD in either the univariable or multivariable analyses. The study does therefore not provide support for the hypothesis that women are more susceptible to the effects of tobacco smoke than men^{83 84}, or that they are inclined to develop more severe COPD than men.⁸⁵

On the contrary, the dose-response gradient of pack-years of cigarette smoking with COPD was less steep in women than in men, which, if anything suggests less susceptibility to the effects of cigarette smoke. However, this result should be interpreted with caution, as the patterns of exposure were very different between men and women. In women the majority were in the 0-10 pack year group and fell nearer the lower end of this category whereas the median in men tended towards the higher end of the category. Moreover, the distribution of smokers with COPD into the other pack-year categories was also different for men and women. Whereas approximately a quarter of women with COPD fell into each of the four pack year categories, just under one quarter of men had a 0 - 10 pack year history and approximately 40% had a 10 - 20 pack year history and 40% had a >20 pack year history (see Table 59).

In South Africa, a respiratory survey of a black Johannesburg workforce showed bronchitic symptoms in men to be related to smoking and previous occupational exposure and in women to relate to smoking, even of low intensity.⁸⁶ Occupational exposure appears to be more significant in women suggesting that women may be more susceptible to developing chronic bronchitis than men, or that their exposures are of a different type and/or intensity. Chen et al (2000) have indicated that an increased biological susceptibility to tobacco smoke among women could be an explanation for the significantly higher hospitalisation rate and the increasing COPD mortality rate for women.⁸⁷ The same could be true for occupational exposures, but this hypothesis is not supported by the LHS2002 or BOLD study.

COPD in never smoking men and women

A significant proportion of both men and women with COPD gave no history of smoking. For Stage I or higher COPD, these proportions of never smokers were 12.6 vs. 4.6% for Stage I or higher and 8.2 vs. 3.1% for Stage II or higher respectively. These differences between the prevalence in non-smoking women and men were only present when the NHANES prediction equations were used, but not with the local equations, indicating a potential masking of disease when local prediction equations from groups with high prevalence of exposures is used. The figure of 12.6% non-smoking women having Stage I or higher COPD is slightly higher than the range reported from other series (5 -12 %)⁸⁸.

It is worth noting that women are more prone to other diseases that can affect respiratory health, and in some instances cause chronic airflow limitation and

respiratory symptoms. These included lung disease associated with autoimmune diseases like rheumatoid arthritis, systemic lupus erythematosus, and bronchiolitis obliterans. In other settings, but not in this study, biomass fuel exposure is a consideration. On the other hand, the low proportion of never smoking men with COPD (4.6%) confirms that tobacco smoking remains the main risk factor for the development of COPD in men in this community. TB in non-smokers has been discussed earlier.

8.4.10. BMI

Prevalence and pattern of exposure

Seventy one percent of women aged ≥ 40 years were either obese (45%) or overweight (26.1%), which is a particularly high prevalence. This can be postulated to be partially due to ingestion of poor quality food (associated with poverty) and a sedentary lifestyle. The factors influencing body weight in women, many of whom are predominantly housebound and multiparous, are beyond the scope of this discussion but could have an impact on respiratory health in so far as the association of obesity with breathlessness and a restrictive abnormality in pulmonary function. The corresponding figures for men were 27.7% overweight, 17.4% obese and 10.6% of men underweight.

Relationship with respiratory symptoms

Underweight men had twice the risk of chronic bronchitis compared to those with normal weight, indicating that these persons may have concurrent COPD with systemic effects. A U-shaped distribution of BMI was noted in relation to wheeze, wheeze with breathlessness and dyspnoea but significant associations were seen only with obesity. This U-shaped distribution has been noted by others in relation to chronic respiratory disorders.⁸⁹ Being underweight was associated with cough and chronic bronchitis. Weight loss is a recognised complication of advanced COPD and is attributed to the non-pulmonary effects of this disease.⁹⁰ Weight loss is a feature of active tuberculosis and is usually temporary. However, in those that develop severe complications like bronchiectasis with chronic lung sepsis, this may be associated with persistent weight loss.

Relationship with COPD in the ≥ 40 age group (as defined by GOLD)

A strong association was observed between being underweight and COPD. It is assumed that the direction of effect is that COPD has caused weight loss. However, owing to the cross sectional nature of the study design, confirmation of the direction of effect is not possible. A fifth of all those persons who were underweight had a history of

past TB (19.4%), and a fifth of all those with a history of TB were underweight (21.4%) but there was no evidence of an interaction between BMI and past TB, confirming their independent associations with COPD.

8.4.11. Other risk factors

The high degree of variation in susceptibility to developing chronic bronchitis and COPD is not fully understood. Apart from alpha1- antitrypsin deficiency, other gene polymorphisms have shown associations, but results have been inconsistent in different populations.⁹¹ Such predilections have not been examined in the studies reported here.

8.5. Implications for health in South Africa and future research

Advocacy for COPD

Adult obstructive lung disease, in particular COPD is a disease that deserves greater emphasis amongst health care providers and, in particular, from primary healthcare practitioners, and from those responsible for health promotion. The high prevalence and severity of disease demonstrated in the LHS2002 and BOLD study predict a heavy burden of morbidity and mortality in this community. Since the Ravensmead/Uitsig suburbs are probably representative of a large proportion of the South African population in terms of socioeconomic status, these findings have significant, if not alarming implications, which require further discussion and planning.

Firstly, in the public health arena, COPD deserves a higher priority status than it currently enjoys.⁹² Although never prominent, it has lost ground in public and health planners' consciousness to the much more pressing problems of HIV/AIDS and tuberculosis. This may be attributed to several factors. Firstly, it is perceived as a condition affecting only older people, many of whom are not economically active. However, this deserves closer scrutiny in South Africa. The current studies confirm, not only a high prevalence, but evidence that the disease affects a significant proportion of people in their 40s and 50s, and even in their 30s when they are at the height of their working careers. Moreover, particularly in working class communities, older persons are the carers for small children of those that are fortunate enough to find work. Failure to make provision for the care of these patients with COPD may result in their being unable to manage such responsibilities. With modern treatments, activities, freedom from exacerbations and quality of life is considerably improved. With good care which includes smoking cessation, pharmacological interventions, avoidance of infections

through a variety of measures and rehabilitation based on sound advice and a modest prescription of activities, patients have long survival and good functionality. This care is not currently available nor viewed as possible in community health facilities in South Africa. Instead, outdated attitudes persist, such as considering COPD as a self-inflicted disease that deserves less attention than other health needs.⁹³ Under-recognition and undertreatment, as confirmed in this study is common. A mechanism for advocacy for patients with COPD is required in South Africa.

Fortunately, at a global level there is an increasing interest and emphasis on improving the recognition of and quality of care offered to patients with COPD. Global initiatives, as described above include GOLD, the development of the BOLD methodology, and several other international initiatives. In March 2006 the WHO launched the Global Alliance Against Chronic Respiratory Diseases (GARD) which has as its goals “increasing awareness of the importance of the burden of chronic respiratory disease (CRD)”, which should be regarded as significant diseases and a serious global health problem by all. Included in the aims of this alliance are the fostering of country-focused initiatives for surveillance, prevention and control of chronic respiratory diseases; improving the quality and the affordability of care to patients with CRD in developing countries; improving the education and training of health care workers and personnel dealing with CRD; and integrating or coordinating initiatives that governmental and international nongovernmental organizations are currently undertaking in developing countries, thus avoiding duplication of efforts and wasting of resources.”

A particular concern is the global shift of these diseases to developing countries and in particular to those with an improving Gross National Product, and potential purchasing power for cigarettes. For COPD, the largest burden is now in low to middle income countries, like South East Asia and China.⁹⁴ In South Africa, the government has made laudable strides in improving tobacco control by banning tobacco advertising and restricting smoking in public places, but it is clear that more action is required.

Addressing smoking

An encouraging feature of COPD is that it is a disease that is almost entirely preventable, and even achieving smoking cessation in patients with established disease improves health status and slows or arrests the rate of deterioration of COPD. The current research has contributed to this approach in several ways. It has confirmed that cigarette smoking remains the major risk factor in almost all men with COPD, and

for a majority of women with COPD. Smoking cessation is essential in those currently affected. Secondly there is a need for intensified effective and aggressive anti-smoking-initiation interventions directed at primary, high schools and even tertiary institutions, as few people start smoking after age 19.⁹⁵ Reviews of the effectiveness of such interventions have shown a reduction in smoking prevalence of between 5 and 30%, and identify the social influence resistance model as the most effective.⁹⁶ However there are concerns about the long-term effect of these interventions are that they have a limited period of effect⁹⁶, so they need to be part of a comprehensive approach to tobacco control which includes increased taxation, media campaigns, advertising restrictions and legislation. This could be the first step to empowering South Africans to make informed choices regarding smoking. It is a well known fact that changing established health-related behaviour in adulthood is a difficult task.⁹⁷

Further research can contribute to this initiative. For example, by examining and addressing factors that perpetuate and entrench smoking behaviour in South Africa, particularly in the Western Cape. Current interventional research in low-income pregnant women at state antenatal facilities in the Western Cape has attempted to address this question, but results are not available yet.^{98 99} In the BOLD study information on the "Stages of Change" of smoking behaviour was collected with the intention that analysis of this will shed some light on the psychosocial aspects of smoking behaviour in Ravensmead/Uitsig that will prove useful in designing smoking cessation and other community programmes.

Monitoring of tobacco usage is a research focus of the national Demographic and Health Surveys. Concomitant monitoring of policy and control efforts and evaluation of their effectiveness is necessary in order to track health consequences of health and control policies. Tobacco control research deserves greater support as a national research priority.

At the provincial level, where the responsibility for the primary and secondary health service lies, motivations need to be made for the provision of nicotine replacement therapy and pharmacological therapy such as bupropion, although other health priorities are currently likely to take precedence. This can be done by presenting health budget planners and resource allocators with an economic analysis of the projected healthcare costs and cost saving that would result from less hospitalisation and fewer exacerbations.

Nurses at the primary care level can be trained to provide brief counselling interventions in addition to physician advice. Moreover, the first target group of such interventions should be healthcare workers themselves in order to strengthen the credibility of the interventions. Smoking prevalences as high as 61% have been reported in Chinese hospital physicians.¹⁰⁰ Similarly, in 2003, 50% of nurses ≥ 40 years working at Tygerberg Hospital (the local tertiary hospital situated at the periphery of the study area), were current smokers, and 48% of smokers started smoking during or after their training.¹⁰¹

At the local authority level, the second important step in prevention is the development of smoking cessation programmes that are widely available and accessible to communities that depend on public primary health care facilities for health advice and care. Several simple tools have been developed to assist carers in their approach to this need. One such method, developed by the U.S. Public Health Service is the five A's (Ask, Advise, Assess, Assist and Arrange).¹⁰² Even if the documented 16% of persons¹⁰³ respond to this intervention, cost saving in terms of productivity, quality of life, mortality and health service costs could be significant. Additional counselling by nurses has been shown to almost double the quit rate.¹⁰⁴

Findings from the LHS2002 have suggested that smoking increases the risk of M.tuberculosis infection.¹⁰⁵ The BOLD study has found that the converse is also true – the lung damage from TB is an aetiological agent for COPD. Including smoking cessation as part of the TB control programme would be a useful intervention, as South Africa faces considerable financial difficulty in merely maintaining their existing healthcare services. Inclusion of smoking cessation into other programmes would prove to be more feasible and cost effective. Programmes for HIV/AIDS, cancer control, cardiovascular disease, family planning and maternal health should be considered because smoking is an independent risk factor for many diseases other than COPD.¹⁰⁶ Brief counselling interventions by pharmacists could be another strategy, as many rely on pharmacists for health information.

A starting point for promoting smoking cessation is at community level in the study area. This has and will be approached in several ways, firstly, through community report-back meetings. The author and colleagues formally communicated the main results of both the studies to the members of the Ravensmead and Uitsig communities at two special community events. The first was held in 2003 and the preliminary results

of the LHS2002 were presented to the communities and the second was held in 2005, informing the community of the results of the BOLD study. These events were intended to be not only an expression of appreciation for the community's involvement in the project, but an opportunity for promoting smoking cessation and lung health. Further local follow-up is planned (see Appendix 6).

An organised national response to COPD is needed. An organisation exists for the prevention and control of asthma (National Asthma Education Programme), which has brought asthma into the public domain. A similar initiative needs to be created for COPD or the National Asthma Education Programme could be expanded to include COPD and links with the existing National Council Against Smoking can be created. Public knowledge on COPD seems to be extremely limited. COPD and smoking need to be put into perspective considering that COPD accounts for much higher morbidity and mortality than lung cancer, which is a better known association.

Addressing tuberculosis and poverty

Both the SADHS and this study have confirmed the role of tuberculosis in contributing to the burden of obstructive lung disease in South Africa.^{107 108} The TB-attributable COPD subgroup requires further investigation in terms of pathophysiological mechanisms associated with airflow limitation.⁹³ Research into the specific characteristics of this subgroup is necessary to characterise the entity in terms of features such as AHR, severity and response to bronchodilators and corticosteroids, which will assist in defining optimal treatment for this group.

The overwhelming issue of poverty and its effects upon lung health also needs to be addressed if the burden of respiratory disease is to be reduced. Low socioeconomic status is itself an independent risk factor for respiratory symptoms. In addition, poverty-associated factors such as overcrowding, smoking, poor nutrition and alcohol abuse create an immune deficient state that predispose individuals to TB and a proportion of these will develop significant airflow limitation that limits quality of life and productivity and increases morbidity, mortality and health system costs. TB control is already a national priority but the management strategies for TB require review in the light of the run-away increase in the incidence of this disease in the face of the HIV/ AIDS epidemic, and the fact that recurrences are being shown to represent transmission rather than reactivation. Prevention of overcrowding, and focused efforts to eradicate poverty are required. Even job creation is not enough, as 67% of wage earners in Cape

Town do not earn enough to push their household above the poverty line, making them the “chronic working poor”.¹⁰⁹

Addressing cannabis smoking

This study has shown that the population prevalence of cannabis smoking is high in the study area, and that a significant proportion of respiratory symptoms can be attributed to this habit. The results also suggest, but do not confirm that heavy cannabis smoking is associated with the development of COPD. The negative respiratory health effects of cannabis need to be highlighted and publicised by health promotive activities in the health service and the media in order to increase public awareness in South Africa, which is currently virtually non-existent. The incorporation of an anti-cannabis smoking message into tobacco smoking cessation programmes is imperative in areas where cannabis smoking is highly prevalent. Indeed, we have no knowledge of where these are, as there is little information on the pattern and prevalence of usage in South Africa. Despite problems of underreporting, the inclusion of questions on cannabis use in the next national Demographic and Health Survey would be helpful to give some idea of the magnitude and distribution countrywide, which would in turn assist in focusing further research and anti- smoking interventions in the appropriate groups. In addition, further research should be directed towards confirming or clarifying the link between cannabis use and COPD, including considering the effects of dose. A further aspect is to clarify the additive roles of tobacco smoking and also methaqualone (Mandrax®) use as part of the cannabis smoking routine, and whether the ‘white pipe’ method of smoking is more harmful to health.

Another important research question is a possible relationship between cannabis smoking and tuberculosis. Recent studies have shown that cannabis reduces immune function by impairing host defences against respiratory pathogens¹¹⁰, and it can be hypothesised that cannabis is a risk factor for both *M.tuberculosis* infection and disease. Further population studies and enquiry into the mechanisms of this association are encouraged to assess this relationship. Data from the LHS2002 will be interrogated to investigate this question in a separate body of work.

Addressing air pollution

This study shows that electrification has been successful in reducing exposures to biomass fuels, as very few participants reported current exposure. Indoor air pollution from biomass fuel confers considerable risk to rural South African women for chronic

bronchitis.⁹⁹ Certain areas of South Africa such as the Northern Province have a large rural population of approximately 88.1%, many of whom are dependent on biomass sources for cooking and heating.¹¹¹ As biomass fuel use is directly related to poverty, suggested interventions include financial support measures through income generation and micro-credit and increasing accessibility of cleaner fuels to the poor.¹¹² However, interventions need to be locally appropriate and participatory in nature if they are to be sustainable and successful, especially if the alternative (biomass) is free.

The goal of country-wide electrification needs to be a continued focus. Short and intermediate term solutions include better indoor ventilation by means of innovative stove and chimney designs such as the ceramic chimney-less stoves¹¹² that have been piloted in other African countries¹¹³, and could be promoted in some parts of South Africa. Substitution of biomass fuels for less polluting agents such as kerosene or liquid petroleum gas is another alternative, but they require funding and are associated with other risks such as accidental poisoning of children.⁹³ Potential solutions need to be novel and cost effective e.g. solar water heating.^{93 114}

It is paradoxical that creation of much South African electricity is via the burning of coal, which itself results in significant outdoor pollution.^{93 115} There is hardly any data on outdoor air pollution in South Africa, apart from the Vaal Triangle study.¹¹⁶ This area of research needs to be extended with the emphasis of monitoring and evaluating the respiratory effects of industrial and urban pollution in the large cities where, like Cape Town, photochemical smog is a visible problem.¹¹⁷ Along with research, awareness of the effects of indoor air pollution needs to be increased at a national governmental level and increased intersectoral¹¹² collaboration with NGOs and health agencies should be promoted so that efforts can be strengthened and supported by unified efforts.

Addressing occupational exposures

The prevention of occupational exposures can be achieved by substitution of hazardous materials, containment of exposures such as dust fumes and gases by engineering processes and by local exhausts or general exhausts or the use of respiratory masks (which are less effective). Key to this process of preventing and reducing exposures is worker education. Statutory occupational dust exposure limits are geared at reducing respiratory hazards, but recent evidence suggests that some are insufficient to protect against the development of COPD.¹¹⁸ Longitudinal studies are

needed to examine the exposure – response relationship between occupational dusts and COPD, including the effect of tuberculosis in the occupational setting, particularly amongst miners.⁹³

The Occupational Health and Safety Act (No. 85 of 1996) and the Mine Health and Safety Act (No. 29 of 1996) stipulate controls for the reduction of workplace exposures. However, enforcement of these measures is not effectively practiced. Reluctance of employers to put the measures into place, owing to cost implications, absent or ineffective risk assessment and monitoring of airborne hazards, occur even in industries with known respiratory risk (e.g. metal and coal mining).⁹³ This lack of ability to control exposures by enforcing existing legislation hampers the process of reducing and eliminating respiratory hazards in the South African occupational context and is due to factors such as skills shortages, fragmentation of enforcement efforts and attenuated trade union power.¹¹⁹

Diagnosis and treatment

Early diagnosis and appropriate treatment of persons with COPD is the aim of published guidelines, but their translation into practice is a challenging process. Local and international guidelines emphasise control of risk factors (especially smoking cessation and known aetiological factors such as occupational exposures), early diagnosis, optimal drug therapy and patient education.^{93 120 121} This study has shown significant underdiagnosis and undertreatment of symptomatic lung disease.

However, there are multiple barriers to the practice of guidelines in the public sector primary care. A barrier to the recognition of obstructive lung disease and guideline practicability is the level of service obtained in state primary health clinics which are overburdened, under serviced, and sometimes lack availability of medication and time.

In addition, the underuse of spirometry as a diagnostic tool and management aid is associated with lack of equipment, skills, practitioner knowledge, in addition to insufficient time. Failure to use even a peak flow meter in the primary care setting is concerning.²⁷ The creation and distribution of appropriate skills is a challenge that is being addressed by the provision of pulmonology skills (particularly clinical technologists) at tertiary and secondary hospitals.¹²² The Practical Approach to Lung Health in South Africa Study (PALSA) is a novel approach that operates in primary care clinics and assists nurse practitioners identify COPD and other priority lung diseases and provide guideline-based treatment. The PALSA guideline is syndromic, and

evidence-based, and is provided in an attractive well-illustrated form that is easy to use and even demonstrate to patients.¹²³ PALSA, which is being rolled out in both the Western Cape and Free State provinces, incorporates in its integrated guideline a module on asking about smoking and a simple guide to counselling patients on smoking cessation. This is a unique package that has been developed for use by health professionals in that it includes the promotion of smoking cessation at the primary care level.¹²³ These and similar initiatives need to be promoted and introduced into other provincial health services.

The contribution of the pharmaceutical industry is important in increasing awareness of COPD. Research into the pathophysiological aspects of obstructive lung disease and optimal drug therapy assist in improving treatment, quality of life and provide hope for COPD patients. However, these improvements reach only the 17% of South Africans in the private health sector, and those that attend private practitioners and receive prescriptions.

Another barrier to improving management of COPD is the high cost of medication, which is particularly important in the resource limited public sector.⁹³ There are many other pressing health issues that compete for funding at the primary health care level, notably HIV-related disease and infections. Health managers need to be made aware of the exact cost comparisons of providing appropriate medical management and the treatment of uncontrolled disease.⁹³ Economic analyses of the projected costs for COPD in South Africa, based on statistical models are essential to motivate for appropriate resource allocation. This is one of the aspects of the BOLD study that will assist in creating a perspective on COPD in South Africa.

8.6. Concluding remarks

The prevalence of respiratory symptoms and COPD in this predominantly low-income urban area of South Africa is high in both men and women reflecting high levels of smoking and past TB in the community. These results highlight the need for prioritisation of COPD as a health problem requiring targeted strategies for prevention, diagnosis and treatment. As smoking confers the highest attributable risk for COPD in most settings, the one practical and achievable goal for the reduction of the burden of obstructive lung disease is to develop a strong initiative to address tobacco control and reduce smoking, of both tobacco and cannabis. Serious attempts need to be made by

the state health service and other health organisations if the predicted damage is to be reduced.

The BOLD study is the first in Africa to use internationally standardised methodology and provides a basis for comparisons of the prevalence of COPD with other parts of South Africa, other countries on the African continent and further afield. In settings where spirometry is not practical, the questionnaire and approach used in the LHS2002 study provides a standardised tool for monitoring of prevalence of symptoms of respiratory diseases, and prevalence of risk factors. This information can be used to develop or strengthen strategies to stem and reverse the tide of obstructive lung disease.

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APPENDIX 1

INFORMATION SHEET FOR LUNG HEALTH SURVEY 2002 RAVENSMEAD AND UITSIG IN PERSONS 15 YEARS AND OLDER IN RAVENSMEAD AND UITSIG.

You are invited to take part in a study to determine the prevalence of TB and chest diseases in people living in Ravensmead and Uitsig. About 5000 people will take part. Information on the study is supplied in this document. A trained fieldworker will be on hand to explain the contents and answer all your questions. Please ensure that you understand everything contained in this document. If you decide to participate, you will be required to give written consent before you take part.

Who is doing the study?

This study is being performed by health workers of the TB Research Centre of the University of Stellenbosch (Tygerberg Hospital) led by Professor Nulda Beyers, and the Lung Institute of the University of Cape Town, led by Prof. Eric Bateman.

Drs Du Toit Loots (tel. 021-9389177), Anamika Jithoo (021-4066877), Emma van Schalkwyk (021-9389594) are responsible for the day- to -day running of the study.

What is the purpose of the study?

In spite of a good TB tracing and treatment programme in the areas of Ravensmead and Uitsig, the number of TB cases remains high. The purpose of this study is to determine the number of people who are currently or have been infected with TB, or have other forms of lung disease like asthma and emphysema. We will look for factors that increase the risk of developing these diseases and the effect of these diseases upon the community. When this survey has been completed, it is our intention to conduct two further studies involving smaller numbers of residents of Uitsig and Ravensmead, who are identified in the first study. We will invite both people without lung disease, and some with chest complaints, to take part in the later studies. Separate information pamphlets and consent forms will be provided for these studies.

What is TB?

Tuberculosis (TB) is an infectious disease caused by bacteria (germs) which are spread through coughing. TB infection affects mainly the lungs, but can also affect other parts of the body, such as the lining of the brain (meningitis), and glands. The areas of Uitsig and Ravensmead, like other parts of the Western Cape has a higher number of TB cases than most other parts of South Africa. In spite of a good programme for tracing and treating persons with active TB infection, many persons with TB are not diagnosed quickly, and go on infecting other people, including friends and family without knowing it. Early infection with the organism can be detected with a skin test, sputum (phlegm) examination, and chest X-Ray. These will be performed on all that enter the study.

Other Lung Diseases that will be studied?

We will be asking questions and looking at X-Rays for signs of other lung diseases like asthma, chronic bronchitis and emphysema. We will also ask questions about your home, habits and work that might have an effect on your lungs. We will also look for evidence of lung damage caused by TB. In this way we will be able to assess how much of a problem lung diseases are in your community.

This research proposal has been approved by the Medical Ethics Committee (Research Ethics) of the Universities of Stellenbosch and Cape Town and is being performed with the permission of the Health Department of the City of Cape Town

Participation in this study is strictly on a voluntary basis. You are free to withdraw from this study at any stage, without any consequences for you. No financial reward will be given to any persons taking part in this study.

Are there any risks for people who take part in this survey?

Taking part in this study does not pose any severe risks to you or your family. However, the following will be required of those taking part:

1) You will be asked to sign a consent form after you have read and understood this information leaflet. You will be given an original copy of this leaflet and the consent form to keep.

2) You will be asked to complete (with the help of a trained interviewer) a detailed questionnaire about your health

3) A TB skin test, called the Tuberculin test, will be performed on all that take part. In about 70% of persons it may form a red, slightly tender lump on the upper arm, at the injection site, within a day, which could last for several days, up to two weeks. Occasionally, it may blister, or form a shallow sore (ulcer), or cause tender glands under the arm. A health worker will record the result of the test after 3 days, when the reaction is strongest. If necessary, shall be will provided some cortisone cream to rub on the area to reduce the pain and swelling.

4) You will be given an appointment and transport to attend the Tygerberg Hospital X-Ray Department for a chest X-Ray within a few days or weeks of completing the questionnaire. At this visit your arm will be examined for a scar from previous TB vaccination. Your height and weight will also be recorded. You will then have a chest X-Ray. If you are female, in privacy, you will be asked if you are pregnant, and if so, your abdomen will be covered by a lead shield, to prevent your baby from being exposed to the X-Ray. The chest X-Ray will be reported on by experienced specialists. The radiation risk of a standard chest X-Ray is very small.

5) You will be asked to try and cough up some phlegm for examination for TB organisms.

What is the benefit for you, of taking part in this study?

The information gained from this study will be used to provide suggestions for improving health services. (Community Health Centres, hospitals, medications etc.)

This study may benefit you if you have a lung problem of which you are not aware.

What will happen if these tests show that you have a lung problem?

After you have completed the questionnaire, the answers will be screened within days for symptoms that suggest lung disease that needs immediate attention. Such persons will be contacted within days, to have a chest X-Ray and be referred to a doctor at either the local Community Health Centre, or if they prefer, to their private doctor. If considered necessary, they might be referred to the Lung Clinics at either Tygerberg or Groote Schuur Hospitals. If the X-Ray or phlegm examination shows TB, you will be referred to the local TB Clinic for treatment.

Confidentiality of information and privacy of the participant

All personal information obtained during this study will remain strictly confidential.

The answers will be transferred to a computer, but your name will not be included, and you will be identified by a coded number. No information about individuals will be released to any other parties but the research team, without your further consent. When the results of research are published(for example, in medical journals), no personal details that might identify individuals, or individual households will be included. Completed questionnaires will be stored in a safe place.

Thank you for reading this information sheet. If you have any questions, please ask them now. The interviewer will be pleased to answer them. If you wish to take part, please read and sign the 2 consent forms.

Please keep this information sheet and a copy of the consent form in a safe place, for your records.

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**INFORMED CONSENT FORM FOR THE LUNG HEALTH SURVEY
(FOR PERSONS AGE 15 YEARS AND OLDER)**

- I confirm that I have read the information sheet, and that the information and procedures involved in my taking part in the survey have been explained to me.
- I confirm that I have had the opportunity to ask questions about the survey and that I am satisfied with the answers and explanations that have been provided.
- I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to take part in this survey.
- I agree to take part in the survey.

Subject's signature: _____ date _____

Subject's name: _____ (please print)

The person who conducts the informed consent discussion must also sign and date this form.

Signature: _____ date _____

Name: _____ (please print)

Signature of witness, if applicable.

Witnessed by: (print name): _____

Signature of Witness: _____ date _____

APPENDIX 2



Please read these 3 instructions carefully before completing the questionnaire:

- 1 - Do not write anywhere outside the spaces provided.
- 2 - Indicate correct answers in check boxes with an X, i.e.
- 3 - If you make a mistake, ask the supervisor for help.

1 Name

2 Address

3 Dwelling number

4 Interviewer number

5 Today's date
d d / m m / Y Y Y Y

6 Sex Male Female

7 Date of birth
d d / m m / Y Y Y Y

8 If you do not know your date of birth, what was your age on your last birthday? years

9 How many years have you lived in the present home? years

10 How many years have you lived in Ravensmead/Uitsig? years

11 Where did you live before this?

12 What is your employment status (**check all that apply**)?

<u>Employed</u>	<u>Unemployed</u>
<input type="checkbox"/> Self-employed	<input type="checkbox"/> Not seeking work
<input type="checkbox"/> Employed by government	<input type="checkbox"/> Seeking work
<input type="checkbox"/> Employed in private sector	<input type="checkbox"/> Student
<input type="checkbox"/> Casual employment, specify: <input style="width: 150px; height: 25px;" type="text"/>	<input type="checkbox"/> Housewife
	<input type="checkbox"/> Pension
	<input type="checkbox"/> Disability grant for chest disease
	<input type="checkbox"/> Disability grant for other disease
	<input type="checkbox"/> Child support grant

If unemployed go to Question 14.

13 If you are employed, please state the nature of your job.

<input type="checkbox"/> Street vendor	<input type="checkbox"/> Taxi driver	<input type="checkbox"/> Factory worker
<input type="checkbox"/> Hair dresser	<input type="checkbox"/> Child minder	<input type="checkbox"/> Office worker
<input type="checkbox"/> Shop owner	<input type="checkbox"/> Health care worker	<input type="checkbox"/> Other (Please specify): <input style="width: 150px; height: 25px;" type="text"/>

14 What is your usual monthly income(from all sources)?

<input type="checkbox"/> Less than R 500	<input type="checkbox"/> R 3 000-R 4 000	<input type="checkbox"/> R 8 000-R 10 000
<input type="checkbox"/> R 500-R 1 000	<input type="checkbox"/> R 4 000-R 5 000	<input type="checkbox"/> R 10 000-R 13 000
<input type="checkbox"/> R 1 000-R 2 000	<input type="checkbox"/> R 5 000-R 6 500	<input type="checkbox"/> Greater than 13 000
<input type="checkbox"/> R 2 000-R 3 000	<input type="checkbox"/> R 6 500-R 8 000	

15 What level of education did you reach?
 Highest grade completed: Initiated tertiary education

16 What is your marital status?

<input type="checkbox"/> Single (never been married)	<input type="checkbox"/> Widowed
<input type="checkbox"/> Married	<input type="checkbox"/> Living with a partner
<input type="checkbox"/> Divorced/separated	



We are now going to ask you some questions about chest problems....

17 Has a doctor/health worker ever told you that you have (check all that apply):

- Heart trouble?
 Chronic Bronchitis / Emphysema?
 Asthma?
 Pleurisy?
 Pneumonia?
 Hay fever?
 TB?
 Other chest trouble? Specify:

18 If you have had TB, when and where was it treated?

	Start of treatment	End of treatment	Clinic/Hospital Name
1	<input type="text"/>	<input type="text"/>	<input type="text"/>
2	<input type="text"/>	<input type="text"/>	<input type="text"/>
3	<input type="text"/>	<input type="text"/>	<input type="text"/>

19 Do you have a **cough** that began recently? Y N

If 'yes', when did it start?

20 Are you **coughing up blood** now or in the last month? Y N

21 Have you coughed up blood in the last 12 months? Y N

If 'yes', when did it start?

22 Do you usually bring up any **phlegm** from your chest **first thing in the morning** in the winter? Y N

23 Do you usually bring up any **phlegm** from your chest during the day, or at night, in the winter? Y N

If 'no', go to question 24.

23.1 Do you bring up phlegm like this on most days for as much as **3 months each year**? Y N

23.2 Have you had coughing and phlegm on most days for a minimum of 3 months a year and for at least **2 successive years**? Y N

24 In the last 12 months, have you had any chest illnesses that have kept you **off work, indoors at home, or in bed**? Y N

If 'no' go to question 25.

24.1 Did you produce **phlegm** with any of these chest illnesses? Y N

24.2 In the last 12 months, how many such illnesses, with (increased phlegm), did you have which lasted **a week or more**?

25 Do you ever have trouble with your breathing? Y N

If 'no' go to question 26.

- 25.1 Do you have this trouble
- Continuously, so that your breathing is never quite right?
 Repeatedly, but it always gets completely better?
 Only rarely?

26 Are you disabled from walking by any condition other than heart or lung disease? Y N

If yes, please describe:



27 Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill? Y N
If 'no', go to Question 28.

27.1 Do you have to walk slower than people of your own age on the level because of breathlessness? Y N

27.2 Do you ever have to stop for breath when walking at your own pace on the level? Y N

27.3 Do you ever have to stop for breath after walking about 100 yards (or after a few minutes) on the level? Y N

27.4 Are you too breathless to leave the house or breathless on dressing or undressing? Y N

28 Have you had wheezing or whistling in your chest at any time in the last 12 months? Y N
If 'no', go to question 29.

28.1 Have you been at all breathless when the whistling noise was present? Y N

28.2 Have you had this wheezing or whistling when you did not have a cold? Y N

28.3 Have you been woken by an attack of shortness of breath or tightness in your chest at any time in the last 12 months? Y N

29 Have you ever had a problem with sneezing, or a runny, or blocked nose when you DID NOT have a cold or the flu? Y N
If 'no', go to question 30.

29.1 In the last 12 months, have you had a problem with sneezing, or a runny, or blocked nose when you DID NOT have a cold or the flu? Y N

30 Do you have to change your clothes or bedding because of night sweats? Y N

If 'yes', when did it start?

d	d	m	m	y	y	y	y
---	---	---	---	---	---	---	---

31 Are you troubled by fever? Y N **If 'yes', when did it start?**

d	d	m	m	y	y	y	y
---	---	---	---	---	---	---	---

32 Are you losing weight? Y N **If 'yes', when did it start?**

d	d	m	m	y	y	y	y
---	---	---	---	---	---	---	---

33 Do you recall having any chest illnesses with cough and shortness of breath when you were a child (<12 years)? Y N
If 'no', go to Question 34.

33.1 Did you have such an illness repeatedly? Y N

33.2 Did you ever sleep in a hospital for such an illness? Y N

33.3 Do you recall the name of the illness? Y N **If 'yes', specify:**

34 Have you smoked cigarettes for a year or longer? Y N
If 'no', go to Question 35.

34.1 How old were you when you started smoking?

34.2 Do you smoke now (within the last month)? Y N

If 'no', how old were you when you stopped smoking?

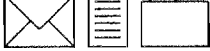
34.3 **On average**, how much do you smoke or did you smoke?

Number of cigarettes per day:

Number of pipe bowls per day:



- 35 Have you ever smoked anything other than tobacco? Y N *If 'no', go to Question 36.*
- 35.1 Have you ever smoked **cannabis**? Y N *If 'no', go to Question 36.*
- 35.2 How old were you when you started smoking cannabis?
- 35.3 Do you smoke now (within the last month)? Y N
If 'no', how old were you when you stopped smoking?
- 35.4 **On average**, how much do you smoke or did you smoke per day?
Number of joints per day: Number of pipes per day:
- 36 Have you ever worked in a job that exposed you to silica dust, or involve sand blasting, grinding, pottery, work in a quarry/mine or grave stone manufacturing? Y N
- 37 Have you ever been exposed to other dusts, gases, strong smells, chemicals, fumes, at work? Y N
If 'no', go to Question 38.
- 37.1 Have you ever had to leave your job because it affected your breathing? Y N
- 38 Do you or your immediate neighbours keep pigeons/birds in a cage (not chickens)? Y N
- 39 Have you ever been told that you snore? Y N *If 'no', go to Question 40.*
- 39.1 According to what others have told you, **please estimate how often you snore.**
- | | |
|--------------------------------------|--|
| <input type="checkbox"/> Rarely | <input type="checkbox"/> 3 to 5 times a week |
| <input type="checkbox"/> Sometimes | <input type="checkbox"/> Every night or almost every night |
| <input type="checkbox"/> Once a week | <input type="checkbox"/> Do not know |
- 39.2 **How loud** have others said your snoring is?
- | |
|--|
| <input type="checkbox"/> only slightly louder than heavy breathing |
| <input type="checkbox"/> about as loud as mumbling or talking |
| <input type="checkbox"/> louder than talking |
| <input type="checkbox"/> extremely loud (can be heard through a closed door) |
| <input type="checkbox"/> do not know |
- 40 According to what others have told you, how often, if ever, do you gasp, choke, or make snorting sounds during sleep?
- | | |
|------------------------------------|--|
| <input type="checkbox"/> never | <input type="checkbox"/> often (at least once a week) |
| <input type="checkbox"/> rarely | <input type="checkbox"/> very often (every night/almost every night) |
| <input type="checkbox"/> sometimes | <input type="checkbox"/> Do not know |
- 41 According to what others have told you, how often, if ever, do you seem to have momentary periods? during sleep, when you **stop breathing, or you breathe abnormally?**
- | | |
|------------------------------------|--|
| <input type="checkbox"/> never | <input type="checkbox"/> often (at least once a week) |
| <input type="checkbox"/> rarely | <input type="checkbox"/> very often (every night/almost every night) |
| <input type="checkbox"/> sometimes | <input type="checkbox"/> Do not know |
- 42 Are you currently taking any medicines (including inhalers, aerosols, or tablets) for any chest diseases, including nasal allergies? Y N *If 'no', go to Question 43.*
- 42.1 For what conditions are you taking these medicines (**check all that apply**)?
- | | |
|--|---|
| <input type="checkbox"/> Chronic Bronchitis / Emphysema? | <input type="checkbox"/> Hay fever? |
| <input type="checkbox"/> Asthma? | <input type="checkbox"/> TB? |
| <input type="checkbox"/> Pleurisy? | <input type="checkbox"/> Other chest trouble? |
| <input type="checkbox"/> Pneumonia? | Specify: <input type="text"/> |



42.2 Where do you receive your **chest medicines**?

- | <u>usually</u>
(check one only) | | <u>occasionally</u>
(check all that apply) |
|------------------------------------|----------------------|---|
| <input type="checkbox"/> | Community clinic | <input type="checkbox"/> |
| <input type="checkbox"/> | Private hospital | <input type="checkbox"/> |
| <input type="checkbox"/> | Provincial hospital | <input type="checkbox"/> |
| <input type="checkbox"/> | Pharmacy | <input type="checkbox"/> |
| <input type="checkbox"/> | Private practitioner | <input type="checkbox"/> |
| <input type="checkbox"/> | Traditional healer | <input type="checkbox"/> |
| <input type="checkbox"/> | A friend | <input type="checkbox"/> |

43 Where do you usually go for medical care for chest problems?

- | <u>usually</u>
(check one only) | | <u>occasionally</u>
(check all that apply) |
|------------------------------------|----------------------|---|
| <input type="checkbox"/> | Community clinic | <input type="checkbox"/> |
| <input type="checkbox"/> | Private hospital | <input type="checkbox"/> |
| <input type="checkbox"/> | Provincial hospital | <input type="checkbox"/> |
| <input type="checkbox"/> | Pharmacy | <input type="checkbox"/> |
| <input type="checkbox"/> | Private practitioner | <input type="checkbox"/> |
| <input type="checkbox"/> | Traditional healer | <input type="checkbox"/> |
| <input type="checkbox"/> | A friend | <input type="checkbox"/> |

43.1 In the last 12 months, have you visited the above for your chest/lung disease? Y N
If 'yes', how many times?

44 Where do you usually go for emergency treatment for your chest problems?

- | <u>usually</u>
(check one only) | | <u>occasionally</u>
(check all that apply) |
|------------------------------------|----------------------|---|
| <input type="checkbox"/> | Community clinic | <input type="checkbox"/> |
| <input type="checkbox"/> | Private hospital | <input type="checkbox"/> |
| <input type="checkbox"/> | Provincial hospital | <input type="checkbox"/> |
| <input type="checkbox"/> | Pharmacy | <input type="checkbox"/> |
| <input type="checkbox"/> | Private practitioner | <input type="checkbox"/> |
| <input type="checkbox"/> | Traditional healer | <input type="checkbox"/> |
| <input type="checkbox"/> | A friend | <input type="checkbox"/> |

45 Have you visited a hospital casualty department or emergency room because of your chest/lung disease in the last 12 months? Y N

If 'yes', how many times?

46 Have you spent at least one night in hospital because of your chest/lung disease in the last 12 months? Y N

If 'yes', how many days?

47 If you are currently employed, have you lost any days of work because of your chest/lung disease in the last 12 months? Y N

If 'yes', how many days?

48 Whatever your working situation, have there been any days when you have had to give up other activities (e.g. looking after the children, the housework, studying) because of your chest/lung disease, in the last 12 months? Y N

If 'yes', how many days, on average, every month?

3096



49 Do you drink **alcohol**? Y N *If 'no', go to Question 50.*

49.1 **How many days** do you drink during the week (Monday to Thursday)? days

49.2 **How many days do** you drink over weekends (Friday to Sunday)? days

49.3 **How much** would you drink on a typical drinking day?

Wine ml shared by persons

Brandy / whisky ml shared by persons

Beer ml shared by persons

Other alcoholic drinks ml shared by persons

50 On average, how much time do you spend in the following modes of transport?

	days/week	hours/day
Taxi	<input type="text"/>	<input type="text"/>
Train	<input type="text"/>	<input type="text"/>
Bus	<input type="text"/>	<input type="text"/>
Private car	<input type="text"/>	<input type="text"/>

Other specify:

51 What amount of time do you spend on average in the following places (other than home)?

	days/week	hours/day
Visiting a friends home	<input type="text"/>	<input type="text"/>
Church/community gatherings	<input type="text"/>	<input type="text"/>
Clinics	<input type="text"/>	<input type="text"/>
Shebeen	<input type="text"/>	<input type="text"/>

Other specify:

52 What fuels are mostly used in the dwelling you spend most of your evenings?

For Cooking
(check one only)

- Wood or coke
- Gas
- Electricity
- Paraffin
- Spirits

For Heating
(check one only)

-
-
-
-
-

53 Have you ever spent time in a prison? Y N *If yes, please specify dates and place:*

From	To	Prison
<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>

APPENDIX 3

INFORMATION SHEET FOR THE BOLD STUDY (LUNG HEALTH SURVEY PART 2): PERSONS 40 YEARS AND OLDER IN RAVENSMEAD AND UITSIG.

You are invited to take part in a study examining how common smoking-related lung disease is. (emphysema and chronic bronchitis) This is a follow up study of the Lung Health Survey 2002, for which you have already answered a questionnaire, in 2002. Information on this further study is supplied here. A trained fieldworker will be on hand to explain the contents and answer any questions. Please be satisfied that you understand everything contained in this document. If you decide to participate, you will be asked to give written consent before you take part. Participation is entirely voluntary.

Who is doing the study?

This study is being performed by the University of Cape Town Lung Institute, led by Professor Eric Bateman and Dr Anamika Jithoo, in conjunction with by health workers of the TB Research Centre of the University of Stellenbosch (Tygerberg Hospital) led by Professor Nulda Beyers.

Dr. Anamika Jithoo (021-4066850) and Sister Christine Johannisen (tel. 021 4066850) and are responsible for the day-to-day running of the study.

What is the purpose of the study?

In our first study last year, you participated in a questionnaire, had a chest X-Ray, a sputum sample for TB, and measurement of your height and weight.

The aim of this study is to measure the breathing capacity of a randomly selected group of participants. This will assess the breathing capacity of the population, which will yield information about smoking related lung disease (emphysema), asthma, occupational lung disease, TB, and the validity of the first questionnaire. Some persons with symptoms of lung disease are also included in this study.

You have been randomly (like the flip of a coin) chosen to perform simple breathing tests that will take up about 30 minutes of your time. Your selection does not mean that you have a lung disease.

What do we mean by smoking-related lung disease?

Smoking related lung disease is most commonly called emphysema and/or chronic bronchitis. People in the medical field refer to these two diseases as Chronic Obstructive Pulmonary Disease.

This disease of the lungs is much more common than many people suspect, and you may not even know that you have it, because the symptoms only occur later in the course of the disease. The symptoms are cough, phlegm production, shortness of breath and wheeze. The same symptoms also occur in persons with asthma and other lung diseases.

Cigarette smoking is the main cause of emphysema. The ingredients of cigarettes, when smoked over a long period of time, cause damage to the lungs, and decrease their function. If one continues to smoke, the damage becomes greater, as time passes. This ongoing damage to the lungs can be stopped by stopping smoking.

What is asthma?

Asthma is a disease of the lungs that causes symptoms of cough, phlegm production, shortness of breath and wheeze or tight chest. It is one of the most common respiratory complaints in the world, and affects many people. Asthma attacks are most commonly triggered by allergies to airborne particles of house-dust mites, grass or tree pollens, fungal spores and skin flakes from furry animals such as cats and dogs. Certain foods and additives can also trigger off asthma, when eaten.

Asthma cannot be cured, but it can be treated and well controlled with inhaled and oral medications, allowing most sufferers to lead a normal life.

What is TB?

Tuberculosis (TB) is an infectious disease caused by bacteria (germs), which are spread through coughing. TB infection affects mainly the lungs, but can also affect other parts of the body, such as the lining of the brain (meningitis), and glands. The areas of Uitsig and Ravensmead, like other parts of the Western Cape has a higher number of TB cases than most other parts of South Africa. In spite of a good programme for tracing and treating persons with active TB infection, many persons with TB are not diagnosed quickly, and go on infecting other people, including friends and family without knowing it. Early infection with the organism can be detected with a skin test, sputum (phlegm) examination, and chest X-Ray. These have been performed on all that have entered

the study. If you suspect that you may have TB, and are not part of the study, you are advised to attend your local clinic for a sputum(phlegm) test.

This research proposal has been approved by the Medical Ethics Committee (Research Ethics) of the University of Cape Town and is being performed with the permission of the Health Department of the City of Cape Town

Participation in this study is voluntary. You are free to withdraw from this study at any stage, without any consequences for you. No financial reward will be given to any persons taking part in this study.

Are there any risks for people who take part in this survey?

Taking part in this study does not pose any significant risks to you or your family. However, the following will be required of those taking part:

1) You will be asked to sign a consent form after you have read and understood this information leaflet. You will be given a copy of this leaflet and the consent form to keep.

2) You and a trained interviewer will complete a questionnaire about your health. Part of this is to assess if it is safe for you to perform lung function tests on the day of your appointment. If not, another appointment may be scheduled. The rest of the questions are on respiratory health.

3) You will be asked to perform lung function tests with an experienced trained clinical technologist. She/he will explain the technique to you. This will involve you blowing into a breathing apparatus (spirometer), up to six times on two occasions, 15 minutes apart. You will be given a noseclip to wear. After the first set of blows, you will be given 2 puffs of Salbutamol, an inhaled medication that assists in opening airways that may be obstructed. You will then blow into the spirometer again. Salbutamol is a safe, well-tested medication. You may briefly experience a rapid heartbeat, and some tremor. These tests are performed in exactly the same manner at any hospital/lung clinic, according to existing guidelines and rules.

A small number of persons may become a dizzy or feel faint after exerting themselves for the test. This is usually temporary, lasts a few seconds only, and passes away with resting. Clinic staff will be able to assist you if there are any complications.

What is the benefit for you, of taking part in this study?

The information gained from this study will be used to provide suggestions for improving health services. (Community Health Centres, hospitals, medications etc.)

This study may benefit you if you have a lung problem of which you are not aware.

What will happen if these tests show that you have a lung problem?

After you have completed the breathing tests, the results will be screened within days by one of the doctors participating in the study for abnormalities that suggest lung disease that needs attention. A copy of the results will be given to each participant, which may be reviewed by his/her own healthcare practitioner. If the results are sufficiently abnormal, you will be contacted within days, and given a letter referring you to a doctor at either the local Community Health Centre, or if you prefer, to your private doctor. If considered necessary, you might be offered an appointment at the Lung Clinics at either Tygerberg or Groote Schuur Hospitals, or the UCT Lung Institute.

If you are not contacted or visited, you may assume that your lung function is normal, and you do not need referral or treatment.

Confidentiality of information and privacy of the participant

All personal information obtained during this study will remain strictly confidential.

The results will be transferred to a computer, but your name will not be included, and a coded number will identify you. No information about individuals will be released to any other parties but the research team, unless in a referral letter. When the results of research are published (for example, in medical journals), no personal details that might identify individuals, or individual households will be included. Completed results of the lung functions will be stored in a safe place.

Thank you for reading this information sheet. If you have any questions, please ask them now. The interviewer will be pleased to answer them. If you wish to take part, please read and sign the 2 consent forms.

Please keep this information sheet and a copy of the consent form in a safe place, for your records.

C:/MyDoc.Jithoo/AdultBOLD

**INFORMED CONSENT FORM FOR THE BOLD STUDY (LUNG HEALTH SURVEY: Part 2)
FOR PERSONS AGED 40 YEARS AND OLDER**

- I confirm that I have read the information sheet, and that the information and procedures involved in my taking part in the study have been explained to me.
- I confirm that I have had the opportunity to ask questions about the survey and that I am satisfied with the answers and explanations that have been provided.
- I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to take part in this survey.
- I agree to take part in the survey.

Subject's signature: _____ date _____

Subject's name: _____ (please print)

The person who conducts the informed consent discussion must also sign and date this form.

Signature: _____ date _____

Name: _____ (please print)

APPENDIX 4

Country Code _____ 1

City Code _____ 2

ID _____ 3

Date: _____ / _____ / _____ 4-6
 d d m m y y y y

BOLD SPIROMETRY QUESTIONNAIRE

Safety Questions

- | | | |
|--|--------------------------------|----|
| 1. In the past three months have you had any surgery on your chest or abdomen? | Yes <input type="checkbox"/> 1 | 7 |
| | No <input type="checkbox"/> 2 | |
| 2. Have you had a heart attack within the past three months? | Yes <input type="checkbox"/> 1 | 8 |
| | No <input type="checkbox"/> 2 | |
| 3. Do you have a detached retina or have you had eye surgery within the past three months? | Yes <input type="checkbox"/> 1 | 9 |
| | No <input type="checkbox"/> 2 | |
| 4. Have you been hospitalized for any other heart problem within the past month? | Yes <input type="checkbox"/> 1 | 10 |
| | No <input type="checkbox"/> 2 | |
| 5. Are you in the last trimester of pregnancy? | Yes <input type="checkbox"/> 1 | 11 |
| | No <input type="checkbox"/> 2 | |
| 6. Does the participant have a resting pulse of greater than 120 beats per minute? | Yes <input type="checkbox"/> 1 | 12 |
| | No <input type="checkbox"/> 2 | |
| 7. Is the participant currently taking medication for tuberculosis? | Yes <input type="checkbox"/> 1 | 13 |
| | No <input type="checkbox"/> 2 | |

If the participant answers "Yes" to any of Questions 1 through 7, do NOT proceed with the test.

- | | | |
|---|--|-----------------------------------|
| 8. Have you had a respiratory infection (cold) in the last three weeks? | Yes <input type="checkbox"/> 1 | 14 |
| | No <input type="checkbox"/> 2 | |
| 9. Have you used any medication for breathing in the last three hours? | Yes <input type="checkbox"/> 1 | 15 |
| | No <input type="checkbox"/> 2 | |
| 10. Spirometry Outcome | Pre-bronchodilator test completed | Yes <input type="checkbox"/> 1 16 |
| | | No <input type="checkbox"/> 2 |
| | Post-bronchodilator test completed | Yes <input type="checkbox"/> 1 17 |
| | | No <input type="checkbox"/> 2 |
| | Unable to obtain satisfactory spirometry (check one) | |
| | The participant did not understand instructions | <input type="checkbox"/> 2 18 |
| | The participant was medically excluded | <input type="checkbox"/> 3 |
| | The participant was unable to physically cooperate | <input type="checkbox"/> 4 |
| | The participant refused | <input type="checkbox"/> 5 |

11. Did the participant experience any adverse events as a result of performing the spirometry test? Yes 1 19
No 2

If yes, please briefly describe event: _____

12. Please note any items about the spirometry test concerning the ability of the participant to adequately perform the maneuver (e.g. kyphosis, dentures, missing limbs, etc.).

13. Fieldworker Number _____ 20

Country Code _____ 1
 City Code _____ 2
 ID _____ 3
 Date: _____ / _____ / _____ 4 6
d d m m y y y y

BOLD CORE QUESTIONNAIRE

Demographics

1. What is the participant's sex? Male 1 7
 Female 2
2. What is your race? _____ 8
3. What is your date of birth? _____ / _____ / _____ 9-11
d d m m y y y y
4. How many years of schooling have you completed? _____ 12
5. What is the highest level of schooling you have completed?

Primary School	<input type="checkbox"/>	1	13
Middle School	<input type="checkbox"/>	2	
High School	<input type="checkbox"/>	3	
Some College (Trade/Professional/Community)	<input type="checkbox"/>	4	
Four-Year College/University	<input type="checkbox"/>	5	
None	<input type="checkbox"/>	6	
Unknown	<input type="checkbox"/>	7	
6. What is the highest level of schooling your father has completed?

Primary School	<input type="checkbox"/>	1	14
Middle School	<input type="checkbox"/>	2	
High School	<input type="checkbox"/>	3	
Some College (Trade/Professional/Community)	<input type="checkbox"/>	4	
Four Year College/University	<input type="checkbox"/>	5	
None	<input type="checkbox"/>	6	
Unknown	<input type="checkbox"/>	7	

Respiratory Symptoms and Disorders

These questions pertain mainly to your chest. Please answer yes or no if possible. If you are in doubt about whether your answer is yes or no, please answer no.

Cough

7. Do you usually cough when you don't have a cold? Yes 1 15
 No 2

[If yes, continue with Question 7A; If no, skip to Question 8]

- 7A. Are there months in which you cough on most days? Yes 1 16
 No 2

[If yes, ask both Questions 7B & 7C; If no, skip to Question 8]

7B. Do you cough on most days for as much as three months each year? Yes 1 17
No 2

7C. For how many years have you had this cough? Less than 2 years 1 18
2-5 years 2
More than 5 years

Phlegm

8. Do you usually bring up phlegm from your chest, or do you usually have phlegm in your chest that is difficult to bring up when you don't have a cold? Yes 1 19
No 2

[If yes, continue with Question 8A; If no, skip to Question 9]

8A. Are there months in which you have this phlegm on most days? Yes 1 20
No 2

[If yes, ask both Questions 8B & 8C; If no, skip to Question 9]

8B. Do you bring up this phlegm on most days for as much as three months each year? Yes 1 21
No 2

8C. For how many years have you had this phlegm? Less than 2 years 1 22
2-5 years 2
More than 5 years 3

Wheezing/Whistling

9. Have you had wheezing or whistling in your chest at any time in the last 12 months? Yes 1 23
No 2

[If yes, ask both Questions 9A & 9B; If no, skip to Question 10]

9A. In the last 12 months, have you had this wheezing or whistling only when you have a cold? Yes 1 24
No 2

9B. In the last 12 months, have you ever had an attack of wheezing or whistling that has made you feel short of breath? Yes 1 25
No 2

Breathlessness

10. Are you unable to walk due to a condition other than shortness of breath? Yes 1 26
No 2

[If yes to Question 10, please describe this condition on the line below and then skip to Question 12. If no, go directly to Question 11.]

Nature of condition(s): _____

11. Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill? Yes 1 27
No 2

[If yes, ask Question 11A through 11D; If no, skip to Question 12]

- 11A. Do you have to walk slower than people of your age on level ground because of shortness of breath? Yes 1 28
No 2
Does not apply 3

- 11B. Do you ever have to stop for breath when walking at your own pace on level ground? Yes 1 29
No 2
Does not apply 3

- 11C. Do you ever have to stop for breath after walking about 100 yards (or after a few minutes) on level ground? Yes 1 30
No 2
Does not apply 3

- 11D. Are you too short of breath to leave the house or short of breath on dressing or undressing? Yes 1 31
No 2
Does not apply 3

12. Has a doctor or other health care provider ever told you that you have emphysema? Yes 1 32
No 2

13. Has a doctor or other health care provider ever told you that you have asthma, asthmatic bronchitis or allergic bronchitis? Yes 1 33
No 2

[If yes, ask Question 13A. If no, skip to Question 14]

- 13A. Do you still have asthma, asthmatic bronchitis or allergic bronchitis? Yes 1 34
No 2

14. Has a doctor or other health care provider ever told you that you have chronic bronchitis? Yes 1 35
No 2

[If yes, ask Question 14A. If no, skip to Question 15]

- 14A. Do you still have chronic bronchitis? Yes 1 36
No 2

15. Has a doctor or other health care provider ever told you that you have chronic obstructive pulmonary disease (COPD)? Yes 1 37
No 2

Management Section

Now I am going to ask you about medicines that you may be taking to help with your breathing. I want to know about medicines that you take on a regular basis and medicines that you may take only for the relief of symptoms. I would like you to tell me each medicine that you take, what form do you take it in, and how often you take it each month.

16. In the past 12 months, have you taken any medications for your breathing (including medications for nasal congestion)? Yes 1 38
No 2

If participant does not take any medications to help their breathing, skip to Question 17.

16A. Medication Name (not entered)								
16B. Medication Code	_____ 39	_____ 44	_____ 49	_____ 54	_____ 59	_____ 64	_____ 69	
16C. Formulation	Pills <input type="checkbox"/> 1 Inhaler <input type="checkbox"/> 2 Nebulizer <input type="checkbox"/> 3 Liquid <input type="checkbox"/> 4 Suppository <input type="checkbox"/> 5 Injection <input type="checkbox"/> 6 Other <input type="checkbox"/> 7	Pills <input type="checkbox"/> 1 Inhaler <input type="checkbox"/> 2 Nebulizer <input type="checkbox"/> 3 Liquid <input type="checkbox"/> 4 Suppository <input type="checkbox"/> 5 Injection <input type="checkbox"/> 6 Other <input type="checkbox"/> 7	Pills <input type="checkbox"/> 1 Inhaler <input type="checkbox"/> 2 Nebulizer <input type="checkbox"/> 3 Liquid <input type="checkbox"/> 4 Suppository <input type="checkbox"/> 5 Injection <input type="checkbox"/> 6 Other <input type="checkbox"/> 7	Pills <input type="checkbox"/> 1 Inhaler <input type="checkbox"/> 2 Nebulizer <input type="checkbox"/> 3 Liquid <input type="checkbox"/> 4 Suppository <input type="checkbox"/> 5 Injection <input type="checkbox"/> 6 Other <input type="checkbox"/> 7	Pills <input type="checkbox"/> 1 Inhaler <input type="checkbox"/> 2 Nebulizer <input type="checkbox"/> 3 Liquid <input type="checkbox"/> 4 Suppository <input type="checkbox"/> 5 Injection <input type="checkbox"/> 6 Other <input type="checkbox"/> 7	Pills <input type="checkbox"/> 1 Inhaler <input type="checkbox"/> 2 Nebulizer <input type="checkbox"/> 3 Liquid <input type="checkbox"/> 4 Suppository <input type="checkbox"/> 5 Injection <input type="checkbox"/> 6 Other <input type="checkbox"/> 7	Pills <input type="checkbox"/> 1 Inhaler <input type="checkbox"/> 2 Nebulizer <input type="checkbox"/> 3 Liquid <input type="checkbox"/> 4 Suppository <input type="checkbox"/> 5 Injection <input type="checkbox"/> 6 Other <input type="checkbox"/> 7	Pills <input type="checkbox"/> 1 Inhaler <input type="checkbox"/> 2 Nebulizer <input type="checkbox"/> 3 Liquid <input type="checkbox"/> 4 Suppository <input type="checkbox"/> 5 Injection <input type="checkbox"/> 6 Other <input type="checkbox"/> 7
16D. Is the Medicine taken on most days, or just when you have symptoms, or both? (If 'most days' ask Q16E, if 'symptoms', ask Q16F, if 'both', ask both Q16E and Q16F.)	Most Days <input type="checkbox"/> 1 Symptoms <input type="checkbox"/> 2 Both <input type="checkbox"/> 3	Most Days <input type="checkbox"/> 1 Symptoms <input type="checkbox"/> 2 Both <input type="checkbox"/> 3	Most Days <input type="checkbox"/> 1 Symptoms <input type="checkbox"/> 2 Both <input type="checkbox"/> 3	Most Days <input type="checkbox"/> 1 Symptoms <input type="checkbox"/> 2 Both <input type="checkbox"/> 3	Most Days <input type="checkbox"/> 1 Symptoms <input type="checkbox"/> 2 Both <input type="checkbox"/> 3	Most Days <input type="checkbox"/> 1 Symptoms <input type="checkbox"/> 2 Both <input type="checkbox"/> 3	Most Days <input type="checkbox"/> 1 Symptoms <input type="checkbox"/> 2 Both <input type="checkbox"/> 3	
16E. When you are taking the medication, how many days a week do you take it?	_____ days 42	_____ days 47	_____ days 52	_____ days 57	_____ days 62	_____ days 67	_____ days 72	
16F. When you are taking the medication, how many months in the past 12 months have you taken it?	0-3 <input type="checkbox"/> 1 43 4-6 <input type="checkbox"/> 2 7-9 <input type="checkbox"/> 3 10-12 <input type="checkbox"/> 4	0-3 <input type="checkbox"/> 1 48 4-6 <input type="checkbox"/> 2 7-9 <input type="checkbox"/> 3 10-12 <input type="checkbox"/> 4	0-3 <input type="checkbox"/> 1 53 4-6 <input type="checkbox"/> 2 7-9 <input type="checkbox"/> 3 10-12 <input type="checkbox"/> 4	0-3 <input type="checkbox"/> 1 58 4-6 <input type="checkbox"/> 2 7-9 <input type="checkbox"/> 3 10-12 <input type="checkbox"/> 4	0-3 <input type="checkbox"/> 1 63 4-6 <input type="checkbox"/> 2 7-9 <input type="checkbox"/> 3 10-12 <input type="checkbox"/> 4	0-3 <input type="checkbox"/> 1 68 4-6 <input type="checkbox"/> 2 7-9 <input type="checkbox"/> 3 10-12 <input type="checkbox"/> 4	0-3 <input type="checkbox"/> 1 73 4-6 <input type="checkbox"/> 2 7-9 <input type="checkbox"/> 3 10-12 <input type="checkbox"/> 4	

17. Please tell me about any other products that you take or things you do to help your breathing that you have not already told me about.

<i>Medicine or Activity</i>	<i>Code</i>
_____	_____ 74
_____	_____ 75
_____	_____ 76
_____	_____ 77

18. Has a doctor or other health care provider ever had you blow into a machine or device in order to measure your lungs (i.e., a spirometer or peakflow meter)? Yes 1 78
No 2

[If yes, ask Question 18A. If no, skip to Question 19]

18A. Have you used such a machine in the past 12 months? Yes 1 79
No 2

19. Have you ever had a period when you had breathing problems that got so bad that they interfered with your usual daily activities or caused you to miss work? Yes 1 80
No 2

[If yes, ask Question 19A. If no, skip to Question 20]

19A. How many such episodes have you had in the past 12 months? _____ episodes 81

[If 19A >0, ask Questions 19B and 19C, else skip to Question 20]

19B. For how many of these episodes did you need to see a doctor or other health care provider in the past 12 months? _____ episodes 82

19C. For how many of these episodes were you hospitalized overnight in the past 12 months? _____ episodes 83

[If 19C >0, ask Question 19C1, else skip to Question 20]

19C1. All together, for how many total days were you hospitalized overnight for breathing problems in the past 12 months? _____ days 84

Tobacco Smoking

Now I am going to ask you about smoking. First I will ask about cigarettes.

20. Have you ever smoked cigarettes? Yes 1 85
No 2

(“Yes,” means more than 20 packs of cigarettes in a lifetime or more than 1 cigarette each day for a year)

[if yes, ask questions 20A through 20D; otherwise, skip to Question 22]

- 20A. How old were you when you first started regular _____ years old 86
cigarette smoking?

- 20B. If you have stopped smoking, how old were you _____ years old 87
when you last stopped? (If the participant has
not stopped smoking, record as code ‘99’.)

- 20C. On average over the entire time that you _____ cigarettes/day 88
smoke(d), about how many cigarettes per
day do (did) you smoke?

- 20D. On average over the entire time that you _____ Manufactured 1 89
smoke(d), do (did) you primarily smoke Hand-rolled 2
manufactured or hand-rolled cigarettes?

[If the participant currently smokes cigarettes (Question 20B is ‘99’), then ask Questions 21A and 21B. Otherwise, skip to Question 22]

- 21A. In the last year, how many times have you quit smoking _____ times 90
for at least 24 hours?

- 21B. Are you seriously thinking of quitting smoking? Yes, within the next 30 days 1 91
Yes, within the next 6 months 2
No, not thinking of quitting 3

22. Have you ever smoked a pipe or cigar? Yes 1 92
No 2

[If yes, ask question 22A. If no, proceed to question 23]

- 22A. Do you now smoke a pipe or cigar? Yes 1 93
No 2

[If the participant has never smoked (answered “no” to **both** Questions 20 and 22), then skip to Question 25. Otherwise, proceed to Question 23]

23. Has a doctor or other health care provider ever advised _____ Yes 1 94
you to quit smoking? No 2

[If yes, ask Questions 23A and 23B. If no, skip directly to Question 24]

23A. Have you received medical advice to stop smoking within the past 12 months? Yes 1 95
No 2

23B. Have you used any medication (prescription or non-prescription), including a nicotine patch, to help you stop smoking? Yes 1 96
No 2

[If yes, ask Question 23B1, then ask Question 24. If no, skip directly to Question 24]

23B1. What kind of medication did you take to help you stop smoking? Nicotine Replacement 1 97
Bupropion 2
Tofranil 3
Other 4

24. Have you used or done anything else to help you stop smoking? Yes 1 98
No 2

[If yes, ask Question 24A, otherwise skip to Question 25]

24A. What did you do? Hypnosis 1 99
Acupuncture 2
Biofeedback 3
Other 4

Occupational Exposure

25. Have you ever worked for a year or more in a dusty job? Yes 1 100
No 2

[If yes, ask Question 25A, otherwise skip to Question 26]

25A. For how many years have you worked in dusty jobs? _____ years 101

Additional Co-morbidities

26. Has a doctor or other health care provider ever told you that you had:

26A. Heart disease Yes 1 102
No 2

26B. Hypertension Yes 1 103
No 2

26C. Diabetes Yes 1 104
No 2

26D. Lung cancer Yes 1 105
No 2

- 26E. Stroke Yes 1 106
No 2
- 26F. Tuberculosis Yes 1 107
No 2
- [If yes to 26F, then ask 26F1; otherwise, skip to Question 27]*
- 26F1. Are you currently taking medicine for tuberculosis? Yes 1 108
No 2
- [If no to 26F1, then ask 26F2; otherwise, skip to Question 27]*
- 26F2. Have you ever taken medicine for tuberculosis? Yes 1 109
No 2
27. Have you ever had an operation on your chest in which a part of your lung was removed? Yes 1 110
No 2
28. Were you hospitalized as a child for breathing problems prior to the age of 10? Yes 1 111
No 2
29. In the past 12 months did you get a flu shot? Yes 1 112
No 2
30. Has a doctor or other health care professional told your father, mother, sister or brother that they had a diagnosis of emphysema, chronic bronchitis or COPD? Yes 1 113
No 2
31. Has anyone living in your home (besides yourself) smoked a cigarette, pipe or cigar in your home during the past two weeks? Yes 1 114
No 2

SF-12

Interviewer: Read the following set of instructions to the participant.

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

32. In general, would you say your health is: (*Check one.*) Excellent 1 115
Very good 2
Good 3
Fair 4
Poor 5
33. The following items are about activities you might do during a typical day. Does your health **now** limit you in these activities? If so, how much?
- 33A. **Moderate activities**, such as moving a table, Yes, limited a lot 1 116
pushing a vacuum cleaner, bowling, or Yes, limited a little 2
playing golf No, not limited at all 3

- 33B. Climbing *several* flights of stairs
- | | | | |
|--|------------------------|----------------------------|-----|
| | Yes, limited a lot | <input type="checkbox"/> 1 | 117 |
| | Yes, limited a little | <input type="checkbox"/> 2 | |
| | No, not limited at all | <input type="checkbox"/> 3 | |
34. During *the past 4 weeks*, have you had any of the following problems with your work or other regular daily activities *as a result of your physical health*?
- 34A. *Accomplished less* than you would like
- | | | | |
|--|-----|----------------------------|-----|
| | Yes | <input type="checkbox"/> 1 | 118 |
| | No | <input type="checkbox"/> 2 | |
- 34B. Were limited in the *kind* of work or other activities
- | | | | |
|--|-----|----------------------------|-----|
| | Yes | <input type="checkbox"/> 1 | 119 |
| | No | <input type="checkbox"/> 2 | |
35. During the *past 4 weeks*, have you had any of the following problems with your work or other daily activities *as a result of any emotional problems* (such as feeling depressed or anxious)?
- 35A. *Accomplished less* than you would like
- | | | | |
|--|-----|----------------------------|-----|
| | Yes | <input type="checkbox"/> 1 | 120 |
| | No | <input type="checkbox"/> 2 | |
- 35B. Didn't do work or other activities as *carefully* as usual
- | | | | |
|--|-----|----------------------------|-----|
| | Yes | <input type="checkbox"/> 1 | 121 |
| | No | <input type="checkbox"/> 2 | |
36. During the *past 4 weeks*, how much did pain interfere with your normal work (including both work outside the home and housework)?
- | | | | |
|--|--------------|----------------------------|-----|
| | Not at all | <input type="checkbox"/> 1 | 122 |
| | A little bit | <input type="checkbox"/> 2 | |
| | Moderately | <input type="checkbox"/> 3 | |
| | Quite a bit | <input type="checkbox"/> 4 | |
| | Extremely | <input type="checkbox"/> 5 | |
37. These questions are about how you feel and how things have been with you *during the past 4 weeks*. For each question, please give the one answer that comes closest to the way you have been feeling.
- How much of the time during the *past 4 weeks*...
- 37A. Have you felt calm and peaceful?
- | | | | |
|--|------------------------|----------------------------|-----|
| | All of the time | <input type="checkbox"/> 1 | 123 |
| | Most of the time | <input type="checkbox"/> 2 | |
| | A good bit of the time | <input type="checkbox"/> 3 | |
| | Some of the time | <input type="checkbox"/> 4 | |
| | A little of the time | <input type="checkbox"/> 5 | |
| | None of the time | <input type="checkbox"/> 6 | |
- 37B. Did you have a lot of energy?
- | | | | |
|--|------------------------|----------------------------|-----|
| | All of the time | <input type="checkbox"/> 1 | 124 |
| | Most of the time | <input type="checkbox"/> 2 | |
| | A good bit of the time | <input type="checkbox"/> 3 | |
| | Some of the time | <input type="checkbox"/> 4 | |
| | A little of the time | <input type="checkbox"/> 5 | |
| | None of the time | <input type="checkbox"/> 6 | |

37C. Have you felt downhearted and blue? All of the time 1 125
Most of the time 2
A good bit of the time 3
Some of the time 4
A little of the time 5
None of the time 6

38. During *the past 4 weeks*, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)? All of the time 1 126
Most of the time 2
A good bit of the time 3
Some of the time 4
A little of the time 5
None of the time 6

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Economic Impact

Work Days Lost

The next questions ask about work and about times when you may have missed work due to health problems.

39. At any time in the past 12 months, did you work for income? Yes 1 127
No 2

[If no, continue with Question 39A; if yes, skip to Question 40]

39A. During the past 12 months, did you not work for income mainly due to breathing problems? Yes 1 128
No 2

39B. During the past 12 months, did you not work for income because you were a full-time homemaker or caregiver? Yes 1 129
No 2

[If yes, continue with Question 39C, if no, skip to Question 44]

39C. During the past 12 months, did health problems stop you from performing your usual homemaking/caregiving tasks? Yes 1 130
No 2

[If yes, continue with Questions 39D & 39E, if no, skip to Question 44]

39D. During the past 12 months, how many **total days** were you unable to perform your homemaking/caregiving tasks due to your health problems? _____ days 131

39E. During the past 12 months, how many **total days** were you unable to perform your homemaking/caregiving tasks specifically due to breathing problems? _____ days 132

[Please skip to question 44]

40. During how many of the past 12 months did you work for income? _____ months 133
41. During the months that you worked, how many days per week _____ days 134
did you work for income?
(when you're working)
42. What is the usual number of hours per day you work for income? _____ hours 135
43. During the past 12 months, did health problems stop you from working for income? Yes 1 136
No 2

[If yes, continue with Questions 43A & 43B, if no, skip to Question 44]

- 43A. During the past 12 months, how many **total days** were _____ days 137
you unable to work for income due to your health
problems?
- 43B. During the past 12 months, how many **total days** were _____ days 138
you unable to work for income specifically due to
breathing problems?

Non-Work Activities Missed

The next questions ask about time when you may have missed your normal activities (such as going shopping, visiting friends/relatives, going to church, or other activities) because of health problems.

44. During the past 12 months, did health problems prevent you from participating in one or more non- work related activities? Yes 1 139
No 2

[If yes, answer Questions 44A & 44B, if no, skip to COMPLETED BY at the end of the questionnaire.]

- 44A. During the past 12 months, how many **total days** did _____ days 140
you not participate in non-work related activities due
to your health problems?
- 44B. During the past 12 months, how many **total days** did _____ days 141
you not participate in non-work related activities
specifically due to breathing problems?

Completed By: _____ 142

Country Code _____ 1

City Code _____ 2

ID _____ 3

Date: _____ / _____ / _____ 4-6
d d m m y y y y

BOLD OCCUPATIONAL QUESTIONNAIRE

1. Have you ever worked for 3 months or more at any of the following?

	Check Yes or No for each	Number of years worked (If less than 01, enter 00)
a. Hard-rock mining	<input type="checkbox"/> Yes 1 _____ <input type="checkbox"/> No 2	_____ years 7-8
b. Coal mining	<input type="checkbox"/> Yes 1 _____ <input type="checkbox"/> No 2	_____ years 9-10
c. Sandblasting	<input type="checkbox"/> Yes 1 _____ <input type="checkbox"/> No 2	_____ years 11-12
d. Working with asbestos	<input type="checkbox"/> Yes 1 _____ <input type="checkbox"/> No 2	_____ years 13-14
e. Chemical or plastics manufacturing	<input type="checkbox"/> Yes 1 _____ <input type="checkbox"/> No 2	_____ years 15-16
f. Flour, feed or grain milling	<input type="checkbox"/> Yes 1 _____ <input type="checkbox"/> No 2	_____ years 17-18
g. Cotton or jute processing	<input type="checkbox"/> Yes 1 _____ <input type="checkbox"/> No 2	_____ years 19-20
h. Foundry or steel milling	<input type="checkbox"/> Yes 1 _____ <input type="checkbox"/> No 2	_____ years 21-22
i. Welding	<input type="checkbox"/> Yes 1 _____ <input type="checkbox"/> No 2	_____ years 23-24
j. Fire fighting	<input type="checkbox"/> Yes 1 _____ <input type="checkbox"/> No 2	_____ years 25-26
k. Farming	<input type="checkbox"/> Yes 1 _____ <input type="checkbox"/> No 2	_____ years 27-28

	<u>Check Yes or No for each</u>	<u>Number of years worked (If less than 01, enter 00)</u>
l. _____	<input type="checkbox"/> Yes 1 → <input type="checkbox"/> No 2	_____ years 29-30
m. _____	<input type="checkbox"/> Yes 1 → <input type="checkbox"/> No 2	_____ years 31-32
n. _____	<input type="checkbox"/> Yes 1 → <input type="checkbox"/> No 2	_____ years 33-34
o. _____	<input type="checkbox"/> Yes 1 → <input type="checkbox"/> No 2	_____ years 35-36
2. In your present job, are you regularly exposed to dust?		Yes <input type="checkbox"/> 1 37 No <input type="checkbox"/> 2
3. In your present job, are you regularly exposed to fumes?		Yes <input type="checkbox"/> 1 38 No <input type="checkbox"/> 2
4. Do you usually wear a mask or respirator at your present work?		Yes <input type="checkbox"/> 1 39 No <input type="checkbox"/> 2
5. What has been your usual occupation or job, the one you have worked at the longest?		_____ 40
5A. For how many years have you worked at this job?		_____ years 41
6. Have you ever had to leave a job because it caused you breathing problems?		Yes <input type="checkbox"/> 1 42 No <input type="checkbox"/> 2

Completed By: _____ 43

Country Code _____ 1

City Code _____ 2

ID _____ 3

Date: _____ / _____ / _____ 4-6
 d d m m y y y y

BOLD BIOMASS QUESTIONNAIRE

1. Has an indoor open fire with coal or coke been used in your home as a primary means of cooking for more than 6 months in your life? Yes 1 7
No 2

If yes to Question 1, ask questions 1A to 1D, else skip to question 2

1A. For how many years has coal or coke been used for cooking in your home?	_____ years	8
1B. On average, for how many hours a day have you personally spent cooking using coal or coke?	_____ hours	9
1C. Is coke or coal still used for cooking in your home?	Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2	10
1D. Did (does) your stove or fire have a chimney or was (is) the smoke vented to the outside?	Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2	11

2. Has an indoor open fire with wood, crop residues or dung been used as a primary means of cooking in your home for more than 6 months in your life? Yes 1 12
No 2

If yes to Question 2, ask questions 2A to 2D, else skip to question 3

2A. For how many years have wood, crop residues or dung been used for cooking in your home?	_____ years	13
2B. On average, for how many hours a day have you personally spent cooking using wood, crop residues or dung?	_____ hours	14
2C. Are wood, crop residues or dung still used for cooking in your home?	Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2	15
2D. Did (does) the stove or fire have a chimney or was (is) the smoke vented to the outside?	Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2	16

BOLD Biomass Questionnaire

3. Have you used an open fire with coal or coke as a primary means of heating your home for more than 6 months in your life? Yes 1 17
No 2

If yes to question 3, ask questions 3A and 3B, else skip to question 4

- | | | |
|--|---|----|
| 3A. For how many years have you used an open fire with coal or coke as a primary means of heating your home? | _____ years | 18 |
| 3B. Do you still use an open fire with coal or coke as a primary means of heating your home? | Yes <input type="checkbox"/> 1
No <input type="checkbox"/> 2 | 19 |

4. Have you used an open fire with wood, crop residues or dung as a primary means of heating your home for more than 6 months in your life? Yes 1 20
No 2

If yes to question 4, ask questions 4A and 4B, else skip to end of questionnaire

- | | | |
|---|---|----|
| 4A. For how many years have you used an open fire with wood, crop residues or dung as a primary means of heating your home? | _____ years | 21 |
| 4B. Do you still use an open fire with wood, crop residues or dung as a primary means of heating your home? | Yes <input type="checkbox"/> 1
No <input type="checkbox"/> 2 | 22 |

Completed By: _____ 23

Country Code _____ 1

City Code _____ 2

ID _____ 3

Date: _____ / _____ / _____ 4-6
 d d / m m / y y y y

BOLD STAGES OF CHANGE QUESTIONNAIRE

Please ask these questions of all participants who are current smokers.

The following statements represent different opinions about smoking. Please rate HOW IMPORTANT each statement is to your decision to smoke according to the following five point scale (*Hand participant a card with the following choices*): 1 = Not important, 2 = Slightly important, 3 = Moderately important, 4 = Very important, and 5 = Extremely important.

- | | | | | |
|---|----------------------|--------------------------|---|----|
| 1. Smoking cigarettes relieves tension. | Not important | <input type="checkbox"/> | 1 | 7 |
| | Slightly important | <input type="checkbox"/> | 2 | |
| | Moderately important | <input type="checkbox"/> | 3 | |
| | Very important | <input type="checkbox"/> | 4 | |
| | Extremely important | <input type="checkbox"/> | 5 | |
| 2. I'm embarrassed to have to smoke. | Not important | <input type="checkbox"/> | 1 | 8 |
| | Slightly important | <input type="checkbox"/> | 2 | |
| | Moderately important | <input type="checkbox"/> | 3 | |
| | Very important | <input type="checkbox"/> | 4 | |
| | Extremely important | <input type="checkbox"/> | 5 | |
| 3. Smoking helps me concentrate and do better work. | Not important | <input type="checkbox"/> | 1 | 9 |
| | Slightly important | <input type="checkbox"/> | 2 | |
| | Moderately important | <input type="checkbox"/> | 3 | |
| | Very important | <input type="checkbox"/> | 4 | |
| | Extremely important | <input type="checkbox"/> | 5 | |
| 4. My cigarette smoking bothers other people. | Not important | <input type="checkbox"/> | 1 | 10 |
| | Slightly important | <input type="checkbox"/> | 2 | |
| | Moderately important | <input type="checkbox"/> | 3 | |
| | Very important | <input type="checkbox"/> | 4 | |
| | Extremely important | <input type="checkbox"/> | 5 | |
| 5. I am relaxed and therefore more pleasant when smoking. | Not important | <input type="checkbox"/> | 1 | 11 |
| | Slightly important | <input type="checkbox"/> | 2 | |
| | Moderately important | <input type="checkbox"/> | 3 | |
| | Very important | <input type="checkbox"/> | 4 | |
| | Extremely important | <input type="checkbox"/> | 5 | |

ID _____

6. People think I'm foolish for ignoring the warnings
about cigarette smoking.

- Not important 1 12
- Slightly important 2
- Moderately important 3
- Very important 4
- Extremely important 5

Completed By: _____ 13

Country Code _____ 1

City Code _____ 2

ID _____ 3

Date: _____ / _____ / _____ 4-6
 d d / m m / y y y y

BOLD MINIMAL DATA/REFUSAL QUESTIONNAIRE

Demographics

1. What is the participant's sex? Male 1 7
Female 2
2. What is your date of birth? _____ / _____ / _____ 8-10
 d d / m m / y y y y

Respiratory Symptoms and Disorders

3. Has a doctor ever told you that you have emphysema, asthma, asthmatic bronchitis, chronic bronchitis or chronic obstructive pulmonary disease (COPD)? Yes 1 11
No 2

Additional Co-morbidities

4. Has a doctor or other health care provider ever told you that you have heart disease, hypertension, diabetes, lung cancer, stroke or tuberculosis? Yes 1 12
No 2

Tobacco Smoking

Now I am going to ask you about smoking.

5. Have you ever smoked cigarettes? Yes 1 13
No 2

["Yes," means more than 20 packs of cigarettes in a lifetime or more than 1 cigarette each day for a year]

[If yes, ask Questions 5A and 5B.]

- 5A. Do you now smoke manufactured or hand-rolled cigarettes? Yes 1 14
No 2

- 5B. How many cigarettes do (did) you smoke per day? _____ cigarettes/day 15

Completed By: _____ 16

Country Code _____ 1

City Code _____ 2

ID _____ 3

Date: _____ / _____ / _____ 4-6
 d d / m m / y y y y

BOLD PARTICIPANT TRACKING QUESTIONNAIRE

1. Age _____ years 7

2. Gender Male 1 8
 Female 2

3. Response Full data collected* 1 9
 Partial data collected (please complete Question 4)# 2
 Refused/Minimal data collected# 3
 Refused/No data collected 4
 Known to have permanently left area 5
 Temporarily out of area 6
 Dead 7
 Age ineligible 8
 Age-sex quota already filled 9
 Untraceable (e.g., bad address and phone) 10
 Unreachable (e.g., never returns mail or answers phone) 11

* For those aged 18-39 years, this is just the minimal questionnaire

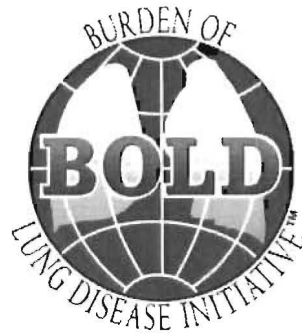
Only applicable for those ages ≥40 years

4. For those participants where only partial data were collected, please indicate whether the following data were completed.

	Yes	No	
Core Questionnaire	<input type="checkbox"/> 1	<input type="checkbox"/> 2	10
Stages of Change Questionnaire	<input type="checkbox"/> 1	<input type="checkbox"/> 2	11
Biomass Questionnaire	<input type="checkbox"/> 1	<input type="checkbox"/> 2	12
Spirometry (including Questionnaire)	<input type="checkbox"/> 1	<input type="checkbox"/> 2	13
Minimal Data/Refusal Questionnaire	<input type="checkbox"/> 1	<input type="checkbox"/> 2	14
Person-Specific Sampling Questionnaire	<input type="checkbox"/> 1	<input type="checkbox"/> 2	15
Occupational Questionnaire	<input type="checkbox"/> 1	<input type="checkbox"/> 2	16

Completed By: _____ 17

APPENDIX 5



BURDEN OF OBSTRUCTIVE LUNG DISEASE (BOLD)

Chapter 6

Questionnaire Administration

INTRODUCTION	3
Helpful Hints for Administering the Questionnaire _____	3
Basic Rules for Administering the Questionnaire _____	3
Interviewer Training _____	4
Recording the Replies to the Questions _____	5

Introduction

The use of a questionnaire to collect information makes it possible to obtain answers to a standard list of questions in a standardized way. The reliability of the questionnaire depends on the behavior of the interviewer, and therefore it is important that the questions are read exactly as they are printed and that no non-verbal clues are given.

Helpful Hints for Administering the Questionnaire

In order to minimize the amount of time needed to administer the questionnaire, it is important to keep the participant focused and not to let the administration of the questionnaire (which is essentially an interview) evolve into a conversation. The following are some general guidelines that may be used to help control the direction and pace of the interview:

1. Before starting the main questionnaire, explain to the participant that the questionnaire is very long, and unless the response categories are specified, the majority of questions require a simple "Yes" or "No" answer. Tell participants that, if they are unsure of an answer, to take their best guess.
2. Explain that you are going to move through the questionnaire quickly so as to take up as little of the participant's time as possible. Move quickly from question to question, since this will allow very little chance for the participant to interject personal comments into the interview. While periodic eye contact with the participant is important, the interviewer may find that the questionnaire takes less time to complete if he/she keeps their eyes focused primarily on the questionnaire.

Basic Rules for Administering the Questionnaire

In addition to the preceding suggestions for completing the interview in a timely manner, the following rules should be followed during the interview.

1. Verbal and nonverbal cues from the interviewer can influence participant responses. Be careful not to give any positive or negative reinforcement by responding to a participant's answer with a nod, gesture, or any verbal cue.
2. In particular, do not express surprise at a given answer, or point out what seems to be an inconsistency in the participant's response to two similar questions.
3. Maintain the participant's right to confidentiality during the interview by conducting it in a comfortable, private setting, away from other staff or family members.
4. Never try to interpret what the respondent means by a given answer. Unless specific instructions are provided for interpreting responses to a given question, the interviewer should offer to read the question again, and if applicable, list the response options.

Encourage the participant to make their best guess. The burden of supplying a response should always be placed on the participant; staff should never try to interpret what the participant meant by a vague response.

5. When the participant does not understand a question, or asks for clarification of what is meant by the question, follow the detailed instructions provided for that question. If no instructions are given, or if the participant is still confused after being given the appropriate clarification, tell the participant to use their own interpretation of the question and to provide the best answer they can. DO NOT try to provide your own explanation of the question, as this can introduce added variability due to different interpretation of the questions from one interviewer to another.
6. If a subject requests further information or clarification of a question that is not possible according to the questionnaire rules, explain that you are required to ask the questions in a standardized manner and that you are not permitted to give further clarification.
7. Words in the question that should be stressed are underlined.
8. Text that is *italicized* should not be read to the participant. Such text is generally used to provide guidance to the interviewer for how to ask or respond to a specific question or series of questions.
9. Carefully follow all the instructions printed on the questionnaire regarding skip patterns. This will assure that all necessary questions are asked and that no unnecessary questions need to be asked.

Interviewer Training

Interviewers should be articulate, able to accurately and easily read the questions out loud, and should be able to follow the instructions. Formal medical training is not necessary, and in fact, it can result in less accurate responses to the questionnaire. Participants often tend to give the answer they think the interviewer wants to hear. This phenomenon, which is known as positive response bias, is more likely to occur when the interviewer is perceived as an authority figure. Second, more educated persons can tend to interpret the participant's responses. If clinicians are to act as interviewers, it is important that they be conscious of this potential problem.

Training of the interviewers requires that they be given the questionnaire and instructions to study for several days so they become familiar with the flow of questions. They also should observe trained interviewers in the process of interviewing both normal and symptomatic subjects. They must practice the interviewing among themselves, and then observe or participate in interviews in which several observers code the responses. Discrepancies in coding must be reviewed and discussed. Recordings of interviews can let trainees review the same interview several times. The process of practicing and becoming accustomed to the questionnaire can take

from several days to several weeks. Individual sites should establish a formal process for training and certifying interviewers. Centralized training is provided by the coordinating center at the outset of the study, although not all staff may be able to attend this training.

Prior to training, staff should have read both the questionnaire and the instructions, and should have practiced administering the questionnaire to co-workers and/or friends. This makes the formalized training session more efficient, since the interviewers are already familiar with the instrument and have some idea of the questions and any difficulties they might have in administering the questionnaire. During the formal training session, the person conducting the training should review each question's purpose and discuss how to ask it; review the interviewer instructions for the questions; and answer any queries staff may have. Staff should then practice administering the questionnaire, both to gain familiarity with its administration and to identify additional queries for the instructor. As part of this process, other staff should role-play different scenarios. Ideally, a pool of healthy and non-healthy volunteers, covering a variety of ages, will also be available for the training.

Following the formal training session, staff should continue to practice the questionnaire, and the "master trainer" should listen to/observe several of these (a minimum of three is suggested). Only staff who are deemed competent in the administration of the questionnaire should be allowed to conduct interviews with study participants.

If multiple interviewers are used in any study, subjects should be assigned randomly to each interviewer, and the interviewer identification should be recorded on the questionnaire along with the time required to conduct the interview.

Specific training and certification requirements are covered in Chapter 11, "Quality Control."

Recording the Replies to the Questions

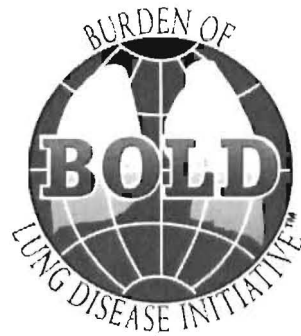
The majority of questions have simple "Yes" or "No" responses. If there is no provision for a "Don't know" reply and the respondent is uncertain of the answer, first repeat the question and ask the participant to make their best guess. If the respondent remains unsure, record the answer as "No."

If the answer to the question is a number, this should be recorded directly on the lines provided. For continuous valued responses (such as number of cigarettes smoked or age started smoking), the respondent may give a range. If this happens, ask the participant to give a single value, if possible. Let them know it does not have to be exact, just their best guess. If participant still replies with a range, record the midpoint of the range.

Where the answer is a date, the date should be written on the lines provided, one number per line. When the answer is a word, it should be legibly written out in full.

In all other cases where the interviewer is unsure how to code a response, he/she should be instructed to write a note in the margin of the questionnaire describing the participant's response. The marginal notation should then be reviewed at the clinical center to determine the proper code. If it cannot be coded at the clinical center, the site should contact the coordinating center for coding instructions.

Some attention should also be given to the legibility of responses. Interviewers should be trained to write numerals (such as one "1" and seven "7") in a standardized way and to check response boxes in a consistent and legible manner in order avoid confusion at the time of data entry.



BURDEN OF OBSTRUCTIVE LUNG DISEASE (BOLD)

Chapter 7

Spirometry

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Overview

Spirometry is a medical test that measures various aspects of breathing and lung function. It is one of the simplest, most effective tests available for the assessment of lung function. The spirometer registers the amount of air a subject inhales or exhales and the rate at which the air is exhaled. The most common spirometric tests require that the subject exhale as forcefully as possible after taking a full, deep breath. The subject's effort is called the *forced expiratory maneuver*.

BOLD uses a spirometer (the NDD EasyOne™ Spirometer) that measures flow and volume by ultrasound transit time. This spirometer is compliant with the American Thoracic Society spirometry standards.

Because the results of the spirometry testing are used to determine COPD status (the primary outcome for BOLD), the measurement must be performed according to strict standards by technicians who have been properly trained and certified in how to conduct the maneuver. In addition, the equipment must be regularly cleaned and the calibration checked. All spirometric maneuvers will be reviewed by a central reading laboratory to assure maximum quality of the data and to provide ongoing feedback to the pulmonary function technicians regarding the adequacy of the maneuvers.

Summary of Measures

The following measurements will be obtained through spirometry testing during the BOLD clinic visits:

- A. **Forced Vital Capacity (FVC)** is the total volume of air exhaled in a forced expiratory maneuver (the act of exhaling as hard and fast as possible after maximal inspiration). The FVC is useful for detecting restrictive diseases, since lower than expected results may be a sign that the lungs cannot inflate normally. The FVC is reduced in people with obstructive and restrictive disorders.
- B. **Forced Expiratory Volume at One Second (FEV₁)** is the amount of air that a person breathes out during the first second of a forced expiratory maneuver. This is reduced in people with airflow obstruction.
- C. **The ratio of FEV₁ to the FVC (FEV₁/FVC)** is the most sensitive and specific index of airways obstruction measured by a spirometer. It is obtained by dividing the FEV₁ by the FVC, and is usually expressed as a percent (i.e., $100 \times \text{FEV}_1/\text{FVC}$).
- D. **Forced Expiratory Volume at Six Seconds (FEV₆)** is the amount of air that a person breathes out during the first six seconds of a forced expiratory maneuver. Increasing interest is being shown in the FEV₆, and more particularly in the FEV₁/FEV₆ ratio, as an alternative to the FEV₁/FVC ratio.
- E. **The ratio of FEV₁ to the FEV₆ (FEV₁/FEV₆)** is an alternative to the FEV₁/FVC ratio. A secondary objective of BOLD is to evaluate the utility of the FEV₁/FEV₆ ratio, particularly with respect to the assessment of COPD.

Setting

Spirometry testing ideally should be performed in a private, temperature-controlled room at a central location (such as a local health clinic). All of the instruments necessary for the test should be in the room. The room should be well lit, preferably with a window, and located in a quiet area of the clinic. These conditions will improve the quality and reproducibility of the results. For safety, the participant should be seated in a chair with no wheels.

For many sites, it may be that testing will be done in mobile settings or in participants' households. The NDD EasyOne™ Spirometer is portable and has been shown to perform well in the field. Nonetheless, this document assumes that testing will be done in a centralized clinic facility. Sites planning to do otherwise should develop corresponding local procedures and document them in their local Manual of Procedures]

Containers with clean mouthpieces (Spirettes™), nose-clips, and spacers should be available in the room, as should be a container to collect used Spirettes™ and another to collect used spacers. A box of facial tissue paper, paper plate or some type of container to place dentures on or in (if needed), and a trash can should be placed close to the participant.

The EasyOne™ Spirometer has been designed to need no calibration. However, a calibration check should be carried out daily to ensure that the spirometer is reading accurately. Instructions for performing the calibration check are in the NDD EasyGuide™ technical manual. The calibration syringe and adapter should always be stored next to the spirometer so that the temperature between the syringe and the spirometer are the same. This will avoid having large differences between room temperature and the spirometer temperature that could affect the results of the calibration tests. If there is the potential for a large temperature difference between the calibration syringe and the spirometer, the technician should pull and push the piston on the syringe several times to correct the problem. If spirometry is done in the field (outside of a clinical center), it is preferable to keep the spirometer and calibration syringe together overnight to avoid temperature differences at the time of calibration.

Medication use prior to testing

In order to provide a valid assessment of bronchial hyper-responsiveness, participants should be asked to refrain from taking their bronchodilator medications during the 6 to 12 hours prior to testing. The exact waiting time depends on the type of medication, as noted below.

<u>Type of medication</u>	<u>period of no use</u>
short-acting beta-2 agonist	6 hours prior to the clinic visit
anticholinergic inhaler	6 hours prior to the clinic visit
oral beta-2 agonist	12 hours prior to the clinic visit
oral theophylline	12 hours prior to the clinic visit
oral antimuscarinic	12 hours prior to the clinic visit
<u>long-acting beta-2 agonist (Serevent)</u>	<u>12 hours prior to the clinic visit</u>

In the event that the participant has not complied with these waiting periods, the spirometry should be done anyway, including both the pre- and post-bronchodilator maneuvers. While the assessment of bronchial hyper-responsiveness may be biased, the post-bronchodilator measurements should be unaffected, and it is these measurements that are used to define COPD

Contraindications for post-bronchodilator testing

Check the participant's pulse and ask certain safety questions to assure that administration of the bronchodilator does not pose a potential health risk. Specifically, post-bronchodilator testing should not be done if the subject has or reports any of the following:

- ñ a heart attack in the last three months
- ñ a **resting** pulse rate more than 120 beats/minute (participant should be sitting for at least 5 minutes prior to pulse rate determination)
- ñ cataract surgery or a major surgical procedure in the past one month
- ñ any other co-morbidity (such as unstable angina or pneumonia) that, in the opinion of a site clinician, may affect the performance of the test or jeopardize the participant's safety

If a participant has or reports any of the conditions above, do the pre-bronchodilator measurement only. Participants may be brought back for retesting at a later date (see below).

Reasons to reschedule any spirometry testing

In some instances, any spirometry testing is contraindicated due to a temporary condition that would affect the validity of the maneuver or endanger the health of the participant. These situations include:

- ñ chest or abdominal surgery in the past 3 months
- ñ third trimester of pregnancy
- ñ respiratory tract infection with unresolved symptoms in the three weeks prior to the visit

Ideally, sites should postpone testing these individuals until the situation is resolved and should re-schedule the visit for a more suitable time. If participants are brought back later for spirometry testing, the site should contact the coordinating center for instructions on processing the data.

Conducting the Visit

A detailed description of the use and operation of the NDD EasyOne™ spirometer, together with instructions for coaching the participant, are included in the NDD EasyGuide™ users' manual. All pulmonary function technicians are expected to have read this document and to be familiar with its contents. A copy of this document should be kept with each spirometer in case questions about the use of the EasyOne™ spirometer arise during testing.

Safety checks

For safety purposes, check each participant's pulse rate prior to spirometry testing. Record the resting pulse rate on the spirometry form. Resting pulse rate is determined by having the participant sit and rest for 5 minutes prior to the measurement. Post-bronchodilator testing should not be done on subjects whose resting pulse is more than 120 beats/minute.

Technicians should also ask the safety questions that are included on the Spirometry form. Depending on the responses, the post-bronchodilator spirometry may be skipped, any spirometry may be rescheduled, or the clinic visit may be rescheduled. Clearly document all potential safety issues in the participant's chart.

Preparing to conduct the spirometry maneuver

In order to minimize the risk of cross-contamination, technicians should wash their hands before the start of the test and should use a tissue to remove a mouthpiece (the Spirette™) from its storage container for the participant to use. Allow the participant to insert the clean Spirette™ into the spirometer. Be careful to ensure that the arrow on the Spirette™ is lined up with the arrow on the spirometer.

Testing should be conducted with the participant in the sitting position. A chair without wheels should be used for the testing, and the participant should sit erect with chin slightly elevated. The purpose of the chair is to support the participant in case s/he faints during the maneuver.

Instruct participant to loosen any tight clothing that might restrict maximal inspiration. Some individuals may have difficulty doing the spirometry maneuver due to urinary incontinence. Offer the participant a chance to use the bathroom prior to testing.

Dentures should be left in place if they are not loose to help keep a tight seal around the mouthpiece. If they are loose, have participant remove them and provide a paper plate or clean container to place them on or in.

All maneuvers should be performed with the participant wearing a nose clip. This clip prevents air from moving through the nose during the test.

Explain the purpose of the spirometry test

Explain that the purpose of the test is to take some measurements to check on the health of the participant's lungs. Emphasize that, although the procedure does not hurt, in order to get useful and valid results he/she must breathe as hard and as fast as possible when told to do so and will need to repeat the procedure a few times. Depending on the cultural setting in which the testing is done, subjects may need repeated assurances that spirometry does not hurt them or damage anything.

Demonstrate the maneuver

Explain that the participant should take in as deep a breath as possible, and when his/her lungs are totally full, quickly position the mouthpiece and BLAST out the air as hard and as fast as possible. A vigorous demonstration of the maneuver will prevent wasted time and effort caused by the participant's lack of understanding. Demonstrate the correct placement of the mouthpiece. Take a deep breath and emphasize the maximal depth of inhalation. Then demonstrate the proper positioning of a demonstration Spirette™ mouthpiece and dramatically blast the air out as fast as possible.

Pre-bronchodilator test

After instructing the participant about the procedure for pulmonary function testing and asking all the safety questions, proceed with the actual testing, following the procedures outlined in sections 5.2 to 5.4 of the NDD EasyGuide™ users' manual. This initial series of maneuvers is performed BEFORE administering the bronchodilator. Follow the computer prompts until a successful test session has been obtained. A successful test session is defined as at least three acceptable maneuvers, with the two best FEV₁s and the two best FVCs from these maneuvers both within 200 ml of each other.

Administer the bronchodilator

After at least 3 acceptable and 2 reproducible maneuvers are obtained, administer two puffs of bronchodilator (beta-agonist) to the participant using a spacer; a timer should be set up to ring 15 minutes after the last administered puff. During the waiting time, begin to administer the study questionnaires. These can be completed after the post-bronchodilator maneuver if necessary.

Post-bronchodilator maneuver

The post-bronchodilator (BD) maneuver can start anytime after the 15-minute wait. The same criteria of at least 3 acceptable and 2 reproducible maneuvers should be followed. It is not critical that the post-BD maneuver be done immediately at 15 minutes, but rather that it be done at least 15 minutes after the last administered puff of bronchodilator. The effect of the bronchodilator will persist, and actually slightly increase, for at least the next 30-40 minutes. Technicians may therefore choose to fully complete the questionnaires between the pre- and post-BD maneuvers.

Print results

Clinical centers wishing to give participants a hardcopy printout of their results can do so following the instructions on page 5.5 of the NDD EasyGuide™ users' manual. Clinical centers choosing to give such printouts to their participants are encouraged to provide guidelines for interpreting the results.

Coaching the participant and troubleshooting problems

Because the adequacy of these maneuvers is highly dependent on participant effort, the technicians must guide the participant through the breathing maneuvers. It is extremely important to inhale maximally and to exhale forcefully and maximally. Tell the participant when to start taking in a deep breath and to put the mouthpiece in his/her mouth. Then tell the participant to blast out the air and to continue exhaling for at least 6 seconds. Observe the body language of the participant as he/she attempts to follow the instructions, and encourage the participant to continue blowing out smoothly without re-breathing. Instruct the participant to remain erect and not to bend over during the maneuver, and to keep their feet flat on the floor.

ACCEPTABLE AND REPRODUCIBLE MANEUVERS

For the purpose of spirometry testing, "acceptable" is defined as a maneuver that is free from error.

"Reproducible" is defined as being without excessive variability between maneuvers.

The following are some errors that can be seen or calculated from a forced expiratory maneuver and that can affect acceptability: hesitation or false starts, cough, variable effort, glottis closure, early termination, and leaks.

Three acceptable maneuvers are needed to determine reproducibility. The two highest values for FVC and FEV₁ taken from acceptable forced expiratory maneuvers must show minimal variability (within 200 milliliters of the second highest FVC and FEV₁). It is also important to inspect the volume-time curves to determine if the size and shapes of the curves are reproducible.

The American Thoracic Society defines FEV₁ and FVC as the best measurements from acceptable and reproducible maneuvers. **It is not necessary that they all come from the same maneuver.** The

FEV₁/FVC and FEV₁/FEV₆ ratios are computed as the ratio of the individual measurements. In order to obtain these results, select the "best value" setting from the system configuration menu (see section 8 of the EasyGuide™ users' manual).

When errors occur, review common errors with the participant before proceeding with additional maneuvers.

Ask the participant to watch the technician perform the FVC maneuver again. The technician should demonstrate the correct placement of the mouthpiece, emphasize the maximum depth of inhalation, and then blast out the air. If the participant tries again and the reproducibility criteria are not met, the technician should continue administering the test as needed (up to a total of five maneuvers), assuming that the subject is able to continue.

Some participants will never be able to provide three acceptable and having two reproducible maneuvers is OK. The goal is to meet the acceptability and reproducibility criteria, but these are not absolute requirements for data to be used. Previous studies have shown that inability to perform reproducible spirometry, even with good coaching, is an important risk factor in predicting future health.

"REFERENCE VALUES"

To interpret spirometric results, they must be compared either to a subject's previous results or to a published set of "predicted reference values." Such predicted reference values typically describe the average lung function for an individual of a given age, height, and sex, and such equations have been published for a variety of racial groups.

Typically, lung function measurements are expressed as a percent of predicted. One hundred percent of predicted represents the average value for the population, but normal, healthy individuals will exhibit a wide range of values about this level. In general, values of 80% or greater for FEV₁ and FVC are considered to be in the normal range. Individuals whose test results are below this level may have an abnormality.

The NDD EasyOne™ spirometer offers a number of published predicted values, most of which were derived from studies of largely Caucasian participants. In this latter case, four ethnic correction settings are available that allow you to customize the amount of adjustment that is made for selected racial groupings. Consult the EasyGuide™ users' manual, sections 8 and 12, for more information regarding the use of prediction equations.

If there are no acceptable reference values for a country, we recommend the use of the NHANES III reference values, which were derived from the 3rd National Health And Nutrition Examination Survey in the United States. This study used a large, randomly selected subset of the entire U.S. population, which included a variety of ethnic groups and strict attention to quality control according to current American Thoracic Society guidelines.

QUALITY CONTROL

The Epidemiology Standardization Project, the American Thoracic Society spirometry standards, and recent evaluations of commercially available spirometers emphasize the importance of spirometry quality control (QC) procedures.

Factors affecting spirometry quality

- a. **Participant:** A subject may not take as deep a breath as possible or exhale as forcefully as possible at the start of the maneuver. Several possibilities will prevent a maneuver from being acceptable: an involuntary epiglottis closure, temporarily cutting off the flow of air; an early termination of the maneuver, preventing the achievement of a plateau; or a variable effort. Coughing during the maneuver or a leakage due to the participant's inability to keep a tight seal also will prevent from obtaining a good maneuver.
- b. **Technician:** Improper coaching or non-standardized coaching procedures will negatively affect the quality of the spirometry testing.
- c. **Equipment:** Leaks in the system, differences in temperature, and poor calibration are all factors that affect the quality of the test results.
- d. **Analysis:** A combination of all factors may affect the quality of the results.

Implementation of QC procedures

- a. **Participant:** To address this source of error, it is very important to have technicians trained to watch the participant closely during the performance and accurately review the displayed flow-volume curves on the computer monitor. The technician thus can guide and explain the source of error to the participant.
- b. **Technician:** The technician should clearly instruct the participant on how to perform this test, demonstrate the maneuver, and watch the participant closely during the performance to avoid unacceptable errors and obtain the best effort from the participants. He/she must be trained to recognize patterns of unacceptable maneuvers and perform equipment checks. BOLD will monitor and provide periodic feedback on each technician's performance.
- c. **Equipment:** Daily spirometer calibration checks should be performed using a 3.00 Liter syringe as the "gold standard". Refer to section 14 of the EasyGuide™ users' manual for instructions.
- d. **Analysis:** Results from the calibration factors, technician's impression of test session quality, and the QC supervisor's impression of test session quality are all integrated to obtain the final FEV₁ and FVC results reported.

SPIROMETER CALIBRATION, MAINTENANCE, AND HYGIENE

The EasyOne™ spirometer is designed to minimize the need for cleaning and maintenance (see sections

13 and 14 in the EasyGuide™ users' manual). The surface of the spirometer and cradle may be cleaned by wiping with a damp cloth. If a more thorough cleaning is desired, the spirometer and its spirette cavity may be cleaned with an alcohol wipe or a soft cloth that has been lightly moistened with isopropyl alcohol. **Do not let liquids flow into the Spirette™ cavity of the spirometer while cleaning.** The disposable Spirette™ eliminates the need for cleaning the spirometer between patients. The Spirettes™ are designed for single patient use only, and must be removed and disposed of after each patient.

Additional guidelines for hygiene and infection control are provided by the American Thoracic Society and include the recommendation that the technician and patient wash their hands after testing and that proper attention be given to environmental controls in settings where tuberculosis or other diseases spread by droplet nuclei are likely to be encountered. Participants with evidence of obvious upper respiratory infections should not be tested, but rather rescheduled for testing at a later date.

Beyond battery replacement and the calibration check described below, no periodic maintenance is required or recommended on the spirometer or cradle. No service should be performed on the spirometer except by manufacturer-authorized personnel.

On each day it will be used, and prior to the first participant tested, the spirometer should be calibrated with a 3.00-Liter syringe that has been stored next to the spirometer. The calibration procedure requires the NDD calibration adapter to connect the syringe with the spirometer.

TROUBLE SHOOTING

Refer to the section 15 of the EasyGuide™ users' manual for troubleshooting tips.

BURDEN OF OBSTRUCTIVE LUNG DISEASE (BOLD)

Chapter 8

Measurement of Height and Weight

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Height

Height is used to predict lung function, so it should be measured as accurately as possible by trained staff. The participant should be standing on a firm, level surface that is perpendicular (at a 90° angle) to the vertical board of the height measurement device (ideally a wall-mounted stadiometer). If a stadiometer is not available, a vertical height bar with centimeter intervals marked or a non-flexible measuring device placed against the wall (or attached to the wall) should be used. Check to be sure that, to the extent possible, the floor is level, the vertical height bar is mounted at a 90-degree angle to the floor, and the wall on which the height bar is mounted is straight.

The participant should be instructed to remove shoes and hat, to stand erect with feet flat on the floor, heels together, and both heels touching the base of the vertical board. The participant should stand erect with back, shoulder blades, and buttocks in contact against the measuring device. If the participant cannot be positioned so that all of the above are in contact with the measuring device, position so that the participant is standing with buttocks in contact with the measuring device. The participant's weight should be evenly distributed on both feet, and arms should remain relaxed at the sides with palms facing inward. The participant should stand facing straight ahead with his/her head in the horizontal (Frankfort) plane. The eyes of the examiner should be at the same level as the height indicator bar to obtain the most accurate measurement (see Figure 1). This may require having the examiner stand on a small stepstool. If this is the case, a stepstool should be available in the examining room (or taken along when doing home visits).

Ask the subject to inhale deeply and maintain a fully erect position without altering the load on the heels. The height board should be brought down snugly, but not tightly, on the top of the participant's head. Record the height to the nearest 0.1 centimeter. Sites should contact the Operations Center if they do not have the ability to measure height to this level of precision.

Weight

Weight is not used in the prediction of lung function, so accuracy is not as critical as it is for height. However, as for all other measurements made, aiming for maximal accuracy is the goal to strive for, and staff should be trained accordingly. A balance beam or digital scale is preferred, but a simple home use (bathroom) scale is satisfactory as long as its accuracy is checked against standard weights. If a site needs to use a home (bathroom) scale, contact the Operations Center for advice about calibration. The scale should be placed on a firm, level surface, and if this surface is carpeted, a sheet of wood or hard plastic should be placed beneath the scale. Staff should therefore take such a sheet with them if doing home visits. Before taking the measurement, the participant should be instructed to remove shoes, hat, coat, and heavy items in the pockets (such as keys or wallet) in order to be weighed in light indoor clothing.

Ask the participant to stand in the center of the scale platform, since standing off-center may affect the weight measurement. Marks should be made on the platform to ensure the proper position of the participant's feet. The participant should stand with arms relaxed at the sides, head erect, and eyes looking straight ahead.

For a balance beam scale

Before each weight is measured, the sliding scale weights must be moved to zero and the scale checked to make sure that the indicator bar is at zero. If it is not, adjust the scale accordingly. Once the participant is on the scale, adjust the sliding scale weights until the indicator is again balanced (reads zero), and record the results to the nearest 0.1 kg. (Sites should contact the Operations Center if they do not have the ability to measure weight to this level of precision.) Use extreme care in adding the lower beam weight to the upper beam weight, as they use different increments. As a further quality assurance measure, staff should write down each number separately before adding them together. Advise the subject to remain standing in position on the scale until the weight has been recorded. This eliminates the possibility of the weight measure being accidentally altered by the balance beam moving as the subject dismounts.

For a digital read-out scale

Make sure the scale reads "0" before the subject stands on the measurement platform. When the digital readout stabilizes, record the observed weight to the nearest 0.1 kg. (Sites should contact the Operations Center if they do not have the ability to measure height to this level of precision.)

In order to minimize the possibility of having transposed numbers, or in the case of the balance beam scale, having incorrectly added the two weights, before the participant dismounts the scale inform the participant of the weight reading and recheck it if participant indicates this is markedly different from what they believe their weight to be. If the repeat readings are within 0.2 cm (for height) or 0.2 kg (for weight), simply record the initial reading.

Equipment Maintenance

BOLD does not have required maintenance procedures for height and weight measurement devices. However, the following guidelines are suggested for optimal quality control.

Ideally, all scales used should be certified on an annual basis by a competent authority. In addition, we recommend bi-monthly in-house checks to ensure accuracy in the range of weights to be measured during the trial. The lower range is checked using 20-30 kg weights and the upper range using 40-50 kg weights. The technician is weighed on the scale first and this weight recorded. The lower weight is then placed on the scale and this weight recorded. The technician then gets on the scale with the weight, and this new weight is recorded. Then the higher weight is placed on the scale by itself and this weight recorded. Then the technician gets on the scale with the higher weight, and weight is again recorded. Scales that fail to meet standards within 0.5 kg at any weight level should not be used for collection of study data and should be immediately reconditioned and recertified by a competent authority.

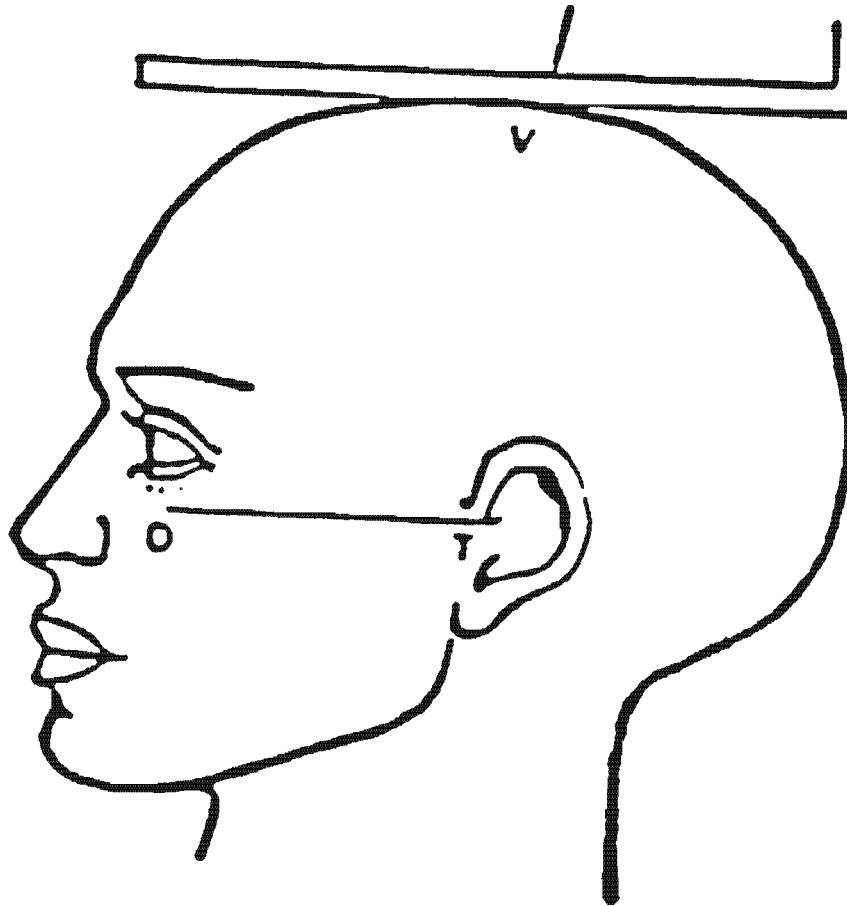
As noted previously, we recommend a wall-mounted stadiometer for measurement of height. The height-measuring devices attached to many balance beam scales can give very unreliable readings.

Staff Training

All staff who will be taking height and weight measurements should be trained to do so according to the above procedures. Training consists of reviewing the above procedures and then performing duplicate measurements on each of two individuals. The trainee should do the first measurement of both the height and weight on the individual and then repeat the process for the second measurement of height and weight on the same individual. The average of the duplicate measurements on a given individual must be within 0.2 kg weight and 0.1 cm height of the trainer's measurement. In addition, both measurements on a given individual must be within 0.2 kg/0.1cm of each other.

Figure 1

Frankfort Plane for measuring body height



ORBITALE: Lower margin of eye socket.

TRAGION: Notch above tragus of ear or at upper margin of zygomatic bone at that point.

FRANKFORT
PLANE: Orbitale tragion line horizontal.



BURDEN OF OBSTRUCTIVE LUNG DISEASE (BOLD)

Chapter 11

Quality Control

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Overview

A goal of the BOLD study is to determine COPD prevalence in many countries and many different settings throughout the world. The many and varied settings and potentially large number of technicians and participants involved make quality control (QC) imperative. QC includes policies and procedures to help assure that study data may be collected, analyzed, compared, and combined as needed. Inadequate QC measures will severely restrict the ability of the BOLD project to achieve its high aims.

QC in the BOLD project falls into three main topic areas: 1) questionnaire administration, 2) spirometry administration and data transfer, and 3) data entry. In order to participate in the BOLD study, sites must have all of the following QC measures documented, in place, and approved by the Operations Center. In addition, sites must have their sampling plans reviewed and approved by the Operations Center.

Initial Training

All BOLD sites are required to complete a training program taught by the Operations Center prior to beginning the study. These trainings are usually held twice yearly, once in the U.S. (usually either just before or after the meeting of the American Thoracic Society) and once outside the U.S. (usually held in the fall). These training sessions cover all three parts of BOLD QC as described above. The review of sampling designs will typically occur independent of the training sessions.

The BOLD study recognizes that sites will not be able to send all staff to the initial training sessions. Therefore, the study is using the “train-the-trainer” model, where one or several people are trained by the Operations Center staff at one of the meetings noted above, and are then authorized by the Operations Center to return to their site and train all site staff on study procedures. The certified trainer will be the primary liaison between the study site and the Operations Center for QC issues.

Questionnaire Administration

At the initial training meeting, general principles of questionnaire administration are discussed, and each questionnaire is reviewed in detail. This review includes an explanation of the intent of each question (which may not always be clear, especially in a cross-cultural context) and specific instructions for asking and responding to queries regarding certain questions. To facilitate the training, site staff are expected to have reviewed the questionnaires and their instructions prior to the training. Site staff should also have translated the questionnaires (where appropriate) and attempted to administer the questionnaire prior to the training. This “pretraining” activity helps identify problem areas that can then be addressed as part of the formal training.

Upon successful completion of this training, site staff receive written certification from the Operations Center certifying them as master trainers for questionnaire administration.

Spirometry Administration and Data Transfer

Prospective master trainers receive specific training and certification regarding use of the NDD EasyOne™ spirometer, proper coaching technique, and spirometry data transfer methods. Upon successful completion of the spirometry training, staff receive written certification from the Operations Center certifying them as master trainers for spirometry administration and data transfer.

Data Entry

All BOLD data (with the exception of the spirometry data) are entered at the site into an Internet-based data entry system, which performs a number of online edit checks that are designed to maximize the completeness and integrity of the study data. During the initial training, staff receive instruction in how to use the system and respond to edit queries. After the initial training is completed, staff are given a set of test data to enter once they return home. This assures not only that staff can use the data entry application, but also that the Internet connections between the Operations Center and the individual site are in place and working correctly. After these test data are entered, the Operations Center reviews them to see that they were entered correctly. If problems exist, the Operations Center contacts the site to resolve them. If the data are correct, then the Operations Center certifies the site staff person(s) as a master trainer in data entry.

Site Training

Certified master trainees from the initial training are authorized by the BOLD study to conduct training at their own sites in questionnaire administration, spirometry administration and data transfer, and data entry. Selected training materials are provided as part of the BOLD MOP.

The criteria for certification of site staff are generally the same as for the trainee at the initial meeting. For questionnaire administration, site staff must in addition successfully administer each of the BOLD study questionnaires three times to a non-study participant while being observed by the site's master trainer, who then informs the Operations Center that the training has taken place and the individual is certified. For spirometry, each staffperson must have a minimum of five sets of tracings deemed acceptable after review by the pulmonary function reading center (PFRC), which then informs the Operations Center that the individual is certified.

All properly certified site personnel receive a formal certification notice from the Operations Center once their training is complete.

Follow-up Training

Ongoing quality control procedures are necessary in order to maintain high standards of data quality throughout the BOLD study. The following procedures/requirements help to assure this goal is met.

Questionnaire Administration

Although direct observation of interviewers on a periodic basis is a desirable method of quality control, this may not be practical. Instead, the local master trainer is expected to review a sample of completed questionnaires from each interviewer for accuracy and completeness, and to

regularly meet with field staff throughout the study in order to review problems that may arise. This review is especially critical in the early stages of the study, so that problems can be identified and addressed early on. The standardization of questionnaire administration should constantly be stressed, and if questions arise that are not explicitly addressed in the instructions that accompany each questionnaire, sites are expected to contact the Operations Center for advice. The Operations Center in turn will post a question and answer (Q&A) document on the Web site so that all BOLD sites receive the same clarifications and instructions.

Spirometry

Data are transferred routinely to the Operations Center in the United States, where they are reviewed for acceptability by the PFRC. The PFRC generates regular QC reports summarizing the quality of each technician's data and transmits these reports to the sites through the Operations Center. If necessary, the PFRC may suggest additional training for some site staff.

Data Entry

The data entry system runs a series of data quality checks both during and after data entry. Sites will be notified of potential data quality issues as they are identified by the Operations Center.

APPENDIX 6

Information sharing and dissemination

Meetings with the National Department of Health

In June 2005, a presentation was made to the National Department of Health Chronic Diseases Directorate in Pretoria, represented by Mr Maluta Tshivase (Head of the Chronic Diseases Directorate) and Mrs Anne Croasdale. Results from the Lung Health Survey were outlined. Preliminary results of the prevalence and risk factors for chronic bronchitis were presented along with the details of methodology and fieldwork for the BOLD study. The problems of under-recognition and under-treatment of obstructive lung disease and very high smoking rates were highlighted. The need for a suitable smoking cessation programmes as part of prevention efforts at primary care level was suggested. The project generated interest and the parties expressed keen interest in obtaining the full results of the study, and the accompanying recommendations.

The Director of the National Council Against Smoking, Dr Yusuf Saloojee, was also present at this meeting in order to create links and involve his organisation as a stakeholder in the process. The organisation currently offers a national telephone quit line in order to assist people in the process of smoking cessation. This service is currently the only formal service for smoking cessation in the country, apart from privately run initiatives, for which individuals have to pay.

Meetings with the Provincial Department of Health.

In August 2005, preliminary results were presented to the Provincial Department of Health (Provincial Administration of the Western Cape) and at a meeting of Provincial Health Promotion section, liaising with Ms Esme Kennel, Patrician De Villiers and Marius Van Wyk. This presentation covered similar content to that of the National Department meeting. However, the preliminary COPD prevalence results for men and women in the study area were included. It was proposed that smoking cessation be included in the provincial programme for management of chronic diseases and offered to assist in developing an appropriate programme. It has already been included in the integrated programme of care for respiratory diseases called PALSAP Plus (Practical Approach to Lung Diseases in South Africa) developed by a team at the UCT Lung Institute which has been adopted for implementation in primary care clinics in the Western Cape and Free State provinces. We will continue communication with the provincial and national authorities to provide whatever assistance we can.

These plans for disseminating results and planning interventions are due to take place in the latter half of 2006 and early 2007, as the final results of the study are available. Other key components of this process are the production of a report, a series of meetings with key stakeholders, and possibly a workshop on tobacco and its impact upon health in South Africa. Partners will be sought to assist in this latter venture. The focus will be to draw attention to the problem in South Africa, share data on the magnitude of the problem and to harness and co-ordinate efforts from a variety of agencies.

Community feedback meeting in Ravensmead/ Uitsig

A community feedback was held in Ravensmead on August 4th 2005. The objectives of the meeting were to provide preliminary results of the survey to those that had taken part, and to any others from the community who wished to attend, to use it as an opportunity to highlight the need to reduce smoking in the area, and to spread the message of smoking cessation amongst those at risk, particularly women and teenagers. It was held on a weekday afternoon, with the intention of targeting women in the home, especially those with responsibility for looking after children. The Lung Health Study has confirmed very high smoking rates amongst both men and women in the community, who in turn expose their growing children to the hazard, and through their example increase the likelihood of children commencing the habit at an early age. The programme was intended to be entertaining, informative, challenging and included a light lunch as a means of thanking the community for their co-operation and assistance with the study. The meeting, attended by more than 300 people, was held in the Ravensmead Civic Centre. Information on lung diseases was presented by Prof Eric Bateman, study details and feedback by the author and a talk on smoking cessation by pulmonologist Dr Rod Dawson, interspersed with songs and jokes by a local entertainer, Mr Alvon Collison who communicated very effectively with the audience, and used humour and challenge, audience participation and a time of questions and answers on health and smoking-related issues. The event attracted considerable media attention (see below).

Publicity

The author and the research team have engaged with a variety of media to inform the public of the project, and raise awareness of the serious health issues surrounding smoking in the region. Firstly the assistance of the staff of the university Media Relations office were employed, who assisted in several ways. They prepared and released a report on August 2nd 2005, and invited interviews between the project

leader and reporters. This resulted in articles in three city newspapers and one local community newspaper, two radio talk shows with Prof Bateman answering questions from the public, and several radio news clips. Effort was made to ensure that a greater audience benefited from the anti – tobacco message.

The highlight of public dissemination activities was a four-minute segment on national television Prime Time News on August 7th 2005, which focussed specifically on the anti-smoking message and COPD with reference to the study and community meeting.

Conferences and planned publications

Results from the Lung Health Survey were presented at the International Union Against Lung Diseases in Preliminary results of the study were presented at the global BOLD sponsors meeting held in Copenhagen on September 18th at the Annual Congress of the European Respiratory Society meeting. Data on COPD prevalence have been presented at the Annual Meeting of the American Thoracic Society in May 2006 (in San Diego) and results of gender differences in COPD in smokers will be presented at the Annual Congress of the European Respiratory Society in Munich, Germany in September 2006. More work will also be presented at the Annual Congress of the South African Thoracic Society in March 2007. Publications on the prevalence of COPD, its associated risk factors and economic impact are planned for 2006/7.

Stakeholders

The academic Departments of Medicine and Public Health in South Africa, the Government Department of Health, the South African Medical Research Council, public sector health facilities, clinical professionals, national and international researchers, community groups, the residents of Ravensmead and Uitsig, and the National Council Against Smoking were identified as having potential interest on the results of these studies.

APPENDIX 7

**Referral Letter for selected BOLD (Burden of Obstructive Lung Disease)
Study participants to Community Health Centre:**

Dear Doctor,

The bearer of this letter.....
participated in a community study of lung function and symptoms of
respiratory disease.

The following findings are abnormal and require further assessment:

- Lung Function tests
- Chronic cough
- Dyspnoea
- wheeze
- other.....

A copy of the reported pre and post bronchodilator spirometry is attached.

Further assessment and possible treatment may be indicated.

If you require assistance with this assessment please refer the patient to
Tygerberg Hospital Respiratory Unit or Groote Schuur Hospital E16
Respiratory Clinic, if necessary.

Thank you for your assistance.

Yours sincerely

Prof E D Bateman and Dr A Jithoo
UCT Lung Institute
Tel : 021 4066850

APPENDIX 8

Chapter 4: Method used for developing weight factors for the Lung Health Survey: by Carl Lombard

A random sample of 15% of the valid addresses (Primary Sample Units – PSU) of Ravensmead and Uitsig was included in the Lung Health Survey. A census (number of people, their age and gender) was done of the PSU's. The following results were obtained

- A. 615 addresses gave full information and consent
- B. 218 addresses did not give consent and only 67 of these gave full census information

The number of addresses in B was replaced by addresses linked to the original PSU by a fixed procedure. Hence

- C. 218 replacement addresses which gave census information and consent.

The census and sample realization of the three address groups (A,B and C) is given in Tables 1-3.(Drafts given to Saskia and Schalk to type). The census and sample (realization or response rate) are broken down by gender and age (0-5,6-14,15-44,45+ years) and the realization proportion (sample/census) is calculated for each of these groups.

The response rate in the A addresses was .898 (3824/4248).

The response rate in the C addresses was .859 (1272/1481).

From tables 1 and 3 it is evident that the response rate of older men (45+) was the lowest of all the subgroups, .836 and .767 in A and C respectively. Although the response rates in A and C subgroups are not that different, separate weights were calculated for them.

The sampling weight (W1) for this study will consist of the following components.

- i) The inverse of the first stage sampling probability of a PSU
- ii) The realization weight of a specific gender and age subgroup within the sample groups A and C. This weight is the inverse of the realization proportion or response rate.

The final weight is the product of the two weights.

Statistical issues:

The PSU's was a single stage random cluster sample of 839 addresses drawn without replacement from a population of 5592 addresses. (Ask Schalk why $615+218=633$ not equal to 639). All residents at a selected address were included in the study. The selection probability for a random address is therefore $839/5592 = .15$. This gives a weight of 6.67. No adjustment is made to this weight for the replacement addresses since they are linked to the original selected address. Using the address weight we assume that the proportion of the population living in the sample address is 15% and that each individual from a complete sample on average represents 6.67 people in the study community.

The realization weight projects the sample results to the corresponding census results of the sample. For the individuals from the A addresses this weight is on average $1/.898=1.114$ and $1/.859=1.164$ for individuals from the B addresses. The product of the address weight and realization weight gives the adjusted number of people represented by the individual. For group A this is on average 7.43 and for group B it is 7.76. Due to the sample realization of

only 90% the individuals in the sample have to represent more people from the study community. This is even more so for the elder men in the sample.

Using the sampling weight in statistical analysis will give unbiased estimates of the population totals, means and prevalences. The (W1) sampling weight can be used for all analyses. This weight will be added to the database of the study together with specific subgroup indicators to facilitate domain analysis. (Required by Stata)

The census profile of the 67 addresses which did not participate in the study is similar to the census profile of the 218 replacement addresses. (See table ..., drafts given to Schalk). Selecting neighbouring addresses for replacement limited the bias effect of this step.

To accommodate simpler analyses (not having to use svyset in Stata) where estimating population totals are not needed three other sampling weights were calculated that only adjusts for differential response rates. These weights only ensure that each address, gender and age subgroup has the same response rate relative to an arbitrary selected reference subgroup.

The three weights are

1. The total sample (W2)
2. The age group 6-14 years (W3)
3. The age group 15-44 years. (W4)

The details of the calculations of the weights are given in ...(handwritten drafts)

To calculate if the sample has the same age and gender distribution as the whole population, the response (realisation) was calculated for different categories dependent on age, gender and whether the address was in the initial sample or whether the address was re-sampled. This response was calculated per category by dividing the number of people in the sample through the number of people that should have been in there theoretically. The latter numbers were obtained from the Census data. Because the response was different in the various groups weight factors should be used to calculate prevalence numbers and associations.

Because the sample consists of 15% of all the households in the population, outcomes should be multiplied by 6.67 to get true numbers in the whole population of Ravensmead and Uitsig. However, because of a different response in the various groups, this multiply factor differs slightly among the various groups. The correction made on this multiply factor for the different groups is weight factor 1 (W1). To calculate true numbers for the population W1 should be used.

For the calculation of prevalence's and associations it is enough to calculate these for the sample. It is not necessary to translate into the whole population first. However, it is important that the numbers of people in the various groups have the same distribution as in the whole population. Therefore different weight factors were calculated. The group(s) that had highest response was used as reference group and got value 1. In comparison with this group(s) the other groups got a weight factor. This is W2.

For children 6 – 14 years there was no big difference in response. Therefore, when only children are used in the analysis, the same weight factor 1 can be used (W3). When only the age group 15 – 44 is included in analysis W4 can be used.

APPENDIX 9

Chapter 4: Analysis Weights for the BOLD study: excerpt of a document by W Vollmer and A Jithoo

Sampling Weight

Since we are treating this is a one-stage cluster sample with clusters selected via simple random sampling, the household sampling weight is just the reciprocal of the probability selection for any given address. The addresses define the primary sampling units (PSUs).

$N_h = \#$ addresses (households) in population = 5592
 $n_h = \#$ addresses in sample (regardless of participation) = 833

$$P_j = P(j^{\text{th}} \text{ PSU is selected}) = (n_h/N_h) \\ = (\# \text{ sampled addresses})/(\text{total } \# \text{ of addresses})$$

Since these probabilities are constant across households, we write the household sampling weight as

$$W_h = 1/(P_j) = N_h/n_h = 5592/833 = 6.71 . \quad (1)$$

Thus each household in the sample represents 6.71 households in the target population. This is a pure sampling weight and does not reflect any adjustment for nonresponse nor any post-stratification adjustment to reflect potential imbalance between the observed age-sex distribution of the sample and the true age-sex distribution of the population.

Weighting Class Adjustment

Since we know nothing about 33 of the original 833 households, we cannot perform a household-based weighting class adjustment. However we can perform a person-based weighting class adjustment to account for participant nonresponse within each household. This adjustment factor, when multiplied by W_h , gives an adjusted person-based sampling weight, W_{ah} , for each individual in any given household. For the residents of any given household, W_{ah} is defined as

$$W_{ah} = W_h * (\# \text{ eligible people in the household}) / (\# \text{ participants from the household}). \quad (2)$$

Thus if there are two age-eligible participants in a household and only one of them participates, then that person's adjusted weight is $2*W_h$.

Post Stratification Adjustment

We still would like to further adjust for the observed differential nonresponse by age and gender. If we had complete enumeration of all of the age-eligible participants from all 833 households, we could have computed a weighting class adjustment by multiplying W_h by the ratio of all eligible people to all actual participants within each age-sex category. That is, we would replace the within household adjustment factor in (2) with a class-specific adjustment factor that is calculated across households.

Since we do not have complete enumeration of the individuals in all 833 households, an alternative adjustment procedure is to compute a post-stratification adjustment that effectively weights the observed age-sex distribution among participants to match the known age-sex distribution in the population.

So we assume that we wish to adjust for the 8 strata defined by gender and age (40-49, 50-59, 60-69, 70+). Let $k=1, \dots, 8$ refer to these strata and N_k and n_k be the number of individuals in the k^{th} strata for the total population of the two townships and for the sample of respondents, respectively. The post-stratification adjustment for individuals in the k^{th} strata, PS_k , is defined by

$$PS_k = \frac{N_k}{\hat{N}_k}$$

where

$$\hat{N}_k = \sum_{i=1}^{n_k} W_{ahi} \quad (3)$$

and the summation is over the n_k individuals in the k^{th} strata. We use the notation W_{ahi} in (3), rather than simply W_{ah} , to reflect the fact that W_{ah} varies across these n_k individuals to the extent that there is nonresponse within households, although realistically it will take on only a limited number of values.

The final weight to be used in the analysis for the i th individual in stratum k is then given by

$$W_{ki}^{final} = PS_k * W_{ahi} ,$$

where again W_{ahi} is the weighting class adjusted weight, per formula (2), for this individual. If the response rates do not differ by age and gender and the age-sex distribution of the sample corresponds to that of the population as a whole, then $PS_k \approx 1$ for all k and the post-stratified weights will resemble the weighting class adjusted weights from formula (2). Otherwise the post stratification adjustment has the effect of forcing the estimated population age-sex distribution to mirror the true population age-sex distribution. For instance if the response rate in stratum k is higher than average, then \hat{N}_k will tend to overestimate N_k , and the post-stratification adjustment will downweight the original sampling weights slightly to compensate for this. Similarly if the response rate in stratum k is lower than average, then \hat{N}_k will underestimate N_k , and the post-stratification adjustment will upweight the original sampling weights slightly. The resulting weights assure that the population prevalence estimates of COPD will be appropriately weighted averages of the prevalences in the eight age-sex strata.

APPENDIX 10

Patient Information

Name
ID 100326
Age 40
Height 158 cm
Weight 71 kg, BMI 28.4
Gender FEMALE
Ethnic CAUCASIAN
Smoker NO
Asthma NO

Test Information

Test Date 21.02.05 14:03
Post Time 14:19
Test Mode DIAGNOSTIC
Interpretation
Predicted Ref Nhanes III
Value Select BEST VALUE
Tech ID 1093
Automated QC ON
BTPS (IN/EX) --/ 1.04

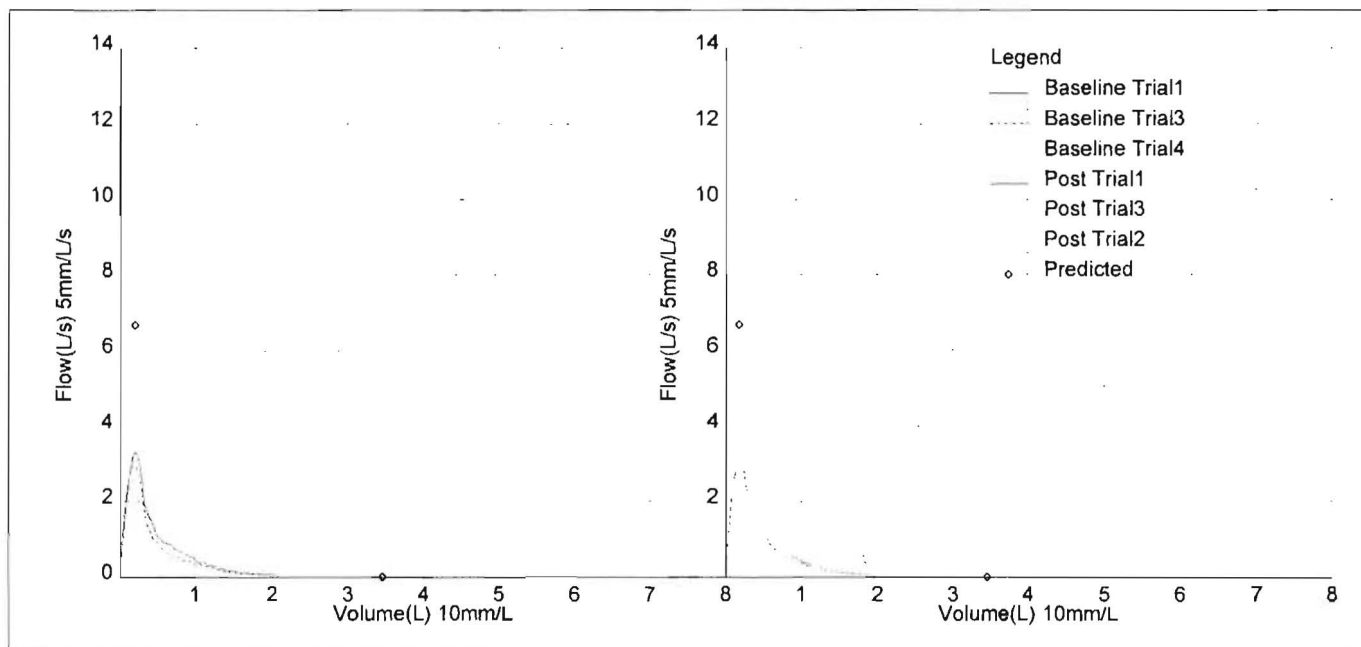
Test Results

Your FEV1 is 35% Predicted

Parameter	Baseline				Pred	%Pred	Post				Chg
	Best	Trial1	Trial3	Trial4			Best	Trial1	Trial3	Trial2	
FVC(L)	2.08*	2.08*	1.91*	1.84*	3.48	60	1.97*	1.97*	1.87*	1.84*	-5%
FEV1(L)	1.01*	1.01*	0.89*	0.85*	2.85	35	0.98*	0.98*	0.95*	0.89*	-2%
FEV1/FVC	0.48*	0.48*	0.47*	0.46*	0.82	59	0.50*	0.50*	0.51*	0.49*	
PEF(L/s)	3.26*	3.26*	2.93*	2.51*	6.70	49	3.15*	3.15*	2.98*	2.76*	-4%
MEF25-75(L/s)	0.33*	0.33*	0.32*	0.28*	3.03	11	0.36*	0.36*	0.32*	0.33*	9%
MEF75(L/s)	1.02	1.02	0.93	0.96	--	--	1.20	1.20	1.13	1.15	
MEF50(L/s)	0.39	0.39	0.39	0.31	--	--	0.42	0.42	0.39	0.38	
MEF25(L/s)	0.12	0.12	0.12	0.11	--	--	0.16	0.16	0.12	0.14	
FET(s)	9.78	9.78	9.22	9.03	--	--	9.26	9.26	8.71	8.63	

* Indicates Below LLN or Significant Post Change

Baseline FEV1 Var=0.11L 11.1%; FVC Var=0.17L 8.2%; Session Quality B
Post FEV1 Var=0.03L 3.6%; FVC Var=0.10L 5.3%; Session Quality A

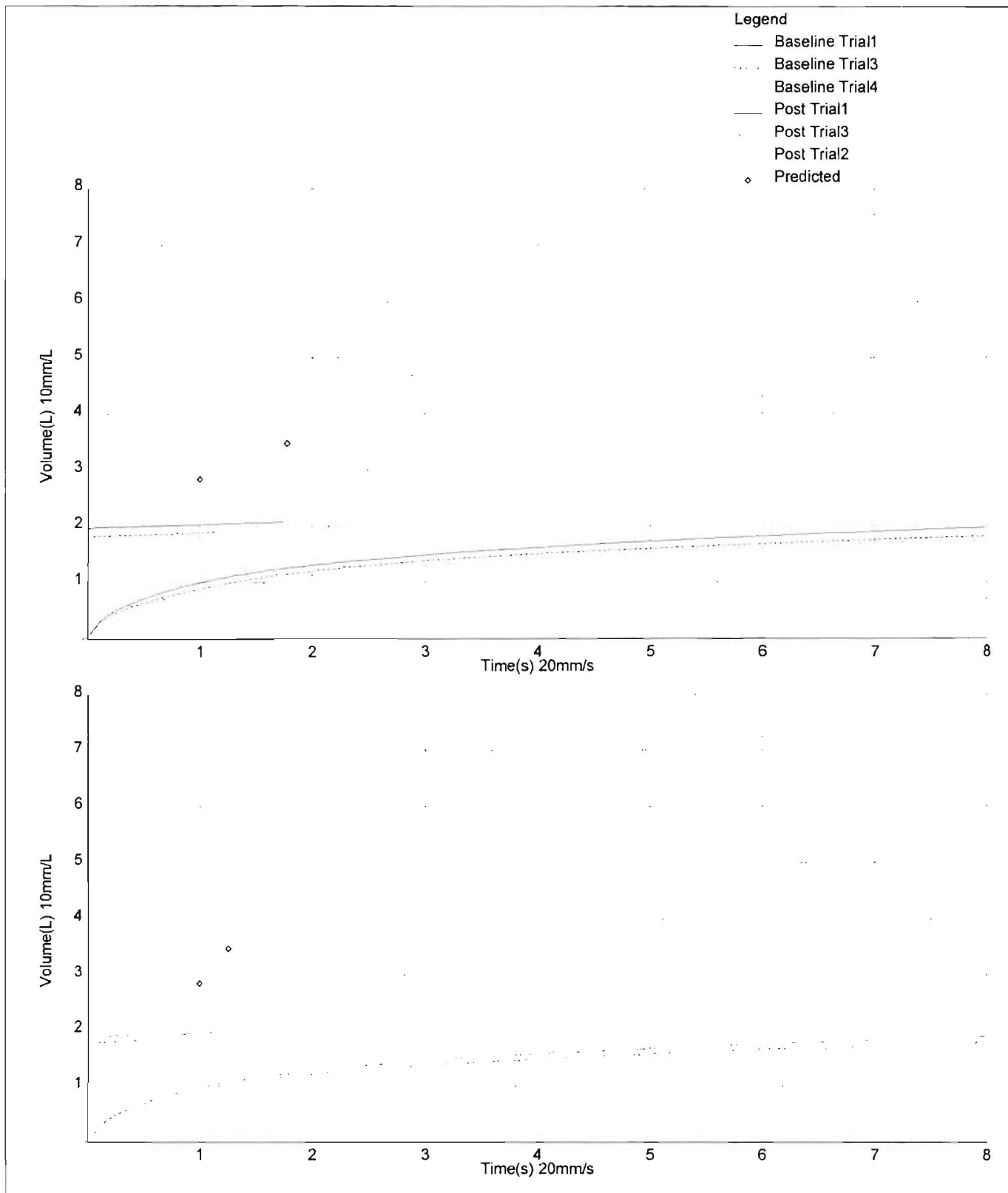


Patient Information

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 Gender FEMALE
 Ethnic CAUCASIAN
 Smoker NO
 Asthma NO

Test Information

Test Date 21.02.05 14:03
 Post Time 14:19
 Test Mode DIAGNOSTIC
 Interpretation
 Predicted Ref Nhanes III
 Value Select BEST VALUE
 Tech ID 1093
 Automated QC ON
 BTPS (IN/EX) --/ 1.04



Patient Information

Name
ID 100175
Age 40
Height 165 cm
Weight 53 kg, BMI 19.5
Gender MALE
Ethnic CAUCASIAN
Smoker YES
Asthma NO

Test Information

Test Date 04.06.05 11:01
Post Time 11:23
Test Mode DIAGNOSTIC
Interpretation
Predicted Ref Nhanes III
Value Select BEST VALUE
Tech ID 1993
Automated QC ON
BTPS (IN/EX) --/ 1.04

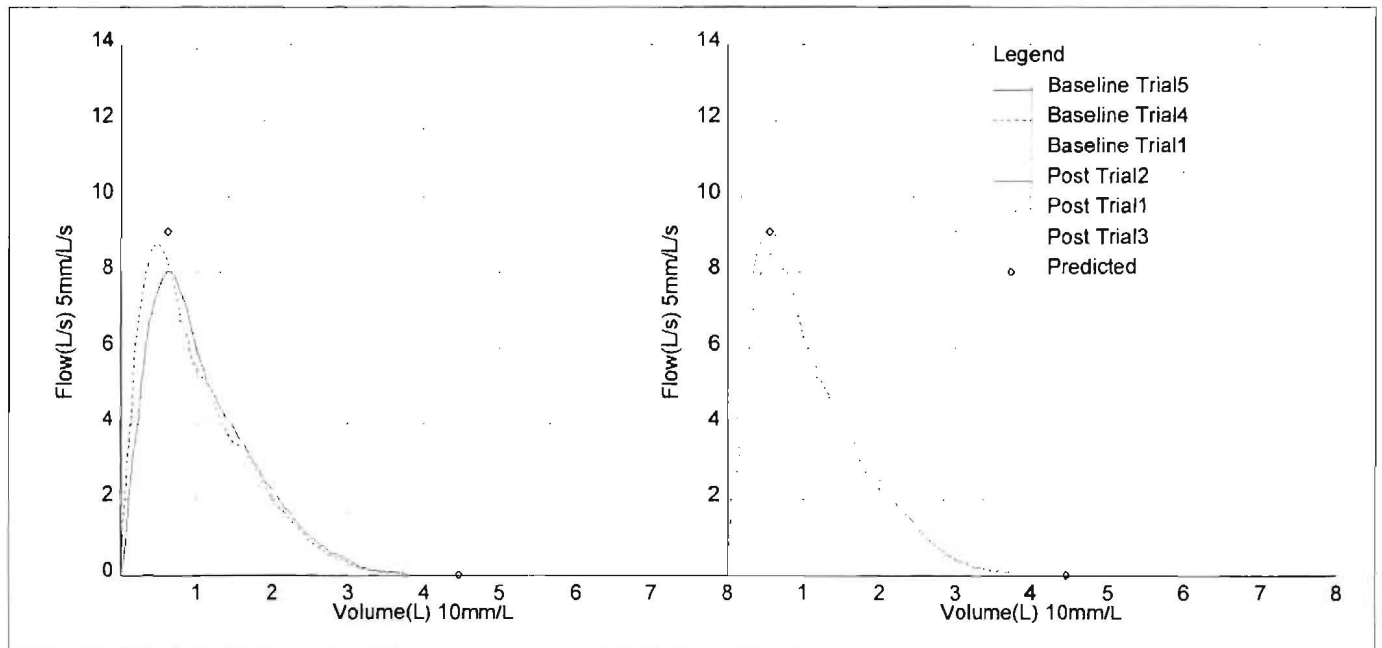
Test Results

Your FEV1 is 74% Predicted

Parameter	Baseline				Pred	%Pred	Post				Chg
	Best	Trial5	Trial4	Trial1			Best	Trial2	Trial1	Trial3	
FVC(L)	3.78	3.75	3.76	3.78	4.48	84	3.86	3.84	3.86	3.83	2%
FEV1(L)	2.66*	2.66*	2.64*	2.62*	3.60	74	2.79*	2.79*	2.77*	2.77*	5%
FEV1/FVC	0.70	0.71	0.70	0.69*	0.80	88	0.72	0.73	0.72	0.72	
PEF(L/s)	7.95	7.95	8.63	7.65	9.07	88	9.02	9.02	8.43	8.09	14%*
MEF25-75(L/s)	1.66*	1.66*	1.57*	1.47*	3.52	47	1.88*	1.88*	1.80*	1.84*	13%*
MEF75(L/s)	6.60	6.60	5.86	5.96	--	--	6.78	6.78	6.87	8.00	
MEF50(L/s)	2.43	2.43	2.38	2.22	--	--	2.75	2.75	2.41	2.72	
MEF25(L/s)	0.54	0.54	0.48	0.44	--	--	0.52	0.52	0.57	0.52	
FET(s)	10.48	10.48	10.79	10.67	--	--	10.17	10.17	10.31	9.99	

* Indicates Below LLN or Significant Post Change

Baseline FEV1 Var=0.02L 0.8%; FVC Var=0.02L 0.5%; Session Quality A
Post FEV1 Var=0.02L 0.7%; FVC Var=0.02L 0.4%; Session Quality A



Patient Information

Name
 ID 100175
 Age 40
 Height 165 cm
 Weight 53 kg, BMI 19.5
 Gender MALE
 Ethnic CAUCASIAN
 Smoker YES
 Asthma NO

Test Information

Test Date 04.06.05 11:01
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