RISK FACTORS FOR TUBERCULOSIS IN A LOW-INCOME URBAN AREA OF CAPE TOWN, SOUTH AFRICA, WITH PARTICULAR REFERENCE TO THE ROLE OF CANNABIS SMOKING

by

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I dedicate this thesis to Sri Gurudev, Swami Sivananda

DECLARATION

I, Anamika Jithoo, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Background: The association between *Mycobacterium tuberculosis* infection and tobacco smoking has recently been highlighted.[24 25] The reason for this association remains unclear, but is postulated to result from the effects of smoking on pulmonary host defences. Cannabis impairs the immune function of alveolar macrophages and has been reported to increase susceptibility to respiratory infections.[77]

Aim: To examine risk factors for both *Mycobacterium tuberculosis* disease and infection, in particular the effects of cannabis smoking.

Methods: A cross-sectional population survey of 3512 persons aged ≥15 years was performed in a predominantly low-income urban area of Cape Town, South Africa. Information on a history of tuberculosis and various risk factors including cannabis smoking was collected by means of an administered questionnaire. Ziehl-Neelson stained sputum smears were examined for acid fast bacilli and cultured on Lowenstein Jensen slants. Tuberculin skin testing (TST) was performed and an induration of ≥10mm read after 48-72 hours was considered positive. One joint year is defined as one joint per day for one year.

Results: The prevalence of ever smoking cannabis was 11.3% (23% in men; 2.6% in women) and 6.4% were current smokers. A history of tuberculosis was reported by 9.7%; current disease confirmed in 1%, and 76% had a positive TST. After adjusting for age, sex, tobacco smoking, income, education, occupational exposure, incarceration, alcohol use and body mass index, persons with a cumulative cannabis exposure of >70 joint years (approximately equivalent to 20 tobacco packyears) had an increased risk of past/current tuberculosis disease (OR 3.2; CI:1.8 – 5.6). Cannabis joint years did not show an association with tuberculosis infection.

Conclusions: This population study shows that cannabis smoking is positively associated with past/current tuberculosis disease, suggesting that cannabis may be a risk factor in the development tuberculous disease.

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CHAPTER 1: INTRODUCTION

This project was conducted in partial fulfilment of the requirements for a Master in Public Health degree at the University of Cape Town. It is a sub-study of a large multicomponent hypothesis-generating study, the Lung Health Survey 2002 (LHS2002). The LHS2002 is a collaborative effort between the Tuberculosis Research group at the University of Stellenbosch (now the Desmond Tutu Centre for TB Research), the University of Cape Town Lung Institute and the City of Cape Town Department of Health.

As an investigator, the candidate was fully involved in the conception of the study and formulation of the research questions, responsible for development of the questionnaire, training of fieldworkers and contributed to the day-to-day management of fieldwork, quality control, supervision of questionnaire administration and data capture. This mini-dissertation, including literature review, data cleaning and analytic strategy, all statistical analysis and data interpretation were performed by the candidate.

One of the aims of the Lung Health Survey LHS2002 was "to determine the prevalence of other lung diseases, and the influence, if any, of co-morbidities and environmental factors like smoking upon lung health" (Lung Health Survey protocol). This mini-dissertation describes a component of this aim, namely an assessment of the role of cannabis smoking upon lung health, specifically tuberculosis (TB) disease and infection.

1.1. Background

Globally, tuberculosis is the second most important cause of death from infectious disease and the 7th leading cause of disability adjusted life years (DALYs).[1 2] Africa has the highest incidence of TB in the world (259/100,000).[3] Much of this burden occurs in Sub-Saharan Africa which has an incidence of 290/100,000.[3 4] Tuberculosis has reached endemic status in South Africa, and is the third leading cause of premature mortality (years of life lost) in South Africa.[5]

In 2000, in the Western Cape province (one of the nine provinces in South Africa) TB accounted for 6.8% of deaths, being the fifth leading single cause of death, and is the third leading cause of premature mortality in the province (7.9% of years of life lost).[6]

Tuberculosis was the leading cause of death in men aged over 45 years and ranked in the top four causes of death in females and in other age groups.

In 2002, the Western Cape had the highest incidence of tuberculosis (917/100,000), and historically has always had the highest notification rate per province, even though in 2003 it did not have the highest number of cases (this occurred in Kwa Zulu Natal which has a larger population and the highest HIV prevalence).[7] The TB epidemic in the Western Cape at the time of this study was thought not to be driven by the HIV epidemic, having preceded it. The HIV prevalence rate in the study area (Western Tygerberg region) was relatively low (7.9%) in 2001 but, as expected, had risen to 15.1% by 2004.[i] It is still however lower than in other areas of Cape Town such as Khayelitsha (33%) and most other provinces.[8]

Since the industrial revolution in Britain in the 1800's, the causes of tuberculosis have been sought. Following Koch's discovery of the tubercle bacillus one hundred years ago and with the advent of antimicrobials in the 1950's, the treatment of tuberculosis has improved. However, the important contributory causes of the epidemic include poor living conditions and other factors that weaken host defences. Many of these factors have been identified and most are aggravated by poverty. Despite the widespread availability of drugs, these poverty-related factors persist and drive the epidemic onwards.

The reason for the high transmission rates, prevalence and incidence of tuberculosis in the Western Cape Province, and particularly in Cape Town have not been fully elucidated, and both host and/or bacterial factors may be responsible.[9] One of these is tobacco smoking, reported to be 57% in men and 40% in women, being the second highest provincial rate in South Africa, with predominantly low to moderate consumption of 1-14 cigarettes per day.[10]

Cannabis smoking is a common practice in Cape Town, but there are few data on its prevalence and attendant consequences. Recent publications from other parts of the world have linked cannabis to outbreaks of tuberculosis[81 85 87], but the mechanisms and factors underlying this association are not clear. Tobacco smoking has also been identified as a risk factor and this begs the question as to whether cannabis smoking

[i] HIV prevalence was measured in pregnant females aged 15-45 years, attending public service antenatal facilities, thought to be a higher risk group. General population prevalence is assumed to be lower.

could also be a potential independent risk factor for tuberculosis, considering the similarity of constituents.

Over the past few decades, risk factors for tuberculosis that have been identified in various studies worldwide include low socioeconomic status (measured by various indicators such as income, education, occupation etc), HIV infection, male sex, older age, ethnic groups in certain geographical areas, homelessness, crowding, known TB contacts, intravenous drug abuse, tobacco smoking, heavy alcohol use, low weight for height, foreign birthplace, residence in hostels and prisons and residential segregation. [11] [12] [13] Cannabis has only recently been associated with tuberculosis in outbreak investigations, and very few data are available as yet.

1.2. The Lung Health Survey 2002

Ravensmead and Uitsig, two adjacent suburbs of Cape Town in the Western Cape Province, are distinguished by a prevalence of tuberculosis that is amongst the highest in the world estimated at 10 per 1000 population and a case notification rate for adults aged ≥15 years of 1029/100,000. [14] [15] Recognised associations of tuberculosis are with urban poverty related to crowding, poor nutrition etc; and the association of TB with tobacco smoking. These two suburbs also have very high rates of tobacco exposure of 67% in men and 50% in women.[16] The incidence of tuberculosis had increased despite having 'moderate quality' Tuberculosis Control programme as rated by the World Health Organisation (WHO) Stop TB Programme.[17]

Partly in response to this increase, the University of Stellenbosch TB Research Unit (now the Desmond Tutu TB Research Centre) in collaboration with the UCT Lung Institute developed a multi-component survey of Ravensmead and Uitsig. This study, the Lung Health Survey 2002 (LHS2002) aimed to establish the prevalence and risk factors for tuberculosis and other common respiratory symptoms and lung diseases by means of a population survey.

The LHS2002 provided an opportunity to study the relationship of tuberculosis with various environmental risk factors. The relationship between TB and cannabis smoking is addressed here.

The initial survey was followed by three separate Part Two studies, performed independently by different investigators. The first was a study of children examining the associations between asthma and allergy and tuberculosis, and the influence of environmental factors on allergic disease.[18] The second study assessed the prevalence and risk factors for asthma in young adults (aged 15 - 44 years).[19] The third was a multi-country initiative known as the Burden of Obstructive Lung Disease (BOLD) study that aimed to assess the prevalence and risk factors for Chronic Obstructive Pulmonary Disease (COPD).[20]

1.3. Mini-dissertation aim and objectives

Aim:

To assess cannabis smoking as a risk factor for both tuberculosis infection and tuberculosis disease in a high tuberculosis prevalence, predominantly low-income urban area of Cape Town, South Africa.

Objectives:

1. To briefly and selectively summarise the literature on risk factors for tuberculosis.
2. To review the literature on cannabis smoking in relation to tuberculosis.
3. To analyse the association of cannabis smoking as a risk factor for tuberculosis infection and disease in the presence of other risk factors such as socioeconomic status, education, tobacco smoking, alcohol abuse, occupational exposures and incarceration.

1.4. Thesis structure

This introductory chapter provides some general background on tuberculosis in South Africa and outlines the aim and objectives of this mini-dissertation. Chapter Two is a brief, selective literature review on the risk factors for tuberculosis, with special reference to the role of cannabis smoking. Chapter Three provides details of the methods of the LHS2002. Chapter Four presents the results of the study in the form of some descriptive tables and an analysis of the outcomes with various risk factors. These results are discussed in Chapter Five.

1.5. Nomenclature and definitions

The following definitions have been used for the purposes of this study:

Tuberculosis infection is defined as a tuberculin skin test (TST) of ≥10mm diameter read between 48-72 hours.

Tuberculosis disease is defined as past and/or present tuberculosis (see below).

Past tuberculosis is defined as questionnaire-based self-reported history of tuberculosis (see Appendix 2, Question 17).

Present tuberculosis is defined as bacteriologically confirmed tuberculosis.[14] Bateriologically confirmed tuberculosis is defined as:

- two smears positive for acid fast bacilli or two positive cultures from different sputum samples OR
- A positive smear and a positive culture from different samples or from the same sample OR
- Either one positive smear or a positive culture with
    a) TB related abnormalities on the chest radiograph OR
    b) A positive smear or culture from sputum samples collected within two months of the sputum sampling for the Lung Health Survey

The Vancouver referencing method is used.[21]

CHAPTER 2: LITERATURE REVIEW: SELECTED RISK FACTORS FOR TUBERCULOSIS

2.1. Introduction

The aim of this chapter is to selectively review certain risk factors for tuberculosis, with special reference to the role of cannabis smoking. Since there is little literature on cannabis smoking and tuberculosis, this part of the review is brief. However, much of the literature on tobacco smoking and tuberculosis is relevant in terms of examining the practice of smoking itself, and potential common mechanisms involved in the risk of tuberculous infection and disease associated with tobacco and cannabis.

For over two centuries, poverty-related risk factors for TB have been clear. Some of these factors continue to remain, especially in developing countries. Low socioeconomic status, poor living conditions, overcrowding and exposure to TB patients are factors for which there is most certainty. However, epidemiological research over the last two decades has provided evidence of several other risk factors.

Known associations with tuberculosis are listed in Table 1, grouped according to the current evidence for the certainty of the association. In addition to cannabis smoking, risk factors that are associated with the inhalation of particulate matter are reviewed; viz. tobacco smoking and indoor air pollution. The large literature on other known risk factors will not be addressed here.

Table 1: Known associations with tuberculosis

Degree of certainty	Environmental factors	Host factors
Established/certain	TB contact	age
		Previous TB
	Certain occupational exposures	sex
	e.g. mining (silicosis)	HIV infection, anergy, low CD4 count[22]
Good evidence	Tobacco smoking	
	Socioeconomic status (education, income etc)	
	Alcohol	BMI/ malnutrition
		Comorbidities causing immunosuppression: e.g. renal failure, malignancy, diabetes, transplant, drugs (cortico-steroid use) etc.
	Region (geographic)	
	Living conditions (crowding)	
	Urban vs. rural	
	Incarceration	
Some evidence	BCG	Family history of TB
	Indoor air pollution (Biomass fuel)	History of asthma (protective)
	Environmental Tobacco Smoke (in children)	Childhood respiratory infection
	Other occupational exposures	
Putative	Outdoor air pollution	Genetic predisposition
	Cannabis smoking	

2.2. Tobacco

The association of tobacco smoking and tuberculosis has been established in many studies. Two recent meta-analyses by Lin et al (2007) and Bates et al (2007) summarise and comment on the association between tobacco smoking and TB disease, TB infection and TB mortality.[24] [25] A modified version of information from case control and cross sectional studies reviewed in these publications are presented in Tables 2 and 3. These list studies of tobacco as a risk factor either for tuberculosis disease (Table 2) or for tuberculosis infection (Table 3). Population based studies related to TB disease and TB infection are of particular relevance.

Bates et al report risk ratios for TB disease of between 2.3 and 2.6. Studies of pulmonary TB (as opposed to any TB) consistently confirm a higher risk of TB disease with tobacco smoking.[24] Several mechanisms of disease causation have been suggested of which a decreased immune response demonstrated as CD4 lymphopaenia, defects in macrophage immune responses, and mucociliary dysmotility are examples.[26] [25]

Ever smokers have a lower risk than current smokers (OR 2.3 – 2.6 vs. 2.7), suggesting that smoking cessation may reduce the risk of TB disease.[25] As with most studies examining smoking as a risk factor, misclassification can be a problem, as can confounding by variables that are not included in the multivariate analysis, such as alcohol. Therefore, examining multiple studies that have adjusted for various risk factors increases confidence in the association with smoking (see "other variables" in Table 2).

There seems to be consistent epidemiological evidence to suggest that tobacco smoking is associated with TB. Most of this data comes from China, the United Kingdom, India and the United States (see Tables 2 and 3) with the earliest association published in 1956 by Lowe et al.[52] The only longitudinal cohort study was that of British doctors by Doll et al (1994) which found that smokers were three to four times more likely to develop TB than non smokers, and three times more likely to die of pulmonary TB than their non-smoking counterparts.[27] Despite being based on small numbers of persons with the outcome, this finding supports the evidence from cross sectional and case control studies.

Several studies found evidence of dose response relationships between tobacco smoking (amount per day and duration in years) and both TB disease and infection. This is evident in the study by Kollapen et al (2002) (see Table 2).[43] Alcaide et al (1996) performed a case control study compared persons with active tuberculosis disease (cases) to others with a positive tuberculin test and no clinical, bacteriological or radiographic evidence of tuberculosis (controls).[48] They found a dose response relationship with tobacco smoking as a risk factor for tuberculosis disease. Other factors (apart from the dose response relationship) that have been associated with an increased risk of pulmonary tuberculosis in adults are early age of initiation of smoking, smoking for >10 years and passive smoking.[28]

Latent TB appears not be confined to the primary lesions in the lungs. As early as 1927 it was noted that mycobacteria could be cultured from histologically normal tissue from the same lungs, even though the primary lesions had become sterile.[29] It is thought that nicotine leads to the reactivation of latent TB by decreasing levels of TNF-alpha production by alveolar macrophages.[30] Since TNF- alpha is essential for maintaining the latent state of TB bacilli within macrophages, reactivation may occur. Another effect of nicotine is that it allows macrophages to survive for prolonged periods by reducing apoptosis, which promotes the killing of mycobacteria. [31 32]

The importance of considering smoking as a risk factor for tuberculosis is that it has one of the greatest potentials for modification, particularly in high TB prevalence regions. In addition, acceptance of tobacco smoking as a risk factor for tuberculosis has implications for the assessment of global tobacco related mortality. For example, Bates et al have reported that 31% of TB cases are attributable to tobacco smoking.[25]

TB infection

A summary risk ratio for TB infection was found to be 1.7 (95% CI: 1.5 – 2.0) in the meta-analysis by Bates et al (2007).[25] Lin et al reported a pooled odds ratio of 2.0 (95% CI: 1.5 – 2.8) when using a 5 mm TST cut-off and 1.8 when using a 10mm cutoff.[24] A point to note is that the two studies that adjusted for alcohol reported lower odds ratios than those that did not, suggesting that alcohol is a significant confounder to the relationship between TB infection and tobacco smoking.

In a study of Lebanese prisoners, Adib et al found that a longer duration of incarceration was associated with an increased risk of TB infection.[60] The association with smoking in this study was weaker than studies that were not performed in prison populations or did not adjust for incarceration in their analyses (OR = 1.2; CI: 1.1 – 1.3). A limitation of not adjusting for other known risk factors in multivariate analyses may mean that confounders were not fully accounted for (see Table 3).

Another prison-based study by Anderson et al (1997) found a positive signal between smoking and TB infection but results were not all significant at the 5% level. They suggested that the cumulative effects related to the duration of smoking may have been more important than the number of cigarettes smoked. The only study that examined a cumulative exposure variable for tobacco smoking was den Boon et al

who observed a dose response related to increasing packyear exposures (packyears take both duration and quantity into account).

Table 2: Studies assessing the risk of tuberculosis disease from tobacco smoking[24 25]

Study	Study design	Country	Population	Outcome	Exposure	Other variables	Main finding
Leung et al. (2004)[33]	Cohort	Hong Kong	42,655 :Elderly Health Services of Hong Kong	Bacteriology/clinical, CXR, or histologic grounds confirmed	Current and former tobacco smoking	Age, gender, alcohol, SES, living conditions, comorbidities	Current smoking associated with pulmonary but not extrapulmonary TB; dose response observed based on quantity
Gajalakshmi et al. (2003)[34]	Cross-sectional	India	235,101 urban men	Self-report	Ever smoking	Age, SES, chewing tobacco	Strong association: ever smoking and TB; dose response (quantity)
Gupta et al. (1997)[35]	Cross-sectional	India	543 rural and 164 urban adults	Radiolology, history, clinical, sputum	Smoking, Wood/cowdung fuel	Age	Association between both use of biomass for fuel (significant) and smoking (nonsignificant)and tuberculosis
Yu et al. (1988)[36]	Cross-sectional	China	30,289 adult residents, Shanghai	Physician diagnosed; criteria not stated	Smoking	Age, gender, TB contact, region, SES	Association :smoking and tuberculosis; increasing effect at higher dose (quantity)
Adelstein et al. (1967)[37]	Cross-sectional	United Kingdom	76,589 adult volunteers: factories, offices,general public	MMR, physician confirmed	Current and former smoking	Age, gender	Association between both current and former smoking; dose response observed (quantity)
Shah et al (1959)[38]	Cross-sectional	India	439 employees	MMR, physician confirmed	Smoking		Association with disease
Shetty et al. (2006)[66]	Case control	India	189 TB outpatients and 189 controls (relatives of non-TB patients)	Pulmonary TB: according to national TB Control Program guidelines	Current and former tobacco smoking; biomass.	Age, gender, SES, living conditions, alcohol, comorbidities, tobacco, biomass	Former smoking, but not current smoking or use of biomass fuels, associated with disease
Jick et al.	Case	United	497 patients and 1,966	All TB: received at	Current and former	Age, gender, region,	Current but not former

(2006)[39]	control	Kingdom	controls from General Practice Research Database	least three anti- TB medications for at least 6 months	tobacco smoking	BMI, comorbidities	smoking associated with disease
Lienhardt et al. (2005)[40]	Case control	West Africa	822 patients, 687 household controls, 816 community controls	Confirmed by sputum smear positivity	Current and former smoking	Age, gender, contact with TB patient, alcohol, BCG, comorbidities	Current and former smoking associated with disease and dose effect reported based on duration of smoking
Wang et al. (2005)[41]	Case control	China	158 patients, 316 controls	smear sputum positivity	Tobacco smoking	Age, gender, SES	Ever smoking associated with disease; dose effect observed for quantity
Crampin et al. (2004)[68]	Case control	Malawi	598 patients and 992 community controls	All culture-confirmed and probable cases of TB	Ex smoking, smoking before onset of TB, biomass	Age, gender, region, HIV	Former smoking and smoking ≥5 cigarettes per day, but not exposure to cooking fires; nonsignificant dose effect for quantity
Ariyothai et al. (2004)[28]	Case control	Thailand	100 adult inpatients and 100 patient controls	bacteriology and/or CXR and histologic	Current, former smoking, passive smoke	Age, alcohol, living conditions,TB contact, BMI, BCG scar	Association with both current and former smoking; dose effect based on duration and quantity; association with passive smoke.
Leung et al. (2003)[42]	Case control	Hong Kong	851 patients from TB registry, 7,835 controls Gen household survey	bacteriology or by clinical, CXR, or histologic grounds	Ever tobacco smoking	Age, gender, alcohol	Ever smoking associated with disease; effect partly reduced by restricting analysis to nondrinkers
Kolappan et al. (2002)[43]	Case control	India	112 adult male patients and 553 community controls	Diagnosed by culture or sputum positivity	Tobacco: cigarettes and "beedi"	Age	Smoking associated with disease; dose effects observed for both quantity

							and duration of smoking
Tekkel et al. (2002)[44]	Case control	Estonia	248 adult inpatients; 248 controls (Estonia Population Registry)	Diagnosed according to WHO European guidelines	Current and former tobacco smoking and passive smoke	Age, gender region, SES	Strong association with disease for both former and current smoking
Tocque et al. (2001)[45]	Case control	United Kingdom	112 adult patients, 198 controls from regional general practitioner databases	Diagnosed by bacteriology	Current, ever , 2 years prior to diagnosis or interview smoking	Age, gender, SES, contact with TB patient, race, comorbidities	Smoking more than 30 y associated with disease but other forms of smoking were not
Dong et al. (2001)[46]	Case control	China	174 adult patients from TB registry and 174 community-based controls	Diagnosed by sputum positivity	Smoking and passive smoking	Age, gender, region, TB contact TB, SES, living conditions, alcohol, dust exposure, BMI, BCG	Nonsignificant association with both smoking and passive smoking; dose response observed on basis of quantity
Gupta et al. (2001)[47]	Case control	India	200 adult patients, 200 chest clinic controls,200 healthy controls	sputum positivity or by CXR and treatment response	Ever smoking (More than 400 lifetime cigarettes)	Age, gender, contact with TB patient, SES	Strong association with smoking compared to both sets of controls; dose response observed on basis of cumulative exposure but not current quantity
Alcaide et al. (1996)[48]	Case control	Spain	46 adult patients and 46 TST positive controls	sputum positivity or clinical, CXR, epi evidence, positive TST	Current smoking and passive smoking	Age, gender SES	Strong association with smoking; dose effect observed based on quantity of cigarettes smoked
Buskin et al. (1994)[49]	Case control	United States	151 adult outpatients; 545 controls screened negative for TB	Diagnosed on the basis of US CDC criteria	Current and former tobacco smoking	Age, gender, alcohol, SES, race, BMI, HIV	Nonsignificant association between both current and former smoking and disease; dose response for duration but not quantity

Lewis et al. (1963)[50]	Case control	United Kingdom	100 male patients and 100 male controls hospitalized	Diagnosed by bacteriology	Tobacco smoking 6 months prior to diagnosis	Alcohol	No effect of smoking after stratification for alcohol; control illnesses may also have been associated with smoking
Brown et al. (1961)[51]	Case control	Australia	100 inpatients and 100 controls hospitalized (all male ex-servicemen)	Probable pulmonary TB; diagnostic method not specified	Tobacco smoking	Alcohol	No effect of smoking after stratification for alcohol; control illnesses may also have been associated with smoking
Lowe (1956)[52]	Case control	United Kingdom	1,200 adult patients, 979 Patient controls	All TB: notification data	Current smoking	Age, gender	Association: current smoking and disease; dose response observed (quantity)
Pe´rez-Padilla et al, (2001)[53]	Case control	Mexico	Patients	WHO criteria	Smoking	Urban/ rural residence, crowding, education, biomass smoke exposure, income	No association with smoking

Table 3: Studies assessing the risk of tuberculosis infection from tobacco smoking[24 25]

Study	Study design	Country	Population	Outcome	Exposure	Other variables	Main finding
Anderson et al (1997)[54]	Case-control	United States	293 prisoners (age 17-54)	TST>10mm or >5mm if HIV+	Current smoking	Age, living conditions, gender, alcohol, HIV, TB contact, BMI	Smoking before and after imprisonment associated with conversion; dose response for duration and quantity. OR = 1.8 for smoking
den Boon et al. (2005)[55]	Cross-sectional	South Africa	2,401 population	TST>10mm	Ever tobacco smoking	Age, gender, SES, BMI	Smoking associated with TST, dose response observed based on pack years
Hussain et al. (2003)[56]	Cross-sectional	Pakistan	425 incarcerated men	TST>10 mm if BCG unvaccinated, >15 mm in BCG vaccinated	Current tobacco smoking	Age, living conditions, SES, BCG	Smoking associated with TST with dose response observed based on quantity
Plant et al. (2002)[57]	Cross-sectional	Vietnam	1,395 adult prospective Migrants	TST>5 mm (n = 898); >10 mm (n = 611); >15 mm (n = 260)	Ever tobacco smoking	Age, gender, contact with TB patient, living conditions, SES	Smoking associated with TST for all cutoffs, but strength of association declined with increasing cutoff
Solsona et al. (2001)[58]	Cross-sectional	Spain	447 residents of homeless shelter	TST>5 mm	Current smoker >10 Cigarettes/day	Age, gender, alcohol, BCG vaccination	Smoking and age, but not alcohol, associated with TST. OR = 1.7 for smoking
McCurdy et al. (1997)[59]	Cross-sectional	United States	296 hispanic migrant farm workers	TST>10 mm	Current and former tobacco smoking	Age, gender, SES	Former smoking more strongly associated with TST than current
Adib et al, (1999)[60]	Cross-sectional	Lebanon	Prisoners	TST>8 mm	Smoking	Residence area, occupation, duration of imprisonment	Age, smoking (OR = 1.2), imprisonment associated with TST.

2.3. Environmental tobacco smoke (passive smoking)

It is well known that passive smoking (environmental tobacco smoke) is a risk factor for respiratory symptoms and illnesses in children.[61] However passive smoking has only recently been considered a potential risk factor for tuberculosis.

A Spanish study by Altet et al (1996) examined TST positive household contacts of TB cases and compared contacts that became cases (93 cases) to those contacts that did not become cases (95 controls).[62] A dose-response relationship was found between the risk of developing TB immediately following infection and the number of cigarettes smoked daily by adults in the home. Younger children were at greater risk than those ≥10 years of age. Passive smoking was strongly associated with TB (adjusted OR 5.39; 95% CI: 2.4 -11.9). An increased risk was present in children exposed both within and outside the home (OR: 6.35; 95% CI: 3.2 - 12.7). Statistically significant differences in urinary cotinine levels were found between contacts with TB disease and contacts without TB disease.

Another two case control studies from Thailand have confirmed the association of passive smoking with tuberculosis disease. Tipayamongkholgul et al (2005) found that risk of TB was nine times greater in children who had close and very close contact with smoking household members (OR 9.3; CI: 3.1 – 27.6).[63] Ariyothai et al (2004) examined passive smoking in adults and showed that exposure in the home and the workplace for >3 days a week increased the risk of pulmonary TB considerably (OR 4.6, 95% CI: 1.7-15.0).

Passive smoking was also associated with an increased risk of tuberculosis infection in a study of children under 5 years (OR 2.7; CI 1.5 – 4.7) in a hospital-based study from India.[64] A suggested mechanism is that tobacco smoke impairs pulmonary defence mechanisms but the authors also suggest that smoking may also reflect poorer health related habits and behaviour that may independently increase the risk of infection. However they confirm that their study suggests an independent association of passive smoking with tuberculosis infection.

2.4. Indoor air pollution/Biomass fuel

Indoor air pollution is a relatively newly identified risk factor for tuberculosis and only five published studies have addressed its contribution to tuberculosis disease.

Mishra et al (1999) was the first to report an association in a study of 260,000 persons aged >20 years of age in the National Family Health Survey of India reporting an OR of 2.58 (95% CI: 1.98-3.37).[65] The authors adjusted for many risk factors such as the availability of a separate kitchen, house type, indoor crowding, age, gender, urban or rural residence, education, religion, caste or tribe, and geographic region. Notably tobacco smoking was not one of the variables considered. The attributable fraction of biomass fuel exposure as a risk factor for tuberculosis in India was significant, calculated to be 51%.

A recent smaller case control study from India did not find an association with biomass fuels, however it is possible that the study lacked the power to demonstrate this association.[66] Both biomass fuels and tobacco smoking were significant in the univariate analyses only.

A case control study by Perez Padilla et al (2001) found the odds of current biomass fuel exposure to be 5.2 (95%CI 3.1-8.9), whereas past or present exposure was 3.4 (95%CI 2.4-5.0) and past exposure was 1.8 (95%CI 1.1-3.0).[67] These associations were found in urban and suburban Mexico City, and this study adjusted for smoking amongst other important risk factors. Delineating the effect of poverty from the exposure to biomass fuels is difficult, but this study did adjust for income and education. The postulated mechanisms for the association of biomass smoke with tuberculosis are similar to those suggested for tobacco smoke, but remain unclear at this stage.

The only African study (from Malawi) showed no association with biomass fuel exposure.[68] The authors suggest that owing to the difficulty in obtaining an accurate estimate of exposure, misclassification may have lead to no effect being found. In addition they cite that there was good ventilation of most houses.

No studies assessing the relationship of indoor air pollution with tuberculosis infection could be found.

2.5. Cannabis

The public health issue of cannabis smoking is of increasing significance as it appears to be on the increase world wide and especially in developing countries.[69] An increase in perceived risk of harm from using cannabis usually predicts a decline in use.

Cannabis use is thought to have doubled in South Africa between 1990 and 2003, possibly due to more having expendable income, more vigorous law enforcement in developed economies resulting in the exploitation of the South African market, and increased import across open borders after 1994.[70] The cost of cannabis in South Africa is very low and an association of cannabis smoking 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.

In South Africa, a case control study of multi drug resistant tuberculosis showed that the strongest risk factor for defaulting tuberculosis treatment was smoking marijuana or methaquolone (OR 17.9, 95% CI 4.7-68.5).[71] Smoking cannabis was also ten times more likely in cases compared to controls. This could suggest that the prior history of smoking increases the risk of acquiring tuberculosis infection and subsequently disease. The assumption that cannabis smoking is merely associated with poor adherence to therapy may be just one facet of the relationship between cannabis smoking and tuberculosis. This relationship needs to be examined in more detail.

Particularly high rates of cannabis smoking have been reported in Cape Town.[72] Cannabis is the most commonly used illicit drug in South African adolescents. A significant proportion of adult patients attending a public hospital trauma unit tested positive for cannabis, suggesting a link with trauma and criminal activity.[72] Lifetime use was reported by 32% of male and 13% of female adolescents in Cape Town, with 21.5% of males and 8.6% of females reporting use in the past year, reflecting what seems to be a predominantly male phenomenon. However, reporting bias and underreporting need to be considered in this context. Seven percent of adolescents reported use in the last year.[73]

As can be seen in Tables 2 and 3, there have been few population-based studies of risk factors for tuberculosis, and none of these have considered cannabis smoking

as a potential risk factor. The relationship between cannabis smoking and tuberculosis has been little researched, and consequently the literature is very scanty. If cannabis is shown to be a risk factor, it raises the question as to whether the risk of infection related to the products of combustion in smoke common to both forms of smoking or whether they relate to specific properties of each – tobacco and cannabis smoke. However, both the specific and common combustible by-products could be factors.

Cannabis smoke shares many constituents with tobacco smoke.[74] These include carbon monoxide, cyanide, benzene, vinyl chlorides, aldehydes, phenols, nitrosamines and polycyclic aromatic hydrocarbons.[74 75] Tobacco smoking has been shown to increase predisposition to lower respiratory tract infections, including tuberculosis, the same may also be true of cannabis smoking.

Studies suggest that cannabis is an immune modulator. In vitro and animal studies have shown that delta tetrahydocannabinol (THC) produces several immunosuppressive effects on T cells, natural killer cells and macrophages and exposed mice were unable to develop a successful immune response against legionella pneumophila.[76] Clinical studies in humans which have recovered alveolar macrophages from the lungs of cannabis smokers showed impaired phagocytosis and bacteriocidal activity. In addition they displayed reduced generation of proinflammatory cytokines including TNF-alpha, granulocyte macrophage-colony stimulating factor (GM-CSF) and interleukin-6 and an inability to use nitric oxide.[77 109] This reduction in immune function might predispose to opportunistic infections (and carcinogenesis) by impairing host defences against lung pathogens. The proposed mechanisms of immune dysfunction are discussed in detail in Chapter 5.

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.[78] 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.[79] This point may be of importance in the thesis study site, because social activities such as drinking alcohol in informal taverns (known as shebeens) have been shown to be associated with the spread of Mycobacterium tuberculosis.[80]

Methods of cannabis smoking associated with tuberculosis

Cannabis **water pipe** smoking has been implicated as a risk factor for tuberculosis, when a cluster of five cases was noted by Munckhof et al (2003) in young males in Queensland, Australia.[81] Of those contacts who shared a cannabis water pipe with a case, 64% had a positive TST, compared to 50% of the total number of contacts. Sharing a cannabis water pipe with a TB case was associated with TB infection (OR 2.2; 95% CI:1.0-5.2), but appears not to be statistically significant. It is difficult to ascertain whether close social contact and sharing of the pipe are the only risk factors or whether it is a combination of the material smoked and the former.

Similarly, the practice of **shotgunning** of cannabis could also be a potential risk factor for tuberculosis. "Shotgunning" drugs (or "doing a shotgun") refer to the practice of inhaling smoke and then exhaling it into another individual's mouth, a practice with the potential for the efficient transmission of respiratory pathogens.[82] Riley et al (2001) found this practice to be commonly reported in a tuberculosis screening programme which used computer-assisted questionnaires in comparison with interviewer assisted questionnaires.[83] An earlier report by Livengood et al (1985) investigating isoniazid resistant tuberculosis found that all contacts who smoked cannabis (14) were TST positive.[84] The small sample sizes in these studies preclude suggesting a causal association for cannabis but alerts to the possibility of one.

More recently, Oeltmann et al (2006) reported another smoking behaviour associated with the transmission of tuberculosis.[85] "**Hotboxing**" refers to smoking marijuana inside a closed car in order to permit repeated inhalation of cannabis smoke in this confined atmosphere. This practice was associated with a tuberculosis outbreak in adolescents in Seattle, Washington. A large proportion of the friends of cases (64%) had positive tuberculin skin test results. Again, both close social contact and the material smoked may be implicated in susceptibility to acquiring tuberculosis infection and disease. This practice of smoking is also relevant because cannabis smoking is often performed in enclosed spaces in order to avoid detection, and the shared airspace increases risk of transmission.[81]

In another study from Seattle, Park et al (2001) found that HIV positive patients with community acquired pneumonia (which included tuberculosis as a common

aetiological agent) were more likely to be cannabis users.[86] Similarly, Sterling et al (2000) reported cannabis smoking as a common finding in 7 out of 20 infected persons in a TB outbreak. Other risk factors such as HIV infection were also common in this group.[87]

None of the papers linking cannabis smoking with tuberculosis infection have suggested that the constituents of cannabis itself or the smoking of cannabis could have been risk factors on the basis of immunosuppression, as is suspected with tobacco smoking. This is probably because all these studies were case series which would not allow for the assessment of cannabis exposure as a risk factor for tuberculosis. No studies have assessed this risk at a population level or even as case control studies. Considering the growing literature on the association of tobacco smoking and tuberculosis, it is plausible that cannabis smoking may likewise be associated with tuberculosis.

The second most commonly abused drug in Cape Town is known as a "white – pipe". This refers to methaquolone (a non-barbiturate sedative hypnotic), cannabis and tobacco smoked in any combination or each alone, using a makeshift pipe fashioned from a broken bottle neck (see Figure 1).[88] This form of drug abuse appears to be unique in South Africa. It is suspected that the true prevalence of cannabis smoking and methaquolone usage may be higher than that reported because self-reported usage is likely to be understated owing to the illegal status of the drugs. There are no South African data on the effect of cannabis smoking on respiratory health in terms of the risk of tuberculosis infection or disease.

Figure 1: "White pipe" method of smoking cannabis in a makeshift "pipe" fashioned from a broken bottle neck[88]

(With kind permission from H. Donson)

The percentage of cannabis smokers that will develop TB infection and TB disease is not known. Quantifying exposures may be difficult, limiting dose-response analyses in population studies. The different methods of smoking cannabis, different sizes of cigarettes or pipe volumes, the tendency for joints to be shared, unreliable self-reporting, varying puff volumes, differing retention times and filtering all pose a challenge to the assessment of associations.[89]

A particularly important factor in the quantification of cannabis use is underreporting. This may cause a significant bias in countries where cannabis is illegal, and is discussed further in Chapter Five.

CHAPTER 3: METHODS OF THE LUNG HEALTH SURVEY

The LHS 2002 was a cross-sectional study of the population of the adjacent suburbs of Ravensmead and Uitsig involving a 15% random sample of addresses and recruiting non-institutionalised persons aged ≥15 years living at the sampled addresses. The methods of the Lung Health Survey have been described in detail elsewhere, and are adapted here.[55 90]

3.1. Study area and study population

The study was performed in two adjacent predominantly low-income suburbs of Cape Town, known as Ravensmead and Uitsig. These suburbs originated from the forced relocation of persons classified as "coloured" by the apartheid/segregation policy of the Nationalist government known as the Group Areas Act in the 1960s. Poor housing is characteristic of this area, ranging from small informal backyard shacks to 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 and an average household size of 7-10 persons.[91] Thirty six percent of the population lives in these dwellings which often are not connected to water, electricity or sewage facilities. 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.[90]

The population pyramid of these suburbs resembled that of a developing country with a high proportion of persons in the younger age groups - forty percent of the population was less than 20 years and 30% less than 15 years. The largest number of persons fell into the 25-34 year age group (>7000). Poverty was a feature with 67% of the population earning less than R3500 in 1996. The TB notification rates had 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.[92 93 100] In view of this increasing prevalence of reported tuberculosis and anecdotal evidence of a high prevalence of cannabis smoking, Ravensmead and Uitsig was an appropriate site in which to investigate risk factors for tuberculosis.

3.2. Study design

This was a cross sectional population study.

3.3. Sampling

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. Geographical Information System (GIS) mapping which combines aerial photography, computer graphics and existing information in order to create a comprehensive map of the area was used. Each location was assigned a specific land-use.[94] 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 2).

The primary sampling unit or cluster was an address. This could be either a physical street address (name and number) or the name and number of a flat. A list of addresses was obtained from the local municipality.

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 was very similar, and ranged from 6.63 to 13.83 in flats and 5.5 - 12.9 in houses. The random sample comprised 839 addresses which was a 15% simple random sample of all addresses (see Figure 2).

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 land, i.e. all residents at each address.[95]

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.

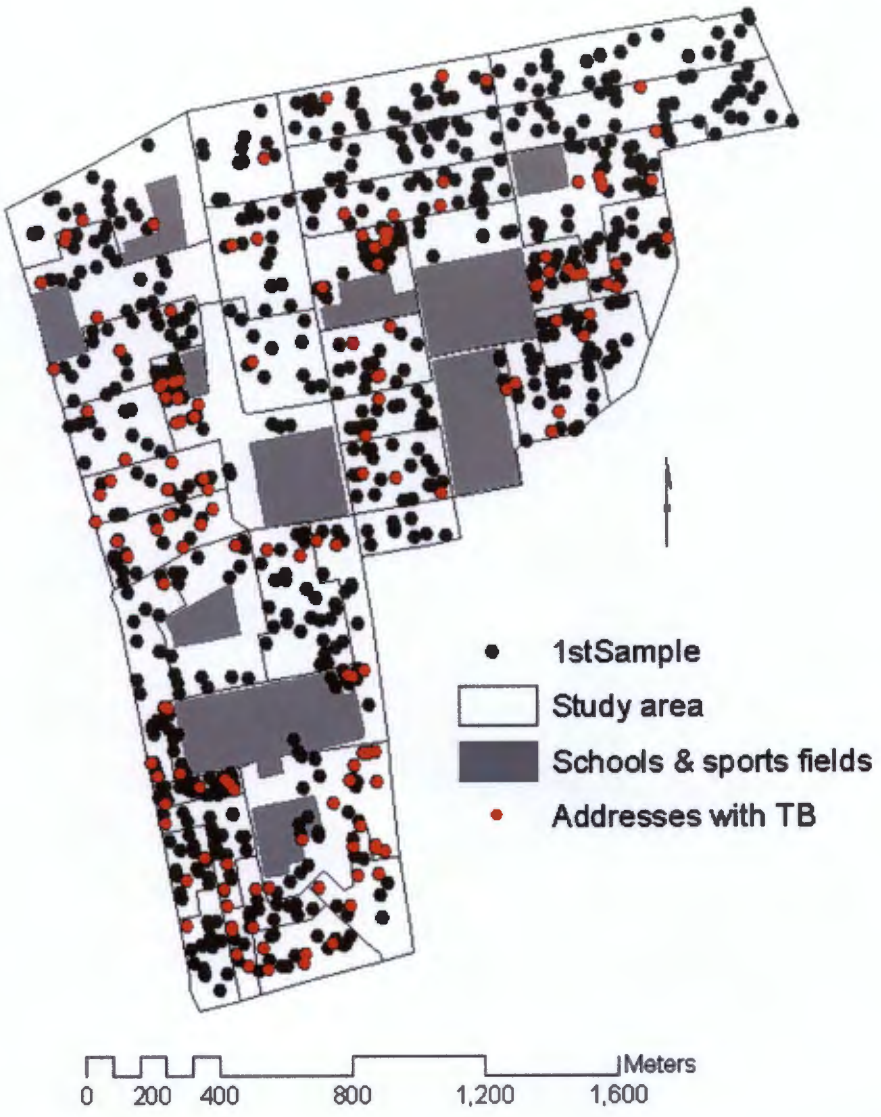


Figure 2: Location of addresses where TB had occurred in relation to the random sample of addresses for the study

3.4. Study procedures

Individuals 15 years and older were assessed as follows:

1. Informed consent
2. 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 sputum samples were set up for culture on Lowenstein Jensen slants.

3.4.1. The questionnaire

A respiratory questionnaire was developed by the candidate 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 disease-specific international questionnaires, such as the European Community Respiratory Health Survey (ECRHS) questionnaire, which had been validated elsewhere. 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, potential risk factors of interest (including confounders) and healthcare utilisation were compiled into a single questionnaire (See Appendix 2). Questions on past TB diagnosis and TB treatment, including the date of treatment/s, were asked.

The vast majority of inhabitants spoke Afrikaans as their first language and 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 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 candidate 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.

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, and the rest between September and December 2002.

3.4.2. Height , weight, Tuberculin Skin test and presence of a BCG scar

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.

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

The Tuberculin Skin Test: The World Health Organisation 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 the nurse.

3.4.3. Sputum sampling and processing

Participants were requested to produce a sputum sample at the health centre where the chest radiograph was performed. Sputum sampling 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 and instructed participants on the active cycle of breathing technique. Adults were asked to expectorate into a wide mouthed plastic sputum jar (with a secure screw-top lid), close it tightly and place it in a plastic bag provided. At the end of each day, all 'cool' boxes were thoroughly cleaned with hycolin.

Sputum samples were transported to the laboratory in 'cool' boxes (at ambient temperature) and processed using standardised methods within three days. The macroscopic appearance of the sputum was recorded. A single smear and a single culture were prepared from each sample. Sputum smears were stained with the Ziehl Neelsen technique and processed using the standard sodium citrate method. Examination for acid fast bacilli (AFB) was performed and the smear was considered positive when there was ≥1 AFB per 100 power field using the scoring system of the International Union Against Tuberculosis and Lung Diseases (IUATLD). Each slide was examined for at least 20 minutes. 'Scanty' smears were also considered positive. Specimens were cultured on Lowenstein Jensen slants and incubated for six weeks at 37 degrees Celsius.

A second sputum sample was requested from participants who had a single scanty smear and/or a positive culture and they were referred to the local clinic for treatment. Participants who attempted but were unable to produce a sputum sample were considered smear- and culture-negative.

3.4.4. Chest radiograph

Participants were requested to present for a chest radiograph at a nearby clinic, and transport was provided. In privacy, all females were asked whether they were pregnant, and if so, the chest radiograph was performed with a lead abdominal shield. Postero-anterior chest radiographs were performed by a trained radiographer, using 200 MA radiograph apparatus producing 35cm by 43cm films. The candidate 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 then formally read by an experienced pulmonologist using a new Chest Radiograph Reading System modelled on the International Labour Organisation (ILO) Classification Reading Form. This Chest Radiograph Reading System was validated and has been reported by den Boon et al (2006).[96] A subsample was reread by another physician in order to assess agreement and evaluate the form as an epidemiological tool. Abnormalities were classified as

consistent with TB or not consistent with TB. The former group were subclassified into non-mutually exclusive groups called pleural abnormalities, parenchymal abnormalities and central structure abnormalities as well as other abnormalities. These will not be reported in detail in this mini-dissertation.

3.4.5. Safety issues: procedure for referral of subjects

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 candidate 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 then contacted and referred to the Respiratory Clinic at Tygerberg Hospital and further action was advised according to medical indications.

3.5. Analysis of data

3.5.1. Data capture and preparation

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 candidate 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 candidate then extracted the data from the database by compiling queries in Access and importing the results of these queries into a STATA database.

3.5.2. Statistical analysis

Analysis was performed using the survey estimation commands in the STATA 9.1® statistical package, taking into account both clustering and weighting. Chapter 4 gives details on the methods used for developing analysis weights.

3.5.3. Categorisation of variables

The two binary outcomes analysed were tuberculosis disease and tuberculosis infection. These are defined in Chapter One.

Characterisation of the population in terms of frequency of exposure to the risk factor variables described below was performed and is presented in a tabular format.

All risk factors that are significant in the univariate analyses were included unless there was a good reason not to include them (e.g. very small numbers with the exposure). In the model building process, suspected interactions such as tobacco and cannabis smoking were tested for significance by including interaction terms in the model. Results from the two multivariable models will be reported in a tabular format.

The exposure variables were categorised in order to allow for clinical interpretation. Where exposure variables were not binary, categorisation of the variables was based on previous such categories in the literature (e.g. BMI categories, pack year categories for tobacco), natural delineations (e.g. education) or related to clinical cutoff points.

Univariate analysis of risk factors was performed and reported. Multivariate models were built based on the results of the univariate analysis and on the *a priori* significance of the variables.

Tobacco smoking was classified into packyear categories (see Table 12)

Number of packyears = number of cigarettes per day/20 X number of years smoked

Cannabis smoking

The categorisation of cannabis exposure has been undertaken in two ways - firstly into non-, former and current cannabis smokers, and secondly into cumulative exposure categories. The following reasons are given for the latter categorisation.

Effort was made to consider the cumulative exposure of cannabis. Tashkin et al have described a measure known as a joint year.[97] A joint year is defined as one joint per day for one year.

The British Thoracic Society published a review stating that the effect of 3-4 cannabis joints is equivalent to 20 tobacco cigarettes with respect to damage of the bronchial mucosa.[98] Since tobacco exposure has been categorised into 0-10 pack years, 10-20 pack years and >20 pack years - for the purposes of comparison, an attempt was made to mirror this categorisation. The equivalent exposure categories for cannabis smoking is 0-35 joint years, 35-70 joint years and >70 joint years.

As some of the cannabis exposure was from pipe smoking, one pipe was considered to be equivalent to 2 joints for the purpose of this categorisation. This choice is based on estimation and is supported by anecdotal evidence only.

Occupational exposure was categorised as follows: a) and/or b)

a) 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?
b) Have you ever been exposed to other dusts, gases, strong smells, chemicals, fumes, at work?

The categorisation of the other independent variables can be seen in Table 12 (age, sex, BMI, education, income, alcohol and imprisonment).

3.6. Ethical considerations and informed consent

The following ethical considerations are in keeping with the Declaration of Helsinki (World Medical Association 2000).[99] Permission to conduct the study was sought and obtained from the Head of the Local Department of Health (Dr Ivan Toms - Cape Metropolitan Council) and the Provincial Department of Health. The study was approved by both the Research Ethics Committee of the Health Sciences (UCT REC REF 160/2002) Faculty at the University of Cape Town and the University of Stellenbosch.

An information leaflet accompanied the informed consent document. This described the study, clearly indicated that participation was voluntary and assured confidentiality. An excerpt from the leaflet is shown below and the interviewers also verbally explained both these key issues:

"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."

The interviewers informed potential participants that taking part in this study did not pose any severe risks to them. They were informed that they would be requested to complete (with the help of a trained interviewer) a detailed questionnaire about their health. The participants were also informed that a TB skin test, called the Tuberculin

test, will be performed on all that take part. They were told that 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 and that occasionally, it may blister, or form a shallow sore (ulcer), or cause tender glands under the arm. Participants were informed that a health worker would record the result of the test after 3 days, when the reaction is strongest, and if necessary, they would be provided some cortisone cream to rub on the area to reduce the pain and swelling.

Participants were informed of the following verbally and in the information leaflet: "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. You will be asked to try and cough up some phlegm for examination for TB organisms."

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. Participants were asked to sign a consent form after they had read and understood the information leaflet. They were given an original copy of both the leaflet and the consent form to keep.

Written signed informed consent was requested and obtained for all participants. 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.

CHAPTER 4: RESULTS

4.1. Response rate

The response rates for the different components and procedures in the project are presented in the following flow chart:

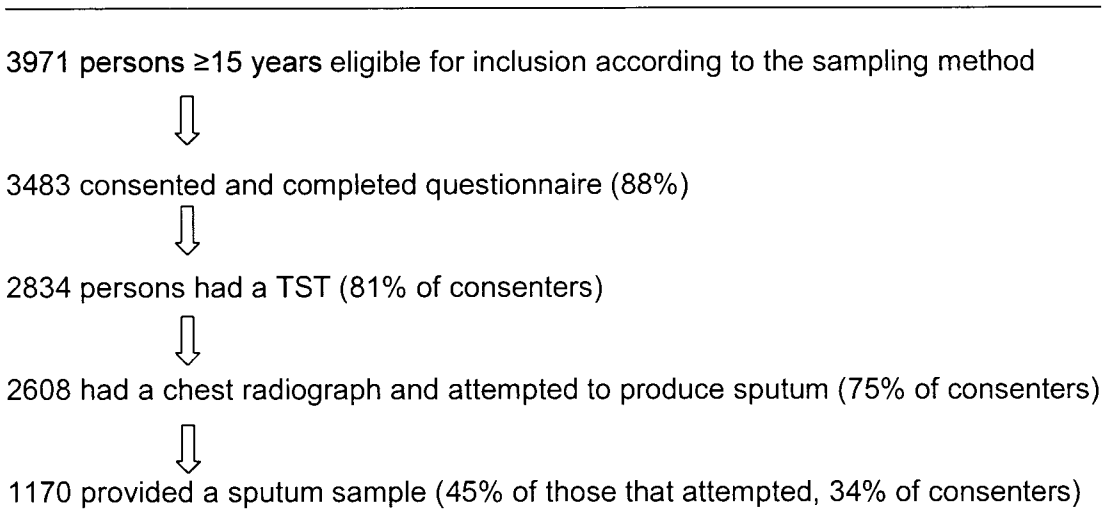


Figure 3: Response rates for the Lung Health Survey

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, two could not be replaced and 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.[14]

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 (Figure 3).

4.2. Development of analysis weight factors

In this survey, the primary sampling unit (PSU) was an address and the analysis takes this clustering into account. The census and sample response rate proportion was calculated for the consenting original and consenting replacement addresses. A response rate for two age and gender categories was calculated (15-44 years and >45 years) and the realisation proportion was calculated for them (unequal response rates in these four sex and age groups)

The address weight which is the selection probability for a random address was 0.15 (839/5592) and therefore the number of persons represented by each of these addresses is the inverse of this i.e. 6.67 persons.

The response rate for the original addresses was 0.898 (3824/4258), and the response rate for the replacement addresses was 0.859 (1272/1481). The response rate for men >45 years was the lowest. Separate weights were calculated for the original consenting and the replacement addresses.

The realisation weight extrapolates the individuals in the sample in terms of how many persons they represent of the population. For persons in the original addresses this weight was 1.114 (1/0.898); and for persons from the replacement addresses it was 1.164 (1/0.859). By multiplying the address weight and the realisation weight, one is able to identify the adjusted number of persons represented by the individual. Persons living at the original addresses represent on average 7.43 persons in the population and persons at the replacement addresses represent 7.76.

The final sampling weight for each individual was a product of the inverse of the first stage sampling probability of an address (original vs. replacement PSUs) and the inverse of the response rate of that individual's specific age and gender subgroup. These weights were linked to each unique identifier in the database. The weights were used by setting the proportion weight as these individual weights and clustering was accounted for by setting the PSU as an address identifier, using the "survey analysis" commands in STATA 9.1®.

4.3. Outcomes

4.3.1. Past/current TB disease

The prevalence of past tuberculosis was based on the question; "Has a doctor/health worker ever told you that you have TB (see question 17, Appendix 2)

Table 4: The prevalence of a history of tuberculosis

Past TB	All n (%)	Men n (%)	Women n (%)	p*
Never	3146 (90.3)	1314 (88.0)	1831 (92.1)	<0.001
Ever	337 (9.7)	179 (12.0)	159(8.0)	

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

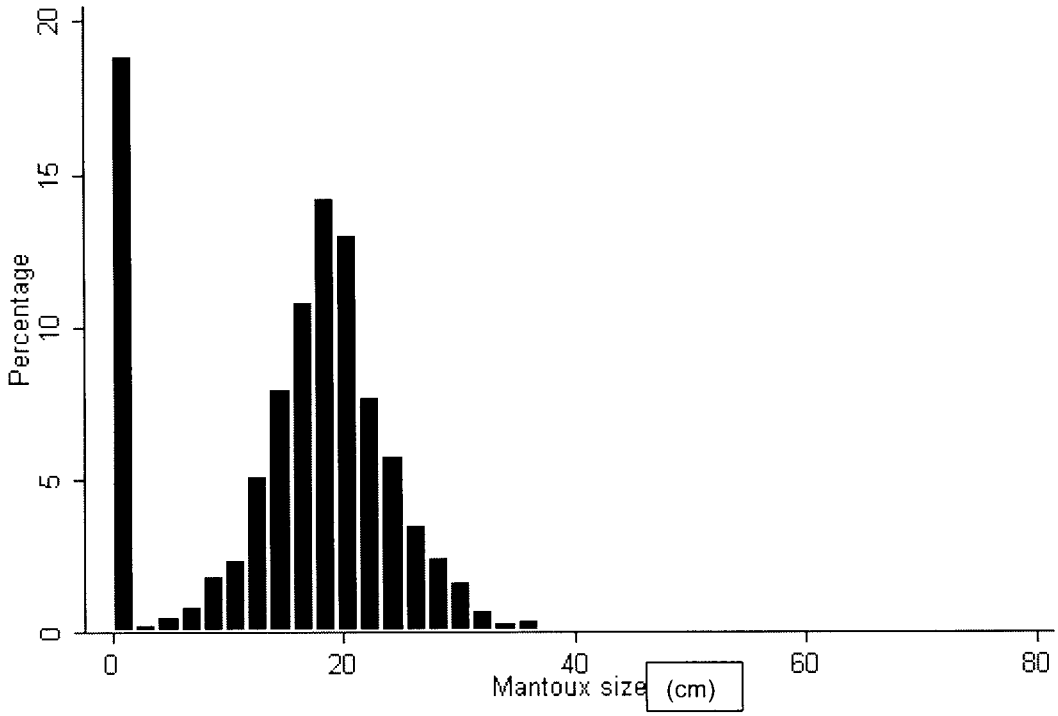
1. The prevalence of past TB was 9.7% (n=337). See Table 4.

2. The prevalence of current bacterially positive TB was 1% (26/2608) (see Chapter 1 for definition). A total of 2608 persons attempted to provide a sputum sample. Persons who attempted but failed to produce a sputum sample were assumed to be smear and culture negative.

Therefore the prevalence of past/current TB disease was 10.4%. (first outcome to be analysed). The age-related prevalence of TB disease is described in Table 13, and shows a steady increase with age and also a significantly greater prevalence in men. (12.7% vs. 8.5%; p <0.001)

4.3.2. TB infection

The prevalence of TB infection was 76% (n= 2194). Figure 4 shows the distribution of TST size. The age related prevalence TST positivity is shown in Table 14. It is high at all ages and decreases slightly with age, with the persons >65 years exhibiting a comparatively lower prevalence of infection (52%)



*also reported in den Boon et al[55]

Figure 4: Histogram of the distribution of tuberculin skin test size in persons ≥15 years (% population vs. TST in centimeters)

4.4. Exposure

Table 5: Prevalence of cannabis smoking (n=3483)

	All: n (%) (n=3483)	Men: n (%) (n=1493)	Women: n (%) (n=1990)	p*
Never smokers	3088 (88.7)	1149 (77.0)	1939 (97.5)	
Ex smokers	173 (5.0)	146 (9.8)	27 (1.4)	
Current 1 – 2 joints per day	89 (2.6)	77 (5.2)	12 (0.6)	<0.001
Current ≥ 3 joints per day	57 (1.6)	51 (3.4)	6 (0.3)	
"Pipe" smoking only	76 (2.2)	70 (4.7)	6 (0.3)	

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

Twelve percent (411) admitted to smoking substances other than tobacco. Most were cannabis smokers (395). Twenty three percent of men and 2.6 percent of women had ever smoked cannabis. The majority of cannabis smokers were male and just under half of male smokers (9.8% of the male population, see Table 5)

were ex-smokers at the time of the survey. A significant proportion of men were current smokers (222 participants - 13.2%).

"Pipe" smoking (a pipe usually being a makeshift 'pipe' – see Figure 1) 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.

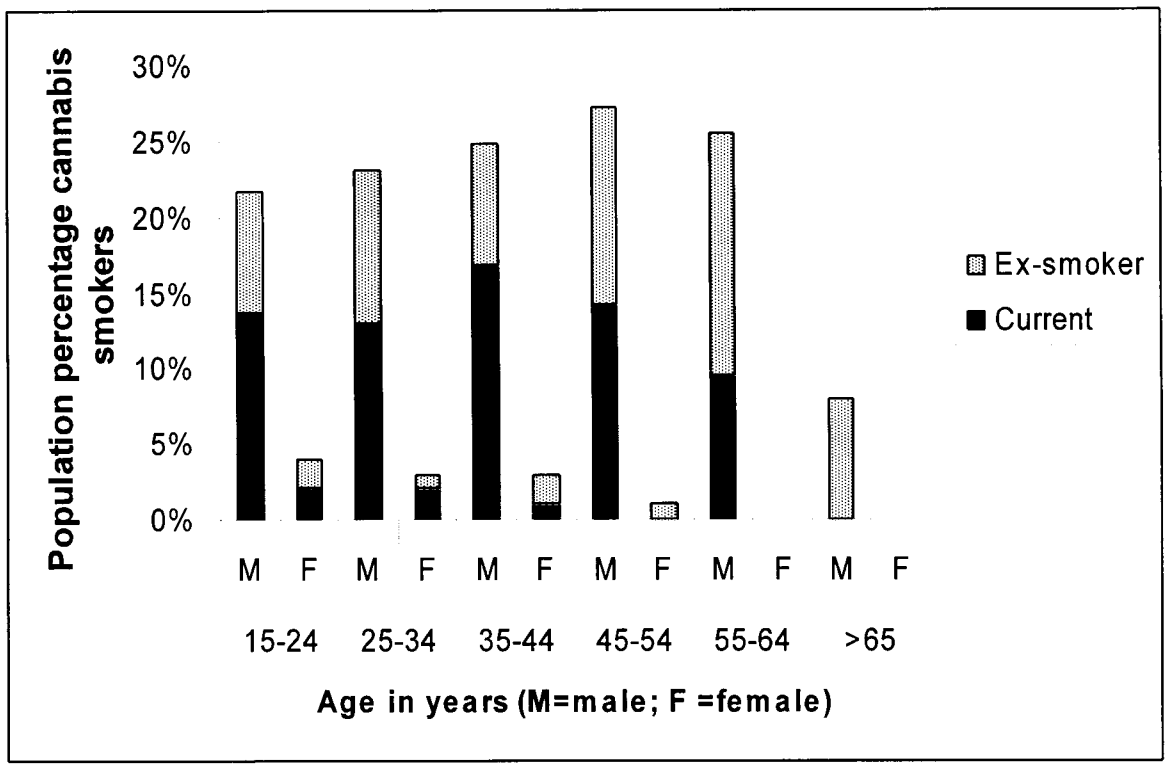


Figure 5: Prevalence of current and previous cannabis smoking in men and women

Figure 5 presents the percentages of male and female cannabis smokers and ex-smokers in different decades of age, and shows that relatively few persons began smoking after the third decade. 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%). The prevalence drops off by almost a half by the sixth decade and few persons older than 55 years smoke cannabis.

Table 6: Lifetime exposure to cannabis smoking (n=395)

	All: median (25^{th} - 75^{th} centile) (n=395)	Men: median (25^{th} - 75^{th}centile) (n=345)	Women: median (25^{th} - 75^{th} 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**	30.0 (10.4 – 88.0)	34 (11.6 - 99.2)	11.7 (4.0 – 30.6)

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

** 1 joint year = an average of 1 joint per day for 1 year[97]

The median age of commencing cannabis smoking was 18. A quarter of smokers had already started smoking by age 16, half by age 18 and three quarters by age 20. Those that stopped did so in their late 20's or early 30's. (Table 6)

Men smoked longer than women (median of 10 vs. 4.3 years).Overall the median time was nine years in a relatively young population (70% of the population was under the age of 45 years). A median number of joint years of 30 was high and the higher prevalence of cannabis smoking in men accounted for higher cumulative exposure

The percentage of ever cannabis smokers with past or current tuberculosis was significantly higher than that for non-cannabis smokers. Table 7 shows that twenty one percent (83/395) of ever cannabis smokers had past/current TB and 8.9% of non cannabis smokers (273/3079) had past TB ($p<0.001$).

Of all persons with current/past TB almost a quarter (23.3%) had smoked cannabis whereas among those with no current/past TB, only 10% had smoked cannabis ($p<0.001$)

Categorisation of cannabis smoking and other variables are discussed in Chapter 3.

Table 7: Relationship between cannabis smoking (ever) and. past or current TB disease

Percentages are presented by row (in bold print) and for each column *(in italics)*

	No Cannabis smoking n (%)	Cannabis smoking n (%)	Total n (%)
No TB disease	2806	312	3118
	90.0%	**10.0%**	**100%**
	91.1%	*79.0%*	*89.8%*
TB disease	273	83.0	356
	76.7%	**23.3%**	**100%**
	8.9%	*21.0%*	*10.3%*
Total	3079	395	3474
	88.6%	**11.4%**	**100%**
	100%	*100%%*	*100%*

Table 8: Distribution of TB disease in cannabis smokers by joint years

Past/current	Joint year categories n (%)				
TB	**0**	**0 – 35**	**35 – 70**	**>70**	**Total**
No	41 (89.1)	151(86.3)	42 (77.8)	56 (60.2)	290 (78.8)
Yes	5 (10.9)	24 (13.7)	12 (22.2)	37 (40.0)	78 (21.2)
Total	46 (100)	175(100)	54 (100)	93 (100)	368(100)*

*27 persons had insufficient information for the accurate calculation of joint years

Increasing joint years was associated with an increasing prevalence of past/current TB disease. Forty percent of cannabis smokers with a >70 joint year history had past/current TB disease. ($p<0.001$)

Table 9: Relationship between cannabis smoking and incarceration (imprisonment).

Percentages are presented by row (in bold print) and for each column *(in italics)*

	No incarceration n (%)	**Incarceration n (%)**	**Total n (%)**
Cannabis(never)	2936	121	3057
	96.0%	**4.0%**	**100%**
	92.5%	*44.3%*	*88.7%*
Cannabis (ever)	238	152	390
	61.0%	**40.0%**	**100%**
	7.5%	*55.7%*	*11.3%*
Total	3174	273	3447
	92.1%	**7.9%**	**100%**
	100%	*100%*	*100%*

*each percentage is rounded to the first decimal place

Forty percent of cannabis smokers had a history of incarceration (Table 9). Approximately 56 percent of persons with a history of incarceration had a history of cannabis exposure. Of all persons with a history of incarceration and cannabis smoking, 25% (38/152) had past TB. Of all those cannabis smokers with no history of incarceration 15.8% (42/266) had past TB.

Table 10: Relationship between cannabis smoking and tobacco smoking

Percentages are presented by row (in bold print) and for each column *(in italics)*

	Tobacco (never) n (%)	**Tobacco (ever) n (%)**	**Total n (%)**
Cannabis(never)	1440	1637	3057
	46.8%	**53.2%**	**100%**
	97.9%	*81.9%*	*88.7%*
Cannabis (ever)	31	363	390
	7.9%	**92.1**	**100%**
	2.1%	*18.2*	*11.3*
Total	1471	2000	3471
	42.4%	**57.6%**	**100%**
	100%	*100%*	*100%*

Of all persons who had ever smoked cannabis, 92.1 percent also ever smoked tobacco (Table 10). There were thus very few exclusive cannabis smokers. Of all those who had ever smoked tobacco, 18.2% had ever smoked cannabis. Of all current tobacco smokers, 11.5% were current cannabis smokers (not shown).

Table 11: Relationship between cannabis smoking and evidence of TB abnormality on chest radiograph

Percentages are presented by row (in bold print) and for each column *(in italics)*

	No TB abnormality on radiograph n (%)	**TB abnormality on radiograph n (%)**	**Total n (%)**
Cannabis(never)	2045	277	2322
	88.1%	**11.9%**	100%
	90.3%	*82.2%*	*89.3%*
Cannabis (ever)	219	60	279
	78.5%	**21.5%**	**100%**
	9.7%	*17.8%*	*10.7%*
Total	2264	337	2601
	87.0%	**13.0%**	**100%**
	100%	*100%*	*100%*

Overall, 13% (337 out of 2608 persons) had an abnormality in keeping with TB on the chest radiograph (Table 11), and 51.5% of persons with past TB had a TB abnormality on CXR (not shown) Of all cannabis smokers, 21.5% had a TB abnormality and 11.9% of non cannabis smokers had a TB abnormality.

Table 12: Sex distribution of other potential risk factors for tuberculosis (n=3483)

Characteristics	All n (%)	Men n (%) 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)	
Cannabis: 0 joint years	3118 (90.6)	1178(80.3)	1940(98.3)	<0.001
0-35 joint years	175 (5.1)	149 (10.2)	26 (1.3)	
35-70 joint years	55(1.6)	50(3.4)	5 (0.3)	
>70 joint years	93(2.7)	91 (6.2)	2 (0.1)	
Tobacco: 0 pack years	1570 (45.1)	527(35.3)	1043 (52.4)	<0.001
0-10 pack years	1335 (38.3)	626 (41.9)	709 (35.6)	
10-20 pack years	305 (8.8)	172 (11.5)	133 (6.7)	
>20 pack years	273 (7.8)	168 (11.3)	105 (5.3)	
Incarceration: No	318 (92.1)	1234 (83.3)	1946 (9807)	<0.001
Yes	274 (7.9)	248 (16.7)	26 (1.3)	
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)	
Occupational exposure: Never	2569 (73.8)	939 (62.9)	1630 (81.9)	<0.001
Ever	914 (26.2)	554 (37.1)	360 (18.1)	
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)	
Alcohol: None	2284 (65.6)	759(50.9)	1525 (76.6)	<0.001
1-2 days/week	762 (21.9)	432 (30.0)	330 (16.6)	
3-4 days/week	307 (8.8)	205 (13.7)	102 (5.1)	
≥5days per week	129 (3.7)	96 (6.4)	33 (1.7)	

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

Table 12 confirms significant differences between the sexes in respect of several factors (other than cannabis use) that may be associated with increased risk of tuberculous infection and disease. These include age, education, income, BMI,

tobacco smoking, imprisonment, and alcohol use and occupational exposure. There was little current exposure to smoky fuels in this community as it is an urban area that is mostly electrified, and no data regarding past exposure was collected.

Most of the population earned less than R1000 per month (63.4%), and almost 70% of women were in this extremely low income category. Just over half the population (52.9%) had a high school education. There were low numbers of men in the >65 age group (79). Almost twice the percentage of men than women reported occupational dust exposure (37.1% vs. 18.1%).

There was a high level of tobacco exposure and the majority of men and women had a 0 – 10 packyear history (38.3%) and a higher percentage of men had greater cumulative exposure. Similarly, the majority of male cannabis smokers fell into the 0-35 joint year category (10.2%), but 6.2% had a >70 joint year exposure.

Twenty five percent of women were overweight and a further 29.7% were obese. Being underweight was more common in men (15.3%) and a history of incarceration was reported by 16.7% of men in this community.

4.4. Risk factor analysis

4.4.1. TB disease

Univariate analysis of risk factors associated with past or current TB was performed. All the *a priori* risk factors were significantly associated with TB disease.

The strongest association was with cannabis smoking of >70 joint-years (OR: 6.8; CI: 4.4 – 10.6) and 35 – 70 joint years (OR 2.9; CI: 1.5 – 5.7) and 0 – 35 joint years (OR 1.6; CI: 1.0 – 2.6), showing a dose dependent association, which was retained in the multivariate analysis, which adjusted for nine other potential risk factors. Cannabis smoking of >70 joint-years was associated with TB disease (OR 3.2; CI: 1.8 – 5.6).

Tobacco smoking of >20 pack years (OR 3.3; CI: 2.3 – 4.7) and 10-20 packyears (OR 1.8; CI: 1.2 – 4.7) and 0 – 10 packyears (OR 1.5; CI: 1.2 – 2.0) also showed a dose dependent association. Income <R1000 per month, lower levels of formal education, increasing age, imprisonment, male gender, alcohol use and being

underweight were all associated with TB disease (see Table 13). There appeared to be a protective effect associated with being overweight or obese.

A multicollinearity matrix was created adjusting for all dependent variables and none of the variables had a coefficient of >0.8, suggesting that there was no need to remove any variables on the basis of multicollinearity. The adjusted Pearson's correlation coefficient for joint years vs. packyears was 0.1972.

In the **multivariate model** of risk factors for past or current TB disease, several risk factors were no longer significant. Those that remained significant were, cannabis smoking of >70 joint years (OR 3.2; CI: 1.8 – 5.6), tobacco smoking of >20 packyears (OR 1.7; CI: 1.1- 2.6), increasing age (see Table 13) and being underweight (OR 1.8; CI: 1.2 – 2.6).

Obesity (OR 0.4; CI: 0.2 – 0.6) and being overweight (OR 0.5; CI: 0.3 – 0.7) retained their apparent protective effect. There were two borderline associations viz. low income and occupational exposure.

Since the models for tobacco and cannabis exposure presented in this chapter were selected in order to examine potential dose-dependent effects of tobacco and cannabis smoking on TB disease they were included as cumulative exposures. However, this categorisation is not well suited for an assessment of interactions with other categorised risk factors as the cell sizes become too small.

Therefore, **further analyses expressing cannabis exposure as non-, ex- and current cannabis smoking** were performed. In this analysis (presented in Appendix 3) a significant association of ex- and current cannabis smoking with tuberculosis disease was observed. However, there was no significant interaction between cannabis smoking and tobacco smoking in this analysis (p =0.27).

Table 13: Logistic regression showing the association of current/past tuberculosis disease with risk factors (n = 2716)

	N with past/current tuberculosis / total N in category	% with past/current tuberculosis	Unadjusted OR (95%CI)	Adjusted OR (95%CI)
Income:** >R2000/month	42/631	6.7%	1.0	1.0
R1000-R2000/month	49/623	7.9%	1.2 (0.9 – 1.8)	1.0 (0.6 – 1.6)
<R1000/month	263/2168	12.1%	**1.9 (1.4 – 2.8)**	1.6 (1.0 – 2.6)
Education: >12 years	44/701	6.3%	1.0	1.0
8-12 years	171/1842	9.3%	**1.5 (1.1 – 2.1)**	1.4 (0.9 – 2.0)
1-7 years	132/832	15.9%	**2.8 (2.0 – 4.0)**	1.5 (1.0 – 2.4)
None	12/106	11.3%	**1.9 (1.0 – 3.7)**	0.8 (0.3 – 2.0)
Age : 15-24	64/969	6.6%	1.0	1.0
25-34	71/742	9.6%	**1.5 (1.0 – 2.1)**	**1.9 (1.2 – 3.0)**
35-44	92/732	12.6%	**2.0 (1.5 – 2.8)**	**2.4 (1.5 – 3.9)**
45-54	62/471	13.2%	**2.1 (1.5 – 3.1)**	**2.4 (1.4 – 4.1)**
55-64	50/331	15.1%	**2.5 (1.7 – 3.7)**	**3.0 (1.8 – 5.0)**
>65	20/237	8.4%	1.3 (0.8 – 2.2)	1.6 (0.8 – 3.1)
Tobacco: 0 pack years	117/1570	7.5%	1.0	1.0
0-10 pack years	147/1335	11.0%	**1.5 (1.2 – 2.0)**	1.1 (0.8 – 1.5)
10-20 pack years	38/305	12.5%	**1.8 (1.2 – 2.6)**	0.8 (0.5 – 1.4)
>20 pack years	57/273	20.9%	**3.3 (2.3 – 4.7)**	**1.7 (1.1 – 2.6)**
Cannabis: 0 joint years	275/3118	8.8%	1.0	1.0
0-35 joint year	24/175	13.7%	**1.6 (1.0 – 2.6)**	1.2 (0.7 – 2.2)
35-70 joint years	12/55	21.8%	**2.9 (1.5 – 5.7)**	1.3 (0.6 – 2.9)
>70 joint years	37/93	39.8%	**6.8 (4.4 – 10.6)**	**3.2 (1.8 – 5.6)**
Occupational exposures:				
Never exposed	236/2569	9.2%	1.0	1.0
Ever exposed	123/914	13.5%	**1.5 (1.2 – 1.9)**	1.3 (1.0 – 1.8)
BMI: normal weight 18.5-25	157/1233	12.7%	1.0	1.0
Overweight BMI >25 & <30	42/653	6.4%	**0.5 (0.3 – 0.7)**	**0.5 (0.3 – 0.7)**
Obese BMI≥30	34/617	5.5%	**0.4 (0.3 – 0.6)**	**0.4 (0.2 – 0.6)**
Underweight BMI <18.5	68/309	22.0%	**1.9 (1.4 – 2.7)**	**1.8 (1.2 – 2.6)**
Gender: Female	170/1990	8.5%	1.0	1.0
Male	189/1493	12.7%	**1.5 (1.2 – 1.9)**	1.0 (0.7 – 1.3)
Alcohol None	202/2284	8.8%	1.0	1.0
1-2 days/week	82/762	10.8%	1.2 (0.9 – 1.6)	1.1 (0.8 – 1.5)
3-4 days/week	48/307	15.6%	**1.9 (1.4 – 2.7)**	1.3 (0.8 – 2.0)
≥5 days/week	27/129	20.9%	**2.7 (1.7 – 4.4)**	1.0 (0.5 – 1.8)
Incarceration No	289/3180	9.1%	1.0	1.0
Yes	67/274	24.5%	**3.2 (2.4 – 4.4)**	1.2 (0.8 – 1.8)

Table 14: Analysis of risk factors for TB infection using survey estimation multiple logistic regression (n=2599)

	N with TB infection / total N in category	% with TB infection	Unadjusted OR (95%CI)	Adjusted OR (95%CI)
Income:** >R2000/month	404/484	83.5%	1.0	1.0
R1000-R2000/month	421/511	82.4%	0.9 (0.7 – 1.3)	1.1 (0.8 – 1.7)
<R1000/month	1340/1797	74.6%	0.6 (0.4 – 0.8)	1.0 (0.7 – 1.3)
Education: >12 years	438/548	79.9%	1.0	1.0
8-12 years	1135/1497	75.8%	0.8 (0.6 – 1.0)	0.9 (0.7 – 1.2)
1-7 years	567/701	80.9%	1.1 (0.8 – 1.4)	1.2 (0.9 – 1.7)
None	52/86	60.5%	0.4 (0.2 – 0.6)	0.7 (0.4 – 1.2)
Age : 15-24	517/780	66.3%	1.0	1.0
25-34	521/583	89.4%	4.3 (3.2 – 5.8)	**4.1 (2.9 – 5.7)**
35-44	516/599	86.1%	3.2 (2.4 – 4.2)	**2.6 (1.9 – 3.6)**
45-54	322/390	82.6%	2.4 (1.8 – 3.3)	**2.0 (1.4 – 2.9)**
55-64	217/290	74.8%	1.5 (1.1 – 2.0)	1.4 (0.9 – 2.0)
>65	100/191	52.4%	0.6 (0.4 – 0.8)	0.5 (0.3 – 0.8)
Tobacco: 0 pack years	928/1301	71.3%	1.0	1.0
0 -10 pack year	861/1060	81.2%	1.7 (1.4 – 2.2)	**1.4 (1.1 – 1.8)**
10-20 pack years	220/247	89.1%	3.3 (2.1 – 5.0)	**2.2 (1.4 – 3.5)**
>20 pack years	185/226	81.9%	1.8 (1.3 – 2.6)	**1.5 (1.0 – 2.3)**
Cannabis: 0 joint years	1952/2564	76.1%	1.0	1.0
0-35 joint year	110/128	85.9%	1.9 (1.2 – 3.1)	1.2 (0.7 – 2.2)
35-70 joint years	35/39	89.7%	2.8 (1.0 – 7.6)	1.0 (0.3 – 2.7)
>70 joint years	64/69	92.8%	4.0 (1.7 – 9.9)	1.4 (0.6 – 3.6)
Occupational exposures:				
Never exposed	1569/2083	75.3%	1.0	1.0
Ever exposed	625/751	83.2%	1.6 (1.3 – 2.0)	0.9 (0.7 – 1.2)
BMI: normal weight 18.5-25	910/1171	77.7%	1.0	
Overweight BMI >25 & <30	499/624	80.0%	1.1 (0.9 – 1.5)	
Obese BMI >30	454/599	75.8%	0.9 (0.7 – 1.1)	
Underweight BMI <18.5	220/291	75.6%	0.9 (0.7 – 1.2)	
Gender: Female	1273/1693	75.2%	1.0	1.0
Male	921/1141	80.7%	1.4 (1.1 – 1.7)	1.1 (0.9 – 1.4)
Alcohol: None	1424/1902	74.9%	1.0	1.0
1-2 days/week	498/600	83.0%	1.6 (1.3 – 2.1)	1.2 (0.9 – 1.6)
3-4 days/week	195/235	83.0%	1.6 (1.1 – 2.4)	0.9 (0.6 – 1.4)
≥5 days per week	76/96	79.2%	1.3 (0.7 – 2.2)	0.7 (0.4 – 1.2)
Incarceration: No	1980/2606	76.0%	1.0	1.0
Yes	193/205	94.2%	5.1 (2.8 – 9.1)	**3.6 (1.8 – 7.1)**

4.4.2. TB infection

A similar process was followed for building the model that examines TB infection. All exposures examined, apart from BMI were significant in the univariate analysis, and were thus included in the multivariate analysis. There appeared to be no association

between cannabis smoking (joint-year categories) and tuberculosis infection (see Table 14).

However, an association of tuberculosis infection and former cannabis smoking (OR 2.0; CI: 1.1- 3.6) was seen in a model categorising cannabis smoking (and tobacco smoking) into non, ex and current smoking, without adjusting for incarceration (see Appendix 3). Incarceration appeared to confound the relationship between former cannabis smoking and tuberculosis infection. However, an interaction term included to test the overall significance of the cannabis/incarceration relationship, proved to be non-significant at the 5% level (p=0.1302). However, the interaction between former cannabis smoking and incarceration was significant (p= 0.046).

4.4.3. Population attributable fractions (PAF)

Population attributable fractions were calculated for the modifiable risk factors of interest. Heavy cannabis smoking had a PAF of 5.6%. Levin's formula was used as follows:

PAF = prevalence of exposure (OR-1)/1 + prevalence of exposure (OR-1)

Table 15: Population attributable fractions for tuberculosis disease

	Percentage exposed to risk factor	Prevalence Odds Ratio (multivariate model)	Population Attributable Fraction (%)
Cannabis smoking >70 joint years	2.7	3.2	5.6
Tobacco smoking >20 pack years	7.8	1.7	5.2
Underweight (BMI <18.5)	11	1.8	8.1

The population attributable fraction for cannabis smoking of >70 joint years was 5.6%.

Table 16: Population attributable fractions for tuberculosis infection

	Percentage exposed to risk factor	Prevalence Odds Ratio (multivariate model)	Population Attributable Fraction (%)
Incarceration	7.9	3.6	17
Tobacco smoking 0 - 10pack years	38.3	1.4	13.3
Tobacco smoking 10-20 pack years	8.8	2.2	9.6
Tobacco smoking >20 pack years	7.8	1.5	3.8

An assessment of reliability and repeatability was performed by administering the questionnaire on a second occasion days or weeks after the first administration, and by a different interviewer. This was performed in a sample of 5% of respondents. Selected questions were analysed for percentage agreement between the first and second interview, and this was found to be acceptable (kappa = 0.7)

CHAPTER 5: DISCUSSION

5.1. Significance of the research question

This study aims to contribute to the field of public health by highlighting cannabis as a potential risk factor for tuberculosis and informing public health policy in terms of the need to address risk factors such as tobacco and cannabis smoking as part of the strategic prevention and management of the tuberculosis epidemic.

Tobacco and cannabis smoking are modifiable risk factors. The strengthening of smoking cessation messages in primary health care is currently underway as part of the Practical Approach to Lung Health in South Africa (PALSA Plus) in conjunction with the South African Department of Health. From a health services and health promotion perspective, understanding the association between smoking of both tobacco and cannabis and TB can add impetus to smoking cessation interventions, and can be used in educational public awareness efforts.[25]

There appears to be a need to include cannabis in anti-smoking messages and interventions, particularly in the high risk communities and to include this in the tuberculosis control programme. The results of this study will be communicated to the Department of Health TB Directorate (national), provincial and local health services, and used to motivate for a smoking cessation service at TB Clinics in the Western Cape, and countrywide.

5.2. Discussion of methodology

5.2.1. Bias

Selection bias

The study design was susceptible to a selection bias in that sampling of clusters (addresses) as the primary sampling unit could result in a biased estimate of the outcomes (TB) arising from common exposure of household contacts to infected individuals in households. This effect would have been reduced by the large sample size; the 15% sample of addresses is considered adequate for this purpose. Moreover, as TB is common throughout the study area, and did not appear to be concentrated in any section of the suburbs sampled (See Figure 1), this influence is likely to have been small, if not insignificant. In addition, the effect of clustering has been corrected for by appropriately weighting the observations (see Chapter 4).

The resampling and replacement procedure is another potential cause of selection bias, but its significance is not possible to estimate. On the one hand, persons at addresses with recent or current tuberculous disease might have felt less inclined to participate owing to fear of stigmatisation. In this scenario, the replacement procedure would have introduced underestimation of the outcome. Conversely, some persons at the sampled addresses would have been more likely to consent if they had experienced TB disease. This would have led to overestimation of the outcome.

Information bias (outcomes and exposure)

In any questionnaire based study some amount of recall bias is inevitable. For example, exposures such as to occupational agents may be overreported and exposures such as cannabis or cigarette smoking may be underreported. The impact of these sources of potential bias cannot be estimated but their direction can be suggested.

Firstly, the definition and recall of the outcome of tuberculosis disease is subject to some limitations. In this study, a history of tuberculosis disease was reported by subjects and not confirmed by the investigators. This is somewhat mitigated by the fact that the information was interrogated further through questions on the number of episodes and the dates of each treatment course. A bias in the assessment of the

outcome of tuberculosis could be caused by stigmatisation of the diagnosis in the community, potentially resulting in underreporting. However, TB is not an acute disease, and its symptoms are protracted. Thus a diagnosis of tuberculosis and treatment for 6 months is likely to be remembered. Another factor that could have counteracted this recall bias is the higher levels of awareness of tuberculosis in this community owing to previous TB research having being conducted in these suburbs for the last 15 years.

Secondly, self reporting of the main exposure of cannabis smoking is subject to recall/reporting bias owing to the illegal nature of the activity and the likely social stigmatisation associated with its use. This would have served to underestimate exposure (joint years), and reduce the strength of association.[101] This may have contributed to or accounted for the lack of evidence of a dose-related effect of cannabis smoking with tuberculosis infection in this study, whereas cruder variables such as non, ex and current smoking showed an association with ex- cannabis smoking in the adjusted analysis.

This bias may differ between sexes, women potentially being more reluctant to admit cannabis use because of the lower background use among women; and it being less socially acceptable for them compared to men in this community.

Interviewers were blinded to the hypothesis and thus the potential of observer bias was reduced. In addition, interviewers were well trained in the standardised method of questionnaire administration which involved not expressing any reaction to participant's answers, so as not to influence their answers

It is acknowledged that risk factor analysis in a population-based study cannot ascribe causality but merely association, and even then the direction of effect is in some cases difficult to ascertain. It also does not address potentially relevant details regarding the type of cannabis smoked and nor does it provide an accurate estimate of the quantity smoked. However, most studies on tobacco smoking also suffer from similar limitations and rely heavily on self reporting.

In spite of these limitations and potential sources of bias, principally resulting in underreporting, the current study, being the first population-based study to address the association between cannabis smoking and tuberculosis, provides some important results that may serve as a guide to further research on this topic.

5.2.2. Misclassification

The outcome of past tuberculosis was not based on the result of an objective test and is therefore prone to misclassification. In the case of current tuberculosis disease and tuberculosis infection, the chances of misclassification are smaller as they were based on standardised quality controlled procedures (sputum microscopy and culture).

Misclassification of smoking behaviour is also a factor to consider. There are multiple ways of classifying smoking patterns, ranging from current and ever smoking to more detailed measures including duration and intensity/amount such as packyears. This misclassification is likely to be non-differential and would have had the effect of reducing risk estimates towards the null.[25]

Exposure to cannabis smoking was obtained from questionnaires alone and was not possible to verify through objective measures in this sort of survey. Tests for current smoking through measurement of urinary tetrahydrocannabinol (THC) would have been useful. This was not logistically feasible in this study, and could be considered in future studies. Nevertheless, the face validity of the data was plausible.

5.3. Discussion of results

5.3.1. Relationship of cannabis smoking and tuberculosis disease

Both the prevalence and cumulative exposure of cannabis smoking is high in men (23% ever smokers and 13% current smokers with a median of 34 joint years) and, surprisingly, was found to be practiced in similar proportions of men in all age deciles (10 – 17 percent). This confirmed that regular cannabis use is not a passing fad of youth, but becomes a life-long habit in this community. In this respect, its use in this community is different to that described in developed countries, where it is used mainly by adolescents and young adults.[102] Although the reasons for this are open to speculation, it might reflect the social use of cannabis smoking as an 'escape' from the harsh realities of poverty and unemployment. On the other hand, its role in perpetuating the 'poverty cycle' through interfering with the regular cannabis smoker's ability to obtain and retain regular employment is also important to consider (amotivational syndrome). Another influence is the potential impact of membership of 'gangs' or informal groupings of cannabis smokers in a sub-culture

within the communities studied. Further research using qualitative methods are required to examine the social behaviour and structures that facilitate cannabis use, and the structure and economics of the supply chain that feeds the habit in this community.

Tobacco and cannabis smoking are clearly linked phenomena. 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 suggesting that both need to be addressed simultaneously in the young. Unlike tobacco smoking, cannabis smoking appears to be 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 5.2.1.).

Rigorous attention was paid to the inclusiveness of the model in order to minimise the possibility of chance associations. All *a priori* risk factors for tuberculosis were included in the multivariate model, if they were significant in the univariate analyses. Of particular importance were incarceration and alcohol use, both of which have not been uniformly addressed as confounders in the majority of studies examining the relationship between tobacco smoking and tuberculosis. Evidence for this can be seen in Tables 2 and 3 in Chapter 2 which list the adjusted variables in each study.

Confounding

In the model building process, the addition of incarceration into the model produced the largest effect in terms of reduction in the strength of association of tuberculosis with cannabis smoking. Sex and tobacco smoking each caused smaller reductions of the association of cannabis with TB disease. The other variables - BMI, education, 'wealth', alcohol, occupational exposure and age each had much smaller effects on the cannabis association. Unmeasured variables such as methaqualone use may also have contributed to confounding.

Co-linearity with tobacco smoking was considered for the multiple logistic regression model in which they were both included. Since 92% of cannabis smokers also smoked tobacco, delineating the separate effects may be difficult, and may limit the interpretation of the results. This was addressed in part by multivariate logistic regression adjusting for both variables as it helps to separate the effects of the different variables on the outcome. Tests for co-linearity between cannabis and tobacco smoking were not significant most probably due to the fact that only 18% of

tobacco smokers smoked cannabis (Pearson correlation coefficient(r) = 0.2). The correlation between the two variables is weak and co-linearity should not be a problem in this model. This was confirmed since the estimated risk measures for cannabis smoking and tobacco smoking were coherent. In the case of models with significant co-linearity the overall model explains a significant component of the variation of the outcome variable but the co-linear factors are not significant or have incoherent results in comparison to a model with one of the risk factors present. Also, finding associations between both tobacco smoking and cannabis smoking and tuberculosis is biologically plausible in view of the many similarities between both types of smoke, at least with respect to their effects on the lungs. Lastly, despite adjusting for many different known variables, the possibility of residual confounding from unknown/unmeasured variables may exist.

A surprising finding however, was the apparent greater strength of the association of TB disease with cannabis than with tobacco smoking. Apart from biological or mechanistic differences, this might also be attributable to differences in the smoking practices and the social context of cannabis smoking, compared to tobacco smoking that might increase opportunities for transmission, and person to person spread of mycobacteria. Examples of the latter include closer social contact in confined areas (prisons, informal shebeens or gang hang-outs) necessitated as much by need for clandestine use, as by the social context and importance of cannabis smoking; and the sharing of joints or pipes. Biological explanations include impairment of host defence mechanisms from the constituents of cannabis. The latter has been proposed as the central hypothesis in the relationship between tobacco and tuberculosis. The mechanisms proposed are explored further below.

Twenty one percent of cannabis smokers reported past or current TB disease compared to 8.9% of non-cannabis smokers ($p<0.001$). Cumulative exposure of cannabis of >70 joint years had the strongest association with past/present TB (roughly equivalent to 20 cigarette pack years with respect to bronchial mucosa damage). More than a quarter (25.3%) of cannabis smokers had this level of exposure. After adjusting for known risk factors, this risk was double that of tobacco smoking of >20 pack years (OR 3.2; CI: 1.8 - 5.6 versus OR 1.7; CI: 1.1 – 2.6)

There was no evidence of a significant interaction between tobacco and cannabis suggesting that they are both independent risk factors.

Temporal relationship between exposures and tuberculosis.

A significant uncertainty in the current study is the temporal relationship between cannabis smoking and both infection and the development of active disease. Since there is no clinical marker useful for timing the date of infection, nor even the onset of disease in a retrospective survey (and particularly since the latter may develop insidiously over months or even years), the questionnaire responses do not permit scrutiny of the temporal associations of these outcomes with smoking. It is thus possible that the outcome may have occurred at any time before or after the exposure. Indeed, few host variables (such as sex and genetic influences) may be viewed as constant risk variables, and even these may be influenced by time if, for example, they only confer risk in a particular age-group.

The cross-sectional study design measures risk factors and outcomes at the same time, and therefore cannot support causality. This would be more likely to be supported by longitudinal studies where the outcome is not yet present and thus is much less likely to "cause" the risk factor (the direction of effect may be clearer).

For example, in this study it is of concern whether current income or current education confers risk on past TB disease. Environmental variables such as socioeconomic status, smoking, incarceration and BMI, alcohol use and occupational exposure may all be subject to change in either direction. In addition, a cumulative increase in risk may occur over time with smoking. An attempt to address this has been made by using cumulative exposure variables for both cannabis and tobacco.

In assessing the public health impact of cannabis smoking, the population attributable fractions (PAF) for >70 joint years exposure was 5.6%. It should be noted that PAFs may be inaccurate tools and it is controversial whether they are a good measure of population impact as they can be non-additive, time insensitive etc.[103] The assumptions made are that they are completely adjusted for confounders, and that the association is causal which is not often the case, especially in cross sectional studies. However, PAFs are useful in that they deliver broad public health messages, but one has to be wary of interpreting them by saying that a certain percentage of tuberculosis is "due to" cannabis smoking.[103]

5.3.2. Relationship of cannabis smoking and tuberculosis infection

There was a very high background prevalence of tuberculosis infection in this community (76% of persons aged ≥ 15 years). However, 87.8% of cannabis smokers had TB infection vs. 76.1% of non cannabis smokers. There was no association between TB infection and cannabis smoking in the model which used joint years to assess cumulative cannabis exposure (it is confounded by incarceration). This could be owing to the fact that most persons in this community acquire TB infection early, before there is time for significant cumulative cannabis exposure. However, this argument does not suffice for tobacco smoking, which has a persistent response in both the presented (Chapter 4) and alternative models (Appendix 3). However, the finding of an association of both tobacco smoking and cannabis smoking with tuberculosis is plausible because of similarities between both types of smoke, at least with respect to their effects on the lungs.

Other factors

Firstly, imprisonment had the strongest association with TB infection in the adjusted analysis (OR 3.6; CI: 1.8 – 7.1).There was a high rate of reported imprisonment in men in this community of 16.7% as a result of juvenile gang warfare, general lawlessness in young men part of a social problem resulting in imprisonment. Exposure to cannabis and habit formation is common in prisons apart from the other known factors that lead to TB infection in prisons. The issue of confounding by incarceration is interesting. Former cannabis smoking was associated with tuberculosis infection (OR 2.0; CI: 1.1 – 3.6) in an alternative model which did not adjust for imprisonment. It is clear that imprisonment is a confounder for cannabis smoking, but one has to also consider the converse in that cannabis smoking may be a confounder for imprisonment as it is illegal and also associated with other reasons for imprisonment. However, for TB infection, imprisonment retains its significance in all models.

The WHO reports the following factors that assist the spread of TB in prisons: Foremost are overcrowding and poor ventilation and high turnover of prisoners.[104] In addition, late case detection, lack of isolation and inadequate treatment are also contributors. Poor nutrition, physical and psychological stress may also weaken the immune response to mycobacterium tuberculosis. It is also common that many persons come to prison already infected. In some countries, many detainees become infected during pre-trial detention.[104]

There are human rights issues regarding imprisonment. Sentencing an individual to a prison where he/she is more likely to contract a potentially lethal disease may contravene the basic human right to life.[104] Alternatives to imprisonment need to be considered by governments in order to decrease tuberculosis transmission.

Secondly, alcohol abuse is a problem in Ravensmead and Uitsig. The density of informal taverns is seventeen per square kilometre.[91] A national survey reported that 30% of women and 33% of men in the Western Cape Province who report current alcohol use are risky drinkers (≥3 drinks per day in women and ≥5 drinks per day in men).[10]

It is possible that the current study lacks sufficient power to show an association with alcohol – the univariate analysis showed an association, but not the adjusted analysis, or that the effect of alcohol is confounded by tobacco. In addition, the classification of the alcohol variable was rather crude which would also bias the results towards the null (this phenomenon is also seen with other crude questionnaire measures of variables such as general occupational dust exposure). In addition reporting bias and sharing of alcohol amongst multiple persons made the accurate quantification of data difficult. The analysis did not take quantity into account, which is a significant limitation.

HIV status is another important risk factor to consider, but was not considered in this study owing to logistic constraints and the relatively low prevalence of HIV infection in this community at the time of the study. The population prevalence of HIV was likely to be lower than that of the 15-45 year old group of pregnant women in which it was reported (antenatal survey). HIV is one of the most important risk factors in the South African setting, and has been associated with atypical signs and symptoms and extrapulmonary dissemination.[105] HIV infected persons are at an extremely high risk of activating latent disease. In addition, the issues of anti-TB drug resistance related to the HIV epidemic and significant drug interactions associated with highly active anti-retroviral therapy (HAART) need to be addressed by public health systems.

5.4. Proposed mechanisms for the association of cannabis smoking with TB:

5.4.1. Droplet spread

Sharing of joints, pipes and waterpipes is the first mode of spread. Cannabis pipe and makeshift pipe ("witpyp" or white-pipe) smoking in particular is a greater risk factor. This may be for more than one reason. Cannabis may be mixed with tobacco, conferring increased risk and may also be smoked in a social context where transmission in the study areas has been shown to be higher. The prevalence and risk conferred by adding methaquolone is not known. Drinking in informal taverns (shebeens) has been identified as a risk factor for tuberculosis.[80] Previously treated smear-positive TB cases from Ravensmead and Uitsig form more than half of the prevalent smear-positive cases. This is considered to be due to reinfection rather than reactivation, as confirmed by DNA fingerprinting studies.[106 107]

Secondly, smoking in enclosed spaces such as cars, bars and rooms where ventilation is deliberately limited, allows for rebreathing of cannabis smoke and potentially also droplet nuclei for long periods of time in greater amounts. Thirdly, cannabis smoking causes cough, which further improves the potential transmission of organisms in enclosed spaces.[85] Better enabling the routes of transmission of tuberculosis has been the main hypothesis explored in the literature. However, immunosuppressive mechanisms may also be potential factors in the transmission of infection and expression of disease.

5.4.2. Host-defence mechanisms

Considering that the constituents of cannabis smoke are very similar to that of tobacco smoke, it is not surprising that cannabis may also be a risk factor for tuberculosis. Exposure to any smoke lowers local bronchial immunity, cellular immunity and antibody production, therefore possibly raising susceptibility to infection. For instance, exposure to biomass smoke and passive tobacco smoke increases the risk of acute respiratory infection in children.[67]

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The differing ingredient of THC is also implicated in impairment of the immune response. The number of cigarettes smoked differs to the number of joints smoked, but it is thought that a smaller number of joints are related to a greater effect on the lungs. Features such as deeper inhalation, longer retention times and absence of

filtration result in a greater deposition of tar deposits compared to tobacco smokers.[77]

Cannabis is responsible for a wide spectrum of impairment of host defences, any or all of which may contribute to the lowering of defences to mycobacterium tuberculosis, particularly in endemic areas and even more so in hosts with other predisposing factors. Outbreak investigations have shown that persons with seemingly little other predisposing factors are at a greater risk for TB disease and infection, as seen where cannabis smoking contacts had a higher rate of infection than non cannabis smoking contacts.[81]

The histological changes that occur are a loss of ciliated epithelium and replacement by mucus secreting surface epithelial cells.[108] The first line of defence of the lung is thus impaired[67] (the mucociliary escalator), thus potentially predisposing to lower respiratory infection, which includes tuberculosis.

Alveolar macrophages are the main cells in the lung's immune response against infection and form the second line of defence.[77] There is a wide spectrum of effects on alveolar macrophages which support the possibility of cannabis smokers being more predisposed to tuberculosis. A review by Tashkin et al (2005) summarises the findings from studies of alveolar macrophage function.[77]
These include:

- "Impairment in fungicidal activity against Candida" spp. in alveolar macrophages from both cannabis smokers and tobacco smokers.[109 110]

- "Impairment in phagocytosis and bacteriocidal activity against staphylococcus aureus by alveolar macrophages" from cannabis smokers but not tobacco smokers.[109]The number of bacteria phagocytised and the rate of phagocytosis are both affected.[67]

- "Reduction in basal superoxide production by alveolar macrophages" from cannabis smokers. Tobacco smoking causes the opposite effect.[110]

- "Impairment in generation of nitric oxide by alveolar macrophages from cannabis smokers (but not tobacco smokers) paralleling their impairment in bacteriocidal activity." [111]

- "Reduction in generation of proinflammatory cytokines, including tumour necrosis factor-alpha (TNF- alpha) and granulocyte macrophage-colony stimulating factor (GM-CSF), by alveolar macrophages" from cannabis smokers when stimulated with bacterial lipopolysaccharide.[109]

Tashkin et al (2005) also suggest that a clinical implication of the impairment in alveolar macrophage function is that cannabis smokers may be at greater risk of pneumonia.[74] As tuberculosis is a common respiratory infection especially in endemic areas, it is likely to be a possible agent. This predisposition to pulmonary infection may occur especially in patients who are immunocompromised e.g. HIV infection. Opportunistic infection in HIV positive patients has been associated with cannabis smoking.[67] There are a few case reports of invasive aspergillosis in patients with AIDS.[112] However, the nature and mechanism of infection from mycobacteria may differ from that of other bacteria, and thus requires further study. Another area of interest that needs to be elucidated is the role of cannabis smoke in the TH1/TH2 balance - two mechanisms that are critical in determining both infection and disease.

5.5. Public Health policy

The relatively high prevalence of cannabis smoking is concerning. Public health efforts to lower the prevalence of cannabis smoking may reduce the prevalence of TB and should be pursued. Promotion of smoking cessation could have an impact on tuberculosis. Education about the harmful effects of cannabis may help to inform the public and assist in both highlighting the risks and reducing other cannabis-related health effects such as chronic bronchitis and trauma. This can be achieved by use of the popular media (TV infomercials, documentaries, magazines, newspapers), as has been done with tobacco smoking in some developed countries.

Secondly there is a need for effective anti-smoking-initiation interventions addressing both tobacco and cannabis, directed at schools and tertiary institutions, as few people start smoking after age 19 after which there are low levels of

quitting.[113] Further research examining factors that initiate, perpetuate and entrench smoking behaviour in South Africa and particularly in the Western Cape, may assist in the promotion of smoking cessation.

5.6. Dissemination

This study will be complied into a paper which will be submitted for publication in a peer reviewed journal dedicated either to respiratory medicine or to tuberculosis, such as the European Respiratory Journal or International Journal of Tuberculosis and Lung Diseases respectively. Findings from this study will also be presented at the American Thoracic Society Meeting in San Francisco, May 2007 and at the Congress of the International Union Against Tuberculosis and Lung Diseases in Cape Town in November 2007. Relevant persons at the local, provincial and national Department of Health will be informed of these findings via an Executive Summary and formal report.

5.7. Concluding remarks

This is the first population-based study to examine cannabis smoking as a risk factor for both tuberculosis disease and infection. This study population was appropriate for the exploration of the hypothesis owing to a high prevalence of both the exposure and outcome. In addition there was a sufficient sample size with which to perform multiple logistic regressions adjusting for various other risk factors.

This study provides further impetus for the promotion of smoking cessation as an important public health measure and suggests that anti-smoking health promotion and interventions need to be inclusive of both tobacco and cannabis. A target group for potential intervention (anti-initiation) would be the under 15 age group, as most smoking is initiated prior to this age. Persons in all other age groups, and particularly men would benefit from a smoking cessation service.

Tuberculosis, apart from being major cause of mortality, has been shown to have lasting effects in terms of respiratory morbidity. TB patients are not the only persons who would benefit from smoking cessation. All smokers would benefit from smoking cessation for a myriad of reasons – this study suggests another reason. However, the social and environmental causes of tuberculosis need to be addressed if any

headway is going to be made in quelling the epidemic, as control programs alone are insufficient.

The cumulative effect of cannabis smoking was found to be an independent risk factor for tuberculosis disease. This finding provides further evidence that cannabis smoking is harmful to health. Efforts are required to combat the existing health burden and inform and enable progressive anti-cannabis legislation and enforcement in addition to anti tobacco legislation. Cannabis smoking is a risk factor that must be considered in future studies of tuberculosis disease and infection. Repeated investigation of this hypothesis in varied settings will provide further information regarding the relationship between cannabis and tuberculosis.

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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.

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

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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**)?

Employed
- ☐ Self-employed
- ☐ Employed by government
- ☐ Employed in private sector
- ☐ Casual employment, specify:

Unemployed
- ☐ Not seeking work
- ☐ Seeking work
- ☐ Student
- ☐ Housewife
- ☐ Pension
- ☐ Disability grant for chest disease
- ☐ Disability grant for other disease
- ☐ Child support grant

If unemployed go to Question 14.

13 If you are employed, please state the nature of your job.
- ☐ Street vendor
- ☐ Hair dresser
- ☐ Shop owner
- ☐ Taxi driver
- ☐ Child minder
- ☐ Health care worker
- ☐ Factory worker
- ☐ Office worker
- ☐ Other (Please specify):

14 What is your usual monthly income(from all sources)?
- ☐ Less than R 500
- ☐ R 500-R 1 000
- ☐ R 1 000-R 2 000
- ☐ R 2 000-R 3 000
- ☐ R 3 000-R 4 000
- ☐ R 4 000-R 5 000
- ☐ R 5 000-R 6 500
- ☐ R 6 500-R 8 000
- ☐ R 8 000-R 10 000
- ☐ R 10 000-R 13 000
- ☐ Greater than 13 000

15 What level of education did you reach?
Highest grade completed: ____ ☐ Initiated tertiary education

16 What is your marital status?
- ☐ Single (never been married)
- ☐ Married
- ☐ Divorced/separated
- ☐ Widowed
- ☐ Living with a partner

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	m m/ Y Y Y Y	m m/ Y Y Y Y	
2	m m/ Y Y Y Y	m m/ Y Y Y Y	
3	m m/ Y Y Y Y	m m/ Y Y Y Y	

19 Do you have a **cough** that began recently? ☐Y ☐N
If 'yes', when did it start? d d/ m m/ Y Y Y Y

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? d d/ m m/ Y Y Y Y

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.**

- ☐ Rarely
- ☐ Sometimes
- ☐ Once a week
- ☐ 3 to 5 times a week
- ☐ Every night or almost every night
- ☐ Do not know

39.2 **How loud** have others said your snoring is?

- ☐ only slightly louder than heavy breathing
- ☐ about as loud as mumbling or talking
- ☐ louder than talking
- ☐ extremely loud (can be heard through a closed door)
- ☐ 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?

- ☐ never
- ☐ rarely
- ☐ sometimes
- ☐ often (at least once a week)
- ☐ very often(every night/almost every night)
- ☐ 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?**

- ☐ never
- ☐ rarely
- ☐ sometimes
- ☐ often(at least once a week)
- ☐ very often(every night/almost every night)
- ☐ 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**)?

- ☐ Chronic Bronchitis / Emphysema?
- ☐ Asthma?
- ☐ Pleurisy?
- ☐ Pneumonia?
- ☐ Hay fever?
- ☐ TB?
- ☐ Other chest trouble?

Specify: ☐

42.2 Where do you receive your **chest medicines?**

usually (check one only)		**occasionally (check all that apply)**
☐	Community clinic	☐
☐	Private hospital	☐
☐	Provincial hospital	☐
☐	Pharmacy	☐
☐	Private practitioner	☐
☐	Traditional healer	☐
☐	A friend	☐

43 Where do you usually go for medical care for chest problems?

usually (check one only)		**occasionally (check all that apply)**
☐	Community clinic	☐
☐	Private hospital	☐
☐	Provincial hospital	☐
☐	Pharmacy	☐
☐	Private practitioner	☐
☐	Traditional healer	☐
☐	A friend	☐

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?

usually (check one only)		**occasionally (check all that apply)**
☐	Community clinic	☐
☐	Private hospital	☐
☐	Provincial hospital	☐
☐	Pharmacy	☐
☐	Private practitioner	☐
☐	Traditional healer	☐
☐	A friend	☐

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 may 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? ☐

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	☐	☐
Train	☐	☐
Bus	☐	☐
Private car	☐	☐
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	☐	☐
Church/community gatherings	☐	☐
Clinics	☐	☐
Shebeen	☐	☐
Other specify:	☐	

52 What fuels are mostly used in the dwelling you spend most of your evenings?

For Cooking (check one only)		**For Heating (check one only)**
☐	Wood or coke	☐
☐	Gas	☐
☐	Electricity	☐
☐	Paraffin	☐
☐	Spirits	☐

53 Have you ever spent time in a prison? ☐Y ☐N ***If yes, please specify dates and place:***

From	**To**	**Prison**
m m / Y Y Y Y	m m / Y Y Y Y	
m m / Y Y Y Y	m m / Y Y Y Y	

APPENDIX 3

Alternative multivariate models

Outcome TB disease

Model assessing the cannabis and tobacco interaction using non, ex- and current cannabis and tobacco smoking

```
xi:svy:logit prespast_tb i.dagga i.age_cat gender_cat  i.smoker  prison i.BMI_cat
i.educ_cat_tert i.wealth
> 3 i.alc_cat occ_exposure i.smoker*i.dagga  ,or
i.dagga           _Idagga_1-3         (naturally coded; _Idagga_1 omitted)
i.age_categor~s   _Iage_categ_1-6     (naturally coded; _Iage_categ_1 omitted)
i.smoker          _Ismoker_1-3        (naturally coded; _Ismoker_1 omitted)
i.BMI_cat         _IBMI_cat_1-4       (naturally coded; _IBMI_cat_1 omitted)
i.educ_cat_tert   _Ieduc_cat__1-4     (naturally coded; _Ieduc_cat__1 omitted)
i.wealth3         _Iwealth3_1-3       (naturally coded; _Iwealth3_1 omitted)
i.alc_cat         _Ialc_cat_0-3       (naturally coded; _Ialc_cat_0 omitted)
i.s~ker*i.dagga   _IsmoXdag_#_#       (coded as above)
(running logit on estimation sample)

Survey: Logistic regression

Number of strata   =         1                  Number of obs      =      2737
bvNumber of PSUs     =       765                  Population size    =     26178
                                                  Design df          =       764
                                                  F(  26,    739)    =      5.50
                                                  Prob > F           =    0.0000

------------------------------------------------------------------------------
             |             Linearized
 prespast_tb | Odds Ratio   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   _Idagga_2 |   2.375152   1.579334     1.30   0.194     .6438657    8.761682
   _Idagga_3 |   3.971371   2.319834     2.36   0.018     1.261628    12.50114
_Iage_cate~2 |   1.946911   .4450712     2.91   0.004     1.242938    3.049599
_Iage_cate~3 |   2.622686   .6099185     4.15   0.000     1.661427    4.140106
_Iage_cate~4 |   2.561159   .6484283     3.71   0.000     1.558079    4.210016
_Iage_cate~5 |   3.119861   .7806793     4.55   0.000     1.908983    5.098805
_Iage_cate~6 |   1.535007   .5062877     1.30   0.194     .8033689    2.932956
  gender_cat |    1.01394   .1627167     0.09   0.931     .7399372    1.389407
   _Ismoker_2 |   1.750261   .4520278     2.17   0.031     1.054193    2.905933
   _Ismoker_3 |   1.169106   .1861421     0.98   0.327     .8552884    1.598067
       prison |   1.302947   .2742143     1.26   0.209     .8619879    1.969483
 _IBMI_cat_2 |   .4535978   .0904306    -3.97   0.000     .3066928    .6708699
 _IBMI_cat_3 |   .3788978   .0842306    -4.37   0.000     .2449042    .5862031
 _IBMI_cat_4 |   1.911929   .3600552     3.44   0.001     1.321049    2.767099
_Ieduc_cat~2 |   1.392097   .2831755     1.63   0.104     .9337837    2.075356
_Ieduc_cat~3 |   1.633269   .3753949     2.13   0.033     1.040171    2.564547
_Ieduc_cat~4 |   .9386734   .3971825    -0.15   0.881     .4090465    2.154053
 _Iwealth3_2 |   1.059796   .2771994     0.22   0.824     .6342047    1.770986
 _Iwealth3_3 |   1.669078    .404292     2.11   0.035     1.037451    2.685257
 _Ialc_cat_1 |   1.039679   .1824861     0.22   0.825     .7366441    1.467373
 _Ialc_cat_2 |   1.242846   .2723687     0.99   0.321     .8083157    1.910968
 _Ialc_cat_3 |   1.089334   .3508452     0.27   0.791     .5788649    2.049959
occ_exposure |   1.199088    .185801     1.17   0.242     .8845987    1.625383
_IsmoXda~2_2 |   .5586657   .4655755    -0.70   0.485     .1088079    2.868427
_IsmoXda~3_2 |   .6062653    .436802    -0.69   0.488     .1473723    2.494075
_IsmoXda~3_3 |   .3263741   .1998532    -1.83   0.068     .0980981    1.085853
------------------------------------------------------------------------------

. testparm _IsmoXda*

Adjusted Wald test

 ( 1)  _IsmoXdag_2_2 = 0
 ( 2)  _IsmoXdag_3_2 = 0
 ( 3)  _IsmoXdag_3_3 = 0

       F(  3,   762) =    1.30
            Prob > F =    0.2747
```

Outcome: TB infection

Model without adjusting for imprisonment

```
xi:svy:logit mtx10 i.age_cat gender_cat i.dagga i.smoker i.alc_cat  occ_exposure
i.educ_cat_tert i.wealth
> 3 ,or
i.age_categor~s   _Iage_categ_1-6     (naturally coded; _Iage_categ_1 omitted)
i.dagga           _Idagga_1-3         (naturally coded; _Idagga_1 omitted)
i.smoker          _Ismoker_1-3        (naturally coded; _Ismoker_1 omitted)
i.alc_cat         _Ialc_cat_0-3       (naturally coded; _Ialc_cat_0 omitted)
i.educ_cat_tert   _Ieduc_cat__1-4     (naturally coded; _Ieduc_cat__1 omitted)
i.wealth3         _Iwealth3_1-3       (naturally coded; _Iwealth3_1 omitted)
(running logit on estimation sample)

Survey: Logistic regression

Number of strata   =         1                  Number of obs      =      3413
Number of PSUs     =       818                  Population size    =     26178
                                                Design df          =       817
                                                F(  19,    799)    =     11.61
                                                Prob > F           =    0.0000
```

mtx10	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
_Iage_cate~2	4.181028	.6762735	8.84	0.000	3.043677	5.743381
_Iage_cate~3	2.692877	.4228978	6.31	0.000	1.978531	3.665137
_Iage_cate~4	2.131814	.3647257	4.42	0.000	1.523715	2.982599
_Iage_cate~5	1.399492	.241707	1.95	0.052	.9971052	1.964265
_Iage_cate~6	.5790874	.1169945	-2.70	0.007	.38951	.8609336
gender_cat	1.205406	.1316939	1.71	0.088	.972746	1.493714
_Idagga_2	**1.974495**	**.605535**	**2.22**	**0.027**	**1.081493**	**3.604861**
_Idagga_3	1.127795	.2658234	0.51	0.610	.7100728	1.791256
_Ismoker_2	1.322509	.2584728	1.43	0.153	.9011395	1.94091
_Ismoker_3	1.648905	.1941524	4.25	0.000	1.308642	2.077639
_Ialc_cat_1	1.163416	.1529705	1.15	0.250	.898772	1.505984
_Ialc_cat_2	.9022128	.1908786	-0.49	0.627	.5956011	1.366666
_Ialc_cat_3	.7018007	.2011536	-1.24	0.217	.3998307	1.231832
occ_exposure	1.027424	.1304618	0.21	0.831	.8007632	1.318242
_Ieduc_cat~2	.9060787	.1219807	-0.73	0.464	.6956697	1.180127
_Ieduc_cat~3	1.255794	.2127706	1.34	0.179	.9005018	1.751267
_Ieduc_cat~4	.6163646	.1636642	-1.82	0.069	.3660004	1.037991
_Iwealth3_2	1.128091	.2059387	0.66	0.509	.7883562	1.614231
_Iwealth3_3	.9826227	.1512195	-0.11	0.909	.7264369	1.329155

Outcome: TB infection

Model adjusting for imprisonment

```
xi:svy:logit mtx10 i.age_cat gender_cat i.dagga i.smoker i.alc_cat prison
occ_exposure i.educ_cat_tert i.
> wealth3 ,or
i.age_categor~s   _Iage_categ_1-6     (naturally coded; _Iage_categ_1 omitted)
i.dagga           _Idagga_1-3         (naturally coded; _Idagga_1 omitted)
i.smoker          _Ismoker_1-3        (naturally coded; _Ismoker_1 omitted)
i.alc_cat         _Ialc_cat_0-3       (naturally coded; _Ialc_cat_0 omitted)
i.educ_cat_tert   _Ieduc_cat__1-4     (naturally coded; _Ieduc_cat__1 omitted)
i.wealth3         _Iwealth3_1-3       (naturally coded; _Iwealth3_1 omitted)
(running logit on estimation sample)

Survey: Logistic regression

Number of strata   =         1                  Number of obs      =      3387
Number of PSUs     =       817                  Population size    =     26178
                                                Design df          =       816
                                                F(  20,    797)    =     11.07
                                                Prob > F           =    0.0000
```

mtx10	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
_Iage_cate~2	4.0956	.6632641	8.71	0.000	2.980331	5.628214
_Iage_cate~3	2.615782	.4129485	6.09	0.000	1.918776	3.565978
_Iage_cate~4	2.072322	.3583602	4.21	0.000	1.475853	2.909857
_Iage_cate~5	1.364246	.239443	1.77	0.077	.9666598	1.925358
_Iage_cate~6	.5699387	.1146197	-2.80	0.005	.3840517	.8457979
gender_cat	1.146987	.1262409	1.25	0.213	.924131	1.423585
_Idagga_2	**1.669535**	**.5201368**	**1.65**	**0.100**	**.9057604**	**3.077357**
_Idagga_3	.8921571	.2152345	-0.47	0.636	.5556258	1.432519
_Ismoker_2	1.337695	.2621172	1.48	0.138	.9105818	1.965147
_Ismoker_3	1.629924	.1912924	4.16	0.000	1.294552	2.052178
_Ialc_cat_1	1.170768	.1542804	1.20	0.232	.9039311	1.516374
_Ialc_cat_2	.9025594	.1939048	-0.48	0.633	.5920154	1.376001
_Ialc_cat_3	.6286767	.1810637	-1.61	0.107	.3571994	1.106481
prison	**3.020794**	**.9465241**	**3.53**	**0.000**	**1.633099**	**5.587655**
occ_exposure	.9942735	.1274154	-0.04	0.964	.7731486	1.278641
_Ieduc_cat~2	.9130833	.1233161	-0.67	0.501	.7004562	1.190254
_Ieduc_cat~3	1.231038	.2093744	1.22	0.222	.8816259	1.718931
_Ieduc_cat~4	.6646113	.1820337	-1.49	0.136	.3882233	1.137769
_Iwealth3_2	1.111587	.202854	0.58	0.562	.7769205	1.590415
_Iwealth3_3	.9373466	.1453793	-0.42	0.677	.6913303	1.27091

Outcome: TB infection

Model assessing the interaction of cannabis with imprisonment

```
xi:svy:logit mtx10 i.age_cat gender_cat i.dagga*prison i.smoker i.alc_cat
occ_exposure i.educ_cat_tert i
> .wealth3 prison,or
i.age_categor~s   _Iage_categ_1-6     (naturally coded; _Iage_categ_1 omitted)
i.dagga           _Idagga_1-3         (naturally coded; _Idagga_1 omitted)
i.dagga*prison    _IdagXpriso_#       (coded as above)
i.smoker          _Ismoker_1-3        (naturally coded; _Ismoker_1 omitted)
i.alc_cat         _Ialc_cat_0-3       (naturally coded; _Ialc_cat_0 omitted)
i.educ_cat_tert   _Ieduc_cat__1-4     (naturally coded; _Ieduc_cat__1 omitted)
i.wealth3         _Iwealth3_1-3       (naturally coded; _Iwealth3_1 omitted)
(running logit on estimation sample)

Survey: Logistic regression

Number of strata   =         1                  Number of obs      =      3387
Number of PSUs     =       817                  Population size    =     26178
                                                Design df          =       816
                                                F(  22,    795)    =     10.33
                                                Prob > F           =    0.0000
```

mtx10	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
_Iage_cate~2	4.095797	.664126	8.70	0.000	2.979289	5.630724
_Iage_cate~3	2.614796	.4146988	6.06	0.000	1.915311	3.569738
_Iage_cate~4	2.074686	.3583833	4.22	0.000	1.478075	2.912113
_Iage_cate~5	1.366791	.2400707	1.78	0.076	.968212	1.929452
_Iage_cate~6	.5714821	.1150473	-2.78	0.006	.3849367	.8484297
gender_cat	1.141959	.1260581	1.20	0.230	.9194943	1.418248
_Idagga_2	**2.210913**	**.8089855**	**2.17**	**0.030**	**1.078076**	**4.534128**
_Idagga_3	.8935735	.2389781	-0.42	0.674	.528623	1.510478
prison	**4.8896**	**2.529311**	**3.07**	**0.002**	**1.771358**	**13.49709**
_IdagXpris~2	**.1860776**	**.156634**	**-2.00**	**0.046**	**.0356547**	**.9711181**
_IdagXpris~3	.6625235	.5302767	-0.51	0.607	.1376882	3.187909
_Ismoker_2	1.333033	.2613298	1.47	0.143	.9072399	1.958662
_Ismoker_3	1.623164	.190873	4.12	0.000	1.288601	2.044592
_Ialc_cat_1	1.164124	.1537535	1.15	0.250	.8982737	1.508656
_Ialc_cat_2	.8862849	.1912402	-0.56	0.576	.5802705	1.353681
_Ialc_cat_3	.6029271	.1760908	-1.73	0.084	.3398551	1.069636
occ_exposure	.9982665	.1284709	-0.01	0.989	.7754241	1.28515
_Ieduc_cat~2	.9040511	.1220921	-0.75	0.455	.6935334	1.17847
_Ieduc_cat~3	1.221171	.2065707	1.18	0.238	.8761431	1.702071
_Ieduc_cat~4	.6606827	.1806899	-1.52	0.130	.3862356	1.130143
_Iwealth3_2	1.116843	.2043413	0.60	0.546	.7798701	1.599419
_Iwealth3_3	.943157	.1466336	-0.38	0.707	.6951047	1.279728

```
testparm _IdagXpris*

Adjusted Wald test

 ( 1)  _IdagXpriso_2 = 0
 ( 2)  _IdagXpriso_3 = 0

       F(  2,   815) =    2.04
            Prob > F =    0.1302
```

Outcome: TB infection

Model assessing the joint-year/prison interaction

```
xi:svy:logit mtx10 i.age_cat gender_cat i.jointpipe_years_cat i.packyear_cat
i.jointpipe_years_cat*priso
> n prison i.alc_cat  occ_exposure i.educ_cat_tert i.wealth3 ,or
i.age_categor~s    _Iage_categ_1-6     (naturally coded; _Iage_categ_1 omitted)
i.jointpipe_y~t    _Ijointpipe_0-3     (naturally coded; _Ijointpipe_0 omitted)
i.packyear_cat     _Ipackyear__0-3     (naturally coded; _Ipackyear__0 omitted)
i.~s_cat*prison    _IjoiXpriso_#       (coded as above)
i.alc_cat          _Ialc_cat_0-3       (naturally coded; _Ialc_cat_0 omitted)
i.educ_cat_tert    _Ieduc_cat__1-4     (naturally coded; _Ieduc_cat__1 omitted)
i.wealth3          _Iwealth3_1-3       (naturally coded; _Iwealth3_1 omitted)
(running logit on estimation sample)

Survey: Logistic regression

Number of strata   =         1                  Number of obs      =      3357
Number of PSUs     =       817                  Population size    =     26178
                                                Design df          =       816
                                                F(  25,    792)    =      8.83
                                                Prob > F           =    0.0000

------------------------------------------------------------------------------
             |             Linearized
       mtx10 | Odds Ratio   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
_Iage_cate~2 |   4.088618   .6637911     8.67   0.000     2.972884    5.623093
_Iage_cate~3 |   2.519595   .4072778     5.72   0.000     1.834572    3.460405
_Iage_cate~4 |   2.024505   .3633349     3.93   0.000     1.423404    2.879451
_Iage_cate~5 |   1.299858   .2326662     1.47   0.143      .914766    1.847064
_Iage_cate~6 |   .5567577   .1116796    -2.92   0.004     .3755525    .8253949
  gender_cat |   1.109564   .1226639     0.94   0.347     .8931226    1.378459
_Ijointpip~1 |    1.28096   .3791758     0.84   0.403     .7164701    2.290199
_Ijointpip~2 |   1.024109   .6112743     0.04   0.968     .3173383    3.304985
_Ijointpip~3 |   1.880886   1.096389     1.08   0.279      .599033    5.905739
_Ipackyear~1 |    1.38213   .1685604     2.65   0.008     1.087889    1.755954
_Ipackyear~2 |   2.174998   .5023414     3.36   0.001     1.382203     3.42252
_Ipackyear~3 |    1.52335   .3155154     2.03   0.042     1.014466    2.287504
      prison |   4.604182   2.171657     3.24   0.001     1.824187    11.62079
_IjoiXpris~1 |    .403586   .3451411    -1.06   0.289     .0753215    2.162485
_IjoiXpris~2 |   .7603707   .9874932    -0.21   0.833     .0594194    9.730221
_IjoiXpris~3 |   .3970144   .4120029    -0.89   0.374     .0517794    3.044075
 _Ialc_cat_1 |   1.223083   .1600886     1.54   0.124     .9459697    1.581375
 _Ialc_cat_2 |   .8883873   .1927957    -0.55   0.586     .5802328    1.360199
 _Ialc_cat_3 |   .6932567   .1901969    -1.34   0.182     .4045923    1.187874
occ_exposure |   .9928107   .1284611    -0.06   0.956     .7701313    1.279877
_Ieduc_cat~2 |   .9083874   .1233553    -0.71   0.479     .6958406    1.185857
_Ieduc_cat~3 |   1.199752   .2040912     1.07   0.285     .8591672     1.67535
_Ieduc_cat~4 |   .6433927   .1785363    -1.59   0.112     .3731845    1.109248
 _Iwealth3_2 |   1.120296   .2075324     0.61   0.540      .778781    1.611574
 _Iwealth3_3 |   .9464232   .1486233    -0.35   0.726     .6953713    1.288113
------------------------------------------------------------------------------

. testparm _IjoiXpris*

Adjusted Wald test

 ( 1)  _IjoiXpriso_1 = 0
 ( 2)  _IjoiXpriso_2 = 0
 ( 3)  _IjoiXpriso_3 = 0

       F(  3,   814) =    0.52
            Prob > F =    0.6690
```